Original Article

Proportion of Thai Patients with Atrial Fibrillation Receiving Warfarin with Labile INR in Each Group of SAMeTT$_2$R$_2$ Score

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Objective: To determine the proportion of Thai AF patients used warfarin with labile INR in each SAMeTT$_2$R$_2$ score.

Materials and Methods: The present retrospective study recruited Thai atrial fibrillation [AF] patients treated at the Central Chest Institute of Thailand. They took warfarin for at least three months before enrollment. The patients that discontinued warfarin during the international normalized ratio [INR] monitoring because of surgery, invasive procedure, hospitalization, or any etiologies were excluded. Each AF patients was measured for the INR to determine the proportion of patients with labile INR in each SAMeTT$_2$R$_2$ score.

Results: Forty AF patients were enrolled. The mean age was 64.35±10.69 years old. Most patients were paroxysmal AF. The average CHA$_2$DS$_2$-VASc score was 3.20±1.56. Half of these patients had hypertension and hypercholesterolemia. Almost one-fifth of these patients had history of ischemic stroke. The study showed the increased proportion of AF patients with labile INR according to the increased SAMeTT$_2$R$_2$ score. The AF patients with SAMeTT$_2$R$_2$ score of 3 or more had a closer proportion of patients with labile INR than those with SAMeTT$_2$R$_2$ score of 2 or less with borderline significance (*p*-value 0.056).

Conclusion: Thai AF patients with increased SAMeTT$_2$R$_2$ score had potential of having labile INR. However, a larger study is needed to use SAMeTT$_2$R$_2$ score for predicting Thai AF patients with labile INR in the future.

Keywords: Atrial fibrillation, Bleeding risk score, Anticoagulant, Labile INR, SAMeTT$_2$R$_2$

Atrial fibrillation [AF] is a common cardiac arrhythmia in the clinical practice. The oral anti-coagulant is indicated in these patients with CHA$_2$DS$_2$-VASc score of 1 or more for prevention of ischemic stroke[1,2]. Warfarin is the most prescribed anticoagulant in Thailand but it has several adverse effects in bleeding risk including intracranial hemorrhage. Those that take warfarin should be monitored with international normalized ratio [INR]. The therapeutic range of INR is between 2 and 3[3-5]. The patients will suffer from the ischemic stroke if their INR level is below 2 and suffer from the intracranial hemorrhage if their INR is above 3.

Presently, there is the novel oral anticoagulant, non-vitamin K antagonist oral anticoagulant [NOAC], in Thailand. This anticoagulant needs no blood level monitoring and is associated with lower risk of intracranial bleeding[6-9]. The NOAC costs more than warfarin. A patient selection criterion appropriate for NOAC is needed.

Many doctors prescribe NOAC to replace warfarin because of labile INR in several patients. Previous study by Apostolakis et al[10] showed that SAMeTT$_2$R$_2$ score of 2 or more can be used to predict patients with labile INR[11].

The present study was conducted to determine the proportion of Thai AF patients that used warfarin with labile INR in each SAMeTT$_2$R$_2$ score.

Materials and Methods

The present study was conducted retrospectively in Thai patients aged 18 years or more with atrial fibrillation using warfarin for three months or more in Central Chest Institute of Thailand between 2000 and 2015. The patients that stopped the warfarin during follow-up period because of invasive procedure, operation, or other causes, those who had their INR values far from each other for more than six months, those with prosthetic heart valve, and those who were

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hospitalized during study were excluded. The $SAMeTT_2R_2$ score included female sex, age less than 60 years, medical history of more than two of following co-morbidities: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, or hepatic or renal disease, treatment with interacting drugs such as amiodarone for rhythm control, tobacco use (doubled), and non-Caucasian race (doubled). The labile INR was defined as the INR level less than 60% of follow-up period, the occurrence of the ischemic stroke when INR was below 2, and the bleeding event when INR was above 3[12]. The study protocol was approved by the Institutional Review Board. The present study complied with the Declaration of Helsinki.

The categorical data are presented as frequency and percentage. The continuous variables are presented as mean ± SD. The Chi-square test or Fisher's Exact test was used to compare the proportion of the patients with labile INR in each $SAMeTT_2R_2$ score. A p-value of 0.05 or less was considered as statistical significance. All statistical analyses were performed with SPSS Statistics software, version 23 (IBM Corp).

Results

Forty AF patients were enrolled. The mean age

Table 1. Baseline characteristics of the patients

Characteristics	Total (n = 40) n (%) or mean ± SD
Age (years)	64.35±10.69
Male gender	18 (45.0)
Paroxysmal AF	37 (92.5)
CHA_2DS_2-VASc score	3.20±1.56
$SAMeTT_2R_2$ score	3.40±0.84
Medical history	
Diabetes mellitus	8 (20.0)
Hypertension	23 (57.5)
Hypercholesterolemia	19 (47.5)
Coronary artery disease	12 (30.0)
Valvular heart disease	16 (40.0)
Chronic kidney disease	2 (5.0)
History of previous ischemic stroke or TIA	7 (17.5)
LVEF (%)	57.00±18.38
Medications	
Beta-blockers	27 (67.5)
Nondihydropyridine CCB	4 (10.0)
Digoxin	14 (35.0)
Warfarin	40 (100)
Aspirin	11 (27.5)
Clopidogrel	4 (10.0)

n = numbers; SD = standard deviation; AF = atrial fibrillation; TIA = transient ischemic attack; LVEF = left ventricular ejection fraction; CCB = calcium channel blockers
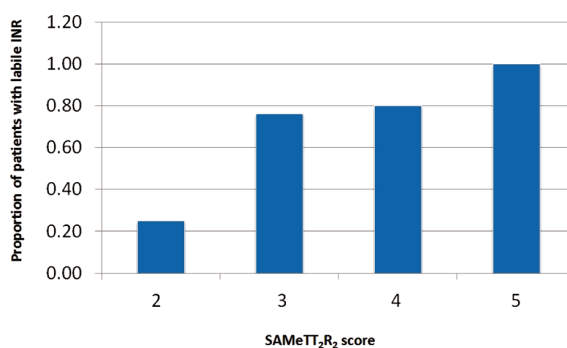

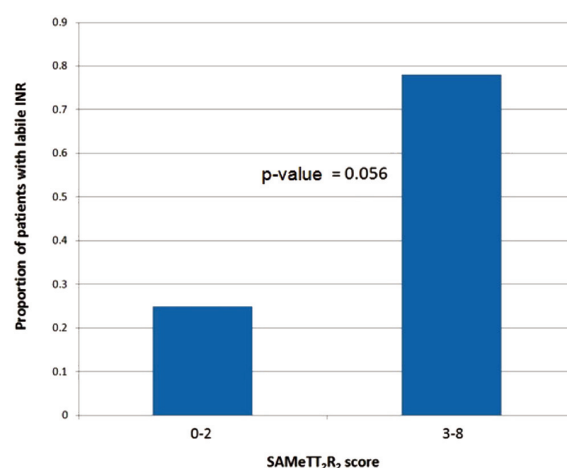**Figure 1.** The proportion of Thai AF patients with labile INR in each group of $SAMeTT_2R_2$ score.

Figure 2. The proportion of Thai AF patients with labile INR between $SAMeTT_2R_2$ score of 2 or less and $SAMeTT_2R_2$ score of 3 or more.

was 64.35±10.69 years old. Most patients were paroxysmal AF. The average CHA_2DS_2-VASc score was 3.20±1.56. Half of these patients had hypertension and hypercholesterolemia. Almost one-fifth of these patients had the history of ischemic stroke. The baseline characteristics of the patients were shown in Table 1.

The present study showed the increased proportion of AF patients with labile INR according to the increased $SAMeTT_2R_2$ score as shown in Figure 1. The AF patients with $SAMeTT_2R_2$ score of 3 or more had similar proportion of patients with labile INR, and more than those with $SAMeTT_2R_2$ score of 2 or less with borderline significance (p-value 0.056) as shown in Figure 2.

Discussion

The present study has shown that the AF patients receiving warfarin had an incremental risk of labile

INR when the $SAMeTT_2R_2$ score increased. This result supported a previous study by Apostolakis et al[10]. However, the $SAMeTT_2R_2$ score predicting the labile INR in the AF patients with warfarin in the present study is still different from the previous study. That study showed the $SAMeTT_2R_2$ score of 2 or more predicted the labile INR in the AF patients with warfarin, while the present study showed the $SAMeTT_2R_2$ score of 3 or more may predict the labile INR in these patients. The different results in the present study came from the racial difference in the two trials. Apostolakis et al studied the AF patients from the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] study[11], which most patients were Caucasian and the few ones were non-Caucasian (9.8%). The present study gave the score of 2 for the non-Caucasian race, so the Asian patients with AF would always have the $SAMeTT_2R_2$ score of 2 or more because of their race. This trial studied in the Thai patients and showed the different results from the Caucasian trial. This trial showed the AF patients with the $SAMeTT_2R_2$ score of 3 or more receiving warfarin had the incremental labile INR with borderline significance (*p*-value 0.056).

The reason that different race has different numbers is because of the different genetic profile. The previous study revealed the Asian AF patients with warfarin[1,15-17] had more bleeding than the western patients[13], while they had similar thromboembolic events. CYP2C9 and VKORC1 polymorphisms can affect the quality control of warfarin. The patients with CYP2C9*2, CYP2C9*3 or VKORC1 A haplotype require a lower dose of warfarin[18-21]. However, the frequency of CYP2C9*2 and CYP2C9*3 is very low (5%) in Thai population, while the frequency of VKORC1 A haplotype is higher in Thai population (63.6%)[22]. Therefore, the labile INR in Thai AF patients may be correlated to VKORC1 A haplotype. However, the Korean study by Park et al revealed the VKORC1 genotype was significantly associated with labile INR, but $SAMeTT_2R_2$ score was not associated with labile INR[23]. The genetic factor may be not the single factor for predicting the labile INR and combined genetic factor and $SAMeTT_2R_2$ score may help to predict these patients.

Moreover, the present study has shown that the race in the $SAMeTT_2R_2$ score cannot be used to predict the labile INR in Thai patients with AF receiving warfarin. If the race was excluded from this score, the average score remained 1.4. The $SAMeTT_2R_2$ score of 1 or more may be used to predict the labile INR in
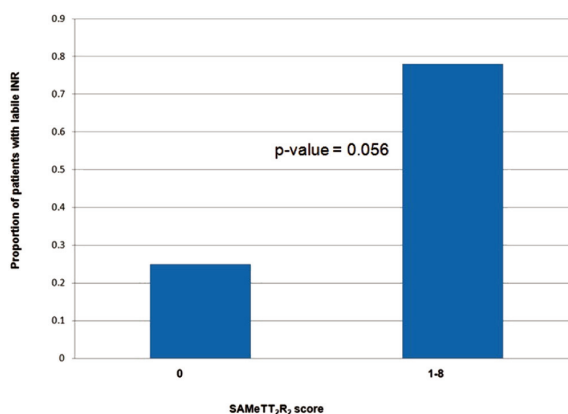

Figure 3. The proportion of Thai AF patients with labile INR between $SAMeTT_2R_2$ score of 0 or less and $SAMeTT_2R_2$ score of 1 or more after exclusion of race.

Thai patients (*p*-value 0.056) in Figure 3.

However, the present study had several limitations. First, the AF patients with the $SAMeTT_2R_2$ score of 3 or more had borderline significance in the labile INR compared with the $SAMeTT_2R_2$ score of 2 or less because of the small sample size in this study. Second, this study was a retrospective study and there were missing data in the medical records. Nevertheless, this study is the first study in Thailand showing the provisional results for a further larger study in the future and the results revealed that different $SAMeTT_2R_2$ score may predict the labile INR in Thai AF patients with warfarin.

Conclusion

Thai AF patients using warfarin had an increased proportion of labile INR according to the increased $SAMeTT_2R_2$ score. However, a larger study is needed to use $SAMeTT_2R_2$ score for predicting Thai AF patients with labile INR in the future.

What is already known on this topic?

The $SAMeTT_2R_2$ score may be used to predict the labile INR in Thai AF patients receiving warfarin.

What this study adds?

The $SAMeTT_2R_2$ score may be used to predict the labile INR in the Thai AF patients receiving warfarin using a different cut-off point from the Caucasian AF patients. The race may not be the predictor of labile INR in Thai AF patients.

Potential conflicts of interest

The author declare no conflict of interest.

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