The importance of time in therapeutic range of warfarin for stroke prevention in atrial fibrillation

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Atrial fibrillation (AF) is associated with significantly higher risk of ischemic stroke [1], and stroke prevention with oral anticoagulants (OACs) is the cornerstone of the management of AF patients [2]. Although non-vitamin K antagonist OACs (NOACs) are more and more commonly prescribed in daily practice [3], warfarin is still important in stroke prevention considering the cost issue. For warfarin, a good treatment quality assessed by the international normalized ratio (INR) and time in therapeutic range (TTR) is crucial since a higher TTR is significantly associated with lower risk of ischemic stroke and intracerebral hemorrhage (ICH) [4]. There are 2 fundamental issues regarding warfarin use — what is the target range of the INR and the goal of TTR?

The target range of the INR of 2–3 has been used for years and was mainly based on relatively small-sized studies performed decades ago. Patients receiving warfarin enrolled in pivotal trials of NOACs provided a great opportunity to re-visit the optimal INR range. In a pooled analysis of warfarin-treated patients (n = 21 883) from three clinical trials (RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48), an INR range between 2.0 and 2.5 appeared to offer a good balance between ischemic stroke and ICH, which was also associated with the lowest rate of all-cause death [5, 6]. These findings were not at variance with the widely adopted INR range of 2–3 but may provide a reasonable indication to keep the INR within the low end of the range for patients with bleeding risk.

Most international AF guidelines have clear suggestions for TTR levels. In the recently published Asia Pacific Heart Rhythm Society (APHRS) AF guidelines, for example, an individual TTR of ≥65% (ideally ≥70%) was suggested [7]. The 2020 AF guidelines of the European Society of Cardiology stated that in patients on warfarin with a low TTR range (e.g. TTR <70%), switching to NOACs to improve TTR was recommended [8]. Although the guidelines have clear recommendations about required TTR levels for warfarin users, large-scale randomized trials comparing the high-quality warfarin treatment (e.g. TTR ≥70%) to NOACs are lacking. The highest quality data currently available were from the sub-analysis of NOAC trials. In the ENGAGE trial, the principal results of the comparisons between the high-dose edoxaban regimen and warfarin were consistent in subgroups with a center level TTR > or ≤66.4% [9]. However, a trend suggested that a greater relative reduction in major bleeding with edoxaban was observed at the centers that achieved a center-based TTR of less than 66.4% (*P* for interaction = 0.06). In the RE-LY trial, the benefits of 150 mg dabigatran in reducing stroke, 110 mg dabigatran in reducing bleeding, and both doses in reducing intracranial bleeding vs. warfarin were consistent irrespective of those centers' TTR (less than 57·1%, 57·1–65·5%, 65·5–2·6%, and greater than 72·6%) [10]. In a pooled analysis of 4 NOAC trials with a median TTR of 65%, it seems that advances of NOACs in reducing major bleeding compared to warfarin were only evident for the subgroup with a center-based TTR <66% (relative risk [RR], 0.69; 95% confidence interval [CI], 0.59–0.81), but not for those with a center-based TTR ≥66% (RR, 0.93;

95% CI 0.76–1.13); *P* for interaction = 0.022 [11]. These data from clinical trials provided important insights into the use of warfarin and emphasized the importance of a high TTR. However, data from routine daily practice on this issue were relatively limited.

In this issue, Aktan and colleagues [12] presented an interesting study to compare the one- and five-year risks of ischemic cerebrovascular disease (CVD)/transient ischemic attack, hemorrhagic CVD, and mortality in 254 patients who received warfarin with effective TTR (>60%) and 886 patients who received NOACs. The results showed that one-year mortality, five-year mortality, and ischemic or hemorrhagic CVD were similar between the warfarin and NOAC groups. The authors should be congratulated on their important work. However, some data may be helpful to make the conclusions applicable in practice more easily. First, for NOAC users, what was the dosing of each NOACs, and how many percentages of these dosing were prescribed according to labelling? A previous study demonstrated that underdosing or overdosing NOACs was not uncommon and was associated with higher risk of ischemic stroke and major bleeding, respectively, compared to on-label dosing [13]. Therefore, the information about NOAC dosing is crucial since it might change the results of the comparisons between warfarin and NOACs. Second, some important safety endpoints, such as risks of major bleeding, gastrointestinal bleeding, and intracranial hemorrhage were not reported. Third, a considerable number of patients crossed over to different OACs (n = 568), and it may potentially confound the authors' analyses. The intention-to-treat design for efficacy endpoints and on-treatment analysis for safety endpoints can further confirm the present findings. Lastly, 554 patients receiving warfarin were actually excluded from the study due to a TTR lower than 60%. This patient number was two-fold higher than the number of patients with effective TTR (n = 245). It may show how difficult it is to maintain a good TTR for warfarin users.

Overall, the study by Aktan et al. [12] provides some unique data, and a high TTR should be encouraged and incorporated into the Atrial Fibrillation Better Care (ABC) Pathway to reduce the risks of adverse clinical outcomes in patients with AF [14].

Article information

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