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Efficacy and safety of non-vitamin K antagonist oral anticoagulants for venous thromboembolism: a meta-analysis

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Summary

Objective: Several trials had compared the efficacy and safety between non-vitamin K antagonist oral anticoagulants and warfarin for acute venous thromboembolism, but the results were incomplete. This updated review comprehensively assessed the efficacy and safety of non-vitamin K antagonist oral anticoagulants for venous thromboembolism.

Design: Meta-analysis of randomised control trials. Six databases were searched from January 2000 to December 2018.

Setting: Adult patients had got non-vitamin K antagonist oral anticoagulants or warfarin for venous thromboembolism.

Participants: Randomised control trials that compared the efficacy and safety between non-vitamin K antagonist oral anticoagulants and warfarin.

Main outcome measures: The efficacy and safety of non-vitamin K antagonist oral anticoagulants .

Results: Seven studies involving 29,879 cases were included, among which 14,943 cases were assigned to non-vitamin K antagonist oral anticoagulants group and 14,936 cases to warfarin group. Meta-analysis showed that compared with warfarin, recurrent venous thromboembolism (odds ratio 0.94 [95% confidence interval 0.81 to 1.11]), death related to venous thromboembolism or fatal pulmonary embolism (odds ratio 1.00 [95% confidence interval 0.63 to 1.60]), symptomatic deep-vein thrombosis (odds ratio 0.88 [95% confidence interval 0.72 to 1.09]), symptomatic nonfatal pulmonary embolism (odds ratio 1.03 [(95% confidence interval 0.82 to 1.30]) and all deaths (odds ratio 0.92 [95% confidence interval 0.76 to 1.12]) are similar in non-vitamin K antagonist oral anticoagulants group, but major bleeding event (odds ratio 0.61 [95% confidence interval 0.50 to 0.75]) and clinically relevant non-major bleeding event (odds ratio [95% confidence interval 0.53 to 0.85]) are less in non-vitamin K antagonist oral anticoagulants group.

Conclusions: For the treatment of venous thromboembolism, non-vitamin K antagonist oral anticoagulants is as effective as warfarin, and has a better safety profile than warfarin.

Keywords

Venous thromboembolism, pulmonary embolism, deep-vein thrombosis, non-vitamin K antagonist oral anticoagulants, warfarin, randomised control trial

Introduction

Acute venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is associated with substantial morbidity and mortality.[1] In the past decades, warfarin and other vitamin K antagonists had been the primary therapy for patients with venous thromboembolism. Although vitamin K antagonists are cheap, they have a narrow therapeutic window and require frequent monitoring, they also have many interactions with food and drugs, which can result in poor adherence.[2]

Alternatively, there are non-vitamin K antagonist oral anticoagulants that have been approved by the US Food and Drug Administration (FDA) for use in venous thromboembolism, and their use has increased substantially. non–vitamin K antagonist oral anticoagulants do not require laboratory monitoring and have fewer food–drug interactions.[3] However, there are some concerns about non–vitamin K antagonist oral anticoagulants, including poor adherence in the absence of monitoring, more cost (three times more expensive than warfarin even when including laboratory monitoring), bleeding risk and current almost absence of a specific antidote.

There are several randomised controlled trials which compared the efficacy and safety between non–vitamin K antagonist oral anticoagulants and warfarin, and showed similar or non-inferiority effect and similar or superior safety of non–vitamin K antagonist oral anticoagulants in treatment of venous thromboembolism. Several meta-analyses have evaluated the efficacy and safety of non–vitamin K antagonist oral anticoagulants compared with

vitamin K antagonists in venous thromboembolism, but only showed part results of the data about efficacy and safety.[4–7] In the present study, we performed a meta-analysis to comprehensively assess the efficacy (recurrent venous thromboembolism, venous thromboembolism related death or fatal pulmonary embolism, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism) and safety (all death, major bleeding event and clinically relevant bleeding event) of non–vitamin K antagonist oral anticoagulants in venous thromboembolism treatment.

Methods

MEDLINE, EMBASE, ScienceDirect, Highwire, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews were searched before conducting the review on January 2019 to ensure that there was no recent review. The review was reported according to the PRISMA guidelines for systematic reviews. After scoping searches, we developed a review protocol, which described the search strategy and methods for data collection and analysis. According to review aims, search terms were generated by patient, intervention, comparison and outcome (PICOS) elements (see Table 1).

Data source and searches

We searched six databases and the reference lists of retrieved reports from January 2000 to December 2018 for studies of efficacy and safety of non–vitamin K antagonist oral anticoagulants versus warfarin in treatment of patients with venous thromboembolism using the terms identified by PICOS (Table 1).

Study selection

Two investigators (Y.Z and L.F.D) independently screened all titles and abstracts to identify studies that examined the efficacy and safety of non–vitamin K antagonist oral anticoagulants in patients with venous thromboembolism. Only reports in English were included in this study. Studies were excluded if the research met any one of the following criteria: (1) the efficacy and safety of non–vitamin K antagonist oral anticoagulants versus warfarin were not

Table 1. PICOS identifiers from research questions (key terms) and database- and thesaurus-derived alternatives (additional terms) used to generate database searches.

	Participants	Interventions	Comparisons	Outcomes	Study design
Key terms	Venous thromboembolism	Anticoagulants	Warfarin	Recurrent venous thromboembolism	Randomised control trial
	Venous thrombosis	Antithrombins		Venous thromboembolism-related death	
	Thromboembolism	Factor a inhibitors		Fatal pulmonary embolism	
	thrombosis			symptomatic deep-vein thrombosis	
	Pulmonary embolism			Symptomatic nonfatal pulmonary embolism	
				all death	
				major bleeding event	
				clinically relevant bleeding event	
Additional terms	Deep vein Thrombosis		Coumarins		
	DVT				
	VTE				
	pulmonary embolisms				

reported, (2) publication only as an abstract and (3) duplicate publication or ongoing/unpublished study.

Data extraction

Two reviewers (Y.Z and L.F.D) extracted relevant data from the included studies using a standardised data extraction form. Randomised studies with follow-up duration at least three months were considered for inclusion. Primary outcome measures were recurrent venous thromboembolism, venous thromboembolism-related death or fatal pulmonary embolism, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism, all death, major bleeding event and clinically relevant bleeding event. Studies reporting efficacy and safety of non–vitamin K antagonist oral anticoagulants on the basis of different drugs were analysed separately, and the total efficacy and safety for all studies (dabigatran, rivaroxaban, endoxaban and apixban) were also analysed.

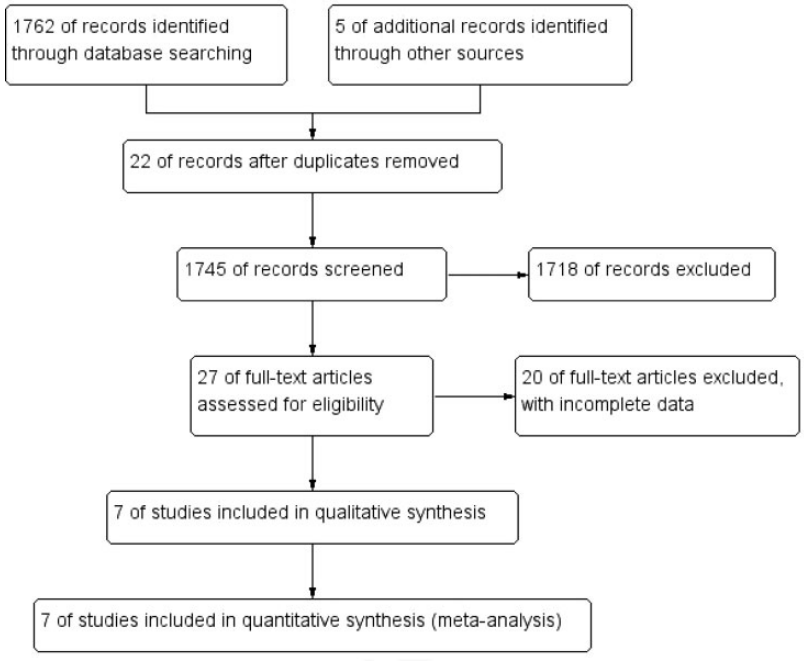
Quality assessment

The quality of included studies was assessed by Cochrane Collaboration Tool, which consisted of seven sections as follows: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other biases.

Data analysis

Statistical analyses were performed using RevMan version 5.3 (The Cochrane Collaboration, Oxford, England), and the results are expressed as odds ratio for dichotomous outcomes, with 95% confidence intervals. We calculated the I^2 statistic to assess the heterogeneity across the trials, and a value greater than 50% was considered substantial heterogeneity then data were pooled using the random-effects model. The efficacy of non–vitamin K antagonist oral anticoagulants in this meta-analysis was assessed using RCTs which were designed as non-inferiority studies with associated non-inferiority margins used to interpret the comparison results, so we also try to use non-inferiority margins to interpret the meta-analysis results. The non-inferiority margins were estimated from studies which evaluated the efficacy of warfarin as compared with no anticoagulation. If the upper boundary of 95% confidence interval for the pooled odds ratio was within reasonable non-inferiority margin, the result may be interpreted as 'similar efficacy'. We conducted

Figure 1. Reports evaluated for inclusion in meta-analysis.



sensitivity analyses by comparing the outcomes using the fixed- versus random-effects model. Publication bias was explored by visual inspection of a funnel plot. $p < 0.05$ was used for statistical significance.

Results

We identified seven studies[8–14] (enrolling 29,879 patients, among which 14,943 cases were assigned to the treatment group and 14,936 cases to the control group) that reported the effects and safety of non–vitamin K antagonist oral anticoagulants in patients with venous thromboembolism. Reports evaluated for inclusion in meta-analysis are shown in Figure 1.

Study characteristics

Baseline characteristics of the studies included in the meta-analysis are listed in Table 2. All patients suffered venous thromboembolism (pulmonary embolism or deep vein thrombosis), the treatment group got fixed dose of non–vitamin K antagonist oral anticoagulants and the control group got dose-adjusted warfarin (achieve an international normalised ratio of 2.0 to 3.0). There are three studies[8,11,14] that compared the efficacy and safety of dabigatran with warfarin; two studies[14,15] compared rivaroxaban with warfarin, one trial[13] compared endoxaban with warfarin and one trial[12] compared apixban with warfarin.

There are seven studies[8–14] that evaluated the recurrent venous thromboembolism, venous thromboembolism-related death or fatal pulmonary embolism, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism, major bleeding event and clinically relevant bleeding event of non–vitamin K antagonist oral anticoagulants, and six studies[8–11,13,14] evaluated all death of non–vitamin K antagonist oral anticoagulants. The primary outcomes of the studies included are listed in Table 3.

Risk of bias assessment

The details on risk for bias are shown in Figure 2. Seven studies[8–14] were judged to be at low risk for bias in the random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Five studies[8,11–14] were judged to have low risk for bias in blinding of participants and personnel. Three studies[8–10] had unclear risk of other bias.

Non-inferiority margin assessment

In order to assess non-inferiority margin to interpret the meta-analysis results, we performed a meta-

Table 2. Characteristics of studies included in the meta-analysis.

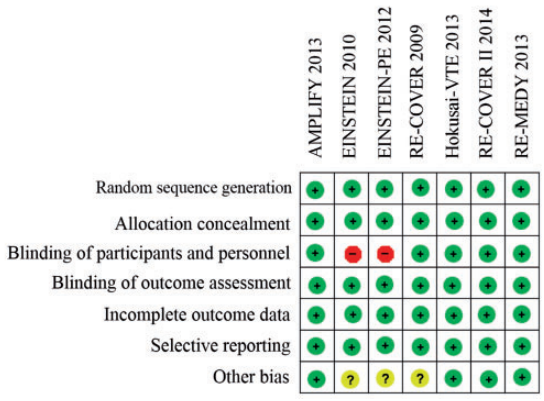
Study, year	Country	Follow-up duration (mo)	Dosage (mg)	Patients, *n*		Age, y		Female %	
				NOAC	VKA	NOAC	VKA	NOAC	VKA
RE-COVER 2009[8]	Multi-nation	6	Dabigatran 150 twice daily	1274	1265	55.0	54.4	42.0	41.1
EINSTEIN 2010[9]	Multi-nation	3,6,12	Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily	1731	1718	55.8	56.4	42.6	43.7
EINSTEIN-PE 2012[10]	Multi-nation	3,6,12	Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily	2419	2413	57.9	57.5	45.9	48.3
Hokusai-VTE 2013[12]	Multi-nation	12	Endoxaban 60 mg once daily, or 30 mg in patients with Ccr < 60 ml	4118	4122	55.7	55.9	42.7	42.8
AMPLIFY 2013[13]	Multi-nation	6	Apixban 10 mg twice daily for 7 days,5 mg twice daily for 6 months	2691	2704	57.2	56.7	39.7	40.9
RE-MEDY 2013[11]	Multi-nation	36	Dabigatran 150 mg twice daily	1430	1426	55.4	53.9	39.1	38.9
RE-COVER II 2014[14]	Multi-nation	6	Dabigatran 150 mg twice daily	1280	1288	54.7	55.1	39.0	39.8

Table 3. The primary outcomes of included studies.

	Recurrent venous thromboembolism		Death related to venous thromboembolism/fatal pulmonary embolism		Symptomatic deep-vein thrombosis		Symptomatic nonfatal pulmonary embolism		All deaths		Major blooding		Clinically relevant non-major bleeding event	
Study, year	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA
RE-COVER 2009[14]	30/1274	27/1265	1/1274	3/1265	16/1274	18/1265	13/1274	7/1265	21/1274	21/1265	20/1274	24/1265	71/1274	111/1265
EINSTEIN 2010[9]	36/1731	51/1718	4/1731	6/1718	14/1731	28/1718	20/1731	18/1718	38/1731	49/1718	14/1718	20/1711	140/1718	139/1711
EINSTEIN-PE 2012[10]	50/2419	44/2413	10/2419	6/2413	18/2419	17/2413	22/2419	19/2413	58/2419	50/2413	26/2412	52/2405	249/2412	274/2405
Hokusai-VTE 2013[12]	73/4118	83/4122	4/4118	3/4122	57/4118	63/4122	49/4118	59/4122	N/A	N/A	56/4118	66/4122	349/4118	423/4122
AMPLIFY 2013[13]	59/2609	71/2635	12/2609	16/2635	20/2609	33/2635	27/2609	23/2635	41/2676	52/2689	15/2676	49/2689	115/2676	261/2689
RE-MEDY 2013[11]	26/1430	18/1426	1/1430	1/1426	17/1430	13/1426	10/1430	5/1426	17/1430	19/1426	13/1430	25/1426	80/1430	145/1426
RE-COVER II 2014[14]	30/1279	28/1289	3/1279	0/1289	25/1279	17/1289	7/1279	13/1289	25/1279	25/1289	15/1279	22/1289	64/1279	102/1289

analysis to assess efficacy of warfarin as compared with no anticoagulation in four studies.[15–18] The results are expressed as odds ratio with 95% confidence intervals. Pooled analysis showed that warfarin could decrease the rate of recurrent venous thromboembolism than no anticoagulation, and the difference was significant (odds ratio 0.55 [95%confidence interval, 0.39 to 0.76], $p = 0.0004$). The noninferiority margin was estimated to correspond to preservation 50% (for assessment of odds ratio) of the lower boundary of the 95% confidence interval for the efficacy of warfarin as compared with no anticoagulation, so the assessed noninferiority margin of odds ratio was 1.14.

Figure 2. Risk of bias summary of all included studies.

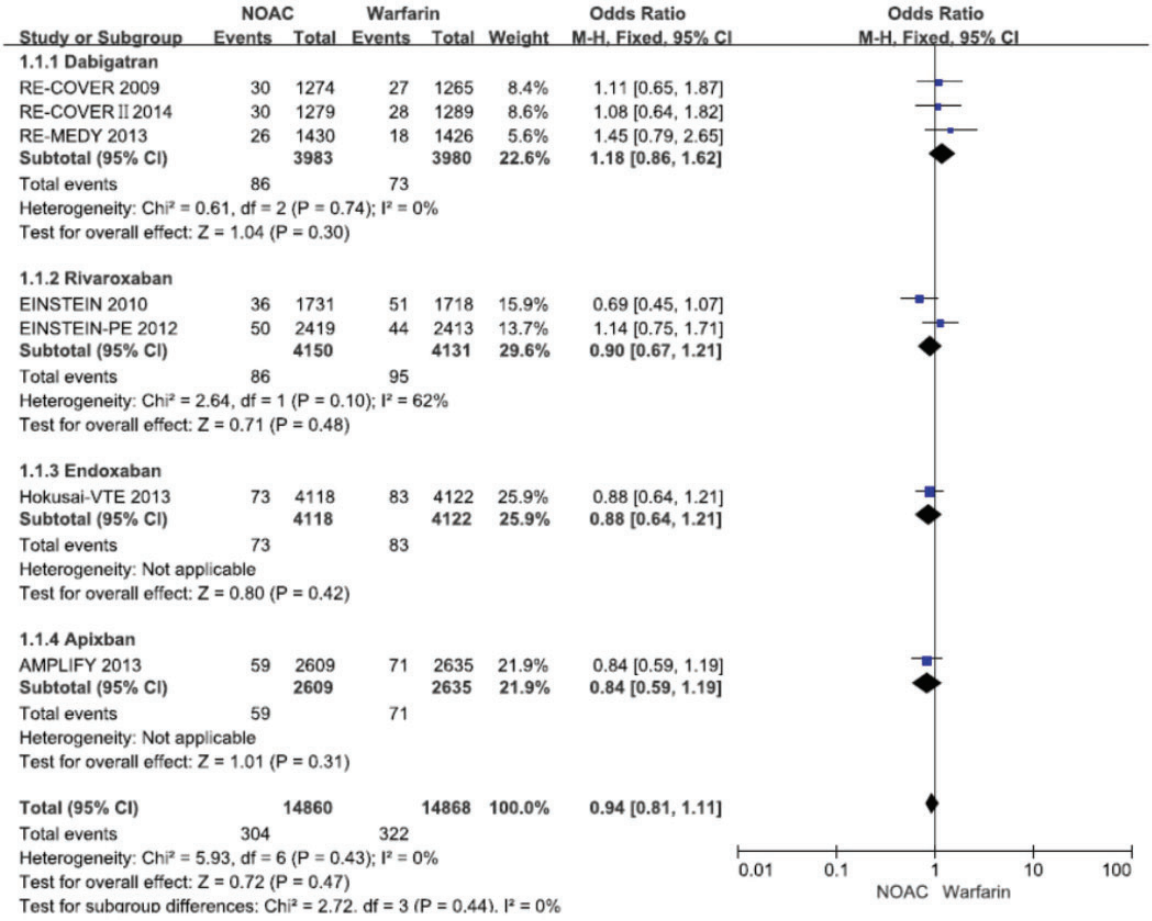


Outcomes

Efficacy outcomes

Recurrent venous thromboembolism. Seven studies[8–14] that included 14,860 patients from non–vitamin K antagonist oral anticoagulants group and 14,868 patients from warfarin group reported recurrent venous thromboembolism. Pooled analysis showed that there was no significant difference in recurrent venous thromboembolism between non–vitamin K

Figure 3. Forest plot of comparison of recurrent venous thromboembolism between NOACs and warfarin.



antagonist oral anticoagulants and warfarin groups in the fixed-effects model (odds ratio 0.94 [95%confidence interval, 0.81 to 1.11], $p = 0.47$). The upper boundary of 95% confidence interval was within the non-inferiority margin, which indicated that the non–vitamin K antagonist oral anticoagulants were non-inferior with regard to the prevention of recurrent venous thromboembolism to warfarin. There was no substantial heterogeneity among the studies ($I^2 = 0\%$, $p = 0.43$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were no significant differences in recurrent venous thromboembolism in dabigatran and rivaroxaban treatment trials (Figure 3).

Venous thromboembolism-related death/ fatal pulmonary embolism

Seven studies[8–14] that included 14,860 patients from non–vitamin K antagonist oral anticoagulants group and 14,868 patients from warfarin group reported venous thromboembolism-related death or fatal pulmonary embolism. Pooled analysis showed that there was no significant difference in venous thromboembolism-related death or fatal pulmonary embolism between non–vitamin K antagonist oral anticoagulants and warfarin groups in the fixed-effects model (odds ratio 1.00 [95%confidence interval 0.63 to 1.60], $p = 0.99$). The upper boundary of 95% confidence interval was beyond non-inferiority margin, which indicated that the non–vitamin K antagonist oral anticoagulants were not similar with regard to the prevention of venous thromboembolism-related death or fatal pulmonary embolism to warfarin. There was no substantial heterogeneity among the studies ($I^2 = 0\%$, $p = 0.59$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were no significant difference in venous thromboembolism-related death or fatal

Figure 4. Forest plot of comparison of death related to venous thromboembolism between NOACs and warfarin.

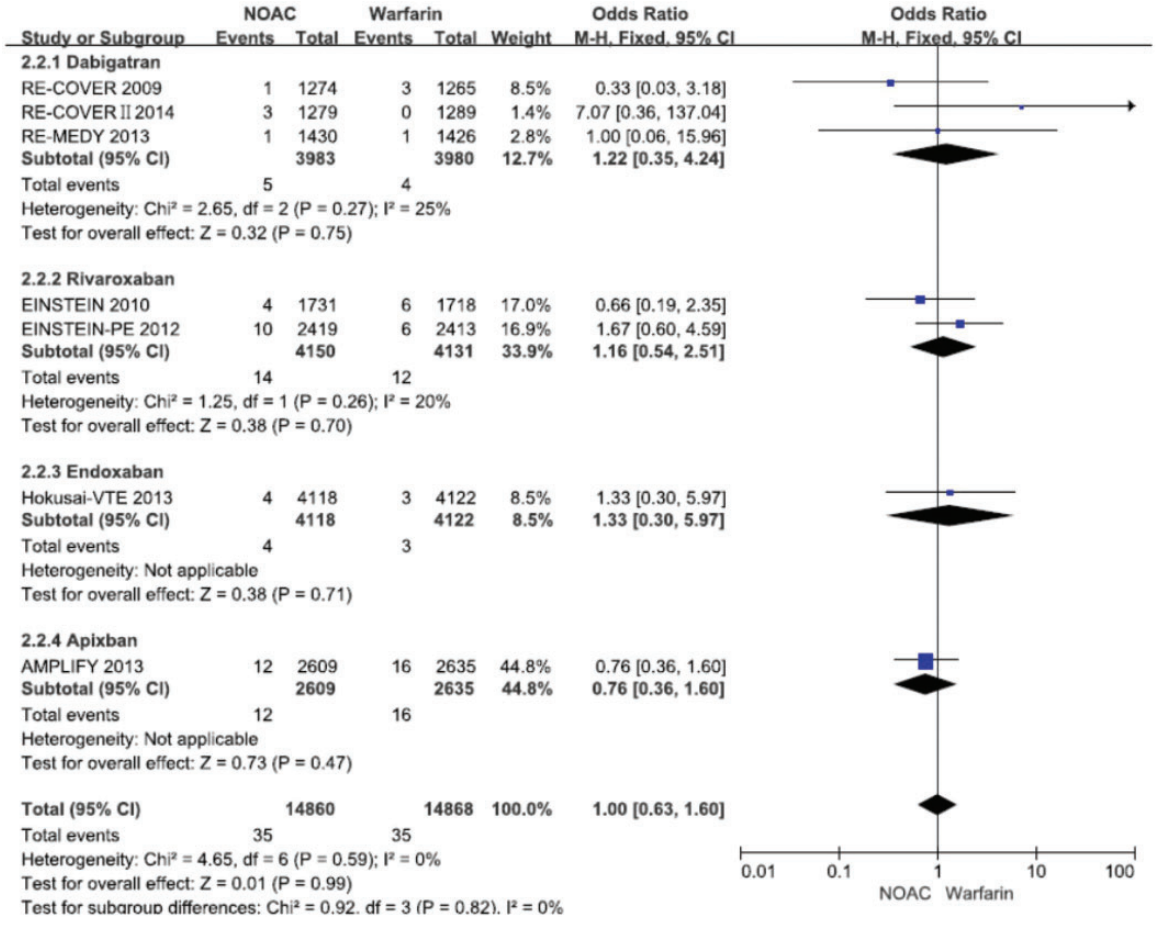
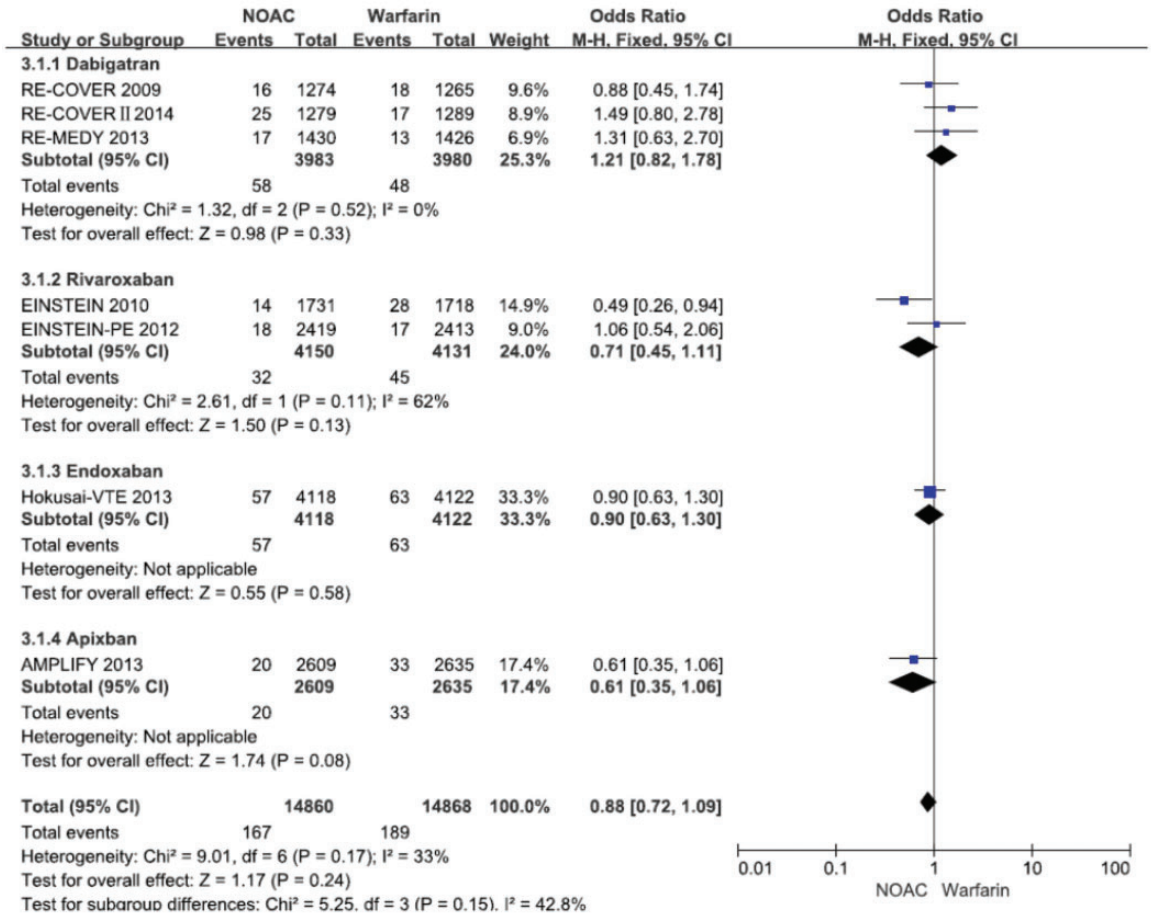


Figure 5. Forest plot of comparison of symptomatic deep-vein thrombosis between NOACs and warfarin.



pulmonary embolism in dabigatran and rivaroxaban treatment trials (Figure 4).

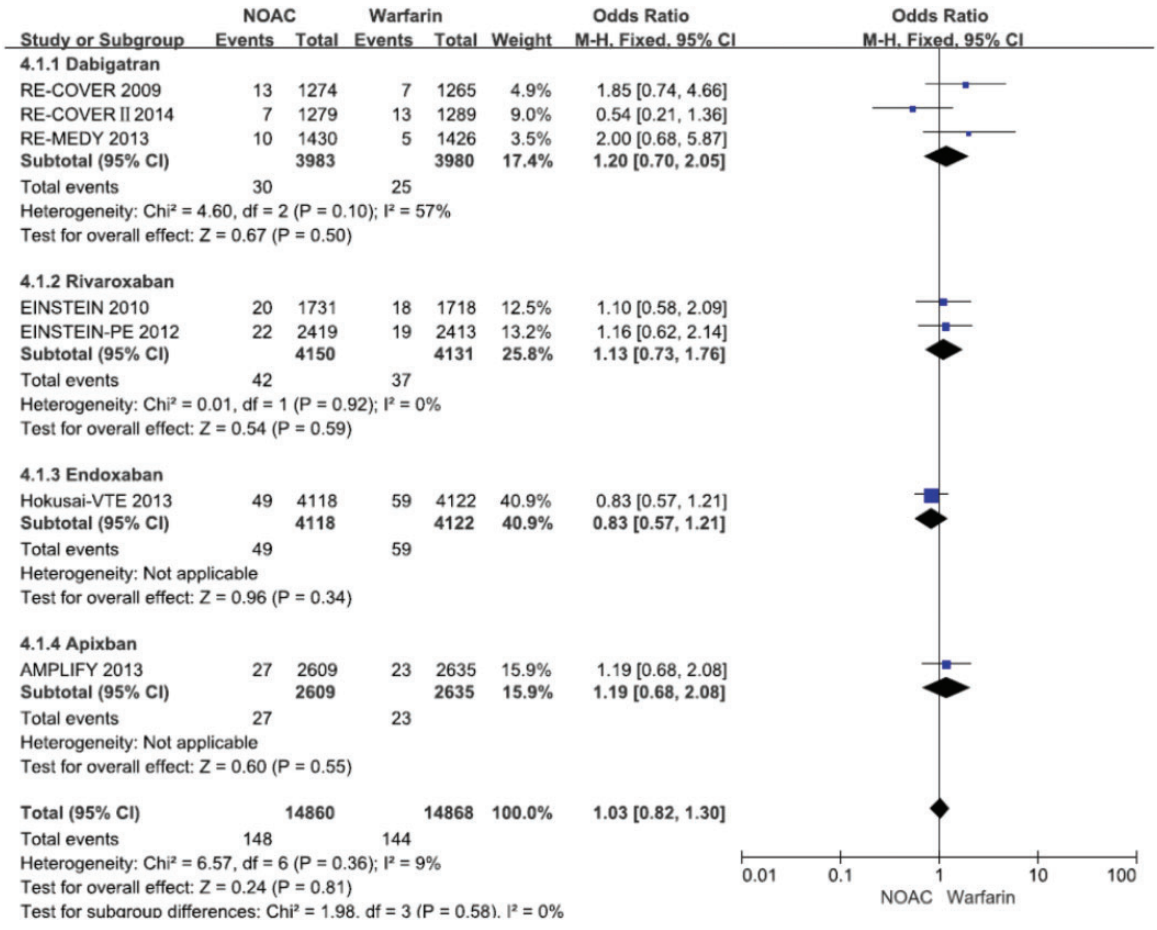
Symptomatic deep-vein thrombosis

Seven studies[8–14] that included 14,860 patients from non–vitamin K antagonist oral anticoagulants group and 14,868 patients from warfarin group reported symptomatic deep vein thrombosis. Pooled analysis showed that there was no significant difference in symptomatic deep vein thrombosis between non–vitamin K antagonist oral anticoagulants and warfarin groups in the fixed-effects model (odds ratio 0.88 [95%confidence interval 0.72 to 1.09], $p = 0.24$). The upper boundary of 95% confidence interval was within non-inferiority margin, which indicated that the non–vitamin K antagonist oral anticoagulants were noninferior with regard to the prevention of symptomatic deep vein thrombosis to warfarin. There was no substantial heterogeneity among the studies ($I^2 = 33.4\%$, $p = 0.17$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were no significant differences in symptomatic deep vein thrombosis in dabigatran and rivaroxaban treatment trials (Figure 5).

Symptomatic nonfatal pulmonary embolism

Seven studies[8–14] that included 14,860 patients from non–vitamin K antagonist oral anticoagulants group and 14,868 patients from warfarin group reported symptomatic nonfatal pulmonary embolism. Pooled analysis showed that there was no significant difference in symptomatic nonfatal pulmonary embolism between non–vitamin K antagonist oral anticoagulants and warfarin groups in the fixed-effects model (odds ratio 1.03 [95%confidence interval 0.82 to 1.30], $p = 0.81$). The upper boundary of 95% confidence interval was beyond non-inferiority margin, which indicated that the non–vitamin K antagonist oral anticoagulants were not similar with regard to the prevention of symptomatic nonfatal pulmonary

Figure 6. Forest plot of comparison of symptomatic nonfatal pulmonary embolism between NOACs and warfarin.



embolism to warfarin. There was no substantial heterogeneity among the studies ($I^2 = 8.7\%$, $p = 0.36$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were no significant differences in symptomatic nonfatal pulmonary embolism in dabigatran and rivaroxaban treatment trials (Figure 6).

Safety outcomes

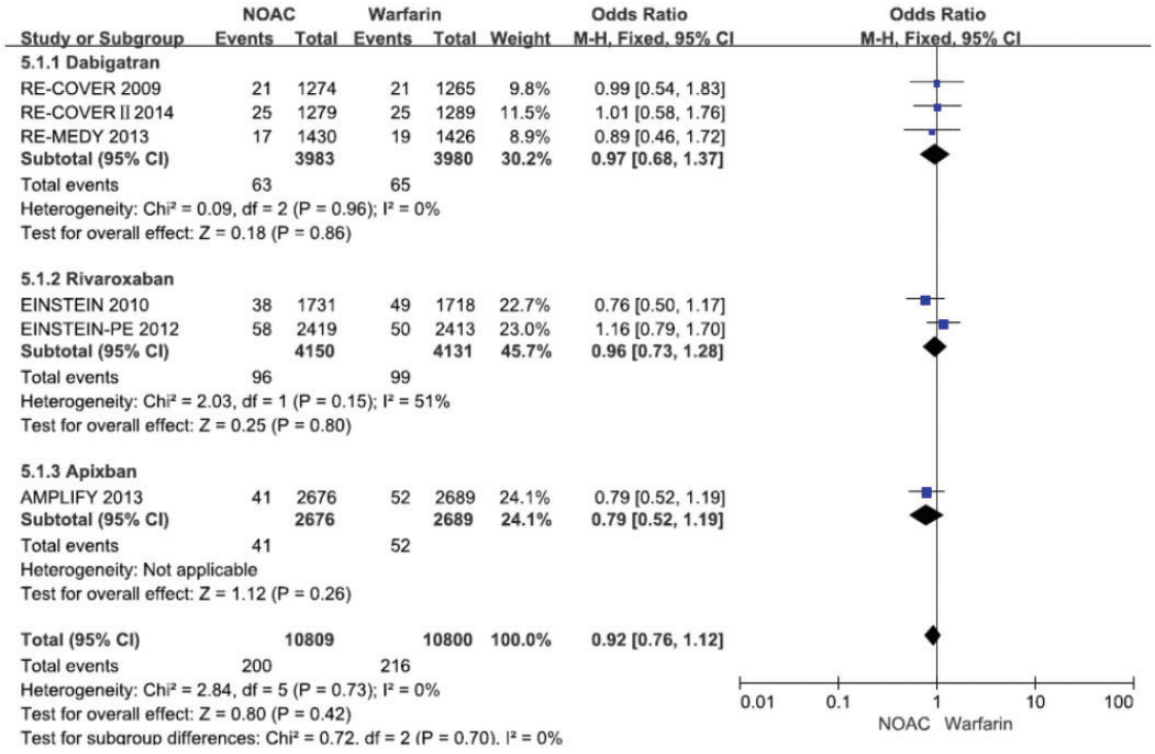
All deaths

Six studies[8–11,13,14] that included 10,809 patients from non–vitamin K antagonist oral anticoagulants group and 10,800 patients from warfarin group reported all death. Pooled analysis showed that there was no significant difference in all death between non–vitamin K antagonist oral anticoagulants and warfarin groups in the fixed-effects model (odds ratio 0.92 [95%confidence interval 0.76 to 1.12], $p = 0.42$). Since the upper boundary of 95% confidence interval was within non-inferiority margin, the indicated non–vitamin K antagonist oral anticoagulants were noninferior with regard to the prevention of all death to warfarin. There was no substantial heterogeneity among the studies ($I^2 = 0\%$, $p = 0.73$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were no significant differences in all death in dabigatran and rivaroxaban treatment trials (Figure 7).

Major bleeding event

Seven studies[8–14] that included 14,907 patients from non–vitamin K antagonist oral anticoagulants group and 14,907 patients from warfarin group reported major bleeding event. Pooled analysis showed that there was significant decrease in major bleeding event in non–vitamin K antagonist oral anticoagulants group in the fixed-effects model (odds ratio 0.61 [95%confidence interval 0.50 to 0.75], $p < 0.00001$). There was no substantial heterogeneity

Figure 7. Forest plot of comparison of all deaths between NOACs and warfarin.



among the studies ($I^2 = 45.4\%$, $p = 0.09$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were significant decreases in major bleeding event in dabigatran and rivaroxaban treatment trials (Figure 8).

Clinically relevant non-major bleeding event

Seven studies[8–14] that included 14,907 patients from non–vitamin K antagonist oral anticoagulants group and 14,907 patients from warfarin group reported clinically relevant non-major bleeding event. Pooled analysis showed that there was significant decrease in clinically relevant non-major bleeding event in non–vitamin K antagonist oral anticoagulants group in the random-effects model (odds ratio 0.67 [95%confidence interval 0.53 to 0.85], $p = 0.001$). There was substantial heterogeneity among the studies ($I^2 = 86.4\%$, $p < 0.00001$). When analysed on the basis of different types of non–vitamin K antagonist oral anticoagulants, there were significant decreases in clinically relevant non-major bleeding event in dabigatran treatment trials, but no significant difference in rivaroxaban treatment trials (Figure 9).

Heterogeneity assessment

Heterogeneity was explored using sensitivity analyses. We analysed the efficacy and safety of non–vitamin K antagonist oral anticoagulants using random- and fixed-effects model and the results did not differ between two models. The results are shown in Table 4.

Publication bias assessment

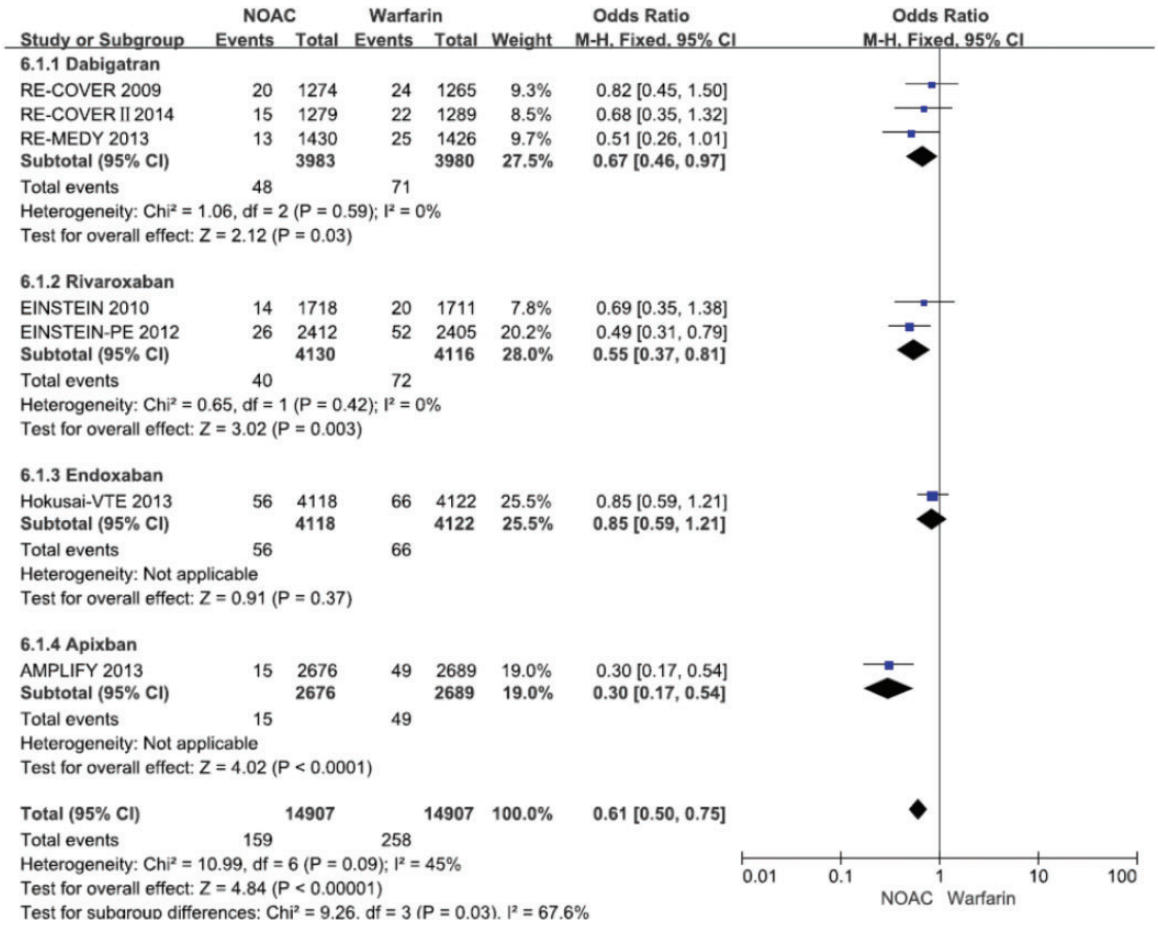
On the basis of funnel plot analysis, the effect points of the seven studies are roughly the inverted funnel type with the centre of the combined effect and the roughly symmetrical distribution, but the number of studies is too small to completely exclude the publication bias of the literature (Figure 10).

Discussion

Summary of evidence

Our study showed that compared with warfarin, recurrent venous thromboembolism, death related to venous thromboembolism or fatal pulmonary

Figure 8. Forest plot of comparison of major bleeding event between NOACs and warfarin.



embolism, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism and all deaths are similar in non–vitamin K antagonist oral anticoagulants group, but major bleeding event and clinically relevant non-major bleeding event decreased in non–vitamin K antagonist oral anticoagulants group. When studies were separately analysed on the basis of types of non–vitamin K antagonist oral anticoagulants, effects and safety showed the same trends.

Comparison with other studies

Our findings were generally consistent with the previous meta-analysis,[5,6] which showed similar or superior efficacy and safety of non–vitamin K antagonist oral anticoagulants compared with warfarin. But indirect comparisons indicate differences in the risk of clinically relevant bleeding events, which weredependent on the pharmacologic properties of non–vitamin K antagonist oral anticoagulants and diseases of patients. For example, dabigatran has a single renal route of elimination and a distinct variability in patients receiving the same dose, which may increase the bleeding risk, especially when using a higher dose.[19] So individualised therapy should be considered in patients with renal impairment.[4] Rivaroxaban has a short half-life, which cause less effective due to its rapid elimination, so the current once-daily regimen may result in insufficient concentrations at the end of a 24-h day.[20] Due to these pharmacologic properties, dabigatran and rivaroxaban may require more individualised dosing.

non–vitamin K antagonist oral anticoagulants' pharmacokinetics is affected by obesity, and meta-analysis showed that compared to vitamin K antagonists/low molecular weight heparin, venous thromboembolism recurrence in patients with obesity and morbid obesity treated with non–vitamin K antagonist oral anticoagulants was similar and non–vitamin K antagonist oral anticoagulants could reduce the risk of major bleeding.[21] When used in cancer-associated venous thromboembolism, oral factor Xa inhibitors reduced

Figure 9. Forest plot of comparison of clinically relevant non-major bleeding event between NOACs and warfarin.

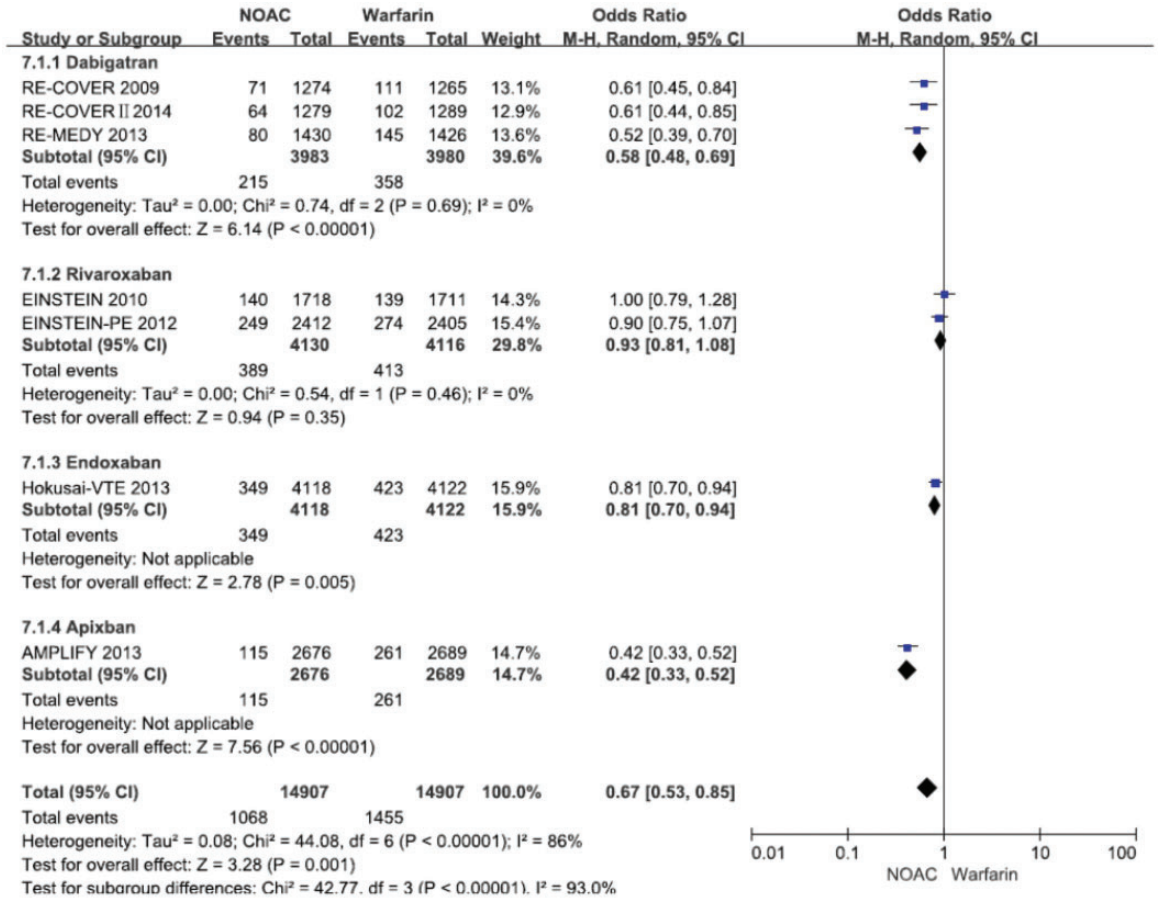


Table 4. The results of efficacy and safety of NOACs by using random- or fixed-effects model.

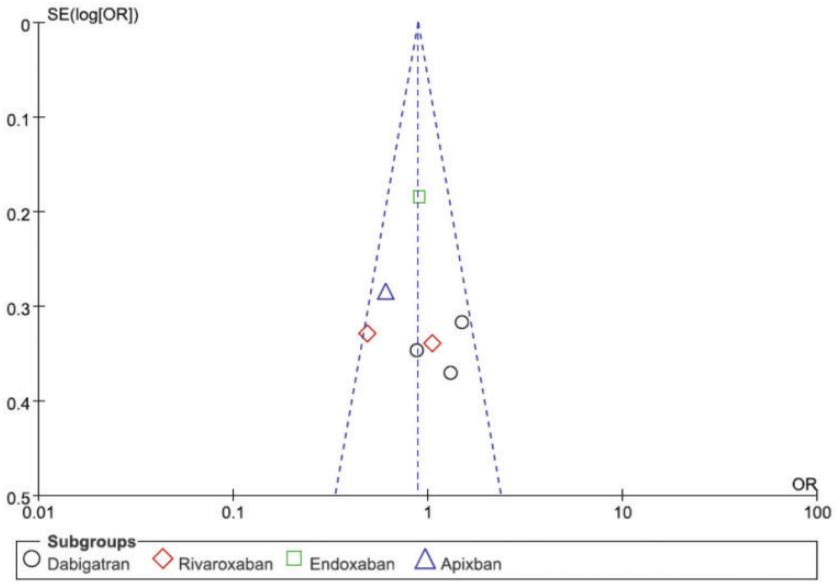
	Recurrent venous thromboembolism	Death related to venous thromboembolism/ fatal pulmonary embolism	Symptomatic deep-vein thrombosis	Symptomatic nonfatal pulmonary embolism	All death	Major bleeding	Clinically relevant non-major bleeding
Fixed-effects model	0.94 (0.8–1.11)	1.0 (0.62–1.60)	0.88 (0.72–1.09)	1.03 (0.82–1.30)	0.92 (0.76–1.12)	0.61 (0.50–0.75)	0.71 (0.66–0.77)
random-effects model	0.94 (0.8–1.11)	0.97 (0.60–1.58)	0.89 (0.68–1.17)	1.04 (0.81–1.34)	0.92 (0.76–1.12)	0.60 (0.45–0.80)	0.67 (0.53–0.85)

the risk of recurrent venous thromboembolism compared with low molecular weight heparin, but the likelihood of major bleeding was inconsistent.[22,23] These characteristics of non–vitamin K antagonist oral anticoagulants indicate the importance of individualised therapy and it is also necessary to look for INR-like indicators to assess the target dose of non–vitamin K antagonist oral anticoagulants.[24]

Strengths and limitations

This review updated the results of efficacy and safety of non–vitamin K antagonist oral anticoagulants for venous thromboembolism, and comprehensively assessed the efficacy (including recurrent venous thromboembolism, venous thromboembolism-related death or fatal pulmonary embolism, symptomatic

Figure 10. Assessment of publication bias by using funnel plot.



deep vein thrombosis, symptomatic nonfatal pulmonary embolism) and safety (including all death, major bleeding event and clinically relevant bleeding event) between non–vitamin K antagonist oral anticoagulants and warfarin.

Our review had limitations that deserve further consideration. First, the results from the study may lack broad generalisability to patients treated in clinical settings due to the presence of highly selective patients in the included randomized controlled trials. Furthermore, several serious flaws in randomized controlled trials comparing non–vitamin K antagonist oral anticoagulants with vitamin K antagonists raised concerns about superiority claims for the non–vitamin K antagonist oral anticoagulants. For example, the outcomes of different studies were adjusted for different confounding factors, which made it difficult to compare the results across the included studies. Second, there are only seven studies included in our meta-analysis and the results for apixaban and edoxaban relied on a single randomized controlled trial, which may omit exact effects and safety of non–vitamin K antagonist oral anticoagulants. Third, we did not review non-English publications. Furthermore, the efficacy and safety of non–vitamin K antagonist oral anticoagulants may be influenced by actual adherence patterns, patient baseline risks and other real-world differences that may not be predicted by randomized controlled trial results.[25]

Conclusions and implications

Our meta-analysis of randomized controlled trials showed that the efficacy of non–vitamin K antagonist oral anticoagulants for venous thromboembolism is comparable to that of warfarin, but the risk of clinical bleeding is lower than that in warfarin. However, randomized controlled trials excluded influences of patient baseline risks, actual adherence patterns and other real-world differences, so more evidence from observational studies is needed for non–vitamin K antagonist oral anticoagulants on their efficacy and safety in the real-world settings.

Declarations

Competing interests: The authors declare that there is no conflict of interest.

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Guarantor: Yan Zhuang.

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