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# Relation of the SAMe-TT<sub>2</sub>R<sub>2</sub> score to quality of anticoagulation control and thromboembolic events in atrial fibrillation patients: Observations from the SPORTIF trials

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### Accepted Manuscript

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### Relation of the SAMe- $TT_2R_2$ Score to Quality of Anticoagulation Control and

#### Thromboembolic Events in Atrial Fibrillation Patients: Observations from the SPORTIF Trials

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#### Abstract

**Background:** Oral anticoagulant therapy is central to the prevention thromboembolic events in atrial fibrillation (AF) patients. The SAMe-TT<sub>2</sub>R<sub>2</sub> score is a simple clinical-derived score designed to aid decision-making on whether or not a patient is likely to achieve good anticoagulation control on Vitamin K Antagonists (VKA, *e.g.* warfarin). Good anticoagulation control is associated with optimal VKA efficacy and safety.

**Methods:** The SAMe- $TT_2R_2$  score was studied in a large cohort of warfarin-treated non-valvular AF patients from the SPORTIF trials, and related to Time in therapeutic range (TTR) as measure of anticoagulation control, and thromboembolism-related outcomes.

**Results:** Among the 3,665 patients originally assigned to the warfarin arm, a SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 was found in 19.5%. In these patients, a linear relationship was reported between SAMe-TT<sub>2</sub>R<sub>2</sub> score and TTR (p<0.001). SAMe-TT<sub>2</sub>R<sub>2</sub> >2 was inversely associated with a higher proportion with TTR >65% (p=0.014) or TTR >70% (p=0.011).

Patients with SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 had a significantly higher event rate of the composite thromboembolism-related outcome, vs SAMe-TT<sub>2</sub>R<sub>2</sub> 0-2 (10.2% vs. 7.9%, p=0.045). On survival analysis, SAMe-TT<sub>2</sub>R<sub>2</sub> >2 was associated with a higher risk for the composite outcome (Log-Rank: 5.471, p=0.019). On Cox regression, a SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 was independently associated with the composite outcome (p=0.020).

**Conclusions:** In this large trial cohort of AF patients, the SAMe-TT<sub>2</sub>R<sub>2</sub> score was able to identify patients more likely to obtain suboptimal anticoagulation control on VKA, with an increase in major thromboembolism-related adverse events consequent upon such poor anticoagulation control.

Key words: atrial fibrillation, anticoagulation control, warfarin

#### Introduction

Oral anticoagulation (OAC) is central to the prevention thromboembolic events in patients with atrial fibrillation (AF)[1]. Despite the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs)[2], many patients worldwide are still treated with the Vitamin K antagonists (VKA, *e.g.* warfarin) for stroke prevention[3,4].

When treating AF patients with VKA, it is important to achieve good anticoagulation control, often quantified as the average time in therapeutic range (TTR) between INR 2.0-3.0[5,6]. TTR is closely related to efficacy and safety of the VKAs. Thus, the National Institute for Health and Care Excellence (NICE) guidelines recommended a TTR level higher than 65% of the total treatment time[7], whereas the European Society of Cardiology advises a TTR higher than 70%[1,8]. Poor anticoagulation control while treated with VKA is one consideration, when considering to switch from VKA treatment to using a NOAC[9].

When starting a newly diagnosed non-anticoagulated AF patient on a VKA, it would be helpful to identify those who are likely to achieve good anticoagulation control if prescribed VKA, whilst those less likely to obtain an optimal TTR could be targeted for more regular follow-up and monitoring, education or use of a NOAC rather than VKA[9,10]. This would avoid a policy of having a 'trial of warfarin' for everyone over 6-9 months, during which those with suboptimal TTR on VKA would be at risk of thromboembolism and bleeding[11,12].

Many common clinical factors are associated with the likelihood of achieving a good TTR on a VKA[13]. By using these common clinical factors to help guide the decision-making process, a simple clinical-based tool was developed, the SAMe-TT<sub>2</sub>R<sub>2</sub> score[13,14]. Patients with SAMe-TT<sub>2</sub>R<sub>2</sub>

>2 are less likely to achieve an optimal TTR level, *i.e.* higher than 65%[13]. Since its original validation, the SAMe-TT<sub>2</sub>R<sub>2</sub> score has been independently validated in several retrospective and prospective cohorts, being able to discriminate those patients likely to do well on VKA treatment, in both AF and venous thromboembolism patients[12,15–21]. Importantly, the SAMe-TT<sub>2</sub>R<sub>2</sub> score was found to be able to identify those at higher risk of adverse outcomes in various VKA-treated 'real world' observational cohorts[12,16,18].

The aims to this study was first, to evaluate the baseline SAMe-TT<sub>2</sub>R<sub>2</sub> score in a large cohort of warfarin-treated non-valvular AF patients from a high-quality, well-conducted multicentre international randomized clinical trial (RCT) population. Second, we evaluated the predictive value of SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 for TTR, independent from prior VKA therapy use. Third, we assessed the adverse outcomes related to high SAMe-TT<sub>2</sub>R<sub>2</sub> score (and thus, poor TTR), *i.e.* clinically relevant major thromboembolic adverse events,

#### Methods

For the present study, we analysed the pooled datasets from the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V studies[22–24]. The SPORTIF trials were two multicentre global phase III clinical trials comparing the efficacy and safety of the direct thrombin inhibitor, ximelagatran, against warfarin in patients with non-valvular AF. SPORTIF III was an open label trial, while SPORTIF V was a double blind study[22]. In the purposes of this study, we only considered the patients assigned to the warfarin arm, as the development of ximelagatran has been discontinued and thus, the results less relevant for clinical practice.

The SAMe-TT<sub>2</sub>R<sub>2</sub> score was calculated (as was previously defined[13]): one point was assigned for female sex; age below 60 years; at least two comorbidities in the previous medical history; and treatment with VKA-interacting drugs; whilst two points were given for current smoking habit and non-Caucasian race. The study population was divided in two categories: (i) patients with SAMe-TT<sub>2</sub>R<sub>2</sub> 0-2, who were likely to do well on warfarin; and (ii) patients with SAMe-TT<sub>2</sub>R<sub>2</sub>>2, who were less likely to achieve good anticoagulation control.

Thromboembolic risk was categorised according to  $CHA_2DS_2$ -VASc scores[25]. "Low risk" patients were defined as males with a  $CHA_2DS_2$ -VASc =0 or females with  $CHA_2DS_2$ -VASc =1; "moderate risk" was defined as male patients with  $CHA_2DS_2$ -VASc=1; and "high risk" with  $CHA_2DS_2$ -VASc  $\geq 2$ .

Anticoagulation control, as reflected by the TTR was calculated using the standardized Rosendaal interpolation method[5], by assigning an INR value to each day between two successive observed INR values, and the percentage of time that the interpolated INR remains between 2 and 3 was used to establish TTR value. In order to verify predictive abilities of SAMe-TT<sub>2</sub>R<sub>2</sub> on different TTR levels, we established three different cut-off points (TTR > 60%, TTR > 65% and TTR > 70%) as sensitivity analyses.

#### Study Outcomes in Warfarin-Treated Patients

Major outcomes were defined according to the original trial protocol, and *independently adjudicated* by an events committee blinded to the trial treatment assignment[22]. To evaluate if SAMe-TT<sub>2</sub>R<sub>2</sub> could identify patients at higher risk for the major adverse events related to poor TTR, a composite outcome of thromboembolism-related complications, that is 'stroke/systemic

embolic event (SEE)/myocardial infarction (MI)/all-cause death' was considered. The relation to major bleeding, as defined according to trial study protocol were also investigated [22].

#### Statistical Analysis

Non-normally distributed variables were expressed as median and interquartile range (IQR) and differences tested using the Mann-Whitney U test. Categorical variables, expressed as counts and percentages, were analysed by chi-squared test. A linear regression analysis between SAMe-TT<sub>2</sub>R<sub>2</sub> and TTR, adjusted for type of AF and previous VKA use, was performed. Moreover, a logistic regression analysis, adjusted for type of AF and previous VKA use, was performed to establish the predictive ability of SAMe-TT<sub>2</sub>R<sub>2</sub> for TTR cut-offs, based on SAMe-TT<sub>2</sub>R<sub>2</sub> as a continuous variable and SAMe-TT<sub>2</sub>R<sub>2</sub> categories (0-2, >2).

A Log-Rank test was performed for SAMe-TT<sub>2</sub>R<sub>2</sub> as a continuous variable and SAMe-TT<sub>2</sub>R<sub>2</sub> categories, and the differences in survival between subgroups were reported as Kaplan-Meier curves. A forward stepwise Cox proportional hazards model, adjusted for type of AF and previous VKA use, according both to SAMe-TT<sub>2</sub>R<sub>2</sub> as a continuous variable and SAMe-TT<sub>2</sub>R<sub>2</sub> categories was performed. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

#### Results

From the original study cohort of 7,329 patients, 3,665 (50.0%) were assigned to the warfarin treatment group. Median age was 72 [IQR 66-77] years, and 1,116 (30.5%) were female. From the warfarin treated arm, 715 patients (19.5%) were categorized as SAMe-TT<sub>2</sub>R<sub>2</sub> >2, with those with SAMe-TT<sub>2</sub>R<sub>2</sub> score= 1 being the most prevalent subgroup [Figure 1].

Baseline characteristics of patients according to SAMe-TT<sub>2</sub>R<sub>2</sub> categories are reported in Table 1. Patients with SAMe-TT<sub>2</sub>R<sub>2</sub> >2 were younger, more commonly female, smokers and diagnosed with hypertension and diabetes mellitus (all p<0.001). Moreover, patients with SAMe-TT<sub>2</sub>R<sub>2</sub> >2 had a higher prevalence of coronary heart disease (CHD), chronic heart failure (CHF) [both p<0.001] and previous stroke or transient ischemic attack (TIA) (p=0.030).

### SAMe-TT<sub>2</sub>R<sub>2</sub> and TTR Levels

TTR was available for 3,624 (98.9%) patients, with median TTR being 68.50% [IQR 55.17-79.32]. TTR values progressively decreased with increasing SAMe-TT<sub>2</sub>R<sub>2</sub> score points (p=0.002) [Table 2]. Patients with SAMe-TT<sub>2</sub>R<sub>2</sub> >2 had a significantly lower median TTR value compared to patients with SAMe-TT<sub>2</sub>R<sub>2</sub> 0-2 (p=0.001) [Table 2].

There was a lower proportion of patients with SAMe-TT<sub>2</sub>R<sub>2</sub> >2 with a TTR >65% and TTR >70% (p=0.014 and p=0.011, respectively), compared to those with SAMe-TT<sub>2</sub>R<sub>2</sub> 0-2 [Figure 2]. A numerical difference between patients with SAMe-TT<sub>2</sub>R<sub>2</sub> 0-2 and SAMe-TT<sub>2</sub>R<sub>2</sub> >2 was found for TTR >60%, of borderline significance (p=0.061).

#### Regression Analyses for SAMe-TT<sub>2</sub>R<sub>2</sub> score and TTR

Linear regression analysis shows that SAMe-TT<sub>2</sub>R<sub>2</sub> was inversely associated with TTR (standardized beta: -0.073, t: -4.470; p<0.001) with an associated linear relationship between SAMe-TT<sub>2</sub>R<sub>2</sub> and TTR. Logistic regression analysis, adjusted for type of AF and previous VKA use, between SAMe-TT<sub>2</sub>R<sub>2</sub> categories and TTR cut-off points [Table 3] found that SAMe-TT<sub>2</sub>R<sub>2</sub> as a continuous variable was inversely associated with all TTR cut-off points (p=0.003, p=0.001 and p=0.001, respectively for TTR >60%, TTR >65% and TTR >70%). Using SAMe-TT<sub>2</sub>R<sub>2</sub> categories, a SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 was inversely associated with TTR >65% and TTR >70% (p=0.014 and p=0.011, respectively).

#### Survival Analysis

After a median follow-up of 563 [IQR 483-651] days, there were a total of 306 (8.3%) events for the composite outcome. Patients with SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 had a significantly higher event rate of the composite outcome, compared to those with SAMe-TT<sub>2</sub>R<sub>2</sub> score 0-2 (10.2% vs. 7.9%, p=0.045). On survival analysis, patients with SAMe-TT<sub>2</sub>R<sub>2</sub> >2 had a significantly higher risk for the occurrence of the composite outcome (Log-Rank: 5.471, p=0.019).

No significant difference was found in event rate for major bleeding was detected for patients with SAMe-TT<sub>2</sub>R<sub>2</sub> score 0-2 and those with score >2 (3.5% vs. 3.5%, p=0.970).

On Cox multivariate regression analysis, adjusted for type of AF and previous VKA use, found that SAMe-TT<sub>2</sub>R<sub>2</sub> score as a continuous variable was significantly associated with the composite outcome (hazard ratio [HR]: 1.14, 95% confidence interval [CI]: 1.04-1.26; p=0.005). Similarly, the SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 category was also significantly associated with the composite outcome (HR: 1.37, 95% CI: 1.05-1.78; p=0.020).

#### Discussion

In this large trial cohort of non-valvular AF patients, almost 20% of had a SAMe-TT<sub>2</sub>R<sub>2</sub> score >2 at baseline and therefore, were predicted to be less likely to achieve good anticoagulation control. Indeed, our second principal finding was that a SAMe-TT<sub>2</sub>R<sub>2</sub> >2 was significantly associated with poor anticoagulation control, as reflected by a TTR <65% or TTR <70%. Third, a high SAMe-TT<sub>2</sub>R<sub>2</sub> score, both as a continuous and categorical variable, was significantly associated with adverse outcomes related to poor TTR (*i.e.* clinically relevant major thromboembolic adverse events), but not with higher major bleeding rates.

Data on the distribution of the SAMe- $TT_2R_2$  score in an AF population has varied in different studies[12,15–19]. The proportion of SAMe- $TT_2R_2$  >2 ranges from 7% to 45% in prior studies, but was 19.5% in the present cohort, perhaps related to the SPORTIF trial protocol which enrolled AF patients at moderate-high stroke risk.

The ability of the SAMe-TT<sub>2</sub>R<sub>2</sub> scores in predicting TTR values has been validated in various retrospective and prospective cohorts[12,13,15–19]. In the original validation paper, for example, the SAMe-TT<sub>2</sub>R<sub>2</sub> score reported good discriminatory ability in identifying patients with the lowest TTR percentile[13]. The SAMe-TT<sub>2</sub>R<sub>2</sub> score has also been significantly associated with other measures of anticoagulation control, including the proportion of INRs in Range (PINRR) >70%[18] and other similar methods (*e.g.* INR variability, time above range)[19]. Our results underline the predictive value of SAMe-TT<sub>2</sub>R<sub>2</sub> in identifying those patients with the lowest TTR values, given the clear linear relationship with the continuous SAMe-TT<sub>2</sub>R<sub>2</sub> score point values and progressively higher TTR. The predictive value of SAMe-TT<sub>2</sub>R<sub>2</sub> was independent of patients' prior VKA use.

More recently, another large observational study in a primary care setting from Spain found that the SAMe-TT<sub>2</sub>R<sub>2</sub> score was able to significantly predict TTR levels although the discriminatory ability was modest, and given the retrospective design of the study, this should be interpreted cautiously [26]. Moreover, the study cohort was part of a study investigating anticoagulation control in non-valvular AF, so patients were well controlled and TTR assessed intensively [26]. Another hospital-based registry study in Hong Kong Chinese reported for the very first time that SAMe-TT<sub>2</sub>R<sub>2</sub> was effective in identifying Asian AF patients who were less likely to perform well on VKAs [27]. I The SAMe-TT<sub>2</sub>R<sub>2</sub> score was also able to predict TTR levels in patients with venous thromboembolism who are initiated on VKA therapy [21].

As far as we are aware, the predictive ability of SAMe-TT<sub>2</sub>R<sub>2</sub> has only been reported in several moderate-sized 'real world' cohorts[12,16,18]. In a large observational cohort of non-valvular AF patients, a SAMe-TT<sub>2</sub>R<sub>2</sub> >2 was predictive of labile INR, as the associated sequelae such as thromboembolism, bleeding and death[12]. Abumuaileq et al. reported that SAMe-TT<sub>2</sub>R<sub>2</sub> was associated with the composite outcome of thromboembolic events, all-cause death and major bleeding (HR: 1.32, p=0.006) and all-cause death (HR: 1.3). Thromboembolic events alone were not significantly increased (HR: 1.01, p=0.90), given the low number of events recorded (1.6% of patients)[18]. Similarly, Gallego et al. reported that SAMe-TT<sub>2</sub>R<sub>2</sub> was associate outcome of all adverse cardiovascular events (p<0.001) and all-cause death (p=0.001)[16]. In the Asian cohort discussed above, patients with a high SAMe-TT<sub>2</sub>R<sub>2</sub> score (hence, more likely to have poor TTR) were at higher risk for incident ischemic stroke [27]. Our data reinforce the concept that SAMe-TT<sub>2</sub>R<sub>2</sub> is useful in predicting a clinically relevant composite outcomes for AF patients. Previously reported data about predictive value of SAMe-TT<sub>2</sub>R<sub>2</sub> for major adverse events

have been reported in VKA-naïve cohorts, different from our cohort which included 21.0% who had prior VKA use.

Use of the SAMe-TT<sub>2</sub>R<sub>2</sub> score may help decision making when deciding on OAC therapy for stroke prevention in AF[10]. Patients with a SAMe-TT<sub>2</sub>R<sub>2</sub> score 0-2 would identify patients likely to achieve good anticoagulation control, whilst those with a score >2 would predict those patients less likely to achieve good TTR and would help clinicians target these patients for more careful follow-up reviews and more intensive education and counselling about VKA therapy, or conversely, prescription of a NOAC (rather than impose a 'trial of warfarin', which may put the patient at risk of thromboembolism due to suboptimal TTR)[6]. Our results also underline how calculation of the simple SAMe-TT<sub>2</sub>R<sub>2</sub> score could help clinicians personalize the optimal approach to using OAC therapy[9]. This is highly relevant since VKA remains the most widely used OAC worldwide, or some healthcare systems still mandate a 'trial of warfarin' for 6-9 months before a NOAC can be prescribed, usually for cost reasons. Thus, the SAMe-TT<sub>2</sub>R<sub>2</sub> score may potentially aid clinical decision making for stroke prevention in AF, and prospective clinical trials testing such a strategy are needed.

#### Limitations and future directions

The main limitation is the post-hoc nature of this study, and the study was not specifically powered to detect differences according to individual SAMe- $TT_2R_2$  points. Since the original trials were run between 2000 and 2002, current clinical practice in managing AF patients could have changed, with implications for the generalizability of our results. Further studies are needed to investigate if a SAMe- $TT_2R_2$  stratified management approach would improve adherence to

treatment and prediction of outcomes in an adequately powered long-term follow-up study of non-valvular AF patients.

#### Conclusions

In this large trial cohort of non-valvular AF patients, the SAMe- $TT_2R_2$  score was able to identify patients more likely to obtain suboptimal anticoagulation control on VKA with an increase in major thromboembolism-related adverse events consequent upon such poor anticoagulation control.

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#### **DISCLOSURES OF INTEREST**

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	SAMe-TT <sub>2</sub> R <sub>2</sub> 0-2	SAMe-TT <sub>2</sub> R <sub>2</sub> >2	р
	N=2,950	N=715	
Age, years median [IQR]	73 [67-78]	68 [59-75]	<0.001
Females, n (%)	787 (26.7)	329 (46.0)	<0.001
BMI, median [IQR]	28.1 [25.2-31.6]	27.7 [24.3-32.5]	0.263
Type of Atrial Fibrillation 3,663	S		0.599
Paroxysmal, n (%)	321 (10.9)	73 (10.2)	
Chronic, n (%)	2,627 (89.1)	642 (89.8)	
Hypertension, n (%)	2,214 (75.1)	598 (83.6)	<0.001
Diabetes, n (%)	600 (20.3)	260 (36.4)	<0.001
Smoking Habit, n (%)	52 (1.8)	282 (39.4)	<0.001
Coronary Heart Disease, n (%)	1,241 (42.1)	378 (52.9)	<0.001
Chronic Heart Failure, n (%)	1,017 (34.5)	355 (49.7)	<0.001
Previous Stroke/TIA, n (%)	585 (19.8)	168 (23.5)	0.030
Previous Bleeding, n (%)	176 (6.0)	32 (4.5)	0.124
<b>Aspirin Use</b> , <i>n</i> (%) 3,662	565 (19.2)	161 (22.5)	0.042
Previous VKA Use, n (%)	2,335 (79.2)	561 (78.5)	0.684
Thromboembolic Risk			0.053
Low Risk, n (%)	9 (0.3)	0 (0.0)	
Moderate Risk, n (%)	369 (12.5)	109 (15.2)	
High Risk, n (%)	2,572 (87.2)	606 (84.8)	

### $\label{eq:table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_table_$

Legend: BMI= body mass index; IQR= Intequartile Range, TIA= Transient Ischemic Attack.

		N (%)	TTR	р	
			Median [IQR]		
SAMe-TT <sub>2</sub> R <sub>2</sub>			Q	0.002	
	0	547 (15.1)	70.36 [59.39-81.54]		
	1	1,228 (33.9)	69.03 [55.07-80.01]		
	2	1,139 (31.4)	68.31 [55.00-79.08]		
	3	463 (12.8)	67.01 [52.50-77.49]		
	4	80 (5.0)	66.91 [54.04-77.73]		
	5-7	67 (1.8)	63.82 [48.56-76.97]		
SAMe-TT <sub>2</sub> R <sub>2</sub> Category				0.001	
	0-2	2,914 (80.4)	69.05 [55.63-79.89]		
	>2	710 (19.6)	66.55 [52.83-77.46]		
Legend: IOR- Interguartile Range: TTR- Time in Therapeutic Range					

### Table 2: TTR Values According to SAMe-TT2R2

Legend: IQR= Interquartile Range; TTR= Time in Therapeutic Range.

**Table 3:** Logistic Regression Analysis\* of SAMe-TT<sub>2</sub>R<sub>2</sub> score to TTR Cut-Off Points

		TTR >60%			°R >65%		TTR >70%		
	OR	95% CI	p	OR S	95% CI p	OR	95% CI	p	
SAMe-TT <sub>2</sub> R <sub>2</sub> (as per point)	0.91	0.86-0.97	0.003	0.91 0.	86-0.96 0.00	1 0.91	0.86-0.96	0.001	
SAMe-TT <sub>2</sub> R <sub>2</sub> >2	0.85	0.71-1.01	0.060	0.81 0.	69-0.96 0.01	4 0.81	0.68-0.95	0.011	

**Legend:** TTR= Time in Therapeutic Range; \*adjusted for type of atrial fibrillation and previous vitamin K antagonist use.

ted for type of atrial norm

#### **FIGURE LEGENDS**

**Figure 1:** Distribution of Patients According to SAMe-TT<sub>2</sub>R<sub>2</sub>

**Figure 2:** TTR Levels According to SAMe-TT<sub>2</sub>R<sub>2</sub> Categories

Legend: TTR= Time in Therapeutic Range.

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