Use of the SAMe-TT_2R_2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients treated with vitamin K antagonists: A review

Running head: The SAMe-TT_2R_2 score: a review

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Abstract

Identifying patients who are likely to achieve and maintain a therapeutic INR when prescribed a vitamin K antagonist (VKA) for stroke prevention in atrial fibrillation (AF) and venous thromboembolism (VTE) is challenging. The SAMe-TT_2R_2 score was developed based on common clinical factors that can highlight patients who may be unable to achieve and maintain good anticoagulation control and for whom a 'trial of warfarin' would be inadvisable. This review summarises the main published prospective and retrospective studies that have validated the SAMe-TT_2R_2 score in AF and VTE patients treated with a VKA and how the SAMe-TT_2R_2 score could aid clinical decision-making; 19 studies were included. Taken together validation studies suggest that the SAMe-TT_2R_2 score is able to predict good or poor anticoagulation control among AF and VTE patients, although data on VTE patients are limited (3 studies). The available evidence suggests that the SAMe-TT_2R_2 score may be a useful tool to aid clinical decision-making for oral anticoagulants (OAC) in AF and VTE patients.

Keywords: SAMe-TT_2R_2 score; atrial fibrillation; venous thromboembolism; vitamin K antagonist; decision-making; oral anticoagulation

Introduction

For decades, vitamin K antagonists (VKA, e.g., warfarin) have been the cornerstone of stroke prevention in atrial fibrillation (AF) and prevention of venous thromboembolism (VTE).[1] However, VKA efficacy and safety requires achievement of an international normalised ratio (INR) between 2.0-3.0. Achieving this target INR alone is an inadequate measure of the therapeutic efficacy of VKA.[1]

Time in therapeutic range (TTR) is one measure that summarises INR control over time. TTR is an important and independent predictor of thromboembolic and bleeding outcomes in AF patients on VKA.[2, 3] An average individual TTR≥65% is recommended by NICE guidelines,[1] while European guidelines[4] recommend TTR≥70% to maximize effectiveness and safety of VKAs.

However, identifying patients who are likely to achieve and maintain a therapeutic INR is more difficult. Based on common clinical factors that influence INR and anticoagulation control in everyday clinical practice, a clinical scoring system, the SAMe-TT_2R_2 score[5] (**Table 1**) was developed in 2013 to identify risk factors highlighting those patients who may be unable to achieve/maintain good anticoagulation control and for whom a 'trial of warfarin' would be inadvisable. The frequency of INR measurements are not factored-in (or intended to be). This score assigns 1 point each to female sex, age <60 years, history of ≥2 co-morbidities (hypertension, diabetes mellitus, coronary artery disease or myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease) and treatment with drugs interacting with VKA (e.g., amiodarone) and 2 points each for current/recent tobacco use (within 2-years) and non-white ethnicity[5] **(Table 1)**. The score can be used to aid decision-making by identifying those patients who would probably do well on VKA (achieving a high TTR, ≥65%) or conversely, those would need additional interventions to achieve good INR control or to be started on/switched to a non-VKA oral anticoagulant (NOAC). The current review summarises studies which have assessed and/or validated the SAMe-TT_2R_2 score in patients treated with VKA for AF or VTE.

Methods

A comprehensive structured literature search was performed using MEDLINE and EMBASE from 2013 until February 2017; the SAMe-TT_2R_2 score was first published in 2013. The search strategy included keywords and MeSH terms relating to AF, deep vein thrombosis, VTE, stroke prevention, warfarin, VKAs, oral anticoagulant, inception cohort, adverse effect, poor control, INR and SAMe-TT_2R_2 score (without MeSH term) individually and in combination. Primary published research articles and abstracts on prospective or retrospective studies validating the SAMe-TT_2R_2 score were included. Studies that did not provide comparative outcomes, information on follow-up time, or were not published in English language were excluded. Manual search of citations was also performed, and discussion with content experts was undertaken to identify any other relevant studies **(Figure 1**).

Results

Searches identified 166 citations. After removal of duplicates and screening of titles and abstracts, 24 full-text articles were assessed for eligibility and 19 studies were included (**see Figure 1**). Current studies assessing the SAMe-TT_2R_2 score are summarised in **Table 2** and baseline patient characteristics of these cohorts in **Table 3**. With the exception of three[6-8] all were performed in AF patients.[2,5,9-22] Most studies (n=11)[5-7,11,14,17,19-22] were performed prospectively, with follow-up duration ranging from six-months[17] to 4.7 years.[15] The number of participants included in VTE cohorts ranged from 135[6] to 1943[8] and between 104[14] to 8120[21] in studies on AF patients.

Fourteen studies were performed in European populations,[5-7,9-12,14,17-22] two in Asian populations,[15, 16](with one reporting a target INR 2.0-3.0[15]) and two in North American populations.[8, 13] Proietti et al[11] studied a mixed indication clinical trial cohort including patients from Europe, Asia and Australasia.

Most studies were performed in elderly (mean/median age ranging from 61-76 years) white-Western populations, mainly using warfarin (13 studies)[5-11,13,15,16,19-21] as the OAC of choice. Most patients had multiple comorbidities with hypertension the most common, except for the study by Lip et al[21] where congestive heart failure was most prevalent. All studies reported a low prevalence of

smoking status and use of amiodarone for rhythm-control, with the exception of the original derivation study; 35% of patients used amiodarone.[21] As the SAMe-TT_2R_2 score categories increase, the mean TTR of their study population decreases, except for one study by Domelo-Rodriguez[6] which showed the opposite relationship (Figure 2).

Five studies[8,12,13,15,18] investigated the relationship between components included in the SAMe-TT_2R_2 score and TTR. Three studies[12,13,18] showed that female sex was associated with poor anticoagulation control; one[18] showed that having ≥2 comorbidities was related to poor TTR and one[13] showed that black ethnicity (as well as NYHA IV) was associated with poorer anticoagulation control. Chan et al[15] also reported that having heart failure and diabetes mellitus independently predicts poor anticoagulation control.

Eight studies[2,5,7-9,12,18, 21] reported the predictive ability of the SAMe-TT_2R_2 score using c-statistics **(Figure 3)**. Taken together these validation studies suggest that the SAMe-TT_2R_2 score is able to predict good or poor anticoagulation control among AF patients better than chance, with c-statistics ranging from 0.56[12] to 0.72;[5] the evidence is less robust in VTE patients (c-statistic 0.52-0.65).[7,8]

Eight studies[11,15,18,20-22] also examined if the SAMe-TT_2R_2 score could discriminate AF patients with clinical events. Five[11,15,18,21,22] demonstrated some positive associations for SAMe-TT_2R_2 score predicting clinical events, with c-statistics ranging from 0.55[21] to 0.62[22] (**Table 4**). Another study,[8] also examined if the SAMe-TT_2R_2 score was associated with clinical outcomes, in particular recurrent VTE and International Society on Thrombosis and Haemostasis (ISTH) major bleeding rates in a VTE cohort; patients with a score>2 had more overall adverse event rates (composite of recurrent VTE and ISTH major bleeding) than those with a score of 0-2 (7.9 vs. 4.5 overall adverse event rates/100 patient-years respectively).[8]

Discussion

This review of studies assessing and validating the SAMe-TT_2R_2 score extends and updates a previous narrative review[23] with the addition of validation studies in VTE populations[6, 7] and validations in Asian AF populations.[15,16] Overall, eight studies[2,5,7-9,12,18,21] suggest that the SAMe-TT_2R_2 score is able

to modestly predict quality of anticoagulation control in AF patients receiving VKA therapy, with c-statistics ranging from 0.56[12] to 0.72.[5] Many risk scores based on clinical factors such as $CHADS_2$, CHA_2DS_2-VASc, Killip and TIMI scores show broadly similar modest c-indexes (approx. 0.6) when used to predict patients categorised at 'high risk' who actually sustain clinical events.[24,25]

The original purpose of developing the SAMe-TT_2R_2 score was to produce a simple clinical schema which could be used routinely in everyday practice to help assess the likelihood of an AF patient being able to achieve and maintain good anticoagulation control on VKA therapy, using patient-related clinical parameters which are readily available. The availability of NOACs worldwide has resulted in increased usage due to their advantages. These include faster onset-of-action (average maximum effect approximately three hours after intake[26] compared to VKA (onset 36-72 hours)), greater reduction in stroke/systemic embolism (+19% compared to VKA[4]), avoidance of INR monitoring with NOACs,[27] and absence of achieving/maintaining adequate TTR (as with warfarin). Achieving a therapeutic INR can take 2-4 weeks and often longer.[3]After termination of study drug in the NOAC trials, of those patients switching to warfarin, <40% achieved a therapeutic INR within 15 days, and <80% after 30 days;[28] more strokes occurred during that period in the patients who went from study drug to VKA than from VKA to VKA.[28,29] This strongly argues for using NOACs over VKAs where possible, however, VKAs are still widely used globally and will not disappear from use especially for AF patients with severe renal impairment, moderate to severe mitral stenosis or mechanical heart valves.[4]

In addition, in low- and middle-income countries where cost plays an important role in options available for OAC treatment VKA is still the first-line antithrombotic agent of choice, therefore the SAMe-TT_2R_2 score will remain an important decision-making tool, currently and in the future, to guide physicians choice of anticoagulant treatment.[30] Most validation studies included in this review demonstrated good predictive ability except two[6,19] which demonstrate that the SAME-TT_2R_2 score was unable to predict anticoagulation control well in their populations. Although both studies were prospective, results should be interpreted with care as both included small numbers of participants (135[6] and 180[19] respectively) and thus may not be adequately powered to test the predictive ability of the SAMe-TT_2R_2 score in regard to anticoagulation control.

Importance of good anticoagulation control

Achieving good anticoagulation control (TTR≥65-70%) as recommended by guidelines[1,4] is essential for managing AF and VTE patients treated with VKA. Numerous studies have demonstrated that a high TTR translates into lower risk of stroke and bleeding.[31-35] A systematic review demonstrated that a 7% and 12% improvement in TTR can lead to a reduction in major bleeding and thromboembolic events, respectively, by 1 event per 100 patient years.[34] A real-world study[32] of 27,458 warfarin-treated AF patients (≥3 INR measurements), showed that in patients with good anticoagulation control (TTR ≥70%), stroke risk was reduced to 79% compared to patients with poor INR control (TTR ≤30%). However, achieving and maintaining a therapeutic INR can be difficult to accomplish and therefore, NOACs are preferred to VKA in the majority of patients requiring OAC initiation.[4]

SAMe-TT_2R_2 score and clinical events

Evident in most studies included in this review,[2,5,7,9-18,20-22] increasing SAMe-TT_2R_2 score demonstrated poorer TTR values which might also translate into poorer clinical outcomes. This can be evidenced by studies that showed the SAMe-TT_2R_2 score relating to severe bleeding[22] and major bleeding (defined by the Bleeding Academic Research Consortium),[21] stroke/TE,[21] adverse cardiovascular events[22] and death[21, 22] during follow-up. In an observational study performed in 911 Spanish AF patients, the SAMe-TT_2R_2 score also successfully predicted the composite outcome of major bleeding, TE complications and death.[18] A Chinese study also demonstrated that a SAMe-TT_2R_2 score of ≤2 vs. SAMe-TT_2R_2 of 3 vs. SAMe-TT_2R_2 ≥4 is associated with lower annual stroke risk (3.49%/year vs. 4.56% per year vs. 6.41%/year, respectively).[15]

Impact of different methods of calculating TTR

Fauchier and colleagues[36] have raised concern about the different methods used to calculate TTR, whether to use TTR based on the Rosendaal method, percentage of INRs in range (PINRR) (traditional method) or percentage of visits in range on a given date (cross-sectional method), as these methods are not interchangeable. In this review, 17 studies[2,5-17,19,20,22] reported TTR using the Rosendaal method, only one[18] calculated time in therapeutic range according to PINRR, while the other reported 'labile INR' as their measure of anticoagulation control.[21] Currently there is no evidence on the optimal method of calculating percentage of INR in range, as each method has its own unique strengths and weaknesses.[37] While TTR via the Rosendaal method calculates the exact percentage of days the INR falls within range, its calculation is more complex than the others and is based on linear extrapolation. In contrast, calculating TTR via the PINRR method is simpler as it only looks at the number of INRs that fall within the therapeutic range divided by the total number of INR tests undertaken. However, the PINNR method does not take into account the actual number of days of anticoagulant treatment and thus might underestimate control in patients with inconsistent INR monitoring, patients who have temporarily discontinued therapy and patients with a long gaps between each INR test, in contrast to the Rosendaal method where these factors will be accounted for, resulting in a lower TTR.

Factors affecting anticoagulation control

In this review, only 5 studies[8,12,13,15,18] investigated the relationship of individual components of the SAMe-TT_2R_2 score with the quality of anticoagulation control. Among these female sex[12,13,18], >2 comorbidities,[18] heart failure and diabetes mellitus[15] (individually) and black ethnicity[5] were associated with poor TTR control, however no studies found any association between age <60 years and smoking with poor TTR.

It is interesting to speculate how some elements of the SAMe-TT_2R_2 score could influence anticoagulation control. Some studies[38,39] investigating predictors of TTR have demonstrated that women have poorer anticoagulation control compared to men (translating into poorer outcomes), although the precise mechanism remains unclear.[5] Similarly, women are known to be at higher risk of AF-related stroke irrespective of warfarin use.[40,41] Tobacco use within 2 years scores 2-points in the

SAMe-TT_2R_2 score, however most validation studies reported low prevalence of smoking (6.3%-30%) except in the external validation study by Apostolakis et al[5] (49% reported as smoker/ex-smoker (within 2 years)). How smoking can influence anticoagulation control is unclear but it may reflect less interest in maintaining good health which may translate into poorer adherence to oral anticoagulants, thus resulting in poor TTR.[5]

The original SAMe-TT_2R_2 score publication suggested that patients who are younger and have more comorbidities probably have adherence issues with VKA therapy which are reflected by poor TTR[3]. In terms of non-white ethnicity, some studies have shown that African-Americans and Hispanics have poorer anticoagulation control compared to whites and suggest that this may be due to various reasons including socioeconomic status, poor understanding of therapy, adherence issues, genetic predisposition, etc.[42,43] However, these aspects need to be further investigated as studies in these areas are lacking.

Another editorial[44] suggests that other factors, not currently within the SAMe-TT_2R_2 score, could be included in the assessment of anticoagulation control, such as distance from home to anticoagulation clinic, which could be the main reason preventing patients attending for regular follow-up. There is clearly the need for a large prospective randomised trial to evaluate the impact of SAMe-TT_2R_2 score-guided therapy with VKA or NOAC not only in relation to anticoagulation control (TTR) but also towards clinical outcomes (stroke and bleeding), which would formalise its utility in clinical practice. Hence, where patients have chosen VKA over a NOAC for stroke prevention or treatment of VTE or where NOACs are contraindicated but a high SAMe-TT_2R_2 score (>2) is present, perhaps more frequent follow-up visits and reviews, educational interventions and counselling[45] may be required to ensure that INRs are within the therapeutic range in order to achieve the best outcomes and minimise treatment complications.

Limitations

The main limitation of the included studies is study design; none utilised a randomised controlled trial design and most were performed in white populations. Given that one of the risk factors for poorer

anticoagulation control is ethnicity, SAMe-TT_2R_2 score in these populations is automatically worse compared to non-whites; thus a lower score predicts better control of VKA therapy. Thus, future studies need to ascertain whether the threshold of the SAMe-TT_2R_2 score used to indicate probability of poorer anticoagulation control (SAMe-TT_2R_2 score $\geq$2) needs to be modified in non-white populations so that the SAMe-TT_2R_2 score is applicable globally. In addition, only three studies have validated the SAMe-TT_2R_2 score in VTE cohorts to date, hence more studies are needed specifically in VTE cohorts to enhance its applicability in these patients. Lastly, only 8 studies reported the c-statistic to quantify the predictive ability of the SAMe-TT_2R_2 score.

Conclusions

Making decisions when choosing OAC therapy can be challenging. The available evidence suggests that the SAMe-TT_2R_2 score is a useful tool to aid decision-making for OAC in AF (and VTE) patients and adequately predicts those who are likely to be able/unable to achieve and maintain good INR control.

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Table 1: The SAMe-TT_2R_2 score

	Component	Score
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history†	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2-years)	2
R	Race (non-white ethnicity)	2
	Maximum total score	**8**

†≥2 of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease.

Table 2: Studies assessing the SAMe-TT_2R_2 score in atrial fibrillation and venous thromboembolism cohorts

	a. Study design **b. Mean follow-up** **c. Method INR monitoring**	**Population** **a. Number** **b. Mean (SD)/median (IQR) age (range, years)** **c. Race/ethnicity** **d. OAC used**	**SAMe-TT_2R_2 score distribution (%); mean TTR (%) ± SD**	**Percentage of patients with dichotomised TTR (%)**
Pivatto Junior[9] **2017** **Brazil**	a. Retrospective b. 1 year c. Hospital OAC clinic	a. 263 AF b. 71.2 (64.1-78.5) c. White d. 97.3% Warfarin	0-1: 138 (52.5); 69.2 ≥2: 125 (47.5); 56.3	-
Kataruka[8] **2017** **USA**	a. Retrospective b. Median 0.56 years ± 1.13 c. Hospital OAC clinic	a. 1943 VTE b. 61.8 (15.7) c. White d. Warfarin	0-1: 665; 57±21 2: 432; 55±22 >2: 846; 50±23	TTR<60:57.6
Bernaitis[16] **2016** **Singapore**	a. Retrospective b. - c. Hospital	a. 1137 AF b. 71 (63-77) c. Asian d. Warfarin	0-1:0 2: 339; 63.2±34.1 >2:798; 55.8±34.1	-
Chan[15] **2016** **Hong Kong**	a. Retrospective b. 4.7 ± 3.6 years c. Hospital	a. 1428 NVAF b. 76.2 (8.7) c. Chinese d. Warfarin	2: 22(14.3); 70[†] 3: 80 (51.9); 70 4: 41 (26.6); 70 5: 7 (4.5); 70 6: 4 (2.6); 70	TTR≥70: 11 TTR<70: 89
Demelo-Rodriguez[6] **2016** **Spain**	a. Prospective b. 72,668 patient-years c. Primary care	a. 135 VTE b. Median 66[#] c. White d. Warfarin	0-1:91; 64.7±19.5 ≥2: 44; 66 ±20.5	-
Gorzelak-Pabis[14] **2016** **Poland**	a. Prospective b. - c. Hospital	a. 104 AF with cognitive impairment b. 75 (10) c. White d. 61% Acenocoumarol	0-1: 64±26 ≥2: 50±28	-

Lip[13] **2016** **USA**	a. Prospective b. 438 days c. Trial setting	a. 229 AF b. 66.7 (11) c. 80.3% White d. Warfarin	0-1:0.571±0.22 ≥2: 0.498±0.24	-
Lobos-Bejarano[12] **2016** **Spain**	a. Retrospective b. >12 months c. Primary care	a. 1524 NVAF b. 77.4 (8.7) c. White d. 94.8% Acenocoumarol	0-1: 69.6% ± 17.4 ≥2: 66.6% ± 18.5	TTR≥65: 60.6 TTR<65: 39.4
Palareti[7] **2016** **Spain**	a. Prospective b. 998 patient-years c. Hospital OAC clinic	a. 1308 VTE b. 68(51-78) c. White d. Warfarin	0-1: 916 (70); 61±22 ≥2: 392 (30); 56±23	TTR≥65: 50.4 TTR<65: 49.6
Proietti[11] **2016** **Europe, Asia, Australasia**	a. Prospective b. Median 563 days c. Trial setting	a. 3665 AF b. 72(66-77) c. Mixed‡ d. Warfarin	0-2: 2914 (80.4); 69.05 (55.63-79.89) >2: 710 (19.6); 66.55 (52.83-77.46)	TTR>70: 46.9 TTR≤70: 53.1
Szymanski [10] **2016** **Poland**	a. Retrospective b. - c. Hospital	a. 211 AF b. 57.1 (10.2) c. White d. 75.4% warfarin	0-1: 114 (54); 52.3 ≥2: 97 (46); 51.3	TTR>70: 25.2 TTR≤70: 74.8
Abumuaileq[18] **2015** **Spain**	a. Retrospective b. 10 months c. Hospital OAC clinic	a. 911 NVAF b. 73 (11) c. White d. 93% Acenocoumarol	0-1:672 (74); 59±18¶ ≥2: 239 (26); 54±19¶	PINRR>65:39 PINRR≤65:61
Roldán[44] **2015** **Spain**	a. Prospective b. 6 months c. Hospital OAC clinic	a. 459 NVAF b. 76 (70-82) c. White d. Acenocoumarol	<2: 253 (55); 67±18 ≥2: 206 (44.8); 61±16	TTR>65:54 TTR≤65:46
Ruiz-Ortiz[2] **2015** **Spain**	a. Retrospective b. Median 27 months c. Cardiology clinic	a. 1056 NVAF b. 73.6 (9.8) c. White d. Acenocoumarol	0-1:613 (58); 65.6±26.2 ≥2: 443 (42); 61.3±25.3	TTR≥65:52.7 TTR≥65:47.3

Gallego[22] **2014** **Spain**	a. Prospective b. Median 952 days c. Hospital OAC clinic	a. 972 NVAF b. 76 (70-82) c. White d. Acenocoumarol	0-1:431 (44); 79.67 ±19.46 ≥2: 332 (34); 78.4 ± 20.28 >2:208 (21); 74.25 ± 20.24	-
Lip[21] **2014** **France**	a. Prospective b. 1016±1018 days c. Clinicians -hospital	a. 8120 AF b. 70 (15) c. White d. Warfarin	0-1: 4504 (55); 77(1.7)[§] ≥2: 2252 (28); 52(2.3)[§] >2:1364 (17); 43(3.2)[§]	-
Poli[20] **2014** **Italy**	a. Prospective b. 4.6 years c. Hospital OAC clinic	a. 1089 AF b. 75 (30-94) c. White d. Warfarin	0-1:624 (57); 72.3 ± 15.3 2: 288 (26); 72.0 ± 15.6 >2:177 (16); 68.2 ±16.4	-
Skov[19] **2014** **Denmark**	a. Prospective b. 1 year c. Hospital OAC clinic	a. 182 AF b. 70.2[#] c. White d. Warfarin	0-1:105 (58); 76 ≥2: 77 (42); 76	-
Apostolakis[5] **2013** **United Kingdom**	a. Retrospective and prospective b. 3.5 years c. Clinical trial (internal-validation)/Hospital OAC clinic (external-validation)	a. 1305 AF b. 69(8)/74(10) c. 8.7%, 19.3 % non-white (internal/external-validation) d. Warfarin	(Internal/External validation) 0: 242 (19); 0.66±0.16/0.7±0.13 1: 413 (32); 0.65±0.18/0.66±0.17 2: 303 (23); 0.63±0.17/0.66±0.16 3:185 (14); 0.59±0.22/0.65±0.17	**Internal validation** TTR>70:35.7 TTR≤70:64.3 **External validation** TTR>70:44.1 TTR≤70:55.9

AF: atrial fibrillation; CV: cardiovascular; INR: international normalised ratio; IQR: interquartile range; Max: maximum; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant/anticoagulation; ROC: area under curve; SD: standard deviation; SAMe-TT_2R_2 score: sex (female), age (<60 years, medical history (≥2 of the following: hypertension, diabetes, coronary artery disease or myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease), treatment with interacting drugs (e.g. amiodarone[all 1 point], current tobacco use and race (non-white) [2 points]; TTR: time to therapeutic; TE: thromboembolism; VTE: venous thromboembolism

†TTR presented as ≥70% and <70% not mean TTR; ‡mixed population: White, Black, Asian, other; §number of patients with labile INR, (%); ¶PINRR % (mean ± SD); [#]no SD or IQR reported; - not reported

Table 3: Baseline characteristics of studies assessing SAMe-TT_2R_2 score in AF and VTE cohorts

Patient characteristic, N (%)	Sex (female)	Age <60 y	Hyperten-sion	Diabetes mellitus	Heart failure	Prior stroke/TIA	Peripheral arterial disease	Renal disease	Coronary artery disease	COPD	Current smoking habit	Previous bleeding	Treatment: Amiodarone
PivattoJunior[9]	113 (43.0)	41 (15.6)	231 (87.8)	108 (41.1)	149 (56.7)	96 (36.5)	25 (9.5)	7 (2.7)	76 (28.9)	36 (13.7)	37 (14.1)	24 (9.1)	26 (9.9)
Kataruka[8]	1017 (52.3)	1060 (54.6)	-	-	-	-	-	-	-	-	575 (29.6)	-	22 (1.1)
Bernaitis[16]	448 (39.4)	172 (15.1)	677 (59.5)	343 (30.2)	88 (7.7)	45 (4.0)	-	156 (13.7)	271 (23.8)	-	84 (7.4)	-	78 (6.9)
Chan[15]	671 (52.5)	48.0 (3.4)	922 (64.6)	387 (27.1)	367 (25.7)	496 (34.7)	102 (7.1)	2.9 (2.0)	407 (28.5)	-	71.0 (5.0)	-	94 (6.6)
Demelo-Rodriguez[6]	(50.4)	-	(51.9)	(18.5)	(3.7)	(5.2)	(3.0)	(15.6)	-	(17.0)	(18.5)	-	-
Gorzelak-Pabis[14]	63 (60.6)	-	92 (88.5)	30 (28.8)	72 (69.2)	15 (14.0)	-	-	-	-	20 (19.2)	-	8 (7.7)
Lip[13]	47 (20.5)	57 (24.9)	206 (90.0)	106 (46.3)	126 (55.0)	26 (11.4)/ 14 (6.1)	31 (13.5)	-	178 (77.7)	-	-	-	46 (20.1)[#]
L-Bejarano[12]	741 (48.6)	66 (4.3)	1223 (80.2)	473 (31.0)	392.0 (25.7)	209.0 (13.7)	99 (6.5)	92 (6.0)	286 (18.8)	-	100 (6.6)	134 (8.8)	100 (6.6)
Palareti[7]	698.0 (53.4)	446 (34.1)	678 (51.8)	107 (8.2)	36.0 (2.8)	66 (5.0)	54 (4.1)	73 (5.6)	99.0 (7.6)	-	134 (10.0)	-	15 (1.1)
Proietti[11]	1116 (30.5)	72[§] (66-77)	2812 (76.7)	860 (23.5)	1372 (37.4)	753 (20.5)	-	-	1619 (44.2)	-	334 (9.1)	208 (5.7)	-
Szymanski[10]	79 (37.4)	108 (51.2)		27 (12.8)	8.0 (3.8)	16 (7.6)	-	-	-	-	31.0 (14.7)	-	17 (8.1)
Abumuaileq[18]	306 (33.6)	-	678 (74.4)	220 (24.1)	343 (37.7)	103 (11.3)	92 (10.1)	36[¶] (4)	127 (13.9)	183 (20.1)	77 (8.5)	115 (12.6)	-
Roldán[17]	237 (53.0)	38 (8.0)	368 (80.0)	141 (31.0)	87 (19.0)	67 (15.0)	-	51 (11.0)	70 (15.0)	50 (11.0)	38 (8.0)	37 (8.0)	72 (16.0)
Ruiz-Ortiz[2]	443 (42.0)	-	884 (83.7)	321 (30.4)	235 (22.2)	150 (14.2)	-	153 (14.5)	215 (20.3)	176 (16.7)	76 (7.2)	56 (5.3)[††]	102 (9.7)

Gallego[22]	494 (51.0)	66 (7.0)	796 (82.0)	249 (26.0)	350 (36.0)	182 (19.0)	-	94 (10.0)	182 (19.0)	-	136 (14.0)	79 (8.0)	-
Lip[21]	3,129 (39)	-	3,405 (42.0)	1,244 (15.0)	4,466 (55.0)	674 (8.0)	-	734 (9.0)	2,434 (30.0)	870 (11.0)	1,053 (13.0)	-	1,670 (35.0)
Poli[20]	412 (37.8)	61 (5.6)	745 (68.7)	216 (19.9)	268 (24.7)	313 (28.8)	143 (13.2)	-	239 (22.1)	-	181 (16.6)	-	200 (18.4)
Skov[19]	54 (29.6)	23 (12.6)	-	-	-	-	-	-	-	-	41 (22.5)	-	27 (14.8)
Apostolakis[5†]	382 (37.5)	147 (14.4)	692 (67.9)	200 (19.6)	197 (19.3)	130 (12.8)	57 (5.6)	53 (5.2)‡‡	173 (17.0)§§	-	64.0 (6.3)	-	129 (12.7)
Apostolakis[5‡]	157 (67.1)	30.0 (10.5)	234 (81.8)	64 (22.4)	45 (15.7)	30.0 (12.8)	8 (2.8)	2.0 (0.7)‡‡	44 (15.4)§§	-	140 (49.0)	-	26 (9.1)

COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; TIA: transient ischemic attack

†Internal validation; ‡external validation; §median age (IQR); ¶eGFR 30 ml/min/1.73m2; # antiarrhythmic; ††Major bleed; ‡‡ hepatic/renal disease; §§ history of MI

Table 4: Predictive ability (c-statistics) of SAMe-TT_2R_2 for anticoagulation control and clinical events

	Anticoagulation control, c-statistics (95% CI)	**Clinical events, c-statistics (95% CI)**
PivattoJunior[9]	TTR≥65: 0.612 (0.544-0.681; p=0.002)	-
Kataruka[8]	TTR<60: 0.61(-) TTR<65: 0.65(-) TTR<70: 0.65 (-)	-
Chan[15]	-	Stroke: 0.54 (0.52-0.57)
Lobos-Bejarano[12]	TTR≥65: 0.562 (0.533-0.592; p<0.001)	-
Palareti[7]	TTR<65: 0.52 (0.48-0.55; p:0.35)	-
Abumuaileq[18]	PINRR ≤70: 0.60 (0.56-0.64; p<0.001)	Composite major bleeding, thromboembolic complication or death: 0.57 (0.51-0.62)
Ruiz-Ortiz[2]	TTR≥65: 0.57 (0.53-0.60; p<0.0005)	-
Gallego[22]	-	Adverse CV event: 0.62 (0.57-0.68; p<0.001) Bleeding: 0.55 (0.49-0.62; p=0.117) All-cause mortality: 0.62 (0.55-0.68; p<0.001)
Lip[21]	Labile INR: 0.589 (0.574-0.603)	Stroke/TE: 0.561 (0.547-0.575) Severe bleeding: 0.552 (0.537-0.566) Major BARC bleeding:0. 574 (0.560-0.589) Death: 0.544 (0.530-0.559)
Apostolakis[5]	TTR 31% internal 0.72 (0.64-0.795) TTR 36% external 0.70 (0.57-0.82)	-

BARC: Bleeding Academic Research Consortium; CV: cardiovascular; INR: international normalised ratio; PINRR: percentage of INR in range; TE: thromboembolism; TTR: time in therapeutic range; - not reported

Figure legends:

Figure 1: Selection of studies for inclusion – PRISMA flowchart

Figure 2: Mean TTR vs. SAMe-TT_2R_2 categories in validation studies

Legend: SAMe-TT_2R_2 categories: black= score 0-1; grey= score of 2; white= score >2

Figure 3: Predictive ability (c-statistics and 95% confidence intervals) of SAMe-TT_2R_2 and anticoagulation control in validation studies