



Evaluation of Warfarin Therapy and Achievement of Target Time in Therapeutic Range in Patients with Atrial Fibrillation at Cardiac Care Center Outpatient Clinic of Dr. Soetomo General Hospital

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Abstract

Warfarin remains an important oral anticoagulant for patients with atrial fibrillation (AF); however, achieving adequate anticoagulation requires appropriate prescribing, individualized dose adjustment, and regular monitoring. This study evaluated warfarin utilization, drug-related problems, and achievement of target time in therapeutic range (TTR) among patients with AF at the Integrated Cardiac Care Center Outpatient Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. This retrospective observational study reviewed the medical records of 106 eligible patients who attended the clinic between December 2023 and January 2024. Warfarin indications, dosing practices, international normalized ratio (INR) monitoring intervals, potential drug–drug interactions, and suspected adverse drug reactions were evaluated. TTR was calculated using the Rosendaal linear interpolation method. Appropriate indications for warfarin therapy were identified in 83.96% of patients. Mean concordance with the warfarin dosing algorithm was 43.20%, while 35.48% of 885 INR monitoring events occurred within the recommended monitoring intervals. Sixty-five potential drug–drug interaction events and nine bleeding events classified as Bleeding Academic Research Consortium (BARC) type 2 were documented. The mean TTR was $43.15 \pm 25.28\%$, and only 18.87% of patients achieved a $TTR \geq 65\%$. These findings indicate that appropriate indications for warfarin therapy did not consistently correspond to adequate anticoagulation control. Warfarin management should therefore emphasize individualized dose adjustment, timely INR monitoring, and systematic medication review. These findings provide a basis for improving anticoagulation management services; however, the retrospective observational design precludes causal inference.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and represents a major global health burden, affecting approximately 50 million people worldwide in 2020 (Tsao et al., 2023). Its prevalence increases substantially with age and varies across ethnic populations, with generally lower rates reported among Asian populations than among European populations (Murakoshi & Aonuma, 2013). In Indonesia, recent national prevalence data remain limited. However, the MONICA observational study conducted in an urban population in Jakarta reported an AF prevalence of approximately 0.2% (PERKI, 2019). AF is characterized by uncoordinated atrial electrical activity resulting in ineffective atrial

contraction and an irregular ventricular response and may present with palpitations, dyspnea, chest discomfort, or no symptoms (Hindricks et al., 2021; Staerk et al., 2017).

AF is associated with serious cardiovascular complications, particularly thromboembolic stroke, heart failure, coronary heart disease, and increased mortality (Kirchhof et al., 2016; Pranata et al., 2017). Patients with AF have an approximately fivefold higher risk of stroke than individuals without AF, and AF-related strokes are generally more severe, more likely to recur, and associated with higher mortality (Hendriks & Heidbüchel, 2019; Tarigan, 2017). AF was reported to account for approximately 20% of cardioembolic strokes and was associated with a substantial burden of cardiovascular mortality in a Canadian population-based study (Gladstone et al., 2009). Furthermore, the prevalence of AF among patients with stroke in Southeast Asia has been reported to range from 2.6% to 23.04%, emphasizing the importance of effective stroke-prevention strategies in this population (Pinzon & Karunawan, 2020).

The management of AF includes ventricular rate control, rhythm control, and anticoagulation for the prevention of thromboembolic events (AHA, 2019; PERKI, 2019). Oral anticoagulant therapy is recommended for eligible patients with AF according to their thromboembolic and bleeding risks, commonly assessed using clinical risk-stratification tools such as the CHA₂DS₂-VASc score (Kirchhof et al., 2016; Lip et al., 2018). Warfarin remains an important vitamin K antagonist (VKA), particularly when direct oral anticoagulants are unsuitable or contraindicated and in specific clinical circumstances requiring VKA therapy. Warfarin therapy has been shown to substantially reduce the risks of stroke and mortality in patients with AF (Kirchhof et al., 2016; PERKI, 2019). For most patients with AF receiving warfarin, the recommended international normalized ratio (INR) target range is 2.0–3.0, although different targets may apply to patients with certain mechanical prosthetic heart valves. Time in therapeutic range (TTR) is widely used to evaluate the quality of warfarin anticoagulation, with higher TTR values indicating more consistent anticoagulation control (Lip et al., 2018).

The difficulty of maintaining adequate anticoagulation control is evident in international research. Singer et al. (2013), analyzing 6,983 warfarin-treated participants from 45 countries in the ROCKET AF trial, reported a mean individual TTR of 55.2%, with regional means ranging from 35.9% to 64.1%. Previous warfarin exposure was also associated with treatment quality: experienced users had a mean TTR of 61.1%, compared with 47.4% among patients without previous VKA treatment. These findings demonstrate substantial variation in anticoagulation control even within a clinical trial setting. They also suggest that anticoagulation quality is influenced by the context in which treatment is delivered, supporting the need for evaluations of routine clinical practice.

Within Southeast Asia, prospective evidence further demonstrates the clinical relevance of anticoagulation quality. Krittayaphong et al. (2023), using data from the Thai COOL-AF registry, examined blood pressure control and TTR among patients receiving care consistent with the Atrial Fibrillation Better Care (ABC) pathway. Achieving the blood pressure target and maintaining TTR $\geq 65\%$ provided additional value in reducing adverse clinical outcomes. These findings support the evaluation of anticoagulation quality alongside other components of AF management. They also provide a regional basis for examining the proportion of patients achieving a specified TTR threshold as a clinically meaningful indicator while recognizing that

the desired quality of anticoagulation control may vary according to the guideline or quality standard applied.

Evidence from Indonesia indicates that suboptimal warfarin control is also a relevant domestic concern. Sekarsari et al. (2021) conducted a descriptive study involving 111 patients with AF at Dr. Kariadi Hospital, Semarang, and reported a mean TTR of 53.75%. Only 29 patients (26.12%) achieved TTR $\geq 70\%$, whereas 82 patients (73.88%) remained below this threshold. These findings demonstrate challenges in maintaining adequate anticoagulation control within an Indonesian hospital setting, although they cannot be generalized to all institutions or patient populations. Differences in clinical characteristics, follow-up arrangements, monitoring practices, and prescribing patterns make institution-specific assessments necessary. Accordingly, evidence from Semarang provides a rationale for evaluating warfarin management in other Indonesian cardiac outpatient settings.

Beyond documenting suboptimal TTR, previous research has investigated potentially modifiable treatment practices. Van Spall et al. (2012) evaluated 6,022 patients with nonvalvular AF from 912 centers in 44 countries participating in the RE-LY trial. Greater adherence to a warfarin dosing algorithm was associated with better anticoagulation control, and each 10% increase in algorithm-consistent dosing at the center level predicted a 6.12% increase in TTR. The analysis also identified an association with a lower rate of the composite outcome of stroke, systemic embolism, or major hemorrhage. These findings support the evaluation of dose-adjustment practices as part of anticoagulation management audits while recognizing that individualized clinical circumstances may justify deviations from standardized dosing algorithms.

Taken together, the reviewed studies demonstrate that TTR varies substantially across clinical settings and that treatment practices warrant closer evaluation. However, differences in study populations and analytical objectives leave an important practical question for the present research: how do prescribing appropriateness, dose adjustment, INR monitoring, potential drug–drug interactions, and documented bleeding events coexist with TTR achievement within the same outpatient population? The research gap addressed in this study is therefore contextual and operational. Evidence from international clinical trials and other Indonesian hospitals cannot directly characterize warfarin management at the Integrated Cardiac Care Center Outpatient Clinic of Dr. Soetomo General Academic Hospital. An integrated local assessment is therefore needed to characterize both anticoagulation quality and the treatment processes associated with its management.

This assessment is particularly relevant during maintenance therapy, when continued warfarin treatment requires appropriate INR monitoring, dose adjustment, medication review, and timely clinical reassessment. At the study clinic, reviewing longitudinal medical records provides an opportunity to evaluate whether warfarin management is consistent with patients' clinical indications and recorded INR values. The importance of this assessment lies in identifying potentially modifiable shortcomings in ongoing anticoagulation management rather than relying solely on individual INR measurements or the presence of an anticoagulant prescription. Evaluating drug-related problems alongside TTR may help clinicians identify areas requiring improvement, including INR monitoring schedules, medication reconciliation, potential drug–drug interactions, and documentation of dose-adjustment decisions.

The distinctive contribution of this study lies in integrating several dimensions of warfarin utilization with a longitudinal measure of anticoagulation quality within an Indonesian cardiac outpatient setting. Its proposed novelty is the combined assessment of warfarin indications, dosing practices, INR monitoring intervals, potential drug–drug interactions, and suspected adverse drug reactions alongside TTR achievement, rather than a claim that these variables have never previously been investigated. This approach provides a detailed institutional profile of warfarin management and therapeutic control. Because the study is retrospective and primarily descriptive, its contribution is limited to characterizing current practice and identifying priorities for improvement; it cannot establish that any particular drug-related problem causes inadequate TTR.

Accordingly, this study aimed to evaluate warfarin utilization and achievement of the target TTR among patients with AF receiving maintenance therapy at the Integrated Cardiac Care Center Outpatient Clinic of Dr. Soetomo General Academic Hospital, Surabaya. Specifically, the study assessed warfarin indications, dose-adjustment practices, INR monitoring intervals, potential drug–drug interactions, and documented suspected adverse drug reactions and calculated TTR using the Rosendaal linear interpolation method. The proportion of patients achieving the study-defined threshold of $TTR \geq 65\%$ was evaluated as an indicator of anticoagulation quality. The findings are expected to provide an evidence base for local clinical audits, coordinated pharmacist–physician medication reviews, and future prospective interventions aimed at improving the consistency, quality, and safety of warfarin management.

METHOD

Study Design and Setting

This retrospective observational study employed a descriptive design to evaluate warfarin utilization among patients with atrial fibrillation (AF) receiving outpatient care at the Integrated Cardiac Care Center of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Medical records of eligible patients who attended the clinic between December 2023 and January 2024 were retrospectively reviewed. The assessment included warfarin-related drug-related problems (DRPs), including the appropriateness of treatment indications and dosing, international normalized ratio (INR) monitoring intervals, potential drug–drug interactions, suspected adverse drug reactions, and anticoagulation quality as measured by time in therapeutic range (TTR). The study protocol was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (Approval No. 1601/LOE/301.4.2/III/2024).

Study Population

The study population consisted of adult patients diagnosed with AF who received warfarin therapy during the maintenance phase at the Integrated Cardiac Care Center Outpatient Clinic. Eligible patients had been receiving warfarin for at least three months and had a minimum of three INR measurements recorded within the previous year, allowing the calculation of TTR using the Rosendaal linear interpolation method. Patients with severe liver disease, advanced chronic kidney disease (CKD stage 4–5 or estimated glomerular filtration rate <30 mL/min/1.73 m²), or active malignancy were excluded because these conditions may substantially alter anticoagulation management and INR stability.

Sampling Method

A total sampling approach was employed. All patients meeting the inclusion and exclusion criteria during the study period were included in the analysis. Patients were eligible if they had a confirmed diagnosis of AF based on electrocardiographic examination, received maintenance warfarin therapy, attended follow-up visits during the study period, and had complete clinical and laboratory data required for analysis.

Data Collection Procedure

Data were obtained retrospectively from patients' electronic medical records using a standardized data collection form. The collected variables included demographic characteristics (age, sex), thromboembolic risk factors, clinical manifestations of bleeding, laboratory parameters (INR, hemoglobin, serum creatinine, and estimated glomerular filtration rate, when available), warfarin therapy characteristics (weekly dose, dosing frequency, and dose adjustment), INR monitoring intervals, concomitant medications, and potential adverse drug reactions.

Warfarin utilization was evaluated by assessing several DRPs, including the appropriateness of indication, dosing, INR monitoring intervals, potential drug interactions, and adverse drug reactions. The appropriateness of warfarin indication for patients with non-valvular AF was assessed using the CHA₂DS₂-VASc score according to current guideline recommendations, whereas all patients with valvular AF were considered to have appropriate indications for anticoagulation. Dose appropriateness was evaluated according to an evidence-based warfarin dosing algorithm. The recommended INR monitoring interval was defined as every 1–3 months for patients with stable therapeutic INR values and every 7–14 days for patients with subtherapeutic or supratherapeutic INR values. Bleeding events were classified according to the Bleeding Academic Research Consortium (BARC) criteria. The quality of anticoagulation control was assessed using the TTR, calculated by the Rosendaal linear interpolation method based on at least three INR measurements obtained during the previous year.

Data Processing and Analysis

Data were entered into a standardized database and verified for completeness prior to analysis. Descriptive statistical analysis was performed to summarize patient characteristics, thromboembolic risk profiles, warfarin utilization patterns, INR monitoring practices, potential drug interactions, adverse drug reactions, and drug-related problems. Continuous variables were presented as means with standard deviations or medians with interquartile ranges, depending on data distribution, whereas categorical variables were reported as frequencies and percentages. TTR values were calculated using the Rosendaal linear interpolation method and expressed as percentages to evaluate the quality of anticoagulation control. All analyses were descriptive because the primary objective of the study was to characterize warfarin utilization and identify DRPs among patients with AF.

RESULTS AND DISCUSSION

This study evaluated warfarin utilization among patients with AF receiving maintenance therapy at the Integrated Cardiac Care Center Outpatient Clinic of Dr. Soetomo General Academic Hospital. The evaluation included warfarin prescribing patterns, dosing regimen, dosing frequency, INR monitoring intervals, TTR, and DRPs, including the appropriateness of

warfarin indication, dosing, INR monitoring intervals, potential drug interactions, and adverse drug reactions. A total of 129 medical records of patients with AF receiving maintenance warfarin therapy were initially screened for eligibility. After applying the predefined inclusion and exclusion criteria and reviewing data from the hospital electronic medical record system, 106 patients met the eligibility criteria and were included in the final analysis.

Patient Characteristics

The characteristics of patients in this study are shown in **Table 1**. Female patients accounted for a slightly higher proportion than males (51.89% vs. 48.11%). Although previous studies have reported that AF is more prevalent in men, women with AF generally have a higher risk of thromboembolic events and stroke, highlighting the importance of appropriate anticoagulation therapy regardless of sex (Siddiqi et al., 2022; Rago et al., 2023). The predominance of female patients observed in this study may reflect the characteristics of the study population after applying the predefined inclusion and exclusion criteria. Most patients were younger than 60 years (72.64%), whereas only 27.36% were aged ≥ 60 years. Although the incidence of AF generally increases with advancing age, the relatively younger population in this study may be explained by the increasing use of non-vitamin K antagonist oral anticoagulants (NOACs) among older patients, leaving younger patients more likely to receive warfarin therapy (Kavousi, 2020; Ko et al., 2022). Regarding occupation, the largest proportion of patients was classified as “others” (43.40%), followed by private employees (27.36%), reflecting the heterogeneous socioeconomic background of the study population. Non-valvular AF was the predominant indication for warfarin therapy, accounting for 86.79% of patients, whereas valvular AF represented only 13.21%. This finding is consistent with previous studies reporting that non-valvular AF is considerably more common than valvular AF in clinical practice (Dhungana & Ghimire, 2020; Okuno et al., 2020). Because therapeutic INR targets differ between valvular AF (2.5–3.5) and non-valvular AF (2.0–3.0), the type of AF has important implications for warfarin dose adjustment and anticoagulation monitoring (January et al., 2019). More than half of the patients had received warfarin therapy for at least one year (53.77%), and the mean number of concomitant medications was 4.00 ± 1.33 . Long-term anticoagulation is recommended for patients with persistent stroke risk when the benefits of therapy outweigh the risk of bleeding, while concomitant medication use may increase the complexity of warfarin management because of its high potential for drug interactions (January et al., 2019; Fox et al., 2013).

Table 1. AF patients’ clinical profiles and sociodemographic data

Characteristics	Category	N = 106	%
Age	<60 years	77	72.64
	≥ 60 years	29	27.36
Gender	Male	51	48.11
	Female	55	51.89
Occupation	Private employee	29	27.36
	Civil servant	2	1.89
	Self-employed	7	6.60
	Homemaker	18	16.98
	Retired	2	1.89
	Student	2	1.89
	Others	46	42.40
Indication for Warfarin Therapy	Valvular AF (female)	4	3.77

Characteristics	Category	N = 106	%
Duration of Warfarin Therapy	Valvular AF (male)	10	9.43
	Non-valvular AF (female)	51	48.11
	Non-valvular AF (male)	41	38.68
	<1 year	49	46.23
	≥1 year	57	53.77
Number of Concomitant Medication, mean ± SD		4.00 ± 1.33	-

Drug Related Problems

Appropriateness of Warfarin Therapy Based on the CHA₂DS₂-VASc Score

The appropriateness of warfarin therapy in patients with non-valvular AF based on the CHA₂DS₂-VASc score is presented in **Figure 1**. Appropriate warfarin prescribing was observed in 85.37% (35/41) of male patients and 78.43% (40/51) of female patients. Overall, 75 of 92 patients (81.52%) with non-valvular AF received warfarin according to the recommended CHA₂DS₂-VASc score criteria. When patients with valvular AF, who all had appropriate indications for anticoagulation, were included, 89 of 106 patients (83.96%) received warfarin appropriately, whereas 17 patients (16.04%) received warfarin without guideline-recommended indications. Current clinical guidelines recommend oral anticoagulation for all patients with valvular AF and for patients with non-valvular AF according to their CHA₂DS₂-VASc score to balance the benefits of stroke prevention against the risk of bleeding. Warfarin therapy was considered appropriate for male patients with a CHA₂DS₂-VASc score ≥1 and for female patients with a CHA₂DS₂-VASc score ≥2, whereas therapy was considered inappropriate for male patients with a score of 0 and female patients with scores of 0–1, in accordance with current guideline recommendations. The high proportion of appropriate prescribing observed in this study suggests that prescribing practices at the study center were generally consistent with contemporary guideline recommendations. However, approximately one-sixth of patients still received warfarin without clear guideline-based indications. Inappropriate anticoagulant prescribing may unnecessarily increase bleeding risk without providing substantial thromboembolic protection, particularly in patients with a low predicted stroke risk. Therefore, routine assessment of the CHA₂DS₂-VASc score before initiating anticoagulation remains essential to optimize the benefit-risk balance of warfarin therapy (Kirchhof et al., 2016; Lip et al., 2018).

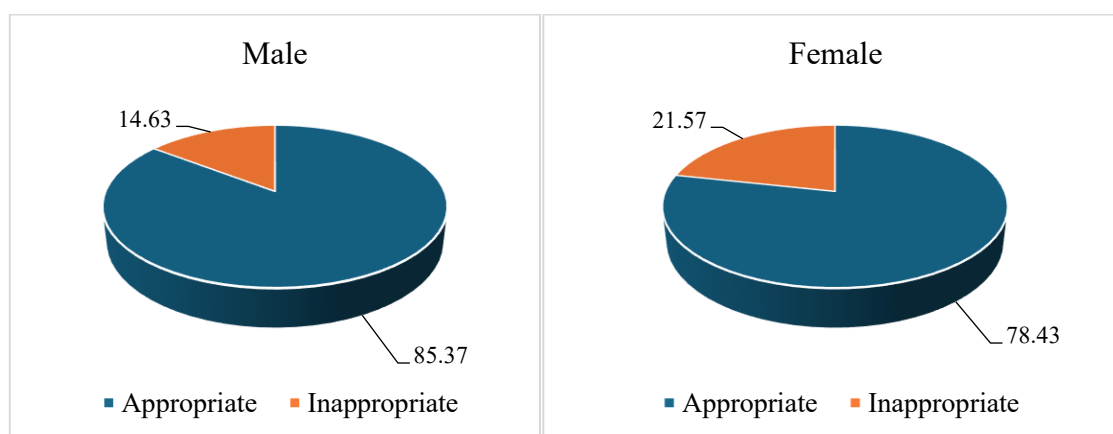


Figure 1. Appropriateness of warfarin therapy indication in patient with non-valvular AF based on CHA₂DS₂-VASc Score

Appropriateness of Warfarin Dose Adjustment According to the Dosing Algorithm

The appropriateness of warfarin dose adjustment according to the dosing algorithm is presented in Table 2. A total of 885 warfarin dosing decisions were evaluated during the study period, with an overall mean appropriateness of $43.20 \pm 22.51\%$. Among 178 dosing decisions requiring a 10–20% dose increase for patients with $\text{INR} \leq 1.50$, 71 (8.02%) were adjusted according to the recommended algorithm, whereas 107 (12.08%) were managed differently. Likewise, among 197 dosing decisions requiring a 10% dose increase for $\text{INR} 1.51\text{--}2.49$, only 9 (1.02%) followed the recommended algorithm. For patients whose INR was within the therapeutic range, 338 dosing decisions were identified, and the majority (284; 32.09%) appropriately maintained the current warfarin dose. In contrast, among 115 dosing decisions requiring a 10% dose reduction for $\text{INR} 3.00\text{--}3.99$, only 9 (1.02%) were consistent with the dosing algorithm. Similarly, of 44 dosing decisions requiring warfarin to be held for one day followed by a 10% dose reduction for $\text{INR} 4.00\text{--}4.99$, only 2 (0.23%) were managed according to the recommended strategy. For 13 dosing decisions with $\text{INR} \geq 5.00$, 6 (0.68%) appropriately followed the recommendation to temporarily hold warfarin and restart therapy with a 10–20% lower dose once the INR had returned to the therapeutic range. During the study period, two patients required individualized dose adjustment because of clinically significant drug interactions involving fenofibrate and amiodarone. Such interactions may alter warfarin pharmacokinetics and increase anticoagulant activity, necessitating closer INR monitoring and individualized dose modification. Although standardized dosing algorithms improve the consistency of warfarin management, clinicians may appropriately deviate from these recommendations when clinically important drug interactions or patient-specific factors are present (van Spall et al., 2012).

Table 2. Appropriateness of warfarin dose adjustment according to the dosing algorithm

Dose Adjustment Recommendation	Dose Adjustment Implemented	N = 885	%
Increase weekly dose by 10–20% if $\text{INR} \leq 1.50$	Increase dose by 10–20%	71	8.02
	Increase dose by <10%	35	3.95
	Increase dose by >20%	21	2.37
	No dose adjustment	40	4.52
	Decrease dose	11	1.24
Increase weekly dose by 10% if $\text{INR} 1.51\text{--}2.49$	Increase dose by 10%	9	1.02
	Increase dose by <10%	53	5.99
	Increase dose by >10%	57	6.44
	No dose adjustment	67	7.57
	Decrease dose	11	1.24
Maintain the current dose if INR is within the therapeutic range	No dose adjustment	284	32.08
	Increase dose	25	2.82
	Decrease dose	29	3.28
	Decrease dose by 10%	9	1.02
Decrease weekly dose by 10% if $\text{INR} 3.00\text{--}3.99$	Decrease dose by <10%	25	2.82
	Decrease dose by >10%	32	3.62
	No dose adjustment	42	4.75
	Increase dose	7	0.79
	Hold warfarin for 1 day and decrease the weekly dose by 10%	2	0.23
Hold warfarin for 1 day and decrease the weekly dose by 10% if $\text{INR} 4.00\text{--}4.99$	Decrease the weekly dose by 10% without holding warfarin	4	0.45
	Decrease the weekly dose by <10%	14	1.58
	Decrease the weekly dose by >10%	16	1.81
	No dose adjustment	7	0.79

Dose Adjustment Recommendation	Dose Adjustment Implemented	N = 885	%
Hold warfarin and restart with a 10–20% lower weekly dose after INR returns to the therapeutic range (INR ≥ 5.00)	Increase dose	1	0.11
	Hold warfarin and restart with a 10–20% lower weekly dose after INR returns to the therapeutic range	6	0.68
	Decrease the weekly dose without holding warfarin	7	0.79

Appropriateness of INR Monitoring Intervals

The appropriateness of INR monitoring intervals according to the dosing algorithm is presented in **Table 3**. A total of 885 INR monitoring events were evaluated. Among 343 monitoring events in which the INR was within the therapeutic range, 204 (59.47%) were monitored at the recommended interval of 1–3 months, whereas 135 (39.36%) were monitored in less than one month and 4 (1.17%) after more than three months. For 542 monitoring events in which the INR was outside the therapeutic range, only 110 (20.29%) were monitored at the recommended interval of 7–14 days. Most patients (415; 76.57%) underwent repeat INR testing more than 14 days later, while 17 (3.14%) were monitored within 7 days. Overall, 314 of 885 monitoring events (35.48%) complied with the recommended monitoring intervals, whereas 571 (64.52%) did not. The low adherence to guideline-recommended INR monitoring intervals may delay dose adjustment in patients with subtherapeutic or supratherapeutic INR values, thereby increasing the risk of inadequate anticoagulation control. Regular INR monitoring enables timely dose modification and improves the likelihood of maintaining INR within the therapeutic range, which is essential for reducing the risks of thromboembolism and bleeding during warfarin therapy (van Spall et al., 2012).

Table 3. Appropriateness of INR monitoring intervals to the dosing algorithm

INR Status	Recommended Monitoring Interval	Actual INR Monitoring Interval	N = 885	%
Within the therapeutic range	Every 1–3 months	1–3 months	204	59.47
		<1 month	135	39.36
		>3 months	4	1.17
	Total INR monitoring		343	100.00
Outside the therapeutic range	Every 7–14 days	7–14 months	110	20.29
		<7 month	17	3.14
		>14 months	415	76.57
	Total INR monitoring		542	100.00

Potential Drug Interactions with Warfarin

Potential warfarin–drug interactions are summarized in Table 4. A total of 14 interacting drugs were identified, with 65 potential interaction occurrences. The most frequently identified interacting drugs were allopurinol (n=14), lansoprazole (n=12), aspirin (n=9), and paracetamol (n=8). Most interactions were classified as moderate, whereas only fenofibrate and amiodarone were categorized as major interactions. Major interactions with fenofibrate and amiodarone may substantially increase the anticoagulant effect of warfarin by elevating INR, thereby requiring close INR monitoring and appropriate warfarin dose adjustment. In contrast, most moderate interactions primarily increased bleeding risk or modestly affected INR, highlighting the importance of routine medication review and regular INR monitoring in patients receiving

multiple concomitant medications to minimize warfarin-related adverse events (Baxter & Stockley, 2010; Bungard et al., 2011; Di Minno et al., 2017).

Warfarin-Related Adverse Drug Reactions

Suspected warfarin-related adverse drug reactions are presented in Table 5. A total of nine bleeding events were identified among 106 patients, comprising petechial bleeding (n=1), gingival bleeding (n=1), ecchymosis (n=1), melena (n=2), hematuria (n=2), hemoptysis (n=1), and ocular bleeding (n=1). All events were classified as BARC type 2 bleeding, indicating clinically overt bleeding that required medical evaluation or intervention without fulfilling the criteria for major bleeding (Mehran et al., 2011). Most bleeding events occurred in patients with supratherapeutic INR values, supporting the established association between excessive anticoagulation and an increased risk of hemorrhage (Harter et al., 2015). Nevertheless, several bleeding events were observed at subtherapeutic INR levels, which may be explained by temporary discontinuation of warfarin before INR measurement or concomitant use of interacting medications such as aspirin, which independently increases bleeding risk (Baxter & Stockley, 2010). These findings highlight the importance of maintaining INR within the therapeutic range through appropriate dose adjustment and regular INR monitoring to minimize bleeding complications during warfarin therapy (January et al., 2019).

Table 5. Suspected warfarin-related adverse drug reactions

Suspected Adverse Drug Reaction	BARC Classification	n	INR at the time of event
Petechial bleeding	Type 2	1	3.39
Gingival bleeding	Type 2	1	4.46
Ecchymosis (skin bruising)	Type 2	1	4.18
Melena	Type 2	2	6.70 and 1.15
Hematuria	Type 2	2	1.54 and 0.86
Hemoptysis	Type 2	1	1.51
Ocular bleeding	Type 2	1	3.67

Therapeutic Outcomes of Warfarin Therapy

Warfarin therapeutic quality was evaluated using time in therapeutic range (TTR) calculated by the Rosendaal interpolation method, with a target TTR of $\geq 65\%$, which is associated with improved anticoagulation quality and a lower risk of thromboembolic and bleeding complications (Rosendaal et al., 1993; Lip et al., 2018). As shown in **Figure 2**, only 20 patients (18.87%) achieved the target TTR ($\geq 65\%$), whereas 86 patients (81.13%) remained below the recommended.

Table 4. Potential Drug–Drug Interactions Identified in Patients Receiving Warfarin Therapy

Interacting Drug	Number of Interactions (n)	Potential Clinical Effect	Interaction Severity	Clinical Recommendations
Fenofibrate	1	Increased INR and anticoagulant effect	Major	Monitor INR closely when initiating or discontinuing therapy and consider reducing the warfarin dose by 10–15%; a reduction of up to 40% may be required.
Amiodarone	1	Increased INR and anticoagulant effect	Major	Monitor INR closely when initiating or discontinuing amiodarone. Consider reducing the warfarin dose by approximately 40%, 35%, 30%, or 25%

Aspirin	9	Increased bleeding risk	Moderate	with amiodarone doses of 400, 300, 200, or 100 mg/day, respectively. Use the lowest effective dose and monitor closely for bleeding, particularly gastrointestinal bleeding.
Clopidogrel	5	Increased bleeding risk	Moderate	Closely monitor for signs and symptoms of bleeding.
Paracetamol	8	Increased INR, particularly at doses >2 g/day	Moderate	Monitor INR when initiating or discontinuing therapy and avoid prolonged use at doses >2 g/day when possible.
Allopurinol	14	Increased INR and anticoagulant effect	Moderate	Monitor INR when initiating or discontinuing therapy and reassess INR within approximately one week.
Diclofenac sodium	3	Increased bleeding risk, particularly gastrointestinal bleeding	Moderate	Avoid concomitant use when possible and monitor closely for gastrointestinal bleeding.
Ibuprofen	1	Increased bleeding risk, particularly gastrointestinal bleeding	Moderate	Avoid concomitant use when possible; if required, use cautiously and monitor for gastrointestinal bleeding.
Mefenamic acid	1	Increased bleeding risk, particularly gastrointestinal bleeding	Moderate	Avoid concomitant use when possible and monitor for gastrointestinal bleeding.
Lansoprazole	12	Increased INR and anticoagulant effect	Moderate	Monitor INR when initiating or discontinuing lansoprazole.
Lactulose	1	Increased INR due to reduced intestinal vitamin K absorption	Moderate	Monitor INR when initiating or discontinuing therapy.
Cilostazol	2	Increased bleeding risk	Moderate	Closely monitor for signs and symptoms of bleeding.
Acarbose	1	Increased INR due to enhanced warfarin absorption	Moderate	Monitor INR when initiating or discontinuing therapy.
Simvastatin	6	Increased INR and anticoagulant effect	Minor to moderate	Monitor INR when initiating or discontinuing therapy and consider an alternative statin with a lower interaction potential.

Description: Each patient can experience more than one potential drug interaction (Baxter and Stockley, 2010; Bungard et al. 2011, Di Minno et al. 2017)

The relatively low TTR observed in this study is consistent with reports from countries where warfarin management remains suboptimal but is still higher than values reported in some low-resource settings. Data from the ROCKET AF trial demonstrated substantial international variation in TTR, ranging from approximately 36% in India to 68.7% in Western Europe and 74% in Sweden, highlighting the influence of healthcare systems and anticoagulation management practices on treatment quality (Singer et al., 2013). Maintaining a high TTR is clinically important because patients who spend more time within the therapeutic INR range experience fewer thromboembolic events, major bleeding episodes, and deaths than those with poor anticoagulation control (Rose et al., 2009; Lip et al., 2018; January et al., 2019).

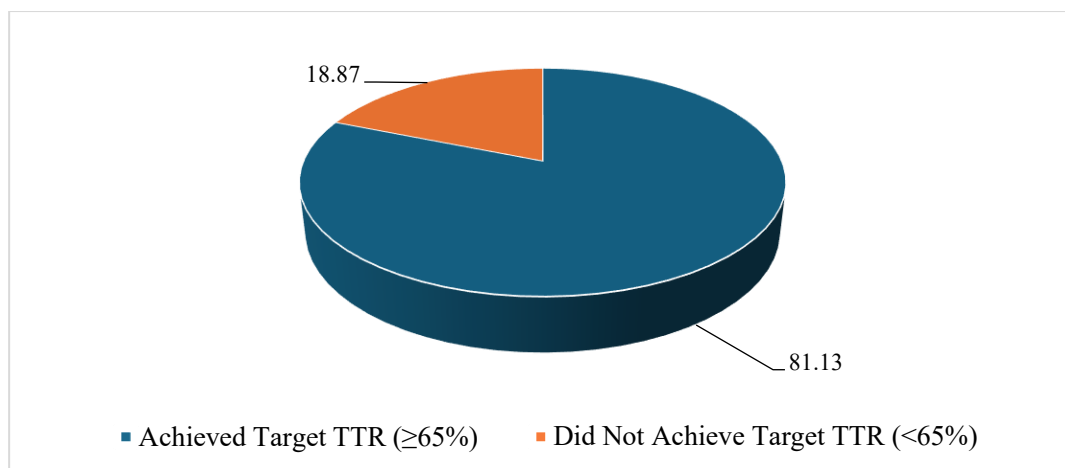


Figure 2. Proportion of patients who Achieved and Did Not Achieve the Target Time in Therapeutic Range (TTR $\geq 65\%$)

As illustrated in Figure 3, patients who achieved the target TTR demonstrated significantly greater adherence to the warfarin dosing algorithm than those who failed to achieve the target ($60.09 \pm 23.12\%$ vs. $39.21 \pm 20.57\%$; $p < 0.001$). This finding suggests that consistent dose adjustment according to INR-based dosing recommendations contributes substantially to maintaining therapeutic anticoagulation. Previous studies have similarly shown that standardized dosing algorithms improve INR stability and increase TTR, particularly in healthcare settings with historically poor anticoagulation control (van Spall et al., 2012).

The low TTR observed in this study is likely multifactorial. In addition to suboptimal adherence to the dosing algorithm, the preceding analyses demonstrated that inappropriate INR monitoring intervals, potential drug interactions, and inappropriate dose adjustments were common drug-related problems identified in this cohort. These factors may prolong periods of subtherapeutic or supratherapeutic anticoagulation, thereby reducing overall TTR and increasing the risk of adverse clinical outcomes (Schachter & Pirmohamed, 2012; January et al., 2019).

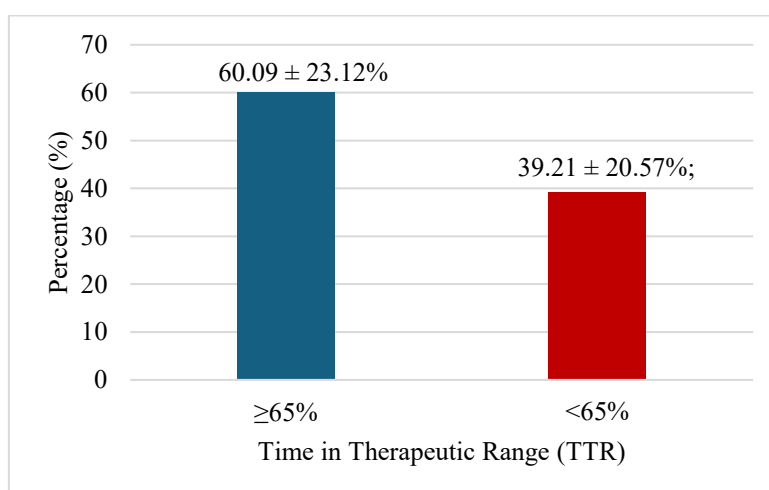


Figure 3. Warfarin Dosing Consistency According to Achievement of the TTR

This study has several limitations. First, the exact duration of warfarin therapy could not be determined because historical patient records were only available from January 2023 onward due to changes in the hospital information system at Dr. Soetomo General Academic Hospital. Second, the retrospective observational design limited the ability to assess patients' adherence to warfarin therapy and the severity of adverse events, as these data were not consistently documented in the medical records. These limitations should be considered when interpreting the study findings and may be addressed in future prospective studies with more comprehensive clinical data collection.

CONCLUSION

The findings of this study indicated that warfarin management among patients with atrial fibrillation (AF) remained suboptimal, despite most patients having an appropriate indication for anticoagulation based on the CHA₂DS₂-VASc score. Although warfarin indications were generally appropriate, concordance with the recommended warfarin dosing algorithm and adherence to recommended international normalized ratio (INR) monitoring intervals were low. Several clinically relevant potential drug–drug interactions were identified, including two classified as major interactions, and bleeding events classified as Bleeding Academic Research Consortium (BARC) type 2 were documented during treatment. Overall, anticoagulation control was suboptimal, with a mean time in therapeutic range (TTR) of $43.15 \pm 25.28\%$ and only 20 patients (18.87%) achieving the study-defined TTR target of $\geq 65\%$. These findings highlight the need to strengthen individualized warfarin dose adjustment, timely INR monitoring, and systematic medication review to improve the quality and safety of anticoagulation management in patients with AF.

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