



## **Recombinant Factor VIIa: A Review on Its Clinical Use**

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### **Abstract**

Recombinant activated factor VII (rFVIIa) (NovoSeven) is a novel hemostatic agent originally developed to treat bleeding episodes in hemophilic patients with inhibitors against coagulation factors VIII and IX. In recent years, rFVIIa has also been employed for the management of uncontrolled bleeding in a number of congenital and acquired hemostatic abnormalities. Based on a literature search including PubMed, references from reviews, and abstracts from the most important meetings on this topic, this review examines the current knowledge on therapy with rFVIIa, from the now well-standardized uses to the newer and less well-characterized clinical applications.

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### **1. Introduction**

Recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk Pharmaceuticals, Bagsværd, Denmark) was originally developed for the treatment of hemophilic patients with inhibitors and then used successfully for treating hemorrhages in patients with acquired hemophilia [1-6]. In the last few years, along with the improvement in the knowledge of its mechanisms of action, rFVIIa has also been used with benefit as a “universal hemostatic agent” in many other nonhemophilic bleeding situations, including congenital FVII deficiencies, quantitative and qualitative platelet disorders, hepatic failure, liver transplantation, major surgery, and trauma [7-12]. This review briefly analyzes the clinical experience regarding rFVIIa treatment and focuses particularly on the newer uses, for which there are only a few randomized, controlled clinical trials. Table 1 summarizes the current approved and “off-label” clinical applications of rFVIIa.

### **2. Mechanisms of Action of rFVIIa**

FVIIa is an important contributor to the initiation of hemostasis [12]. According to a cell-based model of coagula-

tion [13,14], tissue factor (TF) is exposed to circulating blood following injury to the vessel wall, and TF-FVIIa complexes are formed on the TF-bearing cells, where they activate factor X (FX) to produce activated FX (FXa), leading to the conversion of prothrombin to thrombin. The limited amount of thrombin formed activates FV, FVIII, and FXI, as well as platelets, which in turn change shape and expose negatively charged phospholipids, such as phosphatidylserine. These activated platelets provide the template for further FX activation and full thrombin generation with a positive feedback on FV, FVIII, and FXI [15,16]. The extra formation of thrombin results in the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which protects the fibrin clot from premature lysis by down-regulating fibrinolysis [17]. In summary, a full thrombin burst is essential for the formation of a stable fibrin hemostatic plug that is resistant to premature fibrinolysis. In fact, only an initial, limited amount of thrombin dependent on the TF-FVIIa complex is generated in hemophilia, and this amount of thrombin is insufficient to consolidate and sustain the fibrin plug [18]. In a cell-based in vitro model, the addition of increasing amounts of rFVIIa (between 50 and 150 nM) to activated platelets in the presence of FX has been shown to produce a linear increase in the generation of FXa independently of the presence of TF on the platelet surface [15,19-21]. This dose-response mechanism can lead to the generation of significant amounts of thrombin, even in the absence of FVIII and FIX, thus explaining the mechanism of action of rFVIIa in hemophilia patients [12]. The direct activation of FIX on activated platelets in the absence of TF, resulting in improved thrombin generation, may also explain the mechanism of rFVIIa action in acquired coagulopathy following trauma, surgery,

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**Table 1.**

Approved and Potential Clinical Applications of Recombinant Activated Factor VII

Hemophilia and clotting defects
Hemophilia with inhibitors*
Acquired hemophilia*
Congenital factor VII deficiency*
Glanzmann thrombasthenia*
Other platelet disorders (qualitative and quantitative)
Other coagulation factor defects (factor XI and von Willebrand disease)
Emergency bleeds
Intracerebral hemorrhage
Upper gastrointestinal bleeds
Trauma
Oral anticoagulant-induced hemorrhage
Surgery
Liver resection
Orthotopic liver transplantation
Neurosurgery
Cardiac surgery

\*Currently approved in Europe.

or other events [22]. Moreover, the binding of rFVIIa to activated platelets may explain why rFVIIa is localized only to the site of bleeding [12,14]. However, other mechanisms of rFVIIa action have been proposed [23]. In fact, ten Cate and colleagues and subsequently van 't Veer and coworkers proposed a TF-dependent mechanism of rFVIIa action [24,25]. This model was strengthened more recently by the work of Butenas and colleagues, who reported that the local function of rFVIIa was mediated by the combined effect of TF expression and platelet accumulation at the site of a vascular lesion [26,27]. Lisman and De Groot recently analyzed the experimental data available and concluded that both proposed mechanisms of rFVIIa action (ie, TF-dependent and TF-independent) are plausible [23]. In fact, if the TF pathway is usually required for the action of rFVIIa, an rFVIIa-mediated thrombin generation can also occur on the activated platelet surface independently of TF. Moreover, the same authors observed that the enhanced formation of thrombin from rFVIIa not only accelerates clot formation but also inhibits fibrinolysis via TAFI activation [28] and enhances platelet adhesion and aggregation under flow conditions [29]. This last piece of evidence may explain the therapeutic effect of rFVIIa in thrombocytopenic patients. In conclusion, our current knowledge indicates that rFVIIa induces hemostasis by enhancing thrombin generation on thrombin-activated platelet surfaces, thereby providing the formation of a stable, tight fibrin clot that is resistant to premature fibrinolysis.

### 3. Pharmacokinetics, Pharmacodynamics, and Monitoring of rFVIIa

Some peculiar features of the *in vivo* decrease of FVIIa have very important implications for its therapeutic use. rFVIIa is known to compete with plasma FVII for binding to TF, for which both factors have a strong affinity. Once the TF-rFVIIa complex has been formed, it binds to and activates FX (to produce FXa). The TF-rFVIIa-FXa complex is

subsequently inhibited by its binding with the TF plasminogen inhibitor [30]. The rapid decrease of rFVIIa level *in vivo* means that this drug must be given as frequent bolus injections (every 2-4 hours) or as a continuous infusion [31]. However, because the steady state of any drug can be reached only if the dose administered is the same as the drug's clearance (CL) plus the desired increase (minimum level of hemostasis) multiplied by the interval between the bolus doses ( $\tau$ ), it is clear that the most economical form of administering rFVIIa is by continuous infusion, during which  $\tau$  reaches its lowest possible value. In fact, continuous infusion allows an rFVIIa savings of greater than 30% because, unlike bolus injections, continuous infusion does not produce peak drug concentrations greater than the predetermined minimum level of hemostasis, which are not necessary and can be dangerous [32]. However, the recent introduction of single megadoses capable of causing considerable bursts of thrombin has challenged the use of continuous infusions, even though no results of any controlled trials comparing the efficacies of the 2 regimens have been published. It is important to emphasize that each patient's CL must be measured before either method of rFVII administration is used, because there is wide interindividual and intraindividual variability in this parameter. Pharmacokinetic investigations aimed at designing tailored therapy have undoubted financial advantages and are particularly important before the start of prophylaxis or if surgery is being considered [33]. The pharmacokinetic studies published so far have documented that the CL of rFVIIa is much higher than that of FVIII or FIX and that the mean residence time (MRT) and half-life are considerably shorter. Lindley and colleagues performed the first pharmacokinetic study in 1994 on 15 adult patients with hemophilia A or B, with or without inhibitors, and during bleeding episodes or in the nonbleeding state [30]. The median CL was 31 mL/h per kilogram in nonbleeding periods and 32.5 mL/h per kilogram during bleeding episodes. In nonbleeding periods, the median MRT was 3.44 hours, and the median half-life was 2.89 hours. The elimination rate appeared to be higher during bleeding episodes, because the median MRT was 2.97 hours and the median half-life was 2.30 hours. In 1996, Shulman and colleagues reported the first experience with continuous rFVIIa infusion and demonstrated a great variability in the CL, which decreased in one patient from 86.4 to 24.7 mL/h per kilogram [32]. In complete contrast were the results of Ludlam and colleagues, who conducted a multicenter study in 2003 with 9 patients with severe hemophilia A and FVIII inhibitors who underwent elective major orthopedic surgery and received rFVIIa by continuous infusion (initial preoperative bolus of 90  $\mu$ g/kg followed by continuous infusion at a fixed rate of 50  $\mu$ g/kg per hour) [34]. The median total rFVIIa clearance in these 9 patients remained stable during the period of continuous rFVIIa infusion [34]. A pharmacokinetic study of rFVIIa conducted with 28 volunteers anticoagulated with acenocoumarol found interindividual variabilities of 20% for the CL and 16% for the volume of distribution area (VdArea); the latter appeared to be significantly dose dependent [35]. More recently, a randomized controlled multicenter trial compared the pharmacokinetic profiles of rFVIIa (90 or 180  $\mu$ g/kg) in 12 children and 6 adults with hemophilia A

and found that the CL was faster and the VdArea was larger in children than in adults (78 versus 53 mL/h per kilogram for CL and 164 versus 128 mL/kg for VdArea), suggesting that higher rFVIIa doses may be needed in children to achieve the same plasma levels as in adults [36]. Finally, Berrettini and colleagues conducted a pharmacokinetic evaluation of rFVIIa (15 or 30  $\mu\text{g}/\text{kg}$ ) in 5 patients with severe FVII deficiency and found higher dose-independent values of CL and VdArea than those observed in adult hemophilic patients or in volunteers on anticoagulant therapy [37]. These results, which were similar to those observed in hemophilic children, were explained by the absence of competition between the patient's FVII zymogen and infused rFVIIa for binding to TF in such patients. However, in spite of the rapid CL for the TF-rFVIIa complex from the plasma, the faster binding of infused rFVIIa to TF may account for the higher efficacy of rFVIIa and for the lower doses (20  $\mu\text{g}/\text{kg}$ ) required to achieve hemostatic efficacy in such patients compared with those with hemophilia.

As regards laboratory methods for monitoring rFVIIa therapy, measurements of postinjection prothrombin time and FVII activity (FVII:C) have been suggested, although adequate hemostatic levels have not been defined [38]. Recently, an alternative hemostatic laboratory method (the thromboelastogram) has been proposed [39,40]. However, to date no assay has been developed with results that correlate adequately with clinical outcomes in a sufficiently large sample of patients.

#### **4. Use of rFVIIa in Hemophilic Patients with Inhibitors**

Thanks to its ability to bypass the intrinsic coagulation pathway by activating FX directly and independently of the presence of FVIII or FIX, rFVIIa has dramatically changed the treatment of hemophilic patients with inhibitors, thus permitting previously contraindicated major surgery (eg, orthopedic operations) [41,42].

##### *4.1. The Use of rFVIIa in Surgery*

After the first report in 1988 of an open knee joint synovectomy successfully managed with rFVIIa [43], many other elective major surgical procedures have been performed in hemophilic patients with inhibitors. In a prospective double-blind study published in 1998 of hemophilic patients with inhibitors who underwent surgery (29 episodes, 18 minor and 11 major surgeries), Shapiro and colleagues demonstrated that an rFVIIa dose of 90  $\mu\text{g}/\text{kg}$  is an effective first-line option [44]. Hedner and colleagues reported the successful use of rFVIIa at a dose of 60 to 90  $\mu\text{g}/\text{kg}$  every 3 to 4 hours in 6 of 7 patients who underwent dental surgery [45]. In a prospective study published in 1998, Lusher and colleagues used rFVIIa in 103 surgery procedures (21 major and 7 minor surgeries, and 25 dental extractions) with excellent/effective responses in 81%, 86%, and 92% of major, minor, and dental surgical procedures, respectively [1]. In the majority of patients, the initial dose was 90  $\mu\text{g}/\text{kg}$ . Subsequently, Scharrer reported 22 major/minor surgical procedures with an overall effective response to treatment

(median dose, 90  $\mu\text{g}/\text{kg}$ ) of 91% [46]. Recently, Quintana-Molina and colleagues, reporting on their own 20-year experience of surgery on hemophilic patients with inhibitors, documented their good results with rFVIIa (67% in major surgeries and 80% in minor surgeries) [47]. Other data from the literature indicate that rFVIIa is effective in providing hemostatic prophylaxis for central catheter insertion: rFVIIa prophylaxis was judged excellent or effective in 83% (25/30) of evaluable procedures in one case series [48] and in 87% (26/30) of evaluable procedures in another series [49].

##### *4.2. The Use of rFVIIa for Treatment of Joint, Muscle, and Mucocutaneous Bleeding*

A randomized double-blind, dose-finding multicenter study conducted in 1998 by the rFVIIa Study Group compared 35  $\mu\text{g}/\text{kg}$  versus 70  $\mu\text{g}/\text{kg}$  of rFVIIa in treating joint, muscle, and mucocutaneous bleeding episodes in patients with inhibitors against FVIII or FIX [50]. Although both doses achieved excellent/effective results in 71% of hemarthrosis cases, the higher dose achieved a greater number of excellent responses than the lower dose in severe joint bleeds and bleeding in target or damaged joints, and in peripheral intramuscular hemorrhages. In the same year, a study on home treatment of hemophilic patients with inhibitors with rFVIIa showed that a mean of 2.2 injections of 90  $\mu\text{g}/\text{kg}$  at 3-hour intervals was effective at controlling mild to moderate bleeding episodes [51]. The importance of early intervention during home treatment with rFVIIa shown in this study was further outlined by Santagostino and colleagues in a subsequent report that evaluated 53 bleeding episodes in patients with high-titer FVII inhibitors [52]. In fact, earlier treatment with rFVIIa (started within 6 hours from the onset of bleeding) was associated with a better therapeutic response and a smaller number of required doses. Effective home treatment in which hemostasis was achieved in most patients after 2 to 3 bolus injections was also reported by other groups [53,54]. Overall, home treatment with rFVIIa has been shown to be effective in 79% to 92% of mild/moderate hemorrhages in hemophilic patients with inhibitors.

##### *4.3. The Use of rFVIIa for Treatment of Severe Bleeding*

The evidence for the use of rFVIIa in the treatment of severe bleeding is mainly drawn from prospective, uncontrolled compassionate-use studies of patients with hemophilia A or B with inhibitors [42]. An article presented results relating to serious bleeding episodes in 9 hemophilia A patients with high-responding inhibitors who were treated with rFVIIa under a compassionate-use program in Australia between 1991 and 1994 [55]. Treatment with rFVIIa resulted in successful outcomes in all 8 potentially life-threatening retroperitoneal, intracranial, and gastrointestinal bleeds. A second article presented results for patients who received rFVIIa for limb-threatening joint or muscle bleeds as part of the compassionate-use program [3]. Overall, rFVIIa was effective or partially effective in controlling 97% (34/35) of these bleeding episodes. It was effective in 82% (14/17)

of muscle bleeds and 89% (16/18) of joint bleeds. Another article reported on the use of rFVIIa as part of the compassionate-use program to control severe abdominal bleeding in 4 patients with severe hemophilia A with inhibitors who had previously been unresponsive to other therapies [56]. All of these bleeding episodes were successfully controlled with rFVIIa. Similar results were described in another report [57]. Other studies have found that rFVIIa is also effective as treatment for central nervous system (CNS) hemorrhage in hemophilic patients with inhibitors [58]. In fact, Rice et al, presenting pooled data from 2 uncontrolled trials on the use of rFVIIa for serious CNS bleeding, reported a mortality rate of 3%, which compares favorably with an overall mortality rate of 20% to 50% for CNS bleeds in hemophilic patients with and without inhibitors [59].

#### 4.4. Bolus versus Continuous Administration of rFVIIa

The dosing schedules of rFVIIa must take into account this agent's short half-life (approximately 2.9 hours), which necessitates frequent bolus injections [5]. All published studies show that treatment with rFVIIa can be effective at doses between 35 and 120  $\mu\text{g}/\text{kg}$  [5]. Effective doses are independent of the inhibitor titer, with the standard recommended dose being 90  $\mu\text{g}/\text{kg}$  given as a bolus and repeated after 2 hours. When more than 2 doses are necessary to ensure and maintain hemostasis in uncomplicated bleeding episodes, the dose interval may be prolonged to every 4 hours for 1 to 2 days and then every 6 hours until discontinuation, depending on the size and severity of the bleed. In surgical cases or cases of complicated bleeding, rFVIIa must be administered every 2 hours for the first 24 hours, and then the interval is gradually lengthened (from 2 to 6 hours over the next 3 days), depending on the type of surgery [5,11,60]. In most of the surgical trials reported in the literature, rFVIIa was given in association with antifibrinolytic therapy [61-63]. To optimize doses, many groups have considered administering rFVIIa by continuous infusion [64-75]. A commonly used continuous-infusion regimen includes an initial bolus dose of 90 to 180  $\mu\text{g}/\text{kg}$  followed by continuous rFVIIa administration at a rate of 10 to 50  $\mu\text{g}/\text{kg}$  per hour [54]. However, the results are still controversial: a broad range of doses has been used, and the efficacy percentages vary considerably in the different studies (between 63% and 100%) [76]. Moreover, a clear correlation between the doses used and hemostatic efficacy is not always present [34,70,72]. Santagostino and colleagues [75] reported on 25 patients with hemophilia and high-responding inhibitors and 3 patients with nonhemophilic FVIII inhibitors who collectively received 35 courses of rFVIIa by continuous infusion for 10 spontaneous bleeding episodes, 11 major surgical procedures, and 14 minor surgical procedures. A satisfactory hemostatic response was achieved in 30 (88%) of the 35 treatment courses. Disappointing results were conversely obtained by Smith and colleagues [72] for 8 patients with FVIII inhibitors who underwent elective surgery: effective hemostasis was achieved in only 1 of 2 minor procedures and 2 of 6 major operations. Studies are currently evaluating the optimal dose for continuous infusion. This route of rFVIIa administration may be beneficial for prolonged treatment and for surgical procedures.

#### 4.5. Standard versus High Dose of rFVIIa

Cooper et al [77] described the efficacy and the absence of side effects of rFVIIa treatment (at a dosage of 160 to 180  $\mu\text{g}/\text{kg}$  every 2 to 3 hours and of a single bolus dose of 320  $\mu\text{g}/\text{kg}$ ) for a hemophilic child with inhibitors and severe articular bleeding refractory to the standard rFVIIa dosage. Since this report, other studies have used an rFVIIa "megabolo" for treating bleeding episodes in high-titer inhibitor patients with hemophilia. O'Connell et al described the use of rFVIIa at doses of 200  $\mu\text{g}/\text{kg}$  to achieve perioperative hemostasis for the resection of a massive pseudotumor in a patient with high-titer inhibitor hemophilia A [78]. One recent study compared a continuous-infusion protocol with the administration of a single-bolus "megadose" of rFVIIa (300  $\mu\text{g}/\text{kg}$ ) [79] and found that efficacy was higher, resolution of hemarthrosis was quicker, and rFVIIa consumption was lower with the latter schedule. Data from the Hemophilia and Thrombosis Research Society Registry documenting the results of rFVIIa treatment for 555 bleeding episodes in 38 hemophilia patients with inhibitors have recently been published [80]. The patients were divided into 4 groups, depending on the rFVIIa dose range (<100  $\mu\text{g}/\text{kg}$ , 100-150  $\mu\text{g}/\text{kg}$ , 150-200  $\mu\text{g}/\text{kg}$ , and >200  $\mu\text{g}/\text{kg}$ ). A complete response (cessation of bleeding) was observed in 97% of the bleeding episodes in the highest-dose group (>200  $\mu\text{g}/\text{kg}$ ), compared with 84% in the 3 lower-dose groups. Treatment with a single megabolo of rFVIIa may be particularly suitable for the home treatment of hemophilia patients with inhibitors. In fact, although home treatment with repeated boluses of rFVIIa enables faster intervention, it does require adequate compliance from the patient, who must administer the infusions at short intervals and have suitable venous access. These factors can considerably limit the correct use of this therapy, particularly in pediatric patients [81,82]. An ongoing Italian trial (NODOP, or NovoSeven Dose Optimization Study) involving the Italian Association of Hemophilia Centers aims to optimize the home treatment of mild/moderate hemorrhages in hemophilia patients with inhibitors. The results of this study, which compares a single rFVIIa megabolo dose of 270  $\mu\text{g}/\text{kg}$  with the standard regimen of repeated doses of 90  $\mu\text{g}/\text{kg}$ , will contribute to improving the home clinical management of hemophilic patients with inhibitors, particularly pediatric patients who usually require higher doses of rFVIIa because of the higher clearance and shorter half-life of the drug in this age group [60,83].

### 5. Use of rFVIIa in Acquired Hemophilia

After the first successful experiences with rFVIIa in the treatment of hemophilic alloantibody inhibitors, some centers experimented with this drug in the treatment of sporadic cases of acquired hemophilia and obtained positive results [84-90]. In a multicenter retrospective study, Hay and colleagues [91] described the results of rFVIIa treatment of hemorrhages in 38 patients with acquired hemophilia. A good response was noted in all 14 bleeds in which rFVIIa was used as first-line therapy. In the 60 bleeding episodes for which rFVIIa was administered as salvage therapy, the response was good in 75% of the cases, partial in 17%, and

poor in 8%. The conclusion of the analysis was that rFVIIa is a safe, useful, and effective treatment for bleeding in patients with acquired hemophilia. Recently, Baudo and colleagues [92] reported the data collected from the Italian Registry of Acquired Hemophilia. Bleeding was controlled in 90% of the 20 cases in which rFVIIa was used (as first-line therapy in 19 cases and as salvage treatment in 1 case), thus suggesting the drug's efficacy for this clinical condition. More recently, Watts described the case of a patient with hemophilia A and a high-titer inhibitor who underwent an emergency fasciotomy. The initial treatment with FVIII inhibitor-bypassing activity was unsuccessful in controlling bleeding, whereas hemostasis was successfully obtained with rFVIIa treatment [93].

## 6. Use of rFVIIa in Congenital FVII Deficiency

FVII deficiency is a rare coagulation disorder that is characterized by spontaneous bleeding episodes in severely affected patients and bleeding after surgical procedures or trauma in mildly affected ones [94]. Historically, these patients were treated with fresh frozen plasma (FFP) or prothrombin complex concentrates [94]. The development of plasma-derived FVII concentrates represented a substantial improvement in the management of FVII-deficient patients [95,96]. The recent evidence [97-100] on the efficacy of rFVIIa (NovoSeven) in the treatment of bleeding episodes in patients with congenital FVII deficiency has allowed the drug's registration in Europe for the treatment of this rare coagulation defect. Mariani and colleagues [98] reported the results of a randomized study of 17 FVII-deficient patients who were treated with rFVIIa for 27 spontaneous bleeding episodes, 7 major surgical operations, and 13 minor interventions. These investigators found that a mean rFVIIa dose of 22 to 26  $\mu\text{g}/\text{kg}$  was sufficient in all patients for effective hemostasis under these situations. Thus, according to this and other similar evidence [46,101], the most effective dose for rFVIIa-replacement therapy in congenital FVII deficiency can be considered 20 to 25  $\mu\text{g}/\text{kg}$ . Finally, the successful prophylactic treatment of severely FVII-deficient patients with rFVIIa given 2 to 3 times per week has recently been described [102,103]. A possible explanation for this phenomenon, apparently paradoxical given the short half-life of rFVIIa, is that the postinfusion levels of FVII are able to generate the necessary thrombin burst required to maintain hemostasis in these patients [102].

## 7. Use of rFVIIa in Platelet Disorders

The hemostatic effect of pharmacologic doses of rFVIIa seems to be to enhance the rate of thrombin generation on thrombin-activated platelet surfaces, thus providing the thrombin necessary for the formation of a stable fibrin hemostatic plug [6,23]. On the basis of this information, rFVIIa has been employed to treat disorders characterized by impaired thrombin generation, such as quantitative and qualitative platelet defects [104-118]. Kristensen and colleagues [106] studied 74 patients with moderate to severe thrombocytopenia due to impaired platelet production or immune destruction to evaluate the effect of rFVIIa administration. rFVIIa given at a dose of 50 or 100  $\mu\text{g}/\text{kg}$  shortened

the Ivy bleeding time in approximately 50% of the patients, and all 8 patients with overt bleeding had a clinical benefit from rFVIIa administration. No further results of clinical trials have been published since then, and only case reports have appeared in the literature [107,108,119]. rFVIIa had also been used successfully in oncohematologic patients who experienced thrombocytopenia following chemotherapy with or without stem cell transplantation and who had severe bleeding refractory to standard hematologic or hemostatic support. Blatt and colleagues [120] used rFVIIa (boluses of 90-270  $\mu\text{g}/\text{kg}$  with subsequent doses of 90  $\mu\text{g}/\text{kg}$  every 4-24 hours for 3-14 days) for the treatment of severe hemorrhage in 3 transplantation patients, 2 of whom had transient clinical responses. De Fabritiis and colleagues [121] reported on the use of rFVIIa for the treatment of severe bleeding episodes in 7 patients with hematologic malignancies and thrombocytopenia following chemotherapy and documented 2 complete responses, 3 partial responses, and 2 treatment failures. Hicks and coworkers [122] documented the efficacy of rFVIIa for the treatment of diffuse alveolar hemorrhage following bone marrow transplantation.

As regards inherited thrombocytopenia, rFVIIa was reported to enhance local fibrin deposition and to partially restore platelet aggregates in Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS), conditions characterized by impaired thrombin generation [105]. These data supported the use of rFVIIa as a potential hemostatic agent for such conditions. Since the first report in 1996 of a child with GT and severe epistaxis, rFVIIa has been successfully used for the treatment and prophylaxis of bleeding in such patients with and without antibodies to glycoprotein IIb-IIIa [109-116]. Poon and colleagues [110] successfully treated 24 bleeding episodes and prevented bleeding during surgery in 4 children with GT by administering 89 to 116  $\mu\text{g}/\text{kg}$  of rFVIIa every 2 hours in association with antifibrinolytic drugs. In contrast to these reports of success, Almeida and colleagues [117] found that rFVIIa was less satisfactory in the management of 28 acute bleeds and 5 surgical interventions in 7 children with inherited platelet function disorders (5 GT cases, 1 BSS case, and 1 case of storage pool disease). Most children received 3 rFVIIa doses of 100  $\mu\text{g}/\text{kg}$  at 90-minute intervals and tranexamic acid. Although the patients with BSS and storage pool disease responded well to rFVIIa therapy, the children with GT had variable results, with an excellent or good response obtained during surgery or when the severity of bleeding was mild and a poor or ineffective response obtained in severe bleeding episodes. An international registry has been established to obtain more data on the safety, efficacy, optimal dose, and interval of rFVIIa administration in inherited platelet disorders. Data collection is continuing, and updates are published periodically [112,123]. The last update [124] was an analysis of rFVIIa use of during 34 surgical/invasive procedures and 108 bleeding episodes in 59 GT patients. On the basis of the results (rFVIIa was found to be effective in 93% [29/31] of evaluable procedures and in 75% [77/103] of evaluable bleeding episodes), the authors concluded that rFVIIa seems to be a valid alternative to platelet transfusion in GT patients, especially in those with platelet refractoriness. Peters and colleagues

[125] reported on a 5-year-old boy with BSS and severe epistaxis who was unresponsive to standard therapy and who was successfully treated with rFVIIa. Finally, a patient with pseudo-von Willebrand disease was reported to have been treated effectively with rFVIIa [126].

## 8. Use of rFVIIa in Liver Disorders

Bleeding complications are a common cause of morbidity and mortality in patients with liver disease. Bleeding sources include gastrointestinal, variceal, and intracerebral vessels. The coagulopathy of liver disease is multifactorial. Decreased synthesis of vitamin K-dependent coagulation factors (particularly FVII, protein C, and protein S), increased fibrinolysis, and thrombocytopenia may all play a role [127]. Traditional therapies include vitamin K, FFP, desmopressin, and platelets [127,128]. Limited data are available in the literature as regards the hemostatic effect of rFVIIa for the treatment of bleeding in patients with liver disease [8]. Moreover, a wide range of dosages (between 5 and 120  $\mu\text{g}/\text{kg}$ ) has been applied in the different studies, thus making any comparison of results difficult [128]. A preliminary trial conducted by Bernstein and colleagues in 1997 [129] found that rFVIIa transiently corrected prolonged prothrombin time in a group of non-bleeding cirrhotic patients. A randomized double-blind multicenter trial investigated 71 patients with advanced liver disease who underwent laparoscopic liver biopsy under the cover of rFVIIa treatment. These patients were randomly assigned to receive one of 4 doses of rFVIIa (5, 20, 80, or 120  $\mu\text{g}/\text{kg}$ ); 48 (74%) of 65 patients achieved hemostasis within 10 minutes [130]. The authors concluded that this procedure, otherwise contraindicated because of the coagulopathy, could be performed safely in such patients, thanks to the use of rFVIIa. The European Study Group on rFVIIa in Upper Gastrointestinal Haemorrhage recently published the results of a randomized double-blind trial on the use of rFVIIa in 245 cirrhotic patients with upper gastrointestinal bleeding who were randomly assigned to receive 8 rFVIIa doses of 100  $\mu\text{g}/\text{kg}$  or placebo in addition to standard pharmacologic and endoscopic treatment [131]. Although there was no significant difference between the 2 groups for the primary composite end point (failure to control bleeding, failure to prevent rebleeding, and death), there was a significant reduction in the composite end point among the patients with variceal bleeding and more severe liver disease who received rFVIIa. Other studies have examined the use of rFVIIa in patients with cirrhosis and active variceal bleeding [132-134]. Two single-center open-label studies involving small numbers of patients have reported that rFVIIa is effective in controlling variceal bleeding when used as an adjunct to standard treatment [132,133]. In contrast, in a retrospective analysis of the NovoSeven extended-use registry, O'Connell and colleagues [134] found that 6 of the 8 patients who did not respond to rFVIIa had liver disease (3 acute bleeds and 3 liver transplants) with a complex coagulopathy. rFVIIa was also shown to be more effective than conventional therapy with plasma for treating coagulopathy in fulminant hepatic failure [135].

## 9. Use of rFVIIa in Trauma and Surgery

A number of hemostatic changes occur in patients subjected to extensive surgery with substantial bleeding or in patients with acute, severe trauma with profuse bleeding requiring multiple transfusions. These hemostatic changes result in defective thrombin generation [9,136]. In 1999, Kenet and colleagues were the first to successfully use rFVIIa infusions to manage acute, life-threatening traumatic bleeding [137]. Since then, many reports have been published on the use of rFVIIa in posttrauma [138-146], obstetric [147,148], and surgical [149-159] patients. Martinowitz and colleagues [138] reported on 7 massively bleeding, multi-transfused, and coagulopathic trauma patients who were successfully treated with a median of 2 rFVIIa doses ranging from 40 to 120  $\mu\text{g}/\text{kg}$ . In a recent report by the Israeli Multi-disciplinary rFVIIa Task Force of a prospective analysis of rFVIIa use in 36 multitrauma patients, a group of investigators with the same lead author observed a positive effect (cessation of bleeding) in 72% (26/36) of patients and a survival rate of 61% (22/36) [160]. Recently, Mayo and colleagues [139] observed a reduction of blood transfusion requirements after the use of rFVII (2 doses of 90-120  $\mu\text{g}/\text{kg}$ ) in 13 patients with acute, uncontrolled life-threatening bleeding. Geeraedts and colleagues published a retrospective analysis of 8 blunt-trauma patients treated with rFVIIa for uncontrolled bleeding. In all cases, the treatment reduced or stopped bleeding, thus significantly decreasing the requirement for blood components [161]. A large placebo-controlled trial of rFVIIa (400  $\mu\text{g}/\text{kg}$  in 3 doses) in 301 patients with severe blunt and/or penetrating trauma and aiming to achieve a reduction in transfusion requirements has recently been completed. A preliminary report regarding this study showed a significant reduction in red cell transfusions in patients with blunt trauma and a trend toward a reduced incidence of multiple organ failure and acute respiratory distress syndrome in the patients who received rFVIIa. The mortality rate in the blunt-trauma patients who received rFVIIa was 25%, compared with 30% in the placebo group (not statistically significant) [145]. Similar results have been observed in a recent randomized double-blind multicenter Novo Nordisk-sponsored trial (study 2159) involving 277 patients with blunt or penetrating trauma who received the same dose of rFVIIa (400  $\mu\text{g}/\text{kg}$  in 3 doses) [162]. In blunt-trauma cases, rFVIIa significantly reduced the number of red blood cell, FFP, and platelet transfusions and the requirement for massive transfusions (>20 red blood cell units). A significant decrease in the incidence of acute respiratory distress syndrome and multiple organ failure was also observed. Similar trends with respect to transfusion end points, although not statistically significant, were found for penetrating trauma. The use of rFVIIa for blunt trauma is actually under registration by the European Medicines Agency. rFVIIa was also used as a "last chance" in a case of pulmonary hemorrhage after major trauma associated with coagulopathy, heavy transfusion requirements, and multiple organ failure [142]. The bleeding stopped with resolution of the hemothorax after 2 rFVII doses of 60  $\mu\text{g}/\text{kg}$ . A prospective randomized double-blind trial of rFVIIa (a single dose of 20  $\mu\text{g}/\text{kg}$  or 40  $\mu\text{g}/\text{kg}$ ) versus placebo in 36 patients who

underwent radical retropubic prostatectomy found that the patients who received rFVIIa had significantly and dose-dependently less total perioperative blood loss than the placebo recipients [155]. Similar conclusions were drawn by Lodge and colleagues [158] in a double-blind, placebo-controlled multicenter study evaluating the hemostatic efficacy and safety of rFVIIa in 204 patients who underwent partial hepatectomy for neoplasia. The patients were randomly assigned to receive a preoperative injection of either placebo or rFVIIa (20  $\mu\text{g}/\text{kg}$  or 80  $\mu\text{g}/\text{kg}$ ) followed by a second dose 5 hours after surgery began if the anticipated surgery time exceeded 6 hours. Park and colleagues reported on 9 patients with coagulopathy who required urgent neurosurgery. These patients were treated preoperatively with rFVIIa (40-90  $\mu\text{g}/\text{kg}$ ) and had no bleeding or thromboembolic complications [159]. A number of studies have investigated the role of rFVIIa in cardiac surgery, which is often associated with profuse hemorrhage [150-154]. Aggarwal and coworkers [144] reported on a series of 8 surgical patients with intractable bleeding, 6 of whom underwent cardiopulmonary bypass. Bleeding stopped after the administration of 90  $\mu\text{g}/\text{kg}$  of rFVIIa in all but one patient, who required a further bolus. Al Douri and colleagues [150] and Hendricks and colleagues [151] reported that a single rFVIIa dose was an effective treatment for severe intractable bleeding in patients undergoing heart surgery. In a recent study, Karkouti and colleagues compared the outcomes of 51 cardiac surgery patients who received rFVIIa for intractable blood loss with the outcomes of 51 matched control patients and found that rFVIIa at a dose of 35 to 70  $\mu\text{g}/\text{kg}$  was effective in reducing intractable hemorrhage after cardiac surgery [152]. Similar positive results were observed by Razon and coworkers [163] and Halkos and colleagues [164] for small series of pediatric and adult patients treated with rFVIIa for excessive blood loss after cardiovascular surgery. Other reports [153,154] have described the efficacy of rFVIIa in controlling severe bleeding following implantation of mechanical cardiac-assist devices. However, the safety of rFVIIa in cardiac surgery patients was questioned by Dietrich and Spannagl, who claimed that because of the hypercoagulable state following systemic TF activation during cardiac procedures, rFVIIa treatment could be dangerous in such patients [165]. Another situation in which excessive bleeding can occur is during orthotopic liver transplantation. There are reports that rFVIIa treatment is safe and reduces transfusion requirements when administered immediately before the start of transplantation in patients with severe coagulopathy [166-168]. Kalicinski and colleagues [166] reported on 2 pediatric patients who underwent urgent liver transplantation for fulminant liver failure. Conventional therapy with plasma and cryoprecipitate had failed, but the children were successfully treated with 100  $\mu\text{g}/\text{kg}$  of rFVIIa prior to transplantation (one child received an additional intraoperative dose). In another small series, Hendriks and colleagues [167] reported on 6 adult patients who underwent liver transplantation for cirrhosis and received a single rFVIIa dose of 80  $\mu\text{g}/\text{kg}$  prior to skin incision. The authors noted that these patients required significantly fewer red cell and FFP transfusions than the controls. However, 1 patient developed a postoperative hepatic artery thrombosis. These results were contrasted with those of a

recent randomized multicenter study conducted by Planinsic and colleagues [169], who reported no difference in perioperative red cell or FFP transfusions in 83 patients who underwent orthotopic liver transplantation and received placebo or a single prophylactic rFVIIa dose of 20 to 80  $\mu\text{g}/\text{kg}$ . In summary, the experience with rFVIIa use in trauma with excessive bleeding as well as in postoperative profuse bleeding seems to indicate that 1 or 2 rFVIIa doses of 20 to 120  $\mu\text{g}/\text{kg}$  can have a hemostatic effect [146].

## 10. Use of rFVIIa for Reversal of Anticoagulant Therapy

rFVIIa has also been employed in the reversal of warfarin therapy in cases in which the administration of vitamin K alone was found to be insufficient [160-176]. Warfarin is a Coumadin anticoagulant used to treat or prevent primary and secondary venous and arterial thromboembolism. Through vitamin K antagonism, it induces low levels of vitamin K-dependent coagulation factors, in particular FVII, which has been shown to be the earliest and the most sensitive of the coagulation factors to be affected by oral anticoagulant therapy [8]. Spontaneous hemorrhages occur in approximately 10% to 20% of individuals receiving oral anticoagulant therapy [6]. The use of rFVIIa in the reversal of warfarin therapy was first described by Diness and colleagues in 1990 in an animal model [170]. In 1998, a study of 28 healthy volunteers who received warfarin to produce an international normalized ratio (INR) >2 demonstrated that doses from 5 to 320  $\mu\text{g}/\text{kg}$  normalized the INR for periods ranging from 12 to 24 hours [171]. A spontaneous nosebleed in a patient on warfarin with an INR of 2.9 reportedly was treated successfully with 2 rFVIIa doses of 80  $\mu\text{g}/\text{kg}$  [172]. In 2 uncontrolled case series, one of 13 patients with an elevated INR with or without bleeding [173] and the other of 6 patients with CNS bleeding during warfarin prophylaxis [174], rFVIIa treatment (dose range, 10-40  $\mu\text{g}/\text{kg}$  and 15-90  $\mu\text{g}/\text{kg}$ , respectively) rapidly corrected the INR in all cases. In conclusion, rFVIIa at doses between 15 and 90  $\mu\text{g}/\text{kg}$  has been shown to markedly shorten prothrombin time and improve hemostasis in patients with warfarin intoxication [12]. However, because rFVIIa does not influence the other vitamin K-dependent clotting factors (FII, FIX, and FX) [173], only a clinical assessment can be considered as a reliable parameter to assess rFVIIa efficacy. On the other hand, the efficacy of rFVIII in such a situation further confirms the hypothesis that the "thrombin burst" generated on activated platelet surfaces is critical to the hemostatic success of this drug.

## 11. Use of rFVIIa in Other Conditions

There are reports on the use of rFVIIa for a great number of severe bleeding conditions [177-193]. As regards inherited bleeding disorders, Ciavarella and colleagues [177] reported on 2 patients with type III von Willebrand disease and a von Willebrand factor inhibitor who were successfully managed with rFVIIa for dental procedures. Other case reports have described the successful use of rFVIIa for preventing surgical bleeding in patients with severe FXI deficiency with or without inhibitors [178-182]. A pilot study conducted by

O'Connell and colleagues [182] on 14 patients with severe or partial FXI defect who underwent surgical procedures demonstrated that the association of tranexamic acid and rFVIIa (given preoperatively at a dose of 90  $\mu\text{g}/\text{kg}$  and then every 2-4 hours for 2-13 doses, depending on the type of surgery) is effective in preventing bleeding after surgical procedures in such patients.

Recombinant FVIIa has been successfully used for the management of severe hemorrhage in Jehovah's Witnesses, who refuse blood transfusions on religious grounds [183-187]. Tanaka and coworkers [186] described the successful use of 45 to 60  $\mu\text{g}/\text{kg}$  of rFVIIa in 2 Jehovah's Witnesses who bled after cardiac surgery. Similarly, rFVIIa was effective in avoiding blood transfusions after a life-threatening intestinal hemorrhage in an elderly woman with ulcerative colitis and B-cell chronic lymphocytic leukemia [187].

The documented efficacy of rFVIIa in the treatment of CNS bleeding in hemophilia patients with inhibitors [59] led to the extension of its use to nonhemophilic patients with CNS bleeding. Tobias [188] reported the successful use of rFVIIa, after antifibrinolytics and FFP had failed, in the treatment of bleeding complications in 2 children who underwent posterior spinal fusion. In a recent randomized, double-blind, placebo-controlled dose-escalation trial [189], 48 patients with intracranial hemorrhage were treated with placebo or rFVIIa (10, 20, 40, 80, 120, or 160  $\mu\text{g}/\text{kg}$ ). Although no positive effect on hematoma volume was observed with any rFVIIa dose, there was no biochemical or clinical evidence of increased thromboembolic complications. In a more recent double-blind, placebo-controlled multicenter trial involving 399 patients who had primary intracerebral hemorrhage without coagulopathy and had been assigned to receive one of 3 doses of rFVIIa (40, 80, or 160  $\mu\text{g}/\text{kg}$ ) or placebo, the group with the highest rFVIIa dose had a significantly smaller increase in the hematoma volume at 24 hours than the placebo group. Moreover, the combined rFVIIa groups had a lower mortality rate at 3 months than the placebo group (18% versus 29%,  $P = .02$ ). However, these positive results were tempered by the fact that the incidence of serious thromboembolic adverse events was 3 times greater in the rFVIIa groups than in the placebo group (7% versus 2%) [190].

Recombinant FVIIa has also been employed in preterm neonates, a category of patients at particular risk for developing bleeding complications because their frequent low levels of coagulation factor result in a prolonged INR [9]. Greisen and colleagues [191] estimated the effect of rFVIIa on the INR in 16 preterm neonates and observed that the reduction in the INR was dose dependent and significantly better than that achieved with FFP.

Finally, other studies have documented the success of rFVIIa in controlling bleeding in patients with extensive burns [192] or uremia [193].

## 12. Safety of rFVIIa

Relatively few adverse events have been associated with the use of rFVIIa in hemophilia and nonhemophilia settings [6,60]. However, the primary concern regarding the safety of rFVIIa is its potential to induce thrombotic events [194,195],

considering that the concentration of circulating rFVIIa is approximately 1000 times greater than normal when administered at a pharmacologic dose [7,196]. Between 1996, the year in which rFVIIa was licensed, and 2004, more than 750,000 rFVIIa doses of 90  $\mu\text{g}/\text{kg}$  were administered to patients with congenital or acquired FVIII or FIX inhibitors; the reported rate of serious adverse events was less than 1% [196]. A similar rate of serious side effects was observed in a study by the Hemophilia Research Society of North America of 1939 bleeding episodes in 298 patients treated with rFVIIa [196]. Isolated thrombotic events (myocardial infarctions, cerebrovascular accidents, venous thromboembolic events, and cases of disseminated intravascular coagulation) have been reported in such patients in the last few years [196-198]. However, most of the cases reported involved patients with coexisting risk factors (previous cardiovascular disease, advanced age) that may have contributed to the thrombotic event. Recently, Abshire and Kenet revised the clinical experience with rFVIIa in acquired and congenital hemophilia published between 1996 and 2003 and collected 25 thrombotic episodes (7 of acute myocardial infarction, 7 of cerebrovascular thrombosis, 4 of deep vein thrombosis, 1 of pulmonary embolism, 1 of deep vein thrombosis and pulmonary embolism, and 5 of disseminated intravascular coagulation). Most (80%) of these episodes, however, occurred in patients with an additional thrombotic risk factor (ie, age >70 years, concomitant therapy with activated prothrombin complex concentrates and/or antifibrinolytic agents) [60]. Aledort, in reporting data extracted from the MedWatch pharmacovigilance program of the US Food and Drug Administration and supplemented with published case reports, described an incidence rate for thrombotic events of 24.6 per  $10^5$  rFVIIa infusions and reported a higher frequency of cerebrovascular thrombosis than of myocardial infarction and disseminated intravascular coagulation (6.24 versus 1.99 and 0.95 per  $10^5$  infusions, respectively) [195]. Thrombotic complications following rFVIIa administration have also been described rarely in nonhemophilic patients. Bui and colleagues [199] described a death attributed to thrombosis in a lung transplant recipient with postoperative massive bleeding who had received rFVIIa and activated prothrombin complex concentrate. In describing a clinical trial involving patients with FXI deficiency who underwent surgery under the cover of rFVIIa treatment (90  $\mu\text{g}/\text{kg}$  before and after operation), O'Connell [200] reported an acute cerebral vascular accident in an elderly patient with a previous history of acute myocardial infarction. One of the 10 patients enrolled in a trial to prevent rebleeding after subarachnoid hemorrhage experienced cerebral artery thrombosis after receiving rFVIIa [201]. d'Oiron and colleagues [202] reported on a patient with GT who developed a thromboembolic complication that was attributed to the high continuous rate of rFVIIa infusion and the prolonged treatment period. Finally, Laffan and colleagues [203] reported 3 cases of thrombosis after rFVIIa treatment among 40 patients at high risk of thrombosis and thus concluded that this drug is safe and effective in patients without a preexisting coagulopathy. However, there are no reports of thrombotic complications involving high-dose rFVIIa regimens [196]. Together, the available data reported in the literature indicate that rFVIIa is a safe

way of inducing hemostasis in patients with defective thrombin generation and that the risk of thromboembolic complications due to rFVIIa is low.

### 13. Conclusions

From the analysis of the data in the literature, it appears clear that rFVIIa is a well-established, safe, and effective treatment for patients with FVIII or FIX inhibitors, congenital FVII deficiency, and GT. In the last few years, the mechanism of action for rFVIIa has been clarified, and rFVIIa has been successfully employed in a great number of critical bleeding situations characterized by impaired thrombin generation. However, only a few randomized double-blind, placebo-controlled trials have been conducted so far, and most of the published studies are reports on single cases or small series. Larger randomized controlled trials are needed to assess the efficacy, safety, and dosage of rFVIIa in these newer "off-label" clinical applications.

### References

- Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis*. 1998;9:119-128.
- Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci*. 1998;19:163-176.
- Négrier C, Lienhart A. Overall experience with NovoSeven. *Blood Coagul Fibrinolysis*. 2000;11(suppl 1):S19-S24.
- Kessler CM. New products for managing inhibitors to coagulation factors: a focus on recombinant factor VIIa concentrate. *Curr Opin Hematol*. 2000;7:408-413.
- Jurlander B, Thim L, Klausen NK, et al. Recombinant activated factor VII (rFVIIa): characterization, manufacturing and clinical development. *Semin Thromb Hemost*. 2001;27:373-383.
- Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion*. 2002;42:114-124.
- Uhlmann EJ, Eby CS. Recombinant activated factor VIII for non-hemophiliac bleeding patients. *Curr Opin Hematol*. 2004;11:198-204.
- Goodnough LT, Lublin DM, Zhang L, Despotis G, Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion*. 2004;44:1325-1331.
- Ghorashian S, Hunt BJ. "Off-license" use of recombinant activated factor VII. *Blood Rev*. 2004;18:245-259.
- Mathew P. The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics. *Thromb Haemost*. 2004;92:738-746.
- Hedner U. Recombinant factor VIIa (NovoSeven) as a hemostatic agent. *Dis Mon*. 2003;49:39-48.
- Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood*. 2004;104:3858-3864.
- Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. *Thromb Haemost*. 2001;85:958-965.
- Hoffman M. A cell-based model of haemostasis. *Blood Rev*. 2003;17(suppl 1):S1-S5.
- Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. *Br J Haematol*. 1997;99:542-547.
- Rauch U, Bønderman D, Badimon J. Platelets become tissue factor positive during thrombus formation [abstract]. *Blood*. 1998;92:347a.
- Bajzar L, Manuel R, Nesheim ME. Purification and characterization of TAFI, a thrombin-activatable fibrinolysis inhibitor. *J Biol Chem*. 1995;270:14477-14484.
- Cawthern KM, van 't Veer C, Lock JB, DiLorenzo ME, Branda RF, Mann KG. Blood coagulation in hemophilia A and hemophilia C. *Blood*. 1998;91:4581-4592.
- Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. *Br J Haematol*. 2001;114:114-120.
- Hoffman M, Monroe DM 3rd. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. *Semin Hematol*. 2001;38:6-9.
- Lisman T, Adelmeijer J, Heijnen HF, de Groot PG. Recombinant factor VIIa restores aggregation of  $\alpha$ Ib $\beta$ 3-deficient platelets via tissue factor-independent fibrin generation. *Blood*. 2004;103:1720-1727.
- Gabriel DA, Li X, Monroe DM 3rd, Roberts HR. Recombinant human factor VIIa (rFVIIa) can activate factor FIX on activated platelets. *J Thromb Haemost*. 2004;2:1816-1822.
- Lisman T, De Groot PG. Mechanism of action of recombinant factor VIIa. *J Thromb Haemost*. 2003;1:1138-1139.
- ten Cate H, Bauer KA, Levi M, et al. The activation of factor X and prothrombin by recombinant factor VIIa in vivo is mediated by tissue factor. *J Clin Invest*. 1993;92:1207-1212.
- van 't Veer C, Golden NJ, Mann KG. Inhibition of thrombin generation by the zymogen factor VII: implications for the treatment of hemophilia A by factor VIIa. *Blood*. 2000;95:1330-1335.
- Butenas S, Brummel KE, Bouchard BA, Mann KG. How factor VIIa works in hemophilia. *J Thromb Haemost*. 2003;1:1158-1160.
- Butenas S, Brummel KE, Paradis SG, Mann KG. Influence of factor VIIa and phospholipids on coagulation in "acquired" hemophilia. *Arterioscler Thromb Vasc Biol*. 2003;23:123-129.
- Lisman T, Mosnier LO, Lambert T, et al. Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A. *Blood*. 2002;99:175-179.
- Lisman T, Adelmeijer J, Cauwenberghs S, Van Pampus CM, Heemskerk JWM, de Groot PG. Recombinant factor VIIa enhances platelet adhesion and activation under flow conditions at normal and reduced platelet count. *J Thromb Haemost*. 2005;3:742-751.
- Lindley CM, Sawyer WT, Macik BG, et al. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. *Clin Pharmacol Ther*. 1994;55:638-648.
- Berntorp E, Bjorkman S. The pharmacokinetics of clotting factor therapy. *Haemophilia*. 2003;9:353-359.
- Schulman S, Bech Jensen M, Varon D, et al. Feasibility of using recombinant factor VIIa in continuous infusion. *Thromb Haemost*. 1996;75:432-436.
- Erhardtsen E. Pharmacokinetics of recombinant activated factor VIII (rFVIIa). *Semin Thromb Hemost*. 2000;26:385-391.
- Ludlam CA, Smith MP, Morfini M, Gringeri A, Santagostino E, Savidge GF. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *Br J Haematol*. 2003;120:808-813.
- Girard P, Nony P, Erhardtsen E, et al. Population pharmacokinetics of recombinant factor VIIa in volunteers anticoagulated with acenocoumarol. *Thromb Haemost*. 1998;80:109-113.
- Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. *Haemophilia*. 2004;10:352-359.
- Berrettini M, Mariani G, Schiavoni M, et al. Pharmacokinetic evaluation of recombinant, activated factor VII in patients with inherited factor VII deficiency. *Haematologica*. 2001;86:640-645.
- Key NS, Nelsestuen GL. Views on methods for monitoring recombinant factor VIIa in inhibitor patients. *Semin Hematol*. 2004;41:51-54.
- Sørensen B, Ingerslev J. Whole blood clot formation phenotypes in hemophilia A and rare coagulation disorders: patterns of response to recombinant factor VIIa. *J Thromb Haemost*. 2004;2:102-110.
- Gabriel DA, Carr M, Roberts HR. Monitoring coagulation and the clinical effects of recombinant factor VIIa. *Semin Hematol*. 2004;41:20-24.
- Hedner U. Treatment of patients with factor VIII and factor IX inhibitors with special focus on the use of recombinant factor VIIa. *Thromb Haemost*. 1999;82:531-539.
- Lloyd Jones M, Wight J, Paisley S, Knight C. Control of bleeding in

- patients with haemophilia A with inhibitors: a systematic review. *Haemophilia*. 2003;9:464-520.
43. Hedner U, Glazer S, Pinkel K, et al. Successful use of recombinant factor VIIa in a patient with severe haemophilia A during synovectomy. *Lancet*. 1988;2:1193.
  44. Shapiro AD, Gilchrist GS, Keith Hoots WK, Cooper HA, Gastineau DA. Prospective, randomized trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost*. 1998;80:773-778.
  45. Hedner U, Glazer S, Falch J. Recombinant activated factor VII in the treatment of bleeding episodes in patients with inherited and acquired bleeding disorders. *Transfus Med Rev*. 1993;7:78-83.
  46. Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia*. 1999;5:253-259.
  47. Quintana-Molina M, Martinez-Bahamonde F, Gonzalez-Garcia E, et al. Surgery in haemophilic patients with inhibitor: 20 years of experience. *Haemophilia*. 2004;10(suppl 2):30-40.
  48. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Thromb Hemost*. 2000;26:425-432.
  49. DiMichele D. The use of recombinant factor VIIa (NovoSeven) for central catheter insertion: an international experience. *Thromb Haemost*. 1997;77(suppl):167-172.
  50. Lusher JM, Roberts HR, Davignon G, et al. A randomized, double blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors: rFVIIa Study Group. *Haemophilia*. 1998;4:790-798.
  51. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (NovoSeven) in haemophiliacs with inhibitors. *Thromb Haemost*. 1998;80:912-918.
  52. Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. *Br J Haematol*. 1999;104:22-26.
  53. Laurian Y, Goudemand J, Negrier C. Use of recombinant activated factor VII as first line therapy for bleeding episodes in hemophiliacs with factor VIII or IX inhibitors (NOSEPAC study). *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S155-S156.
  54. Ingerslev J, Thykjaer H, Kudsk Jensen O, Fredberg U. Home treatment with recombinant activated factor VII: results from one centre. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S107-S110.
  55. McPherson J, Teague L, Lloyd J, et al. Experience with recombinant factor VIIa in Australia and New Zealand. *Haemostasis*. 1996;26(suppl 1):109-117.
  56. Liebman HA, Chediak J, Fink KI, Galvez AG, Shah PC, Sham RL. Activated recombinant human coagulation factor VII (rFVIIa) therapy for abdominal bleeding in patients with inhibitory antibodies to factor VIII. *Am J Hematol*. 2000;63:109-113.
  57. Bech RM. Recombinant factor VIIa in joint and muscle bleeding episodes. *Haemostasis*. 1996;26(suppl 1):135-138.
  58. Arkin S, Cooper HA, Hutter JJ, et al. Activated recombinant human coagulation factor VII therapy for intracranial hemorrhage in patients with hemophilia A or B with inhibitors: results of the NovoSeven emergency-use program. *Haemostasis*. 1998;28:93-98.
  59. Rice KM, Savidge GF. NovoSeven (recombinant factor VIIa) in central nervous system bleeds. *Haemostasis*. 1996;26(suppl 1):131-134.
  60. Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost*. 2004;2:899-909.
  61. Ingerslev J, Freidman D, Gastineau D, et al. Major surgery in haemophilic patients with inhibitors using recombinant factor VIIa. *Haemostasis*. 1996;26(suppl 1):118-123.
  62. Key NS. Inhibitors in congenital coagulation disorders. *Br J Haematol*. 2004;127:379-391.
  63. Rodriguez-Merchan EC, Rocino A. Literature review of surgery management in inhibitor patients. *Haemophilia*. 2004;10(suppl 2):22-29.
  64. Tagariello G, De Biasi E, Gajo GB, et al. Recombinant FVIIa continuous infusion and total hip replacement in patients with haemophilia and high titre of inhibitors to FVIII: experience of two cases. *Haemophilia*. 2000;6:581-583.
  65. Baudo F, Redaelli R, Caimi TM, Mostarda G, Somaini G, de Cataldo F. The continuous infusion of recombinant activated factor VIIa (rFVIIa) in patients with factor VIII inhibitors activates the coagulation and fibrinolytic systems without clinical complications. *Thromb Res*. 2000;99:21-24.
  66. Gringeri A. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost*. 2001;86:954-958.
  67. Mauser-Bunschoten EP, de Goede-Bolder A, Wielenga JJ, Levi M, Peerlinck K. Continuous infusion of recombinant factor VIIa in patients with haemophilia and inhibitors: experience in the Netherlands and Belgium. *Neth J Med*. 1998;53:249-255.
  68. Montoro JB, Altisent C, Pico M, Cabanas MJ, Vila M, Puig LL. Recombinant factor VIIa in continuous infusion during central line insertion in a child with factor VIII high-titre inhibitor. *Haemophilia*. 1998;4:762-765.
  69. Mauser-Bunschoten EP, Koopman MM, Goede-Bolder AD, et al, and the Recombinant Factor VIIa Data Collection Group. Efficacy of recombinant factor VIIa administered by continuous infusion to haemophilia patients with inhibitors. *Haemophilia*. 2002;8:649-656.
  70. Kenet G, Lubetsky A, Luboshitz J, Gitel S, Varon D, Martinowitz U. Treatment of inhibitor patients with rFVIIa: continuous infusion protocols as compared to a single, large dose [abstract]. *Haemophilia*. 2000;6:279a.
  71. Schulman S, d'Oiron R, Martinowitz U, et al. Experiences with continuous infusion of recombinant activated factor VII. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S97-S101.
  72. Smith MP, Ludlam CA, Collins PW, et al. Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding. *Thromb Haemost*. 2001;86:949-953.
  73. McPherson J, Sutcharitchan P, Lloyd J, et al. Experience with continuous infusion of recombinant activated factor VII in the Asia-Pacific region. *Blood Coagul Fibrinolysis*. 2000;11(suppl 1):S31-S34.
  74. Chuansumrit A, Isarangkura P, Angchaisuksiri P, et al. Controlling acute bleeding episodes with recombinant factor VIIa in haemophiliacs with inhibitor: continuous infusion and bolus injection. *Haemophilia*. 2000;6:61-65.
  75. Santagostino E, Morfini M, Rocino A, Baudo F, Scoraggi FA, Gringeri A. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost*. 2001;86:954-958.
  76. Ewenstein BM. Continuous infusion of recombinant factor VIIa: continue or not? *Thromb Haemost*. 2001;86:942-944.
  77. Cooper HA, Jones CP, Campion E, Roberts HR, Hedner U. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. *Haemophilia*. 2001;7:517-522.
  78. O'Connell N, Chen J, Byrne M, O'Shea E, Smyth H, Smith OP. Massive pseudotumour resection with recombinant factor VIIa (NovoSeven) cover. *Br J Haematol*. 2002;116:645-648.
  79. Kenet G, Lubetsky A, Luboshitz J, Martinowitz U. A new approach to treatment of bleeding episodes in young hemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven). *J Thromb Haemost*. 2003;1:450-455.
  80. Parameswaran R, Shapiro AD, Gill JC, Kessler CM, and HTRS Registry Investigators. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia*. 2005;11:100-106.
  81. Negrier C. The concept of recombinant factor VIIa megadose for treating bleeding episodes in high-titer inhibitor patients with

- hemophilia: toward an expanding indication? *J Thromb Haemost.* 2003;1:423-424.
82. Teitel JM, Barnard D, Israels S, Lillicrap D, Poon MC, Sek J. Home management of haemophilia. *Haemophilia.* 2004;10:118-133.
83. Shapiro A. Inhibitor treatment: state of the art. *Dis Mon.* 2003;49:22-38.
84. Arkin S, Blei F, Fettes J, et al. Human coagulation factor FVIIa (recombinant) in the management of limb-threatening bleeds unresponsive to alternative therapies: results from the NovoSeven emergency-use programme in patients with severe haemophilia or with acquired inhibitors. *Blood Coagul Fibrinolysis.* 2000;11:255-259.
85. Von Depka M. NovoSeven: mode of action and use in acquired haemophilia. *Intensive Care Med.* 2002;28(suppl 2):S222-S227.
86. Majumdar G, Phillips JK, Lavallee H, Savidge GF. Acquired haemophilia in association with type III von Willebrand's disease: successful treatment with high purity von Willebrand's factor and recombinant factor VIIa. *Blood Coagul Fibrinolysis.* 1993;4:1035-1037.
87. Shafi T, Jeha MT, Black L, Al Douri M. Severe acquired haemophilia A treated with recombinant factor VIIa. *Br J Haematol.* 1997;98:910-912.
88. Maliekel K, Rana N, Green D. Recombinant factor VIIa in the management of a pseudotumor in acquired haemophilia. *Haemophilia.* 1997;3:54-58.
89. Papadaki HA, Xylouri I, Valatas W, Petinarkis J, Kontopoulou I, Eliopoulos GD. Severe acquired haemophilia A successfully treated with activated recombinant human factor VII. *Ann Hematol.* 1998;77:123-125.
90. Franchini M, Girelli D, Olivieri O, et al. Clinical heterogeneity of acquired hemophilia A: a description of 4 cases. *Haematologica.* 2005;90:ECR16.
91. Hay CRM, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost.* 1997;78:1463-1467.
92. Baudo F, de Cataldo F, Gaidano G. Treatment of acquired factor VIII inhibitor with recombinant activated factor VIIa: data from the Italian registry of acquired hemophilia. *Haematologica.* 2004;89:759-761.
93. Watts RG. Successful use of recombinant factor VIIa for emergency fasciotomy in a patient with hemophilia A and high-titer inhibitor unresponsive to factor VIII inhibitor bypassing activity. *Am J Hematol.* 2005;79:58-60.
94. Perry DJ. Factor VII deficiency. *Blood Coagul Fibrinolysis.* 2003;14(suppl 1):S47-S54.
95. Mariani G, Mannucci PM, Mazzucconi MG, Capitanio A. Treatment of congenital factor VII deficiency with a new concentrate. *Thromb Haemost.* 1978;39:675-682.
96. Dike GW, Griffiths D, Bidwell E, Snape TJ, Rizza CR. A factor VII concentrate for therapeutic use. *Br J Haematol.* 1980;45:107-118.
97. Billio A, Pescosta N, Rosanelli C, Amaddii G, Fontanella F, Coser P. Successful short term oral surgery prophylaxis with rFVIIa in severe congenital factor VII deficiency. *Blood Coagul Fibrinolysis.* 1997;8:249-250.
98. Mariani G, Testa MG, Di Paolantonio T, Molskov Bech R, Hedner U. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sang.* 1999;77:131-136.
99. Wong WY, Huang WC, Miller R, McGinty K, Whisnant JK. Clinical efficacy and recovery levels of recombinant FVIIa (NovoSeven) in the treatment of intracranial hemorrhage in severe neonatal FVII deficiency. *Haemophilia.* 2000;6:50-54.
100. Weei-Yuan H, Kruskall MS, Bauer KA, Uhl L, Shaz BH. The use of recombinant activated factor VII in three patients with central nervous system hemorrhages associated with factor VII deficiency. *Transfusion.* 2004;44:1562-1566.
101. Ingerslev J, Knudsen L, Hvid I, Tange MR, Fredberg U, Sneppen O. Use of recombinant factor VIIa in surgery in factor VII deficient patients. *Haemophilia.* 1997;3:215-218.
102. Tchong WY, Donkin J, Konzal S, Wong WY. Recombinant factor VIIa prophylaxis in a patient with severe congenital factor VII deficiency. *Haemophilia.* 2004;10:295-298.
103. Mathijssen NC, Masereeuw R, Verbeek K, et al. Prophylactic effect of recombinant factor VIIa in factor VII deficient patients. *Br J Haematol.* 2004;125:494-499.
104. Laurian Y. Treatment of bleeding in patients with platelet disorders: is there a place for recombinant factor VIIa? *Pathophysiol Haemost Thromb.* 2002;32:37-40.
105. Goodnough LT. Experiences with recombinant human factor VIIa in patients with thrombocytopenia. *Semin Hematol.* 2004;41(suppl 1):25-29.
106. Kristensen J, Killander A, Hippe E, et al. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. *Haemostasis.* 1996;26(suppl 1):159-164.
107. Vidarsson B, Onundarson PT. Recombinant factor VIIa for bleeding in refractory thrombocytopenia. *Thromb Haemost.* 2000;83:634-635.
108. Gerotziakas GT, Zervas C, Gavrielidis G, et al. Effective hemostasis with rFVIIa treatment in two patients with severe thrombocytopenia and life-threatening hemorrhage. *Am J Hematol.* 2002;69:219-222.
109. Chuansumrit A, Sangkapreecha C, Hathirat P. Successful epistaxis control in a patient with Glanzmann thrombasthenia by increased bolus injection dose of recombinant factor VIIa. *Thromb Haemost.* 1999;82:1778.
110. Poon MC, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood.* 1999;94:3951-3953.
111. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost.* 1996;75:981-982.
112. Poon MC, d'Oiron R. Recombinant activated factor VII (NovoSeven) treatment of platelet-related bleeding disorders: International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. *Blood Coagul Fibrinolysis.* 2000;11(suppl 1):S55-S68.
113. Caglar K, Cetinkaya A, Aytac S, Gumruk F, Gurgey A. Use of recombinant factor VIIa for bleeding in children with Glanzmann thrombasthenia. *Pediatr Hematol Oncol.* 2003;20:435-438.
114. Chuansumrit A. Confirmation of high dose recombinant factor VIIa in treating patients with Glanzmann thrombasthenia. *J Thromb Haemost.* 2003;1:396.
115. Chuansumrit A, Suwannuraks M, Sri-Udomporn N, Pongtanakul B, Worapongpaiboon S. Recombinant activated factor VII combined with local measures in preventing bleeding from invasive dental procedures in patients with Glanzmann thrombasthenia. *Blood Coagul Fibrinolysis.* 2003;14:187-190.
116. Poon MC, d'Oiron R, Hann I, et al. Use of recombinant factor VIIa (NovoSeven) in patients with Glanzmann thrombasthenia. *Semin Hematol.* 2001;38:21-25.
117. Almeida A, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol.* 2003;121:477-481.
118. Poon MC. Management of thrombocytopenic bleeding: is there a role for recombinant coagulation factor VIIa? *Curr Hematol Rep.* 2003;2:139-147.
119. Culic S. Recombinant factor VIIa for refractive haemorrhage in autoimmune idiopathic thrombocytopenic purpura. *Br J Haematol.* 2003;120:909-910.
120. Blatt J, Gold SH, Wiley JM, Monahan PE, Cooper HC, Harvey D. Off-label use of recombinant factor VIIa in patients following bone marrow transplantation. *Bone Marrow Transplant.* 2001;28:405-407.
121. de Fabritiis P, Dentamaro T, Picardi A, Cudillo R, Masi M, Amadori S. Recombinant factor VIIa for the management of severe hemorrhages in patients with hematologic malignancies. *Haematologica.* 2004;89:243-245.
122. Hicks K, Peng D, Gajewski JL. Treatment of diffuse alveolar hemorrhage after allogeneic bone marrow transplant with recombinant factor VIIa. *Bone Marrow Transplant.* 2002;30:975-978.
123. Poon MC, Katsarou O, Huth-Kuehne A. Recombinant factor VIIa in congenital platelet bleeding disorders [abstract]. *Blood.* 2000;96(suppl 1):256a.

124. Poon MC, d'Oiron R, Von Depka M, et al, for members of the International Data Collection on Recombinant Factor VIIa and Congenital Platelet Disorders Study Group. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost.* 2004;2:1096-1103.
125. Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa. *Thromb Haemost.* 1998;80:352.
126. Fressinaud E, Sigaud-Fiks M, Le Boterff C, Piot B. Use of recombinant factor VIIa (NovoSeven) for dental extraction in a patient affected by platelet-type (pseudo-) von Willebrand disease [abstract]. *Haemophilia* 1998;4:299.
127. Rapaport SI. Coagulation problems in liver disease. *Blood Coagul Fibrinolysis.* 2000;11(suppl 1):S69-S74.
128. Caldwell SH, Chang C, Macik BG. Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: a break from convention in need of controlled trials. *Hepatology.* 2004;39:592-598.
129. Bernstein DE, Jeffers L, Erhardtson E, et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology.* 1997;113:1930-1937.
130. Jeffers L, Chalasani N, Balart L, Pyrsopoulos N, Erhardtson E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology.* 2002;123:118-126.
131. Bosch J, Thabut D, Bendtsen F. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology.* 2004;127:1123-1130.
132. Ejlsers E, Melsen T, Ingerslev J, Andreasen RB, Vilstrup H. Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. *Scand J Gastroenterol.* 2001;10:1081-1085.
133. Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista F, et al. Recombinant activated factor VII as hemostatic therapy in eight cases of severe hemorrhage from esophageal varices. *Clin Gastroenterol Hepatol.* 2004;2:78-84.
134. O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy DF, Laffan MA, Smith OP. Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion.* 2003;43:1711-1716.
135. Shami VM, Caldwell SH, Hespender EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl.* 2003;9:138-143.
136. Grounds M. Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: a review. *Blood Rev.* 2003;17:S11-S21.
137. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet.* 1999;354:1879.
138. Martinowitz U, Holcomb JB, Pusateri AE, Macaitis JM, Hender U, Hess JR. Intravenous rFVIIa administered for haemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma.* 2001;50:721-729.
139. Mayo A, Misgav M, Kluger Y, et al. Recombinant activated factor VII (NovoSeven): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding. *Vox Sang.* 2004;87:34-40.
140. Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive haemorrhage control in adults. *J Trauma.* 2001;51:431-439.
141. O'Neill PA, Bluth M, Gloster ES, et al. Successful use of recombinant activated factor VII for trauma-associated haemorrhage in a patient without preexisting coagulopathy. *J Trauma.* 2002;52:400-405.
142. Kamphuisen PW, van den Akker JM, Kaasjager KAH. Control of life-threatening pulmonary bleeding with activated recombinant factor VII. *Am J Med.* 2002;112:332-333.
143. Svartholm E, Annerhagen V, Lanne T. Treatment of bleeding in severe necrotising pancreatitis with recombinant factor VIIa. *Anesthesiology.* 2002;96:1528.
144. Aggarwal A, Catlett J, Alcorn K. The use of recombinant factor VIIa in the management of intractable bleeding in surgical and trauma patients [abstract]. *Blood.* 2001;98. Abstract 3883.
145. Boffard KD, Warren B, Iau P. Decreased transfusion utilization and improved outcome associated with the use of recombinant factor VIIa as an adjunct in trauma. *J Trauma.* 2004;57:451.
146. Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med.* 2005;33:883-890.
147. Bouwmeester FW, Jonkhoff AR, Verheijen RHM, van Geijn HP. Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII. *Obstet Gynecol.* 2003;101:1174-1176.
148. Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, de Moerloose P. Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature. *BJOG.* 2004;111:284-287.
149. Ng HJ, Koh LP, Lee LH. Successful control of postsurgical bleeding by recombinant factor VIIa in a renal failure patient given low molecular weight heparin and aspirin. *Ann Hematol.* 2003;82:257-258.
150. Al Douri M, Shafi T, Al Khudairi D, et al. Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis.* 2000;11(suppl 1):S121-S127.
151. Hendriks HG, van der Maaten JMAA, de Wolf J, Waterbolk TW, Slooff MJ, van der Meer J. An effective treatment of severe intractable bleeding after heart valve repair by one single dose of activated recombinant factor VII. *Anesth Analg.* 2001;93:287-289.
152. Karkouti K, Beattie WS, Wijesundera DN, et al. Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score-matched case-control analysis. *Transfusion.* 2005;45:26-34.
153. Zietkiewitz M, Garlicki M, Domagala J, et al. Successful use of rFVIIa to control bleeding abnormalities in a patient with a left ventricular assist device. *J Thorac Cardiovasc Surg.* 2002;123:384-385.
154. Potapov EV, Pasic M, Bauer M, Hetzer R. Activated recombinant factor VII for control of diffuse bleeding after implantation of ventricular assist device. *Ann Thorac Surg.* 2002;74:2182-2183.
155. Friederich PW, Henny CP, Messelink EJ, et al. The effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet.* 2003;361:201-205.
156. White B, McHale J, Ravi N, et al. Successful use of recombinant FVIIa (NovoSeven®) in the management of intractable post-surgical intra-abdominal haemorrhage. *Br J Haematol.* 1999;107:677-678.
157. Vlot AJ, Ton E, Mackaay AJC, Kramer MH, Gaillard CA. Treatment of a severely bleeding patient without preexisting coagulopathy with activated recombinant factor VII. *Am J Med.* 2000;108:421-422.
158. Lodge JPA, Jonas S, Oussoultzoglou E, et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology.* 2005;102:269-275.
159. Park P, Fewel ME, Garton HJ, Thompson BG, Hoff JT. Recombinant activated factor VII for the rapid correction of coagulopathy in non-hemophilic neurosurgical patients. *Neurosurgery.* 2003;53:34-39.
160. Martinowitz U, Michaelson M, on behalf of the Israeli Multidisciplinary rFVIIa Task Force. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost.* 2005;3:640-648.
161. Geeraedts LM Jr, Kamphuisen PW, Kaasjager HA, Verwiel JM, van Vugt AB, Frolke JP. The role of recombinant factor VIIa in the treatment of life-threatening haemorrhage in blunt trauma. *Injury.* 2005;36:495-500.
162. Rossaint R, Boffard K, Warren B, et al, and the NovoSeven Trauma Study Group. Decreased transfusion utilization using recombinant factor VIIa as an adjunct in trauma. *J Trauma.* In press.
163. Razon Y, Erez E, Vidne B, et al. Recombinant factor VIIa (NovoSeven) as a hemostatic agent after surgery for congenital heart disease. *Paediatr Anaesth.* 2005;15:235-240.
164. Halkos ME, Levy JH, Chen E, et al. Early experience with activated recombinant factor VII for intractable hemorrhage after cardiovascular surgery. *Ann Thorac Surg.* 2005;79:1303-1306.

165. Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery. *Anesth Analg*. 2002;94:1369-1371.
166. Kalicinski P, Kaminski A, Drewniak T, et al. Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. *Transplant Proc*. 1999;31:378-379.
167. Hendriks HG, Meijer K, de Wolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation*. 2001;71:402-405.
168. Meijer K, Hendriks HGD, de Wolf JTM, et al. Recombinant factor VIIa in orthotopic liver transplantation: influence on parameters of coagulation and fibrinolysis. *Blood Coagul Fibrinolysis*. 2003;14:169-174.
169. Planinsic RM, Testa G, Emre S. Safety and efficacy of single bolus dose of recombinant factor VIIa in patients undergoing orthotopic liver transplantation: a randomized multi-center study [abstract]. *Hepatology*. 2002;36:660A.
170. Diness V, Lund-Hansen T, Hedner U. Effects of recombinant human FVIIa on warfarin-induced bleeding in rats. *Thromb Res*. 1990;59:921-929.
171. Erhardtson E, Nony P, Dechavanne M, Ffrench P, Boissel JP, Hedner U. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. *Blood Coagul Fibrinolysis*. 1998;9:741-748.
172. Berntorp E, Stigendal L, Lethagen S, Olofsson L, Hedner U. NovoSeven in warfarin-treated patients. *Blood Coagul Fibrinolysis*. 2000;11(suppl 1):S113-S115.
173. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant factor VIIa concentrate. *Ann Intern Med*. 2002;137:884-888.
174. Sorensen B, Johansen P, Nielsen GL, Sorensen JC, Ingerslev J. Reversal of the International Normalized Ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. *Blood Coagul Fibrinolysis*. 2003;14:469-477.
175. Veshchev I, Elran H, Salame K. Recombinant coagulation factor VIIa for rapid preoperative correction of warfarin-related coagulopathy in patients with acute subdural hematoma. *Med Sci Monit*. 2002;8:CS98-CS100.
176. Udvardy M, Telek B, Mezey G, Batar P, Altörjay I. Successful control of massive coumarol-induced acute upper gastrointestinal bleeding and correction of prothrombin time by recombinant active factor VII (Eptacog-alpha, NovoSeven) in a patient with a prosthetic aortic valve and two malignancies (chronic lymphoid leukemia and lung cancer). *Blood Coagul Fibrinolysis*. 2004;15:265-267.
177. Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa in the treatment of two patients with type III von Willebrand's disease and an inhibitor against the von Willebrand factor. *Haemostasis*. 1996;26:150-154.
178. Billon S, Niger CL, Escoffre-Barbe M, Vicariot M, Abgrall JF. The use of recombinant factor VIIa (NovoSeven) in a patient with a factor XI deficiency and a circulating anticoagulant. *Blood Coagul Fibrinolysis*. 2001;12:551-553.
179. Hedner U. Factor VIIa in the treatment of haemophilia. *Blood Coagul Fibrinolysis*. 1990;1:307-317.
180. Lawler P, White B, Pye S, et al. Successful use of recombinant factor VIIa in a patient with inhibitor secondary to severe factor XI deficiency. *Haemophilia*. 2002;8:145-148.
181. Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr. Treatment of factor XI inhibitor using recombinant activated factor VIIa. *Haemophilia*. 2005;11:20-25.
182. O'Connell NM. Factor XI deficiency. *Semin Hematol*. 2004;41:76-81.
183. Waddington DP, McAuley FT, Hanley JP, Summerfield GP. The use of recombinant factor VIIa in a Jehovah's Witness with autoimmune thrombocytopenia and post-splenectomy haemorrhage. *Br J Haematol*. 2002;119:286-288.
184. Mindikoglu AL, Anantharaju A, George M, Leone N, Bejna J, Van Thiel DH. Splenic embolization in a Jehovah's Witness: role of recombinant human factor VIIa. *Hepato gastroenterology*. 2003;50:1697-1699.
185. Virchis A, Hughes C, Berney S. Severe gastrointestinal haemorrhage responding to recombinant factor VIIa in a Jehovah's Witness with refractory immune thrombocytopenia. *Hematol J*. 2004;5:281-282.
186. Tanaka KA, Waly AA, Cooper WA, Levy JH. Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology*. 2003;98:1513-1515.
187. Veneri D, Franchini M. Successful treatment of intestinal hemorrhage in a Jehovah's witness patient. *Am J Hematol*. 2005;79:344-345.
188. Tobias JD. Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. *Anesthesiology*. 2002;96:1522-1525.
189. Mayer SA, Brun NC, Broderick J, et al, for the Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74-79.
190. Mayer SA, Brun NC, Begtrup K, et al, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777-785.
191. Greisen G, Andreasen AB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. *Blood Coagul Fibrinolysis*. 2003;14:117-120.
192. Bianchi A, Jackson D, Maitz P, Thanakrishnan G. Treatment of bleeding with recombinant factor VIIa in a patient with extensive burns. *Thromb Haemost*. 2004;91:203-204.
193. Revesz T, Arets B, Bierings M, van den Bos C, Duval E. Recombinant factor VIIa in severe uremic bleeding. *Thromb Haemost*. 1998;80:353.
194. Hay CRM. Thrombosis and recombinant factor VIIa. *J Thromb Haemost*. 2004;2:1698-1699.
195. Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost*. 2004;2:1700-1708.
196. Roberts HS, Monroe DM 3rd, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol*. 2004;41(suppl 1):101-108.
197. Guillet B, Pinganaud C, Proulle V, Dreyfus M, Lambert T. Myocardial infarction occurring in a case of acquired haemophilia during the treatment course with recombinant activated factor VII. *Thromb Haemost*. 2002;88:698-699.
198. Peerlink K, Vermeylen J. Acute myocardial infarction following administration of recombinant activated factor VII (NovoSeven) in a patient with haemophilia A and inhibitor. *Thromb Haemost*. 1999;82:1775-1776.
199. Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT. Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. *J Thorac Cardiovasc Surg*. 2002;124:852-854.
200. O'Connell NM. Factor XI deficiency: from molecular genetics to clinical management. *Blood Coagul Fibrinolysis*. 2003;14(suppl 1):S59-S64.
201. Pickard JD, Kirkpatrick PJ, Melsen T, et al. Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagul Fibrinolysis*. 2000;11(suppl 1):S117-S120.
202. d'Oiron R, Menart C, Trzeciak MC, et al. Use of recombinant factor VIIa in 3 patients with inherited type I Glanzmann's thrombasthenia undergoing invasive procedures. *Thromb Haemost*. 2000;83:644-647.
203. Laffan M, O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy D, Smith OP. Analysis and results of the recombinant factor VIIa extended-use registry. *Blood Coagul Fibrinolysis*. 2003;14(suppl 1):S35-S38.