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 0.95 [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. 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.

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. 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.\textsuperscript{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 apixaban) 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

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**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 edoxaban with warfarin and one trial$^{12}$ compared apixaban 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-analysis of studies included in the meta-analysis.

### 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 |
|-------------|---------|------------------------|-------------|-------------|--------|----------|------|-----|
| RE-COVER 2009 | Multi-nation | 6 | Dabigatran 150 mg twice daily | 1274 | 55.0 | 54.4 | 42.0 | 43.7 |
| EINSTEIN 2010 | Multi-nation | 3, 6, 12 | Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily | 1731 | 55.8 | 56.4 | 42.6 | 42.0 |
| EINSTEIN-PE 2012 | Multi-nation | 3, 6, 12 | Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily | 2419 | 57.9 | 56.3 | 44.8 | 48.3 |
| Hokusai-VTE 2013 | Multi-nation | 12 | Endoxaban 60 mg once daily, or 30 mg in patients with Ccr < 60 ml | 4118 | 55.7 | 55.9 | 42.7 | 42.8 |
| AMPLE 2013 | Multi-nation | 6 | Apixaban 10 mg twice daily for 7 days, 5 mg twice daily for 6 months | 2691 | 57.2 | 56.7 | 39.7 | 40.9 |
| RE-MEDY 2013 | Multi-nation | 36 | Dabigatran 150 mg twice daily | 1430 | 42.6 | 55.4 | 39.1 | 38.9 |
| RE-COVER II 2014 | Multi-nation | 6 | Dabigatran 150 mg twice daily | 1280 | 42.8 | 55.1 | 39.0 | 39.8 |
Table 3. The primary outcomes of included studies.

| Study, year      | Recurrent venous thromboembolism | Death related to venous thromboembolism/fatal pulmonary embolism | Symptomatic deep-vein thrombosis | Symptomatic nonfatal pulmonary embolism | All deaths | Major bleeding | Clinically relevant non-major bleeding event |
|------------------|----------------------------------|---------------------------------------------------------------|----------------------------------|----------------------------------------|------------|----------------|---------------------------------------------|
|                  | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    | NOAC    | VKA    |
| RE-COVER 2009    | 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    | 36/1731 | 51/1718| 4/1731  | 6/1718 | 14/1731 | 28/1718| 20/1731 | 18/1718| 38/1731 | 49/1718| 14/1731 | 20/1711| 140/1718| 139/1711|
| EINSTEIN-PE 2012 | 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 | 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     | 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     | 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 | 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. 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.

**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

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

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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 pulmonary embolism.
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 embolism.
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
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
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 on the basis of clinically relevant bleeding events, which were dependent 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
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

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) |

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
decreased 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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Ethics approval: As a review of existing data, ethical approval was not required.
Guarantor: Yan Zhuang.
Contributorship: Yan Zhuang contributed to study design. Data were collected and analysed by Yan Zhuang and Lin-feng Dai. Yan Zhuang and Ming-qi Cheng drafted/revised the article. The final version has been approved by all authors.
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