



# Plasma Warfarin Level and International Normalized Ratio do not Correlate with Bleeding Events in Indonesian Patients of Minangkabau Ethnicity with Atrial Fibrillation

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## Abstract

**BACKGROUND:** Warfarin is the mainstay of anticoagulant therapy to prevent thromboembolism in atrial fibrillation (AF). It has a narrow therapeutic window, rendering monitoring prothrombin time necessary using the international normalized ratio (INR). However, INR value is not always correlated with the clinical risk of bleeding.

**AIM:** We aimed to monitor plasma warfarin concentration and to analyze its correlation with bleeding events in Indonesian patients of Minangkabau ethnicity with AF.

**METHODS:** We consecutively recruited outpatients with AF from January to November 2017 at a tertiary hospital in West Sumatera, Indonesia. At the time of the study, patients had received at least 5 weeks of warfarin. Their characteristics were obtained from medical records, and INR data were collected. Warfarin plasma concentration was analyzed using high-performance liquid chromatography.

**RESULTS:** There were a total of 45 patients (25 males and 20 females; mean age 54.6 years). The number of patients with INR value lower than, within, and higher than target value (2.0–3.0) was 25, 12, and 8, respectively. Half of the patients (n = 23; 51.1%) had subtherapeutic plasma warfarin levels and nearly half (n = 20; 44.4%) of the patients had therapeutic plasma warfarin levels. INR value was not significantly correlated with plasma warfarin level (r = 0.273; p = 0.07). Bleeding events occurred in 14 patients. INR value was not significantly different (p = 0.12), while the plasma warfarin level was marginally significantly different (p = 0.05) between those with bleeding and no bleeding events.

**CONCLUSION:** Neither warfarin plasma concentration nor INR was correlated with bleeding events in Indonesian patients of Minangkabau ethnicity with AF.

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## Introduction

Atrial fibrillation (AF) is the most common type of arrhythmias and the global burden of AF is increasing progressively [1]. The prevalence of AF in some countries in Europe ranges from 1.9% to 2.9% [2]. The incidence rates in developed regions were significantly higher compared with developing countries [1]. However, AF prevalence in Indonesian National Heart Center in 2013 was 9.8% [3]. The high prevalence of AF makes the treatment of AF and factors contributing to treatment efficacy a critical field to study in Indonesia.

Arrhythmic, particularly AF, patients were commonly treated with the oral anticoagulant warfarin. Warfarin has a narrow therapeutic index. Furthermore, warfarin binds strongly to albumin; therefore, it may shift the bond of other drugs to albumin when given simultaneously, thus reducing the effectiveness of other medications [4]. The amount of administered dose must be individualized by considering each patient's clinical features, by measuring prothrombin

time periodically, and by noting the tendency for the occurrence of bleeding [5]. The therapeutic range of oral anticoagulants is expressed by the International Normalized Ratio (INR) calculated based on prothrombin time. In general, the INR value of 2.0–3.0 is considered within the therapeutic range. INR value is used as a guide for dose adjustment in patients receiving warfarin [6]. Patients with periodical INR value within the therapeutic range 70% of the time or more had a significantly reduced risk of stroke [7]. Determination of warfarin plasma concentration is an objective procedure to ascertain drug concentration in the blood. Some patients may show resistance to warfarin and, thus, may require an increased dose. Warfarin resistance is shown to be associated with genetic abnormalities or the presence of genetic polymorphisms, particularly on *CYP2C9* and *VKORC1* [8], [9]. Asians, African-Americans, and Native Americans combined had lower mean time in therapeutic range compared with European patients receiving warfarin [10]. Ethnic-specific dosing algorithms are thought to be crucial in pharmacogenetics-guided warfarin therapy [11].

However, first, we need to ascertain warfarin plasma level in the ethnic group of interest.

Up until now, there is no data on warfarin plasma concentration in the Indonesian population of Minangkabau ethnic origin suffering from AF. As Indonesia is a multi-ethnic country, ethnic-specific information is valuable in identifying pharmacokinetics variation among patients. The setting of the current study was a general referral hospital in the capital of West Sumatera Province, where Minangkabau ethnic resides. Most patients' medication was covered by a national health insurance system. Patients were referred by primary care physicians to the cardiology department of the hospital to receive specialized care for their AF. In this study, we investigated warfarin plasma concentration to identify pharmacokinetics variation that might impact warfarin efficacy in our patients.

## Materials and Methods

### Study subjects

This study was a cross-sectional study conducted from January to November 2017 in Indonesian patients of Minangkabau ethnicity with AF receiving warfarin therapy at a tertiary hospital in West Sumatra, Indonesia. The study was performed according to the Declaration of Helsinki and approved by the Ethical Committee (Institutional Review Board) of the Faculty of Medicine, Andalas University (Ref No. 177/KEP/FK/2017). Blood samples used in the study were collected at a single time point from patients attending outpatient clinic at the Department of Cardiology and Vascular Medicine, M. Djamil General Hospital, Padang, West Sumatra, who had received oral anticoagulant warfarin for at least 5 weeks. Patients were male or female above 18 years old diagnosed with AF based on standard diagnostic criteria [12]. Those with impaired liver and kidney function and pregnancy were excluded from the study.

Bleeding event as the side effect of oral anticoagulant therapy was defined according to the Bleeding Academic Research Consortium definition [13] and it was assessed by history taking at the time of sample collection. The bleeding event in this study was either Type 0 (no evidence of bleeding) or Type 1 (bleeding that is not actionable and does not cause the patient to seek treatment by a health-care professional) during the past 5 weeks. Patients' 1-year risk of major bleeding was assessed by calculating their hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, and labile INRs (HAS-BLED) score [14]. All patients were taking medications other than warfarin, and these drugs were listed and checked for their interaction with warfarin.

### Plasma warfarin analysis

Plasma warfarin analysis was performed by Pharmametric Laboratory, Jakarta. The method was as followed. Three milliliters of blood was drawn from the vein by using Vacutainer®, inverted and centrifuged at 3,000 rpm for 10 min. Plasma was immediately separated, aliquoted, and stored at  $-20^{\circ}\text{C}$  for <1 month before analysis. High-performance liquid chromatography was used to measure plasma warfarin concentration using a C18 column with mobile phase acetonitrile and 0.5% triethylamine at a ratio of 28:72; pH 6.5; and flow velocity 1.0 ml/min at 386 nm [15], [16], [17].

### Statistical analysis

Categorical data were presented in a frequency distribution, and continuous data were presented in mean, median, and range. The correlation of administered warfarin dose with plasma warfarin level and INR value was analyzed by Spearman's rank correlation due to the non-normal distribution of the data. The difference in INR and plasma warfarin levels in subjects with and without bleeding events was analyzed by the Mann–Whitney U test. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed using IBM® SPSS® Statistics ver.19 (IBM, US).

## Results

There were 45 subjects with AF who met inclusion criteria and agreed to participate in the study with characteristics, as shown in Table 1. The median warfarin plasma concentration was  $0.94\ \mu\text{g/ml}$  with a median maintenance dose of 2.5 mg/day. More than half (55.6%) of patients had INR value  $<2.0$  and only 28.9% of patients reached the desirable INR value of 2.0–3.0, while the rest (15.6%) showed value  $>3.0$  [7].

Warfarin dose was found to be statistically significantly correlated with plasma warfarin level, albeit with moderate positive correlation ( $r = 0.459$ ,  $p = 0.002$ ; Figure 1a). However, warfarin dose and plasma warfarin levels were not significantly correlated with INR ( $r = -0.032$ ,  $p = 0.83$ ; Figure 1b and  $r = 0.273$ ,  $p = 0.07$ ; Figure 1c, respectively).

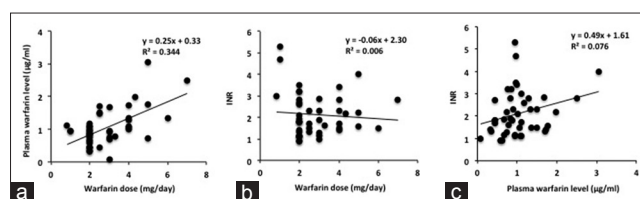


Figure 1: Correlations of warfarin dose with plasma warfarin level (a) and international normalized ratio (INR) (b), and correlation of plasma warfarin level with INR (c) in 45 patients with atrial fibrillation

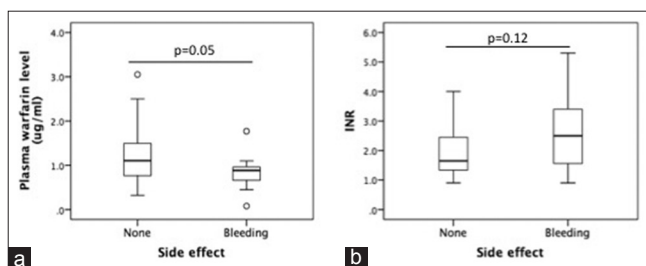
**Table 1: Characteristics of subjects**

Characteristics	n	(%)	AM <sup>a</sup>	GM <sup>b</sup>	Median	Min	Max
Age (year)	45	(100)	54.6			25	80
Sex							
Male	25	(55.6)					
Female	20	(44.4)					
Body mass index (kg/m <sup>2</sup> )	45	(100)	22.9			17.6	29.3
Level of education							
Primary	14	(31.1)					
Secondary	28	(62.2)					
Graduate/postgraduate	3	(6.7)					
Occupation							
Civil servant	5	(11.1)					
Self-employed	13	(28.9)					
Housewife	18	(40.0)					
Retiree	9	(20.0)					
Warfarin dose (mg/day)	45	(100)	2.9	2.6	2.5	0.8	7.0
INR	45	(100)	2.1	1.9	1.8	0.9	5.3
<2.0	25	(55.6)					
2.0–3.0	13	(28.9)					
>3.0	7	(15.6)					
Plasma warfarin (µg/ml)	45	(100)	1.1	0.90	0.94	0.1	3.1
<1.0	23	(51.1)					
1.0–2.0	20	(44.4)					
>2.0	2	(4.4)					
Side effect occurrence	38	(100)					
None	24	(63.2)					
Bleeding	14	(36.8)					

<sup>a</sup>Arithmetic mean  
<sup>b</sup>Geometric mean

INR: International normalized ratio.

To explore the relationship between bleeding event occurrence with plasma warfarin level and INR in our subjects, we compared plasma warfarin level and INR in those without (n = 24) and with (n = 14) bleeding events. Patients whose information on bleeding events unavailable (n = 7) were not included in the analysis. Those with bleeding events had lower plasma warfarin levels (p = 0.05) and higher INR (p = 0.12), albeit statistically non-significant, compared to those without bleeding events (Figure 2).



**Figure 2: Association of plasma warfarin level (a) and international normalized ratio (b) with occurrence of bleeding event in 45 patients with atrial fibrillation**

To predict major bleeding risk in anticoagulated AS patients, we calculated the HAS-BLED score [14] and presented the result in Table 2. More than half (57.8%) of the patients were categorized to moderate risk (HAS-BLED score 1–2) and the rest (42.2%) were categorized to a high risk of major bleeding (HAS-BLED score ≥3).

**Table 2: Bleeding risk in AF patients based on HAS-BLED\* score**

HAS-BLED score	Frequency	Percent	Risk category
1	9	20	Moderate
2	17	37.8	
3	16	35.6	High
4	1	2.2	
5	1	2.2	
6	1	2.2	
Total	45	100	

\*HAS-BLED: Hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile INRs, elderly (age>65), drugs or alcohol. INR: International normalized ratio, AF: Atrial fibrillation.

To consider the possible pharmacokinetic interaction between warfarin and other drugs affecting warfarin plasma levels, we have compiled all the drugs administered to the patients in Table 3. There were four drugs that might have a major and a moderate interaction with warfarin, and there were six drugs that might have minor interaction with warfarin, taken by the patients.

**Table 3: List of drugs administered to the warfarin-taking patients**

Drug class	Drug name	Known interaction with warfarin	Number of patients taking the drug
Antiplatelet	Acetosal	Major	5
	Cilostazol	Major	1
	Clopidogrel	Major	1
Beta-blocker	Bisoprolol	No	40
	Carvedilol	No	4
	Propranolol	Minor	1
Loop-diuretic	Furosemide	Minor	29
Potassium-sparing diuretic	Spironolactone	Minor	21
Angiotensin receptor blocker	Candesartan	No	8
	Telmisartan	Minor	3
ACE-inhibitor	Valsartan	No	1
	Ramipril	No	12
Calcium-channel blocker	Lisinopril	No	1
	Amlodipine	No	4
Cardiac glycoside	Nifedipine	No	1
	Digoxin	No	5
Statin	Atorvastatin	Minor	11
	Simvastatin	Minor	1
Nitrate	Isosorbide dinitrate	No	2
Uric acid medication	Allopurinol	Moderate	3
	Colchicine	No	1
Proton-pump inhibitor	Lansoprazole	Moderate	12
	Omeprazole	Moderate	1
Mucosal protector	Sucralfate	Moderate	2
Laxative	Psyllium	No	1
	Laxadine™	No	1
Antibiotics	Ciprofloxacin	Major	1
Benzodiazepine	Clobazam	No	1
Others	Vitamin B	No	5
	Folic acid	No	1
	Acetyl cysteine	No	1

## Discussion

The mean warfarin plasma concentration of patients with AF in this study was 1.1 ± 0.6 (range,

0.1–3.1)  $\mu\text{g/ml}$ . It was achieved with a maintenance dose of  $2.9 \pm 1.3$  (range, 0.8–7.0) mg/day. This result is higher than that of a study in Chinese patients with heart valve replacement within 1 month of post-operation, where the mean of warfarin plasma concentration was  $0.6 \pm 0.12$   $\mu\text{g/ml}$  [18]. However, our finding is similar to a study in Korean patients ( $1.3 \pm 0.5$   $\mu\text{g/ml}$ ) administered a higher maintenance dose of  $4.1 \pm 1.3$  mg/day (range, 1.7–8.0 mg/day) than our patients [19]. Polymorphisms in a gene such as VKORC1, CYP2C9 [8], [9], [10], [11], and CYP4F2 [20] may contribute to the differences in plasma warfarin levels.

Warfarin is a Vitamin K antagonist with the anticoagulant effect mediated through the prevention of activation of Vitamin K dependent coagulation factors (factor II, VII, IX, and X) [21] age [22], fat-free mass [23], Vitamin K-rich foods, and coadministered drugs [24] are determinants of warfarin pharmacokinetics. It is estimated that pharmacokinetics factors determine up to 40% of warfarin maintenance dose variability [24], [25]. We have listed coadministered drugs in our patients and found that eight patients were taking drugs with significant interaction with warfarin. This possible interaction may influence the correlation between plasma warfarin levels and INR. Furthermore, genetic variations of VKORC1 and Vitamin K intake influence warfarin dose and anticoagulation response [26]. With a narrow therapeutic window and a high inter- and intra-individual variability, warfarin use needs careful laboratory monitoring and dose adjustment to gain antithrombotic protection while minimizing the bleeding risk.

Warfarin dose was found to be correlated with plasma warfarin levels. However, plasma warfarin level was not significantly correlated with INR, despite a trend of increasing INR with increasing plasma warfarin level. These results confirmed the finding of a previous study where the INR is poorly dependent on warfarin concentration [27]. Previous studies in Indonesians receiving low-dose warfarin therapy found that a high INR is associated with polymorphisms in VKORC1 and CYP2C9 [28], and both genes showed significant association with warfarin sensitivity [9]. Whether these major genetic factors played a role in the pharmacokinetics and/or pharmacodynamics in our subjects, remain to be elucidated.

This study finds that less than a third of patients who received doses of 0.8–7.0 mg/day of warfarin had INR value within the optimal warfarin therapy range (2.0–3.0). One study reported that stable anticoagulation was achieved in 80% of patients who received doses of 2–5 mg/day of warfarin [29]. Previous studies had demonstrated the importance of maintaining a stable INR value between 2.0 and 3.0 for reducing strokes and mortality in patients with AF [7]. When INR value remained within the therapeutic range of more than 70% of the time, there is a substantially lower risk of stroke [30]. A previous study showed that

INR value 2.0–3.0 was associated with a reduced risk of clinically significant bleeding [31]. In this study, the INR value was not correlated to the incidence of bleeding. Despite the HAS-BLED score showing our patients having moderate to high risk of major bleeding, the bleeding episodes in this study were minor, and HAS-BLED score was not correlated with plasma warfarin level (data not shown). Diets, age, drug interactions, and genetic polymorphisms are known to link with warfarin metabolism. In this study, age was not associated with INR or plasma warfarin (data not shown).

The limitation of this study was that data were obtained from a single center with a small number of patients. Nevertheless, this is the first plasma warfarin monitoring study in warfarin-treated AF patients from the Indonesian ethnic of Minangkabau. The current study did not encompass patients' clinical outcomes on follow-up, and therefore further studies are warranted.

## Conclusion

Neither warfarin plasma concentration nor INR was correlated with bleeding events in Indonesian patients of Minangkabau ethnicity with AF. Future endeavor is recommended in a more extensive study to explore the genetic variants contributing to warfarin pharmacokinetics/pharmacodynamics in this population.

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