ORIGINAL ARTICLE

Optimal INR Level in Nonvalvular Atrial Fibrillation Patients in Thailand: A Multi-Site Study

Tomon Thongsri, MD[1], Wisit Chanprasertpinyo, MD[1], Wattana Wongtheptien, MD[2], Supharat Wattanasombat, PharmD[3], Chatuphorn Suami, MS[4], Rungroj Krittayaphong, MD[5]

[1] Department of Internal Medicine, Buddhachinaraj Hospital, Phitsanulok, Thailand; [2] Department of Internal Medicine, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; [3] Department of Pharmacy, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; [4] Department of Epidemiology & Biostatistics, Buddhachinaraj Hospital, Phitsanulok, Thailand; [5] Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Warfarin is a common drug for thromboembolic prevention in patients with nonvalvular atrial fibrillation (NVAF). However, hemorrhagic complications are also a concern. The optimal international normalized ratio (INR) level is different in each ethnicity.

Objective: To establish the INR range with lowest all adverse event, optimal INR, in Thai NVAF patients from large data, nationwide Warfarin Registry Network (WaRN).

Materials and Methods: The present study was a retrospective cohort study. It analyzed the data of 31,704 Thai NVAF patient between January 1, 2010 and December 31, 2020. The numbers of thromboembolic and bleeding events were correlated to INR level at the time of event. The six groups of INR range were defined as less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and greater than 3.5.

Results: The data from 797 warfarin clinics were analyzed with an observation period of 21,328.52 patient-years. The median duration of follow-up was 519 days (IQR 172, 1,183). Of the 31,407 patients, 277 patients experienced 319 thromboembolic events, and 3,398 patients experienced 4,860 bleeding events. The thromboembolic events were 4.92, 1.89, 0.86, 0.72, 0.39, 0.36 per 100 patient-years in INR range of less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively. The bleeding events were 12.69, 9.51, 8.41, 15.35, 36.38, 125.03 per 100 patient-years in INR range of less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively. The all-adverse events were 17.61, 11.40, 9.27, 16.07, 36.77, 125.39 per 100 patient-years in the INR range of less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively.

Conclusion: The incidence density of all-adverse events was lowest in INR range of 2.0 to 2.5. This range should be the optimal therapeutic INR level for Thai NVAF patient. However, the INR range can extend to 1.5 to 2.5 in clinical practice.

Keywords: Optimal INR; Nonvalvular Atrial Fibrillation, Bleeding, Thromboembolism

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Atrial fibrillation is a common cardiac arrhythmia[1-3]. The incidence of AF is 1.2% in Western patient[4,5] while it is 3.6% in Thai patient[6].

Thromboembolic events are more common in these patients. So oral anticoagulants, especially warfarin, were widely used to prevent this event. However, bleeding complication is also a common complication of warfarin. The international normalized ratio (INR) must be monitored to balance warfarin levels between bleeding and thromboembolic events optimally. Studies showed the optimal INR was 2.0 to 3.0 for non-valvular atrial fibrillation (NVAF) patients in the Western patients[7,8].

A different INR level is recommended in each country in Asia, 1.5 to 3.0 for Chinese, 1.5 to 2.1 for Japanese and 1.7 to 2.2 for Korean[9-11]. Because of bleeding events, these trials recommended a lower optimal INR. Especially because the risk of intracerebral hemorrhage increases 4-fold in Asian patient[12]. Including Thai patients, the previous study in 2014 recommended 1.5 to 2.9 in NVAF. However, the small sample size may limit the incidence of thromboembolic and bleeding events[13].

For increasing the accessibility and efficacy

Correspondence to:

Thongsri T.

Buddhachinaraj Phitsanulok Hospital, 90 Srithamatripidok Road, Muang, Phitsanulok 65000, Thailand.

Phone: +66-55-270300 ext. 17105

Email: ttomon@hotmail.com

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of warfarin, warfarin clinics have been established in community and provincial hospitals throughout Thailand since 2007. In the Ministry of Public Health (MOPH) strategy, more than 700 clinics were established in 2020. Most of them are under MOPH. Each clinic operates with a doctor, nurse, and pharmacist. The medication, laboratory and tools were provided in these hospitals. Warfarin Registry Network (WaRN), a nationwide web-based online registry, was established in 2008 to evaluate the efficacy and poll patient data.

The present study was conducted to establish the optimal INR level in Thai NVAF patients upon data from WaRN. The optimal INR level was defined as the lowest incidence density of all adverse events, thromboembolic, and bleeding events.

Materials and Methods

The retrospective nationwide cohort study was conducted to analyze data from WaRN. All patients who were given warfarin in each warfarin clinic were recorded in WaRN by pharmacist. All of them followed-up in warfarin clinic. From nationwide warfarin clinics, the data were polled as a database. From this database, the authors selected patients corresponding to inclusion criteria, NVAF patients aged 18 to 80 years old and treated in a warfarin clinic for at least six months between January 1, 2010 and December 31, 2020. In WaRN, the NVAF definition follows the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation[14].

Patients who indicated prosthetic valve replacement, hyperviscosity, venous thrombo-embolism, valvular repair surgery, intracardiac thrombus, and valvular AF were excluded. The valvular AF was defined as rheumatic mitral valve disease, prosthetic heart valve or mitral valve repair. The study protocol was approved by the Buddhachinaraj Phitsanulok Hospital Ethics Committee (No. 050/61).

The electronic database from WaRN was collected. The INR level was classified into six groups, which are less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, as in the previous study[13]. Then the authors analyzed the data as descriptive analytic statistics. The incidence density of thromboembolic or bleeding events was calculated by dividing the numbers of thromboembolic or bleeding events in each INR level with the summary of time that each patient stayed in each INR group. The number of thromboembolic or bleeding events was counted by the INR level during the occurrence of events in each INR. If INR level at the event was not available, it was recorded as missing data.

Thromboembolic events consist of symptomatic ischemic stroke, pulmonary embolism, and recurrent deep vein thrombosis. A bleeding event consists of major and minor bleeding. Major bleeding was defined as 1) fatal bleeding, or 2) bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular bleeding with compartment syndrome, or 3) bleeding causing a fall hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cell. Minor bleeding was defined as bleeding other than major bleeding[15]. These are the definitions of WaRN registry when it was established in 2008.

The Shapiro-Wilk test was used to analyze normal distribution data. The categorical data such as gender and location were presented as frequency and percentage. Continuous variables such as age were presented as mean ± standard deviation (SD). The thromboembolic events including ischemic stroke and bleeding events were analyzed as the chi-square test for two rates. The incidence density of events was compared between each group of INR levels. The optimal INR level was defined as the lowest incidence density of all adverse events, thromboembolic and bleeding events. Cox regression analysis was presented as hazard ratio and 95% confidence interval to define predicting factors were out of therapeutic INR level. The R program version 3.6.2 was used for statistical computing. The incidence density of thromboembolic and bleeding events was calculated with the Rosendaal method[16].

Results

There were 31,407 NVAF patients with 278,931 visits collected between January 1, 2010 and December 31, 2020, from 797 warfarin clinics throughout Thailand. The median follow-up time was 519 days (IQR 172, 1183). The average follow-up time in each visit was 138.43±276.02 days. It contributed to 21,328.52 patient-years. The mean age was 62.2±12.4 years and 53.4% were female. The characteristics are shown in Table 1.

Three hundred nineteen thromboembolic events were reported in 277 patients or 1.49 per 100 patient-years. Almost all of them were ischemic stroke, with 317 events (99.3%). Pulmonary embolism was found in two events (0.63%). Four thousand eight hundred sixty bleeding events were reported in

Table 1. Baseline characteristics of Thai NVAF patients

Characteristics	n=31,407
Age (year)	
Mean±SD	62.2±12.4
≥75	5,389 (17.2)
65 to 74	9,908 (31.6)
Female; n (%)	16,756 (53.4)
Comorbidity; n (%)	
Hypertension	24,999 (79.6)
Congestive heart failure	2,210 (7.0)
Diabetes	9,748 (31.0)
History of stroke/emboli	1,193 (3.8)
Vascular disease	534 (1.7)
CHA_2DS_2-VASc score; n (%)	
Mean±SD	3.5±2.4
Score 0	2 (0.01)
Score 1	5,802 (18.5)
Score 2	13,569 (43.2)
Score 3	7,459 (23.8)
Score 4	1,837 (5.9)
Score 5	1,890 (6.0)
Score 6	726 (2.3)
Location of warfarin clinic; n (%)	121 (0.4)
Bangkok and central region	7,337 (23.4)
North region	10,686 (34.0)
East and North-east region	7,657 (24.4)
South region	5,727 (18.2)

SD=standard deviation

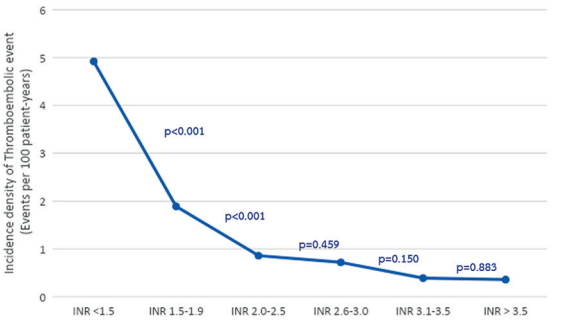

Figure 1. Incidence density of thromboembolic event per 100 patient-years in each INR group.

3,398 patients or 22.79 per 100 patient-years, as in Table 2 and 3. The time of patient stay in INR 2.0 to 3.0, less than 2, and more than 3 were 49.64, 34.24, and 16.12% of total follow-up time, respectively.

The time in therapeutic range (TTR) was 39.22% by the cross section of patient in the range method. The TTR by Rosendaal's method was 32.91%. The incidence density of thromboembolic event was 4.92, 1.89, 0.86, 0.72, 0.39, 0.36 per 100 patient-years in each INR level of less than 1.5, 1.5 to 1.9, 2 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively. In the INR level of less than 1.5 and 1.5 to 1.9, the incidence density of thromboembolic event significantly increased ($p<0.001$), as shown in Figure 1.

Table 2. The incidence of all adverse events

Adverse event	Patient number (n=31,407); n (%)	Event number (total 278,931 visits); n (%)	Per 100 patient-year
Thromboembolism	277 (0.88)	319 (0.11)	1.49
Bleeding	3,398 (10.82)	4,860 (1.74)	22.79
Minor	3,147 (10.02)	4,590 (1.65)	21.52
Major	251 (0.80)	270 (0.09)	1.27
Total	3,675 (11.70)	5,179 (1.85)	24.28

Table 3. Adverse event in each group of INR

Adverse event	Group of INR					
	INR <1.5	INR 1.5-1.9	INR 2.0-2.5	INR 2.6-3.0	INR 3.1-3.5	INR >3.5
Thromboembolism; n (%)	133 (0.05)	87 (0.03)	60 (0.02)	26 (0.01)	6 (0.002)	7 (0.003)
Total bleeding; n (%)	343 (0.12)	438 (0.15)	585 (0.21)	556 (0.20)	560 (0.20)	2,378 (0.86)
Minor	319 (0.11)	430 (0.15)	558 (0.20)	544 (0.20)	548 (0.19)	2,191 (0.79)
Major	24 (0.09)	8 (0.003)	27 (0.01)	12 (0.004)	12 (0.004)	187 (0.07)
Total; n (%)	476 (0.17)	525 (0.18)	645 (0.23)	582 (0.21)	566 (0.20)	2,385 (0.86)
Incidence density of all adverse event (per 100 patient-year)	17.61	11.4	9.27	16.07	36.77	125.39

INR=international normalized ratio

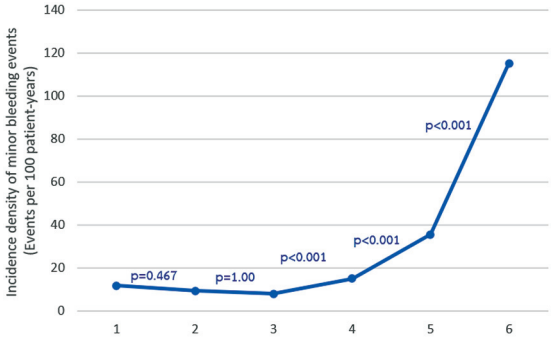

Figure 2. Incidence density of minor bleeding events per 100 patient-years in each INR group.

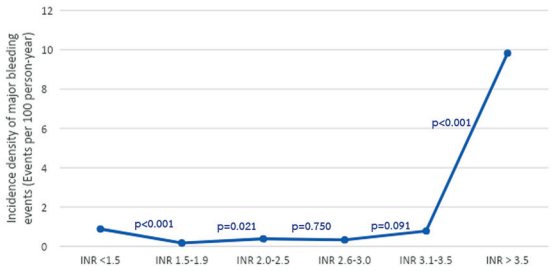

Figure 3. Incidence density of major bleeding events per 100 patient-years in each INR group.

The incidence density of minor bleeding was 11.80, 9.34, 8.02, 15.03, 35.6, 115.19 per 100 patient-years in group of INR of less than 1.5, 1.5 to 1.9, 2 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively, as shown in Figure 2. The incidence density of major bleeding was 0.88, 0.17, 0.38, 0.33, 0.78, 9.83 per 100 patient-years in INR level of less than 1.5, 1.5 to 1.9, 2 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively as shown in Figure 3. For the total bleeding event, the incidence density was 12.69, 9.51, 8.41, 15.35, 36.38, 125.03 per 100 patient-years in INR group of less than 1.5, 1.5 to 1.9, 2 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively. It increased significantly in INR levels 2.6 to 3.0, 3.1 to 3.5, especially in INR level of more than 3.5 ($p<0.001$).

The incidence density of all adverse events, thromboembolic and bleeding events, were 17.61, 11.40, 9.27, 16.07, 36.77, 125.39 per 100 patient-years in INR level of less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5 respectively as shown in Figure 4. Considering to thromboembolism and major bleeding, excluding minor bleeding, the incidence density was 7.71, 4.90, 6.04, 9.40, 11.23, 117.86 per 100 patient-years in INR level of less than 1.5, 1.5 to 1.9, 2.0 to 2.5, 2.6 to 3.0, 3.1 to 3.5, and more than 3.5, respectively.

The incidence density of total bleeding events increases significantly in INR level of more than 2.5 ($p<0.001$, rate ratio 3.87, 95% confidence interval 3.13 to 4.79). The incidence density of thromboembolism increases significantly in INR level of less than 1.5 and 1.5 to 2.0 ($p<0.001$, rate ratio 9.69, 95% confidence interval 5.46 to 17.21). From the results, the authors regrouped and analyzed the all-adverse events in groups of INR levels of less than 1.5, 1.5 to 2.5 and more than 2.5. It increased significantly in INR level of more than 2.5 ($p<0.001$, rate ratio 4.23, 95% confidence interval 3.37 to 5.37). However, there was no significant difference in INR level 1.5 to 2.5 and INR of less than 1.5 ($p=0.094$, rate ratio 2.18, 95% confidence interval 0.59 to 2.97), as shown in Figure 5.

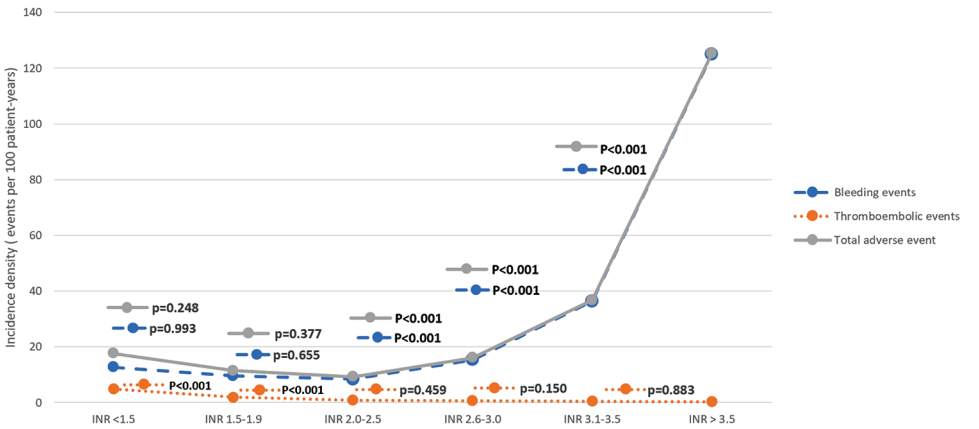

Figure 4. Incidence density of all adverse event, thromboembolic event and bleeding event per 100 patient-years in each INR group.

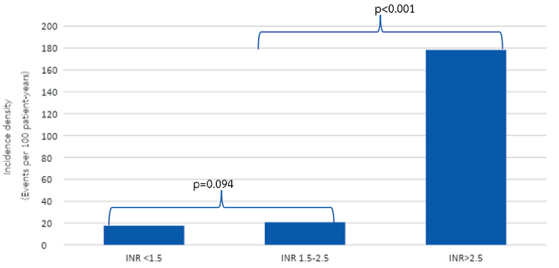

Figure 5. Incidence density of all adverse events per 100 patient-years compared in 3 group of INR range.

Discussion

The present study discovered that Thai NVAF patients who received warfarin had different incidences of thromboembolic and bleeding events from American and European patients. In the previous study, thromboembolic events in Asian patients were similar to European patients. However, the incidence of bleeding events is significantly higher in Asian, at 3.1% to 7.7% versus 2.9%. The bleeding events were very high, at 24.8% in Thai patients[10,11,13,17].

The present study discovered thromboembolic events were low, with only 0.88%. However, the bleeding event was higher than in European patients, with 10.82%. Most of them were minor bleeding events, with 10.02%. The major bleeding events were only 0.80%. This finding supports the data from previous studies.

The TTR in the present study was lower than expected, at less than 65%. In the period of data collection, many warfarin clinics in this registry were just set up and stayed in the developing period. Most of the clinics were in rural areas. Therefore, it may affect compliance and TTR. This TTR was the same as in the GARFIELD registry, the Asian population has lower TTR than the European population[18,19]. However, the incidence of thromboembolic events in Thai patients is still low. Therefore, an optimal target INR should be considered in Thai patients.

Other than TTR, genetic polymorphism is an important factor that affects bleeding events in patients that received warfarin. The patient who has mutant alleles of CYP2C9*2, CYP2C9*3, VKORC1 A haplotype/polymorphism tends to bleed from warfarin[20-23]. Even so, the incidence of CYP2C9*2 and CYP2C9*3 mutation is low in Northern Thai patients, at only 5%. However, the incidence of VKORC1 A haplotype is high, at 63.6%[24]. It is 2-fold higher than the Americans and Europeans. Therefore, the optimal target INR may be adjusted in these patients. The genetic application in patients that received warfarin needs further study.

In the present study, an INR level of more than 2.5 increased the risk of minor bleeding. An INR level of more than 3.5 increased the risk of major bleeding significantly. Therefore, the bleeding event should be special caution when INR is over 3.5. As an unexpected result, the group of INR of less than 1.5 have more incidence of major bleeding event than group of INR 1.5 to 1.9. This result may be related to compliance of patient. The poor compliance of warfarin and antihypertensive drug may affect the INR level and risk of bleeding. Because most of data were collected from warfarin clinics in rural areas and there were many hypertensive patients in the present study, further investigation should be considered. An INR range of 2.0 to 2.5 was an important INR range. The thromboembolic, bleeding and all adverse events were lowest in this INR range. Thromboembolic events increased significantly when INR was less than this range and bleeding events increased significantly when INR was over this range. For the all-adverse event, the incidence density was lowest in groups of INR levels of 2.0 to 2.5. This should be optimal therapeutic level, but it is difficult in real practice.

Therefore, the authors regrouped to an INR level of less than 1.5, 1.5 to 2.5 and more than 2.5 to define optimal INR. The incidence density of all adverse events in the INR of more than 2.5 group was significantly higher than INR 1.5 to 2.5. In the meantime, the incidence density of thromboembolic events significantly increased in INR in the less than 1.5 group. Thus, the authors proposed the optimal INR for Thai NVAF patients is 2.0 to 2.5, the lowest incidence of thromboembolic and bleeding events, similar to a previous Thai study[13].

Even though the present study analyzed large data, this was a retrospective study. There were some confounding factors not included in the present study such as HASBLED score, echocardiographic finding, concomitant medication, and concomitant disease. Because the present study is a real word registry that collected data from well-established and developing warfarin clinics, the TTRs were low in the present study.

Conclusion

The incidence density of all adverse events was lowest in INR range of 2.0 to 2.5. This range was proposed to be the optimal therapeutic INR level for Thai NVAF patient. However, this range can extend to 1.5 to 2.5 in clinical practice.

What is already known on this topic?

The optimal INR in Thai NVAF patients is different from the Western patients. As in other Asian patients, the Thai patients need lower INR to prevent thromboembolic events.

What does this study add?

In this large cohort study, the optimal INR for Thai NVAF patient was different from the previous study. The INR level 2.0 to 2.5 showed the lowest incidence rate of thromboembolic and bleeding events.

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Conflicts of interest

The authors declare no conflict of interest.

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