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Exploring Side Effects of Warfarin in Outpatients at Tertiary Hospital in Indonesia

Fatimatuz Zahra Oviary Satryo[1], Dewi Wahyuni[1], Budi Suprapti[2]*, Wenny Putri Nilamsari[2], Mochamad Yusuf Alsagaff[3], Dewi Makmuroh Nurul Qomar Purnamawati[4], Bambang Subakti Zulkarnain[2]
[1]Master Program of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Cardiology, Faculty of Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia
[4]Department of Pharmacy, Dr. Soetomo General Hospital, Surabaya, Indonesia

*Corresponding author: budi-s@ff.unair.ac.id
Orcid ID: 0000-0001-9060-8041

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Abstract

Background*: Patients with atrial fibrillation, venous thromboembolism, valvular disease, cardioembolic stroke, and acute myocardial infarction are prescribed the oral anticoagulant warfarin to treat thrombi. To guarantee its efficacy and safety, anticoagulants must be closely monitored. Furthermore, warfarin has a narrow therapeutic index, which increases the risk of side effects, particularly in the early stages of treatment.* ***Objective****: This study aimed to analyze the incidence of warfarin side effects in outpatients at Dr. Soetomo General Hospital.* ***Methods****: A retrospective cross-sectional design was adopted for outpatients at the Cardiology Department of Dr. Soetomo General Hospital from March to May 2023. Data were collected on the incidence of side effects in outpatients who received warfarin for a minimum of one month through an interview process. Other data, including age, sex, duration of warfarin therapy, comorbidities, and INR at the last scan, were extracted from medical records. The Chi-Square test was used to examine the data.* ***Results****: The results showed that 88 patients (42.7%) had side effects of bleeding (126 events). These included gum bleeding (22.3%), hematoma (20.4%), melena (7.7%), menometrorrhagia (2.4%), epistaxis (1.9%), hematuria (1.5%), hematemesis (1.0%), hemoptysis (1.0%), spontaneous venous bleeding (1.0%), hematochezia (0.5%), hemostasis during blood sampling (0.5%), tongue bleeding (0.5%), and subconjunctival bleeding (0.5%).* ***Conclusion****: The incidence of side effects during warfarin treatment was high, accounting for approximately 42.7% of cases. Furthermore, one patient experienced more than one side effect.*

Keywords: *outpatients, side effects, warfarin*

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INTRODUCTION

The prevalence of mortality due to cardiovascular disease was quite high, around 17.9 million people in 2016, accounting for 31% of the world's mortality (WHO, 2019). According to data from the Indonesian Ministry of Health, 1.5% of people in Indonesia and the province of East Java had cardiovascular disease in 2018 (based on doctors' diagnoses) (Kemkes RI, 2018). Therefore, oral anticoagulants are essential. In 1941, the FDA approved the clinical use of warfarin for the prevention or treatment of thromboembolism (How, 2015). Warfarin, a vitamin K antagonist anticoagulant, is used to prevent and treat thromboembolic problems linked to atrial fibrillation. In patients with atrial fibrillation, medication has been proven to reduce the risk of stroke by 62% (Touchette et al., 2007). The use of anticoagulants raises concerns because of the associated risk of side effects. Warfarin has a high risk of drug interactions with a narrow therapeutic index, necessitating the determination of a therapeutic dose for each patient. This results in side effects, particularly in the early stages of therapy (Morgan et al., 2009; Hanigan et al., 2021).

The side effects of warfarin are generally mild and do not require intervention. However, some patients with complications are at a higher risk of side effects, such as excessive bleeding (Snipelisky & Kusumoto, 2013). The use of anticoagulants raises concerns because they are associated with adverse effects. A hemoglobin drop of at least 2 g/dL or bleeding that necessitates hospitalization or transfusion is a typical definition of this adverse event. The side effects of warfarin include major bleeding (hematuria), lower gastrointestinal bleeding, upper gastrointestinal bleeding, upper gastrointestinal bleeding, intracranial bleeding, minor bleeding (ecchymosis), intramuscular or intra-abdominal hematoma, epistaxis, hemoptysis, and vaginal and retinal hemorrhage (Ozturk et al., 2019). Other side effects include thromboembolic conditions, such as decreased breath sounds, cough, chest pain, irregular heartbeat, redness or skin rash on the hands, deep vein thrombosis, and edema in the feet or hands (Waheed et al., 2021; Vyas et al., 2022). Necrosis can also occur at the start of warfarin therapy and in cases of systemic embolism or cholesterol microembolism (Ranieri et al., 2015).

Previous studies have shown that several factors influence the risk of bleeding in patients taking warfarin, including sex, age, comorbidities, genetic polymorphisms, and drug interactions (Ozturk et al., 2019; Ababneh et al., 2021; Yabeyu et al., 2022; Aulia et al., 2022). In addition, warfarin has nearly 100% oral bioavailability and reaches peak concentrations within 4 h of administration. This drug has a distribution volume of 0.14 L/kg and 99% protein binding, particularly to albumin. Warfarin binding can be influenced by factors that can increase free drug levels, thereby increasing the risk of side effects (Ranieri, 2015). Apart from these variables, habits such as alcohol consumption, smoking, and a diet of foods containing vitamin K can influence the occurrence of side effects during the use of warfarin (Yabeyu et al., 2022). There are few reports on the side effects of warfarin; therefore, existing data are limited. Furthermore, a larger sample size with bleeding type classification was used in this study than in previous studies. Therefore, this study aimed to analyze the incidence of warfarin side effects in outpatients at Dr. Soetomo General Hospital.

MATERIALS AND METHODS

Study area and period

This study was conducted at the Department of Cardiology at Dr. Soetomo General Hospital, Surabaya, between March and May 2023. These departments are primarily responsible for most hospitalized patients prescribed warfarin. Only outpatient clinic patients who had been taking warfarin for at least one month were included.

Study design

This retrospective cross-sectional study included outpatients who received warfarin at the Department of Cardiology of Dr. Soetomo General Hospital, Surabaya, Indonesia, between March and May 2023.

Sampling and selection of patients

The samples were obtained from total sampling, which included inclusions, from March to May 2023. The inclusion criteria were outpatients at the Cardiology Department of Dr. Soetomo General Hospital who had received warfarin for at least a month and were > 18 years old. The exclusion criterion was cognitive impairment.

Data collection method

Data were collected on the incidence of side effects in outpatients who received warfarin minimum of a month through an interview process. Patient information, such as age, sex, length of warfarin treatment, comorbidities, and INR at the latest scan, was obtained from medical records.

Data analysis

Warfarin side effects were grouped using the Bleeding Academic Research Consortium (BARC) classification. In the absence of bleeding, the BARC

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group was classified as type 0. As type 1 bleeding is "non-actionable," the patient did not seek medical assistance. Similar to type 1, type 2 bleeding is characterized by clinically noticeable symptoms that are "actionable" and necessitate medical diagnosis, hospitalization, or treatment. Type 3, which includes clinical, laboratory, and/or imaging evidence of bleeding with a particular healthcare provider response, is separated into three categories, numbered a to c. Type 3a occurs when hemoglobin levels drop from ≥3 to <5 g/dL, and there is open bleeding that necessitates transfusion. Type 3b is the presence of open bleeding and a decrease in hemoglobin level of ≥5 g/dL, cardiac tamponade, surgical intervention requirement (excluding teeth/nose/skin/hemorrhoids), and intravenous vasoactive drugs. Intracerebral and intraocular hemorrhages that affect vision are classified as type 3c. Type 4 bleeding is linked to coronary artery bypass grafting (CABG) (within 48 h) and type 5 bleeding is lethal. Lethal bleeding is classified as genitourinary, pericardial, pulmonary, retroperitoneal, gastrointestinal, cerebral, or other (Hicks et al., 2011). The Chi-Square tests were conducted to investigate differences between patient demographic characteristics and the incidence of warfarin side effects. A P-value <0.05 indicated a statistical significance of patient demographic characteristics affecting the incidence of warfarin side effects. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital (Surabaya No. 0600/KEPK/II/2023).

RESULTS AND DISCUSSION

From March to May 2023, data were obtained from 206 outpatients taking warfarin at the Department of Cardiology at Dr. RSUD. Soetomo General Hospital. The data extracted from the medical records are presented in Table 1.

Measuring the particle size is essential for determining the dimensions of the particles and ensuring that they meet the desired size range. Typically, the diameter of Nanostructured Lipid Carriers (NLC) ranges from 10 to 1000 nm, with a preferred size of 50–300 nm for targeted drug delivery. For topical applications, such as hair and skin, NLCs are generally the most effective when their maximum particle size is approximately 300-500 nm. Although the human pore diameter ranges from 40–80 μm to 0.05–0.2 mm, achieving an NLC particle size of approximately 300 nm is crucial for optimal product stability and effectiveness.

Table 1. Demographic profile characteristics of warfarin medication in outpatients at the Dr. Soetomo general hospital

	Side Effect		P value
	Absent	Present	
	Subject (n=118)	Subject (n=88)	
Sex			
Male	59 (62.8)	35 (37.2)	0.145
Female	59 (52.7)	53 (47.3)	
Age			
<50 year	59 (60.2)	39 (39.8)	0.419
≥ 50 year	59 (54.6)	49 (45.4)	
Duration of Warfarin Medication			
<1 year	41 (64.1)	23 (35.9)	0.187
≥1 year	77 (54.2)	65 (45.8)	
INR*			
< 2,0	77 (69.4)	34 (30.6)	
2,0-3,0	33 (45.2)	40 (54.8)	-
> 3,0	8 (36.4)	14 (63.6)	
Comorbidity			
Absent	32 (60.4)	21 (39.6)	0.597
Present	86 (56.2)	67 (43.8)	

*recent INR

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The chi-square test yielded a p-value > 0.05, as shown in Table 1, indicating that sex did not significantly influence the incidence of side effects. Other studies have shown no discernible variation in the risk of bleeding between males and females corroborating these findings (Barcellona et al., 2022). According to previous studies, women taking warfarin are at higher risk of bleeding (Gieling et al., 2017). According to another study, women typically have a low TTR, which is associated with a higher risk of bleeding and decreased efficacy (Costa et al., 2021). Several studies have found that men taking warfarin have a greater risk of bleeding (Penttilä et al., 2019; Rydberg et al., 2020). Females have a lower tendency to receive anticoagulant prescriptions than males after considering age, comorbidities, and thromboembolic risk factors (Lee et al., 2023).

According to the other data (Table 1), there was no significant difference in the side effects observed between patients aged ≤ 50 and > 50 years (p > 0.05). The incidence of side events, including bleeding is significantly influenced by the age of warfarin users (Shendre et al., 2018). This study demonstrated that the occurrence of side effects was significantly affected by age. These results contradict those of several studies that have shown a correlation between age and the presence of bleeding side effects when using warfarin. However, determining a set age criterion for evaluating bleeding risk is challenging. Previous studies have found that patients aged 60 years have worse anticoagulant control than older adults. Poor compliance, social factors including employment and alcohol consumption, and clinical considerations that are considered while delivering warfarin safely and effectively are the causes of this adverse event (Abohelaika et al., 2016). In contrast, other studies have stated that bleeding as a complication is prone to occur in patients aged ≥ 65 years owing to the risk of thrombosis when using anticoagulants (Gross & Chan, 2021). In addition to age, the duration of warfarin use should be considered.

Table 1 shows that there were no differences between patients who experienced side effects and patient without have experienced side effects and those who did not in the duration of warfarin medication < 1 year or ≥ 1 year (p > 0.05). According to this study, the risk of side effects was not significantly influenced by the duration of warfarin therapy. However, Al Saikhan (2020) stated that 57.4% of patients in Saudi Arabia had a warfarin medication duration ≥1 year. Another study reported that the use of warfarin for ≥1 year causes major bleeding (Ozturk et al., 2019). Patients taking warfarin for > 12 months require close coagulation monitoring to minimize the risk of bleeding. Monitoring was performed using INR values because thrombus formation still occurs 6-12 months after onset (Ardissino et al., 2003).

Table 1 shows the INR grouping into three groups: INR < 2.0, INR 2.0-3.0, and INR > 3.0 in the groups with and without side effects. The INR value in individuals with long-term warfarin consumption can change even with maintenance doses (Ozturk et al., 2019). To reduce the risk of adverse effects, patients on warfarin therapy must have their INR modified (Shikdar et al., 2018). One parameter that varies with warfarin and other treatments is the INR (Hindricks et al., 2021). INR can be influenced by a wide range of external circumstances, including the use of herbal remedies, alcohol, foods high in vitamin K, diet, and compliance (Al-Momany et al., 2019). A study conducted in 2022 revealed that 14 patients with thromboembolic events had an INR< 3.0, and 23 of the 74 patients who experienced bleeding had an INR < 3.0 (Putriana et al., 2022). Furthermore, Ozturk et al (2019) showed that only major and minor bleeding occurred in patients with an INR of 5-8.9, while major bleeding was quite large in INR ≥ 9 (Ozturk et al., 2019). When the last INR scan was <2, monitoring was performed every day until the individual INR target was reached. However, an INR > 3 requires monitoring every 2-3 d. INR was within the target range; therefore, monitoring was performed for 4-6 months. This is primarily performed in patients with comorbidities (Health, 2024).

Tabel 2. Side effect incidence of warfarin medication in outpatients at the Dr.Soetomo general hospital

BARC Classification	n (%)
Type 0 (absent)	118 (57.3)
Type 1 (gums bleeding, hematoma, melena, menometorrhagia, epistaxis, hematuria, hematemesis, hemoptysis, spontaneous venous bleeding, hematochezia, hemostasis during blood sampling, tongue bleeding, and subconjunctival bleeding.	88* (42.7)

*One patient experienced more than one type of side effect

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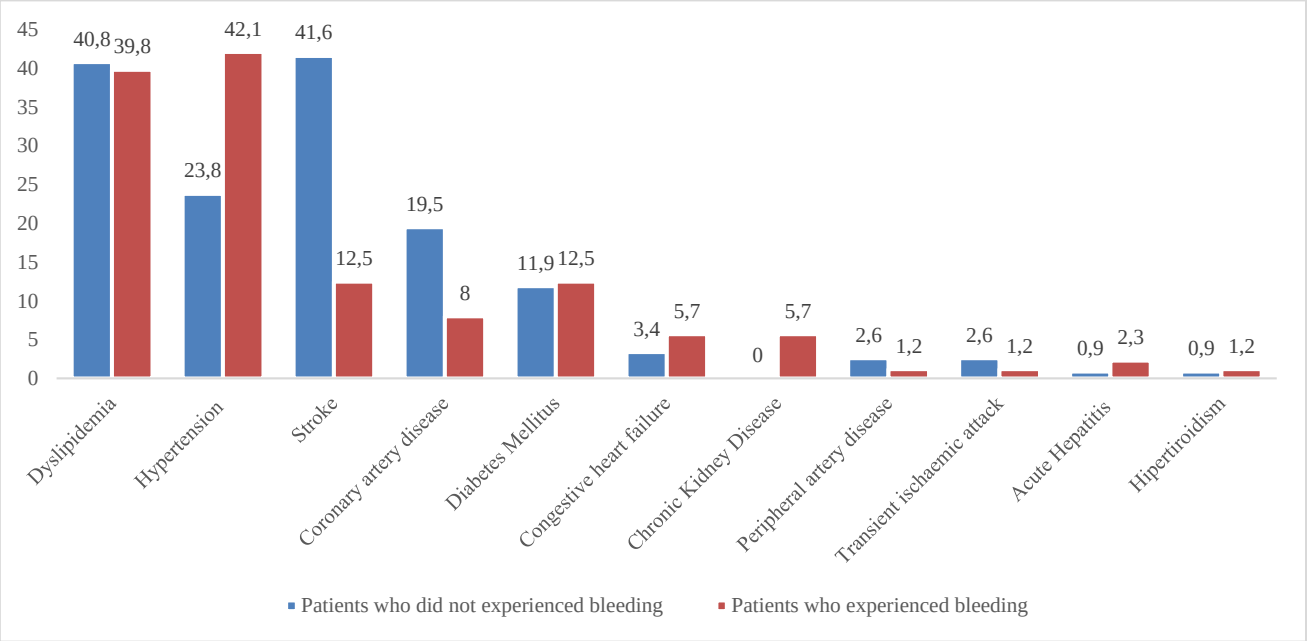

Figure 1. Types of comorbidities in patients receiving warfarin

Table 3. Clinical manifestations of side effects of warfarin medication in outpatients at the Dr.Soetomo general hospital

Side Effect Reaction	n (%)
Gum bleeding	46 (22.3)
Hematoma	42 (20.4)
Melena	16 (7.7)
Menometorrhagia	5 (2.4)
Epistaxis	4 (1.9)
Hematuria	3 (1.5)
Hematemesis	2 (1.0)
Hemoptysis	2 (1.0)
Spontaneous venous bleeding	2 (1.0)
Hematochezia	1 (0.5)
hemostasis during blood sampling	1 (0.5)
tongue bleeding	1 (0.5)
Subconjunctival bleeding	1 (0.5)

The p-value from the *chi-square* test for the presence of comorbidities had no significant influence on the occurrence of side effects ($p > 0.05$) (Table 1). The three most common comorbidities among patients who experienced bleeding were hypertension, dyslipidemia, and stroke (Figure 1). In this study, the most prevalent comorbidity among individuals with bleeding as a side effect was hypertension (Lackland, 2014). Hypertension was the most prevalent comorbid condition in all the black samples (Ciurus et al., 2015). It is possible that the illness may make oral anticoagulants less effective. Individuals without AF who have this comorbidity have been linked to poor anticoagulation control and an elevated risk of stroke (Bertomeu-González et al., 2015). Tapaskar et al (2022) reported that patients using warfarin had several comorbid conditions such as HIV, diabetes mellitus, heart failure, and a previous history of stroke or transient ischemic attack. Warfarin can protect against thrombus formation for 180 days in conditions such as transient ischemic attack, venous thromboembolism, and ischemic stroke (Tapaskar et al., 2022). These conditions are risk factors in increased risk of bleeding in patients with a history of non-cardioembolic stroke, chronic kidney or liver disease, acute, or chronic disease (Ageno et al., 2012).

Patients with comorbidities receive polypharmacy medications, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, and several other drugs, and many other medications can interact with warfarin or elevate the risk of bleeding (Ikeda et al., 2018). For patients with mechanical prosthetic heart valves, combination antithrombotic therapy comprising oral anticoagulants (OAC) and low-dose aspirin (≤100

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mg/day) is recommended (Salem et al., 2004). Currently, this combination is commonly administered to patients with vascular disease, coronary heart disease, and myocardial infarction (MI). This combination increases the risk of bleeding (So & Eckman, 2017). According to previous studies, both non-selective NSAIDs and selective COX-2 inhibitors carry a significant risk of severe hemorrhage. This condition is not easily controlled by INR monitoring and can be avoided by appropriate management. Previous research has shown that the side effects resulting from the use of warfarin vary (Battistella, 2005; Hauta-Aho et al., 2009).

According to the BARC classification, 88 patients (42.7%) experienced side effects in the form of bleeding (Table 2). The various types of bleeding in Table 3 show that a total of 126 events such as gum bleeding (22.3%), hematoma (20.4%), melena (7.7%), *menometorrhagia* (2.4%), epistaxis (1.9%), hematuria (1.5%), hematemesis (1.0%), hemoptysis (1.0%), **s**pontaneous venous bleeding (1.0%), hematochezia (0.5%), hemostasis during blood sampling (0.5%), tongue bleeding (0.5%), and subconjunctival bleeding (0.5%). In this study, the results showed that the most common bleeding reactions were in the form of blood gums, hematoma, and melena. This was supported by the findings of Ozturk et al (2019) which found that the incidence of bleeding in the form of subcutaneous hematoma (10.4%), hematuria (10.4%), and epistaxis (4.2%) was quite large compared to hemoptysis, intracranial bleeding, lower and upper gastrointestinal bleeding (Ozturk et al., 2019). According to Mascolo et al. (2019), the incidence of side effects included epistaxis (40.4%), hematuria (9.8%), melena (7.3%), gum bleeding (4.7%), hematemesis (3.6%), hematoma (2.1%), and gastric bleeding (0.5%) (Mascolo et al., 2019). In geriatric patients, less than 5% of the side effects occur in the form of hematuria (Ningrum et al., 2020). Another study reported that 44% of gastrointestinal bleeding cases occurred during the use of warfarin. In this context, the use of warfarin as monotherapy is associated with the probability of recurrent gastrointestinal bleeding, thus requiring close monitoring (Tapaskar et al., 2022).

According to Kimmel (2008), genetic variables are substantial. Warfarin is influenced by genetic polymorphisms in vitamin K epoxide reductase complex 1 (VKORC1) and cytochrome P450 2C9 (CYP2C9) genes. Warfarin reactivity is also influenced by clinical variables such height, weight, and age (Kimmel et al., 2008). The polymorphisms contribute to the dose variability among ethnic groups (Takahashi et al., 2006). A racemic mixture of R and S enantiomers forms the warfarin. The more potent S-warfarin is metabolized in the liver by cytochrome P450 2C9. Warfarin is metabolized more slowly by the wild-type allele, CYP2C9*1, and the other two alleles, CYP2C9*2 and CYP2C9*3. This allele may increase the risk of bleeding in patients carrying it (Shurin & Nabel).

CONCLUSION

In conclusion, the incidence of warfarin-induced side effects was significant, accounting for approximately 42.7% of the cases. To reduce the risk of warfarin side effects, such as excessive bleeding, drug administrators must ensure close monitoring, including providing education to patients before initial warfarin administration.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.S., W.N., BZ.; Methodology, B.S., W.N., M.Y., F.Z.; Software, F.Z., D.M.; Validation, B.S., W.N., D.M.; Formal Analysis, F.Z., D.W.; Investigation, F.Z., D.M., B.Z.; Resources, M.Y., D.M.; Data Curation, D.W., D.S.; Writing - Original Draft, F.Z., D.W.; Writing - Review & Editing, B.S., W.M.; Visualization, D.W., F.Z.; Supervision, B.S., M.Y., D.M.; Project Administration, F.Z., B.S.; Funding Acquisition, FZ., D.W., B.S.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Ababneh, M., Nasser, S. A., Rababa'h, A. & Ababneh, F. (2021). Warfarin Adherence and Anticoagulation Control in Atrial Fibrillation Patients: A Systematic Review. *European Review for Medical and Pharmacological Sciences*; *25*; 7926-7933. doi: 10.26355/eurrev_202112_27642.

Abohelaika, S., Wynne, H., Avery, P., Robinson, B., Kesteven, P. & Kamali, F. (2016). Impact of Age on Long-Term Anticoagulation and How

P-ISSN: 2406-9388
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Gender and Monitoring Setting Affect it: Implications for Decision Making and Patient Management. *British Journal of Clinical Pharmacology*; *82*; 1076–1083. doi: 10.1111/BCP.13046.

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral Anticoagulant Therapy Antithrombotic Therapy and Prevention of Thrombosis, American College Of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*; *141;* e44S-e88S. doi: 10.1378/chest.11-2292.

Al-Momany, N., Makahleh, Z., Al-Omari, N., & Al-Sarayreh, H. (2019). Analysis of Factors That Interrupt with INR Control in the First Anticoagulation Clinic Monitoring Jordanian Patients. *Clinical and Applied Thrombosis/Hemostasis*; *25*; 1-9. doi: 10.1177/1076029619870252.

Al-Saikhan, F. (2020). Warfarin Therapy Adherence and Health Related Quality of Life Among Patients Using Warfarin in Saudi Arabia. *Nigerian Journal of Clinical Practice*; *23*; 398–407. doi: 10.4103/NJCP.NJCP_608_18.

Ardissino, D., Merlini, P. A., Bauer, K. A., Galvani, M., Ottani, F., Franchi, F., Bertocchi, F., Rosenberg, R. D., & Mannucci, P. M. (2003). Coagulation Activation and Long-Term Outcome in Acute Coronary Syndromes. *Blood*; *102*; 2731–2735. doi: 10.1182/blood-2002-03-0954.

Barcellona, D., Schirru, P., Mameli, A., Cornacchini, S., Fenu, L., & Marongiu, F. (2022). Over-Anticoagulation by Vitamin K Antagonists and Gender Differences. *International Journal of Cardiology*; *362*; 147–151. doi: 10.1016/j.ijcard.2022.05.003.

Battistella, M., Mamdami, M., Juurlink, D. N., Rabeneck, L., Laupacis, A. (2005). Risk of Upper Gastrointestinal Hemorrhage in Warfarin Users Treated with Nonselective NSAIDS or COX-2 Inhibitors. *Arch Intern Med*; *165*. 189-192. doi: 10.1001/archinte.165.2.189.

Bertomeu, G., V, Anguita. M., Moreno, Arribas. J., Cequier, Á., Muñiz, J., Castillo, J., Sanchis, J., Roldán, I., Marin, F., Bertomeu-Martínez, V. (2015). Quality of Anticoagulation with Vitamin K Antagonists. *Clinical Cardiology*; *38*; 357–364. doi: 10.1002/clc.22397.

Chan, P. H., Hai, J. J., Chan, E. W., Li, W. H., Tse, H. F., Wong, I. C. K., Lip, G. Y. H. & Siu, C. W. (2016). Use of The Same-TT2R2 Score to Predict Good Anticoagulation Control with Warfarin in Chinese Patients with Atrial Fibrillation: Relationship to Ischemic Stroke Incidence. *PLOS ONE*; *11*; 1-9. doi: 10.1371/journal.pone.0150674.

Ciurus, T., Cichocka, R. A., & Lelonek, M. (2015). Factors Affecting The Quality of Anticoagulation With Warfarin: Experience of One Cardiac Centre. *Kardiochirurgia i Torakochirurgia Polska*; *12*; 334–340. doi: 10.5114/kitp.2015.56784.

Costa, V. C. da, Silva, P. M. F., & Nunes, de S. (2021). Sex Influence on The Time in Therapeutic Range (TTR) During Oral Anticoagulation with Coumarin Derivatives: Systematic Review and Meta-Analysis. *British Journal of Clinical Pharmacology*; *87*; 4488-4503. doi: 10.1111/bcp.14892.

Gieling, E. M., Van, D., Ham, H. A., Van, O. Hein., Bos, J., Kramers, C., de Boer, A., de Vries, F., Burden, A. M. (2017). Risk of Major Bleeding And Stroke Associated With The Use of Vitamin K Antagonists, Nonvitamin K Antagonist Oral Anticoagulants and Aspirin in Patients with Atrial Fibrillation: A Cohort Study. *British Journal of Clinical Pharmacology*; *83*; 1-7. doi: 10.1111/bcp.13265.

Gross, P. L., Chan, N. C. (2021). Thromboembolism in Older Adults. *In Frontiers in Medicine*; *7*; 1-9. doi: 10.3389/fmed.2020.470016.

Hanigan, S., Kong, X. H., Brian, K. R., Eva, K., Scott, Krol, G., Shah, V., Ali, M., Almany, S., Kozlowski, J., Froehlich, J., & Geofreey, B. (2021). Standard Versus Higher Intensity Anticoagulation for Patients with Mechanical Aortic Valve Replacement and Additional Risk Factors for Thromboembolism. *The American Journal of Cardiology*; *159*; 100–106. doi: 10.1016/j.amjcard.2021.08.023.

Hauta-Aho, M., Tirkkonen, T., Vahlberg, T., & Laine, K. (2009). The Effect of Drug Interactions on Bleeding Risk Associated with Warfarin Therapy in Hospitalized Patients. *Annals of Medicine*; *41*; 619–628. doi: 10.1080/07853890903186168.

Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist, C., Boriani, G.,

P-ISSN: 2406-9388
E-ISSN: 2580-8303

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. Y. H., Pinto, F. J., Thomas, G. N., Valgimigli, M., Van Gelder, I. C., Van Putte, B. P., & Watkins, C. L. (2020). ESC Guidelines for The Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with The European Association. *European Heart Journal*; *42*; 373-498. doi: 10.1161/CIRCULATIONAHA.111.032433.

Health, Q. (2024). Guideline for Warfarin Management in The Community Guideline for Warfarin. https://www.health.qld.gov.au/. Accessed: 10 August 2024.

Hicks, K. A., Stockbridge, N. L., Targum, S. L., Temple, R. J. (2011). Bleeding Academic Research Consortium Consensus Report: The Food and Drug Administration Perspective. *Circulation*; *123*; 2664–2665. doi: 10.1161/CIRCULATIONAHA.111.032433.

How, C. (2015). Novel Oral Anticoagulants for Atrial Fibrillation. *Singapore Medical Journal*; *56*; 657–659. doi: 10.11622/smedj.2015184.

Ikeda, T., Yasaka, M., Kida, M., & Imura, M. (2018). A Survey Of Reasons for Continuing Warfarin Therapy in The Era of Direct Oral Anticoagulants in Japanese Patients With Atrial Fibrillation: The SELECT Study. *Patient Preference and Adherence*; *12*; 135–143. doi: 10.2147/PPA.S152584.

Kementerian Kesehatan RI. (2018). Laporan Riskesdas 2018 Nasional. https://www.badankebijakan.kemkes.go.id/laporan-hasil-survei/. Accessed: 11 August 2024.

Kimmel, S. E., Christie, J., Kealey, C., Chen, Z., Price, M., Thorn, C. F., Brensinger, C. M., Newcomb, C. W., & Whitehead, A. S. (2008). Apolipoprotein E Genotype and Warfarin Dosing Among Caucasians and African Americans. *Pharmacogenomics Journal*; 8; 53–60. doi: 10.1038/sj.tpj.6500445.

Lackland, D. T. (2014). Racial Differences in Hypertension: Implications for High Blood Pressure Management. *The American Journal of the Medical Sciences*; *348*; 135–138. doi: 10.1097/MAJ.0000000000000308.

Lee, K. K., Doudesis, D., Bing, R., Astengo, F., Perez, J. R. P.., Anand, A., McIntyre, S., Bloor, N., Sandler, B., Lister, S., Pollock, K. G., Qureshi, A. C., McAllister, D., Shah, A. S. V., & Mills, N. L. (2023). Sex Differences in Oral Anticoagulation Therapy in Patients Hospitalized with Atrial Fibrillation: A Nationwide Cohort Study. *Journal of the American Heart Association*; 12; 1-22. doi: 10.1161/JAHA.122.027211.

Mascolo, A., Ruggiero, R., Sessa, M., Scavone, C., Sportiello, L., Rafaniello, C., Rossi, F., & Capuano, A. (2019). Preventable Cases of Oral Anticoagulant Induced Bleeding: Data From The Spontaneous Reporting System. *Frontiers In Pharmacology*; *10*; 1-12. doi: 10.3389/fphar.2019.00425.

Morgan, C. L., McEwan, P., Tukiendorf, A., Robinson, P. A., Clemens, A., & Plumb, J. M. (2009). Warfarin Treatment in Patients with Atrial Fibrillation: Observing Outcomes Associated with Varying Levels Of INR Control. *Thrombosis Research*; 124; 37–41. doi: 10.1016/j.thromres.2008.09.2016.

Ningrum, V. D. A., Dyah, W. I., Sufriyanto, Y. B., & Dullah, W. (2020). Bleeding Incidence in Patients Administered with Warfarin At Secondary Hospitals in Yogyakarta Province. *Indonesian Journal of Pharmacy*; *31*; 217–228. doi: 10.22146/ijp.814.

Ozturk, M., Ipekci, A., Kiyak, S. K., Akdeniz, Y. S., Aydin, Y., Ikizceli, I., Sogut, O. (2019). Bleeding Complications in Warfarin Treated Patients Admitted to the Emergency Department. *Journal of Clinical Medicine Research*; *11*; 106. doi: 10.14740/jocmr3669.

Penttilä, Tero., Lehto, Mika., Niiranen, Jussi., Mehtälä, Juha., Khanfir, Houssem., Lassila, Riitta., Raatikainen, Pekka. (2019). Differences In The Risk of Stroke, Bleeding Events, and Mortality Between Female and Male Patients with Atrial Fibrillation During Warfarin Therapy. *European Heart Journal Cardiovascular Pharmacotherapy*; *5*; 29–36. doi: 10.1093/ehjcvp/pvy026.

Putriana, N. A., Rusdiana, T., Rostinawati, T., Akbar, M. R., & Destiani, D. D. (2022). Evaluation of Adverse Drug Reaction in Patients Warfarin Therapy. *Journal of Advanced Pharmaceutical Technology & Research*; *13*; 291. doi: 10.4103/japtr.japtr_439_22.

Ranieri, M. (2015). Casebook in Clinical Pharmacokinetics and Drug Dosing. *American Journal of Health System Pharmacy*; *72*; 1238–1240.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Rydberg, D. M., Linder, M., Malmström, R. E., & Andersen, M. (2020). Risk Factors for Severe Bleeding Events During Warfarin Treatment: The Influence of Sex, Age, Comorbidity and Co-Medication. *European Journal of Clinical Pharmacology*; *76*; 867–876. doi: 10.1007/s00228-020-02856-6.

Salem, D. N., Stein, P. D., Al-Ahmad, A., Henry, B. I., Horstkotte, D., Miller, N., Pauker, S. G. (2004). Antithrombotic Therapy in Valvular Heart Disease-Native and Prosthetic The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest Journal*; *126*; 457S-482S. doi: 10.1378/chest.126.3_suppl.457S.

Shendre, A., Parmar, G. M., Dillon, C., Beasley, T. M., & Limdi, N. A. (2018). Influence of Age on Warfarin Dose, Anticoagulation Control and Risk of Hemorrhage. *Pharmacotherapy*; *38*; 588–596. doi: 10.1002/phar.2089.

Shikdar, S.,Vashisht, R., Zubari, M. T., & Bhattacharya, P. (2023). International Normalized Ratio (INR). *StatPearls Publishing*. https://www.ncbi.nlm.nih.gov/. Accessed: 11 August 2024.

Shurin, S. B., Nabel, E. G. (2008). Pharmacogenomics-Ready for Prime Time? The New England Journal of Medicine;. *https://www.nejm.org/doi/abs/10.1056/NEJMe0800801*. Accessed: 11 August 2024.

Snipelisky & David., Kusumoto. (2013). Current Strategies to Minimize The Bleeding Risk of Warfarin. *Journal of Blood Medicine*; *89*; 1-11. doi: 10.2147/jbm.s41404.

So, C. H., & Eckman, Mark. H. (2017). Combined Aspirin and Anticoagulant Therapy in Patients with Atrial Fibrillation. *Journal of Thrombosis and Thrombolysis*; *43*; 7–17. doi: 10.1007/s11239-016-1425-5.

Takahashi, H., Wilkinson, G. R., Nutescu, E. A., Morita, T., Ritchie, M. D., Scordo, M. G., Pengo, V., Barban, M., Padrini, R., Ieiri, I., Otsubo, K., Kashima, T., Kimura, S., Kijima, S., & Echizen, H. (2006). Different Contributions Of Polymorphisms In VKORC1 and CYP2C9 to Intra and Inter-Population Differences in Maintenance Dose of Warfarin in Japanese, Caucasians and African-Americans. *Pharmacogenetics and Genomics*; *16*; 101–110. doi: 10.1097/01.fpc.0000184955.08453.a8.

Tapaskar, N., Ham, S. A., Micic, D., & Sengupta, N. (2022). Restarting Warfarin vs Direct Oral Anticoagulants after Major Gastrointestinal Bleeding and Associated Outcomes in Atrial Fibrillation: A Cohort Study. *Clinical Gastroenterology and Hepatology*; *20*; 381-389. 10.1016/j.cgh.2020.11.029.

Touchette, D. R. E, Margaret, M., Stoner, S., Shute, D., & Jennifer, M. E. K. (2007). Improving Outpatient Warfarin Use for Hospitalized Patients with Atrial Fibrillation. *Pharmacy practice*; *6*; 43-50. doi: 10.4321/s1886-36552008000100007.

Vyas, V., Sankari, A., & Goyal, A. (2022). Acute Pulmonary Embolism. https://www.ncbi.nlm.nih.gov/books/NBK560551/. Accessed: 4 October 2024.

Waheed, S. M., Kudaravalli, P., Hotwagner, & D. T. (2021). Deep Vein Thrombosis. *StatPearls Publishing*. https://www.ncbi.nlm.nih.gov/books/NBK507708/. StatPearls. Accessed: 12 November 2024.

World Health Organisation (WHO). (2019). Cardiovascular Diseases (CVDs). https://www.who.int/health-topics/cardiovascular-diseases/. Accessed: 12 November 2024.

Yabeyu, A. B., Adugna, A. M., Taye, H. K., & Demelash, K. Z. (2022). Evaluation of Patients Knowledge of Warfarin at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *Metabolism Open*; *13*; 2589–9368. doi: 10.1016/j.metop.2021.1001555.

P-ISSN: 2406-9388
E-ISSN: 2580-8303