

# Comparative risk for intracranial hemorrhage related to new oral anticoagulants

## A network meta-analysis

Tao Ma, MM, Chunbo Liu, MM, Tianwei Jiang, MD, Huaping Qin, MM, Ruhong Wu, MD, Peng Zhou, MM\* 

### Abstract

**Background:** The intracranial hemorrhage (ICH) risk of oral anticoagulants/non-vitamin K antagonist oral anticoagulants (NOACs) remains largely unknown. Patients who need oral anticoagulants such as aspirin or warfarin often suffer from obvious complications.

**Methods:** This network meta-analysis intended to assess the ICH risk in patients taking NOACs. The data from PubMed, the Cochrane database, and Embase were reviewed. All phase III randomized controlled trials of NOACs (apixaban, edoxaban, dabigatran, rivaroxaban), aspirin and warfarin were reviewed.

**Results:** Twenty-three trials involving 137,713 participants were included, involving 6 regimens. Warfarin had the first risk of ICH (surface under the cumulative ranking area: 0.82), followed by dabigatran, edoxaban, aspirin, apixaban, rivaroxaban, and placebo. Dabigatran had the lowest risk of all-cause mortality (surface under the cumulative ranking area: 0.63), followed by apixaban, edoxaban, warfarin, rivaroxaban, aspirin, and placebo.

**Conclusion:** Warfarin significantly increased the risk of ICH in patients taking oral anticoagulants compared with 4 NOACs (dabigatran, edoxaban, apixaban, rivaroxaban) and aspirin. Apixaban is least likely to induce all-cause mortality.

**Abbreviations:** ACS = acute coronary syndrome, AF = atrial fibrillation, CI = confidence interval, DTI = direct thrombin inhibitor, FXa = factor Xa, ICH = intracranial hemorrhage, INR = international normalized ratio, NOAC = non-vitamin K antagonist oral anticoagulant, OR = Odds ratio, PE = pulmonary embolism, RCT = randomized controlled trial, SUCRA = surface under the cumulative ranking curve, VKA = vitamin K antagonist, VTE = venous thromboembolism.

**Keywords:** anticoagulation, intracranial hemorrhage, network meta-analysis, new oral anticoagulants, vitamin K antagonists

## 1. Introduction

Anticoagulants have been widely used in the prevention and treatment of thromboembolic diseases, such as stroke, atrial fibrillation (AF), acute coronary syndrome (ACS), pulmonary embolism (PE), disseminated intravascular coagulation, rheumatic heart disease after valve replacement surgery, and postoperative venous thromboembolism (VTE). However, the

long-term application of antithrombotic drugs can cause abnormal coagulation function in patients. The serious complication of antithrombotic drugs is intracranial hemorrhage (ICH). Once ICH occurs, these patients are more prone to hematoma enlargement, operative hemostasis, and postoperative rebleeding.

Vitamin K antagonists (VKA) including warfarin are effective for preventing stroke in patients with AF. They have the limitations of unpredictable pharmacodynamics or pharmacokinetics and narrow therapeutic index, requiring laboratory monitoring (international normalized ratio [INR]) to adjust the dose. They have also more than doubled the risk of spontaneous intraparenchymal hemorrhage,<sup>[1]</sup> being associated with 12% to 14% of all ICH cases.<sup>[2]</sup> ICH accounts for 90% of all VKA-associated deaths.<sup>[3]</sup> For VKA-related ICH, both mortality rate and functional prognosis are poor.<sup>[4]</sup> NOACs selectively inhibit factors IIa or Xa and overcome the limitations associated with traditional oral anticoagulants.

Traditional head-to-head meta-analyses only compare the effects of 2 individual interventions. A network analysis allows the combination of direct and indirect evidences to compare the effects of 2 interventions and to establish the best intervention measures.<sup>[5]</sup> Therefore, we intended to perform a network analysis to assess the relative effectiveness of apixaban, enoxaparin, edoxaban, dabigatran, rivaroxaban, warfarin, and aspirin on the risk of ICH and mortality.

## 2. Methods

This is a meta-analysis, so ethical approval or informed consent was not necessary.

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The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Department of Neurosurgery, Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou 213003, Jiangsu Province, China.

\* Correspondence: Peng Zhou, Department of Neurosurgery, Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou, 213003, Jiangsu, China (e-mail: jarreddeckerxw@aol.com).

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## 2.1. Search strategy

We searched PubMed, the Cochrane database, and the EMBASE.com database for all randomized controlled trials (RCTs) that investigated the treatments up to May 2020. The following search terms were applied: (“new oral anticoagulants” OR “NOAC” OR “non-vitamin K oral anticoagulants”) and (“Apixaban” OR “Enoxaparin” OR “Dabigatran” OR “Rivaroxaban” OR “Edoxaban” OR “Aspirin” OR “Warfarin”) and (“randomized controlled trials” OR “RCT”) without language restriction. We also manually searched reference lists from cited articles for additional eligible trials.

## 2.2. Eligibility criteria

The studies included in this network meta-analysis met the following criteria:

- (1) NOAC phase III studies.
- (2) Trials comparing any pair of the following interventions: apixaban, dabigatran, enoxaparin, edoxaban, and rivaroxaban against other anticoagulants.
- (3) Trials reporting one of the following outcomes. The primary outcome was ICH.
- (4) RCTs reported in English language.

The following studies were excluded:

- (1) NOAC phase II studies, non-RCTs.
- (2) Duplicated publications from the same author with different interventions.
- (3) Controlled group that did not contain any of apixaban, dabigatran, enoxaparin, edoxaban, and rivaroxaban.
- (4) Research subjects not in accordance with the inclusion criteria.

## 2.3. Data extraction and analysis

Two investigators (Ma and Peng) independently examined publications that met the inclusion criteria. Data of interest were extracted, including report authors, year of publications, study arms, study sample, median age, ICH, and mortality. The Cochrane Collaboration’s tool was adopted to assess the risks of bias as follows: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, etc. Any disagreement with respect to data extraction and integration was discussed with a third researcher (Wu).

## 2.4. Statistical analysis

Pairwise meta-analysis was performed by STATA software (Version 16.0; Stata Corporation, College Station, TX). ICH was defined as the primary endpoint. Mortality was defined as the secondary endpoint. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random-effects model or fixed-effects model for investigating treatment effects. Statistical heterogeneity was assessed by  $I^2$  using the Higgins–Thompson method<sup>[6]</sup>: <25% was no heterogeneity, 25% to 50% was low heterogeneity, 50% to 75% was moderate heterogeneity, and >75% was high heterogeneity.

Node-splitting network meta-analysis was developed in a Bayesian framework using Markov chain Monte Carlo simulation methods provided by Aggregate Data Drug Information System v1.16.6 (Drugis, Groningen, NL). Moreover, the surface

under the cumulative ranking curve (SUCRA) was obtained to rank corresponding interventions. As a transformation of the mean rank, SUCRA provides a hierarchy of treatments and represents the location and variance of treatment effects. Higher accumulative SUCRA value indicates higher possible ranking of the treatment, which is equal to 1 when the treatment is certainly the best.

## 3. Results

### 3.1. Characteristics of included studies

This review included 23 RCTs reporting at least one ICH event (Fig. 1). After retrieving the titles and abstracts, 202 articles were excluded as unrelated studies, 16 as non-RCTs, 43 as non-relevant interventions, 31 as non-included outcomes, and 21 as non-available data. These randomized controlled articles met the inclusion criteria of this network meta-analysis, which were from different countries and published between 1990 and 2018. These studies evaluated a total of 137,713 patients with a mean age ranging from 52 to 78 years. The characteristics of the eligible studies are presented in Table 1.<sup>[7–29]</sup> The included trials evaluated NOACs in the presence of different clinical conditions and settings: patients with venous thromboembolic disease ( $n=4$  RCTs), non-valvular atrial fibrillation (NVAf) ( $n=14$  RCTs), ACS ( $n=1$  RCTs), patients undergoing orthopedic surgery ( $n=2$  RCTs), and patients hospitalized for medical illnesses ( $n=2$  RCTs) (Fig. 2). The risks of bias of the included RCTs are exhibited in Figure 3.

### 3.2. Pairwise meta-analysis

The sum ORs of the corresponding results for each direct comparison were calculated. The results of pairwise meta-analysis are shown in Table 2 and Figure 4. Patients administered with rivaroxaban had an increased risk of ICH compared to those taking placebo (Odds ratio [OR]=3.21, 95% confidence interval (CI)=1.25–8.23,  $P<.001$ ). In contrast, patients administered with rivaroxaban had a significantly lower risk of ICH than those taking edoxaban (OR=0.25, 95% CI=0.07–0.88,  $P<.001$ ). Moreover, patients using warfarin were associated with an increased risk of ICH compared to those administered with apixaban (OR=2.37, 95% CI=1.71–3.29,  $P<.001$ ), while those taking edoxaban were associated with a lower risk of ICH than patients using warfarin (OR=2.46, 95% CI=2.02–3.00,  $P<.001$ ). Furthermore, both dabigatran (OR=1.12, 95% CI=1.00–1.25,  $P<.001$ ) and edoxaban (OR=1.12, 95% CI=1.03–1.23,  $P=.05$ ) were more effective than warfarin in reducing the mortality. Finally, patients taking rivaroxaban had a lower risk of mortality than those administered with placebo (OR=0.80, 95% CI=0.65–0.98,  $P<.001$ ).

The heterogeneity between some studies was not significant, so the fixed-effect model was utilized for comparisons. However, when significant heterogeneity existed in some comparisons (apixaban vs placebo,  $I^2=82.1\%$ ; warfarin vs rivaroxaban,  $I^2=91.9\%$ , in ICH; apixaban vs placebo,  $I^2=97.2\%$ ; rivaroxaban vs placebo,  $I^2=100.0\%$ , in mortality), the random-effects model was employed.

### 3.3. Network meta-analysis

Regarding primary outcome, the pairwise meta-analysis showed that apixaban was more likely to cause ICH than rivaroxaban

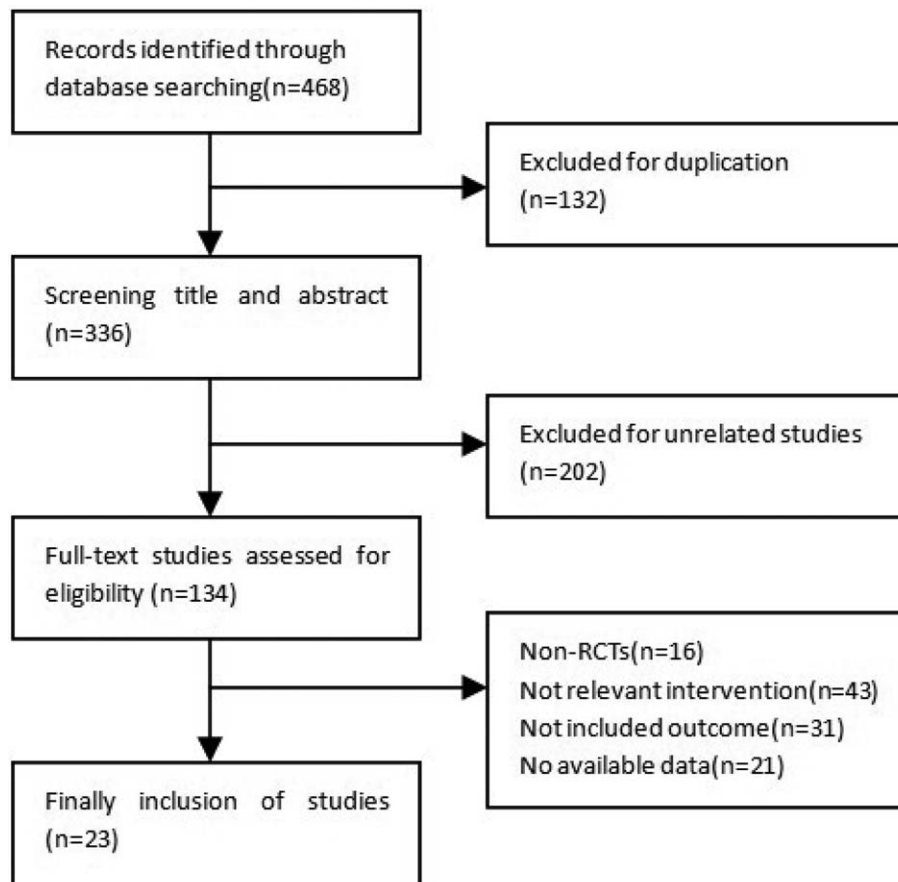


Figure 1. Flow chart of RCT selection. RCT=randomized controlled trial

Table 1

Main characteristics of included studies.

Author	Study	Year	Clinical condition	Intervention and dose	Age (yr)	ICH (n)	Mortality (n)	Patients (n)	Double blind	Follow-up
Goldhaber SZ	ADOPT <sup>[7]</sup>	2011	Medical illnesses	Apixaban 2.5mg twice daily	66.8±12	0	60	3184	Yes	
Lassen MR	ADVANCE-2 <sup>[8]</sup>	2010	Orthopedic surgery	Enoxaparin 40 mg once daily	66.7±12	2	70	3217		
Agnelli G	AMPLIFY-EXT <sup>[9]</sup>	2013	Venous thromboembolism	Apixaban 2.5 mg twice daily	67	0	2	1528	Yes	60 d
Alexander JH	APPRAISE-2 <sup>[10]</sup>	2011	Acute coronary syndrome	Enoxaparin 40 mg once daily	67	0	0	1529		
Granger CB	ARISTOTLE <sup>[11]</sup>	2011	Atrial fibrillation	Apixaban 2.5–5 mg twice daily	56.4	3	66	1653	Yes	12 mo
Mega JL	ATLASACS2-TIMI51 <sup>[12]</sup>	2012	Acute coronary syndrome	Placebo	57.1	4	96	829		
Büller HR	EINSTEIN-PE <sup>[13]</sup>	2012	Pulmonary embolism	Apixaban 5 mg twice daily	67	12	155	3705	Yes	
Singer DE	BAATAF <sup>[14]</sup>	1990	Atrial fibrillation	Placebo	67	3	143	3687		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	70	52	488	9088	Yes	1.8 yr
Giugliano RP	ENGAGE AF-TIMI <sup>[19]</sup>	2013	Atrial fibrillation	Edoxaban 30, 60 mg once daily	70	122	502	9052		
Ezekowitz MD <sup>[20]</sup>		1992	Atrial fibrillation	Warfarin INR 2–3	61.8±9.2	32	245	10,229	Yes	
Büller HR	Hokusai-VTE <sup>[21]</sup>	2013	Venous thromboembolism	Edoxaban 1.0 mg per kilogram twice daily	61.9±9.0	5	153	5113		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	57.9±7.3	3	58	2419	No	
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	57.5±7.2	12	50	2413		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	68.5±8.5	1	11	212	No	
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	67.5±9.3	0	26	208		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	68.0±9.3	1	10	187	Yes	2.5 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	67.4±9.6	0	8	191		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	70±9	11	111	2808	Yes	1.1 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	70±10	13	140	2791		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	71.4±8.7	63	884	12,091	No	2.0 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	71.6±8.6	87	487	6022		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	71±7	1	102	404	Yes	2.3 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	77±8	0	99	378		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	72	177	1510	14,014	Yes	2.8 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	72	211	839	7012		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	67±7	1	15	260	Yes	1.8 yr
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	67±7	0	22	265		
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	55.7±16.3	5	20	4118	Yes	12 mo
Connolly SJ	CAFA <sup>[15]</sup>	1991	Atrial fibrillation	Warfarin INR 2–3	55.9±16.2	18	21	4122		

(continued)

**Table 1**  
(continued).

Author	Study	Year	Clinical condition	Intervention and dose	Age (yr)	ICH (n)	Mortality (n)	Patients (n)	Double blind	Follow-up
Sato H	JAFST <sup>[22]</sup>	2006	Atrial fibrillation	Aspirin 150–200 mg per day	65.5	4	10	426	No	2.1 yr
				Placebo	64.8	2	9	445		
Hori M	J-ROCKET AF <sup>[23]</sup>	2011	Atrial fibrillation	Rivaroxaban 15 mg once daily	71.0	5	7	639	Yes	30 mo
				Warfarin INR 1.6–2.6	71.2	10	5	639		
Turpie AGG	RECORD4 <sup>[24]</sup>	2009	Orthopedic surgery	Rivaroxaban 10 mg once daily	64.4	1	4	1584	Yes	35 d
				Edoxaban 30 mg twice daily	64.7	0	3	1564		
Schulman S	RE-MEDY <sup>[25]</sup>	2013	Venous thromboembolism	Dabigatran 150 mg twice daily	55.4 ± 15.0	8	17	1430	Yes	36 mo
				Warfarin INR 2–3	53.9 ± 15.3	13	19	1426		
Patel MR	ROCKET AF <sup>[26]</sup>	2011	Atrial fibrillation	Rivaroxaban 20 mg once daily	73	55	NR	7111	Yes	1.9 yr
				Warfarin INR 2–3	73	84	NR	7125		
Gullov AL	SCAF <sup>[27]</sup>	1998	Atrial fibrillation	Aspirin 300 mg per day	74.2	1	14	169	No	6 mo
				Warfarin INR 2–3	73.1	2	17	170		
	SPAF <sup>[28]</sup>	1991	Atrial fibrillation	Warfarin	67	1	6	210	Yes	1.3 yr
				Placebo	70	0	8	211		
				Aspirin		1	39	552		
				Placebo		0	50	568		
	SPAFII <sup>[29]</sup>	1994	Atrial fibrillation	Aspirin 325 mg per day	72.5	2	41	357	No	3 mo
				Warfarin INR 2.0–4.5	72	6	36	358		

AF = atrial fibrillation, INR = international normalized ratio, PE = pulmonary embolism, VTE = venous thromboembolism.

(OR = 0.14, 95% CI: 0.05, 0.57). The other groups had similar risks of ICH. The results of direct comparisons are shown in Table 3 and Figure 5.

The SUCRA probabilities of different intervention methods were estimated. Figure 6 shows the ranking of different risks of ICH. The results of indirect comparisons are shown in the lower triangles of Table 3. The absolute effects and rank test indicated that warfarin ranked the first (SUCRA: 0.82), followed by dabigatran, edoxaban, aspirin, apixaban, rivaroxaban, and placebo.

As to secondary outcome, the pairwise meta-analysis showed that apixaban was more likely to reduce mortality than placebo (OR = 1.57, 95% CI: 1.07, 2.37). The other groups had similar risks of mortality. The results of direct comparisons are shown in Table 3.

The SUCRA probabilities of different intervention methods were estimated. Figure 7 shows the ranking of different risks of mortality. The results of indirect comparisons are shown in the

upper triangles of Table 3. The absolute effects and rank test indicated that dabigatran ranked the lowest (SUCRA: 0.63), followed by apixaban, edoxaban, warfarin, rivaroxaban, aspirin, and placebo.

#### 4. Discussion

ICH is a well-known serious complication of antithrombotic drugs. Many previous RCTs have not been analyzed in head-to-head comparisons or network meta-analysis. In this study, direct pairwise meta-analysis and network meta-analysis were conducted to compare the risks of 6 regimens (apixaban, edoxaban, dabigatran, rivaroxaban, aspirin, and warfarin) as OACs and placebo/control. Treatment was selected to match the individual risk of ICH events with specific pharmacokinetic and pharmacodynamic of suppository therapy.

In this network meta-analysis, warfarin had the highest probability of ICH risk among all anticoagulant regimens. Direct pairwise meta-analysis results showed that warfarin augmented the probability of ICH risk than apixaban and edoxaban. After ICH in patients taking VKA, hematoma easily expands and the mortality and disability rates increase obviously than those of the general population.<sup>[30]</sup> Patients should stop using VKA immediately and take vitamin K to correct coagulation dysfunction. Prothrombin complex concentrates, which can correct INR rapidly with milder complications, should be the first choice. The target value of INR should be lower than 1.4.<sup>[31]</sup>

For patients with NVAF, venous thrombosis and PE, direct factor Xa inhibitors (FXas) (including apixaban, edoxaban, and rivaroxaban) can inhibit both free factor Xa (FXa) factor of plasma and FXa factor combination of prothrombinase complexes. The required concentration range for coagulation activation of FXa is wider than that of thrombin, which can reduce the requirement of monitoring the blood coagulation function, because this kind of drug is superior to warfarin. Our direct pairwise meta-analysis results showed that warfarin elevated the probability of mortality risk than dabigatran and edoxaban. Thus, the SUCRA ranking plot did not reveal obvious winners of 4 NOACs (apixaban, edoxaban, rivaroxaban, dabigatran) for ICH.

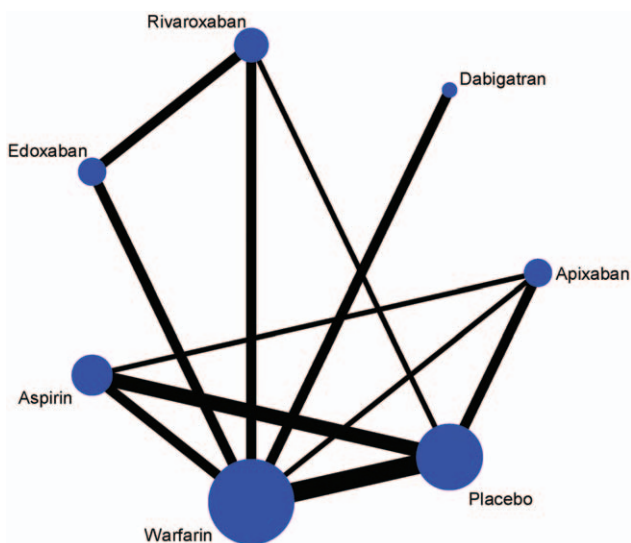


Figure 2. Network plot of treatment comparisons.



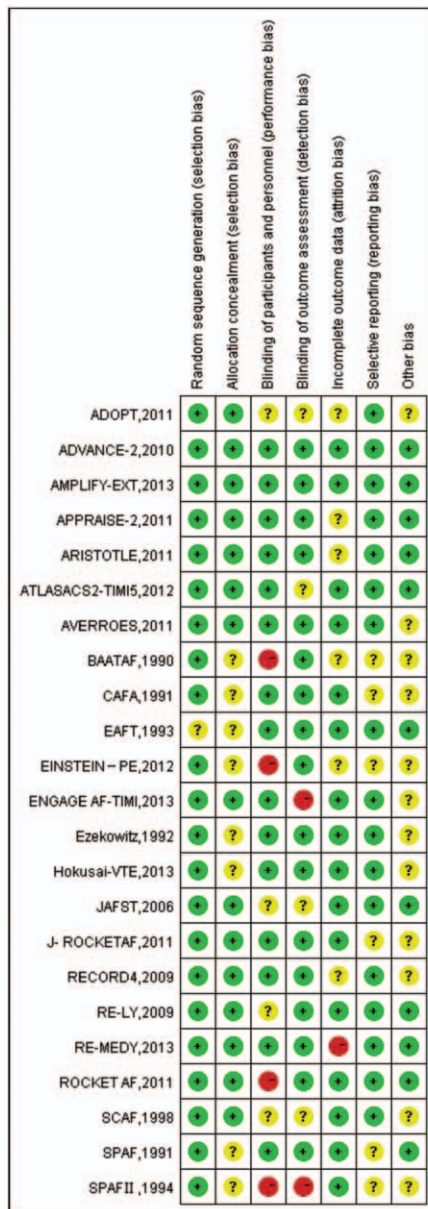
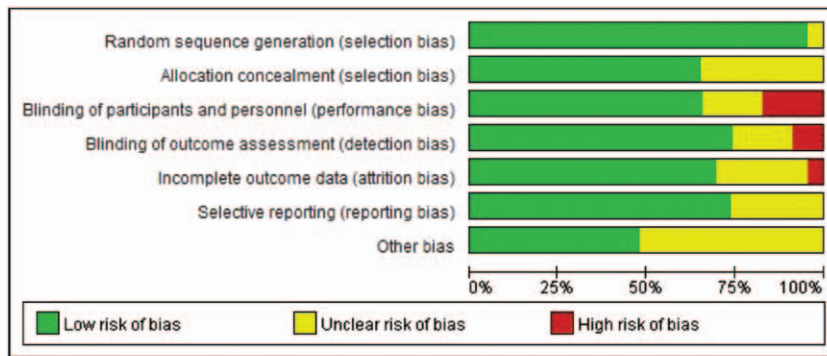
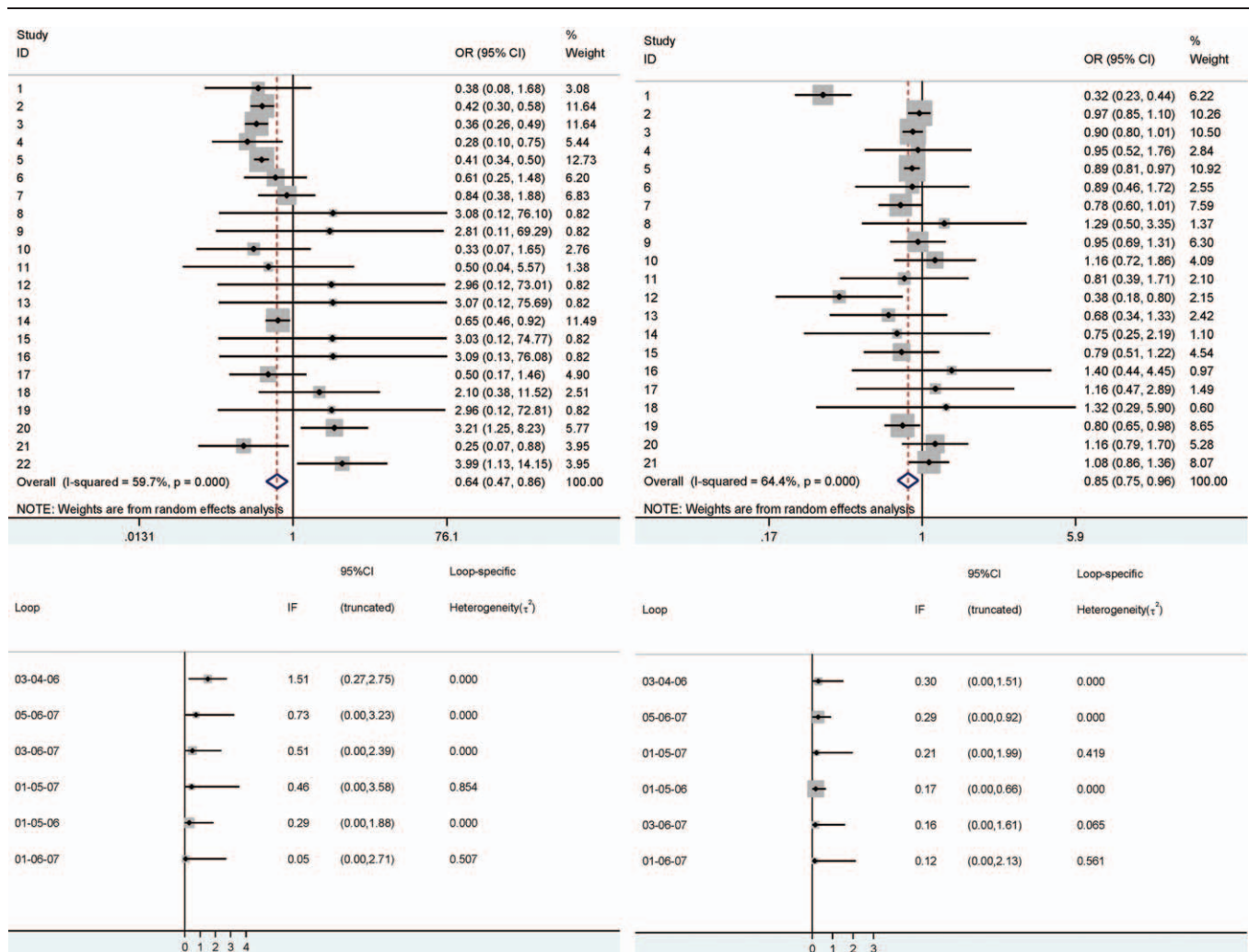


Figure 3. Risks of bias of included RCTs.

**Table 2**  
Pairwise meta-analyses of comparisons.

Endpoints	Direct comparisons	$I^2$	$P_H$ values	OR (95%CI)
ICH	Aspirin vs Apixaban	N/A	0.00	1.19 (0.53,2.66)
	Apixaban vs Placebo	82.1%	5.58	0.79 (0.08,8.00)
	Warfarin vs Apixaban	N/A	0.00	2.37 (1.71,3.29)
	Aspirin vs Placebo	N/A	0.00	0.48 (0.09,2.61)
	Warfarin vs Aspirin	0.0%	0.08	2.66 (0.70,10.14)
	Rivaroxaban vs Edoxaban	N/A	0.00	0.25 (0.07,0.88)
	Warfarin vs Edoxaban	0.0%	0.00	2.46 (2.02,3.00)
	Rivaroxaban vs Placebo	N/A	0.00	3.21 (1.25,8.23)
	Warfarin vs Rivaroxaban	91.9%	12.41	5.96 (0.82,43.57)
Mortality	Aspirin vs Apixaban	N/A	0.00	1.28 (0.99,1.66)
	Apixaban vs Placebo	97.2%	36.16	1.70 (0.51,5.64)
	Warfarin vs Apixaban	N/A	0.00	1.03 (0.91,1.18)
	Aspirin vs Placebo	0.0%	0.78	1.10 (0.86,1.41)
	Warfarin vs Aspirin	0.0%	0.63	0.96 (0.64,1.42)
	Warfarin vs Dabigatran	0.0%	0.00	1.12 (1.00,1.25)
	Rivaroxaban vs Edoxaban	0.0%	0.03	1.17 (0.81,1.69)
	Warfarin vs Edoxaban	0.0%	0.05	1.12 (1.03,1.23)
	Rivaroxaban vs Placebo	100.0%	0.00	0.80 (0.65,0.98)
	Warfarin vs Placebo	26.4%	4.08	0.66 (0.41,1.07)
	Warfarin vs Rivaroxaban	N/A	0.00	0.71 (0.22,2.26)

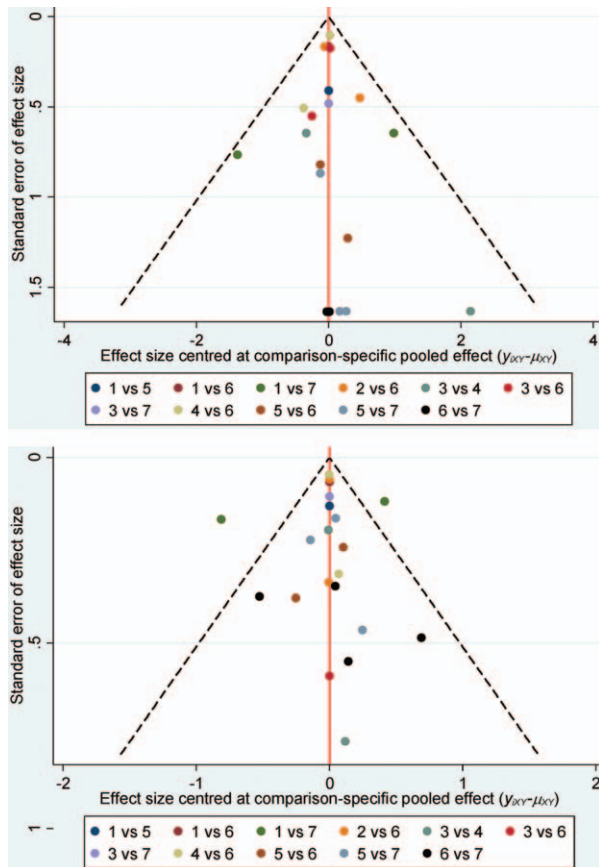
CI=confidence interval, ICH=intracranial hemorrhage, OR=Odds ratio.



**Figure 4.** Contribution plot of included RCTs. The columns refer to direct comparisons and the rows refer to all possible pairwise comparisons. 1: Apixaban; 2: dabigatran; 3: rivaroxaban; 4: edoxaban; 5: aspirin; 6: warfarin; 7: placebo.

**Table 3**  
**Network meta-analyses of comparisons.**

Apixaban	1.30 (0.82,2.04)	0.99 (0.48,2.02)	1.02 (0.55,1.93)	1.57 (1.07,2.37)	1.26 (0.69,2.41)	1.10 (0.71,1.72)
0.78 (0.16,3.23)	Aspirin	0.76 (0.37,1.52)	0.79 (0.43,1.45)	1.20 (0.82,1.77)	0.97 (0.54,1.81)	0.84 (0.56,1.28)
0.49 (0.04,3.86)	0.63 (0.06,5.23)	Dabigatran	1.03 (0.50,2.16)	1.60 (0.83,3.09)	1.28 (0.60,2.78)	1.12 (0.65,1.97)
0.60 (0.07,4.42)	0.77 (0.09,6.05)	1.20 (0.22,8.13)	Edoxaban	1.52 (0.89,2.63)	1.23 (0.72,2.10)	1.07 (0.67,1.69)
2.23 (0.53,9.15)	4.40 (0.93,23.55)	6.86 (0.85,78.82)	5.76 (0.83,48.17)	Placebo	0.80 (0.48,1.37)	0.70 (0.49,1.02)
1.31 (0.15,7.83)	1.72 (0.20,10.08)	2.78 (0.34,18.09)	2.22 (0.46,9.34)	0.39 (0.06,1.67)	Rivaroxaban	0.88 (0.51,1.51)
0.30 (0.06,1.30)	0.31 (0.06,1.46)	0.44 (0.12,1.69)	0.36 (0.10,1.16)	0.06 (0.00,0.33)	0.14 (0.05,0.57)	Warfarin



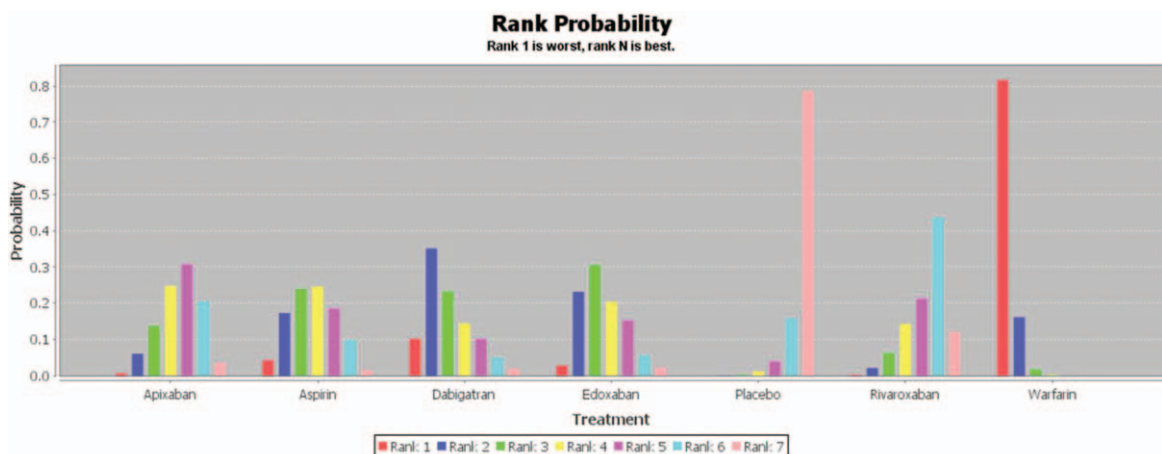
**Figure 5.** Comparison-adjusted funnel plot for the network meta-analysis. 1: Apixaban; 2: dabigatran; 3: rivaroxaban; 4: edoxaban; 5: aspirin; 6: warfarin; 7: placebo.

Direct thrombin inhibitors (DTIs) can inhibit thrombin to exert an antithrombotic effect and suppress free thrombin binding to blood clots, without needing auxiliary factors. They do not react with the fourth factor of platelets, and thus have no risk of thrombocytopenia. The incidence rate of ICH is low in treatment. Direct pairwise meta-analysis results showed that dabigatran reduced the probability of mortality risk of warfarin. As suggested by the SUCRA ranking plot, dabigatran may give the lowest mortality rate among all regimens.

This network meta-analysis still has some limitations related to included studies and analysis methods. For instance, it is based on research rather than the data analysis of individual patient. The collection of data from patients under different clinical conditions is always a methodological concern and should be considered as a limitation.

This network meta-analysis compares different types of treatments including apixaban, edoxaban, dabigatran, rivaroxaban, aspirin, and warfarin. Our findings suggested that warfarin had the most probability of causing ICH with SUCRA value of 82% and dabigatran had the most probability of reducing mortality with SUCRA value of 63%. Due to the limitations in the quantity of currently available evidence, high-quality RCTs with large numbers of participants should be conducted to explore the preferred options for clinical practice.

In conclusion, this network meta-analysis showed that warfarin significantly increased the risk of ICH in patients taking oral anticoagulants compared with 4 NOACs (dabigatran, edoxaban, apixaban, rivaroxaban) and aspirin. Dabigatran had the lowest probability of causing mortality among NOACs. We recommend that future studies focus on the ICH risk to clarify the incidence rate and associated risk.



**Figure 6.** Ranking of different risks of ICH. Rank 1 is worst and Rank 7 is best.

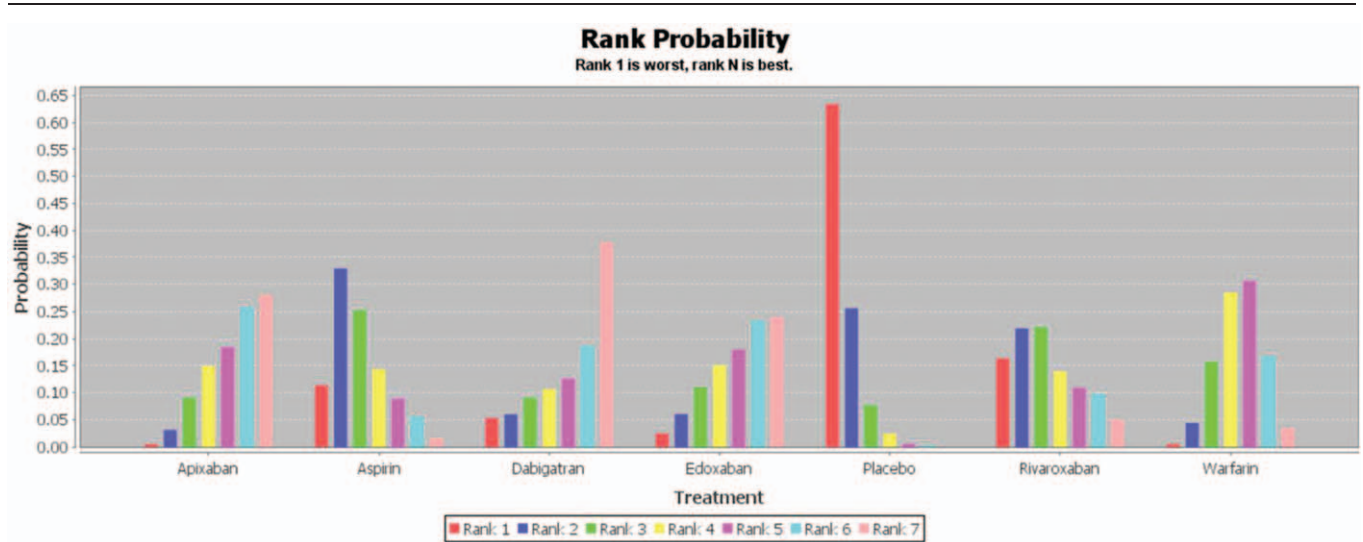


Figure 7. Ranking of different risks of mortality. Rank 1 is worst and Rank 7 is best.

## Author contributions

**Conceptualization:** Tao Ma, Peng Zhou.

**Data curation:** Chunbo Liu.

**Investigation:** Chunbo Liu, Tianwei Jiang, Huaping Qin, Ruhong Wu.

**Methodology:** Chunbo Liu, Tianwei Jiang, Huaping Qin, Ruhong Wu.

**Supervision:** Peng Zhou.

**Writing – original draft:** Tao Ma.

**Writing – review & editing:** Peng Zhou.

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