Jurnal Manajemen dan Pelayanan Farmasi (JMPF)
(Journal of Management and Pharmacy Practice)
ISSN-p : 2088-8139 | ISSN-e : 2443-2946
JMPF Vol 14(2) 2024: 111-123

# Correlation Between Warfarin Levels in the Blood and the Value of Normal INR in Fibrillation Atrium Inpatients

**Masita Wulandari Suryoputri*, Nialiana Endah Endriastuti, Dewi Latifatul Ilma, Alfita Azzahra**
Department of Pharmacy, Faculty of Health Sciences, Jenderal Soedirman University, Central Java, Indonesia

**ARTICLE INFO**
**Submitted : 18-10-2023**
**Revised : 11-01-2024**
**Accepted : 03-05-2024**

**Published : 30-06-2024**

**Corresponding Author:**
**Masita Wulandari Suryoputri**

**Corresponding Author Email:**
**masita.suryoputri@unsoed.ac.id**

## ABSTRACT

**Background:** Warfarin is an anticoagulant inhibitor of vitamin K that is effective in preventing systemic embolization in atrial fibrillation patients. Warfarin has a narrow therapeutic index, so it requires monitoring of rates to prevent the occurrence of toxic effects and to ensure the passage of INR values.

**Objectives:** The study aims to find out the correlation between warfarin levels and normal INR values.

**Methods:** Observational research method with the collection of retrospective data on the medical records of patients treated with atrial fibrillation at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, in January 2019–December 2021. Warfarin levels were calculated pharmacokinetically using the steady-state concentration (Css) and plasma concentration (Cp) formulas. Data analysis is carried out using the Spearman test to determine the correlation between warfarin levels and normal INR values.

**Results:** The number of patients with normal INR values was less than the number of patients with abnormal INR values, namely 21 patients and 48 patients. The Spearman test results show a p-value of 0.31 (p>0.05), showing that the correlation between warfarin levels in the blood and the corresponding INR value is not significant (p> 0.05), and the R value in the Spearman test is 0.122, showing that the direction of the correlation is positive with very weak correlation strength.

**Conclusion:** The correlation between warfarin levels in the blood and the appropriate INR value is not significant (p>0.05), where the R value in the Spearman test shows R=0.122, meaning the direction of the correlation is positive with a very weak correlation strength.

**Keywords: atrial fibrillation; INR; warfarin levels**

## INTRODUCTION

Atrial fibrillation is a heart rhythm disorder characterised by uncoordinated atrial contractions and rapid ventricular response.[1] A person is diagnosed with atrial fibrillation based on the results of an electrocardiogram (ECG) examination. ECG results showed inconsistent, unclear atrial activity (P waves), irregular RR intervals of 30 seconds, and a ventricular rate reaching 90–170 beats per second with an irregular pulse.[2] The prevalence of atrial fibrillation has increased by 33% in the last 20 years. It is known that the number of atrial fibrillation cases in the world in 2017 reached 37,534 million (4,977 cases per million population), and by 2050, it is predicted that this will increase by >60%.[3] The prevalence of atrial fibrillation increases with age. By the age of 80, atrial fibrillation incidence is driven by a lifetime risk of 22%.[4]

Anticoagulant medication is the first choice of treatment for stroke prevention for patients with atrial fibrillation because it is suspected of an increased risk of stroke and has been shown to be involved in 15% of stroke events. Vitamin K antagonists, such as warfarin, and new oral anticoagulants (NOACs), such as rivaroxaban and edoxaban, are examples of oral anticoagulants that can be used. The class of indirect thrombin inhibitors that includes heparin, fondaparinux, and enoxaparin also includes intravenous anticoagulants. Pharmacological rhythm control therapy can use antiarrhythmics such as propafenone and amiodarone. In the meantime,

combination medication, which includes beta-blockers, digoxin, diltiazem, and verapamil, can be prescribed to control heart rate.[2,5]

Patients with atrial fibrillation are able to prevent stroke or systemic embolization with warfarin.[6] Patients with atrial fibrillation can lower their risk of stroke by about 60% using warfarin. By preventing an increase in coagulation factors that are dependent on vitamin K, warfarin has anticoagulant effects. Warfarin's initial therapeutic effect starts with its suppression of factor II, also known as thrombin. The first line of treatment for atrial fibrillation in order to prevent stroke is warfarin. Because of its pharmacokinetic parameters, warfarin has a narrow therapeutic index. Therefore, levels need to be monitored frequently.[7] Therapeutic blood levels of warfarin are in the range of 1 to 4 mg/L.[8] Over-the-therapeutic levels of warfarin might increase the risk of bleeding events such as hematuria, melena, severe bruises, or low haemoglobin.[9] Monitoring drug levels in the blood in Indonesia cannot be done directly because the costs involved are relatively expensive. One way to monitor drug levels in the blood is to calculate drug levels pharmacokinetically using a formula based on the therapeutic dose given to the patient, so that an overview of drug levels in the blood can be obtained.[10] Warfarin levels are measured in the blood using the concentration steady-state (Css) formula for patients who have taken the drug for a minimum of four days and have amounted to steady state, and the plasma concentration (Cp) formula for patients who have taken the medication for one to three days but have not yet reached steady state.[11]

Therapeutic monitoring of anticoagulants in atrial fibrillation patients is measured by the prothrombin time parameter expressed by the International Normalized Ratio (INR).[7] Because one of the side effects of anticoagulant medicine is that blood clots easily, making it difficult to stop bleeding if it happens, an INR is a crucial part of anticoagulant therapy. INR provides an indicator to ensure that the anticoagulant impact is not significantly strong and to avoid these negative effects. When treating atrial fibrillation with warfarin, the ideal INR is 2.5, or between 2 and 3.[12] The research results of Furdiyanti et al. (2014) show that the maintenance dose of warfarin on days 15–30 is an average of 2.24 ± 0.77 mg/day, while the estimated average warfarin level is at steady state or on The 30th was 0.658 ± 0.315 mg/L, and 9 patients (10.47%) had values within the therapeutic range. The results of the INR examination showed that 54 patients (62.79%) did not reach the INR target, and 32 patients (37.21%) reached the INR target. The correlation between the estimated blood warfarin levels and the INR value is not significant with a value of $p = 0.180$ ($p > 0.05$), while the correlation coefficient value of 0.146 indicates a positive correlation direction with a very weak correlation strength.[8] This strengthens the concept of therapeutic drug monitoring. Prof. Dr. Margono Soekardjo Hospital, Purwokerto, has never conducted research on estimating warfarin levels in the blood, so it is necessary to determine the level of warfarin in the blood pharmacokinetically as well as analyze correlations between the level of warfarin in the blood and the observance of the normal INR value in patients with atrial fibrillation. Besides that, further precautions must be taken when using warfarin, a drug with a narrow therapeutic index. The purpose of this study was to determine the blood levels of warfarin using the pharmacokinetic formula and to observe a correlation between the blood levels of warfarin and the atrial fibrillation patients' getting a normal INR value.

## METHODS

This study is a descriptive-analytic one that was conducted utilising medical record data from inpatients diagnosed with atrial fibrillation at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from January 2019 to December 2021. The test participants were not given medication or otherwise engaged in.

### Study design

Observational research method with the collection of retrospective data on the medical records of patients treated with atrial fibrillation in the Prof. Dr. Margono Soekarjo Hospital, Purwokerto period of January 2019–December 2021.

### Population and samples

All inpatient atrial fibrillation patients treated at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from January 2019 to December 2021 comprised the study's population. The total sampling method was used for collecting the data. The study sample included patient medical record data that fulfilled the inclusion criteria. The inclusion criteria in question are as follows: patients with complete medical records that include patient identity (age, gender, weight, and medical history), drug history (dose, interval within warfarin administrations, and length of warfarin administration), and objective data (INR) are those who are diagnosed with atrial

fibrillation and are being treated with oral warfarin therapy. The study excluded patients who died while taking warfarin and those who were pregnant.

### Study instruments

The Case Report Form (CRF) is the tool utilized in this study. The patient's identity, including name, initials, medical record number, age, weight, warfarin dosage and interval, and INR value data, is included on the CRF.

### Data collection

The total sampling method was used to collect research samples. The study was conducted in the medical records division of Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from May 2022 to May 2023.

### Data Analysis

### Univariate Analysis

This analysis aims to describe the characteristics of each variable to be studied. The results of the analysis include age, gender, diagnosis, pattern of warfarin use, calculation of warfarin levels grouped based on levels that are suitable for therapy and levels that are not suitable for therapy based on calculations of drug levels in the blood after administration of warfarin, as well as INR values grouped based on normal INR values and abnormal INR values.

### Bivariate Analysis

The association between two variables—the blood warfarin levels and the INR values of atrial fibrillation patients—was examined using bivariate analysis. The correlation between these two variables was determined using the Spearman's test. Although the Spearman statistic test is non-parametric, it is not required that the data follow a normal distribution. The correlation coefficient value indicates the strength of the correlation between warfarin levels and the accordance of the normal INR value, whereas the significance value in the Spearman test indicates if there is a correlation between the two variables.

### Independent Variable

Blood warfarin levels were the study's independent variable. The average warfarin levels at steady state, minimum warfarin levels at steady state, maximum warfarin levels at steady state, and plasma levels that are still above steady state are all included in the pharmacokinetic formula used for estimating the blood levels of warfarin. Less than 1 mg/dL and more than 4 mg/dL are considered to be above the therapeutic range for warfarin levels. The therapeutic range is referred to as between 1-4 mg/dL. Patients who have taken warfarin for more than four days or who have reached steady state are able to determine the concentration steady-state (Css) formula: [11]

$$Cp = \frac{F \times D \times Ka}{Vd(Ka-K)}(e^{-k.t} - e^{-ka.t})$$

Note : *Cp = Drug levels in the blood* (mg/L); $F$ = *Bioavailability fraction* (99%); $D$ = *Warfarin dosage* (mg); $\tau$ = *Dose intervals* (hour); t = *Peak time* (hour); $Vd$ = *Volume distribution* (Liter) (0.14 L/kg); $K$ = *Elimination rate constant* ($jam^{-1}$); (K = $\frac{0.693}{\frac{t1}{2}elimination}$, $t^1/_2$ elimination = 40 hours); Ka = Absorption rate constant ($jam^{-1}$); (Ka = $\frac{0.693}{\frac{t1}{2}absorption}$, $t^1/_2$ absorption= 0,5 hour)

Through monitoring the patient's blood warfarin levels and using the Concentration Steady State (Css) and Plasma Concentration (Cp) formulas to estimate warfarin levels pharmacokinetically, the study was able to determine the patient's warfarin levels based on the dosage and interval of warfarin administration.[11]

The clearance calculation procedures involve multiplying a volume of distribution, which is determined by multiplying the body weight of each patient by a set value of 0.693 and dividing the result by the 40-hour half-life of warfarin. The concentration steady state average ($C_{SS}$ ave) formula is then filled in with the estimated clearance value. In the meantime, the elimination rate (k), which is determined by dividing the constant value by the warfarin half-life, is used to estimate $C_{SS}$min and $C_{SS}$max. This results in an elimination rate value of 0.0173 hours per day. The 693 and dividing the result by the 40-hour half-life of warfarin. The consentration steady state minimum ($C_{SS}$min) and concentration steady state maximum ($C_{SS}$max) formulas are then filled in using the estimated elimination rate values. The Ka value (absorption rate constant) used for Cp calculations is obtained by dividing the constant value by the absorption half-life of warfarin, which produces a value of 1.386 hours.

When a fixed dose is administered at the same drug administration interval, the concentration steady state average represents the average drug concentration in plasma during the dosing period at steady state. In addition to the concentration steady state average, estimates for concentration steady state maximum and concentration steady state minimum are also obtained. The maximum and lowest drug concentrations in plasma at steady state that result from administering a set dose at the same dosing interval are known as $C_{SS}$max and $C_{SS}$min. Cp is the medication's plasma concentration. For patients whose warfarin usage has occurred for no fewer than four days, steady state warfarin levels (Css) are determined; for patients whose warfarin use has lasted for less than four days, Cp is utilised. The drug's elimination half-life should be taken into consideration while calculating dosage intervals.[11]

### Dependent Variable

The accordance of the usual INR value is the research's dependent variable. When treating atrial fibrillation with warfarin, the preferred INR value is in the range of two and three.[12]

### Eligibility criteria

The study sample included patient medical record data that fulfilled the inclusion criteria. The inclusion criteria in question are as follows: patients with complete medical records that include patient identity (age, gender, weight, and medical history), drug history (dose, interval within warfarin administrations, and length of warfarin administration), and objective data (INR) are those who are diagnosed with atrial fibrillation and are being treated with oral warfarin therapy. The study excluded patients who died while taking warfarin and those who were pregnant.

## RESULTS AND DISCUSSION

The population of inpatient atrial fibrillation patients at Prof. Dr. Margono Soekarjo Hospital in the period January 2019–December 2021 was 697. Of the samples obtained, 63 patients met the inclusion criteria, and 10 patients met the exclusion criteria because they died while using warfarin. Of the 63 patients, there were 6 who used 2 different doses of warfarin, so the total number of cases calculated by pharmacokinetic blood levels of warfarin was 69.

### Patient Characteristics

The characteristics of the 63 patients included in the inclusion criteria are presented in Table I. The results of the study show that the number of male patients is greater than that of female patients, namely 55.56% and 44.44%. The results of this study are in accordance with research by Chung, M.K., et al. (2020), which stated that the prevalence of atrial fibrillation in 1990–2010 was that men had a higher prevalence every year than women.[13] There are several things that influence the difference in the incidence of atrial fibrillation in men and women, such as anatomical factors in the form of the size of the left atrium and hormonal factors. Men have a larger atrium than women.[14] The left atrium plays a major role in cardiac physiology by collecting blood during systole and modulating left ventricular filling during diastole. Left ventricular diastolic dysfunction or mitral valve disease can cause pressure on the left atrium and volume overload, which, if maintained, can result in remodelling and enlargement of the left atrium. In this regard, left atrial enlargement is associated with a higher risk of atrial fibrillation (4–7) and cardiovascular events.[15] Sex hormones also influence the incidence of atrial fibrillation. The incidence of atrial fibrillation in premenopausal women is low but increases after menopause. This is due to post-menopausal hormonal changes, namely estrogen. With reduced oestrogen levels after menopause, blood pressure, cholesterol, metabolic syndrome, and BMI increase, which can develop into atrial fibrillation. In men over 80 years of age, reduced testosterone levels increase the risk of atrial fibrillation threefold.[16] Lifestyle factors can also influence the risk of atrial fibrillation, such as men having a higher prevalence of being overweight, smoking, and consuming alcohol compared to women. Smoking, alcohol consumption, and overweight/obesity showed moderate to strong associations with atrial fibrillation. The risk of atrial fibrillation differed substantially across the spectrum of health behaviours, with a 282% increased risk in people who smoked, drank more alcohol (14 units/week), and were obese compared with normal-weight nonsmokers with no or no alcohol consumption. Avoiding these three health behaviours could help prevent approximately 25% of all cases of atrial fibrillation in the population if a direct causal effect of these behaviours is assumed.[17]

The age characteristics of the patients in this study are categorised based on the World Health Organisation (2021), which states that the age categories of patients are divided into 3 categories: 0–18 years

**Table I. Patient Characteristics**

| Patient Characteristics | Amount (n) | Percentage (%) |
|---|---|---|
| **Gender** | | |
| Male | 35 | 55.56 |
| Female | 28 | 44.44 |
| **Age (WHO, 2021)** | | |
| 19-60 y.o (Adult) | 31 | 49.2 |
| >60 y.o (Elderly) | 32 | 50.8 |
| **Primary Diagnosis** | | |
| **Cardiovascular** | | |
| Atrium Fibrillation | 36 | 57.14 |
| Congestive Heart Failure | 10 | 15.87 |
| Stroke infarct | 4 | 6.34 |
| Premature Ventricular Contractions | 2 | 3.17 |
| Mitral Valve Insufficiency | 2 | 3.17 |
| Bronchopneumonia | 2 | 3.17 |
| Others | 5 | 7.93 |
| **Non-Cardiovascular** | | |
| Pertrochanteric fracture | 1 | 1.58 |
| Leukemia | 1 | 1.58 |
| **Secondary Diagnosis** | | |
| **Cardiovascular** | | |
| Atrium Fibrillation | 27 | 20.3 |
| Congestive Heart Failure | 22 | 16.54 |
| Mitral stenosis | 10 | 7.51 |
| Pneumonia | 10 | 7.51 |
| Cardiomegaly | 9 | 6.76 |
| HHD | 9 | 6.76 |
| Premature ventricular contractions | 7 | 5.26 |
| Bronchopneumonia | 5 | 3.75 |
| Chronic cardiac ischemia | 5 | 3.75 |
| Mitral valve insufficiency | 4 | 3 |
| Others | 25 | 18.79 |
| **Non-Cardiovascular** | | |
| Dyspepsia | 10 | 12.5 |
| Hypokalemia | 9 | 11.25 |
| Kidney failure | 6 | 7.5 |
| Hyperkalemia | 6 | 7.5 |
| Others | 49 | 61.25 |

old is children, 19–60 years old is adults, and over 60 years old is elderly. Based on table I, the characteristics of patients in this study show that there are more elderly patients (> 60 years) than adult patients (19–60 years), namely 50.8% and 49.2%. These results are in accordance with research by Morseth, B., et al. (2021) showing that the incidence of atrial fibrillation increases with age.[18] The prevalence of atrial fibrillation increases exponentially at age 50 and increases rapidly after age 70.[19] When it comes to atrial fibrillation, a 40-year-old man has a 26% chance and a 22.7% risk of experiencing it when he is 80 years old, whereas a 40-year-old woman has a 23% danger and a 21.6% risk when she is 80 years old.[20] Patients who are older than those who are younger are more susceptible to warfarin. These multifactorial age-related alterations in drug response include reduced clearance, albumin binding, and renal excretion, all of which affect pharmacokinetics. Furthermore, through drug-drug and disease-drug interactions, older patients with more concomitant diseases and concurrent medication use may have complex impacts on the effects of warfarin.[21] Patients with structural heart disease, comorbidities, and cardiovascular risk factors are more likely to die from atrial fibrillation. Atrial fibrillation and comorbidities can often lead to heart disease. Hypertension (67–76%), heart failure (22–42%), diabetes (20–

24%), obesity (20–35%), chronic lung disease (10–18%), thyroid dysfunction (8–11%), kidney failure (11–22%), stroke/transient ischemic attack (9–16%), and neuropsychiatric disorders (19%) are among the most common comorbidities.[22] In this study, based on Table I, heart failure is the most common cardiovascular disease that accompanies the incidence of atrial fibrillation, both in primary diagnosis (15.87%) and secondary diagnosis (16.54%).

Heart failure occurs due to tachycardia, fibrosis, and irregular atrial contractions, which are the pathophysiological causes of atrial fibrillation. Diastolic dysfunction, or shortening the heart's relaxation period during diastole when the ventricles fill with blood, occurs when brought on by prolonged tachycardia. A rapid heartbeat shortens the time the ventricles can fill, disrupting ventricular relaxation and leading to heart failure. The ventricles may become rigid due to fibrosis, which makes it difficult for them to contract during diastole. It might also aggravate the symptoms of heart failure.[23] The incidence of atrial fibrillation in heart failure patients was 46.7%, significantly increasing the risk of acute heart failure hospitalisation[24]. Meanwhile, the most common non-cardiovascular disease that accompanies atrial fibrillation is dyspepsia (12.5%).

### Usage Patterns for Oral Warfarin

Based on the results of this study, there were five dosage regimens given to inpatients diagnosed with atrial fibrillation. These doses are 1 mg, 2 mg, 3 mg, 5 mg, and 6 mg, given every 24 hours. Based on Table II, it is known that the warfarin dose of 2 mg every 24 hours is the dose most commonly used in atrial fibrillation patients, with a total of 62 patients (89.87%). The range of warfarin doses used in this study was around 1 mg–6 mg/day, so the warfarin dose used was lower than the dose recommended by PIONAS BPOM (2023), which states that usually the dose of warfarin is a continued support or maintenance dose in adults for atrial fibrillation patients. is 3 mg–9 mg/day, depending on prothrombin time. The usual induction dose of warfarin in adults with atrial fibrillation is 10 mg/day for 2 days, and higher doses are not recommended.[25] However, according to Effendi (2017), the principles of atrial fibrillation therapy are: antithrombotic for stroke prevention, heart rate control, heart rhythm control, and additional therapy. The warfarin dose used must be adjusted to the INR target of 2–3.[26] Following the start of treatment, the frequency of INR testing decreases when the INR response is monitored until an established dose-response correlation is maintained.[27] The amount of warfarin used must be suitable for the patient's condition; otherwise, bleeding events such as hematuria, melena, excessive bruising, or decreased haemoglobin will occur. In addition, taking a high dose of warfarin can result in bleeding or thrombosis.[9,28]

Many variables, including age, gender, comorbidities, nutritional state, concurrent use of drugs, compliance, and genetic polymorphisms, affect a patient's response to warfarin.[29,30] Numerous factors, including age, gender, comorbidities, nutritional condition, concurrent drug usage, compliance, and genetic polymorphisms, affect a patient's reaction to warfarin.[8] Age and genetic variants in VKORC1 and CYP2C9 affect the variability of INR values among Indonesians, while gender, body weight, and concurrent use of other medicines have little effect on INR values.[31] A number of variables, including failure with therapy, drug interactions (pharmaceutical or herbal), dietary or alcohol intake changes, comorbid or systemic disorders, or other unidentified causes, can affect INR values that fluctuate in individuals. Patient noncompliance is one of the variables that can alter the INR.[32]

### Warfarin Levels in Blood Estimated Using Pharmacokinetics

Data used to calculate estimated levels include warfarin dose (mg), warfarin bioavailability (99%), patient body weight, volume of distribution (L), clearance value (L/hour), peak time (hours), and warfarin administration interval (hours). Data regarding warfarin dose (mg), patient weight (kg), and warfarin administration interval were obtained through patient medical record data at Prof. Dr. Margono Soekarjo Hospital, Purwokerto. Data regarding warfarin's bioavailability of 99%, distribution volume of 0.14 L/BW, and warfarin's half-life of 40 hours were obtained from the literature.[33] Patients may suffer toxic effects because the drug concentration is too high (exceeding $C_{SS}$ max) or subtherapeutic effects because the drug concentration is too low (lower than $C_{SS}$ min).[34]

This study's findings showed that 69 inpatient atrial fibrillation cases were treated with warfarin. Of the patients in this case, 4 (5.79%) had warfarin levels that were within the therapeutic limit, and 65 (94.21%) had levels that were below it. The findings of this investigation are consistent with a study conducted in 2020 by Rahmatini, R., et al., which showed that more patients had warfarin concentrations below 1 mg/L than patients with concentrations within the therapeutic range; especially, of a total of 45 patients, 23 patients (51%) had concentrations below 1 mg/L.[35] According to research from Furdiyanti, N.H., et al. (2014), of 86 patients, only

**Table II. Warfarin Use Patterns in Inpatient Atrial Fibrillation Patients Based on Dosage at Prof. Dr. Margono Soekarjo Hospital, Purwokerto**

| Dosage warfarin | Number of Patients | (%) |
|---|---|---|
| 1 mg/24 hours | 2 | 2.9 |
| 2 mg/24 hours | 62 | 89.87 |
| 3 mg/24 hours | 3 | 4.35 |
| 5 mg/24 hours | 1 | 1.44 |
| 6 mg/24 hours | 1 | 1.44 |
| **Total** | **69** | **100** |

10.47% had warfarin levels in the therapeutic range on day 7, only 8.14% had levels in the therapeutic range on day 10, and only 10.47% had levels in the therapeutic range on day 30.[8] Table III shows the pharmacokinetic estimate of warfarin blood levels.

Variations in parameter values in pharmacokinetic calculation, such as volume of distribution (Vd) and clearance (Cl), caused variations in the drug levels in the blood of research respondents. The literature's volume of distribution and clearance values which are often Caucasian in race were collected from studies conducted with non-Indonesian populations.[36] Additionally, variations in the dosages administered, the use of additional medications, and individual variability may have contributed to variations in the drug levels in the blood of the study's participants. It's important to think about dosage settings and delivery frequency to ensure that blood medication levels stay within the therapeutic range. In general, a medicine won't have a therapeutic effect if its level is below the minimum effective concentration (MEC). On the other hand, signs of drug toxicity often manifest if the drug level in the blood surpasses the minimum toxic concentration (MTC). A number of combinations is another significant factor that might have an important effect on the medication levels in a treatment regimen.[37] The measurement of drug levels in the blood is significantly influenced because of individual variability, which includes factors such as body weight, drug dosage, age, gender, and polytherapy.[38]

Table III shows patients with steady-state warfarin levels (Css). Of the four patients who had warfarin levels within the therapeutic range, only two had normal INR values, namely patient no. 17 and patient no. 45, while patients no. 14 and 18 had warfarin levels within the therapeutic range, but based on examination of the INR values, these patients had INRs greater than 3. Based on medical records, patient number 14 experienced clinical improvement in the form of reduced shortness of breath and improvement in vital signs in the form of normal RR (respiratory rate) and pulse. Both patients did not experience symptoms of toxicity such as coughing up blood, nosebleeds, or bloody stools after 4 days of using oral warfarin. In addition, based on patient medical record data, patient No. 17 had warfarin levels in the therapeutic range and had a normal INR range, indicating that the patient had clinical improvement, namely reduced shortness of breath and abdominal pain and improvement in vital signs (normal pulse and respiratory rate). This can be caused because the onset of action of warfarin is usually 24 to 72 hours. The half-life of warfarin is generally 40 hours, so peak therapeutic effects can be seen 5 to 7 days after initiation.[39] Therefore, it can be stated that warfarin's therapeutic effects can endure in the body for a while, even if its levels are below what is suggested.

Besides that, a different administration dose is another factor that affects the impact of variable warfarin levels in the blood on the clinical improvement of the patient. The correlation between dosage and drug concentration in the blood is significant. Higher doses usually result in higher levels, while smaller amounts usually generate lower levels. It's important to think about dosage settings and delivery frequency to ensure that blood medication levels stay within the therapeutic range. In general, a drug can't have a therapeutic effect if its level is below the minimal effective concentration. However, signs of drug toxicity usually surface if the blood drug level is higher than the minimum toxic concentration.[10] The correlation between dosage and plasma, or drug concentration in the blood, serves as a foundation for drug therapy monitoring. Drug levels in the blood can be estimated, and this data can be used to adjust the dosage to get the right concentration and therapeutic effect.[40] According to the study's findings, participants' blood levels of warfarin vary even though they received the same dose of the drug. Age variants, drug interactions during therapy, hepatic and renal function problems, and comorbidities are among the reasons for this.[10,21,41]

Drug interactions also affect warfarin levels in the blood. The presence of combinations in a therapeutic regimen can significantly influence drug levels.[40] Protein-binding interactions are one of the pharmacokinetic mechanisms of drug interactions with warfarin. This interaction may cause warfarin to be eliminated from protein binding sites, increasing warfarin concentrations in free plasma and increasing the potential for warfarin

**Table III. Estimation of steady-state Warfarin levels ($C_{SS}$ ave, $C_{SS}$ max, and $C_{SS}$ min) in Atrial Fibrillation Patients at Prof. Dr. Margono Soekarjo Hospital, Purwokerto.**

| No | Warfarin dose (mg/day) | Vd (L) | Cl (L/hour) | Estimating levels (mg/L) | | | INR |
|---|---|---|---|---|---|---|---|
| | | | | $C_{ss}$ ave | $C_{ss}$ max | $C_{ss}$ min | |
| 1 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 2.76 |
| 2 | 2 | 0.14 | 0.133 | 0.618 | 0.735 | 0.478 | 1.01 |
| 3 | 2 | 0.14 | 0.194 | 0.425 | 0.505 | 0.328 | 1.43 |
| 4 | 3 | 0.14 | 0.158 | 0.523 | 0.622 | 0.404 | 1.02 |
| 5 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.09 |
| 6 | 6 | 0.14 | 0.146 | 0.283 | 0.337 | 0.219 | 1.09 |
| 7 | 2 | 0.14 | 0.097 | 0.850 | 1.010 | 0.657 | 1.20 |
| 8 | 2 | 0.14 | 0.218 | 0.378 | 0.449 | 0.292 | 1.54 |
| 9 | 2 | 0.14 | 0.150 | 0.549 | 0.652 | 0.424 | 1.31 |
| 10 | 2 | 0.14 | 0.150 | 0.549 | 0.652 | 0.424 | 1.34 |
| 11 | 2 | 0.14 | 0.218 | 0.378 | 0.449 | 0.292 | 1.47 |
| 12 | 2 | 0.14 | 0.158 | 0.523 | 0.622 | 0.404 | 1.71 |
| 13 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.03 |
| 14 | 2 | 0.14 | 0.121 | 1.020* | 1.212 | 0.788 | 5.04 |
| 15 | 2 | 0.14 | 0.158 | 0.523 | 0.622 | 0.404 | 6.18 |
| 16 | 2 | 0.14 | 0.170 | 0.486 | 0.577 | 0.375 | 1.92 |
| 17 | 2 | 0.14 | 0.146 | 1.417* | 1.684 | 1.094 | 1.13 |
| 18 | 2 | 0.14 | 0.146 | 1.701* | 2.020 | 1.313 | 6.00 |
| 19 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.64 |
| 20 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 1.21 |
| 21 | 1 | 0.14 | 0.133 | 0.309 | 0.367 | 0.239 | 4.2 |
| 22 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 1.19 |
| 23 | 2 | 0.14 | 0.116 | 0.709 | 0.842 | 0.547 | 3.15 |
| 24 | 2 | 0.14 | 0.116 | 0.709 | 0.842 | 0.547 | 1.99 |
| 25 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.36 |
| 26 | 3 | 0.14 | 0.194 | 0.638 | 0.758 | 0.492 | 1.24 |
| 27 | 2 | 0.14 | 0.158 | 0.523 | 0.622 | 0.404 | 3.60 |
| 28 | 2 | 0.14 | 0.114 | 0.724 | 0.860 | 0.559 | 3.37 |
| 29 | 2 | 0.14 | 0.211 | 0.391 | 0.464 | 0.302 | 1.01 |
| 30 | 2 | 0.14 | 0.124 | 0.667 | 0.792 | 0.515 | 1.49 |
| 31 | 2 | 0.14 | 0.114 | 0.724 | 0.860 | 0.559 | 1.07 |
| 32 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 3.48 |
| 33 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.98 |
| 34 | 2 | 0.14 | 0.177 | 0.466 | 0.554 | 0.360 | 1.23 |
| 35 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.08 |
| 36 | 2 | 0.14 | 0.097 | 0.850 | 1.010 | 0.657 | 0.91 |
| 37 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.36 |
| 38 | 2 | 0.14 | 0.201 | 0.410 | 0.487 | 0.316 | 1.01 |
| 39 | 2 | 0.14 | 0.143 | 0.577 | 0.685 | 0.445 | 1.77 |
| 40 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 4.92 |
| 41 | 2 | 0.14 | 0.170 | 0.486 | 0.577 | 0.375 | 1.92 |
| 42 | 2 | 0.14 | 0.182 | 0.454 | 0.539 | 0.350 | 1.64 |
| 43 | 2 | 0.14 | 0.090 | 0.919 | 1.092 | 0.710 | 1.26 |
| 44 | 2 | 0.14 | 0.107 | 0.773 | 0.918 | 0.597 | 0.92 |
| 45 | 3 | 0.14 | 0.116 | 1.063* | 1.263 | 0.821 | 1.42 |
| 46 | 2 | 0.14 | 0.114 | 0.724 | 0.860 | 0.559 | 7.93 |
| 47 | 2 | 0.14 | 0.182 | 0.454 | 0.539 | 0.350 | 1.15 |
| 48 | 2 | 0.14 | 0.194 | 0.425 | 0.505 | 0.328 | 1.45 |
| 49 | 2 | 0.14 | 0.109 | 0.756 | 0.898 | 0.584 | 2.5 |

**Table III. (Continued)**

| No | Warfarin dose (mg/day) | Vd (L) | Cl (L/hour) | Estimating levels (mg/L) | | | INR |
|---|---|---|---|---|---|---|---|
| | | | | $C_{ss}$ ave | $C_{ss}$ max | $C_{ss}$ min | |
| 50 | 2 | 0.14 | 0.109 | 0.756 | 0.898 | 0.584 | 7.92 |
| 51 | 2 | 0.14 | 0.109 | 0.756 | 0.898 | 0.584 | 7.28 |
| 52 | 2 | 0.14 | 0.099 | 0.830 | 0.986 | 0.641 | 2.94 |
| 53 | 2 | 0.14 | 0.124 | 0.667 | 0.792 | 0.515 | 6.80 |
| 54 | 2 | 0.14 | 0.112 | 0.739 | 0.878 | 0.571 | 1.37 |
| 55 | 2 | 0.14 | 0.133 | 0.618 | 0.735 | 0.478 | 1.42 |
| 56 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 1.45 |
| 57 | 2 | 0.14 | 0.097 | 0.850 | 1.010 | 0.657 | 5.35 |
| 58 | 2 | 0.14 | 0.097 | 0.850 | 1.010 | 0.657 | 4.85 |
| 59 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 1.36 |
| 60 | 2 | 0.14 | 0.124 | 0.667 | 0.792 | 0.515 | 2.24 |
| 61 | 2 | 0.14 | 0.114 | 0.724 | 0.860 | 0.559 | 0.98 |
| 62 | 2 | 0.14 | 0.170 | 0.486 | 0.577 | 0.375 | 1.60 |
| 63 | 2 | 0.14 | 0.170 | 0.486 | 0.577 | 0.375 | 2.43 |
| 64 | 2 | 0.14 | 0.141 | 0.586 | 0.697 | 0.453 | 1.06 |
| 65 | 2 | 0.14 | 0.097 | 0.850 | 1.010 | 0.657 | 1.09 |
| 66 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.81 |
| 67 | 2 | 0.14 | 0.150 | 0.549 | 0.652 | 0.424 | 1.14 |
| 68 | 2 | 0.14 | 0.121 | 0.680 | 0.808 | 0.525 | 1.25 |
| 69 | 2 | 0.14 | 0.146 | 0.567 | 0.673 | 0.438 | 3.05 |

Note = *within the therapeutic range (1-4 mg/L)

toxic exposure.[41] Warfarin concentrations are influenced by liver and kidney function. Damage to the kidneys can change the responsiveness and bioavailability of drugs that are mostly metabolised by the liver, as well as decrease non-renal clearance. Warfarin dosages for patients with moderate to severe renal impairment should be lower than for those without mild renal impairment. Warfarin levels may increase as a result of reduced kidney function, increasing the risk of bleeding.[42] Furthermore, because the liver is the main pathway of warfarin treatment, abnormal liver function may increase warfarin levels, lower coagulation factors, and increase the risk of bleeding. Because the metabolism of warfarin depends on cytochrome P450 enzymes, people with liver diseases or disorders may have changes in the activity of these enzymes.[43]

When using warfarin anticoagulant therapy, the risk of adverse events can be prevented by monitoring therapeutic levels and monitoring INR. Individual patient factors such as compliance, dosage, and INR monitoring play an important role in the success of warfarin therapy in atrial fibrillation patients.[44] The purpose of monitoring INR readings in this study is to keep current with patients' warfarin drugs. An INR of two to three should be considered while treating bleeding in atrial fibrillation.[12] This range is used to lower the risk of systemic embolism and prevent venous thromboembolism in patients with valvular heart disease and atrial fibrillation.[45]

### Correlation of Warfarin Levels with Corresponding Normal INR Values

The purpose of this study was to determine the normal INR value for patients with atrial fibrillation who were taken to Prof. Dr. Margono Soekarjo Hospital, Purwokerto, and the blood levels of warfarin. Spearman For the purpose of finding out if there was a correlation between the two variables, a test analysis occurred. Table IV shows the analysis results.

Based on these results, the number of patients who had normal INR values was smaller than the number of patients who had abnormal INR values, namely 21 patients and 48 patients. The results of the Spearman-test statistical analysis showed a p value of 0.31 ($p > 0.05$), meaning that the correlation between warfarin levels in the blood and the corresponding INR value was not significant. The same results were also shown in research by Furdiyanti, N.H., et al. (2014), showing the results of the Spearman correlative test between warfarin levels in the blood and the INR value, which showed a value of $p = 0.180$ ($p > 0.05$), meaning the correlation between warfarin levels in the blood and insignificant INR values[8]. Separate from that, research by

**Table IV. Correlation of warfarin levels in patients who have normal INR values**

| Compatibility of INR Normal Values | Number of Patients | INR (Mean ± SD) | Warfarin levels (mg/L) (Mean ± SD) | *p value* | *R* |
|---|---|---|---|---|---|
| The normal INR value is appropriate. | 21 | (1.33±0.29) | (1.30±0.32) | 0.31 | 0.122 |
| The normal INR value is not appropriate. | 48 | (4.57±1.85) | (0.61±0.14) | | |
| **Total** | **69** | | | | |

Suryoputri, M.W., et al. (2020) shows drug levels and clinical outcomes obtained in respondents who used monotherapy or polytherapy of valproic acid have no significant correlation ($p > 0.05$).[10]

The Spearman test result for this study's R value is R = 0.122, showing a positive correlation with a very weak correlation strength. This study correlates with that of Furdiyanti, N.H., et al. (2014), who found that the Spearman test correlation coefficient measured an r value of 0.146, indicating a very low, even positive correlation strength and direction.[8] Many variables, such as the amount of the warfarin dose, drug interactions, noncompliance, alcohol, smoking, and genetic factors, may contribute to the failure to achieve a normal INR.[42] In this study, 62 of the 69 patients who had atrial fibrillation received 2 mg of warfarin daily. The AHA/ACC Guideline to Warfarin Therapy (2014) states patients with atrial fibrillation using a dose of 5 mg/day will achieve an INR value > 2 in 5–6 days. Whereas the 5 mg dose had a mean time for achieving the target INR of 2.0–3.0 in a study by Agustini, T., T., et al. (2016), which was significantly different compared to the 2 mg dose and the 4mg dose.[44] However, warfarin dosing is highly individualised for each patient, and maintenance of warfarin dosing can be challenging due to variations in patient characteristics.[46] Drug and/or food interactions can also affect absorption and inhibit the anticoagulant effect of warfarin, requiring higher warfarin doses to achieve therapeutic INR. Factors in warfarin distribution can also influence INR values. Warfarin is highly bound to plasma proteins. Changes in protein levels or protein binding interactions can result in the displacement of warfarin from protein binding sites, increasing free warfarin plasma concentrations, and potentially affecting INR values.[42]

Numerous drugs and herbal products have the ability to either increase or decrease the effects of warfarin levels. According to data obtained from medical records, 52 out of 69 patients in this study used digoxin and warfarin, 21 out of 69 patients used bisoprolol and warfarin, and 13 out of 69 patients used aspirin and warfarin. Digoxin and aspirin use together may increase the risk of bleeding, so warfarin doses must be adjusted based on prothrombin time, or INR. Additionally, vitamin K-rich foods (broccoli, spinach, lettuce, mustard greens, and kale) may increase warfarin levels when combined with warfarin in the body, which decreases warfarin's effectiveness.[47] This risk may further increase with patient age and other diseases.[48] Additionally, other drugs, such as cimetidine, can increase INR by inhibiting the metabolism of R-warfarin. Concomitant use of warfarin with salicylates may cause an increased risk of bleeding because salicylates inhibit platelet aggregation, may cause gastric irritation, and result in increased free warfarin levels because salicylates have a higher affinity for protein binding sites. Phenytoin may cause an increase or decrease in INR. After the initiation of phenytoin, the INR may increase due to the displacement of warfarin from protein binding sites. Meanwhile, there are interactions between warfarin and herbal products. Green tea has been associated with inhibiting the effects of warfarin and decreasing INR due to its high amount of vitamin K.[49]

The amount of warfarin needed to achieve desired anticoagulation and the amount of treatment needed to reach target INR vary significantly among individuals. Clinical or lifestyle factors (e.g., patient age, weight, BMI, gender, smoking status, medical history, and current medications) as well as genetic factors have been shown to relate to some of these differences. The two most significant known genetic predictors of warfarin dosage are the VKORC1 and CYP2C9 genotypes. The enzyme vitamin K epoxide reductase, which has been encoded through the VKORC1 gene, triggers the rate-limiting step in vitamin K recycling, which is the reduction of vitamin K epoxide to vitamin K. Warfarin is another medication that affects this enzyme. Variations in VKORC1 genetics might enable patients to take warfarin at different dosages. Higher warfarin dosages are needed in individuals with elevated VKORC1 enzymes in order to achieve the target concentration. The liver's CYP2C9 enzyme has responsibility for taking down warfarin. In affecting the rate of warfarin metabolism, CYP2C9 variability might have an impact on the body's level of warfarin. This genetic variability may affect the amount of warfarin that needs to be given in order to achieve the necessary INR range.[50]

There might be other medications that can affect warfarin levels because the pharmacokinetic estimation of warfarin levels in this study didn't take into consideration other drug use in patients. It is crucial to take into

consideration other factors that could have an influence on the INR value if it is within the therapeutic range while the warfarin level in the blood remains below the target. Adjusting the warfarin dose is necessary if monitoring shows bleeding events in patients. The warfarin dose is required to be adjusted to enhance clinical outcomes and patient safety. In addition, the limited sample size in this study could have an influence on the correlation between patients' warfarin levels and appropriate INR values.

## CONCLUSION

Based on the results of this study, it can be concluded that the correlation between warfarin levels in the blood and the appropriate INR value is not significant ($p > 0.05$), where the R value in the Spearman test shows $R = 0.122$, meaning the direction of the correlation is positive with a very weak correlation strength.

## ACKNOWLEDGEMENT

The LPPM Jenderal Soedirman University, Purwokerto, is to be acknowledged for contributing funds to the BLU UNSOED research funds at Skim Riset Peningkatan Kompetensi 2022. We give thanks to Prof. Dr. Margono Soekardjo Hospital, Purwokerto, for providing the time, space, and approval required to conduct this research. We also thank the students on our project team, Atika Putri, Alfita Azzahra, Chintia Rahma, and Dwi Aprilia, for helping in collecting data for the study.

## STATEMENT OF ETHICS

This study complies with ethical guidelines and has been granted approval by Prof. Dr. Margono Soekarjo, Hospital, Purwokerto, Ethics Committee under reference number 420/04627, April 2022.

## REFERENCES

1. Siontis, K. C., Geske, J. B. and Gersh BJ. Atrial Fibrillation Pathophysiology and Prognosis: Insights From Cardiovascular Imaging. *Circ Cardiovasc Imaging*. 2015;8(6):3020. doi:doi: 10.1161/CIRCIMAGING.115.003020.
2. Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J.J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G.A., Dilaveris, P.E., Fauchier, L., Filippatos, G., Kalman, J.M., La Meir, M., Lane, D.A., Lebeau, J.P., Lettino, M., Lip, G., Pinto, C. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Hear Journal,*. 2021;42(5):373-498. doi:doi: 10.1093/eurheartj/ehaa612.
3. Lippi, G., Sanchis-Gomar, F. and Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. *Int J Stroke*. 2021;16(2):217-221. doi:doi: 10.1177/1747493019897870.
4. Nesheiwat Z, Goyal A JM. Atrial Fibrillation [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Published 2022. https://www.ncbi.nlm.nih.gov/books/NBK526072/
5. Zimetbaum P. Atrial Fibrillation. *Ann Intern Med*. 2017;166(5):33. doi:doi: 10.7326/AITC201703070.
6. Brunton, L. L., Knollmann, B. C., & Hilal-Dandan R. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. Thirteenth. McGraw Hill Medical.; 2018.
7. Yakobus Y. New oral anticoagulants for Atrial Fibrillation. *Indones J Med Heal*. 2017;8(2):102-109. doi:https://doi.org/10.20885/JKKI.Vol8.Iss2.art5
8. Furdiyanti, N. H., Pramantara, I. D. P., & Wahyono D. 'Evaluasi Dosis Warfarin dan Hasil Terapinya pada Pasien Rawat Jalan. *J Manag Pharm Pract*. 2014;4(3):175-179.
9. Zeid Nesheiwat; Amandeep Goyal; Mandar. *Atrial Fibrillation*. Updated 20. (In: StatPearls, ed.). StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK526072/
10. Suryoputri MW, Mustikaningtias I, Maharani L. Pemantauan Kadar Obat Indeks Terapi Sempit Melalui Estimasi Kadar Obat di Dalam Darah pada Pasien Rawat Inap di RSUD Prof. Dr. Margono Soekarjo, Purwokerto. *Indones J Clin Pharm*. 2020;9(2):105. doi:10.15416/ijcp.2020.9.2.105
11. Rowland, M., dan Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. edisi 4. Wolters Kluwer Health/Lippincott William & Wilkins, Philadelphia.; 2011.
12. Katzung, B. G., Trevor, A., & Kruidering-Hall M. *Katzung & Trevor's Pharmacology: Examination & Board Review (*. 13th ed. McGraw-Hill Education.; 2015.
13. Chung, M. K., Refaat, M., Shen, W.-K., Kutyifa, V., Cha, Y.-M., Di Biase, L., Baranchuk, A., Lampert, R., Natale, A., Fisher, J., & Lakkireddy DR. Atrial Fibrillation. *J Am Coll Cardiol*. 2020;75(14):1689–1713.

doi:https://doi.org/10.1016/j.jacc.2020.02.025
14. Westerman, S., & Wenger, N. Gender Differences in Atrial Fibrillation: A Review of Epidemiology, Management, and Outcomes. *Curr Cardiol Rev*. 2019;15(2):136–144. doi:https://doi.org/10.2174/1573403X15666181205110624
15. Bouzas-Mosquera, A., Broullon, F. J., Alvarez-Garcia, N., Mendez, E., Peteiro, J., Gandara-Sambade, T., Prada, O., Mosquera, V. X., & Castro-Beiras A. Left atrial size and risk for all-cause mortality and ischemic stroke. *Can Med Assoc J*. 2011;183(10):E657–E664. doi:https://doi.org/10.1503/cmaj.091688
16. Odening, K. E., Deiß, S., Dilling-Boer, D., Didenko, M., Eriksson, U., Nedios, S., Ng, F. S., Roca Luque, I., Sanchez Borque, P., Vernooy, K., Wijnmaalen, A. P., & Yorgun, H. Mechanisms of sex differences in atrial fibrillation: Role of hormones and differences in electrophysiology, structure, function, and remodelling. *EP Eur*. 2019;21(3):366–376. doi:https://doi.org/10.1093/europace/euy215
17. Di Benedetto, L., Michels, G., Luben, R., Khaw, K.-T., & Pfister R. Individual and combined impact of lifestyle factors on atrial fibrillation in apparently healthy men and women: The EPIC-Norfolk prospective population study. *Eur J Prev Cardiol*. 2018;25(13):1374–1383. doi:https://doi.org/10.1177/2047487318782379
18. Morseth, B., Geelhoed, B., Linneberg, A., Johansson, L., Kuulasmaa, K., Salomaa, V., Iacoviello, L., Costanzo, S., Söderberg, S., Niiranen, T. J., Vishram-Nielsen, J. K. K., Njølstad, I., Wilsgaard, T., Mathiesen, E. B., Løchen, M.-L., Zeller, T., Blanken RB. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: Results from the MORGAM Consortium. *Open Hear*. 2021;8(2):1624. doi:https://doi.org/10.1136/openhrt-2021-001624
19. Mandalenakis, Z., Von Koch, L., Eriksson, H., Dellborg, M., Caidahl, K., Welin, L., Rosengren, A., & Hansson P-O. The risk of atrial fibrillation in the general male population: A lifetime follow-up of 50-year-old men. *Europace*. 2015;17(7):1018–1022. doi:https://doi.org/10.1093/europace/euv036
20. R. A. Bimandoko, P. Ardhianto and HM. HUBUNGAN FIBRILASI ATRIUM TERHADAP PENURUNAN FUNGSI KOGNITIF. *J Kedokt Diponegoro*. 2016;5(4):1693-1700. doi:https://doi.org/10.14710/dmj.v5i4.15917
21. Shendre, A., Parmar, G. M., Dillon, C., Beasley, T. M., & Limdi NA. Influence of Age on Warfarin Dose, Anticoagulation Control, and Risk of Hemorrhage. *Pharmacother J Hum Pharmacol Drug Ther*. 2018;38(6):588-596. doi:https://doi.org/10.1002/phar.2089
22. Naser, N., Dilic, M., Durak, A., Kulic, M., Pepic, E., Smajic, E., & Kusljugic, Z. The Impact of Risk Factors and Comorbidities on The Incidence of Atrial Fibrillation. *Mater Socio Medica*. 2017;29(4):231-236.
23. Sugumar, H., Nanayakkara, S., Prabhu, S., Voskoboinik, A., Kaye, D. M., Ling, L.-H., & Kistler, P. M. Pathophysiology of Atrial Fibrillation and Heart Failure. *Cardiol Clin*. 2019;37(2):131-138. doi:https://doi.org/10.1016/j.ccl.2019.01.002
24. Diaz, J., Martinez, F., Calderon, J. M., Fernandez, A., Sauri, I., Uso, R., Trillo, J. L., Redon, J., & Forner, M. J. Incidence and impact of atrial fibrillation in heart failure patients: Real-world data in a large community. *ESC Hear Fail*. 2022;9(6):4230–4239. doi:https://doi.org/10.1002/ehf2.14124
25. BPOM. Antikoagulan Oral. Published 2023. Accessed November 3, 2023. https://pionas.pom.go.id/ioni/bab-2-sistem-kardiovaskuler-0/26-antikoagulan-dan-protamin/261-antikoagulan-oral
26. Effendi. Tatalaksana Fibrilasi Atrium. *Cermin Dunia Kedokt J*. 2017;44(2):93-96.
27. Hirsh, J., Fuster, V., Ansell, J., & Halperin, J. L. Circulation. *Am Hear Assoc Coll Cardiol Found Guid to Warfarin Ther*. 2003;107(12):1692–1711. doi:https://doi.org/10.1161/01.CIR.0000063575.17904.4
28. Ashorobi, D., Ameer, M. A., & Fernandez R. Thrombosis. StatPearls Publishing. Published 2023. https://www.ncbi.nlm.nih.gov/books/NBK538430/
29. Wallace JL, Reaves AB, Tolley EA, Oliphant CS, Hutchison L, Alabdan NA, Sands CW ST. Comparison of initial warfarin response in obese patients versus non-obese patients. *J Thromb Thrombolysis*. 2013;36(1):96-101. doi:doi: 10.1007/s11239-012-0811-x. PMID: 23015280.
30. Holbrook, A., Schulman, S., Witt D. M., Vandvik, P. O., Fish, J., Kovacs MJ et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis. *Am Coll Chest Physicians Evidence-Based Clin Pract Guidel*. 2012;141(2):152-184.
31. Rusdiana, T., Araki, T., Nakamura, T., Subarnas, A., dan Yamamoto, K. Responsiveness to Low-Dose Warfarin Associated with Genetic Variants of VKORC1, CYP2C9, CYP2C19, and CYP4F2 in an Indonesian Population. *Eur J Clin Pharmacol*. 2013;69(3):395–405.
32. Clarke, R., Ross, S., Walker, T., dan Woods D. *INR Testing*.; 2006.
33. Patel S, Singh R PC. Warfarin [Updated 2022 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL):

StatPearls Publishing. Published 2022. https://www.ncbi.nlm.nih.gov/books/NBK470313/
34. Shargel, L & Yu AB. *Applied Biopharmaceutics and Pharmacokinetics*. Seventh. McGraw-Hill Companies.; 2016.
35. Rahmatini, R., Aliska, G., Usman, E., Yanni, M., & Ilmiawati, C. Plasma Warfarin Level and International Normalized Ratio do not Correlate with Bleeding Events in Indonesian Patients of Minangkabau Ethnicity with Atrial Fibrillation. *Open Access Maced J Med Sci*. 2020;8(B):192-197. doi:https://doi.org/10.3889/oamjms.2020.3436
36. Lingga HN, Hakim L PI. Evaluasi dosis asam valproat pada pasien epilepsi anak. *J Manag Pharm Pr*. 2013;3(2):137–42. doi:doi: 10.22146/jmpf.112
37. Clarke W DA. *Clinical Challenges in Therapeutic Drug Monitoring: Special Populations, Physiological Conditions, and Pharmacogenomics.*; 2016.
38. Methaneethorn J. A systematic review of population phramacokinetics of valproid acid. *Br J Clin Pharmacol*. 2018;84(5):816-834. doi:doi: 10.1111/bcp.13510
39. Patel S, Singh R PC. Warfarin [Updated 2022 Mar 13]. *Treasure Isl StatPearls Publ*. Published online 2022. https://www.ncbi.nlm.nih.gov/books/NBK470313/
40. Kang, J.-S., & Lee, M.H. Overview of Therapeutic Drug Monitoring. *Korean J Intern Med*. 2009;24(1):1-5. doi:https://doi.org/10.3904/kjim.2009.24.1.1
41. Mullokandov E, Ahn J, Szalkiewicz A. Protein Binding Drug-Drug Interaction between Warfarin and Tizoxanide in Human Plasma. 2014;2(7):7-9.
42. Limdi, N. A., Limdi, M. A., Cavallari, L., Anderson, A. M., Crowley, M. R., Baird, M. F., Allon, M., & Beasley, T. M. Warfarin Dosing in Patients With Impaired Kidney Function. *Am J Kidney Dis*. 2010;56(6):823-831. doi:https://doi.org/10.1053/j.ajkd.2010.05.023
43. Qamar, A., Vaduganathan, M., Greenberger, N. J., & Giugliano, R. P. Oral Anticoagulation in Patients With Liver Disease. *J Am Coll Cardiol*. 2018;71(19):2162-2175. doi:https://doi.org/10.1016/j.jacc.2018.03.023
44. Agustini, T. T., Arifin, H., & Hanif AM. Perbandingan Dosis Warfarin terhadap Durasi Tercapainya Target INR pada Pasien CHF dengan Fibrilasi Atrial. *J Sains Farm Klin*. 2016;2(2):162-167. doi:https://doi.org/10.29208/jsfk.2016.2.2.67
45. Kearon, C., Kahn, S. R., Agnelli, G., Goldhaber, S., Raskob, G. E., & Comerota AJ. Antithrombotic Therapy for Venous Thromboembolic Disease. *Chest*. 2008;133(6):454S-545S. doi:https://doi.org/10.1378/chest.08-0658
46. Mueller, J. A., Patel, T., Halawa, A., Dumitrascu, A., & Dawson NL. Warfarin Dosing and Body Mass Index. *Ann Pharmacother*. 2014;48(5):584-588. doi:https://doi.org/10.1177/1060028013517541
47. Drugs.com. Drug Interaction Checker. Drugs.com. Published 2023. Accessed November 3, 2023. https://www.drugs.com/interactions-check.php?drug_list=883-0,2311-0
48. Ho, L. L., & Brighton, T. Warfarin, antiplatelet drugs and their interactions. *Aust Prescr*. 2002;25(4):81-85. doi:https://doi.org/10.18773/austprescr.2002.073
49. Crader, M. F., Johns, T., & Arnold JK. Warfarin Drug Interactions. StatPearls Publishing.
50. Dean L. Warfarin Therapy and VKORC1 and CYP Genotype. Medical Genetics Summaries.