Research Article

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Evaluation of the Modified SAME-TT₂R₂ Score to Predict Good Anticoagulation Control with Warfarin Among non-valvular Atrial Fibrillation Patients

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ABSTRACT

Background: The SAME-TT₂R₂ Score was developed to identify vitamin K antagonists control outliers before non-valvular atrial fibrillation (AF) patients start treatment. SAME-TT₂R₂ Score was derived and validated using a primarily white Caucasian population to predict TTR. Given that non-Caucasian race already confers 2 points in this score, the SAME-TT₂R₂ score requires validation and/or re-calibration despite race of population.

Method: We conducted a cohort retrospective study that included all non-valvular atrial fibrillation patients who were on warfarin therapy from January to December 2019.

Then we calculated the modified SAME-TT₂R₂ and SAME-TT₂R₂ for all study populations and we correlated the result with patients' TTR. The TTR was calculated through the Rosendaal's method.

Results: We had 662 patient using warfarin therapy, among those 662, 60.9% were under cardiology and using it for cardiac indication, and only 18.1% diagnosed to have non-valvular AF. Modified SAME-TT₂R₂ score has good relation to original SAME-TT₂R₂ score as showed 75.71% (95% CI. 63.99 to 85.17%), 100% (95% CI. 92.89 to 100%) and 15% (95% CI. 3.21 to 77.95%); accuracy, sensitivity and specificity in relation to SAME-TT₂R₂ respectively. In addition to that in this small cohort we found that there is universal relationship between SAME-TT₂R₂ score, Modified SAME-TT₂R₂ score and TTR; TTR >=65% associate with low score (<2) of both SAME-TT₂R₂, Modified SAME-TT₂R₂ score.

Conclusion: The use of Modified SAME-TT₂R₂ score allows clinicians to make an informed decision on whether to start vitamin K antagonist or other non-vitamin K antagonist oral anticoagulant despite the race of the patients.

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Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia, which is associated with a 5-fold higher risk of cerebral stroke and a 3-fold higher risk of congestive heart failure. Nearly 20% of all strokes are caused by cardiogenic embolism associated with AF [1].

AF patients with CHA₂DS₂-VASc ≥ 2 for male, and ≥ 3 for Female, should be started on therapeutic anticoagulation to prevent stroke and systemic embolism. Risk factors for cerebral stroke and systemic embolism included in CHA₂DS₂-VASc score are defined as; (Congestive heart failure/left ventricular dysfunction, hypertension, age from 65 to <75 years, age ≥ 75 years, diabetes, stroke, and female sex) [1].

Vitamin K antagonists (VKAs), are the most commonly used oral anticoagulants. VKAs and target specific oral anticoagulants have been used to reduce the risk of ischemic stroke in AF patients by approximately 60% [2]. The efficacy of treatment with VKAs is directly related to the time in therapeutic range (TTR); which is defined as a measure that summarizes international normalized ratio (INR) control over time [2].

Nation Institute for Care Excellence guidelines recommend a TTR of 65% for an average individual while European guidelines recommend TTR 70% to maximize the effectiveness and safety of VKAs [2]. However, maintaining a 65% to 70 % TTR requires regular monitoring of antithrombotic which makes therapy difficult; since VKAs have a narrow therapeutic window and numerous interactions with food and other medications [1]. Therefore, determining which patients are good candidates

for VKAs would be very useful in therapy. Scores CHADS₂ and CHA₂DS₂-VASc are currently used to assess the risk for thromboembolic events, while other scores HAS-BLED assess the risk of bleeding from that therapy; bleeding risk. Those scores allow us to assess the indication for that therapy and its risk. However, they provide no information on how the patient will respond to treatment, particularly whether the patient will maintain the target TTR [3].

Decision-making could be guided by a strategy that assesses the probability of stabilized anticoagulation during VKAs treatment. Recently, apostolakis et al. have proposed and validated the SAME-TT₂R₂ score (Sex (female), age <60 years, medical history* and treatment* -interacting drugs- "all 1 point"; as well as current tobacco use "2 points" and race (non-Caucasian; 2 points) [4].

*Medical history includes at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease, and treatment interacting drugs, eg, amiodarone [4].

The new 8-point score (SAME-TT₂R₂ score) that was introduced in 2013 states that patients with a score of 0 to 1 (low risk group) should receive VKAs treatment, while patients with a score of 2 or higher (high risk group) are recommended to use non-VKAs oral anticoagulants as an alternative treatment [4]. This score was derived from the AF Follow-up Investigation of Rhythm Management (AFFIRM) trial population and externally validated in a small "real world" cohort of anticoagulated non-valvular AF patients [5].

The SAME-TT₂R₂ Score was developed to identify VKAs control outliers before they start treatment. While the score has been adopted in AF guidelines, the added benefit of this score remains unclear [6]. SAME-TT₂R₂ score, is easy, simple prediction of which AF patients are likely to do well on VKAs (with good average TTR), could guide decision-making between using VKAs and non-VKAs oral anticoagulants.

SAME-TT₂R₂ Score was derived and validated using a primarily white Caucasian population to predict TTR. Given that non-Caucasian race already confers 2 points in this score, the SAME-TT₂R₂ score requires validation and/or re-calibration in a non-Caucasian population [3].

Nevertheless, despite the fact that it is well documented that a lower SAME-TT₂R₂ score is associated with a well-controlled TTR. The clinical benefit of this tool was only established in Caucasian population. Therefore, we are conducting this study to evaluate the applicability of this tool despite the race.

Study objectives

We evaluated the clinical use of modified SAME-TT₂R₂ score

(modified SAME-TT₂R₂ score defined as: SAME-TT₂R₂ score in despite to the race of population) in non-valvular AF.

Methodology

Study Design and Procedure

A cohort retrospective study that was conducted at a single tertiary care hospital in Riyadh, Saudi Arabia. We included all non-valvular AF patients who were on vitamin K antagonist (warfarin) therapy from January to December of 2019.

Then we calculated the modified SAME-TT₂R₂ score (original score without including race) and SAME-TT₂R₂ score for all study population and we correlated the results with the patients TTR. The TTR was calculated through the Rosendaal's method.

Inclusion Criteria

1. Saudi and non-Saudi patients of ≥18 years of age
2. Confirmed diagnosis of non-valvular AF
3. Patients on Warfarin for at least 3 months during the defined study period.

Exclusion Criteria

1. Age <18 years of age
2. Patients using warfarin for indication other than non-valvular AF

Statistical Analysis

All categorical variables such as race, gender, CHF, past medical history, HTN, bleeding etc. presented as numbers and percentages. Continuous variable such as age presented as Mean ± SD. Whereas weight, height, CHADS₂, CHA₂DS₂-VASc, SAME-TT₂R₂ score, and modified SAME-TT₂R₂ score were expressed as Interquartile range (IQR). Whereas test of normality was checked by Kolmogorov Smirnov test. The Receiver operating characteristics (ROC) was carried out to determine the sensitivity and specificity of modified SAME-TT₂R₂ score test for good anticoagulation control. Furthermore, comparative analysis will be applied by Mann-Whitney U test as appropriate. Chi-square / Fisher's exact test was used according to whether the cell expected frequency smaller than 5, and to determine significant association between categorical variables. A P-value of less than 0.05 will be considered as statistically significant. All data will be entered and analyzed through statistical package SPSS 25 (SPSS Inc., Chicago, IL, USA) and MedCalc version 18.16.11.

Results

During the defined study period, we had 662 patients using warfarin therapy, among those 662, 60.9% (403 patients) were under cardiology and using it for cardiac indication, and only 18.1% (73 patients) were diagnosed with non-valvular atrial fibrillation. 95.9% (70 patients) met the inclusion criteria, with a mean age 60.12 ± 14.38 years and female gender representing 54.3% from the total study population, baseline characteristics and median (IQR) scores of study population are presented in Table I and Table II respectively.

Table I: Baseline Characteristics of the Patients (n = 70)

Variables	Description	n(n%)
Race	Saudi	63 (90.0%)
	Non-Saudi	7 (10.0%)
Gender	Male	32 (45.70%)
	Female	38 (54.30%)
Age (years)	Mean ± SD	60.12 ± 14.38
Weight (kg)	Median (IQR)	77.60 (90.00 - 64.50)
Height (cm)	Median (IQR)	1.65 (1.78 - 1.56)
HTN	Yes	18 (26.10%)
	No	51 (73.90%)
Renal	Yes	22 (31.90%)
	No	47 (68.10%)
Previous stroke	Yes	19 (27.50%)
	No	50 (72.50%)
History of bleeding	Yes	8 (11.60%)
	No	61 (88.40%)
Labile INR	Yes	23 (33.30%)
	No	46 (66.70%)
Age > 65	Yes	26 (37.70%)
	No	43 (62.30%)

SD: Standard deviation

Table II: Descriptive Analysis of Different Scores

	Median (IQR)
CHADS ₂	2.00 (3.00 – 1.00)
CHA ₂ DS ₂ -VASc	4.00 (5.00 – 2.00)
HAS-BLED	2.00 (3.00 – 1.00)
SAME-TT ₂ R ₂	4.00 (6.00 – 3.00)
Modified SAME-TT ₂ R ₂	2 (2.25 – 1.00)
TTR	59.1 (69.6 – 37.25)

In order to establish the optimal cut-off/threshold values of modified SAME-TT₂R₂ score of the best sensitivity and specificity for the study outcome, we performed ROC analysis by plotting sensitivity against 100-specificity at different cut-off values of modified SAME-TT₂R₂. By using, the value original SAME-TT₂R₂ score ≥ 2 score detect poor Vitamin-K antagonist effect while original SAME-TT₂R₂ <2 score detect good Vitamin-K antagonist effect. Moreover, Modified SAME-TT₂R₂ score has good relation to original SAME-TT₂R₂ score as showed 75.71% (95% CI. 63.99 to 85.17%), 100% (95% CI. 92.89 to 100%) and 15% (95% CI. 3.21 to 77.95%); accuracy, sensitivity and specificity in relation to SAME-TT₂R₂ score respectively, Table III.

Table III: Predication of Drugs Outcome by ROC Analysis of Modified SAME-TT₂R₂ Score

		Modified SAME-TT ₂ R ₂		P – value
		Positive	Negative	
		(≥2 SAME-TT ₂ R ₂)	(< 2 SAME-TT ₂ R ₂)	
SAME-TT ₂ R ₂	Positive (≥2)	50 (100%)	17 (85%)	*<0.001
	Negative (< 2)	0	3 (15.0%)	
Statistic		Value	95% CI	
Sensitivity		100%	92.89% to 100%	
Specificity		15.00%	3.21% to 37.89%	
Positive Predictive Value		74.63%	59.38 to 77.95%	
Negative Predictive Value		100%		
Accuracy		75.71%	63.99% to 85.17%	

While that SAME-TT₂R₂ score is considered a predictor for good average time in therapeutic range; in this cohort we tested the validity of Modified SAME-TT₂R₂ score by using ROC in relation to original SAME-TT₂R₂ score, that showed good prediction; Modified SAME-TT₂R₂ score in relation to SAME-TT₂R₂ score has AUC 87.3%, Figure I

Figure: ROC Analysis of Modified SAME-TT₂R₂ Score

This curve and corresponding AUC showing that 75.71% diagnostic accuracy (concordance) of the test along the tradeoff (cut off) value of modified SAME-TT₂R₂ score ≥ 2 test has predictability to detect the poor response to VKAs. Whereas accuracy is measured by the area under the curve which is also statistically significant (P < 0.0001).

In addition to that in this small cohort we found that there is universal relationship between- SAME-TT₂R₂ score, Modified SAME-TT₂R₂ score and TTR; TTR ≥65% associate with low score (<2) of both SAME-TT₂R₂ score, Modified SAME-TT₂R₂ score; Table IV and V.

Table IV: Relationship between TTR and SAME-TT₂R₂ score

TTR	SAME-TT ₂ R ₂		P-value
	<2 SAME-TT ₂ R ₂	>= 2 SAME-TT ₂ R ₂	
TTR < 65%	3 (100%)	41 (61.2%)	0.242
TTR >= 65%	0	26 (38.8%)	

Table V: Relationship between TTR and Modified SAME-TT₂R₂ score

TTR	SAME-TT ₂ R ₂		P-value
	<2 Modified SAME-TT ₂ R ₂	>= 2 Modified SAME-TT ₂ R ₂	
TTR < 65%	13 (65.0%)	31 (62.0%)	0.055
TTR >= 65%	7 (35.0%)	19 (38.0%)	

Discussion

Previous studies in patients with non-valvular AF have shown that a low SAME-TT₂R₂ score was a significant predictor for good Vitamin-K antagonist effect while in high SAME-TT₂R₂ score predict poor Vitamin-K antagonist effect that measured by TTR [7]. This study showed Modified SAME-TT₂R₂ is a good predictor for good Vitamin-K antagonist effect.

Noteworthy, we studied Arabic population non Caucasian (medial east), which is considered one of the risk factors for poor time in therapeutic range as per SAME-TT₂R₂ score [8]. In Modified SAME-TT₂R₂ score we do not consider ethnicity as a risk factor for predicting poor Vitamin-K antagonist effect, however this study showed a universal relationship between Modified SAME-TT₂R₂ score and TTR as opposed to what has been shown between SAME-TT₂R₂ score and TTR in previous studies and this could be due to small study size [7,8]. It is important to note that this an observational cohort study with a small study population, observing the relation between modified score to original score as well as TTR only, and to the relation between modified score and solid efficacy and safety outcomes.

Conclusion

The use of modified SAME-TT₂R₂ allows clinicians to make an informed decision on whether to start vitamin K antagonist or other non-vitamin K antagonist oral anticoagulant despite the race of the patients.

Ethical Considerations

The study conducted following King Fahad Medical City policies and procedures of the Research Center. Regarding patient confidentiality and safety, the data retrieved from the patient's information that granted only to the investigators.

Study approved by institution research board with reference number 20-688.

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