

# Consensus Recommendations for the Off-Label Use of Recombinant Human Factor VIIa (NovoSeven®) Therapy

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## ABSTRACT

**Objective:** To rationalize decision-making concerning the growing and costly off-label use of recombinant human factor VII (rFVIIa, NovoSeven®) therapy.

**Options:** Using rFVIIa therapy for patients with bleeding or providing usual care (e.g., continued clotting factor replacement).

**Outcome:** Morbidity and mortality related to continued bleeding or thrombosis.

**Evidence:** A literature review was performed to assess the efficacy and safety of off-label rFVIIa therapy. An expert consensus panel reviewed the data. Most studies were case series or reports. Only four randomized trials were available in the peer-reviewed literature at the time of the panel's deliberations. The Rand Corporation/University of California at Los Angeles Appropriateness Method was used to rate 41 clinical scenarios as "appropriate," "uncertain," or "inappropriate" in a comparison of risks and benefits in an environment



with constrained health care costs.

**Values:** The panel comprised nine geographically diverse clinicians to represent the interests of clinical specialties, including anesthesiology/critical care, surgery, transfusion medicine/hematology, pharmacy, neurology/critical care, and practice environments.

**Benefits, Harms, and Costs:** The panel's recommendations are expected to limit the use of rFVIIa to the most appropriate circumstances, thus minimizing associated risks and costs. These suggestions should be considered consistent with the

quality and quantity of the available evidence and should be adjusted as new evidence emerges.

**Recommendations:** The panel rated the use of rFVIIa as "appropriate" in limited circumstances: (1) cardiac, thoracic aortic, or spinal surgery; hepatic resection; hysterectomy; or postpartum bleeding (when significant clotting factor replacement has failed); (2) for severe multiple trauma (only if surgery and substantial blood replacement are unsuccessful); and (3) for nontraumatic intracranial bleeding (only if less than four hours has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and hematoma expansion).

Doses of 20 to 40 mcg/kg were recommended for non-emergent anticoagulant reversal. Doses of 41 to 90 mcg/kg were recommended for all other scenarios.

## INTRODUCTION

Recombinant coagulation factor VIIa (rFVIIa, NovoSeven®, Novo Nordisk) is an analogue of the naturally occurring proenzyme. In 1999, Novo Nordisk received marketing approval from the Food and Drug Administration (FDA) for rFVIIa to be used to treat bleeding in hemophilia patients with acquired coagulation factor inhibitors. Since then, rFVIIa has been increasingly used in patients without hemophilia for the con-

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trol of refractory bleeding in a variety of clinical situations.<sup>1</sup>

Multiple case series and case reports have described striking benefits in patients with obstetrical bleeding, trauma, and perioperative bleeding.<sup>2,3</sup> Some speculate, however, that because of its mechanism of action, rFVIIa might lead to significant thrombotic complications such as myocardial or cerebral ischemia, deep venous thrombosis, or pulmonary embolism. Limited data are available regarding the safety profile of the drug.

Based upon 500,000 doses used, only 24 thrombotic adverse drug events (ADEs) have been reported.<sup>4</sup> However, this use has been predominantly in patients with hemophilia and coagulation factor inhibitors, in whom the risk of thrombotic complications would be very low compared with that for other acutely ill patients.

Whereas the number of hemophilia patients in the U.S. is modest, the number of potential recipients of this drug, when used "off-label," is substantially larger, particularly to treat active bleeding and bleeding prophylaxis in at-risk patients. At a cost of \$2,000 to \$8,000 per dose, it is not uncommon for hospitals to have rFVIIa expenditures that exceed \$500,000 per year, with most of these costs related to off-label use.<sup>5</sup>

Although numerous reports on the clinical use of rFVIIa are available in the literature, only four prospective randomized, controlled trials had been published prior to the panel's deliberations. Those studies had small sample sizes (totaling only 117 adults), and half of the studies examined the reversal of anticoagulation in healthy individuals. The remaining literature consisted of case reports or case series without control groups; as a result, the potential existed for significant bias in patient selection, variations in drug doses used, and—most important—the likelihood of the submission of only positive data.

Thus, an ample, representative, and statistically valid base of evidence did not exist at the time of the panel's deliberations. In the absence of such evidence, clinicians and hospitals lack scientifically sound guidance and would appear to benefit from an objective and unbiased multidisciplinary clinical assessment.

Using the Rand Corporation/UCLA Appropriateness Method,<sup>6</sup> the Society for the Advancement of Blood Management (SABM) and the University HealthSystem Consortium (UHC) reviewed the literature and developed consensus recommendations for the appropriate clinical situations, doses, and administration related to the off-label use of rFVIIa. In developing these recommendations, we have attempted to balance the risks, benefits, and costs associated with this therapy.

### METHODS

We used the Rand/UCLA Appropriateness Method to develop the recommendations presented in this article.<sup>6-8</sup> These recommendations entailed:

- a computer search of the clinical literature on the efficacy and safety of rFVIIa.
- development of a list of clinical scenarios for which this therapy might be considered.
- convening a geographically diverse, multidisciplinary panel of clinicians to review and rate each clinical scenario (see box below).

### Literature Summary

We conducted an electronic search of the biomedical literature using the National Library of Medicine National Center for Biotechnological Information (NCBI) PubMed (Medline Plus) database, encompassing the time period from 1998 through June 2004. The following search terms were used: "recombinant activated factor vii" or "novoseven" or "rfviiia." The search was limited to English-language studies of human subjects.

We examined the reference lists of papers selected for review, and we used the "related articles" function of the PubMed database to identify papers that were not identified in the electronic search. Appendix 1 (see page 654) presents a detailed schematic of the literature search and selection strategy and its results.

Before the consensus meeting, each panel member received

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Table 1 Medical Evidence Grading System

Evidence Category	Description
Type I	Obtained from at least one properly designed randomized, controlled trial
Type II-1	Obtained from well-designed controlled trials without randomization
Type II-2	Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Type II-3	Obtained from multiple time-series with or without the intervention; dramatic results in uncontrolled experiments could also be regarded as this type of evidence
Type III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

a comprehensive evidence table and a summary review of the clinical literature on the efficacy and safety of the off-label use of rFVIIa in adults. One of the authors (T. Ratko) reviewed, graded, and compiled the literature, and any disagreements were discussed and resolved at the panel meeting.

The evidence grade for each study was based on each study's design, according to the U.S. Preventive Services Task Force definitions (Table 1).<sup>9</sup> In this scheme, data from randomized, controlled trials are generally considered to provide the most reliable evidence of the clinical effectiveness or ineffectiveness of any therapy. Other study designs—primarily non-controlled, open series, cohort studies, retrospective analyses, or case reports—provide less reliable data.

Note that the evidence grading system does not reflect the strength of a recommendation; rather, it measures the strength of the available data, based on study design elements (e.g., the number of patients, the method used to allocate subjects to study groups, statistical analysis, and other parameters). Furthermore, the criteria used to evaluate the clinical effectiveness of rFVIIa (e.g., laboratory data, such as hematocrit, and clinical findings—primarily cessation of active bleeding) were not considered as indicators of the study strength or the validity of the results.

Dr. Ratko repeated the same electronic search for the period from May 31, 2004, through May 31, 2005, to identify relevant articles published since the panel meeting in July 2004. This step was performed because a substantial amount of time had elapsed between the first literature search and the submission of this report. We compared the later published results with the panel's consensus determinations as a qualitative test of the validity of the recommendations.

### Clinical Scenarios

We attempted to create a comprehensive list of all possible clinical scenarios for the off-label use of rFVIIa therapy. We constructed preliminary scenarios, which then underwent a two-round review process by the expert panel. Clinical scenarios were categorized into three broad categories according to their appropriateness of use:

- patients with closed-space (including intracranial) bleeding
- patients with bleeding associated with surgery
- "other" uses (postpartum, post-hysterectomy, severe multiple trauma, active gastrointestinal bleeding, hepatic failure, and prophylaxis prior to major surgery)

Nine scenarios pertained to the recommended dosing of rFVIIa therapy. The panel also evaluated 10 administration topics related to the use of rFVIIa (e.g., prescriber restrictions, bolus injections, patients' body temperature and pH, concomitant coagulation testing, and the use of the agent as salvage therapy).

The scenarios were based on our clinical experience. Cases of bleeding that required treatment with fresh frozen plasma, platelets, and cryoprecipitate were considered as scenarios for the use of rFVIIa. No particular methodology was used, other than listing all possible clinical situations. This information was not considered to be crucial, because we did list the scenarios that were excluded.

For ease of discussion, closed-space bleeding was considered to represent a completely different approach for clinicians, compared with the "rescue" use of the drug. The example used here from the "other" category was for obstetrical patients who continued to experience bleeding after delivery and after emergency hysterectomy.

### Consensus Panel

We convened a panel of nine clinicians in the fields of anesthesiology/critical care (n = 2), surgery (n = 3), transfusion medicine/hematology (n = 2), pharmacy (n = 1), neurology/critical care (n = 1). A pool of potential panel members was identified from a combination of not-for-profit specialty society (SABM) recommendations, UHC member institutions, and authors of key clinical trials.

The final selection balanced the specialty and geographical factors. All members of the consensus panel resided in the U.S. The list of panel members and their specialties appears on page 645. The process of selecting panel members based upon specific characteristics minimizes the potential for bias in terms of specialty or geography.

The panelists received the literature review and an initial set of scenarios by mail. They were requested to study the synthesis of the literature and to rate each scenario using a scale of 1 to 9 (1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate). "Appropriateness" was defined as *the expected health benefits of the therapy exceeding its expected negative health consequences by a sufficiently wide margin to justify prescribing the therapy in an environment with constrained health care costs.*

After this task was accomplished in an independent manner, the results of the initial ratings were compiled.

Finally, the group convened for a two-day consensus

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**Table 2 Summary of Evidence for Off-Label Use of rFVIIa (NovoSeven®)<sup>10-46</sup>**

Clinical Category	Specific Clinical Condition or Setting	Total rFVIIa Recipients	rFVIIa Dose Range (mcg/kg)	No. of Studies	Evidence Grade*; No. of Recipients (Reference No.)
<i>Reversal of anticoagulant therapy</i>	Factor Xa inhibitors	28	90	2	I; 28
	Oral anticoagulants	26	10-90	5	II-3; 13(12) III; 13(13-16)
<i>Perioperative and traumatic blood loss</i>	Cardiac surgery	8	30-180	4	II-3; 5(17) III; 3(18-20)
	General surgery	2	90	2	III; 2(21,22)
	Neurosurgery	13	40-120	3	III; 13(23-25)
	Obstetrics/gynecology	7	10-120	3	III; 7(26-28)
	Trauma	33	30-180	3	III; 33(29-31)
	Urological surgery	26	20-135	3	I; 24 III; 2(32,33)
<i>Hepatic dysfunction</i>	Advanced liver disease (non-transplanted adults)	96	5-137	10	I; 65(34) II-3; 20(35,36) III; 11(37-43)
	Advanced liver disease (pre-transplanted adults)	15	40-80	3	II-3; 13(44,45) III; 2(46)

\*This scoring system indicates the quality of the evidence available in the literature. It does not signify in any way the strength of the individual recommendations. Despite the existence of high-quality scientific studies on a particular topic, such use may be not recommended because the results conflict or the data are insufficient to make a determination.

I = evidence obtained from at least one properly designed, randomized, controlled trial.  
 II-1 = evidence obtained from well-designed, controlled trials without randomization.  
 II-2 = evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.  
 II-3 = evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments may also be regarded as this type of evidence.  
 III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

meeting in Washington, DC (July 17-18, 2004). During the meeting, the panelists reviewed the summarized first-round ratings, revised the structure of the clinical scenarios, reviewed the definition of key terms, and discussed reasons for the degree of agreement or disagreement in the ratings from the first round. The panelists then independently re-rated all clinical scenarios in confidence.

The final rating was the median score of the nine panelists. We considered that clinical scenarios were "appropriate" for median ratings between 7 and 9 (without disagreement), "inappropriate" for median ratings between 1 and 3 (without disagreement), and "uncertain" for median ratings between 4 and 6 or if the panelists disagreed. The consensus method did not force agreement.

We defined "disagreement" as occurring when at least two panelists rated the scenario as "appropriate" and at least two panelists rated the scenario as "inappropriate" regardless of the median rating.

### RESULTS

#### Literature Review

The comprehensive contents of the literature summary and

evidence tables that were provided to the panel are beyond the scope of this article but are available upon request. A brief compilation of the evidence base is included in Table 2.<sup>10-46</sup> The recommendations and discussion herein pertain only to adults.

Efficacy and safety data have been reported for various off-label uses of rFVIIa, including traumatic or surgical blood loss, liver disease, and oral anticoagulant activity. Most of the available peer-reviewed, published data are from type III case reports, case series, or retrospective studies (n = 86 patients) and type II-3 noncontrolled or historically controlled studies (n = 51 patients) (see Table 2). Seven studies examined the use of rFVIIa as reversal of anticoagulant therapy, 18 trials pertained to perioperative or traumatic blood loss, and 13 related to patients with hepatic dysfunction.

When this exercise was conducted, peer-reviewed published data were available from only four randomized, controlled trials (type I evidence) that examined the efficacy of rFVIIa in three clinical settings.<sup>3,10,11,34</sup> These studies were considered to represent the highest-quality literature available and are discussed in detail here (see also Table 2). Details on lower evidence grade studies (types II-3 and III) can be obtained from the authors.

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In the first type I study, a double-blind, placebo-controlled, randomized trial, rFVIIa was administered to control perioperative bleeding in patients with normal coagulation systems undergoing retropubic prostatectomy.<sup>3</sup> In one group of eight patients, rFVIIa was administered by IV bolus at a dose of 20 mcg/kg. A second group of 16 patients received the drug at a dose of 40 mcg/kg, and a third group of 12 received placebo.

Primary outcome measures were safety (particularly potential thromboembolic, laboratory, and cardiac events) and efficacy in terms of reduction of perioperative blood loss and transfusion requirements. Administration of rFVIIa resulted in a dose-dependent significant reduction in perioperative blood loss compared with placebo.

No significant differences were reported between the two dose groups and the placebo group in the mean length of operation or hospital stay. Systemic activation of coagulation was not observed, and no other adverse events (cardiac or thromboembolic) attributable to rFVIIa were reported.

In a second type I study, rFVIIa was investigated as a means of neutralizing the anticoagulant effects of fondaparinux (Arixtra™, Organon), a synthetic pentasaccharide that selectively inhibits factor Xa (FXa).<sup>10</sup> Injection of rFVIIa after fondaparinux corrected the prolonged activated partial thromboplastin time (aPTT) and the prothrombin time (PT), compared with placebo in 16 healthy subjects. Thrombin-generation time and endogenous thrombin potential, which were inhibited by fondaparinux, were normalized after rFVIIa injection. No adverse thromboembolic, cardiac, or laboratory events related to the study drug were reported.

A third type I, randomized, controlled trial examined the ability of rFVIIa to neutralize the anticoagulant effects of idraparinux, a synthetic pentasaccharide that selectively inhibits factor Xa, in normal healthy volunteers.<sup>11</sup> Given three hours after idraparinux, rFVIIa significantly reversed the increased thrombin-generation time (TGT), the increased activated partial thromboplastin time (aPTT), and the reduced prothrombin fragment 1 + 2 levels caused by idraparinux, although no clear effect of the study drug on the endogenous thrombin potential (ETP) was observed. Similar results were achieved in subjects given rFVIIa one week after idraparinux. No adverse thromboembolic, cardiac, or laboratory events caused by

**Table 3 Consensus Recommendations for the Use of rFVIIa (NovoSeven®) Therapy**

### Closed-Space Bleeding

1. *Non-traumatic intracranial bleeding (excluding subarachnoid hemorrhage)*
  - A. < 4 hours since symptom onset
    - i) Not taking warfarin or LMWH **Appropriate**
    - ii) Taking warfarin or LMWH **Appropriate**
  - B. 4 or more hours since symptom onset
    - i) Not taking warfarin or LMWH **Inappropriate**
    - ii) Taking warfarin or LMWH **Uncertain**
2. *Isolated traumatic head injury*
  - A. No evidence of expanding bleeding
    - i) Not taking warfarin or LMWH **Inappropriate**
    - ii) Taking warfarin or LMWH **Uncertain**
  - B. Evidence of expanding bleeding
    - i) Not taking warfarin or LMWH **Uncertain**
    - ii) Taking warfarin or LMWH **Appropriate**
3. *Retroperitoneal bleeding*
  - A. Not taking warfarin or LMWH
    - i) No significant clotting factor replacement **Inappropriate**
    - ii) Attempted significant clotting factor replacement **Uncertain**
  - B. Taking warfarin or LMWH
    - i) No significant clotting factor replacement **Inappropriate**
    - ii) Attempted significant clotting factor replacement **Appropriate**

### Rescue Therapy for Surgical Patients

1. *Cardiac surgery*
  - A. No significant clotting factor replacement **Inappropriate**
  - B. Attempted significant clotting factor replacement\* **Appropriate**
2. *Aortic surgery*
  - A. Thoracic
    - i) No significant clotting factor replacement **Inappropriate**
    - ii) Attempted significant clotting factor replacement\* **Appropriate**
  - B. Abdominal
    - i) No significant clotting factor replacement **Inappropriate**
    - ii) Attempted significant clotting factor replacement\* **Uncertain**
3. *Hepatic resection or liver transplant*
  - A. No significant clotting factor replacement **Uncertain**
  - B. Attempted significant clotting factor replacement\* **Appropriate**
4. *Nontraumatic high blood loss orthopedic surgery*
  - A. Spine
    - i) No significant clotting factor replacement **Inappropriate**
    - ii) Attempted significant clotting factor replacement\* **Appropriate**
  - B. Large joint replacement
    - i) No significant clotting factor replacement: **Inappropriate**
    - ii) Attempted significant clotting factor replacement\* **Inappropriate**

### Other Uses

1. *Postpartum period and after hysterectomy*
  - A. No attempted significant clotting factor replacement **Inappropriate**
  - B. Attempted significant clotting factor replacement\* **Appropriate**

*continued*

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**Table 3 Consensus Recommendations for the Use of rFVIIa (NovoSeven®) Therapy** (continued)

2. Severe multiple trauma (Ongoing bleeding and coagulopathy despite surgical intervention and $\geq 10$ units of blood in six hours)	<b>Appropriate</b>
3. Active GI bleeding	<b>Inappropriate</b>
4. Hepatic failure with GI bleeding or pending invasive procedure A. No attempted significant clotting factor replacement B. Attempted significant clotting factor replacement*	<b>Inappropriate</b> <b>Appropriate</b>
5. Thrombocytopenia with severe bleeding refractory to conventional treatment	<b>Uncertain</b>
6. Prophylactic use before major surgery	<b>Inappropriate</b>

\* 20 ml/kg or 6 units of fresh frozen plasma or 6 units of platelets  $\times 2$  if platelet count  $< 50,000$ , or 10 bags of cryoprecipitate  $\times 2$  if fibrinogen was low or clotting factor replacement was not a feasible alternative because of time or volume constraints.

GI = gastrointestinal; LMWH = low-molecular-weight heparin.

rFVIIa were reported.

A fourth type I study was designed to evaluate the efficacy of four different doses of rFVIIa (5, 20, 80, and 120 mcg/kg) on specific laboratory and clinical hemostatic parameters in patients with liver disease prior to laparoscopic liver biopsy.<sup>34</sup> The PT was corrected to normal levels (in less than 13.1 seconds) in most patients, with a dose-dependent duration of the normalization. Hemostasis was achieved in 48 of 65 patients (74%) within 10 minutes and was maintained for 18 hours. None of the patients required operative intervention or transfusion of blood or blood products to control bleeding.

Safety was assessed by measuring hematological, biochemical, laboratory coagulation parameters, and vital signs. No adverse events occurred that were considered to be related to the study drug.

Details of a multicenter, randomized, placebo-controlled, dose-response trial of rFVIIa were provided at the panel meeting by one of the principal investigators (Dr. Diringer), also a panel member.<sup>47</sup> This trial enrolled 400 patients who had intracerebral hemorrhage, as confirmed by computed tomography. This report was subsequently published in the peer-reviewed literature, but the panel considered it in abstract form because of its clinical implications.<sup>48</sup>

The primary endpoint of the study was to limit hematoma expansion, which occurs in about 40% of patients who present within three hours of symptom onset. Patients were randomly selected to receive rFVIIa (40, 80, or 160 mcg/kg) or placebo within one hour of diagnosis. The percentage of increase in hematoma volume at 24 hours was significantly lower with rFVIIa (11%–16%) than with placebo (29%).

The secondary endpoint of death or disability also achieved statistical significance (49%–55% with rFVIIa vs. 69% with placebo;  $P = .023$ ).

Patients were monitored for the frequency of thrombotic complications at day 90. Serious thromboembolic ADEs,

mainly myocardial or cerebral infarction, occurred in 7% of the rFVIIa patients, which was slightly but not significantly higher ( $P = .12$ ) than that in the placebo patients (2%). Serious thromboembolic ADEs that were possibly or probably related to treatment and that were fatal or disabling occurred in 2% of rFVIIa-treated patients and in 2% of placebo-treated recipients.

### Consensus Findings

Of the 32 clinical scenarios pertaining to possible uses of rFVIIa, the panel rated 34% of the uses “appropriate” ( $n = 11$ ), 44% “inappropriate” ( $n = 14$ ), and 22% “uncertain” ( $n = 7$ ). According to our definition, the panel disagreed about the appropriateness of 3% of the scenarios in the final ratings, falling from 14% in the first-round ratings.

Table 3 lists the consensus recommendations pertaining to rFVIIa therapy for patients with closed-space bleeding, as rescue therapy in surgical patients, and for

other uses. Various recommendations pertain to patients who have already received significant clotting factor replacement. Patients for whom replacement was not a feasible alternative because of time or volume constraints were viewed the same as patients who had received replacement therapy.

For patients who met the criteria for appropriateness of use, the panel rated a dose of 20–40 mcg/kg as “appropriate” for nonemergent anticoagulant reversal and 41–90 mcg/kg as “appropriate” for all other off-label uses. Doses greater than 90 mcg/kg were rated “inappropriate.” Doses of 20–40 mcg/kg were rated “uncertain” (except for nonemergent anticoagulant reversal).

The panel also contemplated a series of administrative and clinical considerations pertaining to the characteristics of delivery, the patients, and their health care providers, as follows:

- rFVIIa given as a bolus infusion
- consultation with a hematologist or blood bank required
- restrictions acceptable to health care providers
- concern about pH, body temperature, and coagulation testing
- unstudied uses during pregnancy and theoretical risks to the fetus
- unstudied uses in other prothrombotic patients and theoretical risks
- the concomitant use of hemostatic agents (e.g., fresh frozen plasma) in patients receiving rFVIIa for reversing the effects of warfarin (Coumadin®, Bristol-Myers Squibb)

The panel chose not to address the use of rFVIIa in children and did not recommend distinct criteria for Jehovah’s Witnesses. In the absence of informed consent, the latter patients are not candidates for blood replacement therapies.

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### DISCUSSION

Ideally, prescribing decisions for rFVIIa should rely upon high-quality clinical evidence to balance risks, benefits, and costs. That evidence, however, is scant for clinicians at the bedside or for hospitals that bear the economic consequences of prescribing decisions. The absence of scientifically sound data is highlighted in Table 2, which summarizes 38 published studies examining the off-label use of rFVIIa in 254 adults. Only four of these studies that were available when the panel met were type I randomized, controlled trials, with healthy volunteers composing 50% of the subjects.

The type I studies available to the panel were relatively well designed and executed, compared with the majority of the published evidence that comprised anecdotal or uncontrolled series (types II and III). However, the small numbers of patients involved in the randomized trials limits extrapolation of the results to broader populations, and the clinical significance of surrogate laboratory evidence proposed to reflect the efficacy of rFVIIa has not been established.

Similarly, rFVIIa appears to be efficacious in stopping or reducing active bleeding when it is administered as an adjunct to traditional therapies (red blood cells, platelets, and cryoprecipitate) in patients with hemostatic dysfunction caused by liver disease or in surgical or traumatically injured patients with coagulation abnormalities caused by underlying physiological or iatrogenic causes. However, several caveats must be considered in this exercise:

1. The number of cases in which rFVIIa was used was relatively small, and there was substantial heterogeneity among cases in terms of their clinical condition, therapies received, outcome measures, and demographics.

2. Most of the studies were uncontrolled case reports or series. Publication bias was probably a factor in the analysis of the literature, in which papers that reported positive findings predominated.

3. Because rFVIIa was usually administered as an adjunct to other therapies, it is difficult to ascribe successful hemostasis solely to rFVIIa activity.

4. We did not attempt to perform a meta-analysis or systematic review, because the literature consisted mostly of uncontrolled reports (or series with no control subjects) that generally mentioned efficacy in a binary manner. This precludes reflecting efficacy in terms of differences between groups or in confidence intervals.

5. Except for the type I studies, investigators generally did not predetermine criteria for analyzing the safety of rFVIIa. They often reported only the absence of ADEs or their occurrence in relation to administration of the study drug, with thromboembolic ADEs of most theoretical concern.

Consequently, most of the time, these findings are reported in qualitative terms based on the literature, buttressed by the knowledge and experience of the expert panelists. This conclusion is supported by a recent systematic review of the off-label use of rFVIIa to treat severe bleeding, which suggests that thromboembolism has occurred in 1.4% of all cases reported. The review further notes that safety data from placebo-controlled studies are scarce.<sup>49</sup>

Although the risk of thromboembolism should be considered before one prescribes off-label rFVIIa, this might not be a rigid contraindication. The product label warns that patients with disseminated intravascular coagulation, advanced atherosclerotic disease, crush injury, or septicemia may be at an increased risk for thrombotic events because of circulating tissue factor or predisposing coagulopathy. Patients who receive the agent should be monitored if they develop signs or symptoms of activation of the coagulation system or thrombosis. Treatment should be stopped, or the dosage should be reduced.

In the absence of definitive evidence and in an effort to provide guidance to providers, the SABM and UHC undertook the collaborative development of consensus recommendations for the off-label use of rFVIIa. A multidisciplinary group of clinicians reviewed the available scientific literature and used the Rand/UCLA Appropriateness Method to evaluate the appropriateness of rFVIIa therapy in 32 separate clinical situations (see Table 3). The panel did not consider pediatric settings, as fewer data are available, and it did not specifically evaluate platelet disorders and other hematological indications except for anticoagulant reversal. This approach provides quantitative ratings of "appropriateness" that compare efficacy and safety for the settings under consideration in an environment with constrained health care costs.

The panel evaluated the use of rFVIIa in surgical, obstetrical, and trauma patients. In the literature review, only one study had a prospective, randomized, controlled design, which pertained to the prophylactic use of rFVIIa in patients undergoing retropubic prostatectomy.<sup>3</sup> No randomized, controlled trials examined the efficacy of this agent in patients already experiencing bleeding.

On the basis of their review of the class II and III evidence and clinical experience, the panel rated the use of rFVIIa "appropriate" as rescue therapy in patients with active intraoperative or perioperative bleeding associated with cardiac, thoracic aortic, spinal surgery; hepatic resection; or liver transplantation—but only after a significant attempt at clotting factor replacement, defined as follows:

- *For thrombocytopenic patients:* 20 ml/kg or 6 units fresh frozen plasma or 6 units of platelets [ $\times 2$ ]  
or
- *For hypofibrinogenemic patients:* 10 bags of cryoprecipitate [ $\times 2$ ]

In the absence of a clotting factor replacement attempt, the panel rated the use of rFVIIa as "inappropriate" in these bleeding surgical patients.

The panel viewed the agent as "appropriate" to use in bleeding postpartum or post-hysterectomy patients or patients with severe, multiple trauma in a similar fashion if routine care had failed (i.e., significant clotting factor replacement in the gynecological patient or ongoing bleeding and coagulopathy despite surgical intervention and 10 units or more of blood transfused in six hours in the trauma patient); otherwise, it was considered "inappropriate." Because of the expectation of less blood loss, the panel rated rFVIIa as "inappropriate" in patients undergoing large-joint replacement despite a trial of clotting

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**Table 4 Summary of Published Evidence for Off-label Use of rFVIIa (NovoSeven®) from May 31, 2004, through May 31, 2005<sup>52-80</sup>**

Reference (Year)	Evidence Grade*	Specific Clinical Condition or Setting	Total rFVIIa Recipients	rFVIIa Dose Range (mcg/kg)	Consistent with recommendations?	Comment
50 (2004)	I	Hepatic failure with GI bleeding or pending invasive procedure	121	100 (eight doses)	Yes	Dose higher than recommended (41–90 mg/kg)
51 (2005)	I	Prophylactic use before major surgery (partial hepatectomy)	132	20 or 80	Yes	Dose within recommended range
48 (2005)	I	Nontraumatic intracranial bleeding (excluding subarachnoid hemorrhage)	303	40, 80, or 160	Yes	Two lower doses within recommended range
52 (2005)	I	Prophylactic use before major surgery (orthopedic)	24	90	Yes	Dose within recommended range
53 (2004)	II-3	Life-threatening bleeding secondary to aneurysm, trauma, abdominal surgery	13	90–120	Yes	Rescue therapy
54 (2004)	III	Cardiac surgery	40	90	Yes	Rescue therapy
55 (2004)	III	Life-threatening bleeding secondary to aneurysm, pancreatitis, trauma, abdominal surgery	10	90 (repeated every 2 hours if bleeding continued and there was an initial response)	Yes	Rescue therapy, but value is uncertain
56 (2004)	III	Hepatic failure with GI bleeding or pending invasive procedure	1	90	Yes	Dose within recommended range
57 (2004)	III	Cardiac surgery	1	90	Yes	Rescue therapy
58 (2004)	III	Cardiac surgery	1	90	Yes	Rescue therapy
59 (2004)	III	Nontraumatic intracranial bleeding (excluding subarachnoid hemorrhage)	7	15–90	Yes	Therapy for warfarin-related acute intracranial hemorrhage
60 (2004)	III	High blood loss in orthopedic surgery	4	16–117	Yes	Rescue therapy
61 (2004)	III	Cardiac surgery	1	70	Yes	Rescue therapy
62 (2004)	III	Active gastrointestinal bleeding	1	4.8 mg	Yes	Post-endoscopic sphincterotomy
63 (2004)	III	Nontraumatic high blood loss in orthopedic surgery	1	90	Yes	Surgical adjunct to fresh frozen plasma and vitamin K
64 (2004)	III	Cardiac surgery	7	90	Yes	Rescue therapy
65 (2005)	III	Postpartum period and after hysterectomy	12	44–120	Yes	Rescue therapy
66 (2005)	III	Cardiac and abdominal surgery; trauma	5	80–120	Yes	Rescue therapy with one patient receiving higher than recommended dose
67 (2005)	III	Life-threatening bleeding secondary to cardiac, general, orthopedic, vascular surgery; trauma	13	75–90	Yes	Rescue therapy

*continued*

## Recommended Uses of Off-Label NovoSeven® Therapy

**Table 4 Summary of Published Evidence for Off-label Use of rFVIIa (NovoSeven®) from May 31, 2004, through May 31, 2005<sup>52-80</sup> (continued)**

Reference (Year)	Evidence Grade*	Specific Clinical Condition or Setting	Total rFVIIa Recipients	rFVIIa Dose Range (mcg/kg)	Consistent with recommendations?	Comment
68 (2005)	III	Hepatic resection or liver transplant	4	90	Yes	Thrombotic events in two patients may have been associated with rFVIIa treatment
69 (2004)	I	Reversal of oral anticoagulants	20	90	No	Unapproved oral anticoagulant
70 (2005)	III	Abdominal surgery	1	60	No	Used as prophylactic therapy because platelets were unavailable
71 (2004)	II-3	Life-threatening bleeding secondary to dengue shock syndrome	15	Not relevant	Not relevant	Pediatric patients
72 (2004)	III	Neurosurgery	8	Not relevant	Not relevant	Pediatric patients
73 (2004)	III	Severe multiple trauma	3	Not relevant	Not relevant	Isolated FVII deficiency
74 (2004)	III	Factor VII deficiency	2	Not relevant	Not relevant	Bleeding in pregnant women with coagulation disorders
75 (2004)	III	Refractoriness to platelet transfusion	59	Not relevant	Not relevant	International survey of Glanzmann's thrombasthenia patients
76 (2004)	III	Hemorrhagic disseminated intravascular coagulation associated with cancer	18	Not relevant	Not relevant	Rescue therapy in patients with underlying advanced or metastatic tumors
77 (2004)	III	Nontraumatic intracranial bleeding (excluding subarachnoid hemorrhage)	1	Not relevant	Not relevant	Pediatric patient with echovirus type 7 and multiple underlying conditions
78 (2004)	III	Cardiac surgery	9	Not relevant	Not relevant	Pediatric patients
79 (2004)	III	Abdominal surgery	1	Not relevant	Not relevant	Glanzmann's thrombasthenia patient

\*This scoring system indicates the quality of the evidence available in the literature. It does not signify in any way the strength of the individual recommendations. Despite the existence of high-quality scientific studies on a particular topic, such use may be not recommended because the results conflict or the data are insufficient to make a determination.

I = evidence obtained from at least one properly designed, randomized, controlled trial.

II-1 = evidence obtained from well-designed, controlled trials without randomization.

II-2 = evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 = evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments may also be regarded as this type of evidence.

III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

factor replacement.

(A rating of "appropriate" does not imply that the action is mandatory, merely that the potential benefits outweigh the potential harms in an environment of constrained health care costs and that it is an acceptable approach to care.)

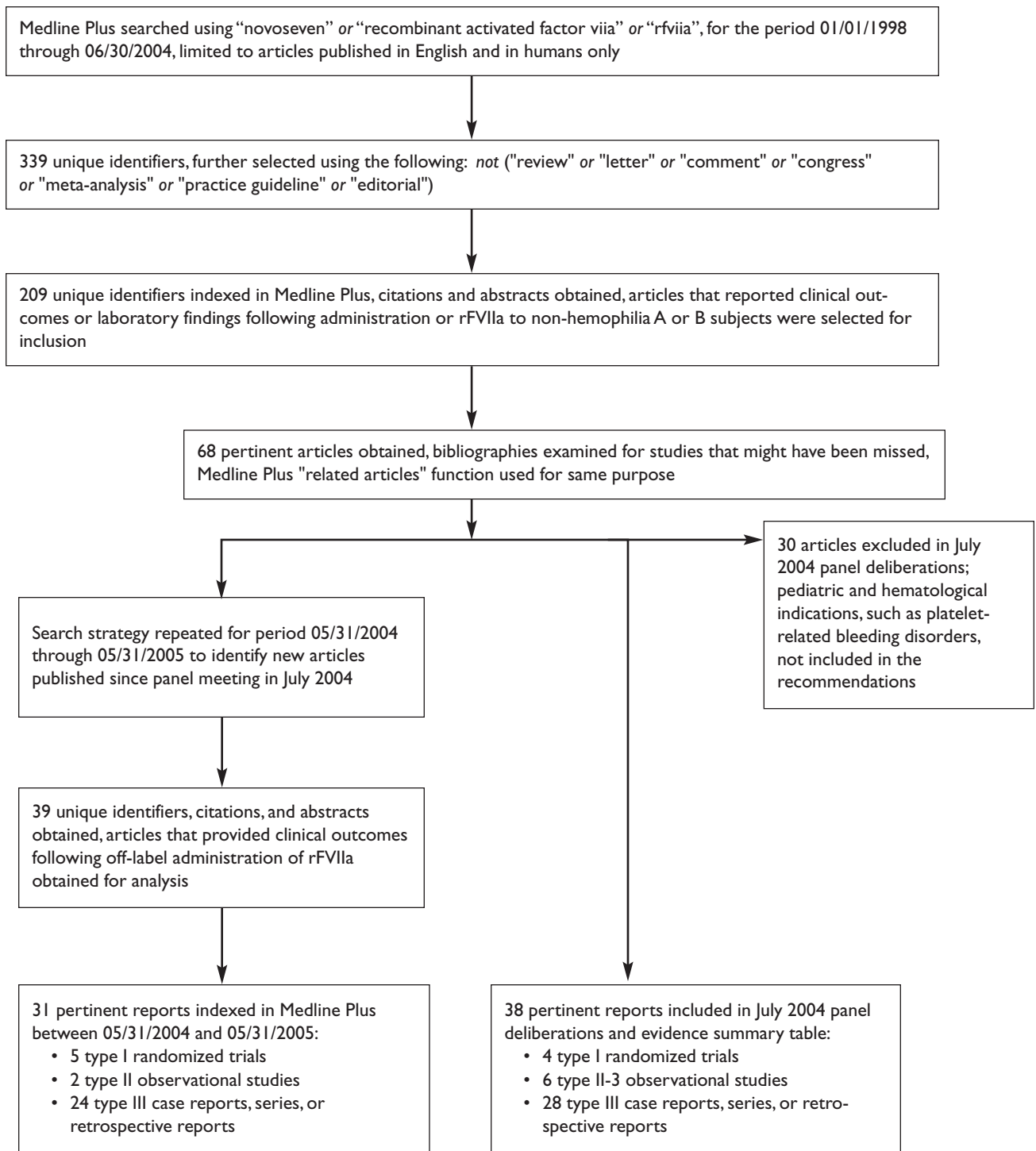
The panel considered the *prophylactic* use of rFVIIa in patients undergoing surgery. Despite the positive evidence for prophylactic use cited earlier in patients undergoing retro-

public prostatectomy,<sup>3</sup> the panel rated it "inappropriate" as a general approach to minimize surgical bleeding unless the patient had hepatic failure. Prophylactic use in hepatic failure was supported by one multicenter, randomized trial.<sup>34</sup>

Patients who present with intracranial bleeding face substantial risks of near-term mortality and long-term disability. Bleeding may occur in patients with normal coagulation parameters as well as in patients receiving warfarin or

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### Appendix I Literature Search Strategy and Results for the Off-Label Use of Recombinant Activated Factor VIIa (NovoSeven®)



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low-molecular-weight heparin (LMWH).

Two randomized, controlled trials in normal volunteers showed that rFVIIa could quickly and effectively reverse the coagulation deficit associated with either idraparinux or fondaparinux.<sup>10,11</sup> rFVIIa may be advantageous as a reversal agent if large doses of plasma severely compromise patients with left ventricular dysfunction and congestive heart failure.

In a study that was unpublished when the panel was convened, patients who presented with intracranial bleeding within four hours of symptom onset showed a statistically significant reduction in hematoma size with various doses of rFVIIa and a statistically significantly improved combined endpoint of mortality and disability compared with those who received placebo.<sup>47</sup> Although these data were unpublished at that time, the panel considered this evidence, along with the lack of good alternative therapy, and rated the use of rFVIIa as “appropriate” in patients within four hours of symptom onset (whether the bleeding occurred with or without warfarin or LMWH).

For patients who experienced bleeding after four hours from the onset of symptoms, the panel rated the use of rFVIIa “inappropriate” or “uncertain” if the bleeding occurred during warfarin or LMWH therapy.

In patients with isolated traumatic head injury, rFVIIa was rated “appropriate” only if patients had evidence of an expanding bleeding episode associated with warfarin or LMWH. These data have since been published in the peer-reviewed literature.<sup>48</sup>

After identifying appropriate candidates for rFVIIa treatment, clinicians must determine the correct dose.<sup>1</sup> The dose selected has a direct impact on the cost of therapy and may also influence the likelihood of thrombosis. For most uses, the panel recommended that the dose be between 41 and 90 mcg/kg and that rFVIIa be given as a bolus infusion. Doses above 90 mcg/kg were rated “inappropriate.” For patients requiring nonemergent anticoagulant reversal, lower doses (20–40 mcg/kg) were rated “appropriate.”

The panel raised concerns about the use of rFVIIa for pregnant women or for patients with prothrombotic states, because theoretical risks exist and inadequate studies have been performed to provide specific guidance. The panel also identified other rFVIIa evidence gaps related to its efficacy in patients with acidosis (low pH) or in those with low body temperature.

From an administrative standpoint, the panel rated it “appropriate” for a hospital to restrict physicians who are able to prescribe rFVIIa or who require a transfusion medicine or hematological consultation (see earlier).<sup>50</sup> The panel also addressed the tendency to use the drug in situations of clinical futility but made no clear recommendations.

The challenges related to the use of rFVIIa are not unique, especially the need to balance the severity of the clinical presentation with the potential benefits of a therapy associated with uncertain efficacy and high cost. Many randomized trials of thrombolysis for patients presenting with cardiac ischemia were required before the panel members agreed about which patients would benefit from the drug.<sup>51</sup> Moreover, even after multiple supportive trials, more than a decade elapsed before textbooks supported thrombolytic therapy.<sup>51</sup>

rFVIIa has an added complication. Although its efficacy remains uncertain, the apparently safe drug profile may encourage broader off-label use. If costs were not a concern, the magnitude of this dilemma would be much smaller.

Since the July 2004 panel meeting, we again searched the biomedical literature in June 2005 to ascertain the extent of new data (see Appendix 1). We were especially interested in determining whether or not newly published data were consistent with the panel’s recommendations. This exercise identified 31 new publications on rFVIIa that mention five type I randomized, clinical trials (including that of Mayer and colleagues<sup>47</sup>), two type II studies, and 24 type III reports. These are listed in Table 4<sup>52–80</sup> and are aligned as closely as possible with the clinical categories considered by the panel. The findings of 20 reports were deemed “consistent” with the panel recommendations, nine were considered “not relevant” because of the settings, and two were rated as “inconsistent.”

Taken together, with the possible exception of one study,<sup>70</sup> the clinical findings from the type I studies that were published subsequent to our expert panel’s deliberations in July 2004 are consistent with the recommendations that were developed at that time for the specific uses under consideration. Similarly, results from the pertinent type II and III studies that became available are either generally consistent with our recommendations or not relevant because they involved children or other settings not considered by the panel.

This exercise highlights one of the main weaknesses of this type of process: it is time-sensitive, and results can change as new studies are published. Thus, it is important that physicians and institutional decision-makers remain apprised of advances in medicine that may have an impact on published guidelines and that they try to place them in the proper context. This will help to ensure that patients receive the most appropriate and safest care based on the most current medical evidence.

### CONCLUSION

No methodology can divine the results of future randomized, controlled trials. In the absence of definitive data, however, clinicians need to make decisions about patient care on a daily basis, and hospitals have economic implications associated with them. Off-label uses of rFVIIa continue to increase despite the lack of definitive, controlled trials. Until this clinical evidence becomes available, we believe that consensus ratings of appropriateness can assist those faced with challenging treatment choices. The “model” consensus recommendations for rFVIIa, developed by the SABM/UHC expert panel, might be able to serve as a starting point for hospitals as they deliberate and determine their own approach to this high-impact pharmaceutical intervention.

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