Who Will Achieve Stable Anticoagulation Therapy With Warfarin?

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Time in therapeutic range (TTR) is the most widely used indicator of the quality of anticoagulation therapy using vitamin K antagonists (VKA), mainly warfarin, and can strongly predict both bleeding and thromboembolic events in patients with atrial fibrillation (AF) receiving anticoagulation therapy. The SAMe-TT2R2 score (Sex female, Age less than 60 years, Medical history [at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease], Treatment [interacting drugs, e.g., amiodarone for rhythm control], Tobacco use [doubled], Race [doubled]) was proposed in 2013 and validated in some other cohorts. Professor Lip proposed a simple and practical decision-making process for choosing an oral anticoagulant using this score: which patients would do well on a VKA with a good TTR (SAMe-TT2R2 score 0–2), and which patients would do worse and need close monitoring and counselling, if a VKA used, or consideration of non-VKA oral anticoagulant (NOACs) prescription (SAMe-TT2R2 score ≥3) (Figure).

Variability of the international normalized ratio (INR) during anticoagulation therapy with VKA, which is calculated by Fihn’s method, has also been reported as a measure that reflects the stability, not intensity, of anticoagulation, whereas the TTR represents the percentage of appropriate intensity of anticoagulation. High INR variability (i.e., unstable anticoagulation intensity) has been shown to be associated with warfarin-associated complications, independent of the TTR, and may be more important prognostically than TTR. However, data on the predictors of
high INR variability remain scarce.

In this issue of the Journal, Numao et al.\(^9\) investigate the predictors of high INR variability in AF patients under warfarin therapy. In their study, symptomatic heart failure (odds ratio [OR] 3.974, 95% confidence interval [CI] 2.510–6.292), older age (≥75 years: OR 2.984, 95% CI 1.844–4.826) and severe renal dysfunction (eGFR <30 mL/min/1.73 m\(^2\): OR 3.918, 95% CI 1.742–8.813) were identified as independent predictors of high INR variability, after multivariate logistic regression analysis of a single hospital-based cohort, the Shinken Database. Their result will assist in the identification of AF patients for whom special attention is needed when using warfarin, as amended in the Figure.

In recent years, NOAC have emerged as an advantageous alternative to warfarin. Despite their gradually increasing use,\(^11,12\) warfarin remains the main oral anticoagulation used in many countries, especially where economic consideration of medications is an important national problem. Warfarin therapy can be challenging, given its requirement for INR monitoring and the narrow therapeutic window. The underlying mechanisms for the high inter- and intra-individual variation in the INR include genetic polymorphisms (cytochrome P450 2C\(\gamma\) gene and vitamin K epoxide reductase complex 1 gene), which are involved in the pharmacokinetics and pharmacodynamics of warfarin, and numerous drug and food interactions, respectively.\(^13\) Thus, the effectiveness and safety of warfarin needs to be evaluated in the setting of the percent TTR with an INR between 2.0 and 3.0. Indeed, the lowest risk of thromboembolic events and bleeding is achieved with the highest TTR.\(^1\) Furthermore, a current meta-analysis in patients with AF shows that the therapeutic benefit of NOAC compared with warfarin depends on the quality of INR control of anticoagulation.\(^14\) The advantage of the NOACs is dependent on the percent TTR of warfarin, and is almost lost when the TTR is >70%, according to the results of this meta-analysis. Given the utility of the SAMe-TT\((2)\)R\((2)\) score for the prediction of who can achieve a high TTR with warfarin therapy (SAMe-TT\((2)\)R\((2)\) score 0–2), this score can help physicians decide on the need for close monitoring and counselling, if warfarin is to be used, or consideration of NOAC usage in patients with higher SAMe-TT\((2)\)R\((2)\) score (≥3).

Unlike the TTR, INR variability has not been widely adopted for the assessment of anticoagulation control in patients on warfarin therapy. This may be partly because the calculation method is complex for use in a routine clinical practice. In addition, there is no agreement on the calculation method or of the cutoff value for INR variability to define stable and unstable anticoagulation, respectively. Previous studies used different thresholds for INR variability when identifying unstable anticoagulation measurements. However, some recent studies reported that combining both treatment quality indicators (TTR and INR variability) could provide helpful information for identifying patients at high risk of bleeding or death as warfarin complications.\(^15\) When making a choice of oral anticoagulant, physician should pay attention not only to the TTR but also INR variability, including the predictors, even before initiation of anticoagulant therapy, as identified by Numao et al.\(^9\) in this issue of the Journal.

Further studies to demonstrate external validation of the predictors for INR variability will be needed in other cohorts and to establish the ‘new score’ for assessment of INR variability that can predict adverse clinical outcomes in AF patients before initiation of anticoagulation therapy.

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### References


12. Olshansky B, Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Relation-Ship of the SAMe-TT(2)R(2) score to poor-quality anticoagula-


21. Olshansky B, Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Relation-Ship of the SAMe-TT(2)R(2) score to poor-quality anticoagula-


23. Fratini J, Ferreira J, Costa F, Carmo P, Cavaco D, Carvalho S, et al. Non-vitamin K antagonist oral anticoagulants compared with warfarin at different levels of INR control in atrial fibrilla-