

Recombinant Activated Factor VII (rFVIIa) as a Hemostatic Agent in Liver Disease: A Break From Convention in Need of Controlled Trials

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The management of coagulopathy in patients with acute and chronic liver disease has undergone little change in many years despite advances in our understanding of the pathogenesis of this problem. In general, deficiency of clotting factors as a result of poor hepatic synthetic function accounts for most of the coagulopathy. However, other processes such as disseminated intravascular coagulation (DIC), hyperfibrinolysis, dysfibrinogenemia, hemolysis, and a decrease in number or function of platelets may be present and thus add to the complexity of the problem. Coexisting portal hypertension and the associated risks of volume expansion, renal failure, and endothelial dysfunction add even more difficulty to the management of these patients. The clinician's despair is only exacerbated by uncertainty regarding the significance of laboratory indices of coagulation and the lack of agreement between health care providers regarding how to use these indices. Simple, conventional interventions such as vitamin K or plasma administration often produce only limited amelioration, and the latter carries the potential disadvantage of volume overexpansion as well as the risk of infection and transfusion reactions. Into this complex and uncertain clinical situation has arrived the antihemophilic agent recombinant activated factor VII (rFVIIa). Its development has led to a fundamental re-evaluation of the classic understanding of the normal clotting cascade. Moreover, use of this product in liver disease patients is increasing despite the lack of definitive studies or literature to guide therapy. Herein we review the mechanism of action of this agent, report the clinical applications in patients with liver disease, address the limitations and risks associated with the drug, and discuss the issue of its cost-effectiveness. (HEPATOLOGY 2004;39:592–598.)

Few areas within the field of hepatology are fraught with as much uncertainty and variation in practice as that of the management of coagulation disorders in patients with liver disease. Clinical experience is replete with anecdotes regarding variation in practice between and within major academic centers. This wide variation in practice has been documented in two reports addressing acceptable cut-offs for coagulation tests in patients undergoing liver biopsy.^{1,2} Adding to the uncertainty in this

area is the lack of good correlation between common coagulation indices and bleeding risks.³ It is clear that we often navigate without a map when managing coagulopathy in the liver disease patient. So, how do we react to a very expensive product approved only for specific forms of hemophilia that commonly corrects the PT after a single dose in liver patients and appears to also augment platelet function even in the setting of thrombocytopenia?

Recombinant Activated Factor VII and Changing Concepts of the Clotting Cascade

Recombinant activated factor VII (rFVIIa) is one of the unusual types of scientific advances whose existence caused a re-evaluation of the general conceptual milieu from which it sprang.⁴ Its development brought with it a new appreciation of the integration of the traditional intrinsic and extrinsic clotting pathways with the humoral and cellular components of the clotting cascade (Fig. 1). Typical clot formation occurs through the interaction of a

Abbreviations: DIC, disseminated intravascular coagulation; rFVIIa, recombinant activated factor VII; FVIIa, activated factor VII; TF, tissue factor; ICP, intracranial pressure.

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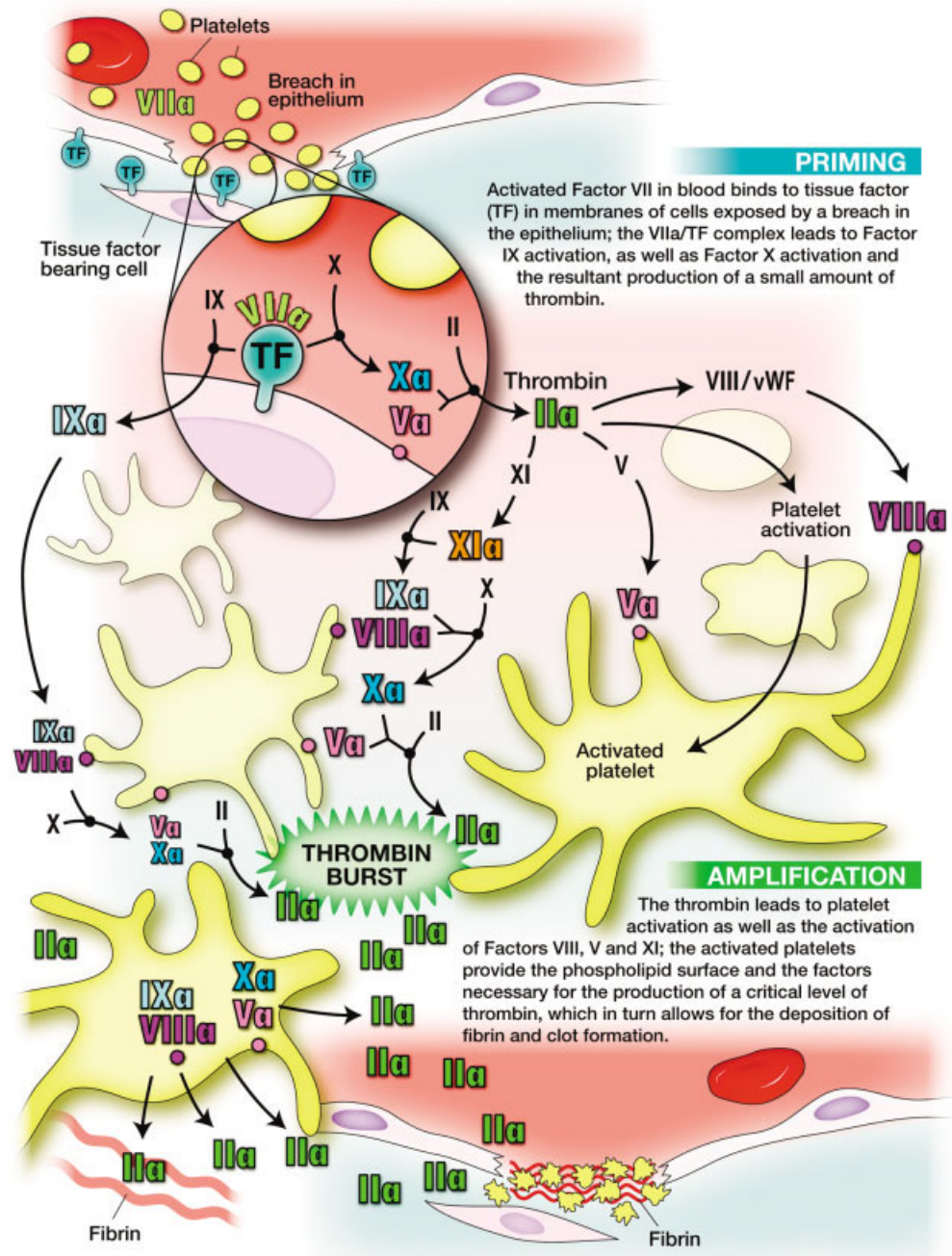


Fig. 1. Current concept of the clotting cascade. Factor VII is critical in setting off a cascade characterized by priming and amplification phases. Clot formation begins with a breach in the vascular endothelium, which exposes tissue factor to circulating FVIIa. A small amount of thrombin is formed in this priming step. An amplification phase follows, during which activated coagulation factors and platelets help to produce a thrombin burst, leading to fibrin and clot formation.

small amount of normally circulating activated factor VII (FVIIa) with tissue factor (TF) that is exposed on certain cell surfaces only after injury to the endothelium—a process facilitated by cell membrane phospholipid.⁵⁻⁷ Once the FVIIa–TF complex forms on the TF-bearing cell, the clotting process can be divided into a “priming” step and a propagating or accelerating step. The FVIIa–TF complex formed on a TF-bearing cell activates factor X, which in turn converts prothrombin (factor II) to thrombin. The small concentration of thrombin generated during priming activates factors VIII, V, and XI and platelets that serve as a scaffold for amplification and propagation of the

enzymatic reactions of the clotting cascade and results in a burst of thrombin activation. Activated platelets, bearing activated factors VIIIa, Va, and XIa, result in further activation of factor X and recruitment of additional platelets. This generates an increasing amount of thrombin, which converts fibrinogen to fibrin, resulting in clot formation. The process is regulated by antithrombin inactivation of FXa and thrombin and blockage of the FVIIa–TF complex by a complex of TF pathway inhibitor and FXa.⁸

Exogenous administration of rFVIIa augments the initial priming and subsequent amplification phases of coag-

ulation at the site of injury (*i.e.*, wherever there is a breach of the vascular tree). It intensifies the thrombin burst at the site of injury with very limited (if any) activation of the clotting cascade outside of the injury site. In normal coagulation, TF-bearing cells play a critical role in localizing and limiting the coagulation reaction to sites where the vascular integrity is impaired. Originally developed for treatment of bleeding in hemophilia A and B patients with inhibitors, use of rFVIIa has been broadened to include patients with cirrhosis despite limited supportive literature.

Clotting time is decreased with single doses of rFVIIa in patients with cirrhosis without a concomitant increase in clot lysis time or fibrinolysis⁹ indicating formation of a viable clot.¹⁰ In factor VIII- or factor IX-deficient nonbleeding hemophiliacs, the half-life of a single dose of rFVIIa is estimated at 2.89 hours; this falls to 2.3 hours in bleeding patients.¹¹ By comparison, in nonbleeding patients with cirrhosis the half-life is approximately 2.3 hours, and no data is available for bleeding patients. The median duration of normalization of the PT is estimated at 2, 6, and 12 hours following a single dose of 5, 20, or 80 $\mu\text{g}/\text{kg}$, respectively.¹² In addition to the effect on clotting times, rFVIIa also augments coagulation in thrombocytopenia by way of enhancement of site-specific activation of platelets that enhance thrombin generation.¹³ For these reasons, in conjunction with the relatively low volume of rFVIIa typically administered (40 $\mu\text{g}/\text{kg}$ constitutes only a few cc in the average adult), rFVIIa is an attractive agent for hemostatic control in patients with liver disease.

Coagulopathy in Liver Disease and the Significance of Clinical Tests

The importance of coagulopathy in acute and chronic liver disease is reflected both in the increased risk of bleeding and by the incorporation of coagulation indices into prognostic scores for both fulminant hepatic failure (such as the King's College criteria and the Clichy criteria)¹⁴⁻¹⁶ and cirrhosis (Child-Pugh-Turcotte score and MELD scores).¹⁷⁻¹⁹ The factor VII level, perhaps because of its very short half-life, has been reported to be one of the single most important prognostic indicators in cirrhosis.²⁰ Although the mechanisms may differ somewhat, dysfunction in both acute and chronic liver disease appears to variably involve all aspects of the clotting system, including the humoral limb, the cellular limb, and possibly function of the endothelium (cirrhotic vasodilation), although less has been written about the latter.

Vitamin K deficiency and impaired gamma-carboxylation of vitamin K-dependent factors may be present in patients with liver disease. However, the major abnormality in most forms of liver disease-associated coagulopathy

involves impaired synthesis of the clotting factors. The liver is the site of synthesis of the majority of clotting proteins, with the notable exception of von Willebrand factor and possibly factor VIII. Although impaired synthesis includes both pro- and anticoagulant components (antithrombin, protein C, and protein S), bleeding tends to be the overriding problem. Additional bleeding risks include thrombocytopenia (from splenic sequestration, antibody expression, or deficient thrombopoietin),^{21,22} hyperfibrinolysis due to impaired clearance of tissue plasminogen activator,²³ dysfibrinogenemia,²⁴ and/or endothelial dysfunction possibly mediated by nitric oxide metabolites. However, thrombosis may also be seen in liver disease and could play a role in disease progression; intrahepatic small vessel thrombi have been implicated by Wanless in the progression of cirrhosis to a state of atrophy (parenchymal extinction).²⁵ Other complicating factors may also be superimposed on the background of synthetic dysfunction, including disseminated intravascular coagulation (DIC)²⁶ and spur cell hemolysis (due to disturbed lipoprotein metabolism). Uremia,²⁷ a common complication of advanced liver disease, and platelet dysfunction²⁸ further contribute to coagulopathy in these patients.

Common laboratory indices of coagulation have prognostic significance in patients with liver disease, but they are not reliable or unequivocal indicators of bleeding risk (either spontaneous bleeding or resulting from invasive interventions). For example, liver bleeding time measured under direct visualization during laparoscopic examination correlated poorly with all common indices of coagulation in one study.²⁹ The lack of correlation raises the practical issue of how to determine bleeding risk for these patients. Nonetheless, at least one study has offered some encouragement. Boks and colleagues³⁰ studied a battery of coagulation indices in 31 patients with both fulminant liver failure and decompensated cirrhosis and compared the results with those obtained in healthy controls. Abnormalities were evident in both the coagulant and anticoagulant systems but with an overall tendency toward increased bleeding risks. Furthermore, they demonstrated a correlation between the Normotest (a variant of the PT) and bleeding from mucosal surfaces and puncture wounds.

However, probably due to the complexity of the bleeding diathesis in liver disease, no coagulation tests are reliably predictive and hence no uniformly accepted guidelines for either therapeutic or prophylactic administration of hemostatic agents exist. In addition, a small degree of variation in one of the common, standard indices, international normalized ratio, or INR, has been reported in patients with liver disease,^{31,32} suggesting some

inherent problems, peculiar to such patients, with the currently available indices. Although the future promises more refined tests to offer an assessment of the speed and quality of clot formation as well as activity of the anticoagulating system based on thromboelastography or other viscoelastic testing methods,³³ currently we are limited largely to the PT and platelet count. It seems likely—though largely conjectural—that these tests may be more predictive with very extreme abnormalities but are far more limited within the range typically encountered.

Specific Interventions, Bleeding Risks, and rFVIIa

Liver Biopsy. Life-threatening bleeding with liver biopsy in patients with liver disease is estimated to occur between 1:1,000 and 1:10,000 individuals—although, as noted above, the relationship between bleeding risk and common measures of coagulation (*e.g.*, the PT and platelet count) is weak.^{34,35} Surface bleeding in lesser amounts is almost universal, but it is unlikely to be seen by any technique other than laparoscopic observation despite its association with localized postprocedure pain.³⁶ In spite of the poor correlation between coagulation tests and bleeding risks, we have not encountered a report that does not recommend some specific target test value beyond which some correction of the coagulopathy is recommended. A number of prophylactic strategies are recommended as reviewed by Grant and Neuberger.³⁴

Limited data is available regarding rFVIIa in this setting. Four different doses of rFVIIa (5, 20, 80, and 120 $\mu\text{g}/\text{kg}$) were studied in 71 mildly coagulopathic patients with cirrhosis undergoing laparoscopic liver biopsy.³⁷ Liver bleeding time, measured by direct observation, was the main endpoint. At baseline, all patients had platelet counts above 60,000/ mm^3 and the PT was 3 to 15 seconds above normal. The majority of patients in all groups achieved transient normalization of the PT within 10 minutes of administration, although the duration of normalization varied significantly between the groups—longer duration was observed at higher doses (10–20 minutes for the 5- μg dose vs. 4 hours of normalization for the 120- μg dose). There was no difference in liver bleeding following the biopsy between the groups, but two patients had complications (one DIC and one portal vein thrombosis) although neither complication was directly attributed to the rFVIIa by the authors. However, the poor correlation between coagulation indices and bleeding risks and the uncertain safety issue warrant caution. It may also be that an agent such as rFVIIa would have a greater effect in more thrombocytopenic patients, although this was not addressed in this study because all

patients had platelet counts above 60,000/ mm^3 . As discussed below, it is our opinion that rFVIIa will likely find a role as a rescue agent for severe postprocedure bleeding rather than as a prophylactic agent; however, this has yet to be investigated.

Fulminant Hepatic Failure. Several studies have reported the use of low doses of rFVIIa in patients with fulminant hepatic failure, usually in the setting of intracranial pressure (ICP) monitor placement for the detection of cerebral edema.^{38–40} As with liver biopsy, there is no wide agreement on acceptable preprocedure coagulation indices, which in the United States often fall to the neurosurgeon to deem as acceptable or not. A number of strategies have been employed to correct preprocedure coagulopathy,⁴¹ including plasma infusion; however, increasing plasma volume may lead to anasarca and theoretical exacerbation of cerebral edema. Using rFVIIa in this setting is particularly attractive given the low volume required to correct the coagulopathy.

Shami and colleagues³⁸ reported on 15 patients with fulminant hepatic failure who met King's College criteria for urgent liver transplantation. Eight consecutive historical controls received plasma alone in an effort to correct the PT and place ICP monitors. rFVIIa was used in seven subsequent consecutive patients. None of patients in the plasma-alone group normalized the PT, and only three were deemed sufficiently stable to undergo ICP monitoring. In contrast, all seven of the patients in the rFVIIa group normalized the PT after a single 40- $\mu\text{g}/\text{kg}$ dose and all underwent ICP monitor placement. The authors noted significantly less anasarca in the rFVIIa group (attributed to less plasma infusion) and a nonsignificant improvement in survival.

Many issues remain unresolved, however, including the use of ICP monitors in general and appropriate dosing of rFVIIa. As with liver biopsy, the lack of safety data warrants a cautious approach. The thrombotic effect of any hemostatic agent needs to be considered, especially in patients treated with artificial liver support devices that may thrombose. In addition, the hemostatic agent may alter coagulation parameters commonly used to establish transplantation criteria.

Variceal Bleeding. As with placement of ICP monitors, volume expansion may be particularly undesirable in managing the patient with variceal bleeding due to adverse effects on portal pressure.^{42,43} At least two trials of rFVIIa as an adjunct to endoscopic therapy of variceal bleeding have been reported.^{44,45} In the controlled trial (available only in abstract), a modest (12 of 65 placebo vs. 3 of 63 treated patients) reduction in early rebleeding was observed in Child-Pugh B/C patients. In the second trial of 10 patients with cirrhosis and variceal bleeding, nor-

malization of PT was observed in all patients following a single 80- μ g/kg dose of rFVIIa. Immediate endoscopic hemostasis was observed in all; however, 6 of 10 patients had rebleeding, and 6 patients died (from bleeding-related causes) suggesting potential short-term benefit of rFVIIa in the setting of endoscopic intervention that does not necessarily translate to lower morbidity/mortality.

Given the prominent role of pressure changes as opposed to coagulation problems in the pathogenesis of variceal bleeding and the high degree of efficacy of conventional pharmacologic and endoscopic therapy, it seems unlikely that a hemostatic agent will have a prominent role in these patients. On the other hand, rescue therapy of uncontrollable bleeding in patients in whom endoscopy cannot be completed seems more plausible as a means of facilitating endoscopic treatment (by allowing a clear field). A recently published trial⁴⁶ reported the use of rFVIIa in this setting. Eight patients with bleeding esophageal varices unresponsive to pharmacologic therapy, endoscopic therapy, or balloon tamponade were given a single dose of rFVIIa. Hemostasis was observed in all cases, with a rebleeding rate of 25%.

Procedures. Bedside procedures are commonly performed in both acute and chronic liver disease patients. Paracentesis rarely requires checking of coagulation indices,⁴⁷ because bleeding more often results from transgression of a peritoneal wall blood vessel collateral, which is best avoided by carefully placing the thin bore anesthetic needle and closely following this track with the larger caliber cannulas without lateral movements (*i.e.*, avoidance of "Z-tracking"). As with variceal bleeding, prepuncture plasma probably engorges the collateral system and may actually exacerbate the bleeding risk. However, in patients requiring a thoracentesis, a more aggressive approach should be considered given the difficulty in detecting bleeding and managing hemothorax. For venous line placements (such as dialysis catheters), existing studies indicate a poor correlation between the coagulation indices and bleeding risk.^{48,49} A few case reports exist regarding the use of rFVIIa in this setting,⁵⁰ but given the difficulty in predicting bleeding, routine use of aggressive measures is probably not necessary.

Likewise, with dental extractions, the low incidence and unpredictable nature of bleeding warrants careful consideration before prophylactic use of rFVIIa. Rescue therapy has been reported for uncontrolled bleeding following dental extractions in two cirrhotic patients with coagulopathy and poor response to conventional therapy.⁵¹ Another interesting application was noted in four cirrhotic patients undergoing colonoscopic polypectomy; however, the use of rFVIIa in this report as a preventive

rather than rescue therapy limits interpretation of this small series.⁵²

Liver Transplantation and Surgery in the Cirrhotic Patient. The literature in the surgical field regarding rFVIIa remains limited because of the mostly uncontrolled nature of the reported studies. Although intraoperative bleeding is associated with a more severe postoperative course, prediction of bleeding based on common coagulation indices has been difficult to establish.⁵³ However, experience with the use of techniques such as the thromboelastogram are much greater in this setting, and some experienced surgeons feel strongly about the use of coagulation indices coupled with other factors such as prior abdominal surgery in predicting intraoperative bleeding. Safety and reduced transfusion requirements have been reported with the use of rFVIIa just before initiating a transplant in severely coagulopathic patients.^{54,55}

Kalicinski and colleagues⁵⁴ reported on two pediatric patients (2.5 and 6 years old) undergoing urgent liver transplantation for fulminant liver failure. Both failed conventional therapy with plasma and cryoprecipitate and subsequently received 100 μ g/kg just before the skin incision and again at 2 hours into the operation in one patient. Baseline INR values were 5.7 and 6.9, respectively, and in both there was normalization after administration of rFVIIa. No complications were noted, and blood loss was assessed as relatively mild. However, both patients also received tranexamic acid prior to surgery (another hemostatic agent), making interpretation more difficult. In another series, Hendriks and colleagues⁵⁵ reported on six adult patients undergoing transplantation for cirrhosis who received a single dose of 80 μ g/kg prior to skin incision. Compared with matched controls, the authors noted less blood loss and fewer transfusions of blood or plasma in the treated group. One patient receiving rFVIIa developed hepatic artery thrombosis on the first postoperative day.

Limitations, Cautions, Risks, and Costs

The efficacy of rFVIIa is limited in patients with low fibrinogen (<100 mg%), and administration of at least a small amount of plasma or cryoprecipitate may be indicated for these patients. Low fibrinogen levels warrant careful consideration, because the level may be an indicator of coexisting DIC or hyperfibrinolysis, which could complicate use of rFVIIa. Prolongation of the PT following a dose of rFVIIa probably indicates a laboratory artifact, because devices used to perform a PT often default to a reading of greater than 100 seconds if the test result is faster than the device's lower limit range. Thus a PT value of less than 8 seconds may be reported as greater than 100.⁵⁶

There are many theoretical safety concerns that must be addressed before rFVIIa becomes routine therapy in liver disease patients. Augmentation of thrombin formation (the thrombin burst) could exacerbate coexisting DIC. Most studies to date show no biochemical evidence of DIC in otherwise stable cirrhotic patients, but both DIC and portal vein thrombosis have been observed in at least one series of liver biopsy patients.³⁷ In addition, we have observed myocardial infarction in a 19-year-old patient with unexplained fulminant liver failure (FDA Med-watch) who received repeated doses of rFVIIa following placement of an ICP monitor and in the setting of high doses of levophed, dobutamine, and norepinephrine therapy for blood pressure support. Cardiac catheterization showed no evidence of thrombus in this case, casting doubt on the role of thrombus as opposed to coronary vasospasm; nevertheless, there remains some grounds for caution.

Finally, given the many uncertainties, one of the greatest concerns is the cost of rFVIIa in light of an uncertain risk–benefit ratio, especially when it is used as a prophylactic agent before invasive procedures. The typical charge for a single 40- μ g/kg dose in an adult liver disease patient may be as high as \$3,000 to \$4,000.

Conclusion

The evolution of our understanding of normal coagulation, which has been nicely reviewed in a recent editorial,⁵⁷ is a fascinating subject that is especially relevant to the liver disease patient. Derangement of this complex system forms an inherent part of both acute and chronic liver disease, and the associated abnormalities are established as important prognostic indices. Varying opinions regarding the coagulopathy associated with liver disease are commonly held by different health care providers including the GI/hepatologist, hematologist, hepatobiliary surgeon, transplant surgeon, interventional radiologist, and anesthesiologist. The development of rFVIIa has brought with it a remarkable re-evaluation of the clotting cascade, and it has provided an almost intoxicating ability to correct common measures of the clotting cascade in patients with liver disease. An encouraging aspect of this development is that it has changed attitudes among many care providers who once regarded the often dire situation of these patients as hopeless.

However, in the absence of more definitive data regarding cost-effectiveness and safety, a cautious approach is warranted. It is now incumbent upon us to evaluate the real use of rFVIIa in controlled trials that measure the clinical outcome and risk–benefit parameters in specific situations. Such studies (some sponsored by the National Heart, Lung, and Blood Institute) are presently in devel-

opment. In addition to clinical trials of rFVIIa—and perhaps of equal or greater importance—it is necessary that we carefully re-evaluate the use of newer tests of coagulation as a means of defining bleeding risk. Until these analyses are complete, the use of rFVIIa should be very carefully weighed to avoid undue costs and unknown risks. In most situations, it is our suspicion that it will find its greatest use as a postprocedure rescue intervention for relatively infrequent bleeding from procedures such as dental extractions, line placements, liver biopsy, and uncontrollable variceal bleeding when the field cannot be endoscopically cleared. As a prophylactic intervention, its major use will likely be limited to particularly risky procedures such as ICP monitor placement, thoracentesis, transplantation in the patient with prior abdominal surgery and severe coagulopathy, and perhaps some types of large bore central line placement (*e.g.*, in the subclavian site) where a bleeding complication may be difficult to recognize early.

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