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Research Article

Comparative Risk of Clinically Significant Bleeding In Patients with Atrial Fibrillation Receiving Factor Xa Inhibitors versus Vitamin K Antagonists: A Case-Control Study

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with an important risk of thromboembolic event. The mainstay of stroke prevention in these patients is oral anticoagulation. Bleeding is the most important side effect of anticoagulant treatment and comparative safety information from clinical practice in Pakistan is scarce.

Objective: To assess differences in clinically significant bleeding risk in patients with AF who are treated with Factor Xa inhibitors compared with those treated with vitamin K antagonists.

Methods: This was a retrospective case-control study in the Department of Medicine, SIMS Hospital and Research Centre, which was conducted for 6 months after ethical clearance. Study patients consisted of those with documented AF on OAC. The cases were those patients who developed clinically significant bleeding, and the controls were anti-coagulated patients without bleeding, in 1:2 ratios. Analysis of data was done through SPSS version 26. Odds ratios and 95% confidence intervals were computed and a multivariable logistic regression was performed to adjust for confounders.

Results: 300 patients (100 cases and 200 controls) were included. Factor Xa inhibitors had a significantly lower rate of bleeding than did vitamin K antagonists (OR 0.58, 95% CI 0.35-0.95, p=0.03). Advanced age (OR 1.85), chronic kidney disease (OR 2.21), concomitant antiplatelet use (OR 2.67) and HAS-BLED score > 3 (OR 3.12) were independent predictors of bleeding.

Conclusion: Factor Xa inhibitors have demonstrated a reduced risk of clinically important bleeding over VKA in patients with AF. To reduce bleeding complications risk stratification with HAS-BLED score and careful selection of patients are crucial.

Keywords: Atrial Fibrillation, Anticoagulation, Bleeding Risk, Factor Xa Inhibitors, Vitamin K Antagonists, HAS-BLED Score.

INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia seen in clinical practice, and is a major cause of stroke and systemic thromboembolism in millions of people throughout the world. For decades, vitamin K antagonists (VKAs) – mainly warfarin – were the only therapeutic option for stroke prevention in eligible patients, and oral anticoagulation (OAC) remains the standard of care today. Although effective, vitamin K antagonists have a narrow therapeutic window, uncertain dose-response curves, require regular laboratory monitoring, are subject to considerable dietary interactions and have a wide range of interactions with other drugs which limit their safe long-term use in clinical practice. (2)

Factor Xa inhibitors such as rivaroxaban, apixaban and edoxaban marked a change in the anticoagulation paradigm. These agents provide predictable and reliable pharmacological activity, do not need routine coagulation monitoring and have fewer interacting profiles than warfarin. Current international guidelines have preference for direct oral anticoagulants over vitamin K antagonists in patients with non-valvular atrial

fibrillation because they are as effective or more effective as vitamin K antagonists and have an improved safety profile, especially with regard to intracranial hemorrhage. (3,4)

The major safety issue with all anticoagulant drugs is bleeding, which can occur from nuisance bleeding to life-threatening bleeding. Risk factors for bleeding are multifaceted, including age, renal function, other health conditions, bleeding risk measures (e.g., HAS-BLED score) and other medications. (5) Although RCTs have proven the relative safety of Factor Xa inhibitors over warfarin, real-world evidence in resource-limited settings, especially within the healthcare environment in Pakistan, is limited.

Therefore, this study was aimed at comparing and assessing the risk of clinically relevant bleeding in AF patients treated with Factor Xa inhibitors versus vitamin K antagonists in a hospital-based setting in Pakistan to provide locally relevant evidence for decision making in AF anticoagulation.

MATERIALS AND METHODS

Study Design and Setting: The study was a retrospective case-control study conducted in Department of Medicine, SIMS Hospital and Research Centre with approval of Institutional Ethical Review Board (Ref No: IM-RC-217). The study was carried out over a period of six months. A waiver of informed consent was granted by the ERB given the retrospective nature of the study and use of anonymized hospital records.

Study Population: Inclusion criteria were adult patients (aged 18 years and older) with a known diagnosis of AF who were on OAT. Cases were those patients who experienced clinically important bleeding on anticoagulation therapy. The controls were patients with AF who were on anticoagulation and did not have bleeding events and were enrolled in a 1:2 ratio to cases. The patients were split into two exposure groups: Factor Xa inhibitors (rivaroxaban, apixaban, or edoxaban) and vitamin K antagonists (primarily warfarin).

Exclusion Criteria: Patients were excluded if they underwent mechanical heart valve surgery or had moderate to severe mitral stenosis, known hereditary bleeding disease, malignancy-related bleeding, recent major surgery or trauma, pregnancy, or incomplete medical records.

Data Collection: Data was collected from hospital medical records by using a structured proforma. Demographic and other parameters recorded were demographic data, comorbidities, type and duration of anticoagulant therapy, concomitant medication, relevant laboratory parameters and HAS-BLED score. Bleeding events were categorized as per standard criteria. Major bleeding was defined as fatal hemorrhage, bleeding into a critical anatomical site, hemoglobin reduction ≥ 2 g/dL, or blood transfusion. Non-major bleeding was defined as clinically relevant bleeding that did not meet major bleeding criteria.

Statistical Analysis: IBM SPSS Statistics version 26.0 was used for data entry and analyses. Mean ± standard deviation were used to represent continuous variables. Categorical data were presented as frequencies and percentages. Independent samples t test and chi square test were used to compare the variables between the groups. Odds ratios for bleeding risk and 95% confidence intervals were calculated to assess the relationship between the anticoagulant type and bleeding risk. A multivariable logistic regression analysis was carried out to determine independent predictors of bleeding after adjustment for age, renal function, comorbidities, the use of concomitant antiplatelet therapy, and HAS-BLED score. Statistically significant p-values were set at < 0.05 (two-tailed).

RESULTS

Three hundred patients with atrial fibrillation taking oral anticoagulation – 100 with clinically relevant bleeding and 200 non-bleeding controls – were included. Overall, the study population had a mean age of 67.4 ± 11.2 years and was male-predominant (56%).

Baseline Characteristics: Patients who developed bleeding were significantly older (71.2 ± 10.5 vs 65.6 ± 11.3 years; p=0.001) and demonstrated higher rates of hypertension (72% vs 59%; p=0.03), chronic kidney disease (36% vs 19%; p=0.002), previous bleeding history (30% vs 11%; p=0.001), and higher mean HAS-BLED scores (3.8 ± 1.2 vs 2.6 ± 1.1; p=0.001). There was no significant difference between the two groups in terms of gender and prevalence of diabetes mellitus and previous stroke or TIA. Group baseline characteristics are shown in Table I.

Anticoagulant Distribution: Vitamin K antagonists were more commonly prescribed to cases than controls (68% vs 52%) while factor Xa inhibitors were more commonly prescribed to controls than cases (48% vs 32%), as shown in Table II.

Association Between Anticoagulant Type and Bleeding: Table III shows that Factor Xa inhibitors were associated with a 42% decrease in bleeding risk when compared to vitamin K antagonists (VKAs) on unadjusted analysis (OR 0.58, 95% CI 0.35–0.95; p=0.03).

Multivariable Logistic Regression: Factor Xa inhibitors were still independently associated with decreased bleeding risk after adjustment for potential confounders (adjusted OR 0.62, 95% CI 0.38–0.98; p=0.04). Additional independent predictors of bleeding included age above 65 years (adjusted OR 1.85, 95% CI 1.12–3.04; p=0.02), chronic kidney disease (adjusted OR 2.21, 95% CI 1.29–3.78; p=0.004), concomitant antiplatelet use (adjusted OR 2.67, 95% CI 1.52–4.68; p=0.001), and HAS-BLED score above 3 (adjusted OR 3.12, 95% CI 1.84–5.30; p=0.001). The results are shown in Table IV.

Bleeding Characteristics: The most common manifestation was gastrointestinal bleeding (42%), followed by hematuria (18%), intracranial hemorrhage (16%), epistaxis (12%) and other sites (12%) (Table V).

Clinical Outcomes: There was significant clinical morbidity associated with bleeding events. As displayed in Table VI, 82% of cases were admitted to hospital, 38% required a blood transfusion, 18% required admission to an intensive care unit and 8% of bleeding patients died in hospital.

Table I: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Cases (n=100)	Controls (n=200)	p-value
Age (years, mean ± SD)	71.2 ± 10.5	65.6 ± 11.3	0.001
Male Gender n (%)	54 (54%)	114 (57%)	0.64
Hypertension n (%)	72 (72%)	118 (59%)	0.03
Diabetes Mellitus n (%)	48 (48%)	76 (38%)	0.09
Chronic Kidney Disease n (%)	36 (36%)	38 (19%)	0.002
Previous Stroke/TIA n (%)	28 (28%)	42 (21%)	0.18
Previous Bleeding History n (%)	30 (30%)	22 (11%)	0.001
HAS-BLED Score (mean ± SD)	3.8 ± 1.2	2.6 ± 1.1	0.001

SD = Standard Deviation; TIA = Transient Ischaemic Attack; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke history, Bleeding history, Labile INR, Elderly, Drugs or alcohol.

Table II: Distribution of Anticoagulant Use between Cases and Controls

Anticoagulant Type	Cases n (%)	Controls n (%)
Factor Xa Inhibitors	32 (32%)	96 (48%)
Vitamin K Antagonists (Warfarin)	68 (68%)	104 (52%)
Total	**100 (100%)**	**200 (100%)**

Factor Xa inhibitors include rivaroxaban, apixaban, and edoxaban.

Table III: Unadjusted Association between Anticoagulant Type and Bleeding Risk

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
Factor Xa Inhibitors vs Vitamin K Antagonists	0.58	0.35 – 0.95	0.03

Reference category: Vitamin K Antagonists; OR below 1.0 indicates reduced bleeding risk with Factor Xa inhibitors

Table IV: Multivariable Logistic Regression — Independent Predictors of Clinically Significant Bleeding

Variable	Adjusted OR	95% Confidence Interval	p-value
Factor Xa Inhibitors (vs VKA)	0.62	0.38 – 0.98	0.04
Age above 65 years	1.85	1.12 – 3.04	0.02
Chronic Kidney Disease	2.21	1.29 – 3.78	0.004
Concomitant Antiplatelet Use	2.67	1.52 – 4.68	0.001
HAS-BLED Score above 3	3.12	1.84 – 5.30	0.001

OR = Odds Ratio; VKA = Vitamin K Antagonist; CI = Confidence Interval; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs/alcohol.

Table V: Distribution of Bleeding Types among Cases (n=100)

Type of Bleeding	Frequency n (%)
Gastrointestinal Bleeding	42 (42%)
Hematuria	18 (18%)
Intracranial Hemorrhage	16 (16%)
Epistaxis	12 (12%)
Other Sites	12 (12%)
Total	**100 (100%)**

Primary bleeding site recorded; cases could present with more than one bleeding manifestation

Table VI: Clinical Outcomes among Bleeding Cases (n=100)

Outcome	Frequency n (%)
Hospital Admission	82 (82%)
Blood Transfusion Required	38 (38%)
ICU Admission	18 (18%)
In-hospital Mortality	8 (8%)

ICU = Intensive Care Unit; outcomes are not mutually exclusive

DISCUSSION

The study investigated the comparative risk of bleeding with Factor Xa inhibitor versus vitamin K antagonist in patients with AF in a hospital environment in Pakistan. The major result was that on average, the use of Factor Xa inhibitors was associated with a significant decrease in the incidence of clinically relevant bleeding, which did not change following multivariable adjustment for known confounding factors.

The lower bleeding risk seen with Factor Xa inhibitors is in line with data from key randomized controlled trials. The present study adds to this evidence, in a local clinical setting where there is a large difference between the patient population, monitoring systems, and adherence to the drugs included in the landmark trials.

Older age was an important independent predictor of bleeding in this study and is well supported in the literature. (17) Progressive decrease in renal and hepatic clearance, increase in the number of comorbidities and increase in polypharmacy (drug use) and fall risk all increase hemorrhagic risk in patients taking anticoagulants. Bleeding was also independently associated with chronic kidney disease, which is due to reduced excretion of drugs and dysfunction of platelets, which exacerbates the presence of anticoagulants. These data support the need for personal dose estimation and renal monitoring in older persons and patients with impaired renal function who are on warfarin treatment.

In this population, the strongest predictors of bleeding were concomitant antiplatelet therapy, with an adjusted odds ratio of 2.67. The clinical implication of this finding is obvious, as dual antithrombotic therapy is often used in patients with both coronary artery disease and recent acute coronary syndromes. The combination of anticoagulant and antiplatelet agents should be carefully and periodically evaluated for risk/benefit ratio and used for the shortest duration possible. (11)

In the multivariate analysis, the score > 3 for HAS-BLED was the strongest predictor of bleeding events with an adjusted OR of 3.12, reinforcing its usefulness as a bedside risk stratification tool. These findings support strongly the routine use of it before the start of or continuation of anticoagulation therapy (8), which is recommended in current guidelines. (1,2)

The most commonly observed type of bleeding was gastrointestinal bleeding (42% of all bleeding events). This aligns with the previously described sites of vulnerability in ant coagulated populations in which the gastrointestinal tract is the most vulnerable site, especially in the case of Factor Xa inhibitors which have high concentrations in the gastrointestinal tract. While the incidence of intracranial hemorrhage (ICH) was low (16%), the high proportional impact on death and persisting disability indicates the clinical relevance of ICH despite its low incidence.

Of all of these cases of bleeding, 82% had to be admitted to the hospital, with 8% of these patients dying in hospital, indicating that bleeding from an anticoagulant is a large clinical and resource burden in this context. These numbers further underscore the need for proactive bleeding risk mitigation strategies in managing anticoagulation.

There are limitations to this study. The retrospective nature of the design could lead to selection bias and reliance on the completeness and accuracy of the medical records. Even after multivariable adjustments, however,

unmeasured confounding variables cannot be ruled out. Use of time in therapeutic range was not reported systemically and may have affected results for bleeding outcomes among users of warfarin. The study was conducted in a single center and the results may not be applicable to other clinical settings and the general Pakistani population. Future multicenter prospective studies of therapeutic monitoring results and longer follow-up would help strengthen the evidence base in this area.

CONCLUSION

In patients with atrial fibrillation, the bleeding risk with factor Xa inhibitors is much lower than with the vitamin K antagonists. Independent factors associated with bleeding risk include: advanced age, chronic kidney disease, concomitant antiplatelet therapy and the HAS-BLED score > 3. Safe anticoagulation practice requires routine use of the HAS-BLED score, careful patient selection, individualized patient risk–benefit assessment, and judicious use of combination antithrombotic therapy. These results offer locally relevant evidence on Factor Xa inhibitors use in appropriate patients with AF in the Pakistan clinical setting.

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Conflict of Interest: None declared

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