2014

Is Apixaban Effective for the Prevention of Stroke in Patients With Non-Valvular Atrial Fibrillation?

Amira Moore
Philadelphia College of Osteopathic Medicine, amiramo@pcom.edu

Is apixaban effective for the prevention of stroke in patients with non-valvular atrial fibrillation?

Amira Moore, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

OBJECTIVE: The objective of this EBM review is to determine whether or not Apixaban is effective for the prevention of stroke in patients with non-valvular atrial fibrillation.

STUDY DESIGN: Review of three English language primary studies published all published in 2011.

DATA SOUCRES: Three double-blind randomized control trials found using the Cochrane Database and PubMed.

OUTCOME(S) MEASURED: Outcomes measured were occurrence of stroke (TIA or CVA), systemic embolism, major bleeding or clinically relevant non-major bleeding, and incidence of death.

RESULTS: Apixaban 2.5mg and 5mg were both superior to Warfarin in the prevention of stroke or systolic embolism and also decreased the rate of intracranial hemorrhage or other clinically relevant bleeding. Apixaban 5mg was also demonstrated superiority compared to aspirin 81-324mg in reduction of stroke, systemic embolism, and death rates.

CONCLUSION: In patients with atrial fibrillation, apixaban was superior to both warfarin (adjusted to an INR 2.0-3.0) and aspirin (81-324mg) in the indication of prevention of stroke or systemic embolism.

KEY WORDS: Apixaban, atrial fibrillation, stroke, prevention

INTRODUCTION

Atrial fibrillation is the most common chronic arrhythmia with an incidence and prevalence that increases with age. Atrial fibrillation can occur in conjunction with other diseases that affect the function of the heart such as rheumatic heart disease, many forms of valvular heart disease, dilated cardiomyopathy, atrial septal defect, coronary heart disease and can also present in patients without any prior history of cardiac disease [5]. The mechanism of cause is still debatable. Current theories involve complex interaction between the initiation and the musculature in the atria that responds to this impulse.

Symptoms of atrial fibrillation include: irregular heartbeat, tachycardia, lightheartedness, extreme fatigue, shortness of breath with chest pain. This condition is routinely diagnosed by ECG interpretation due to its disorganized atrial activity and irregular ventricular response. Episodes of atrial fibrillation can be classified as paroxysmal (hours to days), persistent (lasts for days and is corrected with intervention), or permanent [5]. Atrial fibrillation reduces the amount of blood that is pumped from the atria into the ventricles increasing the chance dangerous clot formation which can go on to embolize and cause infarction. Due to the potential for emboli to reach the brain atrial fibrillation is known to be the cause of 15-20% of ischemic strokes [5]. The focus of this study will be patients that have non-valvular atrial fibrillation, defined as being in of rheumatic heart disease, a prosthetic heart valve or previous valve repair.

Atrial fibrillation, in general, is relatively common with an estimated 2.66 million people having been diagnosed with this disorder in 2010. The average age of a patient with atrial fibrillation is 67 for men and 75 for women [4]. Demographics wise atrial fibrillation is also more prevalent in white than black populations. Occurring to the CDC the estimated cost of treatment for atrial fibrillation was $6.65 billion per year; this figure includes cost of hospitalization, in/outpatient physician care and medications [4.] Though there is not an exact estimate of how many healthcare visits are due to atrial fibrillation complications it is projected that 12 million people will have this condition by 2050. In

addition the mortality rate from atrial fibrillation either as a primary or an underlying cause of death has been increasing for more than two decades [4].

There are multiple methods in which non-valvular atrial fibrillation is treated. Treatment is initiated through the use of medication to control rate and rhythm (amiodarone, verapamil, diltiazem) and surgical ablation therapy. The gold standard anticoagulant prophylaxis for emboli from potential clot formation is warfarin, but other anticoagulant therapeutic agents such as IV heparin and oral aspirin have also been successful in the prevention of stroke and other thromboembolic events [5]. Warfarin is recommended for patients with a INRs (international normalized ratio) in between 2.0-3.0 with increased risk for stroke/thromboembolic events. These risks include previous stroke, TIA, systemic emboli, previous symptomatic heart failure or left ventricular ejection <40%, diabetes, and/or hypertension[3].

Factor Xa inhibitors are another classification of anticoagulants which directly target the clotting factor Xa to prevent clot formation. Traditionally these agents have been used in place of warfarin or LMWH to prevent venous thrombosis after hip or knee replacement surgery. Unlike warfarin these agents have no required need for coagulation monitoring. In 2012 Apixaban, a factor Xa inhibitor was approved for the prevention of stroke in patients with non-valvular atrial fibrillation after exploration of the medications efficacy with studies of this patient population.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is apixaban effective for the prevention of stroke in patients with non-valvular atrial fibrillation”.

METHODS

The studies in this selective Evidence Based Medicine review included men and women diagnosed with atrial fibrillation. The inclusion criteria were based on the following risk factors: ages greater than or equal to 75yrs, history of previous stroke (TIA or cerebral infraction), history systemic

embolism, CHF (left ventricular ejections fraction of less than or equal to 40%), hypertension requiring pharmacological treatment, or a diagnosis of diabetes mellitus. Exclusion criteria included atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, stroke within the previous seven days, severe renal insufficiency (serum creatinine level of >2.5mg or CrCl of <25ml/min) [1,2,3]. The intervention addressed was Apixaban 2.5mg or 5mg BID compared against Warfarin titrated to an INR level between 2.0-3.0 and aspirin dosed 81-324mg given once a daily. Outcomes were measured in the occurrence of stroke and/or systemic embolism, MI, major bleeding, clinically relevant non-major (CRNM) bleeding or death. These three studies compared are double-blind randomized controlled trials using apixaban, compared with warfarin, aspirin or both. In all three of the studies detailed in this review CHADS2 scale was used to measure a patients risk of stroke.

Data sources included both Cochrane and Pubmed databases using the keywords “Atrial fibrillation”, “apixaban”, “stroke”, “warfarin”, and “prevention” between 2003-2013. All articles were published in English in 2011 and were selected based on relevance to patients with atrial fibrillation. Statistics include p-value, RRR, ARR and NNT. Articles were selected based on their relevance to my clinical question and if they included POEMs.

Table 1: Demographics & Characteristics of included studies

Study	Type	#pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Joyner et al[1] (2011)	Double-blind RCT	18201	50 or older	Men or women aged 50 years or older with documented atrial fibrillation that have one or more of the following risk factors for stroke: -Age greater than or equal to 75yrs Previous stroke, TIA or systemic embolism -CHF (left ventricular ejection fraction of less than or equal to 35%) -Documented peripheral artery disease -HTN requiring pharmacologic treatment -DM -Could not be receiving vitamin K antagonist therapy because it was previously proven to be unsuitable for them or it was expected to be unsuitable	Presence of conditions other than atrial fibrillation for which the patient required long-term anticoagulation, Valvular disease requiring surgery Serious bleeding event in the previous 6 months or a high risk of bleeding (active peptic ulcer disease, platelet count under 100,000, hemoglobin level of <10g/dl, stroke within the past 10 days, documented hemorrhagic tendenices, or blood dyscrasias) Current alcohol or drug abuse/psychosocial issues	None (early termination of the study)	Apixaban 5mg 1 tab PO BID
Ogawa, Shinohara, and Kanmuri[2] (2011)	Double-blind RCT	222	20 or older	Men or women with documented atrial fibrillation that have one or more of the following risk factors for stroke: Age greater than or equal to 75yrs CHF (left ventricular ejection fraction of less than or equal to 40%) HTN requiring medication DM History of cerebral infraction or TIA	Recent cerebral infraction (including TIA) Valvular heart disease Sick sinus syndrome or severe conduction disturbance Non-cardiogenic stroke requiring aspirin or aspirin and anti-platelet agents Contraindications for warfarin use Severe or refractory HTN Current thrombocytopenia (platelet count under 100x109 /L or hemoglobin less than 10g/dl) Renal dysfunction (creatinine clearance < 25ml/min) LFT abnormalities (ALTs or AFTs greater than or equal to 2x the upper limit of normal)	0	Apixaban 2.5mg or 5mg 1tab po BID
Granger, Alexandar, McMurray et al.[3] (2011)	Double-blind RCT	5599	50 or older	Men or women with documented atrial fibrillation that have one or more of the following risk factors for stroke: Age greater than or equal to 75yrs Previous stroke, TIA or systemic embolism CHF (left ventricular ejection fraction of less than or equal to 40%) HTN requiring pharmacologic treatment DM	Atrial fibrillation due to a reversible cause Moderate or severe mitral stenosis Conditions other than atrial fibrillation that required anticogulation Stroke with the previous 7 days Need for aspirin at a dose >165mg qd or for both aspirin and clopidogrel Severe renal insufficiency (serum creatinine level of >2.5mg/dl or calculated creatinine clearance of <25ml/min)	N/A	Apixaban 5mg 1 tab po BID

OUTCOMES

All outcomes were measured in relation to the incidence of stroke or other thromboembolic event during the time that patients were using the treatment medication (apixaban, warfarin, or aspirin). Favorable outcomes included a decrease in the rate of stroke or systemic embolism, intracranial bleeding, myocardial infarction or pulmonary embolism. Unfavorable outcomes included an increase in the rate of death, stroke, systemic embolism, clinically relevant major or non major bleeds, myocardial infarction, or death.

Stroke was defined as a focal neurologic deficit, originating from a non-traumatic cause, lasting for at least 24 hours and was categorized as ischemic or hemorrhagic from evaluation of brain imaging studies (MRI, CT without contract). Those in whom imaging or an autopsy was not performed were classified as "uncertain" [3]. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ. Major bleeding was defined as an acute, clinically overt, and with 1 or more of the following: decrease in hemoglobin >2g/dl over a 24hr period; bleeding requiring a transfusion of >2 units of packed red blood cells, or bleeding at the critical site (intracranial, intraspinal, intraocular, intra-articular), or bleeding that was fatal [2]. Clinically relevant non-major bleeding was defined as acute or subacute, clinically overt, not major that lead to hospital admission or physical guided medical or surgical treatment [2].

In the study comparing Apixaban and Warfarin in Patients with Atrial Fibrillation apixaban was administered at a dose of 5mg twice a day or Warfarin titrated to an INR 2.0-3.0. Those participants that were on previously initiated warfarin therapy were asked to discontinue their medication three days before randomization. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. This trial was designed to test for non-inferiority with a secondary objectives of testing for superiority.

In the study comparing the Safety and Efficacy of Oral Direct Factor Xa Inhibitor Apixaban in Japanese Patients with Non-Valvular Atrial Fibrillation apixaban was given in either doses of 2.5mg or

5mg twice a day or open-label warfarin titrated to an INR of 2.0-3.0 for 12 weeks. The endpoint being occurrence of major and clinically relevant non-major bleeding.

In the study Apixaban in Patients with Atrial Fibrillation this patient population consisted of those whom Vitamin K antagonist therapy was unsuitable. Apixaban was dosed at 5mg twice daily and aspirin was compared to aspirin dosed 81-324mg daily. The primary outcome was occurrence of stroke or systemic embolism. This trial was designed to test for superiority of apixaban when compared with aspirin.

RESULTS

In the study Apixaban and Warfarin in Patients with Atrial Fibrillation the rate of the primary outcome (stroke or systemic embolism) were compared with patients given apixaban 5mg and those given Warfarin adjusted to an INR of 2.0-3.0. Rates of stroke or systemic embolism in the apixaban group were decreased when compared to warfarin (Hazard ratio =0.79; 95% CI, 0.66-0.95; $P<0.01$;). With a primary outcome event ratio of apixaban and warfarin 1.27% and 1.60% per year, respectively. Incidence of major bleeding also decreased in the apixaban group compared to the warfarin group (Hazard ratio =0.69, 95% CI 0.60-0.80, $P<0.001$). The yearly event rate of major bleeding in the apixaban and warfarin groups were 2.13% and 3.09%. In addition the net clinical outcomes (stroke, systemic embolism, major bleeding, or death from any cause) were lower in the apixaban group than the warfarin group (Hazard ratio = 0.85, 95% CI 0.78-0.92, $P<0.001$); with event rates 6.13% and 7.20% respectively. When evaluating the treatment effect of apixaban 5mg versus warfarin the RRR was 20%, ARR was 0.33% and the NNT was 303.

Table 2: Rates of Primary and Secondary Event Outcomes in Granger et al 2011

Event Rate (%)	Apixaban (5mg)	Warfarin (INR 2.0-3.0)
Stroke or systemic embolism	1.27%	1.60%
Major bleeding	2.13%	3.09%
Net clinical outcomes*	6.13%	7.20%
* stroke, systemic embolism, major bleeding, or death from any cause		

In the study Safety and Efficacy of Oral Direct Factor Xa Inhibitor Apixaban in Japanese Patients with Non-Valvular Atrial Fibrillation the primary clinical endpoint was major and clinically relevant non-major (CRNM) bleeding, were compared with patients given apixaban 2.5mg or 5mg BID and the warfarin (adjusted to an INR 2.0-3.0) group. Due to the small number of patients in each group no formal statistical testing was conducted and P-values were not calculated for this study. Major and CRNM bleeding events occurred in 1.4% of apixaban 2.5mg BID group (1 out of 72 patients), 1.4% of apixaban 5mg BID group (1 out of 71 patients) and 5.3% (4 out of 75) in the warfarin group. In both apixaban groups there was no incidence of stroke, systemic embolism, MI or death from any cause while in the warfarin group 4.1% (3 patients), had stroke events including: 1 subarachnoid hemorrhage and 2 ischemic strokes. No deaths occurred in the warfarin group. When evaluating the treatment effect of apixaban 2.5mg or 5mg versus warfarin the RRR was 73.5%, ARR was 3.9%, NNT was 26.

In the study Apixaban in Patients with Atrial Fibrillation the primary outcome, occurrence of stroke or systemic embolism, was compared between patients given apixaban 5mg and patients given aspirin doses in the range of 81mg-324mg. These patients where all determined to be unsuitable for warfarin treatment and thus aspirin was used in the control group. Rates of stroke or systemic embolism were decreased in the apixaban group compared to the aspirin group (Hazard ratio 0.45; 95% CI 0.32-0.62; $P<0.001$). The yearly event rates of the primary outcomes are significantly increased in the aspirin group (event rate of 3.7% per year) compared to the apixaban group (event rate of 1.6% per

year). Incidence of major bleeding was similar between both apixaban and aspirin groups (Hazard ratio with apixaban 1.13; 95% CI 0.74 to 1.75; P=0.57). The yearly event ratio of major bleeding for the apixaban group was 1.4% and 1.2% for the aspirin group. In addition the yearly death rate was 3.5% per year in the apixaban group and 4.4% in the aspirin group. When evaluating the treatment effect of apixaban 5mg versus aspirin 81-324mg the RRR was 22.7%, ARR was 0.5%, NNT was 200. Due to the treatment benefit in favor apixaban for the primary outcome which exceeded 4 SD this study was terminated early [1]. Study termination was recommended after the first confirmatory data analysis.

Table 3: Rates of Primary and Secondary Event Outcomes

Event Rates (%)	Apixaban (5mg)	Aspirin (81mg-324mg)
Stroke or systemic embolism	1.60%	3.70%
Major bleeding	1.40%	1.20%
Deaths (from any cause)	3.50%	4.40%

DISCUSSION

Anticoagulation therapy with warfarin is the gold standard therapy for patients with atrial fibrillation, but not only apixaban, but rivaroxaban (another Factor XA inhibitor) and dabigatran (an oral direct thrombin inhibitor) have also been proven to be noninferior or superior to warfarin in regards to stroke prevention[5]. A major complication of warfarin is an increased risk of intracranial bleeding including hemorrhagic stroke. Patients on warfarin are required to their INRs monitored to track their rate of anticoagulation to prevent aforementioned bleeding. In addition patients using warfarin must control their diet for foods that are high in vitamin K (liver, green tea, green leafy vegetables) which is the antidote to the anticoagulative effects of the medication [5]. Apixaban, unlike warfarin, has no required coagulation monitoring nor does the patient have to alter their diet to prevent interactions with the medication. A possible limitation of the studies that included warfarin are due to he studies not being completely blinded. Although randomization occurred blind, those patients on warfarin were required to have INR monitoring.

Apixaban's original indication was prevention of venous thrombosis after hip and knee surgery

and was recently approved by the FDA for the of stroke prevention in patients with atrial fibrillation in Dec 2012. Due to how recent FDA approval was to the time that the research for this study was conducted statistically reliable cost effective studies for apixaban when compared to warfarin are not available. The price of apixaban is partially covered by Medicare Part D but the out-of-pocket prices of the medication vary across insurance providers.

CONCLUSION

Based on the three studies above, it can be concluded that Apixaban is effective in the prevention of stroke in patients with non-valvular atrial fibrillation. Apixaban doses 2.5and 5mg had consistently lower rates of stroke, systemic embolism, and bleeding (major or CRNM) when compared to the groups treated with warfarin [2,3]. Apixaban 5mg was proven to have lower rates of stroke or systemic embolism in patients which Vitamin K antagonist therapy was unsuitable, when compared to aspirin 81-324mg. In addition patients with atrial fibrillation, apixaban was superior to both warfarin (adjusted to an INR 2.0-3.0) and aspirin (81-324mg) in the indication of prevention of stroke or systemic embolism.

REFERENCES

1. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med . 2011;364(9):806-817. doi: 10.1056/NEJMoa1007432; 10.1056/NEJMoa1007432.
2. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor Xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -the ARISTOTLE-J study-. Circ J. 2011;75(8):1852-1859.
3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-992. doi: 10.1056/NEJMoa1107039; 10.1056/NEJMoa1107039.
4. Atrial Fibrillation Fact Sheet. Centers for disease control and prevention website. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm. Accessed September 29 2013.
5. Granger CB, Hranitzky P, Patel MR. Chapter 10. Heart Disease. In: Papadakis MA, McPhee SJ, Rabow MW, Berger TG, eds. *CURRENT Medical Diagnosis & Treatment 2014*. New York: McGraw-Hill; 2013. http://www.accessmedicine.com/content.aspx?aID=3671. Accessed December 20, 2013.