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Research Article

Effects of Switching Dose, Dose Variation, and Warfarin Interaction on the Incidence of Stroke Recurrence in Stroke Patients with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) significantly increases the risk of stroke, necessitating anticoagulation therapy. Warfarin, a commonly prescribed anticoagulant regimen, requires careful monitoring to ensure patient safety. This study aimed to assess the impact of dose switching, dose variation, and potential interactions with warfarin on the incidence of stroke recurrence in stroke patients with AF. The study retrospectively analyzed the treatment records of stroke patients with AF in outpatient settings over one year. The subjects comprised 314 patients who received warfarin prescriptions at two Indonesian Hospitals from January 1, 2015, to December 31, 2019. Out of these patients, 50 had recorded data regarding dose adjustments, variations, and interactions. They were divided into two groups: a case group (n=11) with stroke recurrence and a control group (n=39) without recurrence. Statistical analysis, including chi-square tests and odds ratio calculations, revealed that both warfarin dose switching (OR=7.6) and dose variation (OR=6.6) significantly influenced the incidence of stroke recurrence. It implies that inconsistencies or alterations in warfarin dosing substantially elevate the likelihood of experiencing another stroke, potentially due to inadequate anticoagulation leading to clot formation. Interestingly, the analysis of drug interactions did not significantly impact stroke recurrence. In summary, the recurrence of stroke in patients with AF is notably influenced by warfarin dose adjustments and variations rather than drug interactions. This study highlights the critical importance of precise dosing strategies and vigilant monitoring to enhance the efficacy of anticoagulant therapy in this high-risk population.

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INTRODUCTION

Stroke, a neurological disorder characterized by impaired cerebral blood flow, imposes a significant burden on individuals and healthcare systems worldwide. Hemorrhagic stroke, in particular, requires extensive long-term treatment and incurs substantial costs, often leading to decreased patient productivity[1]. Globally, stroke remains a major health concern, affecting over 101 million people, with an annual incidence of 12.2 million new cases. Alarmingly, 6.5 million individuals succumb to stroke each year. While stroke traditionally impacted older populations, recent data indicate a concerning trend towards younger-onset strokes, with 63% of stroke cases occurring in individuals under 70 years of age in 2019[2]. In the United States, stroke ranks second only to ischemic heart disease as a leading cause of death, with approximately 795,000 individuals experiencing a stroke annually[3].

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Cardioembolic stroke, a type of ischemic stroke, occurs when blood clots (emboli) formed in the heart are carried to the brain, causing neurological deficits. Atrial fibrillation (AF), a cardiac rhythm disorder, is the most common cause of cardioembolic stroke, accounting for 45% of cases[4]. Strokes associated with AF carry a higher risk of recurrence, death, and dependence compared to those without AF, even after one year (42% vs 17.8%; 50% vs 36.1%; 32.2% vs 24.1%)[5,6]. This risk profile increases further in the third year of follow-up.

Anticoagulation therapy is a crucial strategy for reducing stroke risk in patients with AF. The Indonesian Heart Association recommends anticoagulants to mitigate hypercoagulation, prevent cardioembolic stroke, and reduce the risk of postoperative venous thrombosis and pulmonary embolism[7]. The anticoagulant landscape in Indonesia includes both vitamin K antagonists (VKAs) and the newer direct-acting oral anticoagulants (DOACs) like dabigatran, rivaroxaban, and apixaban. VKAs have historically been the mainstay of oral anticoagulation for stroke prevention[8]. However, DOACs have emerged as promising alternatives, offering several advantages in terms of convenience and safety profiles.

Anticoagulant therapy, particularly warfarin, is a cornerstone in preventing stroke events among individuals with a high risk of AF[9]. However, effective warfarin management necessitates careful monitoring due to its susceptibility to interactions with food and medications, as well as the presence of contraindications that can increase the risk of bleeding[10]. Individualized dosing of warfarin is crucial given the wide variability in bleeding rates associated with its use. The International Normalized Ratio (INR) serves as a key indicator for monitoring warfarin therapy, as deviations from the target range necessitate dose adjustments. Interactions between warfarin and other substances can pose significant risks to patients, potentially leading to adverse health outcomes and increased healthcare costs[11].

Drug-drug interactions (DDIs) and bleeding risks are significant concerns among inpatients receiving warfarin therapy in our institution. Clinicians must be vigilant in identifying potential DDIs and closely monitoring INR levels[12]. Previous research has consistently demonstrated the high prevalence of DDI during warfarin therapy, both in inpatients and outpatients[13,14]. To mitigate the risk of adverse events, strategies for identifying and managing warfarin-drug interactions are essential.

Although the absolute and relative risks of AF-associated ischemic stroke have decreased in the past two decades, AF remains a significant risk factor, contributing to approximately one in four ischemic strokes in 2020[15]. This underscores the substantial potential for improving stroke prevention among individuals with AF. Identifying potential drug interactions involving warfarin is crucial to minimizing adverse effects in patients with AF. The risk of adverse events increases with the number of medications administered concurrently with warfarin[16]. This study aimed to investigate the impact of dosage adjustments, variations, and drug interactions on the recurrence of stroke in AF patients receiving warfarin therapy. Two hospitals, a central hospital and a regional hospital, were selected for this study due to their high prevalence of AF-associated stroke cases.

MATERIALS AND METHODS

Materials

This study was conducted at Dr. Sardjito Hospital in Yogyakarta and Dr. Moewardi Hospital in Solo, Central Java, from August 2019 to March 2020. Data collection involved the retrospective review of patient medical records, which were summarized in a standardized data collection form. Data were collected using a standardized Case Report Form (CRF) designed to capture demographic information (medical record number, gender, date of birth, admission date), AF characteristics (anticoagulant medication, dosage, frequency, diagnosis of comorbidities, and in-hospital events), and laboratory data, medication usage, and nursing notes from the patient's medical records. Ethical approval for this study was obtained from the Faculty of Medicine, Universitas Gadjah Mada, and the Medical and Health Research Ethics Committee (MHREC) (Ethics Committee Approval Ref: KE/FK/002/EC/2018).

Methods

This study employed a retrospective case-control design to investigate the relationship between warfarin therapy and recurrent stroke in patients with AF. Data were collected from medical records of patients hospitalized at Dr. Sardjito General Hospital (218 patients) and RSUD Dr. Moewardi (96 patients) between January 1, 2015, and December 31, 2019. Inclusion criteria included patients aged 45 or older, outpatients, diagnosed with AF and stroke (ICD-10 codes I63 and I48),

and receiving warfarin therapy for at least six months and 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,. Exclusion criteria encompassed patients who discontinued warfarin or switched to other anticoagulants, died during the observation period, or had a history of stage IV renal failure, pregnancy, or breastfeeding. A total of 50 patients met these criteria, divided into a case group (11 patients with recurrent stroke) and a control group (39 patients without recurrent stroke). The primary outcome was the incidence of recurrent stroke within one year of warfarin initiation, with consideration of examination frequency and INR therapeutic values.

Data analysis

To investigate the association between warfarin therapy factors (dose switching, dose variance, and drug interactions) and stroke recurrence, data analysis was performed using SPSS version 22. Statistical significance was set at a p-value of <0.05 and a 95% confidence interval. Bivariate analysis was conducted to identify variables associated with stroke recurrence. Chi-square tests were employed to analyze the relationships between predictor variables and the outcome variable. To assess the risk factors associated with AF and stroke recurrence, odds ratios (ORs) were calculated.

RESULTS AND DISCUSSION

As detailed in **Table I**, the study included patients with AF who had experienced a stroke and were receiving warfarin therapy. This retrospective study analyzed outpatient data from a one-year period to evaluate the association between warfarin treatment and stroke recurrence. Our analysis revealed that the timely administration of warfarin, along with appropriate supportive medications, was crucial in preventing stroke recurrence in patients with AF. Adherence to warfarin therapy and the use of additional preventive medications significantly reduced the risk of recurrent strokes. Both case and control groups consisted predominantly of patients over 60 years old (case: 45.5%; control: 71.8%) and a majority of female participants (case: 72.7%; control: 59%). All subjects in both groups received switching doses and utilized Indonesian health insurance for examinations (case: 90.9%, 90.9%; control: 56.8%, 86.8%). Notably, dose variations were observed in 81.8% of case subjects but in only 59.5% of control subjects. Congestive heart failure, hypertension, and diabetes were prevalent comorbidities in both groups.

Warfarin (brand names: Warfarin, Simarc, Notisil) is administered in 2 mg tablets. Dosage is individualized according to patient factors and regular INR monitoring. A review of patient medical records revealed a wide range of prescribed warfarin dosages, from 1 to 7 mg per day, as summarized in **Table II**. As depicted in **Table II**, the most frequent warfarin dosage in the stroke group was 1 mg/2 mg daily, indicating a biphasic dosing regimen with a higher dose on Mondays and Thursdays. In contrast, the non-stroke group exhibited a higher prevalence of 2 mg daily warfarin use. These findings align with the Oxford Haemophilia and Thrombosis Centre Protocols for Outpatient Oral Anticoagulation with Vitamin K Antagonists[17], which recommend a starting dose of 2 mg warfarin for patients with an INR within the target range of 2.6-2.7 after at least 7 days of treatment.

The analysis revealed that patients in this study frequently received non-warfarin medications to manage comorbidities such as congestive heart failure, diabetes mellitus, and hypertension. These medications can interact with warfarin, affecting its therapeutic efficacy and increasing the risk of bleeding events. It is essential to consider these interactions when administering non-warfarin drugs to patients on warfarin therapy. Bisoprolol, furosemide, and candesartan were the most frequently prescribed non-warfarin medications in both the case and control groups, accounting for 64%, 55%, and 44% of prescriptions, respectively. This aligns with the 2017 ACC/AHA/HFSA Focused Update on the 2013 ACCF/AHA Guideline for Management of Heart Failure[18], which recommends beta-blockers, ACE inhibitors or ARBs, and diuretics as a cornerstone of treatment for congestive heart failure.

Drug interactions are a common concern in polypharmacy. While this analysis did not explicitly assess drug interactions, it is important to note the potential for significant, moderate, or minor interactions among the prescribed medications. Careful monitoring and management of drug interactions are crucial to ensure optimal patient outcomes[19]. Drug interactions were classified based on their severity as major, moderate, or minor. Major interactions pose a significant health risk, potentially leading to life-threatening complications or prolonged/permanent damage. Moderate interactions, while not as severe, can

still cause substantial harm if left unaddressed. Minor interactions, although generally not harmful, may still result in some adverse effects[20].

Both the stroke recurrence and non-recurrence groups exhibited a high prevalence of drug interactions, as shown in **Table III**. Major interactions were observed in 81% of the recurrence group and 69% of the non-recurrence group. Moderate interactions were even more prevalent, occurring in 91% and 89% of patients, respectively. Minor interactions were also common, affecting 72% and 87% of patients. There were no statistically significant differences in the frequency of major, moderate, or minor interactions on recurrent stroke outcomes between the groups (p >0.05).

Table I. Patient characteristics.

Variable	Case group (recurrence stroke) N =11(22%)	Control group (non-recurrence stroke) N=39(78%)	p
Age (years)			
40-60	5(45.5)	9(23.1)	0.25
<40	1(9)	2(5.1)	
>60	5(45.5)	28(71.8)	
Sex			
Male	3(27.3)	16(41)	0.50
Female	8(72.7)	23(59)	
Switching dose			
Switching dose	10(90.9)	21(56.8)	0.04
No switching dose	1(9.1)	16(43.2)	
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	10(90.9)	33(86.8)	1.00
Non-Indonesian Social Security and Health	1(9.1)	5(13.2)	
Disease Risk Factor			
Diabetes mellitus			
Yes	2(18.2)	4(10.3)	0.60
No	9(81.8)	35(89.7)	
Hypertension			
Yes	2(18.2)	16(41)	0.28
No	9(81.8)	23(59)	
Congestive heart failure			
Yes	5(45.5)	16(48.7)	1.00
No	6(54.5)	23(51.3)	
Dyspepsia			
Yes	2(18.2)	6(15.4)	1.00
No	9(81.8)	33(84.6)	
Mitral valve insufficiency			
Yes	2(18.2)	14(35.9)	0.48
No	9(81.8)	25(64.1)	
Rheumatic tricuspid valve disease			
Yes	0(0)	7(17.9)	0.32
No	11(100)	32(82.1)	
Congenital malformation of aortic and mitral valve			
Yes	0(0)	4(10.3)	0.56
No	11(100)	35(89.7)	
Osteoarthitis			
Yes	1(9.1)	3(7.7)	1.00
No	10(90.9)	36(92.3)	
Chronic kidney disease			
Yes	0(0)	1(2.6)	1.00
No	11(100)	38(97.4)	
Disorder of lipoprotein metabolism and other lipidemia			
Yes	0(0)	2(5.1)	1.00
No	11(100)	37(94.9)	
Multiple sclerosis			
Yes	1(9.1)	0(0)	0.22
No	10(90.9)	39(100)	
Chronic ischemic heart disease			
Yes	1(9.1)	0(0)	0.22
No	10(90.9)	39(100)	

Table II. Warfarin dose in each group.

Oral warfarin dosage (daily dose)	Case (recurrence stroke) N =11(22%)	Control (non-recurrence stroke) N=39(78%)
1 mg	0(0)	6(15)
1mg/2 mg	4(36)	6(15)
2mg	0(0)	14(36)
2mg/3mg	2(18)	9(23)
2mg/4mg	0(0)	1(3)
3mg	3(27)	1(3)
4mg/6mg	1(9)	2(5)
6mg/7mg	1(9)	0(0)

Table III. Average patient drug interactions.

Drug interactions	Case (recurrence stroke) N =11(22%)	Control (non-recurrence stroke) N=39(78%)	p
Major	81	69	0.30
Moderate	91	89	0.49
Minor	72	87	0.36

Analysis of potential drug interactions is crucial for optimizing patient outcomes. **Table IV** presents the variables associated with recurrent stroke. However, statistical analysis revealed no significant correlation between the three investigated interactions and stroke recurrence (p-value >0.05). Warfarin interactions, categorized as major, moderate, or minor, were not found to be associated with stroke recurrence risk.

Table IV. Warfarin dose switching, variance and warfarin drug interactions in the incidence of recurrent stroke.

Variable	Case (reccurence stroke) N=11(22%)	Control (non-recurrence stroke) N=39(78%)	OR (95% CI)	p
Switching dose				
Yes	10(90.9)	21(56.8)	7.6(0.8-65.8)	0.04
No	1(9.1)	16(43.2)		
Dose variance				
Yes	9(81.8)	15(40.5)	6.6(1.2–34.9)	0.03
No	2(18.2)	22(59.5)		
Major interaction				
Yes	3(27.3)	8(20.5)	1.4(0.3-6.7)	0.68
No	8(72.7)	31(79.5)		
Moderate interaction				
Yes	6(54.5)	19(48.7)	1.2(0.3-4.8)	1.00
No	5(45.5)	20(51.3)		
Minor interaction				
Yes	6(54.5)	29(74.4)	0.4(0.1-1.6)	0.24
No	5(45.5)	10(25.6)		

Several previous studies have demonstrated the effectiveness of anticoagulant therapy in reducing stroke risk for patients with AF. Standard anticoagulants were associated with a 22% reduction in stroke risk compared to aspirin[21]. This aligns with the recommendation that most AF patients should receive long-term oral anticoagulants to prevent ischemic stroke and other stroke types[22]. Warfarin therapy has also been shown to reduce ischemic stroke risk by 43.5%[23]. Additionally, non-VKAs oral anticoagulants are considered safer and equally effective as warfarin in stroke prevention[24]. Our research differs from previous studies in its specific focus. While existing studies have generally examined the effectiveness of various anticoagulant therapies, including warfarin and non-VKAs oral anticoagulants, in reducing stroke risk for AF patients, this study aimed to investigate the relationship between warfarin treatment variables, such as dosage adjustments, dose variability, and drug interactions, and the incidence of stroke recurrence in this population.

The management of warfarin therapy requires careful consideration of dosage adjustments and potential drug interactions. Warfarin can interact with numerous medications, affecting the maintenance dose, particularly when interacting drugs are introduced or discontinued. These interactions can be pharmacokinetic or pharmacodynamic in nature[25]. For patients initiating warfarin therapy, the dose should be adjusted based on regular INR monitoring at specified intervals. The goal is to achieve a therapeutic INR range as quickly as possible, as excessively high INR levels can increase the risk of bleeding, while subtherapeutic INR levels may lead to recurrent stroke[26]. Given the risk of bleeding associated with warfarin therapy, routine monitoring of INR levels is essential. The target INR range is typically 2.0-3.0[27].

In this study, we observed that 90.9% of patients in the case group required routine warfarin dose adjustments within one year. Statistical analysis revealed a significant association between warfarin switching dose prescription and stroke

recurrence (OR = 7.6). This indicates that patients receiving variable warfarin doses had a 7.6-fold higher risk of recurrent stroke compared to those with consistent dosing. Such fluctuations in warfarin dosing can disrupt the delicate balance required for effective anticoagulation, leading to suboptimal blood thinning levels. These deviations create windows of vulnerability where clot formation is more likely, increasing the risk of subsequent strokes in patients relying on warfarin therapy.

Our analysis revealed a significant association between dose variation and stroke recurrence in patients with AF (**Table III**). Approximately 81.8% of patients received variable doses, highlighting the importance of consistent dosing for stroke prevention. Statistical analysis demonstrated that patients with inconsistent dosing had a six-fold higher risk of stroke recurrence (OR = 6.6). These findings underscore the critical need for meticulous monitoring of INR levels and timely dose adjustments to optimize warfarin therapy and minimize the risk of stroke recurrence. In this study, the earliest stroke recurrence occurred three months post-index stroke, while the longest was observed 15 months later. These findings align with previous research indicating a cumulative risk of cardioembolic stroke reaching 10% within the first year and increasing over time[28].

Analysis of drug interactions in stroke recurrence and non-recurrence groups revealed no significant difference in the severity of moderate and minor major interactions. However, both groups experienced a high incidence of drug interactions, with recurrence stroke patients reporting 81% major, 91% moderate, and 72% minor interactions, and non-recurrence stroke patients reporting 69% major, 89% moderate, and 87% minor interactions. To mitigate the risk of drug interactions, strategies such as replacing medications or adjusting dosing intervals should be considered. Consistent with the findings of previous studies, an increase in warfarin prescribing is strongly associated with a higher cumulative incidence of stroke/systemic embolic events (SEEs), major hemorrhage, gastrointestinal hemorrhage, fractures/falls, cardiovascular events, cardiovascular death, and mortality from other causes[29].

An analysis of drug interaction categories revealed no significant difference in the incidence of recurrent stroke for major, moderate, or minor interactions ($p > 0.05$). While statistically insignificant, the potential for drug interactions in stroke patients remains clinically relevant and underscores the risk of adverse drug reactions. The high incidence of drug interactions in this study can be attributed to the large number of medications prescribed to patients, particularly the elderly population, who often have multiple chronic health conditions[30,31].

This study, while offering valuable insights, has several limitations that warrant consideration. Firstly, the focus on two specific hospitals may limit the generalizability of the findings to a broader population. Future studies should consider a multicenter design with a more diverse patient sample to enhance external validity. Secondly, the retrospective nature of the study relies on the quality and completeness of medical records, which may introduce potential biases. While the study can generate hypotheses, it cannot definitively establish causation. Thirdly, the study should be mindful of potential confounding variables, such as age, comorbidities, and other medications, which could influence stroke recurrence risk. Incorporating appropriate statistical methods to control for these factors can strengthen the study's conclusions. Finally, a longer follow-up period might be necessary to capture all potential stroke recurrences, as these events can occur over an extended timeframe. In conclusion, while this study provides valuable insights, particularly regarding clinical relevance and the inclusion of a control group, these limitations should be acknowledged when interpreting the findings. Future research could be enhanced by expanding the sample size, addressing potential confounders, and adopting a multicenter design to improve the generalizability of the results.

Future research on stroke recurrence in patients with AF receiving warfarin therapy should focus on enhancing our understanding of the underlying factors and mechanisms involved. Prospective longitudinal studies with extended follow-up periods are necessary to capture the full spectrum of stroke recurrence patterns over time. Collaborative efforts among multiple medical centers and the implementation of randomized controlled trials can strengthen the evidence base for assessing the impact of various warfarin dosing strategies, including dose variation and switching. Additionally, incorporating pharmacogenomic studies to tailor warfarin dosing based on individual genetic factors can improve treatment efficacy. Comprehensive risk factor analysis, encompassing comorbid conditions, lifestyle variables, and concurrent medications, is essential for a more accurate risk assessment. Evaluating the quality of anticoagulation control, patient-reported outcomes, and the influence of drug interactions on warfarin therapy are crucial areas for future investigation.

CONCLUSION

Our analysis revealed that stroke recurrence in AF patients is significantly influenced by warfarin dosing and dose switching. Inconsistent or altered warfarin dosing increases the risk of recurrent stroke. While major, moderate, and minor DDIs did not exhibit significant differences in stroke recurrence rates, healthcare professionals must remain vigilant in assessing and managing these interactions to optimize anticoagulation therapy.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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