



IAP National Guidelines 2006

(by respective IAP National Consensus Meetings held
under Indian Academy of Pediatrics Action Plan 2006)

IAP GUIDELINES 2006 ON

Recombinant Activated Factor VIIa (rFVIIa)

Recombinant Activated Factor VIIa (rFVIIa)

finalised at the
IAP National Consensus Meeting on rFVIIa
held under the IAP Action Plan 2006 on 3rd June 2006

(Meeting held with Scientific Grant by)

Writing Group: Dr. Anupam Sachdev
Dr. SP Yadav
Dr. Nitin K. Shah
Dr. Bharat Agarwal
Dr. Vinita Jain
Dr. Ruchira Misra
Dr. Deepak Ugra

List of experts invited at the meeting:

Chairperson: Dr. Nitin K. Shah

Conveners: Dr. Anupam Sachdev
Dr. Bharat Agarwal

Members: Dr. HR Badrinath
Dr. Asif Ali
Dr. Dhiren Gupta
Dr. SP Yadav
Dr. Ruchira Misra
Dr. K Chugh
Dr. Vivek Nangia
Dr. Praveen Khilnani
Dr. Dinesh Bhurani
Dr. Vinita Jain
Dr. Arvinder Soin
Dr. Renu Saxena
Dr. MR Lokeshwar
Dr. V P Choudhary
Col. Velu Nair
Dr. Mamta Manglani

IAP Guidelines 2006 On

Recombinant Activated Factor VIIa (rFVIIa)

Introduction

Recombinant Factor VIIa has been successfully used in non-hemophilia patients with acquired antibodies against Factor VIII (acquired hemophilia). Pharmacological doses of rFVIIa have been found to enhance the thrombin generation on already activated platelets and, therefore, may also likely be of benefit in providing hemostasis in other situations characterised by profuse bleeding and impaired thrombin generation, such as patients with thrombocytopenia and in those with functional platelet defects. Because of the recent trends in rFVIIa usage in non-approved settings among physicians from various disciplines, significant concerns about its safety, efficacy, and costs have arisen. Additionally, dosing of rFVIIa for these potentially broad clinical applications is not standardised. Currently, the decision on when and where to use rFVIIa for patients with uncontrolled bleeding continues to be one that must be made by individual physicians, assisted by their hospital pharmacotherapeutics and transfusion committees.

Currently approved clinical settings for use of rFVIIa

1. Patients with FVIII or IX inhibitor

- A) Vigorous bleeding, impending compartment syndrome, or bleeding in critical location: 90 μ g/kg q 2-3 hr until hemostasis is achieved, and less frequently thereafter.
- B) Persistent bleeding, not life or limb threatening: Titrate both dose and interval to obtain adequate hemostasis.
- C) Before invasive procedures: 90 μ g/kg initially, subsequent doses, interval, and duration of transfusion to be titrated to risk of further bleeding.

In a patient with no signs of bleeding and stable hemoglobin level, rVIIa is NOT indicated.

Currently non-approved clinical settings for use of rFVIIa

Qualitative or quantitative platelet disorders with life-threatening bleeding unresponsive to platelet transfusion

- A) Correct coagulopathy and anemia with platelets, Fresh Frozen Plasma (FFP), cryoprecipitate, and Red Blood Cell (RBC) transfusions.
- B) Administer Desmopressin (DDAVP) and EACA.
- C) Dialyze if uremic.
- D) rVIIa 50-100 μ g/kg. If clinical response, titrate dose and interval to maintain adequate hemostasis.

Prolonged INR requiring rapid reversal

A) Minimal or no active bleeding - 10 mg Vitamin K IV or SC.

B) Life threatening or intracranial hemorrhage risk.

50-100 µg/kg of rFVIIa, FFP 15-20mL/kg, and 10 mg vitamin K IV infused over 20 min.

Uncontrollable hemorrhage associated with trauma, surgery, and liver failure

- Replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, platelet transfusion, RBC transfusions.
- Periodically monitor PT, aPTT, fibrinogen, platelet count, hemoglobin level.
- If excessive bleeding continues without apparent response to adequate blood components and no identifiable surgical source has been found, 50-100 µg/kg of rFVIIa. If bleeding does not diminish in 30-60 min, consider one more dose or surgical exploration.

Use rFVIIa with caution in patients at increased risk for thrombotic complications:

- After cardiac surgery.
- Patients with h/o coronary artery disease.
- Patients with h/o venous or arterial thrombosis.
- Patients with DIC.
- Patients on extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD).
- Patients with cerebral vascular disease.

Congenital Factor VII deficiency

- Factor VII activity >25%, expectant management except neurologic, cardiothoracic, or ophthalmologic surgery/trauma.
- Factor VII activity <25% and minor trauma/surgery: Initial treatment: 10-15mL/kg FFP. Repeat 3-6mL/kg at 6- to 8-hr intervals until hemostasis is achieved.
- Factor VII activity <25% and at risk for neurologic, cardiothoracic, ophthalmologic bleeding:
- Initial treatment: rVIIa 20 µg/kg patient q 2 hr until hemostasis is achieved.
- Titrate dose and interval to ongoing bleeding risk.
- Combined treatment with FFP and rFVIIa at lower doses is a consideration, in patients who can tolerate volume infusions.

Specific situations

Acquired Hemophilia

This is a rare condition characterised by development of autoantibodies against Factor VIII. There is no genetic pre-disposition or bleeding history and usually presents with soft tissue hematomas, muscle and compartment bleeds. It may be associated with autoimmune disease in 20% cases, malignancy in 7%, drugs in 6%, and as postpartum complication in 7%. rFVIIa ensures hemostasis in 80-90% of patients with inhibitors. Efficacy is not influenced by level of inhibitor nor is there any anamnestic response. Exclusive use may allow a temporal decrease of the inhibitor level.

The standard (and approved) intravenous (IV) dose of rFVIIa in hemophilia patients with an inhibitor is 90µg/kg until hemostasis is achieved; for surgical patients, repeated doses are administered every 2 hours until hemostasis is achieved, then less frequently thereafter (Table 1). Doses between 35 and 120µg/kg have been used successfully in clinical trials, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved. Most patients are also given anti-fibrinolytic therapy. Successful use of rFVIIa has also been demonstrated in minor surgery and dental surgery (1). rFVIIa has been given to hemophilia patients suffering from serious bleeding in the central nervous system, intraperitoneal and retroperitoneal hemorrhage, as well as muscle (compartment syndrome) bleeding.

Monitoring

Plasma VIIa levels have a linear relationship with FVII:C levels. Peak levels of FVII:C of 30IU/ml are needed to ensure full thrombin burst. 30-40IU/ml in post-op period for effective hemostasis. Prothrombin time is not a good indicator as the INR normalises at FVII: C level of 5 IU/ml. Clinical improvement during rFVIIa treatment is associated with shortening of aPTT to 15-20sec.

Platelet disorders

The availability of platelet procoagulant phospholipids has been demonstrated to be the rate limiting factor for the production of thrombin, so that patients with a decreased number of platelets have impaired thrombin generation (2,3). Single-case reports of a haemostatic effect of rFVIIa in thrombocytopenic (as low as 5000/mL) patients have been published (4). Controlled randomised studies are ongoing to establish the potential role and effective dosage of rFVIIa in patients with thrombocytopenia (5).

Congenital Factor VII Deficiency

Factor VII deficiency is a rare coagulation disorder that is characterised by spontaneous bleeding episodes in severely affected patients and bleeding after surgical challenge or trauma in the mildly affected individuals. Plasma-derived Factor VII concentrates were developed, followed by the development of rFVIIa, both of which have been satisfactorily used in the treatment of Factor VII deficiency (6,7,8). In a randomised study, 17 Factor VII-deficient patients were treated with rFVIIa (7). The doses of rFVIIa ranged from 21 to 27µg/kg, based on calculations of the dose capable of normalising the prothrombin time (PT) 15 minutes after injection. The treatment resulted in excellent resolution of all hemarthroses treated. The recommended dosage for rFVIIa replacement therapy in congenital FVII deficiency is therefore 20µg/kg.

Acquired Factor VII Deficiency

Patients receiving oral anticoagulant therapy

Through vitamin K antagonism, anticoagulant agents induce low levels of functional vitamin K-dependent coagulation factors (Factors prothrombin, VII, IX, and X). Factor VII has been shown to be the earliest and the most sensitive of the coagulation factors to be affected by anticoagulant therapy, monitored indirectly by the international normalised ratio (INR) value. Spontaneous hemorrhages have been reported to occur in approximately 10 to 20 percent of patients receiving oral anticoagulant therapy (9,10). Of these, half occur in patients with INR values outside therapeutic range and half in patients with INR values within therapeutic range. These patients also may require urgent reversal of their prolonged INR when invasive procedures are scheduled or after head trauma. One report describes the use of rFVIIa in seven adult

patients with prolonged INR, three of whom required surgery. The doses administered ranged from 20 to 90 μ g/kg, and all patients were reported to have a positive outcome (2). These observations indicate that rFVIIa may be used to reverse the effect of warfarin or other vitamin K-antagonist therapies in cases in which the administration of vitamin K alone has been found to be insufficient. Two published reports of 15 total patients treated with FVIIa for reversal of excessive anticoagulation with Coumarin support a dosage of 20 μ g/kg, or 1.2 mg for an adult patient (3,4). It is important to note that vitamin K and plasma therapy (15-20 mL/kg, or at least 4 units) should also be administered concomitantly to correct deficiencies of functional prothrombin, IX, and X (Table 1). Controlled randomised studies are required to establish the optimal dose of rFVIIa.

Factor VII and Liver diseases

Patients with impaired liver function

The liver is the principal site for synthesis and clearance of coagulation factors, components of the fibrinolytic system, and naturally occurring anticoagulants. Cirrhotic patients do not generally experience bleeding episodes apart from upper GI bleeding, but they are at an increased risk of bleeding from routine procedures such as liver biopsy and also during major surgery such as liver transplantation (11). A haemostatic effect of rFVIIa has been proven in a limited number of liver disease patients (11,13). It is concluded that the single dose significantly reduced transfusion requirements when compared with the matched controls and that further randomised controlled studies were needed in patients undergoing liver transplantation to establish the optimal and safe dose of rFVIIa.

Recommendations: rFVIIa in Liver Disease

- Prophylactic use should be discouraged – except in high risk liver transplantation/ thoracocentesis or Jehova's witness patients.
- Therapeutic use in variceal bleed, difficult liver transplantation, liver surgery including trauma.
- Must correct hypothermia, acidosis
- Must try conventional measures (enough Packed RBCs, and FFP) first
- Doses: Ped: 50 μ g/kg; adults 60-120 μ g/kg/dose, 1-2 hourly for bleeding and 2-8 hourly for prophylaxis.

Dengue fever and rFVIIa

In the minority of patients of dengue with uncontrolled massive bleeding or prolonged shock, the coagulation abnormality may be difficult to manage and may lead to disseminated intravascular coagulation or may enhance ongoing disseminated intravascular coagulation. Intensive supportive care is the most important aspect in the management of patients with DHF. Prompt treatment with adequate fluid replacement during the critical period and effective control of bleeding episodes are essential for a favorable outcome. Platelet and FFP transfusions are usually required for the control of severe bleeding. rFVIIa appears to be useful as an adjunctive treatment to blood component replacement in controlling active bleeding episodes in children with grade II or grade III DHF when platelet concentrates are not available (14). Concerning safety, patients with DHF grade II or grade III have mild consumptive coagulopathy, and rFVIIa does not appear to aggravate their clinical condition to full-blown DIC.

rFVIIa and trauma

Complex surgery and trauma resulting in profuse bleeding

Acute trauma in humans has been shown to initiate a number of haemostatic changes that are correlated with the severity of the trauma and hemorrhage (15). A decrease in the concentration of coagulation factors as well as platelets occurs due to clotting factor consumption (15). Hemodilution in severely bleeding patients also contributes substantially to the lowered plasma concentrations of the various proteins and platelets (16,17). Most of the plasma substitutes used in hypovolemic patients also contribute to the coagulopathy seen in patients after trauma and excessive bleeding (14,16). A haemostatic effect has been demonstrated after the administration of rFVIIa in a limited number of patients after trauma and bleeding (18,19,20). rFVIIa has been used in patients with serious bleeding secondary to extensive surgery and severe trauma (21). However, data regarding its application in the treatment of severe bleeding associated with disseminated intravascular coagulation (DIC) are very limited (22,23,24). Furthermore, the use of rFVIIa in such cases is highly controversial. Previous clinical experience with rFVIIa suggests that it is a safe treatment, although cases of thrombotic complications have also been reported (11,25,26).

Preliminary Guidelines for the off-Label Use of rFVIIa

Basic Principles

- The indication for rFVIIa must be evaluated in all critical, life-threatening bleeding. If the prognosis is desolate for any reason and possibly necessary resuscitation will not be considered, administration of Factor VIIa should not be considered.
- rFVIIa is not capable of stopping true surgical bleeding (defined as hemorrhages from open vessels). Administration of rFVIIa should therefore be considered only if all surgical attempts failed to localise a source of hemorrhage.
- So far, there is no evidence or experience about using rFVIIa in preclinical settings like at the place of accident or in the ambulance.

Standard of Care (Preconditions before Use of rFVIIa)

Clinical Preconditions

- Exclusion of a true surgical hemorrhage (if time allows)
- Exclusion of a severe hypothermia and/or acidosis (if time allows)
- Exclusion of a substitutable coagulation deficiency

Preconditions Regarding Transfusion Therapy

Continuous bleeding despite:

Adequate platelet substitution (at least >20,000/ul, unless patient is platelet refractory)

Massive transfusion

Adequate substitution of coagulation factors

- **Exception of the above mentioned Preconditions**

Intracerebral bleeding (e.g., trauma, spontaneous, neurosurgery or anticoagulants); *Note: consider localization and extent of bleeding (prognosis!)*

Special cases where conventional haemostatic actions are known to be notoriously ineffective (e.g., pulmonary hemorrhages, invasive aspergillomas etc.)

Indications (Examples)

- **Internal Medicine**

- Life-threatening pulmonary bleeding
- Intracerebral hemorrhages (also due to anticoagulants)
- Severe gastrointestinal bleeding (e.g., unsuccessful local haemostatic therapy)
- Severe hemorrhages after HSCT (e.g., hemorrhagic cystitis)

- **Surgery**

- Bleeding after blunt trauma or burns
- Diffuse hemorrhages after ECC
- Bleeding during/after liver transplantation (e.g., unsuccessful use of aprotinin)
- Diffuse bleedings after mass transfusions
- Bleedings in witness' of Jehova

Thus the one may think and consider using factor VIIa in any patient suffering massive, uncontrolled bleeding that hasn't responded to conventional surgical measures and appropriate blood components. Unsalvageable patients are a contraindication, while pulmonary embolism, deep vein thrombosis, myocardial infarction and cerebrovascular accidents within the last 6 months form a relative contraindication. It is important to evaluate risk/benefit for each patient. Traumatic Brain Injury (TBI) is not a contraindication

All conventional/accessible surgical treatments include-

- Replacement with: FFP- 5-10 ml/kg (4-6 units For 70 kg)
- Cryo.-1-2 U/10kg (10-15 un For 70 kg)
- Platelets- 1-2 U/10kg
- rFVIIa should be administered after adequate PRBC
- Correction of acidosis (minimum pH> 7.1)
- Warming of body

Preconditions associated with the use of Factor VII include:

- Fibrinogen>50mg/dl (preferably >100 mg/dl)
- Platelets >50X10⁹/L (preferably >100X10⁹/L)

rFVIIa – initial dose-120µg/kg IV over 2-5 min. The arrest of coagulopathic bleeding together with the haemodynamic improvement that follows may expose surgical bleeding sites. If given outside OR-“second look” should be considered.

Repeated doses: Then 100µg/kg dose should be repeated if hemostasis is not achieved within 15-20 min. If the response remains inadequate, consider to repeat the replacement therapy +Ca + bicarbonate before the third dose.

Monitoring

No laboratory method to monitor the effect. Watch the cessation of hemorrhage and haemodynamic stabilization. Typically, there should be shortening of PT below normal range.

Factor VII and Intracranial haemorrhage

Intracerebral hemorrhage is one of the most disabling forms of stroke. More than one third of patients with this disorder die within one month after the onset of symptoms, and only 20 percent regain functional independence. There is currently no effective treatment for intracerebral hemorrhage. The volume of the hematoma is a critical determinant of mortality and functional outcome after intracerebral hemorrhage and early hematoma growth is an important cause of neurological deterioration. An increase in volume of more than 33 percent is detectable on repeated computed tomography (CT) in 38 percent of patients initially scanned within three hours after onset; in two thirds of cases with growth in volume, this increase is evident within one hour.

Early hematoma growth occurs in the absence of coagulopathy and appears to result from continued bleeding or re-bleeding at multiple sites within the first few hours after onset. Intervention with so-called ultra-early haemostatic therapy in the emergency department might improve outcomes after intracerebral hemorrhage by arresting ongoing bleeding and minimising increases in the volume of the Hematoma. rFVIIa is approved to treat bleeding in patients with hemophilia who have antibodies to factor VIII or IX, and it has been reported to reduce bleeding in patients without coagulopathy as well (27). In two recent dose-escalation safety studies, it was found that doses of rFVIIa ranging from 5 to 160µg/kg of body weight were not associated with a high frequency of thromboembolic complications in patients with acute intracerebral hemorrhage (28,29).

rFVIIa in Cardiac Surgery

Cardiac surgery is often complicated by excessive blood loss. Management of the blood loss typically involves transfusion of blood components and haemostatic agents. If the bleeding continues, the patient may require a second operation and even this fails in some cases to halt the bleeding. An investigation has been carried out by the Aldouri group to see whether severe uncontrolled bleeding during cardiac surgery can be successfully treated with rFVIIa (7). It proved to be of some benefit.

Conclusions

rFVIIa can be considered for the management of bleeding in a case of hemophilia with inhibitors, the only approved indication of this drug. It can be considered as 'off-label' use for bleeding in some other conditions with uncontrolled bleeding as a last ditch try. However patient should be treated for acidosis and hypothermia if present before giving this drug. Other blood components as appropriate should be given including PRBs, platelet, FFP, Cryoprecipitate and vit. K. Only after these have been given in adequate doses and there is failure to control bleeding one may consider use of rFVIIa. Due to its short half life, the drug has to be injected repeatedly. Lastly the cost of rFVIIa is exorbitant precluding its use routinely.

References

1. Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis* 1998; 9: 119-28.
2. Bequin S, Lindhout T, Hemker HC. The effect of trace amounts of tissue factor on thrombin generation in platelet rich plasma, its inhibition by heparin. *Thromb Haemost* 1989; 61: 25-9.
3. Biggs R, MacFarlane RG. Human blood coagulation and its disorders, 3rd ed. Pg 280 Oxford: Blackwell scientific publications, 1962.
4. Goodnough LT. Experience with recombinant factor VIIa in thrombocytopenic patients. *Sem Hematol* 2004; 41(Suppl): 25-9.
5. Attar S, Boyd D, Layne E, et al. Alterations in coagulation and fibrinolytic mechanisms in acute trauma. *J Trauma* 1969; 9: 939-65.
6. Jesu's Martý'nez, Ana Rosa Cid, Javier de la Rubia and Ricardo Gimeno. Treatment of intra-abdominal bleeding with recombinant activated factor VII in a patient with disseminated intravascular coagulation secondary to septic shock; *Blood Coagulation and Fibrinolysis* 2005, Vol 16 No 4; 297-29
7. Aldouri M, Shafi T, Al Khudairi D, Al Bokhari E, Black L, Akinwale N, Osman Musa M, Al Homaidhi A, Al Fagih M, Borum Andreasen R: Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven®) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinol* 2000; 11 (suppl 1):121-127.
8. Shapiro AD, Gilchrist GS, Hoots WK, et al. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80: 773-8.
9. Lusher JM, Roberts HR, Davignon G, et al. A randomised, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group. *Haemophilia* 1998b; 4: 790-8.
10. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 1998; 80: 912-8.
11. Chuansumrit A, Treepongkaruna S, Phuapradit P. Successful invasive procedures in children with liver failure using recombinant factor VIIa. *Haemophilia* 2000; 6: 348.
12. Papatheodoridis GV, Chung S, Keshav S, et al. Recombinant factor VIIa is used in a Jehovah's witness with liver cirrhosis to correct prothrombin time, bleeding time, and thromboelastographic parameters, enabling safe percutaneous injection of hepatocellular carcinoma (abstract). *Thromb Haemost* 1999; 82 (Suppl): 620.
13. Bernstein DE, Jeffers L, Erhardtsen E, et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology* 1997; 113: 1930-7.
14. Vlot AJ, Ton E, MacKaay AJ, et al. Treatment of severely bleeding patients without pre-existing coagulopathy with activated recombinant factor VII. *Am J Med* 2000; 108: 421-3.
15. Simmons RL, Collins JA, Heisterkamp CA, et al. Coagulation disorders in combat casualties. I. Acute changes after wounding. II. Effects of massive transfusion. III. Post-resuscitative changes. *Ann Surg* 1969; 169: 455-82.
16. Strump DC, Strauss RG, Henriksen RA, et al. Effects of hydroxyethyl starch on blood coagulation, particularly factor VIII. *Transfusion* 1985; 25: 349-54.
17. Aberg M, Hedner U, Bergentz SE. Effect of dextran on factor VIII (antihemophilic factor) and platelet function. *Ann Surg* 1979; 189: 243-7.
18. Goodnough LT. Treatment of bleeding in the intensive care unit. In: Goodnough LT, ed. Recombinant factor VIIa: potential treatment of critical bleeding in the future ICU. *Int Care Med* 2002; 28: A5.

19. Martinowitz U, Kenet G, Segale N, et al. Recombinant activated factor VII in adjunctive hemorrhage control in trauma. *J Trauma* 2001; 51: 431-9.
20. Rapaport SI. Coagulation problems in liver disease. *Blood Coagul Fibrinolysis* 2000;11(Suppl 1): S69-74.
21. Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002; 42: 114-124.
22. Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teerararkul S, Hogeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2000; 11: S101-S105.
23. Moscardo F, Pe rez F, De La Rubia J, Balerdi B, Lorenzo JI, Senent ML, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001; 113: 174-176.
24. Holcomb JB, Neville HL, Fischer CF, Hoots K. Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding in a septic patient. *Curr Surg* 2003; 60: 423-427
25. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. *Blood Reviews*, 2003; 17, 51-55
26. Oliver JA, Monroe DM, Roberts HR, Hoffman MR. Feedback activation of factor XI on platelets in the absence of factor XII. *Arterioscler Thromb Vasc Biol* 1999; 19: 170-177.
27. Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; 361: 201-5. [Erratum, *Lancet* 2003; 361: 1138.]
28. Mayer SA, Brun N, Broderick J, et al. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005; 36: 74-9.
29. Mayer SA, Brun N, Broderick J, Davis S, Diringer MN, Steiner T. Safety and preliminary efficacy of recombinant coagulation factor VIIa in acute intracerebral hemorrhage: U.S. phase 2A study. *Stroke* 2004; 35: 332. abstract.