The risk of postoperative hemorrhage and efficacy of heparin for preventing deep vein thrombosis and pulmonary embolism in adult patients undergoing neurosurgery: a systematic review and meta-analysis

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ABSTRACT

The aim of this meta-analysis was to examine the risk of postoperative bleeding and efficacy of heparin for preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) in adult patients undergoing neurosurgery. MEDLINE, Cochrane, and EMBASE databases were searched until October 31, 2016, for randomized controlled trials (RCTs) and non-randomized comparative studies that assessed the rates of postoperative hemorrhage, DVT, PE, and mortality in adult patients undergoing neurosurgery. Nine eligible studies (five RCTs, four retrospective studies) including 874 patients treated with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and 1033 patients in control group (placebo with or without compression device) were analyzed. The overall analysis revealed that there was an increase in the risk of postoperative hemorrhage in patients who received heparin (pooled OR 1.66, 95% CI 1.01 to 2.72, p=0.046) compared with no treatment group. The risk of postoperative hemorrhage was more significant if only RCTs were included in analysis. Heparin prophylaxis was associated with a decrease in the risk of DVT (pooled OR 0.48, 95% CI 0.36 to 0.65, p<0.001) and PE (pooled OR 0.25, 95% CI 0.09 to 0.73, p=0.011) but it did not affect the rate of mortality. In conclusion, heparin increased the rate of postoperative bleeding, decreased the risk of DVT, PE and venous thromboembolic event (VTE) but it did not affect the mortality of patients undergoing neurosurgery. For the heparin prophylaxis, the trade-off between the risk of postoperative bleeding and benefit of prophylaxis against VTEs requires further investigation.

Significance of this study

What is already known about this subject?

- Heparin prophylaxis decreases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing neurosurgery.
- Heparin prophylaxis may increase the risk of intracranial bleeding.
- The trade-off between the benefit of a reduced incidence of venous thromboembolic events (VTE)s and the increased risk of postoperative bleeding has not been clearly determined.

What are the new findings?

- Heparin prophylaxis increased the risk of postoperative bleeding.
- Heparin prophylaxis decreased the risk of DVT and PE after neurosurgery.
- Heparin prophylaxis did not affect the mortality after neurosurgery.

How might these results change the focus of research or clinical practice?

- Given that heparin prophylaxis decreases the risk of VTE at the cost of increasing the risk of postoperative bleeding, further randomized control trials are required to identify the subgroup of patients that are likely to benefit the most from this trade-off.

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INTRODUCTION

Patients undergoing neurosurgical procedures are at increased risk for life-threatening venous thromboembolic events (VTEs).[1] VTEs are defined as ultrasound-proven proximal deep venous thrombosis (DVT) or clinically detected pulmonary embolism (PE).[2] The risk of PE in neurosurgical patients is as high as 5% with a reported mortality ranging from 9% to 50%,[1] and the risk of DVT in patients undergoing surgery for a brain tumor reaches 31%.[3 4] Many factors are believed to be responsible for the increased risk of VTE in neurosurgery patients including the patient's premorbid state, type of surgical procedure, specific disease (eg, meningiomas are associated with an incidence of VTE of up to 72%), advanced age, tumor-induced hemostatic changes resulting in a hypercoagulable state, and steroid use.[3 5–8]

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Prophylaxis measures against VTEs in surgical patients usually include treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), and compression stockings and have been shown to reduce the incidence of vascular complications such as DVT and PE.[9–12] However, there is a valid concern of intracranial bleeding with the use of anticoagulation prophylaxis against VTEs. While some researchers showed that the risk of postoperative hematoma is increased with the use of early anticoagulation,[13] others did not observe an increased risk of bleeding with early postoperative heparin administration after intracranial surgery.[14] Although several studies attempted to resolve this inconsistency,[15–18] there is still no clear consensus on the use of prophylactic anticoagulation in patients undergoing neurosurgery, and the trade-off between the benefit of a reduced incidence of VTEs and the increased risk of intracranial bleeding has not been clearly determined.

Thus, the purpose of the current study was to perform an updated meta-analysis examining the risk of postoperative hemorrhage and efficacy of UFH and LMWH in preventing DVT and PE in patients undergoing neurosurgery, including intracranial surgery and spinal surgery.

MATERIALS AND METHODS

Search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] MEDLINE, Cochrane, and EMBASE databases were searched from inception until October 31, 2016, using combinations of the following terms: anticoagulant, heparin, LMWH, unfractionated heparin, thromboembolic, thromboembolism, embolic, embolism, hemorrhage, neurosurgery, brain surgery, neurosurgical procedure, intracranial surgery. Reference lists of relevant studies were hand-searched. Searches and study selection were conducted by two independent reviewers, and a third reviewer was consulted for resolution of any disagreements.

Inclusion criteria for the meta-analysis were (1) randomized controlled trials (RCTs) or non-randomized comparative studies, (2) recruited patients received neurosurgery for brain or spinal neoplasm or non-neoplastic diseases, and (3) the studies that compared heparin (UFH or LMWH) with the control or placebo group (without heparin treatment) for the rate of thrombosis. Exclusion criteria were (1) letters, comments, editorials, case reports, proceedings, and personal communications; (2) the studies that compared UFH with LMWH; (3) the studies that compared different doses of UFH or LMWH; and (4) the studies that used multiple types of anticoagulants (eg, warfarin, dabigatran).

Data extraction

Data extraction was performed by two independent reviewers, and a third reviewer was consulted for any uncertainties. The following information was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, patients' demographic data, intervention details, anticoagulant administration, the length of follow-up, and data on primary (rate of postoperative hemorrhage) and secondary outcomes (rates of DVT, PE, and mortality).

Risk of bias assessment

The Cochrane Risk of Bias Tool was used to assess the methodological quality of the included studies.[20] The quality assessment was performed by two independent reviewers, and a third reviewer was consulted if no consensus could be reached.

Outcome measures and statistical analysis

Because the positive outcome (eg, postoperative hemorrhage) is a rare event, the Peto OR with 95% CI was calculated for the primary and secondary outcome measures for both individual studies and the studies combined.[21] Pooled effects were calculated, and a two-sided value of $p<0.05$ was considered to indicate statistical significance. In addition, subgroup analyses were performed according to different anticoagulant therapies (UFH or LMWH). A χ^2-based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistic were determined. Random-effects models of analysis were used if significant heterogeneity was detected (Q statistic $p<0.10$ or $I^2>50\%$). Otherwise, fixed-effects models were employed. Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was assessed by constructing funnel plots if more than 10 studies were included in the analysis.[22] All analyses were performed using Comprehensive Meta-Analysis statistical software V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search

A PRISMA flow diagram of study selection is shown in figure 1. Initially, 270 articles were identified in the database searches and 16 through other sources. A total of 270 publications remained after duplicates were removed. Further titles and abstracts screening based on the exclusion criteria eliminated 233 articles from consideration. The full texts of 37 articles were assessed for eligibility. Subsequently, 28 articles were excluded due to the improper study design (eg, compared UFH with LMWH, UFH and LMWH with LMWH alone) (n=14) and improper control group (eg, patients with other types of anticoagulants) (n=3). In addition, single-arm studies (n=7), studies that did not report an outcome of interest (n=2), and studies that did not report quantitative outcomes (n=2) were excluded. Thus, nine studies were included in the meta-analysis.

Study characteristics

The basic characteristics of the nine studies[2 9 13 23–28] included in the meta-analysis are summarized in table 1. There were four retrospective studies and five RCTs that recruited a total of 1907 patients who underwent intracranial (n=1854) or spinal (n=53) surgery. The underlying diseases included brain neoplasms,[9 13 25–28] spinal neoplasm,[9 27] and movement disorders.[2] A total of 874 patients received either UFH or LMWH and 1033 patients did not receive chemoprophylaxis. The mean patient age ranged from 42 to 61.5 years. In five studies, both treatment group and control group received mechanical compression devices (eg, intermittent pneumatic compression, compression stockings).[2 9 13 23 25]

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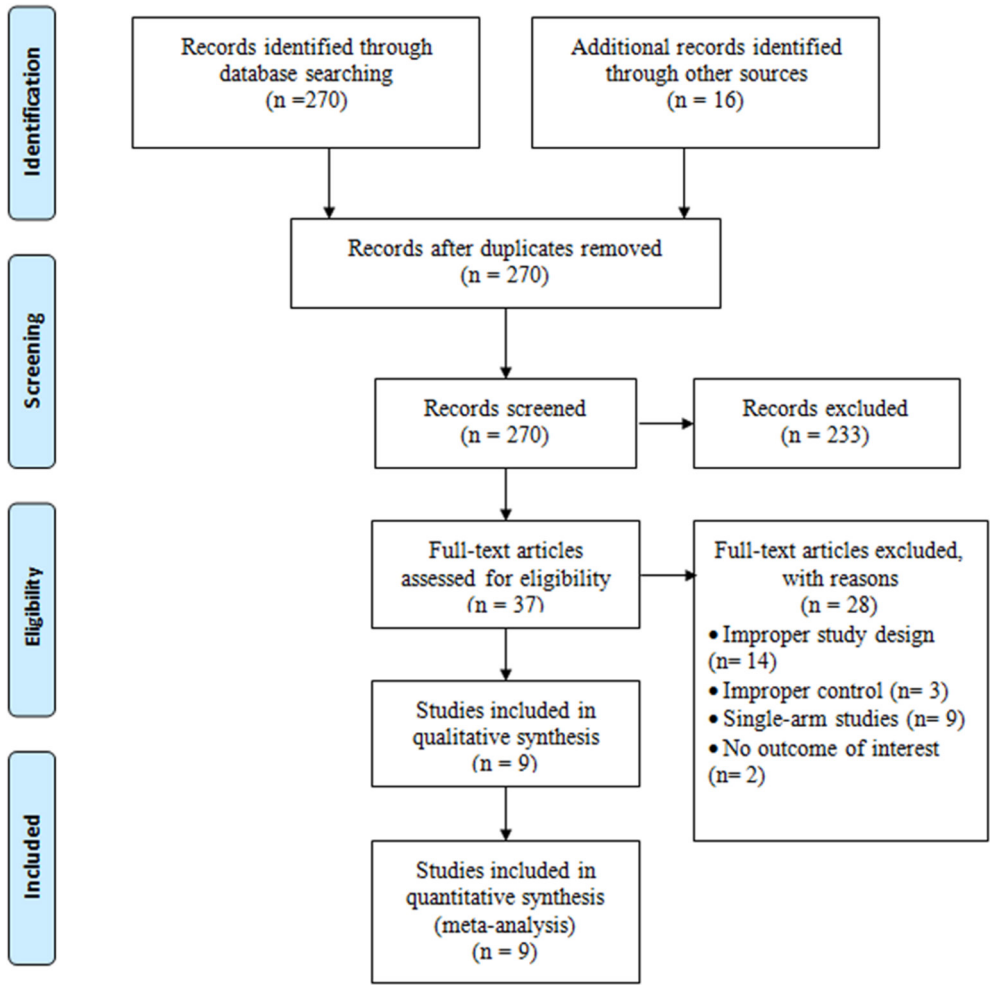

Figure 1 Flow diagram of study selection.

LMWH was used in five studies,[9 13 23 25 27] UFH was used in three studies[2 26 28] and one study used LMWH or UFH.[24]

Meta-analysis

Data of outcome measurements are summarized in the online Supplementary table 1 The results of meta-analysis (Forest plot) are shown in figures 2 and 3.

Postoperative hemorrhage

Seven studies[2 9 24–28] provided complete data with respect to the rate of postoperative hemorrhage (%) and were included in the analysis (figure 2). There was no evidence of significant heterogeneity (Q statistic p=0.327, I^2=13.46%); therefore, a fixed-effects model of analysis was used. The overall analysis revealed that there was a significant difference in the rate of postoperative hemorrhage between patients who received heparin and those in control/placebo group (pooled OR 1.66, 95% CI 1.01 to 2.72, p=0.046).

We also performed subanalysis and assessed the association of heparin prophylaxis with the rate of postoperative bleeding in RCTs only. There was no evidence of significant heterogeneity among four RCTs,[9 26–28] and a fixed-effects model of analysis was used. The analysis indicated that patients treated with heparin had a significantly higher rate of postoperative hemorrhage than those who did not receive anticoagulation treatment (pooled OR 1.91, 95% CI 1.06 to 3.43, p=0.031, table 2).

In addition, we assessed the association of anticoagulation prophylaxis modality (UFH or LMWH) with the rate of postoperative bleeding. For patients treated with UFH,[2 26 28] a fixed-effects model of analysis was performed as there was no evidence of significant heterogeneity between the three included studies. The analysis indicated that there was no difference in the rate of postoperative hemorrhage between patients treated with UFH and those who received no anticoagulants (pooled OR 1.84, 95% CI 0.58 to 1.76, p=0.298) (data not shown). For patients treated with LMWH,[9 25 27] a fixed-effects model of analysis was performed as there was no evidence of significant heterogeneity between the three included studies. The analysis indicated that patients treated with LMWH had a significantly higher rate of postoperative hemorrhage than those who did not receive anticoagulation treatment (pooled OR 1.87, 95% CI 1.05 to 3.31, p=0.033) (data not shown).

Deep vein thrombosis

All nine studies[2 9 13 23–28] provided data with respect to DVT rate. There was no evidence of significant heterogeneity between the studies (Q statistic p=0.153, I^2=33.06%); therefore, a fixed-effects model of analysis was used

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Table 1 Characteristics of studies included in the meta-analysis

First author (publication year)	Study design	Intervention	Patient number	Age (year)	Male (%)	Underlying disease	Anticoagulant administration	Length of follow-up
Daley *et al*[23 23]	Retrospective cohort	SCD+enoxaparin*	45	42±18	84%	Traumatic brain injury	30 or 40 mg daily or 30 mg twice daily postoperation.	During hospitalization
		SCD+No enoxaparin	226	47±21	77%			
Farooqui *et al*[24]	Retrospective	Enoxaparin (Lovenox) or heparin	129	57.4±22.5	58%	Traumatic brain injury	Chemoprophylaxis at 24 hours postinjury, and 24 hours postoperation.	NA
		No Enoxaparin or heparin	107	53.3±22.8	61%			
Cage *et al*[25]	Retrospective cohort	IPC+enoxaparin	24	56 (30–73)	NA	Intracranial meningiomas	Postoperative within 24–48 hours for 1–7 days; 40 mg SC, once a day (30 mg SC for one patient).	30 days
		IPC	62	56 (30–80)	NA			
Bauman *et al*[2]	Retrospective	IPC heparin †	133	60.7	73%	Movement disorders‡	2 hours before surgery and after surgery; 50 mg IV, twice daily.	NA
		IPC	121	61.5	64%			
Constantini *et al*[26]	RCT	Heparin	55	58	49%	Supratentorial brain tumor	Preoperative 2 hours until full ambulation or for 7 days; 50 mg SC.	14 months
		Placebo	48	54	44%			
Agnelli *et al*[27]	RCT	Enoxaparin	Cranial surgery: 122 Spinal surgery: 31	55	45%	Brain or spinal tumors	Postoperative within 24 hours for 8±1 days; 40 mg SC, once a day.	2 month
		Placebo	Cranial surgery: 139 Spinal surgery: 15	58	55%	Brain or spinal tumors		
Dickinson *et al*[13]	RCT	SCD+enoxaparin	23	50 (29–72)	NA	Intracranial neoplasm	Perioperative enoxaparin treatment until discharged; 30 mg SC, twice daily.	20 months
		Enoxaparin	21	43 (28–61)	NA			
		SCD	22	49 (20–72)	NA			
Nurmohamed *et al*[9]	RCT	SCD+nadroparin	Cranial surgery: 238 Spinal surgery: 3	52±15	50%	Brain (n=193) or spinal tumor (n=3) or non-neoplastic diseases: 45	Postoperative 18–24 hours for 10 days or until discharge; 7500U SC, once a day.	56 days
		SCD+placebo	Cranial surgery: 240 Spinal surgery: 4	52±13	58%	Brain (n=207) or spinal tumor (n=3) or non-neoplastic diseases: 34		
Cerrato *et al*[28]	RCT	Heparin	50	53	48%	Brain tumor: 42; non-neoplastic diseases: 8	2 hours preoperative and at least 7 days	8 days
		Control	50	51	54%	Brain tumor: 44; non-neoplastic diseases: 6	Postoperative; 5000U SC, once in 8 hours.	

Data presented as mean.
*Enoxaparin sodium is a low-molecular-weight heparin marketed under the trade names Lovenox, Xaparin and Clexane.
†Fifty milligrams of heparin (heparin chloride) diluted in 1 mL 0.9% NaCl (5000 U heparin) was given.
‡In this study, movement disorders include Parkinson's disease, essential tremor and dystonia. Patients with movement disorders undergo deep brain stimulation (DBS) surgery.
AKI, acute kidney injury; ICH, intracranial hemorrhage; IPC, intermittent pneumatic compression; IV, intravenous injection; NA, not available; RCT, randomized controlled trial; SC, subcutaneous injection; SCD, sequential compression device (thigh-high antiembolic stockings); SDH, subdural hematoma; TBI, traumatic brain injury.

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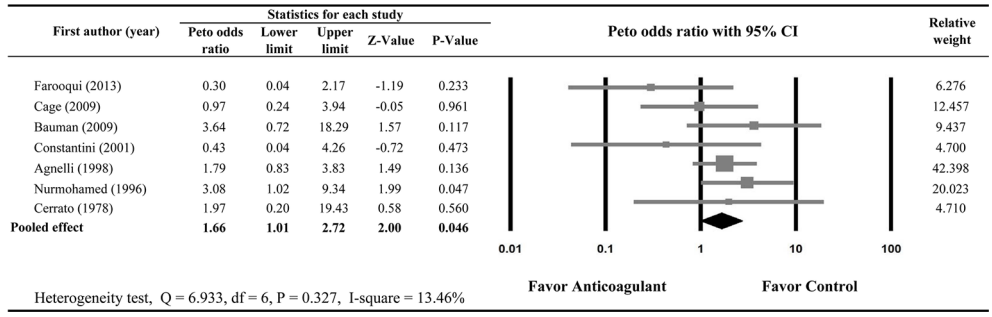

Figure 2 Meta-analysis (Forest plot) of postoperative hemorrhage.

(figure 3A). The overall analysis revealed that patients who received heparin were less likely to experience DVT compared with patients who did not receive anticoagulants (pooled OR 0.48, 95% CI 0.36 to 0.65, p<0.001).

We performed subanalysis and assessed the association of DVT rate and anticoagulant treatment in RCTs only. There was no evidence of significant heterogeneity among five RCTs,[9 13 26–28] and a fixed-effects model of analysis was used. The overall analysis showed that patients who received heparin were less likely to experience DVT compared with patients who did not receive anticoagulants (pooled OR 0.51, 95% CI 0.38 to 0.69, p<0.001).

For subgroup analysis, we assessed the association of anticoagulation prophylaxis modality (UFH or LMWH) with the risk of DVT. For patients treated with UFH,[2 26 28] a fixed-effects model was used as there was no evidence of significant heterogeneity between the three included studies. The overall analysis revealed that patients who received UFH were less likely to experience DVT than those who did not receive anticoagulants (pooled OR 0.23, 95% CI 0.10 to 0.55, p=0.001) (data not shown). For analysis of patients treated with LMWH,[9 13 23 25 27] a fixed-effects model was used as there was no evidence of significant heterogeneity between the five studies. The analysis indicated that patients treated with LMWH had a lower risk of DVT than those who did not receive heparin (pooled OR 0.56, 95% CI 0.41 to 0.77, p<0.001) (data not shown).

Pulmonary embolism

Six studies[2 9 23–25 27] provided complete data with respect to PE risk (figure 3B). There was no evidence of significant heterogeneity between the studies (Q statistic p=0.981, I^2=0%); therefore, a fixed-effects model of analysis was used. The overall analysis demonstrated that patients who received heparin were less likely to experience PE than those who did not receive anticoagulants (pooled OR 0.25, 95% CI 0.09 to 0.73, p=0.011).

Only two RCTs provided data of PE risk.[9 27] A fixed-effects model of analysis was performed as there was no significant heterogeneity between the RCTs. The analysis indicated that there was no difference in the rate of PE between patients treated with heparin and those who received no anticoagulants (pooled OR 0.36, 95% CI 0.05 to 2.55, p=0.306, table 2)

For subgroup analysis, we assessed the association of UFH or LMWH prophylaxis with the risk of PE. Only one of the included studies in UFH subgroup reported the risk of development of clinically significant PE[2]; therefore, no analysis was done for risk of PE in the UFH subgroup. This study reported that 2 out of 121 control patients (1.6%) and no patients in the heparin treatment group developed PE.

For patients treated with LMWH,[9 23 25 27] a fixed-effects model of analysis was used as there was no evidence of significant heterogeneity between the five included studies. The analysis indicated that there was no difference in the rate of PE between patients treated with LMWH and those who received no anticoagulants (pooled OR 0.32, 95% CI 0.07 to 1.43, p=0.135) (data not shown).

Venous thromboembolic events

Five studies[2 9 23 25 27] provided complete data with respect to VTE risk (figure 3C). There was no significant heterogeneity between the studies (Q statistic p=0.128, I^2=44.05%); therefore, a fixed-effects model of analysis was used. The overall analysis revealed that patients who received heparin were less likely to experience VTE than those who did not receive anticoagulants (pooled OR 0.60, 95% CI 0.44 to 0.83, p=0.002).

We performed subgroup analysis and assessed the association of VTE rate and anticoagulant treatment in RCTs only. A random-effects model of analysis was used as there was significant heterogeneity between two RCT studies.[9 27] The analysis indicated that there was no difference in the rate of VTE between patients treated with heparin and those who received no anticoagulants (pooled OR 0.62, 95% CI 0.31 to 1.24, p=0.175, table 2).

For subgroup analysis, we assessed the association of UFH or LMWH prophylaxis with the risk of VTE. Only one of the included studies in UFH subgroup reported the number of patients who developed clinically significant VTE[2]; therefore, the risk of VTE was not analyzed for the UFH treatment. This study reported that 3 of 121 patients in the control group (2.5%) and no patients in the heparin treatment group developed VTE. For patients treated with LMWH,[9 23 25 27] a fixed-effects model of analysis was used as there was no significant heterogeneity between the four included studies. The analysis indicated that patients who received LMWH were less likely to experience VTE than those who did not receive anticoagulants (pooled OR 0.62, 95% CI 0.45 to 0.86, p=0.004) (data not shown).

Mortality

Six studies[9 13 23 25–27] provided complete data with respect to mortality (figure 3D). A random-effects model of analysis was used as there was significant heterogeneity between

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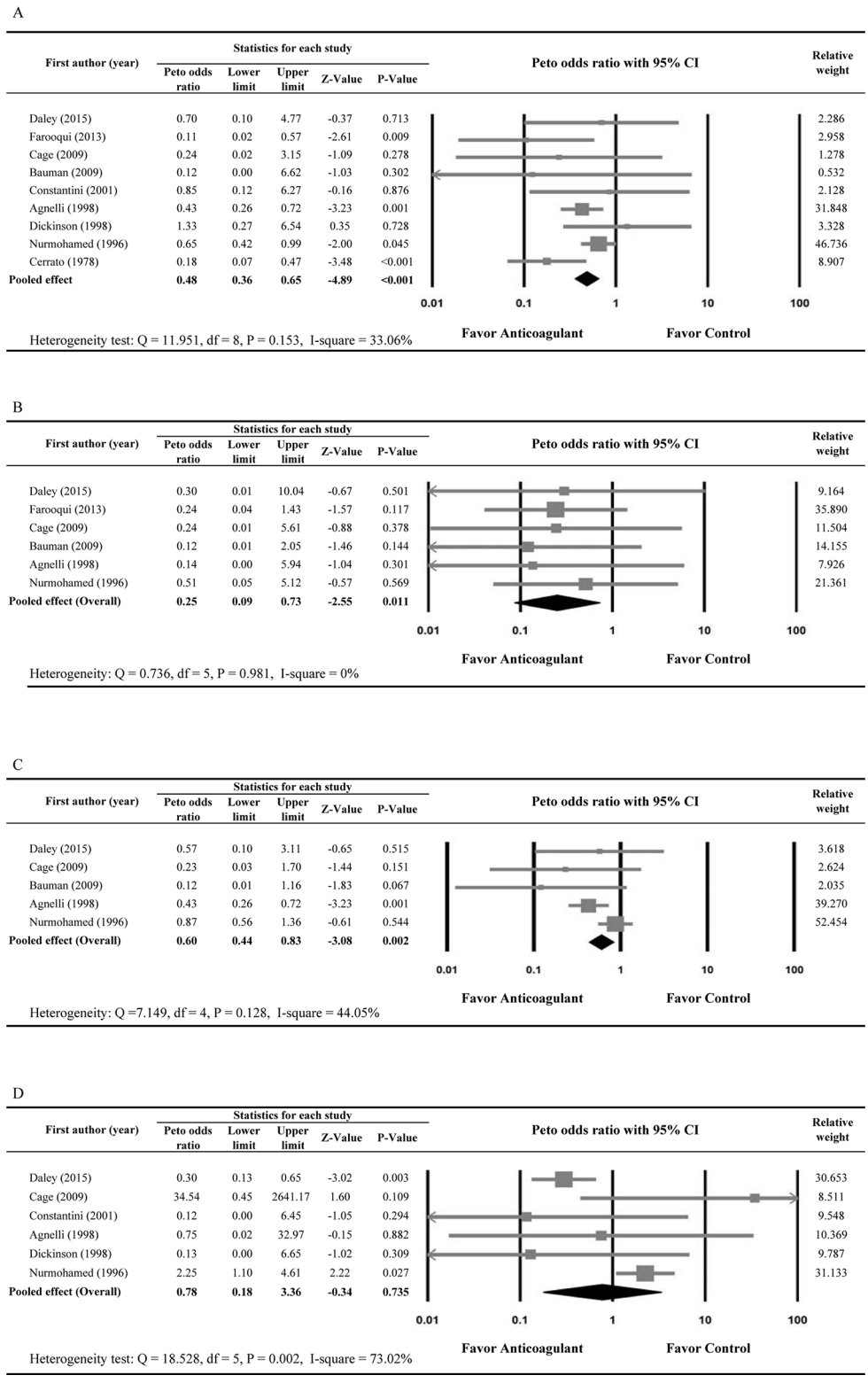

Figure 3 Meta-analysis (Forest plot) of (A) deep vein thrombosis, (B) pulmonary embolism, (C) venous thromboembolism and (D) mortality.

the studies (Q statistic p=0.002, I^2=73.02). The overall analysis revealed that there was no difference in mortality between patients treated with heparin and those who received no anticoagulants (pooled OR 0.78, 95% CI 0.18 to 3.36, p=0.735).

We performed subanalysis and assessed the association between mortality rate and anticoagulant treatment in RCTs only. A fixed-effects model of analysis was used as there was no significant heterogeneity between four RCT studies.[9 13 26 27] The analysis indicated that there was no difference in

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Table 2 Additional meta-analysis for pooled effect of RCTs only

	Number of studies	Homogeneity		Peto OR (95% CI)	p Values
		Cochran Q	I^2		
Postoperative hemorrhage	4	2.365	0.00%	1.91 (1.06 to 3.43)	0.031
Deep vein thrombosis	5	7.827	48.89%	0.51 (0.38 to 0.69)	<0.001
Pulmonary embolism	2	0.346	0.00%	0.36 (0.05 to 2.55)	0.306
Venous thromboembolism	2	4.186	76.11%	0.62 (0.31 to 1.24)	0.175
Mortality	4	4.076	26.40%	1.83 (0.92 to 3.62)	0.083

the mortality between the two treatments (pooled OR 1.83, 95% CI 0.92 to 3.62, p=0.083, table 2).

For subgroup analysis, we assessed the association of anticoagulation prophylaxis modality (UFH or LMWH) with mortality. Only one of the included studies in UFH subgroup reported the mortality risk for this treatment[26]; therefore, no analysis was done for mortality in the UFH subgroup. Of the 103 patients in this study, only one patient died (1%). For patients treated with LMWH,[9 13 23 25 27] a random-effects model of analysis was used as there was significant heterogeneity between the five included studies. The analysis indicated that there was no difference in the rate of mortality between patients treated with LMWH and those who received no anticoagulants (pooled OR 0.95, 95% CI 0.20 to 4.54, p=0.950) (data not shown).

Sensitivity analysis

Sensitivity analyses for the five outcome measures were performed using the leave-one-out approach (table 3). The direction and magnitude of combined estimates for DVT, PE, and mortality did not vary markedly with the removal of individual studies, indicating that the meta-analysis for these outcomes had good reliability and the results were not overly influenced by each study. However, four studies affected the overall estimate for the rate of postoperative hemorrhage,[2 9 27 28] suggesting that the summary effect was heavily influenced by any one of these four studies. For VTE, the results differed when the study by Agnelli *et al*[27] was removed; the pooled effect size became non-significant, suggesting this study may have overly influenced our finding.

Risk of bias assessment

Results of the risk of bias assessment for individual studies are shown in figure 4. Four of the included studies were retrospective studies, and thus selection, performance, and detection biases could have occurred. Additionally, the consequent inadequate blinding of patients and outcome assessors could lead to performance bias and detection bias.

DISCUSSION

Postoperative bleeding can be a catastrophic event in a patient who underwent intracranial surgery. Similarly, a VTE, a common complication in neurosurgical patients, can be life-threatening. While heparin prophylaxis has clearly been shown to reduce the risk of VTEs in surgical patients, its use in neurosurgical patients remains a matter of debate and studies have provided varying results. The trade-off between the risk and benefit has not been clearly established,[1] and practices with respect to VTE prophylaxis vary considerably.[29] The aim of this meta-analysis was to clarify the risks and benefits of heparin for prophylaxis against VTEs in patients undergoing neurosurgery. We found that heparin treatment was associated with an increased risk of postoperative bleeding but a decreased risk of VTEs, including DVT and PE. Nevertheless, it did not reduce or increase mortality in patients undergoing neurosurgery.

Postoperative bleeding

In our study, heparin was only marginally associated with an increased risk of postoperative bleeding (p=0.046). When the reports of RCTs (higher level of evidence) were analyzed separately, the result of analysis indicated that patients treated with heparin had more significant risk of postoperative hemorrhage than those who did not receive anticoagulation treatment (p=0.031), and the OR increased from 1.66 in overall pooled effect to 1.91 in RCT pooled effect, suggesting that included retrospective studies impacted the observed result. In addition, subgroup analysis demonstrated that LMWH prophylaxis lead to a significantly higher rate of postoperative hemorrhage (p=0.033 with CI marginally above 1), while UFH was not associated with the increased rate of postoperative bleeding. Given that the study design was not a head-to-head comparison as well as the number of studies (only three studies) that used UFH for chemoprophylaxis was limited, our meta-analysis does not allow us to conclude that LMWH prophylaxis is less safe compared with UFH prophylaxis in neurosurgery. A head-to-head comparison between the two forms of heparin is required to draw this type of conclusion.

Venous thromboembolic events (DVT and PE)

The results of the overall pooled effect analysis for the rate of DVT (four retrospective and five RCT studies), PE (four retrospective and two RCT studies), and VTE (three retrospective and two RCT studies) revealed that patients who received heparin were less likely to experience DVT (p<0.001), PE (p=0.011) and VTEs (p=0.002) than those who did not receive anticoagulants. However, separate analysis of RCTs indicated that there was no difference in the rate of PE between patients treated with heparin and those who received no anticoagulants (p=0.306). Similarly, analysis of RCTs demonstrated that there was no difference in the rate of VTEs between patients treated with heparin and those who received no anticoagulants (p=0.175), suggesting that retrospective studies did affect the result of overall pooled effect analysis.

When we performed subgroup analysis based on the treatment modality (UFH and LMWH prophylaxis), results indicated that patients who received LMWH were less likely

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Table 3 Sensitivity analysis

First author (year) of the study removed	Statistics with study removed				
	Points	Lower limit	Upper limit	Z value	p Value
Hemorrhage					
Farooqui *et al*[24]	1.86	1.11	3.10	2.37	0.018
Cage *et al*[25]	1.79	1.05	3.04	2.15	0.031
Bauman *et al*[2]	1.53	0.91	2.57	1.59	0.111
Constantini *et al*[26]	1.77	1.07	2.95	2.21	0.027
Agnelli *et al*[27]	1.57	0.82	3.02	1.35	0.177
Nurmohamed *et al*[9]	1.42	0.82	2.47	1.24	0.216
Cerrato *et al*[28]	1.64	0.99	2.73	1.92	0.055
Deep vein thrombosis					
Daley *et al*[23]	0.48	0.36	0.64	−4.89	<0.001
Farooqui *et al*[24]	0.51	0.38	0.68	−4.51	<0.001
Cage *et al*[25]	0.49	0.36	0.65	−4.80	<0.001
Bauman *et al*[2]	0.49	0.36	0.65	−4.83	<0.001
Constantini *et al*[26]	0.48	0.36	0.64	−4.92	<0.001
Agnelli *et al*[27]	0.51	0.36	0.73	−3.72	<0.001
Dickinson *et al*[13]	0.47	0.35	0.63	−5.04	<0.001
Nurmohamed *et al*[9]	0.37	0.25	0.56	−4.83	<0.001
Cerrato *et al*[28]	0.53	0.39	0.72	−4.04	<0.001
Pulmonary embolism					
Daley *et al*[23]	0.25	0.08	0.75	−2.46	0.014
Farooqui *et al*[24]	0.26	0.07	0.97	−2.01	0.045
Cage *et al*[25]	0.25	0.08	0.78	−2.39	0.017
Bauman *et al*[2]	0.28	0.09	0.89	−2.15	0.031
Agnelli *et al*[27]	0.26	0.09	0.80	−2.35	0.019
Nurmohamed *et al*[9]	0.21	0.06	0.69	−2.57	0.010
Venous thromboembolism					
Daley *et al*[23]	0.60	0.43	0.84	−3.01	0.003
Cage *et al*[25]	0.62	0.44	0.86	−2.89	0.004
Bauman *et al*[2]	0.62	0.45	0.86	−2.85	0.004
Agnelli *et al*[27]	0.75	0.50	1.14	−1.36	0.175
Nurmohamed *et al*[9]	0.40	0.25	0.64	−3.83	<0.001
Mortality					
Daley *et al*[23]	1.30	0.28	5.99	0.34	0.737
Cage *et al*[25]	0.56	0.13	2.43	−0.78	0.435
Constantini *et al*[26]	0.95	0.20	4.54	−0.06	0.950
Agnelli *et al*[27]	0.78	0.15	3.91	−0.30	0.761
Dickinson *et al*[13]	0.95	0.20	4.54	−0.07	0.945
Nurmohamed *et al*[9]	0.42	0.11	1.63	−1.26	0.209

to experience VTEs and DVT but there was no difference in the rate of PE between the LMWH group and control group (p=0.135), suggesting that studies using UFH[2 24] did affect the outcome of overall pooled effect analysis of PE. The observed effect can be explained by the fact that Farooqui *et al*[24 24] and Bauman *et al*[2 2] studies had higher relative weight (larger sample size), and their lower and upper limits were closer to CI than other studies. Subgroup analysis for association of UFH treatment with the rates of DVTs, PE and VTEs was not performed due to limited study numbers. A meta-analysis conducting a head-to-head comparison between the LMWH (dalteparin) versus UFH for preventing of VTE in medical-surgical critically ill patients was published recently.[30] In this meta-analysis, no significant treatment effect on proximal leg DVT was found in both groups but a superior effect of dalteparin on PE compared with UFH was demonstrated. Clearly, high-quality RCTs are warranted to establish the safety and efficiency of LMWH and UFH in different clinical scenarios.

Mortality

Acute PE is strongly associated with morbidity and mortality in patients with traumatic brain injury. Even transient episodes of PE may significantly increase early mortality after traumatic brain injury.[23] Although our meta-analysis indicated that heparin might reduce the rate of PE in adult patients undergoing neurosurgery, result of overall pooled effect (four RCTs and two retrospective studies) showed no difference in mortality between patients treated with heparin and those who received no anticoagulants (p=0.735). The result of analysis for

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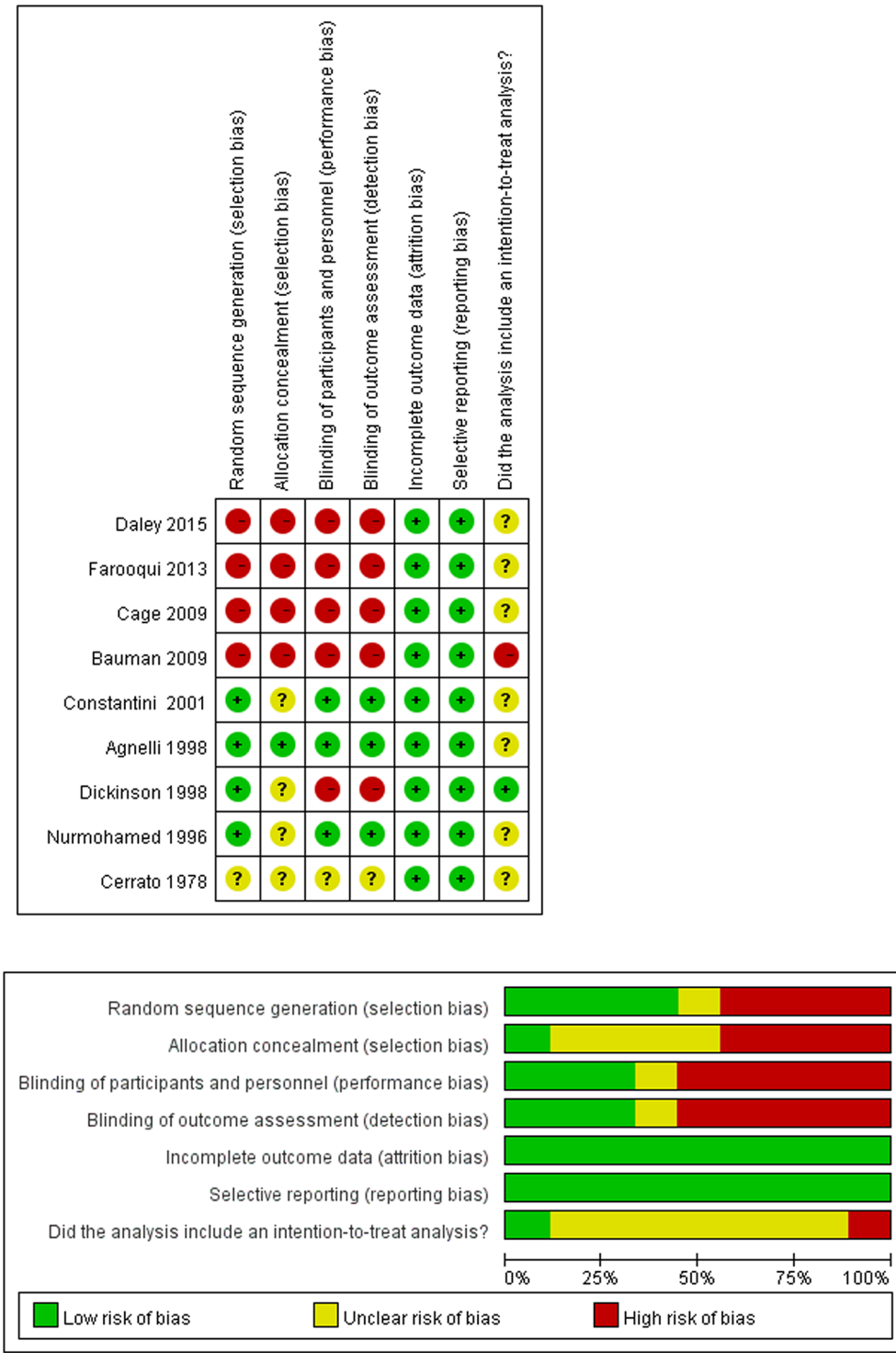

Figure 4 Quality assessment (publication bias) of included studies. (A) Risk of potential bias of individual studies and (B) risk of bias summary of all included studies.

four RCTs was similar to the overall pooled effect for mortality (p=0.083), suggesting that retrospective studies did not influence the result of pooled effect analysis for the mortality outcome. Among included studies, only one study treated the patients with UFH.[26] After exclusion of this study, result of analysis for LMWH-treated patients was still similar to the result of overall pooled effect for mortality (p=0.950). These results suggest that the reduction of VTEs (DVTs and/or PE) by heparin did not reduce the mortality of the patients. It is possible that neurological impairment caused by postoperative hemorrhage could offset the decrease in mortality caused by reduction of VTE-related morbidity. However, it was reported that in either heparin group or placebo group, the deaths

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were usually due to the non-hemorrhagic cerebral complications,[18 27] while the deaths caused by bleeding and PE were rare.[18]

Prior systematic reviews and meta-analysis

Prior systematic reviews and meta-analysis attempted to define the role of heparin (UFH and LMWH) as VTE prophylaxis in patients undergoing neurosurgical procedures. A 2000 meta-analysis by Iorio and Agnelle[18] examined four RCTs, three of which used LMWH, and four uncontrolled studies that evaluated 187 thromboembolic events in 827 patients (22.6%). Heparin prophylaxis resulted in a 45% relative risk reduction of VTEs (OR 0.48, 95% CI 0.35 to 0.66; p<0. 001) and 71% relative risk increase of major bleeding (OR 1.72, 95% CI 0.69 to 4.27, p=0.24). The authors concluded that heparin is effective for prophylaxis of VTEs without excessive bleeding risk. In 2008, Collen *et al*[17] studied both heparin and mechanical devices as VTE prophylaxis in neurosurgical patients. The study analyzed 18 RCTs and 12 cohort studies including 7779 patients, and the results indicated that LMWH and intermittent compression devices were equally effective in reducing the rate of DVT. In head-to-head trials, there was no statistical difference in the rate of intracranial hemorrhage (ICH) between therapy with LMWH and non-pharmacological methods, whereas the pooled rates of ICH and minor bleeding were generally higher with heparin therapy than with non-pharmacological methods. A 2011 systematic review and meta-analysis by Hamilton *et al*[16] examined RCTs that evaluated low-dose UFH or LMWH with respect to VTEs and ICH in patients undergoing elective cranial neurosurgery. Five of six trials reported a significant reduction in the risk of symptomatic and asymptomatic VTE with heparin prophylaxis (pooled risk ratio=0.58, 95% CI 0.45 to 0.75). ICH was more common in patients who received heparin, but the difference was not statistically significantly. Further analysis showed that for every 1000 patients who receive heparin prophylaxis, 91 VTEs will be prevented, whereas seven ICHs and 28 episodes of a minor bleeding will occur. The results led the authors to conclude that while heparin prophylaxis reduces the risk of VTEs, it also increases the risk of bleeding with only slightly favorable benefit to risk ratio. In 2013, Salmaggi *et al*[15] performed a systematic review that identified 13 RCTs which evaluated mechanical methods (eg, intermittent pneumatic compression, compression stockings) or heparin (UFH/LMWH) prophylaxis and included 1932 randomized patients, of whom 1558 were neuro-oncological patients. While no meta-analysis was performed, the authors reported a trend of decreased VTEs in patients treated with mechanical methods and significantly reduced VTEs with the addition of LMWH (enoxaparin) starting the day after surgery (mechanical plus anticoagulant prophylaxis) (OR 0.57, 95% CI 0.39 to 0.82). A non-significant decrease in PE with combined modalities was also observed. However, the incidence of major bleeding increased with addition of LMWH. The author included two trials that reported rates of symptomatic DVT, which did not show significant difference between patients treated with UFH/LMWH and placebo (OR 0.63, 95% CI 0.28 to 1.41).

Limitations

There are several limitations in the current analysis that should be considered. The studies were heterogeneous with respect to the surgical procedures performed (intracranial surgery or spinal surgery), patients' underlying diseases (brain neoplasm or non-neoplasm) and the control group treatments (with or without physical compression device). In addition, the protocol for administration of heparin varied between the studies. Potential bias resulting from inadequate randomization, allocation and blinding in retrospective studies should also be considered when interpreting the conclusions. Lastly, sensitivity analysis using the leave-one-out approach for between-study heterogeneity indicated that four studies affected the overall estimate for the rate of postoperative hemorrhage.[2 9 27 28] Removing any one of these four studies turned the summary effect from significant (p<0.05) into non-significant (p≥0.05), suggesting that several studies overly influenced the findings and may be responsible for the between-study heterogeneity. Those studies might be primarily responsible for the between-study heterogeneity in the rate of postoperative bleeding or intracranial hemorrhage. The between-study heterogeneity also affects the robustness of the conclusions for this meta-analysis. However, as long as the predefined eligibility criteria for the meta-analysis are meaningful and that the data are correct, the between-study heterogeneity may still be acceptable.[31]

Conclusion

In summary, heparin increased the rate of postoperative bleeding, decreased the risk of DVT, PE and VTE but it did not affect the mortality of patients undergoing neurosurgery. However, the pooled effect was heavily influenced by the type of study design (RCT or retrospective study) and the treatment modality (UFH and LMWH prophylaxis) as well as publication bias. For the heparin prophylaxis, the trade-off between the risk of postoperative bleeding and benefit of prophylaxis against VTEs requires further investigation and in-depth subgroup analysis of sufficient RCT data to identify individual risk factors.

Contributors XW is the guarantor of integrity of the entire study, study concepts, manuscript review. YCZ was involved in the study design and definition of intellectual content. WDZ was responsible for the literature research and YS for statistical analysis. PF was involved in the manuscript preparation, DQL in the manuscript editing and HYZ in data acquisition. All authors read and approved the study.

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