

## Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile

*Jerrold H. Levy, Abe Fingerhut, Thomas Brott, Irene H. Langbakke, Elisabeth Erhardtson, and Robert J. Porte*

**BACKGROUND:** In recent years, the hemostatic agent recombinant factor VIIa (rFVIIa) has emerged as a potentially new therapeutic agent for management of coagulopathy in patients with cirrhosis or following severe traumatic injury, a complex problem for clinicians in which standard treatment strategies are not always effective. As with other hemostatic agents, a primary safety concern of rFVIIa therapy is the theoretical possibility that systemic administration could confer an increased risk of thrombotic complications. So far, clinical experience indicates rFVIIa to be a safe treatment for currently approved indications within hemophilia. Little information is available, however, for patient populations outside this clinical setting.

**STUDY DESIGN AND METHODS:** This article reviews critical safety data obtained from 13 Novo Nordisk-sponsored clinical trials of rFVIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury.

**RESULTS:** Thrombotic adverse events were reported for 5.3 percent (23/430) of placebo-treated patients and 6.0 percent (45/748) of patients on active treatment. No significant difference was found between placebo-treated and rFVIIa-treated patients with respect to the incidence of thrombotic AEs, either on an individual trial basis or for these trial populations combined ( $p = 0.57$ ).

**CONCLUSION:** An important determinant for the safety profile reported here is likely to be the specific mechanism of action of rFVIIa, shown in experimental studies to be localized to the site of vascular injury where tissue factor is exposed.

**B**leeding resulting from coagulopathy can occur in a variety of clinical situations outside of hemophilia, developing, for example, because of cirrhosis or severe traumatic injury. Because the liver is the principal site of synthesis and clearance of the vitamin K-dependent coagulation factors (FII, FVII, FIX, and FX), naturally occurring anticoagulants, and components of the fibrinolytic system, moderate to severe cirrhosis is often associated with hemostatic abnormalities that reduce the capacity for optimal fibrin clot formation.<sup>1</sup> As a result, patients with cirrhosis can be at increased risk of bleeding episodes such as upper gastrointestinal (UGI) variceal bleeding<sup>2,3</sup> and are susceptible to hemorrhage during surgical procedures.<sup>4,5</sup> Coagulopathy can also occur after major hemorrhage and often develops in the context of severe traumatic injury.<sup>6-9</sup> In such critical bleeding situations, factors contributing to impaired hemostasis include the loss of coagulation factors through hemorrhage, the consumption of factors at the site of

**ABBREVIATIONS:** AE(s) = adverse event(s); APCC = activated prothrombin complex concentrate; OLT = orthotopic liver transplantation; TF = tissue factor; UGI = upper gastrointestinal.

From the Department of Anesthesiology, Emory University Hospital, Atlanta, Georgia; the Center Hospitalier Intercommunal, Poissy, France; the Mayo Clinic, Jacksonville, Florida; Novo Nordisk A/S, Bagsværd, Denmark; and the Department of Surgery, University Medical Center Groningen, University of Groningen, the Netherlands.

*Address reprint requests to:* Robert J. Porte, Department of Surgery, Section Hepatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, the Netherlands; e-mail: r.j.porte@chir.umcg.nl.

The clinical trials described herein were funded by Novo Nordisk A/S, Bagsværd, Denmark.

Received for publication May 30, 2005; revision received November 4, 2005, and accepted November 4, 2005.

doi: 10.1111/j.1537-2995.2006.00824.x

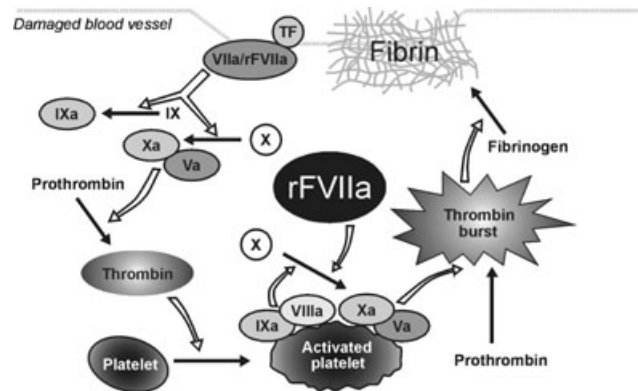
TRANSFUSION 2006;46:919-933.

injury, dilutional coagulopathy consequent to infusing resuscitation fluids and blood components, hypothermia, and metabolic acidosis.<sup>6,7,9-12</sup> Although replacement of blood components lost through hemorrhage is a standard adjunctive therapy to the surgical control of severe bleeding, blood component therapy is subject to delays and does not always adequately correct coagulopathy or stop diffuse, microvascular bleeding.<sup>8,13</sup> In addition, transfusions may carry an increased risk of morbidity through pathogen transmission, transfusion reactions, and transfusion-associated lung injury.<sup>14-19</sup> A reduction in transfusion requirements, through use of more efficient pharmacologic interventions to correct coagulopathy and reduce blood loss, could therefore be of considerable benefit.<sup>20</sup>

In recent years, increasing evidence has suggested that the hemostatic agent recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk, Bagsværd, Denmark) may represent a new treatment in this setting. Originally developed for treating bleeding episodes associated with hemophilia, rFVIIa is approved for hemophilia patients with inhibitors (neutralizing antibodies) against coagulation factors VIII or IX, and in Europe rFVIIa is further licensed for use in acquired hemophilia and congenital FVII deficiency and in patients with Glanzmann's thrombasthenia who are refractory to platelet (PLT) transfusions. Since being licensed in late 1995, however, a growing number of case reports and small, controlled and uncontrolled studies have reported the successful investigational use of rFVIIa in a diverse range of clinical settings outside the hemophilia area. These observations have prompted a continuing program of randomized, controlled clinical trials designed to evaluate the efficacy of rFVIIa in a broad spectrum of potentially new indications including liver surgery and trauma. Although clinical experience so far suggests rFVIIa to be safe in patients with hemophilia,<sup>21</sup> little information is available for other patient populations. This article reviews critical safety data obtained from all 13 completed Novo Nordisk-sponsored clinical trials of rFVIIa in patients with coagulopathy secondary to anticoagulant therapy,<sup>22</sup> cirrhosis,<sup>23-29</sup> or severe traumatic injury,<sup>30</sup> focusing on the incidence of thrombotic adverse events (AEs).

### Mechanism of action of rFVIIa

FVII plays a key role in the initiation and propagation of a series of highly regulated interactions among PLTs, coagulation factors, and components of the blood vessel wall that result in a fibrin clot. In brief, after blood vessel injury, tissue factor (TF) exposed in the subendothelium of the damaged vessel wall binds and activates circulating FVII, resulting in the generation of small amounts of thrombin (Fig. 1). This initial thrombin activates FV and FVIII (to FVa and FVIIIa, respectively) as well as PLTs accumulated



**Fig. 1. Mechanism of action of rFVIIa.** Although rFVIIa binds to TF, at pharmacological doses it directly activates FX on the surface of activated PLTs leading to thrombin generation and fibrin clot formation.

at the site of injury, leading to the activation of FX on the PLT surface. Activated FX then interacts with FVa to produce larger amounts of thrombin (the "thrombin burst"), which leads to the formation of a stable fibrin clot (Fig. 1). In addition to converting fibrinogen into fibrin monomers, thrombin activates FXIII, which covalently cross-links fibrin to form a more stable clot. Further, through the action of thrombin-activatable fibrinolysis inhibitor, the clot is protected from premature fibrinolysis. Because the clot structure is dependent on the rate and amount of thrombin production, sufficient thrombin must be generated to ensure reliable and sustained hemostasis at the site of injury (for a detailed description of the coagulation cascade and mode of action of rFVIIa, see other reviews<sup>21,31</sup>).

At pharmacological concentrations (25-50 nmol/L, corresponding to a dose of 100-200 µg rFVIIa/kg body weight), cell-based studies have indicated that rFVIIa can bind to the surface of locally activated PLTs and directly activate FX (Fig. 1).<sup>32-34</sup> This activation induces a thrombin burst independently of FVIII and F IX and forms the basis of the mechanism by which rFVIIa bypasses a lack of FVIII or F IX activity in hemophilia A and B patients with inhibitors. Under normal or thrombocytopenic conditions, rFVIIa shortens the lag phase of thrombin generation and provides faster PLT activation,<sup>34</sup> suggesting a potential beneficial effect of rFVIIa in situations other than hemophilia. Because rFVIIa only binds to activated PLTs with low affinity, supraphysiological doses of rFVIIa are required to generate an adequate thrombin burst in vivo.<sup>32</sup> TF, however, remains essential for the initiation of coagulation because it is required for initial thrombin generation and local PLT activation (Fig. 1). Further, other studies suggest that the therapeutic efficacy of rFVIIa may be at least partly attributable to displacing zymogen FVII from TF binding sites.<sup>35,36</sup>

### Risk of thrombotic events

A primary safety concern of rFVIIa therapy is the theoretical possibility that the systemic administration of an activated coagulation factor could confer an increased risk of thrombotic complications.<sup>37</sup> Because rFVIIa is not known to bind to circulating inactive PLTs *in vivo*, however, the hemostatic activity of rFVIIa should be restricted to the site of blood vessel injury where TF is exposed and PLTs are locally activated by thrombin. Experimental evidence for this localized effect of rFVIIa has been provided by a comparative study of rFVIIa and the activated prothrombin complex concentrate (APCC) in a rabbit stasis model.<sup>38</sup> In this study, both rFVIIa and APCC promoted clot formation at the site of blood vessel injury. Whereas APCC induced significant dose-dependent decreases in PLT count and fibrinogen levels that suggested a systemic activation of coagulation, however, rFVIIa was without effect on these variables. Further, in contrast to APCC, no changes were observed in antithrombin III levels, nor was there any evidence of a generation of soluble fibrin monomers suggestive of systemic thrombin activity after rFVIIa treatment. Taken together, these data suggest that rFVIIa exerts a local effect at the site of vascular injury without inducing a systemic activation of coagulation.

Since licensing in December 1995 until January 31, 2005, it is estimated that the total amount of rFVIIa released from Novo Nordisk to external customers corresponds to 680,245 standard doses of rFVIIa (defined as 90 µg rFVIIa per kg body weight administered to a 70-kg individual). The proportions of rFVIIa administered either for approved indications or for "off-label" use, however, are not known. Over this postmarketing period, 123 thrombotic AEs have been reported (data derived from published literature, and solicited, spontaneous, and regulatory reports), corresponding to a mean of 1 thrombotic AE reported for every 5530 standard doses of rFVIIa. A recent review of the safety of rFVIIa in patients with acquired and congenital hemophilia with inhibitors concluded that, based on clinical trial data and spontaneous reports, the incidence of thrombotic events associated with the use of rFVIIa in this patient population was low.<sup>21</sup>

## MATERIALS AND METHODS

### Data acquisition and presentation

Data were obtained from all 13 completed Novo Nordisk-sponsored clinical trials of rFVIIa in patients with coagulopathy secondary to anticoagulant therapy,<sup>22</sup> cirrhosis,<sup>23-27,39-41</sup> or severe traumatic injury.<sup>30</sup> Only company-sponsored clinical trials were included to ensure the validity of the data, because these trials were closely monitored with respect to reporting of AEs through frequent monitoring visits. An additional investigator-initiated study in 28 patients with hemorrhagic dengue fever

has been conducted; no thrombotic events were observed in patients receiving rFVIIa, and no safety concerns were raised.<sup>42</sup> A summary of the clinical trials included in this review, including brief details of trial populations, patient demographics, disease severities, dosing regimens, and safety monitoring, is provided in Table 1. Because of differences between trials with respect to patient demographics, baseline characteristics, clinical settings, dosing regimens, and the nature and extent of safety monitoring, all data, as obtained from the original clinical trial reports, are presented on an individual trial basis. Patient selection criteria varied with the different clinical settings under investigation. A common feature was that patients with a perceived increased risk of thrombotic events were excluded from participation in the studies, which is in line with the current dosing recommendations for rFVIIa. Unless otherwise stated, the term "adverse event" includes both nonserious and serious AEs. The criteria used to categorize AEs into either "nonserious" or "serious" did not differ among clinical trials. To provide a complete overview of the incidence of thrombotic AEs, the term "thrombotic AEs" includes both nonserious and serious AEs. All AEs were coded through use of Medical Dictionary for Regulatory Activities terminology<sup>43</sup> and included events with an onset before first trial product administration but evaluated to have worsened after exposure to the trial product. Thrombotic AEs included events coded as thrombosis, emboli, infarctions, and other codes indicating vascular occlusion. The incidence and nature of thrombotic AEs and the mortality rates reported for each clinical trial were reviewed and compared with other reports in the literature (where available) for the investigated patient group and/or clinical setting. Specific details of the nature and severity of other AEs are beyond the scope of this review; this information is provided, where applicable, in the original articles describing these clinical trials. To relate safety data to the therapeutic effectiveness of rFVIIa at the investigated doses, primary efficacy endpoints (and, where appropriate, other data relevant to efficacy) were summarized for each trial.

### Statistical analysis

For trials with a placebo treatment arm (and with reported cases of thrombotic AEs), the risk of experiencing thrombotic AEs on rFVIIa treatment relative to placebo is presented for each trial as an odds ratio (OR) with 95 percent confidence intervals (CIs) and a p value for Fisher's exact test. Further, the overall risk of a thrombotic AE for these trials combined was compared between placebo and rFVIIa groups with a logistic regression model, adjusting for trial effect. The combined OR for rFVIIa relative to placebo is presented with 95 percent CI and a p value for the chi-square test. All statistical analyses were performed

**TABLE 1. Clinical trial details**

Clinical trial (Trial ID)	Trial demography*	Dosing regimen†	Safety monitoring
<b>Experimentally induced coagulopathy<sup>22</sup></b>			
Trial to evaluate the effect of a single dose of rFVIIa in healthy subjects pretreated with an oral anticoagulant.‡	n = 4 (rFVIIa, 4); mean age, ~26 years	Single dose of rFVIIa (10 µg/kg) after administration of acenocoumarol (1-3 mg, twice daily) for 3.5 days.	Standard safety monitoring   up to 8 days after rFVIIa dose.
Dose-ranging trial to evaluate the effect of rFVIIa in healthy subjects receiving an oral anticoagulant.‡	n = 16 (rFVIIa, 16); mean age, ~24 years	Two single doses of rFVIIa (5 and 10, 10 and 20, 20 and 40, 40 and 80, 80 and 120, 120 and 160, 160 and 240, or 10 and 320 µg/kg) separated by 48 hr. The first dose was given on Day 4 of the trial, the second dose on Day 6. Subjects received acenocoumarol (0.5-4 mg, twice daily) from Day 0 to morning of Day 6.	Standard safety monitoring   up to 15 days after second rFVIIa dose.
Trial to evaluate dose response of rFVIIa in healthy subjects receiving an oral anticoagulant.§	n = 12 (rFVIIa, 12); mean age, ~24 years	Single dose of placebo or rFVIIa (5, 20, or 80 µg/kg) separated by 48 hr. The first dose was given on Day 4 of the trial, the second dose on Day 6. Subjects received acenocoumarol (0.5-3 mg, twice daily) from Day 0 to morning of Day 6.	Standard safety monitoring   up to 29 days after second dose.
<b>Cirrhotic patients</b>			
<i>Correction of prolonged prothrombin time</i>			
Dose-escalation trial of rFVIIa in nonbleeding cirrhotic patients.‡ <sup>23</sup>	n = 13 (rFVIIa, 13); mean age, ~46 years; Cirrhosis Child-Pugh score B (n = 6) or C (n = 7)	Three single doses of rFVIIa (5, 20, and 80 µg/kg), each dose separated by 7 days.	Standard safety monitoring   up to 12 hr after final dose.
<i>Dental surgery</i>			
Trial to evaluate the effect of rFVIIa in patients undergoing dental extraction§. <sup>24</sup>	n = 39 (rFVIIa, 30; placebo, 9); mean age, ~53 years; liver disease due to alcoholic cirrhosis or viral hepatitis.	Single dose of placebo or rFVIIa (20 or 80 µg/kg) 10 min before surgery.	Standard safety monitoring   up to 24 hr after surgery.
<i>Liver biopsy</i>			
Two-part trial to evaluate the effect of rFVIIa in patients with advanced liver disease or presumed cirrhosis undergoing a laparoscopic liver biopsy. <sup>25</sup>	n = 71 (rFVIIa, 71); mean age, ~50 years; Cirrhosis Child-Pugh score B (n = 34) or C (n = 36)	Part 1: Single dose of rFVIIa (5 µg/kg) 10 min before biopsy (n = 5)‡. Part 2: Single dose of rFVIIa (5, 20, 80, or 120 µg/kg) 10 min before biopsy.	Standard safety monitoring   up to 18 hr after rFVIIa dose.
<i>Partial hepatectomy</i>			
Trial to evaluate the effect of rFVIIa in cirrhotic patients scheduled to undergo partial hepatectomy due to liver cancer of benign tumors.§ <sup>41</sup>	n = 232 (rFVIIa, 151; placebo, 81); mean age, ~53 years Cirrhosis Child-Pugh score A (n = 224), B (n = 7), or unknown (n = 1)	Single dose of placebo or rFVIIa (50 or 100 µg/kg) 10 min before surgery followed by further identical doses at 2-hr intervals until the end of surgery.	Standard safety monitoring   until discharge from hospital. Doppler ultrasonography of hepatic vasculature (before surgery to 48 hr after surgery) and lower extremities (before surgery to 3 days after surgery).
<b>OLT</b>			
Open-label pilot trial evaluating the effect of rFVIIa in cirrhotic patients undergoing OLT.‡ <sup>26</sup>	n = 6 (rFVIIa, 6); mean age, ~45 years; Cirrhosis Child-Pugh score B (n = 5) or C (n = 1)	Single dose of rFVIIa (80 µg/kg) 10 min before surgery.	Standard safety monitoring   up to 5 days after surgery. Doppler ultrasonography of hepatic vasculature at 1, 3 and 5 days after surgery.
Dose exploratory trial evaluating the effect of rFVIIa in cirrhotic patients undergoing OLT.§ <sup>29</sup>	n = 83 (rFVIIa, 64; placebo, 19); mean age, ~50 years Cirrhosis Child-Pugh score B (n = 37) or C (n = 46)	Single dose of placebo or rFVIIa (20, 40, or 80 µg/kg) 10 min before surgery.	Standard safety monitoring   up to 7 days after surgery. Doppler ultrasonography of hepatic vasculature at 1, 3, and 7 days after surgery (and additional times if hepatic thrombosis was suspected).

TABLE 1. *Continued*

Clinical trial (Trial ID)	Trial demography*	Dosing regimen†	Safety monitoring
Dose exploratory trial evaluating the effect of rFVIIa in cirrhotic patients undergoing OLT.§ <sup>28</sup>	n = 183 (rFVIIa, 121; placebo, 62); mean age, ~53 years Cirrhosis Child-Pugh score A (n = 1), B (n = 107), C (n = 73), or unknown (n = 1)	Single dose of placebo or rFVIIa (60 or 120 µg/kg) 10 min before surgery followed by further identical doses at 2-hr intervals until ~30 min from the completion of surgery. A final dose was administered at the completion of wound closure.	Standard safety monitoring   up to 7 days after surgery. Thrombotic AEs reported for 30 days after surgery. Doppler ultrasonography (as above).
<i>UGI bleeding</i> Trial to evaluate the effect of rFVIIa in the treatment of UGI bleeding.§ <sup>27</sup>	n = 242 (rFVIIa, 121; placebo, 121); mean age, ~53 years Cirrhosis Child-Pugh score A (n = 46), B (n = 124), C (n = 67), or unknown (n = 5); variceal bleeding (n = 161), nonvariceal bleeding (n = 72), unknown (n = 9)	Eight doses of placebo or rFVIIa (100 µg/kg), the first dose within 6 h of hospital admission (or within 6 h of the index bleeding if patient was already hospitalized) with subsequent doses at 2, 4, 6, 12, 18, 24, or 30 hr after the first dose.	Standard safety monitoring   up to 5 days after first dose of rFVIIa. AEs and serious AEs recorded for 5 and 42 days after first trial product administration, respectively. Elective Doppler ultrasonography at some centers?
<b>Noncirrhotic patients</b> <i>Severe traumatic injury</i> Two parallel trials under the same protocol (one in patients with blunt trauma, the other in patients with penetrating trauma) evaluating the effect of rFVIIa in severely injured trauma patients.§ <sup>30</sup>	1) Blunt trauma trial n = 143 (rFVIIa, 69; placebo, 74); median age ~31 years; 2) Penetrating trauma trial n = 134 (rFVIIa, 70; Placebo, 64); median age, ~28 years	Three doses of placebo or rFVIIa (200 + 100 + 100 µg/kg), the first dose administered immediately after transfusion of the 8th unit of RBC and the second and third doses given 1 and 3 hr after the first doses, respectively.	Standard safety monitoring   up to 48 hr after first dose of rFVIIa. Serious AEs recorded until 30 days after first dose.

\* Data refer to the safety population (M, male; F, female).  
† All doses of rFVIIa are expressed in µg of rFVIIa per kg body weight (µg/kg). All patients received rFVIIa or placebo as a slow intravenous bolus injection over a period of approximately 2 minutes. Placebo was administered in the same form and volume as the trial product.  
‡ Open-label trial.  
§ Randomized, double-blind, placebo-controlled trial.  
|| Standard safety monitoring comprised an assessment of AEs, vital signs, physical examination, blood biochemistry (a minimum of serum creatinine, potassium, sodium, calcium, bilirubin, serum albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), hematology (a minimum of Hct, Hb, WBC count, PLT count), coagulation-related parameters (D-dimers, antithrombin III activity, activated partial thromboplastin time [aPTT], fibrinogen, prothrombin fragments 1+2, FVII coagulant activity [FVII:C], international normalized ratio, and PT/aPTT), and coagulation variables (protein S, protein C, FV, FIX, FX, prothrombin).

with computer software (SAS for Windows, Version 8.2, SAS Institute, Cary, NC).

## RESULTS

Table 2 provides a summary of the overall number of AEs, serious AEs, thrombotic AEs, and fatal AEs observed for each trial. For trials with multiple rFVIIa dose groups, AEs were pooled for the active treatment arms. In general, the most commonly reported AEs for both placebo and rFVIIa-treated patients were as expected for the underlying disease and/or condition of the study population or were associated with complications expected with major surgery.

### Experimentally induced coagulopathy

Three clinical trials<sup>22</sup> studied the effect of rFVIIa in healthy subjects treated with an oral anticoagulant to induce a level of coagulation factor deficiency similar to that

observed with impaired liver function. This experimentally induced coagulopathy served as model to test the potential of rFVIIa to correct coagulopathy in patients with liver disease and treat events of acute bleeding arising from oral anticoagulant therapy. For these trials, doses of rFVIIa ranged from a single 10 µg per kg dose to two doses (5-320 µg/kg) over a 48-hour period (maximum cumulative dose of 400 µg/kg; Table 1). At all doses, rFVIIa administration resulted in a normalization of prothrombin time (primary efficacy endpoint), the duration of which was dose-dependent.<sup>22</sup> No thrombotic AEs, serious AEs, or deaths were reported for either the single-dose trial or the two multiple-dose trials.<sup>22</sup> There was no apparent association between rFVIIa dose and the incidence of nonserious AEs.

### Cirrhotic patients

**Correction of prolonged prothrombin time in non-bleeding cirrhotic patients.** One clinical trial evaluated

**TABLE 2. Summary of AEs**

Trial	AEs											
	No. of patients*		All††		Serious‡		Thrombotic‡		Fatal‡			
	Placebo	rFVIIa§	Placebo	rFVIIa§	Placebo	rFVIIa§	Placebo	rFVIIa§	Placebo	rFVIIa§		
Experimentally induced coagulopathy <sup>22</sup>												
Single-dose	0	4	NA	1 (25); 3	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0
Dose-ranging	0	16	NA	12 (75); 34	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0
Dose-response	0	12	NA	6 (50); 20	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0
Cirrhotic patients												
Correction of prothrombin time <sup>23</sup>	0	13	NA	2 (15); 3	NA	1 (8); 1	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0
Dental surgery <sup>24</sup>	9	30	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0
Liver biopsy <sup>25</sup>												
Part 1	0	5	NA	2 (40); 3	NA	1 (20); 1	NA	0 (0); 0	NA	0 (0); 0	NA	0 (0); 0
Part 2	0	66	NA	44 (62); 104	NA	19 (27); 29	NA	1 (1); 1	NA	7 (11); 7	NA	3 (2); 3
Partial hepatectomy <sup>41</sup>	81	151	76 (94); 282	142 (94); 498	2 (2); 2	7 (5); 11	1 (1); 1	3 (2); 3	0 (0); 0	0 (0); 0	0 (0); 0	0 (0); 0
OLT open-label pilot trial <sup>26</sup>	0	6	NA	6 (100); 20	NA	1 (17); 2	NA	2 (33); 3	NA	0 (0); 0	NA	0 (0); 0
OLT dose-exploratory trial <sup>29</sup>	19	64	17 (89); 98	63 (98); 342	6 (32); 9	23 (36); 33	3 (16); 3	7 (11); 9	1 (5); 1	1 (5); 1	6 (9); 6	
OLT dose-exploratory trial <sup>28</sup>	62	121	53 (85); 179	115 (95); 401	12 (19); 17	33 (27); 42	6 (10); 6	19 (16); 21	1 (2); 1	5 (4); 5	5 (4); 5	
UGI bleeding <sup>27</sup>	121	121	95 (79); 288	84 (69); 249	48 (40); 67	42 (35); 55	7 (6); 7	7 (6); 7	11 (9); 11	16 (14); 16	16 (14); 16	
Noncirrhotic patients												
Traumatic injury <sup>30</sup>	74	69	59 (80); 146	53 (77); 123	49 (66); 109	44 (64); 91	3 (4); 3	2 (3); 2	22 (30); 22	17 (25); 17	17 (25); 17	
Blunt trauma	64	70	43 (67); 117	46 (66); 90	36 (56); 76	36 (51); 57	3 (5); 3	4 (6); 4	18 (28); 18	17 (24); 17	17 (24); 17	
Penetrating trauma												

\* Refers to the safety population (i.e., patients exposed to at least one dose of trial product).

† Includes serious and nonserious AEs.

‡ Data are reported as number of patients having an event (percentage of exposed patients having the event); number of AEs reported. NA = not applicable.

§ rFVIIa data are pooled for trials with more than one active treatment arm.

the efficacy and safety of rFVIIa in correcting prolonged prothrombin time in nonbleeding patients with cirrhosis.<sup>23</sup> Thirteen patients were administered 3 successive doses of rFVIIa (5, 20, and 80 µg/kg), each dose separated by an interval of 7 days (Table 1). Prothrombin time was normalized (primary efficacy endpoint) at all dose levels in a dose-dependent manner, remaining within the normal range for approximately 12 hours after the highest dose (80 µg/kg).<sup>23</sup> No thrombotic AEs or deaths were reported (Table 2).

**Dental surgery.** One clinical trial evaluated the effect of rFVIIa in patients with cirrhosis undergoing dental surgery. In this trial,<sup>24</sup> 39 patients received a single dose of placebo, 20 or 80 µg per kg rFVIIa before a pre-molar or molar tooth extraction anticipated to require suturing with one to three stitches (Table 1). No significant difference in the number of patients achieving hemostasis (cessation of bleeding) within 15 minutes of completing the dental procedure (primary efficacy endpoint) was found between treatment groups.<sup>24</sup> No AEs

(including thrombotic AEs) or deaths were reported (Table 2).

**Liver biopsy.** A two-part clinical trial evaluated the effect of rFVIIa in cirrhotic patients undergoing a laparoscopic liver biopsy.<sup>25</sup> In the first pilot phase of the trial, 5 patients received a single 5 µg per kg dose of rFVIIa (Table 1), resulting in a correction of prothrombin time (the primary endpoint) to normal or near normal in all patients.<sup>25</sup> No deaths or thrombotic AEs were reported (Table 2).

In the second part of the trial, patients were evenly randomized to 5, 20, 80, or 120 µg per kg rFVIIa (Table 1). Prothrombin time (the primary efficacy endpoint) was restored to normal in 74 percent of patients, with a significantly longer duration of normalization achieved with higher doses of rFVIIa.<sup>25</sup> No dose-related effect of rFVIIa in the type or frequency of serious and nonserious AEs was evident.<sup>25</sup> One thrombotic AE was reported (1/66 of patients); a portal vein thrombosis occurring in a patient receiving 5 µg per kg rFVIIa (Table 3). Seven

TABLE 3. All thrombotic AEs

Patient (sex/age)	Treatment	AE	Serious (Y/N)	Latency (days)*	Outcome	Comments
Liver biopsy, <sup>25</sup> Part 2						
M/38	5 µg/kg	PVT	Y	6 days	Fatal	Patient with a history of portal vein thrombosis died 13 days after treatment due to peritoneal sepsis.
Partial hepatectomy <sup>41</sup>						
F/55	Placebo	PE	N	5 days	Stabilized	Potential pulmonary embolism suspected by X-ray but not confirmed by spiral-computed tomography.
M/37	50 µg/kg	PVT	N	4 days	Recovered	Clinically asymptomatic. Diagnosed by abnormal blood flow at routine Doppler examination but not confirmed by follow-up Doppler ultrasonography.
M/56	100 µg/kg	MVT	Y	3 days	Recovered	Mesenteric venous thrombosis could not be confirmed upon surgical exploration of the mesenteric vein.
M/56	100 µg/kg	MI	Y	6 hr	Recovered	ECG showed signs consistent with a non Q-wave myocardial infarction. Cardiac enzymes elevated.
OLT <sup>26</sup>						
F/42	80 µg/kg	HAT	Y	1 day	Recovered	The first thrombosis occurred in arteria hepatica propria, the second in the left hepatic artery.
		HAT	Y	70 hr	Recovered with sequelae	
M/39	80 µg/kg	PVT	N	>6 hr	Recovered	Portal vein thrombosis occurred in the anhepatic phase. Doppler ultrasonography at 24 h and at Day 3 and 5 did not reveal flow abnormalities. This portal vein thrombosis is not described in the article by Hendriks et al. <sup>26</sup>
OLT <sup>29</sup>						
M/38	Placebo	HAT	Y	35 days	Recovered	Reduced arterial flow occurred during surgery but no thrombosis was identified.
M/48	Placebo	HAT	Y	4 days	Recovered	Poor quality donor. Hepatic artery graft made from another donor segment.
M/68	Placebo	HVT	Y	0 days	Recovered	Diagnosed during surgery. The thrombosis was preexistent in nature, most likely due to the liver cirrhosis. Known history of deep vein thrombosis.
M/59	20 µg/kg	MI	Y	2 days	Fatal	Acute myocardial infarction at Day 2 after surgery. Hepatic artery thrombosis at Day 7 and rethrombosis at Day 11. The patient died at Day 20. Autopsy report stated septic multiorgan failure as cause of death and furthermore revealed severe arteriosclerotic stenosis of LAD and severe general arteriosclerosis.
		HAT	Y	7 days	Recovered	
		HAT	Y	11 days	Recovered	
M/21	20 µg/kg	HAT	Y	0 days	Recovered	Hepatic artery thrombosis was discovered 40 min after reperfusion of the graft. The patient was hypercoagulable before surgery.

TABLE 3. *Continued*

Patient (sex/age)	Treatment	AE	Serious (Y/N)	Latency (days)*	Outcome	Comments
M/42	20 µg/kg	HVT	Y	0 days	Recovered	Hepatic vein occlusion. Appearance of thrombus indicated presence for a long time. Autopsy of explanted liver showed no fresh thrombus.
M/46	40 µg/kg	HAT	Y	4 days	Recovered	Alternative etiology: The clot originated from an unusual suture in splenic artery stump.
M/58	40 µg/kg	HVT	Y	11 days	Recovered	Patient had intraoperative findings of pre-existing portal vein thrombosis (partial) and underwent thrombectomy in conjunction with OLT.
M/62	80 µg/kg	HAT	Y	6 days	Stabilized	Artery anomalies noted in donor liver.
M/32	80 µg/kg	HAT	Y	5 days	Recovered	Severe stenosis of the donor common HA. Clamp injury suspected.
OLT <sup>28</sup>						
M/51	Placebo	HAT	Y	1 day	Recovered	"Stenosis of truncus coeliacus" reported as alternative etiology.
F/41	Placebo	HAT	Y	1 day	Recovered	Complicated OLT, during which the patient experienced circulatory shock.
F/50	Placebo	HAO	N	0 days	Recovered	
M/66	Placebo	PVT	Y	0 days	Recovered	Previous TIPS with partial thrombosis.
F/38	Placebo	PVT	N	1 day	Recovered	
F/55	Placebo	HAT	Y	2 days	Recovered	Previous TIPS, "Splenic artery steal syndrome" suspected.
F/59	60 µg/kg	AMI	Y	4 days	Recovered	AMI confirmed by ECG and echocardiogram.
M/67	60 µg/kg	PVT	N	1 day	Recovered	
M/39	60 µg/kg	AT NOS	Y	5 days	Recovered	Occlusion of the hepatic artery near the arterial anastomosis.
F/46	60 µg/kg	PE	Y	1 day	Fatal	Autopsy revealed peripheral pulmonary embolism and preexisting recurrent microthromboembolism of the peripheral lung vessels.
F/63	60 µg/kg	HAT	Y	0 days	Recovered	Repeated clamping of the right hepatic artery during anastomosis.
		VGO	Y	5 days	Recovered	
M/51	60 µg/kg	PVT	N	1 day	Recovered	
F/59	60 µg/kg	CI	Y	17 days	Recovered	Infarction verified by CT scan. Medical history of arrhythmia.
F/63	60 µg/kg	PVT	N	0 days	Recovered	
M/60	60 µg/kg	PVT	Y	1 day	Recovered	Old mural recipient portal vein thrombosis detected during OLT. Limited thrombectomy performed.
M/61	60 µg/kg	MI	Y	1 day	Recovered	ECG changes and increased cardiac enzymes.
M/64	60 µg/kg	PVT	N	0 days	Recovered	
F/45	60 µg/kg	HAT	Y	1 day	Stabilized	ECG changes and increased cardiac enzymes.
		PVT	Y	1 day	Recovered	
M/50	120 µg/kg	RVT	N	8 days	Recovered	
M/44	120 µg/kg	PVT	Y	7 days	Recovered	Patient had marked portal hypertension.
F/69	120 µg/kg	SO	N	0 days	Recovered	
M/60	120 µg/kg	HAT	Y	1 day	Recovered	Thrombosis detected during OLT surgery.
F/67	120 µg/kg	HAT	Y	17 days	Recovered	Doppler ultrasonography at Day 5 was suggestive of hepatic artery thrombosis
M/62	120 µg/kg	HAT	Y	21 days	Recovered	Complicated OLT.
M/49	120 µg/kg	HF/PVT	Y	0 days	Fatal	Patient experienced fulminant hepatic failure and was reported as such by investigator. The patient died 29 hr after initiation of OLT: As the event was related to a portal vein thrombosis Novo Nordisk A/S decided to include the event in the analysis.
UGI bleeding <sup>27</sup>						
M/59	Placebo	PVT	Y	23 days	Recovered	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
F/63	Placebo	PVT	Y	2 days	Stabilized	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/54	Placebo	PVT	Y	1 day	Stabilized	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/57	Placebo	PH NOS	N	4 days	Not yet recovered	
M/64	Placebo	PVT	N	4 days	Unknown	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/61	Placebo	PH NOS	N	2 days	Recovered	
M/69	Placebo	PVT	N	2 days	Unknown	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/44	100 µg/kg	PVT	Y	4 days	Unknown	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/58	100 µg/kg	CA	Y	<1 day	Recovered with sequelae	A right hemisphere cerebrovascular accident. CAT scan 3 months before event showed lesions suggestive of a previous infarction in the right cerebral hemisphere. Alcohol abuser and daily smoker.

TABLE 3. *Continued*

Patient (sex/age)	Treatment	AE	Serious (Y/N)	Latency (days)*	Outcome	Comments
M/73	100 µg/kg	CA	Y	<1 day	Fatal	Cerebral infarction. Patient was a nonsmoker without active alcohol abuse, but suffered arterial hypertension.
M/69	100 µg/kg	T NOS	N	<1 day	Recovered	
M/45	100 µg/kg	PVT	Y	1 day	Unknown	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/44	100 µg/kg	PVT	Y	5 days	Stabilized	Clinically asymptomatic event diagnosed through elective Doppler ultrasonography.
M/67	100 µg/kg	PH NOS	N	3 days	Recovered	
Severe traumatic injury <sup>30</sup>						
Blunt trauma						
M/22	Placebo	SVT	Y	13 days	Recovered	Asymptomatic subclavian vein thrombosis at the site of a central venous catheter was diagnosed by ultrasonography.
M/41	Placebo	PE	Y	4 days	Fatal	Suspected pulmonary embolism after removal of vena cava compression.
M/25	Placebo	PE	Y	5 days	Fatal	Pedestrian hit by car. Autopsy revealed pulmonary thromboemboli.
M/18	rFVIIa†	JVT	Y	16 days	Recovered	Thrombosis of internal jugular vein at the site of the central catheter access.
M/33	rFVIIa†	ATL	Y	0 days	Recovered	Driven over by locomotive. Thrombosis diagnosed by angiogram.
Penetrating trauma						
M/27	Placebo	MVT	Y	15 days	Recovered	Stab wounds to abdomen with subsequent surgical repair of vena cava.
M/16	Placebo	CI	Y	1 day	Not yet recovered	Gun shot wound with vascular injuries involving common carotid artery and right subclavian artery. Suspected to be caused by hypotension and cross-clamping.
M/22	Placebo	DVT NOS	Y	7 days	Recovered	Stab wound. Thrombosis at site of subclavian vein repair.
M/25	rFVIIa†	DVT NOS	Y	19 days	Recovered	Paraplegia and splenectomy following trauma. Bed confinement for weeks.
M/41	rFVIIa†	II	Y	0 days	Fatal	Multiple gun shot wounds: Infarction of bowel in superior mesenteric artery territory following ligation of proximal superior mesenteric artery and multiple mesenteric lacerations during damage control.
M/19	rFVIIa†	CI	Y	-1 day	Fatal	Stab wounds to sternoclavicular region. The operative repair necessitated cross clamping of common carotid and brachiocephalic artery.
M/17	rFVIIa†	PHL DVT	Y	4 days	Recovered	Gun shot wound with lacerations and subsequent surgical repair of iliac veins.

\* Time from last study drug administration to onset.

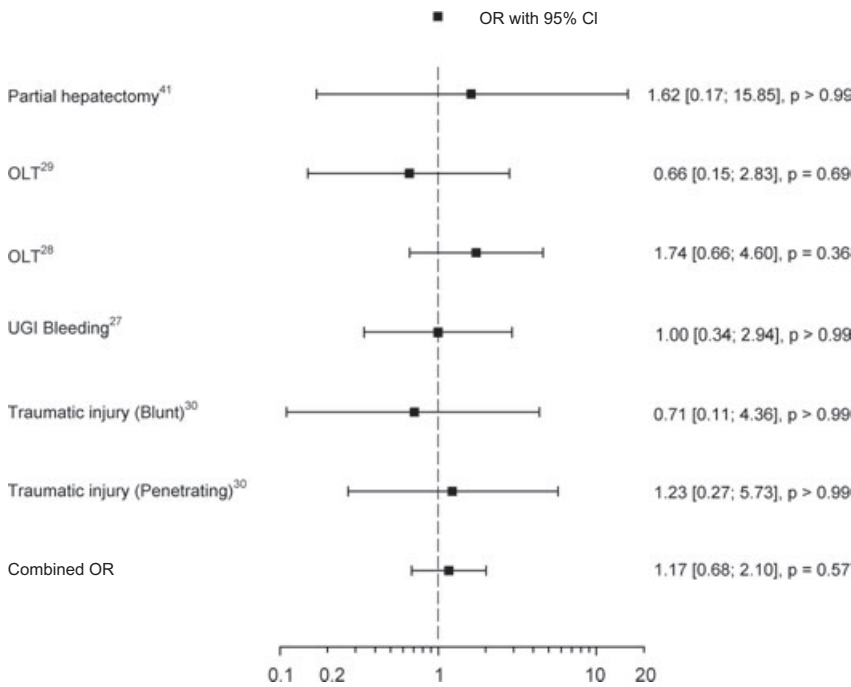
† 200 plus 100 plus 100 µg/kg rFVIIa.

AMI = acute myocardial infarction; AT = arterial thrombosis; ATL = arterial thrombosis limb; CA = cerebrovascular accident; CI = cerebral infarction; DVT = deep vein thrombosis; HAO = hepatic artery occlusion; HAT = hepatic artery thrombosis; HF = hepatic failure; HVT = hepatic venous thrombosis; II = intestinal infarction; JVT = jugular vein thrombosis; MI = myocardial infarction; MVT = mesenteric venous thrombosis; PE = pulmonary embolism; PH = phlebitis; PHL = phlebothrombosis; PVT = portal vein thrombosis; RVT = renal vein thrombosis; SO = shunt occlusion; SVT = subclavian vein thrombosis; T = thrombosis; TIA = transient ischemic attack; VGO = vascular graft occlusion; NOS = not otherwise specified.

deaths (5 µg/kg rFVIIa, 3 deaths; 20 µg/kg rFVIIa, 1 death; 80 µg/kg rFVIIa, 1 death; 120 µg/kg rFVIIa, 2 deaths) occurred between 4 days and 8 months after dosing.

**Partial hepatectomy.** In this study,<sup>41</sup> patients with cirrhosis were evenly randomized to placebo or 50 or 100 µg per kg rFVIIa (Table 1). No significant difference was found between treatment groups in the proportion of patients requiring perioperative red blood cell (RBC) transfusions (primary efficacy endpoint). A similar percentage of patients on placebo and active treatment experienced AEs (serious and nonserious; Table 2), and no association between rFVIIa dose and the type or fre-

quency of AEs was apparent. Thrombotic AEs were reported for 1 percent (1/81) of patients given placebo (pulmonary embolism), 1 percent (1/73) of patients given 50 µg per kg rFVIIa (portal vein thrombosis), and 3 percent (2/78) of patients given 100 µg per kg rFVIIa (mesenteric venous thrombosis, myocardial infarction). For 3 of the above 4 events of thrombosis, the diagnosis could not be confirmed upon follow-up (Table 3). No significant difference in the incidence of thrombotic events was found between placebo and active treatment ( $p > 0.99$ ; Fig. 2). The overall incidence of myocardial infarction (0.4%) was similar to that previously reported for patients undergoing hepatectomy (<0.2%).<sup>44</sup>



**Fig. 2. ORs for thrombotic AEs (rFVIIa vs. placebo).** OR = the odds for a thrombotic AE on rFVIIa relative to placebo (OR 1, equal risk of a thrombotic event with placebo and rFVIIa; OR <1, greater risk of a thrombotic AE on placebo; OR >1, greater risk of a thrombotic AE on rFVIIa). Combined OR = logistic regression model for the above trials combined (with adjustment for trial effect). ORs for individual trials are presented with 95 percent CIs and a p value for Fisher's exact test. The Combined OR is presented with 95 percent CIs and a p value for the chi-square test.

Three patients died during the trial period (50 µg/kg rFVIIa, 1 death; 100 µg/kg rFVIIa, two deaths). All deaths were due to hepatic failure (one death in combination with renal failure). The overall mortality rate of the trial (1.3%) was within the range (1.2%-13%) reported for hepatectomy in patients with cirrhosis.<sup>44-48</sup>

**Orthotopic liver transplantation.** To date, two single-dose trials<sup>26,29</sup> and one multiple-dose trial<sup>28</sup> evaluating the effect of rFVIIa in cirrhotic patients undergoing orthotopic liver transplantation (OLT) have been completed (Table 1). In a pilot trial,<sup>26</sup> 6 patients with cirrhosis undergoing OLT received a single 80 µg per kg dose of rFVIIa before the start of surgery (Table 1). Compared with a group of matched historical controls, a significant reduction in median total RBC transfusion requirements (primary efficacy endpoint) was found for rFVIIa-treated patients. Thrombotic AEs were reported for 2 of 6 (33%) patients (2 patients, 3 events; Table 2) and included 2 cases of hepatic artery thrombosis (experienced on separate occasions by the same patient) and 1 case of portal vein thrombosis (Table 3). No deaths occurred during the trial.

In a subsequent single-dose trial,<sup>29</sup> patients with cirrhosis undergoing OLT were evenly randomized to receive

placebo or 20, 40, or 80 µg per kg rFVIIa (Table 1). No significant differences in perioperative RBC transfusion requirements (primary efficacy endpoint) were found between the placebo and rFVIIa treatment groups. In general, the incidences of AEs (nonserious and serious) were similar for placebo-treated and rFVIIa-treated patients (Table 2), and no notable differences in the type or frequency of AEs were found between rFVIIa dose groups.<sup>29</sup> Thrombotic AEs were reported for 16 percent of patients given placebo (3 patients, 3 events), 17 percent of patients given 20 µg per kg rFVIIa (3 patients, 5 events), 8 percent of patients given 40 µg per kg rFVIIa (2 patients, 2 events), and 8 percent of patients given 80 µg per kg rFVIIa (2 patients, 2 events). No significant difference in the incidence of thrombotic AEs was found between placebo and active treatment (p = 0.69; Fig. 2). The 12 thrombotic AEs reported (Table 3) included 8 cases (in 7 patients) of hepatic arterial thrombosis (2 patients in each of the placebo and 20 and 80 µg/kg rFVIIa groups; 1 patient in the 40 µg/kg rFVIIa group), 3 cases of hepatic venous thrombosis (1 patient in each of the placebo and 20 and 40 µg/kg rFVIIa groups), and 1 acute myocardial infarction (one patient in the 20 µg/kg rFVIIa group). Seven patients died during the trial (placebo, 1 patient; 20 µg/kg rFVIIa, 1 patient; 40 µg/kg rFVIIa, 2 patients; 80 µg/kg rFVIIa, 3 patients).<sup>29</sup>

In a multiple dosing trial,<sup>28</sup> patients with cirrhosis undergoing OLT were evenly randomized to repeated doses of placebo or 60 or 120 µg per kg rFVIIa (Table 1). No significant differences in perioperative RBC transfusion requirements (primary efficacy endpoint) were found between placebo and rFVIIa treatment groups. A significantly higher number of patients in each rFVIIa dose group, however, avoided RBC transfusions when compared with the placebo group.<sup>40</sup> In general, the incidences of AEs (nonserious and serious) were comparable for placebo- and rFVIIa-treated patients (Table 2), and no differences in the type or frequency of AEs were observed between treatment groups.<sup>40</sup> Thrombotic AEs were reported for 10 percent of patients on placebo (6 patients, 6 events), 19 percent of patients on 60 µg per kg rFVIIa (12 patients, 14 events), and 12 percent of patients on 120 µg per kg rFVIIa (7 patients, 7 events; Table 3). No significant difference was found between placebo and active treatment with respect to the proportion of patients experiencing thrombotic AEs (p = 0.36; Fig. 2). Although thrombotic

AEs occurred more frequently in the 60 µg per kg rFVIIa group relative to placebo, a similar incidence was observed for placebo- and 120 µg per kg rFVIIa-treated patients. Twenty-two of 27 thrombotic AEs (81%) originated in the hepatic vessels, of which portal vein thrombosis (2 events in both the placebo and the 120 µg/kg rFVIIa groups, 6 events in the 60 µg/kg rFVIIa group) and hepatic artery thrombosis (placebo, 4 events; 60 µg/kg rFVIIa, 2 events; 120 µg/kg rFVIIa, 3 events) were most frequently reported (Table 3). Five thrombotic AEs were nonhepatic; 1 case each of pulmonary embolism and cerebral infarction and 2 cases of acute myocardial infarction were reported for patients in the 60 µg per kg rFVIIa group, whereas 1 patient in the 120 µg per kg rFVIIa group experienced a renal vein thrombosis (Table 3). No significant difference in the proportion of patients experiencing nonhepatic thrombotic AEs was found between treatment groups (Fisher's exact test,  $p = 0.85$ ).

Six patients died during the trial; one death occurred in each of the placebo and 60 µg per kg rFVIIa groups (2% mortality in each group), whereas 4 deaths occurred in the 120 µg per kg rFVIIa group (7% mortality). No significant differences in patient mortality were found between treatment groups (Fisher's exact test,  $p = 0.29$ ).

For the 3 OLT trials combined, the overall incidences of portal vein thrombosis (placebo, 3.7%; rFVIIa, 5.7%), hepatic artery thrombosis (placebo, 7.4%; rFVIIa, 5.7%), and pulmonary embolism (placebo, 0%; rFVIIa, 0.5%) were within the ranges reported for patients undergoing OLT (2.7-14,<sup>49-51</sup> 2-10,<sup>52-54</sup> and 1%,<sup>55</sup> respectively).

**UGI bleeding.** To date, one trial has been completed that evaluated the effect of rFVIIa in cirrhotic patients with UGI bleeding. In this trial,<sup>27</sup> patients were equally randomized to eight doses of either placebo or 100 µg per kg rFVIIa administered over a 30-hour period as an adjunct to standard pharmacological and endoscopic treatment (Table 1). No significant difference was found between placebo and active treatment with respect to a composite primary endpoint consisting of failure to control bleeding within 24 hours of the first dose of trial product, failure to prevent rebleeding between 24 hours and 5 days, and mortality over the 5-day trial period.<sup>27</sup> An exploratory analysis in the subgroup of patients with bleeding varices (with a Child-Pugh score B or C and more severe coagulopathy), however, found that significantly fewer rFVIIa-treated patients than placebo-treated patients failed on the composite endpoint.<sup>27</sup> No obvious differences in the frequency of AEs and serious AEs were found between treatment groups (Table 2). No significant difference in the incidence of thrombotic AEs was found between placebo and rFVIIa ( $p > 0.99$ ; Fig. 2); thrombotic AEs were reported for 6 percent of patients on placebo (7 patients, 7 events) and 6 percent of patients on active treatment (7 patients, 7 events; Table 2). Clinically asymptomatic por-

tal vein thrombosis was diagnosed through elective Doppler ultrasonography in 4 percent (5/121) of patients on placebo and in 2 percent (3/121) of patients on rFVIIa, for an overall rate of 3.3 percent, well within the range reported for cirrhotic patients (0.6-14%).<sup>2,56</sup> Three cases of thrombophlebitis (placebo, 2 patients; rFVIIa, 1 patient), 1 thrombosis resulting from a blood clot in a central catheter (rFVIIa group), and 2 cerebrovascular events (transient ischemic attack, cerebral infarction; both in the rFVIIa group) were also reported (Table 3).

Twenty-seven deaths occurred during the study; 11 in the placebo group (9% mortality) and 16 in the rFVIIa group (13% mortality; Table 2). The mortality rates observed for this trial compared favorably with the mortality of 15 to 30 percent reported to be associated with initial UGI bleeding episodes.<sup>57-59</sup>

### Noncirrhotic patients

Two randomized trials were conducted in parallel and under the same protocol, one in 143 patients with severe blunt trauma and the other in 134 patients with severe penetrating trauma, to evaluate the efficacy and safety of rFVIIa (200 plus 100 plus 100 µg/kg) or placebo as an adjunct to standard treatment of bleeding in noncirrhotic patients with severe traumatic injury (Table 1).<sup>30</sup>

**Severe traumatic injury—blunt trauma.** For the blunt trauma trial, estimated RBC transfusion (primary efficacy endpoint) was significantly reduced by rFVIIa relative to placebo.<sup>30</sup> The frequencies of AEs and serious AEs were similar for placebo- and rFVIIa-treated patients (Table 2), and no apparent treatment-dependent pattern in the types of AEs was observed.<sup>30</sup> Thrombotic AEs were reported for 4 percent of patients on placebo (3 patients, 3 events) and 3 percent of patients on active treatment (2 patients, 2 events; Table 2). No significant difference in the incidence of thrombotic AEs was found between placebo and rFVIIa ( $p > 0.99$ ; Fig. 2). Of the 5 thrombotic AEs recorded, 2 cases of pulmonary embolism and 1 subclavian vein thrombosis (after central line placement) were reported for the placebo group, whereas 1 jugular vein thrombosis (after central line placement) and 1 arterial limb thrombosis were reported in rFVIIa-treated patients.

In total, 39 patients had an AE with a fatal outcome (placebo, 22 deaths; rFVIIa, 17 deaths) during the 30-day trial period, with mortality rates comparable for placebo (30%) and rFVIIa (25%; Table 2).

**Severe traumatic injury—penetrating trauma.** For the penetrating trauma trial, no significant difference in estimated RBC transfusion requirements (primary efficacy endpoint) was found between treatment groups. No notable differences in the incidence of overall AEs and serious AEs were found between treatment groups (Table 2), and a similar pattern of AEs was observed for

placebo- and rFVIIa-treated patients.<sup>30</sup> No significant difference in the incidence of thrombotic AEs was found between treatment groups ( $p > 0.99$ ; Fig. 2). Thrombotic AEs were reported for 5 percent of patients on placebo (3 patients, 3 events) and 6 percent of patients on active treatment (4 patients, 4 events; Table 3). One cerebral infarction and 1 deep vein thrombosis was observed for each treatment group. In addition, a mesenteric vein thrombosis was recorded in the placebo group and an intestinal infarction (at the site of operation) and an event of phlebothrombosis was observed in the rFVIIa group (Table 3). No difference was found in the mortality rate of placebo- and rFVIIa-treated patients during the 30-day trial period (placebo, 28%; rFVIIa, 24%; Table 2).<sup>30</sup>

For the blunt and penetrating trauma trials combined, the proportion of patients with deep vein thrombosis (placebo, 0.7%; rFVIIa, 0.7%) or pulmonary embolism (placebo, 1.4%; rFVIIa, 0.0%), which are the most common thrombotic complications associated with traumatic injury, was lower than incidences reported for this patient group in the literature (6%, deep vein thrombosis;<sup>60</sup> 2%-22%, pulmonary embolism<sup>61</sup>).

## DISCUSSION

Previously, assessment of the risk of thrombotic complications outside currently approved indications has been difficult. Until recently, results from randomized, placebo-controlled clinical trials were limited, and interpretation of case reports and uncontrolled studies was hampered by possible differences in definitions or methods of detection as well as potential reporting bias.

In this review of 13 controlled clinical trials, comprising 1178 patients with coagulopathy because of anticoagulant therapy, cirrhosis, or severe traumatic injury (the trauma patients typically developed dilutional coagulopathy complicated by acidosis and hypothermia), thrombotic AEs were reported for 5.3 percent (23/430) of placebo-treated patients and 6.0 percent (45/748) of patients on active treatment.

For the 6 trials with a placebo treatment arm (and with reported cases of thrombotic AEs), no significant difference was found between placebo and rFVIIa with respect to the incidence of thrombotic AEs, either on an individual trial basis or from a logistic regression analysis of these trial populations combined ( $p = 0.57$ ; Fig. 2). Further, for trials with more than one active treatment arm, no association between rFVIIa dose and the incidence of thrombotic events was apparent, although this was not formally tested due to the low number of events observed. Because the trials in these analyses were randomized and double-blinded, underlying factors that could potentially predispose to thrombotic complications were expected to be more or less evenly distributed across treatment groups within an individual trial, therefore minimizing the need

to adjust for specific baseline characteristics. Indeed, owing to the low number of thrombotic AEs reported for individual trials, such analyses are unlikely to be meaningful.

For many of the reported thrombotic AEs, the long interval between administration of the last dose of rFVIIa (which has a  $t_{1/2}$  of approximately 2 to 3 hours in patients with hemophilia<sup>62,63</sup>) and the actual event makes a causal relationship less likely, although a potential lag from time of onset to clinical recognition of the thrombotic event remains possible. For placebo- and rFVIIa-treated patients alike, it cannot be excluded that the underlying medical condition of the patient—or in the case of OLT, the intervention—may have contributed to the thrombosis, which in some cases may have been present before the patient received the trial product.

The mortality rates and incidences of specific thrombotic events (both for placebo- and rFVIIa-treated patients) noted for the clinical trials summarized here were similar to and did not exceed those of prior reports for the clinical settings studied. It is recognized, however, that because of variations between studies in trial populations and the methods used to detect thrombosis, it is difficult to make direct comparisons.

For a number of the clinical areas studied, the optimal dose (or dosing regimen) of rFVIIa remains to be defined. At the evaluated individual doses of up to 200  $\mu\text{g}$  per kg (severe traumatic injury), 120  $\mu\text{g}$  per kg (OLT), or 100  $\mu\text{g}$  per kg (UGI bleeding), however, rFVIIa was not associated with an increased risk of thrombotic complications.

It should be noted, however, that although the studies summarized in this article did not detect a greater incidence of thrombotic events in rFVIIa-treated coagulopathic patients, we cannot infer that no increased risks were present. None of the described studies were designed or powered to detect a difference in the incidence of specific thrombotic AEs between treatment groups. Moreover, because most trials had enrollment criteria designed to exclude patients with conditions (e.g., atherosclerotic cardiovascular disease, history of thromboembolism) known to carry a possible risk of thrombotic complications, the selected patient groups of these studies were unlikely to fully reflect those in the general population. Finally, the present conclusions are limited to the coagulopathic patient population included in the studies presented. A recent study in patients with intracerebral hemorrhage, who are typically noncoagulopathic and elderly, showed an increased risk of thrombotic events following rFVIIa administration, although the clinical benefit clearly outweighed the risk.<sup>64</sup>

In summary, based on reported AEs from 13 clinical trials of patients with coagulopathy due to anticoagulant therapy, cirrhosis, or severe traumatic injury, no significant association was found between exposure to rFVIIa and the incidence of thrombotic events. An important

determinant for the safety profile reported here is likely to be the specific mechanism of action of rFVIIa, shown in experimental studies to be localized to the site of vascular injury where TF is exposed.

#### ACKNOWLEDGMENTS

We are indebted to the study coordinators, nurses, physicians, patients, and volunteers who participated in the clinical trials included in this review. We thank Kamilla Begtrup, Paul G. Drake, and Tine M. Sørensen for their valuable contributions in the preparation of the manuscript.

#### REFERENCES

- 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;39:592-8.
- D'Amico G, De Franchis R, Cooperative-Study G. Upper digestive bleeding in cirrhosis: post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;38:599-612.
- Bosch J, Abraldes JG. Management of gastrointestinal bleeding in patients with cirrhosis of the liver. *Semin Hematol* 2004;41:8-12.
- Lodge JP. Hemostasis in liver resection surgery. *Semin Hematol* 2004;41:70-5.
- Silva MA, Muralidharan V, Mirza DF. The management of coagulopathy and blood loss in liver surgery. *Semin Hematol* 2004;41:132-9.
- Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. *Intensive Care Med* 2002;28(Suppl 2):S241-7.
- Hoyt DB, Bulger EM, Knudson MM, et al. Death in the operating room: an analysis of a multi-center experience. *J Trauma* 1994;37:426-32.
- Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfus Med Rev* 2003;17:223-31.
- Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004;57:709-19.
- Valeri CR, Feingold H, Cassidy G, et al. Hypothermia-induced reversible platelet dysfunction. *Ann Surg* 1987;205:175-81.
- Gubler KD, Gentilello LM, Hassantash SA, Maier RV. The impact of hypothermia on dilutional coagulopathy. *J Trauma* 1994;36:847-51.
- Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med* 1992;20:1402-5.
- Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001;51:431-8.
- Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005;105:2266-73.
- Dodd RY. Bacterial contamination and transfusion safety: experience in the United States. *Transfus Clin Biol* 2003;10:6-9.
- Houbiers JG, van de Velde CJ, van de Watering LM, et al. Transfusion of red cells is associated with increased incidence of bacterial infection after colorectal surgery: a prospective study. *Transfusion* 1997;37:126-34.
- Jensen LS, Andersen AJ, Christiansen PM, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992;79:513-6.
- Blumberg N, Heal JM. Effects of transfusion on immune function: cancer recurrence and infection. *Arch Pathol Lab Med* 1994;118:371-9.
- Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg* 2002;68:566-72.
- Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002;62:2193-211.
- 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.
- Erhardtson E, Nony P, Dechavanne M, et al. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. *Blood Coagul Fibrinolysis* 1998;9:741-8.
- Bernstein DE, Jeffers L, Erhardtson E, et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology* 1997;113:1930-7.
- Carreño V, Messner M, Arrieta J, et al. The effect of recombinant factor VIIa (NovoSeven) on haemorrhage following dental surgery in patients with liver cirrhosis—a randomised placebo controlled study. *Thromb Haemost* 2001;(Suppl ISTH XVIII Congress):P2612.
- 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;123:118-26.
- Hendriks HG, Meijer K, De Wolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation. *Transplantation* 2001;71:402-5.
- Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004;127:1123-30.
- Lodge JPA, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005;11:973-9.
- Planinsic RM, van der Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 2005;11:895-900.

30. Boffard KD, Riou B, Warren B, et al. Recombinant Factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005;59:8-15.
31. Roberts HR, Monroe DM, Escobar MA. Current concepts of hemostasis: implications for therapy. *Anesthesiology* 2004;100:722-30.
32. Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. *Br J Haematol* 1997;99:542-7.
33. Allen GA, Monroe DM, Roberts HR, Hoffman M. The effect of factor X level on thrombin generation and the procoagulant effect of activated factor VII in a cell-based model of coagulation. *Blood Coagul Fibrinolysis* 2000;11(Suppl 1): S3-S7.
34. Kjalke M, Ezban M, Monroe DM, et al. 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;114:114-20.
35. 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;95:1330-5.
36. Friederich PW, Levi M, Bauer KA, et al. Ability of recombinant factor VIIa to generate thrombin during inhibition of tissue factor in human subjects. *Circulation* 2001;103:2555-9.
37. Roberts HR, Monroe DM III, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol* 2004;41:101-8.
38. Diness V, Bregengaard C, Erhardttsen E, Hedner U. Recombinant human factor VIIa (rFVIIa) in a rabbit stasis model. *Thromb Res* 1992;67:233-41.
39. Planinsic RM, van de Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005;11:895-900.
40. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005;11:973-9.
41. Shao YF, Yang JM, Chau GY, et al. Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Am J Surg* 2006;191:245-9.
42. Chuansumrit A, Wangruangsattid S, Lektrakul Y, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind placebo-controlled study. *Blood Coagul Fibrinolysis* 2005;16:549-55.
43. Brown EG, Wood L, Wood S. The Medical Dictionary for Regulatory Activities (MedDRA). *Drug Saf* 1999;20:109-17.
44. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 2004;240:698-708.
45. Capussotti L, Borgonovo G, Bouzari H, et al. Results of major hepatectomy for large primary liver cancer in patients with cirrhosis. *Br J Surg* 1994;81:427-31.
46. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995;130:198-203.
47. Fan ST, Ng IO, Poon RT, et al. Hepatectomy for hepatocellular carcinoma: the surgeon's role in long-term survival. *Arch Surg* 1999;134:1124-30.
48. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000;191:38-46.
49. Nonami T, Yokoyama I, Iwatsuki S, Starzl TE. The incidence of portal vein thrombosis at liver transplantation. *Hepatology* 1992;16:1195-8.
50. Davidson BR, Gibson M, Dick R, Burroughs A, Rolles K. Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. *Transplantation* 1994;57:1174-7.
51. Settmacher U, Nussler NC, Glanemann M, et al. Venous complications after orthotopic liver transplantation. *Clin Transplant* 2000;14:235-41.
52. Drazan K, Shaked A, Olthoff KM, et al. Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). *Am Surg* 1996;62:237-40.
53. Parera A, Salcedo M, Vaquero J, et al. Arterial complications after liver transplantation: early and late forms [Estudio comparativo de las complicaciones arteriales precoces y tard?as postrasplante hep?] *Tico Gastroenterol Hepatol* 1999;22:381-5.
54. Porte RJ. Antifibrinolytics in liver transplantation: they are effective, but what about the risk-benefit ratio? *Liver Transpl* 2004;10:285-8.
55. Ishitani M, Angle J, Bickston S, et al. Liver transplantation: incidence and management of deep venous thrombosis and pulmonary emboli. *Transplant Proc* 1997;29:2861-3.
56. Okuda K, Ohnishi K, Kimura K, et al. Incidence of portal vein thrombosis in liver cirrhosis: an angiographic study in 708 patients. *Gastroenterology* 1985;89:279-86.
57. Afessa B, Kubilis PS. Upper gastrointestinal bleeding in patients with hepatic cirrhosis: clinical course and mortality prediction. *Am J Gastroenterol* 2000;95:484-9.
58. del Olmo JA, Peña A, Serra MA, et al. Predictors of morbidity and mortality after the first episode of upper gastrointestinal bleeding in liver cirrhosis. *J Hepatol* 2000;32:19-24.
59. Butt AK, Khan AA, Alam A, et al. Predicting hospital mortality in cirrhotic patients: comparison of Child-Pugh and Acute Physiology, Age and Chronic Health Evaluation (APACHE III) scoring systems. *Am J Gastroenterol* 1998;93:2469-75.
60. Britt LD, Zolfaghari D, Kennedy E, Pagel KJ, Minghini A. Incidence and prophylaxis of deep vein thrombosis in a high risk trauma population. *Am J Surg* 1996;172:13-4.

61. O'Malley KF, Ross SE. Pulmonary embolism in major trauma patients. *J Trauma* 1990;30:748-50.
62. Lindley CM, Sawyer WT, Macik BG, et al. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. *Clin Pharmacol Ther* 1994;55:638-48.
63. 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;10:352-9.
64. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777-85+851. 