

Stroke Prevention in Atrial Fibrillation: Rivaroxaban, Dabigatran, and Warfarin

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Warfarin, a vitamin K antagonist, has previously been the drug of choice for reducing the risk of stroke and systemic embolism in patients with non-valvular AF.⁶ When using warfarin, a patient's INR should be monitored closely and dose adjustments may be required to keep the patient within the therapeutic range.⁶ Many different medications and foods can interact with warfarin, causing INR levels to fluctuate, and necessitating medication and dietary modifications.¹ Due to the complexity of conventional warfarin therapy, new anti-coagulants with different mechanisms of action have been developed.¹ The new oral anti-coagulant agents currently approved by the FDA for this indication are rivaroxaban (Xarelto) and dabigatran (Pradaxa).

Rivaroxaban, an oral direct factor Xa inhibitor, was recently approved by the FDA for the prevention of stroke in patients with non-valvular AF in addition to the previous indication of DVT prophylaxis in knee and hip replacement surgeries.⁴ The ROCKET-AF trial compared once daily rivaroxaban to adjusted dose warfarin therapy in patients with AF and was published in September.¹ This multi-center, randomized, double-blinded trial, in which power was met, found that rivaroxaban was non-inferior to warfarin in preventing stroke and systemic embolism (HR 0.79; 95% CI, 0.66 to 0.96; P<0.001). However, the superiority analysis found that there was not a significant difference between the groups (HR 0.88; 95% CI, 0.74 to 1.03; P=0.12). Patients in the warfarin group were within the target therapeutic range 55% of the time during the study period.

Dabigatran is an oral direct thrombin inhibitor and has been FDA approved for the prevention of stroke and systemic embolism in patients with non-valvular AF.⁵ The RE-LY trial compared two different twice daily dabigatran dosing regimens, 110mg and 150mg, to adjusted dose warfarin therapy. The 110mg dose was found to be non-inferior to warfarin in the prevention of stroke and systemic embolism (RR 0.91; 95% CI, 0.74 to 1.11; P<0.001), while the 150mg dose was found to be superior (RR 0.66; 95% CI, 0.53 to 0.82; P<0.001). Major bleeding events occurred at a rate of 3.36% per year in the warfarin group, compared to 2.71% per year in the 110mg group (P=0.003), and 3.11% per year in the 150mg group (P=0.31). When looking at the net clinical benefit outcome, comprised of major vascular events, major bleeding, and death, the occurrence rate was 7.64% with warfarin, 7.09% with dabigatran 110mg (P=0.10), and 6.91% with dabigatran 150mg (P=0.04). Warfarin treated patients were within the target therapeutic range 64% of the time.

The main adverse event associated with anti-coagulation therapy is an increased risk of bleeding and each of these trials evaluated specific bleeding outcomes. The principal bleeding outcome in the ROCKET-AF trial was defined as major and clinically relevant non-major bleeding events.¹ The rate was numerically greater in the rivaroxaban group (14.9% per year) compared to warfarin (14.5% per year, P=0.44), however the difference was not statistically significant. Rivaroxaban did cause significantly fewer intracranial hemorrhage events (HR 0.67; 95% CI, 0.47 to 0.93; P=0.02), but increased the risk of major bleeding from gastrointestinal sites (3.2% rivaroxaban, 2.2% warfarin; P<0.001). In the RE-LY trial, the bleeding outcome was defined as a reduction in hemoglobin of at least 2g/dL, transfusion of 2 units of blood or more, or symptomatic bleeding in a critical organ.² This rate was found to be 3.36% per year

for warfarin, 2.71% per year in the dabigatran 110mg group (P=0.003), and 3.11% per year in the dabigatran 150mg group (P=0.31).

There are both benefits and concerns associated with the clinical use of rivaroxaban and dabigatran. The potential benefit is that these produce a more consistent and predictable anti-coagulation effect than warfarin and have been shown to be at least as effective. Monitoring is required less frequently which could potentially improve patient compliance and decrease provider workload. These new drugs also have fewer interactions with foods, eliminating the need for patients to change their eating habits.

Concerns with their use are the lack of a widely accepted and validated test to monitor coagulation and a proven antidote to reverse their effects. These can be especially problematic if a patient experiences a major bleeding event and requires prompt reversal of anti-coagulation. A recent placebo controlled trial found that prothrombin complex concentrate (PCC) was able to reverse the effects of rivaroxaban, normalizing the prothrombin time and endogenous thrombin potential.³ PCC contains high concentrations of coagulation factors II, VII, IX, and X and also increases thrombin generation. The effects of dabigatran were not reversed with this treatment. While these results are positive, future studies need to be done that include a larger patient population and use a validated monitoring test.

Currently, warfarin remains the preferred oral anticoagulant for the prevention of stroke in patients with AF due to the proven efficacy, low cost, availability of INR monitoring and an antidote.⁷ Patients who are taking warfarin and have maintained an INR consistently within the therapeutic range should continue taking it.⁷ The newer agents are recommended in patients whose INR control is inadequate on warfarin and when the frequency of monitoring is problematic. When recommending one of the newer agents, dabigatran is preferred because it has been shown to reduce the risk of stroke more than warfarin.⁷ Rivaroxaban is recommended in patients with compliance issues due to the once daily dosing.⁷ When switching from warfarin to rivaroxaban or dabigatran, it is recommended to wait until the INR is less than 2 before initiating treatment with either of the newer agents.⁷

Rivaroxaban and dabigatran are promising new oral anti-coagulants that have the potential to dramatically decrease the risk of stroke and systemic embolism in patients with AF. Rivaroxaban has been shown to be non-inferior to warfarin for the prevention of stroke in patients with AF, while dabigatran 150mg twice daily has been shown to be superior. The decreased amount of clinical monitoring as well as drug and food interactions could have a positive impact on patient compliance. However, the lack of a widely accepted monitoring method and the lack of a proven antidote need to be addressed in future studies.

References

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