Comparing Apixaban Vs Rivaroxaban For Atrial Fibrillation Patients: An Effectiveness And Safety Analysis

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● **Abstract**

Apixaban and Rivaroxaban, two direct oral anticoagulants, are being compared for their efficacy and safety in the treatment of atrial fibrillation as part of the study's aims.

The most common arrhythmia, atrial fibrillation (AF), is expensive for the healthcare system because of its high death and morbidity rates, which are mostly caused by thromboembolic consequences. In order to treat patients with atrial fibrillation, we thoroughly analyze the safety and effectiveness of two novel anticoagulant drugs in this study: rivaroxaban and apixaban.

In conclusion, In our study we try to investigate and compare the relatively new two anticoagulants Apixaban and Rivaroxaban regarding their effectiveness and safety in managing atrial fibrillation.

Keywords: Apixaban; Rivaroxaban; atrial fibrillation; oral anticoagulants; safety; effectiveness.

● Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide. Anatomical and/or electrophysiological anomalies can lead to aberrant impulse generation. An estimated 33.5 million persons had AF by 2010. Even though industrialized countries have carried out more epidemiological studies on AF, the condition's

prevalence and incidence rates are increasing worldwide. The prevalence was 2.3%, 2%, and 1.7% in the US, Europe, and New Zealand, respectively. In contrast, the aging population in the West has been associated with AF, despite the fact that only two hospital-based examinations in Saudi Arabia found variations in the underlying causes of the illness. The effects of AF are expensive in terms of higher healthcare costs and debt, as well as higher rates of thromboembolic complications and heart failure (HF)-related morbidity and mortality. (Mashat et al., 2019)

A major risk factor for stroke is atrial fibrillation (AF). As of right now, the only antithrombotic medications that are approved for use in people with atrial fibrillation (AF) are vitamin K antagonists (VKAs; oral anticoagulants, such warfarin) and the platelet inhibitor acetylsalicylic acid. Although VKAs are useful, their pharmacological effects can vary, therefore it's important to regularly change dosage and check coagulation to ensure that effects stay within the prescribed range. First in the clinical development pipeline, evaluation of safety and efficacy in a short-term indication such as venous thromboembolism (VTE) prophylaxis is often the first step. Subsequent research focuses on treating VTE for longer periods of time, and finally, chronic indications such preventing stroke in individuals with atrial fibrillation (AF) are addressed. Several elements of the coagulation cascade, including Factor Xa (FXa) and Factor IIa (thrombin), can be targeted by novel anticoagulants. Many of the direct, oral FXa inhibitors that are anticipated to avoid the side effects of VKAs are now undergoing various stages of clinical trials. DU-176b, Betrixaban, Rivaroxaban, and Apixaban are a few of these. (Turpie, 2007).

Because these drugs are considered relatively new, their effect and safe use should be thoroughly investigated. In our study we perform a detailed analysis to compare two of the new anticoagulant drugs: Apixaban and Rivaroxaban regarding their effectiveness in managing AF patients and their safety.

- **Significance of the study**

Due to the high incidence of atrial fibrillation and the emergence of new oral anticoagulants with many types, it is essential to investigate them properly, especially with evidence that both Apixaban and Rivaroxaban can cause major side effects like major ischemic or hemorrhagic events (Oldgren et al., 2013) Investigating the drugs' efficacy and safety can help greatly in anticipating those

side effects and dealing with them properly, as well as, helping in setting new guidelines on when and whether or not use them in managing AF patients.

- **Objectives**

1. Determine the efficacy and safety of Apixaban in AF management.
2. Determine the efficacy and safety of Rivaroxaban in AF management.
3. Comparing between the two drugs to decide which is safer and more effective.
4. Determine possible modification in the drugs prescribed for AF management.

- **Literature Review**

i. Atrial Fibrillation (AF) Epidemiology and Risk Factors:

The global epidemic of AF is posing a growing clinical and public health challenge. Not only have large studies from North America and Europe helped establish key epidemiological characteristics of AF in these locations, but they have also brought attention to the underutilization of anticoagulant medication. Research in low- and middle-income countries (LMICs), where AF is becoming more common, has shown that undertreatment and inadequate treatment efficacy monitoring may be even bigger issues than previously thought. Therefore, in order to combat this serious epidemic and enhance patient outcomes, health care providers, national organizations, international societies, and health insurance companies worldwide should acknowledge the significance of treating AF to avoid complications and concentrate on allocating resources as efficiently as possible. (Rahman et al., 2014)

Since AF mostly affects the elderly, it is expected that the percentage of older adults with AF will more than double over the next three decades. a result of population aging. Being older is another independent risk factor for stroke in patients with AF, especially in women. The percentage of strokes linked to AF increases exponentially with age. Furthermore, AF is associated with increased medical costs and hospital admissions, as well as decreased survival and quality of life in the elderly, according to the evaluations written by Drs. Lane and Lip in this issue. In light of these results, further investigation is needed to completely

understand the underlying causes and pathophysiology of AF in the elderly as well as to identify and implement more effective therapeutic and preventative interventions for this increasingly common disease. (Rich, 2009)

Globally, the prevalence of AF is gradually rising, despite significant regional and study-based variations. The discovery that a higher percentage of ischemic stroke patients have atrial fibrillation (AF) either during hospitalization or after post-discharge inquiry raises serious concerns because AF associated with stroke has worse results and a worse prognosis. Better prediction techniques for AF detection as well as increased knowledge among doctors and other healthcare professionals who can identify patients with AF during routine check-ups, flu shots, and hospital admissions may account for this rise in the prevalence of AF. (Zulkifly et al., 2018)

Despite the noticeable differences in demographic variables found in most published epidemiological studies (e.g., varying ages at enrollment, various types of AF investigated), the available data indicate a similar prevalence and incidence of AF throughout the developed globe.According to current estimates, the prevalence of AF among Europeans who are 15 to 20 years of age or older is 2%, with an incidence ranging from 0.23 to 0.41 per 1,000 people annually. Since there are now no proven effective medications for the primary prevention of AF, doctors should concentrate on treating the cardiac conditions and comorbidities that pose a significant risk for the condition. More research is especially needed to better understand the long-term course of people at risk of developing AF in order to prevent issues. (Zoni-Berisso et al., 2014)

As people age, atrial fibrillation (AF) becomes more common. The aging population provides only a partial explanation for the trend of rising incidence and prevalence of AF seen in recent population-based data. According to a recent population research, by 2050 there would be over 10 million Americans living with AF, up from the present 2.3 million. Obesity and sleep apnea are two novel risk factors that could contribute to the present AF epidemic. Studies based on population samples have indicated but not conclusively clarified ethnic variations in the epidemiology of AF. Data based on the general population provide compelling evidence for the heritability of AF. Studies on the genetic epidemiology of AF may provide significant mechanistic insights that eventually may result in new treatment and preventive approaches. (Chen & Shen, 2007)

ii. Anticoagulation in AF Management:

Oral anticoagulant therapy, which can be given with vitamin K antagonists (VKAs) or novel oral anticoagulants like dabigatran, rivaroxaban, and apixaban, is the cornerstone of thromboprophylaxis in patients with atrial fibrillation (AF). The thromboembolic risk factors linked to atrial fibrillation (AF) and the bleeding risk variables related to oral anticoagulant medication are nearly identical. Oral anticoagulant medication has a positive net clinical benefit because the risk of bleeding usually outweighs the individual benefit of avoiding thrombosis. Long-term oral anticoagulant treatment is the most common necessity for the prevention of thromboembolic events due to AF. A patient may experience different clinical scenarios over time (e.g., an acute stroke, an urgent surgical procedure, etc.), which may call for a temporary or long-term adjustment to anticoagulant medication irrespective of the anticoagulant medication taken. This could be especially difficult for doctors because there are still a lot of unanswered questions about the best way to utilize oral anticoagulant medications in certain clinical settings. (Kornej et al., 2013)

The finest people to handle various elements of AF are individuals who have received specialized training in managing AF. Numerous care gaps exist in the general practitioner level of AF management, as has been extensively reported. These concerns concern the choice of patients who should be anticoagulated, the appropriate time for a cardioversion, the transition from rate to rhythm management, and the referral process for catheter ablation. Establishing a specialty clinic under medical supervision could help with education for both doctors and patients because the knowledge would come from one source. This would enable the population to get an evidence-based, unified approach about these novel medicines, in addition to additional information surrounding the paradigms in AF treatment nowadays. A combined specialist and nurse-based AF clinic was linked to a significant decrease in ED visits, hospitalizations, and increased survival, according to earlier research. The purpose of this study was to ascertain whether an integrated management approach combined with physician-supervised, nurse-based care produces repeatable results in other healthcare jurisdictions. (Carter et al., 2016)

Warfarin is a better option than aspirin in this sense because it can cause considerable bleeding while also lowering the risk of stroke in patients with atrial fibrillation. Therefore, physicians stratify

patients according to their risk of stroke in order to ensure a net benefit. The CHA2DS2-VASc stratification system used in the most current guidelines released by the European Society of Cardiology (2010–12) will be explained in this review. The increased sensitivity of this method more accurately determines the patients who should take warfarin as compared to the previous CHADS2. Additionally, the study predicts that a broader range of patients may benefit from the new oral anticoagulants, which significantly lower the risk of cerebral hemorrhage and have equivalent or superior efficacy and/or safety to warfarin without requiringFrequent monitoring of coagulation. (John Camm, 2012)
The course of long-term care for AF is determined by its symptoms and length. Within less than 48 hours of safely cardioverting AF back to sinus rhythm, anticoagulation treatment could be initiated. Any AF that lasts more than 48 hours, there are two recommended courses of action: either start DCCV/pharmacologic cardioversion after 4 weeks of complete anticoagulation, or start DCCV/pharmacologic cardioversion first, followed by transesophageal echo-guided DCCV or pharmacologic cardioversion. The symptoms of the patient, such as palpitations, impaired functional ability, exercise intolerance, and medication tolerance, are utilized to guide the drug therapy used in the rate control method. Pacemakers and AV node ablation are alternatives to rate control therapy in cases where the patient is not responding to pharmaceutical therapy. (Amin et al., 2016)

iii. Mechanisms of Action of Apixaban and Rivaroxaban

Even if the outcomes of a few phase III clinical studies using novel oral anticoagulants are already known, it's nevertheless critical to comprehend how they work. These new medications work as anticoagulants by specifically blocking one factor (such thrombin or Factor Xa) in the coagulation cascade. Rivaroxaban, a small-molecule derivative of oxazolidinone, is the first oral direct Factor Xa inhibitor. It binds to Factor Xa directly and reversibly via the S1 and S4 pockets. Compared to other similar serine proteases, rivaroxaban is more than 10,000 times more selective for Factor Xa and competitively inhibits it. Its anticoagulant action is independent of cofactors such antithrombin. Rivaroxaban inhibits Factor Xa both free and attached to clots, in contrast to indirect Factor Xa inhibitors**,** along with prothrombinase activity, which causes clotting times to be extended. A direct thrombin inhibitor, dabigatran etexilate inhibits thrombin both free and attached to

fibrin. Phase III tests of these novel medicines demonstrated that both thrombin and Factor Xa are effective anticoagulation targets, despite the fact that their mechanisms of action are different. (Samama, 2011)

Two small compounds that reversibly inhibit factor Xa are apixaban and Rivaroxaban. Activated partial thromboplastin time and prothrombin time are less affected by apixaban than by rivaroxaban. To investigate this phenomenon, we used a buffer system with a factor Xa-directed substrate. Although both medications suppressed factor Xa with similar Ki values at equilibrium, kinetic studies revealed that rivaroxaban inhibited factor Xa up to 4-fold faster than apixaban ($p<0.001$). Using a discontinuous chromogenic test to track prothrombinase synthesis in a pure system, rivaroxaban outperformed apixaban four times (Ki values of 0.7 ± 0.3 and 2.9 ± 0.5 nM, respectively; $p = 0.02$). (Kim et al., 2018)

Because of the manner they function, the new oral anticoagulants are referred to as direct oral anticoagulants (DOACs). Whereas rivaroxaban, apixaban, and edoxaban selectively and competitively block the activated Factor X (FXa) by direct inhibition, dabigatran acts as a competitive, selective, and direct inhibitor of thrombin (Factor IIa). The plasma peak concentration of DOACs is rapidly reached, and they exhibit nearly instantaneous anticoagulant action with a relatively short half-life. As a result, they do not require an overlapping parenteral anticoagulant phase. Even though renal function has an impact, their elimination occurs sufficiently quickly after withdrawal. The only DOAC that is given as a prodrug and becomes active upon drug metabolization is dabigatran. Dabigatran is mostly eliminated through the kidneys, while FXa inhibitors are primarily removed through the biliary-fecal system. The main targets of pharmacological interactions with DOACs are medications that operate on P-glycoprotein in the case of dabigatran and on P-glycoprotein and/or cytochrome P3A4 in the case of anti-Xa. Dietary interactions don't exist with DOACs. DOACs don't require routine laboratory monitoring because of their fixed dosage, linear pharmacodynamics (a predictable dose/response relationship) and anticoagulant effect. (Masotti & Campanini, 2013)

The direct oral anticoagulants apixaban and rivaroxaban specifically target and activate factor X (FXa). The exact mechanism by which xabans affect platelet function is currently unknown. The purpose of this single-center observational study was to evaluate

the in vitro platelet function of atrial fibrillation patients taking apixaban or rivaroxaban. It looked at platelet quantitation.

Aggregation measured by light transmission aggregometry in 34 individuals receiving rivaroxaban or apixaban treatment. Two hours after ingesting specific xabans, the thrombin-induced platelet aggregation was considerably lower than the baseline value (69.55±32.15% vs. 44.79±34.97.9%; p<0.0001). Only those patients who took rivaroxaban or apixaban for longer than a week experienced this side effect. When using rivaroxaban or apixaban, patients with cardiovascular disease experience less thrombin-induced platelet aggregation. This decrease is probably contingent upon the The direct oral anticoagulants apixaban and rivaroxaban specifically target and activate factor X (FXa). It is currently unclear how long the treatment will last. It is recommended that future investigations on DOACs and platelet aggregation take treatment duration into account. (Sokol et al., 2018)

iii. Studies comparing Apixaban and Rivaroxaban:

There were no statistically significant increases in the incidence of stroke, systemic embolism, or major bleeding among patients with AF in routine clinical practice, according to propensity-matched assessments of apixaban, dabigatran, and rivaroxaban administered at regular doses. Even though analysis suggests that differences larger than moderate can be excluded, smaller differences cannot be ruled out. (Andersson et al., 2018)

The only source of information that is currently accessible is observational research because there are no head-to-head trials comparing different DOACs. Based on these results, it may be concluded that while apixaban, dabigatran, and rivaroxaban all have similar effects on the risk of ischemic stroke, apixaban may have a lower risk of substantial bleeding than either dabigatran or rivaroxaban. (Douros et al., 2019)

Direct comparisons reveal that apixaban at a lowered dose and dabigatran at a regular dose both have acceptable bleeding risk profiles. There were no variations in efficacy discovered. This research validates earlier indirect DOAC comparisons. Additional research is required. (Jansson et al., 2020)

In general, DOACs were superior to warfarin in preventing strokes; yet, there were notable variations among subgroups identified by a prior ischemic stroke. Regarding the prevention of ischemic stroke, patients with a history of stroke or TIA were found to

benefit from dabigatran more than those without a history (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.48 to 0.85) and those without a history (HR 0.94; 95% CI 0.75 to 1.16; p value for interaction = 0.034). When taking apixaban, dabigatran, or rivaroxaban, patients without a history of stroke or transient ischemic attack did not exhibit a statistically significant increase in their risk of stroke. But when compared to apixaban, rivaroxaban (HR 0.70; 95% CI 0.56 to 0.87) and dabigatran (HR 0.64; 95% CI 0.48 to 0.85) decreased the risk of stroke in people with a history of TIA or stroke (p value for both interactions <0.05). In conclusion, the relative effectiveness of DOACs varies significantly between patients with and without a history of stroke or TIA; in particular, apixaban is less effective in patients with a history of stroke or TIA. (Yang et al., 2020)

- **Conclusion**

In our study we try to investigate and compare the relatively new two anticoagulants Apixaban and Rivaroxaban regarding their effectiveness and safety in managing atrial fibrillation. Although our study is conclusive further future investigations must be done to furtherly perform in detail investigations and avoid any possible limitations and biases in our study.

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