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Clinical characteristics, adherence to anticoagulation therapy and prognosis in patients with atrial fibrillation: a real-life study

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Abstract

Background Atrial fibrillation (AF) is a prevalent tachyarrhythmia, and a comprehensive understanding of its clinical features is essential for optimizing therapeutic management. However, the unregulated use of anticoagulants in AF remains a concern, as their efficacy and safety profiles are not yet fully understood.

Methods Data from AF patients were collected in 2013, 2018, and 2023. First, cross-sectional data on AF patients were gathered during each period to longitudinally evaluate long-term trends in AF characteristics and the progression of anticoagulation therapy. Additionally, predictors of non-regulated dosing of oral anticoagulants (OAC) were analyzed. Second, patients with non-valvular atrial fibrillation (NVAF) were prospectively followed for 24 and 60 months with different NOAC doses to assess the risk of clinical outcome events and to analyze independent risk factors for clinical outcomes.

Results This study included 2825 AF patients, with 394 patients undergoing longitudinal follow-up. Paroxysmal AF (49.70%) and non-valvular atrial fibrillation (NVAF) (86.30%) were the most prevalent forms with advanced age being a prominent characteristic. Independent predictors of unregulated NOAC use included age, renal insufficiency, BMI, diabetes, hypertension, and bleeding risk. At the 24-month follow-up, patients who received overdosed NOAC exhibited a higher mortality rate compared to those who were inappropriately underdosed (18.75 vs.10.92 events/patient-year, $P=0.017$). At the 60-month follow-up, both all-cause mortality (10.00 vs. 6.49 events per patient-year, $P=0.019$; 10.00 vs. 6.21 events per patient-year, $P=0.005$) and the composite endpoint event rate (12.50 vs. 9.61 events per patient-year, $P=0.017$; 12.50 vs. 9.32 events per patient-year, $P=0.013$) were significantly higher in the overdosing group compared to standard and underdosing groups. Age and anemia were identified as risk factors for all-cause mortality, while renal insufficiency was associated with an increased risk of composite endpoint events.

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Conclusion AF remains a major disease burden, especially in elderly patients. For Asians, NOAC underdosing was still effective in preventing stroke, but its efficacy and safety need to be further validated through larger-scale clinical trials. Meanwhile, overdosing of NOAC should be avoided.

Clinical trial number Not applicable.

Keywords Atrial fibrillation, Clinical features, Oral anticoagulants, Inappropriate prescribing, Prognosis

Introduction

Atrial fibrillation (AF) is a common clinical arrhythmia, and its prevalence has significantly contributed to the global burden of disease, driven by population aging and the increasing prevalence of clinical risk factors [1]. Over the past two decades, several epidemiological studies on AF have been conducted in China at different time points, reporting a prevalence ranging from 0.2–2.3% [2–6]. Although these studies varied in terms of population characteristics, regional scope, and methodology, they consistently demonstrated an upward trend in AF prevalence, reflecting the impact of industrialization both nationally and locally. Therefore, regular statistics on AF prevalence and a comprehensive understanding of its clinical features are essential for optimizing patient treatment and overall disease management.

AF increases the risk of ischemic stroke (IS) fivefold [7]. This increased risk is not only attributed to the arrhythmia itself but also to the underlying structural and functional changes in the atria, collectively referred to as atrial myopathy. Atrial myopathy is characterized by atrial fibrosis, inflammation, and endothelial dysfunction, which promote thrombus formation and embolic events, even in the absence of AF [8]. These pathological changes create a prothrombotic state, further exacerbating the risk of stroke in AF patients. Additionally, emerging evidence suggests that genetic factors play a significant role in the pathogenesis of AF. Variants in genes such as PITX2 and KCNN3 have been associated with increased susceptibility to AF, potentially through mechanisms involving atrial electrical remodeling and structural changes [9]. Understanding the interplay between atrial myopathy, genetic predisposition, and AF may provide new insights into stroke prevention strategies.

Anticoagulation therapy remains the cornerstone for preventing IS and systemic thromboembolism in AF patients. Oral anticoagulants (OAC), including traditional warfarin and non-vitamin K antagonist oral anticoagulants (NOAC), are the mainstay of treatment. OAC significantly reduce the risk of IS and thromboembolism in AF patients, and the widespread adoption of NOAC has expanded therapeutic options while improving the safety profile regarding bleeding complications [10–13]. According to the 2024 ESC Guidelines for the management of AF, a personalized, evidence-based approach is crucial for optimizing anticoagulation therapy. The guidelines emphasize the importance of individualized risk assessment, including considerations of stroke risk, bleeding risk, and patient preferences, to guide the choice of anticoagulant and dosage [14].

Despite the availability of diverse anticoagulation options, the quality of anticoagulation in clinical practice varies significantly, often involving inappropriate prescribing or irregular dosing of anticoagulants [15, 16]. Inappropriate use of anticoagulants may bring about serious side effects such as bleeding, stroke and even death. With the increasing use of NOAC, several studies have preliminarily explore the factors associated with inappropriate NOAC use and its impact on patient outcomes [17–23]. However, due to the lack of relevant studies and the influence of different populations and regions on treatment choices, the results of these studies are often inconsistent. As a result, the efficacy and safety of irregular prescribing and non-recommended dosages of NOAC in AF patients remain unclear. Clinicians face the ongoing challenge of accurately assessing the clinical characteristics of AF patients and prescribing NOAC appropriately.

This study aims to summarize the clinical characteristics of AF and evaluate the standardized application of OAC by dynamically collecting baseline data and treatment information from AF patients across different time periods. Additionally, it will follow up on the prognosis of patients receiving different NOAC dosages and explore the factors influencing irregular NOAC prescriptions and their impact on outcomes in non-valvular atrial fibrillation (NVAF) patients. The findings are expected to provide real-world evidence to support more standardized management and treatment of AF.

Materials and methods

Study design

This study adopts a single-center design integrating cross-sectional and prospective research methodologies. The study protocol is structured as follows: (1) Over a 5-year interval, inpatient cases diagnosed with AF in 2013, 2018, and 2023 were systematically extracted from the electronic medical record system based on predefined inclusion and exclusion criteria. (2) The data analysis was divided into two stages:

Phase 1: Cross-sectional Study: A cross-sectional analysis was performed on a cohort of 2,825 AF patients

to delineate the clinical characteristics and treatment patterns across different years. This phase aimed to dynamically evaluate the evolving disease profiles and therapeutic trends in AF patients while identifying independent factors associated with the use of non-standard doses of NOAC in NVAF patients undergoing anticoagulation therapy.

Phase 2: Prospective Follow-up Study: A prospective follow-up study was conducted on 394 NVAF patients treated with varying doses of NOAC. Initially, propensity score matching (PSM) was employed to balance baseline characteristics among patients receiving different NOAC doses, enhancing intergroup comparability. Subsequently, NVAF patients prescribed standard, under-, or over-dosed NOAC regimens were longitudinally followed for 24 and 60 months to assess the efficacy and safety of different NOAC doses (dabigatran and rivaroxaban) [10, 12]. Finally, independent risk factors influencing NVAF patient prognosis were further investigated. Follow-up continued until the occurrence of the first predefined endpoint event or the conclusion of the study (Fig. 1).

Data collection and outcome

Study population

Patients discharged with a diagnosis of atrial fibrillation between 01/01/2013–31/12/2013, 01/01/2018–31/12/2018 and 01/01/2023–31/12/2023 were included in the study. AF diagnoses were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes (Table S1). Definitions of AF types were based on the most recent guideline definitions for the corresponding periods [24–27].

Inclusion criteria: (1) AF rhythms recorded by electrocardiogram (ECG) or 24-hour ambulatory electrocardiogram, or previous medical records with clear ECG findings and AF diagnosis. For patients with recurrent AF hospitalizations within one year, only the last hospitalization was recorded. (2) Discharge date in 2013, 2018, or 2023.

Exclusion criteria: (1) Death or unstable vital signs during hospitalization (2) Incomplete or inadequate medical records. (3) Inability to cooperate in completing this study due to various reasons.

Data collection

Baseline data of patients with AF: type of AF, gender, age, smoking, body mass index (BMI), concomitant diseases, CHA2DS2-VASc score, HAS-BLED score, stroke and bleeding events before and after anticoagulation, history of current medication use (type and dose), cardiac ultrasound, and laboratory parameters (liver, kidney, and coagulation).

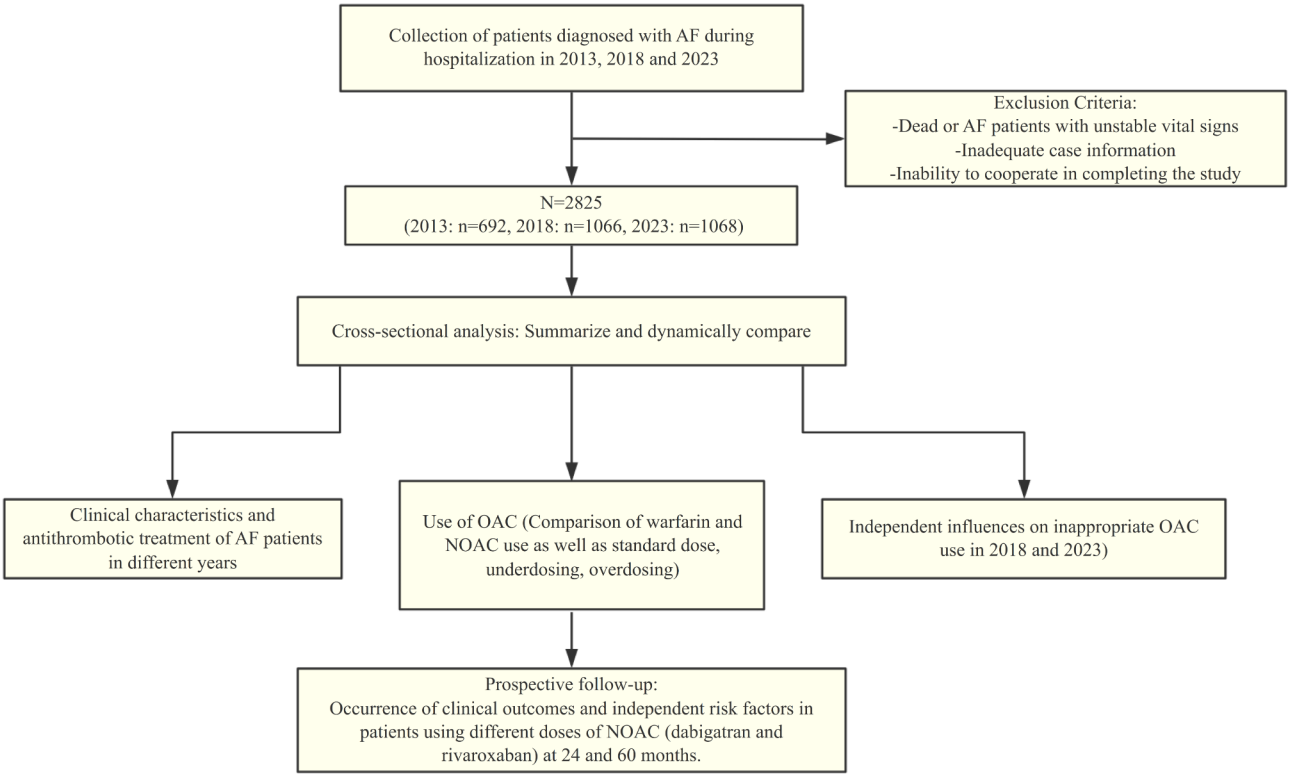

Fig. 1 The process of cross-sectional analysis and prospective follow-up of AF patients in this study. AF: Atrial fibrillation, OAC: Oral anticoagulant, NOAC: Non-vitamin K antagonist oral anticoagulant

Definition of OAC prescribing dose: The OAC prescribing dose was categorized according to the European Medicines Agency (EMA)-approved dosage and dose-adjustment criteria [28](Table S2), the International Normalized Ratio (INR) levels of warfarin users, and the dosage and administration section of the NOAC dosage form.

Standard dose: Compliance with EMA and drug label criteria for indication and dosage, or maintenance of INR levels within the target range of 2–3 for warfarin users [27].

Underdosing: Failure to meet EMA or drug label criteria for dose reduction, or INR < 2.

Overdosing: Failure to reduce the dose when indicated by EMA or drug label criteria, or INR > 3.

Use at low risk of stroke: Prescription of anticoagulants to NVAF patients at low stroke risk (CHA2DS2-VASc score: <2 in males and <3 in females).

Potential influences on NOAC prescribed dosage

Age, sex, weight, BMI, concomitant diseases (coronary artery disease, heart failure, diabetes mellitus, hypertension, renal insufficiency, hyperthyroidism, anemia, cardiomyopathies (dilated cardiomyopathies and hypertrophic cardiomyopathies), chronic obstructive pulmonary disease, peripheral arterial disease, post-PCI, the occurrence of IS or bleeding before anticoagulation, CHA2DS2-VASc score of high risk (≥ 2 points in males and ≥ 3 points in females), and HAS-BLED score of high risk (≥ 3 points).ICD code diagnoses for concomitant diseases are detailed in Table S1.

Follow-up outcome definitions.

(1) All-cause mortality (2) Ischemic stroke/systemic embolism (IS/SE) (3) Bleeding (intracranial or another site) (4) Composite endpoint in which the above events occur (Table S1).

Statistical analyses

Continuous variables were expressed as mean ± standard deviation if they were normally distributed, and comparisons between groups were performed using samples t-test or one-way analysis of variance (ANOVA). For non-normally distributed data, variables were expressed as the interquartile range (P25, P75), and comparisons were made using the Mann-Whitney U test. Categorical variables were presented as frequencies (%), and group comparisons were conducted using the Pearson $\chi 2$ test or Fisher's exact test, as appropriate.

Potential factors showing statistically significant differences in group comparisons of different NOAC doses were further analyzed. A multivariate logistic regression model was constructed to identify independent predictors of inappropriate NOAC dosing, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). Survival analysis was performed using the Kaplan-Meier method to evaluate the risk of outcomes associated with different NOAC doses, and differences in survival curves between groups were assessed using the log-rank test. Multivariate Cox proportional hazards regression was used to analyze independent risk factors for outcome events, with results reported as hazard ratios (HR) and 95% CIs. All statistical tests were two-sided, with a significance level set at $P < 0.05$. Data analysis and visualization were performed using SPSS 26.0, GraphPad Prism 9.0.0, OriginPro 2024, and R 4.4.1.

Results

A total of 2825 AF patients were included in this study (2013: 691, 2018: 1066, 2023: 1068), with the NVAF percentage of 86.3% and the valvular AF percentage of 13.7%. The median follow-up durations were 24 and 60 months. Among 394 AF patients using dabigatran and rivaroxaban in 2018,32 were lost to follow-up, resulting in survival outcome data for 362 patients.

Clinical characteristics and treatment status of AF in different years

The baseline characteristics of AF patients in 2013, 2018 and 2023 are summarized in Table 1. NVAF and paroxysmal AF were the predominant types across all periods ($P < 0.05$). Females constituted 52.7% of the study population, with a slightly higher proportion than males in all years (> 50%). The mean age of AF patients increased yearly ($P < 0.05$). The top three concomitant diseases of AF were heart failure, coronary atherosclerotic heart disease, and hypertension, of which heart failure was the most common concomitant disease (> 60%). The mean CHA2DS2-VASc score was ≥ 3 in AF patients in all years, and 82.4% of AF patients were at high risk of stroke (CHA2DS2-VASc score: ≥2 in males and ≥ 3 in females). The proportion of high risk of stroke in 2023 was higher than that in 2013 and 2018. In addition, 50.1% of AF patients were at high bleeding risk (HAS-BLED score: ≥3), with the HAS-BLED score and the proportion of patients with high bleeding risk increased ($P < 0.05$).

In this study, 55.0% of AF patients received anticoagulation therapy, 13.4% received anticoagulation combined with antiplatelet therapy, 14.8% received antiplatelet therapy alone 6.6% received herbal or transient anticoagulation, and 10.2% did not undergo any antithrombotic therapy. Compared with 2013, anticoagulation became the primary antithrombotic strategy for patients with AF in 2018 and 2023, with a significant increase in anticoagulation prescription rates and a substantial proportion of patients receiving antiplatelet therapy alone ($P < 0.05$) (Fig. 2). Among AF patients at low risk of stroke, anticoagulation remained the primary antithrombotic strategy, with prescription rates increasing annually. However, the

Table 1 Baseline characteristics of AF patients

	2013 *n*=691	2018 *n*=1066	2023 *n*=1068	Total *n*=2825	*P*-value
Age, y	70.93±11.19	72.44±11.44	72.10±12.15		0.026
Female, n(%)	391(56.6%)	548(51.4%)	550(51.5%)	1489(52.7%)	0.063
Paroxysmal atrial fibrillation, n(%)	105(15.2%)	254(23.8%)	166(15.5%)	1404(49.7%)	0.000
Non-valvular AF, n(%)	579(83.8%)	914(85.7%)	945(88.5%)	2438(86.3%)	0.016
CHA2DAS2-VASc	3.72±1.90	3.68±1.86	3.95±1.86		0.000
CHA2DAS2-VASc, n(%) (Male:≥2,Female:≥3),	556(80.5%)	854(80.1%)	917(85.9%)	2327(82.4%)	0.001
HAS-BLED	1.77±0.93	2.77±1.12	2.91±1.07		0.000
HAS-BLED≥3	136(19.7%)	585(54.9%)	695(65.1%)	1416(50.1%)	0.000
Comorbidities, n (%)					
Heart faliure	422(61.1%)	688(64.5%)	686(64.2%)	1796(63.6%)	0.287
Coronary atherosclerotic heart disease	260(37.6%)	488(45.8%)	470(44.0%)	1218(43.1%)	0.003
Hypertension	421(60.9%)	521(48.9%)	602(56.4%)	1544(54.7%)	0.000
Diabetes	159(23.0%)	259(24.3%)	348(32.6%)	766(27.1%)	0.000
Post-PCI	26(3.8%)	110(10.3%)	150(14.0%)	286(10.1%)	0.000
Previous stroke	151(21.9%)	131(12.3%)	104(9.7%)	386(13.7%)	0.000
Antithrombotic strategies, n(%)					
Anticoagulation	212(30.7%)	569(53.4%)	773(72.4%)	1554(55.0%)	0.000
Antiplatelet therapy	311(45.0%)	53(5.0%)	54(5.1%)	418(14.8%)	
Anticoagulation combined with antiplatelet therapy	11(1.6%)	236(22.1%)	132(12.4%)	379(13.4%)	
Other	15(2.2%)	164(15.4%)	8(0.7%)	187(6.6%)	
No antithrombotic therapy	142(20.5%)	44(4.1%)	101(9.5%)	287(10.2%)	
Low risk of stroke(Male:<2,Female:<3)					
Anticoagulation	76(56.3%)	131(61.8%)	113(74.3%)	320(64.1%)	0.000
Antiplatelet therapy	26(19.3%)	6(2.8%)	10(6.6%)	42(8.4%)	
Anticoagulation combined with antiplatelet therapy	0(0.0%)	32(15.1%)	8(5.3%)	40(8.0%)	
Other	1(0.7%)	28(13.2%)	1(0.7%)	30(6.0%)	
No antithrombotic therapy	32(23.7%)	15(7.1%)	20(13.2%)	67(13.4%)	
High risk of stroke(Male:≥2,Female:≥3)					
Anticoagulation	136(24.5%)	438(51.3%)	660(72.1%)	1234(53.1%)	0.000
Antiplatelet therapy	285(51.3%)	47(5.5%)	122(13.3%)	454(19.5%)	
Anticoagulation combined with antiplatelet therapy	11(2.0%)	204(23.9%)	46(5.0%)	261(11.2%)	
Other	14(2.5%)	136(15.9%)	7(0.8%)	157(6.7%)	
No antithrombotic therapy	110(19.8%)	29(3.4%)	81(8.8%)	220(9.5%)	
Use of OAC					
Warfarin: NOAC n%:n%	32%:0.3%	36.9%:38.6%	7.4%:77.2%		0.000

AF: Atrial Fibrillation, PCI: Percutaneous coronary intervention, OAC: Oral anticoagulant, NOAC: Non-vitamin K oral anticoagulant, Statistically different at $P < 0.05$

proportion of patients receiving no antithrombotic intervention was higher in 2013 and 2023 compared to 2018 ($P < 0.05$). Among AF patients at high risk of stroke, 53.1% received anticoagulation, with the highest prescription rate observed in 2023. Nevertheless, 9.5% of high-risk patients still did not receive any antithrombotic therapy ($P < 0.05$). Regarding OAC use, warfarin was predominant in 2013 (warfarin: NOAC = 32.0%:0.3%), while warfarin and NOAC were prescribed at similar rates in 2018 (warfarin: NOAC = 36.9%:38.6%). By 2023 NOAC became the dominant therapy (warfarin: NOAC = 7.4%:77.2%), with a declining trend in warfarin use trend and a significant increase in NOAC prescription rates ($p < 0.05$) (Table 1).

Current status of inappropriate OAC doses in patients with NVAF

Among the total AF patients included 2,438 were diagnosed with NVAF (2013: 579, 2018: 914, 2023: 945). Of these, 147 NVAF patients were on warfarin in 2013, 281 NVAF patients were on warfarin and 394 NVAF patients were on NOAC in 2018, and 774 were on NOAC in 2023. Table 2 provides details on the use of OAC doses in different years. Overall, 28.8% of NVAF patients received a standard dose of OAC, while 52.0% of NVAF patients were underdosed, 3.2% of NVAF patients were overdosed, and 16.0% with a low risk of stroke were treated with OAC. Details of the different OAC doses used are

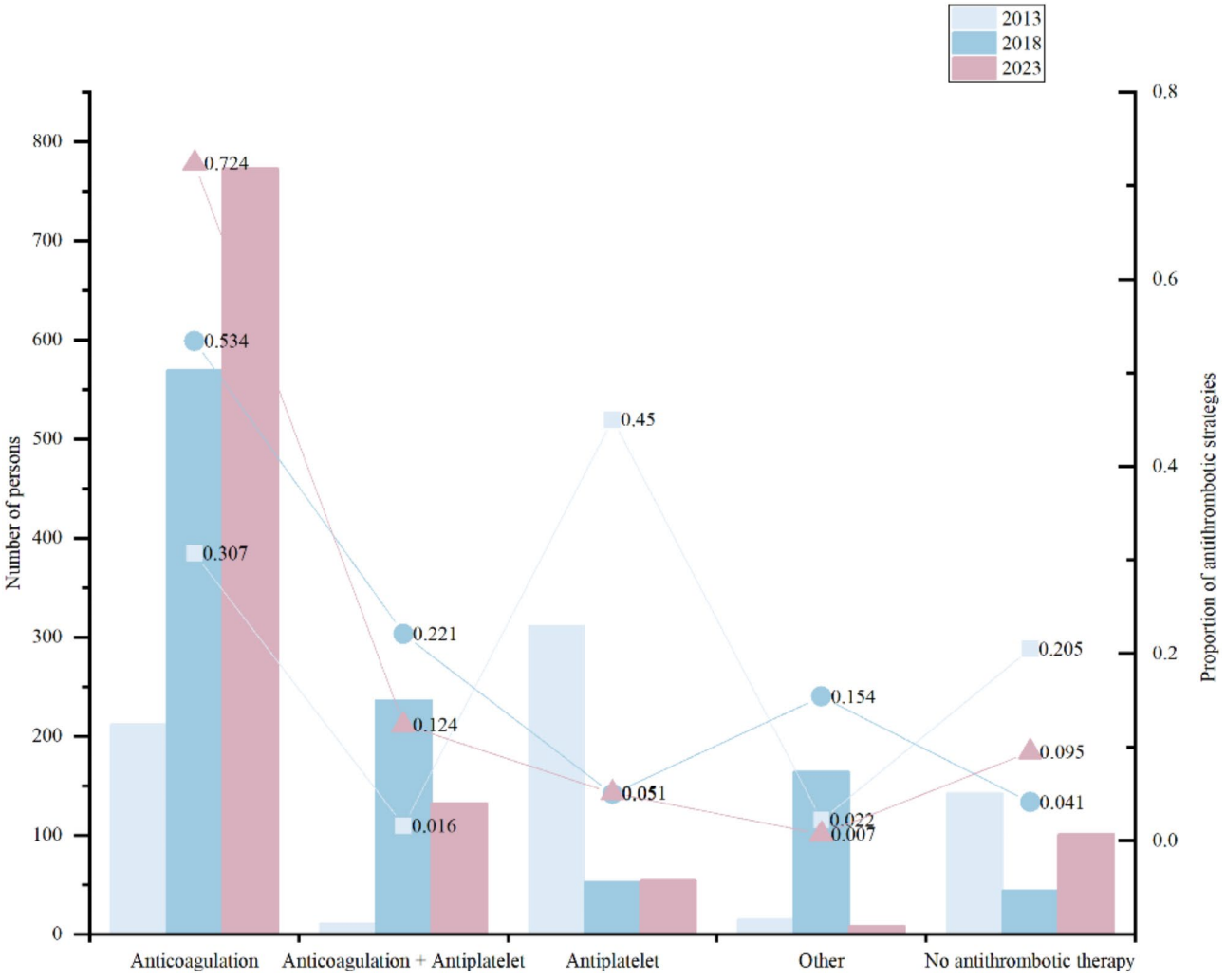

Fig. 2 Application of AF antithrombotic strategies in different years. Different colors and icons represent different years. The left Y-axis and bar chart section indicate the number of atrial fibrillation cases using different antithrombotic strategies, while the right Y-axis and line graph represent the proportion of cases using different antithrombotic strategies

Table 2 OAC use in different years

	Standard Dose	Underdosing	Overdosing	Use at low risk of stroke	*P*-value
OAC					
2013	12(8.2%)	101(68.7%)	3(2.0%)	31(21.1%)	0.000
2018	138(20.4%)	408(60.4%)	13(1.9%)	116(17.2%)	
2023	310(40.1%)	321(41.5%)	35(4.5%)	108(14.0%)	
	460(28.8%)	830(52.0%)	51(3.2%)	255(16.0%)	
Warfarin					
2013	12(8.2%)	101(68.7%)	3(2.0%)	31(21.1%)	0.006
2018	55(19.6%)	185(65.8%)	5(1.8%)	36(12.8%)	
	67(15.7%)	286(66.8%)	8(1.9%)	67(15.7%)	
NOAC					
2018	83(21.1%)	223(56.6%)	8(2%)	80(20.3%)	0.000
2023	310(40.1%)	321(41.5%)	35(4.5%)	108(14.0%)	
	393(33.6%)	544(46.6%)	43(3.7%)	188(16.1%)	

OAC: Oral anticoagulant, NOAC: Non-vitamin K antagonist oral anticoagulant, Statistically different at $P < 0.05$

shown in Fig. 3. From 2013 to 2023, the proportion of standard dose of both warfarin and NOAC increased significantly. In contrast, the rates of inappropriate dosing (underdosing and overdosing) and incorrect use of OAC generally decreased ($P < 0.05$), with underdosing remaining the most common issue (> 40%).

Factors associated with inappropriate NOAC dosing

2018 Cohort analysis

Further analysis of the factors associated with inappropriate NOAC dosing in 2018 revealed that the dose of NOAC used in NVAF patients was significantly associated with the following factors ($P < 0.05$):

Patient Characteristics: Age, body weight, and gender.

Comorbidities: Coronary artery disease, heart failure, diabetes mellitus, hypertension, renal insufficiency, and chronic obstructive pulmonary disease (COPD).

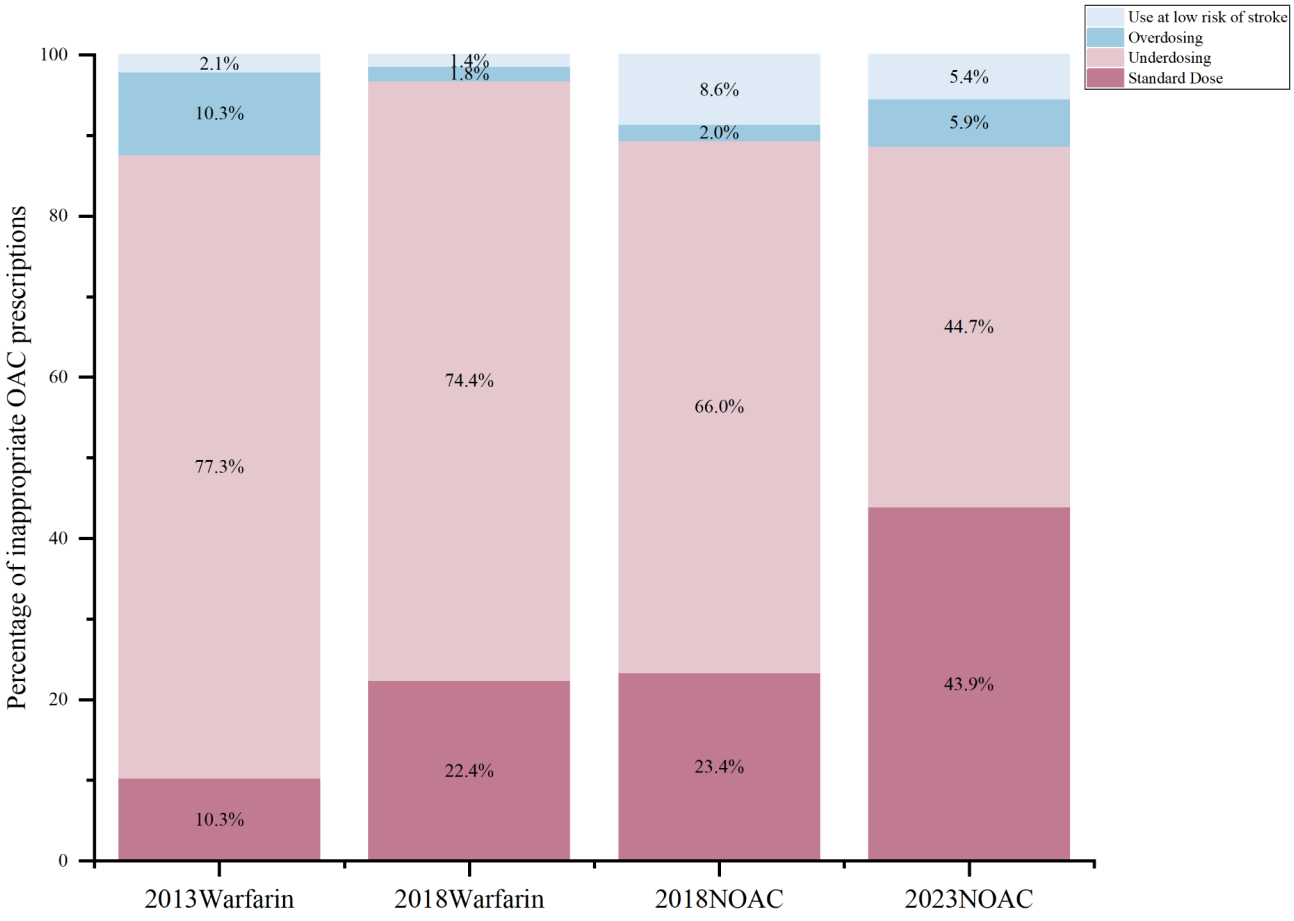

Fig. 3 Inappropriate prescribing of doses of major OAC used in different years. OAC: Oral anticoagulant, NOAC: Non-vitamin K antagonist oral anticoagulant.The X-axis indicates the main OAC categories in different years, the Y-axis indicates the proportion of inappropriate OAC doses, and different colours indicate different dose categories

Clinical indicators: Occurrence of ischemic stroke (IS) before anticoagulation, peripheral arterial disease, a high CHA2DS2-VASc score (indicating elevated stroke risk), and a high HAS-BLED score (indicating elevated bleeding risk).

Multifactorial logistic regression models identified the following independent predictors of inappropriate dosing in 2018:

Inappropriately Low Doses: Renal insufficiency (OR = 0.334, 95% CI: 0.128–0.872, $P = 0.025$).

Overdosing: Diabetes mellitus (OR = 7.080, 95% CI: 1.007–49.761, $P = 0.049$).

2023 Cohort analysis

In 2023, the dose of NOAC used in NVAF patients was associated with all the factors listed above except for COPD. Additionally, the following factors were significantly associated ($P < 0.05$):

Newly identified factors: Gender, body mass index (BMI), and hyperthyroidism.

Multifactorial logistic regression models for the 2023 cohort identified the following independent predictors of inappropriate dosing:

Inappropriately Low Doses: Age (OR = 1.043, 95% CI: 1.020–1.066, $P < 0.001$), renal insufficiency (OR = 0.381, 95% CI: 0.253–0.573, $P < 0.001$), and use of rivaroxaban (OR = 10.725, 95% CI: 6.177–18.622, $P < 0.001$) compared to edoxaban.

Overdosing: BMI (OR = 1.318, 95% CI: 1.040–1.671, $P = 0.022$), renal insufficiency (OR = 2.791, 95% CI: 1.189–6.551, $P = 0.018$), hypertension (OR = 0.323, 95% CI: 0.125–0.833, $P = 0.019$), high bleeding risk (OR = 5.154, 95% CI: 1.555–17.088, $P = 0.007$), and use of dabigatran (OR = 7.274, 95% CI: 1.584–33.391, $P = 0.011$) and rivaroxaban (OR = 6.935, 95% CI: 2.794–17.214, $P < 0.001$) compared to edoxaban (Table 3, Table S3).

Clinical outcomes and independent risk factors associated with inappropriate NOAC doses

First, 291 NVAF patients receiving different doses of NOAC (standard dose, underdosing, and overdosing) in

Table 3 Independent Influences on Prescribing Inappropriate OAC Doses in NVAF Patients

Inappropriate dose	Impact factor	Number of events	OR(95%CI)	P-value
2018				
Standard Dose Underdosing	Renal insufficiency	10 9	0.334(0.128-0.872)	0.025
Standard Dose Overdosing	Diabetes	26 5	7.080(1.007-49.761)	0.049
2023				
Standard Dose Underdosing	Age	-	1.043(1.020-1.066)	0.000
Standard Dose Underdosing	Renal insufficiency	128 87	0.381(0.253-0.573)	0.000
Standard Dose Underdosing	Rivaroxaban	20 109	10.725(6.177-18.622)	0.000
Standard Dose Overdosing	BMI	-	1.318(1.040-1.671)	0.022
Standard Dose Overdosing	Hypertension	185 19	0.323(0.125-0.833)	0.019
Standard Dose Overdosing	Renal insufficiency	128 25	2.791(1.189-6.551)	0.018
Standard Dose Overdosing	HAS-BLED≥3	213 29	5.154(1.555-17.088)	0.007
Standard Dose Overdosing	Dabigatran	9 3	7.274(1.584-33.391)	0.011
Standard Dose Overdosing	Rivaroxaban	20 12	6.935(2.794-17.214)	0.000

OAC: Oral anticoagulant, NVAF: Non-valvular atrial fibrillation, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

-:Continuous variables; Statistically different at $P < 0.05$

2018 were propensity-matched based on baseline characteristics, as detailed in Table 4. Among them, the ratio of NVAF patients in the standard dose group to those in the underdose group was approximately 1:2.7. Subsequently, survival analyses were conducted to evaluate the efficacy and safety of different NOAC dose. Figure 4 presents the cumulative event rates for all-cause death, IS/SE, bleeding, and the composite endpoints during the 24-month and 60-month follow-up periods across different NOAC dose groups. During the 24-month follow-up period, the difference in all-cause mortality among NVAF patients was borderline statistically significant ($P = 0.051$). In contrast, there was no statistically significant difference in stroke, bleeding, and composite endpoint event rates between NOAC dose groups. During the 60-month follow-up period, there was a statistically significant difference in all-cause mortality rate ($P = 0.022$) and composite endpoint event rate ($P = 0.040$) between different NOAC dose groups. Specifically, at 24-month follow-up, the risk of all-cause mortality was higher with overdosing NOAC than with underdosing NOAC (18.75 vs. 10.92 events/patient-years, $P = 0.017$). At 60-month follow-up, overdosing NOAC was associated with higher rates of all-cause mortality (10.00 vs. 6.49 events/patient-years, $P = 0.019$,10.00 vs. 6.21, events/patient-years, $P = 0.005$) and composite endpoint events (12.50 vs. 9.61 events/patient-years $P = 0.017$,12.50 vs. 9.32 events/patient-years $P = 0.013$). No statistically significant differences in outcome events were observed between the standard dose and underdosing groups. Among the 71 patients who used NOAC at low risk of stroke, 34 discontinued the medication either voluntarily or following outpatient physician recommendations several months after discharge. The clinical outcomes of the remaining 37 patients are detailed in Table S4.

Multivariate COX proportional hazards regression analysis was performed, with the all-cause mortality and composite endpoints during follow-up as dependent variables and potential factors influencing NOAC dosing as independent variables. The results are shown in detail in Fig. 5. At 24-month follow-up, age (HR = 1.109,95% CI,1.066–1.154, $P < 0.05$) and anemia (HR = 2.691, 95% CI,1.258–5.756, $P = 0.011$) were identified as independent risk factors for all-cause mortality. At the 60-month follow-up, age (HR = 1.105,95%CI,1.068–1.143, $P = 0.000$, HR = 1.073,95%CI,1.048–1.098, $P = 0.000$) was an independent risk factor for both all-cause mortality and composite endpoints, while renal insufficiency (HR = 1.866,95%CI,1.075–3.239, $P = 0.027$) was an independent risk factor for the composite endpoint.

The study further evaluated the efficacy and safety outcomes of different NOAC (dabigatran and rivaroxaban) at different doses. (Table S5-S6). For NVAF patients on dabigatran, no significant differences in clinical outcomes were observed across different doses during the 24-month and 60-month follow-up periods. Similarly, for rivaroxaban users, no significant differences in clinical outcomes were noted during the 24-month follow-up. However, at the 60-month follow-up, significant differences were observed in all-cause mortality ($P = 0.014$) and endpoint composite events ($P = 0.029$) between dose groups. In particular, compared to standard and underdosing groups, overdosing was associated with significantly higher risks of all-cause mortality (11.43 vs. 5.38 events/patient-years, $P = 0.005$; 11.43 vs. 6.30 events/patient-years, $P = 0.006$) and composite endpoint events (17.14 vs. 11.54 events/patient-years, $P = 0.007$; 17.14 vs. 11.27 events/patient-years, $P = 0.011$). No significant differences in clinical outcomes were observed between standard dose and underdose groups.

Discussion

In this study, we dynamically analyzed the changes in clinical characteristics and the progression of anticoagulation therapy in AF, the prescribing of OAC in patients and the factors influencing it, and the clinical outcomes

Table 4 Baseline Characteristics of AF Patients Regularly Followed With Different Doses of NOAC

	Before propensity match weighting				After propensity match weighting			
	Standard Dose	Underdosing	Overdosing	*P*-value	Standard Dose	Underdosing	Overdosing	*P*-value
Age, y	77.58±8.17	75.63±9.27	79.63±6.48	0.147	77.55±8.13	75.97±9.24	82.43±6.05	0.018
Female, n(%)	41(49.4%)	115(55.8%)	4(50%)	0.608	41(49.4%)	123(55.2%)	4(50%)	0.817
Weight	60.71.19±9.23	60.80±11.64	63.75±8.55	0.751	60.64±9.06	60.63±11.44	63.47±6.93	0.387
BMI	23.86±3.14	23.74±3.71	24.75±2.12	0.721	23.81±2.98	23.71±3.69	24.94±1.99	0.184
Coronary atherosclerotic heart disease	48(62.3%)	123(59.7%)	6(75.0%)	0.638	51(61.4%)	132(59.2%)	6(75.0%)	0.513
Heart faliure	55(71.4%)	133(64.6%)	4(50%)	0.351	60(72.3%)	145(65.0%)	4(50%)	0.974
Diabetes	23(29.9%)	62(30.1%)	5(62.5%)	0.176	26(31.3%)	70(31.4%)	5(62.5%)	0.491
Hypertension	52(67.5%)	120(58.3%)	4(50.0%)	0.297	56(67.5%)	131(58.7%)	4(50.0%)	0.853
Cardiomyopathy (dilated cardiomyopathy and hypertrophic cardiomyopathy)	4(5.2%)	11(5.3%)	0(0.0%)	0.809	4(4.8%)	11(4.9%)	0(0.0%)	0.771
Renal insufficiency	8(10.4%)	8(3.9%)	2(25.0%)	0.386	10(12.0%)	9(4.0%)	2(25.0%)	0.000
Peripheral artery disease	7(9.1%)	9(4.4%)	0(0.0%)	0.090	7(8.4%)	11(4.9%)	0(0.0%)	0.764
Anemic	6(7.8%)	15(7.3%)	0(0.0%)	0.635	6(7.2%)	17(7.6%)	0(0.0%)	0.749
Hyperthyroidism	0(0.0%)	5(2.4%)	0(0.0%)	0.272	1(1.2%)	6(2.7%)	0(0.0%)	0.464
Chronic obstructive pulmonary disease	13(16.9%)	24(11.7%)	1(12.5%)	0.524	13(15.7%)	26(11.7%)	1(12.5%)	0.940
Post-PCI	8(10.4%)	26(12.6%)	2(25.0%)	0.353	8(9.6%)	28(12.6%)	2(25.0%)	0.886
Previous stroke	9(11.7%)	28(13.6%)	2(25%)	0.613	12(14.5%)	30(13.5%)	2(25%)	0.689
Previous-bleeding	7(9.1%)	10(4.9%)	0(0.0%)	0.127	7(8.4%)	10(4.5%)	0(0.0%)	0.771
CHA2DAS2-VASc, n(%),(Male:≥2,Female:≥3)	77(100.0%)	206(100.0%)	8(100.0%)	-	83(100.0%)	223(100.0%)	8(100.0%)	-
HAS-BLED≥3	52(67.5%)	122(59.2%)	5(62.5%)	0.436	56(67.5%)	130(58.3%)	5(62.5%)	0.817

-:Patients in each group were eligible patients with high stroke risk,Statistically different at $P < 0.05$

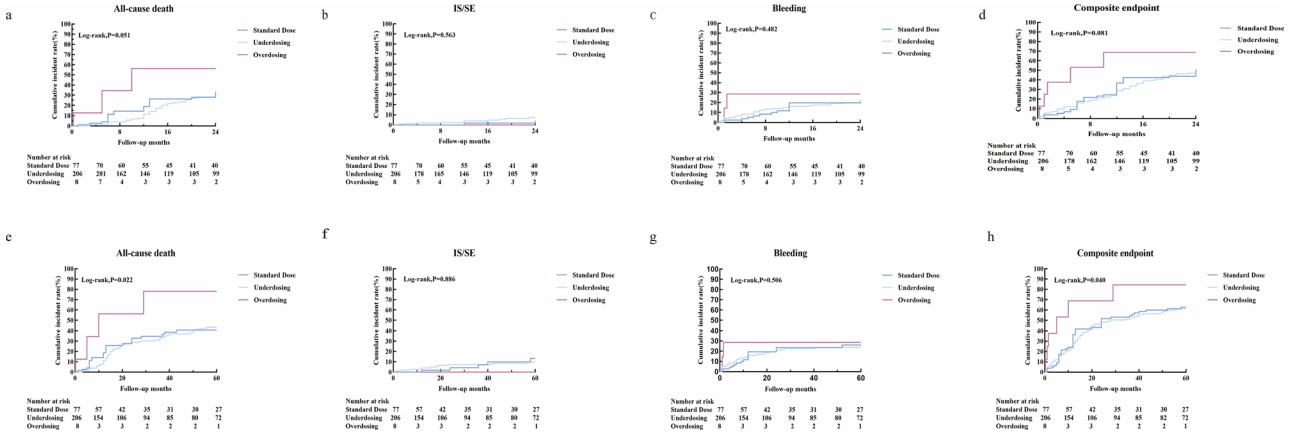

Fig. 4 Cumulative event rates for clinical outcomes at different NOAC doses. **a-d**: clinical outcome events occurring at 24 months of follow-up, **e-h**: clinical outcome events occurring at 60 months of follow-up. Different colors represent cumulative event rates for different NOAC doses. Clinical outcome events included: All-cause death, IS/SE, Bleeding and Composite endpoint. Statistical analysis was performed using log-rank, Statistically different at $P < 0.05$; IS/SE: Ischemic stroke/systemic embolism

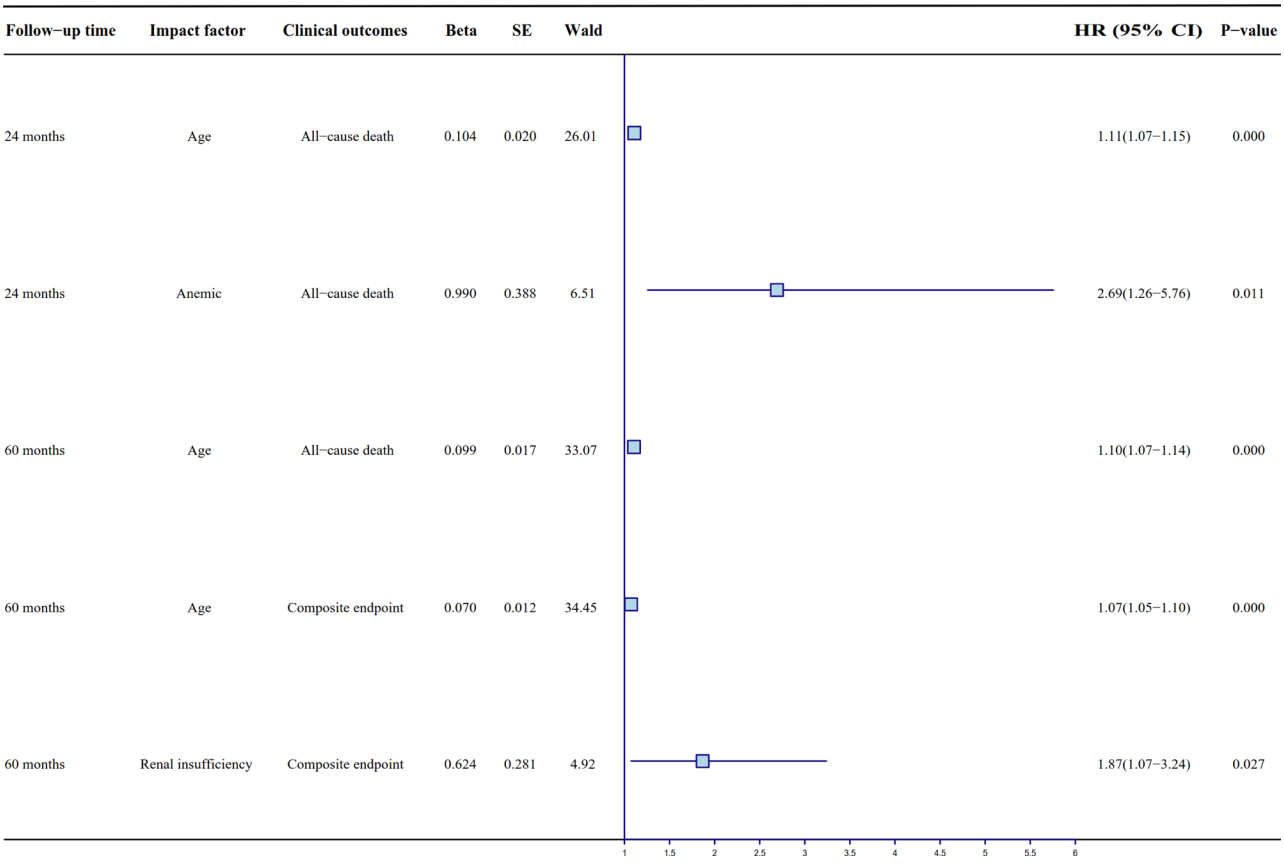

Fig. 5 Forest plot of independent risk factors influencing prognosis at different doses of NOAC. SE: Standard error, HR: Hazard ratio,95%CI: 95% Confidence interval. Each icon represents the corresponding HR, and each horizontal line represents the upper and lower ranges of the 95% confidence interval

and independent risk factors of inappropriately dosed NOAC by collecting data on patients with AF regularly from 2013 to 2023.

Clinical features of atrial fibrillation

Epidemiological findings in patients with AF are often inconsistent due to differences in demographic characteristics, healthcare delivery capacity, and survey methods. In this study, we obtained the dynamic clinical characteristics of patients with AF and the updated status of treatment options through a single-center longitudinal survey. Previous studies have shown that increasing age is the most prominent risk factor for AF and has been included in the AF risk prediction score [1, 29]. Our study extends this finding. It is not difficult to explain that population ageing and concomitant cardiovascular disease are the main drivers of the increasing mean age and development of AF patients [30, 31]. With technological advances, various portable devices for monitoring cardiac rhythms have improved the screening and detection of AF, especially in patients with asymptomatic and paroxysmal AF [32]. The screening findings have increased the rate of patients seeking medical attention, thus increasing the incidence of AF recorded by inpatient ECG. The increasing incidence of AF in our cohort may be partially attributed to the widespread use of wearable devices for rhythm monitoring, which has improved the detection of asymptomatic and paroxysmal AF. However, the specific impact of wearables on AF incidence was not quantified in this study, and thus, this remains a hypothetical explanation that warrants further investigation. Gender differences are also gaining attention in AF epidemiology. The Framingham Heart Study (FHS) and the Global AF Epidemiology Survey have shown that the incidence of AF is higher in men than women. Despite the inconsistent results of gender differences reported in Asia, most studies still show a higher incidence in males than in females or no significant difference [1, 6, 33]. Our study found that the prevalence of AF was slightly higher in females than in males, both 10 years ago and in the most recent data. This is consistent with the finding that the prevalence of males was no longer significant in Western China [34]. This result suggests that regional differences substantially impact epidemiological investigations of AF. Theoretically, it is hypothesized that the older mean age of the AF patients investigated in this study

may be related to the increased risk of cardiovascular disease in postmenopausal women with reduced oestrogen [35].

Trends in anticoagulation therapy

Over the past decade, the management of AF has evolved significantly, with a shift from antiplatelet agents and warfarin to NOAC. Our study observed a substantial increase in OAC prescription rates, reflecting improved awareness and acceptance of anticoagulation therapy among clinicians and patients. In the past 10 years, the American Heart Association (AHA) has continuously updated its guidelines for managing AF, recommending using OAC for stroke risk reduction in patients with AF. The introduction of NOAC, in particular, has given clinicians more choices when it comes to anticoagulation therapy [25–27]. Compared with conventional warfarin, NOAC has the advantages of not requiring routine testing of INR and fewer drug-drug interactions, which improves the rate of anticoagulation prescription [10–13].In addition, the RE-LY and ROCKET AF studies have shown that antiplatelet agents alone are not effective in reducing stroke risk in patients with AF and that anticoagulation is more effective [10, 12]. This finding has significantly increased clinicians' awareness of the correct choice of anticoagulation regimen. Recent data from the Italian Registry in the Setting of Atrial Fibrillation Ablation with Rivaroxaban (IRIS) further support the importance of standardized anticoagulation practices, particularly in patients undergoing AF ablation. The IRIS study highlighted that adherence to NOAC therapy, especially rivaroxaban, significantly reduces thromboembolic events without increasing bleeding risk, emphasizing the need for personalized anticoagulation strategies in AF management [36].Still, the standardization of anticoagulant dosing in clinical practice must be improved. Despite continuous updating of therapeutic guidelines, our study demonstrated that OAC dosage irregularities continue to be predominantly inappropriately underdosing, with varying degrees of overdosing over time. Previous studies, such as the Canadian Primary Care cohort, the ORBIT-AF II Registry, and the FANTASIIA Registry, noted that underdosing was the most prevalent problem, ranging from 7.7-32% [37–39]. Our study observed a higher incidence of underdosing (>40%) over time than previous studies, which may be due to different population characteristics, but the conclusion that underdosing is the main problem is stable in this study based on the longitudinal follow-up in one center, which is consistent with the fact that patients with NVAF in Asia are often prescribed low-dose anticoagulants [40].

Factors influencing inappropriate dosing

Inappropriate dosing of NOAC, particularly underdosing, was a consistent finding across all study years. Advanced age, renal insufficiency, and high bleeding risk scores (HAS-BLED) were identified as independent predictors of underdosing. However, these conclusions are contradictory and may be related to the patient's frailty, comorbidities, and prescriber's concerns about the use of the medication [39, 41, 42]. It is important to note that although patients with renal insufficiency and diabetes mellitus differed between years, renal function was an independent risk factor for dosage impact, and diabetes mellitus was an independent risk factor for overdosing in 2018. Age, weight and BMI were additional independent risk factors in 2023, as they were not statistically different between years. Year comparisons identified renal function as a stable influence on inappropriately low and excessive doses of NOAC. To reduce the risk of bleeding, clinical guidelines usually recommend adjusting the NOAC dose based on renal function, but the complexity of renal function assessment and errors in practice have led to a certain degree of neglect of renal function or inability to correctly assess the risk of bleeding and stroke in NVAF due to the influence of renal function in clinicians' consultations, resulting in the problem of under- or over-dosing of NOAC [43]. Age is one of the factors influencing low doses, which is consistent with other studies [39, 41]. The pharmacokinetics and pharmacodynamics of the organism change significantly with age [44]. For elderly patients, there are often multiple comorbidities and multi-drug combinations, which increase the risk of drug interactions and adverse reactions, which may be the reason why clinicians tend to favour low dosages when prescribing NOAC in elderly NVAF patients.

Diabetes and hypertension, as common co-morbidities in patients with NVAF, are independent influences on the overdosing of NOAC, which has rarely been reported in previous studies. Such patients are often associated with vascular degeneration, atherosclerosis, and metabolic abnormalities and have a high risk of bleeding and embolism [45, 46]. Clinicians may overdose on NOAC for concomitant conditions while ignoring their bleeding-prone risk status. BMI is also one of the major influences on the overdose of NOAC, suggesting that clinicians may subconsciously take obesity into account in dosage considerations. However, guidelines and instructions for NVAF anticoagulation therapy do not emphasize dosing in overweight patients [28]. High bleeding risk and varying NOAC also influence the use of inappropriate doses. Multicenter studies have found a higher rate of inappropriately low-dose use of rivaroxaban than other NOAC agents, especially in NVAF patients with high HAS-BLED scores [15, 47]. Our data results align with this and may be related to the fact that clinicians perceive a wider

adjustable range of rivaroxaban dosage in their practice to avoid the risk of bleeding. Dabigatran is more likely to be used at inappropriately overdosing, which is particularly common in patients with impaired renal function [47], suggesting that renal function assessment should be emphasized for dabigatran use. Compared to dabigatran and rivaroxaban, edoxaban is less prone to inappropriate dose use, possibly due to its fixed-dose regimen and fewer drug-drug interactions, which simplifies dose adjustment [13]. These data suggest that the use of drug dosage, in addition to the correct choice of drug in the use of OAC, is a priority issue in anticoagulation with NVAF. This study also found that none of these potential influences were statistically associated with the use of anticoagulants in patients with a low risk of stroke, suggesting that ignoring stroke risk scores is a direct cause of anticoagulant use in these patients.

Clinical outcomes of inappropriate dosing

Previous studies have focused on the efficacy and safety of inappropriate dose use of NOAC but have not been uniformly conclusive. Two large-scale NOAC randomized controlled trials (RCTs), RE-LY and ENGAGE AF TIMI-48, reported that underdosing anticoagulants were accompanied by higher rates of IS/SE and lower rates of major hemorrhagic events than standard doses [10, 13]. However, analysis of data from the US ORBIT-AF2 registry found no statistical difference between low and standard-dose groups of NOAC in terms of STROKE/SE events and major hemorrhagic events, and only in terms of mortality did the underdosed group show an increased trend [39]. A meta-analysis based on real-world data showed no significant difference between underdosing and standard doses in stroke and bleeding, among other things, but underdosing NOAC increased the risk of death, while overdosing NOAC increased the risk of stroke/SE and significant hemorrhagic events, especially in Asian populations [48]. Further analysis by the SAKURA AF Registry in Japan showed that underdosing NOAC reduced major bleeding events but was comparable to the standard dose in IS/SE event rates [19]. The present study found comparable clinical outcomes between the underdosing and standard dose groups regarding standard follow-up time in the NOAC based phase III trial and long-term prognosis. In contrast the overdosing group showed an increase in all-cause mortality and composite endpoint event rates, especially at long-term follow-up and with the use of rivaroxaban. Several possible reasons could explain the differences between the results of this study and those of previous studies. The first is the different characteristics of the study patients, especially weight differences [19]. Previous studies have focused on European and American countries with significantly higher body weights than Asian countries. Heavier people are usually thought to require larger doses of NOAC, so the underdosing group has a higher risk of IS/SE incidence and death [39, 49]. In addition, the dose standard of rivaroxaban in Japan is 15 mg instead of 20 mg in other countries [19], and their BMI is lower than that in Europe and the United States, so the underdosing of NOAC may be sufficient for the prevention of stroke/SE. Secondly, there are different geographical regions. Data analyses in Europe and the United States have shown mixed results regarding the impact of NOAC underdosing on stroke/embolism and mortality, with some studies reporting an increased risk and others showing no significant difference [10, 13, 39]., whereas neither data analysis from the SAKURA AF Registry in Japan nor the present study found differences in clinical outcomes between the underdosing and the standard dose group [19]. Therefore, low-dose NOAC may be safely applied, especially for Asian populations. A real-world-based meta-analysis reported that the use of overdose NOAC was associated with the risk of stroke/SE, major bleeding, and death in Asian populations. In contrast, there was no significant difference in populations from other regions, consistent with the results of the SAKURA AF study in Japan and the data analysis from the National Health Insurance System (NHIS) in South Korea [18, 19, 48]. The present study similarly confirmed the composite endpoint event rate of increased mortality and adverse event occurrence with overdose use. All of this study suggests that geographic differences may be one of the reasons for overdosing, with Asian NVAF patients being more inclined to be intolerant of overdoses of NOAC. In addition, the patient's accompanying disease state is also an essential factor. The analysis in this study found that age, anemia and renal insufficiency were independent influences on the time to death or composite endpoints due to overdose. Whether it is advanced age, anemia or renal insufficiency, these may exacerbate the patient's debilitating state and increase adverse drug use reactions, resulting in a poor prognosis [50, 51].

Differences across sub-cohorts (2013, 2018, and 2023)

This study is the longitudinal analysis of three distinct sub-cohorts (2013, 2018, and 2023), which revealed evolving trends in AF management. Over the decade, we observed a gradual increase in the mean age of AF patients, reflecting population ageing and improved asymptomatic and paroxysmal AF detection. A shift from antiplatelet therapy to NOAC, driven by updated guidelines and the availability of safer anticoagulation options. Persistent challenges in dosing standardization, with underdosing remaining prevalent despite increased awareness of anticoagulation benefits.

Application of left atrial appendage occlusion (LAAO)

In patients with cardiac amyloidosis, the optimal anticoagulation strategy remains controversial. A recent study demonstrated that combining LAAO with NOAC therapy provides superior stroke prophylaxis compared to NOAC alone, particularly in post-ablation AF patients with high thromboembolic risk [52]. This finding underscores the potential of LAAO as an adjunct to anticoagulation in specific high-risk populations. In elderly patients with AF, particularly those at high risk of bleeding or contraindications to long-term anticoagulation, LAAO has emerged as a promising alternative for stroke prevention. The left atrial appendage is the primary source of thromboembolism in NVAF patients, and LAAO aims to mechanically exclude this structure from the circulation, thereby reducing the risk of stroke without the need for long-term anticoagulation. Recent studies, including the PRAGUE-17 trial and the LAAOS III study, have demonstrated that LAAO is non-inferior to NOAC in preventing stroke and systemic embolism in high-risk patients significantly reducing in major bleeding events [53, 54]. For elderly patients with multiple comorbidities, frailty, or a history of bleeding, LAAO offers a valuable therapeutic option. However, the procedure requires careful patient selection, advanced imaging for procedural planning, and expertise in device implantation. Future research should focus on optimizing patient selection criteria and evaluating the long-term outcomes of LAAO in elderly AF populations.

Implications for clinical practice

This study collected longitudinal AF data through long-term dynamic assessment and follow-up, capturing long-term trends and changes in AF characteristics and treatment progress. In addition, the study paid particular attention to the current status of inappropriate use of OAC. It analyzed and identified predictors of adherence to anticoagulation therapy, which informs the standardized use of OAC dosage. Finally, the study followed up on the clinical outcomes of NOAC and assessed the actual clinical effects and risks of NOAC, which is the focus of this study. It provides valuable real-world anticoagulant dosing data for using NOAC in AF patients. Additionally, the role of LAAO as an adjunct to anticoagulation in high-risk patients warrants further exploration, particularly in those with contraindications to long-term anticoagulation.

Limitations

However, there are some limitations to this study. Firstly, this was a single-center, combined cross-sectional and prospective design study with population selection bias and unavoidable confounding bias. Combined with the reality of clinical unregulated use in NOAC, apixaban is not approved for anticoagulation in Chinese NVAF patients, and the use of edoxaban in the data was mainly concentrated in AF patients in 2023, along with its low rate of unregulated use. Therefore, this study focused on the follow-up of dabigatran and rivaroxaban in NVAF patients with a small follow-up sample size, which limits the comprehensive assessment of the effectiveness and safety of NOAC and the extrapolation of the results. Although this study assessed the risk of increased mortality and composite endpoints in patients with NVAF with overdoses of NOAC and analyzed independent risk factors, clinical outcomes may still be affected by the patient's frail state and the multiple medications taken.

Conclusion

Paroxysmal and non-valvular AF are the main types of AF, and ageing is the most significant disease feature of AF. Physician and patient awareness of anticoagulation for the treatment of AF has increased markedly. Although the adoption of NOAC has improved anticoagulation practices, inappropriate dosing remains a significant problem, and the use of overdosed NOAC should be avoided, especially in high-risk populations. Future research should focus on optimizing dosing strategies, integrating advanced monitoring technologies, and exploring alternative therapies such as LAAO to further reduce the burden of AF-related complications.

Abbreviations

AF	Atrial fibrillation
OAC	Oral anticoagulants
NOAC	Non-vitamin K antagonist oral anticoagulants
NVAF	Non-valvular atrial fibrillation
INR	International normalized ratio
IS/SE	Ischemic stroke/systemic embolism
COPD	Chronic obstructive pulmonary disease
LAAO	Left atrial appendage occlusion
PSM	Propensity score matching

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization: FLQ and HX. Data curation: JCW, SYX, ZX, XYC, HJZ, ZL, NYB and CCL. Formal analysis: FLQ and HX. Funding and acquisition: HX. Investigation: all authors. Methodology: JCW and FLQ. Project administration, resources and supervision: HX. Visualization: FLQ. Writing original draft: FLQ. Writing, review and editing: FLQ and HX. All authors read and approved the final version of the manuscript.

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Data availability
All data generated or analyzed during this study are included in this article and its supplementary information files. Further inquiries during the current study can be available from the corresponding author on reasonable request.

Code availability
Not applicable.

Declarations

Ethical approval
This study involves human participants and was approved by the Ethics Committee of the First Hospital of Chongqing Medical University (reference number K2023-538) and adhered to the guidelines of the Helsinki Declaration.

Consent to participate
Informed consent was obtained from all individual participants included in the study.

Consent for publication
All authors approve to publication.

Competing interests
The authors declare no competing interests.

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