Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Review)

Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C

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[Intervention Review]

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

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ABSTRACT

Background

Recombinant factor VIIa (rFVIIa) is licensed for use in patients with haemophilia and inhibitory allo-antibodies and for prophylaxis and treatment of patients with congenital factor VII deficiency. It is also used for off-license indications to prevent bleeding in operations where blood loss is likely to be high, and/or to stop bleeding that is proving difficult to control by other means. This is the third version of the 2007 Cochrane review on the use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia, and has been updated to incorporate recent trial data.

Objectives

To assess the effectiveness of rFVIIa when used therapeutically to control active bleeding or prophylactically to prevent (excessive) bleeding in patients without haemophilia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and other medical databases up to 23 March 2011.

Selection criteria

Randomised controlled trials (RCTs) comparing rFVIIa with placebo, or one dose of rFVIIa with another, in any patient population (except haemophilia). Outcomes were mortality, blood loss or control of bleeding, red cell transfusion requirements, number of patients transfused and thromboembolic adverse events.

Data collection and analysis

Two authors independently assessed potentially relevant studies for inclusion, extracted data and examined risk of bias. We considered prophylactic and therapeutic rFVIIa studies separately.

Main results

Twenty-nine RCTs were included: 28 were placebo-controlled, double-blind RCTs and one compared different doses of rFVIIa. In the 'Risk of bias' assessment, most studies were found to have some threats to validity although therapeutic RCTs were found to be less prone to bias than prophylactic RCTs.

Sixteen trials involving 1361 participants examined the prophylactic use of rFVIIa; 729 received rFVIIa. There was no evidence of mortality benefit (risk ratio (RR) 1.04; 95% confidence interval (CI) 0.55 to 1.97). There was decreased blood loss (mean difference (MD) -297 mL; 95% CI -416 to -178) and decreased red cell transfusion requirements (MD -261 mL; 95% CI -367 to -154) with rFVIIa treatment; however, these values were likely overestimated due to the inability to incorporate data from trials (four RCTs in the outcome of blood loss and three RCTs in the outcome of transfusion requirements) showing no difference of rFVIIa treatment compared to placebo. There was a trend in favour of rFVIIa in the number of participants transfused (RR 0.85; 95% CI 0.72 to 1.01). However, there was a trend against rFVIIa with respect to thromboembolic adverse events (RR 1.35; 95% CI 0.82 to 2.25).

Thirteen trials involving 2929 participants examined the therapeutic use of rFVIIa; 1878 received rFVIIa. There were no outcomes where any observed advantage or disadvantage of rFVIIa over placebo could not have been observed by chance alone. There was a trend in favour of rFVIIa for reducing mortality (RR 0.91; 95% CI 0.78 to 1.06). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47).

When all trials were pooled together to examine the risk of thromboembolic events, a significant increase in total arterial events was observed (RR 1.45; 95% CI 1.02 to 2.05).

Authors' conclusions

The effectiveness of rFVIIa as a more general haemostatic drug, either prophylactically or therapeutically, remains unproven. The results indicate increased risk of arterial events in patients receiving rFVIIa. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

PLAIN LANGUAGE SUMMARY

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

The purpose of this review was to evaluate the evidence of effectiveness and safety for the use of recombinant factor VIIa (rFVIIa). This drug has been used in patients who are either at risk of major bleeding (e.g. because of planned high-risk surgery), or who have uncontrolled bleeding (e.g. related to trauma). There have been many articles in the literature describing the off-license use of this drug, which often suggest benefit. However, most of the publications are based on small numbers of patients (in case reports or case series) and may be affected by bias. Randomised controlled trials provide higher-quality research findings and allow us to assess the evidence of drug effectiveness with more certainty.

This review included 29 randomised controlled trials with 4290 patients. The trials showed modest reductions in total blood loss or red cells transfused (equivalent to less than one unit of red cell transfusion) with the use of rFVIIa. However, the reductions were likely to be overestimated due to the limitations of the data. We also observed an increase in the risk of having a blood clot in the arteries (such as a heart attack or stroke) in those patients receiving rFVIIa. When taken together, the data supporting the off-license use of recombinant FVIIa are weak. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Recombinant factor VIIa compared with placebo for the prevention and treatment of bleeding in patients without haemophilia

Patient or population: any patients with conditions outside the marketing license for the intervention, particularly those at risk of bleeding or those whose bleeding cannot be controlled by other means
Settings: hospital
Intervention: recombinant factor VIIa
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of studies (participants)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	rFVIIa				
PROPHYLACTIC USE - to prevent bleeding in those at risk of bleeding such as during operations						
Death (follow-up generally not specified, but usually postoperative period)	**Low-risk population**		RR 1.04 (0.55 to 1.97)	15 (1219)	+++O moderate [1,2]	
	0 per 100	0 per 100				
	Medium-risk population					
	15 per 100	16 per 100 (8 to 30)				
	High-risk population					
	30 per 100	31 per 100 (17 to 59)				
Total operative and peri-operative blood loss (mL) (follow-up generally not specified, but usually postoperative period)	The mean ranged across control groups from 381 mL to 8552 mL	Mean difference was 297 mL lower (416 to 178 lower)	NA	10 (707)	++OO low [1,3]	Negative value indicates less blood loss in rFVIIa

Red cell transfusion requirements (mL) (follow-up generally not specified, but usually postoperative period)	The mean ranged across control groups from 450 mL to 5820 mL	Mean difference was 261 mL lower (367 to 154 lower)	NA	12 (774)	++00 low [1,3]	Negative value indicates less transfusion in rFVIIa
Number of patients transfused (follow-up generally not specified, but usually postoperative period)	**Low-risk population**		RR 0.85 (0.72 to 1.01)	8 (868)	++00 low [1,2,4,5]	
	40 per 100	34 per 100 (29 to 40)				
	Medium-risk population					
	70 per 100	60 per 100 (50 to 71)				
	High-risk population					
	100 per 100	85 per 100 (72 to 100)				
Total thromboembolic events (follow-up generally not specified, but usually postoperative period)	**Low-risk population**		RR 1.35 (0.82 to 2.25)	13 (1159)	+++0 moderate [1,2]	
	0 per 100	0 per 100				
	Medium-risk population					
	10 per 100	14 per 100 (8 to 23)				
	High-risk population					
	20 per 100	27 per 100 (16 to 45)				
THERAPEUTIC USE - to treat established bleeding						

Death (follow-up generally not specified, but usually period of hospitalisation)	**Low-risk population**		RR 0.91 (0.78 to 1.06)	13 (2856)	+++O moderate [1,2,5]	
	0 per 100	0 per 100				
	Medium-risk population					
	15 per 100	14 per 100 (12 to 16)				
	High-risk population					
	30 per 100	28 per 100 (24 to 32)				
Numbers of patients with reduced bleeding (follow-up generally not specified, but usually period of hospitalisation)	**Low-risk population**		RR 0.95 (0.88 to 1.03)	4 (616)	++OO low [1,2,6]	
	50 per 100	48 per 100 (44 to 52)				
	Medium-risk population					
	70 per 100	67 per 100 (62 to 72)				
	High-risk population					
	90 per 100	86 per 100 (79 to 93)				
Red cell transfusion requirements (mL) (follow-up generally not specified, but usually period of hospitalisation)	The mean ranged across control groups from 103 mL to 2730 mL	Mean difference was 89 mL lower (264 lower to 87 higher)	NA	5 (911)	++OO low [1,2,7]	Positive value indicates more transfusion in rFVIIa.

Total thromboembolic events (follow-up generally not specified, but usually period of hospitalisation)	**Low-risk population**		RR 1.14 (0.89 to 1.47)	13 (2873)	+++O moderate [1,2]
	0 per 100	0 per 100			
	Medium-risk population				
	20 per 100	23 per 100 (18 to 29)			
	High-risk population				
	40 per 100	46 per 100 (36 to 59)			
THROMBOEMBOLIC EVENTS ACROSS ALL RANDOMISED CONTROLLED TRIALS					
Total thromboembolic events (follow-up generally not specified, but usually period of hospitalisation)	**Low-risk population**		RR 1.18 (0.94 to 1.48)	26 (4032)	+++O moderate [1,2]
	0 per 100	0 per 100			
	Medium-risk population				
	20 per 100	24 per 100 (19 to 30)			
	High-risk population				
	40 per 100	47 per 100 (38 to 59)			
Arterial thromboembolic events (follow-up generally not specified, but usually period of hospitalisation)	**Low-risk population**		RR 1.45 (1.02 to 2.05)	25 (3849)	+++O moderate [1,2]
	0 per 100	0 per 100			
	Medium-risk population				

	20 per 100	29 per 100 (20 to 41)
	High-risk population	
	40 per 100	58 per 100 (41 to 82)

Assumed risks are derived from observed rates in the placebo groups (Low = lowest observed; High = highest observed; Medium = mid-point of highest and lowest observed).

GRADE Working Group grades of evidence

High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality (+++0): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality (++00): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality (+000): We are very uncertain about the estimate.

Concerns identified:

1. Some risks of bias in included studies.
2. Wide confidence intervals.
3. Unable to include studies described as showing ' ' no difference" in meta-analysis. Heavy weighting towards very small studies with apparently very precise estimates of blood loss. Very marked heterogeneity.
4. Some heterogeneity.
5. Evidence of publication bias.
6. Unable to incorporate results of all studies on intracerebral haemorrhage where control of bleeding measured in different manner.
7. Small number of included studies.

BACKGROUND

Recombinant activated factor VII (rFVIIa) (NovoSeven®, Novo Nordisk, Denmark) has been manufactured and used clinically for a number of years for the treatment of bleeding in individuals with haemophilia and inhibitory antibodies to factor VIII (Lusher 1998) as well as other congenital bleeding disorders such as inherited factor VII deficiency and Glanzmann's thrombasthenia. More recently, the potential of rFVIIa to minimise or control severe bleeding in a variety of medical and surgical situations has engendered considerable interest (Hedner 2002). The hypothesis that high-dose rFVIIa would be capable of enhancing haemostasis at the local site of injury, without systemic activation of the coagulation cascade and the risk of widespread inappropriate thrombosis, would clearly be an asset for clinical use (Key 2003a).

The initial evidence on the clinical role of rFVIIa for patients without inherited defects of haemostasis was dominated by case reports and small case series (Ahonen 2005; Greisen 2003; Key 2003b). However, over the years, data from randomised controlled trials have been reported, which should provide the most robust means of evaluating drug effectiveness and safety. These trials have assessed drug use in a variety of clinical scenarios in which rFVIIa may have a role, including excessive surgical bleeding, uncontrolled medical bleeding and trauma. However, bleeding in these clinical settings has multiple causes, including diffuse small vessel oozing, dilution of clotting factors and platelets from massive transfusion, disseminated intravascular coagulation, hyperfibrinolysis, hypothermia (with slowing of the enzymatic reactions in coagulation) and acidosis, and it is unclear what effect rFVIIa would have on haemostasis in the setting of each or a combination of these factors. Many hospitals report that off-label use of rFVIIa as a general or 'universal haemostatic agent' has been increasing at least up until 2008 (Isbister 2008; Logan 2010; Logan 2011; Roberts 2004).

One of the concerns about extending the use of a coagulation factor treatment such as rFVIIa to different patient groups is the potential for adverse effects, in particular the risk of thromboembolism (Levi 2010; O'Connell 2006).

To examine the effectiveness and safety of recombinant factor VIIa with the addition of larger randomised controlled trials, we have produced this third version of the Cochrane review on the use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia, which was first published in 2007.

OBJECTIVES

The objective of this systematic review was to assess the effects of recombinant factor VIIa (rFVIIa) when used for the prophylactic or therapeutic management of haemorrhage in patients without haemophilia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients at risk of blood loss due to surgery, or who had received treatment to manage bleeding. We considered all age groups, but we excluded patients with haemophilia or other haemostatic defects (for example, Glanzmann's thrombasthenia, inherited factor VII deficiency).

Types of interventions

- RCTs comparing rFVIIa to prevent bleeding (for example, before or during surgery) with no rFVIIa.
- RCTs comparing rFVIIa to treat bleeding (for example, in the context of medical or surgical bleeding, or trauma) with no rFVIIa.
- RCTs comparing rFVIIa with alternative treatments for the prevention and/or treatment of haemorrhage.
- RCTs comparing different dose schedules of rFVIIa.

We documented details of co-interventions aimed at managing bleeding, including the use of additional 'haemostatic' drugs and policies for transfusion.

Types of outcome measures

- Survival at fixed, relevant time periods, with mortality evaluated by cause when possible (that is, as either haemorrhagic, an adverse effect of the intervention, or not related to intervention).
- Bleeding (within a predefined follow-up period post-intervention), measured as response of bleeding (for example, prevented, stopped, decreased, increased, no change), number and/or duration of bleeding episodes, or severity of blood loss (for example, by volume, rate or bleeding score).
- Number of red cell transfusions required (whether as units transfused or episodes, in a follow-up period relevant to the bleeding episode).
- Number of patients avoiding transfusions (for prophylactic studies).
- Adverse effects of interventions (for example, thrombosis).

We identified other outcome information (for example, use of blood products other than red cells, impact on operation times and adverse events other than thromboembolic events) in study reports during the preparation of the first version of this review.

In the future, we will explore the value of these data in a separate analysis.

Search methods for identification of studies

The searches were not restricted by language or publication status. Searches were conducted by the authors, working independently from the Cochrane Injuries Group Editorial Base.

Electronic searches

We searched the following databases on 23 March 2011.

- CENTRAL (Cochrane Central Register of Controlled Trials, *The Cochrane Library* 2011, Issue 1)
- MEDLINE (1948 to 23 March 2011)
- EMBASE (1980 to 23 March 2011)
- CINAHL (1982 to 23 March 2011)
- UK Blood Transfusion & Tissue Transplantation Services (UKBTS) Systematic Review Initiative (SRI) Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to 23 March 2011)
- LILACS (1982 to 23 March 2011)
- KoreaMed (1997 to 23 March 2011)
- IndMed (1985 to 23 March 2011)
- PakMediNet (2001 to 23 March 2011)
- ISRCTN Register (23 March 2011)
- ClinicalTrials.gov (23 March 2011)
- EUDRACT (EU Clinical Trials Register) (23 March 2011)
- WHO ICTRP (International Clinical Trials Register Portal) (23 March 2011)

In MEDLINE, we combined the search strategy with the Cochrane optimal RCT search filter described in Chapter 6.4.11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In EMBASE and CINAHL, we combined search strategies with adaptations of this RCT filter. Search strategies can be found in Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

Searching other resources

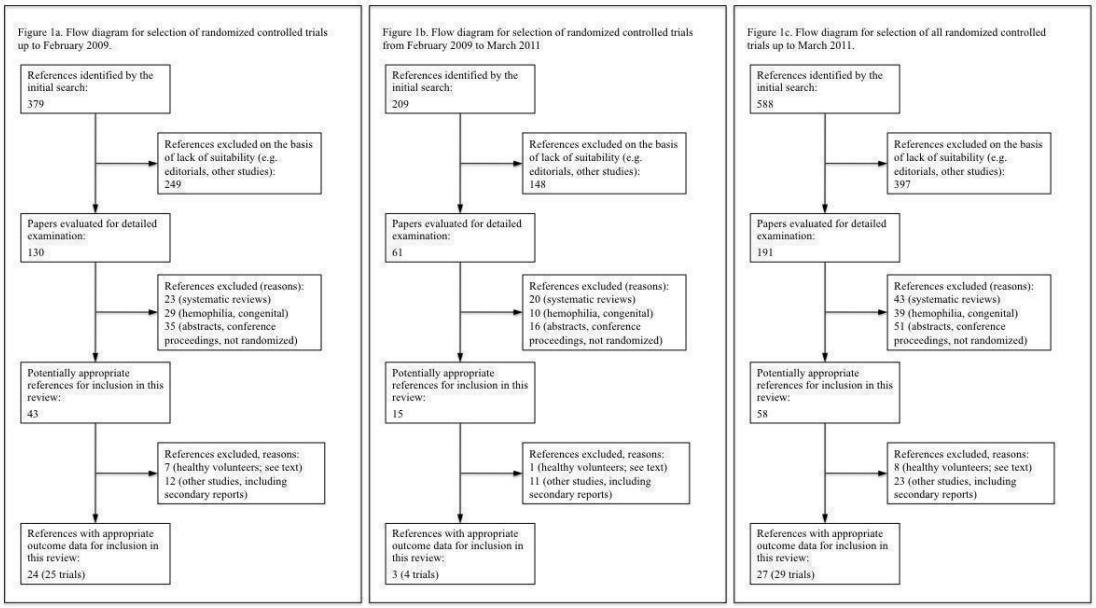
In addition, we checked the reference lists of the RCTs identified and of relevant reviews, including recently published systematic reviews (Hsia 2008; You 2006). We contacted the authors of known trials for information on any further trials of which they may be aware, whether published, unpublished or ongoing, or to provide additional data as required. We also carefully followed up ongoing trials identified in the first version of this review and identified new ongoing trials.

Data collection and analysis

Selection of studies

Two of the authors (ES, YL, SS or JB) screened all titles and abstracts of papers identified by the database searches for relevance. We excluded only clearly irrelevant studies at this stage; we assessed all other studies on the basis of their full text for inclusion/exclusion using the criteria indicated above. At this stage, two authors independently assessed eligibility and noted any discrepancies in their assessments. We only included trials available as full publications up to March 2011 (Figure 1).

Figure 1. Figure 1. Flow diagram for selection of all randomized controlled trials for this review.



Data extraction and management

Aside from details relating to study quality, we extracted the following data.

- Study characteristics - place of publication, date of publication, population characteristics, setting, intervention, comparator and outcomes. A key purpose of these data was to examine clinical heterogeneity in the included studies independently from the analysis of results. Potential sources of clinical heterogeneity in this specific review included details of intervention (dose, frequency) and participant group (condition, clinical setting).
- Results of included studies - we extracted data for each of the main outcomes indicated in the review question. If an included study did not contribute data on a particular outcome we recorded the reason. We considered the possibility of the selective reporting of results on particular outcomes. For dichotomous outcomes, we recorded the numbers of outcomes in treatment and control groups. For continuous outcomes, we recorded means and standard deviations (SD). If median and interquartile range (IQR) were available, we used the median as the mean and converted the IQR to SD.

Two authors extracted data using data extraction forms that were purposely created and piloted for this review. The authors resolved disagreements by consensus, recording the agreed data onto a third summary data extraction form. One author transcribed this into the systematic review computer software Review Manager 5 (RevMan 2008); another author verified all data entry for discrepancies.

Assessment of risk of bias in included studies

All authors used the following criteria for judging risk of bias from the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.1 (Higgins 2011) to evaluate the methodological quality of the included studies:

- generation of a random sequence;
- concealment of treatment allocation schedule;
- blinding of participants, personnel and outcome assessors;
- incomplete outcome data reporting;
- selective outcome reporting; and
- other potential threats to validity.

We rated these criteria using the 'Risk of bias' assessment tool provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This assigns a rating of 'Yes' (adequate), 'Unclear' and 'No' (clearly inadequate) to each specified methodological criterion. In addition, we added a criterion to the table to indicate whether a power calculation was performed for the RCT. A rating of 'Yes' was assigned if both a power calculation was performed and the target sample size was stated (regardless of whether

or not this target was achieved), 'Unclear' if a power calculation was performed but a target sample size was not specified, and 'No' if no power calculation was performed.

We used evaluation of the methodological quality of each included study within the review in the following ways:

- either as a possible explanation for differences in results between studies or to investigate heterogeneity; or
- in sensitivity analyses, examining the effect on overall estimates of excluding studies of poor methodological quality.

Measures of treatment effect

We analysed data qualitatively and quantitatively. The preferred form of summary result was a risk ratio (RR) for binary data and mean difference (MD) for continuous data, both with 95% confidence intervals (CI). When a study reported values on continuous outcomes for subgroups of different doses of rFVIIa, we used the mean of the reported values as an overall summary effect of rFVIIa for the meta-analysis.

Assessment of heterogeneity

We examined statistical heterogeneity using the Chi^2 test, the I^2 statistic and visual inspection of graphs. We considered values of I^2 greater than 25% to indicate a level of heterogeneity at which pooled estimates should be interpreted very cautiously and efforts focused on understanding the cause of between-study variation in results. Where the I^2 was below 25% we explored the robustness of any summary measures, particularly with respect to study quality.

Assessment of reporting biases

We examined publication bias using funnel plots produced using RevMan 5 software for each of the outcome measures.

Data synthesis

We employed meta-analysis, using a fixed-effect model in the first instance, but also evaluated the results from the random-effects model. The results from the random-effects models are given in recognition of the marked clinical heterogeneity between the included studies.

Subgroup analysis and investigation of heterogeneity

One subgroup was pre-specified: rFVIIa dose. The cut-off used to distinguish low from high dose was less than 80 μg/kg and equal to or more than 80 μg/kg of rFVIIa, based on clinical opinion (and was not strictly pre-specified). No differences between the low-dose and high-dose outcomes were seen in the previous versions nor in this version, therefore these analyses are not presented.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

See 'Characteristics of included studies' and 'Characteristics of ongoing studies'.

Results of the search

The updated search (conducted 23 March 2011) identified a total of 140 new records since the last version, which three authors (ES, YL, SS) reviewed independently. Figure 1 shows the study selection sequentially for each of the updates of this review.

Twenty-seven RCTs as full publications up to 23 March 2011 were eligible for inclusion. For the purposes of this review, we considered each of the studies by Boffard et al and Hauser et al as two separate trials, because they both concerned two different types of trauma: blunt (Boffard 2005a; Hauser 2010a) and penetrating (Boffard 2005b; Hauser 2010b). With these sub-populations, there was a total of 29 RCTs for analysis (see 'Characteristics of included studies').

We identified a number of potentially eligible ongoing and completed (unpublished) trials from other registers, including the meta-register of controlled trials (mRCT - includes ClinicalTrials.gov), the National Research Register, ClinicalStudyResults.org and the Novo Nordisk list of rFVIIa trials. These trials are summarised in the 'Characteristics of ongoing studies' table. An additional table (Table 1) has been included in this update summarising the status of the ongoing studies from the last version of this review (Lin 2011). Of the 11 studies in Table 1, five were completed and two were published.

Included studies

See 'Characteristics of included studies'.

Prophylactic trials

Sixteen RCTs assessed rFVIIa given prophylactically to prevent bleeding (Table 2). Nine trials were single-centre and seven were multi-centre. Eight were small with fewer than 50 patients randomised (Diprose 2005; Essam 2007; Friederich 2003; Hanna 2010; Johansson 2007; Ma 2006; Pugliese 2007; Raobaikady 2005).

Participants

The clinical setting of the included studies varied (Table 2). Five studies evaluated patients undergoing cardio-pulmonary bypass (Diprose 2005; Ekert 2006; Essam 2007; Ma 2006; Gill 2009). Six studies evaluated patients undergoing hepatic procedures: one

in liver biopsy (Jeffers 2002), two in partial hepatectomy (Lodge 2005a; Shao 2006) and three in liver transplantation (Lodge 2005b; Planinsic 2005; Pugliese 2007). Five studies evaluated the role of rFVIIa in a variety of other conditions: paediatric craniofacial reconstruction (Hanna 2010), retropubic prostatectomy (Friederich 2003), burn patients requiring excision and grafting (Johansson 2007), pelvic fracture (Raobaikady 2005) and spinal fusion surgery (Sachs 2007). Both Sachs 2007 and Gill 2009 were considered with the prophylactic group as rFVIIa was administered at the time of a defined bleeding trigger in the perioperative setting.

All studies reported predefined exclusion criteria except Pugliese 2007. The main exclusions were evidence of pre-existing 'coagulopathy' in patients with known thromboembolic or vascular disease. In addition, Diprose 2005 and Ma 2006 excluded patients who would refuse blood products while Hanna 2010 also excluded patients with neurological disorders, and both Planinsic 2005 and Lodge 2005b excluded patients who had undergone previous transplantation.

Intervention

Fifteen of 16 trials compared rFVIIa with placebo. rFVIIa was given at a single dose in eight studies and as repeated dosing in eight studies, with three studies administering repeated dosing only if there was ongoing surgery or bleeding (Table 2). Thus there were marked differences in the doses and schedules employed. The differences are more apparent if the total dose administered is considered. This varied from 5 µg/kg (Jeffers 2002) to 360 µg/kg (Lodge 2005b; Sachs 2007).

Co-interventions

The two main groups of important co-interventions were the use of additional 'haemostatic' drugs and transfusion (Table 2). Red cell transfusion protocols were provided in 13 studies with seven studies outlining further guidelines for platelets and/or plasma. Three studies provided no details on transfusion protocols (Ekert 2006; Jeffers 2002; Ma 2006). Co-interventions are also outlined in Table 2. Of particular interest for thromboembolic adverse events, four studies described the use of low molecular weight heparin (LMWH) in the perioperative (Raobaikady 2005) and postoperative settings (Friederich 2003; Johansson 2007; Lodge 2005a).

Outcomes

The prophylactic studies reported a variety of primary outcome measures (Table 2). However, the main outcome focus of the included studies was either blood loss (primary outcome in Friederich 2003; Raobaikady 2005; Sachs 2007), amount of blood transfused (primary outcome in Ekert 2006; Friederich 2003; Johansson 2007; Lodge 2005b; Planinsic 2005; Shao 2006), or number of patients receiving allogeneic transfusion (primary outcome in Diprose 2005; Lodge 2005a; Shao 2006). Four studies did not define a primary outcome but collected data on blood loss and transfusion requirements (Essam 2007; Hanna 2010; Ma 2006; Pugliese 2007). Finally, one study in liver biopsy (Jeffers 2002) used time to haemostasis and duration of normal prothrombin time (PT) as its primary outcomes and one study used a primary outcome of critical serious adverse events (Gill 2009).

All trials except Essam 2007 and Hanna 2010 reported adverse events including deaths and thromboembolic events. Active surveillance (planned ECG, troponin measurements or doppler ultrasound) was performed in five prophylactic studies (Friederich 2003; Lodge 2005a; Lodge 2005b; Planinsic 2005; Shao 2006). Other adverse events were reported, but the focus of this report is on death and thromboembolic events, the latter being of particular concern when using a pro-coagulant agent.

Therapeutic trials

Thirteen RCTs assessed rFVIIa given therapeutically to treat established bleeding (Table 3). All of the trials were multi-centre. Three studies were small with fewer than 50 patients randomised (Chuansumrit 2005; Mayer 2005b; Mayer 2006).

Participants

The clinical setting of the included studies varied (Table 3): four studies in severe trauma (Boffard 2005a; Boffard 2005b; Hauser 2010a; Hauser 2010b), two studies in cirrhosis with acute upper gastrointestinal bleeding (UGIB) (Bosch 2004; Bosch 2008), one study in dengue haemorrhagic fever (Chuansumrit 2005), one study in bleeding post-haematopoietic stem cell transplantation (HSCT) (Pihusch 2005), four studies in spontaneous intracranial haemorrhage (ICH) (Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008) and one study in traumatic ICH (Narayan 2008).

All studies reported pre-defined exclusion criteria. Common exclusions related to the severity of the condition being treated (all trials) and evidence of an underlying clotting or bleeding diathesis (Bosch 2004; Bosch 2008; Mayer 2005a; Mayer 2006; Mayer 2008; Narayan 2008). In all ICH trials, patients were excluded if surgical intervention was planned within 24 hours.

Intervention

All clinical trials were placebo-controlled but the doses of rFVIIa varied widely, as did its administration (Table 3). rFVIIa was given as a single dose in the five ICH trials and as repeated dosing in the other trials, with one study administering repeated dosing only if there was ongoing bleeding (Chuansumrit 2005). The variation in doses was most evident when estimating the total dose of rFVIIa received. The minimum was 5 to 10 µg/kg in Mayer 2006 and Mayer 2005b, extending to 1120 µg/kg in Pihusch 2005, a 100-fold variation.

Co-interventions

The two main groups of important co-interventions were the use of additional 'haemostatic' drugs and transfusion (Table 3). Five studies described transfusion protocols (Bosch 2004; Bosch 2008; Hauser 2010a; Hauser 2010b; Pihusch 2005). The five ICH studies did not provide a transfusion protocol, which was appropriate as these patients are rarely transfused. The remaining three studies (Boffard 2005a; Boffard 2005b; Chuansumrit 2005) did not provide transfusion protocols. Although these studies did not include transfusion protocols, transfusion requirements were cited as the primary outcome in Boffard 2005a and Boffard 2005b.

Outcomes

The therapeutic studies reported multiple outcome measures (see Table 3 and 'Characteristics of included studies'). In the majority of the included trials (Bosch 2004; Bosch 2008; Chuansumrit 2005; Mayer 2005a; Pihusch 2005) the primary endpoint was a measure of change in bleeding. By contrast, Boffard 2005a and Boffard 2005b defined the primary endpoint as transfusion requirements. The primary endpoint in Mayer 2008 was a clinical outcome as defined by the modified Rankin scale at day 90. Mayer 2005b, Mayer 2006 and Narayan 2008 defined their primary outcome as the frequency of adverse events that were (possibly or probably) treatment-related. Hauser 2010a and Hauser 2010b measured all-cause 30-day mortality as the primary outcome.

Again, other secondary outcomes for all included treatment trials included adverse events, particularly deaths and thromboembolic events, which were monitored either clinically or additionally by Doppler ultrasound. Other adverse events were reported, but deaths and thromboembolic events are the focus of this review.

Sources of support

Nine of 16 prophylactic trials were either supported by Novo Nordisk, the manufacturer of rFVIIa or were co-authored by an employee of Novo Nordisk. All therapeutic trials were supported by the company or co-authored by an employee of Novo Nordisk. Details are provided in the 'Characteristics of included studies'.

Risk of bias in included studies

Full details of quality assessments are presented in the 'Risk of bias' table presented with each study in the 'Characteristics of included studies' table. Figure 2 and Figure 3 give visual representations of the assessments of risk of bias across all studies and for each item in the individual studies, respectively.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

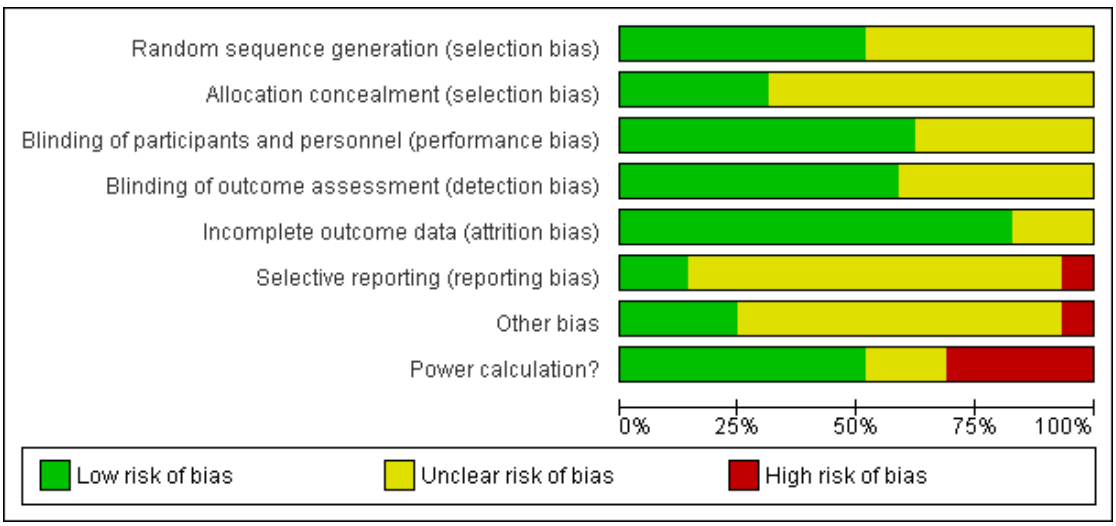
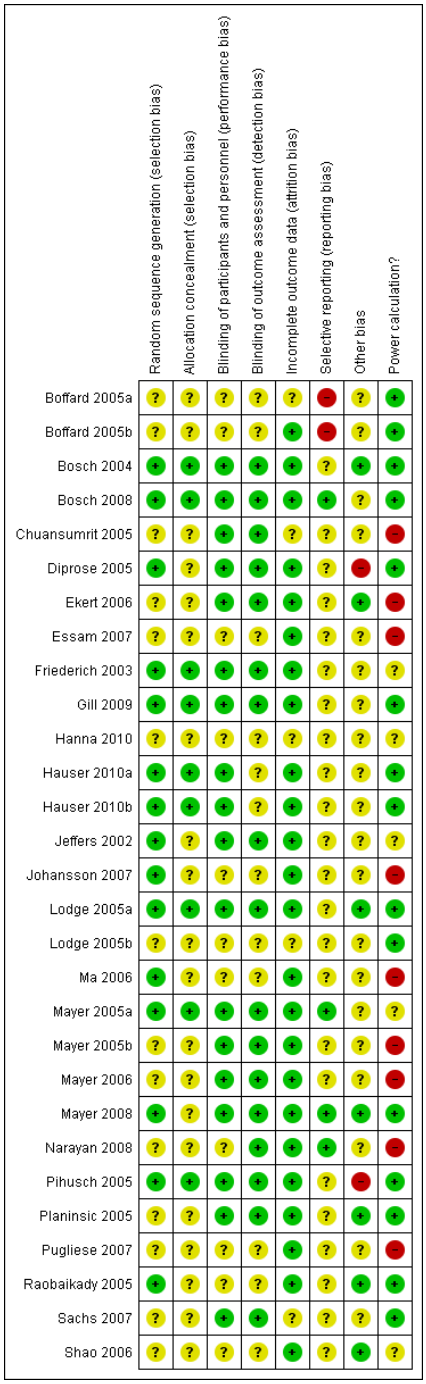


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Prophylactic trials

All prophylactic studies had some threats to validity. For the most part, these potential risks of bias were due to lack of detail provided on the specific criteria and thus were judged as 'unclear'. Using the Cochrane grading system:

- sequence generation was adequate in eight studies and unclear in eight;
- allocation concealment was adequate in three studies and unclear in 13;
- blinding of participants and personnel was adequate in nine studies and unclear in seven;
- blinding of outcome assessment was adequate in nine studies and unclear in seven;
- incomplete outcome data assessment was adequate in 13 studies and unclear in three;
- free of selective outcome reporting assessment was unclear in all studies as study protocols were not available and none of the studies were found to be registered with a clinical trials registry;
- free of other bias assessment was adequate in five studies, unclear in 10 and inadequate in one. The study judged to be inadequate in this category was Diprose 2005 in which there were baseline differences between rFVIIa and placebo groups and the study was underpowered; and
- power calculation was adequate in seven studies, unclear in four and inadequate in five. The studies judged to be inadequate had not performed power calculations.

Two prophylactic trials (Gill 2009; Lodge 2005a) had minimal threats to validity.

Therapeutic trials

For therapeutic studies, the potential risks of bias were mostly due to lack of detail provided on the specific criteria and we thus judged them as 'unclear'. Using the Cochrane grading system:

- sequence generation was adequate in seven studies and unclear in six;
- allocation concealment was adequate in six studies and unclear in seven;
- blinding of participants and personnel was adequate in 10 studies and unclear in three;
- blinding of outcome assessment was adequate in nine studies and unclear in four;
- incomplete outcome data assessment was adequate in 11 studies and unclear in two;
- free of selective outcome reporting assessment was adequate in seven studies (registered with a clinical trials registry), unclear in four studies and inadequate in two studies. The two studies judged to be inadequate were Boffard 2005a and Boffard 2005b where emphasis was placed on the analysis where patients who died within 48 hours were excluded and data for some outcomes were presented for those patients alive at 48 hours;
- free of other bias assessment was adequate in two studies, unclear in 10 and inadequate in one. The study judged to be inadequate was Pihusch 2005 in which there were baseline differences between rFVIIa and placebo groups;
- power calculation was adequate in eight studies, unclear in one and inadequate in four studies where no power calculations were performed.

All 13 RCTs using rFVIIa to treat established bleeding were reported to be double-blind and placebo-controlled, but two (Bosch 2004; Bosch 2008) were felt to be largely free from threats to validity.

When compared to the prophylactic trials, the therapeutic trials were less prone to bias, particularly in the areas of blinding and selective reporting as judged by being registered clinical trials. Therapeutic trials were also on average larger in sample size than prophylactic trials.

Effects of interventions

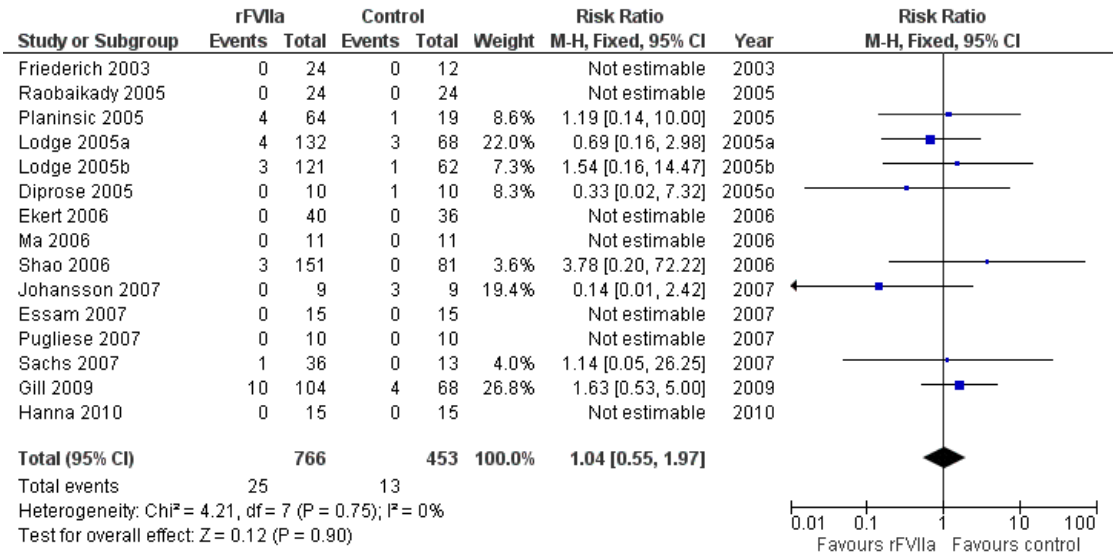
See: **Summary of findings for the main comparison**

Prophylactic trials

Death

Mortality data were included for 15 trials. The individual results from all 15 studies had a 95% confidence interval (CI) that included 1.0 (no difference between rFVIIa and placebo). The pooled risk ratio (RR) was 1.04 (95% CI 0.55 to 1.97), I^2 = 0%, indicating that observed variation in the study results was compatible with chance alone (Figure 4). In six studies (Ekert 2006; Essam 2007; Friederich 2003; Hanna 2010; Pugliese 2007; Raobaikady 2005) no deaths were mentioned; thus the number of deaths was taken to be zero in all study arms. Control arm death rates were generally low across all studies, the maximum being 1/10 (Diprose 2005).

Figure 4. Forest plot of comparison: 1 rFVIIa used prophylactically versus placebo, outcome: 1.1 Death.



Blood loss

Ten studies contributed blood loss outcome data. The pooled mean difference (MD) was -297 mL (297 mL less blood loss in the rFVIIa arms) (95% CI -416 to -178) (Analysis 1.3). There was marked variation in the amount of mean blood loss in the control arms, from 381 mL (Ma 2006) to 8552 mL (Lodge 2005b). Five studies, each with fewer than 40 patients, had a 95% CI not including zero favouring rFVIIa (Essam 2007; Friederich 2003; Hanna 2010; Ma 2006; Pugliese 2007). These studies accounted for 20% of the included patients in the analysis but their MDs accounted for 82% of the pooled estimate.

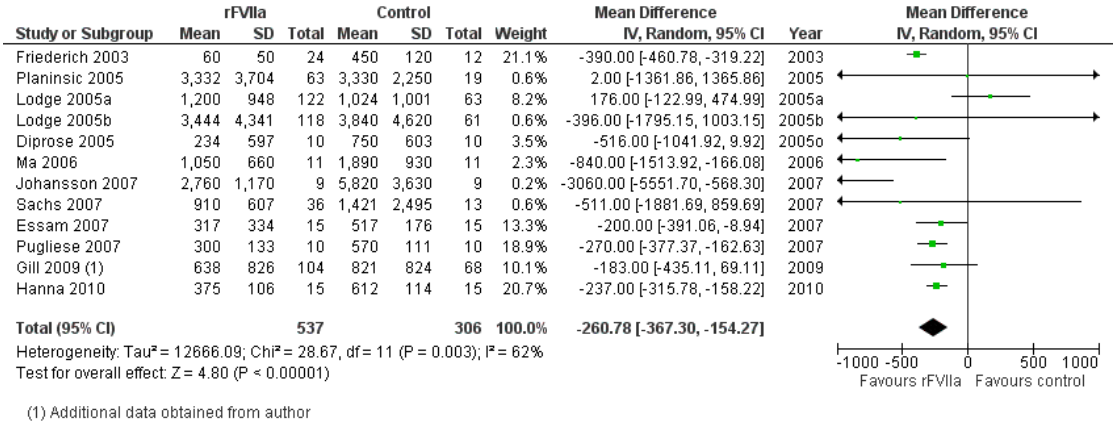
Investigation of the heterogeneity is presented in Analysis 1.4. Heterogeneity was explained in part by the size of the study. When only studies with greater than 50 patients (Gill 2009; Lodge 2005a; Lodge 2005b; Sachs 2007) were included, the I^2 = 0% and the pooled MD was no longer statistically significant (MD -261 mL; 95% CI -550 to 28).

The pooled MD likely represents an overestimate of the effect of rFVIIa as four additional studies, each with more than 40 patients, reported no difference in blood loss and could not be incorporated into the pooled analysis because outcomes were not available as mean/standard deviation (SD) (Ekert 2006; Planinsic 2005; Raobaikady 2005; Shao 2006). The blood loss data were affected by heavy weighting towards several small studies that reported very precise estimation of blood losses.

Use of red cell transfusion

Twelve studies were included in the pooled analysis for red cell transfusion requirements. The pooled MD was -261 mL (261 mL less red cells required in the rFVIIa arms) (95% CI -367 to -154) (Figure 5). There was evidence of significant heterogeneity (I^2 = 62%). Data in units of red cells were converted to millilitres assuming a single unit equated to 300 mL. There was marked variation in the amount of mean red cell transfusion requirements in the control arm, from 450 mL (Friederich 2003) to 5820 mL (Johansson 2007). Six studies had a 95% CI not including zero and favouring rFVIIa (Essam 2007; Friederich 2003; Hanna 2010; Johansson 2007; Ma 2006; Pugliese 2007) and none had more than 50 patients. Studies with fewer than 50 patients accounted for 26% of the included patients in the analysis but their MDs accounted for 81% of the pooled estimate.

Figure 5. Forest plot of comparison: 1 rFVIIa used prophylactically versus placebo, outcome: 1.5 Red cell transfusion requirements (mL).



Further investigation of the heterogeneity is presented in Analysis 1.6. Heterogeneity was explained in part by the size of the study. When only studies with greater than 50 patients (Gill 2009; Lodge 2005a; Lodge 2005b; Planinsic 2005) were included, the I^2 = 14% and the pooled MD was no longer statistically significant (MD -33 mL; 95% CI -260 to 193).

The pooled MD likely represents an overestimate of the effect of rFVIIa as three additional studies reported no difference in red cell requirements and could not be incorporated into the pooled analysis because outcomes were not available as mean/SD (Ekert 2006; Raobaikady 2005; Shao 2006). The red cell transfusion data was also affected by heavy weighting towards several small studies that reported very precise estimation of red cell transfusion requirements.

Number of patients transfused

Eight studies reported and contributed data on the number of patients transfused. The pooled RR was 0.85 (95% CI 0.72 to 1.01) with marked heterogeneity present, I^2 = 57% (Analysis 1.7). Further exploration offered no clear explanation for heterogeneity (Analysis 1.8). There was marked variation in the proportions of patients receiving transfusions in the control arms, ranging from 37% (Lodge 2005a) to 100% (Lodge 2005b). Two studies had a 95% CI that did not include 1.0 (no difference) (Friederich 2003; Lodge 2005b); both studies showed a reduction in the proportion of people requiring transfusion with rFVIIa.

Thromboembolic events

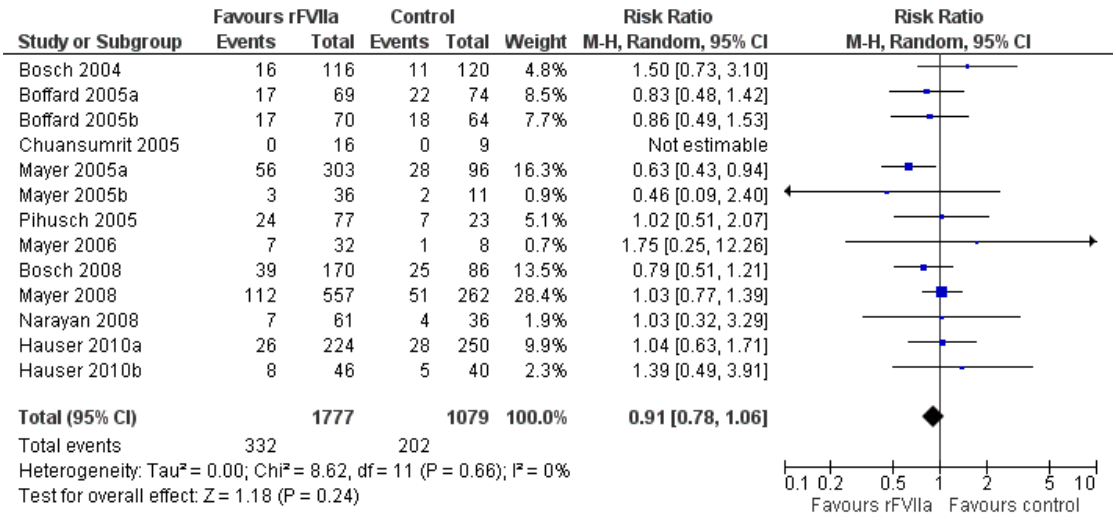
Thirteen studies contributed data on thromboembolic events. The pooled RR was 1.35 (95% CI 0.82 to 2.25) with heterogeneity accounted for by chance alone (I^2 = 0%) (Analysis 1.9). Control event rates were generally low across all studies, the maximum being 2/10 (Diprose 2005). Individually the 95% CIs of all the included studies included 1.0 (no difference between rFVIIa and placebo). Essam 2007 was not included in the pooled analysis as no detail was provided on adverse events.

Therapeutic trials

Death

All included studies contributed data on death. The pooled RR for overall mortality was 0.91 (95% CI 0.78 to 1.06) with no statistical heterogeneity (I^2 = 0%) (Figure 6). The mortality rates in the control group varied from 0/9 (Chuansumrit 2005) to 22/74 (30%) (Boffard 2005a). All studies yielded a RR whose 95% CI included 1.0 when examined in separate dose groups. However, in Mayer 2005a the RR was 0.63 (95% CI 0.43 to 0.94).

Figure 6. Forest plot of comparison: 2 rFVIIa used therapeutically versus placebo, outcome: 2.1 Death.



Control of bleeding

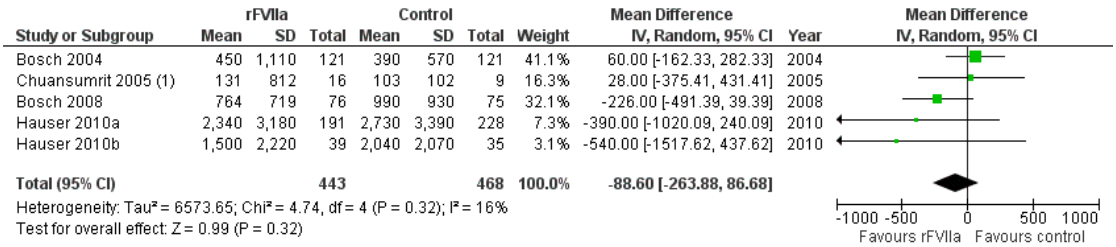
Seven trials reported outcome data on the control of bleeding, four of which (Bosch 2004; Bosch 2008; Chuansumrit 2005; Pihusch 2005) provided data appropriate for meta-analysis. The pooled RR was 0.95 (95% CI 0.88 to 1.03) in favour of rFVIIa, with I^2 = 0% (Analysis 2.3). The proportion of participants achieving bleeding control in the placebo arm ranged from 44% (Chuansumrit 2005) to 84% (Bosch 2004). For all the included studies, the RR 95% CI included 1.0 (no difference).

The five intracranial haemorrhage (ICH) randomised controlled trials (RCTs) (Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008; Narayan 2008) measured bleeding control in a different way from the other studies. Although appropriate to the condition they addressed, this meant that their results could not be combined quantitatively. We thus considered the additional insights they provided qualitatively alongside the above pooled RR. In the initial efficacy study (Mayer 2005a), the trial authors reported a statistically significant reduction in the growth of haemorrhage volume in favour of rFVIIa. Additional data provided suggested that reductions in the increase in haemorrhage volume attributable to rFVIIa were associated with reduced disability as measured by the Modified Rankin Scale, the Extended Glasgow Coma Scale, the Barthel Index and the National Institutes of Health Stroke Scale at 90 days. The second efficacy trial (Mayer 2008) defined its primary endpoint as severe disability or death by a Modified Rankin scale score of 5 or 6. Although this study did show a significant reduction in growth of volume of haemorrhage in the 80 μg/kg rFVIIa group, there was no significant difference in the primary endpoint at 90 days. None of the safety trials (Mayer 2005b; Mayer 2006; Narayan 2008) showed a significant reduction in their secondary endpoints of growth of volume of haemorrhage.

Use of red cell transfusion

Five studies contributed data on the use of red cell transfusions (Bosch 2004; Bosch 2008; Chuansumrit 2005; Hauser 2010a; Hauser 2010b). The pooled MD was -89 mL (95% CI -264 to 87) with minimal heterogeneity (I^2 = 16%) (Figure 7). The use of transfusion in the control groups varied from 103 mL (Chuansumrit 2005) to 2730 mL (Hauser 2010a). The 95% CI for the MD for all the included studies included zero (no difference).

Figure 7. Forest plot of comparison: 2 rFVIIa used therapeutically versus placebo, outcome: 2.5 Red cell transfusion requirements (mL).



(1) Data provided per kg and converted to mL according to average weights for the mean ages indicated

Data from Boffard 2005a and Boffard 2005b were reported as median/range, therefore these could not be incorporated into the pooled analysis. The exclusion of these studies is unlikely to change the pooled MD as there was no significant difference in the primary endpoint of number of red cell units transfused for all patients at 48 hours.

Number of patients transfused

Three of the 13 studies investigating the use of rFVIIa for treating bleeding collected information on the number of patients transfused (Chuansumrit 2005; Hauser 2010a; Hauser 2010b). These studies showed a trend to a lower number of transfused patients in the rFVIIa treatment groups (RR 0.94; 95% CI 0.89 to 1.00) (Analysis 2.7).

Thromboembolic events

All of the treatment trials contributed data on thromboembolic events. The pooled RR was 1.14 (95% CI 0.89 to 1.47) with no heterogeneity beyond chance expectation (I^2 = 0%) (Analysis 2.8). Control event rates were generally low across all studies, the maximum being 3/8 (Mayer 2006). Individually the 95% CIs of all the included studies included 1.0 (no difference between rFVIIa and placebo).

Thromboembolic events across all RCTs

Twenty-six studies were available from prophylactic and therapeutic study groups to contribute to an overall combined estimate of the risk of thromboembolic events. The pooled RR was 1.18 (95% CI 0.94 to 1.48) with no observed heterogeneity (I^2 = 0%) (Figure 8). When considered as individual outcomes, there was no difference in cardiovascular, stroke or venous events. However, there was a significant increase in arterial thromboembolic events (RR 1.45; 95% CI 1.02 to 2.05) (Figure 9).

Figure 8. Forest plot of comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), outcome: 3.1 Total thromboembolic events.

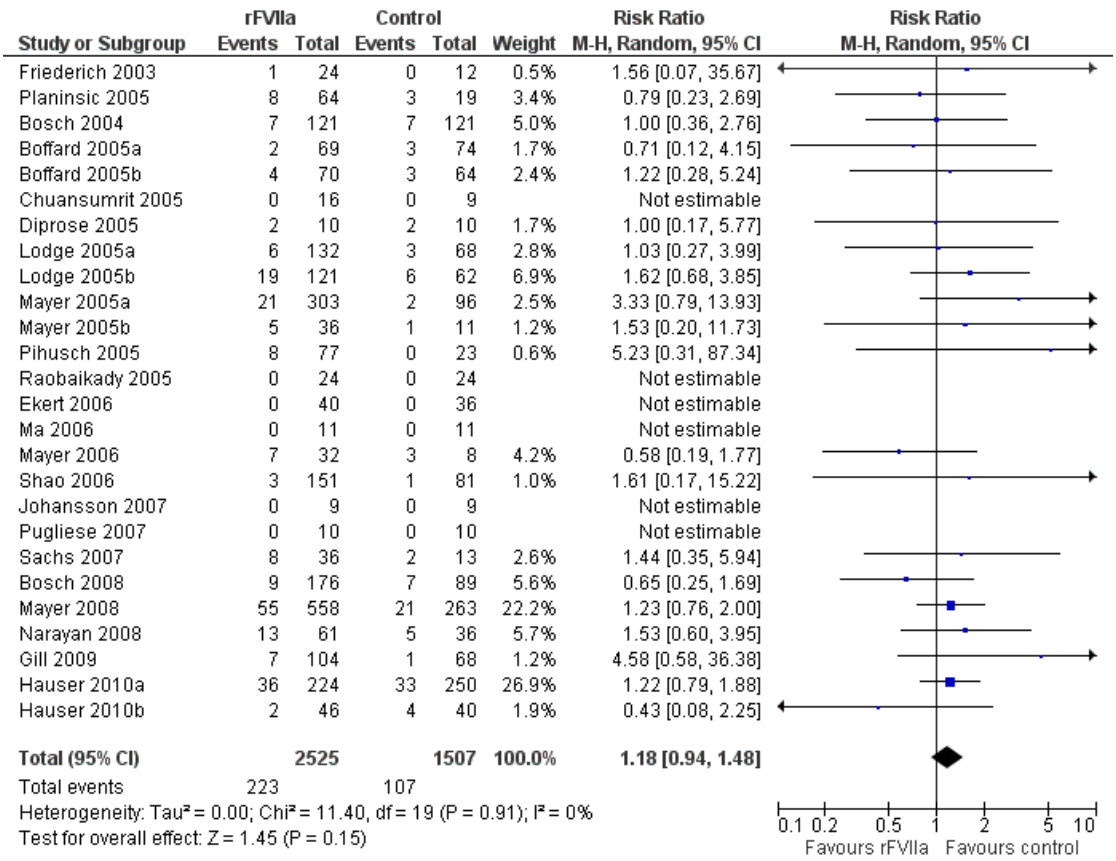
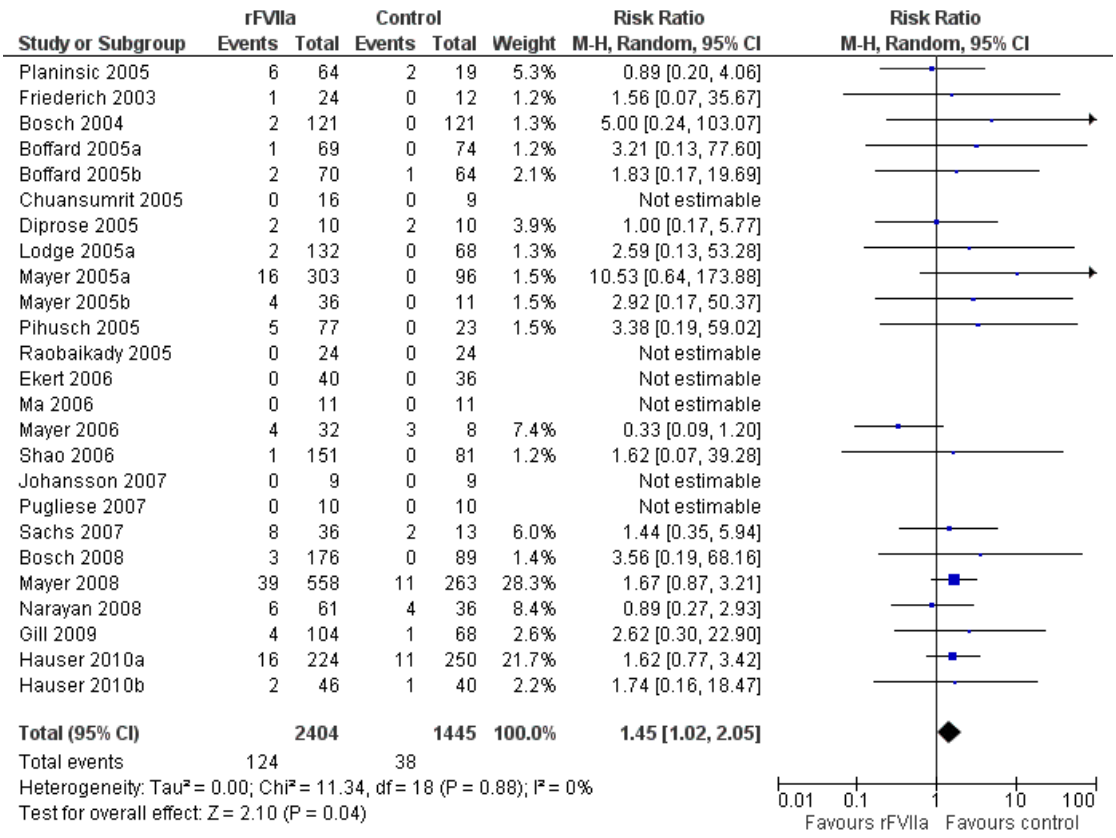


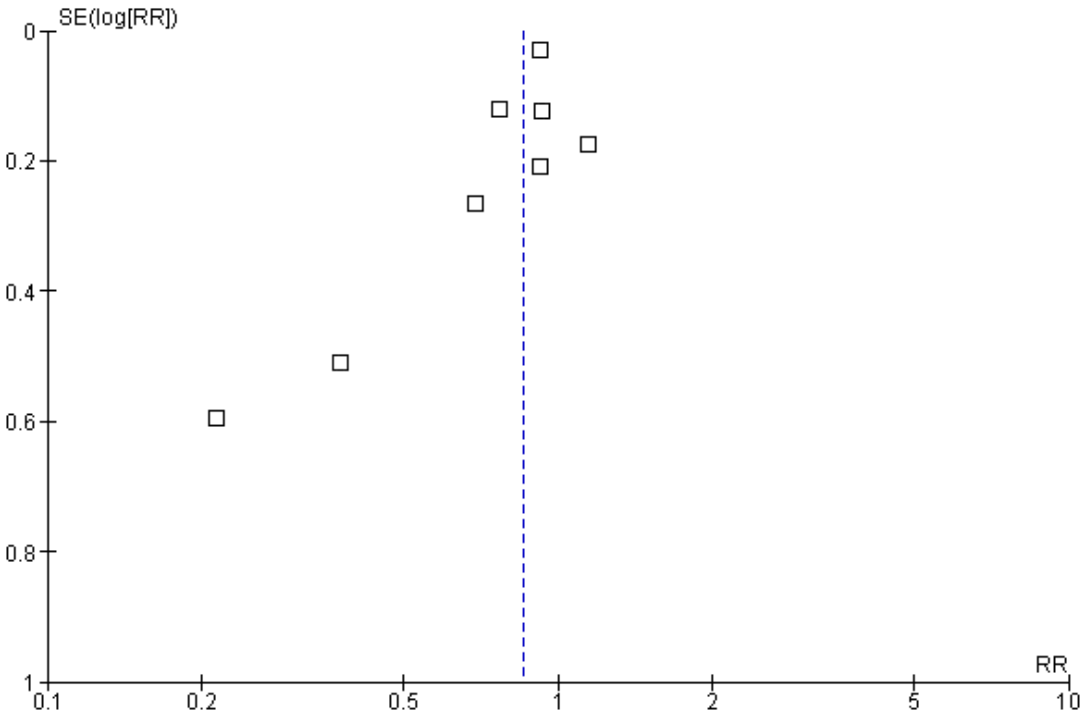
Figure 9. Forest plot of comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), outcome: 3.4 Total arterial events.



Publication bias

We assessed publication bias for each of the outcomes above. In the prophylactic studies, there was little or no asymmetry except for the outcome number of patients transfused. The funnel plot for the analysis number of patients transfused suggested that there may be small missing studies with RR > 1.0 (favouring placebo) (Figure 10). In the therapeutic studies, there was no marked asymmetry in the funnel plots.

Figure 10. Funnel plot of comparison: 1 rFVIIa used prophylactically versus placebo, outcome: 1.7 Numbers of patients transfused.



As noted in the methods section, we did review ongoing studies from our previous update. There has been no reported progress in ongoing studies since the last review despite adequate time for recruitment. This may also be a potential source of publication bias.

How does this update differ from the previous review?

Results: potential benefits of rFVIIa

There was no evidence of a significant mortality benefit with the use of rFVIIa. This finding remains unchanged compared to the previous version of this review (Lin 2011), despite the addition of recent RCTs. In this updated version of the review, the risk of mortality associated with the prophylactic use of rFVIIa changed from a RR of 1.06 (95% CI 0.50 to 2.24) to a RR of 1.04 (95% CI 0.55 to 1.97). For therapeutic studies, the trend towards decreased mortality in the previous Cochrane review with a RR of 0.89 (95% CI 0.77 to 1.03) is similar to the current review with a RR of 0.92 (95% CI 0.79 to 1.08). Looking at the individual studies, Mayer 2005a was the only study that showed a mortality benefit and in this study, mortality was a secondary outcome. The subsequent phase III clinical trial in spontaneous ICH (Mayer 2008) was unable to show an improvement in survival or functional outcome, even though a reduction in haematoma growth was seen. The group receiving 80 μg/kg rFVIIa was found to have a more frequent rate of arterial events when compared to placebo. The question as to whether there may be clinical benefit in a subgroup of high-risk patients with spontaneous ICH is being addressed in two registered clinical trials which, at the time of writing, have just begun recruiting (Flaherty 2008; Gladstone 2011).

As in the previous Cochrane review (Lin 2011), the volume of perioperative blood loss and red cell transfusions for the prophylactic trials remained statistically significant in favour of rFVIIa. However, there was evidence of important statistical heterogeneity for these studies.

In this version, although not statistically significant, there is a trend towards a lower number of patients transfused favouring rFVIIa in the included eight prophylactic trials (RR 0.85; 95% CI 0.72 to 1.01) and three therapeutic trials (RR 0.94; 95% CI 0.89 to 1.00) compared to the previous version (prophylactic RR 0.91; 95% CI 0.82 to 1.02 and therapeutic RR 0.94; 95% CI 0.29 to 3.04). For the prophylactic estimate, potential publication bias may overestimate the benefit of rFVIIa.

Results: potential risks of rFVIIa

In this review, thromboembolic events were not statistically increased in prophylactic (RR 1.35; 95% CI 0.82 to 2.25) or therapeutic (RR 1.14; 95% CI 0.89 to 1.47) studies. Pooling adverse events across both prophylactic and therapeutic studies did lead to an increase in arterial thromboembolic events (RR 1.45; 95% CI 1.02 to 2.05) (Figure 9), which is a new finding compared to the previous version.

DISCUSSION

Summary of main results

Sixteen trials including a total of 1361 participants examined the use of rFVIIa *prophylactically* to prevent bleeding. The studies were conducted in a range of clinical situations including cardiac surgery; liver biopsy; partial hepatectomy; liver transplantation; prostatectomy; burns excision; pelvic reconstruction; craniofacial reconstruction and spinal surgery. The main outcomes were mortality, blood loss, red cell transfusion requirements, numbers transfused and thromboembolic adverse events. All studies were randomised controlled trials (RCTs), but many were prone to bias, particularly through lack of clarity about how participants were randomised. There was no effect on mortality (risk ratio (RR) 1.04; 95% confidence interval (CI) 0.55 to 1.97). Modest benefits were found in the outcomes of blood loss and red cell transfusion requirements (less than one red cell unit saved with rFVIIa treatment); however, these favourable findings were likely overestimated because data were not available from larger negative studies for inclusion in the meta-analysis. A statistically non-significant trend towards an increased risk of thromboembolic events with rFVIIa was also observed (see 'Summary of findings for the main comparison').

Thirteen trials including a total of 2929 participants examined the *therapeutic* role of rFVIIa for the treatment of bleeding. Again the studies were conducted in a range of different clinical scenarios including blunt and penetrating trauma; gastrointestinal haemorrhage; Dengue haemorrhagic fever; intracranial haemorrhage (ICH) and stem cell transplantation. There was no difference in the outcomes of mortality (RR 0.91; 95% CI 0.78 to 1.06), control of bleeding, red cell transfusion requirements, numbers transfused and thromboembolic adverse events. All studies were placebo-controlled, double-blind RCTs. Two trials (Bosch 2004; Bosch 2008) were substantially free from bias; the remainder had threats, particularly lack of detail about randomisation. None of the pooled outcomes showed reliable evidence of an advantage (or disadvantage in the case of adverse events) of rFVIIa over placebo. However, there were trends towards decreased mortality, decreased number of patients transfused and increased thromboembolic adverse events with rFVIIa treatment (see 'Summary of findings for the main comparison').

Although there were no differences seen in the total thromboembolic adverse events, when arterial thrombotic events were considered for all studies combined, a statistically significant increase was observed (RR 1.45; 95% CI 1.02 to 2.05).

Quality of the evidence

Issues relating to methodological quality of the trials have been described in the 'Risk of bias' figures (Figure 2 and Figure 3). Overall, all studies except four (Bosch 2004; Bosch 2008; Gill 2009; Lodge 2005a) had threats to validity. In most cases, the threats to validity were assessed as 'unclear' because details were not provided in the publications. Many of the studies, in particular the prophylactic studies, were also hampered by inadequate power due to small sample size. The clinical settings in which more than one adequately powered trial was conducted included trauma, partial hepatectomy, liver transplantation, cirrhosis with upper gastrointestinal bleeding and spontaneous intracranial haemorrhage.

Potential biases in the review process

Concerning the validity of the findings of this systematic review, there are limitations. We were unable to obtain data from all authors to be used quantitatively in the meta-analysis and often the excluded studies were those that did not favour rFVIIa (specifically in the prophylactic trials, four RCTs in the outcome of total blood loss and three RCTs in the outcome of red cell transfusion requirements showed no difference between rFVIIa and placebo). In the therapeutic studies for the outcome control of bleeding, data from the intracranial haemorrhage studies could not be included in the pooled estimate because they expressed their results in a different manner (appropriately) from other therapeutic RCTs and so were considered qualitatively.

Publication bias remains possible. We examined funnel plots and detected publication bias in the outcome of number of patients transfused in the prophylactic RCTs where there were a lack of studies that favoured placebo over rFVIIa treatment. A potentially more significant source of publication bias was our inability to include unpublished but ongoing trials that have not been completed since the last version of this review.

Agreements and disagreements with other studies or reviews

The findings of this updated review extend and are consistent with other published meta-analyses. The relevant Cochrane systematic reviews include Marti-Carvajal 2007 and You 2006. Marti-Carvajal 2007 examined upper gastrointestinal bleeding (UGIB) in patients with liver disease but at the time of the review, the only RCT included was Bosch 2004. You 2006 considered haemostatic drugs for intracranial haemorrhage (ICH) and

included the first three RCTs of rFVIIa in ICH (Mayer 2005a; Mayer 2005b; Mayer 2006) but not Mayer 2008. The meta-analysis showed reduction in risk of disability and death by the modified Rankin scale score but this was not consistent when an alternative outcome score (extended Glasgow Outcome Scale) was used. The use of rFVIIa was also balanced against a trend towards increased thromboembolic events. Ranucci 2008 performed a meta-analysis of rFVIIa in major surgical procedures and included seven of the prophylactic studies included in this review. They found a significant reduction in the risk of receiving allogeneic packed red blood cells (odds ratio (OR) 0.29; 95% CI 0.10 to 0.80) although the absolute amount of red cell transfusion received was not analysed. Estimates of mortality and thromboembolic events were similar to the estimates in this review for prophylactic studies.

A recent systematic review published by Hsia 2008 reported similar estimates for mortality (OR 0.88; 95% CI 0.71 to 1.09) and thromboembolic events (OR 1.17; 95% CI 0.87 to 1.58). Hsia 2008 also found that rFVIIa reduced the number of patients requiring additional red blood cell transfusion (OR 0.54; 95%CI 0.34 to 0.86). In our current review, the absolute amount of red cell transfusion has been quantified; at least in the prophylactic setting, the estimated absolute amount of total blood loss or red cell transfusion requirement saved with rFVIIa treatment was less than one unit of red blood cells (RBCs) (the assumption in this review was that one red cell unit was equivalent to 300 mL). However, this was likely to be an overestimate of the effect as data from negative studies could not be incorporated into the pooled analyses as described earlier in the results. In the therapeutic setting, Hsia 2008 identified one study (Boffard 2005a) of four included RCTs favouring rFVIIa for the outcome of additional red blood cell transfusion. The numbers used in the meta-analysis and reported in Boffard 2005a for this outcome were based on the percentage of patients alive at 48 hours receiving massive transfusion (more than 20 units of RBCs). The number of patients requiring massive transfusion for all patients was not provided in the publication. Thus, although there may be an advantage to rFVIIa in decreasing blood loss and red cell transfusion requirements, we believe that this advantage is small when the limitations of the data and the absolute amount of blood saved are considered.

In line with the findings of our Cochrane review, a recent meta-analysis of the off-label use of rFVIIa in cardiac surgery, liver transplantation, intracranial haemorrhage, trauma and prostatectomy showed no mortality benefit among patients who received rFVIIa (Yank 2011). In this review, the administration of rFVIIa was reported to increase the risk of arterial thromboembolism among patients with intracranial haemorrhage (risk difference (RD) 0.03; 95% CI 0.01 to 0.06 and RD 0.06; 95% CI 0.01 to 0.11 for medium- and high-dose rFVIIa, respectively) and the rate of all thromboembolic events among cardiac surgery patients (RD 0.05; 95% CI 0.01 to 0.10). Unlike previous studies of the off-label use of rFVIIa, Yank 2011 also reported a decreased risk of acute respiratory distress syndrome among body trauma patients who received rFVIIa (RD -0.05; 95% CI -0.02 to -0.08).

More recently, Levi 2010 reported on the risks related to rFVIIa use, by analysis of data held by Novo Nordisk. The authors reported that individuals who received rFVIIa experienced a higher frequency of arterial thromboembolic events when compared to patients who were given placebo (5.5% versus 3.2%, P = 0.003). This association was more pronounced among older patients over the ages of 65 years (rFVIIa: 9.0% versus placebo: 3.8%, P = 0.003) and 75 years (rFVIIa: 10.8% versus placebo: 4.1%, P = 0.02). In the Levi 2010 study, there was no significant difference in the rates of venous thromboembolism among patients who received rFVIIa as compared to those who received placebo (5.3% versus 5.7%).

How do the conclusions of this update differ from the previous review?

This review provides the most up to date assessment of the effectiveness and safety of RFVIIa. With the addition of four RCTs, there was a significant increase in the number of arterial thromboembolic events observed among patients who received rFVIIa. Despite the greater number of trials, almost all of the findings in support of and against the use of rFVIIa could be due to chance, indicating ongoing uncertainty about the true effectiveness of rFVIIa in patients without haemophilia. Suggestions of a potential benefit of rFVIIa reside in the findings of decreased blood loss and red cell transfusion requirements and a trend towards a decreased number of patients who required blood transfusion and decreased mortality in the therapeutic setting. However, the findings of decreased blood loss and red cell transfusion in this review were modest and are likely overestimates of the true benefit of rFVIIa. There may be publication bias particularly in the number of patients transfused overestimating the benefit of rFVIIa, which has been found in other reviews (Hsia 2008; Ranucci 2008). Moreover, in direct (and even some indirect) comparisons of dose of rFVIIa, there was no evidence of a dose-response effect.

Any (small) benefits of rFVIIa are likely to be offset by its potential thromboembolic risks. These risks are likely to be underestimated and may be more serious and/or frequent in the real world than in the RCT setting when tight inclusion criteria apply. For many of the patients in the clinical settings of the included studies, a higher risk of thrombosis might be expected, for example, related to immobilisation and stroke. In addition, a history of thrombosis or vaso-occlusive disease was a criterion for exclusion in most of the included studies and active surveillance (e.g. scheduled lower extremity ultrasounds or troponin measurements) for adverse events was reported in only 11 of 29 trials. These greater risks are consistent with the analysis of passive surveillance of reports describing thromboembolic events for the Food and Drug Administration Adverse Reporting System, which indicated that many events following rFVIIa use occurred after unlabelled indications and often resulted in serious morbidity and mortality (O'Connell 2006).

Although a large, adequately powered trial with a strict transfu-

sion protocol and active surveillance for adverse events could be designed to address with greater precision the effect size for use of rFVIIa, the results of this review perhaps question the need for such a trial. It seems unlikely that a large benefit for the drug exists based on the findings of 29 trials, and for those trials which initially found evidence of benefit, larger follow-up studies have not confirmed these earlier promising results. This has occurred in the setting of cirrhosis with UGIB where potential benefit in a subgroup of high-risk patients (Bosch 2004) was not confirmed in the RCT looking specifically at this high-risk subgroup (Bosch 2008). In the setting of spontaneous intracranial haemorrhage (ICH), the earlier trial showed benefit in a secondary outcome of disability and death (Mayer 2005a), however this was not borne out in the phase III RCT designed with a primary outcome of disability and death (Mayer 2008). The phase III trial in trauma patients (Hauser 2010a; Hauser 2010b) was terminated early due to a low likelihood of reaching a positive outcome, again not confirming potential benefits seen in the earlier trauma trials (Boffard 2005a; Boffard 2005b).

It is difficult to highlight specific gaps or areas where new RCTs are required now. Although there have been retrospective observational studies supporting the use of rFVIIa in refractory bleeding, such as in the setting of cardiac surgery, these studies are limited by the lack of a control group, lack of transfusion protocols and observer bias. Without performing large RCTs, one cannot exclude an effect of rFVIIa, particularly if compared to the use of another haemostatic agent such as tranexamic acid (which has demonstrated a safer risk profile) or fibrinogen concentrate or even more platelet transfusions in the post-cardiac bypass setting. In these situations, the immediate real risk of life-threatening ongoing haemorrhage is being weighed by clinicians against a potential risk of no benefit from rFVIIa or potential thrombotic harm. These related issues of prescribing behaviour have also been recently summarised by Lipworth 2012.

In summary, the aim of this review was to update the assessment of the effectiveness and safety of rFVIIa in the management of bleeding in patients without haemophilia. We conclude that the clinical value of rFVIIa as a more general haemostatic drug, both as prophylaxis in high blood loss surgery and as therapy to treat uncontrollable bleeding, remains unproven. In addition, its use is associated with an increased risk of adverse arterial thrombotic events. Based on the available RCT data, there is little evidence of benefit for the use of off-label rFVIIa in patients without haemophilia.

AUTHORS' CONCLUSIONS

Implications for practice

Unrestricted, unevaluated administration of rFVIIa outside licensed uses is not justified on the basis of the randomised controlled trials (RCTs) identified and analysed in this review. Administration of rFVIIa outside its current license should be restricted to rigorous research studies and clinical trials, planned to add to existing knowledge in a systematic way.

Implications for research

The results of ongoing research should be actively monitored and systematically reviewed independently of the pharmaceutical companies with a financial interest in this drug. Any future RCTs should be adequately powered, focusing on clinical outcomes such as mortality, rather than blood loss and transfusion use. Continuing close attention to measurement of adverse, particularly thromboembolic, events is required.

REFERENCES

References to studies included in this review

Boffard 2005a *{published data only}*
Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, et al.Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized placebo-controlled double blind clinical trials. *Journal of Trauma* 2005;**59**(1): 8–15.

Boffard 2005b *{published data only}*
Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, et al.Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized placebo-controlled double blind clinical trials. *Journal of Trauma* 2005;**59**(1): 8–15.

Bosch 2004 *{published data only}*
Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez Abraldes J, et al.Recombinant factor VIIa for upper gastrointestinal bleeding patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004;**127** (4):1123–30.

Bosch 2008 *{published data only}*
Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al.Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. *Hepatology* 2008;**47**(5):1604–14.

Chuansumrit 2005 *{published data only}*
Chuansumrit A, Wangruangsatid S, Lektrakul Y, Chua MN, Zeta Capeding MR, Bech OM, et al.Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-

controlled study. *Blood Coagulation & Fibrinolysis* 2005;**16** (8):549–55.

Diprose 2005 *{published data only}*

* Diprose P, Herbertson M, O'Shaughnessy D, Gill R. A pilot double blind randomized placebo-controlled trial of the use of recombinant factor VIIa (rf VIIa) in high transfusion risk cardiac surgery. *European Journal of Anaesthesiology* 2005;**21**(Suppl 33):2–36.
Herbertson M. Recombinant activated factor VII in cardiac surgery. *Blood Coagulation & Fibrinolysis* 2004;**15**(Suppl 1): S31–2.

Ekert 2006 *{published data only}*

Ekert H, Brizard C, Eyers R, Cochrane A, Henning R. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. *Blood Coagulation & Fibrinolysis* 2006; **17**(5):389–95.

Essam 2007 *{published data only}*

Essam MA. Prophylactic administration of recombinant activated factor VII in coronary revascularization surgery. *Internet Journal of Anesthesiology* 2007;**13**(1):10.

Friederich 2003 *{published data only}*

Friederich PW, Geerdink MGF, Keller TT, Messelink EJ, Henny Ch P, Levi M. Novel applications of recombinant factor VIIa: the effect of the administration of recombinant activated factor VII on perioperative blood loss in patients undergoing transabdominal retropubic prostatectomy: the PROSE study. *Infusionstherapie und Transfusionsmedizin* 2001;**28**(2):112–3.
Friederich PW, Geerdink MGF, Spataro M, Messelink EJ, Henny Ch P, Buller HR, et al.The effect of the administration of recombinant activated factor VII on perioperative blood loss in patients undergoing transabdominal retropubic prostatectomy: the PROSE study. *Blood Coagulation & Fibrinolysis* 2000;**11**(Suppl 1): S129–32.
* Friederich PW, Keller T, Buller HR, Levi M. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003;**361**(9353):201–5.

Gill 2009 *{published data only}*

Gill R, Herbertson M, Vuylsteke A, Olsen P S, von Heymann C, Mythen M, et al.Additional data obtained from author 2009.
* Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, et al.Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009;**120**(1):21–7.

Hanna 2010 *{published data only}*

* Hanna MG, Refaie A, Gouda N, Obaya G. Reduction of peri-operative bleeding in craniofacial surgeries in pediatrics. Comparison between recombinant factor VII and tranexamic acid. *Egyptian Journal of Anaesthesia* 2010; **26**:53–61.

Hauser 2010a *{published data only}*

Hauser C J, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, et al.Results of the CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *Journal of Trauma* 2010;**69**(3):489–500.

Hauser 2010b *{published data only}*

Hauser CJ, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, et al.Results of the CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *Journal of Trauma* 2010;**69**(3):489–500.

Jeffers 2002 *{published data only}*

Jeffers L, Chalasani N, Balart L, Pyrsopoulos N, Erhardtsen E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002;**123**:118–26.

Johansson 2007 *{published data only}*

Johansson PI, Eriksen K, Nielsen SL, Rojkjaer R, Alsbjorn B. Recombinant FVIIa decreases perioperative blood transfusion requirement in burn patients undergoing excision and skin grafting - results of a single centre pilot study. *Burns* 2007;**33**(4):435–40.

Lodge 2005a *{published data only}*

* Lodge JP, Jonas S, Oussoultzoglou E, Malago M, Jayr C, Cherqui D, et al.Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005;**102**(2):269.
Lodge JPA. Hemostasis in liver resection surgery. *Seminars in Hematology* 2004;**41**(Suppl 1):70–5.

Lodge 2005b *{published data only}*

* Lodge JP, Jonas S, Jones RM, Olausson M, Mir-Pallardo J, Soefelt S, et al.Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transplantation* 2005;**11**(8):973–9.
Lodge JPA. Hemostasis in liver resection surgery. *Seminars in Hematology* 2004;**41**(Suppl 1):70–5.

Ma 2006 *{published data only}*

Ma B, Wang ZN, Zhang BR, Xu ZY, Yang LX, Chen KB, et al.Effect of recombinant activated factor VIIa on early recovery of patients undergoing cardiac valve replacement under cardiopulmonary bypass: a randomized double-blind placebo-controlled trial. *Academic Journal of Second Military Medical University* 2006;**27**:1110–3.

Mayer 2005a *{published data only}*

Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Medicine* 2002;**28**:S235–40.
* Mayer SA, Nikolai MD, Brun C, Begtrup K, Broderick J, Davis S, et al.Recombinant activated factor VII for acute

intracerebral hemorrhage. *New England Journal of Medicine* 2005;**352**(8):777–85.
Pickard JD, Kirkpatrick PJ, Melsen T, Andreasen RB, Gelling L, Fryer T, et al.Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagulation & Fibrinolysis* 2000;**11** (Suppl 1):S117–20.

Mayer 2005b *{published data only}*
Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Medicine* 2002;**28**:S235–40.
* Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, et al.Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005; **36**(1):74–9.
Pickard JD, Kirkpatrick PJ, Melsen T, Andreasen RB, Gelling L, Fryer T, et al.Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagulation & Fibrinolysis* 2000;**11** (Suppl 1):S117–20.

Mayer 2006 *{published data only}*
Mayer SA, Brun NC, Broderick J, Davis SM, Diringer MN, Skolnick BE, et al.Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocritical Care* 2006;**4**(3):206–14.

Mayer 2008 *{published data only}*
Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al.Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *New England Journal of Medicine* 2008;**358**(20):2127–37.

Narayan 2008 *{published data only}*
Narayan RK, Maas AI, Marshall LF, Servadei F, Skolnick BE, Tillinger MN, rFVIIa Traumatic ICH Study Group. Recombinant factor VIIA in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial. *Neurosurgery* 2008;**62**(4):776–86. [: Clinicaltrials.gov Identifier: NCT00123591]

Pihusch 2005 *{published data only}*
Bacigalupo A. Haemopoietic stem cell transplants: the impact of haemorrhagic complications. *Blood Reviews* 2003; **17**:S6–10.
* Pihusch M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, Hyveled L, et al.Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. *Journal of Thrombosis & Haemostasis* 2005;**3**(9):1935–44.

Planinsic 2005 *{published data only}*
* Planinsic RM, Testa G, Grande L, Candela A, van der Meer J, Porte RJ, et al.Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transplantation* 2005;**11**(8):895–900.

Pugliese 2007 *{published data only}*
Pugliese F, Ruberto F, Summonti D, Perrella S, Cappannoli A, Tosi A, et al.Activated recombinant factor VII in orthotopic liver transplantation. *Transplantation Proceedings* 2007;**39**(6):1883–5.

Raobaikady 2005 *{published data only}*
Raobaikady R, Redman J, Ball JA, Maloney G, Grounds RM. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis and acetabulum: a double-blind randomized, placebo-controlled trial. *British Journal of Anaesthesia* 2005;**94**(5):586–91.

Sachs 2007 *{published data only}*
Sachs B, Delacy D, Green J, Graham RS, Ramsay J, Kreisler N, et al.Recombinant activated factor VII in spinal surgery: a multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial. *Spine* 2007;**32** (21):2285–93.

Shao 2006 *{published data only}*
Shao YF, Yang JM, Chau GY, Sirivatanauksorn Y, Zhong SX, Erhardtsen E, et al.Safety and hemostatic effect of recombinant activated factor VIIa in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *American Journal of Surgery* 2006;**191**(2):245–9.

References to studies excluded from this review

Ashrani 2006 *{published data only}*
Ashrani AA, Gabriel DA, Gajewski JL, Jacobs DRJ, Weisdorf DJ, Key NS. Pilot study to test the efficacy and safety of activated recombinant factor VII (NovoSeven) in the treatment of refractory hemorrhagic cystitis following high-dose chemotherapy. *Bone Marrow Transplantation* 2006;**38**(12):825–8.

Bijsterveld 2002 *{published data only}*
Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, et al.Ability of recombinant factor VIIa to reverses the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002;**106**(20):2550–4.

Bijsterveld 2004 *{published data only}*
Bijsterveld NR, Vink R, van Arken BE, Fennema H, Peters RJG, Meijers JCM, et al.Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *British Journal of Haematology* 2004;**124**(5):653–8.

Boffard 2009 *{published data only}*
Boffard KD, Choong PI, Kluger Y, Riou B, Rizoli SB, Rossaint R, et al.NovoSeven Trauma Study Group. The treatment of bleeding is to stop the bleeding! Treatment of trauma-related hemorrhage. *Transfusion* 2009;**49**(Suppl 5): 240s–7s.

Bysted 2007 *{published data only}*
Bysted BV, Scharling B, Møller T, Hansen BL. A randomized, double-blind trial demonstrating bioequivalence of the current recombinant activated factor VII formulation and a new robust 25 degrees C stable formulation. *Haemophilia* 2007;**13**(5):527–32.

Davis 2004 *{published data only}*

Davis S, Mayer S, Brun N, Broderick J, Diringer MN, Steiner T. Safety of activated recombinant factor VII in acute intracerebral hemorrhage: results of two multi-center placebo-controlled trials. *Internal Medicine Journal* 2004; **34**:1–2.

Diringer 2007 *{published data only}*

Diringer MN, Ferran JM, Broderick JP, Davis S, Mayer SA, Steiner T, et al.Impact of recombinant activated factor VII on health-related quality of life after intracerebral hemorrhage. *Cerebrovascular Diseases* 2007;**23**(2-3): 219–25.

Elgafy 2010 *{published data only}*

Elgafy H, Bransford RJ, McGuire RA, Dettori JR, Fischer D. Blood loss in major spine surgery: are there effective measures to decrease massive hemorrhage in major spine fusion surgery?. *Spine* 2010;**35**(Suppl 9):S47–56. [PUBMED: 20407351]

Ensor 2011 *{published data only}*

Ensor CR, Paciullo CA, Cahoon WD Jr, Nolan PE Jr. Pharmacotherapy for mechanical circulatory support: a comprehensive review. *Annals of Pharmacotherapy* 2011;**45** (1):60–77. [PUBMED: 21205950]

Fridberg 2005 *{published data only}*

Fridberg MJ, Hedner U, Roberts HR, Erhardtsen E. A study of the pharmacokinetics and safety of recombinant activated factor VII in healthy Caucasian and Japanese subjects. *Blood Coagulation and Fibrinolysis* 2005;**16**(4):259–66.

Gurusamy 2009 *{published data only}*

Gurusamy KS, Li J, Sharma D, Davidson BR. Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD008085]

Jilma 2002 *{published data only}*

Jilma B, Marsil C, Mayr F, Graninger MT, Taylor FB, Ribel MC, et al.Pharmacodynamics of active site-inhibited factor VIIa in endotoxin-induced coagulation in humans. *Clinical Pharmacology and Therapeutics* 2002;**72**(4):403–10.

Johansson 2010 *{published data only}*

Johansson PI, Ostrowski SR. Evidence supporting the use of recombinant activated factor VII in congenital bleeding disorders. *Drug Design, Development and Therapy* 2010;**4**: 107–16. [PUBMED: 20689697]

Kolban 2005 *{published data only}*

Kolban M, Balachowska KI, Chmielnicki M. The use of recombinant coagulation factor VIIa in patients undergoing surgical correction of scoliosis with the C-D method. *Ortopedia Traumatologia Rehabilitacja* 2005;**7**(3):285–9.

Larsen 2010 *{published data only}*

Larsen OH, Ezban M, Persson E, Ingerslev J, Sorensen B. Artificial contact pathway activation masks the haemostatic potential of rFVIIa and NN1731 in thrombocytopenic whole blood. *British Journal of Haematology* 2010;**150**(1): 124–7.

Leduc 2009 *{published data only}*

Leduc D, Senikas V, Lalonde AB, Ballerman C, Biringer A, Delaney M, et al.Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *Journal of Obstetrics and Gynaecology* 2009;**31** (10):980–93. [PUBMED: 19941729]

Levi 2010 *{published data only}*

Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *New England Journal of Medicine* 2010;**363**(19): 1791–800. [PUBMED: 21047223]

Lin 2011b *{published data only}*

Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without hemophilia: a systematic review and meta-analysis. *Canadian Medical Association Journal* 2011;**183**(1):E9–19. [PUBMED: 21078742]

Logan 2010 *{published data only}*

Logan AC, Goodnough LT. Recombinant factor VIIa: an assessment of evidence regarding its efficacy and safety in the off-label setting. *Hematology/the Education Program of the American Society of Hematology. American Society of Hematology. Education Program* 2010;**2010**:153–9. [PUBMED: 21239786]

Macieji 2004 *{published data only}*

Macieji K, Ina BK, Slawomir Z, Lukasz K. Use of small doses of recombinant factor VIIa during scoliosis surgery. *Journal of Bone and Joint Surgery (Proceedings)* 2004;**86 B.C.** (Suppl 1):94–9a.

Nishijima 2009 *{published data only}*

Nishijima DK, Zehtabchi S. Evidence-based emergency medicine/critically appraised topic. The efficacy of recombinant activated factor VII in severe trauma. *Annals of Emergency Medicine* 2009;**54**(5):737–44.e1. [PUBMED: 19285753]

Perel 2010 *{published data only}*

Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S. Haemostatic drugs for traumatic brain injury. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD007877.pub2]

Perez 2007 *{published data only}*

Perez AF, Serra C, Macia J, Mayol L. rFVII for pediatric acute intracranial hemorrhage. *Stroke* 2007;**38**(7):E63–4.

Plaat 2007 *{published data only}*

Plaat F. Recombinant factor VIIa should be used in massive obstetric haemorrhage. *International Journal of Obstetric Anesthesia* 2007;**16**(4):354–7.

Pugh 2007 *{published data only}*

Pugh R, Wenstone R. Predicting response to recombinant factor VIIa in non-haemophilia patients with severe haemorrhage (1). *British Journal of Anaesthesia* 2007;**98**(5): 690.

Strydom 2010 *{published data only}*

Strydom J. The rational use of recombinant factor VIIa in the treatment of major intractable bleeding in the

trauma patient. *Southern African Journal of Anaesthesia and Analgesia* 2010;**16**(1):130–3.

Thabut 2011 *{published data only}*
Thabut D, Rudler M, Rousseau G, Poynard T. Recombinant activated factor VII in chronic liver diseases: should we be afraid of thromboembolic events?. *Journal of Hepatology* 2011;**55**(2):483–5. [PUBMED: 21349297]

Van De Velde 2007 *{published data only}*
Van de Velde M. Recombinant factor VIIa should be used in massive obstetric haemorrhage. *International Journal of Obstetric Anesthesia* 2007;**16**(4):357–9.

Vincent 2009 *{published data only}*
Vincent JL, Artigas A, Petersen LC, Meyer C. A multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial assessing safety and efficacy of active site inactivated recombinant factor VIIa in subjects with acute lung injury or acute respiratory distress syndrome. *Critical Care Medicine* 2009;**37**(6):1874–80.

Vink 2004 *{published data only}*
Vink R, Bijsterveld NR, Van Aken BE, Fennema H, Peters RJG, Joost CM, et al.Recombinant factor VIIa reverses the anticoagulant effect of the long-standing anticoagulant idraparinux in healthy volunteers. *Blood* 2004;**102**(11): 812a.

Woltz 2004 *{published data only}*
Woltz M, Levi M, Sarich LC, Bostram SL, Eriksson UG, Eriksson-Lepkoska M, et al.Effect of recombinant factor VIIa on melagatran-induced inhibition of thrombin generation and platelet activation in healthy volunteers. *Thrombosis and Haemostasis* 2004;**91**(6):1090–6.

Yank 2009 *{published data only}*
Yank V, Logan AC, Tuohy CV, Bravata DM, Staudenmayer K, Eisenhut R, et al.Comparison of thromboembolic event rates in randomized controlled trials and observational studies of recombinant factor VIIa for off-label indications. A meta-analysis. ASH Annual Meeting Abstracts. *Blood* 2009;**114**(22).

Yank 2011 *{published data only}*
Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al.Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Annals of Internal Medicine* 2011;**154**(8): 529–40.

Yuan 2010 *{published data only}*
Yuan ZH, Jiang JK, Huang WD, Pan J, Zhu JY, Wang JZ. A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia. *Journal of Clinical Neuroscience* 2010;**17**(6):685–93. [PUBMED: 20399668]

References to ongoing studies

Arai 2005 *{published and unpublished data}*
Arai M. Factor VIIa: Safety of Eptacog Alfa (activated) (genetical recombination) on adverse events and serious adverse events in patients with acute intracerebral haemorrhage. ClinicalTrials.gov 2005. [: ClinicalTrials.gov Identifier: NCT00266006; : Novo Nordisk Clinical Trial ID: F7ICH–1602]

Flaherty 2008 *{published data only}*
Flaherty ML, Jauch EC. The spot sign for predicting and treating intracerebral hemorrhage growth study. Clinicaltrials.gov 2008. [: Clinicaltrials.gov Identifier: NCT00810888]

Gajewski 2005 *{unpublished data only}*
Gajewski JL, Vogelsang G, Key N, Goodnough L. A multi-center, randomized, double-blind, parallel groups, placebo-controlled trial on efficacy and safety of activated recombinant factor VII (rFVIIa/NovoSeven) in the treatment of bleeding in patients following hematopoietic stem cell transplantation (HSCT). Novo Nordisk Clinical Trial ID: F7SCT-1485 2005.

Gladstone 2011 *{published data only}*
Gladstone DJ, Aviv RI, Demchuk AM. "Spot sign" selection of intracerebral hemorrhage to guide hemostatic therapy (SPOTLIGHT). ClinicalTrials.gov 2010. [: ClinicalTrials.gov identifier NCT01359202]

Gris 2006 *{published data only}*
Gris JC. rhuFVIIa in post-partum hemorrhage. ClinicalTrials.gov 2006. [: Clinicaltrials.gov Identifier: NCT00370877]

Imberti 2005 *{published and unpublished data}*
Imberti R. Efficacy and safety of factor VIIa (Eptacog Alfa) on rebleeding after surgery for spontaneous supratentorial intracerebral hemorrhage. A randomized, controlled, open-label, investigator-blinded pilot study. ClinicalTrials.gov 2005. [: ClinicalTrials.gov Identifier: NCT00128050]

Iorio 2006 *{published and unpublished data}*
Iorio A. Randomized, open, prospective, multicenter pilot study to evaluate the efficacy and safety of activated recombinant factor VII in acute intracerebral haemorrhage in patients treated with oral anticoagulants or antiplatelets agents. ClinicalTrials.gov 2006. [: ClinicalTrials.gov Identifier: NCT00222625]

Kelleher 2006 *{published data only}*
Kelleher A. A multi-centre, randomised, double-blind, placebo-controlled, dose-escalation trial of safety and efficacy of activated recombinant factor VII (Rfv11a/NovoSeven) in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass. http://www2.rbht.nhs.uk/research/projects.

McCall 2005 *{published and unpublished data}*
McCall P, Poustie S. "Salvage use" of recombinant activated factor VII after inadequate haemostatic response to conventional therapy in complex cardiac surgery - a randomised placebo-controlled trial. ClinicalTrials.gov 2005. [: ClinicalTrials.gov Identifier: NCT00214656]

Molter 2005 *{published and unpublished data}*
Molter NC, Park MS, Frail EA. Effect of recombinant coagulation factor VIIa on peri-operative blood loss in patients undergoing major burn excision and grafting.

ClinicalTrials.gov 2005. [: ClinicalTrials.gov Identifier: NCT00243243]

Ng 2006 *{published and unpublished data}*

Ng C. Use of recombinant activated factor seven (FVII) in bleeding ECMO patients post cardiac surgery. Randomised prospective study. National Research Register 2005. [: N0012154243; ISRCTN98382551]

Additional references

Ahonen 2005

Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *British Journal of Anaesthesia* 2005;**94**(5):592–5.

Della Corte 2006

Della Corte F. Efficacy and safety of factor VIIa on rebleeding after surgery for spontaneous intracerebral hemorhage (ICH). Clinical Trials.gov 2006. [: Clinicaltrials.gov Identifier: NCT00128050]

Greisen 2003

Greisen G, Andreasen RB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. *Blood Coagulation & Fibrinolysis* 2003;**14**(1):117–20.

Hedner 2002

Hedner U, Erhardtsen E. Potential role for rVIIa in transfusion medicine. *Transfusion* 2002;**42**(1):114–24.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hsia 2008

Hsia CC, Chin-Yee IH, McAlister VC. Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. *Annals of Surgery* 2008;**248**(1):61–8.

Isbister 2008

Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J, Cameron P. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Internal Medicine Journal* 2008;**38**(3):156–65.

Key 2003a

Key NS, Mast AE. Factor VIIa and tissue factor pathway inhibitor. In: Stowell C, Dzik W editor(s). *Emerging Technologies in Transfusion Medicine*. AABB Press, 2003.

Key 2003b

Key NS. Recombinant FVIIa for intractable hemorrhage: more questions than answers. *Transfusion* 2003;**43**(12):1649–51.

Lipworth 2012

Lipworth W, Kerridge I, Little M, Day R. Evidence and desperation in off-label prescribing: recombinant factor VIIa. *BMJ* 2012;**344**:d7926.

Logan 2011

Logan AC, Yank V, Stafford RS. Off-label use of recombinant factor VIIa in U.S. hospitals: analysis of hospital records. *Annals of Internal Medicine* 2011;**154**(8):516–22.

Lusher 1998

Lusher JM, Roberts HR, Davignon G, Joist JH, Smith H, Shapiro A, et al.A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group. *Haemophilia* 1998;**4**(6):790–8.

Marti-Carvajal 2007

Martí-Carvajal AJ, Salanti G, Marti-Carvajal PI. Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD004887.pub2]

O'Connell 2006

O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;**295**(3):293–8.

Ranucci 2008

Ranucci M, Isgro G, Soro G, Conti D, De Toffol B. Efficacy and safety of recombinant activated factor VII in major surgical procedures. *Archives of Surgery* 2008;**143**(3):296–304.

RevMan 2008

The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

Roberts 2004

Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004;**104**(13):3858–64.

You 2006

You H, Al-Shahi R. Haemostatic drug therapies for acute primary intracerebral haemorrhage. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD005951.pub2]

References to other published versions of this review

Lin 2011

Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD005011.pub3]

Stanworth 2007

Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005011.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boffard 2005a

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Severely bleeding blunt trauma Group 1 blunt = 69 (numbers eligible for analysis) Group 2 blunt = 74 Randomised but not given the allocated treatment = 15 All blunt = 158
Interventions	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.
Outcomes	1. (Primary) RBCs transfused in 48 hours after first dose FVIIa/placebo 2. Other transfused products in first 48 hours 3. Mortality (and a composite endpoint of death and critical complications) 4. Days on ventilator 5. Days on ICU 6. Adverse events
Sources of Support	Study supported by Novo Nordisk. One author from Novo Nordisk. 4 authors received consultancy fees from Novo Nordisk
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, but no detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, but no detail

Boffard 2005a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up: 22; 14%
Selective reporting (reporting bias)	High risk	Emphasis on analysis where patients who died within 48 hours were excluded. For number of patients requiring massive transfusion, data for all patients at 48 hours were not presented
Other bias	Unclear risk	Lack of clarity about flow of patients and appropriateness of denominators used in analysis. Equality of distribution of patients between the 32 contributing study centres. No transfusion guidelines provided
Power calculation?	Low risk	Done; target 140 (achieved)

Boffard 2005b

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Severely bleeding penetrating trauma Group 1 penetrating = 70 Group 2 penetrating = 64 Randomised but not given an allocated treatment = 9 All penetrating = 143
Interventions	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.
Outcomes	1. (Primary) RBC transfused in 48 hours after first dose FVIIa/placebo 2. Other transfused products in first 48 hours 3. Mortality 4. Days on ventilator 5. Days on ICU
Sources of Support	Study supported by Novo Nordisk. One author from Novo Nordisk. 4 authors received consultancy fees from Novo Nordisk
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Boffard 2005b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, but no detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, but no detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 13; 9%
Selective reporting (reporting bias)	High risk	Emphasis on analysis where patients who died within 48 hours were excluded. For number of patients requiring massive transfusion, data for all patients at 48 hours were not presented
Other bias	Unclear risk	Lack of clarity about flow of patients and appropriateness of denominators used in analysis. Equality of distribution of patients between the 32 contributing study centres. No transfusion guidelines provided
Power calculation?	Low risk	Done; target 140 (achieved)

Bosch 2004

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Upper gastrointestinal haemorrhage in patients with cirrhosis Group 1 = 121 Group 2 = 121 Randomised but not given allocated treatment = 3 All randomised = 245
Interventions	Group 1. 8 x 100 µg/kg doses of iv rFVIIa. Initial dose given at time = 0, which was within 6 hours of bleed/admission. Subsequent doses given at 0, 2, 4, 6, 12, 18, 24, 30 hours. Total dose 800 µg/kg. Group 2. Placebo at same times.
Outcomes	1. (Primary) Control of acute bleeding within 5 days OR failure to prevent rebleeding between 24 hours and 5 days or death during first 5 days 2. Control of acute bleeding independently

Bosch 2004 (*Continued*)

	3. Prevention of rebleeding independently 4. Active bleeding at first endoscopy 5. 5-day mortality 6. 6-week mortality 7. Transfusion requirements 8. Number of emergency and elective procedures performed 9. Length of stay on intensive care or hospital 10. Frequency of adverse events including thromboembolic events 11. Changes in coagulation related parameters 12. Other haematology and biochemical parameters
Sources of Support	Study supported by Novo Nordisk. Trial planning and steering committee contained Novo Nordisk employees. 2 authors from Novo Nordisk
Notes	Minimal threats to validity (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated. Stratified by trial centre. Central interactive voice response system
Allocation concealment (selection bias)	Low risk	Treatment allocation in sealed envelopes during study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Indicated placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 8; 3%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	Low risk	Done; target 240 (achieved)

Bosch 2008

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Upper gastrointestinal haemorrhage in patients with cirrhosis Group 1 = 85 Group 2 = 85 Group 3 = 86 Randomised but not given an allocated treatment = 9 Total randomised = 265
Interventions	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.
Outcomes	1. (Primary) Treatment failure defined as: failure to control acute bleeding within 24 hours OR failure to prevent rebleeding OR death within 5 days 2. 5-day and 42-day mortality 3. Failure to control 5-day bleeding 4. Failure to control bleeding within 24 hours 5. Failure to prevent rebleeding at 5 days 6. Number of emergency procedures performed within 5 days 7. Transfusion requirements at 24 hours and 5 days 8. Frequency of adverse events up to 42 days 9. Changes in coagulation related parameters
Sources of Support	Study supported by Novo Nordisk. Sponsor designed study, analysed data and assisted in preparation of manuscript
Notes	Minimal threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated and stratified by centre with equal allocation between groups. Central interactive voice-response system
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Active agent and placebo were provided as indistinguishable powders for reconstitution

Bosch 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 9; 3%
Selective reporting (reporting bias)	Low risk	Registered at www.clinicaltrials.gov
Other bias	Unclear risk	Undesired selection bias occurred in several centres, whereby patients with a better prognosis were over-represented
Power calculation?	Low risk	Done; target 258 (not achieved)

Chuansumrit 2005

Methods	Double-blind, placebo-controlled RCT
Participants	Children Dengue haemorrhagic fever Group 1 = 18 Group 2 = 10
Interventions	Group 1. 1 dose of 100 µg/kg of iv rFVIIa. Further dose allowed after 30 minutes if bleeding not controlled. Total dose 100 to 200 µg/kg. Group 2. Placebo given in same manner.
Outcomes	1. Assessment of bleeding control 0.25, 0.5, 0.75, 1, 2, 6, 12, 24 hours after first dose of allocated treatment 2. Blood component requirements 3. Laboratory investigations No primary outcome defined
Sources of Support	Study supported by Novo Nordisk. One author from Novo Nordisk
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given

Chuansumrit 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Indicated that placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up: 3; 11%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small study size. Equality of distribution of patients between the 5 contributing study centres. No specific transfusion guidelines provided
Power calculation?	High risk	No power calculation

Diprose 2005

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Complex non-coronary cardiac surgery requiring cardio-pulmonary bypass Group 1 = 10 Group 2 = 10 Total randomised = 20
Interventions	Group 1. 1 dose of 90 µg/kg rFVIIa iv after bypass and reversal of heparin. Group 2. Placebo; equivalent volume of 0.9% saline.
Outcomes	1. (Primary) The number of patients receiving any allogeneic transfusion 2. Total units of red cells and coagulation products transfused 3. Adverse events 4. Also reported length of stay in intensive care and hospital
Sources of Support	2 authors had consulted for Novo Nordisk. The company had no role in design, execution or interpretation of the study
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Diprose 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind (investigators, patients, and all involved in patient care). All study agents identified, prepared and blinded by pharmacy staff. Placebo was equal volume of saline
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind (investigators, patients and all involved in patient care)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	High risk	Difference in baseline characteristics. Small study which was underpowered
Power calculation?	Low risk	Done; target 64 (not achieved)

Ekert 2006

Methods	Double-blind, placebo-controlled RCT
Participants	Infants less than 1 year of age Congenital heart disease requiring cardio-pulmonary bypass Group 1 = 40 Group 2 = 36 Randomised but not given an allocated treatment = 6 Total randomised = 82
Interventions	Group 1. First dose of 40 μg/kg rFVIIa iv after bypass and reversal of heparin; second dose if excessive bleeding at 20 minutes post-reversal of heparin; third dose if delayed postoperative bleeding in the post-surgery recovery period. All participants had 1 or 2 doses. Total dose 40 to 80 μg/kg Group 2. Placebo, freeze-dried powder for reconstitution, as for group 1
Outcomes	1. (Primary) Time to chest closure after reversal of heparin 2. Units/volume of platelets, FFP and blood transfused in the first 48 to 72 hours 3. Blood loss in the first 12 hours
Sources of Support	Novo Nordisk supplied study agent and placebo but no other stated involvement

Ekert 2006 (*Continued*)

Notes	Some threats to validity noted (see 'Risk of bias' assessment)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Indicated that placebo identical. For primary outcome, operating team was unaware of results of prothrombin time until patient in intensive care unit after chest closure
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 1; 1%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	High risk	No power calculation

Essam 2007

Methods	RCT
Participants	Adults Elective cardiac revascularisation requiring cardio-pulmonary bypass Group 1 = 15 Group 2 = 15 Total randomised = 30
Interventions	Group 1. 1 dose of 90 μg/kg rFVIIa iv after bypass and reversal of heparin. Group 2. No rFVIIa
Outcomes	1. Chest tube drainage during first 24 hours after surgery 2. Blood products transfused during first 24 hours after surgery 3. Serial haematological parameters during first 24 hours after surgery including haemoglobin, INR, PTT, fibrinogen

Essam 2007 (*Continued*)

Sources of Support	No statement made	
Notes	Important threats to validity noted (see 'Risk of bias' assessment)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Randomisation was established through sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given on whether a placebo was given or on outcome assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given on whether a placebo was given or on outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Conclusion overstated for small study size
Power calculation?	High risk	No power calculation

Friederich 2003

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Retropubic prostatectomy Group 1 = 8 Group 2 = 16 Group 3 =12 Total randomised = 36
Interventions	Group 1. 1 dose of 20 µg/kg rFVIIa iv in early operative phase. Group 2. 1 dose of 40 µg/kg rFVIIa iv at same time. Group 3. Placebo, saline, at same time.
Outcomes	1. (Primary) Total of pre-operative blood loss up to 24 hours after surgery 2. (Co-primary) Transfusion requirements 3. Adverse effects, including thromboembolic events

Friederich 2003 (*Continued*)

	4. Duration of operation and length of hospital stay were also reported
Sources of Support	Novo Nordisk supplied study agent and placebo but no other stated involvement
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by a computer-generated scheme
Allocation concealment (selection bias)	Low risk	Statement that treatment allocation concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Active agent and placebo (saline) were provided as indistinguishable solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small study size
Power calculation?	Unclear risk	Done; target not stated

Gill 2009

Methods	Multicentre, double-blind, placebo-controlled RCT
Participants	Adult patients undergoing cardiac surgery requiring CPB and admitted to a postoperative care environment for at least 30 minutes - randomised on reaching prespecified bleeding rate Group 1 = 35 Group 2 = 69 Group 3 = 68 Randomised but not given the allocated treatment = 7 Total randomised = 179

Interventions	Group 1 = rFVIIa 40 μg/kg Group 2 = rFVIIa 80 μg/kg Group 3 = Placebo
Outcomes	1. (Primary) Critical serious adverse events (death, cerebral infarction, myocardial infarction, pulmonary embolism and other thromboembolic events) 2. Rates of reoperation within 30 days after rebleeding 3. Transfusion of allogeneic blood and blood products within 5 days after trial drug administration 4. Drainage volumes from cardiothoracic cavity within 4 hours, 24 hours and 5 days after trial drug administration
Sources of Support	2 authors from Novo Nordisk Sponsor responsible for trial operations and statistical analyses
Notes	Protocol for the use of antifibrinolytics was unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised through interactive voice response system and were always assigned to the lowest available randomisation number
Allocation concealment (selection bias)	Low risk	Masking of treatment allocation maintained until all patient data entered and database locked
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physical appearances of placebo and rFVIIa were identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind. Masking of treatment allocation maintained until all patient data entered and database locked
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	No protocol provided for the use of antifibrinolytic therapy
Power calculation?	Low risk	Based on both safety (based on probability that uneven distribution of critical serious adverse events between rFVIIa and placebo

		groups would be minimised) and efficacy evaluation to detect a 35% reduction in need for any allogeneic transfusions on the highest cohort

Hanna 2010

Methods	Single-centre, placebo-controlled RCT
Participants	Paediatric patients of ASA class I and II with congenital craniofacial malformation scheduled to undergo reconstructive surgery Group 1 = 15 Group 2 = 15 Group 3 = 15 Total randomised = 45
Interventions	Group 1 = Control. No medications. Group 1 = Tranexamic acid at hour 0, tranexamic acid 100 mg/kg over 15 minutes and then maintenance infusion of 1 mg/kg/h until skin closure Group 3 = rFVIIa at hour 0, rFVIIa 10 μg/kg over 15 minutes and then maintenance infusion of 10 μg/kg/h until skin closure
Outcomes	1. Perioperative and intraoperative blood loss 2. Transfusion requirements at 24 h and 48 hours from treatment 3. Serial measurements for platelet count, fibrinogen concentration and FDPs prior to surgery (hour 0), 1 hour and 12 hours following completion of surgery 4. Serial haemoglobin levels were measured hourly
Sources of Support	No statement made
Notes	Some threats to validity were identified (See 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Study described as "double-blind", and the control arm as "placebo". Each patient received a small bag with 2 syringes - for initial dose and maintenance dose. No details provided about whether the formulations looked the same or if the clinical team was blinded
Blinding of participants and personnel (performance bias)	Unclear risk	No details given

Hanna 2010 (*Continued*)

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small sample size
Power calculation?	Unclear risk	No details were provided

Hauser 2010a

Methods	Multi-centre, double-blind, placebo-controlled RCT
Participants	Adult patients who had sustained blunt trauma and who had received a minimum of 4 units of red blood cells (RBCs) but had not yet completed an 8th unit within 12 hours of injury Group 1 = 221 Group 2 = 247 Randomised but not given the allocated treatment = 13 Total randomised = 481
Interventions	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.
Outcomes	Primary: 1. 1^{st} tier endpoint was superiority in all-cause 30-day mortality in blunt trauma 2. If not met, the 2^{nd} tier primary conditional endpoint of non-inferiority of mortality and superiority on durable morbidity (pulmonary and/or renal dysfunction at day 30) was applied Secondary: 3. Transfused units of RBC, plasma, platelets, cryoprecipitate, fibrinogen concentrate and all allogeneic blood products at 24 hours and 48 hours after dosing and number of patients requiring massive RBC transfusion ($\geq$ 10 units of RBC) at 24 hours 4. Number of patients with thromboembolic events, multiple organ failure (MOF), single organ failure (SOF) and days alive and free from MOF, SOF, intensive care unit, hospital or ventilator, and/or renal replacement therapy, through day 30
Sources of Support	Drug supplied by sponsor: Novo Nordisk Sponsor responsible for data management, assisted with trial design Analyses performed by sponsor but also repeated by independent statistician and the latter is presented in the article

Hauser 2010a (*Continued*)

Notes	Inaccurate denominators were used although intention-to-treat analysis was supposed to have been performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in random permuted blocks with allocation of every randomisation block to a specific centre. Randomisation was confirmed through an interactive voice response system set up by the sponsor
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Description of placebo as the same formulation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	FFP differences may have been due to changes in INR, the results of which would have been available to clinicians and the transfusion protocol was based on INR results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available
Other bias	Unclear risk	Study was terminated early due to futility analysis
Power calculation?	Low risk	Aim was to detect a 16.7% mortality reduction with rFVIIa, assuming 30% mortality in placebo patients

Hauser 2010b

Methods	Multi-centre, double-blind, placebo-controlled RCT
Participants	Adult patients who had sustained penetrating trauma and who had received a minimum of 4 units of red blood cells (RBCs) but had not yet completed an 8th unit within 12 hours of injury Group 1 = 46 Group 2 = 40 Randomised but not given the allocated treatment = 6 Total randomised = 92

Hauser 2010b (*Continued*)

Interventions	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.
Outcomes	Primary: 1. 1^{st} tier endpoint was superiority in all-cause 30-day mortality in blunt trauma 2. If not met, the 2^{nd} tier primary conditional endpoint of non-inferiority of mortality and superiority on durable morbidity (pulmonary and/or renal dysfunction at day 30) was applied Secondary: 3. Transfused units of RBC, plasma, platelets, cryoprecipitate, fibrinogen concentrate and all allogeneic blood products at 24 hours and 48 hours after dosing and number of patients requiring massive RBC transfusion ($\geq$ 10 units of RBC) at 24 hours 4. Number of patients with thromboembolic events, multiple organ failure (MOF), single organ failure (SOF) and days alive and free from MOF, SOF, intensive care unit, hospital or ventilator, and/or renal replacement therapy, through day 30
Sources of Support	Drug supplied by sponsor: Novo Nordisk Sponsor responsible for data management, assisted with trial design Analyses performed by sponsor but also repeated by independent statistician and the latter is presented in the article
Notes	Inaccurate denominators were used although intention-to-treat analysis was supposed to have been performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in random permuted blocks with allocation of every randomisation block to a specific centre. Randomisation was confirmed through an interactive voice response system set up by the Sponsor
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Description of placebo as the same formulation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	FFP differences may have been due to changes in INR, the results of which would have been available to clinicians and the transfusion protocol was based on INR results.

Hauser 2010b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available
Other bias	Unclear risk	Study was terminated early due to futility analysis
Power calculation?	Low risk	Aim was to detect a 16.7% mortality reduction with rFVIIa, assuming 30% mortality in placebo patients

Jeffers 2002

Methods	Double-blind RCT
Participants	Adults Cirrhosis and coagulopathy undergoing laparoscopic liver biopsy Group 1 = 16 Group 2 = 14 Group 3 = 17 Group 4 = 19 Total randomised = 66
Interventions	Group 1. 1 dose of 5 μg/kg rFVIIa iv 10 minutes before biopsy. Group 2. 1 dose of 20 μg/kg rFVIIa iv at same time pre-biopsy. Group 3. 1 dose of 80 μg/kg rFVIIa iv at same time. Group 4. 1 dose of 120 μg/kg rFVIIa iv at same time.
Outcomes	1. Time to haemostasis assessed visually 2. Duration of normal PT 3. Serial laboratory parameters after rFVIIa infusion including PTT, fibrinogen, D-dimer, F1+2 and platelets
Sources of Support	One author from Novo Nordisk
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 8 and sequentially assigned to 1 of 4 treatment groups. No details of sequence generation given
Allocation concealment (selection bias)	Unclear risk	No details given

Jeffers 2002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Injection volume per kg body weight was the same regardless of rFVIIa dose administered
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 4; 6%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	No placebo group. No transfusion guidelines provided.
Power calculation?	Unclear risk	Done for outcome of duration of normal PT; target not stated

Johansson 2007

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Thermal burn undergoing skin excision and grafting Group 1 = 9 Group 2 = 9 Total randomised = 18
Interventions	Group 1. First dose of 40 μg/kg rFVIIa iv given immediately before start of surgery; 2nd dose given at 90 minutes later. Total dose 80 μg/kg. Group 2. Placebo as for Group 1.
Outcomes	1. (Primary) Total number of units of blood components transfused per patient and percentage full-thickness wound excised during and up to 24 hours after surgery 2. Operating time 3. Number of patients with microvascular bleeding 4. Percentage graft survival on day 7 after surgery 5. Days spent in intensive care unit after surgery 6. Days of hospitalisation 7. 30-day mortality 8. Postoperative complications 9. Serial laboratory parameters after surgery including PT-INR, FVII activity, thrombin-antithrombin complexes, tissue factor and IL-6
Sources of Support	Study supported by an unrestricted educational grant from Novo Nordisk and an employee from Novo Nordisk assisted in preparation of the manuscript
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Johansson 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using permuted blocks that were derived from random number tables
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small study size
Power calculation?	High risk	No power calculation

Lodge 2005a

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Partial hepatectomy for liver carcinoma/metastasis, benign tumours or anatomical/non-anatomical resection Group 1 = 63 Group 2 = 59 Group 3 = 63 Randomised but not given an allocated treatment = 19 Total randomised = 204
Interventions	Group 1. 20 µg/kg rFVIIa by slow iv, within 5 minutes before the first skin incision; repeated at 5 hours if operation likely to be longer than 6 hours. Total dose 20 or 40 µg/kg. Group 2. 80 µg/kg as for group 1. Total dose 80 or 160 µg/kg. Group 3. Placebo as for group 1.
Outcomes	1. (Primary) Patients requiring erythrocyte (red cell) transfusion during surgery and the 48-hour period after 2. Amount of erythrocytes (red cells) transfused

Lodge 2005a (*Continued*)

	3. Change in haematocrit 4. Proportion of patients who received perioperative transfusions of fresh frozen plasma 5. Total surgery time 6. Blood loss during and after surgery 7. Adverse events especially thromboembolic events
Sources of Support	Novo Nordisk set up randomisation, provided clinical researcher and statistician
Notes	Minimal threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation, blocked by centre, was computer-generated by means of central interactive voice response system
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind. An additional measure was that clotting blood tests were not released from the central lab until the trial end
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 19; 9%. 19 patients lost to follow-up did not undergo partial hepatectomy and lack of clarity on whether losses to follow-up were spread equally across each treatment group
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	Low risk	Done; target 180 (achieved)

Lodge 2005b

Methods	Double-blind, placebo-controlled RCT
Participants	Adults End-stage liver disease with cirrhosis prior to orthotopic liver transplantation Group 1 = 63 Group 2 = 58

Lodge 2005b (*Continued*)

	Group 3 = 61 Randomised but not given an allocated treatment = 27 Total randomised = 209
Interventions	Group 1. Repeated doses of 60 µg/kg rFVIIa iv starting within 10 minutes of skin incision and then repeated every 2 hours. Most participants had 3 doses. Total dose approximately 180 µg/kg. Group 2. As for group 1 but dose 120 µg/kg. Total dose approximately 360 µg/kg. Group 3. Placebo.
Outcomes	1. (Primary) Total number of red cells units transfused during the perioperative period defined as surgery + 24 hours postoperatively 2. Other transfusion requirements (FFP, platelets, crystalloids and colloids) during perioperative period 3. Blood loss during perioperative period and changes in haematocrit during perioperative period 4. Use of other haemostatic drugs, including antifibrinolytics 5. Length of intensive care and hospital stay 6. Surgery time 7. Adverse events especially thromboembolic events and bleeding complications
Sources of Support	One author from Novo Nordisk
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up: 27; 13% (26 withdrawn before dosing and 1 did not complete preanhepatic phase of surgery)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

Lodge 2005b (*Continued*)

Other bias	Unclear risk	Equality of allocation within each of the 14 centres not assured
Power calculation?	Low risk	Done; target 180 (achieved)

Ma 2006

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Cardiac valve replacement requiring cardio-pulmonary bypass Group 1 = 11 Group 2 = 11 Total randomised = 22
Interventions	Group 1. 1 dose of 40 μg/kg rFVIIa iv after bypass and reversal of heparin. Group 2. Placebo at same time.
Outcomes	1. Serial haematological parameters including haemoglobin, haematocrit, platelets, PT, INR, fibrinogen, ACT 2. Postoperative thoracic drainage 3. Postoperative blood transfusion 4. Period of mechanical ventilation 5. Period of ICU stay 6. Hospitalisation costs
Sources of Support	No statement made
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using random number tables
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided

Ma 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small study size. No transfusion guidelines.
Power calculation?	High risk	No power calculation

Mayer 2005a

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Spontaneous intracerebral haemorrhage confirmed by CT scan within 3 hours of onset Group 1 = 108 Group 2 = 92 Group 3 = 103 Group 4 = 96 Total randomised = 400 (one withdrew consent)
Interventions	Group 1. 1 dose of 40 µg/kg of iv FVIIa within 1 hour of scan. Group 2. 1 dose of 80 µg/kg at same time. Group 3. 1 dose of 160 µg/kg at same time. Group 4. Placebo at same time.
Outcomes	1. (Primary) Change in volume of intracerebral haemorrhage as assessed by CT scan between baseline and 24 hours 2. Survival at 90 days 3. Unfavourable Modified Rankin Scale score (4 to 6) at 90 days 4. Unfavourable Extended Glasgow Outcome Scale score (1 to 4) at 90 days 5. Barthel Index score at 90 days 6. NIH Stroke Scale score at 90 days 7. All serious adverse events, particularly thromboembolic, up to 90 days (all adverse events collected to discharge from hospital)
Sources of Support	Study supported by Novo Nordisk. Sponsor responsible for collecting the data. 5 authors received consultancy fees from Novo Nordisk. 3 authors from Novo Nordisk
Notes	Some threats to validity (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4 in sequentially numbered, identical appearing containers

Mayer 2005a (*Continued*)

Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Indicated that placebo identical. CT scans analysed in random order, double-read, blind to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 16; 4%
Selective reporting (reporting bias)	Low risk	Registered at www.clinicaltrials.gov
Other bias	Unclear risk	Half of study patients had complete screening data, precluding full assessment of balance of population characteristics. Equality of distribution of patients between the 73 contributing study centres. Inclusion criteria changed during trial to exclude those with history of thrombotic or vaso-occlusive disease - distribution across final study groups not described. In analysis for surviving patients with missing outcome data, last observation was carried forward
Power calculation?	Unclear risk	Done; target not stated

Mayer 2005b

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Spontaneous intracerebral haemorrhage confirmed by CT scan within 3 hours of onset Groups 1, 2, 3, 4, 5, 6 = 6 Group 7 = 12 Total randomised = 48 (1 withdrew consent)
Interventions	Group 1. 1 dose of 10 µg/kg of iv rFVIIa within 1 hour of scan. Group 2. 1 dose of 20 µg/kg at same time. Group 3. 1 dose of 40 µg/kg at same time. Group 4. 1 dose of 80 µg/kg at same time. Group 5. 1 dose of 120 µg/kg at same time. Group 6. 1 dose of 160 µg/kg at same time. Group 7. Placebo within 1 hour of scan.

Outcomes	1. (Primary) Frequency of adverse events that were possibly or probably treatment related by day 15 or discharge if earlier. Serious adverse events were considered to day 90; predefined events included MI, DVT, PE, cerebral artery or vein thrombosis, consumptive coagulopathy, perihaematoma oedema 2. Change in baseline and 24-hour CT 3. In hospital neurological deterioration between day 0 and day 5 4. Percentage of patients dead, alive with minimal or no disability, or alive and functionally independent at day 90
Sources of Support	Study supported by Novo Nordisk. Statistician from Novo Nordisk
Notes	Some threats to validity (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation schedule was generated and patients were allocated to the next available randomisation number within the dose tier. No details given about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. CT scans analysed in random sequence by 2 independent blinded neuroradiologists
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 1; 2%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small safety study with no power calculation. Equality of distribution of patients between centres. No comparison of population characteristics between study arms
Power calculation?	High risk	No power calculation

Mayer 2006

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Spontaneous intracerebral haemorrhage confirmed by CT scan within 3 hours of onset Group 1 = 8 Group 2 = 8 Group 3 = 8 Group 4 = 8 Group 5 = 8 Randomised but not given an allocated treatment = 1 Total randomised = 41
Interventions	Group 1. 1 dose of 5 μg/kg of rFVIIa iv within 1 hour of CT scan. Group 2. 1 dose of 20 μg/kg at same time. Group 3. 1 dose of 40 μg/kg at same time. Group 4. 1 dose of 80 μg/kg at same time. Group 5. Placebo at same time.
Outcomes	1. (Primary) Frequency of adverse events by day 15 or discharge if earlier. Serious adverse events were considered to day 90. Predefined events included MI, DVT, PE, cerebral artery or vein thrombosis, consumptive coagulopathy, perihaematoma oedema 2. Change in CT scan at 1 and 24 hours after baseline 3. In hospital neurological deterioration between day 0 and day 5 4. Percentage of patients dead, alive with minimal or no disability, or alive and functionally independent at day 90
Sources of Support	Study supported by Novo Nordisk. One author from Novo Nordisk. Agreement to publish results regardless of outcome
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned in 4 sequential dose tiers (n = 10 per tier) to receive placebo (n = 2 per tier) or product at 4 different doses (n = 8 per tier). No details given about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Active agent and placebo were provided as indistinguishable powders for reconstitution

Mayer 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind. CT scans analysed in random sequence by 2 independent blinded neuroradiologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 1; 2%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Small study size. Equality of distribution of patients among centres unclear. 2 patients (5%) were treated beyond 4 hours of onset
Power calculation?	High risk	No power calculation

Mayer 2008

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Spontaneous intracerebral haemorrhage confirmed by CT scan within 3 hours of onset Group 1 = 265 Group 2 = 293 Group 3 = 263 Randomised but not given an allocated treatment = 20 Total randomised = 841
Interventions	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.
Outcomes	1. (Primary) Severe disability or death by modified Rankin scale score of 5 or 6 at day 90 2. Clinical assessment scores at day 90: Barthel index, Extended Glasgow Outcome Scale, NIH Stroke Scale, EuroQoL scale and Revised Hamilton Rating Scale for Depression 3. Change in volume of intracerebral haemorrhage, intraventricular haemorrhage and oedema as assessed by CT scan between baseline, 24 and 72 hours 4. All adverse events until discharge and serious adverse events, particularly thromboembolic, up to 90 days
Sources of Support	Study supported by Novo Nordisk. Sponsor responsible for trial operations including data analysis
Notes	Some threats to validity noted (see 'Risk of bias' assessment)
Risk of bias	

Mayer 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation according to site
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CT scans analysed by 2 independent blinded neuroradiologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 22; 3%
Selective reporting (reporting bias)	Low risk	Registered at www.clinicaltrials.gov
Other bias	Low risk	External generalisability is a concern as less than 10% who were assessed for eligibility for the trial underwent randomisation. In analysis for surviving patients with missing outcome data, last observation was carried forward
Power calculation?	Low risk	Done; target 816 (achieved)

Narayan 2008

Methods	Double-blind, placebo-controlled RCT Dose-escalation trial
Participants	Adult Traumatic brain injury with contusion of total volume of at least 2 mL on CT scan obtained within 6 hours of injury Group 1 = 12 Group 2 = 11 Group 3 = 14 Group 4 = 12 Group 5 = 12 Group 6 = 36 Total randomised = 97
Interventions	Group 1. 1 dose of 40 μg/kg of rFVIIa iv within 2.5 hours of CT scan. Group 2. 1 dose of 80 μg/kg at same time. Group 3. 1 dose of 120 μg/kg at same time.

	Group 4. 1 dose of 160 μg/kg at same time. Group 5. 1 dose of 200 μg/kg at same time. Group 6. Placebo at same time.
Outcomes	1. (Primary) Safety: occurrence of AEs, serious AEs, predefined potential thromboembolic AEs (deep venous thrombosis, pulmonary embolus, myocardial infarction, cerebral infarction, DIC, coagulopathy) and mortality within 15-day trial period 2. Changes in haematoma volume on CT scan at baseline compared with 24 hours and 72 hours after dosing 3. Clinical outcomes at day 15: Glasgow Coma Scale, extended Glasgow Outcome Scale and Barthel Index
Sources of Support	Novo Nordisk supplied study agent and placebo. 2 authors from Novo Nordisk
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	2 independent neuroradiologists assessed CT scans masked to patient, treatment arm and study site information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Low risk	Registered at www.clinicaltrials.gov
Other bias	Unclear risk	Inclusion criteria amended after 8% of patients entered study to improve recruitment (reducing minimal lesion volume from 5 mL to 2 mL; GCS scores changed from 4-13 to 4-14; time of CT scan from within 4 to within 6 hours). External generalisability is a concern as 4% who were assessed for eligibility for the trial underwent randomisation. Follow-up data available up to 15 days post-dosing

Narayan 2008 (*Continued*)

Power calculation?	High risk	No power calculation

Pihusch 2005

Methods	Double-blind, placebo-controlled RCT
Participants	Adults (all included patients > 16 years old, although inclusion criteria allowed > 12 years) Bleeding occurring 2 to 120 days (or 180 days later in study) after haematopoietic stem cell grafts (initially allogeneic, later in study autologous included) for a variety of haematological and oncological conditions Group 1 = 20 Group 2 = 26 Group 3 = 31 Group 4 = 23 Total randomised = 100
Interventions	Group 1. 7 x 40 µg/kg of iv rFVIIa given every 6 hours; total dose 280 µg/kg. Group 2. As for group 1, but 7 x 80 µg/kg; total dose 560 µg/kg. Group 3. As for group 1 but 7 x 160 µg/kg; total dose 1120 µg/kg. Group 4. Placebo.
Outcomes	1. (Primary) Change in bleeding score (5-point scale 0 to 4) from baseline to 38 hours after initial dose 2. Changes in bleeding scores over other periods 3. Use of RBC, platelets and FFP over 96-hour trial period 4. Adverse events and serious adverse events over 96-hour trial period
Sources of Support	Novo Nordisk support in all phases of the trial. 2 authors from Novo Nordisk
Notes	Important threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, using centre blocks with equal allocation ratio between treatment groups
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Indicated that placebo identical.

Pihusch 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 2; 2%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	High risk	Stopped recruiting patients where bleeding event triggering trial entry was haemorrhagic cystitis (HC) ("bleeding from urinary bladder") after an interim analysis (p1938 col2) . However, there was a marked imbalance in patients with HC across study groups being much reduced in the 80 μg/kg treatment group
Power calculation?	Low risk	Done; target 100 (achieved)

Planinsic 2005

Methods	Double-blind, placebo-controlled RCT
Participants	Adults End-stage liver disease prior to orthotopic liver transplantation Group 1 = 18 Group 2 = 24 Group 3 = 22 Group 4 = 19 Randomised but not given an allocated treatment = 4 Total randomised = 87
Interventions	Group 1. 1 dose rFVIIa 20 µg/kg iv within 10 minutes of the first skin incision. Group 2. 1 dose 40 µg/kg FVIIa, otherwise as for group 1. Group 3. 1 dose 80 µg/kg FVIIa, otherwise as for group 1. Group 4. Placebo.
Outcomes	1. (Primary) Total number of red cells units transfused during the perioperative period defined as surgery + 24 hours postoperatively 2. Other transfusion requirements during the perioperative period (FFP, platelets, crystalloids and colloids) 3. Blood loss recorded during the perioperative period 4. Use of other haemostatic drugs, including antifibrinolytics 5. Length of intensive care unit stay 6. Adverse events especially thromboembolic events and bleeding complications
Sources of Support	One author from Novo Nordisk

Planinsic 2005 (*Continued*)

Notes	Some threats to validity noted (see 'Risk of bias' assessment)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	In blocks of 8 equally allocated across 4 treatment groups. No other details
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 5; 5%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	Low risk	Done; target 80 (achieved)

Pugliese 2007

Methods	Double-blind, placebo-controlled RCT
Participants	Adults End-stage liver disease prior to orthotopic liver transplantation Group 1 = 10 Group 2 = 10 Total randomised = 20
Interventions	Group 1. 1 dose of 40 μg/kg rFVIIa iv immediately before anaesthesia induction. Group 2. Placebo at same time.
Outcomes	1. Change in INR 2. Blood products transfused during surgery 3. Blood loss during surgery
Sources of Support	No statement made

Pugliese 2007 (*Continued*)

Notes	Important threats to validity noted (see 'Risk of bias' assessment)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Some results reported in abstract but not in results section
Other bias	Unclear risk	Not enough information to determine if groups were balanced. Small study size
Power calculation?	High risk	No power calculation

Raobaikady 2005

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Reconstructive surgery for traumatic fractures of the pelvis or pelvis and acetabulum Group 1 = 24 Group 2 = 24 Total randomised = 48
Interventions	Group 1. 90 µg/kg rFVIIa iv at first skin incision plus a further dose after 2 hours if there was evidence of significant bleeding. Total dose 90 to 180 µg/kg. Group 2. Placebo.
Outcomes	1. (Primary) Total volume of perioperative blood loss (surgery + 48 hours postoperatively) 2. Transfusion requirements 3. Numbers of patients transfused 4. Volume of crystalloids/colloids infused

Raobaikady 2005 (*Continued*)

	5. Surgery time 6. Time to reach normal body temperature and acid-base status 7. Time in ICU 8. Days in hospital 9. Number of times returned to operating theatre 10. Adverse events focusing on thromboembolic events
Sources of Support	Study supported by Novo Nordisk. Novo Nordisk assisted in preparation of manuscript. One author worked as consultant for Novo Nordisk
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated scheme
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 0; 0%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	Low risk	Done; target 48 (achieved)

Sachs 2007

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Spinal fusion surgery reaching dosing trigger of 10% loss of estimated blood volume with total expected loss of at least 20% estimated blood volume before end of surgery Group 1 = 12 Group 2 = 12 Group 3 = 12

	Group 4 = 13 Randomised but not given an allocated treatment = 11 Total randomised = 60
Interventions	Group 1. 3 x 30 μg/kg rFVIIa iv. First dose at dosing trigger; second dose at 2 hours after initial dose; third dose at 4 hours after initial dose. Total dose 90 μg/kg. Group 2. 3 x 60 μg/kg rFVIIa iv at same times. Total dose 180 μg/kg. Group 3. 3 x 120 μg/kg rFVIIa iv at same times. Total dose 360 μg/kg. Group 4. Placebo, powder for reconstitution, at same times.
Outcomes	1. (Primary) All serious adverse events to 30 days post-surgery, thrombotic serious adverse events, changes in laboratory parameters and all adverse events from baseline visit until discharge 2. (Co-primary) Adjusted volume of blood loss 3. Rate of blood loss 4. Units/volume of allogeneic and autologous RBC, FFP, platelets and cryoprecipitate transfused 5. Duration of surgery 6. Time to drain removal
Sources of Support	Study supported by Novo Nordisk. 2 authors from Novo Nordisk.
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double-blind. Active agent and placebo were provided as indistinguishable powders for reconstitution
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up; 11; 18% (all 11 did not reach dosing trigger)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Unclear if groups were balanced. Power calculation based on assumed increase in thrombotic events from 2% for placebo to 15%

		for rFVIIa leading to an underpowered study. Marked differences between the unadjusted and adjusted analyses.
Power calculation?	Low risk	Done; target 48 (achieved)

Shao 2006

Methods	Double-blind, placebo-controlled RCT
Participants	Adults Partial hepatectomy for liver cancer or benign tumours in patients with cirrhosis Group 1 = 71 Group 2 = 74 Group 3 = 76 Randomised but not given an allocated treatment = 14 Total randomised = 235
Interventions	Group 1. First dose of 50 μg/kg rFVIIa iv within 10 minutes before first skin cut with additional doses given every 2 hours until the end of surgery to a maximum dose of 4 doses. Group 2. 100 μg/kg iv as for Group 1. Group 3. Placebo as for Group 1.
Outcomes	1. (Primary) Proportion of patients receiving RBC transfusions during surgery and the first 48 hours after surgery 2. (Co-primary) Amount of RBCs transfused during surgery and the first 48 hours after surgery 3. Amounts of FFP and platelets transfused during surgery and the first 48 hours after surgery 4. Blood loss 5. Proportion of patients receiving systemic haemostatic drugs 6. Changes in coagulation-related parameters including PTT, platelet counts, fibrinogen, D-dimer, thrombin-anti-thrombin complexes, prothrombin fragments 1+2)
Sources of Support	One author from Novo Nordisk
Notes	Some threats to validity noted (see 'Risk of bias' assessment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind but no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 14; 6%
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	-
Power calculation?	Unclear risk	Done; no target stated

ACT = activated clotting time
AE = adverse event
ASA = acetylsalicylic acid
CPB = cardiopulmonary bypass
CT = computerised tomography
DIC = disseminated intravascular coagulation
DVT = deep vein thrombosis
FDP = fibrin degradation products
FFP = fresh frozen plasma
GCS = Glasgow Coma Scale
ICU = intensive care unit
INR = international normalised ratio
iv = intravenous
MI = myocardial infarction
MOF = multiple organ failure (MOF)
NIH = National Institutes of Health
PE = pulmonary embolism
PT = prothrombin time
RBC = red blood cell
RCT = randomised controlled trial
rFVIIa = recombinant factor VIIa
SOF = single organ failure

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ashrani 2006	Not a randomised controlled trial
Bijsterveld 2002	Study of human volunteers
Bijsterveld 2004	Study of human volunteers
Boffard 2009	Secondary report
Bysted 2007	Study of human volunteers
Davis 2004	Not a randomised controlled trial
Diringer 2007	Not a randomised controlled trial
Elgafy 2010	Systematic review or meta-analysis
Ensor 2011	Systematic review or meta-analysis
Fridberg 2005	Study of human volunteers
Gurusamy 2009	Systematic review or meta-analysis
Jilma 2002	Study of human volunteers
Johansson 2010	Systematic review or meta-analysis
Kolban 2005	Not a randomised controlled trial
Larsen 2010	Laboratory-based study
Leduc 2009	Systematic review or meta-analysis
Levi 2010	Systematic review or meta-analysis
Lin 2011b	Published version of previous Cochrane review
Logan 2010	Narrative review
Macieji 2004	Not a randomised controlled trial
Nishijima 2009	Systematic review or meta-analysis
Perel 2010	Systematic review or meta-analysis

(*Continued*)

Perez 2007	Not a randomised controlled trial
Plaat 2007	Not a randomised controlled trial
Pugh 2007	Not a randomised controlled trial
Strydom 2010	Systematic review or meta-analysis
Thabut 2011	Systematic review or meta-analysis
Van De Velde 2007	Not a randomised controlled trial
Vincent 2009	Study was discontinued prematurely by the Safety Committee based on statistical analysis of the mortality in cohort 3, which suggested that 28-day mortality was significantly higher in this cohort than in the placebo group and time to death was significantly shorter
Vink 2004	Study of human volunteers
Woltz 2004	Study of human volunteers
Yank 2009	Not a randomised controlled trial
Yank 2011	Systematic review or meta-analysis
Yuan 2010	Systematic review or meta-analysis

Characteristics of ongoing studies *[ordered by study ID]*

Arai 2005

Trial name or title	Randomised, double-blind, multicentre, placebo-controlled dose-escalation study to evaluate the safety and preliminary efficacy of activated recombinant factor VII (NN-007) in acute intracerebral haemorrhage
Methods	Double-blind, placebo-controlled RCT Dose-escalation trial
Participants	Adults Spontaneous ICH diagnosed by CT scan within 3 hours of symptom onset Group 1 = 15 Group 2 = 15 Group 3 = 15 Group 4 = 45 Total randomised = 90
Interventions	Group 1. 1 dose of 40 μg/kg of rFVIIa iv within 1 hour of CT scan. Group 2. 1 dose of 80 μg/kg at same time. Group 3. 1 dose of 120 μg/kg at same time.

Arai 2005 (*Continued*)

	Group 4. Placebo at same time.
Outcomes	1. Modified Rankin Scale, Barthel Index scores at 15 days post-dose and 90 days post-dose 2. Change in volume of intracerebral haemorrhage, total haemorrhage volume (intracerebral haemorrhage + intraventricular haemorrhage) and total lesion volumes (ICH + IVH + oedema) as assessed by CT scan from baseline to 24, 48 and 72 hours post-dose 3. Change in Glasgow Coma Scale and the National Institute of Health's Stroke Scale (NIHSS) scores from baseline to 1 hour, 24 hours, 48 hours, 72 hours, 15 days and 90 days post-dose 4. Mortality at 90 days post-dose 5. Occurrence of thromboembolic serious adverse events 6. Changes in laboratory coagulation parameters from prior to dosing to 1, 24, 48 and 72 hours post-dose 7. Occurrence of adverse events until discharge or 90 days post-dose, whichever came first and serious adverse events
Starting date	January 2006 to April 2007
Contact information	Morio Arai MD, PhD, Study Director, Novo Nordisk Pharma Ltd.
Notes	Completed. Not yet published.

Flaherty 2008

Trial name or title	The spot sign for predicting and treating intracerebral haemorrhage growth
Methods	Double-blind, placebo-controlled RCT
Participants	Participants with ICH who are determined by CT angiogram to be at high risk for haemorrhage growth (CT angiogram "spot sign" positive) Estimated enrolment: 184
Interventions	Recombinant FVIIa
Outcomes	1. Life-threatening thromboembolic complications (acute myocardial infarction, acute cerebral ischaemia and acute pulmonary embolism) 2. Rate of haematoma growth 3. Sensitivity and specificity of the spot sign for predicting haematoma growth 4. Incidence of other thromboembolic complications (deep venous thrombosis, elevations in troponin not associated with ECG changes) 5. Modified Rankin Scale score at 90 days 6. Positive and negative predictive values of the spot sign
Starting date	November 2010 to January 2013
Contact information	Janice A. Carrozzella, RN, BA, RT(R)
Notes	Recruiting

Gajewski 2005

Trial name or title	A multi-center, randomized, double-blind, parallel groups, placebo-controlled trial on efficacy and safety of activated recombinant factor VII (rFVIIa/NovoSeven) in the treatment of bleeding in patients following hematopoietic stem cell transplantation (HSCT)
Methods	Double-blind, placebo-controlled RCT
Participants	Patients $\geq$ 12 years Post HSCT with active bleeding Group 1 = 4 Group 2 = 4 Group 3 = 3 Total randomised = 11
Interventions	Group 1. 2 days of rFVIIa 40 μg/kg every 6 hours (7 doses) plus standard therapy. Total dose 280 μg/kg. Group 2. 80 μg/kg as for Group 1. Total dose 560 μg/kg. Group 3. Placebo as for Group 1.
Outcomes	1. (Primary) Effect on bleeding after 38-hour observation period following initial dosing 2. Transfusion requirements for RBCs, platelets, FFP in a 4-day observation period 3. Bleeding evaluation at time points of 24, 48, 72, and 96 hours 4. Adverse events were recorded for the 38-hour observation period plus an additional 58 hours (96 hours of safety assessments) 5. Changes in safety coagulation parameters
Starting date	June 2002 to October 2003
Contact information	James L. Gajewski
Notes	Trial was prematurely terminated due to excessively slow patient recruitment. Planned for 75 (25 per arm)

Gladstone 2011

Trial name or title	"Spot sign" selection of intracerebral hemorrhage to guide hemostatic therapy (SPOTLIGHT)
Methods	Double-blind, placebo-controlled RCT
Participants	Patients with ICH not due to trauma or other known causes with "spot sign" on CT angiography (sign of active bleeding) who can be treated within 6 hours of onset Estimated enrolment: 110
Interventions	Recombinant FVIIa
Outcomes	Primary outcome: ICH size at 24 hours
Starting date	May 2011 to August 2016

Gladstone 2011 (*Continued*)

Contact information	David J Gladstone, MD 416-480-4866 david.gladstone@sunnybrook.ca
Notes	Recruiting

Gris 2006

Trial name or title	rFVIIa as salvage therapy in severe post-partum haemorrhage
Methods	-
Participants	Female patients with post-partum haemorrhage responding to none of the existing medical and surgical treatments
Interventions	Recombinant human activated FVII (rhuFVIIa)
Outcomes	Primary outcomes: Clinical parameters: intensity of haemorrhage before and 1 hour after administration of rhuFVIIa; number of units and volume of RBC, platelets, FFP; haemodynamics-related parameters
Starting date	December 2006 to December 2009
Contact information	Geraldine Lissalde-Lavigne MD, PhD geraldine.lavigne@chu-nimes.fr +33 4 66 68 32 11
Notes	Recruitment status is unknown

Imberti 2005

Trial name or title	Efficacy and safety of rFVIIa on rebleeding after surgery for spontaneous supratentorial intracerebral haemorrhage: a randomised controlled open label investigator blinded pilot study
Methods	-
Participants	Patients receiving surgery for spontaneous supratentorial intracerebral haemorrhage Estimated enrolment: 30
Interventions	rFVIIa (Eptacog alfa, Novo Nordisk)
Outcomes	Primary outcome: Evaluate the efficacy of Factor VIIa (Eptacog alfa) in preventing or reducing rebleeding after surgery for spontaneous supratentorial ICH Secondary outcomes: Safety of product administration

Imberti 2005 (*Continued*)

Starting date	January 2005 to December 2008
Contact information	Roberto Imberti M.D., Principal Investigator, IRCCS Policlinico S. Matteo - Pavia - Italy Roberto Imberti M.D. Tel: +39 0382 502071 r.imberti@smatteo.pv.it
Notes	Completed. Not yet published.

Iorio 2006

Trial name or title	Randomised, open, prospective, multicenter pilot study to evaluate the efficacy and safety of activated recombinant factor VII in acute intracerebral haemorrhage in patients treated with oral anticoagulants or antiplatelet agents
Methods	-
Participants	Acute intracerebral haemorrhage in adult patients on treatment with one of the following: a) oral anticoagulant b) aspirin, whatever dosage Estimated enrolment: 32
Interventions	rFVIIa
Outcomes	Primary outcomes: EFFICACY: change in ICH volume from prior to dosing to 24 hours SAFETY: occurrence of clinical adverse events (thromboembolic events, death) Secondary outcomes: Difference between groups on the modified Rankin Scale, the Barthel Index (BI), the Extended Glasgow Scale (EGCS), and the National Institute of Health's Stroke Scale (NIHSS) at 1 and 3-month follow-up
Starting date	September 2005 to September 2006
Contact information	Alfonso Iorio, Principal Investigator, University Of Perugia Tel: +39 075 578 4306 iorioa@unipg.it
Notes	Recruitment status is unknown

Kelleher 2006

Trial name or title	A multi-centre, randomised, double-blind, placebo-controlled, dose-escalation trial of safety and efficacy of activated recombinant factor VII (Rfv11a/NovoSeven) in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass
Methods	-

Kelleher 2006 (*Continued*)

Participants	Patients post-cardiac surgery
Interventions	rFVIIa (NovoSeven®)
Outcomes	Outcome measures: Critical serious adverse events: death, acute myocardial infarction, cerebral infarction
Starting date	2006
Contact information	Dr Andrea Kelleher, Royal Brompton and Harefield NHS Trust, London SW3 6NP A.Kelleher@rbh.nthames.nhs.uk
Notes	Completed. Not yet published.

McCall 2005

Trial name or title	"Salvage use" of rFVIIa after inadequate haemostatic response to conventional therapy in complex cardiac surgery - a randomised placebo-controlled trial
Methods	-
Participants	Adult patients with scheduled cardiac surgery undergoing the following procedures: - double valve replacements or repair - major thoracic aortic surgery including hypothermic circulatory arrest or descending aortic reconstruction - valve repair or replacement in the setting of endocarditis - complex procedures requiring cardiopulmonary bypass duration anticipated to exceed 180 minutes in patients aged 70 years Expected enrolment: 40
Interventions	rFVIIa
Outcomes	Primary outcome: Adequate haemostasis to enable chest closure after administration of trial medication without the need for further intervention to improve coagulation Secondary outcomes: Percentage of cases that haemostasis after first administration of coagulation factors alone; assessment of surgical field after administration of trial medication; time to closure of chest after administration of trial medication; transfusion requirements in post-bypass period in theatre; transfusion requirements in ICU first 12 hours; mediastinal drainage in ICU first 12 hours; coagulation study results at various sample times; requirement for chest re-exploration; ventilation duration in ICU; duration of stay in ICU
Starting date	June 2005 to June 2008
Contact information	Austin Health Melbourne Victoria 3084 Contact: Peter McCall FANZCA

	Tel: +61 3 94965000 ext.: 3800 peter.mccall@austin.org.au Contact backup: Stephanie J Poustie MPH Tel: +61 3 94965000 ext.: 3800 stephanie.poustie@austin.org.au Investigator: Peter McCall FANZCA, Principal Investigator
Notes	Recruitment status is unknown.

Molter 2005

Trial name or title	Effect of rFVIIa on peri-operative blood loss in patients undergoing major burn excision and grafting: a randomised, double-blind, placebo-controlled parallel assignment efficacy study
Methods	-
Participants	Patients undergoing major burn excision and grafting Estimated enrolment: 52
Interventions	rFVIIa
Outcomes	Reduce perioperative blood loss and transfusion requirements
Starting date	January 2006 to December 2010
Contact information	Nancy C Molter RN, PhD Tel: 210 916 5690 Nancy.Molter@amedd.army.mil
Notes	Active, but not recruiting

Ng 2006

Trial name or title	Use of rFVIIa in bleeding ECMO patients post cardiac surgery. Randomised prospective study
Methods	-
Participants	Patients post-cardiac surgery
Interventions	rFVIIa
Outcomes	a) Amount of postoperative bleeding b) Use of human blood products
Starting date	April 2004

Ng 2006 (*Continued*)

Contact information	Mr C Ng PICU, Great Ormond Street Hospital, Great Ormond Street, London, WC1N 3JH, UK Tel: +44 020 7405 9200
Notes	Recruitment status is unknown

CT = computerised tomography
FFP = fresh frozen plasma
HSCT = haematopoietic stem cell transplantation
ICH = intracranial haemorrhage
ICU = intensive care unit
iv = intravenous
IVH = intraventriculare hemorrhage
RBC = red blood cell
RCT = randomised controlled trial
rFVIIa = recombinant factor VIIa

DATA AND ANALYSES

Comparison 1. rFVIIa used prophylactically versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	15	1219	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.55, 1.97]
2 Death - exploring heterogeneity	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Studies with ≥ 50 patients each	7	995	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.67, 2.78]
2.2 Studies with < 50 patients each	8	224	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.57]
2.3 Studies with adequate allocation concealment	3	408	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.51, 2.89]
2.4 Studies with transfusion protocols	13	1121	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.55, 1.97]
3 Total operative and perioperative blood loss (mL)	10	707	Mean Difference (IV, Random, 95% CI)	-296.97 [-416.32, -177.61]
4 Total operative and perioperative blood loss (mL) - exploring heterogeneity	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Studies with ≥ 50 patients each	4	549	Mean Difference (IV, Random, 95% CI)	-261.01 [-550.32, 28.29]
4.2 Studies with < 50 patients each	6	158	Mean Difference (IV, Random, 95% CI)	-304.87 [-439.60, -170.15]
4.3 Studies with adequate allocation concealment	3	393	Mean Difference (IV, Random, 95% CI)	-604.91 [-1259.77, 49.95]
4.4 Studies with transfusion protocols	9	685	Mean Difference (IV, Random, 95% CI)	-342.30 [-479.01, -205.60]
5 Red cell transfusion requirements (mL)	12	843	Mean Difference (IV, Random, 95% CI)	-260.78 [-367.30, -154.27]
6 Red cell transfusion requirements - exploring heterogeneity	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Studies with ≥ 50 patients each	4	618	Mean Difference (IV, Random, 95% CI)	-33.42 [-260.27, 193.43]
6.2 Studies with < 50 patients each	8	225	Mean Difference (IV, Random, 95% CI)	-310.57 [-413.14, -208.00]
6.3 Studies with adequate allocation concealment	3	393	Mean Difference (IV, Random, 95% CI)	-157.57 [-478.84, 163.70]
6.4 Studies with transfusion protocols	11	821	Mean Difference (IV, Random, 95% CI)	-248.42 [-353.13, -143.70]
7 Numbers of patients transfused	8	868	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
8 Numbers of patients transfused - exploring heterogeneity	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Studies with ≥ 50 patients each	5	764	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.97]
8.2 Studies with < 50 patients each	3	104	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.22, 0.89]

8.3 Studies with adequate allocation concealment	3	324	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.10]
8.4 Studies with transfusion protocols	7	792	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.01]
9 Total thromboembolic events	13	1159	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.82, 2.25]
10 Total thromboembolic events - exploring heterogeneity	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Studies with ≥ 50 patients each	7	995	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.81, 2.37]
10.2 Studies with < 50 patients each	6	164	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.24, 5.13]

Comparison 2. rFVIIa used therapeutically versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	13	2856	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
2 Death - exploring heterogeneity	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Studies with ≥ 50 patients each	10	2744	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.07]
2.2 Studies with < 50 patients each	3	112	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.22, 3.03]
2.3 Studies with adequate concealment allocation	6	1545	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.69, 1.16]
2.4 Studies with transfusion protocols	5	1146	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.77, 1.30]
2.5 Studies without transfusion protocols	8	1704	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.05]
3 Control of bleeding (number of patients with reduced bleeding)	4	616	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
4 Control of bleeding - exploring heterogeneity	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Studies with ≥ 50 patients each	3	571	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
5 Red cell transfusion requirements (mL)	5	911	Mean Difference (IV, Random, 95% CI)	-88.60 [-263.88, 86.68]
6 Red cell transfusion requirements (mL) - exploring heterogeneity	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Studies with ≥ 50 patients each	4	886	Mean Difference (IV, Random, 95% CI)	-131.20 [-360.09, 97.69]
7 Number of patients transfused	3	585	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.00]
8 Total thromboembolic events	13	2873	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.89, 1.47]
9 Total thromboembolic events - exploring heterogeneity	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Studies with ≥ 50 patients each	10	2761	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.91, 1.54]

9.2 Studies with < 50 patients each	3	112	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.27, 1.92]
9.3 Studies with adequate allocation concealment	6	1566	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.70, 1.76]
9.4 Studies with transfusion protocols	5	1167	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.74, 1.52]

Comparison 3. rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total thromboembolic events	26	4032	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.94, 1.48]
2 Cardiovascular events, including myocardial infarction	24	3472	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.85, 2.15]
3 Stroke	23	3289	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.72, 3.07]
4 Total arterial events	25	3849	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.02, 2.05]
5 Total venous events	25	3849	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.26]

Analysis 1.1. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 1 Death.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 1 Death

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Friederich 2003	0/24	0/12		0.0 [0.0, 0.0]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Planinsic 2005	4/64	1/19		1.19 [0.14, 10.00]
Lodge 2005a	4/132	3/68		0.69 [0.16, 2.98]
Lodge 2005b	3/121	1/62		1.54 [0.16, 14.47]
Diprose 2005	0/10	1/10		0.33 [0.02, 7.32]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Shao 2006	3/151	0/81		3.78 [0.20, 72.22]

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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Johansson 2007	0/9	3/9		0.14 [0.01, 2.42]
Essam 2007	0/15	0/15		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	1/36	0/13		1.14 [0.05, 26.25]
Gill 2009	10/104	4/68		1.63 [0.53, 5.00]
Hanna 2010	0/15	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**766**	**453**		**1.04 [0.55, 1.97]**

Total events: 25 (rFVIIa), 13 (Control)

Heterogeneity: $Chi^2 = 4.21$, df = 7 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 0.12 (P = 0.90)

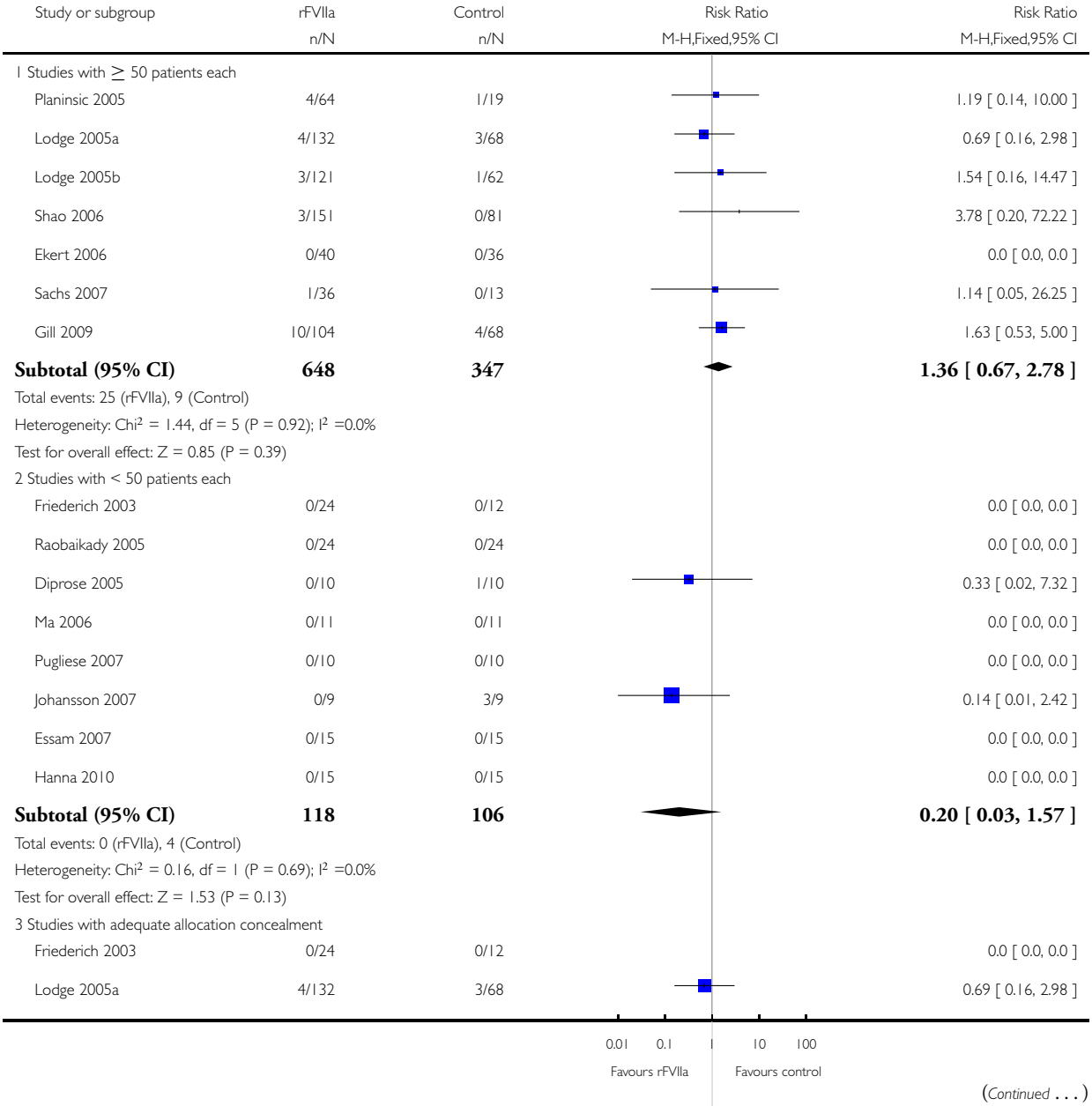
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 2 Death - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 2 Death - exploring heterogeneity



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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gill 2009	10/104	4/68		1.63 [0.53, 5.00]
Subtotal (95% CI)	**260**	**148**		**1.21 [0.51, 2.89]**
Total events: 14 (rFVIIa), 7 (Control)				
Heterogeneity: Chi^2 = 0.85, df = 1 (P = 0.36); I^2 =0.0%				
Test for overall effect: Z = 0.42 (P = 0.67)				
4 Studies with transfusion protocols				
Friederich 2003	0/24	0/12		0.0 [0.0, 0.0]
Planinsic 2005	4/64	1/19		1.19 [0.14, 10.00]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Lodge 2005a	4/132	3/68		0.69 [0.16, 2.98]
Lodge 2005b	3/121	1/62		1.54 [0.16, 14.47]
Diprose 2005	0/10	1/10		0.33 [0.02, 7.32]
Shao 2006	3/151	0/81		3.78 [0.20, 72.22]
Sachs 2007	1/36	0/13		1.14 [0.05, 26.25]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Johansson 2007	0/9	3/9		0.14 [0.01, 2.42]
Essam 2007	0/15	0/15		0.0 [0.0, 0.0]
Gill 2009	10/104	4/68		1.63 [0.53, 5.00]
Hanna 2010	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**715**	**406**		**1.04 [0.55, 1.97]**
Total events: 25 (rFVIIa), 13 (Control)				
Heterogeneity: Chi^2 = 4.21, df = 7 (P = 0.75); I^2 =0.0%				
Test for overall effect: Z = 0.12 (P = 0.90)				

Analysis 1.3. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 3 Total operative and perioperative blood loss (mL).

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 3 Total operative and perioperative blood loss (mL)

Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Friederich 2003	24	1138 (285)	12	2688 (1376)		2.1 %	-1550.00 [-2336.84, -763.16]
Lodge 2005a	122	1227 (1154)	63	1422 (1271)		7.0 %	-195.00 [-569.75, 179.75]
Lodge 2005b	99	7977 (9739)	44	8552 (10658)		0.1 %	-575.00 [-4262.50, 3112.50]
Diprose 2005 (1)	10	438 (344)	10	770 (634)		5.4 %	-332.00 [-779.07, 115.07]
Ma 2006	11	246 (42)	11	381 (69)		21.5 %	-135.00 [-182.74, -87.26]
Pugliese 2007	10	740 (131)	10	1140 (112)		18.9 %	-400.00 [-506.82, -293.18]
Sachs 2007	36	1680 (1285)	13	2270 (2659)		0.6 %	-590.00 [-2095.14, 915.14]
Essam 2007	15	435 (94)	15	620 (108)		20.6 %	-185.00 [-257.46, -112.54]
Gill 2009	104	1397 (1288)	68	1728 (1738)		4.8 %	-331.00 [-812.58, 150.58]
Hanna 2010	15	507 (143)	15	877 (155)		18.9 %	-370.00 [-476.72, -263.28]
Total (95% CI)	**446**		**261**			**100.0 %**	**-296.97 [-416.32, -177.61]**

Heterogeneity: Tau^2 = 16624.40; Chi^2 = 42.63, df = 9 (P<0.00001); I^2 =79%

Test for overall effect: Z = 4.88 (P < 0.00001)

Test for subgroup differences: Not applicable

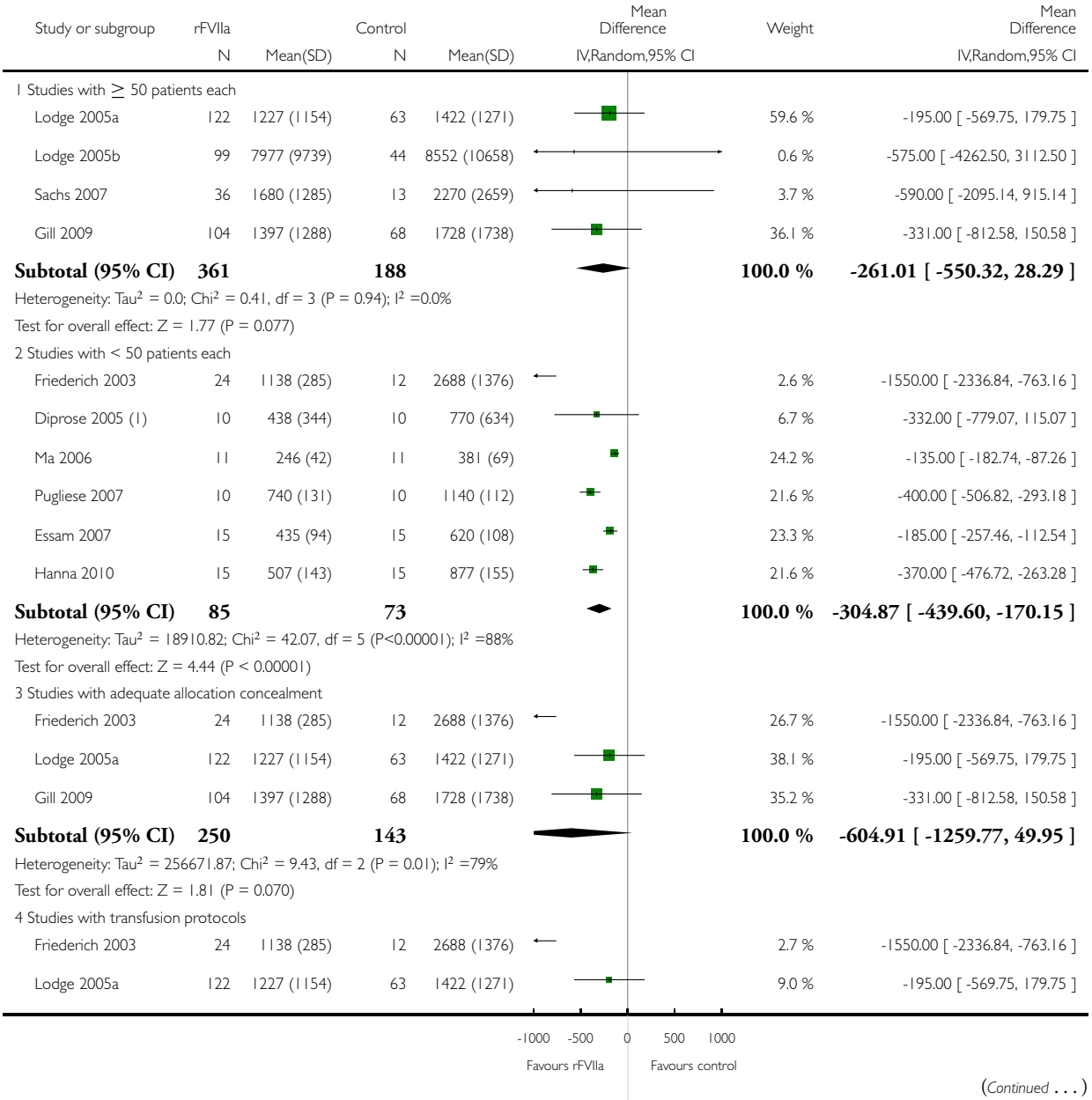
(1) Diprose 2005 = Additional data obtained from author

Analysis 1.4. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 4 Total operative and perioperative blood loss (mL) - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 4 Total operative and perioperative blood loss (mL) - exploring heterogeneity



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Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Lodge 2005b	99	7977 (9739)	44	8552 (10658)		0.1 %	-575.00 [-4262.50, 3112.50]
Diprose 2005 (2)	10	438 (344)	10	770 (634)		7.0 %	-332.00 [-779.07, 115.07]
Pugliese 2007	10	740 (131)	10	1140 (112)		24.0 %	-400.00 [-506.82, -293.18]
Sachs 2007	36	1680 (1285)	13	2270 (2659)		0.8 %	-590.00 [-2095.14, 915.14]
Essam 2007	15	435 (94)	15	620 (108)		26.0 %	-185.00 [-257.46, -112.54]
Gill 2009	104	1397 (1288)	68	1728 (1738)		6.3 %	-331.00 [-812.58, 150.58]
Hanna 2010	15	507 (143)	15	877 (155)		24.0 %	-370.00 [-476.72, -263.28]
Subtotal (95% CI)	**435**		**250**			**100.0 %**	**-342.30 [-479.01, -205.60]**

Heterogeneity: Tau^2 = 17310.50; Chi^2 = 24.61, df = 8 (P = 0.002); I^2 =67%

Test for overall effect: Z = 4.91 (P < 0.00001)

(1) Diprose 2005 = Additional data obtained from author

(2) Diprose 2005 = Additional data obtained from author

Analysis 1.5. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 5 Red cell transfusion requirements (mL).

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 5 Red cell transfusion requirements (mL)

Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Friederich 2003	24	60 (50)	12	450 (120)		21.1 %	-390.00 [-460.78, -319.22]
Planinsic 2005	63	3332 (3704)	19	3330 (2250)		0.6 %	2.00 [-1361.86, 1365.86]
Lodge 2005a	122	1200 (948)	63	1024 (1001)		8.2 %	176.00 [-122.99, 474.99]
Lodge 2005b	118	3444 (4341)	61	3840 (4620)		0.6 %	-396.00 [-1795.15, 1003.15]
Diprose 2005	10	234 (597)	10	750 (603)		3.5 %	-516.00 [-1041.92, 9.92]
Ma 2006	11	1050 (660)	11	1890 (930)		2.3 %	-840.00 [-1513.92, -166.08]
Johansson 2007	9	2760 (1170)	9	5820 (3630)		0.2 %	-3060.00 [-5551.70, -568.30]
Sachs 2007	36	910 (607)	13	1421 (2495)		0.6 %	-511.00 [-1881.69, 859.69]
Essam 2007	15	317 (334)	15	517 (176)		13.3 %	-200.00 [-391.06, -8.94]
Pugliese 2007	10	300 (133)	10	570 (111)		18.9 %	-270.00 [-377.37, -162.63]
Gill 2009 (1)	104	638 (826)	68	821 (824)		10.1 %	-183.00 [-435.11, 69.11]
Hanna 2010	15	375 (106)	15	612 (114)		20.7 %	-237.00 [-315.78, -158.22]
Total (95% CI)	**537**		**306**			**100.0 %**	**-260.78 [-367.30, -154.27]**

Heterogeneity: Tau^2 = 12666.09; Chi^2 = 28.67, df = 11 (P = 0.003); I^2 =62%

Test for overall effect: Z = 4.80 (P < 0.00001)

Test for subgroup differences: Not applicable

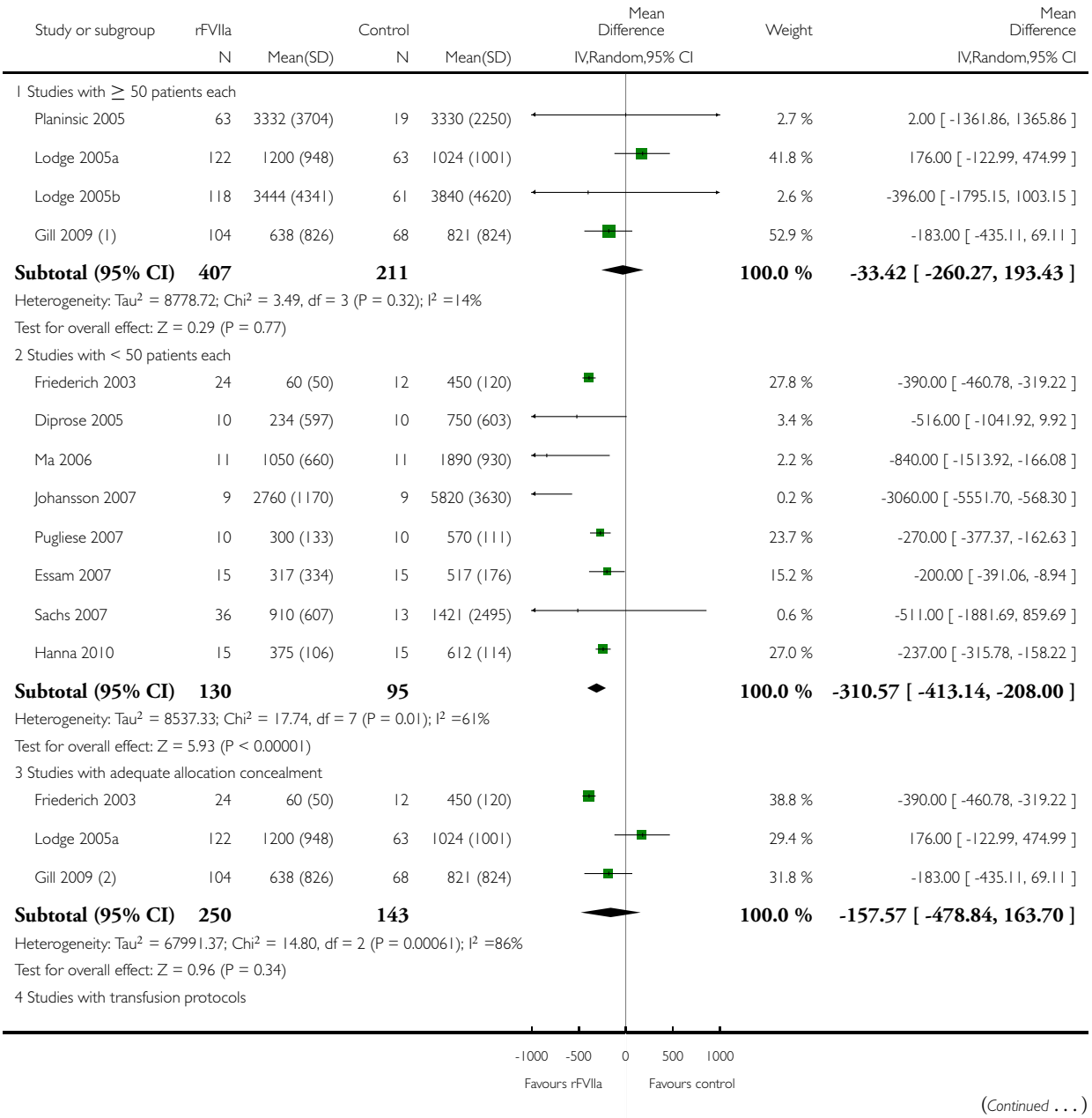
(1) Additional data obtained from author

Analysis 1.6. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 6 Red cell transfusion requirements - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 6 Red cell transfusion requirements - exploring heterogeneity



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Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Friederich 2003	24	60 (50)	12	450 (120)		22.0 %	-390.00 [-460.78, -319.22]
Planinsic 2005	63	3332 (3704)	19	3330 (2250)		0.6 %	2.00 [-1361.86, 1365.86]
Lodge 2005a	122	1200 (948)	63	1024 (1001)		8.2 %	176.00 [-122.99, 474.99]
Lodge 2005b	118	3444 (4341)	61	3840 (4620)		0.5 %	-396.00 [-1795.15, 1003.15]
Diprose 2005	10	234 (597)	10	750 (603)		3.4 %	-516.00 [-1041.92, 9.92]
Pugliese 2007	10	300 (133)	10	570 (111)		19.5 %	-270.00 [-377.37, -162.63]
Sachs 2007	36	910 (607)	13	1421 (2495)		0.6 %	-511.00 [-1881.69, 859.69]
Essam 2007	15	317 (334)	15	517 (176)		13.5 %	-200.00 [-391.06, -8.94]
Johansson 2007	9	2760 (1170)	9	5820 (3630)		0.2 %	-3060.00 [-5551.70, -568.30]
Gill 2009 (3)	104	638 (826)	68	821 (824)		10.1 %	-183.00 [-435.11, 69.11]
Hanna 2010	15	375 (106)	15	612 (114)		21.5 %	-237.00 [-315.78, -158.22]
Subtotal (95% CI)	**526**		**295**			**100.0 %**	**-248.42 [-353.13, -143.70]**

Heterogeneity: Tau^2 = 11668.49; Chi^2 = 26.15, df = 10 (P = 0.004); I^2 =62%

Test for overall effect: Z = 4.65 (P < 0.00001)

(1) Additional data obtained from author

(2) Additional data obtained from author

(3) Additional data obtained from author

Analysis 1.7. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 7 Numbers of patients transfused.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 7 Numbers of patients transfused

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Friederich 2003	3/24	7/12		1.9 %	0.21 [0.07, 0.68]
Raobaikady 2005	11/24	16/24		7.5 %	0.69 [0.41, 1.16]
Lodge 2005a	41/122	23/63		10.4 %	0.92 [0.61, 1.39]
Lodge 2005b	108/118	61/61		28.3 %	0.92 [0.87, 0.98]
Diprose 2005	3/10	8/10		2.5 %	0.38 [0.14, 1.02]
Shao 2006	63/145	29/76		13.0 %	1.14 [0.81, 1.60]
Ekert 2006	30/40	29/36		18.1 %	0.93 [0.73, 1.18]
Gill 2009	24/35	61/68		18.2 %	0.76 [0.60, 0.97]
Total (95% CI)	**518**	**350**		**100.0 %**	**0.85 [0.72, 1.01]**

Total events: 283 (rFVIIa), 234 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.12$, df = 7 (P = 0.02); $I^2 = 57\%$

Test for overall effect: Z = 1.89 (P = 0.058)

Test for subgroup differences: Not applicable

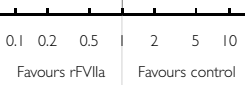
Analysis 1.8. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 8 Numbers of patients transfused - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 8 Numbers of patients transfused - exploring heterogeneity

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Studies with ≥ 50 patients each					
Lodge 2005a	41/122	23/63		2.2 %	0.92 [0.61, 1.39]
Lodge 2005b	108/118	61/61		81.6 %	0.92 [0.87, 0.98]
Shao 2006	63/145	29/76		3.2 %	1.14 [0.81, 1.60]
Ekert 2006	30/40	29/36		6.4 %	0.93 [0.73, 1.18]
Gill 2009	24/35	61/68		6.5 %	0.76 [0.60, 0.97]
Subtotal (95% CI)	**460**	**304**		**100.0 %**	**0.92 [0.86, 0.97]**
Total events: 266 (rFVIIa), 203 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.09, df = 4 (P = 0.39); I^2 =2%					
Test for overall effect: Z = 2.82 (P = 0.0048)					
2 Studies with < 50 patients each					
Friederich 2003	3/24	7/12		23.3 %	0.21 [0.07, 0.68]
Raobaikady 2005	11/24	16/24		48.6 %	0.69 [0.41, 1.16]
Diprose 2005	3/10	8/10		28.1 %	0.38 [0.14, 1.02]
Subtotal (95% CI)	**58**	**46**		**100.0 %**	**0.44 [0.22, 0.89]**
Total events: 17 (rFVIIa), 31 (Control)					
Heterogeneity: Tau^2 = 0.19; Chi^2 = 3.93, df = 2 (P = 0.14); I^2 =49%					
Test for overall effect: Z = 2.30 (P = 0.021)					
3 Studies with adequate allocation concealment					
Friederich 2003	3/24	7/12		11.6 %	0.21 [0.07, 0.68]
Lodge 2005a	41/122	23/63		38.7 %	0.92 [0.61, 1.39]
Gill 2009	24/35	61/68		49.6 %	0.76 [0.60, 0.97]
Subtotal (95% CI)	**181**	**143**		**100.0 %**	**0.71 [0.45, 1.10]**
Total events: 68 (rFVIIa), 91 (Control)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 5.41, df = 2 (P = 0.07); I^2 =63%					
Test for overall effect: Z = 1.52 (P = 0.13)					
4 Studies with transfusion protocols					
Friederich 2003	3/24	7/12		3.1 %	0.21 [0.07, 0.68]
Raobaikady 2005	11/24	16/24		10.9 %	0.69 [0.41, 1.16]



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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lodge 2005a	41/122	23/63		14.3 %	0.92 [0.61, 1.39]
Lodge 2005b	108/118	61/61		29.0 %	0.92 [0.87, 0.98]
Diprose 2005	3/10	8/10		4.0 %	0.38 [0.14, 1.02]
Shao 2006	63/145	29/76		17.0 %	1.14 [0.81, 1.60]
Gill 2009	24/35	61/68		21.7 %	0.76 [0.60, 0.97]
Subtotal (95% CI)	**478**	**314**		**100.0 %**	**0.82 [0.66, 1.01]**
Total events: 253 (rFVIIa), 205 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 16.84, df = 6 (P = 0.01); I^2 =64%					
Test for overall effect: Z = 1.82 (P = 0.068)					

Analysis 1.9. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 9 Total thromboembolic events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 9 Total thromboembolic events

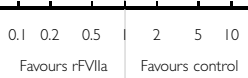
Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Friederich 2003	1/24	0/12		1.56 [0.07, 35.67]
Planinsic 2005	8/64	3/19		0.79 [0.23, 2.69]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Lodge 2005a	6/132	3/68		1.03 [0.27, 3.99]
Lodge 2005b	19/121	6/62		1.62 [0.68, 3.85]
Diprose 2005	2/10	2/10		1.00 [0.17, 5.77]
Shao 2006	3/151	1/81		1.61 [0.17, 15.22]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Sachs 2007	8/36	2/13		1.44 [0.35, 5.94]
Gill 2009	7/104	1/68		4.58 [0.58, 36.38]
Total (95% CI)	**736**	**423**		**1.35 [0.82, 2.25]**

Total events: 54 (rFVIIa), 18 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.60$, df = 7 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable

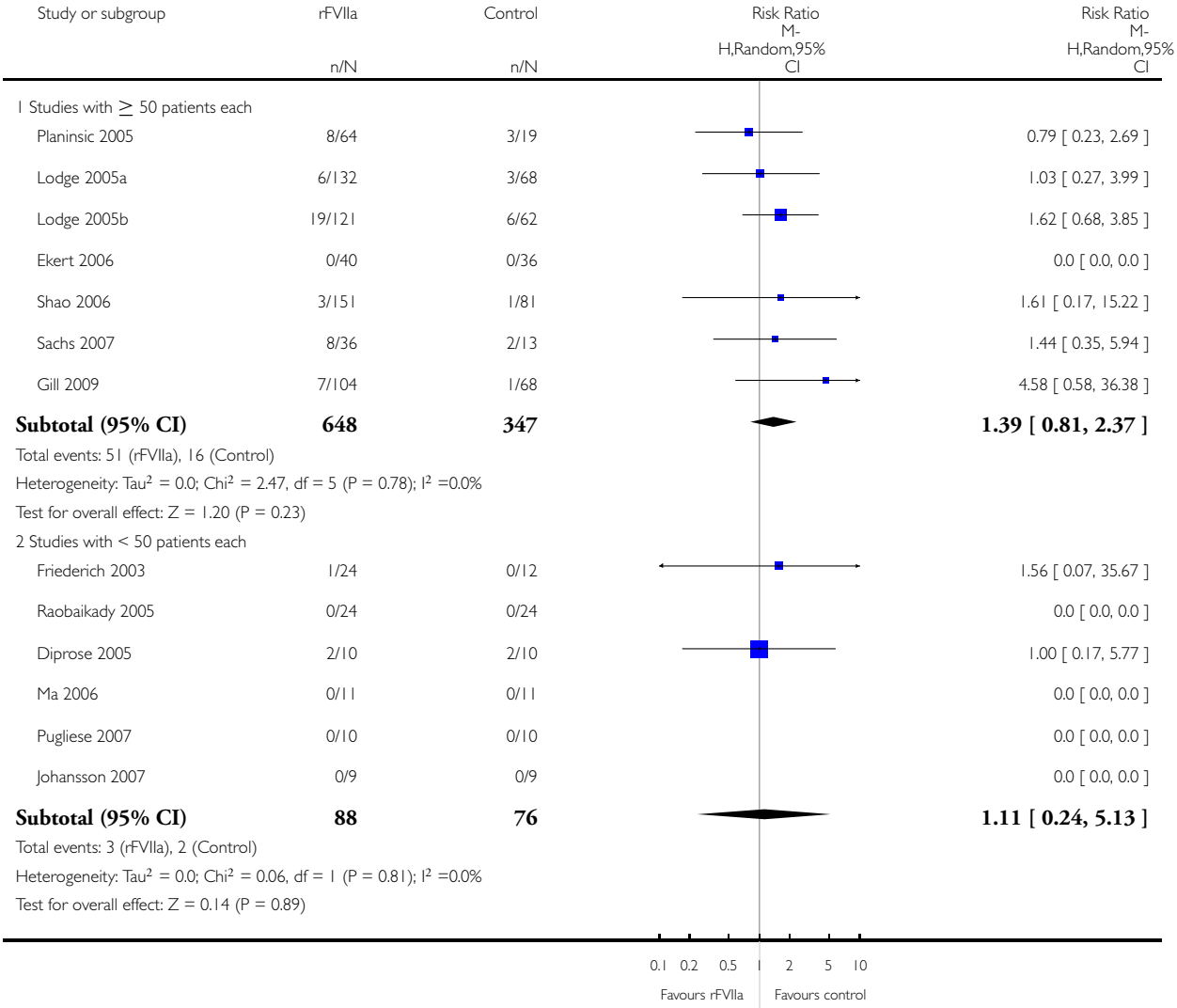


Analysis 1.10. Comparison 1 rFVIIa used prophylactically versus placebo, Outcome 10 Total thromboembolic events - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 1 rFVIIa used prophylactically versus placebo

Outcome: 10 Total thromboembolic events - exploring heterogeneity

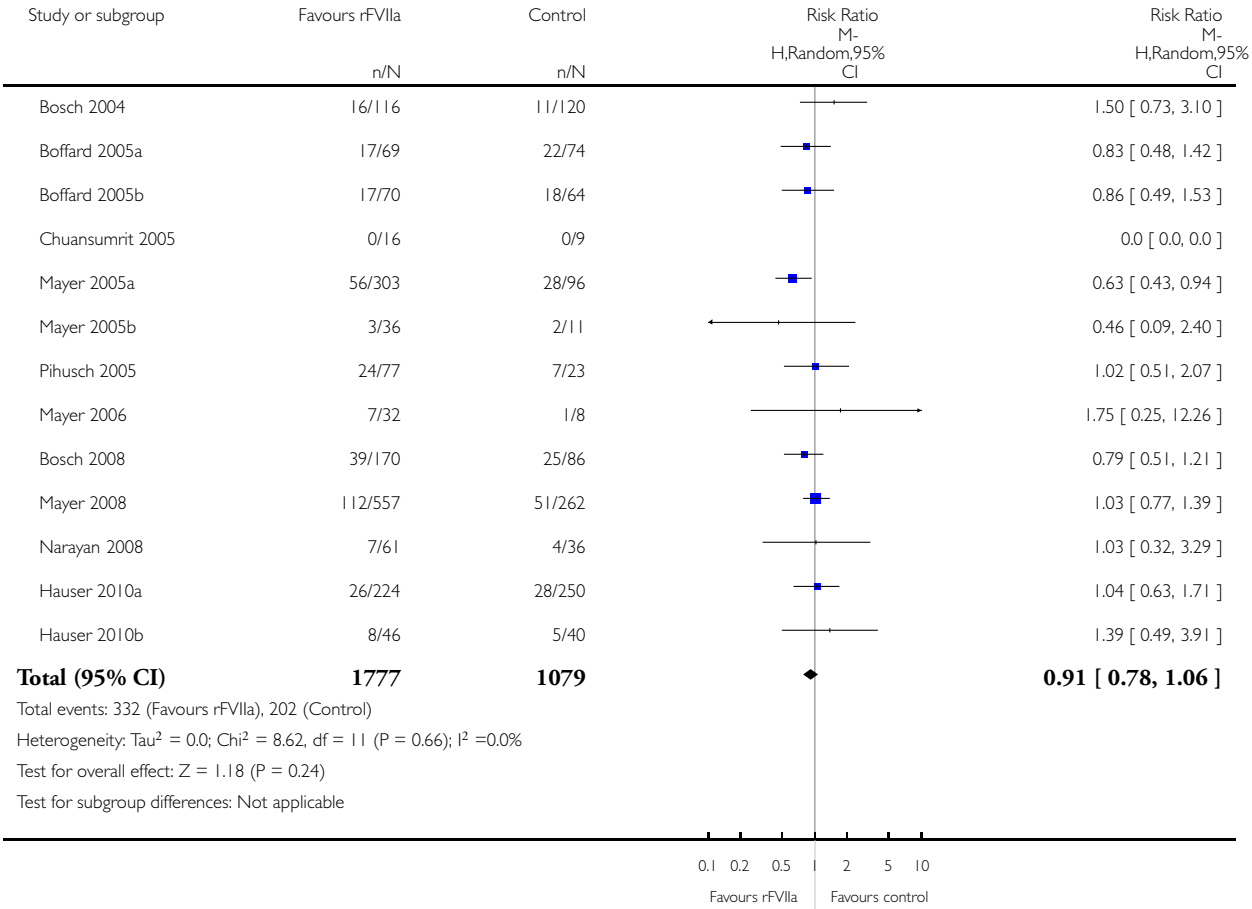


Analysis 2.1. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 1 Death.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 1 Death

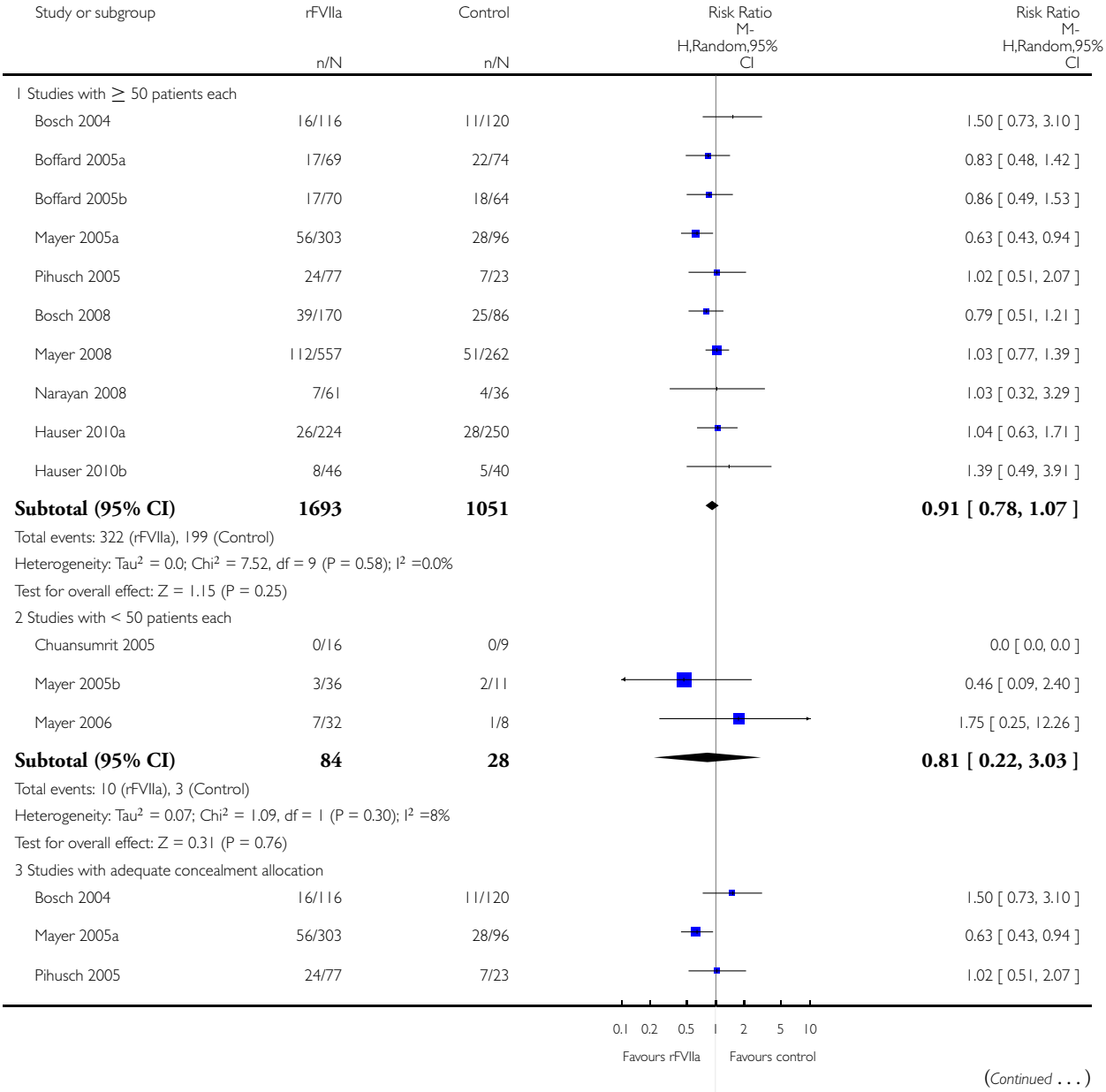


Analysis 2.2. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 2 Death - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 2 Death - exploring heterogeneity



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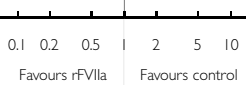
Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bosch 2008	39/170	25/86		0.79 [0.51, 1.21]
Hauser 2010a	26/221	28/247		1.04 [0.63, 1.71]
Hauser 2010b	8/46	5/40		1.39 [0.49, 3.91]
Subtotal (95% CI)	**933**	**612**		**0.90 [0.69, 1.16]**
Total events: 169 (rFVIIa), 104 (Control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.47, df = 5 (P = 0.26); I^2 =23%				
Test for overall effect: Z = 0.83 (P = 0.41)				
4 Studies with transfusion protocols				
Bosch 2004	16/116	11/120		1.50 [0.73, 3.10]
Pihusch 2005	24/77	7/23		1.02 [0.51, 2.07]
Bosch 2008	39/170	25/86		0.79 [0.51, 1.21]
Hauser 2010a	26/221	28/247		1.04 [0.63, 1.71]
Hauser 2010b	8/46	5/40		1.39 [0.49, 3.91]
Subtotal (95% CI)	**630**	**516**		**1.00 [0.77, 1.30]**
Total events: 113 (rFVIIa), 76 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.83, df = 4 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 0.00 (P = 1.0)				
5 Studies without transfusion protocols				
Boffard 2005a	17/69	22/74		0.83 [0.48, 1.42]
Boffard 2005b	17/70	18/64		0.86 [0.49, 1.53]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Mayer 2005a	56/303	28/96		0.63 [0.43, 0.94]
Mayer 2005b	3/36	2/11		0.46 [0.09, 2.40]
Mayer 2006	7/32	1/8		1.75 [0.25, 12.26]
Mayer 2008	112/557	51/262		1.03 [0.77, 1.39]
Narayan 2008	7/61	4/36		1.03 [0.32, 3.29]
Subtotal (95% CI)	**1144**	**560**		**0.86 [0.71, 1.05]**
Total events: 219 (rFVIIa), 126 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.02, df = 6 (P = 0.54); I^2 =0.0%				
Test for overall effect: Z = 1.47 (P = 0.14)				



Analysis 2.3. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 3 Control of bleeding (number of patients with reduced bleeding).

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 3 Control of bleeding (number of patients with reduced bleeding)

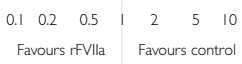
Study or subgroup	Control n/N	rFVIIa n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bosch 2004	100/119	102/118		58.3 %	0.97 [0.87, 1.08]
Chuansumrit 2005	4/9	12/16		1.1 %	0.59 [0.27, 1.30]
Pihusch 2005	13/22	44/76		4.2 %	1.02 [0.69, 1.52]
Bosch 2008	66/86	142/170		36.4 %	0.92 [0.80, 1.05]
Total (95% CI)	**236**	**380**		**100.0 %**	**0.95 [0.88, 1.03]**

Total events: 183 (Control), 300 (rFVIIa)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.00$, df = 3 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 4 Control of bleeding - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 4 Control of bleeding - exploring heterogeneity

Study or subgroup	Control n/N	rFVIIa n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Studies with ≥ 50 patients each					
Bosch 2004	100/119	102/118		59.1 %	0.97 [0.87, 1.08]
Pihusch 2005	13/22	34/56		4.0 %	0.97 [0.65, 1.46]
Bosch 2008	66/86	142/170		36.9 %	0.92 [0.80, 1.05]
Subtotal (95% CI)	**227**	**344**		**100.0 %**	**0.95 [0.88, 1.03]**
Total events: 179 (Control), 278 (rFVIIa)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.18 (P = 0.24)					

Analysis 2.5. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 5 Red cell transfusion requirements (mL).

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

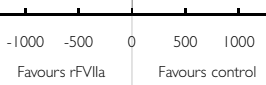
Outcome: 5 Red cell transfusion requirements (mL)

Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bosch 2004	121	450 (1110)	121	390 (570)		41.1 %	60.00 [-162.33, 282.33]
Chuansumrit 2005 (1)	16	131 (812)	9	103 (102)		16.3 %	28.00 [-375.41, 431.41]
Bosch 2008	76	764 (719)	75	990 (930)		32.1 %	-226.00 [-491.39, 39.39]
Hauser 2010a	191	2340 (3180)	228	2730 (3390)		7.3 %	-390.00 [-1020.09, 240.09]
Hauser 2010b	39	1500 (2220)	35	2040 (2070)		3.1 %	-540.00 [-1517.62, 437.62]
Total (95% CI)	**443**		**468**			**100.0 %**	**-88.60 [-263.88, 86.68]**

Heterogeneity: $Tau^2 = 6573.65$; $Chi^2 = 4.74$, df = 4 (P = 0.32); $I^2 = 16\%$

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable



(1) Data provided per kg and converted to mL according to average weights for the mean ages indicated

Analysis 2.6. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 6 Red cell transfusion requirements (mL) - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 6 Red cell transfusion requirements (mL) - exploring heterogeneity

Study or subgroup	rFVIIa N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies with ≥ 50 patients each							
Bosch 2004	121	450 (1110)	121	390 (570)		45.3 %	60.00 [-162.33, 282.33]
Bosch 2008	76	764 (719)	75	990 (930)		38.3 %	-226.00 [-491.39, 39.39]
Hauser 2010b	39	1500 (2220)	35	2040 (2070)		5.1 %	-540.00 [-1517.62, 437.62]
Hauser 2010a	191	2340 (3180)	228	2730 (3390)		11.3 %	-390.00 [-1020.09, 240.09]
Subtotal (95% CI)	**427**		**459**			**100.0 %**	**-131.20 [-360.09, 97.69]**

Heterogeneity: Tau^2 = 17265.85; Chi^2 = 4.44, df = 3 (P = 0.22); I^2 =32%

Test for overall effect: Z = 1.12 (P = 0.26)

Analysis 2.7. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 7 Number of patients transfused.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 7 Number of patients transfused

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chuansumrit 2005	5/16	3/9		0.3 %	0.94 [0.29, 3.04]
Hauser 2010a	191/224	228/250		86.4 %	0.93 [0.87, 1.00]
Hauser 2010b	39/46	35/40		13.4 %	0.97 [0.82, 1.15]
Total (95% CI)	**286**	**299**		**100.0 %**	**0.94 [0.88, 1.00]**

Total events: 235 (rFVIIa), 266 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 1.98 (P = 0.048)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 8 Total thromboembolic events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 8 Total thromboembolic events

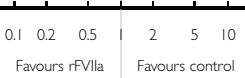
Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bosch 2004	7/121	7/121		1.00 [0.36, 2.76]
Boffard 2005a	2/69	3/74		0.71 [0.12, 4.15]
Boffard 2005b	4/70	3/64		1.22 [0.28, 5.24]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Mayer 2005a	21/303	2/96		3.33 [0.79, 13.93]
Mayer 2005b	5/36	1/11		1.53 [0.20, 11.73]
Pihusch 2005	8/77	0/23		5.23 [0.31, 87.34]
Mayer 2006	7/32	3/8		0.58 [0.19, 1.77]
Bosch 2008	9/176	7/89		0.65 [0.25, 1.69]
Mayer 2008	55/558	21/263		1.23 [0.76, 2.00]
Narayan 2008	13/61	5/36		1.53 [0.60, 3.95]
Hauser 2010a	36/224	33/250		1.22 [0.79, 1.88]
Hauser 2010b	2/46	4/40		0.43 [0.08, 2.25]
Total (95% CI)	**1789**	**1084**		**1.14 [0.89, 1.47]**

Total events: 169 (rFVIIa), 89 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.44$, df = 11 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

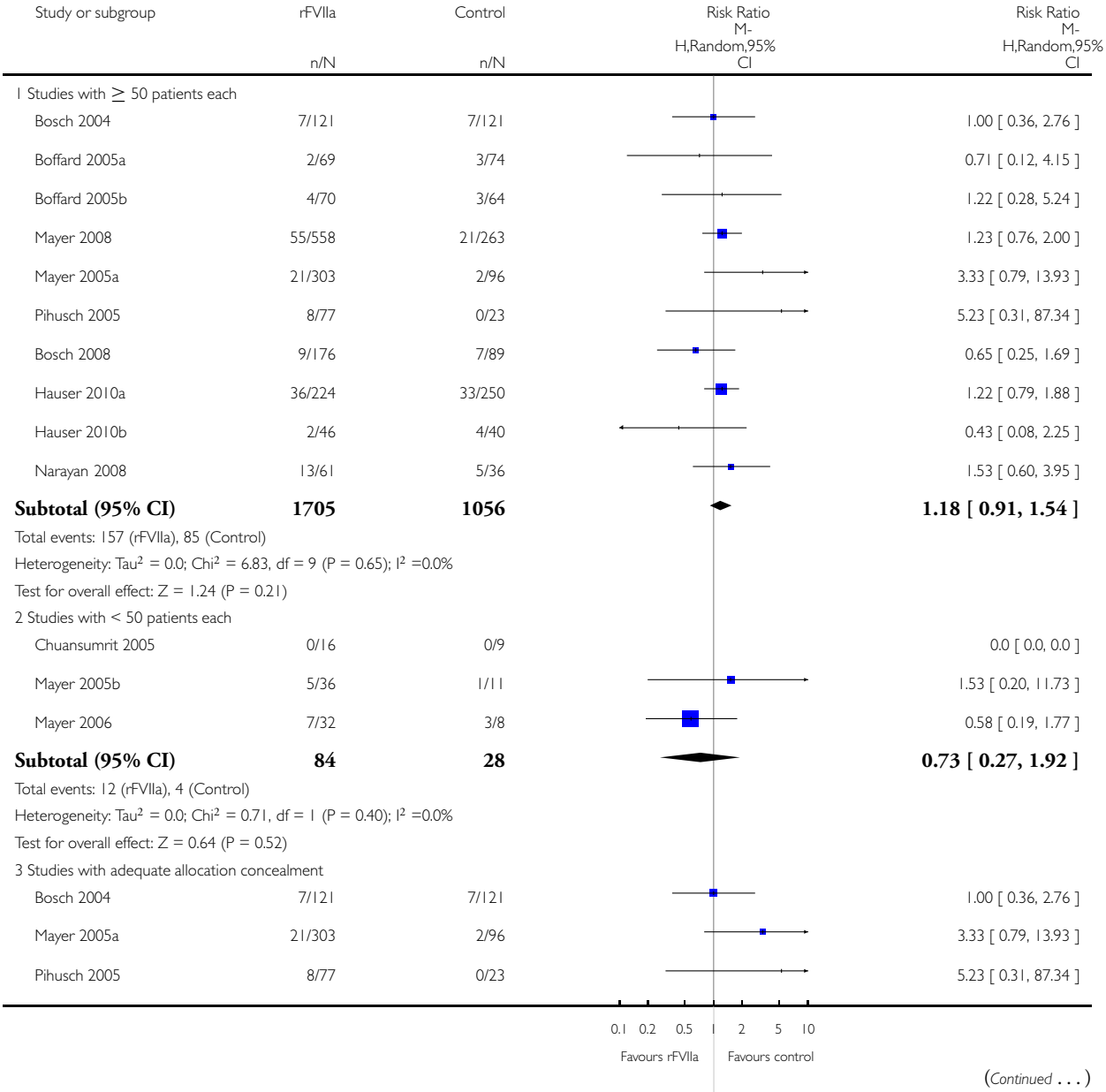


Analysis 2.9. Comparison 2 rFVIIa used therapeutically versus placebo, Outcome 9 Total thromboembolic events - exploring heterogeneity.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 2 rFVIIa used therapeutically versus placebo

Outcome: 9 Total thromboembolic events - exploring heterogeneity



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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bosch 2008	9/176	7/89		0.65 [0.25, 1.69]
Hauser 2010a	36/224	33/250		1.22 [0.79, 1.88]
Hauser 2010b	2/46	4/40		0.43 [0.08, 2.25]
Subtotal (95% CI)	**947**	**619**		**1.11 [0.70, 1.76]**
Total events: 83 (rFVIIa), 53 (Control)				
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.19$, df = 5 (P = 0.29); $I^2 = 19\%$				
Test for overall effect: Z = 0.46 (P = 0.64)				
4 Studies with transfusion protocols				
Bosch 2004	7/121	7/121		1.00 [0.36, 2.76]
Pihusch 2005	8/77	0/23		5.23 [0.31, 87.34]
Bosch 2008	9/176	7/89		0.65 [0.25, 1.69]
Hauser 2010a	36/224	33/250		1.22 [0.79, 1.88]
Hauser 2010b	2/46	4/40		0.43 [0.08, 2.25]
Subtotal (95% CI)	**644**	**523**		**1.06 [0.74, 1.52]**
Total events: 62 (rFVIIa), 51 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.78$, df = 4 (P = 0.44); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.32 (P = 0.75)				

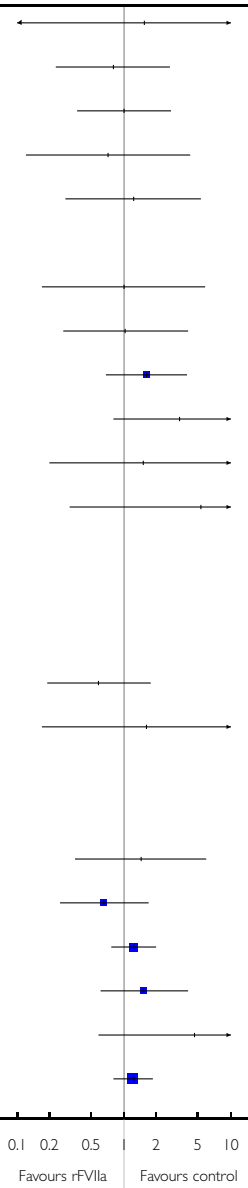
Analysis 3.1. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 1 Total thromboembolic events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 1 Total thromboembolic events

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Friederich 2003	1/24	0/12		1.56 [0.07, 35.67]
Planinsic 2005	8/64	3/19		0.79 [0.23, 2.69]
Bosch 2004	7/121	7/121		1.00 [0.36, 2.76]
Boffard 2005a	2/69	3/74		0.71 [0.12, 4.15]
Boffard 2005b	4/70	3/64		1.22 [0.28, 5.24]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Diprose 2005	2/10	2/10		1.00 [0.17, 5.77]
Lodge 2005a	6/132	3/68		1.03 [0.27, 3.99]
Lodge 2005b	19/121	6/62		1.62 [0.68, 3.85]
Mayer 2005a	21/303	2/96		3.33 [0.79, 13.93]
Mayer 2005b	5/36	1/11		1.53 [0.20, 11.73]
Pihusch 2005	8/77	0/23		5.23 [0.31, 87.34]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Mayer 2006	7/32	3/8		0.58 [0.19, 1.77]
Shao 2006	3/151	1/81		1.61 [0.17, 15.22]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	8/36	2/13		1.44 [0.35, 5.94]
Bosch 2008	9/176	7/89		0.65 [0.25, 1.69]
Mayer 2008	55/558	21/263		1.23 [0.76, 2.00]
Narayan 2008	13/61	5/36		1.53 [0.60, 3.95]
Gill 2009	7/104	1/68		4.58 [0.58, 36.38]
Hauser 2010a	36/224	33/250		1.22 [0.79, 1.88]



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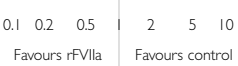
Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hauser 2010b	2/46	4/40		0.43 [0.08, 2.25]
Total (95% CI)	**2525**	**1507**		**1.18 [0.94, 1.48]**

Total events: 223 (rFVIIa), 107 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.40$, df = 19 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 2 Cardiovascular events, including myocardial infarction.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 2 Cardiovascular events, including myocardial infarction

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Planinsic 2005	1/64	0/19		0.92 [0.04, 21.78]
Friederich 2003	1/24	0/12		1.56 [0.07, 35.67]
Bosch 2004	0/121	0/121		0.0 [0.0, 0.0]
Boffard 2005a	0/69	0/74		0.0 [0.0, 0.0]
Boffard 2005b	0/70	0/64		0.0 [0.0, 0.0]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Diprose 2005	1/10	1/10		1.00 [0.07, 13.87]
Lodge 2005a	2/132	0/68		2.59 [0.13, 53.28]
Lodge 2005b	10/121	2/62		2.56 [0.58, 11.33]
Mayer 2005a	7/303	0/96		4.79 [0.28, 83.04]

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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Mayer 2005b	4/36	0/11		2.92 [0.17, 50.37]
Pihusch 2005	2/77	0/23		1.54 [0.08, 30.95]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Mayer 2006	4/32	2/8		0.50 [0.11, 2.26]
Shao 2006	1/151	0/81		1.62 [0.07, 39.28]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	7/36	2/13		1.26 [0.30, 5.32]
Bosch 2008	3/176	0/89		3.56 [0.19, 68.16]
Mayer 2008	25/558	8/263		1.47 [0.67, 3.22]
Narayan 2008	5/61	3/36		0.98 [0.25, 3.87]
Gill 2009	0/104	1/68		0.22 [0.01, 5.30]
Total (95% CI)	**2255**	**1217**		**1.35 [0.85, 2.15]**

Total events: 73 (rFVIIa), 19 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.78$, df = 14 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

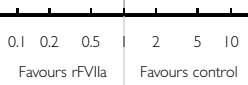
Analysis 3.3. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 3 Stroke.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 3 Stroke

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Planinsic 2005	0/64	0/19		0.0 [0.0, 0.0]
Friederich 2003	0/24	0/12		0.0 [0.0, 0.0]
Bosch 2004	2/121	0/121		5.00 [0.24, 103.07]
Boffard 2005a	0/69	0/74		0.0 [0.0, 0.0]
Boffard 2005b	1/70	1/64		0.91 [0.06, 14.32]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Diprose 2005	1/10	1/10		1.00 [0.07, 13.87]
Lodge 2005a	0/132	0/68		0.0 [0.0, 0.0]
Mayer 2005a	9/303	0/96		6.06 [0.36, 103.21]
Mayer 2005b	0/36	0/11		0.0 [0.0, 0.0]
Pihusch 2005	2/77	0/23		1.54 [0.08, 30.95]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Mayer 2006	0/32	1/8		0.09 [0.00, 2.05]
Shao 2006	0/151	0/81		0.0 [0.0, 0.0]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	1/36	0/13		1.14 [0.05, 26.25]
Bosch 2008	0/176	0/89		0.0 [0.0, 0.0]
Mayer 2008	14/558	4/263		1.65 [0.55, 4.96]
Narayan 2008	1/61	1/36		0.59 [0.04, 9.15]
Gill 2009	4/104	0/68		5.91 [0.32, 108.12]
Total (95% CI)	**2134**	**1155**		**1.49 [0.72, 3.07]**
Total events: 35 (rFVIIa), 8 (Control)				



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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.36, df = 9 (P = 0.70); I^2 =0.0%				
Test for overall effect: Z = 1.07 (P = 0.28)				
Test for subgroup differences: Not applicable				

Analysis 3.4. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 4 Total arterial events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 4 Total arterial events

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Planinsic 2005	6/64	2/19		0.89 [0.20, 4.06]
Friederich 2003	1/24	0/12		1.56 [0.07, 35.67]
Bosch 2004	2/121	0/121		5.00 [0.24, 103.07]
Boffard 2005a	1/69	0/74		3.21 [0.13, 77.60]
Boffard 2005b	2/70	1/64		1.83 [0.17, 19.69]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Diprose 2005	2/10	2/10		1.00 [0.17, 5.77]
Lodge 2005a	2/132	0/68		2.59 [0.13, 53.28]
Mayer 2005a	16/303	0/96		10.53 [0.64, 173.88]
Mayer 2005b	4/36	0/11		2.92 [0.17, 50.37]
Pihusch 2005	5/77	0/23		3.38 [0.19, 59.02]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]

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Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Mayer 2006	4/32	3/8		0.33 [0.09, 1.20]
Shao 2006	1/151	0/81		1.62 [0.07, 39.28]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	8/36	2/13		1.44 [0.35, 5.94]
Bosch 2008	3/176	0/89		3.56 [0.19, 68.16]
Mayer 2008	39/558	11/263		1.67 [0.87, 3.21]
Narayan 2008	6/61	4/36		0.89 [0.27, 2.93]
Gill 2009	4/104	1/68		2.62 [0.30, 22.90]
Hauser 2010a	16/224	11/250		1.62 [0.77, 3.42]
Hauser 2010b	2/46	1/40		1.74 [0.16, 18.47]
Total (95% CI)	**2404**	**1445**		**1.45 [1.02, 2.05]**

Total events: 124 (rFVIIa), 38 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.34$, df = 18 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 5 Total venous events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 5 Total venous events

Study or subgroup	rFVIIa n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Planinsic 2005	2/64	1/19		0.59 [0.06, 6.20]
Friederich 2003	0/24	0/12		0.0 [0.0, 0.0]
Bosch 2004	5/121	7/121		0.71 [0.23, 2.19]
Boffard 2005a	1/69	3/74		0.36 [0.04, 3.36]
Boffard 2005b	2/70	2/64		0.91 [0.13, 6.30]
Chuansumrit 2005	0/16	0/9		0.0 [0.0, 0.0]
Diprose 2005	0/10	0/10		0.0 [0.0, 0.0]
Lodge 2005a	4/132	3/68		0.69 [0.16, 2.98]
Mayer 2005a	4/303	2/96		0.63 [0.12, 3.41]
Mayer 2005b	1/36	1/11		0.31 [0.02, 4.49]
Pihusch 2005	3/77	0/23		2.15 [0.12, 40.24]
Raobaikady 2005	0/24	0/24		0.0 [0.0, 0.0]
Ekert 2006	0/40	0/36		0.0 [0.0, 0.0]
Ma 2006	0/11	0/11		0.0 [0.0, 0.0]
Mayer 2006	3/32	0/8		1.91 [0.11, 33.67]
Shao 2006	2/151	1/81		1.07 [0.10, 11.65]
Johansson 2007	0/9	0/9		0.0 [0.0, 0.0]
Pugliese 2007	0/10	0/10		0.0 [0.0, 0.0]
Sachs 2007	0/36	0/13		0.0 [0.0, 0.0]
Bosch 2008	6/176	7/89		0.43 [0.15, 1.25]
Mayer 2008	17/558	11/263		0.73 [0.35, 1.53]
Narayan 2008	7/61	1/36		4.13 [0.53, 32.23]
Gill 2009	3/104	0/68		4.60 [0.24, 87.67]
Hauser 2010a	29/224	24/250		1.35 [0.81, 2.25]
Hauser 2010b	0/46	4/40		0.10 [0.01, 1.75]

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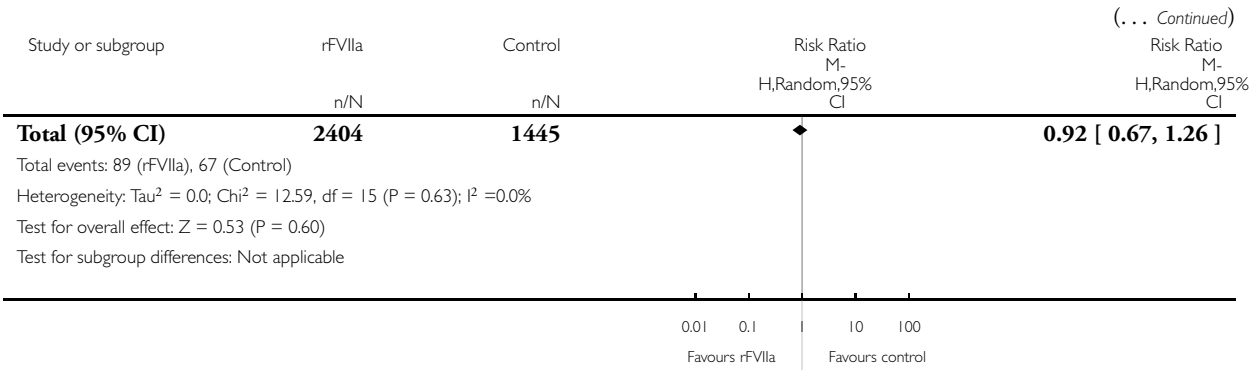

ADDITIONAL TABLES

Table 1. Status of ongoing studies from 2007 Cochrane review

Author	Population	Expected enrolment	Primary outcome	Start date	Status as of 23 March 2011
Arai 2005	Spontaneous ICH	90	TE serious adverse events to 90 days	January 2006	Completed but not yet published
Della Corte 2006	Post-surgical evaluation of intracerebral haematoma	Not stated	Postoperative rebleeding after surgery	Jan 2005	See Imberti 2005
Gaspar-Blaudschun 2004	Post-cardiac surgery	Not stated	Serious adverse events within 30 days	October 2004 to November 2007	Completed. See Gill 2009.
Gris 2006	Post-partum haemorrhage refractory to other treatment	Not stated	Intensity of haemorrhage before and after VIIa; units transfused	December 2006	Recruiting
Imberti 2005	Post-surgical evaluation of intracerebral haematoma	Not stated	Postoperative rebleeding after surgery	Jan 2005 to December 2008	Completed but not yet published
Iorio 2006	ICH in setting of oral anticoagulants or antiplatelets	Not stated	Change in ICH volume at 24 hours	September 2005	Recruiting
Kelleher 2006	Post-cardiac surgery	Not stated	Critical serious adverse events	2006	Completed but not yet published

Table 1. Status of ongoing studies from 2007 Cochrane review (*Continued*)

McCall 2005	Complex cardiac surgery as salvage treatment	40	Adequate haemostasis to enable chest closure	June 2005	Recruiting
Molter 2005	Burn excision and grafting	52	Perioperative blood loss and transfusion	January 2006	Recruiting
Ng 2006	ECMO patients post-cardiac surgery	Not stated	Postoperative bleeding and transfusion	April 2004	Status unknown
Tortella 2006	Trauma	1502	Mortality and morbidity through day 30	May 2006	Terminated early. See Hauser 2010a and Hauser 2010b

EMCO = extracorporeal membrane oxygenation; ICH = intracranial haemorrhage; TE = thromboembolic

Table 2. Prophylactic RCT - overview

Study	Participants	N	Intervention	Co-Intervention(s)	Primary outcome
Diprose 2005	Complex non-coronary cardiac surgery requiring CPB	20	1 dose of 90 µg/kg rFVIIa iv	Transfusion for Hb < 8.5 g/dL Intraoperative cell salvage Aprotinin Protamine for heparin reversal	Number of patients receiving allogeneic transfusion
Ekert 2006	Infants < 1 year with congenital heart disease requiring CPB	82	First dose of 40 µg/kg rFVIIa iv; repeated up to 2 times if ongoing bleeding	No transfusion protocol stated Protamine for heparin reversal	Time to chest closure after reversal of heparin and transfusion requirements
Essam 2007	Elective cardiac revascularisation requiring CPB	30	1 dose of 90 µg/kg rFVIIa iv	Transfusion for Hb < 7 g/dL Intraoperative cell salvage Protamine for heparin reversal	No stated primary outcome but blood loss and transfusion requirements measured
Friederich 2003	Retropubic prostatectomy	36	1 dose of 20 µg/kg or 40 µg/kg rFVIIa iv	Transfusion for Hb < 8 g/dL intraoperatively and < 10 g/dL postoperatively LMWH postoperatively	Blood loss and transfusion requirements
Gill 2009	Adult patients undergoing cardiac surgery requir-	179	1 dose of 40 µg/kg or 80 µg/kg of rFVIIa	Clearly defined transfusion protocol to maintain Hb > 8.0 g/dL	Death, cerebral infarction, myocardial infarction, pulmonary em-

Table 2. Prophylactic RCT - overview (*Continued*)

	ing CPB				bolism and other thromboembolic events
Hanna 2010	Paediatric patients of ASA class I and II with congenital craniofacial malformation undergoing reconstructive surgery	45	First dose of 100 μg/kg at hour 0 over 15 minutes followed by infusion of 10 μg/kg/h until skin closure	Transfusion for Hb < 9 g/dL. However, blood transfusion was instituted immediately whenever severe blood loss occurred or was anticipated	Primary endpoints were not clearly stated, but perioperative blood loss and transfusion requirements measured
Jeffers 2002	Cirrhosis and coagulopathy undergoing laparoscopic liver biopsy	66	1 dose of 5 μg/kg, 20 μg/kg, 80 μg/kg or 120 μg/kg rFVIIa iv	No transfusion protocol stated	Time to haemostasis and duration of normal PT
Johansson 2007	Thermal burn undergoing skin excision and grafting	18	First dose of 40 μg/kg rFVIIa iv; 2nd dose given at 90 minutes later	Transfusion for Hb < 10 g/dL; platelet count < 80 x 10^9/L; and FFP in 1:1 ratio to RBCs for microvascular bleeding LMWH postoperatively	Transfusion requirements
Lodge 2005a	Partial hepatectomy	204	First dose of 20 μg/kg or 80 μg/kg rFVIIa iv; 2nd dose given at 5 hours if operation longer than 6 hours	Transfusion for Hct < 25% and platelet count < 30 x 10^9/L LMWH postoperatively	Number of patients receiving allogeneic transfusion
Lodge 2005b	Liver transplantation	209	First dose of 60 μg/kg or 120 μg/kg rFVIIa iv; repeated every 2 hours until end of surgery	Transfusion for Hct < 25%, platelet count < 30 x 10^9/L; and coagulation ratios > 1.5 times normal	Transfusion requirements
Ma 2006	Cardiac valve replacement requiring CPB	22	1 dose of 40 μg/kg rFVIIa iv	No transfusion protocol stated Protamine for heparin reversal	No stated primary outcome but blood loss and transfusion requirements measured
Planinsic 2005	Liver transplantation	87	1 dose of 20 μg/kg, 40 μg/kg or 80 μg/kg rFVIIa iv	Transfusion for Hct < 25%, platelet count < 30 x 10^9/L; and coagulation ratios > 1.5 times normal	Transfusion requirements
Pugliese 2007	Liver transplantation	20	1 dose of 40 μg/kg rFVIIa iv	Transfusion for Hb < 10g/dL and INR > 1.5	No stated primary outcome but blood loss and transfusion requirements measured

Table 2. Prophylactic RCT - overview (*Continued*)

Raobaikady 2005	Reconstructive surgery for traumatic pelvic fractures	48	First dose of 90 µg/kg rFVIIa iv; 2nd dose given at 2 hours if ongoing bleeding	Transfusion for Hb < 8 g/dL; platelet count < 100 x 10^9/L; and coagulation ratios > 1.5 times normal Intraoperative cell salvage LMWH perioperatively	Blood loss
Sachs 2007	Spinal fusion surgery	60	First dose of 30 µg/kg, 60 µg/kg or 120 µg/kg rFVIIa iv at dosing trigger; repeated in 2 and 4 hours after initial dose	Transfusion for Hb < 9 g/dL; platelet count < 75 x 10^9/L; and coagulation ratios > 1.5 times normal Topical haemostatic agents	Adverse events and blood loss
Shao 2006	Partial hepatectomy	235	First dose of 50 µg/kg or 100 µg/kg rFVIIa iv; repeated every 2 hours until end of surgery to maximum of 4 doses	Transfusion if RBC loss > 500 mL Aprotinin if critical bleeding	Number of patients receiving allogeneic transfusion and transfusion requirements

CPB = cardiopulmonary bypass; Hb = haemoglobin; Hct = haematocrit; INR = international normalised ratio; iv = intravenous; LMWH = low molecular weight heparin; N = number of patients randomised; RBC = red blood cell; rFVIIa = recombinant factor VIIa

Table 3. Therapeutic RCT - overview

Study	Participants	N	Intervention	Co-intervention(s)	Primary outcome
Boffard 2005a	Blunt trauma	158	First dose of 200 µg/kg rFVIIa iv; repeated doses of 100 µg/kg at 1 and 3 hours after initial dose	No transfusion protocol stated	Transfusion requirements
Boffard 2005b	Penetrating trauma	143	First dose of 200 µg/kg rFVIIa iv; repeated doses of 100 µg/kg at 1 and 3 hours after initial dose	No transfusion protocol stated	Transfusion requirements
Bosch 2004	Upper gastrointestinal haemorrhage in patients with cirrhosis	245	First dose of 100 µg/kg rFVIIa iv; repeated doses at 2, 4, 6, 12, 18, 24 and 30 hours after initial dose	Transfusion to maintain Hct 25% to 30% Vasoactive therapy Endoscopic therapy	Combined endpoint of control of bleeding or rebleeding or death
Bosch 2008	Upper gastrointestinal haemorrhage in patients with cirrhosis	265	First dose 200 µg/kg rFVIIa iv; repeated doses at 2, 8, 14 and 20 hours after initial dose; or repeat	Transfusion to maintain Hct 25% to 30% and for platelet count < 30 x 10^9/L	Combined endpoint of control of bleeding or rebleeding or death

Table 3. Therapeutic RCT - overview (*Continued*)

			dose 2 hours after initial dose	Vasoactive therapy Endoscopic therapy Prophylactic antibiotic therapy	
Chuansumrit 2005	Children with dengue haemorrhagic fever	28	First dose of 100 µg/kg rFVIIa iv; repeated dose at 30 minutes if ongoing bleeding	No transfusion protocol stated Nasal packing for epistaxis Ranitidine or omeprazole	Change in bleeding
Hauser 2010a	Adult patients who had sustained blunt trauma	481	First dose of 200 μg/kg of rFVIIa at 0 hour; repeated doses of 100 μg/kg at 1 hour and 3 hours	Evidence-based guidelines and protocols to maintain Hb 8 to 10 g/dL for first 24 hours and Hb > 7 g/dL thereafter (unless haemodynamically unstable) Platelets to maintain > 50 x 10^9/L and FFP/cryoprecipitate to maintain INR < 1.5 or if bleeding	1st tier endpoint was superiority in all-cause 30-day mortality in blunt trauma. If not met, the 2nd tier primary conditional endpoint of non-inferiority of mortality and superiority on durable morbidity was applied
Hauser 2010b	Adult patients who had sustained penetrating trauma	92	First dose of 200 μg/kg of rFVIIa at 0 hour; repeated doses of 100 μg/kg at 1 hour and 3 hours	Evidence-based guidelines and protocols to maintain Hb 8 to 10 g/dL for first 24 hours and Hb > 7 g/dL thereafter (unless haemodynamically unstable) Platelets to maintain > 50 x 10^9/L and FFP/cryoprecipitate to maintain INR < 1.5 or if bleeding	1st tier endpoint was superiority in all-cause 30-day mortality in blunt trauma. If not met, the 2nd tier primary conditional endpoint of non-inferiority of mortality and superiority on durable morbidity was applied
Mayer 2005a	Spontaneous ICH	400	1 dose of 40 µg/kg, 80 μg/kg or 160 μg/kg of rFVIIa iv	No transfusion protocol stated Medical management following AHA guidelines	Change in volume of ICH
Mayer 2005b	Spontaneous ICH	48	1 dose of 10 µg/kg, 20 μg/kg, 40 μg/kg, 80 μg/kg, 120 μg/kg or 160 μg/kg of rFVIIa iv	No transfusion protocol stated Medical management following AHA guidelines	Adverse events

Table 3. Therapeutic RCT - overview (*Continued*)

Mayer 2006	Spontaneous ICH	41	1 dose of 5 μg/kg, 20 μg/kg, 40 μg/kg or 80 μg/kg of rFVIIa iv	No transfusion protocol stated Medical management following AHA guidelines	Adverse events
Mayer 2008	Spontaneous ICH	841	1 dose of 20 μg/kg or 80 μg/kg of rFVIIa iv	No transfusion protocol stated Medical management following AHA guidelines	Severe disability or death
Narayan 2008	Traumatic ICH	97	1 dose of 40 μg/kg, 80 μg/kg, 120 μg/kg, 160 μg/kg or 200 μg/kg of rFVIIa iv	No transfusion protocol stated	Adverse events
Pihusch 2005	Post-haematopoietic stem cell transplantation	100	First dose of 40 μg/kg, 80 μg/kg or 160 μg/kg; repeated every 6 hours x 6 doses	Transfusion for Hb < 8 g/dL and platelet count < 20 x 10^9/L (< 75 x 10^9/L in haemorrhagic cystitis or diffuse alveolar haemorrhage) Heparin, defibrotide, NSAIDs	Change in bleeding

AHA = American Heart Association; FFP = fresh frozen plasma; Hb = haemoglobin; Hct = haematocrit; ICH = intracranial haemorrhage; INR = international normalised ratio; iv = intravenous; N = number of patients randomised; NSAID = non-steroidal anti-inflammatory drug; rFVIIa = recombinant factor VIIa

APPENDICES

Appendix 1. CENTRAL search strategy (*The Cochrane Library*)

#1 FACTOR VIIA single term (MeSH)
#2 factor viia OR factor 7a OR rfviia OR fviia
#3 (activated NEAR/2 factor seven) OR (activated NEAR/2 factor vii) OR (activated NEAR/2 rfvii) OR (activated NEAR/2 fvii)
#4 novoseven* OR novo seven* OR eptacog* OR proconvertin* or novo7
#5 (factor seven OR factor vii OR factor 7):ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 HEMORRHAGE explode all trees (MeSH)
#8 hemorrhag* or haemorrhag* OR bleed* OR bloodloss* OR blood NEAR/3 los* OR ICH
#9 HEMOSTASIS explode all trees (MeSH)
#10 hemosta* OR haemosta* OR surg* or operat* OR perioperat* OR resect* OR transplant* OR *tomy OR trauma* or transfus* or emergenc* or polytrauma* or injur* or accident*
#11 #7 OR #8 OR #9 OR #10

#12 #6 AND #11

Appendix 2. MEDLINE (Ovid) search strategy

1. FACTOR VIIA/
2. (factor viia OR factor 7a OR rfviia OR fviia).tw.
3. ((activated adj2 factor seven) OR (activated adj2 factor vii) OR (activated adj3 rfvii) OR (activated adj2 fvii)).tw.
4. (novoseven* OR novo seven* OR eptacog* OR proconvertin OR novo7).tw.
5 (factor seven OR factor vii OR factor 7).ti.
6. or/1-5
7. exp HEMORRHAGE/
8. (hemorrhag* OR haemorrhag* OR bleed* or bloodloss* or blood loss* OR ICH).tw.
9. exp HEMOSTASIS/
10. (hemosta* OR haemosta* or surg* or operat* or resect* or perioperat* or trauma* or transfus* or emergenc* or polytrauma* or injur* or accident*).tw.
11. or/7-10
12. 6 AND 11

Appendix 3. EMBASE (Ovid) search strategy

1. BLOOD CLOTTING FACTOR 7A/
2. (factor viia OR factor 7a OR rfviia OR fviia).mp.
3. ((activated adj3 factor seven) OR (activated adj3 factor vii) OR (activated adj3 rfvii) OR (activated adj3 fvii)).mp.
4. (novoseven* OR novo ADJ seven* OR eptacog* OR proconvertin).mp.
5. or/1-4
6. exp BLEEDING/
7. (hemorrhag* OR haemorrhag* OR bleed* or bloodloss* or blood near los* OR ICH).mp.
8. HEMOSTASIS/
9. (hemosta* or haemosta*).mp.
10. (surg* or operat* or resect* or perioperat* or trauma* or transfus* or emergenc* or polytrauma* or injur* or accident*).mp.
11. or/6-10
12. 5 AND 11

Appendix 4. CINAHL (NHS Evidence) search strategy

1. (factor AND viia OR factor AND 7a OR rfviia OR fviia).ti,ab
2. ((activated adj2 factor seven) OR (activated adj2 factor vii) OR (activated adj3 rfvii) OR (activated adj2 fvii)).ti,ab
3. (novoseven* OR novo AND seven* OR eptacog* OR proconvertin or novo7).ti,ab
4. (factor seven OR factor vii OR factor 7).ti
5. 1 OR 2 OR 3 OR 4
6. exp HEMORRHAGE/
7. (hemorrhag* OR haemorrhag* OR bleed* OR bloodloss* OR blood AND loss* OR ICH).ti,ab
8. exp HEMOSTASIS/
9. (hemosta* OR haemosta* OR surg* OR operat* OR resect* OR perioperat* OR trauma* OR transfus* OR emergenc* OR polytrauma* OR injur* OR accident*).ti,ab
10. 6 OR 7 OR 8 OR 9
11. 5 AND 10

Appendix 5. OTHER STRATEGIES

PUBMED
("activated factor vii" OR "activated factor seven" OR "recombinant factor vii" OR "factor viia" OR rfviia OR fviia OR "activated rfvii" OR "activated fvii") AND (randomi* OR randomly OR trial OR groups)
LILACS/KoreaMed/IndMed/PakMediNet
factor viia OR activated factor vii OR activated fvii OR activated rfvii OR rfviia OR fviia OR novoseven OR novo seven
TRANSFUSION EVIDENCE LIBRARY/ISRCTN REGISTER/WHO ICTRP Database/EUDRACT (EU Clinical Trials Register)/ClinicalTrials.gov
"factor viia" OR "factor seven" OR rfviia OR fviia OR novoseven OR "activated factor seven" OR "activated factor vii" OR "activated rfvii" OR "activated fvii"

WHAT'S NEW

Last assessed as up-to-date: 23 March 2011.

Date	Event	Description
23 March 2011	New search has been performed	The search for studies was updated to 23 March 2011.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 2, 2007

Date	Event	Description
12 September 2011	New citation required but conclusions have not changed	The search was updated to 23 March 2011. Four new trials have been included in the review. The Results and Discussion sections have been amended accordingly. The authors of the review have changed
29 July 2009	New search has been performed	The search was updated to 25 February 2009. Twelve new trials have been included in the review. The Results and Discussion sections have been amended accordingly. The authors of the review have changed
1 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

CAROLYN DOREE: Searching and protocol development.

SIMON STANWORTH: Protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and content expert.

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CHRIS HYDE: Methodological quality assessment, data extraction and analysis expert.

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DECLARATIONS OF INTEREST

Yulia Lin: The author is a study site investigator for a registry on the off-label use of rFVIIa in Canada funded by an unrestricted educational grant from Novo Nordisk but receives no personal financial payments for participation in the registry.

Chris Hyde was an employee of NHS Blood and Transplant when this review was commenced. This arrangement ended in 2009.

The other authors have no declarations of interest.

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External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

*Hemophilia A; Coagulants [*therapeutic use]; Erythrocyte Transfusion [utilization]; Factor VIIa [*therapeutic use]; Hemorrhage [*drug therapy; mortality; *prevention & control]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]

MeSH check words

Humans