

## Review Article

# Rivaroxaban decreases recurrent venous thromboembolisms in patients with deep vein thrombosis: a meta-analysis

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**Abstract:** Rivaroxaban (RIV), a new anticoagulant, has been widely used in the treatment of venous thromboembolisms. Deep vein thrombosis (DVT) is a common disease with a high mortality rate. This study focused on DVT patients to evaluate the risk of recurrent venous thromboembolisms (rVTE) and fatal bleeding after oral RIV treatment. Data were collected from randomized controlled trials (RCTs) of RIV versus conventional anticoagulants (CAs) in patients with DVT, through PUBMED, MEDLINE, and Cochrane CENTRAL. A total of 41,150 patients in 11 RCTS were included. Compared to CAs, RIV was associated with significant reduction of rVTE [odds ratio (OR) = 0.74; 95% confidence interval (CI) = 0.61-0.87] and fatal bleeding (OR = 0.377; 95% CI = 0.184-0.772). Simultaneously, there were no statistical differences regarding hemoglobin falling ( $\geq 2$  g/dl), transfusions ( $\geq 2$  units) (OR = 0.700; 95% CI = 0.398-1.230), total death (OR = 0.521; 95% CI = 0.244-1.112), and death from cardiovascular disease (OR = 0.685; 95% CI = 0.190-2.470). In conclusion, compared with CAs, oral RIV therapy in DVT patients gained more benefits in reducing risk of rVTE, fatal bleeding, and so forth.

**Keywords:** Rivaroxaban, recurrent venous thromboembolism, rVTE, fatal bleeding, deep vein thrombosis, DVT, meta-analysis

## Introduction

Deep vein thrombosis (DVT) has become a topic medical concern worldwide. More than 1/3 DVT patients may develop pulmonary embolisms (PE) with a high mortality rate [1, 2]. Recurrent venous thromboembolisms (rVTE), including DVT and PE, frequently occur six months after conventional anticoagulant (CAs, enoxaparin/Vitamin K antagonists represented) treatment has been completed [3].

The anticoagulation activity of CAs is unstable, requiring international normalized ratio (INR) monitoring and dose titration [4]. Before CAs treatment, hypodermic injections of low-molecular-weight heparin are essential for patients undergoing VTE [5]. Rivaroxaban (RIV), a new generation of anticoagulant, plays a pivotal role in anti-thrombosis through blocking activated factor X directly without routine INR monitoring

during treatment [6]. Therefore, oral RIV has better compliance than CAs.

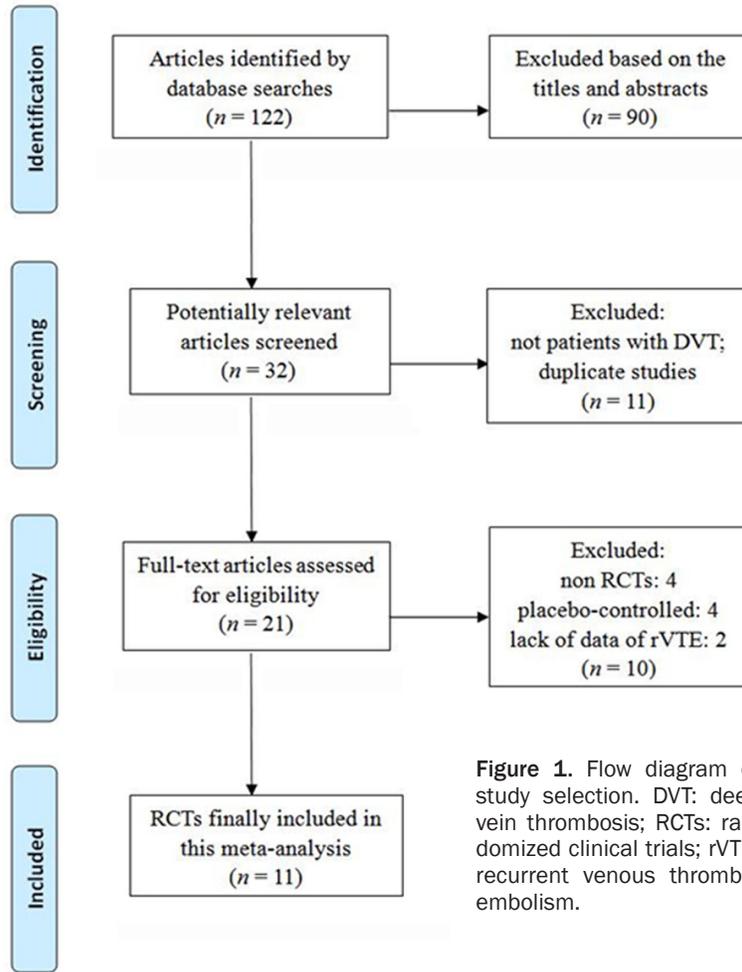
Recently, clinical trials revealed that, compared to CAs, RIV could reduce occurrence of rVTE, without increasing incidence of the first major or non-major bleeding risk during treatment [7-9]. However, some trials recruited only a small number of patients and results might not be convincing, even obtaining opposite conclusions [10]. A published meta-analysis concluded that RIV had more advantages than CAs in preventing DVT but with major bleeding as the main disadvantage [11]. More evidence is needed to verify efficacy and risks of RIV. The present study conducted a meta-analysis to compare the preventive effects of rVTE and risks of fatal bleeding, major or non-major bleeding during treatment, total death during the treatment period, and death from cardiovascular disease.

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**Table 1.** Characteristics of included RCTs

Study	Rupert Bauersachs <i>et al</i> [20]	Bengt I Eriksson <i>et al</i> [7]	Ajay K Kakkar <i>et al</i> [8]	Michael R Lassen <i>et al</i> [9]	Alexander Turpie G G <i>et al</i> [24]	BüllerHR <i>et al</i> [19]	Yuqi Wang <i>et al</i> [18]	Bauersachs RM <i>et al</i> [22]	Ageno W <i>et al</i> [21]	Burness CB <i>et al</i> [23]	Prins MH <i>et al</i> [17]
Multi-center	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Patients, n (RIV/ENO-VKA)	1731/1818	2209/2224	1228/1229	1220/1239	1526/1508	2419/2413	220/219	4150/4131	2619/2149	1731/1718	1731/1718
Male, % (RIV/ENO-VKA)	57.4/56.3	44.8/44.2	45.7/47.0	29.8/33.7	34.0/35.9	54.1/51.7	57.7/51.1	55.5/53.6	55.0/52.0	NR	57.4/56.3
Age, years (Rivo/ENO-VKA)	55.8±16.4/ 56.4±16.3	63.1±21.6/ 63.3±22.1	61.4±13.2/ 61.6±13.7	67.6±18.8/ 67.6±17.9	64.4±9.7/ 64.7±9.7	57.9±7.3/ 57.5±7.2	58.6±15.8/ 59.0±15.0	58±7.5/ 59±7.3	59±7.5/ 66±8.2	NR	55.8±16.4/ 56.4±16.3
Weight, KG (RIV/ENO-VKA)	NR	78.1±37.1/ 78.3±27.0	78.1±37.1/ 78.3±27.0	78.1±37.1/ 78.3±27.0	78.1±37.1/ 78.3±27.0	NR	NR	80±6.7/ 80±6.7	NR	NR	NR
Dose of RIV	15 mg twice daily; 20 mg once daily	10 mg once daily; 40 mg once daily	10 mg once daily; 40 mg once daily	10 mg once daily; 40 mg once daily	10 mg once daily; 30 mg twice daily	15 mg twice daily CD, INR2.0-3.0	15 mg twice daily CD, INR2.0-3.0	15 mg twice daily CD, INR2.0-3.0	15 mg twice daily	10 30 mg twice CD, INR2.0-3	15 mg twice daily 1.0 mg/kg twice daily
ENO VKA	1.0 mg/kg, twice daily, INR2.0-3.0	INR2.0-3.0 NR	INR2.0-3.0 NR	INR2.0-3.0 NR	INR2.0-3.0 NR	INR2.0-3.0 NR	INR2.0-3.0 NR	INR2.0-3.0 NR	CD, INR2.0-3.0; INR2.0-3.0	IN IR2.0-3.0 N NR	INR2.0-3.0 NR
Follow-up months	3/6/12 months	36 days	31-39 days	10-14 days	15 days	3/6/12 months	3/6/12 months	3/6/12 months	3 months	3/6/12 months	3/6/12 months
rVTE, % (RIV/ENO-VKA)	2.1/3.0	0.2/2.0	0.6/5.1	1.0/2.6	1.2/2.0	2.1/1.8	3.2/3.2	2.1/2.3	1.4/2.6	2.1/3.0	2.1/3.0
First bleeding, % (RIV/ENO-VKA)	8.1/8.1	3.2/2.5	3.3/2.8	3.3/2.7	3.2/2.3	10.3/11.4	5.9/9.2	9.3/10.0	11.4/10.1	8.1/8.2	8.1/8.1
Fatal bleeding, (RIV/ENO-VKA)	0.06/0.29	0.05/0.00	0.00/0.00	0.00/0.00	0.07/0.00	0.08/0.12	0.00/0.91	0.07/0.19	0.00/0.09	0.06./0.29	0.06./0.29
Hb falling ≥ 2 g/dl and/or transfusions ≥ 2 units	0.58/0.70	0.09/0.04	0.08/0.00	0.08/0.00	0.26/0.00	0.70/1.08	0.00/0.91	0.65/0.90	NR	NR	0.58/0.70
Total deaths (RIV/ENO-VKA)	2.21/2.86	0.25/0.26	0.23/0.69	0.00/0.33	0.39/0.40	2.40/2.07	NR	NR	NR	NR	2.20/2.85
Death of CVD (RIV/ENO-VKA)	0.12/0.23	0.14/0.04	0.16/0.00	0.00/0.08	0.13/0.20	NR	NR	NR	0.03/0.47	NR	0.12/0.23

RIV: rivaroxaban; ENO: enoxaparin; VKA: vitamin K antagonist; CD: conventional dose; INR: international normalized ratio; First bleeding: first major or clinically relevant nonmajor bleeding during treatment; HB: hemoglobin; CVD: cardiovascular disease; NR: not reported.



**Figure 1.** Flow diagram of study selection. DVT: deep vein thrombosis; RCTs: randomized clinical trials; rVTE: recurrent venous thromboembolism.

operation was repeated until no other qualified trials were found.

*Inclusion and exclusion standards*

Inclusion criteria were as follows: All studies must be RCTs, RIV compared with CAs (enoxaparin/VKAs) directly in patients undergoing DVT, and endpoint events must include rVTE and fatal bleeding, at least. Exclusion criteria were: Not the primitive studies, duplicate articles, lack of rVTE related data, and uncontrolled studies between RIV and CAs.

*Data extraction and quality evaluation*

Two authors reviewed the titles and abstracts of identified articles, separately, to evaluate eligible standards. The following data were collected: author and publication date, number of patients, age, gender, weight, dosage and course of anticoagulation, data of rVTE, fatal bleeding,

first major or non-major bleeding during follow-up, hemoglobin (Hb) falling  $\geq 2$  g/dl and/or transfusions  $\geq 2$  units, total death during the course, and deaths from cardiovascular disease. This study was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for meta-analysis of RCTs [12]. Cochrane risk-of-bias tool was used to evaluate the risk of bias repeatedly. Six items of risk of bias [7] are presented in **Table 1**. Disputes were discussed by several authors until a consensus was reached.

*Outcome measurement*

Main clinical outcomes were rVTE, including symptomatic distal or proximal DVT, and fatal or non-fatal PE [13]. Other endpoints were fatal bleeding, first major or non-major bleeding, Hb falling  $\geq 2$  g/dl and/or transfusions  $\geq 2$  units, total death, and deaths from cardiovascular disease during treatment of DVT. Age and

**Methods**

*Literature search*

Two authors (Juxian Tang and Yihui Lin) searched PubMed, MEDLINE, and Cochrane CENTRAL for relevant articles published up to May 30, 2016. The following search terms were used: Patient: “deep vein thrombosis”, “deep venous thrombosis”, “DVT”; Treatment: “rivaroxaban”, “conventional anticoagulants”, “standard anticoagulants”, “enoxaparin”, “vitamin K antagonists”, “VKAs”, “warfarin”; Primary endpoint events: “recurrent venous thromboembolism”, “rVTE”, “fatal bleeding”. The search contained only human studies and RCTs. Moreover, literature lists were examined to ensure other eligible studies were included. Furthermore, similar trials were also searched from the abstracts of conferences of the National Institute for Health and Clinical Excellence. This

**Table 2.** Risk of bias of included studies

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias*
Rupert Bauersachs <i>et al</i> [20]	Yes	No	No	Yes	Yes	Yes
Bengt I Eriksson <i>et al</i> [7]	Yes	Yes	Yes	Yes	Yes	Yes
Ajay K Kakkar <i>et al</i> [8]	Yes	No	No	Yes	Yes	Yes
Michael R Lassen <i>et al</i> [9]	Yes	Yes	Yes	Yes	Yes	Yes
Alexander Turpie GG <i>et al</i> [24]	Yes	Yes	Yes	Yes	Yes	Yes
Büller HR <i>et al</i> [19]	Yes	No	No	Yes	Yes	Yes
Yuqi Wang <i>et al</i> [18]	Yes	No	No	Yes	Yes	Yes
Bauersachs RM <i>et al</i> [22]	Yes	No	No	Yes	Yes	Yes
Agno W <i>et al</i> [21]	Yes	No	No	Yes	Yes	Yes
Burness CB <i>et al</i> [23]	Yes	No	No	Unclear	Yes	Yes
Prins MH <i>et al</i> [17]	Yes	No	No	Yes	Yes	Yes

\*Including intention-to-treat analysis.

weight were also included as factors for comparative analysis. If disputes occurred, two or three authors discussed the disputes until reaching a consensus.

#### Statistical analysis

Association is expressed as odds ratio (OR) for dichotomous data and weighted mean difference (WMD) is expressed for continuous data with 95% confidence interval (CI). Heterogeneity was checked using the  $I^2$  statistic:  $I^2$  value from 0% to 25% was considered unimportant heterogeneity, 26% to 49% as low heterogeneity, 50% to 74% as moderate heterogeneity, and 75% to 100% as high heterogeneity [14]. To reduce heterogeneity, a random-effects model was conducted. Sensitivity analysis was also performed to assess the impact of each research on the whole risk. Publication bias was evaluated by funnel plots. Egger's linear regression test was used to measure funnel plot asymmetry [15].  $P < 0.05$  is considered statistically significant. Statistical analyses were performed by STATA software version 13.0 (Stata Corporation).

## Results

#### Literature search and selection

A total of 122 studies for RCTs were found from searching PubMed, MEDLINE, and Cochrane CENTRAL. Ninety studies were excluded, according to titles and abstracts, and 11 studies were excluded due to none of the patients

undergoing DVT or duplicate studies. The remaining 21 studies were screened further. Finally, 11 RCTs [7-9, 16-23] were included in this study, according to inclusion criteria. Selection process is shown in **Figure 1**.

#### Characteristics of included studies

A total of 11 RCTs were included in this pooled analysis. **Table 1** lists the main characteristics of these 11 RCTs. These studies were multicenter trials ranging from 2008 to 2015. Clinical follow-up course ranged from 10 days to 12 months. A total of 41,150 cases were collected. Within each study, the RIV group received oral rivaroxaban and the CAs group received enoxaparin, VKAs, etc. Sample sizes ranged from 219 to 4,150. The proportion of male and female patients was basically balanced. Ages of enrolled patients ranged from 56.4 to 67.6 years old with weights ranging from 78.1 to 80.0 kilograms.

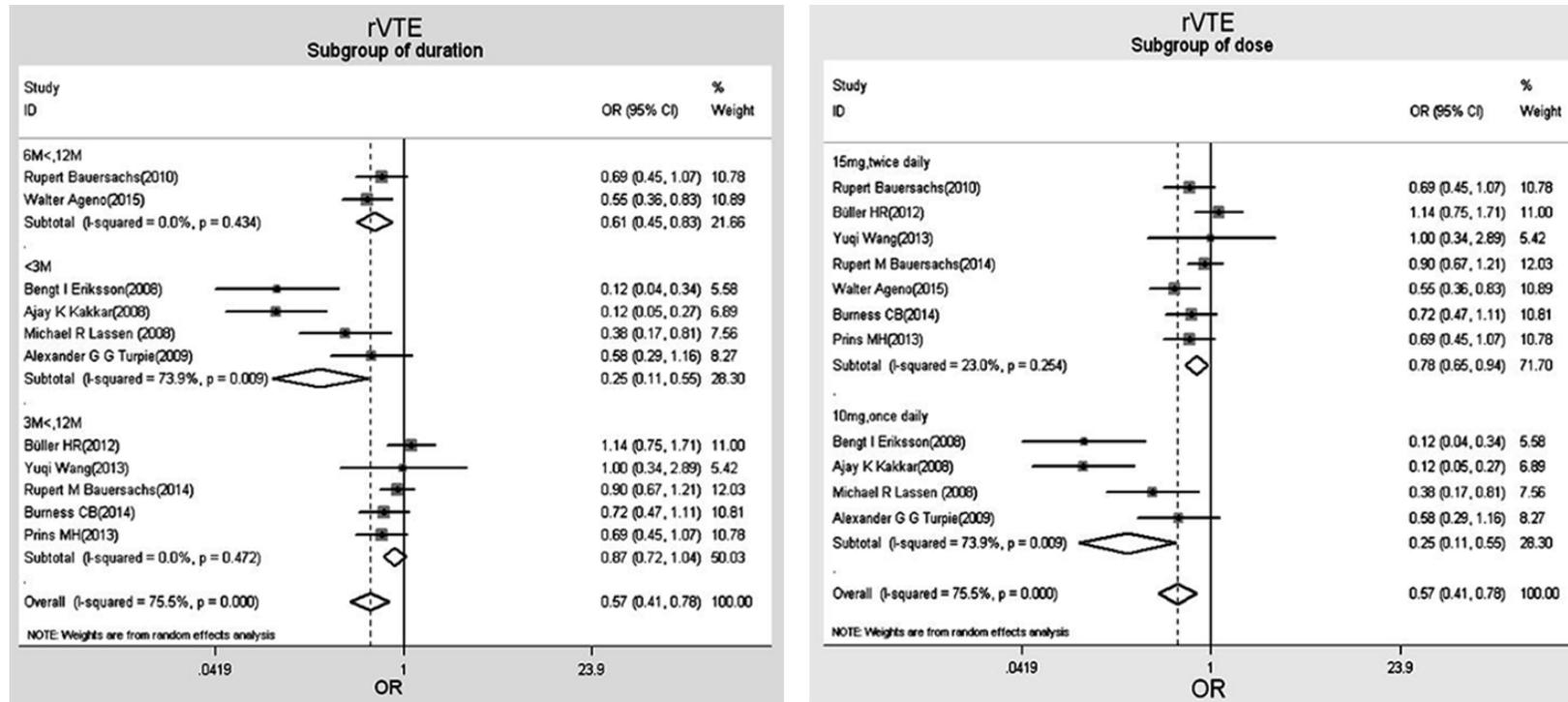
#### Risk of bias

**Table 2** presents the risk of bias for all studies. All researches had adequate randomized sequence generation. There were three studies [23-25] conducted in a double-blinded fashion. All studies were free of selective reporting bias with results addressed completely.

#### Age and weight

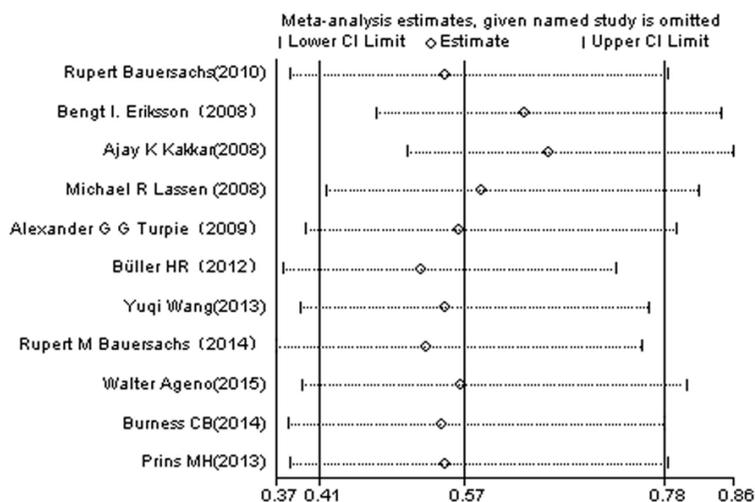
There were no significant differences in terms of age (WMD, -1.009; 95% CI = 3.267-1.250;  $P$

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**Figure 2.** Subgroup analysis of recurrent venous thromboembolism (rVTE) by duration and dose. OR: odds ratio; M: month.

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**Figure 3.** Sensitivity analysis.

= 0.381) and weight (WMD, -0.044; 95% CI, -0.317-0.229;  $P = 0.750$ ).

### Prevention efficacy of rVTE

Eleven studies reported outcomes of rVTE in the follow-up period. There was significant heterogeneity among the studies ( $I^2 = 75.5\%$ ,  $P = 0.001$ ).

Subgroup and sensitivity analysis were conducted to identify sources of heterogeneity. Included studies were divided into three subgroups by duration and two groups by dose of RIV, respectively (**Figure 2**). Subgroup analysis of rVTE showed that when the duration of oral RIV was less than 3 months, there was higher heterogeneity in 4 studies [7-9, 24] ( $I^2 = 73.9\%$ ,  $P = 0.009$ ). These were then divided into the same subgroup by the RIV dose of 10 mg once daily. There was also higher heterogeneity ( $I^2 = 73.9\%$ ,  $P = 0.009$ ).

Sensitivity analysis showed that 2 studies [7, 8] had a significant impact on results and may be major sources of heterogeneity (**Figure 3**). Labbe graph and Galbraith plot for heterogeneity showed similar results (**Figure 4**). Meta regression analysis of rVTE indicated that dose of RIV was one of the heterogeneity sources (Adj  $R^2 = 79.92\%$ ,  $P = 0.008$ ), rather than duration of treatment (Adj  $R^2 = 3.79\%$ ,  $P = 0.269$ ).

Meta-analysis of rVTE was carried out on these 2 studies [7, 8]. A random effects model was used to draw a more conservative and safer conclusion. Statistical analysis revealed that

RIV had significantly lower risk of rVTE than CAs (OR = 0.74; 95% CI = 0.61-0.87;  $P = 0.002$ ), with low heterogeneity in trials ( $I^2 = 32.0\%$ ,  $P = 0.162$ ; **Figure 5**).

### Evaluation of fatal bleeding

Compared to CAs, RIV was associated with a significant reduction of fatal bleeding (OR = 0.377; 95% CI = 0.184-0.772;  $P = 0.008$ ) in patients with DVT.

### Secondary safety endpoints

RIV also did not appear to increase the risk of first major or non-major bleeding during treatment (OR = 1.016; 95% CI = 0.935-1.105;  $P = 0.701$ ). Simultaneously, there were no notable differences in terms of Hb falling  $\geq 2$  g/dl and/or transfusions  $\geq 2$  units (OR = 0.700; 95% CI = 0.398-1.230;  $P = 0.215$ ), total death until the end of the treatment period (OR = 0.521; 95% CI = 0.244-1.112;  $P = 0.092$ ), and deaths from cardiovascular diseases (OR = 0.685; 95% CI = 0.190-2.470;  $P = 0.563$ ).

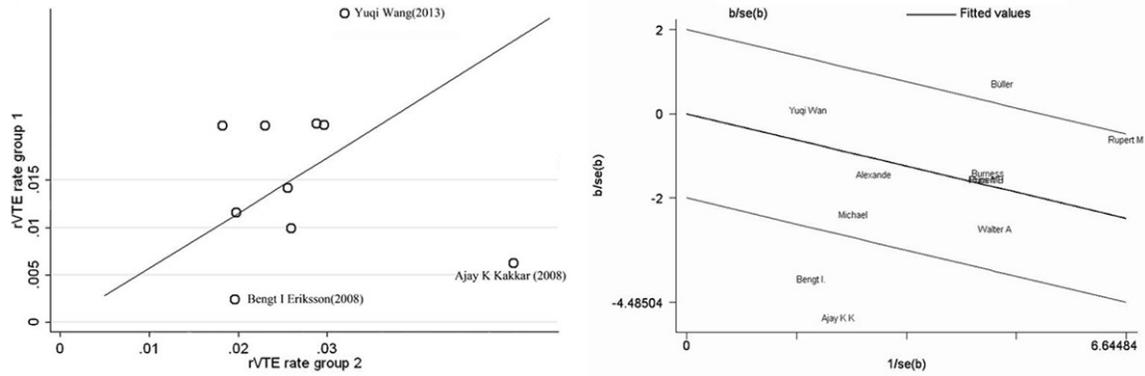
### Publication bias assessment

Publication bias was evaluated by funnel plots and Egger's linear regression test for rVTE, fatal bleeding, and other safety endpoints. Funnel plots were roughly symmetrical. Furthermore, Egger's linear regression test showed normal distribution of rVTE ( $P = 0.356$ ), fatal bleeding ( $P = 0.167$ ), first major or non-major bleeding ( $P = 0.163$ ), and total death until the end of the treatment period ( $P = 0.472$ ).

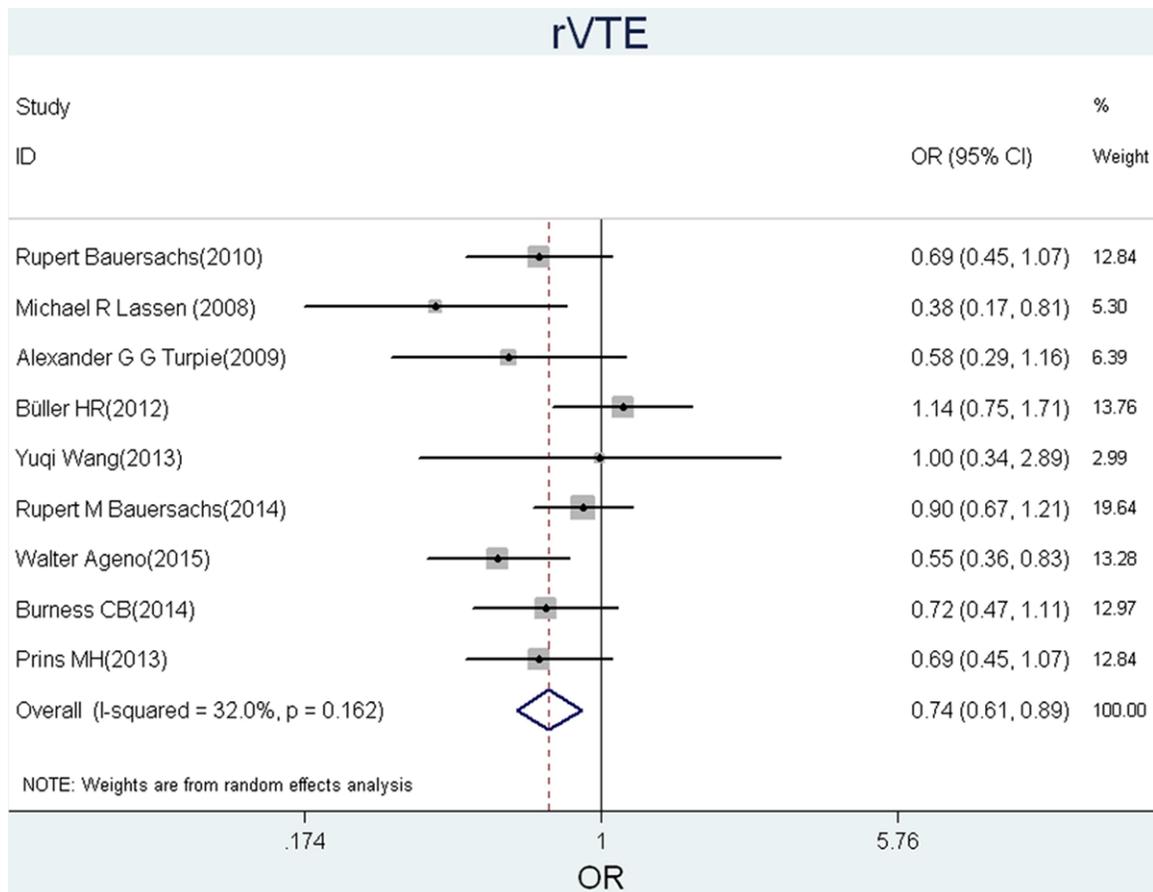
## Discussion

Cohen AT et al [24] conducted a similar research as the present study. However, they included both DVT and PE patients, which may be a potential heterogeneity source. Comparing with each other, it was uncovered that RIV was no better than dabigatran in related hemorrhages. Another study [25] with only PE patients included demonstrated that RIV had a similar efficacy to CAs. In the present study, only patients confirmed with DVT were included and different conclusions were obtained.

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**Figure 4.** The L'abbe graph and Galbraith plot for heterogeneity. rVTE: recurrent venous thromboembolism.



**Figure 5.** ORs of rivaroxaban versus standard anticoagulation after erasing the studies of high heterogeneity. OR: odds ratio; rVTE: recurrent venous thromboembolism.

To produce conservative outcomes, this study strictly adhered to inclusion and exclusion criteria. Outcomes of rVTE in 11 studies had significant heterogeneity. To further analyze sources of heterogeneity, subgroup analysis, and sensitivity analysis was conducted, along

with L'abbe graph and Galbraith plot. Results suggested that 2 studies [7, 8] had a significant impact on results and may be major sources of heterogeneity. Meta regression analysis of rVTE indicated that dose of RIV was one of the heterogeneity sources, rather than duration

of treatment. Statistical analysis showed that oral RIV had significantly lower risk of rVTE than CAs and there was low heterogeneity between trials.

Compared to CAs, RIV was associated with a significant reduction of rVTE. RIV decreased incidence of fatal bleeding and did not appear to increase the risk of first major or non-major bleeding during treatment. There were no significant differences in terms of decrease of Hb  $\geq 2$  g/dl and/or transfusion  $\geq 2$  units, total death until the end of the duration, and cardiovascular mortality.

VTE, including DVT and PE, is a common chronic disease with a higher recurrence rate within 6 to 12 months after anticoagulation treatment [3]. Cancer is also one of the risk factors for rVTE [26, 27]. Some studies [28] have assessed treatment of VTE with VKAs, revealing that incidence of rVTE was decreased while major bleeding did not increase if anticoagulant therapy was continued after the first course. However, approximately 8% patients receiving CAs still experienced rVTE during follow-up [29]. Quon P et al [30] revealed that, compared to CAs, treatment with apixaban resulted in fewer rVTEs, VTE-related deaths, and bleeding events.

Clinical application of direct activated factor X inhibitor RIV has been increasingly accepted in preventing and treating DVT, strokes, and systemic thrombotic incidents in non-valvular atrial fibrillation [31]. It can start and cancel the action more quickly than VKAs [5]. The pharmacology of RIV can be well summarized as follows [6, 32-38]. It is dose-dependent and its bioavailability ranges from 66-100%. It is easily absorbed with a relatively fast metabolism (half-life: 5-17 h). An advantage of RIV is that it can be used in a regular dose, unlike CAs, which are known for unstable anticoagulant effects. CAs also require dose adjustment according to prothrombin time, activated partial thromboplastin time, and INR [4].

According to pooled analysis, compared to CAs, RIV showed a significant reduction in rVTE and fatal bleeding during follow-up treatment, which may be attributed to its pharmacological activity. Clinical advantages of anticoagulant therapy might be offset by a related increase in bleeding (including major and non-major bleed-

ing) complications. However, the present study did not show increased risk of first major or non-major bleeding during treatment, total death until the end of the treatment period, and death from cardiovascular diseases. Moreover, RIV could even reduce the risk of fatal bleeding. Based on this evidence, RIV has more advantages than CAs in preventing rVTE in patients with DVT. It is also safer than CAs.

There were still some limitations to the present study that require careful consideration. First, rVTE in 11 studies showed high heterogeneity. To find out sources of heterogeneity, this study conducted subgroup analysis, sensitivity analysis, L'abbe graph, and Galbraith plot, along with meta regression analysis. Second, included studies were different from their treatment durations and dosage of RIV. Potential heterogeneity might exist. Third, this study was not able to access the raw data of patients, which may be another source of heterogeneity among trials.

In conclusion, compared to CAs, oral RIV therapy in patients with DVT gains more benefits in reducing rVTE and fatal bleeding, without increasing events of non-fatal bleeding, total death, and death from cardiovascular diseases.

### Disclosure of conflict of interest

None.

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