EDITORIAL

New Options in Anticoagulation for Atrial Fibrillation

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The presence of atrial fibrillation significantly increases the risk and burden of thromboembolic stroke.[1] Warfarin is the reference standard treatment for the primary prevention of embolic stroke during atrial fibrillation.[2] However, the long-term use of warfarin has its limitations. Although guidelines suggest a target international normalized ratio (INR) of 2.5 (range, 2.0 to 3.0) for this indication,[2] only about 60% of patients have an INR within the recommended range at a given time in usual clinical practice. This is the reason that is most often given for the search for other oral antithrombotic agents that could be simpler to manage and that might replace warfarin in such patients.

Two recent studies have compared new antithrombotic agents with warfarin for the primary prevention of thromboembolic events in patients with nonvalvular atrial fibrillation. In this issue of the *Journal*, Patel et al.[3] report the results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), in which the investigators compared rivaroxaban, a direct factor Xa inhibitor, with warfarin. This study follows on the heels of the report of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (ClinicalTrials.gov number, NCT00262600),[4] showing that dabigatran, a direct thrombin inhibitor, was not inferior to warfarin. Both studies provide some points to ponder for a condition in which placebo-controlled trials are no longer possible.

One interesting point is how the interpretation of ROCKET AF depends on the results from the three different protocol-specified analyses of the primary outcome of stroke or systemic embolism. The primary analysis included only patients who were treated according to protocol and were followed for outcome events only for the period during which they were actually receiving the assigned treatment (or within 2 days after the last dose). This analysis, designated the "per-protocol, as-treated" analysis, resulted in a conservative test for noninferiority[5] and showed that rivaroxaban was significantly noninferior to warfarin. The authors also tested for superiority using an intention-to-treat analysis, which did not show superiority for rivaroxaban over warfarin.

Between these two analyses, the authors conducted another analysis in the "as-treated safety population." Here, they included all patients who received at least one dose of a study drug and were followed for events while receiving the drug (or within 2 days after the last dose), regardless of adherence to protocol. It is not surprising that the annual event rates in the two study groups in this analysis were much closer to those of the per-protocol analysis than to those in the intention-to-treat analysis. As a consequence, in the safety analysis, the between-group P value was significant, even though the results do not show superiority for rivaroxaban over warfarin, since the intention-to-treat analysis was negative. Thus, the multiple analyses have muddied the waters regarding rivaroxaban's efficacy and effectiveness over warfarin.

Trials comparing new oral antithrombotic agents with warfarin are dependent on the quality of the management of the warfarin cohort. Overall compliance varies. Trials like ROCKET AF and RE-LY use algorithms for imputing the dummy INR of the warfarin placebo in patients who are not receiving warfarin in order to maintain blinding. They also use the concept of "time in thera-

peutic range" to assess the quality of warfarin management. Such trials typically use a method described by Rosendaal et al.,[6] in which the measured INR values and the interval between INR tests are both taken into account. On the basis of this approach, INR values were within the therapeutic range a mean of 55% of the time in ROCKET AF and 64% in the RE-LY trial. So the interpretation of noninferiority in a given trial may also depend both on the homogeneity and treatment accuracy of the warfarin cohort and on the dummy INR algorithm that is used.

Overall, the frequency of major hemorrhagic events in ROCKET AF did not differ significantly between the rivaroxaban group and the warfarin group. A similar finding was seen in the RE-LY study. However, interestingly, both studies showed a reduction in the rate of intracranial hemorrhage with the new oral antithrombotic agent, as compared with warfarin. The reasons for the potential reduction in intracranial hemorrhage that was associated with these agents are not clear, but one possibility is the effect on a single target in the hemostatic system by the new antithrombotic agents versus the multiple targets by warfarin.[7] More intriguing is the possibility that cerebral vascular beds have protective features that are more apparent at the doses of either of the new agents tested. The presence of large amounts of tissue factor in the cerebral vascular neighborhood could modulate vascular hemostatic activity within brain vessels. It is possible that neither rivaroxaban nor dabigatran affects the complex made up of tissue factor and factor VIIa, whereas warfarin decreases factor VII activity. Does this difference influence the risk of hemorrhage? Fundamental studies of cerebral vascular responses to these agents and of the differential risk of intracranial hemorrhage in the two trials would be instructive.

For the management of atrial fibrillation, oral alternatives to warfarin have arrived. Their simplicity of use is attractive, and they appear to have an efficacy similar to that of warfarin, with the proviso that comparisons seem to depend on how easily the patient can be treated with warfarin. An important concern that these clinical trials do not address is the absence of antidotes to rapidly reverse the anticoagulant effects of either rivaroxaban or dabigatran in the case of life-threatening hemorrhage or surgery. All these issues need to be taken into account in clinical decision making. Further studies will be necessary to refine the treatment of a growing population of patients with atrial fibrillation in order to reduce the risk of stroke.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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