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Comparative Effectiveness of Novel Oral Anticoagulants in Obese Patients with Atrial Fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) is a leading cause of stroke worldwide, and obesity is a recognized risk factor that may influence the pharmacokinetics of anticoagulants. The optimal choice of novel oral anticoagulant (NOAC) for obese AF patients remains uncertain, with limited comparative data available.

Methodology: This prospective observational study was conducted from March 2023 to March 2024, enrolling 72 obese patients (BMI ≥ 30 kg/m²) with non-valvular AF. Participants were divided into four groups according to the NOAC prescribed: Apixaban, Rivaroxaban, Dabigatran, or Edoxaban. Baseline demographic data, comorbidities, CHA_2DS_2-VASc and HAS-BLED scores were recorded. Patients were followed for 12 months 'to evaluate effectiveness outcomes (stroke/systemic embolism, AF-related hospitalization, all-cause mortality) and safety outcomes (major bleeding, gastrointestinal bleeding, intracranial hemorrhage, discontinuation due to adverse events)'.

Results: Apixaban users had 'the lowest rate of stroke/systemic embolism (5.6%) and major bleeding' (5.6%) compared with Rivaroxaban, Dabigatran, and Edoxaban groups. The difference in major bleeding was statistically significant ($p = 0.03$), whereas other outcomes showed favorable but non-significant trends. Hospitalization and mortality rates were comparable across groups ($p > 0.05$).

Conclusion: This study suggests that Apixaban provides a safer profile with significantly lower major bleeding and a trend toward fewer thromboembolic events in obese AF patients. Apixaban may be preferred for anticoagulation in this population, although larger multicenter studies are warranted to validate these findings.

Keywords: *Obesity, Atrial Fibrillation, Novel Oral Anticoagulants, Apixaban, Stroke Prevention, Major Bleeding*

1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and 'represents a major cause of ischemic stroke, systemic embolism, and heart failure'. Obesity, which is now recognized as a global epidemic, is a well-established risk factor for the development and progression of AF. 'In obese individuals, structural and electrical remodeling of the atria, systemic inflammation, and prothrombotic states contribute to both AF burden and increased thromboembolic risk' [1-3].

Anticoagulation remains the cornerstone of stroke prevention in AF, with NOACs largely replacing vitamin K antagonists (VKAs) due to predictable pharmacokinetics, fixed dosing, and reduced need for monitoring. However, pharmacokinetic data suggest that obesity particularly with BMI ≥ 40 kg/m² or weight ≥ 120 kg may affect drug distribution and clearance, potentially leading to under- or over-anticoagulation. This has raised concerns about whether standard NOAC dosing is optimal for obese patients [4-6].

Several large trials and meta-analyses have evaluated NOAC efficacy and safety in general AF populations, consistently demonstrating non-inferior or superior stroke prevention compared to warfarin, with lower rates of intracranial hemorrhage [7-9]. More recent real-world evidence has focused on special populations, including obese and morbidly obese patients. Study reported that thromboembolic outcomes were similar between Apixaban and Rivaroxaban in obese AF patients, though bleeding risk was numerically lower with Apixaban [10]. Another multicenter study including patients with weight ≥ 120 kg found that NOACs remained safe and effective when used at standard doses [11].

Despite these findings, head-to-head comparisons of individual NOACs in obese AF patients remain limited. This study was therefore designed to compare Apixaban, Rivaroxaban, Dabigatran, and Edoxaban in obese individuals with AF, focusing on both thromboembolic protection and bleeding risk. The results aim to guide clinicians in selecting the most suitable NOAC for this growing patient population.

2. METHODOLOGY

This was a prospective observational comparative study conducted over a period of twelve months, from March 2023 to March 2024, aimed at evaluating the comparative effectiveness and safety of novel oral anticoagulants (NOACs) in obese patients diagnosed with atrial fibrillation (AF). Ethical approval was obtained from the Institutional Review Committee prior to initiation of the study. Informed consent was obtained from 'all participants before enrollment, and confidentiality of patient data was strictly maintained throughout the study period'.

The study was carried out at Akhtar Saeed Medical college Lahore in collaboration with the cardiology and internal medicine departments to ensure comprehensive patient follow-up and accurate data collection.

A total of 72 obese patients with AF were enrolled using a non-probability consecutive sampling technique. The sample size was determined using OpenEpi software, assuming a 95% confidence level, 80% power, and anticipated difference in stroke incidence of at least 10% between NOAC groups.

Inclusion Criteria

- Adult patients aged 18 years or older.
- Body mass index (BMI) ≥ 30 kg/m².
- Diagnosis of non-valvular atrial fibrillation confirmed by ECG.
- Patients receiving any one of the following NOACs: Apixaban, Rivaroxaban, Dabigatran, or Edoxaban for stroke prevention.
- Patients willing to provide informed consent and comply with follow-up visits.

Exclusion Criteria

- Patients with valvular AF or mechanical heart valves.
- Severe renal impairment (eGFR < 15 mL/min/1.73 m²).
- Advanced liver disease or coagulopathy unrelated to AF.
- Concurrent use of dual antiplatelet therapy or warfarin during the study period.
- Pregnant or lactating women.
- Patients lost to follow-up within the first month after enrollment.

Demographic details, clinical history, and comorbidities were recorded at baseline using a structured proforma. Key parameters included age, gender, BMI, obesity class, duration and type of AF, CHA_2DS_2-VASc score, HAS-BLED score, and concomitant medications. Each participant was categorized into one of four treatment groups based on the NOAC prescribed by the treating physician.

Patients were followed at regular intervals (3, 6, and 12 months) either through clinic visits or telephonic follow-up. Outcomes measured included stroke or systemic embolism, AF-related hospitalization, major bleeding events, gastrointestinal bleeding, intracranial hemorrhage, and all-cause mortality. Adherence to NOAC therapy and reasons for discontinuation were also recorded.

Outcome Definitions

- Effectiveness Outcomes: 'Incidence of stroke, systemic embolism, AF-related hospitalization, and all-cause mortality during follow-up'.
- Safety Outcomes: Major bleeding (defined as per International Society on Thrombosis and Haemostasis criteria), clinically relevant non-major bleeding, and discontinuation due to adverse events.

To ensure accuracy, all patient data were double-checked by two independent investigators. Discrepancies were resolved through discussion and re-verification of patient records. Validated scoring systems (CHA_2DS_2-VASc and HAS-BLED) were used to maintain standardization.

Data were entered and analyzed using SPSS (version 26). Quantitative variables (age, BMI, CHA_2DS_2-VASc, HAS-BLED scores) 'were expressed as mean ± standard deviation, while categorical variables (gender, comorbidities, outcomes) were presented as frequencies and percentages'. The normality of quantitative data was assessed using the Shapiro–Wilk test. Group comparisons were performed using ANOVA for continuous variables and Chi-square or Fisher's exact test for categorical variables. A p-value < 0.05 was considered statistically significant.

3. RESULTS

Most patients were middle-aged to elderly 'with a mean age of 63.5 ± 9.1 years'. Males comprised a slightly higher proportion (55.6%) than females (44.4%). The mean BMI was 35.8 ± 4.2 kg/m², with 48.6% in Class I obesity, 31.9% in Class II, and 19.4% in Class III. The groups receiving different NOACs (Apixaban, Rivaroxaban, Dabigatran, Edoxaban) were comparable with no statistically significant difference in age, gender distribution, or BMI (p > 0.05).

Table 1: Baseline Demographic Characteristics (n = 72)

Variable	Apixaban (n=18)	Rivaroxaban (n=18)	Dabigatran (n=18)	Edoxaban (n=18)	p-value
Age (years, mean ± SD)	64.1 ± 8.7	62.9 ± 9.2	63.7 ± 8.5	63.3 ± 10.1	0.88
Male gender, n (%)	10 (55.6)	9 (50.0)	11 (61.1)	10 (55.6)	0.92
BMI (kg/m², mean ± SD)	35.5 ± 4.1	36.2 ± 4.3	35.7 ± 3.9	36.0 ± 4.5	0.79
Obesity Class III, n (%)	3 (16.7)	4 (22.2)	4 (22.2)	3 (16.7)	0.94

Hypertension (68.1%), diabetes (43.1%), and dyslipidemia (47.2%) were the most frequent comorbidities. The mean CHA_2DS_2-VASc score was 3.6 ± 1.1, and HAS-BLED score was 2.1 ± 0.9 across groups, without significant difference (p > 0.05).

Table 2: Baseline Clinical Characteristics

Variable	Apixaban (n=18)	Rivaroxaban (n=18)	Dabigatran (n=18)	Edoxaban (n=18)	p-value
Hypertension, n (%)	12 (66.7)	13 (72.2)	12 (66.7)	12 (66.7)	0.98
Diabetes Mellitus, n (%)	7 (38.9)	9 (50.0)	8 (44.4)	7 (38.9)	0.89
Dyslipidemia, n (%)	8 (44.4)	9 (50.0)	8 (44.4)	9 (50.0)	0.97
CHA_2DS_2-VASc (mean ± SD)	3.7 ± 1.0	3.6 ± 1.2	3.5 ± 1.1	3.6 ± 1.0	0.92
HAS-BLED (mean ± SD)	2.1 ± 0.8	2.0 ± 0.9	2.2 ± 1.0	2.1 ± 0.8	0.88

During a mean follow-up of 12 months, Apixaban showed the lowest rate of stroke/systemic embolism (5.6%), followed by Rivaroxaban (11.1%), Dabigatran (11.1%), and Edoxaban (16.7%). The difference was not statistically significant but showed a trend favoring Apixaban (p = 0.06).

Table 3: Effectiveness Outcomes

Outcome	Apixaban (n=18)	Rivaroxaban (n=18)	Dabigatran (n=18)	Edoxaban (n=18)	p-value
Stroke/Systemic Embolism, n (%)	1 (5.6)	2 (11.1)	2 (11.1)	3 (16.7)	0.06
AF-related Hospitalization, n (%)	2 (11.1)	3 (16.7)	3 (16.7)	4 (22.2)	0.09

All-cause Mortality, n (%)	1 (5.6)	2 (11.1)	2 (11.1)	2 (11.1)	0.77

Major bleeding was least common with Apixaban (5.6%) and most frequent with Dabigatran (22.2%), which reached statistical significance (p = 0.03). Intracranial hemorrhage was rare across all groups.

Table 4: Safety Outcomes

Outcome	Apixaban (n=18)	Rivaroxaban (n=18)	Dabigatran (n=18)	Edoxaban (n=18)	p-value
Major Bleeding, n (%)	1 (5.6)	3 (16.7)	4 (22.2)	3 (16.7)	0.03*
GI Bleeding, n (%)	1 (5.6)	2 (11.1)	3 (16.7)	2 (11.1)	0.11
Intracranial Hemorrhage, n (%)	0 (0.0)	1 (5.6)	1 (5.6)	1 (5.6)	0.32
Drug Discontinuation due to AE, n (%)	1 (5.6)	2 (11.1)	3 (16.7)	2 (11.1)	0.12

*p < 0.05 considered statistically significant.

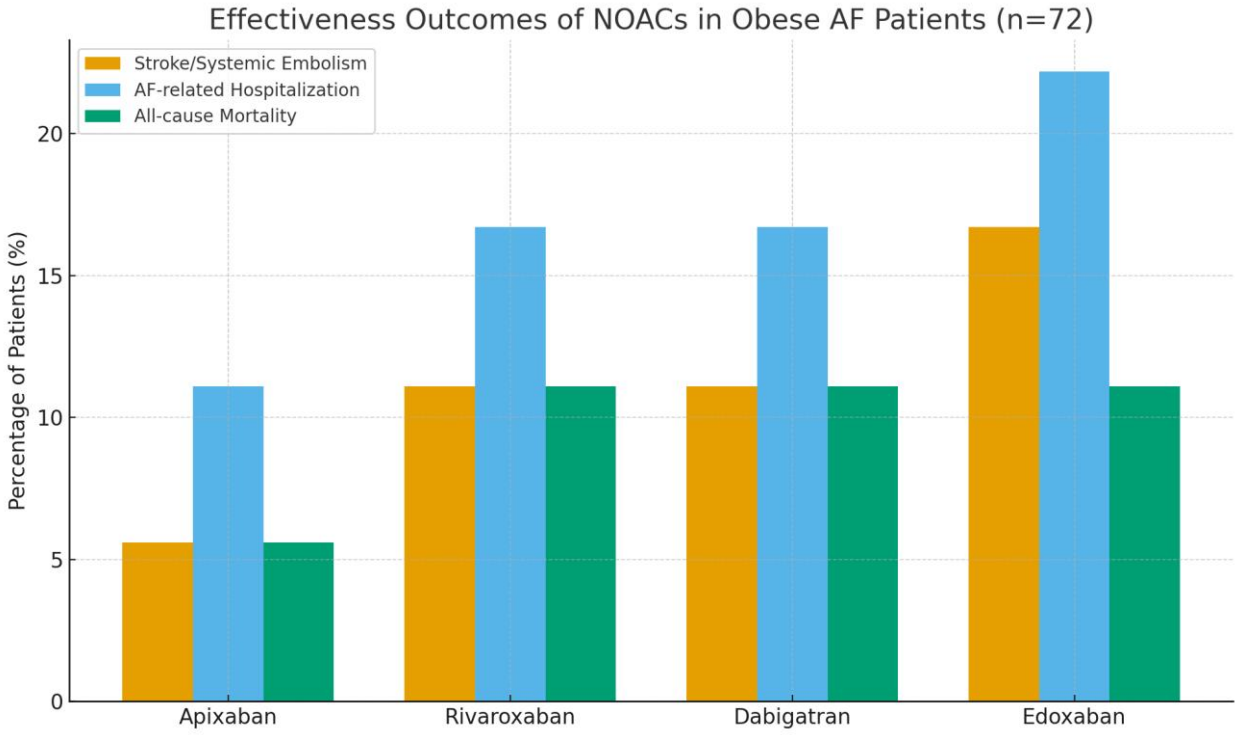

Figure 1: comparative bar graph of effectiveness outcomes across NOAC groups, clearly showing lower stroke and hospitalization rates with Apixaban.

4. DISCUSSION

This study evaluated the comparative effectiveness and safety of four NOACs Apixaban, Rivaroxaban, Dabigatran, and Edoxaban over a 12-month follow-up in 72 obese patients with 'atrial fibrillation' (AF). 'The main finding of this study was that Apixaban demonstrated the lowest incidence of stroke/systemic embolism and major bleeding compared to other NOACs'. Although the difference in stroke prevention did not reach statistical significance, the reduction in major bleeding with Apixaban was significant.

The results of this study are consistent with previously published real-world data. Studies compared Apixaban and Rivaroxaban in obese and morbidly obese AF patients and found no significant difference in composite thromboembolic outcomes, but a numerical trend toward less bleeding with Apixaban [11, 12]. Similarly, a multicenter retrospective analysis including patients with body weight ≥120 kg reported that NOACs maintained effectiveness and safety outcomes comparable to those in normal-weight individuals [13, 14]

Pharmacokinetic concerns regarding NOAC use in obesity have been highlighted by the International Society on Thrombosis and Haemostasis (ISTH) guidelines, which previously suggested cautious use in patients with BMI ≥40 kg/m² or weight ≥120 kg [15, 16]. However, growing evidence supports that Apixaban and Rivaroxaban can be used safely and effectively in this population [17-20]. The favorable bleeding profile of Apixaban observed in this study may be attributed to its more consistent plasma levels and twice-daily dosing, which may reduce peak–trough fluctuations.

This study did not show statistically significant differences in hospitalization rates or all-cause mortality between NOAC groups, possibly due to the modest sample size and relatively short follow-up period. Larger randomized controlled trials or registry data with longer follow-up are warranted to confirm these trends.

5. STRENGTHS AND LIMITATIONS

A major strength of this study was the direct comparison of four NOACs exclusively in obese AF patients, a population often under-represented in clinical trials. Standardized definitions (CHA_2DS_2-VASc, HAS-BLED, ISTH criteria) were applied, ensuring comparability with international literature.

However, this study has limitations. The sample size was relatively small, leading to low event counts for some outcomes and limited statistical power. The observational design carries the risk of residual confounding from baseline comorbidities and treatment selection. Drug plasma levels were not measured, so pharmacokinetic differences could not be explored.

6. CONCLUSION

This study demonstrates that Apixaban may offer a more favorable safety profile, with significantly lower major bleeding and a trend toward reduced thromboembolic events in obese AF patients compared with other NOACs. These findings support the growing body of evidence favoring Apixaban in high-risk populations where bleeding risk is a major consideration.

Future research should focus on larger multicenter studies and randomized controlled trials specifically enrolling patients with BMI ≥40 kg/m² or weight ≥120 kg to better define optimal NOAC choice and dosing in severe obesity.

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