International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Special Issue 2, 2025

Original Article

POTENTIAL OF DRUG INTERACTIONS IN HOSPITALIZED PATIENTS RECEIVING WARFARIN THERAPY FOR THE FIRST TIME

DIAN OKTIANTI[1,2], ZAKKY CHOLISOH[1*], SITI MAISHARAH SHEIKH GHADZI[3], HIDAYAH KARUNIAWATI[1]

[1]Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Central Java, Indonesia. [2]Pharmacy Study Program, Faculty of Health, Universitas Ngudi Waluyo, Central Java, Indonesia. [3]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Gelugor-11800, Pulau Pinang, Malaysia

[*]Corresponding author: Zakky Cholisoh; [*]Email: zakky.cholisoh@ums.ac.id

Received: 19 Mar 2025, Revised and Accepted: 21 May 2025

ABSTRACT

Objective: To identify potential interactions between warfarin and other drugs in hospitalized patients receiving warfarin therapy for the first time and determine parameters that are predicted to increase the risk of drug interactions resulting in major clinical severity. This is the first study in the field that was conducted in a multicenter setting in Central Java.

Methods: Data on the use of concomitant drugs with warfarin were collected from the medical records of hospitalized patients (August 2023-July 2024) who first received warfarin in a retrospective, multicentre study at 4 hospitals. Potential drug interaction was analyzed using a drug interaction checker.

Results: There were 148 patients who met the criteria, 78 patients (53%) were male and aged between 40-64 y. 78 patients (52%) received more than 8 types of drugs. Potential drug interactions occurred in all patients (100%), 62 patients (46.62%) experienced interactions in 6-8 drugs used. The parameter that had the strongest association with the severity of potential drug interactions was the number of drugs consumed with an Adjusted Odds Ratio (AOR) of 3.097 (95% CI 1.495-6.417) and a p-value of 0.002 ($p<0.05$) and Length of Stay (LOS) with an AOR of 0.344 (95% CI 0.125-0.945 and a p-value 0.038 ($p<0.05$).

Conclusion: All hospitalized patients receiving first-time warfarin therapy experienced potential drug interaction events. The strongest predictors contributing to potential drug interactions with major clinical impact severity were the number of drugs taken at the normal dose and length of stay.

Keywords: Warfarin, Drug interaction, Major severity, Hospitalised patients

DOI: https://dx.doi.org/10.22159/ijap.2025.v17s2.14 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Warfarin is an oral anticoagulant recommended for the treatment and prevention of thromboembolism in patients with atrial fibrillation [1]. In Indonesia, the number of heart disease patients with atrial fibrillation has increased by 30% in the last 3 y. This is one of the factors that has led to an increase in the use of warfarin. Warfarin is an oral anticoagulant listed in the national formulary with an indication for the prevention of thromboembolism in patients with atrial fibrillation. Warfarin is the most cost-effective oral anticoagulants [2, 3]. Warfarin has a narrow therapeutic index, interacts with many drugs, and has a risk of causing bleeding. Warfarin metabolism occurs in the liver via cytochrome P450 enzymes, mainly CYP2C9, CYP2C19, CYP2C8, CYP1A2, and CYP3A4 [4]. Genetic factors that play a role in warfarin dose variability are the Cytochrome P450 Family 2 Subfamily C Member 9 (CYP2C9) genes CYP2C9*2 and CYP2C9*3 are very influential on warfarin dose variability because they can reduce the activity of the CYP2C9 enzyme, thus causing a decrease in warfarin metabolism in the body based on research it is known that a decrease in binding affinity leads to an increased risk of bleeding [5]. Competition by some drugs for metabolism through CYP2C9 may reduce elimination of the drug from the systemic circulation. Diuretics (loop and thiazide) and warfarin are highly protein-bound to albumin and are basic substrates for CYP2C9 isoenzyme. The addition of diuretics may enhance the anticoagulant action of warfarin through metabolic competition via CYP2C9, by reduction of warfarin elimination, and displacement of warfarin protein binding from albumin [6, 7]. The risk of side effects due to interactions between warfarin and other drugs will increase when the number of other drugs given simultaneously increases.

In a study conducted on hospitalized patients, the incidence of drug interactions was experienced by 132 (99.2%) of patients, which caused 22 patients (16.5%) to experience bleeding [8]. Based on research conducted in Indonesia at RSUD Wates Yogyakarta Indonesia, it is known that the interaction of warfarin with antibiotics can significantly ($p=0.017$) increase the risk of bleeding. Antibiotics used by patients with bleeding events are azithromycin, ampicillin-sulbactam, cephalosporin group, and quinolone group. Bleeding events that occurred included hematemesis melena (25%), hematuria (50%) and unknown (25%) [9]. A systematic review and meta-analysis showed that a total of 3,735,775 patients receiving warfarin were found to have experienced drug interactions. Increased risk of clinically relevant bleeding when added to warfarin therapy was observed for antiplatelet, nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2 NSAIDs, loop diuretics, and many antibiotics [10]. The highest frequency of drug interactions was found in hospitalized patients taking warfarin compared to patients undergoing outpatient treatment. This is due to the many types of drugs given to hospitalized patients according to their health conditions and comorbidities [11–13]. The aim of this study was to identify potential interactions between warfarin and other drugs in hospitalized patients receiving warfarin therapy for the first time and determine the parameters that are predicted to increase the risk of drug interactions that result in major clinical severity.

MATERIALS AND METHODS

Research design and location

This research was conducted at four hospitals, Roemani Muhammadiyah Hospital Semarang, RSI Sultan Agung Semarang, Gondo Suwarno Hospital Ungaran, and Ken Saras Hospital Ungaran. The design of this study was a retrospective cohort. Research data was obtained retrospectively for the first time from August 2023 to July 2024. Data was collected from medical records of inpatients who underwent warfarin therapy for the first time. Patient consent was waived for retrospective data use and this study adhered to Declaration Helsinki guideline. This research has received ethical approval from the Ethics Committee of Ngudi Waluyo University

with number 327/KEP/EC/UNW/2024. The sampling technique used was purposive sampling with inclusion criteria: inpatients who were using warfarin for the first time and had complete medical record data. The sample calculation used is the total sample based on the appropriate sample. The use of total sampling in this study was due to the small number of populations obtained, so this method was used. The sample used consisted of hospitalized patients who were receiving warfarin therapy for the first time.

Data collection

Data recorded in the data collection sheet included demographic data, indications for use of warfarin, comorbidities, and use of other drugs that were used simultaneously

Assessment of potential drug interactions

The assessment of drug interaction events was analyzed using https://go.drugbank.com/drug-interaction-checker. This application identifies potential interactions between drugs, complete with the level of severity (major, moderate, or minor), as well as an explanation of the interaction mechanism. The severity of the interaction is critical in evaluating the risks and benefits of various treatment options. By adjusting the dose or drug administration schedule, most side effects due to drug interactions can be avoided. Drug interactions refer to interactions between two or more drugs that may affect the effectiveness or safety of those drugs. The severity of drug interactions can be categorized as minor, moderate, or major. Minor interactions generally have mild side effects that may not significantly affect treatment outcomes. Moderate interactions may cause a deterioration in the patient's clinical condition and may require additional treatment. Meanwhile, major interactions have the potential to be life-threatening, such as bleeding [14].

Statistical analysis

To analyze the relationship between the independent variables and the dependent variable, the chi-square test was used. This test is used to see the relationship between categorical variables. The chi-square test was carried out first for the independent variables age, gender, number of comorbidities, length of treatment, and number of drugs used with dependent variables interaction severity. To identify the factors that most influence the potential for bleeding due to drug interactions, logistic regression analysis was carried out. All data analysis was carried out using statistical software IBM SPSS ver 25 with a confidence level of 95%.

RESULTS AND DISCUSSION

This study used medical record data of inpatients who underwent warfarin therapy for the first time from August 2023 to July 2024. Table 1 shows the sociodemographic characteristics.

Table 1: Sociodemographic and clinical characteristics of patients receiving warfarin for the first time (N=148)

Criteria		Number (n)	Percentage (%)
Sociodemographic			
Sex	Male	78	53
	Female	70	47
	Total	148	100
Age	15-39	5	3
	40-64	82	55
	≥65	61	41
	Total	148	100
Clinical			
Indications for the Use of Warfarin	AF	50	33.78
	CHF	41	27.70
	AF+CHF	38	25.68
	CVD	10	6.76
	Cerebral Infraction	6	4.05
	DVT	2	2.03
	Total	148	100
Comorbidities	Hypertension	44	31.08
	DM type 2	32	21.62
	Pneumonia	13	8.78
	CKD	9	6.08
	COPD	8	5.41
	Others	42	27.03
	Total	148	100
Length of stay (LOS) (days)	<3	8	5.41
	3-5	97	65.54
	6-8	38	25.68
	>8	5	3.38
	Mean±SD	5±1,35	
Medication			
First dose of Warfarin (mg)	1	4	2.70
	2	136	91.89
	3	3	2.03
	4	5	3.38
	Total	148	100
The amount of medication per patient	≥ 10	64	43.24
	<10	84	56.76
	Mean±SD	9±1.56	
Number of drug interactions	<3	4	2.70
	3-5	43	29.05
	6-8	69	46.62
	>8	32	21.62
	Mean±SD	7±1.63	

Note: AF: Atrial fibrillation; CHF: Congestive heart failure; CAD: Coronary artery disease; DVT: Deep vein thrombosis; Type 2 DM: Type 2 diabetes mellitus; COPD: Chronic obstructive pulmonary disease, list of drugs that interact with warfarin can be seen in table 2.

Table 2: List of drugs that interact with warfarin

No	Interaction severity	Drug class	Drug	Number	Frequency (%)
1	Major	Antihypertensive	Candesartan	47	75
			Amlodipine	23	(8,76)*
		Antihyperlipidemics	Fenofibrate	4	
		Electrolit	Tolvaptan	1	
2	Moderate	Antihypertensive	Furosemide	86	618
			Bisoprolol	70	(72,20)**
			Valsartan	14	
			Carvedilol	12	
		Antibiotic	Ceftriaxone	30	
			Ampicillin Sulbactam	13	
		NSAID	Acetaminophen	23	
			Ketorolac	10	
		Antidiabetic	Metformin	16	
		Gastrointestinal	Omeprazole	80	
			Ondansetron	47	
			Sucralfate syr	32	
			Lansoprazole	18	
			Ranitidine	15	
		Cardiovasculer	Digoxin	47	
		Antiplatelet	Clopidogrel	32	
			Aspirin	23	
		Antihyperlipidemics	Simvastatin	5	
		Antihistamine	Cetirizine	5	
			Flunarizine	5	
		Antihyperuricemic	Allopurinol	18	
		Corticosteroid	Methylprednisolone	17	
3	Minor	Antihypertensive	Spironolactone	83	163 (19,04)***
		Antibiotic	Cefixime	13	
		NSAID	Tramadol	4	
		Antidiabetic	Glimepirid	8	
			Acarbose	7	
			Glicazid	7	
		Antihyperlipidemics	Atorvastatin	41	

*: % of major interaction" **: % of moderate interaction; ***: % of minor interaction, NSAID: Non Steroid Anti-infammatory drugs

Table 3: Statistical test parameters based on sociodemographic and clinical characteristics to the potential for major drug interactions

No	Parameter	Bivariate test			Multivariate test		
		Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
1	The amount of medicine taken ≥ 10 (64) <10 (84)	2.545	1.299-4.989	0.006	3.097	1.495-6.417	0.002
2	LOS -≥ 7 (23) <7 (125)	0.522	0.210-1.294	0.156	0.344	0,125-0.945	0.038
3	Sex -Male (71) -Female (77)	0.988	0.518-1.886	0.972	0.966	0.494-1.963	0.966
4	Comorbidities ->1 (68) -≤ 1 (80)	1.579	0.822-3.032	0.169	1.498	0.757-2.966	0.246
5	Age (y) ->60 (101) -≤ 60 (47)	1.248	0.624-2.495	0.531	1.438	0.682-3.032	0.340

CI: confidence interval; LOS: length of stay

Table 3 shows the test results to see parameters related with the incidence of drug interactions.

The number of medications used category is based on the WHO definition of hyperpolypharmacy and other studies [15, 16].

LOS is divided into>7 d and<7 d because the ideal length of hospital stay in Indonesia is 6-9 d, based on guidelines from the Ministry of Health and other studies that use this split [16, 17].

DISCUSSION

Based on table 1, there were 148 patients who met the inclusion criteria. As many as 78 patients (53%) were male and 70 patients (47%) were female. The age range of most patients was within the age group of 40-64 y, with 82 people (55%).

Table 1 shows that the main indications for the use of warfarin in patients are for atrial fibrillation (AF) therapy in 53 patients (33.78%) and congestive heart failure (CHF) in 41 patients (27.70%). Most patients (n=136, 91.89%) received a dose of warfarin 2 mg per day. Hypertension (n=44, 31.08%) and type 2 diabetes mellitus (n=32, 21.62%) were the most comorbidities. The average length of patient hospitalization is three to five days (n=97, 65.54%). In addition, majority of patients, 78 patients (52.70%), received more than 8 types of medication during their treatment. The number of potential drug interactions experienced by each

patient is also quite high, with an average of six to eight potential interactions per patient (n=69, 46.62%).

Based on the results of the research in table 1, it is known that majority of patients receiving warfarin therapy were in the age range of 40-64 y, with the main indication being atrial fibrillation. Another study mentions that warfarin is the most used anticoagulant for atrial fibrillation therapy in patients aged>45-65 y [18–20]. With the increasing life expectancy, the incidence of atrial fibrillation has tripled in the last 50 y, where the risk in men is more than four times that of women over the age of 40 [21, 22].

Hypertension and diabetes mellitus (DM) were the most common comorbidities in patients in this study. Age, body mass index, hypertension, diabetes mellitus (DM), myocardial infarction, congestive heart failure (CHF), smoking, and genetic factors are risk factors that increase the incidence of atrial fibrillation (AF). Hypertension is a factor that influences cardiovascular complications, including coronary artery disease, which can ultimately lead to AF. High blood pressure in hypertensive patients causes remodeling of the left ventricular structure [23–25]. The condition of glucose intolerance and insulin resistance in DM patients can trigger modulators that play a role in the onset of AF. People with DM have a 40% higher risk of experiencing AF compared to those without DM [20–23].

The incidence of AF increases with age, so patients with AF often have one or more comorbidities. As the number of comorbidities increases, the likelihood of polypharmacy also increases. Polypharmacy is defined as the use of five or more drugs simultaneously. While polypharmacy is defined by the WHO as the use of more than ten medications. In this study, it was found that 130 patients (56.76%) used more than ten types of medication. Another study also reported that polypharmacy occurred in 76.5% of AF patients who received over six types of medication [30, 31]. One of the unavoidable impacts of polypharmacy is the increased drug interactions, which can elevate the risk of bleeding and death. This presents a unique challenge because AF therapy worldwide generally uses warfarin as an oral anticoagulant, which is known to have many drug interactions. Warfarin can cause more than 6-8 drug interactions in patients who are using it for the first time, with significant potential interactions [26, 27].

In table 2, it is noted that furosemide is the most frequently administered medication to patients, with a total of 86 individuals. Based on the therapy received by the patients, an analysis of potential drug interactions was conducted. The analysis results indicate that potential drug-drug interaction were most likely occurs in three types of drugs (8.76%) with a major severity level, 22 types of drugs (72.20%) with a moderate severity level, and seven types of drugs (19.04%) with a minor severity level. Compared to a prospective study conducted in Ethiopia, almost the same results were obtained. In the study, it was stated that the prevalence of drug interactions was 99.2% and 42.9% experienced interactions with major severity. Whereas in this study, 100% of patients experienced drug interactions and 8.76% experienced major severity [8].

The medications most used with warfarin were antihypertensives, antibiotics, analgesics, antidiabetics, gastrointestinal drugs, cardiovascular drugs, antiplatelets, antihyperlipidemic, and antihyperuricemics. In this study, the medications that have the potential to cause drug interactions with major severity are candesartan, amlodipine, fenofibrate, and tolvaptan. Antihypertensive drugs are the most used group with warfarin. Candesartan and amlodipine have the potential to cause interactions with major severity. Antihypertensive drugs of the ARB class (candesartan, irbesartan, losartan, valsartan, and olmesartan) affect the activity of the CYP2C9 enzyme, with losartan and irbesartan also known to inhibit CYP3A4 [34]. The concurrent use of candesartan with warfarin can lower the plasma concentration of warfarin, so prothrombin time (PT) monitoring is necessary to ensure the target INR value is achieved. Physicians and pharmacists should monitor the INR regularly to ensure that the patient's INR target is being achieved [35]. The potential interaction between warfarin and amlodipine can increase the risk of bleeding, as amlodipine inhibits the CYP3A4 enzyme, which raises warfarin levels [10]. Fenofibrate, when given together with warfarin, will reduce the metabolism of warfarin and displace protein-bound warfarin, thereby increasing the anticoagulant response. To prevent bleeding, the warfarin dose needs to be reduced by 20% in patients of Indian, Chinese, and Malay ethnicity [36, 37]. Whenever starting fenofibrate for patients receiving concurrent warfarin, the INR should be checked 48–72 h as the warfarin dose may need to be reduced [38]. Tolvaptan, a drug used to treat hyponatremia in patients with heart dysfunction, can interact with warfarin through protein binding displacement, thereby increasing the level of free warfarin. This change in clinical effects is marked by an increased INR value, which poses a risk of increased bleeding events, necessitating more frequent INR monitoring [39, 40].

The mechanisms of drugs with a moderate potential for interaction events are discussed below. The antihypertensive drugs that most commonly cause interactions with warfarin are furosemide, bisoprolol, valsartan, and carvedilol. The interaction mechanism between furosemide and hydrochlorothiazide (HCT) with warfarin occurs through the reduction of calcium ion concentration, which enhances the activity of factor X, one of the blood coagulation factors. The decrease in factor X activity will lead to a reduction in blood clotting time and a decrease in the International Normalized Ratio value (INR) [6]. Valsartan, when used together with warfarin, does not cause changes in the pharmacokinetics of warfarin, so no adjustment of the warfarin dose is necessary [41]. According to a study comparing the incidence of bleeding in heart failure (CHF) patients using beta blockers, it was found that carvedilol has a lower bleeding risk compared to atenolol and metoprolol. Therefore, carvedilol is considered safer to use in conjunction with warfarin therapy. Bisoprolol is relatively safe because it does not affect bleeding time [42].

The most used antibiotics were ceftriaxone and ampicillin-sulbactam. The use of cephalosporin antibiotics is suspected to increase the risk of bleeding when used in conjunction with warfarin. The suspected mechanism is the elimination of beneficial bacteria in the gastrointestinal tract that play a role in the synthesis of vitamin K, thereby increasing the risk of bleeding. Some cephalosporins, such as cefazolin, cefuroxime, ceftriaxone, and cefepime, can persist in the gastrointestinal tract for a long time and affect the formation of vitamin K by beneficial bacteria [43]. The interaction between warfarin and ceftriaxone occurs because ceftriaxone increases the INR value in patients using warfarin, which can increase the risk of bleeding. Ceftriaxone could alter prothrombin time (PT) in patients with impaired vitamin K synthesis or low vitamin K stores as in the case of patients receiving warfarin [44]. Other antibiotics should be preferred for infection treatment in patients on warfarin [45]. The use of ampicillin-sulbactam together with warfarin can alter the anticoagulant effects of warfarin, thus requiring special attention for patients receiving this therapy concurrently [7, 46]. In a study conducted in Thailand, it was found that patients receiving warfarin also experienced interactions with cefoperazone sulbacatam, so it is necessary to adjust the dose of warfarin so as not to increase the risk of bleeding [47].

Proton pump inhibitors can interact with warfarin through the inhibition of the CYP2C19 enzyme. However, this inhibition generally does not have significant clinical effects, except in patients with genetic variations in that enzyme [48, 49]. In an Indonesian study in outpatients, there were 14 drugs that could potentially interact with proton pump inhibitors (PPIs), one of which was warfarin [50]. Ranitidine, an H-2 histamine antagonist, is reported to inhibit cytochrome P450, thereby significantly affecting prothrombin time when used concurrently with warfarin. Therefore, close monitoring of increased INR values is necessary to reduce the risk of bleeding [51]. Ondansetron used in conjunction with warfarin can increase the risk of bleeding, as there is competition for binding to the CYP1C2 enzyme, which is also one of the specific action sites of warfarin [10, 52].

Digoxin is the most widely used heart medication, and it has interactions with warfarin that have not been extensively studied. However, there were several case reports indicating that this interaction can cause coagulopathy with an increase in INR values above 10 and bradycardia. This interaction likely occurs due to the

displacement of warfarin protein binding by digoxin, leading to increased warfarin levels and a higher anticoagulant effect [53, 54].

The use of antiplatelet agents together with warfarin is often unavoidable, as the goal is to reduce the incidence of thrombosis. This combination of warfarin and antiplatelet is given for the prevention of Atherosclerotic Screening Cardio Vascular Disease (ASCVD), patients with AF undergoing Percutaneous Coronary Intervention (PCI) and patients with antiphospholipid syndrome. The administration of these two drugs must be done with consideration of the minimal duration of use and the patient's condition. The risk that may arise is an increased risk of bleeding [55].

To identify factors that increase the risk of major drug interactions, a logistic regression analysis was conducted. The complete results of the logistic regression analysis can be seen in table 3. Before the multivariate analysis was conducted, a chi-square test was used to identify the parameters to be included in the analysis. The results of the chi-square test indicate that the number of comorbidities and the number of medications consumed have a significant relationship with the risk of drug interactions. These two variables were then analyzed together using logistic regression. The analysis results show that the number of medications consumed is the strongest factor associated with an increased risk of serious drug interactions.

To determine the parameters of patient characteristics that most influence the potential severity of drug interactions, a multivariate analysis was conducted (table 3). Previously, the parameters of age, gender, number of comorbidities, length of stay, and number of medications consumed were tested bivariate using the Chi-Square test. From the Chi-Square test, it was found that the parameters with a p-value<0.25 were the number of medications taken, the number of comorbidities, and LOS (length of stay). Next, these parameters were analyzed multivariate using logistic regression. The results of the multivariate analysis show that the parameter most strongly associated with the potential severity of drug interactions is the number of drugs consumed by the patient, with an adjusted odds ratio (AOR) of 3.097 (95% CI 1.495-6.417) and a p-value of 0.002 (p<0.05) and LOS with an adjusted odds ratio (AOR) of 0.344 (95% CI 0,125-0,945) and p-value 0.038 (p<0,05). Based on the OR value, it can be determined that the more drugs consumed concurrently with warfarin therapy (≥ 10 types), the 3.097 times higher the likelihood of experiencing a potential drug interaction with major clinical severity compared to patients who consume fewer drugs. The potential occurrence of major interactions is most commonly bleeding. Other studies have also shown that drug interactions can increase the risk of bleeding [8, 56]. In this study, LOS can also affect the incidence of drug interactions significantly with p<0.038 (p<0.05) with an adjusted odds ratio (AOR) of 0.344 (95% CI 0.125-0.945). LOS can increase the incidence of drug interactions because the longer the patient is hospitalized, the higher the potential for drug interactions [57]. More drugs were administered to patients with longer hospital stays, resulting in a higher likelihood of drug-drug interactions. patients with higher disease severity are more likely to be prescribed more drugs and, thus more likely to experience DDIs. Increased length of stay and hospitalization costs can be attributed to possible adverse effects resulting from drug interactions [47, 58, 59].

Patients who are hospitalized generally receive many medications, increasing the risk of drug interactions. Drug interactions may also reduce achievement of the time to therapeutic range (TTR), according to another study [60]. This study is expected to provide information on the potential drug interactions in hospitalized patients who are receiving warfarin for the first time. The use of warfarin requires special attention because it is a drug that has many interactions with other drugs that can increase. The use of warfarin requires special attention because it is a drug that has many interactions with other drugs that can increase the risk of bleeding. There are several limitations to this retrospective study. The unavailability of INR test data in medical records greatly affected the results of this study, resulting in the inability to determine the impact of drug interactions experienced by patients. INR testing requires costs that must be borne by the patient or the government, so it is often neglected [29]. The use of the Drug Interaction Checker (Drugbank) to analyze potential drug interactions cannot describe the influence of patient-specific factors. Lack of genetic testing for CYP2C9/VKORC1 is another limitation of this study. As a result, the achievement of clinical outcomes cannot be accurately observed.

CONCLUSION

From this study, it can be concluded that all inpatients receiving warfarin therapy experience potential drug interactions. Most of the identified drug interactions have a moderate or severe severity level. There are four types of drugs that have the potential to cause drug interactions in the severe or major category. The class of drugs most often used concurrently with warfarin is antihypertensive medications. On average, these antihypertensive drugs have a moderate interaction severity level, necessitating more frequent INR monitoring to prevent the risk of bleeding. The parameter that has the strongest relationship with the potential severity of drug interactions is the number of medications consumed by the patient, with an Adjusted Odds Ratio (AOR) value of 3.097 (95% CI 1.495-6.417) and a p-value of 0.002 (p<0.05). Based on the OR value, it can be determined that the more medications consumed alongside warfarin therapy (≥ 10 types), the 3.097 times higher the likelihood of experiencing a potential drug interaction with major clinical severity compared to patients who consume fewer medications. In this study, LOS can also affect the incidence of drug interactions significantly with p<0.038 (p<0.05) with an adjusted odds ratio (AOR) of 0.344 (95% CI 0.125-0.945). Based on the results of this study, it is recommended that medical personnel be more careful in prescribing drugs to patients undergoing warfarin therapy, especially if the number of drugs consumed reaches or exceeds 10 types. For future research, it is recommended to conduct a prospective observational study supplemented with laboratory data (INR), so that the actual effects of drug interactions on patients can be directly observed. In addition, genetic testing is required to determine the specific dose for each patient.

ACKNOWLEDGEMENT

We would like to thank Roemani Muhammadiyah Hospital Semarang, RSI Sultan Agung Semarang, Gondo Suwarno Hospital Ungaran, and Ken Saras Hospital Ungaran for the opportunity to conduct the study.

FUNDING

The authors would like to acknowledge the financial support provided by DRTPM Kemendikbudristek through the 2024 Doctoral Dissertation Research Grant with contract number 108/E5/PG.02.00. PL/2024.

AUTHORS CONTRIBUTIONS

DO and ZC: conceptual or design the work, collection, data analysis, interpretation, and manuscript draft and final approval of the version to be published. SMSG and HK: development of draft manuscript and revision of manuscript.

CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Patel S, Singh R, Preuss CV, Patel N. Warfarin. Hemostasis and thrombosis. 4th ed; 2023. p. 161-8.
2. Perki. Pedoman tata laksana fibrilasi atrium non valvular. Perhimpunan Dokt Spesialis Kardiovaskuler Indones; 2019.
3. Musnelina L, Handayani F, Hoa VO TH, Pontoan J. Trends in use of direct oral anticoagulants and warfarin in atrial fibrillation patients. Indonesian J Pharm Sci. 2023;21(2):266-72. doi: 10.35814/jifi.v21i2.1475.
4. Crader MF, Johns T, Arnold JK. Warfarin drug interactions. StatPearls; 2023.
5. Putriana NA, Rusdiana T, Rostinawati T, Akbar MR, Megantara S, Hidayanti S. Prediction of the effect of single nucleotide polymorphisme (SNPS) in the CYP2C9 on warfarin metabolism by in silico study. Int J Appl Pharm. 2022 Dec 1;14(5):86-8. doi: 10.22159/IJAP.2022.V14S5.14.

6. Bloukh D, Hijazeen S, Al Noimi F. Effect of diuretics on the pharmacologic action of warfarin. Scholars Acad J Pharm (SAJP). 2018;7(1):54-9. doi: 10.21276/sajp.2018.7.1.8.
7. Vega AJ, Smith C, Matejowsky HG, Thornhill KJ, Borne GE, Mosieri CN. Warfarin and antibiotics: drug interactions and clinical considerations. Life (Basel). 2023;13(8):1661. doi: 10.3390/life13081661, PMID 37629518.
8. Teklay G, Shiferaw N, Legesse B, Bekele ML. Drug-drug interactions and risk of bleeding among inpatients on warfarin therapy: a prospective observational study. Thromb J. 2014 Sep 17;12(1):20. doi: 10.1186/1477-9560-12-20, PMID 25249791.
9. Rahma N, Andayani TM, Nurrochmad A. Risiko kejadian perdarahan pasca rawat inap pada penggunaan bersamaan warfarin dan antibiotik. J Sains Farm Klin. 2021 Aug 6;8(2):164. doi: 10.25077/jsfk.8.2.164-173.2021.
10. Wang M, Zeraatkar D, Obeda M, Lee M, Garcia C, Nguyen L. Drug-drug interactions with warfarin: a systematic review and meta-analysis. Br J Clin Pharmacol. 2021;87(11):4051-100. doi: 10.1111/bcp.14833, PMID 33769581.
11. Timur WW, Ussa RE, Widyaningrum N. Kajian interaksi antar obat terhadap profil glikemik pada pasien diabetes rawat inap rumah sakit islam sultan agung semarang the study of between drug interaction and glycemic profile among in patients with diabetes at sultan agung islamic hospital semarang. J Farmasi Indones. 2022;19(2):221-7. doi: 10.23917/pharmacon.v19i2.18583.
12. Marisya N, Putri A, Fortuna TA, Nyoman N, Mendra Y. Evaluasi drug related problems (DRPS) pada pasien demam tifoid di instalasi rawat inap rumah sakit x di klaten periode Nov 2021-Oct 2022. Usadha J Pharm. 2024;3(2):162-76. doi: 10.23917/ujp.v3i2.318.
13. DE Fatima Colet C, Amador TA, Heineck I. Drug interactions and adverse events in a cohort of warfarin users attending public health clinics. Int J Cardiovasc Sci. 2019;32(2):110-7. doi: 10.5935/2359-4802.20180091.
14. Tatro DS. Drug interaction facts. 8th ed. Vol. 1. Lippincott Williams & Wilkins; 2015.
15. World Health Organization (WHO). Medication Safety in Polypharmacy; 2019.
16. Dagnew SB, Tadesse TY, Zeleke MM, Yiblet TG, Addis GT, Mekonnen GB. Drug-drug interactions among hospitalized elderly in patients at medical wards of Northwest Ethiopia's comprehensive specialized hospitals: a multicenter observational study. Sage Open Med. 2022;10:20503121221135874. doi: 10.1177/20503121221135874, PMID 36385798.
17. Kemenkes. Petunjuk teknis standar pelayanan kefarmasian di rumah sakit; 2019.
18. Du X, Guo L, Xia S, Du J, Anderson C, Arima H. Atrial fibrillation prevalence awareness and management in a nationwide survey of adults in China. Heart. 2021 Apr 1;107(7):535-41. doi: 10.1136/heartjnl-2020-317915, PMID 33509976.
19. Elewa H, Alhaddad A, Al Rawi S, Nounou A, Mahmoud H, Singh R. Trends in oral anticoagulant use in qatar: a 5 y experience. J Thromb Thrombolysis. 2017;43(3):411-6. doi: 10.1007/s11239-017-1474-4, PMID 28138812.
20. Zhang C, Wang J, Yang Y, Ma EL, Lin HW, Liu BL. Prescribing trends of oral anticoagulants from 2010 to 2020 in Shanghai, China: a retrospective study. Clin Appl Thromb Hemost. 2022;28:10760296221132551. doi: 10.1177/10760296221132551, PMID 36250531.
21. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD. 50 y trends in atrial fibrillation prevalence incidence risk factors and mortality in the framingham heart study: a cohort study. Lancet. 2015;386(9989):154-62. doi: 10.1016/S0140-6736(14)61774-8, PMID 25960110.
22. Kornej J, Borschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. Circ Res. 2020;127(1):4-20. doi: 10.1161/circresaha.120.316340, PMID 32716709.
23. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features epidemiology and mechanisms. Circ Res. 2014;114(9):1453-68. doi: 10.1161/circresaha.114.303211, PMID 24763464.
24. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology pathophysiology and clinical outcomes. Circ Res. 2017;120(9):1501-17. doi: 10.1161/circresaha.117.309732, PMID 28450367.
25. Sivakumar V, SS, AM, Kumar NG, CP A. Development of prediction tool for assessment of risk associated with acenocoumarol. Int J Pharm Pharm Sci. 2023;15(1):33-6. doi: 10.22159/ijpps.2023v15i1.46434.
26. Indrawan SA, Yulianti T. Probems IDR (DRPs) pada pasien diabetes mellitus di instalasi rawat jalan. Usadha. J Pharm. 2024;3(1):29-42. doi: 10.23917/ujp.v3i1.301.
27. Muliani K, Lakcita DM, Annisa. Hubungan faktor klinis terhadap drug related problems pada pasien pasien hipertensi rawat inap rumah sakit pusat di jawa tengah. Usadha J Pharm. 2024;3(1):65-79.
28. Leopoulou M, Theofilis P, Kordalis A, Papageorgiou N, Sagris M, Oikonomou E. Diabetes mellitus and atrial fibrillation from pathophysiology to treatment. World J Diabetes. 2023;14(5):512-27. doi: 10.4239/wjd.v14.i5.512, PMID 37273256.
29. Lorenzo Almoros A, Casado Cerrada J, Alvarez Sala Walther LA, Mendez Bailon M, Lorenzo Gonzalez O. Atrial fibrillation and diabetes mellitus: dangerous liaisons or innocent bystanders? J Clin Med. 2023;12(8):2868. doi: 10.3390/jcm12082868, PMID 37109205.
30. Proietti M, Raparelli V, Olshansky B, Lip GY. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. Clin Res Cardiol. 2016;105(5):412-20. doi: 10.1007/s00392-015-0936-y, PMID 26525391.
31. Wang Y, Singh S, Bajorek B. Old age high-risk medication polypharmacy: a trilogy of risks in older patients with atrial fibrillation. Pharm Pract (Granada). 2016;14(2):706. doi: 10.18549/PharmPract.2016.02.706, PMID 27382425.
32. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the aristotle trial. BMJ. 2016;353:i2868. doi: 10.1136/bmj.i2868, PMID 27306620.
33. Shaikh F, Pasch LB, Newton PJ, Bajorek BV, Ferguson C. Addressing multimorbidity and polypharmacy in individuals with atrial fibrillation. Curr Cardiol Rep. 2018;20(5):32. doi: 10.1007/s11886-018-0975-x, PMID 29574524.
34. Kamiyama E, Yoshigae Y, Kasuya A, Takei M, Kurihara A, Ikeda T. Inhibitory effects of angiotensin receptor blockers on CYP2C9 activity in human liver microsomes. Drug Metab Pharmacokinet. 2007;22(4):267-75. doi: 10.2133/dmpk.22.267, PMID 17827781.
35. Guidoni CM, Camargo HP, Obreli Neto PR, Girotto E, Pereira LR. Study of warfarin utilization in hospitalized patients: analysis of possible drug interactions. Int J Clin Pharm. 2016;38(5):1048-51. doi: 10.1007/s11096-016-0336-z, PMID 27365092.
36. Kim KY, Mancano MA. Fenofibrate potentiates warfarin effects. Ann Pharmacother. 2003;37(2):212-5. doi: 10.1177/106002800303700210, PMID 12549950.
37. Ken Wey C, Chee Li Ching E, Jothy Nagesvararao N, Jagan N, Info A. Warfarin fenofibrate interaction: hospital kuala lumpur experience. Malaysian Journal of Pharmacy. 2021;7(1):7-10. doi: 10.52494/YCKM4957.
38. Kim KY, Mancano MA. Fenofibrate potentiates warfarin effects. Ann Pharmacother. 2003 Feb;37(2):212-5. doi: 10.1177/106002800303700210, PMID 12549950.
39. Nimura S, Kitahara K, Ueshima K, Mochizuki Y, Momo K, Shinke T. Potential drug-drug interaction between tolvaptan and warfarin in a geriatric patient with heart failure. Clin Case Rep. 2022;10(4):e05592. doi: 10.1002/ccr3.5592, PMID 35414910.
40. Saito M, Ajioka M, Iwao T, Suzuki T. Enhancement of warfarin anticoagulant reaction in patients with repeated oral tolvaptan administration. Biol Pharm Bull. 2018;41(7):1014-6. doi: 10.1248/bpb.b17-01008, PMID 29760305.
41. Kasichayanula S, Chang M, Liu X, Shyu WC, Griffen SC, LaCreta FP. Lack of pharmacokinetic interactions between dapagliflozin and simvastatin valsartan warfarin or digoxin. Adv Ther. 2012;29(2):163-77. doi: 10.1007/s12325-011-0098-x, PMID 22271159.

42. Berlowitz DR, Miller DR, Oliveria SA, Cunningham F, Gomez Caminero A, Rothendler JA. Differential associations of beta-blockers with hemorrhagic events for chronic heart failure patients on warfarin. Pharmacoepidemiol Drug Saf. 2006;15(11):799-807. doi: 10.1002/pds.1301, PMID 16892457.
43. Thabit AK, Almoalim SY, Altalhi R. Cephalosporins with warfarin increase the risk of bleeding: myth or fact? Expert Opin Drug Metab Toxicol. 2024;20(5):293-6. doi: 10.1080/17425255.2024.2349718, PMID 38712794.
44. Saum LM, Balmat RP. Ceftriaxone potentiates warfarin activity greater than other antibiotics in the treatment of urinary tract infections. J Pharm Pract. 2016;29(2):121-4. doi: 10.1177/0897190014544798, PMID 25092605.
45. Saum LM, Balmat RP. Ceftriaxone potentiates warfarin activity greater than other antibiotics in the treatment of urinary tract infections. J Pharm Pract. 2016;29(2):121-4. doi: 10.1177/0897190014544798, PMID 25092605.
46. Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo YF. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. Am J Med. 2012;125(2):183-9. doi: 10.1016/j.amjmed.2011.08.014, PMID 22269622.
47. Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo). 2011;66(1):9-15. doi: 10.1590/s1807-59322011000100003, PMID 21437429.
48. Henriksen DP, Stage TB, Hansen MR, Rasmussen L, Damkier P, Pottegard A. The potential drug-drug interaction between proton pump inhibitors and warfarin. Pharmacoepidemiol Drug Saf. 2015;24(12):1337-40. doi: 10.1002/pds.3881, PMID 26395871.
49. Tang J, Sharma U, Desai S, Molnar J, Perlmuter L, Feller A. A study of proton pump inhibitors and other risk factors in warfarin associated gastrointestinal bleeding. Cureus. 2021;13(1):e12624. doi: 10.7759/cureus.12624, PMID 33585113.
50. Seesin T, Pengsupsin P, Weesaphen S, Sriphong P, Limpapanasit U, Bhongchirawattana S. Evaluation of cefoperazone/sulbactam and vitamin K use in patients with bacterial infections. Int J Appl Pharm. 2019 Sep 1;11(5):191-3. doi: 10.22159/ijap.2019.v11s5.T0100.
51. Ahmad S, Ali S, Alam N, Alam I, Alam S, Ali D. Drug interactions of h2 receptor antagonists ranitidine: a review. Res J Pharm Technol. 2016;9(3):275-80. doi: 10.5958/0974-360X.2016.00051.2.
52. Blower PR. 5-HT3 receptor antagonists and the cytochrome P450 system: clinical implications. Cancer J. 2002;8(5):405-14. doi: 10.1097/00130404-200209000-00012, PMID 12416899.
53. Rajiv R, Khausik M, Mahajan S, Thakur R. Rare interaction of warfarin and digoxin in a case of digoxin toxicity. J Assoc Physicians India. 2020 Mar;68(3):85-6. PMID 32138495.
54. Sadaf S, Alam SA, Burhan-ul-Haq S, Raza-ul-Haq HM, Amna Y. Warfarin induced coagulopathy: is the digoxin the culprit? Pak Armed Forces Med J. 2024;74(1)s54-6. doi: 10.51253/pafmj.v74iSUPPL-1.10618.
55. Kumbhani DJ, Cannon CP, Beavers CJ, Bhatt DL, Cuker A, Gluckman TJ. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(5):629-58. doi: 10.1016/j.jacc.2020.09.011, PMID 33250267.
56. Berg TM, O Meara JG, Ou NN, Daniels PR, Moriarty JP, Bergstrahl EJ. Risk factors for excessive anticoagulation among hospitalized adults receiving warfarin therapy using a pharmacist-managed dosing protocol. Pharmacotherapy. 2013;33(11):1165-74. doi: 10.1002/phar.1280, PMID 23625787.
57. Moura C, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. Clin Drug Investig. 2011;31(5):309-16. doi: 10.1007/BF03256929, PMID 21344954.
58. Rodrigues AT, Stahlschmidt R, Granja S, Pilger D, Falcao AL, Mazzola PG. Prevalence of potential drug-drug interactions in the intensive care unit of a Brazilian teaching hospital. Braz J Pharm Sci. 2017;53(1):e16109. doi: 10.1590/s2175-97902017000116109.
59. Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci. 2009;12(3):266-72. doi: 10.18433/j35c7z, PMID 20067703.
60. Mathur A, Sharma A. Quality of anticoagulation perdictors and consequences of deranged INR of patient on warfarin. Asian J Pharm Clin Res. 2024 Dec 1;17(12):80-4. doi: 10.22159/ajpcr.2024v17i12.52969.