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Determinants of the Quality of Warfarin Control after Venous Thromboembolism and Validation of the SAMe-TT2-R2 Score: An Analysis of Hokusai-VTE

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Abstract

Background Time in therapeutic range (TTR) measures the quality of vitamin K antagonist (VKA) anticoagulation. In patients with atrial fibrillation, the dichotomized SAMe-TT2-R2 score ($\geq$2 vs. $<$ 2 points) can predict if adequate TTR is unlikely to be achieved.

Aims We validated the SAMe-TT2-R2 score in patients with venous thromboembolism (VTE) randomized to the warfarin arm of the Hokusai-VTE trial.

Patients and Methods A total of 3,874 patients were included in the primary analysis (day 31–180 from randomization). The efficacy and safety outcomes were symptomatic recurrent VTE and major or clinically relevant non-major bleeding.

Keywords
- vitamin K antagonist
- quality of treatment
- warfarin
- venous thromboembolism
- risk assessment model

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Results The rates of recurrent VTE and bleeding events were higher in patients with a TTR below the median (< 66% vs. ≥66%) resulting in an absolute risk difference (ARD) of +0.5% (95% confidence interval: 0%, +1.1%) and +2.2% (0.9%, +3.5%), respectively. Patients with high SAMe-TT2-R2 score were 76% of total and had lower median TTR (64.7% vs. 70.7%). The SAMe-TT2-R2 score exhibited low negative (0.59) and positive (0.52) predictive value (TTR threshold 66%), and poor discrimination (c-statistic, 0.58). ARD between patients with high and low score was 0% (–0.6%, +0.7%) for recurrence and +1.3% (–0.1%, +2.7%) for bleeding. Results were confirmed in sensitivity analyses focusing on the whole study period (day 1–365).

Conclusion In VTE patients, the SAMe-TT2-R2 score showed unsatisfactory discrimination and predictive value for individual TTR and did not correlate well with clinical outcomes. The choice of starting a patient on VKA cannot be based on this parameter and its routine use after VTE may not translate into clinical usefulness.

Introduction

Direct oral anticoagulants (DOACs) represent the drugs of choice for most patients diagnosed with acute venous thromboembolism (VTE) based on the results of large phase III trials, which compared them to conventional international normalized ratio (INR)-adjusted vitamin K antagonist (VKA) anticoagulation.[1] One of the factors contributing to the favourable efficacy and safety of DOACs is their more stable pharmacokinetic profile, which provides steady therapeutic levels following the administration of a fixed-dose regimen.

Despite this, a proportion of patients with acute VTE are still candidates for VKA, especially those with absolute or relative contraindications to DOAC use or taking potentially interacting co-medications.[2–5] National restrictions for drug reimbursement, and patients' or physicians' preferences also influence the choice of anticoagulant therapy for the management of acute VTE. Since the risk of recurrence and bleeding during VKA therapy greatly depends on the quality of anticoagulation, as estimated by the individual time in therapeutic INR range (TTR),[6–8] predicting whether a patient is likely to achieve a good TTR is crucial to select the right therapy for the right patient.

The SAMe-TT2-R2 score (►**Table 1**) was developed to identify patients with atrial fibrillation who would perform well (or not) on VKA and aid therapeutic decision making.[9–11] A position document released by the European Society of Cardiology Working Group on Thrombosis suggested that, in patients with atrial fibrillation and a SAMe-TT2-R2 score predicting poor TTR, DOACs might represent a better option for initial treatment.[12] Only a few adequately sized studies validated the score in VTE patients and investigated correlations with clinical outcomes.[13–15] It remains unclear whether the SAMe-TT2-R2 score may influence the choice of anticoagulant therapy after VTE.

Our objectives were to identify independent predictors of individual TTR in the warfarin arm of the Hokusai-VTE trial, which compared the direct oral anti-Xa inhibitor edoxaban versus standard VKA therapy for the treatment of acute VTE, and provide a temporal, geographical and independent external validation of the SAMe-TT2-R2 score in this setting.

Patients and Methods

Study Design of the Hokusai-VTE

The Hokusai-VTE was a double-blind, double-dummy, placebo-controlled phase III trial that randomized patients diagnosed with acute symptomatic VTE to either edoxaban or warfarin after an initial course of heparin. The study design and results have been previously reported (ClinicalTrials.gov identifier: NCT00986154).[16,17] In brief, patients enrolled in the Hokusai-VTE trial were adults with an episode of objectively confirmed acute, symptomatic proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Main exclusion criteria included severe renal dysfunction (creatinine clearance < 30 mL/min), active cancer, use of chronic dual anti-platelets,

Table 1 The SAMe-TT2-R2 score

Item	Points
Female sex	1
Age < 60 years	1
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)	1
Concomitant medications (interacting drugs, e.g. amiodarone for rhythm control)[a]	1
Tobacco use (within 2 y)[a]	2
Non-Caucasian origins	2
SAMe-TT2-R2 classes	**Total points**
Low probability of not doing well on VKA – Higher TTR expected	0–1
High probability of not doing well on VKA – Lower TTR expected	2 or more

Abbreviations: TTR, time in therapeutic range; VKA, vitamin K antagonist.
[a]For the present study, separate analyses have been performed for (1) all potential interacting drugs, and (2) amiodarone only. Moreover, we only considered 'current tobacco use' at the time of enrolment.

aspirin (> 100 mg/day) and use of non-steroidal anti-inflammatory drugs or potent P-glycoprotein inhibitors. The Hokusai-VTE protocol had been reviewed by the institutional review board at each participating site and all patients provided written informed consent.

Study Treatment

All patients received open-label unfractionated heparin or low-molecular weight heparin for at least 5 consecutive days. Edoxaban or warfarin was given for at least 3 and up to 12 months after enrolment. The length of anticoagulation was individualized and the decision left at the discretion of the treating physicians. Edoxaban was given at a standard dose of 60 mg once daily; the dose was reduced to 30 mg once daily in patients with a creatinine clearance of 30 to 50 mL/min, body weight of ≤60 kg or taking concomitant P-glycoprotein inhibitors. The warfarin dose was adjusted to maintain an INR comprised between 2.0 and 3.0, as measured locally by point-of-care devices.[16,17]

Time in Therapeutic Range

We calculated individual TTR in the warfarin arm of Hokusai-VTE for the period elapsing between day 31 and 180 after enrolment, inclusively. We have chosen this timeframe since day 30 represents the time by which 'stable' therapeutic individualized dosing is achieved after the early inception phase of VKA treatment and acute factors (including INR management during hospitalization) are less likely to play a role.[18] The timeframe for censoring (day 180) has been previously used in similar studies on TTR, phase III trials[18,19] and risk assessment model validations.[20,21]

We additionally performed non-predefined sensitivity analysis focusing on the whole study period (day 1–365) on anticoagulant, provided that initial (day 1–30) TTR may be difficult to predict due to the concomitance of transient influencing factors (e.g. hospitalization, acute infection, co-medications) and, vice versa, that extended VKA anticoagulation may have been preferred in patients who had achieved adequate TTR during the first 6 months of therapy.

We used the method of linear interpolated INR to calculate individual TTR in patients with INR measurement gaps no longer than 42 days.[22] The compliance to the study drug was calculated based on the compliance to placebo edoxaban of patients randomized to the warfarin arm of the study, according with the formula 'number of tablets taken by number of tablets due'.

The SAMe-TT2-R2 Score

The SAMe-TT2-R2 score was derived for each patient by adding one point for any of the following items[9]: (1) female sex, (2) age < 60 years, (3) at least two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease (i.e. chronic obstructive pulmonary disease), hepatic or renal disease, (4) treatment with interacting drugs (mainly amiodarone), and two points for the following: (5) tobacco use (within 2 years) and (6) non-Caucasian origins (►**Table 1**).

The main discrepancy between our analysis and the original SAMe-TT2-R2 score was represented by the item 'tobacco use (within 2 years)'. This variable was not available in the Hokusai-VTE case report form and, therefore, we used 'current tobacco use' for the classification of patients. Furthermore, the score was derived in the atrial fibrillation setting, where amiodarone represented the principal interfering co-medication known to exert an effect on INR levels. Since the proportion of VTE patients taking amiodarone is usually extremely low,[10] and atrial fibrillation was an exclusion criteria in Hokusai-VTE,[17] we calculated the SAMe-TT2-R2 score accounting for the use of (1) major interfering drugs based on the Food and Drug Administration prescribing information (a full list is provided in the ►**Supplementary Material**, available in the online version) and (2) amiodarone only.

The primary evaluation of the score was based on dichotomized classes, namely, low (0–1 point) versus high (2 points or more) SAMe-TT2-R2 score with a high SAMe-TT2-R2 score predicting poor TTR. We performed separate evaluation of the trichotomized score (0–1 point, 2 points, 3 points or more), as previously reported.[15,23,24]

Clinical Outcomes

In Hokusai-VTE, all patients, regardless of treatment duration, were followed for 12 months or until the end-of-study date. For the present analysis, we considered events occurring during anticoagulant treatment between day 31 and 180 from randomization.

The primary efficacy outcome was symptomatic recurrent VTE (defined as DVT and/or fatal, or non-fatal, PE). The principal safety outcome was clinically relevant bleeding (the composite of major and clinically relevant non-major bleeding). Major bleeding was defined as overt bleeding that was associated with a reduction in haemoglobin of ≥2 g/dL or requiring transfusion of two or more units of blood, occurred at a critical site or contributing to death. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but required medical intervention, unscheduled contact with a clinician, interruption of study drug or discomfort or impairment of daily activities.[17] In addition, we focused on a composite outcome including recurrent VTE or clinically relevant bleeding. All suspected outcomes have been adjudicated by an independent committee.[16,17]

Statistical Analysis

We used counts and percentages for describing categorical data and mean/median (standard deviation [SD]/interquartile range [IQR]) for continuous variables, where appropriate. Comparisons between groups were performed using the two-sided Wilcoxon non-parametric test for non-normally distributed data. We used linear mixed regression for our unadjusted and adjusted models to evaluate the impact of independent baseline factors on TTR (dependent variable). The variables were selected on the basis of clinical relevance, frequency of missing values and available literature on this topic: their detailed description has already been provided

elsewhere.[17] The unstandardized regression coefficient for the predictor represents the difference in response in terms of TTR change when baseline factor status changes. The diagnostic quality of the multi-level SAMe-TT2-R2 was evaluated using receiver operator characteristic curve analysis (95% confidence interval [95% CI]) as a measure of discrimination. For the dichotomized SAMe-TT2-R2 score, we calculated odds ratio (OR), sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) accompanied by 95% CI for the outcome of low TTR. Low TTR was primarily defined by using the median value of the study population (66%) as a threshold.

We calculated event rates by dividing the number of patients with an event for the total number of subjects included in the safety population between day 31 and 180. To explore the time distribution of the events, we calculated the monthly rate for each outcome, which provides better visual overview compared with the Kaplan–Meier curve estimator. Finally, we performed univariate Cox regression model analysis to calculate the hazard ratios (HRs; 95% CI) of TTR levels or SAMe-TT2-R2 score classes for the occurrence of thromboembolic and bleeding complications (dependent variables). The difference between groups are also provided as absolute risk reduction (ARD; 95% CI).

Results

A total of 8,292 patients were enrolled in the Hokusai-VTE between 2010 and 2012, of whom 4,122 were randomized to receive warfarin. Median duration of treatment with the study drug was 266 days: 528 (12.8%) patients were treated for 3 months or less, 1,084 (26.3%) for 3 to 6 months and 2,510 (60.9%) for 6 months or longer. Of these, 3,903 completed at least 30 days of anticoagulant treatment and 3,874, who had at least one INR measurement available after day 30, were included in the present analysis. The baseline characteristics of the study population are depicted in ►**Table 2**.

Between day 31 and 180, median individual TTR (range: 2.0–3.0) was 66.0% (IQR: 50.4–80.6%). Mean TTR was 63.7% (SD, 22.4%) with 21.5% (SD, 20.8%) of time spent below and 14.8% (SD, 16.5%) above the therapeutic range (INR: 2.0–3.0). We summarized the drug compliance to placebo edoxaban of patients randomized to the warfarin arm and geographical variations of TTR in ►**Supplementary Tables S1** and **S2** (available in the online version).

Factors Influencing the Time in Therapeutic Range

After adjustment for clinically relevant baseline characteristics reported in ►**Table 2**, we observed that patients of Afro-American or Asian origins had lower individual TTR (–5.2 and –7.1%, respectively) with 95% CI not including zero. Tobacco use (–3.9%), the presence of anaemia at baseline (–4.9%) and the presence of at least one of the following criteria (a creatinine clearance of 30–50 mL/min, body weight < 60 kg or P-glycoprotein inhibitor administration: –2.9%) were also associated with lower TTR. Vice versa, patients taking statin (+2.7%), consuming alcohol (+1.8%) and with PE as the presenting location of acute VTE (+2.6%) had higher TTR. ►**Supplementary Table S3** (available in the online version) depicts the coefficients resulting from the univariate analysis.

Time in Therapeutic Range and Clinical Endpoints

Recurrent VTE occurred in 1.0% of patients with an individual TTR of $< 66\%$ and in 0.5% of patients with TTR $\geq 66\%$ (HR: 2.02; 95% CI: 0.94–4.38), corresponding to an ARD of 0.5% (95% CI: 0.0%, 1.1%). Clinically relevant bleeding occurred in 5.5% (TTR $< 66\%$) and 3.3% (TTR $\geq 66\%$) of patients within the two groups, respectively, for HR of 1.75 (95% CI: 1.28–2.38) and ARD of 2.2% (95% CI: 0.9%, 3.5%; ►**Table 3**). The composite outcome occurred in 6.4% of patients with low and 3.8% with high TTR (HR: 1.76; 95% CI: 1.32–2.35 and ARD 2.7%; 95% CI: 1.3–4.1%). The time distribution of the events appeared to be left skewed with more (especially bleeding) events recorded between day 31 and 90 in patients with low TTR, as depicted in ►**Supplementary Fig. S1** (available in the online version).

External Validation of the SAMe-TT2-R2 Score for the Prediction of TTR Levels

By applying the conventional score threshold (0–1 vs. 2 points or more), 943 (24%) patients were classified in the low and 2,931 (76%) in the high SAMe-TT2-R2 class by considering the use of any potentially interfering co-medications, which was reported in 47% of patients (►**Table 4**). Median TTR was 70.7% (IQR: 56.5–84.0%) in patients with low and 64.7% (IQR: 48.7–79.1%) with high score (Wilcoxon two-sided test, $p < 0.0001$). The time above INR 3.0 was 10.7% in patients with low and 9.5% in patients with high score. The time below INR 2.0 was 12.4 and 18.1% in the two groups, respectively.

High SAMe-TT2-R2 score predicted low TTR with OR of 1.55 (95% CI: 1.34–1.80) for TTR $< 66\%$ (vs. TTR $\geq 66\%$) and OR of 1.86 (95% CI: 1.54–2.26) for TTR $< 50\%$ (vs. TTR $\geq 50\%$). c-Statistics of the continuous SAMe-TT2-R2 score were 0.58 (95% CI: 0.56–0.60) and 0.59 (95% CI: 0.57–0.61) for these two TTR thresholds, respectively. NPV increased from 0.59 (95% CI: 0.56–0.62) for the 66% threshold to 0.84 (95% CI: 0.81–0.86) for the 50% threshold.

We also calculated the score by excluding the item 'treatment with interacting drugs', since none of the patients used amiodarone. In this analysis, 1,400 (36%) patients were classified in the low and 2,474 (64%) in the high SAMe-TT2-R2 class. The performance of the score was similar as considering all potential interfering drugs (►**Supplementary Tables S4** and **S5**, available in the online version).

SAMe-TT2-R2 Score and Clinical Endpoints

In patients with a SAMe-TT2-R2 score calculated accounting for multiple potential interfering drugs, the rate of recurrent VTE was 0.8% in the high (SAMe-TT2-R2 ≥ 2 points) versus 0.7% in the low (SAMe-TT2-R2 < 2 points) risk group for HR of 1.02 (95% CI: 0.42–2.49) and ARD of 0% (95% CI: –0.6%, 0.7%). The rates of clinically relevant bleeding were 4.7% versus 3.4% (HR: 1.34 [95% CI: 0.91–1.97] and ARD: +1.3% [95% CI: –0.1%, +2.7%]), respectively. The composite outcome

Table 2 Baseline characteristics of the study population

Variable	Value[a]	Adjusted effect on TTR, % (95% CI) – Day 31–180	Adjusted effect on TTR, % (95% CI) – Day 1–365
Age, I quartile (18–44 y)	1,026/3,874 (26.5)	Reference	Reference
Age, II quartile (45–56 y)	930/3,874 (24.0)	−0.2 (−2.2; +1.9)	−0.7 (−2.5; +1.0)
Age, III quartile (57–68 y)	1,002/3,874 (25.9)	+1.9 (−0.3; +4.1)	+1.1 (−0.8; +3.0)
Age, IV quartile (69–95 y)	916/3,874 (23.6)	+0.8 (−1.9; +3.5)	−0.4 (−2.8; +1.9)
Female sex, n (%)	1,644/3,874 (42.4)	−0.7 (−2.2; +0.9)	−0.2 (−1.5; +1.2)
Ethnicity			
White	2,730/3,874 (70.5)	Reference	Reference
Afro-American	128/3,874 (3.3)	−5.2 (−9.8; −0.7)	−6.4 (−10.3; −2.4)
Asian	802/3,874 (20.7)	−7.1 (−9.6; −4.6)	−6.0 (−8.2; −3.8)
Other	214/3,874 (5.5)	+1.3 (−2.6; +5.2)	+0.7 (−2.8; +4.2)
Body mass index			
BMI < 18.5	67/3,831 (1.7)	Reference	Reference
BMI 18.5–24.9	1,071/3,831 (28.0)	−1.6 (−7.1; +3.9)	−1.9 (−6.7; +2.8)
BMI 25.0–30.0	1,485/3,831 (38.8)	−0.5 (−6.2; +5.2)	−0.7 (−5.6; +4.1)
BMI > 30.0	1,208/3,831 (31.5)	−0.4 (−6.2; +5.5)	−0.8 (−5.7; +4.2)
Creatinine clearance			
CrCL < 50 mL/min	194/3,669 (5.3)	Reference	Reference
CrCL 50–80 mL/min	832/3,669 (22.7)	−0.7 (−4.3; +2.9)	+1.1 (−2.0; +4.2)
CrCL >80 mL/min	2,643/3,669 (72.0)	−0.7 (−4.6; +3.2)	+1.4 (−1.9; +4.7)
Presenting location of acute venous thromboembolism			
Pulmonary embolism (with or without deep vein thrombosis)	1,548/3,874 (40.0)	+2.6 (+0.9; +4.2)	+1.4 (−0.04; +2.8)
Provoked event	1,324/3,874 (34.2)	+0.9 (−0.7; +2.5)	0.0 (−1.3; +1.4)
Previous venous thromboembolism	704/3,874 (18.2)	+0.5 (−1.4; +2.3)	+1.2 (−0.4; +2.8)
Active cancer	83/3,874 (2.1)	−3.4 (−8.4; +1.6)	−2.9 (−7.1; +1.2)
History of diabetes	396/3,874 (10.2)	−0.8 (−3.3; +1.6)	−0.6 (-2.7; +1.4)
History of chronic heart failure	84/3,874 (2.2)	−3.5 (−8.4; +1.5)	−4.2 (−8.4; +0.1)
History of pulmonary disease	628/3,874 (16.2)	−0.6 (−2.7; +1.4)	−0.9 (-2.7; +0.8)
Anaemia	947/3,874 (24.4)	−4.9 (−6.6; −3.2)	−3.7 (−5.1; −2.2)
History of hypertension	1,547/3,874 (39.9)	+0.6 (1.2; +2.3)	+0.7 (−0.8; +2.2)
Number of co-medications			
0–2	1,122/3,874 (28.9)	Reference	Reference
3–5	1,286/3,874 (33.2)	−0.5 (−2.5; +1.4)	−0.5 (−2.2; +1.1)
> 5	1,466/3,874 (37.8)	−0.8 (−3.1; +1.4)	−0.8 (−2.7; +1.2)
Anti-platelet use	1,194/3,874 (30.8)	−0.5 (−2.2; +1.2)	0 (−1.5; +1.5)
Statin use	484/3,874 (12.5)	+2.7 (+0.3; +5.0)	+3.0 (+1.0; +5.0)
Alcohol use (any amount)	1,314/3,874 (33.9)	+1.8 (+0.1; +3.5)	+0.5 (−0.9; +2.0)
Tobacco use	758/3,874 (19.6)	−3.9 (−5.8; −2.1)	−3.9 (−5.5; −2.3)
CrCl 30–50 mL/min, a body weight ≤60 kg or use of potent P-glycoprotein inhibitors	655/3,874 (16.9)	−2.9 (−5.3; −0.5)	−2.6 (−4.7; −0.5)

Abbreviations: BMI, body mass index; CI, confidence interval; CrCL, creatinine clearance; TTR, time in therapeutic range.
[a]Frequencies refer to subjects satisfying the criteria for inclusion in the primary analysis ($N = 3,874$; day 31–180).

Table 3 Clinical endpoints in patients stratified by TTR and classes of the SAMe-TT2-R2 score

	Group	*n*/*N* (%)	Crude hazard ratio (95% CI)	Absolute risk difference, Δ% (95% CI)
Time in therapeutic range (TTR)				
Recurrent VTE	TTR < 66%	20/1,914 (1.0)	2.02 (0.94–4.38)	0.5 (0.0, 1.1)
	TTR ≥ 66%	10/1,960 (0.5)	Reference	Reference
Clinically relevant bleeding	TTR < 66%	105/1,914 (5.5)	1.75 (1.28–2.38)	2.2 (0.9, 3.5)
	TTR ≥ 66%	64/1,960 (3.3)	Reference	Reference
Recurrent VTE or clinically relevant bleeding	TTR < 66%	123/1,914 (6.4)	1.76 (1.32–2.35)	2.7 (1.3; 4.1)
	TTR ≥ 66%	74/1,960 (3.8)	Reference	Reference
Dichotomized SAMe-TT2-R2 score				
Recurrent VTE	≥2 points	23/2,931 (0.8)	1.02 (0.42–2.49)	0.0 (–0.6, 0.7)
	0–1 points	7/943 (0.7)	Reference	Reference
Clinically relevant bleeding	≥2 points	137/2,931 (4.7)	1.34 (0.91–1.97)	1.3 (–0.1, 2.7)
	0–1 points	32/943 (3.4)	Reference	Reference
Recurrent VTE or clinically relevant bleeding	≥2 points	159/2,931 (5.4)	1.31 (0.91–1.87)	1.4 (–0.3; 2.8)
	0–1 points	38/943 (4.0)	Reference	Reference
Three-class SAMe-TT2-R2 score				
Recurrent VTE	≥3 points	18/2,010 (0.9)	1.16 (0.46–2.94)	0.2 (–0.5, 0.8)
	2 points	5/921 (0.5)	0.72 (0.22–2.32)	–0.2 (–0.9, 0.5)
	0–1 points	7/943 (0.7)	Reference	Reference
Clinically relevant bleeding	≥3 points	104/2,010 (5.2)	1.49 (1.00–2.23)	1.8 (0.3, 3.3)
	2 points	33/921 (3.6)	1.02 (0.63–1.66)	0.2 (–1.5, 1.9)
	0–1 points	32/943 (3.4)	Reference	Reference
Recurrent VTE or clinically relevant bleeding	≥3 points	121/2,010 (6.0)	1.46 (1.01–2.11)	2.0 (0.3; 3.6)
	2 points	38/921 (4.1)	0.99 (0.63–1.56)	0.1 (–1.7; 1.9)
	0–1 points	38/943 (4.0)	Reference	Reference

Abbreviations: CI, confidence interval; TTR, time in therapeutic range; VTE; venous thromboembolism.
Note: Clinical endpoints were accounted between day 31 and 180 from randomization. We calculated the SAMe-TT2-R2 score accounting for all potentially interfering co-medications.

occurred in 5.4 and 4.0% of patients (HR: 1.31; 95% CI: 0.91–1.87 and ARD: 1.4%; 95% CI: –0.3%; 2.8%), respectively (►**Table 3**). No relevant differences were observed by excluding the item 'treatment with interacting drugs' (►**Supplementary Table S5**, available in the online version).

When we considered the trichotomized score (0–1 vs. 2 vs. 3 points or more), patients with 3 points or more had a rate of recurrent VTE of 0.9% (HR: 1.16 for 3 vs. 0–1 points [95% CI: 0.46–2.94] and ARD: +0.2% [95% CI: –0.5%, +3.3%]). The rate of clinically relevant bleeding was 5.2% (HR: 1.49 for 3 vs. 0–1 points [95% CI: 1.00–2.23] and ARD: +1.8% [95% CI: +0.3, +3.3]), respectively (►**Table 3** and ►**Supplementary Table S5**, available in the online version).

Sensitivity Analysis for the Whole Study Period (Day 1–365)

In 3,984 patients with available INR measurements followed during the whole study period, the adjusted linear regression analysis did not lead to the identification of additional baseline factors associated with significant changes in TTR (►**Table 2**). We confirmed the association between low (< 66% vs. ≥66%) TTR and recurrent VTE (HR: 1.91; 95% CI: 1.12–3.25), clinical relevant bleeding (HR: 1.51; 95% CI: 1.23–1.86) and the composite outcome (HR: 1.54; 95% CI: 1.27–1.86).

Consistently with the primary analysis focusing on the period elapsing between day 31 and 180, the SAMe-TT2-R2 score showed poor discrimination (c-statistic: 0.58, irrespective of whether we accounted or not for all potentially interfering co-medications) and low predictive values for individual TTR (data not shown). High (≥2 points or ≥3 points vs. < 2 points) SAMe-TT2-R2 score was associated with clinically relevant bleeding, but showed a tendency for inverse association with recurrent VTE (►**Supplementary Table S6**, available in the online version).

Discussion

The TTR is an indirect, but arguably the best available, measure of the quality of VKA treatment and correlates well with the individual thrombotic and bleeding risk during

Table 4 SAMe-TT2R2 score predicting individual TTR in warfarin-treated patients

	Low SAMe-TT2-R2 score (0–1 points)	High SAMe-TT2-R2 score (≥2 points)
n (%)	943 (24.3)	2,931 (75.7)
Median TTR (IQR)[a]	70.7 (56.5–84.0)	64.7 (48.7–79.1)
Time above INR 3.0, median % (IQR)	10.7 (1.3–24.7)	9.5 (0.0–22.7)
Time below INR 2.0, median % (IQR)	12.4 (2.0–23.8)	18.1 (6.9–33.3)
Dependent variable: TTR < 66% (vs. TTR ≥66%)		
OR (95% CI)	Reference	1.55 (1.34–1.80)
c-Statistic (95% CI)	0.58 (0.56–0.60)	
Sensitivity for TTR < 66% (95% CI)[b]	0.80 (0.78–0.82)	
Specificity for TTR ≥66% (95% CI)[b]	0.28 (0.26–0.30)	
NPV (95% CI)[c]	0.59 (0.56–0.62)	
PPV (95% CI)[c]	0.52 (0.50–0.54)	
Dependent variable: TTR < 50% (vs. TTR ≥50%)		
OR (95% CI)	Reference	1.86 (1.54–2.26)
c-Statistic (95% CI)	0.59 (0.57–0.61)	
Sensitivity for TTR < 50% (95% CI)	0.84 (0.81–0.86)	
Specificity for TTR ≥50% (95% CI)	0.27 (0.25–0.29)	
NPV (95% CI)	0.84 (0.81–0.86)	
PPV (95% CI)	0.27 (0.25–0.28)	

Abbreviations: CI, confidence interval; INR, international normalized ratio; IQR, interquartile range; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; TTR, time in therapeutic range.

[a] $p < 0.0001$ (Wilcoxon two-sided non-parametric test).

[b] Indicating that 80% of patients with a TTR < 66% had a high SAMe-TT2-R2 score and that 28% of patients with a TTR ≥66% had a low SAMe-TT2-R2 score.

[c] Indicating that 59% of patients with a low SAMe-TT2-R2 score had a TTR ≥66% and that 52% of patients with a high SAMe-TT2-R2 score had a TTR < 66%.

anticoagulation.[7,18,19] The SAMe-TT2-R2 score can classify, among VKA-treated patients with atrial fibrillation, those in whom an adequate TTR (e.g. more than 65% of TTR) is likely to be achieved.[11,12] In 3,874 patients randomized to the warfarin arm of the Hokusai-VTE trial,[17] we confirmed the presence of an inverse correlation between TTR and clinical events in VTE patients, identified independent predictors of TTR and provided the largest validation of the SAME-TT2-R2 score. Our results suggest that a low score of less than 2 points could correctly identify patients with an 'adequate' TTR (above a certain threshold) only if this threshold was set very low (e.g. 50%). Moreover, its poor discrimination (c-statistic: 0.58), low predictive value for identifying patients who did not do well on VKA and only marginal correlation with clinical events suggest that the role of the SAMe-TT2-R2 score for identifying potential candidates to VKA therapy is limited in the VTE population.

In the warfarin arm of the Hokusai-VTE trial, TTR during stable anticoagulation after the first month from VTE diagnosis was good (median 66%, mean 64%). A meta-analysis of studies from the literature calculated a weighed mean of 60% for the same treatment period.[18] In our analysis, we identified several factors influencing TTR, most of which were already included in the SAMe-TT2-R2 score. In particular, the Afro-American or Asian ethnicity and tobacco use proved to be strong independent risk factors.[25–27] For ethnicity, it has been speculated that this is a consequence of genetic predisposition, socio-economic status or less experience in VKA monitoring. Furthermore, we identified a few factors significantly associated with poor TTR not included in the score, such as anaemia (which is a well-known risk factor for bleeding after VTE[20,21,28]), the PE presenting location of VTE and statin use.

The results of our analysis indicate (and confirm) that TTR inversely correlates with recurrent thromboembolic (ARD: +0.5% [95% CI: 0–1.1%]) and clinically relevant bleeding (ARD: +2.2% [95% CI: 0.9–3.5%]) events occurring during anticoagulation.[6,19] In particular, it appears that TTR had a greater impact on safety, particularly during the initial period, when the individualized VKA dose is less likely to be identified (►**Supplementary Fig. S1**, available in the online version). These results were confirmed in a sensitivity analysis focusing on the whole period of anticoagulation (day 1–365). It remains to be determined whether patients with low TTR would have had better outcomes under DOACs.

The dichotomized SAMe-TT2-R2 score exhibited poor NPV and PPV if the somehow standard TTR threshold of 66% was used. Moreover, the SAMe-TT2-R2 used as a continuous score had poorer discrimination (c-statistic: 0.58) when compared with the results of the derivation study by Apostolakis et al (0.72), irrespective of the time-frame considered (day 31–180 or day 1–365). Indeed, the c-statistic was similar to other external validation studies.[13,15,29,30] Such differences are not surprising, since the performance of risk prediction models in external validation studies is usually worse than in derivation cohorts.[31] This observation confirms the results of a recent meta-analysis of validation studies[32] and contributes to raise the question about the clinical role of the SAMe-TT2-R2 score, especially if one considers that 76% of patients were classified within the high SAMe-TT2-R2 class ($\geq$2 points). Moreover, since the score correlates with TTR, but not clearly with clinical events, it remains unclear whether its use may improve the management of patients with VTE. We also observed that patients with a high ($\geq$2 points or $\geq$3 points vs. $<$ 2 points) SAMe-TT2-R2 score had a higher risk of developing bleeding events, but somehow exhibited lower recurrence rate, suggesting that the sub-optimal TTR levels might have been due to fluctuations of INR above the therapeutic range.

We acknowledge that our study has limitations. First, this is a post hoc analysis: in Hokusai-VTE, the administration of warfarin was based on randomization, and not guided by the SAMe-TT2-R2 score: this prevents us from drawing firm conclusions regarding the predictive value of the score and its clinical usefulness. Only a management study can minimize the confounding by indication, for example, for the frequency of testing and VKA dose adjustment, and provide substantial evidence regarding the accuracy of the SAMe-TT2-R2 score. Moreover, the prevalence of some important predictors (i.e. non-white ethnicity, amiodarone use) was low and this could have led to an under-estimation of the prognostic value of SAMe-TT2-R2, at least as compared with the derivation cohort.[9] Future studies should investigate whether the threshold of the SAMe-TT2-R2 score needs to be modified in non-white populations or in VTE patients.[10] Indeed, the clinical utility of the score may be diminishing with the increasing use of DOACs, which are often prescribed independently from the quality of warfarin treatment expected at each site or in the individual patient. Finally, the assumption that patients with a poor TTR would do better with one of the DOACs than on VKA is purely speculative, since it implies both a causal association between TTR and clinical outcomes and a positive interaction with DOAC treatment.

In conclusion, TTR, but not the SAMe-TT2-R2 score, showed an inverse correlation with VTE recurrence and clinically relevant bleeding. The SAMe-TT2-R2 score showed unsatisfactory discrimination and predictive value for individual TTR: therefore, its routine use after VTE may not translate into clinical usefulness. Future adequately powered studies must investigate whether the recalibration of the score with other variables, such as the presenting location of acute VTE, anaemia on admission or statin use, would improve its predictive value.

What is known about this topic?

- Vitamin K antagonists (VKAs) are effective anticoagulants, but they require strict monitoring to ensure both efficacy and safety.
- The individual time in therapeutic range (TTR) measures the quality of VKA anticoagulation.
- TTR inversely correlates with the risk of thromboembolic and bleeding events during VKA anticoagulation.
- In patients with atrial fibrillation, the dichotomized SAMe-TT2-R2 score ($\geq$2 vs. $<$ 2 points) can predict if adequate TTR is unlikely to be achieved, but it has not been validated in large cohorts of patients with venous thromboembolism (VTE).

What does this paper add?

- In patients on chronic anticoagulation after acute VTE who were enrolled in the Hokusai-VTE trial, the individual time in therapeutic range (TTR) correlated with clinical outcomes.
- The SAMe-TT2-R2 score showed unsatisfactory discrimination and predictive value for individual TTR. Moreover, it did not correlate well with clinical outcomes.
- We identified additional clinical factors independently associated with TTR and not included in the SAMe-TT2-R2, such as anaemia, the presenting location of VTE and statin use.
- The routine use of the SAMe-TT2-R2 score in VTE patients may not translate into clinical usefulness. The present analysis may help to lead to an improved prediction of adverse outcomes in VKA-treated patients.

Authors' Contributions

Stefano Barco and Serena Granziera: concept and design of the study, interpretation of the results, writing of the manuscript and final approval. George Zhang and Min Lin: statistical analysis, interpretation of the results, critical revision of the manuscript and final approval. Michiel Coppens, Jonathan Douxfils, Mathilde Nijkeuter, Nicoletta Riva, Thomas Vanassche, Pieter W. Kamphuisen, Alexander T. Cohen and Jan Beyer-Westendorf: interpretation of the results, critical revision of the manuscript and final approval.

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Conflict of Interest

Stefano Barco has received congress and travel payments from Bayer HealthCare and Daiichi-Sankyo, lecture honoraria from BTG Interventional Medicine and financial support for the printing costs of his PhD thesis from Pfizer BV, CSL Behring bv, Sanquin Plasma Products, Boehringer Ingelheim bv, Aspen Netherlands and Bayer bv. Serena Granziera has received congress and travel payments from Daiichi-Sankyo, Bayer and Boehringer Ingelheim. Michiel Coppens reports grants from Boehringer Ingelheim, grants, personal fees, non-financial support and other from Bayer, grants, personal fees, non-financial support and other from Daiichi Sankyo, other from Pfizer, personal fees from Bristol Myers Squibb, other from Portola, personal fees and non-financial support from CSL Behring, personal fees from Aspen Pharma Group. J. Douxfils is CEO and founder of QUALIblood s.a. and reports personal fees from Stago and Daiichi-Sankyo. Mathilde Nijkeuter and Nicoletta Riva have no relevant disclosures. Thomas Vanassche has received speaker's fee and/or participated in advisory boards from Boehringer Ingelheim, Pfizer, Daiichi Sankyo and Bayer. George Zhang and Min Lin are employees of Daiichi-Sankyo Inc. Pieter W. Kamphuisen has received honoraria from LEO Pharma. Alexander Cohen reports grants and personal fees from BristolMyers Squibb and Pfizer Limited and personal fees from Boehringer Ingelheim, Johnson & Johnson, Portola, Sanofi Aventis, XO1, Janssen, Bayer HealthCare and grants from Daiichi Sankyo. Jan Beyer-Westendorf reports grants and personal fees from Bayer AG, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer and Portola

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References

1 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149(02):315–352
2 Sindet-Pedersen C, Pallisgaard JL, Staerk L, et al. Temporal trends in initiation of VKA, rivaroxaban, apixaban and dabigatran for the treatment of venous thromboembolism - a Danish nationwide cohort study. Sci Rep 2017;7(01):3347
3 Moustafa F, Pesavento R, di Micco P, et al; RIETE Investigators. Real-life use of anticoagulants in venous thromboembolism with a focus on patients with exclusion criteria for direct oral anticoagulants. Clin Pharmacol Ther 2018;103(04):684–691
4 Cohen AT, Gitt AK, Bauersachs R, et al. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. Thromb Haemost 2017;117 (07):1326–1337
5 Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016;3(01):e12–e21
6 Sandén P, Renlund H, Svensson PJ, Själander A. Bleeding complications and mortality in warfarin-treated VTE patients, dependence of INR variability and iTTR. Thromb Haemost 2017;117(01):27–32
7 Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. Br J Haematol 2005;128(04):513–519
8 Kooistra HA, Gebel M, Sahin K, Lensing AW, Meijer K. Independent predictors of poor vitamin K antagonist control in venous thromboembolism patients. Data from the EINSTEIN-DVT and PE studies. Thromb Haemost 2015;114(06):1136–1143
9 Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. Chest 2013;144 (05):1555–1563
10 Zulkifly H, Lip GYH, Lane DA. Use of the SAMe-TT_2R_2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists: a review. Heart Rhythm 2018;15(04):615–623
11 Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37 (38):2893–2962
12 De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis–Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013; 110(06):1087–1107
13 Palareti G, Antonucci E, Lip GY, et al; START-Register Participants. The SAME-TT2R2 score predicts the quality of anticoagulation control in patients with acute VTE. A real-life inception cohort study. Thromb Haemost 2016;115(06):1101–1108
14 Demelo-Rodríguez P, Postigo-Esteban A, García-Fernández-Bravo I, et al. Evaluation of the SAMe-TT2R2 score to predict the quality of anticoagulation control in a cohort of patients with venous thromboembolism treated with vitamin K antagonists. Thromb Res 2016;147:58–60
15 Kataruka A, Kong X, Haymart B, et al. SAMe-TT_2R_2 predicts quality of anticoagulation in patients with acute venous thromboembolism: the $MAQI^2$ experience. Vasc Med 2017;22(03):197–203
16 Raskob G, Büller H, Prins M, et al; Hokusai-VTE Investigators. Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study–methodological implications for clinical trials. J Thromb Haemost 2013;11(07):1287–1294
17 Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369(15):1406–1415
18 Erkens PM, ten Cate H, Büller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLoS One 2012;7(09):e42269
19 Connolly SJ, Pogue J, Eikelboom J, et al; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118(20):2029–2037
20 van Es N, Wells PS, Carrier M. Bleeding risk in patients with unprovoked venous thromboembolism: a critical appraisal of clinical prediction scores. Thromb Res 2017;152:52–60
21 Klok FA, Barco S, Turpie AGG, et al. Predictive value of venous thromboembolism (VTE)-BLEED to predict major bleeding and other

adverse events in a practice-based cohort of patients with VTE: results of the XALIA study. Br J Haematol 2018;183(03):457–465
22 Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69(03):236–239
23 Lip GYH, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAMe-TT_2R_2 score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest 2014;146(03):719–726
24 Poli D, Antonucci E, Testa S, Lip GY. A prospective validation of the SAME-TT2R 2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Intern Emerg Med 2014;9(04):443–447
25 Yong C, Azarbal F, Abnousi F, et al. Racial differences in quality of anticoagulation therapy for atrial fibrillation (from the TREAT-AF Study). Am J Cardiol 2016;117(01):61–68
26 Golwala H, Jackson LR II, Simon DN, et al; Outcomes Registry for Better Informed Treatment for Atrial Fibrillation (ORBIT-AF) Registry. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: insights from Outcomes Registry for Better Informed Treatment for Atrial Fibrillation Registry. Am Heart J 2016;174:29–36
27 Lip GY, Waldo AL, Ip J, et al; IMPACT Investigators. Determinants of time in therapeutic range in patients receiving oral anticoagulants (a substudy of IMPACT). Am J Cardiol 2016;118(11):1680–1684
28 Klok FA, Barco S, Konstantinides SV. External validation of the VTE-BLEED score for predicting major bleeding in stable anticoagulated patients with venous thromboembolism. Thromb Haemost 2017;117(06):1164–1170
29 Lobos-Bejarano JM, Barrios V, Polo-García J, et al; on behalf the PAULA Study Team. Evaluation of SAMe-TT2R2 score and other clinical factors influencing the quality of anticoagulation therapy in non-valvular atrial fibrillation: a nationwide study in Spain. Curr Med Res Opin 2016;32(07):1201–1207
30 Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, et al. Evaluation of SAMe-TT2R2 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. Europace 2015;17(05):711–717
31 Siontis GC, Tzoulaki I, Castaldi PJ, Ioannidis JP. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol 2015;68(01):25–34
32 van Miert JHA, Bos S, Veeger NJGM, Meijer K. Clinical usefulness of the SAMe-TT2R2 score: a systematic review and simulation meta-analysis. PLoS One 2018;13(03):e0194208