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Editorial Open Access

Edoxaban for the Prevention of Stroke in Patients with Atrial Fibrillation

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Editorial

Atrial fibrillation (AF) is a devastating disease in the United States and affects almost 12% of patients who are between the ages of 75 to 84. Having AF almost increases the risk of stroke by 5-fold, and therefore, anticoagulation therapy is essential for the prevention of stroke in patients with AF [1]. Warfarin has been the sole oral anticoagulation available for decades. From 2010 to 2012, 3 additional novel oral anticoagulation (NOAC) came onto the market, which includes dabigatran, rivaroxaban, and apixaban and offered viable alternatives to warfarin for the management of AF [2-4]. In January 2015, the FDA approved edoxaban, a factor Xa inhibitor, to come onto the market for the prevention of stroke in AF patients. Edoxaban is the third factor Xa inhibitor currently available, in addition to rivaroxaban and apixaban [5,6].

Efficacy of edoxaban for the management of AF was investigated in the ENGAGE-AF TIMI 48 trial. Patients were randomized to receive warfarin, edoxaban 30 mg, or edoxaban 60 mg daily. Doses of warfarin were adjusted to target international normalized ratio (INR) of 2 to 3. Doses of edoxaban were decreased by 50% if patients had renal impairment (creatinine clearance [CrCl] 30-50 ml/min), weight of less than 60 kg, or were on concomitant potent p-glycoprotein inhibitors. The study found that edoxaban, at either dose, was non-inferior to warfarin in the event rates of the primary efficacy endpoint (stroke or systemic embolism) (warfarin 1.50% per year, edoxaban 30 mg 1.61% per year; hazard ratio [HR]: 1.07; 95% confidence interval [CI]: 0.87 to 1.31; p=0.005 for noninferiority, p=0.44 for superiority). Higher dose of edoxaban (60 mg) was also found to be superior to warfarin (edoxaban 60 mg 1.18% per year; HR: 0.79; 95% CI: 0.63 to 0.99; p<0.001 for noninferiority, p=0.02 for superiority). Edoxaban, at either dose, was also associated with lower risks of bleeding as compared to warfarin [7]. The ENGAGE-AF TIMI 48 trial also found that edoxaban patients with CrCl above 95 ml/min were at higher risk for stroke or systemic embolism (edoxaban 60 mg 1% per year vs. warfarin 0.6% per year; HR: 1.87; 95% CI: 1.1 to 3.17) as well as stroke (edoxaban 60 mg 0.9% per year vs. warfarin 0.4% per year; HR: 2.16; 95% CI: 1.17 to 3.97). Edoxaban patients with CrCl between 50 and 80 ml/min were at lower risk for primary endpoints and stroke as compared to the warfarin patients. Therefore, edoxaban was not approved to be used for non-valvular AF in patients with CrCl above 95 ml/min [6].

A subgroup analysis study was subsequently conducted to compare efficacy of edoxaban and warfarin in the US approved population (edoxaban 60 mg if CrCl was between 50 to 95 ml/min; edoxaban 30 mg if CrCl was between 15 to 50 ml/min). The results showed that edoxaban 60/30 mg daily significantly lowered risks of stroke or systemic embolism (edoxaban group 1.11%/yr, warfarin 1.72%/yr; HR: 0.64; 95%CI: 0.51-0.81; p<0.001). Looking at the individual endpoints, edoxaban patients only significantly lower risks for hemorrhagic stroke (0.25% per year for edoxaban vs. 0.53% per year for warfarin; HR: 0.47; 95%CI: 0.31-0.72; p<0.001). No significant difference was found in the rates of ischemic stroke or systemic embolism. Edoxaban patients were also at lower risk for bleeding events [8].

Edoxaban is a newer agent that offers the convenience of once daily dosing. Additionally, it is the only NOAC that reduced the risk of death due to cardiovascular (CV) causes as well as death due to any cause [7]. Apixaban and dabigatran only effectively decreased death rates due to any causes, but not death due to CV causes or vascular causes, based on the results of the ARISTOTLE and RELY trials, respectively [9,10]. Death rates were not significantly different between rivaroxaban and warfarin in the ROCKET-AF trial [11]. However, as edoxaban was shown to increase risks of stroke or system embolism in patients with CrCl above 95 ml/min, its use may be limited in younger patients. Additionally, utilization of edoxaban may be limited due to the lack of available antidote. Investigation on a novel agent, andexanet alfa, as a potential reversal agent for factor Xa inhibitors is currently conducted as a phase 3, randomized trial. Results of the study may be disseminated in the upcoming months [12] Availability of an antidote may increase utilization of edoxaban. Finally, the FDA approved package insert did not require dosing adjustment in patients with lower body weight (less than 60 kg) or concomitantly on P-glycoprotein inhibitors, as were done in the ENGAGE AF-TIMI 48 study [6]. The efficacy and safety of higher doses of edoxaban in that subgroup warrants further research.

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