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Original Article

Comparison of Efficacy and Safety of Apixaban and Warfarin in Patients with Atrial Fibrillation and Chronic Kidney Disease: A Randomised Controlled Trial

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ABSTRACT

Introduction: Atrial fibrillation (AF), the most common kind of cardiac arrhythmia, has a significant role in ischemic stroke and other severe thromboembolic consequences. According to current guidelines, individuals with atrial fibrillation who are at risk (CHA2DS2VASc score above or equal to 2) should receive direct oral anticoagulants (DOACs) instead of vitamin K inhibitors in order to avoid these dangerous side effects. The usefulness of apixaban for people with chronic kidney disease (CKD) without hemodialysis is still up for debate.

Aims/ objective: To compare the efficacy and safety of apixaban versus warfarin in patients with AF and stage 3-5 chronic kidney disease.

Materials and Method: Using web-generated random numbers, each patient with AF and CKD who met our eligibility requirements was assigned to either the warfarin (W) or apixaban (A) group. This was done through consecutive sampling. According to recommendations from the American College of Cardiology (ACC), anticoagulant medication dosages were adjusted. Incidences of ischemic stroke and thromboembolism within 1-year, significant bleeding within 3 months of enrolment and within 6 and 12 months of follow-up, and TTR (time in therapeutic range of INR between 2.0 - 3.0) at 1 year were compared between two groups.

Results: Incidence of major bleeding was lesser in patients on apixaban therapy as compared to patients receiving warfarin and the difference became significant at 12 months ($p<0.05$). Patients on apixaban therapy had longer duration in therapeutic range of INR (2.0-3.0) in comparison to patients on warfarin therapy and the difference was statistically significant ($p<0.0001$). Incidence of stroke and thromboembolism was also lower in patients given apixaban as compared to patients on warfarin therapy but the difference was not statistically significant at this sample size.

Conclusion: apixaban medication reduced the risk of stroke and thrombosis in individuals with atrial fibrillation compared to those treated with warfarin. Moreover, apixaban, at both the conventional and reduced doses, does not increase the risk of serious bleeding when compared to warfarin.

Keywords: Apixaban, Warfarin, Atrial Fibrillation, Chronic Kidney Disease, Bleeding, Stroke, Embolism.

INTRODUCTION

Atrial fibrillation (AF), the most common kind of cardiac arrhythmia, has a significant role in the cerebral ischemic strokes and other severe thromboembolic consequences.[1] According to current guidelines, individuals with atrial fibrillation who are at risks (CHA_2DS_2VASc scores greater than or equal to 2) should receive direct oral anticoagulants (DOACs) instead of vitamin K inhibitors in order to avoid these dangerous side effects. [2–5]

Patients with chronic kidney disease (CKD) have a two- to three-fold greater risk of atrial fibrillation than the general population. [6–8] Chronic renal illness can also result in a prothrombotic condition, increasing the risk of ischemic stroke or systemic thromboembolism.[9–11] Patients receiving renal replacement therapy who have a history of CKD are significantly more likely to experience thromboembolic consequences.[11, 12] Furthermore, patients with an estimated glomerular filtration rate (eGFR) of below thirty mL per min per 1.73 m^2 or between thirty to sixty mL per min per 1.73 m^2 are more likely to experience bleeding when using oral anticoagulant (OAC) medication. [12–14]

Furthermore, most important trials of direct oral anticoagulants excluded participants with severe chronic kidney disease and end-stage kidney disease (ESKD). Real-world data is needed to optimize thromboembolism mitigation while minimizing the risk of hemorrhage in patients with compromised renal function.

Renal function is one factor that influences a patient's choice of oral anticoagulants, and individuals with chronic kidney illness are often prescribed warfarin.[15, 16] Apixaban is currently the only direct oral anticoagulant available for AF patients with an eGFR of below 15 mL per minute, despite approval based on a pharmacokinetics trial involving just eight dialysis recipients with chronic kidney disease.[17] Results of apixaban treatment in patients with end-stage renal disease have also been reported. [18, 19]

Apixaban was linked to a much lower risk of major bleeding than warfarin, despite studies utilizing information gathered by the US Renal Data System (USRDS) between 2010 to 2015 showing no substantial effectiveness in reducing stroke or systemic embolism. [18] There was no correlation observed in a different study comparing apixaban and placebo in patients with AF receiving continuous dialysis to reduce the risk of either fatal or severe intracranial haemorrhage or ischemic stroke. [19] Between 2012 to 2015, USRDS data were used in this investigation.

Subsequently, the FDA revised its apixaban prescribing guidelines to include specific dosage recommendations for individuals with AF. It is recommended to lower the 5-mg twice-day dose to 2.5 mg twice-day if any two of the following criteria are met: age above or equal to to 80 years, serum creatinine more than or equal to 1.5 mg/dL, or weight of the patient below or equal to 60 kg. [20]

In a recent pharmacokinetics study involving seven participants, the area under the concentration-time curve was examined following 2.5 mg twice daily for seven days, and the sufficiency of apixaban dose for dialysis patients was evaluated. A 5-mg BD dose was administered for the following seven days following a wash-out interval. The authors found that whereas the 2.5-mg BD dosage generated levels comparable to the prescribed dosage in individuals regardless of renal impairment, the 5-mg BD dosage generated supra-therapeutic concentrations.[21]

It is yet unknown if apixaban treatment is helpful for people with chronic kidney disease (CKD) who don't undergo haemodialysis, as most research has focused on the need for anticoagulation in patients receiving chronic haemodialysis. To investigate the relative risks of significant bleeding, thromboembolism, and stroke, this study was done to compare the efficacy and safety of apixaban versus warfarin in patients with AF and stage 3-5 chronic kidney disease.

MATERIALS AND METHODS

From January 2023 to December 2024, patients suffering from atrial fibrillation and CKD (chronic kidney disease) participated in an open-label, single-centered randomised controlled study at a tertiary care centre in eastern India. All study participants provided written informed permission after receiving an explanation of the participant information sheet, and the trial was carried out in accordance with Good Clinical Practice principles, having received clearance from the Institutional Ethics Committee.

Inclusion Criteria: Our study included patients of either sex who had been diagnosed with atrial fibrillation or atrial flutter and had an eGFR of below 60 milliliters per minute per m^2 according to KDIGO (kidney disease: Improving Global Outcomes) guidelines, as well as stage 3-5 chronic kidney disease according to ICD (International Classification of Disease) – 9 and 10 regulations. [22–24]

Exclusion Criteria: Within three months of enrolment, we eliminated patients who had been diagnosed as having moderate to severe mitral stenosis, had undergone kidney transplant surgery or cardiac surgery including valve replacement, or were receiving peritoneal dialysis, or were taking other oral anticoagulants.

Every patient with AF and CKD who met our eligibility requirements was enrolled in the trial and assigned to a block that represented their respective CKD stages through the use of consecutive sampling. Using randomly generated numbers from the web, patients were assigned to either the warfarin group (Group W) or the apixaban group (Group A). According to recommendations from the American College of Cardiology (ACC), anticoagulant medication dosages were adjusted.[25]

Study Outcomes

The main outcome of our study was the incidence of severe bleeding within three months of enrolment. Major bleeding was defined by the ISTH (International Society on Thrombosis and Haemostasis) as having one of the following characteristics: bleeding that is lethal, bleeding in a vital organ or region (intracranial, intraspinal, intraocular, retro-peritoneal, intraarticular, pericardial, or intramuscular along with compartment syndrome), or bleeding that causes a drop in haemoglobin levels of more than 2 g/dL or necessitates the transfusion exceeding two units of PRBC (packed red blood cells).[26] To prevent any misunderstandings, a 48-hour window was provided for the drop in haemoglobin.

Secondary outcomes included major bleeding rates with follow-up periods of six and twelve months, ischemic stroke incidences within that time frame, recurrent thromboembolism incidences within that time frame, and TTR (time in therapeutic range of INR between 2.0 to 3.0) at that 12-month mark. The number of documented INR readings in the normal range divided by the overall number of recorded INR values yielded the TTR, which was then translated to a percentage.[27] Patients with significant bleeding or other conditions that prevented them from taking study medications during the study period were excluded. Using a chart assessment and ICD 9 and 10 codes, a confirmed diagnosis of either ischemia or of unknown sort was produced for stroke, which was characterized as a focal neurological deficit with a non-traumatic origin.[22, 23] A confirmed diagnosis of thromboembolism—which is characterized by a fatal or non-fatal pulmonary embolism or deep vein thrombosis—was determined using a chart examination of ICD 9 and 10 codes.

Statistical Analysis

Using Microsoft Excel 365, data on baseline demographic and clinical features as well as outcome variables from patients on warfarin or apixaban treatment were tabulated and then imported into SPSS version 24 for additional statistical analysis. Age, weight, CHA_2DS_2-VASc, TTR, and eGFR were examples of continuous data that were reported as mean ± SD (standard deviation). The unpaired t-test was used to determine the statistical significance of the difference in continuous data between the warfarin and apixaban groups. A p-value of less than 0.05 was considered statistically significant. Categorical data, including gender, CKD stage, usage of concurrent medication, and outcome measures, were reported as percentages and frequencies and analyzed using chi-square or Fisher's exact test.

RESULTS

100 patients were enrolled in the study during the study period of which 8 patients were lost to follow-up in within 1 month of our study and thus excluded from our analysis. Remaining patients were randomised to group A and W with 46 patients in each group. The baseline demographic and clinical characteristics of group A and group W is compared in table 1.

Table 1: Comparison of baseline demographic and clinical characteristics between Group A and W

Variables	Group A (n=46)	Group W (n=46)	P-Value
Age in years, (mean ± SD)	61.69 ± 10.24	59.88 ± 11.39	0.43
Weight in kg, (mean ± SD)	69.38 ± 6.67	70.46 ± 5.85	0.41
eGFR in ml/min/1.73 m^2, (mean ± SD)	39.26 ± 3.59	38.49 ± 4.03	0.33
CHA_2DS_2-VASc, mean ± SD)	4.65 ± 1.43	4.83 ± 1.60	0.57
Haemodialysis, n	8	7	>0.99
Aspirin, n	22	22	>0.99
P2Y12 inhibitors, n	4	5	>0.99
Proton pump inhibitors, n	20	18	0.83
Sex, n			
Male	25	24	>0.99
Female	21	22	
CKD Stage, n			
3a	12	12	0.99
3b	14	13	
4	11	12	
5	9	9	

At baseline, apixaban and warfarin groups were similar with respect to age, sex, stage of CKD, utilization of concomitant medication, haemodialysis, body weight and CHA_2DS_2-VASc with no statistically significant difference between them (P>0.05)

Table 2: Comparison of Incidence of Major Bleeding between Group A and W

Time Period	Group A (n=46)	Group W (n=46)	P-Value
0-3 Months	4	8	0.35
3-6 Months	1	4	0.36
6-12 Months	1	8	**0.03**

Incidence of major bleeding was lesser in patients on apixaban therapy as compared to patients receiving warfarin and the difference became significant at 12 months (p<0.05).

Table 3: Comparison of TTR (Time in Therapeutic Range of INR) between Group A and W

Variables	Group A (n=46)	Group W (n=46)
TTR in Percentage, mean ± SD	64.58 ± 6.08	54.78 ± 7.95
Difference in Mean	9.80	
95% Confidence interval (Difference of Mean)	6.88 to 12.71	
P Value	<0.0001	

Patients on apixaban therapy had longer duration in therapeutic range of INR (2.0-3.0) in comparison to patients on warfarin therapy and the difference was statistically significant (p<0.0001). Patients in stage 5 CKD receiving apixaban also had TTR greater than 60%.

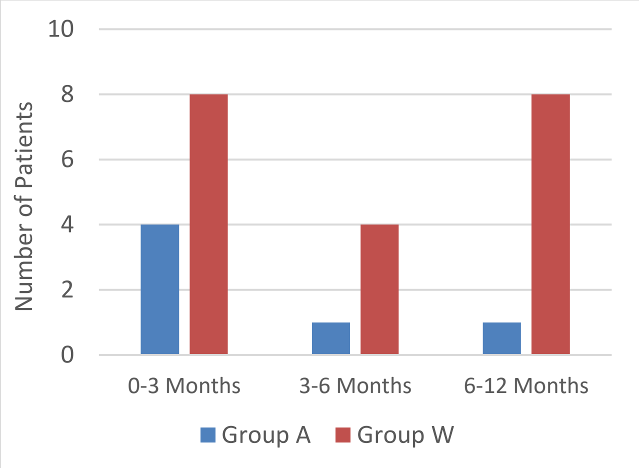

Figure 1: Major Bleeding between Group A and W

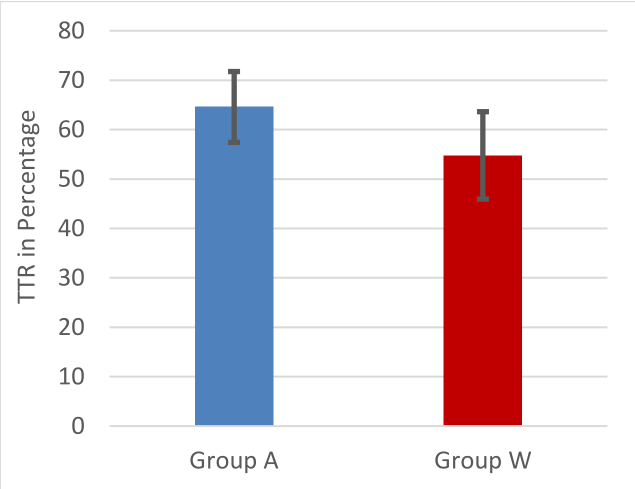

Figure 2: Comparison of TTR between Group A and W

Table 4: Comparison of Incidence of Stroke and Thromboembolism between Group A and W

Outcomes	Group A (n=46)	Group W (n=46)	P-Value
Stroke	2	5	0.43
Thromboembolism	1	3	0.62

Incidence of stroke and thromboembolism was also lower in patients given apixaban as compared to patients on warfarin therapy but the difference was not statistically significant at this sample size.

DISCUSSION

Apixaban appears to have minimal real-world benefit for those with CKD and atrial fibrillation who are not receiving dialysis. This study found that individuals getting apixaban had a reduced incidence of severe bleeding, stroke, or thromboembolism than patients on warfarin treatment. Additionally, apixaban-treated patients spent more time in the therapeutic range of INR. Nonetheless, even while the rate of major bleeding was lower in the apixaban group than in those in the warfarin group throughout every stage of CKD, the difference wasn't of statistical significance up until six months into the follow-up period while becoming significant at twelve months.

The first trial comparing the effectiveness of warfarin and apixaban in treating patients with chronic renal disease was published in 2017. In terms of serious bleeding or thromboembolic events, the trial, which comprised 146 participants with eGFR above 25 mL/min or creatinine levels more than 2.5 mg/dL, did not show statistically significant differences between those receiving apixaban versus warfarin treatment.[28]

Furthermore, no statistically significant difference was observed between the apixaban and warfarin groups with respect to preventing strokes or thromboembolic events and fatalities from all causes in patients with eGFR in the range of 25 to 30 mL/min, according to the most recent subgroup evaluation of results from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[29] In a US Medicare population cohort of 22,739 individuals with atrial fibrillation and stage 3 to 5 chronic kidney disease, apixaban, rivaroxaban, and dabigatran have been compared to warfarin in patients with CKD. It was found that apixaban was associated with a lower risk of stroke.[30] Since most of the patients were diagnosed with stage 3 CKD and were identified by ICD codes, the results were mainly applicable to those without more advanced CKD. The current study's findings about the incidence of ischemic stroke in people with CKD are consistent with previous observational research.[18, 28]

The risk of severe bleeding was lower with apixaban treatment in comparison to warfarin therapy, irrespective of the apixaban dose. This benefit was especially noticeable in older, less physically active individuals and those with serum creatinine levels over 1.5 mg/dL (or reduced eGFR).[29] Additionally, apixaban was observed to be associated with a lower risk of serious bleeding than warfarin among people with an eGFR of between 25 and 30 ml/min. 29 Patients with eGFR in the range of 25 to 30 ml/min generally had more favorable pharmacokinetic profile for apixaban in the typical dose (5 mg twice daily) compared to patients who had higher eGFR (greater than 30 ml/min), according to findings from the ARISTOTLE research.[29] When taken as a whole, the data suggest that individuals with chronic renal disease may safely tolerate the recommended dosage of apixaban.

A sub-analysis of the ARISTOTLE study revealed that East Asians had a significantly lower mean TTR than non-East Asians, and that they also had a longer duration (28.6%) with an INR of less than 2 than non-East Asians (18%).[31, 32] The higher incidence of cerebral hemorrhage among those with lower INRs in comparison to peers aligns with findings from a multi-center trial involving Asian patients on apixaban and dabigatran.[32, 33]

The best therapeutic INR treatment for warfarin depends on both its safety and effectiveness. Patients had an increased risk of systemic embolism when taking warfarin with a higher INR, according to our findings. It's possible that difficult management or poor compliance in certain patients are to blame for the significant variation in INR. Low intensity anticoagulant treatment is a common technique in Taiwan. Interpreting the results of this study requires a discussion of the differences in how Asian and non-Asian people react to warfarin and direct oral anticoagulants.

CONCLUSION

The results of this study suggest that apixaban may be a good substitute for warfarin in patients with chronic renal disease. In summary, apixaban medication reduced the risk of stroke and thrombosis in individuals with atrial fibrillation compared to those treated with warfarin. Additionally, apixaban was beneficial for patients with stage 4 to stage 5 CKD (eGFR below 30 ml/min/1.73 m^2). Moreover, apixaban, at both the conventional and reduced doses, does not increase the risk of serious bleeding when compared to warfarin. To produce more data for the available evidence, a larger sample size study comparing various warfarin and apixaban doses is required.

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