

# The Efficacy of Recombinant Activated Factor VII in Severe Trauma

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**Study objective:** The use of recombinant activated factor VII (rFVIIa) in severe trauma is controversial. This evidence-based emergency medicine review evaluates the existing evidence about the efficacy and safety of rFVIIa for the management of severe trauma.

**Methods:** We searched MEDLINE, EMBASE, the Cochrane Library, and other databases. We limited our review to prospective, controlled trials that involved the therapeutic use of rFVIIa in the emergency department phase of care. We included studies with blunt and penetrating severe trauma. The primary outcome measure of interest was mortality. Secondary patient-important outcome measures included neurologic outcome, delayed surgical intervention, and adverse effects. Standard criteria were used to evaluate the quality of published trials.

**Results:** One randomized, blinded trial met the inclusion criteria. There was no significant difference in mortality or adverse effects between rFVIIa and placebo. Our other selected secondary outcome measures of interest were not reported.

**Conclusion:** Existing evidence suggests that there is no significant difference in mortality between rFVIIa and placebo. Further research is needed to better understand the efficacy and safety of rFVIIa in patients with severe trauma. [Ann Emerg Med. 2009;54:737-744.]

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## CLINICAL SCENARIO

You are the attending physician in a community emergency department (ED). You are beginning your shift and are receiving a sign-out on a 28-year-old man who was involved in a high-speed motor vehicle crash and has experienced multiple rib fractures, bilateral femur fractures, bilateral pneumothoraces, and a grade 1 splenic injury. The patient is intubated and has bilateral chest tubes. He has received multiple units of packed RBCs and fresh frozen plasma and is awaiting transfer to the regional tertiary trauma center. His pregnant wife and his daughter are waiting apprehensively outside of the trauma bay. The accepting trauma surgeon has suggested the use of recombinant activated factor VII (rFVIIa) before transfer, suggesting that this treatment might improve bleeding-related outcomes for this patient. You know that rFVIIa was developed and approved by Food and Drug Administration for the treatment of bleeding episodes in patients with hemophilia who develop antibodies to factor VIII.<sup>1</sup> You are aware that it has also been used off label in a number of bleeding conditions.<sup>2-6</sup> However, neither you nor your colleague who initially treated the patient has administered this medication before. Therefore, you decide to examine the evidence about the use of rFVIIa for severe trauma.

The following evidence-based emergency medicine review seeks an answer to the question posed by this scenario.

## FORMULATING THE QUESTION

Our goal was to investigate the use of rFVIIa in patients with severe trauma. Emergency physicians are at the front line of caring for these patients, and resuscitation of this population is highly relevant to the practice of emergency medicine. To remain focused on a patient population that might be considered for treatment with rFVIIa, we addressed specific patient characteristics, including preexisting coagulopathy, mechanism of injury, and severity of injury.

We excluded studies that focused on patients with preexisting hypocoagulable states such as hemophilia or patients receiving warfarin because of their biological uniqueness.<sup>1,7-10</sup> rFVIIa is licensed and in wide use in patients with hemophilia with inhibitory alloantibodies to factor VIII.<sup>1</sup> Previous reviews have also analyzed patients with and without preexisting hypocoagulable states separately.<sup>11,12</sup>

The coagulopathy after trauma has largely been attributed to dilution from intravenous fluid therapy and massive transfusion, as well as physiologic components such as hypothermia and acidosis.<sup>13</sup> It has also been suggested that the injury itself is associated with coagulopathy caused by the release of mediators

from damaged tissues.<sup>14</sup> Specific injuries such as burns,<sup>15</sup> long bone fractures,<sup>16</sup> and head trauma<sup>14</sup> have been associated with an increased risk of traumatic coagulopathy. However, there is inadequate evidence indicating whether patients with different mechanisms of injury (eg, blunt versus penetrating) experience coagulopathy or would respond differently to its treatment. Given the inadequacy of pathophysiologic knowledge in this area, we were inclined to consider evidence from both penetrating and blunt trauma settings to be relevant to our question about the efficacy of rFVIIa.

We were interested in the benefits of using rFVIIa in patients with severe trauma. Patients with minor or non-life-threatening injuries generally do not require aggressive interventions and frequently have acceptable recovery and desirable outcomes with minor interventions or observation alone. However, there is no standard definition for severe trauma, and it has been defined in the literature in various manners. Some investigators have used trauma scoring systems based on the anatomic classification of injuries (eg, Injury Severity Score)<sup>17</sup> or on physiologic variables (eg, Revised Trauma Score).<sup>18</sup> Other investigators have used biological markers reflecting tissue hypoperfusion and tissue hypoxia such as base deficit and lactate to define severe trauma.<sup>19</sup> Another definition of severe trauma is the use of aggressive measures, such as emergency surgery or the need for massive transfusion.<sup>20,21</sup> Given that there is no clear definition of severe trauma, we considered the biological plausibility of rFVIIa to define our patient population. Because the pharmacologic potential of rFVIIa is hemostasis at the site of local injury, we believed that our target patient population should include trauma patients with significant bleeding not easily corrected by conventional therapeutic measures (eg, surgical intervention, intravenous fluids). We believed that these patients would have the greatest potential for benefit from the use of rFVIIa. Patients with isolated head trauma or injuries that are efficaciously stabilized with prompt surgical intervention or minimal blood product transfusion would likely have less of a benefit from rFVIIa. These injuries are likely to have a different pathophysiology and response to treatment and therefore should be evaluated separately from patients with "severe multisystem trauma." Previous trauma literature involving severe trauma has also excluded isolated head trauma patients.<sup>22-24</sup> Therefore, for the purposes of our review, we considered any reasonable definition for severe trauma as long as the criteria were clearly defined by the investigators and benefit from rFVIIa was plausible.

We did not specify a dosing regimen because we could not find a well-established ideal dosing for rFVIIa in the literature. A Cochrane review compared the use of low-dose (less than 80  $\mu\text{g}/\text{kg}$ ) versus high-dose rFVIIa (equal to or greater than 80  $\mu\text{g}/\text{kg}$ ) in 5 randomized clinical trials.<sup>12</sup> The trials used rFVIIa in a variety of clinical indications and found no statistical difference in the outcome measures of blood loss, transfusion requirements, reduced bleeding, and intracranial hematoma size. None of the 5 trials included

patients being treated for a traumatic condition. A more recent randomized dose escalation trial in patients with traumatic intracranial hemorrhage showed no difference in outcome measures at escalating doses of rFVIIa (40, 80, 120, 160, and 200  $\mu\text{g}/\text{kg}$ ) compared with placebo.<sup>25</sup>

In this review, we focused on patient-oriented outcomes, which are more clinically relevant than disease-oriented outcomes<sup>26-28</sup>; such outcomes are the ones that the patients can comprehend, care about, and directly relate to.<sup>29-31</sup> The outcomes of interest for our review include mortality, neurologic outcomes, the need for surgical intervention (other than emergency resuscitative surgery), and adverse effects of rFVIIa.

Reducing mortality is clearly the most sought-after outcome in severely injured trauma patients. The use of rFVIIa would be best justified if it met this expectation. Therefore, we considered mortality/survival data after any follow-up period such as 48 hour mortality, inhospital mortality, or 30-day mortality.

For assessing neurologic outcome, we planned to consider any reasonable approach that measured patient-oriented outcomes. Previous examples of patient-oriented measurements of neurologic outcome in the literature include the ability to return to work, discharge destination (home as opposed to rehabilitation/special facility), and functional performance.<sup>32,33</sup>

Hemodynamically unstable patients or those with obvious exsanguinations generally go to the operating room or angiography suite early on as part of the resuscitation effort. Administration of rFVIIa is unlikely to prevent these emergency interventions. However, administration of rFVIIa in the ED might prevent delayed surgical interventions aimed at control of hemorrhage or repair of organ injury. Therefore, we were particularly interested in delayed surgical interventions as an outcome.

Previous literature has identified thrombotic complications as the main adverse effect of rFVIIa.<sup>34,35</sup> Therefore we planned to analyze the rate of thromboembolic events in the selected studies to evaluate the safety of rFVIIa.

To maintain our focus on patient-oriented outcomes, we did not include any transfusion-related outcomes in our review. Whether an intervention reduces or increases the number of transfused units in a patient who has already received several units of blood or whether the patient crosses an arbitrary cutoff for massive transfusion (10 units of packed RBCs) is unlikely to be the main concern of a severely injured patient.

Consequently, the reformulated question is: in adult, nonhemophilic patients with severe multisystem trauma requiring large amounts of fluid resuscitation or blood products that is not easily amenable to immediate surgical intervention, does the therapeutic use of rFVIIa at any dosing regimen, compared with placebo, improve the patient-oriented outcomes of mortality, neurologic status, delayed surgical interventions, and adverse effects?

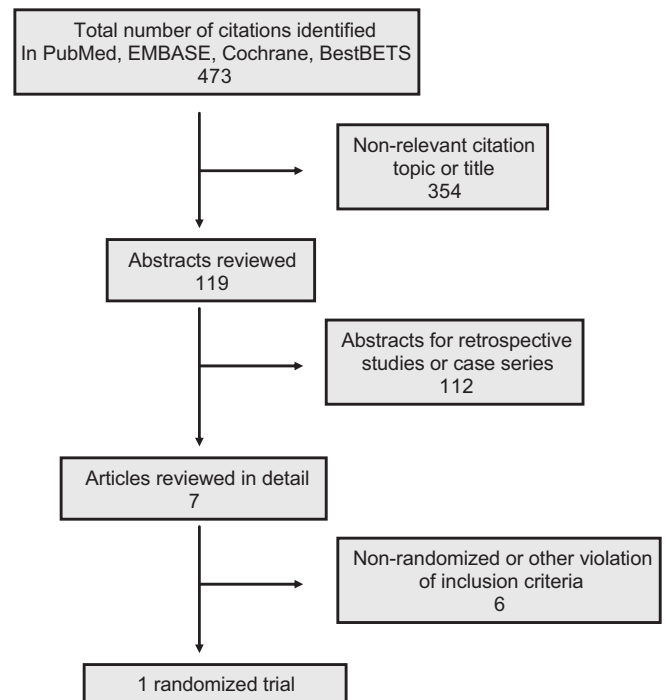
## SEARCHING FOR AND SELECTING THE BEST EVIDENCE

Because this is a clinical question about treatment, this review was confined to randomized, controlled trials that compared administration of rFVIIa to placebo in adult patients with severe trauma. In line with our question, we sought trials enrolling patients of all ages who presented to the ED for treatment of severe trauma requiring transfusion and who received other standard trauma and critical care interventions. We included studies involving the use of rFVIIa in patients with either blunt or penetrating trauma. Our evidence-based emergency medicine review was limited to studies in which rFVIIa was initiated in the out-of-hospital or ED phase of care and to studies reporting major clinical outcomes. The focus of our study was to assess the effectiveness of rFVIIa in improving outcomes of patients with severe trauma with presumed life-threatening injuries in the ED. We therefore considered studies investigating the prophylactic or therapeutic use of rFVIIa in nontrauma patients, or in non-ED settings (intraoperative use or utilization in the ICU) to be outside the scope of our review. We also excluded studies that evaluated the use of rFVIIa for isolated head trauma.

We searched the MEDLINE database from 1966 to July 2008, using the terms “wounds and injuries,” “trauma,” “hemorrhage,” “bleed,” and “factor VII” (for detailed search strategy, see [Appendix E1](#), available online at <http://www.annemergmed.com>). Using the search words “factor VIIa” and “trauma,” we also conducted a search of the databases of EMBASE from 1990 to July 2008, the Cochrane library<sup>36</sup> (all databases in the Cochrane Library, Issue 4, 2008; Chichester: Wiley), Emergency Medical Abstracts<sup>37</sup> from 1988 to July 2008 (available online at <http://ccme.org>), and BestBETS<sup>38</sup> (available online at <http://www.bestbets.org>). The bibliographies of relevant trials and systematic reviews were reviewed for citations of additional eligible studies. We also searched [ClinicalTrials.gov](#) (available at <http://www.clinicaltrials.gov>) and contacted the manufacturers of rFVIIa (Novo Nordisk, Bagsværd, Denmark) for any unpublished or ongoing studies.

These databases and searches yielded a total of 473 results. The process in which clinical trials were selected or excluded is presented in a diagram ([Figure](#)). A recently published randomized controlled trial comparing rFVIIa and placebo in patients with traumatic intracranial hemorrhage was excluded because it was conducted for patients with isolated head trauma.<sup>25</sup> After all the selection criteria were applied, only 1 randomized, placebo-controlled, double-blinded trial by Boffard et al<sup>39</sup> was included in the final review.

We also identified 1 brief review in the BestBETS database,<sup>40</sup> 1 Cochrane Database systematic review,<sup>12</sup> and 3 independent systematic reviews.<sup>34,41,42</sup> The BestBETS review included trials only through 2002 and did not identify any additional eligible controlled trials. The Cochrane<sup>12</sup> and the Hsia et al<sup>41</sup> systematic reviews did not meet the criteria for our review because they included a broad spectrum of nontraumatic clinical trials in



**Figure.** Process of selecting trials suitable for inclusion in the final review.

their analyses such as prophylactic surgical procedures, spontaneous intracranial hemorrhage, and upper gastrointestinal hemorrhage. The other 2 systematic reviews, by Ranucci et al<sup>34</sup> and von Heymann et al,<sup>42</sup> did not meet our inclusion criteria because they assessed major surgical trials exclusive of trauma. These reviews did not identify further studies that met our inclusion criteria. The registry for clinical trials did reveal 1 terminated study.<sup>43</sup> This clinical trial was a phase III, multicenter, industry-sponsored, international trial comparing rFVIIa versus placebo in severe trauma and ran from September 2005 to July 2008. The trial was terminated by the manufacturer after enrollment of 576 patients when the planned futility analysis predicted a very low likelihood of reaching a successful outcome on the primary efficacy endpoint. Contacting the manufacturers did not reveal any unidentified studies.

## ANALYZING THE EVIDENCE

### Description of the Trials

Table 1 summarizes the key features of the Boffard et al<sup>39</sup> study that compared the use of rFVIIa in severe trauma to placebo. This study was conducted in 32 centers in 8 countries. Severe trauma was defined as the transfusion of 6 or more units of packed RBCs within 4 hours of admission and included patients with either blunt or penetrating trauma. The study authors conducted 2 concurrent, parallel trials (one for blunt trauma and one for penetrating trauma), using the same protocol for both arms. If patients had both penetrating and blunt trauma, they were allocated to the blunt trauma arm (1

**Table 1.** Characteristics of randomized trial evaluating the use of rFVIIa in severe trauma.

Study	Patients	Interventions	Comparisons	Outcomes
Boffard et al, 2005 <sup>39</sup>	277 Patients across 32 international trauma centers, with a mean age of 34 y, with severe trauma (143 blunt, 134 penetrating) requiring >6 units of packed RBC within 4 h of admission	rFVIIa 200 µg/kg intravenously (IV) immediately after 8th unit of packed RBC, then 100 µg/kg IV repeated at 1 and 3 h	3 IV Injections of placebo	Primary: 48-h and 30-day mortality Secondary: units of packed RBC transfused in first 48 h, use of other transfusion products, ventilator and ICU days, MOF, ARDS Safety: adverse events, changes in coagulation-related laboratory variables

MOF, multi-organ failure; ARDS, adult respiratory distress syndrome.

**Table 2.** Assessment of susceptibility to important bias in the selected trial.

Criteria	Boffard et al, 2005 (n=277) <sup>39</sup>
Randomization	Yes
Concealment	Unclear, method of concealment not reported
Intention-to-treat analysis	Yes
Balance of study groups with respect to prognostically important variables	Groups similar with respect to age, sex, ISS score, GCS score, time to hospital, time from hospitalization to study treatment, vital signs, and biological variables
Blinding	Patients and care providers were blinded using placebo control group. Unclear whether data analysis was blinded.
Follow-up	3 patients lost to follow-up in rFVIIa group, 2 patients lost to follow-up in placebo group
Cointervention	Standard surgical intervention and resuscitation strategies for both placebo and rFVIIa groups. Transfusion guidelines similar for both groups in all study centers.

ISS, Injury Severity Score; GCS, Glasgow Coma Scale.

patient). Hence, this protocol could be considered to be the equivalent of a single randomized trial in which patients were stratified by presence or absence of blunt trauma. Key exclusion criteria consisted of cardiac arrest before trial drug administration, gunshot wound to the head, Glasgow Coma Scale score less than 8 unless in the presence of a normal computed tomographic scan result, base deficit of greater than 15 mEq/L or severe acidosis with pH less than 7.0, transfusion of 8 units or more of packed RBCs before arrival at the trauma center, and injury sustained greater than 12 hours before randomization.

We assessed the validity and bias in this trial by using published criteria,<sup>44,45</sup> including evaluation of randomization technique, concealment, comparison of baseline characteristics, blinding, follow-up, cointerventions, and intention-to-treat

**Table 3.** Outcome measures in patients who have severe blunt or penetrating trauma and are receiving rFVIIa versus placebo.

Outcome	Boffard et al, 2005 (Severe Trauma) (n=277) <sup>39</sup>		
	rFVIIa, No. (%) (n=139)	Placebo, No. (%) (n=138)	RR (95% CI)
48-h mortality	25 (18)	23 (17)	1.09 (0.59–2.0)
30-day mortality	34 (24)	40 (29)	0.84 (0.57–1.25)
Patients with adverse events (thromboembolism)	6 (4)	6 (4)	0.99 (0.33–3.0)
Massive transfusion*	15 (11)	36 (26)	0.41 (0.24–0.93)
ARDS within 30 days	7 (5)	17 (12)	0.41 (0.18–0.95)
MOF within 30 days	7 (5)	16 (12)	0.43 (0.18–1.02)
Composite outcome of ARDS, MOF, or death (within 30 days)	40 (29)	53 (38)	0.75 (0.54–1.05)

RR, Relative risk, rFVIIa compared with placebo.

\*Massive transfusion defined as patients alive at 48 hours who receive more than 12 units of RBCs within 48 hours of the first dose, which equals greater than 20 units of RBCs, inclusive of the 8 predose units.

analysis. The overall quality of the Boffard et al<sup>39</sup> study using this validity assessment is summarized in Table 2. The strengths of the study include randomization, which achieved balance among the prognostic variables between groups, an acceptable rate of patients lost to follow-up, and adherence to the intention-to-treat analysis. However, on critical appraisal, there were a number of weaknesses identified. The methods of enrollment and concealment of allocation were not completely transparent; there was no description of who determined enrollment, the enrollment rate, or any comparison of enrolled versus missed eligible patients. Although the investigators took appropriate steps to mask patients and caregivers from the treatment assignment, routine monitoring of the coagulation profile may have revealed patient allocation. The failure to report certain important prognostic variables and potential

**Table 4.** Subgroup analysis based on blunt and penetrating mechanism of injury.

Outcome	Boffard et al, 2005 (Blunt Trauma) (n=143) <sup>39</sup>			Boffard et al, 2005 (Penetrating Trauma) (n=134) <sup>39</sup>		
	rFVIIa, No. (%) (n=69)	Placebo, No. (%) (n=74)	RR (95% CI)	rFVIIa, No. (%) (n=70)	Placebo, No. (%) (n=64)	RR (95% CI)
48-h mortality	13 (19)	13 (18)	1.07 (0.54–2.14)	12 (17)	10 (16)	1.10 (0.51–2.36)
30-day mortality	17 (25)	22 (30)	0.83 (0.48–1.42)	17 (24)	18 (28)	0.86 (0.49–1.53)
Patients with adverse events (thromboembolism)	2 (3)	3 (4)	0.72 (0.12–4.15)	4 (6)	3 (4)	1.22 (0.28–5.24)

confounders such as anticoagulant use and cointerventions (fresh frozen plasma, platelets, intravenous fluids, surgical interventions) was another limitation. Finally, there may have been protocol violations because, per study protocol, patients who sustained an injury greater than or equal to 12 hours before enrollment were to be excluded, yet 45 patients (16.2%) were categorized as “unknown time of hospitalization.”

### Results of the Trials

Tables 3 and 4 present the results of the Boffard et al<sup>39</sup> study for all patients combined and also separately for patients with blunt and penetrating trauma. Included are our predefined outcome measures, as well as additional outcome measures reported by the study authors. The relative risk for mortality at 48 hours and 30 days between rFVIIa and placebo was very close to unity, with wide confidence intervals. Neurologic outcome and surgical intervention were not reported in the trial. The study did not find an increase in the rate of thromboembolic events associated with rFVIIa. This is consistent with other systematic reviews that specifically evaluated this adverse effect over a broad range of clinical indications.<sup>12,34,41,42</sup> Study authors report a reduction of massive transfusion favoring rFVIIa (defined as >20 units of packed RBCs transfused, inclusive of the 8 pre-rFVIIa units). However, this endpoint of massive transfusion was defined post hoc and is not consistent with other definitions of massive transfusion in the literature.<sup>20</sup> The investigators also reported other 30-day outcomes that were not among the patient-important outcomes selected for this evidence-based emergency medicine review (ie, acute respiratory distress syndrome, multiorgan failure, and a composite endpoint).

### APPLYING THE EVIDENCE

In the preceding clinical scenario, the clinician wondered whether the use of rFVIIa would benefit our patient with significant trauma and blood transfusion requirements. Our patient is a difficult patient to manage, with a high probability of mortality. Previous studies have shown that increasing severity of trauma and transfusion requirements are associated with a hypocoagulable state, ongoing bleeding, and subsequent mortality.<sup>14,46-49</sup> When there is a delay between the severe injury and definitive control of bleeding (eg, surgical intervention or angiographic embolization), the emergency physician's therapeutic options are limited. rFVIIa is a potential

treatment option in such patients because it has been used in multiple off-label bleeding conditions.<sup>2-6</sup> Although the mechanism of rFVIIa is not completely understood, it is thought to work by promoting thrombin generation by tissue factor and independent pathways.<sup>50,51</sup>

In the study by Boffard et al,<sup>39</sup> investigators found that in patients with severe trauma, the administration of rFVIIa was not associated with a decrease in mortality compared with placebo. Although the authors report a decrease in massive transfusion with rFVIIa, this was not included as one of our predefined outcomes because we could not justify transfusion-related outcomes as patient oriented. Moreover, this outcome measure of massive transfusion (defined as >20 units of RBCs) was defined post hoc by study authors and does not correlate with other previous definitions of massive transfusion.<sup>20</sup> It has been well established that changes in outcomes determined in post hoc analyses are highly subject to bias.<sup>52-54</sup>

Another important consideration is the cost of rFVIIa, approximately \$1 per  $\mu\text{g}$ . At the recommended dose of 90  $\mu\text{g}/\text{kg}$ , the approximate cost for a 70-kg patient is \$6,300 per dose, with the potential for multiple doses.<sup>51</sup> We could not find any formal cost-benefit analysis of rFVIIa for our study population; however, one systematic review in patients with major surgical procedures theorized that if a patient receives greater than 40 units of RBC, the cost of this massive transfusion is greater than the cost of rFVIIa.<sup>34</sup>

Returning to our original clinical scenario, we believe that there is insufficient evidence in the literature to support a clear recommendation for the use of rFVIIa in patients with severe trauma. Although the Boffard et al<sup>39</sup> study suggests that there is no difference in mortality or adverse effects with rFVIIa compared with placebo, further studies are required to elucidate the efficacy and safety of rFVIIa.

### PATIENT COMMUNICATION

With the increasing dissemination and access to medical information, patients are more informed about novel treatment options and frequently ask about issues of safety and benefit of these treatments. The following is an example of how an emergency physician might convey what is known about the benefits and risks of rFVIIa in patients with severe trauma. The following should be modified to reflect the actual clinical circumstance.

“Your family member has sustained significant injury, and we are doing everything possible to save his life. In addition to all the available treatments that we have provided, there is a medication called rFVIIa that has been used in a number of bleeding conditions with the hope of reducing the amount of bleeding. Unfortunately, there is very little scientific research evaluating the use of this medication in severe trauma. The use of this medication might be associated with increased risk of clot formation in the body. The available research does not clearly indicate whether this treatment is helpful or harmful. Therefore, we cannot recommend using or not using this medication.”

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**Critically Appraised Topic (CAT): Recombinant activated factor VII for severe trauma.**

<b>Question</b>	In adult, nonhemophilic patients with severe multisystem trauma requiring large amounts of fluid resuscitation or blood products that is not easily amenable to immediate surgical intervention, does the therapeutic use of rFVIIa at any dosing regimen, compared with placebo, improve the patient-oriented outcomes of mortality, neurologic status, delayed surgical interventions, and adverse effects?
<b>Reviewed by</b>	Nishijima DK, Zehtabchi S
<b>Date of search</b>	September 2008
<b>Expiration date</b>	September 2010
<b>Clinical bottom line</b>	Existing evidence does not show any benefit from using rFVIIa in severe multisystem trauma.
<b>Search strategy</b>	The search for randomized trials included PubMed, EMBASE, BestBETS, and the Cochrane Library, from the date of origin to September 2008.
<b>Citations</b>	1. Boffard KD, Riou B, Warren B, 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. <i>J Trauma</i> . 2005;59:8-18.
<b>Primary study characteristics</b>	<p><b>Study Population</b> 277 Trauma patients requiring at least 6 units of packed RBCs within 4 hours of admission, aged 16–65 years, from 32 centers in 8 countries. Excluded patients with cardiac arrest before drug administration, gunshot wound to the head, pH &lt;7.0, GCS score &lt;8, and injury ≥12 hours before randomization.</p> <p><b>Interventions</b> 3 IV injections of rFVIIa (200, 100, 100 μg/kg), first dose given immediately after the 8th unit of RBC, the second and third doses given at 1 and 3 hours after first dose, respectively.</p> <p><b>Outcome measures</b> Mortality, blood transfusion requirements, ICU days, multiorgan failure and acute respiratory distress syndrome at 30 days, and adverse events.</p>
<b>Critical appraisal</b>	The study was randomized, blinded, achieved balance with respect to baseline characteristics, and adhered to intention-to-treat analysis. The number of patients lost to follow-up was minimal. Methods of randomization, enrollment, and concealment were not completely reported.

**Results**

Trial	RR (95%CI)
Primary outcome: mortality	
<b>48-h Mortality</b>	
Boffard et al	1.09(0.59–2.0)
<b>30-Day mortality</b>	
Boffard et al	0.84(0.57–1.25)

APPENDIX E1. Designed search strategy: PubMed.

Search Order	Search Term
#1	wounds and injuries [MeSH]
#2	multiple trauma [MeSH]
#3	hemorrhage [MeSH]
#4	hemorrhag* [tw]
#5	bleed* [tw]
#6	trauma* [tw]
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	factor VII [MeSH]
#9	nn1731 [tw]
#10	novo seven [tw]
#11	novo nordisk [tw]
#12	eptacog alpha [tw]
#13	#8 or #9 or #10 or #11 or #12
#14	#7 and #13
#15	randomized controlled trial [Publication Type] or randomized controlled trials [MeSH]
#16	Prospective [tw]
#17	#15 or #16
#18	#14 and #17