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Role of anticoagulation with apixaban in left-sided atrial tachycardias

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Abstract

Background Atrial tachycardia poses challenges in patient management due to the associated risks of stroke and systemic embolism. While anticoagulation is recommended in atrial fibrillation (AF), its role in atrial tachycardia remains less defined. This prospective study aimed to evaluate the efficacy and safety of apixaban, a direct oral anticoagulant, in individuals diagnosed with left-sided atrial tachycardias.

Methods Patients diagnosed with left-sided atrial tachycardia (n = 439) were observed over 3 years. Baseline characteristics, medication regimens, and clinical outcomes were assessed. Apixaban-treated individuals (n = 213) received standard or reduced dosages, while the control group (n = 226) received standard care. Primary outcomes included stroke, systemic embolism, bleeding, and mortality rates.

Results Baseline characteristics were comparable between groups. The apixaban cohort showed a lower incidence of stroke (7.0% vs. 9.3%, $p = 0.027$) and decreased all-cause mortality (11.7% vs. 12.8%, $p = 0.012$) compared to controls. No significant differences were found in major bleeding or systemic embolization between groups.

Conclusion Apixaban demonstrated a potential benefit in reducing stroke and mortality rates in patients with left-sided atrial tachycardia. While requiring further validation, these findings suggest a potential role for apixaban in anticoagulation strategies for atrial tachycardia management.

Keywords Atrial tachycardia, Apixaban, Anticoagulation, Stroke prevention, Clinical outcomes

Introduction

Atrial tachycardia (AT) can pose significant challenges in the management of patients due to its association with an increased risk of atrial fibrillation which can lead to stroke and systemic embolism [1]. Current guidelines recommend anticoagulation therapy in patients with atrial fibrillation (AF) to mitigate the risk of thromboembolic events [2]. However, the optimal approach to anticoagulation in individuals with AT remains less defined. Apixaban, a direct oral anticoagulant (DOAC), has emerged as a promising agent for stroke prevention in patients with AF [3]. Its efficacy, safety profile, and convenience in dosing have led to its widespread use [4–8]. Despite its success in AF management, the specific role of apixaban in patients with AT warrants further investigation.

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This prospective study aims to address the gap in knowledge regarding the use of apixaban as an anticoagulant in individuals diagnosed with AT. By evaluating its efficacy in preventing thromboembolic events and assessing its safety profile in this specific patient population, we seek to provide evidence-based insights into the potential benefits and risks associated with apixaban therapy. Through a comprehensive analysis of clinical outcomes, including stroke, systemic embolism, bleeding complications, and overall morbidity and mortality rates, this study endeavors to elucidate whether apixaban could be a viable anticoagulant strategy in the management of AT. The study aims to contribute valuable data that may guide clinicians in making informed decisions regarding anticoagulation therapy for patients diagnosed with AT.

Methods

The retrospective study was done at Abbas Institute of Medical Sciences (study ID # AIMS/23/64) and informed consent was taken from all participants according to the principles of the Declaration of Helsinki. Eligible patients, aged 18 or older and diagnosed with left-sided focal AT, were included after obtaining informed consent. Exclusion criteria comprised individuals with contraindications to apixaban, severe renal impairment (CrCl < 15 mL/min), active bleeding, recent major surgery, or significant comorbidities affecting life expectancy. Participants with diagnosed left-sided AT on EP studies were enrolled. All patient data, demographics, and follow-up data were extracted from medical records. Patients in the apixaban group received oral apixaban per a predetermined dosing regimen. The standard dosage consisted of 5 mg taken orally twice daily [9]. However, a reduced dose of 2.5 mg orally twice daily was administered if patients met specific criteria such as being aged 80 or older, having a body weight of 60 kg or less, or having a serum creatinine level of 1.5 mg/dL or higher [10]. The control group, in contrast, received standard care without apixaban or any other anticoagulant therapy.

Throughout the study's duration, spanning 3 years, all participants underwent regular follow-up assessments at 3-month intervals. These clinical visits were integral for monitoring primary and secondary outcomes. The primary outcomes evaluated in the study included the incidence of stroke, systemic embolism, bleeding complications (Major bleeding was defined according to the criteria of ISTH as clinically overt bleeding which was fatal or associated with any of the following: (a) a fall in hemoglobin level of 2 g/dL or more or documented transfusion of at least 2 units of packed red blood cells, (b) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal).) [11], and overall mortality rates. Secondary outcomes encompassed additional clinical events related to cardiovascular health, such as hospitalizations due to cardiovascular causes or adverse events associated with anticoagulation therapy. The follow-up protocol involved comprehensive assessments of patients' clinical status, laboratory investigations, and any reported adverse events. Patient compliance with the prescribed medication regimen was monitored, and any changes in dosage or medication were duly recorded. This meticulous follow-up and data collection allowed for a comprehensive analysis of the efficacy and safety of apixaban as an anticoagulant in patients diagnosed with AT over the 3-year study period.

Descriptive statistics, such as mean, median, standard deviation for continuous variables, and frequencies or proportions for categorical variables, were calculated to summarize patient characteristics, baseline demographics, comorbidities, and other relevant factors. Student's t-test was performed for continuous variables and Chi-square test for categorical variables. Logistic regression assessed the association between potential predictors and outcomes like bleeding events, strokes, or mortality. Logistic regression models were built for outcome variables. Predictor variables such as age, gender, comorbidities (e.g., hypertension, diabetes), medication adherence (antiplatelet use), and dosage adjustments were included in these models. Kaplan–Meier survival analysis was utilized to estimate survival rates and event-free probabilities over the 3-year follow-up period. This analysis method generated survival curves that depicted the probability of survival without experiencing certain events, such as strokes or mortality. Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) and a p value of < 0.05 was considered significant.

Results

In this study comparing two groups, Group 1 (n = 213) and Group 2 (n = 226), the baseline characteristics were similar across various parameters. Both groups demonstrated comparable rates of comorbidities including hypertension (Group 1: 68.1% vs. Group 2: 67.3%), diabetes mellitus (Group 1: 38.5% vs. Group 2: 42.9%), hyperlipidemia (Group 1: 48.8% vs. Group 2: 50.9%), and coronary artery disease (Group 1: 28.2% vs. Group 2: 31.9%) (Table 1). The dosage of Apixaban was consistent between the groups at 5 ± 1 mg/day. Additionally, the distribution of other medications such as aspirin (Group 1: 30.5% vs. Group 2: 31.9%), clopidogrel (Group 1: 20.2% vs. Group 2: 21.2%), and statins (Group 1: 47.9% vs. Group 2: 48.7%) showed comparable patterns. Both groups had similar mean BMI values (Group 1: 28.4 ± 3.7 kg/m^2 vs. Group 2: 29.1 ± 4.0 kg/m^2) and age distribution (Group 1:

Table 1 Baseline characteristics

Characteristic	Group 1 (n = 213)	Group 2 (n = 226)
Comorbidities		
Hypertension	145 (68.1%)	152 (67.3%)
Diabetes mellitus	82 (38.5%)	97 (42.9%)
Hyperlipidemia	104 (48.8%)	115 (50.9%)
Coronary artery disease	60 (28.2%)	72 (31.9%)
Dosage of apixaban (mg/day)	5 ± 1	5 ± 1
Other medications		
Aspirin	65 (30.5%)	72 (31.9%)
Clopidogrel	43 (20.2%)	48 (21.2%)
Statins	102 (47.9%)	110 (48.7%)
BMI (kg/m^2)	28.4 ± 3.7	29.1 ± 4.0
Atrial fibrillation	26 (12.2%)	25 (11%)
Atrial flutter	7 (3.2%)	5 (2.2%)
Age (years)	62.7 ± 8.5	63.5 ± 7.9
Gender		
Male	110 (51.6%)	120 (53.1%)
Female	103 (48.4%)	106 (46.9%)
CHA2DS2-VASc score	3 ± 1	3 ± 1

62.7 ± 8.5 years vs. Group 2: 63.5 ± 7.9 years). Gender distribution also exhibited no substantial difference between the groups, with Group 1 having 51.6% males and Group 2 having 53.1% males.

Regarding study outcomes, Group 1 demonstrated a lower incidence of stroke compared to Group 2 (7.0% vs. 9.3%) with a statistically significant hazard ratio of 0.60 (95% CI 0.32–1.14, $p = 0.027$) (Table 2). The occurrence of major bleeding was 8.4% in Group 1 and 11.1% in Group 2, although without statistical significance (hazard ratio: 0.77, 95% CI 0.44–1.34, $p = 0.351$). The rates of myocardial infarction were 5.6% and 7.1% in Group 1 and Group 2, respectively, with no significant difference observed between the groups (hazard ratio: 0.80, 95% CI 0.39–1.63, $p = 0.550$). Similarly, systemic embolization rates were 3.8% in Group 1 and 4.9% in Group 2, showing no significant variance (hazard ratio: 0.77, 95% CI 0.30–1.99, $p = 0.587$). Notably, all-cause mortality was lower in Group 1 compared to Group 2 (11.7% vs. 12.8%) with a significant hazard ratio of 0.71 (95% CI 0.45–1.12, $p = 0.012$) (Fig. 1).

Discussion

The investigation aimed to assess the differential effects of Apixaban treatment compared to standard care, focusing on adverse events and clinical outcomes. The outcomes assessment revealed differences between the Apixaban and Control groups. Specifically, the Apixaban group exhibited a significantly lower stroke incidence than the Control group. This finding suggests a potential protective effect or advantage associated with Apixaban therapy in reducing the occurrence of stroke [12–16]. However, further investigations are warranted to elucidate the exact mechanisms behind this observed reduction. Contrarily, the study did not demonstrate statistically significant differences in major bleeding, myocardial infarction, or systemic embolization between the Apixaban and Control groups. These non-significant differences might indicate that Apixaban therapy may not directly influence these specific outcomes or that the study's sample size might not be sufficient to detect significant variances in these less frequent events. Of particular interest is the lower all-cause mortality observed in the Apixaban group compared to the Control group [17–20]. This finding suggests a potential clinical benefit associated with Apixaban therapy, resulting in reduced mortality rates. However, interpreting these results requires caution due to the multifactorial nature of mortality outcomes, and further investigations are essential to validate these findings. A study (ARISTOTLE Trial) enrolled 18,201 patients diagnosed with AF were part of this study, with 2786 (15.3%) experiencing paroxysmal AF and 15,412 (84.7%) having persistent or permanent AF [19]. These patients were randomly assigned to receive either apixaban or warfarin. This analysis aimed to compare the outcomes and effectiveness of apixaban versus warfarin based on the type and duration of AF. The main measure for effectiveness was a combination of ischemic or hemorrhagic stroke or systemic embolism. Another aspect studied was the overall mortality rate. The findings consistently showed that apixaban was more effective than warfarin in reducing

Table 2 Rate of study outcomes

Outcome	Group 1 (n = 213)	Group 2 (n = 226)	Hazard ratio (95% CI)	*p* value
Stroke	15 (7.0%)	21 (9.3%)	0.60 (0.32–1.14)	0.027
Major bleeding	18 (8.4%)	25 (11.1%)	0.77 (0.44–1.34)	0.351
Myocardial infarction	12 (5.6%)	16 (7.1%)	0.80 (0.39–1.63)	0.550
Systemic embolization	8 (3.8%)	11 (4.9%)	0.77 (0.30–1.99)	0.587
All-cause mortality	25 (11.7%)	29 (12.8%)	0.71 (0.45–1.12)	0.012

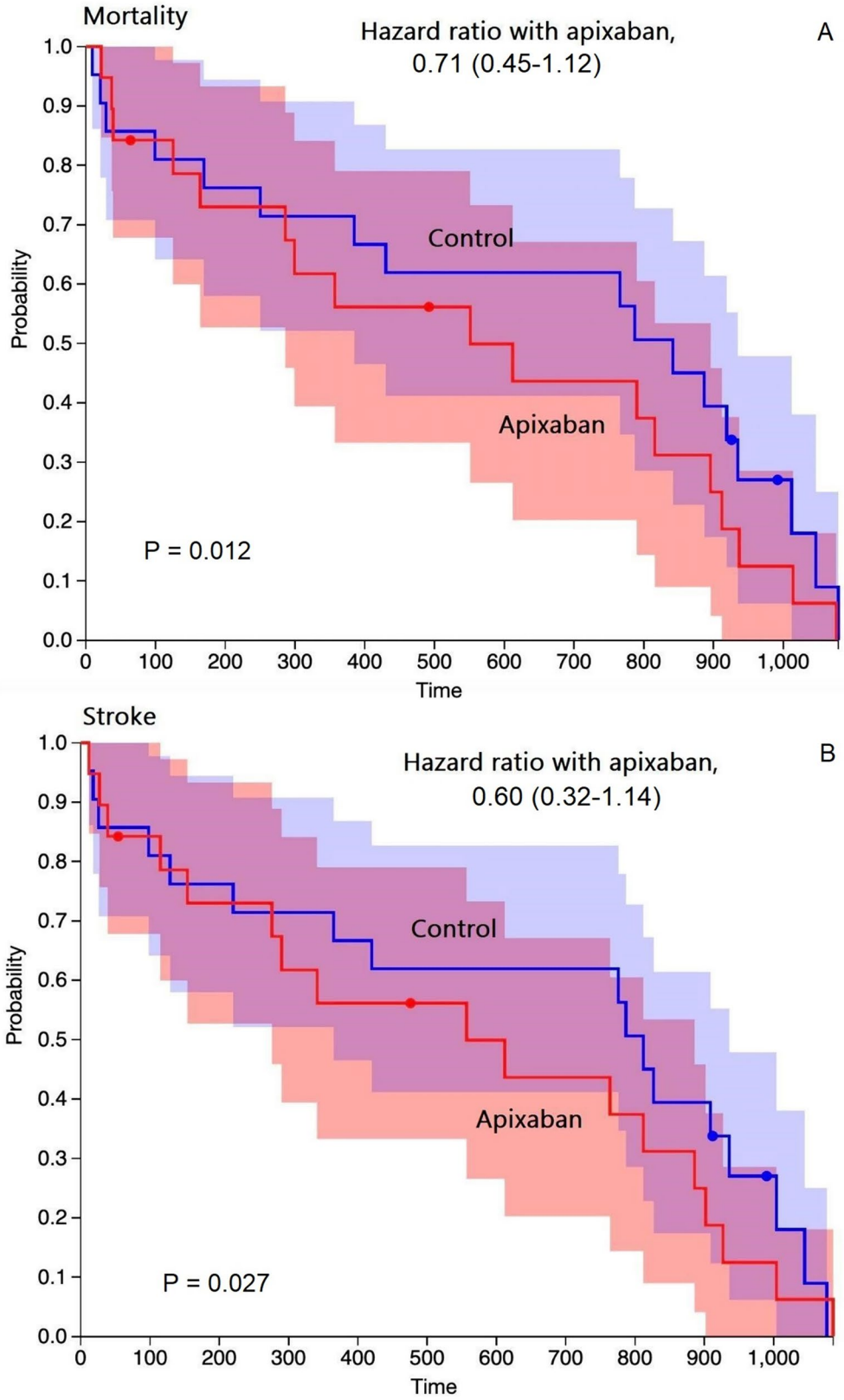

Fig. 1 Cumulative hazard rates for the primary efficacy and safety outcomes **a** shows kaplain meier survival curve for mortality and **b** for stroke

stroke or systemic embolism (with no significant difference between the AF types, lowering all-cause mortality, and decreasing major bleeding, regardless of the duration of AF at the beginning of the study. It was observed that patients with persistent or permanent AF had a notably higher rate of stroke or systemic embolism compared to those with paroxysmal AF (1.52% vs. 0.98%). Moreover, there was a tendency towards higher mortality in patients with persistent or permanent AF (3.90% vs. 2.81%). To investigate apixaban's impact on mortality among patients with AF, a meta-analysis was conducted comparing apixaban versus placebo through an indirect placebo analysis [17]. This analysis utilized data from randomized controlled trials that compared warfarin, aspirin, and no antithrombotic treatment as controls. Two specific trials, comparing apixaban against warfarin and aspirin, were used for this analysis. By employing meta-analysis methods, researchers indirectly assessed apixaban's effect on mortality by comparing it to an estimated placebo. The findings revealed that both warfarin and aspirin demonstrated a lower death rate compared to placebo/no treatment. Combining results from the ARISTOTLE and AVERROES trials, apixaban exhibited a 34% reduction in the risk of death compared to the estimated placebo. The overall analysis indicated a 34% reduction in all-cause mortality associated with apixaban compared to the estimated placebo. These results suggest a significant reduction in the risk of death with the use of apixaban among patients with AF when compared indirectly to a placebo.

Emerging research has highlighted the correlation between AT and ischemic stroke, prompting the consideration of the CHA2DS2VASC score for risk assessment in such cases [21]. The exact mechanisms behind cardioembolic stroke remain not fully comprehended, although studies suggest a link between hypercoagulability and an elevated stroke risk [21]. Investigations by Larsen et al. suggested that excessive supraventricular ectopic activity, particularly in middle-aged and older populations, posed an increased stroke risk beyond just incident AF [22]. Notably, stroke is often presented as the initial clinical manifestation rather than AF in these individuals. According to American Heart Association (AHA) guidelines, there isn't a unanimous consensus regarding anticoagulation in AT or cases of AT with underlying thrombotic factors [23]. Associations between AF and stroke have been well-documented [2, 24, 25]. Current AF management guidelines advocate for oral anticoagulant therapy in patients with a CHA2DS2-VASc score of ≥ 2 in men or ≥ 3 in women to mitigate the risk of stroke [10, 23]. The increased stroke risk in AF may be attributed to factors that trigger the Virchow triad, including stasis in the left atrium and left atrial appendage, endothelial damage due to atrial structural remodeling, and the induction of a prothrombotic and hypercoagulable state [26]. These mechanisms promote platelet activation and initiate the coagulation cascade, resulting in the formation of intracardiac and extracardiac thrombi leading to embolism. Several studies have linked elevated homocysteine levels to vascular diseases like myocardial infarction and stroke [27, 28]. The MTHFR variant C677T, a genetic mutation affecting the enzyme responsible for homocysteine breakdown, may lead to hypercoagulability and an increased thrombosis risk [28].

Several studies have indicated an increased risk of thromboembolism (TE) and AT/AF. However, establishing a clear link between AT/AF episodes and subsequent cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) has proven challenging. Various studies have revealed significant connections between relatively low AT burdens and the risk of CVA or TIA. For instance, analyses of studies like the MOST, TRENDS, and ASSERT trials have shown associations between specific durations of AT and the risk of death, stroke, or systemic embolism [29–31]. However, the correlation isn't always straightforward. Despite observing increased risks, not all patients with AT/AF experiences have had subsequent TE events. Some studies found that a substantial percentage of patients who experienced a TE event didn't show any recorded AT before or in proximity to the event [32]. This lack of a consistent temporal relationship challenges the conventional understanding of how AT/AF might directly lead to TE events. While the closure of the left atrial appendage (LAA) with devices like WATCHMAN has shown some reduction in ischemic stroke rates, implying a connection between intracardiac thrombus and strokes, it's clear that AT/AF might not be the sole cause of TE events in these cases [33, 34]. AT/AF could serve as an indicator of atrial myopathy, which itself may signify heightened vascular risk [35]. In essence, while AT/AF episodes are associated with an increased risk of TE events, the relationship isn't always straightforward or predictable. It suggests that TE events in patients with AT/AF may involve more complex mechanisms beyond mere atrial arrhythmias. Further research is necessary to better comprehend these fundamental principles and their implications for managing stroke risks in these patient populations.

The present study possesses several notable limitations that warrant consideration. Firstly, relying on available data sources introduces potential issues related to data completeness and accuracy. Incomplete or missing data may compromise the depth and reliability of the study findings. Additionally, the observational nature of the study carries inherent risks of selection bias, confounding variables, and unmeasured factors that might influence outcomes, impacting the

internal validity of the results. The relatively small sample size employed in the study might limit its statistical power, hindering the detection of subtle differences in outcomes. Moreover, the study cohort may not fully represent the broader population, thereby restricting the generalizability of the findings. As a retrospective investigation, the study might be susceptible to recall or information bias, which could introduce inaccuracies in data collection or patient history documentation, potentially affecting result accuracy. Unmeasured confounders and variables not included in the analysis might influence observed associations, challenging the interpretation of outcomes. Establishing a direct cause-and-effect relationship remains challenging due to the observational design of the study. Lastly, the study's limitations include the potential lack of diversity in the study population and the possibility of publication bias, impacting the overall interpretation and general applicability of the study outcomes.

Conclusion

In conclusion, our study suggests that the use of apixaban in patients diagnosed with AT exhibits promising outcomes, particularly in reducing the incidence of stroke. While no significant differences were observed in major bleeding, myocardial infarction, or systemic embolization between groups, the lower all-cause mortality in the apixaban-treated group highlights its potential clinical benefit. Further investigations are warranted to validate these findings and establish precise guidelines for anticoagulation strategies in AT management.

Author contributions

Concept; JM. Methodology: FAB, SA, MFK. Data collection: AK, FM, JP, AK. Formal analysis: IA, WA. Validation: JM, WA. First draft: AK, JP, FAB, SA, MFK, IA. Final draft: JM, IA, SA, WA, MFK. Supervision: JM.

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Availability of data and materials

Data is available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The retrospective study was done at our institute (Abbas Institute of Medical Sciences; study ID # AIMS/23/64) and informed consent was taken from all participants according to the principles of the Declaration of Helsinki. As this is a retrospective observational study it was not registered as a clinical trial.

Consent for publication

Yes all participants gave informed consent.

Competing interests

No competing interests to declare.

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