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Evaluation of the Modified SAMe-TT_2R_2 Score to Predict Good Anticoagulation Control with Warfarin Among non-valvular Atrial Fibrillation Patients

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ABSTRACT

Background: The SAMe-TT_2R_2 Score was developed to identify vitamin K antagonists control outliers before non-valvular atrial fibrillation (AF) patients start treatment. SAMe-TT_2R_2 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-TT_2R_2 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-TT_2R_2 and SAMe-TT_2R_2 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-TT_2R_2 score has good relation to original SAMe-TT_2R_2 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-TT_2R_2 respectively. In addition to that in this small cohort we found that there is universal relationship between SAMe-TT_2R_2 score, Modified SAMe-TT_2R_2 score and TTR; TTR >=65% associate with low score (<2) of both SAMe-TT_2R_2, Modified SAMe-TT_2R_2 score.

Conclusion: The use of Modified SAMe-TT_2R_2 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 CHA_2DS_2-**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 CHA_2DS_2-**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 $CHADS_2$ and CHA_2DS_2-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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 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-TT_2R_2 score (modified SAMe-TT_2R_2 score defined as: SAMe-TT_2R_2 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-TT_2R_2 score (original score without including race) and SAMe-TT_2R_2 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, $CHADS_2$, CHA_2DS_2-VASc, SAMe-TT_2R_2 score, and modified SAMeTT_2R_2 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-TT_2R_2 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_2DS_2-VASc	4.00 (5.00 – 2.00)
HAS-BLED	2.00 (3.00 – 1.00)
SAMe-TT_2R_2	4.00 (6.00 – 3.00)
Modified SAMe-TT_2R_2	2 (2.25 – 1.00)
TTR	59.1 (69.6 – 37.25)

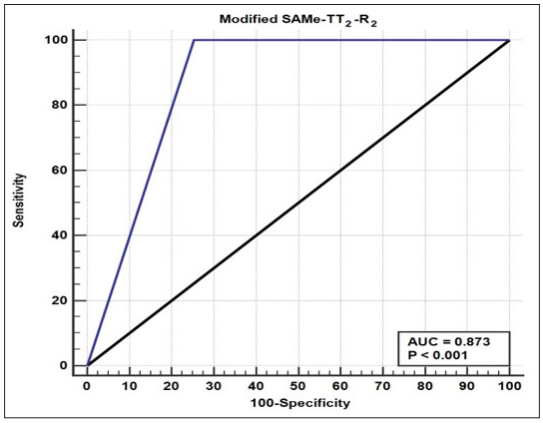
In order to establish the optimal cut-off/threshold values of modified SAMe-TT_2R_2 score of the best sensitivity and specificity for the study outcome, we performed ROC analysis by plotting sensitivity against 100-specificity at different cut-off values of modified SAMe-TT_2R_2. By using, the value original SAMe-TT_2R_2 score ≥ 2 score detect poor Vitamin-K antagonist effect while original SAMe-TT_2R_2 <2 score detect good Vitamin-K antagonist effect. Moreover, Modified SAMe-TT_2R_2 score has good relation to original SAMe-TT_2R_2 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-TT_2R_2 score respectively, Table III.

Table III: Predication of Drugs Outcome by ROC Analysis of Modified SAMe-TT_2R_2 Score

		Modified SAMe-TT_2R_2		*P – value*
		Positive	**Negative**	
		(>=2 SAMe-TT_2R_2)	**(< 2 SAMe-TT_2R_2)**	
SAMe-TT_2R_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-TT_2R_2 score is considered a predictor for good average time in therapeutic range; in this cohort we tested the validity of Modified SAMe-TT_2R_2 score by using ROC in relation to original SAMe-TT_2R_2 score, that showed good prediction; Modified SAMe-TT_2R_2 score in relation to SAMe-TT_2R_2 score has AUC 87.3%, Figure I

Figure: ROC Analysis of Modified SAMe-TT_2R_2 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-TT_2R_2 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-TT_2R_2 score, Modified SAMe-TT_2R_2 score and TTR; TTR >=65% associate with low score (<2) of both SAMe-TT_2R_2 score, Modified SAMe-TT_2R_2 score; Table IV and V.

Table IV: Relationship between TTR and SAMe-TT_2R_2 score

TTR	SAMe-TT_2R_2		*P-value*
	<2 SAMe-TT_2R_2	>= 2 SAMe-TT_2R_2	
TTR < 65%	3 (100%)	41 (61.2%)	0.242
TTR >= 65%	0	26 (38.8%)	

Table V: Relationship between TTR and Modified SAMe-TT_2R_2 score

TTR	SAMe-TT_2R_2		*P-value*
	<2 Modified SAMe-TT_2R_2	>= 2 Modified SAMe-TT_2R_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-TT_2R_2 score was a significant predictor for good Vitamin-K antagonist effect while in high SAMe-TT_2R_2 score predict poor Vitamin-K antagonist effect that measured by TTR [7]. This study showed Modified SAMe-TT_2R_2 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-TT_2R_2 score [8]. In Modified SAMe-TT_2R_2 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-TT_2R_2 score and TTR as opposed to what has been shown between SAMe-TT_2R_2 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-TT_2R_2 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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References

1. Barkan, Sigal, Luís Carlos Amon, Andréia Biolo (2017) "SAMe-TT2R2 Score in the Outpatient Anticoagulation Clinic to Predict Time in Therapeutic Range and Adverse Events Fernando Pivatto Júnior, Rafael Selbach Scheffel, Lucas Ries, Ricardo Roitman Wolkind, Roberta Marobin, Sabrina." Arq Bras Cardiol 108: 290-296.
2. Gorzelak-Pabiś Paulina, Sandra Zyzak, Łukasz Krewko, Marlena Broncel (2016) "Assessment of the mean time in the therapeutic INR range and the SAME-TT." Polskie archiwum medycyny wewnętrznej 126: 494-501.
3. Chan Pak Hei, Jo Jo Hai, Esther W Chan, Wen Hua Li, Hung Fat Tse, et al. (2016) "Use of the SAMe-TT2R2 score to predict good anticoagulation control with warfarin in Chinese patients with atrial fibrillation: relationship to ischemic stroke incidence." PLoS One 11: e0150674.
4. Bryk Agata Hanna, Krzysztof Plens, Anetta Undas (2017) "Prediction of unstable anticoagulation with acenocoumarol versus warfarin in atrial fibrillation." Cardiology Journal 24: 477-483.
5. van Miert Jasper HA, Sarah Bos, Nic JM Veeger JG , Karina Meijer (2018) "Clinical usefulness of the SAMe-TT2R2 score: A systematic review and simulation meta-analysis." PloS one 13: e0194208.
6. Bernaitis, Ms Nijolė (2018) "Predictors of Warfarin Control in Patients with Atrial Fibrillation in South-East Queensland and Singapore." https://research-repository.griffith.edu.au/handle/10072/384289.
7. Pilar Gallego, Vanessa Roldán, Francisco Marin, José Gálvez, Mariano Valdés, et al. (2014) "SAMe-TT2R2 Score, Time in Therapeutic Range, and Outcomes in Anticoagulated Patients with Atrial Fibrillation". The American Journal of Medicine 127: 1083-1088
8. Stavros Apostolakis, Renee M Sullivan, Brian Olshansky, Gregory Y H Lip (2013) "Factors Affecting Quality of Anticoagulation Control Among Patients With Atrial Fibrillation on Warfarin The SAMe-TT 2 R 2 Score". CHEST 2013; 144: 1555-1563.