

## **Stroke Prevention in Atrial Fibrillation**

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People with nonvalvular atrial fibrillation (AF) face a risk of ischemic stroke that is three to five times that of the population in sinus rhythm, increasing with age, and the incremental risk is greatest for those who have experienced a previous ischemic stroke, systemic embolism or transient ischemic attack. Numerous clinical trials have demonstrated that anticoagulation with the vitamin K antagonist warfarin is the most effective therapy available for stroke prophylaxis in patients with AF. The narrow therapeutic index of warfarin requires that the intensity of anticoagulation be maintained within a narrow therapeutic range (INR 2.0-3.0) to optimize efficacy and minimize bleeding. Since the pharmacokinetics of warfarin vary as a consequence of genetic factors and interactions with multiple drugs and foods, maintenance of the INR within this range is difficult to achieve in clinical practice without close coagulation monitoring and frequent dose adjustments. Current guidelines recommend oral anticoagulation for high-risk patients with AF, but the inherent limitations of these agents lead to substantial underuse, particularly among elderly individuals who, on average, take nearly a dozen concomitantly prescribed medications, many of which interact with warfarin.

This state of affairs has stimulated the development of new agents with improved benefit–risk profiles, such as direct thrombin inhibitors and factor Xa inhibitors, which appear to offer a wider therapeutic margin and low potential for drug interactions, allowing more convenient dosing without anticoagulation monitoring. Among these, the agent at the most advanced stage of clinical development, dabigatran etexilate, has been evaluated for stroke prevention in AF in the RE-LY trial, the largest clinical trial of antithrombotic therapy for stroke prevention to date, involving a population of some 18,000 patients with AF at risk of stroke, the results of which will become available shortly before the symposium. The results of other trials, involving rivaroxiban, apixiban and idrabiotaparinux are anticipated in the next 12-18 months.

For well over half a century, the vitamin K antagonists have been the only class of oral anticoagulant drugs available for long-term clinical use. The introduction of a new class of compounds for stroke prevention in patients with AF may increase the number of patients eligible for anticoagulation therapy and offer the potential to prevent thousands of strokes, but present unique challenges to regulatory authorities and clinicians to assure safety and efficacy as these compounds enter the clinical arena.

## References

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