Anticoagulants effectively prevent stroke and systemic thromboembolism in patients with atrial fibrillation (AF) when used properly. In many healthcare systems, vitamin K antagonists (VKA) remain the most commonly used anticoagulant drugs (1). For benefits to exceed risks with these drugs, the international normalised ratio (INR) must be maintained in a therapeutic target range of 2.0–3.0, but maintaining this range remains a challenge. In clinical practice, the average time in therapeutic range (TTR) of INRs can be suboptimal (2, 3), and if the TTR is <65%, expectation of benefits from the VKA may be eliminated. The TTR can be influenced by many patient clinical features, but sometimes guesswork or a ‘trial of warfarin’ was used to see how the previously anticoagulation-naïve patient does after starting VKA.

In 2013, the SAMe-TT$_2$R$_2$ score (sex female, age <60 years, medical history >2 comorbidities, treatment [interacting drugs], tobacco use [doubled], race non-Caucasian [doubled]) was proposed to identify patients likely to have a poor INR control reflected by an average TTR <65%. This simple score, based on easily measurable clinical features, appeared to identify AF patients who could maintain a TTR>65% (SAMe-TT$_2$R$_2$ score of 0–2) or not (SAMe-TT$_2$R$_2$ score >2) (4). However, this score, derived retrospectively from a trial initiated 20 years ago, may not apply now. Thus, independent modern ‘real world’ AF cohorts were needed for validation.

In this issue of the journal, Ruiz-Ortiz et al. (5) evaluated a nationwide population of 1,056 AF patients prescribed VKAs in 120 outpatient cardiology clinics throughout Spain. Of those recruited, the mean TTR was 64 ± 26% with a progressive decline in the mean TTR from a SAMe-TT$_2$R$_2$ score of 0 (68% ± 25%) to ≥4 (53 ± 29%). The score discriminated good anticoagulation control (TTR ≥65%) with a C-statistic of 0.57 (p<0.0005). SAMe-TT$_2$R$_2$ score of 0–1 was associated with a TTR ≥65% (sensitivity, specificity, positive and negative predictive values of 64%, 48%, 58% and 54%, respectively). The odds ratio of having a TTR<65% if the score was ≥2 was 1.64. The Spanish study was meritorious in measuring the TTR and validating the main purpose of the SAMe-TT$_2$R$_2$ score, i.e. identifying patients who will not do well with VKA (8–10). These data support the SAMe-TT$_2$R$_2$ score as a viable predictor of poor (and good) quality of anticoagulation based on the TTR for patients taking VKAs (6) but issues remain.

The TTR methodology – there are problems
A strong relationship between quality of anticoagulation and clinical outcomes has previously been demonstrated, thus supporting its use as a relevant outcome variable (7, 8). At least three different methods are identified for quantifying quality of anticoagulation (9). The TTR, or percent of days with INRs of 2.0–3.0 used by Ruiz-Ortiz and defined by Rosendaal is not as simple as it may seem. The TTR is calculated by incorporating INR measurement frequency and values, assuming that changes between consecutive INR measurements are linear, but interpolation of values not measured creates gaps in credibility. There is variability during the time not measured in practice and there are other flaws in the calculation as well.

The Percent of Visits in Range looks at how many visits had INRs in range and divides by the total number of visits. If the patient had nine visits and six had readings within their therapeutic range, then the patient is considered in range 66% of the time. This usually defines a Percentage of INRs in therapeutic range (PINNR). The PINNR is intuitive but is not the most widely accepted. The TTR and PINNR are not absolutely interchangeable even if they correlate.

The percent of visits in range on a given date, a cross-section method, considers a specific date; all patients are evaluated on the last reading to see if they were within range. The number of patients in range on their last reading is taken as a percentage of the total patients on that date. This method is not relevant for the individual management but is dedicated to evaluation of populations in a trial or in a registry. It may also reflect the quality of the global organisation in different healthcare systems.

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work, in lieu of these data, the SAMe-TT$_2$R$_2$ score appears convincingly validated in highly selected clinical-trial cohorts to real-world populations (4, 10, 12, 16) but does this real-world population represent long-term anticoagulation in all clinical practices?

The quality of anticoagulation is the result of a dynamic process with potential for rapid and long-term variation within the single patient in relation to compliance, health status or intercurrent disease. An inherent problem of the SAMe-TT$_2$R$_2$ score is the assumption that a fixed set of patient characteristics predicts a lifetime course of VKA treatment quality. Some contributing factors (tobacco use and nonwhite race) may be under- or over-represented depending on a particular setting potentially limiting generalisability of the score. In the original report (4), the external validation cohort had a poor TTR (<0.64) only for scores $\geq 6$ limiting the usefulness of the score only to a very select subgroup. It is known that a determinant of the quality of anticoagulation is experience in managing VKA.

Drott et al. reported that the number of patients tested per physician practice was

positively associated with TTR (13), reflecting volume-related drug familiarity and/or better-organised VKA management. The need for an organised management of VKA treatment is one of Best Practices Statement indicated by ACCP Guidelines (2012) (14). Unfortunately, these aspects are not included in the SAMe-TT2R2 score and the effect of a good VKAs management may actually trump individual patient characteristics.

Intrinsically, measures of c-statistic obtained with SAMe-TT$_2$R$_2$ score still remain relatively low (0.55–0.60) although statistically significant and broadly similar to other clinical factor based scores (e.g. CHADS$_2$ for stroke risk stratification in AF). This means that individual identification of a low TTR remains problematic and improvement may be warranted. The addition of alcohol abuse, low eGFR, diabetes mellitus, heart failure and history of malignancy, over SAMe-TT$_2$R$_2$ may improve the score performance for prediction of low TTR and were consistently identified in previous reports (6, 15). However, additional parameters may offer marginal improvement in predictive ability at the cost of losing simplicity and everyday practicality.

**Other limitations of the study**

Ruiz-Ortiz et al. (5) report observational data and several factors of the design could have led to a selection of a population of rather well-controlled anticoagulation by physicians in cardiology departments particularly involved in AF management. The authors did not collect data about educational level, socioeconomic status and distance from care providers which may have an association with the overall quality of anticoagulation. The authors were not able to look at what happened to patients with high SAMe-TT$_2$R$_2$ in terms of clinical events which may be affected by INR out of target. It has previously been found that SAMe-TT$_2$R$_2$ has a good ability to capture the risk of developing major bleeding, thromboembolic complications, and/or death (6, 11). Beyond labile INRs, the SAMe-TT$_2$R$_2$ score predicts stroke, thromboembolic events, severe bleeding, major bleeding and death among the patients taking VKAs but not for other patients (11).

**What to do if SAMe-TT$_2$R$_2$ predicts a low TTR**

Non-valvular AF patients with high CHA$_2$DS$_2$VASc scores benefit from dose-adjusted VKAs or non-VKA oral anticoagulants (NOAC). The latter can be used unless contraindicated, particularly when there are difficulties in keeping the INR within range with VKA (16, 17). A high SAMe-TT$_2$R$_2$ score suggests that choosing a NOAC instead is logical. However, benefits of such a strategy have not been demonstrated and are not yet proposed in current guidelines. A high SAMe-TT$_2$R$_2$ score may be the marker of a low treatment adherence and/or compliance, which may affect the effectiveness of VKAs or NOACs. It may also reveal a higher risk of pharmacological interaction, some of which are specific to VKAs, some other are also possible with NOACs. Whether the SAMe-TT$_2$R$_2$ score identifies patients who would do worse when treated with a NOAC is currently unknown and should be evaluated now. Some caution is in order to assume that a low TTR means that a NOAC will perform better. Conversely, any error or wide swings in anticoagulation will not be
seen at all with the NOAC strategy since no measure of anticoagulation efficacy is possible. This approach may be like sweeping dirt under a rug where it is not seen.

**Next steps**

For now, the SAMe-TT2R2 score may help clinicians to choose a relevant strategy to anticoagulate patients with non-valvular AF from medical and economic perspectives even though these outcome measures have yet to be proven. Many are currently unenthusiastic to use a NOAC as a first-line strategy for AF patients because of cost. Also, VKAs may be as effective as NOACs when the TTR is high (18). Use of an additional score whose only purpose is to predict another score makes little sense unless actionable intervention improves safety, efficacy, survival or costs for those at risk, particularly, for those with lower SAMe-TT2R2 scores. Clinicians may already be beyond score saturation.

However, given the mounting available evidence, the SAMe-TT2R2 score may avoid a crude "VKA strategy for everybody" (a ‘trial of warfarin’ advocated by some physicians and wished by payers) or "NOAC for everybody unless contraindicated" (defended by evidence-based medicine but perhaps too expensive). Instead, the SAMe-TT2R2 score may provide new insights into how we can decide which approach makes most sense when considering the best strategy to prescribe oral anticoagulation for non-valvular AF patients.

**Conflicts of interest**

LF has served as a consultant for Bayer, Boehringer Ingelheim, Medtronic, Novartis and Sanofi-Aventis and has been on the speaker’s bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Boston Scientific and Daiichi Sankyo. DP has received funding for conference travel and educational symposia from Bayer, Boehringer Ingelheim, BMS/Pfizer and Daiichi Sankyo. BO is a consultant for Medtronic, Boston Scientific, Amarin, BioControl, Boehringer Ingelheim, On-X, Biotronik, Daiichi Sankyo and Lundbeck. He has served on DSMB for Amarin, Boston Scientific and Sanofi-Aventis. He is the national coordinator for the GLORIA AF trial sponsored by Boehringer Ingelheim.

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