Optimal INR Level in Thai Atrial Fibrillation Patients Who Were Receiving Warfarin for Stroke Prevention in Thailand

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Objective: *To determine the optimal International Normalized Ratio (INR) level in Thai atrial fibrillation (AF) patients who received warfarin.*

Material and Method: *This retrospective study enrolled 230 AF patients that received warfarin in Siriraj Hospital between January 1, 2005 and December 31, 2009 and collected the lNR level at the time of the event, the numbers of ischemic stroke, and bleeding events. The incidence density of ischemic stroke or bleeding events was calculated by dividing the number of ischemic stroke or bleeding event in each INR level with the summation of the time that each patient stayed in each INR group. The patients with a prosthetic valve were excluded. The INR range was classified into six groups (less than 1.5, 1.5 to 1.9, 2.0 to 2.4, 2.5 to 2.9, 3.0 to 3.4, and greater than 3.4). The optimal INR level was defined as the lowest incidence density of ischemic stroke and bleeding complications.*

Results: *Two hundred thirty AF patients (the mean age 68±12 years) were enrolled, contributing to 737.54 patient-years of observation period. Of the 230 patients, nine patients experienced 12 ischemic events (1.6 per 100 patient-years) and 54 patients experienced 57 bleeding events (7.7 per 100 patient-years). The percentage of patient-time spent within INR 2 to 3, INR less than 2, and INR more than 3 were 40.75, 46.22, and 13.03%, respectively. The INR level more than 3.4 increased both major and minor bleeding events ($p = 0.001$). The INR level of 3.0 to 3.4 increased the minor bleeding events ($p = 0.03$). The INR level less than 1.5 increased incidence of ischemic stroke ($p = 0.03$). The overall event rate was lowest in the INR range from 1.5 to 2.9, which is significantly different from that of INR more than 2.9 ($p<0.0001$), but trend lower than INR less than 1.5 without being statistically significant ($p = 0.198$).*

Conclusion: *An INR of 1.5-2.9 appeared to be associated with the lowest incidence rate of bleeding or ischemic stroke in a cohort of Thai AF patients receiving warfarin therapy for stroke prevention.*

Keywords: *International normalized ratio (INR), Warfarin, Anticoagulation, Atrial fibrillation, Ischemic stroke, bleeding*

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Atrial fibrillation (AF) is the most common cardiac arrhythmias in our clinical practice. Several factors are related to atrial fibrillation such as advanced age, hypertension, diabetes mellitus, coronary artery disease, or valvular heart diseases[14,16].

The management in atrial fibrillation consists of the correction of the precipitating factors, rate control or rhythm control, and anticoagulation for stroke prevention[14,16]. Currently, warfarin is the useful drugs for both primary and secondary stroke prevention in atrial fibrillation patients. It is well known that warfarin inhibits vitamin K epoxide reductase leading to reduce the active form of vitamin K. This action affects the coagulation system including the prothrombin time and international normalized ratio (INR). Its half-life is 36 to 42 hours[14]. The full antithrombotic effect is reached five days after the initial dose of warfarin. Although warfarin has a benefit for stroke prevention in atrial fibrillation patients, it has bleeding complications. The optimal INR level prevents atrial fibrillation patients from ischemic stroke, if low INR level, and bleeding complications, if high INR level.

The previous trials in United States and European countries found that INR level 2 to 3 had the lowest incidences of thromboembolic and bleeding events[2,13]. These data came from western countries. However, there was no data for safety of warfarin in Asian countries including Thailand. In 2000 and 2005, Japan and China completed clinical trials for the optimal INR level in atrial fibrillation patients, respectively[1,9,15]. These trials were suggestive of

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lower optimal INR level in Asian people. However, there is still a lack of data in Thai AF patients.

The present trial is conducted to determine the optimal INR level in Thai AF patients who received warfarin for stroke prevention. The optimal INR level is defined as the lowest incidences of ischemic stroke and bleeding complications.

Material and Method

The present study was done between January 1, 2005 and December 31, 2009. It enrolled Thai patients, aged at least 18 years old who were either paroxysmal or persistent atrial fibrillation and received warfarin for stroke prevention for at least six months, following the ACC/AHA/ESC2006 Guidelines for the Management of Patients with Atrial Fibrillation. Patients were excluded if they had prior ischemic stroke or bleeding complications before January 1, 2005, platelet count was less than 100,000/mm^3 during bleeding occurrence, ischemic stroke from heparin-induced thrombocytopenia, myeloproliferative disorders including essential thrombocythemia, chronic myeloid leukemia, polycythemia vera, agnogenic myeloid metaplasia, or hyperviscosity syndrome, or prosthetic heart valve replacement. The study protocol was approved by the Siriraj Institutional Review Board. The present study was performed in accordance with the Declaration of Helsinki.

We classified the INR level into six groups (less than1.5, 1.5 to 1.9, 2.0 to 2.4, 2.5 to 2.9, 3.0 to 3.4, and more than 3.4) and retrospectively analyzed data from the medical records.

The incidence density of ischemic stroke or bleeding events was calculated by dividing the numbers of ischemic stroke or bleeding event in each INR level with the summation of the time that each patient stayed in each INR group[14].

The numbers of ischemic stroke and bleeding event in each group of INR level were counted by the INR level during or within seven days before the occurrence of the ischemic or bleeding events.

The time that each patient stayed in each INR group was calculated by dividing the half-time between the first and the next INR levels in each pairs of INR level. The first half-time was the time in the first INR level and the last half-time was the time in the next INR level. For example, if one INR was 2.4 and the next INR, 12 weeks later, was 2.6, the time of INR 2.0 to 2.4 was six weeks and INR 2.5 to 2.9 was six weeks.

Ischemic stroke was defined as the sudden neurological deficit whether more than 24 hours or not and normal non-contrast computed tomography with or without significant carotid artery stenosis from carotid doppler ultrasonography or carotid bruit.

Bleeding complications were consist of major and minor bleeding. Major bleeding was defined as 1) gastrointestinal bleeding required at least two units of blood transfusion or led to hemodynamically compromised, 2) intracranial hemorrhages were consist of intraventricular hemorrhage, intracerebral hemorrhage, subarachnoid hemorrhage, and/or subdural hematoma, 3) gross hematuria required continuous bladder irrigation or led to hemodynamically compromised, and 4) hemoptysis required emergent bronchoscopy or bronchial embolization or intubation or led to hemodynamically compromised. Minor bleeding was defined as the bleeding other than major bleeding.

The authors estimated the incidences of thromboembolic events in each INR group such as INR level less than1.5, 1.5 to 1.9, 2.0 to 2.4, 2.5 to 2.9, 3.0 to 3.4, and more than 3.4, respectively to be 0.144, 0.023, 0.022, 0.011, 0, and 0 [modified from Cheung et al, 2005[1]]. We determined 0.05 for type I error and 0.20 for type II error with 80% power. A sample size of 230 patients was calculated to compare populations of more than two groups by Chi-square test.

The categorical data such as sex and comorbid diseases were presented as frequency and percentage. The continuous variables such as age, LVEF, and left atrial size were presented as mean ± standard deviation (SD). The optimal INR level was determined by comparing the incidence density between each group of INR level. The authors compared the incidence density of ischemic stroke and bleeding complications with the Chi-square test for two rates. The optimal INR level was defined as the lowest incidence density of ischemic stroke and bleeding complications.

Results

Two hundred thirty atrial fibrillation patients were enrolled between January 1, 2005 and December 31, 2009 contributing to 737.54 patient-years of observation period. The mean age of the patients was 68±12 years and 62.17% of patients were female. Two-third of patients (65.22%) were non-valvular AF. Hypertension was the most common comorbidity (61.74%). One-fourth of patients (23.04%) had concomitant aspirin, 5.22% had concomitant clopidogrel, and 3.91% had combined aspirin and

Table 1. Baseline characteristics of Thai atrial fibrillation patients

Characteristics	Number (%) or mean ± SD Total n = 230
Age (years)	68.1±12.0
Female sex	143 (62.2)
Nonvalvular AF	150 (65.2)
Comorbidity	
Liver cirrhosis	2 (0.9)
Chronic kidney disease	19 (8.3)
Hypothyroidism	15 (6.5)
Hyperthyroidism	7 (3.0)
Diabetes mellitus	61 (26.5)
Hypertension	142 (61.7)
Dyslipidemia	104 (45.2)
Coronary artery disease	50 (21.7)
Echocardiographic findings	
LVEF (%)	65.0±10.5
Apical aneurysm	1 (0.4)
LA volume index (ml/m^2)	76.0±52.5
LA diameter (mm)	51.6±9.6
Concomitant antiplatelets	
Aspirin	53 (23.0)
Clopidogrel	12 (5.2)
Dual antiplatelets	9 (3.9)

AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction

clopidogrel. Their baseline characteristics were shown in Table 1.

Of the 230 patients, nine patients experienced 12 ischemic events (1.6 per 100 patient-years) and 54 patients experienced 57 bleeding events (7.7 per 100 patient-years). The percentage of patient-time spent within therapeutic INR range 2 to 3, INR less than 2 and INR more than 3 were 40.75, 46.22, and 13.03%, respectively.

The authors analyzed and compared the incidence density of ischemic stroke, major bleeding, minor bleeding, and total bleeding events between each group of INR level with the Chi-square test for two rates as show in Fig. 1-4.

The present trial revealed the INR level more than 3.4 increased the incidence density of total bleeding events significantly (rate ratio 3.55, 95% confidence interval 1.52-9.61, p = 0.001) compared with other groups of INR level. The INR level less than 1.5 increased the incidence density of ischemic stroke significantly (rate ratio 4.03, 95% confidence interval 0.97-23.60, p = 0.03). Although the present trial

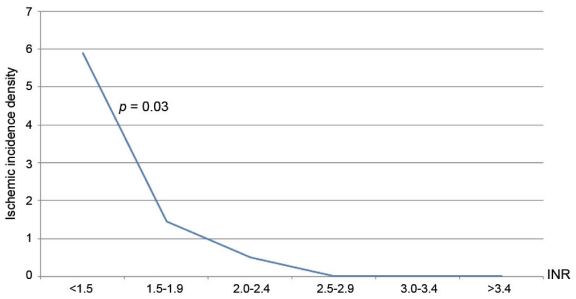

Fig. 1 Incidence density of ischemic stroke (events per 100 patient-years) in each INR group.

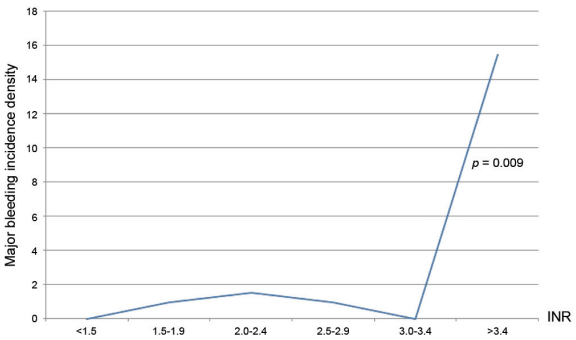

Fig. 2 Incidence density of major bleeding (events per 100 patient-years) in each INR group.

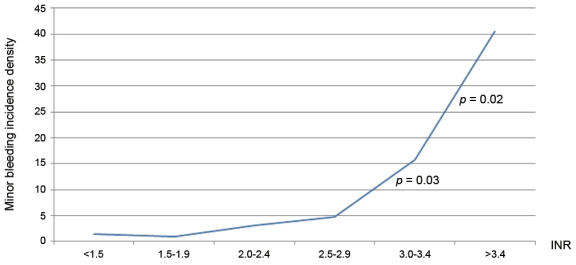

Fig. 3 Incidence density of minor bleeding (events per 100 patient-years) in each INR group.

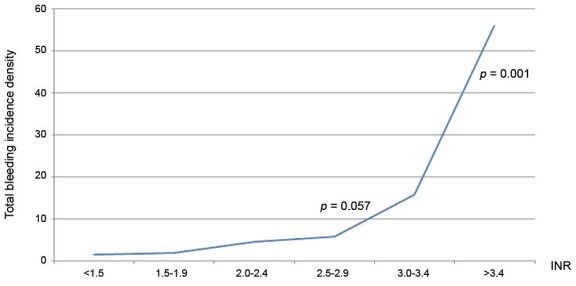

Fig. 4 Incidence density of total bleeding (events per 100 patient-years) in each INR group.

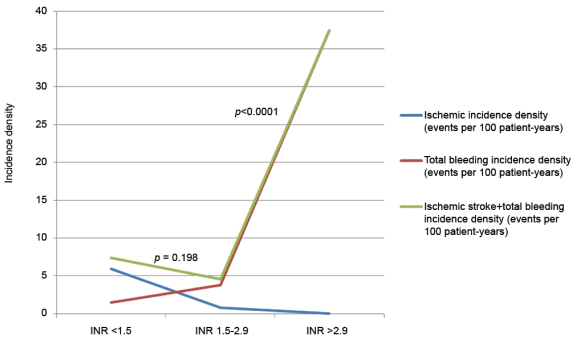

Fig. 5 Incidence density of ischemic stroke and total bleeding (events per 100 person-years) in each INR group.

showed that the INR level 1.5 to 3.4 did not increase the incidence density of ischemic stroke and total bleeding events, the INR level 3.0 to 3.4 increased the incidence density of total bleeding events with borderline significant (rate ratio 2.76, 95% confidence interval 0.79 to 9.93, p = 0.057). The increased incidence density of total bleeding events in the INR level 3.0 to 3.4 was driven by the significantly increased incidence density of minor bleeding events (rate ratio 3.31, 95% confidence interval 0.90-13.22, p = 0.03). Therefore, the authors concluded that the optimal INR level was 1.5 to 2.9. The overall event rate was the lowest in the INR range from 1.5 to 2.9 with significant difference from that of INR level more than 2.9 (rate ratio 0.12, 95% confidence interval 0.07-0.21, p<0.0001), but trend lower than INR level less than 1.5 without statistically significant difference (rate ratio 0.62, 95% confidence interval 0.28-1.45, p = 0.198) as show in Fig. 5.

Discussion

The present trial showed Thai patients with atrial fibrillation required lower INR level than western patients in the previous studies[2,13]. The results in the present trial were similar to the prior trials from Japanese and Chinese populations[1,9,15]. The reasons for the different results from the western population and the same results as Asian population may be from the racial difference between Asian and western populations. Previous trial from EAFT study showed the overall ischemic events were 5.6%, while bleeding events were 2.9%[13]. Later trials were conducted in Japan and Hong Kong, found that the overall thromboembolic events 2.6 to 5.5% were similar to the results from European population, while these trials revealed the bleeding events 3.1 to 7.0% were higher than the European population[1,9,15]. Especially, the Japanese study was terminated prematurely due to significantly higher life-threatening bleeding complications in the conventional-intensity group (INR 2.2-3.5) than the low-intensity group (INR 1.5-2.1)[15]. These Asian trials showed higher bleeding complications in the warfarin users from western population. The present trial was the first study in Thai patients with atrial fibrillation that determined the optimal INR level. The overall event rate from ischemic stroke in this trial was 5.2%, while the overall event rate from bleeding complications was 24.8%. The event rate from bleeding complications was divided as the event rate from major bleeding complications at 6.1% and minor bleeding complications at 18.7%. Therefore, the present trial showed the overall ischemic events were similar to the previous Asian and western trials, while the overall bleeding events were higher than the previous Asian and western trials[1,9,15]. The reason for the higher bleeding events in this trial compared with previous other trials could be because of the present trial included the minor bleeding complications while the previous western and Chinese studies reported only major bleeding complications[1,9,15]. Therefore, the overall major bleeding complications in the present trial were similar to the prior Japanese and Chinese trials[1,13,15]. It also showed the high minor bleeding complications were not studied in the previous trials except the Japanese study that reported the overall bleeding complications including the minor bleeding[15]. Compare with the Japanese study, the present trial showed the higher minor bleeding complications. Therefore, Thai patients with atrial fibrillation may have higher minor bleeding complications and the same ischemic and major bleeding events compare with the previous Asian studies[1,9,15].

The possible explanation for the higher bleeding complications in the present trial may be that one-fourth of patients took the concomitant aspirin, two-third of patients had underlying hypertension, and two-third of patients were female, which increased the risk of bleeding in the warfarin users. Another explanation was from the different CYP2C9 and VKORC1 polymorphisms. CYP2C9 is the cytochrome P450 that metabolized S-enantiomer, which is three times as potent as R-enantiomer of warfarin[4]. If the patients have the mutant alleles, CYP2C9*2 or CYP2C9*3, they require the lower dose of warfarin[4,6,10]. While VKORC1 is a gene encoding vitamin K epoxide reductase that changes the inactive vitamin K to the active vitamin K, the VKORC1 A haplotype leads to

require the lower dose of warfarin[3]. However, the frequencies of CYP2C9*2 and CYP2C9*3 are 5 to 10% in western countries[4,6], while their similar frequencies are in Asian countries. The prevalence of CYP2C9*2 and CYP2C9*3 is very low (5%) in Thai population[11]. The frequency of VKORC1 A haplotype is 37% in European-American population while their frequency is 89% in Asian-American population[12]. In Thai population, the previous study revealed that 63.6% had VKORC1 AA haplotype[11]. Therefore, the requirement for lower warfarin dose in Thai population may be the effect from VKORC1 mutation more than from CYP2C9 polymorphisms.

From the results of the present trial, the authors concluded that the INR 1.5 to 2.9 had the lowest incidence of ischemic stroke and bleeding complications. When the authors combined the INR groups into INR less than 1.5, INR 1.5 to 2.9, and INR more than 2.9. The INR 1.5 to 2.9 had lower combined ischemic and bleeding complications than INR more than 2.9 with statistical significance, while it had lower combined ischemic and bleeding complications than INR less than 1.5 without statistical significance. The reason for non-significant combined ischemic and bleeding complications between INR 1.5 to 2.9 and INR less than 1.5 may be the higher bleeding complications in INR 1.5 to 2.9 compared with INR less than 1.5. Therefore, when the authors calculated the summation of ischemic and bleeding complication, it led to balance effect of lower ischemic stroke and higher bleeding complication in INR 1.5 to 2.9 compared with INR less than 1.5. However, INR 1.5 to 2.9 had higher bleeding complications without statistical significance and lower ischemic stroke with statistical significance than INR less than 1.5.

However, the present trial had several limitations. First, it was a retrospective study, so several confounding factors occurred during the study and some data might be missed because of no data in the medical records such as some minor bleeding complications that were ignored by the physicians or patients. However, the present trial was the first Thai study that revealed the preliminary data about the optimal INR level in patients with atrial fibrillation. A prospective study will be required to confirm these results. Second, the sample size in the present trial may be small because of wide 95% confidence interval. Although the present trial had a small sample size, it could demonstrate statistical significance between each group of INR level.

Conclusion

An INR of 1.5 to 2.9 appeared to be associated with the lowest incidence rate of major/minor bleeding or ischemic stroke in a cohort of Thai atrial fibrillation patients receiving warfarin therapy for stroke prevention. However, further study is required to confirm these results.

What is already known on this topic?

Warfarin is one of the most useful anticoagulant drugs for both primary and secondary stroke prevention in patients with atrial fibrillation. The previous trials in United States and European countries found that the INR level 2 to 3 had the lowest incidences of thromboembolic and bleeding events.

What this study adds?

An INR of 1.5 to 2.9 appeared to be associated with the lowest incidence rate of major/minor bleeding or ischemic stroke in a cohort of Thai patients with atrial fibrillation receiving warfarin therapy for stroke prevention. This study showed the lower optimal INR level in Thai patients with atrial fibrillation compared with western population.

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Potential conflicts of interest

None.

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การศึกษาระดับ INR ที่เหมาะสมในผู้ป่วย atrial fibrillation ที่ได้รับยา warfarin เพื่อป้องกันการเกิดโรคสมองขาดเลือดในประเทศไทย

คมสิงห์ เมธาวีกุล, วรางคณา บุญญพิสิฏฐ์

วัตถุประสงค์: เพื่อหาระดับ international normalized ratio (INR) ที่เหมาะสมในคนไทยที่เป็น atrial fibrillation (AF) ที่ได้รับยา warfarin

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบย้อนหลังในผู้ป่วย AF 230 ราย ที่ได้รับยา warfarin เพื่อป้องกันการเกิดโรคสมองขาดเลือดใน โรงพยาบาลศิริราช ระหว่างวันที่ 1 มกราคม พ.ศ. 2548 ถึง วันที่ 31 ธันวาคม พ.ศ. 2552 เก็บข้อมูลเกี่ยวกับระดับ INR ในขณะที่เกิดโรคสมองขาดเลือดหรือภาวะแทรกซ้อนจากเลือดออกผิดปกติ อัตราการเกิดโรคสมองขาดเลือด และภาวะแทรกซ้อนจากเลือดออกผิดปกติในผู้ป่วยแต่ละกลุ่ม INR ในเวชระเบียน โดยในการศึกษานี้จะคำนวณค่า incidence density ของการเกิดโรคสมองขาดเลือดหรือภาวะแทรกซ้อนจากเลือดออกผิดปกติจากจำนวนผู้ป่วยที่เกิดโรคสมองขาดเลือดหรือภาวะแทรกซ้อนจากเลือดออกผิดปกติหารด้วยผลรวมของระยะเวลาที่ผู้ป่วยอยู่ในระดับ INR แต่ละกลุ่ม โดยผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนลิ้นหัวใจเทียมจะถูกตัดออกจากการศึกษา แล้วจึงแบ่งระดับ INR ออกเป็น 6 กลุ่ม คือ ระดับ INR <1.5, 1.5-1.9, 2.0-2.4, 2.5-2.9, 3.0-3.4 และ >3.4 ระดับ INR ที่เหมาะสมคือระดับ INR ที่มีค่า incidence density ของการเกิดโรคสมองขาดเลือดและมีภาวะแทรกซ้อนจากเลือดออกผิดปกตินอ้ยที่สุด

ผลการศึกษา: ผู้ป่วย AF 230 ราย (อายุเฉลี่ย 68±12 ปี) ที่ได้รับคัดเลือกเข้ามาในการศึกษานี้ซึ่งใช้ระยะเวลาในการศึกษา 737.54 patient-years ในผู้ป่วยทั้งหมด 230 ราย มี 9 ราย เกิดโรคสมองขาดเลือด 12 ครั้ง (คิดเป็น 1.6 ต่อ 100 patient-years) และ 54 ราย เกิดภาวะแทรกซ้อนจากเลือดออกผิดปกติรวม 57 ครั้ง (คิดเป็น 7.7 ต่อ 100 patient-years) ซึ่งในการศึกษาระยะเวลาที่ผู้ป่วยมีระดับ INR อยู่ในระดับการรักษา (2-3), INR <2 และ INR >3 เป็น 40.75, 46.22 และ 13.03% ของระยะเวลาที่ทำการศึกษาทั้งหมดตามลำดับ การศึกษานี้พบว่า ระดับ INR >3.4 มีภาวะแทรกซ้อนจากเลือดออกผิดปกติรวมเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p = 0.001) ในขณะที่ระดับ INR 3.0-3.4 ก็เพิ่มภาวะแทรกซ้อนจากเลือดออกผิดปกติแบบ minor bleeding อย่างมีนัยสำคัญทางสถิติ (p = 0.03) แต่ระดับ INR <1.5 กลับพบว่าเกิดโรคสมองขาดเลือดเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p = 0.03) โดยพบว่า INR 1.5-2.9 เกิดโรคสมองขาดเลือดและภาวะแทรกซ้อนจากเลือดออกผิดปกติต่ำที่สุดเมื่อเทียบกับ INR >2.9 อย่างมีนัยสำคัญทางสถิติ (p<0.0001) และมีแนวโน้มต่ำกว่า INR <1.5 แต่ไม่มีนัยสำคัญทางสถิติ (p = 0.198)

สรุป: ระดับ INR 1.5-2.9 มีความสัมพันธ์กับการเกิดโรคสมองขาดเลือดและภาวะแทรกซ้อนจากเลือดออกผิดปกตินอ้ยที่สุดในคนไทยที่เป็น AF ที่ได้รับ warfarin เพื่อป้องกันการเกิดโรคสมองขาดเลือด