CONTEMPORARY REVIEW

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

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Identifying patients who are likely to achieve and maintain a therapeutic international normalized ratio when prescribed a vitamin K antagonist for stroke prevention in atrial fibrillation (AF) and venous thromboembolism (VTE) is challenging. The SAMe-TT_2R_2 score was developed on the basis of 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 summarizes the main published prospective and retrospective studies that have validated the SAMe-TT_2R_2 score in AF and VTE patients treated with a vitamin K antagonist 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 in 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 in AF and VTE patients.

KEYWORDS Atrial fibrillation; Decision making; Oral anticoagulation; SAMe-TT_2R_2 score; Venous thromboembolism; Vitamin K antagonist

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Introduction

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

Time in therapeutic range (TTR) is a measure that summarizes INR control over time. TTR is an important and independent predictor of thromboembolic and bleeding outcomes in AF patients treated with VKA.[2,3] An average individual TTR of ≥65% is recommended by the National Institute for Care Excellence guidelines,[1] while European guidelines[4] recommend TTR ≥70% to maximize the 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 is not factored in (or intended to be). This score assigns 1 point each to female sex, age <60 years, history of ≥2 comorbidities (hypertension, diabetes mellitus, coronary artery disease or myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, and pulmonary, hepatic, or renal disease), and treatment with drugs interacting with VKA (eg, amiodarone) and 2 points each for current/recent tobacco use (within 2 years) and nonwhite ethnicity[5] (Table 1). The score can be used to aid decision making by identifying those patients who would probably do well when treated with VKA (achieving a high TTR, ≥65%) or, conversely, those who would need additional interventions to achieve good INR control or to be initiated on/switched to a non-VKA oral anticoagulant (NOAC). The present review summarizes studies that have

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Table 1 The SAMe-TT_2R_2 score

Component	Score
S: Sex (female)	1
A: Age (<60 y)	1
Me: Medical history*	1
T: Treatment (interacting drugs, eg, amiodarone)	1
T: Tobacco use (within 2 y)	2
R: Race (nonwhite ethnicity)	2
Maximum total score	*8*

*Two or more of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, and pulmonary, hepatic, or renal disease.

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, VKA, oral anticoagulant (OAC), 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 or information on follow-up time or those that 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 summarized in Table 2, and baseline patient characteristics of these cohorts are summarized in Table 3. Except 3 studies,[6–8] all[2,5,9–22] were performed in AF patients. Most studies (n=11)[5–7,11,14,17,19–22] were performed prospectively, with follow-up duration ranging from 6 months[17] to 4.7 years.[15] The number of participants included in VTE cohorts ranged from 135[6] to 1943[8] and from 104[14] to 8120[21] in studies in AF patients.

Fourteen studies were performed in European populations,[5–7,9–12,14,17–22] 2 in Asian populations[15,16] (with 1 reporting a target INR 2.0–3.0[15]), and 2 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 to 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 being the most common, except for the study by Lip et al,[21] in which congestive heart failure was most prevalent. All studies reported a low prevalence of smoking and use of amiodarone for rhythm control, except 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 1 study by Demelo-Rodríguez et al,[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; 1 study[18] showed that having ≥2 comorbidities was related to poor TTR, and 1 study[13] showed that black ethnicity (as well as New York Heart Association class 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 in 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 whether the SAMe-TT_2R_2 score could discriminate AF patients with clinical events. Five studies[11,15,18,21,22] demonstrated some positive associations for the 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 whether the SAMe-TT_2R_2 score was associated with clinical outcomes, in particular recurrent VTE and International Society on Thrombosis and Haemostasis major bleeding rates in a VTE cohort; patients with a score of >2 had more overall adverse event rates (composite of recurrent VTE and International Society on Thrombosis and Haemostasis major bleeding) than those with a score of 0–2 (7.9 overall adverse event rates per 100 patient-years vs 4.5 overall adverse event rates per 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, 8 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 $CHADS_2$,