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Original Article

Pharmacology Section

Clinical Outcomes of Non Vitamin K Antagonist Oral Anticoagulants versus Vitamin K Antagonist Oral Anticoagulants in Non Valvular Atrial Fibrillation Patients: A Cohort Study in a Rural Tertiary Care Hospital, Gujarat, India

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ABSTRACT

Introduction: Atrial Fibrillation (AF) is the most common arrhythmia, with an increased risk of ischaemic stroke and subsequent morbidity and mortality. Oral anticoagulants such as Vitamin K Antagonists (VKAs) and non VKA Oral Anticoagulants (NOACs) are effective stroke prevention treatments, when used properly. The CHA_2DS_2-VASc and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), and Drugs/alcohol) scores are utilised to guide clinical decision-making in stroke prevention and bleeding risk management for patients with AF. However, real-world evidence on anticoagulation strategies and their effectiveness in rural Indian populations remains limited.

Aim: To evaluate the clinical outcomes of NOACs versus VKAs in Non Valvular Atrial Fibrillation (NVAF) patients in a rural tertiary care hospital in India.

Materials and Methods: An ambidirectional cohort study, conducted from January 2014 to December 2024, evaluated baseline demographic and clinical characteristics and anticoagulation therapy (NOACs or VKAs) in NVAF patients. Clinical outcomes evaluated encompass major (example: ischaemic or haemorrhagic stroke) and minor bleeding, and all-cause mortality. Fisher's exact test was used to compare patient and clinical characteristics between the NOAC and VKA groups. The log-rank test and Cox proportional hazards analysis were used to compare bleeding risk and mortality between NOAC and VKA groups.

Results: Among the 347 patients with NVAF, those prescribed NOACs were significantly older (median age 74 vs. 58 years, p-value <0.0001) and had higher CHA2DS2-VASc scores (median 4 vs. 3, p-value <0.0001) than VKA users. NOAC users also had a higher prevalence of hypertension, diabetes, ischaemic heart disease, prior stroke and chronic kidney disease (p-value <0.0001). Major bleeding was slightly more common in NOAC patients (2.9 vs. 2.1 events per 1,000 person-months, p-value=0.40). The log-rank test showed no significant difference in major bleeding event between NOAC and VKA groups (p-value=0.10). However, all-cause mortality was higher in NOAC users (11.6 vs. 7.7 per 1,000 person-months).

Conclusion: Although NOACs are generally favoured in AF management, this study found higher mortality and bleeding risks among NOAC users in a rural Indian cohort. Older age, higher burden of co-morbidities, being underweight and higher stroke and thromboembolic risk can contribute to adverse outcomes among NOAC users. These findings highlight the need for individualised anticoagulation strategies, particularly in resource-limited settings.

Keywords: Bleeding complications, Risk stratification, Stroke prevention, Treatment outcomes

INTRODUCTION

The AF is the most common type of cardiac arrhythmia, with an estimated global prevalence between 0.5% and 5.5% across different demographic groups [1-4]. The AF prevalence varies significantly in India, ranging from 0.1-1.6% [5-6]. AF can potentially lower living standards, functional capacity and cardiac functions and related complications can lead to healthcare cost and mortality risk [7-9]. Stroke is the most serious complication of AF, accounting for almost 15% of strokes in India [10]. Nearly 60% of AF-related strokes could be prevented with appropriate oral anticoagulation therapy [11]. Long-term oral anticoagulation is essential for the management of cardiovascular conditions such as thromboembolism in AF patients, protecting mechanical heart valves, limiting complications after acute myocardial infarction and secondary prevention after venous thromboembolism [12-15].

VKAs like warfarin, acenocoumarol, phenprocoumon and fluindione have been extensively utilised [16]. However, their efficacy and safety are often compromised due to delayed onset and offset of action, necessitating prolonged hospital stays and increasing healthcare costs. These drugs also exhibit high interindividual variability, require frequent International Normalised Ratio (INR) monitoring and necessitate counselling on dietary interaction, which complicate dose adjustments and increase the risk of thromboembolism and bleeding [17,18]. This significant treatment gap has driven the development of NOACs, which selectively target coagulation factors, especially activated factor X (Xa) and thrombin [19-22]. In the past 15 years, research has focused on the convenient use, effectiveness and efficacy of NOACs for stroke prevention among patients with AF. While the global medical community is more inclined to use NOACs, its safety and efficacy benefits remain unproven without long-term follow-up [23].

There is an evidence gap, particularly from India, with respect to AF's prevalence, aetiology and treatment patterns. Standardised country-specific guidelines on the prevention and management of venous thromboembolism and NVAF in India further muddle the path for clinical decision-making, as these should rely more on factor inputs that are not directly translatable from international

recommendations [24]. The epidemiological data on NVAF and anticoagulation treatment patterns to help NOACs and VKAs in India are crucial to identify areas for intervention to improve clinical outcomes in patients.

This study aimed to assess the safety and efficacy of NOACs (dabigatran, apixaban and rivaroxaban) compared to VKAs (warfarin and acenocoumarol) among NVAF at a rural tertiary care hospital in western India during 2014 to 2024. The two objectives to achieve this aim were: 1) assessing safety outcomes in patients with NVAF treated with either NOACs or VKAs by calculating the incidence of major bleeding events (such as stroke or haemorrhage) and adverse drug reactions; and 2) to evaluate the effectiveness of NOACs versus VKAs in preventing ischaemic stroke, reducing thromboembolic events and improving overall survival in patients with NVAF.

The current research is part of a larger study that also evaluated clinical outcomes in NVAF patients using the CHA_2DS_2-VASc and HAS-BLED score risk assessments. A related paper, submitted independently, has described clinical characteristics and outcomes in NVAF patients using the above mentioned thromboembolic and bleeding risk stratification. The current manuscript focuses on assessing clinically relevant outcomes based on the comparative effectiveness of NOACs and VKAs. While both studies used the same NVAF cohort, they each offer distinct perspectives and do not interpret the same data or duplicate the findings.

MATERIALS AND METHODS

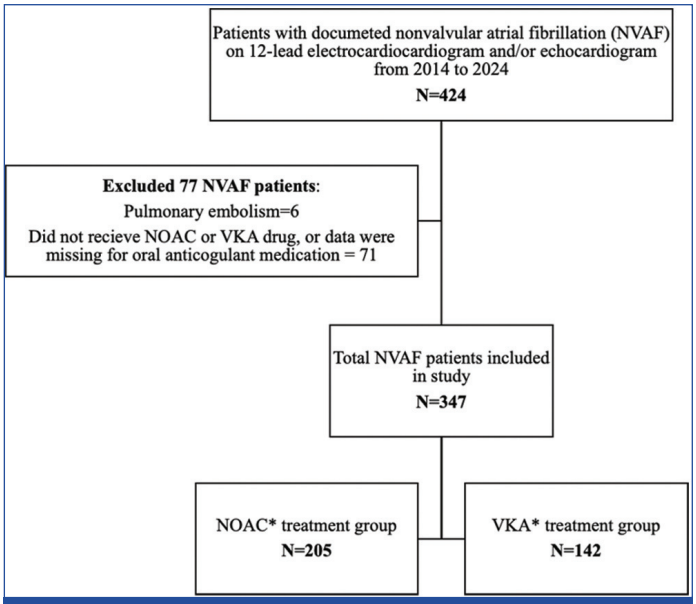
This single-centre, ambidirectional cohort study was conducted at a rural tertiary care hospital- Bhanubhai and Madhuben Patel Cardiac Centre, Shree Krishna Hospital, Bhaikaka University in Karamsad, Gujarat, India. The cohort included patients NVAF treated between January 2014 and December 2024 meeting the study criteria. On 28 September 2022, Bhaikaka University's Institutional Ethics Committee (IEC) approved the study protocol (approval number IEC/BU/140/Faculty/03/222/2022), with a waiver for consent. This study adhered to the ethical standards outlined in the Declaration of Helsinki (1975, revised in 2000). Confidentiality and anonymisation of patient data were strictly maintained throughout the study. A final approval (IEC/BU/2025/Ex.33/110/2025) from the IEC was obtained prior to submission of this manuscript for publication.

A total of 347 study participants, including both male and female patients aged ≥18 years, met the inclusion criteria.

Inclusion criteria: All participants had a documented diagnosis of NVAF and were receiving oral anticoagulation therapy — either VKAs (warfarin or acenocoumarol) or NOACs (apixaban, dabigatran, or rivaroxaban) — between 2014 and 2024 were included in the study.

Exclusion criteria: NVAF patients diagnosed with acute Pulmonary Embolism (PE) or Deep Vein Thrombosis (DVT); patients on anticoagulation therapy for indications other than NVAF, such as PE, DVT, or thrombophilia; patients with End-Stage Renal Disease (ESRD); patients with valvular AF or other co-existing arrhythmias that requiring specific management protocols; and those who had incomplete or missing medical records during study period were excluded from the study.

Sample size calculation: The sample size was calculated using WinPepi software (Version 11.65), which is designed for epidemiological statistics. To achieve a confidence level of 95% and a statistical power of 80%, allowing for a 5% margin of error and based on an expected prevalence rate of 1.6% for AF at the study hospital [6], assuming 50% loss of follow-up (attrition rate), the required sample size was determined to be 348 participants. This inflated sample size of 348 would compensate for the anticipated loss of 50% of participants [Table/Fig-1].



[Table/Fig-1]: Patient enrolment in this study.
*NOAC: Non-vitamin K Antagonist or Nove Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban
**VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin

Study Procedure

Patients meeting the study criteria were identified using hospital medical records. Baseline data, including patient demographics (age and sex) and clinical characteristics such as height, weight, co-morbidities and treatment for corresponding co-morbidities, were documented from medical records. Body Mass Index (BMI) was calculated using height and weight (as kg per square metre). Baseline data were also documented on prescribed anticoagulation therapy, categorised as NOACs (dabigatran, apixaban, rivaroxaban) or VKAs (warfarin, acenocoumarol).

Risk stratification for thromboembolism and bleeding was performed using the CHA_2DS_2-VASc and HAS-BLED scores, respectively, to guide anticoagulation decisions. The HAS-BLED score assessed the risk of major bleeding in patients receiving anticoagulation therapy. It assigns one point for each of the following risk factors: hypertension, abnormal renal/liver function, prior stroke, history of bleeding or predisposition to bleeding, labile INR, elderly (age ≥65 years), and drug/alcohol use. A score of ≥3 indicates a high risk of bleeding that requires closer monitoring or modification of anticoagulation therapy [25].

The CHA_2DS_2-VASc score was used to estimate the stroke risk in NVAF patients. This scoring system assigns points based on the presence of risk factors: congestive heart failure (1), hypertension (1), age ≥75 years (2), diabetes mellitus (1), prior stroke/TIA/thromboembolism (2), vascular disease (1), age 65-74 years (1), and sex category (female) (1). A score of ≥2 in men and ≥3 in women indicates a high risk of stroke, warranting anticoagulation therapy [26].

Follow-up and Outcomes of Interest

From 2014 to 2024, a longitudinal follow-up systematically documented clinical outcomes in patients with NVAF receiving either VKAs for anticoagulation therapy. Follow-up data on outcomes of interest were collected through comprehensive review of medical records and/or structured telephone consultations with patients at uniformly pre-determined intervals — 1, 3, 6, and 12 month post-anticoagulant therapy, and thereafter, annually until 31 December 2024.

Primary Endpoint (Outcome of Interest): Major Bleeding Events and Complications

Outcome and date of occurrence of major bleeding (haemorrhagic) events were documented as primary endpoint. Major bleeding events and complications, according to the International Society

on Thrombosis and Haemostasis (ISTH) criteria [27], included: fatal bleeding episodes; symptomatic bleeding into a critical organ; intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial and intramuscular bleeding with compartment syndrome requiring reoperation; and hospitalisation for bleeding.

Minor bleeding events included clinically relevant, non major bleeding episodes that did not lead to hospitalisation, significant haemodynamic compromise, or transfusion. These included epistaxis, haematuria, subcutaneous haematomas, gingival bleeding and ecchymosis that did not meet the ISTH criteria for major bleeding [28].

Secondary Endpoint (Outcome of Interest): Mortality

Causes and dates of death were documented as secondary endpoints. This composite endpoint included myocardial infarction, stroke (ischaemic or haemorrhagic), fatal thromboembolic complications and cardiovascular-related mortality.

Censoring and Study Completion

Patients who were lost to follow-up, discontinuation of treatment, or did not experience the event were censored at their last follow-up. The study concluded on 31 December 2024, and a total of 60 patients (17.3%) were lost to follow-up during the period from 2014 to 2024.

STATISTICAL ANALYSIS

A comprehensive statistical analysis compared patient characteristics and clinical outcomes between NVAF patients receiving NOACs and VKAs. Categorical variables were summarised as counts and percentages, with Fisher's exact test used for group comparisons. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and compared between treatment groups (NOAC vs VKA) using the Wilcoxon Rank Sum Test.

Incidence rates for all-cause mortality, major and minor bleeding events were calculated using a person-months approach with 95% Confidence Intervals (CI). Incidence rate differences (with 95% CI and Chi-square p-value) compared event rates between treatment groups. Kaplan-Meier curve was used to estimate time-to-event (survival) probabilities for bleeding events (both major and minor), and log-rank test compared these bleeding event probabilities between treatment groups.

Cox proportional hazards models estimated both unadjusted and adjusted Hazard Ratios (HRs) for bleeding events (major and minor) and all-cause mortality (including thromboembolic complications) by patient sex, with adjusted models incorporating covariates such as patient age, BMI, co-morbidities, CHA_2DS_2-VASc and HAS-BLED scores and anticoagulant regimen (including single or dual antiplatelet therapy). Schoenfeld residuals confirmed the proportional hazards assumption and clustering techniques accounted for recurrent bleeding episode within the same patient. A p-value of <0.05 was considered statistically significant and all data management and analyses were completed using Microsoft Excel (Microsoft Office Standard 2016) and statistical software SAS Viya (© 2005 SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Between 2014 and 2024, a total of 347 NVAF patients receiving either NOACs or VKAs were included in the study. The NOAC group had a slight male predominance, with 109 men (53.2%), whereas women comprised the majority in the VKA group (56.3%), though this difference was not statistically significant (p-value=0.10). Patients on NOACs were significantly older (median: 74 years, Interquartile Range (IQR): 16) than those on VKAs (median: 58 years, IQR: 21) (p-value <0.0001). More than half of the patients, 191 (55%), were classified as underweight (BMI <18.5 kg/m^2), with BMI distribution differing significantly between treatment groups (p-value=0.001) [Table/Fig-2].

Demographic and clinical characteristics	Total (N=347)	Treatment group		p-value†
		NOAC (n=205)	VKA (n=142)	
Sex, n (%)				
Men	171 (49.3)	109 (53.2)	62 (43.7)	0.10
Women	176 (50.7)	96 (46.8)	80 (56.3)	
Age (years)				
Median (interquartile range)	69 (21.5)	74 (16)	58 (21)	<0.0001‡
Minimum-maximum	24-94	25-94	24-85	
Body Mass Index (BMI), n (%)				
Underweight (less 18.5)	191 (55.0)	111 (54.2)	80 (56.3)	0.001
Normal (18.5 to less 23)	125 (36.0)	74 (36.1)	51 (35.9)	
Overweight (23 to less than 25)	14 (4.0)	7 (3.4)	7 (4.9)	
Obese (30 and higher)	17 (4.9)	13 (6.3)	4 (2.8)	
Co-morbidities§, n (%)				
Hypertension	200 (57.6)	147 (71.7)	53 (37.3)	<0.0001
Diabetes mellitus	101 (29.1)	76 (37.1)	25 (17.6)	<0.0001
Ischaemic heart disease	68 (19.6)	52 (25.4)	16 (11.3)	<0.0001
Rheumatic heart disease	70 (20.2)	9 (4.4)	61 (43.0)	<0.0001
Congestive heart failure	20 (5.8)	10 (4.9)	10 (7.0)	0.02
Prior ischaemic stroke/transient ischaemic attack	95 (27.4)	70 (34.2)	25 (17.6)	0.001
Prior intracranial haemorrhage	3 (0.9)	3 (1.5)	0	0.27
Venous thromboembolism	2 (0.6)	2 (1.0)	0	0.05
Chronic kidney disease	29 (8.4)	25 (12.2)	4 (2.8)	0.0001
Liver failure	1 (0.3)	1 (0.5)	0	0.07
Cancer	8 (2.3)	5 (2.4)	3 (2.1)	0.04
$CHA2_2$- DS_2- VASc score				
Median (interquartile range)	3 (1)	4 (2)	3 (1)	<0.0001‡
Minimum-Maximum	2-9	2-9	2-5	
HAS BLED score				
Median (interquartile range)	2 (1)	2 (1)	2 (3)	0.53‡
Minimum-Maximum	0-8	0-8	1-5	

[Table/Fig-2]: Oral anticoagulant treatment group by patient demographic and clinical characteristics.
*NOAC: Non-vitamin K Antagonist or Novel Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban; **VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin; †Fisher's-exact test p-value. ‡Wilcoxon Sum Rank test p-value; §Co-morbidities are not mutually exclusive. A patient can have more than one co-existing health condition

Risk stratification showed that the NOAC group had higher CHA_2DS_2-VASc scores (median: 4, IQR: 2) than the VKA group (median: 3, IQR: 1) (p-value <0.0001), whereas HAS-BLED scores were similar across groups (p-value=0.53), indicating comparable bleeding risks. Co-morbidities were significantly more prevalent in the NOAC group, including hypertension, diabetes, ischaemic heart disease, prior stroke/TIA, and chronic kidney disease (all p-value <0.001). Conversely, the VKA group had a higher prevalence of rheumatic heart disease (p-value <0.0001) and congestive heart failure (p-value=0.02). These findings suggest that NOACs were prescribed to older patients with higher thromboembolic risk, while VKAs remained the preferred option for conditions like rheumatic heart disease [Table/Fig-2].

In this study, the most prescribed concomitant medications among NVAF patients were beta-blockers 243 (70%), proton pump inhibitors 192 (55.3%), and statins 189 (54.5%). Statin use was significantly higher in the NOAC group (p-value <0.0001), along with antidiabetic agents (p-value=0.03), clopidogrel (p-value=0.01), and angiotensin receptor blockers (p-value=0.02). Conversely, the VKA group had higher prevalence of digoxin (p-value=0.0003) and diuretics (p-value=0.0007). Given that patients in the VKA group had a higher prevalence of congestive heart failure, they required specific pharmacological management. Similarly, NOAC-treated patients commonly received medications targeting metabolic and

cardiovascular comorbidities such as hypertension, diabetes and ischaemic heart disease [Table/Fig-3].

Other medications§, n (%)	Total (N=347)	Treatment group		p-value‡
		NOAC* (n=205)	VKA** (n=142)	
Angiotensin-Converting Enzyme (ACE) inhibitors	36 (10.4)	16 (7.8)	20 (14.1)	0.07
Angiotensin receptor blockers	44 (12.7)	33 (16.1)	11 (7.8)	0.02
Acetyl Salicylic Acid (ASA) drug	179 (51.6)	108 (52.7)	71 (50.0)	0.66
Clopidogrel	66 (19.0)	48 (23.4)	18 (12.7)	0.01
Proton pump inhibitors	192 (55.3)	122 (59.5)	70 (49.3)	0.06
Alpha blockers	36 (10.4)	27 (13.2)	9 (6.3)	0.05
Beta blockers	243 (70.0)	146 (71.2)	97 (68.3)	0.63
Calcium channel blockers	89 (25.6)	61 (29.8)	28 (19.7)	0.05
Amiodarone	56 (16.1)	37 (18.1)	19 (13.4)	0.30
Digoxin	80 (23.1)	33 (16.1)	47 (33.1)	0.0003
Diuretic	182 (52.4)	92 (44.9)	90 (63.4)	0.0007
Statin	189 (54.5)	132 (64.4)	57 (40.1)	<0.0001
Antidiabetic	71 (20.5)	50 (24.4)	21 (14.8)	0.03

[Table/Fig-3]: Non Valvular Atrial Fibrillation (NVAF) patients receiving other medications for co-existing health conditions by oral anticoagulant treatment group. *NOAC: Non-vitamin K Antagonist Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban; **VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin; †p-value: Fishers-exact test; p<0.05 denotes statistically significant; §Other medications are not mutually exclusive. A patient can be prescribed more than one medication for co-mbordities

Sixty patients (17.3%) with NVAF experienced adverse events, with a significantly higher incidence in the NOAC group compared to the VKA group (p-value <0.0001). Major bleeding events included ischaemic stroke 25 (7.2%), haemorrhagic stroke 5 (1.4%), and combined subdural or epidural bleeding 4 (1.2%) [Table/Fig-4]. These findings underscore the need for stringent monitoring of anticoagulation therapy to balance thromboembolic prevention with bleeding risk in NVAF patients.

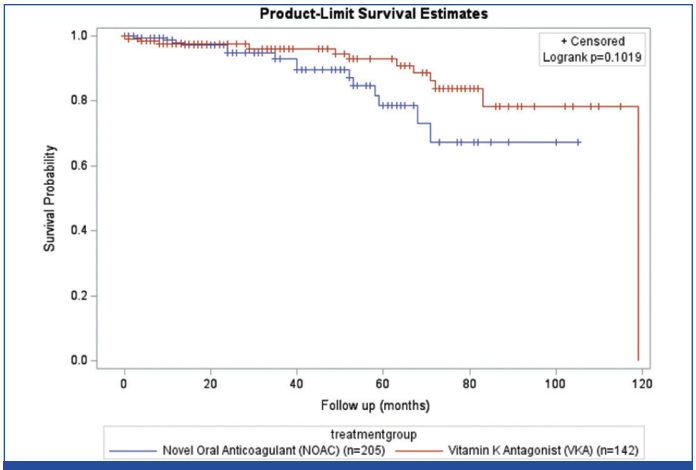
Clinical outcomes, n (%)	Total N=347 Count (%)	Treatment group NOAC* (n=205) Count (%)	Treatment group VKA** (n=142) Count (%)	p-value†
Any adverse event	60 (17.3)	38 (18.5)	22 (15.5)	<0.0001
Any hospitalisations	181 (52.2)	81 (39.5)	100 (70.4)	<0.0001
Major bleeding				
Haemorrhagic stroke	5 (1.4)	3 (1.5)	2 (1.4)	<0.0001
Ischaemic stroke	25 (7.2)	14 (6.8)	11 (7.8)	0.0003
Subdural/epidural bleeding	4 (1.2)	3 (1.5)	1 (0.7)	<0.0001
Minor bleeding				
Gastrointestinal bleeding	8 (2.3)	3 (1.5)	5 (3.5)	<0.0001
Anal fissure bleeding	2 (0.6)	1 (0.5)	1 (0.7)	<0.0001
Contusion	21 (6.1)	17 (8.3)	4 (2.8)	<0.0001
Easy bruising	3 (0.9)	2 (1.0)	1 (0.7)	<0.0001
Gingival bleeding	1 (0.3)	0	1 (0.7)	<0.0001
Haematuria	3 (0.9)	2 (1.0)	1 (0.7)	0.15
Other minor bleeding	47 (13.5)	27 (13.2)	20 (14.1)	0.87
Survival status at the end of study				
Death	104 (30.0)	60 (29.3)	44 (31.0)	0.0013
Alive	183 (52.7)	116 (56.6)	67 (47.2)	
Loss to follow-up	60 (17.3)	29 (14.1)	31 (21.8)	

[Table/Fig-4]: Clinical outcomes in Non Valvular Atrial Fibrillation (NVAF) patients by oral anticoagulant treatment group. *NOAC: Non-vitamin K Antagonist Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban; **VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin; †Fisher's-exact test p-value; p<0.05 denotes statistically significant; ‡Major bleeding event and minor bleeding events are not mutually exclusive. The same patient can have more than one major or minor bleeding event

During 2014-2024 (11-year study period), there were 104 deaths (30%) and 54 bleeding events (27 major and 27 minor) among NVAF patients. Total all-cause mortality was higher in the NOAC group compared to VKA group (p-value=0.04). The total major bleeding events, including ischaemic and haemorrhagic strokes, occurred at a slightly higher rate in the NOAC group, although the difference was not statistically significant (p-value=0.40) [Table/Fig-5]. Kaplan-Meier analysis indicated no significant difference in the long-term bleeding risk between NOAC and VKA therapies (p-value=0.10), suggesting comparable safety profiles for both anticoagulant strategies [Table/Fig-6].

Type of event	Treatment group NOAC* Events	NOAC* Rate† (95% CI)	VKA** Events	VKA** Rate† (95% CI)	IRD§ (95% CI)	p-value‖
Men						
All-cause mortality	31	12.2 (8.6-17.3)	21	8.9 (5.8-13.6)	3.3 (-2.4-9.1)	0.26
Major bleeding	7	2.8 (1.3-5.8)	2	0.8 (0.2-3.4)‡	1.9 (-0.5-4.3)	0.12
Minor bleeding	8	3.1 (1.6-6.3)	3	1.3 (0.4-3.9)‡	1.9 (-0.8-4.5)	0.16
Women						
All-cause mortality	29	11.0 (7.6-15.8)	23	6.9 (4.6-10.3)	4.1 (-0.6-8.8)	0.09
Major bleeding	8	3.0 (1.5-6.0)	10	3.0 (1.6-5.5)	0.04 (-2.7-2.8)	0.98
Minor bleeding	12	4.5 (2.6-8.0)	4	1.2 (0.4-3.2)‡	3.3 (0.7-6.0)	0.01
Total						
All-cause mortality	60	11.6 (9.0 -14.9)	44	7.7 (5.7-10.3)	3.9 (0.2-7.5)	0.04
Major bleeding	15	2.9 (1.7-4.8)	12	2.1 (1.2-3.7)	0.8 (-1.1-2.7)	0.40
Minor bleeding	20	3.9 (2.5-6.0)	7	1.2 (0.6-2.6)‡	2.6 *0.8-4.5)	0.01

[Table/Fig-5]: Event (incident) rates by treatment group. *NOAC: Non-vitamin K Antagonist Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban; **VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin; †Rate per 1,000 person-months; ‡Relative standard error is 30% or more, indicating this rate is unreliable and should be interpreted be caution; §IRD: Incidence rate difference=Rate for NOAC-Rate for VKA; ‖Chi-square p-value; Note: Major bleeding includes including ischaemic stroke, haemorrhagic stroke, subdural or epidural haemorrhagic stroke



[Table/Fig-6]: Probabilities for all bleeding event (major and minor) by treatment group: Kaplan-Meier curve of time to event at follow-up.

After adjusting for key covariates—including age, BMI, HAS-BLED score, co-morbidities and antiplatelet use—the risk of major bleeding among men receiving NOACs was 14.47 times (95% CI: 2.93-71.42) more likely than that of VKA users, at a CHA_2DS_2-VASc score of 3.2 or higher (p-value <0.0001). In contrast, none of these independent variables significantly influenced major bleeding risk in women [Table/Fig-7].

Type of event	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Men				
All-cause mortality	1.15 (0.61-2.18)	0.66	0.67 (0.31-1.48)[a]	0.32
Major bleeding	12.46 (1.76-88.13)	0.01	14.47 (2.93-71.42)[b]	<0.0001
Minor bleeding	3.34 (0.84-13.26)	0.09	1.18 (0.17-19.04)	0.87
Women				
All-cause mortality	1.31 (0.73-2.36)	0.37	0.75 (0.38-1.46)[a]	0.40
Major bleeding	1.13 (0.45-2.85)	0.80	-[c]	-
Minor bleeding	5.58 (1.87-16.65)	0.002	5.96 (0.53-67.54)	0.15

[Table/Fig-7]: Unadjusted and adjusted Hazard Ratios (HR) for NOAC* versus VKA** by patient sex.
*NOAC: Non-vitamin K Antagonist Oral Anticoagulants in this study include Dabigatran, Rivaroxaban and Apixaban; **VKA: Vitamin K Antagonists in this study include Acitrom (coumarin derivative) and Warfarin. VKA is reference group for Cox Proportional Hazard analysis; [a]Adjusted for age; [b]Hazard ratio for major bleeding after controlling for patient age, BMI, HAS BLED score, co-morbidities such as hypertension, diabetes, prior ischaemic stroke, chronic kidney disease, ischaemic heart disease, rheumatic heart disease, venous thromboembolism, and use of other antiplatelet (clopidogrel, acetylsalicylic acid), at $CHA2_2$- DS_2- VASc Score of 3.2; [c]In women, there was no individual effect of treatment, patient age, BMI, HAS BLED score, co-morbidities such as hypertension, diabetes, prior ischaemic stroke, chronic kidney disease, ischaemic heart disease, rheumatic heart disease, venous thromboembolism, and use of other antiplatelet (clopidogrel, acetylsalicylic acid) and $CHA2_2$-DS_2- VASc score on all-cause mortality; Note: Major bleeding includes including ischaemic stroke, haemorrhagic stroke, subdural or epidural haemorrhagic

DISCUSSION

This study highlights clinical outcomes in a rural Indian cohort with NVAF receiving oral anticoagulation therapy- NOACs or VKAs. Patients on NOACs were primarily older, underweight had cardiometabolic co-morbidities and exhibited higher rates of bleeding complications and all-cause mortality compared to those on VKAs. Major clinical trials, systematic reviews and meta-analyses have established NOACs as safer alternatives to VKAs, particularly regarding major bleeding risks [29-32]. However, the current study findings favour VKAs in a rural Indian population. Several key factors contribute to this result, including differences in patient demographics, co-morbidities, prescribing patterns and healthcare infrastructure.

A national claims data analysis over a 10-year period by Engelbertz C et al., in Germany investigated the comparative safety and efficacy of NOACs and VKAs in patients with atrial fibrillation, finding that NOACs—apixaban, edoxaban and rivaroxaban—were associated with higher mortality compared to VKAs, whereas dabigatran showed no significant difference [33]. This was similar to current study findings, indicating VKAs may still be a viable option in specific high-risk populations, particularly where INR monitoring is well managed. The findings of Engelbertz C et al., challenge the general assumption of NOACs' superiority and call for randomised trials to further assess these observations [33].

In contrast, an analysis by Steinberg BA et al., of the Outcomes Registry for Better Informed Treatment of AF II (ORBIT-AF II) registry data showed comparable major bleeding rates between NOACs and warfarin (3.3 vs. 3.5 events per 100 patient-years) [34]. Rates of intracranial haemorrhage and gastrointestinal bleeding in ORBIT-AF II were not significantly different between NOACs and warfarin. Given the ORBIT-AF II included a broader community-based population in their study, they may have had a lower-risk cohort with more controlled anticoagulation management [34]. Similarly, a French nationwide cohort found no significant difference in bleeding or thromboembolic events for dabigatran (one of the NOAC) versus VKA users, and comparable bleeding risk in Rivaroxaban (one of the NOAC) user versus patients on VKA [35].

Studies have shown benefits of NOACs in reducing major bleeding risk and mortality in obese individuals (BMI ≥30 kg/m²) compared to VKA such as warfarin [36-39]. However, there is limited evidence on risk-benefit profile of different NOACs in underweight (BMI ≤18.5 kg/m²) NVAF patients [36]. Shinohara M et al., indicated that low body weight was a significant predictor of bleeding complications in elderly patients with AF receiving anticoagulation therapy [40]. In the present study, a majority of NOAC users were underweight (BMI <18.5) compared to VKA users. Since NOAC are prescribed in fixed doses, it is possible that underweight patients may be receiving higher dose per body weight compared to those in morbid obese category. Standard dosing in underweight individuals may lead to excessive anticoagulation and increased bleeding risk. These findings reinforce the necessity of weight-based dose adjustments and close monitoring to optimise safety in anticoagulated underweight NVAF patients.

Older age is a known risk factor for bleeding-related complications in NVAF patients, which was prevalent among NOAC users (median age 74 years) in the present study. This was consistent with the FRAIL-AF trial (ESC Congress 2023), where frail elderly patients (mean age 83 years) experienced a higher rate (HR=1.69) of bleeding complications when switched from VKAs to NOACs [41]. Both the present study and the FRAIL-AF trial observed no significant reduction in thromboembolic event with NOACs despite the higher bleeding risk. This underscores the need for individualised anticoagulation strategies in older NVAF patients.

In addition to older age, Šinigoj P et al., reported that a prior history of stroke or thromboembolic events was a strong predictor of major bleeding in NOAC users [42]. Presence of other co-morbidities, such as chronic kidney disease, can also play a role in bleeding risk. NOACs are primarily eliminated through the kidneys, which may increase bleeding risk in patients with renal impairment due to the possible drug accumulation [23]. Comparatively, VKAs are primarily metabolised via hepatic clearance and are therefore less dependent on renal mechanisms and potentially at lower risk of major bleeding event [43].

NOACs are widely used for anticoagulation in AF. Their safety profile may, however, differ in high-risk populations such as the elderly, underweight, those with cardiometabolic or chronic kidney disease, or patients on dual antiplatelet therapy. While NOACs can be beneficial in certain populations, clinicians should carefully consider their use in older adults after weighing against bleeding risks. In such cases, VKAs still be the safer and more appropriate option. Frequent INR monitoring can help mitigate the risk of bleeding. Future studies should evaluate long-term INR control in Indian settings and verify whether dose adjustments or specific NOAC choices, such as apixaban versus dabigatran, can influence safety outcomes.

The strengths of this study include real-world data and comprehensive documentation and assessment of baseline and follow-up data for patient demographics, clinical characteristics, treatment strategies, and clinical outcomes.

Limitation(s)

An ambidirectional cohort study design is subject to inherent biases, including confounding and selection bias. Retrospective nature of the data makes it impractical to account for all confounding variables, making it difficult to establish some causal relationships. Information bias from potential differential misclassification may exist, as clinicians likely prescribed NOACs to older and high-risk patients, which could, in turn, increase their bleeding events. The study's single-centre design and small sample size limit generalisability. The absence of long-term INR monitoring data for VKA users prevented a direct assessment of its impact. Future studies should focus on INR variability and the applicability of NOACs in Indian populations. The safety of NOACs in high-risk subgroups, such as the elderly,

underweight patients, and those with chronic conditions, requires further investigation. Additionally, the characteristics of the rural population—such as patient compliance, average diet, and genetic variations regarding drug metabolism—may diverge from those tested in bigger multicentre trials.

CONCLUSION(S)

This study aimed to compare the clinical outcomes of NOACs and VKAs in NVAF patients, assessing their safety and efficacy profiles. While NOACs were associated with a slightly higher risk of major bleeding in men, their overall bleeding risk was comparable to that of VKAs. NOACs offer advantages in stroke prevention; however, clinicians should assess bleeding risks, especially in high-risk subgroups, to ensure personalised and safe anticoagulation management.

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