2012

# What Evidence is Available on Apixaban for the Primary Prevention of Stroke in Patients with Atrial Fibrillation?

Justin Dang
*Midwestern University*

Laura Tsu
*Chapman University*, ltsu@chapman.edu



Recommended Citation
Dang J, Tsu LV. What evidence is available on apixaban for the primary prevention of stroke in patients with atrial fibrillation? *Arizona Journal of Pharmacy* 2012;4:30-1.

# What Evidence is Available on Apixaban for the Primary Prevention of Stroke in Patients with Atrial Fibrillation?

# Question: What evidence is available on apixaban (Eliquis®) for the primary prevention of stroke in patients with atrial fibrillation?

*by Justin Dang, Pharm.D. Candidate, Class of 2013, and Laura Tsu, Pharm.D., Assistant Professor, Midwestern University College of Pharmacy-Glendale*

## Answer:

**Introduction**

Atrial fibrillation is a type of supraventricular tachycardia where the atria beat at rates of 400-600 beats/minute and have disorganized atrial activation. Common symptoms of atrial fibrillation include tachycardia, palpitations, and worsening of heart failure symptoms. Approximately 2.2 million Americans have atrial fibrillation and it is expected to increase to 12-15 million by 2050. The prevalence of atrial fibrillation increases with age, severity of heart failure, and other cardiovascular disease states.[1]

Atrial fibrillation increases the risk of stroke due to atrial stasis and thrombi formation.[1] The American College of Chest Physicians (ACCP) recommends assessing the stroke risk in patients with atrial fibrillation using the $CHADS_2$ scoring system. Patients are given two points if they have had a prior stroke or transient ischemic attack and one point each if they are > 75 years of age or have hypertension, diabetes, or congestive heart failure.[2] The risk of stroke increases for each additional point in the $CHADS_2$ score with a 1.9% risk for a score of 0, 2.8% for a score of 1, 4.0% for a score of 2, 5.9% for a score of 3, 8.5% for a score of 4, 12.5% for a score of 5, and 18.2% for a score of 6.[3] Aspirin can reduce the risk of stroke by 21% compared to no therapy, and warfarin can reduce the risk of stroke by one-half compared to aspirin. The ACCP guidelines recommend that patients with a score of 0, indicating low risk, should receive no therapy, aspirin (75 - 325 mg/day), or aspirin plus clopidogrel. Patients with a $CHADS_2$ score of one, indicating intermediate risk, should receive oral anticoagulation over aspirin or aspirin plus clopidogrel. Lastly, patients with a $CHADS_2$ score of two or greater, indicating high risk, should receive oral anticoagulation.[2]

Despite the proven efficacy of warfarin and aspirin, recommendations for oral anticoagulation now favor the newer oral anticoagulants over warfarin. These novel anticoagulants have shown at least equal efficacy to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation, but lack warfarin's limitations, which include a narrow therapeutic window, need for frequent monitoring, multiple drug-drug interactions, and dietary restrictions (especially foods with high vitamin K content). Currently, the ACCP guidelines give a higher recommendation to dabigatran, an oral direct thrombin inhibitor, over warfarin. Other emerging oral anticoagulants include the factor Xa inhibitors, rivaroxaban and apixaban, which target a common point in both the extrinsic and intrinsic pathways of the clotting cascade and a primary site for signal amplification.[4] Factor Xa inhibitors also have the advantage of not needing international normalized ratio (INR) monitoring and having fewer drug and food interactions than vitamin K antagonists, such as warfarin.[2,4]

The latest factor Xa inhibitor, apixaban, is currently not FDA-approved, but two completed trials have demonstrated apixaban's safety and efficacy compared to aspirin and warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation. In addition, three completed trials have demonstrated apixaban's safety and efficacy compared to enoxaparin in patients undergoing elective total knee replacement and hip replacement surgery, and three ongoing trials are currently investigating apixaban's role in venous thromboembolism (VTE) prophylaxis and treatment.[5] Apixaban is currently dosed at 2.5 or 5 mg twice daily with maximum concentration reached in 1-3 hours for stroke prevention in patients with atrial fibrillation. Apixaban is approximately 25% renally excreted and 15% metabolized by CYP3A4. In clinical trials, apixaban has shown no significant drug-drug interactions and no adverse effects beyond bleeding.[5] In a search of Medline, two randomized controlled clinical trials have investigated the safety and efficacy of apixaban for stroke and systemic embolism prevention in patients with atrial fibrillation.[6,7]

**Clinical Trials**

The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial by Connolly et al. compares apixaban 5 mg twice daily with aspirin at a dose of 81 to 324 mg daily. A reduced dose of apixaban was used (2.5 mg twice daily) if patients met at least two of the following criteria: ≥ 80 years old, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL. The investigators estimated that a total of 5600 patients would be needed to have 90% power to detect a 35% relative reduction in events, as compared to aspirin. The trial randomized 5599 patients with atrial fibrillation who were not taking a vitamin K antagonist because it was unsuitable or expected to be unsuitable and had at least one risk factor for stroke: prior stroke or transient ischemic attack, age > 75 years, hypertension, diabetes mellitus, heart failure (New York Heart Association class II or higher), left ventricular ejection fraction < 35%, or documented peripheral arterial disease. The primary efficacy outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety outcome was the occurrence of major bleeding as defined by the International Society of Thrombosis and Haemostasis (ISTH), which includes a decrease in hemoglobin level of ≥ 2 g/dL over a 24-hour period, transfusion of ≥ 2 packed red blood cells, bleeding at a critical site, or fatal bleeding.[6]

The results of this trial showed 51 primary outcome events (1.6% per year) for patients on apixaban and 113 events (3.7% per year) for patients on aspirin (95% CI, 0.32 to 0.62; P<0.001). The rate of death was 3.5% per year for patients on apixaban and 4.4% per year for patients on aspirin (95% CI, 0.62 to 1.02; P=0.07). There were 44 major bleeding events (1.4% per year) for patients on apixaban and 39 events (1.2% per year) for patients on apixaban (95% CI, 0.74 to 1.75; P=0.57). There were 188 minor bleeding events for patients on apixaban and 153 events for patients on aspirin (95% CI, 1.00 to 1.53; P=0.05). The composite rate of stroke, systemic embolism, myocardial

infarction, death from vascular causes, or major bleeding was 5.3% per year with apixaban and 7.2% per year with aspirin (95% CI, 0.60 to 0.90; P=0.003). The trial was terminated early for efficacy after the first planned interim analysis and confirmatory analysis showed a benefit with apixaban over 4 SD (z=4.76) and P value of 0.000002. The authors of this study concluded that apixaban reduced the risk of stroke or systemic embolism by more than 50% when compared with aspirin without significantly increasing the risk of major bleeding.[6]

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial by Granger et al. compares apixaban 5 mg twice a day with dose-adjusted warfarin to INR of 2-3. Similar to the AVERROES trial, a reduced dose of apixaban was used (2.5 mg twice daily) if patients met at least two of the following criteria: ≥ 80 years old, weight ≤ 60 kg, or SCr ≥1.5 mg/dL. The investigators estimated that 18,000 patients would be needed to achieve 90% power to show at least a 50% relative risk reduction in stroke and systemic embolism compared with warfarin. The trial randomized 18,201 patients with atrial fibrillation and at least one other risk factor for stroke: prior stroke, transient ischemic attack, or systemic embolism; age over 75 years; hypertension (receiving treatment); symptomatic heart failure; or left ventricular ejection fraction less than 40%. The primary efficacy outcome was stroke or systemic embolism, and the key secondary efficacy outcome was death from any cause. The primary safety outcome was major bleeding as defined by ISTH criteria.[7]

The results of the trial showed the primary outcome occurring in 212 patients (1.27% per year) in the apixaban group and 265 patients (1.60% per year) in the warfarin group (95% CI, 0.66 to 0.95; P<0.001 for noninferiority and P=0.01 for superiority). The rate of death from any cause was 3.52% per year in the apixaban group and 3.94% per year in the warfarin group (P=0.047). Major bleeding occurred in 327 patients (2.13% per year) in the apixaban group and 462 patients (3.09% per year) in the warfarin group. This includes a lower rate of intracranial hemorrhage with apixaban versus warfarin (52 versus 122, P<0.001). The authors of this study concluded that apixaban significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% compared with dose-adjusted warfarin.[7]

**Discussion**

The two clinical trials, AVERROES and ARISTOTLE, compared apixaban to aspirin and warfarin, respectively, and demonstrated that apixaban significantly reduced the rate of stroke in patients with atrial fibrillation and at least one risk factor for stroke. Apixaban was also shown to not significantly increase bleeding risk when compared to aspirin and showed a significantly decreased risk of bleeding when compared to warfarin.[6,7]

While apixaban appears to be superior to warfarin in terms of efficacy and safety, there are no controlled trials that directly compare apixaban to the other novel oral anticoagulants, such as dabigatran or rivaroxaban.[6,7] The ACCP guidelines have been revised to favor dabigatran 150 mg twice daily over vitamin K antagonists in patients with a $CHADS_2$ score of two or more based on the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial.[2] This study demonstrated that dabigatran 150 mg twice daily was superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation and showed no difference in the rates of major bleeding. The lower dose of dabigatran 110 mg twice daily was non-inferior to warfarin with respect to prevention of stroke or systemic embolism and had a significantly lower incidence of major bleeding.[8] In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, rivaroxaban 20 mg was non-inferior to warfarin in terms of stroke and systemic embolism prevention, but there were similar rates of major bleeding between the two groups.[9] This is in comparison to apixaban, which has demonstrated superiority in preventing stroke and systemic embolism compared to warfarin, without a corresponding increase in major bleeding. However, it is not possible to state that apixaban is the preferred anticoagulant because while the ARISTOTLE, RE-LY, and ROCKET-AF trials shared similar primary efficacy and safety endpoints, the patient populations were different. The main distinction between the trials lies in the average $CHADS_2$ score, which was 2.1 in the ARISTOTLE trial, 2.2 in the RE-LY trial, and 3.5 in the ROCKET-AF trial.[7-9] The warfarin group in the ROCKET-AF trial also had less optimal management of their INR readings, with only 55% of patients within therapeutic range during the study, compared to 62% in ARISTOTLE and 64% in RE-LY.[7-9] These factors could contribute to the different results from these trials and preclude clinicians from making direct comparisons without additional real-world data.

In comparison to warfarin, apixaban is similar to the other new anticoagulants in that it provides adequate anticoagulation without the need for therapeutic monitoring or dietary restrictions. However, the drawbacks to these new agents include the lack of a reversal agent, no monitoring parameters to determine medication compliance, and multiple daily dosing with dabigatran and apixaban.[3] There have also been no studies evaluating the safety of apixaban in patients with renal insufficiency or with long- term use. Compared to dabigatran and rivaroxaban, apixaban offers the advantage of a lower bleeding rate, fewer drug interactions, and less gastrointestinal side effects. Therefore, apixaban is a promising new anticoagulant that will offer an alternative to the currently available options.

***References:***


*1. Sanoski CA, Bauman JL. The arrhythmias. In: DiPiro JT, Talbert RL, Yee GC et al., eds. Pharmacotherapy: a pathophysiologic approach. 8th ed. New York: The McGraw-Hill Companies, Inc.; 2011.*

*2. You JJ, Singer DE, Howard PA et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (9th Edition). Chest 2012; 141:531S-75S.*

*3. Gage BF, Waterman AD, Shannon W et al. Validation of clinical classification schemes for predicting stroke. JAMA. 2001; 285:2864-70.*

*4. Turpie AG. Oral, factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol. 2007; 27:1238-47.*

*5. Wittkowsky A. Novel oral anticoagulants and their role in clinical practice. Pharmacotherapy. 2011; 31:1175-91.*

*6. Connolly SJ, Eikelboom J, Joyner C et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011; 364:806-17.*

*7. Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365:981-92.*

*8. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361:1140-51.*

*9. Patel MR, Mahaffey KW, Jyotsna G et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365:883-91.*