The efficiency and safety of recombinant factor VIIa for bleeding in patients without haemophilia: a meta-analysis of 12 randomized controlled trials

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Abstract

Background: Despite widely use of recombinant factor VIIa (rFVIIa) for bleeding in patients without haemophilia, its efficiency and safety remain unclear. Therefore, we carried out a meta-analysis on this topic. Methods: We searched Cochrane Library, Web of Science, PubMed and Embase, from January 2008 to July 2019 for randomized controlled trials on the topic. The results of this work are synthesized and reported in accordance with the PRISMA statement. Results: Twelve trials met our inclusion criteria. rFVIIa over 200ug/kg reduced red blood cell (RBC) transfusions within 24 h by 232.34ml (95% confidence interval [CI]; -410.31 to -54.37). rFVIIa did not significantly reduce 30-day mortality (relative risk [RR], 1.00; 95%CI, 0.82-1.21), total thromboembolic events (RR, 1.13; 95%CI, 0.94-1.36), myocardial infarction (RR, 1.37; 95%CI, 0.92-2.05), deep vein thrombosis (RR, 0.83; 95%CI, 0.52–1.33), ICU staying (RR, 0.40; 95%CI, -1.28 to 2.07) and number of patients transfused RBC (RR, 0.94; 95%CI, 0.83-1.08). However, rFVIIa may increase the incidence of arterial thrombotic events (RR, 1.38; 95%CI, 1.08–1.77). Conclusion: rFVIIa over 200ug/kg reduced RBC transfusions for bleeding in patients without haemophilia. However, it may increase the risk of arterial thrombotic events.

Background

Major bleeding is an usually perioperative complication, which not only increases the incidence of homologous blood transfusion but also increases mortality[1,2].Recombinant activated factor VII (rFVIIa), a potent procoagulant that promotes hemostasis at sites of vascular injury [3].It is licensed for the treatment of patients with haemophilia A and B, acquired haemophilia, factor VII deficiency, or Glanzmann thrombasthenia, but it has been successfully used off-label in a very large number of patients with major bleeding [4]. Off-label used of rFVIIa has been reported in severe trauma, liver transplantation, cardiac surgery, spontaneous intracerebral haemorrhage (ICH), and postpartum haemorrhage (PPH) [6-16]. A clinical trial published recently in patients with spontaneous intracerebral hemorrhage (ICH) that the administration of rFVIIa limits hematoma expansion [17]. However, concerns about extending the use of rFVIIa is the potential for adverse effects, in particular the risk of thromboembolism [5]. Mayer SA et al. [18] has reported that rFVIIa used to treatment of acute intracerebral hemorrhage increased thromboembolic. But studies could not show a clear benefit and harmful. Studies considering other systems focused on selected groups of participants or were conducted before many randomized controlled trials (RCT) publications. Therefore, more quality and statistically significant data are needed to guide the off-label applications, new trails are needed to update guidelines to adjust clinical practice. This review will critically evaluate the results of different identification trials and extend the early Cochrane findings for systematic review by including as many additional trials as possible.

Methods

Literature Search and Selection

Four trained investigators independently searched for comprehensive systematic literature in PubMed, Cochrane Library, Embase and Web of Science from January 2008 to July 2019. The search strategy included the following terms: factor VIIa, recombinant activated factor VII, recombinant factor VIIa, NovoSeven, rFVIIa, Factor 7A, Factor Seven A, hemorrhage, bleeding, blood loss, haemorrhage. Moreover, we reviewed the references of included studies and the included research of related reviews to identify additional studies.

This study followed the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21]. This study analyzed the efficiency and safety of rFVIIa in adult non-haemophiliac hemorrhage in randomized controlled trials. The inclusion criteria were as follows: Patients older than 18 years who require hemostatic treatment for hemorrhage. Patients with haemophilia or other haemostatic defects (for example, Glanzmann's thrombasthenia, inherited factorVII deficiency) were excluded; intervention: rFVIIa versus (Vs) placebo; study design: randomized controlled trials.

We excluded non-RCT trials and RCT studies in underage patients on this topic. In addition, studies with fewer than 10 patients were excluded, and we think would affect the accuracy and reliability of the analysis results.

Data Extraction and Assessment of Risk of Bias

Retrieved studies were selected by two independent investigators according to inclusion and exclusion criteria for the final included trials. Data extraction and literature quality assessment were conducted by two researchers separately for the included studies. The baseline details of the included literature were arranged in a table, and the extracted data were recorded in an excel database according to different outcome events. The primary outcome was volume of RBC transfusions with 24h. Secondary outcomes included the 30-day mortality, total thromboembolic events and incidences of patients with myocardial infarction, arterial thrombotic events, deep vein thrombosis, and numbers of patients transfused RBC and ICU-staying. The assessment of the risk of bias was evaluated by the Cochrane risk of bias tool recommended by the Cochrane Collaboration [22]. Two reviewers independently assessed each domain of included studies and any disagreement was resolved by another investigator.

Statistical Analysis

The risk ratio (RR) with 95% confidence intervals (95% CIs) was calculated for categorical varies and the mean difference (MD) was estimated by numeric varies. Heterogeneity among studies was tested using the Cochran Chi-square test and Inconsistency index (I^2), in which I^2> 50% suggested significant heterogeneity. And when I^2>50%, a random-effects model was chosen to pool the results, while the fixed-effects model was used when I^2< 50%. Publication bias was detected using the Funnel plots tests, and the Egger test was recommended for enumeration data [23].Two-tailed P-values < 0.05 were considered statistical significance. The effect of publication bias on study results was analysis with the trim and fill method. In order to evaluate the effect of dose on red blood cell transfusions, we added a subgroup analysis to observe whether using a higher dose of rFVIIa can reduce RBC transfusions and improve the

hemostatic effect. We performed sensitivity analyses of primary outcome events and heterogeneous significant outcomes. All data analysis was conducted by using ReviewManager (RevMan; version 5.3) and STATA, version 12.0 (Stata Corporation, College Station, TX).

Results

Results of search

According to the previous search strategy, 617 studies were obtained from the four databases and 2 studies were found by searching the reference lists and reviewed articles. After removing the duplicates, 416 publications remained in total and 401 records were excluded by browsing title and abstract. Among the remaining 15 records, 4 citations were removed according to our inclusion and exclusion criteria. Finally, 11 full-text studies (12 trials, a study consisted of 2 parallel randomized controlled trials) were suitable for this meta-analysis. (Fig. 1). The characteristics, type of haemorrhageand intervention methods of included studies were summarized in Table 1.

Risk of bias within studies

Bias risk of twelve trials was assessed in Fig.2. Two experiments did not provide a detailed method of random processes. The blinding process was at high risk of bias in two studies and unclear risk of bias in one study. No study had unclear or incomplete descriptions of their outcome data. Five trials did not provide a satisfactory description of reporting bias and nine studies did not indicate the other bias in the article.

Analysis of Primary outcomes

Death

A total of 2,040 patients from nine studies were included in the analysis of 30-day mortality in both rFVIIa and control groups. The results showed that rFVIIa did not increase the incidence of death events from a meta-analysis [220/1217 vs 139/823, RR=1.00 (0.82-1.21), P for effect= 0.98]. No heterogeneity was revealed in the results.[P for heterogeneity =0.83, I2 = 0%] (Fig. 3a).

Total thromboembolic events

Total thromboembolic events occurred in 279 of 1786 patients in the experimental group and 143 of 1,083 in the control group. rFVIIa did not increase the incidence of total thromboembolic events overall from meta-analysis. [RR=1.13 (0.94-1.36), P for effect= 0.20]. No heterogeneity was revealed in the result. [P for heterogeneity =0.54, I2 = 0%] (Fig. 3b).

RBC transfusions

Six trials reported the volume of RBC transfusions, with a total of 907 participants. The results showed that there was no significant difference between the two groups [MD = -168.12 (-381.84–45.60), P for

effect=0.12]. Heterogeneity was revealed in the result. [P for heterogeneity 0.01 I^2 = 76%].

Considering the significant heterogeneity of the experimental results, we performed subgroup analysis to compare the volume of red cells transfusion between the low-dose (200ug/kg) and high-dose (200ug/kg) groups. In the subgroup of patients with low-dose, rFVIIa did not significantly reduce RBC transfusion compared with the control group. [MD = -106.72(-448.33–234.89), P for effect =0.54, P for heterogeneity< 0.0001, I^2 = 90%]. In the subgroup of patients with high-dose, rFVIIa significantly reduced RBC transfusion. [MD=-232.34(-410.31–-54.37), P for effect =0.01, P for heterogeneity=0.77, I2 = 0%]. (Fig.3c).

Analysis of Second outcomes

Arterial thrombotic events

Compared with the control group, rFVIIa significantly increased the incidence of arterial thrombotic events, and there was no significant heterogeneity. [RR = 1.38(1.08–1.77), P for effect =0.01, P for heterogeneity=0.87, I2 = 0%]. (Fig.4a)

Myocardial infarction

In total, 8 studies with 2295 participants reported the incidence of myocardial infarctions after using rFVIIa and placebo. The overall analysis showed no increased risk of myocardial infarction [86/1508 vs 30/787, RR =1.37 (0.92–2.05), P for effect = 0.13, P for heterogeneity =0.43, I2 = 0%]. (Fig.4b)

Deep vein thrombosis

Seven studies reported the incidence of deep vein thrombosis in this meta-analysis. The RR for deep vein thrombosis (DVT) with the use of rFVIIa versus placebo was 0.83 (95% CI 0.51–1.33) which suggested that rFVIIa would not increase the incidence of DVT. No heterogeneity was revealed in the result. [P for heterogeneity =0.59, I2 = 0%] (Fig. 4c).

Number of patients transfused RBC

Number of patients transfused RBC in the rFVIIa group and the control group was 414/497 and 378/433, respectively. rFVIIa did not reduce the number of patients transfused RBC overall from meta-analysis. [RR =0.94 (0.83–1.08), P for effect = 0.39, P for heterogeneity =0.002, I2 = 77%]. (Fig.5a).

ICU-staying

Four trails with a total of 627 participants reported the ICU-stay days. Overall, rFVIIa did not significantly reduce length of ICU-stay. [RR = 0.40(-1.28–2.07), P for effect=0.64, P for heterogeneity=0.77, I^2 = 0%] (Fig. 5b).

Publication Bias and Sensitivity Analysis

Funnel plots showed that there was asymmetric distribution of included studies. Egger tests and trims and fill method demonstrated that there was no publication bias in all the studies. Sensitivity analyses have confirmed that all results are robust. All the results were shown in the Supplementary Figures.

Discussion

The main results in this meta-analyzed show that high dose rFVIIa would significantly reduce RBC transfusions, increase arterial thrombotic events, but did not increase patiences mortality, ICU-stay, total thromboembolic events, deep vein thrombosis and myocardial infarction.

All of the included studies were randomized controlled trials, included cardiac surgery[15,18,22], intracerebral hemorrhage[14,19,21,23], postpartum haemorrhage[16], severe acute pancreatitis[17], trauma[20] and upper gastrointestinal haemorrhage[24]. Besides, there were no heterogeneity among studies on most outcomes and sensitivity analysis also suggested the results were not affected by individual research.

Our study contains 12 trials with 2928 patients (1218 patients in control group Vs 1710 patients in treatment group) and reflects the latest results for the treatment of rFVIIa. rFVIIa over 200ug/kg reduced RBC transfusions within 24 h. rFVIIa did not significantly affect 30-day mortality, total thromboembolic events, myocardial infarction, deep vein thrombosis, ICU-stay and number of patients transfused RBC. However, rFVIIa may increase the incidence of arterial thrombotic events.

Similar to the previous studies, our meta-analysis suggested that rFVIIadid not increase mortality and total thromboembolic events [20]. Compared with previous studies, we analyzed the effects of rFVIIa on different thrombotic events in more detail and performed a subgroup analysis of RBC transfusions. Guidelines recommend different dosage for different patient cohorts. We found that the single-use dose of rFVIIa did not exceed 200ug/kg, and the multiple-use dose exceeded 200ug/kg. Therefore, we set a cut-off point at 200ug/kg. In this experiment, we found that rFVIIa over 200ug/kg reduced RBC transfusions. Besides, we added a comparison of outcome events such as myocardial infarction, deep vein thrombosis, and ICU-stay. There was no statistical difference between the two groups.

We acknowledge some potential limitations in this study. Firstly, heterogeneity due to clinical and methodological diversity was inevitable which may affect the reliability of the analysis results especially in meta-analyses of transfusion. Secondly, we used different measurement units for conversion, which may affect the reliability of the experimental results. In the future, we hope to have more large-scale randomized controlled experiments to research this topic.

Conclusion

The current study systematically reviewed the existing evidence on the efficacy and safety profile of rFVIIa in patients without haemophilia. The results show that high dose rFVIIa would significantly reduce RBC transfusions. rFVIIa did not increase mortality, ICU-stay, total thromboembolic events, deep vein

thrombosis and myocardial infarction. However, rFVIIa increased arterial thrombotic events. Overall, further studies are needed to identify the optimal dose and regime for intravenous use of rFVIIa to achieve the best benefit with the lowest risk.

Abbreviations

rFVIIa: Recombinant human factor VIIa

RCT: randomized controlled trials

RR: risk ratio

CI: confidence intervals

MD: mean difference

I^2:Inconsistency index

Vs: versus

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

YZ, JL and HYZ were involved in the study design, data review, data analysis, writing paper, review and approval of final manuscript. YTW, YFZ and HYZ were involved in data review, data analysis, review and approval of final manuscript. All authors read and approved the final manuscript.

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Not applicable

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Table

Characteristics of included studies

D	Country	No. C/T	Sex F/M	Type of hemorrhage	Intervention
	Canada	37/32	34/35	Acute Intracerebral Hemorrhage	Group1. 1 dose of 80 ug/kg rFVIIa iv within 6 hours from stroke onset in the SPOTLIGHT trial or 6.5 hours in the STOP-IT trial. Group2. Placebo, saline, at same time
15	Iran	18/18	12/24	Cardiac Valve Reoperations	Group1. 1 dose of 40 µg/kg rFVIIa iv after reversal of heparin. Group2. Placebo, saline, at same time
	Switzerland and France	42/42	84/0	Severe Refractory Postpartum Hemorrhage	Group1. 1 dose of 60 µg/kg rFVIIa iv. Group2. No rFVIIa
]	China	33/31	20/44	Severe Acute Pancreatitis	Group1. 1 dose of 40 µg/kg rFVIIa was administered intravenously 10 minutes before surgery. Group2. Placebo, saline, at same time
uid	Saudi Arabia	15/15	NA	Coronary Revascularization Surgery under CPB	Group1. a dose of 90 ug/Kg of rFVIIa was administered following weaning off CPB. Group2. Placebo, saline, at same time
12	Italy	8/13	5/16	Spontaneous Intracerebral Hemorrhage	Group1. 100 mcg/kg of rFVIIa by intravenous infusion in 5-10 minutes immediately after evacuation of the hematoma at the beginning of the closure of the dura. Group2. Placebo, saline, at same time
	26 countries	247/221	NA	Blunt Trauma	Group 1. 3 doses of iv rFVIIa. 200 µg/kg first dose, after 8 units of RBC transfused; 100 µg/kg 1 hour after dose 1; 100 µg/kg 3 hours after dose 1. Total dose 400 µg/kg. Group 2. Placebo given at each of the 3 time points.
	26 countries	40/46	NA	Penetrating Trauma	Group 1. 3 doses of iv rFVIIa. 200 µg/kg first dose, after 8 units of RBC transfused; 100 µg/kg 1 hour after dose 1; 100 µg/kg 3 hours after dose 1. Total dose 400 µg/kg. Group 2. Placebo given at each of the 3 time points.
010	22 countries	558/263	322/519	Spontaneous Intracerebral Hemorrhage	Group 1. 1 dose of 20 µg/kg of rFVIIa iv within 1 hour of CT scan. Group 2. 1 dose of 80 µg/kg at same time. Group 3. Placebo at same time.
14]	13 countries	68/104	44/128	Cardiac Surgery Requiring CPB	Group 1 = rFVIIa 40 µg/kg Group 2 = rFVIIa 80 µg/kg Group 3 = Placebo
08	22 countries	558/263	322/519	Spontaneous Intracerebral Hemorrhage	Group 1. 1 dose of 20 µg/kg of rFVIIa iv within 1 hour of CT scan. Group 2. 1 dose of 80 µg/kg at same time. Group 3. Placebo at same time.

Characteristics of included studies

)	Country	No. C/T	Sex F/M	Type of hemorrhage	Intervention
8	12 countries	86/170	69/187	Upper Gastrointestinal Haemorrhage	Group 1. First dose 200 µg/kg rFVIIa iv followed by doses of 100 µg/kg at 2, 8, 14 and 20 hours after initial dose. Total dose 600 µg/kg Group 2. First dose 200 µg/kg rFVIIa iv followed by second dose of 100 µg/kg at 2 hours and placebo at 8, 14 and 20 hours after initial dose. Total dose 300 µg/kg Group 3. Placebo at same times.

Figures

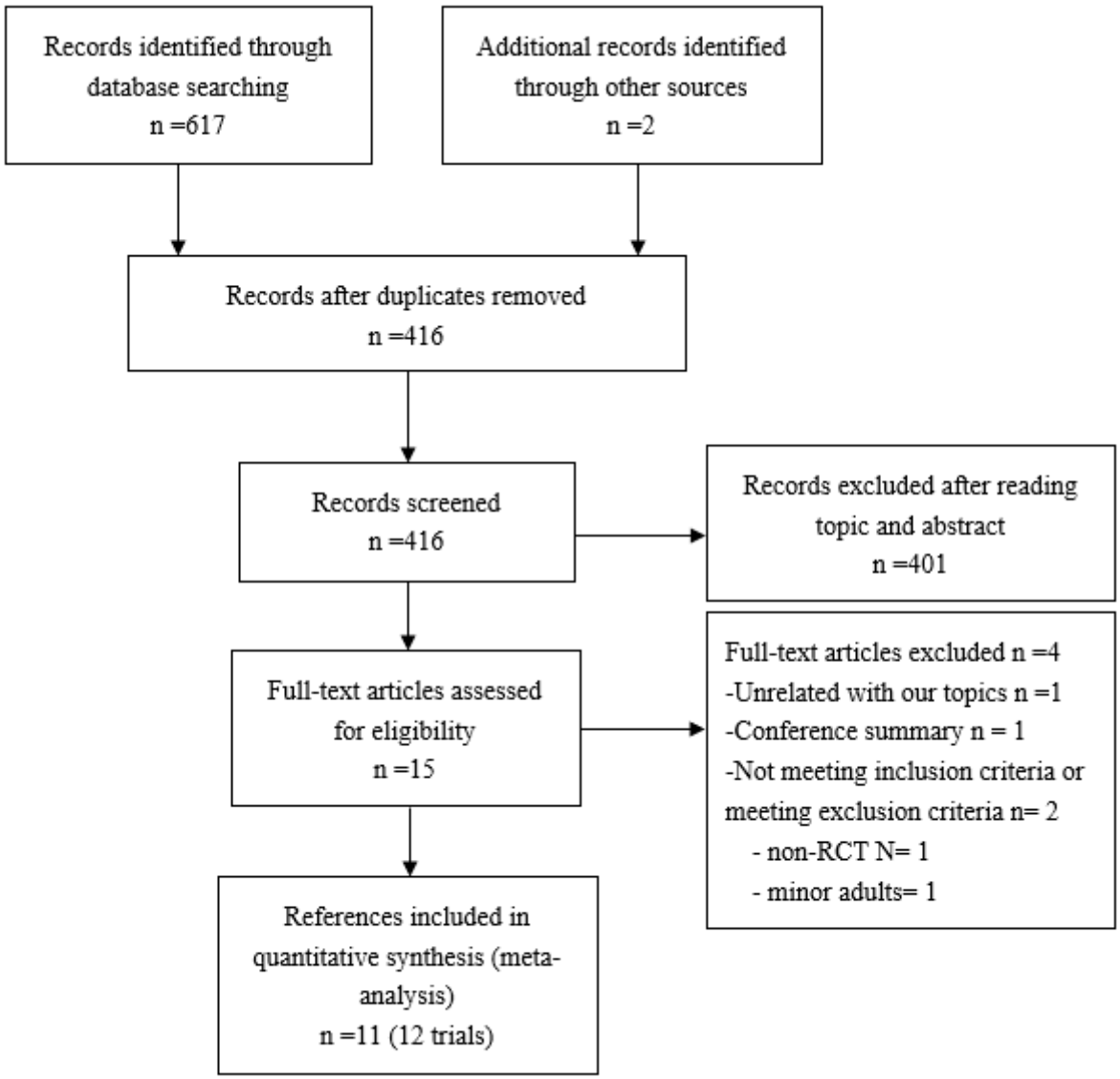

Figure 1

Flow diagram of the literature strategy

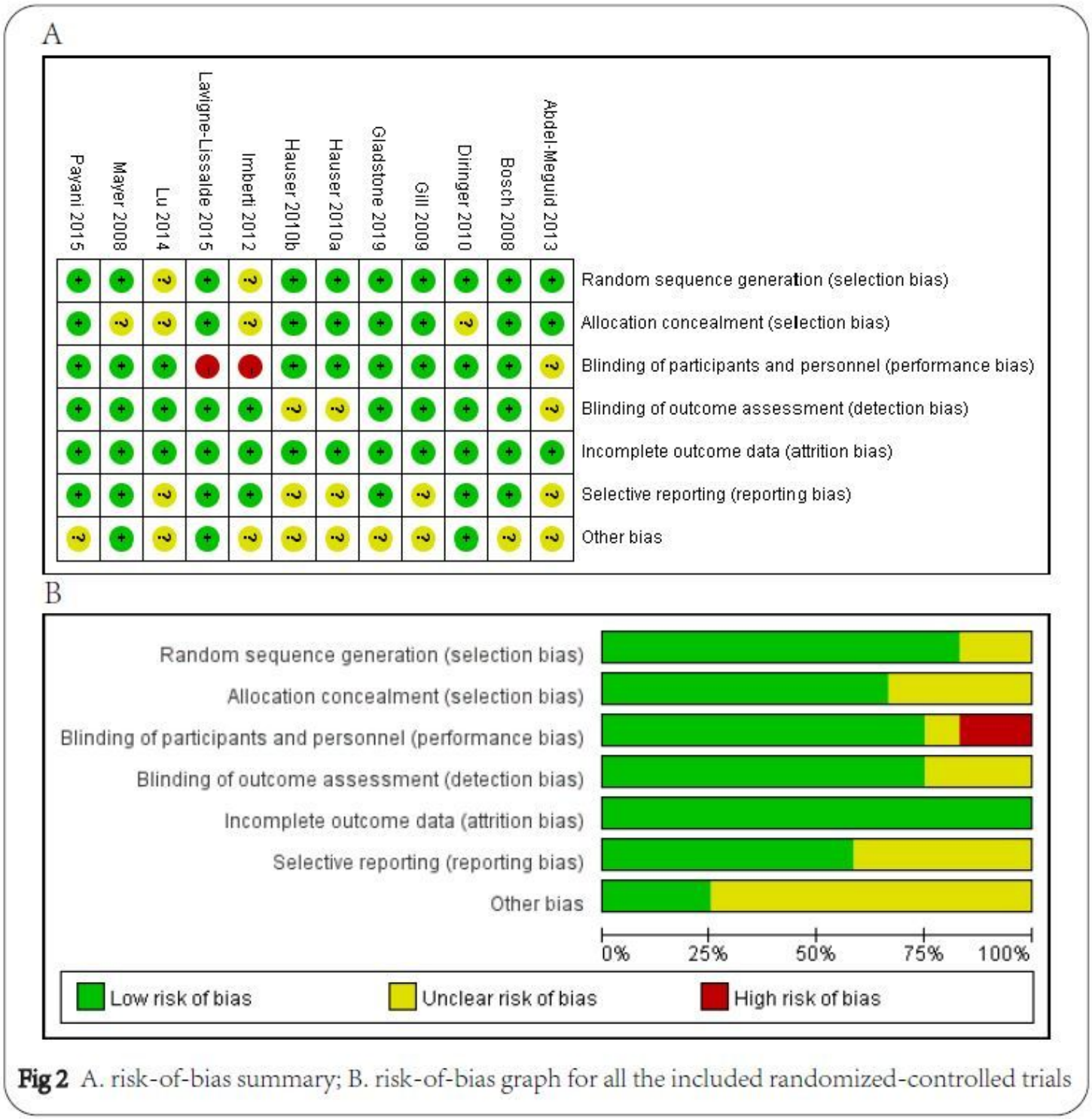

Fig 2 A. risk-of-bias summary; B. risk-of-bias graph for all the included randomized-controlled trials

Figure 2

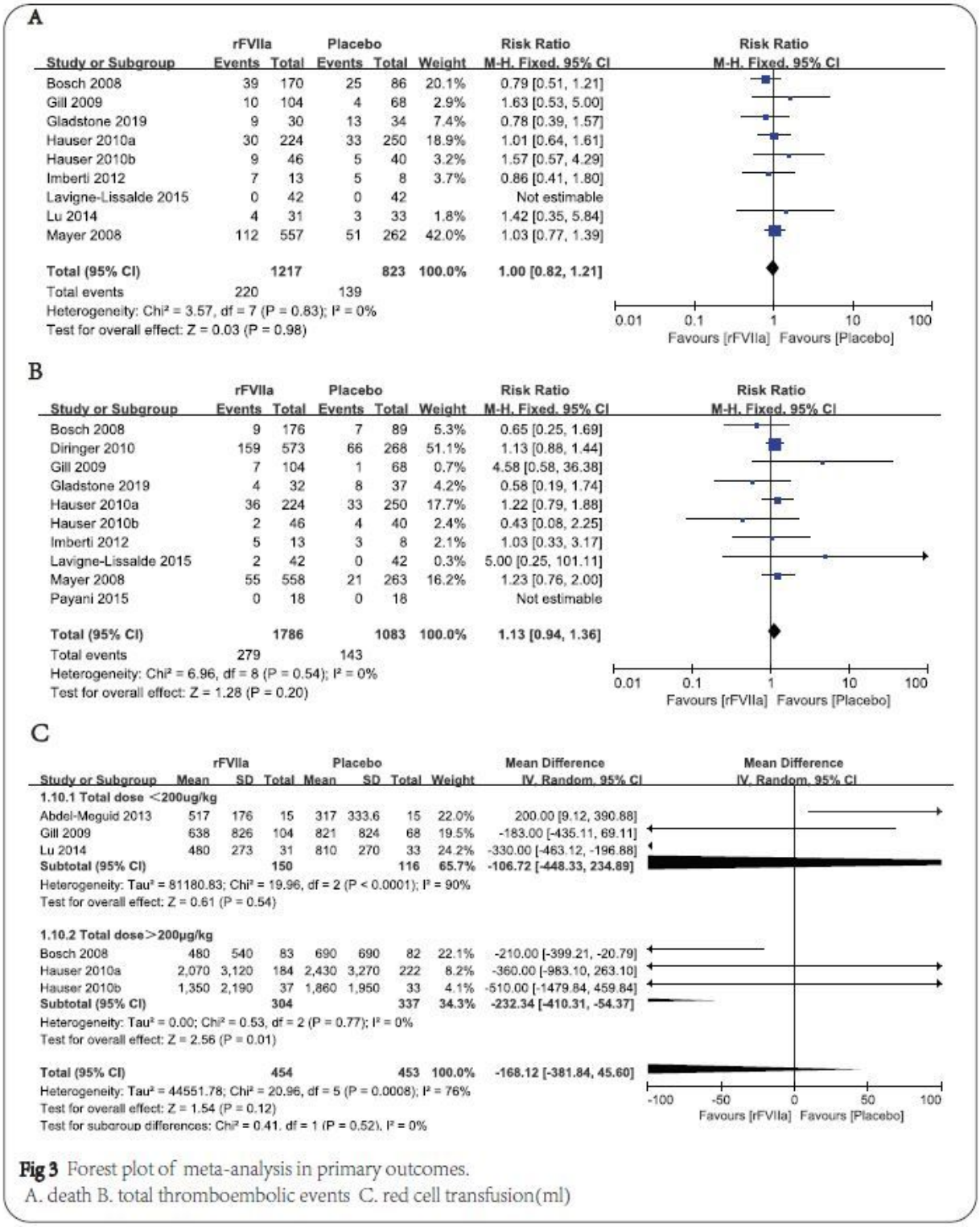

Fig 3 Forest plot of meta-analysis in primary outcomes.
A. death B. total thromboembolic events C. red cell transfusion(ml)

Figure 3

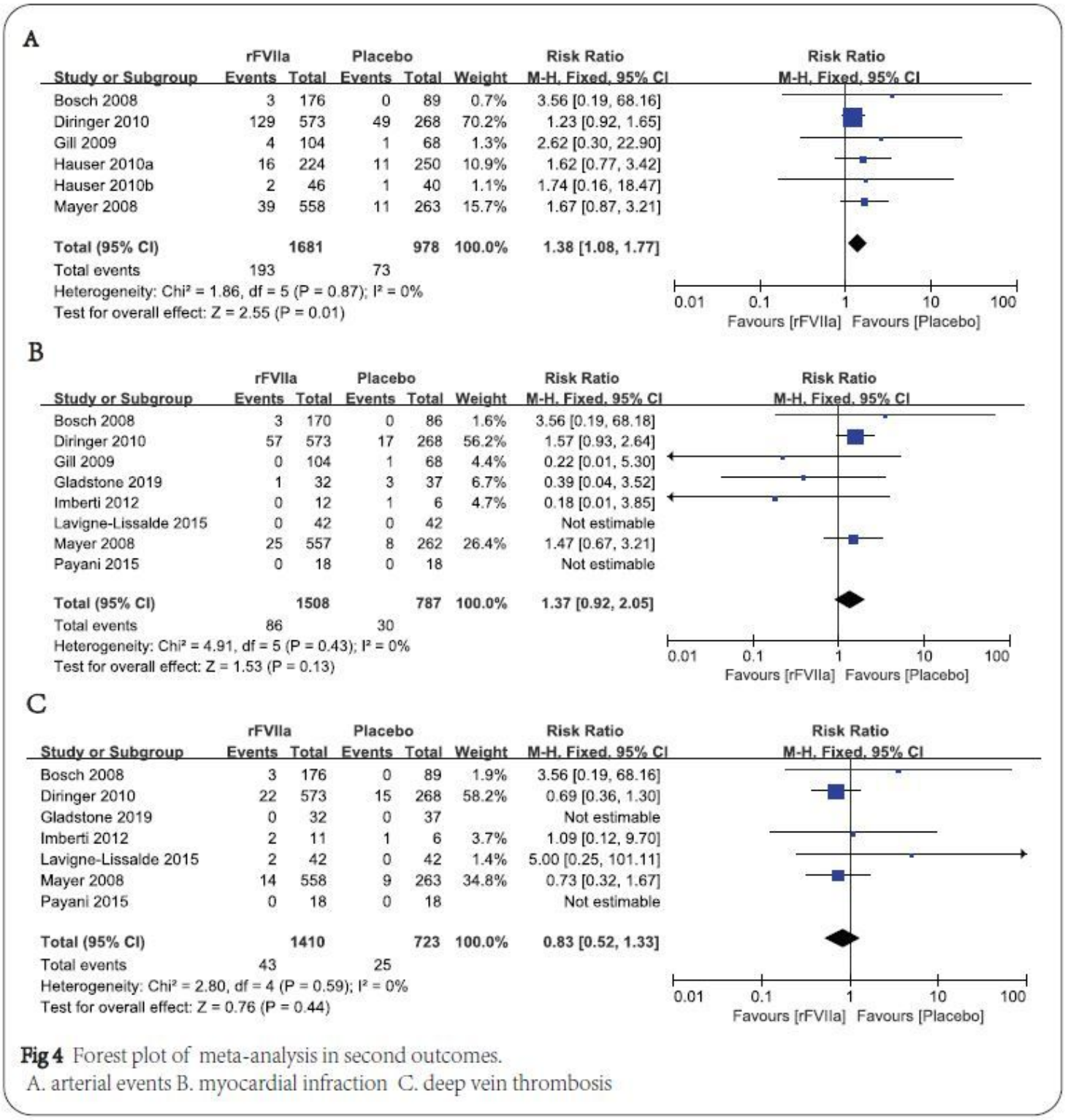

Fig 4 Forest plot of meta-analysis in second outcomes.
A. arterial events B. myocardial infraction C. deep vein thrombosis

Figure 4

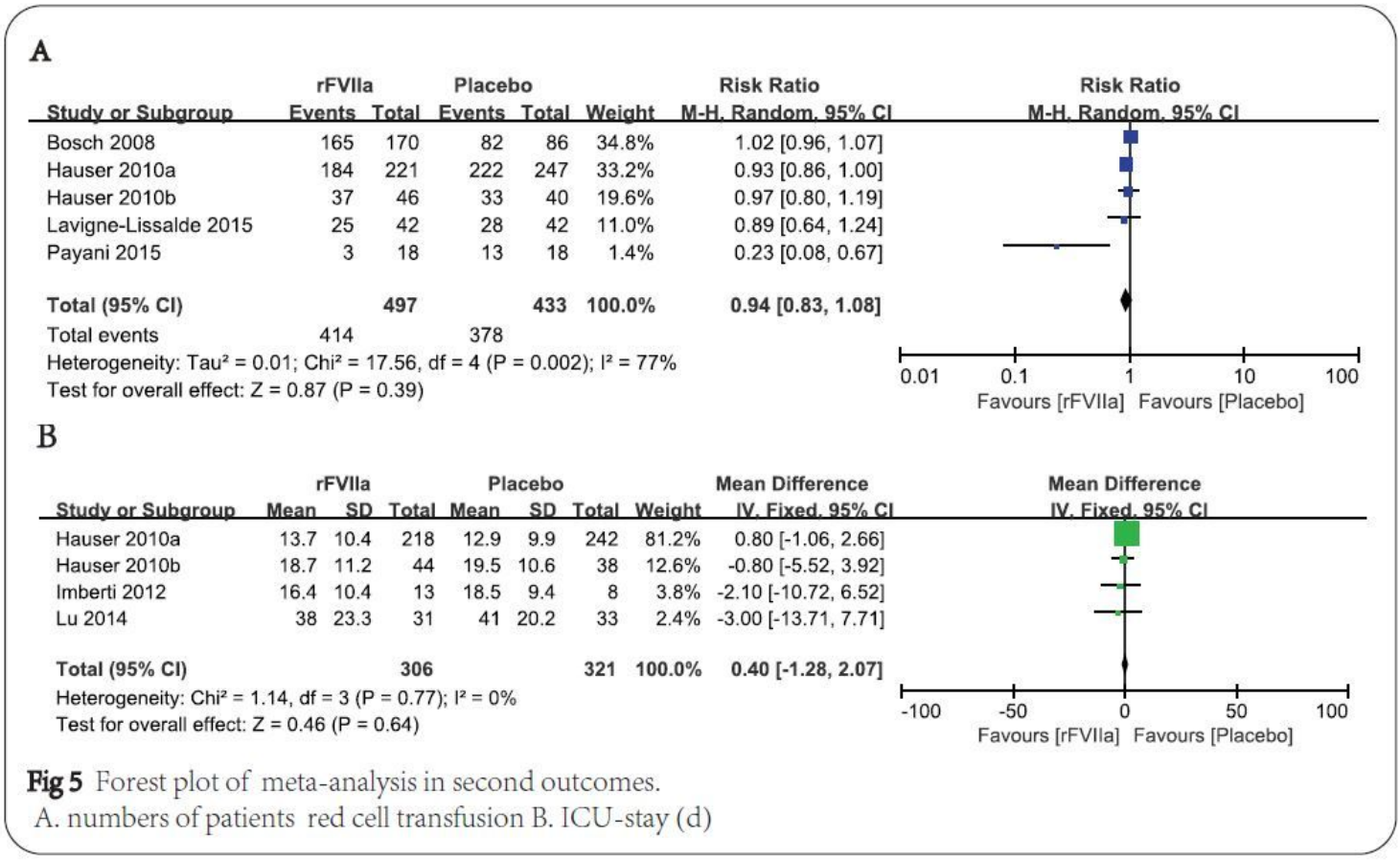

Fig 5 Forest plot of meta-analysis in second outcomes.
A. numbers of patients red cell transfusion B. ICU-stay (d)

Figure 5

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigS2.pdf
- PRISMA2009checklist.doc
- FigS1.pdf
- FigS3.pdf