

Idarucizumab, a humanized monoclonal antibody fragment, for reversal of Dabigatran therapy for atrial fibrillation

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The prevalence of atrial fibrillation (AF) increases with age, and the elderly are the fastest growing subset of the population. It has been estimated that there will be 12 million patients with AF in the United States within the next several decades [1-5]. Actually, AF is the most common sustained arrhythmia encountered in the field of internal medicine. AF has a prevalence of approximately 1% and a lifetime risk of approximately 25% after the age of 40 [1,2]. The annual risk of stroke ranges from 2%-18% depending on other risk factors [3]. Atrial fibrillation shares strong epidemiological associations with other cardiovascular diseases such as heart failure and coronary artery disease [6-10]. Many fundamental aspects of AF have been poorly understood until quite recently, and there are several features on the mechanisms of AF that makes it difficult to manage it properly [10-12]. AF may present in a wide variety of clinical conditions. The optimal management strategy for an individual patient with AF depends on the patient's underlying condition.

AF increases the overall risk of stroke five-fold, and is associated with particularly severe strokes. About 76% of AF patients have a moderate to high risk of embolic complications, and they have also a significant risk factor for stroke recurrence [13-15]. Therefore, AF carries a high risk for thromboembolic events and any patient with at least two moderate risk factors, and probably even one, should be on oral anticoagulation. Balancing the risk of bleeding and thromboembolism is crucial in the management of patients with AF. Antithrombotic therapy reduces the risk of stroke in patients with AF, and Warfarin has been shown to have a relative risk reduction of approximately 60% compared with control and to be significantly more effective than Aspirin [16,17]. Therefore, for over five decades, oral anticoagulation with Warfarin has become the standard of care for stroke prevention in patients with AF [18]. Warfarin, however, has limitations, including multiple interactions with other drugs and foods, genetic variability in metabolism, delayed onset and offset, and the need for frequent monitoring and dose adjustments. Given the limitations of Warfarin, clinicians and clinical investigators have been interested in the development of newer oral anticoagulants [19-21]. Therefore, there have been studies investigating the efficacy and safety of these agents. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a large, multicenter, randomized trial designed to compare two fixed doses of Dabigatran (110 mg and 150 mg), each administered in a blinded manner, with open-label use of Warfarin in AF patients who were at increased risk for stroke [19]. The primary study outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other

outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. The rate of the primary outcome was significantly lower with Dabigatran at a dose of 150 mg twice daily (1.11% per year) than with either Dabigatran at a dose of 110 mg twice daily (1.53% per year) or Warfarin (1.69% per year). Both doses of Dabigatran were noninferior to warfarin ($p < 0.001$), and the higher dose of Dabigatran was even superior to Warfarin ($p < 0.001$). The rate of non-hemorrhagic stroke was also significantly lower with 150 mg of Dabigatran (0.92% per year) than with either 110 mg of Dabigatran (1.34% per year) or Warfarin (1.20% per year). The rates per year of hemorrhagic stroke with the 110-mg and 150-mg Dabigatran doses (0.12% and 0.10%) were significantly lower than that with Warfarin (0.38%). The rate of extracranial hemorrhage was similar in all three groups: 2.51% with 110 mg of Dabigatran, 2.84% with 150 mg of Dabigatran, and 2.67% with Warfarin. In summary, the RE-LY trial showed that compared with Warfarin the oral direct thrombin inhibitor, Dabigatran etexilate given at a dose of 150 mg twice daily reduces stroke with less intracranial bleeding, and Dabigatran 110 mg twice daily has similar efficacy with less bleeding [19]. The rate of major bleeding was 3.36% per year in the Warfarin group, as compared with 2.71% per year in the group that received 110 mg of Dabigatran (relative risk with Dabigatran, 0.80; 95% CI, 0.69 to 0.93; $P = 0.003$) and 3.11% per year in the group that received 150 mg of Dabigatran [19].

Despite this better performance of dabigatran than warfarin in the bleeding scenario, there are still various emergent situations where the presence of Dabigatran in the blood system may worsen the hemorrhagic event [22-24]. Serious bleeding can occur. For example, a life-threatening bleeding complication can occur. Moreover, dabigatran-treated patients may sustain trauma, and may require urgent surgery or intervention. Additionally, dabigatran can increase the risk of perioperative bleeding. In order to improve the medical management of such patients, a specific dabigatran-reversal agent was synthesized. Idarucizumab, a humanized monoclonal antibody

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fragment, binds dabigatran with an affinity that is 350 times as high as that observed with thrombin [25-27]. Consequently, idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity. In healthy young volunteers with normal renal function, as well as, in elderly volunteers with mild or moderate renal impairment, the administration of idarucizumab produced immediate and complete reversal of the anticoagulant effects of dabigatran without procoagulant effects [28-30].

There are interesting studies on Idarucizumab at present time that we can't discuss them all in this editorial. One the most important studies is The RE-VERSE AD study which was undertaken to examine the efficacy and safety of idarucizumab in dabigatran-treated patients who had serious bleeding or required urgent procedures [31]. Idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran in 88 to 98% of the patients who had had elevated clotting times at baseline. Idarucizumab obviated the need for intervention in 1 of the 3 patients in group B who did not undergo a procedure. Among the 36 patients who underwent a procedure, normal hemostasis was reported in 92% and mild-to-moderate impairment in the remaining 8%. The 5-g dose of idarucizumab that was used in this study to reverse the effects of dabigatran was chosen on the basis of the highest range of plasma concentrations measured in the RE-LY trial. Immediately after the administration of idarucizumab, the concentration of unbound dabigatran was reduced to a level at or near the lower limit of quantification in all but 1 patient, resulting in normalization of the dilute thrombin time and the ecarin clotting time. There were no safety concerns among the 90 patients involved in this study. Evidently, the efficient development of idarucizumab to rapidly and completely reverse the anticoagulant activity of dabigatran is an important therapeutic advance with clinical implication. Therefore, idarucizumab is likely to be the treatment of choice for patients who present with dabigatran-induced uncontrolled or life-threatening bleeding or for those AF patients on dabigatran who require urgent surgery or invasive procedures.

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