Am J Transl Res 2025;17(6):4534-4545
www.ajtr.org /ISSN:1943-8141/AJTR0163521

Review Article

Efficacy and safety of oral anticoagulants in elderly patients with non-valvular atrial fibrillation: a meta-analysis

Baocai Fan[1,2], Jun Xia[1,2]

[1]*Department of Medical, Wujin Hospital Affiliated with Jiangsu University, Changzhou 213017, Jiangsu, China;*
[2]*The Wujin Clinical College, Xuzhou Medical University, Changzhou 213017, Jiangsu, China*

Received January 23, 2025; Accepted May 27, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Background: Thromboembolism is a common complication in elderly patients with non-Valvular Atrial Fibrillation (NVAF). Noval oral anticoagulants (NOACs) remain the primary treatment strategy. This study focuses on the optimal dosage and safety of new oral anticoagulants introduced in recent years. Objective: To investigate the optimal dose and safety of NOACs in elderly patients with NVAF through meta-analysis. Methods: A systematic literature search was conducted using both Chinese and international academic databases to identify studies on NOAC therapy in elderly patients with NVAF. A total of 22 studies were included. Meta-analysis was performed using RevMan 5.3 software. Results: The risk of systemic embolism (SSE) in patients receiving warfarin was significantly higher compared to those on both standard-dose and low-dose NOACs. Patients who take conventional doses of new anticoagulants orally have a higher risk of developing SSE ($P < 0.05$). The risk of severe bleeding in patients receiving standard-dose warfarin was higher than those on conventional dose and low-dose NOACs. There was no statistically significant difference in the risk of severe bleeding between patients with conventional and low-dose anticoagulants ($P > 0.05$). Funnel plots for SSE and major bleeding outcomes were symmetrical and centered around the mean, suggesting low publication bias and reliable results. Conclusion: Low-dose NOACs demonstrate favorable efficacy and safety in elderly NVAF patients, appearing superior to warfarin and conventional dose NOACs. These findings support the preferential use of NOACs over warfarin in this population.

Keywords: Elderly patients, non-valvular atrial fibrillation, novel anticoagulants, oral medication, meta-analysis, efficacy, safety

Introduction

Atrial Fibrillation (AF) is a tachyarrhythmic condition, with a global incidence of about 2% to 3% [1]. It is a leading cause of heart failure, ischemic stroke, and death. The risk of concurrent ischemic stroke in AF patients is four to five times higher than in non-valvular atrial fibrillation (NVAF) patients [2]. According to global disease burden reports, the number of AF patients has reached 33.5 million [3], with NVAF being the predominant type in Central Africa. The incidence of NVAF increases with age, and individuals over 60 years old represent a high-incidence group [4], accounting for more than 45% of all AF patients [5]. Due to the significantly high risk of thromboembolic events, NVAF patients are highly prone to thrombotic detachment, death and other serious complications [6, 7]. Therefore, global AF treatment guidelines emphasize the concurrent use of anticoagulant therapy for AF patients [8]. However, elderly patients, who often suffer from multiple chronic conditions, face considerable challenges in managing their medications, especially due to high stroke and bleeding risk scores [9]. For example, elderly patients receiving classical anticoagulant therapy such as warfarin often experience fatigue due to frequent blood monitoring, increasing the medication burden and leading to forgetfulness in monitoring INR levels, which severely impacts adherence to treatment.

Traditionally, oral anticoagulants in clinical practice mainly include vitamin K antagonists, with warfarin being the most widely used. As a classic oral anticoagulant, it has been used for

https://doi.org/10.62347/JOJX2439

more than 70 years and remains stable in anticoagulation therapy. A Time in Therapeutic Range (TTR) ≥ 65% is considered the standard for high-quality anticoagulant therapy. Currently, the TTR values of warfarin anticoagulation in clinical settings is reported to be 57.1% in Canada [10] and 68.8% in Turkey [11]. However, only about 12%-19% of patients in China achieve a TTR ≥ 65% [12], indicating a low rate of high-quality anticoagulation. This low rate of is contributed to factors such as insufficient use of anticoagulant therapy and a low application rate of warfarin. In addition, some researchers have pointed out that race may influence warfarin anticoagulant quality, with Caucasians showing higher rates of high-quality anticoagulation. In 2016, the European College of Cardiology recommended novel oral anticoagulants (NOACs) as the primary anticoagulants for AF patients, and in 2020, the AF guidelines clearly indicated that NOACs can directly replace warfarin [13]. Currently, in China, NOACs such as dabigatrant and rivaroxaban are commonly recommended as alternatives to warfarin for anticoagulation treatment in NVAF patients [14]. Rivaroxaban is a selective factor Xa blocker [15] and is classified as a Class IA anticoagulant in relevant clinical guidelines [16]. Some studies have shown that rivaroxaban is particularly effective in elderly patients [17]. Dabigatrant, a reversible, direct thrombin inhibitor, is characterized by hydrophilicity, poor intestinal absorption, and a high volume of distribution, plasma clearance, and half-life elimination [18]. Both dabigatran and rivaroxaban do not possess intrinsic pharmacological activity; instead, they are mainly absorbed and hydrolyzed in the intestine to form active metabolites that block thrombin's active site, thereby inhibiting fibrin production and exerting an anticoagulant effect.

Current clinical studies on NOACs are independent studies, and results may vary due to factors such as sample size, study design, and patient age. To confirm the optimal dosage of new anticoagulants, this study utilizes meta-analysis to synthesize existing clinical data, improving the effectiveness and reliability of research findings.

Literature retrieval strategy

This study was registered with PROSPERO (CRD42024581748). The following English search terms were used for literature retrieval: "Non-valvular atrial fibrillation", "new oral anticoagulant", "Rivaroxaban", "Dabigatran", "direct oral anticoagulant", "reduced dose", "advanced age", "Warfarin", "different dosage", "Atrial Fibrillation" and "Anticoagulants". Searches were performed across English-language databases, including PubMed, Embase, Web of Science, Cochrane Library, and other. In addition, literature searches were performed in Chinese databases such as China National Knowledge Infrastructure (CNKI) and WanFang Data, using Chinese search terms such as "non-valvular atrial fibrillation", "anticoagulant drugs", "new anticoagulants", "rivaroxaban", "dabigatran", "elderly patients", "low dose", "different doses" and "low dose". The database search covered all published literature from the inception of each database up to May 2023. Two clinical researchers performed the literature retrieval, and the results were cross-checked and summarized.

Literature screening was performed according to the PICOS principle: Population (P): Patients with a confirmed diagnosis of NVAF, including elderly individuals (age ≥ 60 years) according to the age grouping criteria proposed by the United Nations World Health Organization; Intervention (I): Oral administration of dabigatrant or rivaroxaban for thrombosis prevention; Comparison (C): Studies involving different drug doses in the intervention groups; Outcome measures (O): Systemic embolism (SSE) as the efficacy outcome, and severe bleeding complications, including massive gastrointestinal hemorrhage and intracranial hemorrhage, as safety outcome indicators; Study design (S): Prospective or retrospective cohort study.

Exclusion criteria: a. Animal studies; b. Non-Chinese or non-English literature; c. Duplicate publications; d. Review articles, meta-analysis, conference abstracts, systematic reviews, pathological studies, and other non-original research articles; e. Literature published earlier in repeated publications; f. Unclear drug dosage descriptions; g. Sample sizes < 30; h. Incomplete literature content unavailable for full review.

Literature screening and data extraction

Two investigators independently screened the included literature based on the inclusion and exclusion criteria. Valid data were extracted and cross-checked. In case of disagreements,

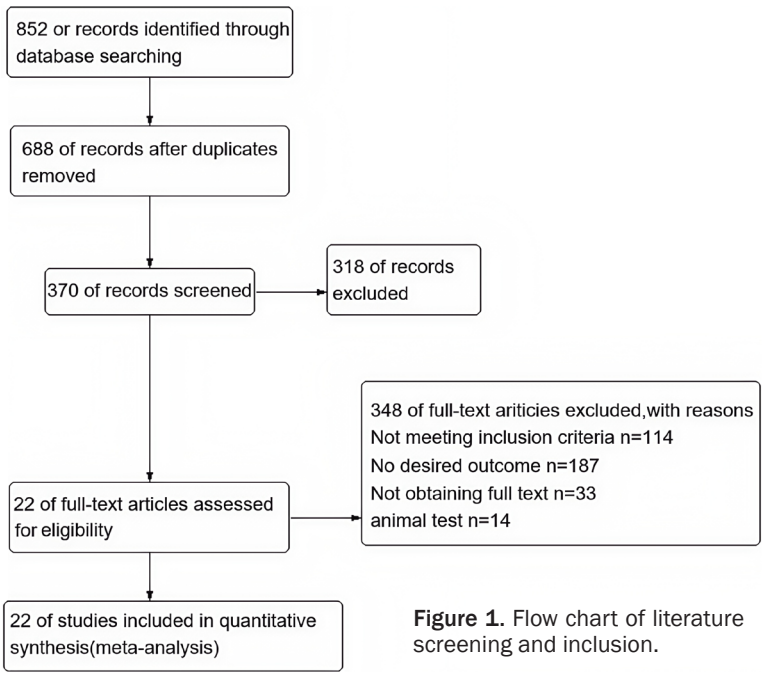

Figure 1. Flow chart of literature screening and inclusion.

the two investigators discussed and resolved the issue through negotiation. A third-party investigator should be consulted for a final decision if the consensus cannot be reached. The data extracted mainly include: (1) Literature information: Author name (first author), publication dates, randomization method, blinding method, etc.; (2) Study information: Number of subjects included in the study, doses administered, etc.; (3) Intervention methods: Oral anticoagulant regimens used in both the study and control groups; (4) Outcome measures.

Literature quality assessment

The Cochrane risk of bias assessment tool was used to evaluate the risk of bias in the included literature. The bias risk in each dimension is divided into three levels: low risk, unclear, and high risk. Literature with a higher risk of bias was excluded. The risk of bias included in the literature was independently assessed by two investigators and cross-checked. Any discrepancies were resolved through discussion. If a consensus could not be reached, a third-party investigator was consulted for final judgment.

Statistical analysis

RevMan 5.3 software was used for metadata analysis. The results were expressed as odds ratios (OR) and 95% confidence interval (CI). Inter-study heterogeneity was evaluated using I^2 and P values. The analytical effect model was selected according to the heterogeneity. If $I^2 \geq 50\%$ or $P > 0.1$, indicating no significant heterogeneity, a fixed effect model was selected; otherwise, if $I^2 \geq 50\%$ or $P \leq 0.1$, indicating significant heterogeneity, a random effects model was selected. Publication bias was analyzed using funnel plot and Eggerr's test.

Results

Literature search results

A total of 852 articles were obtained after retrieval in each database. After eliminating duplicates and screening based on titles, abstracts, and full-text reviews, and comparing with the inclusion and exclusion criteria, 22 articles were ultimately included for meta-analysis (**Figure 1**).

Basic characteristics and quality evaluation of included literature

Among the 22 studies included, 6 were published in English and 16 in Chinese. **Table 1** presents the basic characteristics of included literature. Of these studies, 4 described random sequence generation, while 2 did not provide details. No study showed a high risk of bias across any domain. In the domain of random sequence generation, 81.82% of the studies were classified as low risk and 18.18% as unclear risk. For the domain of allocation concealment, 72.73% of the studies were at low risk, while 27.27% had unclear risk. Blinding of participants and personnel was assessed as low risk in 81.82% of studies, with 18.18% rated as unclear risk. Regarding blinding of outcome assessment, 40.91% were assessed as low risk and 59.09% as unclear risk. Data incompleteness was rated as unclear risk in 54.55% of the studies, and 45.45% had no assessment of bias. Selective reporting was considered low risk in 81.82% of the studies and unclear in 18.18%. All other risks were assessed as low risk. The bias risk assessment of included literature is shown in **Figure 2**.

Table 1. Basic characteristics of included literature

Included Studies	Year	Experimental Design	Interventions		Sample Size		Follow-up Time	Outcome Measures	Age		Gender	
			T	C	T	C			T	C	T	C
Blin [19]	2019	RCT	T_1: Dabigatran (110 mg)	C_1: Dabigatran (150 mg)	T_1:7639 T_2:7639	C_1:8290 C_2:8290	24 months	①, ②	60-80	60-80	4285:3354	4246:4044
Chen [20]	2023	RCT	T_3: Rivaroxaban (15 mg)	C_2: Rivaroxaban (20 mg)	T_1:41 T_2:41	41	3 months	①, ②	T_1:77.49±1.73 T_2:77.81±1.96	77.51±1.69	T_1:21:20 T_2:22:19	23:18
Eikelboom [21]	2011	RCT	T_1: Rivaroxaban (15 mg)	Warfarin	T_1:6015 T_2:6076	6022	12 months	①, ②	T_1:65-85 T_2:65-85	65-85	3217:2798	3318:2704
Gan [22]	2021	RCT	T_2: Rivaroxaban (20 mg)	Warfarin	43	43	3 months	①, ②	71.02±6.51	71.35±6.84	23:20	24:19
Gu [23]	2023	RCT	T_1: Dabigatran (110 mg)	Warfarin	102	98	12 months	①, ②	86.41±6.13	84.51±6.13	54:48	54:44
Lee [24]	2017	Cohort	T_2: Dabigatran (150 mg)	Rivaroxaban (15 mg)	T_1:550 T_2:294	990	12 months	①, ②	67.0-79	63.0-79.0	525:319	652:338
Li [25]	2023	RCT	Dabigatran (110 mg)	Warfarin	T_1:100 T_2:100	100	12 months	①, ②	74.72±7.85	74.83±8.10	44:56	54:46
Liu [26]	2021	RCT	Rivaroxaban (10 mg)	Warfarin	199	92	3 months	①, ②	66.81±6.09	68.41±6.24	120:79	56:36
Navarro-Almenzar [27]	2019	RCT	T_1: Dabigatran (110 mg)	Warfarin	T_1:176 T_2:258	C_1:441 C_2:582	15 months	①, ②	T_1:71±11 T_2:73±12	C_1:76±9 C_2:72±14	T_1:71:106 T_2:101:157	C_1:210:231 C_2:277:305
Peng [28]	2022	RCT	T_2: Dabigatran (150 mg)	C_1: Dabigatran (150 mg)	58	58	12 months	①, ②	66.9±9.7	72.0±8.0	25:33	27:31
San [29]	2023	RCT	T_1: Rivaroxaban (10 mg)	C_2: Rivaroxaban (20 mg)	T_1:34 T_2:28	34	12 months	①, ②	T_1:83.4±5.6 T_2:81.4±2.9	81.6±3.3	T_1:14:20 T_2:13:51	13:21
Shen [30]	2024	RCT	T_2: Rivaroxaban (15 mg)	Rivaroxaban (20 mg)	T_1:20 T_2:20	20	6 months	①, ②	T_1:82.25±3.41 T_2:82.31±3.44	81.61±2.45	T_1:8:12 T_2:9:11	7:13
Song [31]	2021	RCT	Rivaroxaban (10 mg)	Warfarin	T_1:45 T_2:45	45	6 months	①, ②	T_1:68.7±2.3 T_2:68.2±2.1	69.5±2.5	T_1:28:17 T_2:27:18	30:15
Staerk [32]	2018	RCT	T_1: Dabigatran (110 mg)	C_1: Dabigatran (150 mg) C_2: Rivaroxaban (20 mg)	T_1:2098 T_2:4414	C_1:2957 C_2:4185	24 months	①, ②	T_1:81 (76, 85) T_2:71 (65, 77)	C_1:71 (65, 77) C_2:84 (80, 89)	T_1:793:1305 T_2:1766:2648	C_1:1130:1827 C_2:1723:2462
Wallentin [33]	2010	RCT	T_2: Rivaroxaban (15 mg)	Warfarin	T_1:5957 T_2:6029	5965	12 months	①, ②	T_1:70.0±9.5 T_2:71.3±8.8	72.1±8.3	T_1:2567:3390 T_2:2882:3147	2618:3347
Wang [34]	2019	Cohort	Rivaroxaban (15 mg)	Rivaroxaban (20 mg)	85	16	12 months	①, ②	85.76±4.72	84.56±3.37	32:53	5:13
Wang [35]	2021	RCT	T_1: rivaroxaban (10 mg)	Rivaroxaban (15 mg)	73	67	12 months	①, ②	84.3±3.8	86.8±4.0	60:13	51:16
Yang [36]	2022	RCT	T_2: Rivaroxaban (15 mg)	Rivaroxaban (15 mg)	30	30	6 months	①, ②	79.44±3.19	79.13±4.22	18:12	21:9
Yu [37]	2023	RCT	T_1: Rivaroxaban (15 mg) mg)	Warfarin	T_1:72 T_2:24	24	3 months	①, ②	81-105	81-105	T_1:42:30 T_2:14:10	15:9
Zhang [38]	2023	RCT	T_2: Rivaroxaban (20 mg)	Warfarin	T_1:31 T_2:31	31	12 months	①, ②	T_1:82.21±1.10 T_2:82.36±1.12	82.53±1.16	T_1:18:13 T_2:19:12	17:14
Zhao [39]	2023	RCT	T_1: Dabigatran (110 mg)	Rivaroxaban (15 mg)	43	43	3 months	①, ②	82.62±4.66	83.01±5.13	26:17	25:18
Zuo [40]	2022	RCT	T_2: Dabigatran (150 mg)	Warfarin	T_1:46 T_2:46	46	6 months	①, ②	T_1:86.3±2.4 T_2:87.0±2.1	86.5±2.3	T_1:33:13 T_2:30:16	34:12

Note: T represents the study group (T_1 and T_2 represent Study Group 1 and Study Group 2, respectively); C represents the control group (C_1 and C_2 represent Control Group 1 and Control Group 2, respectively); ① represents systemic embolism; ② represents severe hemorrhage.

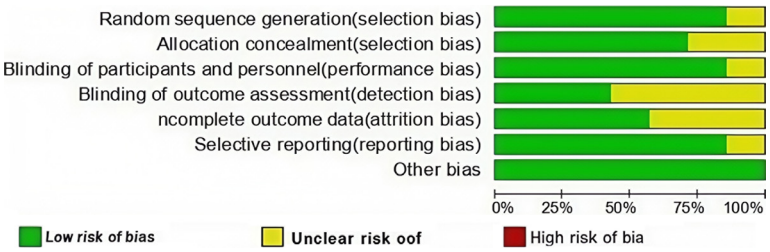

Figure 2. Risk bias plot for included studies.

*Meta-analysis of the incidence of SSEs in NVAF patients (**Table 2**)*

Eleven studies reported the occurrence of SSE after oral administration of conventional doses of NOAC compared with warfarin in NVAF patients. The analysis revealed no heterogeneity (I^2 = 0%, P = 0.78), so a fixed-effects model was used. The overall RR was 0.29 [0.26, 0.32], with a Z-value of 20.71, P < 0.00001, indicating a statistically significant reduction in the risk of SSEs with NOAC compared to warfarin (**Figure 3**).

Thirteen studies reported SSEs after the administration of low-dose new anticoagulants compared with warfarin. Again, no heterogeneity was observed between the literature (I^2 = 0%, P = 0.87), so a fixed-effects model was applied. The RR was 0.21 [0.19, 0.24], with a Z-value of 23.56, P < 0.00001, suggesting a significant reduction in the risk of SSE in low-dose NOAC compared to warfarin (**Figure 4**).

Twenty-two studies compared SSEs between low-dose and conventional doses of new anticoagulants. The analysis showed no heterogeneity (I^2 = 0%, P = 0.72), thus, a fixed-effect model was conducted. The RR was 0.72 [0.65, 0.80], with a Z-value of 6.27, P < 0.00001, suggesting a significant reduction in the risk of SSEs with low-dose new anticoagulants compared to conventional doses (**Figure 5**).

*Meta-analysis of the incidence of severe bleeding in NVAF patients treated with oral low-dose anticoagulants (**Table 3**)*

Eleven studies reported the risk of severe bleeding in NVAF patients after the administration of conventional doses of new anticoagulants versus warfarin. There was no heterogeneity (I^2 = 0%, P = 0.82), and a fixed-effects analysis was performed. The RR was 0.82 [0.75, 0.89], with a Z-value of 4.59, P < 0.00001, indicating a significant reduction in the risk of severe bleeding with new anticoagulants compared to warfarin (**Figure 6**).

Thirteen studies compared the risk of severe bleeding with low-dose new anticoagulants versus warfarin. No heterogeneity was found (I^2 = 0%, P = 0.64), and a fixed-effects model was used. The RR was 0.64 [0.59, 0.70], with a Z-value of 9.73, P < 0.00001, suggesting a significant reduction in the risk of severe bleeding in low-dose new anticoagulants compared to warfarin (**Figure 7**).

Twenty-two studies compared severe bleeding between low-dose and conventional doses of new anticoagulants. Significant heterogeneity was found (I^2 = 86%, P < 0.00001), so a random-effects analysis was conducted. The RR was 1.03 [0.96, 1.11], with a Z-value of 0.90, P = 0.37, suggesting no statistically significant difference in the risk of severe bleeding between low-dose and conventional new anticoagulants (**Figure 8**).

Publication bias

To assess publication bias, funnel plots were created for SSE and severe bleeding risk in both low-dose and conventional anticoagulant groups (**Figures 9**, **10**). The plots are symmetrical and mostly scattered near the mean value, indicating low publication bias and high reliability of the results. Egger's test confirmed no publication bias, with intercepts of -0.153 and -0.203, standard errors of 0.320 and 0.461, t-values of 0.470 and 0.462, and *P*-values of 0.645 and 0.551, respectively. These results suggest that there was no significant publication bias in the meta-analysis findings.

Discussion

Anticoagulation therapy is the main clinical intervention for NVAF patients. Warfarin, as a classic anticoagulant, has a long history of clinical application, and its efficacy is well established. However, the use of warfarin requires careful monitoring due to its significant interactions with food and other medications, along with frequent coagulation tests to adjust the dosage. This need for constant monitoring and dose adjustment complicates its use, especial-

Table 2. Meta-analysis results of SSE incidence

Outcome Measures	Subgroup	Included Studies	Heterogeneity Test Results		Effect Mode	Meta-analysis Results	
			P	I^2 (%)		*OR [95% CI]*	*P*
Incidence of SSE	Regular Dose vs. Warfarin	11	0.79	0	Fixed Effects Mode	0.29 [0.26, 0.32]	0.000
	Low Dose vs. Warfarin	13	0.87	0	Fixed Effects Mode	0.21 [0.19, 0.24]	0.000
	Regular vs. Low Dose	20	0.95	0	Fixed Effects Mode	0.72 [0.65, 0.80]	0.000

Note: SSE represents Systemic embolism.

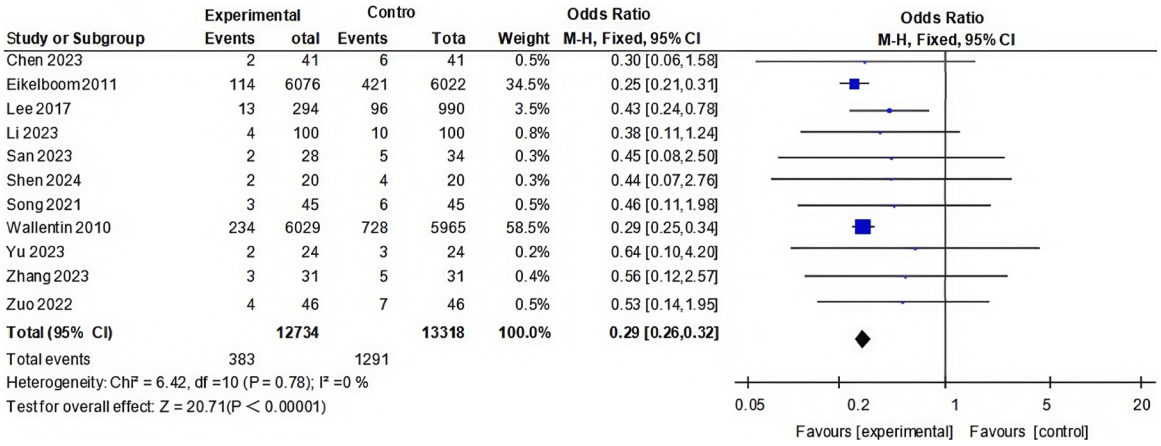

Figure 3. Forest plot of the effect of oral conventional-dose anticoagulants and warfarin on SSE. SSE: systemic embolism.

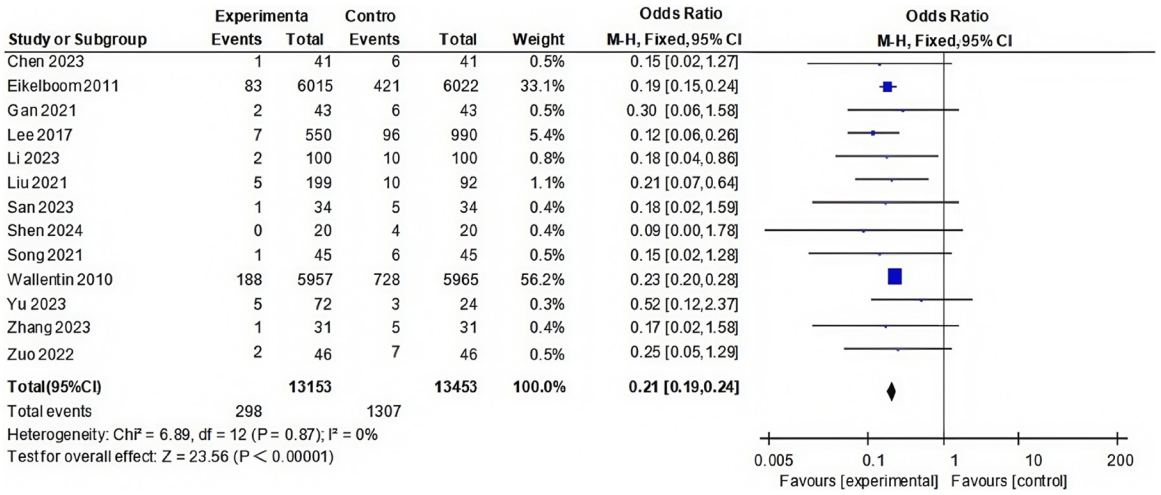

Figure 4. Forest plot of the effect of oral low-dose anticoagulants and warfarin on SSE. SSE: systemic embolism.

ly in elderly patients who often have multiple chronic diseases.

Epidemiological data highlight that the incidence of NVAF increases significantly with age, with elderly individuals having a 10-fold higher risk of developing the condition compared to younger populations. Men are more prone to the condition, accounting for 79.3% of the overall affected population. NVAF is also a major independent risk factor for ischemic stroke, further complicating the management of these patients. Although anticoagulant therapy is clinically advocated in routine treatment for NVAF, its use remains low, especially among elderly patients, as highlighted in recent surveys [41].

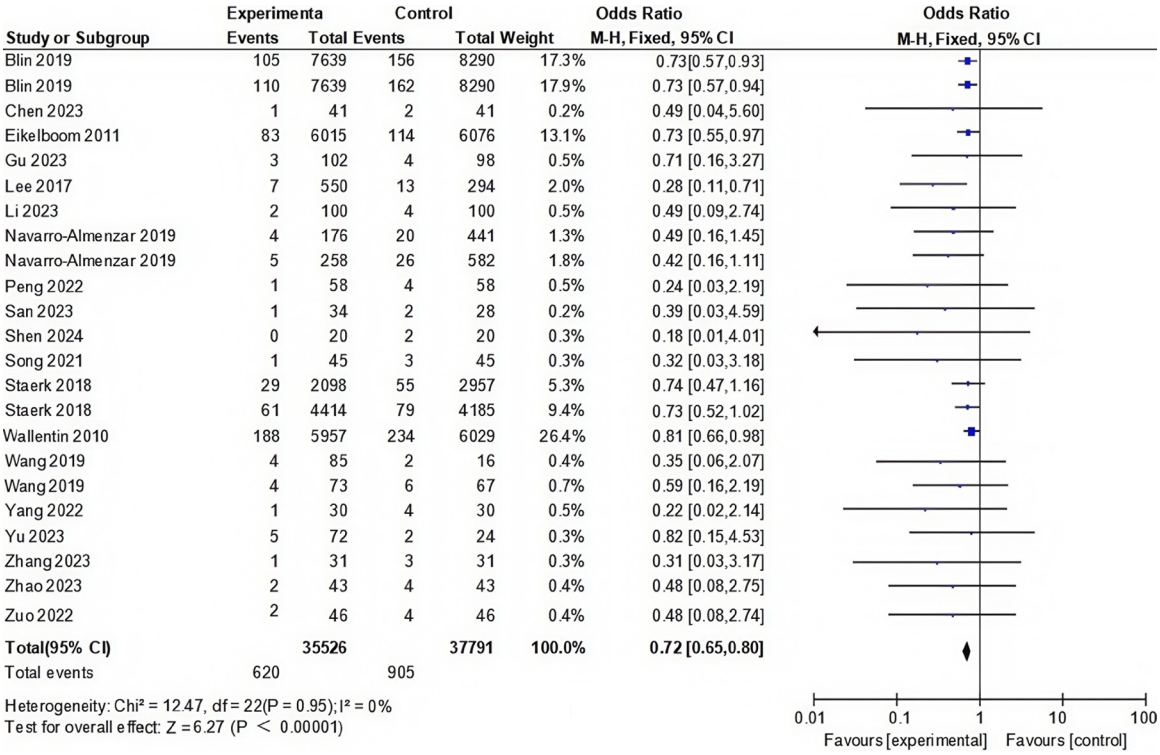

Figure 5. Forest plot of the effect of oral low-dose and conventional anticoagulants on SSE. SSE: systemic embolism.

Table 3. Meta-analysis results of incidence of severe bleeding

Outcome Measures	Subgroup	Included Studies	Heterogeneity Test Results		Effect Mode	Meta-analysis Results	
			P	I^2 (%)		*OR (95% CI)*	*P*
Incidence of serious bleeding	Regular Dose vs. Warfarin	11	1.00	0	Fixed Effects Mode	0.82 [0.75, 0.89]	0.000
	Low Dose vs. Warfarin	13	0.96	0	Fixed Effects Mode	0.64 [0.59, 0.70]	0.000
	Regular vs. Low Dose	20	0.000	86	Random Effects Mode	1.03 [0.96, 1.11]	0.37

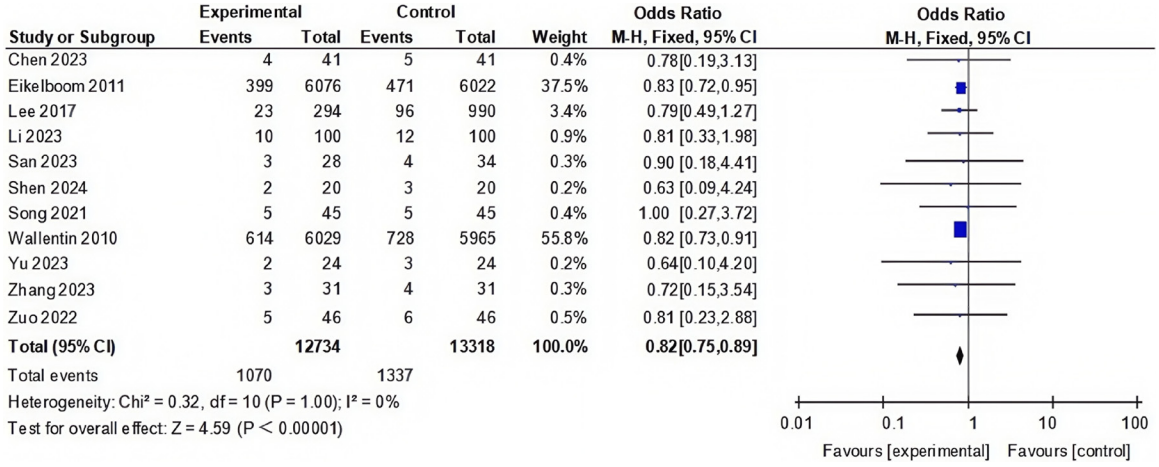

Figure 6. Forest plot of the effect of oral conventional dose anticoagulants and warfarin on severe hemorrhage.

The 2012 guidelines on NVAF management suggested that rivaroxaban and dabigatran could be considered as alternatives to warfarin for anticoagulation therapy in NVAF patients

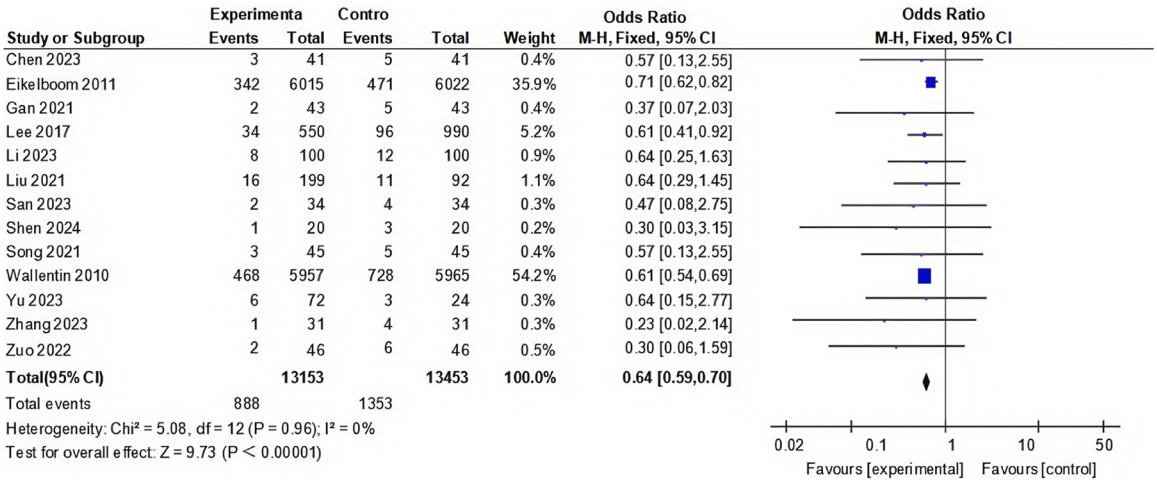

Figure 7. Forest plot of the effect of oral low-dose anticoagulants and warfarin on severe hemorrhage.

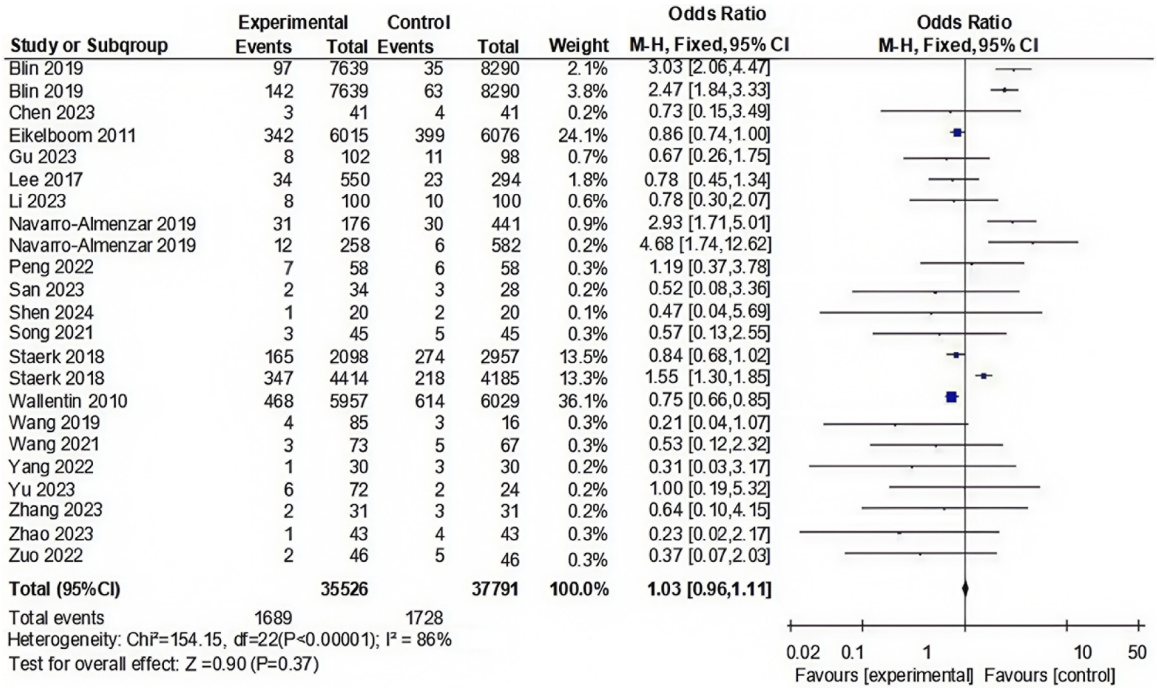

Figure 8. Forest plot of the effect of oral low-dose and conventional anticoagulants on severe hemorrhage.

[42]. More recently, the 2020 ESC Atrial Fibrillation Management Guidelines further emphasized that NOACs should be the preferred choice for patients without contraindications, with warfarin being reserved as a secondary option [43]. Compared with warfarin, the use of NOACs is simpler as they do not require routine coagulation monitoring, and they are less susceptible to dietary or drug interactions. However, NOACs have been in clinical use for a shorter period than warfarin, and there remains some uncertainty regarding the optimal dosage, partly due to limited research on dosing regimens.

The results of this study support the superiority of NOACs over warfarin in terms of both efficacy and safety. Specifically, both conventional and low-dose NOACs demonstrated a lower incidence of SSE and severe bleeding compared to warfarin. These findings are consistent with the work of Zhang et al [38]. At present, low-dose

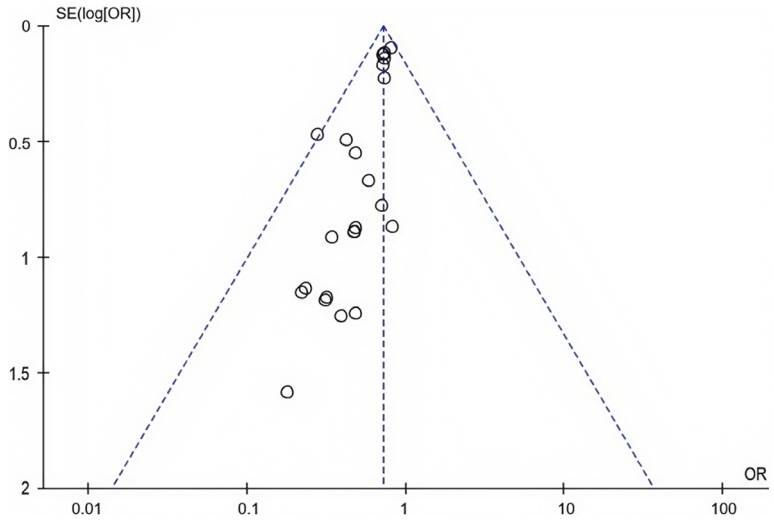

Figure 9. Publishing bias evaluation chart for incidence of SSEs in low-dose and conventional oral anticoagulants. SSE: systemic embolism.

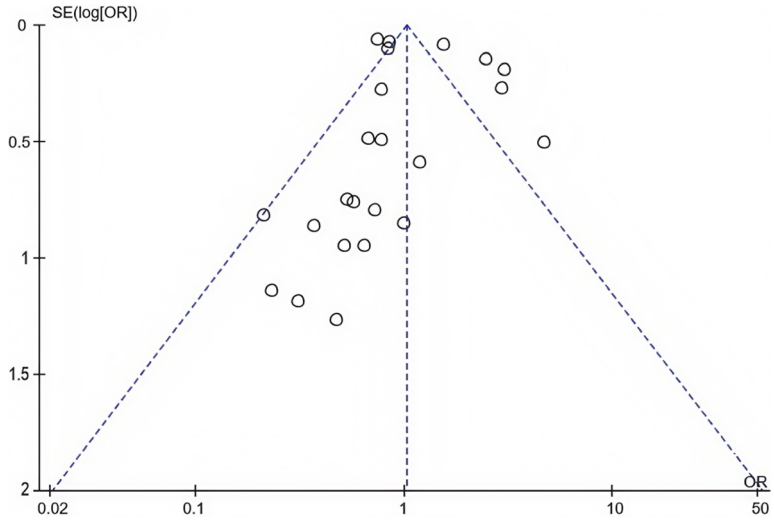

Figure 10. Evaluation of publication bias for incidence of severe bleeding with new oral anticoagulants at low and conventional doses.

dabigatran is commonly used for the treatment of elderly NVAF patients in China, but there is little comparison between conventional dose and low-dose efficacy. Rivaroxaban, as a non-vitamin K antagonist that blocks the coagulation waterfall process by binding to coagulation factor Xa and produces clotting, shows high bioavailability, reaching the peak 2-4 h after oral administration, and minimal individual variability in response. Studies have shown that low-dose rivaroxaban (20 mg/day) offers superior safety compared to higher doses, especially in elderly patients [44]. In conclusion, the use of NOACs, particularly at low doses, offers a safer and more convenient alternative to warfarin for elderly NVAF patients.

NOACs are metabolized primarily by the kidneys, with some also undergoing liver metabolism. Adjusting the dosage of NOACs appropriately in clinical practice can enhance medication safety, while also reducing the impact of these drugs on liver and kidney functions [28]. In this study, a statistical difference in the risk of SSE was observed between low-dose and conventional doses of NOACs, which aligns with the above-mentioned theory. However, no statistically significant difference was found in the incidence of severe bleeding between the two groups, which is inconsistent with those reported by Peng et al [28]. The discrepancy may be stem from the large proportion of international literature included in this study, which may not fully account for the specific characteristics of the Asian population, as Asians are known to have lower coagulation activity and weaker gastrointestinal barrier function than Europeans and Americans, potentially leading to a higher risk of gastrointestinal bleeding [45]. As a result, differences between the results of our meta-analysis and those of clinical studies in China are likely. Thus, although the safety profile of NOACs, particularly low-dose NOACs, is higher than that of warfarin, there are certain regional variations in clinical outcomes.

This study does have some limitations that should be acknowledged: (1) The focus on elderly patients with NVAF resulted in a small number of eligible studies. This limitation restricts the ability to conduct a more comprehensive analysis and comparison; (2) The number of included Chinese studies is small, limiting the generalizability of the results to the Chinese

population. Additional studies from China are needed to validate and further refine the conclusions; (3) Although several types of NOACs are currently used in clinical practice, this study only focused on rivaroxaban and dabigatran, thus the findings may not fully represent the broader landscape of NOAC therapy.

Suggestions for improvement: (1) Appropriately relaxing the inclusion criteria for literature to increase the number and literature included; (2) Increasing the focus on domestic Chines literature would yield findings that are more aligned with the unique clinical conditions in China; (3) Expanding the search to include other NOACs would improve the comprehensiveness of the study.

In conclusion, this study synthesized the results of previous clinical trials and concluded that low-dose NOACs for elderly NVAF patients was superior to conventional warfarin and standard-dose NOACs in terms of efficacy and safety. It is recommended that low-dose NOACs be preferred for the treatment of elderly NVAF patients, with dosage adjusted based on individual patient conditions.

Disclosure of conflict of interest

None.

Address correspondence to: Jun Xia, Department of Medical, Wujin Hospital Affiliated with Jiangsu University, No. 2 Yongning North Road, Changzhou 213017, Jiangsu, China. Tel: +86-0451-85579236; E-mail: xiajun_2023@126.com

References

[1] Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH and Chen SA. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. Chest 2018; 153: 453-466.

[2] Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J and Connolly S. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J 2015; 36: 281-7a.

[3] Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E and Tousoulis D. Atrial fibrillation: pathogenesis, predisposing factors, and genetics. Int J Mol Sci 2021; 23: 6.

[4] Sepehri Shamloo A, Dagres N and Hindricks G. 2020 esc guidelines on atrial fibrillation: summary of the most relevant recommendations and innovations. Herz 2021; 46: 28-37.

[5] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ and Zakirov NU. 2020 esc guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the european association of cardio-thoracic surgery (eacts). Eur Heart J 2021; 42: 373-498.

[6] Andersen JH, Andreasen L and Olesen MS. Atrial fibrillation-a complex polygenetic disease. Eur J Hum Genet 2020; 29: 1051-1060.

[7] Heijman J, Luermans JGLM, Linz D, van Gelder IC and Crijns HJGM. Risk factors for atrial fibrillation progression. Card Electrophysiol Clin 2021; 13: 201-209.

[8] January CT, Wann LS, Calkins H, Chen LY and Yancy CW. 2019 aha/acc/hrs focused update of the 2014 aha/acc/hrs guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2019; 140: e125-e151.

[9] Douxfils J, Ageno W, Samama CM, Lessire S, Ten Cate H, Verhamme P, Dogné JM and Mullier F. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost 2018; 16: 209-219.

[10] Mcalister FA, Wiebe N and Hemmelgarn BR. Time in therapeutic range and stability over time for warfarin users in clinical practice: a retrospective cohort study using linked routinely collected health data in alberta, canada. BMJ Open 2018; 8: e016980.

[11] Kılıç S, Soner Kemal H, Yüce Eİ, Şimşek E, Yağmur B, Memişoğlu Akgül N, Soydaş Çınar C, Zoghi M and Gürgün C. Comparison of warfarin use in terms of efficacy and safety in two different polyclinics. Anatol J Cardiol 2017; 18: 328-333.

[12] Yang YM, Shao XH, Zhu J, Zhang H, Wang J, Wu S and Ren JM. Atrial fibrillation registry study in Chinese emergency department: one year outcomes analysis. Chin J Cardiac Arrhythmias 2020; 24: 376-381.

[13] Hendriks JM and Heidbüchel H. The management of atrial fibrillation: an integrated team approach - insights of the 2016 European Society of Cardiology guidelines for the management of atrial fibrillation for nurses and allied health professionals. Eur J Cardiovasc Nurs 2019; 18: 88-95.

[14] Jan S and Heidbüchel H. European heart rhythm association practical guide on the use of non-vitamin k antagonist oral antico agulants in patients with atrial fibrillation: comment-authors' reply. Europace 2021; 23: 1612-1676.

[15] Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K and Lip GYH. 2021 Focused update consensus guidelines of the asia pacific heart rhythm society on stroke prevention in atrial fibrillation: executive summary. Thromb Haemost 2022; 122: 20-47.

[16] Bando S, Nishikado A, Hiura N, Ikeda S, Kakutani A, Yamamoto K, Kaname N, Fukatani M, Takagi Y, Yukiiri K, Fukuda Y and Nakaya Y. Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: analysis of the shikoku rivaroxaban registry trial (srrt). J Cardiol 2018; 71: 197-201.

[17] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD and Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.

[18] Yi ZM. The use of anticoagulants by elderly people to prevent recurrence of ischemic stroke also benefits. Clin Med J 2017; 15: 89.

[19] Blin P, Dureau-Pournin C, Cottin Y, Benichou J, Mismetti P, Abouelfath A, Lassalle R, Droz C and Moore N. Comparative effectiveness and safety of standard or reduced dose dabigatran vs. rivaroxaban in nonvalvular atrial fibrillation. Clin Pharmacol Ther 2019; 105: 1439-1455.

[20] Chen HM, Zhu HY, Jiao TR, Zhao MZ and Yuan QR. Clinical efficacy and safety of rivaroxaban in treatment of senile nonval-vular atrial fibrillation. Chin J Sch Doctor 2023; 37: 531-534.

[21] Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J and Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (re-ly) trial. Circulation 2011; 123: 2363-2372.

[22] Gan LL and Xu B. The effect of low-dose dabigatran etexilate on coagulation function and platelet activation in patients with non valvular atrial fibrillation. Strait Pharm J 2021; 33: 153-154.

[23] Gu YJ, Liu XM, Liu WL and Chen N. Efficacy and safety of low-dose rivaroxaban in the treatment of non valvular atrial fibrillation in the elderly patients. Henan Med Res 2023; 32: 524-527.

[24] Lee KH, Park HW, Lee N, Hyun DY, Won J, Oh SS, Park HJ, Kim Y, Cho JY, Kim MC, Sim DS, Yoon HJ, Yoon NS, Kim KH, Hong YJ, Kim JH, Ahn Y, Jeong MH, Park JC and Cho JG. Optimal dose of dabigatran for the prevention of thromboembolism with minimal bleeding risk in korean patients with atrial fibrillation. Europace 2017; 19 Suppl 4: iv1-iv 9.

[25] Li NX, Ao Y, Zhao J, Cheng B and Chen XH. Efficacy and safety analysis of low-dose rivaroxaban in the treatment of elderly patients with double high risk of ischemia and bleeding with non-valvular atrial fibrillation. Pract J Clin Med 2023; 20: 141-144.

[26] Liu F, Yu F and Ye L. Comparative study on anticoagulation effect and safety of low-dose rivaroxaban and warfarin in elderly patients with atrial fibrillation. J Hunan Norm Univ Med Sci 2021; 18: 275-278.

[27] Navarro-Almenzar B, Cerezo-Manchado JJ, Caro-Martinez C, García-Candel F, Flores Blanco PJ, Ruiz GE, Andreu Cayuelas JM, Montoya FA, Cascales A, Lova Navarro A, García Alberola A, Andrés Pascual Figal D, Bailen Lorenzo JL and Manzano-Fernández S. Real-life behaviour of direct oral anticoagulants in a spanish cohort with non-valvular atrial fibrillation: refase registry. Curr Med Res Opin 2019; 35: 2035-2041.

[28] Peng C, Shen XF, Wei JR and Li B. Effect and safety evaluation of different doses of rivaroxaban on stroke prevention in elderly patients with non-valvular atrial fibrillation. China J Mod Med 2022; 32: 81-86.

[29] San Y, Chen L, Zhou L, Fan XZ, Chi MY and Yao ZY. Effect of low-dose rivaroxaban on thromboembolism, bleeding events and readmission rates in elderly patients with non-valvular atrial fibrillation. Chin J Clin Healthcare 2023; 26: 332-337.

[30] Shen XF, Zheng JL and Zhang J. Comparison of the rationality and safety of different doses of rivaroxaban in elderly patients with non valvular atrial fibrillation. J Clin Electrocardiol 2024; 33: 25-28.

[31] Song CH. Study on the efficacy of low-dose dabigatran etexilate in the treatment of nonvalvular atrial fibrillation. China Pract Med 2021; 16: 130-132.

[32] Staerk L, Gerds TA, Lip GYH, Ozenne B, Bonde AN, Lamberts M, Fosbøl EL, Torp-Pedersen C, Gislason GH and Olesen JB. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med 2018; 283: 45-55.

[33] Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S and Connolly SJ; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in

atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010; 376: 975-983.
[34] Wang Q, Zhang L, Huang J, Ma Q, Xu YN and Wu J. Usual dose and prognosis of rivaroxiban in octogenarians with nonvalvular atrial fibrillation. South Chin J Cardiovasc Dis 2019; 25: 638-641, 646.
[35] Wang HM, Zhao YZ, Liu ZF, Gao YF, Sun Z, Lin Y, Zhang R, Xu Y and Guo XH. Efficacy and safety of different doses of rivaroxaban in treatment of elderly non-valvular atrial fibrillation. Chin J Multiple Organ Dis Elderly 2021; 20: 481-487.
[36] Yang LQ. The effect of different doses of rivaroxaban on the prevention and treatment of venous thrombosis in elderly patients. Cardiovasc Dis Prev Treat Knowle 2022; 12: 4-6.
[37] Yu SY and Dang DS. Analysis of efficacy and safety of low dose of rivaroxaban in the prevention and treatment of venous thrombosis in elderly patients. Chin J Mod Drug Appl 2023; 17: 104-107.
[38] Zhang RT, Li Z, Zhou C and Ji YY. The application effect of different doses of rivaroxaban in elderly patients with coronary heart disease and atrial fibrillation after PCI. Shenzhen J Integr Tradit Chin West Med 2023; 33: 116-118.
[39] Zhao YF. Effect of low dose rivaroxaban on coagulation function in elderly patients with non valvular atrial fibrillation. Xinjiang Med J 2023; 53: 965-967+990.
[40] Zuo NN and Wang C. Comparative study on efficacy and safety of preventing thromboembolic events with rivaroxaban, dabigatran and warfarin in senile patients with nonvalvular atrial fibrillation. Chin J Thromb Hemost 2022; 28: 7-10.
[41] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G and Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-2747.
[42] Hindricks G. Atrial fibrillation. Herz 2021; 46: 303-304.
[43] Zhang W and Zhang N. Efficacy of low-dose rivaroxaban in the treatment of elderly patients with non-valvular atrial fibrillation. Chin J Thromb Hemost 2021; 27: 412-413.
[44] Peng C, Shen XF, Wei JR and Li B. Effect and safety evaluation of different doses of rivaroxaban on stroke prevention in elderly patients with non-valvular atrial fibrillation. China J Mod Med 2022; 32: 81-86.
[45] Kang J, Park KW, Palmerini T, Stone GW, Lee MS, Colombo A, Chieffo A, Feres F, Abizaid A, Bhatt DL, Valgimigli M, Hong MK, Jang Y, Gilard M, Morice MC, Park DW, Park SJ, Jeong YH, Park J, Koo BK and Kim HS. Racial differences in ischaemia/bleeding risk trade-off during anti-platelet therapy: individual patient level landmark meta-analysis from seven RCTs. Thromb Haemost 2019; 119: 149-162.