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Perspective

Evaluating Rivaroxaban for Nonvalvular Atrial Fibrillation — Regulatory Considerations

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On September 8, 2011, the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration (FDA) discussed data submitted in support of the new drug application for rivaroxaban for preventing stroke and non–central nervous system systemic embolic events in patients with nonvalvular atrial fibrillation. Supportive evidence came primarily from ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ClinicalTrials.gov number, NCT00403767),[1] in which more than 14,000 patients were randomly assigned in a double-blind fashion to either 20 mg of rivaroxaban once daily or warfarin therapy targeting an international normalized ratio (INR) of 2 to 3. The primary aim was to assess whether rivaroxaban was noninferior to warfarin, with a secondary aim of assessing superiority.

In ROCKET-AF, a noninferiority margin of 1.38 for the relative risk of stroke or systemic embolism was based on an approval criterion that rivaroxaban be superior to placebo by at least 50% of the margin by which warfarin is superior to placebo, as estimated from a meta-analysis of six placebo-controlled reference studies. Per-protocol "on-treatment" analyses were prespecified because of concerns in noninferiority trials that events occurring with equal probabilities after patients discontinue randomized treatments might dilute the trials' sensitivity to true treatment differences and thus increase the risk of falsely declaring a treatment noninferior.[2] In the primary analysis, the relative risk of stroke or systemic embolism with rivaroxaban as compared with warfarin was 0.79, with a 95% confidence interval that excluded the prespecified noninferiority margin. The risk of major bleeding events was somewhat higher with rivaroxaban, especially when double counting is avoided by excluding hemorrhagic strokes that were included in the efficacy end point of stroke or systemic embolism.

ROCKET-AF had important strengths, including its double-blind design and the favorable efficacy results noted above. However, thorough analyses provided by the FDA identified important issues affecting interpretation of these results.

In noninferiority trials, the "constancy assumption" must be satisfied: the control treatment, as administered in the new trial, must have the same magnitude of benefit relative to placebo as it had in the reference trials used to estimate its effect. The noninferiority margin might need to be modified if the results in the control group are for a different patient population, intensity of treatment, or measure of outcome than was used in the reference trials. Concerns about nonconstancy in ROCKET-AF were related to the higher-risk patients enrolled in the study, the more than 5% of patients who discontinued follow-up due to "withdrawal of consent," and the fact that the INR for patients in the warfarin group was in the therapeutic range (between 2 and 3) only 55% of the time — considerably less than the 62 to 73% seen in other recent clinical trials. When the FDA analyzed data only from ROCKET-AF sites whose patients' average time in the therapeutic range was above specified thresholds, they found that the relative risk of stroke or systemic embolism with rivaroxaban was considerably higher (near unity) if the threshold was 67%, whereas with a threshold near 55% (corresponding to sites with an average time in the therapeutic range of about 65%), the relative risk was closer to that observed in the study as a whole.

Even in noninferiority trials, per-randomization analyses should be conducted. These analyses avoid the bias that occurs with per-protocol on-treatment analyses when patients discontinue their randomized treatment for reasons related to the treatment itself and the patients who do so have a different risk profile from those who don't. The importance of per-randomization analyses is very apparent in ROCKET-AF. The on-treatment analysis was based on observations that were truncated at 2 days after discontinuation of randomized treatment — a time frame likely to miss events related to inadequate coagulation during the transition to alternative treatment. There was greater risk of such events in the group receiving rivaroxaban, with its 5-to-9-hour half-life, than in the group receiving warfarin, with its 40-hour half-life. There was a much higher rate of stroke or systemic embolism in the rivaroxaban group than in the warfarin group (31 vs. 12 detected events) between day 2 and day 7 after discontinuation of randomized treatment. In the per-randomization analysis that captured these events, the relative risk of stroke or systemic embolism with rivaroxaban was 0.88, with a 95% confidence interval of 0.78 to 1.03, so superiority was not established. A positive trend seen in the per-protocol analysis of myocardial infarctions was similarly attenuated. A striking increase in death rates after the discontinuation of randomized treatment further complicates the noninferiority assessment in ROCKET-AF.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (NCT00262600), which provided the pivotal data in support of dabigatran's approval, compared open-label use of dabigatran with warfarin in more than 18,000 patients. The estimated relative risk of stroke or systemic embolism in a per-randomization analysis was 0.66 (95% confidence interval, 0.53 to 0.82) in a setting in which the average time in therapeutic range with warfarin was 64%.[3] Although the trial was not blinded and dabigatran's effect on the risk of myocardial infarction was slightly unfavorable, the results robustly support the superiority of dabigatran over warfarin. RE-LY is also relevant to deliberations regarding rivaroxaban's approval. According to FDA policy, "It is essential that a new therapy must be as effective as alternatives that are already approved for marketing when the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack)."[2,4] Does rivaroxaban satisfy this criterion? In particular, are additional data needed to evaluate whether rivaroxaban is noninferior to dabigatran?

The RE-LY results and uncertainty about the validity of the constancy assumption in ROCKET-AF raise concerns that rivaroxaban could be inferior to either dabigatran or warfarin, particularly when the latter is "used skillfully." The apparent nonconstancy of warfarin treatment between the two trials is problematic, although it's unclear whether the lower average time in therapeutic range in ROCKET-AF reflects greater difficulty in caring for higher-risk patients or is an artifact of the protocol design and trial conduct, including the mandated blinding of INR monitoring. Further concerns relate to a trend toward higher event rates in the rivaroxaban group than in the warfarin group as patients were transitioned to usual care — excess events that weren't captured in the primary efficacy analyses. The FDA also noted that ROCKET-AF's once-daily dosing of rivaroxaban wasn't really supported by the available pharmacokinetic and pharmacodynamic data. If the apparent noninferiority of once-

daily rivaroxaban to warfarin was due primarily to a low time in therapeutic range in the warfarin group and the exclusion of excess events after randomized treatment was discontinued, then that dosing strategy might be unacceptably inferior to dabigatran. These circumstances could lead to an unproven treatment displacing an effective treatment on the basis of overzealous promotion of more convenient once-daily dosing.

The majority of the advisory committee judged that ROCKET-AF's results supported approval of rivaroxaban for stroke prevention in patients with atrial fibrillation. Justifications included the strength of evidence for noninferiority relative to warfarin in a high-risk population, the expectation that evidence can be obtained to establish that risk will be reduced by short-term continuation of rivaroxaban when transitioning to other anticoagulant therapy, the belief that postmarketing studies can address FDA concerns that a twice-daily dosing regimen is more appropriate, and the interest in having an additional option that (some are convinced) adequately preserves the efficacy of existing treatments. It was suggested that rivaroxaban might be used in patients who have an inadequate response to or cannot take dabigatran or warfarin, although data are not available to directly address rivaroxaban's efficacy and risks in such settings. The FDA will take the advisory committee's discussion and other insights under consideration; the target date for FDA action, according to the agency's Web site, is November 5, 2011.

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

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