Anticoagulation Control in Atrial Fibrillation
Optimizing Risks and Benefits

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A trial fibrillation (AF), the most common sustained arrhythmia in clinical practice, with a prevalence of almost 1 in 10 by the eighth decade of life, is associated with a heavy burden on morbidity, mortality, and healthcare expenditure. To both patients and physicians, a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared and almost 1 in 10 by the eighth decade of life, is associated with a feared consequence of AF is a 5-fold increase in the risk of stroke. To date, the most effective intervention to mitigate the risk of thromboembolic events in patients with AF is adjusted-dose anticoagulation with warfarin. Evidence-based guidelines and performance measures for optimal management of AF have been developed recently, with particular emphasis on patient selection for anticoagulation. Multiple studies assessing risks and benefits of anticoagulation with the vitamin-K antagonist warfarin have had consistent clinical implications. Maintaining patients in the narrow therapeutic range of warfarin, as measured by the international normalized ratio (INR), is critical but represents a major clinical challenge. The benefits of warfarin in prevention of thromboembolic events are accompanied by the risks of bleeding complications, including life-threatening cerebral hemorrhage.

Both the risk of the outcome to be prevented (ie, thromboembolic events) and the potential harm from the intervention (ie, bleeding) are related to the intensity of anticoagulation as measured by the INR. A “subtherapeutic” INR, typically defined as <2.0 for AF, is associated with an increased risk of thromboembolism, whereas the risk of major bleeding significantly increases with INR values >3.5. Given these observations, efforts have been directed at identifying reliable longitudinal measures of monitoring anticoagulation intensity, which could then be used to improve quality of care in patients with AF. An important question about any proposed measure of anticoagulation intensity is how such a measure relates to the 2 feared outcomes in anticoagulated patients with AF: thromboembolism and major bleeding.

That question is addressed by Wan et al in this issue of Circulation: Cardiovascular Quality and Outcomes. On the basis of a comprehensive review of observational studies and randomized controlled trials of patients with AF receiving vitamin-K antagonists (mostly warfarin) and reporting 1 of 2 measures of anticoagulation intensity (percentage of time in therapeutic range [TTR] or percentage of INRs in range), Wan et al make several informative observations. As observed in multiple prior studies of warfarin use in patients with AF, there was considerable variation in the intensity of anticoagulation by either measure, reflecting heterogeneity in the patient population and clinical practice (across the eligible studies, TTR ranged from 29% to 75%, and percent of therapeutic INRs ranged from 34% to 84%). The authors note that in studies reporting both measures, TTR correlated significantly with percentage of INRs in range (P<0.001). Consistent with prior observations, anticoagulation control was significantly better in randomized controlled trials compared with observational studies.

Most notably, Wan et al observed an inverse relationship between TTR and risk of thromboembolic events or major bleeding. On the basis of the observation that studies reporting a higher TTR tended to have a lower rate of thromboembolic events or major bleeding, the authors conclude that TTR may be used to accurately predict reductions in adverse events. Assuming a linear relationship, the authors estimated 1 major bleed prevented per 100 patient-years for every 8% increase in TTR and 1 thromboembolic event prevented for every 10% increase in TTR. Interestingly, this inverse association was only evident in retrospective studies and was not observed in randomized controlled trials. This may be because of the smaller number of included clinical trials reporting TTR (7 versus 19 retrospective studies) and the smaller variation in the risk of outcomes in clinical trials (especially risk of major bleeding). However, given the well-recognized limitations of retrospective studies, the associations reported by Wan et al need to be confirmed in prospective studies.

The observations of Wan et al emphasize the essential clinical message that optimization of risk-benefit ratio of anticoagulation in AF is achieved by maintaining INRs in the therapeutic range as much as possible. Although the findings are clinically intuitive, their implications on clinical practice are not straightforward. Although a statistically significant linear relationship can be described between TTR and outcome rates, careful examination of the scatter plots (eg, Figure 3) reveals considerable variability in the risks of these outcomes for any given TTR. For example, for a TTR...
between 50% and 60%, there is a >2-fold difference in the observed rates of thromboembolic events and an ~7-fold difference in the rates of major hemorrhage. The coefficient of determination ($R^2 = 0.35$) suggests that only about one third of the variability in the risks of these outcomes could be accounted for by differences in TTR.

Despite the many prior studies assessing the risks and benefits of anticoagulant therapy in patients with AF and the analysis of Wan et al.\textsuperscript{14} it is evident that much remains unknown. Additional research is needed to identify patient-and practice-specific factors that may account for the remainder of that variability in outcomes that is not accounted for by TTR alone. For instance, because older patients are at higher risk of thromboembolic or hemorrhagic events, and because physicians may tend to be more cautious with INRs in older patients (hence, such patients may spend less time in the therapeutic range), the relationship between TTR and thromboembolic events may be partly confounded by age. Other factors that need to be considered include the phase of anticoagulation (initiation or maintenance) and concomitant medications and comorbidities that may be related to both the intensity of anticoagulation and the risk of stroke or major bleeding. The role of emerging clinical strategies for optimizing the risk-benefit ratio of warfarin use, such as pharmacogenomic testing and patient monitoring of INRs, needs additional investigation. Such details could only be addressed with access to individual-level data in clinical trials or carefully designed prospective cohort studies.

Fundamentally, the analysis by Wan et al\textsuperscript{14} represents a significant association between a surrogate marker (TTR) and a clinical outcome (thromboembolic event or major hemorrhage). How and whether changing that marker would affect the hard end points is uncertain. Although clinical intuition would suggest that increasing TTR will improve outcomes, one could envision a situation in which intensive efforts at increasing TTR could lead to more aggressive dosing of warfarin in some patients and hence a higher risk of bleeding. The designed intervention is sometimes a more important determinant of the outcome than the surrogate marker that prompted it. Although the study by Wan et al\textsuperscript{14} adds to the available knowledge regarding risks and benefits of anticoagulation therapy in AF patients, further research is needed before TTR can be adopted as a preferred tool to assess quality of anticoagulant therapy.

**Disclosures**

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**References**


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