Editorial

Dabigatran and Mechanical Heart Valves — Not as Easy as We Hoped

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Warfarin is the mainstay of anticoagulation for patients with mechanical heart valves. However, warfarin has well-known limitations, including interactions with food and drugs and the requirement for lifelong monitoring of the international normalized ratio (INR).[1] Variability of the INR is the strongest independent predictor of reduced survival after mechanical valve replacement.[2] Thus, there is a pressing need for alternatives to warfarin, and the advent of the target-specific oral anticoagulants has been highly anticipated.

Eikelboom et al.[3] now report in the *Journal* the results of a study whose primary aim was to validate a new dosing regimen for dabigatran, as compared with warfarin, for the prevention of thromboembolism in patients with mechanical heart valves. In the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN), the investigators evaluated doses that were based on pharmacokinetic simulations in patients with atrial fibrillation who were treated with dabigatran. The starting dose of dabigatran varied according to presurgical renal function, with subsequent dose adjustment based on trough levels of the drug for a target level of 50 ng per milliliter or more. Nearly 80% of patients were started on dabigatran within 3 to 7 days after valve-replacement surgery (population A). The remainder were enrolled more than 3 months after valve replacement (population B).

The study was terminated early because of an excess of both thromboembolic and bleeding events among patients in the dabigatran group. The majority of thromboembolic events occurred within the first 90 days in the group that had recently undergone surgery. All major bleeding episodes occurred in this group and were pericardial in location. Dose adjustment or discontinuation of dabigatran was required in 32% of patients.

Several features of RE-ALIGN may help to explain these results. High on the list is the large majority of patients (nearly 80%) who had recently undergone surgery. The early postoperative period may have been less than optimal for testing a new fixed-dose drug regimen because of the enhanced thrombogenicity inherent in such patients. The postoperative state is characterized by intense inflammation, activated platelets, and circulating procoagulant tissue-factor–

bearing microparticles, which are a recognized alternative mechanism for coagulation activation.[4-6] Because of the heightened thrombogenicity of this early period, bridging therapy with heparin is recommended, with doses closely adjusted according to the activated partial thromboplastin time until a therapeutic INR is achieved. Thus, anticoagulation during this phase is characterized by frequent individualized dose adjustment to precisely match the antithrombotic effect to changing conditions.

Another key consideration in the interpretation of RE-ALIGN is the dabigatran trough target level of 50 ng per milliliter or more. This level was correlated with the prevention of stroke among patients with atrial fibrillation in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Translation of dose across indications is challenging, given the different mechanisms of thrombus formation in different vascular beds, differences in flow and shear stress (aortic vs. mitral position), and patients' characteristics. The lack of association of trough levels with outcome events in RE-ALIGN is not surprising, given individual variation in dose and therapeutic response, unmeasured confounders in the recent surgical period, and the interval between trough measurement and event. All the major bleeding events occurred within the first 2 weeks after surgery and were pericardial in location, which raises additional questions about the surgery itself and the timing of drug initiation, given the rapid onset of action of dabigatran and the delayed time to peak effect of warfarin.

Finally, the lower-than-projected plasma levels of dabigatran in the first 4 weeks after randomization were problematic. Extrapolation of pharmacokinetic models derived from older ambulatory patients with atrial fibrillation to younger patients shortly after valve surgery may have resulted in a greater proportion of patients with trough levels of less than 50 ng per milliliter. The mean age of patients in the RE-LY study was 71 years, as compared with 56 years in RE-ALIGN. Renal function in the younger group was also better. The timing of intervention may also be an influential factor. Because plasma levels of drugs are dependent on bioavailability and drug clearance, gut dysfunction in the postoperative setting caused by opiates, metabolic derangements, or other factors may have altered dabigatran absorption, an important factor given the absolute bioavailability of 3 to 7% for the drug.

Thus, there were calculable reasons for the failure of RE-ALIGN, including the use of a fixed dabigatran dose during a period of anticipated wide fluctuations in endogenous and exogenous confounding factors, a trough level predicated on a stasis thrombosis model, and extrapolation of a dosing regimen derived from a different patient population with a different indication. The Food and Drug Administration and the European Medicines Agency have recommended against the use of dabigatran in patients with mechanical heart valves.[7,8] Off-label use will place patients at undue risk and is rightfully prohibited. The results of RE-ALIGN are disappointing, but there is a palpable downside as well to potential premature abandonment of research into the use of such drugs in patients with mechanical heart valves.