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Inappropriate dosing of direct oral anticoagulants among very older inpatients with atrial fibrillation

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Abstract

Among very older patients with atrial fibrillation (AF), the frequency of inappropriate direct oral anticoagulant (DOAC) dosing, associated factors, and temporal trends in practice are unknown.

This retrospective study included consecutive inpatients aged 80 years or older with a discharge diagnosis of atrial fibrillation who were prescribed DOACs at discharge from Beijing Hospital between January 2018 and August 2023. Patients were stratified into underdosed, overdosed, or recommended dosing groups. Logistic regression analysis was performed to identify risk factors associated with inappropriate dosing, and temporal trends were evaluated using the Cochran–Mantel–Haenszel test.

Among 676 inpatients aged ≥ 80 years with AF (mean age 84.4 ± 3.5 years; 53.1% female) who were prescribed a DOAC at hospital discharge (22.9% dabigatran, 62.3% rivaroxaban, 14.8% edoxaban), recommended dosing was observed in 338 patients (50.6%), underdosing in 308 (45.6%), and overdosing in 30 (4.4%). The overall rate of inappropriate dosing was 49.4%. Factors independently associated with underdosing included advanced age (OR = 1.98, 95% CI: 1.52–2.60, $p < 0.001$), lower creatinine clearance (OR = 0.98, 95% CI: 0.97–0.99, $p = 0.01$), and discharge from non-internal medicine wards (OR = 2.15, 95% CI: 1.33–3.45, $p = 0.002$). Overdosing was associated with younger age (OR = 0.38, 95% CI: 0.19–0.75, $p = 0.005$). Although the proportion of recommended dosing increased over the study period, and inappropriate dosing showed a declining trend, these changes did not reach statistical significance.

Inappropriate DOAC dosing, especially underdosing, remains common in very older AF inpatients. This issue persists despite years passing, emphasizing the need for patient-focused, collaborative AF management and thorough prognostic studies.

Keywords Atrial fibrillation, Anticoagulants, Geriatrics

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Introduction

In recent years, direct oral anticoagulants (DOACs) have gradually replaced warfarin as the preferred medication for anticoagulation therapy in non-valvular atrial fibrillation (NVAF) [1–4]. Compared to warfarin, DOACs offer advantages such as ease of use, no need for frequent INR monitoring, and fewer interactions with food and drugs, while also demonstrating good efficacy and a reasonable safety profile in reducing the risk of stroke and major bleeding. The clinical effectiveness and safety of DOACs stem from appropriate dosing, which is based on guidelines and labeling, taking into account factors including age, renal function, body weight, and concomitant use of medications—particularly P-glycoprotein and CYP3A4 inhibitors, depending on the specific DOAC. However, substantial data indicate that inappropriate use of DOACs is significant and associated with increased risks—such as increased bleeding with DOAC overdosing and increased stroke risk with DOAC underdosing [5, 6].

The inappropriate dosing of DOACs is particularly prevalent among older patients with AF, presenting a significant clinical concern. This issue stems from two primary factors. Firstly, the paucity of clinical evidence due to the exclusion of this demographic from most clinical trials has led to uncertainty regarding the safety and efficacy of currently recommended dosages. Secondly, anticoagulation therapy in older AF patients is inherently complex, compounded by aging process, including multimorbidity, kidney impairment, decreased drug metabolism, elevated fall risk, and increased risk of bleeding [7, 8].

These challenges underscore the critical need for comprehensive studies focusing on DOAC use in the older AF population. To address this gap in knowledge, our investigation aims to elucidate the prevalence of inappropriate DOAC dosing, identify associated risk factors, and analyze temporal trends in this vulnerable patient cohort.

Methods

Study design and participants

We conducted a retrospective chart review of all consecutive patients discharged from Beijing Hospital between January 2018 and August 2023. Inclusion criteria were as follows: (1) age ≥ 80 years; (2) diagnosis of atrial fibrillation based on the discharge diagnosis, including paroxysmal and non-paroxysmal types (including persistent and permanent AF); and (3) prescription of a direct oral anticoagulant (rivaroxaban, dabigatran, or edoxaban) at the time of hospital discharge. Apixaban was not represented in our cohort because it was not available at our institution during the study period. Subjects were excluded from the study if they fulfilled any of the following criteria: (1) underwent left atrial appendage closure; (2) glomerular filtration rate < 15 ml/min/1.73m^2; (3) incomplete data. This study was approved by the Ethics Committee of Beijing Hospital (approval no. 2023BYJYYEC-279-01). Demographic, clinical and non-clinical parameters were obtained by chart review.

Trained personnel abstracted clinical, demographic, laboratory, and treatment characteristics of these participants from the electronic medical record system. This included participants' age, sex, ward of origin (internal medicine ward includes cardiology, respiratory, geriatric, neurology, rehabilitation, and traditional chinese medicine wards), comorbidities (such as diabetes mellitus, hypertension, heart failure, chronic kidney disease, and prior stroke), treatment variables (i.e., complete medication list), and laboratory values including serum creatinine and hemoglobin. Traditional Chinese medicine wards refers to hospital departments where patients receive treatment based on traditional Chinese medicine (TCM) principles, including herbal therapy, acupuncture, and other non-Western medical approaches. Smoking refers specifically to current smoking status at the time of hospital admission. Drinking refers to current alcohol consumption as reported in the medical records at the time of hospital admission. History of bleeding (major bleeding or clinically relevant non-major bleeding), as defined by the International Society on Thrombosis and Hemostasis criteria [9], was also ascertained. Multimorbidity was defined as the number of comorbidities reported at baseline, when a patient presented at least 2 conditions [10]. CrCl (creatinine clearance) was estimated with the Cockcroft-Gault formula. Polypharmacy was defined according to the number of drugs prescribed at baseline, as the presence of ≥ 7 different drugs taken by a patient [11]. Antiplatelet drugs include aspirin, clopidogrel, and ticagrelor. Rhythm control drugs include propafenone, sotalol, and amiodarone. Rate control drugs include beta-receptor blockers, non-dihydropyridine calcium channel antagonists, and digoxin.

Determining appropriateness of DOAC dose

Underdosing and overdosing were, respectively, defined as the administration of a lower or higher DOACs dose than recommended in the European Heart Rhythm Association (EHRA) consensus [12] and package inserts. Inappropriate DOACs was defined as either underdosed or overdosed DOACs. For detailed recommended dosages, see Table S1.

Statistical analysis

Patients were divided into three groups: underdosing, overdosing, or recommended dosing of DOACs at discharge. We summarized continuous variables using means and standard deviations or medians and interquartile ranges, depending on the distribution's

normality. Categorical variables were summarized by count and percentages. We used analysis of variances or Kruskal–Wallis for continuous variables and the chi-square test for categorical variables to compare between groups. In addition, we performed subgroup analyses comparing underdosed versus non-underdosed patients, and overdosed versus non-overdosed patients.

To identify the risk factors of underdosing or overdosing, we conducted backward selection of logistic regression. The candidate risk factors, including age, sex, BMI (body mass index), cardiology ward, internal medicine ward, Paroxysmal AF, CHA_2DS_2-VASc score, HAS-BLED score, multimorbidity, history of bleeding, dementia, ALT (alanine aminotransferase), AST (aspartate aminotransferas), Hb (hemoglobin), CrCI, polypharmacy, antiplatelet drug, rhythm control drug, rate control drug, NSAID (non-steroidal anti-inflammatory drug) were determined through a comprehensive consideration of the literature review, clinical experience, and data imbalance. We used Cochran–Mantel–Haenszel tests to assess the calendar trends of underdosing or overdosing.

Results

Between January 2018 and August 2023, a total of 676 consecutive older AF patients aged ≥ 80 years receiving DOAC treatment were studied (Fig. 1). The mean age was 84.4 ± 3.5 years, 53.1% were female, and the mean body mass index was 24.6 ± 3.7 kg/m2. 60.4% had paroxysmal AF, and the mean CHA_2DS_2-VASc score and HAS-BLED score were 5.0 ± 1.5 and 1.6 ± 0.7, respectively. Figure 2 illustrates the distribution of underdosing, recommended dosing, and overdosing by DOAC type.

DOAC dosing patterns and patient characteristics

308 patients (45.6%) received a DOAC dose lower than recommended, 338 (50.6%) received the recommended DOAC dose, and 30 (4.4%) received a DOAC dose higher than recommended (Table 1; Fig. 2). Compared to those discharged on Non-underdosed DOACs (including recommended and overdosed), patients who received underdosed DOACs were older (85.4 ± 3.7 versus 83.5 ± 3.1 years), had lower BMI (24.2 ± 3.9 versus 25.0 ± 3.5), higher HAS-BLED score (1.7 ± 0.7 versus 1.6 ± 0.7), were less frequently found in Cardiology ward (44.5% versus 57.3%) and Internal Medicine ward (77.9% versus 87.5%), were more bedridden (17.2% versus 9.5%), more frequently had a prior hemorrhage (8.4%

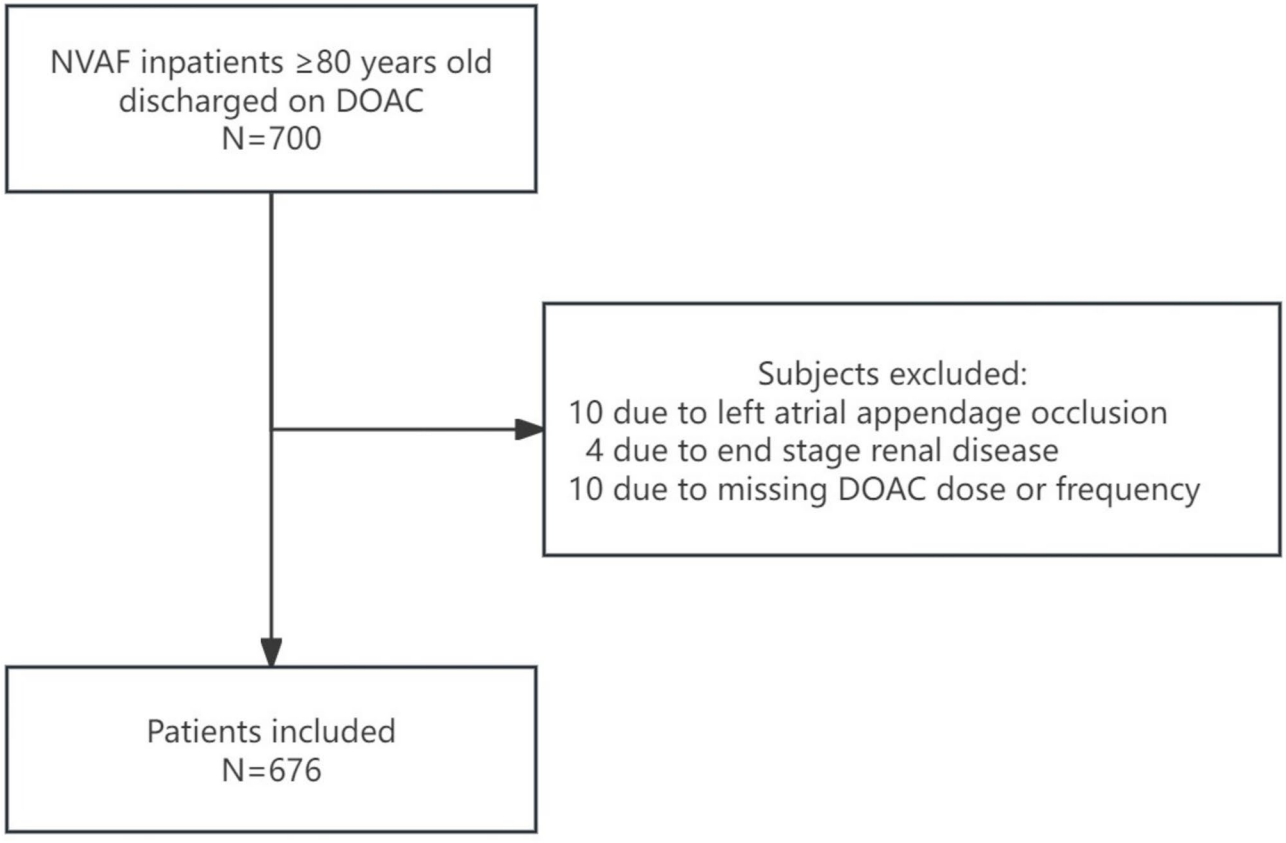

Fig. 1 Flowchart of patient enrollment

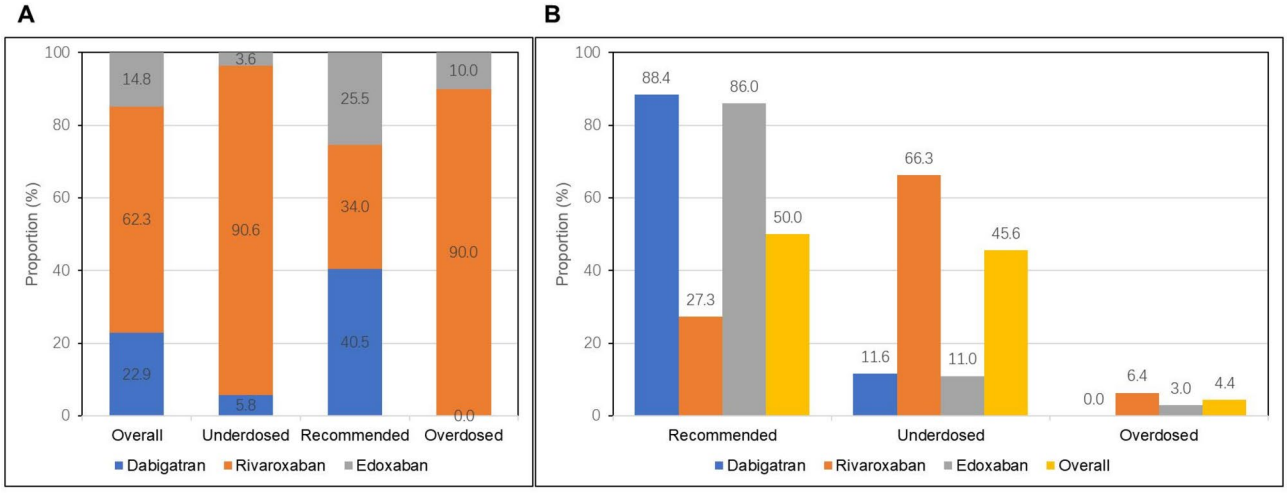

Fig. 2 Frequency of NOAC prescription. (**A**) frequency of overall, underdosing, overdosing, and recommended dosing by each NOAC type; (**B**) frequency of NOAC dosing by recommended dosing, underdosed, or overdosed

versus 3.5%), lower hemoglobin (Hb) (119.7 ± 17.8 versus 124.1 ± 16.9 g/L), CrCl (47.9 ± 15.9 versus 54.3 ± 16.3 ml/min) and albumin (Alb) (36.1 ± 3.9 versus 37.3 ± 4.0 g/l), higher D-dimer (273.0 versus 196.0 ng/ml) (Table S2). Compared to those discharged on Non-overdosed DOACs (including recommended and underdosed), patients who received overdosed DOACs were younger (82.7 ± 2.4 versus 84.4 ± 3.5 years), less frequently found in the Cardiology ward (30.0% versus 52.5%), and had a lower rate of Cardiovascular implanted electronic device (CIED) implantation (6.7% versus 22.1%). They also had higher CrCl (58.8 ± 19.0 versus 51.1 ± 16.3 ml/min) and D-dimer (475.0 versus 221.0 ng/ml) (Table S3).

Risk factors for inappropriate dosing of DOAC

At multivariate logistic regression analysis (Table 2), older age (OR = 1.98, 95% CI: 1.52–2.60, $p < 0.001$), lower CrCl (OR = 0.98, 95% CI: 0.97–0.99, $p = 0.01$), and non-internal medicine ward (OR = 2.15, 95% CI: 1.33–3.45, $p = 0.002$) were independently associated with underdose prescription. Younger age (OR = 0.38, 95% CI: 0.19–0.75, $p = 0.005$) was independently associated with overdose prescription.

Temporal trends

Figure 3 shows temporal trends in the rate of recommended dosing, underdosing, and overdosing of DOACs. Although there were fluctuations and the differences are not significant, it can be observed that the proportion of recommended dosing (51.2% in 2018 to 58.8% in 2023, $p = 0.09$) shows an increasing trend, while the proportions of underdosing (42.7% in 2018 to 39.5% in 2023, $p = 0.19$) and overdosing (6.1% in 2018 to 1.7% in 2023, $p = 0.32$) show a gradually decreasing trend.

Discussion

The main finding of this study are: (1) Inappropriate dosing of DOACs was relatively common among AF inpatients aged ≥ 80 years, with an overall inappropriate dosing rate of 49.4%. (2) Underdosing (45.6%) was more common than overdosing (4.4%). (3) Risk factors associated with underdosing included: older age, compromised renal function (decreased creatinine clearance), and hospitalization in non-internal medicine wards. (4) The main risk factor associated with overdosing was younger age. (5) Although there was no statistically significant difference, from 2018 to 2023, the use of recommended dosages showed an increasing trend (from 51.2 to 58.8%), while the proportions of underdosing and overdosing showed a gradual decreasing trend (from 42.7 to 39.5%, and from 6.1 to 1.7%, respectively).

With global population aging, especially in China, stroke prevention in older patients, particularly those of advanced age with AF, faces unprecedented challenges. More worryingly, the issue of inappropriate DOAC dosing is particularly prominent in the very older AF population. Our results showed that nearly half of the patients received inappropriate DOAC dosing, a finding that is consistent with other studies reporting similarly high rates, highlighting the widespread nature of this issue. A study from Italy showed that among AF patients aged 80 and above, the rate of inappropriate DOAC use was 29%, with 74.4% being underdosed and 25.6% being overdosed [13]. A German study found that in AF patients aged 85 and above, the rate of inappropriate DOAC use was 26.1%, all of which were underdosed [14]. Data from a French medical center indicated that for AF patients aged 80 and above, the rate of inappropriate DOAC use was 40.0%, with 88.0% being underdosed [15]. Another survey of older hospitalized patients with an average age of

Table 1 Baseline patient characteristics

	Underdosed	Recommended	Overdosed	
	n **= 308 (45.6%)**	***n*** **= 338 (50.6%)**	***n*** **= 30 (4.4%)**	***p*** **Value**
Age, y	85.3 ± 3.7	83.6 ± 3.2	82.7 ± 2.4	**< 0.001**
Male	135 (43.8)	165 (48.8)	17 (56.7)	0.25
Smoking	104 (33.8)	92 (27.2)	9 (30.0)	0.19
Drinking	102 (33.1)	93 (27.5)	8 (26.7)	0.28
BMI, kg/m^2	24.2 ± 4.0	25.1 ± 3.5	24.2 ± 3.1	**0.01**
Cardiology Ward	137 (44.5)	202 (59.8)	9 (30.0)	**< 0.001**
Internal Medicine Ward	240 (77.9)	300 (88.8)	22 (73.3)	**< 0.001**
Bedridden	53 (17.2)	30 (8.9)	5 (16.7)	**0.006**
Paroxysmal AF	194 (63.0)	196 (58.0)	18 (60.0)	0.43
CHA2DS2-VASc score	5.1 ± 1.4	5.0 ± 1.5	4.8 ± 1.9	0.41
HAS-BLED score	1.7 ± 0.7	1.5 ± 0.7	1.6 ± 0.7	**0.04**
Multimorbidity	301 (97.7)	327 (96.7)	27 (90.0)	0.06
DVT	31 (10.1)	15 (4.4)	6 (20.0)	**< 0.001**
PE	24 (7.8)	7 (2.1)	6 (20.1)	**< 0.001**
Surgical thromboprophylaxis	10 (3.2)	4 (1.2)	3 (10.0)	**0.007**
HTN	251 (81.5)	265 (78.4)	21 (70.0)	0.27
CAD	151 (49.0)	162 (47.9)	10 (33.3)	0.26
MI	40 (13.0)	31 (9.2)	4 (13.3)	0.28
HF	60 (19.5)	62 (18.3)	4 (13.3)	0.70
CIED	56 (18.2)	87 (25.7)	2 (6.7)	**0.009**
catheter ablation	45 (14.6)	89 (26.3)	8 (26.7)	**< 0.001**
Diabetes	114 (37.0)	124 (36.7)	8 (26.7)	0.52
Stroke/TIA	97 (31.5)	117 (34.6)	10 (33.3)	0.70
SE	10 (3.2)	11 (3.3)	2 (6.7)	0.60
PVD	84 (27.3)	72 (21.3)	11 (36.7)	0.06
OSAS	9 (2.9)	15 (4.4)	0 (0.0)	0.33
CKD	40 (13.0)	30 (8.9)	4 (13.3)	0.23
COPD	24 (7.8)	16 (4.7)	1 (3.3)	0.22
History of bleeding	26 (8.4)	9 (2.7)	4 (13.3)	**0.001**
Dementia	16 (5.2)	9 (2.7)	0 (0.0)	0.13
Hb g/L	119.7 ± 17.8	124.4 ± 16.2	120.3 ± 24.0	**0.003**
ALT U/L	14.0 (10.0,22.0)	15.0 (11.0,21.0)	14.5 (10.0,27.0)	0.71
AST U/L	19.5 (16.0,25.0)	19.0 (16.0,24.0)	19.0 (16.0,24.0)	0.79
Scr umol/L	90.1 ± 32.3	86.2 ± 34.7	80.6 ± 28.5	0.08
CrCl, ml/min	47.9 ± 15.9	53.9 ± 16.0	58.9 ± 19.0	**< 0.001**
Alb, g/l	36.1 ± 3.9	37.4 ± 3.8	35.9 ± 5.6	**< 0.001**
D-dimer, ng/ml	273.0 (130.5, 636.0)	188.0 (105.0, 365.5)	475.0 (196.0, 1625.0)	0.44
Polypharmacy	183 (59.4)	210 (62.1)	23 (76.7)	0.17
Antiplatelet drug	44 (14.3)	38 (11.2)	4 (13.3)	0.51
Rhythm control drug	58 (18.8)	69 (20.4)	2 (6.7)	0.18
Rate control drug	155 (50.3)	195 (57.7)	19 (63.3)	0.11
NSAID	6 (1.9)	2 (0.6)	1 (3.3)	0.20

Note: For continuous variables, values are presented as mean ± SD and compared by analysis of variances or median (interquartile range: 25th to 75th percentiles) and compared by Kruskal–Wallis. For categorical variables, values are summarized by frequencies and percentages, and tested by chi-square tests

Abbreviations: AF = atrial fibrillation; Alb = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CAD = coronary artery disease; CIED = Cardiovascular implanted electronic device; CrCl = creatinine clearance; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; Hb = hemoglobin; HF = heart failure; HTN = hypertension; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; OSAS = obstructive sleep apnea syndrom; PE = pulmonary embolism; PVD = peripheral vascular disease; SE = systemic thromboembolism; Scr = serum creatinine; TIA = transient ischemic attack

Table 2 Risk factors associated with underdosing or overdosing

Factor	Unadjusted Analysis			Adjusted Analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Risk factor of underdosing						
Age	2.22	1.74–2.82	< 0.001	1.98	1.52–2.60	< 0.001
CrCl	0.98	0.97–0.99	< 0.001	0.98	0.97–0.99	0.001
Non-internal medicine ward	2.09	1.39–3.17	< 0.001	2.15	1.33–3.45	0.002
Risk factor of Overdosing						
Age	0.40	0.20–0.80	< 0.010	0.38	0.19–0.75	0.005

Abbreviations: CrCl = creatinine clearance

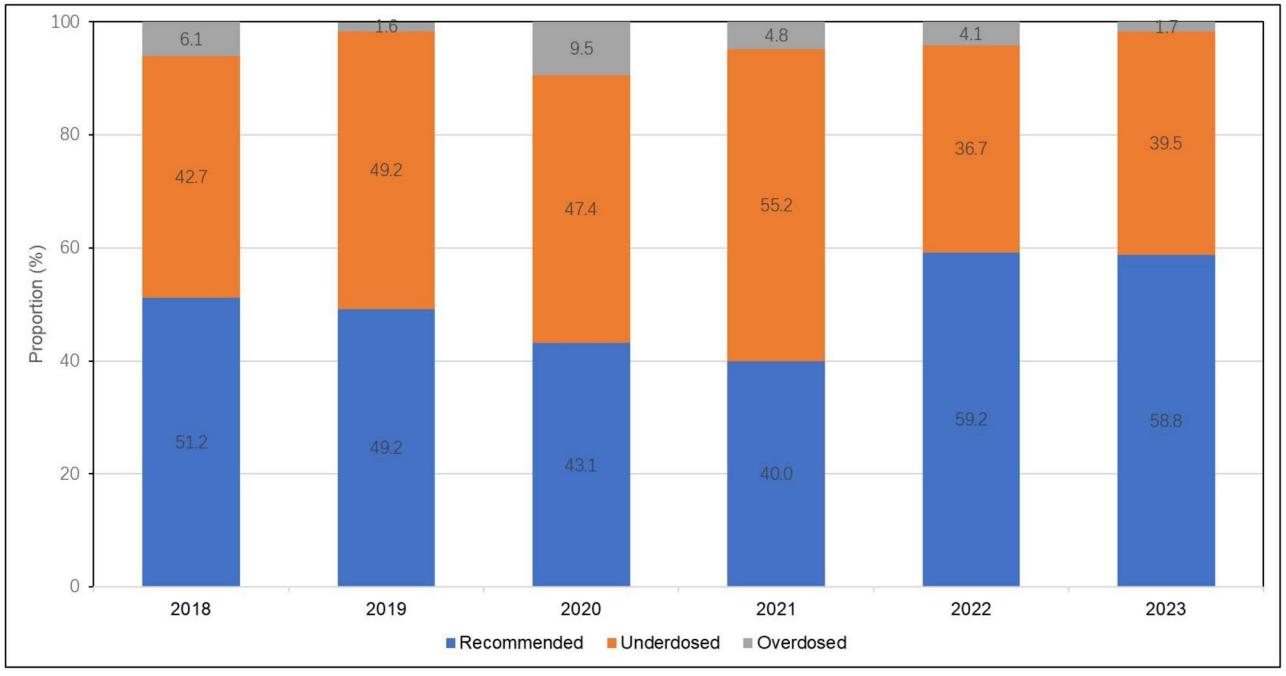

Fig. 3 Trends in the rates of recommended, underdosing, and overdosing of DOAC

82 ± 8 years showed that the rate of inappropriate DOAC use was as high as 54.4%, of which 93.8% were underdosed [16]. These research results indicated that underdosing of DOAC is the most prominent issue among inappropriate DOAC dosing in very older AF populations. Our research findings were consistent with this, with DOAC underdosing accounting for up to 90.7% of cases. Very older AF patients receiving low-dose DOAC typically have the following characteristics: older age, lower BMI or body weight, higher bleeding risk, and poorer renal function. Multiple studies also supported these findings [13, 15]. Additionally, we analyzed the differences between various departments and found that DOAC underdosing was less common in cardiology and internal medicine wards. Interestingly, this contrasts with a previous French study, which found underdosing to be more prevalent in cardiology wards [15]. This phenomenon may reflect differences in experience and education levels regarding stroke prevention in AF across different departments and healthcare systems.

Previous studies [5, 17, 18], including younger AF cohorts, had confirmed that advanced age, renal dysfunction, weight, and bleeding risk were independent risk factors for underdosing of DOACs. However, research on very older AF populations was relatively limited. Carbone et al. [13] found that in very older AF patients, male gender, coronary heart disease, and low BMI were independently associated with underdosing of DOACs. Cavillon Decaestecker et al. [15] reported that neurology wards were negatively correlated with underdosing of DOACs, while the use of antidepressants was positively correlated. Our research analysis also confirmed that in very older AF patients, advanced age and renal dysfunction were independently associated with underdosing of DOACs. Additionally, we explored the correlation between hospital wards and underdosing of DOACs. Similarly, to the analysis by Cavillon Decaestecker et al., [15] our analysis identified internal medicine wards (including neurology) were negatively correlated with underdosing. Physicians in internal medicine and neurology wards may place

greater emphasis on stroke prevention and guideline-adherent dosing. In contrast, other specialties may be more conservative due to heightened concerns about bleeding complications. These findings highlight the need for better interdisciplinary communication and coordination in anticoagulation management, and support the development of multidisciplinary and patient-centered models of care to ensure optimal and individualized DOAC use in older adults with AF. It is also noteworthy that previous studies have demonstrated the influence of ethnicity on the pharmacological response to anticoagulants, particularly vitamin K antagonists (VKAs), and emerging evidence suggests that similar variability may exist with DOACs [17, 19]. Asian populations, including Chinese patients, appear to have a higher susceptibility to bleeding at equivalent doses, which may partially account for the high prevalence of underdosing observed in our cohort. These observations highlight the importance of developing population-specific dosing strategies and conducting further research across diverse ethnic groups. Notably, differences in the prevalence of underdosing among specific DOACs were observed, with underdosing being more common for rivaroxaban and less frequent for dabigatran. One possible explanation for this pattern may relate to differences in formulation. Rivaroxaban is available as a 10 mg tablet, which makes it more convenient for physicians to prescribe at a lower-than-recommended dose. In contrast, dabigatran is formulated as a capsule, and in China, it is only available in 110 mg and 150 mg dosages, which cannot be split or adjusted easily, potentially limiting the occurrence of underdosing in clinical practice.

On the other hand, previous studies and our research had shown that although the proportion was low, there was still a problem of DOAC overdosing in very older AF patients. Carbone et al.'s study had shown that diabetes and history of bleeding were positively correlated with overdosage, while age and BMI were negatively correlated [13]. Our study had also confirmed an independent correlation between age and DOAC overdosing.

It was worth noting that our study found that the appropriateness of DOAC use in very older AF patients had improved from 2018 to 2023, although this improvement was not significant. In contrast, the situation was more optimistic for younger AF patient groups, where the appropriate use of DOACs showed significant annual improvement. The reasons for this difference, besides the complex characteristics of the very older population itself, also lay in the lack of evidence-based medical evidence for this group. On one hand, patients aged 80 and above are typically excluded from clinical trials of DOACs [2–4]. In previous landmark clinical trials of DOACs, the mean or median age of participants ranged from 70 to 73 years [2–4]. Therefore, the clinical guidelines recommending the use of DOACs based on these trials may not be entirely applicable to very older patients. On the other hand, there is still a lack of high-quality research on underdosing than recommended dosing of DOACs. The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial [20] is the only randomized controlled trial to date that has studied underdosing of NOACs in AF patients aged 80 and above. This study demonstrated that a once-daily 15 mg dose of edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding compared to placebo. However, evidence comparing underdosing than recommended dosing of DOAC primarily comes from observational cohort studies, which involved relatively younger subjects and have inconsistent conclusions. The GARFIELD-AF (Global Anticoagulant Registry in the FIELD-AF) study [17], which included patients with an average age of 72 years, revealed in its 2-year follow-up data that underdosing of DOACs was associated with an increased risk of all-cause mortality. Interestingly, despite a significantly reduced bleeding risk, there were no significant differences in the risks of stroke, systemic embolism, or major bleeding compared to recommended doses. Similarly, data from the ORBIT-AF II registry study, focusing on AF patients with an average age of 71 years, showed that patients receiving underdosed DOACs had a significantly higher rate of cardiovascular hospitalization within one year [5]. The two-year follow-up data further indicated an increase in thromboembolic events and mortality among these patients [21]. While these differences weren't statistically significant after adjusting for variables, the overall data trend still leaned towards supporting the use of recommended DOAC doses. Meanwhile, multiple studies from different regions with comparable age groups of study populations have also confirmed that underdosing of DOACs not only fails to reduce the risk of bleeding, systemic embolism, or all-cause mortality in atrial fibrillation patients, but may also significantly increase the risk of stroke and systemic embolism [22, 23]. Data from the Danish Stroke Registry [24], however, revealed no significant differences in stroke severity and 1-year mortality between inappropriate and appropriate direct oral anticoagulant therapy. Notably, this study population was older, with an average age of 78.7 years. Similarly, a nationwide study focusing on older individuals (average age 82 years) demonstrated that over a one-year observation period, underdosed DOAC treatment did not significantly differ in effectiveness compared to recommended-dose DOAC treatment [25]. Interestingly, the underdosed DOAC treatment was associated with a lower bleeding rate. A post hoc analysis of the ENGAGE AF-TIMI 48 randomized clinical trial found that in AF patients 80 years and older, those

receiving edoxaban 30 mg daily had lower major bleeding events compared to those receiving 60 mg daily (in patients without dose-reduction criteria), without an increase in ischemic events [26]. However, conflicting results exist. An Italian multicenter study of AF patients aged 80 and above found no significant differences in thromboembolic events, major bleeding events, and mortality rates among different dose subgroups. Notably, the underdosed group had a significantly lower survival rate compared to the appropriate dose group [13]. A retrospective cohort study from Taiwan's National Health Insurance Research Database (NHIRD) also showed that for AF patients aged 80 and above, low-dose DOACs were associated with higher risks of arterial and venous thrombosis, death, and composite outcomes compared to recommended-dose DOACs [27].

Our study had several limitations. First, the retrospective study design may have led to bias and incompleteness in data collection. Second, the single-center study limited the generalizability of the results. Third, the study was unable to comprehensively capture all factors influencing physicians' decision-making regarding DOAC dosing. For example, we did not assess DOAC plasma concentrations, which may be particularly relevant in frail older patients, as recent studies have indicated that recommended dosing may not always result in optimal drug exposure in this population [28]. In addition, the differences in the distribution of DOAC types across studies may contribute to variations in study outcomes, which should be considered when interpreting the results. Lastly, discrepancies in DOAC dose reduction criteria between China and other countries—particularly for rivaroxaban—may limit the comparability of our findings with international studies. These differences should be taken into account when interpreting cross-national variations in prescribing patterns and dosing appropriateness.

Conclusions

Inappropriate DOAC dosing is very common among very old AF patients, particularly with underdosing, and this situation has not significantly improved over the years. Therefore, there is an urgent need to promote patient-centered multidisciplinary management and shared decision-making models for AF, while also conducting high-quality prognostic studies. Our study contributes to this effort by focusing on real-world prescribing patterns in patients aged 80 and above in a Chinese tertiary hospital, offering insight into clinical decision-making and the underlying factors influencing off-label DOAC dosing in this population.

Abbreviations

AF Atrial fibrillation
BMI Body mass index
CrCl Creatinine clearance
DOAC Direct oral anticoagulant
NVAF Non-valvular atrial fibrillation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05960-3.

Supplementary Material 1: **Supplementary Table S1**: Appropriate dosage levels for NOACs administered to patients aged ≥ 80 years with atrial fibrillation in China. **Supplementary Table S2**: Baseline patient characteristics between underdosed and Non-underdosed group. **Supplementary Table S3**: Baseline patient characteristics between overdosed and Non-overdosed group.

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Author contributions

Ya-Tong Zhang: conceptualization, investigation, write. Jun-Peng Liu: conceptualization, funding acquisition, resources, supervision, write, review & editing. Zi-Nan Zhao, Yi-Fan Na, Tian-Qi Zhang, Min Dong, Yu-Hao Wan and Min Zeng: investigation, formal analysis. Hong-Qiu Gu: formal analysis. Ning Sun and Cheng Wu: investigation, data Curation. Jiefu Yang: resources, supervision. All authors reviewed the draft, made contributions and approved the final manuscript.

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Data availability

Date sharing might compromise patient's individual privacy. Please contact corresponding author for possible data sharing.

Declarations

Ethics approval and consent to participate

The study was adhered to the Declaration of Helsinki. This study was approved by the Ethics Committee Board of Beijing Hospital (approval no. 2023BYJYYEC-279-01). The need for consent to participate was waived by the Institutional Review Board of the Beijing Hospital as the study was retrospective, and all data were anonymized before analysis..

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical Trial registration

ChiCTR2300076161; registration date: 09/26/2023.

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