

# Uses of recombinant factor VIIa in trauma

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## Purpose of review

Despite advances in the care of the injured, the morbidity and mortality of traumatic hemorrhage remain a significant problem. Traumatologists continue to look for ways to treat bleeding and prevent the sequelae of hemorrhagic shock. Recombinant factor VIIa, developed for the treatment of patients with hemophilia, has been used with some success in acute bleeding associated with injuries.

## Recent findings

The mechanism of action is via a tissue factor-dependent effect and/or platelet activation. Coagulation occurs at the site of tissue injury, where tissue factor is exposed. Case series have described the beneficial effects of recombinant factor VIIa in the treatment of acute hemorrhage, early treatment of traumatic brain injury, and reversal of preinjury anticoagulation. In addition, there have been numerous reports of recombinant factor VIIa use in acute bleeds secondary to other causes as well as some evidence that recombinant factor VIIa may be efficacious when used prophylactically in high-risk patients and for high-risk procedures. Typical doses range from 50 to 100 µg/kg as a single bolus. Although there has been concern over the risk of inappropriate thrombosis with recombinant factor VIIa administration, this complication has seldom been described in published series.

## Summary

Although case experience is encouraging, no level 1 evidence has been published that demonstrates clinical or economic benefit of the use of recombinant factor VIIa in trauma patients. Many questions remain to be answered, ideally through randomized, prospective clinical trials. In particular, the issues of patient selection, ideal dosing, and factors associated with futile administration need to be elucidated.

## Keywords

recombinant factor VIIa, hemorrhage, trauma, traumatic brain injury, coagulopathy

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## Abbreviation

rFVIIa recombinant factor VIIa

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## Introduction

Injury is the leading cause of death in the United States among those 1 to 44 years of age and the third leading cause of death overall [1]. Worldwide, injuries represent the leading cause of death among those 5 to 44 years of age [2]. The concept of the trimodal distribution of trauma deaths describes that 50% of deaths from injury occur in the field, 30% occur within the first 4 hours, and 20% are late deaths due to multiorgan system failure and sepsis [3]. Between 30% and 50% of deaths that occur immediately and in the hours after injury are owing to acute blood loss and hemorrhagic shock [4,5,6\*]. Many of the late deaths may also be attributable to the inflammatory sequelae of acute hemorrhagic shock. Advances in trauma care, including damage control laparotomy, hypotensive resuscitation, angiographic management of visceral injury, and maturation of trauma systems have all had a profound effect on outcome after injury. Trauma care professionals continue to develop new ways to mitigate the devastating consequences of exsanguination and prevent death and disability from injury.

In 1990, Hedner [7] described the use of human recombinant factor VIIa (rFVIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) for the treatment of hemophilia. Since that time, rFVIIa has been used extensively in patients with hemophilia with alloantibodies to factor VIII for both prophylaxis and treatment of acute bleeding episodes. During the past 6 years, interest has increased in using rFVIIa "off-label" for the treatment of coagulopathic, surgical, and traumatic bleeding. The increasing experience with rFVIIa in injured patients has been driven by clinicians who believe that there is a significant role for the use of rFVIIa in the treatment of traumatic hemorrhage. rFVIIa is extremely expensive, however, costing more than US\$5000 per 100-µg/kg dose. Because of the expense, widespread adoption of rFVIIa as a standard of care for traumatic injuries will likely depend on a convincing demonstration of its efficacy. We review the literature to date on this topic.

## Normal coagulation mechanisms

Clinical experience with rFVIIa and laboratory work done to elucidate its mechanisms of action have led some

researchers to call into question the classic descriptions of the coagulation cascade [8•,9•]. The mechanisms of clot formation were historically divided into the intrinsic and extrinsic pathways. The extrinsic pathway was initiated by tissue factor, whereas the intrinsic pathway was thought to be an intravascular process. Hoffman [9•] questioned the independence of these pathways and described a cell-based model of coagulation. In this model, there is a series of overlapping steps that lead to coagulation: initiation, amplification, propagation, and termination. To initiate the formation of clot, tissue factor and platelets must come into contact with each other, which normally occurs only at the site of a vascular disruption.

#### Development of traumatic coagulopathy

Traumatic coagulopathy often occurs in the presence of hemorrhagic shock. Injured patients with profuse bleeding enter into a cycle of hemodilution, consumption of clotting factors, fibrinolysis, hypothermia, and profound metabolic disturbance. Massive transfusions are required to maintain blood volume, which leads to the development of further hypothermia, acidosis, and electrolyte derangement. There are also significant long-term consequences of blood transfusions. These include infection, transfusion-related acute lung injury, the systemic inflammatory response syndrome, and, ultimately, multiple organ failure [10•].

The mainstay of therapy for bleeding in the trauma patient is restoration of vascular and tissue integrity, either through surgery or angiographic embolization. However, once a patient becomes coagulopathic, operative or angiographic approaches can fail. If the patient develops the "lethal triad" of hypothermia, acidosis, and coagulopathy, surgical control of bleeding is unlikely to be successful [11]. Attempts to minimize transfusion of blood products and gain early control of bleeding to prevent the lethal triad have led clinicians to look at alternative means of restoring hemostasis, such as rFVIIa.

#### Mechanism of action of factor VIIa

The mechanisms by which rFVIIa enhances hemostasis have been elucidated. It appears that rFVIIa enhances coagulation at sites of tissue injury but not in remote areas. This has led to the hypothesis that rFVIIa acts via a tissue factor-dependent mechanism [12•,13]. Tissue factor is exposed at the site of endovascular injury. rFVIIa binds to the tissue factor and causes the activation of factor X. This activation leads to thrombin formation and activation of both platelets and other clotting factors. This, in turn, leads to amplification of factor X activation and clot formation. The activation of platelets through this mechanism is thought to increase the rate of clot formation. Although some researchers have questioned the significance of the tissue factor-dependent mechanism of rFVIIa, one recent study demonstrated that *in vitro* in the absence of tissue factor, rFVIIa fails to

activate platelets [14]. In a separate study, the absence of tissue factor in an experimental model produced only negligible amounts of thrombin in the presence of rFVIIa [13]. The extent to which these results can be extrapolated to an *in vivo* cell-based model have been questioned, however [15•].

The additional mechanism that has been proposed is a platelet-dependent one, whereby rFVIIa binds to activated platelets and subsequently activates factor X directly. Work by researchers at Duke University Medical Center and the University of North Carolina have elucidated a cell-based model of hemostasis that describes the effect of rFVIIa as occurring primarily through platelet activation [16–18]. This mechanism is thought to function somewhat independently of tissue factor. Several excellent reviews of this theory have been published in the past 2 years [8•,19•,20•]. A schematic of the proposed mechanisms of action of rFVIIa is shown in Figure 1.

#### Uses of recombinant factor VIIa

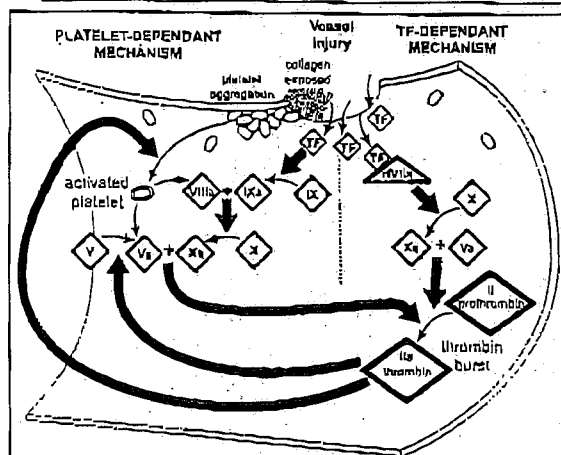
Since Hedner first described rFVIIa, it has been used in thousands of patients with both congenital and acquired hemophilia. Currently, the indications that are approved in Europe and by the U.S. Food and Drug Administration are treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to factor VIII or factor IX (Novo Nordisk, NovoSeven product monograph). rFVIIa is synthesized in baby hamster kidney cells, which have been transfected with human factor VII genes from the liver. Since its development in 1990, rFVIIa has been touted by some as a "universal coagulant" and has been used on an off-label basis for a wide variety of bleeding disorders and conditions.

#### In acute traumatic hemorrhage

In 2001, Martinowitz *et al.* [21] reported a study of intravenous rFVIIa used in experimental liver trauma in swine. They demonstrated that administration of rFVIIa was associated with a decrease in blood loss and restoration of normal coagulation profiles. Subsequently, three additional controlled experimental studies were published that used a swine model of traumatic liver injury [22–24]. In all three, benefits were noted in the rFVIIa groups with no evidence of inappropriate thrombosis. Since 2002, one additional experimental study was published that looked at rFVIIa in trauma [25]. That study failed to demonstrate the utility of rFVIIa as a sole therapy for grade V liver injuries in pigs when used without packing of the abdomen. In reviewing these experimental studies, it should be noted that rFVIIa is derived from a human gene source and may not interact with the coagulation cascade of swine in the same way that it does in humans.

Proposed uses of rFVIIa in trauma patients are shown in Table 1. Early experience with the use of rFVIIa in

Figure 1. A schematic of the proposed mechanisms of recombinant factor VIIa in vessel injury



TF tissue factor; rFVIIa, recombinant factor VIIa; X, factor X; IX, factor IX; VIII, factor VIII; V, factor V. Large arrows indicate activation.

human trauma came from reports from one group in Israel, with the first report published in 1999 [26]. Subsequently, the same group reported on six additional injured patients who were also treated with rFVIIa [27]. All responded to rFVIIa administration with cessation of bleeding and normalization of prothrombin and activated partial thromboplastin time. Three of the seven patients died of causes reportedly unrelated to bleeding or thrombosis. An additional report of 19 patients was published in 2002, in which all but four patients responded with clinical cessation of bleeding [28]. Since 2002, only one report has been published describing rFVIIa use exclusively in trauma patients [29\*]. The series reported on five patients, of whom three survived. The two patients who died both appeared to transiently respond but subsequently exsanguinated. Both of these patients were noted to have profound acidosis and shock and had had cardiac arrests before rFVIIa administration.

The largest reported North American series comes from the Shock Trauma Center of the University of Maryland [30]. In this series, 81 coagulopathic trauma patients were treated with rFVIIa. Forty-six patients were administered rFVIIa for acute hemorrhagic shock, 20 for traumatic brain injury, nine for reversal of warfarin in the presence of life-threatening intracranial or systemic hemorrhage, two for factor VII deficiency before surgery, and

Table 1. Uses of recombinant factor VIIa in trauma patients

Acute hemorrhage
Reversal of anticoagulants
Traumatic brain injury
*Acquired* coagulopathy secondary to multiple organ failure or sepsis
Congenital coagulopathy/factor deficiency

four for acquired hematologic defects. The clinical response rate to rFVIIa administration was reported to be 75% and the overall survival rate was 42%. All patients for whom follow-up coagulation studies were available responded with a significant reduction in prothrombin. The mortality rate was 56% in the acute hemorrhage group (44% of those who responded to rFVIIa). The authors attempted to match patients administered rFVIIa with controls to determine whether a survival advantage was obtained but were unable to identify a control population with similarly profound hemorrhagic shock.

Additional case series have been published since 2002 that have reported on rFVIIa use in acute hemorrhage from both traumatic and nontraumatic causes. In 2003, Eikelboom *et al.* [31\*\*] reported a case series of 21 patients in Australia who were treated with rFVIIa for life-threatening hemorrhage. In this series, only three of the patients were administered rFVIIa for control of acute hemorrhage from trauma. The others had bleeding from nontraumatic causes (eg, hemorrhagic pancreatitis, cardiac surgery). The authors reported that 18 of the 21 patients stopped bleeding after rFVIIa administration and 16 survived 30 days or were discharged alive. The patients who died had received more blood products and were more coagulopathic. There were no reported thrombotic complications.

Another series from the United Kingdom looked at 50 coagulopathic surgical patients, of whom 10 had received rFVIIa [32\*]. Only seven of the 50 patients were bleeding from traumatic causes and only one trauma patient was given rFVIIa. The authors determined that rFVIIa is "ineffective" when given to profoundly coagulopathic patients, despite a reduction or cessation of bleeding in 60% of patients. Of the 10 patients, four died within 24 hours of exsanguination and seven died within 7 days of multiple organ failure.

To date, no randomized, prospective trials on the use of rFVIIa in trauma patients have been published, although trials are ongoing. Results from a phase 2 study of 280 patients have been reported in a press release from Novo Nordisk (Stock Exchange announcement, 2003). The preliminary results demonstrated a reduction in bleeding after rFVIIa administration in patients with a blunt mechanism of injury. In patients with penetrating injury, there was a "strong trend" toward reduction in bleeding.

#### In intracranial bleeding

In the series by Dutton *et al.* [30], rFVIIa was administered to 20 patients with traumatic brain injury for the treatment of coagulopathy. All these patients responded to rFVIIa administration with an improvement in their coagulation profile and a decrease in bleeding, but 75% died of their brain injury. All these patients were admini-

istered rFVII after the development of coagulopathy, however.

Early administration of rFVIIa in patients with intracranial hemorrhage has demonstrated better results. A case report of a man with cirrhosis with a spontaneous intracranial bleed who was successfully treated early with rFVIIa was published in 2003 [33]. A series of five patients with traumatic brain injury was reported in 2004 by a group in Israel who demonstrated "control of intracranial bleeding" with early rFVIIa administration [34]. Another case series of nine patients with coagulopathy in whom rFVIIa was used before neurosurgical intervention was reported in 2003 [35]. Additionally, in 2004, Mayer *et al.* (Paper presented at the 5th World Stroke Congress, Vancouver, 2004) presented the preliminary findings of early use of rFVIIa in patients with intracerebral hemorrhage that demonstrated safety of administration. Subsequently, Novo Nordisk released a stock exchange announcement describing the benefit of early rFVIIa administration in 400 patients with intracranial hemorrhage (Novo Nordisk, Stock Exchange announcement, 2004). Benefits reported include both a reduction in "hematoma growth" and improvement in neurologic and functional recovery. These data have not yet been published.

#### In reversal of anticoagulation

Recombinant factor VIIa has been used to reverse therapeutic anticoagulation in a variety of clinical situations. One report of 13 patients with elevated International Normalized Ratios (INRs) secondary to warfarin use was published in 2002 [36]. These patients required rapid reversal of their anticoagulation for a variety of reasons. All patients had both biochemical and clinical responses to rFVIIa. An additional report of one patient who was being anticoagulated with acenocoumarol who successfully received rFVIIa for an acute upper gastrointestinal bleed was also recently published [37].

In 2003, there was a report on a series of seven patients with either spontaneous or traumatic intracranial hemorrhage or imminent hemorrhage who were administered rFVIIa with favorable results [38]. All these patients had a measured response in INR, and the six who underwent evacuation of their hematomas survived. No thrombotic events were reported. The series from Maryland on rFVIIa use in trauma patients also reported use in nine patients on warfarin with favorable results in terms of bleeding cessation, although five died owing to traumatic brain injury or multiple organ failure [30]. Two excellent reviews on the use of rFVIIa for reversal of anticoagulant therapy have recently been published [39,40].

#### Other uses

Since its first use in patients with hemophilia, rFVIIa has been used for treatment of acute bleeding in a number of

nontrauma patients without congenital bleeding disorders. In 2003, two reports were published from the United Kingdom's extended-use registry, funded by Novo Nordisk [41,42]. The registry reports the use of rFVIIa in 40 patients with acute and postoperative bleeding. Eighty percent of patients responded to rFVIIa administration, but the mortality rate was 57.5%. Other reports have described the use of rFVIIa in patients undergoing cardiac [43,44,45-49] and spinal surgery [50] and patients with cirrhosis undergoing elective procedures [51,52], neurosurgical procedures [35], abdominal aortic aneurysm repairs [53], liver transplantation [54-56], lung transplantation [57], and renal transplantation [58,59]. Several reviews have recently been published describing the use of rFVIIa during hepatectomy [60,61].

Other reports have been published since 2002 on the use of rFVIIa in acute bleeding emergencies in patients without hemophilia, including hemorrhagic pancreatitis [62], extensive burns [63], obstetric hemorrhage [64-68], extracorporeal membrane oxygenation use [69], esophageal varices [70], liver failure [71], and gastrointestinal bleeds [72]. Several reports have also described its use in Jehovah's Witnesses with hemorrhage [49,73,74]. Dutton *et al.* [30] also described the use of rFVIIa in four trauma patients with acute bleeding from acquired coagulopathy from multiple organ failure late in the hospital course. Other reports of rFVIIa use in coagulopathic hemorrhage from sepsis have appeared [75].

The first published randomized, prospective trials of rFVIIa use in surgical patients without hemophilia were also published in 2003. Friederich *et al.* [76] published the results of a double-blind, placebo-controlled, randomized trial in 36 patients undergoing elective radical prostatectomy. They demonstrated a decrease in the need for blood transfusions in the factor VIIa group without any reported complications, but failed to demonstrate an economic benefit [77]. Additionally, no morbidity or mortality benefit was demonstrated, but the sample size was likely too small to detect such an effect. Currently, a prospective, randomized trial is under way in the United Kingdom to determine the efficacy of prophylactic rFVIIa use in cardiac surgery [45].

#### Futility of use

In nearly all the published series on rFVIIa administration for acute hemorrhage in patients without congenital bleeding disorders, there have been some patients in whom therapy was unsuccessful. Patients have failed to respond, responded only transiently, or responded acutely but rebled and exsanguinated. Clark *et al.* [32] reported that "last-ditch" administration of rFVIIa is ineffective, with mortality rates in patients who were treated with rFVIIa similar to those in patient who were

not given the drug. These patients were all thrombocytopenic and coagulopathic. Eikelboom *et al.* [31••], in their report of use in acute bleeding patients, described the patients in whom rFVIIa failed to prevent death as being more coagulopathic and having received more blood products. Laffan *et al.* [41•] described the nonresponders as being more coagulopathic and thrombocytopenic. They also implicated underlying illness as a potential factor in the lack of response.

Dutton *et al.* [30] found that acutely bleeding patients who failed to respond were already in irreversible shock. In addition, several patients who did respond acutely died later in the hospital course of multiple organ failure. Multiple organ failure was likely caused by the initially profound shock state, characterized by hypothermia, acidosis, and thrombocytopenia. Additionally, most patients treated with rFVIIa for severe traumatic brain injury who responded to its administration still died of their brain injury. These patients would likely have expired in the acute phase had rFVIIa not been administered.

An experimental study conducted on the effect of hypothermia and pH determined that acidosis does reduce the efficacy of rFVIIa [78•]. These researchers failed to demonstrate a negative effect of hypothermia, however. Examining our experience at the University of Maryland, we have determined that Revised Trauma Score (RTS) less than 4.1, prothrombin time greater than 17.6 seconds, and lactate greater than 13 mg/dl are all independent predictors of futile rFVIIa administration. Additionally, age greater than 32 may predict futility in profoundly coagulopathic patients (Stein *et al.*, Presented at the 63rd Annual Meeting of the American Association of the Surgery of Trauma, Hawaii, 2004). Additionally, the need for CPR was also predictive of nonresponse to rFVIIa in our patients. The factors that we have identified are shown in Table 2. Clearly more work needs to be done in this area to better elucidate which patients benefit from rFVIIa.

### Dosing

The recommended dose of rFVIIa in patients with hemophilia with acquired inhibitors is 90 µg/kg every 2 hours until hemostasis is achieved (Novo Nordisk, NovoSeven product monograph). Doses as high as 120 µg/kg have been used for surgical cover and "serious" bleeding episodes in those with hemophilia [79••]. Megadoses as high as 240 µg/kg have been recommended [79••], and single doses of 300 µg/kg have been used in children and adolescents [80•]. There is some

evidence that continuous infusion of rFVIIa may be beneficial in those with hemophilia [81].

Because of its off-label use in trauma and other acute bleeding emergencies, the appropriate dosing is currently unknown. In the first reported use in a trauma patient, two doses of 60 µg/kg were used [26]. Since that time, doses as low as 10 µg/kg [36] and as high as 180 µg/kg [31••,42••] have been used successfully. Most of the lower doses have been used for reversal of anticoagulation and intracranial bleeds [46••,38••]. The more common dosing for acute traumatic hemorrhage has been in the range of 50 to 100 µg/kg. For use in the elective settings of retropubic radical prostatectomy, doses of 20 and 40 µg/kg were given [76••]. Perioperative blood loss in this study was, in fact, found to be dose dependent. In experimental work in swine, however, no clinical difference was found between 180 and 720 µg/kg despite a difference in measured VII levels in serum [24]. The currently recognized approach to dosing is to give enough rFVIIa to generate a thrombin burst that will result in stable clot formation. The number of repeated doses for acute hemorrhage in patients without hemophilia has ranged from one to 18 [42••], with a single dose being most typical.

### Monitoring

Monitoring rFVIIa administration has been a source of some debate. Several researchers have attempted to "normalize" the prothrombin and INR with rFVIIa [36]. However, caution in this use has been suggested because of the known therapeutic mechanism of rFVIIa, which is not likely to be appropriately measured with the prothrombin [82•,83•,84]. Most rFVIIa administration in the setting of acute hemorrhage is monitored primarily by clinical effect. Currently, laboratory monitoring of rFVIIa administration can be done using FVII:C levels [84,85] or thromboelastogram assays. The thromboelastogram provides information on the "kinetics" of clot formation and therefore is informative for determining the quality of clot [83•].

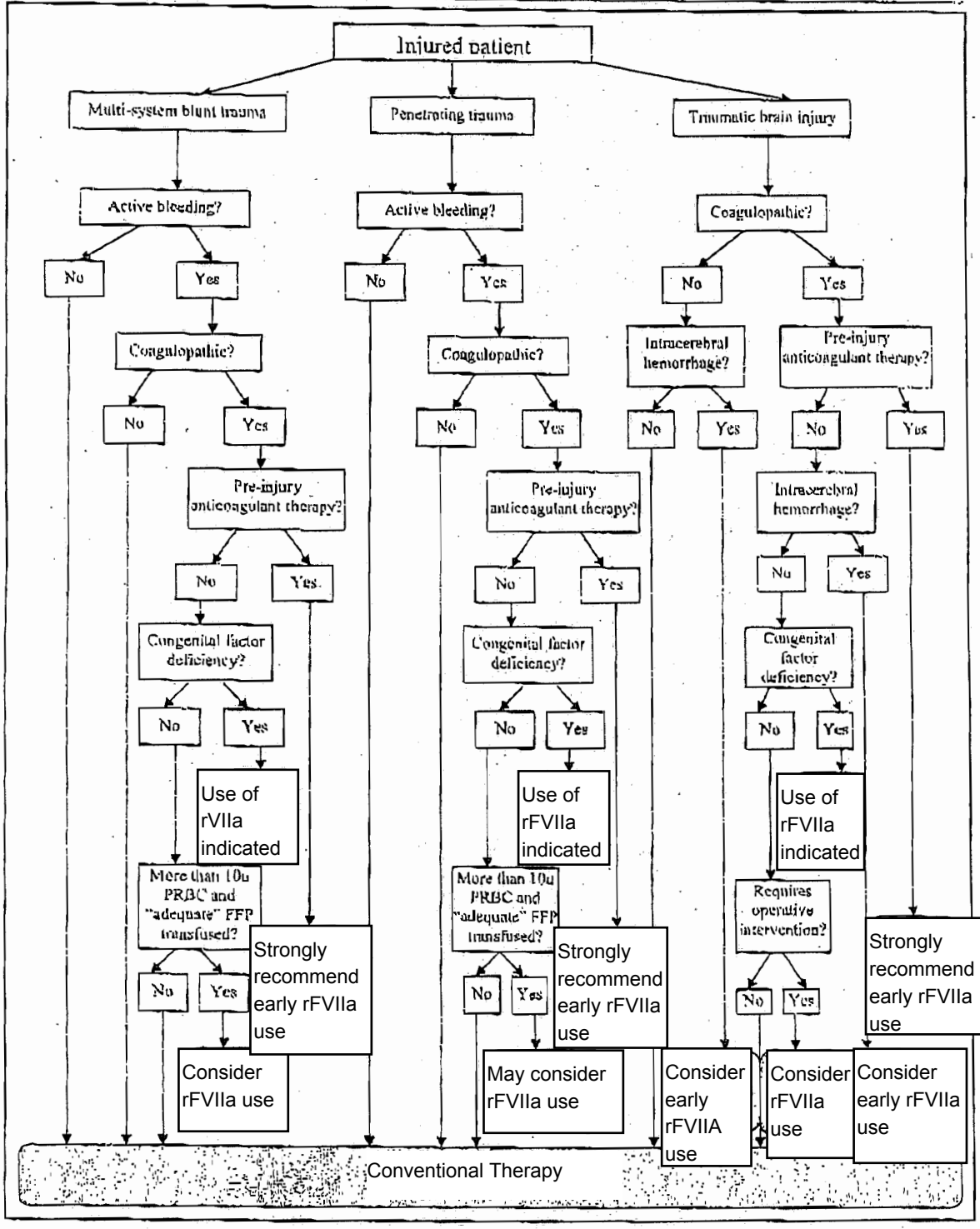
### Side effects

Much concern has been voiced about the safety of rFVIIa administration [86]. Its prohemostatic effect is thought to place patients at risk of diffuse thrombosis. However, clinically, this has seldom been reported [87••]. There have been reports of hemophilia patients with hemophilia experiencing myocardial infarction [88–90], pulmonary embolism [91], and disseminated intravascular coagulation (Novo Nordisk, NovoSeven product monograph). However, given the vast experience of administration in this patient population, these events are relatively rare. In addition, many of these patients who experienced thrombotic complications were concurrently treated with other procoagulants. Roberts [92] reports a

**Table 2. Potential markers of futility of recombinant factor VIIa administration**

Revised trauma score < 4.1
Lactate > 13 mg/dl
Ongoing or previous CPR

Figure 2. A proposed algorithm for the use of recombinant factor VIIa in the acutely injured patient



0.8% incidence of thromboembolic events during clinical trials with NovoSeven.

In 2001, Roberts [93] reported thrombotic episodes in 17 patients treated with rFVIIa for a variety of indications. In patients without hemophilia treated for acute hemorrhage, the larger series have reported few thrombotic complications. The series published by Marrinowitz *et al.* [28] reported one deep vein thrombosis. In the series from the United Kingdom, three thrombotic complications were noted among the 40 patients, although none were attributed to rFVIIa by the authors [41•]. No thrombotic events were reported in the series from Australia [31••]. The incidence of thrombotic complications in the series from Maryland was three of 61, with all three patients developing necrotic bowel that could have been attributable to mesenteric injuries [30]. There are several reports of rFVIIa use in patients with new vascular anastomoses without reported thrombosis [53–55,57–59].

Since 2003, additional reported complications in patients without hemophilia include one report of a thrombosed arteriovenous fistula after rFVIIa administration for coagulopathic bleeding after a thoracotomy [94] and one report of a clotted extracorporeal membrane oxygenation circuit after the patient had received both rFVIIa and Factor Eight Inhibitor Bypass Inhibitor [95]. The prospective trial conducted in patients undergoing radical prostatectomy reported no thrombotic complications [76••].

### Next steps

Although there is a growing body of anecdotal and retrospective reports of rFVIIa use for acute hemorrhage, to date no prospective, randomized trials have been published. Although the early reports from Novo Nordisk's trials in this patient population are encouraging, the data will have to be reviewed before conclusions can be drawn. Clearly, many clinicians have noted favorable clinical responses to rFVIIa when used in patients without hemophilia. A proposed algorithm for the use of rFVIIa in acute trauma is shown in Figure 2.

Recombinant factor VIIa also seems to be safe to administer without a large number of thrombotic complications reported, despite early concerns. However, there is no doubt that large prospective, placebo-controlled trials are indicated to delineate the drug's clinical efficacy. In addition, rFVIIa is expensive and without reliable evidence of its clinical efficacy and economic benefit; it should be used with reserve. Aside from demonstrating clinical benefit, other questions yet to be answered include optimal dosing, number of doses, and determination of criteria that predict futility of administration. These studies are currently ongoing [96••].

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