

## New Anticoagulation Medications for Atrial Fibrillation

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In December 2012, the Food and Drug Administration approves apixaban for reducing risks of stroke and venous thromboembolism in patients with nonvalvular atrial fibrillation (NAF) [1]. Apixaban is the third new oral anticoagulation agent that came into the market [1-3]. Prior to the approval of apixaban, dabigatran (a direct thrombin inhibitor) was approved in 2010, and rivaroxaban (a factor Xa inhibitor) was approved in November 2011. All of these agents have been compared to warfarin in various landmark trials [1-3].

Dabigatran was the first alternative to warfarin, and is currently, the only oral direct thrombin inhibitor available. Efficacy of dabigatran for NAF was studied in the RE-LY trial [4]. The RE-LY trial was a non-inferiority trial, and compared open-label adjusted warfarin dose to two doses of dabigatran, 110 mg or 150 mg by mouth twice a day [4]. The median follow-up was 2 years and the primary endpoint was stroke and systemic embolism. There were 18,113 patients (mean age 71 years old) and a mean CHADS2 score of 2.1. The annual rates for the primary endpoint in patients receiving dabigatran 150 mg BID were 1.11% vs. 1.69% for warfarin (Relative risk [RR]: 0.66; 95% Confidence Interval [CI]: 0.53-0.82, p=0.003). The rates of major bleeding were similar for dabigatran and warfarin (3.11% per year vs. 3.36% per year; P=0.31). Hemorrhagic stroke, however, occurred less frequently in dabigatran group with an annual rate of 0.10% vs. 0.38% with warfarin (p<0.001). There was an increased rate of gastrointestinal (GI) bleeding reported with dabigatran (1.51% per year vs. 1.02% per year; RR 1.5; 95% CI: 1.19-1.89; p<0.001). The warfarin group had 64% in the mean time in therapeutic range and based on the findings, the FDA approved the 150 mg BID dosing regimen. Dabigatran was well tolerated except dyspepsia was more common associated with it versus warfarin (11.3% vs. 5.8% respectively; p <0.001). Note that additionally analysis of RE-LY raised concerns of increased rate of myocardial infarction (MI) was seen with dabigatran compared to warfarin (0.74% per year vs. 0.53% per year; RR 1.38, 95% CI, 1.00-1.91; p=0.048). Twenty-eight more cases of silent MI were identified during the reanalysis period, that changed the statistically significant difference between dabigatran and warfarin for this outcome (0.81% per year vs. 0.64% per year; RR 1.27; 95% CI, 0.94-1.71; p=0.12) [5,6]. Also, Boehringer Ingelheim confirmed serious cases and potentially life-threatening bleeding associated with dabigatran between March 2008 and October 2011 [7,8]. There were 260 fatal bleeding events worldwide that triggered safety concerns and the need for regular assessment of kidney function and dabigatran use.

Rivaroxaban was compared to warfarin in the ROCKET AF trial. The study was a multicentered, randomized, double-blind, double-dummy, event-driven trial, which enrolled 14,264 NAF patients at moderate to high risk for stroke. In contrast to the RE-LY trial, patients who were on warfarin for the ROCKET AF had therapeutic International Normalized Ratio 55% of the time. For the per protocol patient population, rivaroxaban was proven to be noninferior to warfarin in the primary efficacy composite endpoint of stroke and systemic embolism (Hazard Ratio [HR]: 0.79, 95% CI: 0.66-0.96, p<0.001). As for the intention to treat population, rivaroxaban was also noninferior to warfarin, but it fails to show superiority over

warfarin (HR: 0.88, 95% CI: 0.74 to 1.03, p<0.001 for noninferiority, and p=0.12 for superiority). Mortality rates were similar between the treatment groups for the as treated population (HR: 0.85, 95% CI: 0.70 to 1.02, p=0.07) and in the intention to treat population (HR: 0.92, 95% CI: 0.82 to 1.03, p=0.15). Patients in the rivaroxaban group had lower rates of critical bleeding, fatal bleedings, and intracranial hemorrhages (p=0.007, p=0.003, p=0.02, respectively) [9]. Advantages of rivaroxaban over dabigatran are that rivaroxaban is the once daily dosing, and can be crushed and mixed with applesauce in patients who are unable to swallow tablets. For patients with nasogastric tube or feeding tube, rivaroxaban can be crushed and suspended in water. In addition to NAF, rivaroxaban is indicated for the treatment and prevention of deep vein thrombosis and pulmonary embolism. One specific dose is approved for each indication so healthcare professionals need to be extremely cautious when prescribing rivaroxaban [10].

The ARISTOTLE compared apixaban with warfarin in a multicentered, randomized, double-blinded, double dummy study. Eighteen-thousand two hundred patients with NAF and at least 1 risk factor for stroke were enrolled. Patients on warfarin had a therapeutic INR 62.2% of the time. Patients in the apixaban group has lower rates of stroke or systemic embolism (HR: 0.79, 95% CI: 0.66 to 0.95, p<0.001 for noninferiority and p=0.01 for superiority), and lower mortality rates (HR: 0.89, 95% CI: 0.80 to 0.99, p=0.047). Additionally, less patients in the apixaban group experienced intracranial bleeding (HR: 0.42, 95% CI: 0.30-0.58, p<0.001) or major or clinically relevant non-major bleeding (HR: 0.68, 95%CI 0.61-0.75, p<0.001) [11]. Advantages of apixaban are that doses do not need to be adjusted unless patients have at least 2 factors: age of 80 years or greater, serum creatinine of 1.5 mg/dl or greater, or body weight less than 60 kg. Disadvantages include the twice daily dosing, not recommended for CLcr<15 mL/min or hemodialysis, and no information available on crush or administration through feeding tube [11].

All of the new anticoagulants have the advantage of having a predictable drug effect, faster onset of action, and less need for monitoring as compared to warfarin. The decision of selecting one anticoagulant over another may be difficult. Although all of the new anticoagulants were noninferior in preventing stroke or systemic embolism, apixaban is the only one proven to be superior as compared to warfarin, and is the only one shown to reduce risk of death from any cause [4,9,12]. While dabigatran does not reduce risks of death, it reduces risks of death from vascular causes (p=0.04). Based on the

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findings, rivaroxaban may not be the optimal agent for NAF. However, one would have to closely look at the baseline demographics of the studies. In the RE-LY and the ARISTOTLE trials, only 30% of patients had CHADS2 scores of 3 or greater and average CHADS2 score was between 2.1 to 2.2. In the ROCKET AF trial, 87% of patients had CHADS2 score of 3 or greater and average CHADS2 score was 3.48 in the rivaroxaban group and 3.46 in the warfarin group. Therefore, the reduction in mortality rates may be due to inclusion of lower risk patients in the RE-LY and ARISTOTLE trials [4,9,12]. Moreover, only apixaban have shown reductions in any bleeding events as compared to warfarin. Rivaroxaban only showed reduction in risks of fatal bleeding, intracranial bleeding, or critical bleeding while dabigatran only shows reduction in minor bleeding events.

Warfarin could be initiated for patients with atrial fibrillation and with valvular diseases. Rivaroxaban is preferred for patients who are unable to swallow or who has feeding tubes, or for patients who are unlikely to be compliant with twice daily dosing. Other than that, the choice between rivaroxaban, apixaban or dabigatran is at the discretion of the physician. Future studies should be conducted to directly compare all of the agents in order to assist healthcare professionals to select the most appropriate anticoagulation for each individual patient.

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