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Original article

Appropriate international normalized ratio follow-up interval for patients with atrial fibrillation taking warfarin

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Abstract

Background: The recommended follow-up for international normalized ratio (INR) measurement is every 4 weeks in patients with atrial fibrillation (AF) who take warfarin. However, data regarding the appropriate INR follow-up interval are lacking in these patients.

Objective: We aimed to investigate the appropriate INR follow-up intervals in patients with AF receiving warfarin between 6- and 12-week intervals for follow-up appointments.

Methods: We retrospectively enrolled patients with AF taking warfarin at the Central Chest Institute of Thailand between January 2017 and May 2023. The primary outcome was the time in therapeutic range (TTR) for each follow-up interval group, and the secondary outcome was the composite outcome of acute ischemic stroke/transient ischemic attack (TIA)/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality between the 6- and 12-week groups.

Results: A total of 400 patients with AF taking warfarin were recruited for the study. The average CHA_2DS_2-VASc score was 3.6 and 3.7 in the 6- and 12-week groups, respectively. The average HAS-BLED score was 1.8 in both groups. The TTR in the 12-week group was not inferior to that in the 6-week group (absolute difference 1.5 percentage points; 95% confidence interval –2.4 to 5.3; $P < 0.001$ for non-inferiority). In addition, the incidence of acute ischemic stroke/TIA/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality was not significant between patients in the 6- and 12-week groups.

Conclusion: The TTR in the 12-week group was not inferior to that in the 6-week group in patients with AF taking warfarin. Thus, an extended 12-week follow-up interval may be applied in clinical practice. A larger prospective study will be required in the future.

Keywords: Appropriate follow-up interval, atrial fibrillation, INR, TTR, warfarin.

In clinical practice, atrial fibrillation (AF) is a common cardiac arrhythmia. Symptoms that usually bring patients to the hospital include palpitations, dizziness, dyspnea, and chest pain; however, it can also be asymptomatic. [1] The most catastrophic consequence of AF is ischemic stroke, which leads to increased morbidity and mortality in these patients. Moreover, AF increases the risk of death, dementia, myocardial infarction, sudden cardiac death, heart failure (HF), chronic kidney disease, and peripheral artery disease. [2]

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Current international clinical practice guidelines recommend the use of oral anticoagulants in patients with AF and a CHA_2DS_2-VASc score of at least 1 in males and 2 in females. [1 - 4] In Thailand, warfarin is the most commonly used vitamin K antagonist. A previous trial showed that patients with AF taking warfarin had a 68.0% reduced risk of stroke. [5] The poor anticoagulation control estimated by the time in therapeutic range (TTR) is a challenge for patients taking warfarin in clinical practice. A previous trial showed that TTR < 70.0% was associated with a substantially increased risk of stroke/thromboembolism and major bleeding. [6] Moreover, previous trials have shown that patients with AF and well-controlled warfarin (TTR > 65.0%) compared with those taking non-vitamin K antagonist oral anticoagulants (NOACs) had comparable thromboembolic and/or major bleeding events, although they experienced more minor bleeding

events. [7] Overall, the net clinical benefit of warfarin use in AF patients with TTR > 65.0% was greater than that compared with those taking NOACs. [8]

It is recommended for patients taking warfarin that the international normalized ratio (INR) be closely monitored, and each visit should be followed up every four weeks, as previously recommended by the American Guide to Warfarin Therapy. [9] A previous study showed that patients taking warfarin followed up every 12 weeks appeared to be not inferior to every 4 weeks. These patients were prescribed warfarin for AF, heart valve replacement, and venous thromboembolism. [10] To date, data regarding the appropriate INR follow-up interval are lacking in patients with AF taking warfarin. Therefore, this study aimed to investigate the appropriate INR follow-up intervals in patients with AF receiving warfarin between 6- and 12-week intervals for follow-up appointments.

Materials and methods

We retrospectively enrolled patients with AF aged 18 years or older who were taking warfarin for at least 12 months at the Central Chest Institute of Thailand between January 2017 and May 2023. Patients with rheumatic mitral stenosis, a moderate to severe degree of other valvular heart disease, mechanical prosthetic valve, venous thromboembolism including pulmonary embolism and deep vein thrombosis, thrombocytopenia (platelets < 100,000/mm^3), hematologic malignancy, myelodysplastic syndrome, disseminated intravascular coagulation, warfarin discontinuation due to surgery or other invasive medical procedures, follow-up intervals less than 4 weeks or more than 14 weeks, pregnancy, or a life expectancy of less than 6 months were excluded. The study protocol was reviewed and approved by the Human Research Ethics Committee of the Central Chest Institute of Thailand (COA no.026/2566) and was in compliance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines.

The patients' data were obtained from the medical records. The baseline demographic data, such as underlying diseases, current medications, CHA_2DS_2-VASc score, HAS-BLED score, and echocardiographic findings, were collected.

The primary outcome was the TTR in each follow-up interval group. The TTR was calculated using the Rosendaal method. [11] The secondary outcome was the composite outcome of acute ischemic stroke/TIA/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality between the 6- and 12-week groups. The patients in the 6-week group were followed up every 4–8 weeks, while those in the 12-week group were followed up every 10–14 weeks. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis. [12] Bleeding other than major bleeding was defined as minor bleeding.

Statistical analysis

We specified 0.05 for α-error and 0.20 for β-error; therefore, the study power was 80%. We determined 20% for the standard deviation (SD) of TTR in the patients and 2.5% for the mean difference between the TTR of patients in the 6- and 12-week groups.

The statistics employed in this study for the assessment of TTR for the follow-up patients with AF taking warfarin at 6-week intervals compared with 12-week intervals was a non-inferiority test. The non-inferiority margin was 7.5% to prove that the TTR in the 12-week group would not be inferior to the TTR in the 6-week group. [10] We estimated a sample size of 396 patients.

We used descriptive statistics for the analysis of baseline demographic and clinical data. The categorical data were compared using the chi-square test or Fisher's exact test, and continuous data were compared using the Student's *t*-test or Mann–Whitney U test. The categorical data are presented as numbers and percentages, whereas the continuous data are presented as the mean and SD. Interaction analyses were performed based on aspirin/clopidogrel use, a history of HF, the presence of diabetes mellitus (DM), and a history of stroke/intracranial hemorrhage (ICH). $P < 0.05$ was considered statistically significant.

Results

A total of 450 patients with AF were treated with warfarin at the Central Chest Institute of Thailand between January 2017 and May 2023. Of the 450 patients, 400 patients with AF taking warfarin were eligible and subsequently recruited for the study. There were 200 patients in the 6-week group and 200 patients in the 12-week group **(Figure 1).** The average age was 74 and 75 years in the 6- and 12-week groups, respectively. There were more males in the 6-week

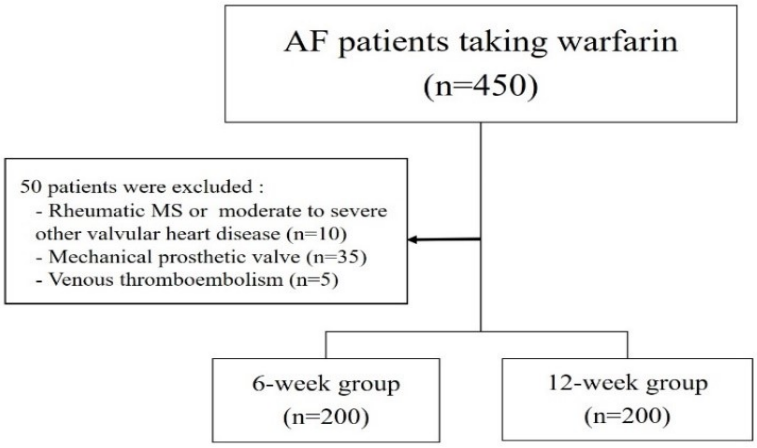

Figure 1. Flow diagram of the study patients (AF, atrial fibrillation; MS, mitral stenosis).

Table 1. Baseline characteristics of patients with AF.

Baseline demographic data	6-week group (n = 200) n (%)	12-week group (n = 200) n (%)	*P* - value
Age (years)	73.7 ± 11.1	75.3 ± 10.0	0.13
Male (sex)	108 (54)	86 (43)	0.04*
Average follow-up interval (weeks)	6.4 ± 1.4	12.2 ± 1.8	< 0.01*
CHA_2DS_2-VASc score	3.6 ± 1.2	3.7 ± 1.1	0.64
HAS-BLED score	1.8 ± 0.6	1.8 ± 0.6	0.80
HAS-BLED score ≥ 3	7 (3.5)	11 (5.5)	0.47
Medical history			
Previous stroke/TIA	10 (5)	12 (6)	0.83
Diabetes mellitus	56 (28)	44 (22)	0.20
History of heart failure	73 (36.5)	66 (33.0)	0.53
Hypertension	174 (87.0)	164 (82.0)	0.21
Previous myocardial infarction	37 (18.5)	39 (19.5)	0.90
Peripheral artery disease	2 (1.0)	1 (0.5)	> 0.99
Liver cirrhosis	2 (1.0)	1 (0.5)	> 0.99
History of major bleeding	2 (1.0)	3 (1.5)	> 0.99
Medications			
Aspirin	9 (4.5)	6 (3.0)	0.60
Clopidogrel	9 (4.5)	11 (5.5)	0.82
Amiodarone	9 (4.5)	18 (9.0)	0.11

*$P < 0.05$ indicates statistical significance.
n, number; SD, standard deviation; TIA, transient ischemic attack.

group (54.0%) compared with the 12-week group (43.0%). The average CHA_2DS_2-VASc score was 3.6 and 3.7 in the 6- and 12-week groups, respectively, and the average HAS-BLED score was 1.8 in both groups. Most patients had hypertension, and approximately one-third of those patients had a history of HF. Furthermore, approximately 10.0% of those patients were prescribed concomitant antiplatelets. The average follow-up time was 391.7 ± 166.0 and 401.1 ± 157.0 days in the 6-week and 12-week groups, respectively. The baseline characteristics are shown in **Table 1.**

Table 2. Primary and secondary outcome of AF patients taking warfarin.

Outcomes	6-week group (n = 200) n (%)	12-week group (n = 200) n (%)	Absolute difference (95% CI), percentage points	*P* - value
Primary outcome: TTR (%)	62.8 ± 19.6	61.3 ± 19.6	1.5 (- 2.4 to 5.3)	0.001 for non-inferiority, 0.45
Secondary outcome			**OR (95% CI)**	***P* - value**
Composite outcome of acute ischemic stroke/TIA/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality	34 (17.0)	26 (13.0)	0.7 (0.4 to 1.3)	0.33
Acute ischemic stroke	4 (2.0)	5 (2.5)	1.26 (0.4 to 4.4)	> 0.99
Major bleeding	7 (3.5)	5 (2.5)	0.71 (0.2 to 2.2)	0.77
Minor bleeding	24 (12.0)	16 (8.0)	0.64 (0.3 to 1.2)	0.24
All-cause mortality	1 (0.5)	0 (0)	N/A	N/A

P are used for superiority unless otherwise indicated.
n, number; CI, confidence interval; SD, standard deviation; OR, odds ratio; TIA, transient ischemic attack; TTR, time in therapeutic range.

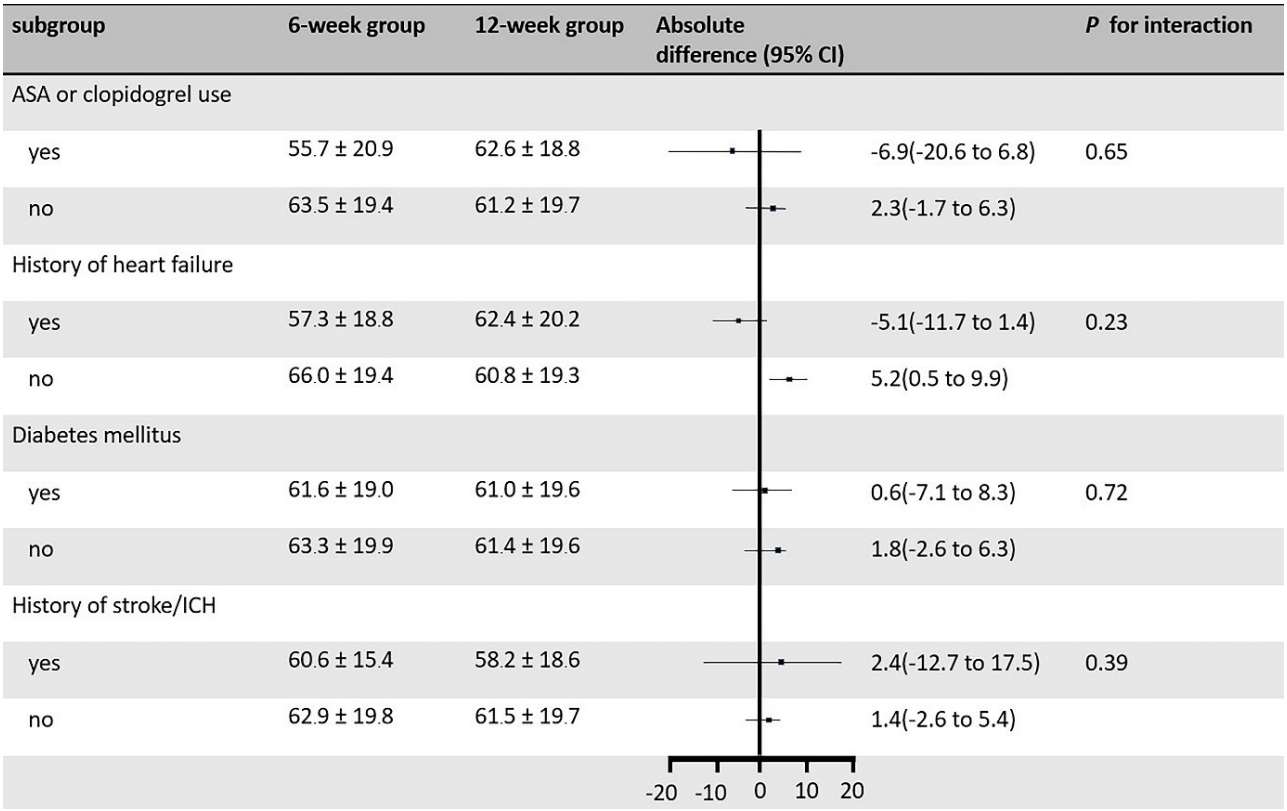

Figure 2. Absolute difference of the primary outcome between 6-week group and 12-week group according to subgroup (CI, confidence interval; ICH, intracranial hemorrhage).

The patients with AF in the 12-week group had an average TTR of 61.3% ± 19.6%, while patients in the 6-week group had an average TTR of 62.8% ± 19.6%. The TTR in the 12-week group was not inferior to that in the 6-week group (absolute difference 1.5 percentage points; 95% confidence interval (CI) –2.4 to 5.3; $P < 0.001$ for non-inferiority). However, the TTR in the 12-week group was not superior to that in the 6-week group ($P = 0.45$). In addition, the rate of a composite outcome of acute ischemic stroke/TIA/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality was not significantly different between patients in the 6- and 12-week groups **(Table 2).**

Moreover, there was no significant interaction of the primary outcome between the 6- and 12-week groups in patients taking antiplatelets (aspirin or clopidogrel use), a history of HF, DM, or a history of stroke/ICH **(Figure 2).**

Discussion

Our study showed that the TTR of patients with AF taking warfarin in the 12-week group was not inferior to that in the 6-week group. These results were consistent across patients taking antiplatelets (aspirin or clopidogrel use), a history of HF, DM, or a history of stroke/ICH. In addition, there was no significant difference between the two groups.

The previous American Guide to Warfarin Therapy recommends that INR testing should be followed up every 4 weeks after the patient's INR has become stable. [9] However, data supporting these recommendations are scarce. A previous study showed that patients taking warfarin with a 12-week follow-up appeared to be not inferior to those who were followed up every 4 weeks. These patients were prescribed warfarin for AF, heart valve replacement, and venous thromboembolism. [10] However, there was a lack of data showing the appropriate follow-up interval in patients with AF taking warfarin. Our study was conducted to prove the appropriate follow-up interval in patients with AF taking warfarin. Nevertheless, the TTR in our study (62.8% in the 6-week group *vs.* 61.3% in the 12-week group) was lower than that in the previous study (74.1% in the 4-week group *vs.* 71.6% in the 12-week group). A previous trial recruited patients taking warfarin with a therapeutic INR level and an unchanged maintenance dose for at least 6 months, whereas, in our study, patients taking warfarin for at least 12 months with no therapeutic INR level requirement were enrolled. The differences in the requirements for patient recruitment may have led to the lower TTR in our study. Moreover, 41.0% of the patients in the previous trial had prosthetic heart valve replacement and thus had a high risk of thrombogenesis. Those patients urgently needed to maintain a therapeutic INR level to prevent prosthetic valve thrombosis. This is different from the patients in our study who had only AF without rheumatic mitral stenosis, a moderate to severe degree of other valvular heart disease, mechanical prosthetic valve, and venous thromboembolism for which oral anticoagulants were indicated, and warfarin dose adjustment was dependent on each physician. In addition, more patients in our study had a history of HF, which resulted in more patients with subtherapeutic INR levels than in the previous study. However, the rate of acute ischemic stroke, major bleeding, or all-cause mortality was not significantly different between patients in the 6- and 12-week groups as in the previous study.

Our study had several limitations. First, our study was performed retrospectively. As a result, it was not feasible to record the accurate follow-up interval; therefore, we used the average follow-up interval. Moreover, there may be missing data or confounding factors in our study. Second, our study had a small sample size, which limited the power for the detection of a clinically meaningful difference in acute ischemic stroke events, major bleeding, or all-cause mortality between the 6- and 12-week groups. Third, although our study revealed that in patients with AF taking warfarin the TTR in the 12-week group was not inferior to that in the 6-week group, the TTR in our study was lower than the recommended TTR (> 65.0%–70.0%) in many standard international clinical practice guidelines. Moreover, the upper limits of the CI for the secondary outcome and its components, especially the acute ischemic stroke events and major bleeding, were wide and suggested that the 12-week follow-up interval might be appreciably worse than the 6-week follow-up interval regarding these clinical events. However, this was the first study in patients with AF taking warfarin to demonstrate that an extended follow-up interval was not inferior to that of a shorter follow-up interval. Lastly, all patients in our study were Thai, which may lead to limited generalizability, and a larger multicenter prospective study will be necessary in the future.

Conclusion

The TTR in the 12-week group was not inferior to those in the 6-week group of patients with AF taking warfarin. Moreover, the rate of acute ischemic stroke/TIA/systemic embolic events, major bleeding, minor bleeding, and/or all-cause mortality was comparable between patients in both groups. Thus, an extended 12-week follow-up interval may be applied in clinical practice.

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Conflict of interest statement

The authors have completed the International Committee of Medical Journal Editors Form for Disclosure of Conflicts of Interest. The authors declare that they have no potential or actual conflict of interest to disclose related to the present article.

Data sharing statement

The dataset used in this study is included in the manuscript. Any other additional data will be made available upon reasonable request to the corresponding author after deidentification from any patent.

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