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Original Article

Comparative safety and effectiveness of non-vitamin K oral anticoagulants versus warfarin in patients with non-valvular atrial fibrillation: A network meta-analysis

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Background: The introduction of non-vitamin K antagonist oral anticoagulants (NOACs), with a non-inferior or superior clinical efficacy profile compared to vitamin K antagonists (VKAs), has significantly improved the safety profile and treatment adherence of patients with non-valvular atrial fibrillation (AF). However, few studies have compared the effectiveness and safety of NOACs. Therefore, we conducted this systematic review and network meta-analysis to compare the safety and clinical effectiveness of NOACs and VKAs in patients with non-valvular AF.

Methods: An online bibliographic search was conducted to retrieve real-world evidence studies published between January 2019 and June 2022.

Results: Dabigatran was associated with lower risks of major bleeding, ischemic stroke, and intracranial hemorrhage than warfarin. Among the NOACs, only dabigatran had a lower risk of all-cause mortality than warfarin. Dabigatran was also associated with lower risks of major bleeding and intracranial hemorrhage than rivaroxaban.

Conclusion: Our meta-analysis confirms that dabigatran's real-world safety and clinical effectiveness align with the results of pivotal clinical trials.

Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and a leading cause of mortality and morbidity worldwide.[1] Patients with AF are prone to increased risk of thromboembolic events, heart failure, dementia, and cardiovascular and all-cause mortality.[2] Nearly 15% of ischemic stroke cases in the US (38% in elderly patients) are attributed to AF, accounting for up to 125,000 events annually.[3] Prophylactic anticoagulants are universally recommended to prevent ischemic stroke in high-risk patients with non-valvular AF.[4] Anticoagulants have well-established efficacy in preventing AF-related thromboembolic events. The vitamin K antagonist (VKA), warfarin, has long been considered the standard anticoagulant for non-valvular AF, and ample evidence supports its efficacy in preventing stroke and related thrombotic events.[5] Despite its effectiveness, the use of warfarin in clinical practice can be problematic due to its slow pharmacokinetic action, interactions with several drugs and foods, and excessive risk of fatal bleeding, necessitating routine monitoring of patients' prothrombin profiles.[6–8]

The introduction of non-VKA oral anticoagulants (NOACs) has revolutionized the management of patients with AF and improved the safety profile and patient adherence. The NOACs rivaroxaban, apixaban, dabigatran, and edoxaban have shown a more favorable safety profile, with non-inferior or superior clinical efficacy, than warfarin in several clinical trials and real-world evidence studies.[9–11] In clinical practice, NOACs are convenient alternatives since they have minimal drug

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interactions, show rapid onset and offset of action, and do not require regular monitoring of patients' coagulation profiles.[12]

Dabigatran etexilate is a reversible direct oral free and fibrin-bound thrombin inhibitor approved by the US and European regulatory bodies at 150 mg bid or 110/75 mg bid for stroke prevention in patients with non-valvular AF. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was superior to warfarin for stroke prevention and had a lower risk of major bleeding.[13] In real-world registries, such as Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients (ARISTOPHANES) and Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation (GLORI-A-AF), dabigatran has a lower risk of stroke and major bleeding than warfarin.[14,15] However, few studies have compared the effectiveness and safety of dabigatran to other NOACs.[16] Therefore, comparing dabigatran and other NOACs is necessary to ensure that the former has a tolerability profile similar to other oral agents. Few clinical studies have directly compared NOACs. A network meta-analysis of real-world evidence could benefit the assessment of the comparative safety and clinical effectiveness of different NOACs. Therefore, we conducted this systematic review and network meta-analysis to compare the safety and clinical effectiveness of NOACs and VKAs in patients with non-valvular AF.

Materials and methods

The manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[17]

Eligibility criteria

Real-world evidence studies (both retrospective registries and prospective cohorts) were included in this systematic review and network meta-analysis if they evaluated the data of adult patients with non-valvular AF who received prophylactic NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) or VKAs for preventing stroke or systemic embolism as part of routine clinical practice. In cases of mixed AF, studies were deemed eligible if $\geq$ 90% of their patients had non-valvular AF. In addition, studies were eligible for inclusion if they compared at least two NOACs and reported on any of the following outcomes: major bleeding, ischemic stroke, myocardial infarction, intracranial hemorrhage, and all-cause mortality. Only studies published between January 2019 and June 2022 were included. There were no restrictions regarding the included studies' geographic location, sample size, and methods for reducing confounders. In the case of multiple data sets, we selected the report with the longest follow-up duration. We excluded articles published in languages other than English, theses, and conference proceedings.

Information sources and search strategy

Studies published from January 2019 to June 2022 were retrieved through an online bibliographic search of the Medline database via PubMed, SCOPUS, Web of Science, and Cochrane Library. The bibliographic search used the following search term combining relevant keywords: (atrial fibrillation OR atrial flutter OR nonvalvular atrial fibrillation) AND (dabigatran OR rivaroxaban OR warfarin OR apixaban OR edoxaban OR Savaysa OR pradaxa OR xarelto OR Eliquis OR bms562247 OR bms-562247-01 OR bay 59–7939 OR bibr 1048 OR factor xa inhibitor OR direct thrombin inhibitor OR NOACs OR direct oral anticoagulant OR DOACs) NOT (editorial OR letter OR lecture note OR review OR case reports OR practice guideline OR animals). The online search was complemented by manual searching of the references in eligible studies.

Selection process

Retrieved articles were imported into EndNote 20 for Windows to remove duplicates. Two independent authors screened unique reports for eligibility, and a third reviewer resolved discrepancies. The two independent authors downloaded and screened the full texts of potentially eligible reports for inclusion in the network meta-analysis. The outcome of the selection process is shown in the PRISMA flowchart (Fig. 1).

Data items and effect measures

Two independent authors extracted the following data from the eligible studies: authors; registry name; publication year; country; enrollment period; data source; sample size; NOAC type; treatment dose and duration; patients' demographic characteristics, history of prior bleeding or stroke, CHA_2DS_2-VASc at treatment initiation, and HAS-BLED score at treatment initiation; and effect measures of interest. The effect measures of interest included major bleeding, ischemic stroke, intracranial hemorrhage, myocardial infarction, and all-cause mortality. Since this network meta-analysis depended on real-world evidence, the effect measures were defined based only on the reporting of the studies included in the analysis; no definitions were created before data extraction. The risk-of-bias assessment was conducted using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[18]

Synthesis methods

The data were analyzed using Stata 16.0 and R 4.1.3 software. Pairwise meta-analysis was performed using R's *Metan* package for pooling time-to-event data and the inverse variance heterogeneity (IVhet) random-effects model for dichotomous data. Missing hazard ratios (HRs) were calculated from Kaplan–Meier curves according to Tierney et al.[19] Following Cochrane Handbook recommendations, heterogeneity was inspected visually and statistically through chi-square and τ^2 tests, using $p < 0.1$ as the significance level for heterogeneity. When significant heterogeneity was detected, further sensitivity analyses were conducted to determine the source of heterogeneity by excluding one study at a time.

The network meta-analysis adopted a mixed treatment approach with a frequentist framework and used R's *Netmeta*, *Mvmeta*, and *Network_graphs* packages. We used node-splitting and loop-specific approaches to ascertain inconsistencies across the network, where a $p < 0.05$ indicated significant inconsistency. A consistency model was used when no significant inconsistency could be detected within the network. Publication bias was examined using comparison-adjusted funnel plots with further Egger's regression and trim-and-fill analyses.

Standard protocol approvals, registrations, and patient consent

This study was approved by the Institutional Review Board of the Ethical Standards Committee of Chang Gung Memorial Hospital. The requirement to obtain informed consent was waived. This study was performed according to the Declaration of Helsinki and relevant local laws, regulations, and guidelines for using human subjects.

Results

The online search of bibliographic databases retrieved 7223 unique records; 7069 records were excluded after title/abstract screening, leaving 154 records for full-text screening. Overall, 143 articles were excluded since they used duplicate data sets ($n = 57$), were published before 2019 ($n = 32$), were randomized controlled trials ($n = 50$), or involved only one NOAC ($n = 4$). Therefore, the network meta-analysis included ten studies (11 articles; Fig. 1).

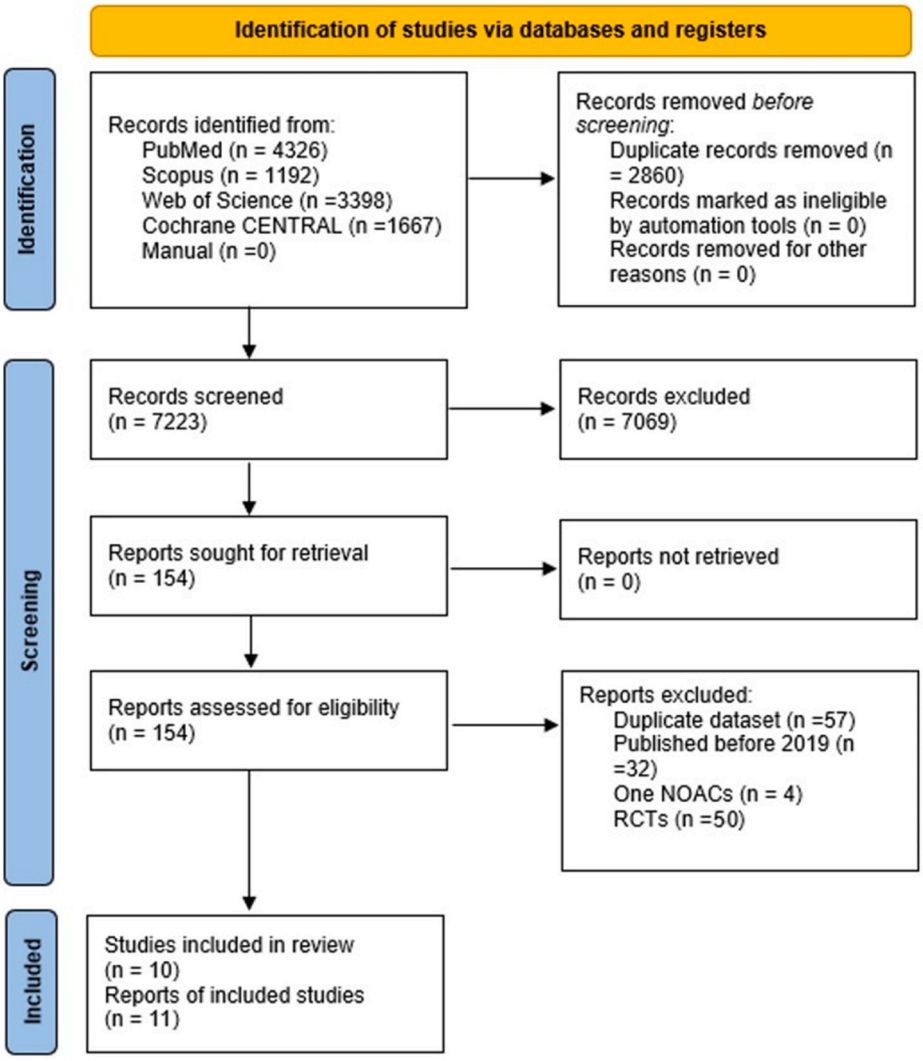

Figure 1. PRISMA flowchart.

Table 1
Summary characteristics of the included studies ($n = 10$).

Author/ Registry	Year of publication	Country	Enrolment period	Data source	No.	NoACs	VKA
Rutherford et al.	2020	Norway	January 2013 and December 2017.	NPR and NorPD.	30401	Apixaban, Dabigatran, Rivaroxaban	Warfarin
Hald et al.	2021	Denmark	2005 to 2018	Danish Stroke Registry	16765	Apixaban, Dabigatran, Rivaroxaban	Warfarin
NAXOS Study	2021	France	2014 and 2016	French National Health System claims data	321501	Apixaban, Dabigatran, Rivaroxaban	Warfarin
Chan et al.	2019	Taiwan	June 1, 2012, to December 31, 2017	Taiwan's National Health Insurance Research Database	89683	Apixaban, Dabigatran, Rivaroxaban, Edoxaban	Warfarin
Kohsaka et al.	2019	Japan	March 2011 to July 2018	372 acute care hospitals in Japan	73989	Apixaban, Dabigatran, Rivaroxaban, Edoxaban	Warfarin
González-Pérez et al.	2022	UK	January 1, 2012, and June 30, 2018	IMRD-UK	45164	Apixaban, Dabigatran, Rivaroxaban	Warfarin
GLORIA-AF Registry	2022	Asia, Europe, North America, Latin America	January 2014 and December 2016.	50 countries	21,300	Apixaban, Dabigatran, Rivaroxaban	Warfarin
Marston et al.	2022	Germany	January 2014 through June 2017	Deutsche Analysedatenbank für Evaluation und Versorgungsforschung	21,038	Apixaban, Dabigatran, Rivaroxaban, Edoxaban	Warfarin
Lee et al.	2019	South Korea	January 2015 to December 2017	National Health Insurance Service Database	116,804	Apixaban, Dabigatran, Rivaroxaban	Warfarin
REAL-T AF	2020	Thailand	January 2012 to April 2018	9 Hospitals in Thailand	2055	Apixaban, Dabigatran, Rivaroxaban	Warfarin

NPR: Norwegian Patient Registry; NorPD: Norwegian Prescription Database; VKA: Vitamin K antagonist; IMRD: IQVIA Medical Research Data; NOACs. Non-vitamin K antagonist oral anticoagulants.

Summary characteristics of the included studies

Four studies were from Asia (Taiwan,[11] South Korea,[20] Japan,[9] and Thailand[21]), and five were from Europe.[10,22–25] The remaining study, the GLORIA-AF registry, was an international registry that included patients from Asia, Europe, North America, and Latin America.[14] The studies' sample sizes ranged from 2055 to 321,501 patients. All studies compared at least three NOACs (apixaban, dabigatran, and rivaroxaban) with warfarin. Data were extracted mainly from national/claims databases, except for the study from Thailand, which retrieved data from the registries of nine hospitals. There was notable variation in patient age across the studies; however, the average age of the patients in the most studied arm was >70 years. The mean CHA2DS2-VASc and HAS-BLED scores ranged from 2.7 to 4.7 and 1.2 to 2.9, respectively (Tables 1 and 2).

Risk of bias assessment

The studies' risk of bias was assessed using the ROBINS-I tool. The overall judgment was a moderate-to-serious risk of bias across all effect measures in the eligible studies. The risk of bias was notably serious due to the study participant selection process, confounding, or deviation from intended interventions. Most studies applied methods, such as propensity score analysis or regression, to reduce the impact of confounders.

Study outcomes

a. Ischemic stroke

In the analysis of ischemic stroke, the contribution plots showed that ten direct comparisons were available. The comparisons of apixaban to rivaroxaban, dabigatran to edoxaban, and dabigatran to rivaroxaban made the greatest relative contributions to the combined/indirect treatment effects (Supplementary Figure 1). The network map shows the relative size and weight of studies in each direct comparison (Fig. 2a). The comparison-adjusted funnel plot indicated asymmetries in all interventions and significant Egger's test results, which can be attributed to the small number of included studies (Supplementary Figure 2). No significant inconsistencies were identified among indirect comparisons, and the τ^2 values indicated low between-study heterogeneity (Supplementary Table 1). The direct and indirect comparison results are detailed in the interval plots in Fig. 3a. Dabigatran achieved a lower incidence of ischemic stroke than warfarin (HR = 0.74, 95% confidence interval [CI] = 0.57–0.96). Apixaban achieved a lower incidence of ischemic stroke than warfarin (HR = 0.60, 95% CI = 0.46–0.78) and rivaroxaban (HR = 0.77, 95% CI = 0.59–1.00). Similarly, edoxaban achieved a lower incidence of ischemic stroke than warfarin (HR = 0.58, 95% CI = 0.43–0.78). In contrast, rivaroxaban had a comparable risk of ischemic stroke to warfarin (HR = 0.78, 95% CI = 0.60–1.01).

b. Myocardial infarction

The contribution plots show the contribution matrix for the myocardial infarction network (Supplementary Figure 3), and the network map shows the relative size and weight of studies used in each direct comparison (Fig. 2b). No significant inconsistencies were identified among indirect comparisons, and the τ^2 values indicated low between-study heterogeneity (Supplementary Table 2). The results of each direct and indirect comparison are shown in interval plots (Fig. 3b). Apixaban (HR = 0.33, 95% CI = 0.13–0.84), dabigatran (HR = 0.38, 95% CI = 0.17–0.84), edoxaban (HR = 0.28, 95% CI = 0.09–0.77), and rivaroxaban (HR = 0.38, 95% CI = 0.15–0.97) had significantly lower risks of myocardial infarction than warfarin.

c. All-cause mortality

The contribution plots and network maps for the relative size and weight of studies used in the pooled analysis of all-cause mortality are shown in Supplementary Figure 1 and Fig. 2c, respectively. No significant inconsistencies were identified among indirect comparisons, and the τ^2 values indicated low between-study heterogeneity (Supplementary Table 3). The results of each direct and indirect comparison showed that only dabigatran (HR = 1.51, 95% CI = 1.00–2.28) reduced the risk of all-cause mortality significantly more than warfarin; the other NOACs did not differ significantly from warfarin.

d. Major bleeding

Five different interventions were analyzed. The contribution plots showed that ten direct comparisons were available. The comparisons of dabigatran to rivaroxaban and apixaban to edoxaban made the greatest relative contributions to the combined/indirect treatment effects (Supplementary Figure 2). The network map shows the relative size and weight of the studies used in each direct comparison (Fig. 2d). We used a comparison-adjusted funnel plot of major bleeding HRs to assess the presence of publication bias. It showed asymmetries in all interventions, with a significant Egger's test indicating a small-study effect (Supplementary Figure 3). The random-effect consistency model showed no significant inconsistencies among the indirect comparisons, and the τ^2 values indicated low between-study heterogeneity (Supplementary Table 4). The results of each direct and indirect comparison are shown in Fig. 4a. Dabigatran achieved a significantly lower risk of major bleeding than warfarin (HR = 0.36, 95% CI = 0.28–0.47) and rivaroxaban (HR = 0.73, 95% CI = 0.56–0.95). Apixaban (HR = 0.33, 95% CI = 0.25–0.44), edoxaban (HR = 0.34, 95% CI = 0.24–0.48), and rivaroxaban (HR = 0.50, 95% CI = 0.38–0.65) had significantly lower risks of major bleeding than warfarin.

e. Intracranial hemorrhage

The contribution plots show the contribution matrix for the intracranial hemorrhage network (Supplementary Figure 4). Network maps were constructed to visually display the relative size and weight of the studies used in each direct comparison (Fig. 2e). No significant inconsistencies were identified among indirect comparisons, and the τ^2 values indicated low between-study heterogeneity (Supplementary Table 5). The results of each direct and indirect comparison are detailed in interval plots (Fig. 4b). Apixaban (HR = 0.35, 95% CI = 0.24–0.51), dabigatran (HR = 0.26, 95% CI = 0.18–0.38), edoxaban (HR = 0.27, 95% CI = 0.17–0.42), and rivaroxaban (HR = 0.40, 95% CI = 0.28–0.58) had significantly lower risks of intracranial hemorrhage than warfarin. In addition, dabigatran had a lower risk of intracranial hemorrhage than rivaroxaban (HR = 0.66, 95% CI = 0.45–0.96).

Discussion

The advantages of dabigatran over VKAs are well-established. The existing body of evidence supports its more tolerable safety profile, superior efficacy in preventing ischemic stroke, more predictable pharmacokinetics, and minimal food or drug interactions compared to warfarin.[26] In addition, dabigatran is more convenient to use in clinical practice because frequent coagulation monitoring is unnecessary.[20] Despite these advantages, few studies have compared it with other NOACs. Real-world studies can provide compelling evidence regarding the comparative safety and clinical effectiveness of NOACs in clinical practice. They can also offer broader evidence on the performance of NOACs in the general non-valvular AF population, including those usually excluded from clinical trials, and assess patient adherence.[20] Therefore, we conducted this systematic review and network meta-analysis to compare the safety and clinical effectiveness of dabigatran to other NOACs and VKAs in patients with non-valvular AF.

Bleeding, which can be fatal, is a common adverse event with any

Table 2
Baseline characteristics of the included studies ($n = 10$).

Author/ Registry	Arm	No.	Dose (mg) (% per total patients)	Age, y Mean (SD)	Female, n (%)	Prior bleeding, n (%)#	Previous stroke/ SE, n (%)#	CHA2DS2-VASc score, mean (SD)	HAS-BLED score, mean (SD)
Rutherford et al.	Apixaban	13786	5 mg bid (55.4%) 2.5 mg bid (44.6%)	80.8 (4.6)	3744 (49.1)	1106 (14.5)	1253 (16.4)	4.3 (1.3)	2.8 (0.98)
	Dabigatran	3857	150 mg bid (24.1%) 110 mg bid (75.9%)	78 (3.5)	386 (41.5)	105 (11.3)	136 (14.6)	3.9 (1.3)	2.6 (0.95)
	Rivaroxaban	6108	20 mg OD (59.4%) 15 mg OD (40.6%)	81 (4.8)	1812 (49.9)	501 (13.8)	600 (16.5)	4.2 (1.3)	2.7 (0.95)
	Warfarin	6650	—	82.9 (5.1)	3316 (49.9)	1225 (18.4)	1096 (16.5)	4.7 (1.4)	2.9 (1.0)
Hald et al.	Apixaban	NR	NR	NR	NR	NR	NR	NR	NR
	Dabigatran	NR	NR	NR	NR	NR	NR	NR	NR
	Rivaroxaban	NR	NR	NR	NR	NR	NR	NR	NR
	Warfarin	NR	—	NR	NR	NR	NR	NR	NR
NAXOS Study	Apixaban	87565	5 mg bid (62.3%) 2.5 mg bid (37.7%)	74.7 (11.5)	42731 (48.8)	NR	NR	3.1 (1.7)	2.2 (1.0)
	Dabigatran	21245	150 mg bid (42.4%) 110 mg bid (57.6%)	72.7 (11.8)	9751 (45.9)	NR	NR	2.8 (1.7)	2.1 (1.0)
	Rivaroxaban	100063	20 mg OD (65.2%) 15 mg OD (34.8%)	72.0 (12.0)	44928 (44.9)	NR	NR	2.7 (1.7)	2.0 (1.0)
	Warfarin	112628	—	78.5 (11.1)	57665 (51.2)	NR	NR	3.9 (1.7)	2.6 (1.1)
Chan et al.	Apixaban	9952	5 mg bid (36%) 2.5 mg bid (64%)	76 (10.5)	4498 (45.2)	139 (1.4)	2060 (20.7)	3.9 (1.6)	2.9 (1.1)
	Dabigatran	22371	150 mg bid (11%) 110 mg bid (89%)	74.2 (10.4)	8792 (39.3)	403 (1.8)	5257 (23.5)	3.7 (1.5)	2.8 (1.1)
	Rivaroxaban	33022	20 mg OD (6%) 10/15 mg OD (94%)	75.3 (10.6)	14629 (44.3%)	627 (1.9)	6604 (20)	3.8 (1.6)	2.9 (1.1)
	Warfarin	19761	—	70.6 (13.4)	8319 (42.1)	415 (2.1)	2846 (14.4)	3.2 (1.8)	2.6 (1.3)
	Edoxaban	4577	60 mg OD (36%) 30/15 mg OD (64%)	74.7 (10.8)	1959 (42.8)	23 (0.5)	586 (12.8)	3.6 (1.6)	2.6 (1.1)
Kohsaka et al.	Apixaban	22752	5 mg bid (44.9%) 2.5 mg bid (55.1%)	76.1 (10.8)	8828 (38.8)	2754 (12.1)	4756 (20.9)	3.8 (1.9)	NR
	Dabigatran	8003	150 mg bid (18.1%) 110 mg bid (81.9%)	75.6 (10.3)	3041 (38)	1002 (12.5)	1624 (20.3)	3.8 (2.0)	NR
	Rivaroxaban	17481	15 mg OD (47.3%) 10 mg OD (52.8%)	76.2 (10.6)	6800 (38.9)	2136 (12.2)	3696 (21.2)	3.8 (1.9)	NR
	Warfarin	19059	—	76.1 (11.9)	7395 (38.8)	2322 (12.2)	4086 (21.4)	3.8 (2.1)	NR
	Edoxaban	12592	60 mg OD (74.5%) 30 mg OD (25.5%)	76.2 (10.8)	4898 (38.9)	1530 (12.2)	2641 (21.0)	3.8 (2.0)	NR
González-Pérez et al.	Apixaban	14701	5 mg bid (69.6%) 2.5 mg bid (30.4%)	72.0 (10.1)	3970 (38.8)	NR	1335 (13.0)	3.2 (1.7)	1.6 (1.0)
	Rivaroxaban	14288	150 mg bid (81.8%) 110 mg bid (18.2%)	73.2 (10.5)	4671 (40.0)	NR	1351 (11.6)	3.2 (1.7)	1.6 (0.9)
	Warfarin	16175	—	73.7 (10.1)	7114 (44.0)	NR	1585 (9.8)	3.2 (1.6)	1.8 (0.9)
GLORIA-AF Registry	Apixaban	4505	5 mg bid (79.5%) 2.5 mg bid (19.5%) Other dose (1.0%)	NR	1960 (47.2)	184 (4.4)	481 (11.6)	NR	NR
	Dabigatran	3839	150 mg bid (52.2%) 110 mg bid (45.0%) 75 mg bid (1.4%) Other dose (1.3%)	70.1 (10.2)	1718 (44.8)	138 (3.6)	441 (11.5)	3.1 (1.4)	1.2 (0.8)
	Rivaroxaban	3785	10 mg OD (2.8%) 15 mg OD (21.3%)	NR	1685 (44.5)	164 (4.3)	268 (7.1)	NR	NR

(*continued on next page*)

Table 2 (*continued*)

Author/ Registry	Arm	No.	Dose (mg) (% per total patients)	Age, y Mean (SD)	Female, n (%)	Prior bleeding, n (%)#	Previous stroke/ SE, n (%)#	CHA2DS2-VASc score, mean (SD)	HAS-BLED score, mean (SD)
			20 mg OD (74.5%) Other dose (1.4%)						
	Warfarin	4836	—	71.2 (10.3)	2152 (44.5)	251 (5.2)	462 (9.6)	3.3 (1.5)	1.3 (0.9)
Marston et al.	Apixaban	6053	5 mg bid (NR)	73.92 (11.75)	2674 (44.18)	NR	762 (12.59)	4.02 (1.86)	2.49 (1.09)
	Dabigatran	1306	110 mg, or 150 mg bid (NR)	71.61 (11.57)	521 (39.89)	NR	226 (17.30)	3.83 (1.91)	2.42 (1.10)
	Rivaroxaban	7013	20 mg OD (NR)	70.93 (12.02)	2931 (41.79)	NR	465 (6.63)	3.52 (1.83)	2.26 (1.09)
	Warfarin	5430	—	74.27 (10.18)	2372 (43.68)	NR	398 (7.33)	4.01 (1.65)	2.45 (1.00)
	Edoxaban	1236	30 mg, or 60 mg OD (NR)	72.33 (10.89)	494 (39.97)	NR	67 (5.42)	3.53 (1.72)	2.34 (1.05)
Lee et al.	Apixaban	22177	5 mg bid (41.2%) 2.5 mg bid (58.2%)	72.7 (10.2)	10778 (48.6)	NR	NR	3.76 (1.41)	2.75 (1.04)
	Dabigatran	17745	150 mg bid (33.8%) 110 mg bid (66.2%)	70.8 (9.9)	7666 (43.2)	NR	NR	3.55 (1.37)	2.67 (1.01)
	Rivaroxaban	35965	20 mg OD (41.3%) 10/15 mg OD (58.7%)	72 (9.9)	16580 (46.1)	NR	NR	3.63 (1.40)	2.77 (1.02)
	Warfarin	25420	—	67.3 (12.6)	9634 (37.9)	NR	NR	3.18 (1.61)	2.58 (1.14)
	Edoxaban	15496	60 mg OD (45.9%) 30 mg OD (53.1%)	71.7 (9.9)	7051 (45.5)	NR	NR	3.58 (1.38)	2.61 (1.01)
REAL-T AF	Apixaban	405	5 mg bid (NR) 2.5 mg bid (NR%)	73.89 (10.24)	201 (49.63)	NR	156 (38.52)	3.86 (1.72)	1.65 (1.00)
	Dabigatran	441	150 mg bid (NR%) 110 mg bid (NR%)	70.26 (11.04)	205 (46.49)	NR	125 (28.34)	3.25 (1.74)	1.59 (1.05)
	Rivaroxaban	604	20 mg OD (NR%) 10/15 mg OD (NR %)	71.12 (10.84)	293 (48.51)	NR	155 (25.66)	3.28 (1.72)	1.39 (1.0)
	Warfarin	605	—	68.40 (11.40)	304 (50.25)	NR	136 (22.48)	3.28 (1.75)	1.27 (0.91)

SD: Standard deviation; SE: systemic embolism; NR: Not reported; OD: Once daily; Bid: Twice daily; #: The percentage was calculated from the available cohort.

anticoagulant. While dabigatran was well-tolerated in pivotal clinical trials (the rate of serious adverse events was <3% per year),[13,27] there have been three case reports describing fatal gastrointestinal bleeding in elderly patients receiving dabigatran.[28] Our pooled analysis showed that dabigatran had a more tolerable safety profile than warfarin and that its safety profile was similar to those of other NOACs. The risk of major bleeding among patients receiving dabigatran was 64% lower than those on warfarin and 27% lower than those on rivaroxaban. Similarly, dabigatran had an 84% lower risk of intracranial hemorrhage than warfarin. The risk of major bleeding did not differ significantly between dabigatran and apixaban or edoxaban. These findings agree with a recent network meta-analysis of real-world evidence that found no significant differences in major bleeding or intracranial hemorrhage between NOACs.[29] In their meta-analysis, Escobar et al. also showed that the risk of major bleeding in patients receiving dabigatran was 23% lower than in patients receiving warfarin.[30] The GLORIA-AF registry demonstrated that the risk of major bleeding with dabigatran was 41% lower than with rivaroxaban and similar to other NOACs.[14] In the ARISTOPHANES study, which pooled data from five sources in the US, the rate of major bleeding was comparable between NOACs and warfarin.[15]

In the RE-LY trial, the risk of myocardial infarction or acute coronary syndrome slightly increased in patients receiving dabigatran than warfarin.[13] A previous meta-analysis of seven trials (two in a non-valvular AF setting) showed an increased risk of myocardial infarction or acute coronary syndrome with dabigatran compared to warfarin,[31] which was attributed to warfarin's better cardiac protection.[32] Our analysis showed that all NOACs, including dabigatran, had a significantly lower risk of myocardial infarction than warfarin. These findings are consistent with the existing evidence showing a lower or similar risk of myocardial infarction with dabigatran compared to warfarin or other NOACs.[29,30] A recent comprehensive meta-analysis of 588,047 patients receiving dabigatran or other anticoagulants demonstrated that the risk of myocardial infarction was similar between dabigatran and other anticoagulants.[33]

Regarding efficacy endpoint, we found that dabigatran was significantly associated with a lower risk of ischemic stroke and all-cause mortality than warfarin. In addition, dabigatran was non-inferior to other NOACs regarding ischemic stroke. Similarly, the ARISTOPHANES study found that NOACs, including dabigatran, had lower risks of ischemic stroke and all-cause mortality than warfarin.[15]

Study limitations

This systematic review and network meta-analysis was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2).[34] We adopted a comprehensive strategy for searching major medical databases and extracted data from propensity score analysis or multivariate regression adjustment analysis, if available, to account for potential confounders. We also excluded multiple reports of the same registry and included the most complete report to avoid statistical overweighting of some registries. The effect measures did not show inconsistencies across the pooled analysis. Nevertheless, we acknowledge that this study had some limitations. We could not conduct a subgroup analysis comparing the results of NOACs according to dosage regimens (standard vs. low doses) due to

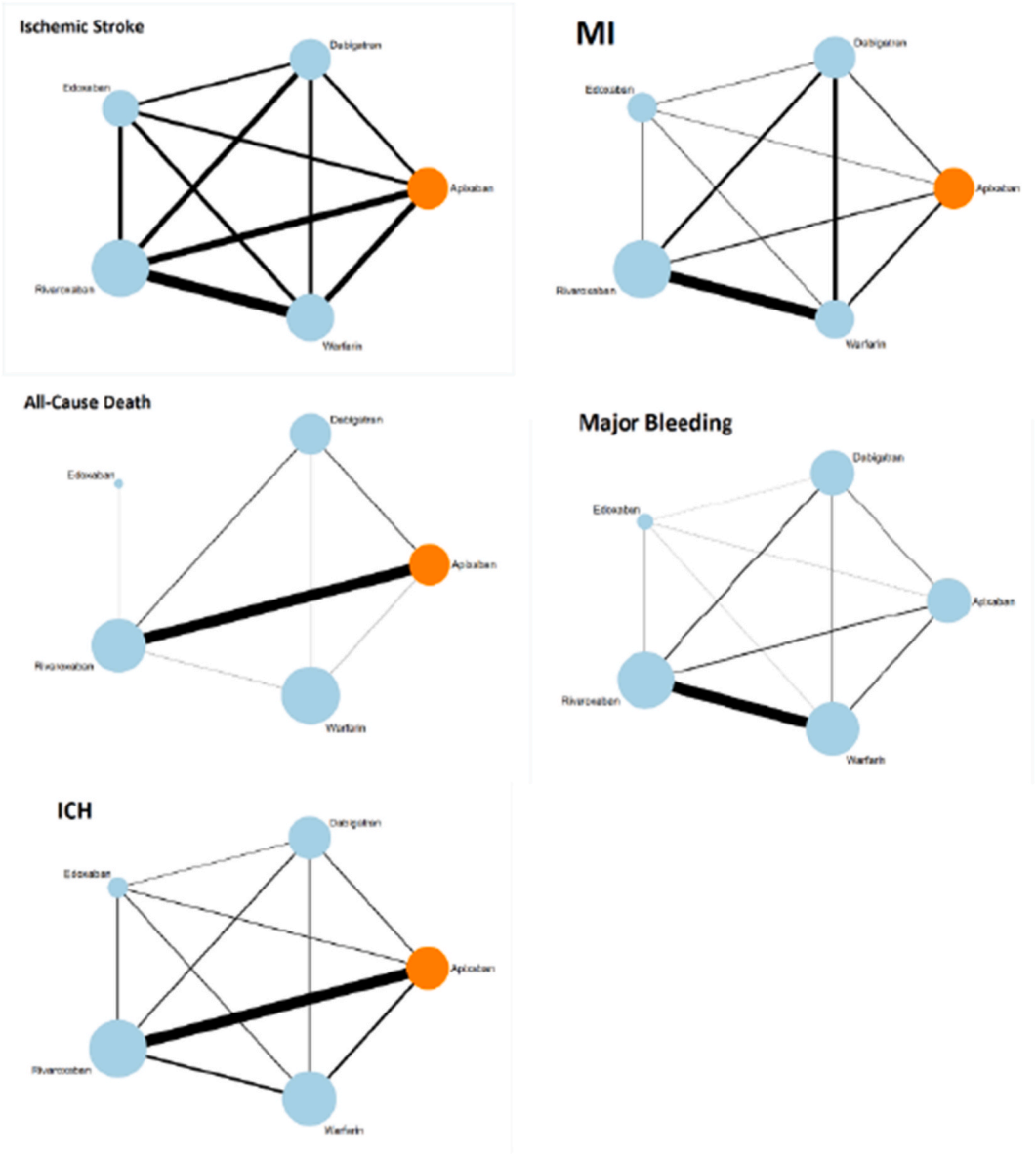

Figure 2. Network maps showing the relative size and weight of studies included in each direct comparison for (a) ischemic stroke, (b) myocardial infarction, (c) all-cause mortality, (d) major bleeding, and (e) intracranial hemorrhage. The network maps were constructed to visually display the relative size and weight of studies involved in each direct comparison, where the node size reflects the sample size of each intervention, and the line thickness depicts the weight of each comparison.

the limited availability of effect measures data in the included studies. In addition, data on the rate of treatment adherence were limited. A separate analysis of industry-sponsored registries was also not feasible due to the limited number of industry-sponsored studies in our network meta-analysis. The generalizability of our findings to may be limited because the bibliographic search was limited to studies published between 2019 and 2022. Another limitation was the moderate-to-serious risk of bias of the included studies, which is attributable to the inherent methodological limitations of real-world evidence studies; registry-based studies can suffer from a lack of standardized definitions of outcomes of interest, a unified clinical pathway, dosing regimens, and monitoring schedule for all patients and inadequate capturing of important confounders (such as comorbidities or other relevant medical histories). Lastly, evidence regarding edoxaban was limited.

Conclusion and future perspectives

In conclusion, this network meta-analysis confirms that dabigatran's real-world safety and clinical effectiveness align with the results of pivotal clinical trials. The pooled estimates showed lower risks of major bleeding, ischemic stroke, and intracranial hemorrhage with dabigatran than warfarin among patients with non-valvular AF. Dabigatran was the only NOAC with a lower risk of all-cause mortality than warfarin. Dabigatran was also associated with lower risks of major bleeding and intracranial hemorrhage than rivaroxaban. However, future research is warranted to compare dabigatran with other NOACs in well-controlled trials to confirm real-world evidence. Future real-world evidence studies should investigate treatment adherence and the impact of treatment switchers on the reported results for NOACs since they have been largely excluded from published reports.

Data sharing and data availability

The data used to support the findings of this study are included within the article.

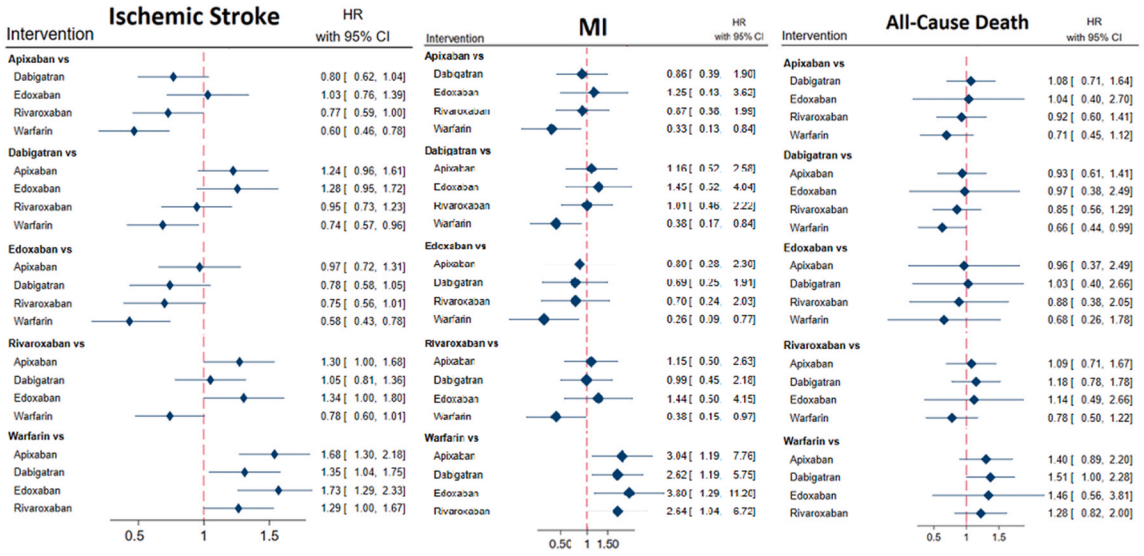

Figure 3. Interval plots showing the results of the multiple treatments network meta-analyses with a frequentist framework for each comparison for (a) ischemic stroke, (b) myocardial infarction, and (c) all-cause mortality. The plots show the estimated treatment effects for each pairwise comparison of interventions, along with CIs (horizontal axis).

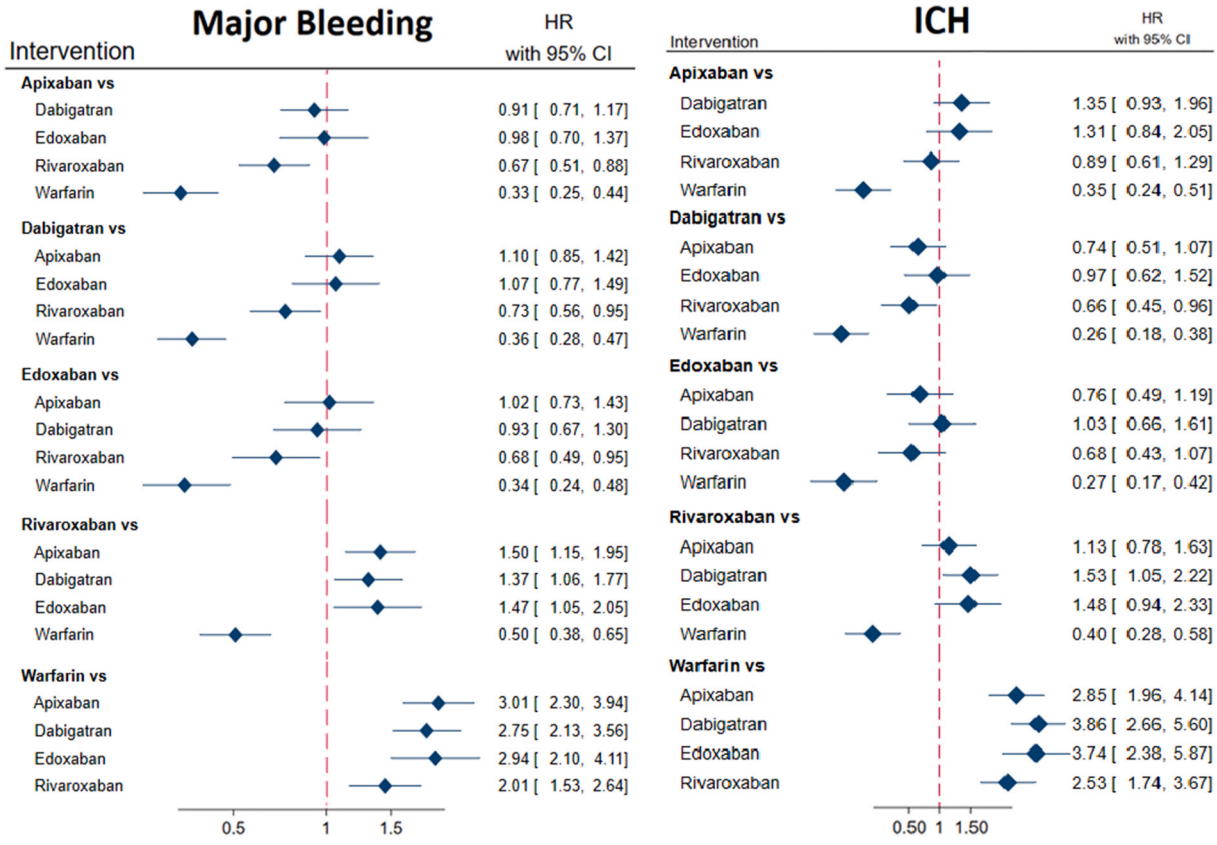

Figure 4. Interval plots showing the results of the multiple treatments network meta-analyses with a frequentist framework for each comparison for (a) major bleeding and (b) intracranial hemorrhage. The plots show the estimated treatment effects for each pairwise comparison of interventions, along with CIs (horizontal axis).

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Author contributions

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2023.10.014.

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