ANTICOAGULANTS FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION

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Dabigatran

Dabigatran etexilate is an oral prodrug that is converted to dabigatran, a direct, competitive thrombin inhibitor. It is important to note that 80% of dabigatran is excreted renally.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared open-label warfarin with two fixed, blinded doses of dabigatran (110 or 150 mg twice daily) in patients with AF and at least 1 additional stroke risk factor (previous stroke or TIA, left ventricular ejection fraction <40%, New York Heart Association heart failure classification of II or higher, age ≥75 years, or age 65–74 years plus diabetes mellitus, hypertension, or coronary artery disease). The primary outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage. (1)

The rates of stroke or systemic embolism with dabigatran 110 mg twice daily (1.53% per year) and dabigatran 150 mg twice daily (1.11% per year) were noninferior to warfarin (1.69% per year); dabigatran 150 mg twice daily was also superior to warfarin (RR, 0.66; 95% CI, 0.53–0.82). Compared with warfarin, the risk of hemorrhagic stroke was lower with both dabigatran 110 mg twice daily (RR, 0.31;95% CI, 0.17–0.56) and dabigatran 150 mg twice daily (RR, 0.26; 95% CI, 0.14–0.49).

Major bleeding was similar for dabigatran 150 mg (3.1% per year; RR, 0.93; 95% CI, 0.81–1.07) and warfarin (3.4% per year) treated patients. The rate of gastrointestinal bleeding was higher with dabigatran 150 mg twice daily (1.5% per year) than with warfarin (1.0% per year). Rates of life-threatening and intracranial bleeding, respectively, were higher with warfarin (1.8% and 0.7%) than with dabigatran 150 mg (1.5% and 0.30%). The rate of MI was higher with dabigatran 150 mg (0.74% per year) than with warfarin (0.53% per year; RR, 1.38; 95% CI, 1.00–1.91). However, a post hoc analysis found that the MI annual rates were not significantly different.

Post marketing, concern about bleeding risk with dabigatran led to an FDA analysis of the reported cases, however this study found that the bleeding rates associated with dabigatran were not higher than warfarin. Patients in the dabigatran arm of the RE-LY trial were followed for another 2 years as part of the Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study. Rates of stroke, systemic embolism and major bleeding on dabigatran were similar to rates observed in the RE-LY trial and demonstrated that dabigatran was safe for up to 4.5 years. (2)

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor, with a serum half-life of 5 to 9 hours. Clearance is both renal (36%) and fecal. It is dosed once a day.

The Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) Trial was a double-blind trial which randomized patients with nonvalvular
AF at moderate to high risk of stroke to rivaroxaban (20 mg/d) or warfarin. (3) The primary end point, ischemic and hemorrhagic stroke and systemic embolism occurred in 1.7% per year in the rivaroxbabn treated subjects as compared to 2.2% per year in the warfarin group (HR, 0.79; 95% CI, 0.66–0.96; P<0.001 for noninferiority).

The primary safety endpoint was a composite of major and non-major clinically relevant bleeding. Clinically significant bleeding occurred in 14.9% of patients per year in the rivaroxaban group and 14.5% in the warfarin group (HR, 1.03; 95% CI, 0.96–1.11; P=0.44). Lower rates of intracranial hemorrhage (0.5% versus 0.7%, P=0.02) and fatal bleeding (0.2% versus 0.5%, P=0.003) were observed in the rivaroxaban group than in the warfarin group.

Apixaban

Apixaban is a direct and competitive factor Xa inhibitor. It has a half-life of 8 to 15 hours. Clearance is both renal (25%) and fecal.

The ARISTOTLE trial was a phase 3 randomized trial comparing apixaban to warfarin for the prevention of stroke (ischemic or hemorrhagic) or systemic embolization among patients with AF or atrial flutter. (4) The doses tested was 5 mg twice daily as well as 2.5-mg twice daily. Warfarin dose was adjusted to achieve a therapeutic INR of 2.0 to 3.0. Additionally, patients in both groups were permitted to receive up to 162 mg of aspirin daily if clinically indicated. 1.3% patients in the apixaban group experienced the primary outcome of stroke or systemic embolization compared with 1.6% of warfarin group (HR, 0.79; 95% CI, 0.66–0.95). Both noninferiority (P<0.001) and superiority (P=0.01) of apixaban were demonstrated. There was significant reduction in hemorrhagic stroke (49% reduction) compared with ischemic or uncertain types of stroke (8% reduction). Secondary end points of death (3.5% versus 3.9%; HR, 0.89; 95% CI, 0.80–0.99; P=0.047) and major bleeding (2.1% versus 3.1%; HR, 0.69; 95% CI, 0.60–0.80; P<0.001) favored apixaban.

Edoxaban

Edoxaban is an oral factor Xa inhibitor which is 50% renally excreted and dosed once a day.

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibirllation-Thrombolysis in Myocardial Infarction 48 (ENGAGE-TIMI 48) trial randomized 21,105 subjects with moderate-high risk nonvalvular atrial fibrillation to either warfarin, low dose edoxaban (30 mg daily), or high dose edoxaban (60mg daily). (5) The primary outcome was stroke or systemic embolism. Major bleeding was the principal safety outcome.

In ENGAGE-TIMI 48, the rate of systemic embolism and stroke was 1.5% with warfarin compared with 1.2% with high-dose edoxaban (hazard ratio, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority) and 1.6% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority).
The rate of major bleeding was 3.4% with warfarin versus 2.8% with high-dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.6% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001).

Reversal Agents
Idarucizumab is a monoclonal antibody fragnment which binds dabigatran and neutralizes its activity. A prospective cohort study examined 90 patients on dabigatran who experienced serious bleeding or required an urgent procedure. Idarucizumab 5g reversed the anticoagulant effects of dabigatran within minutes. One thrombotic event occurred within 72 hours.

Andexanet Alfa, though not yet approved for use, is a recombinant modified human factor Xa decoy protein. Andexanet Alfa (bolus followed by a two hour infusion) was administered to 67 patients who experienced major bleeding with the use of a Factor Xa inhibitor. Hemostasis wa restored in 79% of subjects at 12 hours. Eighteen present of subjects had thrombotic events within 30 days.

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