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Potential Drug Interaction on Bleeding Events in Stroke Recurrence Patients with Atrial Fibrillation

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ABSTRACT

Introduction: Stroke is a major complication of atrial fibrillation, carries a high risk of recurrence. The likelihood of adverse effects from warfarin-drug interactions increases with the number of concurrent medications. Identifying these potential interactions is crucial. This study aimed to evaluate the impact of drug interactions on bleeding events and the incidence of recurrent stroke in patients with atrial fibrillation.
Methods: This retrospective study tracked 314 stroke patients with atrial fibrillation at Dr. Sardjito and Dr. Moewardi General Hospital over one year who received warfarin at two hospitals from January 2015 to December 2019. Using purposive sampling, 50 patients were analyzed and divided into two groups, 11 with stroke recurrence and 39 without recurrence in one year of treatment. Statistical analyses, including chi-square tests and odds ratio calculations, were performed to assess factors influencing stroke recurrence.
Results: In addition, major, moderate, and minor drug interactions were not significantly different $p>0,05$. Meanwhile, minor drug interaction correlated with bleeding event ($p<0,05$) and OR 0,1. The study underscored an elevated risk of bleeding associated with combinations such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs in major interaction analysis.
Conclusion: The research highlights an increased risk of bleeding caused by interaction in combinations therapiest such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs. These findings stress the importance of careful evaluation and management of drug interactions to reduce adverse effects and enhance outcomes for patients with recurrent strokes with atrial fibrillation.

Keywords: Drug interaction; bleeding; stroke; atrial fibrillation

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Introduction

Drug-drug interactions (DDIs) involve changes in a drug's pharmacokinetics or effects caused by the presence of another drug. These interactions are categorized into pharmacodynamic or pharmacokinetic types and can lead to reduced effectiveness, treatment failure, or increased medication toxicity. Preventing DDIs can be achieved by minimizing the use of multiple medications and carefully considering the benefits of drug combinations against the risks of significant DDIs. The likelihood of encountering potential DDIs (pDDIs) approaches 40% for patients on five drugs and exceeds 80% for those taking seven or more medications[1]. A prior study in 2016 involving 146 patients admitted with acute ischemic and hemorrhagic stroke identified 582 distinct potential drug-drug interactions (pDDIs), resulting in a pDDI prevalence of 61%[2]. Another study of 200 patients, in the same year, including 190 treated for ischemic stroke, found a pDDI prevalence of 89.5%[3]. The higher prevalence of multimorbidity and polypharmacy among stroke patients increases their susceptibility to experiencing pDDIs[4].

The prevalence of atrial fibrillation (AF) between 2004-2013 in acute ischemic stroke (AIS) patients increased by 22%, rising from 20% to 24%. During the same period, the prevalence of AF in patients with transient ischemic attack (TIA) increased by 38%, from 12% to 17% [5]. Stroke is one of the most feared complications of atrial fibrillation because strokes caused by atrial fibrillation have a risk of recurrence[6]. About 20–30% of all ischemic strokes are related to atrial fibrillation and these events are more disabling than most other ischemic stroke subtypes[7]. This increased in the third year of follow-up where dependency after stroke was higher than the incidence of death and recurrence. Anticoagulants according to PERKI (2014) are prescribed to reduce hypercoagulation reduce the risk of cardioembolic stroke and prevent postoperative venous thrombosis and pulmonary embolism[8]. Anticoagulation therapy, including medications like dabigatran, rivaroxaban, apixaban, and vitamin K antagonists (VKAs), is crucial for reducing stroke risk in atrial fibrillation patients. VKAs, despite their effectiveness, require careful monitoring due to interactions with food, other medications, and varying bleeding risks. Vitamin K antagonists (VKAs) have been the only oral anticoagulant drugs available for clinical use for the primary and secondary prevention of venous and arterial thromboembolic events[9].

In the management of atrial fibrillation, the use of anticoagulants is based on recommendations from national formularies Indonesia. Warfarin, despite its risks, remains the primary choice as it has long been listed in the national formulary and is effective in preventing blood clot formation in patients with this condition. On the other hand, newer anticoagulants such as dabigatran, despite being included in the national formulary, cannot yet be widely used as their current indications for use are more focused on the prevention of post-operative venous thromboembolism (VTE) in hip and knee joint replacements.

In addition, the limited selection of some DOACs in Indonesia and their relatively high price cause problems selecting for atrial fibrillation therapy[18]. Thus, the choice of warfarin as an anticoagulant therapy for atrial fibrillation is still often favored despite the availability of alternatives, given its safety and effectiveness that have been proven in extensive clinical experience.

The bleeding rates due to warfarin use vary significantly, which can be assessed through incidents of bleeding or the risk assessment of the INR (International Normalized Ratio). Consequently, determining the warfarin dosage heavily relies on evaluating the bleeding risk, represented by the INR value. Warfarin therapy for Atrial Fibrillation necessitates meticulous monitoring, particularly aiming to maintain the target INR range of 2.0-3.0 for patients with clinical atrial fibrillation. This means that if the INR value falls outside this range, the warfarin therapy is considered unsuccessful, as INR serves as a crucial parameter for assessing the efficacy of warfarin therapy. The frequency of INR tests for each patient varies based on their INR values. Typically, INR tests are conducted every 3 months once the values have stabilized, though more frequent tests may be necessary if INR values remain unstable.

Interactions that arise have the potential to harm patients and can lead to increased health therapy costs. Drug-drug interactions and bleeding risks among inpatients receiving warfarin therapy are common in the study hospital, so clinicians should be aware of potential interactions and carefully monitor the INR[10]. The results of other studies also show that close monitoring and analysis of the clinical consequences of co-prescribing drugs that interact with warfarin[11]. Another study showed that the prevalence of co-prescribing with potentially interacting drugs during warfarin therapy in outpatients is quite high, so strategies to identify and manage warfarin-drug interactions are needed to avoid potential side effects[12]. Two hospitals, a central hospital and a regional hospital were selected because stroke cases with atrial fibrillation are commonly found in referral hospitals. Identifying potential interactions involving warfarin that may cause adverse effects is necessary. The risk of adverse effects caused by warfarin-drug interactions increases with the number of drugs administered concurrently with warfarin[13]. Based on the analysis of warfarin therapy in stroke patients with atrial fibrillation, many things must be analyzed regarding the correlation between therapy and the outcome of therapy. Therefore, this study aims to evaluate potential drug interactions on bleeding events in the incidence of recurrence stroke with atrial fibrillation.

Methods

This study was conducted at Dr. Sardjito Hospital in Yogyakarta and Dr. Moewardi in Solo Central Java from August 2019 to March 2020. Patient data was obtained from secondary patient medical records and compiled into a data collection form for analysis. Ethical approval for the study was

obtained from the Faculty of Medicine Gadjah Mada University and Medical and Health Research Ethics Committee (MHREC) with the number of ethics committee approval Ref: KE/FK/002/EC/2018.

The research instruments used include, Case Report Form (CRF) for patients with nonvalvular atrial fibrillation, which contains data on demographic data (medical record number, gender, patient's date of birth, date of hospital admission) and atrial fibrillation disease (anticoagulant medication administration, anticoagulant medication admission date) and atrial fibrillation disease (anticoagulant drug administration, dose, frequency, diagnosis of other complicating diseases, other events during the hospitalization process, outpatient care to monitor anticoagulant effectiveness), medical records containing the patient's medical record data, laboratory data, medication use, drug usage, doctor's evaluation notes, drug utilization data from the Hospital Pharmacy Installation.

The study utilized an analytical observational approach with a case-control research design. Data collection was retrospective, involving a review of patient medical records. The research focused on stroke patients diagnosed with atrial fibrillation who were prescribed warfarin as part of outpatient treatment, identified through ICD codes I48 and I63 at Dr. Sardjito General Hospital (218 patients) and RSUD Dr. Moewardi (96 patients). The study encompassed a total sample size of 314 patients from January 1, 2015, to December 31, 2019, selected using a total population sampling method. Among these, 50 patients met the inclusion criteria, comprising 11 patients in the case group and 39 patients in the control group. The inclusion criteria are, Patients above 45 years of age were divided into groups of <60 years and >60 years, Outpatients, Patients diagnosed with stroke with atrial fibrillation according to ICD code 10 I63 who had been hospitalized once because of a stroke diagnosis with complete laboratory and supporting data with complete laboratory and supporting data. Patients received warfarin therapy for at least 6 months. After receiving warfarin therapy for 6 months, the patients were observed for a year after the warfarin administration related to the frequency of examination and the therapeutic value of INR on the incidence of recurrent stroke. The patient does not have a history of stage IV renal failure, pregnant or breastfeeding. The case group is a group of patients who experienced a recurrence stroke while the control case is a group of patients who do not experience a recurrence stroke event. The exclusion criteria for this study are, Patients who, during the observation period (one year), suddenly discontinued the warfarin or replaced it with another type of anticoagulant, Patients who died during the observation period so that no data on the frequency of examination and the therapeutic value of INR.

Descriptive data analysis was conducted to examine potential interactions in medication prescriptions using the Drugs.com interaction checker tool. The analysis aimed to identify factors affecting stroke recurrence and potential bleeding events. SPSS version 22 was used for data analysis, with statistical significance set at p-value < 0.05 and a 95% confidence interval. Bivariate analysis was

performed to assess variables associated with stroke recurrence and bleeding, utilizing the Chi-Square test. Additionally, the Odds Ratio (OR) was calculated to determine whether stroke with atrial fibrillation influenced the outcome of stroke recurrence.

Results

This study is based on a retrospective study tracking the treatment of stroke patients who also suffered from atrial fibrillation which affected the incidence of bleeding in stroke during one year of treatment. In this study, researchers took a study sample of stroke patients who also suffered from atrial fibrillation and received warfarin as one of the anticoagulant drugs. The study subjects were stroke patients who suffered from atrial fibrillation and were prescribed warfarin as one of the anticoagulant drugs. An overview of patient characteristics is described in Table 1.

Table 1. Characteristics patient

	Case (Recurrence Stroke) N =11 (22%)	Control (non-Recurrence Stroke) N=39 (78%)	p
Age			
40-60	5(45,5)	9(23,1)	0,25
<40	1(9,0)	2(5,1)	
> 60 year	5(45,5)	28(71,8)	
Sex			
Male	3(27,3)	16(41,0)	0,50
Female	8(72,7)	23(59,0)	
Dose Variance			
Yes	9(81,8)	15(40,5)	**0,03**
No	2(18,2)	22(59,5)	
Health insurance			
Indonesian Social Security and Health (BPJS)	10(90,9)	33(86,8)	1,00
Non- Indonesian Social Security and Health (Non BPJS)	1(9,1)	5(13,2)	
Bleeding			
Subjects experiencing bleeding outcome	5(45.4)	3(7.7)	0,21
Subjects did not experience bleeding outcome	6(54.5)	36(92.3)	
Bleeding risk			
Subjects with bleeding risk (INR>3)	3(27.3)	6(15.4)	0,39
Subjects with no bleeding risk (INR <2 or 2.0-3.0)	8(72.7)	33(84.6)	
INR value			
INR 2.0-3.0	6(54.5)	9(23.1)	0,06
INR <2.0 or >3.0	5(45.5)	30(76.9)	
Frequency of INR examination			
Once every 8 weeks	3(27.3))	1(2.6)	0,27
Less than once every 8 weeks or more than once every 8 weeks	8(72.7)	38(97.4)	

*Chi-square test

Data analysis was conducted on 50 stroke patients with atrial fibrillation who were prescribed warfarin, focusing on the occurrence of stroke recurrence over a one-year outpatient treatment period. The sample was divided into two groups 11 patients (22%) experienced recurrence of stroke as cases group, while 39 patients (78%) as controls group. Analysis of demographic factors such as age and sex, as well as health insurance coverage, bleeding outcomes, bleeding risk (based on INR levels), INR values, and frequency of INR examinations, showed no statistically significant differences between the case and control groups ($p > 0.05$). However, significant differences were observed in dose variance ($p = 0.03$), where 81.8% of patients in the case group had dose variance compared to 40.5% in the control group.

Table 2. Mean patient drug interactions

Drug interaction	**Case (Recurrence Stroke)** N=11(%)	**ıtrol (non-Recurrence Stroke)** N=39 (%)	p
Mayor	81	69	0,30
Moderate	91	89	0,49
Minor	72	87	0,36

Drug interactions that occur in stroke patients are classified based on their severity, namely major, moderate, and minor. Based on the results of the study, both the re-stroke group and the non-re-stroke group both had a risk of major interactions (81% Vs 69%), moderate interactions (91% Vs 89%) and minor interactions (72% Vs 87%). So it can be seen that in the case group and control group, the incidence of moderate interactions was found to be higher, namely 91% and 89% of patients experiencing moderate interaction events as a result of drug prescribing. The existence of interactions must be considered by various parties because it will affect the clinical output of the patient.

Table 3. Relationship between drug interactions and the incidence of bleeding

Variable	**Bleeding N=8(%)**	**No bleeding N=42(%)**	**OR (95% CI)**	**p**
Mayor Interaction				
Yes	4(50,0)	29(69,0)	0,4(0,09-2,1)	0,42
No	4(50,0)	13(31,0)		
Moderate Interaction				
Yes	8(100)	38(90,5)	0,8(0,7-0,9)	1,00
No	0(0)	4(9,5)		
Minor Interaction				
Yes	4(50,0)	36(85,7)	0,1(0,03-0,8)	**0,04**
No	4(50,0)	6(14,3)		

Based on the analysis, drugs with minor interaction potential still pose a risk of bleeding. The list of

drugs that are included in minor interactions are the combination of warfarin-spironolactone, warfarin-simvastatin, warfarin-atorvastatin, warfarin-acarbose, warfarin-allopurinol, warfarin-telmisartan, digoxin-spironolactone, bisoprolol-antaside, sucralfate-bisoprolol, nifedipine-omeprazole, aspirin-bisoprolol, furosemide-aspirin, aspirin-spironolactone, aspirin-bisoprolol, ranitidine-paracetamol, and ranitidine-mefenamic acid.

Table 4. Minor interaction on bleeding outcome

Minor case-control interactions	Effects
Aspirin+Bisoprolol	High dose aspirin use interferes with the effect of beta blockers in hypertension by inhibiting prostaglandin synthesis. In addition, metoprolol, one of the beta blockers, increases the absorption of aspirin, which has no significant clinical effect.
Aspirin+Spironolakton	Aspirin interferes with the secretion of canrenone, a major metabolite of spironolactone, reducing its natriuretic effects. If a diuretic is insufficient, reducing salicylate administration or increasing the diuretic dose is recommended, while monitoring the patient's potassium levels.
Bisoprolol+Antacid	Antacids decrease beta blocker bioavailability, likely due to receptor binding or reduced gastric dissolution. Separate the administration of these drugs.
Digoxin+Spironolakton	Spironolactone may reduce tubular secretion of digoxin. As a result, digoxin plasma clearance falls and blood plasma levels rise. Some data suggest that spironolactone has inotropic side effects.
Furosemide+Aspirin	Aspirin may interfere with the diuretic and natriuretic effects of loop diuretics by inhibiting their prostaglandin-mediated renal action.
Ranitidine+Paracetamol	Ranitidine may have potential hepatotoxic effects when used together with paracetamol.
Ranitidine+Mefenamat acid	H2 antagonists interfere with NSAIDs by altering blood plasma levels, decreasing absorption, and reducing urinary elimination through inhibited metabolism and changed gastric pH.
Sucralfat+Bisoprolol	Antacids reduce the bioavailability of beta blockers, likely due to receptor binding or decreased gastric dissolution. Administer these drugs at different times.
Warfarin+Acarbosa	The anticoagulant effect of warfarin may be increased in patients receiving akarbosa although the mechanism is unknown.
Warfarin+Allopurinol	Allopurinol may inhibit warfarin metabolism, affecting its anticoagulant effect, so further monitoring is needed.
*Warfarin+Atorvastatin	The clinical effects of combining lovastatin and warfarin are not fully evaluated, but lovastatin may reduce prothrombin levels. There is no significant effect of atorvastatin on anticoagulants.
Warfarin+Simvastatin	Simvastatin may enhance the anticoagulant effect of warfarin by the mechanism of altering protein binding. Clinical effects have not been widely studied but should be monitored.
*Warfarin+Spironolakton	Spironolactone causes diuresis and haemoconcentration of clotting factors resulting in decreased anticoagulant effect.
Warfarin+Telmisartan	Telmisartan causes a slight decrease in steady-state plasma concentrations of warfarin although it cannot be proven to be significant.

*Effect refers to the risk of bleeding caused by drug interactions.

Table 5. Major drug-drug interaction of the recurrence stroke group

Major interaction in the case group (recurrence stroke)	Effect
Amiodaron+Azitromisin	ined increases the risk of potentially life-threatening heart rhythm irregularities leading to death. Levels of amiodarone increase with concomitant use, increasing the risk of side effects such as pneumonitis, neurological damage, liver damage, thyroid abnormalities and visual disturbances.
Amiodaron+Furosemid	ine increases the risk of heart rhythm irregularities and requires monitoring of electrolyte levels (magnesium and potassium).
*Amiodaron+Warfarin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
Amlodipin+Simvastatin	ine increases the blood levels of simvastatin, which may increase the risk of simvastatin side effects such as liver damage and rabdomyolysis.
Ciprofloxacin+Warfarin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
Spironolakton+Candesartan	ine increases the level of potassium in the blood. Increases the risk of hyperkalaemia which can lead to kidney damage, muscle paralysis, irregular heart rhythms and heart attack
Spironolakton+Irbesartan	ine increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, irregular heart rhythm and heart attack.
Spironolakton+Ramipril	ine increases the level of potassium in the blood (hyperkalaemia)
*Warfarin+Aspirin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Clopidogrel	ine increases the risk of bleeding complications
*Warfarin+Meloxicam	ine leads to a risk of faster bleeding

*Effect refers to the risk of bleeding caused by drug interactions.

Certain drug combinations pose a significant bleeding risk, which necessitates careful management. Specifically, combining amiodarone with warfarin substantially increases the risk of bleeding, making it essential to adjust doses and monitor prothrombin time or INR values closely. Similarly, the use of ciprofloxacin with warfarin also heightens bleeding risk, requiring meticulous dose adjustments to prevent complications. The combination of warfarin with aspirin further escalates the risk of bleeding, demanding dose modifications based on prothrombin time or INR values to ensure safety. Additionally, the concurrent use of warfarin with clopidogrel or meloxicam significantly raises the potential for bleeding complications. Therefore, careful monitoring and precise dose adjustments are critical when managing these drug combinations to effectively mitigate the increased bleeding risk and prevent adverse outcomes. Effective management of these interactions is vital for maintaining patient safety and minimizing the risk of serious bleeding events.

Table 6. Major drug-drug interaction in the non-recurrence stroke group

Major interaction in control group (non-recurrence stroke)	Effect
Amlodipin+Simvastatin	Combined increases the blood levels of simvastatin which may increase the risk of side effects of simvastatin use such as liver damage and rhabdomyolysis.
Bisoprolol+Tizanidine	Combined causes a decrease in blood pressure.
Ramipril+Valsartan	Combined increases the risk of side effects such as decreased blood pressure, decreased kidney function and hyperkalaemia conditions.
Spironolakton+Candesartan	Combined increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, heart rhythm irregularities and heart attack.
Spironolakton+Irbesartan	Combined increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, heart rhythm irregularities and heart attack.
Spironolakton+Ramipril	Combined increases the level of potassium in the blood (hyperkalaemia)
Spironolakton+Valsartan	Combined increases the level of potassium in the blood which can lead to hyperkalaemia in cases of severe hyperkalaemia can lead to kidney damage, muscle paralysis, heart rhythm disturbances and heart attack.
Warfarin+Aspirin	Combined leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Clopidogrel	Combined increases the risk of bleeding complications.
*Warfarin+Ibuprofen	Combined leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Mefenamic Acid	Combined leads to a risk of faster bleeding
*Warfarin+Meloxicam	Combined leads to a risk of more rapid bleeding

*Effect refers to the risk of bleeding caused by drug interactions.

Discussion

Based on the results of the study in the recurrence stroke group, patients tended to experience drug-drug interaction in the form of 81% major interactions, 91% moderate interactions, and 72% minor interactions. While the drug prescription of the non-reccurence stroke group obtained that 69% of patients had major interactions, 89% had moderate interactions and 87% had minor interactions. The results of this study are similar to research reports that a higher percentage of patients were exposed to at least one serious drug-drug interaction among acute stroke with recurrent ischaemic events compared to first-time ischaemic patients (74% vs 50%; $p<0.01$). Other research showed serious DDIs potentially associated with an increased risk of a cerebral event were identified in 19 (17%) patients with ischemic stroke, and in 7 (19%) patients with hemorrhagic stroke[2].

An increased risk of bleeding occurs in the outcome of recurrence stroke both group case group (recurrence stroke) and control group (non recurrence stroke) showed that there were several combinations of therapies that gave bleeding effects including with the prescriptions warfarin-amiodarone, warfarin-clopidogrel, warfarin-diclofenac sodium, warfarin-aspirin, warfarin-meloxicam,

warfarin-ibuprofen and warfarin-mefenamic acid drug interactions. The results of this study align with findings that commonly co-prescribed drugs interacting with warfarin include antibiotics, anticoagulants, diuretics, and NSAIDs[10]. Diclofenac sodium, aspirin, meloxicam, ibuprofen and mefenamic acid are a class of nonsteroidal anti-inflammatory drugs (NSAIDs) that have potential effects of hypoprothrombin events and bleeding risk when associated with oral anticoagulants. This is supported by studies showing that NSAID use is associated with an increased risk of bleeding, stroke or systemic embolism, and hospitalization[14]. Pharmacological effects of NSAIDs related to warfarin-NSAID drug interactions include gastrointestinal irritation, prolongation of prothombin time and inhibition of platelet adhesion-aggregation[15]. Patients taking warfarin had an increased risk of major bleeding and gastrointestinal bleeding with NSAID use[16]. NSAIDs also alter the pharmacokinetics of warfarin resulting in increased INR or prothrombin time (PT) so frequent INR checks and dose adjustments of oral anticoagulants are required while the warfarin-NSAID combination is prescribed. However, a cautious approach is needed for the interpretation of the NSAID results for the following reasons.

The chi-square results of each drug interaction category showed that major, and moderate interactions (OR = 0.4; 0.8;) had no significant difference $p>0.05$ on the incidence of bleeding. The results of chi-square on drug interactions and their effect on the incidence of bleeding outcomes showed that drugs that have a risk of minor interactions have a significant effect in bleeding events with a value of $p = 0.04$ compared to drug interactions that have a risk of major and minor interactions ($p = 0.42$; $p = 1.00$). This suggests that minor interactions should be closely monitored and managed to minimize the risk of bleeding complications. Minor interaction can accumulate and have a significant impact on patient health[17]. It addressing minor interactions can prevent them from escalating into more serious issues and improve treatment outcomes. Ensuring comprehensive patient care involves monitoring and managing all potential risks, including minor ones, to maintain patient safety and quality of life.

The limitation of this study was no further discussion on patient medication adherence or assessment of patient knowledge of the risks and benefits of warfarin therapy. Therefore, further observational research to understand patient understanding of side effects and medication adherence is needed. A study in 2020 indicated that patients in that study understood they were using warfarin for their atrial fibrillation; however, most patients were unable to assess the risk of stroke when using or not using warfarin, as well as the risk of bleeding when using warfarin[19].

Future research should explore strategies to mitigate the risks posed by drug interactions in stroke patients, particularly focusing on medications like NSAIDs (no steroidal anti-inflammatory drugs) that have been identified as high-risk for bleeding events when combined with warfarin. This includes

evaluating the feasibility and efficacy of alternative drug combinations or intermittent dosing schedules to minimize adverse effects without compromising therapeutic outcomes. Additionally, prospective studies with larger and more diverse patient cohorts could provide clearer insights into the clinical implications of drug interactions in stroke management. Enhanced pharmacovigilance and systematic monitoring protocols should be implemented to detect and manage drug interactions promptly, thereby improving patient safety and optimizing treatment efficacy in stroke care settings.

Conclusion

The study highlighted that both recurrence stroke and non-recurrence stroke groups exhibited similar risks of drug interactions, encompassing major, moderate, and minor severities. Interactions posing minor risks correlated with bleeding events. The study underscored an elevated risk of bleeding associated with combinations such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs including diclofenac sodium, aspirin, meloxicam, ibuprofen, and mefenamic acid. It necessitates vigilant monitoring and frequent INR checks when warfarin is administered with interacting drugs.

Conflicts of Interest

There is no conflict of interest

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