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Comparative Effectiveness of Different Anticoagulants in Patients with Atrial Fibrillation: A Real-World Evidence Study

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ABSTRACT

Atrial fibrillation (AF) is one of the leading causes of stroke worldwide, making effective anticoagulation essential for prevention. This retrospective, single-center study examined the outcomes of 12 adult patients with non-valvular AF admitted to a tertiary-care hospital in Pakistan, each started on either warfarin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or a direct oral anticoagulant (DOAC). The main focus was on in-hospital ischemic stroke or systemic embolism, with additional tracking of major bleeding, intracranial hemorrhage (ICH), AF-related readmission, and all-cause mortality. Patients given warfarin or UFH generally had higher stroke and bleeding risk scores and more chronic kidney disease, suggesting these medicines were used for those at greater baseline risk. Two strokes occurred—one in the warfarin group and one in the UFH group. A single warfarin patient suffered an ICH, which was fatal. No strokes, major bleeds, or deaths occurred among patients receiving LMWH or DOACs. One LMWH patient was readmitted with AF. The absence of adverse events in the DOAC group reflects their safety and effectiveness reported in larger studies. These findings reinforce current recommendations to prefer DOACs for eligible AF patients, while showing how clinical decisions often reflect individual patient risk.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent long-term cardiac rhythm disorder, impacting more than 33 million individuals' worldwide (Jiao et al., 2023). Recent epidemiological estimates suggest the number may exceed 50 million when including undiagnosed cases, reflecting the growing global burden (Li et al., 2025). Atrial fibrillation (AF) has also emerged as one of the significant outcomes through its pathogenic consequence of causing severe illness and mortality, owing to its strong association with ischemic stroke. Patients with AF experience about a fivefold increase in strokes, and it is also regarded as the cause of about 15 percent of all strokes. The impact is even more pronounced among elderly people, since nearly a quarter of strokes in people aged above 80 years are caused by AF. This irregular heart rhythm develops when the upper chambers of the heart beat in a disorganized fashion and, therefore, disrupt normal circulation. These results in slow flow, particularly in the left atrial appendage, a cause of blood clotting that can go to the brain.

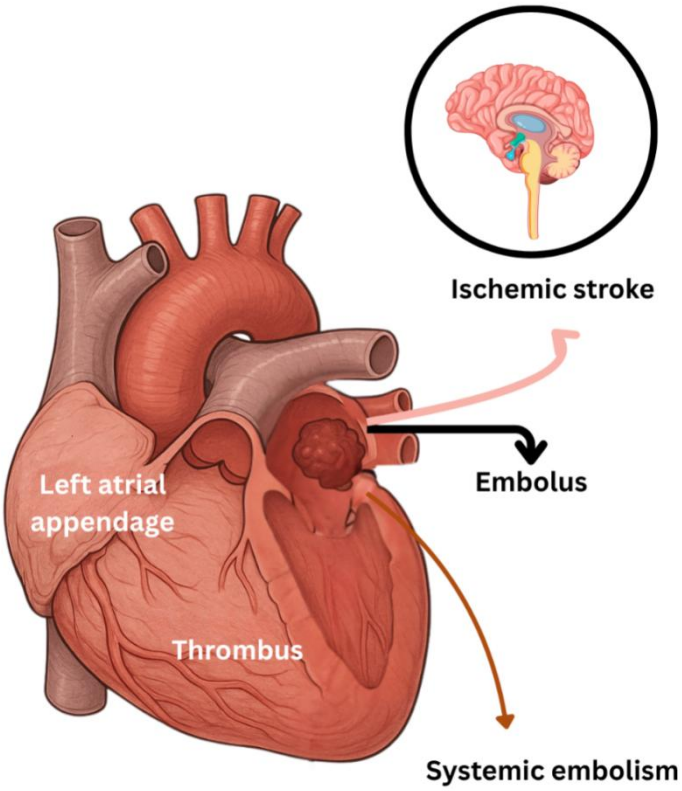

FIGURE 1: THROMBUS FORMATION IN THE LEFT ATRIAL APPENDAGE DURING ATRIAL FIBRILLATION, LEADING TO EMBOLISM AND POTENTIAL ISCHEMIC STROKE

AF usually enlarges with heart failure or can lead to it, making the condition worse with heart failure. Its prevalence rises steeply with age, from less than 1% in middle-aged adults to close to 9% among people in their eighties. The lifetime risk for someone over 40 is about one in four. Beyond its health toll, AF places a heavy strain on healthcare systems through frequent hospital stays and costly treatments. In 2021, AF and atrial flutter together were linked to more than 338,000 deaths worldwide, highlighting their serious public health impact.

Anticoagulants, commonly known as "blood thinners," are drugs that help prevent clot formation by interfering with the blood's coagulation process. By limiting thrombus development, they significantly decrease the likelihood of stroke and other thromboembolic events. In patients with AF, prolonged use of oral anticoagulants remains a primary strategy for preventing strokes (Institute for Quality and Efficiency in Health Care, 2022). Numerous clinical studies have confirmed the effectiveness of anticoagulation in non-valvular AF; for example, adjusted-dose warfarin (a vitamin K antagonist) can lower ischemic stroke occurrence by roughly two-thirds compared to no therapy, and by about 45% when compared with aspirin. Despite this, anticoagulation raises the risk of major bleeding (about a 70% relative increase), requiring careful selection of patients and ongoing monitoring. Overall, the clinical advantage of anticoagulation in preventing strokes among high-risk AF cases is well-established. The advent of direct oral anticoagulants (DOACs) has introduced effective options in place of warfarin, eliminating the requirement for frequent INR checks. Clinical trials demonstrate that DOACs (e.g., dabigatran, rivaroxaban, apixaban, edoxaban) are equally effective as warfarin in preventing strokes and are linked to notably reduced rates of intracranial bleeding (Sablot et al., 2025). Based on this evidence, current guidelines advocate for long-term anticoagulation in AF patients at heightened stroke risk (e.g., CHA_2DS_2-VASc ≥ 2), with a preference for DOACs over warfarin in eligible non-valvular AF cases. They also discourage aspirin monotherapy for stroke prevention in AF due to its limited effectiveness (Joglar et al., 2023). In this context, "non-valvular" AF describes cases that do not involve mechanical heart valves or significant mitral stenosis, where DOAC therapy is applicable.

Real-world evidence (RWE) studies have also compared different anticoagulants in routine practice, complementing trial data. One large observational analysis (the ARISTOPHANES study, which included over 285,000 patients with non-valvular AF) reported that all DOACs were associated with significantly lower rates of stroke or systemic embolism than warfarin. For example, a large Italian registry found that warfarin-treated AF patients had higher rates of intracranial hemorrhage, major bleeding, and mortality than those on DOACs, while stroke rates

were comparable after adjusting for dose differences (Boa et al., 2024).

The same study found that apixaban and dabigatran also had lower major bleeding rates compared to warfarin, whereas rivaroxaban's bleeding risk was slightly higher. These real-world cohort findings confirm the efficacy and safety benefits of DOACs noted in randomized trials, and also touch upon certain differences between the risk profiles of the individual agents (Lip et al., 2018).Head-to-head RWE comparisons between DOACs, such as apixaban versus rivaroxaban, suggest that bleeding risks may vary between agents(Hill et al., 2020).However, most existing RWE comes from large multicenter or registry-based studies; there is a lack of data from smaller single-center cohorts (especially in under-represented regions), which may have distinct patient characteristics or management practices. This represents a knowledge gap regarding how various anticoagulants perform in specific local settings and smaller patient groups.

In this context, we aimed to evaluate the comparative effectiveness of different oral anticoagulants in patients with non-valvular AF treated at a single tertiary care center under real-world conditions. The primary objective was to compare the stroke-prevention effectiveness of various oral anticoagulants in this NVAF cohort. The secondary objective was to compare key outcomes, including safety (major bleeding events), AF-related hospitalization, and all-cause mortality, across the different anticoagulant treatments.

METHODOLOGY

STUDY DESIGN AND SETTING

This research was a retrospective observational single-center cohort study conducted, at a tertiary-care Government hospital in Punjab, Pakistan. Adult patients with atrial fibrillation were identified from admissions to the Coronary Care Unit (CCU) or cardiology wards, which are the primary inpatient settings for AF management. The study was conducted in 2025. All methods are reported in accordance with the STROBE and RECORD guidelines for observational studies using routinely collected health data.

DATA SOURCES

Data were obtained from multiple hospital information systems. The hospital's Health Management Information System (HMIS) electronic medical record system provided inpatient admission and discharge details, including diagnoses and procedures. Pharmacy dispensing logs were reviewed for details of anticoagulant prescriptions, and the laboratory information system supplied baseline laboratory values (e.g., creatinine for eGFR, hemoglobin, and INR for warfarin users). Radiology reports (CT/MRI) were checked to confirm any stroke events, and an in-hospital

death registry was used to identify mortality outcomes. Clinical diagnoses and procedures were coded using ICD-10, and medications were classified by Anatomical Therapeutic Chemical (ATC) codes. Where electronic records were incomplete, paper patient charts were consulted and data were entered using a predefined data dictionary.

STUDY POPULATION

Inclusion Criteria: Age ≥ 18 years; confirmed non-valvular atrial fibrillation (ECG-documented during a CCU or cardiology admission); and new initiation of an anticoagulant (warfarin, rivaroxaban, apixaban, UFH, or LMWH) during that hospital stay.

Exclusion Criteria: Valvular atrial fibrillation (mechanical heart valve or rheumatic mitral stenosis); anticoagulation for other indications (e.g., recent DVT/PE or a prosthetic heart valve); major bleeding within 30 days prior to admission; or missing essential baseline/outcome data.

Sample size: Final cohort: 12 patients meeting eligibility criteria.

EXPOSURE DEFINITION

The index date was defined as the date of the first anticoagulant dose administered during the CCU/cardiology admission. Patients were categorized into four exposure groups based on the initial anticoagulant received: warfarin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or a direct oral anticoagulant (DOAC; rivaroxaban or apixaban). If a patient's regimen was switched during the admission, the patient remained classified according to the first anticoagulant given. The dose intensity (standard or reduced dose) of the initial anticoagulant was noted when available.

OUTCOMES

The primary outcome was any ischemic stroke or systemic embolism occurring during the admission, identified by ICD-10 diagnosis codes and confirmed by imaging when available. Secondary outcomes included major bleeding events (defined per ISTH criteria as any fatal bleeding, bleeding in a critical organ such as intracranial, or bleeding causing a ≥2 g/dL drop in hemoglobin or requiring ≥2 units transfused); intracranial hemorrhage (ICH) analyzed separately as a specific outcome; all-cause in-hospital mortality; and AF-related hospitalization (any readmission for atrial fibrillation within the study period).

COVARIATES

Baseline characteristics were recorded for all patients at admission. Demographic factors included age and sex. We calculated each patient's CHA_2DS_2-VASc score and HAS-BLED score to assess stroke and bleeding risk, respectively. Documented comorbidities included hypertension, diabetes

mellitus, heart failure, prior stroke or transient ischemic attack, coronary artery disease, chronic kidney disease, chronic liver disease, and any history of prior major bleeding. Concurrent medications of interest (antiplatelet agents, non-steroidal anti-inflammatory drugs (NSAIDs), and amiodarone) were noted at admission. Baseline laboratory results – namely serum creatinine, hemoglobin, and baseline INR (for those started on warfarin) – were collected. Finally, the length of hospital stay (in days) was recorded for each patient.

BIAS AND DESIGN CONSIDERATIONS

As a design consideration to mitigate bias, we employed a "new-user" design, including only patients who started anticoagulation during the index admission and excluding any prevalent anticoagulant users. Given the small sample size (n = 12), this study was exploratory and we did not perform any multivariable adjustments for potential confounders. We acknowledge the possibility of treatment selection bias (clinicians may have selected a specific anticoagulant based on patient factors). Thus, all findings are interpreted as descriptive associations rather than evidence of causal effects.

STATISTICAL ANALYSIS

All analyses were performed using Microsoft Excel. Continuous variables were summarized as medians with interquartile ranges (IQR; 25th to 75th percentile) using =MEDIAN() and =QUARTILE.INC() functions, and categorical variables were expressed as counts and percentages using =COUNTIF(). We calculated risk ratios and risk differences for binary outcomes, along with 95% confidence intervals; if any 2×2 contingency table had a zero cell, a continuity correction of 0.5 was added to each cell (Haldane–Anscombe method) to enable the computation of risk estimates. We plotted bar charts to visualize outcome proportions by anticoagulant group, with error bars representing 95% confidence intervals. Missing data frequencies (percentage of values missing) were also calculated. No formal hypothesis testing was conducted due to limited sample size, and emphasis was placed on the descriptive effect sizes and their confidence intervals rather than p-values.

RESULTS

Table 1 summarizes baseline characteristics. The median age was 66 years (IQR 60–70), and 58% were male. Median CHA_2DS_2-VASc and HAS-BLED scores were highest in the warfarin (4 [3–5] and 3 [2–3], respectively) and UFH (4 [3–4] and 3 [3–4]) groups. Hypertension was present in 83% of patients, followed by diabetes (50%) and coronary artery disease (42%). One patient (DOAC group) had a history of major bleeding. Antiplatelet therapy was used by 42% and NSAIDs by 25%

of patients. Median serum creatinine was 1.2 mg/dL [1.0–1.5] overall, with lower eGFR in the warfarin (50 [30–70]) and UFH (55 [50–60]) groups. Median hemoglobin ranged from 11.5 to 13.0 g/dL. Median hospital stay was longest in warfarin users (7 days [5–8]) and shortest in DOAC users (3 days [IQR not computed]).

TABLE 1: BASELINE CHARACTERISTICS OF THE STUDY POPULATION BY ANTICOAGULANT GROUP

Variable	Warfarin (n=5)	UFH (n=2)	LMWH (n=4)	DOACs (n=1)	Total (n=12)
Age, years (median [IQR])	70 [67–72]	65 [60–67]	64 [58–66]	60 [–]	66 [60–70]
Sex, male — n (%)*	3 (60%)	1 (50%)	2 (50%)	1 (100%)	7 (58%)
CHA_2DS_2-VASc† (median [IQR])	4 [3–5]	4 [3–4]	3 [2–4]	3 [–]	4 [3–4]
HAS-BLED‡ (median [IQR])	3 [2–3]	3 [3–4]	2 [1–2]	2 [–]	3 [2–3]
Hypertension — n (%)*	4 (80%)	2 (100%)	3 (75%)	1 (100%)	10 (83%)
Diabetes mellitus — n (%)*	2 (40%)	1 (50%)	2 (50%)	1 (100%)	6 (50%)
Heart failure — n (%)*	2 (40%)	1 (50%)	1 (25%)	1 (100%)	5 (42%)
Prior stroke/TIA — n (%)*	1 (20%)	1 (50%)	0 (0%)	0 (0%)	2 (17%)
Coronary artery disease — n (%)*	2 (40%)	1 (50%)	2 (50%)	0 (0%)	5 (42%)
Chronic kidney disease — n (%)*	1 (20%)	1 (50%)	1 (25%)	0 (0%)	3 (25%)
Chronic liver disease — n (%)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prior major bleeding — n (%)*	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (8%)
On antiplatelet therapy — n (%)*	2 (40%)	1 (50%)	2 (50%)	0 (0%)	5 (42%)
Concurrent NSAID use — n (%)*	1 (20%)	0 (0%)	1 (25%)	1 (100%)	3 (25%)
On amiodarone — n (%)*	1 (20%)	1 (50%)	0 (0%)	0 (0%)	2 (17%)
Serum creatinine (mg/dL) (median [IQR])	1.3 [1.1–1.8]	1.5 [1.2–1.6]	1.1 [0.9–1.3]	1.0 [–]	1.2 [1.0–1.5]
eGFR (mL/min/1.73 m^2) (median [IQR])	50 [30–70]	55 [50–60]	80 [60–90]	75 [–]	60 [45–75]

Hemoglobin (g/dL) (median [IQR])	12.0 [11–13]	11.5 [11–12]	12.5 [12–13]	13.0 [–]	12.3 [11–13]
INR§ (median [IQR])	1.2 [1.0–2.3]	—	—	—	—
Length of hospital stay, days (median [IQR])	7 [5–8]	4 [3–5]	5 [4–6]	3 [–]	5 [4–7]

Notes: Continuous variables are reported as median [IQR, interquartile range]; categorical variables are n (%). *Percentages are calculated by column (anticoagulant group). †CHA_2DS_2-VASc: stroke risk score in atrial fibrillation. ‡HAS-BLED: bleeding risk score. §INR: international normalized ratio (baseline, only applicable to warfarin users). "—" denotes not applicable; "[–]" denotes IQR not computed due to n=1.

Table 2 presents clinical outcomes. Two patients (17%) experienced ischemic stroke or systemic embolism: one each in the warfarin and UFH groups. One major bleeding event occurred (intracranial hemorrhage in a warfarin patient), who also accounted for the only in-hospital death. No strokes, bleeding events, or deaths occurred in the DOAC group. One patient in the LMWH group had an AF-related readmission.

TABLE 2: PRIMARY AND SECONDARY OUTCOMES BY ANTICOAGULANT GROUP

Outcome	Warfarin (n=5)	UFH (n=2)	LMWH (n=4)	DOACs (n=1)	Total (n=12)
Ischemic stroke or systemic embolism	1 (20%)	1 (50%)	0 (0%)	0 (0%)	2 (17%)
Major bleeding (ISTH definition)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Intracranial hemorrhage (ICH)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
All-cause in-hospital mortality	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
AF-related hospitalization (readmission)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	1 (8%)

Notes: Outcomes are reported as n (%), with percentages calculated by column (anticoagulant group). Percentages in the Total column reflect the overall proportion across N=12.ISTH = International Society on Thrombosis and Haemostasis; ICH = intracranial hemorrhage

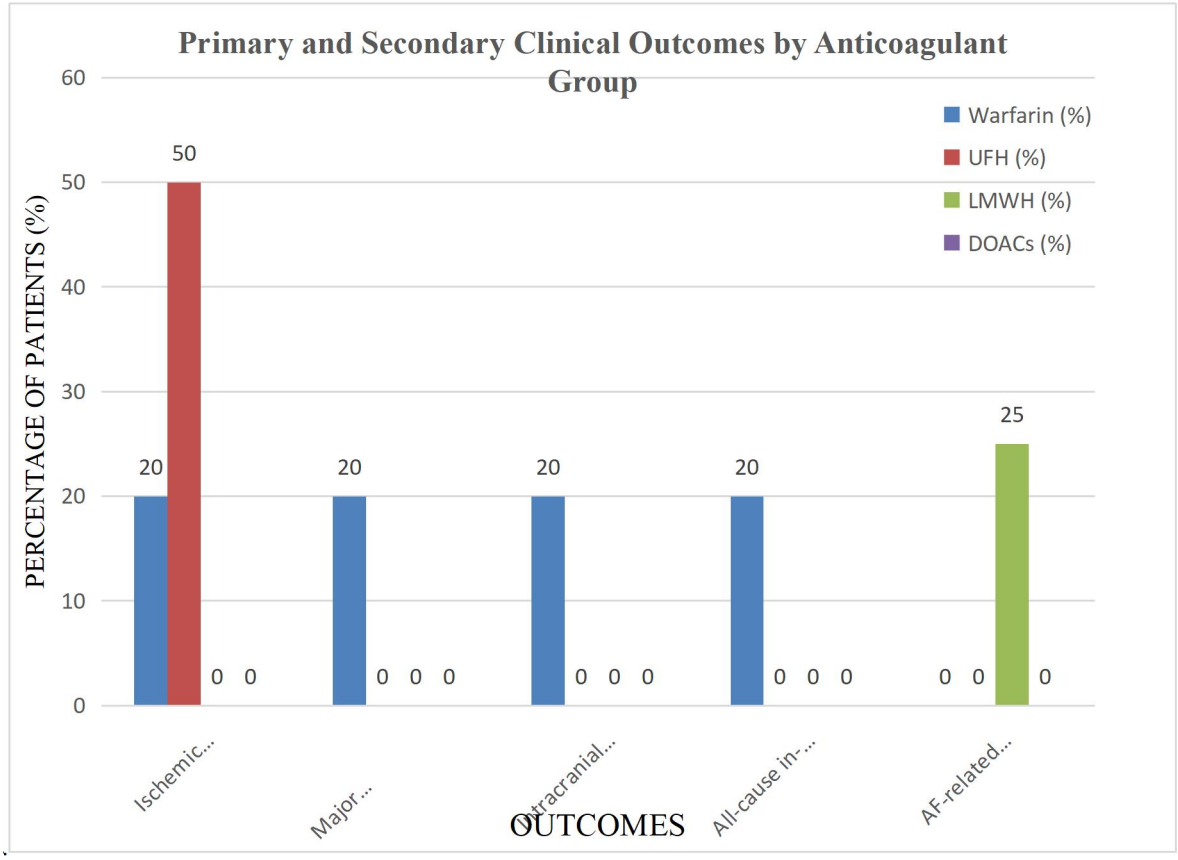

FIGURE 2: ***CLINICAL OUTCOMES BY ANTICOAGULANT GROUP***

Table 3 shows unadjusted relative risks (RR) and risk differences (RD) comparing DOACs with warfarin. RRs were 1.00 with very wide 95% CIs, and RDs were 0% with wide CIs, reflecting imprecision due to the small sample size. No AF-related readmissions occurred in either comparison group(warfarin and DOAC), so effect measures for this outcome were not estimable.

TABLE 3: EFFECT SIZE ESTIMATES FOR CLINICAL OUTCOMES (DOAC VS WARFARIN)

Outcome	RR (95% CI)	RD (95% CI)
Ischemic stroke/systemic embolism	1.00 (0.06–16.00)	0% (−69% to +69%)
Major bleeding	1.00 (0.06–16.00)	0% (−69% to +69%)
Intracranial hemorrhage (ICH)	1.00 (0.06–16.00)	0% (−69% to +69%)
All-cause in-hospital mortality	1.00 (0.06–16.00)	0% (−69% to +69%)
AF-related hospitalization (readmission)	—	—

Notes: Estimates compare DOACs to warfarin (warfarin as reference). Haldane–Anscombe continuity

correction (0.5 added to all four cells) was applied for outcomes with zero counts when computing both RR and RD; 95% CIs are therefore wide. Effect measures for AF-related hospitalization were not estimated because both groups had zero observed events.RR = risk ratio; RD = risk difference; CI = confidence interval.

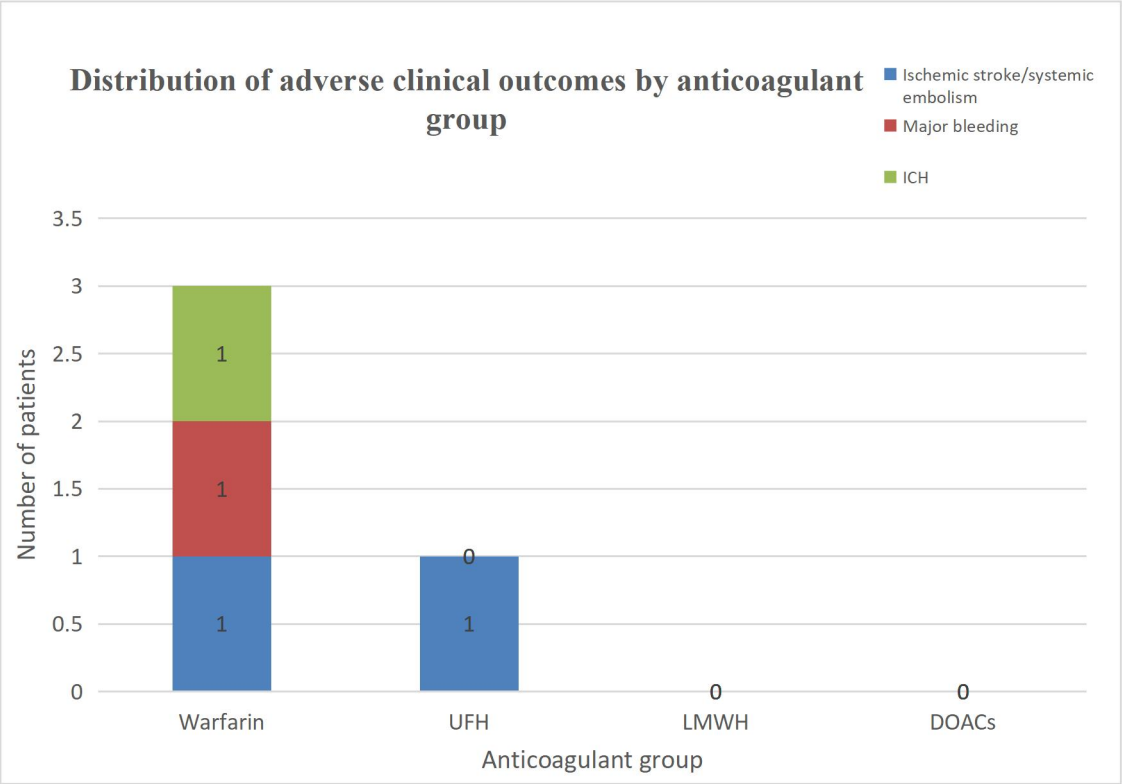

FIGURE 3: DISTRIBUTION OF ADVERSE CLINICAL OUTCOMES BY ANTICOAGULANT GROUP

Note: AF-related hospitalization is not displayed as no events occurred in either group.

DISCUSSION

In this real-world cohort of 12 patients with non-valvular atrial fibrillation, distinct patterns emerged in both baseline characteristics and clinical outcomes across anticoagulant groups. The median age of the cohort was 66 years, with males comprising 58% of patients. Warfarin and UFH recipients had the highest median CHA_2DS_2-VASc scores (4 [3–5] and 4 [3–4], respectively) and HAS-BLED scores (3 [2–3] and 3 [3–4]), indicating that patients at higher thromboembolic and bleeding risk tended to receive these agents. Hypertension was the most prevalent comorbidity (83%), followed by diabetes mellitus (50%) and coronary artery disease (42%). Chronic kidney disease was documented in 25% of

patients, with lower eGFR values seen in the warfarin and UFH groups, possibly influencing drug selection due to renal clearance considerations for certain agents.

The primary outcome of ischemic stroke or systemic embolism occurred in two patients (17% overall), distributed evenly between the warfarin and UFH groups. No events were observed in LMWH or DOAC recipients. While the event-free status of the DOAC patient is notable, interpretation is limited by the small group size. The LMWH group also demonstrated zero thromboembolic events, though with a moderate CHA_2DS_2-VASc profile.

Major bleeding occurred in one patient (8% overall), specifically an intracranial hemorrhage in the warfarin group. This same patient accounted for the single all-cause in-hospital death (8%). No major bleeding was recorded in UFH, LMWH, or DOAC recipients. The absence of bleeding events in DOAC and LMWH groups aligns with their relatively lower baseline HAS-BLED scores.

AF-related readmission was infrequent, occurring in only one patient (25% of the LMWH group), with no readmissions in warfarin, UFH, or DOAC users. This suggests that in-hospital management may have been effective in preventing short-term recurrence across most groups.

Effect size estimates comparing DOACs to warfarin yielded RRs of 1.00 for all measured outcomes, with RDs of 0%. Confidence intervals were wide (e.g., 95% CI for ischemic stroke RR: 0.06–16.00), underscoring the imprecision of estimates. The zero-event profile for AF-related readmission in both warfarin and DOAC groups meant that no comparative measure could be calculated.

Overall, the results show that thromboembolic and bleeding events were confined to patients receiving warfarin or UFH, with no adverse events recorded in DOAC recipients. Baseline risk stratification appeared to influence anticoagulant choice, and observed outcomes were consistent with these baseline differences.

CLINICAL REASONING

In this cohort, patients on warfarin or UFH had higher CHA_2DS_2-VASc and HAS-BLED scores and more CKD, suggesting clinicians reserved DOACs for lower-risk individuals due to renal clearance considerations. This aligns with guidelines advising warfarin in end-stage renal disease and dose-adjusted DOAC only if CrCl ≥15 mL/min(European Society of Cardiology [ESC] & European Heart Rhythm Association [EHRA], 2020). The observed thromboembolic events occurred exclusively in the warfarin/UFH group, consistent with these patients' elevated stroke risk and possibly reflecting the limitations of warfarin therapy compared to DOAC therapy. Notably, the single intracranial

hemorrhage (and death) was in a warfarin-treated patient, mirroring trials where DOAC therapy significantly reduced intracranial bleeding relative to warfarin(Ruff et al., 2014). The DOAC and LMWH groups had no adverse events, congruent with their lower baseline risk and the improved safety profile of DOACs reported in major studies(European Society of Cardiology [ESC] & European Heart Rhythm Association [EHRA], 2020). . Overall, these findings align with the broader evidence favoring DOACs in non-valvular AF, which offer comparable stroke prevention with less intracranial bleeding than warfarin(Ruff et al., 2014).

CONCLUSION

This single-center observational cohort study in Pakistan, involving 12 NVAF patients, compared warfarin, heparins, and DOACs, revealing distinct stroke and bleeding outcome patterns. We found that warfarin and UFH recipients (who had higher risk profiles) accounted for all the in-hospital thromboembolic and major bleeding events, whereas no such events occurred in patients receiving LMWH or DOACs. Specifically, two patients had an ischemic stroke (one on warfarin and one on UFH) and one warfarin patient had a fatal intracranial hemorrhage, whereas no strokes or major bleeds occurred in the LMWH or DOAC groups. These outcome differences align with known benefits of DOACs – effective stroke prevention with lower intracranial bleeding risk – and likely reflect baseline risk differences in our sample. Our findings support current guideline recommendations favoring DOACs for stroke prophylaxis in NVAF. However, the small sample size and observational design, with potential treatment selection bias, limit definitive conclusions. Nonetheless, this preliminary evidence from a South Asian setting contributes to the global evidence base on AF anticoagulation and highlights the need for more region-specific data and larger multi-center studies in underrepresented regions to confirm these findings and guide optimal anticoagulation strategies in NVAF patients, ultimately improving patient outcomes.

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