

## ORIGINAL ARTICLE

## SAME-TT<sub>2</sub>R<sub>2</sub> Score: A Useful Tool in Oral Anticoagulation Decision-Making for Venous Thromboembolism Patients?

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### Abstract

**Background:** The SAME-TT<sub>2</sub>R<sub>2</sub> score was introduced to identify atrial fibrillation patients with a high risk of not achieving a good time in therapeutic range (TTR) during vitamin K antagonists (VKA) therapy.

**Objective:** The aim of this study was to evaluate this score in venous thromboembolism (VTE) patients.

**Patients and methods:** A retrospective cohort study of patients receiving care at the outpatient anticoagulation clinic of a tertiary care teaching hospital. Patients were classified as having low (score 0-1) or high risk (score  $\geq$  2) of not achieving a good TTR. The area under the ROC curve was calculated to assess the ability of the score to predict a TTR  $\geq$  65%. Adverse event-free survival curves according to the SAME-TT<sub>2</sub>R<sub>2</sub> score were calculated by the Kaplan-Meier method and compared by the log-rank test. A p-value  $<$  0.05 was considered statistically significant.

**Results:** We investigated 111 patients during a median follow-up of 2.3 (0.7-6.4) years. Mean age was 54.1  $\pm$  15.7 years and 71 (64.0%) were women. Low- and high-risk groups had similar mean TTR (51.9 vs. 49.6%; p = 0.593). The two groups did not differ significantly in the percentage of patients achieving a TTR  $\geq$  65% (35.6 vs. 25.8%; p = 0.370). The c-statistic was 0.595 (p = 0.113) for TTR  $\geq$  65%. Adverse event-free survival during anticoagulation was also similar in both groups (p = 0.136).

**Conclusions:** The SAME-TT<sub>2</sub>R<sub>2</sub> score does not seem to be a useful tool in oral anticoagulation decision-making for patients with VTE and should not be used in this setting. (Int J Cardiovasc Sci. 2018;31(5)483-491)

**Keywords:** Venous thrombosis; Venous thromboembolism; Pulmonary embolism; Anticoagulants; Decision support techniques.

### Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are clinical manifestations of the same pathological process, collectively termed venous thromboembolism (VTE), which is the third most common cardiovascular condition after myocardial infarction and stroke, with an estimated incidence rate of 0.7-2.0 per 1,000 person-years.<sup>1</sup> Another important feature of the disease is the high mortality rate associated with PE. In Brazil, PE accounted for 0.05% of total hospital admissions (46,421 of 89,499,700) from 2008 to 2015, with a mortality rate of 21.4%.<sup>2</sup> In

a Canadian study including 67,354 definite and 35,123 probable cases of VTE, the 30-day and 1-year case-fatality rates after definite or probable VTE were 10.6 and 23.0%, respectively.<sup>1</sup>

One-quarter to one-third of acute episodes of VTE are recurrences,<sup>3</sup> and VTE has been recognized as a chronic disease associated with short- and long-term morbidity and mortality.<sup>4</sup> Therefore, the management of VTE requires recurrence prevention, often through prolonged anticoagulant treatment, which has been traditionally performed using vitamin K antagonists (VKA), but now can be performed with the use of novel anticoagulants (NOAC). The efficacy and safety of VKA treatment are

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determined mainly by the time in therapeutic range (TTR), i.e., the percentage of days that prothrombin time/international normalized ratio (PT/INR) remains in the interval 2.0-3.0. Thus, the ability to identify patients treated with VKA who will present poor anticoagulation control may be useful in establishing the indication for NOAC rather than VKA.<sup>5</sup>

The SAME-TT<sub>2</sub>R<sub>2</sub> score uses clinical risk factors to identify patients with atrial fibrillation (AF) at high risk of not achieving a good TTR ( $\geq 65\%$ ) during VKA therapy, who are, consequently, suitable candidates for the use of NOAC. It takes into account sex (S, 1 point), age (A, 1 point), medical history (Me, 1 point), treatment - especially interacting drugs, such as amiodarone - (T, 1 point), tobacco use in the previous 2 years (T, 2 points) and race (R, 2 points). The maximum score is 8, and patients scoring 0-1 are most likely to benefit from warfarin because they are also most likely to have a TTR  $\geq 70\%$ , indicating good anticoagulation control. Patients with scores  $\geq 2$  are at risk of suboptimal anticoagulation control. In the original study that developed the score, the score showed good discrimination performance in both the internal (c-statistic of 0.72 for TTR  $\geq 64\%$ ; 95%CI: 0.64-0.79) and external (c-statistic of 0.7 for TTR  $\geq 67\%$ ; 95%CI: 0.57-0.82) validation cohorts.<sup>6</sup> In a previous study conducted at our anticoagulation outpatient clinic, including only patients with AF, the low-risk group (score 0-1) had a better median TTR than the high-risk group (score  $\geq 2$ ): 69.2 vs. 56.3%  $p = 0.002$ . Similarly, the percentage of patients with a TTR  $\geq 65\%$  was higher in the low-risk group (58.7 vs. 36.8%;  $p = 0.001$ ).<sup>7</sup>

Use of the SAME-TT<sub>2</sub>R<sub>2</sub> score in patients with VTE to predict a good TTR during anticoagulant therapy was only recently assessed, with conflicting results. Two studies showed that patients classified as at high risk (score  $\geq 2$ ) had a lower TTR than those at low risk,<sup>8,9</sup> whereas one study found no association between the SAME-TT<sub>2</sub>R<sub>2</sub> score and TTR.<sup>5</sup> Moreover, the results regarding the association of the score with bleeding or thrombotic events were also contradictory. These studies differ in terms of their selection criteria, cutoff points, and study design, which may be a possible explanation for the conflicting results but precludes the widespread applicability of the SAME-TT<sub>2</sub>R<sub>2</sub> score in patients with VTE. The present study was therefore designed to evaluate the SAME-TT<sub>2</sub>R<sub>2</sub> score in patients with VTE and determine its usefulness in predicting TTR and adverse events.

## Material and methods

This was a retrospective cohort study of patients on oral anticoagulant therapy with VKA at the outpatient anticoagulation clinic of a tertiary care teaching hospital in southern Brazil. All patients receiving care at the clinic from January to March 2014 were screened for inclusion in the study (screening period). Patients anticoagulated for lower-limb DVT and/or PE were included. Patients with upper-limb, abdominal or cerebral DVT and those using VKA for other indications (e.g., AF) were excluded. The study was approved by the Research Ethics Committee of the institution. Informed consent was waived due to the retrospective nature of data collection.

The patients' medical records were retrospectively reviewed for outpatient visits, emergency visits, and hospitalizations since the first PT/INR measurement after the start of VKA treatment until the end of treatment or the end of the study. Patients who were lost to follow-up, who died or whose anticoagulant therapy was discontinued were included in the analysis, and, in these cases, TTR was calculated until the last PT/INR measurement available.

For the SAME-TT<sub>2</sub>R<sub>2</sub> score (0-8 points), the following variables were assessed: female sex (1 point), age  $< 60$  years (1 point), presence of  $> 2$  comorbidities (1 point), use of amiodarone to control heart rhythm (1 point), tobacco use within the past 2 years (2 points), and non-white race (2 points). The following conditions were considered comorbidities: previous stroke, diabetes, peripheral artery disease, coronary artery disease, liver disease, pulmonary disease, renal disease, hypertension and heart failure. Based on the SAME-TT<sub>2</sub>R<sub>2</sub> score, patients were divided into two groups: low risk (score 0-1) or high risk (score  $\geq 2$ ) of not achieving a good TTR during VKA therapy.

Coronary artery disease was defined as prior myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery.<sup>10</sup> Patients with left ventricular ejection fraction (LVEF)  $< 40\%$  or with recently decompensated heart failure requiring hospitalization, regardless of LVEF, were classified as having heart failure.<sup>11</sup> LVEF was obtained preferably from the transthoracic echocardiogram and calculated by the Simpson's method in the presence of segmental changes or by the Teichholz method in the absence of segmental changes (if more than one test was available, the lowest value was used for the analysis).

Liver disease was defined as the presence of chronic liver disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2x the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3x the upper limit of normal).<sup>12</sup> Peripheral artery disease was defined as the presence of any of the following: claudication, carotid occlusion or > 50% stenosis, and previous or planned intervention on the abdominal aorta, limb arteries, or carotids.<sup>13</sup> Pulmonary disease was defined as long-term use of bronchodilators or steroids for lung disease.<sup>13</sup> Renal disease was defined as kidney damage for  $\geq 3$  months, as defined by structural or functional abnormalities of the kidney, or glomerular filtration rate  $< 60$  mL/min/1.73m<sup>2</sup> for  $\geq 3$  months.<sup>14</sup>

Thromboembolism during anticoagulation was defined as acute lower-limb DVT, PE, or thromboembolism at other sites, demonstrated by objective diagnostic techniques, such as compression ultrasonography, lung ventilation-perfusion scintigraphy, and computed tomography angiography. Only patients with clinical signs or symptoms of VTE underwent specific evaluation. Major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a drop in hemoglobin level  $\geq 2$  g/dL or leading to transfusion of  $\geq 2$  units of whole blood or red cells.<sup>15</sup>

All decisions regarding the management of anticoagulation were based on the protocol published by Kim et al.<sup>16</sup> The Rosendaal linear interpolation method was used to calculate TTR.<sup>17</sup>

### Statistical analysis

Data were analyzed using SPSS, version 21.0 (IBM, Armonk, NY, USA). Qualitative variables were expressed as absolute and relative frequencies, while quantitative variables were expressed as mean  $\pm$  standard deviation for normally distributed data and as median (25-75<sup>th</sup> percentile) for non-normally distributed data. The Shapiro-Wilk test was used to assess data distribution. Quantitative variables were compared between groups using non-paired Student t test for normally distributed data, and Mann-Whitney U test for non-normally distributed data. The chi-square test was used for categorical variables. Fisher exact test was used in cases of low frequency. Pearson's (if normally distributed) or

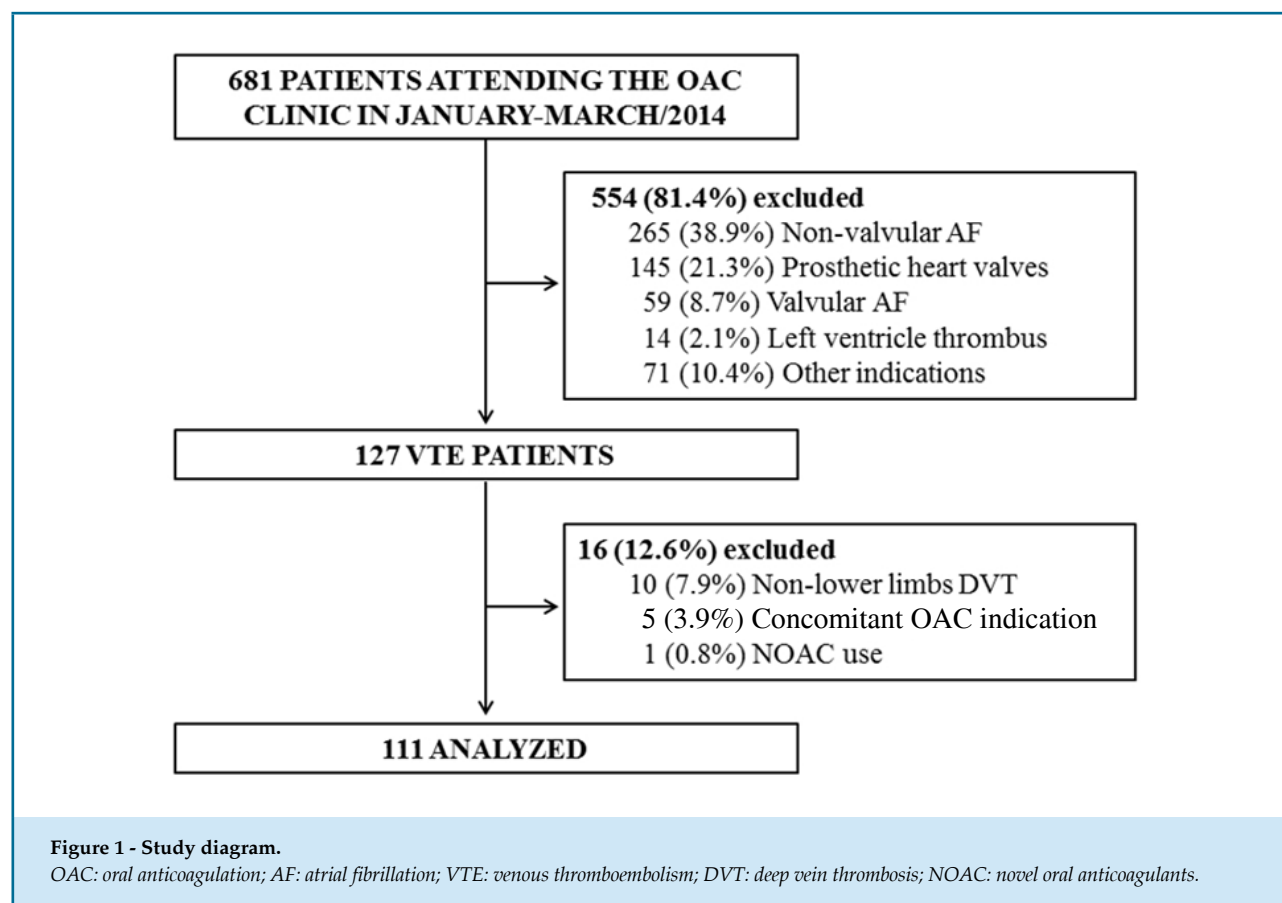
Spearman's (if non-normally distributed) correlation test was used for TTR and the SAME-TT<sub>2</sub>R<sub>2</sub> score. The area under the receiver operating characteristic (ROC) curve was calculated to assess the ability of the SAME-TT<sub>2</sub>R<sub>2</sub> score to predict a TTR  $\geq 65\%$ . Adverse event-free survival curves according to the SAME-TT<sub>2</sub>R<sub>2</sub> score were calculated by the Kaplan-Meier method and compared by the log-rank test. A p-value  $< 0.05$  was considered statistically significant.

### Results

During the screening period, of 681 consecutive patients who received care at the outpatient anticoagulation clinic, 111 (16.3%) were included in the analysis after applying the inclusion and exclusion criteria (Figure 1). The demographic characteristics of the sample are shown in Table 1. Mean patient age was  $54.1 \pm 15.7$  years, and 71 (64.0%) were women. Twenty-five (22.5%) patients had cancer (16 current and 9 previous). Patients with current cancer were initially treated with heparin and then switched to VKA after being in the therapeutic range. Median follow-up was 2.3 (0.7-6.4) years. During this period, 34 (30.6%) patients discontinued anticoagulation following appropriate treatment, 5 (4.5%) due to adverse events (bleeding) and 1 (0.9%) due to switch to NOAC. Nineteen (17.1%) patients were lost to follow-up.

The VKA of choice was warfarin, used in 109 (98.2%) patients. Only 2 (1.8%) patients used phenprocoumon. Anticoagulation monitoring consisted of 5,657 PT/INR measurements. Of these, 2,379 (42.1%) were within the PT/INR interval of 2.0-3.0, over a total treatment time of 438.8 patient-years. The median time between PT/INR measurements was 25.7 (14.7-35.1) days. Mean TTR was  $50.6 \pm 21.9\%$ . Patients were below this range for a median time of 31.3% (16.8-47.9) and above this range for a median time of 12.9% (6.2-20.9). Duration of VKA treatment was  $< 6$  months in 7 (8.1%) cases, 6-12 months in 21 (24.4%) cases, and  $> 12$  months in 58 (67.5%) cases, not including patients who died during the anticoagulant treatment or were lost to follow-up. Forty-four (39.6%) patients were still on VKA treatment at the end of follow-up.

The median SAME-TT<sub>2</sub>R<sub>2</sub> score was 2 (1-2), and 66 (59.5%) patients had a score  $\geq 2$ . The most prevalent score component was female sex (64.0%), followed by age  $< 60$  years (61.3%), medical history of  $> 2$  comorbidities (14.4%), non-white race (10.8%), and tobacco use within the past 2 years (8.1%). No patient was using amiodarone.



Low- and high-risk SAME-TT<sub>2</sub>R<sub>2</sub> groups had similar mean TTR: 51.9 ± 20.1% vs. 49.6 ± 23.1% (p = 0.593) (Figure 2). The results for the two groups remained similar even after excluding patients on anticoagulation for up to 3 months (n = 6, 5.4%): 51.8 ± 19.7% vs. 49.1 ± 22.6% (p = 0.593). The two groups did not differ significantly in the percentage of patients achieving a TTR ≥ 65% (35.6 vs. 25.8%; p = 0.370). The correlation between TTR and SAME-TT<sub>2</sub>R<sub>2</sub> score was poor (r = -0.093; p = 0.330). The c-statistic was 0.595 (95% CI: 0.482 - 0.708; p = 0.113) for TTR ≥ 65%.

Adverse events during anticoagulation are shown in Table 2. There were no cases of stroke, transient ischemic attack or myocardial infarction during follow-up. None of the deaths during follow-up was related to bleeding. Of six deaths, five were cancer-related and one was related to respiratory tract infection. Adverse event-free survival was similar in both low- and high-risk SAME-TT<sub>2</sub>R<sub>2</sub> groups (p = 0.136) (Figure 3).

## Discussion

In the present study, low- and high-risk SAME-TT<sub>2</sub>R<sub>2</sub> groups had similar mean TTR, and the prevalence of

patients with a high TTR did not differ significantly between groups. In addition, the SAME-TT<sub>2</sub>R<sub>2</sub> score had poor accuracy in predicting both good TTR and adverse events during anticoagulation. Therefore, based on these findings, the score does not seem to be a useful tool in oral anticoagulation decision-making for patients with VTE.

The SAME-TT<sub>2</sub>R<sub>2</sub> score has been developed and validated for use in patients with AF,<sup>6</sup> with good results in predicting which patients will have poor anticoagulation control with VKA therapy. Several studies have confirmed the predictive ability of the score in patients with AF<sup>7,18-29</sup> and described its association with adverse events (death, bleeding, and stroke).<sup>7,18-21,25,26</sup> Its use in patients with VTE, however, has only been recently assessed in three studies, with conflicting results. In a multicenter European study including 1,308 patients,<sup>9</sup> high-risk patients (score ≥ 2) had a lower TTR than low-risk patients, both during the first 3 months of treatment (53 vs. 61%; p = 0.0001) and during the entire treatment period (56 vs. 61%; p = 0.017). Despite the promising results, c-statistic was only 0.52 (p = 0.35) for TTR < 65% and there was no association with bleeding or thrombotic events. Conversely, in a

**Table 1 - Demographic characteristics of the sample**

Variable	n = 111
Sex, female	71 (64.0)
Age (years)	54.1 ± 15.7
More than 2 comorbidities	16 (14.4)
Hypertension	49 (44.1)
Diabetes	20 (18.0)
Previous stroke	10 (9.0)
Renal disease	10 (9.0)
Heart failure	9 (8.1)
Coronary artery disease	7 (6.3)
Pulmonary disease	6 (5.4)
Peripheral artery disease	2 (1.8)
Liver disease	1 (0.9)
Thrombophilia	31 (27.9)
Any cancer (current/previous)	25 (22.5)
Race, non-white	12 (10.8)
Tobacco use (within the past 2 years)	9 (8.1)
Previous VTE	37 (33.3)
Isolated DVT	29 (26.1)
Isolated PE	5 (4.5)
DVT + PE	3 (2.7)
VTE on treatment	
Isolated DVT	78 (70.3)
Isolated PE	23 (20.7)
DVT + PE	10 (9.0)
Initial heparin use (LMWH/UFH)*	82 (73.9)

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; (\*) 14 (12.6%) patients without initial treatment data. Data are presented as number (%), mean ± standard deviation, or median (25-75<sup>th</sup> percentile).

compared to a low SAME-TT<sub>2</sub>R<sub>2</sub> score (0-1), a high score (> 2) was associated with both lower TTR (50 vs. 57%) and a higher proportion of patients with a TTR < 60% (63.4 vs. 52.3%;  $p < 0.0001$ ). The SAME-TT<sub>2</sub>R<sub>2</sub> score had a modest predictive ability for poor anticoagulation control (TTR < 60%) (c-statistic of 0.61), and its predictive performance did not change significantly at higher TTR cutoffs (0.65 for TTR < 65 and 70%). High-risk patients also had higher VTE recurrence rates and bleeding (7.9 vs. 4.5/100 patient-years;  $p = 0.002$ ).<sup>8</sup> Taken together, these results demonstrate a modest agreement between the SAME-TT<sub>2</sub>R<sub>2</sub> score and TTR, and only studies with large samples ( $n > 1,000$  patients) were able to detect this association. This indicates that the score has limited clinical usefulness in patients with VTE. Moreover, its ability to predict TTR in this particular population was poor (c-statistic of 0.5 to 0.6). Our results are consistent with these findings, and a larger sample would probably allow greater statistical power to show this association, although without clinical applicability.

The most likely explanation for the difference observed between studies assessing the ability of the SAME-TT<sub>2</sub>R<sub>2</sub> score to predict TTR in patients with AF and VTE is that patients with VTE are usually younger, make less frequent use of amiodarone, and have a lower prevalence of comorbidities, all of which are components of the score. In the study that developed the SAME-TT<sub>2</sub>R<sub>2</sub> score, which included only patients with AF, 14.4% of patients in the internal validation cohort were < 60 years of age.<sup>6</sup> However, this age group accounted for 34.1 and 54.6% of patients with VTE included in the studies conducted by Palareti et al.<sup>9</sup> and Kataruka et al.,<sup>8</sup> respectively. In the present study, the proportion of patients aged < 60 years (61.3%) was almost 4 times that of the original SAME-TT<sub>2</sub>R<sub>2</sub> study.<sup>6</sup> Amiodarone was used by 0-1.1% of patients in VTE studies assessing the SAME-TT<sub>2</sub>R<sub>2</sub> score,<sup>5,8,9</sup> while 12.7% of patients were receiving this drug in the original SAME-TT<sub>2</sub>R<sub>2</sub> study.<sup>6</sup> Regarding comorbidities, previous stroke and heart failure were found in 12.8 and 19.3% of patients in the original SAME-TT<sub>2</sub>R<sub>2</sub> study<sup>6</sup> against only 5.0-5.2% and 2.8-3.7% in VTE studies.<sup>5,9</sup> In addition, patients with VTE are more likely to have other comorbidities that are not included in the score, such as cancer. As pointed out by Rose et al.<sup>30</sup> in a case-control study, compared to matched controls, cancer patients receiving warfarin spend less time in the target PT/INR range, have more variable PT/INR values and more thrombotic events. Contributing factors may include drug interactions, fluctuations in dietary vitamin

Spanish study including 135 patients,<sup>5</sup> no differences were found in TTR between low- and high-risk patients (64.7 vs. 66.0%;  $p = 0.73$ ), similar to our results. The score also had poor accuracy in the ROC curve analysis (c-statistic of 0.517 for TTR ≥ 65%). A study conducted in the United States involving 1,943 patients, excluding individuals with current/previous cancer, showed that,

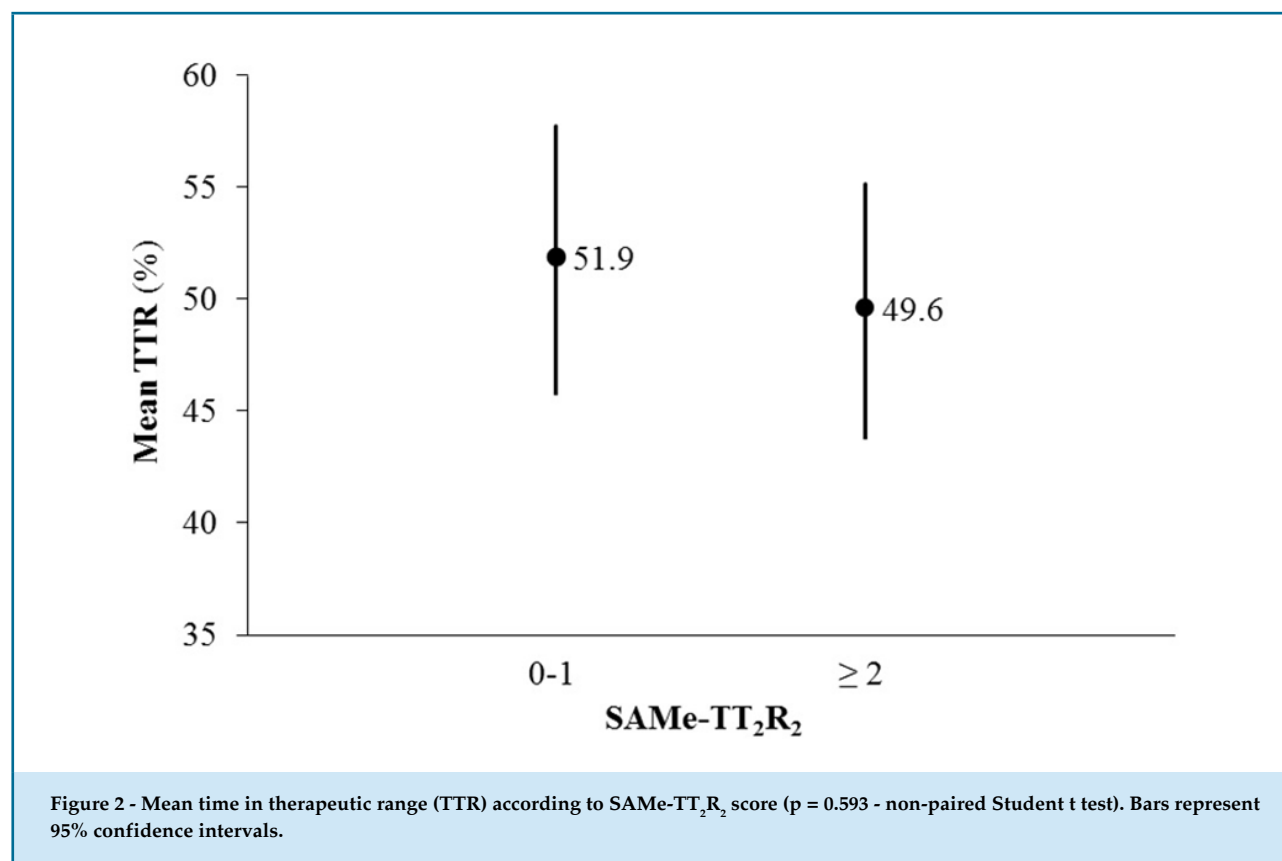


Table 2 - Adverse events during anticoagulation according to the SAME-TT<sub>2</sub>R<sub>2</sub> score

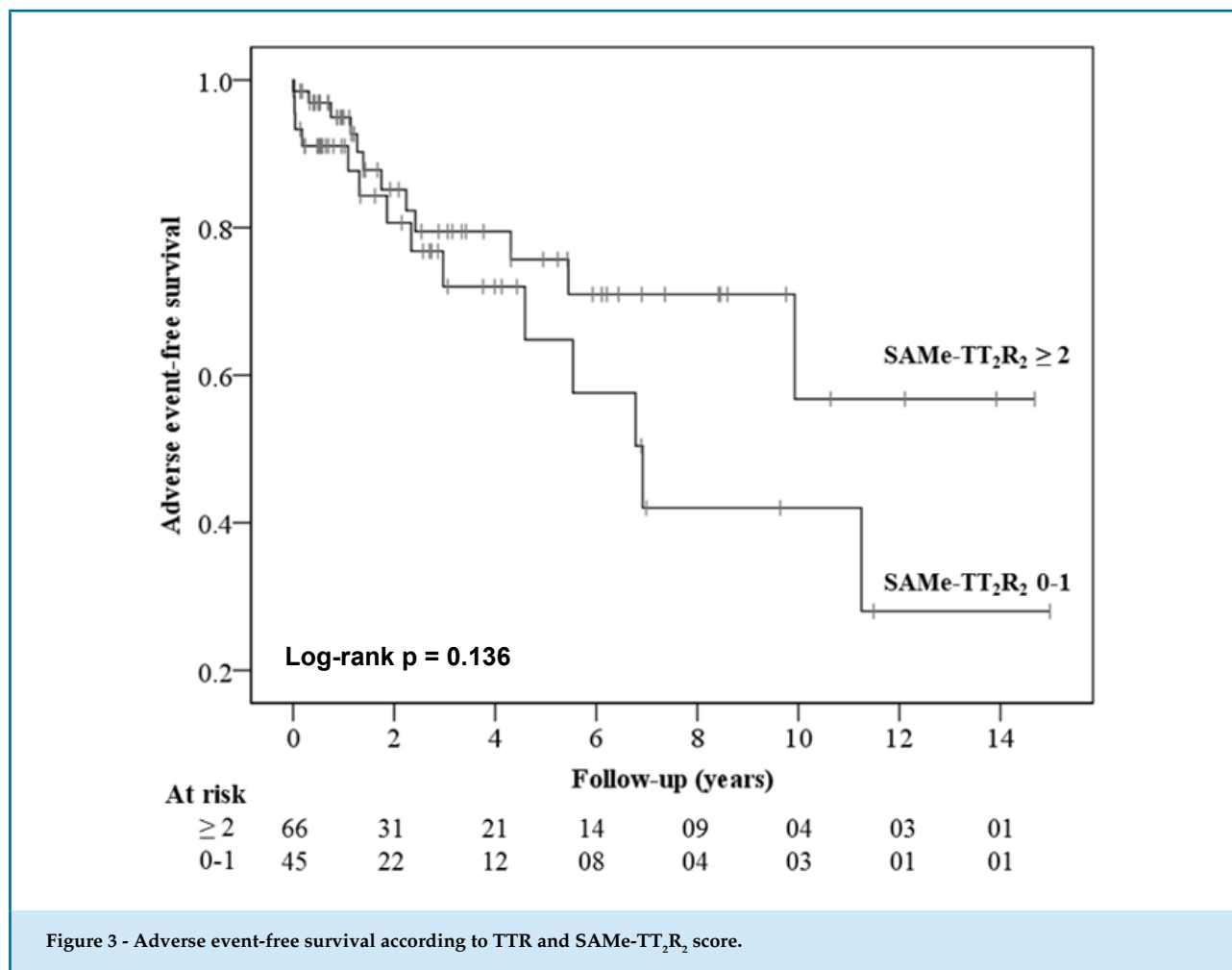
Type of event	n	Incidence rate (/100 patient-years)	Patients with event (n = 111)	SAME-TT <sub>2</sub> R <sub>2</sub> score		P (0-1 vs. ≥ 2)
				0-1	≥ 2	
DVT	11	2.5	11 (9.9)	6 (13.3)	5 (7.6)	0.348 <sup>†</sup>
PE	2	0.5	2 (1.8)	1 (2.2)	1 (1.5)	1.0 <sup>†</sup>
Major bleeding	11	2.5	11 (9.9)	7 (15.6)	4 (6.1)	0.117 <sup>†</sup>
Death	6	1.4	6 (5.4)	2 (4.4)	4 (6.1)	1.0 <sup>†</sup>
Any event	30	6.8	26 (23.4) <sup>*</sup>	14 (31.1)	12 (18.2)	0.177 <sup>‡</sup>

DVT: deep vein thrombosis; PE: pulmonary embolism; (\*) 4 (3.6%) patients had 2 events during follow-up. Data are presented as number (%). <sup>†</sup>Fisher exact test; <sup>‡</sup>Chi-square test.

K intake, treatment interruptions, hepatic dysfunction, mucositis, diarrhea, and the hypercoagulable state induced by cancer itself.

An important methodological aspect of the assessment of the SAME-TT<sub>2</sub>R<sub>2</sub> score is the use of ROC curve analysis, which provides the best statistical method to assess the diagnostic accuracy of a test that has a continuous spectrum of test results.<sup>31</sup> The AUC, also known as

c-statistic or c-index,<sup>31</sup> is an effective and combined measure of sensitivity and specificity that describes the inherent validity of diagnostic tests. The AUC can be interpreted as the probability that a randomly selected diseased individual will be rated or ranked as more likely to be diseased (in our study, with a TTR ≥ 65%) than a randomly selected non-diseased individual.<sup>32</sup> In previous studies assessing the SAME-TT<sub>2</sub>R<sub>2</sub> score in



patients with VTE, the AUC indicated that the score has a unsatisfactory predictive value ( $< 0.7$ ), as observed in the present analysis ( $AUC = 0.595$ ). The values described by Demelo-Rodríguez et al.<sup>5</sup> ( $AUC = 0.517$ ) and Palareti et al.<sup>9</sup> ( $AUC = 0.52$ ) were considered poor ( $0.5 < AUC < 0.6$ ), while the value described by Kataruka et al.<sup>8</sup> ( $AUC = 0.65$ ) was considered only fair ( $0.6 \leq AUC < 0.7$ ).

This study has some limitations. The retrospective design has inherent limitations that may have influenced the quality and consistency of the data collected. Nevertheless, we believe that there was no significant loss of data required for the study, since, at our institution, patients receive systematic care by means of protocols and structured outpatient visits. Thus, most data required for the analysis were systematically collected during outpatient visits. Moreover, the comorbidities were carefully defined to reduce the possibility of misclassification. Another limitation is that the review of medical records allows the identification of only in-

hospital adverse events or events reported by patients during outpatient visits, and some events may have been underestimated. Finally, although the fact that the study was performed at a single center ensured a more organized and consistent follow-up care of patients in this cohort, this might have decreased its external validity.

## Conclusion

Based on the present findings, the SAmE-TT<sub>2</sub>R<sub>2</sub> score does not seem to be a useful tool for determining which patients with VTE are more likely to achieve a good TTR and to have adverse events during anticoagulation with VKA. Population differences between patients with AF and VTE may explain the differences in score performance and highlight the importance of studying scores in specific populations before their clinical application. We believe that our data, derived from a cohort of patients with VTE from a South American

reference center, add to the existing body of knowledge suggesting that the SAME-TT<sub>2</sub>R<sub>2</sub> score should not be used in patients with VTE in its present form. To predict response to VKA therapy in patients with VTE, we believe that a new score or a modification of the SAME-TT<sub>2</sub>R<sub>2</sub> score will be necessary.

## Author contributions

Conception and design of the research: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Scheffel RS. Acquisition of data: Pivatto Júnior F, Salla RF, Cé LC, Führ B. Analysis and interpretation of the data: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Silva ALFA, Scheffel RS. Statistical analysis: Pivatto Júnior F. Writing of the manuscript: Pivatto Júnior F, Salla RF, Cé LC, Blaya MB, Scheffel RS. Critical revision of the manuscript for intellectual content: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Silva ALFA, Führ B, Amon LC, Blaya MB, Scheffel RS. Supervision / as the major investigator: Pivatto Júnior F.

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No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (HCPA) under the protocol number 16-0489. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Free and informed consent was dispensed because of the retrospective nature of data collection.



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