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Arrhythmia

N E W S

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Pradaxa: A Novel Anticoagulant to Reduce Thromboembolism in Patients with Non-Valvular Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice and is associated with increased cardiovascular morbidity and mortality.¹ In particular, AF is associated with a markedly increased risk of stroke, which are larger, more likely to recur, and more likely to cause disability or death than in patients without AF.² Anticoagulation with warfarin reduces the risk of stroke in AF patients by two-thirds. Unfortunately, multiple drug-drug interactions, drug-food interactions as well as recently appreciated genetic polymorphisms that affect warfarin metabolism all contribute to a difficulty in maintaining the desired level of anticoagulation. This contributes to reluctance on the part of physicians to prescribe warfarin and of patients to take the medication. Thus, the need for alternative forms of effective anticoagulation is obvious.

Dabigatran

Dabigatran (trade name: Pradaxa) is a direct thrombin inhibitor. Thrombin acts at the center of the coagulation cascade enabling the conversion of fibrinogen into fibrin. Inhibition of free and clot bound thrombin by dabigatran prevents the development of thrombus.

Dabigatran etexilate (an inactive prodrug) is a small molecule that is rapidly and predictably absorbed (within 1-3 hours) and converted to dabigatran (the active drug) through hydrolysis both in the plasma and in the liver. It is eliminated in the urine (80%) in proportion to the glomerular filtration rate with the remainder excreted in the bile. The elimination half-life is 14-17 hours and increases slightly in the elderly. The dose needs to be reduced in moderate renal insufficiency (creatinine clearance 15-30 cc/min) and it should not be given to patients with severe renal insufficiency (creatinine clearance <15 cc/min). Importantly, plasma levels of dabigatran are not affected by hepatic dysfunction and dabigatran does not act as a substrate, inhibitor or inducer of the cytochrome P450 isoenzymes. Therefore drug-drug interactions are virtually non-existent.

Dabigatran: RE-LY Trial

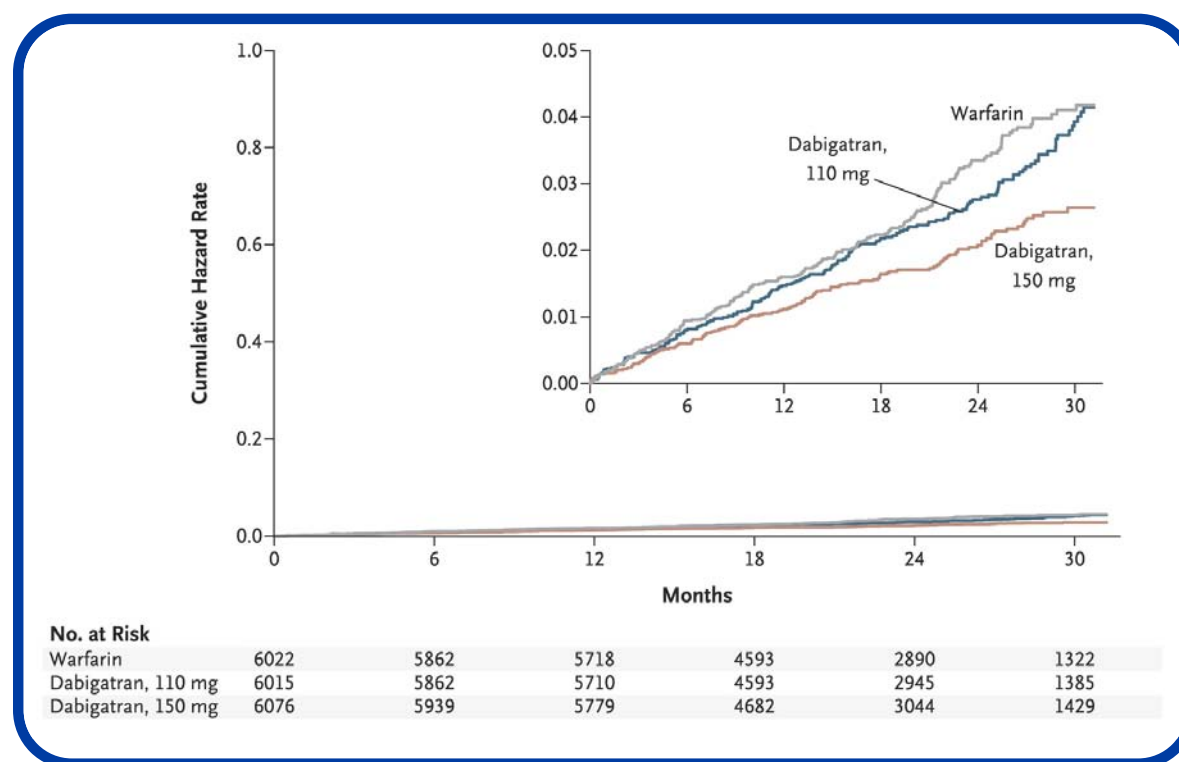
The RE-LY trial randomized 18,113 patients with non-valvular paroxysmal, persistent, or permanent AF and at least one risk factor for stroke (age > 75 or age 65-74 with either hypertension, diabetes mellitus, or coronary artery disease, prior TIA, stroke, or systemic embolism, LVEF<40%, or NYHA ≥ 2 CHF), to either 110 mg or 150 mg dabigatran or to warfarin adjusted to an INR 2-3.³ The primary endpoint of stroke or systemic embolism occurred in 1.69% per year in the warfarin group compared with 1.53% per year in the 110 mg and 1.11% in the 150 mg dabigatran groups. While the 110 mg group was statistically "non-inferior" to warfarin, the 150 mg dose as statistically superior to warfarin (relative risk 0.65; 95% confidence interval

0.52-0.81 for superiority, Figure) Thus, the 110 mg dose was not approved by the FDA for use in the US. The efficacy of 150 mg dabigatran was observed across all major subgroups. (Of note, the FDA approved a 75 mg bid dabigatran dose in patients with moderate renal insufficiency (creatinine clearance 15-30 ml/min) based solely on pharmacokinetic data.)

Major bleeding episodes, the major primary safety endpoint, occurred equally in the 150 mg dabigatran and warfarin groups. Importantly, the rate of hemorrhagic stroke was 0.38% per year in the warfarin group compared with 0.10% in the 150 mg dabigatran group

However, there was a higher risk of gastrointestinal bleeding with dabigatran 150 mg as compared to warfarin (1.6% vs 1.1%). The rate of discontinuation of dabigatran was higher than with warfarin only during the first 3 months of the RE-LY trial. The most frequent adverse events leading to discontinuation of dabigatran were bleeding and gastrointestinal events (e.g., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Restoring sinus rhythm in patients with AF, whether by pharmacologic or electrical cardioversion is associated with an increased risk of thromboembolism for up to 4 weeks. In the absence of therapeutic pre-cardioversion anticoagulation for at least 3 weeks, this risk is increased approximately ten fold. In the RE-LY trial, 1983 cardioversion procedures were performed. The incidence of cerebral and systemic thromboembolism were similar with dabigatran (0.3%) and warfarin (0.6%) treated patients, suggesting that dabigatran is effective in this common clinical situation.⁴



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Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group. Legend (From: Connolly SJ, et al. N Engl J Med 2009;361:1139- 1151)

Dabigatran: Levels

The level of anticoagulation achieved with dabigatran is predictable. Therefore unlike warfarin, blood tests to measure the degree of anticoagulation are unnecessary. Nonetheless, prior to any procedure or in the case on accidental overdose, a method for quantitative assessment of the degree of anticoagulation is clinically desirable. The prothrombin time (PT) a measure of the extrinsic coagulation pathway will increase slightly but bears no relationship to plasma dabigatran levels and is of no clinical value. The aPTT and activated clotting time are reflective of the intrinsic coagulation pathway; however, they are relatively insensitive within the range of dabigatran levels seen clinically. They may be useful in reflecting the presence or absence of dabigatran effect. The thrombin clotting time (TT), Hemoclot thrombin inhibition assay and ecarin clotting time (ECT) provide quantitative, linear measures of dabigatran activity; however, they are not yet widely available. Thus, at present there is no reliable, readily available quantitative method for assessing dabigatran's anticoagulation effect.

Dabigatran: When To Discontinue

In general, dabigatran should be discontinued at least 24-48 hours prior to elective surgical procedures. For patients with normal renal function discontinuation of dabigatran will result in 25% of steady state trough levels at 24 hours and 5-10% at 48 hours. Patients with moderate renal impairment or those undergoing procedures with a high risk of bleeding should hold dabigatran for 3-5 days before their elective surgery.⁵

Dabigatran levels fall quickly upon drug discontinuation. Other than time, there are currently no antidotes. Hemodialysis can reduce plasma levels of the drug; in case of an oral overdose, activated charcoal can be administered within 2 hours of ingestion to limit absorption. Recombinant factor VII and non-activated prothrombin complex have been used clinically although they have not been specifically studied for this purpose.

Conclusion

Dabigatran is an exciting new alternative to warfarin for prevention of thromboembolism in patients with non-valvular AF. The RE-LY study has demonstrated that dabigatran 150 mg administered twice daily is actually superior to warfarin in preventing thromboembolism; importantly, it is not associated with increased major bleeding complications and has much less chance of producing intracranial bleeding. The absence of need for blood testing will be a big attraction for patients. How quickly dabigatran replaces warfarin in routine clinical use, will depend upon its cost, which is likely to come down as other direct thrombin inhibitors and factor Xa inhibitors are approved, and upon patient acceptance, possibly tempered by the need for twice daily dosing and a moderately high incidence of gastrointestinal side effects.