Review and Recommendations for the Off Label Use of Recombinant Activated Human Coagulation Factor VII (Novoseven®)

VA MedSafe, Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

EXECUTIVE SUMMARY

Novoseven® is a recombinant preparation of activated human coagulation factor VII (rFVIIa). The Food and Drug Administration (FDA) approved rFVIIa in March of 1999 for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or IX and in those with congenital Factor VII deficiency. It is also approved for the prevention of bleeding prior to surgical interventions or invasive procedures in similar patients.

Over the past few years, there has been increasing interest in using rFVIIa for off-label indications. This interest is demonstrated by the large amount of published data examining the many off-label uses of rFVIIa. Off-label use has included use for surgery or trauma-related bleeding; use prior to liver biopsy or for variceal bleeding in patients with cirrhosis; perioperative use during orthotopic liver transplantation or liver resection; reversal of anticoagulation therapy; other coagulation defects (e.g. von Willebrand disease, factor V deficiency and factor XI deficiency) and finally as a rescue intervention in patients with intractable bleeding despite other therapeutic measures. However, the bulk of the evidence is in the form of case reports and case series with no control group making it very difficult to determine actual benefit and safety in treating various conditions. In addition, with case reports and case series making up the bulk of the evidence, there is a potential for bias of various types including selection of patients, varied doses and dosing regimens, and finally submitting only positive data for publication. Because there are only a limited number of published controlled trials prospectively evaluating rFVIIa for these various off-label conditions, the appropriate dose for each indication, the dosing interval, whether or not to combine rFVIIa with other hemostatic agents (e.g. antifibrinolytics-aminocaproic acid or tranxemic acid or aPCCs or PCCs), optimal timing for use, need for repeat doses, etc. is not clear. (The available controlled clinical trials are summarized in the text of the document as well as in Appendix A.) There are numerous clinical trials underway in a variety of conditions. For more information, go to http://www.clinicaltrials.gov/ct and type Novoseven® in the search box.

In December 2005, the FDA and Novo Nordisk alerted healthcare professionals of several labeling changes concerning the safety of recombinant coagulation factor VIIa or rFVIIa (Novoseven®) in non-hemophiliac patients. These changes are reflected in the warnings and adverse reactions sections of the label and originate from data from clinical trials in non-hemophiliac patients and from post marketing surveillance. Essentially, the labeling states that the risk for thromboembolism in patients without hemophilia is unknown, but warns of a potentially increased risk associated with rFVIIa in these patients. The changes originate from a study of rFVIIa in elderly non-hemophiliacs presenting with acute intracerebral hemorrhage. In this study, there was a nonsignificant increase in major thromboembolic events (e.g. myocardial ischemia, myocardial infarction, cerebral infarction and/or ischemia) in the group receiving rFVIIa.

In the majority of controlled clinical trials involving rFVIIa, there was not a significantly greater frequency of thromboembolic events compared to placebo. However, in some of the trials, there tended to be a higher risk for more serious thromboembolic events in the rFVIIa groups. Additionally, a group examining thromboembolic adverse events (associated with rFVIIa) reported to the FDA's adverse event reporting system (AERS or MedWatch) raised awareness of the potential thromboembolic risk of rFVIIa. Although a frequency or incidence rate of thromboembolic adverse events cannot be determined because of the limitations of spontaneous reporting systems, like AERS, the paper provides evidence that administration of rFVIIa may be associated with a risk of serious thromboembolic adverse events. The magnitude of the risk in specific patients is not known and as a result the benefit to risk ratio of rFVIIa needs to be thoughtfully considered in individual patients and conditions. **Refer to Page 9 for a summary of the evidence and recommendations.**

INTRODUCTION

Novoseven® is a recombinant preparation of activated human coagulation factor VII (rFVIIa). The Food and Drug Administration (FDA) approved rFVIIa in March of 1999 for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or IX and in those with congenital Factor VII deficiency. It is also approved for the prevention of bleeding prior to surgical interventions or invasive procedures in similar patients.

In December 2005, the FDA and Novo Nordisk alerted healthcare professionals of several labeling changes concerning the safety of recombinant coagulation factor VIIa or rFVIIa (Novoseven®) in non-hemophiliac patients.[1] These changes are reflected in the warnings and adverse reactions sections of the label and originate from data from clinical trials in non-hemophiliac patients and from post marketing surveillance. In the warnings section, it is stated that the risk for thromboembolic events in patients with hemophilia and inhibitors is unknown, but is considered to be low. However, patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs) may have an increased risk for developing a thrombotic event due to circulating tissue factor (TF) or predisposing coagulopathy.

Furthermore, the new labeling includes a statement that the risk for arterial and venous thromboembolism in patients without hemophilia is also not known, but warns of a potential increased risk for these events occurring in non-hemophiliac patients who receive rFVIIa. This change is based upon data from a clinical study of elderly non-hemophiliac patients presenting with acute intracerebral hemorrhage in which there was a nonsignificant trend towards a higher risk of thromboembolic events (e.g. myocardial ischemia, myocardial infarction, cerebral infarction and/or ischemia).[2]

Finally, the changes include incorporation of adverse event information from post marketing clinical trials as well as those reported to the FDA's voluntary safety and adverse events reporting program (AERS or MedWatch).

In this document, the evidence for the effective and safe use of rFVIIa in non-hemophiliacs will be reviewed.

PHARMACOLOGY/rFVIIa PRODUCT INFORMATION[2,3]

Coagulation factor VII (FVII) is a vitamin K dependent glycoprotein that initiates coagulation by binding to tissue factor (TF). Tissue factor is a component of the deep layer of the walls of the blood vessels and is only present in the blood after injury or trauma. Once FVII binds with TF, FVII is converted to its active form (FVIIa) and facilitates activation of factors X and IX leading to thrombin production. Thrombin production then leads to activation of platelets and formation of a clot.[3] Novoseven was developed using recombinant DNA technology and is almost identical in structure and function to the plasma derived FVIIa.[4-6]

Pharmacokinetics

The median half-life of rFVIIa, after a single bolus dose, is 2.3 hrs (range 1.7-2.7 hrs) in adults. However, the half-life may be reduced during active bleeding.

Drug-Drug Interactions

It is not known if there is an increased risk for thromboembolic events when rFVIIa is combined with other coagulation factor concentrates. Although not prospectively evaluated, many patients in the trials received antifibrinolytic agents (e.g. tranxemic acid, aminocaproic acid) in combination with rFVIIa with no apparent adverse outcomes.

Contraindications

Recombinant activated FVII is contraindicated in patients with a known hypersensitivity to mouse, bovine or hamster proteins.

Monitoring

Laboratory coagulation parameters (e.g. PT, aPTT) may be monitored together with monitoring for clinical signs of a hemostatic response. However, there is no evidence correlating achievement of hemostasis and an effect of rFVIIa on these coagulation parameters.

Dose

The recommended dose and dosing interval for rFVIIa are available for FDA approved indications (e.g. hemophilia A or B with inhibitors prior to surgery or during active bleeding), but are outside of the scope of this document.

At this time, there is not sufficient evidence to suggest a particular dose for off-label indications. Additionally, from the available data, there is not a clear dose-response relationship for achieving hemostasis. However, one group has recommended a 4.8 mg vial in appropriate patients providing a dose of 50-100 mcg/kg in individuals weighing 50-100 kg.[11] While another group has recommended a dose of 20-40 mcg/kg for nonemergent anticoagulation reversal and doses of 41-90 mcg/kg for other appropriate scenarios.[7]

OFF-LABEL USES OF NOVOSEVEN

There is a considerable amount of published data examining the off-label uses of rFVIIa. Off-label use has included use for surgery or trauma-related bleeding; use prior to liver biopsy or for variceal bleeding in patients with cirrhosis; perioperative use during orthotopic liver transplantation or liver resection; reversal of anticoagulation therapy; other coagulation defects (e.g. von Willebrand disease, factor V deficiency and factor XI deficiency) and finally as a rescue intervention in patients with intractable bleeding despite other therapeutic measures. However, the bulk of the evidence is in the form of case reports and case series with no control group making it very difficult to determine actual benefit and safety in treating various conditions. In addition, with case reports and case series making up the bulk of the evidence, there is a potential for bias of various types including selection of patients, varied doses and dosing regimens, and finally submitting only positive data for publication. Because there are only a limited number of published controlled trials prospectively evaluating rFVIIa for these various off-label conditions, the appropriate dose for each indication, the dosing interval, whether or not to combine rFVIIa with other hemostatic agents (e.g. antifibrinolyics-aminocaproic acid or tranxemic acid or aPCCs or PCCs), optimal timing for use, need for repeat doses, etc. is not clear.

As evidenced by the published literature, there is interest in using rFVIIa for a variety of bleeding disorders and/or coagulopathies for which it has not been adequately studied or FDA approved. Some of the stated advantages of rFVIIa, as opposed to other hemostatic treatments (aPCCs, PCCs, fresh frozen plasma (FFP), platelet concentrates, red blood cell transfusion (RBC) and cryoprecipitate), include a belief that since rFVIIa is not active unless it binds with TF, it will not induce systemic coagulation. Second, the activity of rFVIIa is not altered by the presence of clotting factor inhibitors. Third, there is no risk for transmission of infection since rFVIIa is not a human derived blood product. However, since Novoseven® may contain trace foreign proteins from the manufacturing process, there is a potential for a harmful antibody response in some persons. Finally, since only small amounts of fluid are introduced with rFVIIa, it may be more advantageous in those individuals where volume overload is a concern. However, because of the unknown risk for thromboembolic adverse events in non-hemophiliac patients and the significant cost associated with the use of rFVIIa, several authors have reviewed the available evidence for its off-label use and have attempted to provide rationale guidance for appropriate use.[3,7-11]

Since randomized, controlled clinical trials are considered the best available evidence, only those studies will be included in detail in this section. **(See Appendix A-Clinical Trials)** There are numerous clinical trials underway in a variety of conditions. For more information, go to http://www.clinicaltrials.gov/ct and type Novoseven® in the search box.

I. Liver Disease

Dysfunctional coagulation systems are commonly observed in patients with acute and chronic liver disease. Since the liver is responsible for producing the majority of clotting proteins, impairment of synthesis of these proteins or clotting factors (generally, FVII deficiency is the most pronounced) is the primary abnormality leading to bleeding diatheses in these patients. There are other factors that may contribute to bleeding risk including disseminated intravascular coagulation (DIC), uremia (in more severely diseased livers) and platelet dysfunction.[10] Because the liver is also responsible for the synthesis of anticoagulant proteins like protein C, protein S and antithrombin, thrombosis can also be a concern. However, bleeding tends to be the more common problem in this population. As a result, there is considerable interest in identifying agents, like rFVIIa, to reduce the likelihood of bleeding in patients with more advanced hepatic dysfunction including reducing the risk of bleeding and/or time to hemostasis after undergoing limited invasive procedures (e.g. prophylaxis prior to liver biopsy), and in achieving hemostasis if spontaneous bleeding (e.g. variceal, mucosal) does occur.

Available evidence supports that common laboratory indices of coagulation (e.g. elevated PT, reduced platelet count) do correlate with prognosis in patients with liver disease. However, evidence does not support using these indices to predict bleeding risk in these patients.[10] Because of the complexity of bleeding diathesis in liver disease, and the inability to predict bleeding risk based upon examination of coagulation tests, there is not a consensus on when to use hemostatic agents. As a result, the decision of when (e.g. prophylaxis prior to an invasive procedure or for spontaneous bleeding) to use a product such as rFVIIa is especially difficult because of its high cost and unknown benefit to risk profile in this population.

Ia. Normalization or Reduction in Prothrombin Time (PT)

There are several trials in which the ability of rFVIIa to normalize or reduce the prothrombin time (PT) prior to invasive procedures, such as liver biopsy, in patients with elevated PT has been investigated.[12-14] In these studies, the PT was normalized or reduced significantly in the majority of patients within approximately 10-30 minutes. However, normalization or reduction in PT does not necessarily reflect resolution of the clotting defect or correlate with hemostasis.[8-10] The duration of PT normalization in response to administration of rFVIIa was observed to range from 20 minutes to nearly 12 hrs and appeared to be dose-dependent with higher doses leading to more prolonged duration of PT normalization.[12-14] However, in one of those studies, there was no correlation between escalating doses of rFVIIa and post-procedural bleeding, suggesting no dependence upon dose.[12]

Ib. Upper Gastrointestinal Bleeding (UGIB)-Variceal in Origin

Because variceal bleeding is a major cause of morbidity and mortality in patients with cirrhosis, one group of investigators has examined the effect of rFVIIa as a hemostatic agent in a randomized, double-blind, placebo controlled trial.[15] Bosch et al., sought to determine if administration of rFVIIa would result in a better outcome in terms of bleeding, rebleeding and death compared to placebo in 245 patients with UGIB (variceal in origin) and cirrhosis. All patients were to receive standard therapy for variceal bleeding including vasoactive pharmacologic and endoscopic therapy. The primary endpoint was a composite of cessation of acute bleeding in 24 hrs, prevention of rebleeding from 24 hrs to 5 days and death at 5 days. Secondary endpoints included analysis of the individual endpoints of the composite primary endpoint, need for transfusion, and death at 6 weeks. There was no difference in the primary endpoint between groups or any of the secondary endpoints. Of interest, there was a nonsignificant trend towards a higher rate of death in the rFVIIa group compared to placebo (5 days: 7/118 (6%) vs. 4/119 (3%); 6 weeks: 16/116 (14%) vs. 11/120 (9%), respectively). Although p-values weren't provided, it appeared that a higher number of patients given placebo were classified as having a Child-Pugh Grade of C (more severe disease). The authors reported in a post-hoc analysis they found that patients with moderate to severe cirrhosis (Child-Pugh Grades of B and C) did derive statistically significant benefit from receiving rFVIIa vs. placebo. However, they also stated that use of Cox regression analysis revealed that the severity of disease, and not the active drug, influenced the outcome.

Ic. Liver Transplantation/Liver Resection or Partial Hepatectomy

Surgical procedures involving the liver are known to be associated with excessive blood loss. It has been estimated that as many as 25-40% of patients undergoing hepatic resection will require perioperative blood

transfusion.[16] To date, there have been four randomized, placebo-controlled trials evaluating the effect of rFVIIa on red blood cell (RBC) transfusion requirements. Two trials[16-17] involved patients requiring surgical resection or partial hepatectomy for liver cancer or benign tumors (one in cirrhotics and one in noncirrhotics), while the other two trials[18-19] involved patients requiring orthotopic liver transplantation (OLT). Single and repeat doses of rFVIIa were evaluated. Doses of rFVIIa ranged from 20 mcg/kg to 120 mcg/kg.

In the liver resection study by Lodge, et al[16], 20 or 80 mcg/kg of rFVIIa or placebo was given preoperatively and then repeated after 5 hours if surgery was expected to exceed 6 hours. In the study by Shao, et al[17], rFVIIa 50 or 100 mcg/kg or placebo was administered preoperatively and repeated every 2 hours during surgery up to a maximum of four doses. In both trials, there was no significant effect of rFVIIa treatment vs. placebo in efficacy endpoints. Endpoints included proportion of patients requiring RBC transfusion, number of RBC units transfused, use of other hemostatic agents and use of fresh frozen plasma (FFP) or platelet concentrates (PC). There were a small number of thromboembolic events with no statistical differences between active and placebo groups.

In the OLT studies, single and repeated doses of rFVIIa were evaluated. In the study by Lodge, et al[18] repeat doses of rFVIIa 60 or 120 mcg/kg were compared to placebo. In the second trial by Planinsic, et al[19], a single dose of 20, 40 or 80 mcg/kg vs. placebo was administered. In both trials, rFVIIa was not associated with a reduction in the number of RBC units transfused or blood loss during surgery compared to placebo. However, in the study by Lodge, et al. involving 183 patients, there was a significant reduction in the proportion of patients avoiding RBC transfusions in the rFVIIa groups vs. placebo (9.6% (4/56), 7.1% (6/62) and 0% (0/61), respectively, p=0.0331).

As shown above, there have been a number of trials evaluating the effectiveness and safety of rFVIIa in patients with impaired liver function. In the case of normalizing PT, rFVIIa was very effective at reducing the PT test to normal values with the duration of normalization being dose-dependent. However, since the PT test is highly sensitive to VIIa, the effect of rFVIIa on the PT may be an *ex vivo* effect rather than a true correction of the coagulopathy. As for the effect of rFVIIa vs. placebo in the cessation of bleeding, rebleeding and death as a result of bleeding varices, there was no apparent advantage. Finally, in the case of surgical interventions involving the liver, administration of rFVIIa demonstrated no significant advantage over placebo with the exception of a reduced proportion of patients receiving RBC transfusions in one of the four studies. As for safety, the number of thromboembolic events was not different between rFVIIa and placebo, however the numbers were small. Finally, there was a nonsignificant trend towards a higher rate of death at 5 days and 6 weeks in cirrhotic patients with variceal bleeding in the rFVIIa group vs. placebo.

II. Acute Intracerebral Hemorrhage

It has been estimated that 37,000-52,000 cases of intracerebral hemorrhage (ICH) occur in the United States annually and account for approximately 10-15% of all strokes.[20] It is reportedly the most disabling form of stroke and is associated with a high incidence of one-year mortality.[20] A critical factor in death or functional outcome is hematoma volume. Early hematoma growth (33% in volume within 3 hours), due to continued bleeding or rebleeding at multiple sites, occurs in about one-third of patients and is a crucial factor in neurologic deterioration.[21] As a result, Mayer, et al.,[21] set out to determine whether treatment with rFVIIa would limit hematoma growth in patients with acute intracerebral hemorrhage and in turn improve functional outcomes.[21] In this study, 399 patients presenting within three hours of symptom onset were randomized to a single dose of rFVIIa 40, 80, 160 mcg/kg or placebo. Treatment was administered within one hour of computerized tomography (CT) scan and no later than four hours after symptom onset. There were multiple exclusion criteria including Glasgow Coma Scale 3-5 (representing deep coma); planned surgical evacuation of hematoma with 24 hours of admission; intracerebral hemorrhage resulting from aneurysm, arteriovenous malformation or trauma; use of oral anticoagulants; thrombocytopenia, coagulopathy; sepsis, disseminated intravascular coagulation; preexisting disability, and symptomatic thrombotic or vaso-occlusive disease within the past 30 days. The last criterion was modified midway through the trial to exclude any patient with a history of thrombotic or vaso-occlusive disease. The reason for that change was not stated. All but one patient received treatment within four hours of symptom onset.

The primary outcome measure was the mean percent increase in hematoma volume.

Table 1

Variable-ICH	Placebo (n=96)	40 mcg/kg (n=108)	80 mcg/kg (n=92)	160 mcg/kg (n=103)	Combined (n=303)
Estimated mean relative change in Volume from baseline (%)	29%	16%, p=0.07, 98.3% CI 4-28	14%, p=0.05, 98.3% CI 2-27	11%, p=0.02*, 98.3% CI 0-23	14%, p=0.01*, 98.3% CI 7-21
Estimated mean absolute increase from baseline (ml)	8.7 ml	5.4 ml, p=0.13, 98.3% CI 1.7-9	4.2 ml, p=0.04, 98.3% CI 0.3-8	2.9 ml, p=0.008*, 98.3% CI -0.8-6.6	4.2 ml, p=0.01*, 98.3% CI 2-6.3

Data extracted from Table 2. in reference 21
P value represented is vs. placebo (threshold of significance=0.0167 due to Bonferroni's correction for 3 doses of rFVIIa)
* Represents statistical significance

As noted in the table, there was a significant reduction in hematoma growth in the 160 mcg/kg and combined rFVIIa groups vs. placebo. There appeared to be a dose-response relationship in limiting hematoma growth based upon testing for trends.

Four outcome scales were used to measure death and functional outcomes at 90 days. Global outcomes were assessed using the modified Rankin Scale (0 indicates full recovery, 6 death) and the extended Glasgow Outcomes Scale or E-GOS (8 indicates minimal or no disability, 1 death). In analyzing global outcomes, moderately severe to severe disability and death were combined and counted as poor or unfavorable outcomes to control for the possibility that rFVIIa would reduce death but result in a greater number of those severely disabled. Activities of daily living were assessed using the Barthel Index (100 indicates independence, 0 bedridden and dependence) and neurologic impairment with the National Institutes of Heath Stroke Score (NIHSS) (0 indicates no deficits, 45 coma and quadriplegia).

Table 2

Variable	Placebo (n=96)	40 mcg/kg (n=108)	80 mcg/kg (n=92)	160 mcg/kg (n=103)	Combined (n=303)
Death (%) OR for survival (95% CI)	29% --	18%, p=0.05 1-3.8	17%, p=0.10 0.9-3.6	19%, p=0.11 0.9-3.3	18%, p=0.02 1.1-3
Modified Rankin Scale (% Unfavorable outcome) OR for improvement*	69% --	55% 1.1-4.0, p=0.02	49% 1.3-4.6, p=0.008	54% 1.1-4.1, p=0.02	53% 1.3-3.8, p=0.004
E-GOS (% Unfavorable outcome) OR for improvement*	81% --	72% 0.9-3.8, p=0.09	72% 0.7-3.2, p=0.28	75% 0.7-3, p=0.36	73% 0.9-3, p=0.14
Barthel Index (Median Score), p-value	25	55, p=0.07	67.5, p=0.01	55, p=0.02	60, p=0.006
NIHSS, p-value	12.5	6, p=0.03	5, p=0.004	7, p=0.02	6, p=0.008

E-GOS=Extended Glasgow Outcome Scale OR=odds ratio
Unfavorable outcome: Modified Rankin 4-6, E-GOS 1-4, *Odds for improvement is the likelihood of improving by 1 scale vs. placebo 95% CI. Data extracted from Table 3 in reference 21

In the table above, there was a benefit in the active treatment groups in terms of fewer patients having an unfavorable outcome in the Modified Rankin Scale but not different in the E-GOS. Scales examining activities of daily living and neurologic status were more favorable in the rFVIIa groups combined vs. placebo. However, a clear dose-response relationship is not apparent.

Subgroup analysis reveals that early intervention in administering treatment within three hours of symptom onset (n=269) resulted in a significant reduction in hematoma volume from baseline in the combined rFVIIa groups vs. placebo (13% increase vs. 34% increase from baseline, respectively, p=0.004; 4.4 ml vs. 10.7 ml, respectively, p=0.009). Among those treated longer than 3 hours after onset of symptoms (n=115), the mean increase in hematoma growth was not different between rFVIIa groups and placebo (16% vs. 14%, respectively, p=0.86; 3.8 vs. 3.1, respectively, p=0.76).

The primary safety endpoint was the rate of serious thromboembolic events between groups. Of note, midway through the trial, one criterion excluding patients with recent (within 30 days) thrombotic or vaso-occlusive disease was changed to excluding patients with a history of these conditions. Seven percent of patients receiving rFVIIa experienced a serious thromboembolic event vs. 2% of those receiving placebo (p=0.12). No clear dose-response relationship.

Table 3

Serious Thromboembolic Adverse Events	Placebo (n=96)	40 mcg/kg (n=108)	80 mcg/kg (n=92)	160 mcg/kg (n=103)	Combined (n=303)
Total	2 (2%)	7 (6%)	4 (4%)	10 (10%)	21 (7%)
Arterial	0	6 (6%)	2 (2%)	8 (8%)	16 (5%)*
Venous	2 (2%)	1 (1%)	2 (2%)	2 (2%)	5 (2%)

Total ADE: NNH=20

*7 MI, 9 strokes. Data abstracted from Table 3 in reference 21

The authors of this study concluded from the results that administration of rFVIIa within 4 hours of onset of symptoms of ICH reduces the growth of the hematoma, reduces mortality and improves functional outcomes at 90 days with a small increase in the frequency of thromboembolic events.

An accompanying editorial discusses limitations of this study including not analyzing the effect of blood pressure on outcomes.[22] Blood pressure, either high or low, has been shown to be a prognostic factor in ICH. Also there is a lack of adjustment for withdrawal of care, which may have impacted the results. However, investigators did attempt to remedy this limitation by combining severe disability with death in their evaluation of global outcomes at 90 days. Finally, the editorialist states that although the results are encouraging, the use of rFVIIa at 160 mcg/kg in this population should be tempered by the limited number of patients exposed to this dose and the potential for serious thromboembolic events.

III. Complex Surgeries/Bleeding Associated with Trauma

There have been a number of case reports and case series describing the perioperative use of rFVIIa to reduce blood loss and transfusion requirements in patients undergoing various types of surgical interventions. Currently, there are seven published randomized clinical trials evaluating the effect of rFVIIa on blood loss and transfusion requirements as a result of surgery. In three of four trials, involving patients undergoing liver transplantation or liver resection, no difference was observed in transfusion requirements or the proportion of patients transfused between rFVIIa and placebo.[16,17,19] However, in one trial, although there was no difference in the number of red cells transfused, the proportion of patients avoiding RBC transfusion was statistically greater in the rFVIIa group vs. placebo.[18]

The fifth trial was conducted in 36 patients undergoing retropubic prostatectomy. In this double-blind trial, patients were randomized to receive rFVIIa (20 or 40 mcg/kg) or placebo in the early operative period. The primary endpoints were perioperative blood loss and requirement for transfusion. Median blood loss in the placebo group was 2688 ml (Interquartile range (IQR) 1707-3565 ml), vs. 1235 ml (IQR 1022-1407 ml) in the 20 mcg/kg group vs. 1089 ml (IQR 928-1320 ml) in the group receiving 40 mcg/kg (p=0.001 for both rFVIIa groups vs. placebo). Fifty-eight percent of patients in the placebo vs. 38% of the 20 mcg/kg group vs. none of the 40 mcg/kg group required a transfusion of red cells (NS difference between placebo and 20 mcg/kg, p=0.001 in favor of the 40 mcg/kg group vs. placebo). There were no thromboembolic events reported with the exception of one MI in the 20 mcg/kg group occurring two weeks after the surgery and not considered to be related to treatment.[24]

The sixth study involved 48 patients undergoing reconstructive surgery for traumatic fracture of the pelvis or pelvis and acetabulum.[41] In addition to standard treatment, these patients were randomized to double-blind treatment with rFVIIa 90 ug/kg or placebo to be administered upon skin incision. The primary outcome measure was total perioperative blood loss (intraoperative period and 48 hours after rFVIIa or placebo). Other outcome measures included perioperative transfusion requirement, number of patients transfused, etc. There were no differences in any outcome measure between groups with the exception of postoperative blood loss (rFVIIa 240 mg vs. 370 mg placebo, p=0.02). There were no differences in adverse events.

The final study was conducted in patients undergoing complex noncoronary cardiac surgery. In this study, 20 patients were randomized to receive rFVIIa 90 ug/kg or placebo after being removed from cardiopulmonary bypass and reversal of heparin. The primary endpoint was the total number of patients receiving any allogeneic transfusion, the total number of red cells transfused and occurrence of adverse events. A power calculation was conducted and determined that a total of 32 patients be included in each group. However, because of a lack of funding, the group decided to conduct a pilot study. In the intention

to treat analysis, there were no statistically significant differences between groups. The authors admit that there are major limitations to their pilot study in that it was underpowered and prone to type 1 error among other shortcomings that they do discuss.

There is also a great deal of interest in identifying agents to reduce or control bleeding associated with trauma. As with the other previously discussed off-label uses for rFVIIa, there are numerous case reports and case series describing experiences with rFVIIa. There is currently one published clinical trial in which investigators set out to determine the effect of rFVIIa on blood loss and red cell units transfused in surviving trauma patients at 48 hours.[25] In this trial, trauma was categorized as either blunt or penetrating and the data were analyzed separately. One hundred and forty-three blunt trauma and 134 penetrating trauma cases were analyzed for a total of 301 patients. Patients were randomized to receive 200 mcg/kg initially, 100 mcg/kg 1 hour later and 100 mcg/kg three hours later or placebo in addition to standard treatment. The initial treatment with rFVIIa or placebo occurred after the 8th unit of transfused red cells. In the blunt trauma patients, the number of red cell units transfused was reduced by 2.6 units in the rFVIIa group (p=0.02) and the need for massive transfusion (defined post-hoc as >20 units RBC) was reduced (14% vs. 33%, p=0.03) vs. placebo. The authors noted a trend towards reduced complications (adult respiratory distress and multiple organ failure) in the rFVIIa group compared to placebo but the study was not powered for clinical endpoints. No differences in 48 hr or 30 day mortality were observed. In penetrating trauma, there was no statistically significant difference between groups for reduced RBC transfusions or other endpoints.

In the case of excessive or massive bleeding from trauma or surgery, there are inconsistencies in the benefit of rFVIIa as a "last ditch" or futile intervention and the evidence originates from case reports and case series.[26-27] There are a lack of clinical trials in this varied group because of their heterogeneity in cause for the bleeding and the difficulty in conducting a clinical trial in the midst of their emergent condition. As a result, choosing the appropriate patient that may most benefit from rFVIIa as well as the appropriate dose and dosing schedule can present a challenge. Available evidence supports a significantly reduced benefit of rFVIIa in patients with severe acidosis and profound shock.[28] One group performed a retrospective evaluation to determine if they could identify factors that would help predict response to rFVIIa in order to reduce the costly and potentially futile use of rFVIIa. They determined that a Revised Trauma Score (RTS) of <4.09; PT prolongation of 17.6 seconds or greater; and severe metabolic acidosis was independently associated with a failure to respond and may be considered contraindications to using rFVIIa.[29]

In the case of excessive and/or intractable bleeding associated with cardiac surgery, there are numerous case reports, case series[43-46] and case-control publications[47-48] examining the efficacy and safety of rFVIIa. Doses ranged from 30-90 ug/kg with most reporting a significant reduction in bleeding after administration of rFVIIa. In one case-control study (retrospective), the "incremental" benefit of rFVIIa (above that achieved with standard therapies for hemostasis) in patients with refractory bleeding after cardiac surgery was examined.[50] In that analysis, the authors concluded that rFVIIa was safe when given as a rescue but was not incrementally beneficial over traditional hemostatic therapies.

In two case-control studies[47-48] , authors observed a reduction in bleeding and transfusion requirements but there was a trend towards greater morbidity or complications in those that received rFVIIa vs. placebo. The difficulty in drawing conclusions regarding the efficacy or safety of rFVIIa with the available evidence is the lack of a parallel control group and in the case of safety, the group receiving rFVIIa may have started with a worse prognosis. The vast majority of these authors conclude that randomized controlled trials are desperately needed to determine the true efficacy and safety, the proper timing of administration and dose of rFVIIa for patients with severe bleeding associated with cardiac surgery. One other very important question that remains to be answered is the safety of this agent in patients who have severe intractable bleeding status post coronary artery bypass grafting. The risk for thrombosis with rFVIIa in these patients is not know but theoretically may be increased due to circulating tissue factor and atherosclerotic plaque in other coronary arteries. At this time, there are no randomized controlled trials examining the efficacy and safety versus standard treatments for excessive bleeding associated with cardiac surgery. However, there is one randomized, placebo-controlled trial of this agent underway in patients with critical bleeding associated with cardiac surgery. Primary endpoints include incidence of critical or serious adverse events within 30

days. Secondary outcomes include number of transfusions and surgical drainage. The study was begun in October of 2004 with plans to enroll 210 patients.

IV. Reversal of Anticoagulation Therapy

As with other off-label uses of rFVIIa, much of the available data for the reversal of anticoagulation with rFVIIa exists in the form of case reports and case series.[30-31] In some cases, patients are not experiencing active bleeding but their International Normalized Ratios (INRs) are felt to be excessively elevated. Administration of rFVIIa 15-90 mcg/kg reduced INRs to normal levels. In other cases, active bleeding with warfarin is reportedly controlled and INRs reduced with administration of rFVIIa. However, in the cases with elevated INRs and no active bleeding, there is no comparison with traditional therapies such as vitamin K. In those with elevated INR and bleeding, there is no comparison to other hemostatic therapies such as administration of vitamin K and fresh frozen plasma.

There is one small trial in 16 healthy males evaluating the effect of rFVIIa on reversing the anticoagulation caused by fondaparinux.[32] Fondaparinux is a selective factor Xa inhibitor producing prolonged anticoagulation because of its half-life of 17 hours. With all anticoagulants, there is a concern for bleeding. Because there is no antidote for reversing the anticoagulation caused by fondaparinux, investigators set out to determine if rFVIIa would be efficacious in this setting. In this study, males aged 18-45 were given a single dose of fondaparinux 10 mg and rFVIIa 90 mcg/kg (n=8), fondaparinux and placebo (n=4) or placebo and rFVIIa (n=4). The effect of rFVIIa on thrombin generation, aPTT and PT were evaluated. The time to generate thrombin was doubled with fondaparinux. Although rFVIIa did shorten thrombin generation times, times was not reduced to baseline. Fondaparinux increased aPTT from 33.5 to 38.5 seconds. Activated partial thromboplastin times (aPTT) were reduced to nearly baseline from 2-6 hours after rFVIIa administration but began to increase thereafter. Prothrombin time increased from 13.2 to 14.3 seconds after fondaparinux and was reduced in the presence of rFVIIa from 2-8 hours. The authors comment that although coagulation times were altered, it is unclear if the results correlate with cessation of bleeding. There are currently no case reports in which bleeding was stopped with rFVIIa in the presence of fondaparinux.

In an ex vivo study, rFVIIa did accelerate thrombin generation in the presence of fondaparinux, but it did not completely reverse the anticoagulation caused by fondaparinux.[33]

V. Other Coagulopathies

Although rFVIIa was originally developed and intended as a bypassing agent to achieve hemostasis in patients with hemophilia A or B with inhibitors to factors VIII and IX, it has been used off-label in a relatively small number of patients with other hereditary or acquired bleeding disorders. Use of rFVIIa in these disorders has been documented in the form of case reports and case series. These disorders have included factor VII, V, and XI deficiencies, type III Von Willebrand disease, Glanzmann thrombasthenia, Bernard-Soulier syndrome, platelet-type (pseudo) von Willebrand disease, and thrombocytopenia (platelet counts should be 5,000-30,000/mcgL or higher).[8-9, 11, 34-36]

SAFETY OF rFVIIa

The warnings section of rFVIIa's product information states that the risk for thromboembolic events in patients with hemophilia and inhibitors is unknown, but is considered to be low. However, patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) may have an increased risk for developing a thrombotic event due to circulating tissue factor (TF) or predisposing coagulopathy. Because there is concern regarding an increased potential for thrombosis with rFVIIa in patients without hemophilia, the incidence of thromboembolic events has been monitored and reported in clinical trials of rFVIIa. In the majority of trials, there was not a statistically significantly greater frequency of thromboembolic events in those receiving rFVIIa compared to placebo. However, there did tend to be a higher risk for more serious thromboembolic events in the rFVIIa groups. Additionally, the number of patients included in the trials is small.

Recently, there were some product labeling changes made in response to a statistically nonsignificant increase in the risk for serious thromboembolic events (stroke and MI) observed in a clinical trial of elderly patients with ICH receiving rFVIIa compared to placebo.[21] Midway through the trial, criteria were altered to exclude patients with any history of thrombotic or vaso-occlusive disease. The authors do not provide information on the reason for this modification. Despite the change, 7% of patients receiving rFVIIa vs. 2% receiving placebo (p=0.12) had a thromboembolic event. In a registry of 40 patients who received rFVIIa for intractable bleeding, 3 patients (7.5%) developed a thrombotic event.[26]

In response to concern regarding the potential for thrombotic events with rFVIIa, a group of investigators reviewed the FDA's adverse events reporting system (AERS) database for thromboembolic events associated with rFVIIa. They reviewed events reported to AERS between March 25, 1999 and December 31, 2004.[37] Events reported to AERS include spontaneously reported events as well as those reported by manufacturers from post licensure clinical trial data. A total of 168 reports described 185 thromboembolic events. All of the thromboembolic events reported from clinical trials were in patients without hemophilia. Eighty-four percent of spontaneous reports were off-label use as well. The most common uses were for prevention or cessation of bleeding in surgical cases (e.g. cardiothoracic, liver transplantation/resection, or trauma). See table four below for location of thromboembolic events. In 102 reports that included a statement regarding cause of event, nearly 80% felt that rFVIIa was a probable or possible cause of the thromboembolic event. Of the 50 reported deaths, 72% (n=36) were attributed to the thromboembolic event either by autopsy or definitive clinical information (e.g. ECG, cardiac enzymes or other studies).

Table 4

Location	Number of Reports	Percentage of Total Events
Arterial (Total)	99	54.1%
Cerebrovascular accident	39	21.3%
Acute Myocardial Infarction	34	18.6%
Other Arterial thromboembolic (includes hepatic, pulmonary, renal, splenic, and iliac arter occlusion)	26	14.2%
Venous (Total)	74	40.4%
Other than Pulmonary Embolus	42	22.9%
Pulmonary Embolus	32	17.5%
Device Occlusion	10	5.5%

*2 spontaneous reports were not included because location of thrombosis was not stated. Table adapted from reference 37.

In this analysis, a frequency or incidence rate of thromboembolic adverse events cannot be determined because of the limitations of spontaneous reporting systems like AERS. It is understood that the number of events reported is influenced by many factors and certainly does not capture all events. However, at least the paper provides evidence that administration of rFVIIa is associated with a risk of serious adverse thrombotic events, although the magnitude of that risk in specific types of patients is not known. Therefore, the risk benefit ratio of rFVIIa needs to be thoughtfully considered in individual patients and conditions.

As far as the comparative safety and efficacy of other hemostatic or coagulation agents compared to rFVIIa, there are no direct clinical trials examining this issue. However, there is another report using data obtained from AERS as well as published and unpublished reports (of thromboembolic events) in which the number of thromboembolic events is compared between which Factor VIII Bypass Activity (FEIBA) and rFVIIa. FEIBA is an anti-inhibitor coagulant complex containing sterile human plasma fraction with FVIII bypassing activity. Its use is limited primarily to hemophiliac patients with spontaneous bleeding or during surgical interventions. There is very limited off-label use with FEIBA but it may be effective in patients with acquired inhibitors to Factors VIII, XI or XII. In this study, the authors reported a higher rate of thrombotic events reported by infusion of bypassing agents with rFVIIa versus FEIBA (24.6 per 10^5 infusions vs. 8.24 per 10^5 infusions, respectively; 95% CI 1.71-5.52). However, as previously stated, there are limitations to spontaneous reporting systems and differences in safety between agents cannot necessarily be concluded from these data. In addition, there is much greater off-label use of rFVIIa vs. FEIBA and the thromboembolic risk may be different in non-hemophiliacs.[38]

USE OF rFVIIa IN VHA

A review of VA purchasing records and query of usage data of this product by VISN indicates that there is currently limited use of rFVIIa in VHA.

COST OF rFVIIa

rFVIIa Vial Size	Cost per Vial
1.2 mg	$766.00
2.4 mg	$1,495.53
4.8 mg	$2,961.61

Single Dose (mcg/kg)	Dose for an 80 kg Patient	Vials Needed For Dose	Cost of Therapy
80	6.4 mg	1.2 mg+4.8 mg=6 mg	$3,727.61
90	7.2 mg	2.4 mg+4.8 mg=7.2 mg	$4,457.14
120	9.6 mg	4.8 mg+4.8 mg=9.6 mg	$5,923.22
160	12.8 mg	4.8 mg x2+2.4 mg=12 mg	$7,418.75

*Refer to page 3 for dosing considerations.

CONCLUSIONS/RECOMMENDATIONS

As evidenced by the number of case reports, case series and ongoing randomized clinical trials of rFVIIa, there is a great deal of interest in using this product for a wide variety of off-label indications. However, because of the small number of randomized clinical trials evaluating its safe and effective use for off-label indications, we make the following recommendations:

SUMMARY OF EVIDENCE FROM RANDOMIZED TRIALS

Off-Label Indication	Trials (n)	Summary of Findings	Recommendation	Quality of evidence/ Strength of Recommendation +[39-40]
PT Reversal in Liver Disease*	Jeffers[12] (71) Bernstein[13] (case series) (13) Ejlersen[14] (case series (10)	PT normalized in all 3 studies within 30 minutes regardless of dose. Duration of normal PT was dependent on dose in 2 studies up to 80 mcg/kg but the 120 mcg/kg dose did not result in a longer duration of normal PT values vs. 80 mcg/kg dose.	Recommendation against use of rFVIIa to normalize PT prior to invasive procedures such as liver biopsy in patients with elevated PT and cirrhosis.	3C Unknown effectiveness since acutely reducing PT values has not been correlated with cessation of bleeding.
Cessation of Variceal Bleeding/Prevention of Rebleeding in Cirrhosis	Bosch[15] (245)	No difference in acute bleeding cessation within 24 hrs, rebleeding and death at 5 days. Trend towards higher death in rFVIIa group vs. placebo.	Recommendation against use since no apparent effect of rFVIIa to control acute bleeding and prevent rebleeding in patients with cirrhosis and bleeding varices in one well designed study.	1B (one study) Likely to be ineffective or harmful
Major Liver Resection	Lodge[16] (204) Shao[17] (234)	No difference in proportion of patients requiring RBC transfusion or number of RBC units transfused.	Recommendation against use since no apparent effect of rFVIIa to reduce proportion of patients requiring RBC transfusion or number RBC units.	1A Unlikely to be beneficial
Orthotopic Liver Transplantation	Lodge[18] (183) Planinsic[19] (83)	No differences in the number of RBC units transfused or blood loss during surgery between groups. However, a secondary endpoint in the Lodge study (repeated doses), showed a significant reduction in the	Recommendation against use since no apparent effect of rFVIIa on number of RBC units transfused or blood loss during surgery.	1A Unlikely to be beneficial

		proportion of patients requiring RBC transfusion. But the numbers were very small. No other secondary endpoint differed.		
Intracerebral Hemorrhage	Mayer[20] (399)	If given within 4 hrs of symptom onset, dose-related significant reduction in percent change in intracerebral hemorrhage volume at 24 hrs. Clinical outcomes and death were also improved at 90 days in the rFVIIa groups. No clear dose-related effect on clinical outcomes or death. Subgroup analysis reveals most benefit if given within 3 hrs of symptom onset.	Recommendation for consideration of rFVIIa within 4 hrs, preferably <4hrs, in patients with GCS >5 and no plan for surgical evacuation in 24 hrs with no history of thrombotic or vaso-occlusive disease. Patients with any history of thrombotic or vaso-occlusive disease were excluded from trial. Statistically nonsignificant increase in serious thromboembolic events in rFVIIa group (7% vs. 2%)	1B (one study) Likely to be beneficial but may also be harmful in certain groups due to thromboembolic risk.
Reconstructive surgery for traumatic fracture of pelvis or pelvic-acetabulum	Raobaikady[41] (48)	No difference in transfusion of blood products or number of patients transfused	Recommend against use of rFVIIa to reduce blood loss associated with this type of surgery	1B Likely to be ineffective
Complex Noncoronary Cardiac Surgery	Diprose[42] (20)	Study underpowered. Trend towards reduce number of allogeneic transfusions an patients transfused (NS)	Insufficient evidence-exhaust standard measures for bleeding cessation prior to rFVIIa.	3C Unknown effectiveness
Severe, intractable Bleeding Associated with Cardiac Surgery	Vanek[43] (7) Al Douri[44] (5) Bishop[45] (12) Al Douri[46] (5) Karkouti[47] (51) Romagnoli[48] 15)	Case series and case-control studies in patients with intractable bleeding as a result of cardiac surgery. Doses ranged from 30-90 mcg/kg. Most reported reduced bleeding but there was not a parallel control group.	Insufficient evidence-exhaust standard measures for bleeding cessation prior to rFVIIa. Caution should be used in patients with intractable bleeding s/p CABG since most patients in these trials did not have a CABG.	3C Unknown effectiveness Unknown potential for graft thrombosis in patients undergoing CABG.
Retropubic Prostatectomy	Friederick[24] (36)	Blood loss and RBC transfusion requirements were significantly reduced in 36 patients undergoing retropubic prostatectomy in the 40 mcg/kg group vs. placebo.	Insufficient evidence-exhaust standard measures for bleeding cessation prior to rFVIIa. There is only one small study with 1B evidence with only 12 patients exposed to 40 mcg/kg dose. **Use in other surgeries not determined.	1B (One small study of only 36 patients) Insufficient evidence
Trauma	Boffard[25] (blunt- 143, penetrating-134)	The initial treatment with rFVIIa or placebo occurred after the 8th unit of transfused red cells. In blunt trauma patients, the number of red cell units transfused was reduced by 2.6 units in the rFVIIa group (p=0.02) and the need for massive transfusion (>20 units RBC) was reduced (14% vs. 33%, p=0.03) vs. placebo. No difference in penetrating trauma.	Insufficient evidence-exhaust standard measures for bleeding cessation prior to rFVIIa in patients with uncontrolled bleeding despite use of FFP, cryprecipitate, platelets and RBC transfusion associated with blunt trauma. Recommendation against use in patients with Revised Trauma Score (RTS) of <4.09; PT prolongation of 17.6 seconds or greater; and severe metabolic acidosis. Recommendation against use in penetrating trauma	1B (one study) Likely to be beneficial for reducing RBC transfusion and massive transfusion in patients with blunt trauma 1B (one study)
Reversal of Anticoagulation	Bijsterveld[32] (16)	PT normalization by rFVIIa in healthy subjects after single dose of fondaparinux. Thrombin generation times did not completely resolve with rFVIIa In the case of excessive anticoagulation with warfarin (in bleeding or nonbleeding	Recommend against use: No data in bleeding associated with fondaparinux. PT and aPTT normalization have not been correlated with bleeding cessation. No data comparing reversal of excessive anticoagulation with	3C Unknown effectiveness

		subjects,) rFVIIa was not compared to traditional therapies such as FFP or vitamin K.	warfarin of rFVIIa to FFP or vitamin K.	
Other Hereditary Coagulation Disorders/ platelet function defects	No controlled trials		Recommend consideration ONLY after other standard treatments have proven to be inadequate and/or patient has developed inhibitors or antibodies to clotting factors. There are a couple of reports of development of FVII antibodies after treatment with rFVIIa in patients with severe FVII deficiency.	3C Unknown effectiveness

*Reversal of PT has not been correlated with cessation of bleeding
+Study Quality: Level 1 evidence from good quality patient oriented-evidence; level 2 evidence from limited quality patient-oriented evidence; level 3 evidence from consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented intermediate or physiologic evidence, or case series.
Strength of Recommendation: A is based upon consistent and good-quality patient-oriented evidence; B is based upon inconsistent or limited-quality patient-oriented outcomes; C is based on consensus, usual practice, opinion, disease-oriented intermediate evidence, or case series.

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Appendix A: Randomized Controlled Trials Involving rFVIIa in Non-Hemophiliac Patients

Study	Population	Intervention/Primary Outcome Measure	Results	Adverse Events/Comments
Liver Disease				
Jeffers[12] 2002 R, DB Dose ranging study (n=71)	a) 71 (5 run-in) patients with advanced liver disease undergoing liver biopsy. b) Inclusion Criteria: Plts ≥60,000 mm^3, Child-Turcotte B or C, PT 3-15 seconds >NL c) Exclusion Criteria: (not inclusive) MI or stroke W/I 6 months, SCr>1.5 mg/dL or abnormal flow in portal, hepatic or mesenteric venous circulation.	a) One dose of rFVIIa 5, 20, 80 or 120 mcg/kg, 10 min. prior to liver biopsy. b) Primary endpoint: Normalization of PT and time to achieve post-biopsy hemostasis	A) 62 completed the study. Dose (mcg/kg) / N / Median Duration NPT (min)/Range 5 / 11 / 9.6/0-76 20 / 12 / 29.4/0-143 80 / 13 / 280.7/0-454 120 / 16 / 83.7/0-714 Dose (mcg/kg) / N / % achieving hemostasis in 10 min 5 / 16 / 69 20 / 14 / 71 80 / 16 / 81 120 / 19 / 74 The 80 mcg and 120 mcg/kg doses produced a statistically prolonged normalization of PT vs. the 2 lower doses. Those not achieving hemostasis were reportedly distributed equally among the groups.	ADE: hepatic failure and bleeding (GI tract or hematoma) that the authors considered being associated with this population. One patient developed a portal vein thrombosis 6 days after the rFVIIa which was not believed to be related to treatment. Comments: Thirteen of 17 patients not achieving hemostasis within 10 minutes post-biopsy received a rescue dose of rFVIIa so were not included in the duration of NPT analysis. No control group was used so it is difficult to determine whether there would be less bleeding in patients receiving traditional therapies like FFP or supportive care post-biopsy vs. those receiving rFVIIa. The authors noted that FFP would not be as desirable in this pop. due to potential volume overload.
Bernstein[13] 1997 SC, Dose escalation (n=13)	a) 13 patients with cirrhosis and PT >2 seconds above NL.	a) Given vitamin K. If PT still abnormal, given rFVIIa 5, 20, 80 mcg/Kg during 3 successive weeks. b) Primary outcome: PT normalization	a) 10 patients were to receive 3 escalated doses of rFVIIa. PT was normalized within 10 minutes of each dose of rVIIa. The duration of normalized PT was dose related with the 5 mcg/kg dose lasting 2 hrs, 20 mcg/kg lasting 6 hrs, and the 80 mcg/kg lasting 12 hrs.	No thromboembolic events were reported.
Ejlersen[14] 2001 SC, OL (n=10)	a) 10 patients with cirrhosis and variceal bleeding. 5 patients with Child-Pugh Class B and 5 with Class C	a) A single dose of rFVIIa 80 mcg/kg in combination with routine treatment for bleeding varices b) Primary outcome: Normalization of PT Clinical outcomes, bleeding were recorded over 12 hrs	a) 10 patients with elevated PT were given rFVIIa with normalization of PT within 30 minutes. Duration of normal PT values was 4 hrs in 7 patients and 2 hrs in 3 patients. The 3 patients with normal PTs for only 2 hrs had baseline PTs >20 seconds. b) Bleeding was reported to be controlled after rFVIIa in all patients. Median number of red cells transfused was 2. 2 patients rebleed within 12 hrs.	One patient rebled after 12 hrs, 3 received a TIPS W/I 24 hrs and 6 patients died 2-10 days after study period. All deaths related to bleeding. No thromboembolic events or DIC was reported.
Bosch[15] 2004 R, MC, DB, PC (n=245)	a) 245 patients with UGIB (variceal in origin) requiring hosp. and volume replace. All patients were to receive standard therapy for variceal bleeding (vasoactive therapy and/or endoscopic therapy) b) Inclusion Criteria: Presence of cirrhosis and portal HTN, requiring endoscopy W/I 12 hrs. c) Exclusion Criteria: Many-Known hypercoagulopathy or hereditary bleeding disorder, PE or DVT	a) A single dose of 100 mcg/kg rFVIIa or placebo was given before endoscopy or W/I 6 hrs of admission. Subsequent 100 mcg/kg or placebo was given at 2, 4, 6, 12, 24 and 30 hrs after the initial dose. b) Primary outcome: composite of- failure to control bleeding W/I 24 hrs, failure to prevent rebleeding W/I 24 hrs or death W/I 1-5 days. Secondary outcomes included 5-day and 6 week mortality, transfusion needs, emergency or elective	a) 242 completed the study. Composite: % reflect failures to control bleeding, prevent rebleeding or death: Pla: 19/119 (16%) vs. rFVIIa 16/118 (14%), p=0.72 Individual components: Failure to stop bleeding W/I 24 hrs: Pla: 10/199 (8%) vs. rFVIIa 7/118 (6%), p=0.31 Failure to prevent rebleeding: Pla: 10/116 (9%) vs. 9/116 (8%), p=1 5 day Death: Pla 4/119 (3%) vs. rFVIIa 7/118 (6%), p=0.38 42 day Death: Pla 11/120 (9%) vs. rFVIIa 16/116 (14%), p=0.31 No difference in transfusion requirements.	There were 14 thromboembolic events reported. Seven in each group. 8 cases of asymptomatic portal vein thromboses (5 placebo, 3 active product), 3 cases of phlebitis (2 pla, 1 rFVIIa), 1 nonserious blood clot in the central catheter in rVIIa group. Two CVAs in those on rVIIa. One patient died, the other with mild neurologic sequelae. The authors noted that in a post-hoc analysis, there appeared to be a benefit with the active product in those with Child-Pugh grades B and C. There were 9% more patients with Child-Pugh C in the placebo group. Using Cox regression analysis, it was reported

	W/I 6 months, portal vein thrombosis, angina, MI, PVD, ischemic TIA/CVA, etc.	procedures, etc.		that the Child-Pugh grade and not the active product influenced findings. Although not statistically significant, there was a trend towards higher death with rFVIIa.
Lodge[16] 2005 R, MC, DB, PC (n=204)	a) 204 noncirrhotics undergoing major liver resection cancer/ metastasis, benign tumors or both. b) Exclusion Criteria: known bleeding d/o, planned blood transfuse, dialysis, portal or deep vein thrombosis, severe CV disease or MI or stroke W/I 6 months	a) rFVIIa 20, 80 mcg/kg or placebo 5 min prior to skin incision and repeated in 5 hrs if surgery expected to exceed 6 hrs. b) Primary endpoint: RBC transfusion required intraoperative or W/I 48 hrs post-surgery (perioperative period). Also, change in HCT, intraoperative FFP, and duration of surgery.	a) 185 patients were available for efficacy analysis. Need for RBC transfusion: 20 mcg/kg=41% 80 mcg/Kg=25% placebo=37% (p=0.09) Mean red cell volume needed: 20 mcg/kg=1,354 ml 80 mcg/kg=1,036 ml placebo=1,354 ml (p=0.78) No differences between groups in need for FFP, platelet conc., other hemostatic drugs. No differences in operating time, blood loss during or after surgery. The only difference in favor of rFVIIa 80 mcg/kg was less reduction in HCT during surgery.	4 patients w/d before dosing, 15 did not have liver resection and were not included in efficacy analysis. 3 patients in each group had a thromboembolic event: Placebo: 2 asymptomatic DVT, one partial portan vein thrombosis 20 mcg/kg: PE, 2 MI 80 mcg/kg: PE, 2 DVT
Shao YF[17] 2006 R, MC, DB, PC (n=234)	a) 234 cirrhotic patients requiring partial hepatectomy for liver cancer or benign tumors b) Exclusion Criteria: h/o portal vein thrombosis, DVT, severe CV disease, MI, PE, stroke or dialysis.	a) rFVIIa 50, 100 mcg/kg or placebo before surgery and every 2 hrs during surgery or for a max of 4 doses. b) Primary Endpoint: Proportion of patients requiring RBC transfusions, amount of RBCs during first 48 hrs after surgery. Other endpoints: FFP, platelet conc., blood loss, proportion of patients receiving hemostatic drugs.	a) 221 patients were evaluated for efficacy. There were no differences in the primary or secondary endpoints between the rVIIa groups and placebo.	Data was lost on 2 patients in the placebo group. 11 patients did not have hepatectomy. Thromboembolic events: 100 mcg/kg: mesenteric vein thrombosis, MI, 3 abnormal Doppler studies in hepatic vessels 50 mcg/kg: portain vein thrombosis, 1 abnormal Doppler study in hepatic vessel placebo: PE
Lodge[18] 2005 R, MC, DB, PC (n=183)	a) 183 patients with Child-Turcotte-Pugh class B or C) and undergoing orthotopic liver transplantation (OLT)	a) rFVIIa 60, 120 mcg/kg or placebo, starting with 1st dose within 10 minutes of incision and every 2 hrs during OLT ceasing 30 minutes prior to reperfusion on new liver. Final dose at closure of skin. b) Primary endpoint: RBC transfusions required	a) There were no differences in the number of RBC units transfused between groups or blood loss during surgery. There was also no difference in the numbers requiring antifibrinolytics, crystalloid or colloid replacement or blood loss. b) 9.6% (4/56), 7.1% (6/62) and 0% (0/61) of patients receiving 60, 120 mcg/kg or placebo, respectively avoided RBC transfusion. (p=0.0331).	a) 57% of patients received 3 doses of study product. Only 1 patient received 6 doses. No info on numbers receiving 4 or 5 doses. b) Patients experiencing serious ADEs: Placebo 19%, 60 mcg/kg 27%, 120 mcg/kg 28% Thromboembolic events: Placebo 10%, 60 mcg/kg 19%, 120 mcg/kg 12%. No details on thromboembolic events provided. And no statistical analysis.
Planinsic[19] 2005 R, DB, dose-ranging trial (n=83)	a) 83 patients with end-stage liver disease and undergoing orthotopic liver transplantation (OLT).	a) rFVIIa 20, 40, 80 mcg/kg or placebo prior to surgery b) Primary endpoint: Need for RBC transfused perioperative	a) 82 patients underwent OLT There were no differences in number of red cell blood units transfused between placebo and rFVIIa.	Number of ADE was comparable between all groups and no pattern of ADEs was present. Thromboembolic events occurred in a similar number of patients between groups.
Intracerebral Hemorrhage				
Mayer[20] 2005 R, MC, DB, PC (n=399)	a) 399 patients with acute ICH W/I 3 hrs of symptom onset b) Exclusion Criteria: GCS 3-5, planned surgical evacuation of hematoma, known use of anticoagulants,	a) rFVIIa 40, 80 or 160 mcg/kg or placebo (single dose) W/I 4 hrs of symptom onset. b) Primary endpoint: Percent change in hematoma volume of ICH at 24 hrs. Clinical	a) 399 patients with acute ICH were randomized. **Mean Absolute Change in Lesion Volumes on CT at 24 hrs-Baseline-ml (% Inc. from baseline)** Dose / ICH / ICH+IVH Pla / 8.7 / 10.8	Serious thromboembolic events occurred in 2% of placebo recipients vs. 7% of rFVIIa (7 MI, 9 strokes) (p=0.12) Placebo: 2 venous, 0 arterial RFVIIa: 5 venous, 16 arterial (NNH=20)

	coagulopathy, DIC, sepsis, trauma, symptomatic thrombotic or vaso-occlusive disease (angina, DVT, Stroke or MI) W/I 30 days, etc. Midway through trial, exclusion criteria modified to exclude any patient with history of thrombotic or vaso-occlusive disease.	outcomes were assessed via varied methods (Modified Rankin Scale, Extended GCS, Barthel Index, NIHSS) at 90 days.	<table><tr><td></td><td>(29%)</td><td>(31%)</td></tr><tr><td>40</td><td>5.4 (16%)</td><td>7.2 (16%)</td></tr><tr><td>80</td><td>4.2 (14%)</td><td>5.1 (14%)</td></tr><tr><td>160</td><td>2.9 (11%)</td><td>4 (13%)</td></tr><tr><td>Combined (rFVIIa)</td><td>4.2 (14%)</td><td>5.4 (14%)</td></tr></table> *Effect was dose dependent with significant differences between 160 mcg/kg dose and combined groups vs. placebo Clinical outcomes at 90 days: a) Mortality: 29% placebo, 18% combined rFVIIa groups (NNT 9) b) 3 of 4 outcomes scales showed a statistically favorable global outcome for rFVIIa groups vs. placebo. The benefit was observed with the 80 and 160 mcg/kg doses. However, for moderate to severe disability or death, the outcome did not appear to be related to dose. Although this analysis was not provided in the paper. Modified Rankin (to avoid unfavorable outcome) NNT=6.25 Extended GCS (to avoid unfavorable outcome) NNT=12.5	
Surgery and Trauma				
Friederich 2003[24] R, SC, DB, PC (n=36)	a) 36 patients undergoing retropubic prostatectomy for enlarged prostate or cancer. b) Exclusion Criteria: treatment with anticoagulants W/I 24 hrs of surgery, ASA <7 days prior, coagulation disorder, unstable angina, history of thromboembolic disorder, liver disease	a) Single-dose rFVIIa 20 (n=8), 40 mcg/kg (n=16) or placebo (n=12) in the early operative phase. b) Primary endpoint: Blood loss and transfusion requirements	Median blood loss: (IQR) <table><tr><td>Placebo</td><td>2688 ml (1707-3565)</td></tr><tr><td>20 mcg/kg</td><td>1235 ml (1022-1407)</td></tr><tr><td>40 mcg/kg</td><td>1089 ml (928-1320)</td></tr></table> *p=0.001 for both vs. placebo % Requiring Red Cell Transfusion <table><tr><td>Placebo</td><td>58%</td><td>---</td></tr><tr><td>20 mcg/kg</td><td>38%</td><td>P=0.65</td></tr><tr><td>40 mcg/kg</td><td>0</td><td>P=0.001</td></tr></table> P vs. placebo	One MI noted in the 20 mcg/kg group occurring 14 days after surgery. Felt not to be related to treatment. Small study
Boffard 2005[25] R, DB PC (n=301)	a) 301 patients with severe traumatic injuries to control bleeding b) Inclusion Criteria: 6 units of RBC W/I 4 hrs of admission c) Exclusion Criteria: GCS<8, severe acidosis, transfused 8 or > units of RBC prior to arrival at hospital, GSW to the head, etc.	a) After 8 units of RBC, patients given 200 mcg/kg, 100 mcg/kg at 1 hr and 100 mcg/kg at 3 hrs or placebo b) Primary Endpoint: Number of RBC units transfused at 48 hrs in surviving patients	143 Blunt Trauma: Reduction in RBC transfused by approx. 2.6 units (p=0.02). Massive transfusion (defined post-hoc >20 RBC units) 14% rFVIIa vs. 33 % placebo (p=0.03). No difference in deaths. Trend towards reduced ARDS/MOF in favor of rFVIIa. 134 Penetrating Trauma: Reduction in RBC transfused by approx. 1 unit (p=0.1). Massive transfusion 7% rFVIIa vs. 19% placebo (p=0.08)	No difference in ADEs noted between groups.
Raobaikady R, 2005[41] R, DB, PC (n=48)	Patients with normal hemostasus and undergoing surgery for major traumatic fracture of the pelvis or pelvis and acetabulum 1) Inclusion Criteria: Reconstructive surgery as above and expected	a) rFVIIa 90 mcg/kg or placebo was give upon first skin incision. A second dose could be given after 2 hrs if transfusion of RBCs were indicated (hgb <8 g/dl). b) Primary Endpoint:	Median perioperative blood loss: rFVIIa=2070 ml, Placebo=1534 (p=0.79) Intraoperative blood loss: rFVIIa=1598 ml Placebo=1188 (p=0.57) Postoperative blood loss: rFVIIa=240 ml Placebo=370 ml (p=0.022)	There were no differences in adverse events between groups. The authors conclude that early use of rFVIIa does not reduce blood loss in patients with normal hemostasis undergoing major pelvic-acetabular fracture surgery.

	to lose >50% circulating blood volume 2) Exclusion Criteria History of thrombosis, severe head injury, severe acidosis, known congenital bleeding disorder, etc.	Total volume of perioperative blood loss (Perioperative-after rFVIIa or placebo through 48 hrs after) c) Secondary Endpoint: Perioperative transfusion requirements	There were no differences in number of blood products transfused or in the number of patients requiring transfusion	
Diprose P, 2005[42] R, DB, PC pilot study (n=20)	Patients undergoing complex noncoronary cardiac surgery. 1) Inclusion Criteria: Repeat non-coronay cardiac surgery, multiple valve surgeries, aortic root or arch replacements and surgery for endocarditis and aortic dissection. 2) Exclusion Criteria: Recent thrombotic disease or refuse blood products.	a) rFVIIa 90 mcg/kg or placebo after removal from CPB and reversal of heparin. b) Primary Endpoint: Number of patients receiving any allogeneic transfusion, total number of RBC and coagulation products transfused and adverse events.	Power calculations were based upon a reduction in exposure to transfused blood products by 50%. (n=32 in each group) Intent to treat group: No difference in number of blood product transfusion prior to ICU, during ICU stay or total during the study. However, trend was in favor of rFVIIa group.	Study was significantly underpowered. Expected to have 32 patients in each group but only had 10). No difference in adverse events Authors admit to major limitations of study including being underpowered and prone to type 1 error.
Reversal of Anticoagulation				
Bijsterveld 2002[32] R, SB, PC (n=16)	a) 16 male healthy volunteers 18-45 years of age.	a) Fondaparinux 10 mg+rFVIIa (n=8), fondaparinux+placebo (n=4), placebo+rFVIIa (n=4) b) Primary Endpoint: Thrombin generation time, aPTT, PT	a) Thrombin generation time doubled in presence of fondaparinux. RFVIIa reduced time to thrombin generation but not completely. b) aPTT was increased with fondaparinux from 33.5-38.5 sec, rFVIIa reduced to baseline from 2-6 hrs. c) PT was increased by fondaparinux from 13.2-14.3 sec, rFVIIa reduced to baseline from 2-8 hrs	No adverse events noted. Coagulation parameters do not correlate with cessation of bleeding. Thrombin generation times not restored.

ARDS=adult respiratory distress syndrome, ADE=adverse events, CPB=cardiopulmonary bypass, DB=double-blind, DVT=deep vein thrombosis, FFP=fresh frozen plasma, GCS=Glasgow coma scale, GSW=gun shot wound, HCT-hematocrit, HTN=hypertension, ICH=intracerebral hemorrhage, MI=myocardial infarction, MOF=multiple organ failure, NIHSS=National Institutes of Health Stroke Scale, NL=normal, NPT=normalized prothrombin time, PC=placebo-controlled, PE=pulmonary embolism, Plt=platelets, R=randomized, RBC=red blood cell, SC=single center, TIPS=transjugular intrahepatic portosystemic shunt, W/I=within,