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Effects of oral anticoagulant therapy in atrial fibrillation patients with comorbidities

Edited by
Wengen Zhu, Ping Yuan and Jianyong Ma

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Effects of oral anticoagulant therapy in atrial fibrillation patients with comorbidities

Topic editors

Wengen Zhu — First Affiliated Hospital of Sun Yat-sen University, China
Ping Yuan — Second Affiliated Hospital of Nanchang University, China
Jianyong Ma — University of Cincinnati, United States

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EDITED AND REVIEWED BY
Nicola Mumoli,
ASST Ovest Milanese, Italy

*CORRESPONDENCE
Ping Yuan
727769220@qq.com
Jianyong Ma
majy@ucmail.uc.edu
Wengen Zhu
zhuwg6@mail.sysu.edu.cn

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Editorial: Effects of oral anticoagulant therapy in atrial fibrillation patients with comorbidities

Runkai Li[1], Ping Yuan[2]*, Jianyong Ma[3]* and Wengen Zhu[1]*

[1]Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [2]Department of Cardiology, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [3]Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, OH, United States

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oral anticoagulant therapy, atrial fibrillation, comorbidities, bleeding, stroke

Editorial on the Research Topic
Effects of oral anticoagulant therapy in atrial fibrillation patients with comorbidities

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and remains one of the primary contributors to cardiovascular diseases and mortality on a global scale. The incidence of AF increased exponentially with age, especially in the elderly with comorbidities such as hypertension, coronary artery atherosclerosis, valvular heart disease, acute or chronic kidney disease, or respiratory diseases. According to data from 2017, AF contributes to 0.51% of the burden of the global cumulative mortality. Moreover, the mortality associated with AF has increased by approximately 81% in the past 20 years (1). Among the complications of AF, stroke or systemic embolism (SSE) is the leading cause of morbidity and mortality, particularly with respect to cerebrovascular events. Studies have estimated that AF patients have a two-fold risk of stroke-related death compared to non-AF patients (2). Therefore, anticoagulant therapy for preventing thromboembolic events plays a crucial role in the long-term comprehensive management of AF patients, as it has important implications for improving patient prognosis, enhancing the quality of life, and extending overall survival (3).

As the cornerstone of anticoagulant therapy for AF patients, oral anticoagulants (OACs) significantly reduce the risk of thromboembolic events and all-cause mortality in AF patients (4). However, while anticoagulant therapy has clinical benefits, it may also be accompanied by corresponding bleeding side effects in clinical practice. Therefore, to establish the definite clinical benefits of OAC therapy in AF patients, several studies published in our research topic specifically focused on patients at a high risk of bleeding. The results revealed that in AF patients with a history of gastrointestinal (Zhao et al.) or intracranial hemorrhage (Liu et al.), OAC therapy can still reduce the risk of thromboembolic events, ischemic stroke, and all-cause mortality, and non-vitamin K antagonist oral anticoagulants (NOACs) exhibited more pronounced clinical benefits compared to vitamin K antagonists (VKAs). However, OAC therapy in AF patients with a history of intracranial bleeding also carries a higher risk of major bleeding. Furthermore, we also pay special attention to elderly AF patients, as this population has common characteristics such as impaired liver

and kidney function, polypharmacy, multiple comorbidities, increased risk of falls and bleeding, a higher propensity for bleeding, and poor adherence to medication. As a result, selecting appropriate drugs and dosages for anticoagulant therapy in this population becomes crucial. To strike a balance between the risks of stroke-related mortality and anticoagulant-related bleeding in these patients, Zhao et al. developed and established a clinically applicable prediction model for the inappropriate use of NOACs based on a multicenter cohort of elderly AF patients. As the first prediction model for NOAC-related risks in elderly AF patients, it has important clinical value in evaluating anticoagulant-related bleeding risks in high-risk populations and optimizing anticoagulant therapy for AF patients.

In order to reduce the risk of bleeding in AF patients undergoing anticoagulant therapy, the precise assessment of bleeding event risks has been a focal point of clinical research. Currently, Liu et al. have conducted a meta-analysis to further clarify the comparative accuracy of prediction, suggesting that the ORBIT score did not show a significant advantage over the classic HAS-BLED score in terms of predicting bleeding risks. In addition, regular monitoring of coagulation function is crucial for AF patients on long-term anticoagulant therapy, particularly those using warfarin. However, in certain situations that require urgent surgical or interventional procedures, routine laboratory tests are not suitable for promptly assessing coagulation function. Viscoelastic tests can rapidly provide information on residual levels of NOACs in plasma, which has significant value in understanding patients' coagulation function status, formulating specific surgical plans, preparing preoperative measures, and assessing surgical risks in emergency care. However, there is still controversy regarding the accuracy of measuring residual NOAC plasma concentrations with viscoelastic tests. Therefore, Sahli1 et al. conducted a meta-analysis of relevant articles on viscoelastic tests and the results indicated that viscoelastic tests still have important value in providing real-time information about residual NOAC activity, although the sensitivity for quantifying residual NOAC concentrations in plasma needed to be improved.

In the selection of oral anticoagulants, NOACs have gained widespread attention since their introduction. Compared to VKAs, NOACs selectively inhibit the activity of a single molecular target, either thrombin or factor Xa, and do not require monitoring of coagulation function or frequent dose adjustments. NOACs are also not restricted by interactions with other foods or drugs, offering a stable anticoagulant effect and a favorable safety profile with lower bleeding risk (5). However, when anticoagulant therapy is required for AF patients with concurrent comorbidities such as cardiovascular, pulmonary or renal diseases, some factors may complicate the situation, such as changes in drug metabolism and clearance, the necessity of drug dose adjustments, increased bleeding risk, and consideration of alternative treatment options. Therefore, Ren et al. previously investigated the effectiveness and safety of NOACs in subpopulations of AF patients with different comorbidities. Their results showed that compared to VKAs, the use of NOACs in populations at risk of kidney disease can reduce the risk of acute kidney injury in AF patients. In addition, Li et al. found that in AF patients with concomitant end-stage renal disease on dialysis, the use of NOACs showed at least similar effectiveness and safety results compared to VKAs. For patients with concomitant pulmonary diseases, the effects of VKAs and NOACs on reducing the risk of recurrent thromboembolic events were not significantly different statistically, but oral anticoagulant therapy significantly reduced the risk of death in AF patients with concomitant pulmonary hypertension, pulmonary embolism, and chronic obstructive pulmonary disease (Lai et al.). Furthermore, several authors also analyzed the use of anticoagulant therapy in AF patients with cardiovascular diseases such as myocardial infarction and heart failure, suggesting that NOACs were superior to warfarin in stroke prevention (Yu et al. Lee et al. Wulamiding et al.).

In conclusion, while emphasizing the importance of anticoagulation therapy in patients with AF, it is also crucial to evaluate the bleeding risk of individual patients. Oral anticoagulant therapy has demonstrated significant benefits in preventing ischemic stroke and reducing mortality in AF patients with comorbidities. A series of clinical studies have confirmed the effectiveness and safety of oral anticoagulant therapy, especially NOACs, in patients with AF. Similarly, for individual patients, a personalized anticoagulation management plan needs to be established based on the assessment of the bleeding risks. However, the safety of NOACs in certain populations, such as AF patients with concomitant mitral stenosis or aortic stenosis, pulmonary arterial hypertension or pulmonary fibrosis, and severe renal insufficiency, remains controversial, which requires further well-designed trials with a larger sample size to validate previous findings.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Meta-Analysis of Oral Anticoagulants and Adverse Outcomes in Atrial Fibrillation Patients After Intracranial Hemorrhage

Xin Liu[1†], Siyu Guo[2†] and Zhicheng Xu[3*]*

[1] Department of Critical Care Medicine, The First Affiliated Hospital of Gannan Medical University, Ganzhou, China, [2] Medical Department, Queen Mary School, Nanchang University, Nanchang, China, [3] Department of Cardiology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, China

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Edited by:
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

Reviewed by:
Lin Shin Yi,
National Taiwan University, Taiwan
Zi Amber Ye,
Royal North Shore Hospital, Australia

***Correspondence:**
Siyu Guo
1046204733@qq.com
Zhicheng Xu
532141796@qq.com

[†]*These authors share first authorship*

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Background: Intracranial hemorrhage (ICH) is excluded in most anticoagulation randomized clinical trials (RCTs), so oral anticoagulant (OAC) therapy is still the conventional treatment for patients with atrial fibrillation (AF) after ICH. Therefore, we conducted a meta-analysis to determine the effectiveness and safety outcomes of OAC for these patients.

Methods: We systematically searched the PubMed and Embase databases up to March 2022 for RCTs and observational studies exploring the effect of OAC in patients with AF after ICH. The effectiveness outcomes included stroke or systemic embolism, ischemic stroke, and all-cause death, whereas the safety outcomes were major bleeding and recurrent ICH. Hazard ratios (HRs) and 95% confidence intervals (CIs) from each study were pooled using a random-effects model.

Results: A total of 14 studies were included. The OAC therapy that was performed reduced the risks of stroke or systemic embolism (HR = 0.65, 95% CI 0.53–0.81), ischemic stroke (HR = 0.70, 95% CI 0.60–0.82), and all-cause death (HR = 0.43, 95% CI 0.27–0.70) but had a higher risk of major bleeding (HR = 1.50, 95% CI 0.94–2.40) and showed no difference in recurrent ICH (HR = 0.91, 95% CI 0.53–1.55) compared to the no OAC therapy. With the use of non-vitamin K antagonist oral anticoagulant (NOAC) therapy, a lower risk of stroke or systemic embolism (HR = 0.83, 95% CI 0.70–0.98), all-cause death (HR = 0.67, 95% CI 0.53–0.84), and recurrent ICH (HR = 0.68, 95% CI 0.54–0.86) was observed against the use of vitamin K antagonists (VKA) therapy.

Conclusion: The OAC therapy (especially VKA) revealed superior effectiveness in patients with AF after ICH, and the superiority of NOAC was also found, but some related evidence was limited.

Keywords: atrial fibrillation, intracranial hemorrhage, anticoagulation, prognosis, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is a well-documented risk factor for stroke and systemic embolism (1, 2). The prevention of non-fatal and fatal thromboembolic events is a key goal for the management of patients with AF. Oral anticoagulants (OAC) are recommended in patients with AF to reduce the risk of stroke and thromboembolic events by national and international clinical practice guidelines (3). However, since intracranial hemorrhage (ICH) [especially symptomatic ICH (sICH)] is the most fatal complication of long-term anticoagulation (4), patients with previous ICH are regarded as an excluded population in the majority of randomized clinical trials (RCTs) of stroke prevention in AF. Hence, whether patients with AF after ICH derive net clinical benefit (including efficacy and safety outcomes) from antithrombotic therapy is still unclear, given that the effect of ischemic stroke reduction is needed to balance against increased bleeding recurrence in this population. A previous meta-analysis by Korompoki et al., which pooled seven observational studies and 2,452 ICH survivors with AF, demonstrated that anticoagulation with vitamin K antagonists (VKA) correlated with a lower rate of ischemic stroke and no significantly increased ICH recurrence, as compared with antiplatelet agents or no antithrombotic medication (5, 6). Nevertheless, because of the limited high-grade evidence in this specific population (7), whether to use anticoagulation therapy and the specific therapy window for patients with AF after ICH is still inconclusive.

Although OAC including the non-vitamin K antagonist oral anticoagulants (NOAC; i.e., factor Xa inhibitors and direct thrombin inhibitor) and warfarin are all effective in preventing AF-related stroke, NOAC has been shown to correlate with a significantly lower risk of ICH than VKA in patients with AF without prior ICH (8). Moreover, our recent meta-analysis of 17 retrospective cohort studies found that apixaban was superior to dabigatran or rivaroxaban in stroke prevention with lower bleeding risk in patients with AF (9). However, in the clinical trials performed by Schreuder et al., the apixaban allocated group elaborated the annual risk of non-fatal stroke or vascular death and a higher risk of major bleeding compared with the no anticoagulation treated group (10). Moreover, by analyzing the result of Lewis et al., the OAC-treated group demonstrated lower rates of recurrent ICH than the no OAC group, but the level of evidence was relatively weak to draw this explicit conclusion (11). Therefore, we aimed to investigate the effectiveness and safety of OAC (NOAC and VKA) compared with no OAC and evaluated the effect of the NOAC therapy versus the VKA therapy in patients with AF after ICH.

METHODS

We conducted this meta-analysis based on the criteria of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2). The results were presented according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) 2020 statement (**Supplementary Table 1**; 12).

Search Strategy

Two reviewers performed the literature search, systematically searching the PubMed and Embase database sources up to March 2022 for studies exploring the effect of OAC compared with no OAC in patients with AF after ICH. The following search terms were used: (1) "AF" OR "atrial flutter," (2) "ICH" OR "intracranial bleeding" OR "intracerebral hemorrhage" OR "hemorrhagic stroke" OR "ICH," (3) "OAC" OR "vitamin K antagonist" OR "VKA" OR "warfarin" OR "non-vitamin K antagonist oral anticoagulant" OR "direct oral anticoagulant" OR "novel oral anticoagulant" OR "NOAC" OR "DOAC" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban." The aforementioned three categories of search terms were combined using the Boolean operator "and." The detailed search strategies are shown in **Supplementary Table 2**. In addition, the reference lists of the retrieved articles and prior reviews were manually checked for additional eligible studies.

Inclusion and Exclusion Criteria

Randomized clinical trials or observational (prospective or retrospective cohort) studies were included if they focused on at least one of the effectiveness and safety outcomes of OAC compared with no OAC in non-valvular AF patients after ICH. The OAC included VKA or NOAC, whereas those in the reference were patients with antiplatelet or no antithrombotic agents. Since the pooled analysis could be performed for the outcome that was simultaneously reported in at least two included studies, we chose the effective outcomes including stroke or systemic embolism, ischemic stroke, and all-cause death, and the safety outcomes, including major bleeding and recurrent ICH. Based on the definition of major bleeding, according to the International Society on Thrombosis and Hemostasis criteria, gastrointestinal, genitourinary, respiratory tract, ICH/sICH, and other fatal and symptomatic bleeding in critical organs were regarded as severe hemorrhagic events for hospitalization. The definitions of these outcomes were applied according to the originally included studies. For the observational studies, the confounders were adjusted *via* the propensity score methods (e.g., matching, inverse probability of treatment weighting) or the regression model adjustment. The effects of OAC on the studied outcomes were expressed as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

We excluded the studies focusing on AF patients with non-ICH bleeding (e.g., any bleeding, gastrointestinal bleeding, major bleeding, and microbleed) or patients with cardioversion, ablation, or left atrial appendage (LAA). The studies without adjustment or with a sample size of <100 were excluded, due to limited convincing evidence being provided. In addition, we also excluded certain publication types (e.g., reviews, comments, case reports, case series, letters, editorials, and meeting abstracts) due to insufficient data or study details. If there were overlapping data among two or more studies, we included the one with the largest sample size or the longest follow-up duration.

Study Selection and Data Abstraction

Two reviewers independently screened the titles and abstracts of the retrieved studies from the electronic databases. Subsequently, based on the pre-defined inclusion criteria, we selected the eligible studies after the full-text screenings. Disagreements were resolved through discussion between the two reviewers or after consulting with the corresponding authors. The following data of the included studies were abstracted: study characteristics (first author, year of publication, data source, study period, and study design), study population, and baseline characteristics (age, male ratio, sample size, stroke and bleeding risk prediction scores, and drugs in the OAC group), effectiveness and safety outcomes, follow-up period, and outcome data (sample size and the number of events between groups, and adjusted HRs). For those studies reporting adjusted data with multiple models, we applied the most adjusted one.

Study Quality Assessment

The bias risks of RCTs were assessed using Cochrane's Risk of Bias tool, which mainly included six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other risk biases. The level of the bias risk in each domain was scored as "low," "unclear," or "high" risk. In addition, the Newcastle-Ottawa Scale (NOS) tool was used to assess the quality of observational cohort studies. In this meta-analysis, the NOS of $\geq$6 and $<$6 points were scored as moderate-to-high quality and low quality, respectively, (9, 13).

Statistical Analysis

All the statistical analyses of this meta-analysis were conducted using Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark)[1].

The statistical heterogeneity across the included studies was assessed using the p-value of the Cochrane Q test and the I^2 statistic, where a p-value of $<$0.10 in the Cochrane Q test or an I^2 value of $>$50% suggested significant heterogeneity. We excluded the included studies one by one to find out the potential source of high heterogeneity. In the pooled analysis, the effectiveness and safety outcomes in patients with AF after ICH were examined among three comparisons, namely OAC versus no OAC, VKA versus no VKA, and NOAC versus VKA. The adjusted HRs and 95% CIs were converted to the natural logarithms [Ln (HR)] and their corresponding standard errors [Ln (upper CI)-Ln (lower CI)/3.92], which were pooled by a DerSimonian and Laird random-effects model with an inverse variance method. The subgroup analysis and sensitivity analysis were not conducted due to the limiting included studies. The publication bias for the reported effect estimates was assessed using the funnel plots in which the logHRs were plotted against their standard errors. In addition, Egger's and Begg's tests for each outcome were applied to examine the statistical publication bias.

[1]https://community.cochrane.org/

RESULTS

Study Selection

The flow chart of literature retrieval is shown in **Figure 1**. A total of 3,790 records were retrieved in the two databases of PubMed and Embase; after the first phase of the title and abstract screenings, 36 remaining studies were potentially suitable and further assessed by full-text screenings. According to the pre-defined inclusion and exclusion criteria, we subsequently excluded 22 studies because (1) the sample size was less than 100 (n = 5); (2) the studies did not report adjusted or weighted HRs (n = 6); (3) the studies focused on a mixed population, and the AF subgroup was not separately analyzed (n = 3); (4) the studies did not report the studied outcomes (n = 4); and (5) the studies focused on AF patients with non-ICH bleeding (n = 4; **Supplementary Table 3**). Finally, a total of 14 studies (2 RCTs and 12 observational cohorts; 10, 11, 14–25) were included in our meta-analysis.

Baseline characteristics of the included studies are presented in **Table 1**. Among the included studies, three are from Denmark, two from Korea, three from Taiwan, and one each from the United Kingdom, Netherlands, Sweden, United States, Canada, and Germany. The mean age of patients ranged from 68.5 to 83.0 years, with a sample size between 101 and 12,917. Evaluated CHA2DS2-VASc, congestive heart failure/left ventricular ejection fraction $\leq$40%, hypertension, age $\geq$ 75 years (2 points), diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism (2 points), vascular disease, age 65-74 years, female sex; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly scores ranged from 3.26 to 6.0, and 2.0 to 4.4, respectively. Data on a specific classification of ICH were not available in seven studies (**Supplementary Table 4**). The adjusted risk factors in each included study are shown in **Supplementary Table 5**.

Risk of Bias Within Studies

The risk of bias assessment for RCT is presented in **Supplementary Table 6**, and quality assessment for observational cohorts is shown in **Supplementary Table 7**. These two assessments revealed that these 12 included observational cohorts and two RCTs' quality were relatively high and the result is convincing. Schreuder et al. showed a high risk of selection and performance bias lacking blindness in participants, their treating physicians, and local investigators.

Effect of Oral Anticoagulants Versus no Oral Anticoagulants in Atrial Fibrillation Patients After Intracranial Hemorrhage

As shown in **Figure 2**, our pooled results based on the random-effects model showed that, compared with no OAC, the use of OAC (NOAC or VKA) was significantly correlated with reduced risks of effectiveness outcomes

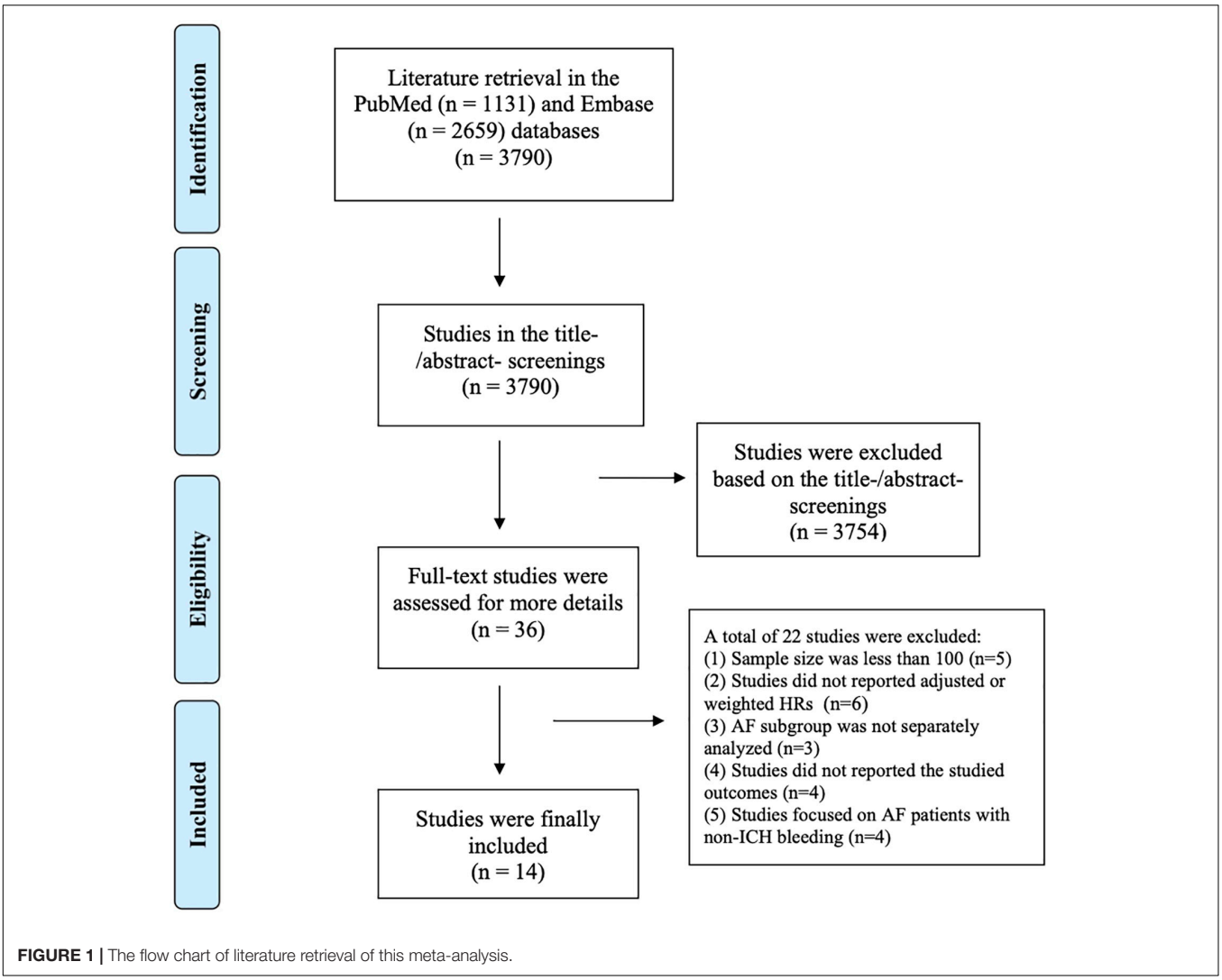

FIGURE 1 | The flow chart of literature retrieval of this meta-analysis.

including stroke or systemic embolism (HR = 0.65, 95% CI 0.53–0.81; I^2 = 8%), ischemic stroke (HR = 0.70, 95% CI 0.60–0.82; I^2 = 0%), and all-cause death (HR = 0.43, 95% CI 0.27–0.70; I^2 = 90%) and showed an upward trend toward major bleeding (HR = 1.50, 95% CI 0.94–2.40; I^2 = 37%) but showed no difference in recurrent ICH (HR = 0.91, 95% CI 0.53–1.55; I^2 = 84%) between the two studied groups. Although we failed to find the source of high heterogeneity, the results were stable when excluding each included study at a time.

As presented in **Figure 3**, compared with no VKA, the use of VKA was correlated with decreased risks of stroke or systemic embolism (HR = 0.56, 95% CI 0.41–0.77; I^2 = 21%) and all-cause death (HR = 0.38, 95% CI 0.27–0.52; I^2 = 38%). There was no difference in recurrent ICH (HR = 1.00, 95% CI 0.45–2.22, I^2 = 90%) between VKA versus no VKA; however, this should be interpreted cautiously due to a quite wide CI and significant heterogeneity. In addition, we did not assess the effect of NOAC versus no NOAC in patients with AF after ICH because only the included study by Komen et al. (14) reported this comparison.

Effect of Non-vitamin K Antagonist Oral Anticoagulants Versus Vitamin K Antagonists in Atrial Fibrillation Patients After Intracranial Hemorrhage

A total of five included studies reported the effects of NOAC versus VKA in patients with AF after ICH. As shown in **Figure 4**, our results based on the random-effects model showed that, compared with VKA, the use of NOAC was significantly correlated with reduced risks of stroke or systemic embolism (HR = 0.83, 95% CI 0.70–0.98; I^2 = 0%), all-cause death (HR = 0.67, 95% CI 0.53–0.84; I^2 = 75%), and recurrent ICH (HR = 0.68, 95% CI 0.54–0.86, I^2 = 0%), but there was no significant difference in major bleeding (HR = 0.54, 95% CI 0.26–1.10, I^2 = 84%).

Publication Bias

As shown in **Supplementary Figures 1–3**, we observed no potential publication biases for the effectiveness and safety outcomes by assessing the funnel plots. Egger's and Begg's tests

TABLE 1 | Baseline characteristics of the included studies in this meta-analysis.

Studies	Database source	Inclusion period	Study design	Study population	Age (y)	Males (%)	Sample size (N)	CHA 2DS2-VASc	HAS-BLED	OAC group	No OAC group	Follow-up	Time to prescription of OACs
Lewis	SoSTART; United Kingdom	2018–2020	RCT	AF patients who had survived at least 24 h after symptomatic spontaneous ICH	79.0	63	203	4.0	2.0	DOACs (dabigatran apixaban, rivaroxaban, edoxaban) or VKAs (warfarin, acenocoumarol, phenindione)	Antiplatelets* or no antithrombotic agents	1.2 year	24 h
Schreuder et al. (10)	APACHE-AF; Netherlands	2015–2016	RCT	Patients with a spontaneous ICH in the prior 7–90 days during anticoagulation for AF	78.0	54	101	4.0	NA	DOACs (apixaban)	Antiplatelets or no antithrombotic agents	1.9 year	45 (22–70) days
Komen et al. (14)	The Stockholm Healthcare Database; Sweden	2011–2018	Observational cohort	AF patients who were diagnosed with ICH	80.2	NA	3,006	NA	NA	DOACs (dabigatran apixaban, rivaroxaban, edoxaban) or VKAs (Warfarin)	No anticoagulants and no antiplatelets	90 day	NA
Lee et al. (15)	The Korean Health Insurance Review and Assessment database; South Korea	2010–2018	Observational cohort	Asian patients with AF and a history of ICH	72.4	56.9	5,712	4.0	4.4	DOACs (dabigatran apixaban, rivaroxaban, edoxaban) or VKAs (Warfarin)	None	9.27 year	3.1 ± 2.8 (years)
Tsai et al. (16)	The National Health Insurance Research Database; Taiwan	2012–2016	Observational cohort	Asian patients with AF and a history of ICH	76.0	58.4	4,540	5.55	4.31	DOACs (dabigatran apixaban, rivaroxaban) or VKAs (Warfarin)	None	5.0 year	NA
Newman et al. (17)	Medicare Part D Claims Data; United States	2010–2016	Observational cohort	AF who experienced an OAC-related ICH and survived at least 6 weeks after the ICH	NA	43.7	1,502	NA	NA	DOACs (dabigatran apixaban, rivaroxaban) or VKAs (Warfarin)	Antiplatelets or no antithrombotic agents	780 day	6 weeks
Nielsen et al. (18)	Danish nationwide databases; Denmark	2003–2017	Observational cohort	AF patients sustaining an ICH and who subsequently claimed an OAC prescription	76.1	60.9	622	4.4	NA	DOACs (dabigatran apixaban, rivaroxaban) or VKAs (Warfarin)	None	3.0 year	2 months

(Continued)

TABLE 1 | (Continued)

Studies	Database source	Inclusion period	Study design	Study population	Age (y)	Males (%)	Sample size (N)	CHA 2DS2-VASc	HAS-BLED	OAC group	No OAC group	Follow-up	Time to prescription of OACs
Perreault et al. (19)	The Quebec Régie de l'Assurance Maladie du Québec and Med-Echo administrative databases; Canada	1995–2015	Observational cohort	AF patients with an incident ICH requiring admission to a hospital	83.0	46.9	683	3.9	2.6	DOACs or VKAs	No anticoagulants and no antiplatelets	1.0 year	6 weeks
Nielsen et al. (20)	Danish nationwide databases; Denmark	1998–2016	Observational cohort	AF patients sustaining an ICH (hemorrhagic stroke or traumatic ICH) and who subsequently claimed an OAC prescription	77.1	61.3	2,415	3.9	3.6	VKAs (Warfarin)	Antiplatelets or no antithrombotic agents	1.0 year	10 weeks
Chao et al. (21)	The National Health Insurance Research Database; Taiwan	1996–2011	Observational cohort	Asian patients with AF and a history of ICH	74.7	57.0	12,917	6.0	NA	VKAs (Warfarin)	No anticoagulants and no antiplatelets	3.3 year	30 days
Park et al. (22)	The Institutional Review Board of Severance Cardiovascular Hospital, Seoul; South Korea	2009–2013	Observational cohort	Patients with AF and a history of ICH	68.5	34.1	428	3.26	3.48	VKAs (Warfarin)	Antiplatelets or no antithrombotic agents	39.5 m	117.5 ± 235.7 (days)
Nielsen et al. (23)	Danish nationwide databases; Denmark	1997–2013	Observational cohort	AF patients sustaining an ICH and who subsequently claimed an OAC prescription	78.0	62.0	1,752	3.9	3.2	DOACs (dabigatran apixaban, rivaroxaban, edoxaban) or VKAs (coumarin)	No anticoagulants and no antiplatelets	1.0 year	6 months
Kuramatsu et al. (24)	19 German tertiary care centers; Germany	2006–2012	Observational cohort	AF patients had OAC-associated ICH※	75.0	61.0	566	NA	NA	VKAs (Warfarin)	Antiplatelets or no antithrombotic agents	1.0 year	95 (44–180) minutes
Lin et al. (25)	Health and Welfare Database; Taiwan	2011–2017	Observational cohort	Asian patients with AF and a history of ICH	76.4	58.7	2,640	5.1	NA	DOACs or VKAs (Warfarin)	Antiplatelets or no antithrombotic agents	0.6 year	42 (10–127) days

**Aspirin and/or P2Y12 antagonist treatment. ※ICH patients with AF were only a part of the whole population in the included study. #only used in the subgroup analysis of VKAs versus no VKAs. AF, atrial fibrillation; ICH, intracranial hemorrhage; OAC, oral anticoagulation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; RCT, randomized controlled Trial; SoSTART, the start or stop anticoagulants randomized trial; APACHE-AF, the apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral hemorrhage in patients with atrial fibrillation; CHA2DS2-VASc, congestive heart failure/left ventricular ejection fraction ≤ 40%, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism (2 points), vascular disease, age 65–74 years, female sex; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; and NA, not available.*

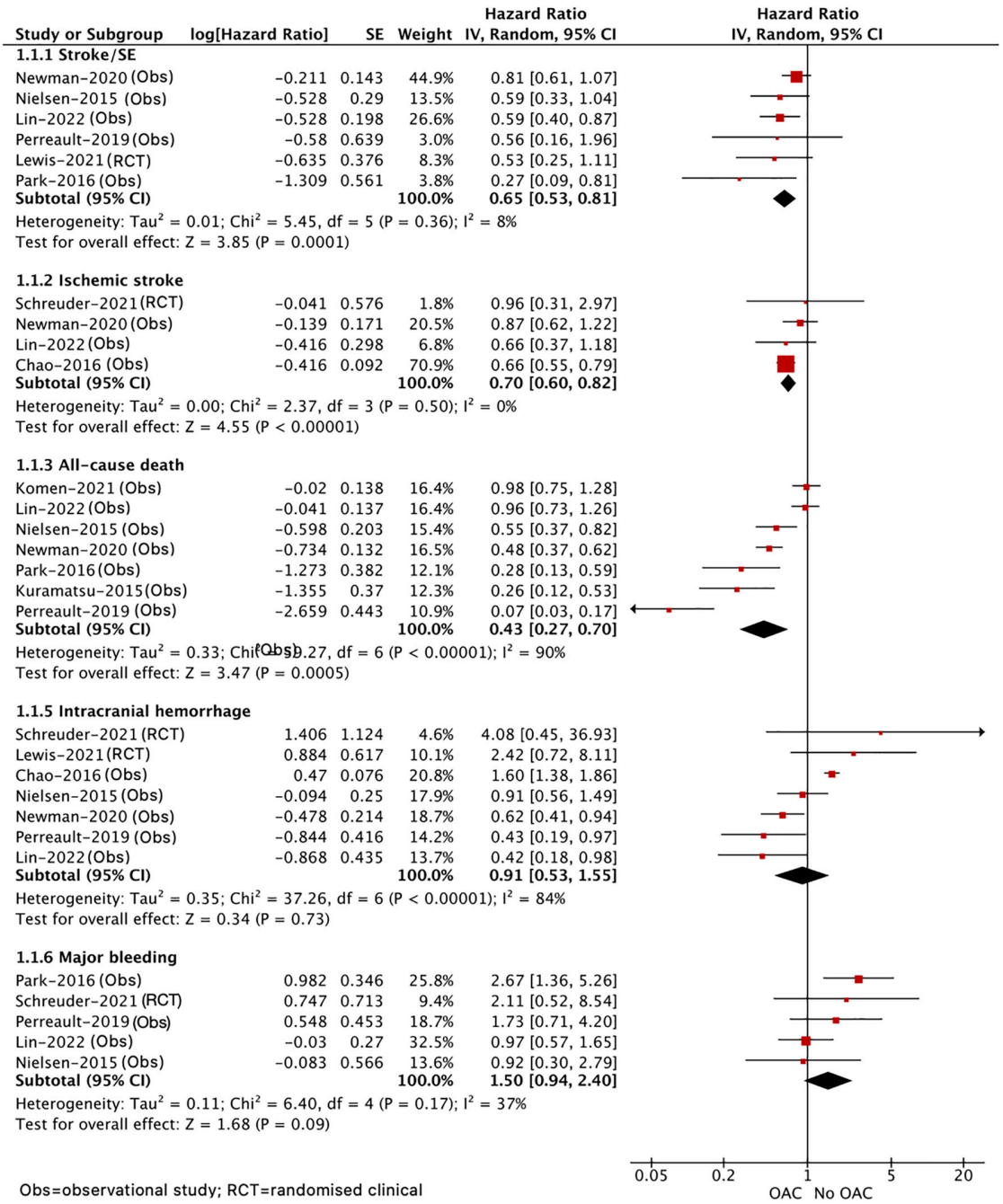

FIGURE 2 | Comparing the efficacy of OAC with no OAC in patients with AF after ICH. AF, atrial fibrillation; ICH, intracranial hemorrhage; OAC, oral anticoagulants; CI, confidence interval; IV, the inverse of the variance; SE, standard error; and SE, systemic embolism.

also suggest no publication biases for most outcomes ($p > 0.1$; **Supplementary Table 8**).

DISCUSSION

The main findings of our meta-analysis on the effectiveness and safety outcomes of OAC versus no OAC in patients with AF after ICH are summarized as follows: (1) OAC was correlated with a lower risk of stroke or systemic embolism, ischemic stroke, and all-cause death but a similar risk of major bleeding and major recurrent ICH compared with no OAC; (2) VKA treatment had significantly reduced risks of stroke or systemic embolism and all-cause death but a similar risk of recurrent ICH compared with no VKA treatment; (3) NOAC had better effectiveness and safety outcomes than VKA,

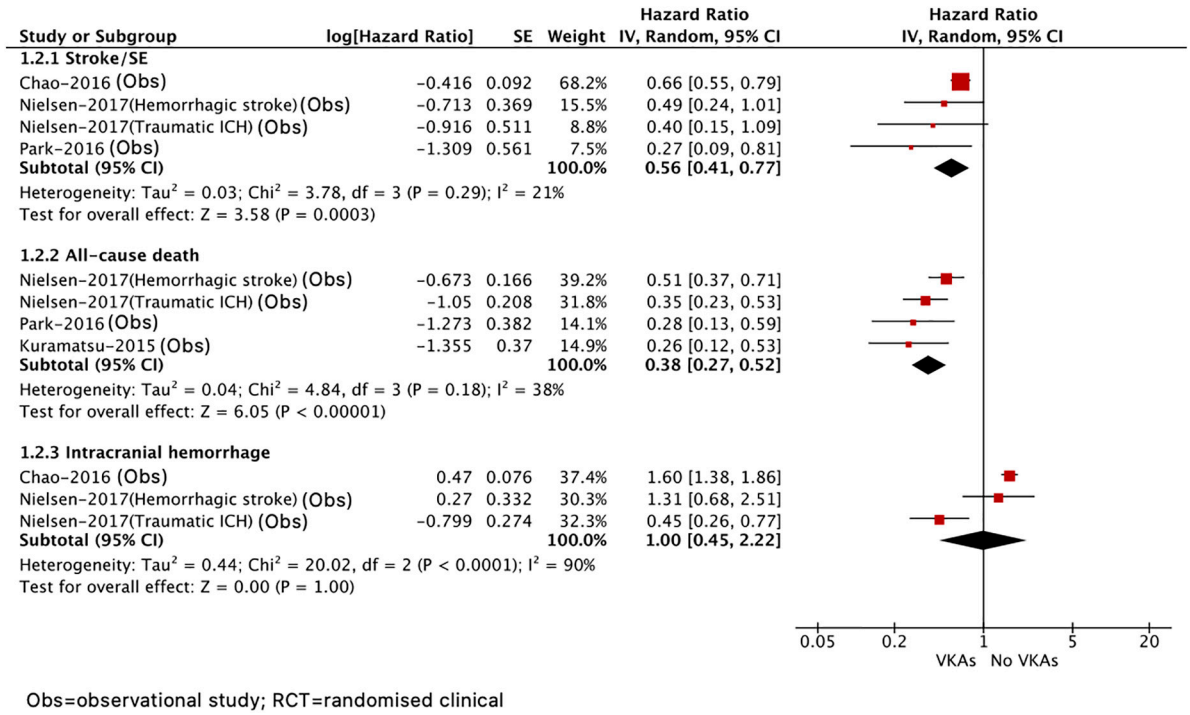

FIGURE 3 | Comparing the efficacy of VKAs with no VKAs in patients with AF after ICH. AF, atrial fibrillation; ICH, intracranial hemorrhage; VKAs, vitamin K anticoagulants; CI, confidence interval; IV, the inverse of the variance; and SE, standard error.

demonstrating a significant reduction of ischemic stroke, all-cause death, and lower risk of recurrent ICH, but no significant difference in major bleeding. Although these results should be interpreted cautiously because of limited evidence, VKA might not be the preferred option because of their higher risk of recurrent ICH than NOAC in patients with AF after ICH. Our results may provide valuable evidence for the current uncertain management of stroke prevention for AF patients with ICH (26).

Based on hematoma-mediated inflammation, antithrombotic drug interruption, and common vascular risk factors, survivors of ICH are at a higher risk of ischemic stroke compared with the general population (27, 28); therefore, stroke prevention is crucial for this specific population. Previous observational studies have provided evidence in favor of recommencing anticoagulation therapy. Several prior studies showed that anticoagulation was correlated with reduced risks of ischemic stroke or systemic embolism and all-cause death (20–22). A recent observational study by Newman et al., which enrolled 1,502 OAC-related ICH survivors, demonstrated that anticoagulation was correlated with a lower risk of ICH (17). In our analysis, after integrating all the available data, it was found that OAC-treated patients had a reduced risk of stroke or systemic embolism, all-cause death and also an upward trend toward major bleeding as compared with no anticoagulants. Given that VKA and NOAC are both effective anticoagulants for the prevention of thromboembolic events in patients with AF, it is logical to observe a favorable effectiveness profile of OAC treatment in patients with AF after ICH. In the present study, no significant difference in recurrent ICH risk was also observed between patients with and without OAC treatment, which was consistent with those reported by recent RCTs in patients with AF after ICH (10, 11). These safety outcomes suggest that OAC therapy may not serve as a promoter for secondary hemorrhagic stroke occurrence. Compared with those with no OAC therapy, the VKA-treated group demonstrates superior effectiveness of anticoagulation and no significant difference in recurrent ICH, which is consistent with the result of the OAC group versus no OAC group. However, due to only one related study, we did not perform the analysis of the NOAC group versus the no NOAC group to evaluate the effectiveness and safety profiles of the NOAC therapy in patients with AF after ICH. In addition, because the sample size of these two recent RCTs is relatively small, further research should be warranted to provide highly correlated evidence for identifying the association between anticoagulant treatment and ICH prevention in patients with AF after ICH.

Considering the increased risk of bleeding with anticoagulants, a treatment strategy that provides a better safety profile may be the optimal option for patients with AF after ICH. Focusing on the east Asian population with cardiovascular diseases, patients who were prescribed antithrombotic agents were predisposed to bleeding events, such as gastrointestinal bleeding and ICH, etc. (29). Data from the present studies demonstrated superior effectiveness and safety outcomes of NOAC in stroke or systemic embolism and recurrent ICH compared with VKA, which was consistent with associated

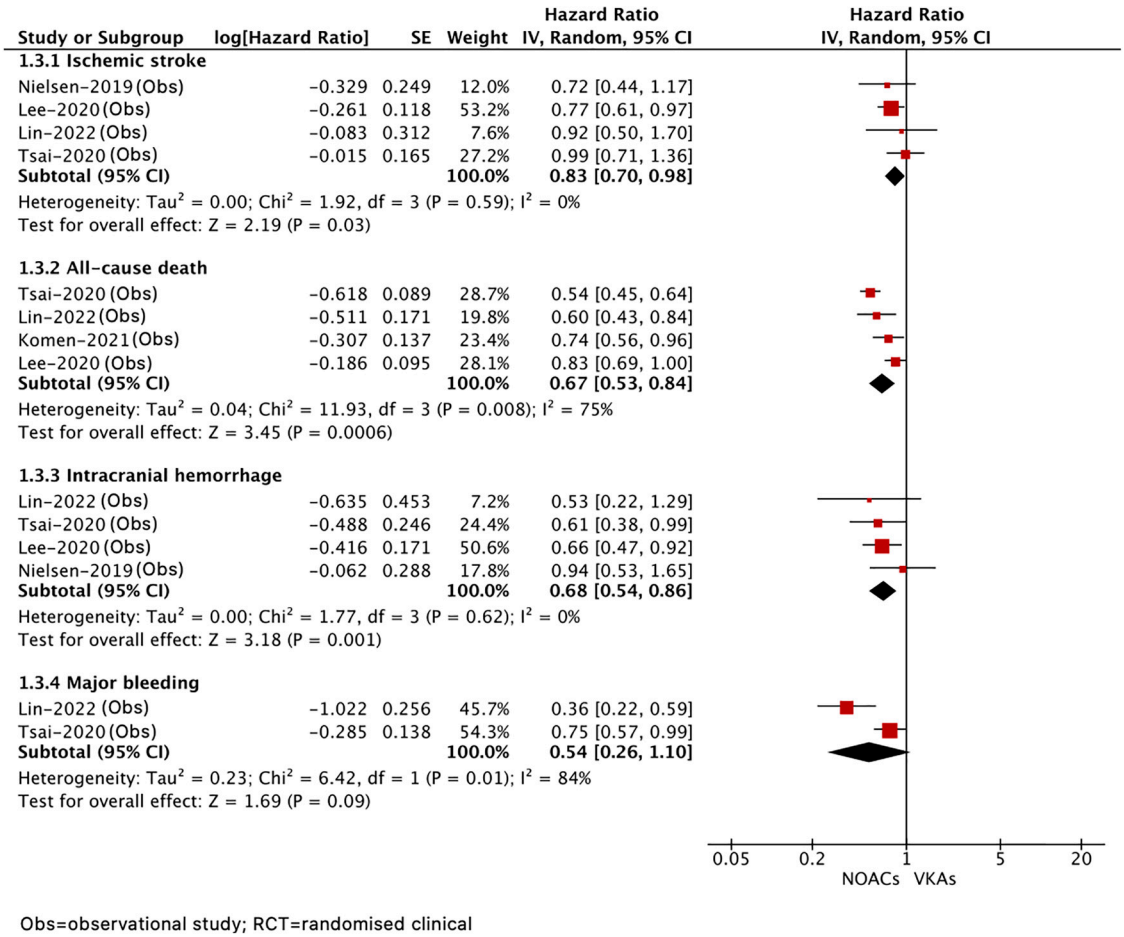

FIGURE 4 | Comparing the efficacy of NOACs with VKAs in patients with AF after ICH. AF, atrial fibrillation; ICH, intracranial hemorrhage; VKAs, vitamin K anticoagulants; NOACs, non-vitamin K oral anticoagulants; CI, confidence interval; IV, the inverse of the variance; and SE, standard error.

RCTs and observational cohorts in AF patients with previously diagnosed ICH (11, 23–25). A prior meta-analysis, which pooled 48 randomized trials and 71,683 patients with AF, suggested that the superior effectiveness and safety profiles of NOAC were attributed to the prevention of stroke, which included ICH and ischemic stroke (8). Moreover, a previous observational study by Hagii et al. elaborated that the size of hematoma in NOAC-associated ICH was smaller than that of VKA-associated ICH (30). Consequently, by reducing the incidence of hemorrhagic stroke, NOAC was significantly correlated with a lower risk of recurrent ICH, which was a crucial safety outcome in the risk-benefit assessment of anticoagulant therapy in patients with AF (31–34). In the current stage, at least 4 pivotal randomized trials (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48) confirm the superior safety outcomes (especially for lower bleeding risk) of NOAC versus VKA, and our results are consistent with this significant finding.

In addition, NOAC treatment confers benefits for survival in patients with AF after ICH as compared with VKA treatment. This beneficial effect is correlated with the prevention of stroke or systemic embolism and the reduction of recurrent ICH in NOAC treatment. Our findings are consistent with that of a previously published meta-analysis, with almost 50% lower risk of ICH in AF patients without previous ICH, though no obvious difference in OAC-ICH was found between the use of NOAC and VKA (6, 8). It reveals that NOAC may be recommended to VKA-tolerant patients with AF after ICH to prevent ICH recurrence. Nevertheless, further studies focusing on specific NOAC subgroups should be performed to analyze consequent all-cause death. Our meta-analysis provides a future research orientation to analyze the discrepancies among secondary outcomes of different NOAC subgroups. Besides anticoagulant treatment, another available and radical approach for AF patients after ICH management is LAA occlusion. In several national observational studies and RCTs (PROTECT AF and PREVAIL), it was demonstrated that, compared with VKA treatment, the LAA occlusion was non-inferior to preventing stroke and major bleeding (35–37). The LAA occlusion is a potential alternative approach for patients with AF who are contraindicated to anticoagulant treatment. However, the limited RCTs comparing anticoagulant treatment (especially for NOAC therapy) with LAA occlusion are performed to identify the effectiveness and

safety outcomes of LAA occlusion. There are two ongoing RCTs: CLEARANCE (NCT04298723), assessing LAA occlusion plus a short-term anticoagulant therapy versus anticoagulant treatment in 550 AF patients with ICH; STROKECLOSE (NCT02830152), a study of LAA occlusion versus other medical therapies (NOAC, VKA, antiplatelet therapy, and no antithrombotic therapy at all) in 750 AF patients after ICH. Further associated research should be performed to provide more convincing evidence.

LIMITATION

Our study had several limitations. First, we pooled data from mostly observational studies and two recent RCTs with a limited sample size, which might limit the data quality. Second, the severity, imaging, and dysfunction of prior stroke/transient ischemic attack or ICH were not addressed and adjusted, which may bring heterogeneity to the pooled result. For example, for patients with a high risk of ICH recurrence, clinical physicians may tend to not prescribe VKA. In addition, the different criteria for major bleeding definition exist in our involving research. Third, due to limited data sources of comparison between OAC and no OAC treatment in AF patients with previous ICH, our study did not divide the patients into four subgroups with traumatic, OAC-related, spontaneous, and no classification ICH for subgroup analysis. Fourth, the limited data were not available for evaluating the effectiveness and safety outcomes among different NOAC strategies and NOAC versus no NOAC. Further research is warranted to examine the outcomes of dabigatran, apixaban, rivaroxaban, and edoxaban in patients with AF after ICH, respectively. Moreover, due to the diverse anticoagulation commencement time presented by our 14 included studies, early or late anticoagulation strategy may have a different effect on ischemic stroke, major bleeding, ICH, and other outcomes, but we did not perform a subgroup analysis to stratify patients into distinct OAC prescription time. Finally, the volume of hemorrhage also plays an important role in anticoagulation decisions, but we were unable to perform the related subgroup analysis.

CONCLUSION

Oral anticoagulant treatment exhibited superior effectiveness profiles in patients with AF after ICH, without increasing the risk of recurrent ICH and major bleeding. Especially, NOAC exerted more favorable effects on stroke prevention and mortality with a lower risk of recurrent ICH as compared with VKA. However, due to insufficient evidence provided by limited RCTs, further research should be performed to identify the superiority of NOAC.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/ **Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.961000/full#supplementary-material

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Zexuan Wu,
First Affiliated Hospital of Sun Yat-sen University, China
Yumeng Shi,
The Second Affiliated Hospital of Nanchang University, China
Zi Amber Ye,
Royal North Shore Hospital, Australia

*CORRESPONDENCE
Xiaojuan Wu
xiger6666@126.com
Siyuan Li
turbolsy@163.com

†These authors share first authorship

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Effectiveness and safety of oral anticoagulant therapy in patients with atrial fibrillation with prior gastrointestinal bleeding: A systematic review and meta-analysis

Jie Zhao[1†], Xiaojuan Wu[2*†], Siyuan Li[3*] and Qiuping Gu[2]

[1]Department of Cardiovascular Medicine, Wuhan Third Hospital & Tongren Hospital of Wuhan University, Wuhan, China, [2]Department of Gastroenterology, Ganzhou People's Hospital, Ganzhou, China, [3]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Background: Gastrointestinal bleeding (GIB) commonly complicates anticoagulant therapy for patients with atrial fibrillation (AF). However, AF patients with prior GIB were excluded from most randomized controlled trials on anticoagulation therapy. Therefore, we conducted a systematic review and meta-analysis to assess the effect of oral anticoagulant (OAC) therapy in this specific population.

Methods: Randomized trials and observational studies reporting the data about the resumption of OAC therapy among AF patients with prior GIB were included. The search was performed in the PubMed and Embase databasesup to March 2022. The adjusted hazard ratios (*HR*s) and 95% confidence intervals (*CI*s) were pooled by a random-effects model with an inverse variance method.

Results: A total of 7 studies involving 57,623 patients were included. Compared with no anticoagulant therapy, OAC therapy was associated with decreased risks of stroke or systemic embolism (*HR* = 0.71, 95% *CI*: 0.59–0.84) and all-cause death (*HR* = 0.66, 95% *CI*: 0.60–0.72), but there was no significant difference in the risk of recurrent GIB (*HR* = 1.22, 95% *CI*: 0.94–1.59). Compared with vitamin K antagonists, non-vitamin K antagonist oral anticoagulants (NOACs) were associated with reduced risks of stroke or systemic embolism (*HR* = 0.61, 95% *CI*: 0.54–0.68), all-cause mortality (*HR* = 0.86, 95% *CI*: 0.75–0.99), major bleeding (*HR* = 0.75, 95% *CI*: 0.66–0.84), and GIB recurrence (*HR* = 0.83, 95% *CI*: 0.72–0.96).

Conclusions: In AF patients with prior GIB, OAC therapy (especially NOACs) demonstrated superior effectiveness compared with no anticoagulant therapy.

KEYWORDS

atrial fibrillation, gastrointestinal bleeding, anticoagulation, prognosis, meta-analysis

Introduction

It is estimated that there were over 6 million cases of ischemic stroke worldwide in 2013, of which approximately 20% are attributed to atrial fibrillation (AF) (1). Oral anticoagulant (OAC) therapy, including vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs), has become the backbone of AF management (2–5). However, OAC therapy often comes at the expense of an increased risk of bleeding. Tensions grounded in the history of bleeding events often play a key role in the assessment of all patients taking OAC, particularly in patients with prior gastrointestinal bleeding (GIB).

A large cohort study demonstrated that during the 5-year anticoagulation therapy, 5.7% of elderly patients with AF developed GIB, some of which were at a high risk of mortality (6). Furthermore, although NOACs show a positive role in convenient dosing adjustment and the reduction of risk of stroke, mortality, and intracranial bleeding events, an increased occurrence of GIB has been examined in the same trials (7–11). With such concern, the management of post-GIB medications is extremely difficult in balancing the benefits of stroke prevention against a high perceived risk of recurrent bleeding.

The previous meta-analysis showed that the resumption of OACs in patients following GIB was associated with reduced thromboembolic events and death, with a statistically significant increase in recurrent GI bleeding compared with no-starters (12). However, it was conducted primarily on patients taking VKAs, such as warfarin, and the population was not strictly limited to patients with AF. For patients with AF at a high risk of GIB, a recent network meta-analysis found that resumption of NOACs appeared to be the preferred option compared with warfarin (13). The European Society of Cardiology (ESC) Guidelines recommend that a VKA or another NOAC preparation should be preferred over dabigatran 150 mg two times daily, rivaroxaban 20 mg one time daily, or edoxaban 60 mg one time daily, although lacking strong evidence (14). Therefore, we performed a systematic review and meta-analysis to demonstrate the effectiveness and safety of restarting OAC therapy in AF patients with prior GIB, and further compare the effects of NOACs with VKAs.

Methods

The meta-analysis was designed and conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2) and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement. Ethical approval was not required since we only included articles of published data in the public domain.

Literature search

Two reviewers searched PubMed and Embase database sources from inception to March 2022. The following search terms were used: (1) "atrial fibrillation" OR "atrial flutter," (2) "gastrointestinal bleeding" OR "gastrointestinal hemorrhage" OR "intestinal bleeding" OR "intestinal hemorrhage" OR "GIB," and (3) "oral anticoagulant" OR "vitamin K antagonist" OR "VKA" OR "warfarin" OR "non-vitamin K antagonist oral anticoagulant" OR "direct oral anticoagulant" OR "novel oral anticoagulant" OR "NOAC" OR "DOAC" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban." The above three categories of search terms were linked by the Boolean command "AND," and the complete depiction of the search strategy is given in the **Supplementary Table 1**. In addition, reference lists of the included studies were also searched to identify any studies not found in the initial database search.

Inclusion and exclusion criteria

The criteria for inclusion were as follows: (1) the study design was a randomized clinical trial (RCT) or an observational (prospective or retrospective cohort) study; (2) the study included AF patients with prior GIB who received VKA or NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban); and (3) effect estimates were adjusted hazard ratios (*HRs*) and 95% confidence intervals (*CIs*), reporting for safety and effectiveness outcomes among patients who resumed OACs and those who did not.

Studies were excluded if the participants had non-GIB [e.g., any bleeding, intracerebral hemorrhage (ICH), major bleeding, and microbleed] or a mixed population without being separately analyzed in the subgroup. In addition, we also excluded certain publication types (e.g., reviews, comments, case reports, case series, letters, editorials, and meeting abstracts) due to insufficient data or study details. If there were overlapping data among two or more studies, we included the one with the largest sample size or the longest follow-up duration. The outcomes considered in our study were SSE, recurrent GIB, and all-cause death. If there are sufficient data on the time to resume anticoagulation, comparisons will be made between different times to resumption. Definitions of the outcomes for each study included in the meta-analysis are shown in **Supplementary Table 3**.

Study selection and data abstraction

In this study, two reviewers screened the titles and abstracts of the retrieved studies from the electronic databases. Subsequently, we selected the eligible studies after the full-text screenings based on the pre-defined inclusion criteria.

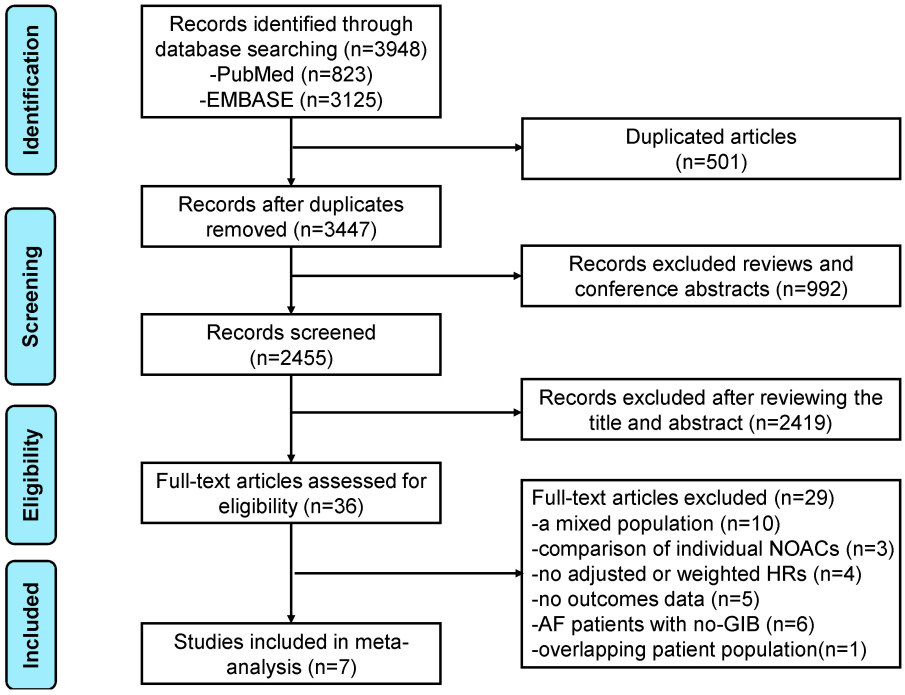

FIGURE 1
The preferred reporting items for systematic review and meta-analysis (PRISMA) flowchart of this meta-analysis.

Reviewers compared and discussed results and consulted a third reviewer in case of any disagreement. The reviewer's abstracted data on the following characteristics: study contexts (first author and year of publication), study design (cohort or RCTs and duration of follow-up), study population (sample size, age, stroke, or bleeding risk prediction scores), outcomes [stroke and systemic embolism (SSE), all-cause death, major bleeding, and recurrent GIB], and measures of association (sample size and the number of events between groups and adjusted *HR*s).

Study quality assessment

We assessed the quality of the *post hoc* analysis of an RCT or observational cohort by using the Newcastle-Ottawa Scale (NOS) tool. This tool had three domains with a total of nine points: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcomes (0–3 points). In this meta-analysis, the NOS of ≥ 6 and < 6 points were scored as moderate-to-high quality and low-quality, respectively (15).

Statistical analysis

This meta-analysis's statistical analyses were conducted using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Center Copenhagen, Denmark).[1]

In this study, significant heterogeneity was indicated by an I^2 value of $> 50\%$, which led to the use of random-effects models and the exploration of a potential source of heterogeneity. When these tests were negative for heterogeneity, fixed-effects models were chosen to calculate pooled *HR*s through the inverse-variance method. In the pooled analysis, the adjusted *HR*s and 95% *CI*s were converted to the natural logarithms (Ln [*HR*]) and their corresponding standard errors (SEs) (Ln [upper CI]-Ln [lower CI]/3.92), which were pooled by a DerSimonian and Laird random-effects model with an inverse variance method. Funnel plots for assessing the potential publication bias for the reported effect estimates were not performed due to the small number of included studies ($n < 10$).

Results

Study selection

The flowchart of literature retrieval is shown in **Figure 1**. A total of 3,948 records were retrieved from the two databases of PubMed and Embase. After removing duplicates, there

1 https://community.cochrane.org/

were 3,447 bibliographic records identified. Following the elimination of reviews and conference abstracts, the remaining 2,455 articles were under the first phase of the title- and abstract- screenings. After that, 36 remaining studies were potentially available, and further assessed under the full-text screenings. According to the pre-defined inclusion and exclusion criteria, we subsequently excluded 29 studies because (1) studies compared the effects of NOACs (n = 3); (2) studies did not report adjusted or weighted *HR*s (n = 4); (3) studies focused on a mixed population, and the AF patients with GIB subgroup was not separately analyzed (n = 10); (4) studies did not report the studied outcomes (n = 5); (5) studies focused on AF patients with no-GIB (n = 6); and (6) studies with an overlapping patient population (n = 1). Finally, a total of seven studies [one *post hoc* analysis of RCT and six observational cohorts (16-22)] were included in our meta-analysis.

Baseline characteristics

Baseline characteristics of the included studies are presented in **Table 1**. Among the included studies, three were from the United States, one was from Denmark, one each from Sweden and Korea, and one from multiple countries. The mean age of patients ranged from 73.5 to 78.3 years, and the sample size was from 784 to 42,048. The study populations in the OAC group across studies were administrated with NOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) or VKAs. A risk of bias evaluation was performed as shown in **Supplementary Table 2**. All the studies had an NOS of $\geq$ 6 points suggesting moderate-to-high quality. The inclusion criteria and primary outcomes varied across studies with different adjusted risk factors in the included studies (**Supplementary Tables 3**, **4**).

Synthesis of results

Effect of OACs vs. no OACs in patients with atrial fibrillation after gastrointestinal bleeding

As shown in **Figure 2**, our pooled results based on the random-effects model showed that compared with no OACs, the use of OACs (NOACs or VKAs) was significantly associated with reduced risks of effectiveness outcomes, including SSE (*HR* = 0.71, 95% *CI*: 0.59–0.84; I^2 = 0%) and all-cause death (*HR* = 0.66, 95% *CI*: 0.60–0.72; I^2 = 0%). There was no significant difference in the risk of recurrent GIB between the two studied groups (*HR* = 1.22, 95% *CI*: 0.94–1.59; I^2 = 68%). We re-analyzed our data, excluding one study at a time to examine if a specific study influenced the results. The risk of recurrent GIB was materially altered by the study conducted by Tapaskar et al. (18).

Specifically, as presented in **Supplementary Figures 1**, **2**, we performed the subgroup analysis by drug regimen (NOACs vs. no NOAC and VKAs vs. no VKAs) on the results of SSE and recurrent GIB. There was no subgroup difference in the risk of recurrent GIB (p = 0.56). In terms of the risk of SSE, although no statistically significant subgroup difference was observed (p = 0.98), the reduced rate of SSE in patients resuming NOACs was not statistically significant when compared with those who did not take NOACs (*HR* = 0.71, 95% *CI*: 0.50–1.01; I^2 = 0%), whereas the use of VKAs was associated with the decreased risk of SSE compared with no VKAs (*HR* = 0.71, 95% *CI*: 0.58–0.87; I^2 = 0%).

Effect of non-vitamin K antagonist oral anticoagulants vs. vitamin K antagonists in patients with atrial fibrillation after gastrointestinal bleeding

A total of three included studies reported the effects of NOACs vs. VKAs in patients with AF after GIB. As shown in **Figure 3**, our results based on the random-effects model showed that compared with VKAs, the use of NOACs was significantly associated with reduced risks of SSE (*HR* = 0.61, 95% *CI*: 0.54–0.68, I^2 = 0%), all-cause death (*HR* = 0.86, 95% *CI*: 0.75–0.99, I^2 = 16%), major bleeding (*HR* = 0.75, 95% *CI*: 0.66–0.84, I^2 = 0%), and recurrent GIB (*HR* = 0.83, 95% *CI*: 0.72–0.96, I^2 = 0%).

Timing of restarting anticoagulation

Three studies provided data on the timing of resuming anticoagulation. As shown in **Figure 4**, our results showed that there was no statistically difference in the risk of SSE between refilling anticoagulation within and after 30 days (*HR* = 0.90, 95% *CI*: 0.68–1.17, I^2 = 25%), whereas the resumption of anticoagulation within 30 days was associated with an increased risk of recurrent GIB (*HR* = 1.43, 95% *CI*: 1.11–1.82, I^2 = 0%). It was worth noting that there was an upper-bound limit on the time according to the included studies. Qureshi et al. defined the longest time of discontinuance as 6 months and Tapaskar et al. classified patients based on the first claim within 90 days of discharge (18, 19). In the study conducted by Sengupta et al., the median time to refill a claim for NOACs after GIB was 40 days (22).

Discussion

In this meta-analysis, we provided evidence that OAC therapy in AF patients with prior GIB was associated with a significant reduction in SSE and all-cause death compared with

TABLE 1 General characteristics of the included studies in the meta-analysis.

Study-year	Location	Study type	Data source	Study period	Sample size	Mean age (y)	HAS-BLED	CHA2DS2-VASc	Follow-up	NOS
(19)	The United States	Retrospective	anticoagulation clinic of Henry Ford Health System (majority of Southeast Michigan, United States)	January, 2005–December 2010	1,329	75	3 (median)	3 ($CHADS_2$, median)	2 years	8
(25)	The United States	Retrospective	IBM MarketScan Research Databases	January 2008–December2017	2,991	77 (warfarin) 78 (NOAC)	NA	NA	6 months	7
(22)	The United States	Retrospective	Truven Health MarketScan Commercial Claims and Encounters Database (Truven Health Analytics, Inc., Ann Arbor, MI, United States)	January 01, 2010–December 31, 2014	1,338	79 (median)	NA	NA	6 months	7
(16)	Korea	Retrospective	Korean Health Insurance Review and Assessment database	January 2010–April 2018	42,048	73 (median)	4	≥4	0.6 year	7
(20)	Sweden	Retrospective	Stockholm Healthcare database	July 2011–June 2018	4,291[a]	77.8 (NOAC) 78.4 (warfarin)	2.25 (NOAC) 2.26 (warfarin)	4.21 (NOAC) 4.26 (warfarin)	90 days	6
(17)	America, Europe, Asia Pacific	*Post hoc* analysis of RCT	ARISTOTLE	December 19, 2006–April 02, 2010	784	73.5	NA	NA	1.8 years	8
(19)	Denmark	Retrospective	Nationwide cohort study using Danish registries	January 01, 2005–July 31, 2017	4,842	NA	NA	NA	36 months	7

NA, not available; ICH, intracranial bleeding; GIB, gastrointestinal bleeding; SE, systemic embolism; HIRA, Health Insurance Review and Assessment; CMS, Centers for Medicare & Medicaid Services; RCT, randomized controlled trails; [a] Number of patients with a severe GIB after their diagnosis of AF.

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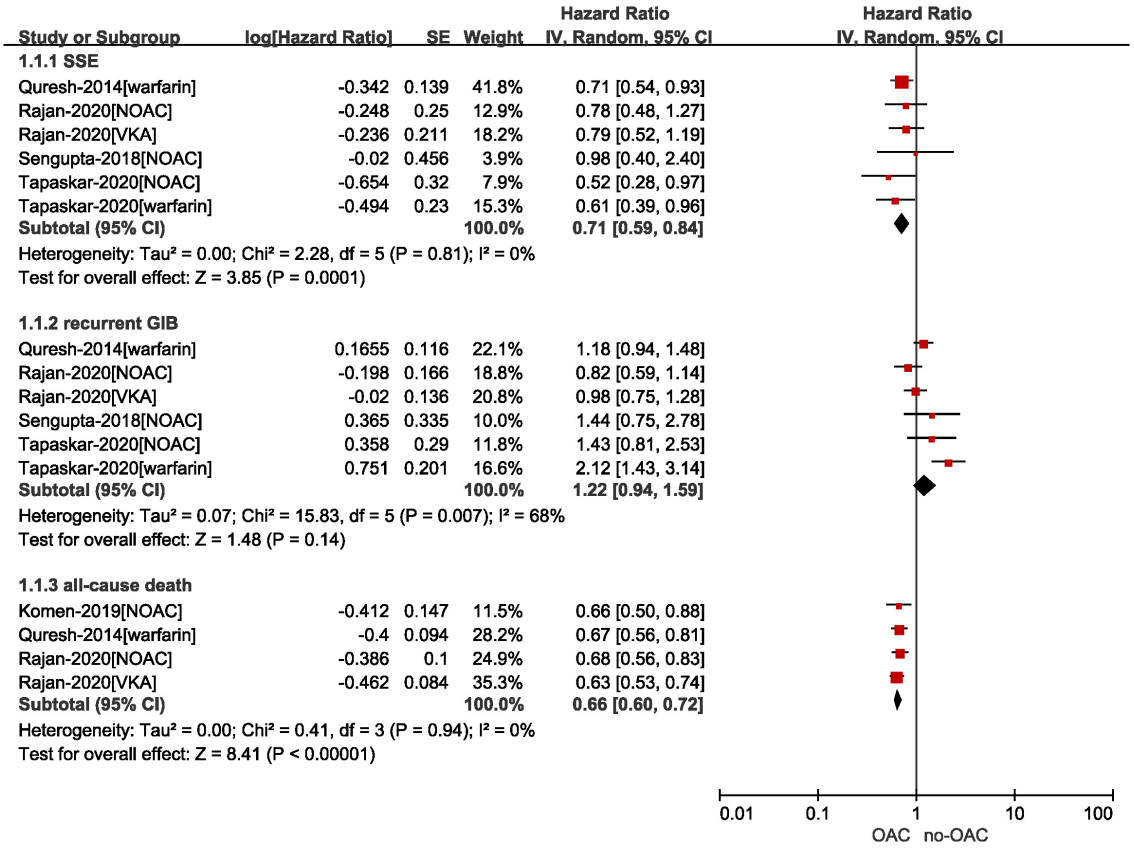

FIGURE 2
Comparing the effect of OAC with no OAC in AF patients with GIB. AF, atrial fibrillation; GIB, gastrointestinal bleeding; OAC, oral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulants; CI, confidence interval; IV, inverse of the variance; SE, standard error; SSE, stroke and systemic embolism.

no anticoagulant therapy, but there was no significant difference in the risk of recurrence GIB between the two groups. In addition, NOACs showed better benefits in SSE, all-cause death, major bleeding, and recurrent GIB compared with VKAs.

When tailoring the treatment of an individual patients with AF, physicians will focus primarily on the risk of stroke and bleeding according to clinical guidelines to ensure patients will derive an immense benefit from anticoagulation. The safety profile of OACs has improved significantly with the widespread use of NOACs, whose favorable risk-benefit profile for stroke, ICH, and mortality was well established, except for GIB (11). Therefore, concern grounded in the rate of GIB often plays a critical role in the prescription. In many cases, AF patients with GIB require temporary discontinuation of OAC therapy in the case of potentially life-threatening bleeding (23, 24). However, coincident with the reduction in bleeding risk, the prevalence of thromboembolism increases. Additionally, many RCTs exclude patients with recent bleeding, making clinical decision-making in specific populations more difficult. Two previous meta-analyses have shown that the resumption of OAC after GIB was associated with a reduced risk of SSE and mortality at the expense of an increased risk of GIB recurrence (12, 25). Recently, Suah et al. (26) performed a subgroup analysis for AF patients with prior GIB and found that NOACs were associated with a reduced risk of ischemic stroke, major bleeding, and GIB compared with warfarin, only using the data by Garcia et al. (17), Kwon et al. (16), and Tapaskar et al. (18). Additionally, a network meta-analysis comparing the effect of resuming NOACs and VKAs in AF patients with prior GIB demonstrated that the resumption of DOACs may be a safer therapy (13).

In terms of effectiveness, our results showed that OACs were associated with a reduced risk of SSE and all-cause death compared with no anticoagulation resumption, which was consistent with two previous meta-analyses. Additionally, subgroup analyses of different drug regimens were performed (NOACs vs. no NOAC and VKAs vs. no VKAs), showing no significant group differences. However, the resumption of VKAs was associated with a reduced risk of SSE compared with non-restarters, but NOACs did not differ. It may be related to the fact that the data of Sengupta et al. (22) were

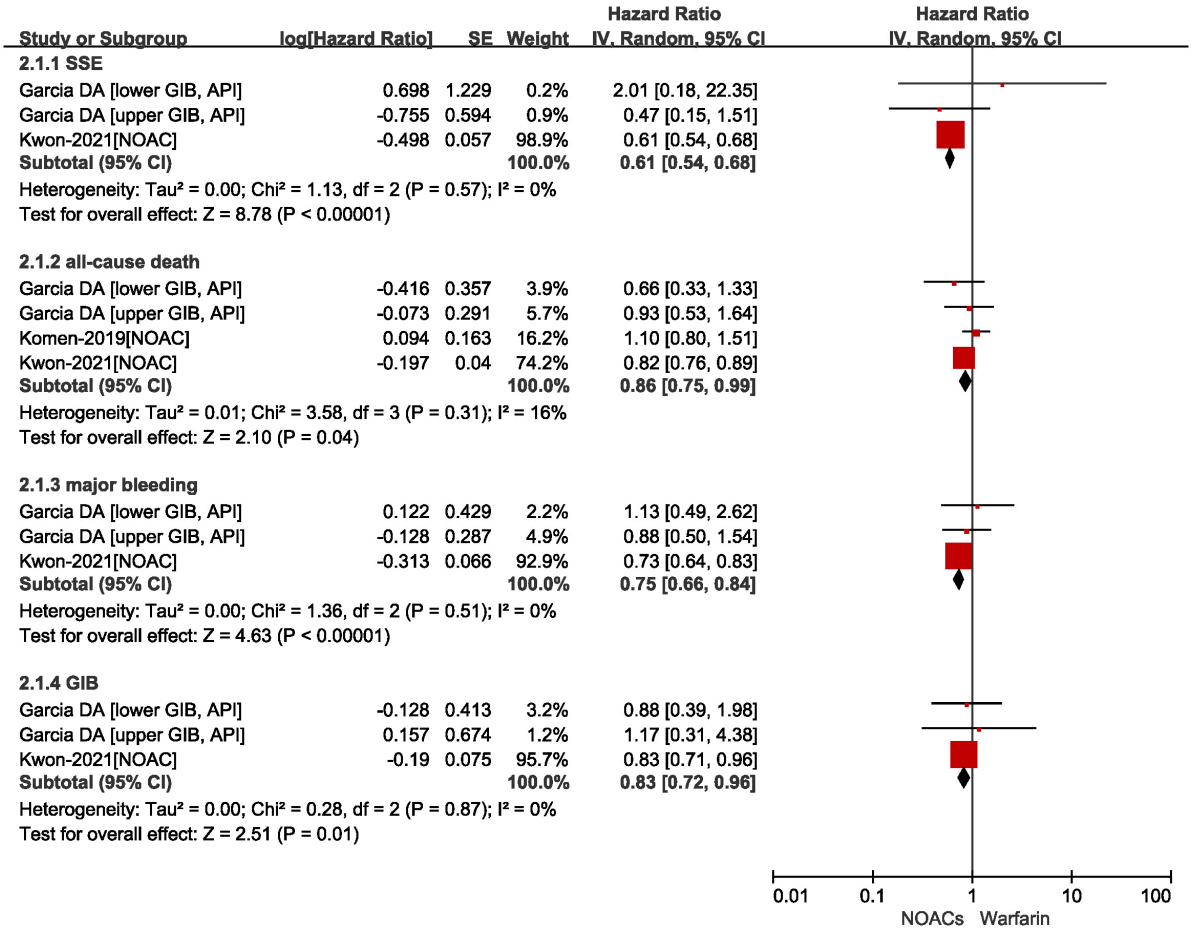

FIGURE 3
Comparing the effect of NOACs with VKAs in AF patients with GIB. AF, atrial fibrillation; GIB, gastrointestinal bleeding; VKAs, vitamin K anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulants; CI, confidence interval; IV, inverse of the variance; SE, standard error; SSE, stroke and systemic embolism.

reliant on billing claims, which is likely to underestimate the occurrence of adverse outcomes and patients may not take their medication as prescribed. Additionally, a discrepancy may exist between the date of patients' resumption and the day when they filed a claim in the insurance plan. Besides, in some situations, physicians may not strictly follow the standard dosing regimen in an attempt to minimize the risk of bleeding, which reduced the effectiveness of NOACs. Further comparisons between NOACs and VKAs demonstrated that NOACs were associated with a better effect on SSE and all-cause death compared with VKAs. However, in the SSE results of Garcia DA et al., there was a wide range of the 95% *CI* due to the small numbers in the lower GIB group. The upper limit of the *CI* for all-cause mortality result was so close to 1 that it needs to be interpreted with caution.

In the risk of bleeding, our results showed no significant difference between patients with the resumption of OAC and those who did not restart in the risk of relapse in GIB, while Tapaskar et al. and Little et al. concluded that the resumption of anticoagulation was associated with a significant increase in recurrent GIB (12, 25). There are several potential reasons why our results are inconsistent with previous findings. First, we restricted our analysis to individuals with AF, while the previous meta-analyses also included patients with venous thromboembolism, ischemic heart disease, and prosthetic valves. A relatively larger number of NOACs-users included in our study should also be considered, as it may make the bleeding risk slightly lower. Additionally, another major part of the difference has been due to the fact that we calculated pooled *HR*s using inverse variance–weighted meta-analysis with random effects. In comparing NOACs with VKAs, Kwon et al. found that NOACs were associated with lower risks of major bleeding than warfarin (16). Similarly, Hu et al. showed that the increased risk of recurrent GIB was associated with the resumption of

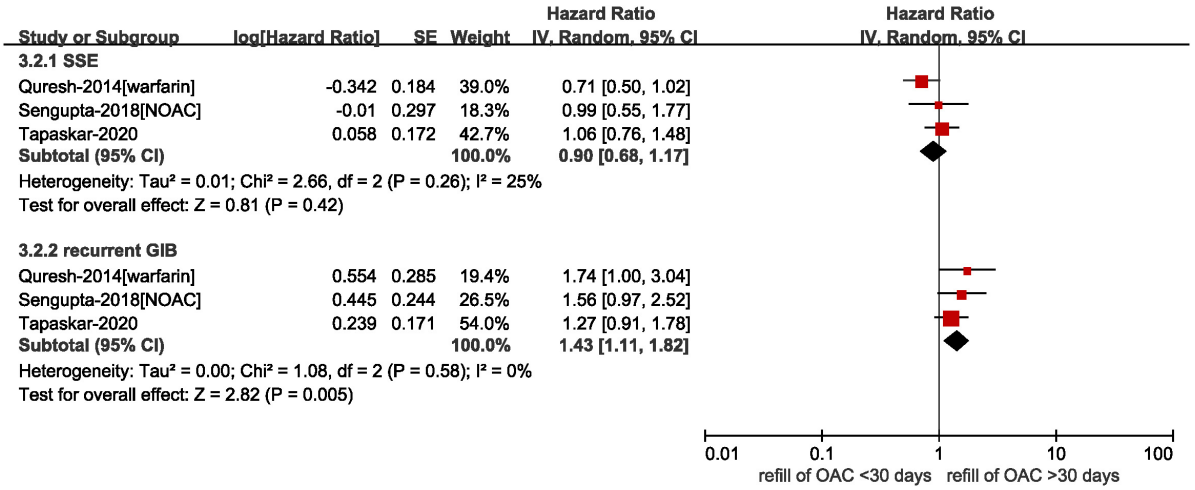

FIGURE 4
Comparing the effect of different time to resume anticoagulation in AF patients with prior GIB. AF, atrial fibrillation; GIB, gastrointestinal bleeding; OAC, oral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulants; CI, confidence interval; IV, inverse of the variance; SE, standard error; SSE, stroke and systemic embolism.

warfarin but not with NOACs. Our study drew the consistent conclusion that NOACs were associated with a reduced risk of major bleeding and recurrent GIB compared with VKAs. Moreover, for patients with AF, the administration of rivaroxaban was found to be associated with a higher incidence of overall GIB, compared with apixaban or dabigatran (27). Thus, head-to-head comparisons were required to explore whether a similar conclusion would be considered for AF patients with prior GIB.

Finally, we tried to analyze the optimal timing to resume anticoagulation. Due to the small number of relevant articles identified, our results were based on only three articles. In the study by Qureshi et al., compared with patients restarting warfarin after 30 days of interruption, patients who refilled prescriptions within the first week presented a significant higher risk of recurrent GIB (19). Sengupta et al. showed that the resumption of NOACs within 30 days after GIB was not associated with either 90-day or 6-month readmissions for thromboembolic events or recurrent GIB (22). Our results showed that the resumption of anticoagulation within 30 days was associated with an increased risk of recurrent GIB compared with prescription after 30 days. As critical as it is, more high-quality studies are desperately required for making the optimal decision to resume OAC.

Limitations

Our study still had several limitations. First, we pooled data from observational studies with limited sample size, decreasing our finding's reliability. Second, the studies did not account for medications, such as non-steroidal anti-inflammatory drugs and aspirin, which might increase the risk of GIB. Similarly, it has been demonstrated that the reduction in GIB associated with NOACs was only statistically significant in patients with no use of proton pump inhibitors and was not significant in those using proton pump inhibitors (27). Third, due to insufficient data, our analysis cannot either derive the specific optimal anticoagulant or elucidate the optimal timing of resumption of the anticoagulant. Fortunately, the "Non-warfarin Oral Anti-Coagulant Resumption After Gastrointestinal Bleeding in Atrial Fibrillation Patients (ClinicalTrials.gov NCT03785080)" is an ongoing RCT investigating how early an NOAC can be safely restarted after acute GIB, which will help provide robust evidence for this issue.

Conclusion

In AF patients with prior GIB, OAC therapy revealed superior effectiveness profiles compared with no anticoagulant therapy. In addition, NOACs exerted superior effectiveness profiles compared with VKAs.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

SL and QG contributed to conception and design of the study. JZ organized the database. XW performed the statistical analysis. JZ wrote the first draft of the manuscript. XW, SL, and QG wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.937320/full#supplementary-material

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EDITED BY
Jianyong Ma,
University of Cincinnati, United States

REVIEWED BY
Yidan Wang,
Capital Medical University, China
Ke Zhuang,
The First People's Hospital of Yunnan Province, China

*CORRESPONDENCE
Jiangui He
hejiangui@163.com
Zexuan Wu
wuzx27@mail.sysu.edu.cn

†These authors share first authorship

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Non-vitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with heart failure and preserved, mildly reduced, and reduced ejection fraction: A systemic review and meta-analysis

Kaisaier Wulamiding[1,2†], Zixuan Xu[3†], Yili Chen[1,2], Jiangui He[1,2*] and Zexuan Wu[1,2*]

[1]Department of Cardiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]NHC Key Laboratory of Assisted Circulation, Sun Yat-sen University, Guangzhou, China, [3]Department of Emergency, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Patient prevalence of atrial fibrillation (AF) and heart failure (HF) is increasing, and anticoagulation for patients from heterogeneous backgrounds with both conditions remains controversial. In this meta-analysis, we are aiming to compare the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in AF patients with HF and preserved (HFpEF), mildly reduced (HFmrEF), and reduced (HFrEF) ejection fraction.

Methods and results: We systematically searched the PubMed, Cochrane, and Embase databases until January 2022. The primary effectiveness and safety outcomes were stroke or systemic embolism (SSE) and major bleeding, respectively. We abstracted risk ratios (RR) and 95% confidence intervals (CIs) and compiled them using a random-effects model. We analyzed data of 266,291 patients from 10 studies. By comparing NOACs with warfarin, patients with AF and HF have reduced the risk of SSE (RR: 0.83, 95% CI 0.76–0.91), all-cause mortality (RR: 0.85, 95% CI 0.80–0.91), major bleeding (RR: 0.79, 95% CI 0.69–0.90), and intracranial hemorrhage (RR: 0.54, 95% CI 0.46–0.63). Further analyses based on the HF subtypes showed that NOACs reduced the chances of SSE (RR: 0.71, 95% CI 0.53–0.94) in the HFrEF group and major bleeding (RR: 0.74, 95% CI 0.57–0.95) in HFmrEF and HFpEF groups. There were no differences regarding SSE (RR: 0.91, 95% CI 0.76–1.09) in HFmrEF and HFpEF groups and major bleeding (RR: 0.99, 95% CI 0.79–1.23) in the HFrEF group.

Conclusion: For patients with AF and HF, NOACs have better or similar effectiveness and safety than warfarin, but the stroke prevention superiority of NOACs over warfarin varies in different HF subtypes.

KEYWORDS

atrial fibrillation, anticoagulants, heart failure, warfarin, meta

Introduction

As the most frequent sustained cardio rhythm disorder, atrial fibrillation (AF) frequently exists alongside heart failure (HF) and is linked to a higher risk of stroke and all-cause mortality (1). Anticoagulant therapy, an essential component of the integrated Atrial fibrillation Better Care (ABC) pathway in patients with AF, has been demonstrated to reduce the potential adverse outcomes (2). Current guidelines consistently recommend non-vitamin K antagonist oral anticoagulants (NOACs) as a priority of anticoagulants for patients with AF (3, 4). Traditionally, HF was divided into two phenotypes: HF with reduced (HFrEF) or preserved EF (HFpEF) ejection fraction (EF) (5). Recently, the European Society of Cardiology (ESC) recommends three HF subtypes: HF and preserved (HFpEF, EF $\geq$ 50%), mildly reduced (HFmrEF, EF 41–49%), and reduced (HFrEF, EF $\leq$ 40%) EF (6, 7). Although HFrEF and HFpEF share some similar clinical manifestations, they represent entirely different diseases in the HF spectrum, and they are studied and treated separately (8).

For patients in conjunction with AF and HF, some randomized controlled trial (RCT) *post hoc* analyses have shown that NOACs are non-inferior or even better than vitamin-K antagonists (VKAs) in terms of effectiveness and safety (9–12). An earlier meta-analysis by Chen et al. demonstrated that compared to warfarin, NOACs led to significantly fewer stroke or systemic embolism (SSE) and major bleeding risks in patients with concomitant AF and HF (13). The American Heart Association's scientific statement encouraged a decision-making process for AF and HFrEF including guideline-directed HF treatment therapy, lifestyle, risk factor adjustment, oral anticoagulation based on the CHAD2DS2-VASc score, pharmacological rate control, and cardioversion if necessary (including catheter ablation and antiarrhythmic treatment) (14). As for AF and HFpEF, there is still a lack of corresponding guidelines and clinical evidence. In addition, a comparison of NOACs and VKAs in AF patients with different HF subtypes (HFpEF, HFmrEF, and HFrEF) remain unknown. Therefore, our study evaluated the safety and effectiveness of NOACs against VKAs in patients with AF accompanied by HF, especially in different subtypes of HF.

Methods

We conducted the meta-analysis based on the Cochrane Systematic Review Handbook (15), and the writing followed the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16) (list of checkpoints displayed in **Supplementary Table 1**). The included studies were reviewed by the relevant ethics committee before publication, so we did not need ethical approval.

Criteria for study eligibility

For our analysis, the following criteria were used to select studies: (1) population: adult patients with non-valvular AF complicated with HFpEF, HFmrEF, or HFrEF; (2) outcome measures and intervention: studies assessing at least one effectiveness or safety outcome of NOACs (edoxaban, rivaroxaban, apixaban, or dabigatran) versus VKAs; and (3) study design: RCTs and observational (prospective or retrospective cohort) studies.

We excluded studies where cross-sections, reviews, reports on cases, editorials, letters, or meeting abstracts had insufficient data or study details. For studies that met our inclusion criteria but had overlapping populations, our priority was to study long-term follow-ups or large sample sizes.

Search strategy

We systematically searched all the studies published on electronic databases, such as Cochrane Library, Embase, and PubMed, without linguistic limits (up to January 2022). **Supplementary Table 2** presents a listing of the retrieval strategies used: (1) heart failure, AND (2) atrial fibrillation OR atrial flutter, AND (3) non-vitamin K antagonists OR direct oral anticoagulants OR novel oral anticoagulants OR new oral anticoagulants OR edoxaban OR apixaban OR rivaroxaban OR dabigatran, and (4) acenocoumarol OR warfarin OR coumadin OR phenprocoumon OR indandione OR vitamin-K antagonists OR phenindione OR anisindione.

Selection of studies and data extraction

A team of two reviewers reviewed all retrieved studies and abstracted relevant data independently. Based on the qualifications for inclusion, we reviewed the titles and abstracts of the studies and then read the full text in detail to determine the truly eligible studies. In the case of conflict between two reviewers, we reached a consensus by consulting with a third reviewer. We collected the following data from the studies we included: author, publication year, country of the population, data source, study duration, study design, demographics of patients, follow-up period, types of NOACs and dosages, and outcome data (size of sample, count of events in a group, and adjusted effect estimates).

Study outcomes

The effectiveness outcomes included SSE, all-cause death, and ischemic stroke, whereas major bleeding, gastrointestinal bleeding, and intracranial bleeding were the safety outcomes. SSE and major bleeding were the primary effectiveness and safety outcomes, whereas others were the secondary outcomes. All the outcomes included in this meta-analysis and definitions of the primary outcomes are shown in **Supplementary Table 3**.

Quality assessment

The Newcastle-Ottawa Scale (NOS) items were used to evaluate observational studies. The RCT *post hoc* analyses were used as an observational study for quality evaluation. A total of nine points were allocated to the NOS tool's three domains: cohort selection (0–4 points), cohort comparability (0–2 points), and outcome assessment (0–3 points). NOS scores of 6 or more points were considered medium to high quality, and a score below six points was regarded as low quality (17).

Statistical analysis

Cochrane Q test and I^2 values were used to determine heterogeneity between studies in statistical terms. A p-value of < 0.1 or I^2 value $> 50\%$ indicated significant heterogeneity across studies. The study effect was estimated with adjusted risk ratios (RRs) and 95% confidence intervals (CIs). The RR natural logarithm and its corresponding standard deviation ((Ln[upper CI]-Ln[lower CI])/3.92) were calculated. Because there were different types and doses of NOACs included in this study, the random-effects model was used in conjunction with the inverse variance method to pool the natural logarithms. Subgroups were performed based on taking 40 and 50% as the left ventricular ejection fraction (LVEF) boundary, study type, renal function, CHA2DS2-VASc score, types of NOACs, New York Heart Association (NYHA) class, and follow-up time. The bias of publication was examined by visually inspecting the funnel plots in which the logRRs were plotted against their standard errors. In addition, Egger's and Begg's tests for each outcome were applied to examine publication bias.

Review Manager version 5.4 (the Cochrane Collaboration 2014, Rigshospitalet, Nordic Cochrane Centre Copenhagen, Denmark) was used to perform all the statistical analyses. p-values of < 0.05 were considered statistically significant.

Results

Study identification and selection

The literature retrieval flowchart is presented in **Figure 1**. We identified 2,106 articles using the PubMed, Embase, and Cochrane Library databases through our search strategy. A total of 415 studies were duplicated, and 1,691 articles were excluded after screening the title and abstract. The remaining 18 studies were assessed by reading the full text and eight articles were removed for eligibility. Finally, our meta-analysis included 10 studies (4 RCT *post hoc* analyses and six observational studies) comprising 266,291 patients (9–12, 18–23).

Study characteristics

A summary of study characteristics at baseline is shown in **Table 1**. Among them, four studies were *post hoc* analyses of RCTs, including RE-LY (dabigatran), ROCKET AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF-TIMI 48 (edoxaban) trials (9–12). The other 6 studies were observational studies from the United States ($n = 4$) (18, 19, 21, 22), Japan ($n = 1$) (23), and Sweden ($n = 1$) (20), respectively. Sample sizes ranged from 4,904 to 49,448 patients, and the duration of median follow-up time was 0.4–2.8 years. The definition of HF was extracted from the originally included studies and shown in **Supplementary Table 3**. As a measure of quality, the NOS tool was used to assess the included studies, all of which were judged to be medium-to-high and deemed qualified (**Supplementary Table 4**).

Effectiveness and safety outcomes in atrial fibrillation with and without heart failure population

Among AF with HF patients, in comparison with warfarin (**Supplementary Figure 1**), the use of NOACs was linked to lower risks of SSE (RR: 0.83, 95% CI 0.76–0.91) and all-cause death (RR: 0.85, 95% CI 0.80–0.91), while a significant

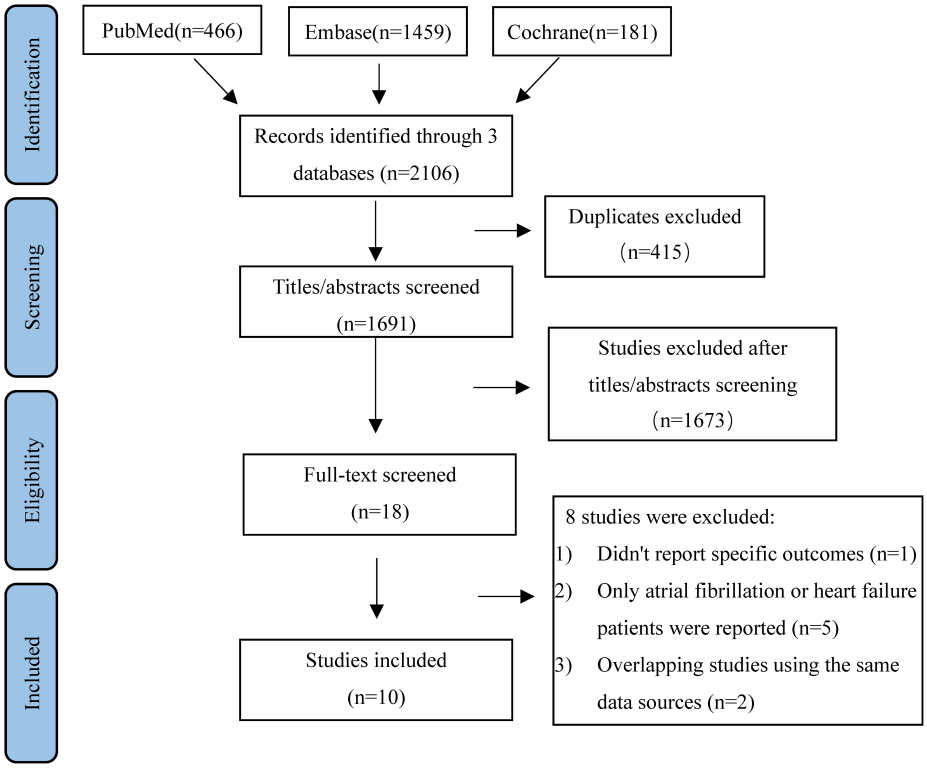

FIGURE 1
Flowchart of studies identified, screened, excluded, and included in the meta-analysis.

difference was not observed in ischemic stroke (RR: 0.88, 95% CI 0.74–1.04). As for the safety outcomes compared to warfarin (**Supplementary Figure 2**), NOACs in patients with AF and HF were found to reduce major bleeding (RR: 0.79, 95% CI 0.60–0.90) and intracranial bleeding (RR: 0.54, 95% CI 0.46–0.63) risks significantly, but the risk of gastrointestinal bleeding (RR: 1.00, 95% CI 0.76–1.31) was not different between the two groups.

The effectiveness and safety of NOACs and warfarin in AF patients without HF were consistent with those in patients with AF and HF. In AF patients without HF (**Supplementary Figure 3**), NOACs reduced the risk of SSE (RR: 0.83, 95% CI 0.71–0.97), all-cause mortality (RR: 0.85, 95% CI 0.78–0.92), major bleeding (RR: 0.77, 95% CI 0.68–0.89) and intracranial hemorrhage (RR: 0.46, 95% CI 0.35–0.61) than warfarin, but there was no significant difference in the risks of ischemic stroke (RR: 0.91, 95% CI 0.74–1.12) and gastrointestinal bleeding (RR: 1.08, 95% CI 0.72–1.64).

Effectiveness and safety outcomes in different heart failure subtypes

Effects of NOACs on primary effectiveness and safety outcomes in HFrEF and HFpEF subgroups were analyzed taking 40 and 50% as the LVEF boundary, respectively (**Figure 2**). Compared with warfarin, the use of NOACs was related to lower SSE risks in patients with HFrEF independent of the LVEF boundary of 40 or 50%.

When categorizing HF into different types of HFpEF, HFmrEF, and HFrEF, NOACs against warfarin significantly decreased SSE (RR: 0.71, 95% CI 0.53–0.94) risks in patients with AF and HFrEF (**Figure 3A**). However, no significant statistical difference in the risks of SSE (RR: 0.91, 95% CI 0.76–1.09) was indicated in AF patients with HFmrEF or HFpEF. As presented in **Figure 3B**, in AF patients with concomitant HFmrEF or HFpEF, as compared to warfarin, NOACs reduced the risk of major bleeding (RR: 0.68, 95% CI 0.57–0.82), whereas major bleeding (RR: 0.86, 95% CI 0.66–1.10) risks did not differ in patients with AF and HFrEF.

Subgroup analyses

Subgroup analyses were performed based on study type (RCT *post hoc* analysis and observational study), class of NYHA (NYHA I-II and NYHA III-IV), renal function (creatinine clearance was 50 ml/min as the boundary), CHA2DS2-VASc score (≤3, 4–9), types of NOACs (factor Xa inhibitors,

TABLE 1 Patients' characteristics of the selected studies for this meta-analysis.

References	Location	Database source	Age (years)	CHA2DS2-VASc score	HAS-BLED score	OAC	Antiplatelet agents, n (%)	NYHA class III or IV, n (%)	Follow-up Period (y)	LVEF subgroup boundary	Outcomes used in this meta-analysis
(12)	Multinational	ENGAGE AF-TIMI 48 trial, 11/2008–11/2010; *post hoc* analysis of RCT	75	4.5	2.4	EDO warfarin	2,437 (29.9) NA	1,801 (13)	2.8	<50% (n = 3,103) ≥50% (n = 3,236)	SSE, MB
(11)	Multinational	ARISTOTLE trial, 12/2006–04/2010; *post hoc* analysis of RCT	71	NA	NA	API warfarin	2,089 (35.2) NA	1,335 (22.5)	1.5	≤40% (n = 3,207) >40% (n = 2,736)	SSE, IS, All-cause death, MB, HS, GIB
(10)	Multinational	ROCKET AF trial, 12/2006–06/2009; *post hoc* analysis of RCT	74	5.1	NA	RIV warfarin	1,373 (30.3) 1,428 (31.7)	1,329 (30.0) 1,316 (29.9)	1.9	<40% (n = 2,145) ≥40% (n = 6,888)	SSE, MB
(9)	Multinational	RE-LY trial, 12/2005–12/2007; *post hoc* analysis of RCT	73	NA	NA	DA warfarin	NA NA	NA	2.0	≤40% (n = 1,258) >40% (n = 1,631)	SSE, MB
(18)	United States	HealthCore Integrated Research Environment, 11/2009–01/2016; retrospective cohort	70	3.3	2.1	DA RIV API warfarin	1,699 (19.9) 745 (20.2) 1,722 (20.5) 4,733 (20.2)	NA	0.4*/0.5	NA	MB
(20)	Sweden	Cross-linked national registers, 12/2011–12/2014; retrospective cohort	74	3.3	NA	NOACs warfarin	2,367 (12.7) 7,215 (14.6)	NA	0.7/1.7*	NA	SSE, All-cause death, MB
(22)	United States	Truven MarketScan Commercial and Medicare supplemental database, 11/2011–12/2016; retrospective cohort	74	4.0	2.0	RIV warfarin	578 (16.9) 612 (17.9)	NA	1.4	NA	SSE, IS, MB, ICH
(23)	Japan	Fukushima Medical University Hospital, 2011-015; retrospective cohort	70	4.3–4.4	2.7–2.8	NOACs warfarin	108 (42.0) 62 (41.3)	8 (3.1) 4 (2.7)	3.0	<50% (n = 127) ≥50% (n = 101)	All-cause death
(19)	United States	The Center for Medicare and Medicaid Services, 01/2012–09/2016; retrospective cohort	79–80	5.2–5.4	3.5–3.7	DA RIV API warfarin	887 (20.64) 3,788 (24.11) 2,786 (26.36) NA	NA	0.6	NA	SSE, IS, All-cause death, MB, ICH, GIB
(21)	United States	Veterans Administration databases, 10/2010–08/2017; retrospective cohort	72	4.1	3.37–3.57	NOACs warfarin	10,561 (40.9) 9,548 (40.4)	NA	1.4*/1.5	<40% ≥40%	All-cause death, MB, GIB

Data were presented as mean for age, CHA2DS2-VASc score, HAS-BLED score and follow-up period; *: represents the median follow-up time of warfarin group, when there are two follow-up times. CHA2DS2-VASc, Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, age 75 years of age and older, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65–74 years, Sex (female); HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; OAC, oral anticoagulants; LVEF, left ventricular ejection fraction; NOACs, non-vitamin K antagonist oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; SSE, stroke or systemic embolism; MB, major bleeding; IS, ischemic stroke; ICH, intracranial hemorrhage; GIB, gastrointestinal bleeding; NOS, Newcastle-Ottawa Scale; NA, not available.

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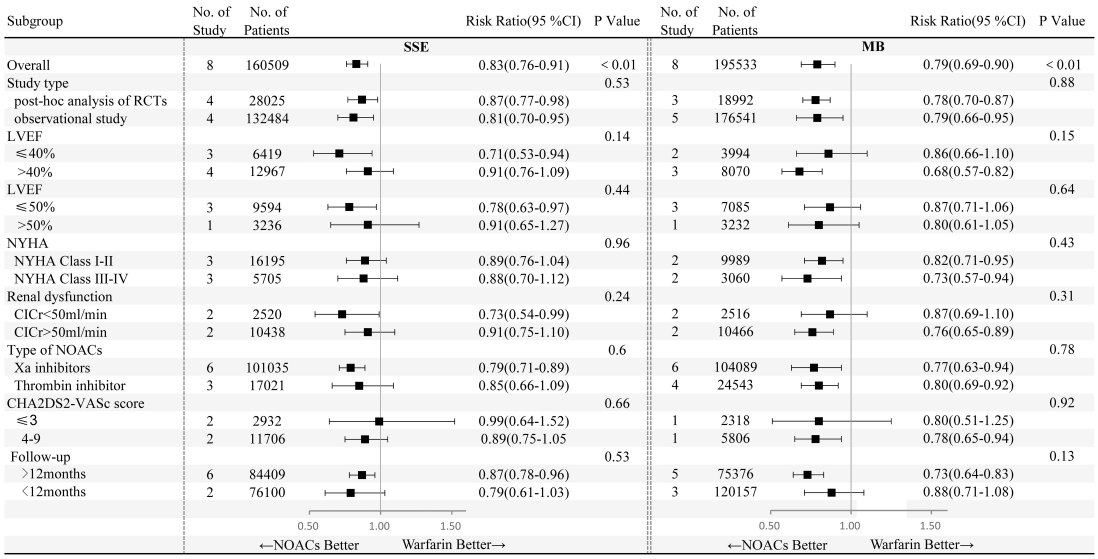

FIGURE 2
Primary effectiveness and safety outcomes of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin according to different subgroups. NYHA, New York Heart Association; ClCr, creatinine clearance; CI, confidence interval.

thrombin inhibitor), and follow-up time (12 months as the boundary) (**Figure 2**).

In comparison with warfarin users, lower SSE and major bleeding risks were associated with factor Xa inhibitor, whereas thrombin inhibitor users had smaller major bleeding risks and similar SSE risks. In addition, during long-term follow-up (>12 months), NOACs versus warfarin significantly decreased the risks of SSE and major bleeding. In other subgroup analyses based on NYHA class, renal dysfunction, study type, LVEF with 50% as the boundary, and the CHA2DS2-VASc score, NOACs and warfarin were at least as safe and effective as each other for the prevention of strokes.

Bias in publication

Publication bias was evaluated through a visual check of the asymmetry of the funnel plots (**Supplementary Figures 4**, **5**). No obvious publication biases were found for SSE, ischemic stroke, all-cause mortality, and major bleeding. Egger's and Begg's tests did not indicate publication biases for the primary outcomes. However, the funnel plot for intracranial hemorrhage or gastrointestinal bleeding was asymmetrical possibly because only a few studies were included in terms of these outcomes. Therefore, the pooled data should be interpreted cautiously.

Discussion

We evaluated the adverse outcomes of NOACs across different HF subtypes by performing a meta-analysis in this study. We found that in comparison with warfarin, NOACs use was significantly linked to reduced risks of SSE, all-cause mortality, intracranial bleeding, and major bleeding, whereas risks of ischemic stroke and gastrointestinal bleeding did not differ significantly between the treatment groups. In addition, NOACs outweighed warfarin in decreasing the risks of SSE in the HFrEF group and major bleeding in HFmrEF or HFpEF groups.

The coexistence of AF and HF was common with a patient prevalence of AF in HF exceeding 20% (24). It has been reported that SSE and all-cause mortality risks were increased when both conditions were present (11). As recommended by the current guidelines, NOACs are more effective and safer than warfarin in stroke prevention for AF patients (25). In this meta-analysis, we found that for patients with AF and HF, NOACs were also superior to warfarin in the reduction of SSE, all-cause mortality, intracranial bleeding, and major bleeding. This was consistent with prior meta-analyses which demonstrated that despite the increasing death rate among patients with HF and AF, SSE, major, and intracranial bleeding in AF patients with concomitant HF were significantly reduced by NOACs compared with warfarin (13, 26).

The prevalence of AF and prognosis vary across different HF subtypes. According to the ESC heart failure long-term registry, the prevalence of AF increases with the increase of LVEF (HFrEF: 27%, HFmrEF: 29%, and HFpEF: 39%) (27). Patients with HFpEF are usually older, more likely to be women, and usually have multiple comorbidities, including hypertension, obesity, and diabetes, making the CHA2DS2-VASc score much higher than those with HFrEF (28). However,

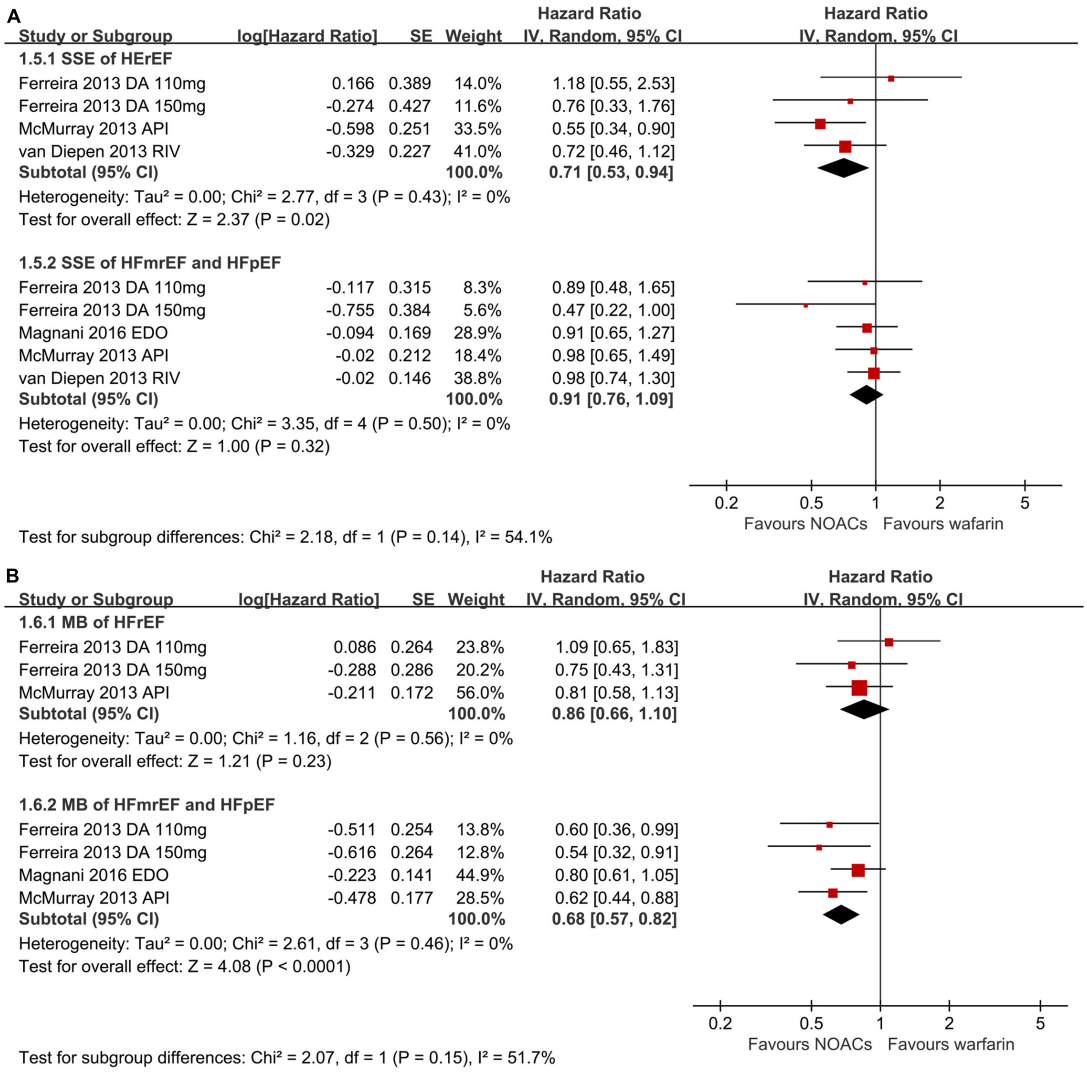

FIGURE 3
Forest plot for primary effectiveness **(A)** and safety **(B)** outcomes in HFrEF, HFmrEF, and HFpEF. HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CI, confidence interval.

the annual incidence of stroke was linearly increasing by 0.054% per each 1% of LVEF decrease (29). Indeed, patients with HFrEF had the highest risks of stroke and mortality despite a relatively lower CHA2DS2-VASc score compared with HFpEF (29). In our meta-analysis, NOACs were linked to reduced SSE (RR: 0.71, 95% CI 0.53–0.94) risks significantly in AF patients with HFrEF but not those with HFmrEF or HFpEF. However, limited evidence was available in terms of the superiority of NOACs over warfarin in patients with AF and different phenotypes of HF. Further robust clinical trials were warranted to investigate the safety and efficacy of NOACs in patients with AF among different phenotypes (11, 12).

In addition, the definition of HF and the cut-off value of HFpEF, HFmrEF, and HFrEF were also heterogeneous. Therefore, the results derived from the included studies may not reflect the real therapeutic effects of NOACs and should be interpreted cautiously.

Limitations

Our meta-analysis had several limitations that should be further addressed. First, the choice of drugs for these patients depends on many factors, and it is difficult to directly compare NOACs with each other given the differences in trial design and study population among the four *post hoc* analyses of RCTs. Second, the definition of HF and the cut-off valve of HFpEF, HFmrEF, and HFrEF differ in the included studies in this meta-analysis, hence the results should be interpreted cautiously.

Further robust clinical trials with consistent definitions and categories of HF are warranted.

Conclusion

Our current evidence of this meta-analysis suggested that in patients with AF and HF, NOACs have better or similar effectiveness and safety than warfarin, but the stroke prevention superiority of NOACs over warfarin varies in different HF subtypes.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

JH and ZW designed the study and revised the manuscript. KW and ZX carried out the literature search, article screen, assessing quality, and statistics. KW wrote the manuscript. ZW and YC reformulated the manuscript and revised the English grammar. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.949726/full#supplementary-material

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EDITED BY
Jianyong Ma,
University of Cincinnati, United States

REVIEWED BY
Yalin Cao,
Guizhou Provincial People's Hospital, China
Junyi Sun,
The First Affiliated Hospital of Sun Yat-sen University, China

*CORRESPONDENCE
Xin Liu
17041037@qq.com
Shuo Xu
396116462@qq.com

†These authors have contributed equally to this work

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Effects of oral anticoagulant therapy in patients with pulmonary diseases

Jiying Lai[1†], Shenghui Feng[2†], Shuo Xu[3*] and Xin Liu[1*]

[1]Department of Critical Care Medicine, The First Affiliated Hospital of Gannan Medical University, Ganzhou, China, [2]Queen Mary School, Medical Department, Nanchang University, Nanchang, China, [3]Department of Respiratory and Critical Care Medicine, The Ganzhou People's Hospital, The Affiliated Ganzhou Hospital of Nanchang University, Ganzhou, China

Background: To evaluate the effect of oral anticoagulants (OACs) therapy, including vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC) in patients with pulmonary diseases.

Methods: Literature from PubMed, MEDLINE, and Cochrane Library were screened until June 2022. Studies assessing OACs for pulmonary hypertension (PH), pulmonary embolism (PE), pulmonary fibrosis (PF), or chronic obstructive pulmonary disease (COPD) were evaluated for inclusion.

Results: Our study indicated that in patients with PH, PE, and COPD, OACs could significantly reduce the mortality risk, and the effects of VKA and DOACs without statistical difference in reducing the risk of recurrent embolism events. In patients with sclerosis-associated pulmonary arterial hypertension (SSc-PAH) or idiopathic pulmonary fibrosis (IPF), vitamin K antagonist (warfarin) significantly increased the mortality risk, while DOACs were not. As for the safety outcome of OACs, existing studies indicate that compared with patients treated with warfarin, the users of DOAC have a lower risk of major bleeding, while there is no statistical significance between them in non-major bleeding events. In current guidelines, the anticoagulation regimen for patients with pulmonary disease has not been defined. The results of our study confirm that DOACs (apixaban, rivaroxaban, dabigatran, and edoxaban) are superior to VKAs in the efficacy and safety outcomes of patients with pulmonary disease.

Conclusions: Oral anticoagulant therapy brings benefits to patients with PH, PE, or COPD, while the anticoagulation regimen for patients with SSc-PAH or IPF requires serious consideration. Compared with VKA, DOAC is a non-inferior option for anticoagulation in pulmonary disease treatment. Further studies are still needed to provide more reliable evidence about the safety outcome of pulmonary disease anticoagulation.

KEYWORDS

direct oral anticoagulants, pulmonary hypertension, pulmonary embolism, pulmonary fibrosis, chronic obstructive pulmonary disease

Introduction

Oral anticoagulants (OACs) bring benefits to patients with a history of atrial fibrillation or flutter, recent major surgery, heart valve replacement, ischemic stroke, and other thrombotic event (1, 2). Common OACs include vitamin K antagonists (VKA, i.e., warfarin) and direct oral anticoagulants (DOACs). The major mechanism of VKA is antagonizing vitamin K, which can inhibit the production of vitamin K involved coagulation factors II, VII, IX and X in the liver. Warfarin has been applied in clinical use for several decades, its indications include the prevention of cardioembolic ischemic stroke, deep venous thrombosis, and pulmonary embolism. However, with a slow onset of action and a narrow therapeutic window, warfarin is closely associated with multiple drug-related life-threatening events. Its anticoagulation effect could be influenced by multiple food and drug interactions: the simultaneous use of warfarin and aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), or clopidogrel will significantly increase the risk of bleeding (3, 4). DOACs directly inhibit coagulation factors Xa and IIa, which do not influence the function of vitamin K. In recent years, DOACs have been confirmed with the function of reducing the risk of stroke and systemic embolism in patients with atrial fibrillation and other artery diseases (5, 6), and they have been approved for the prevention and treatment of venous thromboembolism and systemic and cerebral embolism in patients with atrial fibrillation. Since their anticoagulant effects are more predictable and stable (i.e., less affected by food and drug interactions), the clinical application of DOAC was considered safer than VKA (1).

Pulmonary disease is one of the major threats to human health, which includes pulmonary hypertension (PH), pulmonary embolism (PE), pulmonary fibrosis (PF), and chronic obstructive pulmonary disease (COPD). Pulmonary hypertension is a chronic and progressive disease associated with several cardiovascular conditions, including atrial fibrillation and heart failure. According to distinct mechanisms, PH was divided into five subgroups with similar pathological manifestations and clinical features (7, 8). Lifelong anticoagulation therapy is recommended for patients with pulmonary atrial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), since abnormally high shear stress was identified secondary to excessive vasoconstriction in patients with PAH (9), which could induce vascular remodeling, coagulation cascade derangement, and aberrant platelet function (9). In addition, the decreased fibrinolysis, increased clot formation, endothelium dysfunction, and procoagulant mediators released by platelets could also be detected (9), which significantly increase the risk of thrombosis. CTEPH is characterized by incomplete or abnormal resolution of acute pulmonary embolism, which induces residual emboli to become organized and fibrotic (10). Therefore, it is necessary to use OAC to inhibit thrombosis in patients with PH. As for pulmonary embolism, anticoagulation could reduce mortality by preventing the extension of thrombosis, embolization, and/or formation of new thrombi (11). Associations between idiopathic pulmonary fibrosis (IPF) and many thrombotic vascular diseases, including deep vein thrombosis (DVT), PE, and acute coronary syndromes (ACS) have also been reported by previous studies (12–14). The understanding of IPF etiology remains incomplete, the imbalance between thrombosis and fibrinolysis has been detected in the alveolar compartment in IPF patients, and the systemic pro-thrombotic state might also appear (15). In addition, COPD as one of the most challenging chronic diseases, is closely related to inflammation. Venous thromboembolism (VTE) is a common and potentially fatal complication of COPD, whose morbidity could be significantly increased by COPD (odds ratio between 2 and 9) (16, 17). Moreover, PE is also common comorbidity of COPD (18–20), which might induce disease deterioration. Since all of those pulmonary diseases are associated with vasoconstriction, thrombosis, embolism, or the dysregulation of coagulation (21, 22), OACs have been used for pulmonary disease treatment.

The purpose of this systemic review is to evaluate the existing literature and help clinicians select the appropriate oral anticoagulant regimen for patients with pulmonary diseases.

Methods

Two investigators searched electronic databases independently. Relevant articles were screened from PubMed, Embase, and Cochrane Library by using the following keywords: (pulmonary disease OR pulmonary hypertension OR pulmonary fibrosis OR Chronic obstructive pulmonary disease OR pulmonary embolism) AND (oral anticoagulant OR OAC OR vitamin-K antagonist OR VKA OR warfarin OR non-vitamin K oral antagonist OR NOAC OR direct oral antagonist OR DOAC OR apixaban OR rivaroxaban OR edoxaban OR dabigatran OR betrixaban OR novel oral anticoagulant). The last retrieval date was 16th June 2022, and the retrieval process is exhibited in Figure 1.

Eligibility criteria

Studies were included if they met the following criteria: (1) patients in the study were receiving oral anticoagulants, including vitamin K antagonist warfarin, and non-vitamin K oral anticoagulants such as dabigatran, edoxaban, rivaroxaban, apixaban, or betrixaban; (2) patients with pulmonary disease, including pulmonary hypertension, pulmonary embolism, pulmonary fibrosis, and COPD; (3) case series, case-control studies, cohort studies, or randomized clinical trials were considered to be included in this study; (4) only studies written by English were included in this study; (5) the results were

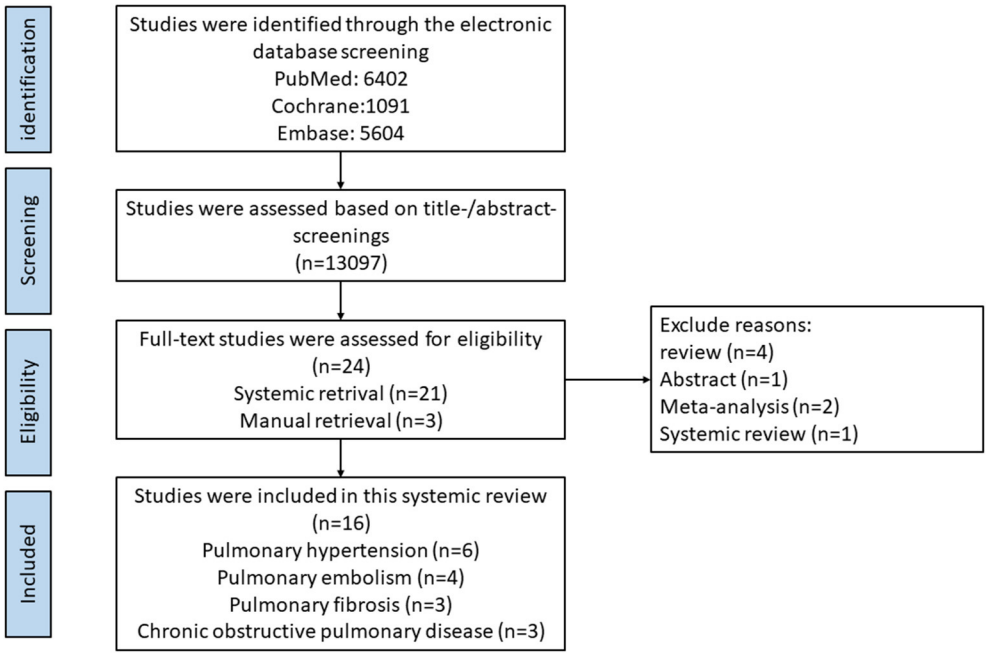

FIGURE 1
Flow diagram of literature retrieval process of our systemic review.

reported as OR, RR or HR value with 95%CI. Specific literature forms including letters, meta-analyses, systemic reviews, cross-sectional studies, reviews, case reports, case series, editorials, and meeting abstracts were excluded in this study. In the pulmonary embolism part, studies investigating venous thromboembolism rather than specific for pulmonary embolism were also considered for exclusion.

Study selection and data extraction

After screening the titles and abstracts of publications, two authors extracted data independently. Then the full-text screening was conducted to determine whether the literature met the inclusion criteria. Disagreements were resolved by discussing with the third researcher. The baseline information of each study was recorded, including the name of the first author, publication year, the types of anticoagulants, study design, baseline characteristics of the investigated population, and the study outcome.

Study quality assessment

The quality of eligible cohort studies was assessed by the Newcastle-Ottawa Scale tool, which assesses three aspects of the included studies. The results were marked from 0 to 9 stars, including the cohort selection (0–4 stars), cohort comparability (0–2 stars), and the study outcomes (0–3 stars). Studies with assessment results of <6 stars were considered as low quality. The quality of included randomized controlled trials was evaluated by the Cochrane risk-of-bias tool version 2 for randomized controlled trials. The corresponding results were recorded in Supplementary Tables 1, 2.

Results

Pulmonary hypertension

According to ACC/AHA/American College of Chest Physicians guidelines, VKA with the therapeutic INR 1.5–2.5 is suitable for patients with idiopathic PAH (IPAH), and the European Society of Cardiology PH guideline suggests that either VKAs or DOACs could be used as the anticoagulation regimen for CTEPH treatment (23, 24). Totally six investigations evaluated the therapeutic effect of oral anticoagulants in patients with PH were included in our study (Table 1). Only one retrospective cohort study from Sena et al. compared the effect and safety outcomes of warfarin with three different DOACs in patients with CTEPH (25). The rest included studies assessed the therapeutic effect between anticoagulation and non-anticoagulation treatment (26–30), however, whether OAC treatment could increase the risk of bleeding events was not reported in these studies. In most eligible studies comparing

TABLE 1 Summary of included studies of OACs in patients with pulmonary hypertension.

Author (year)	Pulmonary disease	Oral anticoagulants	Study design	Baseline characteristics of investigated population	Efficacy outcome	Safety outcome
Sena et al. (2020) (25)	Pulmonary hypertension (CTEPH)	Warfarin, rivaroxaban, dabigatran, apixaba	An observational retrospective study	Chronic thromboembolic pulmonary hypertension Age (mean): 53.54 Female: 50.7% BMI (mean): 28.15	Venous thromboembolism recurrence: warfarin vs. rivaroxaban: 10.1% vs. 8.9% (HR: 1.21, 95% CI, 0.64–2.23; $P = 0.55$). Mortality rates: warfarin vs. rivaroxaban 13.8% vs. 9.7% (HR: 1.61, 95% CI, 0.89–2.99; $P = 0.11$)	Bleeding: warfarin vs. rivaroxaban 27.1% vs. 24.6% (HR: 1.28, 95% CI, 0.86–1.88; $P = 0.22$) Major bleeding: warfarin vs. DOAC (8.9% vs. 14.8%; HR = 1.94, 95% CI = 1.05–3.62, $P = 0.03$) Death according to bleeding events: warfarin vs. rivaroxaban 4.85% vs. 2.2% (HR: 4.75, 95% CI: 1.12–20.16; $P = 0.03$)
Ngian et al. (2012) (26)	Pulmonary hypertension (CTD-PAH)	Warfarin	A cohort study	Patients with right heart catheter proven CTD-PAH	Warfarin therapy: mortality HR = 0.20 (0.05–0.78) $P = 0.02$, 95% CI	NR
Olsson et al. (2014) (27)	Pulmonary hypertension (IPAH, SSc-PAH)	(93%) vitamin K antagonists, heparins (6%) and novel oral anticoagulants (1%).	An observational study	Anticoagulants vs. non-anticoagulants: age: 70 (58–76) vs. 66 (52–75); $P = 0.001$ Female: 64% vs. 63%, $P = 0.77$	Death: IPAH: anticoagulation treatment: HR = 0.79 (0.66–0.94) $P = 0.007$ SSc-PAH: HR = 1.82; 95% CI, 0.94–3.54; $P = 0.08$)	NR
Jonson et al. (2012) (29)	Pulmonary hypertension (SSc-PAH and IPAH)	Warfarin	A cohort study	No warfarin vs. warfarin: SSc-PAH: female: 45 vs. 44%; mean pulmonary artery pressure (mmHg): 38.8 vs. 42.5 IPAH: female: 22% vs. 21%; mean pulmonary artery pressure (mmHg): 51.6 vs. 47.5	Mortality: warfarin vs. no warfarin: SSc-PAH: HR = 1.06 (0.70, 1.63); IPAH: HR = 1.07 (0.57, 1.98)	NR
Preston et al. (2015) (28)	Pulmonary hypertension (SSc-PAH and IPAH)	Warfarin	A cohort study	Warfarin vs. no warfarin: IPAH: age: 50.7 vs. 52.1; female: 80.6% vs. 79.2%; 6MWD: 345.9 vs. 375.1 SSc-PAH: age: 62.8 vs. 64.1; female: 79.1% vs. 90.7%; 6MWD: 290.9 vs. 338.4	Survival: warfarin vs. no warfarin: (adjusted HR) SSc-PAH: HR = 1.60 (0.84–3.06, 95%CI, $P = 0.15$); IPAH: HR = 1.37 (0.84–2.25, 95%CI, $P = 0.21$) SSc-PAH patients receiving warfarin vs. no warfarin in previous 1 year: HR = 1.57; 95% CI, 1.04–2.36; $P = 0.031$) or any time post-baseline HR = 1.49; 95% CI, 1.01–2.20, $P = 0.046$	NR
Kang et al. (2015) (30)	Pulmonary hypertension (IPAH)	Warfarin	A cohort study	Warfarin vs. no warfarin: female: 80% vs. 71.4%; age 32.5 vs. 34.0; 6-MWD (m): 409.0 vs. 451.5	Survival: no warfarin vs. warfarin: OR = 0.210 (0.045–0.976, 95% CI, $P = 0.047$)	NR

CTD-PAH, connective tissue disease associated pulmonary arterial hypertension; SSc-PAH, sclerosis-associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; 6-MWD, 6-min walk distance.

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warfarin with non-anticoagulation therapy, the administration of warfarin shows non-inferiority. This is consistent with the results of a previous meta-analysis (31). As for the subgroup analysis, four studies reported the efficacy outcome of warfarin in patients with IPAH: two of them indicated that warfarin is not associated with the increased survival (28, 29), while the results of another two studies confirmed the benefits of warfarin treatment (27, 30). Four studies specific for patients with connective tissue disease-associated PAH (CTD-PAH) showed inconsistent results: Ngian et al. (26) reports the benefits of warfarin use in reducing the risk of death, while Olsson et al. and Johnson et al. (29) indicated that there was no statistical difference in terms of survival between warfarin and non-warfarin group in patients with sclerosis-associated pulmonary arterial hypertension (SSc-PAH). In contrast with previous studies, Preston et al. (28) revealed that compared with the non-anticoagulation group, warfarin is associated with poorer survival. A corresponding meta-analysis reported that anticoagulation could significantly reduce the risk of mortality in the overall PAH cohort, the administration of OAC will not increase the mortality risk of CTD-PAH, while it could increase the risk of death in SSc-PAH patients (31). As for the options of OAC, Sena et al. indicated that DOAC shows no inferiority in terms of venous thromboembolism recurrence and mortality. In addition, DOAC and VKA did not exhibit a statistical difference in bleeding events, while DOAC could significantly reduce the risk of major bleeding and the mortality risk according to bleeding events. Collectively, except for SSc-PAH treatment, existing studies tend to indicate that OACs show non-inferiority in reducing mortality risk in patients with PH. Compared with VKA, DOAC is associated with decreased risk of major bleeding, which could be considered as the preference for OAC treatment.

Sclerosis-associated pulmonary arterial hypertension is the consequence of progressive remodeling of pulmonary vasculature, which is a type of CTD-PAH. It is believed that inflammation and endothelial injury are closely related to SSc-PAH (32). Inflammation is capable of inducing the disequilibrium between vasoactive, proliferative mediators and antiproliferative vasodilators within the endothelium. Under these conditions, pulmonary artery vasoconstriction and cellular proliferation might occur and be exacerbated by platelets releasing serotonin (33). Simultaneously, increased sympathetic excitability, hypoxemia, and ischemia-reperfusion injury of pulmonary vessels promote more cytokine release, which further promote vascular remodeling, fibrosis, and intraluminal microthrombosis (34). Therefore, theoretically, anticoagulation could bring benefits to SSc-PAH patients. However, the outcomes of existing studies are contrary to the theoretical expectations, and the specific reasons are still unclear. Although previous investigations indicated that gastrointestinal vascular lesions seem more commonly in patients with SSc-PAH than IPAH, the increased occurrence of major gastrointestinal bleeding events was not reported in SSc-PAH patients receiving anticoagulants (31). Therefore, the specific reasons for OAC increase the risk of death in patients with SSc-PAH deserves further study, and it is necessary to include more clinical data to further verify the existing research results. In addition, the number of investigations about the safety effects of OAC in PH treatment is still deficient, it is necessary to conduct more relevant experiments to provide reasonable evidence for the choice of anticoagulation regimen in patients with PH.

Pulmonary embolism

Anticoagulation is also a crucial step for PE treatment. Previous research has indicated that the mortality rate of untreated acute PE has reached 25% (35). The use of anticoagulants is capable of reducing pulmonary embolism-induced mortality rate by preventing the extension of thrombosis, embolization, and/or formation of new thrombi (11). In the past few decades, unfractionated heparin (UFH) and VKAs have been applied to clinics as anticoagulants for PE treatment. After that, since the pharmacodynamic and biological limitations of UFH remain to exist, low-molecular-weight heparins (LMWHs) and the indirect factor Xa (FXa) inhibitor fondaparinux were developed to simplify the management of PE (36). However, the limitations of fondaparinux and VKAs still cannot be eradicated. At present, DOAC is being used in clinics to improve the anticoagulation effect of PE. There are four existing studies reporting the corresponding results, including three randomized trials and one pooled-analysis which pooled the pulmonary embolism-related data from two randomized trials (37–40) (Table 2). Among them, most DOACs have been investigated, including apixaban, edoxaban, rivaroxaban, and dabigatran. The results of existing studies indicate that with the respect to preventing recurrent VTE or VTE-related death, there is no statistical difference between DOACs (including dabigatran, edoxaban, apixaban) and warfarin. As for the safety outcome, two of the included studies reported bleeding events in patients with PE (37, 39). Rivaroxaban and dabigatran could significantly reduce the risk of major bleeding. The risk of first major bleeding or clinically relevant non-major bleeding was only reported in a study focusing on rivaroxaban and warfarin, and the results did not show a statistical difference between them (37). The safety outcome of other DOAC in the PE cohort was not specifically investigated, which deserves further study in the future. In general, current studies support that compared with warfarin, the efficacy of most DOACs shows non-inferiority. In terms of safety outcomes, DOACs significantly reduce the risk of major bleeding. Therefore, they can be used as alternatives to vitamin K antagonists.

TABLE 2 Summary of included studies of OACs in patients with pulmonary embolism.

Author (year)	Pulmonary disease	Oral anticoagulants	Study design	Baseline characteristics of investigated population	Efficacy outcome	Safety outcome
The EINSTEIN–PE Investigators	Pulmonary embolism	Rivaroxaban: 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily Edoxaban, warfarin, acenocoumarol: 1.0 mg/kg of body weight twice daily	A randomized, open-label, event-driven, non-inferiority trial	Patients with acute, symptomatic pulmonary embolism with objective confirmation, with or without symptomatic deep-vein thrombosis	Symptomatic recurrent venous thromboembolism: Rivaroxaban vs. standard therapy*: 2.1% vs. 1.8% (HR = 1.12, 95% CI, 0.75–1.68, $P = 0.003$)	First major or clinically relevant non-major bleeding: Rivaroxaban vs. standard therapy: 10.3% vs. 11.4% (HR = 0.90; 95% CI, 0.76–1.07; $P = 0.23$) Major bleeding: Rivaroxaban vs. standard therapy: 1.1% vs. 2.2%, (HR = 0.49; 95% CI, 0.31–0.79; $P = 0.003$)
Goldhaber et al. (2016) (39)	Pulmonary embolism	Warfarin (therapeutic INR range, 2.0–3.0), dabigatran 150 mg twice daily for 6 months (double-dummy, 'oral-only' treatment period).	A pooled analysis	Dabigatran vs. warfarin: age: 55.6 vs. 55.6; male: 52.8% vs. 53.4%	In patients with PE, recurrent VTE/VTE-related death: dabigatran vs. warfarin: 2.9 % vs. 3.1 % (HR = 0.93, 0.53–1.64, $P = 0.4848$)	Major bleeding: dabigatran vs. warfarin HR= 0.60, 0.36–0.99
The Hokusai-VTE Investigators	Pulmonary embolism	Edoxaban: 60 mg once daily, or 30 mg once daily; warfarin	A randomized, double-blind, non-inferiority study	Edoxaban vs. warfarin: age: 57.1 vs. 57.4; male: 52.3% vs. 52.4%	First recurrent VTE or VTE-related death: Edoxaban vs. warfarin: 2.8% vs. 3.9%, HR = 0.73 (0.50–1.06), 95%CI	NR
Agnelli et al. (2013) (40)	Pulmonary embolism	Apixaban group: 10 mg of apixaban twice daily for the first 7 days, followed by 5 mg twice daily for 6 months Conventional therapy: enoxaparin 1 mg/kg of body weight every 12 h for at least 5 days. Warfarin: INR between 2.0 and 3.0	A randomized, double-blind study	Apixaban vs. conventional therapy: age: 57.2 vs. 56.7; male: 58.3% vs. 59.1%	Recurrent symptomatic venous thromboembolism or death related to venous thromboembolism: apixaban vs. conventional group: 2.3% vs. 2.6%, RR = 0.90; 95% CI, 0.50–1.61	NR

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IPF

Idiopathic pulmonary fibrosis is a type of fatal disease, whose 5-year survival is even worse than many cancers. The understanding of IPF etiology remains incomplete, and its diagnosis often requires the cooperation of multidisciplinary teams (46, 47). Associations between IPF and many thrombotic vascular diseases, including deep vein thrombosis (DVT), pulmonary embolism, and acute coronary syndromes (ACS) have been reported in previous studies (12–14). In addition, the imbalance between thrombosis and fibrinolysis has been detected in the alveolar compartment in IPF patients, and the systemic pro-thrombotic state could also appear in IPF patient (15). Therefore, theoretically, the application of oral anticoagulants could improve the therapeutic effect of IPF, and the benefits of warfarin use were reported in previous randomized trials (41, 48). After literature screening, three studies meet the inclusion criteria: the first one is a randomized trial, which compared warfarin and placebo in IPF patients (Table 3). The corresponding results showed that warfarin was associated with increased mortality risk in the IPF population lacking other indications for anticoagulation (41). The second study detected the influence of mortality and transplantation in the non-anticoagulation group and patients using warfarin or DOAC for anticoagulation (22). The adjusted result indicated that warfarin is associated with increased mortality and reduced transplant-free survival, while DOACs were not. Then the result of the third study compared the efficient outcome of DOAC and warfarin, which confirmed the advantages of DOAC in reducing the mortality risk in IPF patients (42). All of these three studies did not evaluate the safety outcome of oral anticoagulation in IPF treatment. Collectively, warfarin is associated with an increased mortality risk in IPF patients and DOACs seem more suitable for their anticoagulation treatment.

Warfarin interferes with the metabolism of vitamin K, disturbing the production of carboxylated vitamin K-dependent clotting factors. In addition, vitamin K is also essential for the production of the endogenous anticoagulant protein C (46). The administration of warfarin could induce the deficiency of protein C before vitamin K-dependent clotting factors depletion, leading to a transient procoagulant state (46). Protein C can also alter the expression level of inflammatory and apoptotic genes, down-regulate the release of inflammatory mediators, reduce the expression of cell adhesion molecules and maintain the barrier function of endothelial cells (49). Interference with these protective pathways might be the reason for worse outcomes in IPF treatment. However, the major difference between warfarin and DOAC is their influence on vitamin K, there is no existing study reporting whether the function of vitamin K will affect the survival of IPF, which deserves more attention in the future.

COPD

Chronic obstructive pulmonary disease is associated with neutrophilic inflammation and T-lymphocytes activation (17). In recent years, macrophages have also been confirmed to be involved in COPD: the inhaled particles activate alveolar macrophages, which then release cytokines and chemokines, including interleukins (IL)-1α, IL-1β, IL-33, and IL-18 (50). These cytokines inhibit plasminogen activators. The procoagulant effect is initiated by tissue factor, IL-6, and the tumor necrosis factor (17). All of the above cytokines contribute to the amplification of procoagulant processes, therefore, COPD could induce the occurrence of venous thromboembolism and pulmonary embolism. A previous multicentral cross-sectional study indicated that PE could be detected in 5.9% of patients with COPD (19), and the correlation between COPD and the risk of embolism might be the basis of its poor prognosis (51). Previous studies have confirmed the effect of anticoagulation in COPD treatment: improved lung function has been detected in patients hospitalized for COPD deterioration and treated with low molecular weight heparin (LMWH). After anticoagulation treatment, FEV1, and PaO_2 were increased and $PaCO_2$ was decreased, and therefore the reduction of D-Dimers and blood clotting parameters was observed (52). Anticoagulation is capable of improving the hemorheological indexes, circulatory and pulmonary functions, which can also reduce patients' blood viscosity.

As for OAC treatment in patients with COPD, totally three studies were included in our systemic review (43–45) (Table 4). All of them indicated that the use of oral anticoagulants could reduce the mortality risk of COPD, and the efficacy outcome between apixaban and warfarin did not exhibit statistical difference. The safety outcome of OAC in COPD treatment was only reported by Durheim et al. in 2018 (45), which indicated that compared with no anticoagulation, OAC will not increase the risk of major bleeding. Considering that current reported data about the efficacy and safety of OAC in COPD treatment are relatively limited, in future research, the safety outcome of different OACs deserves special attention, which could provide suggestions for clinical medication.

Future directions

Totally 16 studies were included in our systemic review to present the efficacy and safety outcomes of OAC therapy in patients with pulmonary diseases. However, in terms of the selection of anticoagulation regimen, multiple crucial clinical questions remain uncertain. First of all, existing investigations have shown that the use of OAC will increase the risk of death in patients with SSc-PAH. However, the relevant theoretical mechanism is still unclear, and more clinical data need to

TABLE 3 Summary of included studies of OACs in patients with pulmonary fibrosis.

Author (year)	Pulmonary disease	Oral anticoagulants	Study design	Baseline characteristics of investigated population	Efficacy outcome	Safety outcome
Noth et al. (2012) (41)	Pulmonary fibrosis	Study subjects were provided two strengths of warfarin tablets (1 and 2.5 mg) or matching placebos	Randomized trial	Patients aged 35–80 years with progressive Idiopathic pulmonary fibrosis Warfarin vs. placebo: age: 67.3 vs. 66.7; Female: 33% vs. 21%; FVC % predicted: 58.9 vs. 58.7	Primary outcome: the composite outcome of time to death, hospitalization (non-bleeding, non-elective), or a 10% or greater absolute decline in FVC: warfarin vs. placebo: HR = 1.32 (0.70, 2.47), $P = 0.271$ All-cause mortality: warfarin vs. placebo: HR = 4.85 (1.38, 16.99), $P = 0.005$ Combined all-cause mortality or non-elective, nonbleeding hospitalizations: warfarin vs. placebo: HR = 2.12 (1.00, 4.52), $P = 0.02$ Combined all-cause mortality or >10% FVC drop: warfarin vs. placebo: HR = 1.44 (0.69, 2.99), $P = 0.28$	NR
Naqvi et al. (2021) (42)	Pulmonary fibrosis	Warfarin or DOACs including apixaban, rivaroxaban, or dabigatran	A retrospective cohort study	Patients with IPF, warfarin vs. DOAC: age 73.29 vs. 74.09; male: 50% vs. 57.8%; atrial fibrillation: 57.1% vs. 64.4%; CHA_2DS_2-VASc (median, IQR): 4 (1.5) vs. 4 (1.25); Thromboembolism: 28.6 vs. 35.6%; Inherited coagulopathy with thrombotic event: 10.7% vs. 2.2%	One year follow-up of mortality: DOAC vs. warfarin: OR = 77.4, 95% CI, 5.94–409.3, $P = 0.007$	NR
King et al. (2021) (22)	Pulmonary fibrosis	Warfarin, DOACs (apixaban, rivaroxaban, dabigatran)	Cohort study	Patients with Interstitial Lung Disease in the Pulmonary Fibrosis Foundation Patient Registry DOAC vs. warfarin vs. none: age: 70.45 vs. 70.40 vs. 67.37; Male: 73.1% vs. 71.6% vs. 62.2%; BMI: 29.48 vs. 30.22 vs. 29.35	Reduced transplant-free survival: (adjusted data) warfarin (HR = 2.566; 95% CI, 1.095–6.0165, $P = 0.014$); DOACs (HR = 1.368; 95% CI, 0.500–3.737)	NR

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TABLE 4 Summary of included studies of OACs in Patients with COPD.

Author (year)	Pulmonary disease	Oral anticoagulants	Study design	Baseline characteristics of investigated population	Efficacy outcome	Safety outcome
Durheim et al. (2016) (43)	Atrial fibrillation, COPD	Apixaban, warfarin	Insights of the results of prospective, multi-center cohort study	NR between apixaban and warfarin groups	stroke or systemic embolism: Apixaban vs. warfarin: HR = 0.92 [95% CI 0.52–1.63] All-cause mortality: apixaban vs. warfarin: HR = 0.80 [95% CI 0.62–1.04]	NR
Andersson et al. (2019) (44)	COPD, right-sided heart failure	Warfarin (96%), DOAC (4%)	Cohort study	NR between patients treated with or without oral anticoagulants	Death: oral anticoagulants treatment vs. no oral anticoagulants treatment: HR = 0.88 (0.85–0.92, 95% CI)	NR
Durheim et al. (2018) (45)	COPD	OAC (warfarin and dabigatran)	Cohort study	NR between OAC and no OAC groups	All cause death: OAC vs. no OAC: HR = 0.77 (95% CI; 0.59–1.01) Cardiovascular death: OAC vs. no OAC: HR = 0.76 (95% CI; 0.49–1.18) Non-cardiovascular death: OAC vs. no OAC: HR = 0.81 (95% CI; 0.58–1.15) 1st cardiovascular hospitalization: OAC vs. no OAC: HR = 0.97 (95% CI; 0.79–1.21)	1st major bleed: OAC vs. no OAC: HR = 1.22 (95% CI; 0.84–1.75) 1st bleeding hospitalization: HR = 1.12 (95% CI; 0.72–1.66)

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be included in the analysis to confirm the reliability of this conclusion. Secondly, the results of our study indicated that warfarin is associated with increased mortality risk in patients with IPF, while DOACs were not. Considering that the major difference between VKA and DOAC is the action of vitamin K, it is reasonable to suspect that vitamin K plays a role in reducing the risk of death in IPF patients. However, existing studies can only provide some theoretical evidence about this assumption, there is no study reporting the relationship between Vitamin K and IPF survival, which deserves further investigation. Thirdly, the results about the safety effect of OAC in pulmonary diseases are still very limited. Our conclusion is based on the evaluation of the corresponding results in patients with PH and PE. The risk of OAC treatment-associated bleeding events specific to IPF patients has not been reported in the included studies, and there are only comparison results between anticoagulation and non-anticoagulation groups in COPD population. It is necessary to investigate more about the safety outcome of OAC in patients with different pulmonary diseases in the future. In addition, obtaining more data comparing the safety results of VKA and DOAC in different pulmonary diseases will help to provide more accurate recommendations for the selection of clinical anticoagulation regimen. Finally, included studies in our systemic review only reported the corresponding results of apixaban, dabigatran, edoxaban, and rivaroxaban, none of them assessed the effects of betrixaban in patients with pulmonary diseases. Completely investigating all types of DOAC will be more conducive to accurately evaluate its effect in the treatment of pulmonary diseases.

Conclusion

Oral anticoagulant (including VKA and DOAC) could significantly reduce the mortality risk in patients with PH, PE, and COPD, and the effects of DOAC in mortality-reducing and VTE recurrence preventing are no less than warfarin. In patients with IPF or SSc-PAH, warfarin could significantly increase the mortality risk and reduce the transplant-free survival, while DOACs are not. Compared with warfarin, DOACs show non-inferiority in the bleeding events, and they can also significantly reduce the risk of major bleeding. DOAC therapy should be regarded as a non-inferior option for stroke and embolism prevention in patients with pulmonary diseases.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Wengen Zhu,
The First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Wenyu Lin,
Tri-Service General Hospital, Taiwan
Jinzhu Hu,
Nanchang University, China

*CORRESPONDENCE
Eue-Keun Choi
choiek17@snu.ac.kr

†These authors have contributed equally to this work and share first authorship

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Net clinical benefit of antithrombotic therapy for atrial fibrillation patients with stable coronary artery disease

So-Ryoung Lee[1†], Jin-Hyung Jung[2†], Eue-Keun Choi[1,3*], Seung-Woo Lee[2], Soonil Kwon[1], Ji-Suck Park[1], Jeehoon Kang[1], Kyung-Do Han[4], Kyung Woo Park[1,3], Seil Oh[1,3] and Gregory Y. H. Lip[3,5,6]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Department of Medical Statistics, College of Medicine, Catholic University of Korea, Seoul, South Korea, [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [4]Department of Statistics and Actuarial Science, Soongsil University, Seoul, South Korea, [5]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest and Heart Hospital, Liverpool, United Kingdom, [6]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Objectives: To compare the net clinical benefit of oral anticoagulant (OAC) monotherapy to OAC plus single antiplatelet therapy (SAPT) in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) at 1- and 3-year after percutaneous coronary intervention (PCI).

Background: It has not been studied whether the net clinical benefit of the antithrombotic treatment options differs depending on the elapsed time from the index PCI.

Methods: Using the Korean nationwide claims database, we included AF patients who underwent PCI from 2009 to 2019 and constructed two cohorts: 1- and 3-year after PCI. In each cohort, the baseline characteristics of two groups were balanced using propensity score weighting. Ischemic stroke, myocardial infarction, major bleeding, and composite clinical outcomes were analyzed.

Results: Among patients with 1-year after PCI, OAC monotherapy (n = 678), and OAC plus SAPT (n = 3,159) showed comparable results for all clinical outcomes. In patients with 3-year after PCI, OAC monotherapy (n = 1,038) and OAC plus SAPT (n = 2,128) showed comparable results for ischemic stroke and myocardial infarction, but OAC monotherapy was associated with a lower risk of composite clinical outcomes (HR 0.762, 95% CI 0.607–0.950), mainly driven by the reduction of major bleeding risk (HR 0.498, 95% CI 0.345–0.701).

Conclusion: Oral anticoagulant monotherapy may be a comparable choice for patients with AF and stable CAD compared to OAC plus SAPT. In patients with stable CAD more than 3-year

after index PCI, OAC monotherapy would be a better choice, being associated with less major bleeding and a positive net clinical benefit.

KEYWORDS

atrial fibrillation, coronary artery disease, antithrombotic therapy, oral anticoagulant, antiplatelet agent

Introduction

Oral anticoagulant (OAC) monotherapy is generally recommended in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) (1–4). In a previous meta-analysis, OAC monotherapy showed a comparable risk of major adverse cardiovascular events and a lower risk of major bleeding than OAC plus single antiplatelet agent (SAPT) (5). There have also been two randomized clinical trials that evaluated the optimal antithrombotic therapy for patients with AF and stable CAD (6, 7). The OAC-ALONE trial was the first randomized trial comparing OAC monotherapy vs. OAC plus SAPT in patients with AF and stable CAD beyond 1-year after undergoing percutaneous coronary intervention (PCI) (6). However, non-inferiority of OAC monotherapy to OAC plus SAPT for the composite of major adverse cardiovascular events was not established because of inadequate statistical power (6). Recently, the AFIRE trial showed that rivaroxaban monotherapy was non-inferior for efficacy and superior for safety to rivaroxaban plus SAPT in patients with AF and stable CAD (7).

Although the AFIRE trial demonstrated that rivaroxaban monotherapy is superior to rivaroxaban plus SAPT in primary safety outcomes, there have been conflicting data regarding the comparative effectiveness and safety of OAC monotherapy vs. OAC plus SAPT according to the time from index PCI to study enrollment (8, 9). Considering the temporal dynamic of the risk of stent thrombosis after PCI and thromboembolic risk in patients with AF (10), we can hypothesize that the efficacy and safety of antithrombotic treatment strategies can temporally vary. However, it has not been studied whether the net clinical benefit of the antithrombotic treatment options differs depending on the elapsed time from the index PCI.

In this study, we aimed to compare the effectiveness, safety, and net clinical benefit of OAC monotherapy to OAC plus SAPT in patients with AF and stable CAD at 1- and 3-year after PCI in a contemporary real-world observational cohort.

Materials and methods

Data source, study design, and study population

This analysis was performed based on the Korean nationwide claims database from the Korean Health Insurance Review Agency (HIRA) database. In South Korea, all citizens are subscribed to the medical insurance system, called the Korean National Health Insurance Service (NHIS) provided by the Korean government (11). Information on subscribers' medical use is collected for NHIS operation, and information on medical use, which becomes insurance coverage, is submitted from health care providers. The submitted information is reviewed by the Korean HIRA, which is a quality control department that provides a review of the medical costs incurred. The Korean HIRA database contains all medical expenses claim data of the entire Korean population, including subscribers' demographic information, diagnoses, examinations, prescriptions, and procedures for both inpatient and outpatient services (11, 12). Diagnoses were coded based on the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes (11, 12).

Using the Korean nationwide claims database, we included AF patients who underwent PCI from January 1, 2009 to February 28, 2019. Considering dynamic changes in antithrombotic therapy according to the period after receiving PCI, the index antithrombotic treatment was independently defined at different times after receiving PCI and we constructed two cohorts: 1- and 3-year after PCI (**Figure 1**). Cohort 1 consisted of patients who had just passed 1 year after PCI. Patients with AF who underwent PCI between September 1, 2009 and June 30, 2017, were firstly identified. Patients who died before 1-year after PCI and underwent repeated PCI before 1-year after PCI were excluded. Among these, the OAC monotherapy group and OAC plus SAPT group were defined by identifying prescriptions between 12 and 15 months from PCI (**Figure 1A**). Cohort 2 was defined as patients 3 years after PCI. Patients with AF who underwent PCI between September 1, 2009 and June 30, 2015, were included. Similar to cohort 1, patients who died before 3-year after PCI and

underwent repeated PCI before 3-year after PCI were excluded. OAC monotherapy group and OAC plus SAPT group were identified by the prescription between 36 and 39 months from PCI (**Figure 1B**).

The study design was approved by the Institutional Review Board of the Seoul National University Hospital (E-1911-052-1078). The review board waived informed consent since each patient is de-identified and encrypted in the HIRA database to ensure patient privacy.

Covariates

Subjects' age, sex, comorbidities including hypertension, diabetes, dyslipidemia, heart failure, prior myocardial infarction, peripheral artery disease, prior ischemic stroke/transient ischemic attack/systemic embolism, prior intracranial hemorrhage, prior gastrointestinal bleeding, renal disease, and liver disease were ascertained by the prespecified operational definitions summarized in **Supplementary Table 1** (13, 14). Concomitant medications include renin-angiotensin-aldosterone system inhibitors, beta-blockers, calcium channel blockers, loop diuretics, statins, non-steroidal anti-inflammatory drugs, and proton-pump inhibitors were ascertained based on the prescription records. The type of OAC [warfarin or direct oral anticoagulant (DOAC) including rivaroxaban, dabigatran, apixaban, and edoxaban], dose of DOAC, type of antiplatelet agents among aspirin, clopidogrel, prasugrel or ticagrelor were also identified. CHA_2DS_2-VASc score and modified HAS-BLED score were calculated by the operational definitions of comorbidities and medical history including concomitant medication (**Supplementary Table 1**) (13, 14).

Study outcomes and follow-up

During the follow-up period, composites of ischemic stroke and myocardial infarction occurrence were identified for effectiveness evaluation. For safety evaluation, major bleeding was defined as a composite of intracranial hemorrhage, gastrointestinal bleeding, and extracranial/unclassified major bleeding. We identified the major bleeding that occurred during the follow-up period. To assess net clinical benefit, composite clinical outcomes of ischemic stroke, myocardial infarction, and major bleeding were ascertained. Furthermore, we reported each component of effectiveness and safety outcome as follows: ischemic stroke, myocardial infarction, intracranial hemorrhage, gastrointestinal bleeding, and gastrointestinal bleeding requiring transfusion. Clinical outcomes were defined by the ICD-10-CM codes and detailed definitions of clinical outcomes are summarized in **Supplementary Table 1**.

To evaluate the accuracy of the operational definitions of clinical outcomes including ischemic stroke, myocardial infarction, intracranial hemorrhage, and gastrointestinal bleeding, we conducted a validation study in a tertiary hospital with 200 randomly chosen patients with the relevant ICD-10-CM codes for each event (15). Patients' medical records were reviewed by two physicians (JP and SK). The positive predictive values of the operational definitions were 91.2, 92, 95.1, and 91.7% for ischemic stroke, myocardial infarction, intracranial hemorrhage, and gastrointestinal bleeding (15). In each cohort, the index date was the first date of OAC monotherapy or OAC plus SAPT prescription. Patients were censored at the outcome events or the end of the study period (February 28, 2019), whichever came first.

Statistical analysis

Continuous variables are presented as mean (standard deviation) and median (interquartile ranges, IQR). Categorical variables are presented as number and percentage. For each clinical outcome, the crude incidence rate for each clinical outcome was estimated by dividing the number of incidents during the follow-up period by the number of 100 person-years at risk. Unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were analyzed for estimation of the risk of clinical outcomes using the Cox proportional hazards regression models.

To compare the OAC monotherapy and OAC plus SAPT groups, propensity score methods were used (16). A logistic regression model with all baseline factors (except for DOAC dose) was used to determine the probability score for being in each treatment group. To balance baseline characteristics across the two treatment groups, time-to-event analyses were conducted using inverse probability of treatment weighting (IPTW) analysis with stabilized weights computed from the propensity score (17, 18). Following IPTW, the covariate balance between the two groups was determined using the absolute standardized difference (ASD) (19). In a covariate, an ASD of $\leq$0.1 (10%) indicated that the two groups were well-balanced, with a negligible difference. The weighted number of events throughout the follow-up period was divided by 100 person-years at risk to calculate the weighted incidence rates. Survival analysis with the Kaplan-Meier method (log-rank test) and weighted Cox proportional hazards regression models with IPTW were used to determine the risk of clinical outcomes for OAC monotherapy and OAC plus SAPT (reference).

To provide complementary results, we conducted multivariable Cox analyses for a sensitivity analysis. Age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior myocardial infarction, peripheral artery disease, prior stroke/transient ischemic attack/systemic embolism, prior intracranial hemorrhage, prior gastrointestinal bleeding, renal disease, liver disease, CHA_2DS_2-VASc score, modified HAS-BLED score, and OAC type (warfarin or DOAC) were included for the multivariable-adjusted Cox analyses.

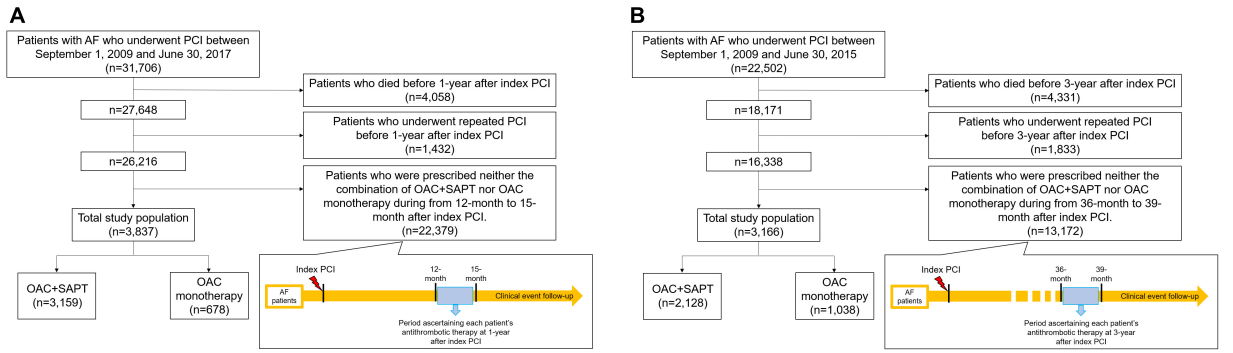


FIGURE 1
Study design and patient enrollment flow. **(A)** Cohort 1: patients with AF who underwent PCI, 1-year after index PCI. **(B)** Cohort 2: patients with AF who underwent PCI, 3-year after index PCI. AF, atrial fibrillation; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet agent.

SAS software, version 9.3 (SAS Institute, Cary, NC, United States), was used for all statistical analyses, and a two-tailed *p*-value of 0.05 was considered statistically significant.

Results

In cohort 1 among patients 1-year after PCI, 678 patients with OAC monotherapy and 3,159 patients with OAC plus SAPT were included. In cohort 2 among patients 3-years after PCI, 1,038 patients with OAC monotherapy and 2,128 patients with OAC plus SAPT were enrolled.

Baseline characteristics are presented in **Tables 1**, **2**. In cohort 1, the OAC monotherapy group were older, more likely to be women, and had higher CHA_2DS_2-VASc scores than OAC plus SAPT group. OAC monotherapy group showed a higher prevalence of prior ischemic stroke/transient ischemic attack/systemic embolism than the OAC plus SAPT group. Regarding OAC types, the OAC monotherapy group was more likely to be prescribed DOAC rather than warfarin compared to OAC plus SAPT group. Among DOAC users, the OAC plus SAPT group was more likely to be prescribed a reduced dose of DOAC than the OAC monotherapy group. Among SAPT for OAC plus SAPT group, clopidogrel was the most commonly prescribed (65.9%), followed by aspirin (33.8%). In cohort 2, similar differences between the two groups were observed as in cohort 1. OAC monotherapy group were older, more likely to be women, and had higher CHA_2DS_2-VASc scores compared to OAC plus SAPT group. Diabetes mellitus was more prevalent in OAC plus SAPT group than in the OAC monotherapy group. DOAC prescription was more common in the OAC monotherapy group. Among DOAC users, reduced dose DOAC use was more common in patients with OAC plus SAPT. Among SAPT for OAC plus SAPT group, aspirin was the most commonly prescribed (52.2%), followed by clopidogrel (47.7%). The baseline characteristics were well-balanced after IPTW between the two groups in both cohorts except for the DOAC dose (**Tables 1**, **2** and **Supplementary Figure 1**).

Effectiveness, safety, and net clinical benefit of oral anticoagulant plus single antiplatelet therapy vs. oral anticoagulant monotherapy in patients 1-year after percutaneous coronary intervention

A median follow-up duration of cohort 1 was 2.3 (IQR, 1.2–4.2) years. Crude incidence rates of clinical outcomes and unadjusted HRs for clinical outcomes are presented in **Supplementary Table 2**. **Figure 2A** showed weighted cumulative incidence curves of effectiveness, safety, and composite clinical outcomes of cohort 1. Weighted incidence rates and weighted HRs are presented in **Figure 3A**. After IPTW, OAC monotherapy and OAC plus SAPT showed comparable risks for a composite of ischemic stroke and myocardial infarction, major bleeding, and composite clinical outcomes (**Figures 2A**, **3A**). OAC monotherapy and OAC plus SAPT did not show any significant differences for the individual components of the effectiveness and safety outcomes.

Effectiveness, safety, and net clinical benefit of oral anticoagulant plus single antiplatelet therapy vs. oral anticoagulant monotherapy in patients with 3-year after percutaneous coronary intervention

A median follow-up duration of cohort 2 was 2.5 (IQR, 1.3–4.2) years. Crude incidence rates of clinical outcomes

TABLE 1 Baseline characteristics of oral anticoagulant (OAC) plus single antiplatelet therapy (SAPT) and OAC monotherapy groups at 1-year after index percutaneous coronary intervention (PCI).

	Before IPTW			Post IPTW		
	OAC + SAPT (*n* = 3,159)	OAC monotherapy (*n* = 678)	ASD	OAC + SAPT (*n* = 3,159)	OAC monotherapy (*n* = 676)	ASD
The year of index PCI						
2009	122 (3.9)	33 (4.9)		119 (3.8)	35 (5.2)	
2010	194 (6.1)	44 (6.5)		189 (6.0)	50 (7.4)	
2011	178 (5.6)	40 (5.9)		172 (5.5)	47 (6.9)	
2012	237 (7.5)	50 (7.4)		232 (7.3)	55 (8.1)	
2013	291(9.2)	63 (9.3)		283 (8.9)	72 (10.6)	
2014	429(13.6)	70 (10.3)		426 (13.5)	69 (10.3)	
2015	503(15.9)	104 (15.3)		508 (16.1)	98 (14.5)	
2016	742(23.5)	172 (25.4)		758 (24.0)	158 (23.4)	
2017	463(14.7)	102 (15.0)		474 (15.0)	92 (13.6)	
Age, years			0.068			0.005
Mean (SD)	70.4 ± 9	71.03 ± 9.32		70.51 ± 9.05	70.46 ± 9.14	
Median (IQR)	72 (65–77)	72 (65–78)		72 (65–77)	71 (65–77)	
Age group						
<65 years	733 (23.2)	159 (23.5)		728 (23.1)	162 (24.0)	
65–74 years	1323 (41.9)	242 (35.7)		1295 (41.0)	269 (39.8)	
≥75 years	1103 (34.9)	277 (40.9)		1136 (36.0)	245 (36.3)	
Women	1029 (32.6)	264 (38.9)	0.133	1065 (33.7)	229 (33.9)	0.003
Comorbidities						
Hypertension	2873 (91.0)	619(91.3)	0.012	2875 (91.0)	614 (90.8)	0.006
Diabetes mellitus	1225 (38.8)	249 (36.7)	0.042	1213 (38.4)	255 (37.7)	0.013
Dyslipidemia	2621 (83.0)	547 (80.7)	0.059	2608 (82.6)	558 (82.5)	0.001
Heart failure	1451 (45.9)	339 (50.0)	0.081	1475 (46.7)	320 (47.3)	0.011
Prior myocardial infarction	1075 (34.0)	221 (32.6)	0.030	1068 (33.8)	231 (34.1)	0.007
Peripheral artery disease	797 (25.2)	170 (25.1)	0.003	798 (25.2)	173 (25.6)	0.008
Prior ischemic stroke/TIA/SE	632 (20.0)	167 (24.6)	0.111	658 (20.8)	141 (20.8)	0.000
Prior intracranial hemorrhage	16 (0.5)	9 (1.3)	0.086	21 (0.7)	4.7 (0.7)	0.004
Prior gastrointestinal bleeding	204 (6.5)	57 (8.4)	0.074	215 (6.8)	47 (6.9)	0.005
Renal disease	458 (14.5)	100 (14.8)	0.007	460 (14.5)	98 (14.5)	0.001
Liver disease	1049 (33.2)	218 (32.2)	0.022	1042 (33.0)	219 (32.3)	0.014
CHA_2DS_2-VASc score			0.159			0.004
Mean (SD)	3.69 ± 1.78	3.97 ± 1.81		3.74 ± 1.8	3.75 ± 1.78	
Median (IQR)	3 (2–5)	4 (3–5)		4 (2–5)	4 (2–5)	
Modified HAS-BLED			0.050			0.005
Mean (SD)	3.33 ± 0.94	3.38 ± 0.97		3.34 ± 0.95	3.33 ± 0.95	
Median (IQR)	3 (3–4)	3 (3–4)		3 (3–4)	3 (3–4)	
Concomitant medications						
RAAS inhibitors	2612 (82.7)	552 (81.4)	0.033	2111 (66.8)	449 (66.3)	0.010
Beta-blockers	2682 (84.9)	572 (84.4)	0.014	2685 (85.0)	571 (84.4)	0.014
Calcium channel blockers	2211 (70.0)	476 (70.2)	0.004	2213 (70.1)	468 (69.3)	0.017
Loop diuretics	1875 (59.4)	432 (63.7)	0.089	1887 (59.7)	423 (62.5)	0.057
Statins	2787 (88.2)	579 (85.4)	0.083	2783 (88.1)	585 (86.5)	0.046
NSAID	2106 (66.7)	458 (67.6)	0.018	2111 (66.8)	449 (66.3)	0.010
Proton pump inhibitors	1595 (50.5)	339 (50)	0.009	1612 (51.0)	32 (47.5)	0.070

(Continued)

TABLE 1 Continued

	Before IPTW			Post IPTW		
	OAC + SAPT (*n* = 3,159)	OAC monotherapy (*n* = 678)	ASD	OAC + SAPT (*n* = 3,159)	OAC monotherapy (*n* = 676)	ASD
Antithrombotic therapy						
OAC type			0.191			0.004
Warfarin	1718(54.38)	304(44.84)		1665(52.7)	355 (52.5)	
DOAC	1441(45.62)	374(55.16)		1494 (47.3)	322 (47.5)	
DOAC dose			0.320			0.355
Standard dose DOAC	320 (22.2)	137 (36.6)		329 (22.0)	122.3(38.04)	
Reduced dose DOAC	1121 (77.8)	237 (63.4)		1166 (78.0)	199 (62.0)	
DOAC type						
Rivaroxaban	565 (17.9)	149 (22.0)		585 (18.5)	131 (19.3)	
Dabigatran	260 (8.2)	69 (10.2)		271 (8.6)	58 (8.6)	
Apixaban	432 (13.7)	106 (15.6)		448 (14.2)	89 (13.1)	
Edoxaban	184 (5.8)	50 (7.4)		190 (6.0)	44 (6.5)	
Antiplatelet agent type						
Aspirin	1069 (33.8)	0 (0)		1063 (33.7)	0 (0)	
Clopidogrel	2081 (65.9)	0 (0)		2087 (66.1)	0 (0)	
Prasugrel or ticagrelor	9 (0.3)	0 (0)		9.2 (0.3)	0 (0)	

IQR, interquartile ranges; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; SE, systemic embolism; TIA, transient ischemic attack.

and unadjusted HRs for clinical outcomes are presented in **Supplementary Table 2**. **Figure 2B** showed weighted cumulative incidence curves of effectiveness, safety, and composite clinical outcomes of cohort 2. Weighted incidence rates and weighted HRs are presented in **Figure 3B**. In cohort 2 with 3-year after PCI, OAC monotherapy and OAC plus SAPT showed a comparable risk for a composite of ischemic stroke and myocardial infarction, however, OAC monotherapy was associated with a lower risk of composite clinical outcomes (HR 0.762, 95% CI 0.607–0.950), mainly driven by a reduction of major bleeding risk (HR 0.498, 95% CI 0.345–0.701) compared to OAC plus SAPT (**Figures 2B**, **3B**).

For each component of effectiveness and safety outcomes, OAC monotherapy and OAC plus SAPT group showed comparable risks for both ischemic stroke and myocardial infarction (**Figure 3B**). OAC monotherapy was associated with lower risks of intracranial hemorrhage, gastrointestinal bleeding, and gastrointestinal bleeding requiring transfusion than OAC plus SAPT (**Figure 3B**).

Sensitivity analyses

Multivariable Cox analyses showed consistent results with the IPTW analyses in two cohorts (**Supplementary Table 2**).

Discussion

In this nationwide population-based observational study, our principal findings are as follows: (1) a substantial proportion of AF patients who had been receiving PCI for more than a year was prescribed OAC plus SAPT rather than OAC monotherapy; (2) among patients who had just passed 1 year after PCI, OAC monotherapy showed comparable risks for ischemic stroke, myocardial infarction, and major bleeding compared to OAC plus SAPT; (3) among patients 3 years after PCI, OAC monotherapy was associated with a lower risk of the composite clinical outcomes of ischemic stroke, myocardial infarction, and major bleeding than OAC plus SAPT, mainly driven by a lower risk of major bleeding. From these results, OAC monotherapy results in positive net clinical benefits by reducing bleeding risk in AF patients with sufficiently stable CAD after PCI (**Figure 4**). From the results of this study and previous clinical trials, OAC monotherapy would be the most reasonable option for patients with AF with stable CAD (1-year beyond PCI) as the current guidelines (1–4).

In a previous observational study based on the Danish nationwide cohort, warfarin-based OAC monotherapy was suggested as the most optimal antithrombotic therapy regimen in patients with stable CAD defined as 12 months from an acute coronary event (20). Compared to warfarin, single or dual antiplatelet therapy without anticoagulation was

TABLE 2 Baseline characteristics of OAC plus SAPT and OAC monotherapy groups at 3-year after index PCI.

	Before IPTW			Post IPTW		
	OAC + SAPT (*n* = 2128)	OAC monotherapy (*n* = 1038)	ASD	OAC + SAPT (*n* = 2129)	OAC monotherapy (*n* = 1036)	ASD
The year of index PCI						
2009	225 (10.6)	78 (7.5)		210 (9.9)	89 (8.6)	
2010	242 (11.4)	95 (9.2)		227 (10.7)	106 (10.3)	
2011	266 (12.5)	112 (10.8)		248 (11.6)	132 (12.7)	
2012	304 (14.3)	130 (12.5)		297 (14.0)	134 (12.9)	
2013	369 (17.3)	206 (19.9)		386 (18.1)	203 (19.6)	
2014	471 (22.1)	251 (24.2)		494 (23.2)	222 (21.4)	
2015	251 (11.8)	166 (16.0)		267 (12.6)	151 (14.6)	
Age, years			0.185			0.001
Mean (SD)	68.06 ± 9.07	69.71 ± 8.74		68.61 ± 9.09	68.6 ± 8.85	
Median (IQR)	69 (63–74)	71 (65–76)		70 (64–75)	70 (63–75)	
Age group						
<65 years	645 (30.3)	256 (24.7)		603 (28.3)	299 (28.9)	
65–74 years	969 (45.5)	439 (42.3)		944 (44.3)	454 (43.8)	
≥75 years	514 (24.2)	343 (33.0)		582 (27.3)	283 (27.3)	
Women	595 (28.0)	385 (37.1)	0.195	660 (31.0)	321 (31.0)	0.000
Comorbidities						
Hypertension	1911 (89.8)	948 (91.3)	0.052	1924 (90.4)	940 (90.7)	0.011
Diabetes mellitus	799 (37.6)	328 (31.6)	0.125	757 (35.6)	370 (35.7)	0.002
Dyslipidemia	1698 (79.8)	834 (80.4)	0.013	1704 (80.1)	832 (80.3)	0.005
Heart failure	860 (40.4)	430 (41.4)	0.020	865 (40.6)	419 (40.4)	0.004
Prior myocardial infarction	691 (32.5)	327 (31.5)	0.020	684 (32.1)	331 (31.9)	0.004
Peripheral artery disease	511 (24.0)	247 (23.8)	0.005	513 (24.1)	250 (24.2)	0.001
Prior ischemic stroke/TIA/SE	417 (19.6)	206 (19.9)	0.006	422 (19.8)	206 (19.9)	0.002
Prior intracranial hemorrhage	13 (0.6)	8 (0.8)	0.019	14 (0.6)	6 (0.6)	0.002
Prior gastrointestinal bleeding	134 (6.3)	77 (7.4)	0.044	144 (6.7)	70 (6.7)	0.000
Renal disease	244 (11.5)	123 (11.9)	0.011	248 (11.6)	122 (11.8)	0.005
Liver disease	659 (31.0)	356 (34.3)	0.071	683 (32.1)	335 (32.3)	0.004
CHA_2DS_2-VASc score			0.137			0.005
Mean (SD)	3.32 ± 1.71	3.56 ± 1.79		3.4 ± 1.74	3.41 ± 1.73	
Median (IQR)	3 (2–4)	3 (2–5)		3 (2–5)	3 (2–5)	
Modified HAS-BLED			0.138			0.007
Mean (SD)	3.18 ± 0.94	3.31 ± 0.93		3.23 ± 0.94	3.24 ± 0.93	
Median (IQR)	3 (3–4)	3 (3–4)		3 (3–4)	3 (3–4)	
Concomitant medications						
RAAS inhibitors	1820 (85.5)	861 (83.0)	0.070	1822 (85.6)	860 (83.0)	0.071
Beta-blockers	1809 (85.0)	877 (84.5)	0.014	1811 (85.1)	877 (84.6)	0.011
Calcium channel blockers	1493 (70.2)	745 (71.8)	0.035	1506 (70.8)	737 (71.1)	0.007
Loop diuretics	1174 (55.2)	606 (58.4)	0.064	1188 (55.8)	591 (57.0)	0.023
Statins	1819 (85.5)	906 (87.3)	0.052	1826 (85.7)	905 (87.3)	0.046
NSAID	1390 (65.3)	696 (67.1)	0.036	1405 (66.0)	683 (65.9)	0.002
Proton pump inhibitors	782 (36.8)	405 (39.0)	0.046	800 (37.6)	387 (37.3)	0.005
Antithrombotic therapy						
OAC type			0.271			0.001
Warfarin	1320 (62.0)	505 (48.7)		1226 (57.6)	596 (57.5)	

(Continued)

TABLE 2 Continued

	Before IPTW			Post IPTW		
	OAC + SAPT (n = 2128)	OAC monotherapy (n = 1038)	ASD	OAC + SAPT (n = 2129)	OAC monotherapy (n = 1036)	ASD
DOAC	808 (38.0)	533 (51.4)		903 (42.4)	440 (42.5)	
DOAC dose			0.205			0.283
Standard dose DOAC	220 (27.2)	196 (36.8)		236 (26.2)	173 (39.4)	
Reduced dose DOAC	588 (72.78)	337 (63.2)		666 (73.8)	267 (60.6)	
DOAC type						
Rivaroxaban	327 (15.4)	209 (20.1)		364 (17.1)	173 (16.7)	
Dabigatran	179 (8.4)	114 (11.0)		198 (9.3)	97 (9.3)	
Apixaban	190 (8.9)	137 (13.2)		214 (10.1)	110 (10.6)	
Edoxaban	112 (5.3)	73 (7.0)		126 (5.9)	61 (5.9)	
Antiplatelet agent type						
Aspirin	1110 (52.2)	0(0)		1098 (51.6)	0(0)	
Clopidogrel	1015 (47.7)	0(0)		1028 (48.3)	0(0)	
Prasugrel or ticagrelor	3 (0.1)	0(0)		3 (0.1)	0(0)	

IQR, interquartile ranges; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; SE, systemic embolism; TIA, transient ischemic attack.

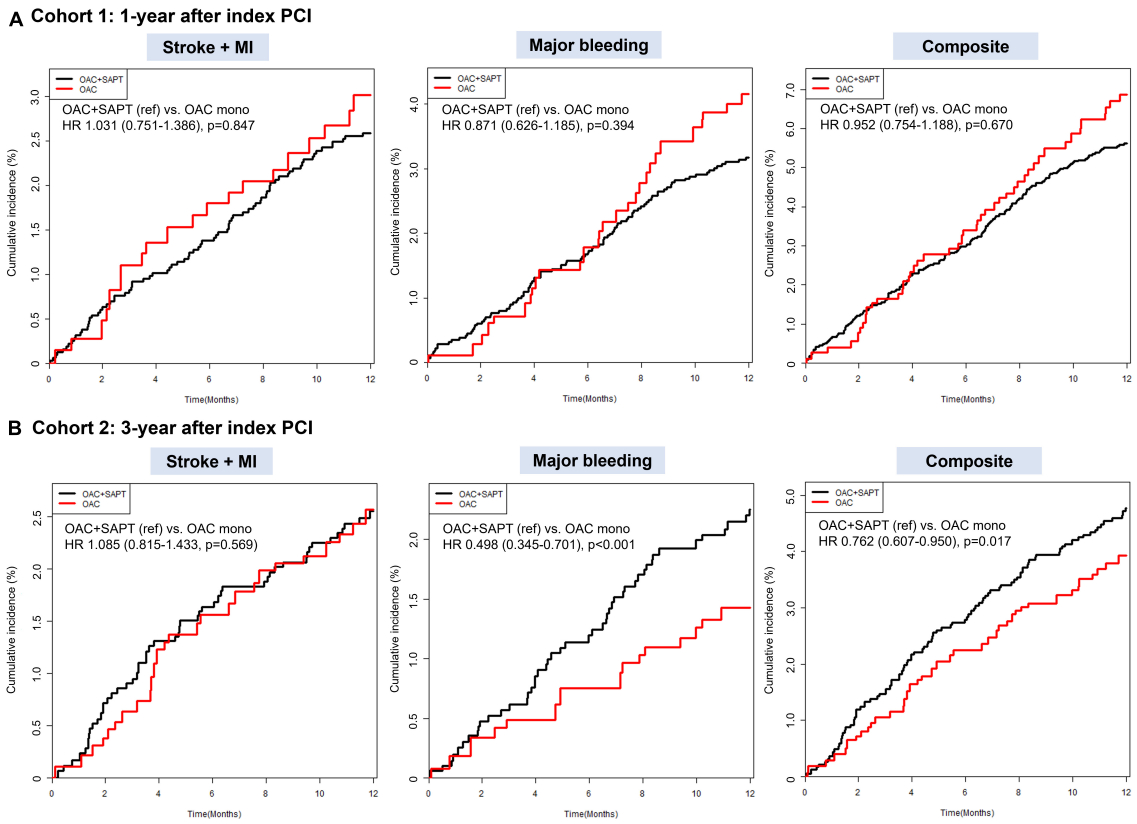
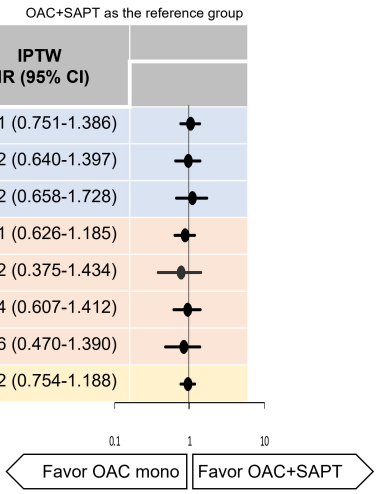


FIGURE 2
Weighted cumulative incidence curves for ischemic stroke/myocardial infarction, major bleeding, and composite clinical outcome: OAC plus SAPT vs. OAC monotherapy. **(A)** Cohort 1: patients with AF who underwent PCI, 1-year after index PCI. **(B)** Cohort 2: patients with AF who underwent PCI, 3-year after index PCI. HR, hazard ratio; OAC, oral anticoagulant; SAPT, single antiplatelet agent.

A Cohort 1: 1-year after index PCI

OAC+SAPT (n=2804) vs OAC (n=678)	Weighted IR		IPTW HR (95% CI)
	OAC +SAPT	OAC	
Ischemic stroke + Myocardial infarction	2.45	2.52	1.031 (0.751-1.386)
Ischemic stroke	1.58	1.52	0.962 (0.640-1.397)
Myocardial infarction	0.93	1.00	1.092 (0.658-1.728)
Major bleeding	2.59	2.23	0.871 (0.626-1.185)
Intracranial hemorrhage	0.64	0.49	0.772 (0.375-1.434)
Gastrointestinal bleeding	1.37	1.28	0.944 (0.607-1.412)
Gastrointestinal bleeding requiring transfusion	0.92	0.76	0.836 (0.470-1.390)
Composite clinical outcome	4.97	4.67	0.952 (0.754-1.188)



B Cohort 2: 3-year after index PCI

OAC+SAPT (n=2128) vs OAC (n=1038)	Weighted IR		IPTW HR (95% CI)
	OAC +SAPT	OAC	
Ischemic stroke + Myocardial infarction	2.45	2.68	1.085 (0.815-1.433)
Ischemic stroke	1.74	1.71	0.975 (0.685-1.367)
Myocardial infarction	0.72	0.99	1.352 (0.832-2.161)
Major bleeding	2.73	1.36	0.498 (0.345-0.701)
Intracranial hemorrhage	0.58	0.25	0.423 (0.173-0.894)
Gastrointestinal bleeding	1.48	0.88	0.590 (0.370-0.907)
Gastrointestinal bleeding requiring transfusion	1.04	0.56	0.532 (0.296-0.990)
Composite clinical outcome	5.12	3.92	0.762 (0.607-0.950)

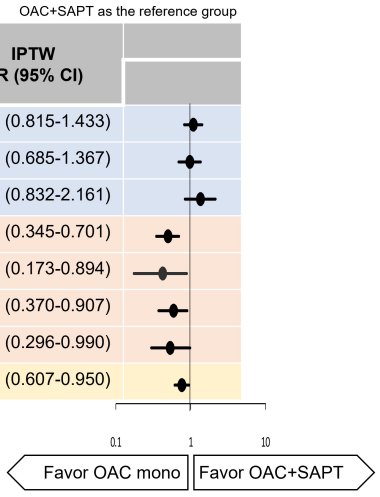


FIGURE 3
Hazard ratios of ischemic stroke, myocardial infarction, major bleeding, and composite clinical outcome: OAC plus SAPT vs. OAC monotherapy. **(A)** Cohort 1: patients with AF who underwent PCI, 1-year after index PCI. **(B)** Cohort 2: patients with AF who underwent PCI, 3-year after index PCI. IR, 100 person-years. CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; SAPT, single antiplatelet agent.

associated with increased risks of myocardial infarction, thromboembolism, death from the coronary event, and all-cause death. A combination of warfarin and single or dual antiplatelet therapy was related to the excessive bleeding risk compared to warfarin monotherapy.

Based on the consistent results of several observational studies (5), the guidelines have therefore advocated prescribing OAC monotherapy in AF patients 1 year following PCI as a Class IIa recommendation (21). However, the evidence generated through RCTs *per se* may be insufficient. The first RCT comparing OAC alone vs. OAC plus SAPT in patients with AF beyond 1 year after PCI, the OAC-ALONE trial, was reported (6). The median time from the last PCI was 4.4 (IQR 1.8–7.7) years in the OAC monotherapy group or 4.6 (IQR 2.4–7.4) years in OAC plus SAPT group, respectively. Among the total study population, only 25% were prescribed DOAC. Hence, the main results of the OAC-ALONE trial were inconclusive. More recently, the results of the AFIRE study, which included a large number of patients and used rivaroxaban as anticoagulation therapy, were published (7). This trial showed rivaroxaban monotherapy was significantly safer and more effective than rivaroxaban plus SAPT in patients with AF and stable CAD.

Despite the recommendations of the latest guidelines and updated evidence, a substantial proportion of patients with AF and stable CAD still do not receive guideline adherent antithrombotic therapy (22, 23). In contrast to the high rates of dual antiplatelet treatment, the overall rates of OAC were low after PCI in patients with AF. Since the emergence of DOACs, the usage of triple anti-thrombotic therapy in periprocedural antithrombotic regimens has shifted significantly, particularly

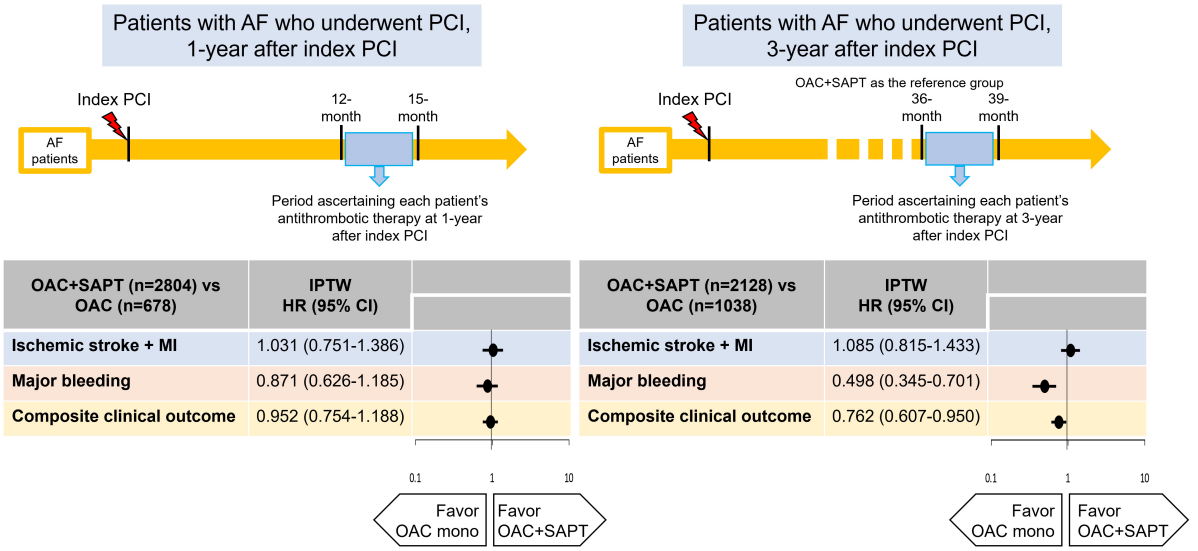


FIGURE 4
Hazard ratios of ischemic stroke, myocardial infarction, major bleeding, and composite clinical outcome: OAC plus SAPT vs. OAC monotherapy. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet agent.

in DOAC-based regimens. Regarding antithrombotic therapy 1 year after PCI, DAPT was more prevalent than OAC therapy. Also, OAC monotherapy 1 year after PCI was significantly lower than OAC plus SAPT therapy even in the DOAC era. In clinical practice, most patients with AF who underwent PCI continued to receive antiplatelet agents beyond 1-year post-PCI (23). This could be seen as a reflection of physicians' preference for continuing to utilize the antiplatelet therapy in patients undergone PCI while omitting anticoagulation therapy because of the concern of excessive bleeding.

There have been two recent conflicting observational studies for patients with AF who underwent PCI beyond 1-year (8, 9). In a previous study including patients with AF who were at "early" stable period from PCI (immediate after 1-year), OAC plus SAPT seemed to be more effective than OAC monotherapy, without a difference in safety (8). In another previous study enrolled AF patients who were stable for more than 1-year after PCI, the mean time difference between the last PCI and the index date was 24 ± 18 months (9). OAC monotherapy showed similar efficacy to OAC plus SAPT and was associated with a lower risk of hospitalization due to bleeding compared to OAC plus SAPT. Neither net clinical benefit nor survival benefit of OAC monotherapy was documented.

Considering the results of previous studies and the trade-off of ischemic risk and bleeding risk after PCI (8–10, 24), the clinical benefits of OAC monotherapy over OAC plus SAPT may differ depending on how long it has elapsed since a year from PCI. However, there have been no studies attempting to analyze whether the benefit of treatment varies with the elapsed time after PCI in RCTs or observational studies. Recently, a *post-hoc* analysis of AFIRE study including patients who had undergone PCI has been reported which showed that in the PCI subgroup, the main results were consistently observed that rivaroxaban monotherapy was associated with lower risks of the primary efficacy and safety endpoints, compared to combination therapy (25). The median time from PCI to index date was 48 (IQR, 21–91) months, and most were more than 24 months after PCI. When analyzing the efficacy and safety endpoints over time after PCI, the differences in efficacy endpoints were not significant according to the time after PCI; however, in terms of safety endpoint, the longer the time elapsed after PCI, the more the OAC monotherapy benefits were accentuated compared to OAC plus SAPT. Overall, the net clinical benefit also became more evident with the longer time between PCI and enrollment. Our study showed consistent results through a large real-world observational cohort that the benefit of OAC monotherapy is more certain to reduce bleeding risk in patients with AF that are sufficiently stable after PCI.

While two RCTs have been reported (6, 7), more evidence is still needed for AF patients with stable CAD, and the results of the EPIC-CAD trial (NCT03718559), are awaited (26).

Study limitations

First, there is a possibility of residual confounding, although we ascertained available variables and matched the balance between the two treatment groups. Among possible confounders, these data did not include information about the characteristics and numbers of coronary stents, the complexity

of PCI procedure, and the presence of remaining significant coronary lesions. Second, this study is an observational study, which would include more comprehensive patients than RCTs in which patients are highly selected, but patients who died within 1 or 3 years or who received repeated PCI were excluded from the study design. However, if a physician considers prescribing patients without additional coronary events for several years after PCI, our data can be applied practically. Third, OAC monotherapy and OAC plus SAPT do not represent the majority of prescriptions in AF patients with stable CAD in Korea, who are often prescribed with antiplatelet agents only (22, 23). Therefore, the number of study subjects is limited, and it should be considered when interpreting the results that patients who received OAC prescriptions in real-world practice were selected by physicians. Fourth, the Korean HIRA database did not include laboratory findings such as serum creatinine. Therefore, to indirectly measure renal dysfunction, we included "renal diseases" as one of the baseline covariates defined using the operational definition adopted in previous observational studies based on the claims database (14, 22, 23). Fifth, among DOAC users in OAC plus SAPT group, a higher proportion of patients were prescribed reduced dose DOAC than those in the OAC monotherapy group. In previous observational studies and even in the RCT (6, 9), reduced dose DOAC was preferred in OAC plus SAPT group. In this dataset, patients' body weight and creatinine clearance were not available, thus, DOAC dosing adherence could not be evaluated. Notwithstanding the higher proportion of reduced dose DOAC in the OAC plus SAPT group than in the OAC monotherapy group, a combination of OAC and SAPT still showed a higher risk of bleeding than OAC monotherapy. Sixth, two types of antiplatelet agents (aspirin and clopidogrel) were prescribed for the most of patients in the OAC plus SAPT group. Although which antiplatelet agents are better than others also can be an important question for clinical practice, the primary objective of this study was the comparison between OAC and OAC plus SAPT in patients with AF and stable CAD. The number of the study population was not sufficient to explore the better antiplatelet type or the better OAC type for these populations. Further clinical or observational studies are needed to answer this question.

Conclusion

Oral anticoagulant monotherapy may be a comparable choice for patients with AF and stable CAD compared to OAC plus SAPT. In patients with stable CAD more than 3-year after index PCI, OAC monotherapy would be a better choice, being associated with less major bleeding and a positive net clinical benefit.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Seoul National University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

S-RL and J-HJ: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing – original draft, figures and tables generation, and writing – review and editing. E-KC: conceptualization, formal analysis, investigation, methodology, resources, validation, funding acquisition, project administration, supervision, and writing – review and editing. S-WL, SK, and J-SP: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, and validation. JK, K-DH, KP, SO, and GL: conceptualization, investigation, methodology, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

E-KC: research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd., Medtronic, Samjinpharm, Seers Technology, and Skylabs. GL: consultant

and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.991293/full#supplementary-material

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Fuwei Liu,
Ganzhou People's Hospital, China
Jinzhu Hu,
Nanchang University, China

*CORRESPONDENCE
Zhi-Chun Gu
guzhichun213@163.com
Pei-Zhi Ma
mpeizhi@126.com

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Prevalence, risk factors, and prediction of inappropriate use of non-vitamin K antagonist oral anticoagulants in elderly Chinese patients with atrial fibrillation: A study protocol

Shu-Juan Zhao[1], Bo-Ya Chen[1], Xue-Jiao Hong[1], Yin-Ping Liu[1], Hai-Xia Cai[1], Song Du[2], Zhi-Chun Gu[3]* and Pei-Zhi Ma[1]*

[1]Department of Pharmacy, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, School of Clinical Medicine, Henan University, Zhengzhou, China, [2]Department of Cardiovascular Medicine, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, School of Clinical Medicine, Henan University, Zhengzhou, China, [3]Department of Pharmacy, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Atrial fibrillation (AF) is an arrhythmia that is prevalent globally, and its incidence grows exponentially with aging. Non-vitamin K antagonist oral anticoagulants (NOACs) have been developed in recent years, and it challenges the supremacy of warfarin for thromboembolism prophylaxis in AF. Nevertheless, there are limited data specifically evaluating the real-life use of NOACs in elderly patients with AF in China.

Methods: This is a national, multicenter, non-interventional, cross-sectional study that enrolls patients with AF aged 75 years and above from 31 institutions across China. Data were collected using the Hospital Information System. The primary outcomes include (1) profiles of NOAC use in the elderly; (2) frequency of inappropriate NOAC use based on guidelines and approved labeling recommendations; (3) exploring potential risk factors related to NOACs inappropriate use; and (4) creating a prediction tool for inappropriate NOACs use.

Conclusion: The results of this study reveal the prevalence, risk factors, and corresponding prediction tool of inappropriate NOACs use in older patients with AF in China, as well as provide valuable insights into the clinical application of NOACs in high-risk populations in the real-world setting.

Clinical trial registration: www.ClinicalTrials.gov, identifier: NCT 05361889.

KEYWORDS

atrial fibrillation, elderly, non-vitamin K antagonist oral anticoagulants, drug utility, real-world, risk factors, prediction, machine learning

Introduction

Atrial fibrillation (AF) is an arrhythmia that is prevalent globally, and its incidence grows exponentially with aging (1). AF increases the risk of stroke and its sequelae. It also leads to severe complications, such as impaired quality of life, heart failure, dementia, disability, and even death. More frequent hospitalization and treatment of these complications substantially increase the economic burden of the disease (2–5).

Oral anticoagulants (OACs) are the cornerstone of stroke and/or systemic embolism (SE) prevention for patients with non-valvular atrial fibrillation (NVAF) (6, 7). Although dose-adjusted warfarin has been the primary treatment for oral anticoagulation for decades, non-vitamin K antagonist oral anticoagulants (NOACs) have been developed more recently and have challenged the supremacy of warfarin for thromboembolism prophylaxis in NVAF (8–11). NOACs comprise dabigatran (factor IIa inhibitor), rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors), and each of these agents has been proven to be equivalent to or even better than warfarin in terms of effectiveness and safety for stroke prevention in NVAF (12). Current guidelines recommend NOACs as the first-line OAC agents, including for the older adult population (6, 7, 12, 13).

Although advanced chronological age by itself is not a contraindication for anticoagulation in AF, in the real clinical context, the appropriate use of NOAC prescriptions is still challenging for several reasons. First, on the subjective side, many clinicians are hesitant to comply with approved NOAC dosing recommendations for older adults due to concerns posed by frailty, liver or kidney function impairment, polypharmacy, complex comorbidities, prior falls, contraindications, and history of bleeding or potential bleeding risk (14). Second, dosages may be varied to account for ethnic factors. For instance, Asian patients with AF tend to be leaner and shorter and have a greater bleeding risk. This population often receives off-label dose-reduced NOAC more frequently than in Western countries (15). Third, approval was granted by the NOACs' National Medical Products Administration (NMPA) at specific doses as adjusted for age, renal function, body weight, or concomitant administration of other drugs. Therefore, the optimal use of NOACs depends on a thorough understanding of drug labels and the knowledge of definitive guidelines and consensus opinions (16). Finally, some hospitals do not have reliable access to important NOAC formulations (17), precluding their rational use. In previous studies, such inappropriate use of NOACs was problematic because it is associated with adverse events and harmful clinical outcomes, including an increased risk of stroke, thromboembolism, cardiovascular hospitalizations, bleeding, and even all-cause mortality (18, 19).

Since most available data on NOAC practices have been established within the framework of a cardiology setting and in the general population, data on Chinese-specific real-life NOACs use, such as in older adults, are underrepresented. Of note, older Chinese individuals with AF account for a high percentage of the total number of patients with AF. This population is considered to be more susceptible to bleeding. The net clinical benefit of vitamin K antagonist (VKA) use in older adults with AF is barely satisfactory (20). Therefore, collecting data on case mix, clinical characteristics, and treatment for older adults with AF is valuable for improving the management of OAC use in real-world practice. In addition, some studies explored risk factors that influence the appropriateness of NOACs. However, they did not establish the related prediction model (21, 22). Therefore, we will conduct a study to (a) investigate profiles of NOAC use in older individuals, (b) determine the rate of inappropriate NOAC use, (c) explore potential risk factors related to inappropriate NOAC use, and (d) conduct a model for inappropriate use of NOACs.

Materials and methods

Data sources

This study is proposed as a national, multicenter, non-interventional, cross-sectional study. Individual patient data will be obtained from the ReAl-life multIceNter outcomes registry for Better antithrOmbotic strategies in patients With AF (RAINBOW-AF), an ongoing national AF registration conducted at 31 secondary- or tertiary-care hospitals in China. The purpose of the RAINBOW-AF registry is to collect medical records data of contemporary patients with AF and to determine the relationship between comprehensive assessment and better anticoagulation outcomes in patients with AF. In this study, we will include older adults (aged ≥75 years) who will be receiving a NOAC for NVAF. Considering that this population is regarded as high-risk in the stroke risk-stratification tool (CHA_2DS_2-VASc score of at least 2) for NVAF, all selected patients will have strong indications for anticoagulation. The study initiative will be performed based on the Hospital Information System (HIS) (Figure 1). As part of the assessment, this study will be applied for the expansion and spread of a quality promotion initiative for a better NOAC strategy.

Site selection

The study will be carried out using data given by inpatients from 12 provinces, two municipalities, and one autonomous region across mainland China, with a focus on regions and medical staff features. Suitable site enrollment will be adopted to guarantee geographic heterogeneity and diversity across

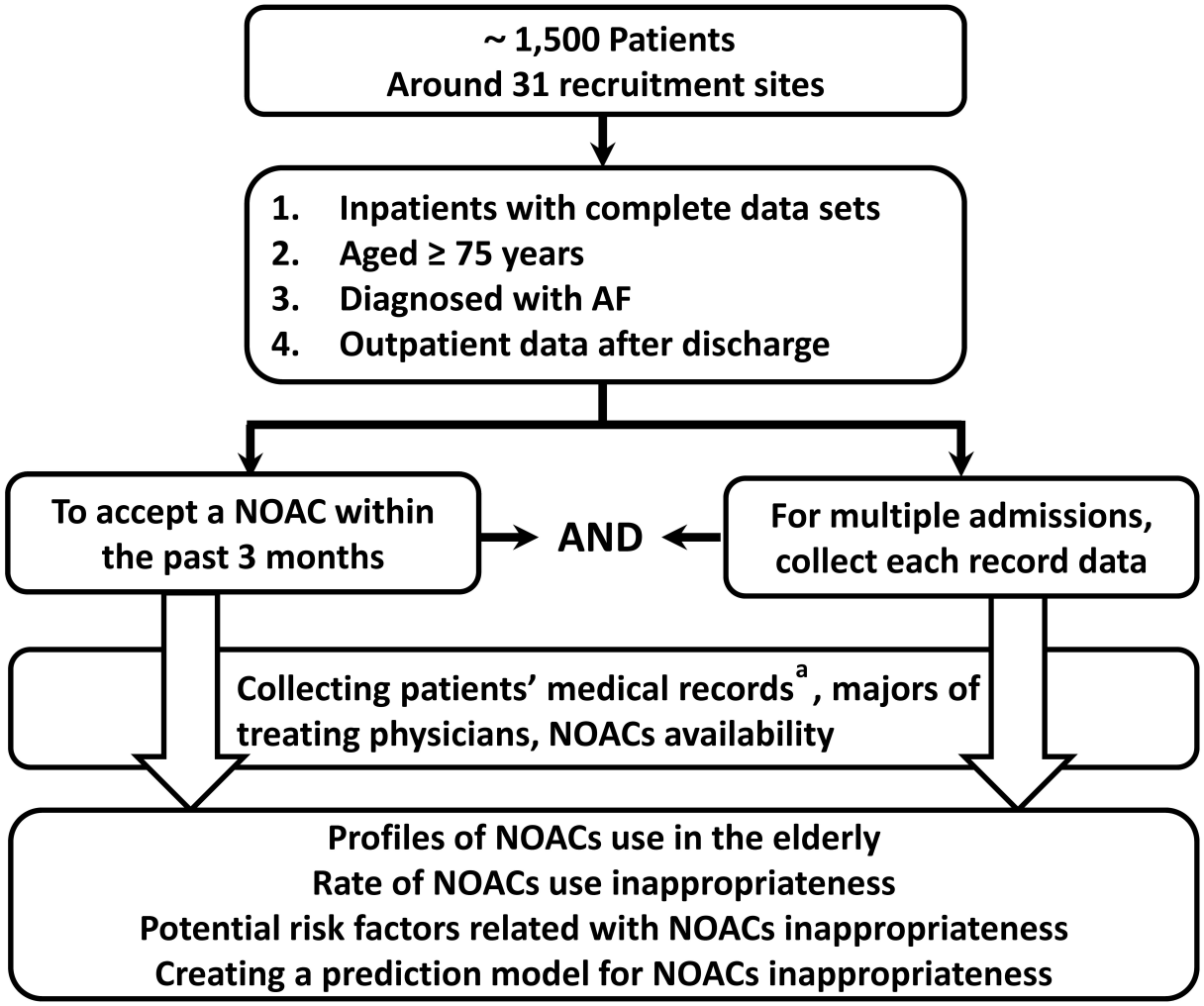

FIGURE 1
Design schematic of this registry. NOAC, non-vitamin K antagonist oral anticoagulant. a: Including the following details: basic information, disease information, history, latest laboratory data, co-administrations with NOACs, risk factors for thromboembolism (CHA_2DS_2-VASc score), and risk factors for bleeding (HAS-BLED score).

practice categories (e.g., secondary graded and tertiary hospitals; teaching and general hospitals) and prescriber type (e.g., general practitioner, neurologist, cardiologist, electrophysiologist, and other specialists). In this way, we expect to register a representative sample of patients with NVAF in mainland China; this will limit any bias introduced by the selection of patient criteria, physician specialty, or extent of experience. Around 31 recruitment sites will be activated to select participants for the study.

Patient recruitment criteria

Eligibility criteria include the following: inpatients with complete data sets; age ≥75 years; diagnosis of AF confirmed by electrocardiogram; use of Holter monitor, pacemaker, implantable device or clinic note, or hospital record of such intervention; or documentation of NOAC therapy for AF regardless of prescriber within the past 3 months. For multiple related admissions, each admission data will be recorded to avoid an omission. To minimize the deviation in the selection of the population and to obtain more sufficient information, the outpatient follow-up data after discharge will also be documented using HIS (Table 1).

Exclusion criteria include NVAF due to reversible causes (e.g., thyroid disease, postoperative AF, and pulmonary embolism), having an additional indication for anticoagulation treatment apart from AF (e.g., venous thromboembolism and hip/knee replacement surgery), bleeding history in critical organs, current participation in an ongoing clinical trial of

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Inpatients with complete data sets. To minimize the deviation in the selection of the population and obtain more sufficient information, the outpatient follow-up data after discharge will also be documented *via* Hospital Information System	• AF resulting from reversible causative factors (e.g., thyroid disease, postoperative AF, pulmonary embolism)
• Aged ≥ 75 years	• Have additional indication for anticoagulation treatment apart from AF (e.g., venous thromboembolism, hip/knee replacement surgery, left atrial/ventricular thrombus)
• Diagnosed with AF (e.g., by electrocardiogram, Holter monitor, pacemaker, implantable device, or a history of these interventions in any clinic note or hospital record)	• Bleeding history in critical organs (e.g., intracranial, intraocular, or gastrointestinal bleeding)
• To accept a prescription of NOAC therapy for AF whoever the prescriber within the past 3 months (with the rationale that such patients may have exceptional circumstances preventing long-term anticoagulation or lack of an appropriate indication for long-term anticoagulation)	• Current participation in an ongoing clinical trial of NOAC anticoagulation for AF
• For multiple related admissions, each admission data will be recorded to avoid an omission. For example, patients with variable bleeding factors that could be a relative contraindication or an absolute contraindication that could still be inappropriately used	• Illogical data, missing or insufficient data

AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

NOAC anticoagulation for AF, and incomplete information (illogical data and missing or insufficient data); any patients with such history will also be excluded.

Ethics and informed consent

The study will be organized and coordinated by the Henan Provincial People's Hospital. The study protocol complies with Good Clinical Practice standards for drugs and the ethical guidelines specified in the revised Declaration of Helsinki (2013). The Henan Provincial People's Hospital Institutional Review Board has approved the RAINBOW-AF registry (approval number: 2022-0406), and the trial was registered at ClinicalTrials.gov (NCT 05361889). Data extracted from medical records will be de-identified and anonymized before analysis; therefore, informed consent is waived for this study. This study will also follow the STROBE reporting checklist and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines.

Data collection

Data will be entered into a web-based case report form, enabled with dynamic data reviews for patient features, expected data ranges, and mandatory fields. It will be derived primarily from three different sources: patients' electronic medical records (including demographics, clinical characteristics, medical management, laboratory measurements, imaging parameters, and drug information), the grade level of treating physicians, referring to the clinical expertise or academic background of clinicians, and the availability of NOACs at each hospital. The specific details include participants' sex, age, body weight, lifestyle, comorbidities (such as diabetes, coronary heart disease, and heart failure), history, latest laboratory data, and risk factors for thromboembolism and bleeding. In addition, co-administration of drugs (such as antiplatelet agents and antiarrhythmic therapy), appearances after NOAC treatment (incidence of inappropriate use), the expertise of physicians, and NOAC availability from that institution will also be documented (Table 2).

Evaluation of the appropriate NOACs use

Different nations do not always adopt the standard indications for NOAC prescription. Local policies, such as formulary committees, regulatory approval, and cost-effectiveness, all influence NOAC labeling recommendations (23). In this study, we will adopt an adaptive design to account for a summary of product characteristics, and analyze prevalent NOAC strategies based on indications, NOAC selection, or dosages (Figure 2). We use the recommendations given by NMPA for each agent and the 2021 European Heart Rhythm Association (EHRA) practical guide on the use of NOACs for patients with AF (24). Patients for whom the selected NOAC was

TABLE 2 Details of data collection.

Data collection	Interpretation
• Basic information	Participants' sex, age, body weight, marital status, lifestyle (current smoking and drinking status), educational status, place of residence (rural or urban)
• Disease Information	Type of AF, comorbidities (correlate with stroke and bleeding risk, e.g., anemia, MI, PAD), procedures or surgical history (PCI, CABG, or RFCA)
• History	History of thromboembolism and related hemorrhagic events (major bleeding is defined based upon ISTH criteria and incidences apart from major bleeding are considered as non-major bleeding), fall history
• Latest laboratory data	Serum creatinine levels, hemoglobin, bilirubin, liver function (Child-Pugh score), and renal function (CrCl, calculated using Cockroft-Gault formula)
• Co-administration with NOACs	NOAC medication type, antiplatelet agent, interacting combination medications with NOACs, such as antiarrhythmic therapy, itraconazole, ketoconazole, ritonavir, etc.
• Risk factors for thromboembolism (CHA_2DS_2-VASc score)	CHA_2DS_2-VASc score is a rating of risk for stroke in patients with AF, items of 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, Age 65–74 years, sex category [female], and 2 points each for a history of a stroke, TIA, or age $\geq$ 75 years)
• Risk factors for bleeding (HAS-BLED score)	HAS-BLED score is a rating of risk for bleeding in patients with AF, 1 point each for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age 65 years or greater, drugs/alcohol concomitantly
• Expertise of prescriber	Cardiologist or not
• NOACs availability from that institution	Some institutions do not have access to certain NOACs, which can influence the NOAC inappropriateness

AF, atrial fibrillation; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; RFCA, radiofrequency catheter ablation; ISTH, International Society of Thrombosis and Hemostasis; CrCl, creatinine clearance rate; TIA, transient ischemic attack; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

contraindicated can be categorized as inappropriate use. If there exist no absolute contraindications, the protocol can evaluate appropriateness according to patient-specific features, like age, weight, renal function, Child-Pugh classification, specific drug–drug interactions, hemoglobin level, and bleeding risk. In cases of discrepancy between the EHRA recommendations and the NMPA recommendations, we adopt the NMPA-approved label recommendations as the standard for determining the appropriateness (Table 3). Patients will be classified as either (a) NOAC-appropriate (rational use of NOAC according to the standardized criteria) or (b) NOAC-inappropriate (irrational use of NOAC according to the standardized criteria).

Since apixaban has not been fully studied in Chinese populations, the NMPA did not approve the NVAF indication for apixaban; thereby, we have excluded it from this study. Rivaroxaban, given 15 mg daily (or 10 mg, based on creatinine clearance rate [CrCl]), in combination with clopidogrel, was also used in patients with AF and recent percutaneous coronary intervention (PCI) or acute coronary syndromes (ACS) in the PIONEER AF-PCI trial. Therefore, we considered that both doses are appropriate for such patients in our study. The NMPA recommends a daily dose of 220 mg for dabigatran, which can be given to patients with CrCl 30–50 ml/min, aged $\geq$75 years, or with increased bleeding risk. The NOAC prescription was deemed reasonable for patients aged $\geq$75 years.

Quality control

Standard criteria for NOAC appropriateness were drafted by the two highly experienced pharmacists (S-JZ and B-YC) after obtaining consent from all collaborators. A steering committee, comprising of an independent panel of experts (organized by Z-CG) blinded to RAINBOW-AF data independently checked the entire algorithm program (including recommendation-consistency, under-dosing, or over-dosing) to validate its results. A standard electronic data capture form was devised to accumulate data. To explain each data element as clearly as possible, consensus must be met prior to the entry of study data to discuss the specifics. RAINBOW-AF health personnel who are involved in the care of the study participants will receive rigorous training with periodical quality control inspection prior to the study. All study outcomes are defined based on the diagnosis at the first discharge to avoid misclassification. Manual chart review results must conform to the program of the algorithm revealed above in all cases. Data monitoring will be implemented by the coordinating administrators to determine the integrity and accuracy of data input.

Primary outcomes

The primary outcomes include (a) profiles of NOAC use in the elderly; (b) the rate of inappropriate NOAC use

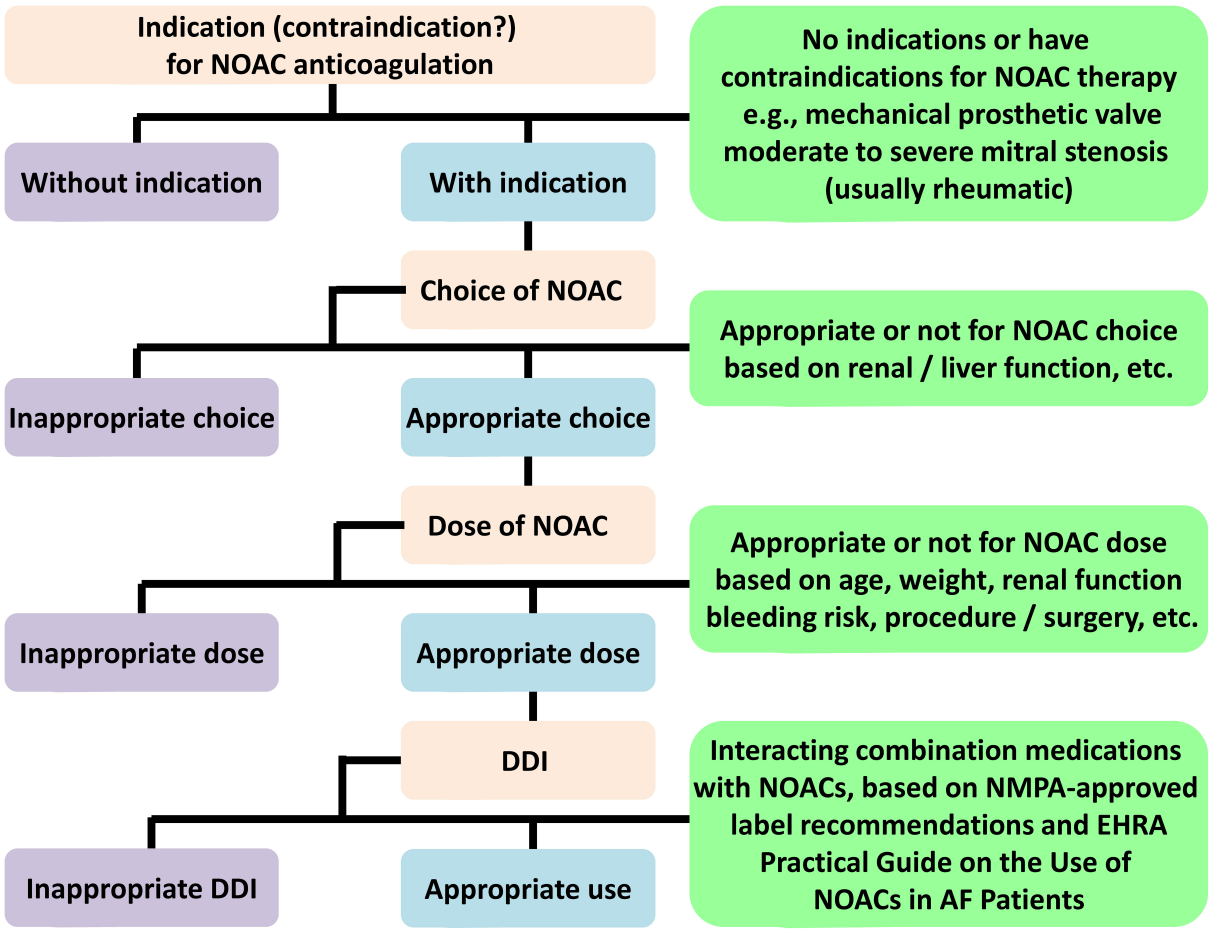

FIGURE 2
NOACs evaluation flowchart. NOAC, non-vitamin K antagonist oral anticoagulant; DDI, drug-drug interaction; NMPA, National Medical Products Administration; EHRA, European Heart Rhythm Association; AF, atrial fibrillation.

according to the guidelines and labeling recommendations; (c) potential risk factors related to inappropriate NOAC use; and (d) creation of a prediction model for inappropriate NOAC use. First, we will try to identify the characteristics of participants who were given appropriate NOAC agents and those who were not from a number of several variables (e.g., demographics, clinical, management, expertise of treating clinicians, NOAC availability, and the prevalence of potentially inappropriate NOAC use). Next, using this binary outcome, a logistic model will be fitted to quantify risk factors correlated with these variables with selections of NOAC-inappropriate regimens. Lastly, we will create a prediction model using both logistics and machine learning method for predicting inappropriateness in the entire cohort.

Sample size calculation

This study is designed as a multicenter cross-sectional study. Assuming that each institution can treat 300–500 patients with AF per year, patients over 75 years old account for 20–30% and the rate of NOAC use is ∼50–70%, with a 2% error range and 95% confidence interval (CI). The drop-out rate is not considered in the calculation as the primary outcomes will be evaluated during hospitalization; the drop-out rate is expected to be very low. To get a representative result, we calculated that a sample size of 1,500 patients would be sufficient. Since this is an event-driven study (the rate of inappropriate NOAC use), the total number of patients may change as necessary according to the cumulative number of target events.

TABLE 3 Approved dosing regimens for the NOACs package inserts for NVAF in the Mainland China.

Medication	Regulations from the NMPA (Mainland China)
	NMPA (Mainland China) (Revised: 06/2020)
Dabigatran	• Full dose: 150 mg twice daily
	• 110 mg twice daily, if:
	-age ≥ 80 years
	-concomitant verapamil
	• Daily dose of 300 mg or 220 mg according to an individual evaluation of the thromboembolic risk and bleeding risk:
	-age 75–80 years
	-moderate renal impairment (CrCl 30–50 mL/min)
	-gastritis, esophagitis, or gastroesophageal reflux
	-other increased bleeding risk [a]
Rivaroxaban	NMPA (Mainland China) (Revised: 07/2020)
	• Full dose: 20 mg once daily with food when CrCl ≥ 50 mL/min
	• 15 mg once daily with food, if:
	-CrCl 15 – 49 mL/min
Apixaban	NMPA (Mainland China) (Revised: 02/2019)
	• Not approved
Edoxaban	NMPA (Mainland China) (Revised: 07/2021)
	• Full dose: 60 mg once daily
	• 30 mg once daily with one or more of the following clinical factors:
	-CrCl 15 – 50 mL/min
	-body weight ≤ 60 kg
	-concomitant use of the following P-gp inhibitors: ciclosporin, erythromycin, dronedarone, or ketoconazole

NVAF, non-valvular atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulants; NMPA, National Medical Products Administration; P-gp, P-glycoprotein; CrCl, creatinine clearance rate. a: Other increased bleeding risks include: Strong P-gp inhibitors; mild to moderate P-gp inhibitor co-medication (e.g., quinidine, verapamil, ticagrelor, and amiodarone); low body weight (< 50 kg); acetylsalicylic acid (ASA) and other platelet aggregation inhibitors, e.g., clopidogrel; selective serotonin norepinephrine re-uptake inhibitors (SNRIs), selective serotonin re-uptake inhibitors (SSRIs), and non-steroidal anti-inflammatory drugs (NSAID); other medicinal products that may impair hemostasis; functional platelet defects or thrombocytopenia; major trauma and recent biopsy; and bacterial endocarditis.

Model development process

Predictors and outcomes

Based on demographics, clinical, medical management, patient characteristics, CHA_2DS_2-VASc score, HAS-BLED score, the expertise of treating physicians, NOAC availability, and clinical relevance, we can identify the variables potentially related to inappropriate NOAC use. Variables above will be extracted from the medical records in each participating institution using an *a priori* designed form. The target outcome will be NOAC inappropriateness. Patients with more than 30% missing data will be excluded. For patients with partially missing data, the Random Forest (RF) algorithm will be used for data-level computation.

Data separation and feature filtering

In this process, the data will be randomly divided into training and test sets in a ratio of 8:2, which will be used for the model establishment and verification, respectively. Feature selection will be performed using the Sequence Forward Selection algorithm based on RF. For each group, the algorithm will search from the empty set and subsequently add one variable to the feature subset each time to achieve an optimal performance, which is measured by the F1 score.

Machine learning model establishment, evaluation, and interpretation

Both linear and non-linear machine learning models will be applied to the sets, which include logistic regression, RF, support vector machine, gradient boosting tree (such as XGBoost, LightGBM, Adaboost, and Catboost), and attentive interpretable tabular learning (TabNet). The prediction performance of all models will be evaluated through five measures (area under the receiver operating characteristics [AUROC] curve, precision, recall, F1 score, and accuracy). The acceptably performing machine learning models will be selected according to AUROC. Next, we will calculate the importance scores of the features using the above-chosen algorithms. Features with higher importance scores are more closely related to the accurate prediction of NOAC inappropriate use. Finally, features ranked

in the top 50% based on normalized importance scores in selected models will be determined as major predictors and depicted in radar plots.

Statistical analyses

Categorical data will be presented as frequencies and be compared by Chi-squared or Fisher's exact test as appropriate. Continuous data will be reported as mean ± standard deviation or median and interquartile range (IQR) and analyzed by either Student's *t*-test or the Mann–Whitney *U* test. In this study, data will be extracted and summarized using Excel 2016. Univariate and multivariate logistic regression analyses will be applied to ascertain the correlation between candidate variables and NOAC inappropriate use. Multicollinearity between the variables will be shifted based on the variance inflation factor (VIF; VIF $>$ 5 is considered strong collinearity) (25). Two criteria will be considered necessary for a variable to be incorporated into the final prediction model: (a) a univariate *p*-value indicative of NOAC prescription inappropriateness $\leq$0.05 and (b) a plausible connection with risk factors from NOAC inappropriate prescriptions based on previously published research. The risk tendency of inappropriate NOAC use among risk stratifications will be evaluated by the Cochran-Armitage trend test (26). Machine learning algorithms will be built based on the Scikit-learn package (version 0.22.2). Interaction analyses will be used to compare predictive performance between machine learning models. Statistics will be performed employing STATA software (version 12.0, Stata Corporation LLC, College Station, United States), and a $p < 0.05$ will be considered to be statistically significant.

Discussion

This is a national, multicenter, non-interventional, cross-sectional study driven by pharmacists to explore NOAC use appropriateness in older adults with AF in the real-world setting, which includes the prevalence of potentially inappropriate NOAC use and relevant influencing factors, and to derive a clinically practical prediction model for predicting the risk of inappropriate NOAC use based on explored risk factors. The prediction model will be applied in routine clinical practice to identify patients potentially at risk due to inappropriate NOAC use and to optimize anticoagulation management for older adults with AF.

The research data will come from the RAINBOW-AF registry, which will function as a post-marketing surveillance study after the transition from a single available traditional OAC (warfarin) to the target-specific NOAC agents. The RAINBOW-AF registry enables aggregation and integration of information on OAC use, safety, and effectiveness from 31 medical institutions in 7 different regions of China (East, South, Central, North, Northwest, and Northeast China and Southwest Asia). From the cohort perspective, baseline characteristics, contemporary anticoagulant management practices, and treatment outcomes will be described in the setting of real clinical scenarios in Chinese patients with AF. A remarkable feature of the RAINBOW-AF register is that it includes patients from all levels of medical institutions in mainland China, including those from secondary-graded hospitals or general departments. Thus, patients can be well-represented at all levels in mainland China, regardless of anticoagulant strategies. We plan to include patients who have been discharged after only a short stay in the hospital and their outpatient follow-up information because these groups of patients also frequently take NOACs.

High-quality anticoagulant treatment is crucial in guaranteeing the effectiveness and safety of OAC administration in AF patients. The benefits of OACs in NVAF may be impossible to achieve if anticoagulant regimens are prescribed inappropriately (27). As NOAC use has become more pervasive, off-label prescribing has become a global issue. Several studies have outlined the adverse clinical consequences of off-label prescribing. The ENGAGE AF-TIMI 48 trial illustrated the outcome of under-dosing of edoxaban (11). The edoxaban 30/15 mg group posed a significantly higher ischemic stroke risk when compared to the well-controlled vitamin K antagonist group; this resulted in the disapproval of this dosing regimen for clinical application (11). In the ORBIT-AF II registry, off-label doses of NOACs presented an increased risk for adverse events than the recommended NOAC dosage protocols (27). In particular, NOAC over-dosing was associated with increased all-cause mortality, while NOAC under-dosing was associated with higher rates of hospitalization for cardiovascular conditions (27). Another study demonstrated that inappropriate NOAC prescriptions were more likely to occur in the older adult population (28). This is the most worrisome finding because the risk of stroke increases significantly with age. Inappropriate dosage exposes high-risk patients to potential hazards of disabling or even fatal strokes.

Previous studies report relevant risk factors for inappropriate NOACs use. In the SAGE-AF (Systematic Assessment of Geriatric Elements in Atrial Fibrillation) cohort, a potentially inappropriate NOAC dose was prescribed to nearly a quarter of older adults. This stemmed from patients being older, having poor renal function, and higher CHA_2DS_2-VASc scores (16). Another Korean study found that NOAC label adherence was approximately 60%, and the risk factors of NOAC under-dosing were independently related to old age ($\geq$75 years), female sex, lower body weight ($<$ 60 kg), renal impairment (CrCl $<$ 50 ml/min), hypertension, previous

stroke/transient ischemic attack (TIA)/thromboembolic events, bleeding history, and concomitant dronedarone or antiplatelet agent use (29). In the ORBIT-AF II registry (18), compared with those whose NOAC dose was appropriately reduced, patients accepting inappropriate dose reductions were younger and had lower bleeding risk scores. Physician assessment may have a strong impact on inappropriate NOAC dosing; however, there may also be drug-specific factors. In Mainland China, information on practice patterns of NOAC administration and the use of NOACs for licensed indications in older patients remains scarce.

Currently, few studies have focused attention on the prediction model of the risk factors of NOAC inappropriateness in elderly patients with AF. Considering that inappropriate NOACs doses are prescribed to a fair percentage of older patients with AF, with most being under-dosed, the development of a practical prediction model with reliable predictability is of great value. To our knowledge, this will be the first study to establish a feasible prediction model for predicting inappropriate NOAC use in older Chinese patients with AF. In the prediction model of probabilistic estimation, we will combine the above independent predictors and the risk factor variables from previously published research. Accordingly, we believe that the prediction model could be applied as a simpler and more effective tool for clinical decision-making for elderly patients with AF.

Strengths and limitations

The main strengths of this study are believed to be as follows: First, we will include data from a national, comprehensive, and diversified cohort of older patients with AF and will perform in-depth phenotyping of NOAC use to help refine best practices for older adults with AF. Second, most studies evaluating the appropriateness of NOAC primarily focus on dosage in the general population, while our study will evaluate the rationale of NOAC decision-making for older adults from multiple perspectives: patient factor (patients' demographics and categories of treating physicians) and institution layer (the availability of certain NOACs in that center). Additionally, this study will build the first prediction model to predict the inappropriateness of NOAC in older Chinese patients with AF.

Inevitably, this study has some inherent limitations. First, due to the inherent restriction placed by its design, this study will not evaluate the outcomes of older adults with AF treated with inappropriate anticoagulation therapy, nor will there be a follow-up for efficacy evaluation. Nevertheless, its primary purpose is to establish a reliable prediction model in older adults with NVAF receiving NOAC. Second, data will be dependent on the quality of medical record extraction, so that residual and unmeasured covariates among the associated variables may influence the results, even after strict measurement and recording of crucial variables and avoidance of confounding factors. Last, the prediction model needs independent validation in other cohorts to establish its utility for clinical use, not least in older outpatients taking NOACs.

Conclusion

This study will provide unique and valuable data on the feasibility of NOAC use in older adults with AF. This will be the first study to establish a prediction model to predict inappropriate NOAC use in this high-risk population.

Ethics statement

The studies involving human participants were reviewed and approved by Henan Provincial People's Hospital Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

P-ZM and Z-CG are the guarantors of the entire manuscript. S-JZ and Z-CG participated in the study conception and design, drafting, and critical revision. S-JZ and B-YC contributed to the project administration. All authors contributed to the acquisition, analysis, and interpretation of data, and they agreed to be held accountable for all aspects of the work and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Jinzhu Hu,
Nanchang University, China
Ye Zhu,
Yangzhou University, China

*CORRESPONDENCE
Liangxi Yuan
yuanlx116@163.com

†These authors have contributed equally to this work and share first authorship

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Efficacy and safety evaluation of rivaroxaban vs. warfarin among non-valvular atrial fibrillation patients undergoing lower extremity revascularization

Qingyuan Yu[1†], Cheng Chen[2†], Jinyan Xu[1†], Yu Xiao[1], Junmin Bao[1] and Liangxi Yuan[1*]

[1]Department of Vascular Surgery, Changhai Hospital, Navy Military Medical University, Shanghai, China, [2]ChangZheng Hospital, Navy Military Medical University, Shanghai, China

Introduction: The efficacy and safety of antithrombotic strategies remain uncertain in patients with atrial fibrillation undergoing lower-extremity revascularisation.

Materials and methods: Between January 2011 and November 2021, 319 patients with atrial fibrillation after lower-extremity revascularisation received rivaroxaban or warfarin treatment as anticoagulation regimens with different antiplatelet therapy strategies. The primary efficacy outcome was the composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, clinically driven target lesion revascularisation, and death from vascular causes. The safety outcomes were major bleeding events according to the International Society on Thrombosis and Haemostasis classification criteria.

Results: A total of 178 and 141 patients received rivaroxaban and warfarin treatments, respectively, after revascularisation with or without antiplatelet regimens. The incidence of the primary efficacy outcome at 36 months in the rivaroxaban group (44 patients, 24.7%) tended to be lower than that in the warfarin group (43 patients, 30.5%) (hazard ratio, 0.870; 95% confidence interval, 0.565–1.339; P = 0.527). The incidence of the secondary efficacy outcomes decreased in the rivaroxaban group (56 patients, 31.6%) compared with that in the warfarin group (61 patients, 43.2%). Major bleeding events occurred in three patients (1.7%) in the rivaroxaban group and five patients (3.5%) in the warfarin group; no significant difference in fatal or intracranial bleeding was observed between the groups.

Conclusion: This study describes practical experience regarding the use of rivaroxaban and warfarin in patients with peripheral arterial disease

complicated by non-valvular atrial fibrillation following endovascular intervention. The efficacy and safety outcomes do not differ significantly between rivaroxaban and warfarin.

KEYWORDS

oral anticoagulants, nonvalvular atrial fibrillation, peripheral arterial disease, lower extremity revascularization, revascularization

Introduction

The prevalence of atrial fibrillation (AF) in patients with peripheral arterial disease (PAD) is 10–13% (1, 2). AF and PAD have similar epidemiological patterns and risk factors that are associated with increased cardiovascular (CV) events and mortality. It has been reported that patients with AF and PAD have a higher incidence of adverse events; among them, the presence of PAD is significantly associated with a 1.3–2.5-fold increased risk of stroke, and the risk of thrombotic events, including ischaemic stroke, is increased up to 2-fold (3, 4).

The current guidelines recommend oral anticoagulant (OAC) therapy instead of antiplatelet therapy (APT) for patients with AF and PAD; meanwhile, the combination of OAC therapy and APT can be considered for patients with AF and PAD undergoing intravascular revascularisation (3, 5). However, OAC therapy combined with APT may increase severe bleeding, including intracranial bleeding (4, 6). To guide in the selection of OAC therapy, few studies have investigated the outcome of adverse limb events in patients with AF and concomitant PAD post-procedure receiving OAC or APT regimens; further, it is uncertain whether new oral anticoagulants (NOACs) or warfarin is more effective (7, 8).

Therefore, the aim of this study was to investigate the efficacy and safety outcomes of NOACs compared with those of warfarin in patients with AF and concomitant PAD following endovascular intervention.

Materials and methods

This single-centre retrospective study included all sequential patients who were prescribed rivaroxaban or warfarin after endovascular intervention for chronic lower-extremity arterial occlusive disease or acute embolic thrombus occlusion with concomitant non-valvular atrial fibrillation (NVAF) between January 2011 and November 2021. Patient demographics, comorbidities, lesion characteristics, pre-procedural medications, CHA_2DS_2-VASc score, HAS-BLED score, and procedural details were recorded. The comorbidities included hypertension, diabetes, smoking-related conditions, coronary artery disease, ischaemic stroke, and chronic renal failure.

Patients were excluded when they had significant haemorrhagic transformation, mechanical/prosthetic heart valves, haemodynamically significant mitral stenosis, end-stage renal disease, or a recent stroke or systemic embolic event or were at risk of bleeding or switching between two anticoagulants postoperatively.

Definitions

The CHA_2DS_2-VASc score (age of 75 years or above, 2 points; previous stroke or transient ischaemic attack, 2 points; congestive heart failure, hypertension, diabetes, vascular disease, age of 65–74 years, and female sex, 1 point) was calculated to quantify the risk of thromboembolic events in the patients with AF. The HAS-BLED score [hypertension, renal or liver dysfunction, stroke, history of bleeding, unstable international normalised ratio (INR), age of 65 years or older, antiplatelet drug use, or alcohol use] was calculated to assess the bleeding risk in the patients with AF treated with OACs (9, 10).

Periprocedural anticoagulation regimen

Rivaroxaban was prescribed at a dose of 10 mg, once daily. All patients in the warfarin group were bridged with unfractionated or low-molecular-weight heparin periprocedurally, and their INR was maintained between 2 and 3. The patients were required to take the planned rivaroxaban/warfarin dose and continue antiplatelet drug use after surgery.

Outcomes

Efficacy outcomes

The primary efficacy outcome was the composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, clinically driven target lesion revascularisation (CD-TLR), or death from vascular causes. The secondary efficacy outcomes included the composite

of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, CD-TLR, or death from any cause. The composite of major adverse limb events included acute limb ischaemia, major amputation for vascular causes, and CD-TLR.

Safety outcomes

The primary safety outcome was major bleeding defined by the International Society on Thrombosis and Haemostasis as intracranial or severe bleeding that was sufficient to result in death, surgery, cessation of therapy, dropping of the haemoglobin level to 2.0 g/dL, or transfusion of 2 units of blood (11, 12). Gastrointestinal bleeding was assessed as the secondary safety outcome.

Data collection

Outpatient monitoring of INR was conducted once every week of discharge and the dose of warfarin was adjusted until the value achieve and maintain the therapeutic INR between 2 and 3. All patients were followed up within 30 days after surgery and planned to return every 3 months in the first year after treatment and every 6 months thereafter. Preoperative and postoperative evaluation data included clinical manifestations, symptoms, complications, anticoagulant use, and ultrasound findings. Follow-up imaging was mainly performed using dual-function ultrasound scanning. Computed tomography angiography was performed when symptoms recurred, or more than 50% restenosis was detected on Doppler ultrasound. The clinical secretary conducted a monthly telephone follow-up to assess the incidence of bleeding. The follow-up period was defined as 3 years of discharge or the end date of the study period (31st May 2022), whichever occurred first.

Statistical analyses

All analyses were performed using the SPSS software (version 26.0, Chicago, IL, United States). Continuous data were expressed as means ± standard deviations, categorical data as numbers and percentages, and non-normally distributed data as medians and interquartile ranges. Differences between the two cohorts were compared using the chi-square test and Fisher's exact test for categorical variables and the *t*-test for continuous variables. Statistical significance was set at $P < 0.05$. The event probability was expressed as a Kaplan–Meier estimate of the 3-year cumulative incidence. Factors identified in the univariate analysis ($P < 0.3$) and other variables considered likely to have important prognostic values were tested in the multivariate Cox proportional hazard model, which was used to generate hazard ratios (HRs) and 95% confidence intervals (CIs) (**Supplementary Tables 1**, **2**).

Results

Baseline characteristics

The baseline characteristics were well balanced between the groups (**Table 1**). The median patient age was 80 years, and 47% of the patients were women. Approximately one-third of the patients had atherosclerosis obliterans (39.8%), and two-thirds underwent thrombus embolisation (60.2%). The risk factors were common: 26.3% of the patients had diabetes mellitus; 26.3% had chronic renal failure; and 19.4% were smokers. Approximately 31% of the patients had a previous ischaemic stroke; 30.1% had a previous coronary artery disease; and 69.6% had hypertension. The CHA_2DS_2-VASc and HAS-BLED scores were higher in the rivaroxaban group than in the warfarin group. Approximately 87.8% of the patients had *de novo* lesions, and 62.7% had lesions > 10 cm in length. A total of 55 patients (17.2%) underwent index revascularisation for critical limb ischaemia, and 67.4% underwent thrombus debulking. In terms of pre-procedural medications, 26% received single APT, while 3.8% received dual APT. Post-procedurally, without accounting for anticoagulant treatments, 82.4% received single APT, while 17.6% received dual APT. The median clinical follow-up period was 36 months (interquartile range, 17.5–36 months).

Efficacy outcomes

The rivaroxaban and warfarin groups did not differ significantly regarding the efficacy outcomes (**Figure 1** and **Table 2**). The primary composite outcome occurred in 44 patients in the rivaroxaban group and 43 patients in the warfarin group, and the Kaplan–Meier estimates of the incidence at 3 years were 29.6% and 31.4%, respectively (HR, 0.87; 95% CI, 0.57–1.34; $P = 0.527$) (**Figure 1A** and **Table 2**). The incidence of the first secondary outcome was lower in the rivaroxaban group than in the warfarin group (HR, 0.73; 95% CI, 0.51–1.07; $P = 0.102$) (**Figure 1B** and **Table 2**); the Kaplan–Meier estimates of the incidence at 3 years were 35.5% and 43.6%, respectively. The all-cause mortality was lower in the rivaroxaban group than in the warfarin group (HR, 0.79; 95% CI, 0.49–1.27; $P = 0.331$); the Kaplan–Meier estimates of the incidence at 3 years were 22.3 and 27.9%, respectively (**Figure 1C** and **Table 2**). The incidence of vascular death was higher in the rivaroxaban group than in the warfarin group (HR, 1.07; 95% CI, 0.58–1.98; $P = 0.817$); the Kaplan–Meier estimates of the incidence at 3 years were 14.6% and 13.5%, respectively (**Figure 1D** and **Table 2**). The incidence of major adverse limb events was not lower in the rivaroxaban group than in the warfarin group (HR, 0.72; 95% CI, 0.42–1.42; $P = 0.406$); the Kaplan–Meier estimates of the incidence at 3 years were 15.3% and 17.1%, respectively (**Figure 1E** and **Table 2**). The rivaroxaban and warfarin groups did not

TABLE 1 Baseline clinical characteristics of the patients.

Baseline characteristic	Total(N = 319)	Rivaroxaban(N = 178)	Warfarin(N = 141)	P Value
Median age, years	80.0 (71.0–84.0)	80.0 (66.0–94.0)	81.0 (69.0–93.0)	0.688
Sex				0.198
Male	169 (53.0%)	100 (56.2%)	69 (48.9%)	
Female	150 (47.0%)	78 (43.8%)	72 (51.1%)	
CHA2DS2-VASc score	5.07 ± 1.455	5.09 ± 1.478	5.04 ± 1.431	0.970
HAS-BLED score	2.28 ± 0.968	2.30 ± 0.984	2.25 ± 0.950	0.529
Duration				0.334
Acute	185 (58.0%)	99 (55.6%)	86 (61.0%)	
Chronic	143 (42.0%)	79 (44.4%)	55 (39.0%)	
Diagnosis				0.509
ASO	127 (39.8%)	68 (38.2%)	59 (41.8%)	
Thrombus Embolization	192 (60.2%)	110 (61.8%)	82 (58.2%)	
Lesion characteristics				0.935
De Novo	280 (87.8%)	156 (87.6%)	124 (87.9%)	
Restenosis	39 (12.2%)	22 (12.4%)	17 (12.1%)	
Lesion length				0.559
> 10cm	198 (62.1%)	113 (63.5%)	85 (60.3%)	
< 10cm	121 (37.9%)	65 (36.5%)	56 (39.7%)	
Thrombus Debulking	215 (67.4%)	121 (68.0%)	94 (66.7%)	0.804
Critical limb ischemia	248 (77.7%)	141 (79.2%)	107 (75.9%)	0.478
History of index-limb revascularization	55 (17.2%)	36 (20.2%)	19 (13.5%)	0.113
Risk factors and coexisting conditions				
Hypertension	222 (69.6%)	129 (72.5%)	93 (66.0%)	0.209
Diabetes mellitus	84 (26.3%)	42 (23.6%)	42 (29.8%)	0.212
Smoking status	62 (19.4%)	40 (22.5%)	22 (15.6%)	0.124
Coronary artery disease	99 (31.0%)	52 (33.3%)	47 (29.2%)	0.430
Ischemic stroke	96 (30.1%)	52 (29.2%)	44 (31.2%)	0.700
Chronic Renal failure	20 (6.3%)	11 (6.2%)	9 (6.4%)	0.941
Pre-procedural medication				0.467
No	224 (70.2%)	121 (68.0%)	103 (73.0%)	
Single antiplatelet	83 (26.0%)	51 (28.7%)	32 (22.7%)	
Dual antiplatelet	12 (3.8%)	6 (3.4%)	6 (4.3%)	
Post-procedural medication				0.266
Single antiplatelet	263 (82.4%)	143 (80.3%)	120 (85.1%)	
Dual antiplatelet	56 (17.6%)	35 (19.7%)	21 (14.9%)	

Data are shown as number (percentage), median (interquartile range) or mean ± SD.

differ significantly regarding the efficacy outcomes of CD-TLR, acute limb ischaemia, major amputation for vascular causes, or ischaemic stroke (Figures 1F–I and Table 2).

Chronic renal failure increased the risk of the primary efficacy outcomes. There was no risk increase in the efficacy of the primary outcome across the other major risk factors, including those based on the diagnosis, critical limb ischemia, and hypertension risk factors (Figure 2A). Similarly, there was no risk increase in terms of pre-procedural APT, post-procedural APT, post-procedural anticoagulation, or thrombus debulking; meanwhile, there was significant risk increase in terms of chronic renal failure. There was also significant risk increase in the efficacy of the secondary outcomes of chronic renal failure, post-procedural APT, and critical limb ischemia (Figure 2B). Conversely, there was significant risk increase in terms of post-procedural APT (Figure 2C).

Safety outcomes

The rivaroxaban and warfarin groups did not differ significantly regarding the safety outcomes. The primary safety outcome of major bleeding during follow-up occurred in three patients in the rivaroxaban group and five patients in the warfarin group, with Kaplan–Meier estimates of the incidence at 3 years of 2.6 and 3.7%, respectively (HR, 0.51; 95% CI,

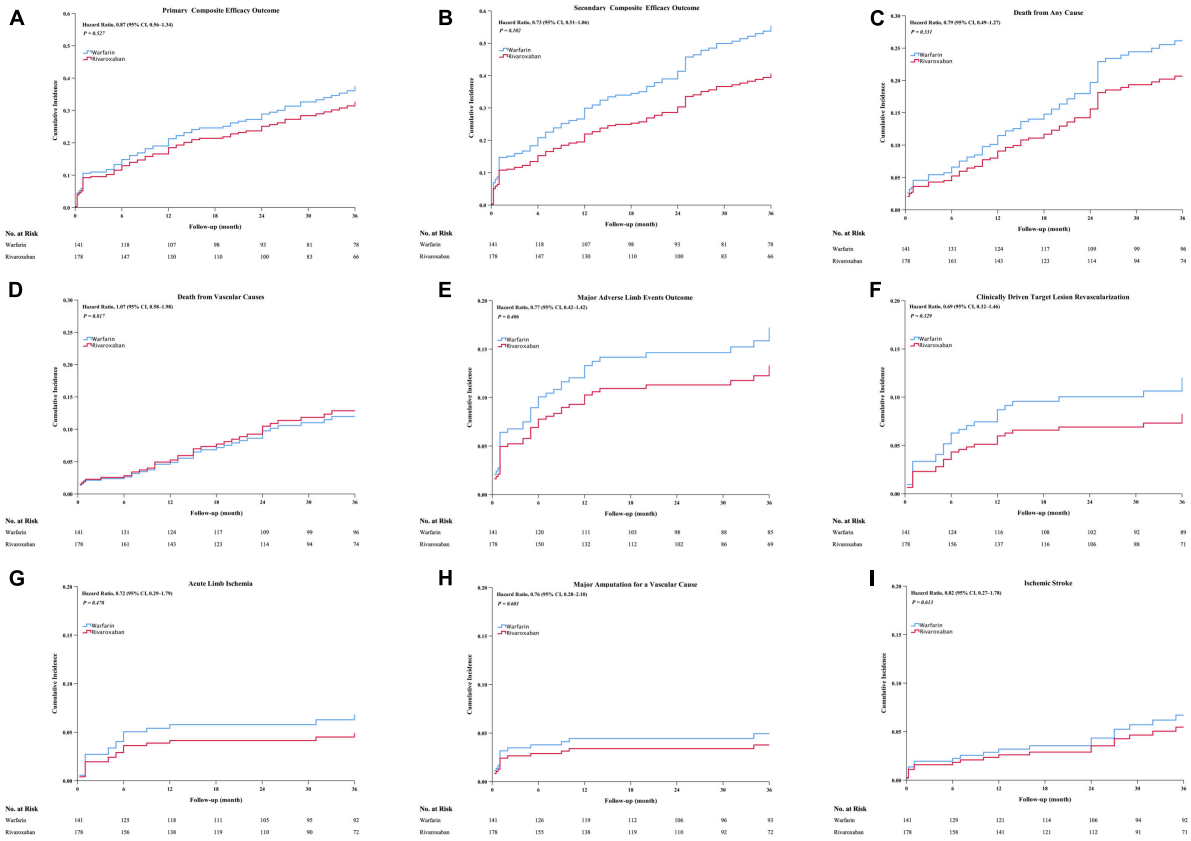

FIGURE 1
The cumulative incidence outcomes occurred between the rivaroxaban group and the warfarin group, including cumulative incidence of primary composite efficacy outcome **(A)**, secondary composite efficacy outcome **(B)**, death from all cause **(C)**, death from vascular cause **(D)**, major adverse limb events outcome **(E)**, CD-TLR **(F)**, acute limb ischemia outcome **(G)**, major amputation for a vascular cause **(H)**, Ischemia stroke **(I)**. CI, confidence intervals. CD-TLR, clinically driven target lesion revascularization. Major adverse limb events: Acute limb ischemia, major amputation for a vascular cause, or CD- TLR.

0.12–2.07; P = 0.343) (**Table 3**). The composite outcome of intracranial or fatal bleeding occurred in two patients in each group (HR, 0.93; 95% CI, 0.121–7.13; $P = 0.943$). The secondary safety outcome of gastrointestinal bleeding occurred in four patients in the rivaroxaban group and two patients in the warfarin group; the Kaplan–Meier estimates of the incidence at 3 years were 2.6% and 1.7%, respectively (HR, 2.33; 95% CI, 0.42–12.82; $P = 0.33$) (**Table 3**).

Discussion

Among patients with PAD, those with AF are usually older than those with sinus rhythm, and most of them are complicated with diseases, such as hypertension, diabetes, chronic renal disease, coronary artery disease, and/or heart failure (13). According to the Rutherford classification, patients with AF have more severe PAD symptoms and a higher incidence of in-hospital complications, and PAD-related AF is an independent predictor of stroke, amputation, and death (2, 14).

However, in patients with AF undergoing lower-extremity revascularisation, antithrombotic strategies remain a challenge in clinical practice. The risk of ischaemic and haemorrhagic events must be carefully balanced (15). In patients with AF and PAD, there is a significant 56% reduction in the incidence of acute limb events when receiving rivaroxaban compared with that when receiving warfarin (1), and current clinical practice is more inclined to the use of NOACs, such as rivaroxaban. The following advantages of rivaroxaban should be noted: no temporary hypercoagulable state, stable anticoagulation effect, fewer drug–food or drug–drug interactions, and less unnecessary INR monitoring to adjust the dose (8, 16, 17). Previous studies have indicated that rivaroxaban affects protease-activated receptors to inhibit cell signalling in atrial myocytes or endothelial cells, thus playing an important role in the pro-inflammatory response to prevent related adverse events (8, 18).

The current guidelines for the optimal dose of rivaroxaban when considering efficacy and safety are based on global trial

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TABLE 2 Primary and secondary efficacy outcomes.

Outcome	Total (*N* = 319)	Rivaroxaban(*N* = 178)		Warfarin(*N* = 141)		Hazard Ratio (95% CI)	*P* Value
	Patients with event No. (%)	Patients with event No. (%)	K–M Estimate at 3 Yr %	Patients with event No. (%)	K–M Estimate at 3 Yr %		
Primary efficacy outcome:acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, CD- TLR or vascular death.	87 (27.3)	44 (24.7)	29.6	43 (30.5)	31.4	0.870 (0.565–1.339)	0.527
Acute limb ischemia	20 (6.3)	10 (5.6)	6.8	10 (7.1)	7.8	0.718 (0.287–1.794)	0.478
Major amputation for vascular causes	16 (5.0)	8 (4.5)	5.3	8 (5.7)	6.0	0.764 (0.279–2.096)	0.601
Myocardial infarction	8 (2.5)	5 (2.8)	3.6	3 (2.1)	2.3	1.848 (0.442–7.718)	0.400
Ischemic stroke	19 (6.0)	8 (4.5)	5.9	11 (7.8)	9.1	0.815 (0.370–1.797)	0.613
CD- TLR	30 (9.4)	15 (8.4)	10.1	15 (10.6)	11.9	0.688 (0.324–1.459)	0.329
Vascular death	38 (11.9)	20 (11.2)	14.6	18 (12.8)	13.5	1.074 (0.584–1.975)	0.817
Secondary efficacy outcomes							
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, CD-TLR or death from any cause	117 (36.7)	56 (31.6)	35.6	61 (43.2)	43.6	0.733 (0.506–1.064)	0.102
Major adverse limb events	45 (14.1)	23 (12.9)	15.3	22 (15.6)	17.1	0.772 (0.419–1.421)	0.406
Death from any cause	73 (22.9)	34 (19.1)	22.3	39 (27.7)	27.9	0.791 (0.494–1.268)	0.331

Data are shown as number (percentage). K–M denotes Kaplan–Meier. CI, confidence intervals. CD-TLR, clinically driven target lesion revascularization. Major adverse limb events: Acute limb ischemia, major amputation for a vascular cause, or CD- TLR.

results (19). Most NOAC trials included a low proportion of Asian participants, such as 6.5% in the ROCKET-AF trial (19). To date, several studies have focused on the issue of reduced rivaroxaban doses in Asian populations. Asians are more prone to anticoagulant-related and intracranial bleeding than Caucasians owing to differences in race and lifestyle (15). Another study showed that in healthy Chinese individuals, 10 mg rivaroxaban may be sufficient to reach 83% of inhibition of factor Xa activity caused by a 20-mg dose (17). Furthermore, the Korean Heart Rhythm Society set 75–80 years of age as the standard age for rivaroxaban dose reduction (19). Thus, off-label rivaroxaban dose reduction is a common clinical practice in Asia.

In our research, the dose of rivaroxaban administered to the patients was 10 mg per day, and the dose reduction was mainly attributed to the following: (i) The median age of the patients in our cohort was 80.0 years (range, 71.0–84.0 years), which is higher than those in AF registry trials (e.g., 73 years in the ROCKET-AF trial; 71.5 years in the XANTUS trial). (ii) For these patients, renal creatinine clearance probably declines, and the time for rivaroxaban to be metabolised in the body will be prolonged (18, 20, 21). (iii) More importantly, a considerable number of patients in our cohort required single -antiplatelet or dual APT regimens postoperatively. Considering that standard doses may increase the risk of bleeding in patients, a reduced dose of 10 mg rivaroxaban per day for patients with AF who have

A

Primary Composite Efficacy Outcome

Risk factors	Rivaroxaban	Warfarin	HR (CI)	P value
Diagnosis				0.639
ASO	68 (21.3%)	59 (18.5%)	*Reference*	
Thrombus Embolization	110 (34.5%)	82 (25.7%)	1.137 (0.665−1.945)	
Hypertension	129 (40.4%)	93 (29.2%)	0.696 (0.440−1.100)	0.121
Chronic renal failure	11 (3.4%)	9 (2.8%)	2.266 (1.076−4.772)	0.031*
Pre−procedural APT				0.173
No	121 (37.9%)	103 (32.3%)	*Reference*	
Single antiplatelet	51 (16.0%)	32 (10.0%)	1.523 (0.952−2.437)	0.079
Dual antiplatelet	6 (1.9%)	6 (1.9%)	1.605 (0.575−4.484)	0.367
Post−procedural APT				0.163
Single antiplatelet	143 (44.8%)	120 (37.6%)	*Reference*	
Dual antiplatelet	35 (11.0%)	21 (6.6%)	1.468 (0.855−2.519)	
Post−procedural anticoagulation				0.527
Warfarin	/	141 (44.2%)	*Reference*	
Rivaroxaban	178 (55.8%)	/	0.870 (0.565−1.339)	
Thrombus debulking	121 (37.9%)	94 (29.5%)	1.165 (0.687−1.978)	0.571
Critical limb ischemia	141 (44.2%)	107 (33.5%)	1.537 (0.839−2.814)	0.164

B

Secondary Composite Efficacy Outcome

Risk factors	Rivaroxaban	Warfarin	HR (CI)	P value
Age	80.0 (66.0−94.0)	81.0 (69.0− 93.0)	1.009 (0.989−1.030)	0.363
Duration				0.797
Acute	99 (31.0%)	86 (27.0%)	*Reference*	
Chronic	79 (24.8%)	55 (17.2%)	1.055 (0.702−1.584)	
Ischemic stroke	52 (16.3%)	44 (13.8%)	0.793 (0.525−1.198)	0.270
Chronic renal failure	11 (3.4%)	9 (2.8%)	2.307 (1.270−4.191)	0.006*
Lesion procedural history	36 (11.3%)	19 (6.0%)	0.620 (0.283−1.358)	0.232
Lesion Lenth				0.176
＞10cm	113 (35.4%)	85 (26.6%)	*Reference*	
＜10cm	65 (20.4%)	56 (17.6%)	0.759 (0.509−1.131)	
Pre−procedural APT				0.18
No	121 (37.9%)	103 (32.3%)	*Reference*	
Single antiplatelet	51 (16.0%)	32 (10.0%)	1.307 (0.871−1.961)	0.195
Dual antiplatelet	6 (1.9%)	6 (1.9%)	1.885 (0.812−4.379)	0.140
Post−procedural APT				0.010*
Single antiplatelet	143 (44.8%)	120 (37.6%)	*Reference*	
Dual antiplatelet	35 (11.0%)	21 (6.6%)	1.782 (1.145−2.774)	
Post−procedural anticoagulation				0.102
Warfarin	/	141 (44.2%)	*Reference*	
Rivaroxaban	178 (55.8%)	/	0.733 (0.506−1.064)	
Lesion characteristics				0.798
De Novo	156 (48.9%)	124 (38.9%)	*Reference*	
Restenosis	22 (6.9%)	17 (5.3%)	0.889 (0.360−2.195)	
Critical limb ischemia	141 (44.2%)	107 (33.5%)	1.710 (1.010−2.898)	0.046*

C

Major Adverse Limb Events Outcome

Risk factors	Rivaroxaban	Warfarin	HR (CI)	P value
Duration				0.947
Acute	99 (31.0%)	86 (27.0%)	*Reference*	
Chronic	79 (24.8%)	55 (17.2%)	1.026 (0.486−2.163)	
Diagnosis				0.436
ASO	68 (21.3%)	59 (18.5%)	*Reference*	
Thrombus Embolization	110 (34.5%)	82 (25.7%)	1.402 (0.599−3.280)	
Hypertension	129 (40.4%)	93 (29.2%)	0.582 (0.303−1.116)	0.103
Chronic renal failure	11 (3.4%)	9 (2.8%)	1.362 (0.405−4.575)	0.617
Lesion procedural history	36 (11.3%)	19 (6.0%)	1.003 (0.322−3.125)	0.995
Lesion Lenth				0.230
＞10cm	113 (35.4%)	85 (26.6%)	*Reference*	
＜10cm	65 (20.4%)	56 (17.6%)	0.672 (0.351−1.286)	
Pre−procedural APT				0.120
No	121 (37.9%)	103 (32.3%)	*Reference*	
Single antiplatelet	51 (16.0%)	32 (10.0%)	1.710 (0.884−3.305)	0.111
Dual antiplatelet	6 (1.9%)	6 (1.9%)	2.614 (0.765−8.929)	0.125
Post−procedural APT				0.045*
Single antiplatelet	143 (44.8%)	120 (37.6%)	*Reference*	
Dual antiplatelet	35 (11.0%)	21 (6.6%)	2.099 (1.016−4.338)	
Post−procedural anticoagulation				0.406
Warfarin	/	141 (44.2%)	*Reference*	
Rivaroxaban	178 (55.8%)	/	0.772 (0.419−1.421)	
Lesion characteristics				0.385
De Novo	156 (48.9%)	124 (38.9%)	*Reference*	
Restenosis	22 (6.9%)	17 (5.3%)	0.524 (0.122−2.251)	
Thrombus debulking	121 (37.9%)	94 (29.5%)	1.818 (0.808−4.091)	0.148
Critical limb ischemia	141 (44.2%)	107 (33.5%)	1.420 (0.586−3.437)	0.437

FIGURE 2

(A) Forest plot comparing the efficacy of the primary composite outcome across the risk factors. **(B)** Forest plot comparing the efficacy of the secondary composite outcome across the risk factors. **(C)** Forest plot comparing the efficacy of the major adverse limb events outcome across the risk factors.

TABLE 3 Safety outcomes.

Outcome	Total (N = 319)	Rivaroxaban(N = 178)		Warfarin(N = 141)		Hazard Ratio (95% CI)	*P* Value
	Patients with Event No. (%)	Patients with Event No. (%)	K–M Estimate at 3 Yr %	Patients with Event No. (%)	K–M Estimate at 3 Yr %		
Principal safety outcome: ISTH major bleeding	8 (2.5)	3 (1.7)	2.6	5 (3.5)	3.7	0.506 (0.124–2.068)	0.343
Intracranial or fatal bleeding	4 (1.3)	2 (1.2)	1.7	2 (1.4)	1.4	0.929 (0.121–7.132)	0.943
Secondary safety outcome							
Gastrointestinal bleeding	6 (3.1)	4 (2.2)	2.6	2 (1.4)	1.7	2.325 (0.422–12.820)	0.333

Data are shown as number (percentage). K–M denotes Kaplan–Meier. CI, confidence intervals.

undergone lower-extremity revascularisation is appropriate in clinical practice.

Herein, we also compared the efficacy and safety of rivaroxaban with those of warfarin in the patients with AF who underwent lower-extremity revascularisation using the Cox proportional hazard model. Similar to other studies, our study revealed a non-significant trend toward an overall lower incidence of the primary composite efficacy outcome in the rivaroxaban group than in the warfarin group. Although there was no significant difference between the two groups, rivaroxaban was associated with a reduced risk of adverse limb events. In terms of the secondary efficacy outcomes, our study also demonstrated a similar result for rivaroxaban. In the ROCKET-AF trial, rivaroxaban has not been reported to be related to a significantly higher risk of stroke or systemic embolism than warfarin (22). Lee et al. noted that NOACs were associated with a similar risk of ischaemic stroke and a reduced risk of acute myocardial infarction, major adverse limb events, and major bleeding events (3). Compared with the incidence in these previous studies, the high incidence of systemic embolism or vascular death in our study is probably attributed to the following: an older age (median age: 80.0 years in our study vs 73 years in the ROCKET-AF trial); a higher incidence of concomitant coronary or cerebral artery diseases; a higher CHA_2DS_2-VASc score (warfarin group: 5.04 ± 1.43 in our study vs 4.43 ± 1.65 in the study by Lee et al.; rivaroxaban group: 5.09 ± 1.48 in our study vs 4.41 ± 1.67 in the study by Lee et al.). Moreover, our research focused on patients with PAD requiring endovascular procedures rather than a broad population of patients with PAD. Taken together, rivaroxaban has the advantage of reducing the risk of composite efficacy outcomes. In our subgroup analysis, although not significant, the advantage of rivaroxaban over warfarin persisted in reducing the risks of acute limb ischaemia, major amputation for vascular causes, revascularisation for recurrent limb ischaemia, and all-cause death.

Another major finding was that low-dose rivaroxaban was non-inferior to warfarin in terms of the primary safety outcomes, including major and intracranial or fatal bleeding. The incidence of gastrointestinal bleeding was slightly higher in the rivaroxaban group than in the warfarin group. No difference in the overall bleeding events was observed between the rivaroxaban and warfarin groups during the follow-up period, with only 1.2% of the patients experiencing fatal or intracranial bleeding and 2.2% experiencing gastrointestinal bleeding in the rivaroxaban group. Contrary to our study, the ROCKET-AF trial demonstrated that rivaroxaban yielded a higher bleeding risk than did warfarin but also reported that the excessive bleeding events with rivaroxaban were the result of non-fatal mucosal bleeding. We hypothesised that the different opinions regarding haemorrhagic safety events in current studies may be related to the different bleeding definitions used by investigators. The incidence of fatal and intracranial bleeding, which required a specific focus, is similar in each study. Available evidence suggests that peri-procedural measures of anticoagulation or antiplatelet regimens and use of PPI, glycoprotein IIb/IIIa inhibitors, and other factors may be considered to further prevent bleeding (23).

In our study, 82.4% of all patients received single APT, while 17.6% received dual APT. Triple therapy has been widely demonstrated to cause an increase in the incidence of bleeding events, with no apparent benefit in the prevention of postoperative restenosis and systemic thrombosis. In the VOYAGER PAD study, the efficacy and safety of dual-pathway inhibition regimens were consistent with those of aspirin. The addition of clopidogrel did not further reduce the risk of limb and CV events, whereas its combination increased the risk of bleeding. This also provides support for postoperative drug use in patients with AF who have undergone lower-extremity revascularisation.

Limitations

This study was a retrospective analysis with a relatively small sample size. Further randomised and prospective studies are necessary to evaluate limb prognosis in patients with AF and concomitant PAD treated with NOACs and warfarin. Additionally, no further subgroup analysis was conducted, and the heterogeneity results of the main subgroups need to be further verified.

Conclusion

This study describes practical experience regarding the use of rivaroxaban and warfarin in patients with PAD complicated by NVAF following endovascular intervention. The efficacy and safety outcomes do not differ significantly between rivaroxaban and warfarin.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

LY: conception and design, analysis and interpretation, critical revision, approval of the manuscript, agreement to be accountable, statistical analysis, and obtaining funding. QY: data collection, analysis and interpretation, writing the manuscript, critical revision, approval of the manuscript, agreement to be accountable, and statistical analysis. CC: conception and design, writing the manuscript, critical revision, approval of the manuscript, agreement to be accountable, and statistical analysis. JX: analysis and interpretation, writing the manuscript, approval of the manuscript, and agreement to be accountable. YX: analysis and interpretation, critical revision, approval of the manuscript, and agreement to be accountable. JB: conception and design, critical revision, approval of the manuscript, and agreement to be accountable. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.978639/full#supplementary-material

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EDITED BY
Ping Yuan,
Second Affiliated Hospital of Nanchang University, China

REVIEWED BY
Junyi Sun,
The First Affiliated Hospital of Sun Yat-sen University, China
Siyuan Li,
Nanchang University, China

*CORRESPONDENCE
Haidong Zhang
1013722016@qq.com
Dewang Zeng
derek1119@126.com

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Use of non-vitamin K antagonists oral anticoagulants in atrial fibrillation patients on dialysis

Wenhao Li[1], Yanxia Zhou[2], Siqi Chen[1], Dewang Zeng[1]* and Haidong Zhang[3]*

[1]Department of Nephrology, Affiliated Huadu Hospital, Southern Medical University (People's Hospital of Huadu District), Guangzhou, China, [2]Department of Nephrology, Leliu Hospital Affiliated to Shunde Hospital of Guangzhou University of Chinese Medicine, Foshan, China, [3]Department of Nephrology, Peking University Third Hospital, Beijing, China

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) showed a benefit-risk profile superior to that of warfarin in atrial fibrillation (AF) patients with mild to moderate chronic kidney disease. However, the effectiveness and safety of NOACs in AF patients with end-stage renal disease (ESRD) on dialysis remain unclear. Therefore, we performed a meta-analysis regarding the effect of NOACs vs. warfarin in AF patients undergoing dialysis.

Methods: A search of the Pubmed and EMBASE databases until November 2021 was performed. Adjusted risk ratios (RRs) and 95%confidence intervals (CIs) were pooled by a random-effects model with an inverse variance method.

Results: Six studies involving 3,744 NOAC- and 26,973 warfarin- users were deemed to meet the criteria. In the pooled analysis, the use of mixed NOACs had similar incidences of effectiveness and safety outcomes compared with warfarin use. And factor Xa inhibitors (rivaroxaban or apixaban) did not have significantly better effectiveness than warfarin. For the safety outcomes, the use of factor Xa inhibitors was associated with a reduced risk of gastrointestinal bleeding (RR = 0.81, 95% CI 0.70–0.95), but not major bleeding and intracranial bleeding.

Conclusion: Compared with warfarin, the use of NOACs, especially factor Xa inhibitors (rivaroxaban or apixaban), showed at least similar effectiveness and safety outcomes in AF patients on dialysis.

KEYWORDS

non-vitamin K antagonist oral anticoagulants, warfarin, atrial fibrillation, dialysis, meta-analysis

Introduction

Patients with chronic kidney disease [CKD, especially end-stage renal disease (ESRD)] and atrial fibrillation (AF) are at higher risk of stroke or systemic thromboembolism (SSE) (1). Incidence of AF and worsening of CKD are linked with each other as they share several common risk factors (2). AF accelerates the progression to ESRD in patients with

CKD, nearly doubles the mortality, and increases the stroke risk by ∼6-fold in patients on dialysis (3), becoming one of the most important causes accounting for death among ESRD patients (4). An altered internal environment in CKD patients such as platelet dysfunction and hypercoagulability contributes to the development of AF in these patients. Dialysis is thought to be a trigger of AF in patients with ESRD as a high incidence of new-onset AF was observed after dialysis initiation (5).

AF is the most common indication for anticoagulation in patients with CKD (6). Warfarin has been used in patients with AF for decades (7). A prior meta-analysis showed that warfarin led to a much higher risk of bleeding in AF patients with ESRD on dialysis compared to those without anticoagulation (8). This might result from warfarin accumulation in these patients as CYP2C9 is downregulated in patients with ERSD (7, 9). And warfarin needs close monitoring of prothrombin time (10), deteriorates vascular calcification (11), and sometimes induces anticoagulant-related nephropathy (12).

NOACs [i.e., dabigatran (a direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors)] are alternatives for warfarin in AF-related stroke prevention. Several studies including different randomized clinical trials (13–16) and meta-analyses (17–19) have indicated a benefit-risk profile of NOACs superior to that of warfarin in patients with mild to moderate CKD, and other studies have demonstrated that there was no difference in bleeding rates between ESRD patients receiving apixaban and warfarin (20). One meta-analysis by Kuno et al. (21) investigated the efficacy of apixaban and warfarin in AF patients on dialysis and found they were not associated with a significant decrease in stroke and/or SSE. However, this analysis did not provide enough evidence as only 2 of 16 included studies in this meta-analysis investigated NOACs and the outcomes of dabigatran and rivaroxaban were limited to major bleeding events due to lack of data. Therefore, the effect of NOACs compared with warfarin in AF patients with ESRD on dialysis remains unclear. And the level of evidence and class of recommendation suggesting benefit or at least similar effect of NOACs compared with warfarin in this population was low and needed to be improved urgently. In this meta-analysis, we summarized the available data to compare the effectiveness and safety of NOACs vs. warfarin in this specific AF population.

Methods

This meta-analysis was performed according to the guidance from the Cochrane Handbook for Systematic Reviews, the results of which were presented based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) items. Two reviewers (WH-L and YX-Z) independently performed the literature search, study selection, data abstraction, quality assessment, and data analysis. Disagreements were resolved by discussion between two reviewers, or consultation with the corresponding authors.

Inclusion and exclusion criteria

We included randomized controlled trials (RCTs) or observational cohort studies if they compared at least one of the effectiveness and safety outcomes of NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) vs. warfarin in AF patients with ESRD on dialysis (hemodialysis or peritoneal dialysis). The effectiveness outcomes were a composite of SSE, ischemic stroke, and all-cause death, whereas the safety outcomes were major bleeding, intracranial bleeding, and gastrointestinal bleeding. The definitions of the studied outcomes were applied that were reported in the originally included studies. We excluded studies focusing on AF patients with cardioversion, ablation, or left-atrial appendage occluder. We also excluded studies with a sample size of <100. Certain publication types were excluded (e.g., reviews, comments, case reports, case series, letters, editorials, and meeting abstracts) due to insufficient data.

Literature search

We systematically searched the PubMed and Embase databases until November 7, 2021, for identifying studies about the effectiveness and safety of NOACs compared with warfarin in AF patients with ESRD on dialysis. The search terms combined with "AND" were applied as follows: (1) "atrial fibrillation", (2) "dialysis" OR "hemodialysis" OR "peritoneal dialysis" OR "end-stage kidney disease" OR "end-stage renal disease" OR "advanced renal disease", (3) "vitamin K antagonist" OR "warfarin", (4) "non-vitamin K antagonist oral anticoagulant" OR "direct oral anticoagulant" OR "novel oral anticoagulant" OR "NOAC" OR "DOAC" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban". The detailed search strategies of this meta-analysis are presented in Supplementary Table 1. No linguistic restrictions were applied in the literature search.

Study screenings and data abstraction

We first screened the titles and abstracts of the retrieved studies, and subsequently read the full texts of the potential studies. Eligible studies would be chosen based on the pre-defined inclusion criteria. The following information of the included studies was collected: first author, year of publication, study design, data source and study period, patient characteristics (study population, sample size, age, and sex), type

and dosage of NOACs, follow-up time, and the effectiveness and safety outcomes.

Study quality assessment

We assessed the bias risk of RCTs using the Cochrane Collaboration's tool on the selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. For each domain of this tool, the level of the bias risk was scored as "low," "unclear," or "high" risk. In addition, the Newcastle-Ottawa Scale (NOS) tool was used to assess the quality of the observational cohort studies. The NOS tool had three domains with a total of nine points: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcome (0–3 points). In this meta-analysis, studies with an NOS of <6 points were defined as a low quality (22, 23).

Statistical analysis

The statistical heterogeneity across the included studies was assessed using the *P*-value of the Cochrane *Q*-test and the I^2 statistic, where a *P*-value of < 0.10 in the Cochrane *Q*-test or an I^2-value of $> 50\%$ suggested significant heterogeneity. For the included studies reporting unadjusted effect estimates, we collected the sample size and the number of events in the warfarin- or NOAC- groups and then calculated the unadjusted event rates between the two groups, which were expressed as the odds ratios. For those studies reporting adjusted data with multiple models, we applied the most adjusted risk ratios (RRs) and 95%confidence intervals (CIs). In the main pooled analysis, the effect estimates were converted to the natural logarithms and standard errors, which were pooled by a DerSimonian and Laird random-effects model with an inverse variance method. In the secondary analysis, since the use of dabigatran had limited evidence in AF patients with ESRD on dialysis, we excluded the data of dabigatran and re-performed the meta-analysis. The subgroup analysis was performed based on the type and dosage of NOACs. In the sensitivity analysis, we re-performed the above-mentioned analysis using a fixed-effects model. We also excluded the unadjusted data or the data of RCT in the pooled analysis. According to the Cochrane book, we did not perform the publication bias analysis if the number of the included studies was <10.

All the statistical analyses of this meta-analysis were performed using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Center Copenhagen, Denmark; https://community.cochrane.org/). In this study, a *P*-value of <0.05 was considered statistically significant.

Results

Study selection

The flow chart of the literature retrieval is presented in Supplementary Figure 1. A total of 736 retrieved studies were retrieved in the Pubmed and Embase databases. After the first phase of the title- and abstract- screenings, 11 remaining studies were potentially available, which were assessed by the full-text screenings. Subsequently, we excluded 5 studies because (1) warfarin was not the reference ($n = 2$) (24, 25); (2) study focused on ESRD patients with AF or venous thromboembolism ($n = 1$) (20); (3) study included a sample size of <100 in the analysis ($n = 1$) (26); and (4) study with an overlapping data ($n = 1$) (27). Finally, a total of 6 studies (1 RCT and 5 observational cohorts) (28–33) involving 3,744 NOAC- and 26,973 warfarin- users were included in this meta-analysis.

Baseline characteristics of the included studies

Table 1 shows the baseline characteristics of the included studies. In hemodialysis patients with AF, a prior RCT in 2020 published by De Vriese et al. (27) compared the primary endpoint of the progression of cardio-aortic calcium deposits among warfarin, rivaroxaban, and rivaroxaban plus vitamin K2 with a follow-up of 18 months. In this trial, they additionally followed for at least 18 months and compared the effectiveness and safety outcomes of rivaroxaban compared with warfarin (29). Although the studies by See et al. (28) and Lin et al. (31) used the same data source of Taiwan's National Health Insurance Research Database, See et al. (28) reported a mixed type of NOACs including dabigatran, rivaroxaban, apixaban, and edoxaban, whereas Lin et al. (31) focused on the use of rivaroxaban. Therefore, the data of See et al. (28) and Lin et al. (31) were applied in different parts of our meta-analysis. Chan et al. (33) assessed the effect of dabigatran and rivaroxaban separately, whereas Ionescu et al. (30) and Siontis et al. (32) focused on the use of apixaban. The administrated dosages of different NOACs in patients in the included studies are listed in Table 1. For the quality assessment, the Valkyrie study by De Vriese et al. (29) had a low risk of bias, details of the assessment are presented in Supplementary Table 2. All 5 observational cohorts had an acceptable quality with the NOS tool of ≥6 points.

Effect of mixed NOACs vs. warfarin in dialysis patients with AF

In the main pooled analysis, our results based on the random-effects model showed that compared with warfarin

TABLE 1 Baseline characteristics of the included studies.

References	Database source	Study design	AF patients on dialysis	Age (y)/Sex	Sample size	NOAC dose	Follow-up (y)	Quality assessment
De Vriese et al. (29)	The Valkyrie study	RCT	Patients on chronic hemodialysis	71.5–84.3/both	Rivaroxaban ($n = 88$); Warfarin ($n = 44$)	Rivaroxaban 10 mg QD (100%)	1.88	Low risk of bias
See et al. (28)	Taiwan's National Health Insurance Research Database; 06/2012–12/2017	Retrospective cohort	ESRD patients on chronic dialysis	74.8/both	Dabigatran ($n = 150$); Rivaroxaban ($n = 224$); Apixaban ($n = 72$); Edoxaban ($n = 17$); Warfarin ($n = 8,064$)	Dabigatran 110 mg BID (92%); Rivaroxaban 15/10 mg QD (96%); Apixaban 2.5 mg BID (82%); Edoxaban 30 mg BID (89%)	NA	NOS = 7 points
Ionescu et al. (30)	Academic healthcare system in Southeast Michigan, USA	Retrospective cohort	Patients on chronic hemodialysis	67.2/both	Apixaban ($n = 144$); Warfarin ($n = 563$)	Apixaban 5 mg BID (36%) and 2.5 mg BID (64%)	NA	NOS = 6 points
Lin et al. (31)	Taiwan's National Health Insurance Research Database; 02/2013–09/2017	Retrospective cohort	ESRD patients on regular dialysis	69.0/both	Rivaroxaban ($n = 173$); Warfarin ($n = 3,185$)	Rivaroxaban 20 mg QD (10.4%), 15 mg QD (38.7%), and 10 mg QD (50.8%)	1.59	NOS = 7 points
Siontis et al. (32)	Medicare beneficiaries included in the United States Renal Data System; 10/2010–12/2015	Retrospective cohort	ESRD patients on peritoneal dialysis or hemodialysis	68.2/both	Apixaban ($n = 2,351$); Warfarin ($n = 7,053$)	Apixaban 5 mg BID (44%) and 2.5 mg BID (56%)	NA	NOS = 8 points
Chan et al. (33)	Fresenius Medical Care North America ESRD database; 10/2010–10/2014	Retrospective cohort	Patients on hemodialysis	70.4/both	Dabigatran ($n = 281$); Rivaroxaban ($n = 244$); Warfarin ($n = 8,064$)	Dabigatran 150 mg BID (15.3%) and 75 mg BID (84.7%); Rivaroxaban 20 mg QD (32.1%) and 15 mg QD (67.8%)	2.0	NOS = 8 points

AF, atrial fibrillation; RCT, Randomized Controlled Trial; ESRD, end-stage renal disease; NOACs, non-vitamin K oral anticoagulants; NOS, Newcastle-Ottawa Scale; NA, not available.

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TABLE 2 Effectiveness and safety outcomes between NOACs and warfarin in dialysis patients with AF.

	Stroke or systemic embolism	Ischemic stroke	All-cause death	Major bleeding	Intracranial bleeding	Gastrointestinal bleeding
Main analysis: mixed NOACs						
No. of effect estimates	6	4	2	5	3	4
RRs and 95% CIs	0.95 (0.68, 1.31)	0.93 (0.55, 1.60)	0.84 (0.71, 1.00)	0.96 (0.65, 1.43)	0.75 (0.50, 1.14)	0.87 (0.74, 1.01)
P-value	0.74	0.8	0.05	0.85	0.18	0.07
I^2 statistic	51%	41%	0%	89%	0%	0%
Secondary analysis: factor Xa inhibitors						
No. of effect estimates	4	3	2	4	3	4
RRs and 95% CIs	0.64 (0.41, 1.01)	0.75 (0.39, 1.43)	0.84 (0.71, 1.00)	0.82 (0.52, 1.29)	0.72 (0.48, 1.09)	0.81 (0.70, 0.95)
P-value	0.05	0.38	0.05	0.39	0.12	0.009
I^2 statistic	57%	34%	0%	83%	0%	0%
Subgroup analysis						
1) Rivaroxaban						
No. of effect estimates	3	2	-	3	1	2
RRs and 95% CIs	0.51 (0.22, 1.20)	0.76 (0.26, 2.23)	-	0.84 (0.43, 1.63)	0.62 (0.24, 1.61)	0.63 (0.41, 0.96)
Apixaban						
No. of effect estimates	2	-	-	1	2	2
RRs and 95% CIs	0.85 (0.68, 1.08)	-	-	0.72 (0.59, 0.87)	0.77 (0.49, 1.22)	1.44 (0.43, 4.77)
2) High dose of NOACs						
No. of effect estimates	1	-	-	3	-	-
RRs and 95% CIs	0.64 (0.42, 0.97)	-	-	1.57 (0.63, 3.90)	-	-
Low dose of NOACs						
No. of effect estimates	3	-	-	5	-	-
RRs and 95% CIs	0.51 (0.18, 1.44)	-	-	0.85 (0.56, 1.29)	-	-
Sensitivity analysis						
1) Only included adjusted data						
No. of effect estimates	2	1	1	4	2	2
RRs and 95% CIs	0.97 (0.73, 1.29)	0.62 (0.24, 1.61)	0.85 (0.71, 1.01)	1.10 (0.74, 1.63)	0.79 (0.51, 1.21)	0.88 (0.75, 1.04)
P-value	0.83	-	-	0.65	0.27	0.13
I^2 statistic	30%	-	-	90%	0%	0%

(Continued)

TABLE 2 (Continued)

	Stroke or systemic embolism	Ischemic stroke	All-cause death	Major bleeding	Intracranial bleeding	Gastrointestinal bleeding
2) Deleting the data of RCT						
No. of effect estimates	5	3	1	4	3	3
RRs and 95% CIs	1.02 (0.79, 1.32)	1.14 (0.74, 1.77)	0.85 (0.71, 1.01)	1.10 (0.74, 1.63)	0.75 (0.50, 1.14)	0.87 (0.74, 1.01)
P-value	0.89	0.55	-	0.65	0.18	0.07
I^2 statistic	28%	8%	-	90%	0%	0%
3) Re-analysis with a fixed-effects model						
No. of effect estimates	5	4	2	5	3	4
RRs and 95% CIs	0.95 (0.79, 1.14)	1.02 (0.69, 1.51)	0.84 (0.71, 1.00)	1.05 (0.93, 1.18)	0.75 (0.50, 1.14)	0.87 (0.74, 1.01)
P-value	0.58	0.92	0.05	0.46	0.18	0.07
I^2 statistic	51%	41%	0%	89%	0%	0%

AF, atrial fibrillation; RR, risk ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants; RCT, Randomized Controlled Trial.

use, the use of NOACs was not significantly associated with the effectiveness outcomes including SSE (RR = 0.95, 95% CI 0.68–1.31; $P = 0.74$; $I^2 = 51\%$), ischemic stroke (RR = 0.93, 95% CI 0.55–1.60; $P = 0.80$; $I^2 = 41\%$), and all-cause death (RR = 0.84, 95% CI 0.71–1.00; $P = 0.05$; $I^2 = 0\%$), and safety outcomes including major bleeding (RR = 0.96, 95% CI 0.65–1.43; $P = 0.85$; $I^2 = 89\%$), intracranial bleeding (RR = 0.75, 95% CI 0.50–1.14; $P = 0.18$; $I^2 = 0\%$), and gastrointestinal bleeding (RR = 0.87, 95% CI 0.74–1.01; $P = 0.07$; $I^2 = 0\%$) (Supplementary Figures 2, 3).

Effect of factor Xa inhibitors vs. warfarin in dialysis patients with AF

In the secondary analysis, we excluded studies with the data of dabigatran (28, 33) and assessed the effect of factor Xa inhibitors (rivaroxaban or apixaban) compared with warfarin in dialysis patients with AF. As shown in Table 2, our pooled results based on the random-effects model showed that the use of factor Xa inhibitors did not alter the risk of SSE (RR = 0.64, 95% CI 0.41–1.01; $P = 0.05$; $I^2 = 57\%$) and risk of all-cause death (RR = 0.84, 95% CI 0.71–1.00; $P = 0.05$; $I^2 = 0\%$) significantly compared to warfarin (Figure 1). For the safety outcomes, compared with warfarin use, the use of factor Xa inhibitors was associated with a decreased risk of gastrointestinal bleeding (RR = 0.81, 95% CI 0.70–0.95; $P = 0.009$; $I^2 = 0\%$), but there were no differences in major bleeding (RR = 0.82, 95% CI 0.52–1.29; $P = 0.39$; $I^2 = 83\%$) and intracranial bleeding (RR = 0.72, 95% CI 0.48–1.09; $P = 0.12$; $I^2 = 0\%$) between the two groups (Figure 2).

Subgroup analysis and sensitivity analysis

In terms of SSE and major bleeding, the subgroup analysis based on the NOAC type showed that there were no interactions between rivaroxaban vs. apixaban. In addition, there were also no significant differences in SSE and major bleeding between the high vs. low dose of NOACs (Table 2).

As shown in Table 2, for the effectiveness and safety outcomes, re-analysis with the fixed-effects model showed similar results as the main pooled analysis with the random-effects model. In addition, we also observed similar results as the main analysis when excluding the studies with unadjusted data or excluding the RCT of De Vriese et al. (29).

Discussion

Our current study indicated that the use of mixed NOACs had similar incidences of effectiveness and safety outcomes compared with warfarin use in AF patients with ESRD on dialysis. Specifically, the use of factor Xa inhibitors (rivaroxaban or apixaban) had a decreased risk of gastrointestinal bleeding compared with warfarin use. This specific effect might result from decreased absorption function of the gastrointestinal

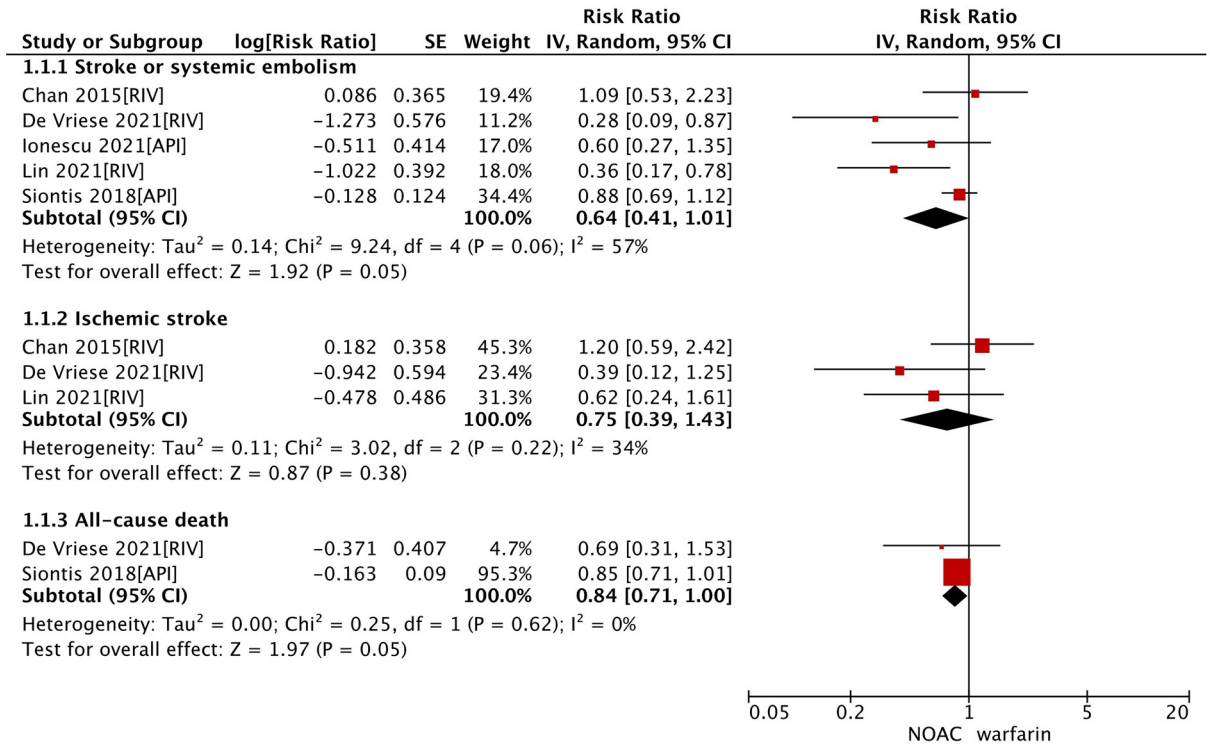

FIGURE 1
Effectiveness outcomes of NOACs vs. warfarin in dialysis patients with atrial fibrillation. CI, confidence interval; SE, standard error; IV, inverse of the variance.

tract in patients with uremia. In uremia, the absorption of NOACs becomes slower and a larger amount of NOACs accumulates in the gastrointestinal tract. This process might be even more obvious in rivaroxaban as the bioavailability of it increases if it is taken together with food (1). Such an assumption could be proved by a mouse model in the future. Overall, the use of NOACs, especially factor Xa inhibitors (rivaroxaban or apixaban), showed at least similar effects compared with warfarin use in dialysis patients with AF.

We queried the outcomes of the prior meta-analysis by Kuno et al. (21) as only 2 included studies investigated NOACs and the sample size is relatively small. In addition, a similar study conducted by Chen et al. (9) summarized that the use of rivaroxaban or apixaban might be associated with reduced risks of all-cause death and gastrointestinal bleeding in AF patients with stage 4–5 CKD or on dialysis. And another meta-analysis by See et al. (28) suggested similar effectiveness and safety outcomes between NOACs and warfarin among AF patients with stage 4–5 CKD on dialysis. These two studies by Chen et al. (9) and See et al. (28) did not focus on the AF patients with ESRD on dialysis and thus the effect of NOACs in this specific population remained debatable for us to investigate. However, the data we summarized showed the use of factor Xa inhibitors (rivaroxaban or apixaban) did not alter the risks of SSE and all-cause death significantly compared to warfarin as both confidence intervals cross one (95% CI 0.41–1.01 for risks of SSE and 95% CI 0.71–1.00 for all-cause mortality, respectively). We hoped future observational studies or RCTs could focus on hazard ratio and bring a new answer to the question of whether NOACs could lengthen the survival time of AF patients on dialysis or not. In terms of gastrointestinal bleeding, a previous meta-analysis by Burr et al. (34) demonstrated that factor Xa inhibitors were associated with a reduced risk of all severities of gastrointestinal bleeding compared with warfarin, but not specifically in AF patients with ESRD on dialysis. We remedied this weakness and the summarized data indicated that in this specific population the use of factor Xa inhibitors was associated with a decreased risk of gastrointestinal bleeding. Our findings support the FDA's recommendation of rivaroxaban and apixaban in patients with ESRD and AF (2). While European guideline recommended patients on dialysis as well as patients with severe renal dysfunction (CrCl $<$ 15 mL/min) should refrain from NOACs use (35), our study supported that factor Xa inhibitors (apixaban and rivaroxaban) in AF patients with ESRD on dialysis is at least not a worse choice compared to warfarin. In fact, anticoagulation

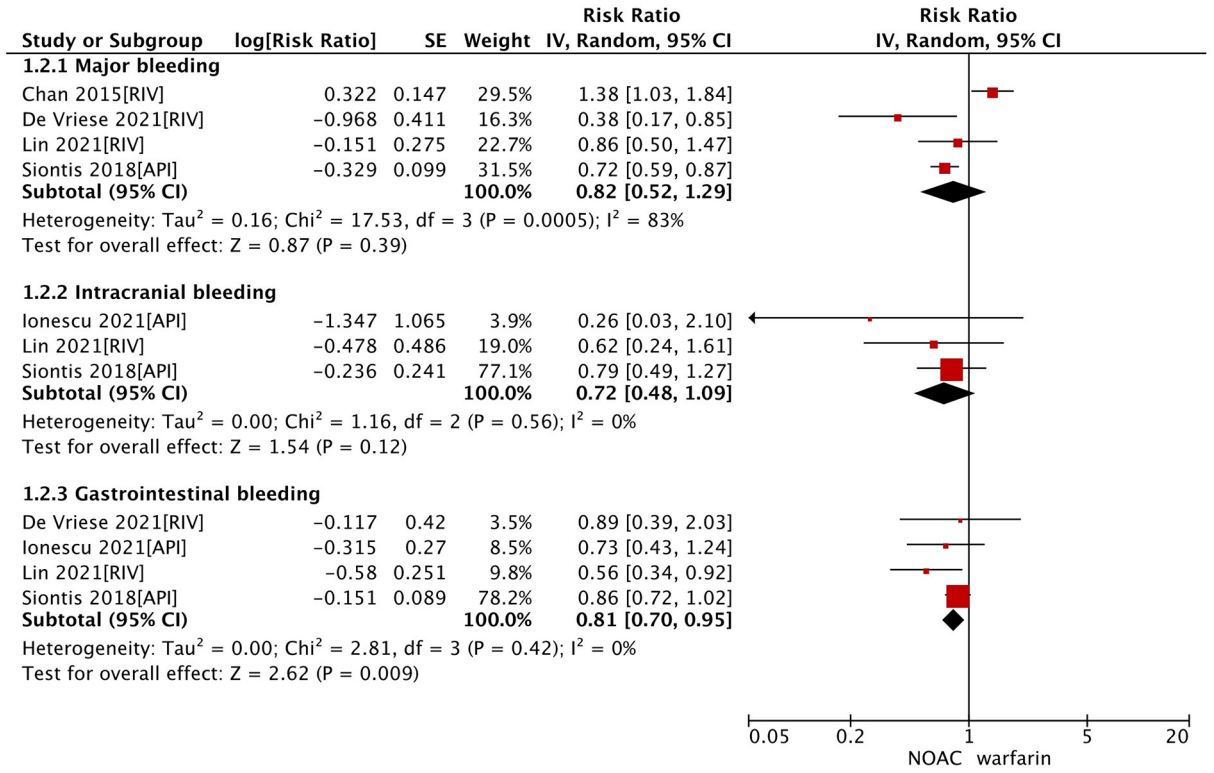

FIGURE 2
Safety outcomes of factor Xa inhibitors (rivaroxaban or apixaban) vs. warfarin in dialysis patients with atrial fibrillation. CI, confidence interval; SE, standard error; IV, inverse of the variance.

in this specific population must be individualized through a multidisciplinary approach.

Although apixaban and rivaroxaban show potential advantages over warfarin, the dosage of these drugs for a better effectiveness and safety outcome in AF patients with ESRD on dialysis remains unclear. In one of our included studies, Siontis et al. (32) compared the different roles of different dosages of apixaban in this population, suggesting that a standard dose (5 mg twice daily) is associated with lower risks of SSE and death, whereas a low dose (2.5 mg twice daily) presents a lower risk of major bleeding. Kuno et al. (21) reported that apixaban 5 mg twice daily was associated with a lower risk of mortality for patients with AF on long-term dialysis compared to other treatments (apixaban 2.5 mg twice daily or no anticoagulants). Because of this uncertain benefit-to-harm ratio of NOACs in AF patients on dialysis, the nephrological guidelines KDIGO (Kidney Disease: Improving Global Outcomes) still recommend warfarin as the first choice drug for anticoagulation (36).

The effectiveness and safety outcomes of NOACs seemed to improve after we excluded the data of dabigatran, suggesting low effectiveness and safety of dabigatran in AF patients with ESRD on dialysis. This could be explained by the pharmacokinetic and pharmacodynamic characteristics of dabigatran. First, the effect of dabigatran might be reduced in hemodialysis patients as 50–60% of dabigatran is dialyzable (1). Second, clinical use of dabigatran shortly after its approval in the United States showed high rates of major and non-major bleeding in patients with hemodialysis (37), this might result from the high renal clearance rate of dabigatran (∼80%) (38) and accumulation of dabigatran in patients with severe renal impairment (a 6.3-fold higher AUC in these patients) (39). Therefore, rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for use in patients with severe CKD, with a reduced dose regimen. In view of individual pharmacokinetics, edoxaban might be another NOAC with clinical effectiveness and safety comparable to apixaban and rivaroxaban as hemodialysis only led to a minor decrease in a total exposure of edoxaban and hemodialysis did not affect edoxaban's concentration in 24 h (40). However, the effectiveness and safety of edoxaban in AF patients with ESRD on dialysis remains unclear due to limited data. Only one RCT by Bohula et al. (14) and one observational study by Yu et al. (41) reported edoxaban was associated with reduced bleeding risk in patients with GFR 30–50 ml/min, respectively. Further studies on

the data of edoxaban with a larger sample size might help establish its clinical effect in AF patients with ESRD on dialysis.

Limitations

Our current meta-analysis still had several limitations. First, it's still insufficient to make recommendations of NOACs for AF patients on dialysis based on our study as we only included 1 RCT and 5 observational cohorts. More data from large RCTs are considered to be a preferable way to bring clarity to this question. And the all-cause death endpoint was evaluated in only 2 of the 6 meta-analyzed studies. Second, although we performed the subgroup analysis based on the type and dosage of NOACs, dosage variability of NOACs in our study showed no difference in SSE and major bleeding, further scrutinized analysis is restricted given the limited patients number. The results of subgroup analyses should be interpreted cautiously. The data of dabigatran could not be assessed in the subgroup analysis because only one study by Chan et al. (33) studied the use of dabigatran vs. warfarin. In addition, comparative effectiveness and safety outcomes of edoxaban compared with warfarin were not assessed because of the limited data. Third, according to the Cochrane handbook, the publication bias was not formally assessed when the number of included studies was <10. As such, the results of publication bias should be interpreted cautiously and further assessed. Fourth, we pooled the unadjusted and adjusted data in the main analysis. Although we observed similar findings as the main analysis when only including the studies with adjusted data, the potential unmeasured confounders still existed. Fifth, ESRD patients on peritoneal dialysis and hemodialysis were not separately analyzed in our present study due to the limiting data. Finally, this review was not pre-registered online.

Conclusion

The use of NOACs, especially factor Xa inhibitors (rivaroxaban or apixaban), showed at least similar effectiveness and safety outcomes compared with warfarin use in dialysis patients with AF.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1005742/full#supplementary-material

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EDITED BY
Wengen Zhu,
The First Affiliated Hospital, Sun Yat-sen University, China

REVIEWED BY
Zi Amber Ye,
Royal North Shore Hospital, Australia
Yuxiang Zheng,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

*CORRESPONDENCE
Huizhuang Guo
doctorguo84@sina.com

†These authors share first authorship

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Oral anticoagulant therapy for patients with new-onset atrial fibrillation following acute myocardial infarction: A narrative review

Shenglong Yu[1†], Chenxi Li[2†] and Huizhuang Guo[3*]

[1]Department of Cardiovascular, Panyu Central Hospital, Guangzhou, China, [2]Medical Department, Queen Mary School, Nanchang University, Nanchang, China, [3]Department of Radiology, Panyu Central Hospital, (Medical Imaging Institute of Panyu District), Guangzhou, China

Background: To evaluate the advantages and disadvantages of anticoagulant therapy and provide a piece of information on anti-thrombotic treatment strategies for patients with new-onset atrial fibrillation (NOAF) and acute myocardial infarction (AMI).

Methods: Literature from PubMed and Google scholar were screened until August 2022. Studies assessing oral anticoagulant (OAC) treatments for NOAF in patients with AMI were evaluated for inclusion.

Results: Three retrospective cohort studies were included. In the study performed by Madsen et al., patients with previously diagnosed AMI with or without NOAF were followed up for 5.8 years. About 38% of NOAF patients with anticoagulant therapies, which could reduce long-term mortality [adjusted hazard ratio (HR): 0.69; 95% confidence interval (CI): 0.47–1.00]. Hofer et al. performed a single-center cohort study containing 1,372 patients with AMI with an 8.6-year follow-up period. Dual anti-thrombotic therapy (DAT) did not show the effect on the survival in NOAF (adjusted HR: 0.97; 95% CI: 0.65–1.57), while triple antithrombotic therapy (TAT) could reduce long-term cardiovascular mortality (adjusted HR: 0.86; 95% CI: 0.45–0.92). Petersen et al. also did a cohort study with 1-year follow-up duration. It showed that anticoagulant therapies demonstrated positive results (HR: 0.78; 95% CI: 0.41–1.47).

Conclusion: Recent studies have shown that anticoagulant therapy in AMI-NOAF patients can obviously reduce the mortality of AMI-NOAF patients, especially OAC therapy. Further clinical trials could confirm these findings.

KEYWORDS

atrial fibrillation, new-onset, myocardial infarction, antithrombotic therapy, review

Introduction

Acute myocardial infarction (AMI) and atrial fibrillation (AF) are the most common cardiovascular disease and cardiac arrhythmia in the settings, respectively (1–3). The two diseases share common risk factors, (4) and the presence of either can lead to an increased risk of the other (5–7). Patients with AMI are frequently accompanied by new-onset atrial fibrillation (NOAF) based on multiple mechanisms, such as atrial ischemia, atrial stretch, severe autonomic activation, and hormonal activation (8–11). Recent studies have shown that NOAF following AMI (AMI-NOAF) is strongly correlated to the increased risks of stroke, recurrence of MI, and both short- and long-term mortality (12–16). Thus, the monitoring and treatment of these patients have been taken into serious consideration.

The antithrombotic therapy for AMI-NOAF patients is contradictory. For AMI, dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is indicated to prevent stent thrombosis, (17) while in AF patients, oral anticoagulant (OAC) therapies including vitamin K antagonists (VKAs) or non-vitamin K oral anticoagulants (NOACs) are more effective in preventing stroke and other thromboembolic events (18, 19). However, triple therapy combining DAPT with an anticoagulant is usually associated with an increased rate of excessive bleeding, which limits the clinical application (20). During the past decades, large randomized clinical trials showed that using NOACs in patients with AF who had undergone percutaneous coronary intervention (PCI) may reduce the risk of bleeding compared to VKAs and DAPT without increasing the incidence of thrombotic events (21–23). Therefore, in this review, we evaluated the advantages and disadvantages of anticoagulant therapy and provided a piece of information on anti-thrombotic treatment strategies for patients with AMI-NOAF.

Methods

Two investigators searched the electronic database until August 2022 independently. Relevant articles were screened from PubMed and Google scholar by using the following keywords: (AMI OR acute coronary syndrome) AND (atrial fibrillation) AND (non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban OR VKAs OR warfarin). Studies were included if they assessed oral anticoagulant treatments (NOACs or VKAs) for NOAF in patients with AMI.

The corresponding searched results were recorded in **Supplementary Table 1**. After screening titles and abstracts of publications, two authors extracted data independently. Then, the full-text screening was performed to determine whether the literature met the inclusion criteria. Disagreements were resolved by discussing with the third researcher. The baseline information of each study was recorded, including the name of the first author, publication year, the types of anticoagulants, study design, baseline characteristics of the investigated population, and the study outcome.

Results

Figure 1 shows the diagram of the retrieved study selection for this review. A total of 143 retrieved records were retrieved from the PubMed database. Firstly, titles and abstracts of all these records were screened, and then 120 studies were excluded according to the predetermined criteria. In the full-text screenings, we further excluded 20 studies because of the following reasons: (1) nine studies did not focus on new-onset AF, but the pre-existing AF, (2) seven studies were not written in English, and (3) four studies were reviews. Finally, three studies in total (24–26) (all of these studies were retrospective cohort studies) were included in this narrative review.

Table 1 shows the baseline characteristics of all included studies. Each study was published in 2021. The inclusion sample size for all included studies ranged from 1372 to 161266. A total of 170,257 patients in total with previously diagnosed AMI or acute coronary syndrome (ACS) and with or without NOAF. The following-up period was from the range of 1 to 8.6 years. The primary and second outcome results were also shown in **Table 1**.

Madsen et al. described a sizeable single-center cohort including 7,944 patients with ST-segment elevation myocardial infarction (STEMI) treated with PCI between 1999 and 2016 to investigate the prognostic implication of OAC therapy for AMI-NOAF, of which 75.2% were males (24). Among these patients with STEMI, 296 (3.7%) of them developed NOAF. It was reported that patients with NOAF were older, more frequently non-smoking women and often more likely to have cardiovascular comorbidities. NOAF can lead to increased long-term mortality [adjusted hazard ratio (HR) for STEMI with NOAF vs. without NOAF: 1.48; 95% confidence interval (CI): 1.20–1.82]. It can also increase the risk of bleeding leading to hospitalization (adjusted HR: 1.36; 95% CI: 1.00–1.85). About 38% of NOAF patients were treated with OAC therapy, which can decrease long-term mortality (adjusted HR: 0.69; 95% CI: 0.47–1.00).

Hofer et al. also performed a single-center retrospective cohort study containing 1,372 patients with AMI to observe the development of *de novo* AF. They found that in the acute phase of AMI, 149 (10.9%) patients developed NOAF. After 8.6 years of following up analysis showed that 30.5% of patients died because of cardiovascular diseases. These included 93 (62.4%) patients in the NOAF group. It was reported that NOAF has a strong correlation with long-term cardiovascular mortality (adjusted HR: 1.45; 95% CI: 1.19–2.57). Dual anti-thrombotic therapy (DAT) did not show the effect on the

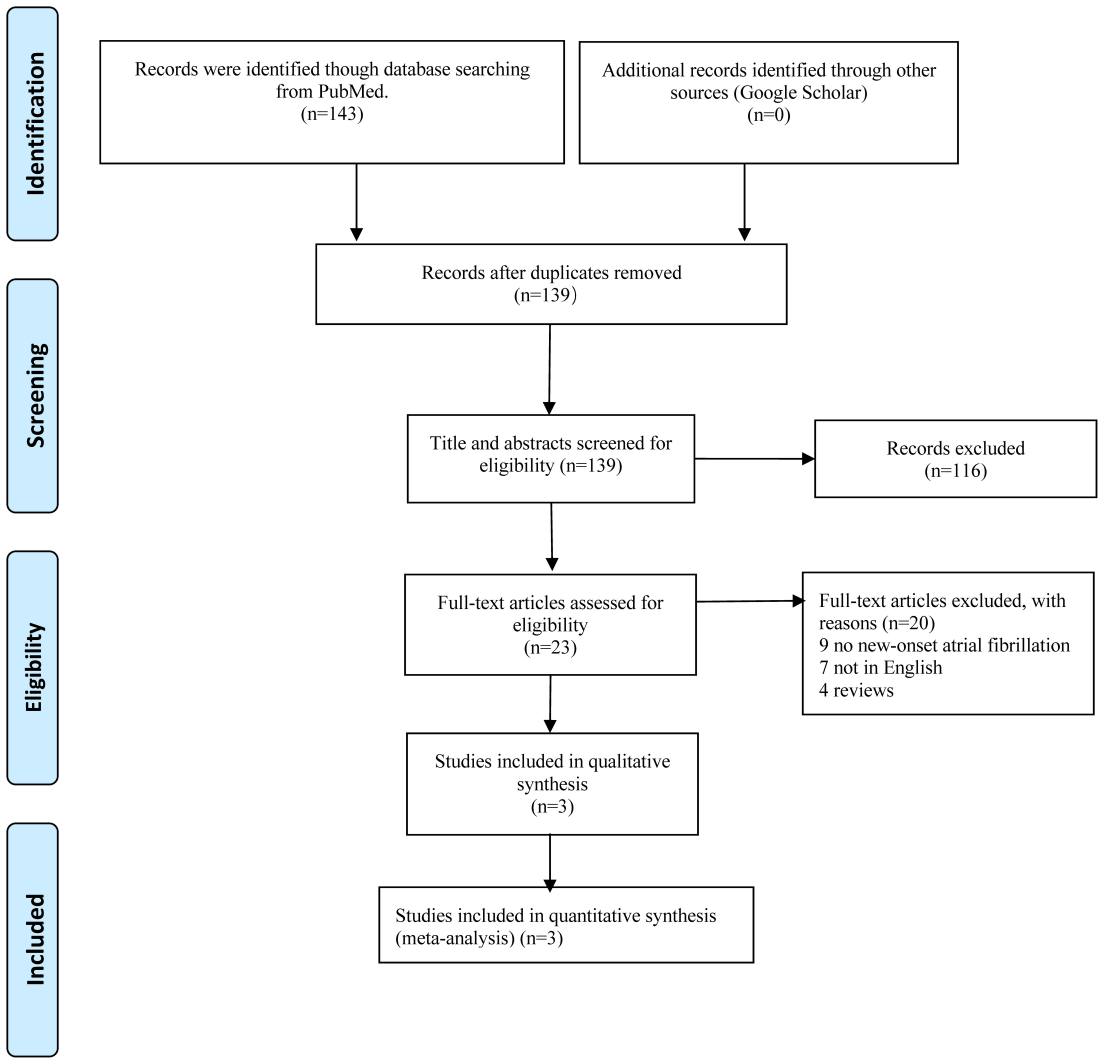

FIGURE 1
Diagram of retrieved study selection of this review.

survival in NOAF (adjusted HR: 0.97; 95% CI: 0.76–1.21). While triple antithrombotic therapy (TAT) can reduce long-term cardiovascular mortality (adjusted HR: 0.86; 95% CI: 0.45–0.92). But a recent meta-analysis showed that DAT can reduce bleeding and has a similar effect on preventing AF with ACS or PCI (27). Thus, the optimal treatment regimen should be decided by experts in specific conditions.

Petersen et al. did a nationwide cohort study; 161,266 ACS patients were included. In patients with newly diagnosed AF, a high incidence of ischemic stroke was observed (HR: 1.38; 95% CI: 1.22–1.56). Also, compared to patients without AF, a higher mortality rate was in the NOAF group (HR: 1.52; 95% CI: 1.43–1.62). As for the recurrence of myocardial infarction, there was no significant difference was found in patients with firstly diagnosed AF (HR: 0.99; 95% CI: 0.91–1.07). And patients with NOAF also showed an increased rate of bleeding (HR: 1.28; 95% CI: 1.15–1.43). OAC treatment also showed positive results. It had the lowest incidence of ischemic stroke in both pre-existing AF (HR: 0.87; 95% CI: 0.63–1.20) and new-onset AF (HR: 0.78; 95% CI: 0.41–1.47), although the difference was not statistically significant.

There are also some limitations in these three studies. The study of Madsen et al. does not contain information on the cause of death. And some asymptomatic patients may have undiagnosed previous paroxysmal atrial fibrillation which may give rise to an underestimated incidence. Additionally, due to a lack of power, the analysis of OAC therapy in NEW-AF which may be a confounding factor was not included. The limitations of Hofer's study were that there was no non-fatal data of ischemic stroke or bleeding complications, which may have an effect on the final results. Additionally, the follow-up visits of patients using DAT and TAT were not completed and the

TABLE 1 Summary of the relevant studies of this review.

References	Definition of NOAF	Study design	Follow-up period	Primary outcome results	Secondary outcome results
Madsen et al. (24)	A diagnosis of AF within 30 days after STEMI	Single-center, retrospective cohort study, only STEMI patients (n = 7,944)	5.8 years	Long-term all-cause mortality: STEMI with NOAF (n = 296) vs. without NOAF (n = 7,648): HR (95% CI) = 1.48 (1.20–1.82), $P < 0.001$; NOAF with OAC therapy (n = 113) vs. NOAF without OAC therapy (n = 183): HR (95% CI) = 0.69 (0.47–1.00), $P = 0.049$	Bleeding leading to hospitalization: STEMI with NOAF vs. STEMI without NOAF: HR (95% CI) = 1.36(1.00–1.85), $P = 0.050$; NOAF with OAC therapy vs. NOAF without OAC therapy: HR (95% CI) = 1.31(0.75–2.27), $P = 0.34$
Petersen et al. (25)	A diagnosis of AF during admission with ACS with no prior history of AF	Nationwide, retrospective cohort study, first-time admission with ACS (n = 161,266)	1 year	Ischemic stroke: ACS with a history of AF (n = 18,961), or NOAF (n = 6,427) vs. free of AF (n = 161,266): HR (95% CI) = 1.38 (1.22–1.56), 1.67 (1.38–2.01); OAC vs. antiplatelet therapy in patients with history of AF (n = 6,679), or NOAF (n = 2,331): HR (95% CI) = 0.87 (0.63–1.20), 0.78 (0.41–1.47)	All-cause mortality: With a history of AF, or with NOAF vs. without AF: HR (95% CI) = 1.25 (1.21–1.31), 1.52 (1.43–1.62); OAC vs. antiplatelet therapy in patients with history of AF, or with NOAF: HR (95% CI) = 0.75(0.68–0.84), 0.75(0.61–0.91); Bleeding: With a history of AF (6.9%), or with NOAF (5.7%) vs. without AF (3.6%): HR (95% CI) = 1.22(1.14–1.30), 1.28 (1.15–1.43); OAC vs. antiplatelet therapy in patients with history of AF, or with NOAF: HR (95% CI) = 1.18 (0.99–1.41), 1.11 (0.83–1.49)
Hofer et al. (26)	A new onset of atrial fibrillating impulses at the time of admission or during the hospitalization	Single-center, retrospective cohort study, AMI (STEMI or NSTEMI) patients	8.6 years	Long-term cardiovascular mortality: NOAF (n = 149) or pre-existing AF (n = 90) vs. free of AF (n = 1,133): HR (95% CI) = 1.45 (1.19–2.57), 0.70 (0.35–0.98); DAT (n = 21) or TAT therapy (n = 56) vs. DAPT only therapy (n = 32) in patients with NOAF: HR (95% CI) = 0.97 (0.65–1.57), 0.86 (0.45–0.92)	Fatal bleeding events: No difference between different treatment strategies: NOAF (n = 4): 2.6% vs. pre-existing AF (n = 2): 2.2%, $P = 0.824$

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; CI, confidence interval; DAPT, dual antiplatelet therapy; DAT, dual anti-thrombotic therapy: the combination of single anti-platelet therapy (aspirin or clopidogrel) and VKA; HR, hazard ratio; NOAF, new-onset atrial fibrillation; OAC, oral anticoagulant; STEMI: ST-segment elevation myocardial infarction; TAT: triple antithrombotic therapy: OAC plus DAPT; PCI, percutaneous coronary intervention; $P2Y_{12}$-I, $P2Y_{12}$ inhibitors.

rates of AF episodes were not evaluated during the observation period. What's more, this investigation was limited to VKAs. Because at that time, NOACs haven't been approved by FDA and EMA. As for the limitations of Petersen's study, first, this is an observational study, since the risk of residual confounding cannot be excluded, the assessment of antithrombotic therapy is challenging. Second, bleeding cannot be sorted by criteria. Third, the treatment regimens were drastically changed during the treatment period.

Discussion

Epidemiology of acute myocardial infarction-new-onset atrial fibrillation

Arrhythmia is not uncommon during the acute phase of AMI. The incidence of NOAF in patients with AMI varies among studies with a wide range from 2 to 21% (28–30). Approximately half of NOAF developed within 30 days of the onset of AMI (31). Notably, the onset of NOAF was not evenly distributed, as 30% of events occurred at the time or within 2 days after AMI, 16% during the intermediate stage of 3 to 30 days after AMI, while 54% occurred more than 30 days with gradually decreased during follow-up (31). Previous studies have shown that the incidence of NOAF after AMI ranges from 3.7 to 22.6% (3–7). Due to the loss of effective atrial contraction, increased ventricular rate, shortened ventricular diastolic time, irregular RR interval and other factors during AF, the decrease in ventricular filling and ejection, the decrease in coronary blood supply and the increase of myocardial oxygen consumption aggravates the degree of cardiac injury in patients with AMI. In addition, after the loss of normal atrial systolic function, atrial blood flow stagnation or turbulence can easily lead to thrombosis. These factors make patients with AMI more prone to hospital complications.

Risk factors of acute myocardial infarction-new-onset atrial fibrillation

Atrial fibrillation shares a couple of risk factors with AMI, such as aging, hypertension, obesity, diabetes, alcohol consumption, and sleep-disordered breathing (4, 5, 18). Therefore, the two diseases may share similar

pathophysiological pathways, and the co-occurrence of these two diseases seems not to be avoidable (4). The cause of AMI-NOAF is multifactorial with older age, female sex, hypertension, cardiogenic shock, and congestive heart failure have been identified as risk factors (32, 33). The conventional view holds that infarct size and severity contribute to the development of AF after AMI (34, 35). In contrast, a recent community cohort study of 3,220 people conducted by Jabre et al. found that AMI characteristics and indicators of severity, except anterior location, higher Killip levels, and lower left ventricular ejection fraction, are mostly irrelevant to the occurrence of NOAF (31). NOAF occurs in a short time after AMI. Atrial ischemia, atrial infarction, atrial dilatation and elevated intraatrial pressure may be the main causes in the early stage, while inflammation, oxidative stress and atrial remodeling involved in autonomic nerves may be the main causes in the later stage (8–11). The mechanism of NOAF after AMI is complex and has not been fully elucidated at present.

Mechanisms of acute myocardial infarction-new-onset atrial fibrillation

Since coronary occlusion is the pathogenesis of AMI, the resulting further myocardial ischemia is considered the most critical mechanism for the onset of NOAF. A case-control study conducted by Alasady et al. (36) demonstrated that approximately half of the AMI-NOAF patients had a critical lesion in the sinoatrial nodal branch originating from the right coronary or left circumflex arteries, which was 25-times more than the patients free of AF. Therefore, the atrial branch affected by coronary artery disease is considered a strong predictor of AMI-NOAF. Hofer et al. (26) and Alasady et al. (36) found that patients with AMI-NOAF were significantly less likely to receive timely PCI and stent implantation compared to those free of AF, resulting in broader tissue damage and scar formation. The peak creatinine kinase value is a surrogate marker for evaluating the infarct size (37), while the N-terminal proB-type natriuretic peptide (NT-proBNP) level indicates cardiac strain. In the research mentioned above, both creatinine kinase and NT-proBNP were elevated significantly in the AMI-NOAF patients, suggesting that the tissue damage and overstretch as the results of myocardial ischemia may develop an extended electrical and structural remodeling of the heart, and trigger the onset of AF. In animal models, ligation of the atrial branch of the right coronary artery would result in isolated atrial ischemia. In the ischemia region, there is a significantly decreased conduction velocity of atrial cardiomyocytes, which may promote and stabilize reentry that maintains AF (38). Additionally, inflammation reaction may also relate to AF. Psychari et al. (39) showed that the level of IL-6 in AF patients is obviously higher than it in non-AF patients. Thus, patients with AMI may generate systemic inflammatory response which may be responsible for NOAF. Yoshizaki et al. (40) demonstrated that in patients with NOAF following AMI, the level of white blood cell and C-reaction protein are higher than in patients with no NOAF (41).

Prognosis of acute myocardial infarction-new-onset atrial fibrillation

The general clinical characteristics of patients with NOAF after AMI are old age, low blood pressure, higher admission heart rate, higher Killip grade, more severe coronary artery disease and so on. Poor general condition directly affects the patient's condition and increases the difficulty of treatment, which increases the risk of in-hospital heart failure, re-infarction, cerebral infarction and hemorrhage, resulting in poor short-term and long-term prognosis and increased mortality. The SPRINT trial compared the pre-thrombolytic era with the thrombolytic era, the 30-day and 1-year mortality rates of patients with AF after AMI in the pre-thrombolytic era were 27.6 and 42.5%, respectively, and the 30-day and 1-year mortality rates of patients with paroxysmal AF after MI in the thrombolytic era were 25.1 and 38.4%, respectively (42). Through further multivariate adjustment, it was found that the mortality of patients with AF after MI in the thrombolytic era was significantly lower than that in the pre-thrombolytic era. The incidence of NOAF after PCI in the OACIS study was 12.0% (7). A meta-analysis including 43 studies (278,854 participants) showed that among patients with AMI, the presence of AF would lead to at least a 40% higher mortality rate than those with sinus rhythm, while this poor prognosis persists regardless of the timing of AF onset (29). Notably, AMI-NOAF was still associated with an increased risk of death, even after adjusting for risk factors such as age, diabetes, hypertension, prior AMI, heart failure, and coronary revascularization status (29). Nevertheless, the prognosis of cardiovascular disease and death related to the first detection of AF in ACS remains to be further elucidated.

Antithrombotic therapy for acute myocardial infarction-new-onset atrial fibrillation

Myocardial infarction is usually caused by a rupture of the plaque on the basis of a severe stenosis of the coronary artery, leading to thrombosis. AMI can initiate atherosclerotic plaques which are prone to rupture, owing to the high level of lipids and apoptotic cells, which leads to a fatty core and thin fibrous cap (43). Thus, thrombosis is formed and endothelial coverage is lost. This triggers two main pathways. One is coagulation activation, the other is platelet activation (44). Platelet recruitment is also related to two pathways. The first is dependent on the coagulation cascade. The second is associated with tissue factor release. AF can also lead to coagulation

disorder through thrombogenesis by affecting the coagulation cascade (45). Thus, antithrombotic therapy is necessary for AMI-NOAF treatment.

Because there are plenty of pathways and factors in the coagulation process which is related to thrombosis formation. It is crucial to block any of them so that can people effectively decrease the risk of thrombosis formation. There are some examples. First, inhibiting platelet aggregation is essential for the whole treatment process. There are three main stages of the process being focused on, including the blocking of TXA_2 formation, the $P2Y_{12}$ ADP receptor and the IIbIIIa integrin. Second, aspirin is also an important anticoagulant drug. It contains acetylsalicylic acid (ASA) which can irreversibly block COX-1 and COX-2 through acetylation of the active sites. Therefore, the production of thromboxane and prostaglandin (PGs) from platelets-membrane arachidonate can be blocked. The inhibition of COX-1 can decrease the formation of prostaglandin H_2, a metabolic precursor of TXA_2, which can activate platelet. Additionally, inhibiting coagulation is also a major process. It can be obtained both directly and indirectly. Direct anticoagulation involves the direct inhibition of thrombin or factor Xa, while indirect anticoagulation requires antithrombin activation which can activate thrombin to react.

In clinical practice, physicians usually face the dilemma of choosing appropriate antithrombotic therapy for patients with AMI concomitant AF. Aspirin and a $P2Y_{12}$ inhibitor as the standard DAPT should be indicated to AMI patients, especially during the acute phase, to prevent recurrent MI and stent thrombosis, and to further reduce major adverse cardiac events (MACE), (46, 47) while anticoagulants (VKAs or NOACs) are recommended in patients with AF with a CHA_2DS_2-VASc score greater than 2 for preventing stroke and systemic embolic events, no matter whether it is new-onset or prior existent (48).

Unfortunately, TAT comprising DAPT combined with anticoagulant would increase the incidence of bleeding as reported previously, which was thought to be positively associated with the mortality rate (49–51). Therefore, how to balance the efficacy and safety in AMI-NOAF patients is a significant challenge for the optimal antithrombotic treatment, and several retrospective studies have made suggestions on this topic. Although there are enormous new antithrombotic drugs invented for treatment, how to choose an appropriate treatment for different patients is also a big point to focus.

Future directions

We included 3 studies in our narrative review to explore the efficacy and safety of antithrombotic therapy in AMI patients following new-onset AF. The data of these studies was well collected which increases the credibility and quality of this narrative review. According to the previous studies, we can obviously conclude that antithrombotic therapy plays a significant role in preventing thrombosis formation and reducing the mortality rate in AMI-NOAF patients. And it can also improve the prognosis of these patients. However, there are also some limitations of our study. Firstly, the number of studies included is very small. More clinical studies are needed to increase credibility. Secondly, the study performed by Hofer showed that DAT has a good effect on previously existing AF while there is no improvement in the prognosis of NOAF patients. But TAT exhibits better efficacy in NOAF patients than in pre-existing AF patients. However, some randomized controlled trials demonstrated that compared to TAT, DAT can significantly reduce bleeding events. And the use of TAT has a bias. Only patients with low bleeding risk can choose TAT treatment. Thus, how to choose the optimal regimen is still worthy of serious consideration. Finally, the efficacy of OAC is not evaluated in this review. OAC is a novel drug for these patients, however, there are not many clinical studies on OAC in the treatment of AMI-NOAF patients (46). But what is clear is that OAC can reduce the mortality rate.

Conclusion and further implications

Atrial fibrillation is a common complication of AMI. At present, the understanding of this complication has been gradually deepened. The pathogenesis of NOAF is not completely clear, further clinical or basic experiments will help to further explore the pathogenesis and break through the bottleneck for precision treatment. Finally, due to prolonged hospitalization, high incidence of hospital complications, high mortality, increased difficulty in hospital treatment management and poor long-term prognosis in patients with AMI complicated with NOAF, efforts should be made to identify those high-risk patients who can be monitored during hospitalization and who can benefit from early treatment. There are some studies showing the benefit of antithrombotic therapy such as OAC, TAT, and DAT, which can prevent thrombosis formation and reduce the risk of bleeding under certain conditions. Antithrombotic therapy for AMI-NOAF patients brings a promising future.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1046298/full#supplementary-material

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EDITED BY
Jianyong Ma,
University of Cincinnati, United States

REVIEWED BY
Dimitrios Tsakiris,
University of Basel, Switzerland
Nicolas Gendron,
Hôpital Européen Georges Pompidou, France

*CORRESPONDENCE
Alexander Kaserer
alexander.kaserer@usz.ch

†These authors share first authorship

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The impact of direct oral anticoagulants on viscoelastic testing – A systematic review

Sebastian D. Sahli[1†], Clara Castellucci[1†], Tadzio R. Roche[1], Julian Rössler[2], Donat R. Spahn[1] and Alexander Kaserer[1*]

[1]Institute of Anesthesiology, University and University Hospital Zurich, Zurich, Switzerland, [2]Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, United States

Background: In case of bleeding patients and in acute care, the assessment of residual direct oral anticoagulant (DOAC) activity is essential for evaluating the potential impact on hemostasis, especially when a timely decision on urgent surgery or intervention is required. Viscoelastic tests are crucial in a modern goal-directed coagulation management to assess patients' coagulation status. However, the role of viscoelastic test to detect and quantify residual DOAC plasma levels is controversially discussed. The aim of this review was to systematically summarize the evidence of viscoelastic tests for the assessment of residual DOAC activity.

Method: PubMed, Embase, Scopus, and the Cochrane Library were searched for original articles investigating the effect of rivaroxaban, apixaban, edoxaban, or dabigatran plasma levels on different viscoelastic tests of the adult population from database inception to December 31, 2021.

Results: We included 53 studies from which 31 assessed rivaroxaban, 22 apixaban, six edoxaban, and 29 dabigatran. The performance of viscoelastic tests varied across DOACs and assays. DOAC specific assays are more sensitive than unspecific assays. The plasma concentration of rivaroxaban and dabigatran correlates strongly with the ROTEM EXTEM, ClotPro RVV-test or ECA-test clotting time (CT) and TEG 6s anti-factor Xa (AFXa) or direct thrombin inhibitor (DTI) channel reaction time (R). Results of clotting time (CT) and reaction time (R) within the normal range do not reliable exclude relevant residual DOAC plasma levels limiting the clinical utility of viscoelastic assays in this context.

Conclusion: Viscoelastic test assays can provide fast and essential point-of-care information regarding DOAC activity, especially DOAC specific assays. The identification and quantification of residual DOAC plasma concentration with DOAC unspecific viscoelastic assays are not sensitive enough, compared to recommended anti-Xa activity laboratory measurements.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=320629], identifier [CRD42022320629].

KEYWORDS

DOAC, point-of-care, ROTEM, TEG, ClotPro, FXa inhibitor, FII inhibitor

Introduction

Direct oral anticoagulants (DOACs) are prescribed for stroke prevention in atrial fibrillation, for the prevention and treatment of venous thromboembolism and for secondary cardiovascular prevention (1, 2). Currently, five substances are approved with regional differences for clinical use by medical regulatory authorities: rivaroxaban, apixaban, edoxaban, and dabigatran (3). The prescription and use of DOACs is steadily increasing since the introduction in 2008 (4). They are taken orally as fixed-dose regimens with no regular monitoring required (5).

In acute care, the assessment of residual DOAC activity is essential for evaluating the potential impact on hemostasis, especially when a timely decision on urgent surgery or intervention is required (6–9). Residual DOAC plasma levels can be quantified by high-pressure liquid chromatography-tandem mass spectrometry (HPLC-MS) or by chromogenic anti-Xa and anti-IIa assays (10). However, both measurements are more time-consuming compared to point-of-care assays. HPLC-MS measurement requires on average 2 h, whereas specific DOAC anti-Xa assays deliver results within 30 min. No standardized point-of-care test is currently available to evaluate the anticoagulant effects of DOACs (7, 8). Viscoelastic tests are crucial in a modern-goal directed coagulation management to assess patients' coagulation status (11, 12). The role of viscoelastic test to detect residual DOAC plasma levels in acute care is controversially discussed. Therefore, this systematic review compiles the existing evidence on the accuracy of point-of-care viscoelastic tests to assess residual DOAC effects.

Viscoelastic assays

Different from standard coagulation assays, viscoelastic tests are point-of-care systems analyzing in whole blood the process of clot formation and subsequent lysis in real time with on-line graphic display. The rotational thrombelastic system (ROTEM, Werfen, Bedford, MA, USA) and thrombelastographic system (TEG, Haemonetics Corporation, Boston, MA, USA) provide similar information but operate with different techniques. While ROTEM delta uses a rotating pin, the TEG 5000 uses a cup oscillating around the pin. The new ROTEM sigma operates by the same principle as delta but is automated with ready-to-use cartridges for simultaneous testing. The new TEG 6s system uses a resonance method, is fully automated and uses prefabricated cartridges, too. Differences in the terminology of the results between both devices are shown in **Figure 1**. ClotPro (Haemonetics Corporation, Boston MA, USA; formerly enicor GmbH, Munich, Germany) provides six channels for parallel testing. It has a unique Active-Tip technology with the dried reagents contained in a sponge at the pipette tip.

With the different viscoelastic systems, several assays can be performed depending on the clinical question (13). For ROTEM and ClotPro, the clotting time (CT) and for TEG the reaction time (R) is defined as the time from the beginning of the test until a clot firmness amplitude of 2 mm is achieved which reflects the velocity of thrombin generation.

Methods

This systematic review follows the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (**Figure 2**). We defined the PICO question for this review as "In adult patients taking DOACs (Population), are results in point-of-care viscoelastic tests (Intervention) compared to standardized laboratory tests or DOAC naïve blood (Control) altered by the drug (Outcome)?" This work was registered on the international prospective register of systematic reviews PROSPERO (registration ID # CRD42022320629).

Eligibility criteria and study selection

We included original articles addressing the coagulation profile of DOACs assessed with viscoelastic assays of the adult population (>18 years old) from database inception to December 31, 2021. Articles were excluded if they did not consider apixaban, edoxaban, rivaroxaban, and dabigatran; did not involve whole blood viscoelastic assays; instruments for measuring activated clotting time (ACT) solely; or referred to animal studies. Non-commercially available assays were considered beyond the scope of this review and are mentioned, but not further described. Poster abstracts and case reports were excluded too.

Search strategy

Four electronic databases have been queried: US National Library of Medicine (MEDLINE via PubMed), Excerpta Medica Database (EMBASE), Scopus database by Elsevier, and the Cochrane Library for Trials. We used following keywords and operators: (ROTEM or TEG or sonoclot or clotpro or reorox or viscoelastic or "viscoelastic hemostatic assay" or "viscoelastic test" or thrombelastometry or thrombelastography or thrombelastography or "hemostatic assay") AND (DOAC or "direct oral anticoagulant" or NOAC or "new oral anticoagulants" or "non-vitamin k anticoagulants" or rivaroxaban or dabigatran or apixaban or edoxaban).

References of articles were retrieved for the inclusion of related articles. Publications in English and German language were considered.

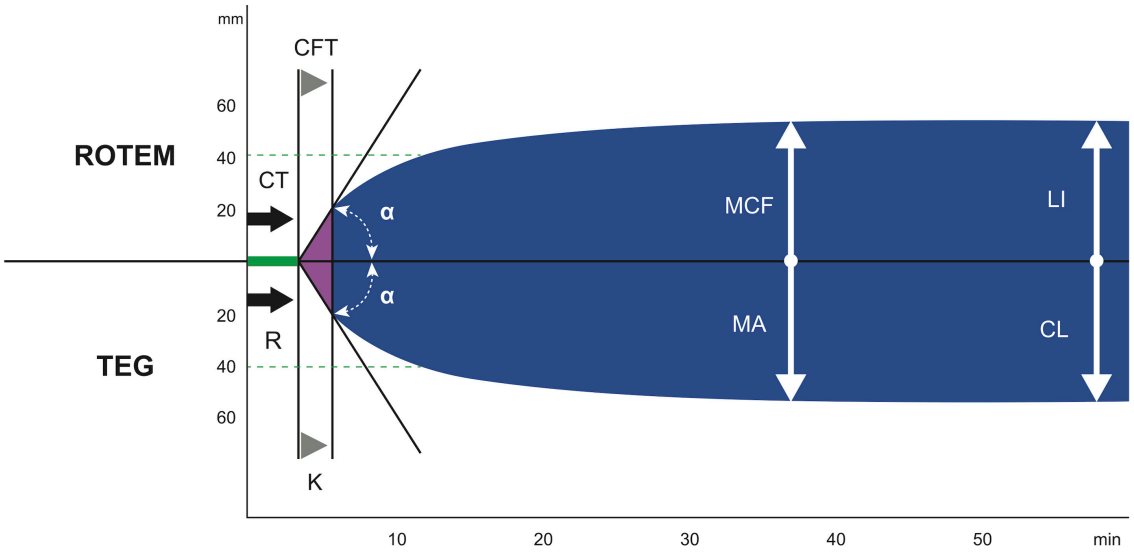

FIGURE 1
The difference in the terminology of the most important results between ROTEM and TEG. ROTEM parameters: CT, clotting time; CFT, clot formation time; α, α angle; MCF, maximum clot firmness; LI (30/60), lysis index 30 and 60 min after CT. TEG parameters: R, reaction time; k, kinetics; α, α angle; MA, maximum amplitude; CL (30/60), clot lysis after 30 and 60 min (89). With reprint permission by Georg Thieme Verlag KG.

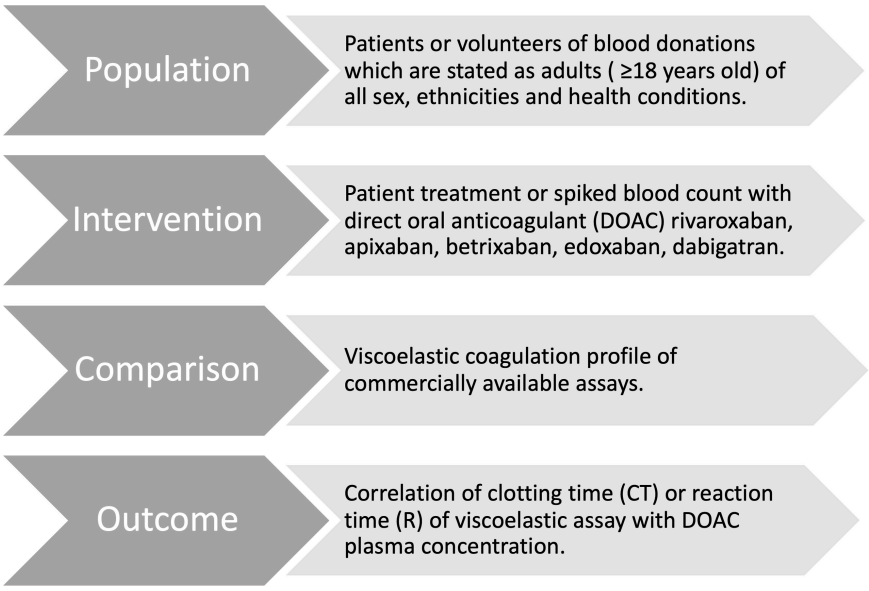

FIGURE 2
Clinical questions for evidence-based practice.

Selection process

Two reviewers (CC and SDS) examined studies independently by reading the titles and abstracts. The studies corresponding to the inclusion criteria were read and the reviewers abstracted data. Any discrepancies between the reviewers were resolved by discussion.

Data items

A standard form was used to extract the following data: author(s), year of publication, study site and country, study design, number of overall patients, anticoagulant(s) examined, viscoelastic test(s) used, plasma concentrations of anticoagulant(s), main findings.

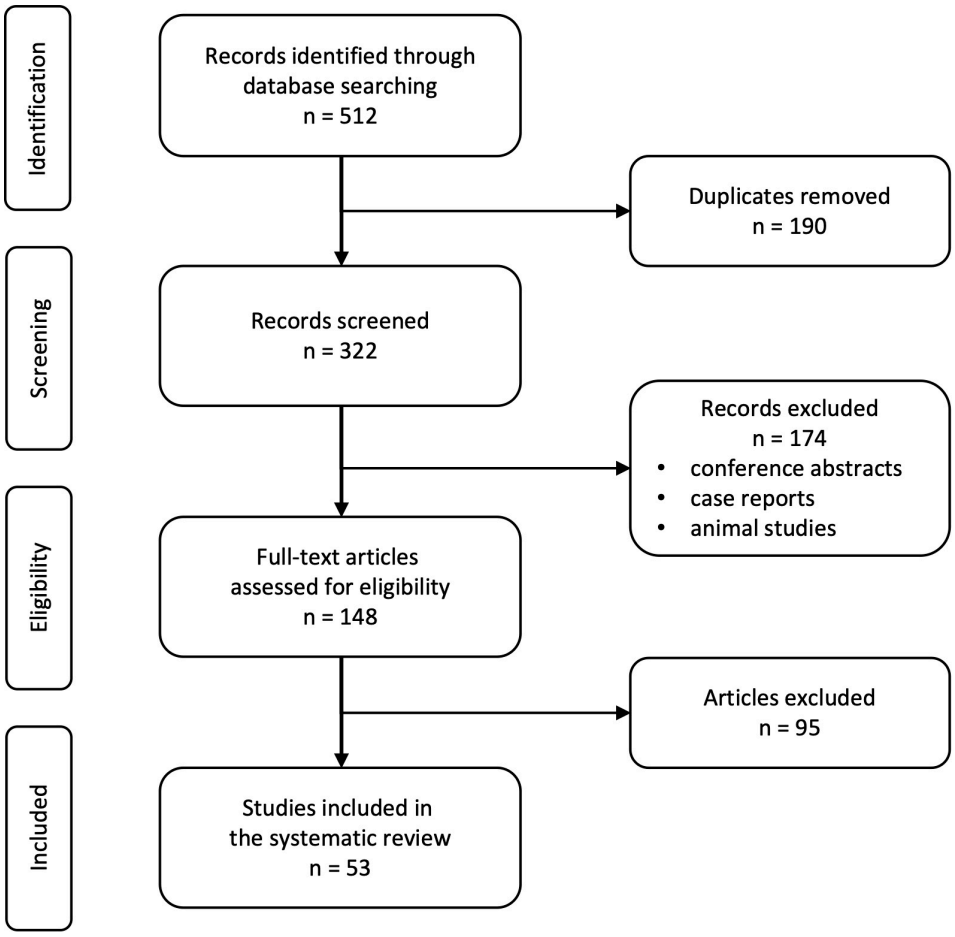

FIGURE 3
PRISMA flow chart of the selection process.

Risk of bias

The methodological quality of each included article was evaluated by the Newcastle Ottawa Scale (NOS) (14) (**Supplementary Table 1**). Three independent authors performed the evaluation (SDS, CC, and TRR). Disagreement was solved by discussion.

Statistics

We labeled the strength of the association, for absolute values of r, the following: 0 to 0.19 is regarded as very weak, 0.2 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.6 to 0.79 as strong and 0.8 to 1 as very strong correlation (15). Regression analyses values of R^2 were converted into an effect size f according to Cohen (16), where f = 0.10 represents a weak effect, f = 0.25 a moderate effect and f = 0.40 a strong effect (17).

Results

We identified 512 records in the mentioned databases of which 190 duplicates were automatically removed (**Figure 3**). The remaining 322 records were screened for suitability and a total of 148 full-text articles were proofread. A total of 53 studies met the pre-defined quality and inclusion criteria.

Viscoelastic analysis of direct factor Xa inhibitors

Rivaroxaban

We identified 31 studies describing rivaroxaban action in whole blood with viscoelastic methods (18–48) (**Supplementary Tables 2.1–2.3**). Except for the well-documented viscoelastic parameters clotting time (CT) and reaction time (R), rivaroxaban showed either no significant influence or was not analyzed for other parameters besides individual and

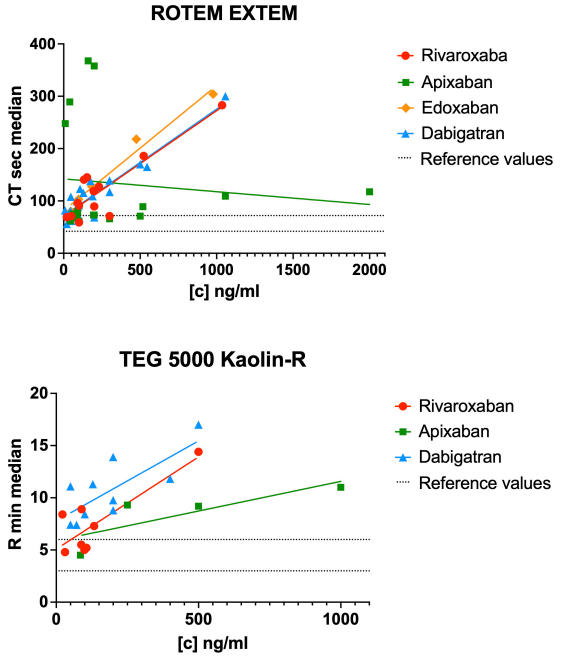

FIGURE 4
Reported clotting time (CT) and reaction time (R) in relation to the DOAC plasma concentration of the included studies for the ROTEM EXTEM and TEG 5000 kaolin assays. [c] DOAC plasma concentration in ng/ml. The dashed lines represent the lower and upper reference values for ROTEM EXTEM CT [42, 72 s (88)] and TEG 5000 R [3, 6 min (90)].

heterogenous nominations. The CT and R in relation to the rivaroxaban plasma concentration are shown in **Figure 4**.

Rivaroxaban and rotational thrombelastometry

Seventeen studies assessed rivaroxaban measurements in whole blood with ROTEM (Werfen, Bedford, MA, USA) (18, 19, 23, 24, 27, 28, 30, 31, 34, 36, 39–41, 44, 45, 47, 48) (**Supplementary Table 2.1**). A significant correlation between rivaroxaban plasma concentration and duration of clotting time (CT) was shown for EXTEM (strong to very strong correlation) (24, 28, 30, 34, 44, 45), INTEM (moderate to strong correlation) (24, 28, 30, 34, 45), NATEM (strong correlation) (19), FIBTEM (strong correlation) (44), and HEPTEM (strong correlation) (28) assays (**Table 1.1**). One study did not find any significant effect of rivaroxaban on ROTEM parameters (31).

Three studies examined modified ROTEM assays (18, 40, 48). Some of these non-commercially available modified ROTEM activators showed promising results in detecting rivaroxaban plasma levels (**Table 2.1**).

Rivaroxaban and thrombelastography

Thirteen studies described rivaroxaban action in whole blood with TEG (Haemonetics Corporation, Boston MA, U.S.A.) (20–22, 25, 26, 31–33, 35, 37, 42, 43, 46) (**Supplementary Table 2.2**). Of these, four studies did not report the exact rivaroxaban concentration under which conditions the viscoelastic tests were performed (22, 25, 32, 33). Four studies investigated with the new cartridge-based anti-factor-Xa [AFXa] channel of TEG 6s (20–22, 25), to the best of our knowledge not yet commercially available at the time of manuscript preparation (**Table 1.2**).

A significant correlation between rivaroxaban plasma concentration and reaction time (R) have been reported for the specific anti-factor-Xa channel [AFXa] (strong to very strong correlation) (20, 21, 37), and for citrated kaolin channel (moderate to strong correlation) (35, 37).

The study of Kaaber et al. mentions that approximately 65% of the patients treated with rivaroxaban presented with RapidTEG^{TM} activated clotting time within the normal reference, but that those with an activated clotting time above this level had a significantly increased risk of severe bleeding with high transfusion demands (33). Three studies did not find any significant effect of rivaroxaban on TEG 5000 parameters (31, 32, 42). One study compared the results descriptively only (46) (**Table 2.2**).

Rivaroxaban and ClotPro analyzer

Two studies reported results from the ClotPro analyzer (29, 38) (**Supplementary Table 2.3**). The commercially available Russel's viper venom test (RVV-test) for the detection of factor Xa antagonists showed strong to very strong correlations between rivaroxaban plasma concentration and clotting time (CT) (29, 38) (**Tables 1.3**, **2.3**).

Viscoelastic thresholds for rivaroxaban concentrations

Rivaroxaban plasma concentrations between 30 and 150 ng/ml can be detected by threshold values of the viscoelastic parameters CT and R (18–22, 24, 30, 38, 40) (**Figure 5** and **Tables 1.1**–**1.3**). In particular, the RVV-test of ClotPro and the AFXa channel of TEG 6s show high sensitivity and specificity. It is important to mention that the study of Bliden et al. analyzed the results of rivaroxaban and apixaban in a pooled setting (22).

Apixaban

Twenty-two studies were identified analyzing the effects if apixaban on viscoelastic testing (18, 20–22, 25–27, 29, 32, 33, 35, 38, 40, 45, 46, 48–54) (**Supplementary Tables 2.1**–**2.3**). The CT and R in relation to the apixaban plasma concentration are shown in **Figure 4**.

Apixaban and rotational thrombelastometry

We revealed nine studies assessing the effects of apixaban on ROTEM (18, 27, 40, 45, 48–52) (**Supplementary Table 2.1**). Out of these, three studies used modified or *ad hoc* designed assays (18, 40, 48), whereas the other studies focused on the EXTEM (27, 45, 49–52), INTEM (27, 45), NATEM (50) and FIBTEM (45) assays. Apixaban caused a statistically significant

TABLE 1.1 Study defined ROTEM clotting time (CT) thresholds for detection of the residual DOAC plasma concentration stratified by assays.

Assay	Threshold ng/ml	CT sec	Sensitivity %	Specificity %	Study
Rivaroxaban					
EXTEM	30	60	96	75	Henskens et al. (30)
	153	79	92	62	Chojnowski et al. (24)
INTEM	30	195	77	80	Henskens et al. (30)
	153	200	77	69	Chojnowski et al. (24)
NATEM	30	715	81	83	Aranda et al. (19)
Modified					
m-ROTEM	20	197 [&]	85	100	Pailleret et al. (40)
	30	197 [&]	90	85	Pailleret et al. (40)
	100	197 [&]	96	64	Pailleret et al. (40)
LowTF	0	426	90	88	Adelmann et al. (18)
	200	524	98	96	Adelmann et al. (18)
Apixaban					
Modified					
m-ROTEM	20	197 [&]	85	100	Pailleret et al. (40)
	30	197 [&]	90	85	Pailleret et al. (40)
	100	197 [&]	96	64	Pailleret et al. (40)
LowTF	0	432	96	97	Adelmann et al. (18)
	200	548	95	74	Adelmann et al. (18)
Dabigatran					
EXTEM	20	90	85	100	Taune et al. (69)
	30	60	91	75	Henskens et al. (30)
INTEM	30	195	52	50	Henskens et al. (30)
Modified					
Thrombin-b	20	154	100	100	Taune et al. (69)

[&] Analysis pooled with apixaban and rivaroxaban cases. Reference ranges: 2.5 to 97.5 percentiles [median] of EXTEM CT: 42 to 74 s [55 s]; INTEM CT: 137 to 246 s [184 s] (88). NATEM, non-activated rotational thromboelastometry; EXTEM, extrinsic activated rotational thromboelastometry; INTEM, intrinsic activated rotational thromboelastometry; Modified assays customized by study team; m-ROTEM, assay activated with tissue factor and phospholipid vesicles; LowTF, assay activated with low tissue factor; Thrombin-b, assay activated with thrombin-based trigger.

prolongation of CT in EXTEM (27, 49, 51), with a greater sensitivity than CT in INTEM (27, 45). In comparison to the other factor Xa inhibitors, apixaban had the lowest effect on CT, often requiring supra-therapeutic doses to achieve a significant CT prolongation (27, 45). Also, apixaban plasma levels beneath 50 ng/ml could not be detected by EXTEM CT changes (45, 51). The significance of a dose dependent effect of apixaban plasma concentrations on CT length was shown for EXTEM [strong correlation (45)], INTEM [strong correlation (45)], and NATEM [weak correlation (50)] assays (**Table 2.1**).

Our search identified four studies analyzing modified ROTEM assays (18, 40, 48, 50). Overall, the experimental changes to ROTEM resulted in CT prolongation, with some studies requiring lower concentrations than those done with commercially available channels (**Table 1.1**).

Apixaban and thrombelastography

Ten studies investigated the effects of apixaban on TEG with a focus on R value, using either the TEG 6s anti-factor Xa channel [AFXa] (20–22, 25), or TEG 5000 system (26, 32, 33, 35, 46, 53, 54) (**Supplementary Table 2.2**). A statistically significant, dose-dependent correlation of reaction time (R) and apixaban plasma concentration was shown with the anti-factor Xa channel [very strong correlation (20, 21)] and kaolin-TEG [moderate correlation (35)] (**Tables 1.2**, **2.2**).

Two studies reported no statistically significant effect of apixaban plasma levels on reaction time (R) (32, 53).

Apixaban and ClotPro analyzer

Using the ClotPro analyzer, Oberladstätter et al. (38) found a statistically strong correlation between apixaban plasma concentrations and clotting time (CT), which, compared to the other anti-factor Xa inhibitors used in the study, showed weaker correlation (**Tables 1.3**, **2.3**, and **Supplementary Table 2.3**).

Viscoelastic thresholds for apixaban concentrations

There is no result with ROTEM EXTEM and INTEM for apixaban thresholds detection. Apixaban plasma

TABLE 1.2 Study defined TEG 6s reaction time (R) thresholds for detection of residual DOAC plasma concentration stratified by assays.

Assay	Threshold ng/ml	R min	Sensitivity %	Specificity %	Study
Rivaroxaban					
AFXa channel	30	1.7	98	86	Artang et al. (21)
	50	2.1	95	80	Artang et al. (21)
	50	1.8	100	100	Artang et al. (20)
	50	1.95 [&]	92	95	Bliden et al. (22)
	100	2.6	96	85	Artang et al. (21)
	100	3.4	100	91	Artang et al. (20)
Apixaban					
AFXa channel	30	2.5	100	100	Artang et al. (20)
	50	1.7	100	96	Artang et al. (21)
	50	2.5	100	92	Artang et al. (20)
	50	1.95 [&]	92	95	Bliden et al. (22)
	100	2.6	100	63	Artang et al. (20)
	100	2.2	98	81	Artang et al. (21)
Dabigatran					
DTI channel	30	2.6	100	92	Artang et al. (21)
	30	2.1	92	100	Artang et al. (20)
	50	3.1	94	83	Artang et al. (21)
	50	2.5	100	90	Artang et al. (20)
	50	1.9	94	96	Bliden et al. (22)
	100	3.4	100	82	Artang et al. (21)
	100	3.0	100	96	Artang et al. (20)

[&] Analysis pooled with apixaban and rivaroxaban cases. Normal reference range estimated using a non-parametric method (97.5% of population) and mean (SD) for AFXa R time: 0.6 to 1.5 min and 0.9 (0.2) min; DTI R time: 1.6 to 2.5 min and 2.0 (0.2) min (25). AFXa, anti-factor Xa channel; DTI, direct thrombin inhibitor channel.

TABLE 1.3 Study defined ClotPro clotting time (CT) thresholds for detection of residual DOAC plasma concentration stratified by assays.

Assay	Threshold ng/ml	CT sec	Sensitivity %	Specificity %	Study
Rivaroxaban					
RVV-test	50	177	90	100	Oberladstätter et al. (38)
	100	196	100	91	Oberladstätter et al. (38)
Apixaban					
RVV-test	50	136	80	88	Oberladstätter et al. (38)
	100	191	67	88	Oberladstätter et al. (38)
Edoxaban					
RVV-test	50	168	100	100	Oberladstätter et al. (38)
	100	188	100	75	Oberladstätter et al. (38)
Dabigatran					
ECA-test	50	189	100	90	Oberladstätter et al. (38)
	100	315	92	100	Oberladstätter et al. (38)

Reference range for CT in the ecarin test (ECA-test) is 68 to 112 sec, and that for the Russell is viper venom test (RVV-test) is 49 to 79 s (38). RVV-test, Russell's viper venom activated test; ECA-test, ecarin activated test.

concentrations of ≥30 and of ≥50 ng/ml can be detected by threshold values of the AFXa channel by TEG 6s and RVV-test by ClotPro (20–22, 38) (**Figure 5** and **Tables 1.1–1.3**). No differences in R times between apixaban peak and through samples were found in another study (25).

TABLE 2.1 Correlation of DOAC plasma concentration and ROTEM clotting time (CT) for different assays.

Assay	DOAC plasma concentration (ng/mL)	Coefficient	Study
Rivaroxaban			
EXTEM	0 to 1000	0.96	Seyve et al. (45)
	NA	0.83	Fontana et al. (28)
	84 (20 to 341); 206 (43 to 350)	0.69	Klages et al. (34)
	153 (107 to 198)	0.68	Chojnowski et al. (24)
	0 to 700	0.63	Schenk et al. (44)
	187 (± 139)	0.58	Henskens et al. (30)
INTEM	0 to 1000	0.86	Seyve et al. (45)
	187 (± 139)	0.69	Henskens et al. (30)
	NA	0.62	Fontana et al. (28)
	84 (20 to 341); 206 (43 to 350)	0.60	Klages et al. (34)
	153 (107 to 198)	0.56	Chojnowski et al. (24)
NATEM	18 (± 31); 185 (± 65)	0.79	Aranda et al. (19)
HEPTEM	*NA*	0.62	Fontana et al. (28)
FIBTEM	0 to 700	0.69	Schenk et al. (44)
Modified			
LowTF	60 to 420; 535 (± 147)	0.95	Adelmann et al. (18)
	60 to 420; 535 (± 147)	0.81	Adelmann et al. (18)
PiCT	60 to 420; 535 (± 147)	0.84	Adelmann et al. (18)
	60 to 420; 535 (± 147)	0.59	Adelmann et al. (18)
Apixaban			
EXTEM	0 to 1000	0.70	Seyve et al. (45)
INTEM	0 to 1000	0.77	Seyve et al. (45)
Modified			
LowTF	50 to 420; 64 (± 56)	0.96	Adelmann et al. (18)
	50 to 420; 64 (± 56)	0.81	Adelmann et al. (18)
PiCT	50 to 420; 64 (± 56)	0.60	Adelmann et al. (18)
	50 to 420; 64 (± 56)	0.38	Adelmann et al. et al. (18)
Edoxaban			
EXTEM	0 to 500	0.94	Havrdová et al. (55)
	0 to 1000	0.94	Seyve et al. (45)
INTEM	0 to 1000	0.92	Seyve et al. (45)
FIBTEM	0 to 500	0.91	Havrdová et al. (55)
Dabigatran			
EXTEM	0 to 1000	0.97	Seyve et al. (45)
	0 to 1000	0.95	Comuth et al. (58)
	74 (11 to 250); 120 (31 to 282)	0.92	Sokol et al. (64)
	86 (29 to 150); 175 (67 to 490)	0.92	Taune et al. (70)
	129 (81 to 204)	0.84	Herrmann et al. (31)
	34 (0 to 228); 82 (18 to 252)	0.77	Klages et al. (34)
INTEM	0 to 1000	0.93	Seyve et al. (45)
	0 to 1000	0.92	Comuth et al. (58)
	107 (91 to 305)	0.88	Körber et al. (60)
	74 (11 to 250); 120 (31 to 282)	0.84	Sokol et al. (64)
	34 (0 to 228); 82 (18 to 252)	0.79	Klages et al. (34)
	87 (29 to 150); 175 (67 to 490)	0.72	Taune et al. (69)
	129 (81 to 204)	0.68	Herrmann et al. (31)
FIBTEM	0 to 1000	0.98	Comuth et al. (58)
	88 (29 to 150); 175 (67 to 490)	0.93	Taune et al. (69)
Modified			

(Continued)

TABLE 2.1 (Continued)

Assay	DOAC plasma concentration (ng/mL)	Coefficient	Study
ECATEM	107 (91 to 305)	0.90	Körber et al. (60)
	47 (28 to 147)	0.77	Körber et al. (60)
	9 (0 to 59)	0.65	Körber et al. (60)
LowTF	89 (29 to 150); 175 (67 to 490)	0.36	Taune et al. (70)

DOAC plasma concentration presents as median and interquartile range, mean and standard deviation, or total range. Coefficients refer to correlation test of the original study either to Spearman's, Pearson's, or regression analysis. NATEM, non-activated rotational thromboelastometry; EXTEM, extrinsic activated rotational thromboelastometry; INTEM intrinsic activated rotational thromboelastometry; HEPTEM, intrinsic activated rotational thromboelastometry with added heparinase; FIBTEM, extrinsic activated rotational thromboelastometry with added cytochalasin D; Modified assays customized by study team; LowTF, assay activated with low tissue factor; PiCT, prothrombinase induced clotting time reagent; ECATEM, uses ecarin to initiate rotational thromboelastometry.

TABLE 2.2 Correlation of DOAC plasma concentration and TEG reaction time (R) for different assays.

Assay	DOAC plasma concentration (ng/mL)	Coefficient	Study
Rivaroxaban			
AFXa channel	206 (94 to 318)	0.93	Artang et al. (20)
	29 to 99	0.92	Artang et al. (21)
	88 (27 to 221)	0.68	Myers et al. (37)
Kaolin-TEG	88 (27 to 221)	0.67	Myers et al. (37)
	99 (48 to 311)	0.54	Kopytek et al. (35)
Apixaban			
AFXa channel	29 to 99	0.84	Artang et al. (21)
	104 (74 to 145)	0.83	Artang et al. (20)
Kaolin-TEG	85 (40 to 105)	0.55	Kopytek et al. (35)
Dabigatran			
DTI channel	92 (41 to 197)	0.94	Artang et al. (20)
	29 to 99	0.93	Artang et al. (21)
Kaolin-TEG	0 to 400	0.89	Solbeck et al. (67)
	71 (39 to 98)	0.79	Kopytek et al. (35)
	269 (54 to 837), 179 (26 to 687)	0.74	Solbeck et al. (65)
$CaCl_2$ TEG	90 (± 71)	0.54	Pipilis et al. (63)

DOAC plasma concentration presents as median and interquartile range, mean and standard deviation, or total range. Coefficients refer to correlation test of the original study either to Spearman's, Pearson's, or regression analysis. AFXa, anti-factor Xa channel; DTI, direct thrombin inhibitor channel; Kaolin-TEG, intrinsic activated assay; $CaCl_2$ TEG, contains calcium chloride solution.

Edoxaban

Six studies (25, 29, 38, 45, 46, 55) were identified analyzing the effects if edoxaban on viscoelastic testing (**Supplementary Tables 2.1–2.3**). The CT and R in relation to the edoxaban plasma concentration are shown in **Figure 4**.

Edoxaban and rotational thrombelastometry

By the time literature review was concluded there were only two studies assessing the effects of edoxaban on ROTEM showing significant prolongations of EXTEM clotting time (CT) even in therapeutic doses (45, 55) (**Table 2.1**).

Edoxaban and thrombelastography

Two studies described effects of edoxaban on the anti-factor-Xa channel [AFXa] of the TEG 6s and TEG 5000 system (**Supplementary Table 2.2**). The one study reported a pooled analysis of various DOACs together, not allowing for an individual result analysis (56). The other reported a change in parameters at doses several times higher than peak plasma levels (46) (**Table 2.1**).

Edoxaban and ClotPro analyzer

Alterations of ClotPro parameters by edoxaban were found in two studies (**Supplementary Table 2.3**). Main changes occurred to CT of the russel viper venom test, showing high sensitivity and specificity for a low threshold (38). Further, a statistically significant prolongation of the CT for this test was only seen in patients taking edoxaban compared to the other anti-factor Xa inhibitors rivaroxaban and apixaban (29) (**Tables 1.3**, **2.3**).

Viscoelastic thresholds for edoxaban concentrations

Edoxaban plasma concentrations of 50 and 100 ng/ml can be detected by threshold values of clotting time (CT) (38) (**Figure 5** and **Table 1.2**).

TABLE 2.3 Correlation of DOAC plasma concentration and ClotPro clotting time (CT) for different assays.

Assay	DOAC plasma concentration (ng/ml)	Coefficient	Study
Rivaroxaban			
RVV-test	0 to 650	0.88	Oberladstätter et al. (38)
Apixaban			
RVV-test	0 to 400	0.74	Oberladstätter et al. (38)
Edoxaban			
RVV-test	0 to 450	0.93	Oberladstätter et al. (38)
Dabigatran			
ECA-test	*NA*	1.00	Groene et.al. (29)
	0 to 375	1.00	Oberladstätter et al. (38)

DOAC plasma concentration presents as median and interquartile range, mean and standard deviation, or total range. Coefficients refer to correlation test of the original study either to Spearman's, Pearson's, or regression analysis. RVV-test, Russell's viper venom activated test; ECA-test, ecarin activated test.

Viscoelastic analysis of direct factor II inhibitor

Dabigatran

29 studies described dabigatran action in whole blood with viscoelastic methods (20–22, 25–27, 29–31, 34, 35, 38, 45, 48, 57–71) (**Supplementary Tables 2.1–2.3**). As already mentioned for the factor Xa inhibitors, dabigatran showed either no significant influence or was not analyzed for other parameters except for the viscoelastic parameters clotting time (CT) and reaction time (R). The CT and R in relation to the dabigatran plasma concentration are shown in **Figure 4**.

Dabigatran and rotational thrombelastometry

Fourteen studies assessed dabigatran in whole blood with ROTEM (27, 30, 31, 45, 48, 58, 60, 61, 68–71) (**Supplementary Table 2.1**). Out of these, one study did not report the exact dabigatran concentration under which conditions the viscoelastic tests were performed (48). Most studies analyze the EXTEM (27, 30, 31, 34, 45, 58, 60, 64, 68–70) and INTEM (27, 30, 31, 34, 45, 58, 60, 64, 68, 70) original assays, with less data published on NATEM (61, 68) and FIBTEM (34, 45, 58, 70). Four studies reported results obtained from *ad hoc* designed or modified original assays (48, 60, 69, 70).

The majority of studies describe a correlation between plasma dabigatran concentrations with a linear increase of clotting time (CT), some highlighting a higher sensitivity of EXTEM over INTEM (27, 31, 34, 45, 58, 64, 68, 70, 72). In detail, a significant correlation between dabigatran plasma concentration and duration of clotting time (CT) varied from strong [EXTEM (34), INTEM (34, 70)] to very strong [EXTEM (45, 58, 64, 70), INTEM (45, 58, 60, 64) and FIBTEM (58, 70)] (**Table 2.1**).

Dabigatran and thrombelastography

Four studies investigated dabigatran action with the new cartridge-based direct thrombin inhibitor [DTI] channel of TEG 6s (20–22, 25), to our knowledge not yet commercially available at the time of manuscript preparation. Of these, two (22, 25) did not report the exact dabigatran concentration under which conditions the viscoelastic tests were performed.

The further studies investigated parameters with the TEG 5000 system (26, 31, 35, 57, 62, 63, 65–67) (**Supplementary Table 2.2**).

Dabigatran treated whole blood led to a significant prolongation of reaction time (R) when compared to baseline or control values in regard to the direct thrombin inhibitor channel (20), the citrated kaolin channel (26, 35, 67, 73), RapidTEG^{TM} channel (26, 62), and calcium chloride ($CaCl_2$) channel (63). One study did not find any effect of dabigatran on TEG 5000 parameters (57).

A significant correlation between dabigatran plasma concentration and reaction time (R) was shown for the direct thrombin inhibitor channel [very strong correlation (20, 21)], for the citrated kaolin channel [strong to very strong correlation (35, 65, 67)], and calcium chloride channel [moderate correlation (63)] (**Table 2.2**).

Dabigatran and ClotPro analyzer

The three studies performed with ClotPro showed moderate (59) to very high (29, 38) correlation between plasma dabigatran concentration and clotting time (CT) of pathway, specific for the detection of factor IIa antagonist (**Supplementary Table 2.3**).

Viscoelastic thresholds for dabigatran concentrations

Dabigatran plasma concentrations between 20 and 100 ng/ml can be detected by threshold values of the viscoelastic

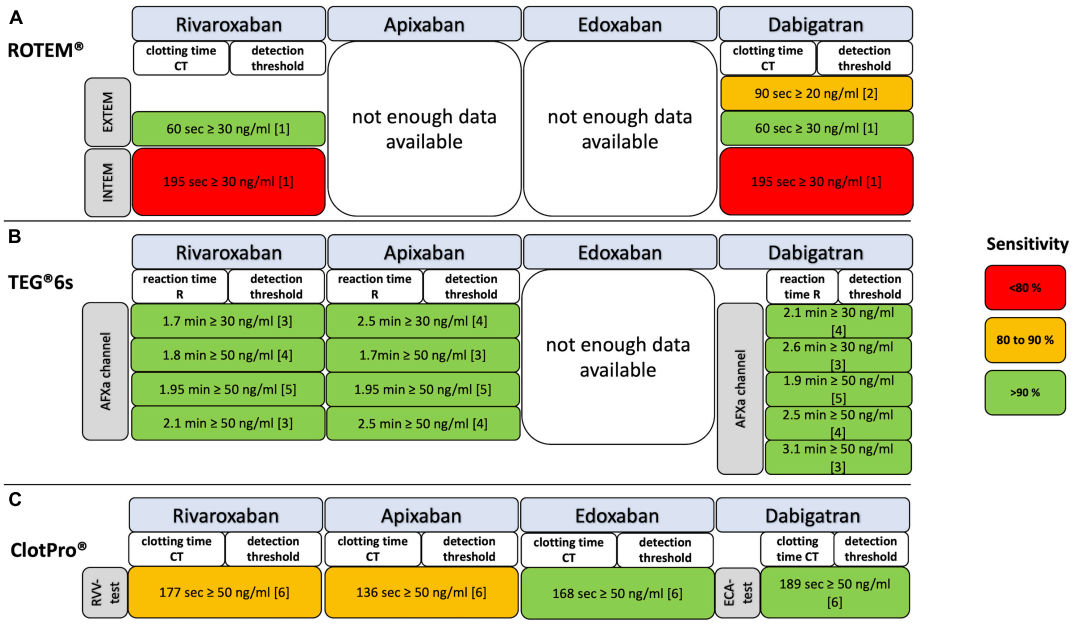

FIGURE 5
Detection of residual DOAC plasma concentrations with ROTEM, TEG, and ClotPro assays coded for test accuracy by sensitivity. **(A)** EXTEM, ROTEM assay extrinsic activated; INTEM, ROTEM assay intrinsic activated; NATEM, ROTEM assay natively activated; **(B)** DTI, direct thrombin inhibitor channel of TEG 6s; AFXa, anti-factor-Xa channel of TEG 6s; **(C)** ECA, ecarin-activated ClotPro test; RVV, Russell's viper venom-activated ClotPro test. References: [1] Henskens et al. (30); [2] Taune et al. (69); [3] Artang et al. (21); [4] Artang et al. (20); [5] Bliden et al. (22); [6] Oberladstätter et al. (38).

parameters CT and R (20–22, 30, 38, 69) (**Figure 5**; **Tables 1.1**–**1.3**). In particular, the ECA-test of ClotPro and the DTI channel of TEG 6s show consistent statistical sensitivity and specificity.

Impact of andexanet alfa and idarucizumab on viscoelastic testing

The specific antagonists andexanet alfa and idarucizumab have been developed for the reversal of direct oral anticoagulants. There is limited to no published information on viscoelastic coagulation testing for specific DOAC reversal (3) despite this method being of particular importance, as the treatment monitoring after administration of andexanet alfa should not be based on commercial anti-FXa activity assays (74, 75). In these assays, the FXa inhibitor dissociates from andexanet alfa resulting in the detection of falsely elevated anti-FXa activity levels.

We found two studies reporting viscoelastic testing after the specific reversal of DOAC (68, 76). No data is available for ROTEM on behalf of andexanet alfa. Takeshita et al. investigated the reversal of dabigatran by adding idarucizumab, which resulted in both INTEM and EXTEM clotting time reversal toward reference ranges (68). Oberladstätter et al. investigated the specific reversal of dabigatran with ClotPro ecarin clotting time (ECA-test CT) and apixaban, edoxaban, and rivaroxaban with ClotPro Russell's viper venom test clotting time (RVV-test CT) (76). Idarucizumab substantially reduced ECA-CT, whereas andexanet alfa did not normalize the RVV-CT. Andexanet alfa spiking of non-anticoagulated blood prolonged RVV-CT, potentially as a consequence of a competitive antagonism with human factor Xa.

Discussion

This review shows the effect of the DOACs rivaroxaban, apixaban, edoxaban, and dabigatran on viscoelastic point-of-care tests. A total of 53 studies were included and qualitatively analyzed. Mainly, studies report ROTEM and TEG measurement methods, with rivaroxaban and dabigatran being the most studied.

Correlation of direct oral anticoagulant plasma concentration with viscoelastic tests

Direct oral anticoagulants (DOACs) show a clear influence on CT and R, resulting in being the main focus of studies. Other ROTEM and TEG parameters (e.g., MCF, A10, LI 60, or alpha angle) were either not further analyzed or showed no to minor changes in the reported studies. By using different activators, viscoelastic tests distinguish extrinsic, intrinsic or total pathways

of coagulation in relation to the DOAC effect. The most specific results are produced by viscoelastic assays that reflect thrombin generation by measuring the physiological constitutional change of blood from the viscous to the clotted state. In principle, this reflects the length of CT as well as R. Accordingly, most significant concentration-dependent changes are described for ROTEM INTEM/EXTEM-CT and for TEG AFXa/DTI as well as CK channel R time. Overall, the results of the analyzed studies were trending toward DOACs showing a higher correlation of CT with drug concentration in the EXTEM channel over INTEM and FIBTEM. With TEG, the greatest affinity resulted with the AFXa or DTI channel, which are currently not yet available. Stronger correlations were demonstrated in assays with alternative not commercially available activators, but these are isolated examples and beyond the scope of this review. Not only is it important to consider the right cartridge and channel, but also the mechanism of action of the DOAC, distinguishing between dabigatran and factor-Xa inhibitors. In regards to the latter, the two most analyzed drugs, rivaroxaban and apixaban, show distinct differences in their affinity, even in identical conditions, potentially explaining the discrepancies in CT with apixaban (77). ROTEM tests were only poorly impacted by low levels of rivaroxaban, edoxaban or dabigatran, and apixaban had only a low effect even at high concentrations.

Detection of clinically relevant direct oral anticoagulant plasma concentrations with viscoelastic tests

Of particular interest are threshold values of clotting time CT or reaction time R at which a certain DOAC concentration must be assumed. It was shown that a cut-off value of 50 ng/ml does not exacerbate ongoing hemorrhage in bleeding patients (78, 79). For surgery with high bleeding risk, a preoperative DOAC concentration less than 30 ng/ml is proposed (78, 80, 81). In surgery with high expected blood loss, a calculated rivaroxaban concentration of greater than 100 ng/ml was associated with a significant increase of perioperative red blood cell loss (82). For thrombolysis in patients with acute ischemic stroke, plasma concentrations up to 100 ng/ml have been suggested to be acceptable (83). According to current guidelines, administration of reversal agents in bleeding patients on DOACs should be considered if plasma concentrations exceed 50 ng/ml (80). Most of the research regarding perioperative bleeding thresholds focuses on rivaroxaban, as this is the most prescribed DOAC (79, 81). We are not aware of any study investigating the interchangeability of above mentioned perioperative bleeding thresholds between different DOACS.

Most data are available for rivaroxaban and dabigatran. We revealed a good sensitivity of viscoelastic parameters in patients using DOAC and might therefore be a good candidate for emergency testing. The added advantage is that the results are readily available and there is uniform performance. But it must be assumed that viscoelastic methods are not sensitive enough to determine specific DOAC concentrations. Results within the normal reference range do not reliably exclude relevant residual DOAC plasma levels and limit their clinical implications. Further, traditional viscoelastic coagulation monitoring assays were not designed to measure the effects of DOACs. Of interest, the costs of DOAC specific laboratory measurements, such as anti-Xa-activity or liquid-chromatography mass-spectrometry (a more accurate method compared to HP-LC) are $40USD and $130USD, with a turnaround time of approximately 30–60 min and 2-4 h, respectively. Moreover, liquid-chromatography mass-spectrometry measurements may not be available 24/7. Viscoelastic tests cost on average about $70USD per analysis and provide first results within minutes. However, there may be price differences depending on the manufacturer and country-specific health system.

Monitoring the specific direct oral anticoagulant reversal

The use of commercially available anti-FXa assays to measure rivaroxaban or apixaban concentrations in patients after reversal with andexanet alfa has limitations. One of the limitations is the large sample dilution in the assay set-up, which causes dissociation of the inhibitor from the andexanet alfa-inhibitor complex, resulting in an erroneous elevation of the anti-FXa activity (5). For rivaroxaban, the residual drug concentration 4 h after treatment with andexanet alfa was approximately 42% lower than the pretreatment concentration (84). A concentration that can still affect hemostasis. Thus, viscoelastic testing may play an important role in monitoring after andexanet alfa reversal (85).

For dabigatran reversal, there appears to be a rebound or dissociation effect after 12 to 24 h (5). Measurements of dabigatran may predict the need for secondary dosing of this reversal agent. In a retrospective study, it has been shown that no plasma dabigatran rebound was observed after reversal in patients with dabigatran plasma level <264 ng/mL at baseline (86). Further, in a case of ongoing bleeding by chronic accumulation of dabigatran showed impressively ongoing redistribution of dabigatran necessitates repetitive application of idarucizumab to neutralize dabigatran (87). Accordingly, repeated and timely coagulation monitoring is required.

Limitation

The studies are heterogeneous, and their replication of results was not constant. For apixaban in particular, there are heterogeneous data for the effect on CT EXTEM in ROTEM. This may be attributed to methodological differences in the

work of Escolar et al. and Pujadas-Mestres et al. (49, 51). Most studies are based on a small study population or sample collection. The analyses reflect different populations including healthy volunteers with spiked samples and *in vitro* analyses. Furthermore, there is a lack of international reference values among the different tests. On the other hand, this work includes a large number of studies. Direct conclusions for the treatment of patients under DOAC can be made for clinical use from this review. We omitted betrixaban from our review as the drug was discontinued by the manufacturer in April 2020 for independent business reasons and never received approval from the European Medicines Agency.

Conclusion

Viscoelastic test assays can provide fast and essential point-of-care information regarding residual DOAC activity, especially DOAC specific assays. Even with strong correlation between the DOAC plasma concentration and viscoelastic parameter clotting time (CT) or reaction time (R), the results could be within the normal reference range. The quantification of residual DOAC plasma concentration with DOAC unspecific viscoelastic assays is not sensitive enough, compared with recommended anti-Xa activity laboratory measurements.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

SDS, DRS, and AK contributed to conception and design of the study. SDS and CC organized the database. SDS wrote the first draft and processed the manuscript. CC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

AK received honoraria for lecturing from Bayer AG Switzerland. DRS's academic department receives grant support from Vifor SA, and Vifor (International) AG. He is co-chair of the ABC-Trauma Faculty, sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, CSL Behring GmbH, LFB Biomédicaments, and Octapharma AG. He has received honoraria/travel support for consulting or lecturing from: Alexion Pharmaceuticals Inc., AstraZeneca AG, Bayer AG, B. Braun Melsungen AG, CSL Behring GmbH, Celgene International II Sàrl, Daiichi Sankyo AG, Haemonetics, Instrumentation Laboratory (Werfen), LFB Biomédicaments, Merck Sharp & Dohme, Novo Nordisk Health Care AG, PAION Deutschland GmbH, Pharmacosmos A/S, Pfizer AG, Pierre Fabre Pharma, Portola Schweiz GmbH, Roche Diagnostics International Ltd, Sarstedt AG & Co., Shire Switzerland GmbH, Takeda, Tem International GmbH, Vifor Pharma, Vifor (International) AG, and Zuellig Pharma Holdings.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.991675/full#supplementary-material

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-Sen University, China

REVIEWED BY
Yalin Cao,
Guizhou Provincial People's Hospital, China
Sherzod Abdullaev,
Republican Specialized Scientific-Practical Medical Center of Nephrology and Kidney Transplantation, Uzbekistan

*CORRESPONDENCE
Shucheng Liang
liangshch2001@gmail.com
Zeyu Guan
e363006910@gmail.com
Ke Zhu
1304465587@qq.com

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Effect of direct oral anticoagulants in patients with atrial fibrillation with mitral or aortic stenosis: A review

Guigao Guo[1], Shucheng Liang[2]*, Zeyu Guan[2]* and Ke Zhu[1]*

[1]Department of Cardiovascular, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Zhuzhou, China, [2]Faculty of Medicine, Macau University of Science and Technology, Macau, Macau SAR, China

Background: Several studies have summarized the clinical performance of direct oral anticoagulants (DOACs) in atrial fibrillation (AF) patients with mitral stenosis or aortic stenosis. The significance of this review was to provide clinicians the latest update of the clinical application of DOACs in managing this specific population.

Methods: Literatures from the PubMed database up to July 2022 were screened for inclusion. Studies on the effect of DOACs in patients suffering from AF with mitral or aortic stenosis were assessed for further selection.

Results: Results from four studies were gathered: the RISE MS trial, the DAVID-MS study, and two observational studies. In the Korean observational study with a 27-month follow-up duration and a sample population consisted of patients with mitral stenosis and AF, the thromboembolic events happened at a rate of 2.22%/ year in the DOAC group and 4.19%/year in the warfarin group (adjusted hazard ratio: 0.28; 95% CI: 0.18–0.45). Intracranial hemorrhage occurred at rates of 0.49% and 0.93% in the DOAC and the warfarin groups, respectively (adjusted hazard ratio: 0.53; 95% CI: 0.22–1.26). In the Danish observational study, which had a sample pool with AF patients with aortic stenosis, reported that the adjusted hazard ratios for thromboembolism and major bleeding were 1.62 (95% CI, 1.08–2.45) and 0.73 (95% CI, 0.59–0.91) for DOACs compared with warfarin during 3 years of follow-up. In the RISE-MS trial involving AF patients with mitral stenosis, there were no differences in ischemic stroke, systemic embolic events, or major bleeding between the rivaroxaban vs. warfarin groups during a 1-year follow-up as well as equal rate of increased thrombogenicity in the left atrial appendage at 6 months. The rate of silent cerebral ischemia at 12 months was higher in the warfarin group (17.6%) than that in the rivaroxaban group (13.3%).

Conclusions: Current published studies supported DOACs' effectiveness in preventing thromboembolism in patients of AF with mitral or aortic stenosis. Further clinical trials could confirm these findings.

KEYWORDS

direct oral anticoagulants, warfarin, atrial fibrillation, mitral stenosis, aortic stenosis

Introduction

Valvular heart disease (VHD) has a rising prevalence in the elderly population over 75 years old (1). Among the moderate-to-severe VHDs, mitral or aortic stenosis happen with rates of 11 and 9%, respectively. Mitral stenosis (MS) is the most common valve stenosis, characterized by the narrowing of the mitral valve, which is crucial to prevent backflow from the left ventricle, followed by the occurrence of life-threatening complications such as atrial fibrillation (AF) and heart failure (2). Aortic stenosis (AS) is featured by the narrowing of the aortic valve which subsequently restricts the ejection of blood from the left ventricle, leading to high ventricular pressure and serious complications like AF (3). It has been shown that patients develop AF associated with MS and AS in a rate of 66.6% (4) and >9% (5) respectively, of which 3–7.5% of the patients are complicated by thromboembolic stroke.

Current guidelines of anticoagulation for AF in patients with non-valvular heart disease recommend that warfarin, a vitamin-K-dependent anticoagulant (VKA), is the drug of choice (6–8). However, such guidelines do not include AF combined with VHDs like mitral or aortic stenosis, which leaves patients developing both VHDs and AF with less therapeutic options beyond traditional warfarin administration. There is an urgent need for the establishment of a more inclusive guideline that provides alternative anticoagulation involving the usage of direct oral anticoagulants (DOACs) for patients with both VHD and AF (9). More recent studies have shown that DOACs are superior to warfarin for the prevention of systemic embolism in patients with AF (10–14), and even have a significant reduction in intracranial hemorrhage (12, 15–19). The better effect of DOACs compared with warfarin is also found in the AF specific population (20–24) and is well supported by cohort studies (25–28). However, only a few have specifically studied the efficacy and safety outcomes of DOACs compared with warfarin in AF patients with MS or AS (29–33). In this review, we discussed all the relevant studies regarding the effect of DOACs in AF patients with MS or AS.

Methods and results

Two investigators conducted independent searches on online database. Combinations of the following keywords were used to generate a search for relevant articles on the PubMed database up to July 2022: dabigatran, rivaroxaban, apixaban, edoxaban, direct oral anticoagulants, novel anticoagulants, DOAC, NOAC, warfarin, atrial fibrillation, mitral stenosis, aortic stenosis, and valvular heart disease. Observational studies or randomized controlled trials (RCTs) were selected if they satisfied the following criteria: AF patients with mitral or aortic stenosis treated with DOACs compared with warfarin.

A total of 698 articles were identified from the database for initial screening, 30 of which met the inclusion criteria and were retrieved for full-text article reading. Upon assessment for eligibility, 19 articles were excluded for not being either a RCT or observational study, seven articles were removed due to irrelevance. Only four articles eventually out of 30 matched the criteria and were included in this review. Among the four articles reviewed, two are observational in design, both are multicenter retrospective cohort studies, one using 1 to 1 propensity score matching, the other one using target trial emulation. The rest two studies are RCTs, one of which is still a protocol, with results not yet available. The whole search and selection process is summarized in Figure 1. The study design and baseline information of the studies are demonstrated in Table 1.

Among four studies included in this review (29–31, 33), the primary outcomes and safety outcomes are summarized in Table 1. The Korean observational study by Kim et al. (33) included 2,230 AF patients with MS, of which 30.6% were males. It was reported that thromboembolic events occurred at a rate of 2.22%/year in the DOAC group and 4.19%/year in the warfarin group (adjusted hazard ratio for DOACs vs. warfarin: 0.28; 95% CI: 0.18–0.45), while intracranial hemorrhage occurred in 0.49% in DOACs group and 0.93% in warfarin group (adjusted hazard ratio for DOACs vs. warfarin: 0.53; 95% CI: 0.22–1.26). The incidence rates of all-cause death were 3.45%/year in the DOAC arm and 8.08%/year in the warfarin arm. The overall survival curve showed a lower all-cause death in the DOAC group compared with the warfarin group. The estimated 3-year major bleeding-free survival was 87.6% for DOACs and 83.6% for warfarin. In the RISE-MS pilot RCT (29), 37 patients with AF and MS were recruited and randomized into either rivaroxaban (n = 18) or warfarin (n = 19) groups. This study reported no symptomatic ischemic stroke or systemic embolic events during the 1-year follow-up. For the safety outcomes, there was no major bleeding in neither group, but 1 clinically relevant nonmajor bleeding in the rivaroxaban group which was explained by increased menstrual bleeding. For exploratory outcomes, the rates of increased thrombogenicity in the left atrial appendage (LAA) assessed by transesophageal echocardiography (TEE) at 6 months and silent cerebral ischemia at 12 months assessed by brain magnetic resonance imaging (MRI) were explored. There were 11 patients in each group agreed to undergo the TEE assessment. There were 15 patients in the rivaroxaban group and 17 patients in the warfarin group accepted the MRI assessment. As results, both groups reported 27.2% rates of increased LAA thrombogenicity, whereas the rates of silent cerebral ischemia were 13.3 and 17.6% in the rivaroxaban and warfarin groups, respectively. Zhou et al. (31) published the protocol of the DAVID-MS trial on the effect of dabigatran vs. warfarin in patients with AF and MS.

The Danish observational study by Melgaard et al. (30) included 3,726 patients with AF and AS who had been prescribed for either a DOAC (n = 2,357) or warfarin (n = 1,369).

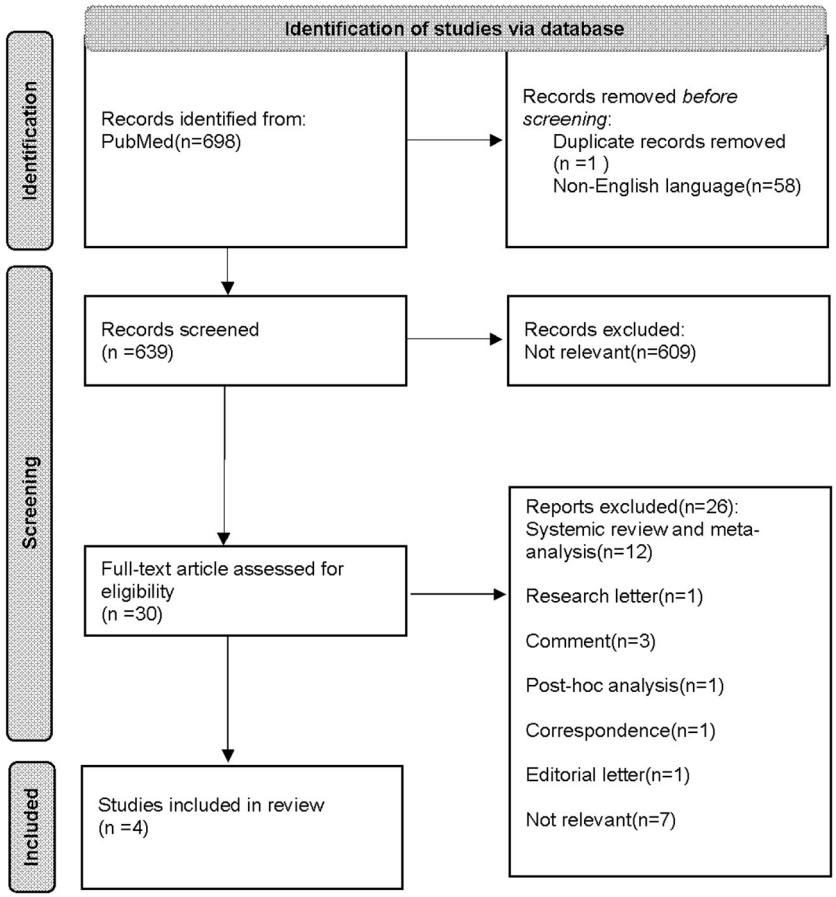

FIGURE 1
PRISMA flow diagram that summarizes the literature search process.

During a median follow-up 14 months, the adjusted hazard ratio for thromboembolism was 1.62 (95% CI, 1.08–2.45) for DOACs compared with warfarin. The estimated 3-year thromboembolic-free survival was 94% in the DOACs group and 96% for the warfarin group. For the safety outcomes, the adjusted hazard ratio for major bleeding was 0.73 (95% CI, 0.59–0.91) for DOACs compared with warfarin.

Discussion

One of the earliest studies looking into the effect of DOACs in patients with MS was conducted by Kim et al. (33) in 2019. This study presented a retrospective analysis to validate the effectiveness and safety outcomes of DOACs vs. warfarin in patients with MS. Patients were selected using the Korean health insurance database between 2008 and 2017 that were identified with AF and MS. A total of 2,230 patients were enrolled with matching baseline characteristics and 1:1 propensity score matching, of which patients in the DOACs or warfarin group were divided evenly. The primary outcomes of interest were ischemic stroke and systemic embolism over a follow-up of 27 months, and the safety outcomes were intracranial hemorrhage and all-cause death over the same course of follow-up. Thromboembolic events happened in rates of 4.19% per year and 2.22% per year and intracranial bleeding occurred in rates of 0.93% per year and 0.49% per year in warfarin and DOACs groups, respectively. Although the results seemed to support that DOACs were more effective and safer than warfarin, since the use of DOACs was off-label administered, it was difficult to overcome the confounding factors given a narrow range of baseline characteristics. Moreover, comparing to RCTs, observational retrospective studies have less restrictions as well as less consistency in terms of experimental design due to the fact that the data gathered was collected from different healthcare providers. Such characteristics of all observational analysis make them prone to selection bias. Therefore, results from such observational study should be interpreted critically and the data should only be used for "hypothesis-generating".

In another observational study conducted in 2021, Melgaard et al. (30) collected data from Danish nationwide registries

TABLE 1 The baseline data of the included studies in this review.

References	Study treatment	Study design	Baseline characteristics of the population	Efficacy outcome results	Safety outcome results
Kim et al. (33)	Apixaban (n = 192), dabigatran (n = 367), rivaroxaban (n = 472), or edoxaban (n = 84) vs. Warfarin (n = 1,115), dosage unmentioned	Multicentre, retrospective cohort study; 1 to 1 propensity score matching	Age: DOAC 69.2 vs. warfarin 70.2 years; Hypertension: DOAC 1076 vs. Warfarin 2080; previous stroke: DOAC 518 vs. Warfarin 521; mean CHA DS 2 2-VASc score = 5.2	Stroke or systemic embolism: DOAC 2.22%/year ($n = 30$) vs. Warfarin 4.19%/year ($n = 146$)	Intracranial hemorrhage: DOAC 0.49%/year ($n = 7$) vs. Warfarin 0.93%/year ($n = 36$)
Sadeghipour et al. (29)	Rivaroxaban 20 mg/day or 15 mg/day (CrCl<50ml/min; $n = 20$) vs. Warfarin with target INR 2-3 ($n = 20$). Study discontinued due to concerns raised by COVID-19.	Single center, open-labeled, parallel-group, pilot registered RCT (RISE MS)	Age: Rivaroxaban 60 vs. Warfarin 56 years; BMI: Rivaroxaban 27.1 vs. Warfarin 27.8 kg/m2 Hypertension: Rivaroxaban 5(25%) vs. Warfarin 4 (20%) HAS-BLED score: Rivaroxaban 0 vs. Warfarin 0	Stroke or systemic embolism: DOAC (n = 0) vs. Warfarin ($n = 0$)	Major bleeding: Rivaroxaban ($n = 0$) vs. Warfarin ($n = 0$); Clinically nonmajor bleeding: Rivaroxaban ($n = 1$) vs. Warfarin ($n = 0$)
Melgaard et al. (30)	Apixaban ($n = 1105$), Dabigatran ($n = 323$), edoxaban ($n = 38$) or rivaroxaban ($n = 891$) vs. Warfarin ($n = 1369$)	Multicenter, retrospective "target trial" emulation	Median age: NOAC 82 vs. Warfarin 79 years; Previous aortic valve intervention: NOAC 497 (21.1%) vs. Warfarin 432 (31.6%); Hypertension: NOAC 1616 (68.6%) vs. Warfarin 957 (69.9%); Heart failure: NOAC 1008 (42.8%) vs. Warfarin 670 (48.9%)	Thromboembolism: Per protocol analysis: Warfarin (n = 19) vs. NOAC (n = 62); Intention-To-Treat analysis: Warfarin (n = 36) vs. NOAC (n = 77);	Major bleeding: Per protocol analysis: Warfarin ($n = 119$) vs. NOAC ($n = 163$) Intention-To-Treat analysis: Warfarin ($n = 171$) vs. NOAC ($n = 184$)
Zhou et al. (31)	Dabigatran 110/150 mg BD ($n = 343$) vs. Warfarin ($n = 343$; INR 2-3 and TTR > 65%) protocol	Protocol, randomized, open-label study (DAVID-MS)	N/A	Stroke or systemic embolism	Ischemic stroke, systemic embolism, hemorrhagic stroke, intracranial hemorrhage, major bleeding and death

N/A, not applicable.

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between 2013 and 2018 with the intent to compare effectiveness and safety of DOACs with warfarin in patients with AF and AS. Similar to the situation regarding treatment for patients with both AF and MS, there is lack of information and update about the guidelines on the usage of DOACs for patients carrying AF and AS. Melgaard et al. has highlighted the necessity of exploring the efficacy of DOACs for such indication in the observational study. A total of 3,726 patients with AF and AS satisfied selection criteria, in which 2,357 patients initiated DOACs and 1,369 patients used warfarin. Throughout 3 years of follow-up, thromboembolism happened in a rate of 3.3% in the DOAC group and 2.6% in the warfarin group, indicating a higher risk of thromboembolism in treatment with DOACs, whereas major bleeding occurred in a rate of 13% and 7.8% in the DOACs and warfarin groups, respectively. A major drawback of this study is its non-randomized design, which is common in every observational study as discussed above, making confounding factors unavoidable. Another limitation is that even though the comparison is between DOACs and warfarin, the study did not specifically compare two single drugs. Instead, patients prescribed with apixaban, dabigatran, edoxaban, and rivaroxaban were all counted into analysis, which potentially increased heterogenicity. Inarguably, this study provided new information regarding the use of DOACs in patients with AF and complicated with AS. However, the lack of randomization renders it unpowerful to draw any definite conclusion.

The RISE MS is a pilot RCT (29) initiated in Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. From May 2019 to February 2020, researchers of the study recruited 37 patients 18 to 75 years old out of a pool of 237 and they were subsequently randomized to receive either rivaroxaban 20 mg daily or warfarin (with a target international normalized ratio [INR] of 2–3) in a 1:1 ratio. Based on the inclusion criteria, the recruited patients must be diagnosed with moderate-to-severe MS and AF within the prior 12 months. The exclusion criteria excluded all the patients with high risk of bleeding, left atrial thrombi, renal impairments, or allergies to DOACs or VKA. The dosages of drugs were tightly monitored. Patients who had never been administered with anticoagulants were monitored with shorter intervals until reaching a therapeutic INR level. The primary outcomes consisted of symptomatic ischemic strokes and systemic embolic events occurred during the 12-month follow-up. TEE and brain MRI were taken at the beginning of the study, the 6th and 12th month after randomization and the results were used to evaluate thrombogenicity in the LAA and silent cerebral ischemia, respectively. There are several limitations in the study. First, the small sample size made it difficult to report robust results for primary outcomes. Furthermore, the study was discontinued for two reasons. The first reason indicated that COVID-19 was associated with higher risk of thrombotic complications. The second reason was local COVID-19 restrictions rendered a rigorous and consistent follow-up impossible. The COVID-19 restrictions also limited the patient participation in imaging examinations due to the concerns of COVID-19 contamination in the imaging center. The authors also highlighted a concern in patient enrollment. Since almost all the patients were advised with their family practitioner, sever patients with moderate to severe MS refused to participate in the study, which could become a major selection bias and confront outcome analysis. Despite the limitations, the study has generated new clinical data for the application of DOACs. The primary outcome results supported that DOACs were at least as effective as VKAs for lowering thrombotic risks in AF patients with moderate to severe MS.

With the urgency of filling the knowledge gap regarding DOACs' efficacy in treating patients with AF and MS, Zhou et al. (31) has submitted a protocol of dabigatran for stroke prevention in AF patients with moderate or severe MS (the DAVID-MS trial). According to the protocol, this will be the first open-label, multicenter, randomized clinical trial to compare the efficacy and safety of dabigatran and warfarin therapy for stroke prevention in patients with AF and moderate or severe MS. The targeted patients are those with AF aged 18 or over with moderate to severe MS without schedule for valvular intervention in the coming 12 months. Patients will be randomized in a 1:1 ratio to receive either two-doses of dabigatran (110 mg or 150 mg two times per day) or warfarin with an INR of 2–3 along with a follow-up of 12 months. The primary outcomes compose of stroke and systemic embolism and the secondary outcomes include ischaemic stroke, intracranial hemorrhage, and major bleeding. The sample size is estimated to require 686 participants and the study will be conducted mainly in Hong Kong and Mainland China. It is worth mentioning that Zhou et al. decided to use dabigatran as a comparison to warfarin not only because dabigatran appears to be more effective in stroke prevention with less intracranial bleeding than warfarin but also because of the availability of its antidote idarucizumab, granting more protection for patients involved in the DAVID-MS trial.

In summary, the guidelines for DOACs regarding its administration in AF with mitral or aortic stenosis are lacking. On the other hand, only a handful of works are done to fill in the knowledge gap. As far, there are four studies completed to explore the efficacy of DOACs in treating patients with AF and MS or AS. The two observational studies, one conducted in Korean (33) and the other one in Denmark (30), looked at the effect of DOACs in reducing thromboembolic events in patients with AF and MS or AS, respectively. The RISE-MS is a pilot RCT (29) to compare rivaroxaban to warfarin about their ability to lower risk of thromboembolism in patients with both AF and MS. DAVID-MS is a registered RCT to compare dabigatran to warfarin for the same indication above. The DAVID-MS trial (31), however, has not yet been conducted. Both the observational study by Kim et al. and the pilot RCT

have reported non-inferior efficacy of DOACs compared to warfarin. The observational study conducted by Melgaard et al. (30), however, reported that DOACs are associated with higher rate of thromboembolism than warfarin. The two observational studies were subject to a variety of bias due to their retrospective nature. Therefore, their results should merely be considered as hypothesis generating but not clinically significant. The pilot RCT supported that DOACs possessed higher efficacy than warfarin, yet the study was limited to small sample size. Although DOACs have already been used widely as alternatives to traditional blood thinners such as warfarin in treatments for patients with AF, its applications in other indications like AF complicated with MS or AS have only been lightly explored. Such knowledge gap awaits elucidation as it will potentially open new windows for patients suffering from both AF and MS or AS (32).

Future work

Although DOACs have been branded and extensively used for more than a decade, there is always ongoing research regarding their safety efficacy. A recent study conducted in Italy found that the use of DOACs is associated with higher rate of recurrent thromboembolism than VKA in patients with antiphospholipid syndrome (34). In this review, no study has included antiphospholipid syndrome in their baseline characters. Recruiting patients with the syndrome would overestimate the bleeding risk and undermine the safety outcome. Therefore, in future observational studies, researchers must consider the syndrome in baseline characteristics to avoid bias.

Another baseline characteristic that can help to optimize baseline characteristic design is VKORC genotyping (35). Patients with the VKORC gene are more susceptible to warfarin overdose, as warfarin has a narrow therapeutic window. Genetic screening on these patients can help clinicians to estimate dosages more precisely and lower the effect of VKORC polymorphism on the time required to reach targeted INR and the time required to reach stable therapeutic plasma concentration for warfarin so to lower the risk of hemorrhage (36). In the mentioned studies of our review, no information was given regarding patients' VKORC polymorphism, which could be a potential confounding factor as some patients in the warfarin arm were more likely to bleeding upon warfarin treatment (37). This could overstate the bleeding risk of warfarin compared to DOACs. Hence, we suggested that in further studies, researchers need to normalize the results along with patients' VKORC screening results.

A retrospective review conducted in Denmark reported inclusively on all-cause mortality, stroke, and bleeding in patients with AF and valvular heart disease and treated with either rivaroxaban, apixaban, or VKA (38). The goal of the study was to compare the risk of the mentioned safety event in order to infer which drug is safer. The results showed that there was non-significant absolute 2-year risk difference between VKA and DOACs groups for all outcomes measured, suggesting that apixaban and rivaroxaban possess at least equal, if not better, safety profile as VKA. Nevertheless, the limitations in this study were obvious. For instance, there was a possible detection bias that patients treated with VKA were more often in contact with practitioners and professionals and were therefore more likely to be diagnosed with arisen problems, making the VKA arm more subject to false positive detection. The other problem was that populations in the study were not stratified according to their VHD degree. This proposed a major problem in data analysis since patients with more severe VHD are more susceptible to bleeding. Therefore, if patients with different VHD severity were mixed in the same group instead of being stratified, the total bleeding events could be exaggerated or understated as there were more moderate-severe VHD patients or mild-moderate VHD patients, respectively.

Connection to the INVICTUS trial

In the INVICTUS trial, which is the most recent RCT of DOACs, the efficacy and safety of rivaroxaban and warfarin for stroke prevention in patients who had AF due to rheumatic heart disease have been updated (39). Patients with AF and echocardiographically diagnosed rheumatic heart disease and satisfy the following criteria were enrolled: CHA2DS2VASc score of at least 2 (with higher scores suggesting a higher risk of stroke) and a mitral-valve area of no more than 2 cm^2. In the end, there were over 80% of enrolled members in both arms with moderate-to-severe mitral stenosis. The patients were randomized in a 1:1 ratio to receive either 20 mg daily rivaroxaban or VKA. The efficacy outcomes included total stroke and systemic embolism and safety outcomes included myocardial infarction and death from vascular causes. The results showed that of 4,531 patients included in the on-treatment analysis, the occurrence rates of all stroke events of rivaroxaban and VKA groups were 1.39 and 0.87%, respectively. The rates of fatal bleeding, however, were 0.07 and 0.22 in rivaroxaban and VKA groups, respectively. In addition, VKA group also showed higher restricted mean survival time compared to rivaroxaban group, which was 1,686 days vs. 1,619 days ($p = 0.002$).

In connection to our review, since the INVICTUS enrolled mostly MS patients with rheumatic heart disease and AF, we can make inference accordingly. Compared to the observational studies in our review, the data from INVICTUS supported otherwise opposite conclusion as the INVICTUS have suggested that for preventing thromboembolic events in rheumatoid heart disease patients with AF, VKA is associated with better efficacy and lower mortality rate compared to rivaroxaban, although with higher bleeding rate. However, the authors of

INVICTUS indicated that there was no relation between AF-related stroke prevention and reduced mortality rate. VKA also did not slow down the deterioration of heart-valve, which suggested that the better efficacy in preventing stroke and lower mortality in the VKA group was not related to MS progression. On the other hand, although the rivaroxaban group had higher mortality rate, there was no evidence to suggest rivaroxaban increased mortality among the patients, as it has been shown that rivaroxaban lowers mortality substantially in patients with atherosclerotic vascular disease (40). Hence, if VKA did not lower mortality through optimizing AF-related stroke prevention or slowing MS progression, it appeared more likely that VKA had a direct effect on the disease process of rheumatic heart disease. This information is important because if the efficacy of stroke prevention of VKA or DOACs is dependent on rheumatic heart disease progression, such condition should strictly be included as one of the exclusion criteria when studying the effectiveness of stroke prevention of DOACs vs. VKA in patients with AF and MS.

Conclusions

Among the reviewed studies (29–31, 33), two of them showed non-inferiority of DOACs to warfarin in treating patients with AF and mitral or aortic stenosis, and one observational study showed the opposite results. Due to their own limitations, the use of DOACs in AF patients with MS or AS is still controversial. A more adequately designed RCT with a larger sample size is needed to verify the results from the previous studies. Warfarin would remain the drug of choice for such patients as per the guideline, due to the lack of clinical data, until a more definitive trial showed otherwise.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jianyong Ma,
University of Cincinnati, United States

REVIEWED BY
Junyi Sun,
The First Affiliated Hospital of Sun Yat-sen University, China
Ting-Chun Huang,
National Cheng Kung University Hospital, Taiwan

*CORRESPONDENCE
Xuyang Liu
lxy0136@163.com
Linjuan Guo
727456372@qq.com

†These authors share first authorship

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HAS-BLED vs. ORBIT scores in anticoagulated patients with atrial fibrillation: A systematic review and meta-analysis

Xuyang Liu[1*†], Shengnan Wang[2†], Wenfeng He[2] and Linjuan Guo[3*]

[1]Department of Cardiology, Affiliated Hospital of Jinggangshan University, Jinggangshan University, Ji'an, Jiangxi, China, [2]Department of Medical Genetics, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China, [3]Department of Cardiology, Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang, Jiangxi, China

Background: The 2021 UK National Institute for Health and Care Excellence guidelines tend to recommend the ORBIT score for predicting bleeding risk in patients with atrial fibrillation (AF) with anticoagulants. Herein, we comprehensively re-assessed the predicted abilities of the HAS-BLED vs. ORBIT score since several newly published data showed different findings.

Methods: We comprehensively searched the PubMed electronic database until December 2021 to identify relevant studies reporting the ORBIT vs. HAS-BLED scores in anticoagulated patients with AF. Their predicted abilities were assessed using the C-index, reclassification, and calibration analysis.

Results: Finally, 17 studies were included in this review. In the pooled analysis, the ORBIT score had a C-index of 0.63 (0.60–0.66), 0.59 (0.53–0.66), and 0.57 (0.48–0.67) for major bleeding, any clinically relevant bleeding, and intracranial bleeding, respectively, while the HAS-BLED score had a C-index of 0.61 (0.59–0.63), 0.59 (0.56–0.63), and 0.57 (0.51–0.64) for major bleeding, any clinically relevant bleeding, and intracranial bleeding, respectively. There were no statistical differences in the accuracy of predicting these bleeding events between the two scoring systems. For the outcome of major bleeding, the subgroup analyses based on vitamin K antagonists vs. direct oral anticoagulants suggested no differences in the discrimination ability between the HAS-BLED and ORBIT scores. Reclassification and calibration analyses of HAS-BLED vs. ORBIT should be further assessed due to the limited and conflicting data.

Conclusion: Our current findings suggested that the HAS-BLED and ORBIT scores at least had similar predictive abilities for major bleeding risk in anticoagulated (vitamin K antagonists or direct oral anticoagulants) patients with AF, supporting the use of the HAS-BLED score in clinical practice.

KEYWORDS

atrial fibrillation, ORBIT, HAS-BLED, bleeding risk, review

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, the leading cause of cardiovascular diseases and death worldwide (1). Generally, the most worrisome complication of AF is cardiac stroke. Effective stroke prevention requires the use of oral anticoagulants, including vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) (2). However, bleeding events will occur after receiving anticoagulation therapy, and it is very important to accurately assess the risk of embolism and bleeding in clinical practice. Over the past few decades, various bleeding risk scores have been proposed (3–5). Among these proposed bleeding risk scores, the HAS-BLED score (hypertension [H, 1 point], abnormal liver/renal function [A, 1 point each], stroke [S, 1 point], bleeding history or predisposition [B, 1 point], labile international normalized ratio [L, 1 point], elderly [E, 1 point], and drugs/alcohol concomitantly [D, 1 point each]) have become increasingly popular in the clinical settings (6, 7). Patients with HAS-BLED < 3 are divided into the low-risk group, while those with HAS-BLED ≥ 3 are divided into the high-risk group (2, 8).

In 2015, O'Brien et al. (9) derived and validated another bleeding risk score, ORBIT, which consists of 1 point for age $\geq$ 75 years, 2 points for reduced hemoglobin/hematocrit/history of anemia, 2 points for bleeding history, and 1 point for impaired renal function ($<$60 mL/min/1.73 m^2). The previous meta-analysis comparing the HAS-BLED score with the ORBIT score showed that the HAS-BLED score was no better than the ORBIT score in predicting major bleeding events in anticoagulated patients with AF (10). However, this meta-analysis (10) did not compare the predictive power of the ORBIT and HAS-BLED scores for bleeding risk in different oral anticoagulant use statuses. Given recently updated research comparing the ORBIT and HAS-BLED scores, whether the ORBIT or HAS-BLED score has better predictive power for bleeding in patients with AF remains controversial. In addition, the 2021 UK National Institute for Health and Care Excellence guidelines tend to recommend the ORBIT score for predicting bleeding risk in patients with AF with anticoagulants (11). Therefore, we performed a systematic review and meta-analysis aiming to re-assess the diagnostic accuracy of the HAS-BLED vs. ORBIT scores for predicting bleeding risks in anticoagulated (VKAs or DOACs) patients with AF.

Methods

Literature search

We comprehensively searched the PubMed electronic database until December 2021 to identify relevant literature reporting the ORBIT vs. HAS-BLED scores in anticoagulated patients with AF. The following keywords in the search strategies were used: (1) atrial fibrillation AND (2) vitamin K antagonists OR warfarin OR coumadin OR phenprocoumon OR acenocoumarol OR indandione OR fluindione OR phenindione OR anisindione OR non-vitamin K antagonists OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban AND (3) HAS-BLED. We did not search "ORBIT" in this study. In addition, we checked previous reviews for additional studies (4, 5, 10, 12). Studies published in English were included in this study.

Eligibility criteria

We included the studies if they met the inclusion criteria: (1) adult non-valvular patients with AF treated with VKAs or DOACs; (2) studies reported the diagnostic performance of the ORBIT vs. HAS-BLED scores; (c) major bleeding and any other bleeding events, such as any clinically relevant bleeding, any bleeding, intracranial bleeding, and gastrointestinal bleeding; (d) at least one of the following data were reported: C-index, net reclassification improvement (NRI) and integrated discrimination improvement [IDI] values, and calibration data. We excluded studies with insufficient data, such as reviews, case reports, comments, editorials, letters, or abstracts.

Study selection and data extraction

Two authors independently assessed the relevant studies based on the predetermined criteria. We included the qualified articles after the title/abstract screenings and the full-text screenings. Disagreements were resolved through discussion or consultation with a third reviewer. Data were abstracted from the included studies. We abstracted the following data: author, year of publication, study type, data source, baseline patient characteristics (age, sex ratio, sample size, and type of anticoagulants), study outcomes, and follow-up time.

Quality assessment

The quality assessment was performed using the prediction model risk of bias assessment tool (PROBAST),[1] consisting of four domains including participants, predictors, outcomes, and analysis.

Statistical analyses

The consistency of the included studies was assessed through the Cochrane Q-test and I^2 index. Significant heterogeneity was considered if the P-value of the Cochrane Q-test < 0.1 or if the I^2 value of $>50\%$. In the discrimination analysis, the C-index and 95% confidence interval (CI) were abstracted from each included study and pooled by a random-effects model with an inverse variance method. The Z-statistic was calculated to compare the two C-indexes of the ORBIT vs. HAS-BLED models (10). For the primary major bleeding events, the subgroup analyses were conducted on the basis of VKAs vs. DOACs or available vs. unavailable labile INRs (**Supplementary Table 1**). We used the funnel plots to examine the publication bias, and visual inspection of asymmetry indicated a bias. In addition, we performed narrative analyses on the improvement

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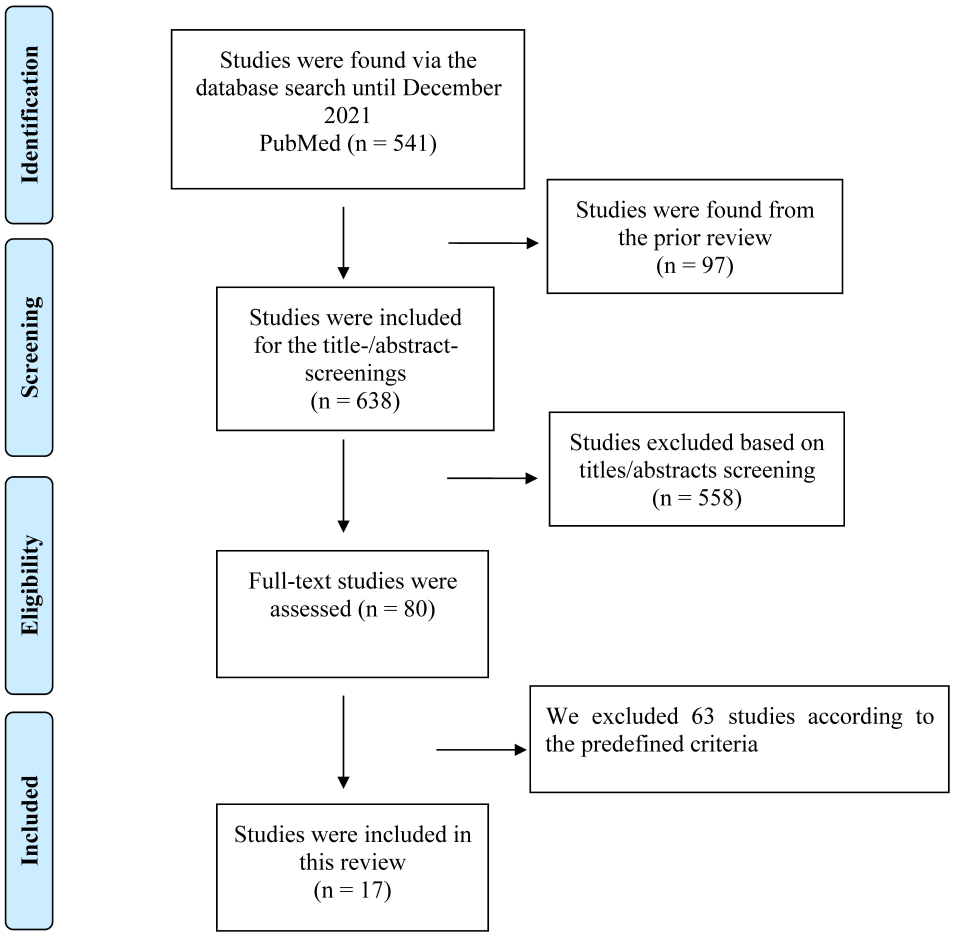

FIGURE 1
Flowchart of document retrieval and screening process of this review.

TABLE 1 Baseline characteristics of the included studies containing the HAS-BLED and ORBIT scores.

Included studies	Data source	Study type	Anticoagulated patients	Anticoagulated types	Study outcomes of interest	Bleeding definitions	Follow-up duration (y)	PROBAST
O'Brien et al. (9)	The ORBIT-AF registry in the USA	Prospective cohort	7,411	Dabigatran; Warfarin	Major bleeding	ISTH	2.0	Unclear
	The ROCKET-AF validation cohort	Retrospective cohort	14,264	Rivaroxaban, warfarin	Major bleeding	ISTH	1.9	
Senoo et al. (13)	The AMADEUS trial	Retrospective cohort	2,293	Warfarin	Major bleeding; Any clinically relevant bleeding	ISTH	1.18	High risk
Proietti et al. (14)	The SPORTIF III and V clinical trials	Retrospective cohort	3,551	Warfarin	Major bleeding	ISTH	1.6	Unclear
Esteve-Pastor et al. (15)	The FANTASIIA registry; Spanish	Prospective cohort	1,276	DOACs; VKAs	Major bleeding	ISTH	1.0	Unclear
Yao et al. (16)	OptumLabs Data Warehouse; US; 2010–2015	Retrospective cohort	39,539	DOACs	Major bleeding	NA	0.6	High risk
Caro Martínez et al. (17)	Three hospitals in Spain	Retrospective cohort	973	DOACs	Major bleeding; Gastrointestinal bleeding	ISTH	1.77	Unclear
Rivera-Caravaca et al. (18)	Single anticoagulation centre in a tertiary hospital in Murcia, Spain	Retrospective cohort	1,361	Acenocoumarol	Major bleeding	ISTH	6.5	Unclear
Beshir et al. (19)	University of Malaya Medical Centre and Institut Jantung Negara or the National Heart Institute of Malaysia	Retrospective cohort	1,017	Warfarin, rivaroxaban, dabigatran	Major bleeding; Any clinically relevant bleeding	ISTH	1.0	High risk
Chao et al. (20)	National Health Insurance Research Database, Taiwan	Retrospective cohort	40,450	Warfarin	Major bleeding; Intracranial bleeding	NA	4.6	Unclear
Lip et al. (21)	Three Danish nationwide databases	Retrospective cohort	57,930	DOACs	Any bleeding	ICD codes	2.5	Unclear

(Continued)

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TABLE 1 (Continued)

Included studies	Data source	Study type	Anticoagulated patients	Anticoagulated types	Study outcomes of interest	Bleeding definitions	Follow-up duration (y)	PROBAST
Proietti et al. (22)	The RE-LY trial, whole cohort	Retrospective cohort	18,113	Dabigatran; warfarin	Major bleeding; Intracranial bleeding	ISTH	2.0	Unclear
Claxton et al. (23)	The derivation (MarketScan, 2007–2014) and validation (Optum Clinformatics, 2009–2015) cohorts	Prospective cohort	81,285	DOACs; Warfarin	Major bleeding	ISTH	1.0	High risk
Rutherford et al. (24)	Norwegian Patient Registry and Norwegian Prescription Database	Retrospective cohort	21,248	DOACs	Any clinically relevant bleeding	ICD codes	0.5	High risk
Mori et al. (25)	The DIRECT registry in Japan	Prospective cohort	2,216	DOACs	Major bleeding	ISTH	0.86	High risk
Adam et al. (26)	Multicenter cohort study in Switzerland	Prospective cohort	2,147	DOACs; VKAs	Any clinically relevant bleeding	ISTH	4.4	Unclear
Watanabe et al. (27)	J-RHYTHM Registry	Prospective cohort	7,406	VKAs	Major bleeding	NA	2.0	Unclear
Proietti et al. (28)	ESC-EHRA EORP-AF General Long-Term Registry	Prospective cohort	3,018	DOACs	Major bleeding	NA	2.0	Unclear

Only analyzed in the analysis of the DOAC subgroup based on the occurrence of intracranial hemorrhage and major extracranial hemorrhage during the follow-up.
HAS-BLED, hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; ORBIT, outcomes registry for better informed treatment of atrial fibrillation; ICD, International Classification of Diseases; ISTH, International Society of Thrombosis and Haemostasis; VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants; NA, not available.

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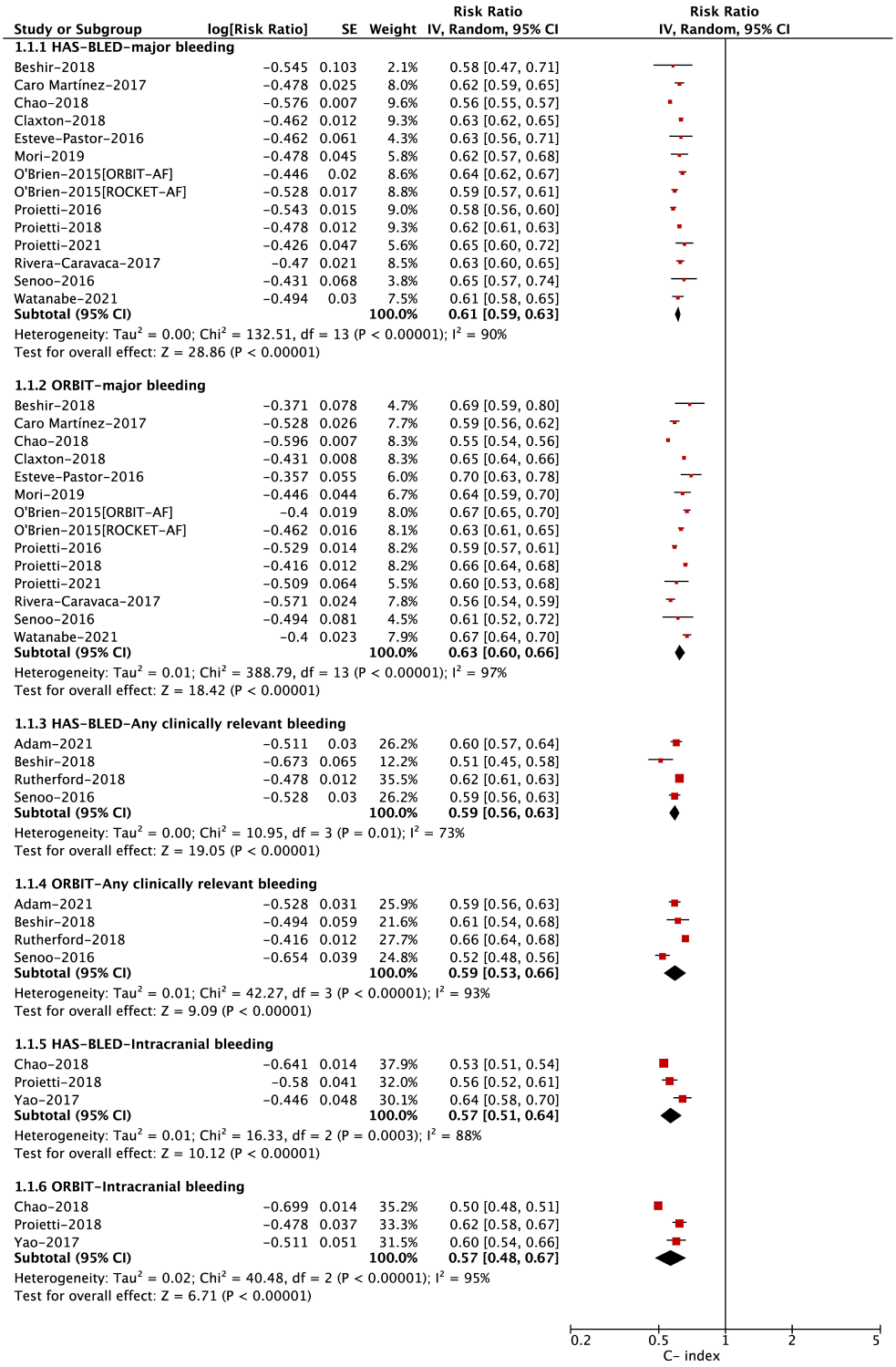

FIGURE 2
Pooled C-index for bleeding events in anticoagulated patients with atrial fibrillation.

in predictive accuracy by the reclassification analysis, including the NRI and IDI values. Calibration data represented the extent to which predicted risks correspond to observed risks.

All the statistical analyses were carried out using the Review Manager 5.4 software. A *P*-value of <0.05 indicated statistical significance.

TABLE 2 *C*-statistics and 95% CIs between the HAS-BLED and ORBIT scores.

	Major bleeding	Any clinically relevant bleeding	Intracranial bleeding
Overall			
No. of studies	14	4	3
C-statistic: HAS-BLED	0.61 (0.59–0.63)	0.59 (0.56–0.63)	0.57 (0.51–0.64)
C-statistic: ORBIT	0.63 (0.60–0.66)	0.59 (0.53–0.66)	0.57 (0.48–0.67)
Subgroup analysis			
DOAC-group			
No. of studies	6		
C-statistic: HAS-BLED	0.64 (0.62–0.65)	–	–
C-statistic: ORBIT	0.65 (0.62–0.68)	–	–
VKA-group			
No. of studies	7		
C-statistic: HAS-BLED	0.60 (0.58–0.62)	–	–
C-statistic: ORBIT	0.60 (0.56–0.63)	–	–

HAS-BLED, hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; ORBIT, outcomes registry for better informed treatment of atrial fibrillation; VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants; CI, confidence interval.

Results

The flowchart of the document retrieval and screening process is shown in **Figure 1**. We initially retrieved 541 studies through an electronic search of the PubMed database. We also found additional 97 studies from the prior reviews. After the screenings of the titles and abstracts, 80 studies were assessed in full-texts, and 63 of these studies were excluded according to the predefined criteria. Finally, a total of 17 studies were included in this meta-analysis (9, 13–28).

Table 1 shows the baseline characteristics of the 17 studies included in this review. The quality assessment by the PROBAST is shown in **Supplementary Table 2**, suggesting that all of the included studies had a high or unclear risk of biases.

Discrimination analysis between HAS-BLED and ORBIT

The discrimination analysis was assessed by the C-index between the HAS-BLED and ORBIT scores. In the pooled analysis shown in **Figure 2** and **Table 2**, the ORBIT score had a C-index of 0.63 (0.60–0.66), 0.59 (0.53–0.66), and 0.57 (0.48–0.67) for major bleeding, any clinically relevant bleeding, and intracranial bleeding, respectively. Similarly, the HAS-BLED score had a C-index of 0.61 (0.59–0.63), 0.59 (0.56–0.63), and 0.57 (0.51–0.64) for major bleeding, any clinically relevant bleeding, and intracranial bleeding, respectively. The *Z*-statistics suggested that the two scoring systems had no statistical differences in the accuracy of predicting bleeding events (major bleeding, any clinically relevant bleeding, and intracranial bleeding) after anticoagulation in patients with AF. For the outcome of major bleeding, the subgroup analyses based on the OAC type suggested that there were no differences in the discrimination ability between the HAS-BLED and ORBIT scores in either the DOAC or VKA group (**Figure 3** and **Table 2**). In addition, the subgroup analyses based on available vs. unavailable labile INRs also showed no difference.

Reclassification analysis between HAS-BLED and ORBIT

The NRI and IDI data between the HAS-BLED and ORBIT scores are presented in **Supplementary Table 3**. For the primary outcome of major bleeding, only four included studies reported the NRI and IDI values between the two studied risk scores. Consistently, the HAS-BLED score in these four studies showed positive NRI and IDI values compared with the ORBIT score, although not significant in each included study. In addition, for the outcome of intracranial bleeding, Chao et al. reported that the HAS-BLED score had a significantly positive NRI value (+4.8%, $P < 0.001$) compared with the ORBIT score. No NRI and IDI data were reported about any other bleeding outcomes.

Calibration analysis between HAS-BLED and ORBIT

Calibration data between the HAS-BLED and ORBIT scores from seven included studies are displayed in **Supplementary Table 4**. However, we found that their findings of this part were not consistent among the included studies. Proietti et al., Lip et al., O'Brien et al., and Watanabe et al. showed that ORBIT had a better calibration than HAS-BLED, while Proietti et al. acquired the opposite finding. Beshir et al. and Mori et al. found no difference in the calibration data between ORBIT and HAS-BLED.

Publication bias

As shown in **Supplementary Figure 1**, when analyzing the C-index, we found no potential publication biases when inspecting the funnel plot.

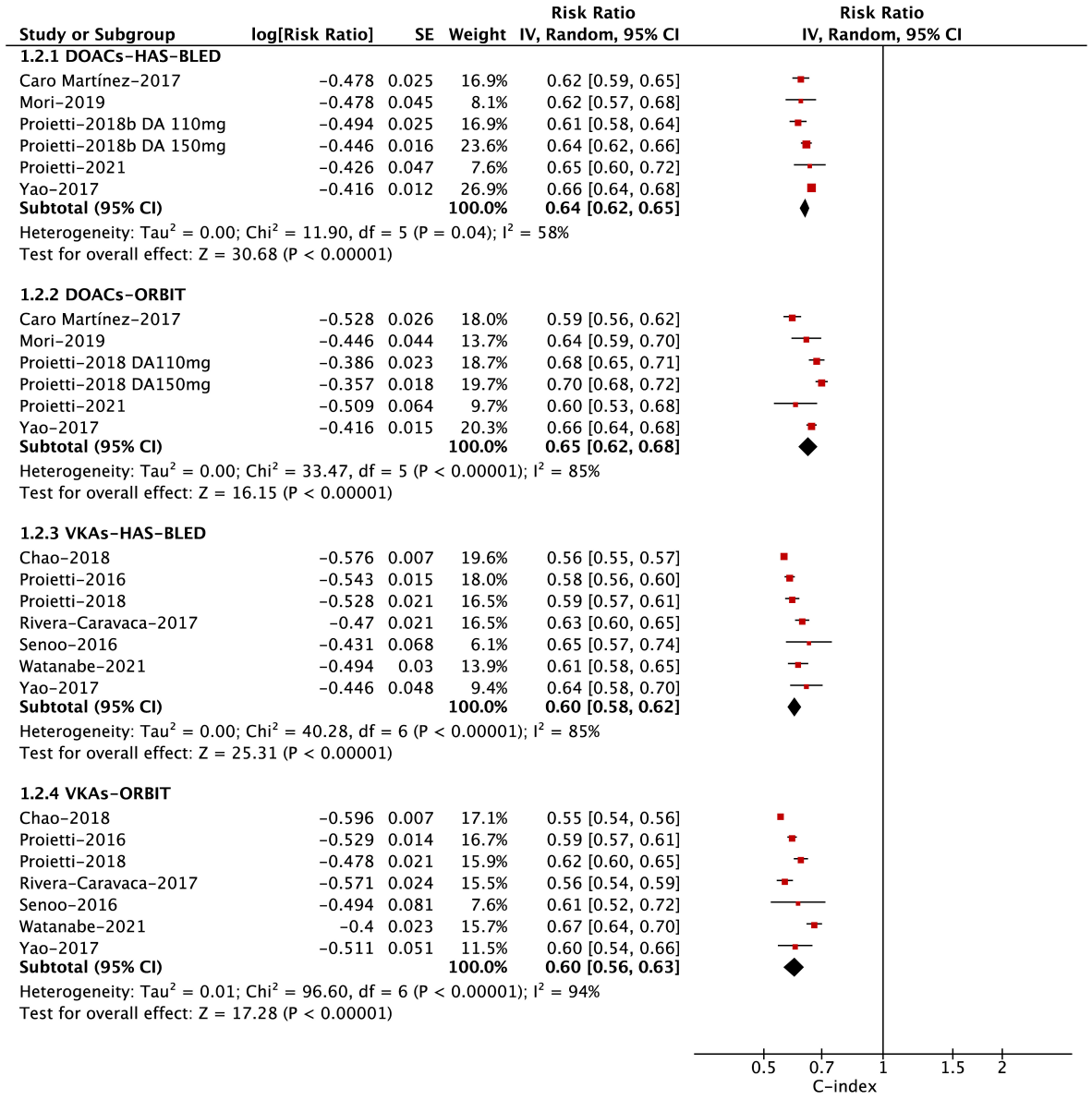

FIGURE 3
Pooled analysis of the *C*-statistics of different subgroups by using DOAC or VKA for major bleeding.

Discussion

The goal of anticoagulation in patients with AF is to minimize the occurrence of adverse events (especially the risk of stroke) by preventing thrombosis, while the risk of bleeding is significantly increased during anticoagulation. Therefore, the accurate prediction of patients with AF with a high bleeding risk is helpful. To date, multiple bleeding risk scores have been created for the assessment of bleeding risk in patients with AF on anticoagulation (29). Moreover, the HAS-BLED and ORBIT scores have been validated in different populations, especially patients with AF using DOACs. These two scores, especially the HAS-BLED score, are currently the most commonly used score in trials and clinical practice systems. Therefore, this study mainly conducted a meta-analysis on the predictive power of the ORBIT vs. HAS-BLED scores in patients with AF with different anticoagulants (VKAs or DOACs).

Our results showed that ORBIT was comparable to the HAS-BLED score in predicting major bleeding, any clinically relevant bleeding, and intracranial hemorrhage in patients with AF treated with anticoagulation. However, the HAS-BLED score was found to be more predictive than the ORBIT score in terms of NRI and IDI values. Because the criterion of "unstable INR" is difficult to be defined and detected, the

HAS-BLED score is less suitable for patients with AF who have received anticoagulation therapy with DOACs or have not received anticoagulation therapy. By contrast, the ORBIT score no longer includes "unstable INR." Subsequent studies comparing the ORBIT with the HAS-BLED score showed greater variability in the predictive values (13, 16, 28, 30). Some cohort studies showed that the HAS-BLED was superior to the ORBIT score in predicting bleeding risk in patients with VKAs or DOACs (28), potentially consistent with our current findings. While in patients with AF receiving VKAs, the ORBIT score was less predictive in ultimately identifying patients with truly "low risk" of major bleeding but was ultimately in identifying truly "low risk" major bleeding in patients with AF receiving VKA anticoagulation. The exclusion of unstable INR or alternative assessment of anticoagulation-related outcomes (reduced hemoglobin/hematocrit/history of anemia) may have resulted in an underestimation of bleeding risk by the ORBIT score. Interestingly, the revised ORBIT (including the unstable INR) showed better clinical utility and higher predictive power than the original ORBIT score. Senoo et al. compared the ORBIT score with TTR or not; for the ORBIT score, adding time in the therapeutic range (TTR) would result in a significant improvement in AUC ($p = 0.002$), with an NRI of 0.26 ($p < 0.001$) and IDI of 0.0065 ($p < 0.001$), compared with ORBIT score without TTR. The difference in AUC between the HAS-BLED score and the ORBIT score was also significant ($p = 0.002$), while NRI and IDI values were not evaluated (13). Proietti et al. made the same comparison, and the result was significantly raised in AUC ($p = 0.106$), with an NRI of 0.2508 ($p = 0.0054$) and IDI of 0.0023 ($p = 0.0092$) (14). Rivera-Caravaca et al. also produced similar results with an NRI of 0.1097 ($p < 0.001$) and IDI of 0.0270 ($p < 0.001$) (18). Ultimately, we believe that the ORBIT score is not significantly better than the HAS-BLED score as it is unlikely to underestimate the bleeding risk in patients anticoagulated with VKAs or DOACs.

In addition, in the subgroup analysis based on the OAC type (VKAs vs. DOACs), we found that the HAS-BLED and ORBIT scores had similar moderate abilities for predicting major bleeding. Therefore, for patients with AF treated with VKA or DOAC anticoagulation, it is still recommended to use the HAS-BLED score for bleeding risk assessment among patients with AF. Moreover, the assessment of bleeding risk is not a "static" process, and patients with AF need to be repeatedly assessed throughout the course of anticoagulation therapy. The main role of the bleeding risk score is to "mark" patients who may be at risk of bleeding for more careful evaluation and follow-up.

Limitations

Several limitations in this meta-analysis should be noted. First, there was high heterogeneity in the C-index analysis and limiting data of the NRI and IDI values, calibration, and decision curve analysis between the two studied scores. Second, the study quality assessed by the PROBAST was relatively low for each included study, potentially limiting the reliability of our findings. Third, beyond major bleeding, the predictive ability of other bleeding events between the HAS-BLED and ORBIT scores should be further explored.

Conclusion

The HAS-BLED and ORBIT scores had similar predictive abilities for major bleeding risk in VKA- or DOAC-treated patients with AF, supporting the recommendation of the HAS-BLED score in the AF settings.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1042763/full#supplementary-material

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Junyi Sun,
The First Affiliated Hospital of Sun Yat-sen University, China
Zhao Jie,
Wuhan Third Hospital, China

*CORRESPONDENCE
Dehui Liu
✉ liudehui2008@126.com

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Effects of direct oral anticoagulants vs. vitamin K antagonists on acute kidney injury in patients with atrial fibrillation: A systematic review

Chengfa Ren[1], Yudan Zhao[2] and Dehui Liu[1]*

[1]Department of Nephrology, Ganzhou People's Hospital Affiliated to Nanchang University, Ganzhou, Jiangxi, China, [2]Medical Department, Queen Mary School, Nanchang University, Nanchang, China

Background: Patients with atrial fibrillation (AF) are routinely prescribed oral anticoagulants to prevent thromboembolism. Concerns regarding the efficacy and safety of oral anticoagulants, such as vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), arise for patients with non-valvular atrial fibrillation (NVAF) because of their widespread use in clinical practice. Even though there have been an abundance of studies on this topic, it is still not clear if DOAC users with NVAF have a lower risk of acute kidney injury (AKI) than warfarin users.

Methods and results: We conducted electronic searches in PubMed, Embase, and the Cochrane Library to identify relevant studies for this systematic review. We included randomized clinical trials and observational studies that reported on the incidence rate, hazard ratio (HR), and 95% confidence interval (95% CI) of AKI in patients using oral anticoagulants. This systemic review included six observational studies and four randomized clinical trials (RCT). The overall results showed that DOACs were associated with a lower AKI risk than warfarin. However, for NVAF patients with severe renal dysfunction, DOACs may not have a reduced risk of AKI compared to warfarin.

Conclusion: The overall results suggest that, except for edoxaban, patients using DOACs may experience a reduced risk of AKI. However, it is uncertain whether this is also the case for patients with severe renal dysfunction. Further research is needed to confirm the effect of DOACs on this population.

KEYWORDS

direct oral anticoagulants, vitamin K antagonists, acute kidney injury, atrial fibrillation, systematic review

Introduction

Atrial fibrillation (AF) is a common type of arrhythmia that affects many adults. It occurs when abnormal electrical signals in the heart, produced by an ectopic focus1 rather than the heart's normal pacemaker (called the sinus node), cause the heart to beat irregularly and too fast. The incidence and prevalence of AF have been on the rise due to an aging population and the ability to more accurately diagnose the condition (1). Therefore, there has been a greater focus on improving the treatment of AF and preventing its complications, such as stroke and heart failure. Thromboembolism, caused by irregular myocardial cell contraction, is frequently observed in patients with AF without the use of anticoagulants. It has been reported that patients with AF have a mortality risk from a stroke that is two times that of patients without AF (2). For this reason, patients with non-valvular atrial fibrillation (NVAF) are prescribed anticoagulation therapy based on their CHA2DS2-VASc score, which is essential for their treatment (3, 4).

Direct oral anticoagulants (DOACs) include factor Xa inhibitors and direct thrombin inhibitors (DTI). The former inhibits both the direct and indirect coagulation pathways by

occupying the active site of the factor Xa molecule. DTI, as its name implies, acts directly on the prothrombin transformation process to prevent fibrin formation. Vitamin K antagonists (VKA) exert their pharmacological function by inhibiting vitamin K epoxide reductase (VKOR). This enzyme catalyzes the conversion of vitamin K to dihydroquinone, which is required for glutamic acid carboxylation (5, 6). Although anticoagulants reduce the incidence of thrombus formation in patients, the oral administration of warfarin to patients with AF may result in renal injuries and accelerated progression of chronic kidney disease (CKD), known as "warfarin-related nephropathy" (WRN) (7, 8). Some studies reported that DOAC users are less likely to experience unfavorable renal outcomes than warfarin users (9). In this systemic review, we aimed to compare the risk of AKI in patients with NVAF caused by agents in DOACs and VKA.

Previous meta-analyses have revealed that, compared with warfarin, using DOACs is linked to a lower risk of developing AKI (10). However, due to differences in the action mechanisms of these drugs, it might be inappropriate to evaluate their renal outcomes together. The drugs in the DOACs group were analyzed separately in this systemic review to provide clinicians with more accurate guidance when deciding which oral anticoagulants should be given to patients with NVAF who require anticoagulation therapy.

Methods

We conducted an electronic search in PubMed, Embase, and the Cochrane Library. The restricted date range was from 1 January 2000 to 20 November 2022. We searched the database using keywords and free-text words on atrial fibrillation, acute kidney injury and oral anticoagulants. Following the search, strategies were applied: (acute kidney injury OR acute renal injury OR acute renal failure OR acute kidney failure OR warfarin related nephropathy OR AKI OR ARF OR WRN) AND (atrial fibrillation OR auricular atrial fibrillation OR non-valvular atrial fibrillation OR NVAF) AND (oral anticoagulants OR OAC OR warfarin OR vitamin K antagonist OR VKA OR non-vitamin K antagonist oral anticoagulant OR NOAC OR direct oral anticoagulant OR DOACs OR novel oral anticoagulant OR dabigatran OR apixaban OR rivaroxaban OR edoxaban). Then, the studies were assessed based on their title and abstract. Afterward, we performed a selection process based on the full texts of the literature. All the processes were conducted independently by two investigators. The process of selecting the studies is displayed in Figure 1.

Eligibility criteria

Eligible studies must include patients with NVAF receiving anticoagulation therapy. The anticoagulants used by those patients are either DOACs or VKA. Studies focusing on comparing the difference in the risk of AKI induced by DOACs and warfarin were included. The included studies must be case-control studies, cohort studies, or randomized clinical trials (RCT). For all the included studies, the results need to be reported in the form of an odds ratio (OR), relative risk (RR), or hazard ratio (HR). Moreover, a clear definition of AKI needs to be given in the studies. All the studies included were written in English.

Study selection

The eligibility of studies was determined through a review of their titles, abstracts, and full texts. Once selected, baseline information was extracted from these studies, including the author, year of publication, study design, characteristics of the study population, types of oral anticoagulants used, and results. This information was used to assess the suitability of the studies for inclusion in the analysis.

Study quality assessment

To evaluate the overall quality of the research, the Newcastle–Ottawa tool was used to evaluate the quality of the included observational studies (11). Selection of the population, comparability of the included subjects, and study outcomes were considered when evaluating the included literature. Literature with seven or more stars was considered superior. For the randomized clinical trials, an assessment based on the Cochrane risk-of-bias tool was performed. The results are shown in Supplementary Tables 1, 2. The publication bias of all included studies was assessed by the Egger test ($P = 0.091$).

Results

Apixaban and acute kidney injury

Four observational studies and one randomized clinical trial comparing the effects of apixaban and warfarin on AKI risk in patients with NVAF were included in this review (12–16). The eligible studies included populations from different regions, such as Asia, North America, and Europe. All five studies assessed the risk of AKI as a renal outcome, while efficacy outcomes were only discussed in the RCT, which suggests that apixaban-treated patients have a significantly lower risk of stroke compared to the warfarin-treated population. The results of the included studies suggest that apixaban is associated with a reduced risk of AKI (Table 1). Subgroup analysis was performed in three studies based on renal function, and one study divided patients into two groups based on the presence of chronic kidney disease (CKD). Divergence from the general conclusion could be observed in patients with severe renal impairment. Jung-Im Shin et al. found that patients treated with apixaban were more likely to develop AKI than patients treated with warfarin (13). However, another study conducted by Ziv Harel et al. indicates they have a significantly lower risk of AKI compared to another group (15). For this reason, it is currently unclear whether apixaban is superior to warfarin in terms of AKI for those patients with severe renal dysfunction. On the basis of current studies, patients taking apixaban tend to have a lower risk of developing AKI among most strata of renal function. However, for those with severe kidney dysfunction, further studies are required.

Dabigatran and acute kidney injury

In this systemic review, five studies comparing the AKI risk induced by dabigatran and warfarin were included (Table 2)

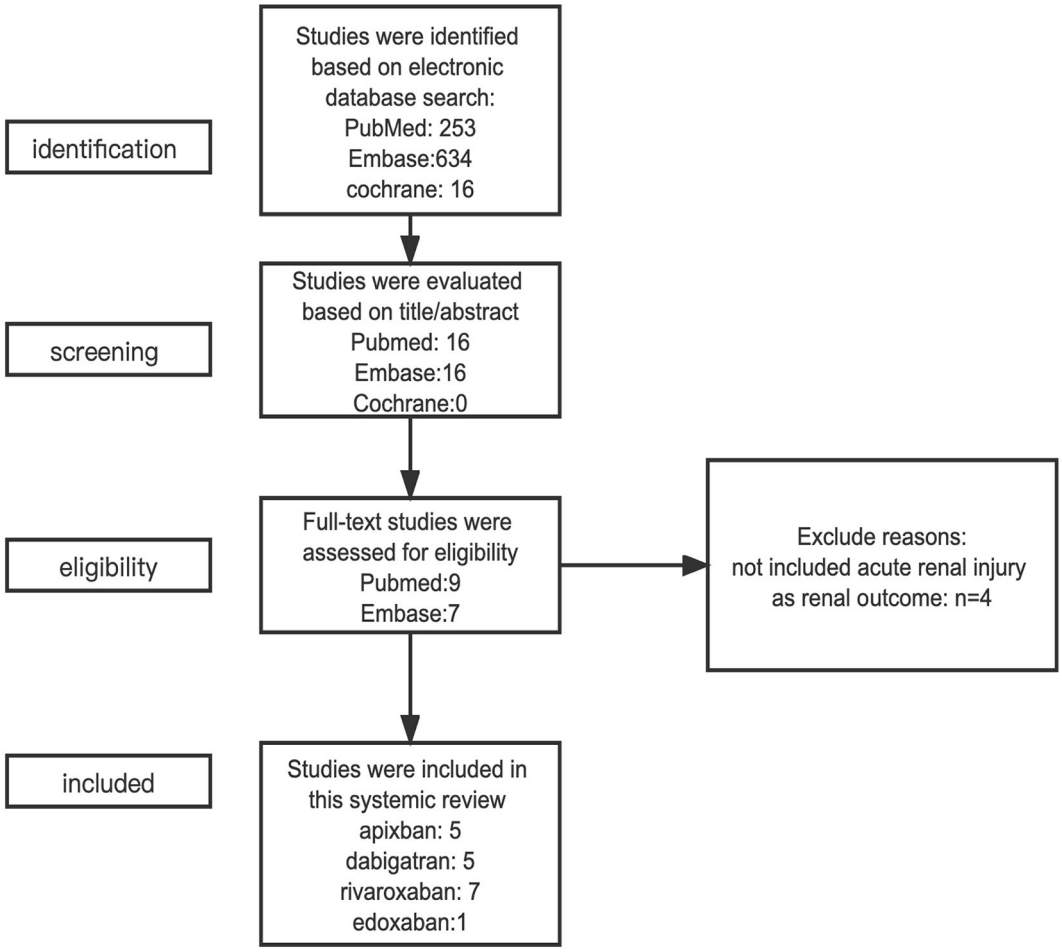

FIGURE 1
The process of selecting eligible studies.

(12–15, 17). The efficacy outcomes were discussed in the study conducted by Connonlly et al., which revealed that high-dose dabigatran has a significantly lower risk of stroke, whereas such an advantage cannot be detected in low-dose therapy. Based on the overall results of the included studies, patients with NVAF have a lower risk of AKI when treated with dabigatran. All included studies suggest that dabigatran is associated with a reduced risk of AKI compared to warfarin, except for the one conducted by Connonlly et al. (17), which indicates that dabigatran shows no superiority over warfarin in terms of a decreased AKI risk, with RRs of 1.203 and 1.075 for the low dose and high dose groups, respectively. Based on the overall results of the included studies, patients with NVAF tend to have a lower risk of AKI when treated with dabigatran. Three of the eligible studies performed subgroup analyses of the AKI risk induced by dabigatran and warfarin in patients with different renal functions. One study (13) suggests that, for patients with severe renal dysfunction, dabigatran has an increased risk of AKI relative to warfarin, while another study (15) did not report the result due to the small sample size. According to the results of the present studies, it is unclear whether dabigatran-treated patients with severe renal deficiency could have a lower risk of AKI compared to the warfarin-treated population.

Rivaroxaban and acute kidney injury

This review included seven studies conducted in various regions, including Asia, North America, and Europe (12–15, 18–20). Only one study evaluated an efficacy outcome, which showed that the risk of stroke was similar between the low-dose rivaroxaban group and the warfarin group, while high-dose rivaroxaban therapy was associated with a significantly lower risk of stroke compared to warfarin (20). In comparison to warfarin, the overall results revealed that using rivaroxaban is associated with a lower risk of developing AKI (Table 3). Five studies included a subgroup analysis; four were based on the stratification of renal function, and one divided the cohorts into CKD and CKD-free groups. Yao et al. (12) suggested that, for patients with deficient renal function (eGFR <60 ml/min per 1.73 m^2), the AKI risk induced by rivaroxaban does not differ significantly from that of warfarin. Divergence from the general conclusion could be observed in the population with severe renal dysfunction; the study conducted by Jung-Im Shin et al. (13) indicated that rivaroxaban is related to a higher risk of AKI, while the results of the other two studies suggest that the risk of AKI associated with rivaroxaban is not significantly different from that of warfarin (15, 19). According to current studies, rivaroxaban may not be superior to warfarin

TABLE 1 Summary of studies comparing the risk of AKI induced by apixaban and warfarin.

Author	Medication	Study design	Baseline characteristics of investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Xiaoxi et al. (12)	Apixaban ($n = 1883$) Warfarin ($n = 4185$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in the United States Apixaban vs. Warfarin: age(yrs.): 72.9 vs. 73.2 eGFR (ml/min per 1.73 m^2): 67.6 vs. 66.9 Women (%): 47.8 vs. 44.8 CHA_2DS_2-VASc: 4.0 vs. 4.2	Hospitalization or emergency department with a diagnosis code of AKI at the primary or secondary position	Acute kidney injury: Apixaban vs. Warfarin: HR = 0.84 95 %CI (0.66,1.07) $P = 0.16$ eGFR ≥60ml/min per 1.73 m^2 Sample size: NR HR = 0.75 95% CI (0.49, 1.14) eGFR<60 ml/min per 1.73 m^2 Sample size: NR HR = 0.94 95% CI (0.71, 1.25)	NR
Shin et al. (13)	Apixaban ($n = 1029$) Warfarin ($n = 1029$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in the United States Age (mean, yrs.): 72 years eGFR (ml/min per 1.73 m^2): 69 Women (%): 47	Hospitalization or emergency department with a diagnosis code of AKI (ICD-9 clinical modification code 584. x.) at the primary or secondary position.	Acute kidney injury: Apixaban vs. Warfarin: Overall: HR = 0.86, 95% CI (0.68, 1.10) $P = 0.233$ eGFR≥60 ml/min per 1.73 m^2: Sample size: NR HR = 0.67, 95% CI (0.45, 1.00) $P = 0.052$ eGFR 30-59 ml/min per 1.73m^2: Sample size: NR HR = 1.01, 95% CI (0.72,1.41) $P = 0.956$ eGFR <30 ml/min per 1.73m^2: Sample size: NR HR = 1.23, 95% CI (0.58,2.61) $P = 0.593$	NR
Chan et al. (14)	Apixaban ($n = 5875$) (std. dose 5mg b.i.d : 39% Low dose 2.5mg b.i.d : 61%) Warfarin ($n = 21135$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in Taiwan CKD-free cohort (Dabigatran vs. Warfarin) Age(mean): 71 vs. 70 Women (%): 43 vs. 43 CHA_2DS_2-VASc: 3.05 vs. 2.94 CKD cohort (Dabigatran vs. warfarin) Age(mean): 77 vs. 76 Women (%): 39 vs. 38 CHA_2DS_2-VASc: 3.99 vs. 3.99	The outcomes of AKI were defined as those who received a diagnosis coded as ICD-9-CM 580.X, 584.X, or 586 (until Jan 1, 2016) and ICD-10-CM N17.x (from Jan 1, 2016, to Dec 31, 2016) during hospitalization or an outpatient visit at least once.	Acute kidney injury: Apixaban vs. Warfarin: CKD-free cohort: Sample size: 4368 vs. 16,908 HR = 0.65, 95% CI (0.60,0.72) CKD cohort: Sample size: 1507 vs. 4227 HR = 0.50, 95% CI (0.45,0.56)	NR

(Continued)

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TABLE 1 (Continued)

Author	Medication	Study design	Baseline characteristics of investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Harel et al. (15)	Apixaban ($n = 8217$) Warfarin ($n = 8383$)	Retrospective cohort study	Canadian patients diagnosed with atrial fibrillation. apixaban vs. warfarin: (mean) age(yrs.): 80 vs. 80 eGFR (ml/min per 1.73 m^2): 65 vs. 65 Female (%): 54.85 vs. 53.64 CHA_2DS_2-VASc: 4.0 vs. 4.0	Hospitalization or emergency department presentation with AKI defined as a ≥50% increase in serum creatinine concentration from baseline, an absolute increase of ≥0.3 mg/dl, or the receipt of acute dialysis	Acute kidney injury: Apixaban vs. Warfarin: Overall: HR = 0.79, 95% CI (0.66, 0.94) eGFR≥60 ml/min per 1.73 m^2: sample size: 5007 vs.5128 HR = 0.97, 95% CI (0.73,1.12) eGFR 30-59 ml/min per 1.73m^2: sample size: 3,025 vs. 3065 HR = 0.76, 95% CI (0.64,0.91) eGFR <30 ml/min per 1.73m^2: sample size: 158 vs. 189 HR = 0.54, 95% CI (0.35,0.83)	NR
Granger et al. (16)	Apixaban ($n = 9,088$, 5 mg b.i.d: 95.3% 2.5 mg b.i.d: 4.7%) Warfarin ($n = 9,052$ 5 mg b.i.d: 95.6% 2.5 mg b.i.d: 4.4%)	Randomized clinical trials	Patients from North America, Latin America, Europe, and Asia Pacific diagnosed with atrial fibrillation. Apixaban vs. warfarin Age(yrs): 70 vs. 70 $CHADS_2$ score: 2.1 vs. 2.1 The proportion of patients with moderate to severe renal impairment: 16.5% vs. 16.7%	NR	Acute kidney injury: RR:0.615 95% CI (0.403, 0.938)	Stoke: HR = 0.79 95% CI (0.65,0.95)

NR, not reported in the included studies; AKI, acute kidney injury; yrs, years; ICD-9, international classification of disease ninth revision; ICD-10, international classification of disease tenth revision; HR, hazard ratio; 95% CI, 95% confidence interval; std dose: standard dose; b.i.d: bis in die, twice daily; RR: risk ratio; eGFR, estimated glomerular filtration rate.

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TABLE 2 Summary of studies comparing the risk of AKI induced by warfarin and dabigatran.

Author	Medication	Study design	Baseline characteristics of the investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Xiaoxi et al. (12)	Dabigatran ($n = 1216$) Warfarin ($n = 4185$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in the United States Dabigatran vs. warfarin: age(yrs.): 72.1 vs. 73.2 eGFR (ml/min per 1.73 m^2): 67.8 vs. 66.9 Women (%): 43.0 vs. 44.8 CHA_2DS_2-VASc: 3.9 vs. 4.2	Hospitalization or emergency department with a diagnosis code of AKI at the primary or secondary position	Acute kidney injury: Apixaban vs. Warfarin: HR = 0.55 95 %CI (0.40,0.77) $p < 0.001$ eGFR ≥60ml/min per 1.73 m^2 Sample size: NR HR = 0.63 95% CI (0.39, 1.03) eGFR<60 ml/min per 1.73 m^2 Sample size: NR HR = 0.54 95% CI (0.34, 0.84)	NR
Shin et al. (13)	Dabigatran ($n = 852$) Warfarin ($n = 852$)	Cohort study	Patients with non-valvular atrial fibrillation in the United States Age (mean): 72 years eGFR (ml/min per 1.73 m^2): 69 Women (%): 47	Hospitalization or emergency department with a diagnosis code of AKI (ICD-9 clinical modification code 584. x.) at the primary or secondary position.	Acute kidney injury: Dabigatran vs. Warfarin: Overall: HR = 0.70 95% CI (0.52, 0.96) $P = 0.025$ eGFR≥60 ml/min per 1.73 m^2: HR = 0.66 95% CI (0.43, 1.02) $P = 0.063$ eGFR 30–59 ml/min per 1.73m^2: HR = 0.60, 95% CI (0.37,0.98) $P = 0.040$ eGFR <30 ml/min per 1.73m^2: HR = 1.52, 95% CI (0.53,4.38) $P = 0.440$	NR
Chan et al. (14)	Dabigatran, ($n = 20145$) (std. dose 150 mg b.i.d: 11% low dose: 110 mg b.i.d 89%) warfarin ($n = 21135$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in Taiwan CKD-free cohort (dabigatran vs. warfarin) Sample size: 16,945 vs. 16,908 Age(mean): 71 vs. 70 Women (%): 43 vs. 43 CHA_2DS_2-VASc: 3.05 vs. 2.94 CKD cohort (dabigatran vs. warfarin) Sample size: 3200 vs. 4227 Age(mean): 77 vs. 76 Women (%): 39 vs. 38 CHA_2DS_2-VASc: 3.99 vs. 3.99	The outcomes of AKI were defined as those who received a diagnosis coded as ICD-9-CM 580.X, 584.X, or 586 (until Jan 1, 2016) and ICD-10-CM N17.x (from Jan 1, 2016, to Dec 31, 2016) during hospitalization or an outpatient visit at least once.	Acute kidney injury: Dabigatran vs. Warfarin: CKD-free cohort: HR = 0.68, 95% CI (0.64,0.74) CKD cohort: HR = 0.54, 95% CI (0.49,0.59)	NR

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TABLE 2 (Continued)

Author	Medication	Study design	Baseline characteristics of the investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Harel et al. (15)	Dabigatran, ($n = 2,277$) Warfarin ($n = 2,269$)	Retrospective cohort study	Canadian patients with non-valvular atrial fibrillation Dabigatran vs. warfarin: age(yrs.): 78 vs. 78 eGFR (ml/min per 1.73 m^2): 69 vs. 69 Women (%): 44.56 vs. 44.05 CHA_2DS_2-VASc: 4 vs. 4	Hospitalization or emergency department presentation with AKI defined as a ≥50% increase in serum creatinine concentration from baseline, an absolute increase of ≥0.3 mg/dl, or the receipt of acute dialysis	Acute kidney injury: Dabigatran vs. Warfarin: Overall: HR = 0.54, 95% CI (0.43,0.69) eGFR≥60 ml/min per 1.73 m^2: sample size: 1,535 vs. 1,543 HR = 0.69, 95% CI (0.52, 0.90) eGFR 30-59 ml/min per 1.73m^2: sample size: 727 vs. 712 HR = 0.60, 95% CI (0.44,0.82) eGFR ≤30 ml/min per 1.73m^2: NR	NR
Connonlly et al. (17)	Dabigatran ($n = 12042$. 110mg b.i.d : 5,983 150mg b.i.d: 6,059) Warfarin ($n = 5998$)	Randomized clinical trial	Patients from North America, Latin America, Europe, and Asia Pacific diagnosed with atrial fibrillation. Dabigatran (110mg b.i.d) vs. Dabigatran (150 mg b.i.d) vs. Warfarin: Age(yrs): 71.4 vs. 71.5 vs. 71.6 Women (%): 35.7 vs. 36.8 vs. 36.7 $CHADS_2$ score: 2.1 vs. 2.2 vs. 2.1	NR	Acute kidney injury: Low-dose (110mg b.i.d) group: Dabigatran vs. warfarin RR = 1.203 95% CI (0.769, 1.881) High-dose (150 mg b.i.d) group: RR=1.075 95% CI (0.680, 1.699)	Stroke Low-dose (110mg b.i.d) group: Dabigatran vs. warfarin HR = 0.91 95% CI (0.74, 1.11) High dose (150 mg b.i.d) group: HR = 0.66 95% CI (0.53,0.82)

NR, not reported in the included studies; AKI, acute kidney injury; yrs, years; ICD-9, international classification of disease ninth revision; ICD-10, international classification of disease tenth revision; HR, hazard ratio; RR, risk ratio; 95% CI, 95% confidence interval; eGFR, estimated glomerular filtration rate; std dose: standard dose; b.i.d: bis in die, twice a day; CKD, chronic kidney disease.

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TABLE 3 Summary of studies comparing the risk of AKI induced by rivaroxaban and warfarin.

Author	Medication	Study design	Baseline characteristics of the investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Xiaoxi et al. (12)	Rivaroxaban ($n = 2,485$) Warfarin ($n = 4,185$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in the United States Rivaroxaban vs. warfarin: age(yrs.): 72.3 vs. 73.2 eGFR (ml/min per 1.73 m^2): 69.0 vs. 66.9 Women (%): 43.8 vs. 44.8 CHA_2DS_2-VASc: 3.9 vs. 4.2	Hospitalization or emergency department with a diagnosis code of AKI (ICD-10M) at the primary or secondary position.	Acute kidney injury: Rivaroxaban vs. Warfarin Overall: Sample size: 2,485 vs. 4185 HR = 0.69 95 %CI (0.57,0.84) $p < 0.001$ eGFR ≥60ml/min per 1.73 m^2 Sample size: HR = 0.62 95% CI (0.44, 0.87) eGFR<60 ml/min per 1.73 m^2 Sample size: NR HR = 0.81 95% CI (0.63, 1.03)	NR
Shin et al. (13)	Rivaroxaban, ($n = 1,325$) Warfarin ($n = 1,325$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in the United States Age (mean): 72 years eGFR (ml/min per 1.73 m^2): 69 Women (%): 47	Hospitalization or emergency department with a diagnosis code of AKI (ICD-9 clinical modification code 584. x.) at the primary or secondary position.	Acute kidney injury: Rivaroxaban vs. Warfarin: Overall: HR = 0.83 95% CI (0.66, 1.05) $P = 0.114$ eGFR≥60 ml/min per 1.73 m^2: HR = 0.79 95% CI (0.50, 0.98) $P = 0.037$ eGFR 30-59 ml/min per 1.73m^2: HR = 0.95 95% CI (0.68,1.33) $P = 0.764$ eGFR <30 ml/min per 1.73m^2: HR = 1.48 95% CI (0.63,3.49) $P = 0.36$	NR
Chan et al. (14)	Rivaroxaban, ($n = 28,066$) (std. dose: 93% Low dose: 7%) Warfarin ($n = 21,135$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation in Taiwan CKD-free cohort (rivaroxaban vs. warfarin) Age(mean): 71 vs. 70 Women (%): 43 vs. 43 CHA_2DS_2-VASc: 3.04 vs. 2.94 CKD cohort (rivaroxaban vs. warfarin) Age(mean): 76 vs. 76 Women (%): 38 vs. 38 CHA_2DS_2-VASc: 3.99 vs. 3.99	The outcomes of AKI were defined as those who received a diagnosis coded as ICD-9-CM 580.X, 584.X, or 586 (until Jan 1, 2016) and ICD-10-CM N17.x (from Jan 1, 2016, to Dec 31, 2016) during hospitalization or an outpatient visit at least once.	Acute kidney injury: Rivaroxaban vs. Warfarin: CKD-free cohort: Sample size: 22,301 vs. 16,908 HR = 0.73 95% CI (0.68,0.79) CKD cohort: Sample size: 5765 vs. 4227 HR = 0.53 95% CI (0.49,0.58)	NR
Hernandez et al. (18)	Rivaroxaban ($n = 10,017$) (std dose 20mg o.d ,: 77.4% Low dose 15mg o.d: 22.6%). Warfarin ($n = 11665$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation and a baseline history of type 1 or type 2 diabetes in the United States Age(median): 70 years CHA_2DS_2-VASc (median): 3	Based on the definition of acute kidney injury in ICD-10 code.	Acute kidney injury: Rivaroxaban vs. warfarin HR = 0.83 95% CI (0.74-0.92) Stage 3-4 CKD cohort: HR = 0.63 95% CI (0.49-0.79) No Stage 3-4 CKD: HR = 0.89 95% CI (0.78-1.00)	NR

(Continued)

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TABLE 3 (Continued)

Author	Medication	Study design	Baseline characteristics of the investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Harel et al. (15)	Rivaroxaban ($n = 5,263$) Warfarin ($n = 5,363$)	Retrospective cohort study	Canadian patients with atrial fibrillation Rivaroxaban vs. warfarin: age(yrs.): 78 vs. 78 eGFR (ml/min per 1.73 m^2): 70 vs. 70 Women (%): 51.97 vs. 50.39 CHA_2DS_2-VASc: 4 vs. 4	Hospitalization or emergency department presentation with AKI defined as a ≥50% increase in serum creatinine concentration from baseline, an absolute increase of ≥0.3 mg/dl, or the receipt of acute dialysis	Acute kidney injury: Rivaroxaban vs. Warfarin: Overall: HR = 0.77 95% CI (0.63, 0.93) eGFR≥60 ml/min per 1.73 m^2: sample size: 3,777 vs. 3,898 HR = 0.94 95% CI (0.76, 1.14) eGFR 30–59 ml/min per 1.73 m^2: sample size: 1,439 vs. 14,118 HR = 0.70 95% CI (0.57, 0.86) eGFR <30 ml/min per 1.73m^2: sample size: 47 vs. 47 HR = 0.83 95% CI (0.35,1.95)	NR
González-Pérez et al. (19)	Rivaroxaban ($n = 6,436$ Dose: 15/20 mg/day) Warfarin ($n = 7,129$)	Retrospective cohort study	Patients with non-valvular atrial fibrillation registered in IMRD-UK Rivaroxaban vs. warfarin: age(yrs.): 74.4 vs. 74.2 eGFR (ml/min per 1.73 m^2): 70.5 vs. 70.4 Female (%): 42.7 vs. 43.7 CHA_2DS_2-VASc: 3.2 vs. 3.3	Based on recorded SCr values using validated Aberdeen AKI phenotyping. AKI is determined if any of following 3 criteria were met: 1) Serum creatinine ≥1.5 times higher than the median of all creatinine values 8-365 days ago. 2) Serum creatinine ≥1.5 times higher than the lowest creatinine within 7 days. 3) serum creatinine >26 μmol/L higher than the lowest creatine within 48 hours.	Acute kidney injury Rivaroxaban vs. warfarin Overall: HR = 0.80, 95%CI (0.68,0.93) eGFR>50 ml/min/1.73m^2: Sample size: 5547 vs. 6043 HR = 0.79 95% CI (0.66,0.94) eGFR ≤50 ml/min/1.73m^2: Sample size: 889 vs. 1,086 HR = 0.82 95% CI (0.59,1.14)	NR
Manesh R Patel et al. (20)	Rivaroxaban ($n = 7,131$, 20 mg o.d, 15 mg o.d. for patients with CrCL 30–49 ml /minute) Warfarin ($n = 7,133$, adjusted dose to target INR, 2.0 to 3.0)	Randomized clinical trials	Patients with non-valvular atrial fibrillation from 45 countries. Rivaroxaban vs. warfarin: 71.2 vs. 71.2 Female (%): 39.6 vs. 39.7	NR	Acute kidney injury: Rivaroxaban vs. warfarin: HR = 0.806 95% CI (0.523, 1.241)	Stroke Low-dose (110mg b.i.d) group: Dabigatran vs. warfarin HR = 0.91 95% CI (0.74, 1.11) High dose (150 mg b.i.d) group: HR = 0.66 95% CI (0.53,0.82)

NR, not reported in the included studies; AKI, acute kidney injury; yrs, years; ICD-9, international classification of disease ninth revision; ICD-10, international classification of disease tenth revision; HR, hazard ratio; RR, risk ratio; 95% CI, 95% confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; std dose: standard dose; o.d.:omni die, once daily; IMRD-UK: the IQVIA Medical Research Data UK, a database representative of UK general population.

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TABLE 4 Summary of studies comparing the risk of AKI induced by edoxaban and warfarin.

Author	Medication	Study design	Baseline characteristics of investigated population	Definition of acute kidney injury	Renal outcome	Efficacy outcome
Giugliano et al. (21)	Edoxaban, High dose (60mg o.d.): 7,012 Low dose (30 mg o.d.): 7,012 Warfarin: (Dose adjusted to achieve INR, 2.0 to 2.0)	Randomized clinical trial	Patients with non-valvular atrial fibrillation from Asia (13.7%), America (82.3%) Age (yrs): High-dose edoxaban vs. low-dose edoxaban vs. warfarin (median) 72 vs. 72 vs.72 Women (%): 37.9 vs. 38.8 vs. 37.5 $CHADS_2$ score: 2.8 vs. 2.8 vs. 2.8	NR	Acute kidney injury: Low dose edoxaban vs. warfarin HR = 0.984 95% CI (0.694, 1.395) High dose edoxaban vs. warfarin HR = 0.841 95% CI (0.585, 1.210)	Stroke Low dose (30mg o.d) HR = 1.13 95% CI (0.97,1.31) High dose (60mg o.d.) HR = 0.88 95% CI (0.75,1.03)

NR, not reported in the included studies; HR, hazard ratio; RR: risk ratio; 95% CI, 95% confidence interval; o.d.: omni die, once daily; yrs, years.

in reducing AKI risk for NVAF patients with severely impaired renal function.

Edoxaban and acute kidney injury

A single randomized clinical trial (21) was conducted to analyze the effect of edoxaban on NVAF patients (Table 4). The study participants were divided into three groups based on the dosage and type of treatment they received. The results indicated that patients in both the low-dose edoxaban group and the high-dose edoxaban group had a slightly lower risk of AKI compared to the warfarin group. In terms of safety outcomes, the low-dose edoxaban group had a higher risk of stroke, while the high-dose group had a slightly lower, but not statistically significant, risk of stroke.

The overall results suggest that DOACs, except for edoxaban, are associated with a lower risk of AKI than warfarin in patients with NVAF from various regions. Subgroup analysis based on eGFR stratification revealed that, for patients with severe renal deficiencies, DOACs may not provide a significantly lower risk of AKI compared to warfarin.

Discussion

Six observational studies and four randomized clinical trials were included in our systemic review to compare the risk of AKI caused by warfarin and DOACs (rivaroxaban, dabigatran, apixaban, and edoxaban). Instead of being analyzed as a group, agents belonging to DOACs were analyzed individually. The results indicate that DOACs, except for edoxaban, are associated with a lower incidence of AKI compared to warfarin. The conclusion of this systemic review is consistent with that of prior analyses, which also focused on the renal outcomes of DOACs (10, 22, 23). The result of edoxaban might be caused by the lack of edoxaban-related studies. Subgroup analysis based on the stratification of renal function was also involved. The results demonstrate that DOACs may not be superior to warfarin in terms of AKI risks in patients with severe renal impairment.

Thrombin inhibition and vascular calcification caused by vitamin K deficiency may explain why populations treated with DOACs have a lower AKI incidence compared to warfarin-treated populations. Erythrocytes and the cast of red blood cells can be observed under a microscope in renal biopsies of patients with WRN, an injury that has long been demonstrated, indicating the presence of endothelial wall impairment (24, 25). The damage to endothelial wall integrity is assumed to be associated with thrombin since it participates in the maintenance of the endothelial barrier by activating protease-activated receptors (26–28). Moreover, another hypothesis suggests that vascular calcification induced by vitamin K deficiency is related to renal deterioration. Matrix G1α protein (MGP), a protein whose activation requires vitamin K-dependent carboxylase, can inhibit bone morphogenic protein-2 (BMP_2), which can elevate the expression level of osteogenesis markers within a cell (29, 30). In the absence of sufficient vitamin K, the level of BMP_2 rises, resulting in vascular calcification, which is believed to have a direct relationship with a decline in renal function (31).

The results also revealed that DOACs may not be superior to warfarin with respect to AKI risk for patients with severe renal deficiency. However, previous meta-analyses (32) revealed that

patients treated with DOACs were less likely to experience renal deterioration than those treated with warfarin; this conclusion may not apply to those with severe renal dysfunction since patients with severe kidney dysfunction were excluded in the original studies (16, 17, 20, 21). The pharmacokinetics and pharmacodynamic properties of DOACs may account for the results in patients with severe renal dysfunction. Agents belonging to DOACs undergo renal elimination, with proportions being approximately 80%, 35%, 27%, and 50% for dabigatran, rivaroxaban, apixaban, and edoxaban, respectively. In contrast, warfarin molecules are not eliminated through the kidneys (33). In patients whose renal functions are severely compromised, using DOACs increases the burden on the kidney, resulting in acute deterioration of kidney function. Moreover, the improper usage of DOACs in clinical practice may also provide an explanation for the results. According to the guidelines, reduced doses of DOACs are recommended for patients with renal insufficiency (34). However, a survey conducted by Yao et al. (35) demonstrated that a large proportion of patients potentially overdosed, which contributes to undesired renal outcomes.

Among the observational studies included, only one study included the Asian population. Notably, compared to other populations, Asian populations are more likely to receive low-dose DOACs. This finding is consistent with a prior clinical trial that claimed that, for patients with NVAF in Asia, low-dose treatment is favored because of the relatively higher prevalence of CKD in the Asian population (36, 37). This can result in a lower risk of renal injury since the kidney injury induced by DOACs is dose-dependent (38). Moreover, Asian patients are reported to have poorer quality control, which can induce a higher risk of WRN compared to the non-Asian populations (36). Although the conclusion of the study conducted in the Asian population is consistent with that for other populations, further studies are required to analyze the risk of AKI among Asian NVAF populations taking a standard dose of DOACs.

Admittedly, there are some limitations to this review. First, the majority of the included studies are observational. In four of the included studies, instead of diagnosing AKI based on recorded data, the diagnoses of AKI were largely based on the physician's judgment in clinical practice since the codes that indicate AKI in the International Classification of Disease (ICD) are applied. In addition, we found in these studies that AKI can be caused by factors other than warfarin. Moreover, as WRN is dose-dependent, the daily dose of DOACs and time in the therapeutic range (TTR) of warfarin-treated patients, for instance, may influence the final results (38). The daily dose of the drugs and TTR were not reported in most of the eligible studies, which may introduce bias into the results. Second, efficacy outcomes were not evaluated in most of the included studies. Efficacy outcomes must be included to provide more detailed guidance so that physicians can make better decisions after weighing the pros and cons. In addition, most of the present studies are conducted in the non-Asian population. The only study conducted in an Asian population included a large proportion of patients taking low-dose DOACs. For this reason, whether the conclusion in this review can be applied to Asian populations taking a standard dose of DOACs remains unclear.

Despite these limitations, our review also has some advantages over the others, and it provides directions for future research and clinical practice. First, only one clinical trial focusing on edoxaban was included. With the increased application of edoxaban in clinical practice, more studies examining its efficacy and safety should be conducted. Second, our review suggests that more studies are required in patients with severe renal insufficiency. Given that AF and chronic kidney disease are two diseases with shared risk factors and have a bidirectional relationship with each other (39), clarifying the correlation between decreased kidney function and AKI risk induced by DOACs will assist doctors in making more accurate choices when selecting oral anticoagulants for their patients. Furthermore, a few of the current studies investigate the difference in AKI risk among DOACs. The agents in DOACs do not perform their roles with identical mechanisms. For example, dabigatran specifically acts on thrombin, while the other three act pharmacologically on coagulation factors. As discussed above, thrombin inhibition may also induce renal injury. Therefore, agents in DOACs may correlate to different AKI risks, and elucidating the variance among DOACs aids in more accurate usage of DOACs. In addition, the study conducted in Asian populations suggests that the usage of DOACs in Asians differs from that in other populations. More studies focusing on the efficacy and safety of DOACs should be conducted in this population. Indeed, low-dose DOACs provide a lower risk of AKI for Asian patients, but whether low-dose therapy has the same effect on reducing stroke risk remains unclear in the included study. Efficacy outcomes should also be included in future studies.

Except for providing potential directions for further study, our findings also provide directions for clinical practice. For patients with normal or relatively preserved renal function, DOACs are favored since they can provide a lower risk of AKI. However, for patients with severe renal insufficiency, the use of anticoagulants needs to be individualized, and comprehensive evaluations are required before deciding the agent and its dosage for the patient. The results also indicate that renal functions should be routinely monitored when anticoagulants are prescribed to patients. The dose of DOACs should be adjusted immediately after the detection of severe renal insufficiency since an overdose of DOACs induces a higher risk of renal impairment in those patients.

Conclusion

Patients with NVAF who are treated with DOACs have a lower risk of developing AKI compared to those treated with warfarin. However, the effects of DOACs on patients with impaired renal functions remain unclear, and more studies are required to determine whether they are better options for those with severe renal dysfunction.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1068269/full#supplementary-material

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EDITED BY
Wengen Zhu,
First Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Feria Ladha,
University of Connecticut, United States
Zi Amber Ye,
Royal North Shore Hospital, Australia

*CORRESPONDENCE
Wenfeng He
✉ fengfeng_982366@126.com

†These authors share first authorship

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Genetic variants, pathophysiological pathways, and oral anticoagulation in patients with hypertrophic cardiomyopathy and atrial fibrillation

Shengnan Wang[1†], He Chen[2†], Chunju Liu[3†], Mengxian Wu[3], Wanlei Sun[4], Shenjian Liu[2], Yan Zheng[1,2] and Wenfeng He[1,2*]

[1]Department of Medical Genetics, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [2]Jiangxi Key Laboratory of Molecular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [3]Department of Clinical Laboratory, Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Nanchang, China, [4]Department of Clinical Laboratory, The Second Affiliated Hospital of Nanchang University, Nanchang, China

Atrial fibrillation (AF) is commonly prevalent in patients with hypertrophic cardiomyopathy (HCM). However, whether the prevalence and incidence of AF are different between genotype-positive vs. genotype-negative patients with HCM remains controversial. Recent evidence has indicated that AF is often the first presentation of genetic HCM patients in the absence of a cardiomyopathy phenotype, implying the importance of genetic testing in this population with early-onset AF. However, the association of the identified sarcomere gene variants with HCM occurrence in the future remains unclear. How the identification of these cardiomyopathy gene variants should influence the use of anticoagulation therapy for a patient with early-onset AF is still undefined. In this review, we sought to assess the genetic variants, pathophysiological pathways, and oral anticoagulation in patients with HCM and AF.

KEYWORDS

atrial fibrillation, hypertrophic cardiomyopathy, genotype, mechanism, anticoagulation

Introduction

Atrial fibrillation (AF) is commonly seen in patients with hypertrophic cardiomyopathy (HCM). The estimated prevalence of AF in HCM patients is 22.3%, and the incidence of AF is 2.5 cases per person-years (1). Genes encoding thick-filament (MYH7, MYBPC3; nearly 40%) and thin-filament (TNNT2, TNNI3, TPM1, TNNC1, ACTC1; nearly 5%) proteins are the two most common types associated with HCM development, followed by other sarcomeric genes (e.g., TTN, MYL2, MYL3, OBSCN, TRIM63, JHP2, ACTN2, CRSP3, MYZO2) (2). Recent evidence has suggested that AF is often the first presentation of genetic HCM patients in the absence of a cardiomyopathy phenotype, implying the importance of genetic testing in this population with early-onset AF. However, the association of the identified sarcomere gene variants with HCM occurrence in the future remains unclear. In this review, we aimed to assess the genetic variants, pathophysiological pathways, and oral anticoagulation in patients with HCM and AF.

Prevalence and incidence of AF in inherited HCM patients

AF is the most common persistent cardiac arrhythmia disease, affecting 1% to 4% of the general population, which leads to an increased risk of heart failure and stroke, further causing substantial morbidity and mortality. More recently, a growing body of evidence has found that some gene variants accounting for inherited cardiomyopathies, such as dilated cardiomyopathy (DCM), HCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC), are also primarily related to substantial AF penetrance (3).

In the study of Butters et al., the incidence of AF in hereditary cardiomyopathy was HCM (31%), left ventricular noncompaction cardiomyopathy (LVNC) (18%), DCM (17%), and ARVC (14%) (3). Bongini et al. analysed the prevalence and clinical correlates of AF in relation to genotype and evaluated 237 patients with HCM followed for 14 ± 10 years. AF occurred in 74 patients with HCM (31%), with no differences among groups (31% in MYBPC3, 37% in MYH7% and 18% in other genotypes) (4). Akhtar et al. recruited 537 TTN gene carriers with truncating variants (TTNtv) in DCM and followed them for a median of 49 (18–105) months. In the final assessment, 31% of the patients had AF (5). Currently, only a few dozen patients with SCN5A-mediated cardiomyopathies have been described. Mutations are associated with DCM, ARVC, and atrial standstill. These cardiomyopathies are usually characterized by a wide range of rhythm disorders. The incidence of AF with SCN5A reported by Zaklyazminskaya was 40%–60% (6). However, there are no data on the incidence of AF in different hereditary cardiomyopathies in the same type of gene mutation. Currently, most data describing the prevalence and impact of AF in patients with cardiomyopathy have focused on HCM, with limited data describing patients with LVNC, DCM or ARVC.

The prevalence of AF in HCM has been found to be not different between genotype-positive vs. genotype-negative patients in previous studies (7–11). Among these studies, Olivotto et al. (7) reported that the prevalence of paroxysmal or chronic AF in HCM patients at baseline was independent of the genetic background. However, when chronic AF was independently analysed, it was more prevalent in genotype-positive patients with HCM than in genotype-negative controls. Moreover, the AF prevalence and baseline left atrial diameter were comparable between thin-filament and thick-filament mutation-associated HCM patients (12). In the study of Bongini et al. (4), the studied HCM population was divided into three genotypes, namely, MYBPC3 (58%), MYH7 (28%), and other sarcomeric genes (14%), suggesting no differences in the prevalence of paroxysmal/persistent AF, paroxysmal evolved to permanent AF, or chronic AF only among the three subgroups.

A meta-analysis of 51 studies with 7,675 HCM individuals found that 18% of HCM patients with MYBPC3 variants, 24% of MYH7, 33% of TNNT2, 30% of TNNI3, and 17% of genotype-negative (no pathogenic variants in sarcomere genes) patients showed supraventricular tachycardia, such as AF. Lee et al. (13) found that 19% of HCM patients with sarcomeric gene variants developed new-onset AF. In the Genotyped HCM Cohort (14), when compared with genotype-negative patients with HCM, sarcomere mutation carriers (pathogenic or likely pathogenic variant [hazard ratio (HR) = 2.41, 95% confidence interval (CI): 1.98–2.94], sarcomere variant of unknown significance at present [HR = 1.90, 95% CI: 1.38–2.64]) had an increased risk of incident AF after controlling for proband status, sex, and race. However, the AF risk was similar regardless of whether the sarcomere variant was pathogenic or of unknown significance at present (14), suggesting that these variants of unknown significance in sarcomere genes could affect the HCM prognosis. In the follow-up, the genetic subtype was seemingly not an independent predictor of new-onset AF (thin vs. thick-filament: 11% vs. 9%, $P = 0.527$ [Coppini et al.] and MYBPC3 vs. MYH7 vs. other genotypes: 31% vs. 37% vs. 18%, $P = 0.15$ [Bongini et al.]) in HCM patients (4, 12). Of note, in the study by Bongini et al. (4), HCM patients with MYH7 variants had a higher risk of AF than other genotypes, although the difference was not significant. Indeed, a subsequent study by Lee et al. (13) further demonstrated that HCM patients with likely pathogenic or pathogenic MYH7 variants had a higher risk of incident AF than other sarcomeric genes (MYBPC3, thin filament genes). In addition, patients with sarcomeric gene (e.g., MYH7, TNNT2) variants in hot spot sites that are more frequently associated with HCM development may have higher AF vulnerability in the future than those with gene variants in non-hot spot sites (13, 15).

Cardiomyopathy gene variants and early-onset AF

Previous studies have implicated the genetic basis of AF and found that both common and rare variants in ion-channel genes, gap junction and transcription factor genes, or structural genes are likely associated with AF pathogenesis (16, 17).

For the ion channels, the KCNQ1 and SCN5A genes, encoding the pore-forming α-subunit of the cardiac potassium-channel IKs and the α-subunit of the cardiac sodium channel, respectively, are involved in current processes that alter the voltage dependence of channel gating, which are associated with early-onset AF. Their variants are also linked to DCM, Brugada syndrome, and ventricular fibrillation (16, 18). In addition, mutations in genes related to signalling molecules also play a role in the development of AF. It has been postulated that GATA4 and GATA5, cardiac transcription factors involved in myocardial development, directly coregulate SCN5A. GATA4, GATA5 and GATA6 are linked to decreased transcriptional activity and may play a role in reducing the levels of NKX2.5 and other target proteins, which could have further downstream effects on cardiac development and function or electrical activity (16, 17). The LMNA gene variants interact with the NUP155 gene, encoding lamin A/C and nucleoporin 155. The latter reduces nuclear envelope permeability by affecting the overall nuclear pore complex and subsequently leads to shortened action potential duration (APD), which is thought to be related to the occurrence of AF, DCM and muscular dystrophy. Myozap, a myocardial

ribbon adhesion protein encoded by MYZAP, is primarily expressed in the human heart and is thought to be associated with a subtype of atrial cardiomyopathy. KLF15 is specifically expressed in myocytes and fibroblasts, playing a role in inhibiting hypertrophy and fibrosis. Li et al. found a KLF15 mutant (K229*) in a large family with AF. The affected individuals also manifested as premature ventricular contractions, and several manifested as ventricular tachycardia and HCM (17, 19).

More recently, a growing body of evidence has found that rare gene variants accounting for inherited ventricular cardiomyopathies (e.g., DCM, HCM, and ARVC) or arrhythmias (e.g., long QT syndrome) are predominantly associated with substantial AF penetrance (20). Furthermore, the identified gene variants are more often linked to inherited cardiomyopathies than arrhythmia syndrome (3, 21). Yoneda et al. (22) found that disease-associated variants in patients with early-onset AF were most frequent in genes associated with DCM (7.2%), followed by ARVC (3.3%) and HCM (2.9%). Some rare variants in genes affecting cardiac structure, such as MYH7, MYBPC3, MYL4 and TTN, have been associated with AF incidence (16). MYH7 and MYBPC3 account for more than 40% of HCM patients with pathogenic variants (23). The increased expression of MYH7 may lead to extensive myocardial disease and reduce cardiac performance, which may be related to the high occurrence of AF (16). MYL4 encodes atrial light chain-1, a protein that is expressed in foetal and adult cardiac atrial tissue. Loss-of-function variants of MYL4 can cause early atrial fibrosis, resulting in atrial cardiomyopathy and atrial arrhythmia, as well as atrial contractile failure and atrial enlargement. Titin is a giant sarcomere protein encoded by TTN, which may be associated with impaired sarcomere function caused by loss-of function variants of TTN, leading to an increased susceptibility to arrhythmia, such as early-onset AF (16, 17, 21). Vad et al. found that rare loss-of-function variants in DCM-related cytoskeletal genes (DMD, PDLIM3, and FKTN) may play a role in the development of atrial cardiomyopathy and early-onset AF (16, 17). FLNC encodes filamin-C, a cytoskeletal protein that anchors membrane proteins to the cytoskeleton in both skeletal and cardiac muscle by stabilizing polymerized actin. Variants in FLNC may present with AF, conduction disease, or ventricular arrhythmias prior to a diagnosis of cardiomyopathy (20). The SGCG gene encodes the gamma-sarcoglycan protein, and it has previously been associated with DCM. Furthermore, the SGCG gene is thought to be linked to AF in a large genome-wide association study (24). In addition, prior clinical and genetic studies indicated that pathogenic variants in other sarcomere protein genes, including TNNT2, TNNI3, TPM1, MYL2, MYL3 and ACTC1, were associated with the occurrence of ventricular and atrial arrhythmias (particularly AF) (15, 23).

Several case-control studies have demonstrated the positive association of gene variants linked to cardiomyopathies with early-onset AF (21, 24, 25). Nevertheless, whether patients with unexplained AF should be screened for cardiomyopathy-associated gene variants remains controversial (26). A recent observational prospective cohort study (22) by Yoneda et al. enrolled 1,293 patients with early-onset AF (defined as AF diagnosed at <66 years of age) and performed whole genome sequencing using the major commercial cardiomyopathy and arrhythmia-susceptibility gene panels (145 genes), identifying a disease-associated variant in 10.1% of patients. More interestingly, the authors found that the prevalence of disease-associated variants was approximately the same (10%) in the 40- to 60-year age group but up to 16.8% with AF onset before 30 years of age. These findings potentially support the use of genetic testing in early-onset AF, especially for patients before 30 years of age.

Of note, no study has evaluated the subsequent occurrence of the cardiomyopathy phenotype when a pathogenic cardiomyopathy gene variant has been identified in patients with early-onset AF. Nevertheless, after a median of 10 years of follow-up, the presence of a pathogenic or likely pathogenic variant in cardiomyopathy genes was associated with a 1.5-fold higher risk of all-cause mortality among patients with early-onset AF (27). These studies may support the use of genetic testing in early-onset AF. The consensus on how to appropriately measure the impact of genetic assessment and testing on clinical risk-benefit analyses is still developing. In addition to these limitations, the interpretation of genetic testing is extremely challenging and should be approached with caution. As larger datasets become available, it is reasonable to expect that more pathogenic variants will be discovered and provide important prognostic information for patients with early-onset AF.

Pathophysiological mechanisms of AF remodelling in HCM

AF has been found to be secondary to an underlying atrial cardiomyopathy encompassing primary atrial disorders and secondary atrial remodelling (28). Multiple factors (i.e., environmental, clinical, and genetic) potentially lead to different pathophysiological and histological subtypes of atrial cardiomyopathy, responsible for AF vulnerability (28, 29). Genetic variants have been found to be prevalent in patients with both AF and HCM (30). However, whether HCM-associated gene variants have direct or indirect potential for AF development is not well defined. Previously, experts regularly thought that genetic variants first caused ventricular cardiomyopathy and increased left ventricle (LV) filling pressures, which subsequently led to increased atrial filling pressures, atrial stretch, and atrial dilation, ultimately causing AF development. Nevertheless, which underlying genetic HCM contributes to the atrial substrate predisposing to AF remains unclear.

More recently, the coexistence of a genetic atrial substrate in HCM patients has been increasingly considered the primary culprit of AF. This alternative hypothesis is potentially supported by several observations. Variants in atria-specific genes may be the direct drivers of AF among individuals with HCM. For instance, MYH6 encodes the α-subunit of myosin heavy chain predominantly expressed in atrium. Myosin, an ATPase cellular motor protein whose heavy chain subunit is a main component

of the sarcomere, is the building block of the contractile system of cardiac muscle. The overexpression of MYH6 in HL-1 and isolated rat atrial cardiomyocytes results in sarcomere impairment, electrophysiological abnormalities, and a slower conduction velocity, suggesting the potential role of MYH6 gene variants in atrial structure and function. Comparable pathways may play a role in mutant MYH6-induced AF (31, 32). MYL4 is a chamber-specific expression restricted to the atria, which encodes atrial Light Chain-1, a key sarcomeric component. E17K transgenic zebrafish showed myofibrillar disarray and absent Z-disks under electron microscopy. Z-disks can form T-tubules that have a high density of LTCCs through cell membrane invaginations. The activation of LTCC triggers ryanodine receptor activation, resulting in the further release of calcium from the sarcoplasmic reticulum and subsequent sarcomere activation and contractility. Hence, the E11K-MYL4 mutation causes destabilization of the F-actin–Z-disk complex, which may impair calcium signalling and cause atrial myopathy, leading to atrial arrhythmias, especially in AF (33, 34). Among the HCM-related individual genes, it is speculated that some ventricular cardiomyopathy genes expressed in both the atria and ventricles could give rise to an atrial cardiomyopathy phenotype, subsequently manifesting as electrophysiological or structural changes affecting the atria and developing AF. For instance, TTN encodes a sarcomeric protein, titin, and is widely expressed in both the atria and ventricles. Loss-of-function variants in TTN are the most common in early-onset AF. Ahlberg et al. observed compromised assembly of the sarcomere in both the atria and ventricle, a prolonged PR interval, and a higher degree of atrial fibrosis in heterozygous adult zebrafish, suggesting that TTNtv is an important risk factor for AF (22, 25, 35–37). The next most commonly affected gene is MYH7 (22). Patients with HCM attributable to MYH7 (encoding β-MyHC) gene variants have a higher risk of AF than those with variants in other sarcomeric genes. Furthermore, in the early stages of HCM, genetic variation in MYH7 is related to higher levels of propeptide of type I procollagen, a marker of collagen synthesis, indicating that fibrosis can mediate a link between MYH7 and AF (3, 13). However, the underlying genetic aetiology for AF in patients with HCM is still unclear.

Examining the atrial substrate in the HCM mouse model may help explain AF development in HCM. The missense mutation Glu180Gly in the α-tropomyosin gene was previously detected in familial patients with HCM (38). A transgenic mouse model with the α-tropomyosin Glu180Gly variant was established. Compared with nontransgenic and control mice expressing wild-type α-tropomyosin, mutant mice at baseline presented severe biatrial remodelling and diastolic dysfunction (39–41), although whether mutant mice displayed an LV hypertrophy phenotype varied across studies (39, 41). The left atrial size of α-tropomyosin Glu180Gly mice was clearly larger than that of their controls (40), which is an independent risk factor for AF development. In a transgenic HCM mouse model with the cardiac troponin-I Gly203Ser variant, Lim et al. (42) first tried to assess atrial structural and electrophysiological alterations and circulating biomarkers. Compared with control mice, HCM mice with the troponin-I Gly203Ser variant showed enlarged left and right atria, increased atrial myocardial mass, significant atrial structural (myocyte hypertrophy and fibrosis) and electrophysiological (conduction) abnormalities, increased levels of blood biomarkers of extracellular matrix remodelling (MMP-2, MMP-3), and inflammation (VCAM-1). Nevertheless, Lim et al. did not document any inducible AF in the murine atrium in ex vivo electrophysiological experiments, which warrants further examination by telemetric electrocardiography in conscious animals. In addition, Pioner et al. found that HCM mouse models expressing TNNT2 variants ("hot-spot" site-R92Q and "sporadic" site-E163R) displayed atrial structural and electrophysiological remodelling. More interestingly, the pathogenesis of atrial cardiomyopathy and AF occurrence were TNNT2 variant-dependent, where E163R increased myofilament tension cost but showed no atrial arrhythmic propensity, whereas R92Q increased atrial myofilament calcium sensitivity, representing an intrinsic arrhythmogenic mechanism promoting AF. Overall, TNNT2 E163R promotes and sustains AF due to atrial cardiomyopathy induced by LV diastolic dysfunction in HCM, whereas R92Q causes AF related to the mutation itself. The sarcomere mutation-driven mechanism may help individualized treatment for AF in patients with HCM. However, although atrial myopathy may play a crucial role in providing a substrate predisposing to AF development in HCM patients, the specific molecular basis of AF occurrence caused by mutations in cardiac sarcomeric proteins is unclear.

Anticoagulation for AF in patients with HCM

AF is common in patients with HCM and further elevates the risks of stroke and other thromboembolic events. Atrial cardiomyopathy in AF has been found to be associated with an increased stroke risk, potentially caused by atrial fibrosis-related hypocontractility, hypercoagulability, and endothelial dysfunction (43). Some genetic variants in cardiomyopathy are associated with a higher risk of early-onset AF, and tools are now becoming available to better understand and address arrhythmias in genetic cardiomyopathy, raising the prospect of therapies specific to mechanism, gene, and mutation. For instance, mavacamten is a new therapy targeted to decrease hypercontractility in HCM. It is an allosteric modulator developed to inhibit myosin ATPase activity and will soon be used to treat symptoms of outflow tract obstruction and improve the capacity to exercise in obstructive HCM. It is not clear how the specific genetic variants will affect the clinical responses to mavacamten, but studies with human induced pluripotent stem cells have shown that the ACTC1 variant responds more to mavacamten than the more common MYH7 variant (20). Furthermore, ranolazine is capable of normalizing Ca-handling in human HCM myocardium and in the ventricles of R92Q mice by blocking late sodium current, potentially reducing Ca-dependent arrhythmias in R92Q atria. Ranolazine is able to selectively inhibit peak sodium current in the atria, also destabilizing atrial reentry circuits. These observations prompt us towards further tests of ranolazine as a

drug to prevent AF in selected HCM patients with a high-risk mutation (15). Similarly, SCN5A codes for the Nav1.5 channel, which is the target for sodium channel blockers, such as flecainide. KCNH2 encodes the Kv11.1 channel, which is the target for potassium channel inhibitor drugs, such as amiodarone (16). An intron-mediated TTN enhancer promotes cardiac-specific TTN expression in similarly derived cardiomyocytes, thus promoting normal TTN expression in mice. In addition, adenoviral-mediated modulation of RNA splicing with an HCM-related MYBPC3 mutation in induced pluripotent stem cells is able to correct the hypertrophic phenotype. Danon disease, an HCM phenotype, has been reported for 3 patients with the first-in-human gene transfection of the LAMP2 gene. The rationale to expand genetic testing extends from current management of patients and families to accelerate an exciting future. Tailored preventive treatments for AF can be identified in selected genotyped HCM subgroups to develop novel first-in-class agents that target specific molecular mechanisms in cardiomyopathy subtypes, correcting their underlying molecular defects and reducing the incidence of AF in HCM.

The HA/ACC Guideline recommends that, in patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 h' duration for a given episode, anticoagulation is recommended with direct-acting oral anticoagulants (NOACs) as a first-line option and vitamin K antagonists (VKAs) as a second-line option, independent of CHA2DS2-VASc score (44). Hence, early detection of AF is extremely crucial to recognize and treat AF in a timely manner. In conclusion, we recommend close and thorough investigations using ECG, Holter ECG and implantable loop recorders on a regular basis in HCM patients at high risk for AF. As such, every HCM patient with documented AF should be immediately given lifelong oral anticoagulant treatment because AF is necessary for patients with HCM regardless of the CHA2DS2-VASc score.

Beyond VKAs, several observational studies have assessed the effect of nonvitamin K NOACs compared with VKAs in HCM patients with AF (45–49). Among the published studies, a study in the US commercial insurance database showed that NOACs use in HCM patients with AF was associated with a lower risk for ischaemic stroke and bleeding after a mean follow-up of 0.56 years compared with warfarin use (48). Data from patients with AF and HCM from the Korean National Health Insurance Service database showed that, compared with those with VKAs, patients with NOACs had significant reductions in the risks of all-cause mortality and composite fatal cardiovascular events during a median follow-up of 16 months (46). Other data from the Korean Health Insurance Review and Assessment Service database showed that the use of NOACs vs. VKAs significantly decreased the risks of ischaemic stroke and the composite outcome during 1.6 years of follow-up (45). A subsequent systematic review by Rujirachun et al. including published articles observed that the use of NOACs vs. VKAs showed a significantly lower risk of all-cause death in HCM patients with AF, but the risks of ischaemic stroke, major bleeding and intracranial bleeding were not significantly different (50). In addition, Zhou et al. compared the effect of NOACs with VKAs in patients with HCM and AF, and they found that the use of NOACs was associated with reduced risks of ischaemic stroke, all-cause death, and intracranial haemorrhage (51). In sum, these data support the notion that, compared with VKA use, the use of NOACs showed similar or lower risks of thromboembolic and bleeding events in HCM patients with AF (50–52). In addition, NOACs at least have similar effects as VKAs in patients with HCM undergoing catheter ablation for AF (53). Further head-to-head randomized clinical trials in this population could confirm the use of NOACs. It is also not known whether there are differences in anticoagulation effects regarding positive vs. negative genotypes in patients with HCM and AF. Further studies could explore whether the HCM genotype affects treatment with anticoagulants in this specific population.

Conclusions and further implications

Recent evidence has suggested that AF could be the first presentation of genetic HCM patients in the absence of a cardiomyopathy phenotype. However, data are currently limited as to whether genetic testing should be performed in this population with early-onset AF. After sarcomere gene variants are identified in an individual with AF, the question regarding the association of sarcomere gene variants with HCM occurrence in the future also remains unanswered. Whether a cardiomyopathy variant directly or indirectly leads to the incidence of AF remains controversial and needs further examination. Moreover, how the identification of these sarcomere gene variants should influence clinical care (e.g., anticoagulation therapy) for a patient with early-onset AF is still undefined.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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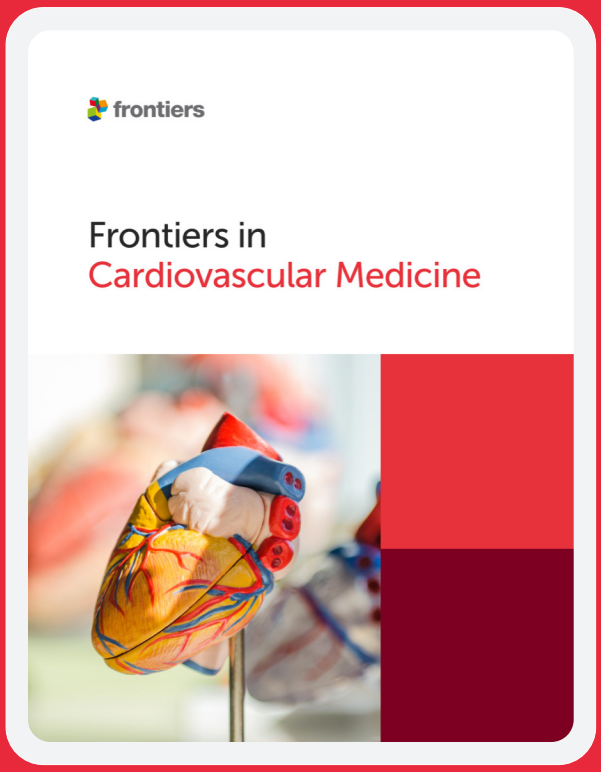

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