Systematic review

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Relative efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation by network meta-analysis

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Background **Much direct evidence has proved that the novel oral anticoagulants (NOACs) are noninferior or superior to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation, and lead to a relevant decrease in bleeding profiles. However, no study has compared NOACs with each other head-to-head. The current study is a network meta-analysis aiming to assess the efficacy and safety of NOACs.**

Methods **Cochrane library, Pubmed NCBI, EMBASE and MEDLINE were systematically searched for randomized controlled trials that assessed the efficacy and safety profiles of NOACs compared with warfarin. The primary outcome was the rate of stroke or systemic embolism, and the secondary outcome was the rate of bleeding events. Network meta-analysis was performed using Markov chain Monte Carlo methods.**

Results **A total of four phase III randomized controlled trials ($n = 71683$) met the inclusion criteria. All NOACs except low dose of edoxaban showed noninferior efficacies to warfarin in stroke prevention. In the field of hemorrhage, apixaban was safer than edoxaban 60 mg in any bleeding events and had fewer major bleeding events compared with dabigatran 150 mg and rivaroxaban.**

Conclusion **NOACs are promising candidates for stroke prevention in patients with nonvalvular atrial fibrillation due to a favorable risk–benefit profile. All NOACs other than edoxaban 30 mg had parallel efficacies with respect to stroke prevention. Apixaban had an advantage over the other NOACs in safety.**

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Keywords: atrial fibrillation, network meta-analysis, novel oral anticoagulants, stroke prevention

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Background

Atrial fibrillation is one of the most common clinical cardiac arrhythmias.[1] The current prevalence of atrial fibrillation estimated in the developed countries was approximately 1.5–2% of the general population.[2] The incidence of atrial fibrillation increased with age, and it was estimated that both incidence and prevalence of atrial fibrillation were likely to rise from 2010 to 2030 due to the extension of survival.[3] Patients with atrial fibrillation were at high risk of stroke.[4] Such risk factors included heart failure, hypertension, age, diabetes, previous stroke, vascular disease, and sex category, which were expressed by the CHA_2DS_2-VASc scores.[5] Stroke increased the burden of economic cost on the healthcare system, so it was necessary to search for an effective preventive therapy.[6] Warfarin was the conventional drug for stroke prevention in patients with atrial fibrillation. However, with the disadvantages of the unstable international normalized ratio (INR) and high rates of bleeding, INR had to be frequently monitored, and dosages of warfarin had to be carefully adjusted according to it, which led to the poor medication adherence.[7,8] Therefore, the novel oral anticoagulants (NOACs) were developed as alternatives to warfarin, such as the direct thrombin inhibitor dabigatran, and the direct factor Xa inhibitors apixaban, rivaroxaban, and edoxaban. Four large phase III randomized controlled trials (RCTs),[9–12] registering approximately 70 000 participants, demonstrated that NOACs were noninferior to warfarin for the prevention of stroke or systemic embolism. However, there was no head-to-head evidence to compare NOACs with each other. Network meta-analysis (NMA) was a statistical method to assess the degree of agreement between direct and indirect comparisons.[13] We therefore aimed to assess the relative efficacy and safety of interventions for stroke prevention using the NMA approach.

Method

Literature search

We systematically searched for relevant RCTs in Cochrane, PubMed, EMBASE, and MEDLINE from inception through April 2014 using the following keywords: nonvalvular atrial fibrillation, stroke prevention, novel oral anticoagulants, dabigatran, apixaban, rivaroxaban, edoxaban, and warfarin. There were no language or publication status restrictions. In addition, the reference lists of published articles and previous meta-analyses were manually searched. This meta-analysis was carried

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out in accordance with the preferred reporting items for systematic reviews and meta-analyses.[14]

Study selection and data extraction

Studies were eligible to be included in the meta-analysis if they were prospective, randomized controlled, double-blinded or open-labeled, phase III trials, comparing any of the following four NOACs – dabigatran, apixaban, rivaroxaban, and edoxaban – with vitamin K antagonists in patients diagnosed with nonvalvular atrial fibrillation and at least one risk factor for stroke. The reporting data of included studies were mainly on the relevant outcomes of stroke and bleeding. We excluded nonrandomized studies, substudy of the RCTs, ongoing trials, and those involving children (<18 years of age) or patients who had a valvular atrial fibrillation, recent stroke, or a condition with a risk of bleeding. Internal validity of RCTs was assessed according to the *Cochrane Handbook of Systematic Reviews*. Two investigators (W.F., J.G.) independently performed the literature search and assessed the relevance of the research objects. Disagreements were resolved by consensus or in consultation with a third author (Z.S.).

Qualitative assessment

The quality of the studies was assessed by two authors (W.F., J.G.) independently according to the criteria described in the *Cochrane Handbook 5.1.0*. The criteria included the following items: sequence generation, allocation sequence concealment, blinding of participants, incomplete outcome data, and selective outcome reporting. Each criterion was categorized as 'yes', 'no', or 'unclear', and the summary assessment of the risk of bias for each important outcome within and across studies was categorized as 'low risk of bias', 'unclear risk of bias', or 'high risk of bias'.[15] Disagreements were resolved by discussion or in consultation with a third author (Z.S.).

Statistical analysis

We performed NMA within a Bayesian framework using Markov chain Monte Carlo methods, which combined direct and indirect evidence for any given treatments in one joint analysis.[16] The analysis not only increased statistical power of the direct comparisons but also provided insights into the relative effectiveness of interventions that have never been directly compared. We did both fixed and random effects models and estimated the fitness by calculating the totresdev and deviance information criterion (DIC). When totresdev equaled the total number of the original data, the model fit the best. DIC was an estimate of expected predictive error.[17] In the current NMA, the values of DIC and totresdev were similar for all results of fixed and random effects models, so there was almost no difference in model fitness. In analyses including a few studies, the random effects model will produce poor estimates of the variation.[18] Given that the NMA included only four RCTs, we chose the fixed-effects model to avoid poor estimates of variation. The odds ratios (ORs) and appropriate 95% confidence intervals (CIs) of outcomes were calculated to assess the compared interventions, and the P values below 0.05 were used to assess significance. Heterogeneity was assessed with the data including TTR, $CHADS_2$ score, age, and sex. Two sensitivity analyses were performed including a meta-analysis of the factor Xa inhibitors only, the thrombin inhibitor dabigatran removed, and an analysis combining all doses of all NOACs. Statistical analyses were conducted using STATA version 12.0 (StataCorp, College Station, Texas, USA), R version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria), and WinBUGS 1.4.3 (MRC Biostatistic Unit, Cambridge, UK) through the package R2winbugs.[19]

Results

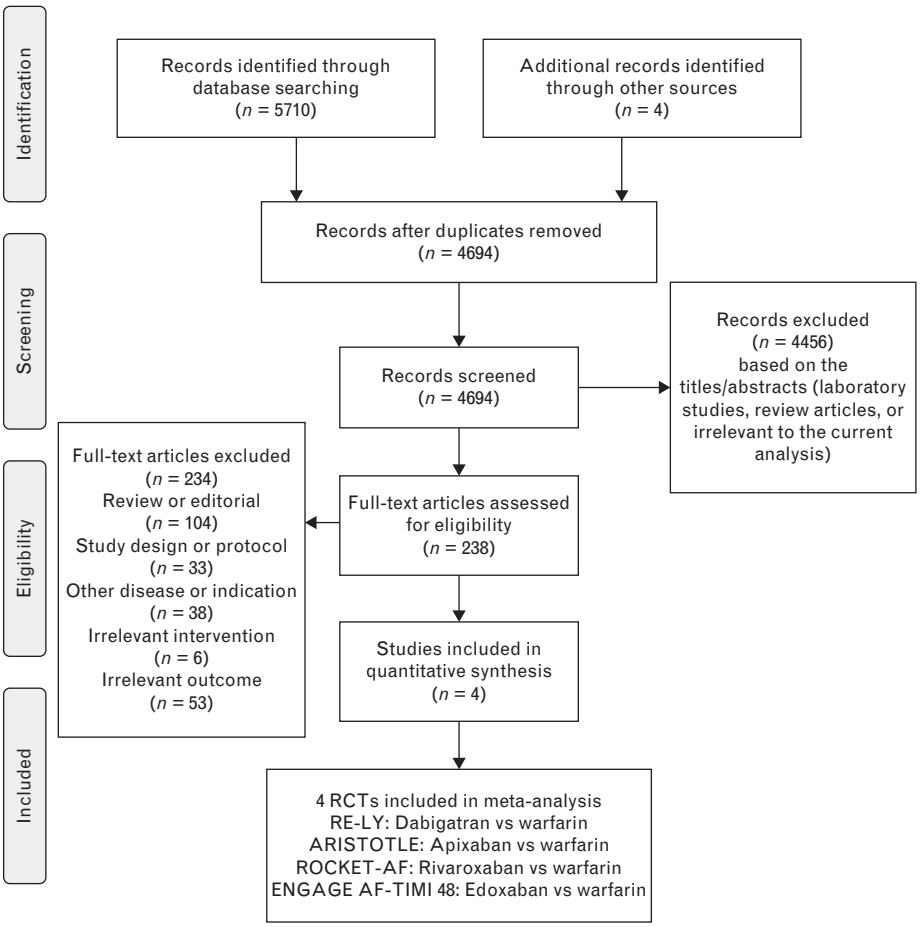
Study selection and description

Our electronic searches yielded 4694 studies after elimination of duplicate results, through a review of titles and abstracts; 4456 studies were rejected for laboratory studies, were review articles, or were irrelevant to the current analysis. The remaining 238 articles were reviewed and assessed for satisfaction of the inclusion or exclusion criteria (Fig. 1). Since clinical and methodological diversity always occurs in a meta-analysis, statistical heterogeneity is inevitable.[18] There was also notable heterogeneity in the remaining articles. To decrease statistical heterogeneity and increase comparable ascertainment, we restricted phase III trials comparing NOACs with warfarin in the current study, and did not incorporate any phase II dose-ranging studies because of their small sample size and short follow-up. We did not include the J-ROCKET-AF[20] trial mainly because of its smaller sample size ($n = 1278$) compared with the global ROCKET-AF ($n = 14\,264$). To minimize heterogeneity and confirm the reliability, we had to restrict RCTs whose sample sizes were similar. Finally, four RCTs ($n = 71\,683$) fulfilled our inclusion criteria: the RE-LY evaluated dabigatran,[9] ARISTOTLE trial investigated apixaban,[10] ROCKET-AF evaluated rivaroxaban,[11] and edoxaban investigated in ENGAGE AF-TIMI 48.[12] The study design and baseline patient characteristics are shown in Table 1. The qualitative assessment and risk of bias for each trial are reported in Supplementary Fig. 1 (http://links.lww.com/JCM/A54). The network geometry is shown in Supplementary Fig. 2 (http://links.lww.com/JCM/A54). Sensitivity analyses removing dabigatran and combining all doses of all NOACs also showed similar results.

Network meta-analysis

The results of NOACs vs. warfarin and NOAC vs. NOAC are respectively summarized in Table 2 and Table 3 for the outcomes of stroke or systemic embolism, any stroke, hemorrhagic stroke, ischemic stroke, disabling or fatal stroke, all-cause mortality, myocardial infarction (MI),

Fig. 1



Flow diagram of selection process of randomized controlled trials included in meta-analysis.

major bleeding, gastrointestinal bleeding, intracranial hemorrhage (ICH), and any bleeding.

Novel oral anticoagulants versus warfarin

Other than edoxaban 30 mg, the remaining NOACs demonstrated numerically lower hazards of stroke or systemic embolism, and any stroke compared with warfarin. It reached statistical significance for apixaban and dabigatran 150 mg in prevention of stroke or systemic embolism and any stroke, whereas edoxaban 60 mg only in stroke or systemic embolism. All NOACs were associated with a significant reduction in the risk of

Table 1 Summary of the trials used to conduct the network meta-analysis

Study characteristics						Baseline patient characteristics			
Trial name	Study design	Number of patients	Follow-up period	Treatment groups	Dose	Age (years)[a]	Male sex (%)	$CHADS_2$ (mean)	Mean TTR (%)
RE-LY[9]	Randomized, open-label	18113	2 years	Dabigatran 110 mg	110 mg b.i.d.	71.5 ± 8.7	64.3	2.1	
				Dabigatran 150 mg	150 mg b.i.d.		63.2	2.2	
				Dose-adjusted warfarin	INR 2.0–3.0		63.3	2.1	64%
ARISTOTLE[10]	Randomized, double-blind	18201	1.8 years	Apixaban	5 mg b.i.d.[b]	70 [63–76]	64.4	2.1	
				Dose-adjusted warfarin	INR 2.0–3.0		65.0	2.1	62%
ROCKET-AF[11]	Randomized, double-blind	14264	1.9 years	Rivaroxaban	20 mg q.d.[c]	73 [65–78]	60.3	3.48	
				Dose-adjusted warfarin	INR 2.0–3.0		60.3	3.46	55%
ENGAGE AF-TIMI 48[12]	Randomized, double-blind	21105	2.8 years	Edoxaban 30mg	30 mg q.d.	72 [64–78]	61.2	2.8	
				Edoxaban 60 mg	60 mg q.d.		62.1	2.8	
				Dose-adjusted warfarin	INR 2.0–3.0		62.5	2.8	64.9%

b.i.d., Twice daily; INR, International Normalized Ratio; q.d., once daily; TTR, time in therapeutic range. [a] RE-LY: mean ± SD, ROCKET-AF, ARISTOTLE, ENGAGE AF: median (interquartile range). [b] A dose of 2.5 mg b.i.d. was used in patients with two or more of the following criteria: an age of at least 80 years, a body weight of not more than 60 kg, or a serum creatinine level of 1.5 mg/dl (133 μmol/l) or more. [c] A dose of 15 mg q.d. was used in patients with a creatinine clearance of 30–49 ml/min.

Table 2 Results of the network meta-analysis in novel oral anticoagulants vs. warfarin[a]

	Stroke or systemic embolism	Any stroke	Hemorrhagic stroke	Ischemic stroke	Disabling or fatal stroke	All-cause mortality	MI	Major bleeding	GI bleeding	ICH	Any bleeding
Warfarin vs. dabigatran 110 mg	1.10 (0.90;1.35)	1.09 (0.88;1.35)	**3.46 (1.80;6.14)**	0.89 (0.70;1.11)	1.06 (0.82;1.37)	1.10 (0.96;1.25)	0.73 (0.52;1.03)	**1.25 (1.07;1.46)**	0.91 (0.69;1.19)	**3.38 (2.19;5.41)**	**1.36 (1.26;1.46)**
Warfarin vs. dabigatran 150 mg	**1.53 (1.23;1.92)**	**1.55 (1.22;1.95)**	**4.09 (2.06;7.51)**	**1.32 (1.03;1.67)**	**1.51 (1.12;1.98)**	1.14 (0.99;1.30)	**0.72 (0.50;0.99)**	1.07 (0.92;1.24)	**0.66 (0.52;0.82)**	**2.52 (1.65;3.74)**	**1.15 (1.06;1.24)**
Warfarin vs. apixaban	**1.27 (1.05;1.52)**	**1.27 (1.05;1.52)**	**2.02 (1.35;2.94)**	1.09 (0.88;1.32)	**1.46 (1.08;1.91)**	**1.13 (1.01;1.26)**	1.15 (0.85;1.51)	**1.44 (1.26;1.67)**	1.15 (0.87;1.48)	**2.44 (1.72;3.38)**	**1.46 (1.37;1.56)**
Warfarin vs. rivaroxaban	1.14 (0.97;1.37)	1.12 (0.94;1.34)	**1.76 (1.15;2.71)**	1.02 (0.83;1.21)	1.28 (0.99;1.62)	1.10 (0.97;1.23)	1.10 (0.84;1.38)	0.98 (0.84;1.13)	**0.69 (0.55;0.83)**	**1.57 (1.09;2.23)**	0.98 (0.90;1.06)
Warfarin vs. edoxaban 30 mg	0.92 (0.77;1.10)	0.87 (0.76;1.02)	**3.12 (1.99;4.66)**	**0.69 (0.59;0.81)**	0.89 (0.71;1.13)	**1.16 (1.04;1.29)**	0.83 (0.67;1.02)	**2.16 (1.85;2.52)**	**1.50 (1.19;1.89)**	**3.33 (2.34;4.65)**	**1.58 (1.45;1.71)**
Warfarin vs. edoxaban 60 mg	**1.30 (1.07;1.58)**	1.14 (0.96;1.34)	**1.88 (1.30;2.63)**	0.99 (0.83;1.22)	1.03 (0.80;1.30)	1.10 (0.99;1.22)	1.07 (0.85;1.35)	**1.27 (1.10;1.45)**	**0.82 (0.67;0.99)**	**2.22 (1.63;2.97)**	**1.19 (1.11;1.28)**

GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; NR, not reported. [a]Results are presented as odds ratios (95% confidence intervals). Results shown in boldface are significantly different.

hemorrhagic stroke. Compared with warfarin, dabigatran 150 mg could significantly reduce the risk of ischemic stroke, whereas edoxaban 30 mg could significantly increase the risk of ischemic stroke. Dabigatran 150 mg and apixaban could significantly reduce the risk of disabling and fatal stroke. All-cause mortality was numerically reduced by all NOACs, especially by apixaban and edoxaban 30 mg. Only dabigatran 150 mg could increase the risk of MI significantly. Concerning the safety results, apixaban, dabigatran110 mg, and both doses of edoxaban exhibited lower rates of major bleeding and any bleeding compared with warfarin. A significantly lower hazard for dabigatran 150 mg in any bleeding was also observed. All NOACs demonstrated significant reductions in ICH compared with warfarin. Dabigatran 150 mg, rivaroxaban, and edoxaban 60 mg were associated with significantly increased gastrointestinal bleeding; however, edoxaban 30 mg was the opposite.

Indirect comparisons among novel oral anticoagulants

Compared with dabigatran 150 mg, rivaroxaban showed significantly higher hazards of stroke or systemic embolism, any stroke, and hemorrhagic stroke. The hazards of stroke or systemic embolism, any stroke, ischemic stroke, and disabling or fatal stroke were significantly higher for edoxaban 30 mg compared with dabigatran 150 mg. A similar pattern in any stroke was observed for edoxaban 60 mg compared with dabigatran 150 mg. There were significantly higher risks of stroke or systemic embolism, any stroke, ischemic stroke, and disabling or fatal stroke for edoxaban 30 mg compared with apixaban. A similar pattern, with the exception of stroke or systemic embolism, was seen in the comparison of edoxaban 30 mg and rivaroxaban. The results of efficacy achieved no statistical significance for edoxaban 60 mg compared with apixaban, rivaroxaban, and dabigatran 110 mg, respectively. Edoxaban 60 mg had significantly lower risks of stroke or systemic embolism, any stroke, and ischemic stroke, than edoxaban 30 mg. Lower risks of stroke or systemic embolism, any stroke, and ischemic stroke were observed in dabigatran 150 mg compared with dabigatran 110 mg. Apixaban, rivaroxaban, and edoxaban 60 mg could significantly reduce the risk of MI compared with dabigatran 150 mg. Regarding the bleeding outcomes, the hazards of major bleeding, gastrointestinal bleeding, and any bleeding were significantly higher for rivaroxaban vs. apixaban and edoxaban 30 mg. A similar pattern was observed for both doses of dabigatran vs. edoxaban 30 mg and for dabigatran 150 mg vs. apixaban. The hazards of major bleeding, ICH, and any bleeding were significantly higher for rivaroxaban vs. dabigatran 110 mg. The hazards of major bleeding were significantly lower for edoxaban 30 mg than apixaban, and similar results were observed in edoxaban 60 mg vs. rivaroxaban. The hazard of ICH was significantly lower for edoxaban 30 mg than for rivaroxaban. The hazard of any bleeding was significantly higher for edoxaban 60 mg than for dabigatran 110 mg, and

Table 3 **Results of the network meta-analysis in novel oral anticoagulant vs. novel oral anticoagulant**[a]

	Stroke or systemic embolism	Any stroke	Hemorrhagic stroke	Ischemic stroke	Disabling or fatal stroke	All-cause mortality	MI	Major bleeding	GI bleeding	ICH	Any bleeding
Dabigatran 150 mg vs. dabi 110 mg	**0.73 (0.53;0.97)**	**0.71 (0.51;0.99)**	0.94 (0.34;2.04)	**0.69 (0.48;0.96)**	0.72 (0.48;1.04)	0.97 (0.80;1.18)	1.06 (0.64;1.65)	1.17 (0.95;1.47)	1.39 (0.97;1.99)	1.40 (0.75;2.48)	**1.18 (1.06;1.31)**
Apixaban vs. dabigatran 110 mg	0.88 (0.66;1.15)	0.87 (0.64;1.13)	1.78 (0.79;3.44)	0.83 (0.61;1.11)	0.74 (0.49;1.08)	0.98 (0.81;1.17)	0.65 (0.40;1.03)	0.87 (0.70;1.07)	0.80 (0.54;1.13)	1.43 (0.82;2.46)	0.93 (0.84;1.02)
Rivaroxaban vs. dabigatran 110 mg	0.97 (0.75;1.26)	0.99 (0.74;1.31)	2.07 (0.92;4.03)	0.88 (0.64;1.18)	0.85 (0.59;1.18)	1.01 (0.83;1.21)	0.68 (0.43;1.02)	**1.29 (1.04;1.59)**	1.34 (0.95;1.88)	**2.23 (1.23;3.90)**	**1.39 (1.23;1.54)**
Edoxaban 30 mg vs. dabigatran 110 mg	1.21 (0.93;1.57)	1.26 (0.95;1.65)	1.17 (0.50;2.44)	1.29 (0.97;1.66)	1.21 (0.83;1.69)	0.95 (0.80;1.13)	0.90 (0.58;1.35)	**0.58 (0.47;0.71)**	**0.61 (0.42;0.86)**	1.05 (0.59;1.80)	**0.86 (0.77;0.95)**
Edoxaban 60 mg vs. dabigatran 110 mg	0.86 (0.64;1.14)	0.96 (0.73;1.26)	1.90 (0.90;3.57)	0.90 (0.66;1.20)	1.05 (0.74;1.49)	1.00 (0.85;1.18)	0.70 (0.45;1.04)	0.99 (0.79;1.22)	1.12 (0.79;1.55)	1.56 (0.92;2.58)	**1.14 (1.02;1.27)**
Apixaban vs. dabigatran 150 mg	1.22 (0.89;1.60)	1.23 (0.90;1.63)	2.10 (0.97;4.11)	1.22 (0.87;1.65)	1.06 (0.69;1.54)	1.01 (0.84;1.19)	**0.64 (0.39;0.94)**	**0.75 (0.61;0.90)**	**0.59 (0.41;0.82)**	1.06 (0.61;1.74)	**0.79 (0.71;0.87)**
Rivaroxaban vs. dabigatran 150 mg	**1.34 (1.02;1.76)**	**1.40 (1.05;1.83)**	**2.45 (1.05;5.17)**	1.31 (0.94;1.77)	1.21 (0.82;1.73)	1.04 (0.86;1.23)	**0.66 (0.43;0.99)**	1.11 (0,90;1.35)	0.98 (0.71;1.29)	1.66 (0.93;2.68)	**1.17 (1.05;1.30)**
Edoxaban 30 mg vs. dabigatran 150 mg	**1.67 (1.26;2.21)**	**1.79 (1.34;2.33)**	1.38 (0.57;2.77)	**1.92 (1.43;2.56)**	**1.73 (1.13;2.42)**	0.98 (0.82;1.18)	0.88 (0.57;1.25)	**0.50 (0.40;0.62)**	**0.45 (0.32;0.60)**	0.78 (0.43;1.29)	**0.73 (0.65;0.81)**
Edoxaban 60 mg vs. dabigatran 150 mg	1.19 (0.91;1.58)	**1.37 (1.03;1.80)**	2.25 (0.98;4.30)	1.33 (0.98;1.78)	1.49 (0.99;2.16)	1.04 (0.87;1.22)	**0.68 (0.44;0.99)**	0.85 (0.69;1.02)	0.82 (0.61;1.09)	1.16 (0.69;1.93)	0.97 (0.87;1.07)
Rivaroxaban vs. apixaban	1.11 (0.86;1.43)	1.15 (0.88;1.46)	1.20 (0.66;2.06)	1.08 (0.79;1.40)	1.16 (0.78;1.66)	1.03 (0.88;1.23)	1.07 (0.71;1.54)	**1.49 (1.21;1.81)**	**1.70 (1.16;2.31)**	1.61 (0.96;2.48)	**1.49 (1.36;1.64)**
Edoxaban 30 mg vs. apixaban	**1.39 (1.06;1.80)**	**1.46 (1.13;1.87)**	0.68 (0.37;1.17)	**1.59 (1.19;2.02)**	**1.66 (1.15;2.31)**	0.98 (0.84;1.14)	1.41 (0.96;1.98)	**0.67 (0.53;0.82)**	0.78 (0.54;1.08)	0.75 (0.45;1.16)	0.92 (0.83;1.02)
Edoxaban 60 mg vs. apixaban	0.99 (0.75;1.28)	1.12 (0.87;1.43)	1.11 (0.63;1.85)	1.11 (0.82;1.45)	1.44 (0.95;2.04)	1.03 (0.88;1.19)	1.09 (0.75;1.61)	1.14 (0.93;1.36)	1.41 (0.99;1.95)	1.12 (0.68;1.70)	**1.23 (1.12;1.35)**
Edoxaban 30 mg vs. rivaroxaban	1.26 (0.96;1.60)	**1.28 (1.02;1.61)**	0.59 (0.32;1.02)	**1.48 (1.14;1.86)**	**1.45 (1.02;1.99)**	0.95 (0.81;1.12)	1.34 (0.96;1.83)	**0.46 (0.37;0.56)**	**0.46 (0.33;0.61)**	**0.48 (0.28;0.75)**	**0.62 (0.55;0.70)**
Edoxaban 60 mg vs. rivaroxaban	0.89 (0.69;1.13)	0.98 (0.77;1.23)	0.97 (0.54;1.58)	1.03 (0.77;1.36)	1.26 (0.88;1.78)	1.00 (0.84;1.17)	1.04 (0.73;1.45)	**0.77 (0.63;0.93)**	0.84 (0.62;1.13)	0.72 (0.45;1.12)	**0.83 (0.74;0.91)**
Edoxaban 60 mg vs. edoxaban 30 mg	**0.72 (0.54;0.92)**	**0.77 (0.61;0.96)**	1.72 (0.94;2.91)	**0.70 (0.53;0.90)**	0.88 (0.61;1.22)	1.06 (0.92;1.22)	0.79 (0.57;1.07)	**1.71 (1.37;2.10)**	**1.85 (1.37;2.54)**	1.54 (0.95;2.34)	**1.33 (1.19;1.49)**

GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction. [a]Results are presented as odds ratios (95% confidence intervals). Results shown in boldface are significantly different.

similar results were observed in rivaroxaban vs. dabigatran 150 mg, edoxaban 60 mg vs. apixaban, and rivaroxaban vs. edoxaban 60 mg. The hazards of major bleeding, gastrointestinal bleeding, and any bleeding were significantly higher for edoxaban 60 mg than edoxaban 30 mg; the hazard of any bleeding was significantly higher for dabigatran 150 mg compared with dabigatran 110 mg.

Discussion

The current NMA aimed to compare the efficacy and safety of NOACs for stroke prevention in patients with nonvalvular atrial fibrillation. NMA is necessary as no studies compared NOACs with each other head-to-head, and such a trial is difficult to implement due to a large number of involved population and expense. NMA is a method that synthesizes direct and indirect evidence at the same time. The results of indirect comparison are usually, but not always, consistent with the direct ones. When direct evidence of RCTs is insufficient, indirect comparison can provide useful complementary information.[21] Adjusted indirect comparison may be less biased than the direct one.[22] Therefore, to minimize heterogeneity and confirm reliability, the current NMA was restricted to four RCTs whose outcomes were sufficiently similar and balanced.

The results comparing NOACs and warfarin from the current analysis were consistent with the direct ones and confirmed the findings from direct analysis. The application and development of anticoagulant drugs aim at seeking balances between hemorrhage and thrombosis, as higher efficacy in stroke prevention is related to higher risk of major bleeding events.[23] Therefore, when we evaluated new treatments, both results of stroke prevention and bleeding had to be carefully considered, rather than estimating clinical efficacy in isolation. According to the results of the NMA, apixaban, edoxaban 60 mg, and dabigatran 150 mg were found to have significantly better efficacy in prevention of stroke or systemic embolism than warfarin. Similarly, apixaban, both doses of edoxaban, and dabigatran 110 mg have significantly demonstrated lower hazards of major bleeding.

Moreover, a meta-analysis including the four RCTs was published recently,[24] which demonstrated similar results for the four NOACs compared with warfarin, but there were no comparisons among NOACs. Although an indirect comparison analysis among NOACs has been recently published,[25] it used the so-called Bucher method,[26] which can only be used for testing with two arms.[27] However, the Bayesian model used in the current NMA did not have such a limitation. Moreover, in the four included trials, there were direct comparisons between two doses of dabigatran and edoxaban. Three arms partly existed in the network geometry, so we think the results in our analysis were more robust. Similar results between the two methods were observed, but the CI was larger in our analysis. Other early published NMAs[28,29] only provided comparisons in the outcomes of stroke or systemic embolism and major bleeding. According to the results from indirect comparisons, edoxaban 60 mg and apixaban were better than dabigatran 150 mg and rivaroxaban in bleeding events, and were more favorable compared with dabigatran 110 mg and edoxaban 30 mg with respect to stroke prevention. Apixaban significantly revealed better results than edoxaban 60 mg in any bleeding events. In conclusion, apixaban was considered to have an advantage over the other NOACs in terms of safety.

It is, however, still necessary to further investigate these findings by real-world applications and studies.

Limitations

Although the similarity assessment was conducted by inclusion criteria applied for the selection of studies, there remained to be some study-designed differences between the included trials. ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 were designed as double-blinded, double-dummy trials. Only RE-LY was an open-labeled study that might have increased selection bias and overestimated the therapeutic effect.[30] The studies differed in outcome definitions. Moreover, ARISTOTLE and RE-LY studies enrolled patients who had a $CHADS_2$ score of at least 1, whereas patients with higher risk ($CHADS_2$ score of ≥ 2) were enrolled in ROCKET-AF and ENGAGE AF-TIMI 48. The therapeutic ranges (TTR) of 2.0–3.0 for warfarin were different in all the four trials. Efficacy and safety analyses of the RE-LY study were based on the intention-to-treat (ITT) population. However, in the other three trials, efficacy analyses were conducted on the ITT population and safety analyses on the on-treatment population. Moreover, the network geometry was not well connected to form a closed loop; thus, the results were possibly inconsistent.[16] These inherent limitations led to heterogeneity of the network.

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