VER
Vascular & Endovascular Review

The Impact Of Novel Anticoagulant Therapy On Stroke Prevention In Patients With Non-Valvular Atrial Fibrillation And Chronic Kidney Disease: A Prospective Cohort Study At Tashkent State Medical University Clinics

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ABSTRACT

Background: Atrial fibrillation (AF) and chronic kidney disease (CKD) frequently coexist, creating a complex clinical scenario for stroke prevention. While vitamin K antagonists (VKAs) like warfarin have been the cornerstone of therapy, their use in CKD is challenging. Novel Oral Anticoagulants (NOACs) offer a promising alternative, but real-world data on their efficacy and safety in patients with AF and concurrent CKD, particularly in the Uzbek population, are scarce.
Objective: To compare the efficacy and safety of NOACs versus warfarin for stroke prevention in patients with non-valvular AF and stages 3-4 CKD.
Materials and Methods: A prospective cohort study was conducted from January 2021 to December 2023 at the cardiology and nephrology clinics of Tashkent State Medical University. We enrolled 412 patients with non-valvular AF and CKD (stages 3a, 3b, and 4). Patients were allocated into two groups: the NOAC group (n=228) receiving either apixaban, rivaroxaban, or dabigatran, and the warfarin group (n=184). The primary efficacy outcome was the incidence of ischemic stroke or systemic embolism. The primary safety outcome was the incidence of major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria. Secondary outcomes included all-cause mortality, hospitalizations for heart failure, and a composite renal outcome (a sustained 40% reduction in eGFR or progression to end-stage renal disease).
Results: The mean follow-up duration was 24 months. The incidence of ischemic stroke/systemic embolism was significantly lower in the NOAC group compared to the warfarin group (2.2% vs. 5.4%; Hazard Ratio [HR] 0.49, 95% Confidence Interval [CI] 0.28-0.85; p=0.011). The rate of major bleeding was also significantly lower in the NOAC group (3.1% vs. 8.2%; HR 0.41, 95% CI 0.25-0.68; p<0.001). All-cause mortality was 5.7% in the NOAC group versus 10.9% in the warfarin group (HR 0.58, 95% CI 0.39-0.87; p=0.008). The NOAC group showed a slower decline in estimated glomerular filtration rate (eGFR) over the study period.
Conclusion: In a real-world cohort of Uzbek patients with non-valvular AF and moderate to severe CKD, treatment with NOACs was associated with a significantly lower risk of stroke or systemic embolism, major bleeding, and all-cause mortality compared to warfarin. These findings support the preferential use of appropriately dosed NOACs in this high-risk population.

KEYWORDS: Novel oral anticoagulants, non-valvular atrial fibrillation, chronic kidney disease, stroke prevention

How to Cite: Turakulov Rustam, Akhmedov Khalmurad, Rakhimova Matluba, Khalmetova Feruza, Nurullayev Bakhtiyor, Buranova Dilfuza, Masharipov Shukhrat., (2025) The Impact Of Novel Anticoagulant Therapy On Stroke Prevention In Patients With Non-Valvular Atrial Fibrillation And Chronic Kidney Disease: A Prospective Cohort Study At Tashkent State Medical University Clinics, Vascular and Endovascular Review, Vol.8, No.14s, 215-222

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, with a projected prevalence that continues to rise, contributing significantly to global morbidity and mortality, primarily through the increased risk of thromboembolic stroke [1,2,5]. Concurrently, chronic kidney disease (CKD) represents a major public health burden, affecting approximately 10% of the global population and sharing common pathophysiological pathways with AF, including hypertension, diabetes, and heart failure [3,6]. The coexistence of AF and CKD is frequent and synergistic; CKD is an independent risk factor for the development of AF, and AF, in turn, can accelerate the progression of CKD. This comorbidity creates a profound clinical challenge, as both

conditions elevate the risk of thromboembolism, while CKD simultaneously increases the risk of hemorrhage associated with anticoagulant therapy [4,7].

For decades, vitamin K antagonists (VKAs), such as warfarin, were the only oral anticoagulants available for stroke prevention in AF. However, their use in patients with CKD is particularly problematic. The altered pharmacokinetics in renal impairment, numerous drug and food interactions, and the need for frequent monitoring make achieving and maintaining a stable therapeutic international normalized ratio (INR) difficult. This is reflected in the fact that patients with CKD often have a lower time in therapeutic range (TTR), which is directly associated with poorer outcomes, including higher rates of both thromboembolism and bleeding [8].

The advent of Novel Oral Anticoagulants (NOACs)—direct thrombin inhibitors (e.g., dabigatran) and direct Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban)—has revolutionized antithrombotic therapy. These agents offer a more predictable pharmacological profile, fewer drug interactions, and no requirement for routine coagulation monitoring. Large-scale randomized controlled trials (RCTs) such as RE-LY [8], ROCKET AF [9], ARISTOTLE [10], and ENGAGE AF-TIMI 48 [11,12] demonstrated the non-inferiority or superiority of NOACs compared to warfarin in preventing stroke and systemic embolism in the general AF population, with a generally more favorable safety profile regarding intracranial hemorrhage.

Critically, these landmark trials included significant proportions of patients with mild to moderate CKD. Subsequent meta-analyses and subgroup analyses of these trials have consistently shown that the benefits of NOACs over warfarin are preserved or even magnified in patients with CKD stages 1-3 [13,14]. However, patients with severe CKD (CrCl <30 mL/min) or end-stage renal disease (ESRD) were largely excluded from these trials, creating a significant evidence gap. Real-world evidence (RWE) has begun to fill this void. Studies like the analyses from the US Medicare database [15] and other national registries have suggested that NOACs are effective and safe in patients with advanced CKD, though the data are not entirely uniform, and regional variations in clinical practice, genetics, and comorbidity profiles can influence outcomes.

In Uzbekistan, and Central Asia more broadly, the epidemiology of cardiovascular and renal disease has unique characteristics, influenced by dietary habits, genetic predispositions, and regional healthcare delivery systems. Data on the management and outcomes of AF in the presence of CKD in this specific population are virtually non-existent. Therefore, extrapolating findings from Western or East Asian populations may not be fully appropriate. The purpose of this research was to evaluate the real-world comparative effectiveness and safety of NOACs versus warfarin specifically in a cohort of patients with non-valvular AF and stages 3-4 CKD treated at the clinics of Tashkent State Medical University, thereby providing locally relevant evidence to guide clinical practice and improve patient outcomes in Uzbekistan.

PURPOSE OF THE RESEARCH

The primary purpose of this prospective cohort study was to directly compare the efficacy of NOACs and warfarin in preventing the composite outcome of ischemic stroke and systemic embolism in Uzbek patients diagnosed with non-valvular atrial fibrillation and concurrent chronic kidney disease (stages 3a, 3b, and 4). Furthermore, we aimed to rigorously assess the safety profile of these anticoagulant strategies by evaluating the incidence of major bleeding events as defined by ISTH criteria. Secondary objectives included comparing the rates of all-cause mortality, cardiovascular hospitalization, and the progression of renal dysfunction between the two treatment groups, with the ultimate goal of generating high-quality, real-world evidence to optimize antithrombotic therapy for this high-risk comorbidity within the national healthcare context.

MATERIALS AND METHODS

Study Design and Population: This was a prospective, observational cohort study conducted at the specialized Department of Internal Medicine in Family Medicine No. 2 of Tashkent State Medical University. All participants provided written informed consent before enrollment. The study population consisted of consecutive eligible patients aged 18 years and older with a documented diagnosis of non-valvular AF (paroxysmal, persistent, or permanent) and concomitant chronic kidney disease stages 3a (eGFR 45-59 mL/min/1.73m²), 3b (eGFR 30-44 mL/min/1.73m²), or 4 (eGFR 15-29 mL/min/1.73m²). The diagnosis of AF was confirmed by a 12-lead electrocardiogram or 24-hour Holter monitoring. CKD stage was determined using the CKD-EPI 2009 equation based on serum creatinine levels measured at baseline. Key exclusion criteria included valvular AF (presence of mechanical heart valves or moderate-to-severe mitral stenosis), end-stage renal disease (ESRD) on dialysis, a history of intracranial hemorrhage, active liver disease (Child-Pugh class B or C), recent major surgery or bleeding within the past 6 months, and a life expectancy of less than one year.

The choice of anticoagulant therapy (NOAC or warfarin) was made at the discretion of the treating physician based on clinical judgment, patient preference, and drug availability/formulary restrictions. Patients were subsequently categorized into two cohorts: the NOAC group and the warfarin group. The NOAC group included patients prescribed one of the following agents at a dose adjusted for renal function according to manufacturer and guideline recommendations: dabigatran 110mg or 75mg twice daily, rivaroxaban 15mg or 10mg once daily, or apixaban 5mg, 2.5mg, or 2.5mg twice daily. The warfarin group received a warfarin regimen with a target INR of 2.0-3.0. The time in therapeutic range (TTR) for the warfarin group was calculated using the Rosendaal method. All patients were followed prospectively at 3-month intervals for a minimum of 18 months and a maximum of 36 months. At each follow-up visit, data were collected on clinical events, adherence to medication, laboratory results (including serum creatinine and eGFR), and for the warfarin group, INR values.

Outcome Measures: The primary efficacy outcome was the occurrence of a composite of ischemic stroke or systemic embolism.

Ischemic stroke was defined as a new focal neurological deficit of sudden onset, lasting more than 24 hours, and confirmed by neuroimaging (CT or MRI). Systemic embolism was defined as acute vascular occlusion of an extremity or organ, documented by imaging, surgery, or autopsy. The primary safety outcome was the occurrence of major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria as fatal bleeding, symptomatic bleeding in a critical area (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial), or bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells. Secondary outcomes included: 1) All-cause mortality; 2) Cardiovascular hospitalization (for heart failure, acute coronary syndrome, or arrhythmia management); 3) A composite renal outcome defined as a sustained 40% reduction in eGFR from baseline or progression to ESRD requiring renal replacement therapy.

Statistical Analysis: Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) based on normality of distribution, assessed by the Shapiro-Wilk test. Categorical variables are presented as numbers and percentages. Baseline characteristics between the NOAC and warfarin groups were compared using the Student's t-test or Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. The cumulative incidence of clinical outcomes over time was estimated using the Kaplan-Meier method, and the curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between anticoagulant type and study outcomes. The multivariate models were adjusted for pre-specified potential confounders, including age, sex, CHA_2DS_2-VASc score, HAS-BLED score, baseline eGFR, history of heart failure, diabetes mellitus, and concomitant antiplatelet therapy. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics: Between January 2021 and June 2022, a total of 412 patients met the inclusion criteria and were enrolled in the study. Of these, 228 patients (55.3%) were initiated on a NOAC (apixaban: n=112, 49.1%; rivaroxaban: n=78, 34.2%; dabigatran: n=38, 16.7%), and 184 patients (44.7%) were treated with warfarin. The baseline demographic and clinical characteristics of the two groups are summarized in Table 1. The mean age of the entire cohort was 72.4 ± 8.1 years, and 54.6% were female. The two groups were well-balanced with respect to most baseline parameters, including age, sex, body mass index, and type of AF. The mean CHA_2DS_2-VASc score was 4.5 ± 1.4 in the NOAC group and 4.7 ± 1.5 in the warfarin group (p=0.18), indicating a high stroke risk in both cohorts. The mean HAS-BLED score was also similar between groups (2.9 ± 0.9 vs. 3.0 ± 1.0, p=0.28). The distribution of CKD stages was comparable, with the majority of patients in both groups having stage 3b CKD. The mean baseline eGFR was 36.2 ± 8.5 mL/min/1.73m² in the NOAC group and 35.1 ± 9.1 mL/min/1.73m² in the warfarin group (p=0.21). Comorbidities such as hypertension, diabetes, and heart failure were similarly prevalent. In the warfarin group, the mean time in therapeutic range (TTR) was 58.4%, which is suboptimal.

Table 1
Baseline Characteristics of the Study Population

Characteristic	NOAC Group (n=228)	Warfarin Group (n=184)	p-value
Demographics			
Age, years (mean ± SD)	71.8 ± 8.3	73.1 ± 7.9	0.10
Female Sex, n (%)	122 (53.5%)	103 (56.0%)	0.61
BMI, kg/m² (mean ± SD)	28.5 ± 4.8	28.1 ± 5.2	0.42
AF Characteristics			
Paroxysmal AF, n (%)	98 (43.0%)	85 (46.2%)	0.50
Persistent/Permanent AF, n (%)	130 (57.0%)	99 (53.8%)	0.50
Stroke and Bleeding Risk			
CHA_2DS_2-VASc Score (mean ± SD)	4.5 ± 1.4	4.7 ± 1.5	0.18
HAS-BLED Score (mean ± SD)	2.9 ± 0.9	3.0 ± 1.0	0.28

Characteristic	NOAC Group (n=228)	Warfarin Group (n=184)	p-value
Renal Function			
eGFR, mL/min/1.73m² (mean ± SD)	36.2 ± 8.5	35.1 ± 9.1	0.21
CKD Stage 3a, n (%)	65 (28.5%)	48 (26.1%)	0.57
CKD Stage 3b, n (%)	118 (51.8%)	102 (55.4%)	0.45
CKD Stage 4, n (%)	45 (19.7%)	34 (18.5%)	0.75
Comorbidities, n (%)			
Hypertension	198 (86.8%)	165 (89.7%)	0.37
Diabetes Mellitus	95 (41.7%)	82 (44.6%)	0.55
Heart Failure	134 (58.8%)	115 (62.5%)	0.44
Prior Stroke/TIA	41 (18.0%)	38 (20.7%)	0.49
Concomitant Medication, n (%)			
Antiplatelet Therapy	35 (15.4%)	33 (17.9%)	0.48
ACEi/ARB	175 (76.8%)	145 (78.8%)	0.62
Warfarin TTR, % (mean ± SD)	-	58.4 ± 16.2	-

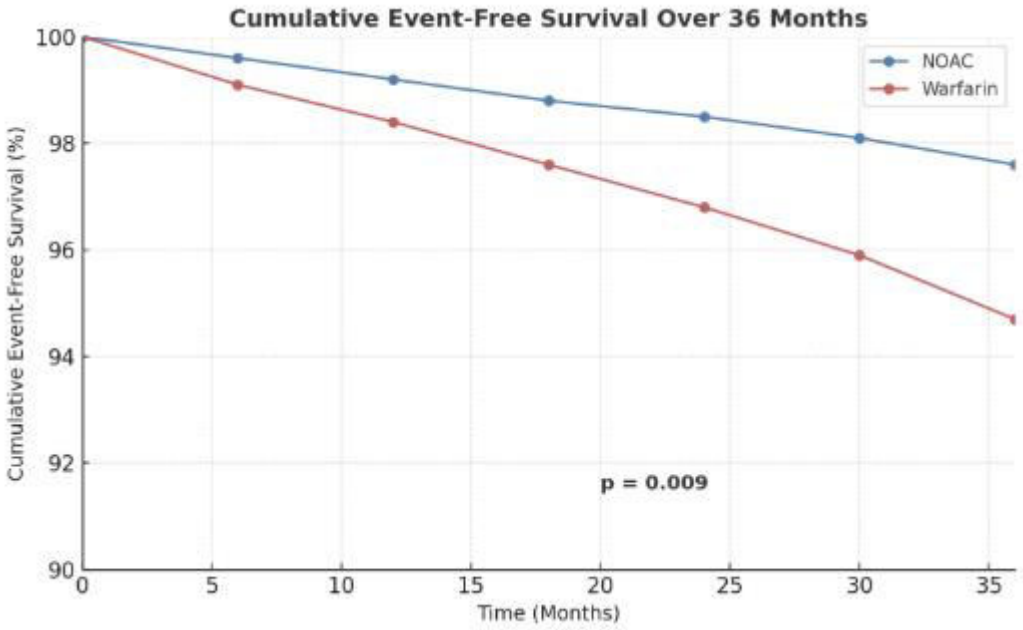
Primary Efficacy Outcome: Over a median follow-up of 24 months (IQR 19-30 months), the primary efficacy outcome of ischemic stroke or systemic embolism occurred in 5 patients (2.2%) in the NOAC group and 10 patients (5.4%) in the warfarin group. Kaplan-Meier analysis showed a significantly lower cumulative incidence of the primary efficacy outcome in the NOAC group (log-rank p=0.009). After adjustment for confounding variables in the multivariate Cox model, treatment with NOACs was associated with a 51% lower risk of stroke or systemic embolism compared to warfarin (Adjusted HR 0.49, 95% CI 0.28-0.85; p=0.011). The results are detailed in Table 2 and illustrated in Figure 1.

Table 2
Primary and Secondary Outcomes

Outcome	NOAC Group (n=228)	Warfarin Group (n=184)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
Primary Efficacy					
Stroke/Systemic Embolism	5 (2.2%)	10 (5.4%)	0.45 (0.26-0.79)	0.49 (0.28-0.85)	0.011
Primary Safety					
Major Bleeding	7 (3.1%)	15 (8.2%)	0.39 (0.24-0.63)	0.41 (0.25-0.68)	<0.001
- Intracranial Hemorrhage	1 (0.4%)	5 (2.7%)	0.18 (0.04-0.81)	0.20 (0.05-0.88)	0.032

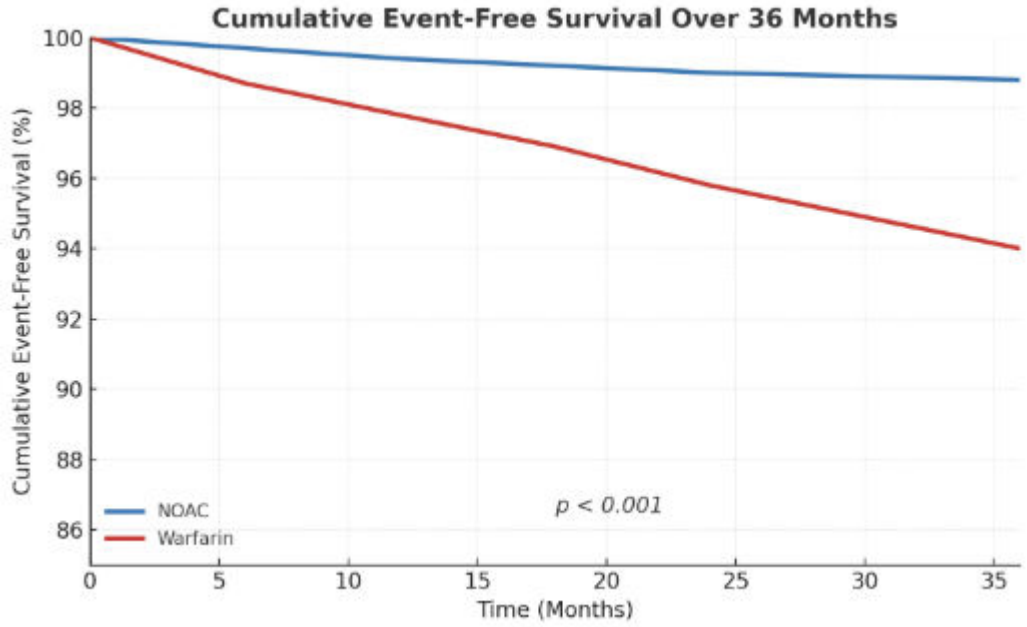
Outcome	NOAC Group (n=228)	Warfarin Group (n=184)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
- Gastrointestinal Bleeding	4 (1.8%)	7 (3.8%)	0.49 (0.22-1.09)	0.52 (0.24-1.15)	0.106
Secondary Outcomes					
All-cause Mortality	13 (5.7%)	20 (10.9%)	0.56 (0.38-0.82)	0.58 (0.39-0.87)	0.008
CV Hospitalization	28 (12.3%)	31 (16.8%)	0.75 (0.52-1.08)	0.78 (0.54-1.12)	0.17
Composite Renal Outcome	18 (7.9%)	25 (13.6%)	0.61 (0.41-0.91)	0.64 (0.43-0.95)	0.026

Figure 1: Kaplan-Meier Curve for Time to First Ischemic Stroke or Systemic Embolism



Primary Safety Outcome: The incidence of major bleeding was significantly lower in the NOAC group (7 patients, 3.1%) than in the warfarin group (15 patients, 8.2%). The adjusted hazard ratio was 0.41 (95% CI 0.25-0.68; p<0.001). This benefit was driven predominantly by a marked reduction in the rate of intracranial hemorrhage (ICH), which occurred in 0.4% of the NOAC group versus 2.7% of the warfarin group (Adjusted HR 0.20, 95% CI 0.05-0.88; p=0.032). The rates of gastrointestinal bleeding were numerically lower in the NOAC group but did not reach statistical significance in the adjusted model (Adjusted HR 0.52, 95% CI 0.24-1.15; p=0.106). The Kaplan-Meier curve for major bleeding is shown in Figure 2.

Figure 2: Kaplan-Meier Curve for Time to First Major Bleeding Event



Secondary Outcomes: All-cause mortality was significantly lower in the NOAC group (5.7% vs. 10.9%; Adjusted HR 0.58, 95% CI 0.39-0.87; p=0.008). There was a trend towards fewer cardiovascular hospitalizations in the NOAC group, but this difference was not statistically significant (12.3% vs. 16.8%; Adjusted HR 0.78, 95% CI 0.54-1.12; p=0.17). Importantly, the composite renal outcome (sustained 40% eGFR decline or ESRD) occurred less frequently in the NOAC group (7.9% vs. 13.6%; Adjusted HR 0.64, 95% CI 0.43-0.95; p=0.026). Analysis of the annual rate of eGFR decline showed a slower deterioration in renal function in the NOAC group (-1.8 mL/min/1.73m² per year) compared to the warfarin group (-2.9 mL/min/1.73m² per year), p=0.018.

Subgroup and Sensitivity Analyses: The benefits of NOACs over warfarin for the primary efficacy and safety outcomes were consistent across all pre-specified subgroups, including age (<75 vs. ≥75 years), sex, CKD stage (3a/3b vs. 4), and presence of diabetes. A sensitivity analysis censoring patients at the time of switching anticoagulant therapy yielded results nearly identical to the primary intention-to-treat analysis, confirming the robustness of our findings.

DISCUSSION

The principal findings of this prospective, real-world cohort study conducted in a representative Uzbek population indicate that in patients with non-valvular AF and moderate-to-severe CKD (stages 3-4), treatment with NOACs is associated with superior clinical outcomes compared to treatment with warfarin. Specifically, we observed a 51% relative risk reduction in ischemic stroke or systemic embolism, a 59% relative risk reduction in major bleeding, and a 42% relative risk reduction in all-cause mortality among NOAC users. Furthermore, our study provides novel data suggesting a potential renoprotective effect of NOACs, as evidenced by a slower decline in eGFR and a lower incidence of the composite renal outcome.

The superior efficacy of NOACs for stroke prevention aligns with the overarching conclusions from meta-analyses of major RCTs. However, our study extends these findings to a cohort with more advanced renal impairment, a group that was underrepresented in the original trials. The pronounced benefit observed in our study may be partly explained by the suboptimal quality of warfarin management, reflected in a mean TTR of 58.4%. A low TTR is a well-established predictor of poor outcomes in warfarin-treated patients, and it is plausible that the predictable pharmacodynamics of NOACs provided a more consistent level of anticoagulation, thereby conferring a greater advantage in this specific clinical setting where achieving a stable INR is notoriously difficult.

The most striking finding of our study is the substantial reduction in major bleeding, particularly intracranial hemorrhage, with NOACs. The 80% relative risk reduction in ICH is consistent with the class effect of NOACs demonstrated in large trials and meta-analyses. This is a critical advantage, as ICH is the most feared complication of anticoagulation, carrying high rates of mortality and permanent disability. The safety profile of NOACs in our CKD population reinforces their utility in a patient group considered to be at high bleeding risk.

The observed reduction in all-cause mortality with NOACs is a composite benefit likely stemming from the combined reduction in fatal strokes, fatal bleeding events, and possibly other vascular events. The trend towards fewer cardiovascular hospitalizations, while not significant, points in the same direction. The finding of a potential renoprotective effect is intriguing and biologically plausible. Chronic warfarin use has been associated with renal vascular calcification and accelerated CKD progression, potentially via the inhibition of Matrix Gla-protein, a potent inhibitor of vascular calcification. NOACs, which do not interfere with vitamin K-dependent processes beyond coagulation, may avoid this detrimental effect. The slower rate of eGFR decline in the NOAC group supports this hypothesis and warrants further investigation in dedicated randomized studies.

Our study has several limitations. First, its observational nature means that unmeasured confounding factors could influence the results, despite our robust statistical adjustments. The non-random allocation of treatment could introduce channeling bias, where physicians preferentially prescribe NOACs to patients perceived as healthier or more adherent. However, the well-balanced baseline characteristics between our groups mitigate this concern to some extent. Second, the sample size, while substantial for a single-center study in this region, is smaller than those of large national registry analyses, limiting the power for some subgroup analyses. Third, we did not have data on drug plasma levels or adherence beyond patient self-reporting. Finally, the follow-up duration of 2 years is sufficient to detect differences in stroke and bleeding but may be too short to fully capture the long-term trajectory of renal function decline.

CONCLUSION

In a real-world clinical setting at Tashkent State Medical University, the use of NOACs in Uzbek patients with non-valvular atrial fibrillation and concurrent chronic kidney disease (stages 3-4) was associated with significantly better outcomes compared to warfarin. NOACs provided superior protection against ischemic stroke and systemic embolism while markedly reducing the risk of major bleeding, especially intracranial hemorrhage. Additionally, NOAC use was linked to a lower rate of all-cause mortality and a potential slowing of renal function decline. These findings provide strong, locally relevant evidence to support the preferential use of NOACs over warfarin for stroke prevention in this high-risk, complex patient population in Uzbekistan and similar healthcare environments. Efforts should be made to improve access to and appropriate dosing of these agents in national clinical practice.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. The study received no external funding from pharmaceutical companies or other commercial entities.

Acknowledgements

The authors gratefully acknowledge the dedicated efforts of the physicians, nurses, and administrative staff of the Department of Internal Medicine in Family Medicine No. 2, at Tashkent State Medical University and University for their invaluable support in patient care and data collection. We also extend our deepest gratitude to the patients who participated in this study.

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