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Evaluation of SAMe-TT_2R_2 Score on Predicting Success With Extended-Interval Warfarin Monitoring

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Abstract

Background: In patients with stable international normalized ratios, 12-week extended-interval warfarin monitoring can be considered; however, predictors of success with this strategy are unknown. The previously validated SAMe-TT_2R_2 score (considering sex, age, medical history, treatment, tobacco, and race) predicts anticoagulation control during standard follow-up (every 4 weeks), with lower scores associated with greater time in therapeutic range. **Objective:** To evaluate the ability of the SAMe-TT_2R_2 score in predicting success with extended-interval warfarin follow-up in patients with previously stable warfarin doses. **Methods:** In this post hoc analysis of a single-arm feasibility study, baseline SAMe-TT_2R_2 scores were calculated for patients with ≥1 extended-interval follow-up visit. The primary analysis assessed achieved weeks of extended-interval follow-up according to baseline SAMe-TT_2R_2 scores. **Results:** A total of 47 patients receiving chronic anticoagulation completed a median of 36 weeks of extended-interval follow-up. The median baseline SAMe-TT_2R_2 score was 1 (range 0-5). Lower SAMe-TT_2R_2 scores appeared to be associated with greater duration of extended-interval follow-up achieved, though the differences between scores were not statistically significant. No individual variable of the SAMe-TT_2R_2 score was associated with achieved weeks of extended-interval follow-up. Analysis of additional patient factors found that longer duration (≥24 weeks) of prior stable treatment was significantly associated with greater weeks of extended-interval follow-up completed (P = 0.04). **Conclusion and Relevance:** This pilot study provides limited evidence that the SAMe-TT_2R_2 score predicts success with extended-interval warfarin follow-up but requires confirmation in a larger study. Further research is also necessary to establish additional predictors of successful extended-interval warfarin follow-up.

Keywords

anticoagulation, interval, monitoring, SAMe-TT2R2, warfarin, vitamin K antagonist

Introduction

Appropriate anticoagulant selection is paramount to achieving quality patient outcomes for myriad conditions. Warfarin, the most frequently used anticoagulant, requires close monitoring of the international normalized ratio (INR) for therapeutic effect and safety.[1] The typical interval for warfarin follow-up in the United States is every 4 weeks, though contemporary guidelines suggest extending follow-up to 12-week intervals in select patients with stable INRs.[2] Extended-interval warfarin follow-up is thought to reduce patient burden and costs through fewer laboratory monitoring visits, which may in turn increase patient acceptance of treatment.[3] However, research has shown that maintenance of extended-interval warfarin follow-up may be difficult for many patients, even among select patients with prior stable INRs over an extended duration.[4,5] Currently, no tool has been validated to predict anticoagulation stability in extended-interval follow-up, which limits the ability to safely increase monitoring intervals beyond 4 weeks.

Stability of INR control in standard-interval warfarin follow-up can be predicted by the SAMe-TT_2R_2 risk tool,[6] which allocates 1 or 2 points based on risk factors, for a total maximum score of 8. Total scores greater than 2 are predictive of poor INR control and increased risk of adverse

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clinical outcomes.[7] In this pilot study, we aimed to assess the extent to which the SAMe-TT_2R_2 risk tool predicts maintenance of extended-interval warfarin follow-up.[4] We hypothesized that, among patients with previously stable INRs, lower SAMe-TT_2R_2 scores would be associated with achieving a longer duration of extended-interval warfarin follow-up.

Methods

Study Population and Design

The Feasibility of Extended-interval Follow-up for Patients Receiving Warfarin (FADE-OUT) study has been described previously.[4] Briefly, FADE-OUT was a prospective, single-arm intervention study conducted from September 2012 to February 2014 investigating the real-world feasibility of extended-interval follow-up for patients taking warfarin. Patients aged 18 to 90 years were enrolled from 5 outpatient anticoagulation clinics within the University of Florida Ambulatory Care Research Network. Patients were eligible for the study if they required at least 6 months of anticoagulation, were on a stable dose of warfarin for at least 12 weeks, and had been followed by the same anticoagulation clinic for the 12 weeks prior to enrollment, per guideline recommendations.[2] FADE-OUT excluded patients with a recent thromboembolic event, life expectancy <24 months, or recent diagnosis of cancer and those receiving cancer treatment. A total of 47 enrolled patients were transitioned from usual care (follow-up intervals up to 4 weeks) to extended-interval follow-up in a stepwise fashion. Specifically, first study follow-up occurred after 6 weeks, then after an additional 8 weeks, then every 12 weeks thereafter. Patients continued extended-interval follow-up for up to 68 weeks or until they were no longer a candidate for extended-interval follow-up. Key criteria for discontinuing extended-interval follow-up were warfarin dose change, out-of-range INR, or clinician discretion (eg, up-coming procedure requiring closer monitoring). Patients who did not meet criteria for continuation of extended-interval follow-up at or before week 26 were allowed to enter "second-chance" procedures, provided a dose adjustment was not required and the INR excursion was anticipated to be temporary. During second-chance procedures, patients were required to follow-up in 1 to 2 weeks to confirm that INR had returned to goal. Follow-up visits were then subsequently extended out at intervals of 4 and 8 weeks, and then 12 weeks thereafter. Patients were allowed to enter second-chance procedures only once during the study. The study was approved by the University of Florida Institutional Review Board. Informed consent was obtained from all individual participants at the time of enrollment in FADE-OUT.

Data Collection and Analysis

The present study was a post hoc analysis of FADE-OUT. Patients enrolled in FADE-OUT were included in the analysis if they completed at least 1 follow-up visit (including second chance visits). Baseline SAMe-TT_2R_2 scores were calculated as described in a previously published study.[6] Demographic and baseline data used for SAMe-TT_2R_2 score calculation included sex, age, medical history, concomitant medications, tobacco use, and race. Patients were assigned 1 point for each of the following: female sex, age <60 years, >2 comorbidities (ie, hypertension, diabetes, coronary artery disease, peripheral arterial disease, congestive heart failure, previous stroke, hepatic or renal insufficiency), and concomitant amiodarone use. Two points were assigned if the patient was a tobacco user (within the past 2 years) or minority (ie, African American, Hispanic). An individual could achieve a maximum total of 8 points.

The primary analysis was comparing median weeks of extended-interval follow-up between baseline SAMe-TT_2R_2 scores. The secondary analysis assessed median weeks of extended-interval follow-up completed for patients with low SAMe-TT_2R_2 scores (0-2) versus high SAMe-TT_2R_2 scores (>2). Exploratory analyses were conducted to test the association between individual variables of the SAMe-TT_2R_2 risk tool and completed weeks of extended-interval follow-up. Additional analyses explored achieved weeks of extended-interval follow-up by baseline alcohol use (any vs none), prior weeks of stable treatment (defined as number of weeks without a change in warfarin dose prior to the baseline visit), and use of any interacting medications at baseline. For prior weeks of stable treatment, we dichotomized the duration into 2 groups based on previous studies using 6 months as the minimum duration[5,8]: (1) patients with ≥24 weeks of prior stable INRs and (2) patients with ≥12 up to <24 weeks of prior stable INRs. Regarding interacting medications, we assessed prescription medications commonly seen in an ambulatory care setting with at least a moderate interaction to either increase or decrease the INR (ie, amiodarone, dronedarone, quinidine, propafenone, gemfibrozil, fenofibrate, allopurinol, and statins [except atorvastatin]).[9] Descriptive statistics were used to characterize the study population. The Kruskal-Wallis test was used to compare achieved weeks of extended-interval follow-up by baseline SAMe-TT_2R_2 scores. The Wilcoxon rank-sum test was used for bivariate analyses. A P value <0.05 was considered statistically significant. We performed all analyses using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 47 patients from the FADE-OUT study were included. Baseline characteristics of the study cohort are

Table 1. Baseline Characteristics of 47 Patients From FADE-OUT.

Characteristic	n (%) or Mean ± SD
Age, years	66.8 ± 12.5
Female	24 (51)
Race/ethnicity	
White (non-Hispanic)	35 (74.5)
African American	10 (21.3)
Hispanic/Latino	1 (2.1)
Other (Native American)	1 (2.1)
Tobacco use	5 (10.6)
Alcohol use	10 (21.3)
Prior weeks with consistent INR	33 ± 27.8
Duration of chronic warfarin use, years	6.74 ± 6.0
SAMe-TT_2R_2 score, median (IQR)	1 (1-3)
Indication for chronic warfarin	
Nonvalvular AF or atrial flutter	25 (53.2)
Recurrent DVT/PE prophylaxis	14 (29.8)
CVA (non-AF/flutter related)	3 (6.4)
Antiphospholipid syndrome	2 (4.3)
Other	2 (4.3)
Comorbidities	
Hypertension	34 (72.3)
Diabetes	11 (23.4)
Coronary artery disease	11 (23.4)
Peripheral arterial disease	1 (2.1)
Congestive heart failure	4 (8.5)
Previous stroke	6 (12.8)
Hepatic or renal insufficiency	7 (14.9)
Interacting medications	
Amiodarone	3 (6.4)
Other antiarrhythmic agents (dronedarone, quinidine, propafenone)	2 (4.2)
Fibrates (gemfibrozil, fenofibrate)	2 (4.3)
Allopurinol	5 (10.6)
Statins (except atorvastatin)	19 (40.4)

Abbreviations: AF, atrial fibrillation; CVA, cerebral vascular accident; DVT, deep-vein thrombosis; IQR, interquartile range; PE, pulmonary embolism.

summarized in Table 1.[4] The mean age of the cohort was 66.8 years, and approximately 51% were women. Patients completed a median 36 weeks (interquartile range [IQR] = 13-52) of extended-interval follow-up from enrollment. The median SAMe-TT_2R_2 score was 1 (IQR = 1-3), with a range of 0 to 5. The most common comorbidity was hypertension (72.3%), followed by diabetes (23.4%) and coronary artery disease (23.4%). Three patients (6.4%) were prescribed amiodarone at baseline.

As SAMe-TT_2R_2 score increased, indicating a greater number of risk factors for INR instability, patients appeared to complete fewer median weeks of extended-interval follow-up (Figure 1). However, no significant difference was observed comparing across all baseline SAMe-TT_2R_2 scores (P = 0.48). One patient in the study had a SAMe-TT_2R_2 score of 5; this patient also completed 63 weeks of extended-interval follow-up. Exclusion of this patient from the analysis had no impact on the differences between scores (P = 0.69). We likewise observed no significant difference in achieved weeks of follow-up comparing patients with low SAMe-TT_2R_2 scores (0-2; n = 35 [75%]), who achieved a median of 36 (IQR = 14-55) weeks of follow-up, to those with high SAMe-TT_2R_2 scores (>2; n = 12 [25%]), who achieved a median of 20 (IQR = 10-49.5) weeks of follow-up (P = 0.55).

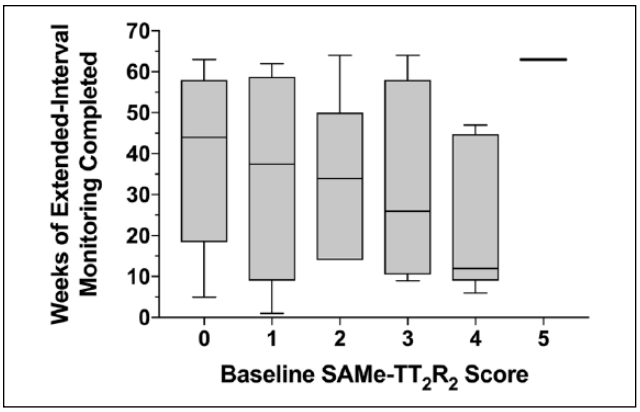

Figure 1. Comparison of total weeks of extended-interval monitoring achieved between baseline SAMe-TT_2R_2 scores.

No individual components of the SAMe-TT_2R_2 risk tool revealed significant associations with weeks of extended-interval follow-up completed (Table 2). Patients who were younger than 60 years of age appeared to complete numerically fewer median weeks of extended-interval follow-up (19 vs 38 weeks), although the difference was nonsignificant (P = 0.17). Likewise, patients taking amiodarone at baseline appeared to complete fewer median weeks of extended-interval follow-up (14 vs 37 weeks; P = 0.11). Table 2 also summarizes subgroup analyses of additional patient characteristics not included in the SAMe-TT_2R_2 score. Patients with longer duration (≥24 weeks) of prior stable treatment completed more weeks of extended-interval follow-up compared with patients with shorter duration (≥12 to <24 weeks) of prior stable INRs (45.5 vs 24 weeks; P = 0.04). Additionally, patients who were prescribed at least 1 interacting medication at baseline appeared to complete fewer median weeks of extended-interval follow-up (24 vs 45 weeks), though the between-group difference was not statistically significant (P = 0.09).

Discussion

In this study of predictors of success with extended-interval warfarin monitoring, we found inconclusive

Table 2. Weeks of Follow-Up Duration According to Individual Components of the SAMe-TT_2R_2 and Other Patient Characteristics.

Variable	n (%)	Weeks of Follow-up Completed, Median (IQR)	*P* Value
Individual SAMe-TT_2R_2 components			
Sex (S)			0.68
Female	24 (51.1)	34 (14-53.5)	
Male	23 (48.9)	37.5 (12-52)	
Age (A)			0.17
<60 years	12 (25.5)	19 (12-45.5)	
≥60 years	35 (74.5)	38 (14-60)	
Comorbidities (Me)			0.52
>2	9 (19.1)	24 (10-50)	
0 to 2	38 (80.8)	37 (14-52)	
Amiodarone use (T)			0.11
Yes	3 (6.4)	14 (6-14)	
No	44 (93.6)	37 (13-53.5)	
Tobacco use (T_2)			0.43
Yes	5 (10.6)	34 (26-63)	
No	42 (89.4)	36 (12-52)	
Race (R_2)			0.99
Minority	12 (25.5)	40 (11-49.5)	
Caucasian	35 (74.5)	34 (14-55)	
Additional patient factors			
Alcohol use			0.24
Yes	10 (21.3)	50 (36-60)	
No	37 (78.7)	28 (12-51)	
Prior weeks with stable INRs			0.04
<24 weeks	23 (48.9)	24 (10-50)	
≥24 weeks	24 (51.1)	45.5 (19.5-60)	
≥1 Interacting drug(s)			0.09
Yes	23 (48.9)	24 (6-51)	
No	24 (51.1)	45 (19.5-57.5)	

Abbreviations: INR, international normalized ratio; IQR, interquartile range.

evidence that the SAMe-TT_2R_2 score is predictive of achieving greater duration of extended-interval follow-up in the clinical setting. Although we observed possible trends that were consistent with our prespecified hypothesis—that is, that lower SAMe-TT_2R_2 scores would be associated with greater duration of achieved monitoring—these results were clearly nonsignificant, likely, at least in part, because of the small sample size available in this pilot study. Nevertheless, these findings are noteworthy in that we observed wide variation in the achieved duration of follow-up according to baseline SAMe-TT_2R_2 score, suggesting that other factors may influence a patient's ability to maintain a therapeutic INR during extended-interval follow-up. To our knowledge, this is the first study to investigate the predictive ability of SAMe-TT_2R_2 for success with extended-interval INR monitoring.

The SAMe-TT_2R_2 was originally developed in an atrial fibrillation cohort, in which investigators found that as SAMe-TT_2R_2 scores increased, time in therapeutic range decreased.[6] Since then, the score has been validated in other populations, including among patients with acute venous thromboembolism.[10-14] In the present study, we included patients with varied and multiple indications for anticoagulation to reflect real-world use of extended-interval monitoring and provide a wider application of the SAMe-TT_2R_2 risk tool. Prior literature has shown that scores of 2 or less have been associated with better INR control in standard-interval warfarin follow-up.[10,11,14] Although the present analysis does not provide sufficient evidence to convincingly extend these findings to extended-duration warfarin follow-up, our results are qualitatively similar. Furthermore, prior studies have shown that lower SAMe-TT_2R_2 scores are associated with lower risk for thromboembolism and major bleeding.[7,11] In FADE-OUT, 2 patients experienced bleeding (nose bleed and rectal bleed), leading to discontinuation of extended-interval follow-up, and no thromboembolic events occurred throughout the study period.[4] Given the low rates of clinical adverse events

in FADE-OUT, we were unable to assess whether the SAMe-TT_2R_2 risk score was also associated with clinical outcomes in an extended-interval monitoring population. Therefore, it remains to be seen whether lower SAMe-TT_2R_2 scores will also be associated with lower risks for bleeding and thromboembolism in patients undergoing extended-interval follow-up.

Our study also explored whether individual components of the SAMe-TT_2R_2 score predicted success with extended-interval follow-up. Although we found no statistically significant associations, interesting observations were seen. Similar to previous studies evaluating SAMe-TT_2R_2 score in standard-interval follow-up,[6,14] we found that younger patients (age <60 years) and patients using amiodarone at baseline may have more difficulty with maintaining extended-interval follow-up. Conversely, female sex, tobacco use, and minority status showed no discernable trends in predicting weeks of follow-up completed.

We also observed interesting findings between other patient characteristics and achieved weeks of extended-interval follow-up. Our group previously reported that duration of prior stability with warfarin therapy trended toward a positive correlation with weeks of extended-interval follow-up completed.[4] In this study, we dichotomized the duration of stable warfarin therapy prior to baseline based on 2 previous extended-interval follow-up studies, which included patients with stable doses of warfarin for at least 6 months prior to baseline.[5,8] We found that longer durations of stable INR prior to extended-interval follow-up were significantly associated with greater weeks of extended-interval follow-up achieved. Our results are concordant with previous data indicating that a duration of ≥24 weeks for prior warfarin stability may be a more reasonable criterion compared with contemporary guidelines, which suggest extending follow-up intervals after ≥3 months of consistent INRs not requiring dose adjustment.[2] However, given the exploratory nature of our study, an ideal threshold for this variable as it relates to optimally predicting success with extended-duration monitoring remains unknown. Further investigations will be necessary to assess the sensitivity and specificity across various thresholds of prior weeks with stable warfarin treatment. Additionally, interacting medications other than amiodarone (eg, fibrates, statins, allopurinol) were not included in the original development of SAMe-TT_2R_2.[6] However, these drugs can have clinically relevant effects on INR stability. We found that patients prescribed at least 1 interacting medication appeared to have more difficulty with maintaining extended-interval follow-up, potentially underscoring that medications other than amiodarone may also have an impact on maintaining stability during extended-interval follow-up. Dietary vitamin K intake may also theoretically influence stability of warfarin on extended-interval follow-up; however, we were unable to analyze this observation because specific details of dietary intake were not collected in the original FADE-OUT study. Nonetheless, the inclusion and exclusion criteria likely resulted in an enrolled patient population that had relatively stable dietary vitamin K intake. Further investigation is necessary to determine whether these additional factors should be incorporated into the existing SAMe-TT_2R_2 risk tool or into a revised tool for predicting extended-interval warfarin monitoring.

Our study has noteworthy limitations. First, the small sample size available likely underpowered the study to detect differences in achieved weeks of follow-up, comparing baseline SAMe-TT_2R_2 scores. Thus, whether our nonsignificant results stem from low power or a true lack of association is not known. Second, the inclusion criteria for FADE-OUT selected for patients at low risk of INR instability. As a result, our analysis included few patients with SAMe-TT_2R_2 scores ≥4, which may have reduced the ability of the score to predict success with extended-interval monitoring. However, practically speaking, few of these patients are likely to have a sufficiently stable INR history to warrant extended-duration warfarin monitoring. Third, we performed a number of exploratory analyses within our post hoc study and cannot rule out the possibility of spurious findings of statistical significance. Therefore, these exploratory findings will need to be confirmed in future studies with larger samples.

Conclusion and Relevance

Implementing extended-interval follow-up with warfarin is challenging and requires careful patient selection and shared decision making between the patient and provider. The SAMe-TT_2R_2 risk tool has previously been validated to predict INR stability on standard-interval follow-up. Our study found limited utility for this tool in its current form to predict success with extended-interval monitoring among patients with previously stable INRs. However, numerical differences in achieved weeks of extended-interval follow-up comparing baseline SAMe-TT_2R_2 scores indicate that additional study, in a larger sample of patients, may be indicated before ruling out any clinical utility with this tool. Other patient-related factors not included in the risk tool (eg, weeks of prior INR stability) also may provide further insight into variables that influence stability of warfarin on extended-interval monitoring. Additional studies are needed to confirm the predictive ability of SAMe-TT_2R_2 or to refine it through the consideration of additional risk factors.

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