Original Article

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

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ABSTRACT

Introduction: The most prevalent form of cardiac arrhythmia, atrial fibrillation (AF), is an important contributor in cerebral ischemic stroke and other serious thromboembolic complications. Current recommendations state that DOACs (direct oral anticoagulants) rather than vitamin K inhibitors should be provided to atrial fibrillation patients at risk (CHA2DS2VASc scores greater than or equal to 2) to prevent these serious consequences. It is still unclear if apixaban medication is beneficial for those with chronic kidney disease (CKD) who are not on haemodialysis.

Aims/ objective: To compare the efficacy and safety of apixaban and warfarin in patients with atrial fibrillation and stage 3-5 CKD and to compare the relative risks of stroke, thromboembolism, and major bleeding between two groups.

Materials and Method: Consecutive sampling was done and each patient of AF and CKD fulfilling our eligibility criteria were allocated either to apixaban or warfarin group using web generated random numbers. Doses of anticoagulation therapy was adjusted based on ACC (American College of Cardiology) guidelines. Incidence of major bleeding within 3 months of enrolment and within 6 and 12 months of follow-up, incidences of ischemic stroke and thromboembolism within 12 months, and TTR (time in therapeutic range of INR between 2.0 and 3.0) at 12 months were compared between two groups.

Results: Incidence of major bleeding was lower in patients receiving apixaban as compared to patients on warfarin therapy and the difference became significant at 12 months ($p<0.05$). Patients receiving apixaban spent more time in therapeutic range of INR (2.0-3.0) as compared to patients on warfarin therapy and the difference comes out to be statistically significant ($p<0.0001$). Patients in stage 5 CKD also had TTR more than 60% in apixaban group. Incidence of stroke and thromboembolism was also lower but not statistically significant.

Conclusion: In conclusion, patients with atrial fibrillation who received apixaban therapy had a lower incidence of stroke or thrombosis than those who were given warfarin, and those with stage 4 and stage 5 CKD were also benefited from apixaban.

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

INTRODUCTION

The most prevalent form of cardiac arrhythmia, atrial fibrillation (AF), is an important contributor in cerebral ischemic stroke and other serious thromboembolic complications.[1] Current recommendations state that DOACs (direct oral anticoagulants) rather than vitamin K inhibitors should be provided to atrial fibrillation patients at risk (CHA_2DS_2VASc scores greater than or equal to 2) to prevent these serious consequences. [2-5]

Compared to the population as a whole, patients with CKD (chronic kidney disease) have a prevalence of atrial fibrillation that is two to three times greater. [6–8] A prothrombotic state is also a result of chronic kidney disease, which raises the dangers of an ischemic stroke or a systemic thromboembolism. [9–11] In patients with chronic kidney disease (CKD) undergoing renal replacement treatment, the risk of thromboembolic complications is substantially higher. [11, 12] Additionally, while taking oral anticoagulant (OAC) medication, patients with an eGFR (estimated glomerular filtration rate) of less than 30 mL per min per 1.73 m^2 as well as those with an eGFR ranging from 30 and 60 mL per min per 1.73 m^2 are at a greater chance of bleeding. [12–14]

Furthermore, individuals with end-stage renal disease (ESRD) and severe chronic kidney disease were excluded from the majority of key studies of direct oral anticoagulants. In order to maximize the mitigation of thromboembolism while still reducing the risk of haemorrhage in patients with impaired kidney function, real-world data is required.

One aspect that affects the choice of an oral anticoagulants for a patient is their renal function, and patients with chronic kidney disease frequently receive warfarin prescriptions.[15, 16] The only direct oral anticoagulant for atrial fibrillation patients with eGFR of less than 15 mL per min is at present apixaban, although approval was given on a pharmacokinetic trial of just eight patients with chronic kidney disease who were receiving dialysis.[17] Additionally, apixaban treatment outcomes in ESRD patients have been also documented. [18, 19]

Although apixaban did not have significant efficacy in preventing stroke or systemic embolism from research using data from the US Renal Data System (USRDS) from 2010 to 2015 however it was associated with a considerably lower risk of serious bleeding than warfarin. [18] Another trial comparing apixaban with placebo in patients undergoing chronic dialysis with atrial fibrillation found no association between apixaban therapy and risk improvements in either ischemic stroke or fatal or serious intracranial bleeding. [19] This analysis used USRDS data from 2012 to 2015.

Later, the American Food and Drug Administration (FDA) updated the prescribing guidelines for apixaban to include precise dose advice for those with AF. If two of the following conditions are satisfied: age greater than or equal to 80 years, serum creatinine greater than or equal to 1.5 mg/dL, or body weight less than or equal to 60 kg then the 5-mg twice-day dose is advised to be reduced to 2.5 mg twice a day. [20]

In an additional recent pharmacokinetics research with 7 patients, the area under the curve of concentration-time was measured after 2.5 mg twice per day for seven days while apixaban dose adequacy in patients on dialysis was assessed. After a wash out period, a 5-mg twice-daily dose was given for the next seven days. The 5-mg twice-daily dosage resulted in supra-therapeutic levels, according to the authors, while the 2.5-mg twice-daily dosage produced concentrations comparable to the recommended dosage in people with or without renal impairment.[21]

Given that the majority of research mainly concentrated on the requirement of anticoagulation in the patients undergoing chronic haemodialysis, it is still unclear if apixaban medication is beneficial for those with chronic kidney disease (CKD) who are not on haemodialysis. In order to examine the relative risks of stroke, thromboembolism, and major bleeding, this study was done to compare the efficacy and safety of apixaban and warfarin in patients with atrial fibrillation and stage 3-5 CKD.

MATERIALS AND METHODS

This was an open label, single cantered randomised controlled trial conducted on patients with atrial fibrillation and chronic kidney disease from July 2021 to June 2023 in tertiary care centre of eastern India. The study was conducted as per guidelines of Good Clinical Practice after getting approval from Institutional Ethics Committee and written informed consent was taken from all study participants after providing and explaining participant information sheet.

Inclusion Criteria: Patients of either sex of age greater than or equal to 18 years diagnosed with atrial fibrillation or atrial flutter and of stage 3-5 CKD as per ICD (International Classification of Disease) – 9 and 10 codes and eGFR less than 60 ml/min/1.73 m^2 as per KDIGO (Kidney Disease: Improving Global Outcomes) guidelines were included in our study. [22-24]

Exclusion Criteria: Patients diagnosed with moderate or severe mitral stenosis or having history of cardiac surgery with valve replacement or renal transplant surgery or on peritoneal dialysis or on oral anticoagulants within 3 months of enrolment were excluded from our study.

Consecutive sampling was done and each patient of AF and CKD fulfilling our eligibility criteria were included in the study and allocated to block representing his/her CKD stages. Patients were allocated either to apixaban or warfarin group using web generated random numbers. Doses of anticoagulation therapy was adjusted based on ACC (American College of Cardiology) guidelines.[25]

Study Outcomes

Incidence of major bleeding within 3 months of enrolment was primary end point of our study. The ISTH (International Society on Thrombosis and Haemostasis) established major bleeding as having one of the following elements: fatal bleeding, bleeding in a critical region or organs (intra-cranial, intra-spinal, intra-ocular, retro-peritoneal, intraarticular, pericardial, or intra-muscular along with compartment syndrome), or bleeding that results in a haemoglobin level drop of more than 2 g/dL or requires the transfusion of more than two units of PRBC (packed red blood cells).[26] A 48-hour window for the haemoglobin decline was added to avoid any misinterpretation.

Major bleeding rates with 6 and 12 months of follow-up, incidences of ischemic stroke within 12 months, recurrent thromboembolism within 12 months, and TTR (time in therapeutic range of INR between 2.0 and 3.0) at 12 months were secondary outcomes. TTR was calculated by dividing the number of INR values in the normal range by the total number of INR values recorded and converted into percentage.[27] Patients were excluded if they had major bleeding or other contraindication to study drugs within the study period. Stroke was defined as a focal neurological dysfunction with a nontraumatic origin and was classified as either ischemic or of unidentified kind, with a confirmatory diagnosis made using a chart assessment and ICD 9 and 10 codes.[22, 23] Using a chart review of ICD 9 and 10 codes, a confirmed diagnosis of thromboembolism was made and it was defined as a fatal or non-fatal pulmonary embolism or deep vein thrombosis.

Statistical Analysis

Data regarding baseline demographic & clinical characteristics and outcome measures from patients receiving apixaban or warfarin therapy were presented in tabular form using Microsoft Excel 365 and transferred to SPSS version 24 for further statistical analysis. Continuous data such as age, weight, CHA_2DS_2-VASc, TTR and eGFR were checked for normality distribution for Shapiro-Wilk test and expressed as mean ± SD (standard deviation) or median and IQR (inter-quartile range) for normally and non-normally distributed data respectively. Statistical significance of difference in continuous data between apixaban and warfarin group was checked using unpaired

t-test or Mann Whitney U test for normally and non-normally distributed data respectively. Categorical data such as gender, CKD stage, use of concomitant medication, and outcome measures were expressed as percentage and frequency and compared using chi-square or fisher's exact test with p-value of less than 0.05 as a measure of statistical significance.

RESULTS

192 patients were enrolled in the study during the study period of which 16 patients were lost to follow-up in within 1 month of our study and thus excluded from our analysis. Remaining patients were randomised to apixaban and warfarin group with 88 patients in each group. The baseline demographic and clinical characteristics of study participants in apixaban and warfarin group is compared in table 1.

Table 1: Comparison of baseline demographic and clinical characteristics between apixaban and warfarin group

Variables	Apixaban Group (n=88)	Warfarin Group (n=88)	P-Value
Age in years, mean ± SD)	63.58 ± 11.08	61.76 ± 12.76	0.31
Weight in kg, median (IQR)	70.13 (54.58-86.89)	72.37 (56.42-88.67)	0.34
eGFR in ml/min/1.73 m^2, median (IQR)	39.26 (25.85-52.79)	37.38 (23.84-50.59)	0.87
CHA_2DS_2-VASc, mean ± SD)	4.77 ± 1.54	4.71 ± 1.49	0.79
Haemodialysis, n	16	13	0.68
Aspirin, n	41	43	0.88
P2Y12 inhibitors, n	8	9	>0.99
Proton pump inhibitors, n	40	36	0.65
Sex, n			
Male	46	43	0.76
Female	42	45	
CKD Stage, n			
3a	23	24	0.43
3b	28	26	
4	19	22	
5	18	16	

At baseline, both groups were comparable with respect to age, sex, stage of CKD, use of concomitant medication, dialysis status, weight and CHA_2DS_2-VASc with no statistical significant difference between them (P>0.05)

Table 2: Comparison of Incidence of Major Bleeding between Apixaban and Warfarin Group

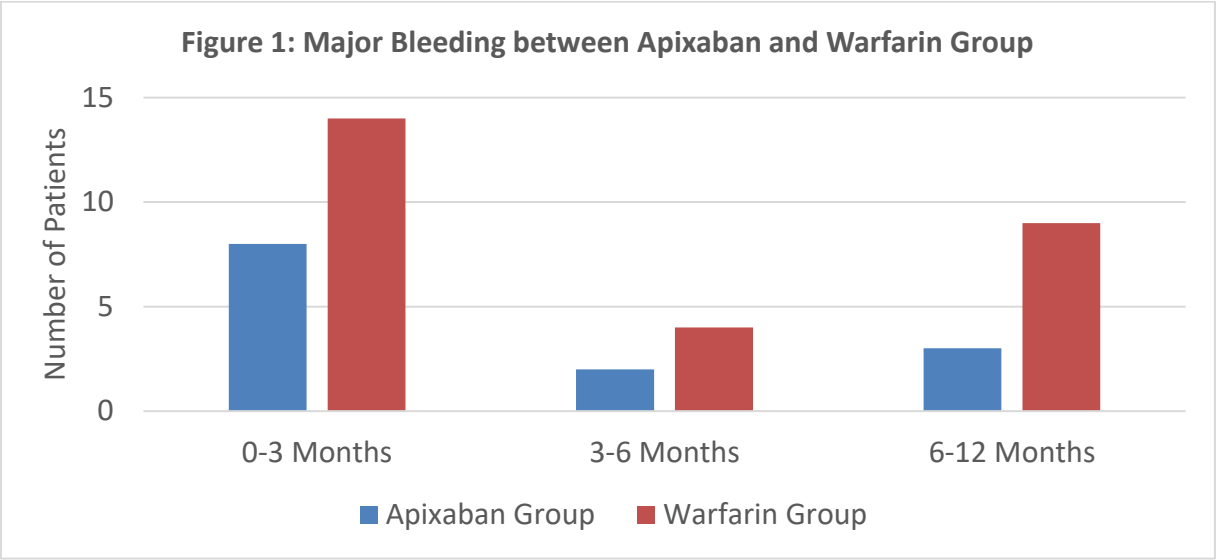
Time Period	Apixaban Group (n=88)	Warfarin Group (n=88)	P-Value
0-3 Months	8	14	0.25
3-6 Months	2	4	0.68
6-12 Months	3	9	**0.047**

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

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

Variables	Apixaban Group (n=88)	Warfarin Group (n=88)
TTR in Percentage, mean ± SD	66.49 ± 7.17	55.67 ± 8.84
Difference in Mean	10.82	
95% Confidence interval (Difference of Mean)	8.42 to 13.21	
P Value	<0.0001	

Patients receiving apixaban spent more time in therapeutic range of INR (2.0-3.0) as compared to patients on warfarin therapy and the difference comes out to be statistically significant (p<0.0001). Patients in stage 5 CKD also had TTR more than 60% in apixaban group.



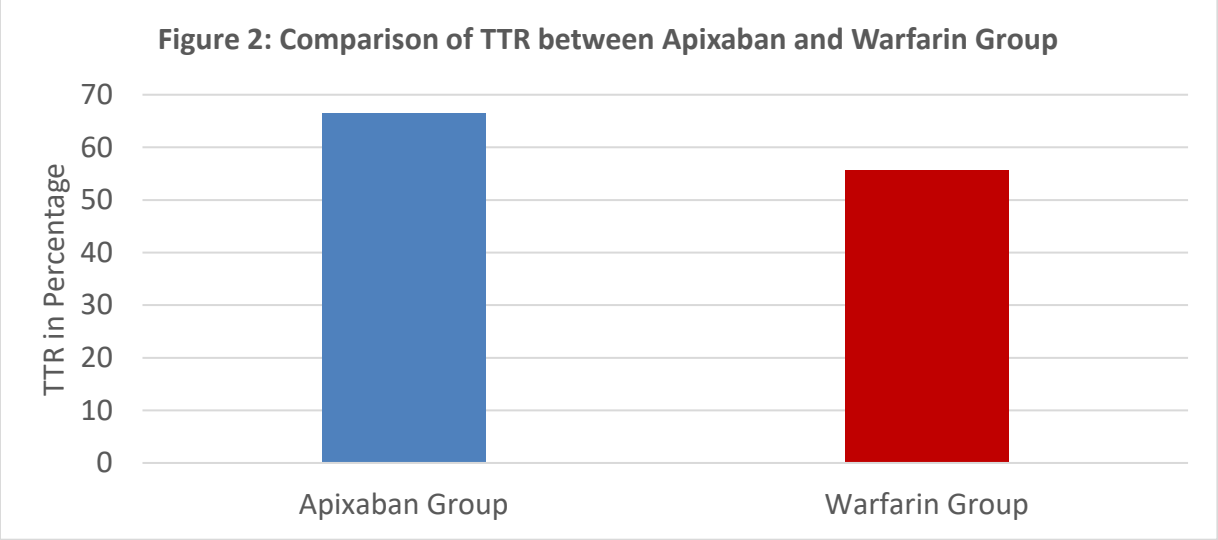


Table 4: Comparison of Incidence of Stroke and Thromboembolism between Apixaban and Warfarin Group

Outcomes	Apixaban Group (n=88)	Warfarin Group (n=88)	P-Value
Stroke	4	8	0.37
Thromboembolism	3	7	0.33

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

There is little actual evidence that apixaban is beneficial for patients with atrial fibrillation and CKD who are not on dialysis. According to this study, incidence of major bleeding, stroke or thromboembolism was lower in patients receiving apixaban as compared to patients on warfarin therapy. Also, patients receiving apixaban spent more time in therapeutic range of INR. However, despite the fact that the rate of serious bleeding was reduced in the apixaban group compared to it was in the warfarin group across all stages of CKD, the difference was not statistically significant up to 6 months of follow-up but it became significant at 12 months of follow-up.

In 2017, the first experimental study comparing the efficacy of apixaban versus warfarin in patients with chronic kidney disease was released. The trial, which included 146 individuals with eGFR greater than 25 mL/min or serum creatinine greater than 2.5 mg/dL, demonstrated no statistically significant differences between the pharmacotherapy of apixaban and warfarin in terms of major bleeding or thromboembolic complications.[28]

Additionally, a latest subgroup analysis of data from the ARISTOLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial found no significant difference between apixaban group and warfarin group in terms of preventing stokes or thromboembolic

events and mortality from all causes in patients with eGFR between 25 to 30 mL/min.[29] Apixaban, rivaroxaban, and dabigatran had been compared with warfarin in patients with chronic kidney disease (CKD) in a US Medicare population cohort of 22,739 patients with atrial fibrillation and stage 3-5 CKD, and it was shown that apixaban was linked with a decreased risk of stroke.[30] The majority of the patients had stage 3 CKD, and as they were recognized by ICD codes, the findings could only be applied to individuals without advanced CKD. The frequency of ischemic stroke in individuals with chronic kidney disease (CKD) in the current research is similar to that in earlier observational studies.[18, 28]

Regardless of the apixaban dose, the risk of significant bleeding was reduced with apixaban therapy than with warfarin therapy, with the advantage being more pronounced in individuals who were elderly, less physically active, and had serum creatinine levels greater than 1.5 mg/dL (or lower eGFR).[29] Additionally, among individuals with eGFR of 25 to 30 ml/min, apixaban was found to be linked with decreased incidence of severe bleeding than warfarin. [29] In general, data from the ARISTOTLE study showed that patients with eGFR between 25 to 30 ml/min had a better pharmacokinetic distribution of apixaban in standard dose (5 mg twice a day) than do patients with greater eGFR (more than 30 ml/min).[29] Collectively, the results imply that patients with chronic kidney disease may tolerate the recommended dose of apixaban without adverse effects.

We were unable to compare the relative benefits and drawbacks of apixaban to those of warfarin due to the low frequency of use of oral anti-coagulants in patients with eGFR more than 60 ml/min/1.73 m^2 in the present research. However, the findings confirm that in patients with eGFR less than 30 ml/min/1.73 m^2, the chance of stroke or thromboembolism was lower with apixaban therapy than with warfarin therapy, and apixaban was more advantageous in patients who had reduced eGFR values than in those who had elevated eGFR values, in line with prior findings. [29, 31] However, the current study failed to clarify the impact of apixaban dose on the relationship between renal function and the likelihood of stroke, thromboembolism, and serious bleeding.

Apixaban had an average time in therapeutic range (TTR) of 62 percent with an INR (international normalized ratio) of 2.0 to 3.0 in the ARISTOLE study, which indicated that it was non-inferior to warfarin.[4] According to a sub-analysis of the ARISTOTLE study, East Asians had a substantially reduced mean TTR than non-East Asians, and their duration with an INR of less than 2 was also longer in East-Asians (28.6%) than it was in non-East Asians (18%).[32] The greater prevalence of cerebral bleeding in those with lower INRs relative to counterparts is consistent with results in Asian patients from multi-centred study of apixaban and dabigatran.[32, 33]

Warfarin's ideal therapeutic INR management is related to both its efficacy and safety. When using warfarin with an elevated INR, we found that patients had a high rate of systemic embolism. The substantial fluctuation of INR may be caused by poor compliance in some patients or challenging management.[32, 34] In Taiwan, low intensity anticoagulant therapy is a frequent procedure. It is crucial to discuss the disparities between Asian and non-Asian individuals' responses to direct oral anticoagulants and warfarin when interpreting the findings of this study.[32, 33]

Patients taking apixaban in this trial received a range of doses. Because some of the patients received the wrong dosage, it would be impossible to establish an accurate dose-bleeding association. The majority of the patients who received the wrong dose also received an underdose. Our study did not emphasize dose; therefore, it is unlikely to significantly clarify the problem. Future research assessing the optimum dose is still required.

CONCLUSION

Apixaban appears to be a suitable replacement for warfarin in individuals with chronic kidney disease, according to the findings of the current research. In conclusion, patients with atrial fibrillation who received apixaban therapy had a lower incidence of stroke or thrombosis than those who were given warfarin, and those with stage 4 and stage 5 CKD (eGFR less than 30 ml/min/1.73 m^2) were also benefited from apixaban. Furthermore, neither the standard nor the lower dose of apixaban raises the risk of severe bleeding in comparison to warfarin. There is a need for study of more sample size comparing different doses of warfarin and apixaban to generate more data for current evidences.

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