Indonesian Journal of Pharmacy

VOL 34 (4) 2023: 665–674 | RESEARCH ARTICLE

Challenges in Achieving Optimal Warfarin Anticoagulation Control: A Comprehensive Exploration and Proposed Holistic Approach

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Article Info

Submitted: 16-05-2023
Revised: 09-09-2023
Accepted: 23-11-2023

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ABSTRACT

Warfarin is the most commonly prescribed oral anticoagulant in Indonesia. However, the time in the therapeutic range (TTR) remains low across different countries worldwide. This study aimed to analyze the challenges associated with achieving optimal warfarin control. The analysis consisted of two distinct stages. The first stage was a prospective observational study that aimed to analyze anticoagulation control, dosing consistency, INR monitoring compliance, medication adherence, and knowledge of warfarin. Meanwhile, in the second stage, focus group discussion was used to propose strategies for overcoming the challenges. The result showed that the average TTR was 49.4 ± 32.1, where only 37.5% of patients had values ≥ 65%. The average dosing consistency obtained was 62.33 ± 32.42%. The majority of patients with supratherapeutic INR values required a 1-month monitoring interval after dose adjustment. Further analysis indicated that only 43.8% of patients were classified as adherent and 39.5% had good knowledge of warfarin, suggesting the level of medication adherence and knowledge was not optimal. Approximately 14.6% of patients received other drugs that potentially interacted with warfarin, causing fluctuations in INR. In conclusion, this study found several challenges associated with achieving optimal warfarin control including barriers to dosing consistency, INR monitoring, medication adherence, and knowledge of warfarin, as well as drug interactions. The proposed solution is a holistic approach combining multifaceted strategies to address each barrier.

Keywords: warfarin, low TTR, challenges, holistic approaches

INTRODUCTION

Warfarin is the most commonly prescribed anticoagulant for preventing stroke in patients with valvular and non-valvular atrial fibrillation (AF), heart valve disease, prosthetic heart valves, deep vein thrombosis, and other coagulation disorders (Nishimura et al., 2017). Despite the discovery of *Novel Oral Anticoagulants* (NOACs) with more predictable pharmacokinetic and pharmacodynamic properties, the *American Heart Association* (AHA)/*American College of Cardiology* (ACC) only recommends warfarin for patients with prosthetic heart valves, moderate to severe mitral stenosis, and valvular AF due to its proven safety and effectiveness (January et al., 2014; Nishimura et al., 2017). Furthermore, the substantial cost associated with NOACs has resulted in a majority of patients with non-valvular AF still relying on the use of warfarin. In Indonesia, the anticoagulant is presently the sole oral medication included in the national formulary for preventing thromboembolism in AF, prosthetic heart valves, and valvular heart disease (Minister of Health of Indonesia, 2021).

The management of warfarin remains challenging primarily due to the suboptimal achievement measured by *Time in the Therapeutic Range* (TTR). The CHEST guidelines recommend a TTR of at least 65%, but a study on warfarin achievement in Indonesia reported suboptimal results. According to (Putriana et al. 2017), the percentage of patients whose *International Normalized Ratio* (INR) values reached the therapeutic range was only 52.5% of the population. A study by (Rahmatini et al. 2020) reported a lower rate of 28.9%. Another study found that only 26.12% of the population could reach TTR > 65% (Sekarsari et al., 2021). Furthermore, among hemodialyzed patients using warfarin, none achieved the expected target (Akbar et al., 2022). A previous study also showed that fewer than half of the patients had TTR ≥ 65%.

Warfarin exhibits a narrow therapeutic index, making the safety and effectiveness of its therapy highly dependent on maintaining an INR range of 2.0 to 3.0. Additionally, this anticoagulant is subject to genetic polymorphisms, resulting in significant dose-response variability. It is also susceptible to the influence of vitamin K-rich diets and interacts extensively with various medications, necessitating regular monitoring of INR levels. These characteristics raise the possibility of suboptimal outcomes in the therapy.

Many developed and developing countries have implemented specialized management programs aimed at enhancing the quality of warfarin therapy. These initiatives include the establishment of warfarin clinics, where pharmacists play a crucial role. Studies indicated that pharmacist-led warfarin clinics could effectively improve therapy outcomes. However, Indonesia lacks a comprehensive management approach, resulting in uncoordinated care. Sociodemographic and healthcare provider practices also differ among several countries. This study aimed to analyze the challenges associated with achieving optimal warfarin control from the perspectives of healthcare professionals, patients, and health policies, as well as develop strategies to overcome these challenges. This is the first study in Indonesia on this topic, and the results are crucial to developing standardized care for warfarin.

MATERIALS AND METHODS

Study Design and Location

This study consisted of two stages, the first was a quantitative analysis aimed to identify challenges in achieving optimal warfarin control. A prospective observational approach was used and it was conducted for 3 months at one of the University Hospitals in East Java, Indonesia. Meanwhile, the second stage was a qualitative study (Focus Group Discussion/FGD) which aimed to propose a strategy to address the challenges.

Population and Sample

The first stage

The samples consisted of patients diagnosed with AF, valvular heart disease, heart valve replacement, or deep vein thrombosis who were prescribed warfarin in January 2021. The inclusion criteria were patients 1) aged ≥ 18 years, 2) in the maintenance phase, and 3) willing to sign informed consent. Meanwhile, the exclusion criteria included 1) patients who could not be accessed by phone and 2) those with severe cancer, and kidney or liver disorders.

The second stage

Focus group discussion (FGD) was attended by 4 cardiologists, 4 clinical pharmacists, and hospital stakeholders who play a role in policy-making.

Anticoagulation Control

The anticoagulation control was measured by TTR, a parameter used to assess the quality of warfarin therapy. The calculation was conducted with the Rosendaal method using the linear interpolation of INR values obtained over the last 3 months, from January to March 2021 (Rosendaal et al., 1993).

Dosing Consistency

Algorithm-based dosing consistency was expressed as the average percentage (%) of all instructions consistent with the algorithm for each patient over 3 months. The dosing protocol was adapted from the guideline by VanSpall *et al*. with slight modifications (van Spall et al., 2012). These weekly dose changes included INR 2.0-3.0 (no dose changes), INR ≤ 1.5 (increased by 10%-20%), INR 1.50-1.99 (increased by 10%), and INR 3.00-3.99 (reduced by 10%). For INR 4.00-4.99, warfarin was stopped for 1 day and the weekly dose was reduced by 10%, while for INR 5.00-8.99, warfarin was stopped and 2-4 mg of vitamin K was considered. Finally, a dose 10%-20% lower was started when the INR was within the therapeutic range. This algorithm applied to compliant patients, while the non-compliant ones received no dose adjustments.

Table I. Sociodemography and Characteristics of Study Participants

Sociodemographics and Characteristics	N	%
Age (years)		
< 50	8	16.6%
≥ 50	40	83.3%
Gender		
Male	25	52.1%
Female	23	48.9%
Education Level		
Elementary School	-	0%
Junior School	6	12.5%
High School	28	58.3%
Diploma	1	2.1%
Bachelor or above	13	27.1%
Indication for Warfarin		
Non-valvular atrial fibrillation	27	56.2%
Valvular atrial fibrillation	12	25.0%
Valvular atrial fibrilation + embolic stroke	2	4.2%
Prosthetic heart valves	2	4.2%
Mitral stenosis	2	4.2%
Others	5	10.5%
Quantity of other drugs (average)	4.6 ± 1.8	
Warfarin Duration of Warfarin Therapy		
< 1 year	12	25,0%
≥ 1 year	36	75.0%
Bleeding and Thromboembolic Events		
Gum bleeding	3	6.2%
Nosebleed	1	2.1%
Bruises	3	6.2%
Thromboembolic	0	0.0%

INR Monitoring Compliance

INR monitoring compliance was determined by calculating the percentage consistent with the guidelines compared to the total number of tests. For patients with stable INR values of **2.0-3.0** in less than 6 months, the monitoring was considered consistent with the guidelines when performed at least once a month. However, for those stable in over 6 months, compliance required testing at least once every 3 months. Among patients with unstable INR values below 2.0 or above 3.0, the monitoring was considered consistent with the guidelines when performed at least once every 7-14 days.

Adherence to Medication

The adherence of patients to medication was assessed by administering the ARMS questionnaire, a validated and reliable tool for calculating adherence in populations with chronic diseases (Kripalani et al., 2009). An ARMS score of 11 was defined as adherent, while those > 11 were defined as non-adherent. The questionnaire has been confirmed to be valid and reliable.

Knowledge of Warfarin

The knowledge of warfarin among the patients was measured using a knowledge questionnaire consisting of 22 multiple-choice questions with one correct answer for each. The questionnaire was created by pharmacists and cardiologists. Correct and incorrect answers were scored 1 and 0, with a total score ranging from 0 to 22. A minimum score of 16 was considered to represent good knowledge. The knowledge questionnaire has been tested for its validity and reliability.

Statistical Analysis

Descriptive analysis was used to describe TTR results, dosing consistency, INR monitoring, adherence to medication, and knowledge of warfarin. Linear regression analysis was utilized to test the correlation between dosing consistency and TTR**.** The difference in the percentage of adherent patients, as well as those having good knowledge in the TTR < 65% and ≥ 65% groups, was determined with the Chi-square test. All statistical analyses were conducted with the JASP software.

Ethics Statement

The methodology of this study was approved by the Ethics Committee of the Health Research of Airlangga University Hospital Surabaya with number 119/KEP/2020. All patients were asked for informed consent to participate as respondents.

RESULTS AND DISCUSSION

A total of 48 patients participated in this study, and the sociodemographic characteristics (Table I). The most common indication for warfarin was non-valvular and valvular AF at 56.2% and 25.0%, respectively. The majority were over 50 years old, accounting for 83.3% of the sample. This result was consistent with other studies that reported an increased prevalence of AF with age, namely from 0.12%-0.16% in individuals younger than 49 years, 1.7%-4.0% in those aged 60-70 years, and 13.5%-17.8% among others above 80 years (Kavousi, 2020). Meanwhile, the percentage of males (52.1%) and females (48.9%) gender was almost equal. This was consistent with the study by Magnussen et al. (2017), where cases of AF were less common in females than in males (Magnussen et al., 2017). The average number of other drugs received was 4.6 ± 1.8, and 75.0% of the patients had been using warfarin for more than 1 year. Approximately 14.5% observed minor adverse events during the 3-month study period, but none experienced major bleeding or thromboembolism.

Anticoagulation Control

Anticoagulation control was calculated using the TTR parameter based on the INR in the last 3 months. The average TTR of the patients was 49.4 ± 32.1, where 37.5% and 62.5% had values ≥ 65% and < 65%, respectively (Table II). These results indicated that the quality of warfarin therapy achievement was sub-optimal considering the CHEST guideline specifically recommended a minimum TTR of 65% (Lip et al., 2018). The values obtained were almost the same as the results reported by another study conducted in Indonesia (Sekarsari et al., 2021)

Table II. Description of TTR

TTR	N	%
≥65%	18	37.5%
< 65%	30	62.5%
Mean	49.4 ± 32.1	

The data from the ROCKET AF study showed differences in the average TTR among various countries, including India, developing countries in East Asia, and Europe with values of 29%, 49%, and 70%. The differences were attributed to the varying levels of aggressiveness in achieving the INR point target of 2.5, variation in support systems to manage warfarin, and different regional barriers to frequent monitoring and dose adjustment (Singer et al., 2013). Another study showed that sites with pharmacist-led warfarin clinics recorded a fairly good TTR (Noor et al., 2021; Alghadeeer S et al., 2020; Wang et al., 2021).

Dosing Consistency Challenges

The dosing of warfarin during the initiation and maintenance phase must follow a specific algorithm. Several studies showed that consistent dosing based on algorithms affected the achievement of warfarin therapy. For example, van Spall et al. (2012) reported that this approach served as a strong predictor of TTR, predicting 65% of the variation. Other studies also found similar results, where higher consistency in dosing increased the chances of INR within the therapeutic range (Kim et al., 2010; Wilson et al., 2022). Linear regression analysis was used to test the correlation between dosing consistency and TTR. The average value obtained was 62.33 ± 32.42%, indicating suboptimal dosing consistency. Furthermore, the results showed an adjusted R^2 of 0.467 meaning that 46.7% of the TTR variable was determined by the dosing consistency variable.

This study examined dose adjustment deviations observed among patients with (1) subtherapeutic INR levels but no reported dosing increment, or cases where the dosing increment exceeded the recommended range (2) INR within the therapeutic range and also experienced dosing increment (3) supratherapeutic levels and excessive dose reduction.

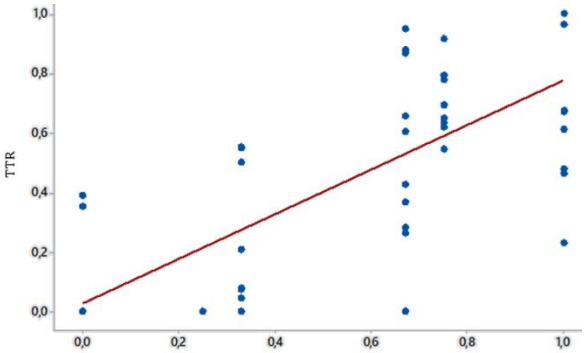

Figure 1. Scatterplot TTR vs. Dosing Consistency

The first identified cause of deviation was the lack of a detailed dosing protocol in the institution where this study was conducted, resulting in wide and non-uniform dosage adjustment variations. The second cause was the absence of a decision support tool that can facilitate dose adjustment, such as computer-based dosing. According to several studies, the use of computer-based dosing may increase TTR (Dimberg et al. 2012; Woller et al. 2015). The third cause was the limited awareness that patient non-adherence was a contributing factor to the failure to achieve the target INR, resulting in unnecessary dosing increment.

The proposed strategy was to conduct a critical review of algorithm-based dosing and develop guidelines disseminated to healthcare professionals responsible for the care of warfarin patients, with subsequent implementation. The use of dosing tools such as paper-based or software programs can also facilitate dose adjustment calculations. The guidelines were not intended to replace clinical justification, but to increase standardization and support clinical decision-making. Efforts to integrate evidence-based dosing into daily practice were critical to achieving good warfarin management. This was in line with recommendations from the US Department of Health and Human Services (USDHHS), and the Joint Commission (TJC) (USDHHS, 2014; TJC, 2017). Additionally, fostering collaboration between clinicians and pharmacists was deemed crucial. Pharmacists could actively assess the adherence of patients, providing necessary information to support dosage adjustment decisions. To ensure timely communication, a centralized warfarin service with collaboration between clinicians and pharmacists might be a more effective solution than having both professionals in separate locations. Establishing a collaborative anticoagulant clinic was deemed more appropriate for Indonesia than autonomous ones such as those in developed countries.

INR Monitoring Challenge

The challenge identified in this study was that almost all patients with INR values outside the therapeutic range (92 INR tests) during the maintenance phase had their monitoring interval set to 1 month after the dose adjustment. According to a previous study, INR monitoring should be conducted every 7-14 days after dose adjustment until the value falls within the therapeutic range. Patients who underwent dose adjustments in that timeframe achieved the therapeutic range faster (Rose et al., 2011).

The underlying problems contributing to this challenge included (1) the high cost of INR testing using traditional laboratory methods, (2) the absence of locally agreed-upon monitoring protocols disseminated to relevant healthcare professionals, and (3) the refusal of patients to visit the hospital more frequently due to transportation costs, and the need for additional time off work. Typically, patients require 2 days, with the first day for INR examination in the laboratory and the second day for receiving results and consulting with the doctor.

To address these issues, the proposed strategy in FGD was to create INR monitoring guidelines and distribute to relevant healthcare professionals. Additionally, it was suggested to centralize anticoagulant services using point-of-care testing, except for those with supratherapeutic INR. This approach would enable patients to check their results and consult with the doctors on the same day. Numerous studies have shown that point-of-care testing provides valid results comparable to laboratory examination, except for supratherapeutic INR values (Bhat et al. 2020; Vazquez et al., 2017). Moreover, intensive education can be provided on the significance of more frequent INR monitoring in subtherapeutic or supratherapeutic conditions to understand the importance of dose adjustment.

Compliance and Knowledge Challenges

Patients with good knowledge and compliance tend to have better anticoagulant control (Chen et al., 2013; Sevilla-Cazes et al., 2017; Balkhi et al., 2018).

The 43.8% and 56.2% of the patients were categorized as compliant and non-compliant respectively (Table III). Based on the Chi-square

test, the percentage of patients who were compliant in the TTR group ≥ 65% was significantly higher than the < 65% group (p=0.001). Warfarin was considered a high-risk drug due to its effectiveness and safety being dependent on a narrow range of INR. Therefore, compliance is a critical factor to maintain patients within their therapeutic range (Ageno et al., 2012).

Table III. Description of Compliance Among Patients

Level of Compliance	Percentage (%)
Compliant	43.8%
Non-compliant	56.2%

The reasons for non-compliance included (1) forgetting to take medication, (2) missing appointments due to work, (3) self-adjusting dose, usually because patients felt the dose received was very high (patients were afraid and did not understand dose adjustment according to the INR value), and (4) refusing to take medication due to the absence of symptoms, or poor understanding of the therapy objective. These observations suggested the need for an educational strategy to improve the compliance of patients in taking their medication. This was consistent with a study by Wang et al. (2014), which reported warfarin compliance of 34.5%, with only 39.1% of patients achieving optimal TTR control (Wang et al., 2014). According to other studies in Korea and China, only 27.0% and 32.3% of patients were compliant with warfarin treatment, respectively (Kim et al., 2010; Zhao et al., 2017).

Several studies showed that the knowledge levels of patients regarding warfarin were related to the outcome of therapy (Hanssens and Kheir, 2010; Matalqah et al., 2013; Al-Saikhan et al., 2018; Li et al., 2018). In this study, 39.5% and 60.5% of patients were found to have good and poor knowledge, respectively. The Chi-square test indicated that the percentage of patients with good knowledge was significantly higher in the TTR ≥ 65% than in the < 65% group (p=0.021). The areas of low knowledge were (1) monitoring INR when the target was not achieved, (2) interaction with diet, (3) the importance of informing the doctor/pharmacist when taking the new medication, (4) interaction with herbal remedies, (5) therapy targets, (6) the impact of not taking medication, (7) the purpose of therapy, and (8) how to manage missed doses. The results were consistent with studies conducted in other countries, where the areas of lowest knowledge included warfarin interaction with other drugs, the importance of maintaining dietary consistency, and the management of missed doses (Hanssens & Kheir, 2010; Smith et al., 2010; van Damme et al., 2011; Wang et al., 2014; Al-Saikhan et al., 2018).

Adequate knowledge is required to improve medication adherence, maintain consistent diets containing vitamin K, and avoid over-the-counter (OTC) drugs, supplements, or herbs interacting with warfarin. Moreover, patients are expected to actively inform healthcare providers about their ongoing therapy when receiving medications from doctors to avoid any potential drug interactions.

As a complex drug, warfarin therapy requires the provision of comprehensive education to patients in various areas. However, the existing education components do not include all the necessary areas for safe and effective use. The method predominantly utilized relied on verbal communication, which was less appealing and resulted in low retention. As a solution, a standardized education protocol was proposed, covering all the essential knowledge areas needed to properly use warfarin. The creation of a protocol was deemed necessary to ensure patients received consistent educational materials. Additionally, more engaging media are needed such as audiovisual materials, to enhance interest and comprehension. Several studies have shown that standardized education can increase TTR (Clarkesmith et al. 2013)

Drug-Drug Interactions Challenges

Based on the results, 14.6% of patients received other drugs that potentially interacted with warfarin, including amiodarone, azithromycin, rifampicin, and ciprofloxacin. The concomitant use of multiple medications impacted the INR, resulting in fluctuating, subtherapeutic, and supratherapeutic values. However, no major bleeding incidence was observed as a consequence of this drug interaction. Patients receiving rifampicin needed frequent dose increments to achieve therapeutic INR, as also reported by a previous study (Yang et al., 2021). Meanwhile, others receiving amiodarone required frequent monitoring and dosing reduction due to increased INR (Sanoski et al., 2002, Holm et al., 2017). The strategies proposed to minimize these challenges included 1) more frequent monitoring for patients receiving other drugs interacting with warfarin. Several publications recommend monitoring at specific time intervals depending on the type of

drug (Sanoski et al., 2002, Holm et al., 2017, Lane et al., 2014). INR monitoring at these specific times is crucial for dose adjustments to avoid supratherapeutic and subtherapeutic conditions. This was also a challenging task due to the cost required for testing and the willingness of patients to visit the hospital. 2) There is an urgent need to prepare local guidelines for the management of drug interactions and distribute to all concerned health workers. The availability of these guidelines is expected to facilitate the implementation by healthcare providers. This will promote a more standardized approach to treatment for each patient. 3) Comprehensive reconciliation **is** needed regarding other drugs/supplements/herbs consumed by patients from other polyclinics and those purchased on a self-medication basis. This would help ensure that no critical information is missing and facilitate appropriate management of potential interaction. 4) The drug interaction component should be explained more intensively in patient education materials.

CONCLUSION

In conclusion, various challenges were found to be associated with achieving optimal warfarin control. These included dosing consistency, INR monitoring, medication adherence, and knowledge of warfarin among patients, as well as drug interactions. Several important strategies were also proposed to address these challenges. A holistic and systematic approach combining various solutions may prove to be the most appropriate way forward. This includes developing validated algorithm dosing protocols, using adjustment tools, establishing INR monitoring protocols, utilizing point-of-care testing, and centralizing anticoagulant services in one location to enhance collaboration between healthcare professionals. Additionally, creating standardized and engaging educational materials to improve knowledge and adherence, as well as providing training to all healthcare professionals may be necessary steps to improve the management of anticoagulation therapy.

ACKNOWLEDGMENTS

The authors are grateful to Airlangga University for the financial support provided and also to Airlangga University Teaching Hospital for granting permission to use the data provided in this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Alghadeeer, S., Alzahrani, A. A., Alalayet, W. Y., Alkharashi, A. A., & Alarifi, M. N. (2020). Anticoagulation control of warfarin in pharmacist-led clinics versus physician-led clinics: A prospective observational study. *Risk Management and Healthcare Policy*, *13*, 1175–1179. https://doi.org/10.2147/RMHP.S248222.

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*(2), e44S-e88S. https://doi.org/10.1378/CHEST.11-2292.

Akbar, M. R., Febrianora, M., & Iqbal, M. (2023). Warfarin usage in patients with atrial fibrillation undergoing hemodialysis in the Indonesian population. *Current Problems in Cardiology*, *48*(5), 101104.https://doi.org/10.1016/j.cpcardiol.2022.101104.

Al-Saikhan, F. I., Abd-Elaziz, M. A., Ashour, R. H., & Langaee, T. (2018). Anticoagulation Therapy: For Patients Attitude, Knowledge and Concerns Regarding their Effects on International Normalized Ratios in Saudi Arabia. *Inter J Pharmacol*, *14*(2), 285-90. https://doi.org/10.4066/biomedicalresearch.29-17-2761.

Balkhi, B., Al-Rasheedi, M., Elbur, A. I., & Alghamadi, A. (2018). Association between satisfaction with and adherence to warfarin therapy on the control of international normalized ratio: a hospital-based study in Saudi Arabia. *Saudi Pharmaceutical Journal*, *26*(1), 145-149.https://doi.org/10.1016/J.JSPS.2017.11.010.

Bhat, M., Abuzied, Y., Fagih, Z., Wani, T., Gawan, I., Andalay, E. M., & AlSheef, M. (2020). Efficacy of point-of-care for INR testing compared to standard laboratory methods at a tertiary care hospital in Saudi Arabia. Global Journal on Quality and Safety in Healthcare, 3(3), 98-104.https://doi.org/10.36401/JQSH-19-36

Chen, S. Y., Wu, N., Gulseth, M., LaMori, J., Bookhart, B. K., Boulanger, L., ... & Schein, J. (2013). One-year adherence to warfarin treatment for venous thromboembolism in high-risk

patients and its association with long-term risk of recurrent events. *Journal of Managed Care Pharmacy*, *19*(4), 291-301. https://doi.org/https://doi.org/10.18553/jmcp.2013.19.4.291.

Clarkesmith, D. E., Pattison, H. M., Lip, G. Y., & Lane, D. A. (2013). Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomized trial. *PloS one*, *8*(9), e74037. https://doi.org/10.1371/journal.pone.0074037

Dimberg, I., Grzymala-Lubanski, B., Hägerfelth, A., Rosenqvist, M., Svensson, P., & Själander, A. (2012). Computerized assistance for warfarin dosage—effects on treatment quality. *European journal of internal medicine*, *23*(8), 742-744. https://dx.doi.org/10.1016/j.ejim.2012.07.0

Khudair, I. F., & Hanssens, Y. I. (2010). Evaluation of patients' knowledge on warfarin in outpatient anticoagulation clinics in a teaching hospital in Qatar. *Saudi Med J*, *31*(6), 672-677.

Holm, J., Lindh, J.D., Anderson, M.L. Mannheimer, B., (2017). The Effect Of Amiodaron On Warfarin Anticoagulation; A Register-Based Nationwide Cohort Study Involving The Swedish Population. *J Thromb Haemost*. 15;446-453. https://doi.org/10.1111/jth.13614.

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., Conti, J. B., Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Murray, K. T., Sacco, R. L., Stevenson, W. G., Tchou, P. J., Tracy, C. M., & Yancy, C. W. (2014). 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*, *64*(21), e1–e76. https://doi.org/10.1016/J.JACC.2014.03.022.

Kavousi, M. (2020). Differences in Epidemiology and Risk Factors for Atrial Fibrillation Between Women and Men. *Frontiers in Cardiovascular Medicine*, *7*(3). https://doi.org/10.3389/FCVM.2020.00003/BIBTEX.

Kim, Y. K., Nieuwlaat, R., Connolly, S. J., Schulman, S., Meijer, K., Raju, N., Kaatz, S., & Eikelboom, J. W. (2010). Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in the therapeutic range: A pilot study. *Journal of Thrombosis and Haemostasis*, *8*(1), 101–106. https://doi.org/10.1111/j.1538-7836.2009.03652.x.

Kripalani, S., Risser, J., Gatti, M. E., & Jacobson, T. A. (2009). Development and evaluation of the Adherence to Refills and Medications scale (ARMS) among low-literacy patients with chronic disease. *Value in Health*, *12*(1), 118–123. https://doi.org/10.1111/j.1524-4733.2008.00400.x.

Lane, M. A., Zeringue, A., & McDonald, J. R. (2014). Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *American Journal of Medicine*, *127*(7), 657-663.e2. https://doi.org/10.1016/j.amjmed.2014.01.044.

Li, X., Sun, S., Wang, Q., Chen, B., Zhao, Z., & Xu, X. (2018). Assessment of patients' warfarin knowledge and anticoagulation control at a joint physician- and pharmacist-managed clinic in China. *Patient Preference and Adherence*, *12*, 783. https://doi.org/10.2147/PPA.S156734.

Lip, G. Y. H., Banerjee, A., Boriani, G., Chiang, C. E., Fargo, R., Freedman, B., Lane, D. A., Ruff, C. T., Turakhia, M., Werring, D., Patel, S., & Moores, L. (2018). Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*, *154*(5), 1121–1201. https://doi.org/10.1016/j.chest.2018.07.040.

Magnussen, C., Niiranen, T. J., Ojeda, F. M., Gianfagna, F., Blankenberg, S., Njølstad, I., Vartiainen, E., Sans, S., Pasterkamp, G., Hughes, M., Costanzo, S., Donati, M. B., Jousilahti, P., Linneberg, A., Palosaari, T., de Gaetano, G., Bobak, M., den Ruijter, H. M., Mathiesen, E., … Schnabel, R. B. (2017). Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: Results from the biomarcare consortium (Biomarker for cardiovascular risk assessment in Europe). *Circulation*, *136*(17), 1588–1597. https://doi.org/10.1161/CIRCULATIONAHA.117.028981.

Matalqah, L. M., Radaideh, K. M., Sulaiman, S. A. S., Hassali, M. A., & Kader, M. A. S. A. (2013). Relationship between patients' warfarin knowledge and anticoagulation control: results of a validated tool in Malaysia. Affiliation. *J Pharm Biomed Sci*, *30*(30), 967–974.

Minister of Health of Indonesia. (2021). *Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/6485/2021 Tentang Formularium Nasional*. Retrieved from Kmk No. Hk.01.07-menkes-6485-2021 Ttg Formularium Nasional [nl2z4zwwy2l8] (doku.pub).

Nishimura, R. A., Otto, C. M., Bonow, R. O., Carabello, B. A., Erwin, J. P., Fleisher, L. A., Jneid, H., Mack, M. J., McLeod, C. J., O'Gara, P. T., Rigolin, V. H., Sundt, T. M., & Thompson, A. (2017). 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *70*(2), 252–289. https://doi.org/10.1016/J.JACC.2017.03.011.

Noor, A., Khan, M. A., Warsi, A., Aseeri, M., & Ismail, S. (2021). Evaluation of a pharmacist vs. Haematologist-managed anticoagulation clinic: A retrospective cohort study. *Saudi pharmaceutical journal*: *SPJ*: *the official publication of the Saudi Pharmaceutical Society*, *29*(10), 1173–1180. https://doi.org/10.1016/j.jsps.2021.08.015.

Putriana, N. A., Lestari, K., Barliana, M. I., & Hartini, S. (2017). Effects of Pharmacist Counseling on Compliance and International Normalized Ratio Score on Outpatients Receiving Warfarin at Dr. Hasan Sadikin Bandung Hospital West Java, Indonesia. *Asian Journal of Pharmaceutical and Clinical Research*, 10(Special Issue May): 72–75. https://dx.doi.org/10.22159/ajpcr.2017.v10s2.19492.

Rahmatini, R., Aliska, G., Usman, E., Yanni, M., & Ilmiawati, C. (2020). Plasma warfarin level and international normalized ratio do not correlate with bleeding events in Indonesian patients of Minangkabau ethnicity with atrial fibrillation. Open Access Macedonian Journal of Medical Sciences, 8(B), 192-197. https://doi.org/10.3889/oamjms.2020.3436.

Rose, A. J., Hylek, E. M., Berlowitz, D. R., Ash, A. S., Reisman, J. I., & Ozonoff, A. (2011). Prompt repeat testing after out-of-range INR values, a quality indicator for anticoagulation care. *Circulation: Cardiovascular Quality and Outcomes*, *4*(3), 276–282. https://doi.org/10.1161/CIRCOUTCOMES.110.960096.

Rosendaal, F. R., Cannegieter, S. C., van der Meer, F. J. M., & Briet, E. (1993). A method to determine the optimal intensity of oral anticoagulant therapy. *Thrombosis and Haemostasis*, *69*(3), 236–239. https://doi.org/10.1055/S-0038-1651587/ID/OR_8.

Sanoski, C. A., & Bauman, J. L. (2002). Clinical observations with the amiodarone/warfarin interaction: dosing relationships with long-term therapy. *Chest*, 121(1), 19-23. https://dx.doi.org/10.1378/chest.121.1.19

Sekarsari DD, Ardhianto P, Kresnoadi E, & Sobirin, M. A. (2021). Time in Therapeutic Range (TTR) in atrial fibrillation with warfarin therapy in Semarang, Indonesia. *Jurnal Kedokteran Diponegoro*, *10(5)*, 315-319. https://doi.org/10.14710/dmj.v10i5.30046.

Sevilla-Cazes, J., Finkleman, B. S., Chen, J., Brensinger, C. M., Epstein, A. E., Streiff, M. B., & Kimmel, S. E. (2017). Association Between Patient-Reported Medication Adherence and Anticoagulation Control. *The American Journal of Medicine*, *130*(9), 1092-1098.e2. https://doi.org/10.1016/J.AMJMED.2017.03.038.

Singer, D. E., Hellkamp, A. S., Piccini, J. P., Mahaffey, K. W., Lokhnygina, Y., Pan, G., Halperin, J. L., Becker, R. C., Breithardt, G., Hankey, G. J., Hacke, W., Nessel, C. C., Patel, M. R., Califf, R. M., Fox, K. A. A., & ROCKET AF Investigators. (2013). Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *Journal of the American Heart Association*, *2*(1). https://doi.org/10.1161/JAHA.112.000067.

Smith, M. B., Christensen, N., Wang, S., Strohecker, J., Day, J. D., Weiss, J. P., Crandall, B. G., Osborn, J. S., Anderson, J. L., Horne, B. D., Muhlestein, J. B., Lappe, D. L., Moss, H., Oliver, J., Viau, K., & Bunch, T. J. (2010). Warfarin Knowledge in Patients with Atrial

Fibrillation: Implications for Safety, Efficacy, and Education Strategies. *Cardiology*, *116*(1), 61–69. https://doi.org/10.1159/000314936.

The Joint Commission. (2017). Ambulatory health care 2018 national patient safety goals. Retrieved from https://www.jointcommission.org/assets/1/6/NPSG_Chapter_AHC_Jan2018.pdf.

U.S. Department of Health and Human Services, Office of Disease Promotion and Prevention. (2014). National action plan for adverse drug event prevention. Retrieved from https://health.gov/hcq/pdfs/ade-action-plan-508c.pdf.

van Damme, S., van Deyk, K., Budts, W., Verhamme, P., & Moons, P. (2011). Patient knowledge of and adherence to oral anticoagulation therapy after mechanical heart-valve replacement for congenital or acquired valve defects. *Heart & Lung*, *40*(2), 139-146. https://doi.org/10.1016/J.HRTLNG.2009.11.005.

van Spall, H. G., Wallentin, L., Yusuf, S., Eikelboom, J. W., Nieuwlaat, R., Yang, S., ... & Connolly, S. J. (2012). Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. *Circulation*, 126(19), 2309-2316. https://doi.org/10.1161/CIRCULATIONAHA.112.101808.

Vazquez, S. R., Fleming, R. P., & Johnson, S. A. (2017). Comparison of two point-of-care international normalized ratio devices and laboratory method. B*lood Coagulation & Fibrinolysis*, 28(7), 534-539. https://doi.org/10.1097/MBC.0000000000000633.

Wang, N., Qiu, S., Yang, Y., Zhang, C., Gu, Z. C., & Qian, Y. (2021). Physician-Pharmacist Collaborative Clinic Model to Improve Anticoagulation Quality in Atrial Fibrillation Patients Receiving Warfarin: An Analysis of Time in Therapeutic Range and a Nomogram Development. *Frontiers in pharmacology*, 12, 673302. https://doi.org/10.3389/fphar.2021.673302.

Wang, Y., Kong, MC, Lee, LH, Ng, HJ, & Ko, Y. (2014). Pengetahuan, kepuasan, dan kekhawatiran mengenai terapi warfarin dan hubungannya dengan kepatuhan warfarin dan kontrol antikoagulasi. *Penelitian trombosis*, *133* (4), 550-554. https://doi.org/10.1016/j.thromres.2014.01.002.

Wilson, A. S., Vazquez, S. R., Saunders, J. A., & Witt, D. M. (2022). Concordance of experienced-based maintenance warfarin dosing vs. algorithm-based dosing. *Thrombosis Update*, *6*, 100093. https://doi.org/10.1016/j.tru.2021.100093.

Woller, S. C., Stevens, S. M., Towner, S., Olson, J., Christensen, P., Hamilton, S., ... & Elliott, C. G. (2015). Computerized clinical decision support improves warfarin management and decreases recurrent venous thromboembolism. *Clinical and Applied Thrombosis/Hemostasis*, *21*(3), 197-203. https://doi.org/10.1177/1076029614550.

Yang, C. S., Boswell, R., & Bungard, T. J. (2021). A case series of the rifampin-warfarin drug interaction: focus on practical warfarin management. European Journal of Clinical Pharmacology, 77, 341-348. https://doi.org/10.1007/s00228-020-03057-x

Zhao, S., Zhao, H., Wang, X., Gao, C., Qin, Y., Cai, H., Chen, B., & Cao, J. (2017). Factors influencing medication knowledge and beliefs on warfarin adherence among patients with atrial fibrillation in China. *Patient Preference and Adherence*, *11*, 213–220. https://doi.org/10.2147/PPA.S120962.