

## **Variation in Time in Therapeutic Range (TTR) of Warfarin Use in Atrial Fibrillation Patients at Hospital X, Banten**

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### **Abstract**

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and a major cause of stroke due to thromboembolism. Stroke prevention is therefore a key therapeutic goal, with warfarin widely used as an oral anticoagulant. Despite its effectiveness, warfarin has a narrow therapeutic window and requires close monitoring of the international normalized ratio (INR). The quality of anticoagulation is commonly measured using Time in Therapeutic Range (TTR), which indicates the proportion of time a patient's INR remains within the target range of 2.0–3.0. This study aimed to evaluate TTR levels and their association with bleeding and stroke risks in AF patients receiving warfarin therapy. A retrospective review of 78 medical records from January to December 2022 was conducted. TTR was calculated using the Rosendaal method, bleeding risk assessed with the HAS-BLED score, and stroke risk with the CHA<sub>2</sub>DS<sub>2</sub>VASc score. Results showed that only 15.38% (12 patients) achieved optimal TTR (>70%), while 84.62% (66 patients) had suboptimal control. Most patients with low TTR presented moderate to high HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>VASc scores, reflecting increased risks of bleeding and stroke. These findings emphasize the importance of optimizing warfarin management and monitoring strategies to improve safety and clinical outcomes in AF patients.

**Keywords :** TTR, INR, Warfarin, Atrial Fibrillation

### **1. INTRODUCTION**

Atrial fibrillation is closely associated with increased morbidity and mortality. It also imposes a significant burden on patients, public health, and healthcare economics (Hindricks et al., 2021). Patients with atrial fibrillation have a fivefold greater risk of experiencing stroke compared to those without the condition. Stroke complications resulting from atrial fibrillation can be prevented through anticoagulant therapy. There are two main classes of anticoagulants used in Atrial Fibrillation patients: warfarin, a Vitamin K Antagonist (VKA), and non-vitamin K antagonist oral anticoagulants (NOACs) (Hindricks et al., 2021). The use of NOACs has increased, in South Korea, due to their significant reduction in the risk of stroke and mortality (Lee et al., 2020). However, in Indonesia, warfarin remains widely used. Warfarin therapy was administered to 50% of patients with atrial fibrillation undergoing hemodialysis (Akbar et al., 2023).

Warfarin is effective for long-term use in preventing recurrent cardioembolic ischemic stroke, which is commonly observed in patients with atrial fibrillation. Warfarin has been shown

to reduce the risk of stroke by 64% and mortality by 26% compared to placebo (Hindricks et al., 2021). However, warfarin also carries the potential risk of bleeding as an adverse effect, necessitating close monitoring to ensure the appropriateness of anticoagulant therapy. The incidence of major bleeding associated with warfarin use is approximately 1.3% per year, compared to only 1% with placebo, indicating that uncontrolled warfarin therapy may present a higher risk of bleeding than no anticoagulation at all (Perhimpunan Dokter Spesialis Kardiovaskular Indonesia, 2019).

Time in Therapeutic Range (TTR) is a key parameter for assessing the quality of warfarin management and the effectiveness of anticoagulant therapy. TTR serves as a monitoring tool for warfarin by indicating the percentage of time a patient's International Normalized Ratio (INR) remains within the target range. A subtherapeutic INR may lead to ineffective anticoagulation and an increased risk of stroke, whereas a supratherapeutic INR can elevate the risk of bleeding (Dokter & Kardiovaskular, 2019). Warfarin is considered effective in preventing stroke when the TTR exceeds 70% (Hindricks et al., 2021). Conversely, low TTR values are associated with a higher risk of stroke, bleeding, and mortality in patients (Krittayaphong et al., 2020).

Based on the aforementioned background, it is important to understand the TTR profile among patients using warfarin in hospitals across Indonesia. This aligns with the principles of quality control and cost-effectiveness in the Indonesian healthcare system. Therefore, the researcher is interested in conducting a study on the variation of Time in Therapeutic Range (TTR) in warfarin use among atrial fibrillation patients at Hospital X in Banten.

## **2. METHOD**

### **Research Plan**

This study employs an observational design involving atrial fibrillation patients who were prescribed warfarin oral. Data were collected retrospectively from medical records covering the period from January 1, 2022, to December 31, 2022.

### **Research Subject**

The sample in this study was obtained using purposive sampling. The sample consisted of all atrial fibrillation patients who met the inclusion and exclusion criteria. The inclusion criteria for this study were: outpatients diagnosed with atrial fibrillation who were receiving warfarin therapy, aged over 18 years, and had regularly undergone monthly INR monitoring for a duration of six months (within the period of January 1, 2022 – December 31, 2022).

### Data Analysis

Data analysis was conducted descriptively, and the results were presented in the form of tables and graphs. The tabulated data included potential drug interactions, patient demographic characteristics, and the incidence of warfarin-related complications. Graphical data included the variation in Time in Therapeutic Range (TTR) analyzed using the Rosendaal method.

Time in Therapeutic Range (TTR) : (Number of Days Within Therapeutic Range ÷ Total Monitoring Days) × 100%

The distribution of comorbidities, and the risk of bleeding and stroke complications assessed using the HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>VASc scores. The CHA<sub>2</sub>DS<sub>2</sub>VASc classification is divided into three categories: low risk with a score of 0, intermediate risk with a score of 1, and high risk with a score above 1. According to the HAS-BLED score, patients with atrial fibrillation are stratified into three risk categories: a score of 0 indicates low risk, scores of 1–2 indicate moderate risk, and a score of 3 indicates high risk (Zhu et al., 2015).

**Table 1.** Risk Assesment CHA<sub>2</sub>DS<sub>2</sub>-VASc (Queensland Health, 2024)

Clinical Characteristic (CHA <sub>2</sub> DS <sub>2</sub> -VASc)	Score
C – Congestive Heart Failure	1
H – History of Hypertension	1
A – Age ≥ 75 years	2
D – Diabetes Mellitus	1
S <sub>2</sub> – Stroke or Transient Ischaemic Attack (TIA)	2
V – Vascular Disease	1
A – Age 65–74 years	1
Sc – Sex Category (Female)	1
Total Score (maximum 9)	

**Table 2.** Risk Assesment HAS-BLED (Queensland Health, 2024)

Letter	Clinical Characteristic	Score
C	Congestive Heart Failure	1
H	History of Hypertension	1
A	Age ≥75 years	2
D	Diabetes Mellitus	1
S <sub>2</sub>	History of Stroke or Transient Ischemic Attack	2
V	Vascular Disease	1
A	Age 65–74 years	1
Sc	Sex category (female)	1

**Total Score:** maximum 9

### 3. RESULTS AND DISCUSSION

#### Demographic Characteristics of Patients

In this study, the sample consisted of atrial fibrillation patients who met the inclusion and exclusion criteria. A total of 78 patients were included in the study, 7 of whom were diagnosed with Mitral Valve Replacement (MVR). Patient demographic data are presented in Table 3. The results showed that the majority of samples were in the age group of 46–65 years (50%), followed by >65 years (44.87%), 31–45 years (3.85%), and 18–30 years (1.28%). The gender distribution of the sample showed 47.44% female and 52.56% male.

**Table 3.** Patient Demographics

<b>Demographic Data</b>	<b>Number of Samples (n=78)</b>	<b>Percentage (%)</b>
<b>Age (Years)</b>		
18–30	1	1.28
31–45	3	3.85
46–65	39	50
>65	35	44.87
<b>Gender</b>		
Female	37	47.44
Male	41	52.56
<b>AF with MVR</b>	7	8.97

#### International Normalized Ratio (INR) Categories

The therapeutic range plays a crucial role in the success of treatment, as staying within the appropriate range ensures that the therapy received is both optimal and aligned with the patient's needs (Dincer, 1002). Atrial fibrillation patients receiving warfarin as an anticoagulant require careful monitoring of their therapeutic range to minimize the risk of complications.

The International Normalized Ratio (INR) is used as a therapeutic parameter for patients undergoing anticoagulant therapy. For atrial fibrillation patients on warfarin, the target INR range is typically 2.0–3.0, while for those with Mitral Valve Replacement (MVR), the recommended range is 2.5–3.5. The results of this study show that INR values were categorized into three groups, as illustrated in table 4. A majority of patients (52.01%) had INR values below the therapeutic range, 33.53% were within range, and 14.46% were above the target range. The low proportion of patients within the therapeutic range indicates inadequate control of warfarin's anticoagulant effect in most patients. The majority of patients who have an INR below the target range receive medications that can interact with warfarin.

**Table 4.** INR Category Data

INR Category	INR Value	Percentage (%)
<b>Below Target</b>	< 2.00	52.01
<b>Within Target Range</b>	2.00–3.00 and 2.50–3.50 in AF with MVR	33.53
<b>Above Target</b>	> 3.00	14.46

INR values can be influenced by various factors, including drug interactions with warfarin, herbal supplements, dietary patterns, and overall health status. In this study, the factors analyzed were drug interactions and comorbidities. Lowering the target INR may reduce the incidence of bleeding but increases the risk of thromboembolism in patients with atrial fibrillation (Pandey et al., 2020).

### Comorbidities of Atrial Fibrillation

In this study, the analyzed factors included drug interactions and comorbidities. Comorbidities referred to other medical conditions diagnosed in patients apart from atrial fibrillation. Hypertension was identified as the most common comorbidity, followed by hypertensive heart disease (HHD), coronary artery disease (CAD), dyslipidemia, congestive heart failure (CHF), and others, as shown in Table 3. These findings are consistent with a study by Lee et al. (2020), which involved 420 patients with atrial fibrillation and found hypertension to be the most prevalent comorbidity.

**Table 5.** Comorbidities Data

No	Comorbidities	Number (n=78)	Percentage (%)
1	Hypertension	37	46.84
2	HHD (Hypertensive Heart Disease)	33	41.77
3	CAD (Coronary Artery Disease)	31	39.74
4	Dyslipidemia	27	34.18
5	CHF (Congestive Heart Failure)	21	26.58
6	DM (Diabetes Mellitus)	21	26.58
7	Hyperuricemia	20	25.32
8	CKD (Chronic Kidney Disease)	16	20.25
9	CVDNH (Cerebrovascular Disease)	15	18.99
10	MR (Mitral Regurgitation)	13	16.46
11	RHD (Rheumatic Heart Disease)	12	15.18
12	AKI (Acute Kidney Injury)	9	11.39
13	Stroke	8	10.13
14	Pseudobulbar ODS	8	10.13
15	OA genu (Osteoarthritis)	8	10.13

Diseases of the circulatory system represented the most frequently diagnosed category. Comorbidities are also associated with an increased risk of complications. In addition, several comorbidities linked to a higher likelihood of atrial fibrillation (AF)—including hypertension, diabetes, congestive heart failure, dyslipidemia, coronary artery disease, sleep apnea, smoking, and obesity—are also recognized as risk factors for stroke. These systemic vascular risk factors contribute to abnormal atrial changes or atrial cardiomyopathy, which can trigger both AF and thromboembolism. Once AF occurs, atrial contractile function further declines, worsening the underlying cardiomyopathy. This progression increases the risk of thromboembolism and explains the heightened stroke risk following the onset of AF (Elsheikh et al., 2024). Based on cohort study findings in patients with atrial fibrillation, those who maintained target Systolic Blood Pressure (SBP) and a Time in Therapeutic Range (TTR)  $\geq 65\%$  experienced fewer adverse clinical outcomes (Krittayaphong et al., 2023).

**Patient Medications**

**Table 6. Drug Classification**

No	Drug Class	Number (n=686)	Percentage (%)
1	Cardiovascular	327	47.67
2	Gastrointestinal	65	9.48
3	Vitamins, Minerals, and Anti-anemia	32	4.66
4	Musculoskeletal System	31	4.52
5	Analgesics	29	4.23
6	Neurologic	23	3.35
7	Endocrine System	20	2.92
8	Respiratory System	19	2.77
9	Antibiotics	18	2.62
10	Antipsychotics	14	2.04
11	Psychiatric	13	1.89
12	Reproductive System	8	1.17
13	Antihistamines and Other Allergy Drugs	8	1.17
14	Corticosteroids	6	0.87
15	Dementia and Alzheimer’s	5	0.73
16	Antidotes and Detoxifying Agents	3	0.44
17	Systemic Hemostatics	2	0.29
18	Other Drugs	77	11.22
19	Unspecified	0	0

The presence of comorbidities in patients with atrial fibrillation necessitates the concurrent use of other medications alongside warfarin. The classification of all prescribed medications is presented in Table 6, while the most frequently prescribed individual drugs are listed in Table 7. The cardiovascular drug group was the most commonly prescribed, with a total of 327 prescriptions. There were 20 drugs most frequently prescribed to patients, with bisoprolol being the most common (92.31%), followed by candesartan (44.87%). These findings are consistent with the high prevalence of hypertension as a comorbidity among patients, as bisoprolol is commonly used as an antihypertensive agent.

**Table 7.** The Most Frequently Prescribed Individual Drugs

No	Drug Name	Number of cases (n)	Percentage (%)
1	Bisoprolol	72	92.31
2	Candesartan	35	44.87
3	Atorvastatin	34	43.59
4	Simvastatin	33	42.31
5	Amlodipine	30	38.46
6	Ramipril	24	30.77
7	Lansoprazole	22	28.21
8	Furosemide	22	28.21
9	Allopurinol	21	26.92
10	Paracetamol	15	19.23
11	Spirolactone	14	17.95
12	Acetylcysteine	14	17.95
13	Eplerenone	14	17.95
14	Sodium bicarbonate	10	12.82
15	Nifedipine	10	12.82
16	Folic acid	10	12.82
17	Omeprazole	8	10.26
18	Gabapentin	8	10.26
19	Metformin	7	8.97
20	Calcium lactate	7	8.97

**Potential Interactions of Other Medications with Warfarin**

The concomitant use of other drugs with warfarin has the potential to cause drug interactions due to warfarin’s high interaction profile. In this study, only interactions between warfarin and other co-administered drugs were included as data. For patients receiving fixed-dose combination drugs, each active ingredient was individually assessed for its interaction with warfarin. Drug interactions were evaluated using the MEDSCAPE interaction checker, which classifies the level of interaction for each drug. This study identified 30 drugs that potentially interact with warfarin, as presented in Table 8, along with their respective

frequencies of use. Among the 30 interacting drugs, 26 drugs (87%) were found to decrease the effect of warfarin, while 4 drugs (13%) increased its effect. Simvastatin, which increases the effect of warfarin, was prescribed to 42% of patients. The enhanced effect of warfarin may elevate the risk of bleeding in patients. Conversely, the diminished effect of warfarin increases the risk of stroke, as the reduced anticoagulant activity raises the likelihood of thromboembolic events.

**Table 8.** Drugs Interacting with Warfarin and Their Interaction Mechanism

No	Mechanism of Interaction	Drug Name	Interaction Category	Number (n=78)	Percentage (%)
1	Increases Warfarin Effect	Simvastatin	Monitor Closely	33	42%
2	Increases Warfarin Effect	Allopurinol	Serious – Use Alternative	21	27%
3	Increases Warfarin Effect	Paracetamol	Monitor Closely	15	19%
4	Increases Warfarin Effect	Nifedipine	Monitor Closely	10	13%
5	Increases Warfarin Effect	Omeprazole	Monitor Closely	10	13%
6	Increases Warfarin Effect	Meloxicam	Monitor Closely	7	9%
7	Increases Warfarin Effect	Clopidogrel	Monitor Closely	7	9%
8	Increases Warfarin Effect	Fenofibrate	Monitor Closely	6	8%
9	Increases Warfarin Effect	Methylprednisolone	Monitor Closely	6	8%
10	Increases Warfarin Effect	Lactulose	Monitor Closely	6	8%
11	Increases Warfarin Effect	Ketorolac	Monitor Closely	5	6%
12	Increases Warfarin Effect	Acetylsalicylic acid	Monitor Closely	4	5%
13	Increases Warfarin Effect	Levofloxacin	Monitor Closely	3	4%
14	Increases Warfarin Effect	Amitriptyline	Monitor Closely	3	4%
15	Increases Warfarin Effect	Azithromycin	Monitor Closely	3	4%

No	Mechanism of Interaction	Drug Name	Interaction Category	Number (n=78)	Percentage (%)
16	Increases Warfarin Effect	Cefixime	Monitor Closely	2	3%
17	Increases Warfarin Effect	Levothyroxine	Monitor Closely	2	3%
18	Increases Warfarin Effect	Entacapone	Monitor Closely	1	1%
19	Increases Warfarin Effect	Ibuprofen	Monitor Closely	1	1%
20	Increases Warfarin Effect	Ciprofloxacin	Monitor Closely	1	1%
21	Increases Warfarin Effect	Sertraline	Monitor Closely	1	1%
22	Increases Warfarin Effect	Diclofenac sodium	Monitor Closely	1	1%
23	Increases Warfarin Effect	Cefadroxil	Monitor Closely	1	1%
24	Increases Warfarin Effect	Amiodarone	Monitor Closely	1	1%
25	Increases Warfarin Effect	Ticagrelor	Monitor Closely	1	1%
26	Increases Warfarin Effect	Ceftriaxone	Monitor Closely	1	1%
27	Decreases Warfarin Effect	Glimepiride	Monitor Closely	6	8%
28	Decreases Warfarin Effect	Methimazole (Thyrozol®)	Monitor Closely	4	5%
29	Decreases Warfarin Effect	Phenytoin	Monitor Closely	3	4%
30	Decreases Warfarin Effect	Vitamin K (phytomenadione)	Monitor Closely	2	3%

The results of drug interaction analysis are presented in Table 6. From the total of 30 drugs identified as having potential interactions with warfarin, 29 were categorized as “Monitor Closely,” while only one drug (allopurinol) was classified as “Serious.” Drugs in the “Serious” category require careful consideration due to their potential to significantly affect the therapeutic outcomes of warfarin therapy. Drug interactions should be avoided as much as possible in pharmacotherapy, particularly with warfarin, which is known to interact with many medications. The mechanisms of drug interactions vary depending on the pharmacological action of each interacting drug.

Such interactions may occur through pharmacodynamic mechanisms, for example protein binding, in which another drug with a higher affinity for the same protein may displace warfarin, thereby increasing its effectiveness (Page Clivon & Pitchford Simon, 2021)

**Time in Therapeutic Range (TTR)**

A specific analysis was conducted for patients using allopurinol to evaluate their Time in Therapeutic Range (TTR). It was found that only 14.29% of patients on allopurinol had TTR values >70%, while 85.71% of them had TTR values below the target. This finding indicates that a majority of patients using allopurinol experienced suboptimal anticoagulation control, suggesting that the interaction between warfarin and allopurinol may contribute to reduced TTR values. Consequently, this interaction may increase the risk of treatment-related complications.

Time in Therapeutic Range (TTR) is a method used to assess the quality of anticoagulant therapy in patients receiving warfarin. TTR is calculated and analyzed using the Rosendaal method, which estimates the proportion of time a patient's International Normalized Ratio (INR) remains within the therapeutic range. This method assumes that INR changes linearly between two measurements, implying a consistent daily rate of change (Rosendaal et al., 1993).

**Table 9.** Data on Time in Therapeutic Range (TTR)

No	TTR Classification	% TTR	Number (n=78)	Percentage (%)
1	High	≥70	12	15.38%
2	Low	<70	66	84.62%

A low TTR value may indicate two possible conditions: the INR is either below or above the target range (Rivera-Caravaca et al., 2017). In this study, TTR values for each patient were analyzed and categorized into two groups: high and low. A TTR value is considered high if it exceeds 70%. Based on the findings, 15.38% of patients achieved this target, while 84.62% had TTR values below the recommended threshold. Improving TTR values can reduce the incidence of complications such as stroke and bleeding (Vestergaard et al., 2017). Low TTR values are associated with an increased clinical risk of mortality, stroke, and bleeding (Krittayaphong et al., 2020).

**HAS-BLED Categories**

The potential risk of bleeding complications can be assessed using the HAS-BLED score. In this study, three categories were identified: low, moderate, and high, as shown in Table 8. The moderate HAS-BLED category had the highest percentage, with 64.10% of patients falling into this group. The percentage of patients with a high HAS-BLED score was 30.77%,

while 5.13% were classified as low risk. These data indicate that the majority of patients are in the moderate and high-risk categories, suggesting a substantial potential for bleeding complications.

**Table 10.** HAS-BLED Score Categories

No	HAS-BLED Category	HAS-BLED Score	Frequency (n=78)	Percentage (%)
1	Low	0	4	5.13
2	Moderate	1.00–2.00	50	64.1
3	High	>3	24	30.77

### HAS-BLED Score and Bleeding Events

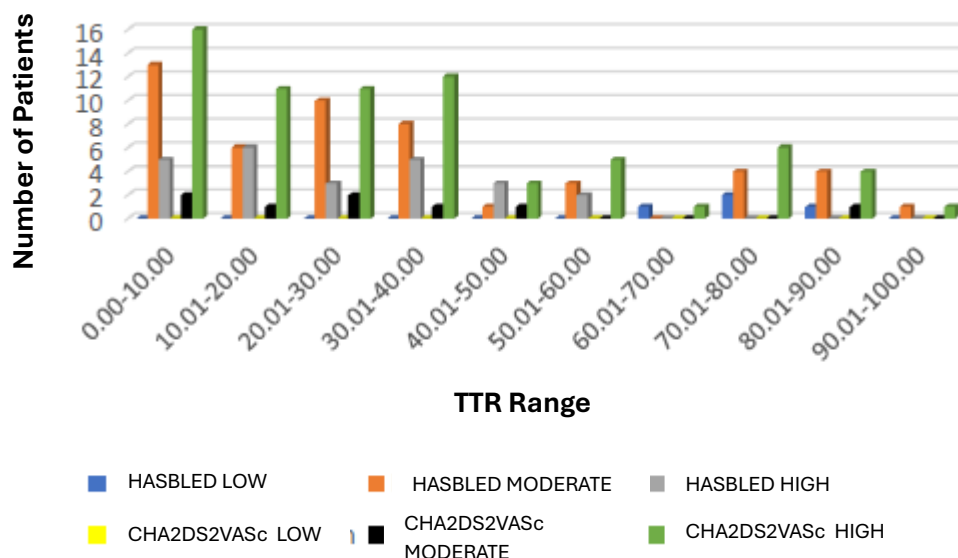
The risk assessment for potential stroke complications was conducted using the CHA<sub>2</sub>DS<sub>2</sub>VASc scoring method. This assessment is categorized into three levels: low, moderate, and high. The data analysis based on this assessment is presented in Table 9, showing that 0% of patients were classified as low risk, 10.26% as moderate risk, and the majority, 89.74%, were classified as high risk. These data indicate that 89.74% of patients fall into the high-risk category for experiencing a stroke.

**Table 11.** CHA<sub>2</sub>DS<sub>2</sub>-VASc Score Categories

No	CHA <sub>2</sub> DS <sub>2</sub> -VASc Category	Frequency (n=78)	Percentage (%)
1	Low (score 0)	0	0
2	Moderate (score 1)	8	10.26
3	High (score >1)	70	89.74

### TTR Values in Relation to HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores

The variation in TTR among patients indicates that warfarin therapy must be tightly controlled. This variability broadly demonstrates that anticoagulation treatment with warfarin in atrial fibrillation patients has not yet reached optimal quality, as the number of patients with subtherapeutic TTR exceeds those with target TTR levels. Both HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in the moderate to high categories predominate across all TTR ranges, as illustrated in Figure 1. These data show that patients with low TTR values are at higher risk of bleeding and stroke complications compared to those with target or above-target TTR values.



**Figure 1.** Time in Therapeutic Range (TTR) in Association with HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASc Scoring Systems

Improving TTR in atrial fibrillation patients receiving warfarin is crucial to ensure optimal anticoagulation therapy. Monitoring co-administered medications is also necessary to minimize potential drug interactions that may affect the patient's INR values. The high prevalence of moderate-to-high HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>VASc scores further supports the need for closer monitoring and stricter control of medication regimens to optimize anticoagulation outcomes.

The proportion of patients with high TTR, currently at only 15%, could potentially be increased through therapeutic modification using NOACs such as Dabigatran, Apixaban, Edoxaban, or Rivaroxaban. These agents do not require TTR or routine INR monitoring, making their pharmacologic effects more predictable.

#### 4. CONCLUSION

There is a variation in the Time in Therapeutic Range (TTR) values among atrial fibrillation patients using warfarin. Only 15.38% of patients achieved the target TTR (>70%), while 84.62% were below the recommended threshold. The risk of bleeding and stroke complications is associated with suboptimal TTR. Most patients with low TTR had HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in the moderate to high-risk categories. Improving TTR values may reduce the potential risk of bleeding and stroke complications in atrial fibrillation patients receiving warfarin therapy.

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