ROCKET-AF Trial Results Under Fire

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Concern that equipment error may have led to higher doses of warfarin than necessary call the huge trial's findings into question.

The novel oral anticoagulants (NOACs) are now common drugs in our arsenal to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation (AF). With multiple well-conducted clinical trials providing evidence of their non-inferiority to, or, in some cases superiority over warfarin, the new drugs came to market relatively quickly and are now widely available. The news that results of one of the primary clinical trials are now under review has raised many critical questions.

A recent report calls into question the validity of the large ROCKET-AF trial1 (rivaroxaban [Xarelto] vs warfarin in nonvalvular AF), published in the New England Journal of Medicine in 2011 and which served as evidence on which rivaroxaban was granted FDA approval. Given the trial's large size (n=14,264) as well as the backing of the Duke Clinical Research Institute (DCRI) and oversight by future FDA commissioner candidate Robert Califf (director of the DCRI), it is no surprise that findings from the study were quickly embraced and put into clinical practice. What has come to light, however, is that the point-of-care device (Alere INRatio and INRatio2 PT/INR Monitor System) used to monitor INR values and adjust warfarin doses in ROCKET-AF was recalled by the FDA for an underreporting error. Apparently, the INR values obtained from the device (which were used to adjust the warfarin dosing) were lower than what would be obtained if the INR had been tested in a laboratory setting.

The findings of the ROCKET-AF trial demonstrated the noninferiority of rivaroxaban (event rate 1.7% per year) compared with warfarin (event rate 2.2% per year) for stroke/systemic embolism. Similarly, it showed no difference in major and nonmajor clinically relevant bleeding between the agents but did show a significant reduction in intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal hemorrhage (0.2% vs. 0.5%, p=0.003) with rivaroxaban. But if the device used to monitor the INR was systematically underestimating the true INR, and so leading to overdosing in the warfarin arm, the faulty equipment may have introduced significant bias into the results (particularly the bleeding results) of ROCKET-AF.

Given the emergence of this new information, the results of the trial are being re-evaluated by the European Medicines Agency. At this time, the FDA has not restricted use of rivaroxaban for nonvalvular AF and we should not alter our clinical practice in any way. However, the issue is a sharp reminder that the clinical trials we rely upon so heavily to ensure our patients’ clinical safety are, in fact, subject to error and that even small errors in trial execution could result in faulty conclusions and the potential for significant harm.

References:

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