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# Safety Profile of Recombinant Factor VIIa

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**Recombinant factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) has been used for many years in the successful management of bleeding episodes in patients with hemophilia and inhibitors. More recently, rFVIIa has also shown considerable success as a hemostatic agent in trauma and surgery patients without pre-existing coagulopathy. Despite extensive and varied usage of rFVIIa, the incidence of serious adverse events associated with its use is less than 1%; however, there remain concerns regarding the agent's potential to induce thrombosis. This paper will review the safety profile of rFVIIa by examining existing clinical evidence, and will demonstrate that the isolated thrombotic events reported following rFVIIa treatment are due primarily to an improvement in the coagulation mechanism rather than rFVIIa treatment per se. The demonstrated safety of rFVIIa is probably due to its localization to injured areas of the vascular tree by binding to tissue factor (TF) and activated platelets at the bleeding site, thus avoiding systemic activation of coagulation. Finally, those situations in which rFVIIa therapy may not be safe, such as disseminated intravascular coagulation (DIC) and sepsis, will also be discussed.**

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FOR OVER A DECADE, recombinant factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) has been used successfully for the treatment and prophylaxis of bleeding episodes in hemophilia patients with inhibitors to either factor VIII (FVIII) or factor IX (FIX).<sup>27</sup> The efficacy of rFVIIa in this indication has led to its increasing use during surgical procedures, not only in hemophilia patients,<sup>13,19,27,42,43</sup> but also in those with disorders of platelet function.<sup>8,47</sup> Furthermore, improved understanding and better definition of the agent's mechanism of action have facilitated its increasingly widespread use as an adjunctive hemostatic therapy following trauma<sup>23,34</sup> or during surgery<sup>2,10,15,30</sup> in individuals without pre-existing coagulopathy.

Despite extensive use of rFVIIa (over 400,000 doses—defined as 90 µg/kg for a 70-kg individual) in a growing number of varied applications over recent years—including administration in the home treatment setting—the incidence of serious adverse events remains low.<sup>39</sup> Importantly, rFVIIa continues to demonstrate a favorable safety profile even when high or “mega” doses are administered,<sup>1,7,24,36</sup> allowing hemostatic efficacy to be achieved rapidly and safely in those patients who fail to respond to standard dosing regimens<sup>7</sup> and potentially reducing the number of repeat doses required.<sup>24</sup>

Clinical experience to date therefore suggests that rFVIIa is a safe and effective hemostatic agent; however, isolated reports of thrombotic events resulting from rFVIIa treatment<sup>8,12,25,37</sup> have given rise to concerns regarding the safety of the agent and its potential to induce serious adverse effects. Clearly, this is a highly significant issue. This paper will ask why concerns remain over the possible thrombogenicity of rFVIIa therapy, and will examine both current clinical evidence and the agent's mode of action in order

to review and evaluate its safety profile and thrombotic potential. Those conditions in which experimental or clinical data suggest that rFVIIa may not be safe—such as disseminated intravascular coagulation (DIC) and sepsis—will also be reviewed.

## rFVIIa and Thrombosis—Why the Concern?

Although rFVIIa has a highly favorable safety record to date, there remain concerns regarding its potential ability to induce thrombotic events. The widely acknowledged thrombotic problems associated with use of the early prothrombin complex concentrates (PCCs) are undoubtedly partially responsible for the current apprehension over the safety of rFVIIa<sup>39,40</sup>; in addition, several features and characteristics of the agent are suspected to be direct inducers of thrombosis. For instance, rFVIIa is an activated factor that initiates coagulation and, when administered at pharmacological doses, circulates at a concentration 1,000 times greater than normal. In addition, the agent's half-life (~2.5 hours) is considerably longer than that of other activated factors. It cannot be inhibited by antithrombin, and inhibition via tissue factor pathway inhibitor (TFPI) can only occur when rFVIIa has formed a complex with tissue factor (TF)

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**Table 1.** Number of Spontaneously Reported Thrombotic Events in Hemophilia Patients With Inhibitors, or Patients With Acquired Inhibitors, Receiving rFVIIa Since Approval in 1996

Type of Thrombotic Event	Hemophilia Patients
Cerebrovascular thrombosis	2
Cerebrovascular accident	1
Acute myocardial infarction	7
Disseminated intravascular coagulation	2
Deep vein thrombosis (including 1 pulmonary embolism)	6
<b>Total</b>	<b>18</b>

and FXa.<sup>26</sup> Finally, as demonstrated in an experimental study by Telgt and colleagues,<sup>44</sup> rFVIIa effectively reduces the prothrombin time (PT) and activated partial thromboplastin time (aPTT) in both normal plasma and plasma deficient in FVIII, FIX, FXI, and FXII. This reduction of the PT and aPTT has been attributed to the ability of rFVIIa to directly activate FX, even in the absence of TF.<sup>44</sup>

These factors all appear to indicate that treatment with rFVIIa should result in a hypercoagulable state, thus increasing the propensity towards the development of thrombosis. The current clinical picture, however, does not support this assumption.

### Clinical Experience With rFVIIa: Focus on Safety Considerations and Thrombotic Events

As of November 2002, more than 400,000 standard doses (90  $\mu\text{g}/\text{kg}$ ) of rFVIIa had been administered; even after extensive use in many situations that predispose to thrombosis, the rate of serious adverse events was less than 1% (Table 1). Similar incidences of side effects were found in a study by the Hemophilia Research Society of North America (HRS). A total of 1,939 bleeding episodes of 298 unique patients worldwide were treated with rFVIIa, producing an incidence of 1% and 8% for serious and nonserious treatment-related adverse events, respectively.

Despite these favorable data, isolated thrombotic events have occurred following rFVIIa therapy in a small number of patients with acquired or congenital hemophilia with inhibitors (Table 1). Seven patients have suffered acute myocardial infarction (MI) after rFVIIa administration, although five patients were older than 70 years of age and the majority showed pre-existing atherosclerosis that may have increased the risk of thrombosis. A case presented by Guillet and coworkers<sup>12</sup> described how a 75-year-old male patient with acquired hemophilia A developed a massive and fatal MI 3 days after initiation of rFVIIa therapy (90  $\mu\text{g}/\text{kg}$  with tranexamic acid every 3 hours) for the treatment of massive melena following

surgery for a rectal adenocarcinoma. The authors suggested, however, that rFVIIa was not the sole trigger of the MI; this elderly patient also presented with mild hypercholesterolemia type IIb, a dysrhythmia with moderate left ventricular hypertrophy, and hypertension, all of which may have contributed to thrombus formation.<sup>12</sup> A further case of MI has been reported in a patient with hemophilia A and inhibitor treated with rFVIIa (bolus dose of 102  $\mu\text{g}/\text{kg}$  followed by continuous infusion at 30  $\mu\text{g}/\text{kg}/\text{h}$ ) and tranexamic acid prior to and during dental extraction.<sup>37</sup> Although rFVIIa was considered to be the cause of the MI, the agent was nevertheless used again 18 hours post-MI to cover removal of a catheter sheath.

Cerebrovascular thrombotic events have been observed in six patients, three of whom were participants in a clinical trial. Three of the patients were greater than 55 years old and several presented with pre-existing risk factors for cerebrovascular thrombosis, such as cardiovascular disease, multi-infarct dementia, previous cerebrovascular accident, and hypertension. Following prophylaxis with rFVIIa to cover craniotomy for a subdural hematoma, an 8-year-old male experienced an occipital infarct that may have been caused by a thrombotic event in the left occipital region, although further use of rFVIIa was not associated with additional infarction. This patient had received prior therapy with FVIII, porcine FVIII, and aPCCs (data on file, Novo Nordisk).

Other thrombotic events involving the pulmonary vasculature, right internal jugular vein, colon microvasculature, or cephalic-basilic vein have been found in six patients (one additional patient had thrombophlebitis at the injection site). Resolution of the thrombosis was achieved in five patients, but one patient who had received prior porcine FVIII and FEIBA (Baxter Corp) therapy, and had suffered a deep vein thrombosis and pulmonary embolism 2 days after receiving rFVIIa, died (data on file, Novo Nordisk).

The current literature also contains several further isolated reports of thrombotic events that may be related to rFVIIa use. In a study of rFVIIa treatment in three patients with Glanzmann's thrombasthenia, one 72-year-old woman received rFVIIa (90  $\mu\text{g}/\text{kg}$  followed by continuous infusion of 30  $\mu\text{g}/\text{kg}/\text{h}$  for 16 days) to cover laparotomy and segmental intestinal resection. Five days after discontinuation of rFVIIa therapy, the patient experienced severe bilateral venous thrombosis of the legs and a pulmonary embolism of the left lung. Heparin therapy successfully resolved the thromboses, which were attributed to the high continuous infusion rate of rFVIIa and the prolonged treatment period.<sup>8</sup>

These cases illustrate how many patients experiencing thrombotic events following rFVIIa treatment

also demonstrate underlying pathological conditions that predispose to the development of thrombosis, such as atherosclerosis, diabetes, or hypertension. Thus, thromboembolic events in such patients are typical of the type that may be expected with underlying comorbidities that predispose to thrombosis when thrombin generation is enhanced or normalized. It would seem, therefore, that most thrombotic events that have been associated with rFVIIa use are related to underlying pathology, and result from improvements in the clotting mechanism rather than rFVIIa therapy per se.<sup>40</sup> As well, it is perhaps worth noting that approximately one third of the patients having thrombotic events had been previously treated with aPCCs or antifibrinolytic agents.

### rFVIIa in the Home Treatment Setting

The early treatment of bleeding episodes in hemophilia patients is considered to be considerably more effective than later intervention, and is thought to minimize the damage caused by hemorrhage and reduce the amount of product required.<sup>28,29</sup> Accordingly, home treatment with rFVIIa has been found to produce cost savings, reduce morbidity, and provide greater convenience.<sup>28,29,41</sup> It is therefore vital that rFVIIa demonstrates a favorable safety profile in the home treatment setting.

Key et al<sup>25</sup> conducted a multicenter, open-label study to determine the efficacy and safety of fixed-dose rFVIIa in the treatment of mild to moderate bleeds in hemophilia patients. Of 60 patients enrolled, 56 had at least one bleed and self-administered up to three doses of rFVIIa (90  $\mu\text{g}/\text{kg}$  at 3-hour intervals). Effective hemostasis was achieved in 92% of 614 evaluable bleeding episodes after a mean of 2.2 doses. A superficial thrombophlebitis was the only thrombotic complication observed, but the affected patient did not withdraw from treatment.<sup>25</sup> Although this study was uncontrolled and nonblinded, it involved a large patient population experiencing many bleeding episodes, and the results demonstrate that home treatment with rFVIIa is both safe and effective.

Two smaller studies have also highlighted the safety of rFVIIa when administered at home. In 1994, a home-treatment program was initiated to investigate the use of rFVIIa in the early intervention of minor bleeds in hemophilia patients with high-responding inhibitors.<sup>20</sup> Seven patients were instructed to inject one dose of 90 to 100  $\mu\text{g}/\text{kg}$  rFVIIa at the onset of a new bleed, followed by a second dose after 3 hours if required. A mean of 2.1 doses was required to effectively manage 114 bleeding episodes. No thromboembolic adverse events were observed, leading to the conclusion that home treatment with rFVIIa is safe and effective in the management of minor bleeds.<sup>20</sup> Similar results were obtained in a

later study involving 10 inhibitor patients.<sup>41</sup> Home treatment with up to four doses of rFVIIa (90  $\mu\text{g}/\text{kg}$  every  $3 \pm 1$  hours) produced effective or partially effective results in 79% and 11% of patients, respectively, after a median of two doses. Despite mild side effects in 2.6% of patients, no thromboembolic events were encountered.<sup>41</sup>

These studies confirm that rFVIIa can be used safely for the treatment of mild to moderate bleeds in hemophilia patients in the home setting. This means that hemorrhagic episodes can be treated earlier than a hospital visit would otherwise allow, producing more effective results and subsequent cost-benefits.

### High-Dose rFVIIa Does Not Increase Thrombotic Potential

To date, treatment with rFVIIa has repeatedly demonstrated a high level of safety. We must also ask ourselves if the agent remains safe even when administered at doses far higher than the recommended levels.

One of the first recipients of “mega-dose” rFVIIa was a boy with hemophilia B and high-titer inhibitors. He first received rFVIIa in 1994, when three doses of 100  $\mu\text{g}/\text{kg}$  were required to manage persistent bleeding from the nose and mouth. One year later, a severe right knee bleed failed to resolve after six doses of 120  $\mu\text{g}/\text{kg}$ , necessitating further treatment with six doses of 180  $\mu\text{g}/\text{kg}$ . In 1997, the patient developed a severe knee bleed that did not respond well to conventional doses (90 to 120  $\mu\text{g}/\text{kg}$ ), and subsequent development of bilateral knee-joint flexion contractures led to confinement in a wheelchair. Shortly afterwards he developed a target joint in his right elbow, and a therapeutic regimen involving a bolus dose of 160  $\mu\text{g}/\text{kg}$  rFVIIa followed by continuous infusion of 16  $\mu\text{g}/\text{kg}/\text{h}$  failed to provide hemostatic efficacy. Based on these observations and the patient’s failure to respond to a dose of less than 160  $\mu\text{g}/\text{kg}$ , it was decided to treat any further significant bleeds with a dose of 320  $\mu\text{g}/\text{kg}$ . This dose was later administered to treat a soft tissue bleed in the left forearm, with an excellent hemostatic response. The discovery of an effective dose level meant that the patient could begin an intensified physiotherapy program to eliminate the need for a wheelchair. He was given 240  $\mu\text{g}/\text{kg}$  rFVIIa every 6 hours for 48 hours during the physiotherapy regimen, with the dose interval gradually lengthening to 24 hours over the next 25 days. No bleeding into the knee or other joints was noted, indicating the prophylactic efficacy of high-dose rFVIIa. Furthermore, no adverse events or thromboembolic complications resulted from the high-dose regimen.<sup>7</sup>

The HRS investigated mega-dose rFVIIa therapy in 556 bleeding episodes in hemophilia patients with

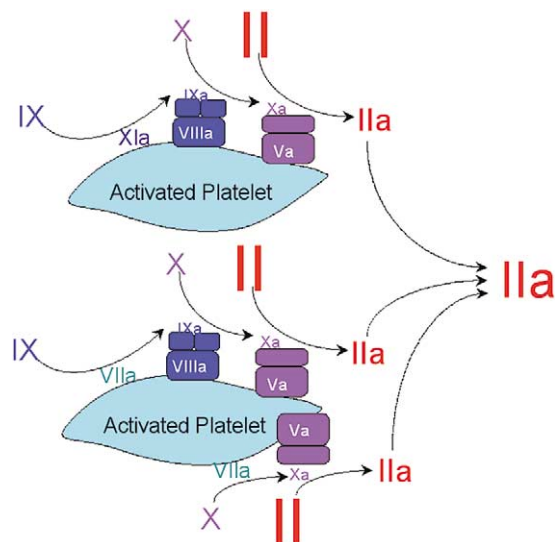
inhibitors. A median dose of 360  $\mu\text{g}/\text{kg}$  administered over 72 hours produced an effective response in 97% of episodes; greater hemostatic efficacy was achieved with higher doses ( $>200 \mu\text{g}/\text{kg}$ ). No safety concerns were raised.<sup>36</sup>

Based on such observations, Abshire<sup>1</sup> recommends that a mega-dose of 300  $\mu\text{g}/\text{kg}$  can be considered for uncomplicated bleeding incidents in children if treatment can be initiated within a few hours of bleed onset. Recently, Kenet and colleagues<sup>24</sup> confirmed the validity of this recommendation in an open-label, single-center study examining the efficacy and safety of 300  $\mu\text{g}/\text{kg}$  rFVIIa as a treatment for bleeds in three young hemophilia patients with inhibitors. Of 114 bleeds, 95 responded to a single dose, and 19 required a second bolus injection (200 to 300  $\mu\text{g}/\text{kg}$ ) within 3 to 4 hours. One patient experienced two incidents of unexplained fever that subsided spontaneously, but no other side effects or thrombotic events were observed. The rFVIIa mega-dose of 300  $\mu\text{g}/\text{kg}$  was considered to be safe, effective, and more convenient than recurrent injections or continuous infusion.<sup>24</sup> Despite this success in pediatric patients, however, Abshire<sup>1</sup> suggests that the standard dosing regimen (90  $\mu\text{g}/\text{kg}$  every 2 to 3 hours) should still be used in adult patients until more safety data from this population are accumulated.

Finally, further support for the safety of high-dose rFVIIa is provided by two cases of accidental rFVIIa overdose in which no adverse events were encountered. One hemophilia B patient received a single dose of 352  $\mu\text{g}/\text{kg}$ , and a patient with hemophilia A was given several doses ranging between 246 and 986  $\mu\text{g}/\text{kg}$  on 5 consecutive days. There were no reported complications in either case, indicating that massive doses of rFVIIa are not necessarily associated with an increased thrombotic potential (NovoSeven Prescribing Information). The demonstrated safety of rFVIIa when administered at higher doses not only provides a greater degree of hemostatic efficacy in patients who lack response to standard regimens, but also allows a dosing flexibility that is both patient-specific and related to the potential for bleeding.<sup>7</sup>

### Mode of Action of rFVIIa in Patients Without Pre-existing Coagulopathy

Recombinant FVIIa has been used extensively on an investigational basis in bleeding patients without pre-existing coagulopathy. This patient group includes those individuals with trauma- or surgery-associated hemorrhage,<sup>2,10,15,23,30,34</sup> pulmonary hemorrhage,<sup>16,22,35</sup> or bleeding following bone marrow transplantation.<sup>3</sup> The apparent safety of even high-dose rFVIIa treatment can perhaps be explained by the agent's mode of action in patients with ostensibly normal coagulation.



**Figure 1.** Mechanism of action of rFVIIa in patients with normal coagulation.

In patients without coagulopathy, rFVIIa has no effect on platelet or fibrinogen levels but increases the level of fragment 1 + 2 (F1 + 2) and other coagulation products, such as thrombin anti-thrombin (TAT).<sup>9</sup> This is thought to be caused by the diffusion of rFVIIa to the extravascular space at the site of vessel damage, where it interacts with TF to initiate coagulation and increase levels of F1 + 2. Consequently, rFVIIa is able to enhance or “drive” the TF pathway at the injury site, thus enhancing thrombin generation in the localized area of vessel damage. Further localization of rFVIIa to the bleeding site is also achieved through TF-independent binding to activated platelets that adhere to the area of vessel injury via interactions with von Willebrand factor (VWF; Fig 1).<sup>17,18,32</sup> High levels of platelet-bound rFVIIa then activate factors X and IX on the surface of activated platelets, leading to the assembly of prothrombinase complexes and subsequent local thrombin formation (Figs 2 and 3).<sup>17</sup>

In hemophilia patients, localization of rFVIIa activity is achieved in the same way: binding to TF exposed at the injury site “drives” the TF pathway, and binding to activated platelets generates sufficient FXa on the platelet surface to support a burst of thrombin generation, even in the absence of FIXa/FVIIIa. These mechanisms for the localization of rFVIIa to the site of injury not only help to explain its clinical efficacy,<sup>17,33</sup> but also ensure that the agent's activity is restricted to the bleeding site, thus avoiding systemic activation of the clotting system and the subsequent risk of thrombosis (Fig 1).<sup>17</sup>

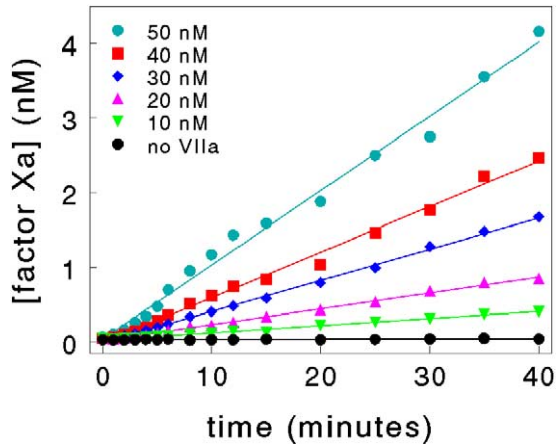


Figure 2. rFVIIa activation of FX on the platelet surface.

### Is rFVIIa Safe to Use in DIC and Sepsis?

Despite the highly favorable safety profile that has been demonstrated by rFVIIa in a variety of situations, indications, and patient populations, there still remains considerable controversy surrounding the issue of whether it should be administered in the presence of DIC or sepsis. DIC and septicemia are contraindications of rFVIIa therapy, due to the potentially increased risk of developing thrombosis as a result of circulating TF or predisposing coagulopathy (NovoSeven Prescribing Information). During infection and subsequent septic shock, TF is rapidly induced on blood mononuclear cells and vascular endothelium, resulting in systemic activation of coagulation,<sup>6,31</sup> consumption of coagulation factors,<sup>48</sup> and depletion of coagulation inhibitors such as antithrombin III.<sup>31</sup> These factors all contribute to the development of DIC, and affected patients exhibit a severely hypercoagulable state.<sup>48</sup>

Furthermore, several workers have shown that inactivated rFVIIa (rFVIIai)—which acts as an anti-thrombotic agent by competing with FVII for binding sites on TF, thus blocking FVIIa activity<sup>38</sup>—has an anti-inflammatory effect in endotoxin-induced sepsis.<sup>4,14,21</sup> These findings clearly indicate that TF/FVIIa activity is an early event in the pathogenesis of sepsis and DIC.

It would therefore seem reasonable to assume that the administration of rFVIIa under conditions of DIC or sepsis may enhance the thrombotic predisposition already established by the presence of widespread fibrin deposition and consumption of coagulation inhibitors. For this reason, the use of rFVIIa in cases where such pathology is present remains controversial.<sup>6</sup> Despite these observations, however, there exists experimental evidence suggesting that rFVIIa does not produce or enhance a hypercoagulable state *in vitro*.<sup>11</sup> A second study also found that neither low-

nor high-dose rFVIIa exacerbates endotoxin-induced DIC in monkeys (data on file, Novo Nordisk).

In accordance with these experimental findings, there is a growing number of clinical reports in which rFVIIa has been administered to patients with DIC or sepsis, with effective results and no evidence of thromboembolic events. In the first reported use of rFVIIa in a trauma patient, a 19-year-old soldier with a high-velocity rifle injury presented with life-threatening hemorrhage and DIC, along with hypothermia, ketoacidosis, and profound hypovolemic shock. Intravenous administration of rFVIIa 60  $\mu\text{g}/\text{kg}$  immediately corrected the coagulopathy and stopped the bleeding, with no evidence of thrombotic effects or adverse events.<sup>23</sup> Another report describes the case of a 19-year-old woman with cardiogenic shock after intraoperative cardiac arrest, resulting in hepatic dysfunction and DIC. As the subsequent coagulopathy did not respond to treatment with fresh-frozen plasma (FFP), a bolus injection of rFVIIa 70  $\mu\text{g}/\text{kg}$  was administered, producing cessation of hemorrhage and normalization of coagulation. No adverse or thrombotic events were encountered.<sup>45</sup>

A more recent case involved intra-abdominal bleeding in a patient with DIC caused by septic shock. Treatment with rFVIIa 80  $\mu\text{g}/\text{kg}$  was initiated when conventional replacement therapy using FFP and red blood cells failed to provide a hemostatic response; the bleeding stopped rapidly with no evidence of thrombosis or other adverse effects, and surgery to drain the intra-abdominal blood was performed uneventfully.<sup>6</sup>

Recombinant FVIIa has also been administered to pediatric patients with symptoms of DIC. Tobias et al<sup>46</sup> conducted a retrospective review of rFVIIa therapy in 10 pediatric patients with coagulopathies of varying etiologies, including DIC, dilutional coagulopathy, and hepatic insufficiency. Following administration of rFVIIa (dose range, 50 to 100  $\mu\text{g}/\text{kg}$ ),

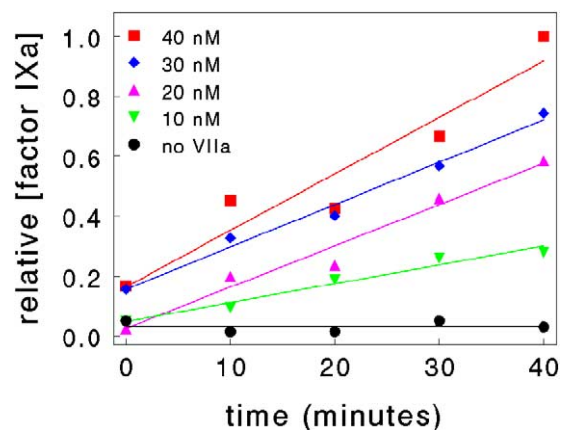


Figure 3. rFVIIa activation of FIX on the platelet surface.

**Table 2. Benefit and Risk Summary of rFVIIa Therapy**

Benefits	Risks
<ul style="list-style-type: none"> <li>● Effective in 90% of cases</li> <li>● It is a recombinant product, and therefore free from viral contamination</li> <li>● No evidence of antigenicity or transfusion reactions</li> <li>● Effective when other treatments fail or are contraindicated</li> <li>● Not subject to blood supply shortages, and may provide a safer and more effective alternative to blood transfusions</li> <li>● High doses are safe and effective, and allow reduced frequency of dosing</li> <li>● Safe and effective in a range of bleeding disorders, and in individuals without pre-existing coagulopathy</li> </ul>	<ul style="list-style-type: none"> <li>● Incidence of adverse events: 13%</li> <li>● Incidence of serious adverse events: &lt;1%</li> </ul>

clinically evident bleeding stopped in all cases, and no rFVIIa-associated adverse events were identified. In a second study, Chuansumrit and coworkers<sup>5</sup> reported the cases of three children with acute bleeding resulting from liver failure and DIC. Cases 1 and 2 received rFVIIa combined with conventional replacement therapy, whereas case 3 received rFVIIa alone; all three children received a bolus dose of 40 to 180  $\mu\text{g}/\text{kg}$  followed by continuous infusion of 16.5 to 33  $\mu\text{g}/\text{kg}/\text{h}$ . The bleeding resolved in all patients following rFVIIa therapy, with no adverse events.

Although rFVIIa has been used to effectively and safely treat DIC in the studies and case reports discussed here, it must be emphasized that such therapy is not appropriate for all such patients. If rFVIIa is used under conditions of DIC or other hemostatic disturbances, the patient must be carefully monitored before, during, and after infusion. It is also possible that all cases diagnosed as DIC did not have true DIC; hence, critical analysis of the data is needed before rFVIIa can be assumed to be safe under these conditions.

### Summary

There exists some concern over the safety of rFVIIa treatment, particularly with regard to its potential thrombogenicity. Although certain characteristics of rFVIIa appear likely to increase the risk of thrombosis, analysis of existing clinical data suggests that the agent demonstrates a highly favorable safety and efficacy profile that far outweighs any observed risk (Table 2). Evidence in the current literature indicates that rFVIIa is a safe and effective treatment in hemophilia and other disorders of hemostasis, and even in patients without pre-existing coagulopathy; to date, the incidence of serious adverse events is less than 1%. Several reports even suggest that high megadoses of rFVIIa do not induce an increased thrombotic risk, allowing greater flexibility of treatment for those patients who fail to respond to more conventional doses. Therapy with rFVIIa in the home treatment setting has also shown considerable success,

safely facilitating more effective management of bleeding episodes and significant cost benefits.

Although isolated cases of thrombotic events have been reported following rFVIIa use, they are primarily found in elderly patients with underlying pathology that predisposes to thrombosis under conditions in which thrombin generation is improved. In such cases, the thromboembolic events may not be directly due to rFVIIa itself, but may instead be caused by improvement in the patient's coagulation status.

The demonstrated safety of rFVIIa in a variety of indications and situations may be provided by the localization of rFVIIa to the site of injury, thus avoiding systemic activation of coagulation and the subsequent risk of thrombosis. This is achieved through the binding of rFVIIa to TF and activated platelets that are exposed at damaged areas of the vascular tree. Despite these mechanisms for the localization of rFVIIa, however, its use in DIC and sepsis remains controversial. Several reports in the literature suggest that rFVIIa may be used safely and effectively in such situations, without induction of thrombotic events, although it cannot be recommended that the agent should be used in all similar cases. Indeed, patients who have bleeding problems with underlying pathologies that predispose to thrombosis should be carefully monitored before, during, and after rFVIIa therapy.

Finally, it should be noted that use of rFVIIa is approved by the Food and Drug Administration (FDA) only for the treatment of bleeding in patients with hemophilia A and B who have inhibitors against factors VIII and IX, respectively. Its use under other conditions represents off-label use not approved by the FDA in the United States.

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