

# Evaluation of the Validity of SAME-TT<sub>2</sub>R<sub>2</sub> Score in a Cohort of Venous Thromboembolism Patients Treated With Warfarin

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## Abstract

Low SAME-TT<sub>2</sub>R<sub>2</sub> score of <2 was validated as a predictor of optimum anticoagulation control, reflected by mean time in therapeutic range (TTR) above 65% to 70%, among warfarin-treated atrial fibrillation patients. This study aimed to validate the ability of SAME-TT<sub>2</sub>R<sub>2</sub> score and its individual components in predicting anticoagulation control (mean TTR and clinical events) among a cohort of venous thromboembolism (VTE) patients in Qatar. A total of 295 patients were retrospectively evaluated. There was a trend toward statistical significance in mean TTR between low (<2) and high ( $\geq 2$ ) SAME-TT<sub>2</sub>R<sub>2</sub> score groups ( $P = .05$ ), a difference that was not sustained when a cutoff of 3 was used (ie, a score of 3 or more). Patients with poor INR control (TTR <70%) were numerically less likely to have SAME-TT<sub>2</sub>R<sub>2</sub> score of <2 compared with those with good INR control, though the difference was not statistically significant (16.7% vs 83.3%, respectively,  $P = .4$ ). No thromboembolic events were reported, and no association was found between the score and risk of bleeding. Non-Caucasian origin was the only significant predictor of good anticoagulation in the studied cohort. In conclusion, SAME-TT<sub>2</sub>R<sub>2</sub> score could not predict quality of anticoagulation control in a cohort of VTE patients treated with warfarin in Qatar. Contribution of other clinical factors and whether a different scoring may yield better prediction of anticoagulation control remains to be tested.

## Keywords

SAME-TT<sub>2</sub>R<sub>2</sub> score, venous thromboembolism, anticoagulation control, time in therapeutic range

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## Introduction

Despite major advancement in anticoagulation field, warfarin, as well as other vitamin K antagonists (VKA), remain a mainstay for the treatment and prevention of venous thromboembolism (VTE).<sup>1</sup> Compared to warfarin, the newer direct oral anticoagulants (DOACs) have limited use in patients with some thromboembolic conditions such as cerebral venous thrombosis as well as advanced kidney and liver dysfunction.<sup>2-6</sup> They were also shown to be less effective than warfarin in the prevention of thrombosis associated with Antiphospholipid Antibody Syndrome, particularly in high risk patients (ie, test positive for all 3 antiphospholipid antibodies) and with history of arterial thrombosis).<sup>7-9</sup> Moreover, DOACs are contraindicated in patients with prosthetic heart valves, mitral stenosis, and

in pregnancy.<sup>2-5</sup> Increased cost of DOACs compared to warfarin is another reason why many patients may opt to use warfarin over DOACs.

However, it is well recognized that achieving and maintaining optimum anticoagulation with warfarin is quiet challenging. Several variables are known to influence patients'

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**Table 1.** SAME-TT<sub>2</sub>R<sub>2</sub> Score.<sup>14</sup>

S	Sex (female)	1
A	Age (<60 years)	1
M	Medical history <sup>a</sup>	1
e		
T	Treatment (interacting Rx, eg, amiodarone for rhythm control)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2

<sup>a</sup>Defined as more than 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.

response to warfarin and subsequent dose requirements such as age, dietary vitamin K intake, disease states, drug interactions, and pharmacogenetics. Thus, such factors should be continuously assessed in order to achieve and maintain a therapeutic International Normalized Ratio (INR).<sup>10</sup>

Quality of anticoagulation control in warfarin-treated patients is usually measured by the time spent in therapeutic range (TTR), which is a good surrogate marker for clinical outcomes such as bleeding and thrombosis, with maximum benefits proven when the TTR is greater than 70%.<sup>11-13</sup>

In view of the challenges associated with predicting and sustaining quality of anticoagulation control in warfarin-treated patients, a clinical tool or a score that can preemptively identify high risk patients who are less likely to maintain therapeutic targets was deemed necessary. Such patients would benefit from more frequent surveillance, extra emphasis on education and considering DOACs as an alternative, when feasible. In 2013, utilizing data of 2080 patients in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, Apostolakis et al developed the SAME-TT<sub>2</sub>R<sub>2</sub> score (Table 1). The score incorporated simple clinical and demographic factors that were significantly associated with the level of anticoagulation control. It was found that SAME-TT<sub>2</sub>R<sub>2</sub> score of 0 to 1 could predict patients who may benefit from warfarin by achieving high TTR (> 65%-70%) and that high SAME-TT<sub>2</sub>R<sub>2</sub> score (≥ 2) predicts patients who may not benefit from warfarin due to low TTR (<65%-70%). The score was further validated externally in a prospective cohort of patients receiving anticoagulation therapy, and it illustrated good discrimination performance in both the internal and external validation cohorts (c-statistics 0.72; 95% CI: 0.64-0.795; and c-statistics 0.7; 95% CI: 0.57-0.82, respectively).<sup>14</sup> The clinical utility of the SAME-TT<sub>2</sub>R<sub>2</sub> score was subsequently proven upon testing in varying real-world populations of patients.<sup>15-19</sup> Based on the above evidence, SAME-TT<sub>2</sub>R<sub>2</sub> score was endorsed by atrial fibrillation (AF) treatment guidelines.<sup>20</sup>

However, data regarding the validity of the score in predicting the quality of anticoagulation control among warfarin-treated patients with VTE including deep vein thrombosis and pulmonary embolism is still limited and contradicting. In a study of 1943 warfarin recipients with acute VTE, SAME-TT<sub>2</sub>R<sub>2</sub> score was shown to have a modest predictive value for the quality of anticoagulation and adverse clinical events.<sup>21</sup> A

finding that was not confirmed in a subsequent Spanish study of 135 acenocoumarol-treated patients, where TTR did not vary significantly between low and high SAME-TT<sub>2</sub>R<sub>2</sub> score groups (ie, ≤1 and >2). However, the study did not evaluate adverse events (bleeding, thrombosis), which are important indicators of anticoagulation quality.<sup>22</sup>

In this study, we sought to investigate the clinical utility of SAME-TT<sub>2</sub>R<sub>2</sub> score in predicting the quality of anticoagulation control, measured by TTR as well as warfarin-related adverse events (thromboembolism and bleeding), and to explore whether an association between individual elements of the score and quality of anticoagulation control exists in a cohort of VTE patients treated with warfarin.

## Methods

### Research Design

This was an observational retrospective cohort study conducted among warfarin-treated patients at Hamad Medical Corporation (HMC), Qatar's leading governmental health care provider.

### Study Setting and Timeline

Patients were recruited from ambulatory anticoagulation clinics in 2 facilities within HMC, namely Hamad General Hospital and Al-Wakra Hospital. International Normalized Ratio results were collected over at least 6 months period and up to 1 year, excluding the first 6 weeks of treatment (to avoid the initiation phase). The frequency of patients' visits to the clinics and INR testing were decided by the treating clinicians according to the patients' factors and INR stability, and in compliance with a standardized warfarin management protocol that is approved by the Pharmacy & Therapeutics Committee in each facility.

### Study Population and Sampling

Patients were enrolled in the study if they fulfill the following inclusion criteria: (1) age ≥18 years, (2) receiving warfarin for a confirmed diagnosis of VTE (eg, deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, portal/mesenteric vein thrombosis, and other venous thrombosis at unusual sites), (3) INR target 2-3, and (4) treatment duration of 6 months or more. Patients were excluded if they had less than 10 retrievable INR measurements, therapy interruption of more than 2 weeks, reported poor compliance to warfarin and/or clinic visits and/or loss of follow-up with the clinic. The sample size of this cohort was 295.

### Data Collection and Outcome Measures

In addition to the collection of INR readings as described above, baseline demographic and clinical information including: age, gender, ethnicity, weight, smoking status, comorbidities, and concomitant medications were collected by electronic

chart review through Cerner. Anticoagulation control was assessed by mean time in therapeutic range (TTR), reported events of bleeding and thromboembolism. Time in therapeutic range was calculated for each patient using the linear interpolation method of Rosendaal et al, which adds each patient's time within the therapeutic range and divides by the total time of observation.<sup>23</sup> A target TTR of  $\geq 70\%$  was utilized as a cutoff value for "good anticoagulation control," in accordance with the European Society of Cardiology's recommended target, thus patients were categorized into 2 groups accordingly (ie, poor anticoagulation control = TTR  $<70\%$  vs good anticoagulation control TTR  $\geq 70\%$ ).<sup>24</sup> Bleeding events were classified as major and clinically relevant nonmajor bleeding according to internationally recognized criteria.<sup>25,26</sup>

The 6 items of the SAME-TT<sub>2</sub>R<sub>2</sub> score were retrieved through chart review and subsequently the score was calculated (Table 1). For interacting medicines, drugs with warfarin interaction category (D and X) in lexi-comp were considered, as unlike AF patients, amiodarone may not be commonly prescribed in our population of VTE patients. This was based on similar or more significant level of interaction between amiodarone and warfarin (category D) on the drug database utilized.<sup>27</sup> Patients were categorized into low and high SAME-TT<sub>2</sub>R<sub>2</sub> score using two cutoffs of 2 and 3 (ie, low = 0-1 vs high = 2 or more, and low = 0-2 vs high = 3 or more, respectively). Using a cutoff of 2, demographic characteristics of patients in low and high score groups were compared.

### Statistical Analysis

Descriptive statistics was used to analyze baseline demographics. Depending on their normal distribution, numerical data were presented as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR). Continuous variables were tested for normality tests including Kolmogorov-Smirnov and Shapiro-Wilk. Categorical variables were presented as frequencies and percentages and analyzed using  $\chi^2$  test.

SAME-TT<sub>2</sub>R<sub>2</sub> score (median, IQR) and TTR (mean  $\pm$  SD) as well as mean ( $\pm$  SD) and median number of follow-up visits were calculated. The effect of SAME-TT<sub>2</sub>R<sub>2</sub> individual factors (example: gender, tobacco use, etc) on TTR was evaluated by Student *t*-test. The difference in patients' demographics between low and high SAME-TT<sub>2</sub>R<sub>2</sub> score groups was evaluated by  $\chi^2$  testing.

The association between SAME-TT<sub>2</sub>R<sub>2</sub> score (low vs high) and quality of anticoagulation control (low vs high) was tested by  $\chi^2$  test. ANOVA testing was used to compare the mean TTR in the different SAME-TT<sub>2</sub>R<sub>2</sub> score groups. Sensitivity, Specificity, positive predictive value and negative predictive value, and odds ratio of SAME-TT<sub>2</sub>R<sub>2</sub> model on poor quality of anticoagulation were explored using logistic regression. A *P* value of less than .05 was considered statistically significant. All statistical tests were carried using the IBM Statistical Package for Social Sciences, SPSS version 26.0 (IBM Corp).

### Ethical Approval

As data were analyzed anonymously, consent was waived. The study was approved by Medical Research Center in HMC (MRC-01-17-053) and conducted in full accordance with rules and regulations of research at HMC.

### Results

A total of 295 patients were included (55.9% males), with majority being from Arabic origin (59%) and younger than 60 years old (77.3%). Hypertension and diabetes were the 2 most common comorbid conditions in the cohort (32.9% and 26.4%, respectively). Tobacco use was reported in 22 patients only (7.5%). Mean ( $\pm$  SD) and median number of follow-up visits were 14.5 ( $\pm$  6.8) and 14, respectively, with a follow-up period that ranged between 6 and 12 months.

The mean TTR ( $\pm$  SD) was 76.7 ( $\pm$  18.6). Median SAME-TT<sub>2</sub>R<sub>2</sub> was 3 (IQR = 1). Majority of patients had SAME-TT<sub>2</sub>R<sub>2</sub> score of 3 (n = 130, 44.1%) and 4 (n = 104, 35.3%; Table 2).

### Association of SAME-TT<sub>2</sub>R<sub>2</sub> With Anticoagulation Control (TTR)

None of the factors in the SAME-TT<sub>2</sub>R<sub>2</sub> score had a significant effect on the TTR except for the ethnicity (Caucasians vs non-Caucasians) where TTR was significantly lower in non-Caucasians (n = 283) compared to Caucasians (n = 12; 76.1%  $\pm$  18.6% vs 89.2%  $\pm$  13.7%, *P* = .017). There was a trend of reduction in mean TTR as SAME-TT<sub>2</sub>R<sub>2</sub> score increased, however, it did not reach statistical significance (*P* = .183; Figure 1).

Upon categorizing patients into 2 groups based on SAME-TT<sub>2</sub>R<sub>2</sub> score; group 1 (SAME-TT<sub>2</sub>R<sub>2</sub> score of 0, 1) and group 2 (SAME-TT<sub>2</sub>R<sub>2</sub> score of 2 or more), a trend toward statistical significance in mean TTR between the 2 groups was revealed (90.9% vs 76.4%, *P* = .05; Figure 2), however such difference was not sustained when a cutoff of 3 was used (ie, 0-2 score group vs 3 or more group). Chi-square testing revealed a numerically higher proportion of patients achieving good anticoagulation control (TTR  $\geq 70$ ) in the SAME-TT<sub>2</sub>R<sub>2</sub> group of (0-1) than those achieving poor anticoagulation control (TTR  $<70\%$ ; 83.3% vs 16.7%), however the difference was not statistically significant (*P* = .4).

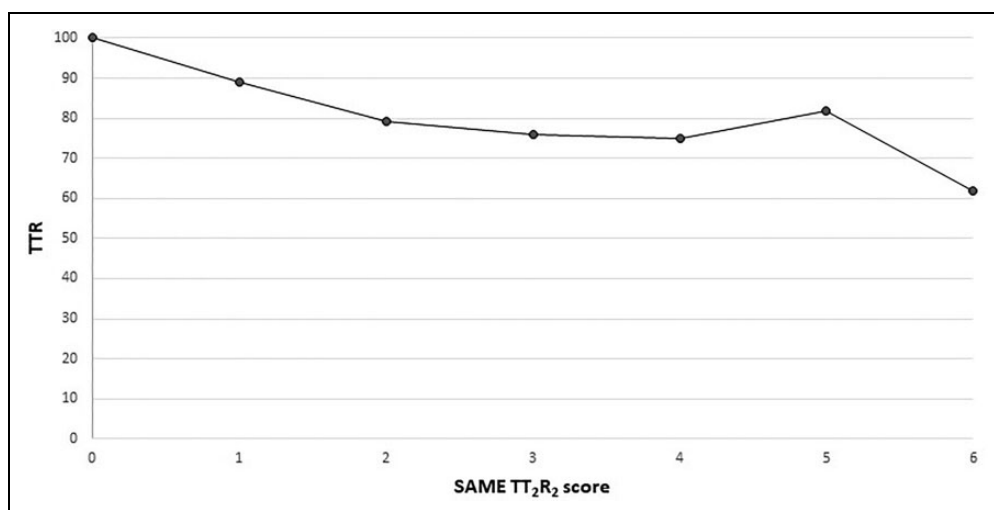
The only significant differences in patients' demographics between low and high SAME-TT<sub>2</sub>R<sub>2</sub> score groups were male gender, ethnicity, and the diagnosis of peripheral arterial disease, as all patients in the low score group (n = 6) were Caucasian males (Table 2).

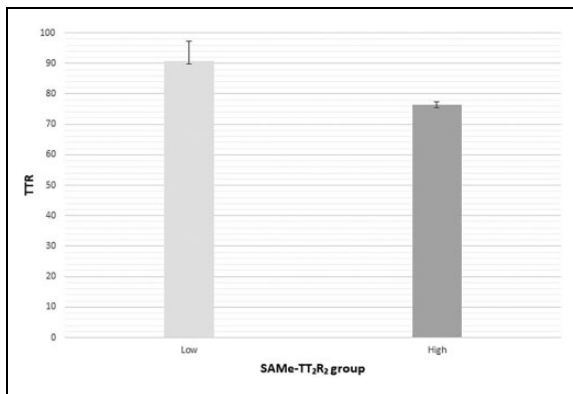
The model as a whole had very good sensitivity (98.9%) but lacked specificity (2.5%). The corresponding positive and negative predictive values were 32.87% and 83.33% (Table 3).

**Table 2.** Demographics and Baseline Characteristics of Patients in the Overall Cohort, and After Stratification Into Low (0-1) and High SAME-TT<sub>2</sub>R<sub>2</sub> ( $\geq 2$ ) Score Groups.

Demographic	Overall frequency (%), (n = 295)	Low SAME-TT <sub>2</sub> R <sub>2</sub> group (0-1), (n = 6)	High SAME-TT <sub>2</sub> R <sub>2</sub> ( $\geq 2$ ), (n = 289)	P value
Age <60 years	228 (77.3)	4 (66.7)	224 (77.5)	.53
Gender, male	165 (55.9)	6 (100)	159 (55)	.03 <sup>a</sup>
Smoker no. (%)	22 (7.5)	0 (0)	22 (7.6)	.48
Race				
Arab	174 (59)	0 (0)	174 (60.2)	.001 <sup>a</sup>
Asian	94 (31.9)	0 (0)	94 (32.5)	
African	15 (5.1)	0 (0)	15 (5.2)	
Caucasian	12 (4.1)	6 (100)	6 (2.1)	
SAME-TT <sub>2</sub> R <sub>2</sub> score				
Zero	1 (0.3)	1 (16.7%)		
1	5 (1.7)	5 (83.3)		
2	25 (8.5)		25 (8.7)	
3	130 (44.1)		130 (45)	
4	104 (35.3)		104 (36)	
5	28 (9.5)		28 (9.7%)	
6	2 (0.7)		2 (0.7%)	
Concomitant disease				
Hypertension	97 (32.9)	3 (50)	94 (32.5)	.37
Diabetes mellitus	78 (26.4)	1 (16.7)	77 (26.6)	.85
Coronary artery disease/myocardial infarction	17 (5.8)	1 (16.7)	16 (5.5)	.25
Peripheral artery disease	2 (0.7)	1 (16.7)	1 (0.3)	.001 <sup>a</sup>
Congestive heart failure	11 (3.7)	0 (0)	11 (3.8)	.62
Previous stroke	17 (5.8)	1 (16.7)	16 (5.6)	.25
Pulmonary disease	25 (8.5)	0 (0)	25 (8.7)	0.45
Hepatic disease	9 (3)	0 (0)	9 (3.1)	.66
Renal disease	30 (10.2)	0 (0)	30 (10.4)	.40
>2 of the above conditions	32 (10.8)	1 (16.7)	31 (10.7)	.64
Cancer	4 (1.4%)	0 (0)	4 (1.4)	.51
Receiving interacting medication	13 (4.4)	0 (0)	13 (4.5)	.59

<sup>a</sup>P value is less than .05 as measured using  $\chi^2$  test comparing low (0-1) and high SAME-TT<sub>2</sub>R<sub>2</sub> ( $\geq 2$ ) score groups.

**Figure 1.** Mean TTR in SAME-TT<sub>2</sub>R<sub>2</sub> score groups.



**Figure 2.** Mean TTR in low (0-1) versus high ( $\geq 2$ ) SAME-TT<sub>2</sub>R<sub>2</sub> score groups.

**Table 3.** Capability of SAME-TT<sub>2</sub>R<sub>2</sub> Model to Predict Poor Quality of Anticoagulation.<sup>a</sup>

	TTR<70%
Sensitivity (%)	98.96
Specificity (%)	2.5
Positive predictive value (%)	32.87
Negative predictive value (%)	83.33
OR (95% CI) <sup>b</sup>	2.5 (0.28-21.25)
P value <sup>b</sup>	0.4

Abbreviations: CI, confidence interval; OR, odd ratio.

<sup>a</sup>SAME-TT<sub>2</sub>R<sub>2</sub> score of 1 was used as the cutoff in this model.

<sup>b</sup>OR (95% CI) and P value were measured using logistic regression.

As tobacco use was poorly reported and the majority of patients were non-Caucasians, SAME-TT<sub>2</sub>R<sub>2</sub> score was recalculated after omission of these 2 components. However, mean TTR did not differ significantly between the 2 SAME-TT<sub>2</sub>R<sub>2</sub> groups (0-1 vs  $\geq 2$ ;  $P = .68$ ).

There were only 25 reported cases of minor bleeding (8.5%), 1 case of major bleeding (0.3%), and no cases of thromboembolic events. No association was found between SAME-TT<sub>2</sub>R<sub>2</sub> score and risk of bleeding.

## Discussion

The current study demonstrated that SAME-TT<sub>2</sub>R<sub>2</sub> score could not predict quality of anticoagulation control in a cohort of VTE patients treated with warfarin in Qatar. There was a trend of decline in TTR as the score increased, however, the association was not statistically significant.

Despite vast body of evidence that supports the ability of the score in predicting anticoagulation control among AF patients,<sup>14-19</sup> the score's utility in VTE patients seems to be limited. Palareti and colleagues were the first to investigate the efficacy of SAME-TT<sub>2</sub>R<sub>2</sub> score in predicting quality of anticoagulation among a cohort of 1308 VTE patients treated with VKA in Italy. Time in therapeutic range was significantly lower in patients with score  $\geq 2$  compared to score 0-1 ( $58.5\% \pm 20\%$  vs  $61.5\% \pm 19\%$ , respectively,  $P = .046$ ). The

difference in TTR between the 2 score groups was strikingly high in the first 3 months of therapy ( $53\% \pm 26\%$  vs  $61\% \pm 26\%$ , respectively;  $P = .0001$ ), which was mostly due to more time spent below therapeutic INR. However, the study utilized TTR only as a surrogate marker of anticoagulation control and did not evaluate any clinical outcomes.<sup>28</sup>

The score was subsequently validated by Kataruka et al in a cohort of 1943 warfarin-treated patients with acute VTE. Patients were divided into 3 categories according to the SAME-TT<sub>2</sub>R<sub>2</sub> score (low 0-1, borderline 2, high  $>2$ ) and a TTR cutoff of  $<60\%$  was applied as a marker of poor anticoagulation control. Increments in the SAME-TT<sub>2</sub>R<sub>2</sub> score significantly increased odds of poor anticoagulation control (TTR  $<60\%$ ), (odds ratio [OR]: 1.18, 95% confidence interval [CI]: 1.11-1.26,  $P < .0001$ ). Compared to low score group (0-1), high score group ( $>2$ ) demonstrated lower TTR (50% vs 57%), higher percentage of patients achieving a TTR  $<60\%$  (63.4% vs 52.3%,  $P < .0001$ ), and higher rates of recurrent VTE (69 vs 57 per 100 patient years,  $P = .0003$ ). The rate of major bleeding was numerically increased in patients with a SAME-TT<sub>2</sub>R<sub>2</sub> score  $>2$  but did not reach statistical significance. Interestingly, the score's discriminative ability was consistent when different TTR cutoffs of  $<60\%$ ,  $<65\%$ , or  $<70\%$  were tested through sensitivity analysis (c-statistics of 0.61, 0.65, and 0.65, respectively).<sup>21</sup>

Our findings are in agreement with results of a previous Spanish study, where SAME-TT<sub>2</sub>R<sub>2</sub> score could not predict INR control among 135 acenocoumarol-treated patients. In the study, no significant differences in INR controls within, above, or below range between patients with score 0-1 versus a score of  $\geq 2$  were found. The study also analyzed the predictive capacity of the test, using a TTR cutoff of 65%, a sensitivity of 31.8%, a specificity of 66.7%, and demonstrated a positive predictive value of 47.7% and negative predictive value of 50.6%. Moreover, area under the curve of the receiver operating characteristic curve for the score groups (0-1,  $\geq 2$ ) was 0.517, revealing a low score's capacity of discrimination.<sup>22</sup>

The authors contributed these findings to the remarkable variation in individual components of the score (particularly concomitant amiodarone and cardiovascular diseases) among the evaluated cohort and those in studies validating the score among AF patients.

In our study, prevalence of myocardial infarction, congestive heart failure, ischemic heart diseases, and peripheral arterial diseases was low as well. However, we accounted for potential drug interactions of "moderate" to "severe" significance and did not limit it to amiodarone only.

A more recent study confirmed the limited usefulness of SAME-TT<sub>2</sub>R<sub>2</sub> score in predicting anticoagulation control and adverse clinical outcomes in VTE populations. The study analyzed 3874 VTE patients randomized to warfarin arm of the Hokusai-VTE trial for up to 6 months, excluding first month of therapy. Majority of patients had a high score of  $\geq 2$  (76%), which was associated with numerically lower median TTR (64.7% vs 70.7%). Nonetheless, for a TTR threshold of 66%, the score revealed low negative and positive

predictive values (0.59 and 0.52, respectively) as well as poor discrimination (c-statistic, 0.58). Additionally, comparison of symptomatic recurrent VTE and bleeding events (major or clinically relevant nonmajor bleeding) between low and high score groups revealed low absolute risk difference of 0 (−0.6%, +0.7%) and +1.3% (−0.1%, +2.7%), respectively. The results were further confirmed by sensitivity analysis evaluating whole study duration.<sup>29</sup>

In our study, evaluation of the score's individual components demonstrated that Caucasian origin was the only significant predictor of the quality of anticoagulation control, as they exhibited significantly higher mean TTR. Additionally, ethnic origin and gender were significantly different between low and high score groups as the 6 patients in the low score group were Caucasian males. However, due to the small number of patients, the clinical significance of this finding is limited.

Previous literature demonstrated that European Americans were significantly more likely to achieve good (ie, TTR  $\geq$  60 < 70%) and excellent (TTR  $\geq$  70%) anticoagulation control compared to African Americans. Moreover, they experienced significantly lower bleeding episodes (Incidence rate ratio: 1.38, 95% CI: 1.01, 1.89,  $P = .045$ ) and were at significantly lower relative risk of major hemorrhagic events (HR: 1.58; 95% CI: 1.04-2.41;  $P = .03$ ) despite adjusting for clinical and genetic factors and TTR.<sup>30</sup> In the study of Kataruka et al,<sup>21</sup> none of the score's factors was independently associated with predicting poor anticoagulation control. Analysis identified weight, history of previous VTE, and alcohol consumption, which are risk factors not included in the SAME-TT<sub>2</sub>R<sub>2</sub> score, as significant predictors of low TTR (<60%). However, when these factors were incorporated into the score and a new model created, only marginal improvement in the score's performance characteristic and ability to predict TTR <60% was noted (c-statistic = 0.64 vs 0.61). Furthermore, the study investigated whether including patients with nonactive malignancy could affect the score's predictive ability, but the effect turned to be insignificant (OR point estimate [1.18, 95% CI: 1.11-1.25], c-statistic = 0.59).

It is noteworthy that only 12 patients evaluated in our study were classified as Caucasians (white-origin) compared to 70% of VTE patients in the first Italian study of score validation. Thus, one may question the validation and/or need for recalibration of the score in a non-Caucasian population, such as those evaluated in our study, given that non-Caucasian race already accounts for 2 points in the score. However, the score was validated in previous Asian studies of AF patients.<sup>31,32</sup> In a Chinese study of 1428 nonvalvular AF patients, where the lowest possible score was 2, a significant and progressive decline in TTR was confirmed as SAME-TT<sub>2</sub>R<sub>2</sub> score increased ( $P = .016$ ).<sup>32</sup> As mentioned earlier, the association between anticoagulation control and SAME-TT<sub>2</sub>R<sub>2</sub> score, when calculated without ethnic origin, did not vary significantly in our study.

Of note, the relatively high TTR (76.7 [ $\pm$  18.6]) reported in this study is in line with previous data from Qatar.<sup>33,34</sup> In one study, mean TTR in pharmacist managed anticoagulation clinic

was remarkably high and significantly higher than that observed in a historical cohort from a doctor-based clinic (81.8% vs 69.8%,  $P < .001$ ).<sup>33</sup> Another study revealed an overall patients' median TTR of 70% (range 19-100) with a numerically higher mean TTR in Arabs than in Asian patients (71%  $\pm$  15% vs 67%  $\pm$  17%,  $P = .15$ ).<sup>34</sup>

Excluding patients with reported poor compliance to warfarin and/or clinic visits may have also contributed to this high TTR. However, data about the exact number of such excluded patients is unavailable. Additionally, since point of care INR testing is the mainstay testing we use at our clinics, it has an error margin of  $\pm$  0.2. Thus, we consider INRs of 1.8 to 3.2 as "within therapeutic range." This may have also slightly overestimated the TTR. However, this should not affect our overall result since we applied the same methodology for all included subjects regardless of their SAME-TT<sub>2</sub>R<sub>2</sub>.

Our study has some limitations. Reported rate of cardiovascular diseases included in the score and the use of amiodarone among evaluated patients were low. However, all drug interactions of "moderate" to "severe" significance were included in the score calculation. In addition, despite our efforts to account for most of factors that could affect INR control (such as age, gender, common comorbidities, significant drug interactions, etc), other factors could be potentially missed due to the retrospective observational nature of the study. Social habits that may have an influence on INR control such as smoking (only 7.5% reported to be tobacco users) and alcohol consumption are poorly documented in patients' records; however, we adjusted for all these variables in the linear regression analysis. Moreover, genetic factors (Polymorphisms of the vitamin K epoxide reductase complex subunit 1 gene [VKORC1] and the cytochrome P450 (CYP)2C9 gene), which are important determinants of maintenance dose, were not addressed in this study, but their evaluation is costly and not always feasible. It is important also to note that with regard to ethnic group, as this was a retrospective chart review, and medical records system does not identify ethnic origin, classification was based on recorded nationality, and only patients of European, Australian, and North American nationalities were considered as Caucasians in this analysis, which may not be accurate. Moreover, as the majority of patients were non-Caucasians (95.9%) the study included 6 patients only in the low score group, which limits the interpretation of our findings. This low number has also reduced the statistical power of the cohort to determine the association between SAME-TT<sub>2</sub>R<sub>2</sub> and the quality of anticoagulation. Of note, when the score was calculated without race and tobacco use, a significant association between the score and mean TTR was not observed. In conclusion, it appears that despite evidence of the clinical utility of the SAME-TT<sub>2</sub>R<sub>2</sub> score in predicting anticoagulation quality among AF patients, evidence seems to be less promising in VTE patients.

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