The SAMe-TT$_2$R$_2$ score and quality of anticoagulation in atrial fibrillation: a simple aid to decision-making on who is suitable (or not) for vitamin K antagonists

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This editorial refers to ‘Evaluation of SAMe-TT$_2$R$_2$ risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists’ by R.R.-Y. Abumuaileq et al., on page 711–717.

Maintaining the therapeutic range in patients treated with vitamin K antagonists (VKAs) had always been challenging whilst the potential consequences of deviating from the optimal average time in therapeutic range (TTR) are deleterious in patients with atrial fibrillation (AF), given the risk for thromboembolic and bleeding events.\(^1,2\)

Various clinical decision-making tools have been developed to help decision-making in the management of AF patients. In 2013, a new score—with the acronym SAMe-TT$_2$R$_2$—was proposed to help identify those patients who were likely to have a propensity to poor INR control (as reflected by average time in the therapeutic range $\leq$65%). This simple score based on clinical features may help identify those AF patients who would do well on VKA (SAME-TT$_2$R$_2$ score $= 0–2$), or conversely, those who might require additional interventions to achieve acceptable anticoagulation control (SAME-TT$_2$R$_2$ score $>2$).\(^3\) This score was derived from a trial cohort and thus independent validation in ‘real-world’ AF cohorts would be needed.

In the current issue of EP-Europace, Abumuaileq et al.\(^4\) performed a retrospective analysis of a cohort of outpatients with non-valvular AF and found that SAMe-TT$_2$R$_2$ could indeed represented a useful clinical tool to identify a poor quality of anticoagulation control with VKAs. The predictive ability of SAMe-TT$_2$R$_2$ was acceptable for identifying low TTR and improved when integrated with other clinical characteristics.

A strong relationship between quality of anticoagulation and clinical outcomes has previously been demonstrated, thus supporting its use as a relevant outcome variable.\(^5,6\) At least three different methods are identified for quantifying quality of anticoagulation. All three metrics have known advantages and disadvantages and may be utilized for clinical management or research.\(^7\)

Time in the therapeutic range, or percent of days in the therapeutic range, has been defined with a methodology described by Rosendaal, but it is not as simple to calculate as it might seem. It is calculated by incorporating the frequency of INR measurements and their actual values, and assuming that changes between consecutive international normalized ratio (INR) measurements are linear over time. This calculation looks at the amount of time between visits to determine how long the patient might have been within the therapeutic range. If an INR (the therapeutic range 2.0–3.0), tested in 1 January is 2.5, then 3.5 when tested in 31 January, one may think that the patient slowly moved from 2.5 to 3.5 over those 30 days. It is assumed that 15 days were in the therapeutic range, and 15 days were out of the range within the 30-day time period, which means the patient was within the range 50% of the time. Assessment of TTR with such linear interpolation is the only method that incorporates time. The calculation is obviously becoming more complex and will often need a computer as soon as the results are not as archetypal as in our example and when tests are not performed on a perfectly regular basis.

The per cent of visits in the range looks at how many visits had INR results in the therapeutic range, and divides by the total number of visits. If the patient has had nine visits, and six had INR readings within the therapeutic range, then the patient is considered to be in the range 66% of the time. This method was used in the study by Abumuaileq et al.\(^4\) The authors defined it as the percentage of INRs in therapeutic range (PINNR). The two methods of assessment—TTR and PINNR—are different and not absolutely interchangeable. The evaluation of quality of anticoagulation with PINNR is not the
most widely used methodology for clinical research and the application of linear interpolation to the results could have given different results. The PINRR method is still a recognized method and generally has a high correlation with TTR. It is quick, may not need a computer, and is thus the easiest to apply for the clinician in daily practice.

The percent of visits in the range on a given date is a cross-section method. It takes a specific date, and all patients are evaluated on the last reading to see whether they were within the range. The number of patients in the range (on their last reading) is taken as a percentage of the total patients on that date. This method is not relevant for an individual patient and is dedicated to evaluation of populations in a trial or in a registry.

The Spanish results with PINNR confirm prior reports validating the SAMe-TT2R2 score and add some new observations. However, this is a rather small study of 911 patients with short follow-up. The mean PINNR was 58% and this value is rather at the lower range of what may be obtained. Nevertheless, SAMe-TT2R2 performed similarly with different PINNR cut-off points. Regarding the PINNR 65% cut-off point, the P-value was 0.06 but the study was likely underpowered to make a strong statement in comparison with other reported data.8–10 Crucially, these results validate the main purpose of the SAMe-TT2R2 score, i.e. identifying patients who will not do well with VKA and additionally suggest that the SAMe-TT2R2 score may be similarly applicable in populations with different PINNR.

The SAMe-TT2R2 score has initially been built using a secondary analysis of the randomized AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial, performed including patients with more than 12 months of uninterrupted VKA treatment and more than eight INR values available.4 The study included an additional external validation cohort with patients from two hospitals in the UK with TTR calculated using the Rosendaal method. Considering the present work and other recent studies, the SAMe-TT2R2 score has now been convincingly validated in different independent study cohorts, ranging from highly selected clinical trial cohorts to real-world populations.3,4,8–10

Interestingly, the authors identified new factors that may improve the clinical value of the SAMe-TT2R2. Intrinsically, measures of c-statistic obtained with SAMe-TT2R2 score remain relatively low (0.55–0.60) although statistically significant. This means that the 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 to the SAMe-TT2R2 improved the score performance for prediction of low PINNR or events, and these observations were consistent with previous reports.11 However, additional parameters (and biomarkers, e.g. eGFR) may offer marginal improvement in the predictive ability at the cost of losing the simplicity, ease of use, and everyday practicality.

This study has other limitations. The authors did not have data about dose adjustments, frequency of INR measurements and their specific relations to other risk factors. Also, they did not collect data on other variables such as educational level, socioeconomic

### Figure 1
Possible strategy for choosing oral anticoagulation in patients with non-valvular AF.1 Medical history defined as more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease. NOAC, non-VKA oral anticoagulant; VKA, vitamin K antagonists.
status, and distance from care providers who may have an association with the overall quality of anticoagulation.

The authors also look at what happened to patients with high SAMe-TT2R2 in terms of clinical events which may be affected by INR out of target. They found that SAMe-TT2R2 has a good ability to capture the risk of developing the composite outcome of major bleeding, thromboembolic complications, and death. The ability of SAMe-TT2R2 for predicting major bleeding as an individual outcome was not statistically significant, but the study was likely underpowered to assess the relationship between SAMe-TT2R2 and major bleeding (the number of events was only 30). This actually contrasts with another study with by far a larger number of 724 bleeding events.12

One may worry that the score captures a higher risk of events as currently well achieved with the validated CHA2DS2-VASc and HASBLED scores.12 However, it has recently been demonstrated that beyond labile INR, the SAMe-TT2R2 score was predictive of stroke/thromboembolism, severe bleeding, major bleeding and death among the patients taking VKAs whilst this was not the case for patients not taking VKAs.9 This clearly suggests that the higher risk is not only a matter of intrinsic superior hazard of events but it is mediated by the use of VKA in AF patients.

Most AF patients require appropriate antithrombotic prophylaxis and oral anticoagulation, and either dose-adjusted VKAs or non-VKA oral anticoagulants (NOAC) can be used for this purpose unless contraindicated.12 In patients with a high SAMe-TT2R2 score, choosing an NOAC would sound logical. However, the benefit of such a strategy has not been demonstrated so far and is not proposed in current guidelines.

A high SAMe-TT2R2 score may also be the marker of a low treatment adherence and/or compliance, which may affect the effectiveness of either VKAs or NOACs. It may also reveal a higher risk of pharmacological interaction, some of which are specific to VKAs and other are also possible with NOACs. Whether the SAMe-TT2R2 score may also identify patients who would do worse when treated with NOAC is currently unknown and should be evaluated.

For now, the SAMe-TT2R2 score allows clinicians to have an informed way (rather than guesswork) to choose the best OAC strategy for patients with non-valvular AF, from both medical and economical perspectives. Many healthcare systems are currently unenthusiastic to propose a first-line strategy with an NOAC for AF patients because the higher cost is a significant issue and VKAs may be as efficacious as NOACs when TTR is high.13 It is likely that a minority of patients account for a majority of the out-of-range INRs and events. Therefore, if poor control is improved in the minority, it should reduce most complications. Although some physicians may be reluctant to use an additional scoring system for the only purpose of identifying the risk of a low TTR with VKA, such a tool may avoid simplistic strategies with ‘VKA strategy for everybody’ (a ‘trial of warfarin’ strategy advocated and sometimes imposed by payers) or ‘NOAC for everybody unless contraindicated’ (rather defended by evidence-based medicine but maybe too expensive) (Figure 1). In other words, using the SAMe-TT2R2 score for decision-making for OACs may be part of responsible prescribing and (given the increasing data supporting its use) evidence-based medicine.

Conflict of interest: L.F. has served as a consultant for Bayer, Boehringer Ingelheim, Medtronic, Novartis, and Sanofi Aventis and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Boston Scientific, and Daiichi Sankyo. D.A. has received funding for conference travel and educational symposia from Astra Zeneca, Eli-Lilly, Novartis, Bayer, MSD, Amgen, Pfizer. G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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