



# Effective Health Care Program

## Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care

### Executive Summary

#### Background

This report evaluates the level of evidence currently available to support the effectiveness and safety of using recombinant activated coagulation factor VII (rFVIIa) for clinical indications not approved by the U. S. Food and Drug Administration (FDA). rFVIIa is approved for a variety of uses in hemophilia patients who have developed antibody inhibitors that compromise the use of standard factor replacement. Use of this costly biologic product has expanded beyond these hemophilia-related indications to encompass a range of off-label uses, most of which are in-hospital uses. These uses differ substantially from the drug's FDA approved label. The purpose of this report is two-fold: (1) To document the full range of clinical indications for which rFVIIa is being used and the types of studies available to evaluate these uses and (2) To provide a comparative effectiveness review of rFVIIa vs. usual care for several in-hospital clinical indications: intracranial hemorrhage, massive bleeding secondary to trauma, and the selected surgical procedures of cardiac surgery, liver transplantation, and prostatectomy.

#### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).



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*Off-label drug use* refers to any use of a medication that deviates from the product labeling approved and required by the FDA. The FDA drug approval process mandates randomized clinical trials that demonstrate efficacy and safety for specific indications prior to marketing. Once approval is given, however, the FDA does not regulate whether drugs are prescribed for off-label indications. In most instances, the data supporting off-label drug use falls short of the rigor that accompanies FDA review. This uncertainty may be acceptable, as when a drug's use is infrequent. Nevertheless, concerns increase when off-label use is clinically distinct from approved indications, when off-label use becomes frequent, when a drug is costly, or when a drug is used in different clinical settings (e.g., shifts from outpatient to in-hospital use).

rFVIIa is a form of human factor VII produced by recombinant technology. This intravenously delivered product works as a potent procoagulant by effectively bypassing parts of the clotting process normally required for clotting. It can facilitate control of bleeding in situations where standard human blood product transfusions have failed. Novoseven® is the only form of rFVIIa available commercially. Developed in the late 1980s, rFVIIa was approved by the FDA in 1999 for use in patients with Hemophilia A and Hemophilia B with antibody inhibitors that lead to unresponsiveness to factor VIII or factor IX, respectively. Both of these X-linked genetic conditions are rare, and most hemophilia patients never require rFVIIa for treatment of bleeding episodes. While the hemophilia population has remained stable over the past decade, in-hospital, off-label use of rFVIIa has increased.

## Key Questions

The purpose of this report is to define current patterns of in-hospital, off-label rFVIIa use through the analysis of U.S. hospital practice patterns of its administration and to conduct an effectiveness review of five selected off-label indications for rFVIIa use. Our goal is to answer the following Key Questions:

### Key Question 1. Current patterns of rFVIIa Use:

Note that this focus on “patterns of use” is directed at in-hospital populations (for whom off-label rFVIIa is more prominent):

- Which clinical populations are receiving off-label rFVIIa and which populations have been scientifically examined?
- What are the characteristics of comparative studies evaluating off-label rFVIIa use?

### Key Question 2. Use of rFVIIa for selected indications in patient with/undergoing intracranial hemorrhage

### Key Question 3. Use of rFVIIa for selected indications in patient with/undergoing massive bleeding from trauma

### Key Question 4a. Use of rFVIIa for selected indications in patient with/undergoing liver transplantation

### Key Question 4b. Use of rFVIIa for selected indications in patient with/undergoing cardiac surgery

### Key Question 4c. Use of rFVIIa for selected indications in patient with/undergoing prostatectomy

**Key Questions 2-4.** For each of these clinical areas we will answer the following questions:

- Does the use of rFVIIa reduce mortality and disability compared to usual care?
- Are there patient subpopulations more likely to benefit from rFVIIa use?
- Does rFVIIa use increase thrombosis-related events?
- Are there patient subpopulations where harms are more likely?
- Which patient subpopulations experience net benefits of rFVIIa and does this vary by timing and dosage?

## Methods

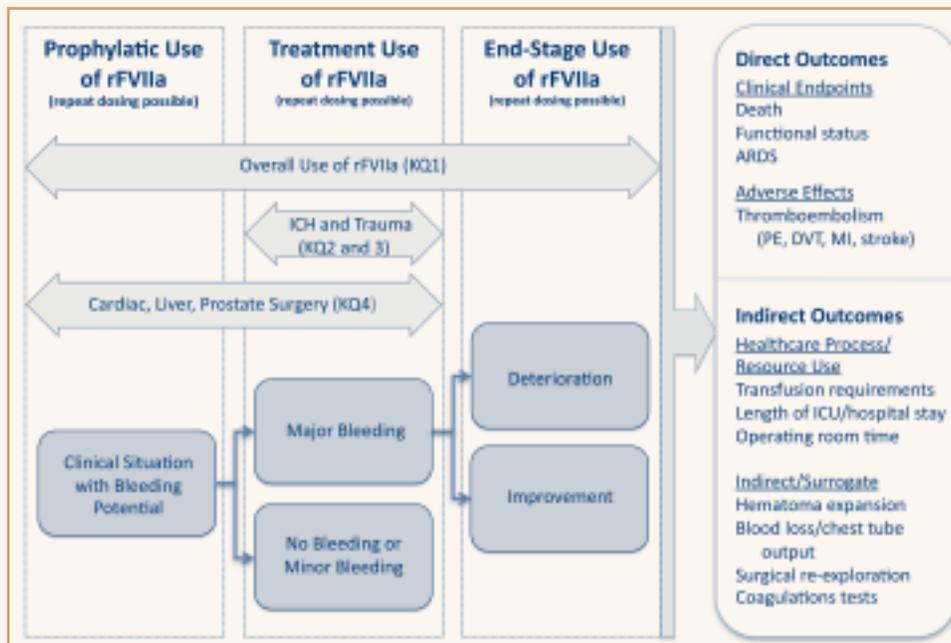
### Framework for Analyzing Outcomes for rFVIIa Use

Our analytic framework for evaluating the off-label use of rFVIIa is shown in Figure A, which represents the trajectory of a patient who receives off-label rFVIIa at some point during in-hospital medical care. Possible

times for drug administration include prophylactic, treatment, and end-stage use. The thick horizontal arrows represent the overlap between the Key Questions (KQs) addressed by this report and the different types of rFVIIa use described above. The potential outcomes examined in this report are shown on the right side of the figure. These cover a range, from indirect outcomes (process/resource use and intermediate/surrogate

outcomes) to direct clinical endpoints (e.g., functional outcome, adverse events, or death). Ideally, this report would focus primarily on the direct clinical outcomes for each of the key questions, but this is not always possible given that the studies and other data sources may only report indirect outcome measures or may only have a few events of this type.

**Figure A. Framework for analyzing outcomes for rFVIIa use**



### Premier Database Analysis to Assess In-Hospital Use of rFVIIa

#### Data Source

We used 2000 through 2008 data from the Perspective Comparative Database of Premier, Inc., in Charlotte, NC. The Premier database includes information on 40 million annual hospitalizations occurring in 615 U.S. hospitals. These hospitals are nationally representative based on bed size, geographic location, designation (urban vs. rural), and teaching status (academic vs. nonacademic). The Premier database provides detailed information on the demographics, diagnoses, and resource utilization of de-identified hospitalized patients. Each hospitalization has an associated statistical weight that allows projection to national levels of in-hospital use.

#### Data Measures and Unit of Analysis

We classified hospitalizations where rFVIIa use was reported into discrete, mutually exclusive indication categories based on the clinical information associated with each hospitalization. We constructed a descending hierarchy of ICD-9 codes to categorize each hospitalization. This hierarchy started with the FDA-approved indications of Hemophilia A and B, followed by those unapproved indications that are similar to hemophilia. In turn, hospitalizations not yet classified were categorized as brain trauma (if any diagnosis indicated a noniatrogenic cause of brain trauma), body trauma, intracranial hemorrhage, brain surgery, cardiovascular surgery (divided into adults and pediatric populations), obstetrics, aortic aneurysm, prostate surgery, other vascular surgical procedures, liver transplantation, liver biopsy, variceal bleeding, other

liver disease-related bleeding, other gastrointestinal bleeding, other hematologic conditions, pulmonary conditions, cancer-associated use, all other surgical procedures, and, finally, other diagnoses not involving surgery.

The unit of analysis was any hospital “case” of rFVIIa use—defined as any application during a patient hospitalization. We favored this case-based unit of analysis because it captures the medical decisionmaking component of care about whether to use or not use rFVIIa for a given patient. Alternative methods of analyzing rFVIIa use by dosing were also considered, including the number of times rFVIIa was dispensed by the inpatient pharmacy and the total volume of rFVIIa dispensed. But we determined that these strategies of examining dosing had significant disadvantages, including: (1) possible discrepancies between dispensed rFVII and the amount actually administered to the patient, (2) lack of consistent hospital coding of rFVIIa dispensing (e.g., missing or variable reporting of units [such as milligrams dispensed vs. vials dispensed]), and (3) outlier cases. Examination of the dosing information on outlier cases indicated substantial variation in the dose of rFVIIa dispensed during individual hospitalizations. Some cases received a fraction of a 1.2 mg vial while others received more than 100 vials. Individual cases with very large aggregate dosages were not limited only to hemophilia patients. Analyses by dosing, rather than cases of use, could have different findings. The Premier database does not provide information on patients with similar clinical indications for rFVIIa use but for whom the drug was not given, so that we were unable to determine the overall denominator of potential rFVIIa usage (i.e., total number of patients eligible for use) by specific clinical indication.

### **Statistical Analysis**

The goals of our statistical analysis of the Premier database were: (1) to provide an overview of trends and range of clinical conditions in which in-hospital, off-label rFVIIa is used, (2) to examine the clinical and demographic characteristics of cases, and (3) to evaluate the relevance of the indications selected for in-depth effectiveness review to actual in-hospital use of off-label rFVIIa.

## **Systematic Review of Off-label rFVIIa Use**

### **Data Sources and Criteria for Included Studies**

We searched the following databases: PubMed, EMBASE, Cochrane Database of Systematic Reviews, ACP Journal Club, D.A.R.E., CCTR, CMR, HTA, NHS EED, and BIOSIS. In addition, we searched the “grey literature” (sources other than published materials) and contacted the authors of abstracts regarding subsequent full publications. Finally, we reviewed files supplied by the manufacturer of rFVIIa (Novo Nordisk), searched the bibliographies of identified meta-analyses and systematic reviews, and contacted experts in the field to uncover studies not already identified by our searches.

We excluded studies of: (1) human (rather than recombinant) factor VIIa and of modified forms of rFVIIa still under development, (2) rFVIIa use in hemophilia A or B and congenital factor VII deficiency, which are the FDA-approved indications, and (3) rFVIIa applied to populations of patients that are substantially similar to those for whom on-label indications have been approved (e.g., Hemophilia C [factor XI deficiency] and Glanzmann’s thrombasthenia). We also excluded studies performed on humans but in which the outcome measures were not clinically relevant to efficacy or effectiveness (e.g., studies of drug half-life) and studies published only in abstract form. At least two authors independently abstracted data onto pretested abstraction forms. Conflicts regarding data abstraction were resolved by re-review, discussion, and input from others, as necessary.

### **Types of Evidence**

Our systematic review of existing research involves three components: (a) analysis of the research available on the spectrum of rFVIIa off-label use (Key Question 1), (b) analysis of the effectiveness of rFVIIa for the five AHRQ-selected indications (in Key Questions 2-4), and (c) analysis of the potential harms for the five indications (in Key Questions 2-4). For these components, we made use of different categories of studies classified by study design and quality:

- Randomized controlled trials (RCTs) on the five selected indications of intracranial hemorrhage, massive bleeding secondary to trauma, cardiac surgery, liver transplantation, and prostatectomy were used in our analyses of comparative

effectiveness (Key Questions 2-4), as well as in the survey of existing research and the analysis of potential harms. RCTs on the other indications were included in our survey of existing research (Key Question 1).

- Comparative observational studies on Key Questions 2-4 that were graded as either *fair* or *good* quality (see Assessment of Quality) were also reviewed in detail in our analyses of comparative effectiveness, as well as in the survey of existing research and harms analysis. Studies on other indications were included in our survey of existing research.
- Comparative observational studies on Key Questions 2-4 graded as *poor* quality were not reviewed in detail in our comparative effectiveness analyses but were used for qualitative sensitivity testing and the harms analysis. Studies on other indications were included in our survey of existing research.
- Noncomparative observational studies on Key Questions 2-4 were included in the harms analysis if these studies were registry studies or these studies included 15 or more patients.
- Noncomparative observational studies that were not registries or contained fewer than 15 patients were not included in our analysis.

### Assessment of Quality

We used nine predefined criteria to assess the quality of included studies identified by performing a review of the literature and the AHRQ Effective Health Care Program's Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide, available at: [http://effectivehealthcare.ahrq.gov/repFiles/2007\\_10DraftMethodsGuide.pdf](http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf)). Most of the criteria (six of the nine) applied to both RCTs and observational studies types (e.g., subject selection, comparability of groups, protections against bias in outcomes). But three criteria were unique to either RCTs (methods of allocation) or observational studies (sample size and methods to characterize exposure). A study's quality was not downgraded because of an identified conflict of interest. Using these criteria, two independent assessors assigned a quality grade of *good*, *fair*, or *poor* to each study.

Disagreements were resolved by discussion, with accommodation made for involvement of a third reviewer, if necessary, but this was never required.

### Strength of Evidence and Applicability

We applied the strength-of-evidence rating system developed and published by the Evidence-based Practice Center (EPC) workgroup on grading strength of evidence. Two reviewers independently assessed the strength of evidence for the major outcomes in each of the Key Questions 2-4. First, they assigned individual scores to each of the four evidence domains: risk of bias, consistency, directness, and precision. Based on these scores, they then assigned an overall "strength-of-evidence rating" to each clinical outcome. The two reviewers also independently evaluated the applicability to real-world practice of the total body of evidence within a given clinical indication (Key Questions 2-4) using the PICOTS framework (population, intervention, comparator, outcome, timing, and setting). Disagreements were resolved by discussion, with accommodation made for involvement of a third reviewer (an expert on strength of evidence grading), if necessary and this was required in only one case regarding a strength-of-evidence assessment.

### Analysis of Comparative Studies

When there were sufficient studies to warrant meta-analytic evaluation, we performed these analyses. Although most of the research synthesis literature analyzes effect sizes from independent studies in which there is a single treatment group vs. a control group, many of the included studies available on rFVIIa had multiple intervention arms for different doses of rFVIIa compared with a single control arm. As necessary, we used a meta-analytic methodology developed specifically for this type of study design. Intervention and control arms were compared for continuous variables (e.g., hematoma volume for intracerebral hemorrhage [ICH] patients) using a random effects model for standardized mean difference effect size. Dichotomous outcomes (e.g., mortality and thromboembolic events) were compared using a random effects model with two different effect size metrics, the risk difference and the arcsine standardized mean difference, which provided a sensitivity analysis for the use of different metrics. The former, the risk difference, was chosen as a measure of effect size for

the report because it is easy to interpret and the risks for different outcomes were similar across studies, such that the disadvantages of using the risk difference approach to estimate effect size (e.g., as compared to other common metrics such as the odds ratio) were minimized. The arcsine metric is a less well-known approach but has the advantage of generating less-biased estimates of the difference between treatment and control arms when there are sparse data or multiple outcomes with zero observations (e.g., zero deaths) for proportions and dichotomous responses. We performed formal assessments of heterogeneity using the  $Q$  statistic for heterogeneity (and  $I^2$  statistic, as appropriate).

### Analysis of Noncomparative Studies for Data on Harm

To evaluate evidence of harm from rFVIIa in noncomparative studies, we described the unadjusted summary event rates for mortality and thromboembolic events from the noncomparative studies, as well as event rates from the intervention arms of the comparative studies.

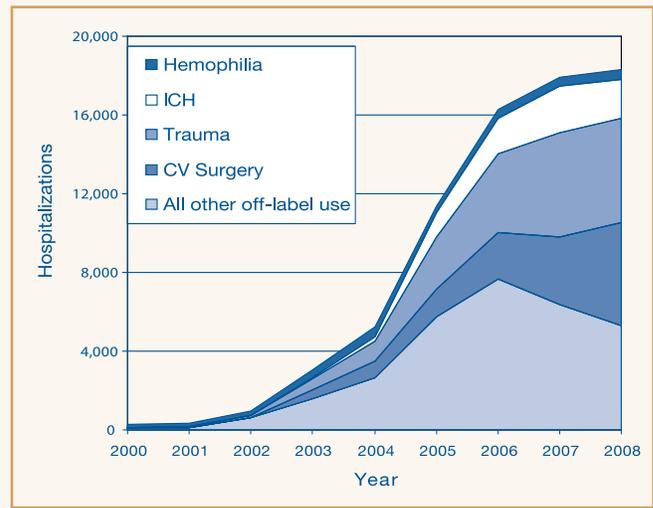
## Results

Our searches identified 5,668 potentially relevant articles of which 74 studies met our inclusion criteria: 24 were RCTs, 31 were comparative observational studies, and 19 were noncomparative reports from registries or cohorts. Overall, these studies were of *fair* quality and had small sample sizes insufficient to evaluate mortality differences. There was substantial variation in the dose and timing of rFVIIa provided making it difficult to assess the importance of the dosing or the timing of drug administration. It also was difficult to identify patient subpopulations that were more likely to experience benefits or harms from rFVIIa use.

### Key Question 1. Indications and populations for which off-label rFVIIa has been used in-hospital

We did not evaluate outpatient rFVIIa use. The majority of use of rFVIIa occurs in the outpatient setting, and the majority of outpatient use is for on-label indications related to hemophilia. According to the Premier database on in-hospital use in the United States, cases of use for the approved hemophilia indications

**Figure B. Growth of in-hospital, off-label vs. on-label use of rFVIIa in the Premier database, 2000-2008**



remained stable over time, whereas cases of in-hospital, off-label use increased. In-hospital, off-label rFVIIa use, estimated to be 125 cases in 2000, underwent a moderate increase until 2005 when use became more frequent and was estimated to be 11,057 cases. By 2008 its use was estimated to be 17,813 cases (97 percent of all of the estimated 18,311 in-hospital cases) (see Figure B). The rate of increase may be plateauing for many indications (Figure B). Use was reported in 235 of the 615 hospitals (38 percent) represented in the Premier database. Most of these hospitals had minimal and sporadic use of rFVIIa, while the highest volume hospitals accounted for 46 percent of all use. In 2008, cardiac surgery (adult and pediatric combined) and trauma (body and brain combined) were the leading indications (29 percent for both), followed by intracranial hemorrhage (11 percent) (Figure B). Cardiac surgery demonstrated more rapid and sustained growth and broader hospital diffusion than other indications. Other off-label uses in 2008 included gastrointestinal bleeding (4 percent), primary clotting disorders (4 percent), secondary clotting disorders (4 percent), and aortic aneurysm and other vascular procedures (4 percent). There was very limited use in liver transplantation (0.3 percent) and prostatectomy (0.0 percent). rFVIIa is used in patients who experience substantial in-hospital mortality (27 percent). This report's subsequent focus on intracranial hemorrhage, trauma, and cardiac surgery is justified by the prevalence of these uses.

### Key Question 1. Indications, populations, and characteristics of comparative studies of off-label rFVIIa use

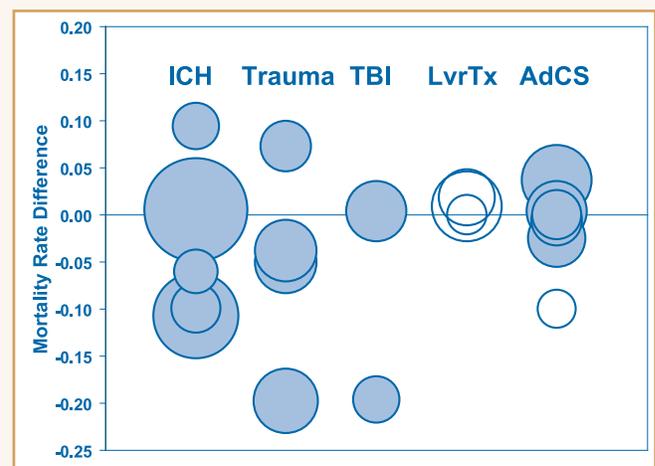
There were 24 randomized clinical trials and 31 comparative observational studies available on rFVIIa use across a variety of clinical indications. rFVIIa use in cardiac surgery (12 studies), trauma (9 studies), intracranial hemorrhage (ICH) (8 studies), liver transplantation (8 studies), and other liver disease (5 studies) accounted for 57 percent of the 74 included studies. In relationship to patterns of use, comparative studies were especially lacking for primary clotting disorders (other than hemophilia), and secondary clotting disorders and gastrointestinal bleeding outside of liver disease. In contrast, studies were available for indications (prostatectomy and liver transplantation) where rFVIIa is not used frequently in the community. Many studies examined only prophylactic use of rFVIIa for clinical indications where treatment or end-stage use may also be frequent. Patients included in the comparative studies were generally younger and had lower clinical acuity in comparison to cases in the Premier database. With the exception of use in ICH, study sample sizes were small (median of 24 treated patients). The doses used in the studies that are the focus of this effectiveness review varied from 5 to 956 mcg/kg of patient weight, and only for intracranial hemorrhage was there a sufficient range of doses to assess the impact of rFVIIa dosing on outcomes. Most studies used indirect endpoints as their primary outcomes, particularly red blood cell (RBC) transfusion requirements. Direct outcomes, such as mortality, functional status, or thromboembolic events, were frequently reported, but most studies were individually underpowered to evaluate them. Most clinical research on rFVIIa has been directed and sponsored by Novo Nordisk, the product's manufacturer. The strength of evidence available from existing studies was thereby compromised by small study size, use of indirect outcomes, and heterogeneity in dosage and indication. The applicability was diminished by less acutely ill patients and a mismatch between existing research and real-world patterns of indication and types of use.

### Key Question 2. Intracranial hemorrhage

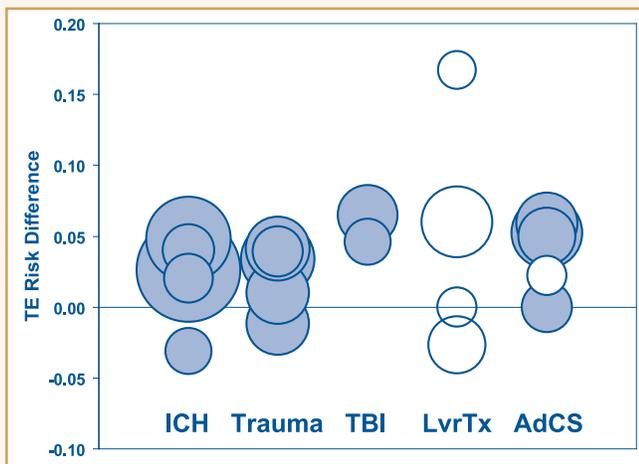
For intracranial hemorrhage, because there were indications in the literature regarding a possible dose–response relationship between rFVIIa and certain outcomes (e.g., thromboembolic events) and multiple doses of rFVIIa were analyzed in each RCT, we chose a priori to analyze the data according to low-, medium-, and high-dose rFVIIa groups, defined as less than or equal to 40 µg/kg, greater than 40 but less 120 µg/kg, and at least 120 µg/kg, respectively. There were four RCTs (two *good* quality, two *fair* quality) and one small comparative observational studies (*fair* quality) that assessed 968 patients who received rFVIIa. The RCTs evaluated patients who were not on oral anticoagulation therapy (OAT) and had intracerebral hemorrhage (ICH), whereas the observational study examined patients on OAT who could have experienced ICH or other forms of intracranial hemorrhage (e.g., subdural bleeding). These studies yielded moderate strength of evidence with good applicability for treatment use in the population targeted by the RCTs—patients with intracerebral hemorrhage who were not on anticoagulation therapy.

In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include:

**Figure C. Mortality differences (rFVIIa minus usual care)**



**Figure D. Thromboembolic event risk differences (rFVIIa minus usual care)**



- There was no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 (95 percent CI -0.086 to 0.024), medium-dose group: 0.020 (95 percent CI -0.076 to 0.036), high-dose group: 0.027 (95 percent CI -0.121 to 0.068); *p* value of the *Q* statistic for all risk differences is 0.248) (also see Figure C: each circle represents a study; larger circles correspond to larger studies; shaded circles represent studies on treatment use of rFVIIa, and white circles represent studies on prophylactic use of rFVIIa). rFVIIa use also did not reduce the rate of poor functional outcome as measured on the modified Rankin Scale (risk difference: low-dose group: 0.024 (95 percent CI -0.093 to 0.045), medium-dose group: 0.029 (95 percent CI -0.099 to 0.041), high-dose group: 0.040 (95 percent CI -0.154 to 0.075); *p* value of the *Q* statistic for all risk differences is 0.088).
- There was an increased rate of arterial thromboembolic events with rFVIIa use vs. usual care for the medium- and high-dose groups (risk difference: low-dose group: 0.025 (95 percent CI -0.004 to 0.053), medium-dose group: 0.035 (95 percent CI 0.008 to 0.062), high-dose group: 0.063 (95 percent CI 0.011 to 0.063); *p* value of the *Q* statistic for all risk differences is 0.277) (see Figure D).
- rFVIIa use significantly decreased the percent relative hematoma expansion (standardized mean difference: low-dose group: 0.146 (95 percent CI -0.291 to -0.001), medium-dose group: 0.240 (95 percent CI -0.385 to -0.095), high-dose group:

0.334 (95 percent CI -0.579 to -0.090); *p* value of the *Q* statistic for all risk differences is 0.840).

- In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other for rFVIIa use in the ICH subgroup of intracranial hemorrhage.

Regarding subpopulations of patients, our findings include:

- Earlier administration of rFVIIa for ICH may increase benefits, but this finding may be confounded by earlier CT scanning among these patients.
- There may be greater benefits in younger patients with smaller initial hematoma size.
- There was no evidence of a dose effect for any endpoint.
- Evolution of intracranial hemorrhage management may reduce the size of the population in which there is a potential benefit of rFVIIa.
- There were insufficient studies to assess the impact of rFVIIa on patients taking oral anticoagulation therapy and/or with other forms of intracranial hemorrhage (e.g., subdural bleeding).

### Key Question 3a. Bleeding from body trauma (Trauma)

There were two RCTs (both published in a single paper and of *fair* quality) and three comparative observational studies (all *fair* quality) with 267 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with blunt or penetrating trauma who were not censored for early in-hospital death (defined as 24 hours or 48 hours depending on the study).

Regarding the benefits and harms of rFVIIa, our findings include:

- There was no effect of rFVIIa on mortality (Figure C) or thromboembolism (Figure D) relative to usual care.
- For acute respiratory distress syndrome, the blunt trauma RCT demonstrated a significant reduction with rFVIIa use vs. usual care, while the remaining two studies that evaluated this outcome

(the penetrating trauma RCT and one observational study) showed a nonsignificant trend in the same direction.

- There was conflicting evidence regarding RBC transfusion requirements. These were significantly decreased among patients receiving rFVIIa vs. usual care in one RCT ( $p = 0.02$ ) and nonsignificantly decreased in the other RCT ( $p = 0.10$ ). In contrast, the one observational study that independently measured this found a significant increase in RBC transfusion requirements ( $p = 0.02$ ).
- Overall, current evidence of low strength suggests the potential for benefit and little evidence of increased harm.

Regarding subpopulations of patients, our findings include:

- Patients with blunt trauma may experience greater benefits than those with penetrating trauma.
- Greater benefits are also possible in patients with higher baseline pH, shorter time to administration, and higher platelet counts.
- There was inadequate information available to assess the effect of rFVIIa dosage.

### **Key Question 3b. Bleeding from brain trauma (i.e., traumatic brain injury [TBI])**

There was one RCT (*fair* quality) and one comparative observational study (*fair* quality) with a total of 79 patients who received rFVIIa. This yielded low strength of evidence with fair applicability for treatment use in the population targeted—patients with intracranial hemorrhage secondary to TBI who were not on anticoagulation therapy.

Regarding the benefits and harms of rFVIIa, our findings include:

- There was no effect of rFVIIa on mortality (Figure C) or thromboembolic event rate (Figure D).
- rFVIIa use vs. usual care had no effect on hematoma growth but, in the one study that evaluated it, reduced the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level).

- Current evidence of low strength is too limited to compare harms and benefits.

Regarding subpopulations of patients, our findings include:

- Patients with coagulopathy may have increased benefits.
- Patients experiencing blunt trauma to the cerebral vessels may have a greater risk of thromboembolic events when rFVIIa is used.
- There was inadequate information available to assess the effect of rFVIIa dosage.

### **Key Question 4a. Liver transplantation**

There were four RCTs (two *fair* quality, two *poor* quality) and one comparative observational study (*fair* quality) with 215 patients who received prophylactic rFVIIa at initiation of liver transplantation. This yielded low strength of evidence with fair applicability for prophylactic use in the population targeted—patients with cirrhosis of Child’s class B or C.

Regarding the benefits and harms of rFVIIa, our findings include:

- There was no effect of rFVIIa use on mortality (Figure C) or thromboembolism (Figure D) relative to usual care.
- There was a trend across studies toward reduced RBC transfusion requirements with rFVIIa use vs. usual care.
- Neither operating room time nor ICU length of stay were reduced with rFVIIa use compared to usual care.
- Current evidence of low strength is too limited to compare harms and benefits.

Regarding subpopulations of patients, our findings include:

- Patients who refuse blood product transfusions, such as Jehovah’s Witnesses, may experience benefits from rFVIIa use, but there was inadequate information to assess this.
- There was inadequate information available to assess the effect of rFVIIa dosage.

#### Key Question 4b.i. Adult cardiac surgery

There were two RCTs (one *good* quality, one *fair* quality) and four comparative observational studies (two *good* quality, two *fair* quality) with 251 patients receiving rFVIIa. One of the RCTs assessed prophylactic rFVIIa use, whereas the rest of the studies evaluated treatment use. These yielded a moderate strength of evidence for the outcome of thromboembolic events but a low strength of evidence for the remainder of the outcomes. The studies had fair applicability for rFVIIa use in the population targeted—patients undergoing cardiac surgery, including straightforward procedures (e.g., isolated coronary artery bypass grafting [CABG]) and more complex procedures (e.g., ascending aortic dissection repair).

In all cases where meta-analyses were performed, the results of the risk difference and arcsine metrics were consistent. The risk difference summary statistics are reported below. Regarding the benefits and harms of rFVIIa, our findings include:

- There was no effect of rFVIIa on mortality (risk difference 0.007; 95 percent CI -0.049 to 0.063; *p* value for the *Q* statistic is 0.63) (also see Figure C).
- rFVIIa use was associated with a higher thromboembolic event rate (risk difference 0.053; 95 percent CI 0.01 to 0.096; *p* value for the *Q* statistic is 0.99) (also see Figure D).
- RBC transfusion needs were possibly reduced with rFVIIa, but the trend was only apparent across the higher quality studies that reported on this outcome (one RCT and one good quality cohort study, *p* = 0.11 and *p* < 0.001, respectively; the other RCT only reported on total transfusion needs, which were significantly reduced). The findings across the *fair* quality observational studies were conflicting.
- There were conflicting results among studies regarding ICU length of stay.
- Current evidence of moderate strength (for thromboembolic events) or low strength (for all other outcomes) suggests that neither benefits nor harms substantially exceed each other.

Regarding subpopulations of patients, our findings include:

- There was a suggestion that earlier treatment use of rFVIIa increases its benefits.
- There was inadequate information available to assess the effect of rFVIIa dosage.

#### Key Question 4b.ii. Pediatric cardiac surgery

A total of 40 patients received rFVIIa prophylaxis in one *poor* quality RCT, (the only included study). This yielded an insufficient strength of evidence and fair applicability for the population targeted—infant patients with congenital heart defects requiring surgical repair.

Regarding the benefits and harms of rFVIIa, our findings include:

- There were no data reported on mortality from the single RCT available.
- The effect of rFVIIa on thromboembolic events cannot be discerned from existing data due to limited events. RBC transfusion requirements demonstrated a nonsignificant decrease among patients receiving rFVIIa vs. usual care: 77 mL and 127 mL, respectively, *p* = 0.15.
- Time from end of cardiopulmonary bypass to chest closure was increased significantly in rFVIIa patients: 99 minutes (SD = 27) for rFVIIa vs. 55 minutes (SD = 29) for usual care, *p* = 0.03.
- Current evidence is insufficient for comparing harms and benefits.

Regarding subpopulations of patients, our findings include:

- Patients on extracorporeal membrane oxygenation (ECMO) may be more likely to experience thromboembolic events.
- There was inadequate information available to assess the effect of rFVIIa dosage.

#### Key Question 4c. Prostatectomy

There was one *fair*-quality RCT on prophylactic use of rFVIIa in 24 patients undergoing prostatectomy. This yielded an insufficient strength of evidence and poor applicability for the population targeted—patients

undergoing retropubic prostatectomy for prostate cancer or benign hyperplasia but not on anticoagulation therapy. These data have limited relevance given the major changes in usual care since the RCT was performed and the lack of reported use of rFVIIa for prostatectomy in the United States in 2008.

Regarding the benefits and harms of rFVIIa, our findings include:

- Mortality and thromboembolic events could not be evaluated due to limited reported events (one thromboembolic event in a rFVIIa patient, no deaths in either group).
- RBC transfusion needs were significantly decreased by rFVIIa, with a possible greater effect at higher doses: 1.5 units (SD = 0.4) for usual care, 0.6 units (SD = 0.3) for 20 mcg/kg, 0 (0) for 40 mcg/kg ( $p < 0.01$ ).
- Operating room time was significantly reduced with rFVIIa (122 minutes [SD = 17] for rFVIIa vs. 180 minutes [SD = 16] for usual care,  $p < 0.01$ ).
- Current evidence is insufficient for comparing harms and benefits.

Regarding subpopulations of patients, our findings include:

- There was inadequate information available to assess the effect of rFVIIa dosage on outcomes other than RBC transfusion requirements.

## Conclusions

Available evidence on off-label rFVIIa use is limited across a wide spectrum of off-label indications. Considering the evidence as a whole, off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. Of the indications we studied, the benefit-to-risk ratio may be more favorable for body trauma than for other indications, because its use may reduce the occurrence of acute respiratory distress syndrome (ARDS); however, the

strength of evidence is low for this as well as most other outcomes, which precludes definitive conclusions. Available evidence does not indicate that use of off-label rFVIIa reduces mortality or improves other direct outcomes for the indications we studied. Thromboembolic events are increased by use of rFVIIa in intracranial hemorrhage and adult cardiac surgery. Despite this state of evidence, in-hospital, off-label cases of rFVIIa use have increased in the last decade, particularly for cardiac surgery, trauma, and intracranial hemorrhage.

## Full Report

This executive summary is part of the following document: Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Stave CD, Zehnder JL, Olkin I, McDonald KM, Owens DK, Stafford RS. Comparative Effectiveness of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care. Comparative Effectiveness Review No. 21. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. 290-02-0017.) Rockville, MD: Agency for Healthcare Research and Quality. May 2010. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

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**Table A. Summary of results and conclusions from overview and Comparative Effectiveness Review**

Number of studies		Total number of patients	Outcome <sup>a</sup> and strength of evidence <sup>b</sup>					Effectiveness review conclusions	
RCT	OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	Units RBCs transfused	Other indirect outcome		
<b>KQ1a. Overview of Premier database information on in-hospital, off-label use</b>									
NA	rFVIIa: 73,746 hospital cases, 2000-2008 UC: Not available from Premier database	By KQ indication: • Intracranial hemorrhage: 0.34 • Body trauma: 0.33 • Brain trauma: 0.33 • Liver transplantation: 0.38 • Adult cardiac surgery: 0.23 • Pediatric cardiac surgery: 0.22 • Prostatectomy: 0	NA	NA	NA	NA	NA	<ul style="list-style-type: none"> <li>The majority of use of rFVIIa occurs in the outpatient setting, and the majority of outpatient use is for on-label indications related to hemophilia.</li> <li>In-hospital rFVIIa cases (any application during a given discharge) in the United States have increased since 2000 almost solely due to rising off-label use. This use was estimated to be 125 cases in 2000, underwent a slow increase until 2005 when use became more frequent and was estimated to be 11,057 cases, and by 2008 was estimated to be 17,813 cases (97 percent of all of the estimated 18,311 in-hospital cases), although the slope of increase may be leveling off for many indications.</li> <li>In 2008, cardiac surgery, trauma, and intracranial hemorrhage were the leading off-label indications, while there was limited use in liver transplantation and none in prostatectomy. Other off-label uses included GI bleeding, primary/secondary clotting disorders, and aortic aneurysm/other vascular procedures.</li> </ul>	
<b>KQ1b. Overview of published literature</b>									
RCT: 24	rFVIIa: 937 in non-KQ studies <sup>c</sup> (N=10) UC: 589	NA	NA	NA	NA	NA	NA	<ul style="list-style-type: none"> <li>Published studies of rFVIIa are often limited by small study size, inconsistent study quality, use of indirect outcomes, and heterogeneity by dosage and indication.</li> </ul>	
OBS: 31	in non-KQ studies <sup>c</sup> (N=7)	NA	NA	NA	NA	NA	NA		
<b>KQ2. Intracranial hemorrhage</b>									
RCT: 4	rFVIIa: 968							Use of rFVIIa compared to usual care, within the ICH subgroup of intracranial hemorrhage	
OBS: 1	UC: 414	Moderate rFVIIa: 0.08-0.22 UC: 0.13-0.29	Moderate rFVIIa: 0.04-0.11 UC: 0-0.13	Poor functional status <sup>d</sup> Moderate rFVIIa: 0.44-0.53 UC: 0.46-0.69	NA	NA	Percent hematoma expansion Moderate rFVIIa: 4-79 UC: 11-29	<ul style="list-style-type: none"> <li>Did not affect mortality or rate of poor functional status</li> <li>Was associated with an increased rate of arterial TE events</li> <li>Was associated with a decrease in the percent hematoma expansion</li> </ul> In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other.	

**Table A. Summary of results and conclusions from overview and Comparative Effectiveness Review (continued)**

Number of studies	Total number of patients	Outcome <sup>a</sup> and strength of evidence <sup>b</sup>					Effectiveness review conclusions
		Mortality	TE events	Other direct outcome	Units RBCs transfused	Other indirect outcome	
<b>RCT</b>	<b>rFVIIa</b>						
<b>OBS</b>	<b>Usual care</b>						
<b>KQ3a. Body trauma</b>							
RCT: 2	rFVIIa: 267	Low	Low	ARDS	Low	NA	Use of rFVIIa compared to usual care
OBS: 3	UC: 429	rFVIIa: 0.07-0.31 UC: 0-0.51	rFVIIa: 0.03-0.12 UC: 0-0.08	rFVIIa: 0.02-0.06 UC: 0.04-0.16	rFVIIa: 6.9-16.0 UC: 7.7-14.0	NA	<ul style="list-style-type: none"> <li>• Did not affect mortality or TE event rate</li> <li>• May decrease the rate of ARDS</li> <li>• Had an unclear impact on RBC transfusion requirements</li> </ul> In summary, current evidence of low strength suggests the potential for benefit and little evidence of increased harm.
<b>KQ3b. Brain trauma</b>							
RCT: 1	rFVIIa: 79	Low	Low	NA	NA	NA	Use of rFVIIa compared to usual care
OBS: 1	UC: 53	rFVIIa: 0.12-0.33 UC: 0.11-0.53	rFVIIa: 0.15-0.22 UC: 0.08-0.18	NA	NA	NA	<ul style="list-style-type: none"> <li>• Did not affect mortality or TE event rate</li> <li>• Did not reduce hematoma growth but may reduce the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level)</li> </ul> In summary, current evidence of low strength is too limited to compare harms and benefits.
<b>KQ4a. Liver transplantation</b>							
RCT: 4	rFVIIa: 215	Low	NA	NA	Low	OR time (min)	Use of rFVIIa compared to usual care
OBS: 1	UC: 117	rFVIIa: 0-0.08 UC: 0-0.02	rFVIIa: 0-0.22 UC: 0-0.16	NA	rFVIIa: 1.2-13.0 UC: 2.3-11.1	Low rFVIIa: 268-554 UC: 432-598 ICU LOS (day) Low rFVIIa: 3.0-4.8 UC: 3.0-5.2	<ul style="list-style-type: none"> <li>• Did not affect mortality or TE event rate</li> <li>• May reduce RBC transfusion requirements</li> <li>• Did not reduce OR time or ICU length of stay</li> </ul> In summary, current evidence of low strength is too limited to compare harms and benefits.

**Table A. Summary of results and conclusions from overview and Comparative Effectiveness Review (continued)**

Number of studies		Outcome <sup>a</sup> and strength of evidence <sup>b</sup>				Effectiveness review conclusions	
RCT	OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	Units RBCs transfused	Other indirect outcome
<b>KQ4bi. Adult cardiac surgery</b>							
RCT: 2		rFVIIa: 251	Low	Moderate	NA	Low	ICU LOS (day)
OBS: 4		UC: 216	rFVIIa: 0-0.33 UC: 0.06-0.33	rFVIIa: 0-0.22 UC: 0-0.20		rFVIIa: 0-9.1 UC: 2-17	Low rFVIIa: 2.5-14 UC: 1-18.5
Use of rFVIIa compared to usual care							
<ul style="list-style-type: none"> <li>• Did not affect mortality</li> <li>• Was associated with a higher TE event rate</li> <li>• May reduce RBC transfusion requirements</li> <li>• Had an unclear impact on ICU length of stay</li> </ul> In summary, current evidence of moderate strength (TE event rate outcome) or low strength (all other outcomes) suggests that neither benefits nor harms substantially exceed each other.							
<b>KQ4bii. Pediatric cardiac surgery</b>							
RCT: 1		rFVIIa: 40	Not reported	Insufficient	NA	mL RBC transfused	Time to chest closure (min)
OBS: 0		UC: 36		rFVIIa: 0 UC: 0		rFVIIa: 77 UC: 127	Insufficient rFVIIa: 98.8 UC: 55.3
The one included study cannot comment on use of rFVIIa compared to usual care on mortality (because these data were not reported) or on TE event rate (because there were limited events). Use of rFVIIa compared to usual care							
<ul style="list-style-type: none"> <li>• May reduce RBC transfusion requirements</li> <li>• Was associated with an increase in time to chest closure</li> </ul> In summary, current evidence is insufficient for comparing harms and benefits.							
<b>KQ4c. Prostatectomy</b>							
RCT: 1		rFVIIa: 24	Insufficient	Insufficient	NA	Insufficient	OR time (min)
OBS: 0		UC: 12	rFVIIa: 0 UC: 0	rFVIIa: 0-0.13 UC: 0		rFVIIa: 0-0.6 UC: 1.5	Insufficient rFVIIa: 120-126 UC: 180
The one included study cannot comment on use of rFVIIa compared to usual care on mortality or TE event rate because there were limited events. Use of rFVIIa compared to usual care							
<ul style="list-style-type: none"> <li>• Was associated with reduced RBC transfusion requirements and OR time</li> </ul> In summary, current evidence is insufficient for comparing harms and benefits.							

KQ=Key Question; RCT=randomized controlled trial; OBS=comparative observational study; TE=thromboembolic; RBC=red blood cell; NA=not applicable; UC=usual care; ARDS=acute respiratory distress syndrome; OR=operating room; ICU LOS=intensive care unit length of stay; GI=gastrointestinal; ICH=intracerebral hemorrhage.

<sup>a</sup>Outcome is given as a range of rates, unless otherwise stated. Each outcome range encompasses the lowest and highest rate/unit measured across all studies and, as such, should not be used to directly compare between the rFVIIa and UC care groups. Direct comparisons between groups are described in detail in the main report and are summarized in the “conclusions” column of this table.

<sup>b</sup>Strength of evidence is based on scores within four evidence domains (risk of bias, consistency, directness, and precision) and is rated as “low,” “moderate,” “high,” or “insufficient.”

<sup>c</sup>Only non-KQ studies are listed here because the studies on Key Questions 2-4 are subsequently reviewed lower in the table.

<sup>d</sup>Poor functional status is defined as a modified Rankin Scale (mRS) score of 4-6.

