Original Article

Optimal INR to Prevent Stroke in Thai Patients with Rheumatic Mitral Stenosis and Atrial Fibrillation Who are Receiving Warfarin

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Objective: To determine the optimal international normalized ratio (INR) level to prevent stroke and bleeding in patients with rheumatic mitral stenosis and atrial fibrillation (AF) receiving warfarin.

Materials and Methods: The present study was a retrospective study that enrolled patients with rheumatic mitral stenosis and AF who received warfarin at King Chulalongkorn Memorial Hospital between January 1, 2010 and December 31, 2015. The INR range was classified into six groups, which were 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 and more.

Results: One hundred eighty-four patients (mean age of 55.7 years, 79.3% female) were enrolled, for a follow-up of 714.4 patient-year. Twenty-eight patients had 35 ischemic stroke events (4.90 per 100 patient-years) and 36 patients had 55 bleeding events (7.70 per 100 patient-years). The time rate in the INR range of 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 and more were 14.0%, 26.7%, 29.5%, 17.4%, 7.1%, and 5.2%, respectively. The percentage of patient-time spent within INR range 2 to 3, INR less than 2, and INR more than 3 were 46.9%, 40.7%, and 12.3%, respectively. The INR level less than 2.00 increased the incidence rate of ischemic stroke (relative risk [RR] 1.57; 95% confidence interval [CI] 1.19 to 2.13; p=0.028). The INR level more than 2.99 to 3.5 increased the incidence rate of total and major bleeding events (RR 2.47; 95% CI 1.88 to 3.23; p<0.001 and RR 3.07; 95% CI 2.44 to 3.87; p<0.001, respectively). The overall of ischemic stroke and bleeding event rate was lowest in the INR range from 2.00 to 2.99.

Conclusion: In this large cohort of patients with rheumatic mitral stenosis and AF, an INR level between 2.00 to 2.99 was associated with the lowest incidence of ischemic stroke and bleeding. This optimal INR level is higher than the optimal INR as previously shown in other studies of Asian patients with non-valvular AF.

Keywords: Atrial fibrillation, Rheumatic mitral stenosis, INR, Stroke, Warfarin

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Rheumatic mitral stenosis with atrial fibrillation (AF) is a common cause of valvular AF in clinical practice. Currently, warfarin is the only useful drugs for stroke prevention in valvular AF. Warfarin has narrow therapeutic range. Previous trials in Europe and United States found the incidences of thromboembolic events combined with bleeding events were lowest when the international normalized ratio (INR) level was between 2 to 3 for non-valvular AF and valvular AF except for mechanical valve AF[1]. However, many studies in Asian countries, including Thailand, showed different INR level for safety of warfarin. A Thai retrospective study enrolled 230 AF patients and showed that INR of between 1.5 and 2.9 appeared to be associated with the lowest incidence rate of bleeding or ischemic stroke[2]. However, there is still a lack of data in Thai rheumatic mitral stenosis with AF patients who have higher risk of stroke than non-valvular AF. The present trial was conducted to determine the optimal INR level to prevent stroke and bleeding in patients with rheumatic mitral stenosis and AF. The optimal INR level is defined as the lowest incidence rate of ischemic stroke and bleeding complications.

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Materials and Methods

The present study was a retrospective study that enrolled consecutive patients with the ICD-10 coding of rheumatic mitral stenosis and AF at King Chulalongkorn Memorial Hospital between January 1, 2010 and December 31, 2015. The study enrolled Thai patients, aged at least 18 years old who were either paroxysmal, persistent, or permanent AF and any severity of rheumatic mitral stenosis. All patients received warfarin for stroke prevention with follow-up period of at least 12 months if there was no ischemic stroke or bleeding events. The study excluded patients with prosthetic valve replacement or valve repaired, did not receive warfarin, participated with other study, pregnant, had platelet less than 100,000/mm^3, heparin-induced thrombocytopenia, and myeloproliferative disorders including essential thrombocythemia, chronic myeloid leukemia, polycythemia vera, agnogenic myeloid metaplasia, or hyperviscosity syndrome.

Patient demographics, dates, and results of all INR assessments, lNR level at the time of the event, the numbers of ischemic stroke, and bleeding events were collected. The INR range was classified into six groups, which were 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 3.5 or more. The time rate in each INR level, which take consideration of INR level and duration, was used for analysis. The incidence rate of ischemic stroke and bleeding events in each INR group was calculated by dividing the numbers of ischemic stroke and bleeding event in each INR group with the summation of the time that each patient stayed in each INR group. The numbers of ischemic stroke and bleeding event in each group of INR level were counted by the INR level within seven days of the ischemic or bleeding events. The time each patient stayed in each INR group was calculated by dividing the half-time between the first and the next INR levels of each pairs of INR level. The first half-time was the time in the first INR level and the last half-time for the next INR level.

Ischemic stroke was defined as clinical and physical examination of sudden neurological deficit with abnormal finding of ischemic stroke by computed tomography or magnetic resonance imaging of brain. Bleeding complications consisted of major bleeding and minor bleeding. Major bleeding was defined as 1) gastrointestinal bleeding requiring at least two units of blood transfusion or hemodynamically compromised, 2) intracranial hemorrhages consisting of spontaneous of intraventricular hemorrhage, intracerebral hemorrhage, subarachnoid hemorrhage, and/or subdural hematoma, spinal hemorrhage, without history of trauma, 3) gross hematuria requiring intervention with continuous bladder irrigation or hemodynamically compromised, 4) hemoptysis requiring emergent bronchoscopy or bronchial embolization or intubation or hemodynamically compromised, 5) intramuscular bleeding and compartment syndrome requiring intervention or blood transfusion or hemodynamically compromised, and 6) retroperitoneal bleeding requiring intervention or blood transfusion or hemodynamically compromised. Minor bleeding was defined as any bleeding other than major bleeding and not requiring intervention or blood transfusion or hemodynamically compromised. The study estimated the incidences of thromboembolic events in each INR group such as INR level 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 to be 0.144, 0.023, 0.022, 0.011, 0, and 0 (modified from Cheung et al, 2005[3]), respectively, and calculated by two independent proportions with minimal clinical difference of 20. A p-value of less than 0.05 was considered statistically significant. The authors determined 0.20 for type II error with 80% power. A sample size of 150 patients was calculated to compare populations of more than two groups by chi-square test. PAWS statistics program version 18.0 was used for statistical analysis. The categorical data such as gender of AF, severity mitral stenosis, and comorbidity diseases were presented as frequency and percentage. The continuous variables such as age, mitral valve area (MVA), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF), and dose of warfarin were presented as mean and standard deviation (SD). The optimal INR level was determined by comparing the incidence rate of ischemic stroke and bleeding events between each group of INR level with Stata program version 12 for two rates. The optimal INR level was defined as the lowest incidence rate of ischemic stroke and bleeding complications.

Results

One hundred eighty-four rheumatic mitral stenosis with AF patients were enrolled between January 1, 2010 and December 31, 2015, contributing to 714.44 patient-years of observation period. The mean age of the patients was 55 years (maximum 87, minimum 24), and 79.35% of patients were female. All of the patients were rheumatic mitral stenosis [mild severity in three patients (1.63%), moderate in 23 patients (12.50%), and severe in 151 patients (82.07%)]. Dyslipidemia and hypertension were the most common comorbidity (31.0% and 27.7%,

Table 1. Basline characteristics of Thai patients with rheumatic mitral stenosis and atrial fibrillation

Characteristic	Total n=184 n (%)
Age (years), Mean±SD	55.7±12.5
Sex: female	146 (79.4)
AF type	
Paroxysmal AF	29 (15.8)
Persistent AF	4 (2.2)
Permanent AF	151 (82.1)
Comorbidity	
HT	51 (27.7)
DLP	57 (31.0)
DM	21 (11.4)
Chronic kidney disease	10 (5.4)
Cirrhosis	5 (2.7)
Hypothyroidsm	1 (0.5)
Hyperthyroidism	1 (0.5)
CAD	9 (4.9)
• PCI	3 (1.6)
• CABG	2 (1.1)
ICD	2 (1.1)
PAD	1 (0.5)
Carotid stenosis (s/p stent)	2 (1.1)
Vital sign, Mean±SD	
HR (bpm)	76.5±12
SBP (mmHg)	116.8±16
CHA2DS2 VASc risk score, Mean±SD	3.0±1.5
CHA2DS2 VASc risk score=0	4 (2.1)
CHA2DS2 VASc risk score=1	19 (10.2)
CHA2DS2 VASc risk score=2	61 (32.6)
CHA2DS2 VASc risk score=3	32 (17.1)
CHA2DS2 VASc risk score=4	38 (20.3)
CHA2DS2 VASc risk score=5	14 (7.5)
CHA2DS2 VASc risk score=6	11 (5.9)
CHA2DS2 VASc risk score=7	4 (2.1)
CHA2DS2 VASc risk score=8	1 (0.5)
HASBLED score, Mean±SD	1.8±0.9

AF=atrial fibrillation; HT=hypertension; DLP=dyslipidemia; DM=diabetes mellitus; CAD=coronary artery disease; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; ICD=intracardiac defibrillator; PAD=peripheral arterial disease; HR=heart rate; SBP=systolic blood pressure; SD=standard deviation

Table 2. Echocardiographic findings

Echocardiographic findings	Total n=184 n (%)
Severity MS	
Mild MS	3 (1.6)
Moderate MS	23 (12.5)
Severe MS	158 (85.9)
MVA, Mean±SD	1.06±0.3
Co incidence with MR	151 (82.1)
• No MR	33 (17.93)
• Mild MR	88 (47.83)
• Moderate MR	45 (24.46)
• Severe MR	18 (9.78)
Co incidence with AS	21 (11.41)
Co incidence with AR	103 (55.99)
LVEF, Mean±SD	61.6±9.7
LVEF <35%	5 (2.7)
LA size (mm), Mean±SD	52.7±9.6
LAVI (ml/m^2), Mean±SD	89.2±53.7
LV mass index, Mean±SD	108.3±39.2
Incidence LA thrombus	28 (15.22)
Incidence LV thrombus	1 (0.54)

MS=mitral stenosis; MVA=mitral valve area; MR=mitral regurgitation; AS=aortic stenosis; AR=aortic regurgitation; LVEF=left ventricular ejection fraction; LA=left atrial; LV=left ventricular; LAVI=left atrial volume index; SD=standard deviation

respectively). Five patients (2.70%) had concomitant aspirin, one patient (0.54%) had concomitant clopidogrel, and none had combined aspirin and clopidogrel. Their baseline characteristics are shown in Table 1, echocardiographic findings in Table 2, and medication used in Table 3. The present study showed no correlation between severity mitral stenosis with incidence stroke (p=0.509), mitral regurgitation with incidence stroke (p=0.290), aortic stenosis with incidence stroke (p=0.900), aortic regurgitation with incidence stroke (p=0.269), but it showed correlation between reduce LV dysfunction (LVEF of less than 35%) with incidence stroke (p=0.005), and LA enlargement (LA diameter of more than 40 mm) with incidence stroke (p=0.452).

Of the 184 patients, 28 patients experienced 35 ischemic events (4.9 per 100 patient-years) and 36 patients experienced 55 bleeding events (7.7 per 100 patient-years). The time rate in the INR range of less

Table 3. Medication

Medication	Total n=184 n (%)
Warfarin, Mean±SD	
Dose of warfarin (mg/week)	21.0±9.9
Day per week	6±0.6
Aspirin	5 (2.70)
Clopidogrel	1 (0.54)
Aspirin and clopidogrel	0 (0.0)
Drug for rate or rhythm control	
No medication for rate or rhythms control	8 (4.3)
Digoxin	101 (54.9)
Propanolol	6 (3.3)
Atenolol	54 (29.3)
Carvedilol	29 (15.8)
Metropolol	29 (15.8)
Bisoprolol	2 (1.1)
Nebiverlol	1 (0.5)
Diltiazem	10 (1.6)
Amiodarone	5 (2.7)
Combination of digoxin with beta blocker	51 (27.7)
Combination of digoxin or beta blocker with amiodarone	5 (2.7)
Other medication use	
ACEI	30 (16.3)
ARB	13 (7.1)
Dihydropyridine CCB	9 (4.9)
Aldosterone blockage	33(16.9)
Furosemide	123 (66.8)
Statin	55 (29.9)
Proton pump inhibitors	40 (21.7)
Oral antiglycemic drug	11 (6.0)
Insulin	3 (1.6)
Antiretroviral	3 (1.6)
Herb	2 (1.1)

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CCB=calcium channel blocker; SD=standard deviation

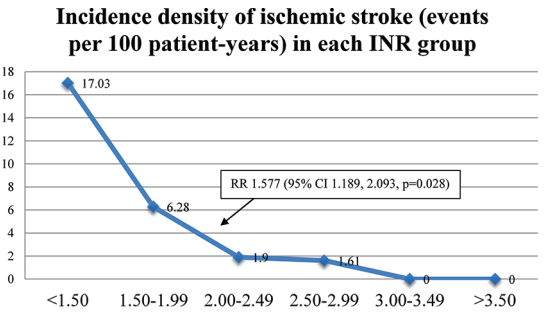

Figure 1. Incidence density of ischemic stroke (events per 100 patient-years) in each INR group.

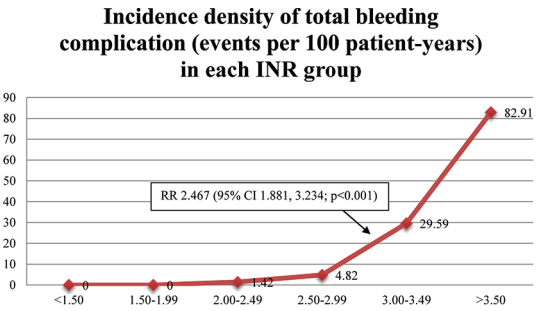

Figure 2. Incidence density of total bleeding complication (events per 100 patient-years) in each INR group.

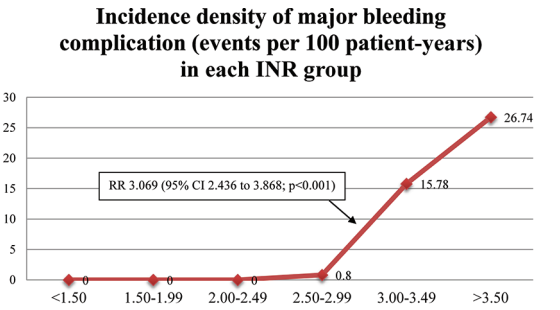

Figure 3. Incidence density of major bleeding complication (events per 100 patient-years) in each INR group.

than 1.50, 1.50 to 1.99, 2.00 to 2.49, 2.50 to 2.99, 3.00 to 3.49 and 3.5 or more were 14.0%, 26.7%, 29.5%, 17.4%, 7.1%, and 5.2%, respectively. The percentage of patient-time spent within therapeutic INR range 2 to 3, INR less than 2 and INR more than 3 were 46.9%, 40.7%, and 12.3%, respectively. The INR level less than 2.00 increased incidence rate of ischemic stroke (relative risk [RR] 1.57; 95% confidence interval [CI] 1.19 to 2.13; p=0.028). The INR level more than 2.99 increased incidence rate of total and major bleeding events (RR 2.47; 95% CI 1.88 to 3.23; p<0.001 and RR 3.07; 95% CI 2.44 to 3.87; p<0.001, respectively).

Table 4. Incidence density of ischemic stroke

INR level	Time (year)	Event of ischemic stroke	Incidence density of ischemic stroke (patient-year)	Relative risk (95% CI)	p-value
<1.50	99.84	17	17.03	1.708 (1.258 to 2.319)	0.006
1.50 to 1.99	190.99	12	6.28	1.577 (1.189 to 2.093)	0.028
2.00 to 2.49	210.66	4	1.90	1.06 (0.602 to 1.867)	0.848
2.50 to 2.99	124.38	2	1.61	1 (0 to 1)	0.367
3.00 to 3.49	50.70	0	0.00	NA	NA
≥3.50	37.39	0	0.00	NA	NA
Total	713.95	35	4.90		

INR=international normalized ratio; CI=confidence interval; NA=not available

Table 5. Incidence density of total bleeding event

INR level	Time (year)	Event of total bleeding event	Incidence densityof total bleeding (patient-year)	Relative risk (95% CI)	p-value
<1.50	99.84	0	0.00	NA	NA
1.50 to 1.99	190.99	0	0.00	NA	NA
2.00 to 2.49	210.66	3	1.42	1.907 (1.897 to 1.916)	0.099
2.50 to 2.99	124.38	6	4.82	1.796 (1.131 to 2.85)	0.066
3.00 to 3.49	50.70	15	29.59	2.467 (1.881 to 3.234)	<0.001
≥3.50	37.39	31	82.91	1.588 (1.298 to 1.942)	<0.001
Total	713.95	55	7.70		

INR=international normalized ratio; CI=confidence interval; NA=not available

Table 6. Incidence density of major bleeding event

INR level	Time (year)	Event of major bleeding	incidence density of major bleeding (patient-year)	Relative risk (95% CI)	p-value
<1.50	99.84	0	0.00	NA	NA
1.50 to 1.99	190.99	0	0.00	NA	NA
2.00 to 2.49	210.66	0	0.00	NA	NA
2.50 to 2.99	124.38	1	0.80	2.694 (2.674 to 2.713)	0.193
3.00 to 3.49	50.70	8	15.78	3.069 (2.436 to 3.868)	<0.001
≥3.50	37.39	10	26.74	1.309 (0.866 to 1.979)	0.26
Total	713.95	19	2.66		

INR=international normalized ratio; CI=confidence interval; NA=not available

The overall of ischemic stroke and bleeding event rate was lowest in the INR range from 2.00 to 2.99 (Table 4-7, Figure 1-5).

Discussion

Mitral stenosis leads to structural changes in the left atrium, causing chronic atrial stretch from pressure and volume overload resulting in fibrotic changes that secondarily alter atrial electrophysiology remodeling and predispose to the development of AF. Mitral stenosis, essentially on a rheumatic basis, is high risk of thromboembolism, probably related to the low-flow patterns occurring in the remodeling left atrium[4].

The CHA2DS2 VASc risk score, even with the presence or absence of heart failure symptoms, comorbidity as diabetic and hypertension is not

Table 7. Incidence density of minor bleeding event

INR level	Time (year)	Event of major bleeding	incidence density of major bleeding (patient-year)	Relative risk (95% CI)	p-value
<1.50	99.84	0	0.00	NA	NA
1.50 to 1.99	190.99	0	0.00	NA	NA
2.00 to 2.49	210.66	3	1.42	1.906 (1.897 to 1.916)	0.099
2.50 to 2.99	124.38	4	3.22	1.539 (0.810 to 2.923)	0.273
3.00 to 3.49	50.70	8	15.78	2.197 (1.406 to 3.436)	0.011
>3.50	37.39	21	56.16	1.766 (1.426 to 2.188)	0.0005
Total	714.44	36	4.89		

INR=international normalized ratio; CI=confidence interval; NA=not available

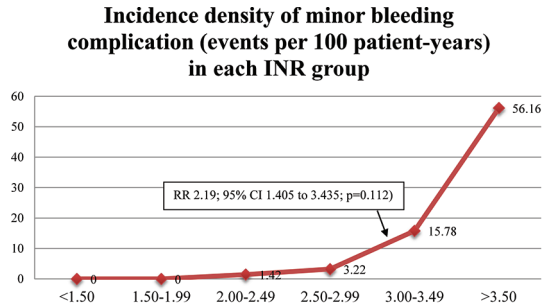

Figure 4. Incidence density of minor bleeding complication (events per 100 patient-years) in each INR group.

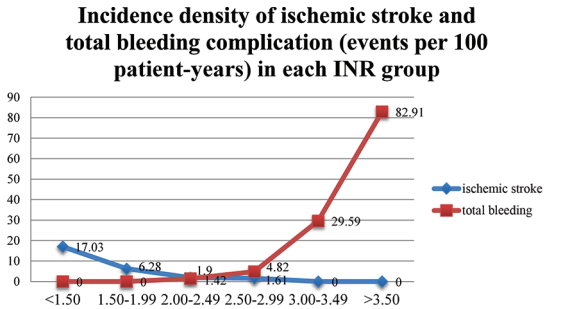

Figure 5. Incidence density of ischemic stroke and total bleeding complication (events per 100 patient-years) in each INR group.

a correlated thromboembolic event in valvular AF. It is no correlation between the occurrence of thromboembolic event and mitral orifice dimensions or severity of mitral stenosis with AF. Embolic events can be the first presentation of mitral stenosis with any severity. The mitral stenosis patients with AF who have a history of embolic event have recurrences at a rate of 15 to 40 events per 100 patient-months, which is a higher rate than non-valvular AF[5]. Therefore, the CHA2DS2 VASc risk score is recommended for patients with non-valvular AF. Thus, for patients with valve AF, particularly rheumatic mitral stenosis, the CHA2DS2 VASc risk score is not recommended.

The 2016 European Society of Cardiology (ESC) Guidelines for the management of AF, developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), suggest a level of INR 2.0 to 3.0 or higher for vitamin K antagonist therapy. This is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves. It is a class I recommendation where the level should be the same for INR as non-valvular AF patients[6]. However, many trials showed that Thai and Asian patients with non-valvular AF required lower INR level than western patients in the previous studies. The present study showed higher incidence of ischemic stroke in rheumatic mitral stenosis with AF than non-valvular AF (incidence of 15.21% and incidence rate of 4.9 per 100 patient-year versus incidence of 3.91% and incident rate of 1.6 per 100 patient-year, respectively), and required INR level higher than non-valvular AF (INR range from 2.00 to 2.99 versus 1.5 to 2.9).

A previous study in Thai patients with non-valvular AF determined that the optimal INR level showing overall event rate from ischemic stroke was 5.2%, and overall event rate bleeding complications was 24.8%[2]. The present study showed a higher event rate from ischemic stroke at 19.0% and overall event rate bleeding complications at 29.9%, which is slightly higher than the previous study. The bleeding complication in many Asian trials showed higher than western population. Previous trial from European Atrial Fibrillation Trial (EAFT) showed that the

overall bleeding events were 2.9%[7].

However, the present study had many limitations. The study was retrospective and had a long period follow-up where some data might be missed because of loss of medical records. Some minor bleeding complications might be ignored by the physicians or patients. Some major bleeding or death might have occurred at other hospital and was not collected. Some laboratory data may not have been collected due to the loss of medical record. A large prospective study to confirm the optimal INR level to prevent stroke and bleeding complications in Thai and Asian population with non-valvular AF and valvular AF as rheumatic mitral stenosis will be required to generate a new recommendation.

Conclusion

In this large cohort of patients with rheumatic mitral stenosis and AF, an INR level between 2.00 and 2.99 was associated with the lowest incidence of ischemic stroke and bleeding. This optimal INR level is higher than the optimal INR shown in previous studies of Asian patients with non-valvular AF.

What is already known on this topic?

Warfarin is the only drug for primary and secondary stroke prevention in patients with rheumatic mitral stenosis and AF. Previous trials in Asia and Thai for non-valvular AF found the INR was lower than guidelines recommendation.

What this study adds?

This present trial showed that the optimal INR to prevent stroke in Thai patients with rheumatic mitral stenosis and AF who are receiving warfarin is between 2.00 to 2.99. The optimal INR for Thai patients with rheumatic mitral stenosis and AF is higher than optimal INR for non-valvular AF in a previous study in Asia including Thai trials.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335:540-6.
2. Methavigul K, Boonyapisit W. Optimal INR level in Thai atrial fibrillation patients who were receiving warfarin for stroke prevention in Thailand. J Med Assoc Thai 2014;97:1274-80.
3. Cheung CM, Tsoi TH, Huang CY. The lowest effective intensity of prophylactic anticoagulation for patients with atrial fibrillation. Cerebrovasc Dis 2005;20:114-9.
4. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart disease. Circulation 2012;125:945-57.
5. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. Eur Heart J 2014;35:3328-35.
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
7. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet 1993;342:1255-62.