The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in severely injured hemorrhaging trauma patients

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INTRODUCTION: Transfusion therapy in hemorrhaging trauma patients is associated with the development of thromboembolic events. It is unknown whether current resuscitation strategies, including large volumes of plasma and early administration of procoagulant therapy, increases this risk.

METHODS: A systematic search was conducted in MEDLINE, PubMed, and Embase. Studies were screened by two independent reviewers and included if they reported on thromboembolic events in patients with severe trauma (injury severity score ≥16) who received transfusion of at least 1 unit of red blood cells. The ratio by which blood products were transfused, as well as use of procoagulant or antifibrinolytic medication, was recorded.

RESULTS: A total of 40 studies with 11.074 bleeding trauma patients were included, in which 1.145 thromboembolic events were reported, yielding an incidence of 10% thromboembolic events. In studies performing routine screening for thromboembolic complications, the incidence ranged from 12% to 23%. The risk of thromboembolic events was increased after administration of tranexamic acid (TXA; odds ratio [OR], 2.6; 95% confidence interval [CI], 1.7-4.1; $p < 0.001$) and fibrinogen concentrate (OR, 2.1; 95% CI, 1.0-4.2; $p = 0.04$). Blood product ratio, the use of prothrombin complex concentrate or recombinant factor VIIa were not associated with thromboembolic events.

CONCLUSION: This systematic review identified an incidence of thromboembolic events of 10% in severely injured bleeding trauma patients. The use of TXA and fibrinogen concentrate was associated with the development of thromboembolic complications.

Traumatic injury is a leading cause of death and morbidity worldwide and is therefore a major global health problem.[1] Hemorrhage is responsible for approximately one-half of trauma-related mortality.[2] In the past decades, it has been recognized that trauma-induced coagulopathy (TIC) importantly contributes to exsanguination. This has resulted in marked changes in resuscitation strategies. In the Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) trial, bleeding trauma patients who received plasma, platelets, and red blood cells (RBCs) with a 1:1:1 (high) ratio were less likely to die from exsanguination when compared to patients who were transfused with a 1:1:2 (low) ratio. Since the publication of this trial, most hospitals have adopted the strategy of transfusing patients with traumatic bleeding with a high ratio.[3] In addition to blood product ratio, antifibrinolytic

ABBREVIATIONS: DVT = deep venous thrombosis; FC = fibrinogen concentrate; ISS = injury severity score; PCC = prothrombin complex concentrate; PE = pulmonary embolism; RCTs = randomized controlled trials; rFVIIa = recombinant activated factor VII; TEEs = thromboembolic events; TIC = trauma-induced coagulopathy; TXA = tranexamic acid.

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and procoagulant medications, including tranexamic acid (TXA), fibrinogen concentrates, and prothrombin complex concentrate, have been shown to either reduce TIC[4,5] or improve outcome of traumatic bleeding.[6,7] Therefore, these interventions have become an accepted strategy to treat TIC, as reflected in trauma guidelines.[8]

While one-half of trauma-related deaths occur in the first hours after injury due to bleeding, the other one-half occurs during hospital admission.[2] The development of thromboembolic events is an important contributor to morbidity and late mortality.[9,10] Several risk factors that predispose trauma patients to the development of thromboembolic events have been identified, such as the severity and type of injury, operative procedures, comorbidities,[10] presence of shock,[11] and duration of immobility.[12] Transfusion, particularly massive transfusion, is also associated with thromboembolic complications.[12,13] Blood product ratio[14-17] as well as procoagulant therapies[6,18-23] may also contribute to the risk of thromboembolic complications in trauma. Although individual studies on the efficacy of procoagulant interventions in trauma have not reported an increased risk, they may have been underpowered to detect differences in thromboembolic complications.

Therefore, it is important to characterize risk factors for the development of these events. This systematic review summarizes the incidence and risk for developing thromboembolic events associated with current transfusion and resuscitation strategies in trauma patients. Results may help guide the administration of thromboprophylaxis and whether there is a need for (standard) screening for thrombosis.

METHODS

This review was reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study selection

An electronic search was conducted in MEDLINE, PubMed, and Embase (see Appendix S1, available as supporting information in the online version of this paper). In addition, we searched for ongoing trials on www.controlled-trials.com and www.clinicaltrials.gov.

The target population was patients 16 years of age or older with severe trauma (injury severity score [ISS] ≥16) resulting in hemorrhage, who received at least 1 unit of RBCs. Randomized controlled trials (RCTs) and observational studies investigating resuscitation strategies in bleeding trauma patients with thromboembolic events as an outcome were eligible for inclusion. Moreover, these studies had to have a follow-up of at least 1 week, since thromboembolic events most often occur during the first week in the hospital.[13] Only articles written in English, German, and Dutch were included. If the number of transfused blood components or the use of procoagulant medication was not reported, studies were excluded from analysis. Reviews, correspondences, editorials, experimental (animal) studies and case reports/series were excluded. Studies on burn victims were also excluded because of the difference in fluid management in this particular population. In case of several publications from the same data set, the most informative study was selected. The bibliographies of both the eligible studies and the excluded studies were reviewed for citations of additional suitable studies. Reviewing of the articles was conducted by two independent researchers (MRW and DVS). Any discrepancies in the included studies were resolved by discussion between the reviewers. An independent reviewer was consulted if no consensus could be reached.

Definitions

Thromboembolic events (TEEs) were defined as deep venous thrombosis (DVT), pulmonary embolism (PE), cerebral vascular infarction, myocardial infarction, mesenteric thrombosis, intestinal infarction, subclavian vein thrombosis, jugular vein thrombosis, or arterial limb thrombosis. In the included studies, TEEs were diagnosed either when patients showed clinical symptoms and/or by routine screening with ultrasound or computed tomography scan.

From the included studies, the amount of transfused units of RBCs, plasma and platelets were collected, as well as the ratio of blood products. If the ratio was not reported, it was calculated based on the mean number of blood products transfused. If only the median number of blood products was reported, an estimated mean was calculated, as done before.[24]

The plasma-to-RBC ratio was categorized into three groups: <1:2 (low ratio), 1-2:2 (high ratio) and > 1:1 (inverse ratio). In the low-ratio group, studies were selected that reported more than two transfused RBC units for every plasma unit transfused. In the high-ratio group, studies were selected that reported transfusion of 1 or 2 plasma units for every 2 transfused RBC units. In the inverse-ratio group, studies were selected that reported to have given more plasma units than RBC units.

In case of studies reporting the use of pooled platelet concentrates, the number of platelets transfused was divided by the number of donors that were pooled in preparation of the platelet product. When apheresis platelets were used, the number of platelet units reported in the study was used. When pooled platelet concentrates as well as apheresis platelets were used, the number of platelets units reported in the study was used. The platelet-to-RBC ratio was categorized into the same ratio groups (low, high, and inverse). In the low-ratio group, studies were selected that reported 10 or more RBC units transfused, for every platelet unit transfused. In the high-ratio group, studies were

selected that reported 5 to 10 RBC units being transfused for every platelet unit. In the inverse-ratio group, studies were selected that reported to have given less than 5 RBCs for every platelet unit transfused.

Data synthesis

The main outcome of this study is the development of thromboembolic events. Computer software (Review Manager 5, The Nordic Cochrane Centre) was used for the meta-analysis. Pooled data were analyzed using a random-effects model. If the heterogeneity, expressed by I^2, had a value greater than 50%, no pooling of the results was done. Kruskal-Wallis statistics were used to analyze differences in calculated incidences between the different ratio groups, with use of statistical software (SPSS version 24, IBM Corp.). A quality assessment of the included RCTs was performed with the Cochrane Collaboration tool for assessing risk of bias. The quality of the included cohort studies was evaluated using the Newcastle-Ottawa Scale.

RESULTS

Our electronic search identified a total of 2552 articles. After removal of duplicates, 1442 studies remained, of which title and abstract were screened for eligibility. A total of 1143 articles were excluded, after which 299 articles were assessed for eligibility based on the full text. Of these, 36 articles complied with our inclusion criteria and were selected for analysis. Reviewing the bibliographies of the included studies and of the excluded reviews resulted in inclusion of an additional four studies (Fig. 1).

A total of 11,074 severely injured and bleeding trauma patients were included in this systematic review, in which a total of 1145 TEEs were reported (incidence, 10.3%), consisting of 502 DVTs, 251 PEs, 143 other events, and 249 TEEs that were not specified. In studies performing routine screening, an incidence of 12% to 23% of TEEs was found. In the included studies, a median of 10.5 (5.5-15.6) RBC units, 8.4 (4.7-12.3) fresh frozen plasma units, and 1.4 (0.8-2.6) platelet units were transfused.

Quality of included studies

The score of the included studies on the Newcastle-Ottawa scale ranged from 5 to 9, with a median of 6, suggesting a moderate to good quality of the cohort studies (Tables S2 and S3, available as supporting information in the online version of this paper). Regarding RCTs, overall quality was also moderate to good. In particular, performance and detection bias is high in these trials due to the difficulty of blinding for transfusion status of patients.

Effect of blood product ratio on the risk of TEEs

A total of five studies[15,25-28] specifically investigated blood product ratio. These studies comprised a group of 1781 trauma patients, in whom 249 TEEs were recorded (163 DVTs, 64 PEs, and 22 other TEEs). The mean incidence of TEEs did not differ between patients receiving a low, high, or inverse ratio of plasma-to-RBC or platelet-to-RBC products (Fig. 2). For the analysis of the impact of plasma dose, four studies were available that evaluated the relation between plasma-to-RBC ratio and outcome,[15,25,27,28] including one RCT,[15] two observational studies,[25,27] and one subanalysis of an observational study.[28] Results of three of these studies could be pooled based on their definition of high and low transfusion ratio, which showed no increased risk for TEEs with the use of high plasma-to-RBC ratios when compared to a low plasma-to-RBC ratio (OR, 1.34; 95% CI, 0.28-1.56; p = 0.34; Fig. 3). Only one study reported on patients being transfused in an inverse ratio and could therefore not be pooled in our analysis. Regarding platelets, only one study focused on the platelet-to-RBC ratio and outcome.[26] Therefore, a systematic analysis of the impact of platelet dose was not possible.

Effect of TXA on the risk of thromboembolic events

The effect of TXA on the development of TEEs was reported in four observational studies in 1984 trauma patients in whom 152 TEEs were recorded, consisting of 28 DVTs, 38 PEs, 31 other TEEs, and 55 undefined TEEs.[29-32] Of these four studies, three were performed in a military population[29-31] and one in a trauma intensive care unit population.[33] All studies followed a standard major hemorrhage protocol consisting of a standard TXA dosing regimen of an intravenous bolus of 1 g followed by a 1-g infusion (over 8 hr) at the discretion of the clinicians. The military studies reported significantly higher incidences of TEEs in patients receiving TXA compared to those that did not.[29-31] In the civilian trauma population,[32] a higher percentage of TEEs was reported in patients receiving TXA compared to patients not receiving TXA, which did not reach a statistical significant difference. Although it does increase the risk of developing a hypercoagulable state, no association with TEEs could be found.[33]

Not all study results could be pooled, as heterogeneity was too high (I^2 = 78%). However, all studies performed subanalyses in massively transfused patients, reducing the heterogeneity of the studies, allowing results to be pooled.[29-32] A pooled analysis of massively transfused patients showed an odds ratio (OR) of 2.60 (95% confidence interval [CI], 1.65-4.11; p < 0.0001) for the development of thromboembolisms after TXA administration (Fig. 4).

Effect of prothrombin complex concentrate on the risk of TEEs

Our search identified four observational studies on the use of prothrombin complex concentrate (PCC) in traumatic bleeding, either as an adjunct to plasma transfusion or as a stand-alone therapy. All studies were performed by the same research group.[34-37] A total of 463 trauma patients

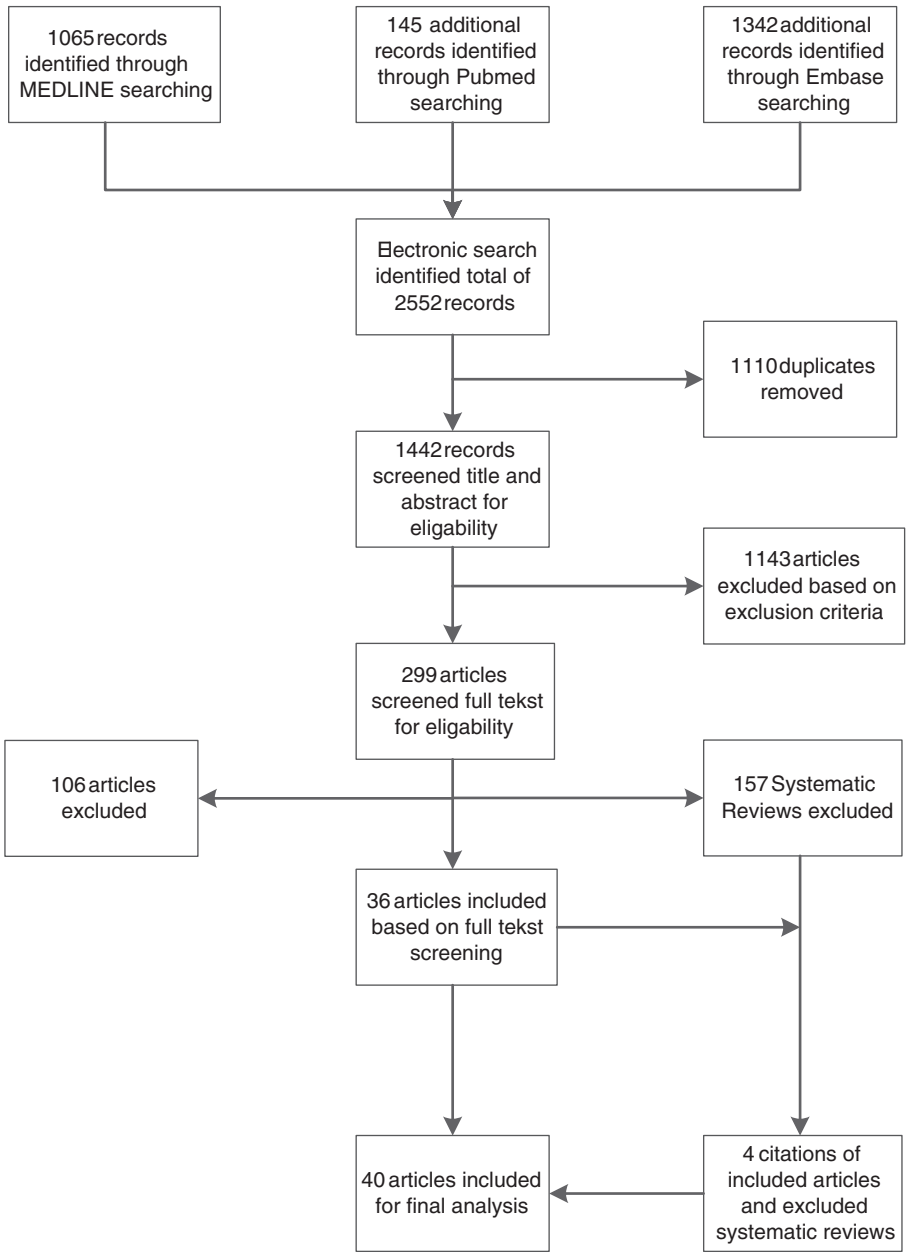


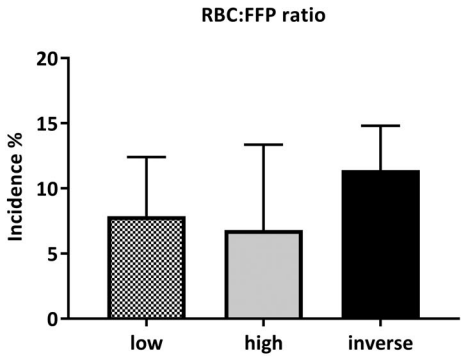
Fig. 1. Flowchart of selection process of studies suitable for inclusion in the final review.

were included, with 18 TEEs (13 DVTs and five other events).

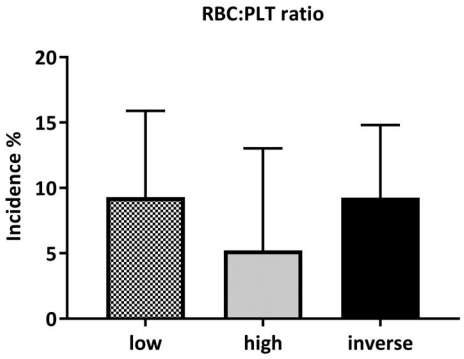
None of the individual studies showed an association between PCC and TEEs. Of note, very low incidences of TEEs have been reported in these studies, ranging from 1.2% to 11.1%, which may have been a result of the small sample size of the studies. Results of two studies could be pooled and showed no increased risk for the development of TEE in the PCC arm (OR, 1.82; 95% CI, 0.60-5.53; p = 0.29; Fig. 5).[34,37] The comparisons made in the other two studies did not allow for pooling of the results.

Effect of fibrinogen concentrate on the risk of TEEs

Four studies reported on the effect of fibrinogen concentrate (FC) administration and the development of TEEs[5,7,38,39] in a total of 871 patients. Triggers for administering FC, as well as dosing, differed among studies. Two studies used viscoelastic assays to guide FC administration, ranging from 25 to 50 mg/kg body weight;[7,39] one study administered a standard dose of 6 g,[5] while the last study did not report on dosing.[38] The median dose of fibrinogen administered in these studies was 5 g. A total of 66 thromboembolic complications (5 DVTs, 7 PEs, 12 other thromboembolisms, and 42



No of study groups	12	47	11
No of patients	2615	6595	747
No of TEE	275	639	85
ISS (median, IQR)	26 (24-29)	27 (24-31)	28 (20-35)
BD (median, IQR)	3,5 (3,0-3,5)	8 (7,1-10,0)	4,3 (4,2-4,3)
SBP (median, IQR)	119 (109-125)	102 (97-111)	109 (106-126)
INR (median, IQR)	2,1 (1,2-2,6)	1,6 (1,4-1,9)	1,9 (1,3-2,3)



No of study groups	26	27	11
No of patients	3666	4903	1036
No of TEE	406	431	136
ISS (median, IQR)	25 (22-32)	28 (25-29)	27 (22-33)
BD (median, IQR)	7,5 (7,0-9,5)	8,0 (4,5-11,2)	7,7 (6,1-8,7)
SBP (median, IQR)	109 (99-121)	108 (100-118)	105 (100-109)
INR (median, IQR)	1,4 (1,4-1,9)	1,5 (1,3-2,1)	1,6 (1,3-1,9)

Fig. 2. Incidence of thromboembolic events according to blood product ratio. Values are presented as median and interquartile range. BD = base deficit; FFP = fresh frozen plasma; INR = international normalized ratio; PLT = platelet; SBP = systolic blood pressure.

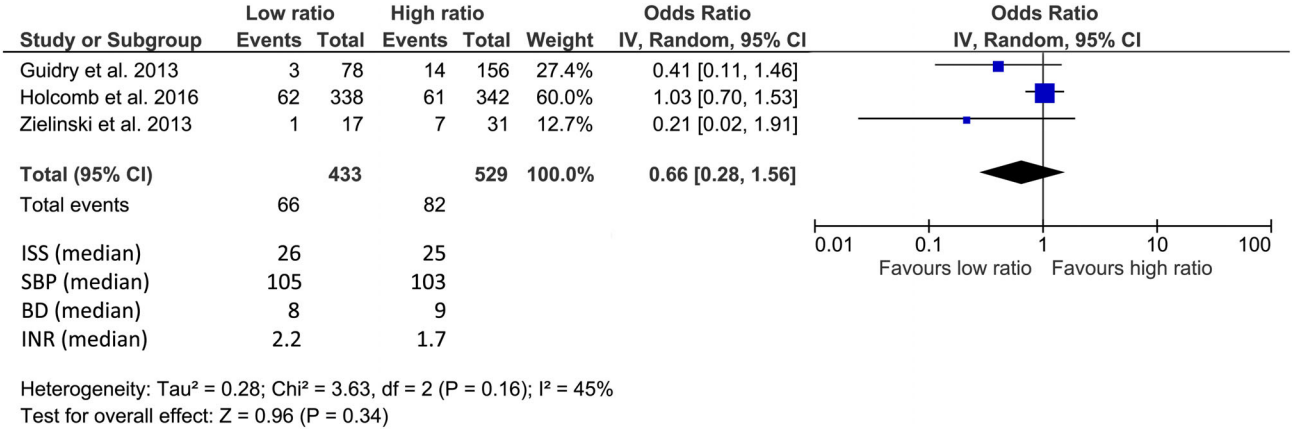


Fig. 3. RBC-to-FFP ratio and the development of thromboembolic events in trauma. BD = base deficit; INR = international normalized ratio; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

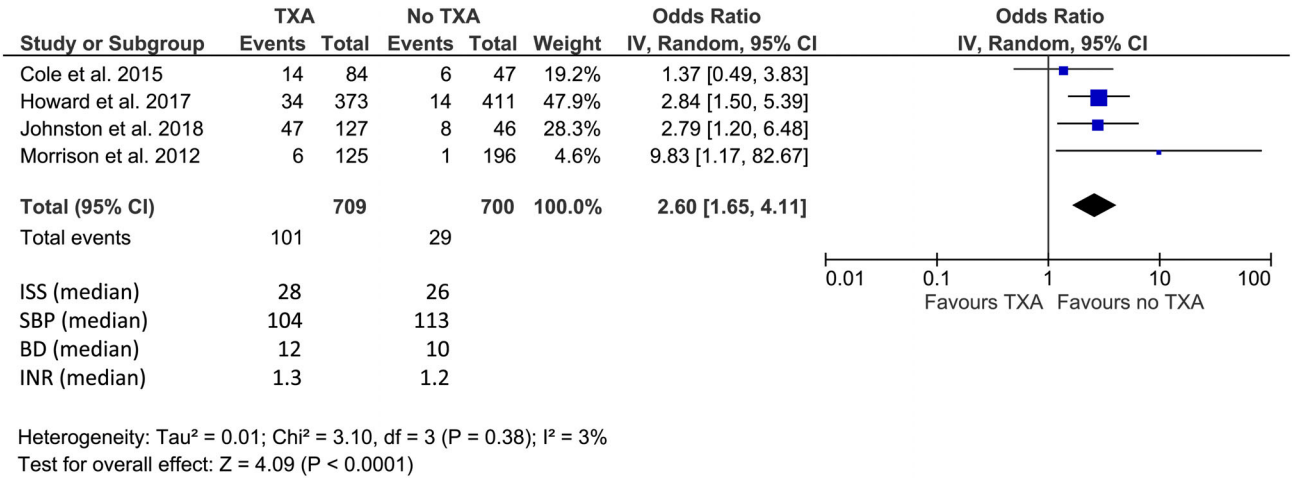


Fig. 4. Use of TXA and the development of TEEs in trauma. BD = base deficit; INR = international normalized ratio; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

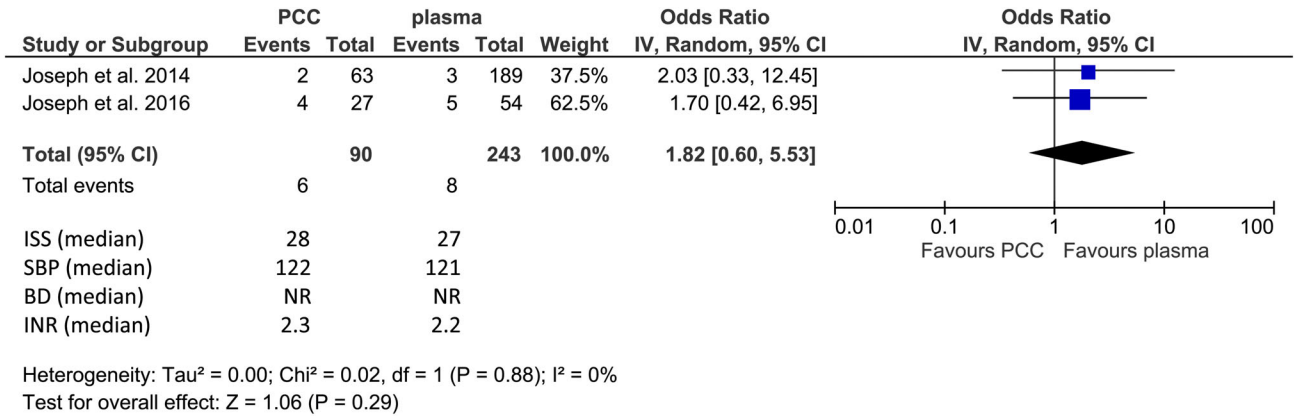


Fig. 5. Use of PCC and the development of TEEs in trauma. BD = base deficit; INR = international normalized ratio; NR = not reported; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

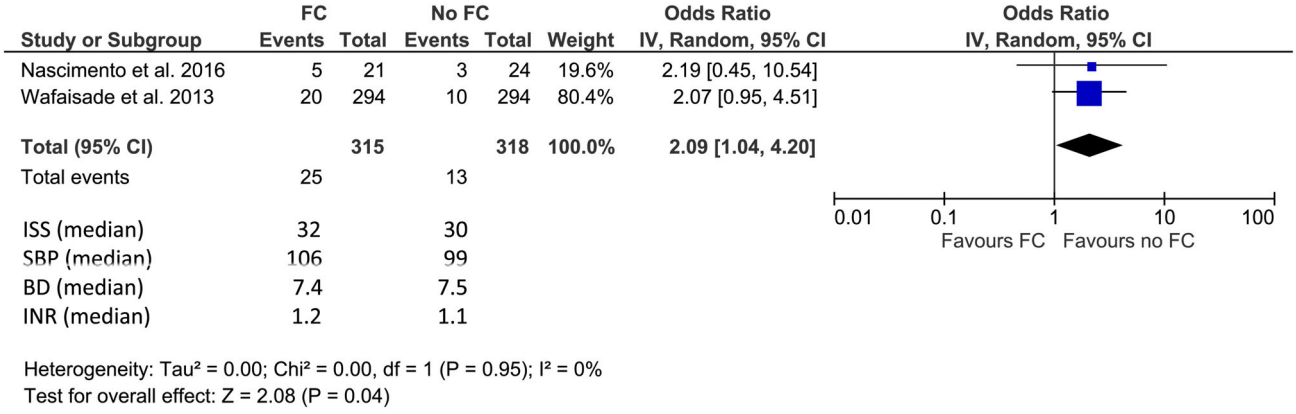


Fig. 6. Use of fibrinogen concentrate and the development of thromboembolic events in trauma. BD = base deficit; INR = international normalized ratio; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

undefined ones) were reported. There were two RCTs[5,7] and two observational studies.[38,39] The RCTs did not see any differences in TEEs. In another study that matched patients that had received FC to patients that had not, a trend toward higher TEE rates was observed in patients receiving FC (6.8% vs. 3.4%; p = 0.06). Of note, in two studies, patients in the FC arm also differed in terms of plasma treatment.[7,39] For this reason, results of these studies were not pooled, as the effect of FC alone on the risk of TEE could not be assessed. The remaining two studies were pooled, which showed an increased risk for the development of TEE in the FC arm (OR, 2.09; 95% CI, 1.04-4.20; p = 0.04; Fig. 6).[5,38]

Patients receiving cryoprecipitate were analyzed separately from patients receiving FC. A small, unblinded RCT investigated the addition of cryoprecipitate as a source of fibrinogen administration to a standard massive transfusion protocol at two civilian major trauma centers.[40] In their "per treatment" analysis, an arterial thrombus was reported in 23 patients receiving cryoprecipitate, while two DVTs and one PE were reported in patients treated with the standard massive transfusion protocol. Although this did not reach statistical significance, it must be noted that groups were small and the study was not powered to detect differences in this outcome. In addition, patients in the standard arm were more severely injured and more shocked, which may have confounded the thromboembolic occurrences.

Effect of recombinant activated factor VII on the risk of thromboembolic events

A total of 16 studies were identified that investigated the use of recombinant activated factor VII (rFVIIa) in a total of 4369 trauma patients.[18,19,41-54] A total of 481 TEEs were reported in these studies, consisting of 192 DVTs, 120 PEs, 63 other TEEs, and 102 TEEs that were not specified.

Most smaller studies found no evidence of TEEs following rFVIIa treatment.[41,43,47,52,53] In the larger cohort studies,[44,46,49,51] which were performed in both military and

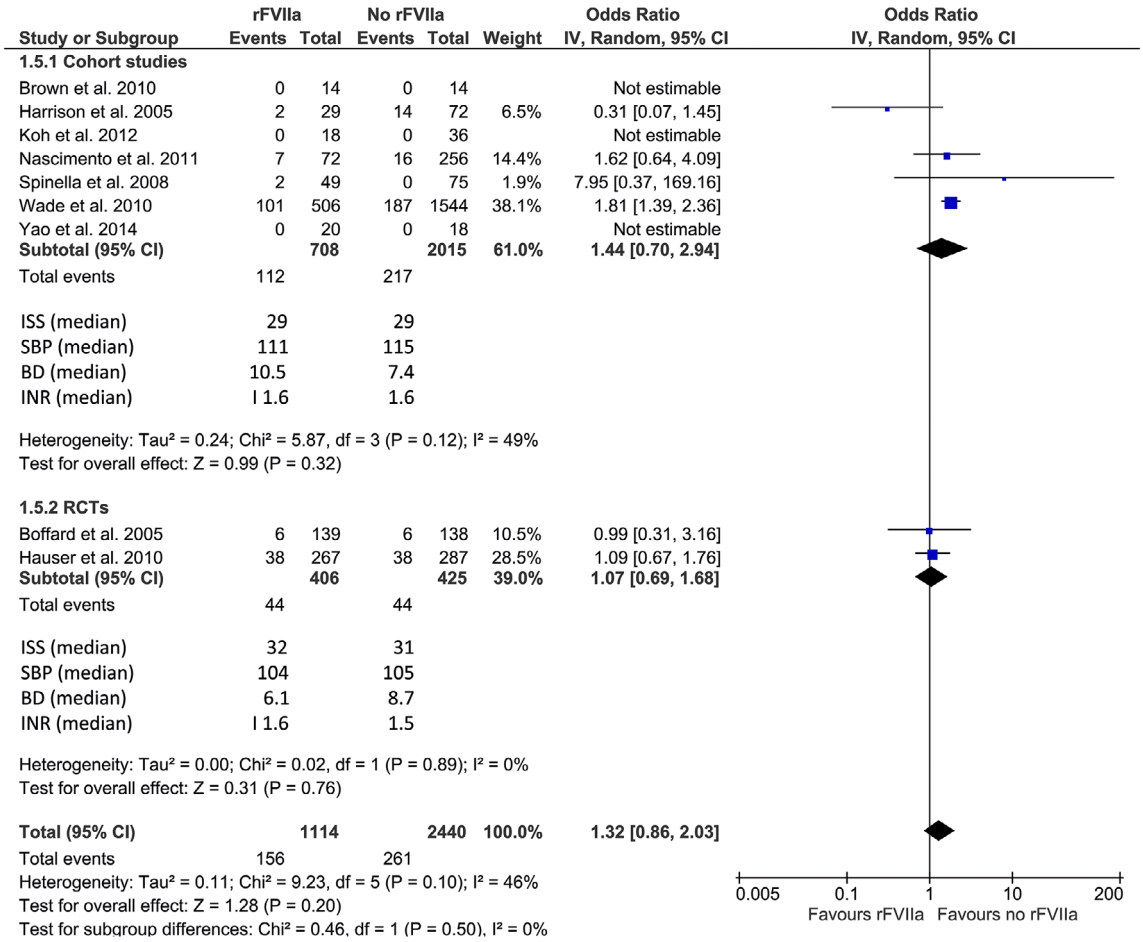


Fig. 7. Use of rFVIIa and the development of thromboembolic events in trauma. BD = base deficit; INR = international normalized ratio; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

civilian populations, patients trended toward a higher incidence of TEEs after rFVIIa but never reached statistical significance. There were two RCTs investigating the use of rFVIIa.[18,19] Pooled results showed that rFVIIa was not associated with an increased risk for the development of TEEs (OR, 1.32; 95% CI, 0.86-2.03; p = 0.20; Fig. 7). Of note, patients receiving rFVIIa were often more severely injured compared to the patients not receiving rFVIIa. However, analysis of only the included RCTs[18,19] also did not find an increased risk for TEEs after rFVIIa administration (Fig. 7).

DISCUSSION

The incidence of TEE is 10% in a population of patients with traumatic bleeding. Results of this review suggest that use of TXA and FC, but not blood product ratio, PCC, or rFVIIa, is associated with an increased risk of TEE in trauma patients who have survived the initial bleeding phase.

It can be hypothesized that the sickest patients who survive the initial bleeding phase have the highest risk of developing a TEE, as well as the highest risk of receiving more plasma and platelets and other therapies when compared to less severely bleeding patients. However, ISS as well as markers of shock did not differ between groups, suggesting that injury severity did not account for any differences that we found between groups. This does not rule out survival benefit, however, which may have skewed the results. In observational studies, adjustment for these confounders is notoriously difficult. Therefore, the finding that TXA and FC are associated with the development of TEEs should be interpreted with caution, as most studies were observational. Conversely, the finding of an absence of increased TEE risk may be less influenced by the confounding effect of bleeding severity than a finding of an increased risk. In other words, the finding of this review that blood product ratio, PCC, and rFVIIa were not associated with increased risk of TEE may not have been influenced by disease severity.

To determine the risk of plasma:RBC ratio, only three studies were available for pooling. However, these studies comprised a fair amount of patients and events, suggesting that high plasma volume is not a risk factor for TEE. Unfortunately, studies on PLT:RBC ratio were scarce. However, TEE incidence in different ratio groups was similar, suggesting no relation between TEEs and the amount of platelet transfusions.

The analysis of the risk of PCC for the development of TEEs was done on two observational studies from the same research group, in which only a few TEEs were reported. Therefore, we feel that we cannot rule out with certainty that PCC is a risk factor for TEE. For rFVIIa, more studies were available for pooling, including three RCTs. Of note, very high mortality rates are reported in the included cohort studies, ranging from 28% to 58%.[18,19] Therefore, the relatively low incidence of thromboembolisms in these patients may be a reflection of the decreased life expectancy in this particular group of patients, as they die before a TEE may have developed. Also, the studies differed in their comparator to rFVIIa. However, a fair number of patients were pooled with an acceptable heterogeneity. Our analysis suggests that the risk of TEE following rFVIIa is not increased.

Our analysis suggests that TXA is a risk factor for the development of TEEs in trauma patients. In this analysis, four observational studies were included, of which three were performed in the military setting. The studies in the military population all showed a trend toward increased risk, which was not found in a smaller civilian population. In addition, in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, TXA given more than 3 hours after onset of bleeding was associated with increased mortality.[6] Possibly, TEEs were responsible for the association between late mortality and late administration of TXA. However, as already discussed, the finding of an increased risk is susceptible to bias of disease severity, as the question remains what the impact of bleeding severity on risk of TEE was in these studies.

FC administration also showed a twofold higher risk of a TEE compared to patients who did not receive FC. However, only two studies were included in the meta-analysis. One study was an RCT, and one study compared FC to a number of other comparators, rendering the comparison somewhat difficult. Several trials on FC administration in trauma are currently ongoing, such as the Pilot Randomized Trial of Fibrinogen in Trauma Haemorrhage (ProoF-iTH)[23] and the Fibrinogen Early in Severe Trauma Study (FEISTY) trial,[55] which may generate more conclusive data about the safety of FC administration.

The high incidence of TEE raises the question whether routine screening is warranted. Current practices regarding screening vary widely across trauma centers.[56] Although implementing a routine screening practice for all trauma patients is costly and time consuming,[57] selecting patients at risk (such as patients receiving TXA or FC) may be useful and cost effective.[58] Although no firm recommendation regarding routine screening can be made based on our analysis, more well-adjusted studies or trials are needed to consider the use of universal screening in these patients.

Our review is limited by the use of different definitions for a TEE. Besides DVT and PE, some studies reported stroke or myocardial infarctions as well, while others did not. Moreover, the way in which a TEE was diagnosed differed among the studies. Some studies performed only diagnostics based on clinical symptoms, while in other studies the patients were subjected to routine screening. Quality of studies also differed, with the majority of studies showing a moderate- to good-quality grading. Also, the management of traumatic bleeding differs widely between hospitals. Finally, it must be noted that it is difficult to analyze the effect of procoagulant medication and blood components individually, as in clinical practice, multiple interventions occur simultaneously.

In conclusion, this systematic review of the literature identified an TEE incidence of 10% in severely injured trauma patients who survived the initial phase of bleeding. We found several associations between resuscitation therapy components and the development of TEEs, including the use of TXA and FCs.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Supporting Information..