Atrial fibrillation (AF) remains a prominent cause of ischemic stroke worldwide. The incidence of AF increases with age and prevalence reaches 10% in octogenarians. The proportion of strokes attributable to this common arrhythmia will continue to rise as our population ages. In the Framingham Study, almost one fourth of all strokes that occurred in patients aged >80 years were attributable to AF. Furthermore, cerebral infarctions in patients with AF tend to be larger than strokes caused by most other etiologies and result in high rates of both disability and mortality.

In use for >50 years, the anticoagulant warfarin was first shown to prevent stroke in patients with AF 2 decades ago. A series of randomized trials demonstrated an exceptional level of efficacy (relative risk reductions close to 70%) for prevention of ischemic stroke and surprisingly low rates of intracerebral hemorrhage or major systemic bleeding.

Despite this remarkable performance in clinical trials and strong endorsement by international guidelines, both physicians and patients have been reluctant to embrace warfarin therapy in AF. Underuse is typically attributed to the inconvenience of coagulation monitoring, complexities associated with drug and dietary interactions as well as the perception that hemorrhage rates may have been underestimated in the clinical trials. It is estimated that only approximately half of warfarin-eligible patients with AF actually receive anticoagulation. Furthermore, even those who are treated are often not maintained in the therapeutic range. This is due in part to warfarin’s nonlinear pharmacokinetics, but also its interaction with multiple other heptatically metabolized drugs and dietary intake of vitamin K that competes with warfarin’s synthetic inhibition of vitamin K-dependent clotting factors. Although patients enrolled in clinical trials typically remain in the target therapeutic international normalized ratio range (ie, international normalized ratio of 2.0 to 3.0) approximately two thirds of the time, the “real-world” experience with warfarin suggests widespread suboptimal control. This is highly clinically relevant because warfarin’s efficacy is powerfully related to the amount of time spent in the therapeutic range.

Because of warfarin’s liabilities, an intensive search for a safe, effective, and less cumbersome antithrombotic for stroke prevention in patients with AF has transpired. Early challengers, including an assortment of antiplatelet agents and combinations of low-dose warfarin with aspirin, could not match the efficacy of dose-adjusted warfarin. More recently, attention has shifted to more specific inhibitors of the clotting cascade such as factor Xa antagonists or direct thrombin (IIa) inhibitors. Key features of the new contenders are freedom from coagulation monitoring, simpler kinetics, more rapid onset and offset, and decreased or absent drug–drug and food interactions. Ideally, an antidote would exist as would a bioassay for drug activity.

Appreciating the fact that exceeding the efficacy of warfarin is nearly unattainable, recent trials of new anticoagulants typically used a noninferiority design. A finding of noninferiority for prevention of stroke and systemic embolism could result in a preference for the new agent if it was substantially more “user-friendly” than warfarin. The first medication to nearly succeed with this approach was ximelagatran, a direct thrombin inhibitor that was shown to be noninferior to warfarin and have comparable bleeding risk in 2 large randomized AF trials. Unfortunately, rare but potentially life-threatening liver toxicity proved too great an obstacle for regulatory approval and the drug was abandoned. Therefore, after 2 decades of competition in randomized AF trials, warfarin remained undefeated until now.
Results of the recently published Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial indicate warfarin’s supremacy for stroke prevention in AF is in jeopardy. RE-LY is the largest stroke prevention trial in patients with AF ever undertaken; over 18,000 patients with AF and at least 1 additional vascular risk factor were randomized to receive 1 of 2 doses of dabigatran or dose-adjusted warfarin. Like ximelagatran, dabigatran etexilate (a prodrug of the active moiety dabigatran) is another direct thrombin inhibitor. Dabigatran is already approved in Europe and Canada for the prevention of venous thromboembolism after hip and knee replacement surgery. This oral compound has a rapid onset (1 to 2 hours) and a relatively short half-life (12 to 17 hours). Because dabigatran leads to a predictable level of anticoagulation with a low potential for drug–drug or food interactions, blood monitoring is unnecessary. There is an interaction with amiodarone, an important consideration in an AF population.

In RE-LY, the dabigatran group received twice-daily dosing of either 110 mg or 150 mg. In an earlier Phase II trial of dabigatran in patients with AF, a 300-mg twice-daily dose appeared to induce excessive bleeding risk, whereas a 50-mg twice daily was associated with a higher rate of thromboembolism. Warfarin was administered open-label in RE-LY with adjudication of efficacy and safety end points performed in a blinded manner. The overall excellent control of anticoagulation (patients on warfarin spent 64% of the time in the therapeutic range) coupled with its established efficacy resulted in few clinical end points of stroke or systemic embolization (1.69%/year) in the warfarin arm. Remarkably, there were even fewer end points in the higher-dose dabigatran arm: 1.11%/year, representing a relative risk of 0.66 (0.53 to 0.82; \( P<0.001 \) for superiority). Furthermore, highly statistically significant benefits were documented for the secondary end points of hemorrhagic stroke as well as fatal or disabling stroke; these findings are unprecedented.

The low absolute event rate in this trial translates to a large number of patients who would need to be treated with the higher dose of dabigatran, rather than warfarin, to prevent 1 stroke (>350 patients). However, a much larger number of strokes will be prevented if a substantial percentage of high-risk patients with AF who are currently averse to taking warfarin are willing to try dabigatran.

The low-dose dabigatran group had a similar stroke rate compared with the warfarin group but a significant decrease in the number of hemorrhagic complications. This dichotomy between the 110 mg twice-a-day group and the 150 mg twice-a-day group suggests that dosing of this new drug could potentially be customized: the lower dose for patients at lower embolic risk but higher bleeding risk and the higher dose for patients at greater stroke risk.

Assuming regulatory approval, the small absolute difference in event rates will provide only limited rationale to switch patients who are stable on warfarin to dabigatran. Warfarin-naive patients, patients who are hard to maintain in the therapeutic range, those who have bleeding complications attributable to warfarin, or those taking multiple medications are the most likely candidates for dabigatran.

Cost considerations will be important; the new agent will probably be expensive. However, elimination of monitoring will likely mediate some of the medication costs.

As encouraging as the results of RE-LY are, a few important outstanding issues remain. The follow-up in RE-LY was relatively short (2.0 years); the safety of dabigatran, particularly in regard to hepatic toxicity, needs to be assessed over a longer duration. There was a small but significant increase in myocardial infarction in the high-dose dabigatran group compared with warfarin (relative risk 1.38 [1.00 to 1.91]; \( P=0.048 \)) that will require ongoing investigation. The benefits and risks of combining dabigatran with antiplatelet agents (approximately 20% of the patients in RE-LY received concomitant aspirin therapy) also require clarification. Dabigatran is largely metabolized and cleared by the kidneys; therefore, the safety and efficacy in patients with AF with renal insufficiency is an important issue. Patients with a creatinine clearance of <30 mL/min were excluded from RE-LY. Importantly, there is no known antidote or reversal agent for dabigatran. Although the half-life is short compared with warfarin, situations will certainly arise when rapid reversal in the setting of hemorrhage or emergent surgery is required. The effect of Factor VII or prothrombin complex concentrate on anticoagulation with dabigatran is not established. Furthermore, the lack of a laboratory test for monitoring can be seen as a double-edged sword. A biomarker would be useful to help assess treatment failures or evaluate patients who are bleeding.

Overall, the results of RE-LY are robust and very exciting. This landmark study represents one of the great advances in the field of stroke prevention. The promise of a safe, effective, and easy-to-use alternative to warfarin is finally on the horizon.

Disclosures

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References


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Dabigatran Challenges Warfarin's Superiority for Stroke Prevention in Atrial Fibrillation

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