# Potential role of recombinant activated factor VII for the treatment of severe bleeding associated with disseminated intravascular coagulation: a systematic review

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**Recombinant activated factor VII (rFVIIa) is a novel hemostatic agent, originally developed for the treatment of hemorrhage in hemophiliacs with inhibitors, which has been successfully used recently in an increasing number of nonhemophilic bleeding conditions. In the present systematic review we report the existing literature data on the use of this hemostatic agent in severe bleeding, unresponsive to standard treatment, associated with disseminated intravascular coagulation. A total of 99 disseminated intravascular coagulation-associated bleeding episodes treated with rFVIIa were collected from 27 published articles: in the majority of the cases, the underlying disorder complicated by disseminated intravascular coagulation was a postpartum hemorrhage, while in the remaining cases it was a cancer, trauma, sepsis or liver failure. Although limited, the data available suggest that rFVIIa could have a potential role in this clinical setting. Large randomized trials are needed, however, to confirm the preliminary results and to assess the safety and dosing regimens of this agent in refractory bleeding associated with disseminated intravascular coagulation.** ***Blood Coagul Fibrinolysis*** **18:589–593 © 2007 Lippincott Williams & Wilkins.**

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## Introduction

Disseminated intravascular coagulation (DIC) is a disorder characterized by a massive systemic intravascular activation of coagulation, leading to a widespread deposition of fibrin in the circulation, a consumption of platelets and a deficiency of coagulant and anticoagulant pathways [1–3]. If the vascular and microvascular fibrin deposition, compromising an adequate blood supply to various organs, can contribute to multiple organ failure, bleeding and thrombosis can therefore occur simultaneously, resulting in a difficult problem for clinicians. DIC, however, is not a disease itself but is always secondary to an underlying disorder [4]. In fact, a variety of clinical conditions may cause systemic activation of coagulation including systemic Gram-positive and Gram-negative infections [5], severe trauma or burns [6], and solid and hematologic cancers [7–9]. Finally, some obstetric conditions such as abruptio placentae, amniotic fluid embolism and placenta previa may be frequently complicated by DIC [10]. The management of DIC is based on the treatment of the underlying disorder, replacement therapy (i.e. fresh-frozen plasma), anticoagulants (i.e. unfractioned and low-molecular-weight heparin) and the restoration of anticoagulant pathways (i.e. antithrombin and recombinant human activated protein C). Among the newer agents used for the control of disrupted coagulation mechanisms in DIC patients, recombinant activated factor VII (rFVIIa), a bypassing hemostatic agent originally developed for the treatment of bleeding episodes in hemophiliac patients with inhibitors, is one of the most promising.

In the present systematic review we analyze present knowledge on the use of rFVIIa in the treatment of severe, refractory bleeding associated with DIC.

## Mechanisms of action of recombinant activated factor VII

According to current knowledge, activated factor VII functions primarily through two mechanisms. The first pathway is tissue factor (TF) dependent and involves the formation, following a vessel injury, of a TF–activated factor VII complex, which in turn activates factor X leading to the conversion of prothrombin to thrombin. The initial limited amount of thrombin formed subsequently activates factor VIII, factor V and platelets so that the tenase complex (activated factor VIII/activated factor IX) and the prothrombinase complex (activated factor X/ activated factor V) assembled on the activated platelet surface lead to a full thrombin generation. This 'thrombin burst' is essential for the formation of a stable fibrin clot that is resistant to premature fibrinolysis, and thus provides reliable and maintained hemostasis. The hemostatic

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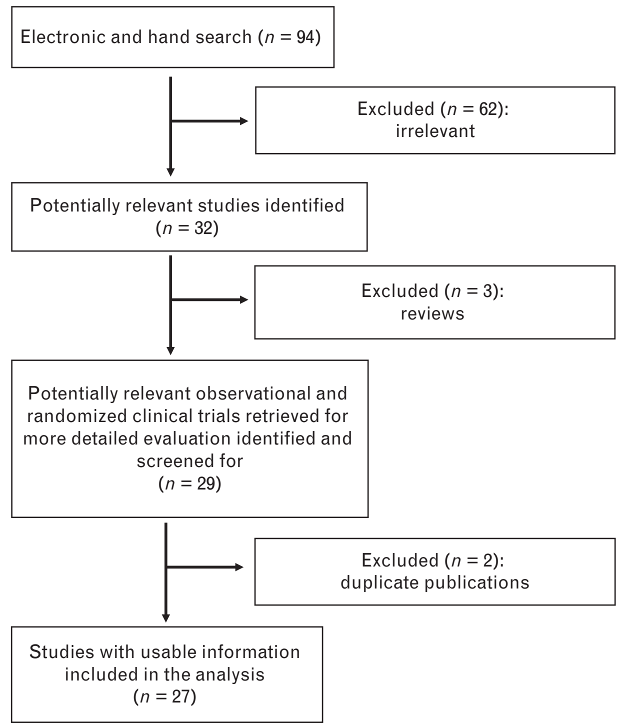
process, however, is not systemic but confined to the surface of the thrombin-activated platelets and the TF-bearing cells at the site of vascular injury. The local activation of hemostasis constitutes the rationale for the use of rFVIIa in DIC-associated severe bleeding. The second pathway involves a TF-independent mechanism. In fact, recent data suggest that rFVIIa can directly activate factor X on phospholipid vesicles and on the surface of activated platelets and monocytes [11–13]. This mechanism, which is the most important mode of action of rFVIIa at pharmacologic doses, optimizes thrombin generation independently of the presence of TF.

## Literature search

We first performed an electronic search on DIC and rFVIIa on MEDLINE, EMBASE, SCOPUS, OVID and the Cochrane Library without temporal limits using different combinations of the following keywords: 'disseminated intravascular coagulation', 'systemic intravascular coagulation', 'DIC', 'leukemia', 'promyelocytic leukemia', 'cancer', 'sepsis', 'septicemia', 'hemorrhage', 'bleeding', 'recombinant activated factor VII', 'rFVIIa'. Only articles with at least an abstract in English were considered. In addition, the bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. Unpublished works were identified by searching the abstract books of the most important conferences on this topic. In total, we identified 94 references through the electronic and hand searches. After reading the titles and abstracts, we excluded 62 irrelevant references and retrieved 32 references for further assessment. A further five studies were excluded because they were reviews (three articles) or duplicates (two articles). A total of 27 articles/abstracts, including 99 patients with DIC treated with rFVIIa, were therefore retrieved from this literature search [14–40]. All the articles found were uncontrolled studies. Figure 1 shows the flowchart of inclusion of studies.

**Fig. 1**




Flowchart of inclusion of studies.

## Use of recombinant activated factor VII in disseminated intravascular coagulation

Most of the literature data available on the use of rFVIIa in DIC patients regard the postpartum hemorrhage (PPH), a rare but life-threatening obstetric complication that may often be complicated by systemic activation of coagulation. DIC plays a significant role in the deaths associated with massive obstetric hemorrhage [41]. Such use of rFVIIa in this clinical setting was firstly described by Moscardo and colleagues [14] in a 33-year-old woman who presented at 31 weeks of a twin pregnancy with severe DIC, liver dysfunction and renal failure, and developed severe intra-abdominal bleeding following cesarean section. Despite intensive transfusion support and a hysterectomy, the bleeding persisted and rFVIIa was given, with a reduction in the bleeding observed after the first two doses. The largest case series was that recently published by Sobieszczyk and colleagues [28]. Among the 25 cases collected from an international internet-based registry, eight (32%) were complicated by DIC. In five out of the eight cases (62.5%), hysterectomy was necessary to control bleeding. In all cases a single dose of rFVIIa (mean 31.6 μg/kg) was sufficient to control the bleeding. Segal and colleagues [23] managed 10 women with PPH over 3 years after conventional blood product repletion was unsuccessful. rFVIIa at doses of 90–100 μg/kg (median 1.2 doses) was administered in the seven patients with associated DIC, and bleeding was stopped in four patients and reduced or controlled in three patients. Table 1 presents the studies so far published on the use of rFVIIa in DIC associated with PPH. A total of 32 cases were collected among the 15 studies retrieved in the literature. The median age of patients was 33.3 years and uterine atony was the leading cause of PPH (10/32, 31.2%). The majority of patients underwent cesarean section (19/25 valuable cases, 76%) and hysterectomy (18/32 cases, 56.3%). The mean dose of rFVIIa administered was 67.6 μg/kg, while the mean number of doses was 1.9. A single dose of rFVIIa, however, was effective to control hemorrhage (26/32 cases, 81.3%). As regards the assessment of the effectiveness of rFVIIa, the majority of the authors defined a positive result when rFVIIa led to cessation or significant reduction in

**Table 1 Use of recombinant activated factor VII (rFVIIa) in obstetric bleeding complications (postpartum hemorrhage) associated with disseminated intravascular coagulation: literature results**

| Reference | Number of patients | Age[a] (years) | Concomitant disease | Type of delivery | Number of hysterectomies | Initial dose of rFVIIa (μg/kg)[a] | Number of doses[a] | Response[b] |
|---|---|---|---|---|---|---|---|---|
| Moscardo *et al.* [14] | 1 | 33 | 1 Atony | 1 CS | 1 | 90 | 9 | 1 |
| Breborowicz *et al.* [15] | 4 | 32.7 (26–40) | 3 Atony, 1 PP | 3 CS, 1 VD | 3/4 (75.0%) | 30.1 (16.7–48) | 1 | 4/4 (100%) |
| Zupancic *et al.* [16] | 1 | 31 | 1 HELLP | 1 CS | 0 | 90 | 1 | 1 |
| Sokolic *et al.* [17] | 1 | 31 | 1 HELLP | 1 CS | 0 | 90 | 1 | 1 |
| Kretzschmar *et al.* [18] | 1 | 35 | 1 AFE | 1 CS | 1 | 60 | 1 | 1[c] |
| Bouwmeester *et al.* [19] | 1 | 30 | 1 Atony | 1 VD | 1 | 60 | 2 | 1 |
| Lim *et al.* [20] | 1 | 26 | 1 AFE | 1 VD | 0 | 90 | 1 | 1 |
| Brice *et al.* [21] | 2 | 33.5 (27–40) | 2 Atony | 2 CS | 1/2 (50.0%) | 60 | 1 | 2/2 (100%) |
| Boehlen *et al.* [22] | 1 | 31 | 1 Atony | 1 VD | 1 | 120 | 19 | 1 |
| Segal *et al.* [23] | 7 | NR | 1 Atony, 3 PA; 3 UR | NR | 4/7 (57.1%) | 91.7 (90–100) | 1.2 (1–2) | 7/7 (100%) |
| Price *et al.* [24] | 1 | 32 | 1 HELLP | 1 CS | 0 | 90 | 1 | 1 |
| Gidiri *et al.* [25] | 1 | 38 | 1 PA | 1 CS | 0 | 170 | 1 | 1 |
| Holub *et al.* [26] | 1 | 28 | 1 Atony | 1 CS | 1 | NR | 1 | 1 |
| Pepas *et al.* [27] | 1 | NR | 1 HELLP | 1 CS | 0 | 90 | 2 | 1 |
| Sobieszczyk *et al.* [28] | 8 | 35.6 (29–44) | 1 UM, 1 Sepsis, 6 NR | 6 CS, 2 VD | 5/8 (62.5%) | 31.6 (15.4–48) | 1 | 8/8 (100%) |
| Total | 32 | 33.3 (26–44) | | 19 CS/6 VD | 18/32 (56.3%) | 67.6 (15.4–120) | 1.9 (1–19) | 32/32 (100%) |

AFE, amniotic fluid embolism; CS, cesarean section; HELLP, hemolysis elevated liver enzymes and low platelets; NR, not reported; PA, placenta accreta; PP, placenta previa; UM, uterus myomatosus; UR, uterine rupture; VD, vaginal delivery. [a] Absolute number or median (range). [b] Defined as cessation of or significant reduction of bleeding. [c] rFVIIa had reduced bleeding but the patient died due to multiorgan failure.

either blood loss or need for blood transfusion. Using this definition, a positive result was obtained in all the 32 cases reported. We advise particular caution in interpreting this result, however, as all data available in the literature were derived from uncontrolled studies including single cases or small series of patients. The real effectiveness of rFVIIa in these bleeding situations could therefore be overestimated, those cases with a positive outcome being preferentially reported. The impact of rFVIIa on avoiding the need for emergency hysterectomy and preservation of reproductive function is difficult to determine as in many cases this surgical procedure was performed before the drug was administered. Another important consideration that emerges from the analysis of the literature on the use of rFVIIa in DIC associated with PPH is that an early use of this hemostatic agent appears crucial for its success. On the other hand, as stated by Vincent and colleagues [42], rFVIIa should not be considered a substitute for, nor should it delay, the performance of life-saving medical (i.e. replacement transfusion therapy) or invasive (i.e. arterial embolization or surgery) procedures to control PPH and DIC.

rFVIIa has also been used for the treatment of critically ill trauma patients, who frequently suffer from coagulopathy abnormalities resembling DIC [43,44]. After the first successful use of this agent in an exsanguinating trauma patient [29], Martinowitz and colleagues [30] described a series of seven massively bleeding coagulopathic trauma patients, in whom conventional medical and surgical hemostatic techniques had failed. The administration of one to three doses of rFVIIa (median dose 120 μg/kg) resulted in the cessation of diffuse bleeding with a significant decrease of blood requirements. Three of the seven patients died from causes other than bleeding or thrombotic events, and no thromboembolic complications were reported in any patient.

Holcomb and colleagues [31] reported the successful use of rFVIIa (single dose of 120 μg/kg) to control diffuse intraperitoneal bleeding in a patient with DIC related to sepsis. Similarly, Martinez and colleagues [32] described the control of severe intra-abdominal bleeding with a single dose (90 μg/kg) of rFVIIa in a patient with DIC secondary to septic shock. Cetin and colleagues [33] reported the successful response to rFVIIa (a dose of 120 μg/kg repeated for three times) in a preterm infant with massive pulmonary hemorrhage resulting from clinical sepsis/DIC-induced severe coagulopathy.

Another clinical condition, not rarely associated with DIC, where rFVIIa could be of benefit for the management of bleeding complications, is liver disease [45]. Chuansumrit and colleagues [34] described three children with acute bleeding resulting from systemic coagulopathy associated with liver failure (two girls with Dengue hemorrhagic fever and prolonged shock, and one boy with a left-lobe hepatectomy for a hepatoblastoma). rFVIIa (a bolus dose of 40–180 μg/kg followed by 16.5–33 μg/kg per h continuous infusion) was able to control bleeding in all patients. A further seven cases of DIC associated with Dengue hemorrhagic fever were described by the same authors [35], with an effective response after rFVIIa administration (single or repeated doses of 100 μg/kg) in four cases. Interestingly, a case of DIC was observed by Jeffers and colleagues [36] in a patient with drug-related acute liver failure, following the administration of a dose of 80 μg/kg rFVIIa. The event, however, was not considered by the investigator to be related to rFVIIa treatment.

Among the 12 patients with pancreatitis and bleeding described by Laffan and colleagues [37], seven also had DIC and in all but one patient the bleeding stopped or was reduced following rFVIIa (a single dose ranging from

18.5 to 120 μg/kg). In a retrospective multicenter study conducted by MacLaren and colleagues [40], rFVIIa was administered for prevention or treatment of bleeding to 315 nonhemophilic patients, 6% of whom (19 patients) had DIC. In the prophylaxis group, rFVIIa was effective in preventing bleeding in 85.7% of patients, while in the treatment group the drug stopped bleeding within 6 h of administration in 52.6% of the patients.

Sallah and colleagues [38] reported the use of rFVIIa in 18 patients with hemorrhagic DIC associated with the presence of underlying advanced or metastatic cancers (three prostate cancer, three lung cancer, two breast cancer, two gastric cancer, two pancreatic cancer, two soft tissue cancer, one colon cancer, one renal cancer, one unknown, one acute leukemia). The dose of rFVIIa was 90 mg/kg and the median number of doses administered was five (range, 3–10). Of the 18 patients, 15 (83.3%) responded with cessation of bleeding and improvement in coagulation data. No thromboembolic complications were observed following rFVIIa administration.

Finally, Zver and colleagues [39] described the effective treatment with rFVIIa (two doses of 90 μg/kg) of a life-threatening bleeding in a patient with acute promyelocytic leukemia, a condition in which DIC is characterized by a severe hyperfibrinolytic state associated with the systemic activation of coagulation.

Another open issue regards the safety of rFVIIa in severe bleeding associated with DIC, particularly considering the recent report of a high rate of thromboembolic adverse events after the use of rFVIIa in patients without a pre-existing coagulopathy [46]. Although no drug-related adverse reactions, especially thrombotic episodes, have so far been reported in the literature, we advise the physicians to follow experts' recommendations [42] as regards the dose and timing of rFVIIa administration and to monitor closely such patients not only for their clinical bleeding conditions but also for the onset of thrombotic complications.

In conclusion, it could be a paradox to use rFVIIa in a clinical setting characterized by systemic activation of coagulation. Comprehension of the molecular mechanisms of action of rFVIIa and the clinical evidence from the literature, however, suggest the potential role of this bypassing hemostatic agent in the treatment of refractory bleeding associated with DIC.

The data published in the literature regarding this topic are limited, however, and randomized, controlled trials on large populations of patients are needed to confirm these preliminary positive results and to assess the safety, the most appropriate dose and the frequency of administration of rFVIIa in DIC.

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