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CLINICAL RESEARCH

Evaluation of SAMe-TT_2R_2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists

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Aims Clinicians need to get better at identifying patients who would have poor quality of anticoagulation control with vitamin-K antagonists (VKAs). We assessed the predictive ability of SAMe-TT_2R_2 score, recently conceived for the prior purpose, and examined its relationship with major bleeding, thromboembolic (TE) complications, and death.

Methods and results Retrospectively, 911 consecutive patients with non-valvular atrial fibrillation (NVAF) started on VKAs within 8 months were studied. The percentage of international normalized ratios in therapeutic range (PINRR) at different levels was used as a metric of anticoagulation quality. We also tested the SAMe-TT_2R_2 predictability for major bleeding, TE complications, and death throughout 10 ± 3 months. The PINRR decreased from 62% at zero point to 53% at ≥ 4 points of SAMe-TT_2R_2. 82.1% of patients who achieved PINRR $\geq$ 70% had 0 or 1 point of SAMe-TT_2R_2. SAMe-TT_2R_2 performed significantly better at PINRR 70% than at 65 and 60% (c-statistic = 0.60 vs. c-statistic = 0.56). The calibration of SAMe-TT_2R_2 was excellent (Hosmer–Lemeshow test *P*-values $\geq$ 0.6). SAMe-TT_2R_2 showed significant association with the composite outcome of major bleeding, TE complications, and death [$n = 98$; hazard ratio (HR) = 1.32; 95% confidence interval (CI) 1.08–1.60]; the c-statistic was 0.57 (95% CI: 0.51–0.62) and $P = 0.03$. As individual outcomes, SAMe-TT_2R_2 was significantly associated with death ($n = 60$; HR = 1.3; 95% CI: 1.03–1.69), but not with either major bleeding ($n = 30$; HR = 1.2; 95% CI: 0.85–1.76) or TE complications ($n = 15$; HR = 1.01; 95% CI: 0.58–1.77).

Conclusion Among NVAF patients, SAMe-TT_2R_2 could represent a useful clinical tool to identify patients who would have poor quality of anticoagulation control with VKAs. SAMe-TT_2R_2 successfully predicts the composite outcome of major bleeding, TE complications, and death.

Keywords Atrial fibrillation • SAMe-TT_2R_2 • Vitamin-K antagonists • Anticoagulation quality control

Introduction

Vitamin-K antagonists (VKAs) are highly effective for the prevention of thromboembolic (TE) complications in patients with non-valvular atrial fibrillation (NVAF),[1] and are still the most used oral anticoagulants in these patients.

However, achieving the best benefit and safety from VKAs in the clinical practice remains a major challenge mainly because of their unpredictable anticoagulant response. Several reports indicate a strong association between international normalized ratio (INR) controls out of range and the increased rates of both stroke and major haemorrhage in patients on VKAs.[2–4]

With the availability of new oral anticoagulants (NOACs), the landscape of anticoagulation management in NVAF has been revolutionized.[5] Clinicians now need to get better at identifying the patients who would do well on VKAs and those less likely to do well, for whom the use of NOACs can be considered as an alternative therapeutic option aiming to avoid stroke and bleeding.

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What's new?

- The clinicians are in continuous need to refine their judgment regarding the correct identification of patients who would do well on vitamin-K antagonists; our study provides a good and unique advancement in this regard.
- Our study shows that SAMe-TT_2R_2 appeared to be an acceptable predictor of the quality of anticoagulation control in patients with non-valvular atrial fibrillation on vitamin-K antagonists, and its prediction ability can be improved significantly if integrated with the physician judgment, which takes into account the overall patients clinical characteristics.
- The analysis of our study demonstrated that if other important risk factors of having low anticoagulation quality are added as strong independent predictors to SAMe-TT_2R_2 score, the discriminative power and its clinical utility can be improved substantially in a real-world practice.

Recently, Apostolakis *et al.*[6] proposed the SAMe-TT_2R_2 [Sex (female); Age < 60 years; Medical history (more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled)] score to help in identifying individuals who will have or not good INRs control.

In this study, we aimed to assess the ability of the new SAMe-TT_2R_2 risk score at predicting different levels of anticoagulation control in a real-world cohort of NVAF patients. We also examined the relationship of SAMe-TT_2R_2 score with major bleeding, TE complications, and all-cause mortality; either as a composite outcome or as individual events.

A secondary goal of our analysis was to investigate some of the cardinal variables that have a widely held belief as strong predictors of poor anticoagulation control.

Methods

Patient's sample

Retrospectively, we identified all consecutive patients of ≥18 years of age with a confirmed diagnosis of atrial fibrillation (AF) on VKAs attending outpatient cardiology consultations at a tertiary hospital between January 2011 and February 2013. Only patients who fulfilled the following criteria were included in this study: patients with permanent or paroxysmal AF recently started on VKAs (i.e. not more than 8 months passed since the beginning of their VKAs therapy), and who have regular visits for INR measurements. Patients with prosthetic valve ($n = 452$), rheumatic heart disease ($n = 43$), active cancer ($n = 41$), dementia ($n = 26$), and/or interrupted VKA >3 days ($n = 73$) were excluded. Thus, the final analysed cohort consisted of 911 patients. A detailed medical history was recorded for each patient, and the basal clinical characteristics at study entry together with information on follow-up were carefully gathered by cardiologists.

The vast majority of patients were on acenocoumarol (93%; and the remaining patients were on warfarin). The INRs measurements were performed at the outpatient anticoagulation clinics in our institution. The available consecutive INRs values for each patient (after excluding the INR measurements during the first month of VKAs initiation) were used to measure the quality of anticoagulation control.

We used the percentage of INRs within the therapeutic range (PINRR) as an index of the quality of oral anticoagulation control. The PINRR method utilizes the number of INRs within the target range (i.e. INR between 2 and 3) divided by the overall number of INRs during that selected time interval.

Patients were followed up to 1-year after the enrolment or until major bleeding, TE complications, or death occurred, whichever comes first. Data on major bleeding and TE complications were gathered from the cardiology clinic visits and records, and through hospital files as well as through primary care centres reports.

The study was approved by the Clinical Research Ethics Committee of our hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

SAMe-TT_2R_2 score calculation

The recently published SAMe-TT_2R_2 score[6] was applied to the database, to evaluate its performance at predicting poor anticoagulation quality controls. For each patient, the SAMe-TT_2R_2 score was calculated as the sum of points after adding one point each for female gender, age < 60 years, medical history of >2 co-morbidities (e.g. hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, prior stroke, pulmonary disease, hepatic, or renal disease), treatment (interacting drugs, e.g. Amiodarone for rhythm control), and two points each for tobacco use and non-White race.

Since all patients in our study were Whites, the maximum score will be of six points.

Patients with SAMe-TT_2R_2 score between 0 and 1 were classified as having low risk of not doing well on VKAs, and ≥2 as at high risk of not doing well with VKAs, as was early described by Apostolakis *et al.*[6]

Variables and definitions

We defined renal dysfunction as glomerular filtration rate <30 mL/min/1.73m^2, while liver disease was defined as cirrhosis or elevated liver transaminases enzymes >3 times higher than the upper limit of normal and elevated total bilirubin >2 times higher than the upper limit of normal. Alcohol abuse was defined as a daily consumption of ≥40 g of ethanol. Past history of malignant disease was assigned, if there is non-active cancer and not being under chemotherapy or radiotherapy in the 6 months previous to the study entry.

We used the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria to define major bleeding.[7] Thus, a major bleeding event was adjudicated if one of the following criteria was met: fatal bleeding and/or symptomatic bleeding in a critical area or organ (e.g. such as intracranial, intraspinal, intraocular, retroperitoneal, atraumatic intraarticular, pericardial, or intramuscular with compartment syndrome); and/or bleeding causing drop of haemoglobin of ≥2 g/dL, or leading to transfusion of ≥2 units of whole blood or packed red blood cells.

A TE complication was defined as the occurrence of ischaemic stroke, transient ischaemic attack, or peripheral embolism. Diagnosis of stroke or transient ischaemic attack required an acute neurological deficit lasting for more than or <24 h, respectively, which could not be explained by other causes and with at least one image test (CT or MRI) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism leading to an abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in the absence of another mechanism such as atherosclerosis, instrumentation, or trauma.

Statistical analysis

Qualitative data were expressed as frequencies and percentages, while quantitative data were summarized as mean and standard deviation. Comparison between qualitative data was performed using the χ^2 test or the Fisher's exact test, as appropriate. The Student's *t*-test or analysis of variance (ANOVA) test was used to compare quantitative data.

Since there is no firm global consensus on the acceptable level of anticoagulation control, and different anticoagulation control levels proved to be meaningful in different reasonable studies,[2,3,8,9] the performance of SAMe-TT_2R_2 risk score was tested regarding different meaningful levels of anticoagulation control: namely PINRR 70, 65, and 60%. This was done by entering the SAMe-TT_2R_2 score, either as a continuous or categorical variable, into separate univariate logistic regression models.

For a better understanding of the effects of the component variables on SAMe-TT_2R_2, we also entered all of the SAMe-TT_2R_2 individual variables into a logistic regression model to test their relationship with PINRR at 65%. We used this cutoff point (i.e. 65%) because it was recently advised to be used for the validation of SAMe-TT_2R_2.[6]

We also attempted to identify other variables correlated with the PINRR cutoff point at 65%. This was used by univariate logistic regression analyses. The effect of variables comprising the SAMe-TT_2R_2 as well as the effect of other variables, which were found to be correlated with PINRR at 65%, were reported as odds ratio (OR) and 95% confidence interval (CI).

All the covariables demonstrating significant association with PINRR at 65% were added to SAMe-TT_2R_2 (as a continuous variable). Thereafter, we analysed the improvement in the performance of SAMe-TT_2R_2 by comparing the c-statistic values of the original score and after adding the above-mentioned covariables. This comparison was done using the Delong method.

We also tested the ability of SAMe-TT_2R_2 to predict major bleeding, TE complications, or all-cause mortality, either as a composite outcome or as individual events, by using Cox proportional hazard models.

The discriminative capacity of the SAMe-TT_2R_2 score to distinguish between patients who will and who will not develop an event of interest was determined by calculating the c-statistic, which is equivalent to the area under the receiver-operating characteristic curve.

The calibration of the model was assessed with the Hosmer–Lemeshow goodness-of-fit test. This test is commonly used to validate models that have just been developed, but it is equally useful for validating (using an external database) the existing logistic models, such as the SAMe-TT_2R_2 model. This test determines how closely the predicted event rate approximates the observed event rate over a range of scores. A significant value of *P* indicates a lack of fit.

A two-sided $P < 0.05$ was considered statistically significant for all analyses. All the analyses were performed with SPSS 21, and by using the MedCalc statistical software version 13.

Results

Baseline characteristics

Our cohort consisted of 911 patients with NVAF on VKAs. *Table 1* summarizes the baseline characteristics of the patients included in the study. Mean age was 73 ± 11 years, and 66.4% were men.

Mean PINRR of the study cohort was 58% ± 18%. Every patient had at least nine consecutive INR measurements (range: 9–15 INR measurements) with intervals <42 days.

Table 1 Baseline characteristics

Age, years	73 ± 11
Men	605 (66.4%)
Systolic blood pressure at study entry	139 ± 28
Hypertension	678 (74.4%)
Current smoking	77 (8.5%)
Diabetes mellitus	220 (24.1%)
Heart failure	343 (37.7%)
Peripheral arterial disease	92 (10.1%)
History of stroke or TIA	103 (11.3%)
Coronary artery disease	127 (13.9%)
COPD	183 (20.1%)
CHA_2DS_2-VASc	
= 0	62 (6.8%)
≥ 1	849 (93.2%)
≥ 2	772 (84.7%)
History of malignancy	135 (14.8%)
HAS-BLED	
0	47 (5.2%)
1	160 (17.6%)
2	365 (40.1%)
3	261 (28.6%)
4	69 (7.6%)
5	6 (0.7%)
6	3 (0.3%)
Alcohol consumption ≥40 g/daily	81 (8.9%)
Prior bleeding	115 (12.6%)
Thyroid disorder:	
Hyperthyroidism	14 (1.5%)
Hyporthyroidism	79 (8.7%)
Anaemia	178 (19.5%)
eGFR < 30 mL/min/1.73m^2	36 (4%)
Abnormal liver function[a]	9 (1%)
PINRR	58% ± 18%

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke, vascular disease, female sex category; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HAS-BLED, uncontrolled Hypertension: systolic >160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly > 65 years, Drugs/alcohol concomitantly; TIA, transient ischaemic attack. PINRR, percentage of INRs in therapeutic range.

[a]Defined as cirrhosis or elevated liver transaminases enzymes >3 times higher than the upper limit of normal and elevated total bilirubin >2 times higher than the upper limit of normal.

Predictive ability of SAMe-TT_2R_2

The relation between SAMe-TT_2R_2 (either as a continuous or a categorical scale) and the anticoagulation quality in terms of mean PINRR values is presented in *Table 2*. The mean PINRR values decreased from 62% at zero point to 53% at ≥4 points of SAMe-TT_2R_2 (ANOVA *P*-value < 0.001). Moreover, the anticoagulation quality clearly decreased from 59% in the low risk to 54% in the high SAMe-TT_2R_2 risk group ($P = 0.001$).

As *Figure 1* illustrates, the majority of patients (82.1%) who achieved a high level of anticoagulation control (i.e. PINRR ≥ 70%)

Table 2 Percentage of INRs in therapeutic range across the different SAMe-TT_2R_2 scores and categories

	Number of patients	PINRR % (mean ± SD)
Continuous SAMe-TT_2R_2		
0	247	62 ± 18
1	425	58 ± 18
2	174	54 ± 19
3	46	55 ± 15
≥4	19	53 ± 18
Categorical SAMe-TT_2R_2		
Low risk: 0–1 point	672	59 ± 18
High risk: ≥2 points	239	54 ± 19

INR indicates international normalized ratio; PINRR, percentage of INRs in therapeutic range; SAMe-TT_2R_2, Sex female, Age < 60 years, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled), and Race (doubled); SD, standard deviation.

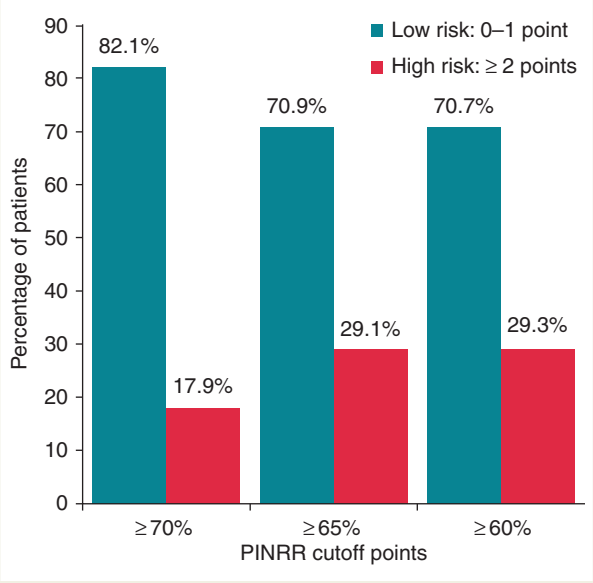

Figure 1 The rate of patients in each risk strata of the SAMe-TT_2R_2 score at different PINRR cutoff points. SAMe-TT_2R_2 indicates Sex female; Age < 60 years; Medical history [more than two comorbidities]; Treatment [interacting drug, e.g. Amiodarone]; Tobacco use [doubled], and Race [doubled]); INR, international normalized ratio; PINRR, percentage of INRs in therapeutic range.

had 0 or 1 point of SAMe-TT_2R_2. However, we found that the prior rate was significantly reduced when we set the PINRR below 70% (70.9% for PINRR ≥ 65%, and 70.7% for PINRR set at ≥60%; $P < 0.001$ for comparisons with PINRR set at ≥70%).

The performance of the SAMe-TT_2R_2 score, in terms of OR and c-statistic, at different PINRR cutoff points is represented and compared in *Table 3*. The best SAMe-TT_2R_2 performance was found at the highest PINRR cutoff point of 70%, regardless of whether it was considered as a continuous or categorical variable: OR = 1.5 and the c-statistic = 0.60 (95% CI: 0.56–0.64, $P < 0.001$) for continuous SAMe-TT_2R_2, and OR = 1.9 with the c-statistic = 0.56 (95% CI: 0.53–0.60, $P < 0.001$) for categorical SAMe-TT_2R_2.

The significant difference ($P = 0.01$), however, was found during the comparison between the continuous SAMe-TT_2R_2 at predicting PINRR ≥ 70% and continuous SAMe-TT_2R_2 for predicting PINRR < 70%.

The calibration of continuous SAMe-TT_2R_2 was excellent regardless of the cutoff points used (*P*-value of Hosmer–Lemeshow being ≥0.6).

The effect of the individual variables comprising SAMe-TT_2R_2 at predicting PINRR cutoff point of 65% (the advised cutoff point to use SAMe-TT_2R_2)[6] is summarized in *Table 4*. Three of the five variables forming SAMe-TT_2R_2, namely female sex (OR = 1.48, 95% CI: 1.12–1.96), medical comorbidities (OR = 2.19; 95% CI: 1.61–2.98), and treatment interaction (e.g. amiodarone) (OR = 1.48, 95% CI: 0.98–2.24), were independent predictors of poor quality of anticoagulation control with VKAs.

The effect of alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or left ventricular ejection fraction (LVEF) < 40%, history of malignancy, and chronic liver disease on the quality of INR control (PINRR < 65%) is presented in *Table 4*. All of these six variables except chronic liver disease were significantly associated with poor quality of INR control defined as having PINRR < 65%.

Adding all of the prior five clinical covariables—showing significant association with poor INR control—as independent predictors over the SAMe-TT_2R_2 score, resulted in a substantial and significant improvement in the score performance for predicting PINRR cutoff point of 65%: the c-statistic = 0.65 (95% CI: 0.61–0.68, $P < 0.0001$), as compared with the c-statistic value of 0.56 (95% CI: 0.53–0.60, $P = 0.001$) when using solely the original SAMe-TT_2R_2 model.

SAMe-TT_2R_2 and the composite outcome of major bleeding, thromboembolic complications, or death

During the follow-up (10 ± 3 months), 98 (10.8%) patients developed major bleeding, TE complications, or death. There was a significant association between SAMe-TT_2R_2 and the composite outcome [hazard ratio (HR) = 1.32; 95% CI: 1.08–1.60, $P = 0.006$]; the c-statistic was 0.57 (95% CI: 0.51–0.62, $P = 0.03$).

The addition of alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or left ventricular ejection fraction (LVEF) < 40%, and history of malignancy, over SAMe-TT_2R_2, significantly improved the score performance: c-statistic = 0.70 (95% CI 0.65–0.75) ($P = 0.007$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

SAMe-TT_2R_2 and major bleeding

Thirty (3.3%) patients developed major bleeding events during the follow-up. There was no significant association between SAMe-TT_2R_2 and major bleeding (HR = 1.2; 95% CI: 0.85–1.76, $P = 0.28$); the c-statistic was 0.57 (95% CI: 0.47–0.67, $P = 0.20$).

The performance of SAMe-TT_2R_2 significantly improved by adding the above-mentioned five clinical variables over the score: c-statistic = 0.68 (95% CI: 0.59–0.77) ($P < 0.001$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

Table 3 Performance of SAMe-TT_2R_2 at different PINRR cutoff points

	PINRR ≤ 70% *n* = 671	PINRR ≤ 65% *n* = 554	PINRR ≤ 60% *n* = 433
Continuous SAMe-TT_2R_2			
OR (95% CI)	1.5 (1.2–1.8)	1.3 (1.1–1.5)	1.2 (1.1–1.4)
c-statistic (95% CI)	0.60 (0.56–0.64)*	0.56 (0.53–0.60)	0.56 (0.52–0.59)
Categorical SAMe-TT_2R_2			
OR (95% CI)	1.9 (1.3–2.7)	1.5 (1.1–2.0)	1.4 (1.0–1.8)
c-statistic (95% CI)	0.56 (0.52–0.60)†	0.54 (0.50–0.57)	0.53 (0.49–0.57)

CI refers to confidence interval; OR, odds ratio; INR, international normalized ratio; PINRR, percentage of INRs in therapeutic range; SAMe-TT_2R_2, Sex female; Age < 60 years; Medical history (more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled); SD, standard deviation.
*$P = 0.01$ for the comparison of c-statistic value of continuous SAMe-TT_2R_2 at predicting PINRR ≤ 70% vs. the remaining c-statistic values.
†$P = 0.6$ for the comparison of c-statistic values of SAMe-TT_2R_2 at predicting different PINRR cutoff points.

Table 4 Individual SAMe-TT_2R_2 variables and other risk factors in relation with PINRR < 65%

	OR (95% CI)	*P*-value
Female sex	1.48 (1.12–1.96)	0.006
Age < 60 years	1.38 (0.93–2.04)	0.11
More than two medical comorbidities	2.19 (1.61–2.98)	<0.0001
Treatment interaction (e.g. Amiodarone)	1.48 (0.98–2.24)	0.06
Tobacco	1.17 (0.92–1.50)	0.21
Alcohol abuse	3.08 (1.73–5.48)	<0.0001
eGFR < 30 mL/min/1.73 m^2	1.49 (1.11–2.01)	0.008
History of malignancy	1.93 (1.29–2.91)	0.002
Diabetes mellitus	1.56 (1.13–2.16)	0.007
Heart failure or LVEF < 40%	1.66 (1.27–2.20)	<0.0001
Liver disease	1.61 (0.31–8.38)	0.57

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PINRR, percentage of INRs in therapeutic range.

SAMe-TT_2R_2 and thromboembolic complications

Fifteen (1.6%) TE events occurred during the follow-up (10 strokes, 2 transient ischaemic attacks, and 3 peripheral embolisms). The SAMe-TT_2R_2 was not significantly associated with TE complications (HR = 1.01; 95% CI: 0.58–1.77, $P = 0.90$); the c-statistic was 0.49 (95% CI: 0.35–0.63, $P = 0.94$). However, the addition of the above-mentioned five clinical variables over SAMe-TT_2R_2 significantly improved its performance: c-statistic = 0.62 (95% CI: 0.49–0.75) ($P = 0.02$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

SAMe-TT_2R_2 and all-cause mortality

During the follow-up, 60 (6.6%) patients died. The increase in the SAMe-TT_2R_2 score was significantly associated with all-cause mortality HR = 1.3 (95% CI: 1.03–1.69); the c-statistic value was 0.57 (95% CI: 0.50–0.64, $P = 0.08$).

The performance of SAMe-TT_2R_2 improved significantly by adding alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, heart failure or LVEF < 40%, and history of malignancy over the score (c-statistic = 0.75 (95% CI 0.69–0.81) ($P < 0.001$ for comparison with the c-statistic from SAMe-TT_2R_2 alone).

Discussion

The VKAs represent the most commonly used oral anticoagulant therapy in patients with NVAF, but in everyday practice there are still many difficulties in reaching an optimal management with VKAs.[4] There is now a great interest in identifying those patients who are at risk of having a poor anticoagulation control with VKAs and therefore could be potential candidates for prescribing NOACs which have more predictable anticoagulant effect, and were found to be superior to VKAs, particularly as long as the level of anticoagulation control is decreasing.[8,9]

In our cohort analysis, we studied for the first time, the predictive ability of the new SAMe-TT_2R_2 at different interesting and clinically meaningful levels of anticoagulation control, in a real-world cohort of patients with NVAF. Generally, we observed that SAMe-TT_2R_2 exhibited a statistically significant ability to predict the quality of anticoagulation control with VKAs.

Since absolute difference of 5% in the level of anticoagulation control has been considered as constituting a meaningful difference in performance and probably the standard for clinically important differences,[10] we tested the performance of SAMe-TT_2R_2 at different interesting PINRR cutoff points (i.e. 60, 65, and 70%) which had shown clinical significance in various studies and in a reasonable recommendation.[2,3,8,9] Remarkably, the SAMe-TT_2R_2 predictive model showed a significantly better predictability at a relatively high PINRR cutoff point of 70%, as compared with lower PINRR cutoff points (i.e. 60 and 65%). In addition, SAMe-TT_2R_2 as a categorical scale demonstrated that patients classified as at high risk of having poor quality of INR control had significantly lower PINRR value (*Table 2*). This finding is consistent with a recent validation study of SAMe-TT_2R_2 in which there was a clear decline of the mean level of anticoagulation control from 74% in low risk to 68% in the high-risk category.[11]

The fact that in our analysis SAMe-TT_2R_2 showed incremental improvement in its performance from PINRR cutoff point of 60%

across 65–70% may partially reflect the findings described in the original SAMe-TT_2R_2 validation cohort[6] in which the best performance of SAMe-TT_2R_2 was tested at the outliers groups, and not on the average level of anticoagulation control.

On the other hand, Apostolakis *et al.*[6] advised using a mean level of anticoagulation of ~65%, given that at this value the SAMe-TT_2R_2 score could aid in the decision making by identifying patients with AF who would have high quality of anticoagulation control with VKA (score = 0–1) from those who are at risk of suboptimal anticoagulation (score ≥ 2). However, in our analysis, at PINRR cutoff point of 65%, the performance of categorical SAMe-TT_2R_2 (0–1 point vs. ≥2 points) was rather modest (c-statistic = 0.54; P = 0.06). In this regard, our results are concordant with the recent finding of Lip *et al.*,[12] who evaluated the SAMe-TT_2R_2 score at predicting labile INR and reported a modest performance with the c-statistic value of 0.58.

In the present paper, we also tested the ability of other risk factors, beyond the SAMe-TT_2R_2 variables, at predicting the PINRR cutoff point of 65% (*Table 4*). We found that five of them (history of cancer, alcohol abuse, eGFR < 30 mL/min/1.73 m^2, diabetes mellitus, and heart failure/LVEF < 40%) were significant predictors of having TTR < 65%. Notably, these five strong prognosticators found in our study also had demonstrated a strong independent association with low level of anticoagulation control in the inception and experienced periods of the VARIA study.[13]

Moreover, in our study, it stands to reason that these five cardinal risk factors significantly improved the discriminative capacity of SAMe-TT_2R_2 (c-statistics improved from 0.56 to 0.65, P = 0.004 for comparison). This interesting finding could improve the clinical utility and accuracy of SAMe-TT_2R_2 in a real-world practice if the prior five risk factors are taken into account. Therefore, in the present analysis we provide a reasonable and logistic assumption that the SAMe-TT_2R_2 score can be improved significantly by including more variables such as the variables found in our study. In this regard, SAMe-TT_2R_2 can be improved significantly if it is integrated with the physician judgment which takes into account other clinical risk factors that had a widely held belief about their role in the dilemma of INR control.

In the present study, we found that SAMe-TT_2R_2 has a good ability to capture the baseline risk of developing the composite outcome of major bleeding, TE complications, and death. However, the ability of SAMe-TT_2R_2 for predicting major bleeding as an individual outcome was not better than chance, as was also recently reported in another study with similar sample size to our cohort.[11] Nonetheless, a recent study by Lip *et al.*[12] showed a significant association between SAMe-TT_2R_2 and major bleeding in 4637 AF patients on VKA.[12] Another study by Gallego *et al.*[14]—including 972 NVAF patients on acenocumarol—demonstrated a trend towards prediction of major bleeding (HR = 1.23; 95% CI: 0.99–1.53, P = 0.059).[14]

Similarly, we found no relationship between SAMe-TT_2R_2 and TE complications. This might be explained by the very few number of TE events in our study which could limit the capacity of the score to discriminate between patients who did and those who did not develop a TE complication. In an Italian study of about 1000 AF patients with 63 stroke/transient ischaemic attack, SAMe-TT_2R_2 was not significantly associated with stroke/transient ischaemic attack.[11] However, it is noteworthy that another recent study in which 379 stroke/TE events were recorded, a significant association was found between SAMe-TT_2R_2 and stroke/TE events. Anyhow, it should be noted that there are another specific scoring systems for predicting bleeding as well as TE complications in AF patients.[15,16]

With the availability of NOACs, the landscape of anticoagulation management in NVAF has been revolutionized,[5] and clinicians appreciate the methods and tools designed to refine their judgment regarding the correct identification of patients who would have high quality of anticoagulation control with VKAs and distinguish them from those less likely to do well on VKAs for whom the use of NOAC should be proposed as an alternative therapeutic option aiming to avoid the excess risk of stroke and bleeding.[17,18] For this purpose, SAMe-TT_2R_2 may represent an acceptable clinical tool which can facilitate the physicians decision-making process to optimize the oral anticoagulation management.

Limitations

The main limitation of our study is its retrospective design, but it has interesting strong points as it reflects real-world practice by enrolment of consecutive NVAF patients attending our outpatient cardiology clinics with the advantage of careful follow-up and data collection by cardiologists and of recording successive INR values, which give a reasonable index of the quality of anticoagulation control.

Of note, our study could be criticized by the fact that we used the PINRR method as an index of the quality of anticoagulation control. However, the quality of anticoagulation can be measured by a number of methods and no standardized consensus exists as to which is the best measure, and as such, all of the available methods have specific and known advantages and disadvantages. Additionally, the PINRR method is still a recognized method and proved to have a significant correlation with the Rosendaal method (r = 0.99, P < 0.001).[19]

Although we excluded groups of patients (i.e. believed to have poor adherence, more frequent INR measurements, and/or more dose adjustments) with active cancer, dementia, and interrupted VKAs, residual confounding is likely as we did not have enough data about the magnitude of dose adjustments in regard to the frequency of INR measurements and their specific relations to the other risk factors. Also, we were not able to collect data about other possible confounding variables such as educational level, socioeconomic status, and distance from the anticoagulation clinics, which may have an association with the overall quality of anticoagulation. The sample size is another limitation of our study that could limit the likelihood of detecting small effects or significant relationships from the data. Finally, the applicability of our findings in other populations with different races and other patient characteristics should be addressed in other studies.

Conclusions

In conclusion, the SAMe-TT_2R_2 score constitutes a user-friendly tool for predicting the quality of anticoagulation control with VKAs, especially at high level. The SAMe-TT_2R_2 score successfully predicts mortality and the composite outcome of major bleeding, TE complications, and mortality. However, SAMe-TT_2R_2 does not appear to predict major bleeding or TE complications among our NVAF patients on VKAs.

Our study also indicates that the performance of SAMe-TT_2R_2 could be improved by taking into account other cardinal risk factors related to poor INR control.

Conflict of interest: none declared.

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