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Yatabe, Tomoaki ; Inoue, Shigeaki ; Sakamoto, So ; Sumi, Yuka ; Nishida, Osamu ; Hayashida, Kei ; Hara, Yoshitaka ; Fukuda, Tatsuma ;…

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Title:

The anticoagulant treatment for sepsis induced disseminated intravascular coagulation; network meta-analysis.

Running title:

The anticoagulant treatment for septic DIC

Author:

Tomoaki Yatabe[1], Shigeaki Inoue[2], So Sakamoto[3], Yuka Sumi[4], Osamu Nishida[5], Kei Hayashida[6], Yoshitaka Hara[5], Tatsuma Fukuda[7], Asako Matsushima[8], Akihisa Matsuda[9], Hideto Yasuda[10], Kazuto Yamashita[11], Moritoki Egi[12]

[1]Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School,
Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan

[2]Department of Emergency and Critical Care Medicine, Tokai University Hachioji Hospital,
1838 Ishikawa-cho, Hachioji, Tokyo, 192-0032, Japan

[3]Department of Emergency and Critical Care Medicine, Juntendo University Nerima Hospital,
3-1-10 Takanodai, Nerima-ku, Tokyo, 177-8521, Japan

[4]Healthcare New Frontier Promotion Headquarters Office, Kanagawa Prefectural Government,
1Nihon-odori, Naka-ku, Yokohama, Kanagawa, 231-8588, Japan

[5]Department of Anesthesiology and Critical Care Medicine, Fujita Health University School of Medicine,
1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan

[6]Department of Emergency and Critical Care Medicine, School of Medicine, Keio University,
35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan

[7]Depertment of Emergency and Critical Care Medicine, Graduate School of Medicine, University of the Ryukyus,
207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan

[8]Department of Advancing Acute Medicine, Nagoya City University Graduate School of Medical Sciences,
1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, 467-8602, Japan

[9]Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital,

1715 Kamagari, Inzai, Chiba, 270-1694, Japan

[10]Department of Intensive Care Medicine, Kameda Medical Center,

929 Higashi-cho, Kamogawa, Chiba, 296-8602, Japan

[11]Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University,

Yoshida Konoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan

[12]Department of Anesthesiology, Kobe University Hospital,

7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

Corresponding author:

Moritoki Egi

Department of Anesthesiology, Kobe University Hospital,

7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

E-mail: moriori@tg8.so-net.ne.jp

Tel: +81-78-382-6172

Fax: +81-78-382-6189

Author's COI:

The authors declare that they have no conflict of interest.

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Abstract

Introduction: The benefits and harm caused by anticoagulant treatments for sepsis induced disseminated intravascular coagulation (DIC) remain unclear. Therefore, we performed a network meta-analysis to assess the effect of available anticoagulant treatments on patient mortality, DIC resolution and the incidence of bleeding complication in patients with septic DIC.

Materials and Methods: We considered all studies from four recent systematic reviews and searched the PubMed, MEDLINE, and Cochrane databases for other studies that investigated anticoagulant treatment for septic DIC using antithrombin, thrombomodulin, heparin, or protease inhibitors in adult critically ill patients. These four anticoagulants and placebo were compared. The primary outcome in this study was patient mortality, and the secondary outcomes were the DIC resolution rate and incidence of bleeding complications.

Results: The network meta-analysis included 1340 patients from nine studies. There were no significant differences in the risks of mortality and bleeding complications among all direct comparisons and the network meta-analysis. Using a placebo was associated with a significantly lower rate of DIC resolution, compared to antithrombin in the direct comparison (odds ratio [OR]: 0.20, 95% credible interval [95% CrI]: 0.046–0.81) and in the network meta-analysis (OR: 0.20, 95% CrI: 0.043–0.84).

Conclusions: Our study revealed no significant differences in the risks for mortality and bleeding complications when a placebo and all four anticoagulants were compared in septic DIC patients. The results also indicated that antithrombin was associated with a five-fold higher likelihood of DIC resolution, compared to placebo.

Keywords: anticoagulant treatment, disseminated intravascular coagulation, sepsis, network meta-analysis

INTRODUCTION

In septic patients, disseminated intravascular coagulation (DIC) is common and can worsen patient outcomes [1]. There are number of anticoagulants proposed as possible treatments to resolve DIC and improve outcomes in patients with septic DIC [2]. However, their benefit on the outcomes is still unclear [3, 4]. For example, administration of an anticoagulant in one study had the potential to increase the risk of bleeding and worsen patients outcomes [5]. To determine the benefit and harm caused by anticoagulant treatments in this cohort, several meta-analyses were conducted [6-9]. Although available randomized controlled trials (RCTs) exploring this topic had assessed the effect of various anticoagulants such as antithrombin, thrombomodulin, and heparin, traditional meta-analyses can compare only 2 interventions. Thus, it was difficult to evaluate and make conclusions regarding the effect of individual anticoagulation treatments, especially to rank each treatment and placebo in accordance with the effect.

Network meta-analyses allow for comparisons of multiple treatments, by summarizing a comprehensive and coherent set of comparisons [10,11]. This approach allows for direct comparisons of interventions within RCTs, as well as indirect comparisons across trials based upon a common comparator (e.g., placebo or a standard treatment) [12]. Accordingly, we performed a network meta-analysis to assess the effect of each anticoagulant treatment on mortality, DIC resolution, and the incidence of bleeding complications in patients with septic DIC.

METHODS

For the current study, we performed a network meta-analysis using randomized controlled trials to assess the effect of anticoagulant treatments in adult critically ill patients with septic DIC. This study was conducted according to the recommendations and checklist from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for network meta-analysis [10]. We developed a review protocol before starting the review process.

Eligible inclusion

Studies were considered eligible if they fulfilled the following criteria: (1) studies that were RCTs; (2) studies with full-text publication in English; (3) studies that included adult critically ill patients with sepsis induced DIC; (4) studies that aimed to assess the effect of anticoagulant treatment on mortality, DIC resolution rate, and the incidence of bleeding complications.

Although there are various definitions of DIC, we included all definitions of DIC mentioned in the studies. These definitions were based on the International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria, ISTH non-overt DIC criteria [13], the Japanese Association for Acute Medicine (JAAM) DIC criteria [14], or the authors' original criteria. The primary outcome in this study was short term mortality. The secondary outcomes were the DIC resolution rate and incidence of bleeding complications. DIC resolution was defined as a score of less than the thresholds of DIC criteria in each study.

Search strategy

For the network meta-analysis, we searched the PubMed, MEDLINE, and Cochrane databases to June 18, 2017 using the following search terms: ("disseminated intravascular coagulation") AND ("randomized" or "randomized"). In addition, we considered all studies from four recent systematic reviews [6-9]. We also evaluated the reference lists of the relevant clinical trials to identify additional studies.

Study selection

All authors participated in the review process. Two reviewers independently screened titles and abstracts to determine potential eligibility. These reviewers also independently assessed the eligibility of each full-text paper. If the opinion of two reviewers conflicted in the process, another reviewer also independently evaluated the studies. We then finalized the decisions through group discussion.

Data collection

We created the abstracted data, which included the first author's name, year of publication, number of study sites, number of patients, cause of DIC, age, sex, diagnostic criteria for DIC, dose and duration of intervention drug and control treatment. We also collected the information for outcomes including mortality, definition of mortality, DIC resolution rate, and incidence of bleeding complications. Methodological quality was evaluated using the Cochrane risk of bias assessment tool, which evaluates randomization, allocation concealment, blinding of the study participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective outcome reporting, and other potential sources of bias [15].

Statistical analysis

The network meta-analysis was performed within a Bayesian framework using JAGS software (version 4.1.0), R software (version 3.1.1), and the rjags and gemtc packages [16, 17]. Comparative odds ratios (OR) were reported with their 95% credible intervals (CrI), and a random effects model was selected. Furthermore, a Bayesian framework meta-analysis provided a rank probability for each of the anticoagulant treatments and placebo and outcome. Inconsistencies were assessed using Bayesian P-values based on a node splitting analysis from the rjags and gemtc packages. Substantial heterogeneity was defined as an I^2 value of ≥50% [18,19].

Our primary analysis was attempted in all studies including those with a post-hoc subgroup analysis. We then further performed the same analysis excluding these studies.

RESULTS

Study selection

Figure 1 shows the flowchart indicating the steps of the study selection. In our literature search, we identified 254 publications through the PubMed search, 244 publications through the MEDLINE search, and 115 publications through the Cochrane search. In addition, we found 49 studies that were included in the four previous systematic reviews [6-9]. After screening the titles and abstracts of all searched articles, we selected 26 studies. After the full-text screening, we excluded 17 studies (Supplementary appendix 1). Accordingly, our analysis included 1340 patients from nine studies [20-28]. Two studies were subgroup analyses of main RCTs [21, 26].

Study characteristics.

Table 1 shows the detailed information for each study. Among nine studies, five were multicenter studies [20,21,23,24,26]. The number of included patients was a median of 60 patients (IQR; 36–161). The mean age of the patients varied from 49 to 76 years.

A total of four studies assessed antithrombin III; three of these studies compared antithrombin III with a placebo [20-22] and one compared antithrombin III with gabexate mesilate [23]. There were three studies that assessed thrombomodulin; two of these studies compared thrombomodulin with a placebo [24,25], and one compared thrombomodulin with heparin. There was one study that assessed gabexate mesilate and one study that assessed heparin, and both studies compared each drug with a placebo.

In regard to the definition of DIC, three studies used the JAAM criteria for diagnosing DIC [20,23,24], two studies used the ISTH criteria [21, 24], another two studies used the Japanese Ministry of Health and Welfare criteria [26,27] and the last two studies used the authors' original criteria [22,28]. The risks of bias for each study are shown in Figure 2.

Mortality

The network of eligible comparisons for the meta-analysis for mortality (nine RCTs) is shown in Figure 3A. The forest plot for mortality is shown in Figure 3B. There were no significant differences in these outcomes for all direct comparisons and the network meta-analysis. The rank probabilities for the four anticoagulant treatments and placebo treatment are shown in Table 2. This analysis suggested that antithrombin had a 50.1% probability of being the best treatment for reducing in-hospital mortality, while heparin had a 46.0% probability of being the worst treatment for reducing in-hospital mortality.

DIC resolution rate

The network of eligible comparisons for the meta-analysis for the DIC resolution rate (five RCTs) is shown in Figure 4A. No studies evaluated the effects of protease inhibitors on the DIC resolution rate. Antithrombin treatment was associated with a significantly higher DIC resolution rate compared to a placebo in the direct comparison (OR: 0.20, 95% CrI: 0.046–0.81) and the network meta-analysis (OR: 0.20, 95% CrI: 0.043–0.84) (Figure 4B). The rank probabilities indicated that antithrombin had a 74.2% probability of being the best treatment for promoting DIC resolution (Table 2).

Bleeding complications

The network of eligible comparisons for the meta-analysis for bleeding complications (six RCTs) is shown in Figure 5A. No studies evaluated the effects of protease inhibitors on bleeding complications. The forest plot for bleeding complications is shown in Figure 5B. There were no significant differences for all direct comparisons and the network meta-analysis. The rank probabilities indicated that antithrombin had a 40.1% probability of being the best treatment in terms of the risk of bleeding complications. In contrast, heparin had a 95.2% probability of being the worst treatment (Table 2).

Additional analysis

We performed an additional analysis excluding two RCTs [21, 26] conducted as a post-hoc subgroup analysis. In this sensitive analysis, there were no significant differences for all direct comparisons and the

network meta-analysis (seven RCTs). The analysis of rank probability indicated that heparin and antithrombin had similar probabilities for being the best treatment (Table 2). In terms of the DIC resolution rate (four RCTs), antithrombin was associated with a significantly higher DIC resolution rate, compared to a placebo in the direct comparison (OR: 0.20, 95% CrI: 0.045–0.85). For bleeding complications (four RCTs), there were no significant differences for all direct comparisons and the network meta-analysis. The rank probabilities indicated that antithrombin might be the best treatment in these two outcomes (79.7%, 87.4%, respectively) (Table 2).

DISCUSSION

We conducted this network meta-analysis to assess the effect of each anticoagulant treatment on mortality, DIC resolution and the incidence of bleeding complication in patients with septic DIC. The results revealed that there were no significant differences in the risks of mortality and bleeding complications for all comparisons of the four anticoagulant treatments and placebo treatment. However, antithrombin treatment was associated with a five-fold higher likelihood of DIC resolution, compared to the placebo treatment. Even after excluding two post-hoc studies, these results were not altered. The sepsis induced DIC was one of the major complications; however, there is no specific treatment for this condition so far. Therefore, our results are relevant and require further discussion.

The use of heparin for septic DIC

The ISTH recommendation for heparin use was based on the experimental studies that reported on the inhibition of coagulation activity using heparin in a DIC setting [29]. However, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG2016) recommended not using heparin as a standard treatment in sepsis-associated DIC (Level D, expert consensus) [30]. There was no recommendation for the use of heparin in the 2016 Surviving Sepsis Campaign guidelines [4].

In 2015, Zarychanski et al conducted a systematic review and reported that the use of heparin tended to decrease mortality [RR, 0.88 (95% CI, 0.77–1.00), p=0.05] without a risk for major bleeding [RR, 0.79 (95% CI, 0.53–1.17)] compared with a placebo or usual care in septic patients [9]. However, among the nine RCTs in the systematic review by Zarychanski et al, there was only one RCT conducted in patients with sepsis-induced DIC. This RCT was excluded from our analysis because not all the patients were critically ill or admitted to the ICU. In the meta-analysis conducted in the J-SSCG2016, the use of heparin did not affect the 28-day mortality rate [RR 1.13, (95% CI, 0.62-2.06), p=0.69], and had a non-significant tendency to increase the incidence of bleeding complications [RR 2.84, (95% CI, 0.27-29.88), p=0.38] [30]. Similar results were reported in a meta-analysis conducted by Umemura et al [7]. Considering the above studies and our results, using heparin in patients with septic DIC should be done with caution due to the risk of bleeding.

The use of antithrombin for Septic DIC

The 2016 SSCG recommended not to use antithrombin for the treatment of sepsis and septic shock (moderate quality of evidence, strong recommendation) [4]. The J-SSCG2016 recommended to use antithrombin for patients with sepsis-associated DIC with ≤ 70% of antithrombin activity (Level 2B, weak recommendation) [30]. The ISTH had also recommended to use an antithrombin in DIC patients (potentially recommended) [29].

In 2016, Allingstrup M et al. conducted a systematic review and reported that antithrombin had no impact on mortality of severe sepsis and DIC patients [RR 0.95 (95% CI, 0.88–1.03), p = 0.19] with significantly higher risk of bleeding complication [RR 1.58 (95 % CI, 1.35–1.84), p < 0.001] [6]. However, in another systematic review conducted by Umemura et al, the use of antithrombin significantly reduced mortality in septic DIC patients compared with the control group [RR 0.63 (95% CI, 0.45–0.90), p = 0.01] [7]. A meta-analysis conducted by the J-SSCG2016 also indicated that antithrombin significantly reduced mortality but not the risk of bleeding complications in septic DIC patients [RR 0.68 (95% CI, 0.49–0.93), p = 0.02; RR 1.17 (95% CI, 0.45–3.01), p = 0.75] [30].

The above controversies on the use of antithrombin may be explained by the KyberSept trial [5]. Umemura [7] and the J-SSCG2016 [30] used the results of subgroup analysis of the KyberSept study conducted on septic DIC patients by Kienast et al [21]. In contrast, Allingstrup [6] used the results of the whole cohort in the KyberSept study [5], which suggested the increase of risk of bleeding complication without any significant effect on mortality for the use of antithrombin.

Considering the bias associated with including the post-hoc subgroup analysis, we conducted the sensitive analysis excluding the two subgroup studies [21, 26]. Even after excluding the post-hoc studies, the use of antithrombin still had a significantly higher rate of DIC resolution, with lower probabilities of bleeding complications. Overall, our results and the results of other studies suggest that antithrombin should be used in septic DIC patients and not in septic patients without DIC. Future studies are warranted to confirm or refute this hypothesis.

The use of thrombomodulin for Septic DIC

In SSCG 2016 [4], there was no recommendation for the use of thrombomodulin in septic patients. In J-SSCG2016, there is no clear recommendation for the use of thrombomodulin in sepsis-associated DIC (Level B, expert consensus) [30]. The ISTH had recommended to use thrombomodulin in DIC patients (potentially recommended) [29]. The recommendation of ISTH was based on an RCT which reported that thrombomodulin significantly increased the resolution rate when compared to heparin in patients with DIC [31].

In 2015, Yamakawa et al. conducted a systematic review and reported that the use of thrombomodulin in septic DIC patients did not differ when compared to a control group in terms of mortality, DIC resolution rate, and bleeding complications [RR 0.81 (95% CI, 0.62–1.06), p = 0.12; RR 1.28 (95% CI, 0.93–1.75), p = 0.13, RR 0.83 (95% CI, 0.22–3.11), p = 0.78, respectively] [8]. Considering past analysis and our results, there would be insufficient information to elucidate the risk and benefit of thrombomodulin in septic DIC patients.

Limitations

The present study has several limitations. First, the meta-analysis only included nine studies, despite the fact that we searched three databases and examined the reference lists from four recent systematic reviews. In seven RCTs, the number of patients in each arm was less than 50 (range 8-47). Thus, there is insufficient evidence regarding the effects of anticoagulant treatment for septic DIC. Second, the included studies used different criteria for diagnosing DIC, as well as different doses and durations of the anticoagulant treatments. In nine RCTs, five different criteria were used. In addition, DIC resolution was evaluated on different days, namely, day 1 [24], 3 [20], 4 [22] and day 7 [25, 26]. The total dose of antithrombin in one study [20] was approximately 5250 U over 3 days, as opposed to 30 000 U over 4 days in another study [21]. Similarly, Aikawa et al. [26] used heparin at a dose of 192 U/kg/day over 6 days, while Liu et al. [28] used it a dose of 70 U/kg/day over 5-7 days. It is very likely that the various definitions and treatments affected our results. Finally, the incidence of bleeding complications was very low. Although six RCTs reported the incidence of bleeding complications, the number of patients who experienced bleeding was quite low with only 0-3 in four RCTs. Unfortunately, the number of patients included in the study was too limited to evaluate the incidence of bleeding complications accurately. Therefore, we think that further large RCTs are needed to clarify the effect and potential danger of using anticoagulants in septic DIC patients.

Conclusions

Our study revealed no significant difference in the risk for mortality and bleeding complications when the placebo treatment and all four anticoagulant treatments were compared in septic DIC patients. The results also indicated that antithrombin treatment was associated with a five-fold higher likelihood of DIC resolution, compared to the placebo treatment. However, there is insufficient evidence regarding the effects of anticoagulant treatments for septic DIC because only nine RCTs were eligible for inclusion.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Figure legend

Figure 1. Flow diagram of study selection.

SR: systematic review, DIC: disseminated intravascular coagulation, RCT: randomized controlled trial, AT: antithrombin, TM: thrombomodulin

Figure 2. Risk of bias in the included randomized controlled trials.
The Cochrane Collaboration tool was used to assess the risk of bias. The authors' judgments were used to assign the risk of bias for each included study. + (green), low risk of bias; − (red), high risk of bias; empty space, unclear risk of bias.

Figure 3. Mortality. A) The network of all eligible comparisons for the meta-analysis. B) Forest plot.
N: number of studies, AT: antithrombin, TM: thrombomodulin, GM: gabexate mesilate, OR: odds ratio, 95% CrI: 95% credible intervals, no direct comparison: there were no studies directly comparing these anticoagulants or placebo, number of patients: the number of patients per each groups.

B) The upper row indicates the pairwise meta-analysis result (black) and the lower row indicates the network meta-analysis result (blue).

Figure 4. DIC resolution rate. A) The network of all eligible comparisons for the meta-analysis. B) Forest plot.
N: number of studies, AT: antithrombin, TM: thrombomodulin, OR: odds ratio, 95% CrI: 95% credible intervals, no direct comparison: there were no studies directly comparing these anticoagulants or placebo, number of patients: the number of patients per each groups.

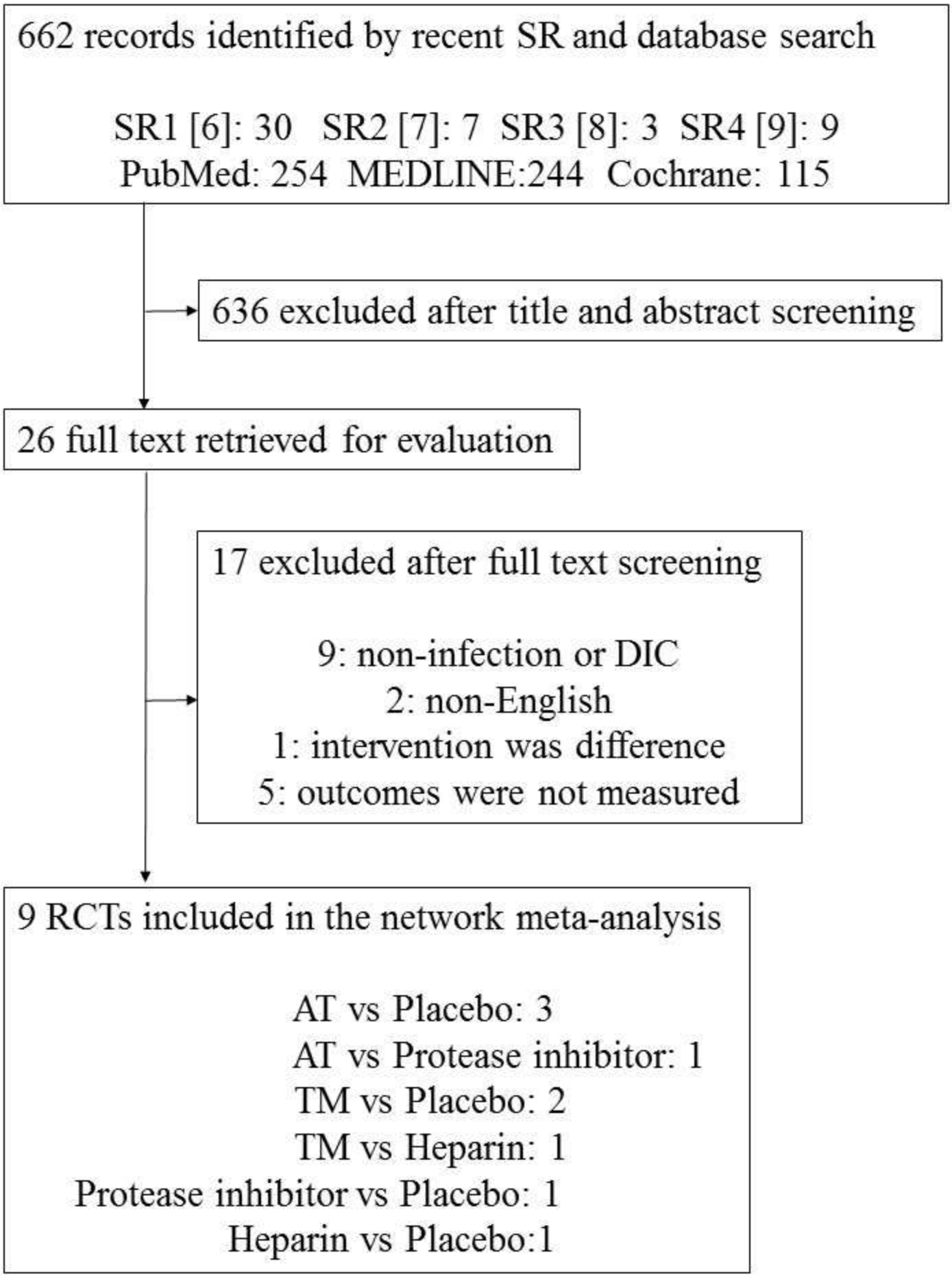
B) The upper row indicates the pairwise meta-analysis result (black) and the lower row indicates the network meta-analysis result (blue).

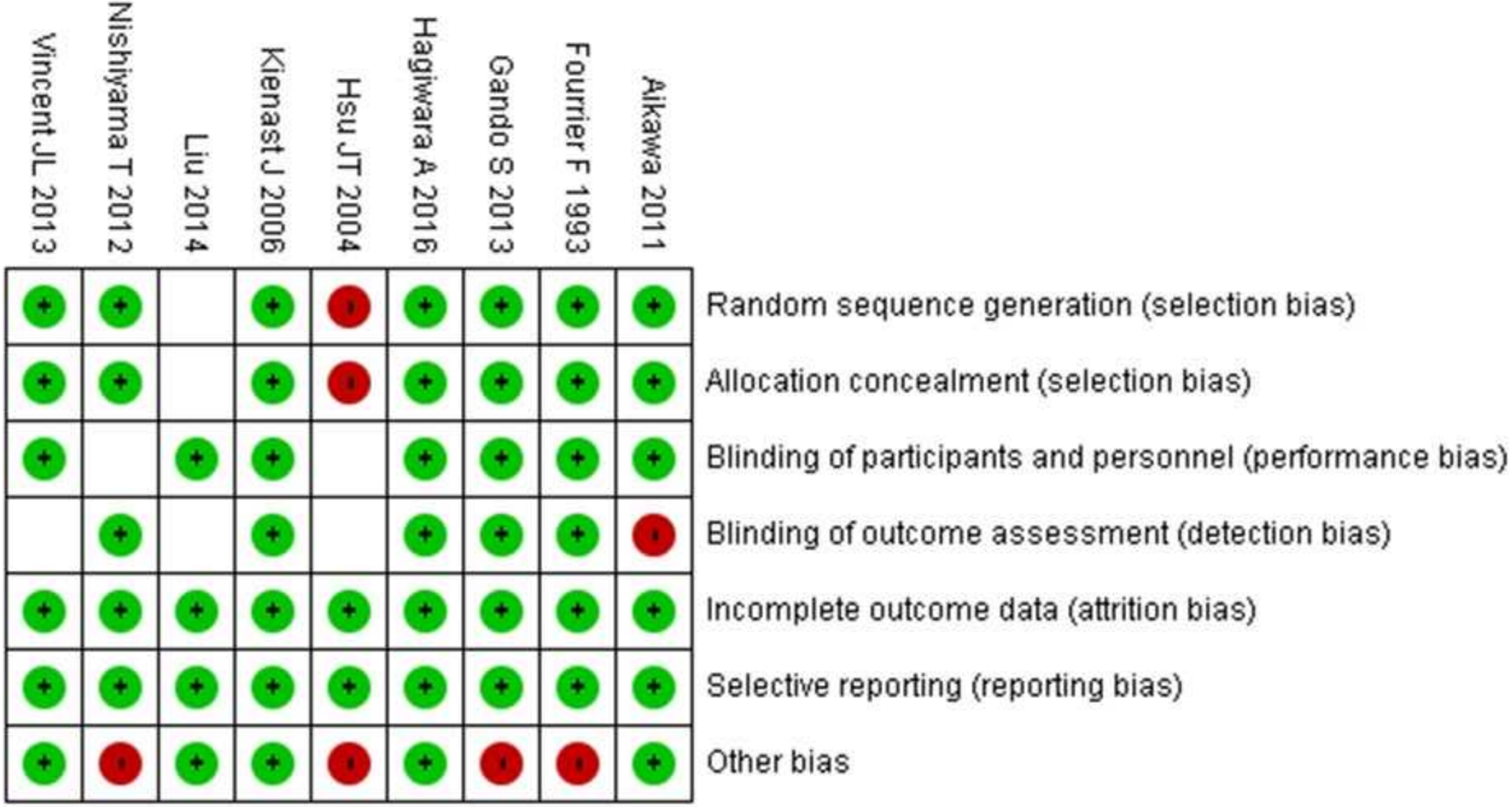
Figure 5. Bleeding complications. A) The network of all eligible comparisons for the meta-analysis. B) Forest

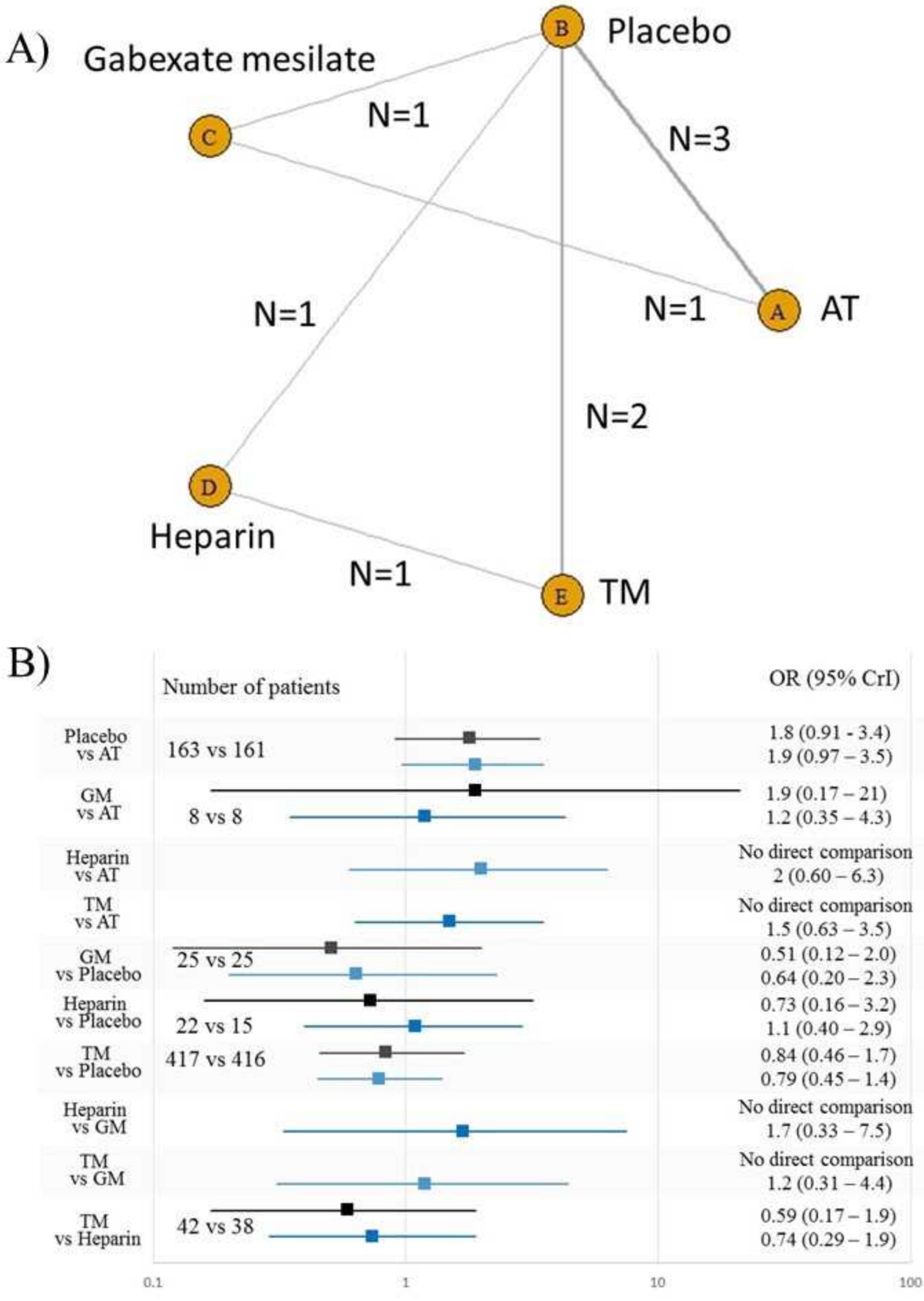
plot.

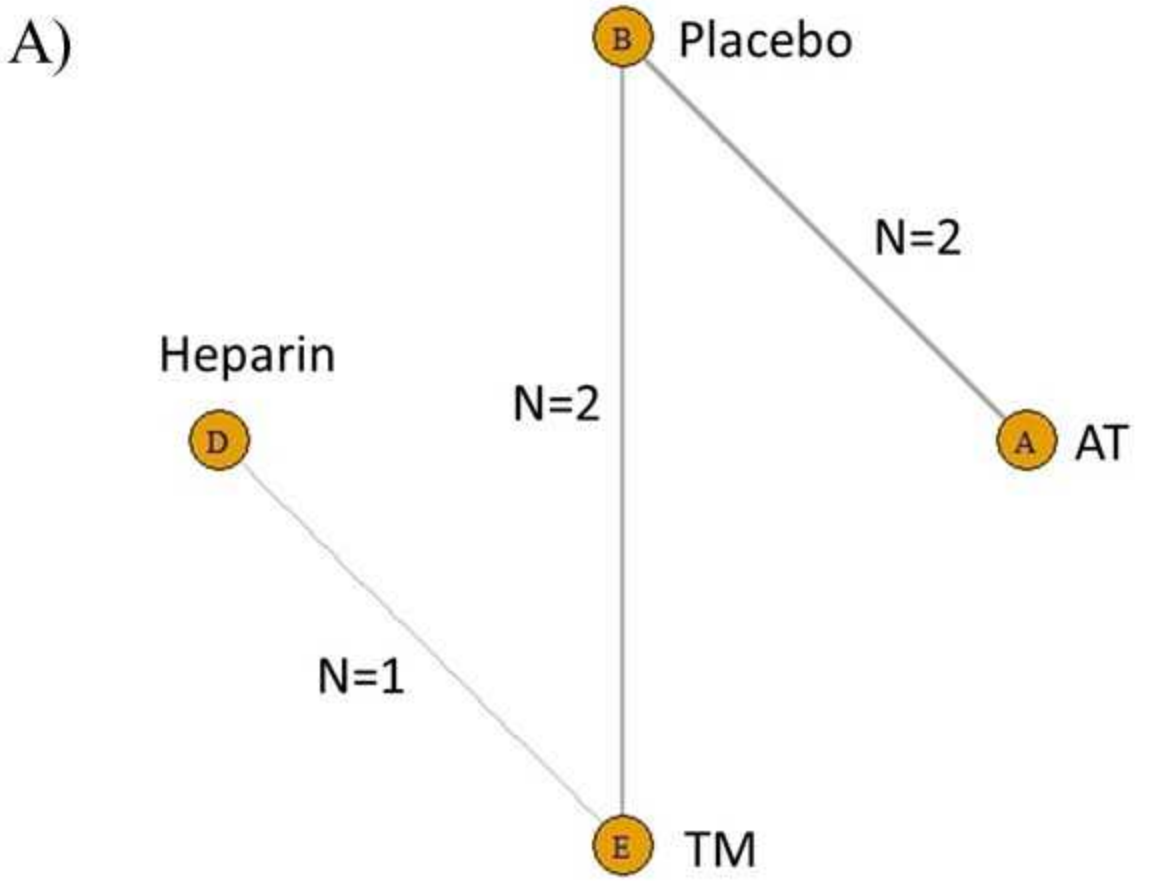
N: number of studies, AT: antithrombin, TM: thrombomodulin, OR: odds ratio, 95% CrI: 95% credible intervals, no direct comparison: there were no studies directly comparing these anticoagulants or placebo, number of patients: the number of patients per each groups.

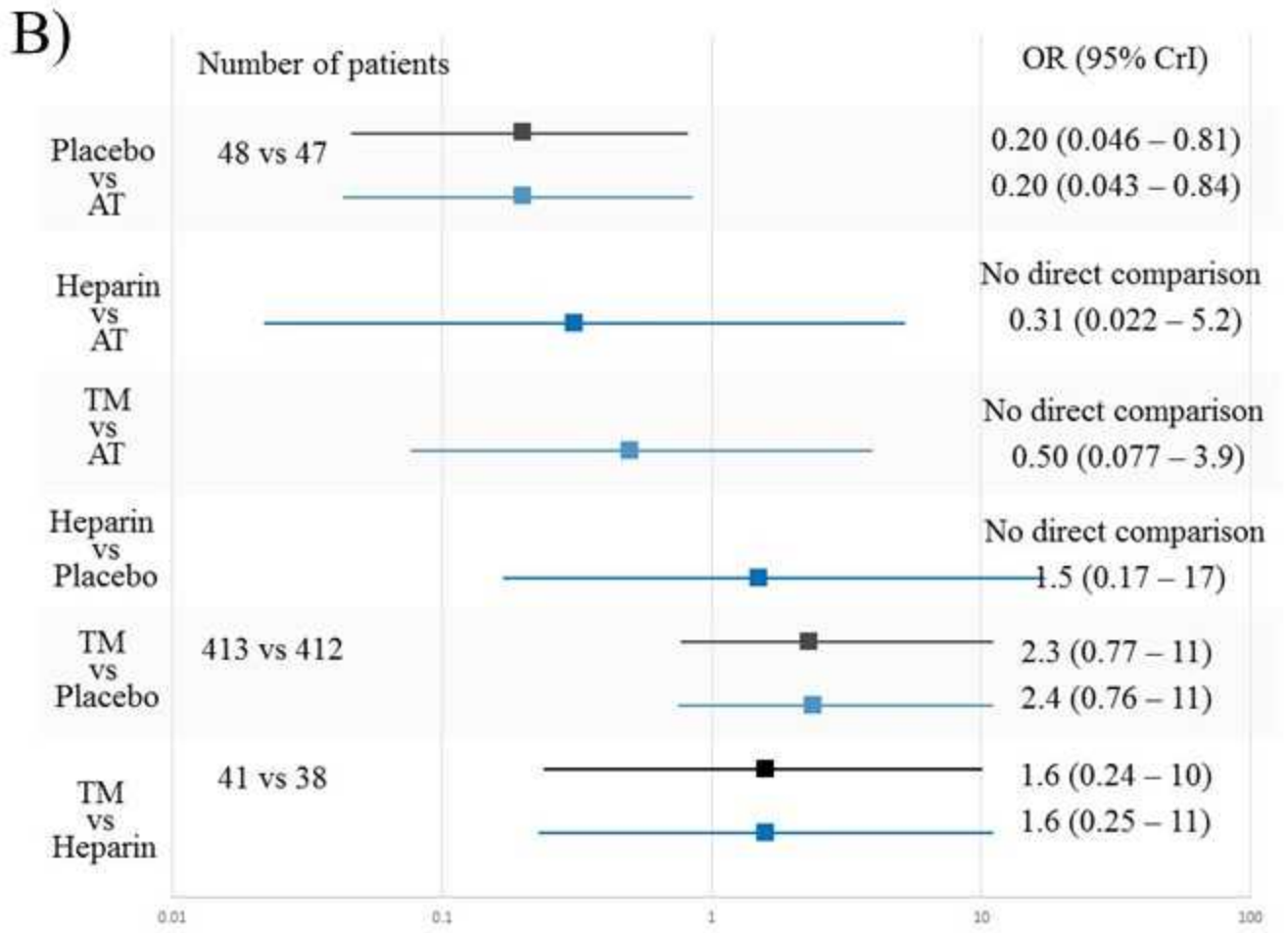
B) The upper row indicates the pairwise meta-analysis result (black) and the lower row indicates the network meta-analysis result (blue).


662 records identified by recent SR and database search
SR1 [6]: 30 SR2 [7]: 7 SR3 [8]: 3 SR4 [9]: 9
PubMed: 254 MEDLINE:244 Cochrane: 115
636 excluded after title and abstract screening
26 full text retrieved for evaluation
17 excluded after full text screening
9: non-infection or DIC
2: non-English
1: intervention was difference
5: outcomes were not measured
9 RCTs included in the network meta-analysis
AT vs Placebo: 3
AT vs Protease inhibitor: 1
TM vs Placebo: 2
TM vs Heparin: 1
Protease inhibitor vs Placebo: 1
Heparin vs Placebo:1


Aikawa 2011
Fourrier F 1993
Gando S 2013
Hagiwara A 2016
Hsu JT 2004
Kienast J 2006
Liu 2014
Nishiyama T 2012
Vincent JL 2013
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias


A)
Gabexate mesilate
Placebo
B
C
D
E
A
AT
Heparin
TM
N=1
N=3
N=1
N=1
N=2
N=1
B)
Number of patients
OR (95% CrI)
Placebo vs AT
163 vs 161
1.8 (0.91 - 3.4)
1.9 (0.97 – 3.5)
GM vs AT
8 vs 8
1.9 (0.17 – 21)
1.2 (0.35 – 4.3)
Heparin vs AT
No direct comparison
2 (0.60 – 6.3)
TM vs AT
No direct comparison
1.5 (0.63 – 3.5)
GM vs Placebo
25 vs 25
0.51 (0.12 – 2.0)
0.64 (0.20 – 2.3)
Heparin vs Placebo
22 vs 15
0.73 (0.16 – 3.2)
1.1 (0.40 – 2.9)
TM vs Placebo
417 vs 416
0.84 (0.46 – 1.7)
0.79 (0.45 – 1.4)
Heparin vs GM
No direct comparison
1.7 (0.33 – 7.5)
TM vs GM
No direct comparison
1.2 (0.31 – 4.4)
TM vs Heparin
42 vs 38
0.59 (0.17 – 1.9)
0.74 (0.29 – 1.9)
0.1
1
10
100


A)
B
Placebo
N=2
Heparin
N=2
D
A
AT
N=1
E
TM


B)
Number of patients
OR (95% CrI)
Placebo vs AT
48 vs 47
0.20 (0.046 – 0.81)
0.20 (0.043 – 0.84)
Heparin vs AT
No direct comparison
0.31 (0.022 – 5.2)
TM vs AT
No direct comparison
0.50 (0.077 – 3.9)
Heparin vs Placebo
No direct comparison
1.5 (0.17 – 17)
TM vs Placebo
413 vs 412
2.3 (0.77 – 11)
2.4 (0.76 – 11)
TM vs Heparin
41 vs 38
1.6 (0.24 – 10)
1.6 (0.25 – 11)
0.01
0.1
1
10
100

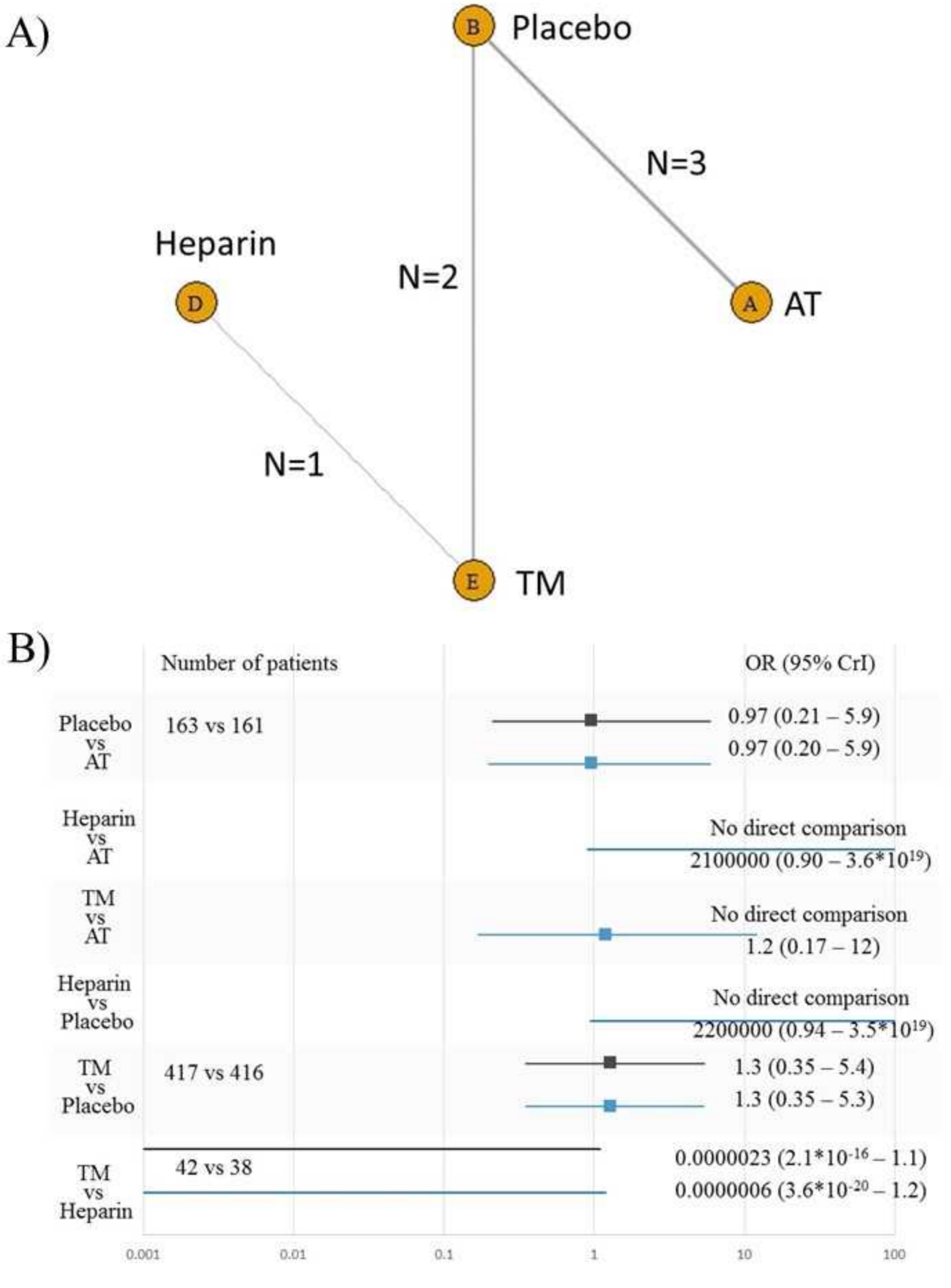

A)
B
Placebo
N=3
Heparin
N=2
D
A
AT
N=1
E
TM
B)
Number of patients
OR (95% CrI)
Placebo vs AT
163 vs 161
0.97 (0.21 – 5.9)
0.97 (0.20 – 5.9)
Heparin vs AT
No direct comparison
2100000 (0.90 – 3.6*10^19)
TM vs AT
No direct comparison
1.2 (0.17 – 12)
Heparin vs Placebo
No direct comparison
2200000 (0.94 – 3.5*10^19)
TM vs Placebo
417 vs 416
1.3 (0.35 – 5.4)
1.3 (0.35 – 5.3)
TM vs Heparin
42 vs 38
0.0000023 (2.1*10^-16 – 1.1)
0.0000006 (3.6*10^-20 – 1.2)
0.001
0.01
0.1
1
10
100

Table 1. Characteristics of included randomized controlled trials

Author, year	No. of sites	No. of patients	Patients	Age (yr)	Male (%)	Diagnosis of DIC	Intervention	Control	Mortality	Mortality rate (%)
Gando S 2013 [19]	13	60	DIC with sepsis AT 50-70%	70	58.3	JAAM	AT 30 IU/kg 3 days	No intervention	28 days	10 vs 13.3
Kienast J 2006 [20]	211	229	Severe sepsis with DIC	NA	NA	ISTH	AT 6000 IU bolus 6000 IU 4 days	1% Albumin	28 days	25.4 vs 40
Fourrier F 1993 [21]	1	35	Septic shock with DIC	52	57.4	Original	AT 90-120 IU/kg bolus 90-120 IU/kg 4days	0.6 % Albumin	28 days	41.2 vs 50
Nishiyama T 2012 [22]	2	16	DIC with infection	70.5	68.8	JAAM	AT 1500 IU 5days	gabexate mesilate 2000mg 5days	28 days	25 vs 37.5
Vincent JL 2013 [23]	233	741	Sepsis with DIC	57.2	61.4	ISTH	Thrombomodulin 0.06 mg/kg/d 6 days	Placebo	28 days	17.8 vs 21.6
Hagiwara A 2016 [24]	1	92	Severe sepsis with DIC	75.9	65.2	JAAM	Thrombomodulin 380 U/kg 6 days	No intervention	28 days	16 vs 17
Aikawa N 2011 [25]	113	80	DIC with infection	NA	65	JMHW	Thrombomodulin 0.06 mg/kg/d 6 days	unfractionated heparin 8 U/kg/h 6 days	28 days	21.4 vs 31.6
Hsu JT 2004 [26]	1	50	DIC with infection	59.6	70	JMHW	gabexate mesilate 1mg/kg/h 5days	No intervention	1 month	24 vs 36
Liu XL 2014 [27]	1	37	Sepsis with pre-DIC	49.3	56.8	Original	Heparin 70 U/kg/24h 5-7 days	Placebo	28 days	31.8 vs 40

NA: not available, No. of sites: number of study sites, DIC: disseminated intravascular coagulation, AT: antithrombin, JAAM: Japanese Association for Acute Medicine, ISTH: International Society on Thrombosis and Haemostasis, JMHW: Japanese Ministry of Health, Labour, and Welfare DIC diagnostic criteria.

Table 2. Summary of network meta-analysis and rank probability

1) 9 RCTs

Outcome	Comparison	OR (95% CrI)	Best	Worst
Mortality	Placebo vs AT	1.9 (0.97-3.5)	Antithrombin 50.1%	Heparin 46.0%
	GM vs AT	1.2 (0.35-4.3)		
	Heparin vs AT	2 (0.60-6.3)		
	TM vs AT	1.5 (0.63-3.5)		
	GM vs Placebo	0.64 (0.20-2.3)		
	Heparin vs Placebo	1.1 (0.40-2.9)		
	TM vs Placebo	0.79 (0.45-1.4)		
	Heparin vs GM	1.7 (0.33-7.5)		
	TM vs GM	1.2 (0.31-4.4)		
	TM vs Heparin	0.74 (0.29-1.9)		
DIC resolution rate	Placebo vs AT	**0.20 (0.043-0.84)**	Antithrombin 74.2%	Placebo 64.9%
	Heparin vs AT	0.31 (0.022-5.2)		
	TM vs AT	0.50 (0.077-3.9)		
	Heparin vs Placebo	1.5 (0.17-17)		
	TM vs Placebo	2.4 (0.76-11)		
	TM vs Heparin	1.6 (0.25-11)		
Bleeding complications	Placebo vs AT	0.97 (0.20-5.9)	Antithrombin 40.1% Placebo 34.5%	**Heparin 95.2%**
	Heparin vs AT	2100000 (0.90-3.6*10^{19})		
	TM vs AT	1.2 (0.17-12)		
	Heparin vs Placebo	2200000 (0.94-3.5*10^{19})		
	TM vs Placebo	1.3 (0.35-5.3)		
	TM vs Heparin	0.0000006 (3.6*10^{-20}-1.2)		

2) 7 RCTs

Outcome	Comparison	OR (95% CrI)	Best	Worst
Mortality	Placebo vs AT	1.6 (0.59-4.8)	Heparin 34.7% Antithrombin 32.0%	Placebo 34.5%
	GM vs AT	1.1 (0.28-4.7)		
	Heparin vs AT	1.1 (0.17-7.6)		
	TM vs AT	1.4 (0.42-4.7)		
	GM vs Placebo	0.67 (0.20-2.2)		
	Heparin vs Placebo	0.68 (0.15-3.3)		
	TM vs Placebo	0.84 (0.47-1.6)		
	Heparin vs GM	1.0 (0.16-7.2)		
	TM vs GM	1.2 (0.33-5.0)		
	TM vs Heparin	1.2 (0.23-6.3)		
DIC resolution rate	Placebo vs AT	**0.20 (0.045-0.85)**	Antithrombin 79.7%	**Placebo 93.5%**
	TM vs AT	0.48 (0.078-3.9)		
	TM vs Placebo	2.3 (0.78-11)		
Bleeding complications	Placebo vs AT	280 (0.32-4.4*10^{7})	**Antithrombin 87.4%**	Thrombomodulin 61.1%
	TM vs AT	350 (0.37-5.8*10^{7})		
	TM vs Placebo	1.2 (0.37-4.7)		

DIC: disseminated intravascular coagulation, RCT: randomized controlled trial, OR: Odds ratios, 95% CrI: 95% credible intervals, Best: Best treatments, Worst: Worst treatments, AT: antithrombin, GM: gabexate mesilate, TM: thrombomodulin