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Optimal INR level in patients with atrial fibrillation with EHRA type 2 valvular heart disease receiving warfarin

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Abstract

Background: To date, there has been no study that compares the efficacy and safety of warfarin in atrial fibrillation (AF) patients with Evaluated Heartvalves, Rheumatic or Artificial (EHRA) type 2 valvular heart disease (VHD). This study was conducted to determine the optimal INR in these patients.

Methods: This retrospective study enrolled AF patients with EHRA type 2 VHD receiving warfarin in Central Chest Institute of Thailand between January 2016 and December 2018. The incidence density of thromboembolic or bleeding events was calculated. The International normalized ratio (INR) was classified into six groups (less than 1.50, 1.50 to 1.99, 2.00 to 2.49, 2.50 to 2.99, 3.00 to 3.49, and 3.50 or more). The optimal INR level was defined as the lowest incidence density of thromboembolic events and bleeding complications.

Results: A total of 200 AF patients with EHRA type 2 VHD receiving warfarin were enrolled, contributing to 289 patient-years of observation period. There were 13 thromboembolic events (4.5 per 100 patient-years) and 16 bleeding events (5.5 per 100 patient-years). The incidence density of thromboembolic events was significantly increased in the INR level below 2.00 (P = .03), while the INR level of 3.50 or more was significantly increased in the incidence density of major bleeding events (P = .03). Total bleeding and minor bleeding were increased significantly in INR level of 2.50 or more (P = .04).

Conclusions: The INR of 2.00 to 2.49 was appeared to be associated with the lowest incidence density of thromboembolic and bleeding events in these patients.

KEYWORDS

atrial fibrillation, bleeding, INR, thromboembolism, warfarin

1 | INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia in clinical practice. It increases the risk of ischemic stroke. Vitamin K antagonist (VKA), such as warfarin, is a common anticoagulant therapy for the prevention of ischemic stroke. It can reduce the stroke risk by 65%. To date, CHA_2DS_2-VASc score is an effective tool for predicting stroke risk in patients with nonvalvular AF (NVAF). Those with non-sex CHA_2DS_2-VASc of 1 or more are indicated for oral anticoagulant drugs.

Patients with AF usually have concomitant valvular heart disease (VHD). Recent European joint consensus proposes valvular

AF is outdated and a functional Evaluated Heartvalves, Rheumatic or Artificial (EHRA) categorization for prevention of thromboembolic events in AF patients with VHD is proposed.[1] They categorized AF patients with VHD into two groups such as EHRA type 1 including those with moderate to severe rheumatic mitral stenosis or mechanical prosthetic valve replacement, and EHRA type 2 including those with native VHD, mitral valve repair, bioprosthetic valve replacements, and trans-aortic valve intervention (TAVI). They recommend AF patients with EHRA type 1 should be prescribed VKA and those with EHRA type 2 should be prescribed either VKA or non-VKA oral anticoagulants (NOACs) for stroke prevention.[1,2]

Until now, standard clinical practice guidelines recommend the initiation of VKA in NVAF patients with CHA_2DS_2-VASc of 1 or more in male gender and/or 2 or more in female gender.[3] The optimal international normalized ratio (INR) in those is 2 to 3. However, Asian studies, especially Chinese and Japanese trials[4–6], have demonstrated the optimal INR may be lower than those from western countries. In Thailand, a study by Methavigul K et al have shown that the optimal INR in Thai AF patients is similar to Japanese and Chinese trials.[7]

However, there has been limited study about the efficacy of oral anticoagulant drugs for prevention of thromboembolism in EHRA type 2 VHD AF patients. Previous NOACs trials have demonstrated use of NOACs in AF patients with VHD had more bleeding complications than those without VHD.[8–12] To date, there are lacking of data about the optimal INR in AF patients with EHRA type 2 including bioprosthetic valve replacement, valve repair, native VHD etc. This study was conducted to determine the optimal INR in patients with AF with EHRA type 2 VHD receiving warfarin.

2 | METHODS

This study was a retrospective chart review in Central Chest Institute of Thailand among January 2016 to December 2018. AF patients with EHRA type 2 VHD over 18 years of age receiving warfarin were recruited. Patients with previous ischemic stroke before initiation of warfarin, thrombocytopenia (platelet count less than 100 000/mm^3) at the time of bleeding events, heparin-induced thrombocytopenia, myeloproliferative disorders, hyperviscosity syndrome, and those receiving warfarin less than 6 months were excluded. The study protocol was approved by the Institutional Review Board. The present study complied with the Declaration of Helsinki.

The data were collected from medical records including demographic data such as the types of VHD and management according to EHRA type 2, medications, thromboembolic, or bleeding events. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type 3 or more and minor bleeding was defined as BARC type 1 to 2.[13]

The INR level was divided into six categories (less than 1.50, 1.50-1.99, 2.00-2.49, 2.50-2.99, 3.00-3.49, and 3.50 or more). The incidence density of thromboembolic events and bleeding events in each category was calculated by the formula below.

$$\text{Incidence density} = \frac{\text{Numbers of thromboembolic and/or bleeding events in each INR level}}{\text{Summation of the time that each patient stayed in each INR group}}$$

TABLE 1 Baseline characteristics of the patients

Demographic data	Total n = 200 n (%) or mean ± SD
Age (y)	64.80 ± 11.70
≥75 y	36 (18.00%)
Male gender	125 (62.50%)
Medical history	
Diabetes mellitus	27 (13.50%)
Hypertension	81 (40.50%)
Dyslipidemia	54 (27.00%)
Coronary artery disease	16 (8.00%)
Congestive heart failure	81 (40.50%)
Chronic kidney disease	7 (3.50%)
CHA_2DS_2-VASc score	2.16 ± 1.40
0	22 (11.00%)
1	51 (25.50%)
≥2	127 (63.50%)
HAS-BLED score	1.10 ± 0.94
0-2	188(94.00%)
≥3	12(6.00%)
Medication	
ACEIs/ARBs	68 (34.00%)
Beta-blocker	116 (58.00%)
Calcium channel blocker	15 (7.50%)
Digoxin	90 (45.00%)
Amiodarone	61 (30.50%)
Aspirin	29 (14.50%)
Clopidogrel	7 (3.50%)
PPI	61 (30.50%)
LVEF	59.92 ± 12.29
<40%	8 (4.00%)
40%–49%	18 (9.00%)
≥50%	174 (87.00%)
Type of valvular heart disease	
Valve repair	156 (78.00%)
Bioprosthetic valve	48 (24.00%)
TAVI	1 (0.50%)
Moderate to severe native valve	19 (9.50%)

Abbreviations: ACEIs, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; n, number; PPI, proton pump inhibitor; SD, standard deviation; TAVI, trans-aortic valve intervention.

Numbers of thromboembolic and/or bleeding events in each INR level were counted during or within 7 days of INR measurement.

The time that each patient stayed in each INR group was calculated by halving the time between the first and next INR category.

The authors determined 0.05 for type I error and 0.20 for type II error with 80% power. The effect size was 0.30. A sample size of 220 patients or more was calculated by using G*Power 3 (Erdfelder et al, 2007).[14,15]

The demographic and clinical data were interpreted by using descriptive statistics. The categorical data are presented as frequency and percentage. The continuous data are presented as mean ± standard deviation (SD). The incidence density of thromboembolic and bleeding events was compared between each group of INR level by chi-square test. The optimal INR level was defined as the INR level had lowest thromboembolic and bleeding events. A P-value of 0.05 or less was considered the statistical significance.

3 | RESULTS

A total of 200 AF patients with EHRA type 2 VHD receiving warfarin were enrolled, contributing to 289 patient-years of the observation period. The average age was 64.8 ± 11.7 years. Most patients were male (62.5%). The most common comorbidities were hypertension and congestive heart failure (40.5%). About one-fifth of those were prescribed concomitant antiplatelet drugs. About two-third of those had a CHA_2DS_2-VASc score of 2 or more. The most common valvular interventions were surgical valve repair (78.0%). The baseline characteristics are shown in Table 1.

There were 13 thromboembolic events (4.5 per 100 patient-years) in 13 patients. The incidences of thromboembolic event rate in each type of VHD were 5.8%, 6.3%, and 10.5% in patients with surgical valve repair, bioprosthetic valve replacement and moderate to severe native valve disease, respectively. All of those had ischemic stroke. Sixteen patients experienced 16 bleeding events (5.5 per 100 patient-years). The incidences of bleeding event rate in each type of VHD were 8.3%, 6.3%, and 15.8% in patients with surgical valve repair, bioprosthetic valve replacement, and moderate to severe native valve disease, respectively. The characteristics of patients with thromboembolic events and major bleeding are shown in Tables 2 and 3, respectively. The percentage of patient-time spent within therapeutic INR range (2-3), INR below 2.00, and INR above 3.00 were 33.5%, 53.5%, and 12.6%, respectively. Comparison between incidence density of ischemic stroke, minor bleeding, major bleeding, and total bleeding in each INR level categories by using chi-square test are shown in Figures 1-4.

This study demonstrated the incidence density of thromboembolic events was significantly increased in the INR level below 2.00 (P = .03), while the INR level of 3.50 or more had a significant increase in the incidence density of major bleeding events (P = .03). Total bleeding and minor bleeding were increased significantly in the INR level of 2.50 or more (P = .04). This study also revealed the INR level of 2.00-2.49 had the lowest incidence density of thromboembolic and bleeding events as shown in Figure 5.

4 | DISCUSSION

To the best of our knowledge, the optimal INR in patients with NVAF is 2 to 3 in western trials while the optimal INR in those is lower in Asian trials. However, there are scarce data about the optimal INR in AF patients with EHRA type 2 VHD according to recent European joint consensus. Previous NOACs trials have demonstrated use of NOACs in AF patients with VHD had more bleeding complications than those without VHD.[7–12]

This study demonstrated AF patients with EHRA type 2 VHD receiving warfarin had the lower therapeutic INR level compared with western trials in NVAF patients while those had higher lowest

TABLE 2 Characteristics of patients with thromboembolic events

Patient	Age (y)	Gender	Type of thromboembolic event	INR during events
14	80	Male	Ischemic stroke	1.26
21	73	Male	Ischemic stroke	1.65
42	53	Female	Ischemic stroke	1.80
44	54	Male	Ischemic stroke	1.31
45	80	Male	Ischemic stroke	1.80
80	72	Male	Ischemic stroke	1.18
114	63	Male	Ischemic stroke	1.27
121	67	Male	Ischemic stroke	1.04
129	67	Male	Ischemic stroke	1.76
163	84	Female	Ischemic stroke	1.46
169	58	Female	Ischemic stroke	1.45
191	55	Male	Ischemic stroke	1.31
194	71	Male	Ischemic stroke	1.78

Abbreviations: INR, International normalized ratio; y, years.

TABLE 3 Characteristics of patients with major bleeding

Patient	Age (y)	Gender	Bleeding site	INR during events
2	66	Female	GI bleeding	4.44
73	72	Male	ICH	4.57
143	75	Male	Hematuria	7.37
181	70	Male	Hematuria	6.22
192	72	Female	ICH	8.98

Abbreviations: INR, International normalized ratio; y, years.

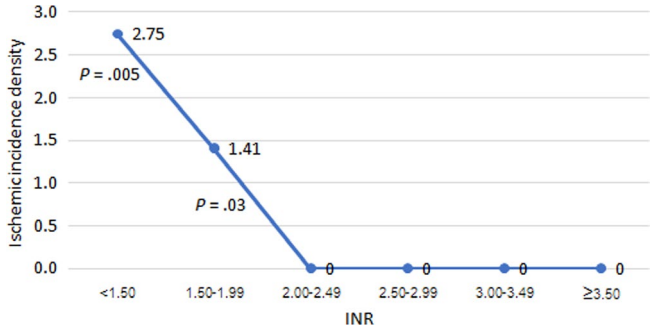

FIGURE 1 Incidence density of ischemic stroke (events per 100 patient-years) in each INR group

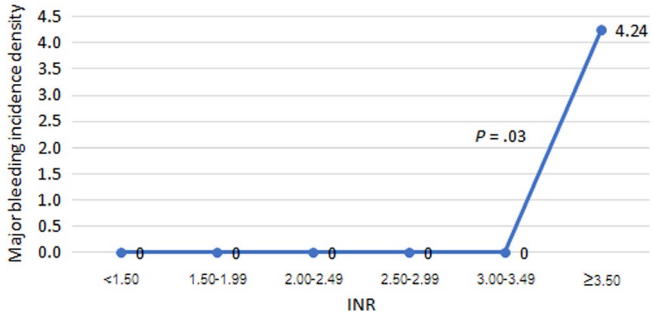

FIGURE 2 Incidence density of major bleeding (events per 100 patient-years) in each INR group

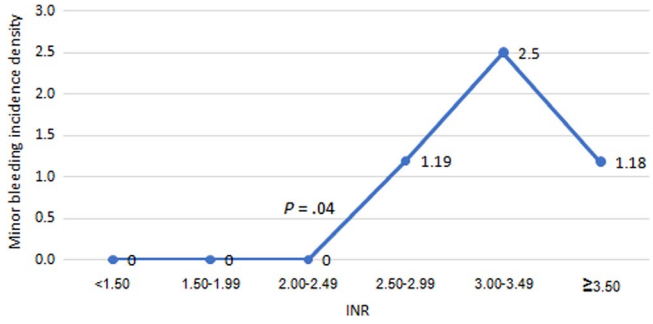

FIGURE 3 Incidence density of minor bleeding (events per 100 patient-years) in each INR group

limit of optimal INR than previous Asian trials.[4–7] This finding implied these patients had more thromboembolic events than Asian NVAF patients and more bleeding events than western NVAF patients.

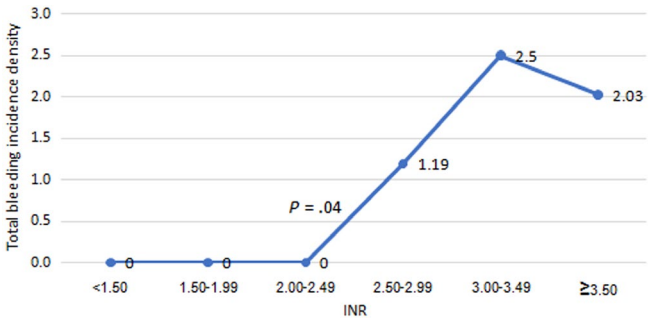

FIGURE 4 Incidence density of total bleeding (events per 100 patient-years) in each INR group

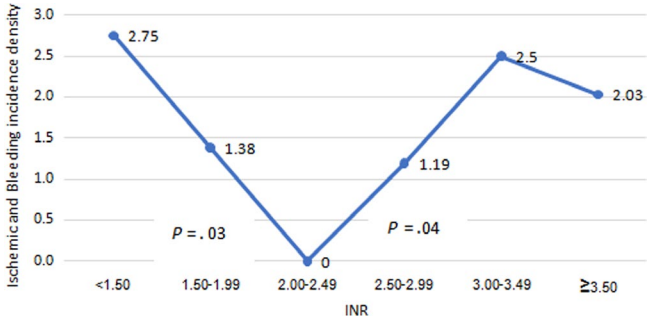

FIGURE 5 Incidence density of ischemic stroke and bleeding events (events per 100 patient-years) in each INR group

Compared to previous Thai study[7], the thromboembolic events in this study (4.5%) were higher, but the bleeding events (5.5%) were slightly lower than NVAF patients.

There were several reasons for higher bleeding than western NVAF patients. First, Bleeding events in this study were used following the BARC criteria of bleeding[13] while those in other Asian trials were used the different bleeding definition. This was a reason for the different bleeding events. Second, Thai patients had lower body weight than western patients leading to increase risk of bleeding. Lastly, Thai patients had CYP2C9 and VKORC1 polymorphisms that were different from western patients. However, the prevalence of CYP2C9*2 and CYP2C*3 was very low (5%), while the prevalence of VKORC1 AA haplotype was 63.6% in Thai patients.[16] The effect of VKORC1 AA haplotype may be affected to the requirement of lower dose of warfarin in Thai patients.

The thromboembolic events were higher than Thai NVAF patients may be from the different population. This study recruited AF patients with EHRA type 2 VHD which 88% of those had a history of surgical valvular repair or bioprosthetic valve replacement. Most patients in this study had higher thromboembolic risk compared with native VHD or non-VHD patients. This demographic profile supported the higher lowest INR level than previous Thai NVAF patients.

The optimal INR level in this study was 2.00-2.49 because of the lowest incidence of thromboembolic and bleeding events. The combined thromboembolic and bleeding complications were higher in the group with INR below 2.00 and INR of 2.50 or more because of increased incidence density of thromboembolism with statistical significance in INR below 2.00 and more bleeding events in INR of 2.50 or more with statistical significance.

However, there were several limitations in this study. First, this study was a retrospective chart review, so some data might be missed because of the absence of documentation in the medical records. Second, the sample size was small and less than expected to be recruited leading to limited for clinical application in general population. Finally, some patients had no INR level during nonsignificant bleeding within 7 days or discontinued warfarin before INR measurement. This affected the interpretation of the bleeding events in some groups of INR. Nevertheless, this study was a preliminary data about the optimal INR in AF patients with EHRA type 2 VHD.

5 | CONCLUSIONS

The INR of 2.00-2.49 was appeared to be associated with the lowest incidence density of thromboembolic and bleeding events in AF patients with EHRA type 2 VHD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for this article.

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