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Efficacy, safety, and bleeding risk factor analysis of oral anticoagulants in AF patients ≥ 65 years of age: a multicenter retrospective cohort study

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Abstract

Background Stroke prevention in elderly patients with atrial fibrillation (AF) is challenging and requires a balance between thromboembolic prevention and bleeding. The comparison of novel oral anticoagulants (NOACs) and warfarin in clinical practice in elderly Asian patients has not been well studied. The purpose of this study was to evaluate the efficacy and safety of NOACs versus warfarin in elderly patients with AF in conjunction with data from real-world observational studies.

Methods This was a retrospective multicenter cohort study conducted in 4 centers in China, where patient information and clinical events were collected through an average of 15 months of follow-up and case queries. Clinical outcomes included major bleeding, minor bleeding, total bleeding, thrombosis, and all-cause mortality.

Results A total of 3450 elderly patients with AF were enrolled. 2656 patients were treated with at least 1 NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban), and 794 patients were treated with warfarin. After correcting for confounders, NOACs significantly reduced the risk of minor bleeding [OR 0.70 (95% CL, 0.49–1.01),$P=0.049$] and all-cause mortality [OR 0.57(95% CI, 0.44–0.75),$P<0.001$] compared with warfarin, however, major bleeding events [OR 1.51 (95% CL, 0.98–2.42),$P=0.075$] and thrombotic events [OR 0.79 (95% CL, 0.57–1.13),$P=0.187$] were not significantly different. There was no heterogeneity between clinical outcomes of NOACs and warfarin in subgroup analyses of age (65–74, 75–84, ≥ 85 years), sex (male, female), BMI (≥ 25, < 25), comorbidities (including hypertension, diabetes and no hypertension, no diabetes), except in female subgroup, where NOACs significantly reduced the risk of minor bleeding [OR 0.56 (95% CL, 0.34–0.91),$P=0.018$] and increased the risk of major bleeding [OR 2.28 (95% CL, 1.12–5.14),$P=0.032$] compared with warfarin.

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Conclusion Compared with warfarin, NOACs significantly reduced the risk of minor bleeding, all-cause mortality, and there were no statistically significant differences in major bleeding or thrombotic events. NOACs were not more effective than warfarin in thrombotic and bleeding events, regardless of the subgroup analyses on age, male, BMI and comorbid hypertension and diabetes.

Keywords Atrial fibrillation, Elderly patients, NOACs, Warfarin, Effectiveness, Bleeding

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, with a worldwide prevalence of 2–4%, and the prevalence of AF increases with age [1]. A study by Singer et al. [2] suggested that age is a continuous risk factor for increased risk of thromboembolism in patients with AF, with an increased risk of thromboembolism in patients with AF between the ages of 65 to 74 years, 75 to 84, and ages ≥ 85 years by a factor of 2.38, 4.46, and 8.14, respectively. Therefore, oral anticoagulant (OAC) therapy is recommended to reduce the risk of stroke or systemic embolism in elderly patients with AF who have risk factors for stroke [3]. In AF patients, stroke prevention can be performed in high risk patients based on the CHA2DS2-VASc score, and anticoagulation prophylaxis with warfarin has traditionally been recommended. However, overcoming some of the limitations of warfarin, and with the advantages of a predictable pharmacological effect and no need for routine coagulation monitoring, novel oral anticoagulants (NOACs) have become the most commonly prescribed medication for the prevention of ischaemic stroke in patients with nonvalvular atrial fibrillation (NVAF) and for the treatment and prevention of venous thromboembolism (VTE) [4], and these advantages may improve the convenience of medication for elderly patients. However, the comparison between NOACs and warfarin in clinical practice in elderly Asian patients has not been well studied.

Four large randomized controlled trials (RCTs) have shown that NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are noninferior to warfarin in preventing the risk of stroke and systemic embolism as well as major bleeding [5–8]. However, in elderly patients with AF, there are some discrepancies in populations of different ages and countries [9–12]. In addition, older patients in RCT are usually a selected group who are relatively healthy and have fewer comorbidities such as hypertension, diabetes mellitus, heart failure, and coronary atherosclerosis [13, 14]. However, in real-world trials [15, 16], elderly patients with AF are often accompanied by cardiovascular and cerebrovascular diseases, hepatic and renal insufficiency, and extreme body weight, all of which can affect the pharmacokinetics of NOACs, and increase the risk of adverse events (e.g., hemorrhage) [17]. Real-world populations differ from those in RCT, and these differences may have a significant impact on the benefit-risk ratio of NOACs, compared with warfarin [18]. Therefore, it is important to analyze the effectiveness and safety of NOACs use in real-world elder adults.

In addition, Asian patients with AF are at higher risk of stroke and bleeding than Western populations [19], and elder patients with AF were largely underrepresented in clinical trials (RCTs) on the efficacy and safety of NOACs. Therefore, more real-world data are urgently needed to assess the thromboembolic risk and bleeding risk of NOACs in elderly Asian patients. To test the hypothesis that NOACs have at least as much efficacy and safety as warfarin in elderly Asian patients with AF, the aim of our study was to characterize the efficacy and safety of using NOACs in elderly AF patients ≥ 65 years of age in actual clinical practice in Asia.

Method

Study design

From January 2019 to August 2023, we conducted a retrospective multicenter registry in 4 centers in China. The distribution of hospitals in each center is shown in Supplementary Table 1. The Ethics Committee of Fujian Maternity and Child Health Hospital approved the scheme (registration number: ChiCTR2300067734). Due to the retrospective nature of this study, the institutional review board waived the patient informed consent requirement. The inclusion criteria for this study were as follows: (1) Age ≥ 65 years; (2) Diagnosis of AF; (3) Treatment with OAC. The exclusion criteria are listed below: (1) Discharged from the hospital without OAC; (2)Patients with haemorrhagic disease due to acute liver failure; (3)Patients with incomplete basic data such as age and gender. A total of 3450 AF patients treated with OAC were eligible to participate in this study after meeting the inclusion criteria. Of these, 2656 patients were treated with NOACs and 794 with warfarin. The flowchart for the study population selection is shown in Fig. 1. We also explored the efficacy and safety of NOACs and warfarin in the treatment of elderly AF patients with comorbid hypertension and diabetes, respectively.

Data collection and definition

Demographic information was collected through the hospital medical records system. Data were collated and recorded by a specialized pharmacist, and included patients with AF who were treated with NOACs and aged greater or equal to 18 years. We obtained clinical events through follow-up visits with patients or relatives. Basic

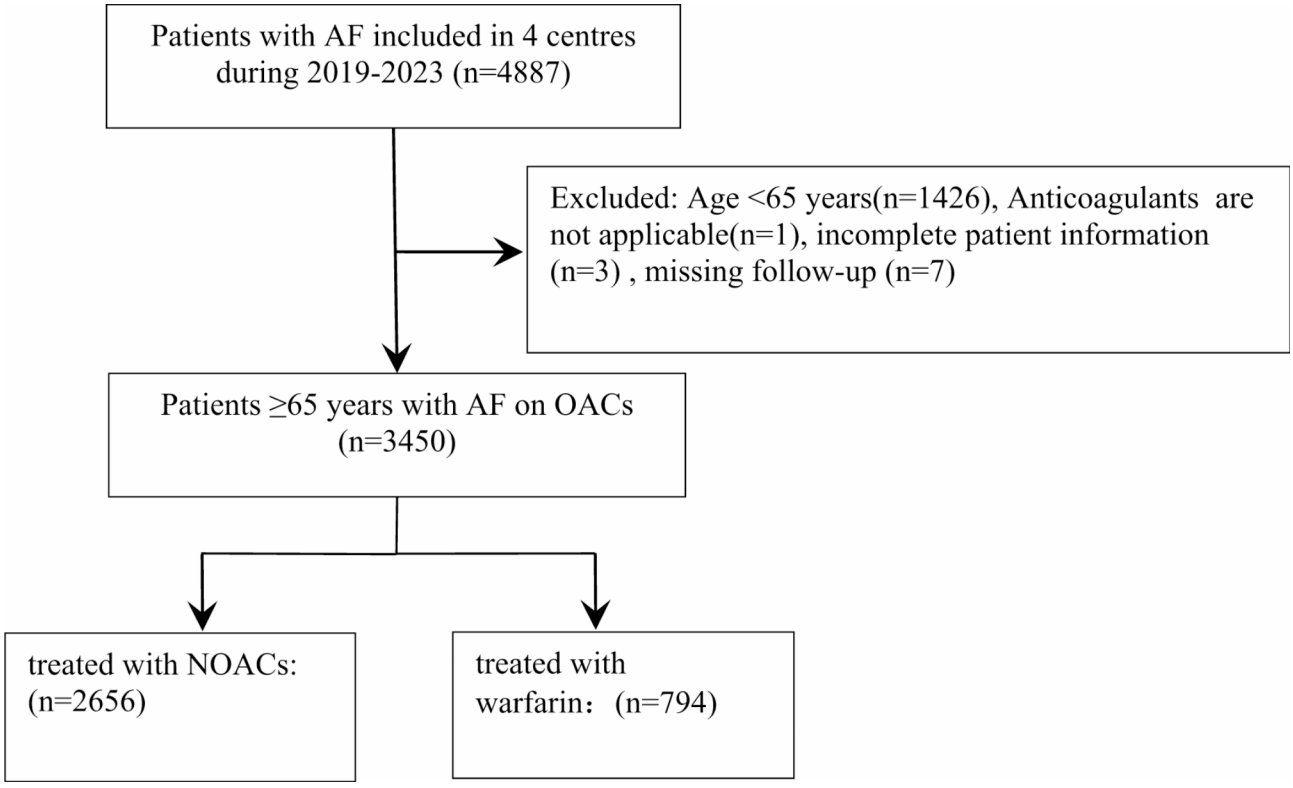

Fig. 1 The flowchart of the study population selection

statistics such as age, gender, height, weight, smoking and alcohol consumption were collected. We also collected information on comorbidities such as hypertension, diabetes mellitus, coronary artery disease, heart failure, malignancy, peripheral vascular disease, hepatic insufficiency, renal insufficiency, and chronic obstructive pulmonary disease (COPD), as well as medication use information such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), β-blockers, calcium channel blockers, statins, anti platelet drugs, digoxin, amiodarone, and nonsteroidal anti-inflammatory drugs (NSAIDs) in combination. Information on bleeding, thrombotic events, and all-cause mortality in patients taking OAC was collected through follow-up. Based on the patients' clinical data, we performed the CHA2DS2-VASC score [20] (including congestive heart failure/left ventricular insufficiency, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65–74 years, and gender) and the HAS-BLED score [21] (hypertension, abnormalities in liver function, abnormal kidney function, stroke, bleeding, age > 65 years, drugs and alcohol).

Study outcomes

The safety outcomes in this study were total bleeding, major bleeding, and minor bleeding, and the efficacy outcomes were thromboembolic events as well as all-cause mortality. Total bleeding includes all bleeding events, including major and minor bleeding. The International Society for Thrombosis and Hemostasis (ISTH) defines major bleeding as bleeding leading to death, occurring in a critical organ (intracranial, intraspinal, intraocular, retrofibular, intra-articular or intrapericardial, intramuscular fascial compartment syndrome), or a decrease in the hemoglobin level of at least 2 g/dl or a transfusion of at least 2 units of red blood cells [22]. Minor bleeding events were defined as not meeting the criteria for major or clinically significant bleeding. Thromboembolic events include ischemic stroke and systemic embolism. Systemic embolization is defined as acute vascular occlusion of an extremity or organ documented by imaging, surgery, or autopsy [23].

Statistical analysis

Data were presented as mean and standard deviation or median and interquartile range for continuous variables and as proportions for categorical variables. Continuous variables were tested for normality and described by the mean ± standard deviation if they conformed to a normal distribution, or by the median (interquartile range) if they did not. If they conformed to a normal distribution, Student's t-test was used to compare the differences in continuous variables. If not, non-parametric statistical

tests were used. Differences between categorical variables were compared by the chi-square test. For comparing the risk of total bleeding, major bleeding, minor bleeding, thrombosis and all-cause deaths in elderly AF patients after taking NOACs, logistic regression was used to analyze potential confounders affecting major bleeding, minor bleeding, total bleeding, thrombosis and all-cause deaths. We also compared the risk of one year clinical events, two years clinical events and three years clinical events of total bleeding, major bleeding, minor bleeding, thrombosis and all-cause deaths in elderly AF patients after taking NOACs. Therefore, we identified covariates of different clinical outcomes based on clinical risk factors for thromboembolism, bleeding and all-cause deaths, as well as significant variables in two groups in the baseline table. The covariates of bleeding include: age, gender, body mass index (BMI), smoking, alcohol consumption, history of bleeding, history of ischemic stroke, hypertension, peripheral arterial disease, diabetes mellitus, renal insufficiency, hepatic insufficiency, antiplatelet agents, statins, PPI, NSAIDs, ACEIs, ARBs, digoxin. The covariates of thromboembolism include: age, gender, BMI, smoking, alcohol, history ischemic stroke, historyTIA, hypertension, diabetes, peripheral arterial disease, coronary heart disease, heart failure, cancer, hepatic insufficiency, renal insufficiency, antiplatelet agents, PPI, statins, ACEIs, ARB. The covariates of all-cause deaths include: age, gender, BMI, smoking, alcohol, history ischemic stroke, historyTIA, history of bleeding, hypertension, diabetes, peripheral arterial disease, coronary heart disease, heart failure, cancer, hepatic insufficiency, renal insufficiency, antiplatelet agents, NSAIDs, PPI, statins, ACEIs, ARB, digoxin.

For further analysis, we performed the following subgroup comparisons of outcome events between the NOACs and warfarin groups using above covariates of clinical outcomes: (1) Sex (male, female); (2) Age (65–74, 75–84, ≥85);(3) BMI (≥25, <25);(4) Comorbidities, including hypertension, diabetes mellitus; (5) Non-complicated diseases, including no hypertension, no diabetes. Odds ratios (OR), 95% confidence intervals (Cl) and *P* values were calculated. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 26.0 (IBM Corporation, Armonk, NY, USA).

Result

Baseline characteristics

A total of 3450 patients with AF were included in this study, of whom 2656 were treated with NOACs and 794 with warfarin. Figure 1 shows a flowchart of the patient screening process. Table 1 shows the baseline information of the patients. Compared with patients treated with warfarin, the NOACs group had older patients, more male patients, a slightly higher proportion of smokers and drinkers, a higher burden of comorbid hypertension, diabetes mellitus, peripheral arterial disease, coronary arterial disease, and hepatic and renal insufficiency disease, and a slightly lower burden of comorbid heart failure disease. Regarding combinations, patients in the NOACs group used more statins and ARBs. The HAS-BLED scores were higher in the NOACs group than in the warfarin group. Table 1 shows the baseline information of the patients.

Overall clinical results

The mean follow-up time was 15 months. There were 327 (9.48%) bleeding events, 198 (5.74%) thrombotic events, and 339 (9.83%) all-cause deaths among the 3450 patients included in the study. Bleeding events included 157 (4.56%) major bleeding events and 173 (5.01%) minor bleeding events. Compared with the warfarin group, patients receiving NOACs had lower rates of thrombotic events, minor bleeding events, and all-cause mortality, and higher rates of major bleeding, particularly in the GI tract. The specific results for the NOACs and warfarin groups are shown in Table 2. One year, two year and three year events of clinical outcomes of NOACs versus warfarin in elderly AF patients are shown in Supplementary Table 2, Supplementary Tables 3 and Supplementary Table 4.

Safe endings

The incidence of total bleeding in the NOACs group was 9.41%, major bleeding was 4.97%, and minor bleeding was 4.56%; in the warfarin group, the incidence of total bleeding was 9.70%, major bleeding was 3.15%, and minor bleeding was 6.55%. The risk of major bleeding [OR1.51 (95%CL, 0.76–1.35), $P=0.947$] and gastrointestinal bleeding [OR1.64 (95%CL, 1.02–2.78), $P=0.051$] in patients using NOACs were not significantly different from warfarin group after adjusting for confounders. But NOACs had the distinct strength of significantly reduced risk of minor bleeding compared with warfarin [OR 0.70 (95%CL,0.49–1.01),$P=0.049$]. NOACs also had the distinct strength of significantly reduced risk of all-cause death compared with warfarin in the follow-up period of one year, two years or three years.(Supplementary Table 2, Supplementary Tables 3 and Supplementary Table 4).

Effective endings

The incidence of thrombosis was 5.50% in the NOACs group and 6.55% in the warfarin group. The risk of thrombosis was similar in both groups after adjusting for confounders [OR 0.79 (95%CI, 0.57–1.13),$P=0.187$]. The risk of all-cause mortality in AF patients in the NOACs group was lower than in the warfarin group after adjusting for confounders, with a significant difference [OR

Table 1 Baseline characteristics of elderly AF patients with NOACs and warfarin

	NOACs (*n* = 2656)	warfarin (*n* = 794)	*P* value
Age			< 0.001
65–74, n (%)	1208(45.48)	487(61.33)	< 0.001
75–84, n (%)	1052(39.61)	263(33.12)	
≥ 85, n (%)	396(14.91)	44(5.14)	
Median, Median(25%, 75%)	75(70–82)	72(68-77.25)	< 0.001
Sex, Femal, n (%)	1107(41.68)	393(49.50)	< 0.001
BMI, Median(25%, 75%)	23.31(21.22–25.78)	23.04(21.20-25.65)	0.499
≥ 25, n (%)	811(30.53)	235(29.60)	0.614
<25, n (%)	1845(69.47)	559(70.40)	
Smoking, n (%)	291(10.96)	67(8.44)	0.041
Alcohol, n (%)	332(12.50)	72(9.07)	0.008
History of bleeding, n (%)	140(5.27)	37(4.66)	0.493
Anaemia, n (%)	733(27.60)	209(26.32)	0.479
History of ischaemic stroke, n (%)	657(24.74)	188(23.68)	0.543
History of TIA, n (%)	23(0.87)	11(1.39)	0.194
Hypertension, n(%)	1708(64.31)	427(53.78)	< 0.001
coronary heart disease, n(%)	1089(41.00)	297(37.41)	0.070
Heart failure, n(%)	1202(45.26)	432(54.41)	< 0.001
Peripheral artery disease, n(%)	859(32.34)	224(28.21)	0.028
Active cancer, n(%)	75(2.82)	21(2.64)	0.788
COPD, n (%)	379(14.27)	105(13.22)	0.457
Diabetes, n(%)	629(23.68)	158(19.90)	0.026
Arthrolithiasis, n(%)	134(5.05)	30(3.78)	0.141
Hepatic insufficiency, n(%)	164(6.17)	34(4.28)	0.044
Renal inadequacy, n(%)	486(18.30)	135(17.00)	0.404
Combined medication, n (%)			
Antiplatelet drugs, n (%)	921(34.68)	324(40.81)	0.002
PPI	1281(48.23)	485(61.08)	0.000
Statins	1757(66.15)	479(60.33)	0.003
Amiodarone	297(11.18)	81(10.20)	0.438
NSAID	457(17.21)	149(18.77)	0.311
ACEI	114(4.29)	85(10.71)	< 0.001
ARB	899(33.85)	215(27.08)	< 0.001
CCB	675(25.41)	186(23.43)	0.256
β-Blockers	1549(58.32)	476(59.95)	0.413
Digoxin	415(15.63)	262(33.00)	< 0.001
score			
CHA2DS2-VASc, Median(25%, 75%)	5(4–6)	5(3–6)	0.045
CHA2DS2-VASc ≥ 2, n (%)	2606(98.12)	786(98.99)	0.092
HAS-BLED, Median(25%, 75%)	2(1–2)	1(1–2)	< 0.001
HAS-BLED ≥ 3, n (%)	484(18.22)	127(15.99)	0.149

Table 2 Clinical outcomes of NOACs versus warfarin in elderly AF patients

Clinical Outcomes	NOACs(*n* = 2656)		warfarin(*n* = 794)					
	Incident number(n)	Incidence rate(%/n)	Incident number(n)	Incidence rate(%/n)	OR(95% CI)	*P*-value	Adjusted OR(95% CI)	Adjusted *P*-value
Thromboembolism	146	5.50	52	6.55	0.83(0.60–1.15)	0.263	0.79(0.57–1.13)	0.187
Total bleeding	250	9.41	77	9.70	1.03(0.78–1.35)	0.853	1.01(0.76–1.35)	0.947
Major bleeding	132	4.97	25	3.15	1.61(1.04–2.47)	0.031	1.51(0.98–2.42)	0.075
Minor bleeding	121	4.56	52	6.55	0.68(0.49–0.95)	0.024	0.70(0.49–1.01)	0.049
Gastrointestinal bleeding	116	4.37	20	2.52	1.77(1.09–2.86)	0.019	1.64(1.02–2.78)	0.051
Intracranial haemorrhage	18	0.68	5	0.63	1.08(0.40–2.91)	0.884	1.06(0.40–3.35)	0.914
All-cause death	237	8.92	102	12.85	0.67(0.52–0.85)	< 0.001	0.57(0.44–0.75)	< 0.001

Table 3 Subgroup ending of clinical outcomes of NOACs versus warfarin in elderly AF patients

	NOACs(*n* = 2656)		warfarin(*n* = 794)			
	Incident Number (n)	Incident Number (%)	Incident Number (n)	Incidence Rate(%)	Adjusted OR(95% CI)	*P*-value
Thromboembolism						
All	146	5.50	52	6.55	0.79(0.57–1.13)	0.187
65 ≤ Age < 74	64	5.29	29	5.95	0.94(0.59–1.54)	0.801
75 ≤ Age < 84	54	5.41	19	7.22	0.66(0.38–1.18)	0.144
Age ≥ 85	28	7.07	4	9.09	0.65(0.22–2.43)	0.479
Male	73	4.71	27	6.73	0.64(0.40–1.04)	0.065
Female	73	6.59	25	6.36	1.01(0.62–1.69)	0.964
BMI < 25	106	5.75	41	7.33	0.76(0.52–1.14)	0.171
BMI ≥ 25	40	4.93	11	4.68	1.01(0.50–2.20)	0.978
Hypertension	105	6.15	27	6.32	0.57(0.32–1.03)	0.057
No Hypertension	41	4.32	25	6.81	1.00(0.64–1.60)	0.996
Diabetes	29	4.61	7	4.43	0.81(0.56–1.19)	0.262
No Diabetes	117	5.77	45	7.08	0.84(0.36–2.21)	0.709
Major bleeding						
All	132	4.97	25	3.15	1.47(0.93–2.31)	0.098
65 ≤ Age < 74	52	4.30	13	2.67	1.58(0.85–3.15)	0.166
75 ≤ Age < 84	55	5.23	10	3.80	1.43(0.73–3.09)	0.328
Age ≥ 85	25	6.31	2	4.54	1.49(0.38–10.17)	0.619
Male	78	5.04	16	3.99	1.14(0.66–2.09)	0.655
Female	54	4.88	9	2.29	2.28(1.12–5.14)	0.032
BMI < 25	84	4.55	17	3.04	1.39(0.82–2.50)	0.243
BMI ≥ 25	48	5.92	8	3.40	1.65(0.79–3.92)	0.214
Hypertension	87	5.09	12	2.81	1.34(0.70–2.73)	0.394
No Hypertension	45	4.75	13	3.54	1.72(0.95–3.39)	0.090
Diabetes	27	4.29	2	1.27	1.39(0.87–2.30)	0.180
No Diabetes	105	5.18	23	3.62	3.45(0.97–22.12)	0.103
Minor bleeding						
All	121	4.56	52	6.55	0.69(0.48–0.98)	0.038
65 ≤ Age < 74	67	5.55	37	7.59	0.73(0.47–1.15)	0.166
75 ≤ Age < 84	39	3.71	14	5.32	0.58(0.31–1.15)	0.101
Age ≥ 85	15	3.79	1	2.27	3.77(0.63–74.90)	0.233
Male	70	4.52	19	4.74	0.93(0.55–1.66)	0.803
Female	51	4.61	33	8.40	0.56(0.34–0.91)	0.018
BMI < 25	88	4.77	38	6.80	0.72(0.47-1.0)	0.115
BMI ≥ 25	33	4.07	14	5.96	0.64(0.32–1.32)	0.207
Hypertension	82	4.80	24	5.62	0.60(0.35–1.05)	0.068
No Hypertension	39	4.11	28	7.63	0.85(0.531–1.41)	0.517
Diabetes	24	3.82	9	5.70	0.70(0.47–1.04)	0.071
No Diabetes	97	4.79	43	6.76	0.71(0.32–1.69)	0.408

0.57 (95% CI, 0.44–0.75), $P < 0.001$]. NOACs had the distinct strength of significantly reduced risk of thromboembolism compared with warfarin in the follow-up period of one year, two years or three years. (Supplementary Table 2, Supplementary Tables 3 and Supplementary Table 4)

Subgroup analysis

Subgroup analyses of age (65–74, 75–84, ≥ 85 years), sex (male, female), BMI (≥ 25, < 25), comorbidities (including hypertension, diabetes mellitus), and non-comorbidities (including no hypertension, no diabetes mellitus) were performed to compare for bleeding events and thrombotic events in elderly AF patients treated with NOACs and warfarin (Table 3).

In terms of thrombosis events, the risk of thrombosis bleeding was similar for NOACs compared with warfarin in all subgroups after adjusting for confounders, with no significant difference ($P > 0.05$).

In terms of minor bleeding events, NOACs had higher major bleeding events than warfarin in the female subgroup after adjusting for confounders, with statistically significant differences ([OR 2.28 (95%CI, 1.12–5.14), $P = 0.032$]), and also fewer minor bleeding events than

warfarin in the female subgroup after adjusting for confounders, with statistically significant differences ([OR 0.56 (95%CI, 0.34–0.91), $P = 0.018$]) respectively (Tanle 3). The remaining subgroups had a similar risk of minor bleeding and major bleeding event after adjusting for confounders, with no significant differences.

Discussion

Based on a multicenter retrospective cohort from four hospitals in China, this study was designed to investigate the efficacy, safety, and bleeding risk factor of NOACs and warfarin for the treatment of elderly patients ≥ 65 years with AF. After adjusting confounders using logistic regression analysis, the main results of our study are as follows: (1) In elder patients ≥ 65 years of age with AF, NOACs are associated with a reduced risk of minor bleeding and all-cause deaths compared with warfarin; (2) The risk of thromboembolism and major bleeding is similar for NOACs and warfarin; (4) There were no significant differences between NOACs and warfarin in the risk of thromboembolism, major and minor bleeding in the age strata ($65 \le Age < 74$, $75 \le Age < 84$, $Age \ge 85$);(5) In elderly AF patients with comorbid hypertension, diabetes mellitus, there was no significant difference in the risk of thromboembolism, major bleeding, and minor bleeding between NOACs and warfarin.

Our findings suggest that NOACs are associated with a significantly lower risk of minor bleeding than warfarin in elderly AF patients ≥ 65 years of age, with no significant difference in thromboembolic events and major bleeding events. Our study is consistent with previous findings on bleeding rates in AF patients specifically studied with oral anticoagulants [24], and in this large national cohort study comprising 32,675 AF patients (median age 74 years), the risk of clinically non-major bleeding was lower in patients receiving NOAC (5.09%) compared with those receiving warfarin. A direct long-term head-to-head comparison of the risk-benefit profile between warfarin and NOACs in 254,478 AF patients (328,796 person-years of follow-up), with a mean age of 76.3 ± 10.1 and 70.9 ± 12.1 years for NOACs and warfarin users, respectively, resulted in a significant reduction in the risk of major bleeding from clinically relevant nonmajor bleeding (MB/ CRNMB) risk of major bleeding was significantly reduced in the NOACs group [25].

We found no significant differences in effectiveness outcomes between NOACs and warfarin, but they varied in safety outcomes. There were no significant differences between NOACs and warfarin in terms of major bleeding. For site-specific bleeding incidence, there was a 1.64-fold increased risk of gastrointestinal haemorrhage in the DOAC group compared to the warfarin group [OR1.64, 95% Cl (1.02–2.78)], and a 1.06-fold increased risk of intracranial haemorrhage [OR 1.06, 95% CL (0.40–3.35)]. It has been shown that there is a higher risk of major bleeding with rivaroxaban compared to warfarin [26], and the majority of patients with NOACs in our study were on rivaroxaban, which may be a reason for the higher rate of major bleeding with NOACs than warfarin in our study. In addition, another meta-analysis showed safety differences between individual NOACs in elderly AF patients [27], and in addition to the overall clinical status of the patient (e.g., patients with comorbidities, elderly frail patients, patients with extreme body weights, and other therapies), it is also important to consider the effect of drug interactions, such as verapamil, dronedarone, or amiodarone, which are used in patients with AF, as well as antifungal drugs, antibiotics of the macrolide class, and antiretroviral protease inhibitors, all of which can increase plasma concentrations of NOACs and increase the risk of bleeding. Most of the patients in our study were elderly patients with multiple comorbid underlying diseases and co-administered multiple medications, which underlie the frail population. Recently, the results of the FRAIL-AF study were published in Circulation [28], a randomised, multicentre, open-label clinical trial of frail elderly patients with AF, where conversion of INR-guided warfarin therapy to non-vitamin K oral anticoagulants (NOACs) was shown to increase the risk of bleeding in frail elderly patients with non-valvular atrial fibrillation (NVF), compared with continuation of vitamin K antagonist (VKA) therapy. anticoagulants (NOACs) was associated with more bleeding complications and no reduction in thromboembolic complications. The above studies overlapped with the results of the present study.

In our subgroup analyses, overall, efficacy and safety results were consistent with the main trials. In investigating whether different age, gender, BMI category, comorbidities (hypertension and diabetes) and non-comorbidities had an effect on the efficacy and safety of NOACs and warfarin, we found that there were no statistically significant differences in the risk of minor bleeding, major bleeding and thromboembolism in patients treated with NOACs and warfarin in the subgroup of age, BMI, comorbidities (hypertension and diabetes) and non-comorbidities. However, in terms of female patients, NOACs had significantly fewer minor bleeding compared to warfarin ($p < 0.05$). This is inconsistent with the findings of a study analysing individual patient data from four pivotal trials of NOACs versus warfarin for patients with AF, which demonstrated that NOACs reduced the risk of embolism, death and haemorrhage compared to warfarin, irrespective of gender [29], but the age of the patients in that study had a relatively small proportion of older patients. In contrast, our study had a higher proportion of older patients using NOACs, with 90% of NOACs and only 10% of warfarin in patients ≥ 85

years of age. Meanwhile, elderly patients with multiple comorbidities and weakened hepatic and renal functions can lead to higher plasma drug concentrations, which can increase bleeding, and physicians usually give lower doses of NOACs in clinical practice due to concerns about the risk of bleeding, which leads to inconsistent results between real-world data and randomised controlled trials [16]. Based on this, it is necessary to further investigate the differences in real-world NOACs in specific populations. In the meantime, our findings must be interpreted with caution when comparing them with reported pivotal outcome trials, as well as observational studies, because of differences in study populations, definitions of haemorrhage, and healthcare systems, as well as other factors that are difficult to interpret.

We also observed that the choice of prescriptions for NOACs was related to underlying patient characteristics, with the use of NOACs in patients who were older, had comorbid hypertension, comorbid diabetes mellitus, comorbid coronary atherosclerosis, comorbid heart failure, comorbid peripheral arterial disease, use of antiplatelet medications, a high risk of bleeding, and a high risk of embolism, possibly because NOACs were safer, more stable, and had a higher risk of drug interactions are superior or noninferior to warfarin. History of cerebral infarction, coronary atherosclerosis, antiplatelet drugs, and nonsteroidal anti-inflammatory drugs were risk factors for hemorrhage and thrombosis in patients ≥ 65 years of age with AF, in contrast to a study by Rohla M et al. [30], which found that abnormal liver function, previous stroke or transient ischemic attack, antiplatelet or nonsteroidal anti-inflammatory drug combinations, heart failure, and advanced age (≥ 75 years of age) were associated with thromboembolism and hemorrhagic events Independently associated with thromboembolic and major bleeding events. The inconsistent risk factors may be due to the different populations included; the patients with AF in the Rohla M study were from several European countries, whereas the present study was a multicenter retrospective study in China, which suggests that different risk factor outcomes may be expected in different ethnic groups.

In real-world everyday practice, participants in randomised controlled trials are not always representative of the broad range of people with AF. Evidence from real-world studies sometimes complements or contradicts the results of randomised controlled trials. Based on published trials of NOACs and real-world studies, our real-world data suggest that the use of NOACs is not inferior to warfarin in Asian patients with AF, that NOACs are associated with a reduced risk of small haemorrhages, and that NOACs may be effective and safe for stroke prevention in Asians, suggesting that NOACs may be an attractive therapeutic option for stroke prevention in Asian patients.

Several strengths of this study are worth mentioning. First, the main strength of this study is the focus on older adults who are underrepresented in randomized controlled trials, using real-world data that are more representative of older adults treated with anticoagulants in clinical practice. Second, our study is a multicenter retrospective cohort analysis from a large sample size in China, with > 3000 cases included in the cohort, making our data and results representative. Third, this study examined differences in major bleeding, minor bleeding, thrombosis, and all-cause mortality in elderly patients with AF using NOACs and warfarin, stratified by patient age (65–74, 75–84, ≥ 85), BMI, gender, and presence of comorbidities (hypertension, diabetes mellitus, heart failure, and coronary artery atherosclerosis), with a more refined patient population.

This study also has some limitations. First, due to the retrospective nature of this study, information about the results may be incomplete. Second, the possibility of unclear or confused memory is unavoidable for most elderly patients during follow-up. Finally, no separate validity and safety analyses were conducted for specific NOACs. We hope to refine our results in the future using studies with larger samples.

Conclusion

Compared with warfarin, NOACs significantly reduced the risk of minor bleeding, all-cause mortality, and there were no statistically significant differences in major bleeding or thrombotic events. NOACs were not more effective than warfarin in thrombotic and bleeding events, regardless of the subgroup analyses on age, males, BMI and comorbid hypertension and diabetes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05838-4.

Supplementary Material 1

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Not applicable.

Author contributions
JZ initiated the study. YL, JC, XH, CY, SJ collected and entered the data. YL, JC performed data collation. YL, JC and PN performed data extraction and analyses. YL drafted the first version of the manuscript. YL, JC, PN and XH and JZ critically reviewed the manuscript and revised it. PN and YLworked on data validation. YL, JC performed the graphical revisions. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data relevant to the study are included in the article.

Declarations

Ethics approval and consent to participate
The study complied with the Declaration of Helsinki and was authorized by The Ethics Committee of Fujian Maternal and Child Health Hospital (registration number: ChiCTR2300067734). The review committee waived informed consent of patient because of the retrospective nature of this study.

Competing interests
The authors declare no competing interests.

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