ORIGINAL ARTICLE

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Modified application of SAMe-TT_2R_2 scoring system in Asian patients with atrial fibrillation for the selection of oral anticoagulants

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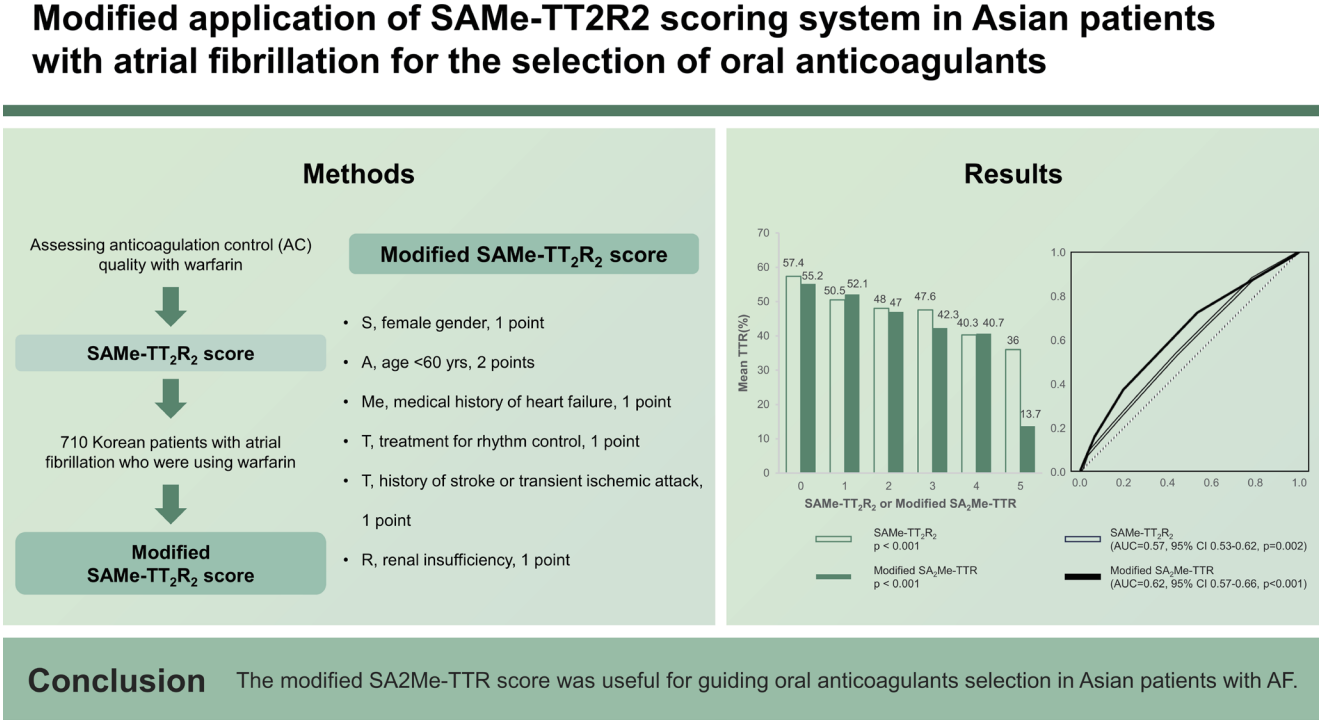

Background/Aims: The SAMe-TT_2R_2 score is used for assessing anticoagulation control (AC) quality with warfarin. However, it is hard to apply SAMe-TT_2R_2 score in Asian patients with atrial fibrillation (AF), because it has not been proven in those populations. This study aimed to validate the SAMe-TT_2R_2 score in Asian patients with AF and suggest a modified SAMe-TT_2R_2 score for this population.

Methods: We analyzed 710 Korean patients with AF who were using warfarin. The AC quality was assessed as the mean time in therapeutic range (TTR). Each component of SAMe-TT_2R_2 score was evaluated for the relationship with AC. Further

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clinical factors that predict AC were analyzed. Identified factors were re-assorted and constructed as SA_2Me-TTR scoring system.

Results: Of the components of the SAMe-TT_2R_2 score, female, age, and rhythm control were associated with AC. Heart failure and renal insufficiency were newly identified factors associated with AC. The modified SA_2Me-TTR score was reconstructed with the relevant risk factors (S, female gender, 1 point; A, age < 60 yr, 2 points; Me, medical history of heart failure, 1 point; T, treatment for rhythm control, 1 point; T, history of stroke or transient ischemic attack, 1 point; R, renal insufficiency, 1 point). The modified SA_2Me-TTR score demonstrated an excellent relationship with the grading of AC. The modified SA_2Me-TTR score ≤ 1 identified patients with good AC (hazard ratio 2.46, 95% CI 1.75–3.47).

Conclusions: The modified SA_2Me-TTR score was useful for guiding oral anticoagulants selection in Asian patients with AF.

Keywords: Warfarin; Prothrombin time; Atrial fibrillation; Thromboembolism; Safety

INTRODUCTION

Despite of emergence of non-vitamin K antagonist oral anticoagulants (NOACs), warfarin is still used for many patients [1]. Warfarin is inexpensive and is a very potent anticoagulant. However, it has critical limitations including the need to monitor individualized titration, such as the target prothrombin time (PT) and international normalized ratio (INR) of 2.0–3.0 [2-5]. Warfarin interacts with numerous other drugs and food, making it difficult to maintain the therapeutic range of PT INR in certain patients. The European Society of Cardiology (ESC) recommends the "time in therapeutic range (TTR)" should be kept as high as possible in the patients who are treated with warfarin, and the crude value of the target TTR is at least 70%. Current guidelines suggest that switching warfarin to a NOAC and maintaining an adequate TTR cannot be sustained [2-5]. Therefore, the quality of anticoagulation control (AC) prediction model with TTR is needed, and the SAMe-TT_2R_2 scoring system (Sex, female; Age, < 60 yr; Medical history, more than two comorbidities; Treatment, interacting drug, e.g., Amiodarone; Tobacco use (doubled); and Race (doubled) is available for this purpose [6-17]. The patients with SAMe-TT_2R_2 score more than 1 point are less likely to achieve a good TTR and alternative strategies may be required [8].

The SAMe-TT_2R_2 score is hard to apply to Asian patients because it has not been proven in the Asian population, and the Asian race is already a risk factor ("R", race). If the SAMe-TT_2R_2 scoring is applied to Asian patients, they would already have at least 2 points by default, leading to NOAC being recommended rather than warfarin. The pharmacodynamics of warfarin in the Asian population differ substantially from Caucasians' [18,19]. The necessity of a tailored guideline for Asians with atrial fibrillation (AF) has come to the fore. Therefore, a modified scoring system is required which is adaptable to Asian patients who are on warfarin.

We aimed to validate the SAMe-TT_2R_2 scoring system in Asian patients with non-valvular AF (NVAF) and to evaluate the relationship of each component of the SAMe-TT_2R_2 score with good INR control. We also aimed to suggest and validate a modified scoring system for the Asian population for anticoagulation therapy decision-making (warfarin or NOAC). Our objective is to contribute a guideline for anticoagulant selection for Asian patients with AF.

METHODS

Study population

This cross-sectional analysis included 2,971 Asian patients with AF who are using oral anticoagulants from the Department of Cardiology and Neurology, a Chonnam National University Hospital (Gwangju, Korea), between January 2016 and December 2018. The inclusion criteria were patients with NVAF, ≥ 18 years, CHA_2DS_2-VASc score ≥ 1, and on warfarin. The exclusion criteria were patients with valvular heart disease (> moderate severity mitral stenosis), the presence of an artificial valve, and previous changes to the class of oral anticoagulants prescribed (e.g., from warfarin to NOAC, and vice versa). In total, 732 patients (66% male; mean age, 69 yr) who had taken warfarin for up to 2 years (median time 596 d) and whose INR were measured serially were included in the study. The patients with insufficient medical records were also excluded. Finally, the analysis

included 710 Korean patients with NVAF and on warfarin. The study was approved by the ethics committee at Chonnam National University Hospital, Gwangju, South Korea (CNUH-2018-109). As the study was retrospective in nature, informed consent was waived.

Definition

The quality of AC was assessed by TTR using the Rosendaal method, which uses linear interpolation to assign an INR value to each day between two successive observed INR values [20]. The target range of INR was 2.0–3.0. A TTR of 60% or more was defined as good AC during a 2-year follow-up. Each component of the SAMe-TT_2R_2 score, except race, was used to re-evaluate AC, because all of the patients were Koreans.

We used the estimated glomerular filtration rate (eGFR) as an indicator of renal function. The CKD-EPI creatinine formula ($141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black]) was used for calculating eGFR. An eGFR of < 50 mL/min/1.73 m^2 was defined as renal insufficiency.

Cardiac systolic function was reflected by left ventricular ejection fraction (LVEF) which was calculated from the apical 2- and 4-chamber images using the bi-plane Simpson's rule in two-dimensional transthoracic echocardiogram. In this study, heart failure was defined as an LVEF reduction of < 40%.

"More than 2 morbidities" was defined as more than two of the following in the original SAMe-TT_2R_2 score: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease. To re-evaluate other clinical factors relevant to Asians, all of the factors, such as hypertension, diabetes, coronary artery disease, heart failure, renal insufficiency, and specific medications including antiarrhythmic drugs (AAD), were analyzed for the prediction of good AC during warfarin therapy. AAD including class I (e.g., propafenone, flecainide), and class III (e.g., amiodarone, dronedarone, sotalol) AAD were included.

Statistical analysis

Continuous variables were presented as means, standard deviations, and 95% confidence intervals (CIs) of the means, while discrete variables were expressed as frequencies and percentages and the differences between groups were analyzed using a chi-square test or Fisher's exact test between groups as appropriate. All potentially relevant variables including age, sex, hypertension, diabetes mellitus, previous history of angina, myocardial infarction or documented coronary artery disease, smoking, renal dysfunction, heart failure, and concomitant drugs, were analyzed using univariate analysis. Univariate analyses were used to correlate between mean TTR and the presence of clinical factors. The ratio of factor-present patients with good or poor AC group was considered. Statistical significance was defined as values of $p < 0.05$, but the clinical relevance between a single factor and good AC was defined as $p < 0.20$.

Covariates associated with TTR at a p value of < 0.20 in the univariate analyses were incorporated into a multivariate

Table 1. Mean TTR according to the factors included in SAMe-TT_2R_2 score and the distribution of each factors according to the status of anticoagulation quality

Variable	Mean TTR			Numbers of factor-present		
	Factor present	Factor absent	*p* value	Good TTR (n = 233)	Poor TTR (n = 477)	*p* value
Sex (female)	48.2 ± 21.8	50.6 ± 22.1	0.182	67 (28.8)	176 (36.9)	0.032
Age (< 60 yr)	39.7 ± 21.2	51.9 ± 21.6	< 0.001	22 (9.4)	102 (21.4)	< 0.001
Medical history (≥ 2 comorbidities)	48.8 ± 21.7	50.4 ± 22.5	0.364	89 (38.2)	188 (39.4)	0.755
Treatment (AAD)	45.8 ± 21.6	51.2 ± 22.1	0.004	47 (20.2)	143 (30.0)	0.006
Tobacco	48.8 ± 22.7	49.9 ± 21.8	0.589	56 (25.6)	113 (25.2)	0.910
Race	-	-	-	-	-	-

Values are presented as mean ± standard deviation or number (%).
AAD, antiarrhythmic drugs; TTR, time in therapeutic range.

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stepwise linear regression model. Based on the regression coefficients, we gave weight to each extracted factor and collated them into a modified predictive scoring system. The risk score was calculated as the sum of the points of the following: S (Sex, female gender, 1 point), A (Age, < 60 yr, 2 points), Me (Medical history of heart failure, 1 point), T (Treatment for rhythm control, any AAD, 1 point), T (sTroke, history of stroke or TIA, 1 point), and R (Renal insufficiency, eGFR < 50 mL/min/1.73 m^2, 1 point). The predictive accuracy of the scoring system was then assessed using the area under the receiver operator characteristics (c statistics). Analysis was performed with SPSS, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean TTR according to individual SAMe-TT_2R_2 factors

Univariate analysis was performed for each component of the SAMe-TT_2R_2 score, except R_2. The mean TTR (according to the factors present) was significantly different for female gender (48.2% vs. 50.6%, $p = 0.182$), age < 60 years (39.7% vs. 51.9%, $p < 0.001$), and the use of AAD (45.8% vs. 51.2%, $p = 0.004$). In contrast, "two or more comorbidities" and "tobacco use" were not significantly different (Table 1). The SAMe-TT_2R_2 score demonstrated a linear association with mean TTR (Fig. 1A, $p < 0.001$)

The relationship between good AC and individual SAMe-TT_2R_2 factors

We divided the patients into two groups (TTR ≥ 60% [Good AC] and < 60% [Poor AC]) and analyzed the ratio of factor-present patients for each component of SAMe-TT_2R_2 score, except R_2. The results for mean TTR according to the presence of the factor were statistically significant. Female gender (28.8% vs. 36.9%, $p = 0.032$), age < 60 years (9.4% vs. 21.4%, $p < 0.001$), and the use of AAD (20.2% vs. 30.0%, $p = 0.006$) and the ratio of factor-present patients were statistically significant. In contrast, "two or more comorbidities" and "tobacco use" were not significant (Table 1). The SAMe-TT_2R_2 score was significantly associated with the ratio of patients with good AC but it failed to show a linear association because the ratio of good AC in patients with 4 points was lower than that of patients with 5 points (Fig. 1B, $p = 0.010$).

Identification of new factors associated with good AC

First, the mean TTR was analyzed according to the presence of each factor (Table 2). The mean TTR did not significantly differ for factors, such as hypertension, diabetes, smoking, angina history, myocardial infarction, coronary artery disease, and comorbidities (≥ 1, ≥ 2). A lower mean TTR was significantly associated with female gender (48.2% vs. 50.6%, $p = 0.182$), < 60 years (39.7% vs. 51.9%, $p < 0.001$), renal insufficiency (51.7% vs. 56.0%, $p = 0.153$),

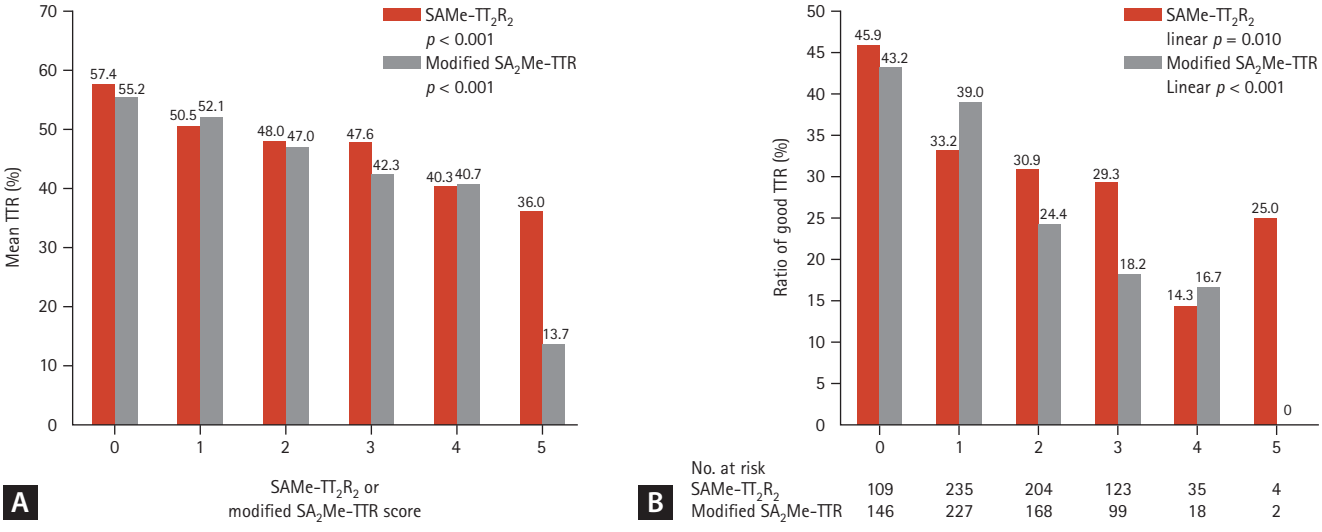

Figure 1. Mean TTR and the ratio of patients with good TTR according to the SAMe-TT_2R_2 and modified SA_2Me-TTR scores. (A) The mean TTR according to the SAMe-TT_2R_2 and the modified SA_2Me-TTR score. (B) The ratio of patients with good TTR according to the SAMe-TT_2R_2 and the modified SA_2Me-TTR. TTR scores. Patients with good TTR had a TTR of ≥ 60%. TTR, time in the therapeutic range.

Table 2. Mean TTR according to the various clinical factors and the distribution of each factors according to the status of anticoagulation quality

Variable	Mean TTR			Numbers of factor-present			
	Factor present	Factor absent	*p* value	All (n = 710)	Good TTR (n = 233)	Poor TTR (n = 477)	*p* value
Sex (female)	48.2 ± 21.8	50.6 ± 22.1	0.182	243 (34.2)	67 (28.8)	176 (36.9)	0.032
Age (yr)				69.4 ± 9.8	72.3 ± 8.4	68.0 ± 10.1	< 0.001
< 50	33.3 ± 22.6	50.3 ± 21.8	< 0.001	23 (3.2)	3 (1.3)	20 (4.2)	0.043
< 60	39.7 ± 21.2	51.9 ± 21.6	< 0.001	124 (17.5)	22 (9.4)	102 (21.4)	< 0.001
Hypertension	49.9 ± 21.9	49.4 ± 22.2	0.806	344 (51.5)	114 (52.1)	230 (51.2)	0.840
Diabetes mellitus	47.9 ± 23.3	50.1 ± 21.7	0.310	135 (20.2)	44 (20.1)	91 (20.3)	0.958
Smoking	48.8 ± 22.7	49.9 ± 21.8	0.589	169 (25.3)	56 (25.6)	113 (25.2)	0.910
Previous history of angina	46.8 ± 22.3	50.0 ± 22.0	0.251	71 (10.6)	23 (10.5)	48 (10.7)	0.941
Previous history of MI	50.5 ± 20.4	49.6 ± 22.1	0.822	33 (4.9)	9 (4.1)	23 (5.3)	0.489
Previous history of CAD	47.9 ± 22.1	49.9 ± 22.0	0.407	93 (13.9)	30 (13.7)	63 (14.0)	0.907
Previous history of renal insufficiency (eGFR < 50 mL/min/1.73 m^2)	51.7 ± 20.5	56.0 ± 21.0	0.153	55 (8.5)	12 (5.6)	43 (9.9)	0.045
Previous history of heart failure	50.8 ± 19.9	56.2 ± 21.1	0.062	60 (9.0)	19 (6.5)	41 (11.0)	0.045
Previous stroke or TIA	48.8 ± 22.6	51.7 ± 20.4	0.130	196 (29.3)	63 (27.0)	153 (32.1)	0.169
More than 2 comorbidities	48.8 ± 21.7	50.4 ± 22.5	0.364	277 (39.0)	89 (38.2)	188 (39.4)	0.755
More than 1 comorbidity	50.3 ± 21.9	48.6 ± 22.3	0.361	513 (72.3)	173 (74.2)	340 (71.3)	0.407
Antiplatelet therapy	47.5 ± 23.6	50.2 ± 21.8	0.241	110 (15.5)	33 (14.2)	77 (16.1)	0.494
Aspirin	47.7 ± 23.5	50.1 ± 21.8	0.305	102 (14.4)	31 (13.3)	71 (14.9)	0.573
Clopidogrel	44.2 ± 25.1	50.0 ± 21.9	0.199	27 (3.8)	7 (3.0)	20 (4.2)	0.437
Statin	51.0 ± 23.1	48.9 ± 21.2	0.202	308 (43.4)	108 (46.4)	200 (41.9)	0.264
ACEI	51.5 ± 22.1	49.6 ± 22.0	0.472	72 (10.1)	28 (12.0)	44 (9.2)	0.247
ARB	50.7 ± 22.6	49.1 ± 21.6	0.343	312 (43.9)	104 (44.6)	208 (43.6)	0.795
ACEI/ARB	50.8 ± 22.4	48.5 ± 21.5	0.167	384 (54.1)	132 (56.7)	252 (52.8)	0.337
Dihydropyridine	48.1 ± 23.5	50.1 ± 21.7	0.376	115 (16.2)	35 (15.0)	80 (16.8)	0.552
Verapamil	56.8 ± 18.9	49.7 ± 22.1	0.396	7 (1.0)	2 (0.9)	5 (1.0)	0.810
Diltiazem	50.5 ± 23.7	49.6 ± 21.5	0.632	167 (23.5)	61 (26.2)	106 (22.2)	0.243
Digoxin	50.5 ± 23.0	49.6 ± 1.8	0.679	118 (16.6)	42 (18.0)	76 (15.9)	0.482
BB	47.8 ± 22.2	50.8 ± 21.9	0.088	243 (34.2)	78 (33.5)	165 (34.6)	0.769
Class III AAD	46.0 ± 20.6	50.4 ± 22.2	0.062	103 (14.5)	25 (10.7)	78 (16.4)	0.046
Amiodarone	44.6 ± 19.9	50.3 ± 22.2	0.048	67 (9.4)	17 (7.3)	50 (10.5)	0.173
Dronedarone	51.8 ± 24.1	49.8 ± 22.0	0.810	7 (1.0)	2 (0.9)	5 (1.0)	0.583
Sotalol	47.5 ± 21.0	49.9 ± 22.1	0.550	31 (4.4)	6 (2.6)	25 (5.2)	0.103
Flecainide	43.8 ± 21.0	50.2 ± 22.1	0.043	51 (7.2)	11 (4.7)	40 (8.4)	0.076
Propafenone	47.7 ± 22.9	49.9 ± 22.0	0.490	52 (7.3)	16 (6.9)	36 (7.5)	0.744
Any AAD	45.8 ± 21.6	51.2 ± 22.1	0.004	190 (26.8)	47 (20.2)	143 (30.0)	0.006

Values are presented as mean ± standard deviation or number (%).
AAD, antiarrhythmic drugs; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; TIA, transient ischemic attack; TTR, time in therapeutic range.

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heart failure (50.8% vs. 56.2%, $p = 0.062$), and stroke or TIA history (48.8% vs. 51.7%, $p = 0.130$). Comparing the mean TTR according to the use of cardiovascular drugs demonstrated that aspirin, clopidogrel, statin, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), calcium channel blocker (CCB), digoxin, and beta-blocker (BB) did not associated significantly with the mean TTR. In analyzing the AAD, amiodarone (44.6% vs. 50.3%, $p = 0.048$), flecainide (43.8% vs. 50.2%, $p = 0.043$), class III AAD (46.0% vs. 50.4%, $p = 0.062$), and any other AAD (45.8% vs. 51.2%, $p = 0.004$) showed a significant difference in the mean TTR.

The factors were analyzed according to the ratio of patients in the good AC and poor AC groups (Table 2). Factors, such as hypertension, diabetes, smoking, history of angina, myocardial infarction, coronary artery disease, and comorbidities (≥ 1, ≥ 2) had no association with good AC. Female gender (28.8% vs. 36.9%, $p = 0.032$), < 60 years (9.4% vs. 21.4%, $p < 0.001$), renal insufficiency (5.6% vs. 9.9%, $p = 0.045$), EF < 40% (6.5% vs. 11.0%, $p = 0.045$), stroke or TIA history (27.0% vs. 32.1%, $p = 0.169$) were lower in the good AC group than in the poor AC group. We also compared the ratio of cardiovascular drugs used between the good AC and poor AC groups. Aspirin, clopidogrel, statin, ACEI, ARB, CCB, digoxin, and BB were not statistically significant. Patients with good AC used fewer AAD including amiodarone (7.3% vs. 10.5%, $p = 0.173$), sotalol (2.6% vs. 5.2%, $p = 0.103$), flecainide (4.7% vs. 8.4%, $p = 0.076$), class III AAD (10.7% vs. 16.4%, $p = 0.046$), and any AAD (20.2% vs. 30.0%, $p = 0.006$) than the poor AC group.

In linear regression analysis, sex, age, medical history (heart failure), treatment, stroke, renal insufficiency (GFR < 50 mL/min.1.73 m^2) were significantly associated with a lower ratio of good AC (Table 3). Considering factors for

Table 3. Factors associated for anticoagulation quality

Variable	Good TTR (n = 233)	Poor TTR (n = 477)	Unadjusted HR (95% CI)	*p* value
Sex – female	67 (28.8)	176 (36.9)	1.45 (1.03–2.03)	0.032
Age – < 60 yr	22 (9.4)	102 (21.4)	2.61 (1.60–4.26)	< 0.001
Medical Hx – comorbidities ≥ 2	89 (38.2)	188 (39.4)	1.05 (0.76–1.45)	0.755
Treatment – any AAD	47 (20.2)	143 (30.0)	1.69 (1.16–2.47)	0.006
Tobacco	56 (25.6)	113 (25.2)	0.98 (0.68–1.42)	0.910
Race	-	-	-	-
Medical Hx – heart failure	19 (6.5)	41 (11.0)	1.78 (1.01–3.13)	0.047
sTtroke	63 (27.0)	153 (32.1)	1.26 (0.91–1.77)	0.169
Renal insufficiency – eGFR < 50 mL/min/1.73 m^2	12 (5.6)	43 (9.9)	1.83 (0.95–3.56)	0.073

Values are presented as number (%).
AAD, antiarrhythmic drugs; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; TTR, time in therapeutic range.

Table 4. The original SAMe-TT_2R_2 score and modified SA_2Me-TTR score

SAMe-TT_2R_2 score			Modified SA_2Me-TTR score		
	Characteristic	Score		Characteristic	Score
Sex	Female	1	Sex	Female	1
Age	< 60 yr	1	Age	< 60 yr	2
Medical Hx	≥ 2 comorbidities	1	Medical Hx	Heart failure	1
Treatment	AAD	1	Treatment	AAD	1
Tobacco use	Smoking	2	sTroke	Previous stroke or TIA	1
Race	Non-caucasian	2	Renal insufficiency	eGFR < 50 mL/min/1.73 m^2	1

AAD, antiarrhythmic drugs; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; TTR, time in therapeutic range.

satisfying both mean TTR and the ratio of good TTR control, sex, age, medical history (heart failure), treatment, stroke, and renal insufficiency were risk factors for poor AC. Furthermore, among the original factors included in the SAMe-TT_2R_2 scoring system, medical history as "more than 2 comorbidities"; this and tobacco use were not associated with good AC. In contrast, heart failure, stroke, and renal insufficiency were associated with good AC. Therefore, the risk factors included in the SAMe-TT_2R_2 score were modified. The original components: medical history (Me), tobacco (T), and race (R), were substituted with medical history of heart failure (Me), stroke (T), and renal insufficiency (R). The modified SA_2Me-TTR included the relevant risk factors for the Asian population including S, female gender (1 point); A, age < 60 years (2 points); Me, medical history of heart failure (1 point); T, treatment for rhythm control (1 point); T, stroke or TIA history (1 point); R, renal insufficiency (1 point) (Table 4).

Validation of the original SAMe-TT_2R_2 and the modified SA_2Me-TTR scores

For the original SAMe-TT_2R_2 score, race (R) was designated as 0. According to the original SAMe-TT_2R_2 system score, the mean TTR decreased in a stepwise manner (57.4% vs. 50.5% vs. 48.0% vs. 47.6% vs. 40.3% vs. 36.0%, linear $p < 0.001$). However, the original SAMe-TT_2R_2 score did not demonstrate a linear relationship for the ratio of good AC, with a sudden incremental increase at score 5. According to the modified SA_2Me-TTR system score, the mean TTR decreased in a stepwise manner (55.2% vs. 52.1% vs. 47.0% vs. 42.3% vs. 40.7% vs. 13.7%, linear $p < 0.001$). Additionally, the modified SA_2Me-TTR scoring system demonstrated an excellent linear relationship with the ratio of patients with good AC (43.2% vs. 39.0% vs. 24.4% vs. 18.2% vs. 16.7% vs. 0.0%, linear $p < 0.001$) (Fig. 1B).

The prediction of good AC (score ≤ 1) was validated for

Table 5. Comparison of the mean TTR and the ratio of the patients with good AC according to the SAMe-TT_2R_2 score and modified SA_2Me-TTR score

TTR	SAMe-TT_2R_2 score				m-SA_2Me-TTR score			
	≤ 1 point	> 1 point	Unadjusted HR (95% CI)	*p* value	≤ 1 point	> 1 point	Unadjusted HR (95% CI)	*p* value
Mean TTR	52.7 ± 21.7	47.0 ± 22.1		0.001	53.1 ± 22.1	44.8 ± 21.0		< 0.001
Good TTR	128 (54.9)	105 (45.1)	1.47 (1.08–2.02)	0.016	171 (73.4)	62 (26.6)	2.46 (1.75–3.47)	< 0.001

Values are presented as mean ± standard deviation or number (%).
AC, anticoagulation control; CI, confidence interval; HR, hazard ratio; TTR, time in therapeutic range.

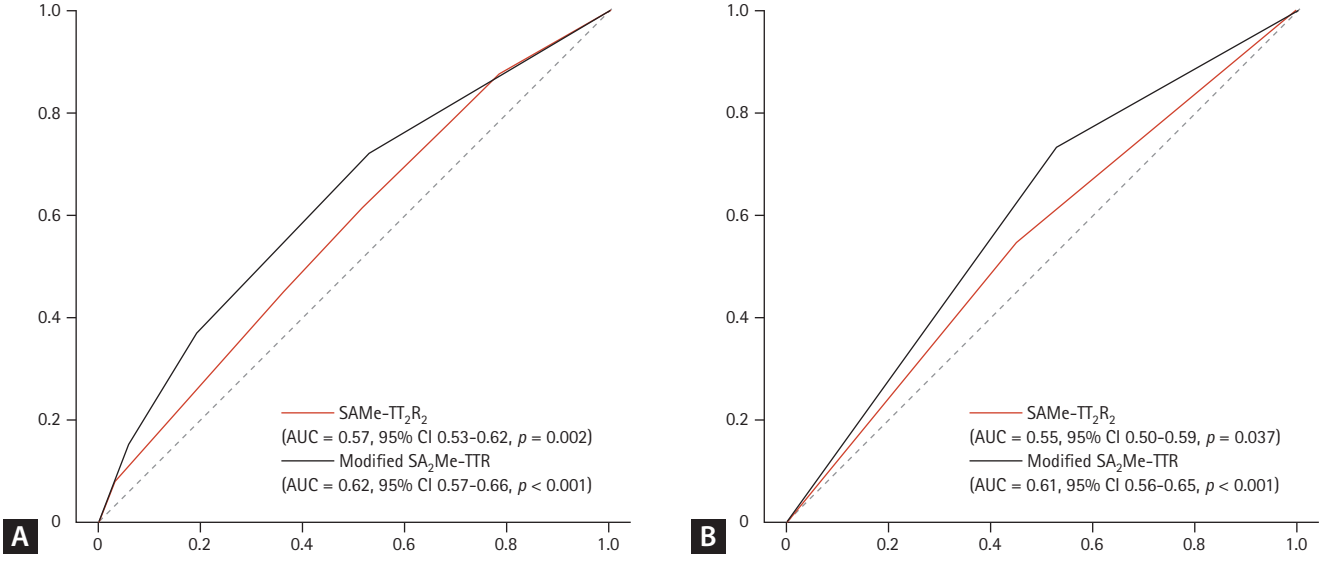

Figure 2. The predictive accuracy of the SAMe-TT_2R_2 and modified SA_2Me-TTR scoring systems. (A) The scores as continuous variables. (B) The scores as dichotomous variables. AUC, area under the curve; CI, confidence interval; TTR, time in the therapeutic range.

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the original SAMe-TT_2R_2 and the modified SA_2Me-TTR scoring systems (Table 5). For the mean TTR, both the original SAMe-TT_2R_2 (52.7 ± 21.7% vs. 47.0 ± 22.1%, $p = 0.001$) and the modified SA_2Me-TTR (53.1 ± 22.1% vs. 44.8 ± 21.0%, $p < 0.001$) scores showed significant discrimination power. For the ratio of good AC, both the original SAMe-TT_2R_2 (54.9% vs. 45.1%, odds ratio [OR] 1.47, 95% CI 1.08–2.02, $p = 0.016$) and the modified SA_2Me-TTR (73.4% vs. 26.6%, OR 2.46, 95% CI 1.75–3.47, $p < 0.001$) systems showed significant discrimination power.

For the model performance evaluation, a ROC curve was created (Fig. 2). Considering the scores as continuous variables, both the original SAMe-TT_2R_2 (area under the curve [AUC] = 0.57, 95% CI 0.53–0.62, $p = 0.002$) and the modified SA_2Me-TTR (AUC = 0.62, 95% CI 0.57–0.66, $p < 0.001$) scoring systems demonstrated good predictive power. Considering the scores as dichotomous variables (1), both the original SAMe-TT_2R_2 (AUC = 0.55, 95% CI 0.50–0.59, $p = 0.037$) and the modified SA_2Me-TTR (AUC = 0.61, 95% CI 0.56–0.65, $p < 0.001$) systems demonstrated good predictive power. Comparing the two systems (as dichotomous variables) for the prediction of good AC, the modified SA_2Me-TTR scoring system showed better predictive power than the original SAMe-TT_2R_2 scoring system ($p < 0.001$).

Good AC as determined by both the scoring systems were evaluated against hard clinical outcomes. In terms of the original SAMe-TT_2R_2 system, there was no difference in the rate of stroke, major bleeding, mortality, or composite clinical outcomes (the sum of stroke or major bleeding, and the sum of stroke, major bleeding, or death) between the good and poor AC groups. similarly, when considering the modified SA_2Me-TTR system, there was no difference in the rate of stroke, major bleeding, mortality, or composite clinical outcomes (the sum of stroke or major bleeding, and the sum of stroke, major bleeding, or death) between the good and poor AC groups (Table 6).

DISCUSSION

The SAMe-TT_2R_2 scoring system is used to identify patients who cannot maintain appropriate therapeutic INR (cut-off value = 2). For patients who score > 2, good AC is unlikely and the clinician may prescribe NOAC instead of warfarin [7]. Meta-analyses have proven that the score is a potent predictor of TTR [21]. However, to date, the meta-analyses have excluded Asian studies because they all have 2 or more points due to the factor R (race) in the scoring system, which makes analysis and direct comparison difficult. Furthermore, Asian studies of the SAMe-TT_2R_2 score are limited.

This study is the first report to suggest a modified version of the SAMe-TT_2R_2 scoring system for Asian patients with AF. In a study by Park et al., the SAMe-TT_2R_2 scoring system was applied to Korean patients with AF in the Department of Neurology [22]. They collected clinical and genetic data from Korean patients with AF and concluded that the time in specific INR ranges depended on the VKORC1 genotype but not on the SAMe-TT_2R_2 score. This led to the suggestion that the scoring system may not be predictive of good AC in Asian populations including Koreans. Although studies of various sample sizes of Asian patients with AF have been conducted, the results relating to the SAMe-TT_2R_2 score have been inconsistent [9,10,22,23]. When compared to Western populations, Asian populations generally have a

Table 6. Clinical according to the SAMe-TT_2R_2 score and modified SA_2Me-TTR score

Variable	SAMe-TT_2R_2 score			Modified SA_2Me-TTR score		
	≤ 1 point	> 1 point	*p* value	≤ 1 point	> 1 point	*p* value
Stroke	11 (3.2)	19 (5.2)	0.187	17 (4.0)	13 (4.5)	0.740
Ischemic stroke	7 (2.0)	15 (4.1)	0.113	12 (2.8)	10 (3.5)	0.625
Hemorrhagic stroke	2 (0.6)	5 (1.4)	0.452	3 (0.7)	4 (1.4)	0.449
Major bleeding	13 (3.8)	12 (3.3)	0.718	13 (3.1)	12 (4.2)	0.432
Death	9 (2.6)	11 (3.0)	0.754	9 (2.1)	11 (3.8)	0.178
Stroke, major bleeding	22 (6.4)	26 (7.1)	0.707	28 (6.6)	20 (7.0)	0.856
Stroke, major bleeding, death	26 (7.6)	32 (8.7)	0.565	32 (7.6)	26 (9.1)	0.476

Values are presented as number (%).
TTR, time in therapeutic range.

lower body mass index and different pharmacodynamics to various drugs [24,25]. Even among Asians, some characteristics may differ depending on the specific race. Hence, heterogeneous results in studies that validated the SAMe-TT_2R_2 score in Asians may be caused by racial differences. A multi-center multi-ethnic cohort study that included Malay, Chinese, and non-Malay patients showed that the SAMe-TT_2R_2 score failed to predict a TTR ≥ 65% [23]. Subgroup analyses revealed that the median TTR significantly differed for each ethnic group and hospital setting.

The objectives of the present study were to validate the SAMe-TT_2R_2 score for an Asian population. Considering the factor R as 0 points, we investigated the predictability of TTR using the SAMe-TT_2R_2 score. Our results showed that the categorical application of the SAMe-TT_2R_2 score (0–1 vs. ≥ 2) was predictive of poor AC. In contrast, the original SAMe-TT_2R_2 score failed to show a linear association with the mean TTR in Asian patients. Moreover, some original components of the SAMe-TT_2R_2 score, such as smoking or comorbidities, were not significantly associated with good AC. Consequently, we suggested a modified version that considered renal insufficiency and stroke history instead of smoking and comorbidities. We verified the modified SA_2Me-TTR score among Asian patients, and demonstrated superior predictability for AC relative to the original SAMe-TT_2R_2.

A good AC quality determined by the SAMe-TT_2R_2 or the modified SA_2Me-TTR scores of ≤ 1 was not associated with a reduced risk of hard clinical outcomes. Composed risk factors both in risk factors might explain the reason. Old age is the strongest risk factor for stroke, major bleeding, and mortality in patients with AF [2,4,5]. However, in both scoring systems, younger ages (< 60 yr) were considered for poor AC. Recent studies confirmed that good rhythm control is associated with a reduced risk of stroke or death [26,27]. AADs are fundamental to improving rhythm control. Yet, both scoring systems considered AAD use as a risk factor for poor AC. Race, specifically non-Caucasians, in the SAMe-TT_2R_2 score, is not a known risk factor for stroke or major bleeding. Hence, the inclusion of non-relevant and opposing risk factors to recognize stroke risks in the SAMe-TT_2R_2 or the modified SA_2Me-TTR scores in the prediction of AC interrupted the relation between improved clinical outcomes and good AC. These findings suggest that the utilization of the SAMe-TT_2R_2 or the modified SA_2Me-TTR scores is not useful for predicting stroke, major bleeding, or death in patients with AF and on warfarin.

This study has some limitations. First, this is a retrospective single-center study. It is difficult to fully represent Asian patients with AF from the present data. Second, the recommended TTR in warfarin-treated patients is ≥ 70% but we utilized 60% as the cut-off value of good AC. This was because at a TTR of 70%, the number of patients in the good AC group was too small, which limits adequate comparisons. Conversely, this could also be a testament to the difficulty of maintaining adequate AC in Asian patients who are placed on warfarin therapy. Therefore, a more accurate tool for the prediction of TTR in Asians is warranted.

The study also has some strengths. In this study, not only each component of the SAMe-TT_2R_2 score but also other clinical factors, such as underlying diseases, and concomitant medications, were also considered when analyzing the association between TTR and good AC. Based on these analyses, we modified the scoring system for Asians and validated the modified model. We concluded that the modified model predicted TTR better than the original SAMe-TT_2R_2 score in Asians. Our findings are especially useful for clinicians who treat patients with NVAF.

KEY MESSAGE

1. The SAMe-TT_2R_2 scoring system is not suitable for Asians who are using warfarin.
2. Some factors in the SAMe-TT_2R_2 scoring system did not correlate with TTR prediction in the Asian population.
3. The modified version of the SA_2Me-TTR score was re-evaluated against the identified factors. Then, the SA_2Me-TTR scoring system was constructed for Asian patients with NVAF.
4. It consists of 6 factors with a maximum of 7 points (S, female gender, 1 point; A, age < 60 yr, 2 points; Me, medical history of heart failure, 1 point; T, treatment for rhythm control, 1 point; T, history of stroke or TIA, 1 point; and R, renal insufficiency, 1 point).
5. The modified SA_2Me-TTR score shows better TTR predictability for Asian patients with NVAF.
6. The modified SA_2Me-TTR score can assist clinicians in identifying Asian patients who do not tolerate warfarin.

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