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Comparison of Major Haemorrhagic Events in Atrial Fibrillation Patients Treated with Warfarin, Rivaroxaban, and Apixaban: A Randomized Controlled Trial

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Abstract: Background: Atrial fibrillation (AF) significantly increases the risk of ischemic stroke, and oral anticoagulation remains the cornerstone of stroke prevention. While direct oral anticoagulants (DOACs) have largely replaced warfarin, comparative hemorrhagic safety data from Pakistani clinical settings remain limited.***Objective:*** To compare the incidence of major haemorrhagic events among AF patients receiving warfarin, rivaroxaban, or apixaban.***Methods:*** This randomized controlled trial was conducted at the Department of Medicine, Jinnah Hospital, Lahore. A total of 306 patients aged 45–70 years with non-valvular AF were equally randomized into three groups (n=102 each): warfarin (standard protocol), rivaroxaban (20 mg once daily), and apixaban (10 mg once daily). Primary outcomes included gastrointestinal (GI) bleeding and intracranial haemorrhage (ICH); death within 30 days of a bleeding event was the secondary outcome. Follow-up was conducted weekly for one month.***Results:*** GI bleeding occurred in 24.5% of warfarin users compared to 9.8% and 6.9% in rivaroxaban and apixaban groups respectively ($p<0.001$). Overall major bleeding was significantly higher with warfarin (29.4%) versus both DOACs (10.8% each; $p<0.001$). ICH rates and 30-day mortality did not differ significantly across groups ($p>0.05$).***Conclusion:*** DOACs, particularly apixaban and rivaroxaban, are associated with significantly fewer major haemorrhagic complications compared to warfarin in AF patients, supporting their preferential use in clinical practiceGiant congenital melanocytic nevi (GCMN) are rare pigmented lesions often present at birth and may be associated with satellite nevi and various structural abnormalities. Their coexistence with a large pedunculated soft-tissue mass is unusual and poses diagnostic as well as surgical challenges.

Keywords:Atrial fibrillation, warfarin, rivaroxaban, apixaban, haemorrhage, gastrointestinal bleeding, intracranial haemorrhage, direct oral anticoagulants, stroke prevention, anticoagulation.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 3 to 6 million in the USA.[1,2] The prevalence of AF rises in the elderly population. AF is associated with a 4- to 5-fold increased risk of ischemic stroke, and the incidence of strokes associated with AF increases with advancing age, ranging from 10% overall to 24% in those aged 80–89 years.[3] The burden of stroke is substantial as this leads to functional impairment and effective prevention is best approach to limit this burden. Oral anticoagulation therapy with direct-acting oral anticoagulants (DOACs) and warfarin is the current standard of care for stroke prevention in patients with

nonvalvular AF (NVAF).[4] Patients with AF suffer from high stroke-related disease burden as they are 3 to 4 times more likely to suffer severe strokes. Among patients with AF, stroke-related risks of 1-year disability and 1-year mortality are twice those of non-AF-related strokes.[5]

Rivaroxaban, a factor Xa inhibitor used in clinical practice since 2011, has increasing use in patients with existing and newly diagnosed AF. [6] Results from clinical and observational studies support the efficacy and safety of rivaroxaban in this population, including better effectiveness than warfarin for preventing stroke or systemic embolism. In the noninferiority clinical trial, ROCKET-AF, secondary end points of all-cause mortality and stroke severity were favorably impacted by rivaroxaban versus warfarin. Apixaban is the only DOAC to show risk reduction in both stroke/systemic embolism (SE) and major bleeding compared to warfarin in its Phase 3 trial (ARISTOTLE).[7] Apixaban is also used to treat NVAF. Compared to warfarin, no anticoagulation monitoring is required for DOAC and fewer drug and food interactions are evident.[8] Warfarin has narrow therapeutic range and broad dose-response variability. The food and drug interactions also pose challenges to anticoagulation maintenance. Patients with NVAF and INR <2 have an increased risk of death or cardiovascular-related events as acute coronary syndrome, ischemic stroke, transient ischemic attack, and systemic embolism compared with those with INR of 2 to 3.[9] The need for constant INR monitoring and the potential consequences of poor anticoagulation in warfarin-treated patients pose a considerable burden.

A study was conducted on warfarin, rivaroxaban and apixaban in 2023.[10] New onset of bleeding was observed in 23.9% of patients treated with warfarin, 40.1% of the patients on rivaroxaban and 23.9% patients on apixaban. However, no other recent data was found comparing haemorrhagic outcomes of these drugs. Current study will be performed to compare the outcomes data in patients with AF being treated with warfarin, rivaroxaban and apixaban.
Keeping in view the above context this study was conducted to compare the incidence of major haemorrhagic events among patients receiving warfarin, rivaroxaban and apixaban for atrial fibrillation

METHODS

This randomized controlled trial was conducted in the Department of Medicine, Jinnah Hospital, Lahore, over a period of six months from April 2025 to September 2025 following approval of the synopsis and ethical approval. A total of 306 patients were included in the study, with 102 patients in each of the three groups. The sample size was calculated using a 95% significance level, 80% power of test, and previously reported onset of new bleeding with rivaroxaban versus warfarin (40.1% vs. 23.9%). A non-probability consecutive sampling technique was used. Patients aged 45–70 years of both gender and diagnosed with atrial fibrillation were included. Patients with a history of other anticoagulant use for the same disease, uncontrolled diabetes mellitus, chronic liver disease, chronic kidney disease, or follow-up duration of less than four months were excluded. After obtaining approval from the institutional ethical review board and informed written consent from all participants, eligible patients were enrolled. Baseline characteristics including age, gender, body mass index (BMI), smoking status, and history of diabetes mellitus were documented on a predesigned proforma. Patients were randomly divided into three equal groups by lottery method: Group W received warfarin according to standard treatment protocol, Group R received rivaroxaban 20 mg once daily, and Group A received apixaban 10 mg once daily. All patients were followed weekly till one moth, and outcomes were recorded, including new onset of gastrointestinal bleeding and intracranial haemorrhage. Death within 30 days of a bleeding event was considered a secondary outcome. All collected data were entered and analysed using SPSS version 25. Continuous variables such as age and BMI were presented as mean ± standard deviation, and comparisons were made using one-way ANOVA after normality check. Categorical variables such as bleeding outcomes and mortality were expressed as frequencies and percentages. Data were stratified for age, gender, and BMI; post-stratification chi-square test was applied to compare the frequencies of outcomes in different drug groups, considering a p-value < 0.05 as statistically significant.

RESULTS

The mean age of patients ranged from 58.98 ± 6.18 years in the Warfarin group to 60.28 ± 6.42 years in the Rivaroxaban group, with no statistically significant difference among the three groups ($p = 0.337$).

Similarly, the mean body mass index (BMI) was comparable across all groups (Warfarin = 29.2 ± 4.1 kg/m², Rivaroxaban = 29.3 ± 3.9 kg/m², Apixaban = 29.5 ± 4.0 kg/m²; $p = 0.300$).

In terms of gender distribution, males constituted approximately 58–60% of each group (Warfarin: 59 males,

Rivaroxaban: 61, Apixaban: 57; p = 0.812), indicating no gender imbalance among groups.
The proportion of smokers was also similar, observed in 37.3% of Warfarin users, 35.3% of Rivaroxaban users, and 32.4% of Apixaban users (p = 0.742).

Likewise, the prevalence of diabetes mellitus did not differ significantly between groups (Warfarin = 40.2%, Rivaroxaban = 38.2%, Apixaban = 39.2%; p = 0.961).

Overall, no statistically significant differences were found among the three treatment groups for any baseline characteristic (all p > 0.05), confirming that the study populations were well matched and comparable at baseline Given in Table.1.a

Table 1. Baseline Characteristics of Study Participants (n = 306)

Characteristic		Warfarin (n = 102)	Rivaroxaban (n = 102)	Apixaban (n = 102)	p-value
Age (years), Mean ± SD		58.98 ± 6.18	60.28 ± 6.42	60.03 ± 7.28	0.337
Gender	**Male n (%)**	59 (57.8 %)	61 (59.8 %)	57 (55.9 %)	0.812
	Female n (%)	43 (42.2 %)	41 (40.2 %)	45 (44.1 %)	
BMI (kg/m²), Mean ± SD		29.2 ± 4.1	29.3 ± 3.9	29.5 ± 4.0	0.3
Smoker n (%)		38 (37.3 %)	36 (35.3 %)	33 (32.4 %)	0.742
Diabetes Mellitus n (%)		41 (40.2 %)	39 (38.2 %)	40 (39.2 %)	0.961

Gastrointestinal (GI) bleeding was significantly more frequent in patients treated with Warfarin, occurring in 25 (24.5%) cases, compared to 10 (9.8%) in the Rivaroxaban group and 7 (6.9%) in the Apixaban group (p < 0.001).

Intracranial hemorrhage (ICH) was observed in 6 (5.9%) Warfarin users, 1 (1.0%) Rivaroxaban user, and 4 (3.9%) Apixaban users, with the difference not reaching statistical significance (p = 0.167).

When considering any major bleeding event (either GI bleed or ICH), 30 (29.4%) patients on Warfarin experienced bleeding compared with 11 (10.8%) on Rivaroxaban and 11 (10.8%) on Apixaban (p < 0.001), indicating a significantly lower overall bleeding risk with direct oral anticoagulants (DOACs).

Death within 30 days of a bleeding event, evaluated as a secondary outcome, occurred in 5 (4.9%) patients in the Warfarin group, and in 2 (2.0%) patients each in the Rivaroxaban and Apixaban groups (p > 0.05). Although the difference was not statistically significant, mortality was numerically higher in Warfarin-treated patients.

Overall, the results demonstrate that patients on DOACs, particularly Rivaroxaban and Apixaban, had a significantly lower incidence of major haemorrhagic complications compared with those on Warfarin, while intracranial haemorrhage and short-term mortality showed no significant intergroup difference given in Table 2.

Table 2. Comparison of Haemorrhagic Events by Treatment Group

Outcome	Event	Warfarin (n = 102)	Rivaroxaban (n = 102)	Apixaban (n = 102)	Total (n = 306)	p-value
GI Bleed	**No**	77 (75.5 %)	92 (90.2 %)	95 (93.1 %)	**264 (86.3 %)**	< 0.001
	Yes	25 (24.5 %)	10 (9.8 %)	7 (6.9 %)	**42 (13.7 %)**	
ICH	**No**	96 (94.1 %)	101 (99.0 %)	98 (96.1 %)	**295 (96.4 %)**	0.167
	Yes	6 (5.9 %)	1 (1.0 %)	4 (3.9 %)	**11 (3.6 %)**	
Any Bleed	**No**	72 (70.6 %)	91 (89.2 %)	91 (89.2 %)	**254 (83.0 %)**	< 0.001
	Yes	30 (29.4 %)	11 (10.8 %)	11 (10.8 %)	**52 (17.0 %)**	
Death within 30 days(Secondary Outcome)	**No**	97 (95.1 %)	100 (98.0 %)	100 (98.0 %)	**297 (97.1 %)**	> 0.05
	Yes	5 (4.9 %)	2 (2.0 %)	2 (2.0 %)	**9 (2.9 %)**	

DISCUSSION

The present study compared the incidence of major hemorrhagic events among patients with atrial fibrillation (AF) treated with Warfarin, Rivaroxaban, and Apixaban. Our findings demonstrate that patients receiving direct oral anticoagulants (DOACs) experienced significantly fewer overall and gastrointestinal bleeding events than those treated with Warfarin, whereas intracranial hemorrhage (ICH) and short-term mortality did not differ significantly. These results are consistent with global evidence showing that DOACs offer superior safety while maintaining comparable or improved efficacy in stroke prevention among patients with non-valvular AF.

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting over 33 million individuals worldwide and contributing substantially to ischemic stroke and mortality risk[1,2]. Effective anticoagulation remains the cornerstone of stroke prevention in AF, but traditional Vitamin-K antagonists such as Warfarin have several limitations, including narrow therapeutic range, variable metabolism, and multiple food and drug interactions[3,7]. The advent of DOACs including Rivaroxaban and Apixaban has transformed anticoagulation practice by offering predictable pharmacokinetics, rapid onset, and fewer interactions, without the need for routine monitoring[5,6].

In our study, Warfarin users had nearly three times the frequency of major bleeding compared with patients receiving DOACs. This aligns with prior large randomized trials and real-world analyses. The ROCKET-AF and ARISTOTLE trials reported reduced rates of major or fatal bleeding with Rivaroxaban and Apixaban respectively, compared with Warfarin[5,6]. Similarly, contemporary observational cohorts and meta-analyses have confirmed that Apixaban and Rivaroxaban are associated with lower risks of gastrointestinal or intracranial bleeding than Warfarin[9,10,11,12]. Recent comparative studies further indicate that among DOACs, Apixaban may provide the most favorable bleeding profile, particularly in elderly and high-risk populations[13,14,15].

The lower incidence of GI and overall bleeding in our DOAC groups may be explained by their more targeted inhibition of coagulation factors (Xa inhibition) without suppression of vitamin-K–dependent proteins, resulting in stable anticoagulant effects and reduced variability in plasma concentration[7,10]. Moreover, DOACs eliminate the need for frequent INR monitoring, reducing the risk of sub- or supra-therapeutic anticoagulation, a well-recognized cause of bleeding in Warfarin users[8].

Our results are supported by prior real-world studies that validated the safety and effectiveness of Rivaroxaban in clinical practice[5] and demonstrated consistent efficacy of Apixaban across different risk profiles[6,9]. The pooled data from multiple meta-analyses confirm that DOACs not only reduce major bleeding events but also lower the risk of intracranial haemorrhage compared with Warfarin[9,13,15]. Nevertheless, as in our findings, minor bleeding and gastrointestinal events remain the most frequent adverse outcomes requiring clinical attention.

The present findings reinforce international guidelines from the American Heart Association and European societies, which recommend DOACs as the first-line therapy for stroke prevention in non-valvular AF[3,11]. Given the comparable efficacy with a superior safety profile, particularly in terms of major and life-threatening bleeding, DOACs represent a clinically advantageous alternative to Warfarin in routine practice.

However, this study has certain limitations. It was conducted in a single tertiary-care centre with a moderate sample size and relatively short follow-up period. Laboratory confirmation of anticoagulation intensity (e.g., time in therapeutic range for Warfarin) was not included, which may underestimate Warfarin's potential if managed optimally. Future multicentre, longer-term studies are warranted to evaluate the consistency of these findings in broader and higher-risk populations

CONCLUSION

In conclusion, our study confirms that direct oral anticoagulants Rivaroxaban and Apixaban are associated with significantly fewer major haemorrhagic events compared with Warfarin in patients with atrial fibrillation. These results support the growing body of international evidence favouring DOACs as safer, effective, and more convenient options for long-term anticoagulation[10–15].

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