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Comparative efficacy and safety of oral anticoagulants for the treatment of venous thromboembolism in the patients with different renal functions: a systematic review, pairwise and network meta-analysis

Xiaole Su,[1,2] Bingjuan Yan,[2] Lihua Wang,[2] Hong Cheng,[1] Yipu Chen [1]

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[1]Department of Nephrology, Beijing Anzhen Hospital, Capital Medical University, Chaoyang District, Beijing, China
[2]Department of Nephrology, Shanxi Medical University Second Hospital, Shanxi Kidney Disease Institute, Taiyuan, Shanxi, China

Correspondence to
Dr Yipu Chen;
chen_yipu@163.com

ABSTRACT

Objectives To compare the efficacy and safety of direct oral anticoagulants (DOACs) in patients with venous thromboembolism (VTE) and different renal functions.

Design Systematic review containing pairwise and Bayesian network meta-analysis of randomised controlled trials (RCTs).

Data sources MEDLINE, EMBASE and Cochrane Library.

Eligibility criteria RCTs reporting the efficacy and safety outcomes of DOACs in different creatinine clearance (CrCl) subgroups.

Data extraction and synthesis Data extraction and quality assessment were undertaken by two independent reviewers. Data were pooled using the DerSimonian-Laird method in pairwise meta-analysis. Network meta-analysis within a Bayesian framework was conducted.

Results Data from 10 RCTs were included. In the treatment of acute VTE, DOACs did not significantly reduce recurrent VTE or VTE-related death (OR, 0.96; 95% CI, 0.82 to 1.11) but significantly reduced bleeding events (0.76, 0.68 to 0.90) compared with warfarin. In the extended treatment of VTE, DOACs produced significant benefits in recurrent VTE or VTE-related death (0.23, 0.16 to 0.29), but significantly increased bleeding events (1.86, 1.04 to 3.33) compared with placebo/aspirin. There were no significant differences in efficacy and safety of DOACs among the three CrCl stratified subgroups in acute and extended treatment of VTE (p for subgroup heterogeneity >0.1). Bayesian network meta-analysis suggested that apixaban 2.5 mg and 5 mg two times per day were associated with a lower risk of bleeding than dabigatran, rivaroxaban, warfarin and aspirin in the subgroup with CrCl >80 mL/min.

Conclusions For the treatment of acute VTE, DOACs are similar to warfarin in reducing recurrent VTE and VTE-related death but are significantly superior to warfarin in reducing the risk of bleeding. For the efficacy and safety of DOACs across different CrCl stratifications (30–50, 50–80 and more than 80 mL/min), no significant difference was found. In light of minimal evidence, apixaban might be associated with a lower risk of bleeding in patients with VTE and CrCl >80 mL/min.

Strengths and limitations of this study

- ► The systematic review, pairwise and network meta-analysis included 10 high-quality randomised controlled trials comprising 37 298 patients and attempted to assess the efficacy and safety of direct oral anticoagulants (DOACs) in the patients with venous thromboembolism (VTE) and different renal functions.
- ► Data were classified and pooled based on the creatinine clearance (CrCl) levels in patients receiving acute or extended treatment of VTE.
- ► Network meta-analysis within a Bayesian framework was conducted to explore the relative efficacy and safety profiles of different DOAC interventions in three CrCl stratifications and to attempt to explain partly the source of heterogeneity in pairwise meta-analysis.
- ► The Grading of Recommendations Assessment, Development and Evaluation guidelines and the Confidence in Network Meta-analysis internet application were used to determine the strength of evidence in pairwise and network meta-analysis.
- ► The inadequate sample size and lower event rate in patients with mild to moderate renal impairment (CrCl 30–50 and 50–80 mL/min, respectively) might affect the results of our research.

PROSPERO registration number CRD42018090896.

INTRODUCTION

With a prevalence reaching 10.5%–13.1%, the incidence of chronic kidney disease (CKD) is increasing.[1] Venous thromboembolism (VTE), with an estimated incidence of 0.7–1.4 per 1000 person-years,[2] which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease. There is an increased risk of VTE in patients with nephrotic syndrome,[3]

those receiving maintenance dialysis[4] and kidney transplant recipients.[5 6] In a large prospective cohort study, a glomerular filtration rate (GFR) of less than 45 mL/min was associated with a 2.13-fold increased risk of VTE compared with a GFR of more than 90 mL/min.[7]

The introduction of direct oral anticoagulants (DOACs), including direct inhibitors of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban), has changed the landscape of VTE treatment. Based on several landmark randomised controlled trials (RCTs),[8–11] the 2014 European Society of Cardiology Guidelines on acute PE suggested that rivaroxaban, apixaban or dabigatran should be considered as an alternative to vitamin K antagonist (VKA) during extended oral anticoagulation (OAC) therapy.[12] The 2016 American College of Chest Physicians Treatment Guideline for VTE suggested DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) over VKA therapy in patients with VTE and no cancer.[13]

The different pharmacokinetic characteristics of the four DOACs, including the half-life, the elimination process, the administration and the fluctuation of plasma concentrations, might result in different efficacy and safety profiles, especially for the patients with VTE and impaired renal function. In patients with different renal functions, there are currently no RCTs to directly compare the efficacy and safety of the different DOAC regimens, leading to uncertainty in the selection of clinical treatment regimens. Therefore, whether there is a relatively optimal DOAC treatment regimen in patients with VTE and impaired renal function is a prominent issue.

In this systematic review, our aim was to synthesise all the available data from RCTs and then evaluate the therapeutic benefits and adverse effects of DOACs in patients with VTE stratified by different creatinine clearance (CrCl) levels. Furthermore, we attempted to explore whether there is heterogeneity among DOACs by means of a network meta-analysis within a Bayesian framework.

METHODS

Data sources and searches

This systematic review is performed according to a prespecified protocol[14] registered at the International Prospective Register of Systematic Reviews (CRD42018090896), and the report is in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] We searched MEDLINE via Ovid, EMBASE via Ovid and the Cochrane Library database (before July 2019) for RCTs (see online supplemental item 1 for full search terms). The ClinicalTrials.gov website was also searched for RCTs that were registered as completed but not yet published. If a trial was published in more than one publication, we used the most detailed publication.

Study selection and outcome definition

We included RCTs of adult patients with VTE (DVT, PE or both) treated with DOACs (dabigatran, rivaroxaban, apixaban or edoxaban), which reported outcomes in different renal function subgroups. The acute and extended treatment of VTE were both included in our analysis. The control groups included anticoagulant-control group (using warfarin as a control, including warfarin alone and enoxaparin followed by warfarin) and non-anticoagulant-control group (using aspirin or placebo as a control). All trials must have an assessment of the efficacy and safety outcomes of DOACs. The efficacy outcome included recurrent VTE and VTE-related death. The safety outcome included major bleeding and clinically relevant non-major bleeding, which were defined individually by each trial. The definitions of efficacy outcome and safety outcome in every trial are presented in online supplemental table 1. The CrCl was calculated by Cockcroft-Gault formula in all trials, which were expressed as mL/min.

Data extraction and quality assessment

Published reports were obtained for each eligible trial, and relevant information was extracted into a spreadsheet by investigator pairs on the basis of methodological and clinical experience. We used the new Cochrane risk of bias tool for RCTs to assess methodological quality of each study.[16] The literature search, study selection, data extraction and quality assessment were undertaken independently by two authors (XS and BY) using a standardised approach according to the predefined protocol. Disagreement was resolved by consensus or by a third-party arbitrator.

Data synthesis and analysis

Data were classified based on the CrCl levels in patients receiving acute or extended treatment of VTE. The random-effects model was applied to generate the summary values according to DerSimonian-Laird method[17] and the CIs according to Knapp-Hartung modified method.[18] All of the above operations were run using the software Stata V.12.0 (StataCorp). ORs and 95% CIs of individual study were calculated from event numbers and the total population at risk extracted from each trial. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. X^2 test was used to assess the between-subgroup heterogeneity.

Four DOACs were pooled as a whole and compared with controls in pairwise meta-analysis. Network meta-analysis within a Bayesian framework was conducted to explore the relative efficacy and safety profiles of different OAC interventions and to attempt to explain partly the source of heterogeneity in pairwise meta-analysis. Relative effects of different OACs were measured by OR and its 95% credible intervals. The above operations are run by WinBUGS V.1.4.3 and the R2WinBUGS package of the R software V.3.1.1. We used non-informative priors with vague normal (mean, 0; variance, 100 000) and uniform (0–5) prior distributions for parameters such as the means and SDs, respectively.[19] For each analysis, we generated 200 000 simulations for each of the two sets of

different initial values and discarded the first 80 000 simulations as the burn-in period. Convergence was reached when Rhat, the potential scale reduction factor, was close to 1 for each of the parameters using the Brooks-Gelman-Rubin statistic.[20] We selected the model with a lower value of deviance information criterion (DIC), which suggests a more parsimonious model.[21] We used the surface under the cumulative ranking curve (SUCRA) probabilities to rank the treatments.

We summarised strength of evidence (SOE) for each outcome individually according to the Grading of Recommendations Assessment, Development and Evaluation guidelines.[22] The Confidence in Network Meta-analysis internet application was used to determine the confidence in network estimates.[23] Confidence was initially considered to be high and was maintained or downgraded to moderate, low or very low according to the assessment of the quality of the evidence.[24]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of our research.

RESULTS

Study search and study characteristics

A total of 6089 records were identified during our search, and 601 potentially eligible full-text articles were retrieved (figure 1). Overall, 10 RCTs reported in eight articles,[8–10 25–29] comprising 37 298 eligible patients, were eventually included in our analysis (see online supplemental table 2 for the details of included studies). All 10 trials were multicentre studies with an average study sample size of 3730 participants. The DOACs in these trials included dabigatran, rivaroxaban, apixaban and edoxaban. In all five trials for the treatment of acute VTE, DOACs were compared with warfarin alone[26] or enoxaparin followed by warfarin.[8–10 29] For the extended treatment of VTE, DOACs were compared with placebo in three trials,[25–27] with aspirin in one trial,[28] and with warfarin in one trial.[27] To date, no RCT has conducted head-to-head comparisons between different DOACs. Eight RCTs excluded patients with a CrCl of <30 mL/min, whereas the cut-off was slightly lower (<25 mL/min) in the two RCTs that included apixaban treatment.[8 25] Nine RCTs involved three CrCl stratifications (25/30–50 mL/min, 50–80 mL/min and >80 mL/min), and one RCT involved two CrCl stratifications (30–50 and >50 mL/min).[10] The detailed results of the risk of bias assessment in the included trials are summarised in online supplemental table 3. The overall methodological quality of the 10 RCTs was moderate to high.

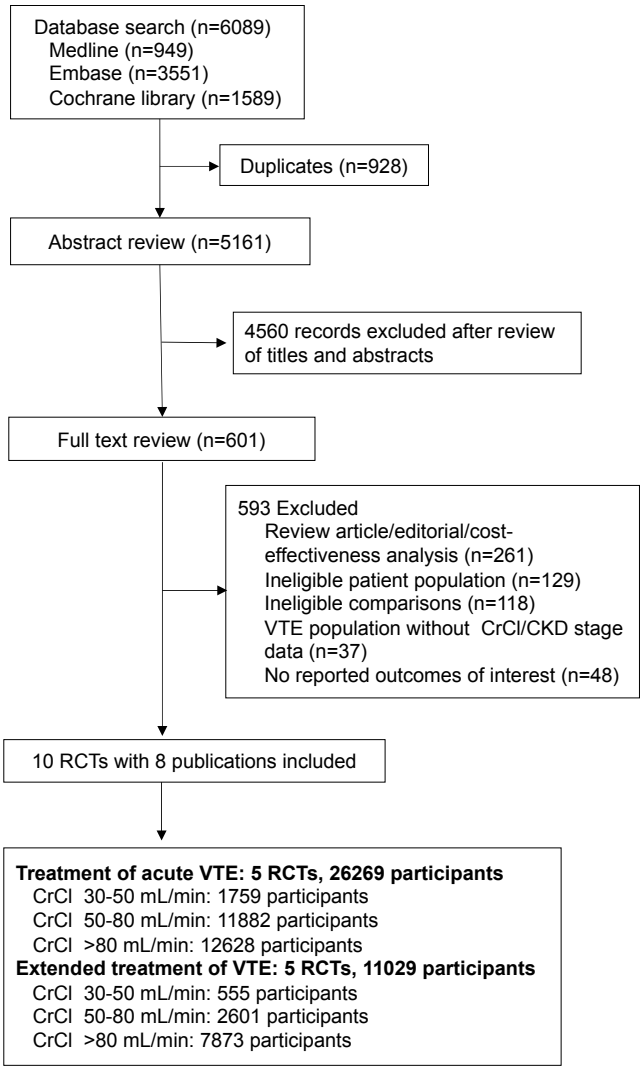

Figure 1 Summary of trial identification and selection. CKD, chronic kidney disease; CrCl, creatinine clearance; RCTs, randomised controlled trials; VTE, venous thromboembolism.

Pairwise meta-analysis

The efficacy outcome

No statistically significant difference was observed between DOACs as a whole and warfarin for recurrent VTE or VTE-related death in patients with acute VTE (OR, 0.96; 95% CI, 0.82 to 1.11; 5 RCTs enrolled 26 269 patients with 703 events; high SOE) without significant heterogeneity (I^2=0%). In patients with extended treatment for VTE, the use of DOACs produced significant benefits for recurrent VTE or VTE–related death compared with placebo/aspirin (OR, 0.23; 95% CI, 0.16 to 0.29; 4 RCTs enrolled 8205 patients with 260 events; moderate SOE) without significant heterogeneity (I^2=0%).

The effects of DOACs on recurrent VTE or VTE-related death in patients with acute and extended treatment of VTE were not significantly different among the three subgroups of CrCl stratifications (p values for subgroup heterogeneity were 0.45 and 0.78, respectively). The RE-MEDY trial comparing dabigatran with warfarin is the only trial designed to specifically evaluate the efficacy of DOAC against VKA during the extended treatment of VTE, in which no significant difference was found for recurrent VTE or VTE-related death among the subgroups of different CrCl stratifications.[27]

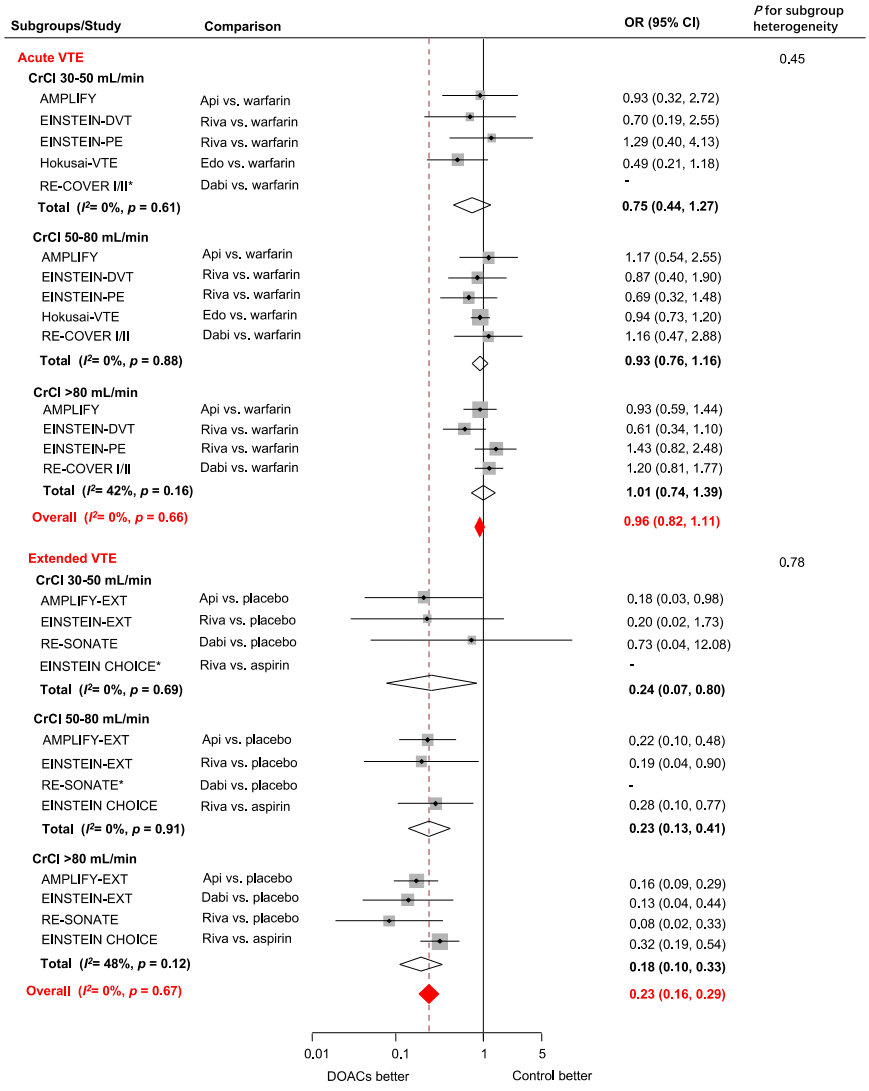

Figure 2 Summary of the efficacy outcome of DOACs therapy according to different CrCl subgroups. *Zero event in at least one treatment arm. Api, apixaban; CrCl, creatinine clearance; Dabi, dabigatran; DOACs, direct oral anticoagulants; Edo, edoxaban; Riva, rivaroxaban; VTE, venous thromboembolism.

The details of the efficacy outcomes are presented in figure 2.

The safety outcome

In patients with acute VTE, DOACs therapy significantly reduced the risk of bleeding events compared with warfarin (OR, 0.76; 95% CI, 0.68 to 0.90; 26 182 patients with 2473 events; moderate SOE). Conversely, in patients with extended treatment of VTE, the use of DOACs significantly increased the risk of bleeding events compared with aspirin/placebo (OR, 1.86; 95% CI, 1.04 to 3.33; 6859 patients with 209 events; low SOE). However, significant heterogeneity was found in the safety outcome for both acute and extended VTE treatment (I^2=47.6% and 55.1%; p for heterogeneity=0.02 and 0.02, respectively). The subgroup analysis suggested that the main contribution of heterogeneity across studies was from the subgroup of CrCl >80 mL/min (I^2=85% in acute treatment and 78.5% in extended treatment).

In patients with acute and extended treatment of VTE, no significant difference in bleeding events was found among the three subgroups of CrCl stratifications (p for subgroup heterogeneity=0.63 and 0.21, respectively).

The details of the safety outcomes are presented in figure 3. The SOE grades (low, moderate or high) and the details of all comparisons and outcomes are summarised and provided in online supplemental table 4.

Bayesian network meta-analysis

Network meta-analysis within a Bayesian framework was conducted to explore the relative efficacy and safety of different treatment regimens and to attempt to explain the source of heterogeneity in pairwise meta-analysis. There were seven, nine and eight treatment regimens in patients with VTE with CrCl of 30–50, 50–80 and more than 80 mL/min, respectively. The networks of eligible comparisons are shown in online supplemental figure 1. The DIC values from the fixed consistency model were

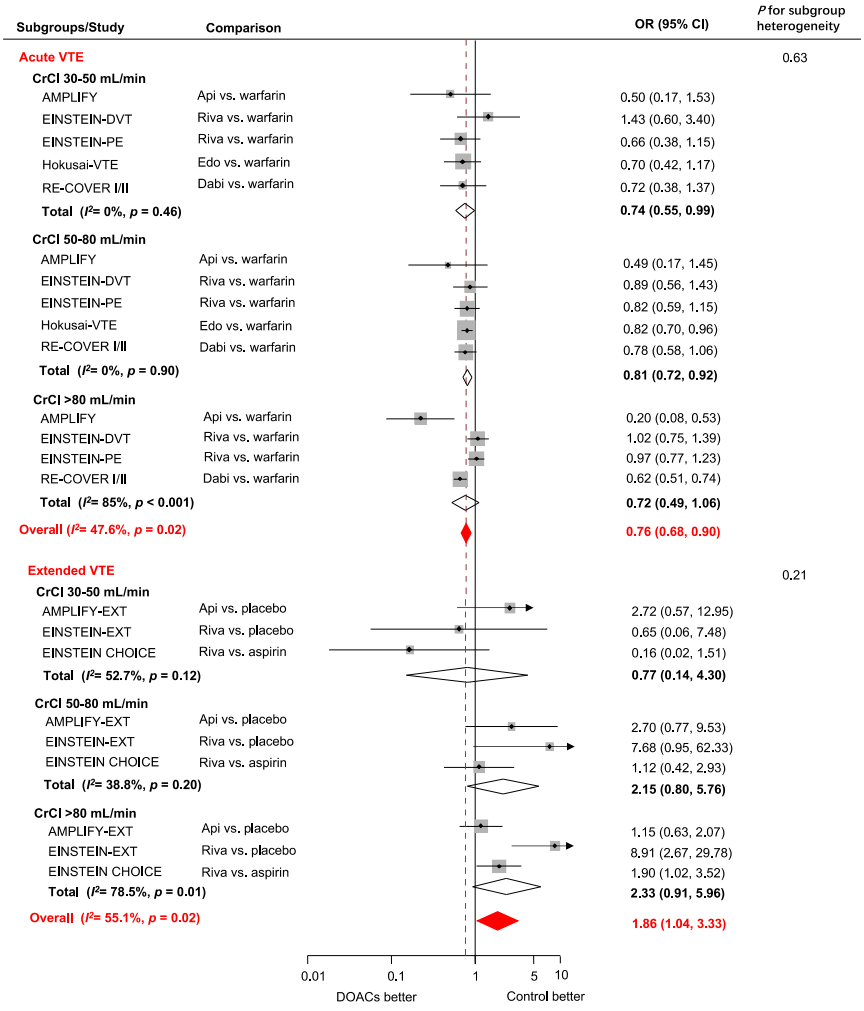

Figure 3 Summary of the safety outcome of DOACs therapy according to different CrCl subgroups. Api, apixaban; CrCl, creatinine clearance; Dabi, dabigatran; DOACs, direct oral anticoagulants; Edo, edoxaban; Riva, rivaroxaban; VTE, venous thromboembolism.

the lowest, which indicates that it was the preferred model (online supplemental table 5). The primary outcomes of the Bayesian network meta-analysis from the three CrCl subgroups, including recurrent VTE or VTE-related death and bleeding events, are summarised in figure 4.

In patients with VTE with CrCl of 30–50 mL/min and 50–80 mL/min, there was no significant difference in recurrent VTE or VTE-related death and bleeding events between any two OACs (figure 4A,B).

In patients with VTE with CrCl greater than 80 mL/min, the significant differences between treatment regimens were mainly from the safety outcomes (figure 4C, the upper triangle with yellow shading). Apixaban 2.5 mg and 5 mg two times per day were associated with reduced bleeding risks compared with the other treatment regimens, including dabigatran 150 mg two times per day, rivaroxaban 10 mg and 20 mg once daily, warfarin and aspirin. No significant difference was found between apixaban 2.5 mg and 5 mg two times per day. Dabigatran 150 mg two times per day was superior to rivaroxaban 20 mg once daily and warfarin in reducing bleeding events: the ORs (95% CIs) were 0.61 (0.47 to 0.81) and 0.62 (0.51 to 0.74), respectively. These results might partly explain the source of heterogeneity in pairwise meta-analysis, especially when bleeding events were analysed in the subgroup of CrCl greater than 80 mL/min.

Because almost all the 95% CIs of the SUCRAs overlapped widely in all three CrCl subgroups, the implications of SUCRA might be limited (online supplemental table 6). Only one to two closed loops were formed, and no significant inconsistency was identified (online supplemental figure 2). The confidence ratings for the effect estimates of outcomes are presented in online supplemental table 7, most of which were low and very low.

DISCUSSION

How to carry out reasonable anticoagulation therapy for VTE in the patients with renal insufficiency is a very important clinical issue. For acute and extended treatments in patients with VTE with different kidney functions, the subgroup analyses of several large RCTs have

A: CrCl 30-50 mL/min								
Api 5 mg	1.20 (0.43,3.45)	1.04 (0.31,3.45)	1.09 (0.33,3.57)	0.66 (0.17,2.56)	1.52 (0.56,4.55)	0.48 (0.11,1.75)	—	—
0.97 (0.21,2.99)	Riva 20 mg	0.85 (0.39,1.75)	0.88 (0.45,1.75)	0.54 (0.09,2.94)	1.27 (0.81,1.99)	0.38 (0.07,1.85)	—	—
5.66 (0.38,28.83)	6.79 (0.56,26.94)	Dabi 150 mg	1.03 (0.47,2.27)	0.65 (0.09,3.85)	1.47 (0.83,2.86)	0.46 (0.08,2.63)	—	—
2.04 (0.39,6.39)	2.55 (0.63,7.65)	0.92 (0.06,3.73)	Edo 30 mg	0.61 (0.11,3.13)	1.41 (0.83,2.51)	0.43 (0.08,2.22)	—	—
0.85 (0.03,4.32)	1.23 (0.04,6.51)	0.49 (0.01,2.61)	0.75 (0.02,3.33)	Api 2.5 mg	2.27 (0.47,14.29)	0.71 (0.15,3.33)	—	—
0.85 (0.25,2.20)	1.06 (0.43,2.35)	0.39 (0.03,1.41)	0.52 (0.18,1.05)	5.46 (0.16,29.1)	Warfarin	0.31 (0.06,1.41)	—	—
0.19(0.02,0.72)	**0.24(0.02,0.85)**	**0.09(0.01,0.42)**	**0.13(0.01,0.54)**	0.58 (0.04,2.09)	**0.26(0.02,0.88)**	Placebo	—	—
B: CrCl 50-80 mL/min								
Api 5 mg	1.71 (0.73,6.17)	1.49 (0.62,5.56)	1.67 (0.71,5.81)	0.98 (0.28,6.71)	0.81 (0.32,2.48)	1.08 (0.34,6.45)	2.04 (0.88,7.19)	**0.24(0.08,0.91)**
1.87 (0.75,3.89)	Riva 20 mg	0.86 (0.59,1.28)	0.96 (0.72,1.32)	0.59 (0.24,2.14)	0.35 (0.11,1.93)	0.64 (0.26,2.28)	1.17 (0.92,1.55)	**0.11(0.03,0.55)**
1.17 (0.39,2.82)	0.68 (0.23,1.49)	Dabi 150 mg	1.09 (0.77,1.56)	0.66 (0.24,2.67)	0.39 (0.11,2.09)	0.71 (0.26,2.61)	1.34(1.00,1.92)	**0.13(0.04,0.69)**
1.61 (0.71,3.32)	0.92 (0.47,1.64)	1.56 (0.65,3.18)	Edo 60 mg	0.61 (0.23,2.39)	0.36 (0.11,1.98)	0.65 (0.25,2.34)	1.21(1.00,1.53)	**0.12(0.04,0.58)**
1.36 (0.09,6.02)	0.72 (0.05,2.74)	1.32 (0.08,5.89)	0.86 (0.06,3.71)	Riva 10 mg	0.42 (0.11,4.59)	0.91 (0.33,3.17)	1.43 (0.54,5.24)	0.13 (0.03,1.25)
1.03 (0.24,2.89)	0.64 (0.13,2.02)	0.40 (0.03,1.57)	0.72 (0.16,2.28)	2.47 (0.11,14.52)	Api 2.5 mg	1.03 (0.25,9.43)	1.94 (0.63,11.36)	0.25 (0.07,1.16)
0.41 (0.04,1.59)	**0.22(0.02,0.74)**	1.03 (0.22,3.47)	**0.26(0.03,0.96)**	0.41 (0.09,1.09)	0.55 (0.03,2.52)	Aspirin	1.36 (0.54,4.93)	0.13 (0.03,1.18)
1.49 (0.69,2.93)	0.85 (0.48,1.38)	1.44 (0.63,2.88)	0.94 (0.73,1.22)	3.32 (0.25,15.36)	2.06 (0.43,5.72)	8.87 (0.99,37.71)	Warfarin	**0.11(0.03,0.49)**
0.18(0.06,0.38)	**0.11(0.03,0.26)**	**0.18(0.05,0.41)**	**0.12(0.04,0.29)**	0.43 (0.02,2.42)	**0.22(0.06,0.48)**	1.15 (0.11,5.36)	**0.13(0.04,0.29)**	Placebo
C: CrCl >80 mL/min								
Api 5 mg	**5.26(2.78,14.29)**	**3.33(1.64,8.33)**	**3.98(1.82,14.29)**	0.65 (0.35,1.28)	**2.33(1.01,8.33)**	**5.26(2.71,14.29)**	0.68 (0.39,1.28)	—
1.12 (0.32,4.66)	Riva 20 mg	**0.61(0.47,0.81)**	0.76 (0.45,1.39)	**0.11(0.04,0.31)**	0.44 (0.20,1.01)	1.00 (0.83,1.20)	**0.11(0.05,0.27)**	—
0.99 (0.35,4.49)	0.90 (0.29,3.21)	Dabi 150 mg	1.20 (0.69,2.44)	**0.17(0.07,0.51)**	0.71 (0.36,1.59)	**1.61(1.35,1.96)**	**0.18(0.09,0.46)**	—
1.92 (0.29,13.21)	1.68 (0.40,7.43)	1.91 (0.25,11.18)	Riva 10 mg	**0.13(0.05,0.43)**	0.55 (0.29,1.23)	1.22 (0.71,2.33)	**0.13(0.05,0.41)**	—
0.98 (0.27,3.93)	0.88 (0.18,5.14)	0.97 (0.17,4.52)	0.52 (0.06,4.07)	Api 2.5 mg	**3.33(1.33,14.29)**	**7.69(3.33,24.99)**	0.96 (0.52,2.08)	—
0.44 (0.07,2.35)	0.41 (0.09,1.38)	0.44 (0.05,1.98)	0.38(0.05,1.79)	0.44 (0.05,3.08)	Aspirin	**2.04(1.05,4.35)**	**0.22(0.09,0.77)**	—
1.08 (0.39,3.48)	0.96 (0.41,2.36)	1.07 (0.41,2.34)	0.57 (0.12,3.14)	1.09 (0.21,5.03)	2.42 (0.61,14.97)	Warfarin	**0.11(0.05,0.28)**	—
0.13(0.04,0.41)	**0.11(0.03,0.35)**	**0.13(0.03,0.36)**	**0.07(0.01,0.36)**	**0.13(0.03,0.48)**	0.29 (0.05,1.64)	**0.12(0.04,0.34)**	Placebo	—

Figure 4 Summary of the primary results of Bayesian network meta-analysis from the three CrCl subgroups. (A) CrCl 30–50 mL/min; (B) CrCl 50–80 mL/min; (C) CrCl more than 80 mL/min. Note: column-to-row ORs and 95% CIs for incidence of VTE or VTE-related death (on the lower triangle, light blue shading) and bleeding events (on the upper triangle, yellow shading) were shown. An OR >1 favours the row-defining treatment and means that the treatment in the row is associated with a lower risk of VTE or VTE-related death and bleeding events than the treatment in the column. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. Api and dabi were administered two times per day, while the other treatments were administered once daily. Api, apixaban; CrCl, creatinine clearance; Dabi, dabigatran; Edo, edoxaban; Riva, rivaroxaban; VTE, venous thromboembolism.

been performed to explore the effectiveness and safety of DOACs therapy. Our study systematically reviewed these research results, which consisted with CrCl stratifications. There were two key findings. First, the efficacy and safety of DOACs had no statistically significant change across different CrCl stratifications (30–50, 50–80 and more than 80 mL/min). Specifically, in patients with acute VTE, DOACs showed similar efficacy to warfarin for the prevention of recurrent VTE or VTE-related death with fewer bleeding events, while in patients with extended treatment of VTE, DOACs significantly reduced the risk of recurrent VTE or VTE-related death, but a significant increase in bleeding complications was found compared with aspirin/placebo. Second, regardless of acute or extended treatment of VTE, significant heterogeneity for bleeding events was found, especially in patients with a CrCl of more than 80 mL/min. The results of the Bayesian network meta-analysis further demonstrated the differences between treatment interventions in patients with a CrCl of more than 80 mL/min: apixaban 2.5 mg or 5 mg two times per day was superior to dabigatran 150 mg two times per day, rivaroxaban 10 mg or 20 mg once daily, aspirin and warfarin, and dabigatran 150 mg two times per day was superior to rivaroxaban 20 mg once daily and warfarin in reducing the risk of bleeding events.

Our systematic review and meta-analysis included only patients with VTE who were treated with OACs, homogenising the research subjects. Furthermore, we attempted to assess the efficacy and safety of DOACs in patients with different renal functions, especially CKD. Subgroup analysis of CrCl stratification was performed for the first time to explore the influence of the severity of renal insufficiency on the actions of OACs. The source of heterogeneity in the outcome of bleeding events in the pairwise meta-analysis is partly explained in Bayesian network meta-analyses. These findings suggest that in terms of safety, there may be some differences between DOACs. However, there are some limitations that may be

considered in our systemic review. First, the inadequate sample size and lower event rate in patients with mild to moderate renal impairment (CrCl 30–50 and 50–80 mL/min, respectively) might affect the results of our research. Second, our study only included RCT data, which may affect the universality of the results because it is generally believed that the risk of bleeding events in clinical trials is often lower than that in clinical practice, especially in patients with severe renal insufficiency. Third, networks are very sparse, so the majority of SOE grades in network meta-analysis were low or very low. Therefore, the findings of our network meta-analysis study should be viewed as hypothesis generating and need to be confirmed in further studies.

In 2019, Ha *et al*[30] published a systematic review and meta-analysis that compared the benefits and harms of various oral and injection anticoagulants in the treatment of patients with CKD with renal insufficiency (CrCl of 20–60 mL/min, estimated GFR 15–60 mL/min/1.73 m^2 or serum creatinine ≥1.5 mg/dL). In Ha *et al*'s study, the indications for anticoagulation treatment included not only VTE but also other disorders, such as atrial fibrillation, cardiovascular diseases other than atrial fibrillation and thromboprophylaxis in the perioperative period. The results showed that DOACs were similar to VKAs in reducing recurrent VTE or VTE-related death in the treatment of acute VTE. In terms of reducing the risk of major bleeding, an analysis combining all indications (not just VTE) showed that DOACs were superior to VKAs, but the difference had not yet reached statistical significance (Risk ratio [RR], 0.75; CI, 0.56 to 1.01). Ha *et al*'s study is a meaningful study, but they did not stratify the patient's renal function, nor did they explore the impact of the severity of renal insufficiency on the efficacy and safety of OACs. Our results further confirm and reinforce Ha *et al*'s findings. In the subgroup analyses of CrCl stratification, we did not find that there were significant differences in the efficacy and safety of DOACs among the three groups (CrCl of 30–50, 50–80 and >80 mL/min, respectively). However, it is still impossible to deny that the severity of renal insufficiency can affect the actions of OACs due to inadequate sample size and a lower event rate. The pairwise meta-analysis by Alhousani *et al*[31] included 10 RCTs and suggested that DOACs, VKA and low-molecular-weight heparin (LMWH) showed no significant difference in preventing recurrent VTEs among patients with CKD, but DOACs had a significantly lower risk of bleeding events irrespective of the level of renal impairment compared with VKAs. The conclusions were essentially consistent with the results of acute VTE treatment in our pairwise meta-analysis. Our analysis divided subjects into acute and extended treatment groups, which is consistent with the original study design and may be more suitable for clinical practice.

Prior to our network meta-analysis, some studies also observed the differences between DOACs. A network meta-analysis published in 2014 showed that rivaroxaban and apixaban had the lowest risk of bleeding compared with other therapeutic regimens, including LMWH with dabigatran and LMWH with edoxaban, in the treatment of acute VTE.[32] Another Bayesian network meta-analysis published in 2015 showed that in the treatment of acute VTE, apixaban was superior to dabigatran, rivaroxaban and edoxaban in the reduction of major bleeding or clinically relevant non-major bleeding.[33] More recently, a retrospective population-based cohort study involving 15 254 patients with acute VTE showed that the use of apixaban was associated with a decreased risk of major bleeding compared with rivaroxaban.[34] The study by Wang *et al*[35] consisted of both direct and indirect analyses and only included four RCTs with 6003 patients in the analysis of patients with VTE. The results showed that rivaroxaban was safer than warfarin in patients with VTE with CrCl 30–79 mL/min, while apixaban's superiority regarding bleeding events was only presented in patients with VTE with CrCl 50–79 mL/min. All the data, including our finding, suggest that differences between DOACs are objective and that apixaban may have advantages in reducing the risk of bleeding compared with other DOACs. In our network meta-analysis, 10 RCTs with 37 298 patients were included and the results appear to be more credible due to the increased study number and sample size.

When DOACs are used in patients with renal insufficiency, due to the difference in pharmacokinetic properties, especially the difference in renal clearance ratio,[36 37] the difference in safety between them may become more obvious. In this case, DOACs with high renal clearance are more likely to accumulate in the body and cause bleeding than those with low renal clearance. However, our research results are contrary to this; that is, differences in DOACs were observed in the subgroup with normal renal function, but not in the subgroup with mild and moderate renal impairment. One possible explanation is that this contradiction is related to the huge differences in sample size and number of events among the three subgroups (the subgroup with CrCl 30–50 mL/min: 2127 patients with 234 bleeding events; 50–80 mL/min: 13 496 patients with 1219 bleeding events; more than 80 mL/min: 33 041 patients with 2682 bleeding events), which led to a decline in statistical power in the first two subgroups, so that the differences between DOACs could not be detected sensitively. Therefore, it is impossible to conclude from this result that there is no difference in DOACs between these two subgroups with impaired renal function. In the future, it will be necessary to expand the sample size and conduct head-to-head RCTs between DOACs for further testing.

Pharmacokinetic studies suggested that the peak-to-trough ratio of rivaroxaban 10–20 mg once daily was approximately 10.4–13.8,[38] and the ratio of edoxaban (at a dose of 90 mg once daily) was 25.8,[39] whereas the average ratios were 3 for apixaban 5 mg two times per day[40] and 1.88 for dabigatran 150 mg two times per day.[41] Peak-to-trough ratios were similarly lower for the two times per day than the once daily dosing regimens, providing less

fluctuation in drug exposure over the dosing interval. A separate analysis comparing DOACs dosed two times per day (dabigatran and apixaban) with those dosed once daily (rivaroxaban and edoxaban) in the atrial fibrillation population found a more favourable safety profile with DOACs dosed two times per day and speculated that the decreased peak-to-trough ratios afforded by two times per day DOACs probably played an important role.[42] Our results of the network meta-analysis seem to confirm the results of this analysis.

Thus, the current study supports the use of DOACs for preventing recurrent VTE or VTE-related death with fewer bleeding events than warfarin in patients with acute VTE and CrCl greater than 30 mL/min in clinical practice. For extended treatment of VTE in patients with different kidney functions, DOACs significantly reduced the risk of recurrent VTE or VTE-related death, while they should be prescribed with caution because of the increased bleeding risk compared with placebo/aspirin. Our study does not permit a definitive conclusion about the preferred DOAC based on low-quality evidence, although we found a trend of apixaban being associated with a reduced risk of bleeding events for patients with VTE with a CrCl of more than 80 mL/min. Detailed characterisation of individual patient risk profiles, careful selection of patients for OAC therapy and intensive monitoring and treatment of patients with atrial fibrillation and CKD may improve outcomes in this high-risk population.

To further verify our results, head-to-head comparative studies with high quality between different DOACs are needed. Currently, a study named 'the Comparisons of Bleeding Risk Between Rivaroxaban and Apixaban' for the treatment of acute VTE is underway (ClinicalTrials.gov identifier: NCT03266783) and has been widely noticed.[43] Moreover, patients with severe renal insufficiency are at a particularly high risk of both thromboembolism and bleeding, but no high-quality evidence-based recommendations exist to guide the management of these patients. Further research in this area is needed.

In summary, the results of meta-analyses suggest that DOACs as a whole are similar to warfarin in reducing recurrent VTE and VTE-related death but are significantly superior to warfarin in reducing the risk of bleeding in the treatment of acute VTE. Furthermore, the possible effects of renal insufficiency on the efficacy and safety of DOACs have not been confirmed, which needs further study after expanding the sample size in the future. The results of network meta-analyses suggest that DOACs are heterogeneous in terms of safety, and the preferred agents of different DOACs remain inconclusive although our study showed that apixaban may be superior to other DOACs in reducing the risk of bleeding. In clinical practice, the use of OACs, including DOACs, to treat VTE in patients with renal insufficiency still needs to be very carefully and closely monitored.

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ORCID iD

Yipu Chen http://orcid.org/0000-0002-5079-4334

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