

# Efficacy and risks of anticoagulation for cerebral venous thrombosis

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## Abstract

**Background and purpose:** Cerebral venous thrombosis (CVT) is a rare but life-threatening disease. Timely and proper treatments are the keys in saving patients' life and preventing from permanent neurological deficits. We performed this network meta-analysis to evaluate the role of anticoagulation in CVT, especially for the patients accompanied with hemorrhagic stroke.

**Methods:** PubMed, Embase, Web of Science, Cochrane Database, and Chinese Biomedical (CBM) databases were searched comprehensively to select eligible articles (up to 30 June 2017). Network meta-analysis was performed based on classical frequency statistics.

**Results:** Around 14 studies comprising 1135 cases were included. Overall analysis showed that low-molecular weight heparin (LMWH) and unfractionated heparin (UFH) were more effective (LMWH vs placebo: OR 4.76, 95%CI: 2.56–8.33; UFH vs placebo: OR 4.12, 95%CI: 2.17–8.33), and safe (LMWH vs placebo: OR 0.22, 95%CI: 0.069–0.65; UFH vs placebo: OR 0.28, 95%CI: 0.058–0.99) than placebo in the management of CVT. Besides, LMWH showed more advantages than UFH; As for the patients accompanied with hemorrhagic stroke, LMWH and UFH were also better than placebo (efficacy: LMWH vs placebo: OR 20, 95%CI: 5.56–100; UFH vs placebo: OR 12.5, 95%CI: 3.7–33.3; safety: LMWH vs placebo: OR 0.18, 95%CI: 0.04–0.77; UFH vs placebo: OR 0.16, 95%CI: 0.04–0.6) in the management of CVT. In addition, LMWH was more effective than UFH for the patients accompanied with hemorrhagic stroke.

**Conclusion:** Anticoagulant treatment with heparin is safe and beneficial for patients with CVT, even for those accompanied with hemorrhagic stroke. Besides, LMWH is better than UFH in the management of CVT.

**Abbreviations:** CBM = Chinese Biomedical, CVST = cerebral venous sinus thrombosis, CVT = cerebral venous thrombosis, F = female, LMWH = low-molecular weight heparin, M = male, NA = not available, OR = odds ratio, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin.

**Keywords:** cerebral venous thrombosis, anticoagulation, heparin, meta-analysis, network

## 1. Introduction

Cerebral venous thrombosis (CVT), which accounts for 1% to 2% of all strokes, is a rare but life-threatening disease.<sup>[1]</sup> It may cause cerebral venous infarcts, which are frequently hemorrhagic and may lead to epilepsy, neurological deficits, or even death.<sup>[2,3]</sup>

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Timely and proper treatments are the keys in saving patients' life and preventing from permanent neurological deficits.

Currently, the first-line treatment for CVT is anticoagulation with intravenous UFH or subcutaneous low-molecular weight heparin (LMWH).<sup>[4,5]</sup> The heparin could reduce the incidence of cerebral infarcts and help patients to recovery from neurological deficits. However, anticoagulation also bears potential risks of bleeding, immune-mediated thrombocytopenia, and heparin-induced osteoporosis.<sup>[6,7]</sup> The efficacy and safety of heparin in the treatment of CVT are varied across reported studies, most of which are limited to case reports. No network meta-analysis is available in the literature to comprehensively assess the effects of heparin, especially for the patients accompanied with hemorrhagic stroke. So, we performed this network meta-analysis to evaluate the role of heparin in the treatment of CVT and further explore the advantages and disadvantages of LMWH and UFH.

## 2. Methods and materials

This study was warranted by the ethics committee of Zhejiang University.

### 2.1. Data sources and searches

We conducted this meta-analysis according to the PRISMA guidelines (Supplemental Table I, <http://links.lww.com/MD/C243>).

PubMed, Embase, Web of Science, Cochrane Database, and Chinese Biomedical (CBM) databases were searched systematically to pick out eligible published articles (up to 30 May 2017)

using the combination of free-text words and MeSH terms as follows: “anticoagulation” or “heparin” or “LMWH” or “UFH”, and “cerebral venous thrombosis” or “cerebral sinus thrombosis” or “dural sinus thrombosis” or “vein sinus thrombosis” or “CVT” or “DCVT” or “CVST.” Furthermore, additional articles were identified by manual search from the references of original studies or review articles pertaining to this topic.

The selection process of eligible studies was performed by 2 independent authors (WLX and LSG).

## 2.2. Selection criteria

The following inclusion criteria were used: Only prospective cohort studies or randomized controlled trials (RCTs) were included; At least one type of heparin was used for the treatment of CVT; For each study, data on efficacy and safety of drugs vs nondrugs users used to generate OR and 95% CIs could be extracted; The minimum number of patients included in each study was 20; There were no overlapping subjects across publications; and language of the eligible studies was either Chinese or English.

The exclusion criteria are as follows: The study did not meet the inclusion criteria; reviews, editorials, clinical conference, abstracts, case reports, comment, congresses.

## 2.3. Data extraction and quality assessment

Data of interest were extracted as follows: Identity: authors, years, countries; Design: prospective studies or RCTs; Patients included in each study: age, gender; Treatments: LMWH or UFH or placebo; Outcomes: good recovery, moderate neurological deficits, severe neurological deficits, mortality; Complications: additional intracranial and extracranial bleeding, and other complications; Recanalization rate.

The related data from eligible studies were collected and summarized by 2 of the authors, respectively (WLX and TL). Any discordance was settled by a third author (JMZ).

The methodological quality of each study was assessed by using the domain-based Cochrane Collaboration’s tool.<sup>[8]</sup> Any dispute was resolved by a third author (AWS).

## 2.4. Outcome

There are some different scores (mRS, NIHSS, or Barthel Index) to assess neurofunction among the included studies. Although there are differences among these different scores, all the scores could be divided into 4 grades: normal neurofunction or slight deficits without affecting working and living; moderate deficits that could affect working and living; severe deficits which could not live by himself; death.

In order to comprehensively evaluate the efficacy and safety of anticoagulation for CVT, we set several eligible types of outcomes in both overall analysis and subgroup analysis: good recovery or complete recovery; moderate neurological deficits; severe deficits; death; poor prognosis (severe deficits + death); re-bleeding; recanalization rate; overall complications.

## 2.5. Statistical analysis

Firstly, we performed pairwise analysis based on the Review Manager Version 5.0 software (The Cochrane Collaboration, Software Update, Oxford, UK), which was provided by the

Cochrane Collaboration, and Stata 14. The efficacy and safety were assessed by using pooled ORs, along with its 95% confidence interval (CI) for dichotomous variables. Heterogeneity across each study was evaluated with Chi-square test and I-square test.<sup>[9]</sup>

Secondly, we conducted a network meta-analysis with Stata14.0 (StataCorp LP, College Station, TX) based on classical frequency statistics. The effect sizes were assessed with ORs and their credible intervals (CrI).

Then, we estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. Besides, the treatment hierarchy was also judged according to the surface under the cumulative ranking curve (SUCRA).<sup>[10]</sup>

As for public bias, we performed a comparison-adjusted funnel plot to detect the presence of any dominant publication bias in the network meta-analysis.<sup>[10]</sup>

Additionally, our network was a closed triangular circular network including both direct and indirect evidences. Ifplot command proposed by Chaimani et al<sup>[11]</sup> was adopted to assess the consistency of direct and indirect estimates.

## 3. Results

### 3.1. Study screening and its characteristics

Searches of PubMed, Embase, Web of Science, Cochrane Database, and Chinese Biomedical (CBM) identified 383, 595, 105, 104 and 910 citations, respectively. After screening the records for duplications, 1940 studies remained for further titles and abstracts screening. There were 32 records potentially eligible left after titles and abstracts screened for further full text assessment. After the removal of reviews and case reports, some articles still contained the data; however, the data could not be extracted as it was overlapping. Finally, 14 articles containing 1135 cases filled in all inclusion and exclusion criteria were enrolled in the network meta-analysis.<sup>[12–25]</sup> The PRISMA flow diagram of the study selection process was displayed in Figure 1, and the basic characteristics of all 14 studies are summarized in Supplemental Table II, <http://links.lww.com/MD/C243>.

The final analysis included 14 articles, of which 4 were prospective studies and 10 were RCTs. The sample cases from each included study ranged from 20 to 421. There were 1135 cases identified and enrolled in the overall analysis.

Around 7 studies compared the effects and risks of LMWH with UFH in treating CVT, 5 studies compared LMWH with placebo, and 2 studies compared UFH with placebo.

We qualitatively judged the quality test of each study and the summary analysis is shown in Figure 2. We determined that most of the studies had low or indeterminate risk of bias.

### 3.2. Outcome

**3.2.1. Overall analysis.** A total of 397 Patients treated with LMWH, 517 patients with UFH and 127 patients with placebo were included in the group of good neurological function recovery. The network of comparisons was shown in Figure 3A. Direct and indirect results suggested that the patients treated with LMWH and UFH were more likely to obtain good recovery than placebo after CVT (Table 1). Besides, we also made ranking graph of distribution of probabilities in Figure 4A. The results based on SUCRA indicated that LMWH (87.1) ranked the first in helping patients to obtain good recovery, UFH (62.9) ranked the second and the last was placebo (0). The heterogeneity test showed that no severe heterogeneity was observed (Table 1).

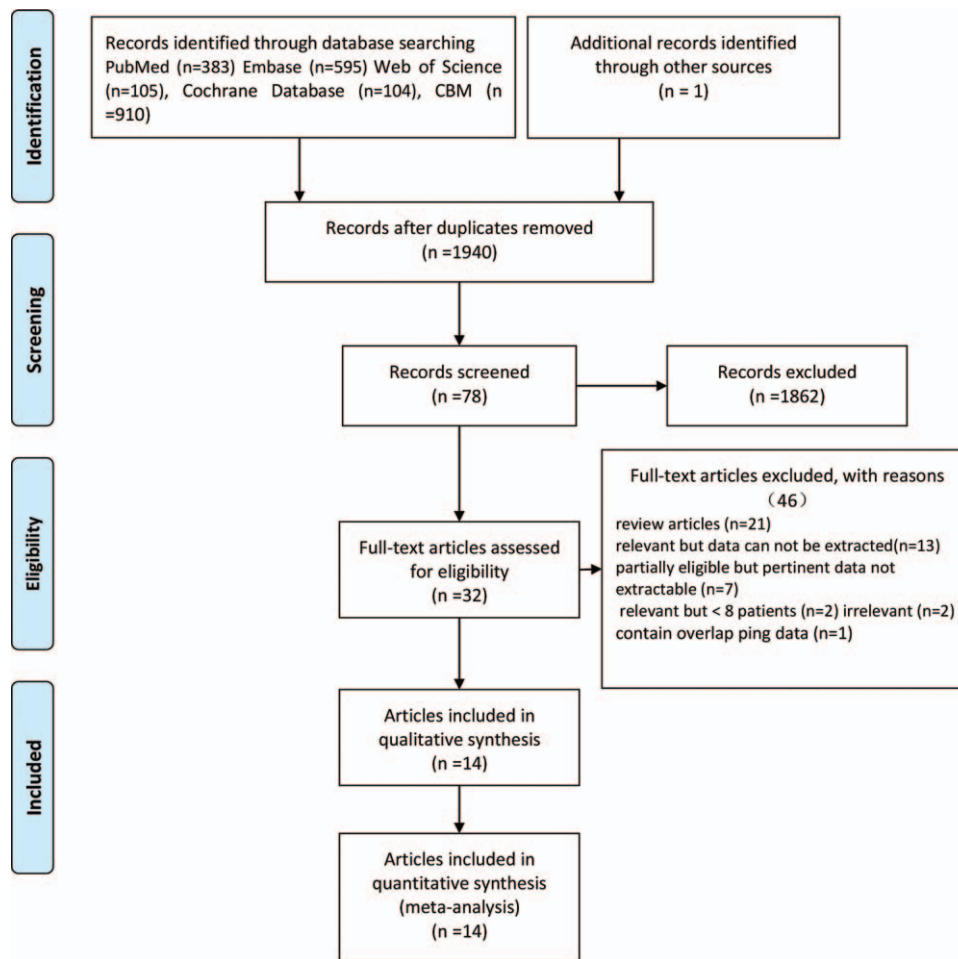


Figure 1. Flow diagram of the study selection process.

In terms of neurological deficits, 397 Patients treated with LMWH, 517 patients with UFH and 127 patients with placebo were enrolled. The network of comparisons between these 3 regimens was shown in Figure 3B. Direct and indirect results

suggested that patients receiving LMWH and UFH had lower rate of neurological deficits (Table 1). However, the comparison between LMWH and UFH had no significant differences based on direct results ( $P > .05$ ). Besides, we also made ranking graph of

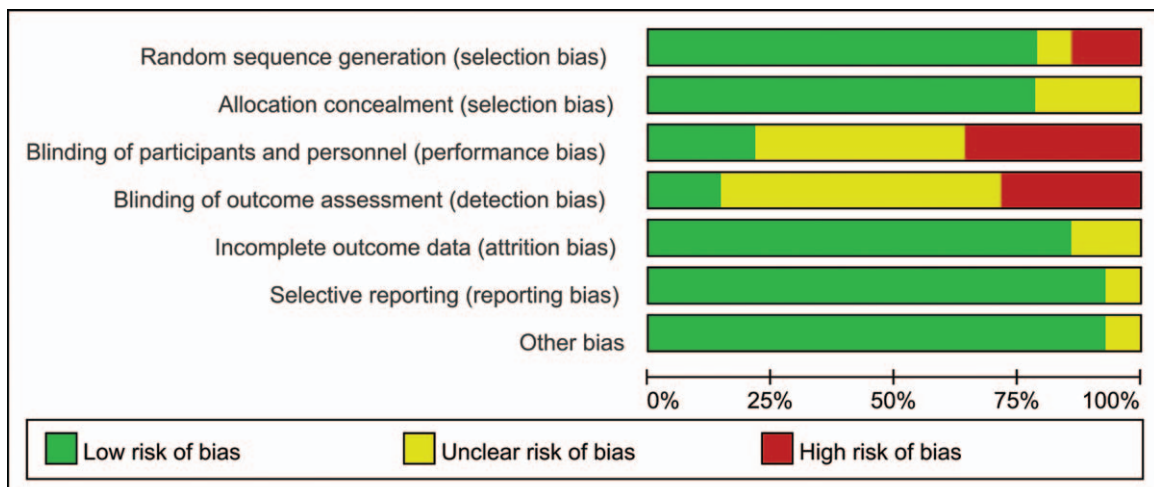
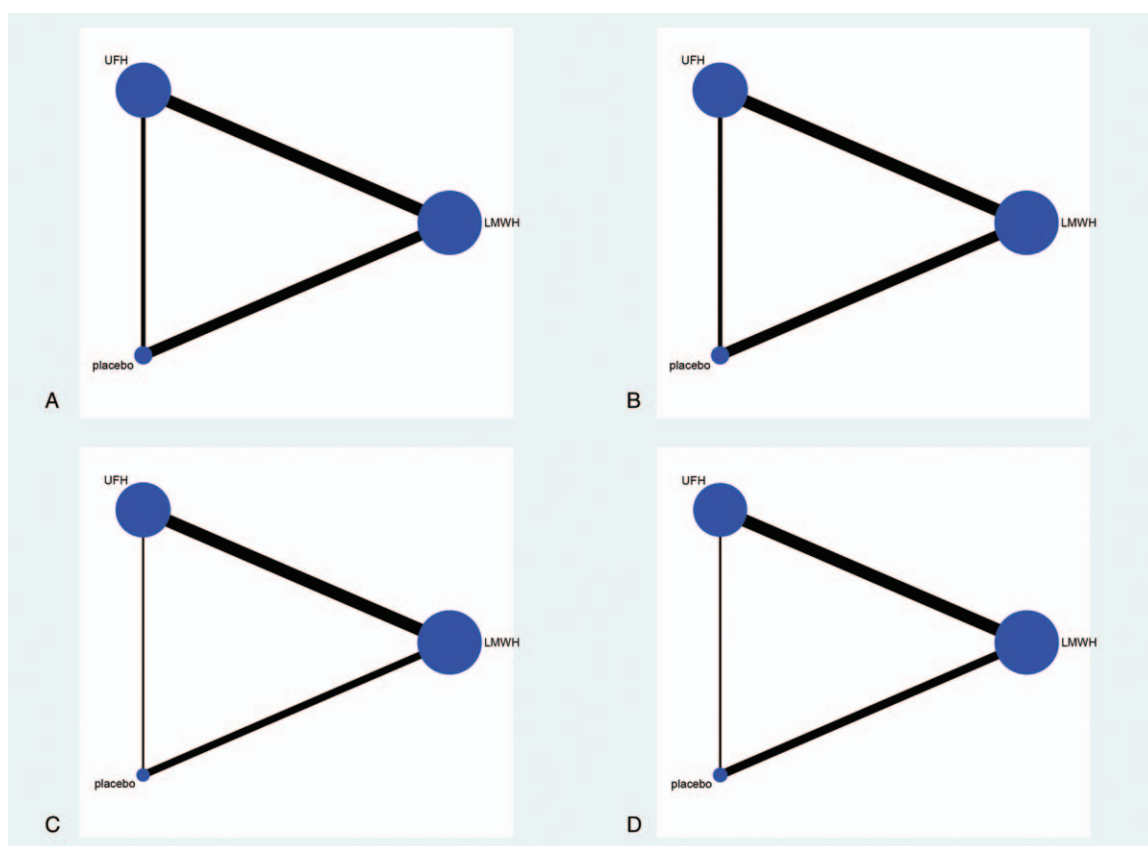


Figure 2. Risk of bias percentile chart.



**Figure 3.** Network of eligible comparisons for efficacy and safety based on overall analysis. (A) Good recovery; (B) Neurological deficits; (C) Death; (D) Bleeding.

distribution of probabilities in Figure 4B. The results based on SUCRA indicated that placebo (100) ranked the first, LMWH (29.2) ranked the second and UFH (20.8) ranked the third in the rate of neurological deficits. The heterogeneity test showed that no severe heterogeneity was observed (Table 1).

As for mortality, 405 patients treated with LMWH, 515 patients with UFH and 90 patients with placebo were enrolled. The network of comparisons was shown in Figure 3C. Direct and indirect results suggested that the incidence of mortality was lower in patients treated with LMWH and UFH than those with placebo (Table 1). Besides, LMWH was more effective in lowering the mortality than UFH. The results based on SUCRA were also consistent with the conclusion above (SUCRA: placebo 98.5; UFH 41.2; LMWH 10.3) (Fig. 4C). No severe heterogeneity was observed (Table 1).

Regarding the complication of bleeding, 355 patients treated with LMWH, 463 patients with UFH and 90 patients with placebo were included. The network of comparisons was shown in Figure 3D. Direct and indirect results demonstrated that the patients treated with LMWH and UFH were less likely to be suffered from intracranial and extracranial bleeding than those with placebo, and LMWH was better than UFH (Table 1). Besides, the ranking graph of distribution of probabilities was shown in Figure 4D. The results based on SUCRA indicated that placebo (77) ranked the first, UFH (60.2) ranked the second and LMWH (12.8) ranked the third in the rate of bleeding. No severe heterogeneity was observed. The results of overall complications were similar to that of the bleeding (Table 1).

The results about poor prognosis and recanalization rate were shown in Table 1 (Supplemental Figure I and II, <http://links.lww.com/MD/C243>).

**3.2.2. Subgroup of patients accompanied with hemorrhagic stroke before anticoagulation.** Around 110 patients treated with LMWH, 206 patients with UFH, and 31 patients with placebo were included in the subgroup analysis of good neurological function recovery. The network of comparisons was shown in Supplemental Figure IIIA, <http://links.lww.com/MD/C243>. Direct and indirect results suggested that the patients treated with LMWH and UFH had higher rates of obtaining good recovery than placebo after CVT (Table 2). Besides, we also made ranking graph of distribution of probabilities in Supplemental Figure IVA, <http://links.lww.com/MD/C243>. The results based on SUCRA indicated that LMWH (96.6) ranked the first in helping patients to obtain good recovery, UFH (53.4) ranked the second and the last was placebo (0).

As for neurological deficits, 125 patients treated with LMWH, 206 patients with UFH, and 45 patients with placebo were enrolled. The network of comparisons between these 3 regimens was shown in Supplemental Figure IIIB, <http://links.lww.com/MD/C243>. Direct and indirect results demonstrated that patients with LMWH and UFH were likely to be suffered from neurological deficits (Table 2). Besides, we also made ranking graph of distribution of probabilities in Supplemental Figure IVB, <http://links.lww.com/MD/C243>. The results based on SUCRA indicated that placebo (100) ranked the first, UFH (32.8) ranked



**Table 1**  
**Results of direct and indirect comparison for the overall analysis.**

Groups	Studies	Cases	Heterogeneity (I <sup>2</sup> )	Direct comparison (95%CI)	Indirect comparison (95%CI)	Inconsistency
Good recovery	13	1041				2.78 (1.00, 12.47)
LMWH vs UFH	6	779	22%	1.21 (0.8, 1.81)	1.11 (0.8, 1.54)	
LMWH vs placebo	5	202	0%	3.83 (1.97, 7.42)	4.76 (2.56, 8.33)	
UFH vs placebo	2	60	32%	10.48 (1.90, 57.85)	4.12 (2.17, 8.33)	
moderate	13	1041				3.648 (1.00, 20.93)
LMWH vs UFH	6	779	0%	1.46 (0.96, 2.2)	1.56 (1.00, 2.43)	
LMWH vs placebo	5	202	0%	1.13 (0.54, 2.38)	0.88 (0.44, 1.79)	
UFH vs placebo	2	60	0%	0.21 (0.05, 0.98)	0.57 (0.26, 1.23)	
severe	13	1041				1.551 (1.00, 9.18)
LMWH vs UFH	6	779	0%	0.57 (0.31, 1.03)	0.6 (0.34, 1.04)	
LMWH vs placebo	5	202	0%	0.27 (0.13, 0.59)	0.25 (0.13, 0.60)	
UFH vs placebo	2	60	0%	0.31 (0.07, 1.37)	0.42 (0.19, 1.16)	
deficit	13	1041				2.467 (1.00, 10.07)
LMWH vs UFH	6	779	0%	0.98 (0.68, 1.4)	1.04 (0.74, 1.47)	
LMWH vs placebo	5	202	0%	0.42 (0.22, 0.78)	0.35 (0.20, 0.61)	
UFH vs placebo	2	60	0%	0.17 (0.05, 0.58)	0.34 (0.18, 0.63)	
death	12	1010				3.359 (1.00, 101.01)
LMWH vs UFH	7	823	0%	0.72 (0.36, 1.43)	0.75 (0.38, 1.49)	
LMWH vs placebo	4	167	0%	0.25 (0.07, 0.81)	0.22 (0.069, 0.65)	
UFH vs placebo	1	20	na	0.1 (0, 2.28)	0.28 (0.058, 0.99)	
poor	14	1085				2.184 (1.00, 12.47)
LMWH vs UFH	7	823	0%	0.51 (0.32, 0.83)	0.55 (0.34, 0.86)	
LMWH vs placebo	5	202	0%	0.14 (0.06, 0.34)	0.17 (0.08, 0.33)	
UFH vs placebo	2	60	0%	0.17 (0.04, 0.79)	0.31 (0.12, 0.67)	
bleeding	11	908				5.576 (1.00, 88.50)
LMWH vs UFH	6	721	0%	0.66 (0.39, 1.12)	0.74 (0.39, 1.39)	
LMWH vs placebo	4	167	21%	0.95 (0.25, 3.69)	0.58 (0.22, 1.56)	
UFH vs placebo	1	20	na	0.26 (0.02, 3.06)	0.79 (0.28, 2.27)	
complications	11					4.058 (1.00, 42.790)
LMWH vs UFH	6	721	0%	0.63 (0.37, 1.07)	0.68 (0.40, 1.12)	
LMWH vs placebo	4	167	21%	0.95 (0.25, 3.69)	0.69 (0.26, 1.85)	
UFH vs placebo	1	20	na	0.38 (0.05, 2.77)	1.03 (0.36, 2.94)	
recanalization rate	5	191				2.897 (1.00, 42.51)
LMWH vs UFH	2	90	0%	1.2 (0.44, 3.28)	1.03 (0.41, 2.63)	
LMWH vs placebo	2	61	0%	7.87 (2.40, 25.78)	10 (3.33, 25)	
UFH vs placebo	1	40	na	19 (2.12, 170.38)	9.09 (2.63, 33.33)	

CI=confidence interval, LMWH=low-weighted molecular heparin, NA=not available, UFH=unfractionated heparin.

the second and LMWH (17.2) ranked the third in the rate of neurological deficits.

In terms of mortality, 125 patients treated with LMWH, 206 patients with UFH and 45 patients with placebo were enrolled. The network of comparisons was shown in Supplemental Figure IIIC, <http://links.lww.com/MD/C243>. Direct and indirect results suggested that the incidence of mortality was lower in patients treated with LMWH and UFH than those with placebo (Table 2). However, the comparison between LMWH and UFH had no significant differences based on direct results ( $P > .05$ ). The results based on SUCRA indicated that placebo (99.2) ranked the first, LMWH (32.2) ranked the second and UFH (19.2) ranked the third in the rate of death (Supplemental Figure IVC, <http://links.lww.com/MD/C243>).

Regarding the complication of bleeding, 110 patients treated with LMWH, 206 patients with UFH and 31 patients with placebo were included. The network of comparisons was shown in Supplemental Figure IIID, <http://links.lww.com/MD/C243>. Direct and indirect results demonstrated that the patients treated with placebo had a higher incidence of re-bleeding than those with LMWH and UFH, and LMWH was better than UFH (Table 2). Besides, the ranking graph of distribution of

probabilities was shown in Supplemental Figure IVD, <http://links.lww.com/MD/C243>. The results based on SUCRA indicated that placebo (99.7) ranked the first, UFH (48.9) ranked the second, and LMWH (1.3) ranked the third in the rate of bleeding.

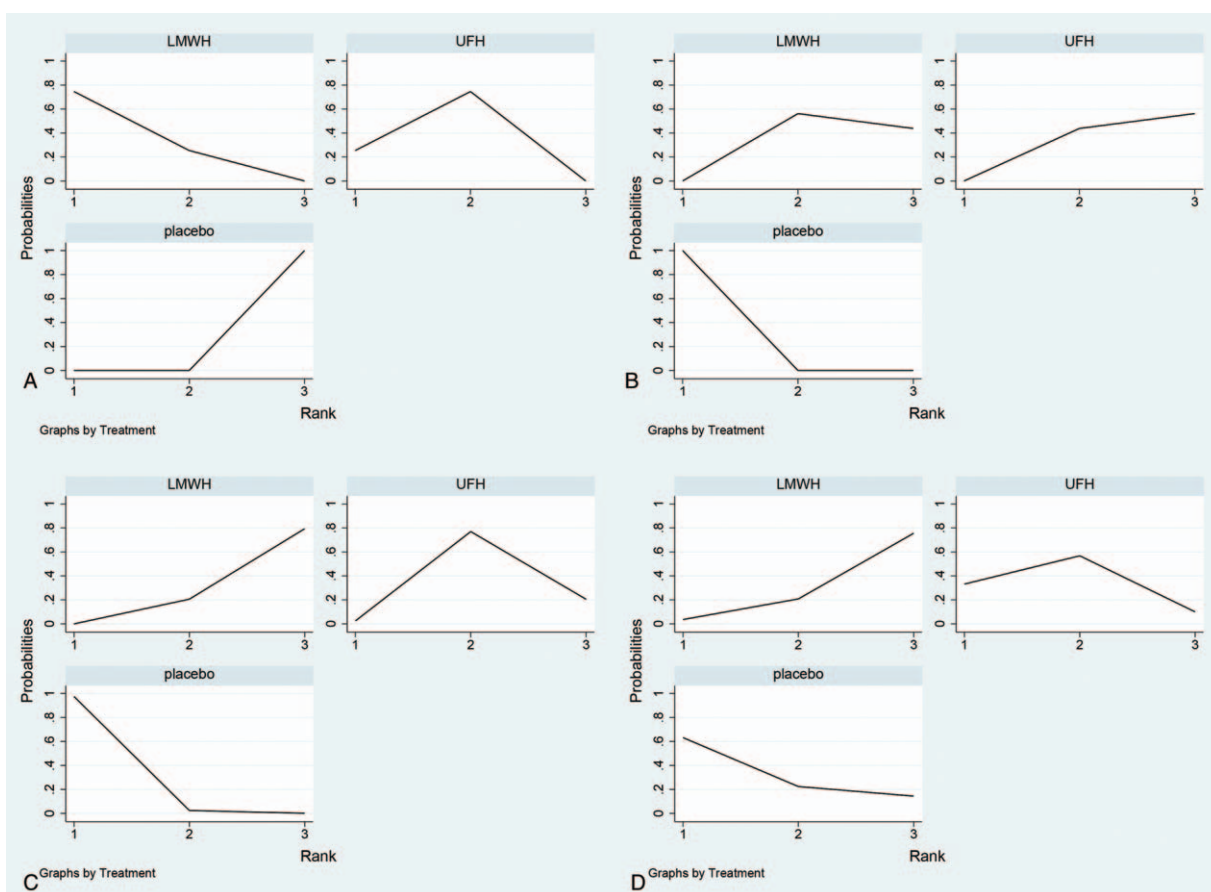
No heterogeneity was observed across each study included in the subgroup analysis (Table 2).

### 3.3. Publication bias

Comparison-adjusted funnel plots show no evidence of dominant asymmetry (Supplemental Figure V, <http://links.lww.com/MD/C243>).

## 4. Discussion

Anticoagulation is the first-line treatment of CVT. Heparin could prevent thrombosis from progression and causing further infarction. However, concerns are also raised that it may cause hemorrhagic complications, with increased neurological deficits. But the efficacy and safety of anticoagulation for CVT have not been systematically reviewed. Most of the studies regarding the anticoagulation of CVT were limited to small case series due to



**Figure 4.** Ranking of treatment strategies based on probability of their effects on the efficacy and safety of anticoagulation from overall analysis. (A) Good recovery; (B) Neurological deficits; (C) Death; (D) Bleeding.

**Table 2**

**Results of direct and indirect comparison for the patients accompanied with hemorrhagic stroke.**

Groups	Studies	Cases	Heterogeneity (I2)	Direct comparison (95%CI)	Indirect comparison (95%CI)	Inconsistency
Good recovery	5	347				3.16 (1.00, 54.50)
LMWH vs UFH	2	267	0%	1.87 (0.9, 3.88)	1.72 (0.85, 3.45)	
LMWH vs placebo	1	20	na	9 (0.81, 100.14)	20 (5.56, 100)	
UFH vs placebo	2	60	0%	15.22 (4.02, 57.60)	12.5 (3.7, 33.3)	
Deficit	6	376				7.135 (1.00, 52.57)
LMWH vs UFH	2	267	0%	1 (0.56, 1.77)	0.81 (0.29, 2.0)	
LMWH vs placebo	2	49	0%	0.56 (0.17, 1.79)	0.11 (0.03, 0.37)	
UFH vs placebo	2	60	0%	0.42 (0.00, 109.05)	0.14 (0.03, 0.49)	
Death	6	342				3.358 (1.00, 39.97)
LMWH vs UFH	2	267	0%	0.92 (0.36, 2.39)	1.19 (0.38, 33.3)	
LMWH vs placebo	2	49	0%	0.31 (0.06, 1.55)	0.18 (0.04, 0.77)	
UFH vs placebo	2	26	67%	0.17 (0.01, 3.01)	0.16 (0.04, 0.60)	
Poor	6	376				7.135 (1.00, 52.57)
LMWH vs UFH	2	267	0%	0.54 (0.26, 1.11)	0.81 (2.90, 2.27)	
LMWH vs placebo	2	49	0%	0.25 (0.07, 0.92)	0.11 (0.03, 0.37)	
UFH vs placebo	2	60	0%	0.07 (0.02, 0.25)	0.14 (0.04, 0.48)	
Bleeding	5					6.241 (1.00, 382.18)
LMWH vs UFH	2	267	0%	0.4 (0.16, 0.97)	0.43 (0.18, 1.03)	
LMWH vs placebo	1	20	0%	0.1 (0.00, 2.28)	0.04 (0.005, 0.28)	
UFH vs placebo	2	60	31%	0.04 (0.00, 0.82)	0.08 (0.01, 0.62)	

CI=confidence interval, LMWH=low-weighted molecular heparin, NA=not available, UFH= unfractionated heparin.

low incidence of CVT. So, we performed this network meta-analysis to evaluate the role of anticoagulation in CVT, especially for the patients accompanied with hemorrhagic stroke before receiving any treatments.

The results of this study demonstrated that anticoagulation could significantly alleviate the neurological deficits and improve the rate of recanalization than those receiving non-anticoagulant. Besides, no additional hemorrhagic complications were observed during anticoagulation. The mortality in the anticoagulant group was also lower than those receiving non-anticoagulant. When it comes to the type of anticoagulants, LMWH shows dominant advantages over UFH in the efficacy and safety of anticoagulation. These results were consistent with the results reported in the literature. Currently, direct data were limited in comparing the use of LMWH and UFH in cerebral venous thrombosis. Most of the studies were focused on leg vein thrombosis or pulmonary embolism. van Dongen and colleagues<sup>[26]</sup> collected as many studies as possible to comprehensively assess the effects of LMWH compared with UFH for the treatment of VTE. Their results showed that the patients receiving LMWH had a lower rate of thrombotic complications, major hemorrhages, mortality, thromboembolic recurrences and higher rate of reduction in thrombus size and recanalization. Besides, compared with UFH, the application of fixed-dose of LMWH was more safe and reliable as suboptimal or overdose anticoagulation with UFH would lead to a worse outcome of CVT.<sup>[27]</sup> However, UFH is better for the critical ill patients who need immediate surgery or other invasive operations as the activated partial thromboplastin time could return to normal within 1 hour after stopping use of UFH.<sup>[28]</sup>

As for patients accompanied with hemorrhagic stroke before any treatments, concerns are raised that anticoagulation may enlarge the bleeding and lead to severe neurological deficits. However, the results of this study demonstrated that anticoagulation would not increase the rate of re-bleeding. Besides, the patients receiving anticoagulation had more preferable outcomes and lower mortality. Experts and guidelines also recommended heparin as standard treatment for CVT, even in the presence of intracerebral lesions, because the benefit outweighs this risk.<sup>[29,30]</sup> In addition, this meta-analysis also showed the advantages of LMWH over UFH in anticoagulation for the patients with hemorrhagic stroke.

## 5. Limitations

There are some limitations in our meta-analysis that cannot be ignored.

Firstly, although no severe heterogeneity was observed, the studies included varied in study design, dose, duration of therapy. Potential heterogeneity may affect the results of this study. Besides, the consistency between direct and indirect analysis was not satisfied in some groups. So, the results from this study should be cautiously interpreted. Secondly, several subgroups, such as dose or duration of therapy, with clinical significance cannot be performed due to limited data, although we had tried to make as extensive analysis as possible. Thirdly, although there was no dominant public bias observed, only papers published in English and Chinese with full-text were included in this meta-analysis. This may leave out other eligible studies that were unpublished or reported in other languages.

## 6. Conclusions

Anticoagulant treatment with heparin is safe and beneficial for patients with CVT, even those with hemorrhagic stroke. Besides, LMWH is better than UFH in the management of CVT. However, the results from this study should be cautiously interpreted due to its limitations.

## Author contributions

This study was designed by Weilin Xu. The data were extracted by Weilin Xu, Liansheng Gao and Tao Li. Anwen Shao and Tao Li performed statistical analysis. The manuscript was written by Weilin Xu and Liansheng Gao. Jianmin Zhang and Anwen Shao participated in discussion development and provided expert guidance. This manuscript was originally written and finally approved by all the authors.

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**Software:** Weilin Xu, Liansheng Gao, Tao Li.

**Supervision:** Anwen Shao, Jianmin Zhang.

**Validation:** Liansheng Gao, Anwen Shao, Jianmin Zhang.

**Visualization:** Jianmin Zhang.

**Writing – original draft:** Weilin Xu.

**Writing – review & editing:** Tao Li, Anwen Shao, Jianmin Zhang.

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