

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



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Comparative Effectiveness Review

Number 21

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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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.

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:

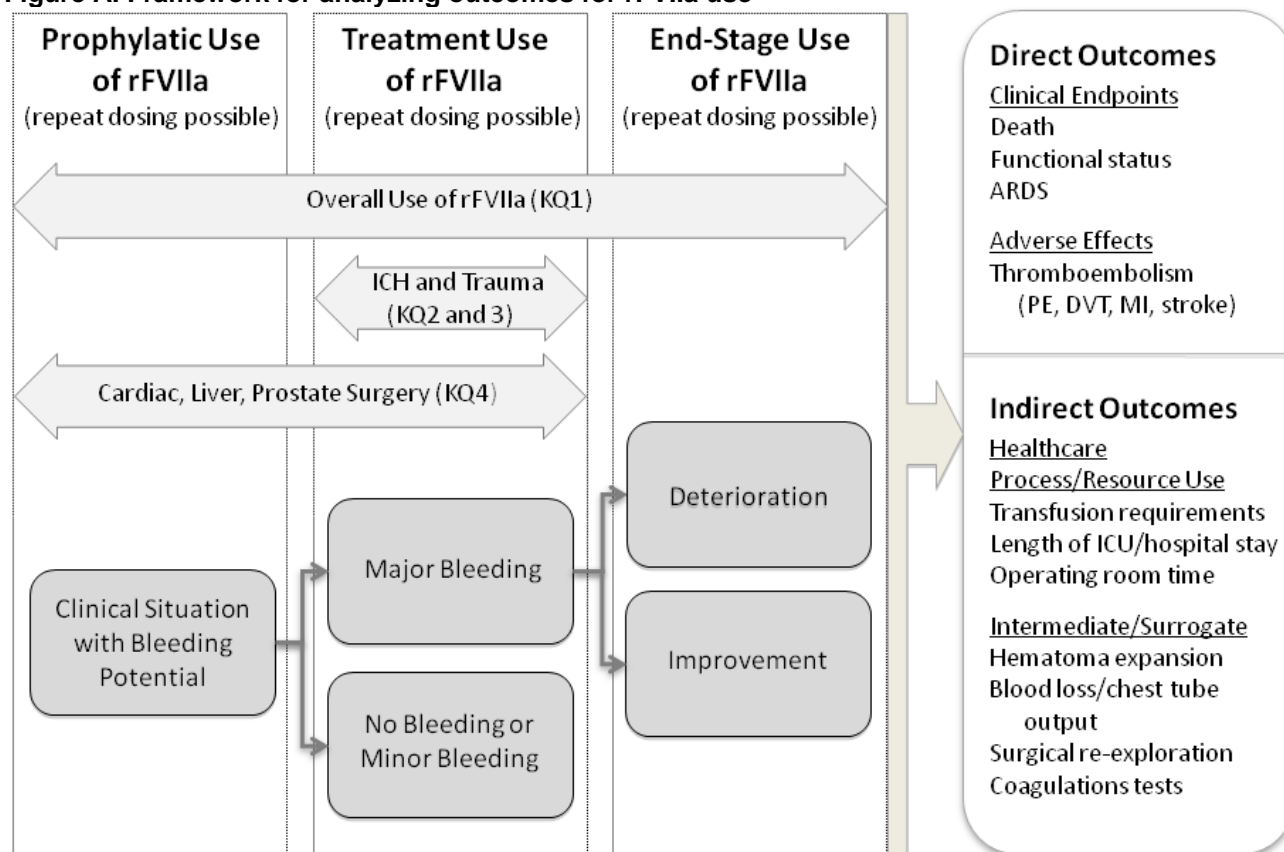
- Does the use of rFVIIa reduce mortality and disability compared to usual care?
- Are there patient subpopulations more likely to benefit from rFVIIa use?
- Does rFVIIa use increase thrombosis-related events?
- Are there patient subpopulations where harms are more likely?
- Which patient subpopulations 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). 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

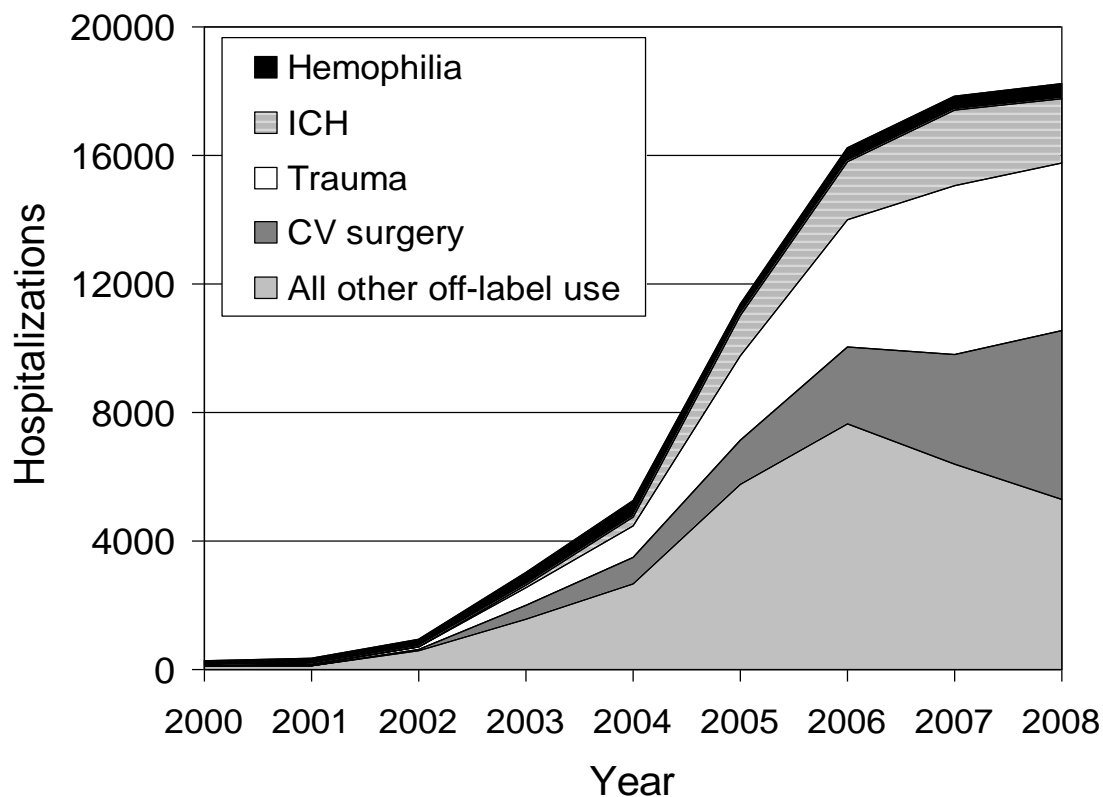
To evaluate evidence of harm from rFVIIa in noncomparative studies, we described the unadjusted summary event rates for mortality and thromboembolic events from the noncomparative studies, as well as event rates from the intervention arms of the comparative studies.

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

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



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 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)

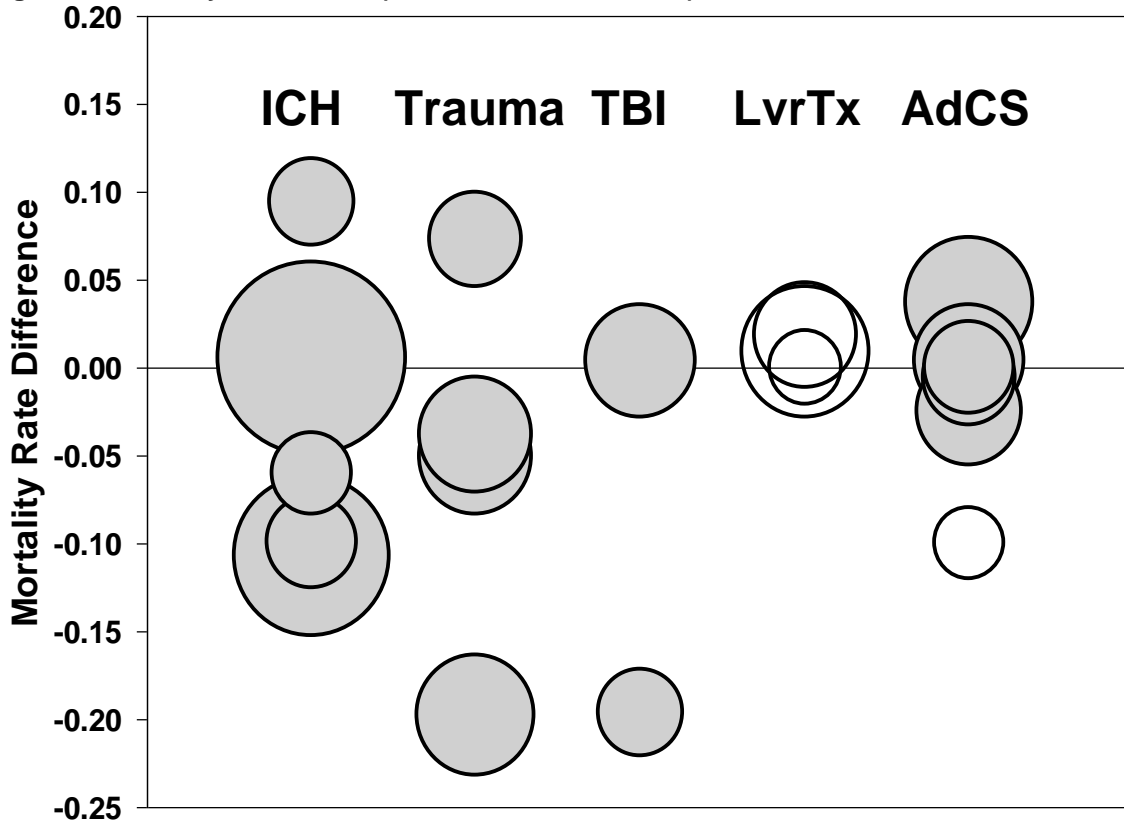
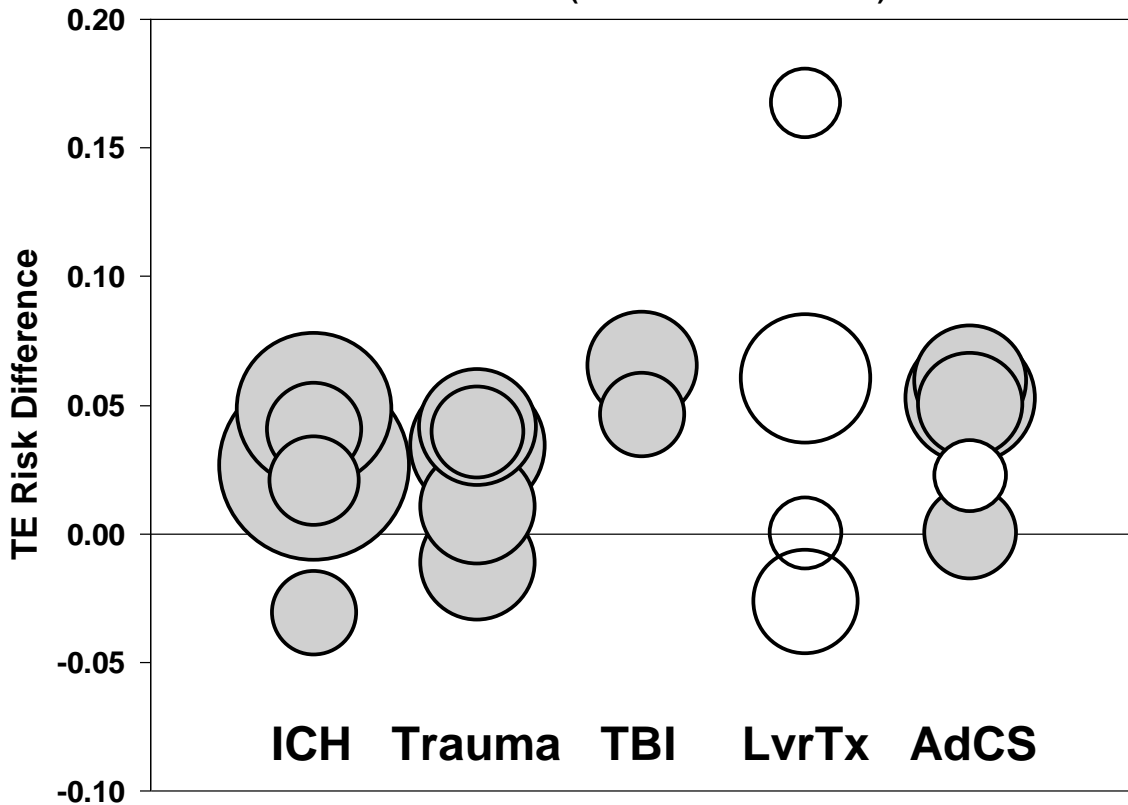


Figure D. Thromboembolic event risk differences (rFVIIa minus usual care)



- 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.

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

Number of studies	Total number of patients	Outcome ^a <u>and</u> strength of evidence ^b					Effectiveness review conclusions
RCT OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	Units RBCs transfused	Other indirect outcome	
KQ1a. Overview of Premier database information on in-hospital off-label use							
NA	rFVIIa: 73,746 hospital cases, 2000-2008 UC: Not available from Premier database	By KQ indication: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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. • In-hospital rFVIIa cases (any application during a given discharge) in the U.S. 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. • 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.
KQ1b. Overview of published literature							
RCT: 24 OBS: 31	rFVIIa: 937 in non-KQ studies ^c (N=10) UC: 589 in non-KQ studies ^c (N=7)	NA	NA	NA	NA	NA	<ul style="list-style-type: none"> • Published studies of rFVIIa are often limited by small study size, inconsistent study quality, use of indirect outcomes, and heterogeneity by dosage and indication.

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

Number of studies	Total number of patients	Outcome ^a <u>and</u> strength of evidence ^b					Effectiveness review conclusions
RCT OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	Units RBCs transfused	Other indirect outcome	
KQ2. Intracranial hemorrhage							
RCT: 4 OBS: 1	rFVIIa: 968 UC: 414	<i>Moderate</i> rFVIIa: 0.08-0.22 UC: 0.13-0.29	<i>Moderate</i> rFVIIa: 0.04-0.11 UC: 0-0.13	<i>Poor functional status^d</i> <i>Moderate</i> rFVIIa: 0.44-0.53 UC: 0.46-0.69	NA	<i>Percent hematoma expansion</i> <i>Moderate</i> rFVIIa: 4-79 UC: 11-29	Use of rFVIIa compared to usual care, within the ICH subgroup of intracranial hemorrhage <ul style="list-style-type: none"> • Did not affect mortality or rate of poor functional status • Was associated with an increased rate of arterial TE events • Was associated with a decrease in the percent hematoma expansion <p><u>In summary</u>, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other</p>
KQ3a. Body trauma							
RCT: 2 OBS: 3	rFVIIa: 267 UC: 429	<i>Low</i> rFVIIa: 0.07-0.31 UC: 0-0.51	<i>Low</i> rFVIIa: 0.03-0.12 UC: 0-0.08	<i>ARDS</i> <i>Low</i> rFVIIa: 0.02-0.06 UC: 0.04-0.16	<i>Low</i> rFVIIa: 6.9-16.0 UC: 7.7-14.0	NA	Use of rFVIIa compared to usual care <ul style="list-style-type: none"> • Did not affect mortality or TE event rate • May decrease the rate of ARDS • Had an unclear impact on RBC transfusion requirements <p><u>In summary</u>, current evidence of low strength suggests the potential for benefit and little evidence of increased harm</p>
KQ3b. Brain trauma							
RCT: 1 OBS: 1	rFVIIa: 79 UC: 53	<i>Low</i> rFVIIa: 0.12-0.33 UC: 0.11-0.53	<i>Low</i> rFVIIa: 0.15-0.22 UC: 0.08-0.18	NA	NA	<i>Absolute hematoma expansion (mL)</i> <i>Low</i> rFVIIa: 7.0 UC: 10.4	Use of rFVIIa compared to usual care <ul style="list-style-type: none"> • Did not affect mortality or TE event rate • Did not reduce hematoma growth but may reduce the time to neurosurgical intervention (e.g., by normalizing the INR to an acceptable level) <p><u>In summary</u>, current evidence of low strength is too limited to compare harms and benefits</p>

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

Number of studies	Total number of patients	Outcome ^a and strength of evidence ^b					Effectiveness review conclusions
		RCT OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	
KQ4a. Liver transplantation							
RCT: 4 OBS: 1	rFVIIa: 215 UC: 117	<i>Low</i> rFVIIa: 0-0.08 UC: 0-0.02	<i>Low</i> rFVIIa: 0-0.22 UC: 0-0.16	NA	<i>Low</i> rFVIIa: 1.2-13.0 UC: 2.3-11.1	<u>OR time (min)</u> <i>Low</i> rFVIIa: 268-554 UC: 432-598 <u>ICU LOS (day)</u> <i>Low</i> rFVIIa: 3.0-4.8 UC: 3.0-5.2	Use of rFVIIa compared to usual care <ul style="list-style-type: none"> • Did not affect mortality or TE event rate • May reduce RBC transfusion requirements • Did not reduce OR time or ICU length of stay <u>In summary</u> , current evidence of low strength is too limited to compare harms and benefits
KQ4bi. Adult cardiac surgery							
RCT: 2 OBS: 4	rFVIIa: 251 UC: 216	<i>Low</i> rFVIIa: 0-0.33 UC: 0.06-0.33	<i>Moderate</i> rFVIIa: 0-0.22 UC: 0-0.20	NA	<i>Low</i> rFVIIa: 0-9.1 UC: 2-17	<u>ICU LOS (day)</u> <i>Low</i> rFVIIa: 2.5-14 UC: 1-18.5	Use of rFVIIa compared to usual care <ul style="list-style-type: none"> • Did not affect mortality • Was associated with a higher TE event rate • May reduce RBC transfusion requirements • Had an unclear impact on ICU length of stay <u>In summary</u> , 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

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

Number of studies	Total number of patients	Outcome ^a and strength of evidence ^b					Effectiveness review conclusions
		RCT OBS	rFVIIa Usual care	Mortality	TE events	Other direct outcome	
KQ4bii. Pediatric cardiac surgery							
RCT: 1 OBS: 0	rFVIIa: 40 UC: 36	Not reported	<i>Insufficient</i> rFVIIa: 0 UC: 0	NA	<i>Insufficient</i> rFVIIa: 77 UC: 127	<i>Insufficient</i> 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"> • May reduce RBC transfusion requirements • Was associated with an increase in time to chest closure <u>In summary</u> , current evidence is insufficient for comparing harms and benefits
KQ4c. Prostatectomy							
RCT: 1 OBS: 0	rFVIIa: 24 UC: 12	<i>Insufficient</i> rFVIIa: 0 UC: 0	<i>Insufficient</i> rFVIIa: 0-0.13 UC: 0	NA	<i>Insufficient</i> rFVIIa: 0-0.6 UC: 1.5	<i>Insufficient</i> 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"> • Was associated with reduced RBC transfusion requirements and OR time <u>In summary</u> , 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.

^aOutcome 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.

^bStrength 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.”

^cOnly non-KQ studies are listed here because the studies on Key Questions 2-4 are subsequently reviewed lower in the table.

^dPoor functional status is defined as a modified Rankin Scale (mRS) score of 4-6.

Introduction

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 beyond those approved by the 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 that differ from the drug's FDA approved label. The purpose of this report is two-fold: (1) To profile 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 versus usual care for several clinical indications: intracranial hemorrhage, massive bleeding secondary to trauma, and the selected surgical procedures of cardiac surgery, liver transplantation, and prostatectomy.

The spectrum of rFVIIa use is broad, involving a range of surgical and medical specialties. In the first part of this report, we provide a full description of the evolution of rFVIIa's off-label in-hospital uses through 2008 based on both a literature review and analysis of national hospital data. While a comparative effectiveness review for every off-label use of rFVIIa is beyond the scope of this report, in the first part of this report (Key Question 1) we document the randomized controlled trials and comparative observational studies of rFVIIa for the full spectrum of clinical conditions to which it has been applied. These analyses identify what other clinical indications beyond those selected for comparative effectiveness review might also warrant focused attention in the future.

In the second part of this report (Key Questions 2-4), we present a comparative effectiveness review of the benefits and harms of rFVIIa versus usual care for the selected clinical indications of intracranial hemorrhage, bleeding secondary to trauma, cardiac surgery, liver transplantation, and prostatectomy. These off-label indications have been prominent in debates about the effectiveness and safety of rFVIIa, including potentially ambiguous benefits and the occurrence of infrequent but catastrophic adverse events. We compare rFVIIa to usual care because there is currently no notable competing product for the clinical indications assessed. We focus on randomized clinical trials (RCTs) as the primary source of information on rFVIIa's potential benefits, but also rely on a range of observational studies to more fully characterize its potential for harm.¹ When adequate information exists, we perform meta-analyses. For each indication, we also provide an overall assessment of the balance of rFVIIa benefits and harms. Because benefits and harms may vary by subpopulation or medication dose, we also evaluate outcomes according to these variables, when possible. Finally, we suggest critical gaps in evidence that might be usefully filled by future clinical research.

Organization of Report

This report begins in the Introduction with a Background on Off-label Medication Use, with a particular focus on its relevant advantages and disadvantages. We provide an Introduction to rFVIIa, including its biology, known patterns of use, regulatory history, and current uncertainty regarding its safety and benefits. We provide a summary of Areas of Anticipated Challenge that we recognized as we undertook the project.

In the Methods, we describe our approach to analyzing rFVIIa off-label use, including the Analytic Framework, Methods to Describe the Spectrum of rFVIIa Off-label Use and Methods of

rFVIIa Comparative Effectiveness Review for intracranial hemorrhage, traumatic bleeding, and the three selected surgical procedures.

Our Results on rFVIIa Off-label Use provide a description of the evolution of rFVIIa off-label use, as well as the extent to which studies exist that evaluate this use at the level of individual indications. The rFVIIa Comparative Effectiveness Results presents our findings in detail, both at the level of individual research studies and in aggregate (as appropriate).

Our Discussion interprets our comparative effectiveness results in light of prior systematic reviews and current trends of rFVIIa use. Where adequate evidence exists, we provide an overall assessment of the value of rFVIIa for each prominent off-label use. Where it does not exist, we identify critical gaps in information recommended as targets for future study.

Background on Off-Label Medication Use

Defining Off-Label Drug Use

Off-label use refers to any use of a medication (or medical device) that differs from the product labeling approved and required by the United States Food and Drug Administration (FDA). The FDA drug approval process requires randomized clinical trials that demonstrate efficacy for specific indications prior to marketing. Once approval is given, however, the FDA does not regulate whether drugs are prescribed for “off-label” indications. Although the extent of evaluation and evidence supporting the efficacy and safety of off-label use may vary tremendously by drug, in all but rare many instances it falls short of the extensive research and scientific scrutiny that accompanies initial FDA review.² In cases where drugs are being used infrequently, this uncertainty may be acceptable. On the other hand, concern increases when larger populations are served, when off-label indications become more clinically or biologically distinct from the approved indications, when the drug is costly, when the safety and response to therapy in anecdotal cases may be over-generalized, and when a drug is used in a different clinical setting.

Regulatory Context

The FDA’s review of a New Drug Application (NDA) evaluates a product’s use for specific indications prior to allowing the product to be marketed. Each distinct indication requires a series of RCTs that demonstrate safety and efficacy for that condition. The FDA focuses on controlling market entry. After approval, physicians are free to use the medications as they wish, and the FDA is specifically enjoined from influencing the practice of medicine. While supplemental NDAs are an available mechanism for adding indications to an existing approval, manufacturers may not seek them, particularly if the indications are difficult or costly to evaluate. There are a great variety of ways in which drug use may differ from FDA labeling. Off-label use can extend the clinical logic from the approved indication to others, such as milder forms of the approved indication (e.g., using antidepressants for dysthymia) or clinically related conditions (e.g., applying asthma treatments to COPD). In addition, drugs may be used for patient subpopulations not approved by the FDA (e.g., children and adolescents)³ or used as monotherapy when approved only as an adjunct therapy (and vice versa).⁴

Advantages and Disadvantages

There is a range of conflicting perspectives on off-label use. Payers question the need to pay for unproven products, physicians want autonomy to meet individual patient needs, and the pharmaceutical industry may identify additional indications for which they could potentially seek FDA approval. For their part, consumers expect drugs that are safe, effective, evidence-based, and affordable, but are often willing to lower their standards in the case of new therapies.⁵

Off-label use has a number of advantages, including facilitating innovation in clinical practice, offering clinical solutions when approved treatments fail, offering earlier access to potentially valuable medications, allowing adoption of new practices based on emerging evidence, providing the only available treatments for orphan conditions, and, occasionally, providing less expensive therapy.⁵ rFVIIa might share many of these attributes to the extent that its use proves safe and efficacious for its off-label indications.

On the other hand, off-label use carries important disadvantages, not the least of which is the way it may undercut public and physician expectations about the full evaluation of drug safety and efficacy.⁵ Off-label use can also increase health care costs, especially when newer, more expensive drugs are used. It may undermine incentives for the pharmaceutical industry to perform the additional rigorous clinical studies needed for FDA approval of new indications. Finally, off-label use may indirectly discourage evidence-based practice if it reduces the expectation that available evidence guides clinical practice.⁶

Unique Aspects of Biologics and Off-Label Use

There are several special issues when biologics, such as rFVIIa, are used off-label. The high cost of development leads to an even higher product cost—for example, in the case of rFVIIa, up to \$10,300 for a single 90 µg/kg dose in a 70 kg patient,⁷ with total in-hospital U.S. sales of rFVIIa in 2007 estimated to have been \$138.5 million.⁸ The injectable form of most biologics limits the potentially available population to severe conditions not treatable with oral medications. While these products are often deployed initially in life threatening situations on a limited number of patients, their application is often expanded into milder forms of disease or into distinctly different conditions, which appears to be the case for rFVIIa.

rFVIIa occupies a unique niche in that its approved indication is relatively rare. The U.S. prevalence of Hemophilia A and Hemophilia B (conditions in which individuals have deficiencies in clotting factors VIII and IX, respectively): 1:10,000 and 1:25,000, respectively.⁹ Of these individuals, relatively few ever require rFVIIa for treatment as a result of developing antibody inhibitors to the exogenous coagulation factors given to replace the deficient factor. Inhibitors to factor VIII develop in 0.45-1.5 patients with Hemophilia A per 10,000 patient-years, with population rates of 0.3 percent in patients with mild Hemophilia A and 30 percent in those with severe forms.¹⁰ In contrast, development of a Factor IX inhibitor in Hemophilia B occurs in only 1-3 percent of the patients. Development of inhibitors appears equally likely in patients receiving plasma-derived replacement therapy and those receiving recombinant products.¹¹ Among those patients with inhibitors, a fraction can be desensitized and can again become responsive to factor replacement, although this process is time consuming and expensive. In most cases, the approved population requires rFVIIa to bypass these inhibitors and promote clotting only during bleeding crises or for surgery and procedures. During the past decade, however, off-label use of rFVIIa has transitioned from infrequent use to more frequent applications for which evidence may be limited.

Introduction to rFVIIa

Procoagulant Products Preceding rFVIIa

The broad therapeutic territory occupied by rFVIIa involves situations where life-threatening bleeding is occurring or anticipated to occur in the absence of treatment alternatives. Its FDA-approved indication of use in hemophilia not amenable to standard factor concentrate therapy is a narrow niche within this broader spectrum of use. Prior to the advent of rFVIIa in 1998, therapeutic options included drugs that facilitate clotting and predecessor products derived from pooled human blood. Products derived from pooled blood samples carry the potential for the transmission of human viruses and increased allergic reactions.

For the FDA-approved indication in hemophilia, rFVIIa has virtually replaced procoagulant products that preceded it. Prior to the manufacture of rFVIIa, human-derived and purified FVII was occasionally used in hemophilia patients with inhibitors, but the mainstay of therapy were Factor Eight Inhibitor Bypassing Agent (FEIBA) followed historically by aPCC. These products also were used outside of hemophilia, but their range of indications has been far narrower than for rFVIIa.¹² FEIBA is a heterogeneous and variable concentrate of vitamin-K-dependent human clotting factors derived from pooled human plasma. It is not clear which component or components are vital for its function. The function of FEIBA may depend on its concentration of rFVIIa.¹³ Activated Prothrombin Complex Concentrate (aPCC) is the successor to FEIBA. It is similar to FEIBA in that it is a human-derived concentrate of clotting factors, but it is processed to convert these into their active forms. This product is FDA-approved only for use in hemophilia patients with inhibitors.

There is also a range of other situation-specific procoagulants often used with limited success in situations where rFVIIa is now used off-label. Protamine is used for heparin reversal and vitamin K is used for subacute reversal of warfarin anticoagulation. The lysine analogues epsilon-aminocaproic acid and tranexamic acid are fibrinolysis inhibitors and are used for bleeding in a wide range of medical conditions and surgical procedures, and are still often used in conjunction with rFVIIa. Aprotinin, a serine protease inhibitor, was used in patients in some surgical procedures with a risk of massive bleeding (e.g., coronary artery bypass grafting (CABG) and other cardiac surgeries) but was removed from the market in November 2007 because of evidence of increased morbidity and mortality.¹⁴⁻¹⁶ Since that time, there has been a shift toward use of tranexamic acid during cardiac surgery.

rFVIIa Biology

rFVIIa is a form of activated human factor VII produced through recombinant technology. The molecule is 406 amino-acids in length and has a molecular weight of 50 kDaltons. As a protein-based therapy, it must be given intravenously to facilitate coagulation at sites of bleeding and has a half-life of 2.5 hours. Currently, Novoseven[®] is the only form of rFVIIa available commercially. rFVIIa is also known by its international nonproprietary name of activated eptacog alfa, although this term is infrequently used. rFVIIa promotes clotting in two ways:

1. At physiologic levels and in association with tissue factor (e.g., on damaged tissue), it activates factors IX and X to initiate the clotting cascade that ultimately leads to formation of a thrombin plug, which allows for clot stability. This normal physiological mechanism suggests that rFVIIa's action is targeted to areas of tissue damage.

2. In pharmacological doses, it also binds to activated platelets and drives the process of thrombin clot formation forward via factor X activation, even in the absence of tissue factor. This mechanism is relatively specific to areas of tissue damage because clotting is fostered primarily where platelet aggregation occurs, the first step in the clotting process.¹⁷⁻¹⁹

These mechanisms effectively bypass portions of the clotting process that are normally required for clotting to occur. Thus, clotting can occur despite factor deficiencies (in factors VII, VIII, IX, and XI) or when the number or function of platelets is reduced.

History of rFVIIa

The development of rFVIIa, under the brand name Novoseven,[®] began in 1985 by Novo Industries of Bagsværd, Denmark (which became Novo Nordisk in a 1989 merger). rFVIIa was developed as an injectable procoagulant for use in hemophilia A or B with inhibitors (antibodies that inactivate exogenous factor VIII or factor IX, respectively). Use of human plasma derived factor VIIa was reported in 1983.²⁰ The first published report of rFVIIa use was in 1989.²¹ Between 1989 and 1999, rFVIIa was provided on a compassionate basis by the manufacturer for use in Hemophilia A or B with inhibitors. The first non-hemophilia-related use was reported for the clinical indication of thrombocytopenia in 1996.²² Since 1999, the FDA has approved four separate applications that have gradually expanded the scope of rFVIIa use for hemophilia:

1. Hemophilia A or B with inhibitors for bleeding episodes (March 25, 1999).
2. Bleeding and surgery in congenital factor VII deficiency (July 11, 2005).
3. Surgery and invasive procedures in Hemophilia A or B with inhibitors (August 12, 2005).
4. Bleeding and surgery in acquired hemophilia (October 13, 2006).

On November 25, 2005, the FDA required Novo Nordisk to make changes in drug labeling and issue a warning letter regarding the possibility of increased arterial thrombotic adverse events with rFVIIa use based on trial results for intracerebral hemorrhage (ICH), a subset of intracranial hemorrhage.²³ Furthermore, in January 2010, the FDA required that a “black box” warning be added to the drug labeling that highlights a possible increase in venous and arterial thromboembolic events with use.²⁴ On May 9, 2008, the FDA approved Novoseven RT, a reformulated form of rFVIIa capable of being stored at room temperature rather than requiring refrigeration. The U.S. patent for Novoseven expires in February 2011.

Similar regulatory histories exist in most developed nations. The European Medicines Agency (EMA) approved rFVIIa on February 23, 1996 for use in Hemophilia A or B with inhibitors and subsequently added the indications of Glanzmann’s thrombasthenia and congenital FVII deficiency. Novo Nordisk applied to the EMA for approval of rFVIIa use in ICH on October 5, 2005, but withdrew this application on April 6, 2006. In Australia and New Zealand, rFVIIa is approved for prophylactic use in hemophilia with inhibitors (2008). The Japanese patent for Novoseven expired in 2008, while the European Union patent will expire in November 2010.

New Forms of rFVIIa and Other Development Trends

The goals of development of alternatives to the current formulation of rFVIIa are to increase the effective half-life of rFVIIa so that dosing can be less frequent, to increase the rapidity of onset so that hemostasis occurs more promptly, and to increase the localization of

therapeutic effect so that remote thromboembolic events do not occur. Several products are under development:

1. Novo Nordisk, with Neose Technologies (formerly of Horsham, PA), developed NN7128, a product with greater glycosylation and other changes that create a longer acting rFVIIa. Phase I clinical trials were completed before Neose sold the drug rights to Novo Nordisk.
2. Novo Nordisk is developing NN1731, an analogue of rFVIIa designed to deliver faster but sustainable hemostasis with greater potency than Novoseven rFVIIa. This product is now in Phase II trials.
3. Novo Nordisk is also developing a subcutaneously absorbed form of rFVIIa. This product is in Phase I trials.
4. Maxygen (Redwood City, CA) developed Maxy-VII as a form of rFVIIa with increased platelet binding and more glycosylation to increase product half-life. Although approved for Phase I trials in 2008 by the FDA, these have not yet been conducted.
5. Factor VIIa-albumin fusion protein, with a reported 6-9 fold increase in half-life, is being developed by CLS Behring (King of Prussia, PA).
6. Bio Affinity Company (Naarden, Netherlands) is developing a version of rFVIIa to be produced by transgenic cows, a less expensive production strategy than cell culture.

Recombinant factor XIII is another Novo Nordisk product currently undergoing testing as a hemostatic agent in cardiac surgery patients. This glycoprotein facilitates clotting by cross-linking fibrin molecules, a process that stabilizes nascent, unstable clots. This mechanism may lead to less risk of inappropriate thrombosis because factor XIII acts only at the site of early clots, rather than participating in new clot formation.

Off-Label Indications

The use of rFVIIa for off-label clinical indications originates in rFVIIa's ability to "bypass" multiple defects in the coagulation pathway. These uses can be defined by their relative proximity to the FDA approved uses. The following categories suggest increasing extension of rFVIIa use into clinical areas with diminishing similarity to the FDA approved uses.

1. Chronic prophylactic use in Hemophilia A and B in the absence of bleeding episodes or procedures. While not approved by the FDA, this form of use has been approved in Australia.
2. Episodic use in other congenital and acquired clotting factor defects, including Hemophilia C, von Willebrand's disease, and factor VII deficiency, as well as in other rare coagulopathies.
3. Episodic use for isolated congenital or acquired clotting defects that arise from deficiency or dysfunction of other components of the coagulation process. This includes platelet dysfunction, such as Glanzmann's thrombasthenia, which has been approved by the EMEA but not the FDA.
4. Episodic use in disease states where impaired coagulation is but one manifestation. Liver disease is a prominent example, but other conditions include leukemia, lymphoma, and other cancers.
5. Episodic use where anticoagulant therapy contributes to bleeding problems beyond what would exist otherwise. This includes patients on warfarin and those undergoing cardiac surgery with cardiopulmonary bypass that requires heparin anticoagulation.

6. Clinical circumstances where a consumptive coagulopathy has developed as the result of substantial and rapid blood loss. In practice, this often includes trauma patients and those with massive gastrointestinal bleeding.
7. Situations where significant blood loss is anticipated in the absence of pre-existing coagulopathy, as with prophylactic use of rFVIIa in prostatectomy or vascular surgery.
8. Clinical situations where prompt cessation of traumatic, surgical or spontaneous bleeding in non-coagulopathic patients is needed because hemorrhage extension is associated with significant adverse outcomes, as occurs with intracranial hemorrhage, brain surgery, and pulmonary hemorrhage.

Among these categories, there is less rationale for an effectiveness review of the first three (#1-3). These uses are closely connected with the FDA approved uses, are relatively infrequent and difficult to study, and may have been scrutinized by other national drug review systems. For these reasons, we have not examined in detail the off-label uses that comprise these categories, but do present data evaluating trends related to these clinical indications. The other categories warrant considerable attention given their high prevalence and their biological remoteness from use in hemophilia. The purpose of this report is to evaluate the evidence of rFVIIa use for five specific off-label indications that cover at least some aspects of the remaining categories of rFVIIa application: intracranial hemorrhage, massive bleeding from trauma, liver transplantation, cardiac surgery, and prostate surgery.

Past Systematic Reviews as Context for the Report

As we review in greater detail in the Discussion section, there have been a number of systematic reviews published on rFVIIa use for a variety of off-label indications, including some of those under consideration in this report.²⁵⁻⁶³ The most recent systematic reviews have largely concluded that there is insufficient evidence to fully evaluate the benefits or harms of rFVIIa. As a generalization across off-label clinical indications, and in the aggregate, these past reviews suggest that for rFVIIa use compared to usual care:

1. There is limited evidence of clinical benefit for some indications when measured by indirect/surrogate end-points.
2. There is insufficient evidence available to evaluate the impact of rFVIIa use on direct clinical outcomes such mortality and functional status.
3. The evidence is inconclusive, but there are non-significant trends that suggest an increase in thromboembolic harms for some indications.

These past systematic reviews varied in their quality of methodology and in the types and quality of the studies included. Given the ambiguity of past reviews, the rapid expansion of knowledge on off-label use, and practice trends that are outstripping the available evidence, re-evaluation of the current literature on off-label rFVIIa use is warranted.

Clinical Considerations of Heterogeneity

In contemplating this task, we noted that some prior systematic reviews pooled data from studies that assessed multiple disparate clinical indications. We felt that evaluation of rFVIIa globally required combining conditions that are so clinically heterogeneous that the results were likely to be extremely difficult to interpret. So we agreed, in general, with the different approach encompassed in the original Key Questions of the report, which differentiate by clinical

indication of use. We acknowledge, however, that selection of the appropriate degree of specificity is difficult and may be controversial. For instance, as discussed in detail below, we determined that certain subgroups within trauma and cardiac surgery warranted further division beyond what was originally encompassed in the Key Questions, and, therefore, we chose to evaluate these subgroups separately. We also included within each Key Question a section on qualitative considerations of heterogeneity to provide further context for our decisions to pool or not pool data from individual studies or particular patient populations.

Areas of Anticipated Challenge

We identified a number of areas of anticipated challenges for our review.

Lack of comparison to predecessor products. No prior studies compare rFVIIa to predecessor products that might be considered alternative therapies in certain clinical scenarios (e.g., aPCC, aminocaproic acid, and tranexamic acid). This means that rFVIIa is compared to “usual care” for the evaluations of effectiveness.

Comparisons to usual care. Unlike a comparison to an alternative pharmaceutical agent, comparisons to usual care are particularly susceptible to bias. Site-to-site variations in usual care inevitably exist, and this lack of comparator uniformity may be substantial for trials conducted in multiple centers and multiple countries. In addition, advances in usual care may evolve over time, which creates additional heterogeneity, diminishes the relevance of past comparisons to current practice, and may diminish the marginal benefit of rFVIIa added to “usual care.”

Manufacturer with intensive involvement in research studies. Novo Nordisk’s sponsorship and involvement in rFVIIa clinical research is extensive, as might be expected of a manufacturer producing the only available product in a drug class. Its likely role in past decisions about research topics and design creates a potential conflict of interest. While these circumstances are not infrequent and do not equate with biased research findings, it does require special care in evaluating the possibility of bias in published studies examining rFVIIa’s use for off-label indications. At the same time, the manufacturer has funded studies on off-label uses of rFVIIa that would otherwise likely have not been undertaken.

Use of drug in emergency situations. In 1996, the FDA and Departments of Health and Human Services issued new guidelines on the study of drugs in emergency situations, allowing for a deferral of informed consent in a rule commonly referred to as Emergency Medicine Exception From Informed Consent.^{64,65} While policies and practices in Europe are in flux,⁶⁶ similar allowances are made in some European countries.⁶⁷ In the United States, the exception can be made only when the following criteria are met: the condition being studied is acute and life threatening, current therapies are inadequate, the window of opportunity for intervention is brief, it is not possible to obtain informed consent from the patient or legally authorized representative, there is the potential of direct benefit to the participant, and the risks of participation are reasonable in proportion to the potential benefits. These criteria might apply in a number of indications covered in this effectiveness review, namely intracranial hemorrhage, traumatic bleeding, and, in some cases, bleeding related to surgery. Patients may withdraw their “deferred consent” at such time as they are able to do so, which *de facto* occurs after randomization. The withdrawals can occur in a differential fashion based on the participant’s ability to survive long

enough to object to enrollment. Thus, one can imagine a situation in which a group with more favorable survival actually has an increased rate of withdrawal solely on the basis of withdrawal of deferred consent by the patients who have lived long enough to object to being enrolled in a study. Note that this issue does not imply the lack of ethical trial conduct, but represents a potential difficulty in interpreting the results of these trials.

Variability in dose, repeat dosing, and prophylactic versus rescue use of rFVIIa. Studies vary widely in the doses of rFVIIa used. This issue is most challenging when rFVIIa is used in dose escalation studies. In the absence of demonstrable dose-effect relationships, inclusion of all doses may be reasonable. Studies also vary in their protocols regarding the acceptability of repeat dosing. Finally, within some clinical indications, separate studies evaluate use of rFVIIa as prophylaxis or treatment therapy, which increases the potential heterogeneity of clinical context and patient characteristics.

Special subgroups within trauma and cardiac surgery. Within the trauma indication for rFVIIa use, patients who have bleeding associated with traumatic brain injury (TBI) form a distinct subgroup of patients, which can present unique challenges that overlap with—and yet are distinct from—the challenges faced in managing other types of trauma-related hemorrhage. Similarly, cardiac surgeries for congenital abnormalities, generally performed in infancy, can differ greatly from cardiac surgeries performed in adults. For these reasons, we anticipated the need to distinguish between these subgroups of patients with hemorrhage: patients with brain trauma versus body trauma, and patients undergoing pediatric versus adult cardiac surgery.

Key Questions that Guide the Current Report

This report has two primary objectives:

1. To document the complete range of clinical indications where rFVIIa is being used off-label, including information on real-world in-hospital practice patterns and the clinical studies available to evaluate these uses
2. To provide a comparative effectiveness review of rFVIIa versus usual care for selected off-label clinical indications: intracranial hemorrhage, massive bleeding secondary to trauma, and the surgical procedures of liver transplantation, cardiac surgery, and prostatectomy.

We were guided in our exploration of these issues by a set of Key Questions developed in preparation for the project by AHRQ. Construction of these questions included substantial input from key stakeholders, as well as refinement by the research team during the initiation of the project. These Key Questions helped define the scope and approach of this project. As below, Key Question 1 pertains to our first objective of documenting the range of rFVIIa off-label use. Note that this focus on “patterns of use” is directed solely at in-hospital populations (which is the population to whom off-label rFVIIa is applied, *not* outpatient populations). The other Key Questions reflect the emphasis of this report on the selected indications.

Key Question 1

Recombinant factor VIIa is being administered and studied in an increasingly wide range of disease conditions and patient populations beyond the scope of its current labeled indications. With the intent of providing an overview of the range of off-label clinical conditions for which rFVIIa has been administered and/or studied:

1. What are the different indications and populations for which rFVIIa has been used and/or studied outside the currently labeled indications?
2. What is the clinical setting, dosage range, study design/size, comparator, and outcomes measured in past comparative studies investigating off-label rFVIIa?

Key Question 2

Considering patients presenting with **intracranial bleeding**:

1. Does rFVIIa use reduce mortality and/or disability compared with currently accepted usual care?
2. Are there subpopulations of patients based on demographic or clinical factors who are more likely to benefit from rFVIIa use?
3. Does rFVIIa use increase thrombosis-related events compared with usual care?
4. Are there subpopulations of patients based on demographic or clinical factors who are more likely to experience harm from the use of rFVIIa compared with usual care?
5. In whom do the benefits of rFVIIa use outweigh the harms (evidence of net benefit), and does net benefit vary by issues such as timing and dosage used?

Key Question 3

Considering patients with acquired, coagulopathic **massive bleeding from trauma**:

1. Does rFVIIa use reduce mortality and/or disability compared with currently accepted usual care?
2. Are there subpopulations of patients based on demographic or clinical factors who are more likely to benefit from rFVIIa use?
3. Does rFVIIa use increase thrombosis-related events compared with usual care?
4. Are there subpopulations of patients based on demographic or clinical factors who are more likely to experience harm from the use of rFVIIa compared with usual care?
5. In whom do the benefits of rFVIIa use outweigh the harms (evidence of net benefit), and does net benefit vary by issues such as timing and dosage used?

Key Question 4

Considering patients undergoing liver transplantation, cardiac surgery, or prostatectomy:

1. Does salvage and/or prophylactic rFVIIa use reduce mortality and/or disability and treatment-related outcomes compared with currently accepted usual care?
2. Are there subpopulations of patients based on demographic or clinical factors who are more likely to benefit from rFVIIa use?
3. Does rFVIIa use increase thrombosis-related events compared with usual care?
4. Are there subpopulations of patients based on demographic or clinical factors who are more likely to experience harm from the use of rFVIIa compared with usual care?
5. In whom do the benefits of rFVIIa use outweigh the harms (evidence of net benefit), and does net benefit vary by issues such as timing and dosage used?

Methods

Topic Development

The topic for this comparative effectiveness review (CER) was nominated in a public process that solicited input from professional societies, health systems, employers, insurers, providers, consumer groups, and manufacturers, amongst others. The draft Key Questions were developed by the Scientific Resource Center (SRC) on behalf of the AHRQ Effective Health Care Program and, after approval from AHRQ, were posted on a public website for public commentary. After reviewing the public commentary, as well as input from experts and stakeholders, the SRC made further revisions to the Key Questions. The Key Questions were then presented to the Stanford-UCSF Evidence-based Practice Center (EPC), and minor revisions were made on the basis of joint discussions between the Stanford-UCSF EPC, Technical Expert Panel (TEP), AHRQ, and the SRC.

Framework for Analyzing Outcomes for rFVIIa Use

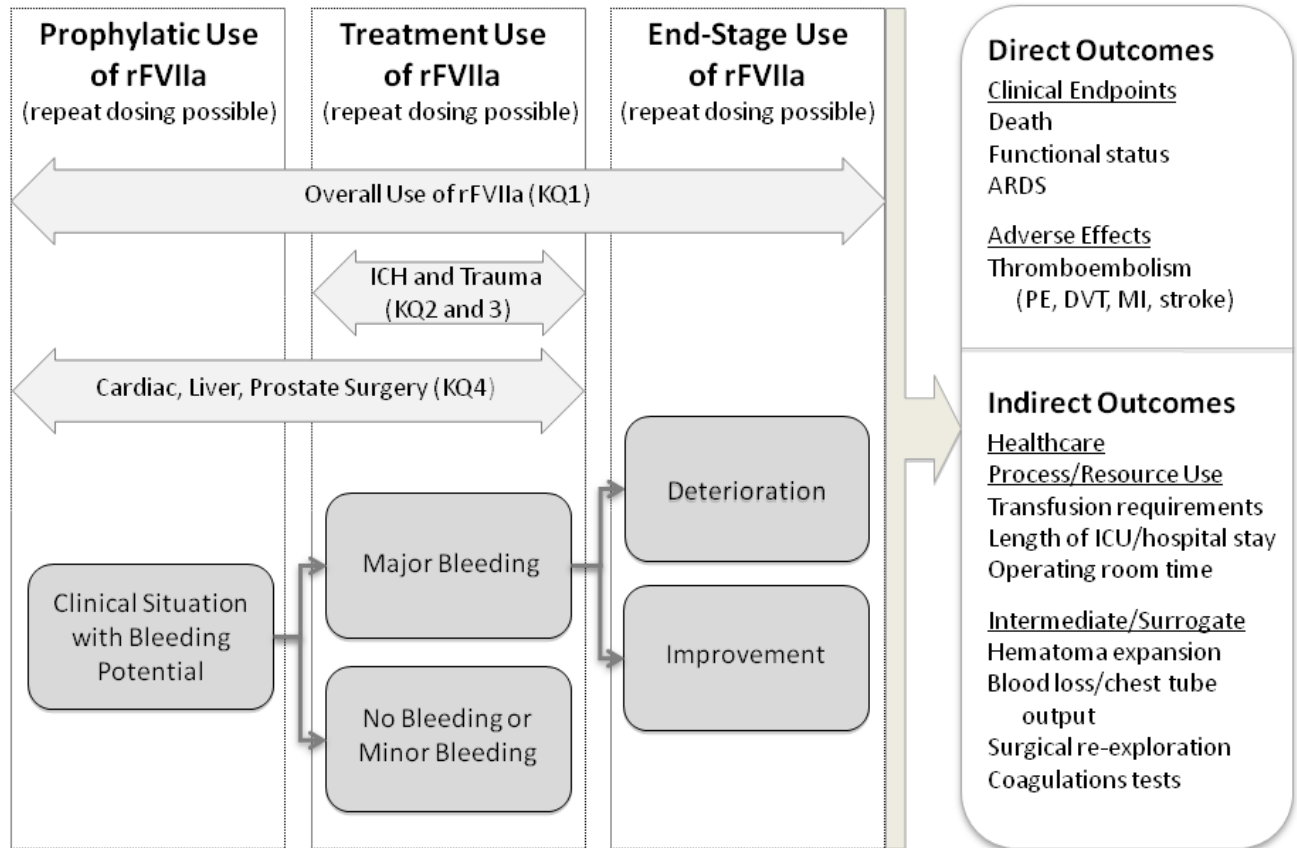
Our analytic framework for evaluating the off-label use of rFVIIa is shown in Figure 1. The figure represents the trajectory of a patient who receives rFVIIa at some point during inpatient medical care. The first possible time of drug administration is in the case of prophylactic use (to limit blood loss) during a potentially bloody surgery, such as liver transplantation or cardiac surgery. The second possible time of drug administration is in the case of treatment use, which occurs as an attempt to arrest ongoing bleeding and is employed in numerous clinical scenarios, including intracranial hemorrhage and trauma. The final possible time of drug administration is in the case of end-stage use, as a last-ditch effort to salvage a patient who is dying from massive hemorrhage and for whom other interventions have failed. Repeat doses of rFVIIa are possible during any of the above applications, for example during a long surgery or for ongoing hemorrhage.

Thick horizontal arrows near the top of the figure represent the overlap between the Key Questions (KQs) addressed by this report and the different types of rFVIIa use described above. For example, the bar representing KQ1 (Overall use of rFVIIa) spans the entire range of potential uses—prophylaxis, treatment, and end-stage—whereas the bar representing KQ2 (intracranial hemorrhage) encompasses only treatment use.

At the right side of the figure are examples of potential outcomes of rFVIIa use. These encompass a range, from indirect outcomes—of process/resource use or intermediate/surrogate outcomes (which are perhaps the easiest to measure but are not always closely connected to patient status)—to direct clinical endpoints such as death, adverse events, or functional outcome (which are the most relevant to patient well being but are often more difficult to measure or occur less frequently than the other outcomes). An important point to note in relation to studies of rFVIIa is that some of them presuppose the plausible—but as-of-yet unproven—assumption that cessation of bleeding, as measured via intermediate endpoints such as blood loss or transfusion requirements, is associated with improvements in direct outcomes, such as mortality. One of the goals of this analytic framework, and indeed the effectiveness reviews, is to attempt to evaluate whether this assumption (of improvements in intermediate outcomes being linked to improvements in direct outcomes) is substantiated by the evidence. Ideally, the report would focus primarily on 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 have few events of this type.

Figure 1. Framework for analyzing outcomes for rFVIIa use



Search Strategy

Premier Database on Hospital Use of rFVIIa

We analyzed nationally representative data on patients who received rFVIIa during a hospitalization. Our analytic goals were:

1. To provide an overview of trends in in-hospital rFVIIa use, particularly for off-label uses.
2. To portray the range of clinical conditions for which rFVIIa has been administered in-hospital.
3. To examine the clinical and demographic characteristics of in-hospital rFVIIa users in relation to the populations studied in comparative studies.
4. To validate the relevance of the five indications selected by AHRQ for in-depth systematic review.

We used 2000 through 2008 data from the Perspective Comparative Database of Premier, Inc. (Charlotte, NC) (subsequently referred to as “Premier database”). The Premier database is the largest hospital-based, service-level comparative database in the country. On an annual basis, the Premier database includes information on 40 million hospitalizations occurring in 615 U.S.

hospitals. The Premier database excludes federally-funded (e.g., Veterans Affairs) hospitals. Otherwise, included hospitals are nationally representative based on bed size, geographic location, designation as urban versus rural, and teaching status (academic versus non-academic). The Premier database provides detailed information on the demographics, diagnoses, and resource utilization of de-identified hospitalized patients, as well as hospital and billing information (Table 1). We received data on all hospital discharges from January 2000 through December 2008 where rFVIIa use was reported. There were a total of 12,644 hospitalizations involving rFVIIa use (“cases”) that occurred in 235 hospitals within the Premier database hospital sample. In addition, we included 78 cases reported uses at these hospitals that did not result in a hospitalization (i.e., patients who received hospital-based outpatient treatment and comprised 0.6 percent of total cases).

Table 1. Data variables available from the Premier database

Data Category	Types of Data
Patient characteristics	Hospitalization and patient ID Primary and secondary ICD-9 Diagnosis and Procedure codes Diagnosis Related Group Patient age, gender, and race/ethnicity Attending and consulting physician specialties Length of hospital stay Primary payer Admission type and source (ER, SNF, transfer, home) Discharge status (deceased, transfer, SNF, home)
Hospital characteristics	Bed size Geographic region and area Teaching status Urban/rural designation
Other billing information	For services patients received each day during their hospitalization, individual service items, quantity, costs, and charges for all service departments were provided (e.g., drug quantity/cost, operating room charges, laboratory tests performed, and diagnostic imaging performed).

Each hospitalization encounter has an associated statistical weight that allows extrapolation to the volume of hospitalizations estimated for the U.S. as a whole. These weights are based on the inverse of the sampling probabilities associated with each hospital in relationship to the universe of non-federal acute care hospitals, stratified by hospital characteristics, so that the aggregate of hospitalizations approximates the number and distribution of discharges from acute care, non-federal hospitals.

Data Sources for Included Studies

At the broadest level, we sought to identify all comparative studies evaluating off-label clinical applications of rFVIIa. Delineation of this evidence base is the foundation of the overview of studies of off-label rFVIIa use. The sub-sets of identified studies that were directed at the five selected indications of intracranial hemorrhage, trauma, liver transplantation, cardiac surgery, and prostatectomy could then also be used in the comparative effectiveness reviews of each of these indications. Because of the importance of evaluating the potential for harm caused by rFVIIa, we also searched for non-comparative studies that reported on harms for the selected indications. Finally, we also sought to identify relevant systematic reviews or meta-analyses.

We searched the following databases using search strings described in detail in Appendix A: PubMed, EMBASE, Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, and BIOSIS through August 4, 2009. In addition, a librarian at

the Scientific Resource Center, who is an expert at searching the “grey literature” (sources other than published materials indexed in bibliographic databases such as Medline), searched regulatory sites (FDA, Health Canada, Authorized Medicines for EU), clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, and WHO Clinical Trials), abstract and conference proceedings (Conference Papers Index and Scopus), grant and federally funded research sites (NIH RePORTER and HSRPROJ), and other miscellaneous sources (Hayes, Inc. Health Technology Assessment and NY Academy of Medicine’s Grey Literature Index) and also contacted the authors of abstracts regarding subsequent full publications. Because we confirmed with the manufacturer (Novo Nordisk) that all of its trials were listed on the ClinicalTrials.gov website, we did not search the European Union’s EMEA database of trials. Finally, we reviewed the manufacturer’s website and files supplied by the manufacturer, searched the bibliographies of identified meta-analyses and systematic reviews, and contacted experts in the field to identify relevant publications.

Study Selection

We applied criteria for inclusion and exclusion based on the indication for rFVIIa use, outcome measures, and types of evidence specified in the Key Questions. We retrieved full-text articles of potentially relevant abstracts to which we re-applied inclusion and exclusion criteria.

Exclusion Criteria

Abstracts only. Results published only in abstract form were not included in our analyses.

Inappropriate intervention or outcome. We excluded studies of human (rather than recombinant) FVIIa and modified forms of rFVIIa that are still under development (e.g., pegylated forms). We also excluded studies that were performed on humans but in which the outcome measures were not deemed to be clinically relevant to efficacy or effectiveness. Examples include pharmacologic studies solely directed at metabolism or half-life or studies in healthy volunteers directed at monitoring parameters such as INR or thromboelastin time. We also excluded studies that were *in vitro* only (i.e., performed in a laboratory setting without translation to a patient).

Clinical indication for rFVIIa use. We excluded studies of on-label applications of rFVIIa in the U.S., which include use in hemophilia A or B with inhibitors and congenital factor VII deficiency. We also excluded studies of rFVIIa applied to populations of patients that are substantially similar to those for whom on-label indications have been approved. We sought expert input from an hematologist to define these patient populations, which were determined to include: Glanzmann’s thrombasthenia (for which rFVIIa is approved in Europe), hemophilia C, von Willebrand disease, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome, and other congenital bleeding disorders.

Comparison Group of “Usual Care”

Key Questions 2-4 compare the effectiveness of rFVIIa with “usual care.” Based on our initial review of the literature and discussion with experts, we noted both evolution over time and regional or hospital differences in the parameters of “usual care” for almost all of the selected indications.⁶⁸ Given these differences, we were concerned that the marginal benefit of rFVIIa

when added onto “usual care” might vary according to the standard of care employed. An example of such a situation might be when the baseline level of anticipated blood loss from a surgical intervention diminishes substantially over time, thus minimizing the marginal benefit of rFVIIa. For this reason, we built into our data abstraction tool a section for the prospective collection of data on the standard of care employed in each study.

Types of Evidence

Overview of comparative off-label studies. For Key Question 1, we limited our article selection to those with comparative study designs that would be expected to provide evidence on effectiveness, which included RCTs and comparative observational studies. Based on an initial review of the literature, we identified clinical categories of significant off-label rFVIIa use that were separate from the five indications that are the focus of the comparative effectiveness section of this report. We prospectively coded the studies identified in these categories which include bleeding related to: other liver disease, obstetrics/gynecology, hematology/oncology, other gastrointestinal bleeding, other surgery, and all other.

Comparative effectiveness reviews on Key Questions 2 through 4. For the comparative effectiveness review of the selected indications of intracranial hemorrhage, trauma, liver transplantation, cardiac surgery, and prostatectomy, we were especially concerned about capturing possible evidence of rare harms. For this reason, we expanded our article selection beyond comparative studies to non-comparative studies. While non-comparative data are open to many sources of bias, lack generalizability, and thus are clearly a weaker source of evidence than comparative studies, they also may report rare events not identified in RCTs. Thus, they can still be an important source of information regarding harm. The non-comparative observational studies we chose to include were registries and cohorts with at least 15 patients, because we believe that the risk of bias (e.g., selective reporting) is likely increased in small reports; the selection of 15 patients as the cut-off point was arbitrary. Table 2 provides a schematic of which study types were used to conduct which assessments in this report.

Although five discrete indications were defined by the AHRQ Key Questions, our review made it evident that two of these indications were too heterogeneous for valid aggregation in the systematic review. Patients with traumatic bleeding can be divided into two distinct, albeit overlapping, groups: (1) those primarily with TBI and (2) those primarily with body trauma. Cardiac surgery, particularly as it pertains to rFVIIa use, also encompasses two populations of patients: (1) those with congenital heart defects requiring surgical correction beginning in infancy, and (2) those with cardiac problems as adults who require cardiac surgery to repair pathology generally resulting from degenerative or atherosclerotic processes. Based on these distinctions, we present a total of seven systematic reviews for each of the following rFVIIa indications: intracranial hemorrhage, body trauma, brain trauma, liver transplantation, adult cardiac surgery, pediatric cardiac surgery, and prostatectomy.

Independent determination of agreement on selection. To determine whether a given study met inclusion criteria, two authors independently reviewed the title, abstract, and full text (as necessary). Conflicts between reviewers were resolved through re-review and discussion. The overwhelming majority of conflicts regarding inclusion or exclusion related to the assignment of a specific reason for exclusion (i.e., there were often multiple reasons for exclusion of a given

article but one needed to be assigned primacy), rather than disagreement over whether a particular article should be included or excluded.

Table 2. Use of different study types for each component of this comparative effectiveness review

Study Category		Use in the Comparative Effectiveness Review			
		Survey of Existing Research (KQ1)	Evaluation of Effectiveness (KQ2-4)		Evaluation of Harms (KQ2-4)
			Systematic Review	Meta-Analysis	
Randomized clinical trials	Five key indications	X	X	X*	X
	Other indications	X		Outside Project Scope [†]	
Comparative observational studies	Five key indications and good quality	X	X	X*	X
	Five key indications and fair quality	X	X	Insufficient Quality	X
	Five key indications and poor quality	X		Insufficient Quality for detailed review**	X
	Other indications	X		Outside Project Scope [†]	
Non-comparative observational studies	Five key indications and ≥ 15 patients	Outside Project Scope [†]	Contributes No Information		X
	Other indications or < 15 patients reported		Outside Project Scope [†]		

X represents use of this study category for each component.

*For the indications where a sufficient number of quality studies existed to justify the use of meta-analytic tools. We defined a sufficient number to be a total of at least two studies of fair or better quality, including at least one study of good quality.

**Poor quality comparative observational studies were not reviewed in detail in the evaluation of effectiveness, but their data were included in the outcomes tables so that qualitative sensitivity analyses could be performed by placing their findings in the context of the findings of the higher quality studies.

[†]Because certain study categories fell outside of the project scope, they were not used for the indicated evaluations in the comparative effectiveness review.

Data Extraction

We extracted the following data from all of the included studies: study design; setting; patient characteristics; inclusion and exclusion criteria; detailed information about the dosing and administration of rFVIIa; numbers of patients eligible, enrolled, and lost to follow-up; details about outcome ascertainment; and information about “usual care” (because of difference over time and between regions/hospitals for the latter⁶⁸).

Table 3 provides additional details on the important baseline characteristics and outcomes that were assessed for all studies and according to clinical indication. These were determined *a priori* through discussion with experts and review of the literature. At least two investigative team members, including one clinical and one non-clinical member, independently abstracted data onto pre-tested abstraction forms (Appendix E). Conflicts regarding data abstraction were resolved by re-review, discussion, and input from others, as necessary.

Table 3. Important baseline data and outcomes according to clinical indication

Clinical Indication	Baseline characteristics pertinent to propensity for poor clinical outcome	Outcomes
All	International normalization ratio (INR) Prior thromboembolic events Other risk factors for thromboembolic events	Transfusion requirements Mortality Thromboembolic events
Intracranial hemorrhage	Hematoma volume Presence of intraventricular hemorrhage Glasgow Coma Scale (GCS) score NIH Stroke Scale (NIHSS) score Systolic blood pressure	Relative or absolute change in hematoma volume Functional outcome as measured by the modified Rankin Scale (mRS)
Body trauma	Type of trauma (blunt versus penetrating) Injury Severity Score (ISS) Presence of acidosis/base deficit	Acute respiratory distress syndrome (ARDS)
Brain trauma	GCS score	Relative or absolute change in hematoma volume
Liver Transplantation	Child-Pugh Score Status as repeat surgery Ischemia time of donor liver	Operating room (OR) time Intensive care unit (ICU) length of stay
Adult cardiac surgery	Cardiopulmonary bypass (CPB) time Status as complex or emergency surgery	ICU length of stay
Pediatric cardiac surgery	CPB time Status as complex surgery Weight	Time to chest closure in operating room
Prostatectomy	Type of surgery	OR time

Quality Assessment of Individual Studies

Criteria

We used predefined criteria to assess the quality of included studies. We generated these criteria 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) to identify articles on the study quality of RCTs and comparative observational studies. We found general agreement in the literature on key components of RCT study quality, but less agreement regarding comparative observational studies. Therefore, we felt that existing quality assessment tools were not complete in assessing key criteria for both RCTs and comparative observational studies and chose to consolidate the areas of criteria overlap, but leave distinct the criteria pertinent only to RCTs or observational studies, respectively. All criteria were culled from the existing literature of quality assessment tools or expert consensus statements on important quality criteria. For RCTs, the quality criteria were based on the Jadad score,⁶⁹ studies of the methodologic quality of RCTs and its impact on treatment effect estimates,⁷⁰⁻⁷² the CONSORT statement,^{73,74} and the Methods Guide.^{75,76} For observational studies, the quality criteria were selected as those most consistently cited by experts in a published systematic review of quality tools,⁷⁷ a Health and Technology Assessment Report on the evaluation of non-randomized studies,⁷⁸ the STROBE statement,^{79,80} and the Methods Guide.^{75,76} Table 4 indicates the quality domains and criteria we used to evaluate RCTs and comparative observational studies, respectively. Most quality criteria apply to both study types (six total—subject selection, comparability of groups, protections against bias in outcomes, follow-up, and protections against bias in analyses, and conflict of interest). But three criteria were unique to either RCTs (methods of allocation) or observational studies (sample size and methods to characterize exposure). We gave certain criteria, indicated in bold in the table, the most weight in our qualitative evaluations,

because our review of the literature indicated that the data and experts most agree on their importance to a determination of methodological quality. A study's quality was not downgraded because of an identified conflict of interest (all of which were identified as manufacturer sponsorship or affiliation); rather, this information is discussed further in the methods below and was included in the results table on general characteristics of all included studies (Table 11).

Table 4. Quality domains and criteria for assessing RCTs and comparative observational studies

Quality domain	Quality criteria	
	RCTs	Comparative observational studies
Subject selection	Appropriate subject selection	Appropriate populations selected Appropriate protections against selection bias between groups
Methods of allocation	*Randomization *Allocation concealment	-
Sample size	-	Adequate sample size
Comparability of groups	Baseline comparability of groups	*Study design appropriate to generate comparability of groups (e.g., strict inclusion criteria) Baseline comparability of groups
Methods to characterize exposure	-	Valid methods to identify and characterize exposure
Protections against bias in outcomes	*Blinding of subjects and providers *Blinding of outcomes assessors Use of valid outcome measures	*Blinding of outcomes assessors Use of valid outcome measure
Follow-up	*Absence of differential follow-up or high rates of drop-outs, withdrawals, or missing data	*Absence of differential follow-up or high rates of missing data
Protections against bias in analyses	Appropriate statistical analyses Intention-to-treat analyses	*Appropriate methods to control for confounding (e.g., adjustment for baseline characteristics known to be associated with prognosis) Appropriate methods to address design issues other than confounding Appropriate statistical analyses
Conflicts of interest	Absence of important sources of conflict of interest	Absence of important sources of conflict of interest

*Criteria that were given special emphasis by experts in our literature review, and hence in our quality review, are shown in bold.

Financial Support from the Manufacturer of rFVIIa

We evaluated the degree of financial support provided by the manufacturer, Novo Nordisk, according to the following schema: sponsorship of the study or the author or statistician being a Novo Nordisk employee was deemed to be substantial support and was labeled as “funding,” while other financial ties (e.g., being member of speakers bureau, getting some measure of research funding from Novo Nordisk, etc.) were noted as “affiliation.”

Assessment

Using the above criteria, two assessors independently assigned a quality grade to each study after coming to a qualitative determination of its overall methodological quality. The assigned categorical grade could be one of three, as suggested by the Methods Guide:⁷⁶ good, fair, or poor (Table 5). Disagreements were resolved by discussion, with accommodation made for involvement of a third reviewer, if necessary, but this was never required. This grading system attempted to assess the comparative quality of studies that share the same study design

(e.g., two RCTs)—but *not* the comparative quality of studies of different types (e.g., an RCT versus an observational study). For example, an RCT assigned a grade of “fair” was not judged to have equal methodological quality to a comparative observational study assigned a grade of “fair.” Rather, both study design and study quality were considered when evaluating the overall validity of a study.

Use of poor quality studies in the report. Using the above logic, all RCTs, including those of poor quality, were included in the evaluations of effectiveness for each clinical indication, whereas poor quality comparative observational studies were not reviewed in detail in the comparative effectiveness review but were used for qualitative sensitivity testing (by placing their findings in the context of those of the higher quality studies) and the harms analysis at the end of the report (Table 2).

Table 5. Criteria for assigning quality grade to individual included studies

Quality Grade	Criteria
Good	Study has the least bias and results are considered valid. It has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients; has a low dropout rate; and uses appropriate means to prevent bias; measure outcomes; analyze and report results.
Fair	Study is susceptible to some bias, but probably not sufficient to invalidate the results. It may be missing information, making it difficult to assess limitations and potential problems. As the “fair-quality” category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	Study has significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Assessing the Strength of Evidence and Applicability for Each Key Question

Strength of Evidence

We applied the strength of evidence rating system recommended by the EPC working group on evidence grading.⁷⁶ Specifically, two reviewers independently assessed the strength of evidence for the major outcomes in each of the Key Questions 2-4. To accomplish this, they first assigned individual scores to the four evidence domains defined further in Table 6: risk of bias, consistency, directness, and precision. Additional information on how the reviewers assessed the specific domain of “risk of bias” is included in Table 7: it was determined by both the type and aggregate quality of the studies on a given clinical outcome.

Based on the individual scores the reviewers assigned to the evidence domains, they then assigned an overall “strength of evidence rating” (defined in Table 8) to each clinical outcome. The reviewers’ domain scores and overall strength of evidence ratings were compared, and 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. (See Appendix F for the strength of evidence evaluation form used by the reviewers.)

Table 6. The four domains of strength of evidence and their definition and scoring

Domain	Definition	Scoring
Risk of bias	The degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: study design and the aggregate quality of studies under consideration. The aggregate quality is based on the quality grades assigned to the individual studies.	Low risk of bias Medium risk of bias High risk of bias
Consistency	The degree to which reported effect sizes from included studies appear similar, assessed through two main elements: effect sizes have the same sign and the range of effect sizes is narrow.	Consistent Inconsistent Unknown (e.g., single study)
Directness	The degree to which the intervention can be directly linked to patient-centered outcomes (“direct” outcomes) using head-to-head comparisons rather than intermediate or surrogate outcomes (“indirect” outcomes).*	Direct Indirect
Precision	The degree of certainty regarding an effect size estimate. When a meta-analysis is performed, precision is indicated by the confidence interval around the summary effect size. An <i>imprecise</i> estimate is one for which the confidence interval is wide enough to include the clinically distinct conclusions of superiority or inferiority (e.g., risk difference crosses zero).	Precise Imprecise

*Note that a second type of *indirectness*, the need for extrapolation from multiple comparisons because a head-to-head comparison was not available, was not relevant to our sample of studies in which rFVIIa was always compared to usual care.

Table 7. Scoring the risk of bias for a given clinical outcome: determined by both the type and aggregate quality of studies

	Study type		
	RCT	Comparative observational	
Aggregate study quality	Good	Low risk of bias	Medium risk of bias
	Fair	Medium risk of bias	High risk of bias
	Poor	High risk of bias	Very high risk of bias

Table 8. Strength of evidence grading schema

Grade	Definition
High	There is high confidence that the evidence reflects the true effect.
Moderate	Further research may change the estimate of effect or the level of confidence in the effect.
Low	Further research is likely to change the estimate of effect or the level of confidence in the effect.
Insufficient	Evidence is either unavailable or does not permit a conclusion.

Applicability

Two independent assessors also evaluated the applicability to clinical practice of the total body of evidence within a given clinical indication in Key Questions 2-4. Disagreements were resolved by discussion, with accommodation made for involvement of a third reviewer, if necessary, but this was not required. Following the recommendations of the draft guidance document provided to EPCs,⁸¹ we used the PICOTS (population, intervention, comparator, outcome, timing, and setting) format to assess applicability. Table 9 describes the process and criteria we used for these assessments. On the basis of these criteria we rated the applicability of an area of evidence as poor, fair or good. Evidence for a given indication could only earn a “good” applicability rating when the applicability for each criterion within the PICOTS format was deemed to be good. The “fair” rating was broadest category and was achieved as long as the evidence for an indication did not earn a “poor” in more than one PICOTS criterion. A “poor” summary applicability rating was assigned if the evidence for an indication was deemed to “poor” in more than one PICOTS criterion.

Table 9. PICOTS criteria for assessing the applicability of evidence in Key Questions 2-4

	Describe Available Evidence	Note Conditions That May Limit Applicability	Describe Overall Implications for Applicability
Population	<ul style="list-style-type: none"> - Eligibility criteria and proportion of screened patients enrolled - Demographic characteristics - Severity or stage of illness - Event rates in treatment and control groups 	<ul style="list-style-type: none"> - Narrow eligibility criteria and high exclusion rate - Large differences between demographics of study population and that of patients in the community - Narrow or unrepresentative severity or stage of illness - Event rates much higher or lower than observed in population-based studies 	Describe how enrolled populations differ from target population and how this might affect risk of benefits or harms
Intensity or quality of intervention	<ul style="list-style-type: none"> - Dose, schedule, and duration of medication 	<ul style="list-style-type: none"> - Doses or schedules not reflected in current practice - Co-interventions that are likely to modify effectiveness of therapy 	Describe how studied interventions compare to those in routine use and how this might affect risk of benefits or harms
Choice of, and dosing of, the comparator	<ul style="list-style-type: none"> - Whether comparator is the best available alternative to the treatment under study 	<ul style="list-style-type: none"> - Use of sub-standard alternative therapy 	Describe whether comparators reflect best alternative treatment and how this may influence treatment effect size
Outcomes	<ul style="list-style-type: none"> - Effects of intervention on most important benefits and harms, and how they are defined 	<ul style="list-style-type: none"> - Using surrogate rather than clinical outcomes - Using composite outcomes that mix outcomes of different significance 	Describe whether measured outcomes reflect most important clinical benefits and harms
Timing and intensity of follow-up	<ul style="list-style-type: none"> - Range and intensity of follow-up 	<ul style="list-style-type: none"> - Follow-up too short to detect important benefits or harms - Follow-up duration unclear - Follow-up not intense enough to ascertain important benefits or harms 	Describe whether follow-up used is sufficient to detect clinically important benefits and harms
Setting	<ul style="list-style-type: none"> - Geographic setting - Clinical setting (e.g. referral center versus community) 	<ul style="list-style-type: none"> - Settings where standards of care differ markedly from setting of interest - Specialty population or level of care that differs importantly from that seen in community 	Describe whether the studies' settings differ meaningfully from settings in which the intervention may be applied

Data Synthesis

Analysis of Premier Database on In-Hospital Use of rFVIIa

Data measures. We used SAS Version 9.1 (SAS Institute, Cary, NC) to analyze data from the Premier database on in-hospital use of rFVIIa. We classified hospitalizations into discrete, mutually exclusive indication categories based on the clinical information associated with each hospitalization, which included multiple diagnoses and procedures. For our sample of 12,644 hospitalizations, a total of 286,113 diagnosis and procedure codes were reported. We therefore constructed a descending hierarchy of ICD-9 codes to categorize each hospitalization (Table 10; also see Appendix C, Appendix Table 1, for a full listing of ICD-9 codes). This hierarchy started with the most relevant, most reliable, and most specific clinical diagnoses, followed successively by less relevant, less reliable, or less specific diagnoses. We also created diagnostic categories that corresponded to reported rFVIIa indications in the literature, including the five key indications identified for in-depth review in this report. The hierarchy was based on both primary and secondary ICD-9 diagnostic codes, as well as ICD-9 procedure codes. A hospitalization was assigned to a diagnostic category based on the ICD-9 code that placed it in the highest category within the descending hierarchy.

Table 10. Diagnostic hierarchy for analysis of Premier database

Rank in Hierarchy	Description	Most Frequent Conditions or Procedures
1	Hemophilia A and B	Hemophilia A, Hemophilia B
2	Hemophilia-related off-label	Other clotting factor deficiencies, Glanzmann's
3	Brain trauma	Subdural hemorrhage, subarachnoid hemorrhage
4	All other trauma	Motor vehicle accident, fall, assault
5	Intracranial hemorrhage	Intracerebral hemorrhage, subdural hemorrhage
6	Brain surgery	Excision of lesion, craniotomy
7	Pediatric cardiac surgery	Transposition of the great vessels, atrial septal defect
8	Adult cardiac surgery	Aortic valve replacement, CABG, mitral valve
9	Obstetrics	Immediate post-partum hemorrhage, pre-eclampsia
10	Neonatal conditions	Respiratory distress syndrome, cesarean section
11	Aortic aneurysm	Abdominal aortic aneurysm, thoracic aortic aneurysm
12	Prostatectomy	Retropubic prostatectomy
13	Other vascular	Vascular bypass, intrabdominal venous shunt
14	Liver transplantation	Liver transplantation
15	Liver biopsy	Closed biopsy of liver, open biopsy of liver
16	Esophageal varices	Esophageal varices
17	Other liver disease	Non-alcoholic cirrhosis, alcoholic cirrhosis
18	Other gastrointestinal bleed	Unspecified gastrointestinal bleed, ischemic bowel
19	Other hematological	Unspecified coagulation defect, defibrination syndrome
20	Pulmonary	Closed bronchial biopsy, hemoptysis
21	Cancer	Acute lymphoid leukemia, acute myeloid leukemia
22	Other surgical procedures	Various
23	Other, without procedures	Various

Because of our focus on off-label use, our top priority diagnoses in this hierarchy were the FDA approved indications of Hemophilia A and B, followed by those unapproved indications that are similar to hemophilia or approved in other nations. If these diagnoses were noted, the hospitalization was classified into that category regardless of whether other prominent potential indications were noted during the same hospitalization. In turn, hospitalizations not classified as hemophilia and related conditions were categorized as brain trauma if any diagnosis indicated a non-iatrogenic cause of brain injury. Those cases not classified to this indication were then evaluated as to the presence of any diagnosis indicating a non-iatrogenic cause of injury, thus creating a category of trauma in the absence of head injury. This same process was used successively for the categories of intracranial hemorrhage, brain surgery, cardiovascular surgery, obstetrics, neonatal conditions, aortic aneurysm, prostate surgery, other vascular surgical procedures, liver transplantation, liver biopsy, variceal bleeding, other liver disease, other sources of gastrointestinal bleeding, other hematologic conditions, pulmonary conditions and procedures, cancer-associated use, all other surgical procedures, and, finally, other diagnoses not involving surgery. We further divided the cardiovascular surgery category into adult and pediatric populations. We also divided the “other hematologic conditions” category into two very different groups. We gave high priority to conditions that represent distinct and usually isolated defects in the clotting process, including other congenital factor deficiencies and Glanzmann’s thrombasthenia. We gave relatively low priority to less specific conditions that are less often isolated defects in clotting, but more likely the end product of other pathological conditions (particularly a variety of secondary thrombocytopenias). Where feasible, we captured the proximal causes of these coagulation problems earlier in the hierarchy, as with traumatic bleeding causing consumptive coagulopathy or the disruption of clotting produced by liver disease. We performed several sensitivity analyses to determine the impact of hierarchy order on these categorizations by moving indications up or down in the hierarchy to determine whether this changed their reported frequency.

Unit of analysis. The unit of analysis was any hospital “case” of rFVIIa use—defined as any application during a patient hospitalization. We favored the use of this case-based unit of analysis because of its advantages, particularly because it captures the medical decision-making 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 examined, including the number of times rFVIIa was dispensed by the inpatient pharmacy and the total dose of rFVIIa dispensed. However, we determined that these strategies of examining dosing had significant drawbacks, 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 versus vials dispensed)), and (3) outlier cases. Examination of the dosing information on outlier cases indicates substantial variation in the dose of rFVIIa dispensed during individual hospitalizations with some cases being dispensed a fraction of a 1.2 mg vial while others received more than a hundred vials. Individual cases with large aggregate dosages included both hemophilia and non-hemophilia cases. Analyses by dosing, rather than cases of use, could have different findings.

Lack of denominator. 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 we were unable to determine the overall denominator of potential rFVIIa usage (i.e., total number of patients eligible for use) for a given clinical indication.

Statistical analysis. Our statistical analysis focused on documenting annual trends in national estimates of in-hospital rFVIIa cases of use. We also analyzed and plotted aggregate rFVIIa use by quarter to characterize the most recent trends. To characterize patterns of use by indication, we produced a simple cross-tabulation of indication category by year. The data presented below combine several of the categories developed within the hierarchy that were not frequent, although we retained all five indication categories subjected to detailed systematic review in this report. This allowed us to gauge whether the volume of real-world use of rFVIIa for each of these indications warranted their selection by AHRQ for such in-depth examination. We reported characteristics of the population receiving rFVIIa, specifically age, gender, and in-hospital mortality rates, to allow for qualitative comparisons to the populations represented in the comparative studies. We also examined the hospital characteristics of teaching hospital status and regional location.

We employed statistical weights associated with each hospital by quarter. These weights allow for nationally representative projections of hospital activities. The weights are derived by Premier Inc. based on the relationship of the Premier hospital sample to the universe of non-federal, acute care hospitals. The statistical weights varied from around 10 in 2000 to around 5.5 in 2008 as a function of the increasing number of hospitals included in the Premier database. To weight the few non-hospitalized patient encounters, we used the corresponding weights for the same quarter and hospital.

Analysis of Comparative Studies

Issues of heterogeneity. We first addressed issues of heterogeneity at the level of the Key Questions. We determined that studies of trauma needed to be separated into those on body trauma and those on brain trauma because the challenges faced in managing these patients, while

overlapping, are distinct enough to warrant separate evaluation. Similarly, we determined that studies of cardiac surgery needed to be separated into those in pediatric patients (generally infants requiring correction of congenital cardiac abnormalities) and those in adult patients (generally patients in the sixth to eighth decades of life with cardiac problems related to age-related degeneration or dysfunction and with very different underlying thromboembolic risks than infants). For the remaining indications, we discuss issues of heterogeneity between studies within the effectiveness review of the given indication.

Statistical analysis. We considered studies eligible for meta-analysis regardless of study type (RCT versus comparative observational) as long as they met the quality criteria of being good or fair, and as long as they had similar interventions and patient populations in terms of baseline clinical characteristics. We performed meta-analyses when there were sufficient studies to warrant meta-analytic evaluations. We defined sufficient studies (for a given indication) as a total of at least two studies of fair or better quality, including at least one study of good quality.

Intervention and control arms were compared for continuous variables (e.g., hematoma volume for ICH patients) using a random effect 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,⁸² 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.⁸² It is calculated as:

$$\begin{aligned} \text{arcsin difference}(p_T, p_C) &= \arcsin(\sqrt{p_T}) - \arcsin(\sqrt{p_C}) \\ &\approx \sqrt{p_T} - \sqrt{p_C} \end{aligned}$$

We performed formal assessments of heterogeneity using the Q statistic for heterogeneity (and I² statistic as appropriate) and performed all meta-analytic calculations using the R statistics package (Version 2.10.0, "meta" and "rmeta" packages).

For the intracranial hemorrhage indication, there were special statistical considerations, and we made several *a priori* decisions regarding the statistical analyses to be performed. 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 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. However, in all of the RCTs, the different levels of treatment dosage were compared to a common control. In addition, some studies did not contain all levels of the treatment dosage. Because of these complexities, we applied methods developed by Olkin et al⁸² to analyze this kind of data when generating the summary effect sizes. Second, because there were suggestions in the literature of a possible association between rFVIIa and arterial thromboembolic events but not venous events and both types of data were available to us

from the ICH RCTs, we chose to analyze arterial and venous thromboembolic events separately for this indication. In contrast, we evaluated all thromboembolic events together for the remainder of the indications. Finally, while the summary effect sizes for the intracranial hemorrhage analyses are indeed accurate, their graphical representation using forest plots is complicated by their use of a common control for the different treatments dosages, so should be considered an aide to interpretation rather than a strict representation of the underlying metrics employed.

Analysis of Non-Comparative Studies for Data on Harm

To evaluate the evidence of harm of rFVIIa in the non-comparative study literature included in our review (registries and non-comparative cohorts with 15 or more patients), we report the unadjusted summary event rates for mortality and thromboembolic events from the non-comparative studies, the intervention arms of the comparative studies, and the Premier database.

Peer Review and Public Commentary

A draft of this Evidence Report was reviewed by experts in hematology, trauma surgery, liver transplantation, cardiac surgery, and prostatectomy (Appendix D). These experts were either directly invited by the EPC or offered comments through a public review process. The draft report was also reviewed by staff from the Scientific Resource Center at Oregon Health Science University and AHRQ staff. Revisions to the draft were made, where appropriate, based on the reviewer comments. However, the findings and conclusions are those of the authors who are responsible for the contents of the report.

Results

Summary of Studies and Data on In-Hospital, Off-Label rFVIIa Use

Table A in the Executive Summary provides an overall “snapshot” of the data and results for each of the Key Questions, as well as the conclusions of our effectiveness review.

Summary of Included and Excluded Studies

Our searches for studies on off-label use of rFVIIa identified 5,668 potentially relevant articles of which 1,326 merited full-text review (Figure 2). A total of 74 articles met our inclusion criteria for this review (Table 11). Seventeen of these only met our inclusion criteria for the first part of this report, the section on delineating the breadth of use of rFVIIa and the comparative studies of its use for the clinical indications not covered in Key Questions 2-4. An additional 57 articles met our inclusion criteria for the comparative effectiveness review, of which 14 were RCTs, 24 were comparative observational studies, and 19 were non-comparative reports from registries or cohorts (cohorts limited to those with at least 15 participants). Table 11 gives summary data on the characteristics of included studies. Most of the studies had small to moderate sample sizes, and there was great variability in the doses of rFVIIa administered. Tables 12 and 13 summarize the distribution of included studies by indication, design, and how they are used in this report. While the majority of studies reported data on mortality and thromboembolic events, almost none were powered to distinguish important differences in the rates of these between treatment groups (Appendix C, Appendix Table 2). Instead, most studies used indirect endpoints (e.g., change in hematoma volume or transfusions requirements) as their primary outcomes (Appendix C, Appendix Table 2).

Unpublished Studies in the Grey Literature

Studies identified via online databases where clinical trials are registered but without a subsequent publication. Our search of online resources (e.g., ClinicalTrials.gov or the manufacturer’s website) for ongoing or completed RCTs that were registered on an online database identified 29 trials with and without subsequent publications, either in the form of an abstract or published article (Appendix Table 4). Of the completed RCTs on Key Questions 2-4, 11 of 16 (69%) have been published: 71% (5/7) on intracranial hemorrhage, 50% (2/4) on body trauma, 50% (1/2) on adult cardiac surgery, and 100% on brain trauma (1/1), liver transplantation (1/1), and pediatric cardiac surgery (1/1). Three of five of the unpublished studies (one on intracranial hemorrhage and two in body trauma) were sponsored by the manufacturer.

Abstracts identified without subsequent publications. Our literature search identified 76 abstracts for which we were unable to find a subsequent full publication. All but three of these were excluded based on our exclusion criteria. Of these three abstracts, one described an RCT of rFVIIa use in liver transplantation with 12 patients in each of the treatment and placebo arms.⁸³ The remaining two abstracts described case series, containing 17 and 24 adult cardiac surgery patients, respectively.^{84,85}

Non-English language studies. We found 134 articles written in 15 different languages: 45 potentially addressing Key Questions 2-4 indications (intracranial hemorrhage, body and brain trauma, liver transplantation, adult and pediatric cardiac surgery, and prostatectomy) and 89 addressing other indications. Because we were not in a position to translate all of the different languages, we relied on English language abstracts and information in indexing databases to determine if articles met our inclusion criteria. Of the 45 articles on Key Questions 2-4 indications, 37 (82%) were excluded because they met other exclusion criteria. The remaining 8 (17%) were excluded solely on the basis of being published in a non-English language (Appendix Table 5). Of these, two were comparative studies. One was an RCT on adults who underwent cardiac surgery in China (11 patients each in the rFVIIa and placebo groups); this article was used for sensitivity analyses in the adult cardiac surgery section of Key Question 3. The other was a comparative cohort study of brain trauma with seven patients in the treatment group. The remaining six articles were case series (range of 15 to 34 patients). Of the 89 articles on other indications, 83 (93%) were excluded because they met other exclusion criteria; of the remaining six that were excluded on the basis of non-English language, four were case series, one was a comparative observational study and for one the study design was unclear.

Quality of Studies Included in Key Questions 2-4

The assigned grades of the two independent assessors never differed by more than one level of the categorical grading schema (good, fair, or poor). Of the RCTs assessed, there was initial agreement on the grade assignment in 13 of 14 (92%). Of the comparative observational studies assessed, there was initial agreement on the grade assignment in 22 of 24 (91%). All disagreements related to whether to categorize the given study as “poor” or “fair.” These were successfully resolved by discussion.

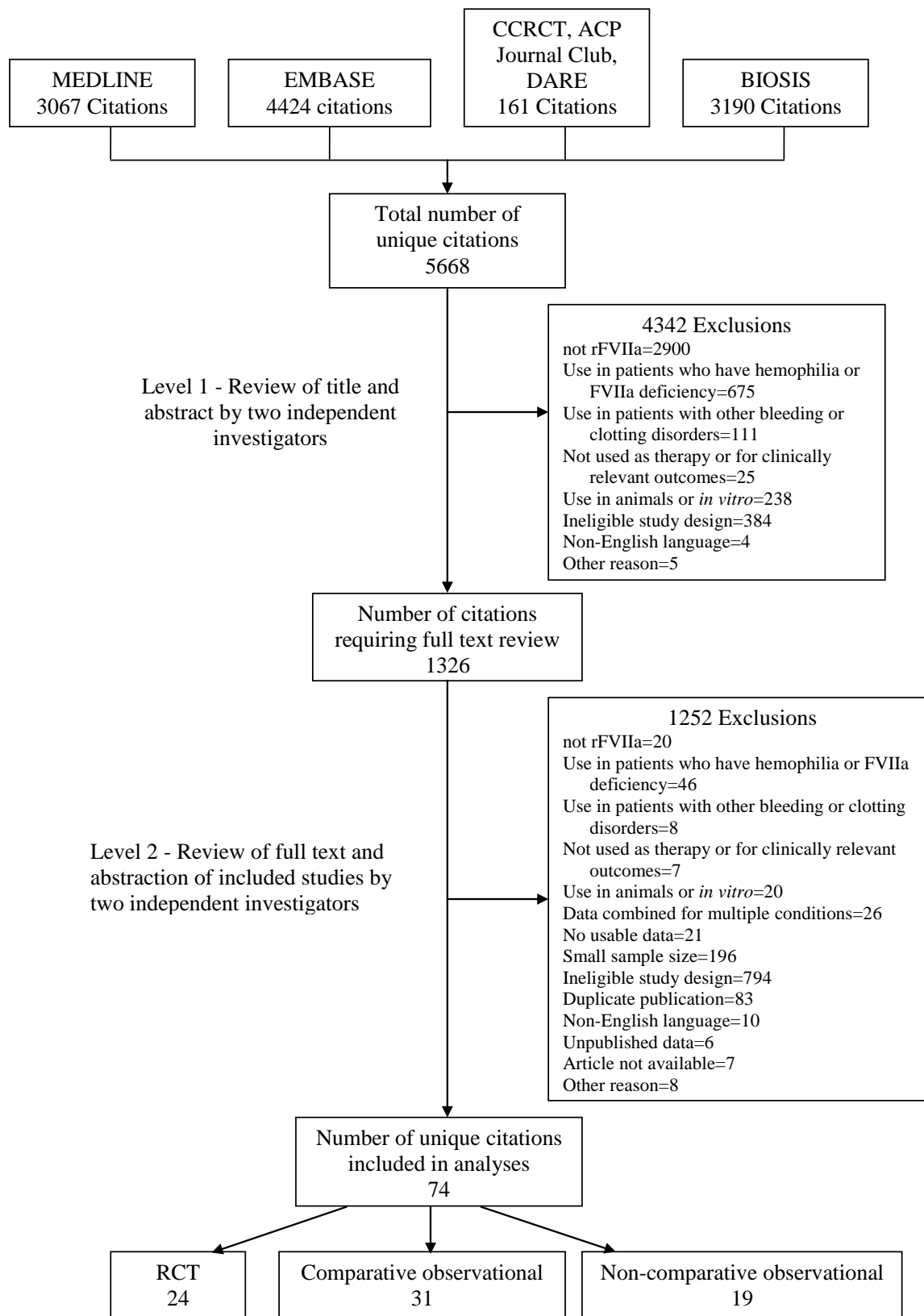
Overall, the published literature contained relatively few fair or good quality comparative studies within any given clinical indication (Table 14). Three of 14 (21 percent) RCTs were determined to be poor quality. In all cases, there was little or no description of the methods of randomization or allocation concealment or of the blinding of subjects, providers, or outcomes assessors, along with other methodologic shortcomings. Poor quality RCTs were still included in the evaluations of effectiveness for each clinical indication. In contrast, 14 of 24 (58 percent) comparative observational studies were judged to be of poor quality and were not included in the comparative effectiveness review but were used for qualitative sensitivity testing, and their data on harm (in the patients who received rFVIIa) were included in the results section on non-comparative evidence of harm. In all cases where comparative observational studies were determined to be of poor quality, there were study designs that were inappropriate for generating comparability of groups, inadequate methods to control for confounding, lack of blinding of outcomes assessors, or differential follow-up/high rates of missing data, among other methodological shortcomings.

Summary of Data from the Premier Database

The search of the Premier database identified nationally representative information on patterns of inpatient use of rFVIIa from 235 U.S. hospitals of the 615 hospitals in the database (38 percent). From 2000 through 2008, the database identified a total of 12,644 hospital cases (any use during a patient hospitalization) where rFVIIa use was reported. Our results indicated that real-world application of rFVIIa was concentrated among three of the key clinical indications that are the focus of this report: intracranial hemorrhage, body trauma, and cardiac

surgery. Application to these indications encompassed 55 percent of hospital cases of rFVIIa use from 2000 to 2008, and 68 percent of hospital cases in 2008 alone. There was variability in use for other indications, as discussed below under Key Question 1.

Figure 2. Search results for included studies



“Small sample size” applies only to non-comparative studies with less than 15 patients. “Duplicate publication” includes studies with overlapping patient populations.

Table 11. General characteristics of all included studies by clinical indication

Article	Study design	Time period	Country or Region	Setting	Sample size [#]		Mean age*, years (SD) [Range]		rFVIIa dose, µg/kg	Manufacturer Sponsorship
					rFVIIa	UC	rFVIIa	UC		
Intracranial hemorrhage										
Mayer 2005a ²³	RCT	8/2002-3/2004	Australia, Europe, Asia, North America	73 centers	303 (3 arms)	96	64 - 67	68 (12)	40; 80; 160	Funding
Mayer 2005b ⁸⁶	RCT	8/2001-10/2002	Australia, Europe, Asia	14 centers	36 (6 arms)	11	51 - 68	66 (14)	10; 20; 40; 80; 120; 160	Funding
Mayer 2006 ⁸⁷	RCT	11/2001-3/2003	USA	17 centers	32 (4 arms)	8	60 - 72	67 (13)	5; 20; 40; 80	Funding
Mayer 2008 ⁸⁸	RCT	5/2005-2/2007	Australia, Europe, Asia, North America	122 centers	573 (2 arms)	268	65 (14)	65 (14)	20; 80	Funding
Ilyas 2008 ⁸⁹	Retrospective comparative	1/2000-NR	USA	1 university hospital	24	30	76.5 (11)	76.4 (12.4)	10-100	NR
Pickard 2000 ⁹⁰ †	Prospective comparative	NR	NR	Multicenter	5	5	NR	NR	80; 80+3.5CI; 7.0 CI	Affiliation
Brody 2005 ⁹¹ †	Retrospective comparative	3/2002-1/2003	USA	1 university hospital	12	15	71 (13)	77 (7)	Mean: 4.8 mg SD: 2.1 mg	NR
Hallevi 2008 ⁹² †	Retrospective comparative	NR	USA	1 university hospital	46	148	60 [38-87]	58 [40-80]	40; 80	Affiliation
Sutherland 2008 ⁹³ †	Retrospective non-comparative	3/2005-12/2006	Canada	2 centers	15	-	68 ^U [25-81]	-	Median: 60 Range: 25-81	Funding
Herbertson 2008 ⁹⁴ †	Retrospective non-comparative	6/2001-12/2003	International	Online registry	20	-	7.7 (5.8)	-	Median: 100 Range: 9-393	Funding
(also reports on body trauma)										
Nussbaum 2009 ⁹⁵ †	Retrospective non-comparative	NR	USA	1 center	18	-	56.8 [42-85]	-	Range: 40-160	NR
Body trauma										
Boffard 2005 ⁹⁶	Two RCTs	3/2002-9/2003	Australia, Canada, Europe, Israel, South Africa	32 centers	139 (2 arms)	138 (2 arms)	29 – 33	32 – 35	200 followed by two 100	Funding
Rizoli 2006 ⁹⁷	Retrospective comparative	1/2000-1/2005	Canada	1 university center	38	204	37	41	NR	Affiliation
Spinella 2008 ⁹⁸	Retrospective comparative	12/2003-10/2005	Iraq	Combat support hospitals	49	75	NR	NR	120	NR

Table 11. General characteristics of all included studies by clinical indication (continued)

Article	Study design	Time period	Country or Region	Setting	Sample size [#]		Mean age*, years (SD) [Range]		rFVIIa dose, µg/kg	Manufacturer Sponsorship
					rFVIIa	UC	rFVIIa	UC		
Fox 2009 ⁹⁹	Retrospective comparative	4/2006-8/2007	Iraq	Combat support hospitals	41	12	28 (9)	24 (10)	90-120	None
Dutton 2004 ^{100†}	Retrospective comparative	6/2001-12/2003	USA	1 university hospital	81	32-449 [^]	41(21)	NR	50; 100	Affiliation
Harrison 2005 ^{101†}	Retrospective comparative	2/2003-12/2003	USA	1 hospital	29	72	41 (21)	42 (22)	Mean: 60	NR
Cameron 2007 ^{102†}	Retrospective non-comparative	1/2001-9/2006	Australia, New Zealand	53 centers	108	-	38 ^U [11-91]	-	Median: 90 IQR: 78-105	Funding
Felfernig 2007 ^{103†}	Retrospective non-comparative	9/2000-8/2003	Europe and Australia	Haemostasis database	45	-	31 [5-81]	-	Mean: 74 SD: 27	Funding
Martinowitz 2005 ^{104†}	Retrospective non-comparative	NR	Israel	Trauma registry	36	-	19.5 [14-65]	-	Median: 140 Range: 70-540	Affiliation
Alten 2009 ^{105†}	Retrospective non-comparative	1999-2006	USA	1 university center	15	-	7 [IQR 1.1-14]	-	Median: 88 Range: 27-160	None
Brain trauma										
Narayan 2008 ¹⁰⁶	RCT	8/2004-5/2006	Canada, Europe, Asia	38 centers	61	36	52 (22)	51 (20)	40; 80; 120; 160; 200	Funding
Stein 2008 ¹⁰⁷	Retrospective comparative	7/2002-6/2006	USA	1 university center	29	34	40 (25)	38 (20)	Range: 8 -140	Affiliation
Tawil 2008 ^{108†}	Retrospective comparative	1/2004-12/2005	USA	1 university center	31	353	NR	NR	NR	NR
Bartal 2007 ^{109†}	Prospective non-comparative	NR	NR	1 center	15	-	61 (11)	-	Mean: 59 Range: 40-90	NR
Liver transplantation										
Lodge 2005 ¹¹⁰	RCT	8/2001-9/2003	Australia, Europe, North America	14 centers	121 (2 arms)	61	53 (10)	52 (12)	60; 120	Affiliation
Planinsic 2005 ¹¹¹	RCT	2/2000-9/2000	Europe, USA	9 centers	64 (3 arms)	19	49 – 52	50 (11)	20; 40; 80	Affiliation
Pugliese 2007 ¹¹²	RCT	11/2003-7/2004	Italy	1 university center	10	10	NR	NR	40	NR
Liu 2009 ¹¹³	RCT	3/2003-7/2006	China	1 university center	14	14	51.9 [36-54]	47.5 [41-65]	70-80	NR
Hendriks 2001 ¹¹⁴	Prospective comparative	12/1998-9/1999	Netherlands	1 center	6	6	43 ^U [37-61]	48 ^U [34-63]	80	Affiliation
De Gasperi 2005 ^{115†}	Retrospective comparative	2/2003	Italy	1 center	6	6	45 (4)	47 (9)	20; 40	NR

Table 11. General characteristics of all included studies by clinical indication (continued)

Article	Study design	Time period	Country or Region	Setting	Sample size [#]		Mean age*, years (SD) [Range]		rFVIIa dose, µg/kg	Manufacturer Sponsorship
					rFVIIa	UC	rFVIIa	UC		
Kalicinski 2005 ^{116†}	Retrospective comparative	NR	Poland	1 center	28	61	13 (4)	11 (6)	Mean: 52 Range: 30-100	NR
Niemann 2006 ^{117†}	Retrospective comparative	2000-2004	USA	1 university center	11	11	48 (15)	41 (17)	Mean: 58 SD: 18	NR
Adult cardiac surgery										
Diprose 2005 ¹¹⁸	RCT	NR	UK	1 center	10	10	70 ^U [64-77] ^l	63 ^U [59-66] ^l	90	Funding
Gill 2009 ¹¹⁹	RCT	8/2004-11/2007	13 countries	30 centers	104	68	63-68	62 (16)	40; 80	Funding
Karkouti 2005 ¹²⁰	Retrospective comparative	11/2002-2/2004	Canada	1 center	51	51	56	59	Mean: 60 SD: 13	None
Gelsomino 2008 ¹²¹	Retrospective comparative	9/2005-6/2007	Italy	1 center	40	40	70 (9)	76 (10)	Median: 19 IQR: 6-16	NR
Tritapepe 2007 ¹²²	Retrospective comparative	1/2003-12/2005	Italy	1 center	23	23	62 (9)	62 (9)	Mean: 82	NR
von Heymann 2005 ¹²³	Retrospective comparative	6/2000-3/2003	NR	1 center	24	24	65	65	60-80 with possible repeat doses	NR
Bowman 2008 ^{124†}	Retrospective comparative	1/2001-12/2006	USA	1 center	36	385	58 (15)	NR	Mean: 100	NR
Trowbridge 2009 ^{125†}	Prospective comparative	NR	USA	1 center	17	187	70 (9)	67 (11)	NR	None
Filsoufi 2006 ^{126†}	Retrospective non-comparative	6/2003-12/2005	USA	1 center	17	-	63 (15)	-	Mean: 103 SD: 30	NR
Gandhi 2007 ^{127†}	Retrospective non-comparative	1/2003-8/2005	USA	1 center	17	-	53 [38-64]	-	Mean: 78 Range: 24-189	NR
Hyllner 2005 ^{128†}	Retrospective non-comparative	1/2004-8/2004	Sweden	1 center	24	-	60 ^U [34-82]	-	Mean: 72	NR
McCall 2006 ^{129†}	Retrospective non-comparative	12/2002-8/2005	Australia	1 center	53	-	68 [55-75] ^l	-	Mean: 90 SD: 15	Affiliation
Raivio 2005 ^{130†}	Retrospective non-comparative	6/2002-10/2004	Finland	1 center	16	-	60 (15)	-	Mean: 65 Range: 24-192	NR
Aggarwal 2004 ^{131†}	Retrospective non-comparative	6/2001-6/2003	USA	1 center	24	-	65 ^U [26-85]	-	90	NR
Karkouti 2008 ^{132†}	Retrospective non-comparative	1/2003-12/2006	Canada	18 centers	503	-	62 (15)	-	Median: 62 IQR: 40-89	Funding
Dunkley 2008 ^{133†}	Retrospective non-comparative	1/2001-9/2006	Australia, New Zealand	21 centers	293	-	63 (15)	-	Median: 92 IQR: 82-103	Funding
Bruckner 2009 ^{134†}	Retrospective	1/2004-	USA	1 center	32	-	51 (17)	-	Range: 10-20	NR

Table 11. General characteristics of all included studies by clinical indication (continued)

Article	Study design	Time period	Country or Region	Setting	Sample size [#]		Mean age*, years (SD) [Range]		rFVIIa dose, µg/kg	Manufacturer Sponsorship
					rFVIIa	UC	rFVIIa	UC		
(2 doses)	non-comparative	11/2006			30	-	51 (17)	-	Range: 30-70	
Masud 2009 ^{135†}	Retrospective non-comparative	1/2004-9/2005	USA	1 university hospital	93	-	60.6 (14.5)	-	Mean: 56.2 SD: 26.5	Affiliation
Hsia 2009 ^{136†}	Retrospective non-comparative	1/2003-6/2007	United Kingdom	1 center	23	-	55 [18-84]	-	NR	NR
Pediatric cardiac surgery										
Ekert 2006 ¹³⁷	RCT	NR	Australia	1 center	40	35	4 months	4 months	Mean: 63	NR
Agarwal 2007 ^{138†}	Retrospective comparative	1/2000-12/2004	USA	1 center	24	22	10 days [4-3285]	7 days [2-240]	Mean: 43 SD: 23	None
Tobias 2004 ^{139†}	Prospective comparative	1/2003	Dominican Republic	1 center	9	8	9 (4)	10 (3)	90	Affiliation
Niles 2008 ^{140†}	Retrospective comparative	2004-2006	USA	1 center	15	15	60 days (99); 5293 days (471)**	16 days (19); 4531 days (2758)**	Range: 76-282; 26-956**	None
Prostatectomy										
Friederich 2003 ¹⁴¹	RCT	NR	Netherlands	1 center	24 (2 arms)	12	61 – 64	63 (8)	20; 40	Affiliation
Other liver disease										
Jeffers 2002 ¹⁴²	Non-comparative RCT [#]	NR	USA	3 centers	71 (5 arms)	-	46 – 52	-	5; 20; 80; 120	Affiliation
Bosch 2004 ¹⁴³	RCT	4/2001-4/2002	Europe	26 centers	121	121	54 (11)	53 (12)	800	Funding
Shao 2006 ¹⁴⁴	RCT	7/2001-12/2002	China, Taiwan, Thailand	7 centers	155 (2 arms)	76	53 – 54	49 ^U [30-75]	50; 100	Affiliation
Bosch 2008 ¹⁴⁵	RCT	4/2004-8/2006	12 countries in Europe and Asia	31 centers	170 (2 arms)	86	55 (12)	54 (10)	300; 600	Funding
Shami 2003 ¹⁴⁶	Retrospective comparative	12/1999-NR	USA	1 center	7	8	34 [16-64]	28 [7-45]	40; 80	NR
Obstetrics/gynecology										
Ahonen 2007 ¹⁴⁷	Retrospective comparative	NR	Finland	1 center	26	22	33 (4)	35 (4)	Mean: 100 SD: 14	NR
Hossain 2007 ¹⁴⁸	Retrospective comparative	3/2005-10/2006	Pakistan	1 center	18	16	29 ^U [26-32] ^l	29 ^U [26-30] ^l	70	NR
McMorrow 2008 ¹⁴⁹	Retrospective comparative	2003-2006	Ireland	1 center	6	6	34 (3)	31 (5)	NR	NR
Hematology/oncology										
Chuansumrit 2005 ¹⁵⁰	RCT	7/2001-12/2002	Thailand, Philippines	5 centers	16	9	9 (4)	11 (3)	100; 200	Funding

Table 11. General characteristics of all included studies by clinical indication (continued)

Article	Study design	Time period	Country or Region	Setting	Sample size [#]		Mean age*, years (SD) [Range]		rFVIIa dose, µg/kg	Manufacturer Sponsorship
					rFVIIa	UC	rFVIIa	UC		
Pihusch 2005 ¹⁵¹	RCT	4/2001-10/2003	Australia, Europe	21 centers	77 (3 arms)	23	36 – 38	39 ^U [18-64]	280; 560; 1120	Funding
Gupta 2007 ¹⁵²	Retrospective comparative	1/2002-12/2004	USA	1 center	24	63	NR	NR	NR	None
Other surgery										
Lodge 2005 ¹⁵³	RCT	1/2001-1/2002	France, Spain, Germany, UK	13 centers	122 (2 arms)	63	56 (13)	56 (14)	20; 80	Funding
Raobaikady 2005 ¹⁵⁴	RCT	8/2002-3/2004	UK	1 center	24	24	44 ^U [18-57]	38 ^U [18-57]	90; 180	Funding
Johansson 2007 ¹⁵⁵	RCT	6/2001-12/2003	Denmark	1 center	9	9	54 ^U [22-85]	38 ^U [19-81]	80	Funding
Sachs 2007 ¹⁵⁶	RCT	7/2004-2/2006	USA	13 centers	36 (3 arms)	13	45 – 46	50 [17-65]	90; 180; 360	Funding
Roitberg 2005 ¹⁵⁷	Retrospective comparative	7/2001-11/2002	USA	1 center	29	24	60	67	NR	NR
Kolban 2006 ¹⁵⁸	Retrospective comparative	2000-2003	Poland	1 center	26	26	17 [10-22]	16 [12-19]	Mean: 23	NR

†For Key Question 2-4 indications, these studies did not meet inclusion criteria for the comparative effectiveness analyses due to poor quality (Table 14) (so are included in qualitative sensitivity discussions within their respective indication and for the harms analyses) or because they were non-comparative studies (so are included only in the harms analyses).

*For RCTs with more than one dosing arm, the range of mean ages of each dosing arm is presented.

**Patients were divided into 2 groups: those <30kg (N=11) and those >30kg (N=4), respectively;

[#]The sample size presented is the largest sample size the study reported for each treatment arm. Sample size may vary for each outcome reported within a study.

[^]Dutton 2004¹⁰⁰ has multiple control groups. The range of sample sizes is presented.

[#]Jeffers 2002¹⁴² did not have a usual care (i.e. placebo) group, but randomized patients in a double-blind fashion to doses of 5, 20, 80, and 120 ug/kg rFVIIa.

^UMedian;

^IIQR;

UC=usual care; NR=not reported; IQR=interquartile range;

Funding=Novo Nordisk funded the study or an author or statistician was an employee of Novo Nordisk; Affiliation=an author belonged to the Novo Nordisk speakers bureau, or received fees, payments, or funding for other projects or work from Novo Nordisk.

Table 12. Clinical indication and study type of included studies

Clinical Indication	Number of studies N (percent)			
	Total N=74	RCT N=24	Comparative observational N=31	Non-comparative observational N=19
Key Question 1 Indications				
Other liver disease	5	4 (17)	1 (3)	NC
Obstetrics/gynecology	3	0 (0)	3 (10)	NC
Hematology/oncology	3	2 (8)	1 (3)	NC
Other surgery	6	4 (17)	2 (7)	NC
Key Questions 2-4 Indications				
Intracranial hemorrhage	11	4 (17)	4 (13)	3 (16)
Body trauma	11	1 (4)	5 (16)	2 (11)
Brain trauma	4	1 (4)	2 (7)	1 (5)
Liver transplantation	8	4 (17)	4 (13)	0
Adult cardiac surgery	19	2 (8)	6 (19)	11 (58)
Pediatric cardiac surgery	4	1 (4)	3 (10)	0
Prostatectomy	1	1 (4)	0 (0)	0

Note: Data from non-comparative observational studies were used to analyze harms associated with rFVIIa use.
NC=not collected

Table 13. Study categories by study design and use in analysis

Study Category		Use in this Comparative Effectiveness Review			
		Survey of Existing Research (KQ1)	Evaluation of Effectiveness (KQ2-4)		Evaluation of Harms (KQ2-4)
			Used for Systematic Review	Used for Meta-Analyses	
Randomized clinical trials	Five key indications	14	14	6*	14
	Other indications	10		Outside Project Scope†	
Comparative observational studies	Five key indications and good quality	2	2	2*	2
	Five key indications and fair quality	8	9	Insufficient Quality	9
	Five key indications and poor quality	14	Insufficient Quality for Detailed Review**		14
	Other indications	7	Outside Project Scope†		
Non-comparative observational studies	Five key indications and ≥ 15 patients	19	Contributes No Information		19
	Other indications or < 15 patients		Outside Project Scope†		

*For the indications of intracranial hemorrhage and adult cardiac surgery only.

**Poor quality comparative observational studies were not reviewed in detail for the comparative effectiveness part of the report, but their data were included in the outcomes tables so that qualitative sensitivity analyses could be performed by placing their findings in the context of the findings of the higher quality studies.

†Because certain study categories fell outside of the project scope, they were not used for the indicated evaluations in the comparative effectiveness review.

Table 14. Study quality assessments

Study reference	Study type	Quality	Study is subsequently included and reviewed in detail in the following	
			Comparative effectiveness analyses	Harms analyses
Intracranial hemorrhage				
Mayer 2005a ²³	RCT	Good	X	X
Mayer 2005b ⁸⁶	RCT	Fair	X	X
Mayer 2006 ⁸⁷	RCT	Fair	X	X
Mayer 2008 ⁸⁸	RCT	Good	X	X
Ilyas 2008 ⁸⁹	Comparative observational	Fair	X	X
Halleivi 2008 ⁹²	Comparative observational	Poor*		X
Pickard 2000 ⁹⁰	Comparative observational	Poor*		X
Brody 2005 ⁹¹	Comparative observational	Poor*		X
Body trauma				
Boffard 2005 ⁹⁶	RCT	Fair	X	X
Rizoli 2006 ⁹⁷	Comparative observational	Fair	X	X
Spinella 2008 ⁹⁸	Comparative observational	Fair	X	X
Fox 2009 ⁹⁹	Comparative observational	Fair	X	X
Dutton 2004 ¹⁰⁰	Comparative observational	Poor*		X
Harrison 2005 ¹⁰¹	Comparative observational	Poor*		X
Brain trauma				
Narayan 2008 ¹⁰⁶	RCT	Fair	X	X
Stein 2008 ¹⁰⁷	Comparative observational	Fair [†]	X	X
Tawil 2008 ¹⁰⁸	Comparative observational	Poor*		X
Liver transplantation				
Lodge 2005 ¹¹⁰	RCT	Fair	X	X
Planinsic 2005 ¹¹¹	RCT	Fair	X	X
Pugliese 2007 ¹¹²	RCT	Poor	X	X
Liu 2009 ¹¹³	RCT	Poor	X	X
Hendriks 2001 ¹¹⁴	Comparative observational	Fair	X	X
Kalicsinski 2005 ¹¹⁶	Comparative observational	Poor*		X
Neimann 2006 ¹¹⁷	Comparative observational	Poor*		X
De Gasperi 2005 ¹¹⁵	Comparative observational	Poor*		X
Adult cardiac surgery				
Gill 2009 ¹¹⁹	RCT	Good	X	X
Diprose 2005 ¹¹⁸	RCT	Fair	X	X
Gelsomino 2008 ¹²¹	Comparative observational	Good	X	X
Karkouti 2005 ¹²⁰	Comparative observational	Good	X	X
Von Heymann 2005 ¹²³	Comparative observational	Fair	X	X
Tritapepe 2007 ¹²²	Comparative observational	Fair	X	X
Bowman 2008 ¹²⁴	Comparative observational	Poor*		X
Trowbridge 2008 ¹²⁵	Comparative observational	Poor*		X
Pediatric cardiac surgery				
Ekert 2006 ¹³⁷	RCT	Poor	X	X
Agarwal 2007 ¹³⁸	Comparative observational	Poor*		X
Tobias 2004 ¹³⁹	Comparative observational	Poor*		X
Niles 2008 ¹⁴⁰	Comparative observational	Poor*		X
Prostatectomy				
Friederich 2003 ¹⁴¹	RCT	Fair	X	X

RCT=randomized controlled trial;

*Poor quality comparative observational studies were not included in the comparative effectiveness analyses, but their data were included in the outcomes tables so that qualitative sensitivity analyses could be performed by placing their findings in the context of the findings of the higher quality studies.

[†]This study was deemed “fair” for the data on patients with isolated TBI only, and these data were included in the comparative effectiveness analysis.

Key Question 1. Overview of off-label rFVIIa use in-hospital and comparative studies

Overview of Trends in Factor VIIa Use in United States Hospitals, 2000-2008

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. Nonetheless, in-hospital U.S. sales of rFVIIa in 2007 are estimated to have been \$138.5 million.⁸ Data from the Premier sample of 615 U.S. hospitals provide nationally representative information (via weighted estimates) about patterns of inpatient rFVIIa use. From 2000 through 2008, there were an estimated 73,747 hospital discharges in the U.S. where rFVIIa use was reported. Over this period, there was growth in in-hospital use of rFVIIa where the unit of analysis was a “case” of use (any application during a patient hospitalization). While most cases were limited to hemophilia and several related hematologic conditions from 2000-2001, such use has leveled over time. In contrast, recent years have witnessed more frequent off-label in-hospital cases. Off-label in-hospital rFVIIa use was 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, and by 2008 was estimated to be 17,813 cases (97 percent of all of the estimated 18,311 in-hospital cases), although the rate of increase may be plateauing for many indications (Figures 3 and 4). The most prominent and rapidly increasing indications are cardiac surgery and traumatic bleeding, with cardiac surgery demonstrating the most sustained increase in use. More modest use is associated with non-traumatic intracranial hemorrhage, liver disease, gastrointestinal bleeding, and aortic aneurysm (Table 15 and Figures 3 and 4).

Hemophilia A and B, and related conditions. Initial use of rFVIIa was limited to the FDA-approved indications, including hemophilia A and B, as well as related conditions, such as other factor deficiencies, von Willebrand Disease and Glanzmann’s thrombasthenia. Over time, cases of use for hemophilia A and B increased 3.7-fold since 2000 (131 during 2000 versus 498 during 2008) but then plateaued, while there has been a 7.4-fold increase in cases for related conditions (107 during 2000 versus 792 during in 2008). These two groups remained the most frequent cluster of indications from 2000 through 2003. Together, they accounted for 10 percent of all reported cases, but their representation among indications for in-hospital use fell over time, from 92.9 percent of cases in 2000 to just 7.1 percent of cases in 2008 (498 cases). Hemophilia A and B, by themselves, accounted for only 2.7 percent of cases in 2008.

Cardiovascular surgery. rFVIIa use in cardiac surgery was initially observed in 2002, and by 2008 was the most frequent (29% of cases, along with trauma) and most rapidly rising indication. Use in pediatric cardiac surgery, largely for repair of congenital anomalies, increased only modestly, accounting for 2.3 percent of cases overall and 2.1 percent in 2008. On the other hand, rFVIIa use in adult cardiac surgery, largely for aortic valve, mitral valve and CABG procedures, rapidly increased over time, accounting for 16.4 percent of cases overall and 26.6 percent in 2008. By 2008, use in all cardiac surgery (5,250 cases) was nearly four times higher than in 2005 (1,375 cases), indicating rapid adoption of rFVIIa use for this indication, although the frequency of use may be leveling off.

Trauma. Traumatic bleeding represents the first area of major rFVIIa usage beyond hemophilia and related conditions. Sizable use began in 2002 and it remained the dominant indication for

off-label in-hospital cases of rFVIIa use until it was matched by cardiac surgery (at 29% of cases) in 2008. Use of rFVIIa for trauma grew continuously between 2002 and 2007 but leveled off in 2008, the first indication of stabilization in usage patterns. Nevertheless, trauma other than brain trauma remained the second most frequent indication for rFVIIa use and accounted for 15.9 percent of overall 2000-08 cases and 17.6 percent of cases in 2008 (3,214 cases). Use in brain trauma, particularly traumatic subdural hematoma, grew over time to constitute 9.7 percent of overall 2000-08 cases and 11.1 percent of cases in 2008 (2,033 cases).

Table 15. Summary data from Premier database according to clinical indication for rFVIIa use

Clinical Indication	Hospital Discharges, 2000-2008 (Sample=12644)		Hospital Discharges, 2008 (Sample=3245)	
	Number	Percentage of Total	Number	Percentage of Total
All patients treated with rFVIIa	73747	100.0	18311	100.0
Indications that are the focus of our effectiveness evaluation				
Intracranial hemorrhage	7760	10.5	2008	11.0
Body trauma	11689	15.9	3214	17.6
Brain trauma	7158	9.7	2033	11.1
Liver transplantation	132	0.2	58	0.3
Adult cardiac surgery	12086	16.4	4862	26.6
Pediatric cardiac surgery	1684	2.3	387	2.1
Prostatectomy	120	0.2	0	0.0
Total	40629	55.1	12562	68.6
Other off-label indications				
Liver Biopsy/Resection	867	1.2	122	0.7
Variceal Bleeding	897	1.2	235	1.3
Other Liver Disease	2451	3.3	539	3.0
Neurosurgery	500	0.7	108	0.6
Obstetrical Hemorrhage	672	0.9	220	1.2
Cancer/Stem Cell Transplant	1094	1.5	138	0.8
Other Gastrointestinal Bleeding	3881	5.3	713	3.9
Neonatal	729	1.0	135	0.7
Pulmonary Hemorrhage	1119	1.5	275	1.5
Aortic Aneurysm	1216	1.7	306	1.7
Other Vascular	1530	2.1	390	2.1
Primary Clotting Disorders	4104	5.6	792	4.3
Secondary Clotting Disorders	3744	5.1	766	4.2
Other Procedures	3867	5.2	407	2.2
Other Diagnoses	3346	4.5	117	0.6
Total	30017	40.7	5263	28.7
FDA approved indication				
Hemophilia A and B	3121	4.2	498	2.7

*Weighted to be nationally representative

Figure 3. Growth of in-hospital, off-label vs. on-label uses of rFVIIa in Premier database

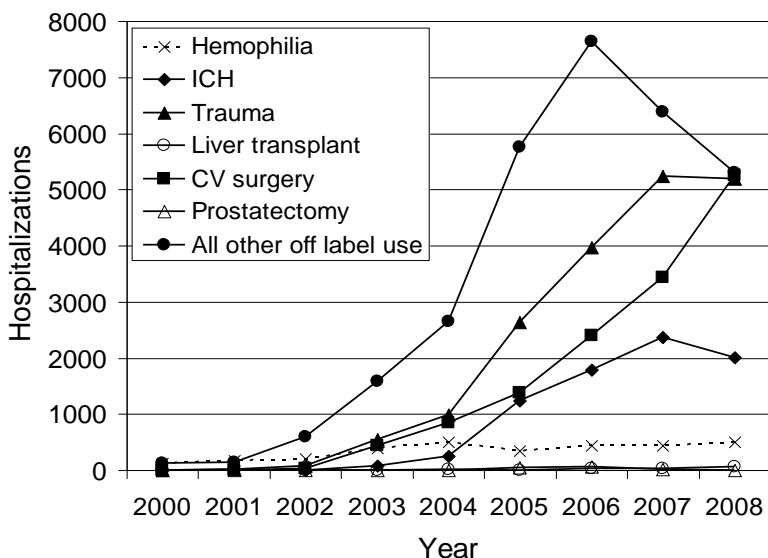
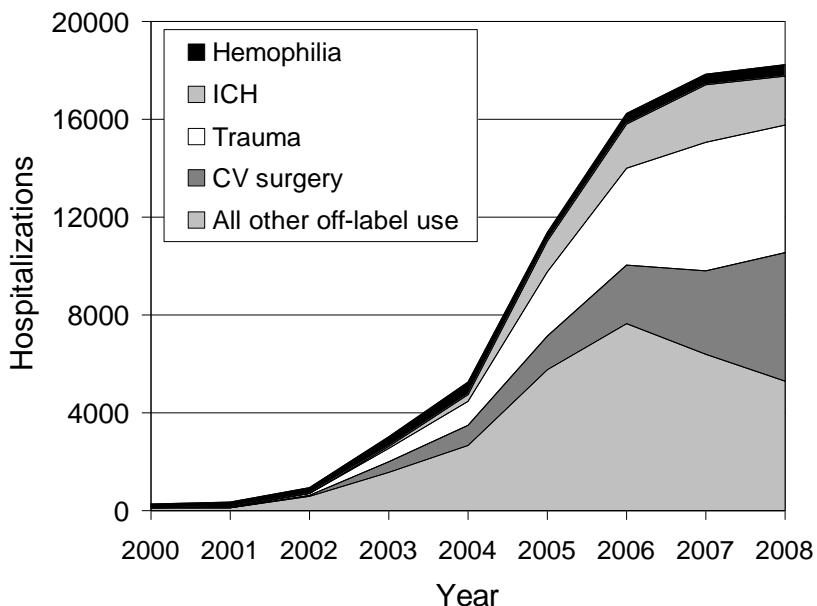


Figure 4. Growth of in-hospital, off-label vs. on-label uses of rFVIIa in Premier database, 2000-2008



Figures 3 and 4 present similar information. However, “all other” in Figure 4 includes liver transplantation and prostatectomy, as well as all of the other indications.

Intracranial hemorrhage. rFVIIa use in non-traumatic intracranial hemorrhage, particularly intracerebral hemorrhage (ICH), reached sizable scale only in 2005. Use for this indication then grew rapidly, with cases in 2008 (2,005 cases) nearly 8-fold higher than was reported in 2004 (253 cases). Notably, however, use of rFVIIa for intracranial hemorrhage fell slightly from 2007 to 2008. Intracranial hemorrhage accounted for 10.5 percent of rFVIIa cases overall and 11 percent in 2008.

Liver disease. A range of indications related to liver disease collectively constitute another cluster of modest rFVIIa use. Overall, these uses accounted for six percent of all cases, including liver transplant (0.2 percent), liver biopsy (1.2 percent), variceal bleeding (1.2 percent), and other liver indications (3.3 percent). There were 954 cases estimated for 2008, which was down from a peak of 1023 cases in 2007.

Other conditions. Other gastrointestinal bleeding, particularly hemorrhage from the colon, accounted for 5.3 percent of cases overall. Management of aortic aneurysm, in the presence and absence of surgical intervention, contributed modestly and stably to overall use of rFVIIa, with 1.7 percent of cases overall and in 2008. Other vascular surgery accounted for 2.1 percent of cases overall and in 2008. A range of other conditions contributed minimally to rFVIIa use, including pulmonary indications (1.5 percent of cases overall, particularly biopsy and lung transplant), cancer-related conditions (1.5 percent, particularly leukemia), neonatal use (1.0 percent), and obstetrical conditions (0.9 percent, particularly post-partum hemorrhage). A variety of other hematologic conditions were associated with rFVIIa use (5.1 percent of cases overall, 4.2 percent in 2008), particularly secondary thrombocytopenias and complications of warfarin anticoagulation. rFVIIa use also was associated with a wide variety of other surgical procedures, although none are individually prominent. Together, these procedures account for 5.3 percent of cases overall and 2.2 percent in 2008. Brain surgery, as the most frequent procedure among these, constituted 0.6 percent of cases overall and 0.7 percent in 2008. Of note, despite its prominence in this report, prostate surgery was an exceedingly rare indication for rFVIIa use, comprising only an estimated 120 cases nationally from 2000 through 2008 with no cases noted in 2008. As a whole, procedural use of rFVIIa declined between 2006 and 2008.

Age and gender distribution. Age and gender distribution. Overall, about 26 percent of in-hospital rFVIIa cases were in patients under the age of 45 years of age. Consistent with the growth of off-label indications, there was a significant increase in the mean age of patients from 3 years in 2000 to 59 years in 2008. The age distribution of rFVIIa use varied enormously by indication. Use for Hemophilia A and B was predominantly in patients 25 years of age and younger (73 percent). At the other extreme, 58 percent of rFVIIa cases in intracranial hemorrhage were for patients 65 years of age and older, with 36 percent in those 75 years and older. Beyond intracranial hemorrhage, other conditions where use in the elderly (>65 years) was prominent included aortic aneurysm (82 percent of cases), prostatectomy (66 percent), brain trauma (58 percent), adult cardiac surgery (57 percent), and gastrointestinal bleeding (57 percent) (Table 16).

In-hospital use of rFVIIa in the early 2000s was almost exclusively in males (98 percent of cases in 2000), as is expected from the inheritance pattern of Hemophilia A and B. Given the expansion of use into off-label indications this differential has diminished over time. A male predominance persisted (63 percent in 2008) largely due to a preponderance of men treated for the most frequent indications of adult cardiac surgery (68 percent) and body trauma (68 percent).

In-hospital mortality. Overall, in-hospital mortality was substantial among patients receiving rFVIIa, with 27 percent of patients dying while hospitalized (Table 16). Only 43 percent of patients were discharged directly home. A small percentage of patients receiving rFVIIa were discharged to hospice (2 percent). Most of the remaining patients were transferred to other facilities, including nursing homes, rehabilitation hospitals, and other acute care facilities (29

percent). Mortality increased substantially over time from five percent in 2000 to a peak of 31 percent in 2004, before it declined to 27 percent in 2008. Across all of the reported indications, mortality was infrequent only for rFVIIa use in Hemophilia A and B (4 percent). The most substantial mortality rates were associated with aortic aneurysm (54 percent), neonatal use (47 percent), variceal bleeding (39 percent), other liver disease (40 percent), liver biopsy (36 percent), vascular procedures (39 percent), intracranial hemorrhage (34 percent), brain trauma (33 percent), body trauma (33 percent), and gastrointestinal bleeding (30 percent). The populations receiving rFVIIa for adult and pediatric cardiac surgery experienced 23 and 22 percent in-hospital mortality rates, respectively, in contrast to patients undergoing prostatectomy who had a mortality rate of zero.

Table 16. Mean age and disposition of patients who received rFVIIa during hospitalizations from 2000-2008

Indication	Total number of hospitalizations	Mean age	Disposition			
			Died [†] (percent)	Hospice (percent)	Other [‡] (percent)	Home (percent)
Hemophilia	3121	26.0	3.8	0.8	10.6	84.8
Intracranial hemorrhage (ICH)	7755	64.7	34.4	5.8	43.9	15.9
Body trauma	11689	52.8	33.1	1.4	35.3	30.2
Brain trauma	7158	63.3	33.1	4.8	39.4	22.7
Liver transplantation	132	51.8	38.1	0.0	14.3	47.6
Adult cardiac surgery	12086	65.3	23.3	0.3	28.2	48.2
Pediatric cardiac surgery	1684	2.6	21.7	0.5	4.5	73.3
Prostatectomy	120	68.9	0.0	12.3	6.8	80.9
Other primary hematologic	4104	48.8	16.8	2.1	23.9	57.2
Other secondary hematologic	3744	55.8	30.1	2.7	25.9	41.3
Liver biopsy	867	49.3	35.9	6.2	12.7	45.2
Varices	897	52.4	39.0	2.2	26.6	32.2
Other liver disease	2451	53.3	40.4	5.1	22.6	31.9
Other gastrointestinal bleed	3881	63.7	29.7	3.3	27.5	39.5
Other vascular	1530	55.6	38.5	2.5	27.8	31.2
Aortic aneurysm	1216	72.8	54.4	1.1	25.5	19.0
Pulmonary	1119	53.4	24.5	1.8	27.9	45.8
Cancer	1094	55.6	13.8	4.7	14.1	67.4
Neonatal	729	0.01	46.7	0.9	14.1	38.3
Obstetric	672	30.6	14.6	0.0	7.8	77.6
Other procedure	4351	57.6	9.4	0.9	25.1	64.6
Other diagnosis	3346	59.2	5.8	0.3	17.2	76.7
Total	73746		26.5	2.3	28.5	42.7

[†] In-hospital deaths.

[‡] Inter-hospital transfers and transfers to skilled nursing and rehabilitation facilities.

Hospital characteristics. rFVIIa 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, whereas the ten hospitals with the highest number of uses by discharge accounted for 46 percent of all rFVIIa cases of use. These same hospitals had a particularly large share of pediatric cardiac surgery. They had a much smaller share of adult cardiac surgery, consistent with the

wider diffusion of rFVIIa use to other hospitals for this indication. A majority of rFVIIa use occurred in non-teaching hospitals (68 percent of cases). Over time, the proportion of use of rFVIIa in non-teaching hospitals grew from just 10.6 percent of cases in 2000 to a peak of 73 percent in 2005 and a similar but lower proportion of 67 percent in 2008. The majority of cases of rFVIIa use for each indication occurred in non-teaching hospitals, with the exception of hemophilia (41 percent) and liver transplantation (10 percent). Fifty-six percent of cases occurred in hospitals with less than 500 beds.

Geographically, a majority of cases of rFVIIa use occurred in the South (52 percent), with much smaller shares in the West (25 percent), Midwest (12 percent), and Northeast (11 percent). While the South is the most populous region in the U.S., the cases of rFVIIa use were disproportionate to its share of population (36 percent), total hospitalizations (38 percent), and hospital procedures (40 percent). In contrast, the Midwest and Northeast together (with 23 percent of cases) comprised comparable shares of population (40 percent), hospitalizations (41 percent), and hospital procedures (39 percent). These regional variations were present for most indications, including the FDA-approved indication of hemophilia, where 47 percent of cases occurred in the South and only 7 percent in the West.⁶⁸

Sensitivity analyses. We also conducted several sensitivity analyses of the coding scheme we used to define clinical indications for rFVIIa. In general, moving indications up or down in the hierarchy did not greatly change their reported frequency. While still modest, the greatest change occurred when trauma was moved to near the bottom of the hierarchy, reflecting the co-occurrence of other indications in patients with trauma (e.g., when a patient with liver disease experiences a traumatic injury). Nonetheless, we believe that it is reasonable to give trauma priority as a diagnosis in these instances, as it was likely trauma and not the associated diagnoses which instigated the use of rFVIIa.

Overview of All Identified Comparative Studies of Off-Label rFVIIa Use

Our literature search identified 55 comparative studies on any off-label indication of rFVIIa use. Seventeen (31 percent) of these addressed clinical indications not assessed in Key Questions 2-4 of this review (Table 17).

Indications and populations for which rFVIIa has been studied. Comparative studies available for rFVIIa use in cardiac surgery (12), trauma (9), intracranial hemorrhage (8), liver transplantation (8), and prostatectomy (1) accounted for 69 percent (38/55) of all such studies. Additional indications included other liver disease (liver resection, liver biopsy, variceal bleeding, and all other liver-related indications), skin grafting, a variety of cranial and spinal neurosurgical procedures, orthopedic surgery, dengue hemorrhagic fever, and hematopoietic stem cell transplantation and other cancer treatment-related conditions.

While the leading off-label uses of rFVIIa (cardiac surgery, trauma, and intracranial hemorrhage) were each represented by a number of studies, beyond these indications there were different types of mismatches between patterns of in-hospital community practice use and the availability of comparative studies. There were prominent community uses that lacked studies, such as primary clotting disorders other than hemophilia, secondary clotting disorders, and gastrointestinal bleeding not related to liver disease. Other indications with no studies included aortic aneurysm, other vascular procedures, and neonatal use (beyond cardiac surgery). In contrast, there were indications that had been studied but where community use was limited.

According to the Premier database, from 2005 to 2008 there were fewer than 30 annual cases of rFVIIa use in prostatectomy and liver transplantation. Use in pelvic fracture, skin grafting, and spine surgery also was limited. Finally, many studies examined only the mode of prophylactic rFVIIa use for clinical indications where treatment or end-stage use may also be frequent.

In general, study patients were younger and had lower clinical acuity than did patients in community practice (Table 16). This was particularly true for body trauma where the mean age in the community was 53 years compared to 32 years in the trauma RCTs. In addition, mortality rates in community practice (Table 16) generally were higher than those noted in the comparative studies. For example, in the intracranial hemorrhage RCTs, the reported 90 day mortality was 20 percent compared to 34 percent in-hospital mortality in the Premier database.

In summary, some study populations overlap with the major off-label indications for in-hospital rFVIIa use in community practice, while others represent indications with minimal use. Anticipated applicability of existing studies may be compromised by study of less acutely ill patients and a mismatch between indications studied and patterns of community use by indication and mode of use (i.e., prophylaxis versus treatment versus end-stage therapy).

Characteristics of comparative studies. The comparative studies of rFVIIa use compared this product to the usual care of hospitalized patients. There were 24 RCTs and 31 comparative observational studies (38 on Key Question 2-4 indications of which 22 (57.8 percent) had fair or better quality (Table 14)) available on rFVIIa use across a wide variety of clinical indications. Because the clinical circumstances of rFVIIa use differ so fundamentally between different indications, the suitability of pooling information across clinical indications is controversial.

Study sample sizes in existing comparative studies were generally small. Across all studies, the median and mean number of patients receiving rFVIIa were 24 and 58, respectively. For RCTs, the median and mean were 62.5 and 95, respectively. In addition, where multiple doses were studied it was typical to have fewer than 20 patients in each dosage arm. Evaluations of intracranial hemorrhage were the exception to the general rule of relatively low sample sizes, with the two largest RCTs together containing information on almost 900 patients treated with rFVIIa.

rFVIIa dosages varied enormously from 5 to 956 mcg/kg of patient weight for the studies examined in the effectiveness reviews. The 5 mcg/kg dose was reported in several dose ranging studies. The large doses were used in studies where multiple doses were given over an extended time period and, given the 2.5 hour half-life of rFVIIa, the aggregate effect of these sequential doses may not have been greater than the effect of the single doses of 160-200 mcg/kg given in other studies.

The primary outcomes of most of the comparative studies were indirect outcomes that assessed surrogate markers or components of the health care process rather than patient-centered outcomes. Common outcomes included RBC transfusion requirements, blood loss, and duration of surgery or ICU stay. While these outcomes may be correlated with direct clinical outcomes, this correlation is incomplete and there are many instances where discrepancies are expected. Many studies included direct outcomes as secondary end-points. These included mortality, thromboembolic events, functional status, and other clinical events such as acute respiratory distress syndrome. Unfortunately, most studies were individually underpowered to evaluate these direct outcomes, although some studies of intracranial hemorrhage were an important exception.

It is also notable that most clinical trial research on rFVIIa was sponsored by Novo Nordisk, the product's manufacturer. In many instances, clinical trials were directed and their data analyzed and reported with the involvement of the manufacturer.

Based on the characteristics of the published studies reviewed above, it is anticipated that the strength of evidence of these studies may be compromised by small study size, inconsistent study quality, heterogeneity by dosage and indication, use of indirect outcomes, and potential conflicts of interest.

Table 17. General characteristics of all comparative studies on off-label rFVIIa use for clinical indications not assessed in Key Questions 2-4

Article	Indication for rFVIIa use	Study Design	Study Setting Time Period	Sample Size and Dose, µg/kg	Mean Age (SD) [Range]	Outcomes Evaluated		
						Direct	Indirect	
Other liver disease in cirrhotic patients								
Jeffers 2002 ¹⁴²	Liver biopsy (cirrhotic patients)	Non-comparative RCT [^]	3 centers	USA	All Rx: 71 5*: 5 5: 16 20: 14 80: 17 120: 19	Rx: 5*: 46 (7) 5: 51 (10) 20: 49 (7) 80: 52 (9) 120: 50 (13)	Mortality	Time to hemostasis
	Prophylaxis		Time period NR				*First 5 patients received a 5 µg/kg dose and were part of a non-randomized pilot study.	
Bosch 2004 ¹⁴³	GI bleeding (cirrhotic patients)	RCT	26 centers	Europe	Rx: 121	Rx: 54 (11) Ucare: 53 (12)	Mortality	Transfusion requirements††
	Treatment		4/2001-4/2002		Dose: 100 µg/kg administered 8 times (800 µg/kg total) before first endoscopy and at 2, 4, 6, 12, 18, 24, and 30 hours later.		Adverse events including TE events	
Shao 2006 ¹⁴⁴	Liver resection (cirrhotic patients)	RCT	7 centers	China, Taiwan, Thailand	All Rx: 155 50*: 71 100*: 74	Rx: 50: 53 ^U [22-76] 100: 54 ^U [23-72]	Mortality	Transfusion requirements††
	Prophylaxis		7/2001-12/2002		*1 st Dose at time of skin cut, additional doses every 2 hours. Maximum of 4 doses.	Ucare: 76 49 ^U [30-75]	Adverse events including TE events	

Table 17. General characteristics of all comparative studies on off-label rFVIIa use for clinical indications not assessed in Key Questions 2-4 (continued)

Article	Indication for rFVIIa use	Study Design	Study Setting Time Period	Sample Size and Dose, µg/kg	Mean Age (SD) [Range]	Outcomes Evaluated	
						Direct	Indirect
Bosch 2008 ¹⁴⁵	Variceal bleeding (cirrhotic patients)	RCT	31 centers	All Rx: 170 300*: 85 600*: 85	Rx: 300: 55 (12) 600: 55 (11) Ucare: 54 (10)	Mortality	Efficacy of bleeding control
	Treatment		12 countries in Europe and Asia 4/2004-8/2006	Ucare: 86 *Total dose. Patients in the 600 µg/kg group given 200 + 4 x 100. Patients in the 300 µg/kg group given 200, 100 + 3 x placebo.		Adverse events including TE events	
Shami 2003 ¹⁴⁶	Fulminant hepatic failure	Retrospective comparative observational	1 center	Rx: 7	Rx: 34 [16-64] Ucare: 28 [7- 45]	Mortality	Transfusion requirements††
	Prophylaxis		Charlottesville, VA, USA 12/1999-NR	Ucare: 8 Dose: 40 µg/kg, which could be repeated after placement of ICP transducer.			Ability to place ICP transducer Efficacy of bleeding control
Obstetrics/gynecology							
Ahonen 2007 ¹⁴⁷	Postpartum hemorrhage	Retrospective comparative observational	1 center	Rx: 26	Rx: 33 (4) Ucare: 35 (4)	Mortality	Transfusion requirements††
	Treatment		Helsinki, Finland Time period NR	Ucare: 22 Mean dose: 100 µg/kg; SD: 14 µg/kg		Adverse events including TE events	Blood loss
Hossain 2007 ¹⁴⁸	Postpartum hemorrhage	Retrospective comparative observational	1 center	Rx: 18	Rx: 29 ^U [26- 32] ^I Ucare: 29 ^U [26-30] ^I	Mortality	Transfusion requirements††
	Treatment		Karachi, Pakistan 3/2005-10/2006	Ucare: 16 Dose: 70 µg/kg, which was repeated in 3 patients.		TE events	
McMorrow 2008 ¹⁴⁹	Postpartum hemorrhage	Retrospective comparative observational	1 center	Rx: 6	Rx: 34 (3) Ucare: 31 (5)	Mortality	Transfusion requirements††
	Treatment		Dublin, Ireland 2003-2006	Ucare: 6 Dose not reported		Adverse events including TE events	

Table 17. General characteristics of all comparative studies on off-label rFVIIa use for clinical indications not assessed in Key Questions 2-4 (continued)

Article	Indication for rFVIIa use	Study Design	Study Setting Time Period	Sample Size and Dose, µg/kg	Mean Age (SD) [Range]	Outcomes Evaluated	
						Direct	Indirect
Hematology/oncology							
Chuansumrit 2005 ¹⁵⁰	Dengue hemorrhagic fever (pediatric) Treatment	RCT	5 centers Thailand, Philippines 7/2001-12/2002	Rx: 16 Ucare: 9 Dose: 100 µg/kg with possible second dose 30 minutes later if bleeding not controlled	Rx: 9 (4) Ucare: 11 (3)	Mortality Adverse events including TE events	Transfusion requirements†† Efficacy of bleeding control
Pihusch 2005 ¹⁵¹	Bleeding following hematopoietic stem cell transplantation Treatment	RCT	21 centers Australia, Europe 4/2001-10/2003	All Rx: 77 40*: 20 80*: 26 160*: 31 Ucare: 23 *study drug administered seven times over 36 hours.	Rx: 40: 36 ^U [20-58] 80: 38 ^U [20-61] 160: 37 ^U [16-57] Ucare: 39 ^U [18-64]	Mortality Adverse events including TE events	Transfusion requirements†† Efficacy of bleeding control
Gupta 2007 ¹⁵²	Alveolar hemorrhage in hematopoietic stem cell transplant recipients Treatment	Retrospective comparative observational	1 center Houston, TX, USA 1/2002-12/2004	Rx: 24 Ucare: 63 Dose not reported	Age not reported.	Mortality Adverse events including TE events	Requirement for positive pressure ventilation Hospital length of stay
Other surgery							
Lodge 2005 ¹⁵³	Liver resection (non-cirrhotic patients) Prophylaxis	RCT	13 centers France, Spain, Germany, UK 1/2001-1/2002	All Rx: 122 20: 63 80: 59 Ucare: 63	Rx: 20: 56 (13) 80: 56 (14) Ucare: 58 (12)	Mortality Adverse events including TE events	Transfusion requirements†† Blood loss Operating time

Table 17. General characteristics of all comparative studies on off-label rFVIIa use for clinical indications not assessed in Key Questions 2-4 (continued)

Article	Indication for rFVIIa use	Study Design	Study Setting Time Period	Sample Size and Dose, µg/kg	Mean Age (SD) [Range]	Outcomes Evaluated	
						Direct	Indirect
Raobaikady 2005 ¹⁵⁴	Reconstruction surgery for traumatic fracture of pelvis Prophylaxis	RCT	1 center London, UK 8/2002-3/2004	Rx: 24 Ucare: 24 Dose: 90 µg/kg given at first skin incision. Second dose given 2 hours later if transfusion of allogenic RBCs indicated.	Rx: 44 ^U [18-57] Ucare: 38 ^U [18-57]	Adverse events including TE events	Transfusion requirements†† Blood loss Operating time Hospital and ICU LOS
Johansson 2007 ¹⁵⁵	Burn patients undergoing excision and skin grafting Prophylaxis	RCT	1 center Copenhagen, Denmark 6/2001-12/2003	Rx: 9 Ucare: 9 Dose: Two 40 µg/kg doses given at start of surgery and 90 minutes later.	Rx: 54 ^U [22-85] Ucare: 38 ^U [19-81]	Mortality Adverse events including TE events	Transfusion requirements†† Operating time Hospital and ICU LOS
Sachs 2007 ¹⁵⁶	Spinal surgery Treatment	RCT	13 Centers USA 7/2004-2/2006	All Rx: 36 30*: 12 60*: 12 120*: 12 Ucare: 13 *3 doses given. First dose at bleeding trigger (10% loss of blood volume), second and third doses 2 and 4 hours later, respectively.	Rx: 30: 46 [18-62] 60: 46 [17-69] 120: 45 [18-63] Ucare: 50 [17-65]	Mortality Adverse events including TE events	Transfusion requirements†† Blood loss
Roitberg 2005 ¹⁵⁷	Neurosurgery Treatment	Retrospective comparative observational	1 center Chicago, IL, USA 7/2001-11/2002	Rx: 29 Ucare: 24 Dose not reported.	Rx: 60 Ucare: 57	Mortality TE events Functional outcome (Glasgow outcome scale)	

Table 17. General characteristics of all comparative studies on off-label rFVIIa use for clinical indications not assessed in Key Questions 2-4 (continued)

Article	Indication for rFVIIa use	Study Design	Study Setting Time Period	Sample Size and Dose, µg/kg	Mean Age (SD) [Range]	Outcomes Evaluated	
						Direct	Indirect
Kolban 2006 ¹⁵⁸	Scoliosis surgery (adolescents)	Retrospective comparative observational	1 center	Rx: 26	Rx: 17 [10-22]	Mortality	Transfusion requirements††
	Prophylaxis		Szczecin, Poland	Ucare: 26	Ucare: 16 [12-19]	Adverse events including TE events	
			2000-2003	Mean dose: 23 ug/kg			Blood loss

^UMedian; ^IInterquartile range; †Examples of transfusion requirements were red blood cells and fresh frozen plasma

[^]Dutton 2004¹⁰⁰ has multiple control groups. The range of sample sizes is presented.

*Jeffers 2002 did not have a usual care (i.e. placebo) group, but randomized patients in a double-blind fashion to doses of 5, 20, 80, and 120 ug/kg rFVIIa.

Rx=treatment group(s); Ucare=usual care; NR=not reported; IQR=interquartile range; LOS=length of stay

Key Question 2. Intracranial hemorrhage and comparative effectiveness of rFVIIa

Background

All of the RCTs evaluated in this section focus on intracerebral hemorrhage (ICH), rather than other forms of intracranial bleeding (e.g., subarachnoid or subdural hemorrhage). In the one comparative observational study, half of the patients had ICH while the other half had isolated subdural hematomas. Intracerebral hemorrhage is associated with high levels of mortality and functional disability. Over one third of patients die within one month, 50 percent have poor functional status at time of discharge, and 20 percent remain institutionalized at three months.^{159,160} Early hematoma growth occurs even in the absence of detectable systemic coagulopathy and is an important independent predictor of mortality and morbidity.^{33,161} There are no proven therapies for ICH.¹⁶² The purpose of this section is to describe the comparative studies of rFVIIa versus usual care for the treatment of intracranial hemorrhage, but the section necessarily focuses primarily on ICH because the majority of studies focused on this form of hemorrhage.

Usual care during the time frame of included studies. While there remains wide variation in practice patterns, usual care for ICH has evolved over the time span during which the studies included in this effectiveness review were conducted (February 2000 to February 2007). The most notable change in practice is the trend toward less tolerance of “permissive hypertension” because of the suggestion in recent studies, albeit far from conclusive, of increased hematoma expansion with higher blood pressures and potentially better outcomes with the control of blood pressure within six hours.¹⁶³⁻¹⁶⁵ The largest and highest quality studies discussed below are those RCTs that were conducted most recently, between May 2005 and February 2007. The included trials did not specify hypertension management.

General Characteristics of Studies of Intracranial Hemorrhage

In the area of ICH, we identified four published RCTs (two good quality,^{23,88} two fair quality^{86,87} (Table 14)) and one comparative observational study⁸⁹ (fair quality) that examined treatment use of rFVIIa in 968 intervention patients. The 944 patients who received rFVIIa in the RCTs were *not* on anticoagulation therapy and had experienced intracerebral hemorrhage (ICH), a subset of intracranial hemorrhage. All of the trials were performed by the same study group, were sponsored by the manufacturer of rFVIIa, and had at least one author or biostatistician who was an employee of the manufacturer. We identified an additional RCT on the Novo Nordisk site that appears to have been performed by a different research group and also sponsored by the manufacturer,¹⁶⁶ but this study has not yet been published in any form, enrollment is small (45 patients in treatment and control groups, respectively), and the online posting gives only summary details. In the comparative observational study by Ilyas 2008,⁸⁹ half of the patients had experienced ICH and the other half had experienced subdural hematomas as their manifestation of intracranial hemorrhage.

Place of studies within analytic framework. All of the included studies of intracranial hemorrhage evaluated rFVIIa for treatment use (versus prophylaxis or end-stage use, which are other potential uses, as outlined in our Analytic Framework (Figure 1)). The RCTs had well-

documented approaches to data collection and analysis of direct outcomes such as mortality, thromboembolic events, and functional outcome, although only one of them was powered to analyze direct outcomes as its primary outcome, and it used a combined endpoint of “severe disability or death.”⁸⁸ The Ilyas observational study examined time to correction of INR as its primary endpoint.

Qualitative considerations of heterogeneity. Intracranial hemorrhage can occur inside the hemispheres of the brain (i.e., intracerebral hemorrhage, or ICH) or around the hemispheres (e.g., subdural or subarachnoid bleeding). Because the underlying causes and associated risks of these types of bleeding can vary, we considered results for them separately. Second, baseline coagulopathy is another source of potential heterogeneity, because patients who are coagulopathic—generally from oral anticoagulation therapy with warfarin—may differ in important ways from those who are not coagulopathic. Again, we considered these patient groups separately in our discussion. Third, 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 rFVI were analyzed in each RCT, we chose to analyze the data according to low, medium, and high dose rFVIIa groups, as described in our methods and 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. Finally, three of the RCTs defined “poor functional outcome” as a modified Rankin scale score of 4-6, whereas the fourth RCT defined it as a score of 5-6 but also included a graphical representation of the scores which allowed us to perform our own calculation of the proportion of patients with scores of 4-6, such that the data could be combined with the other RCTs.

Comparison to studies on other indications. The RCTs on ICH had the longest and most comprehensive follow-up of all of the indications. The largest of them also enrolled more patients than studies in any other indication. On average, the patients tended to be older than those in most other indications, but were similar to those in adult cardiac surgery and prostatectomy. The dose range of rFVIIa was from the low-to-middle range of doses used across indications.

Patient Characteristics and Study Design

RCTs. Table 18 summarizes important characteristics of each of the trials, all of which had similar patient populations and methodologies. The two large RCTs randomized a total of 399 and 841 patients respectively,^{23,88} whereas the smaller trials randomized 47 and 40 patients, respectively.^{86,87} In all of the trials, important inclusion criteria were that patients were required to have received a baseline CT scan within 3 hours of symptoms onset and study drug within 4 hours. Similarly, important shared exclusion criteria were that a patient was known to be taking oral anticoagulants, was in a deep coma, or was anticipated to need surgical evacuation within 24 hours. Overall, the groups randomized to rFVIIa versus usual care were similar on key baseline characteristics such as age, location of hemorrhage, Glasgow Coma Scale (GCS) score (a scale of neurological function), blood pressure, and time to treatment with rFVIIa or placebo. A possible exception to the groups being well-matched occurred in the largest and most recent RCT, which identified a higher rate of baseline intraventricular hemorrhage in the group that received 80 mcg/kg of rFVIIa compared to the usual care group.⁸⁸ The mean age of patients in

the aggregate treatment and usual care groups in every trial was between 61 and 68 years, with standard deviations in the range of 12-15. In general, the RCTs used appropriate methods of blinding, in particular with the blinding of the two radiologists who independently measured the hematoma size and growth on all of the head computed tomography (CT) scans. In addition, the RCTs had appropriately long follow-up periods of 90 days, had very low rates of loss to follow-up, applied an intention-to-treat approach, and used appropriate statistical analyses.

Comparative observational study. Unlike the above RCTs, the one comparative observational study by Ilyas⁸⁹ included patients on oral anticoagulation therapy with warfarin (INR>1.4) and with subdural hematomas or ICH (50 percent apiece). It retrospectively compared 24 patients treated with rFVIIa to 30 usual care patients.

Intervention Characteristics

RCTs. The rFVIIa dose was administered similarly in all of the studies: packaged in identical vials to placebo and administered as a single dose within one hour of baseline head CT scan and four hours of symptoms onset. The doses varied widely, however. The smaller dose-finding studies had the widest variation, with doses of 10, 20, 40, 80, 120, and 160 µg/kg,⁸⁶ and 5, 20, 40, and 80 µg/kg,⁸⁷ respectively, with equal numbers of patients per dose tier in a given study. The larger studies had less variation in dose range, with 20 and 80 µg/kg,²³ and 40, 80, and 160 µg/kg,⁸⁸ respectively, and also had similar numbers of patients within each dose tier.

Comparative observational study. There was a wide dose range of 10-100 µg/kg among treated patients in the Ilyas study.⁸⁹

Outcomes

As explained in our methods, for the intracranial hemorrhage indication there were special statistical considerations, such that we made several *a priori* decisions regarding statistical analyses. Because there were indications in the literature regarding a possible dose response relationship between rFVIIa and certain outcomes (e.g., thromboembolic events and hematoma volume) and multiple doses of rFVI were analyzed in each RCT, we chose 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. However, in all of the RCTs, the different levels of treatment dosage were compared to a common control. In addition, some studies did not contain all levels of the treatment dosage. Because of these complexities, we applied meta-analytic methods developed by Olkin et al⁸² to analyze this kind of data when generating the summary effect sizes. Second, because there were suggestions in the literature of a possible association between rFVIIa and arterial thromboembolic events, but not venous events, and both types of data were available to us from the ICH RCTs, we chose to analyze arterial and venous thromboembolic events separately for this indication. Third, while the summary effect sizes for all analyses (included in both the text and figures) are indeed accurate, their graphical representation using forest plots is complicated by their use of a common control for the different treatments dosages, so should be considered an aide to interpretation rather than a strict representation of the underlying metrics employed. Fourth, among the studies included in the risk difference meta-analyses, assessments of the significance and magnitude of heterogeneity by the Q and I² statistics did not identify significant

heterogeneity for any outcome. Finally, meta-analytic results using the arcsine metric were consistent in all cases with those described below for the risk difference (Appendix C, Appendix Figures 1-9).

Direct (patient-centered) outcomes. There were no dose-dependent trends in the outcomes reported. Because the RCTs had similar patient populations and measured comparable outcomes, we were able to perform meta-analyses of their data for all major outcomes. The direct (patient-centered) outcomes are presented in Tables 19 and 20 and in Figures 5-18. We also plotted mean differences in mortality and thromboembolic event rates for each comparative study and according to each rFVIIa indication using circle charts, with the area of each circle approximating the total sample size of its respective study (Figures 5 and 6).

Mortality. Meta-analytic evaluation of mortality rate indicated no difference between the aggregate rFVIIa patients and the usual care patients (Figures 7-9) (risk difference: low dose -0.031 (95 percent CI -0.086 to 0.024), medium dose -0.020 (95 percent CI -0.076 to 0.036), high dose -0.027 (95 percent CI -0.121 to 0.068); P value of the Q statistic for all risk differences 0.248). The mean mortality rate differences between rFVIIa and usual care groups by study are shown and placed in the context of other indications in Figure 5. The Ilyas observational study of patients on warfarin also found no difference in mortality between groups (Table 19).

Poor modified Rankin Scale. Poor modified Rankin Scale (mRS) score is the most widely accepted, validated measure of functional outcome in ICH. Note that other functional outcome measurements were assessed in most of the ICH studies and had similar outcomes to those reported for the mRS. Meta-analytic evaluation of poor mRS score indicated no difference in outcomes between the aggregate rFVIIa patients and the usual care patients (Figures 10-12) (risk difference: low dose -0.024 (95 percent CI -0.093 to 0.045), medium dose -0.029 (95 percent CI -0.099 to 0.041), high dose -0.040 (95 percent CI -0.154 to 0.075); P value of the Q statistic for all risk differences 0.088).

Thromboembolic events. Meta-analytic evaluation of arterial thromboembolic events identified significantly higher rates with rFVIIa use compared to usual care for the medium and high dose groups and a similar, but non-significant, finding for the low dose group (Figures 13-15) (risk difference: low dose 0.025 (95 percent CI -0.004 to 0.053), medium dose 0.035 (95 percent CI 0.008 to 0.062), high dose 0.063 (95 percent CI 0.011 to 0.063); P value of the Q statistic for all risk differences 0.277). These results suggest that there is an increase in arterial thromboembolic events with rFVIIa use versus usual care. There were no differences between groups in venous thromboembolic events (risk difference: low dose 0.010 (95 percent CI -0.018 to 0.038), medium dose -0.004 (95 percent CI -0.030 to 0.022), high dose -0.012 (95 percent CI -0.049 to 0.026); P value of the Q statistic for all risk differences 0.935). The Ilyas observational study of patients on warfarin noted only one thromboembolic event in any group, a myocardial infarction in a rFVIIa patient (Table 20). Figure 6 displays for each study, and also in the context of studies of the other indications, the mean rate differences for all thromboembolic events (venous and arterial) between the rFVIIa and usual care groups.

Indirect (surrogate) outcomes. Relative hematoma expansion. Meta-analytic evaluation of relative hematoma expansion demonstrated significant reductions in the rFVIIa group compared

to the usual care group at all dosing levels (standardized mean difference: low dose -0.146 (95 percent CI -0.291 to -0.001), medium dose -0.240 (95 percent CI -0.385 to -0.095), high dose -0.334 (95 percent CI -0.579 to -0.090); P value of the Q statistic for all standardized mean differences 0.840) (Figures 16-18). While the large Mayer 2005a²¹ study reported a significant dose-response effect of reduced hematoma growth with higher doses of rFVIIa, statistical tests for differences between dosing levels in our meta-analyses found no significant dose effect. The Ilyas study did not report on this outcome (Table 21).

Consideration of poor quality comparative observational studies. In the poor quality comparative observational studies by Pickard,⁹⁰ Brody,⁹¹ and Hallevi,⁹² the findings on mortality, poor functional outcome, and thromboembolic events are within the range of those described above (Tables 19 and 20). Other outcomes were not reported.

Other Considerations

Timing of rFVIIa and Changes in ICH Volume

Background. Until recently, increases in ICH volume were thought to be completed within minutes of onset, but recent studies have shown continued growth of the hemorrhage up to several hours after symptoms onset.¹⁶⁷ Additionally, this late growth of the ICH has been associated with neurological deterioration and poor clinical outcome.^{33,167} A pooled meta-analysis of individual patient data from the earlier RCTs^{23,86,87} and a study by Brott et al.¹⁶⁷ showed that for each 10 percent increase in ICH between the baseline CT scan (performed within 3 hours of symptoms onset) and follow up CT performed 24 hours after the baseline, the hazard rate of dying increased by five percent. Similarly, the hazard ratio of increasing the modified Rankin Scale by one point (toward worse functional outcomes), was 16 percent for each 10 percent increase in ICH growth.³³ In this section we explore the association between timing of rFVIIa and hemorrhage growth.

Results. Table 22 shows the published data from the largest of the earlier 2 ICH RCTs, Mayer 2005a,²³ but compares those patients treated within three hours of symptoms onset to those treated after three hours from symptoms onset, but still within the four-hour time window established by the study as an inclusion criterion. The data suggest diminished hematoma expansion in the group that received earlier treatment. The subsequent large RCT, Mayer 2008,⁸⁸ reported hematoma expansion occurring in “under 2 hours,” “under 3 hours,” and “at any time (i.e., within the four hour protocol of the study),” such that the data are not directly comparable to those of the earlier study. However, the findings suggest a similar pattern to the earlier RCT, one of diminished hematoma expansion when rFVIIa is administered earlier.

Discussion. Relative to later treatment, earlier treatment with rFVIIa may reduce hematoma growth. One drawback to our analysis is that the patients received rFVIIa within the relatively short time window of four hours. Using timing of treatment as a predictor of hematoma growth also presents analytical problems. Although it is now known that hematoma growth can continue for several hours after symptoms onset, much of ICH growth occurs prior to the baseline CT scan. Therefore, “growth” of the ICH as documented by sequential CT scans may be highly confounded by the timing of the CT scans relative to symptom onset and whether the baseline

scans occur in the earliest, highest growth phase of hematoma formation or in the later, more modest growth phase. Existing studies have not explored this potential source of confounding in great detail.

Post-hoc analyses of age and other factors. Post-hoc analyses in the Mayer 2008 study posited improved functional outcomes with rFVIIa therapy when patients had a combination of younger age, lower baseline hematoma volume, and earlier rFVIIa administration. Additional post hoc analyses identified increased age and previous use of an antiplatelet agent as possible independent risk factors for thromboembolic events.⁸⁸

Comparison with Premier Database

Study patients were approximately the same age (mid 60s) and had lower mortality rates than the mortality rate of 0.34 among patients in the Premier database. Application of rFVIIa to intracranial hemorrhage in the Premier database was very low prior to 2005 but experienced a notable increase in use that year, the same year in which the first Mayer RCT²³ was published (Figures 3 and 4).

Strength of Evidence

We judged the strength of evidence grade to be moderate for all outcomes based on having four RCTs with a low risk of bias and nearly 900 patients on rFVIIa therapy. However, it is important to note that effect size estimates for all outcomes—other than arterial thromboembolic events and changes in hematoma volume—were imprecise, which precludes definitive conclusions about their effects. Another frequent component to limit the strength of evidence was inconsistency, which was due to both the variability of effect sizes and differences in direction of effect. We found no clear evidence (across any dosing level) that rFVIIa has an effect on mortality, poor modified Rankin Scale score, or venous thromboembolic events, but did find that it is associated with an increased rate of arterial thromboembolic events and a decrease in relative hematoma expansion (Table 23).

Applicability

The overall applicability of the evidence for this indication was good for treatment use in the population targeted by the RCTs—adult patients with intracerebral hemorrhage who were not on anticoagulation (Table 24). For instance, the evidence had good duration and intensity of follow-up and also encompassed a range of outcomes that included important measures of functional ability, morbidity, and mortality. The evidence is less applicable to patients on anticoagulation therapy (e.g., warfarin), who had isolated subdural or subarachnoid bleeding, or for whom surgical interventions were planned, because such patients were excluded from the RCTs. The only study to include patients on anticoagulation therapy (with subdural hemorrhage or ICH) was a small comparative observational study of fair quality, which limits applicability.

Conclusions

For patients of mean age 65 without anticoagulation use who present for spontaneous ICH (a subset of intracerebral hemorrhage), current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other. Use of rFVIIa compared to usual care appears to attenuate hematoma growth but also increase the risk of arterial thromboembolic

events without having a significant impact on mortality or functional outcome. Notably, these patients have lower rates of mortality than do patients in the Premier database. Whether patients who are on oral anticoagulation therapy, have other forms of intracranial hemorrhage (e.g., subdural or subarachnoid hemorrhage), are treated earlier with rFVIIa, are younger, have lower baseline hematoma volumes, or have no prior use of antiplatelet agents may experience better outcomes (relative to the populations already studied) remains unclear.

Table 18. General characteristics of comparative studies on off-label rFVIIa use for intracranial hemorrhage

Article	Study Design	Study Setting/ Time Period	Sample Size and Dose, µg/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Mayer 2005a ²³	RCT Treatment	73 centers	All Rx: 303	Rx: 40: 67 (12)	Inclusion: -spontaneous ICH -treatment within 4 hrs of symptoms onset -over 18 years old Exclusion: -deep coma (GCS 3-5) -surgical hematoma evacuation planned within 24h -secondary ICH (e.g. related to trauma) -known oral anticoagulant use, history of coagulopathy, or thrombocytopenia -any history of thrombotic disease* -previous disability (mRS>2)	Mortality	Change in hematoma volume
		Australia, Europe, Asia, North America	40: 108 80: 92 160: 103	80: 65 (12) 160: 64 (13)			
		8/2002-3/2004	Ucare: 96	Ucare: 68 (12)		Poor functional outcome (mRS 4-6)	
Mayer 2005b ⁸⁶	RCT Treatment	14 centers	All Rx: 36	Rx: 10: 51 (9)	Inclusion: -spontaneous ICH -treatment within 4 hrs of symptoms onset -over 18 years old Exclusion: -deep coma (GCS 3-5) -surgical hematoma evacuation planned within 24h -secondary ICH (e.g. related to trauma) -known oral anticoagulant use, history of coagulopathy, or thrombocytopenia -any history of thrombotic disease -previous disability (mRS>2)	Mortality	Change in hematoma volume
		Australia, Europe, Asia	10: 6 20: 6 40: 6 80: 6 120: 6 160: 6	20: 68 (22) 40: 68 (16) 80: 58 (11) 120: 64 (14) 160: 53 (12)			
		8/2001-10/2002	Ucare: 11	Ucare: 66 (14)		Poor functional outcome (mRS 4-6)	

Table 18. General characteristics of comparative studies on off-label rFVIIa use for intracranial hemorrhage (continued)

Article	Study Design	Study Setting/ Time Period	Sample Size and Dose, µg/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Mayer 2006 ⁸⁷	RCT Treatment	17 centers USA 11/2001- 3/2003	All Rx: 32 5: 8 20: 8 40: 8 80: 8 Ucare: 8	Rx: 5: 72 (10) 20: 60 (15) 40: 64 (13) 80: 62 (12) Ucare: 67 (13)	Inclusion: -spontaneous ICH -treatment within 4 hrs of symptoms onset -over 18 years old Exclusion: -deep coma (GCS 3-5) -surgical hematoma evacuation planned within 24h -secondary ICH (e.g. related to trauma) -known oral anticoagulant use, history of coagulopathy, or thrombocytopenia -any history of thrombotic disease -previous disability (mRS>2)	Mortality Adverse events including TE events Poor functional outcome (mRS 4-6)	Change in hematoma volume
Mayer 2008 ⁸⁸	RCT Treatment	122 centers Australia, Europe, Asia, North America 5/2005-2/2007	All Rx: 573 20: 276 80: 297 Ucare: 268	Rx: 20: 65 (14) 80: 65 (13) Ucare: 65 (14)	Inclusion: -spontaneous ICH -treatment within 4 hrs of symptoms onset -over 18 years old Exclusion: -deep coma (GCS 3-5) -surgical hematoma evacuation planned within 24h -secondary ICH (e.g. related to trauma) -known oral anticoagulant use, history of coagulopathy, or thrombocytopenia -known recent thrombotic disease (within 30 days of enrollment) -previous disability (mRS>2)	Mortality Adverse events including TE events Poor functional outcome (mRS 5-6, but with extrapolation possible to mRS 4-6)	Change in hematoma volume
Ilyas 2008 ⁸⁹	Retrospective comparative Treatment	1 University hospital USA 2/2000-NR	Rx: 24 Range 10-100 Ucare:30	Rx: 76.5 (11) Ucare: 76.4 (12.4)	Inclusion: -new or evolving intracranial hemorrhage (ICH or subdural hematoma) -use of warfarin -INR>1.4 Exclusion: NR	Mortality Adverse events including TE events	Time to correction of INR

Table 18. General characteristics of comparative studies on off-label rFVIIa use for intracranial hemorrhage (continued)

Article	Study Design	Study Setting/ Time Period	Sample Size and Dose, µg/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Pickard 2000 ^{90†}	Prospective comparative	Multicenter	All Rx: 5 80: 2 80+3.5/h CI: 2 80+7.0/h CI: 1	Rx: NR	Inclusion: -subarachnoid hemorrhage (grade I, II, or III on World Federation of Surgeons scale) confirmed on head CT or lumbar puncture Exclusion: NR	Adverse events including TE events	PET scan markers of cerebral blood flow and oxygen extraction
	Treatment	NR	UCare: 5				
Brody 2005 ^{91†}	Retrospective comparative	1 University hospital	Rx: 12 Mean 4.8 mg SD 2.1 mg	Rx: 71 (13)	Inclusion: -spontaneous warfarin-associated ICH -INR>1.3 Exclusion: NR	Adverse events including TE events	Mortality ICU and hospital LOS
	Treatment	USA 3/2002-1/2003	UCare 15	UCare: 77 (7)			
Hallevi 2008 ^{92†}	Retrospective comparative	1 University hospital	All Rx: 46 40 (on warfarin): NR	Rx: 60 [38-87]	Inclusion: -spontaneous ICH (could include those on warfarin) Exclusion: -GCS<5 -Recent thromboembolic event	Adverse events including TE events	Mortality Change in hematoma volume
	Treatment	USA NR	80 (not on warfarin): NR UCare: 148	UCare: 58 [40-80]			

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report;

*Mayer 2005a²³ excluded patients with symptomatic thrombotic or vaso-occlusive disease within 30 days of symptoms onset. This was amended midway through the trial to exclude patients with any history of thrombotic or vaso-occlusive disease;

Rx=treatment group(s); Ucare=usual care; GCS=Glasgow Coma Scale; mRS=modified Rankin Scale; CI=continuous infusion; ICU=intensive care unit; LOS=length of stay

Table 19. Mortality and poor outcome on modified Rankin Scale score in comparative studies of rFVIIa use in intracranial hemorrhage

Article	Study Design and rFVIIa use	Mean rFVIIa dose (ug/kg) (SD) [Range]	Sample size^		Mean age (SD) [Range]		Mortality rate			Poor functional outcome on mRS* rate		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Mayer 2005a ²³	RCT Treatment	40	108		67 (12)		0.176		p=.05	0.546		p=.02
		80	92	96	65 (12)	68 (12)	0.185	0.292	p=.10	0.495	0.688	p=.008
		160	103		64 (13)		0.194		p=.11	0.544		p=.02
	All Patients				-	-	0.185	0.292	p=.02	0.530	0.688	p=.004
Mayer 2005b ⁸⁶	RCT Treatment	10	6		51 (9)		0			0		
		20	6		68 (22)		0			0.333		
		40	6	11	68 (16)	66 (14)	0.167	0.182	NR	0.667	0.455	NR
		80	6		58 (11)		0			0.5		
		120	6		64 (14)		0.167			0.5		
	160	6		53 (12)		0.167			0.667			
All Patients				-	-	0.083	0.182	NR	0.444	0.455	NR	
Mayer 2006 ⁸⁷	RCT Treatment	5	8		72 (10)		0.25			0.625		
		20	8	8	60 (15)	67 (13)	0.25	0.125	NR	0.375	0.500	NR
		40	8		64 (13)		0.375			0.625		
	80	8		62 (12)		0			0.25			
All Patients				-	-	0.219	0.125	NR	0.469	0.500	NR	
Mayer 2008 ⁸⁸	RCT Treatment	20	276	268	65 (14)	65 (14)	0.181	0.190	p=.38	0.492		1.0 [0.6-1.6] [#]
		80	297		65 (13)		0.209		p=.75	0.505		1.4 [0.9-2.2] [#]
	All Patients				-	-	0.195	0.190	NR	0.499	0.466	NR
RCTs Unweighted sum	All RCTs	5-40	426				0.181			0.502		
		80	403	383	-	-	0.196	0.214		0.497	0.522	
	All Patients	120-160	115		-	-	0.191			0.548		
All Patients				-	-	0.189	0.214		0.506	0.522		
Ilyas ⁸⁹	Retrospective comparative Treatment	[10-100]	24	30	76.5 (11)	76.4 (12.4)	0.21	0.27	p=.86	NR	NR	NR
Pickard 2000 ^{90†}	Prospective comparative Treatment	80; 80+3.5/h CI; 80+7.0/h CI	5	5	NR	NR	NR	NR	NR	NR	NR	NR

Table 19. Mortality and poor outcome on modified Rankin Scale score in comparative studies of rFVIIa use in intracranial hemorrhage (continued)

Article	Study Design and rFVIIa use	Mean rFVIIa dose (ug/kg) (SD)	Sample size [^]		Mean age (SD) [Range]		Mortality rate			Poor functional outcome on mRS* rate		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Brody 2005 ⁹¹ †	Retrospective comparative <i>Treatment</i>	4.8 ^{&} (2.1)	12	15	71 (13)	77 (7)	0.42	0.13	NR	\$	\$	NR
Hallevi 2008 ⁹² †	Retrospective comparative <i>Treatment</i>	40;80	46	148	60 [38-87]	58 [40-80]	0.13	0.14	NR	0.57	0.54	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

[^]This is the largest sample size reported in each study, which is the correct sample size for mortality. Sample size for poor functional outcome on the modified Rankin Scale (mRS) was smaller in Mayer NEJM 2005²³ and Mayer NEJM 2008.⁸⁸ 108, 91, 103, and 96 in the 40, 80, 160, and usual care groups, respectively in Mayer NEJM 2005²³, and 264, 293, and 262 in the 20, 80, and usual care groups, respectively in Mayer NEJM 2008⁸⁸

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies, wherever possible.

*Poor outcome defined as modified Rankin Scale (mRS) score of 4-6. Data for mRS scores of 4-6 in Mayer NEJM 2008⁸⁸ were derived graphically from figure 3 in the paper. The proportion of patients with mRS scores of 5-6 was reported as 0.261, 0.287, 0.237 for the 20 ug/kg, 80 ug/kg, and usual care groups, respectively. The odds ratio reported for Mayer NEJM 2008⁸⁸ is based upon the proportion of patients with mRS scores of 5-6.

[#]Odds ratio for poor functional outcomes and 95 percent confidence interval (CI), based upon the proportion of patients with mRS scores of 5-6.

[&]Mean dose in mg rather than ug/kg of body weight.

[§]Brody 2005⁹¹ reports median (range) GCS score at discharge by group (15=normal, 0=dead): rFVIIa 13.5 (13-15), usual care 15 (13-15).
mRS=modified Rankin Scale; NR=not reported; CI=continuous infusion

Table 20. Thromboembolic events (arterial and venous) in comparative studies of rFVIIa use in intracranial hemorrhage

Article	Study Design and rFVIIa use	Mean rFVIIa dose (ug/kg) (SD)	Sample size^^		Mean age (SD) [Range]		Total Thromboembolic Event Rate**			Arterial Thromboembolic Event Rate**			Venous Thromboembolic Event Rate**		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Mayer 2005a ²³	RCT <i>Treatment</i>	40	108		67 (12)		0.065			0.056			0.009		
		80	92	96	65 (12)	68 (12)	0.043	0.021	NR	0.022	0	NR	0.022	0.021	NR
		160	103		64 (13)		0.097			0.078			0.019		
	All Patients						0.069	0.021	p=.12	0.053	0	p=.01	0.017	0.021	NR
Mayer 2005b ⁸⁶	RCT <i>Treatment</i>	10	6		51 (9)		0			0			0		
		20	6		68 (22)		0.333			0.167			0.167		
		40	6	11	68 (16)	66 (14)	0.333	0.091	NR	0.333	0	NR	0	0.091	NR
		80	6		58 (11)		0			0			0		
		120	6		64 (14)		0			0			0		
		160	6		53 (12)		0			0			0		
	All Patients						0.111	0.091	NR	0.083	0	NR	0.028	0.091	NR
Mayer 2006 ⁸⁷	RCT <i>Treatment</i>	5	8		72 (10)		0			0			0		
		20	8		60 (15)	67 (13)	0.25	0.125	NR	0	0.125	NR	0.25	0	NR
		40	8	8	64 (13)		0.125			0			0.125		
		80	8		62 (12)		0			0			0		
	All Patients						0.094	0.125	NR	0	0.125	NR	0.094	0	NR
Mayer 2008 ⁸⁸	RCT <i>Treatment</i>	20	265	263	65 (14)	65 (14)	0.098	0.087	NR	0.057	0.046	NR	0.042	0.042	NR
		80	293		65 (13)		0.126			0.092		p=.04	0.034		NR
	All Patients						0.113	0.087	NR	0.075	0.046	NR	0.038	0.042	NR
Unweighted Sum	All RCTs	5-40	415				0.096			0.058			0.039		
		80	399	378			0.103	0.071		0.072	0.034		0.030	0.037	
		120-160	115				0.087			0.070			0.017		
	All Patients						0.098	0.071		0.066	0.034		0.032	0.037	
Ilyas 2008 ⁸⁹	Retrospective comparative <i>Treatment</i>	[10-100]	24	30	76.5 (11)	76.4 (12.4)	0.04	0	NR	0.04	0	NR	0	0	NR

Table 20. Thromboembolic events (arterial and venous) in comparative studies of rFVIIa use in intracranial hemorrhage (continued)

Article	Study Design and rFVIIa use	Mean rFVIIa dose (ug/kg) (SD) [Range]	Sample size		Mean age (SD) [Range]		Total Thromboembolic Event Rate**			Arterial Thromboembolic Event Rate**			Venous Thromboembolic Event Rate**		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Pickard 2000 ⁹⁰ †	Prospective comparative <i>Treatment</i>	80; 80+3.5CI; 7.0 CI	5	5	NR	NR	0.2	0	NR	0.2	0	NR	0	0	NR
Brody 2005 ⁹¹ †	Retrospective comparative <i>Treatment</i>	4.8 ^{&} (2.1)	12	15	71 (13)	77 (7)	0.25	0	NR	0.08	0	NR	0.17	0	NR
Hallevi 2008 ⁹² †	Retrospective comparative <i>Treatment</i>	40;80	46	148	60 [38-87]	58 [40-80]	0.15	NR	NR	0.09	NR	NR	0.07	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report. Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies, wherever possible.

^^Sample size for thromboembolic events in Mayer NEJM 2008⁸⁸ is smaller than reported for mortality and poor mRS because thromboembolic event rates were calculated based upon the “safety population” (i.e. patients exposed to a study agent) rather than the patients subjected to randomization.

**Thromboembolic event rates were calculated by dividing the number of thromboembolic *events* by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from the rates reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

[&]Mean dose in mg rather than ug/kg of body weight.

CI=continuous infusion; NR=not reported; NS=not significant

Table 21. Indirect outcomes in comparative studies of rFVIIa use in intracranial hemorrhage

Article	Study Design/ rFVIIa use	rFVIIa dose (ug/kg) (SD) [Range]	Sample size		Mean age (SD) [Range]		Relative hematoma expansion, % [95 percent CI], (SD)			Absolute hematoma expansion, mL [95 percent CI], (SD)		
			rFVIIa	UC	rFVIIa	UC	rFVIIa	UC	Sig	rFVIIa	UC	Sig
Mayer 2005a ²³	RCT <i>Treatment</i>	40	108		67 (12)		16 [4-28]*		p=.07	5.4 [1.7-9.0]*		p=.13
		80	92	96	65 (12)	68 (12)	14 [2-27]*	29 [16- 44]*	p=.05	4.2 [0.3-8.0]*	8.7 [4.9- 12.4]*	p=.14
		160	103		64 (13)		11 [0-23]*		p=.02 [^]	2.9 [-0.8-6.6]*		p=.008 [^]
All Pts: p=.01 [^]										All Pts: p=.01 [^]		
Mayer 2005b ⁸⁶	RCT <i>Treatment</i>	10	6		51 (9)							
		20	6		68 (22)							
		40	6	11	68 (16)	66 (14)	"same"	"same"	Not significant	NR	NR	NR
		80	6		58 (11)							
		120	6		64 (14)							
Mayer 2006 ⁸⁷	RCT <i>Treatment</i>	5	8		72 (10)		64 (106)			13 (19)		
		20	8	8	60 (15)	67 (13)	79 (172)	11 (18)	Not significant	10 (21)	2 (4)	Not significant
		40	8		64 (13)		37 (51)			1 (2)		
		80	8		62 (12)		4 (9)			1 (2)		
Mayer 2008 ⁸⁸	RCT <i>Treatment</i>	20	276	268	65 (14)	65 (14)	18 [13-24]	26 [20- 32]	p=.09	4.9 [2.9-7.0]	7.5 [5.4- 9.6]	p=.08
		80	297		65 (13)		11 [6-17]		p=<.001	3.7 [1.7-5.7]		p=.009
Ilyas 2008 ⁸⁹	Retrospective comparative <i>Treatment</i>	[10-100]	24	30	76.5 (11)	76.4 (12.4)	NR	NR	NR	NR	NR	NR
Pickard 2000 ⁹⁰ †	Prospective comparative <i>Treatment</i>	80; 80+3.5/h CI; 80+7.0/h CI	5	5	NR	NR	NR	NR	NR	NR	NR	NR
Brody 2005 ⁹¹ †	Retrospective comparative <i>Treatment</i>	4.8 ^{&} (2.1)	12	15	71 (13)	77 (7)	NR	NR	NR	NR	NR	NR
Hallevi 2008 ⁹² †	Retrospective comparative <i>Treatment</i>	40;80	46	148	60 [38-87]	58 [40- 80]	11.6 (14.6)	NR	NR	1.09 (1.37)	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, "Consideration of poor quality comparative observational studies") and in the overall harms analyses near the end of this report;

.Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

*In Mayer 2005a,²³ 98.3 percent confidence interval is used;

[^]The comparison was statistically significant according to the prespecified Bonferroni-corrected threshold of p=0.0167 in Mayer 2005a²³;

[&]Mean dose in mg rather than ug/kg of body weight;

UC=usual care; CI=continuous infusion; NR=not reported

Figure 5. Mean differences in mortality rates, by study and rFVIIa indication (rFVIIa minus usual care)

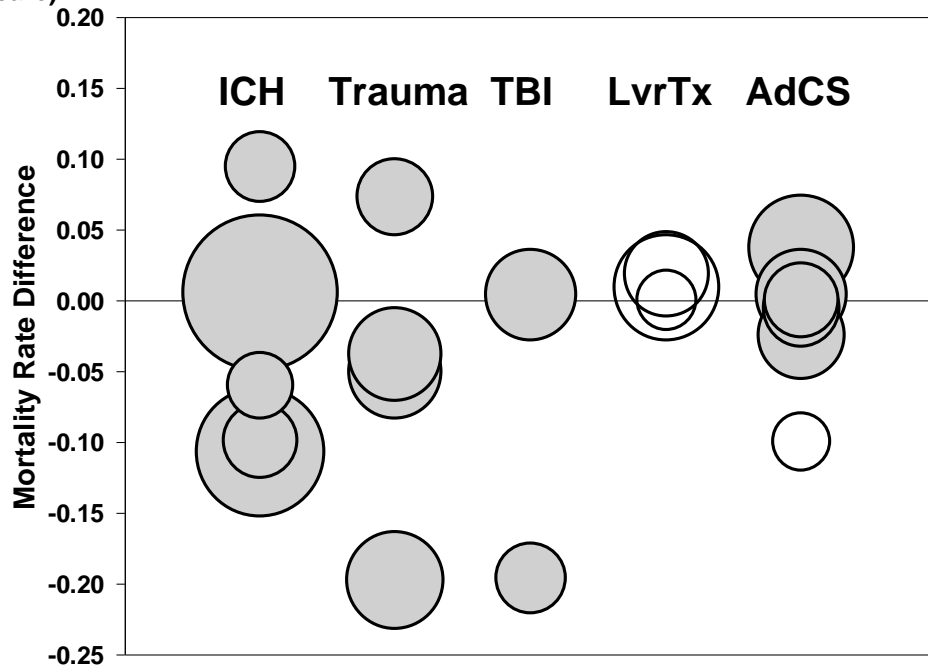
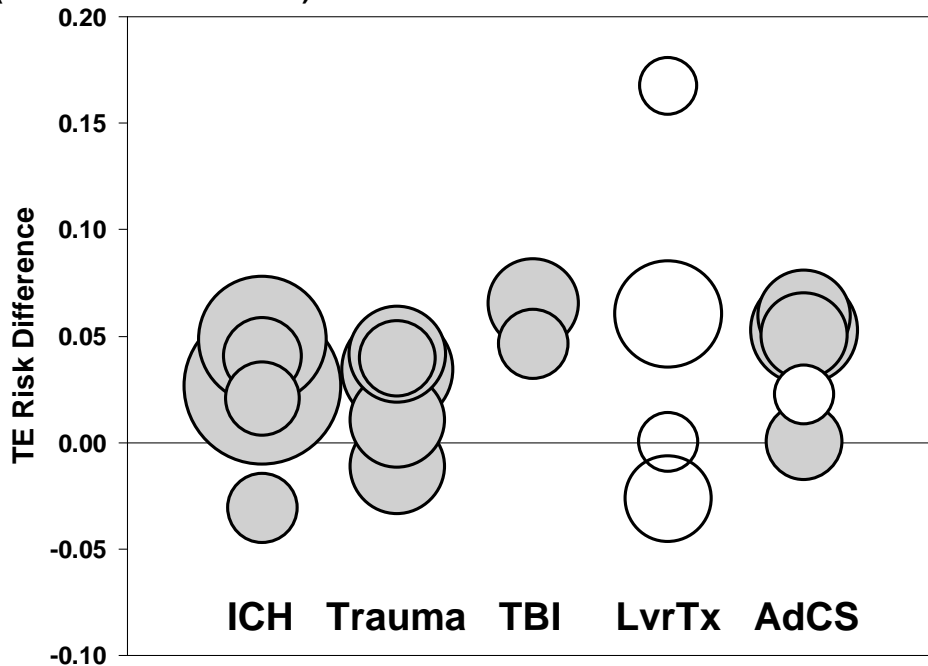


Figure 6. Mean differences in rates of thromboembolic events, by study and rFVIIa indication (rFVIIa minus usual care)



ICH=intracranial hemorrhage here—although in rest of report “ICH” indicates a subset of intracranial hemorrhage, namely intracerebral hemorrhage; Trauma=body trauma; TBI=brain trauma (traumatic brain injury); LvrTx=liver transplantation; AdCS=adult cardiac surgery. The figures show mean differences in mortality and thromboembolic event rates, respectively, for each comparative study and according to each rFVIIa indication. The area of each circle approximates the total sample size of each respective study; shaded circles represent studies on treatment use of rFVIIa and clear circles represent studies on prophylactic use of rFVIIa.

Figure 7. Mortality in ICH (low rFVIIa dose)

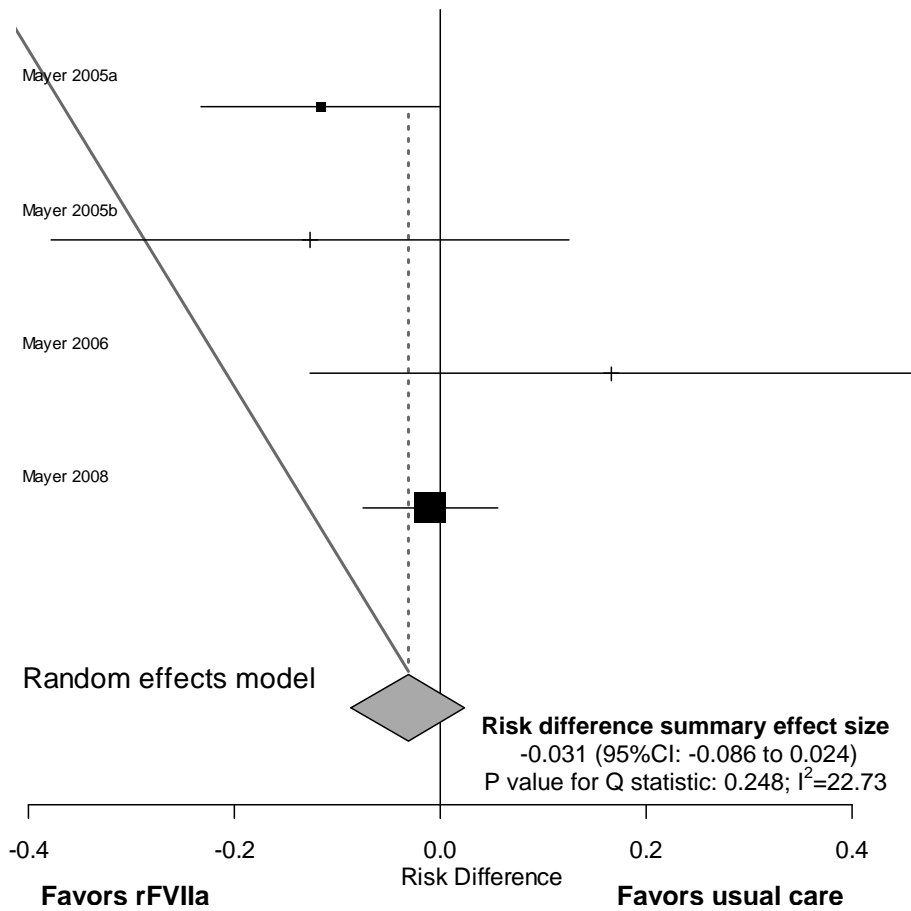
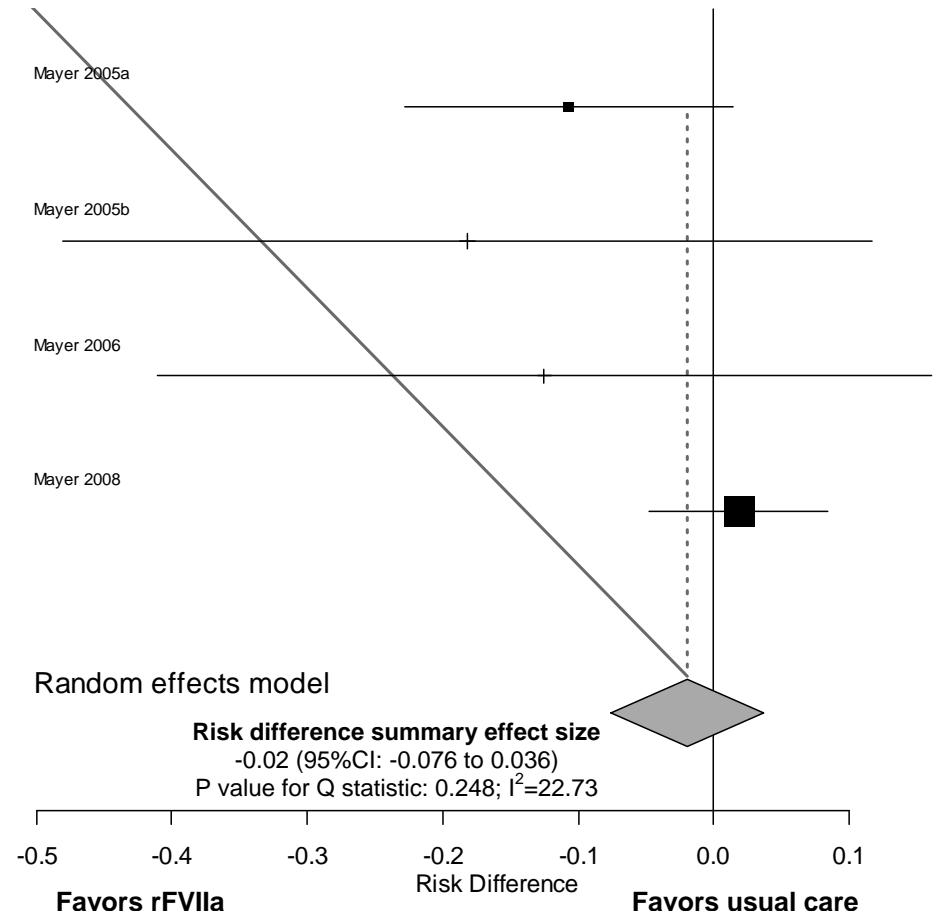
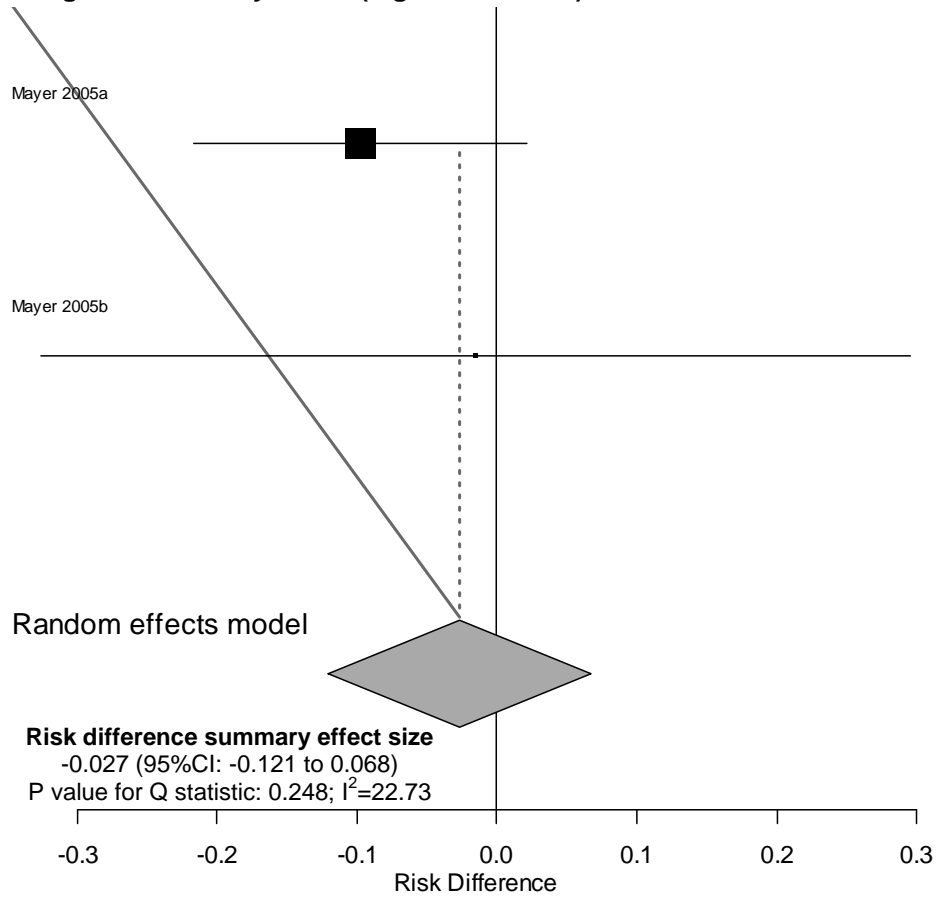


Figure 8. Mortality in ICH (medium rFVIIa dose)



Article	Deaths/total patients (low dose)		Deaths/total patients (medium dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	19/108	28/96	17/92	28/96
Mayer 2005b	1/18	2/11	0/6	2/11
Mayer 2006	7/24	1/8	0/8	1/8
Mayer 2008	50/276	51/268	62/297	51/268

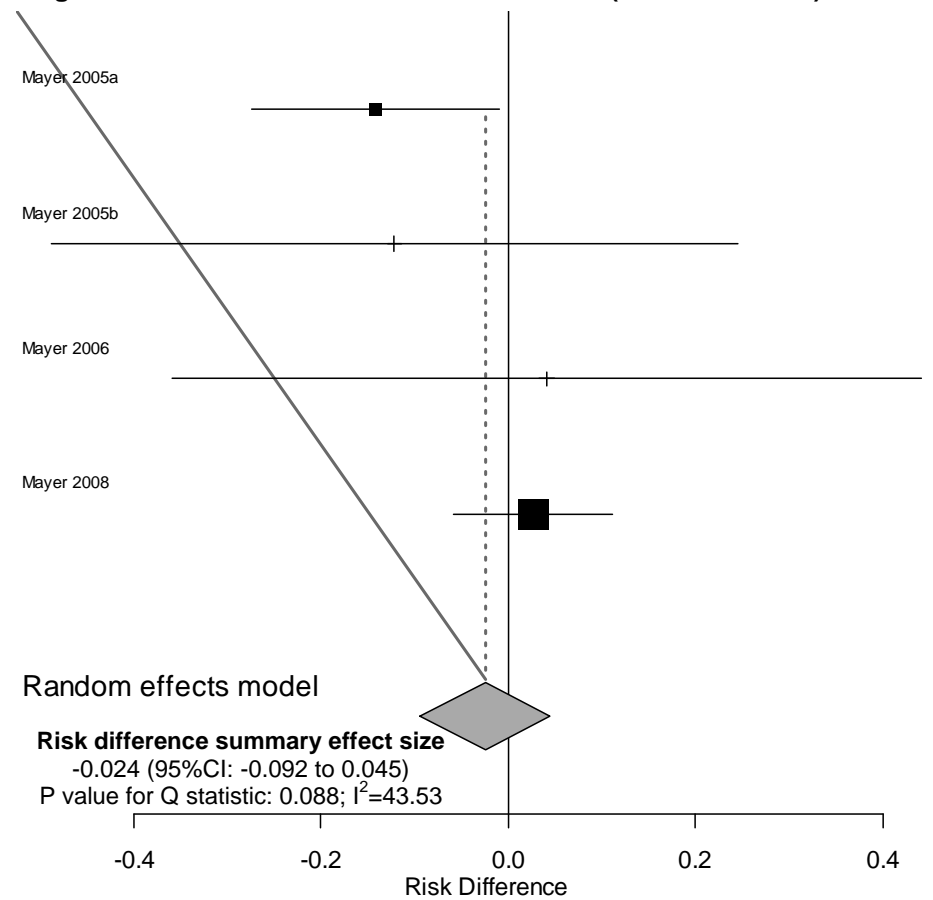
Figure 9. Mortality in ICH (high rFVIIa dose)



Favors rFVIIa **Favors usual care**

Article	Deaths/total patients (high dose)	
	rFVIIa	Control
Mayer 2005a	20/103	28/96
Mayer 2005b	2/12	2/11

Figure 10. Poor modified Rankin score in ICH (low rFVIIa dose)



Favors rFVIIa **Favors usual care**

Article	Poor mRS/total patients (low dose)	
	rFVIIa	Control
Mayer 2005a	59/108	66/96
Mayer 2005b	6/18	5/11
Mayer 2006	13/24	4/8
Mayer 2008	130/264	122/262

Figure 11. Poor modified Rankin score in ICH (medium rFVIIa dose)

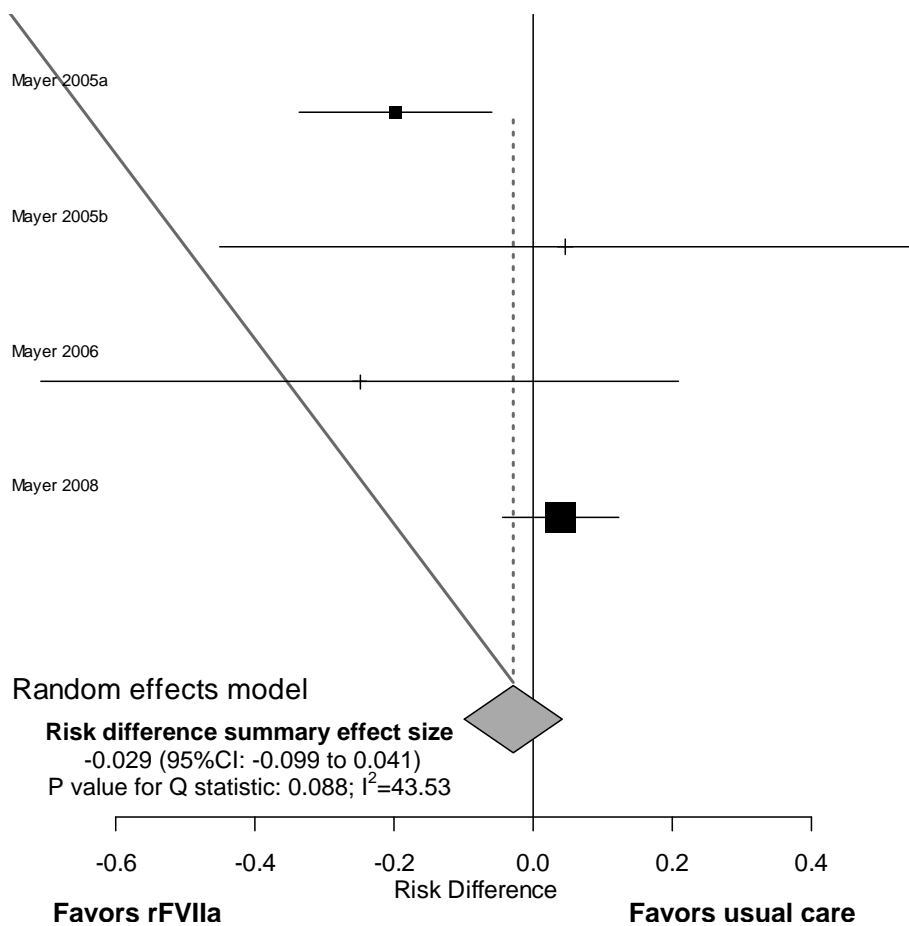
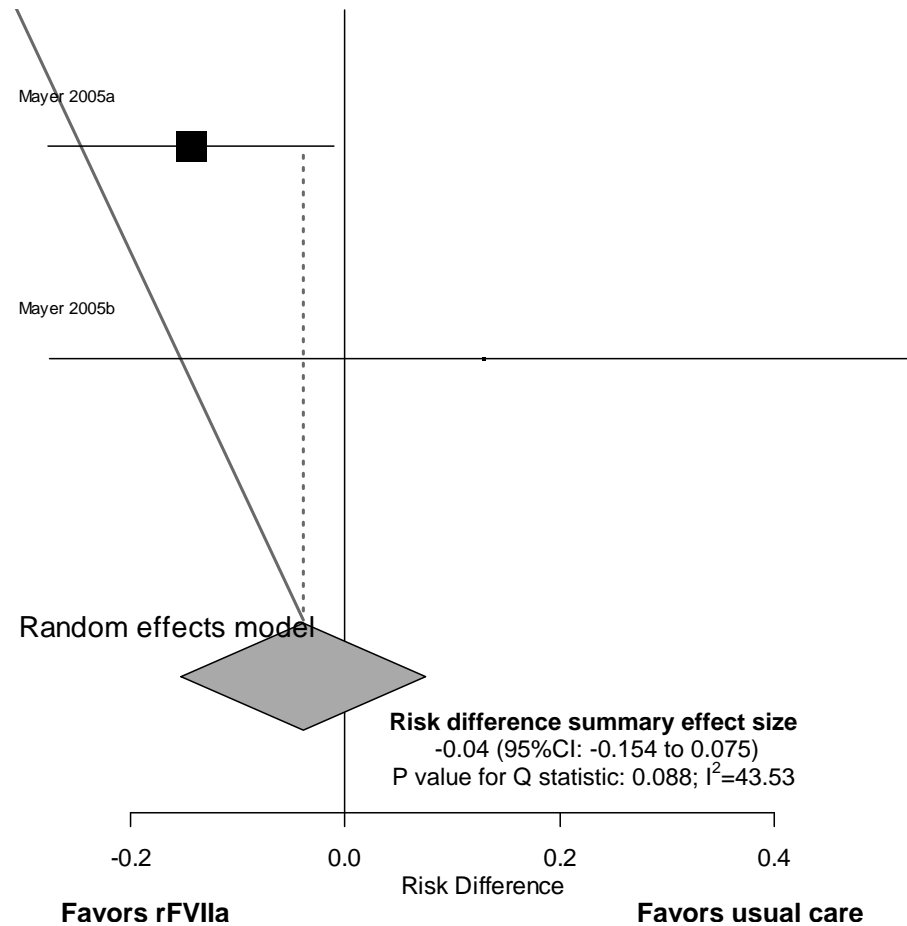


Figure 12. Poor modified Rankin score in ICH (high rFVIIa dose)



Article	mRS/total patients (medium dose)		mRS/total patients (high dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	45/91	66/96	56/103	66/96
Mayer 2005b	3/6	5/11	7/12	5/11
Mayer 2006	2/8	4/8	NA	NA
Mayer 2008	148/293	122/262	NA	NA

Figure 13. Arterial TE events in ICH (low rFVIIa dose)

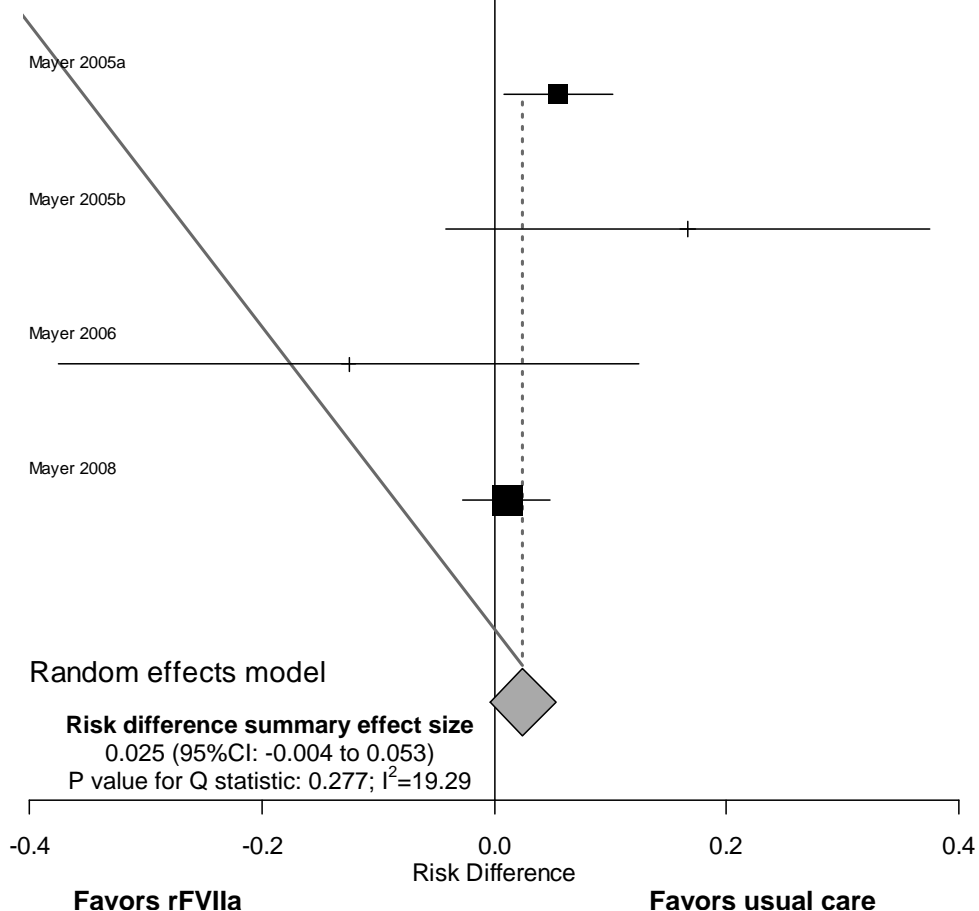
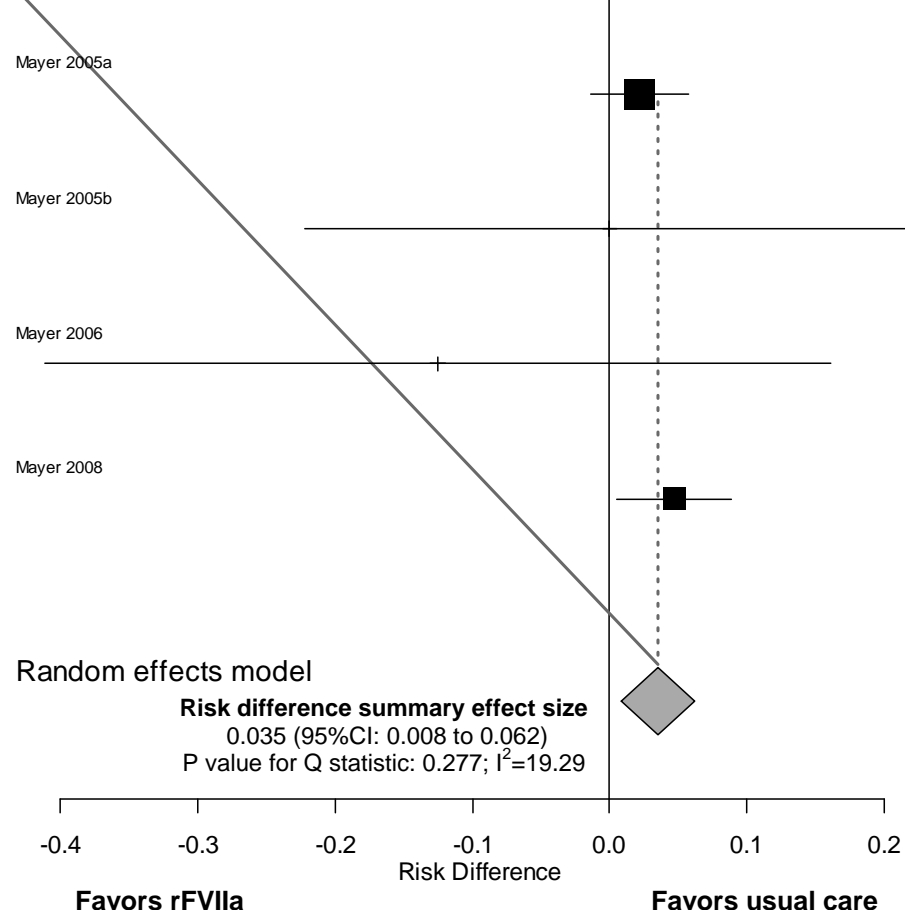


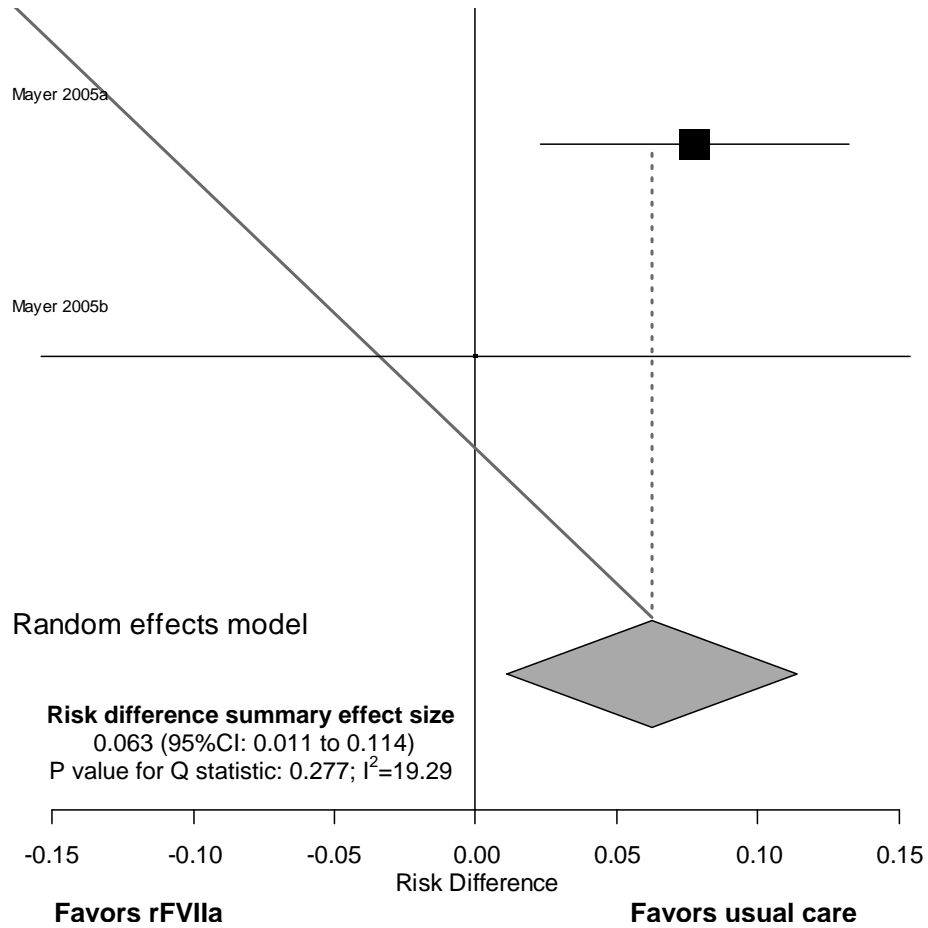
Figure 14. Arterial TE events in ICH (medium rFVIIa dose)



Article	Favors usual care		Favors rFVIIa	
	Arterial TE events /total patients (low dose)		Arterial TE events/total patients (medium dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	6/108	0/96	2/92	0/96
Mayer 2005b	3/18	0/11	0/6	0/11
Mayer 2006	0/24	1/8	0/8	1/8
Mayer 2008	15/265	12/263	27/293	12/263

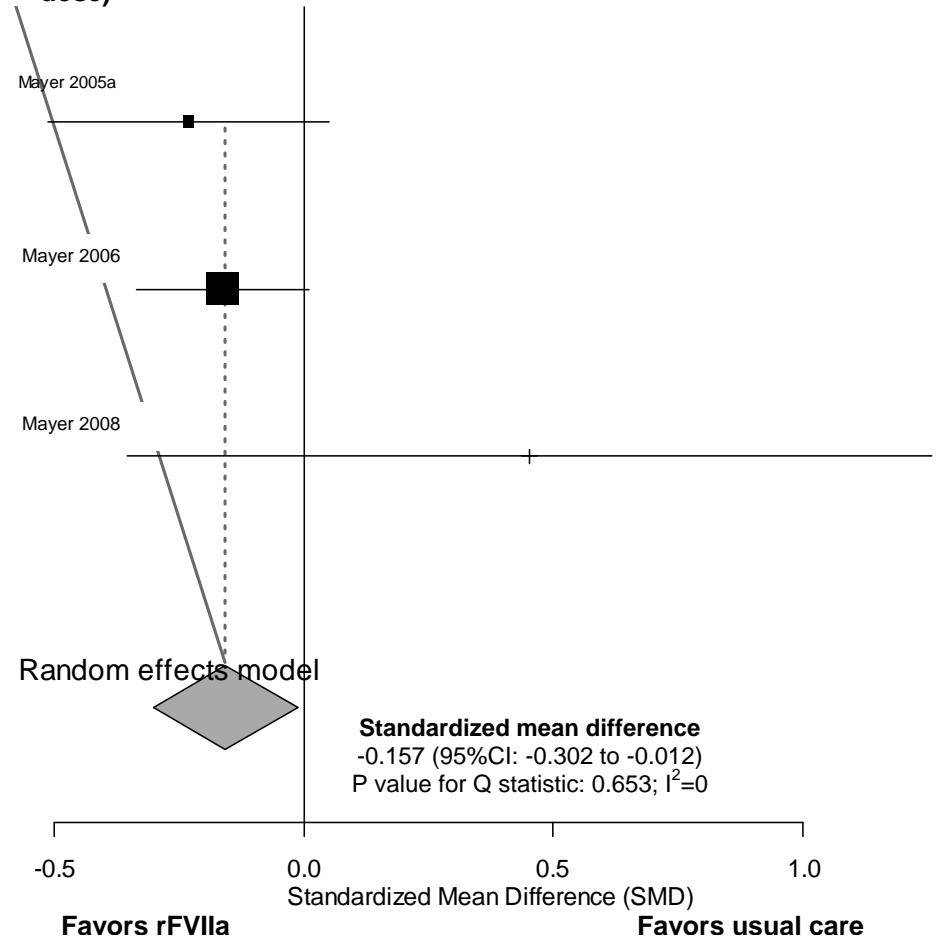
Regarding the Arterial TE events in ICH: Here the weights appear “backwards” to the way they appear in the arcsine analysis (see Appendix Figure 8) and counterintuitive, because Mayer 2008 has a much larger sample size than, for example, Mayer 2005a. These apparent contradictions arise with the use of the risk difference metric because of its use of a 0.5 correction factor in calculations where there are zero cells. Despite these differences, the results remain consistent between the risk difference and arcsine metrics.

Figure 15. Arterial TE events in ICH (high rFVIIa dose)



Article	Arterial TE events/total patients (high dose)	
	rFVIIa	Control
Mayer 2005a	8/103	0/96
Mayer 2005b	0/12	0/11

Figure 16. Relative change in hematoma volume for ICH (low rFVIIa dose)



Article	Mean percent change in hematoma volume/total patients (low dose)	
	rFVIIa	Control
Mayer 2005a	16/101	29/94
Mayer 2006	60/8	11/8
Mayer 2008	18/259	26/254

Table 22. Post-hoc evaluations of rFVIIa use in ICH before versus after 3 hours from time of symptoms onset

Article	Study Design	Dose (ug/kg)	Timing Group*	Sample Size		Mean time from onset to dosing, minutes (SD) [Range]	Mean Relative Change in ICH Volume, % (SD) [95% CI]			Mean Absolute Change in ICH Volume, mL (SD) [95% CI]			Relative Reduction in ICH Volume [^] , mL [95% CI]	
				rFVIIa	Usual Care		rFVIIa	Usual Care	Sig	rFVIIa	Usual Care	Sig		
Mayer 2005a ²³	RCT	All Doses (i.e. 40, 80, 160 combined)	all pts	287	94	167 (32)	14 [7-21] [#]	29 [16-44] [#]	p=.01	4.2 [2.0-6.3] [#]	8.7 [4.9-12.4] [#]	p=.01	-4.5	
			<3 hrs	199	68	-	13	34	p=.004	4.4	10.7	p=.009	-6.3	
			3-4 hrs	88	26	-	16	14	p=0.86	3.8	3.1	p=0.76	0.7	
Mayer 2008 ⁸⁸	RCT	80	all pts	285	254	160 (36)	11 [6-17]	26 [20-32]	p<.001	3.7 [1.7-5.7]	7.5 [5.4-9.6]	p=.009	-3.8	
			<3 hrs	211	183	-	-	-	-	-	-	-	-	-4.5 [-8.0 to 1.0]
			<2 hrs	-	-	-	-	-	-	-	-	-	-	-5.6 [-13.1 to 2.0]

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

*Timing group refers to the stratification of study patients based upon timing of treatment. For example, “<3 hrs” includes all patients who received study drug within three hours of ICH symptoms, and “3-4 hrs” includes all patients who received study drug more than 3 hours after the onset of ICH symptoms. Note that only 1 patient each in Mayer 2005²³ and Mayer 2008,⁸⁸ and 2 patients in Hallevi 2008⁹² received rFVIIa more than 4 hours after the onset of ICH symptoms.

[^]Relative reduction in ICH volume equals the absolute change in ICH volume (mL) in the usual care group minus the absolute change in ICH volume (mL) in the rFVIIa group. A negative value indicates a smaller increase in ICH volume in the rFVIIa group than in the usual care group (i.e. favors rFVIIa), while a positive value indicates a larger increase in ICH volume in the rFVIIa group than the usual care group (i.e. favors usual care).

[#]98.3% confidence interval instead of 95% confidence interval.

Table 23. Strength of evidence for rFVIIa use in intracranial hemorrhage

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Level						
Mortality (90 day)	4 ^{23, 86-88}	944	384	RCT	Good	Low	Inconsistent	Direct	Imprecise	No Effect	No	Moderate
	1 ⁸⁹	24	30	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Arterial Thrombo-embolic Events	4 ^{23, 86-88}	944	384	RCT	Good	Low	Inconsistent	Direct	Precise	Increase with rFVIIa	No	Moderate
	1 ⁸⁹	24	30	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Venous Thrombo-embolic Events	4 ^{23, 86-88}	944	384	RCT	Good	Low	Consistent	Direct	Imprecise	No Effect	No	Moderate
mRS Score	4 ^{23, 86-88}	944	384	RCT	Good	Low	Inconsistent	Direct	Imprecise	No Effect	No	Moderate
Change in Hematoma Volume	4 ^{23, 86-88}	1040	384	RCT	Good	Low	Inconsistent	Indirect	Precise	Decrease with rFVIIa	No	Moderate

mRS=modified Rankin Scale (validated measure of functional outcome); RCT=randomized controlled trial; RBCs=red blood cells. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 24. Applicability assessment of intracranial hemorrhage studies

Available Evidence	Overall Implications for Applicability
Population Patients presenting with CT confirmed intracerebral hemorrhage without signs of grave prognosis Mean age 65 years, male = 60 percent High mortality rate (20%) and low probability of symptom-free recovery (5%) Patients with intact clotting systems Exclusions: Patients on anticoagulation, in whom hematoma aspiration is planned, and/or who have other forms of intracranial hemorrhage (other than the small number of patients on anticoagulation and with subdural hematomas in one comparative observational study)	Gaps to applicability exist for patients on oral anticoagulation therapy (e.g., warfarin) and/or those who experience isolated subdural or subarachnoid bleeding Other approaches to intracranial bleeding may reduce the role of rFVIIa, including more aggressive management of hypertension
Intervention Use of rFVIIa as a treatment at doses of 5 to 160 mcg/kg Deliver of rFVIIa within 4 hours of symptoms onset	Lack of clear dose-response relationships hinders applicability to dose selection decisions Difficult to interpret impact of delivery of rFVIIa earlier or later than time frame used in the studies
Comparator Usual care via randomization	Other hemostatic agents potential comparators, but not used in this setting
Outcomes Primary outcomes: Expansion of hematoma volume and poor modified Rankin score Secondary outcomes: thromboembolic events, mortality	Hematoma volume is a surrogate/indirect outcome that is incompletely correlated with clinical outcomes Modified Rankin score captures important information that relates to functional outcome. No meaningful outcomes omitted
Timing and intensity of follow-up 90 day follow-up for neurological status Detailed protocol for ascertainment of MI and DVT	Highly applicable with appreciation for direct, patient-centered outcomes
Setting Multi-center international settings with likely presence of considerable heterogeneity in clinical practice	Heterogeneity may limit applicability to U.S. stroke centers

Key Question 3.a. Acquired, coagulopathic massive bleeding from body trauma and comparative effectiveness of rFVIIa

Background

Trauma is the leading cause of death in young men between the ages of 15 and 40. Hemorrhage is the leading cause of early death (within 24-48 hours) in trauma and second only to traumatic brain injury (TBI) as the overall cause of mortality.¹⁶⁸ Hemorrhage after traumatic injury is associated with an acquired coagulopathy known as the “acute coagulopathy of trauma.”¹⁶⁹⁻¹⁷¹ The coagulopathy develops when there is tissue injury in combination with hypotension. The severity of coagulopathy increases with increasing injury severity and is associated with worse outcomes.¹⁷² Resuscitation of these patients can worsen the coagulopathy. The dilution of blood due to rapid infusion of crystalloid, the development of hypothermia, and persistent acidosis occur during resuscitation and are known together as the “lethal triad,” which conspires to impede coagulation. Not surprisingly, the conditions which lead to the development of lethal triad are worse in cases of severe hemorrhage, particularly in those cases that require massive transfusions (most frequently defined as the use of 10 or more units of packed red blood cells (RBCs) within 24 hours of injury). This acquired coagulopathy potentiates further bleeding, which in turn leads to further physiologic derangements, increased morbidity, and increased mortality. Unfortunately, blood products that are used to replace lost blood and to treat coagulopathy can carry risks of their own. In particular, studies have highlighted increased risks of acute respiratory distress syndrome (ARDS), multiorgan failure (MOF), and sepsis with higher levels of blood product transfusions.¹⁷³⁻¹⁷⁵ rFVIIa has been investigated in trauma as an adjunct to control bleeding and thereby reduce the above risks.

Usual care during the time frame of included studies. As noted above, there is growing evidence of an association between coagulopathy and poor outcomes after trauma. A recent trend in the “usual care” of traumatic bleeding has been to address coagulopathy early in cases of a massive transfusion. This has been achieved by using fresh frozen plasma (FFP) earlier during the resuscitation and in greater amounts. Recent data from civilian databases and the Iraq war suggest that a 1:1 ratio of RBCs:FFP may have a survival advantage when compared to ratios closer to 4:1. In addition, some experts advocate for early transfusion of platelets as well, with a RBCs:FFP:platelet ratio of 1:1:1.¹⁷⁶ As transfusing large quantities of blood products and maintaining a high ratio of FFP to RBCs is challenging, many institutions have implemented “massive transfusion protocols.”¹⁷⁷ These protocols facilitate coordination between the physicians and the blood bank, have been associated with improved survival, and may include include rFVIIa as part of the protocol. The studies evaluated in this section contain data on patients treated during the period of flux. Both plasma-rich transfusion practices and massive transfusion protocols were being implemented contemporaneously and after the published studies included in this section. This means that comparison to “usual care” is limited and does not necessarily reflect current practice. Two published RCTs (published in one paper) were conducted from March 2002 to September 2003,⁹⁶ while the three comparative observational studies⁹⁷⁻⁹⁹ evaluated data on patients treated from January 2000 to February 2005, December 2003 to October 2005, and April 2006 to August 2008, respectively. Another RCT, as of yet unpublished, was conducted from October 2005 to June 2008.

General Characteristics of Studies of Traumatic Bleeding

For this indication, among the published literature, we identified two RCTs (both fair quality) and three comparative observational studies (all fair quality) with 267 patients who received rFVIIa for treatment use. The RCTs were two trials conducted in parallel by the same investigators and published in the same article. One of the trials enrolled patients with blunt trauma and the other with penetrating trauma.⁹⁶ The two trials are evaluated separately in this review. The trials were sponsored by Novo Nordisk, and the trial statistician was an employee of the company. Another RCT was completed in June 2008 and presented at an international meeting in March 2009, but it has not yet been published.^{178,179} It also evaluates rFVIIa in both blunt and penetrating trauma and is sponsored by the manufacturer. Three retrospective cohort studies were also analyzed. They were not sponsored by the manufacturer, and the authors or statisticians were not employed by Novo Nordisk.

Place of studies within analytic framework. All of the included studies evaluated rFVIIa for treatment use (versus prophylaxis or end-stage use), as outlined in our Analytic Framework (Figure 1). However, the censoring of deaths within the first 48 hours in the randomized controlled trials⁹⁶ and within 24 hours in one of the observational studies⁹⁸ raises the question of whether some end-stage use might have occurred. The RCTs reported direct outcomes (e.g., mortality, thromboembolic events) but were underpowered to detect a difference in these. Therefore, they have as their primary outcome the surrogate endpoint of RBC transfusion. The comparative observational studies all examined direct outcomes as their primary outcomes. Mortality was the primary outcome in the Rizoli and Spinella studies,^{97,98} and limb revascularization is the primary outcome in the Fox cohort.⁹⁹

Qualitative considerations of heterogeneity. The RCTs and observational trials included both blunt and penetrating mechanisms and were from both civilian and military populations. Different anatomic mechanisms of injury often result in the final common pathways of severe tissue injury and hypotension, and these conditions are thought to drive the coagulopathy of trauma. Therefore, despite the differences in injury mechanisms, injuries of sufficient severity do share physiologic characteristics. The role of rFVIIa is to act upon these physiologic disturbances. For this reason, despite the heterogeneous mechanisms, we felt it appropriate to assess the patient populations together in this analysis.

Comparison to studies on other indications. These studies had younger patients, on average, than studies in any other adult indication. The RCTs evaluated the highest dose of rFVIIa used in any indication, although the observational studies applied much lower doses.

Patient Characteristics and Study Design

RCTs. The two double-blind RCTs by Boffard (both published in a single paper and both fair quality (Table 14)) enrolled patients from 32 hospitals in eight countries that did not include the U.S. (namely, Australia, Canada, France, Germany, Israel, Singapore, South Africa, and the United Kingdom) and were of modest sample sizes (Table 25). Approximately 70 patients were enrolled in the rFVIIa group in each trial. Inclusion criteria included hemorrhage from a blunt or penetrating traumatic injury requiring at least six units of RBCs within four hours of hospitalization. Exclusion criteria included low GCS score (less than eight), severe base deficit

(over 15 mEq/L) or acidosis (pH under 7.0). There was good baseline similarity between treatment groups. A limitation of the trials was that there were instances of missing outcomes data. For example, the primary outcome of the studies was the number of RBC units transfused. The numbers of patients for whom data was reported was lower than the number of patients who were said to have completed the trials. Another important contextual factor was the investigators' choice to exclude from further analysis those patients who died within the first 48 hours of hospitalization, which comprised nearly 20 percent of patients in each treatment group.

The more recent but unpublished RCT was conducted at 100 sites in 26 countries, including 23 sites in the United States.¹⁷⁸ It was terminated prematurely after a pre-planned interim futility analysis performed by the Data and Safety Monitoring Committee indicated that “the mortality observed in all enrolled patients was lower than expected during study design, meaning that the study as a whole would be underpowered to assess the primary endpoint [of mortality].” Therefore, “the sponsor chose to close the study.”¹⁸⁰ Prior to terminations, the trial enrolled 468 patients with blunt trauma (221 rFVIIa, 247 placebo) and 86 with penetrating trauma (46 rFVIIa, 40 placebo). Limited data were obtained on the ClinicalTrials.gov and manufacturer's websites. These data were used for qualitative sensitivity analyses but not included in the primary analyses.

Withdrawal of deferred informed consent. The FDA rules for the study of emergency therapies (and similar policies in other countries) allow for deferral of informed consent.^{64,65} The publication of the Boffard RCTs states in the methods section, “Because of the emergency conditions and the possible absence of relatives at enrollment into the trial, waived informed consent was authorized by the ethics committees. However, whenever a patient was included without written informed consent, such consent was promptly sought from the legally authorized representative and subsequently from the patient. Adequate confirmation of consent was not obtained for six patients, and their data were excluded from analysis.”⁹⁶ The publication reported that the withdrawals of deferred consent—described as “consent not confirmed” following “waived informed consent”—occurred after randomization and dosing (whether of rFVIIa or placebo), but did not note the treatment arm of the patients who withdrew. Five patients in the blunt trauma trial were withdrawn for this reason versus one patient in the penetrating trauma trial.

Comparative observational studies. The Spinella retrospective cohort study⁹⁸ assessed data from a military database, the Joint Theatre Trauma Registry. Patients in this registry sustained wartime injuries in Iraq. Patients were included in the registry if they had suffered severe trauma (defined by Injury Severity Score over 15) and required transfusion of 10 or more units of RBCs within the first 24 hours of hospitalization. The time period of data collection was 2003 to 2005. Similar to the RCTs, this study excluded from further analyses those patients who had early in-hospital death, although in this case, early death was defined as occurring within the first 24 hours. Among this cohort, investigators identified 49 patients who received rFVIIa and 75 who did not. The groups were relatively well matched at baseline. The authors evaluated for confounding by testing for interactions between rFVIIa use and other variables when evaluating the primary outcome of mortality at 30 days.

The second retrospective cohort study⁹⁷ by Rizoli identified all trauma patients who were managed at a level I trauma center in Canada and were transfused with eight units of RBCs within the first 12 hours of hospitalization. Among this cohort, investigators identified 38

patients who received rFVIIa and 204 who did not. Groups were relatively well matched at baseline, except that the rFVIIa group received higher numbers of transfusions in the first six hours of admission. The mean time from admission to rFVIIa administration was six hours. The primary outcome was mortality at 24 hours and the secondary outcome was in-hospital mortality. Investigators used univariate analysis followed by multivariable logistic regression analysis to address issues of confounding. Importantly, investigators noted that five of the 38 patients in their cohort who received rFVIIa were also included in one of the above trauma RCTs, although the particular trial (blunt versus penetrating) was not specified.

The final retrospective cohort study by Fox,⁹⁹ like the Spinella study, examined data from the Joint Trauma Registry but for patients treated during a later timeframe—from 2006 to 2007. Patients were included in the study if they suffered life-threatening vascular injuries and required transfusion of over four units of RBCs. Patients were not censored for early in-hospital death. Investigators identified 41 patients who received rFVIIa and 12 patient who did not. Groups were relatively well matched at baseline, with the possible exception of somewhat higher mean Injury Severity scores in the treatment group versus controls (29 versus 22, respectively), although this difference was not statistically significant. The authors did not evaluate for confounding.

Intervention Characteristics

RCTs. The Boffard RCTs both used the same dosing schema consisting of three sequential infusions of rFVIIa (200,100, and 100 $\mu\text{g}/\text{kg}$) or placebo. The first dose was administered after the eighth unit of RBCs, the second one hour later, and the third three hours later. rFVIIa patients in the unpublished RCT¹⁷⁸ received the same regimen as above, except that the first dose was given earlier during the resuscitation—after the fourth unit of RBCs. As noted above, the unpublished trial was used only for sensitivity analysis.

Comparative observational studies. In the observational studies, the exact dose of rFVIIa administered was not clear. In the Spinella study, it was noted that military guidelines recommended a dose of 120 $\mu\text{g}/\text{kg}$, but the actual drug dose administered was not reported.⁹⁸ The Rizoli study⁹⁷ did not report the doses of drug administered except to say that initial practice at their center was to start with a dose of 17.1 $\mu\text{g}/\text{kg}$, which was liberalized over time to higher doses, and that repeat doses were common. The Fox study⁹⁹ described the doses of rFVIIa as “typically 90-120 $\mu\text{g}/\text{kg}$.” The range of rFVIIa doses administered across studies thus appears to be potentially quite broad (from 17.1 $\mu\text{g}/\text{kg}$ to 120 $\mu\text{g}/\text{kg}$). In all cases, drug administration was triggered by the patient reaching a transfusion threshold that was variably defined but considered to be massive or life-threatening bleeding.

Outcomes

Direct (patient-centered) outcomes. Results are summarized in Table 26. Dose-reponse relationships were not apparent for these outcomes.

Mortality. All of the studies reported on mortality, but none were powered to detect differences in mortality. There were differences between studies in the exclusion from analysis of those patients who experienced “early” in-hospital death (defined to be death within 48 hours in the

RCTs and 24 hours in the Spinella study), so comparisons across studies must be interpreted with caution. Among patients who survived at least 48 hours, the RCTs noted no difference in 30-day mortality, although mortality was lower in both rFVIIa groups compared to controls. In the unpublished RCT, there was also no difference in mortality rate between groups, whether measured for blunt or penetrating trauma or at 30 or 90 days.¹⁷⁸ The Spinella study noted a significant decrease in 30-day mortality for patients who received rFVIIa and survived at least 24 hours. The Rizoli study identified a significant improvement in 24-hour mortality with rFVIIa. In-house mortality was lower after rFVIIa but was not significant. The Fox study noted no difference in mortality between groups at 24 hours. To place the mortality differences in the context of the comparable findings for the other clinical indications, also see Figure 5 (in the Key Question section on intracranial hemorrhage). (Note that the Rizoli study is not included in this figure because its findings were reported as an odds ratio rather than event rate.)

Thromboembolic events. Of the published studies, the Boffard RCTs and two of the retrospective trials (Spinella and Fox) evaluated thromboembolic complications. While the retrospective study by Rizoli did not report on thromboembolic complications, an extension of the study by Nascimento¹⁸¹ did report this. None of the studies found any difference between the rFVIIa and usual care groups for such events. However, the absolute number of events was low, so the studies were likely underpowered to detect any difference between groups. The unpublished RCT also found no differences between groups in thromboembolic event rates.¹⁷⁸ To place the differences in thromboembolic event rates in the context of the comparable findings for the other clinical indications, see Figure 6 (in the Key Question section on intracranial hemorrhage).

Acute respiratory distress syndrome (ARDS). Only the Boffard RCTs and Spinella study evaluated the rate of ARDS at 30 days. The blunt trauma RCT identified a significantly lower rate of ARDS in the rFVIIa group compared to the usual care group, while the penetrating trauma RCT and Spinella study together suggested a trend in the same direction. Event rates for ARDS were low, which again raises concern that the studies did not have adequate power to detect a difference for this outcome. Of note, we did not evaluate the outcome of multi-organ failure (MOF), because it was not clear how MOF was defined in the study or if these cases overlapped with cases diagnosed with ARDS.

Indirect (surrogate) outcomes. Results are summarized in Table 27. Dose-response relationships are not apparent for these outcomes.

Red Blood Cell (RBC) transfusion. All of the studies reported on some aspect of RBC transfusion, although comparisons across studies are difficult for this outcome because of the variable censoring of patients who experienced early in-hospital death. For patients who survived to 48 hours, the blunt trauma RCT reported a significant reduction in the 48-hour RBC transfusion rate for patients who received rFVIIa versus controls. In the penetrating trauma RCT, there was a similar but non-significant finding of reduced RBC transfusions in the rFVIIa group. In the unpublished RCT, there were comparable findings: a significant reduction in RBC transfusions for rFVIIa patients in blunt trauma and a non-significant reduction in penetrating trauma.¹⁷⁸ In contrast, the Spinella study identified a significant increase in transfusion requirements with rFVIIa. The Rizoli and Fox studies did not independently assess this outcome.

Consideration of poor quality comparative observational studies. Two studies which were considered to be of “poor quality” were compared with the other studies. In the studies by Dutton¹⁰⁰ and Harrison,¹⁰¹ the findings on mortality, thromboembolic events, and RBC transfusions were consistent with those described above (Tables 26 and 27). Other outcomes were not reported.

Other Considerations

Differences in baseline mortality rate. Both the Rizoli⁹⁷ and Spinella⁹⁸ studies suggest that the higher baseline mortality rates in the patients they studied account for the greater and significant decreases in mortality they observed compared to the Boffard RCTs.⁹⁶ They also cite higher rates of markers of injury severity. For instance, both cohort studies cite higher transfusion requirements within the first 24 hours, and the Spinella study describes lower admission SBP and pH among their patients versus the Boffard RCT patients.

Possible interactions with acidosis, thrombocytopenia, and timing and era of administration. In a post-hoc subgroup analysis of the patients who received rFVIIa, the Rizoli study identified an association between patients with higher baseline pH and platelet counts and increased survival. The Spinella study found a similar post-hoc association between shorter time to intervention and increased survival. Of note, in the unpublished RCT¹⁷⁸ patients were administered rFVIIa earlier in the resuscitation than in the published RCTs (after 4 units of RBCs versus 8 units). In addition, the trial was conducted during the time period when “usual care” more often included the use of matched transfusion ratios of RBCs to FFP (1:1) and massive transfusion protocols. This may explain why the baseline mortality rate among controls appears to be lower than it was for the Boffard RCTs.

Comparison to Premier Database

Study patients, mean ages 28-41, were younger by 20 years, on average, than patients in the Premier database (mean age 53 years). However, mortality rates were comparable to the Premier mortality rate of 0.33. Use of rFVIIa in the Premier patients started slowly in the early 2000s, but increased sharply in 2005, the same year the Boffard RCTs were published (Figures 3 and 4).

Strength of Evidence

The overall strength of evidence was low for all of the outcomes evaluated, including the outcome for which rFVIIa was weakly but non-significantly favored, namely ARDS. These determinations were based primarily on weaknesses in two strength of evidence domains: the “risk of bias” domain, which had ratings of a “medium” or “high” overall risk of bias for all outcomes, and the “precision” domain, which had ratings of “imprecise” for all outcomes. The rating of “imprecise” was based on wide confidence intervals for the major outcomes which in turn were due to low event rates in studies that were underpowered to detect mortality and major morbidity outcomes (Table 28).

Applicability

The overall applicability of the evidence was fair for treatment use in the population targeted—adult 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). Specifically, the types of trauma and practice settings represented by the evidence likely have good applicability to major trauma centers in the U.S., as well as combat settings experienced by U.S. troops. On the other hand, the “usual care” of such patients has likely changed at least moderately since the studies were conducted (e.g., with the introduction of massive transfusion protocols and 1:1 transfusion ratios for RBCs:FFP). The applicability of the mortality outcomes is also difficult to interpret given the censoring of patients who experienced early in-hospital mortality. Finally, the follow-up of 30 days may be insufficient to judge applicability to general practice (Table 29).

Conclusions

The available evidence has low strength and does not permit definitive conclusions regarding the impact of rFVIIa use compared to usual care. The two RCTs, in blunt and penetrating trauma and with mean ages of 29 to 33 years old, reported no improvement in mortality with rFVIIa. However, the conclusions which can be drawn from this are limited by their lack of power for evaluating mortality and the censoring of deaths which occurred within the first 48 hours. One observational study found a significantly reduced death rate with treatment, while the other had non-significant findings in the same direction. For acute respiratory distress syndrome, the blunt trauma RCT demonstrated a significant reduction for rFVIIa patients, while across the remaining two studies that evaluated this outcome (the penetrating trauma RCT and one observational study) there was a trend in the same direction. There was no evidence of an increase in thromboembolic harm with treatment, but again the strength of evidence for this outcome was low. Thus, current evidence of low strength suggests the potential for benefit and no evidence of harm. Importantly, the patients were younger in the studies than in the Premier database, but nonetheless had similar mortality rates. The importance and nature of interactions between outcomes and the era of rFVIIa administration remain unclear, as does the relationship between outcomes and the timing of rFVIIa administration or baseline levels of acidosis or thrombocytopenia.

Table 25. General characteristics of comparative studies of off-label rFVIIa use for massive bleeding due to body trauma

Article	Study Design	Study Setting and Time Period	Sample Size and Dose, µg/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Boffard 2005 ⁹⁶	RCT Treatment	32 centers Australia, Canada, France, Germany, Israel, Singapore, South Africa and UK 3/2002-9/2003	All Rx: 139 -Blunt: 69 -Pen: 70 Usual care: 138 -Blunt: 74 -Pen: 64 Dose: 200 µg/kg after transfusion of eighth unit RBCs, followed by two 100 µg/kg doses at 1 and 3 hrs	Rx: Blunt: 33 (13) Pen: 29 (10) Usual care: Blunt: 35 (13) Pen: 32 (10)	Inclusion: -severe trauma (i.e., 6 units of RBCs transfused within 4 hrs of admission) -between 16 and 65 years old Exclusion: -cardiac arrest before trial drug administration -gunshot wound to head -GCS<8 -base deficit of 15 mEq/L or pH<7.0 -transfusion of 8 units or more RBCs before arrival at trauma center -injury sustained >12 hrs before randomization	Mortality Adverse events including TE events	Transfusion requirements (e.g. RBCs, FFP) Hospital and ICU length of stay
		1 center University of Toronto Health Sciences Centre, Toronto, Canada 1/2000-1/2005	All Rx: 38 Ucare: 204 Dose of rFVIIa is not reported	Rx: 36.8 [30.6-43.1] ^{CI} Usual care: 41.1 [38.1-44.1] ^{CI}	Inclusion: -traumatic hemorrhage -8 or more units RBCs during first 12 hrs of hospitalization Controls: Patients who met above inclusion criteria, but did not receive rFVIIa.	Mortality	Transfusion requirements (e.g. RBCs, FFP)
Spinella 2008 ^{98b}	Retrospective comparative Treatment	Combat support hospitals in Iraq. Data from Joint Theatre Trauma Registry (JTTR) 12/2003-10/2005	All Rx: 49 Usual care: 75 Dose: Institutional guidelines suggested 120 µg/kg	Age not reported	Inclusion: -severe trauma (i.e. ISS>15) -massive transfusion (i.e. transfusion of 10 units or more RBCs in 24 hrs) Controls: Patients who met above inclusion criteria, but did not receive rFVIIa.	Mortality Adverse events including TE events	Transfusion requirements (e.g. RBCs, FFP)

Table 25. General characteristics of comparative studies of off-label rFVIIa use for massive bleeding due to body trauma (continued)

Article	Study Design	Study Setting / Time Period	Sample Size and Dose, µg/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Fox 2009 ⁹⁹	Retrospective comparative	Combat support hospitals in Iraq. Data from Joint Theatre Trauma Registry (JTTR)	All Rx: 41 Usual care: 12	Rx: 27.5 (9.4) Usual care: 24 (10)	Inclusion: -life-threatening hemorrhage (requiring > 4U PRBCs) from penetrating trauma that caused vascular injury which required repair -received damage control resuscitation (minimal crystalloid use, use of whole blood or high ratio of plasma to RBCs (<1:1.4), and liberal replacement of platelets and cryoprecipitate Exclusion: NR	Mortality Adverse events including TE events	Transfusion requirements††
	Treatment	4/2006-8/2007	Dose: "typically" 90-120				
Dutton 2004 ^{100†}	Retrospective comparative	1 University hospital	All Rx: 81		Inclusion: -Receipt of at least 10 units PRBCs, 8 units FFP, and 1 pheresis unit platelets (the equivalent of 1 blood volume transfusion in components), with ongoing hemorrhage and evidence of coagulopathy (abnormal PT and PTT) -Patient viability for meaningful longterm survival as determined by institutional gatekeeper Exclusion: -Lack of patient viability	Mortality Adverse events including TE events	Transfusion requirements†† Hospital LOS
	Treatment	USA 6/2001-12/2003	Usual care: 32-449^ Dose: 100 for hemorrhagic shock; 50 for congenital or pharmacologic coagulopathy	Rx: 41 (21) Usual care: NR			
Harrison 2005 ^{101†}	Retrospective comparative	1 Hospital	All Rx: 29	Rx: 41 (21)	Inclusion: -Inclusion in prospectively collected trauma registry database Exclusion: -No historical matched control could be identified -Isolated closed head injury without hemorrhage -Jehovah's witness patient who declined all transfusions	Mortality Venous TE events	Transfusion requirements †† Hospital and ICU LOS
	Treatment	USA 2/2003-12/2003	Usual care: 72 Dose: 60	Usual care: 42 (22)			

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, "Consideration of poor quality comparative observational studies") and in the overall harms analyses near the end of this report.

^C95% confidence interval; ^UMedian; Pen=penetrating; SD=standard deviation; Rx=treatment group(s); TE=thromboembolic; RBCs=red blood cells; FFP=fresh frozen plasma; ISS=injury severity scale; ICU=intensive care unit

††Examples of transfusion requirements were red blood cells and fresh frozen plasma

^aNascimento et al.¹⁸¹ was used instead of Rizoli et al.⁹⁷ in the harms analysis of thromboembolic events. Nascimento et al. is a continuation of Rizoli et al. with more patients.

^bPerkins 2007¹⁸² was used instead of Spinella 2008⁹⁸ in the harms analysis of mortality and TE events. Perkins 2007 is an overlapping non-comparative study with more patients.

[^]Dutton 2004¹⁰⁰ has multiple control groups. The range of sample sizes is presented.

Table 26. Mortality, thromboembolic events, and ARDS in comparative studies of rFVIIa use in body trauma

Article	Study Design/ rFVIIa use	rFVIIa dose	Sample size		Mean age (SD)		30-day Mortality rate			Thromboembolic event rate			ARDS rate		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Boffard 2005 ⁹⁶ (blunt arm)	RCT <i>Treatment</i>	400	69	74	33 (13)	35 (13)	0.246	0.297	p=.58	0.029	0.041	NR	0.043	0.162	p=.03
Boffard 2005 ⁹⁶ (penetrating arm)	RCT <i>Treatment</i>	400	70	64	29 (10)	32 (10)	0.243	0.281	p=.69	0.057	0.047	NR	0.057	0.078	p=.74
Rizoli 2006 ⁹⁷	Retrospective comparative <i>Treatment</i>	NR	38	204	36.8 [30.6-43.1] ^{CI}	41.1 [38.1-44.1] ^{CI}	*	*	CI 0.8-7.6*	NR	NR	NR	NR	NR	NR
Nascimento 2008 ^{181&}		-	72	256	-	-	-	-		0.097	0.063	p=.31	-	-	-
Spinella 2008 ⁹⁸	Retrospective comparative <i>Treatment</i>	120	49	75	NR	NR	0.306	0.507	p=.03	0.041	0	p=.15	0.020	0.040	p=1.0
Fox 2009 ⁹⁹	Retrospective comparative <i>Treatment</i>	90-120	41	12	28 (9)	24 (10)	0.073†	0†	p=1	0.122	0.083	p=1	NR	NR	NR
Dutton 2004 ^{100†}	Retrospective comparative <i>Treatment</i>	50; 100	81	32-449 [^]	41(21)	NR	0.580	0.438; 0.325 [^]	NR; p=.60 [^]	0	NR	NR	NR	NR	NR
Harrison 2005 ^{101†}	Retrospective comparative <i>Treatment</i>	60	29	72	41 (21)	42 (22)	0.414**	0.403* *	NR	0.069 [#]	0.197 [#]	p=0.2	NR	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

^{CI}95% confidence interval;

ARDS=acute respiratory distress syndrome; NR=not reported

*This study generated odd ratios for survival using a multivariate model, which included independent predictors of in-hospital survival (baseline pH, platelet count, age, head injury (AIS), and transfusion during the resuscitation period) as covariates. Prior to modeling, the unadjusted in-hospital mortality rates were 0.500 in the rFVIIa group and 0.485 in the usual care group. In the multivariate models, rFVIIa was shown to have no significant impact on in-hospital survival (OR: 2.5, 95% CI: 0.8-7.6) but to improve 24-hour survival (OR: 3.4, 95% CI: 1.2-9.8).

& Nascimento2008¹⁸¹ is an extension of Rizoli 2006⁹⁷ with more patients. It also reports data on thromboembolic events not reported in the original publication.

[^] Dutton 2004¹⁰⁰ has multiple control groups. The range of sample sizes is presented. For purposes of outcome data, rates for the most narrow sample (n=32) and most broad sample (n=449) are given, respectively.

[#] Venous thromboembolic events only.

**28-day mortality;

†24-hour mortality

Table 27. RBC transfusion in comparative studies of rFVIIa use in body trauma

Article	Study Design and rFVIIa use	rFVIIa dose	Sample size*		Mean age (SD)		24-Hour RBC transfusion, units (SD) [IQR]		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig
Boffard 2005 ⁹⁶ (blunt arm)	RCT <i>Treatment</i>	400	52	59	33 (13)	35 (13)	6.9 (6.2) ^{&}	10.9 (9.3) ^{&}	p=.02 ^{&}
Boffard 2005 ⁹⁶ (penetrating arm)	RCT <i>Treatment</i>	400	57	52	29 (10)	32 (10)	4.5 (5.3) ^{&}	7.7 (9.9) ^{&}	p=.10 ^{&}
Rizoli 2006 ⁹⁷	Retrospective comparative <i>Treatment</i>	NR	38	204	36.8 [30.6-43.1] ^{CI}	41.1 [38.1-44.1] ^{CI}	#	#	#
Spinella 2008 ⁹⁸	Retrospective comparative <i>Treatment</i>	120	49	75	NR	NR	16 ^U [13-27]	14 ^U [11-19]	p=.02
Fox 2009 ⁹⁹	Retrospective comparative <i>Treatment</i>	90-120	41	12	28 (9)	24 (10)	NR	NR	NR
Dutton 2004 ^{100†}	Retrospective comparative <i>Treatment</i>	50; 100	81	32-449 [^]	41(21)	NR	^	NR	NR
Harrison 2005 ^{101†}	Retrospective comparative <i>Treatment</i>	60	29	72	41 (21)	42 (22)	18.3** (7.5)	22** (9.7)	p=.04

†The studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

^{CI}95% confidence interval; ^UMedian.

*The sample size for RBC transfusions is smaller in Boffard 2005⁹⁶ because patients who died within the 48-hour observation period for RBC transfusions were excluded.

[^] Dutton 2004¹⁰⁰ has multiple control groups. The range of sample sizes is presented. 24-hour transfusion results are only given for patients who received rFVIIa divided into 2 groups: “responders” who received 4.5 (SD 8.0) units RBCs and “non-responders” who received 22.6 (SD 14.7) units RBCs.

[&]48hr RBC transfusions. Mean and standard deviation was derived graphically from figure 2 in Boffard 2005⁹⁶. P-values are based on 48-hour RBC transfusions in patients who survived at least 48 hours (blunt arm: rFVIIa group: median: 7.0 units, range: 0-29 units; usual care group: median: 7.5 units, range: 0-35 units. Penetrating arm: rFVIIa group: median 3.9 units, range: 0-30 units; usual care group: 4.2 units, range: 0-41 units). P-values were calculated using the one-sided Wilcoxon-Mann-Whitney rank test.

[#]This study used multivariate modeling to generate odd ratios for survival in the rFVIIa group versus control group. The model adjusted for independent predictors of in-hospital survival, which included “transfusion during the resuscitation period.” Without adjustment for differences in important baseline covariates, RBC transfusions during the first 24 hours were 24.9 units (95% CI: 21.5-28.3) in the rFVIIa group and 14.9 units (95% CI: 14.0-15.8) in the usual care group, p<.0001.

**72-hour RBC transfusions.

RBCs=red blood cells; NR=not reported

Table 28. Strength of evidence for rFVIIa use in body trauma

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Overall Risk						
Mortality (30 days)	2 ⁹⁶	139	138	RCT	Fair	Medium	Consistent	Direct	Imprecise	No effect	Unknown	Low
	3 ⁹⁷⁻⁹⁹	128	279	COBS	Fair	High	Consistent	Direct	Imprecise	Weakly favors rFVI	Unknown	
Thrombo-embolic Events	2 ⁹⁶	139	138	RCT	Fair	Medium	Consistent	Direct	Imprecise	No effect	Unknown	Low
	3 ^{98, 99, 181}	162	331	COBS	Fair	High	Consistent	Direct	Imprecise	No effect	Unknown	
Units of RBCs Trans-fused	2 ⁹⁶	139	138	RCT	Fair	Medium	Consistent	Indirect	Imprecise	Favors rFVIIa	Unknown	Low
	1 ⁹⁸	49	75	COBS	Fair	High	Unknown	Indirect	Imprecise	Favors Usual Care	Unknown	
ARDS	2 ⁹⁶	139	138	RCT	Fair	Medium	Consistent	Direct	Imprecise	Weakly favors rFVIIa	Unknown	Low
	1 ⁹⁸	49	75	COBS	Fair	High	Unknown	Direct	Imprecise	Weakly favors rFVIIa	Unknown	

ARDS=acute respiratory distress syndrome; RBCs=red blood cells; RCT=randomized controlled trial; COBS=comparative observational study. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 29. Applicability assessments of studies of body trauma

Available Evidence	Overall Implications for Applicability
<p>Population</p> <p>Patients presenting bleeding secondary to blunt or penetrating trauma requiring massive transfusion of RBCs (variably defined) prior to rFVIIa dose Patients with coagulopathy of trauma Mean age 32 Exclusions: In several studies, patients who died within 24h or 48h (censoring point varies with study) or with symptoms/signs indicating grave prognosis</p>	<p>The population included may be infrequent in clinical practice, especially outside of major regional referral centers for trauma. Community practice may involve greater use of rFVIIa as end-stage therapy in patients with poor prognosis</p>
<p>Intervention</p> <p>As series of treatment doses of 200, 100 and 100 mcg/kg during treatment for trauma Transfusion protocol in place at most sites</p>	<p>RCT dose is relatively high compared to other studies</p>
<p>Comparator</p> <p>Usual care via randomization or matched controls Studies implemented prior to current consensus regarding 1:1 ratio of transfusion products and implementation of institutional massive transfusion protocols</p>	<p>Other prophylactic hemostatic agents potential comparators, but not used in this setting Usual care has likely changed moderately since the studies were conducted.</p>
<p>Outcomes</p> <p>Primary outcomes: RBC transfusion requirements in RCTs (over 48 hours) and patient mortality Secondary outcomes: thromboembolic events, ARDS</p>	<p>Surrogate/indirect outcomes without necessary link to clinical outcomes Mortality outcomes less applicable due to censoring (need to survive 24h or 48h post-trauma (censoring point varies with study)) Insufficient sample size to meaningfully assess other clinical outcomes Quality of life or functional status measures absent</p>
<p>Timing and intensity of follow-up</p> <p>Follow-up for duration of hospitalization, one COBS with 30-day mortality information Detailed protocol for ascertainment of MI and DVT</p>	<p>Longer term outcomes desirable</p>
<p>Setting</p> <p>Highly specialized trauma centers in Australia, Canada, France, Germany, Israel, Singapore, South Africa, and U.K., as well as a combat support hospital in Iraq</p>	<p>Experience likely similar to specialized U.S. trauma centers, but some cross-national differences likely exist, and military hospitals may also differ from civilian ones</p>

Key Question 3.b. Bleeding from **brain trauma** and comparative effectiveness of rFVIIa

Background

Traumatic brain injury (TBI) is the leading cause of overall death and disability after trauma.¹⁸³ In severe cases, mortality rates are as high as 30-50 percent.¹⁸⁴ Bleeding within the brain parenchyma is a significant contributor to these poor outcomes. The mechanisms are complex and poorly understood but differ in important ways from spontaneous ICH, which typically consist of more localized areas of bleeding at sites of prior atherosclerotic or thrombotic injury. In the presence of the coagulopathy of trauma,¹⁵⁵ it is more likely that injured parenchyma, and even non-injured parenchyma, will become ischemic. Medical management includes optimization of cerebral blood flow and oxygen delivery. Surgical evacuation for large hemorrhagic lesions secondary to TBI is the only existing treatment for large bleeds (when decompression must be performed to relieve increased intracranial pressure), but often can not be attempted expeditiously secondary to the presence of concurrent coagulopathy, whether due to the trauma itself or the need for resuscitation fluids for hemorrhage at other regions of the body. Of note, TBI is a well-established risk factor for the development of deep vein thrombosis (DVT).

Usual care during the time frame of included studies. The changes in approach to treatment of coagulopathy noted in the above section on body trauma also apply to patients with TBI. Patients with bleeding due to TBI are now recognized to have similar problems with the coagulopathy of trauma.¹⁸⁵ There is growing understanding within the field regarding the need to address this coagulopathy early in the course of therapy. In addition, new evidence suggests that patients with bleeding from TBI experience significant hematoma expansion within the first 24 hours of injury and that this expansion contributes to subsequent morbidity and mortality.^{186,187} However, specific interventions to ameliorate this expansion have not been systematically studied in the TBI literature or have not been shown to help. For example, an RCT of plasma (FFP) use in TBI found that treatment was associated with increased mortality.¹⁸⁸ For large hematomas, the only widely available current therapy is neurosurgical evacuation. But coagulopathy must be corrected prior to surgery, which is accomplished by plasma infusions that may be high in volume and poorly tolerated by older patients or those with cardiac dysfunction.¹⁰⁷ Thus, any therapy that can address TBI-associated coagulopathy and allow for earlier neurosurgical intervention—while also limiting or stopping hemorrhage—is eagerly sought.

General Characteristics of Studies of Traumatic Bleeding

On this topic, we identified one RCT (fair quality) and one comparative observational study (fair quality), which together had 79 patients who received rFVIIa. The RCT, Narayan 2008, both was sponsored and had one author employed by the manufacturer of rFVIIa.¹⁰⁶ The comparative observational study selected for inclusion was the earlier of two published by Stein and colleagues with overlapping patient populations. While the latter cohort study¹⁸⁹ included more patients, these patients were more likely to have significant concurrent trauma elsewhere at the body and were less well matched to controls at baseline. The retrospective cohort chosen for inclusion, Stein 2008, was not sponsored and had no authors or statisticians employed by the manufacturer.¹⁰⁷ The full Stein 2008 cohort study included some patients with traumatic injuries

at areas of the body other than the brain, but also performed subgroup analyses on patients with isolated TBI (Table 30). We evaluated the data on the patients with isolated TBI-associated bleeding, and when evaluated in this light, the study quality was determined to be fair, with good baseline matching of groups.

Place of studies within analytic framework. The two included studies of brain trauma evaluated rFVIIa for treatment use (versus prophylaxis or end-stage use, which are other potential uses, as outlined in our Analytic Framework (Figure 1)). While the Narayan RCT¹⁰⁶ did not define its primary outcome, it reported on important direct outcomes (e.g., mortality, thromboembolic events) but was likely underpowered for these. It also reported on the indirect outcome of change in hematoma volume. The Stein comparative observational study¹⁰⁷ did not define a primary outcome but did examine a number of different direct (e.g., mortality, thromboembolic events) and surrogate (e.g., time to neurosurgical intervention, ICU length of stay) endpoints.

Qualitative considerations of heterogeneity. As noted above, we identified one important source of potential heterogeneity among studies as the inclusion of patients with significant body trauma (as well as brain trauma) among the study population. We addressed this concern by confining our assessment to studies or sub-groups of studies that effectively excluded such patients by focusing primarily on hemorrhage from isolated TBI.

Comparison to studies on other indications. The populations in these studies were young compared to most of the non-trauma studies in adults for other indications, with mean age in the Narayan RCT of 51 in both groups and 45-50 in the Stein cohort study. The rFVIIa dose range of 40-200 µg/kg in the RCT and 8-140 µg/kg in the cohort study were in the low to middle range of those used for rescue treatment across indications.

Patient Characteristics and Study Design

RCTs. The Narayan 2008 RCT was a fair quality dose-finding and safety trial with small sample sizes: 36 patients in the usual care group and 61 patients in the aggregate rFVIIa group (divided relatively evenly between five dosing groups containing an average of 12 patients per group).¹⁰⁶ It was conducted at 38 hospitals in 10 countries, but not the U.S. Inclusion criteria included intracranial hematoma volume of at least two mL, baseline CT scan within six hours of injury, and administration of trial drug within 2.5 hours of baseline CT scan. Important exclusion criteria included known vitamin K antagonist use and planned neurosurgical intervention within 24 hours of admission. There was acceptable baseline similarity between groups among the patients, blinding of the two radiologists who independently evaluated the CT scans for hematoma size and growth, and no loss to follow-up at day 15, the endpoint of the trial. The most problematic aspect of study design was the extremely low enrollment rate of four percent of those screened, which might have been even lower if the investigators had not amended their protocol mid-way to change the minimum lesion volume size required for enrollment from five mL to two mL. The primary outcome was not defined, but the study states that its focus was on “safety endpoints,” namely those of thromboembolic complications (including DVT) and mortality at 15 days.

Comparative observational study. The Stein 2008 retrospective cohort study evaluated patients from the trauma registry of the Shock Trauma Center at the University of Maryland.¹⁰⁷ Patients were included if they were found to have “severe” TBI (defined as a GCS score under nine and an abbreviated Injury Severity Score of four or five) and coagulopathy (defined as INR greater than or equal to 1.4), and were “deemed appropriate for immediate neurosurgical intervention” at the time of hospital admission. Patients who received vitamin K antagonists such as warfarin were included in the study. Among this cohort’s subgroup of patients with isolated TBI, which is the focus of our evaluation, there were small sample sizes: 18 patients received rFVIIa and 17 received usual care. These groups were well-matched at baseline, with the possible exception of a higher rate of pre-injury warfarin use in the rFVIIa group. Investigators did not perform any statistical analyses to evaluate or adjust for residual confounding. One limitation of the study design relates to the determination at the time of admission of appropriateness for immediate neurosurgical intervention, which was not further defined in the paper. The primary outcome was time to neurosurgical intervention, the only widely available definitive therapy for large bleeds. The paper also reported on mortality and thromboembolic events.

Intervention Characteristics

RCT. The RCT intervention group received single doses of rFVIIa (40, 80, 120, 160, or 120 µg/kg), while controls received placebo, delivered within 2.5 hours of the baseline CT scan. No repeat doses were given.

Comparative observational study. The vast majority of patients who received rFVIIa were administered a single dose but the doses varied widely from 8 to 140 µg/kg. The dose was apparently determined by the choice to administer the entire 1.2 mg vial in which the rFVIIa is packaged, rather than by a weight-based calculation for a given patient. It is unclear at what time in the hospital course rFVIIa was delivered, but as neurosurgical intervention occurred within a mean of 185 minutes from arrival, rFVIIa was clearly given within a mean time of less than that amount.

Outcomes

Direct (patient-centered) outcomes. Summary results are reported in Table 31.

Mortality. The Narayan 2008 RCT reported no difference between groups in mortality at 15 days, with rates of 11 percent in each group (seven of 61 in the combined rFVIIa group, four of 36 in the usual care group). The Stein 2008 cohort study did not clearly define the length of follow-up for the patients, but this is likely equal to the hospital length of stay (LOS) given the retrospective nature of the study. The mean hospital LOS was 14.6 days and 19.1 days for the rFVIIa and usual care groups, respectively, which is roughly equivalent to the 15-day follow-up time of the RCT. Among patients with isolated TBI, the Stein cohort identified a reduced mortality with rFVIIa compared to usual care but this was a non-significant finding: 33.3 percent (6 of 18) versus 52.9 percent (9 of 17) in the two groups, respectively. The findings in both studies are limited by low event rates. To place the mortality differences in the context of the comparable findings for the other clinical indications see Figure 5 above (in the Key Question section on intracranial hemorrhage).

Thromboembolic events. Event rates are also low for thromboembolic outcomes. Across the studies there was a trend toward higher rates of thromboembolic events in the rFVIIa group compared to usual care group. In the Narayan RCT the event rates were 16.4 percent (10 of 61) in the rFVIIa group versus 5.6 percent (2 of 36) in the usual care group. Five of the 10 events in the rFVIIa group consisted of DVTs, all of which were symptomatic. In the Stein cohort study the event rates were 22.2 percent (4 of 18) in the rFVIIa group versus 17.6 percent (3 of 17) in the usual care group. The one DVT among these occurred in the usual care group. To place the differences in thromboembolic event rates in the context of the comparable findings for the other clinical indications, see Figure 6 above (in the Key Question section on intracranial hemorrhage).

Indirect (surrogate) outcomes. Summary results are reported in Table 31.

Hematoma expansion. Only the Narayan 2008 RCT reported on hematoma change at 24 hours, which it defined as the mean volume change in hematoma size from baseline. Of note, baseline hematoma volume was well-matched at 11.3 mL (SD 10.9) in the combined rFVIIa group and 10.4 mL (SD 10.8) in the usual care group. The study noted a non-significant reduction in expansion in the rFVIIa group compared to controls (7.0 mL (SD 12.9) versus 10.4 mL (25.0), respectively).

Time to neurosurgical intervention. Only the Stein cohort study evaluated this outcome, which was its primary outcome. The study found that, with treatment, there was a significant decrease in absolute minutes to neurosurgical intervention: 185.3 (SD 219.9) for the rFVIIa group versus 518.6 (SD 409.8) for the usual care group (p=0.005).

Consideration of poor quality comparative observational study. In the poor quality comparative observational study by Tawil,¹⁰⁸ the findings on thromboembolic events are consistent with those described above (Table 31). Other outcomes were not reported.

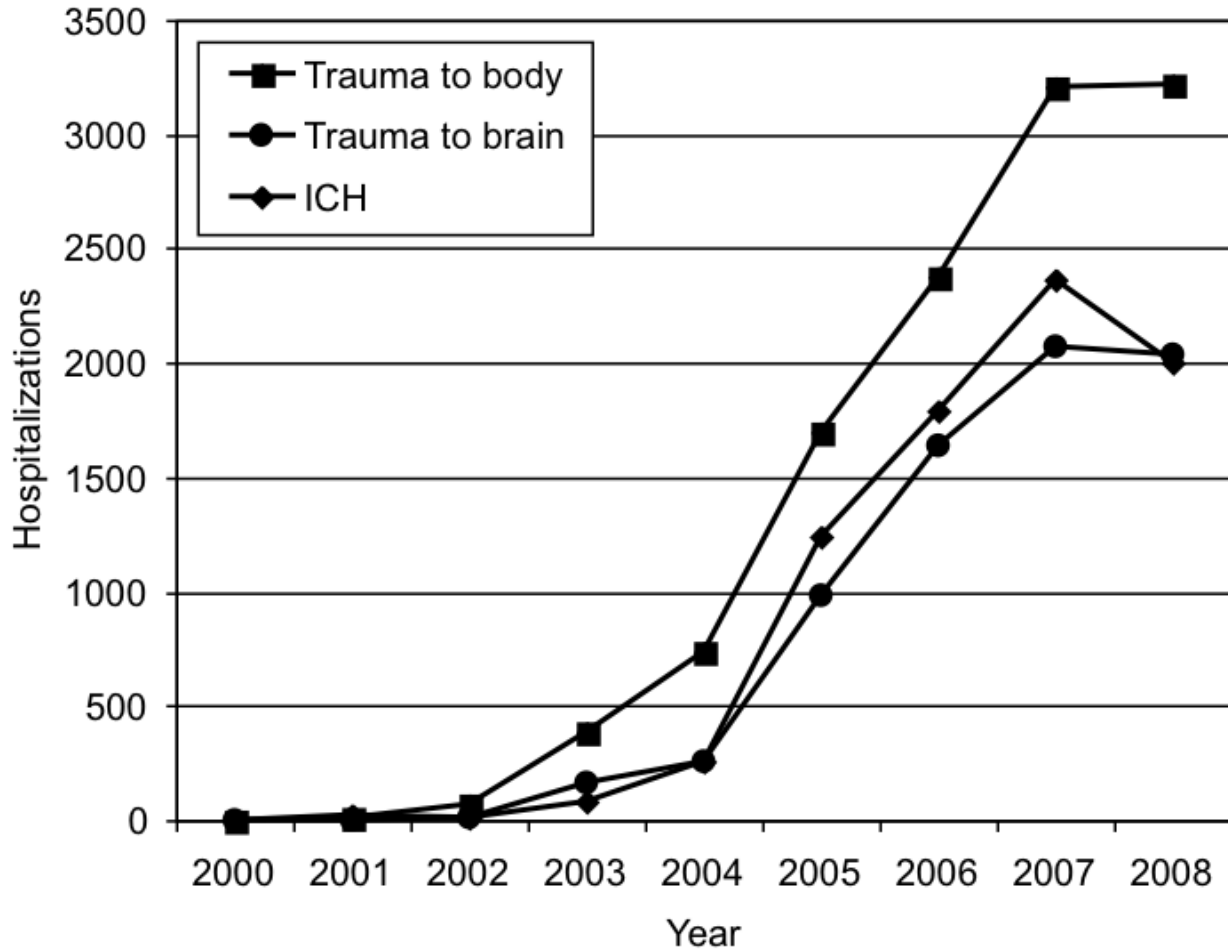
Other Considerations

Possible interactions with coagulopathy, CHF, or blunt trauma injuries to the cerebral vasculature. The Stein cohort study enrolled only patients with baseline derangements in laboratory markers of coagulopathy, defined as INR equal to or greater than 1.4. While the Narayan RCT had no comparable inclusion criteria, it performed post hoc analyses of the subgroup of patients with platelets less than 100K, PT > 14, aPTT > 45 seconds, or INR > 1.2 (13 rFVIIa, 8 placebo). These analyses note a difference between groups, favoring rFVIIa, in the degree of hematoma expansion but are based on small sample sizes. Another subgroup that the Stein study proposed may have the potential for greater benefit from rFVIIa are those patients who have poor toleration of large volume infusions (e.g., the elderly and those with congestive heart failure (CHF)) and yet require rapid correction of coagulopathy to allow for neurosurgical intervention.¹⁰⁷

Other authors have raised concerns regarding a subgroup of patients who might have the potential for increased harm with rFVIIa administration.¹⁰⁸ These are patients who have experienced blunt trauma to the cerebral vessels and thus may already be at increased risk for post-traumatic cerebral infarction, a well recognized complication of TBI.¹⁹⁰ Limited cohort

study data suggest that rFVIIa administration to this group of patients may increase the risk of post-traumatic cerebral infarction even further.¹⁰⁸

Figure 19. Premier database rFVIIa use in intracranial hemorrhage and trauma of the body and brain



Comparison to Premier Database

Study patients, with mean ages 36-52, were younger by 15-20 years, on average, than patients in the Premier database (mean age 63 years). Those in the Stein cohort study experienced a mortality rate comparable to the rate of 0.34 in the Premier database, but the RCT patients had a lower mortality rate than either of these. The Premier database indicated a low level of rFVIIa use for brain trauma in the early 2000s but, similar to the intracranial hemorrhage and body trauma indications, there was an increase in use in 2005 and a possible leveling off more recently (Figure 19).

Strength of Evidence

The strength of evidence assigned to all outcomes was low, on the basis of determinations of a medium to high risk of bias for all study types (driven by the uniformly “fair” quality scores) and imprecise estimates of effect. The imprecision of effects for the direct

morbidity and mortality outcomes was driven by the low event rates for these outcomes—or in the case of change in hematoma volume, a small absolute effect size—among small patient populations, suggesting that these studies were underpowered for these outcomes (Table 32).

Applicability

The overall applicability is fair for treatment use in the population targeted—patients with intracranial hemorrhage secondary to TBI, most of whom were not on anticoagulation (Table 33). The population applicability of both included studies is only fair. The Narayan RCT was limited by the small percent of patients screened who were ultimately enrolled (four percent), just as the data we evaluated from the Stein cohort was limited, in our analysis, by the inclusion of only those patients with isolated TBI rather than those with both TBI and body trauma, the latter of which is a more common pattern of injury. Another important limitation to applicability derives from the small sample sizes, which preclude meaningful determinations regarding the most direct measures of morbidity and mortality. Similarly, while the studies made admirable attempts at ascertainment of thromboembolic harms, their follow-up of 15 days is likely insufficient to make important determinations regarding the long-term health ramifications of rFVIIa therapy. Finally, the study settings at specialized trauma centers in multiple countries are likely comparable to trauma centers in the U.S.

Conclusions

Current evidence of low strength is too limited to compare the harms and benefits of rFVIIa versus usual care for intracranial bleeding due to brain trauma. The lone RCT identified no difference in mortality, while the one cohort study identified a non-significant reduction with rFVIIa treatment. There was a trend across the two studies toward increased thromboembolic events with therapy. The cohort study found a significant reduction in time to neurosurgical intervention. Across studies, event rates for mortality and thromboembolism were low, and there was low strength of evidence for all effect estimates. Study patients were younger than those in the Premier database, and compared to Premier patients, those in the RCT had a lower mortality rate, while those in the cohort study had a comparable mortality rate. The importance and nature of interactions between rFVIIa administration and coagulopathy, congestive heart failure, or blunt trauma injuries to the cerebral vasculature remain unclear.

Table 30. General characteristics of comparative studies on off-label rFVIIa use for bleeding due to brain trauma

Article	Study Design	Study Setting and Time Period	Sample Size and Dose, ug/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Narayan 2008 ¹⁰⁶	RCT Treatment	38 centers Canada, Finland, Germany, India, Israel, Italy, Singapore, Spain, Switzerland, and Taiwan	All Rx: 61 -40: 12 -80: 11 -120: 14 -160: 12 -200: 12 Ucare: 36	All Rx: 51.5 (21.5) Ucare: 51.4 (19.5)	Inclusion: -clinical evidence of traumatic intracranial hemorrhage on admission CT scan -GCS 4-14* -contusion volume of at least 2 mL on baseline CT within 6 hrs of injury* -trial drug administration within 2.5 hrs of baseline CT Exclusion: -penetrating head or spinal cord injury -life expectancy of less than 24 hrs at hospital admission -planned surgical evacuation of hematoma within 24 hrs after dosing -isolated SAH, IVH, or subdural hematomas -significant cardiovascular disease -history of hypercoagulability or thromboembolism -current anticoagulant use	Mortality Adverse events including TE events	Change in hematoma volume (relative and absolute)
		8/2004-5/2006					
Stein 2008 ¹⁰⁷	Retrospective comparative Treatment	1 center University of Maryland School of Medicine, Baltimore, MD, USA	All Rx: 18# Ucare: 17# Dose range: 8-140 ug/kg	Rx: 39.9 (25.3) Ucare: 38.1 (19.8)	Inclusion: -severe TBI (GCS<9, AIS>3) -coagulopathic at admission (INR>1.4) -deemed appropriate for neurosurgical intervention at admission Controls: Patients who met above inclusion criteria, but did not receive rFVIIa.	Mortality TE events	Time to neurosurgical intervention ICU and hospital length of stay
		7/2002-6/2006					

Table 30. General characteristics of comparative studies on off-label rFVIIa use for bleeding due to brain trauma (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose, ug/kg	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Tawil 2008 ¹⁰⁸ †	Retrospective comparative Treatment	1 center University of New Mexico, Albuquerque, New Mexico, USA 1/2004-12/2005	All Rx: 31 Ucare: 353 Dose is not reported	Age for Rx and Ucare combined: 36 [11-90]	Inclusion: -severe traumatic brain injury defined as GCS<9 and brain Abbreviated Injury Scale (AIS)>2 -survival>24 hours Exclusion: -diffuse cerebral infarction due to hypoperfusion -primary cerebrovascular accident -stroke secondary to angiographic complications	Cerebral infarction (odds ratio only)	

†This study did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but is included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

*Original inclusion criteria for the first 8% of patients in Narayan 2008¹⁰⁶ required GCS scores of 4-13, minimum contusion volume of 5 mL, and time from injury to CT scan of 4 hours.

#Data is for patients with isolated traumatic brain injury only.

SD=standard deviation; Rx=treatment group(s); Ucare=usual care; TE=thromboembolic; GCS=glasgow coma scale; TBI=traumatic brain injury; AIS=abbreviated injury scales; SAH=subarachnoid haemorrhage; IVH=intraventricular hemorrhage; INR=international normalized ratio.

Table 31. Mortality, thromboembolic events, and absolute change in hemotoma volume in comparative studies of rFVIIa use in brain trauma

Article	Study Design /rFVIIa use	rFVIIa dose	Sample size		Mean age (SD) [Range]		Mortality rate			Thromboembolic event rate*			Absolute change in hematoma volume, mL (SD)					
			rFVIIa	UC	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig			
Narayan 2008 ¹⁰⁶	RCT Treatment	40	12							0			11.8 (13)		p=.96			
		80	11							0			5.0 (5.3)		p=.38			
		120	14	36		All Rx:				0.071	0.111	NR	0.214	0.083	NR	8.9 (17.7)	10.4	p=.96
		160	12			(21.5)	51.4	(19.5)		0.167			0			3.9 (10.4)	(25)	p=.27
		200	12						0.333				0.167			4.9 (13)		p=.86
	All Patients		61	36	51.5	51.4	(21.5)	(19.5)	0.115	0.111	NR	0.148	0.083	3.3 [0.69-16.2]^	7.0 (12.9)	10.4 (25)	p=0.48	
Stein 2008 ¹⁰⁷	Retrospective comparative Treatment	Range: 8-140	18 [#]	17 [#]	49.8	44.8	(26.9)	(20.6)	0.333	0.529	p=0.24	0.222	0.176	p=0.74	NR	NR	NR	
Tawil 2008 ^{108†}	Retrospective comparative Treatment	NR	31	353	Age for Rx and Ucare combined: 36 [11-90]				NR	NR	NR	higher**	**	3.1 [1.1-8.0]**	NR	NR	NR	

†This study did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but is included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

*Thromboembolic event rates were calculated by dividing the number of thromboembolic events by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from those reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

[#]Data are for patients with isolated traumatic brain injury only.

^Odds ratio and 95% confidence interval.

**Odds ratio and 95% confidence interval. Multivariate analyses demonstrate higher adjusted odds ratio of cerebral infarction with rFVIIa treatment.

Rx=treatment; NR=not reported; SD=standard deviation; Rx=treatment group

Table 32. Strength of evidence for rFVIIa use in brain trauma

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Overall Risk						
Mortality (15 days)	1 ¹⁰⁶	61	36	RCT	Fair	Medium	Unknown	Direct	Imprecise	No Effect	Unknown	Low
	1 ^{107*}	18	17	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Thrombo-embolic Events (72 hours)	1 ¹⁰⁶	61	36	RCT	Fair	Medium	Unknown	Direct	Imprecise	No Effect	No	Low
	1 ^{107*}	18	17	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Glasgow Coma Scale (15 days)	1 ¹⁰⁶	61	36	RCT	Fair	Medium	Unknown	Direct	Imprecise	No Effect	Unknown	Low
	1 ^{107*}	18	17	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Hematoma Volume Change	1 ¹⁰⁶	61	36	RCT	Fair	Medium	Unknown	Indirect	Imprecise	No Effect	Unknown	Low

*Includes only those patients in this study with isolated traumatic brain injury

RCT= randomized controlled trial; COBS= comparative observational study

See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations

Table 33. Applicability assessment of studies on brain trauma

Describe Available Evidence	Describe Overall Implications for Applicability
Population Patients experiencing traumatic brain injury with CT confirmed hematoma > 2 cc (initially set at 5 cc) Includes subdural and subarachnoid hemorrhage, as well as intracerebral hemorrhage Patients primarily with intact clotting systems Mean age 50 Exclusions: Most patients on anticoagulation	The population included may be infrequent in clinical practice, especially outside of major regional referral centers for trauma As with non-traumatic causes of intracranial hemorrhage, other advances may make rFVIIa less important in the future
Intervention A single treatment dose of 40 to 200 mcg/kg upon confirmation of intracranial hemorrhage Usual care, including transfusion protocol	Lack of apparent dose-response relationship reduces possible guidance on dose selection
Comparator Usual care via randomization or matched controls	Other prophylactic hemostatic agents potential comparators, but not used in this setting
Outcomes Primary outcomes: Time to neurosurgical intervention Secondary outcomes: mortality, thromboembolic events, hematoma volume change, GCS score	Surrogate/indirect outcomes related to process of care without direct link to clinical outcomes Insufficient sample size to meaningfully assess clinical outcomes
Timing and intensity of follow-up Follow-up for 15 days after injury Had detailed protocol for ascertainment of thromboembolic events in the RCT	Longer term outcomes desirable
Setting Highly specialized trauma centers in Canada, Germany, Israel, Finland, Italy, Switzerland, Taiwan and Singapore, and Baltimore, MD	Likely applicable to similar U.S. trauma centers despite some variations in practice

Key Question 4.a. **Liver transplantation** and comparative effectiveness of rFVIIa

Background

Liver transplantation is associated with considerable, and in some cases massive, blood loss, not the least because the patients who undergo surgery have significant chronic, acquired coagulopathies related to their advanced liver disease. They often require intraoperative transfusions to correct for the coagulopathies and surgical blood loss. Such transfusions are associated with increased rates of post-operative mortality, multi-organ dysfunction, and infection, as well as reduced graft survival.¹⁹¹⁻¹⁹⁴ The use of prophylactic rFVIIa at the initiation of surgery was investigated for its potential to lower the number of intraoperative transfusions required, thereby ameliorating some of these risks. However, there were concerns about rFVIIa increasing the risk of clotting at unforeseen and unwelcome sites. For instance, thrombosis of the hepatic vessels is a well-recognized complication of liver transplantation that can be devastating.¹⁹⁵ Hepatic artery thrombosis occurs in approximately five percent of transplantations, generally early after transplantation, and results in graft failure.

Usual care during the time frame of included studies. Over the past 10 years, the average transfusion requirement during liver transplantation has decreased dramatically.¹⁹⁶ Much of this change has been attributed to advances in surgical and anesthetic technique, improved understanding and management of coagulopathy, and recognition of the significant risks associated with transfusions that are described above.¹⁹⁷ Although wide variation between centers still exists, the current median RBC transfusion requirement per transplantation is estimated to be less than five units. This compares to a median of 20 or more units in the past. A small but growing proportion of patients is now surviving liver transplantation without the transfusion of any blood products.¹⁹⁸

Jehovah's Witnesses as a special population. For religious reasons, Jehovah's Witnesses refuse the transfusion of blood products (whole blood, red blood cells, white blood cells, platelets, and plasma). However, the religion enjoins its members to make personal determinations regarding the appropriateness of infusion of blood fractions such as cryoprecipitate, recirculated autologous blood, cell-saved blood, albumin, and recombinant products, which some Jehovah's Witness patients will accept. The first liver transplantation in a Jehovah's Witness patient occurred in 1994.¹⁹⁹ But there have been a growing number since that time, and the challenge of these are discussed in the transplantation literature.^{200,201} Usual care in these patients can include pre-operative use of recombinant erythropoietin and intra-operative use of recirculated autologous and cell-saved blood, aprotinin, cryoprecipitate, and albumin. Products that minimize blood loss in such patients are eagerly sought and may change their risk-benefit ratio of transplantation.

General Characteristics of Studies of Bleeding in Liver Transplantation

We identified four RCTs (two fair quality, two poor quality) and one comparative retrospective cohort study (fair quality) that examined the prophylactic use of rFVIIa in 215 liver transplant recipients (Table 34). The RCTs by Planinsic¹¹¹ and Lodge¹¹⁰ both had authors employed by the manufacturer of rFVIIa. The RCTs by Pugliese¹¹² and Liu¹¹³ reported no

financial ties to the manufacturer. The comparative observational study by Hendriks¹¹⁴ had one author employed by the manufacturer.

Place of studies within analytic framework. Liver transplantation is the one indication for which all of the included studies evaluated rFVIIa for prophylactic use (versus treatment or end-stage use, which are other potential uses, as outlined in our Analytic Framework (Figure 1)). Among the four RCTs, those by Lodge,¹¹⁰ Planinsic,¹¹¹ and Pugliese¹¹² reported at least minimal comparative data on the direct outcomes of mortality and thromboembolic events and the indirect outcomes of RBC transfusion requirements, operating room (OR) time, and ICU length of stay, whereas the Liu RCT¹¹³ only reported comparative data on OR time. Furthermore, only the Lodge and Planinsic studies explicitly identified a “primary outcome” (in this case, two for both)—RBC transfusion requirements during the procedure itself *and* during the first 24 hours post-operatively. The Hendriks observational study did not identify a primary outcome, but reported on the direct endpoints of thromboembolic events and the surrogate endpoints of transfusion requirements, blood loss, and operating time.

Comparison to studies on other indications. The studies of rFVIIa use in liver transplantation all evaluated its prophylactic application in comparison to the treatment use to which it was applied in most of the other indications. The mean age of patients was approximately 50 years, which is similar to those in the studies of brain trauma and younger than those in the studies of intracranial hemorrhage or adult cardiac surgery. The dose of rFVIIa was broad, with an approximate range of 20-360 µg/kg. All but one study evaluated a single dose of rFVIIa.

Patient Characteristics and Study Design

None of the studies described having enrolled patients who were Jehovah’s Witnesses.

RCTs. We identified four RCTs (two fair quality, two poor quality (Table 14)). The first, by Lodge,¹¹⁰ was a double-blind study with modest sample sizes: 61 patients in the usual care group and 121 patients in the aggregate rFVIIa group (divided relatively evenly between two dosing groups). It was conducted in 14 hospitals in Europe between August 2001 and September 2003. Inclusion criteria targeted adults with end-stage liver disease (defined as Child-Pugh class B or C) requiring liver transplantation. Important exclusion criteria included previous liver transplantation and multiorgan transplantation, both of which are associated with higher rates of bleeding during surgery. The groups were well-matched at baseline, with the possible exception of the rFVIIa patients having a slightly higher rate of B scores on the Child-Pugh scale (i.e., they may have been slightly less sick) than the usual care group.

The Planinsic RCT¹¹¹ was a double-blind study with small sample sizes: 19 patients in the usual care group and 64 patients in the aggregate rFVIIa group (divided relatively evenly between three dosing groups). It was conducted in nine hospitals in the U.S. and Europe between February and September 2000. The inclusion and exclusion criteria, baseline matching, and primary outcomes were essentially the same as those described for the Lodge RCT above.

The primary outcomes reported were the number of RBC units transfused both intraoperatively and in the first post-operative 24 hours.

The Pugliese RCT¹¹² was a double-blind study with very small sample sizes: 10 patients in the usual care group and 10 in the rFVIIa group. It was conducted at a single Italian center from November 2003 to July 2004, and had an extremely short six hour time frame of data

collection and follow-up. Inclusion criteria included patients “who underwent OLT [orthotopic liver transplantation]” (Child-Pugh class not specified) and who also had hemoglobin greater than eight mg/dL, INR greater than 1.5, and fibrinogen greater than 100 mg/dL. Exclusion criteria and the primary outcome were not specified.

The Liu RCT¹¹³ contained no description of blinding and was also small, with 14 patients in both the treatment and usual care groups. It was conducted at a single center in China from March 2003 to July 2006 and does not designate the timeframe of follow-up. The sole inclusion criterion appears to have been need for liver transplantation, and the exclusion criteria and primary outcome were not specified.

Comparative observational study. The fair quality Hendriks cohort study evaluated patients treated at a single hospital in the Netherlands.¹¹⁴ It evaluated only 12 patients who received usual care matched in a 2:1 ratio with six patients who received rFVIIa. Inclusion criteria were similar to those of the Lodge and Planinsic RCTs, namely adult patients with end-stage liver disease (defined as Child-Pugh class B or C) requiring liver transplantation. Controls were chosen from the hospital database of patients who had received a liver transplantation. They were matched in a 2-to-1 ratio with rFVIIa patients on the characteristics of year of transplantation, Child-Pugh score, blood urea nitrogen levels, and cholestatic versus non-cholestatic liver disease. The groups were well matched at baseline, with the possible exception of longer cold ischemia time for the livers transplanted into the usual care group. The primary outcome was not specified.

Intervention Characteristics

RCTs. Patients in the four RCTs received infusions of rFVIIa or placebo at the initiation of surgery. In the Lodge study,¹¹⁰ treated patients received one dose of either 60 or 120 µg/kg at the initiation of surgery, repeat doses in the same amount every two hours while still in the OR, and a final dose in the same amount at the time of wound closure. Most patients in the study received a total of three doses for approximate cumulative doses of 120 and 360 µg/kg, respectively. In the remainder of the studies, treated patients received a single dose of rFVIIa: in the Planinsic study¹¹¹ a dose of 20, 40, or 80 µg/kg; in the Pugliese study¹¹² a dose of 40 µg/kg; and in the Liu study¹¹³ a dose of “70-80 µg/kg.”

Comparative observational study. Treated patients in the Hendriks cohort study¹¹⁴ received a single 80 µg/kg dose of rFVIIa at initiation of surgery.

Outcomes

Direct (patient-centered) outcomes. There were no dose-dependent trends in the outcomes reported and the events rates for these outcomes were low. Therefore, the event rates in the text are given for the aggregate rFVIIa group compared to the usual care group. Table 35 also summarizes these findings.

Mortality. The Liu RCT¹¹³ did not report on mortality. The remaining three RCTs failed to define explicitly the time to follow-up for the mortality endpoint. However, all of them reported on the number of transfusions within the first 24-hour post-operative period and/or the

subsequent ICU length of stay, such that the minimum follow-up time for mortality may reasonably be expected to be 24 hours. There were no differences between groups in mortality rates, although the studies were not powered for this outcome. The Lodge study¹¹⁰ noted “6 deaths” in the text but provided further details on only four of these in its associated table, for minimum mortality rates of two percent (3 of 121) in the aggregate rFVIIa group and two percent (1 of 61) in the usual care group. The Planinsic study¹¹¹ stated that “seven deaths occurred during the study period,” but described only five deaths for the following minimum mortality rates: six percent (4 of 64) in the aggregate rFVIIa group and five percent (1 of 19) in the placebo group. The Pugliese study¹¹² reported no deaths in either group. The Hendriks cohort study¹¹⁴ also did not report on mortality. To place the mortality differences in the context of the comparable findings for the other clinical indications, also see Figure 5 above (in the Key Question section on intracranial hemorrhage).

Thromboembolic events. There were no differences between groups noted by any of the studies for this outcome. The Lodge RCT¹¹⁰ noted 16 percent (19 of 121) in the aggregate rFVIIa group and 10 percent (6 of 61) in the usual care group. The Planinsic RCT¹¹¹ described thromboembolic event rates of 13 percent (8 of 64, comprised of five arterial thromboses, one myocardial infarction, and two episodes of thrombophlebitis) in the aggregate rFVIIa group and 16 percent (3 of 19, comprised of two arterial thromboses and one episode of thrombophlebitis) in the usual care group. The Pugliese¹¹² RCT stated that no thromboembolic events occurred in either group. The Liu RCT¹¹³ only stated that no events occurred in the treatment group, without commenting on the control group. The Hendriks cohort study¹¹⁴ reported only one thromboembolic event in the study—thrombosis of the hepatic artery in a patient who received rFVIIa: an event rate of 17 percent (1 of 6), versus 0 of 12 in the usual care group. To place the differences in thromboembolic event rates in the context of the comparable findings for the other clinical indications, also see Figure 6 above (in the Key Question section on intracranial hemorrhage).

Indirect (surrogate) outcomes. There were no dose-dependent trends noted for the indirect outcomes described in detail below and summarized in Table 36.

RBC transfusion during the 24-hour post-operative period. Among the RCTs, the Lodge study identified a non-significant reduction and the Pugliese study identified a significant reduction in the 24-hour post-operative RBC transfusion requirements with treatment, whereas the Planinsic study found no difference between groups. The Liu study did not report this outcome, but did note a significant reduction in blood loss. In the Hendriks cohort study¹¹⁴ the treatment group had significantly lower RBC transfusion requirements.

OR time. Only the Liu RCT identified a significant difference between groups in OR time, with transplantation taking over 200 minutes less in the rFVIIa group compared to placebo. None of the other studies identified a difference between groups. Both the Lodge¹¹⁰ and Planinsic¹¹¹ RCTs reported “no notable difference between study groups” for this outcome but gave no further details. While the OR times were slightly shorter for the rFVIIa patients compared to controls in both the Pugliese RCT and Hendriks cohort study (in minutes, 408 versus 432 and 554 versus 598, respectively), these differences were not significant.

ICU length of stay (LOS). None of the RCTs reporting on this outcome found a difference between groups in ICU LOS. The Planinsic RCT¹¹¹ stated only that “the mean number of intensive care unit days was comparable between study groups,” whereas the Lodge and Pugliese RCTs did report duration for each group. The Liu RCT and Hendriks cohort did not report on this outcome.

Consideration of poor quality comparative observational studies. In the poor quality comparative observational studies by De Gasperi,¹¹⁵ Kalicinski,¹¹⁶ and Niemann,¹¹⁷ the findings on mortality, thromboembolic events, and RBC transfusions requirements were consistent with those described above (Tables 35 and 36). Other outcomes were not reported.

Comparison to Premier Database

The mean age of study patients of approximately 50 years was comparable to the mean age of 52 years for Premier patients. Mortality rates among patients in all of the comparative studies were considerably lower than the mortality rate of 0.38 for patients who underwent liver transplantation in the Premier database.

Strength of Evidence

The strength of evidence assigned to all outcomes was low (Table 37). These assessments were made, in part, on the basis of the poor to fair quality scores of the included studies, which prompted a determination that the studies had a medium or high risk of bias in all cases. In addition, there was little certainty regarding the effect size estimates, leading to uniform imprecision on that determinant. Low event rates for all of the morbidity and mortality outcomes contributed to the imprecision for these outcomes, while wide confidence intervals contributed to the imprecision for the surrogate outcomes.

Applicability

The overall applicability was fair for prophylactic use in the population targeted—adult patients with cirrhosis of Child’s class B or C. Such patients represent the usual population requiring liver transplantation for cirrhosis. The range of rFVIIa doses administered limits applicability in terms of choice of prophylactic dose. Another limitation is the emphasis on indirect (surrogate and process) outcomes, rather than direct measures of mortality and morbidity, which would have required much larger studies. Follow-up times were short and poorly defined, and in most cases there were limited descriptions of ascertainment for harms, which reduces study applicability in these areas. Finally, the setting of the studies in regional referral centers in the U.S. and abroad has good applicability to U.S. centers where liver transplantations are performed (Table 38). The evidence is not applicable to treatment or end-stage use of rFVIIa for this indication or to patients who require liver transplantation for indications other than Child’s B or C cirrhosis, because such patients were excluded.

Conclusions

The available evidence of low strength is too limited to compare the benefits and harms of prophylactic use of rFVIIa compared to usual care in liver transplantation. There was no evidence of impact on mortality or thromboembolic events but event rates were low. There was a weak trend toward reduced RBC transfusion requirements in the studies as a whole, but no

differences between groups for the other indirect outcomes (OR time and ICU length of stay). Study patients were comparable in age to those in the Premier database but had lower mortality rates. The impact of rFVIIa on the care of Jehovah's Witness patients remains unclear, in the absence of comparative study data in this population.

Table 34. General characteristics of comparative studies on off-label rFVIIa use for liver transplantation

Article	Study Design	Study Setting/ Time Period	Sample Size / Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Lodge 2005 ¹¹⁰	RCT Prophylaxis	14 centers 8/2001-9/2003	All Rx: 121 60*: 63 120*: 58 Ucare: 61 *rFVIIa patients received between 3 and 6 doses	Rx: 60: 53.3 (11.2) 120: 52.6 (9.2) Ucare: 52.3 (11.5)	Inclusion: -undergoing OLT -cirrhosis (Pugh class B or C) -over 18 years old Exclusion: -previous liver transplantation -split liver transplantation -scheduled multiorgan transplantation -scheduled living related-donor transplantation -renal insufficiency requiring dialysis -documented coagulation disorder -history or presence of portal vein thrombosis	Mortality Adverse events including TE events	Transfusion requirements†† Hospital and ICU length of stay
Planinsic 2005 ¹¹¹	RCT Prophylaxis	9 centers 2/2000-9/2000	All Rx: 64 20: 18 40: 24 80: 22 Ucare: 19	Rx: 20: 49.4 (13.4) 40: 49.7 (10.1) 80: 51.9 (8.8) Ucare: 49.9 (11)	Inclusion: -undergoing OLT -cirrhosis (Pugh class B or C) -over 18 years old Exclusion: -previous liver transplantation -split liver transplantation -scheduled multiorgan transplantation -scheduled living related-donor transplantation -renal insufficiency requiring dialysis -documented inherited coagulation disorder -history or presence of portal vein thrombosis	Mortality Adverse events including arterial TE events	Transfusion requirements††
Pugliese 2007 ¹¹²	RCT Prophylaxis	1 center Rome, Italy 11/2003- 7/2004	All Rx: 10 Ucare: 10 Dose: 40 µg/kg	Age not reported.	Inclusion: -OLT -Hb>8 mg/dL, INR>1.5, fibrinogen>100 mg/dL	Mortality Adverse events including TE events	Transfusion requirements†† Blood loss Operating time Hospital and ICU LOS

Table 34. General characteristics of comparative studies on off-label rFVIIa use for liver transplantation (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Mean Age (SD) [Range]	Population Characteristics		Outcomes Evaluated	
					Inclusion/Exclusion Criteria	Direct	Indirect	
Liu 2009 ¹¹³	RCT	1 center	All Rx: 14	Rx: 51.9 [36-54]	Inclusion: -OLT	TE events	Blood loss	
	Prophylaxis	Guangzhou, China 3/2003-7/2006	Ucare: 14 Dose: 70-80 µg/kg	Ucare: 47.5 [41-65]				Operating time
Hendriks 2001 ¹¹⁴	Prospective comparative	1 center Netherlands	All Rx: 6 Ucare: 12	Rx: 43 ^U [37-61]	Inclusion: -undergoing OLT -cirrhosis (Pugh class B or C) -over 18 years old Exclusion: -"overt major bleeding" -known hereditary bleeding disorder -history of venous or arterial thrombosis -clinically overt atherosclerosis -renal insufficiency (serum creatinine>1.7 mg/dL) -fulminant hepatic failure -use of NSAIDs within 2 weeks of transplantation	Adverse events including TE events	Transfusion requirements† † Operating time	
	Prophylaxis	12/1998-9/1999	Dose: 80 µg/kg	Ucare: 48 ^U [34-63]				Controls: Historical and contemporary controls (11/1997-9/1999) matched 2:1 on year of transplantation, Child-Pugh classification, and urea nitrogen levels. These covariates were previously identified by the authors to be independent predictors of transfusion requirements.
De Gasperi 2005 ¹¹⁵ †	Retrospective comparative	1 center Milan, Italy	All Rx: 6 Ucare: 6	Rx: 45 (4)	Inclusion: -OLT	Mortality	Transfusion requirements† † Blood loss	
	Prophylaxis	2/2003	Dose: 20 µg/kg at the start of surgery. Additional 20 µg/kg 30-40 minutes after reperfusion for significant bleeding.	Ucare: 47 (9)				

Table 34. General characteristics of comparative studies on off-label rFVIIa use for liver transplantation (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Mean Age (SD) [Range]	Population Characteristics		Outcomes Evaluated	
					Inclusion/Exclusion Criteria	Direct	Indirect	
Kalicinski 2005 ¹¹⁶ †	Retrospective comparative	1 center Poland	All Rx: 28 Ucare: 61	Rx: 13.2 (4.2)	Inclusion: -OLT from cadaveric donor	Mortality	Transfusion requirements† †	
	Prophylaxis	Time period not reported.	Mean dose: 51.5 µg/kg; Range: 30-100 µg/kg	Ucare: 11.3 (5.6)	Exclusion: -patients receiving retransplants or transplants from living related donors	Adverse events including TE events	Operating time Hospital and ICU LOS	
Niemann 2006 ¹¹⁷ †	Retrospective comparative	1 center University of California, San Francisco, CA, USA	All Rx: 11 Ucare: 11	Rx: 48 (15)	Inclusion: -OLT in adult patients with MELD score>20 and PT>1.5-2 times normal control	Mortality	Transfusion requirements† †	
	Prophylaxis	2000-2004	Mean dose: 58 µg/kg, SD=18 µg/kg	Ucare: 41 (17)	Exclusion: -Re-transplantation or combined transplantation -rFVIIa given within 24 hours prior to surgery or given during surgery but >30 minutes from incision	Adverse events including TE events	Blood loss Operating time Hospital LOS	

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

^UMedian;

††Examples of transfusion requirements are red blood cells and fresh frozen plasma;

OLT=orthotopic liver transplantation; SD=standard deviation; Rx=treatment group(s); Ucare=usual care; TE=thromboembolic; RBCs=red blood cells; FFP=fresh frozen plasma; INR=international normalized ratio; NSAID=non-steroidal anti-inflammatory drugs; LOS=length of stay

Table 35. Mortality and thromboembolic events in comparative studies of rFVIIa use in liver transplantation

Article	Study Design and rFVIIa use	Mean dose (SD) [Range]	Sample size		Mean age (SD) [Range]		Mortality rate			Thromboembolic event rate ^{&}		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Lodge 2005 ¹¹⁰	RCT	180 [#]	63		53.3 (11.2)		0.016*		NR	0.190 [^]		
	Prophylaxis	360 [#]	58	62	52.6 (9.2)	52.3 (11.5)	0.034*	0.016*	NR	0.121 [^]	0.097 [^]	NS
Planinsic 2005 ¹¹¹	RCT	20	18		49.4 (13.4)		0.056*		NR	0.222		
	Prophylaxis	40	24	19	49.7 (10.1)	49.9 (11)	0.083*	0.053*	NR	0.083	0.158	NR
		80	22		51.9 (8.8)		0.045*		NR	0.091		
Pugliese 2007 ¹¹²	RCT	40	10	10	NR	NR	0	0	NR	0	0	NR
Liu 2009 ¹¹³	RCT				51.9	47.5			NR			
	Prophylaxis	[70-80]	14	14	[36-54]	[41-65]	NR	NR	NR	0	NR	NR
Hendriks 2001 ¹¹⁴	Cohort	80	6	12	43 ^U	48 ^U			NR			
	Prophylaxis				[37-61]	[34-63]	NR	NR	NR	0.167	0	NR
De Gasperi 2005 ^{115†}	Retrospective comparative								NR			
	Prophylaxis	[20-40]	6	6	45 (4)	47 (9)	0	0	NR	NR	NR	NR
Kalicinski 2005 ^{116†}	Retrospective comparative								NR			
	Prophylaxis	52 [30-100]	28	61	13 (4)	11 (6)	0.071	0.082	NR	0	0.098	NR
Neimann 2006 ^{117†}	Retrospective comparative								NR			
	Prophylaxis	58 (18)	11	11	48 (15)	41 (17)	0	0.09	NR	0	0.09	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

&Thromboembolic event rates were calculated by dividing the number of thromboembolic events by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from those reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

*Mortality rate is underestimated in Lodge 2005¹¹⁰ and Planinsic 2005¹¹¹ because in each study two additional deaths were not reported by trial arm.

[^]Lodge 2005¹¹⁰ reports arterial thromboembolic events only.

[#] The majority of patients in Lodge 2005¹¹⁰ received 3 doses of either 60 or 120 ug/kg rFVIIa (range: 3-6 dose).

NR=not reported; NS=not significant; ^UMedian

Table 36. Indirect outcomes in comparative studies of rFVIIa use in liver transplantation

Article	Study Design/ rFVIIa use	Mean dose (SD) [Range]	Sample size		Mean age (SD) [IQR]		Mean RBC transfusion (SD) [IQR]			OR time, minutes (SD)			ICU LOS, days (SD)		
			rFVIIa	UC	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Lodge 2005 ¹¹⁰	RCT <i>Prophylaxis</i>	180 [#]	62*	61	53.3 (11.2)	52.3 (11.5)	7.0 ^U [0-76.5] ^R	8.2 ^U [1.5-100.0] ^R	NS	"same"	"same"	NS	3.5	3.0	NS
		360 [#]	56*		52.6 (9.2)	6.3 ^U [0-76.4] ^R	10.0 ^U [3.0-18.0]	3.0							
Planinsic 2005 ¹¹¹	RCT <i>Prophylaxis</i>	20	18	19	49.4 (13.4)	49.9 (11.0)	13.0 ^U [7.0-24.0]	11.1 ^U [7.0-17.0]	NS	"same"	"same"	NS	"same"	"same"	NS
		40	23		49.7 (10.1)	10.0 ^U [3.2-21.0]	7.0								
		80	22		51.9 (8.8)	10.0 ^U [3.2-21.0]	7.0								
Pugliese 2007 ¹¹²	RCT <i>Prophylaxis</i>	40	10	10	-	-	1.2 (0.53)	2.3 (0.44)	p=.02	408 (56)	432 (48)	NS	4.8 (1.3)	5.2 (1.2)	NS
Liu 2009 ¹¹³	RCT <i>Prophylaxis</i>	[70-80]	14	14	51.9 [36-54]	47.5 [41-65]	**	**	**	268 (42)	485 (65)	p<.01	NR	NR	NR
Hendriks 2001 ¹¹⁴	Cohort <i>Prophylaxis</i>	80	6	12	43 ^U [37-61] ^R	48 ^U [34-63] ^R	3.0 ^U [0-5] ^R	9.0 ^U [4-40] ^R	p=.002	554	598	p=.26	NR	NR	NR
De Gasperi 2005 ^{115†}	Retrospective comparative <i>Prophylaxis</i>	[20-40]	6	6	45 (4)	47 (9)	9 (4)	7 (2.5)	NS	NR	NR	NR	NR	NR	NR
Kalicinski 2005 ^{116†}	Retrospective comparative <i>Prophylaxis</i>	52 [30-100]	28	61	13 (4)	11 (6)	^	^	^	522 (110)	534 (118)	p=.35	7.03 (5.94)	6.15 (5.55)	p=.32
Neimann 2006 ^{117†}	Retrospective comparative <i>Prophylaxis</i>	58 (18)	11	11	48 (15)	41 (17)	3.9 (2.6)	6.9 (2.3)	p=.01	416 (104)	430 (84)	p=.7	##	##	##

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, "Consideration of poor quality comparative observational studies") and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

[#]The majority of patients in Lodge 2005¹¹⁰ received 3 doses of either 60 or 120 ug/kg rFVIIa (range: 3-6 doses);

*1 patient in the 180 ug/kg group and 2 patients in the 360 ug/kg group were excluded from the analysis;

**Liu 2009¹¹³ does not report on RBC transfusion but does report blood loss: rFVIIa 2250 mL (SD 350), placebo 6214 mL (SD 750), p<0.01; ^ Total intraoperative blood transfusion volume (not isolated to RBCs): rFVIIa, 1980 mL; usual care, 1527 mL (NS); ^{##} Total hospital length of stay (not isolated to ICU length of stay): rFVIIa, 11 (SD 7.3) days; 7.9 (SD 2.7) days (p=0.2); ^RDenotes range instead of IQR; ^UMedian; NR=not reported; NS=not significant; UC=usual care; "same" means that both studies stated, "No notable differences between study groups were found with respect to ... operation duration," (Lodge 2005¹¹⁰ and Planinsic 2005¹¹¹) or that "The mean number of intensive care units days was comparable between studies." (Lodge 2005¹¹⁰).

Table 37. Strength of evidence grade for rFVIIa use in liver transplantation

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Overall Risk						
Mortality (timeframe unclear)	3 ¹¹⁰⁻¹¹²	195	90	RCT	Fair	Medium	Consistent	Direct	Imprecise	No Effect	No	Low
	1 ¹¹⁴	6	12	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Thrombo-embolic Events	3 ¹¹⁰⁻¹¹²	195	90	RCT	Fair	Medium	Consistent	Direct	Imprecise	No Effect	No	Low
	1 ¹¹⁴	6	12	COBS	Fair	High	Unknown	Direct	Imprecise	No Effect	Unknown	
Units of RBCs Transfused in 24 hours	3 ¹¹⁰⁻¹¹²	195	90	RCT	Fair	Medium	Consistent	Indirect	Imprecise	Weakly Favors rFVIIa	No	Low
	1 ¹¹⁴	6	12	COBS	Fair	High	Unknown	Indirect	Imprecise	Weakly Favors rFVIIa	Unknown	
OR Time	1 ^{112, 113}	24	24	RCT	Poor	High	Inconsistent	Indirect	Imprecise	No Effect	Unknown	Low
	1 ¹¹⁴	6	12	COBS	Fair	High	Unknown	Indirect	Imprecise	No Effect	Unknown	
ICU Length of Stay	3 ¹¹⁰⁻¹¹²	195	90	RCT	Fair	Medium	Consistent	Indirect	Imprecise	No Effect	No	Low

RCT= randomized controlled trial; ICU=intensive care unit; COBS=comparative observational study; RBCs=red blood cells; OR=operating room. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 38. Applicability assessment of studies on liver transplantation

Describe Available Evidence	Describe Overall Implications for Applicability
Population Patients undergoing orthotopic liver transplantation with Child's class B or C cirrhosis Mean age 50 Patients with abnormal clotting systems secondary to liver disease There is no mention of Jehovah's witness patients within the study populations Exclusions: Patients who require transplantation for indications other than Child's class B or C cirrhosis and/or who are on anticoagulation	rFVIIa use for this indication is very rare in U.S. but nonetheless the study findings are likely applicable to many of those undergoing liver transplantation, and may be relevant to select subgroups such as Jehovah's witness patients, although such patients do not appear to have participated in the studies Other approaches available to minimize blood loss
Intervention Prophylactic use of rFVIIa, either as a single dose of 20 to 80 mcg/kg prior to surgery, or as repeating doses for an aggregate dose of 213 or 412 mcg/kg. Usual care, including transfusion protocol	Dose is variable, with high dose studies higher than for other prophylactic uses
Comparator Usual care via randomization or matched controls	Other prophylactic hemostatic agents potential comparators, but not used in this setting
Outcomes Primary outcomes: Red blood cell transfusions over 24h and perioperative blood loss Secondary outcomes: length of stay, operative time, thromboembolic events, coagulation lab parameters	Surrogate/indirect outcomes related to process of care without direct link to clinical outcomes Insufficient sample size to meaningfully assess clinical outcomes Quality of life or functional outcomes are absent
Timing and intensity of follow-up Follow-up for duration of hospitalization Seldom had protocol for ascertainment of harms	Longer term outcomes and a protocol for ascertainment of harms is desirable
Setting Academic hospitals in the U.S. and Western Europe that serve as regional referral centers	Highly applicable to U.S. transplantation centers

Key Question 4.b.i. **Adult cardiac surgery** and comparative effectiveness of rFVIIa

Background

Despite advances in methods to control blood loss during and after cardiac surgery, perioperative blood transfusions are required in up to 80 percent of adult patients, and 3-5 percent of these patients require post-operative transfusions of over 10 RBC units.²⁰²⁻²⁰⁴ Mediastinal exploration for ongoing post-operative bleeding is necessary in 3-10 percent of patients.^{205,206} Post-operative bleeding that is refractory to surgical re-exploration or conventional hemostatic therapy is felt to be multifactorial, with contributions from the use of antiplatelet agents prior to surgery and various causes of coagulopathy triggered by the surgery itself: residual heparin effect after cardiopulmonary bypass (CPB), hypothermia, hemodilution causing both thrombocytopenia and dilutional coagulopathy, consumption of coagulation factors, hyperfibrinolysis, inflammatory cascade activation, and platelet consumption and dysfunction.^{207,208}

Because anticoagulation is necessary during the period on CPB, the optimal time period for potential use of rFVIIa is some time after discontinuation of CPB and reversal of the anticoagulation. For “prophylaxis” of post-CPB bleeding, rFVIIa is administered immediately after conclusion of CPB. For “treatment” of post-CPB bleeding, rFVIIa is given at such time (variably defined) when excessive bleeding is identified and felt to require treatment. One group of patients known to be at increased risk for excessive bleeding includes those who have undergone complex cardiac surgeries: repeat surgeries, surgeries involving more than one procedure (e.g., multiple valve replacements or repairs), aortic root or arch replacements, and surgeries for aortic dissection or endocarditis.²⁰²

Usual care during the time frame of included studies. Ten years ago, 25-95 percent of adult cardiac surgery patients in the U.S. and U.K. received at least one unit of RBCs post-operatively, with wide variations in local practice. But recent studies have exposed the potential detrimental effects of post-operative transfusion.²⁰⁹ Murphy and Angelini evaluated studies published from 1996 to 2006 and found consistent evidence that transfusions increased the likelihood of infection, stroke, renal failure, prolonged ventilation, and both short- and long-term mortality.²¹⁰ Thus, usual care appears to be shifting toward limiting the practice of post-operative transfusion, whenever possible. All of the included studies were completed by November 2007, when the antifibrinolytic drug aprotinin—commonly used during cardiac surgeries until that time—was removed from the U.S. market due to safety concerns. Since then, tranexamic acid has become the antifibrinolytic agent of choice during cardiac procedures.

General Characteristics of Studies of Adult Cardiac Surgery

We identified for inclusion two RCTs (one good quality, one fair quality) and four comparative observational studies (two good quality, two fair quality) with 252 patients given rFVIIa as prophylaxis or treatment use following completion of CPB. One RCT examined the efficacy of rFVIIa as *prophylaxis* for bleeding and given immediately after termination of CPB in complex, non-coronary artery bypass grafting (non-CABG) surgery (Table 39). It stated that it was not sponsored by Novo Nordisk.¹¹⁸ A second RCT evaluated rFVIIa use following any cardiac surgery requiring CPB, including isolated CABG, as *treatment* for excessive post-

operative bleeding in the ICU, similar to the comparative observational studies described below. This latter study was sponsored by the manufacturer. A third RCT, Ma 2006,²¹¹ was published in Chinese but contained an abstract and data tables in English. It examined prophylactic administration of rFVIIa immediately following CPB. It is not included in our primary analyses but is used for sensitivity analyses.

The remainder of the studies, one prospective cohort²¹² and four retrospective cohorts,¹²⁰⁻¹²³ also evaluated rFVIIa used as *treatment* for excessive post-operative bleeding, typically in patients with non-CABG surgery. A certain number of patients receiving isolated CABG were included in some of the studies,^{121,123} most notably in the Gelsomino cohort, of which approximately 45 percent received an isolated CABG.¹²¹ The definition of “excessive bleeding” across studies was variable, but generally included some combination of the following criteria: bleeding that compromised hemodynamics, prevented chest closure, or crossed a certain threshold in the first post-operative hour (range 100-500 mL/h) or for a certain number of consecutive hours thereafter (range 100-300 mL/h). The majority of the patients in each study, and in some cases all of them, received the study drug in the ICU. One of these studies made no mention of manufacturer sponsorship,¹²¹ while the other three explicitly stated that they had no such sponsorship.^{120,122,123}

Place of studies within analytic framework. Adult cardiac surgery was the only indication for which there were comparative studies on more than one type of use of rFVIIa, namely prophylactic and treatment dosing (but not end-stage use) (see our Analytic Framework (Figure 1)). The Diprose RCT¹¹⁸ examined prophylactic use, while the Gill RCT¹¹⁹ examined treatment use, although in both cases, rFVIIa was given after termination of CPB. The remaining four studies,¹²⁰⁻¹²³ all of which were observational, examined treatment use. All of the studies provided comparative data of some sort on the direct outcomes of mortality and thromboembolic events and the surrogate outcomes of RBC (or in the case of the Gill RCT, total) transfusion requirements, as well as ICU length of stay.

Qualitative considerations of heterogeneity. One obvious source of potential heterogeneity among the adult cardiac surgery studies is the distinction between prophylactic and treatment use. However, in both types of use, rFVIIa is administered after CPB has concluded, when the effects of the many potential causes of coagulopathy discussed above may already be in full force—including the effects of residual heparin from CPB, hypothermia, hemodilution, platelet consumption and dysfunction, and the like. For this reason, we determined that patients in the one study on prophylactic rFVIIa use, the Diprose RCT, might be expected to respond to the drug similarly to the patients in the remaining studies of treatment use, and we therefore chose to analyze the studies together.

Comparison to studies on other indications. Like the Diprose RCT (and the Ma RCT in Chinese used for sensitivity analyses), the other indications that assessed prophylactic use of rFVIIa are those of liver transplantation, pediatric cardiac surgery, and prostatectomy. In contrast, the Gill RCT and all of the cohort studies evaluated treatment use of rFVIIa for bleeding during or after surgery, similar to the ICH and trauma indications. The mean age in the studies ranged from the mid to high 60s, which is comparable to the mean ages in the intracranial hemorrhage and prostatectomy studies. The rFVIIa dose was on the lower end of those studied

(17-90 µg/kg) and was typically only given in the form of 1-2 infusions, rather than the multiple infusions seen in some of the other indications.

Patient Characteristics and Study Design

RCTs. The fair quality Diprose RCT¹¹⁸ was a small double blind study of prophylactic use of rFVIIa conducted in one U.K. hospital with 10 patients in the usual care group and 10 patients in the rFVIIa group, and with the administration of the study drug or placebo at the conclusion of CPB. To qualify for inclusion, patients had to have undergone complex cardiac surgery, defined as repeat non-coronary surgery, multiple valve surgeries, surgery at the aortic root or arch or for aortic dissection, or surgery for endocarditis. All patients in the study received a set dose of aprotinin during surgery. While the study identified no single primary outcome, it reported on various transfusion requirements for the intention-to-treat population. However, the outcomes of mortality, thromboembolic events, and ICU length of stay were reported only for the per-protocol population, which excluded one patient from the rFVIIa group for incurring “multiple transfusion protocol violations” after being unblinded at the request of the surgeon.

The good quality Gill RCT¹¹⁹ evaluated treatment use of rFVIIa for excessive post-operative bleeding in the ICU, was conducted in the U.S. and 12 other countries (in Africa, Asia, Europe, and South America), and enrolled 172 patients total, including 68 patients in the usual care group and 104 patients in the rFVIIa group. The description on the ClinicalTrials.gov website indicates that the trial was terminated in November 2007 “without proceeding to the highest dosing cohort [of 160 µk/kg] as this no longer reflects common clinical practice.”²¹³ To qualify for inclusion, patients had to have undergone cardiac surgery that required CPB, which could include simple CABG (12 to 14 percent of patients in each group received only CABG), and also have reached a prespecified bleeding rate (>200 mL/h or >2mL/kg/h for 2 consecutive hours) after a 30 minute stabilization period in the ICU. Patients were excluded if they were determined to require urgent re-operation or had a history of stroke or non-coronary thrombotic disorder. In the publication there is no mention of whether patients received aprotinin or tranexamic acid for antifibrinolysis during surgery. The primary outcome was the incidence of critical serious adverse events at 30 days, which could include death, myocardial infarction (MI), stroke, pulmonary embolus (PE), or other symptomatic thromboembolic events. Other outcomes reported in the publication included total transfusion volume and blood loss, but not ICU length of stay.

The Ma RCT²¹¹ published in Chinese and used for sensitivity analyses evaluated prophylactic rFVIIa use immediately following conclusion of CPB in 11 usual care patients versus 11 treatment patients. All patients underwent valve repair surgery, with a sub-set undergoing a double valve repair (27 percent rFVII group, 36 percent placebo); there were no other types of surgery performed. Because we have limited access to methodological information and outcomes data—based only on the English-language abstract and results tables—we used the data for sensitivity analyses but did not include them in the primary analyses.

Comparative observational studies. We identified four comparative observational studies (two good quality, two fair quality (Table 14)). Again, all of these studies assessed the treatment use of rFVIIa compared to usual care for ongoing bleeding after discontinuation of CPB. The two highest quality comparative observational studies were the Karkouti and Gelsomino cohorts,

both of which earned “good” scores and were subsequently included with the Diprose and RCTs in the meta-analyses of direct outcomes.

The Karkouti cohort study assessed the first 51 patients treated with rFVIIa for cardiac surgery bleeding at a single Canadian institution between November 2002 and February 2004.¹²⁰ The institutional policy required that a consultant hematologist approve the release of rFVIIa and that bleeding be “massive and refractory,” as defined in the paper. The attending physician could then choose between two doses of rFVIIa which were based on drug vial contents rather than patient weight: a 4.8 mg vial (an approximate 70 µg/kg bolus) or a 2.4 mg vial (an approximate 35 µg/kg bolus). Data were abstracted by a blinded research nurse and research assistant. Each patient who received rFVIIa was matched to a single control selected from the hospital’s database of patients who had undergone cardiac surgery in a similar time frame and using a propensity score that modeled for massive perioperative blood loss. Patients were well matched at baseline on most characteristics, such as complex surgery and mean CPB time, but did have significant differences on baseline rates of re-exploration, blood loss, and transfusion products, all of which were higher in the rFVIIa group. No single primary outcome was identified, but the study reported on outcomes of RBC transfusion requirements, mortality, stroke, MI, PE, deep vein thrombosis (DVT), and ICU LOS, amongst others.

The Gelsomino cohort study¹²¹ assessed 40 patients treated at one Italian center, between September 2005 and June 2007, who had all types of cardiac surgeries, including isolated CABG, and received rFVIIa for “significant and refractory bleeding,” as defined in the paper. The dose of rFVIIa was the lowest administered for this indication, consisting of a uniform dose of 1.2 mg (a median dose of 18 µg/kg for included patients) that could be repeated once for continued bleeding. rFVIIa patients were matched 1:1 with 40 controls who received cardiac surgery at the hospital over the same time frame using a propensity score. Patients were well matched at baseline for important characteristics, such as the proportion undergoing complex cardiac surgery (approximately 40 percent in each group) and baseline transfusion requirements. The one possible exception to successful matching was the 30 minute longer CPB time in the usual care group (p=0.06). No single primary outcome was identified, but the study reported on outcomes of RBC transfusion requirements, mortality, stroke, respiratory failure, and ICU LOS, amongst others.

The von Heymann cohort¹²³ identified 26 patients who received 1-3 doses of 60 µg/kg rFVIIa at a median of 14 hours following CPB at one German institution between June 2000 and March 2003. The majority of patients received a single dose. The study subsequently excluded two patients because they died during the initial 24-hours after treatment. The remaining 24 treated patients were matched 1:1 with controls from a similar time frame and the same hospital. The controls had to have experienced blood loss over 1000 mL in the first 14 hours after CPB, and were also matched to rFVIIa patients based on the “complexity” of the surgery (defined as single procedure (e.g., isolated CABG or single valve) or combined procedure (e.g., CABG plus valve replacement)). While groups were well-matched at baseline on APACHE II scores, there were possibly important differences in rates of emergency or redo surgeries (higher in the usual care group) and liver failure and endocarditis (higher in the rFVIIa group). No single primary outcome was identified, but the study reported on outcomes of RBC transfusion requirements, need for reexploration, mortality, thromboembolic events, and ICU LOS, amongst others.

The Tritapepe cohort¹²² was the only study to report on patients who received a single type of surgery, in this case repair of proximal type A aortic dissections, a high-risk, complex cardiac surgery. It identified 23 consecutive patients who received at least one 70 µg/kg dose of

rFVIIa for refractory bleeding between January 2000 and March 2006. The majority of patients received a single dose. Usual care patients were matched 1:1 with rFVIIa patients based on a propensity score for “use of rFVIIa,” the modeling of which did not include a variable for baseline bleeding or transfusion requirements. The groups were otherwise well-matched on baseline characteristics, with the possible exception of higher rates of Bentall procedures in the rFVIIa group. No single primary endpoint was identified, but the study reported on outcomes of RBC transfusion requirements, mortality, stroke, and ICU LOS, among others.

Intervention Characteristics

RCTs. In the Diprose RCT¹¹⁸ the patients received a single, prophylactic bolus of 90 µg/kg of study drug or placebo immediately following the conclusion of CPB. rFVIIa patients in the Gill RCT¹¹⁹ received one of two possible single doses after a 30-minute stabilization period in the ICU: 35 received 40 µg/kg and 68 received 80 µg/kg. In the Ma RCT²¹¹ published in Chinese, which we are using for sensitivity analyses, a single, prophylactic dose of 40 µg/kg was administered immediately after CPB.

Comparative observational studies. In the cohort studies, rFVIIa was administered as treatment for excessive post-CPB bleeding. Compared to the doses used for treatment (rather than prophylaxis) in other clinical indications, these doses were on average much lower: first-time median doses ranged from 18-70µg/kg, with the majority of patients receiving only a single dose. In the Karkouti cohort,¹²⁰ attending physicians could choose between two doses of rFVIIa which were based on drug vial content rather than patient weight: a 4.8 mg vial (an approximate 62 µg/kg bolus) or a 2.4 mg vial (an approximate 37 µg/kg bolus). The majority of patients received just one dose. Patients in the Gelsomino cohort¹²¹ received the lowest doses of rFVIIa in all of the cohort studies, consisting of a uniform dose of 1.2 mg (which was equal to a median doses of 18 µg/kg) that could be repeated once for continued bleeding—but a repeat dose was required in only three patients. Patients in the von Heymann cohort¹²³ could receive 1-3 doses of 60 µg/kg rFVIIa a median of 14 hours following CPB, but the majority required only a single dose. The Tritapepe cohort¹²² used an initial treatment dose of 70 µg/kg dose rFVIIa, and, again, the majority of patients received only a single dose.

Outcomes

Direct (patient-centered) outcomes. Overall, mortality and thromboembolic event rates were consistently reported for the included RCTs and cohort studies. Table 40 summarizes the morbidity and mortality outcomes for the adult cardiac surgery studies. Given the limitations of the data, we were not able to evaluate for a dose-response relationship for these outcomes. As described further below, among the studies included in the meta-analyses, assessments of the significance and magnitude of heterogeneity by the Q and I² statistics did not identify significant heterogeneity.

Mortality. No study reported a significantly higher mortality rate in the rFVIIa group. Among the RCTs and good quality cohort studies, there were non-significant reductions in mortality with rFVIIa treatment compared to usual care in the Diprose RCT and Gelsomino cohort, exactly equal mortality rates between groups in the Karkouki cohort, and a non-significant increase in

mortality in the Gill RCT. The remaining cohort studies, deemed fair on quality scoring,^{122,123} demonstrated equal mortality rates with rFVIIa use versus usual care. The meta-analysis of mortality for the RCT and good quality cohort studies found no difference in mortality with rFVIIa versus usual care (risk difference 0.007; 95 percent CI -0.049 to 0.063; P value for the Q statistic 0.63) (Figure 21), a finding that remained when sensitivity analyses were performed using the data from the Ma RCT²¹¹ published in Chinese (risk difference 0.006; 95 percent CI -0.046 to 0.059; P value for the Q statistic 0.78) (Figure 22). To place the mortality differences in the context of the comparable findings for the other clinical indications, see Figure 5 above (in the Key Question section on intracranial hemorrhage).

Thromboembolic events. The rFVIIa and control groups in the Diprose RCT had the same rates of thromboembolic events, whereas the Gill RCT had higher rates in the treatment group. The two good quality cohort studies together demonstrated a weak trend toward increased events with rFVIIa. The fair quality cohorts had low but equal rates in both groups. The meta-analysis of the RCTs and good quality cohort studies identified a higher rate of thromboembolic events in the rFVIIa group compared to controls (risk difference 0.053; 95 percent CI 0.01 to 0.096; P value for the Q statistic 0.99) (Figure 23). This finding was replicated on the sensitivity analyses that incorporated data from the Ma RCT²¹¹ published in Chinese (risk difference 0.049; 95 percent CI 0.008 to 0.091) (Figure 24). To place the different thromboembolic event rates in the context of the comparable findings for the other clinical indications, see Figure 6 above (in the Key Question section on intracranial hemorrhage).

Indirect (surrogate) outcomes. These results are summarized in Table 41.

RBC transfusion during the 24-hour post-operative period. The Karkouti study did not report comparative data on this outcome. The Diprose RCT and the only good quality cohort study to report on the outcome, the Gelsomino cohort, respectively demonstrated a non-significant and significant difference between groups that favored a reduction with rFVIIa use (p values 0.11 and <0.001, respectively). While the Gill RCT did not report on isolated RBC transfusions, it did report significant differences between the two treatment groups (40 and 80 µg/kg) and controls in total blood transfusion volume. The Ma RCT (published in Chinese and used only for sensitivity analyses) reported a significant reduction in units of RBCs transfused (rFVIIa 3.5 (SD 2.2) versus control 6.3 (SD 3.1) (p<0.01)).²¹¹ There were inconsistent findings among the remaining studies—namely, the fair quality cohorts. The von Heymann study found no difference between groups, and the Tritapepe study found a significant effect against the rFVIIa group (i.e., increased transfusions with treatment).

ICU length of stay. The Diprose RCT found no significant difference between groups, although the absolute difference in means indicated an increased ICU LOS within the rFVIIa group. The publication of the Gill RCT¹¹⁹ does not comment on ICU LOS, but the synopsis on the manufacturer's website states that there was “no difference” between groups for this outcome.²¹⁴ The Ma RCT (published in Chinese and used only for sensitivity analyses) reported a significantly shorter ICU LOS for the rFVIIa group (2.7 day (SD 0.5) versus 3.3 days (SD 0.7) for controls (p<0.05)).²¹¹ There were inconsistent findings among the cohort studies as well. The good quality Karkouti cohort study identified a significantly longer ICU LOS for rFVIIa patients compared to controls. However, the other good quality cohort study by Gelsomino had

significant findings in the opposite direction—in favor of reduced time for the treatment group. The Tritatpepe study had non-significant findings in the same direction, whereas the remaining cohort study by von Heymann found no difference between groups.

Consideration of poor quality comparative observational studies. In the poor quality comparative observational studies by Bowman¹²⁴ and Trowbridge,¹²⁵ the findings on mortality, thromboembolic events, and RBC transfusions were generally consistent with those described above (Tables 40 and 41). Other outcomes were not reported.

Other Considerations

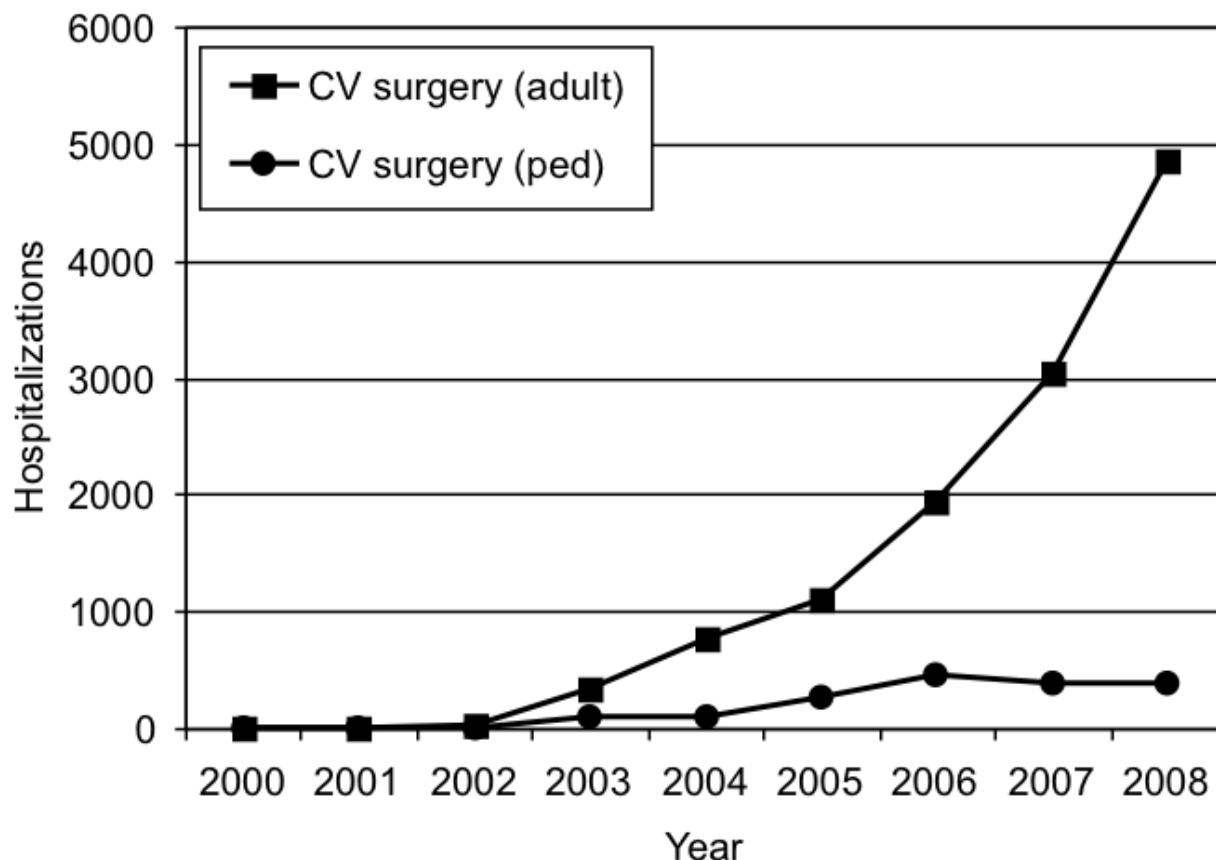
Timing of administration. The Karkouti cohort study¹²⁰ overlapped substantially with another study by the same group,²¹⁵ which was excluded from subsequent analysis on the basis of that overlap and because it focused on “determinants of complications” rather than the comparison of rFVIIa with usual care and had methodological limitations. Nevertheless, it highlighted an important question regarding the timing of treatment use of rFVIIa in cardiac surgery patients.

The study findings should be interpreted with caution, but did identify a non-significant increased risk of adverse events when rFVIIa was given “late” in the resuscitation—with “late” defined as infusion after nine or more units of RBCs had already been administered. None of the included studies performed a similar evaluation of the impact of timing of rFVIIa administration on outcomes.

Comparison to Premier Database

The age of study patients (mid 60s) was comparable to the mean age of 65 years for the Premier patients. The mortality rate of 0.23 among the Premier patients was higher than the rate found for rFVIIa patients in the RCTs but relatively comparable to those identified for the cohort studies. According to the Premier database, rates of use for the adult cardiac surgery indication have continued to increase in the community (with a much slower rate of increase followed by a recent leveling off for pediatric cardiac surgery patients who are discussed further in the subsequent section) (Figure 20).

Figure 20. Premier database rFVIIa use in adult and pediatric cardiac surgery



Strength of Evidence

The strength of evidence assigned to the thromboembolic event outcome was moderate, based on the consistency and precision of findings on the meta-analyses of the higher quality studies for these outcomes (Table 42). The remainder of the outcomes were assigned a low strength of evidence based primarily on weaknesses in two strength of evidence domains: the risk of bias domain—which had ratings of a medium or high—and the precision domain—which had ratings of imprecise. The rating of imprecise was based on wide confidence intervals for the major outcomes which in turn were due to low event rates in studies that were underpowered to detect mortality and major morbidity outcomes.

Applicability

The overall applicability of the evidence for this indication is fair for both prophylactic and treatment use in the population targeted—adult patients undergoing cardiac surgery, including more straightforward procedures (e.g., isolated CABG) and complex surgeries (e.g., ascending aortic dissection repair) (Table 43). Such study populations are diverse, giving them good applicability. The relatively narrow rFVIIa dose range that was studied may also be relevant to practice. However, the variability among studies in use of rFVIIa for prophylaxis versus treatment may be a limitation. The follow-up time was no longer than one month in any study, and the methods of ascertainment for harm was generally not well described, which limits

applicability. The study settings were primarily academic centers, which may be more applicable to regional referral centers than community hospitals.

Conclusions

There is evidence of moderate strength to suggest that the use of rFVIIa in adult cardiac surgery increases the rate of thromboembolic events compared to usual care. The strength of evidence was low for the remainder of outcomes, including for the finding of no effect of rFVIIa use on mortality. Among the RCTs and higher quality cohort studies, there was a trend toward reduced transfusion requirements with therapy, but no difference in ICU length of stay. Thus, 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. Study patients were similar in age to those in the Premier database. Compared to Premier patients, those in the cohort studies had comparable mortality rates, whereas those in the RCTs had somewhat lower mortality rates. The importance and nature of interactions between the timing of treatment use of rFVIIa and important clinical outcomes remain uncertain.

Table 39. General characteristics of comparative studies on off-label rFVIIa use for adult cardiac surgery

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Diprose 2005 ¹¹⁸	RCT Prophylaxis	1 Center Southampton, UK	All Rx: 10 Ucare: 10	Rx: 69.5 ^U [63.5-76.5] ^I	Inclusion: -scheduled to undergo complex non-coronary cardiac surgery requiring CPB. -over 18 Exclusion: -recent thrombotic disease	Mortality	Transfusion requirements††
		Time period not reported.	Dose: 90 µg/kg	Ucare: 63 ^U [59-66] ^I		TE events (stroke and MI only)	Blood loss Hospital and ICU LOS
Gill 2009 ¹¹⁹	RCT Treatment	30 Centers 13 countries	All Rx: 104 40: 35 80: 69	Rx: 40: 68 (12) 80: 63 (16)	Inclusion: -completed cardiac surgery requiring CPB and had been admitted to postoperative care environment for at least 30 minutes and who were bleeding at a prespecified rate based on blood volume from mediastinal drains. Exclusion: -required urgent re-operation -history of stroke or other non-coronary thrombotic disorder -procedure involving transplantation or implantable ventricular assist device -congenital clotting or bleeding disorder	Mortality	Transfusion requirements††
		8/2004-11/2007	Ucare: 68	Ucare: 62 (16)		Adverse events including TE events	Blood loss
Karkouti 2005 ¹²⁰	Retrospective comparative Treatment	1 Center Toronto, Canada	All Rx: 51 Ucare: 51	Rx: 56 Ucare: 59	Inclusion: -massive blood loss (blood loss>2000 mL or required transfusion of at least 4 units RBCs precluding terna closure, or blood loss>100 mL/hr in the ICU). -refractory blood loss (e.g. surgical source of bleeding excluded, antifibrinolytics administered, transfusion protocol completed, coagulation measures corrected to within 50% of normal) SAS Greedy 5 → 1 method was used to match one control patient to each study patient according to propensity score.	Mortality	Blood loss
		11/2002-2/2004	Mean Dose: 62 µg/kg SD: 13 µg/kg			Adverse events including TE events	Hospital and ICU LOS

Table 39. General characteristics of comparative studies on off-label rFVIIa use for adult cardiac surgery (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Von Heymann 2005 ¹²³	Retrospective comparative	1 Center Study location not reported.	All Rx: 24 Ucare: 24	Rx: 65 Ucare: 65	Inclusion: All patients receiving rFVIIa for cardiac surgery. rFVIIa could be administered "if despite adequate conventional hemostatic therapy, excessive bleeding continued." Controls: Historical controls (1998-2002) with blood loss during first 14 hours >1000 mL, matched on baseline and perioperative characteristics (e.g. single procedure versus combined procedure, implantation of ventricular assist device, need for emergency surgery)	Mortality	Transfusion requirements††
	Treatment	6/2000-3/2003	Dose: 60-80 µg/kg with possible second and third doses if blood loss continued at >100 mL/hr.				
Tritapepe 2007 ¹²²	Retrospective comparative	1 Center Rome, Italy	All Rx: 23 Ucare: 23	Rx: 62.4 (9.4)	Inclusion: -Aortic dissection surgery -"life-threatening" postcardiac surgery hemorrhage (i.e. blood loss > 150 mL/hr) -surgical source of bleeding excluded by >2 hours of surgical exploration Controls: SAS Greedy 5 → 1 method was used to match one control patient to each study patient according to propensity score.	Mortality	Transfusion requirements††
	Treatment	1/2000-3/2006	Mean dose: 82 µg/kg	Ucare: 62.2 (9.1)			
Gelsomino 2008 ¹²¹	Retrospective comparative	1 Center Florence, Italy	All Rx: 40 Ucare: 40	Rx: 70.1 (9.2)	Inclusion: -significant bleeding (i.e. >500 mL/hr during first postoperative hour, >300 mL/hr for three consecutive hours after chest closure, or >1200 mL/hr after fifth postoperative hour) -refractory blood loss (e.g. surgical source of bleeding excluded, antifibrinolytics administered, transfusion protocol completed, coagulation measures corrected to within 50% of normal) Controls: SAS Greedy 5 → 1 method was used to match one control patient to each study patient according to propensity score.	Mortality	Transfusion requirements††
	Treatment	9/2005-6/2007	Median Dose: 18.3 µg/kg, IQR: 9-16 µg/kg	Ucare: 75.8 (9.8)			

Table 39. General characteristics of comparative studies on off-label rFVIIa use for adult cardiac surgery (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Bowman 2008 ¹²⁴ †	Retrospective comparative Treatment	1 Center South Carolina, USA 1/2001-12/2006	All Rx: 36 Ucare: 385 Mean dose: 100 ug/kg	Rx: 58 (15) Ucare: NR	Inclusion: -adults undergoing “high-risk” cardiac surgeries (transplantation, aortic surgery, redo operations, or multiple cardiac procedures in one operation) -exclusion of surgical bleeding, failure to reverse coagulopathy with standard means, correction of core body temperature to normal, adequate heparin reversal, and (for those in the ICU) chest tube output of at least 3 mL/kg/h for at least 2h Controls: contemporaneous cohort of adults undergoing “high-risk” cardiac surgeries.	Mortality Adverse events including TE events	Transfusion requirements†† (rFVIIa pts only)
Trowbridge 2008 ¹²⁵ †	Prospective comparative	1 Center Pennsylvania, USA Time period not reported.	All Rx: 17 Ucare: 187 Mean dose not reported.	Rx: 69.6 (8.9) Ucare: 66.5 (11.3)	Inclusion: -adult cardiac surgery patients with “uncontrolled hemorrhage” (e.g., non-surgical bleeding, platelet count>100), thereby meeting institutional guidelines for “rescue therapy” with rFVIIa Controls: contemporaneous cohort of adult cardiac surgery patients without “uncontrolled hemorrhage”	None reported	Transfusion requirements††

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

^UMedian; ^IInterquartile range; ††Examples of transfusion requirements are red blood cells and fresh frozen plasma

IQR=interquartile range; SD=standard deviation; Rx=treatment group(s); Ucare=usual care; NR=not reported; TE=thromboembolic; INR=international normalized ratio; LOS=length of stay

Table 40. Mortality and thromboembolic events in comparative studies of rFVIIa use in adult cardiac surgery

Article	Study Design and rFVIIa use	Mean rFVIIa dose (SD) [IQR]	Sample size		Mean age (SD) [IQR]		Mortality rate			Thromboembolic events rate ^{&}		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Diprose 2005 ¹¹⁸	RCT <i>Prophylaxis</i>	90	9 [^]	10	63 ^U [59-66]	69.5 ^U [63.5-76.5]	0	0.1	p=1	0.222	0.2	NR
Gill 2009 ¹¹⁹	RCT <i>Treatment</i>	40 80	35 69	68	68 (12) 63 (16)	62 (16)	0.114 0.087	0.059	NR	0.086 0.058	0.015	NR
Karkouti 2005 ¹²⁰	Retrospective comparative <i>Treatment</i>	51.1	51	51	56	59	0.137	0.137	NS	0.157	0.098	NR
Gelsomino 2008 ¹²¹	Retrospective comparative <i>Treatment</i>	18 [9-16]	40	40	70.1 (9.2)	73.2 (7.8)	0.05	0.075	p>0.9	0.05	0	NR
von Heymann 2005 ¹²³	Retrospective comparative <i>Treatment</i>	89.3	24	24	63.5	63.5	0.333*	0.333*	p=1	0	0	NR
Tritapepe 2007 ¹²²	Retrospective comparative <i>Treatment</i>	82.2	23	23	62.4 (9.4)	62.2 (9.1)	0.13	0.13	p=1	0.087	0.087	NR
Bowman 2008 ¹²⁴ †	Retrospective comparative <i>Treatment</i>	100	36	385	58 (15)	NR	0.083	0.044 to 0.047†	NR	0.111	0.055	p=.15
Trowbridge 2008 ¹²⁵ †	Prospective comparative <i>Treatment</i>	NR	17	187	70 (9)	67 (11)	NR	NR	NR	NR	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

&Thromboembolic event rates were calculated by dividing the number of thromboembolic *events* by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from those reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

[^] Diprose 2005¹¹⁸ excluded 1 patient who violated the study protocol after randomization. This patient was not evaluated for mortality or thromboembolic events.

*“Hospital mortality”. The mortality rates at 6 months were 0.583 in the rFVIIa group and 0.417 in the usual care group.

†These data were extrapolated as the range of possible mortality for the usual care group given the mortality rates reported for the rFVIIa group and the group of all patients combined.

NR=not reported; NS=not significant; ^Umedian

Figure 21. Mortality in adult cardiac surgery

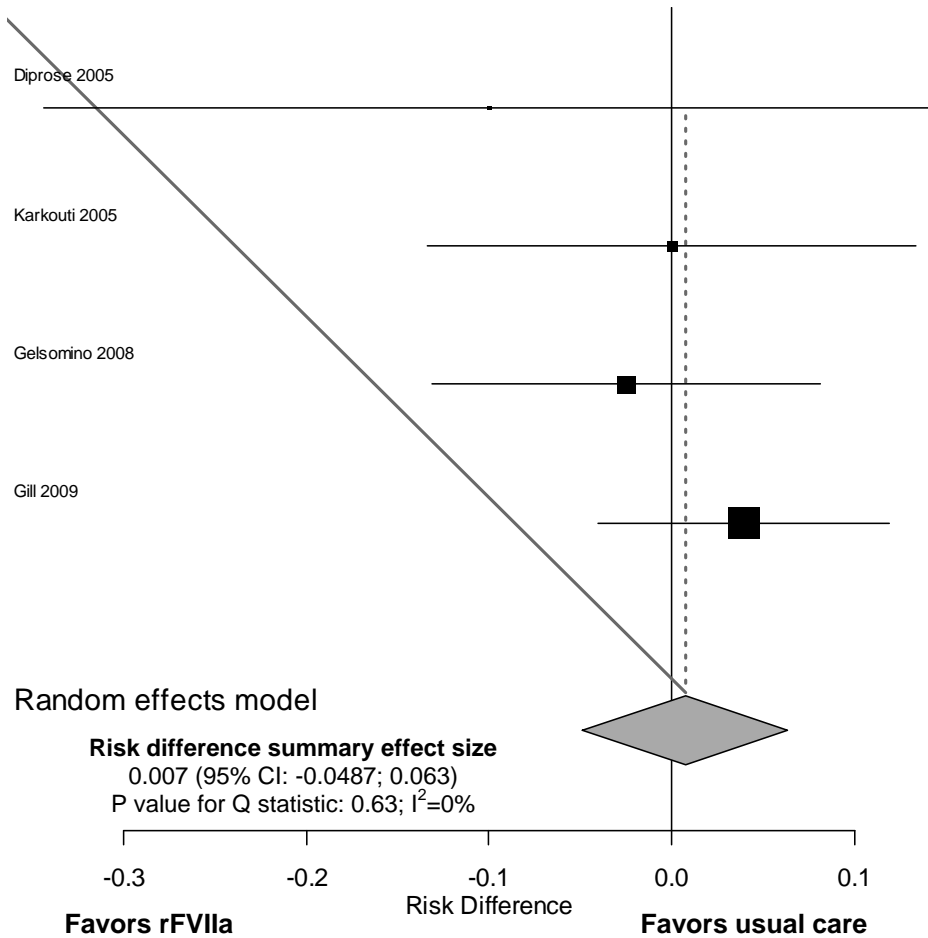
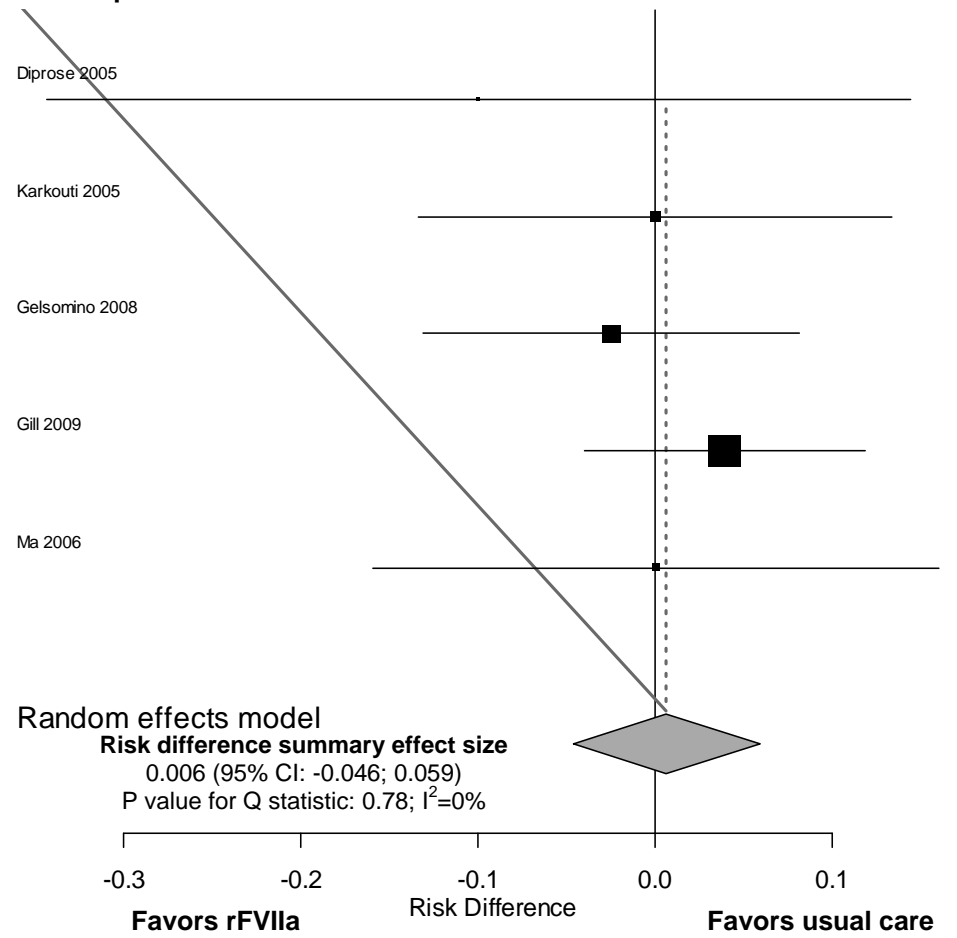


Figure 22. Sensitivity analysis: mortality in adult cardiac surgery that incorporates Chinese RCT data



Article	Deaths/total patients	
	rFVIIa	Control
Diprose 2005	0/9	1/10
Karkouti 2005	7/51	7/51
Gelsomino 2006	2/40	3/40
Gill 2009	10/103	4/69
Ma 2006	0/11	0/11

Figure 23. All thromboembolic events in adult cardiac surgery

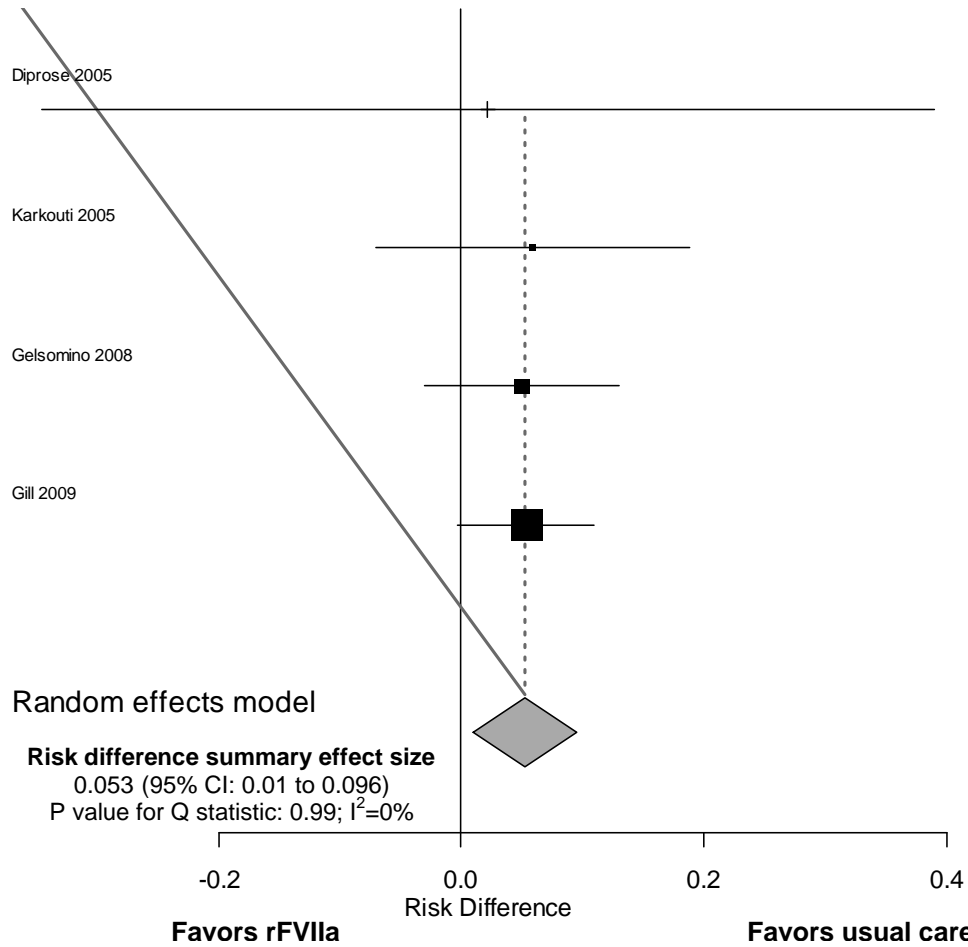
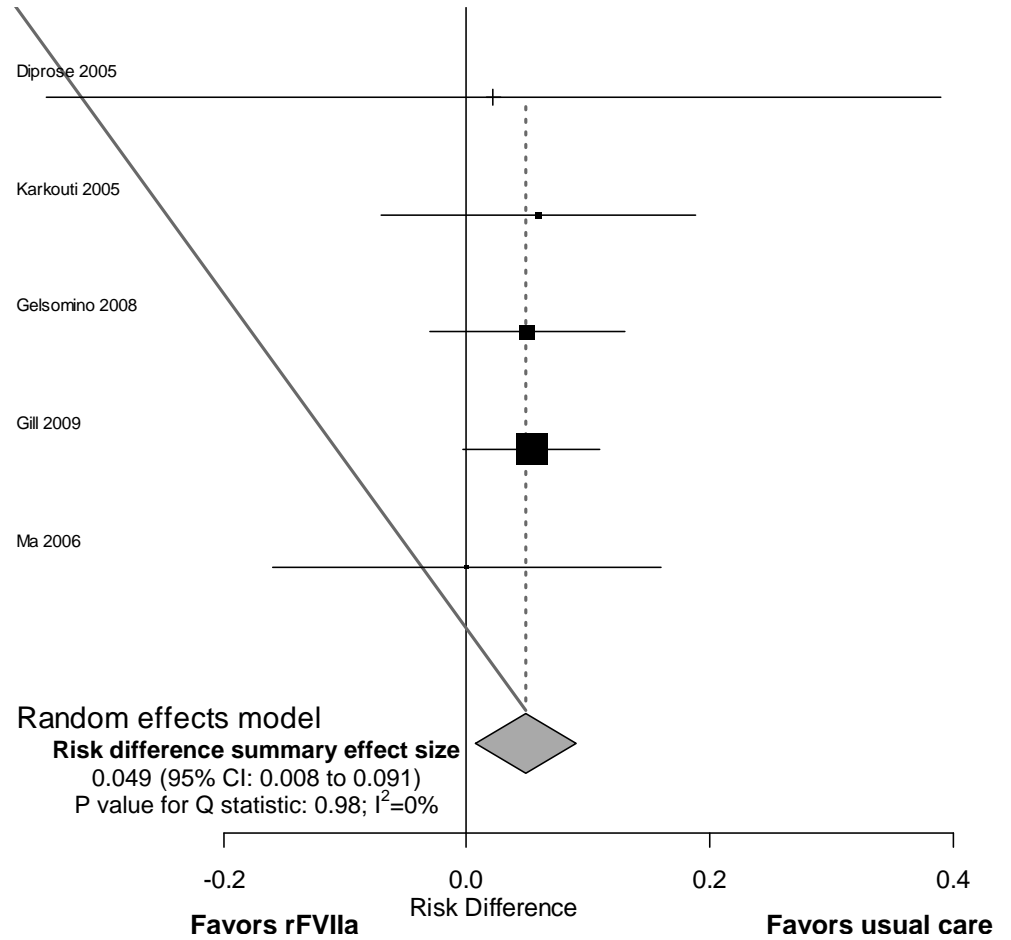


Figure 24. Sensitivity analysis: all thromboembolic events in adult cardiac surgery that incorporates Chinese RCT data



Article	TE Events/total patients	
	rFVIIa	Control
Diprose 2005	2/9	2/10
Karkouti 2005	8/51	5/51
Gelsomino 2006	2/40	0/40
Gill 2009	7/103	1/69
Ma 2006	0/11	0/11

Table 41. Indirect outcomes in comparative studies of rFVIIa use in adult cardiac surgery

Article	Study Design and rFVIIa use	Mean rFVIIa dose (SD) [IQR]	Sample size		Mean age (SD) [IQR]		Mean RBC transfusion (SD) [IQR]			Mean ICU LOS (days) (SD) [IQR]		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Diprose 2005 ¹¹⁸	RCT <i>Prophylaxis</i>	90	9	10	63 ^U [59-66]	69.5 ^U [63.5-76.5]	0* [0-0.75]	2* [1-3.5]	p=0.11 *	2.5 ^U [1-3.5]	1 ^U [1-4]	p=.43
Gill 2009 ¹¹⁹	RCT <i>Treatment</i>	40 80	35 69	68	68 (12) 63 (16)	62 (16)	^	^	^	"no diff" [†]	"no diff" [†]	NR
Karkouti 2005 ¹²⁰	Retrospective comparative <i>Treatment</i>	51.1	51	51	56	59	2 ^U [0-3]	NR	NR	6 ^U [3.5-11.5]	3.5 ^U [1-10]	p<.05
Gelsomino 2008 ¹²¹	Retrospective comparative <i>Treatment</i>	18 [9-16]	40	40	70.1 (9.2)	73.2 (7.8)	6.5 ^U [4-8.5]	17 ^U [12-19.5]	p<.001	6.3 ^U [3.9-7.3]	18.5 ^U [16.2-24]	p<.001
von Heymann 2005 ¹²³	Retrospective comparative <i>Treatment</i>	89.3	24	24	63.5^	63.5^	4.0&	2.6&	p=.44	14 [6.5-34.5] ^R	15 [6.0-29.5] ^R	p=.96
Tritapepe 2007 ¹²²	Retrospective comparative <i>Treatment</i>	82.2	23	23	62.4 (9.4)	62.2 (9.1)	9.1 (3.0)	5.3 (3.2)	p<.001	8.2 (9.0)	10.0 (8.4)	p=.08
Bowman 2008 ¹²⁴ †	Retrospective comparative <i>Treatment</i>	100	36	385	58 (15)	NR	3.1 [#]	NR	NR	NR	NR	NR
Trowbridge 2008 ¹²⁵ †	Prospective comparative <i>Treatment</i>	NR	17	187	70 (9)	67 (11)	0.6 (1.2)**	5.4 (3.5)**	p<.001	NR	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, "Consideration of poor quality comparative observational studies") and in the overall harms analyses near the end of this report.

*Intention to treat data was used (rFVIIa group sample size equals 10 instead of 9). One patient who violated the study protocol in Diprose 2005¹¹⁸ was excluded from the analysis of mortality, thromboembolic events, and ICU length of stay, but was included in the intention to treat analysis of RBC transfusions. If this patient is excluded, median RBC transfusions are 0 units (range: 0-0 units) in the rFVIIa group and 2 units (range 1 to 3.5 units) in the usual care group (p=.03).

^ Total blood transfusion volume (not isolated to RBCs): 40 ug/kg rFVIIa, 640 mL [IQR 0-1920] (p= 0.047 versus usual care); 80 ug/kg rFVIIa, 500 mL [IQR 0-1750] (p=0.042 versus usual care); usual care, 825 mL [IQR 326.5-1893].

† There was "no difference" noted in ICU length of stay between groups in the trial synopsis posted on the manufacturer's website. This outcome was not reported in the published article. [&]Estimated graphically from figure 2 in von Heymann 2005¹²³

[#] Estimated graphically from figure 1 in Bowman 2008¹²⁴.

**Post-CPB transfusion without adjustment for timing of rFVIIa administration.

NR=not reported; NS=not significant;

^UDenotes median

^RRange instead of IQR.

Table 42. Strength of evidence for rFVIIa use in adult cardiac surgery

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Overall Risk						
Mortality (in-hospital)	2 ^{118, 119}	113	78	RCT	Good	Low	Consistent	Direct	Imprecise	No Effect	Unknown	Low
	4 ¹²⁰⁻¹²³	138	138	COBS	Good	Medium	Consistent	Direct	Imprecise	No effect	Unknown	
	4 ¹¹⁸⁻¹²¹	204	169	M-A	Good	Low	Consistent	Direct	Imprecise	No effect	Unknown	
Thrombo-embolic Events	2 ^{118, 119}	113	78	RCT	Good	Low	Consistent	Direct	Imprecise	Weak increase with rFVIIa	Unknown	Moderate
	4 ¹²⁰⁻¹²³	138	138	COBS	Good	Medium	Consistent	Direct	Imprecise	Weak increase with rFVIIa	Unknown	
	4 ¹¹⁸⁻¹²¹	204	169	M-A	Good	Low	Consistent	Direct	Precise	Increase with rFVIIa	Unknown	
Units of RBCs Transfused	1 ¹¹⁸	10	10	RCT	Fair	Medium	Unknown	Indirect	Imprecise	Weakly favors rFVIIa	Unknown	Low
	3 ^{120, 122, 123}	98	98	COBS	Fair	High	Inconsistent	Indirect	Imprecise	No effect	Unknown	
ICU Length of Stay	1 ¹¹⁸	9	10	RCT	Fair	Medium	Unknown	Indirect	Imprecise	Weak increase with rFVIIa	Unknown	Low
	4 ¹²⁰⁻¹²³	138	138	COBS	Good	Medium	Inconsistent	Indirect	Imprecise	No effect	Unknown	

RCT=randomized controlled trial; ICU=intensive care unit; COBS=comparative observational study; RBCs=red blood cells. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 43. Applicability assessment of studies on adult cardiac surgery

Available Evidence	Overall Implications for Applicability
<p>Population</p> <p>Adults undergoing cardiovascular surgery, in many cases complex procedures, including ascending aortic dissection repair, but also including more straightforward surgeries, such as isolated CABG</p> <p>Mean age 64 years</p> <p>High mortality rate (13 percent) in patients receiving rFVIIa in response to bleeding</p> <p>Patients generally with intact clotting systems at baseline, but also with effects of CPB (e.g., residual impact of intraoperative heparin, hypothermia, etc.) and possible prior use of antiplatelet agents</p> <p>Minimal exclusions overall, but usually no underlying coagulopathy and RCTs excluded patients with prior thrombotic disorders</p>	<p>Other approaches available to minimize blood loss</p> <p>Lack of comparison between prophylactic use and use for treatment</p>
<p>Interventions</p> <p>Prophylactic use of rFVIIa as a single dose of 90 mcg/kg prior to surgery</p> <p>Low dose treatment doses of 18 mcg/kg</p> <p>Higher dose treatment doses of 40 to 90 mcg/kg</p>	<p>Dose for prophylaxis is narrow and comparable to prophylactic doses used in studies on other indications and in practice</p> <p>Doses for treatment is lower than observed for treatment in other situations</p>
<p>Comparator</p> <p>Usual care via randomization or matched controls</p>	<p>Other prophylactic and therapeutic hemostatic agents are potential comparators, but not used in this setting</p>
<p>Outcomes</p> <p>Primary outcome: Red blood cell transfusions over 24 hours (in most studies)</p> <p>Secondary outcomes: mortality, thromboembolic events, ICU length of stay, operative time, coagulation lab parameters</p>	<p>Surrogate/indirect outcomes related to process of care without direct link to clinical outcomes</p> <p>Insufficient sample size to assess some clinical outcomes</p> <p>No measure of patient functional status</p>
<p>Timing and intensity of follow-up</p> <p>Follow-up for duration of hospitalization or 30 days</p> <p>Seldom had protocol for ascertainment of harms</p>	<p>Longer term outcomes and a protocol for ascertainment of harms is desirable</p>
<p>Setting</p> <p>Academic hospitals in the U.S., U.K., and Italy that serve as regional referral centers</p>	<p>Likely applicable to U.S. regional referral centers, perhaps less applicable to community hospitals</p>

Key Question 4.b.ii. **Pediatric cardiac surgery** and comparative effectiveness of rFVIIa

Background

The infant population that requires cardiac surgery to correct congenital heart defects is particularly susceptible to dilutional coagulopathies that can cause excessive bleeding. RBC or whole blood transfusions are frequently required during operative or post-operative periods. No hemostatic agents have been found to be consistently useful in such surgeries. While a meta-analysis of aprotinin compared to usual care demonstrated reduced need for transfusions,²¹⁶ these findings are not uniform²¹⁷ and the drug is no longer available in the U.S. due to safety concerns. Multiple studies have shown that DDAVP does not reduce transfusion requirements during surgery for children with congenital heart disease.²¹⁸⁻²²⁰ Pediatric cardiac surgery is further complicated by the frequent need post-surgery for the infant to remain on extracorporeal membrane oxygenation (ECMO) machines, despite the well recognized increased risk of thromboembolism with ECMO use.²²¹

Usual care during the time frame of the included study. Pediatric cardiac surgeons differ in their preference for packed RBCs versus whole blood for transfusion support during surgery based on conflicting evidence in recent trials.^{222,223} Furthermore, recent studies have begun to explore whether transfusion use in pediatric cardiac surgery is associated with adverse effects, such as an increased risk of infection, similar to what has been suggested in the adult cardiac surgery literature.²²⁴

RCT Design and Intervention

We found only one study on prophylactic use of rFVIIa in pediatric cardiac surgery, a poor quality RCT. This small, double-blind, placebo-controlled trial by Ekert did not report any Novo Nordisk sponsorship.¹³⁷ It initially enrolled 82 patients, but six patients (four in the usual care group and two in the rFVIIa group) “did not receive trial medication” and were subsequently excluded from the intention-to-treat analysis, which left 36 control and 40 rFVIIa patients to be evaluated. Treatment with 40 µg/kg of rFVIIa (or placebo) was administered immediately after termination of CPB in children under one year of age who were undergoing repair of complex congenital heart defects. A second dose could be administered 20 minutes later in the operating room at the discretion of the surgeons. A third dose does not appear to have been required in any case. The mean cumulative dose administered was 63µg/kg. Groups were similar at baseline in age, weight, type of surgery, and CPB time. The primary outcome was time to chest closure. The study also reported on outcomes of transfusion requirements of “blood” (which could include packed cells or whole blood) and thromboembolic events. It did not explicitly comment on mortality. There was no mention of ECMO use in the study (Table 44). While attempts at a six-week follow-up were made, these were largely unsuccessful because of considerable missing data.

Place of studies within analytic framework. The Ekert RCT evaluated prophylactic use of rFVIIa in pediatric cardiac surgery (versus treatment or end-stage use, which are other potential uses, as outlined in our Analytic Framework (Figure 1)).

Comparison to studies on other indications. This was the only included study on a solely pediatric patient population, in this case infants. The mean rFVIIa dose of 63 µg/kg was similar to the doses used in adults studies of prophylactic use.

Outcomes

The study identified no thromboembolic events and did not explicitly report mortality (Table 45). With respect to the primary endpoint, rFVIIa patients had a longer time to chest closure than did controls (98.8 minutes (SE 27.3) versus 58.3 minutes (SE 29.2), $p=0.026$). Nonetheless, there was a non-significant decrease in transfusion requirement for RBCs and/or whole blood in the rFVIIa group (Table 46).

Consideration of poor quality comparative observational studies. Unlike the RCT, the poor quality comparative observational studies by Tobias,¹³⁹ Agarwal,¹³⁸ and Niles¹⁴⁰ evaluated treatment use of rFVIIa. Nonetheless, their findings on thromboembolic events and RBC transfusions were consistent with those described above (Tables 44 and 45), with the possible exception of the Agarwal study, which noted a higher rate of thromboembolic events in patients who received rFVIIa versus usual care (6 of 24 (25 percent) and 0 of 22, respectively) and also raised the possibility of an increased risk of severe events among the subgroup of patients on ECMO, which is discussed in the section immediately below. Among these studies, only the one by Tobias reported mortality data, noting no deaths in either group. Other outcomes were not reported.

Other Considerations

Risk of thromboembolic complications in the setting of ECMO use. A comparative cohort study by Agarwal et al. that did not meet criteria for inclusion in the effectiveness review due to methodological limitations nonetheless raises important questions about a subgroup of patients who might experience increased risk for harm within the population of infants undergoing congenital heart surgery.¹³⁸ The Agarwal study evaluated a subgroup of 12 patients on ECMO who received therapeutic rFVIIa for bleeding after CPB completion, two of whom experienced life-threatening thromboembolic adverse events. In the first, the ECMO circuit clotted to the point where blood flow was compromised and the infant required emergent resuscitation and exchange of the circuit. The second patient, who underwent unsuccessful placement of a femoral arterial line after surgery and then received rFVIIa, developed an ipsilateral ischemic lower extremity, which required amputation, as well as both atrial and pericardial thrombi, which required surgical evacuation. In contrast, none of the 15 control patients on ECMO who received usual care were noted to have thromboembolic events of any kind. Given methodological limitations and small sample sizes, these findings should be interpreted with due caution.

Comparison to Premier Database

The Premier database indicates a low but steady level of use of rFVIIa among pediatric cardiac surgery patients (Figure 20). The mortality rate of 0.22 in the Premier database cannot be compared to any mortality rate in the RCT, because the RCT did not report this outcome. The mean age of study patients (3.9-4.0 months) was lower than the mean age of Premier patients (2.6 years). Whereas study patients were receiving their first surgical intervention at the time of rFVIIa administration, the Premier database may include patients undergoing repeat cardiac

procedures, because the full repair of congenital heart defects often involves staged surgeries performed over time, which may explain their older age compared to study patients.

Strength of Evidence

The strength of evidence was insufficient for all outcomes. This determination was made on the basis of having only one small, poor quality study for this indication, which put it at high risk for bias and limited its precision (Table 47).

Applicability

The overall applicability of the evidence for this indication is fair for prophylactic use in the population targeted—infant patients with congenital heart defects requiring cardiac surgery for repair. This population, while limited in absolute number, has good applicability to similar populations at specialized referral centers like the institution that was the setting for the RCT. The low dose of rFVIIa is likely applicable as an appropriate amount for prophylaxis. The emphasis on indirect outcomes rather than mortality and morbidity outcomes is a limitation to applicability. While attempts at adequate follow-up were made, these were unsuccessful, and the method of ascertainment of harms was not described, making the follow-up applicability poor (Table 48).

Conclusions

Current evidence is insufficient for comparing the harms and benefits of rFVIIa use in infant patients undergoing cardiac surgery for congenital heart defect repair. The importance and nature of interactions between rFVIIa administration, ECMO use, and the risk of thromboembolic events remain uncertain.

Table 44. General characteristics of comparative studies on off-label rFVIIa use for pediatric cardiac surgery

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Ekert 2006 ¹³⁷	RCT Prophylaxis	1 center Victoria, Australia Time period NR	All Rx: 40 Ucare: 35 Dose: 63.0 ug/kg	Rx: 4.0 months Ucare 3.9 months	Inclusion: -children under 1 year with complex congenital heart disease requiring surgery with CPB Exclusion: -liver failure -known thrombotic disorder -prior treatment with antifibrinolytic agents -indication for a Norwood procedure -patients on ventilation assistance -occurrence or preoperative sepsis or coagulopathy -expected lifespan of <=3 months	Adverse events including TE events	Transfusion requirements†† Blood loss Time to chest closure
Tobias 2004 ^{139†}	Retrospective comparative Treatment	1 center Santo Domingo, Dominican Republic 1/2003	All Rx: 9 Ucare: 8 Dose: 90 ug/kg	Rx: 9 years (4) Ucare: 10 years (3)	Inclusion: -children who received rFVIIa and with postoperative bleeding of at least 4 mL/kg/hm for 3h consecutively Controls: contemporaneous cohort who had lower bleeding rates and did not receive rFVIIa	Adverse events including TE events	Blood loss Need for surgical re-exploration
Agarwal 2007 ^{138†}	Retrospective comparative Treatment	1 center Nashville, TN, USA 1/2000-12/2004	All Rx: 24 Ucare: 22 Mean Dose: 43 ug/kg SD: 22.9 ug/kg	Rx: 9.5 days ^U [4-3,285] Ucare: 7 days ^U [2-240]	Inclusion: -children who received rFVIIa without a known bleeding disorder and with “severe” postoperative mediastinal bleeding, defined for neonates/infants as over 10 mL/h and for others as over 100 mL/h -includes children placed on ECMO after surgery Controls: contemporaneous cohort who met above criteria but did not receive rFVIIa	TE events	Transfusion requirements†† Blood loss Need for surgical re-exploration

Table 44. General characteristics of comparative studies on off-label rFVIIa use for pediatric cardiac surgery (continued)

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics		Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria	Direct	Indirect
Niles 2008 ^{140†}	Retrospective comparative	1 center Iowa City, IO, USA	All Rx: 15 Ucare: 15	Rx: 60 days (99); 5293 days (471)** Ucare: 16 days (19); 4531 days (2758)**	Inclusion: -cardiac surgery requiring CPB Controls: historical controls who underwent cardiac surgery requiring CPB and were matched for weight > or < 30 kg	Mortality	TE events
	Treatment	2004-2006	Dose not reported				

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

SD=standard deviation; Rx=treatment group(s); Ucare=usual care; TE=thromboembolic;

††Examples of transfusion requirements are red blood cells and fresh frozen plasma

^uMedian

Table 45. Mortality and thromboembolic events in RCT on rFVIIa use in pediatric cardiac surgery

Article	Study Design and rFVIIa use	Mean rFVIIa Dose (µg/kg) (SD) [Range]	Sample size		Mean age (SD)		Mortality rate			Thromboembolic events rate ^{&}		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Ekert 2006 ¹³⁷	RCT Prophylaxis	63 (20.2)	40	36	4 months	3.9 months	NR	NR	NR	0	0	NR
Tobias 2004 ^{139†}	Prospective comparative Treatment	90	9	8	9 years (4)	10 years (3)	NR	NR	NR	0	NR	NR
Agarwal 2007 ^{138†}	Retrospective comparative Treatment	43 (23)	24	22	10 days [4-32850]	7 days [2-240]	NR	NR	NR	0.25	0	NR
Niles 2008 ^{140†}	Retrospective comparative Treatment	[76-282]; [26-956]	15	15	60 days (99); 5293 days (471)**	16 days (19); 4531 days (2758)**	0	0	NR	0	0	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

&Thromboembolic event rates were calculated by dividing the number of thromboembolic events by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from those reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

**Patients were divided into 2 groups: those <30kg (N=11) and those >30kg (N=4), respectively;

NR=not reported;

Table 46. Indirect outcomes in RCT on rFVIIa use in pediatric surgery

Article	Study Design and rFVIIa use	Mean rFVIIa Dose (µg/kg) (SD)	Sample size		Mean age (SD)		RBC transfusion (mL) (SD) [Range]			Time to chest closure (minutes) (SD)		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Ekert 2006 ¹³⁷	RCT <i>Prophylaxis</i>	63 (20.2)	40	36	4 months	3.9 months	77 [25-250]	127 [12-400]	p=.15	98.8* (27.3)^	55.3* (29.2)^	p=.026*
Tobias 2004 ¹³⁹ †	Prospective comparative <i>Treatment</i>	90	9	8	9 years (4)	10 years (3)	NR	NR	NR	NR	NR	NR
Agarwal 2007 ¹³⁸ †	Retrospective comparative <i>Treatment</i>	43 (23)	24	22	10 days [4-32850]	7 days [2-240]	75.1 (75.3)	153.7 (132.2)	p<.001	NR	NR	NR
Niles 2008 ¹⁴⁰ †	Retrospective comparative <i>Treatment</i>	[76-282]; [26-956]	15	15	60 days (99); 5293 days (471)**	16 days (19); 4531 days (2758)**	NR	NR	NR	NR	NR	NR

†These studies did not meet inclusion criteria for detailed review in the comparative effectiveness analyses due to being poor quality (Table 14), but are included in the qualitative sensitivity discussions for this indication (in the section above, “Consideration of poor quality comparative observational studies”) and in the overall harms analyses near the end of this report.

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

^Denotes standard error

*Intention to treat data was used. Sample size=35 for usual care group because one patient had no time to chest closure data. If “per protocol” data are used (sample size=23 rFVIIa; 18 usual care) mean time to chest closure is 62.4 (5.6) in the rFVIIa group and 57.1 (6.4) in the usual care group (p=.052). Those excluded from the per protocol analysis fulfilled the primary and secondary efficacy endpoints, but either did not have 6 week followup (n=22) or had a delay in short-term followup (n=12).

**Patients were divided into 2 groups: those <30kg (N=11) and those >30kg (N=4), respectively.

Table 47. Strength of evidence for rFVIIa use in pediatric cardiac surgery

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade	
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision				
				Design	Quality	Overall Risk							
Mortality	1 ¹³⁷	40	36	RCT	Poor	No Data	No Data	No Data	No Data	No Data	No Data	No Data	Insufficient
Thrombo-embolic Events	1 ¹³⁷	40	36	RCT	Poor	High	Unknown	Direct	Imprecise	Unknown	Unknown	Unknown	Insufficient
Units of WholeBl/RBCs Tx	1 ¹³⁷	40	36	RCT	Poor	High	Unknown	Indirect	Imprecise	Weakly Favors rFVIIa	Unknown	Unknown	Insufficient
Time to Chest closure	1 ¹³⁷	40	36	RCT	Poor	High	Unknown	Indirect	Imprecise	Increase with rFVIIa	Unknown	Unknown	Insufficient

RCT=randomized controlled trial; WholeBl=whole blood; RBCs=red blood cells. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 48. Applicability assessment of study of pediatric cardiac surgery

Describe Available Evidence	Describe Overall Implications for Applicability
Population	
Patients under 1 year of age undergoing initial surgery for correction of a range of congenital cardiac abnormalities Mean age 4 months, mean weight 5.2 kg Patients with intact clotting systems Exclusions: Patients on anticoagulation or with limited life expectancy	The population included may be infrequent in clinical practice outside of major regional referral centers for pediatric cardiac surgery but compose an important subgroup of cardiac surgery patients
Intervention	
An initial prophylactic dose of 40 mcg/kg at heparin reversal then repeated if needed (55 percent) for mean dose 63 µg/kg Detailed protocol of study visits	Dose is low compared to use as treatment
Comparator	
Usual care via randomization	Other prophylactic hemostatic agents potential comparators, but not used in this setting
Outcomes	
Primary outcomes: Time to chest closure Secondary outcomes: Blood loss, transfusion requirement, length of stay, operative time, thromboembolic events, coagulation lab parameters	Surrogate/indirect outcomes related to process of care without direct link to clinical outcomes Insufficient sample size to meaningfully assess clinical outcomes
Timing and intensity of follow-up	
Initially short follow-up, but then with 6 week follow-up at return visit (but with considerable missing data) Lack of detailed protocol or reporting of thromboembolic events or other harms	More consistent, longer term outcomes desirable
Setting	
Highly specialized Australian pediatric surgical center	Likely applicable to similar cardiovascular surgery referral centers

Key Question 4.c. **Prostatectomy** and comparative effectiveness of rFVIIa

Background and Changes in Usual Care

The usual care of patients who require prostatectomy has changed considerably over the time period encompassing and since the performance of the Friederich RCT¹⁴¹ on rFVIIa use in prostatectomy (the one included study for this indication). Whereas radical retropubic prostatectomy and the Millin prostatectomy were frequent in decades past, they have been supplanted in most centers by laparoscopic approaches, which are associated with significantly less bleeding and fewer transfusions.²²⁵ For example, the authors of a letter to the editor on the Friederich RCT noted that they do not routinely prepare blood for transfusion prior to their procedures, because in most surgeries they have no transfusion requirements,²²⁶ which has been the case for others as well.²²⁷ Other changes in surgical approaches, including the use of robotics, have greatly reduced blood loss and hence transfusion requirements. These changes in practice likely account for the negligible use of rFVIIa noted in the Premier database.

RCT Design and Intervention Characteristics

The only identified study of rFVIIa use in prostatectomy was the small Friederich RCT¹⁴¹ that did not report any Novo Nordisk sponsorship and was deemed to be of fair quality (Table 49). It evaluated placebo versus prophylactic use rFVIIa in patients who were not on anticoagulation and were undergoing one of two possible procedures: radical retropubic prostatectomy for prostate cancer or the Millin procedure for benign prostatic hypertrophy. Study drug or placebo was administered after lymph node dissection in the former and placement of guiding sutures in the latter. The RCT enrolled 12 usual care patients and an aggregate of 24 rFVIIa patients, of whom eight received 20 µg/kg and 16 received 40 µg/kg, with the patients who received the different procedures being well balanced between groups. Groups also appeared well balanced at baseline on age and weight, but there was no other information given on other potentially relevant characteristics. Analyses were intention-to-treat and follow-up occurred at 10 days. There was no single primary outcome identified, but the study reported on RBC transfusion requirements, mortality, thromboembolic events, and the duration of operation (OR time).

Place of studies within analytic framework. The Friederich RCT examined prophylactic use of rFVIIa in prostatectomy (versus treatment or end-stage use, which are other potential uses, as outlined in our Analytic Framework (Figure 1)).

Comparison to studies on other indications. Studies of adult cardiac and liver transplantation also evaluated prophylactic use of rFVIIa. The mean age of the prostatectomy patients (61-64) was comparable to that of the intracranial hemorrhage and adult cardiac surgery patients. The single-dose infusion of either 20 or 40 µg of rFVIIa encompassed the lowest mean dose of any indication.

Outcomes

There were no deaths in either study group (Table 50). One patient in the 20 µg/kg dose group experienced a myocardial infarction at day 14, the only thromboembolic event identified

in the study. The RBC transfusion requirements were significantly reduced in the rFVIIa group, as was the OR time (Table 51).

Comparison to Premier Database

The very few Premier database patients who received rFVIIa were older (mean age, 69 years) than the study patients (mean age, 61-64 years). There were no deaths in either sample.

Strength of Evidence

The strength of evidence was insufficient for all outcomes (Table 52). While the RCT was fair in quality, the patient sample size was low, which limits certainty regarding effect size estimates. In addition, the low event rates for thromboembolic events and mortality outcomes contributed to the determination of imprecision for these outcomes.

Applicability

Overall applicability of the evidence is poor for prophylactic use in the populations targeted—patients undergoing retropubic prostatectomy for prostate cancer or benign hyperplasia but not on anticoagulation (Table 53). The baseline transfusion requirements and amount of bleeding are much higher in the study patient population than in the general population of patients undergoing prostatectomy and study patients may be younger as well, both of which make the population applicability poor. In addition, the “usual care” approach to prostatectomy has evolved into something very different, in most cases, from the surgeries evaluated in the included RCT, thereby making the applicability of the comparator also poor. Specifically, surgeons now favor laparoscopic or robotic approaches and alternative surgeries that, on average, incur much less blood loss than their predecessor procedures, thus altering the context of rFVIIa administration. Regarding other criteria of applicability, the dose of rFVIIa was on the lower end of those observed, but was relatively narrow, granting it fair applicability. Other limitations to applicability include the emphasis on surrogate measures, the short follow-up time (10 days), and the setting of the study being an academic rather than community hospital, the latter of which is more common in practice.

Conclusions

Current evidence is insufficient for comparing the harms and benefits of rFVIIa use in prostatectomy. In addition, the usual care for prostatectomy has likely evolved far beyond the standard of care employed in the RCT, making its relevance to current practice uncertain.

Table 49. General characteristics of comparative studies on off-label rFVIIa use for prostatectomy

Article	Study Design	Study Setting and Time Period	Sample Size and Dose (µg/kg)	Population Characteristics			Outcomes Evaluated	
				Mean Age (SD) [Range]	Inclusion/Exclusion Criteria and Other Patient Characteristics	Direct	Indirect	
Friederich 2003 ¹⁴¹	RCT Prophylaxis	1 center Amsterdam, Netherlands	All Rx: 24 20: 8 40: 16	Rx: 20: 61 (8.9) 40: 64 (8.5)	Inclusion: -age 18-85 -scheduled to undergo radical retropubic prostatectomy for prostate cancer, or Millin prostatectomy for prostate hypertrophy Exclusion: -treatment with anticoagulants within 48 hours preoperatively, or treatment with aspirin within 7 days preoperatively -known congenital or acquired hemostatic disorder -unstable coronary artery disease or angina pectoris class III/IV -history of venous thromboembolism of known thrombophilic state -known advanced liver disease, liver cirrhosis, or acute hepatitis	Mortality	Transfusion requirements (e.g. RBCs, FFP)	
		Time period not reported.	Ucare: 12	Ucare: 63 (8.3)				Adverse events including TE events

SD=standard deviation; Rx=treatment group(s); Ucare=usual care; NR=not reported; TE=thromboembolic; RBCs=red blood cells; FFP=fresh frozen plasma;

Table 50. Mortality and thromboembolic events in RCT on rFVIIa use in prostatectomy

Article	Study Design and rFVIIa use	rFVIIa Dose (µg/kg)	Sample size		Mean age (SD)		Mortality rate			Thromboembolic events rate ^{&}		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Friederich 2003 ¹⁴¹	RCT <i>Prophylaxis</i>	20 40	8 16	12	61 (8.9) 64 (8.5)	63 (8.3)	0 0	0	NR	0.125 0	0	NR

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the study.

[&]Thromboembolic event rates were calculated by dividing the number of thromboembolic events by the sample size, not the number of patients who experienced thromboembolic events. Therefore, the rates reported here may differ slightly from those reported in each study. The tests of statistical significance presented are those reported by the individual studies and are not based upon the thromboembolic event rates reported in this table.

Table 51. Indirect outcomes in RCT on rFVIIa use in prostatectomy

Article	Study Design and rFVIIa use	rFVIIa indication and dose (µg/kg)	Sample size		Mean age (SD)		RBC transfusion (SD)			OR time (minutes) (SD)		
			rFVIIa	Usual care	rFVIIa	Usual care	rFVIIa	Usual care	Sig	rFVIIa	Usual care	Sig
Friederich 2003 ¹⁴¹	RCT <i>Prophylaxis</i>	20	8	61 (8.9)	0.6 (0.3)							
		40	16	64 (8.5)	0 (0)	1.5 (0.4)	p=.057 p=.0003	126 (21) 120 (15)	180 (16)	p=.034 p=.014		

Sig=tests of statistical significance between the usual care and rFVIIa group(s). The p-values presented are those reported by the individual studies.

Table 52. Strength of evidence for rFVIIa use in prostatectomy

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
		rFVIIa	Usual Care	Domains Pertaining to Risk of Bias			Consistency	Directness	Precision			
				Design	Quality	Overall Risk						
Mortality (10 day)	1 ¹⁴¹	24	12	RCT	Fair	Medium	Unknown	Direct	Imprecise	Unknown	Unknown	Insufficient
Thrombo-embolic Events	1 ¹⁴¹	24	12	RCT	Fair	Medium	Unknown	Direct	Imprecise	Unknown	Unknown	Insufficient
Units of RBCs Transfused	1 ¹⁴¹	24	12	RCT	Fair	Medium	Unknown	Indirect	Imprecise	Favors rFVIIa	Yes	Insufficient
OR Time	1 ¹⁴¹	24	12	RCT	Fair	Medium	Unknown	Indirect	Imprecise	Favors rFVIIa	No	Insufficient

RCT=randomized controlled trial; RBCs=red blood cells; OR=operating room. See Tables 4 to 7 for definitions of study quality and strength of evidence domains and designations.

Table 53. Applicability assessment of study on prostatectomy

Describe Available Evidence	Describe Overall Implications for Applicability
Population Two distinct populations are studied: -Retropubic prostatectomy for cancer -Retropubic prostatectomy for benign hyperplasia -Patients with intact clotting system Exclusions: Patients on anticoagulation	rFVIIa use for this indication very rare in U.S. and evidence is not relevant Transfusion requirements and blood loss are much higher for the control group than they are in the general population of patients undergoing prostatectomy
Intervention Prophylactic use of rFVIIa at 20 or 40 mcg/kg Usual care, including transfusion protocol	Dose is low compared to use as treatment or even to prophylactic use in other indications
Comparator Usual care via randomization	Advances in usual care have led to the application of other surgical approaches that minimize blood loss (e.g., TURP, laparoscopic surgery) Other prophylactic hemostatic agents potential comparators, but not used in this setting
Outcomes Primary outcomes: Red blood cell transfusions and perioperative blood loss Secondary outcomes: length of stay, operative time, thromboembolic events, coagulation lab parameters	Surrogate/indirect outcomes related to process of care without direct link to clinical outcomes Insufficient sample size to meaningfully assess clinical outcomes
Timing and intensity of follow-up Follow-up for duration of hospitalization (but with long, 10 day stays) Detailed protocol for ascertainment of MI and DVT	Longer term outcomes would be desirable
Setting An academic hospital in the Netherlands	May have limited applicability to U.S. practices

Evaluation of Harms in Patients Who Received rFVIIa: Comparing the Premier, RCT, and Observational Study Data

Given concerns about the potential harms of rFVIIa, we sought to compare and contrast the absolute rates of morbidity and mortality associated with the use of rFVIIa across different types of evidence—that is, comparative and non-comparative data. We therefore examine mortality and thromboembolic event outcomes for the Premier database, RCTs, and observational studies. Additionally, we sought to evaluate the association of key predictors (study design, clinical indication for the use of rFVIIa, mean patient age, and total dose of rFVIIa) with these outcomes. For these analyses, we included data from the intervention arms of the RCTs and comparative observational studies, and from those non-comparative observational studies that reported relevant data for 15 or more patients (Table 54).

In prior sections of the report only comparative observational studies of fair or good quality were reviewed in detail. However, in this section all comparative observational studies are included, along with their non-comparative counterparts. Also note that we are unable to report on thromboembolic events following rFVIIa use in the Premier database.

Findings

Across clinical indications, the mortality rate ranged extremely widely from 0 to 0.87 and the thromboembolic event rate ranged from 0 to 0.39, depending on the clinical indication for use of rFVIIa, age, dose, and study design. Figure 25 presents the adjusted mortality rates by age and indication for the rFVIIa groups in the RCTs—it shows the enormous heterogeneity of effects across indications. Adjusted thromboembolic rates varied similarly (Figure 26).

For each indication, Figures 27 and 28 present the mean mortality and thromboembolic event rates, respectively, by study design. In general, the mortality rates were lowest in the RCTs and highest in the Premier database. Similarly, in general, the thromboembolic rates were generally lowest in the RCTs and highest in the observational studies.

Figures 29 through 32 present the mortality and thromboembolic rates by mean age and total rFVIIa dose. In general, there was no apparent pattern relating age and mortality or age and thromboembolic events, although it is notable that the ages tended to cluster for a given indication. There was also no apparent pattern between dose and mortality or dose and thromboembolic events (with the possible exception of brain trauma, which is discussed further below). Figure 33 displays the mortality by thromboembolic event rate, and, again, there was no readily apparent pattern of association.

Intracranial Hemorrhage. In contrast to other clinical indications, most of the harms data for rFVIIa use in intracranial hemorrhage comes from RCTs rather than comparative observational studies (Figures 27 and 28 and Table 54). Four RCTs evaluated harms for ICH: in their various dosing arms mortality ranged from 0 to 0.375 and total thromboembolic events ranged from 0 to 0.33. Four comparative observational studies reported harms for ICH and, in a small number of patients, other forms of intracranial hemorrhage. Mortality ranged from 0.13 to 0.43, and total thromboembolic events ranged from 0.04 to 0.2. Mortality in the Premier database was higher (0.34) than in the aggregate RCTs and observational studies. Thromboembolic events were higher in the observational studies than in the RCTs.

The RCTs excluded patients on anticoagulants, whereas these patients were included in the observational studies and the Premier database. One observational study⁹¹ had a significantly higher mortality than the other studies (0.42). It specifically analyzed patients with warfarin-related ICH and other patients who were considered to be at “especially high risk” for hematoma growth.

Body trauma. Across study designs, mortality rates among patients receiving rFVIIa for body trauma were among the highest of all the clinical indications, although, again, the range was wide. The two RCTs reported the following event rates: mortality 0.25 and thromboembolism 0.03 in the blunt trauma trial and mortality 0.24 and thromboembolism 0.06 in the penetrating trauma trial. Twelve observational studies reported mortality and/or thromboembolic event rates among trauma patients. Rates for mortality ranged from 0.07 to 0.58 and thromboembolism ranged from 0 to 0.12. Mortality in the Premier database (0.33) was somewhat higher than that of the RCTs (Figures 27 and 28 and Table 54).

The wide range of mortality across study types may be due to differences in inclusion criteria. The RCT⁹⁶ excluded patients over 65 years, those receiving greater than eight units of RBCs prior to arrival at the hospital, and those with severe acidosis or base deficit. Another study^{98, 182} of combat trauma patients reported that only 28 percent of patients would have met inclusion for the RCT.⁹⁶ Several of the observational studies included patients on warfarin or other anticoagulants. As noted earlier in the report, we are aware of a recently concluded phase III trial of rFVIIa in trauma that also uses restrictive inclusion criteria—only two percent of patients from the largest Australian registry¹⁰² would have met its inclusion criteria.

The rate of thromboembolic events in trauma was somewhat lower than for other clinical indications. This may be the case because trauma patients were generally younger and healthier than patients receiving rFVIIa for other indications. It may also reflect differences in harms ascertainment, given the high rate of mortality in trauma (i.e., if patients die early, other harms may not be attributed to them). One observational study²²⁸ with a protocol for identifying thromboembolic complications among trauma patients who received rFVIIa (N=242) identified a thromboembolic event rate of 0.11—which was higher than the rates identified for the RCTs but still lower than the rates reported for other rFVIIa indications, particularly cardiac surgery.

Brain trauma. One RCT evaluated harms among rFVIIa patients with bleeding due to TBI. This study had five arms, each of which evaluated a different rFVIIa dose. Mortality in this study ranged from 0 to 0.33 between dosing arms and may be linear with dose, although the study was quite small, so that no definitive conclusions can be made. Interestingly, total thromboembolic events ranged from 0 to 0.21 and did not appear to be associated with dose. The comparative observational study and non-comparative observational study reported quite different mortality and thromboembolic rates from each other (0.34 and 0.07 for the former and 0.21 and 0 for the latter). Patients included in the Premier database had higher mortality (0.33) and were generally older than the patients in the RCTs (Figures 27 and 28 and Table 54).

Mortality in the comparative observational study¹⁰⁷ was significantly higher than in the RCT.¹⁰⁶ This may be due to differences in inclusion criteria: the RCT included patients with a Glasgow Coma Scale (GCS) of 4 to 14 and excluded patients with planned neurosurgery, whereas the observational study limited rFVIIa use to coagulopathic patient with possibly more severe TBI (GCS less than 9, INR greater than 1.4) who required neurosurgical management of their hemorrhage.

Liver Transplantation. Four RCTs evaluated liver transplantation patients: their reported mortality ranged from 0.02 to 0.08. However, two RCTs^{110, 111} did not report mortality by arm (treatment versus placebo); thus, this range underestimates the true mortality rate among patients receiving rFVIIa in RCTs. Rates of thromboembolic events ranged from 0 to 0.19. Again, this range underestimates the total thromboembolic event rate for patients in RCTs because one study¹¹¹ did not report venous events by arm (treatment versus placebo). Four observational studies evaluated harm in liver transplantation: mortality ranged from 0 to 0.07, and the rate of thromboembolic events ranged from 0 to 0.17. Mortality was substantially higher in patients from the Premier database (0.38) than in other studies (Figures 27 and 28 and Table 54).

The treatment dose administered in the RCT by Lodge¹¹⁰ was substantially higher than in the other RCTs,¹¹¹⁻¹¹³ and Lodge¹¹⁰ reported a significantly higher rate of thromboembolic events—although it may be that the other studies simply under reported such harms. All studies of liver transplant recipients provided rFVIIa prophylactically and, in most cases, at lower doses (with the exception of the Lodge RCT) than in other indications. This may account, in part, for the relatively lower rates of mortality and thromboembolic harms among liver transplant recipients compared to patients who received rFVIIa for other indications.

Adult Cardiac Surgery. Two RCTs reported data on adult cardiac surgery. The reported mortality rates in the rFVIIa arms of the RCTs ranged from 0 to 0.11 and total thromboembolic event rates ranged from 0.06 to 0.22. Mortality in the Premier database (0.23) was high compared with the RCTs and comparative observational studies (Figures 27 and 28 and Table 54).

The mortality rates in the observational studies of cardiac surgery were generally higher than those reported in the RCTs (mortality, range 0 to 0.87). This may have to do with differences in inclusion criteria—namely, that the RCTs typically excluded the most severely ill patients, whereas observational studies often included such patients. For instance, one observational study¹²⁷ included only patients undergoing orthotopic heart transplant or LVAD implantation, and another¹²² enrolled patients undergoing aortic dissection repair.

Pediatric Cardiac Surgery. Harms were reported in the intervention groups of the one RCT and three observational studies of pediatric cardiac surgery. Overall, the rates of thromboembolic events were lower in the pediatric cardiac surgery studies than in the adult studies (Table 54). Mortality was not reported in the RCT, but was lower in the observational studies than in the adult studies or the Premier database.

Prostatectomy. There was one RCT of prostatectomy which reported no mortality and one myocardial infarction (Table 54).

Conclusions

Because this analysis includes data from observational studies and the Premier database, as well as from RCTs, it usefully highlights areas of consistency and contrast among different data sources. Across all indications except for prostatectomy (where no deaths were reported in any data set), mortality rates among patients in the Premier database were uniformly higher than the mortality rates in the RCTs, emphasizing that patients receiving rFVIIa in practice may differ in important ways from those in the included trials. Such distinctions may alter the risk-benefit

profile of rFVIIa administration for real-world populations. Because of the limitations of our data, we can not comment further on how to interpret these differences, except to say that extrapolation from our comparative effectiveness review to real-world contexts, where the patients appear generally to be older and sicker, should be undertaken with appropriate caution.

Table 54. Harms noted in the analysis of rFVIIa use

Study Design	Number of Studies	Study References	Mean Age Range (yrs)	Mean rFVIIa dose (mcg/kg)	Sample Size	Mortality	Thromboembolic Events
Intracranial hemorrhage							
Premier	-		64.7	-	1235	0.34	-
RCT	4 (with 2 to 6 arms)	Mayer 2005a ²³ , Mayer 2005b ⁸⁶ , Mayer 2008 ⁸⁸ , Mayer 2006 ⁸⁷	51 to 72	5 to 160	6 to 297 per arm	0 to 0.38	0 to 0.33
Comparative observational	4	Hallevi 2008 ⁹² , Brody 2005 ⁹¹ , Pickard 2000 ⁹⁰ , Ilyas 2008 ⁸⁹	60 to 77	80	5 to 46	0.13 to 0.43	0.04 to 0.2
Non-comparative Observational	3	Sutherland 2008 ⁹³ , Herbertson 2008 ⁹⁴ , Nussbaum 2009 ⁹⁵	8 to 68	60 to 100	15 to 20	0.13 to 0.22	0 to 0.44
Body trauma							
Premier	-		52.8	-	2136	0.33	-
RCT	1-Blunt	Boffard 2005 ⁹⁶	33	400	69	0.25	0.03
	1-Penetrating	Boffard 2005 ⁹⁶	29	400	70	0.24	0.06
Comparative Observational	5	Rizoli 2006 ⁹⁷ , Fox 2009 ⁹⁹ , Dutton 2004 ¹⁰⁰ , Harrison 2005 ¹⁰¹ , Nascimento 2008 ¹⁸¹	28 to 41	60 to 100	29 to 81	0.07 to 0.58	0.07-0.12*

Table 54. Harms noted in the analysis of rFVIIa use (continued)

Study Design	Number of Studies	Study References	Mean Age Range (yrs)	Mean rFVIIa dose (mcg/kg)	Sample Size	Mortality	Thromboembolic Events
Non-comparative Observational	7	Cameron 2007 ¹⁰² , Felfernig 2007 ¹⁰³ , Thomas 2007 ²²⁸ , Martinowitz 2005 ¹⁰⁴ , Perkins 2007 ¹⁸² †, Alten 2009 ¹⁰⁵ , Herbertson 2008 ⁹⁴	7 to 44	68 to 140	15 to 242	0.13 to 0.42	0 to 0.11
Brain trauma							
Premier	-		63.3	-	1224	0.34	-
RCT	1 (with 5 arms)	Narayan 2008 ¹⁰⁶	51.5	40 to 200	11 to 14 per arm	0 to 0.33	0 to 0.21
Comparative observational	1	Stein 2008 ¹⁰⁷	29.9	-	29	0.34	0.21
Non-comparative Observational	1	Bartal 2007 ¹⁰⁹	61	59	15	0.07	0
Liver transplantation							
Premier	-		51.8	-	33	0.38	-
RCT	4 (with 1 to 3 arms)	Lodge 2005 ¹¹⁰ , Planinsic 2005 ¹¹¹ , Pugliese 2007 ¹¹² , Liu 2009 ¹¹³	49 to 53	20 to 412	10 to 63 per arm	0.02 to 0.08 [#]	0 to 0.19 [^]
Comparative Observational	4	Hendriks 2001 ¹¹⁴ , Kalicinski 2005 ¹¹⁶ , Niemann 2006 ¹¹⁷ , De Gasperi 2005 ¹¹⁵	13 to 48	30 to 80	6 to 28	0 to 0.07	0 to 0.17
Adult cardiac surgery							
Premier	-		65.3	-	2419	0.23	-
RCT	2 (with 1 to 2 arms)	Diprose 2005, ¹¹⁸ Gill 2009 ¹¹⁹	63 to 64	40 to 90	9 to 68	0 to 0.11	0.06 to 0.22
Comparative Observational	4	Bowman 2008 ¹²⁴ , Gelsomino 2008 ¹²¹ , von Heymann 2005 ¹²³ , Trowbridge 2008 ¹²⁵	58 to 70	18 to 100	17 to 40	0.05 to 0.38	0 to 0.11
Non-comparative Observational	13	Karkouti 2006 ²¹⁵ , Tritapepe 2007 ¹²² , Filsoufi 2006 ¹²⁶ , Gandhi 2007 ¹²⁷ , Hyllner 2005 ¹²⁸ , McCall 2006 ¹²⁹ , Raivio 2005 ¹³⁰ , Aggarwal 2004 ¹³¹ , Karkouti 2008 ¹³² , Dunkley 2008 ¹³³ , Bruckner 2009 ¹³⁴ , Masud 2009 ¹³⁵ , Hsia 2009 ¹³⁶	51 to 68	15 to 103	16 to 503	0 to 0.87	0 to 0.39

Table 54. Harms noted in the analysis of rFVIIa use (continued)

Study Design	Number of Studies	Study References	Mean Age Range (yrs)	Mean rFVIIa dose (mcg/kg)	Sample Size	Mortality	Thromboembolic Events
Pediatric cardiac surgery							
Premier	-		2.6	-	274	0.22	-
RCT	1 (with 1 arm)	Ekert 2006 ¹³⁷	0.3	63	40	-	0
Comparative Observational	3	Agarwal 2007 ¹³⁸ , Tobias 2004 ¹³⁹ , Niles 2008 ¹⁴⁰	0 to 9	60 to 286	4 to 24	0	0 to 0.08
Prostatectomy							
Premier	-		68.9	-	15	0	-
RCT	1 (with 2 arms)	Friederich 2003 ¹⁴¹	61 to 64	20 to 40	8 to 16	0	0 to 0.13

*The rate of thromboembolic events is based on a continuation of Rizoli et al.⁹⁷ with 72 patients.²²⁹

†Data on mortality and thromboembolic events from Perkins et al.¹⁸² (an overlapping non-comparative study) are used instead of Spinella et al.⁹⁸ (a comparative observational study analysed in the body trauma section above) because the former has a larger sample size.

#Mortality is underestimated because 2 deaths each in Lodge et al.¹¹⁰ and Planinsic et al.¹¹¹ were not reported by treatment arm.

^Thromboembolic events are underestimated because only arterial thromboembolic events were counted in Planinsic et al.¹¹¹

Figure 25. Adjusted mortality rate by age from the RCTs

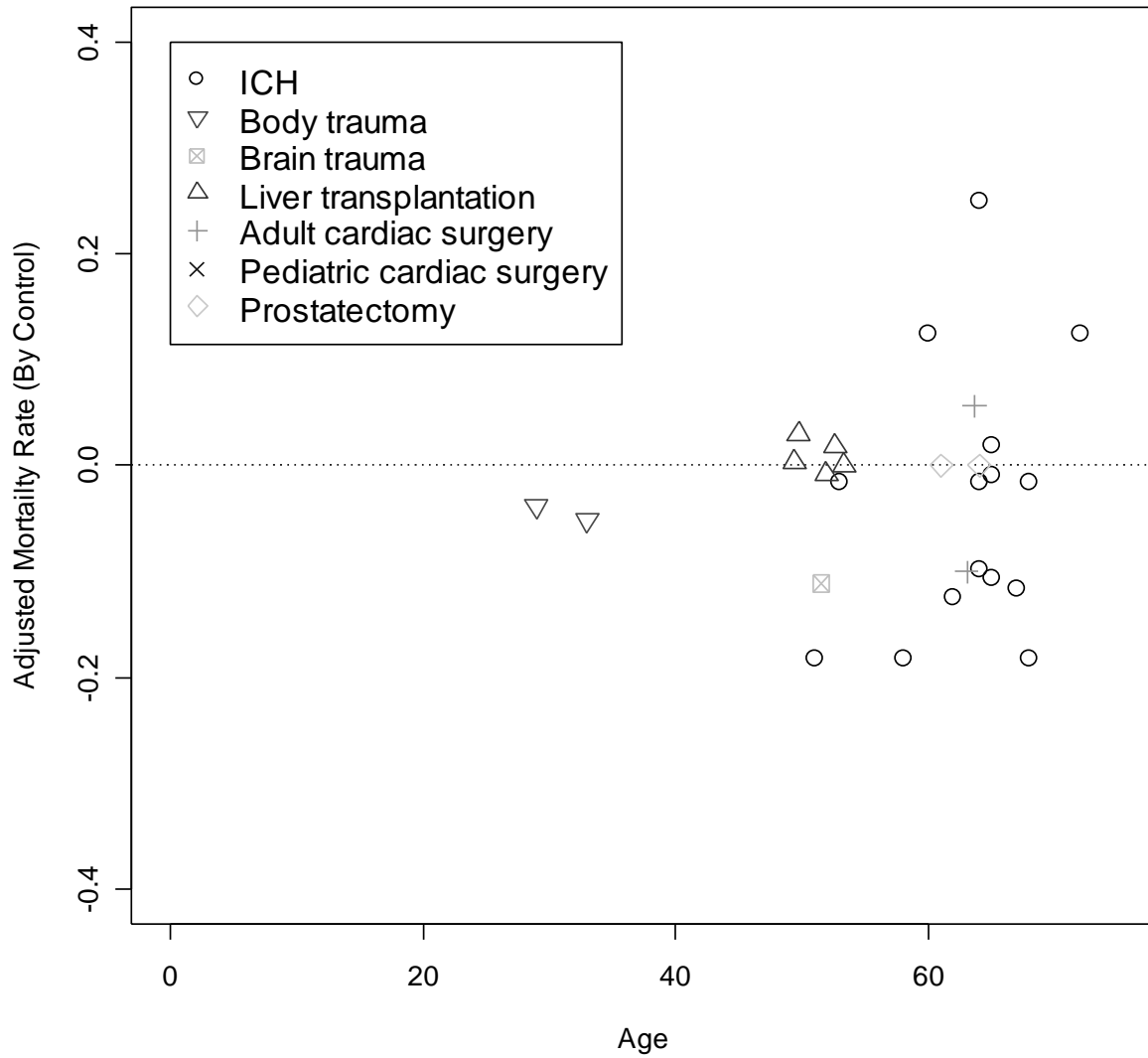


Figure 26. Adjusted all thromboembolic event rate by age from the RCTs

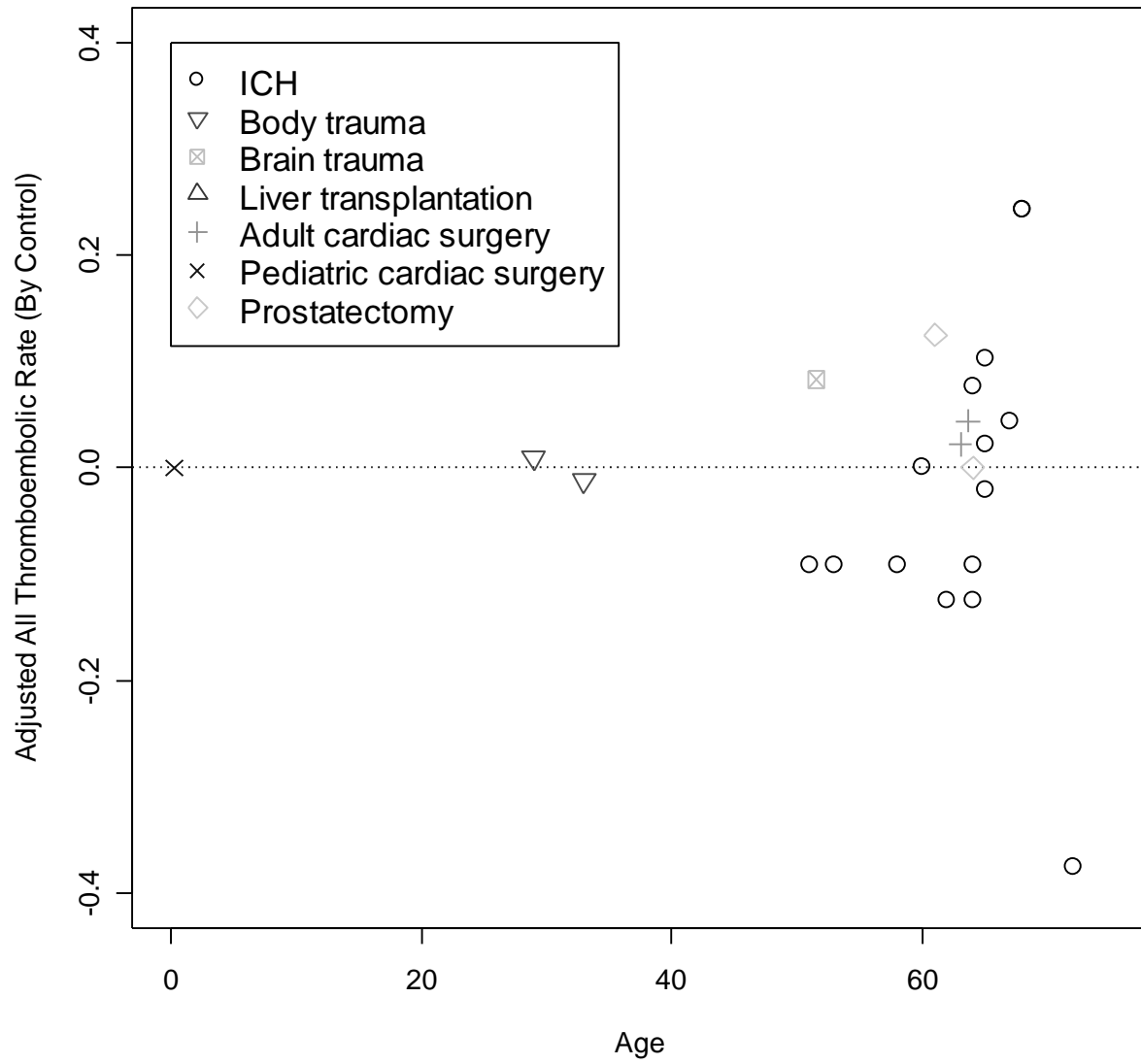


Figure 27. Weighted mean mortality (95 percent CI) by study design for each indication

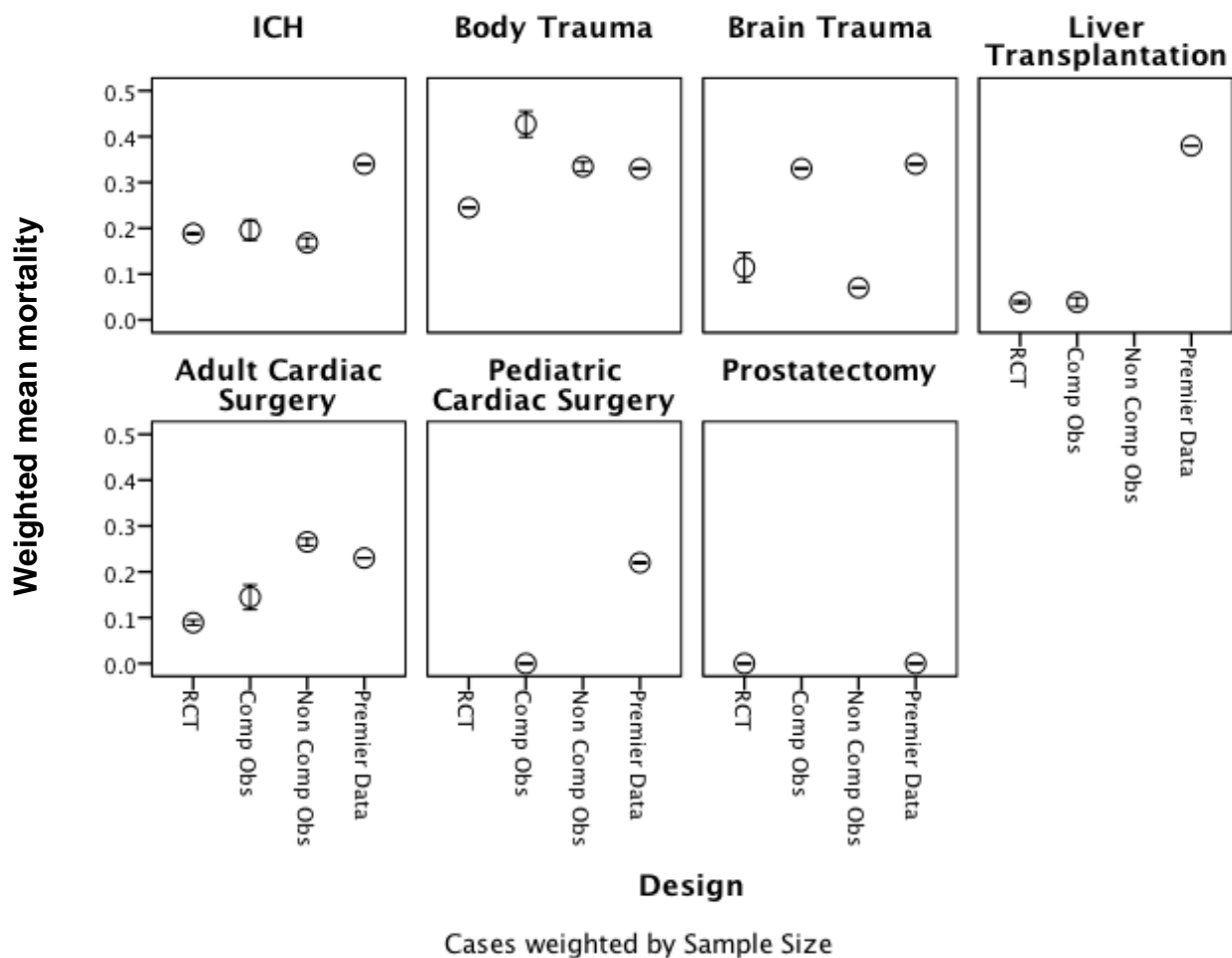


Figure 28. Weighted mean total thromboembolic event rate (95 percent CI) by study design for each indication

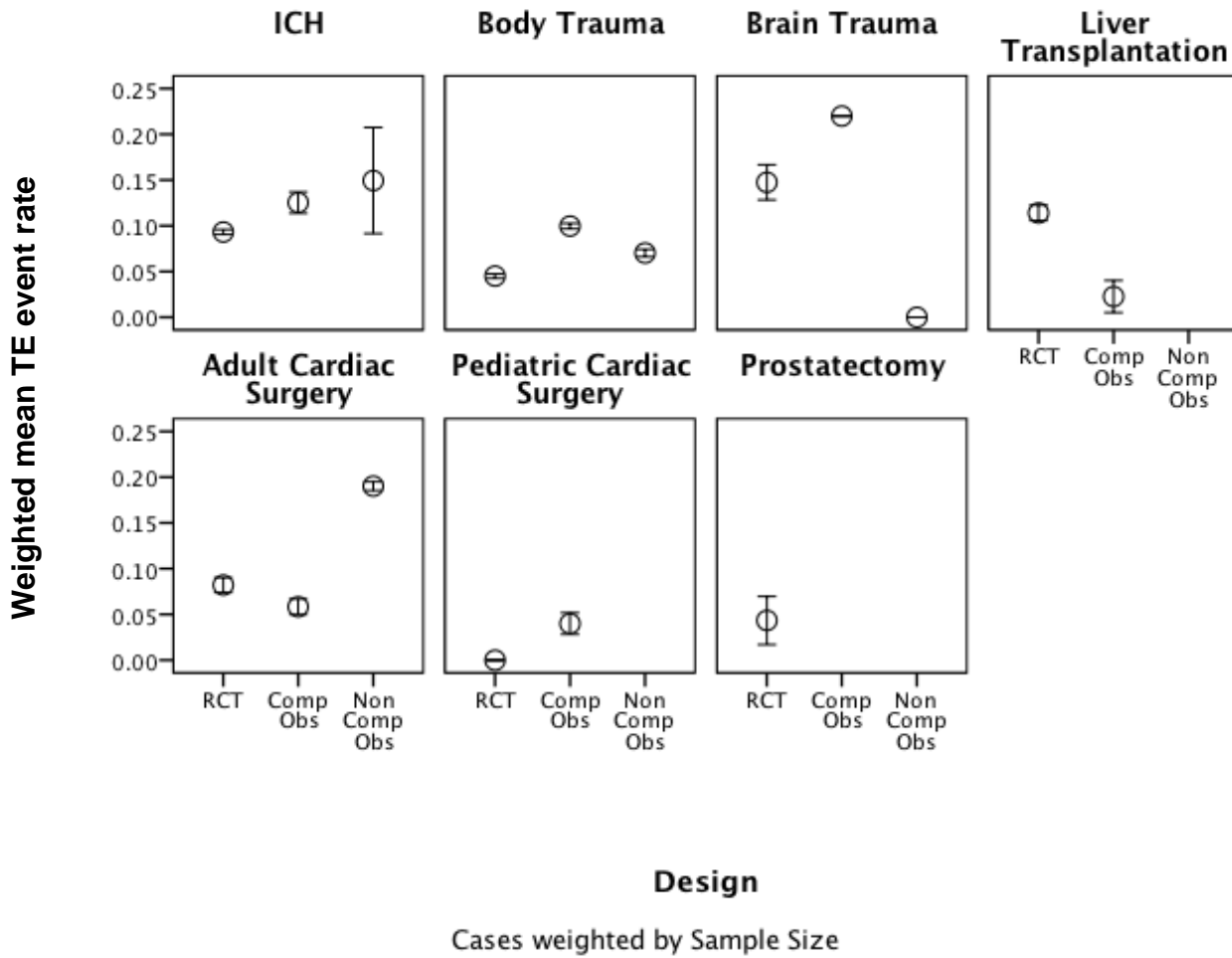
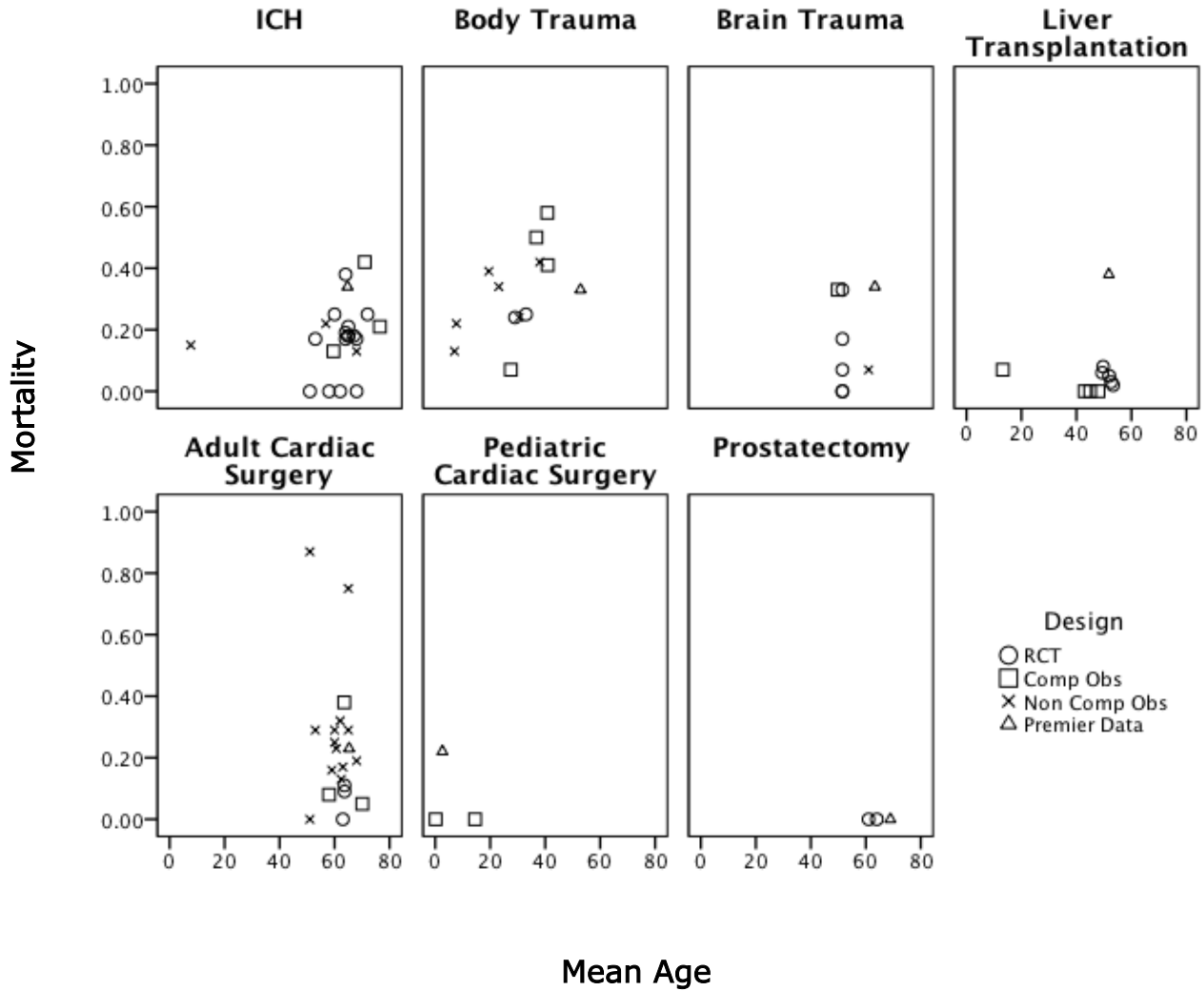
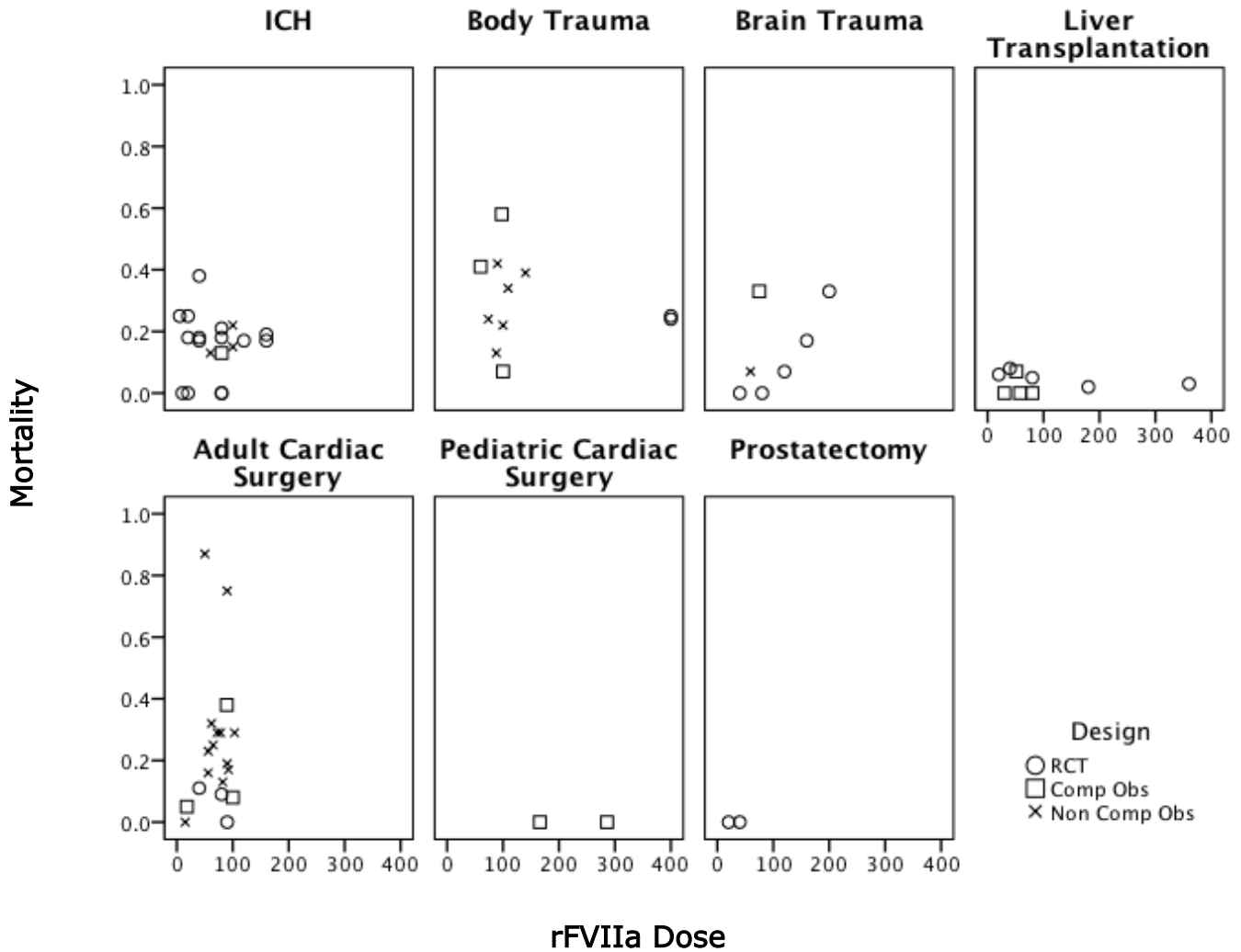


Figure 29. Mortality by mean age per indication



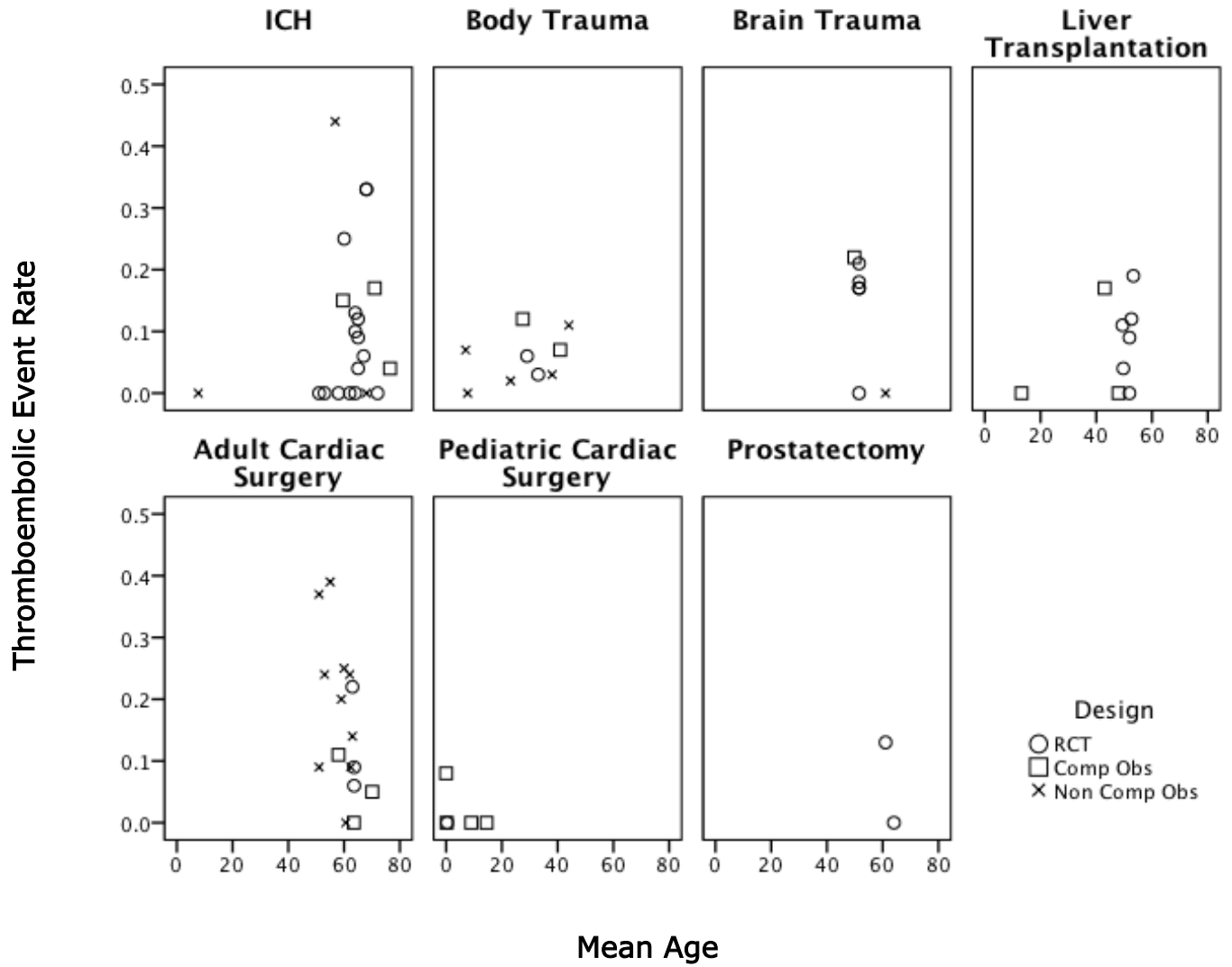
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 30. Mortality by rFVIIa dose per indication



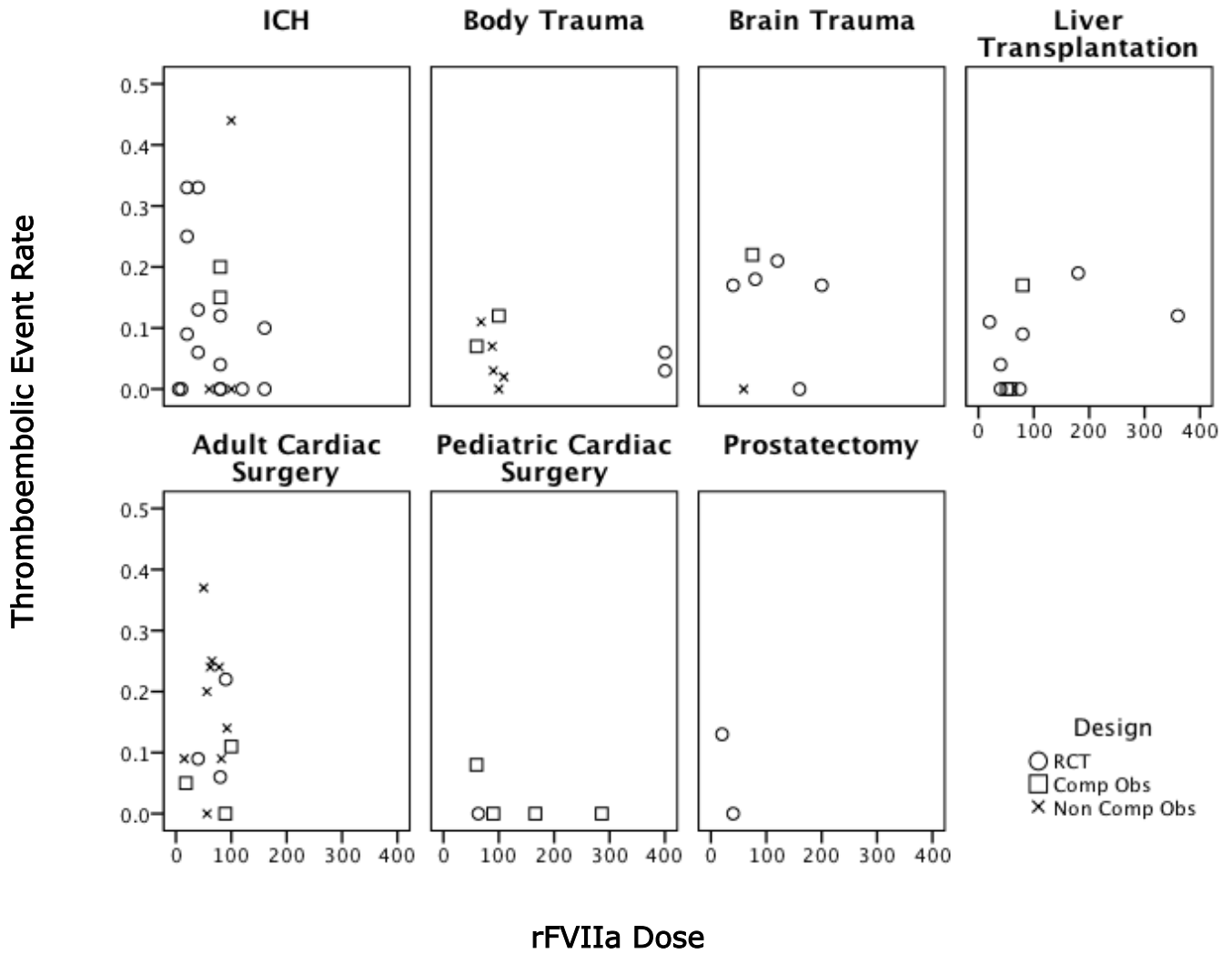
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 31. Thromboembolic events by mean age per indication



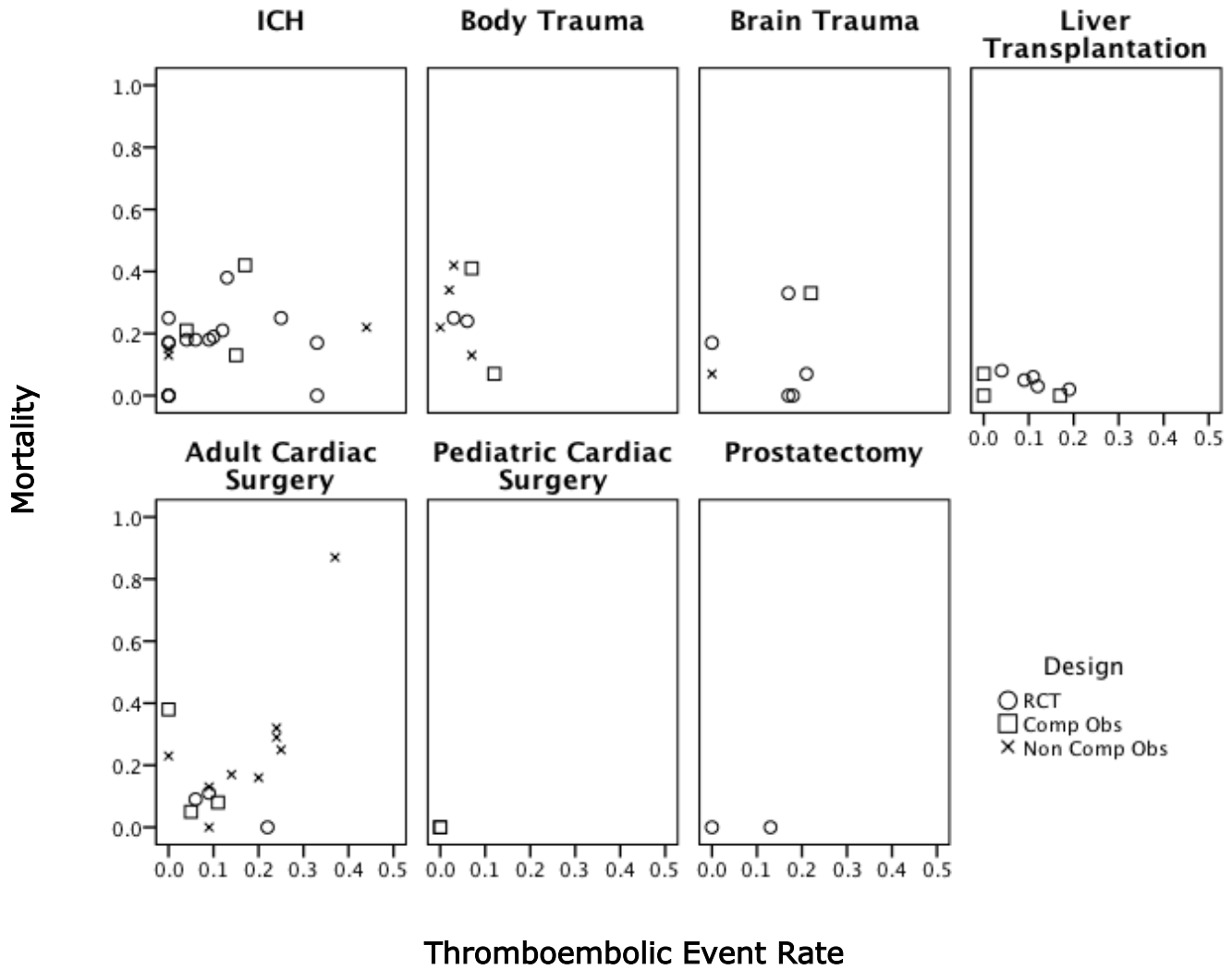
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 32. Thromboembolic events by rFVIIa dose per indication



Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 33. Association of mortality and thromboembolic event rate



Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Summary and Discussion

Findings

The use of rFVIIa is increasingly frequent for a range of indications not directly related to its FDA approved use in hemophilia. The drug's biology suggests the potential for hemostatic benefits in uncontrolled bleeding and a risk of thromboembolic adverse effects. Wide in-hospital diffusion of this expensive medication (approximately \$10,000 for a single 90 µg/kg dose in a 70 kg patient) has occurred despite limited comparative information.

Based on our evaluation of the Premier database, off-label in-hospital use was estimated to be 125 “cases” (defined as any rFVIIa use during hospitalization) 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 rate of increase may be plateauing for many indications. In 2008, the most frequent off-label in-hospital indications for rFVIIa use were adult cardiac surgery, trauma (both at the body and brain), and intracranial hemorrhage, which together account for 68 percent of such use. In contrast, uses for the indications of liver transplantation and prostatectomy were rare. The mean in-hospital mortality rate of 27 percent among cases suggests that rFVIIa is being used in high-risk patient populations that may be more uniformly sick than patients enrolled in studies of rFVIIa. We chose to analyze use by case because it captures the medical decision-making component of care about whether to use or not use rFVIIa for a given patient. Analyses by dosing, rather than cases of use, could have different findings.

Evaluation of the comparative effectiveness of rFVIIa versus usual care for specific indications is limited by a narrow evidence base. We present a summary of our findings in Figure 34. Seventy-four articles met our inclusion criteria for review. Seventeen (23 percent) evaluated off-label indications not included in our subsequent comparative effectiveness review of intracranial hemorrhage, trauma, liver transplantation, cardiac surgery, and prostatectomy. The most frequent indications for rFVIIa use among these were bleeding related to liver disease other than transplantation, obstetrics, neurosurgical procedures, and hematologic malignancies.

Based on the Premier database analysis, these additional off-label indications that are frequently present in the evaluative literature but are not assessed for effectiveness in this report, accounted for eight percent of in-hospital community practice use in 2008. There were other off-label indications that were prominent in the Premier database but *not* in the literature—including gastrointestinal bleeding not related to liver disease and primary and secondary clotting disorders, which together account for 12 percent of off-label rFVIIa use in clinical practice. Finally, mortality rates among patients in the Premier database were often higher than the rates among patients who received rFVIIa for similar indications in our effectiveness review, which may suggest that rFVIIa is administered more frequently for end-stage use in the community than it is in published studies (where it is more frequently employed for treatment use).

For the indications whose efficacy we evaluated, there remained 57 studies: 14 randomized controlled trials, 24 comparative observational studies, and 19 non-comparative reports from registries or cohorts (with cohorts limited to those with at least 15 patients). Of the comparative observational studies, the 10 with the highest quality were used for detailed analyses (of effectiveness and harms), while the remaining 12 were used primarily for the harms analyses.

Overall study quality was fair to poor and the strength of evidence low, with the exception of randomized controlled trials for ICH and certain meta-analyses of adult cardiac

surgery outcomes. These determinations were made on the basis, most frequently, of the presence of a high risk of bias and imprecise estimates of effect. In addition, clinical efficacy was often defined via indirect/surrogate outcomes, such as transfusion requirements, rather than through direct endpoints such as mortality or functional outcome. In cases where we had evidence regarding both indirect and direct outcomes, a close link between improvements in intermediate outcomes (e.g., cessation of bleeding) and improvements in direct outcomes (e.g., mortality) was not substantiated by the evidence. Possible explanations for this are that use of rFVIIa, despite its reversal of bleeding, cannot reverse more systemic derangements that ultimately influence direct outcomes or that potential harms produced by the administration of rFVIIa (e.g., thromboemboli or other harms not yet identified) outweigh the benefits observed for some selected intermediate outcomes.

There was considerable heterogeneity around the dose and administration of rFVIIa, which made comparisons across studies difficult. Most randomized controlled trials evaluated the effectiveness of a single injection of rFVIIa, albeit with wide dosing range. In contrast, most comparative cohort studies evaluated the use of rFVIIa with more flexible dosing strategies: those that allowed for repeated doses of rFVIIa and determinations by the physicians regarding the exact dose infused. For certain indications, rFVIIa was studied solely as a prophylactic agent (e.g., in liver transplantation) or a treatment agent (e.g., intracranial hemorrhage and traumatic bleeding), whereas in still others it was evaluated, in separate studies, as both a prophylactic and therapeutic agent (e.g., cardiac surgery). The tendency, again not uniform, was for the mean dose of rFVIIa to be lower in prophylaxis trials than in therapeutic trials, and lower for repeated doses in studies of therapeutic efficacy, particularly those that were observational.

The potential for publication bias is an important consideration in any systematic review. The drug's manufacturer, Novo Nordisk, has played a substantial role in sponsoring, designing, directing, analyzing, and publishing much of the RCT evidence available on rFVIIa. The potential conflict inherent in this role warrants special attention to several forms of bias that may affect the validity of research findings. In particular, publication bias may affect validity both through the failure to publish unfavorable results and delay in publishing results. We have found no definitive instances of publication bias regarding rFVIIa. We note, however, that the results of one intracranial hemorrhage and two body trauma RCTs—directed by Novo Nordisk and completed in 2007 and 2008, respectively—have yet to be published. The small number of studies available on rFVIIa precludes the use of standard meta-analytic tools, such as funnel plots, that would allow for the evaluation of publication bias across the aggregate of studies available. Beyond publication bias, multiple steps in the process of designing, implementing and reporting on RCTs are potentially susceptible to bias. We have found no definitive instances of decisions in clinical trial design and conduct that reflect such bias. We also note, however, that the available studies rely heavily on surrogate/indirect outcomes that could be more likely to yield favorable findings, but may not fully reflect the drug's effect on direct outcomes. Likewise, the selection of usual care as the comparator, rather than a pre-existing hemostatic agent such as aPCC, could increase the likelihood of favorable findings. These choices do not imply direct or indirect bias, however, and are easily justified as pragmatic decisions seeking to make efficient use of limited research resources.

As evidenced by our harms analyses, there was variability in estimates of mortality and thromboembolic events among the different data sources: the Premier database, RCTs, and comparative and non-comparative observational studies. The higher mortality rates in the Premier database patients may be explained by the real-world application of rFVIIa to patients in

extremis, as a last attempt to control hemorrhage, versus what one might imagine is more controlled use in study settings where patient inclusion and exclusion criteria are designed to give the studied agent a realistic chance of performing better than usual care. The harms analyses also indicate, in general, that observational studies reported higher thromboembolic event rates than did RCTs. This is not surprising and, indeed, is part of the reason for including observational studies in any evaluations of harm.

Among the specific clinical indications, there were four RCTs and one observational study of intracranial hemorrhage that evaluated 968 rFVIIa patients. These provided a moderate strength of evidence for all outcomes. The findings are most applicable to patients in their 60s without prior anticoagulation who present for spontaneous intracerebral hemorrhage. In such cases, rFVIIa limits expansion of hematoma volumes but also increases the risk of arterial thromboembolic events when compared to usual care, without having a significant impact on mortality or functional outcome. The currently available evidence thus suggests that neither benefits nor harms substantially exceed each other, which argues against use of rFVIIa in most patients.

The studies of massive bleeding due to body trauma evaluated 267 treated patients in two RCTs and two cohort studies. These suggested no difference in mortality and a possible reduced rate of ARDS (most likely to be present in blunt trauma patients) in patients treated with rFVIIa compared to usual care. There was little evidence of increased risk of thromboembolic events with treatment. But the findings were complicated by the exclusion of patients with early mortality from both of the RCTs and one of the cohort studies. Given that the risks of thromboembolic events in this patient population appear low, the risk-benefit profile of rFVIIa therapy may weigh in favor of its use for body trauma, but this assessment is based on a low strength of evidence that does not permit definitive conclusions. Thus, current evidence of low strength suggests the potential for benefit and little evidence of increased harm.

Trials of hemorrhage secondary to brain trauma were limited to one RCT and a sub-set of one cohort study, which included a total of 79 patients treated with rFVIIa. There was no evidence of treatment effect on either mortality or thromboembolic events. Therefore, current evidence of low strength is too limited to compare harms and benefits.

There were four RCTs and one comparative observational study with 215 patients who received prophylactic rFVIIa at initiation of liver transplantation. There was no evidence of treatment effect on either mortality or thromboembolic events. These studies yielded a current evidence of low strength that is too limited to compare harms and benefits. Findings are of questionable relevance given the limited use of rFVIIa reported for this indication.

For the indication of bleeding secondary to cardiac surgery in adults, 251 patients who received rFVIIa were assessed in two RCTs and four cohort studies. From the meta-analyses of the RCTs and good quality observational studies, there was a moderate strength of evidence to suggest an increase in thromboembolic events with use of rFVIIa compared to usual care but a low strength of evidence for the finding of no effect on mortality. The risk-benefit profile of rFVIIa therefore remains unclear.

In pediatric patients undergoing congenital heart defect repair, the one study, an RCT, provided insufficient evidence to determine the effects of prophylactic use of rFVIIa on mortality and morbidity or for comparing harms and benefits. The subgroup of patients requiring ECMO was not evaluated in the RCT included in the comparative effectiveness evaluation.

Finally, the findings in the one study on prostatectomy, an RCT, have been made obsolete by the evolution of care away from the surgeries examined and toward less invasive and less bloody interventions.

In summary, 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 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.

Context

In general, our systematic review differs from most previous reviews by including information about real-world patterns of use, incorporating data from comparative observational studies (not just RCTs) in the effectiveness review, using non-comparative observational studies in the evaluation of harms, and assessing the impact of dosing level of rFVIIa on outcomes when warranted. Our use of the Premier database accomplished two objectives. First, it provided a method of gauging the relevance of past studies. This allowed us to reinforce the importance of examining rFVIIa use in cardiac surgery, trauma, and intracranial hemorrhage, at the same time pointing to the debatable relevance of investigating rFVIIa use in liver transplantation and prostatectomy. Second, high in-hospital mortality and the limited number of patients discharged home allowed us to conclude that patients in real-world practice who receive rFVIIa are likely more ill than are patients in most studies. Our use of comparative observational studies in the effectiveness review and non-comparative observational studies for a closer examination of the potential harm of rFVIIa corresponds to a growing skepticism of relying on RCTs alone for the assessment of harms.¹ Despite increasing the complexity of our literature review, it allowed us to highlight that, for many indications, the mortality and thromboembolic event rates associated with rFVIIa use were higher in the observational studies than in the RCTs. We also assessed the potential need for evaluation of the differential impact of rFVIIa by dosing level. For intracranial hemorrhage, we found evidence that this might be the case and so, *a priori*, made the decision to evaluate the RCT evidence by low, medium, and high dose use of rFVIIa (see Key Question 2 above for details). Finally, our analysis also included several key trials completed and/or published only recently. Particularly, in the areas of intracranial hemorrhage and cardiac surgery, these trials added important new evidence that might have altered assessment of the harms and benefits of rFVIIa in prior reviews. Despite these potential differences, we discuss below that our findings are similar to those of most other meta-analyses and systematic reviews.

Reviews of rFVIIa use across off-label indications by Cochrane Collaboration researchers and by Squizzato and colleagues did not come to definitive conclusions regarding safety or efficacy,^{27,63} although the Cochrane review did note a “trend against rFVIIa for increased thromboembolic adverse events.” Hsia and colleagues found trends toward decreased transfusion requirements and possibly mortality but also toward increased arterial thromboembolic events.²³⁰

These results are consistent with our findings of significantly increased rates of arterial and total thromboembolic events with rFVIIa use in studies of intracranial hemorrhage and adult cardiac surgery, respectively. Finally, a recently released technology report from the Canadian Agency for Drugs and Technologies in Health²³¹ performed separate comprehensive assessments of rFVIIa use in RCTs on ICH, trauma (both at the body and brain), gastrointestinal bleeding, and spinal surgery. Investigators for that report found no statistically significant evidence of effect on mortality or thromboembolic events for any indication.

Other reviews and meta-analyses have confined themselves to more narrow clinical indications, but, again, primarily evaluated RCTs. Regarding ICH, a recent meta-analysis on the topic did not incorporate data from the Mayer 2008 trial,⁸⁸ so that its findings are outdated.³⁴ A recently-updated Cochrane review that included the Mayer 2008 trial evaluated RCTs of “hemostatic drug therapies” for ICH, including rFVIIa. All but two of the 975 participants in the intervention arms of the included trials received rFVIIa, while the two outliers received epsilon-aminocaproic acid (EACA). The review concluded that, with rFVIIa treatment, there was no reduction in mortality but that there was a “trend” toward increased thromboembolic serious adverse events.²³² These findings are consistent with ours, with the exception that we focused on all arterial thromboembolic events and found evidence of significantly higher rates with rFVIIa use, but nonetheless found no evidence of differences in outcome by dosing level (whether low, medium, or high).

We identified two systematic reviews of rFVIIa use in body trauma.^{233,234} Both evaluated RCTs, comparative observational studies, and non-comparative observational studies and cited evidence from the Boffard blunt trauma trial⁹⁶ that rFVIIa use is associated with decreased RBC transfusion requirements. But, both also concluded that there was no evidence to suggest decreased mortality with treatment in either blunt or penetrating trauma. These findings are generally consistent with those of our effectiveness review, which determined that the risk-benefit profile of rFVIIa therapy may favor its use for this indication, but that this assessment is based on a low strength of evidence that does not permit definitive conclusions.

There have been several systematic reviews of rFVIIa use in cardiac surgery. A meta-analysis on this indication observed no effect on mortality, a non-significant reduction in the rate of surgical re-exploration, and a trend toward an increase in the rate of perioperative stroke,²³⁵ but was published prior to the publication of the Gill RCT.¹¹⁹ These findings are consistent with our determination that rFVIIa has no effect on mortality but does differ from our finding of a significantly increased rate of thromboembolic events with rFVIIa use. The other reviews, which did not include meta-analytic evaluations, were perhaps more supportive of rFVIIa use. One found that adequate evidence of efficacy was lacking but that rFVIIa use appeared “promising and relatively safe.” This review calculated an associated thromboembolic event rate of 5.3 percent,⁵¹ which is lower, in general, than the rates in the studies we evaluated, but which was calculated using data from studies in pediatric, as well as adult, patients, while we evaluated pediatric patients separately. A Canadian Consensus Conference on application of rFVIIa in cardiac surgery reviewed the literature and then provided expert consensus opinion—namely, that rFVIIa not be used as prophylaxis, given a pattern of higher thromboembolic events with use, but that it might reasonably be used as rescue therapy.²⁶ The Audit and Guidelines Committee of the European Association for Cardio-Thoracic Surgery (EACTS) reached a similar conclusion that “after cardiac surgery, intractable bleeding refractory to conventional haemostatic intervention may be treated successfully with factor VIIa, but there is a small risk of serious or fatal thrombotic complications (Grade C recommendation).”²³⁶

Interestingly, reviews of rFVIIa use in other types of surgery have reached similar conclusions and have generally highlighted a lack of evidence of increased thromboembolism. A meta-analysis of case series and RCTs on patients receiving abdominal, vascular, and urologic surgery noted a reduction in bleeding and no increased risk of thromboembolism,⁵⁰ although a similar study of vascular surgeries alone identified three cases of arterial thrombosis.²⁵ Another meta-analysis of patients undergoing major surgical procedures found a reduction in transfusion requirement and, again, no increased risk of thromboembolism.⁴⁵ A meta-analysis of applications of rFVIIa to vascular surgery concluded that rFVIIa may reduce hemorrhage,⁵⁰ but that more study was needed.

Specific to the topic of harm, O'Connell and colleagues published an important evaluation of data on post-marketing adverse events associated with off-label rFVIIa use reported to the FDA's Adverse Event Reporting System (AERS).²³⁷ They documented many instances of arterial and thromboembolic events, which often resulted in serious morbidity and mortality. A subsequent review of the safety profile of rFVIIa for patients with coagulopathy due to anticoagulation, cirrhosis, or trauma found a six percent thromboembolism rate.⁴³ Such studies raised specific concerns regarding the safety of the drug for off-label indications. Since that time, many of the studies, including the meta-analyses noted above, have emphasized safety evaluations, but few have found definitive evidence of increased risk. In our analyses, which had the benefit of recently published trials and of evaluating comparative observational studies in addition to RCTs, we note an increased risk of arterial thromboembolism in use of rFVIIa for ICH and cardiac surgery. However, we found little evidence of increased risk of such events for the other clinical indications; albeit the strength of evidence for these is low or insufficient.

Limitations of the Premier Database Analysis

There are several limitations that must be acknowledged regarding our analysis of in-hospital rFVIIa prescribing practices. Most relevant are those limitations connected to the Premier database itself and our hierarchical definition of indications for rFVIIa use.

First, the Premier database is largely a convenience sample of non-federal U.S. hospitals that are willing to provide detailed cost and billing information. Although the sample is nationally representative in terms of hospital characteristics, there may be important differences between participating and non-participating U.S. hospitals. It provides no information about use in federal hospitals or outside the U.S. The database also captures only in-hospital use of rFVIIa. Second, it fails to include office-based rFVIIa administration, which is certainly pertinent to on-label use in patients with hemophilia and inhibitors, and may be considerable. Third, the data elements available are collected for administrative purposes, rather than designed to capture all clinically relevant information. For example, the data do not allow use as prophylaxis versus treatment versus end-stage use to be distinguished. In addition, we are unable to identify cases where rFVIIa use is linked to important harms outcomes, such as thromboembolic events. Fourth, there may be overlap between the patients identified in the Premier database and the U.S. patients reported in the research studies analyzed. Given the relatively few American patients included in the largest clinical trials, however, this overlap is likely quite limited. In fact, the experience represented by the Premier database is several-fold larger than the aggregate international experience reported in research studies. Fifth, we are limited to the calculation of in-hospital mortality. Given the substantial fraction of rFVIIa patients discharged to skilled nursing facilities and rehabilitation hospitals, in-hospital mortality may substantially underestimate total mortality attributable to patients' underlying indications or to treatment with

rFVIIa itself. Finally, but importantly, our ability to define cohesive indication categories is limited by the relatively sparse clinical information available. Our hierarchy of clinical indications thus may not precisely define the reason for rFVIIa use in all cases. For example, by prioritizing trauma above many other indications we run the risk of misclassifying patients into this category who have minor trauma but also have another more direct indication for rFVIIa (e.g., gastrointestinal bleeding from a non-traumatic cause). Our hierarchical scheme for assigning a single indication may fail to recognize patients with more than one indication (e.g., ICH in a patient with liver disease).

Limitations of the Systematic Review

A weakness of the systematic review component of this report is the limited evidence foundation upon which it builds. There are few large, high quality studies in any clinical indication. The strength of evidence for any particular outcome was almost uniformly low. We encountered further limitations in the areas below.

Non-English Language Articles

Because we were not in a position to translate articles on Key Questions 2-4 that were published in non-English languages, we were unable to fully incorporate these into our systematic review. However, there were only eight such articles that were otherwise eligible for inclusion, and six of these were case series with 35 or fewer patients. The one identified non-English language RCT²¹¹ was used for sensitivity analyses for the adult cardiac surgery indication.

Unpublished Studies Identified in the Grey Literature

We identified five clinical trials on Key Questions 2-4 that were registered on online databases (e.g., ClinicalTrials.gov) and completed, but for which we were unable to identify a subsequent publication: two on ICH, two on body trauma, and one on adult cardiac surgery. We did not have the data from these trials, and so were unable to assess them in our effectiveness review or use them to evaluate for evidence of publication bias. We also identified three abstracts reporting on studies that appeared to meet all other inclusion criteria for Key Questions 2-4 but for which we were unable to identify a subsequent full publication. One of these was an RCT on liver transplantation,⁸³ while the others were case series with 24 or fewer patients.

Predecessor Products

As expected, we found no studies comparing use of rFVIIa to predecessor products.

Comparisons to Usual Care

We found evidence of significant evolution in usual care in the area of prostatectomy, enough so as to make the findings of the single RCT on the topic likely obsolete for common practice.¹⁴¹ Similar, although less striking, concerns arose when considering the evolution of practice toward fewer transfusions and more limited blood loss in liver transplantation and adult cardiac surgery. In addition, we found evidence of important changes regarding transfusion practice (including the 1:1 ratio of transfused blood products and institution of massive transfusion protocols) in the treatment of massive hemorrhage in body trauma, which may reduce the marginal benefit of rFVIIa use for this indication.

Manufacturer with Intensive Involvement in Research Studies

As noted above, we found no evidence of bias associated with manufacturer involvement in the majority of RCTs. However, because there were so few comparative studies on any single indication, we were unable to perform formal assessments for publication bias, such as with funnel plots.

Use of Drug in Emergency Situations

At least two of the trials (in body trauma) experienced withdrawal of consent by patients who had been enrolled under some version of an emergency exception to informed consent. In this case, there was no information provided on which treatment arm the patients had been assigned to, so we were unable to assess whether differential withdrawal of consent may have introduced bias, however unavoidable.

Variability in Dose, Repeat Dosing, and Context of rFVIIa Use

Studies varied widely in the doses of rFVIIa used, as well as in their protocols regarding repeat dosing. In addition, within the adult cardiac indication, separate studies evaluated use of rFVIIa for prophylactic and therapeutic purposes, which had the potential to increase the heterogeneity of clinical context and patient characteristics (although this does not appear to have been the the case).

Pediatric Patients

We found evidence of substantial use of rFVIIa among pediatric populations in the Premier database (primarily for cardiac surgery and neonatal applications). Yet we identified only four comparative studies conducted in children and only one that met our inclusion criteria for detailed review, a poor quality RCT on repair of infant congenital heart defects. Although rFVIIa is being used in pediatric patients on ECMO, there were no fair or good quality studies that evaluated such patients.

Figure 34. Study summary

Context:

The use of recombinant activated clotting factor VII (rFVIIa) is common for a range of indications not directly related to its Food and Drug Administration approved use in hemophilia. The drug's biology suggests the potential for hemostatic benefits in uncontrolled bleeding but a risk of thromboembolic adverse effects. Wide diffusion of this expensive medication (approximately \$10,000 for a single 90 µg/kg dose in a 70 kg patient) has occurred despite limited comparative data on its effectiveness.

Contributions:

- Based on data from U.S. hospitals, off-label in-hospital rFVIIa use was estimated to be 125 cases (defined as any use during hospitalization) 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 rate of increase may be plateauing for many indications. The leading indications in 2008 were cardiac surgery, trauma, and intracranial hemorrhage
- Randomized clinical trials (RCTs) and comparative observational studies of rFVIIa have examined the efficacy and safety of rFVIIa use across a variety of uses, most prominently cardiac surgery, trauma, intracranial hemorrhage, and liver disease.
- Overall study quality is fair to poor and strength of evidence is low, with the exception of meta-analyses of intracranial hemorrhage which had moderate strength of evidence for all outcomes and of a meta-analysis of adult cardiac surgery studies which had moderate strength of evidence for the thromboembolic event outcome. Clinical efficacy is often defined via indirect/surrogate outcomes, such as transfusion requirements, change in hematoma volume, or ICU length of stay. Safety is defined via thromboembolic events and mortality, but individual studies often lack the statistical power to assess these outcomes.
- Evidence of rFVIIa benefit is suggested for several indications, but largely via the surrogate outcomes used in the included studies and with an uncertain relationship to improved patient survival or functional status. In addition, for some uses rFVIIa produces an increased risk of thromboembolism. Current evidence of low strength suggests the potential for benefits to exceed harms for bleeding from body trauma. There are no indications where potential risks are likely to greatly exceed the benefits.
- Intracranial hemorrhage: There are four RCTs and one observational study involving 968 rFVIIa-treated patients. Treatment with rFVIIa reduces expansion of intracranial hematoma volume relative to usual care, but increases the risk of arterial thromboembolic events and does not reduce the rates of mortality or poor functional outcome. Current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other.

Figure 34. Study summary (continued)

- **Body trauma:** There are two RCTs and two comparative observational studies examining rFVIIa treatment in 257 patients experiencing massive blood loss from trauma. These suggest a possible reduced rate of ARDS, most likely to be present in cases of blunt trauma, but these findings are complicated by the exclusion of patients with early mortality from both of the RCTs and one of the cohort studies. There is no evidence of effect on mortality or of increased thromboembolic events with treatment. Current evidence of low strength suggests the potential for benefit and little evidence of increased harm.
- **Brain trauma:** There is one RCT and a sub-set of one cohort study where 79 patients received rFVIIa as a treatment for bleeding secondary to traumatic brain injury. These studies fail to show an effect of rFVIIa on direct outcomes or indirect outcomes. Current evidence of low strength is too limited to compare harms and benefits.
- **Liver transplantation:** There are four RCTs and one comparative observational study that examine prophylactic use of rFVIIa in 215 liver transplant patients. These studies fail to show an effect of rFVIIa on either direct outcomes or indirect outcomes, although there was a trend toward reduced RBC transfusion requirements. rFVIIa is rarely used in liver transplantation in the U.S. Current evidence of low strength is too limited to compare harms and benefits.
- **Adult cardiac surgery:** There are two RCTs and four included comparative observational studies with 251 patients receiving prophylactic or therapeutic rFVIIa. These studies show that rFVIIa likely increased the risk of thromboembolic events, but fail to show an effect of rFVIIa on other outcomes, including mortality. rFVIIa use for this indication is increasing in the U.S.
- **Pediatric cardiac surgery:** There is one RCT where 40 infants were administered prophylactic rFVIIa. Current evidence is insufficient for comparing harms and benefits.
- **Prostatectomy:** A single RCT examined 24 patients receiving prophylactic rFVIIa. Current evidence is insufficient for comparing harms and benefits. rFVIIa is almost never used during prostatectomy in the U.S.

Implications:

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 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.

Future Research

Evidence Gaps

Our review can usefully comment on evidence gaps for applications of rFVIIa to clinical indications in two ways: areas in which published studies exist but may not yet have been synthesized (as in a systematic review or meta-analysis) and areas in which rFVIIa is being used (as in the Premier database) but where no or few studies have been published.

Our review of the literature identified five RCTs and comparative observational studies on the use of rFVIIa in patients with liver disease but for indications other than liver transplantation. These might be a useful target for future evidence synthesis. Other indications examined in multiple studies include bleeding in obstetrics and gynecology and in hematologic disease states, for which we identified three comparative studies apiece (Table 12).

Our review of the Premier database also identified notable areas of rFVIIa use in clinical practice. Similar to areas targeted in the published literature, applications to patients with liver disease, even outside of liver transplantation, are frequent, as are those to patients with obstetrical hemorrhage, hematologic malignancies and disorders, and non-congenital clotting disorders. However, areas not explored in depth in the published literature but for which real-world application of rFVIIa are not insignificant include bleeding from non-variceal gastrointestinal sources unrelated to liver disease, aortic aneurysm, pulmonary sources, neurosurgery, and neonatal disease states (Table 15). Finally, the high mortality rates among patients on the Premier database who received rFVIIa suggests that community application may be more heavily weighted toward end-stage use than is use in the context of studies. This suggestion, in no way definitive, emphasizes another potential disjunct between community use and the evidence base available for analysis. While end-stage use of rFVIIa is likely extremely difficult to study, this is another potential area for future inquiry.

Of the areas covered by the Key Questions for this project, further research recommendations are described below according to the specific concern or clinical indication.

Need for Better Delineation of Withdrawal of Deferred Consent

Our comparative effectiveness review has implications for future research on the treatment of patients with life-threatening bleeding. For instance, a comment is in order on those RCTs performed in emergency situations. These potentially operate under the purview of the FDA rule on enrollment of patients in extremis (or similar guidelines in other countries, which allows for deferral of informed consent.^{64,65} However, patients (or their legal representatives) may withdraw at a subsequent time, when made aware of the study. This has the potential to introduce bias, albeit for ethical reasons that are unavoidable, via differential withdrawal of consent. Therefore, in the future, such studies should explicitly report on the treatment arm of those patients who do decide to withdraw their (deferred) consent, so that the potential for introduction of bias on the basis of differential withdrawal can be better assessed.

Future Research by Indication

Intracranial Hemorrhage. Despite the promise of earlier studies, there is a lack of evidence of benefit for intracranial hemorrhage patients, specifically those with ICH, on clinically important

outcomes. Thus, if future studies are undertaken, they might best target subgroups of patients who can reasonably be expected to benefit more than those already studied. Because post-hoc analyses suggest that early infusion of rFVIIa may be the most beneficial, such administration may warrant further investigation. In addition, because there are no RCTs investigating the use of rFVIIa in patients on anticoagulation therapy or those with isolated subdural or subarachnoid bleeding, these populations may merit careful study.

Body trauma. Given that the balance of benefits versus harms in this area may favor rFVIIa use, future studies appear warranted. Studies thus far have highlighted possible complex associations between the degree of acidosis, thrombocytopenia, and other markers of baseline injury severity and the impact of rFVIIa. Future studies might attempt to better delineate these relationships and attempt to identify subgroups of patients who might most benefit from therapy.

Brain trauma. Given the lack of evidence of benefit for rFVIIa use on direct outcomes, if future studies are undertaken, they might best target patients felt to be at increased risk for poor outcomes with usual care, such as those who require rapid neurosurgical intervention but can not tolerate the usual care approach of large volume plasma infusions (e.g., patients with congestive heart failure) to correct for the coagulopathy of trauma. Similarly, future studies might avoid enrolling patients who might reasonably be felt to be at increased risk for harm from rFVIIa, such as those with blunt injuries to the cerebral vessels.

Liver transplantation. Because there is little evidence to suggest benefit on direct outcomes of prophylactic use of rFVIIa, future studies might best focus on its therapeutic use or its use in special populations. Jehovah's Witnesses are one such population in which rFVIIa therapy is being regularly applied during liver transplantation without systematic evaluation of its impact.

Adult cardiac surgery. There is moderate evidence to suggest that rFVIIa may increase the rate of thromboembolic events without having an effect on mortality. Because these findings are in the context of increasing community use of rFVIIa for this indication, future studies may be considered, but carefully so. Existing studies have raised the possibility that patients experience greater benefit when rFVIIa is given earlier rather than later during treatment use for massive post-operative bleeding, such that if future studies are undertaken, exploration of the issue of timing of administration would be useful.

Pediatric cardiac surgery. What little evidence there is on rFVIIa use for congenital heart surgery, from one RCT, indicates no benefit and the potential for harm in terms of a longer time to chest closure. Because of this, future studies might be undertaken with great care. In particular, patients who might reasonably be expected to be at higher risk for thromboembolism, such as those on ECMO, might need special consideration in terms of weighing potential benefits and harms.

Prostatectomy. We see little reason for future studies of prophylactic use of rFVIIa on this indication, given that current surgical approaches have diminished bleeding rates to low or even negligible amounts.

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Abbreviations

Acronym or Abbreviation	Definition
ACP Journal Club	American College of Physicians Journal Club
AHRQ	Agency for Healthcare Research and Quality
APACHE II	Acute Physiology And Chronic Health Evaluation
ARDS	Acute respiratory distress syndrome
BIOSIS	Bibliographic database covering worldwide research on all biological and biomedical topics. Records contain bibliographic data, indexing information, and abstracts for most references
BPH	Benign prostatic hypertrophy
CABG	Coronary artery bypass grafting
CCTR	Cochrane Central Register of Controlled Trials
CMR	Cochrane Methodology Register
CPB	Cardiopulmonary bypass
CT	Computed Tomography
DARE	Database of Abstracts of Reviews of Effectiveness
DRG	Diagnosis-related group
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EMBASE	Biomedical database of bibliographic records produced by Elsevier
EMA	European Medicines Agency
EPC	Evidence-based Practice Center
EU	European Union
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
HTA	Health Technology Assessments
ICD-9	International Classification of Diseases, Ninth Revision
ICU	Intensive care unit
INR	International normalization ratio
ISS	Injury Severity Score
LOS	Length of stay
MeSH	Medical Subject Headings
MI	Myocardial infarction
MOF	Multiorgan failure
mRS	Modified Rankin Scale
NHSEED	NHS Economic Evaluation Database
NIHSS	NIH Stroke Scale
NNH	Number needed to harm
NNT	Number needed to treat
OLT	Orthotopic liver transplantation
OR	Operating room
PE	Pulmonary embolus
PubMed	Biomedical database of bibliographic records produced by the National Library of Medicine
RBCs	Red blood cells
RCT	Randomized controlled trial
rFVIIa	Recombinant Clotting Factor VIIa
SRC	Scientific Resource Center
TBI	Traumatic brain injury
TEP	Technical Expert Panel
UCSF	University of California, San Francisco
UK	United Kingdom
U.S.	United States

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

Appendixes

Appendix A. Search Strategies

OID MEDLINE

1948 to August 4, 2009

Search 1: Factor VIIa Off-Label Use

Rather than trying to represent “off-label” use with MeSH terms or keywords, this search included any article on Factor VIIa *except* case reports, editorials, animal-only studies and non-systematic reviews. This search does include systematic reviews.

1. exp factor viia/ OR ("factor viia" OR "factor 7a" OR rfviia OR fviia) OR (novoseven OR eptacog* OR Niastase OR proconvertin OR "novo-seven") OR ec 3 4 21 21.rn. OR ((7a or viia) adj5 (factor OR rfactor)) OR (("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated))

2. case reports OR editorial OR "review"

3. animals/ not humans/

1 NOT (2 OR 3 OR “ALL RESULTS FROM THE NEXT THREE SEARCHES”)

Number of citations: 1684

Search 2: Intracranial Hemorrhages AND Factor VIIa

1. exp factor viia/ OR ("factor viia" OR "factor 7a" OR rfviia OR fviia) OR (novoseven OR eptacog* OR Niastase OR proconvertin OR "novo-seven") OR ec 3 4 21 21.rn. OR ((7a or viia) adj5 (factor OR rfactor)) OR (("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated))

2. exp Intracranial Hemorrhages/ OR exp brain/ OR exp skull/ OR intracranial.mp. OR intracerebral.mp. OR "basal ganglia".mp. OR brain*.mp. OR "posterior fossa".mp. OR cerebral.mp. OR parenchymal.mp. OR subdural.mp. OR subarachnoid.mp. OR pituitary.mp. OR epidural.mp

3. animals/ not humans/

(1 AND 2) NOT 3

Number of citations: 293

Search 3: Trauma AND Factor VIIa

1. exp factor viia/ OR ("factor viia" or "factor 7a" OR rfviia OR fviia) OR (novoseven or eptacog* OR Niastase OR proconvertin OR "novo-seven") OR ec 3 4 21 21.rn. OR ((7a or viia) adj5 (factor OR rfactor)) OR (("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated))

2. exp "Wounds and Injuries"/ OR (traum* or injur* or wound*).mp.

3. animals/ not humans/

(1 AND 2) NOT 3

Number of citations: 459

Search 4: Liver Transplantation/Cardiac Surgery/Prostatectomy AND Factor VIIa

1. exp factor viia/ OR ("factor viia" or "factor 7a" OR rfviia OR fviia) OR (novoseven or eptacog* OR Niastase OR proconvertin OR "novo-seven") OR ec 3 4 21 21.rn. OR ((7a or viia) adj5 (factor OR rfactor)) OR (("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated))

2. exp liver transplantation/ OR ((liver* or hepatic) adj3 (transplan* or graft*).mp. OR exp Cardiovascular Diseases/su [Surgery] OR exp cardiovascular surgical procedures/ OR ((heart* or cardi*) and surg*).mp. OR exp Prostatectomy/ OR (Prostatectom* or (resect* and prostat*).mp.

3. animals/ not humans/

(1 AND 2) NOT 3

Number of citations: 294

Total number of citations from OVID/MEDLINE search: 3067

EMBASE (DIALOG) 1974 to August 4, 2009

Search 1: FACTOR VIIa NOT Letters, NOT Animal-only Studies

S1 FACTOR VIIA! OR FACTOR()VIIA OR FACTOR()7A OR RFVIIA
OR FVIIA OR NOVOSEVEN OR EPTACOG? OR NIASTASE OR PROCONV-
ERTIN OR NOVO()SEVEN

S2 (7A OR VIIA)(5N)(FACTOR OR RFACTOR)

S3 (FACTOR()VII OR FACTOR()7 OR FVII OR RFVII OR FACTOR-
()SEVEN)(5N)(ACTIVE OR ACTIVATED)

S4 DT=LETTER

S5 (ANIMALS/DE OR NONHUMANS/DE) NOT (HUMANS/DE OR HUMAN-
/DE)

S6 S1 OR S2 OR S3

S7 S6 NOT (S4 OR S5)

**Search 2: FACTOR VIIa AND Intracranial Hemorrhage NOT Animal-only
Studies**

S9 BRAIN! OR SKULL! OR INTRACRANIAL OR INTRACEREBRAL OR
BASAL()GANGLIA OR BRAIN? OR POSTERIOR()FOSSA OR CEREBRAL
OR PARENCHYMAL OR SUBDURAL OR SUBARACHNOID OR PITUITARY -
OR EPIDURAL

S10 BRAIN HEMORRHAGE! OR INTRACRANIAL HEMORRHAGES!

S11 (STROKE! OR CVA OR STROKE OR APOPLEXY OR BRAIN()VASC-
ULAR()ACCIDENT? OR CEREBROVASCULAR()ACCIDENT OR CEREBROV-
ASCULAR ACCIDENT/DE) AND (HEMORRHAGE! OR BLEEDING! OR H-
EMORRHAG? OR BLEED?)

S12 S6 NOT S5

S13 s12 AND (S24 OR S13 OR S18)

Search 3: FACTOR VIIa and Liver Transplantation/Heart Surgery/Prostatectomy NOT Animal-
only Studies

S15 LIVER TRANSPLANTATION!

S16 (LIVER? OR HEPATIC)(5N)(TRANSPLANT? OR GRAFT?)

S17 CARDIOVASCULAR SURGICAL PROCEDURES! OR CARDIOVASCULAR
SURGERY!

S18 CARDIOVASCULAR DISEASES!

S19 S32(L)SU

S20 CARDIOVASCULAR DISEASE!

S21 S20(L)SU

S22 (HEART? OR CARDI?) AND (SURG? OR PRESURG? OR POSTSURG? OR PERIOPERAT? OR OPERATION? OR OPERATIVE OR PERIOPERAT? OR PREOPERAT? OR POSTOPERAT? OR RESECT?)/TI,AB,DE

S23 PROSTATECTOMY!

S24 PROSTATECTOM? OR ((SURG? OR PRESURG? OR POSTSURG? OR PERIOPERAT? OR OPERATION? OR OPERATIVE OR PERIOPERAT? OR PREOPERAT? OR POSTOPERAT? OR RESECT?) AND PROSTAT?)

S25 (S15-S24 combined with OR) AND S12

Search 4: FACTOR VIIa and Trauma NOT Animal-only Studies

S27 DC='C21.866.' (WOUNDS AND INJURIES)

S28 TRAUM? OR INJUR? OR WOUND?

S29 S12 AND (S27 OR S28)

Total number of citations from EMBASE search: 4424

All OVID EBM Review Databases (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED) No date restrictions. Searched up to August 4, 2009

Factor VIIa Off-Label Use

"factor viia" or "factor 7a" OR rfvia OR fvia OR novoseven or eptacog* OR Niastase OR proconvertin OR "novo-seven" OR (7a or viia) adj5 (factor OR rfactor) OR ("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated)

Number of citations: 161

BIOSIS (ISI) 1926 to August 4, 2009

Factor VIIa Off-Label Use

Broad search aimed at retrieving all articles on Factor VIIa, but excluding letters and animal-only studies.

"factor viia" or "factor 7a" OR rfvia OR fvia OR novoseven or eptacog* OR Niastase OR proconvertin OR "novo-seven" OR (7a or viia) adj5 (factor OR rfactor) OR ("factor vii" OR "factor 7" OR fvii OR rfvii OR "factor seven") adj5 (active OR activated)

1 NOT Letters

2 NOT animals NOT humans

Number of citations: 3190

Total number of unique citations from all databases (after removing duplicate citations): 5668

Appendix B. List of Excluded Studies

Excluded article	Reason for exclusion
Abdullah F, Hunter C, Hargrove C, et al. Recombinant factor VIIa for treatment of massive liver fracture in a premature infant. <i>J Pediatr Surg</i> 2006;41(10):1764-1767.	Ineligible study design
Abraldes JG, Dell'Era A, Bosch J. Medical management of variceal bleeding in patients with cirrhosis. <i>Can J Gastroenterol</i> 2004;18(2):109-113.	Ineligible study design
Abu-Hajir M, Hollowell J, Nagargoje G. Management of 2 patients with subdural hematoma and coagulopathy with recombinant human activated Factor VII (novoseven, rVIIa). <i>Blood</i> . 2001;98(11 Part 2):79b.	Small sample size
Adams GL, Manson RJ, Turner I, et al. The balance of thrombosis and hemorrhage in surgery. <i>Hematol Oncol Clin North Am</i> 2007;21(1):13-24.	Ineligible study design
Afessa B, Peters SG. Major complications following hematopoietic stem cell transplantation. <i>Semin Respir Crit Care Med</i> 2006;27(3):297-309.	Ineligible study design
Agarwal MB, Patnaik M. Recombinant activated factor VII (rFVIIa, NovoSeven). <i>Journal of the Association of Physicians of India</i> 2005;53:717-720.	Ineligible study design
Agarwal N, Spahr JE, Rodgers GM. Successful management of intra-abdominal hemorrhage in the presence of severe alcoholic liver disease with activated recombinant factor VII (rFVIIa; NovoSeven): a case report and review of the literature on approved and off-label of rFVIIa. <i>Blood Coagulation & Fibrinolysis</i> 2007;18(2):205-207.	Ineligible study design
Aggarwal A, Catlett J, Alcorn K. Use of recombinant activated factor VII (rFVIIa) in the management of intractable bleeding in surgical and trauma patients. <i>Blood</i> . 2001;98(11 Part 2):66b.	Small sample size
Aguilar C, Lucia JF. Successful control of severe postoperative bleeding with recombinant factor VIIa in a case of refractory idiopathic thrombocytopenic purpura. <i>Am J Hematol</i> 2007;82(3):246-247.	Ineligible study design
Aguilar MI, Dernaerschalk BM. Intracerebral Hemorrhage. <i>Seminars in Neurology</i> . 2007;27(4):376-384.	Ineligible study design
Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion.[erratum appears in <i>Mayo Clin Proc</i> 2007 Mar;82(3):387]. <i>Mayo Clinic Proceedings</i> 2007;82(1):82-92.	Ineligible study design
Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage[see comment]. <i>British Journal of Anaesthesia</i> 2005;94(5):592-595.	Ineligible study design
Aitken MG. Recombinant factor VIIa. <i>Emerg Med Australas</i> 2004;16(5-6):446-455.	Ineligible study design
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Al Sobhi E. Successful outcome of using recombinant activated factor VII (rFVIIa) in liver biopsy in a patient with liver failure. <i>J Thromb Haemost</i> 2006;4(9):2073-2074.	Ineligible study design
Alameri A, Baker NS. Successful use of recombinant activated factor VII in the treatment of vitreous haemorrhage: a report of seven cases. <i>Blood Coagulation & Fibrinolysis</i> 2005;16(8):573-578.	Small sample size
Alavi AA, Jalali SM, Rasouli MR, et al. Administration of recombinant activated factor VII in major thoracic operations comment]. <i>Archives of Surgery</i> 2008;143(10):1021; author reply 1021.	Other: unpublished data

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Aldouri M. The use of recombinant factor VIIa in controlling surgical bleeding in non-haemophiliac patients. <i>Pathophysiology of Haemostasis & Thrombosis</i> 2002;32 Suppl 1:41-46.	Small sample size
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Aledort LM. Adverse reactions related to rVIIa? <i>Am J Hematol</i> 2001;67(3):213.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity.[see comment]. <i>Journal of Thrombosis & Haemostasis</i> 2004;2(10):1700-1708.	Ineligible study design
Aledort LM. MedWatch: an important instrument for postlicensing surveillance.[comment]. <i>Journal of Thrombosis & Haemostasis</i> . 2006;4(7):1637.	Ineligible study design
Aledort LM. Recombinant factor VIIa is a pan-hemostatic agent? <i>Thromb Haemost</i> 2000;83(5):637-638.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Aledort LM. rFVIIa--its thrombogenicity. <i>Thromb Haemost</i> 2000;84(3):522-523.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Alfirevic Z, Elbourne D, Pavord S, et al. Use of recombinant activated factor VII in primary postpartum hemorrhage - The northern European registry 2000-2004. <i>Obstetrics & Gynecology</i> 2007;110(6):1270-1278.	Ineligible study design
Alfirevic Z, Elbourne D, Pavord S, et al. Use of recombinant activated factor VII in primary postpartum hemorrhage: the Northern European registry 2000-2004. <i>Obstet Gynecol</i> 2007;110(6):1270-1278.	Ineligible study design
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Alimoghaddam K, Ghavamzadeh A, Jahani M. Use of Novoseven for arsenic trioxide-induced bleeding in PML. <i>American Journal of Hematology</i> 2006;81(9):720.	Ineligible study design
Al-Khuwaitir TS, Al-Moghairi AM, Sherbeeni SM, et al. Rift Valley fever hepatitis complicated by disseminated intravascular coagulation and hepatorenal syndrome. <i>Saudi Med J</i> 2004;25(4):528-531.	Ineligible study design
Allard S, Earley J, Davies JK, et al. Hospital blood transfusion services in a mass casualty situation: lessons to be learned from July 2005 London bombings. <i>British Journal of Haematology</i> 2006;133(Suppl. 1):2.	Ineligible study design
Allen GA, Hoffman M, Roberts HR, et al. Recombinant activated factor VII: its mechanism of action and role in the control of hemorrhage. <i>Canadian Journal of Anaesthesia</i> 2002;49(10):S7-S14.	Ineligible study design
Allen KB, Heimansohn DA. Activated recombinant factor VII: Safety assessment in cardiovascular surgery patients at high risk for postoperative bleeding. <i>Chest</i> 2006;130(4, Suppl S):187S.	Small sample size
Al-Ruzzeh S, Mahmoud A, Shah S, et al. Caution with the use of recombinant activated factor VII in treating postoperative hemorrhage in cardiac surgery. <i>Ann Thorac Surg</i> 2007;83(1):355; author reply 355-356.	Ineligible study design
Al-Said K, Anderson R, Wong A, et al. Recombinant factor VIIa for intraoperative bleeding in a child with hepatoblastoma and review of recombinant activated factor VIIa use in children undergoing surgery. <i>Journal of Pediatric Surgery</i> 2008;43(4):e15-e19.	Ineligible study design

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Al-Shahi R, You H. Hemostatic Drug Therapies for Acute, Nontraumatic Intracerebral Hemorrhage. <i>Stroke</i> 2006.	Ineligible study design
Al-Trabolsi H, Carcao MD, Freedman J, et al. Factor VIIa overdose: Clinical and laboratory observations. <i>Blood</i> 1998;92(10 Suppl 1 Part 1-2):104B.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Altuncu E, Berrak S, Bilgen H, et al. Use of recombinant factor VIIa in a preterm infant with coagulopathy and subdural hematoma. <i>Journal of Maternal-Fetal & Neonatal Medicine</i> 2007;20(8):627-629.	Small sample size
Alving BM. Platelet substitutes: The reality and the potential. <i>Vox Sanguinis</i> 2002;83(Suppl 1):287-288.	Ineligible study design
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Anderson JAM, Cook MK, Ludlam CA. Can factor VIIa alone secure haemostasis in patients with liver cirrhosis? <i>Haemostasis</i> 2000;30(Suppl 1):197-198.	Ineligible study design
Andonova R, Gavrilova N, Bogdanova R, et al. Initial experience with recombinant activated factor VII (NovoSeven(R)) in trauma and surgery paediatric cases of uncontrolled bleeding. <i>Anaesthesiology and Intensive Care</i> 2006;33(2):7-12.	Unable to obtain publication
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Anonymous. 21st Annual Meeting of the European-Association-of-Cardiothoracic-Anaesthesiologists, Venice, Italy, May 24-27, 2006. <i>European Journal of Anaesthesiology</i> 2006;23(Suppl 38):1-47.	Other: conference proceedings
Anonymous. 40th Annual Meeting of the German-Society-for-Transfusion-Medicine-and-Immunohematology, Friedrichshafen, Germany, September 18-21, 2007. <i>Transfusion Medicine and Hemotherapy</i> 2007;34(Suppl 1):1-74.	Other: conference proceedings
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Ansari S, Salehi S. Coagulopathy after spider bites to a 6-year-old boy. <i>Pediatr Hematol Oncol</i> 2007;24(3):233-523.	Ineligible study design
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Apostolidou I, Sweeney MF, Missov E, et al. Acute left atrial thrombus after recombinant factor VIIa administration during left ventricular assist device implantation in a patient with heparin-induced thrombocytopenia. <i>Anesth Analg</i> 2008;106(2):404-408, table of contents.	Small sample size
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Argall J, Teece S, Mackway-Jones K. Factor VIIa for intractable blood loss in trauma. <i>Emerg Med J</i> 2002;19:556-557.	Ineligible study design
Argall J, Teece S. Towards evidence based emergency medicine: best BETs from Manchester Royal Infirmary. Factor VIIa for intractable blood loss in trauma. <i>Emerg Med J</i> 2002;19(6):556-557.	Ineligible study design

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Arthurs Z, Cuadrado D, Beekley A, et al. The impact of hypothermia on trauma care at the 31st combat support hospital. <i>American Journal of Surgery</i> 2006;191(5):610-614.	No usable data
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Ashrani AA, Gabriel DA, Gajewski JL, et al. Pilot study to test the efficacy and safety of recombinant factor VIIa (rFVIIa, NovoSeven (TM)) in the treatment of refractory hemorrhagic cystitis following high dose chemotherapy. <i>Blood</i> 2004;104(11 Part 1):322A.	Ineligible study design
Athale UH, Chan AK. Hemorrhagic complications in pediatric hematologic malignancies. <i>Semin Thromb Hemost</i> 2007;33(4):408-415.	Ineligible study design
Atkison PR, Jardine L, Williams S, et al. Use of recombinant factor VIIa in pediatric patients with liver failure and severe coagulopathy. <i>Transplant Proc</i> 2005;37(2):1091-1093.	Ineligible study design
Auer RN, Sutherland GR. Primary intracerebral hemorrhage: pathophysiology. <i>Canadian Journal of Neurological Sciences</i> . 2005;32 Suppl 2:S3-S12.	Ineligible study design
Auriel E, Bornstein NM. Treatment of acute intracerebral hemorrhage. <i>Israel Medical Association Journal: Imaj</i> 2006;8(11):812-814.	Ineligible study design
Bacigalupo A. Haemopoietic stem cell transplants: The impact of haemorrhagic complications. <i>Blood Reviews</i> 2003;17(Suppl 1):S6-S10.	Ineligible study design
Badjatia N, Rosand J. Intracerebral hemorrhage. <i>Neurologist</i> 2005;11(6):311-324.	Ineligible study design
Badra G, El-Abassy M, Loffy M, et al. A life-sustaining single dose of recombinant activated factor VII for an Egyptian patient with hemorrhagic crisis. <i>Saudi Med J</i> 2007;28(6):979-981.	Ineligible study design
Baker DS, Shenoy S. Treatment of non-hemophilic disorders in children with recombinant FVIIa - A review of dosing, safety, and efficacy. <i>Blood</i> 2005;106(11 Part 2):122B.	Ineligible study design
Baldi G, Altomonte F, Altomonte M, et al. Intracranial haemorrhage in patients on antithrombotics: clinical presentation and determinants of outcome in a prospective multicentric study in Italian emergency departments. <i>Cerebrovasc Dis</i> 2006;22(4):286-293.	Small sample size
Balen S, Roganovic I, Vukelic-Damiani N. Recombinant factor VIIa in treatment of severe thrombocytopenic patients: case report. <i>Vox Sanguinis</i> 2005;89(Suppl 1):195.	Ineligible study design
Ballen J, Raabe M, Muirhead B. Aortic dissection and hypothermic arrest in a Jehovah's Witness patient: a case for recombinant factor VIIa? [see comment]. <i>Canadian Journal of Anaesthesia</i> 2006;53(4):353-356.	Small sample size
Barbui T, Caruso V, Tognoni G, et al. Prognosis of veno-occlusive disease after stem cell transplantation in the DF-VOD trial. On behalf of the DF-VOD investigators. <i>Blood</i> 2004;104(11 Part 1):322A.	Not on rFVIIa
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Barkagan ZS. Pathogenesis and therapy of hemostatic disorders in cancer patients. <i>Terapevticheskii Arkhiv</i> 1997;69(7):65-67.	Ineligible study design
Barkagan ZS. The role of hemostasis system components in therapy of DIC-syndrome and thrombophilias. <i>Gematologiya i Transfuziologiya</i> 2005;50(6):9-12.	Ineligible study design
Barnes C, Blanchette V, Canning P, et al. Recombinant FVIIa in the management of intracerebral haemorrhage in severe thrombocytopenia unresponsive to platelet-enhancing treatment. <i>Transfusion Medicine</i> 2005;15(2):145-150.	Small sample size
Barro C, Wroblewski I, Piolat C, et al. Successful use of recombinant factor VIIa for severe surgical liver bleeding in a 5 month-old baby. <i>Haemophilia</i> 2004;10(2):183-185.	Ineligible study design
Basile VS, Silver FL. Recombinant activated factor VII given within 4 hours of intracerebral hemorrhage reduced hematoma growth [comment]. <i>ACP Journal Club</i> 2005;143(2):34.	Duplicate
Baudo F, Caimi TM, Mostarda G, et al. Critical bleeding in pregnancy: a novel therapeutic approach to bleeding. <i>Minerva Anestesiologica</i> 2006;72(6):389-393.	Ineligible study design
Bauza G, Hirsch E, Burke P, et al. Low-dose recombinant activated factor VII in massively transfused trauma patients with coagulopathy. <i>Transfusion</i> 2007;47(4):749-751.	Small sample size

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Baxter MS, Schroeder WS, Cheng Y, et al. Diminished response to recombinant factor VIIa in a patient with idiopathic thrombocytopenic purpura. <i>Annals of Pharmacotherapy</i> 2006;40(11):2053-2058.	Ineligible study design
Becton D, Saylor R, Morris J, et al. Treatment of bleeding with rFVIIa (NovoSeven(R)) in four diverse cases. <i>Blood</i> 2001;98(11 Part 1):263a.	Small sample size
Beldowicz BC, McDonald JM, Needham CS. Confirmed graft flow following use of recombinant factor VIIa in coronary artery bypass grafting: a case report and literature review. <i>Journal of Cardiac Surgery</i> 2006;21(5):483-486.	Small sample size
Bendtsen F, Krag A, Moller S. Treatment of acute variceal bleeding. <i>Dig Liver Dis</i> 2008;40(5):328-336.	Ineligible study design
Benharash P, Bongard F, Putnam B. Use of recombinant factor VIIa for adjunctive hemorrhage control in trauma and surgical patients. <i>American Surgeon</i> 2005;71(9):776-780.	Small sample size
Ben-Tal O, Misgav M, Kluger Y, et al. Recombinant activated factor VII (NovoSevenTM), an adjunct to replacement therapy in acute, uncontrolled, life threatening bleeding. <i>Blood</i> 2003;102(11):132b.	Ineligible study design
Berkhof FF, Eikenboom JC, Berkhof FF, et al. Efficacy of recombinant activated Factor VII in patients with massive uncontrolled bleeding: a retrospective observational analysis. <i>Transfusion</i> 2009;49(3):570-577.	Small sample size
Bernstein D. Effectiveness of the recombinant factor VIIa in patients with the coagulopathy of advanced child's B and C cirrhosis. <i>Seminars in Thrombosis and Hemostasis</i> 2000;26(4):437-438.	Ineligible study design
Bernstein DE, Glazer S, Jeffers LJ, et al. Recombinant VIIa (rFVIIa) in the treatment of prolonged prothrombin times (PT) in cirrhotics. <i>Hepatology</i> 1995;22(4 part 2):289A.	Ineligible study design
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Berntorp E, Stigendal L, Lethagen S, et al. NovoSeven in warfarin-treated patients. <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S113-S115.	Ineligible study design
Berntorp E. Recombinant FVIIa in the treatment of warfarin bleeding. <i>Seminars in Thrombosis and Hemostasis</i> 2000;26(4):433-435.	Ineligible study design
Berthier AM, Guillygomarc'h A, Messner M, et al. Use of recombinant factor VIIa to treat persistent bleeding following dental extractions in two cirrhotic patients. <i>Vox Sang</i> 2002;82(3):119-121.	Ineligible study design
Betensley AD, Yankaskas JR. Factor viia for alveolar hemorrhage in microscopic polyangiitis. <i>Am J Respir Crit Care Med</i> 2002;166(9):1291-1292.	Ineligible study design
Bhalla A, Hargroves D. Does early medical intervention have a role in the management of intracerebral haemorrhage? <i>Int J Clin Pract</i> 2008;62(4):633-641.	Ineligible study design
Bhullar IS, Braman R, Block EF. Recombinant factor VII as an adjunct to control of hemorrhage from chest trauma in a Jehovah's Witness. <i>Am Surg</i> 2007;73(8):818-819.	Small sample size
Bhuskute N, Kritzing S, Dakin M. Recombinant factor VIIa in massive obstetric haemorrhage. <i>Eur J Anaesthesiol</i> 2008;25(3):250-251.	Ineligible study design
Bianchi A, Jackson D, Maitz P, et al. Treatment of bleeding with recombinant factor VIIa in a patient with extensive burns. <i>Thromb Haemost</i> 2004;91(1):203-204.	Ineligible study design
Biancofiore G, Bisa M, Bindi LM, et al. Liver transplantation due to Herpes Simplex virus-related sepsis causing massive hepatic necrosis after thoracoscopic thymectomy. <i>Minerva Anesthesiol</i> 2007;73(5):319-322.	Small sample size
Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. <i>Circulation</i> 2002;106(20):2550-2554.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
Billio A, Morello E, Amaddii G, et al. Treatment of Refractory Thrombocytopenic Bleeding with rFVII: A Case Report. <i>Blood</i> 2002;100(11):Abstract No. 3806.	Ineligible study design
Birchall J, Stanworth SJ, Duffy MR, et al. Evidence for the use of recombinant factor VIIa in the prevention and treatment of bleeding in patients without hemophilia. <i>Transfusion Medicine Reviews</i> 2008;22(3):177-187.	Ineligible study design
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Biss TT, Hanley JP. Recombinant activated factor VII (rFVIIa/NovoSeven) in intractable haemorrhage: use of a clinical scoring system to predict outcome. <i>Vox Sang</i> 2006;90(1):45-52.	Small sample size

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Biss TT, Hanley JP. Recombinant activated factor VII (rFVIIa/NovoSeven) in intractable haemorrhage: use of a clinical scoring system to predict outcome [see comment]. <i>Vox Sanguinis</i> 2006;90(1):45-52.	Small sample size
Biss TT, Hanley JP. The use of recombinant factor VIIa in the management of major haemorrhage: Experience within the northern region of the UK. <i>British Journal of Haematology</i> 2005;129(Suppl 1):20.	Data combined for multiple conditions
Biss TT, Hanley JP. Use of recombinant factor VIIa (rFVIIa) in the management of intractable haemorrhage: a survey of current UK practice. <i>British Journal of Haematology</i> 2007;138(1):126-128.	Ineligible study design
Blansfield JS, Nekervis MA. A memorable Marine: the battle of coagulopathy. <i>Journal of Emergency Nursing</i> 2007;33(6):545-549.	Small sample size
Blasco V, Leone M, Visintini P, et al. Medical-surgical management of traumatic cardiac rupture: Relevance of recombinant activated factor VII. <i>Annales Francaises d'Anesthesie et de Reanimation</i> 2008;27(9):719-722.	Small sample size
Blatny J, Dusek L, Smid R, et al. "UniSeven" - Registry for life threatening bleeding treated with rFVIIa. Medical and technical background and first output. <i>Blood</i> 2004;104(11 Part 2):88B.	Data combined for multiple conditions
Blatt J, Gold SH, Wiley JM, et al. Off-label use of recombinant factor VIIa in patients following bone marrow transplantation. <i>Bone Marrow Transplantation</i> 2001;28(4):405-407.	Ineligible study design
Blonski W, Siropaides T, Reddy KR. Coagulopathy in liver disease. <i>Current Treatment Options in Gastroenterology</i> 2007;10(6):464-473.	Ineligible study design
Boehlen F, Morales MA, Fontana P, et al. Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature. <i>Bjog</i> 2004;111(3):284-287.	Ineligible study design
Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. <i>J Trauma</i> 2005;59(1):8-15; discussion 15-8.	Duplicate
Boldt J, Papsdorf M. Modern therapeutical strategies in intensive care medicine - are they established in Germany? Results from a questionnaire. <i>DMW Deutsche Medizinische Wochenschrift</i> 2005;130(3):87-91.	Ineligible study design
Bontempo FA, Friedlander L, Van Thiel DH. The use of recombinant human factor VIIa concentrate for short term reversal of coagulopathy in patients undergoing liver biopsy. <i>Blood</i> 2003;102(11):106b.	Ineligible study design
Bormanis J. Development of a massive transfusion protocol. <i>Transfusion & Apheresis Science</i> 2008;38(1):57-63.	Ineligible study design
Bosch J, Abraldes JG. Management of gastrointestinal bleeding in patients with cirrhosis of the liver. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):8-12.	Ineligible study design
Bosch J, Thabut D, Albillos A, et al. Recombinant factor VIIA (RFVIIA) for active variceal bleeding in patients with advanced cirrhosis: A multi-centre randomized double-blind placebo-controlled trial. <i>Journal of Hepatology</i> 2007;46(Suppl 1):S295-S296.	Duplicate
Bosch J, Thabut D, Albillos A, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. <i>Hepatology</i> 2008;47(5):1604-1614.	Duplicate
Bosch J, Thabut D, Albillos A, et al. Recombinant factor VIIa (Rfviiia) for active variceal bleeding in patients with advanced cirrhosis: A multi-center randomised double-blind placebo-controlled trial. <i>Gastroenterology</i> . 2007;132(4 Suppl 2):A728.	Duplicate
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Cimic N, Tulleken JE, Zijlstra JG, et al. Recombinant factor VIIa for refractory hemorrhage after lung transplantation. <i>Transplantation</i> 2005;79(6):741-742.	Ineligible study design
Clark AD, Gordon WC, Walker ID, et al. 'Last-ditch' use of recombinant factor VIIa in patients with massive haemorrhage is ineffective. <i>Vox Sanguinis</i> 2004;86(2):120-124.	Small sample size
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Cosmi B. Review: recombinant factor VIIa does not differ from placebo for prevention or treatment of bleeding in patients without hemophilia [comment]. <i>ACP Journal Club</i> 2007;147(3):70.	Ineligible study design
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Criddle LM. Recombinant factor VIIa and the trauma patient. <i>Journal of Emergency Nursing</i> 2006;32(5):404-408.	Ineligible study design
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Dargaud Y, Bordet JC, Lienhart A, et al. Use of the thrombin generation test to evaluate response to treatment with recombinant activated factor VII. <i>Seminars in Hematology</i> 2008;45(2 Suppl 1):S72-S73.	Animal or in-vitro study
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De Fabritiis P, Dentamaro T, Picardi A, et al. Recombinant factor VIIa for the management of severe hemorrhages in patients with hematologic malignancies. <i>Haematologica</i> . 2004;89(2):243-245.	Ineligible study design
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de Miranda PAP. "Evaluation of off-label recombinant activated factor VII for multiple indications in children" by Reiter et al. <i>Clinical & Applied Thrombosis/Hemostasis</i> 2008;14(2):247; author reply 247.	Ineligible study design
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de Wolf JT, Hendriks HG, Meijer K, et al. Impressive reduction of blood requirements in orthotopic liver transplantation due to recombinant factor VIIa (rFVIIa, NovoSeven). <i>Transfusion (Bethesda)</i> 1999;39(10 Suppl):87S.	Small sample size
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DelGaudio JM, Martinez EJ. Endoscopic sinus surgery in patients with chronic hepatic failure awaiting liver transplant. <i>American Journal of Rhinology</i> 2004;18(4):253-258.	Ineligible study design

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Dement'eva I, Gladysheva VG, Charnaia MA, et al. [On the mechanism of action of recombinant activated factor VII in massive non-hemophylic bleeding in cardiosurgical patients]. <i>Vestn Ross Akad Med Nauk</i> 2006(12):21-25.	Foreign language
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Fishman PE, Drumheller BC, Dubon ME, et al. Recombinant activated factor VII use in the emergency department. <i>Emergency Medicine Journal</i> 2008;25(10):625-630.	Ineligible study design
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Franchini M, Zaffanello M, Veneri D. Recombinant factor VIIa. An update on its clinical use. <i>Thromb Haemost</i> 2005;93(6):1027-1035.	Ineligible study design
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Fraser IS, Porte RJ, Kouides PA, et al. A benefit-risk review of systemic haemostatic agents: part 1: in major surgery. <i>Drug Safety</i> 2008;31(3):217-230.	Ineligible study design
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Hardy JF, de Moerloose P, Samama CM. The coagulopathy of massive transfusion. <i>Vox Sanguinis</i> 2005;89(3):123-127.	Ineligible study design
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Heisel M, Nagib M, Madsen L, et al. Use of recombinant factor VIIa (rFVIIa) to control intraoperative bleeding in pediatric brain tumor patients. Pediatric Blood & Cancer 2004;43(6):703-705.	Ineligible study design
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Helie F, Hardy J-F. Anesthesiologists and the pharmaceutical industry: awareness is paramount. Canadian Journal of Anesthesia 2007;54(12):1026-1027.	Ineligible study design
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Heslet L, Nielsen JD, Levi M, et al. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. <i>Critical Care (London, England)</i> 2006;10(6):R177.	Ineligible study design
Hess JR, Zimrin AB. Massive blood transfusion for trauma. <i>Current Opinion in Hematology</i> 2005;12(6):488-492.	Ineligible study design
Heuer L, Blumenberg D. Accidental overdosage of recombinant factor VIIa due to mistaken package size. <i>Thrombosis and Haemostasis</i> 2004;91(6):1249-1250.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Heuer L, Mathias D, Mathine K, et al. Recombinant Factor VIIa [rFVIIa - NovoSeven(R)] for Diffuse Intractable Bleedings. <i>Anesthesiology Abstracts of Scientific Papers Annual Meeting 2002:Abstract No. A-391</i> .	Small sample size
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Hoffman M, Hoffman M. FVIIa: you've come a long way, baby [comment]. <i>Blood</i> 2008;112(8):3002-3003.	Animal or in-vitro study
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Hoffman M, Monroe DM, Roberts HR. Platelet-dependent action of high-dose factor VIIa. <i>Blood</i> 2002;100(1):364-365; author reply 365.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Hoffman M. A cell-based model of coagulation and the role of factor VIIa. <i>Blood Rev</i> 2003;17 Suppl 1:S1-S5.	Animal or in-vitro study
Hoffman M. Laboratory monitoring of high-dose factor VIIa therapy [comment]. <i>Annals of Internal Medicine</i> 2003;139(9):791.	Ineligible study design

Excluded article	Reason for exclusion
Hoffman R, Mahajana A, Agmon P, et al. Successful use of recombinant activated factor VII (Novoseven(R)) in controlling severe intra-abdominal bleeding after liver needle biopsy. <i>Thrombosis and Haemostasis</i> 2002;87(2):346-347.	Ineligible study design
Holcomb JB, Hoots K, Moore FA. Treatment of an acquired coagulopathy with recombinant activated factor VII in a damage-control patient. <i>Military Medicine</i> 2005;170(4):287-290.	Small sample size
Holcomb JB, Neville HL, Fischer CF, et al. Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding in a septic patient. <i>Curr Surg</i> 2003;60(4):423-427.	Ineligible study design
Holcomb JB. Methods for improved hemorrhage control. <i>Critical Care (London, England)</i> 2004;8 Suppl 2:S57-S60.	Ineligible study design
Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. <i>J Trauma</i> 2005;58(6):1298-1303.	Ineligible study design
Hollnberger H, Gruber E, Seelbach-Goebel B. Major post-partum hemorrhage and treatment with recombinant factor VIIa. <i>Anesth Analg</i> 2005;101(6):1886-1887.	Ineligible study design
Hoots WK. Challenges in the therapeutic use of a "so-called" universal hemostatic agent: recombinant factor VIIa. <i>Hematology</i> 2006:426-431.	Ineligible study design
Hoots WK. Hemorrhage following hematopoietic stem cell transplantation--which arrows belong in the quiver? [comment]. <i>Journal of Thrombosis & Haemostasis</i> 2005;3(9):1933-1934.	Ineligible study design
Horton JD, DeZee KJ, Wagner M. Use of rFVIIa in the trauma setting--practice patterns in United States trauma centers. <i>American Surgeon</i> 2008;74(5):413-417.	No usable data
Hossain NH, Farzana TF, Shamsi TS, et al. Use of activated recombinant factor VII for the control of post partum hemorrhage (PTH). <i>Blood</i> 2006;108(11 Part 2):84B-85B.	Ineligible study design
Hoyt DB. A clinical review of bleeding dilemmas in trauma. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):40-43.	Ineligible study design
Hsia CC, Chin-Yee IH, McAlister VC, et al. Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. <i>Annals of Surgery</i> 2008;248(1):61-68.	Ineligible study design
Hsia CC, Zurawska JH, Tong MZY, et al. Recombinant activated factor VII (rFVIIa) in the treatment of non-hemophilia patients: Physician underreporting of thromboembolic adverse events. <i>Blood</i> 2007;110(11 Part 1):924A.	Data combined for multiple conditions
Hsieh A, Cheong I. Use of recombinant activated factor VII in a Jehovah's Witness patient. <i>Am J Emerg Med</i> 2007;25(9):1085 e1-2.	Ineligible study design
Hsieh PC, Awad IA, Getch CC, et al. Current updates in perioperative management of intracerebral hemorrhage. <i>Neurol Clin</i> 2006;24(4):745-764.	Ineligible study design
Hu Q, Brady JO. Recombinant activated factor VII for treatment of enoxaparin-induced bleeding. <i>Mayo Clin Proc</i> 2004;79(6):827.	Ineligible study design
Huang WY, Kruskal MS, Bauer KA, et al. The use of recombinant activated factor VII in three patients with central nervous system hemorrhages associated with factor VII deficiency. <i>Transfusion</i> 2004;44(11):1562-1566.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Hyde CJ, Stanworth SJ, Murphy MF. Can you see the wood for the trees? Making sense of forest plots in systematic reviews 2. Analysis of the combined results from the included studies. <i>Transfusion</i> 2008;48(4):580-583.	Not on rFVIIa
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Imberti R. Efficacy and safety of factor VIIa on rebleeding after surgery for spontaneous intracerebral hemorrhage (ICH). <i>ClinicalTrials.gov</i> . 2005.	No usable data
Inagaki M, Mori T, Tsunematsu Y, et al. Use of recombinant activated factor VII to control bleeding in a young child with qualitative platelet disorder: a case report. <i>Blood Coagul Fibrinolysis</i> 2006;17(4):317-322.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Ingerslev J, Sneppen O, Hvid I, et al. Treatment of acute bleeding episodes with rFVIIa. <i>Vox Sang</i> 1999;77 Suppl 1:42-46.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Ingerslev J, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation [see comment]. <i>Journal of Postgraduate Medicine</i> 2007;53(1):17-22.	Small sample size
Ionita CC, Ferrara J, McDonagh DL, et al. Systemic hemostasis with recombinant-activated factor VII followed by local thrombolysis with recombinant tissue plasminogen activator in intraventricular hemorrhage. <i>Neurocrit Care</i> 2005;3(3):246-248.	Small sample size
Iorio A. Latrogenic causes of an ICH: OAT therapy. <i>European Journal of Anaesthesiology</i> . 2008;25(Suppl 42):8-11.	Ineligible study design
Iorio A. rFVIIa in ICH in patients treated with anticoagulants or anti-platelets. <i>ClinicalTrials.gov</i> . 2005.	No usable data
Ippoliti C, Hey D, Donato ML, et al. Use of activated recombinant factor VII (rFVIIa) for treatment of pulmonary hemorrhage in stem cell transplantation recipients. <i>Blood</i> 2002;100(11):Abstract No. 3308.	Ineligible study design
Isbister J, Phillips L, Dunkley S, et al. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. <i>Intern Med J</i> 2008;38(3):156-165.	Data combined for multiple conditions
Islam J, Azhar S, Alperin JB, et al. Recombinant factor VIIa for uncontrolled bleeding in 2 different cases of coagulopathy. <i>J Am Board Fam Pract</i> 2003;16(6):549-552.	Ineligible study design
Jabbour N, Gagandeep S, Peilin AC, et al. Recombinant human coagulation factor VIIa in Jehovah's Witness patients undergoing liver transplantation. <i>Am Surg</i> . 2005;71(2):175-9.	Small sample size
Jaffe J, Alkhawam L, Du H, et al. Outcome predictors and spectrum of treatment eligibility with prospective protocolized management of intracerebral hemorrhage. <i>Neurosurgery</i> 2009;64(3):436-445.	No usable data
Jaggers J, Lawson JH. Coagulopathy and inflammation in neonatal heart surgery: mechanisms and strategies. <i>Annals of Thoracic Surgery</i> 2006;81(6):S2360-S2366.	Ineligible study design
James KMH, Melikian CN, Chowdary P, et al. Thromboelastography-guided recombinant factor VIIa administration in a patient with refractory autoimmune idiopathic thrombocytopenia. <i>Anesthesia & Analgesia</i> . 2008;107(2):402-405.	Ineligible study design
Jansen JO, Thomas R, Loudon MA, et al. Damage control resuscitation for patients with major trauma. <i>BMJ</i> 2009;338:b1778.	Ineligible study design
Jaschinski U, Ried M, Lichtwarck-Aschoff M, et al. Bleeding diathesis due to failed antagonism of heparin: successful treatment with recombinant factor VIIa. <i>Anesth Analg</i> 2004;99(6):1872.	Small sample size
Jayr C, Kuhlman L, Lodge P, et al. Recombinant factor VIIa in partial hepatectomy: a randomized, placebo-controlled, double-blind clinical trial. <i>Anesthesiology Abstracts of Scientific Papers Annual Meeting 2003:Abstract No. A-151</i> .	Duplicate
Jeffers L, Balart L, Erhardtson E, et al. Efficacy and safety of rFVIIa in patients with severe coagulopathy undergoing laparoscopic liver biopsy. <i>Blood</i> 1999;94(10 Suppl 1 Part 1):236a.	Duplicate
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Jha A, Balasubramanian M, Charania R, et al. Treatment of diffuse alveolar hemorrhage with recombinant factor VIIa in patients with hematologic malignancies. <i>Blood</i> 2005;106(11 Part 1):607A.	Ineligible study design
Jimenez-Saenz M. Recombinant factor VIIa for variceal bleeding: when, why, and how? <i>Gastroenterology</i> 2005;128(4):1150-1151; author reply 1151.	Ineligible study design
Jirapinyo M, Manonai J, Herabutya Y, et al. Effectiveness of recombinant activated factor VII (rFVII a) for controlling intractable postpartum bleeding: report of two cases and literature review. <i>J Med Assoc Thai</i> 2007;90(5):977-981.	Ineligible study design
Johannessen M, Nielsen G, Nordfang O. Comparison of the factor VII:C clot analysis and a modified activated factor VII analysis for monitoring factor VII activity in patients treated with recombinant activated factor VII (NovoSeven). <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S159-S164.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Johansson PI, Eriksen K, Alsbjorn B. Rescue treatment with recombinant factor VIIa is effective in patients with life-threatening bleedings secondary to major wound excision: a report of four cases. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2006;61(4):1016-1018.	Ineligible study design
Johansson PI. Off-label use of recombinant factor VIIa for treatment of haemorrhage: results from randomized clinical trials. <i>Vox Sang</i> 2008.	Ineligible study design
Johansson PI. Off-label use of recombinant factor VIIa for treatment of haemorrhage: results from randomized clinical trials. <i>Vox Sanguinis</i> 2008;95(1):1-7.	Duplicate
Johnson SJ, Ross MB, Moores KG. Dosing factor VIIa (recombinant) in nonhemophilic patients with bleeding after cardiac surgery. <i>Am J Health Syst Pharm</i> 2007;64(17):1808-1812.	Ineligible study design
Jureczko L, Kolacz M, Trzebicki J, et al. Perioperative use of recombinant activated factor VII in liver transplantation. <i>Ann Transplant</i> 2003;8(4):40-42.	Small sample size
Jureczko L, Trzebicki J, Zawadzki A, et al. Application of recombinant activated factor VII for treatment of impaired haemostasis during liver transplantation in recipients with Wilson's disease--a report of two cases. <i>Annals of Transplantation</i> 2002;7(3):52-54.	Small sample size
Jurlander B, Thim L, Klausen NK, et al. Recombinant activated factor VII (rFVIIa): characterization, manufacturing, and clinical development. <i>Seminars in Thrombosis & Hemostasis</i> 2001;27(4):373-384.	Ineligible study design
Juvela S, Kase CS. Advances in intracerebral hemorrhage management. <i>Stroke</i> 2006;37(2):301-304.	Ineligible study design
Kabakchieva R, Kenderova V, Perenovska P, et al. Recombinant factor VIIa - NovoSeven in pediatric practice. <i>Acta Physiologica Congress</i> :P1424.	Ineligible study design
Kalainov DM, Valentino LA, Kalainov DM, et al. Recombinant activated factor VII as a temporary reversal agent for warfarin anticoagulation: a cautionary report on an off-label application. <i>American Journal of Orthopedics (Chatham, NJ)</i> 2008;37(11):572-574.	Ineligible study design
Kaleelrahman M, Minford A, Parapia LA. Use of recombinant factor VIIa in inherited platelet disorders [comment]. <i>British Journal of Haematology</i> 2004;125(1):95-96.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Kalenka A, Munch E, Fiedler F. Recombinant factor VIIa to treat traumatic bleeding in a children. <i>Paediatric Anaesthesia</i> 2005;15(11):1025-1027.	Small sample size
Kalicenski P, Kaminski A, Drewniak T, et al. Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. <i>Transplant Proc</i> 1999;31(1-2):378-379.	Small sample size
Kamphuisen PW, van den Akker JM, Kaasjager KA, et al. Control of life-threatening pulmonary bleeding with activated recombinant factor VII. <i>Am J Med</i> 2002;112(4):332-333.	Small sample size
Karadimov D, Binev K, Nachkov Y, et al. Use of activated recombinant Factor VII (NovoSeven) during neurosurgery. <i>Journal of Neurosurgical Anesthesiology</i> 2003;15(4):330-332.	Ineligible study design
Karadimov D, Bochev D, Cherkezov J, et al. Preoperative preparation of patients with liver cirrhosis and massive bleeding from oesophageal varices. <i>Anaesthesiology and Intensive Care</i> 2005;32(1):28-31.	Unable to obtain publication
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Karalapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery (vol 53, pg 926, 2006). Canadian Journal of Anesthesia 2006;53(12):1271.	Ineligible study design
Karimi M, Zakerinia M, Khojasteh HN, et al. Successful treatment of cyclophosphamide induced intractable hemorrhagic cystitis with recombinant FVIIa (NovoSeven) after allogenic bone marrow transplantation. Journal of Thrombosis & Haemostasis 2004;2(10):1853-1855.	Ineligible study design
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Karkouti K, Wijeyesundera D, McCluskey S, et al. Efficacy and safety of recombinant factor VIIa (rF-VIIa) for treating refractory blood loss after cardiac surgery: an open-label single-arm clinical trial. Anesthesiology Abstracts of Scientific Papers Annual Meeting 2003:Abstract No. A-164.	Duplicate
Karkouti K, Yau TM, Riaz S, et al. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. Canadian Journal of Anaesthesia 2006;53(8):802-809.	Duplicate
Kase CS. Advances in intracerebral haemorrhage management. European Journal of Anaesthesiology - Supplement 2008;42:16-22.	Ineligible study design
Kase CS. Hemostatic treatment in the early stage of intracerebral hemorrhage: the recombinant factor VIIa experience. Stroke 2005;36(10):2321-2322.	Ineligible study design
Kashyap AS, Kashyap S. The clot thickens! In thin air. Arch Intern Med 2002;162(15):1783.	Not on rFVIIa
Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. Ann Thorac Surg 2002;74(3):910-912.	Small sample size
Kaw Jr LL, Coimbra R, Potenza BM, et al. The use of recombinant factor VIIa for severe intractable bleeding during spine surgery. Spine 2004;29(12):1384-1387; discussion 1388.	Small sample size
Kempton CL, Harvey III RD, Roberts HR. Novel therapeutic agents in the management of hemorrhage and thrombosis. Cardiovascular & Hematological Agents in Medicinal Chemistry 2006;4(4):319-334.	Ineligible study design
Kenet G, Walden R, Eldad A, et al. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet 1999;354(9193):1879.	Small sample size
Kenet G. Recombinant FVIIa for profuse bleeding in trauma and surgery. Journal fur Anesthesie und Intesivbehandlung 2001;8(3):112.	Unable to obtain publication
Kessler C, Knudsen JB. Recombinant factor VIIa in patients without congenital coagulation disorders - a new registry on investigational use. Blood 2002;100(11):Abstract No. 4051.	No data reported
Kessler C, Szurlej D, Heymann Cv. Recombinant factor VIIa (rFVIIa) reverses refractory post-operative cardiac bleeding: results from cases reported to the haemostasis.com registry. Blood 2002;100(11):Abstract No. 4050.	Small sample size
Kessler C. Haemorrhagic complications of thrombocytopenia and oral anticoagulation: is there a role for recombinant activated factor VII? Intensive Care Medicine 2002;28 Suppl 2:S228-S234.	Ineligible study design
Kessler C. Haemostasis.com: clinical experiences in the investigational use of rFVIIa in the management of severe haemorrhage. British Journal of Haematology 2004;127(2):230.	Ineligible study design
Kessler CM. Antidotes to haemorrhage: recombinant factor VIIa. Best Pract Res Clin Haematol 2004;17(1):183-197.	Ineligible study design
Kessler CM. Current and future challenges of antithrombotic agents and anticoagulants: Strategies for reversal of hemorrhagic complications. Seminars in Hematology 2004;41(1 Suppl 1):44-50.	Ineligible study design
Kessler CM. New perspectives in hemophilia treatment. Hematology 2005:429-435.	Ineligible study design
Key N. Current insights on the risk of thrombogenicity with off-label use of rFVIIa. Clinical Advances in Hematology & Oncology 2006;4(1):34-35.	Ineligible study design
Key NS, Christie BA, Jones B, et al. Evaluation of the in vivo effect of rFVIIa (Novoseven) using the clot signature analyzer (CSA). Haemostasis 2000;30(Suppl 1):43.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)

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Key NS. Recombinant FVIIa for intractable hemorrhage: more questions than answers. <i>Transfusion</i> 2003;43(12):1649-1651.	Ineligible study design
Khan AZ, Parry JM, Crowley WF, et al. Recombinant factor VIIa for the treatment of severe postoperative and traumatic hemorrhage. <i>American Journal of Surgery</i> 2005;189(3):331-334.	Small sample size
Khan ZH, Soltani AE, Rahmani P. Postoperative pulmonary thromboembolism possibly associated with recombinant activated factor VII infusion for the treatment of uncontrolled hemorrhage during vertebral instrumentation. <i>J Anesth</i> 2007;21(2):258-260.	Small sample size
Kim JY, Lee KS, Kwon SH, et al. Successful treatment of intractable gastrointestinal hemorrhage with low dose of recombinant FVIIa (Novoseven (R)) in pediatric patient without coagulation deficiencies. <i>Blood</i> 2004;104(11 Part 2):79B.	Ineligible study design
Kissela BM, Eckman MH. Cost effectiveness of recombinant factor VIIa for treatment of intracerebral hemorrhage. <i>BMC Neurology</i> 2008;8:17.	Ineligible study design
Kjalke M, Ezban M, Hedner U. Increased initial thrombin generation may explain the efficacy of high-dose factor VIIa in thrombocytopenia. <i>Blood</i> 1999;94(10 Suppl 1 Part 1):451a.	Animal or in-vitro study
Klamroth R, Gottstein S, Landgraf H. Successful use of recombinant factor VIIa to prevent bleeding during major surgery in a patient with severe immune thrombocytopenia. <i>Blood</i> 2002;100(11):Abstract No. 3779.	Ineligible study design
Klitgaard T, Nielsen TG. Overview of the human pharmacokinetics of recombinant activated factor VII. <i>British Journal of Clinical Pharmacology</i> 2008;65(1):3-11.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
Klitgaard T, Tabanera y Palacios R, Boffard KD, et al. Pharmacokinetics of recombinant activated factor VII in trauma patients with severe bleeding. <i>Critical Care (London, England)</i> 2006;10(4):R104.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
Klitgaard T. Application of trial simulation in the design of a clinical study of recombinant factor (rFVIIa) in cirrhotic patients with active varicose bleeding. <i>Clinical Pharmacology & Therapeutics</i> 2004;75(2):P40.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
Kluger Y, Riou B, Rossaint R, et al. Safety of rFVIIa in hemodynamically unstable polytrauma patients with traumatic brain injury: post hoc analysis of 30 patients from a prospective, randomized, placebo-controlled, double-blind clinical trial. <i>Critical Care (London, England)</i> 2007;11(4):R85.	Duplicate
Knight M, Ukoss. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage [see comment]. <i>BJOG: An International Journal of Obstetrics & Gynaecology</i> 2007;114(11):1380-1387.	Ineligible study design
Kogan A, Berman M, Kassif Y, et al. Use of recombinant factor VII to control bleeding in a patient supported by right ventricular assist device after heart transplantation. <i>Journal of Heart & Lung Transplantation</i> 2005;24(3):347-349.	Small sample size
Kogan A, Berman M, Stein M, et al. Recombinant factor VIIa use in cardiac surgery--expanding the arsenal therapy for intractable bleeding? <i>Journal of Cardiovascular Surgery</i> 2004;45(6):569-571.	Small sample size
Kogler VM, Slobodnjak Z, Samarzija M, et al. Successful use of activated recombinant factor VII in life-threatening bleeding after thoracic surgery. <i>Swiss Medical Weekly</i> 2007;137(27-28):407-410.	Ineligible study design
Korte WC, Moor S. Near fatal hemorrhage in traumatic bilateral leg amputation with coagulopathy, acidosis, and hypothermia and salvage therapy with recombinant factor VIIa. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2007;63(1):E1-E4.	Small sample size
Kositchaiwat C, Chuansumrit A. Experiences with recombinant factor VIIa for the prevention of bleeding in patients with chronic liver disease undergoing percutaneous liver biopsies and endoscopic retrograde cholangiopancreatography (ERCP). <i>Thromb Haemost</i> 2001;86(4):1125-1126.	Ineligible study design
Kotsi P, Gavalaki M, Anastasopoulou I, et al. The use of recombinant FVIIa (rFVIIa) in patients with uncontrollable surgical or post surgical bleeding. <i>Vox Sanguinis</i> 2006;91(Suppl 3):172.	No eligible outcomes
Kotze A. Recombinant activated factor VII in trauma: case report and review of published guidelines. <i>British Journal of Intensive Care</i> 2007;17(2):66-69.	Small sample size

Excluded article	Reason for exclusion
Kovesi T, Royston D. Pharmacological approaches to reducing allogeneic blood exposure. <i>Vox Sanguinis</i> 2003;84(1):2-10.	Ineligible study design
Kozek-Langenecker S. Management of massive operative blood loss. <i>Minerva Anestesiologica</i> 2007;73(7-8):401-415.	Ineligible study design
Krafft A, Asmis LM, Zimmermann R. Treatment of midgestational placental haemorrhage with recombinant factor VIIa. <i>Thrombosis and Haemostasis</i> . 2008;100(1):154-155.	Ineligible study design
Kretzschmar M, Zahm DM, Remmler K, et al. Pathophysiological and therapeutic aspects of amniotic fluid embolism (anaphylactoid syndrome of pregnancy): Case report with lethal outcome and overview. <i>Anaesthesist</i> 2003;52(5):419-426.	Ineligible study design
Kristeller JL. Recombinant factor VIIa attenuates bleeding due to enoxaparin. <i>Pharmacotherapy</i> 2003;23(10):1372.	Ineligible study design
Kristensen J, Alizadeh H, Shammas V, et al. Recombinant FVIIa effectively control bleedings when patients are properly selected. Retrospective analysis. <i>Haematologica-The Hematology Journal</i> 2008;93(Suppl 1):496	Small sample size
Kristensen J, Killander A, Hippe E, et al. Recombinant factor VIIa (rFVIIa) reduces the bleeding time in patients with thrombocytopenia. <i>Blood</i> 1993;82(10 Suppl 1).	Ineligible study design
Kristensen J, Killander A, Hippe E, et al. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. <i>Haemostasis</i> 1996;26 Suppl 1:159-164.	Ineligible study design
Ku G, Ting WC, Lim ST, et al. Life-threatening coagulopathy associated with use of Campath (alemtuzumab) in maintenance steroid-free renal transplant given before surgery. <i>Am J Transplant</i> 2008;8(4):884-886.	Ineligible study design
Kubisz P, Plamenova I, Chudej J, et al. Recombinant activated factor VIIa in patients at the high risk of bleeding. <i>Blood</i> 2003;102(11):103b.	Small sample size
Kubisz P, Stasko J. Recombinant activated factor VII in patients at high risk of bleeding. <i>Hematology</i> 2004;9(5-6):317-332.	Ineligible study design
Kulkarni R, Daneshmand A, Guertin S, et al. Successful use of activated recombinant factor VII in traumatic liver injuries in children. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2004;56(6):1348-1352.	Small sample size
Kulkarni R, Daneshmand A, Guertin SR, et al. Successful use of recombinant factor VIIa (rFVIIa) in traumatic liver injuries in children. <i>Pediatric Research</i> 2002;51(4 Part 2):251A.	Small sample size
Kumar S, Badrinath HR. Early recombinant factor VIIa therapy in acute intracerebral hemorrhage: promising approach. <i>Neurol India</i> 2006;54(1):24-27.	Ineligible study design
Kumar S. Expansion of traumatic intracerebral hemorrhage: treatment implications with recombinant factor VIIa [comment]. <i>Neurology India</i> 2007;55(1):81.	Ineligible study design
Kurekci AE, Atay AA, Okutan V, et al. Recombinant activated factor VII for severe gastrointestinal bleeding after chemotherapy in an infant with acute megakaryoblastic leukemia. <i>Blood Coagulation & Fibrinolysis</i> 2005;16(2):145-147.	Ineligible study design
Labattaglia MP, Ihle B. Recombinant activated factor VII: current perspectives and Epworth experience. <i>Heart Lung Circ</i> 2007;16 Suppl 3:S96-S101.	Small sample size
Lacheva A, Georgiev S, Pilosoff V, et al. Administration of recombinant factor VIIa for the management of massive postoperative blood loss in children with congenital heart defects. <i>Anaesthesiology and Intensive Care</i> 2008;35(2):3-8.	Foreign language
Laffan M, O'Connell NM, Perry DJ, et al. Analysis and results of the recombinant factor VIIa extended-use registry. <i>Blood Coagulation & Fibrinolysis</i> 2003;14 Suppl 1:S35-S38.	Small sample size
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Laffan MA, Tait RC, Blatny J, et al. Use of recombinant activated factor VII for bleeding in pancreatitis - A case series. <i>Pancreas</i> 2005;30(3):279-284.	Ineligible study design
Laffan MA, Tait RC, Blatny J, et al. Use of recombinant activated factor VII for bleeding in pancreatitis: a case series. <i>Pancreas</i> 2005;30(3):279-284.	Ineligible study design
Laird R, Carabine U. Recombinant factor VIIa for major obstetric haemorrhage in a Jehovah's Witness. <i>International Journal of Obstetric Anesthesia</i> 2008;17(2):193-194.	Ineligible study design
Lam MS, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. <i>Ann Pharmacother</i> 2005;39(5):885-891.	Ineligible study design
Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. <i>Annals of Pharmacotherapy</i> 2005;39(5):885-891.	Ineligible study design
Lamarche Y, Demers P, Poirier NC, et al. Safety and efficiency of recombinant activated factor VII in postcardiotomy massive hemorrhage. <i>Can J Cardiol</i> 2007;23(10):809-813.	Small sample size

Excluded article	Reason for exclusion
Langendonck L, Appel IM, van Kessel-Bakvis CL. Effective treatment with recombinant factor VIIa in a patient with storage pool deficiency. <i>Haemostasis</i> 2000;30(1-2):74.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Lapchak PA, Araujo DM. Advances in hemorrhagic stroke therapy: conventional and novel approaches. <i>Expert Opinion on Emerging Drugs</i> 2007;12(3):389-406.	Ineligible study design
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Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):55-64.	Ineligible study design
Leblebisatan G, Sasmaz I, Antmen B, et al. Management of refractory hemorrhage in a kala-azar patient with thrombocytopenia and coagulopathy by using recombinant factor VIIa (rFVIIa). <i>Blood</i> 2005;106(11 Part 2):103B.	Ineligible study design
Leblebisatan G, Sasmaz I, Antmen B, et al. A successful use of recombinant factor VIIa in a patient with inhibitors, for bilateral cataract operation and circumcision. <i>Haemophilia</i> 2006;12(2):187-189.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Leblebisatan G, Sasmaz I, Mert K, et al. Management of refractory intracranial hemorrhage in a coagulopathic patient with liver disease by using recombinant factor VIIa (rFVIIa). <i>Blood</i> 2005;106(11 Part 2):102B-103B.	Small sample size
Lecumberri R, Panzio C, Paramo JA, et al. Acquired inhibitor of the intrinsic pathway in a non-haemophilic patient. Control of bleeding by recombinant factor VIIa. <i>Br J Haematol</i> 2002;119(1):284-285.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Lees K, Christensen MC, Raiko M, et al. Cost-effectiveness of recombinant activated factor VII in the treatment of acute intracerebral haemorrhage in the UK. <i>European Journal of Neurology</i> 2006;13(Suppl 2).	Ineligible study design
Leibovitch L, Kenet G, Mazor K, et al. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. <i>Pediatric Critical Care Medicine</i> 2003;4(4):444-446.	Small sample size
Leung T, Han J, Hao Q, et al. The 9th International Symposium on Thrombolysis and Acute Stroke Therapy (TAST 2006), 2-3 December 2006 Hong Kong. <i>Int J Stroke</i> 2007;2(2):77-79.	Ineligible study design
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Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. <i>Critical Care Medicine</i> 2005;33(4):883-890.	Ineligible study design
Levi M, Vink R, de Jonge E. Prevention and treatment of bleeding by pro-hemostatic treatment strategies. <i>Wien Med Wochenschr</i> 2003;153(19-20):421-425.	Ineligible study design
Levi M. Efficacy and safety of prohemostatic agents. <i>Vox Sang</i> 2008;95(Suppl 1):35.	Ineligible study design
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Levi M. Recombinant factor VIIa: a general hemostatic agent? Not yet [comment]. <i>Journal of Thrombosis & Haemostasis</i> 2004;2(10):1695-1697.	Ineligible study design
Levi M. Use of recombinant factor VIIa in the perioperative period. <i>Hamostaseologie</i> 2009;29(1):68-70.	Ineligible study design
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Levy JH, Tanaka KA. The anticoagulated patient: Strategies for effective blood loss management. <i>Surgery (St Louis)</i> 2007;142(4 Suppl S):S71-S77.	Ineligible study design
Levy JH. Hemostatic agents. <i>Transfusion (Malden)</i> 2004;44(12 Suppl S):58S-62S.	Ineligible study design

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Levy JH. Novel concepts in treatment and prevention of bleeding. <i>Anesthesia & Analgesia</i> 2005(Suppl. S):43-47.	Ineligible study design
Levy JH. Overview of clinical efficacy and safety of pharmacologic strategies for blood conservation. <i>American Journal of Health-System Pharmacy</i> 2005;62(18 Suppl 4):S15-S19.	Ineligible study design
Levy JH. Pharmacologic methods to reduce perioperative bleeding. <i>Transfusion</i> 2008;48(1 Suppl):31S-38S.	Ineligible study design
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Liebekind DS. American Stroke Association--28th International Conference. 13-15 February 2003, Phoenix, AZ, USA. <i>IDrugs</i> . 2003;6(4):288-289.	Ineligible study design
Liem AK, Biesma DH, Ernst SM, et al. Recombinant activated factor VII for false aneurysms in patients with normal haemostatic mechanisms. <i>Thromb Haemost</i> 1999;82(1):150-151.	Small sample size
Lin J, Hanigan WC, Tarantino M, et al. The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. <i>Journal of Neurosurgery</i> 2003;98(4):737-740.	Small sample size
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Lodge JPA. Hemostasis in liver resection surgery. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):70-75.	Ineligible study design
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Loudon B, Smith MP. Recombinant factor VIIa as an adjunctive therapy for patients requiring large volume transfusion: a pharmacoeconomic evaluation. <i>Internal Medicine Journal</i> 35(8):463-467.	Ineligible study design
Louie R, Thomas B, Irwin R, et al. rFVIIa and obstructive hydronephrosis. <i>Pediatric Blood & Cancer</i> 2008;50(2):431.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)

Excluded article	Reason for exclusion
Louie R, Thomas B, Irwin R. rFVIIa and obstructive hydronephrosis. <i>Pediatr Blood Cancer</i> 2008;50(2):431.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Lund-Hansen T. NovoSeven--virus safety. <i>Haemostasis</i> 1996;26 Suppl 1:96-97.	Animal or in-vitro study
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Lusher JM. Recombinant clotting factors: a review of current clinical status. <i>Biodrugs</i> 2000;13(4):289-298.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Lynn M, Jeroukhimov I, Klein Y, et al. Updates in the management of severe coagulopathy in trauma patients. <i>Intensive Care Medicine</i> 2002;28 Suppl 2:S241-S247.	Ineligible study design
Ma B, Wang ZN, Zhang BR. Effect of recombinant activated factor VII a on early recovery of patients undergoing cardiac valve replacement under cardiopulmonary bypass: a randomized double-blind placebo-controlled trial. <i>Dier Junyi Daxue Xuebao</i> 2006;27(10):1110-1113.	Foreign language
Macdonald JA, Fraser JF, Foot CL, et al. Successful use of recombinant factor VII in massive hemoptysis due to community-acquired pneumonia. <i>Chest</i> 2006;130(2):577-579.	Ineligible study design
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Mackonochie M, Chan D. Oral and poster presentations. 13-17 March 2005, San Diego, CA, USA. <i>IDrugs</i> . 2005;8(4):285-287.	Not on rFVIIa
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Malato A, Lo Monte AI, Anastasio R, et al. Successful treatment of gastrointestinal bleeding with recombinant factor VIIa after kidney transplantation in patients with pancytopenia. <i>Transplant Proc</i> 2006;38(4):1031-1033.	Ineligible study design
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Mallarkey G, Brighton T, Thomson A, et al. An evaluation of eptacog alfa in nonhaemophiliac conditions. <i>Drugs</i> 2008;68(12):1665-1689.	Ineligible study design
Mandell BF. Messing with mother nature [comment]. <i>Cleveland Clinic Journal of Medicine</i> 2005;72(4):265.	Ineligible study design
Manning BJ, Hynes N, Courtney DF, et al. Recombinant factor VIIa in the treatment of intractable bleeding in vascular surgery. <i>European Journal of Vascular & Endovascular Surgery</i> 2005;30(5):525-527.	Ineligible study design
Mannucci PM, Levi M. Prevention and treatment of major blood loss. <i>N Engl J Med</i> 2007;356(22):2301-2311.	Ineligible study design
Mannucci PM. Intracerebral haemorrhage and recombinant factor VIIa: not so good news! <i>Internal & Emergency Medicine</i> 2007;2(3):235-236.	Ineligible study design
Marietta M, Facchini L, Girardis M, et al. More on: Platelet count and the use of recombinant factor VIIa for the treatment of bleeding complications after hematopoietic stem cell transplantation [comment]. <i>Journal of Thrombosis & Haemostasis</i> 2006;4(1):288.	Ineligible study design
Marietta M, Facchini L, Pedrazzi P, et al. Pathophysiology of bleeding in surgery. <i>Transplantation Proceedings</i> 2006;38(3):812-814.	Ineligible study design
Marietta M, Pedrazzi P, Girardis M, et al. Intracerebral haemorrhage: an often neglected medical emergency. <i>Internal & Emergency Medicine</i> 2007;2(1):38-45.	Ineligible study design
Markiewicz M, Kalicinski P, Kaminski A, et al. Acute coagulopathy after reperfusion of the liver graft in children correction with recombinant activated factor VII. <i>Transplant Proc</i> 2003;35(6):2318-2319.	Small sample size
Marson F, Farnia A, Callegher L, et al. Use of recombinant activated factor VII (rFVIIa-NovoSeven) in the treatment of uncontrolled postsurgical hemorrhage in a patient with deep venous thrombosis and caval filter. A case report. <i>Minerva Anestesiol</i> 2006;72(7-8):675-682.	Ineligible study design
Marti-Carvajal A, Salanti G, Marti-Carvajal P. Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> 2008(2).	Ineligible study design
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Martinez J, Cid AR, de la Rubia J, et al. Treatment of intra-abdominal bleeding with recombinant activated factor VII in a patient with disseminated intravascular coagulation secondary to septic shock. <i>Blood Coagulation & Fibrinolysis</i> 2005;16(4):297-299.	Ineligible study design
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Martinowitz U, Kenet G, Luboshitz J, et al. Recombinant FVIIa (rFVIIa) for salvage of surgical patients suffering uncontrolled bleeding. <i>Blood</i> 1999;94(10 Suppl 1 Part 1):461a.	Small sample size
Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2001;51(3):431-438; discussion 438-439.	Small sample size

Excluded article	Reason for exclusion
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Martinowitz U, Schulman S. Coagulation factor concentrates by continuous infusion. <i>Transfusion Medicine Reviews</i> 1997;11(1):56-63.	Animal or in-vitro study
Martinowitz U, Zaarur M, Yaron BL, et al. Treating traumatic bleeding in a combat setting: possible role of recombinant activated factor VII. <i>Mil Med</i> 2004;169(12 Suppl):16-18, 4.	Ineligible study design
Matevosyan K, Madden C, Aung FM, et al. Management of Warfarin Associated Intracranial Hemorrhage with a 3-Factor Prothrombin Complex Concentrate and Low Dose Recombinant Factor VIIa. <i>Blood</i> 2008;112(11):1165-1166	No usable data
Matherne D, Begtrup K, Grotta J. Validation of the ICH score in the recombinant factor VIIa ICH trial. <i>Neurology</i> 2007;68(12 Suppl 1):A220-A221.	Duplicate
Mathew P, Simon TL, Hunt KE, et al. How we manage requests for recombinant factor VIIa (NovoSeven). <i>Transfusion</i> 2007;47(1):8-14.	Ineligible study design
Mathew P, Winter SS, Frost JD, et al. Novel applications of recombinant factor VIIa for the management of pediatric coagulopathic diseases. <i>Journal of Pediatric Hematology/Oncology</i> 2003;25(6):499-502.	Small sample size
Mathew P, Winter SS, Frost JD, et al. Successful control of pediatric coagulopathic diseases using recombinant factor VIIa (rFVIIa). <i>Blood</i> 2001;98(11 Part 2):82b-83b.	Small sample size
Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders--a 2006 review. <i>Haemophilia</i> 2006;12(5):457-472.	Ineligible study design
Mathew P. The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics. A systematic review. <i>Thrombosis & Haemostasis</i> 2004;92(4):738-746.	Ineligible study design
Matic I, Titlic M, Lucic I, et al. Recombinant activated factor VII in refractory gastrointestinal haemorrhage of unknown aetiology. <i>Bratislavske Lekarske Listy</i> 2008;109(10):438-440.	Ineligible study design
Matijevic V, Supe S, Poljakovic Z, et al. Treatment with rFVIIa (NovoSeven) in acute intracerebral hemorrhage. <i>Neurologia Croatica</i> 2007;56(3/4):59-68.	Small sample size
Mausser-Bunschoten EP, de Goede-Bolder A, Koopman MMW, et al. Different efficacy of continuous infusion of recombinant factor VIIa in dental surgery compared to other bleeds and surgical interventions. <i>Blood</i> 1999;94(10 Suppl 1 Part 2):120b.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Mayer S, Brun N. Safety and preliminary efficacy of activated recombinant factor VII in acute intracerebral hemorrhage. <i>Stroke</i> 2003;34(1).	Duplicate
Mayer SA, Broderick J, Davis S, et al. The FAST trial: randomised, placebo-controlled, double-blind, multicenter, phase III study to assess recombinant activated factor VII efficacy in acute intracerebral haemorrhage. International Stroke Conference 2006.	Duplicate
Mayer SA, Brun N, Broderick J, et al. Safety and preliminary efficacy of recombinant coagulation factor VIIa in acute intracerebral hemorrhage: US Phase 2A Study. <i>Stroke</i> 2004;35(1).	Duplicate
Mayer SA, Brun N, Broderick J, et al. Predictors and clinical impact of hematoma growth in the NovoSeven ICH Trial. <i>European Journal of Neurology</i> 2004;11(Suppl 2).	Duplicate
Mayer SA, Brun N, Broderick J, et al. Recombinant factor VIIa for acute intracerebral hemorrhage. <i>Stroke</i> 2004;35(6).	Duplicate
Mayer SA, Brun NC, Begtrup K, et al. Randomized, placebo-controlled, double-blind phase III study to assess rFVIIa efficacy in acute intracerebral hemorrhage: the FAST trial. <i>Cerebrovascular Diseases</i> 2007;23(Suppl 2).	Duplicate
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Mayer SA, Brun NC. Safety and feasibility of ultra-early hemostatic therapy for intracerebral hemorrhage: The NovoSeven ICH Trial. 27th International Stroke Conference 2002.	Duplicate
Mayer SA, Committee FTS. Complications in patients with intracerebral hemorrhage treated with recombinant factor VIIa [comment]. <i>Neurology</i> 2007;69(3):319-320.	Ineligible study design

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Mayer SA, Davis SM, Begtrup K, et al. Subgroup analysis in the Fast trial: a subset of intracerebral hemorrhage patients that benefit from recombinant activated factor VII? <i>Stroke</i> 2008;39(2):528.	Duplicate
Mayer SA, Davis SM, Skolnick BE, et al. Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII? <i>Stroke</i> 2009;40(3):833-840.	Duplicate
Mayer SA, Rincon F. Treatment of intracerebral haemorrhage. <i>Lancet Neurol</i> 2005;4(10):662-672.	Ineligible study design
Mayer SA, Rincon F. Ultra-early hemostatic therapy for acute intracerebral hemorrhage. <i>Seminars in Hematology</i> 2006;43(1 Suppl 1):S70-S76.	Duplicate
Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. <i>Intensive Care Medicine</i> 2002;28 Suppl 2:S235-S240.	Ineligible study design
Mayer SA. NovoSeven intracerebral hemorrhage trial. <i>Stroke</i> 2002;33(10).	Duplicate
Mayer SA. Recombinant activated factor VII for acute intracerebral hemorrhage. <i>Stroke</i> 2007;38(2 Suppl):763-767.	Duplicate
Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. <i>Stroke</i> 2003;34(1):224-229.	Ineligible study design
Mayer SA. Ultra-early hemostatic therapy for primary intracerebral hemorrhage: a review. <i>Canadian Journal of Neurological Sciences</i> 2005;32 Suppl 2:S31-S37.	Ineligible study design
Mayo A, Misgav M, Kluger Y, et al. Recombinant activated factor VII (NovoSeven): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding. <i>Vox Sanguinis</i> 2004;87(1):34-40.	Small sample size
Mazer CD, Leong-Poi H, Mahoney J, et al. Vascular injury and thrombotic potential: a note of caution about recombinant factor VIIa. <i>Seminars in Cardiothoracic & Vascular Anesthesia</i> 2007;11(4):261-264.	Ineligible study design
Mazzara R, Escolar G, Castillo R, Ordinas A. Alternatives to platelet transfusions. <i>Sangre (Saragossa)</i> 1998;43(4):331-338.	Ineligible study design
McCabe CJ, Warren RL. Trauma: an annotated bibliography of the recent literature--2005. <i>American Journal of Emergency Medicine</i> 2006;24(5):517-539.	Ineligible study design
McClelland 3 rd S, Won EK, Lam CH. Utilization of recombinant activated factor VII for intracranial hematoma evacuation in coagulopathic nonhemophilic neurosurgical patients with normal international normalized ratios. <i>Neurocrit Care</i> 2007;7(2):136-139.	Small sample size
McCloy M, Iverson A, Crawley C, Laffan M. Recombinant activated factor VIIa for intractable haematuria in sickle cell disease. <i>CME Bulletin Haematology</i> 2000;3(2):42-44.	Ineligible study design
McCormick PA, Murphy KM. Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. <i>Best Practice & Research in Clinical Gastroenterology</i> 2000;14(6):1009-1031.	Ineligible study design
McDonald V, Ryland K. Coagulopathy in trauma: optimising haematological status. <i>Trauma</i> 2008;10:109-123.	Ineligible study design
McEwan A. Aspects of bleeding after cardiac surgery in children. <i>Paediatr Anaesth</i> 2007;17(12):1126-1133.	Ineligible study design
McIlroy DR, Silvers AJ. Recombinant factor VIIa for life-threatening bleeding in high-risk cardiac surgery despite full-dose aprotinin. <i>Anesth Analg</i> 2004;99(1):27-30.	Small sample size
McLeod A, Karkouti K, Yeo E, et al. Recombinant factor VIIa (rF-VIIa) for intractable blood loss after cardiac surgery: A single-arm pilot trial in twenty patients. <i>Blood</i> 2003;102(11):308a.	No eligible outcomes
McLintock C. Postpartum haemorrhage. <i>Thrombosis Research</i> 2005;115 Suppl 1:65-68.	Ineligible study design
McMorrow RC, Ryan SM, Blunnie WP, et al. Use of recombinant factor VIIa in massive post-partum haemorrhage. <i>European Journal of Anaesthesiology</i> 2008;25(4):293-298.	Duplicate
McMullin NR, Kauvar DS, Currier HM, et al. The clinical and laboratory response to recombinant factor VIIa in trauma and surgical patients with acquired coagulopathy. <i>Current Surgery</i> 2006;63(4):246-251.	Data combined for multiple conditions
McPherson J, Sutcharitchan P, Lloyd J, et al. Experience with continuous infusion of recombinant activated factor VII in the Asia-Pacific region. <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S31-S34.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
McRoberts RJ, Beard D, Walsh TS. A study of blood product use in patients with major trauma in Scotland: analysis of a major trauma database. <i>Emergency Medicine Journal</i> 2007;24(5):325-329.	No usable data

Excluded article	Reason for exclusion
Mealy NE, Bayes M. Eptacog alfa (activated). <i>Drugs of the Future</i> . 2005;30(5):528-530.	Ineligible study design
Meijer K, Hendriks HGD, De Wolf JTM, et al. Recombinant factor VIIa in orthotopic liver transplantation: influence on parameters of coagulation and fibrinolysis. <i>Blood Coagulation & Fibrinolysis</i> 2003;14(2):169-174.	Duplicate
Mendez P, Acebo W, Jeffers L, et al. Incidence of subcapsular and intrahepatic hematoma following laparoscopic liver biopsy after intravenous factor VIIa administration in cirrhotic patients with coagulopathy [abstract]. <i>Hepatology</i> 1998;28(Suppl 4).	Other: unpublished data
Mercer KW, Gail Macik B, Williams ME. Hematologic disorders in critically ill patients. <i>Seminars in Respiratory & Critical Care Medicine</i> . 2006;27(3):286-296.	Ineligible study design
Mercier FJ, Van de Velde M. Major obstetric hemorrhage. <i>Anesthesiology Clinics</i> 26(1):53-66.	Ineligible study design
Miall FM, Barton LM, Ayyash R, et al. Recombinant activated factor VII (rVIIa): Predicting response in intractable bleeding. <i>British Journal of Haematology</i> 2005;129(Suppl 1):20.	No eligible outcomes
Michalska-Krzanowska G, Czuprynska M. Recombinant factor VII (activated) for haemorrhagic complications of severe sepsis treated with recombinant protein C (activated). <i>Acta Haematol</i> 2006;116(2):126-130.	Ineligible study design
Michalska-Krzanowska G, Sajdak R, Stasiak-Pikula E. Effects of recombinant factor VIIa in haemorrhagic complications of urological operations. <i>Acta Haematol</i> 2003;109(3):158-160.	Small sample size
Mieli G, Tosi P, Marcheselli S, et al. Early haemostatic therapy for spontaneous intracranial haemorrhage. <i>Neurological Sciences</i> 2005;26 Suppl 1:S34-S36.	Ineligible study design
Midathada MV, Mehta P, Waner M, et al. Recombinant factor VIIa in the treatment of bleeding. <i>Am J Clin Pathol</i> 2004;121(1):124-137.	Ineligible study design
Millar CG, Stringer MD, Sugarman I, et al. The use of recombinant factor VIIa for bleeding in paediatric practice. <i>Haemophilia</i> 2005;11(2):171-174.	Ineligible study design
Mindikoglu AL, Anantharaju A, George M, et al. Splenic embolization in a Jehovah's Witness: role of recombinant human factor VIIa. <i>Hepatogastroenterology</i> 2003;50(53):1697-1699.	Ineligible study design
Mindikoglu AL, Anantharaju A, George M, et al. Acute intracranial hemorrhage in a cirrhotic controlled with recombinant factor VIIa. <i>Dig Dis Sci</i> 2003;48(6):1130-1135.	Small sample size
Mindikoglu AL, Anantharaju A, Villanueva J, et al. Pericardiocentesis and pancreatic aspiration needle biopsy in coagulopathic and thrombocytopenic cirrhotic patient. <i>Chest</i> 2003;123(3):956-958.	Ineligible study design
Minniti C, Weinthal J. Use of recombinant activated factor VII (rFVIIa) in two children with idiopathic thrombocytopenic purpura (ITP). <i>Blood</i> 2001;98(11 Part 2):62b.	Ineligible study design
Mitchell JG, Speake WJ, Russell NK, et al. Recombinant factor VIIa: a useful tool for life-threatening colonic bleeding. Report of a case. <i>Dis Colon Rectum</i> 2007;50(12):2238-2240.	Ineligible study design
Mittal S, Watson HG. A critical appraisal of the use of recombinant factor VIIa in acquired bleeding conditions. <i>Br J Haematol</i> 2006;133(4):355-363.	Ineligible study design
Moeller MS. Indications for use of recombinant factor VIIa: a case study with implications for research. <i>Journal of Trauma Nursing</i> 2006;13(4):190-192.	Small sample size
Mohr AM, Holcomb JB, Dutton RP, et al. Recombinant activated factor VIIa and hemostasis in critical care: a focus on trauma. <i>Critical Care (London, England)</i> 2005;9 Suppl 5:S37-S42.	Ineligible study design
Mohr JP. Report of the 16th European Stroke Conference, Glasgow, May 29 to June 1, 2007. <i>Cerebrovasc Dis</i> 2007;24(4):385-386.	Ineligible study design
Moisescu E, Ardelean L, Simion I, et al. Recombinant factor VIIa treatment of bleeding associated with acute renal failure. <i>Blood Coagul Fibrinolysis</i> 2000;11(6):575-577.	Ineligible study design
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Monroe DM, Hoffman M, Allen GA, et al. The factor VII-platelet interplay: Effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopenia. <i>Seminars in Thrombosis and Hemostasis</i> 2000;26(4):373-377.	Ineligible study design

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Monroe DM. Modeling the action of factor VIIa in dilutional coagulopathy. <i>Thrombosis Research</i> 2008;122(Suppl 1):S7-S10.	Animal or in-vitro study
Moondi P, Cordingley J, Pepper J. Successful use of recombinant factor VIIa for the management of severe haemorrhage after cardiac surgery. <i>British Journal of Intensive Care</i> 2004;14(4):136-138.	Ineligible study design
Morante L, Guasch EV, Palacio F, et al. Activated recombinant factor VII to reverse oral anticoagulants for emergent cesarean delivery. <i>Anesth Analg</i> 2006;102(6):1902-1903.	Ineligible study design
Morenski JD, Tobias JD, Jimenez DF. Recombinant activated factor VII for cerebral injury-induced coagulopathy in pediatric patients. Report of three cases and review of the literature. <i>Journal of Neurosurgery</i> 2003;98(3):611-616.	Small sample size
Morey AF. Factor VIIa for correction of traumatic coagulopathy. <i>J Urol</i> 2005;174(3):968.	Ineligible study design
Morris S, Ridley S, Munro V, et al. Cost effectiveness of recombinant activated factor VII for the control of bleeding in patients with severe blunt trauma injuries in the United Kingdom. <i>Anaesthesia</i> 2007;62(1):43-52.	Ineligible study design
Morris S, Ridley S, Munro V, et al. Cost effectiveness of recombinant activated factor VII for the control of bleeding in patients with severe blunt trauma injuries in the United Kingdom. <i>Anaesthesia</i> 62(1):43-52.	Ineligible study design
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Mousa SA. Tissue factor/VIIa in thrombosis and cancer. <i>Methods Mol Med</i> 2004;93:119-132.	Not on rFVIIa
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Murkin JM. A novel hemostatic agent: the potential role of recombinant activated factor VII (rFVIIa) in anesthetic practice. <i>Canadian Journal of Anaesthesia</i> 2002;49(10):S21-S26.	Ineligible study design
Muslimani A, Daw H. Using recombinant activated factor VII (rFVIIa) in refractory bleeding: A community hospital experience. <i>Blood</i> 2006;108(11 Part 2):90B-91B.	Ineligible study design
Muslimani AA, Walia HK, Ahluwalia MS, Daneschvar HL, Daw HA. Successful use of recombinant factor VIIa in reversal of life threatening bleeding caused by coagulopathy. <i>Blood</i> 2005;106(11 Part 2):100B.	Ineligible study design
Nadir Y, Brenner B. Hemorrhagic and thrombotic complications in bone marrow transplant recipients. <i>Thrombosis Research</i> 2007;120(Suppl 2):S92-S98.	Ineligible study design
Nagarsheth NP, Shander A, Malovany R, et al. Bloodless surgery in a Jehovah's Witness patient with a 12.7-kg uterine leiomyosarcoma. <i>J Surg Educ</i> 2007;64(4):212-219.	Ineligible study design
Naik VN, Mazer CD, Latter DA, et al. Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass. <i>Can J Anaesth</i> 2003;50(6):599-602.	Small sample size
Narayan RK, Maas AIR, Marshall LF, et al. Recombinant factor VIIa in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial. <i>Neurosurgery</i> 2008;62(4):776-786; discussion 786-788.	Duplicate
National Horizon Scanning Centre. Recombinant factor VIIa in haemostasis - horizon scanning review (Brief record). <i>Health Technology Assessment Database</i> 2009; Issue 3	Duplicate
Negrier C, Dargaud Y, Bordet JC. Basic aspects of bypassing agents. <i>Haemophilia</i> 2006;12 Suppl 6:48-52; discussion 52-53.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
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Nelson SC, Heisel MA, Christie B, et al. Use of recombinant factor VIIA in children undergoing radioactive synovectomy. <i>Blood</i> 1995;86(10 Suppl 1):882A.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Neubauer P, Mursula A. Biotechnology - 12th European Congress. <i>Idrugs</i> . 2005;8(10):809-812.	Ineligible study design
Ng HJ, Koh LP, Lee LH. Successful control of postsurgical bleeding by recombinant factor VIIa in a renal failure patient given low molecular weight heparin and aspirin. <i>Ann Hematol</i> 2003;82(4):257-258.	Ineligible study design
Ng HJ, Loh SM, Tan DC, et al. Thrombosis associated with the use of recombinant activated factor VII: profiling two events. <i>Thromb Haemost</i> 2004;92(6):1448-1449.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Ng SS, Yiu RY, Lee JF, et al. Portal venous gas and thrombosis in a Chinese patient with fulminant Crohn's colitis: a case report with literature review. <i>World J Gastroenterol</i> 2006;12(34):5582-5586.	Ineligible study design
Nga HJ, Crowther MA. New anti-thrombotic agents: Emphasis on hemorrhagic complications and their management. <i>Seminars in Hematology</i> 2006;43(1 Suppl 1):S77-S83.	Ineligible study design
Nicklin J, Perrin L, Crandon A, et al. Re: Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. <i>Australian & New Zealand Journal of Obstetrics & Gynaecology</i> 2008;48(4):447.	Ineligible study design
Nohira T, Osakabe Y, Suda S, et al. Successful management by recombinant activated factor VII in a case of disseminated intravascular coagulopathy caused by obstetric hemorrhage. <i>Journal of Obstetrics & Gynaecology Research</i> 2008;34(4 Pt 2):623-630.	Ineligible study design
Nold J, Hargens L, Hagen E, et al. The use of recombinant factor VIIa (rFVIIa) to control bleeding in a neonate with disseminated intravascular coagulation and liver failure. <i>Blood</i> 2003;102(11):101b-102b.	Ineligible study design
Nonthasoot B, Nivatvongs S. Multiple doses of recombinant factor VIIa in orthotopic liver transplantation: a case report. <i>Transplant Proc</i> 2003;35(1):427-428.	Small sample size
Novak V, Mitov L, Rancić Z, et al. The use of recombinant activated factor VII in traumatic intracranial haemorrhage. <i>Srpski Arhiv Za Celokupno Lekarstvo</i> 2008;136 Suppl 3: 193-198.	Foreign language
NovoSeven for massive, uncontrollable, life-threatening haemorrhage in non-haemophiliacs - Early Warning on New Health Technology. Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) 2003;2(1).	Ineligible study design
NovoSeven for non-hemophilia hemostasis. <i>Medical Letter on Drugs & Therapeutics</i> 2004;46(1181):33-34.	Ineligible study design
O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. <i>JAMA</i> 2006;295(3):293-298.	Data combined for multiple conditions
O'Connell NM, Perry DJ, Hodgson AJ, et al. Recombinant FVIIa in the management of uncontrolled hemorrhage. <i>Transfusion</i> 2003;43(12):1711-1716.	Data combined for multiple conditions
O'Connor JV, Stein DM, Dutton RP, et al. Traumatic hemoptysis treated with recombinant human factor VIIa. <i>Ann Thorac Surg</i> 2006;81(4):1485-1487.	Small sample size
Odeyemi IA, Friederich PW, Levi M. Economic impact of recombinant activated factor VII in the control of bleeds associated with abdominal prostatectomy. <i>Journal of Medical Economics</i> 7:107-115.	Ineligible study design
Odeyemi IAO, Friederich PW, Levi M. Economic impact of recombinant activated factor VII in control of bleeds associated with abdominal prostatectomy. <i>J Med Econ</i> 2004;7:107-115.	Ineligible study design
Oh JJ, Akers WS, Lewis D, et al. Recombinant factor VIIa for refractory bleeding after cardiac surgery secondary to anticoagulation with the direct thrombin inhibitor lepirudin. <i>Pharmacotherapy</i> 2006;26(4):569-577.	Small sample size
O'Keefe T, Refaai M, Tchorz K, et al. A massive transfusion protocol to decrease blood component use and costs. <i>Archives of Surgery</i> 2008 143(7):686-690; discussion 690-681.	No usable data
Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. <i>J Perinatol</i> 2002;22(8):672-674.	Ineligible study design

Excluded article	Reason for exclusion
Olomu N, Kulkarni R, Mano-Johnson M. Treatment of intrapulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight (VLBW) infants on mechanical ventilation in a community level III neonatal intensive care unit (NICU). <i>Blood</i> 2001;98(11 Part 1):262a-263a.	Ineligible study design
O'Neill PA, Bluth M, Gloster ES, et al. Successful use of recombinant activated factor VII for trauma-associated hemorrhage in a patient without preexisting coagulopathy. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2002;52(2):400-405.	Small sample size
Overdevest GM, Heetveld MJ. Open pelvic fractures: experience with recombinant factor VIIa, degloving and bowel injury. <i>Injury</i> 2007;38(3):384-391.	Small sample size
Owen PS, Golightly LK, MacLaren R, et al. Formulary management of recombinant factor VIIa at an academic medical center. <i>Annals of Pharmacotherapy</i> 2008;42(6):771-776.	Ineligible study design
Ozcelik T, Ozkocaman V, Ozkalemkas F, et al. Use of recombinant activated factor VII in a patient with severe thrombocytopenia due to myelodysplastic syndrome with uncontrolled gastrointestinal bleeding. <i>Blood Coagul Fibrinolysis</i> 2007;18(4):385-386.	Ineligible study design
Ozier Y, Klinck JR. Anesthetic management of hepatic transplantation. <i>Curr Opin Anaesthesiol</i> 2008;21(3):391-400.	Ineligible study design
Ozier Y, Schlumberger S. Pharmacological approaches to reducing blood loss and transfusions in the surgical patient. <i>Canadian Journal of Anaesthesia</i> 2006;53(6 Suppl):S21-S29.	Ineligible study design
Page MJ, Key NS, Rockwood T. Patient/caregiver assessment of convenience in the use of recombinant activated factor VII (rVIIa; NovoSeven) in home therapy. <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S51-S52.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Palacios Jaraquemada JM. Real efficacy of factor VIIa in the treatment of the postpartum hemorrhage. <i>Acta Obstet Gynecol Scand</i> 2005;84(11):1130; author reply 1131.	Ineligible study design
Palomino MA, Chaparro MJ, de Elvira MJ, et al. Recombinant activated factor VII in the management of massive obstetric bleeding. <i>Blood Coagul Fibrinolysis</i> 2006;17(3):226-227.	Ineligible study design
Panek G, Pawel D, Bidzinski M, et al. Successful use of activated recombinant factor FVIIa in the management of intra abdominal haemorrhage after cytoreductive surgery for advanced carcinoma of the ovary - a case report. <i>Nowotwory</i> 2002;53(4):308-311.	Ineligible study design
Pang G, Donaldson A. Probable right atrial thrombus immediately after recombinant activated factor VII administration. <i>British Journal of Anaesthesia</i> 2007;99(2):221-225.	Small sample size
Panya A, Jackson G, Wingmore T, et al. Management of surgery-associated bleeding in cancer patients. <i>Current Anaesthesia & Critical Care</i> 2008;19:59-69.	Ineligible study design
Papatheodoridis GV, Chung S, Keshav S, et al. Correction of both prothrombin time and primary haemostasis by recombinant factor VII during therapeutic alcohol injection of hepatocellular cancer in liver cirrhosis. <i>J Hepatol</i> 1999;31(4):747-750.	Ineligible study design
Pape H-C. Recombinant factor viia for life-threatening hemorrhage in trauma patients: review of the literature. <i>European Journal of Trauma</i> 2006;32(5):439-448.	Ineligible study design
Papia G, Klein D, Lindsay TF. Intensive care of the patient following open abdominal aortic surgery. <i>Curr Opin Crit Care</i> 2006;12(4):340-345.	Ineligible study design
Pardo M, Bartolome J, Carreno V, et al. Benefit of rFVIIa administration for cirrhotic patients undergoing surgery. <i>World J Surg</i> 2003;27(6):758-759.	Ineligible study design
Pardo Sanchez M, Nebreda JB, Carreno Garcia V. Recombinant activated factor VII prevents bleeding during a surgical procedure in a patient with uncontrollable rectal hemorrhage. <i>American Journal of Gastroenterology</i> 2002;97(5):1266-1267.	Ineligible study design
Park P, Fewel ME, Garton HJ, et al. Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. <i>Neurosurgery</i> 2003;53(1):34-38; discussion 38-39.	Ineligible study design
Parker PJ, Adams SA, Williams D, et al. Forward surgery on Operation Telic--Iraq 2003. <i>Journal of the Royal Army Medical Corps</i> 2005;151(3):186-191.	Small sample size
Paschold JC, Macik BG. Recombinant activated factor VII for correction of the coagulopathy in a patient with cirrhosis requiring surgical drainage of a large epidural abscess. <i>Blood</i> . 2001;98(11 Part 2):76b.	Ineligible study design
Pastores SM, Papadopoulos E, Voigt L, et al. Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: Treatment with recombinant factor VIIa. <i>Chest</i> 2003;124(6):2400-2403.	Ineligible study design
Patanwala AE, Patanwala AE. Factor VIIa (recombinant) for acute traumatic hemorrhage. <i>American Journal of Health-System Pharmacy</i> 2008;65(17):1616-1623.	Ineligible study design

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Paterson NA. Validation of a theoretically derived model for the management of massive blood loss in pediatric patients. <i>Paediatric Anaesthesia</i> 2009;19(5):535-540.	Ineligible study design
Pattaras JG, Ogan K, Martinez E, et al. Endourological management of urolithiasis in hepatically compromised patients. <i>Journal of Urology</i> 2008;179(3):976-980.	Ineligible study design
Pavese P, Bonadona A, Beaubien J, et al. FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: a report of four cases. <i>Can J Anaesth</i> 2005;52(1):26-29.	Small sample size
Payne EM, Brett SJ, Laffan MA. Efficacy of recombinant activated factor VII in unselected patients with uncontrolled haemorrhage: a single centre experience. <i>Blood Coagulation & Fibrinolysis</i> 2006;17(5):397-402.	Data combined for multiple conditions
Pejin D, Popovic S, Gebauer E, et al. The treatment of the life-threatening bleeding in haemophiliacs and in patients with acute leukaemia. Our experience. <i>Blood Reviews</i> 2007;21(Suppl 1):S100-S101.	Not on rFVIIa
Peon M-C. The evidence for the use of recombinant human activated factor VII in the treatment of bleeding patients with quantitative and qualitative platelet disorders. <i>Transfusion Medicine Reviews</i> 2007;21(3):223-236.	Ineligible study design
Pepas LP, Arif-Adib M, Kadir RA. Factor VIIa in puerperal hemorrhage with disseminated intravascular coagulation. <i>Obstet Gynecol</i> 2006;108(3 Pt 2):757-761.	Ineligible study design
Pepas LP, Arif-Adib M, Kadir RA. Factor VIIa in puerperal hemorrhage with disseminated intravascular coagulation. <i>Obstetrics & Gynecology</i> 2006;108(3 Part 2):757-761.	Ineligible study design
Pepe PE, Dutton RP, Fowler RL. Preoperative resuscitation of the trauma patient. <i>Current Opinion in Anaesthesiology</i> 2008;21(2):216-221.	Ineligible study design
Pepion C, Becq MC, Jacob L. Deep vein thrombosis after recombinant factor VIIa infusion to control severe recurrent postoperative bleeding. <i>Anesthesiology</i> 2006;104(4):892-893.	Ineligible study design
Perel P, Roberts I, Shakur H, et al. Haemostatic drugs for acute traumatic brain injury. <i>Cochrane Database of Systematic Reviews</i> 2009(3).	Ineligible study design
Perkins JG, Schreiber MA, Wade CE, et al. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2007;62(5):1095-1099; discussion 1099-1101.	Duplicate
Persson E. Variants of recombinant factor VIIa with increased intrinsic activity. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):89-92.	Not on rFVIIa
Pettersson M, Fischler B, Petrini P, et al. Recombinant FVIIa in children with liver disease. <i>Thrombosis Research</i> 2005;116(3):185-197.	Ineligible study design
Pfau G, Schilling T, Kozian A, et al. A single dose of recombinant activated factor VII (NovoSeven (R)) did not impair the function of the coronary artery bypass grafts - Successful treatment of critical bleeding after cardiac surgery in two cases. <i>Transfusion Medicine and Hemotherapy</i> 2007;34(3):204-207.	Small sample size
Pfliegler GP, Kovacs E, Nemeth H, et al. Oral anticoagulant induced angiosarcomatosis and disseminated intravascular coagulation. <i>Blood</i> 2007;110(11 Part 2):54B.	Ineligible study design
Phelan JT, II, Broder J, Kouides PA. Near-fatal uterine hemorrhage during induction chemotherapy for acute myeloid leukemia: A case report of bilateral uterine artery embolization. <i>American Journal of Hematology</i> 2004;77(2):151-155.	Ineligible study design
Philipson MR, Parker PJ. Damage Control Orthopaedics. <i>Trauma</i> 2007;9:245-254.	Ineligible study design
Piggott KD, Riedel PA, Baron HI. Multifocal lymphoendotheliomatosis with thrombocytopenia: a rare cause of gastrointestinal bleeding in the newborn period. <i>Pediatrics</i> 2006;117(4):e810-e813.	Ineligible study design
Plaat F. Recombinant factor VIIa should be used in massive obstetric haemorrhage. <i>Int J Obstet Anesth</i> 2007;16(4):354-357.	Ineligible study design
Planinsic RM, Testa G, Emre S, et al. Safety and efficacy of single bolus dose of recombinant factor VIIa in patients undergoing orthotopic liver transplantation: A randomized multi-center study. <i>Hepatology</i> 2002;36(4 Part 2):660A.	Duplicate
Planinsic RM. Use of recombinant factor VIIa (rFVIIa) in liver transportation [4]. <i>Liver Transplantation</i> 2006;12(7):1178-1179.	Ineligible study design
Plews DE, Thomas AE. Novel uses of recombinant factor VIIa. <i>Blood</i> . 1999;94(10 Suppl 1 Part 2):83b.	Ineligible study design
Poon MC, d'Oiron R. Recombinant activated factor VII (NovoSeven) treatment of platelet-related bleeding disorders. International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S55-S68.	Ineligible study design

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Poovalingam V, Kenoyer DG, Mahomed R, et al. Superwarfarin poisoning: A report of 4 cases. <i>SAMJ (South African Medical Journal)</i> . 2002;92(11):874-876.	Not on rFVIIa
Popovic L, Peklic M, Kern J. Croatian experience in treatment with recombinant activated factor VII in pediatric liver transplantations. <i>Paediatr Croat</i> 2006;50:127-129.	Small sample size
Porte RJ, Caldwell SH. The role of recombinant factor VIIa in liver transplantation [comment]. <i>Liver Transplantation</i> 2005;11(8):872-874.	Ineligible study design
Porte RJ, Leebeek FWG. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. <i>Drugs</i> 2002;62(15):2193-2211.	Ineligible study design
Potapov EV, Pasic M, Bauer M, et al. Activated recombinant factor VII for control of diffuse bleeding after implantation of ventricular assist device. <i>Annals of Thoracic Surgery</i> 2002;74(6):2182-2183.	Small sample size
Powner DJ, Hartwell EA, Hoots WK. Counteracting the effects of anticoagulants and antiplatelet agents during neurosurgical emergencies [see comment]. <i>Neurosurgery</i> 2005;57(5):823-831; discussion 823-831.	Ineligible study design
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Pratt EL, Tarantino MD. The cost of bridging protocols for anticoagulation in children enduring surgery. <i>Pediatric Research</i> 2002;51(4 Part 2):260A.	Ineligible study design
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Proceedings of the 6th Novo Nordisk Symposium on Treatment of Bleeding and Thrombotic Disorders. Copenhagen, Denmark, May 3-4, 2001. <i>Seminars in Hematology</i> 2001;38(4 Suppl 12):1-50.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
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Pugh R, Wenstone R, Goh N. Recombinant activated factor VIIa (rFVIIa) in intractable haemorrhage: use of a clinical scoring system [comment] [erratum appears in <i>Vox Sang</i> 2006 Jul;91(1):91 Note: Wenstone R [corrected to Wenstone R]]. <i>Vox Sanguinis</i> 2006;90(4):331; author reply 332.	Ineligible study design
Pugh R, Wenstone R. Predicting response to recombinant factor VIIa in non-haemophiliac patients with severe haemorrhage [comment]. <i>British Journal of Anaesthesia</i> 2007;98(5):690; author reply 690-691.	Ineligible study design
Pugh RJ, Wenstone R, Martlew VJ, et al. Use of recombinant factor VIIa for major haemorrhage. <i>Eur J Anaesthesiol</i> 2005;22(7):548-550.	Small sample size
Punzalan RC, Ghanayem NS, Gill JC, et al. Off-label use of recombinant activated factor VII (rFVIIa) in children. <i>Blood</i> 2003;102(11):137b.	Small sample size
Pusateri AE, Park MS. Mechanistic implications for the use and monitoring of recombinant activated factor VII in trauma. <i>Critical Care (London, England)</i> 2005;9 Suppl 5:S15-S24.	Ineligible study design
Pychynska-Pokorska M, Moll JJ, et al. The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass [see comment]. <i>Pediatric Critical Care Medicine</i> 2004;5(3):246-250.	Small sample size
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Pyrasopoulos N, Chalasani N, Balart L, et al. Recombinant factor VIIa safe in patients with liver disease undergoing laparoscopic liver biopsy [abstract]. <i>Hepatology</i> 2001;34(4).	Duplicate
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Excluded article	Reason for exclusion
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Raj R. An approach to a child with recurrent bleeding. <i>Indian Journal of Practical Pediatrics</i> 2003;5(1):21.	Unable to obtain publication
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Recombinant factor VIIa (NovoSeven) for life-threatening surgical and traumatic bleeding in non-haemophiliacs - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC) 2004.	Ineligible study design
Recombinant factor VIIa (NovoSeven) for prevention and treatment of bleeding in patients with underlying disease - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC) 2003:7.	Ineligible study design

Excluded article	Reason for exclusion
Recombinant factor VIIa (NovoSeven) in intracerebral haemorrhage (ICH) - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC) 2004:5.	Ineligible study design
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Reyes G, Carrasco N, Munoz T, et al. Management of massive pulmonary embolism using recombinant activated factor VII. <i>European Journal of Cardio-Thoracic Surgery</i> 2008;33(6):1144-1145.	Small sample size
Rezende SM, Pimentel BD, Araujo JPB. Knocking down the price of factor concentrates in Brazil. <i>Haemophilia</i> 2005;11(3):290-291.	Ineligible study design
Riazi S, Karkouti K, Heggie J. Case report: management of life-threatening oropharyngeal bleeding with recombinant factor VIIa. <i>Canadian Journal of Anaesthesia</i> 2006;53(9):881-884.	Small sample size
Richards M, Kinsey S, Stringer M. Recombinant FVIIa for surgical bleeding in childhood. <i>British Journal of Haematology</i> 2003;121(Suppl 1):36.	Ineligible study design
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Roberts HR, Monroe 3rd DM, Hoffman M. Safety profile of recombinant factor VIIa. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):101-108.	Ineligible study design
Roberts HR, Monroe DM, Key NS. Clinical role of recombinant factor VIIa in bleeding disorders; 2008. (Tanaka K, Davie EW, Ikeda Y, et al., eds. <i>Recent Advances in Thrombosis and Hemostasis</i> 2008).	Ineligible study design
Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. <i>Blood</i> 2004;104(13):3858-3864.	Ineligible study design
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Robertson JD. Prevention of intraventricular haemorrhage: a role for recombinant activated factor VII? <i>Journal of Paediatrics & Child Health</i> 2006;42(6):325-331.	Ineligible study design
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Roitberg B. Research news and notes. <i>Surgical Neurology</i> 2005;63(6):495-496.	Ineligible study design
Romagnoli S, Bevilacqua S, Gelsomino S, et al. Small-dose recombinant activated factor VII (NovoSeven) in cardiac surgery. <i>Anesth Analg</i> 2006;102(5):1320-1326.	Duplicate
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Excluded article	Reason for exclusion
Romero JR, Sakai O, Rice MB, et al. Intracranial hemorrhage sparing meningioma in an anticoagulated patient. <i>J Neuroimaging</i> 2007;17(3):246-250.	Small sample size
Romero R, Pellicer F, Jimenez M, et al. Recombinant activated factor VII (rFVIIa) in the treatment of four cases of severe hemorrhage from portal hypertension (PH). <i>Gastroenterology</i> 2002;122(4 Suppl 1):A79.	Ineligible study design
Romero R, Pellicer F, Jimenez M, et al. Recombinant activated factor VII (RFVIIA) in the treatment of seven cases of severe and active bleeding esophageal varices. <i>Digestive Disease Week Abstracts and Itinerary Planner</i> 2003:Abstract No. M1784.	Ineligible study design
Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista F, et al. Recombinant-activated factor VII as hemostatic therapy in eight cases of severe hemorrhage from esophageal varices. <i>Clin Gastroenterol Hepatol</i> 2004;2(1):78-84.	Ineligible study design
Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista F, et al. Refractory bleeding after endoscopic sphincterotomy: A new indication for recombinant factor VII therapy? <i>American Journal of Gastroenterology</i> 2004;99(10):2063-2065.	Ineligible study design
Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista FJ, et al. A case of bleeding gastric varices treated with recombinant factor VII. <i>Rev Esp Enferm Dig</i> 2001;93(10):675-676.	Ineligible study design
Romero-Castro R, Pellicer-Bautista F, Jimenez-Saenz M, et al. Recombinant activated factor VII (rFVIIa) in the treatment of 13 patients with severe and active bleeding esophageal varices. <i>Gastroenterology</i> 2004;126(4 Suppl 2):A386.	Ineligible study design
Rose L. Recombinant factor VIIa: review of current "off license" indications and implications for practice. <i>AACN Advanced Critical Care</i> 2007;18(2):141-148.	Ineligible study design
Rosovsky RP, Crowther MA, Rosovsky RP, et al. What Is the Evidence for the Off-label Use of Recombinant Factor VIIa (rFVIIa) in the Acute Reversal of Warfarin? <i>Hematology</i> 2008:36-38.	Ineligible study design
Ross KB. Emergent interventions for intracerebral hemorrhage. <i>Journal of Medical Speech-Language Pathology</i> . 2005;13(4):ix-xii.	Ineligible study design
Rossaint R, Duranteau J, Stahel PF, et al. Nonsurgical treatment of major bleeding. <i>Anesthesiology Clinics</i> ;25(1):35-48.	Ineligible study design
Rossaint R, Riou B, Boffard K, et al. A randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt trauma: a reanalysis following the exclusion of early (< 48 hours) deaths. <i>Critical Care</i> 2005;9(Suppl 1):337.	Duplicate
Rott H, Trobisch H, Kretschmar E. Use of recombinant factor VIIa, Novo Seven, in the management of acute haemorrhage. <i>Current Opinion in Anaesthesiology</i> 2004;17(2):159-163.	Ineligible study design
Rudisill CN, Hockman RH, Degregory KA, et al. Implementing guidelines for the institutional use of factor VIIa (recombinant): a multidisciplinary solution. <i>American Journal of Health-System Pharmacy</i> 2006;63(17):1641-1646.	Ineligible study design
Rumyantsev AG, Babkova NV, Chernov VM. Clinical application of recombinant activated coagulation factor VII. <i>Gematologiya i Transfuziologiya</i> 2002;47(5):36-41.	Ineligible study design
Sachs B, Delacy D, Green J, et al. Recombinant activated factor VII in spinal surgery. <i>Spine</i> 2007;32(21):2285-2293.	Duplicate
Saeed G, Ganster G, Friedel N, et al. Was systemic venous thrombosis really due to the administration of recombinant factor VIIa? or was it possibly a manifestation of Lemierre syndrome? <i>Texas Heart Institute Journal</i> 2008;35(3):373-374; author reply 374-376.	Ineligible study design
Sahni R, Weinberger J. Management of intracerebral hemorrhage. <i>Vasc Health Risk Manag</i> 2007;3(5):701-709.	Ineligible study design
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Sajdak S, Moszynski R, Opala T. Bleeding from endometrial and vaginal malignant tumors treated with activated recombinant factor VII. <i>Eur J Gynaecol Oncol</i> 2002;23(4):325-326.	Ineligible study design
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Salek SZ, Sokolic V, Viskovic T, et al. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. <i>Acta Haematologica (Basel)</i> 2002;108(3):162-163.	Ineligible study design

Excluded article	Reason for exclusion
Sallah AS, Wan J, Sigounas GD, et al. Recombinant activated factor VII can control the bleeding manifestations of disseminated intravascular coagulation in patients with cancer. <i>Blood</i> 2002;100(11):Abstract No. 3873.	Ineligible study design
Sallah S, Husain A, Nguyen NP. Recombinant activated factor VII in patients with cancer and hemorrhagic disseminated intravascular coagulation. <i>Blood Coagulation & Fibrinolysis</i> 2004;15(7):577-582.	Ineligible study design
Sallah S, Isaksen M, Seremetis S, et al. Comparative thrombotic event incidence after infusion of recombinant factor VIIa vs. factor VIII inhibitor bypass activity--a rebuttal. <i>J Thromb Haemost</i> 2005;3(4):820-822; author reply 822.	Ineligible study design
Samama CM. Preemptive use of recombinant activated factor VII: many questions but few answers. <i>Canadian Journal of Anesthesia</i> 2006;53(4):336-338.	Ineligible study design
Sanchez MP, Nebreda JB, Garcia VC. Recombinant activated factor VII prevents bleeding during a surgical procedure in a patient with uncontrollable rectal hemorrhage. <i>Am J Gastroenterol</i> 2002;97(5):1266-1267.	Ineligible study design
Sanchis Cervera J, Andres Blasco CJ, Mena-Duran AV. Treatment of acute bleeding with recombinant factor VIIa in a patient with IgA deficit receiving anticoagulant therapy. <i>Acta Haematol</i> 2003;110(1):51-52.	Ineligible study design
Sander M, von Heymann C, Kox WJ, et al. Recombinant factor VIIa for excessive bleeding after thrombectomy prior to kidney transplantation. <i>Transplantation</i> 2004;77(12):1912-1913.	Ineligible study design
Sapsford W. The potential use of recombinant activated factor VII in trauma and surgery. <i>Scandinavian Journal of Surgery: SJS</i> 2004;93(1):17-23.	Ineligible study design
Sattin JA, Zivin JA. Emerging therapies for acute ischemic stroke. <i>American Journal of Therapeutics</i> 2007;14(3):291-298.	Ineligible study design
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Saxonhouse MA, Sola MC. Platelet function in term and preterm neonates. <i>Clinics in Perinatology</i> 2004;31(1):15-28.	Ineligible study design
Scarpelini S, Rizoli S. Recombinant factor VIIa and the surgical patient. <i>Current Opinion in Critical Care</i> . 2006;12(4):351-356.	Ineligible study design
Schlifka B. Lessons learned perspective from OIF: A neurosurgical. <i>Journal of Trauma Injury Infection and Critical Care</i> . 2007;62(6 Suppl S):S103-S104.	Ineligible study design
Schmid S, Friesenecker B, Lorenz I, et al. Administration of recombinant activated factor VII (NovoSeven) in three cases of uncontrolled bleeding caused by disseminated intravascular coagulopathy. <i>Clinical & Applied Thrombosis/Hemostasis</i> 2007;13(3):313-317.	Ineligible study design
Schneck MJ, Biller J. Hemorrhagic stroke in the tropics. <i>Semin Neurol</i> 2005;25(3):300-306.	Ineligible study design
Schreiber MA. Coagulopathy in the trauma patient. <i>Current Opinion in Critical Care</i> 2005;11(6):590-597.	Ineligible study design
Schreiber MA. Damage control surgery. <i>Critical Care Clinics</i> 2004;20(1):101-118.	Ineligible study design
Schulman S, Bech Jensen M, Varon D, et al. Feasibility of using recombinant factor VIIa in continuous infusion. <i>Thromb Haemost</i> 1996;75(3):432-436.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Schulman S, Jensen MB, Varon D, et al. Feasibility of using recombinant factor VIIa in continuous infusion. <i>Blood</i> 1995;86(10 Suppl 1):191A.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Schulman S, Lindstedt M, Alberts KA, et al. Recombinant factor VIIa in multiple surgery. <i>Thromb Haemost</i> 1994;71(1):154.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Schulman S. Safety, efficacy and lessons from continuous infusion with rFVIIa. rFVIIa-CI Group. <i>Haemophilia</i> 1998;4(4):564-567.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)

Excluded article	Reason for exclusion
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Searle E, Pavord S, Alfirevic Z. Recombinant factor VIIa and other pro-haemostatic therapies in primary postpartum haemorrhage. <i>Best Practice & Research in Clinical Obstetrics & Gynaecology</i> 2008;22(6):1075-1088.	Ineligible study design
Seeburger J, Groesdonk H, Borger MA, et al. Quadruple valve replacement for acute endocarditis. <i>Journal of Thoracic and Cardiovascular Surgery</i> 2009;137(6):1564-1565	Ineligible study design
Segal S, Shemesh IY, Blumental R, et al. The use of recombinant factor VIIa in severe postpartum hemorrhage. <i>Acta Obstet Gynecol Scand.</i> 2004;83(8):771-772.	Ineligible study design
Segal S, Shemesh IY, Blumenthal R, et al. Treatment of obstetric hemorrhage with recombinant activated factor VII (rFVIIa). <i>Arch Gynecol Obstet</i> 2003;268(4):266-267.	Ineligible study design
Selin S, Tejani A. Recombinant activated factor VII for bleeding in patients without inherited bleeding disorders. <i>Issues Emerg Health Technol</i> 2006(82):1-4.	Ineligible study design
Shah NL, Caldwell SH, Berg CL, et al. The role of anti-fibrinolytics, rFVIIa and other pro-coagulants: prophylactic versus rescue? <i>Clinics in Liver Disease</i> 2009;13(1):87-93.	Ineligible study design
Shalmi M, Aurup P. Off-label reports of new biologics: exciting new therapy or dubious research? Examples from recombinant activated factor VII.[comment]. <i>Journal of Intensive Care Medicine</i> 2006;21(4):247-248.	Ineligible study design
Shamsi T, Tufail M, Aftab M, et al. Role of recombinant activated factor VII in securing haemostatic failure in gun shot trauma. <i>J Pak Med Assoc</i> 2006;56(5):238-241.	Small sample size
Shamsi TS, Hossain N, Soomro N, et al. Use of recombinant factor VIIa for massive postpartum haemorrhage: case series and review of literature. <i>J Pak Med Assoc</i> 2005;55(11):512-515.	Ineligible study design
Shander A, Javidroozi M. Invited commentary. <i>Ann Thorac Surg</i> 2008;85(3):844.	Ineligible study design
Shander A, Moskowitz D, Rijhwani TS. The safety and efficacy of "bloodless" cardiac surgery. <i>Semin Cardiothorac Vasc Anesth</i> 2005;9(1):53-63.	Ineligible study design
Shapiro AD. Recombinant Factor VIIa: A Viewpoint by Amy D. Shapiro. <i>Biodrugs</i> 1999;12(1):78-79.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Sheares KKK, Mahadeva R. Recombinant factor VIIa and intravenous immunoglobulin therapy for diffuse alveolar haemorrhage: A cautionary tale? <i>Respiratory Medicine Extra</i> 2005;1:120-123.	Ineligible study design
Sheth KN. Recombinant activated factor VII for acute intracerebral hemorrhage. <i>N Engl J Med</i> 2005;352(20):2133-2134; author reply 2133-2134.	Ineligible study design
Shopnick RI. Reversal of warfarin using recombinant factor VIIa prior to invasive procedures. <i>Blood</i> 2001;98(11 Part 2):99b.	Ineligible study design
Siegel LJ, Gerigk L, Tuettenberg J, et al. Cerebral sinus thrombosis in a trauma patient after recombinant activated factor VII infusion. <i>Anesthesiology</i> 2004;100(2):441-443.	Small sample size
Silva MA, Muralidharan V, Mirza DF. The management of coagulopathy and blood loss in liver surgery. <i>Seminars in Hematology.</i> 2004;41(1 Suppl 1):132-139.	Ineligible study design
Silva Z-S. Rapid Reversal of anticoagulant bleeding- rfviiia an option? <i>Journal of Postgraduate Medicine</i> 2007;53(1):3-4.	Ineligible study design
Silver DA, D'Ambra MN. Recombinant activated factor VII in cardiac surgery--will we ever know for sure? <i>Crit Care Med</i> 2007;35(7):1782-1783.	Ineligible study design
Skolnick BE, Brun NC, Kruse P, et al. Safety and laboratory results for recombinant activated coagulation factor VII in patients with acute intracerebral hemorrhage. <i>Blood</i> 2003;102(11 Part 1).	Duplicate
Slappendel R, Huvers FC, Benraad B, et al. Use of recombinant factor VIIa (NovoSeven(R)) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. <i>Anesthesiology (Hagerstown)</i> 2002;96(6):1525-1527.	Ineligible study design
Slappendel R, Huvers FC, Benraad B, et al. Use of recombinant factor VIIa (NovoSeven) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. <i>Anesthesiology</i> 2002;96(6):1525-1527.	Ineligible study design
Smythe MA, Dager WE, Patel NM. Managing complications of anticoagulant therapy. <i>Journal of Pharmacy Practice</i> 2004;17(5):327.	Ineligible study design

Excluded article	Reason for exclusion
Sniecinski RM, Chen EP, Levy JH, et al. Coagulopathy after cardiopulmonary bypass in Jehovah's Witness patients: management of two cases using fractionated components and factor VIIa. <i>Anesth Analg</i> 2007;104(4):763-765.	Small sample size
Snorr J. Risk, benefits and complications of epidural steroid injections: a case report. <i>AANA</i> 2007;75(3):183-188.	Ineligible study design
Sobel BE, Schneider DJ. Platelet function, coagulopathy, and impaired fibrinolysis in diabetes. <i>Cardiology Clinics</i> 2004;22(4):511-V.	Not on rFVIIa
Sobieszczyk S, Breborowicz GH, Platcanov V, et al. Recombinant factor VIIa in the management of postpartum bleeds: an audit of clinical use. <i>Acta Obstet Gynecol Scand</i> 2006;85(10):1239-1247.	Ineligible study design
Soghier LM, Brion LP, Weinberg G, et al. Use of recombinant activated factor VII for refractory hemorrhage in a neonate. <i>Blood</i> 2003;102(11):100b.	Ineligible study design
Sokolic V, Bukovic D, Fures R, et al. Recombinant factor VIIa (rFVIIa) is effective at massive bleeding after caesarean section--a case report. <i>Coll Antropol</i> 2002;26 Suppl:155-157.	Ineligible study design
Sorensen B, Fenger-Eriksen C, Ingerslev J. Recombinant factor VIIa fails to correct coagulopathy induced by haemodilution with colloid. <i>Br J Anaesth</i> 2005;94(6):862-863.	Animal or in-vitro study
Sorensen B, Ingerslev J. Thromboelastography and recombinant factor VIIa: Hemophilia and beyond. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):140-144.	Ineligible study design
Sorensen B, Johansen P, Nielsen GL, et al. Reversal of the International Normalized Ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. <i>Blood Coagulation & Fibrinolysis</i> 2003;14(5):469-477.	Small sample size
Soudry E, Stein M. Prehospital management of uncontrolled bleeding in trauma patients: nearing the light at the end of the tunnel. <i>Israel Medical Association Journal: IMAJ</i> 2004;6(8):485-489.	Ineligible study design
Sousa C, Pedroto I, Campos M, et al. Spontaneous hematoma of the colon. <i>Endoscopy</i> 2000;32(12):S74.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Spahr JE, Maul JS, Rodgers GM. Superwarfarin poisoning and review of: A report of two cases the literature. <i>American Journal of Hematology</i> . 2007;82(7):656-660.	Ineligible study design
Spalding GJ, Hartrumpf M, Sierig T, et al. Cost reduction of perioperative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM). <i>European Journal of Cardio-Thoracic Surgery</i> 2007;31(6):1052-1057.	Ineligible study design
Spalding GJ, Hartrumpf M, Sierig T, et al. Cost reduction of perioperative coagulation management in cardiac surgery: value of 'bedside' thrombelastography (ROTEM). <i>European Journal of Cardio-Thoracic Surgery</i> ;31(6):1052-1057.	Ineligible study design
Special report: recombinant activated factor VII for uncontrolled bleeding in non-hemophiliac patients. <i>Technol Eval Cent Asses Program Exec Summ</i> 2006;21(10):1-2.	Ineligible study design
Spivey M, Parr MJA. Therapeutic approaches in trauma-induced coagulopathy. <i>Minerva Anestesiologica</i> 2005;71(6):281-289.	Ineligible study design
Squizzato A, Ageno W. Recombinant activated factor VII as a general haemostatic agent: evidence-based efficacy and safety. <i>Curr Drug Saf</i> 2007;2(2):155-161.	Ineligible study design
Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. <i>Annals of Pharmacotherapy</i> 2002;36(5):882-891.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Stanworth S, Birchall J, Doree C, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> 2008(2).	Ineligible study design
Stanworth SJ, Birchall J, Doree CJ, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. <i>Cochrane Database Syst Rev</i> 2007(2):CD005011.	Ineligible study design
Stein DM, Dutton RP, Hess JR, et al. Low-dose recombinant factor VIIa for trauma patients with coagulopathy. <i>Injury</i> 2008;39(9):1054-1061.	Duplicate
Stein DM, Dutton RP, Kramer ME, et al. Reversal of coagulopathy in critically ill patients with traumatic brain injury: recombinant factor VIIa is more cost-effective than plasma. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2009;66(1):63-72; discussion 73-65.	Duplicate

Excluded article	Reason for exclusion
Stein DM, Dutton RP, O'Connor J, et al. Determinants of futility of administration of recombinant factor VIIa in trauma. <i>J Trauma</i> 2005;59(3):609-615.	Duplicate
Stein DM, Dutton RP. Uses of recombinant factor VIIa in trauma. <i>Curr Opin Crit Care</i> 2004;10(6):520-528.	Ineligible study design
Stein SC, Smith DH. Coagulopathy in traumatic brain injury. <i>Neurocritical Care</i> 2004;1(4):479-488.	Ineligible study design
Steiner ME, Key NS, Levy JH. Activated recombinant factor VII in cardiac surgery. <i>Current Opinion in Anaesthesiology</i> 2005;18(1):89-92.	Ineligible study design
Steiner T, Diener HC, Unterberg A, et al. Spontaneous intracerebral haemorrhages - What is new? <i>Aktuelle Neurologie</i> 2006;33(5):251-256.	Ineligible study design
Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. <i>Neurosurgery</i> 2006;59(4):767-773; discussion 773-774.	Duplicate
Steiner T, Juettler E, Ringleb P. Acute stroke therapy. <i>Current developments. Nervenarzt</i> 2007;78(10):1147-1154.	Ineligible study design
Steiner T, Mayer S, Brun N. Safety and preliminary efficacy of activated recombinant factor VII (novoseven) in acute intracerebral haemorrhage. <i>Cerebrovascular Diseases</i> 2003;16(Suppl 4).	Duplicate
Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. <i>Stroke</i> 2006;37(1):256-262.	Ineligible study design
Steiner T, Schneider D, Mayer S, et al. Impact of intraventricular haemorrhage on outcomes after recombinant activated Factor VII treatment in patients with acute intracerebral haemorrhage. <i>Cerebrovascular Diseases</i> 2005;19(Suppl 2).	Duplicate
Steiner T, Schneider D, Mayer SA, et al. Impact of intraventricular haemorrhage on outcomes following recombinant activated factor VII treatment in patients with acute intracerebral haemorrhage. <i>Journal of the Neurological Sciences</i> 2005;238(Suppl 1).	Duplicate
Stepinska J, Banaszewski M, Konopka A, et al. Activated recombinant factor VII (rFVIIa) in bleeding management after therapy with IIb/IIIa-inhibitor tirofiban. <i>Thrombosis and Haemostasis</i> 2002;87(2):355-356.	Ineligible study design
Sternbach M, Dragomir A, Crowther MA, et al. Unexpected harmful side effects triggered by immune modulation. <i>Blood</i> 2006;108(11 Part 2):80B.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Stocker CF, Shekerdeman LS. Recent developments in the perioperative management of the paediatric cardiac patient. <i>Current Opinion in Anaesthesiology</i> 2006;19(4):375-381.	Ineligible study design
Stratmann G, deSilva AM, Tseng EE, et al. Reversal of direct thrombin inhibition after cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. <i>Anesthesia & Analgesia</i> 2004;98(6):1635-1639.	Small sample size
Stratmann G, Russell IA, Merrick SH. Use of recombinant factor VIIa as a rescue treatment for intractable bleeding following repeat aortic arch repair. <i>Annals of Thoracic Surgery</i> 2003;76(6):2094-2097.	Small sample size
Strauss RA, Gloster ES. Off-Label Use of Recombinant Activated Factor VII (rFVIIa) for Enucleation Following Eye Trauma. <i>Blood</i> 2002;100(11):Abstract No. 3910.	Small sample size
Streif W, Borum Andreassen R, Paes B, et al. Influence of activated factor VII concentrates on thrombin generation in full-term and preterm neonates. <i>Blood Coagul Fibrinolysis</i> 2000;11 Suppl 1:S133-S134.	Animal or in-vitro study
Stromqvist BN. The use of recombinant factor VIIa for severe intractable bleeding during spine surgery - Point of view. <i>Spine</i> 2004;29(12):1388.	Ineligible study design
Subramaniam S, Demchuk A, Watson TWJ, et al. Unexpected post hemorrhagic hydrocephalus in patients treated with recombinant activated factor VII (rFVIIa): A cause for concern? <i>Neurology</i> 2006;66(5 Suppl 2):303.	Small sample size
Subramaniam S, Demchuk AM, Watson T, et al. Unexpected posthemorrhagic hydrocephalus in patients treated with rFVIIa [see comment]. <i>Neurology</i> 2006;67(6):1096.	Small sample size
Sugg RM, Gonzales NR, Matherne DE, et al. Myocardial injury in patients with intracerebral hemorrhage treated with recombinant factor VIIa. <i>Neurology</i> 2006;67(6):1053-1055.	Duplicate

Excluded article	Reason for exclusion
Sugg RM, Gonzales NR, Matherne DE, et al. Myocardial injury in patients with intracerebral hemorrhage treated with recombinant factor VIIa [see comment]. <i>Neurology</i> 2006;67(6):1053-1055.	Duplicate
Sumann G, Kampfl A, Wenzel V, et al. Early intensive care unit intervention for trauma care: what alters the outcome? <i>Current Opinion in Critical Care</i> 2002;8(6):587-592.	Ineligible study design
Surbek D, Huber A, Alberio L, et al. The role of recombinant factor VIIa in the treatment of severe post partum hemorrhage: Can fertility be preserved? <i>American Journal of Obstetrics and Gynecology</i> 2006;195(6 Suppl S):S92.	Ineligible study design
Surudo T, Wojcicki M, Milkiewicz P, et al. Rapid correction of prothrombin time after low-dose recombinant factor VIIa in patients undergoing orthotopic liver transplantation. <i>Transplant Proc</i> 2003;35(6):2323-2325.	Small sample size
Sutherland GR, Auer RN. Primary intracerebral hemorrhage. <i>Journal of Clinical Neuroscience</i> 2006;13(5):511-517.	Ineligible study design
Svartholm E, Annerhagen V, Lanne T. Treatment of bleeding in severe necrotizing pancreatitis with recombinant factor VIIa. <i>Anesthesiology</i> 2002;96(6):1528.	Ineligible study design
Sykora M, Diedler J, Steiner T. Repetitive asystole in right insular haemorrhage. <i>J Neurol Neurosurg Psychiatry</i> 2007;78(11):1282-1283.	Small sample size
Szabo T, Ali S, Camporesi EM. Intraoperative recombinant activated factor VII for emergent epidural hematoma evacuation. <i>Anesthesia & Analgesia</i> 99(2):595-597.	Small sample size
Takabe K, Holman PR, Herbst KD, et al. Successful perioperative management of factor X deficiency associated with primary amyloidosis. <i>J Gastrointest Surg</i> 2004;8(3):358-362.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Taketomi T, Szlam F, Levy JH, et al. Warfarin reversal with prothrombin complex concentrate confers better antifibrinolytic activity compared with recombinant activated factor VII. <i>Blood Coagulation & Fibrinolysis</i> 2008;19(1):106-108.	Animal or in-vitro study
Taketomi T, Szlam F, Levy JH, et al. Warfarin reversal with prothrombin complex concentrate confers better antifibrinolytic activity compared with recombinant activated factor VII. <i>Blood Coagulation & Fibrinolysis</i> 2008;19(1):106-108.	Animal or in-vitro study
Talkad A, Mathews M, Honings D, et al. Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke. <i>Neurology</i> 2005;64(8):1480-1481.	Ineligible study design
Tanaka KA, Waly AA, Cooper WA, et al. Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). <i>Anesthesiology</i> 2003;98(6):1513-1515.	Small sample size
Tancabelic J, Haun SE. Management of coagulopathy with recombinant factor VIIa in a neonate with echovirus type 7. <i>Pediatr Blood Cancer</i> 2004;43(2):170-176.	Ineligible study design
Tanchev S, Platikanov V, Karadimov D. Administration of recombinant factor VIIa for the management of massive bleeding due to uterine atonia in the post-placental period. <i>Acta Obstet Gynecol Scand</i> 2005;84(4):402-403.	Ineligible study design
Tanos M, Dunning J. Is recombinant activated factor VII useful for intractable bleeding after cardiac surgery? <i>Interactive Cardiovascular & Thoracic Surgery</i> 2006;5(4):493-498.	Ineligible study design
Tawfick WA, Tawfik S, Hynes N, et al. Critical bleeding in vascular surgery: expanding the indication of recombinant activated factor VII. <i>Vascular</i> 2006;14(1):32-37.	Ineligible study design
Teitel J, Poon MC. The safety of recombinant factor VIIa: a rebuttal [comment]. <i>Journal of Thrombosis & Haemostasis</i> 2004;2(11):2078; author reply 2079.	Ineligible study design
Teitel JM. Unexpected bleeding disorders: Algorithm for approach to therapy. <i>Clinical & Laboratory Haematology</i> 2000;22 Suppl 1:26-29; discussion 30-32.	Ineligible study design
Thabut D, de Franchis R, Bendtsen F, et al. Efficacy of activated recombinant factor VII (RFVIIa; NOVOSEVEN) in cirrhotic patients with upper gastrointestinal bleeding: A randomised placebo-controlled double-blind multicenter trial [abstract]. <i>Journal of Hepatology</i> 2003;38(Suppl 2).	Duplicate
Thakar MS, Liedel JL, Rubin CM, et al. FVIIa for peri-operative bleeding in the PICU and NICU. <i>Pediatric Research</i> 2004;55(4 Suppl S, Part 2):307A-308A.	Data combined for multiple conditions
Thomas GO, Dutton RP, Hemlock B, et al. Thromboembolic complications associated with factor VIIa administration. <i>J Trauma</i> 2007;62(3):564-569.	Duplicate
Thompson AR. When all else fails to stop massive bleeding from trauma [comment]. <i>Journal of Thrombosis & Haemostasis</i> 2005;3(4):638-639.	Ineligible study design
Thompson KM, Gerlach SY, Jorn HKS, et al. Files JA. Advances in the care of patients with intracerebral hemorrhage. <i>Mayo Clinic Proceedings</i> 2007;82(8):987-990.	Ineligible study design

Excluded article	Reason for exclusion
Thompson RC. Intracerebral hemorrhage: the least treatable form of stroke [comment]. <i>Southern Medical Journal</i> 2005;98(8):760.	Ineligible study design
Tien H, Nascimento Jr B, Callum J, et al. An approach to transfusion and hemorrhage in trauma: current perspectives on restrictive transfusion strategies. <i>Canadian Journal of Surgery</i> 2007;50(3):202-209.	Ineligible study design
Tien HC, Gough MR, Farrell R, et al. Successful use of recombinant activated coagulation factor VII in a patient with massive hemoptysis from a penetrating thoracic injury. <i>Ann Thorac Surg</i> 2007;84(4):1373-1374.	Small sample size
Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. <i>World Journal of Surgery</i> . 2007;31(5):1055-1064.	Ineligible study design
Tinmouth AT, McIntyre LA, Fowler RA, et al. Blood conservation strategies to reduce the need for red blood cell transfusion in critically ill patients. <i>CMAJ Canadian Medical Association Journal</i> 2008;178(1):49-57.	Ineligible study design
Tinmouth AT, McIntyre LA, Fowler RA. Blood conservation strategies to reduce the need for red blood cell transfusion in critically ill patients. <i>CMAJ Canadian Medical Association Journal</i> 2008;178(1):49-57.	Ineligible study design
Tobias JD, Berkenbosch JW, Muruve NA, et al. Correction of a coagulopathy using recombinant factor VII before removal of an intra-aortic balloon pump. <i>J Cardiothorac Vasc Anesth</i> 2002;16(5):612-614.	Ineligible study design
Tobias JD, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. <i>Pediatr Crit Care Med</i> 2003;4(1):49-51.	Small sample size
Tobias JD, Berkenbosch JW. Synthetic factor VIIa concentrate to treat coagulopathy and gastrointestinal bleeding in an infant with end-stage liver disease. <i>Clin Pediatr (Phila)</i> 2002;41(8):613-616.	Ineligible study design
Tobias JD, Groeper K, Berkenbosch JW. Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. <i>South Med J</i> 2003;96(1):12-16.	Small sample size
Tobias JD. Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. <i>Anesthesiology</i> 2002;96(6):1522-1525.	Ineligible study design
Toffolon EP. Correcting PT with factor 7 may not improve clotting. <i>Gastroenterology</i> 1998;115(3):800.	Ineligible study design
Tofil NM, Winkler MK, Watts RG, et al. The use of recombinant factor VIIa in a patient with Noonan syndrome and life-threatening bleeding [see comment]. <i>Pediatric Critical Care Medicine</i> 2005;6(3):352-354.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
Tong MZ, Chin-Yee I, Eckert K, et al. Efficacy and questionable safety of recombinant activated factor VII in intractable bleeding following cardiac surgery. <i>Canadian Journal of Cardiology</i> 2007;23(Suppl C):291C.	Other: unpublished data
Towfighi A, Greenberg SM, Rosand J. Treatment and prevention of primary intracerebral hemorrhage. <i>Seminars in Neurology</i> 2005;25(4):445-452.	Ineligible study design
Tran KM, Flake AW, Kalawadia NV, et al. Emergent excision of a prenatally diagnosed sacrococcygeal teratoma. <i>Paediatr Anaesth</i> 2008;18(5):431-434.	Ineligible study design
Traynor K. Budget-busting drug gets institutional oversight. <i>American Journal of Health-System Pharmacy</i> 61(9):866.	Ineligible study design
Trowbridge CC, Stammers AH, Ciccarelli N, et al. Dose titration of recombinant factor VIIa using thromboelastograph monitoring in a child with hemophilia and high titer inhibitors to factor VIII: a case report and brief review. <i>Journal of Extra-Corporeal Technology</i> 2006;38(3):254-259.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Tsochatzis E, Papatheodoridis GV, Elefsiniotis I, et al. Prophylactic and therapeutic use of recombinant activated factor VII in patients with cirrhosis and coagulation impairment. <i>Dig Liver Dis</i> 2007;39(5):490-494.	Ineligible study design
Tuhim S. Intracerebral hemorrhage--improving outcome by reducing volume? [comment]. <i>New England Journal of Medicine</i> 2008;358(20):2174-2176.	Ineligible study design
Ucar C, Caliskan U. Successful treatment of acute lymphoblastic leukemia with L-asparaginase-induced intracranial hemorrhage to activated recombinant factor VIIa in a child. <i>Pediatric Hematology & Oncology</i> 2006;23(4):339-345.	Small sample size

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Udvardy M, Telek B, Mezey G, et al. Successful control of massive coumarol-induced acute upper gastrointestinal bleeding and correction of prothrombin time by recombinant active factor VII (Eptacog-alpha, NovoSeven) in a patient with a prosthetic aortic valve and two malignancies (chronic lymphoid leukaemia and lung cancer). <i>Blood Coagulation & Fibrinolysis</i> 2004;15(3):265-267.	Ineligible study design
Udy A, Vaghela M, Lawton G, et al. The use of recombinant activated factor VII in the control of haemorrhage following blunt pelvic trauma [see comment]. <i>Anaesthesia</i> 2005;60(6):613-616.	Small sample size
Uhlmann EJ, Eby CS. Recombinant activated factor VII for non-hemophiliac bleeding patients. <i>Curr Opin Hematol</i> 2004;11(3):198-204.	Ineligible study design
Uhrig L, Blanot S, Baugnon T, et al. Use of recombinant activated factor VII in intractable bleeding during pediatric neurosurgical procedures. <i>Pediatr Crit Care Med</i> 2007;8(6):576-579.	Small sample size
Vaishnav A. International Stroke Conference 2006 16-18 February 2006, Kissimmee, Florida, CA USA. <i>Expert Rev Neurother</i> 2006;6(5):629-630.	Ineligible study design
Valadka AB, Robertson CS. Surgery of cerebral trauma and associated critical care. <i>Neurosurgery (Hagerstown)</i> . 2007;61(1 Suppl S):203-220.	Ineligible study design
van de Garde EM, Bras LJ, Heijmen RH, et al. Low-dose recombinant factor VIIa in the management of uncontrolled postoperative hemorrhage in cardiac surgery patients. <i>J Cardiothorac Vasc Anesth</i> 2006;20(4):573-575.	Small sample size
van de Minkelis JL, Steenvoorde P, Baranski AG. Liver rupture in a patient with HELLP syndrome successfully treated with extensive surgery combined with recombinant factor VIIa. <i>Acta Chir Belg</i> . 2006;106(5):602-604.	Ineligible study design
Van De Velde M. Massive obstetric hemorrhage due to abnormal placentation: uterotonic drugs, cell salvage and activated recombinant factor seven. <i>Acta Anaesthesiologica Belgica</i> 2008;59(3):197-200.	Ineligible study design
Van de Velde M. Recombinant factor VIIa should be used in massive obstetric haemorrhage. <i>Int J Obstet Anesth</i> 2007;16(4):357-359.	Ineligible study design
van der Linden J. Novel antithrombotic agents and the risk of bleeding. <i>Transfusion</i> 2008;48(1 Suppl):47S-50S.	Ineligible study design
Van Der Schueren B, Hammer F, Verschuren F, et al. Angiographic documentation of the efficacy of recombinant activated factor VII (NovoSeven) to control diffuse bleeding in major trauma. <i>Thromb Haemost</i> 2005;94(6):1327-1328.	Small sample size
van 't Veer C, Mann KG. The regulation of the factor VII-dependent coagulation pathway: Rationale for the effectiveness of recombinant factor VIIa in refractory bleeding disorders. <i>Seminars in Thrombosis and Hemostasis</i> 2000;26(4):367-372.	Animal or in-vitro study
Van Thiel DH, Anantharaju A, Mindikoglu AL, et al. Modulation of endothelial cell inflammatory integrins and stress markers with rh-factor VIIa in patients with advanced chronic hepatitis C. <i>J Viral Hepat</i> 2003;10(4):310-317.	In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes
Van Thiel DH, Farr DE, Mindikoglu AL, et al. Recombinant human factor VIIa-induced alterations in tissue factor and thrombomodulin in patients with advanced liver cirrhosis. <i>Journal of Gastroenterology & Hepatology</i> 2005;20(6):882-889.	No eligible outcomes
Van Thiel DH, George M, Anantharaju A, et al. Acute consumption of plasma tissue factor and thrombomodulin with the administration of recombinant human factor VIIa to individuals with advanced liver disease. <i>Gastroenterology</i> 2002;122(4 Suppl 1):A655.	Ineligible study design
van Veen EJW, Monteban-Kooistra WE, Meertens JHJM, et al. Recombinant human activated factor VII in postpartum hemorrhagic shock: the dark side. <i>Intensive Care Medicine</i> 2008;34(1):211-212.	Ineligible study design
Vanek T, Straka Z, Hrabak J, et al. Use of recombinant activated factor VII in cardiac surgery for an effective treatment of severe intractable bleeding. <i>Jpn Heart J</i> 2004;45(5):855-860.	Small sample size
Vater Y, Levy A, Martay K, et al. Adjuvant drugs for end-stage liver failure and transplantation. <i>Medical Science Monitor</i> 2004;10(4):RA77-RA88.	Ineligible study design
Veldman A, Hoffman M, Ehrenforth S. New insights into the coagulation system and implications for new therapeutic options with recombinant factor VIIa. <i>Curr Med Chem</i> 2003;10(10):797-811.	Ineligible study design
Veldman A, Josef J, Fischer D, et al. A prospective pilot study of prophylactic treatment of preterm neonates with recombinant activated factor VII during the first 72 hours of life. <i>Pediatr Crit Care Med</i> 2006;7(1):34-39.	Small sample size

Excluded article	Reason for exclusion
Veldman A, Neuhaeuser C, Akintuerk H, et al. rFVIIa in the treatment of persistent hemorrhage in pediatric patients on ECMO following surgery for congenital heart disease. <i>Paediatr Anaesth</i> 2007;17(12):1176-1181.	Small sample size
Velik-Salchner C, Sergi C, Fries D, et al. Use of recombinant factor VIIa (Novoseven) in combination with other coagulation products led to a thrombotic occlusion of the truncus brachiocephalicus in a neonate supported by extracorporeal membrane oxygenation. <i>Anesth Analg</i> 2005;101(3):924.	Small sample size
Verre M, Bossio F, Mammone A, et al. Use of recombinant activated factor VII in a case of severe postpartum haemorrhage. <i>Minerva Ginecol</i> 2006;58(1):81-84.	Ineligible study design
Verrijckt A, Proulx F, Morneau S, et al. Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation. <i>J Thorac Cardiovasc Surg</i> 2004;127(6):1812-1813.	Small sample size
Veshchev I, Elran H, Salame K. Recombinant coagulation factor VIIa for rapid preoperative correction of warfarin-related coagulopathy in patients with acute subdural hematoma. <i>Med Sci Monit</i> 2002;8(12):CS98-CS100.	Small sample size
Vick LR, Islam S. Recombinant factor VIIa as an adjunct in nonoperative management of solid organ injuries in children. <i>J Pediatr Surg</i> 2008;43(1):195-198; discussion 198-199.	Small sample size
Vidarsson B, Onundarson PT. Recombinant factor VIIa for bleeding in refractory thrombocytopenia. <i>Thromb Haemost</i> 2000;83(4):634-635.	Ineligible study design
Vidarsson B, Onundarson PT. Successful use of recombinant factor VIIa in a bleeding patient with refractory thrombocytopenia undergoing chemotherapy for acute leukemia. <i>Blood</i> 1999;94(10 Suppl 1 Part 2):239b.	Ineligible study design
Viles-Gonzalez JF, Gaztanaga J, Zafar UM, et al. Clinical and experimental experience with factor Xa inhibitors. <i>American Journal of Cardiovascular Drugs</i> 2004;4(6):379-384.	Not on rFVIIa
Vilstrup H, Markiewicz M, Biesma D, et al. Recombinant activated factor VII in an unselected series of cases with upper gastrointestinal bleeding. <i>Thrombosis Research</i> 2006;118(5):595-601.	Ineligible study design
Vincent JL, Rossaint R, Riou B, et al. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding. A European perspective. <i>Annales Francaises d'Anesthesie et de Reanimation</i> 2007;26(2):145-156.	Ineligible study design
Vincent J-L, Rossaint R, Riou B, et al. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding--a European perspective. <i>Critical Care (London, England)</i> 2006;10(4):R120.	Ineligible study design
Virchis A, Hughes C, Berney S. Severe gastrointestinal haemorrhage responding to recombinant factor VIIa in a Jehovah's Witness with refractory immune thrombocytopenia. <i>Hematol J</i> 2004;5(3):281-282.	Ineligible study design
Vlot AJ, Ton E, Mackaay AJ, et al. Treatment of a severely bleeding patient without preexisting coagulopathy with activated recombinant factor VII. <i>Am J Med</i> 2000;108(5):421-423.	Ineligible study design
Voils S. Pharmacologic interventions for the management of critical bleeding. <i>Pharmacotherapy</i> 2007;27(9 Pt 2):69S-84S.	Ineligible study design
Volk T, von Heymann C, Kox WJ. Recombinant activated factor VII and perioperative blood loss.[comment]. <i>Lancet</i> 2003;361(9370):1745; author reply 1745-1746.	Ineligible study design
von Heymann C, Hotz H, Konertz W, et al. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass graft surgery. <i>J Cardiothorac Vasc Anesth</i> 2002;16(5):615-616.	Small sample size
von Heymann C, Jonas S, Spies C, et al. Recombinant activated factor VIIa for the treatment of bleeding in major abdominal surgery including vascular and urological surgery: a review and meta-analysis of published data. <i>Critical Care (London, England)</i> 2008;12(1):R14.	Ineligible study design
von Heymann C, Schoenfeld H, Sander M, et al. Clopidogrel-related refractory bleeding after coronary artery bypass graft surgery: a rationale for the use of coagulation factor concentrates? <i>Heart Surg Forum</i> 2005;8(1):E39-E41.	Small sample size
von Heymann C, Ziemer S, Kox WJ, et al. Caveat against the use of feiba in combination with recombinant factor viia.[comment]. <i>Journal of Thoracic & Cardiovascular Surgery</i> 2003;126(5):1667-1668.	Ineligible study design
Vyas H, Kulkarni R, Guertin S, et al. Use of recombinant activated FVII (rFVIIa) for the treatment of uncontrolled bleeding episodes in pediatric patients in a community hospital. <i>Pediatric Research</i> 2004;55(4 Suppl S, Part 2):308A.	Small sample size

Excluded article	Reason for exclusion
Vyas H, Kulkarni R, Guertin S, John F. Recombinant activated FVII (rFVIIa) for the treatment of severe bleeding episodes in pediatric patients in a community hospital. <i>Blood</i> 2003;102(11):100b.	Small sample size
Waddington DP, McAuley FT, Hanley JP, et al. The use of recombinant factor viia in a Jehovah's witness with auto-immune thrombocytopenia and post-splenectomy haemorrhage. <i>Br J Haematol</i> 2002;119(1):286-288.	Ineligible study design
Wahed S, Karagounis AP, Niranjana G, et al. Successful graft patency after factor VIIa use for bleeding in coronary artery surgery: an unusual complication of a coronary artery bypass surgery. <i>Journal of Cardiac Surgery</i> 2007;22(5):424-427.	Small sample size
Wahlgren CM, Swedenborg J. The use of recombinant activated factor VII to control bleeding during repair of a suprarenal abdominal aortic aneurysm. <i>Eur J Vasc Endovasc Surg</i> 2003;26(2):221-222.	Ineligible study design
Walsham J, Fraser JF, Mullany D, et al. The use of recombinant activated factor VII for refractory bleeding post complex cardiothoracic surgery. <i>Anaesth Intensive Care</i> 2006;34(1):13-20.	Small sample size
Waner M. Novel hemostatic alternatives in reconstructive surgery. <i>Seminars in Hematology</i> 2004;41(1 Suppl 1):163-167.	Ineligible study design
Warkentin TE, Crowther MA. Reversing anticoagulants both old and new. <i>Canadian Journal of Anesthesia</i> 2002;49(6 Suppl):S11-S25.	Ineligible study design
Warkentin TE, Jay RM, Makris M, et al. Platelet-activating anti-platelet factor 4/polyanion antibodies without preceding heparin therapy: A transient autoimmune disorder resembling heparin-induced thrombocytopenia ("spontaneous HIT"). <i>Blood</i> 2006;108(11 Part 1):311A-312A.	Not on rFVIIa
Warren O, Mandal K, Hadjianastassiou V, et al. Recombinant activated factor VII in cardiac surgery: a systematic review. <i>Annals of Thoracic Surgery</i> 2007;83(2):707-714.	Ineligible study design
Warren OJ, Alcock EM, Choong AM, et al. Recombinant activated factor VII: a solution to refractory haemorrhage in vascular surgery? <i>Eur J Vasc Endovasc Surg</i> 2008;35(2):145-152.	Ineligible study design
Warren OJ, Darzi AW, Athanasiou T. Recombinant activated factor VII in cardiac surgery - first, do no harm. <i>Journal of Cardiothoracic Surgery</i> 2007;2:50.	Ineligible study design
Wartenberg KE, Mayer SA. Reducing the risk of ICH enlargement. <i>Journal of the Neurological Sciences</i> 2007;261(1-2):99-107.	Ineligible study design
Watson HG, Salamat AA, Tait J, et al. Successful treatment of life-threatening haemorrhage with rVIIa during autologous peripheral blood stem cell transplantation complicated by platelet refractoriness. <i>Blood</i> 2002;100(11):Abstract No. 3783.	Ineligible study design
Watts RG, Hilliard LM. Use of recombinant factor VIIa for uncontrolled bleeding in critically ill children with malignancy. <i>Blood</i> 2001;98(11 Part 2):85b-86b.	Ineligible study design
Weant KA, Flynn JF, Akers WS. Management of antiplatelet therapy for minimization of bleeding risk before cardiac surgery. <i>Pharmacotherapy</i> 2006;26(11):1616-1625.	Ineligible study design
Webert KE, Arnold DM, Carruthers J, et al. Utilization of recombinant activated factor VII in southern Ontario in 85 patients with and without haemophilia. <i>Haemophilia</i> 2007;13(5):518-526.	Data combined for multiple conditions
Webert KE, Blajchman MA. Randomized trials in patients with blunt and penetrating trauma [comment]. <i>Journal of Trauma-Injury Infection & Critical Care</i> 2006;60(1):242-243; author reply 243-244.	Ineligible study design
Wehbi MA, Obideen K, Martinez E, et al. Recombinant factor VIIa (rFVIIa) as a safe and effective therapeutic option for the correction of moderate to severe hepatic coagulopathy. <i>Hepatology</i> 2003;38(4 Suppl 1):482A.	Ineligible study design
Wei Y-F, Ho C-C, Lin M-T, et al. Successful treatment of intractable hemothorax with recombinant factor VIIa in a nonhemophilic patient. <i>Journal of the Formosan Medical Association</i> 2006;105(9):765-769.	Ineligible study design
Weinberger J. Recombinant activated factor VII for acute intracerebral hemorrhage. <i>Current Cardiology Reports</i> 2006;8(1):8.	Ineligible study design
Weiskopf RB. Intraoperative use of recombinant activated coagulation factor VII. <i>Anesthesiology</i> . 2002;96(6):1287-1289.	Ineligible study design
Weiskopf RB. Recombinant-activated coagulation factor VIIa (NovoSeven): current development. <i>Vox Sanguinis</i> 2007;92(4):281-288.	Ineligible study design
Weiskopf RB. The use of recombinant activated coagulation factor VII for spine surgery. <i>Eur Spine J</i> 2004;13 Suppl 1:S83-S88.	Ineligible study design

Excluded article	Reason for exclusion
Welsby IJ, Monroe DM, Lawson JH, et al. Recombinant activated factor VII and the anaesthetist. <i>Anaesthesia</i> 2005;60(12):1203-1212.	Ineligible study design
Welsby IJ, Ortel TL. Invited commentary. <i>Ann Thorac Surg</i> 2007;84(1):168-169.	Ineligible study design
Welsh A, McLintock C, Gatt S, et al. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage [see comment]. <i>Australian & New Zealand Journal of Obstetrics & Gynaecology</i> 2008;48(1):12-16.	Ineligible study design
Welsh A, McLintock C, Gatt S, et al. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. <i>Australian & New Zealand Journal of Obstetrics & Gynaecology</i> 2008;48(1):12-16.	Ineligible study design
Wheater MJ, Mead GM, Bhandari S, et al. Recombinant factor VIIa in the management of pulmonary hemorrhage associated with metastatic choriocarcinoma. <i>J Clin Oncol</i> 2008;26(6):1008-1010.	Ineligible study design
White B, Martin M, Kelleher S, et al. Successful use of recombinant FVIIa (Novoseven) in the management of pulmonary haemorrhage secondary to Aspergillus infection in a patient with leukaemia and acquired FVII deficiency. <i>Br J Haematol</i> 1999;106(1):254-255.	Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)
White B, McHale J, Ravi N, et al. Successful use of recombinant FVIIa (Novoseven) in the management of intractable post-surgical intra-abdominal haemorrhage. <i>Br J Haematol</i> 1999;107(3):677-678.	Ineligible study design
White CE, Schrank AE, Baskin TW, et al. Effects of recombinant activated factor VII in traumatic nonsurgical intracranial hemorrhage. <i>Curr Surg</i> 2006;63(5):310-317.	Small sample size
White II GC. Congenital and acquired platelet disorders: Current dilemmas and treatment strategies. <i>Seminars in Hematology</i> 2006;43(1 Suppl 1):S37-S41.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
White MC, Pryn SJ, Monk CR. Thrombogenic side-effects of recombinant factor VIIa after use in coronary artery bypass surgery. <i>Anaesth Intensive Care</i> 2006;34(5):664-667.	Small sample size
Whitlock R, Crowther MA, Ng HJ. Bleeding in cardiac surgery: its prevention and treatment—an evidence-based review. <i>Crit Care Clin</i> 2005;21(3):589-610.	Ineligible study design
Wiesenack C, Arlt M, Liebold A, et al. Successful use of one dose of recombinant factor VIIa to control severe bleeding after emergency aortic arch replacement in deep hypothermic circulatory arrest. <i>Journal of Thoracic & Cardiovascular Surgery</i> 2004;128(6):941-943.	Small sample size
Wijdicks EFM. Limiting cerebral hematoma expansion. <i>Reviews in Neurological Diseases</i> 2005;2(3):163-165.	Duplicate
Williams AP, Gettinger A. Transfusion therapy in the intensive care unit. <i>Current Opinion in Anaesthesiology</i> 2006;19(2):127-131.	Ineligible study design
Williams D, McCarthy R. Recombinant activated factor VII and perioperative blood loss [comment]. <i>Lancet</i> 2003;361(9370):1745; author reply 1745-1746.	Ineligible study design
Williams DJ, Thomas GO, Pambakian S, et al. First military use of activated Factor VII in an APC-III pelvic fracture. <i>Injury</i> 2005;36(3):395-399.	Small sample size
Wilson SJ, Bellamy MC, Giannoudis PV. The safety and efficacy of the administration of recombinant activated factor VII in major surgery and trauma patients. <i>Expert Opin Drug Saf</i> 2005;4(3):557-570.	Ineligible study design
Wittenstein B, Ng C, Ravn H, et al. Recombinant factor VII for severe bleeding during extracorporeal membrane oxygenation following open heart surgery. <i>Pediatr Crit Care Med</i> 2005;6(4):473-476.	Small sample size
Wojcicki M, Lubikowski J, Wrzesinski M, et al. Outcome of emergency liver transplantation including mortality on the waiting list: a single-center experience. <i>Transplantation Proceedings</i> 2007;39(9):2781-2784.	Small sample size
Wong WY, Huang WC, Miller R, et al. Clinical efficacy and recovery levels of recombinant FVIIa (NovoSeven) in the treatment of intracranial haemorrhage in severe neonatal FVII deficiency. <i>Haemophilia</i> 2000;6(1):50-54.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Woo YJ. Cardiac surgery in patients on antiplatelet and antithrombotic agents. <i>Semin Thorac Cardiovasc Surg</i> 2005;17(1):66-72.	Ineligible study design

Excluded article	Reason for exclusion
Wordliczek J, Serednicki W, Grabowska I, et al. A 43-year-old man was admitted to the hospital with the diagnosis of acute pancreatitis of 4 days' duration. <i>Pancreas</i> 2003;26(1):101-102.	Ineligible study design
Wrobel G, Dobaczewski G, Patkowski D, et al. Experiences with recombinant activated factor VII in the treatment of severe refractory thrombocytopenia. <i>Pediatr Blood Cancer</i> 2006;47(5 Suppl):729-730.	Ineligible study design
Wu JK, Keith RH, George SG. Use of recombinant activated factor VII (rFVIIa) for acute reversal of warfarin in a child. <i>Blood</i> 2002;100(11):Abstract No. 3964.	Ineligible study design
Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. <i>Lancet Neurology</i> 2006;5(1):53-63.	Ineligible study design
Yadav SP, Chugh K, Gupta D, et al. Use of recombinant factor VIIa in children with uncontrolled bleeding - A single centre experience. <i>Blood</i> 2006;108(11 Part 2):94B-95B.	Ineligible study design
Yadav SP, Sharma SD, Kharya G, et al. Control of massive bleeding in dengue hemorrhagic fever with severe thrombocytopenia by use of KhamRho-IV Anti D (R). <i>Blood</i> 2007;110(11 Part 1):621A.	Ineligible study design
Yan Q, Chang AC. Pharmacologic therapy for postoperative bleeding in children after cardiac surgery: when will the bleeding stop?[comment]. <i>Pediatric Critical Care Medicine</i> 2004;5(3):297-298.	Ineligible study design
Yang L, Jankovic Z. Orthotopic liver transplantation in Jehovah's Witnesses. <i>Current Anaesthesia & Critical Care</i> 2008;19:31-41.	Ineligible study design
Yildirim H, Ucgun I, Yalcin AU, et al. Recombinant factor VIIa treatment for life-threatening haemoptysis. <i>Respirology</i> 2006;11(5):652-654.	Ineligible study design
Yildirim Z, Branda RF. Use of recombinant activated factor VII (rFVIIa) to correct coagulopathy due to congestive liver failure in preparation for surgery. <i>Blood</i> 2002;100(11):Abstract No. 3888.	Ineligible study design
Yilmaz D, Karapinar B, Balkan C, et al. Single-center experience: use of recombinant factor VIIa for acute life-threatening bleeding in children without congenital hemorrhagic disorder. <i>Pediatric Hematology & Oncology</i> 2008;25(4):301-311.	Small sample size
Yilmaz D, Karapinar B, Balkan C, et al. Single-center experience: Use of recombinant factor VIIa for acute life-threatening bleeding in children without congenital hemorrhagic disorder. <i>Pediatr Hematol Oncol</i> 2008;25(4):301-311.	Ineligible study design
You H, Al-Shahi R. Haemostatic drug therapies for acute primary intracerebral haemorrhage [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> 2008(2).	Ineligible study design
You H, Al-Shahi R. Haemostatic drug therapies for acute primary intracerebral haemorrhage. <i>Cochrane Database of Systematic Reviews</i> 2006;3:CD005951.	Ineligible study design
Young G, Lloyd S, Nugent DJ. Recombinant factor VIIa in patients with liver failure undergoing surgery. <i>Blood</i> 2000;96(11 Part 1):267a.	Ineligible study design
Young G, Nugent DJ. Prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa. <i>Hematology</i> 2001;6(5):341-346.	Ineligible study design
Yovtchev V, Gancheva S. The use of recombinant activated factor VII (rFVIIa) for patients with massive hemorrhage provoked by different cases. <i>Anaesthesiology and Intensive Care</i> 2006;33(2):13-16.	Unable to obtain publication
Yusim Y, Perel A, Berkenstadt H, et al. The use of recombinant factor VIIa (NovoSeven) for treatment of active or impending bleeding in brain injury: broadening the indications. <i>Journal of Clinical Anesthesia</i> 2006;18(7):545-551.	Small sample size
Zaaroor M, Soustiel JF, Brenner B, et al. Administration off label of recombinant factor-VIIa (rFVIIa) to patients with blunt or penetrating brain injury without coagulopathy. <i>Acta Neurochirurgica</i> 2008;150(7):663-668.	Small sample size
Zahuranec DB. The 2005 International Stroke Conference, New Orleans, Louisiana, February 2-4, 2005. <i>Journal of Neuro-Ophthalmology</i> 2005;25(2):150-151.	Ineligible study design
Zakhary RG, Seremetis S. Recombinant activated Factor VII in major surgery and trauma patients: a response [comment]. <i>Expert Opinion on Drug Safety</i> 2005;4(5):813-814.	Ineligible study design
Zangrillo A, Mizzi A, Biondi-Zoccai G, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. <i>Journal of Cardiothoracic & Vascular Anesthesia</i> 2009;23(1):34-40.	Ineligible study design
Zibaitis A, Schumann R. Abdominal compartment syndrome following complete abruption of the placenta, fetal demise and consumptive coagulopathy. <i>Anesthesiology (Hagerstown)</i> 2004;100(5):B67.	Ineligible study design

Excluded article	Reason for exclusion
Zietkiewicz M, Garlicki M, Domagala J, et al. Successful use of activated recombinant factor VII to control bleeding abnormalities in a patient with a left ventricular assist device. <i>J Thorac Cardiovasc Surg</i> 2002;123(2):384-385.	Small sample size
Zimmerman RD, Maldjian JA, Brun NC, et al. Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by CT scan. <i>ANNR: American Journal of Neuroradiology</i> 2006;27(3):666-670.	Duplicate
Zimring JC. Appropriate use of recombinant factor VIIa: an expanding and unanswered question. <i>Transfusion</i> 2004;44(11):1544-1546.	Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)
Zirphile X, Debien B, Perez JP, et al. Is Novoseven (R) useful in war traumatology? <i>Medecine et Armees</i> 2008;36(1):3-9.	Ineligible study design
Zulfikar B, Kayiran SM. Successful treatment of massive gastrointestinal hemorrhage in acute biphenotypic leukemia with recombinant factor VIIa (NovoSeven). <i>Blood Coagulation & Fibrinolysis</i> 2004;15(3):261-263.	Ineligible study design
Zupancic Salek S, Sokolic V, Viskovic T, et al. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. <i>Acta Haematol</i> 2002;108(3):162-163.	Ineligible study design
Zupancic-Salek S, Kovacevic-Metelko J, Radman I. Successful reversal of anticoagulant effect of superwarfarin poisoning with recombinant activated factor VII. <i>Blood Coagulation & Fibrinolysis</i> 2005;16(4):239-244.	Ineligible study design
Zuppa AF, Nadkarni VM. Recent developments in the pharmacologic approach to pediatric critical care. <i>Current Opinion in Anaesthesiology</i> 2004;17(3):223-228.	Ineligible study design

Appendix C. Additional Analyses, Tables, and Figures

Appendix Table 1. Diagnostic hierarchy and ICD-9-CM diagnosis and procedure codes

Rank in Hierarchy	Description	ICD-9-CM Codes (PR for procedure codes) Coding based on the presence of any eligible code within a hospitalization
1	Hemophilia A and B	286.0, 286.1
2	Hemophilia-related off-label	286.2, 286.3, 286.4, 286.5, 287.1, 287.3, 287.9
3	Brain trauma	852, 853
4	Body trauma	All E-codes except E85, E87, E92, E93, E94; PR 81-90, 92-95, 98
5	Intracranial hemorrhage	430, 431, 432
6	Brain surgery	PR 1
7	Pediatric cardiac surgery	PR 35, 36, 37 (except 37.2) and age <18
8	Adult cardiac surgery	PR 35, 36, 37 (except 37.2) and age ≥18
9	Obstetrics	72, 73, 74, 75; PR 63, 64, 65, 66, 67 (except 67.8)
10	Neonatal conditions	V3, 76, 77 (except for 76.0, 76.1, 76.2, 76.3) and age < 1 year
11	Aortic aneurysm	441
12	Prostatectomy	PR 60
13	Other vascular surgery	PR 39 (except 39.94, 39.95, 39.96)
14	Liver transplantation	PR 50.5
15	Liver biopsy	PR 50.1, 50.2
16	Esophageal varices	456.0, 456.1, 456.2
17	Other liver disease	571, 572
18	Other gastrointestinal bleed	530.4, 531-535, 537, 557, 562, 569, 578
19	Other secondary hematological conditions	287 (except 287.1, 287.3, 287.9), 446.6, 283.1, 286.6, 286.7, 286.9, 964.2, V58.61, V58.63, E585.2, E934.2
20	Pulmonary disease	786.3, 770.3; PR 32, 33, 34
21	Cancer	140-230
22	Other surgical procedures	PR ≤ 87 (except 39.8)
23	Other, without procedures	All remaining codes

Appendix Table 2. Characteristics of included studies: Sample sizes, patient age, rFVIIa dose, and outcomes

Study Design	Number of Studies	Total Number of rFVIIa Patients	rFVIIa Sample Size Range	rFVIIa Mean Age Range	rFVIIa Mean Dose Range, ug/kg	Important Outcomes Evaluated	
						Direct	Indirect
KQ2-4 Indications							
Intracranial hemorrhage							
RCT	4	944	36 - 573	51 - 72	5 - 160	Mortality, TE events, Functional outcome	Change in hematoma volume
Comparative observational	4	88	5 - 46	60 - 77	10 - 100	Mortality, TE events, Functional outcome	Change in hematoma volume
Non-comparative	3	53	15 - 20	8 - 68	60 - 100	Mortality, TE events, Functional outcome	Change in hematoma volume
Body trauma							
RCT (1 article reports on 2 RCTs)	2	139	139	29 - 33	400	Mortality, TE events, ARDS	Transfusion requirements, Hospital/ICU length of stay
Comparative observational	5	264	29 - 81	28 - 41	50 - 120	Mortality, TE events, ARDS	Transfusion requirements, Hospital/ICU length of stay
Non-comparative	4	204	15 - 108	7 - 38	74 - 140	Mortality, TE events	Transfusion requirements
Brain trauma							
RCT	1	61	61	52	40 - 200	Mortality, TE events	Change in hematoma volume
Comparative observational	2	60	29 - 31	40	NR	Mortality, TE events	Time to neurosurgery, Hospital/ICU length of stay
Non-comparative	1	15	15	61	59	-	-
Liver transplantation							
RCT	4	209	10 - 121	49 - 53	20 - 360	Mortality, TE events	Transfusion requirements, Blood loss, Hospital/ICU length of stay, Operating time
Comparative observational	4	51	6 - 28	13 - 48	20 - 80	Mortality, TE events	Transfusion requirements, Blood loss, Hospital/ICU length of stay, Operating time
Non-comparative	0	-	-	-	-	-	-
Adult cardiac surgery							
RCT	2	114	10 - 104	63 - 70	40 - 90	Mortality, TE events	Transfusion requirements, Blood loss, Hospital/ICU length of stay
Comparative observational	6	191	17 - 51	56 - 70	19 - 100	Mortality, TE events	Transfusion requirements, Blood loss, Hospital/ICU length of stay, Need for surgical re-exploration
Non-comparative	11	1125	16 - 503	51 - 68	10 - 103	Mortality, TE events	Transfusion requirements, Blood loss, Need for surgical re-exploration

Study Design	Number of Studies	Total Number of rFVIIa Patients	rFVIIa Sample Size Range	rFVIIa Mean Age Range	rFVIIa Mean Dose Range, ug/kg	Important Outcomes Evaluated	
						Direct	Indirect
Pediatric cardiac surgery							
RCT	1	40	40	0.33	63	TE events	Transfusion requirements, Blood loss, Time to chest closure
Comparative observational	3	48	9 - 24	0.03 - 9	43 - 282	TE events	Transfusion requirements, Blood loss, Need for surgical re-exploration
Non-comparative	0	-	-	-	-	-	-
Prostatectomy							
RCT	1	24	24	61 - 64	20 - 40	Mortality, TE events	Transfusion requirements, Blood loss, Hospital/ICU length of stay, Operating time
Comparative observational	0	-	-	-	-	-	-
Non-comparative	0	-	-	-	-	-	-
KQ1 Indications:							
Other liver disease							
RCT	4*	517	71 - 170	46 - 55	5 - 800	Mortality, TE events	Transfusion requirements, Blood loss, Efficacy of bleeding control
Comparative observational	1	7	7	34	40 - 80	Mortality	Transfusion requirements, Efficacy of bleeding control, Ability to place ICP transducer
Obstetrics/gynecology							
RCT	0	-	-	-	-	-	-
Comparative observational	3	50	6 - 26	29 - 34	70 - 100	Mortality, TE events	Transfusion requirements, Blood loss
Hematology/oncology							
RCT	2	93	16 - 77	9 - 23	100 - 1120	Mortality, TE events	Transfusion requirements, Efficacy of bleeding control
Comparative observational	1	24	24	NR	NR	Mortality, TE events	Requirement for positive pressure ventilation, Hospital/ICU length of stay
Other surgery							
RCT	4	191	9 - 122	44 - 56	20 - 360	Mortality, TE events	Transfusion requirements, Blood loss, Operating time, Hospital/ICU length of stay
Comparative observational	2	55	26 -29	17 - 60	23	Mortality, TE events, Functional outcome	Transfusion requirements, Blood loss

Study Design	Number of Studies	Total Number of rFVIIa Patients	rFVIIa Sample Size Range	rFVIIa Mean Age Range	rFVIIa Mean Dose Range, ug/kg	Important Outcomes Evaluated	
						Direct	Indirect
Total							
RCT	24	2310	9 - 573	0.33 - 72	5 - 1120		
Comparative observational	31	756	5 - 81	0.03 - 71	17 - 120		
Non-comparative	19	1166	15 - 503	20 - 68	59 - 140		

RCT=randomized controlled trial; TE=thromboembolic; ICU=intensive care unit

Appendix Table 3. Mortality and thromboembolic events in studies included in harms analyses

Article	Study Design	Sample Size	Mean Age (SD) [Range]	Mean Dose (ug/kg) (SD) [Range]	Mortality	TE Rate
Intracranial hemorrhage						
Mayer 2005a ²³ (3 arms)	RCT	108	67 (12)	40	0.18	0.06
		92	65 (12)	80	0.18	0.04
		103	64 (13)	160	0.19	0.10
Mayer 2005b ⁸⁶ (6 arms)	RCT	6	51 (9)	10	0	0
		6	68 (22)	20	0	0.33
		6	68 (16)	40	0.17	0.33
		6	58 (11)	80	0	0
		6	64 (14)	120	0.17	0
		6	53 (12)	160	0.17	0
Mayer 2006 ⁸⁷ (4 arms)	RCT	8	72 (10)	5	0.25	0
		8	60 (15)	20	0.25	0.25
		8	64 (13)	40	0.38	0.13
		8	62 (12)	80	0	0
Mayer 2008 ⁸⁸ (2 arms)	RCT	276	65 (14)	20	0.18	0.09
		297	65 (13)	80	0.21	0.12
Pickard 2000 ⁹⁰	Comparative Observational	5	NR	80	NR	0.20
Brody 2005 ⁹¹	Comparative Observational	12	71 (13.1)	NR	0.42	0.17
Hallevi 2008 ⁹²	Comparative Observational	46	59.6 [38-87]	80 ^U [40;80]	0.13	0.15
Ilyas 2008 ⁸⁹	Comparative Observational	15	76.5 (11)	24 [10-100]	0.21	0.04
Sutherland 2008 ⁹³	Non-Comparative Observational	15	68.0 ^U [25 -81]	60 ^U [40-92]	0.13	0
Nussbaum 2009 ⁹⁵	Non-Comparative Observational	18	56.8	100	0.22	0.44
Herbertson 2008 ⁹⁴	Non-Comparative Observational (Pediatric)	20	7.7	100	0.15	0
Body trauma						
Boffard 2005 ⁹⁶ (blunt arm)	RCT	69	33 (13)	400	0.25	0.03
Boffard 2005 ⁹⁶ (penetrating arm)	RCT	70	29 (10)	400	0.24	0.06
Rizoli 2006 ^{97a}	Comparative Observational	38	36.8 [30.6-43.1]	NR	0.50	NR
Nascimento 2008 ^{181a}	Comparative Observational	72	NR	NR	NR	0.10
Harrison 2005 ¹⁰¹	Comparative Observational	29	40.9 (20.8)	60 [40-80]	0.41	0.07
Fox 2009 ⁹⁹	Comparative Observational	53	27.5 (9.5)	100 [90-120]	0.07	0.12
Dutton 2004 ^{100b}	Comparative Observational	81	40.8 (21)	97.8	0.58	NR
Cameron 2007 ¹⁰²	Non-Comparative Observational	108	38.0 ^U [11-91]	90 ^U [78-105] ^l	0.42	0.03
Felfernig 2007 ¹⁰³	Non-Comparative Observational	45	30.5 [5-81]	73.6 (27)	0.24	NR
Thomas 2007 ^{228b}	Non-Comparative Observational	242	44.0 (21)	68 ^{&} (45)	NR	0.11
Martinowitz 2005 ¹⁰⁴	Non-Comparative	36	19.5	140 ^U	0.39	NR

Article	Study Design	Sample Size	Mean Age (SD) [Range]	Mean Dose (ug/kg) (SD) [Range]	Mortality	TE Rate
	Observational		[14-65]	[70-540]		
Perkins 2007 ^{182c}	Non-Comparative Observational	53	23.1	109 ^{&}	0.34	0.02
Alten 2009 ¹⁰⁵	Non-Comparative Observational (Pediatric)	15	7	88	0.13	0.07
Herbertson 2008 ⁹⁴	Non-Comparative Observational (Pediatric)	37	7.7	100	0.22	0
Brain trauma						
Narayan 2008 ¹⁰⁶ (5 arms)	RCT	12	51.5 (21.5) [^]	40	0	0.17
		11		80	0	0.18
		14		120	0.07	0.21
		12		160	0.17	0
		12		200	0.33	0.17
Stein 2008 ^{107b}	Comparative Observational	29		[8-140]	0.35	0.21
Bartal 2007 ¹⁰⁹	Non-Comparative Observational	15	61.0 (11)	59 ^{&} [40-90]	0.07	0
Liver Transplantation						
Pugliese 2007 ¹¹²	RCT	10	NR	40	NR	0
Lodge 2005 ¹¹⁰ (2 arms)	RCT	63	53.3 (11.2)	180	0.02 [#]	0.19
		58	52.6 (9.2)	360	0.03 [#]	0.12
Planinsic 2006 ¹¹¹ (3 arms)	RCT	18	49.4 (13.4)	20	0.06 [#]	0.11 [*]
		24	49.7 (10.1)	40	0.08 [#]	0.04 [*]
		22	51.9 (8.8)	80	0.05 [#]	0.09 [*]
Liu 2009 ¹¹³	RCT	14	51.9 [36-54]	47.5 [41-65]	NR	0
Hendriks 2001 ¹¹⁴	Comparative Observational	6	43 ^U [37-61]	80	0	0.17
Kalicsinski 2005 ¹¹⁶	Comparative Observational	28	13.2 (4.2)	51.5 [30-100]	0.07	0
Niemann 2006 ¹¹⁷	Comparative Observational	11	48 (15)	58 (18)	0	0
De Gasperi 2005 ¹¹⁵	Comparative Observational	6	45 (4)	30 ^{&} [20-40]	0	NR
Adult Cardiac Surgery						
Diprose 2005 ¹¹⁸	RCT	9	63 ^U [59-66] ^l	90	0	0.22
Gill 2009 ¹¹⁹ (2 arms)	RCT	35	63.6 [^]	40	0.11	0.09
		68	63.6 [^]	80	0.09	0.06
Gelsomino 2008 ¹²¹	Comparative Observational	40	70.1 (9.2)	18 ^U [9-16] ^l	0.05	0.05
von Heymann 2005 ¹²³	Comparative Observational	26	63.5 (12.87)	89.3 ^{&}	0.38	0
Bowman 2008 ¹²⁴	Comparative Observational	36	58	100 ^{&}	0.08	0.11
Trowbridge 2009 ¹²⁵	Comparative Observational	17	70 (9)	NR	NR	NR
Tritapepe 2007 ¹²²	Non-Comparative Observational	23	62.4 (9.4)	82 ^{&}	0.13	0.09
Karkouti 2006 ^{215d}	Non-Comparative Observational	114	59.0 (17)	56 (25)	0.16	0.20

Article	Study Design	Sample Size	Mean Age (SD) [Range]	Mean Dose (ug/kg) (SD) [Range]	Mortality	TE Rate
Dunkley 2008 ¹³³	Non-Comparative Observational	293	63.0 (15)	92.3 ^U [82-103] ^I	0.17	0.14
Filsoufi 2006 ¹²⁶	Non-Comparative Observational	17	65.0 (18)	103.1 (30.2)	0.29	NR
Gandhi 2007 ¹²⁷	Non-Comparative Observational	17	53.0 [38-64]	78.3 [24-189]	0.29	0.24
Hyllner 2005 ¹²⁸	Non-Comparative Observational	24	60.0 [34-82]	72.2 [*] [19.2-104]	0.29	NR
McCall 2006 ¹²⁹	Non-Comparative Observational	53	68.0 [55- 75] ^I	90 (15)	0.19	NR
Raivio 2005 ¹³⁰	Non-Comparative Observational	16	60 (14.9)	65 [24-192]	0.25	0.25
Aggarwal 2004 ¹³¹	Non-Comparative Observational	24	65.0 ^U [26-85]	90	0.75	NR
Karkouti 2008 ¹³²	Non-Comparative Observational	503	62.0 (15)	62 ^U [40-89] ^I	0.32	0.24
Bruckner 2009 ¹³⁴ (2 doses)	Non-Comparative Observational	32 30	51 51	15 20	0 0.87	0.09 0.37
Masud 2009 ¹³⁵	Non-Comparative Observational	93	60.6	56.2	0.23	0
Hsia 2009 ¹³⁶	Non-Comparative Observational	23	NR	NR	NR	0.39
Pediatric Cardiac Surgery						
Ekert 2006 ¹³⁷	RCT	40	0.33	63 [40-80]	NR	0
Agarwal 2007 ¹³⁸	Comparative Observational	24	0.0 ^U [0.01-6.53]	59.8 ^{&}	NR	0.08
Tobias ¹³⁹	Comparative Observational	9	9 (4)	90	NR	0
Niles 2008 ¹⁴⁰ (2 groups)	Comparative Observational	11 4	60 days (99) 14.5	166 [76-282] 286 [26-956]	0 0	0 0
Prostatectomy						
Friederich 2003 ¹⁴¹ (2 arms)	RCT	8 16	61 (8.9) 64 (8.5)	20 40	0 0	0.13 0

Fair+ Comparative Observational, fair or good quality comparative observational studies also included in the effectiveness review in Key Questions 2-4; Variance (e.g. standard deviation, range, or IQR) left blank if not reported.

^UMedian

^IInterquartile Range

[^]Mean age (and standard deviation) for all study arms combined.

[#]Mortality is underestimated because 2 deaths each in Lodge et al.¹¹⁰ and Planinsic et al.¹¹¹ were not reported by treatment arm.

^{*}Thromboembolic events are underestimated because only arterial thromboembolic events were counted in Planinsic et al.¹¹¹

[&]Mean dose estimated from mean or median size of individual doses, or converted from mg to ug/kg by assuming an average patient weight.

^aNascimento et al.¹⁸¹ was used instead Rizoli et al.⁹⁷ for the analysis of thromboembolic events. Nascimento et al. is a continuation of Rizoli et al. with more patients.

^bDutton et al.¹⁰⁰ and Thomas et al.²²⁸ have overlapping patient populations. Dutton et al. was used for the mortality analysis and Thomas et al. was used in the analysis of thromboembolic events for body trauma. Thomas et al. included traumatic brain injury patients, some of which were included in Stein et al.¹⁰⁷ Thus, some patients are double counted between the brain trauma and the body trauma analyses of thromboembolic events.

^cData on mortality and thromboembolic events from Perkins et al.¹⁸² (an overlapping non-comparative study) are used instead of Spinella et al.⁹⁸ (a comparative observational study analysed in the body trauma section above) because the former has a larger sample size.

^dData from the 2006 study by Karkouti et al.²¹⁵ was used instead of the 2005 study by Karkouti et al.¹²⁰ The 2006 study is an overlapping non-comparative study with more patients.

Appendix Table 4. Clinical trials on the off-label use of rFVIIa that are registered on an online database

Trial ID	Topic	Sponsor	End date	Primary associated publications
Key Question 2-4 Indications				
Novo Nordisk trial # F7ICH-1389	Intracranial hemorrhage	Novo Nordisk	Oct 2002	Article: 2005 ⁸⁶
Novo Nordisk trial # F7ICH-2073	Intracranial hemorrhage	Novo Nordisk	Mar 2003	Article: 2006 ⁸⁷
NCT00426803	Intracranial hemorrhage	Novo Nordisk	Jun 2004	Article: 2005, ²³
NCT00222625	Intracranial hemorrhage	University of Perugia	Sep 2006	Article: 2008 ²³⁸
NCT00127283	Intracranial hemorrhage	Novo Nordisk	Feb 2007	Article: 2008 ²³⁹
NCT0026606	Intracranial hemorrhage	Novo Nordisk	Apr 2007	None*
NCT00128050	Intracranial hemorrhage	IRCCS Policlinico S. Matteo	Dec 2008	None
NCT00770718	Intracranial hemorrhage	University of Utah	Apr 2010	NA
NCT00810888	Intracranial hemorrhage	University of Cincinnati	Apr 2013	NA
Novo Nordisk trial # F7TRAUMA-2159	Body trauma (2 RCTs merged) [^]	Novo Nordisk	Sep 2003	Article: 2005 ⁹⁶
NCT00184548 merged with NCT00323570	Body trauma (2 RCTs merged) [^]	Novo Nordisk	Sep 2008 (terminated) [†]	None*
NCT 00123591	Brain trauma	Novo Nordisk	May 2006	Article: 2008 ¹⁰⁶
Novo Nordisk trial # F7LIVER-1256	Liver transplantation	Novo Nordisk	Sep 2003	Article: 2005 ¹¹⁰
NCT00154427	Adult cardiac surgery	Novo Nordisk	Nov 2007 (terminated) [‡]	Article: 2009 ¹¹⁹
NCT00214656	Adult cardiac surgery	Austin Health	Jun 2008	None
Novo Nordisk trial # F7CPB-3343	Pediatric cardiac surgery	Novo Nordisk	NS	Article: 2006 ¹³⁷
Other Indications				
Novo Nordisk trial # F7-3015	Children with dengue hemorrhagic fever	Novo Nordisk	Dec 2002	Article: 2005 ¹⁵⁰
Novo Nordisk trial # F7LIVER-1313	Partial hepatectomy in patients with cirrhosis	Novo Nordisk	Dec 2002	Article: 2006 ¹⁴⁴
Novo Nordisk trial # F7BMT-1360	Allogenic stem cell transplantation	Novo Nordisk	Oct 2003	Article: 2005 ¹⁵¹
Novo Nordisk trial # F7SCT-1485	Allogenic stem cell transplantation	Novo Nordisk	Oct 2003 (terminated) [§]	None*
Novo Nordisk trial # F7HAEM-2080	Hemorrhagic cystitis	Novo Nordisk	Nov 2003	Article: 2006 ²⁴⁰
NCT00104455	Bleeding in healthy volunteers	Novo Nordisk	Nov 2004	Abstracts 2005 ²⁴¹⁻²⁴³

Trial ID	Topic	Sponsor	End date	Primary associated publications
Novo Nordisk trial # F7ORTHO-1506	Acetabular reconstruction surgery	Novo Nordisk	Mar 2005	Article: 2005 ¹⁵⁴
NCT0010237	Spinal surgery	Novo Nordisk	Feb 2006	Article: 2007 ¹⁵⁶
NCT00154492	Variceal bleeding	Novo Nordisk	Aug 2006	Abstract 2007 ²⁴⁴
Novo Nordisk trial # F7HAEM-1825	Bleeding in healthy volunteers treated with warfarin	Novo Nordisk	Jul 2008	None*
NCT00370877	Postpartum hemorrhage	Centre Hospital University of Nimes	Dec 2009	NA
NCT00192933	Hemorrhage††	Rigshospitalet, Denmark	Dec 2010	NA
NCT00243243	Burns	United States Army Institute of Surgical Research	Dec 2010	NA

NA=not applicable. NS=not stated (checked via applicable websites and subsequent publications)

*Synopsis of results available at Novo Nordisk website: www.novonordisk.com (last accessed 10/19/09)

^According to manufacturer web site, each of these trials included 2 related RCTs: one directed at patients with blunt trauma and the other at patients with penetrating trauma.

†According to the manufacturer web site, “The decision to discontinue the F7TRAUMA-1711 trial is not due to any safety concerns. The result of the pre-planned futility analysis performed in June 2008 predicted a very low likelihood of reaching a successful outcome on the primary efficacy endpoint at the end of the trial and as a consequence, the company has decided to close the trial at this juncture.”

‡According to manufacturer web site, “The trial was terminated after recruiting 172 patients but without proceeding to the highest dosing cohort as this no longer reflects common clinical practice.”

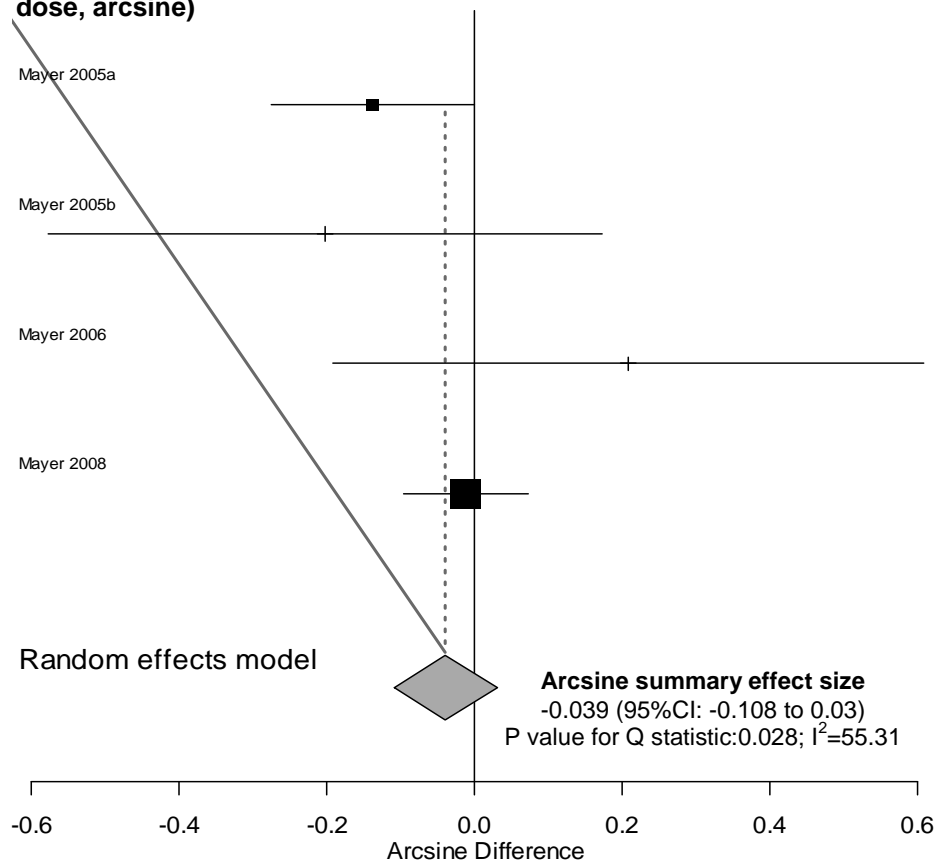
§According to the manufacturer web site, “Trial enrollment of this study was prematurely terminated due to excessively slow patient recruitment.”

††May be a prospective cohort study, rather than a clinical trial.

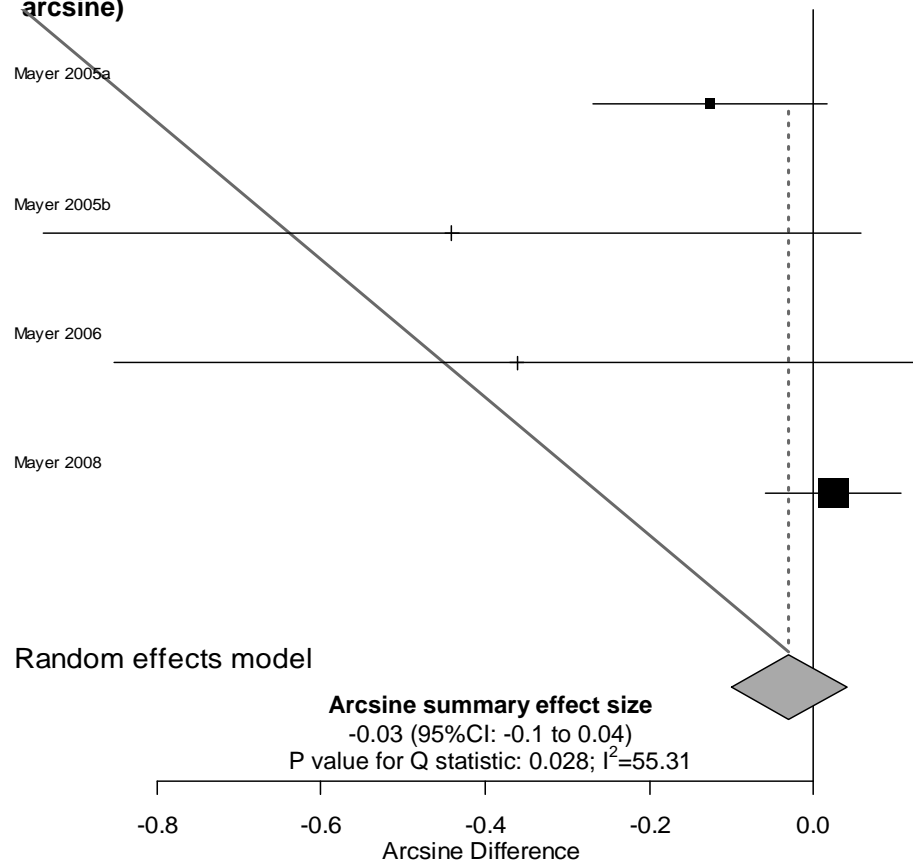
Appendix Table 5. Non-English language articles on key questions 2-4 indications excluded on the basis of language

Article citation	Language	Information available for review in English	Clinical indication	Patient information
RCT				
Ma B, Wang ZN, Zhang BR. Effect of recombinant activated factor VII a on early recovery of patients undergoing cardiac valve replacement under cardiopulmonary bypass: a randomized double-blind placebo-controlled trial. Dier Junyi Daxue Xuebao. 2006;27(10):1110-3.	Chinese	Abstract and tables within full publication	Adult cardiac surgery	11 rFVIIa, 11 placebo
Comparative observational study				
Novak V, Mitov L, Rancić Z, Petrović B, Novak M. The use of recombinant activated factor VII in traumatic intracranial haemorrhage. Srpski Arhiv Za Celokupno Lekarstvo 2008;136 Suppl 3: 193-8.	Serbian	Abstract and tables within full publication	Brain trauma	7 rFVIIa, number of controls unclear
Case report, case series, or registry				
Grintescu I, Tulbure D, Mirea L. [Activated recombinant factor VII (Novoseven) in multiple trauma patients: an outcome analysis]. Chirurgia (Bucuresti). 2006;101(6):615-24.	Romanian	Abstract	Body trauma	34 patients
Demytyeva II, Sandrikov VA, Charnaya MA, Morozov YA, Trekova NA, Eremenko AA. The "NovoSeven" (rFVIIa) hemostatic in massive hemorrhages in patients operated on the heart and aorta. Anesteziologiya i Reanimatologiya. 2004(5):11-13.	Russian	Abstract	Adult cardiac surgery	25 patients
Demytyeva II, Gladysheva VG, Charnaya MA, Morozov YA. Influence of recombinant activated factor VIIa thrombocytic hemostasis. Gematologiya i Transfuziologiya. 2005;50(6):12-15.	Russian	Abstract	Adult cardiac surgery	15 patients
Dement'eva I, Gladysheva VG, Charnaia MA, Morozov lu A. [On the mechanism of action of recombinant activated factor VII in massive non-hemophylic bleeding in cardiosurgical patients]. Vestn Ross Akad Med Nauk. 2006(12):21-5.	Russian	Abstract	Adult cardiac surgery	35 patients
Gong ZY, Gao CQ, Xiao CS, et al. [The use of recombinant activated factor VII for blood loss after cardiovascular surgery]. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery]. 2008;46(19):1497-501.	Chinese	Abstract	Adult cardiac surgery	16 patients
Lacheva A, Georgiev S, Pilosoff V, Lazarov S, Mitev P. Administration of recombinant factor VIIA for the management of massive postoperative blood loss in children with congenital heart defects. Anaesthesiology and Intensive Care. 2008;35(2):3-8.	Bulgarian	Abstract	Pediatric cardiac surgery	30 patients

Appendix Figure 1. Mortality in ICH (low rFVIIa dose, arcsine)



Appendix Figure 2. Mortality in ICH (medium rFVIIa dose, arcsine)



Favors rFVIIa

Favors usual care

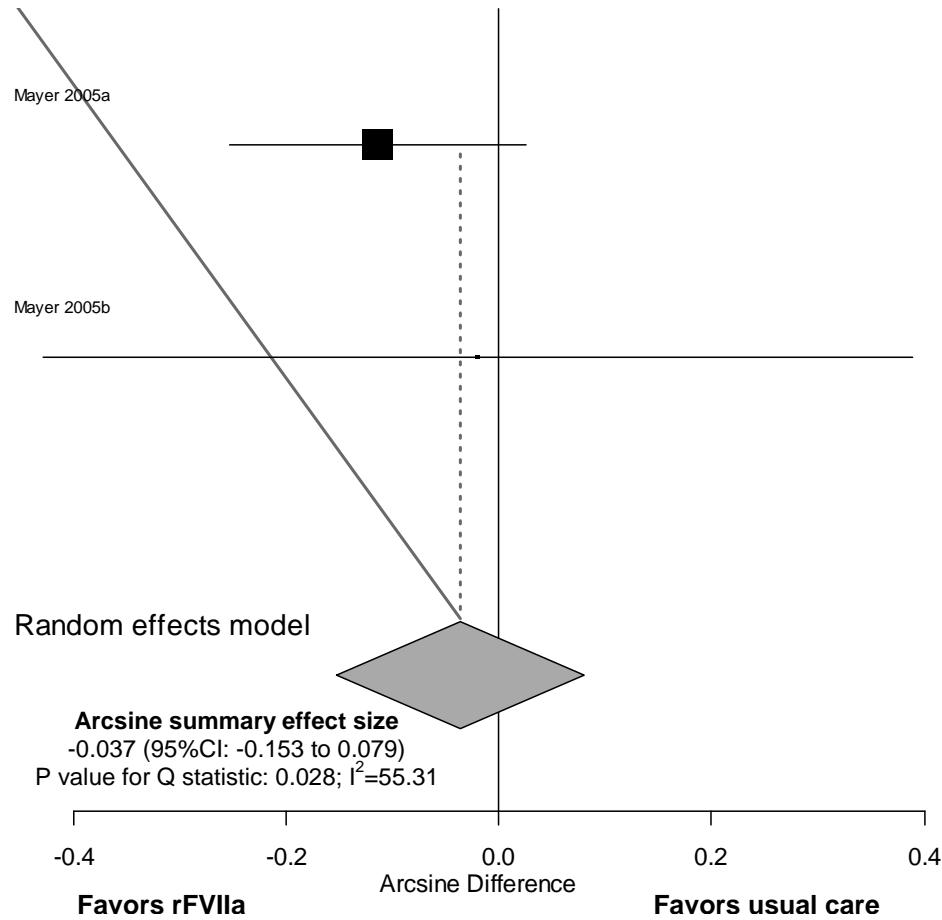
Favors rFVIIa

Favors usual care

Article	Deaths/total patients (low dose)		Deaths/total patients (medium dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	19/108	28/96	17/92	28/96
Mayer 2005b	1/18	2/11	0/6	2/11
Mayer 2006	7/24	1/8	0/8	1/8
Mayer 2008	50/276	51/268	62/297	51/268

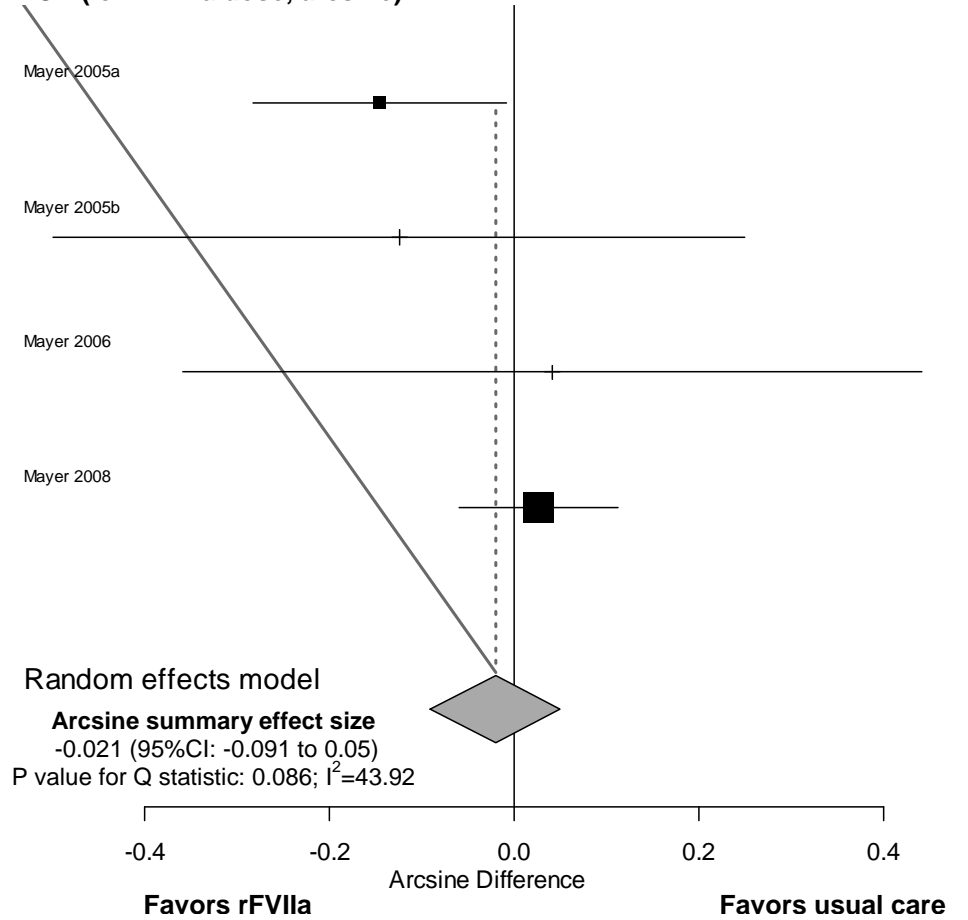
Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95% CI by a diamond.

Appendix Figure 3. Mortality in ICH (high rFVIIa dose, arcsine)



Article	Deaths/Total patients (high dose)	
	rFVIIa	Control
Mayer 2005a	20/103	28/96
Mayer 2005b	2/12	2/11

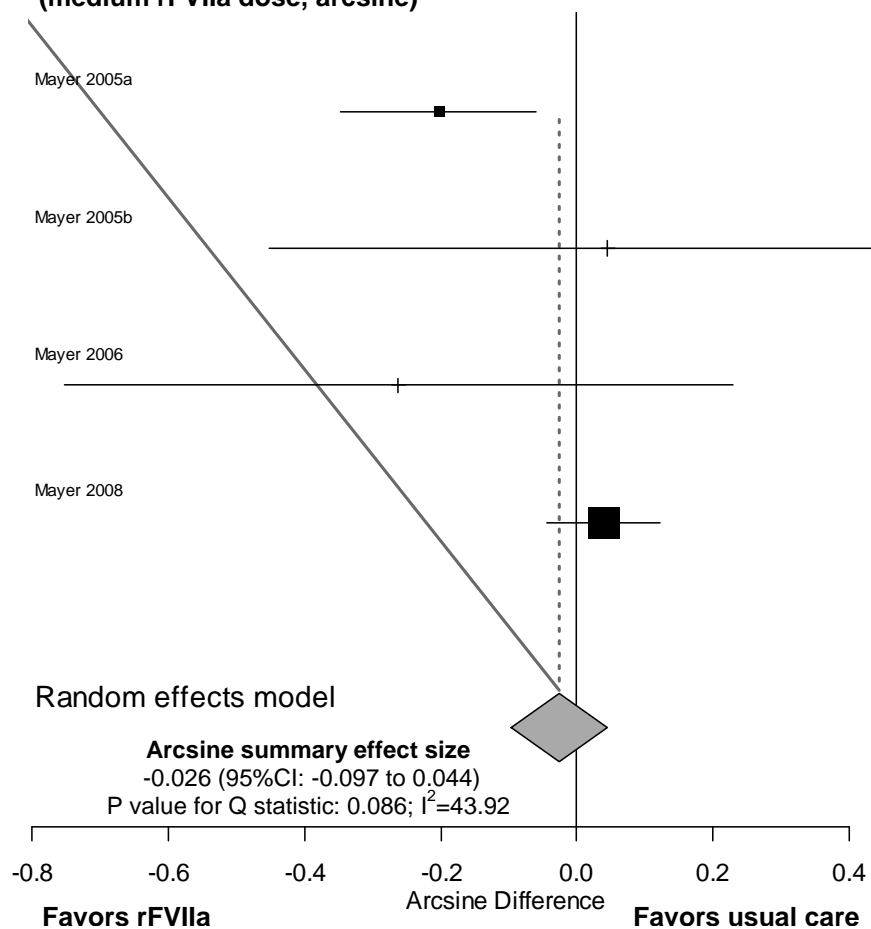
Appendix Figure 4. Poor modified Rankin score in ICH (low rFVIIa dose, arcsine)



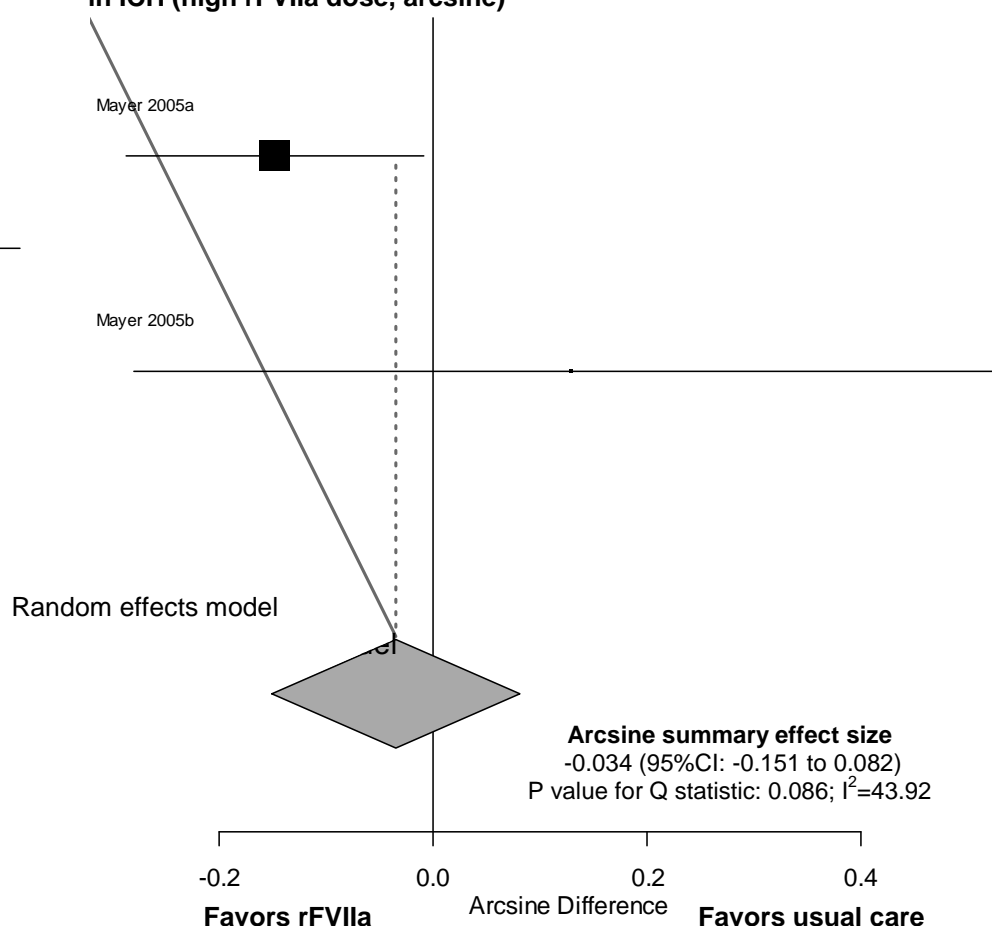
Article	Poor mRS/Total patients (low dose)	
	rFVIIa	Control
Mayer 2005a	59/108	66/96
Mayer 2005b	6/18	5/11
Mayer 2006	13/24	4/8
Mayer 2008	130/264	122/262

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

Appendix Figure 5. Poor modified Rankin score in ICH patients (medium rFVIIa dose, arcsine)



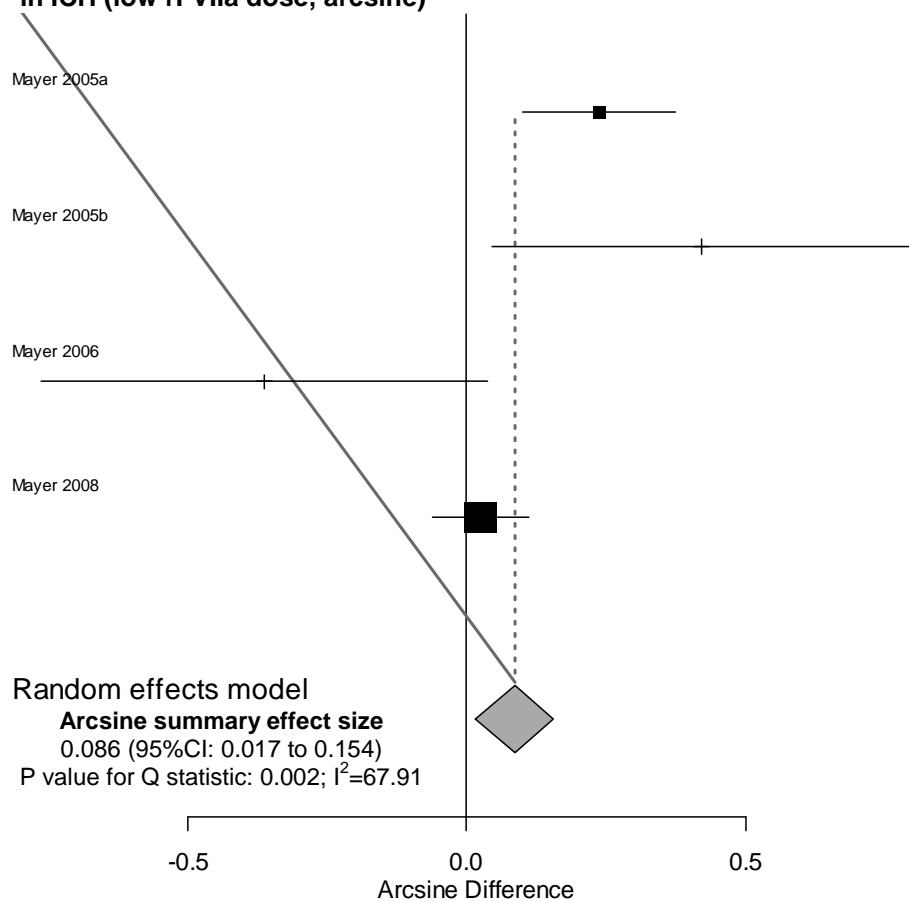
Appendix Figure 6. Poor modified Rankin score in ICH (high rFVIIa dose, arcsine)



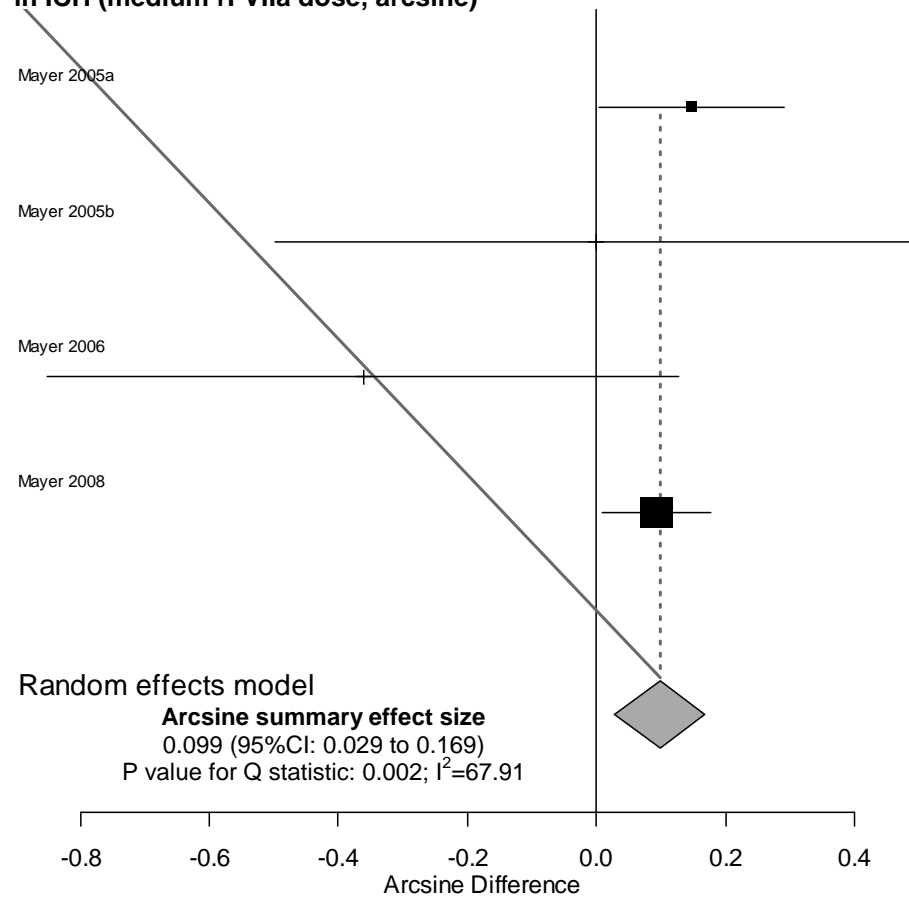
Article	Poor mRS/total patients (medium dose)		Poor mRS/total patients (high dose)	
	rFVIIa	Control	rFVIIa	Control
2005a	45/91	66/96	56/103	66/96
2005b	3/6	5/11	7/12	5/11
2006	2/8	4/8	NA	NA
2008	148/293	122/262	NA	NA

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

Appendix Figure 7. Arterial thromboembolic events in ICH (low rFVIIa dose, arcsine)



Appendix Figure 8. Arterial thromboembolic events in ICH (medium rFVIIa dose, arcsine)

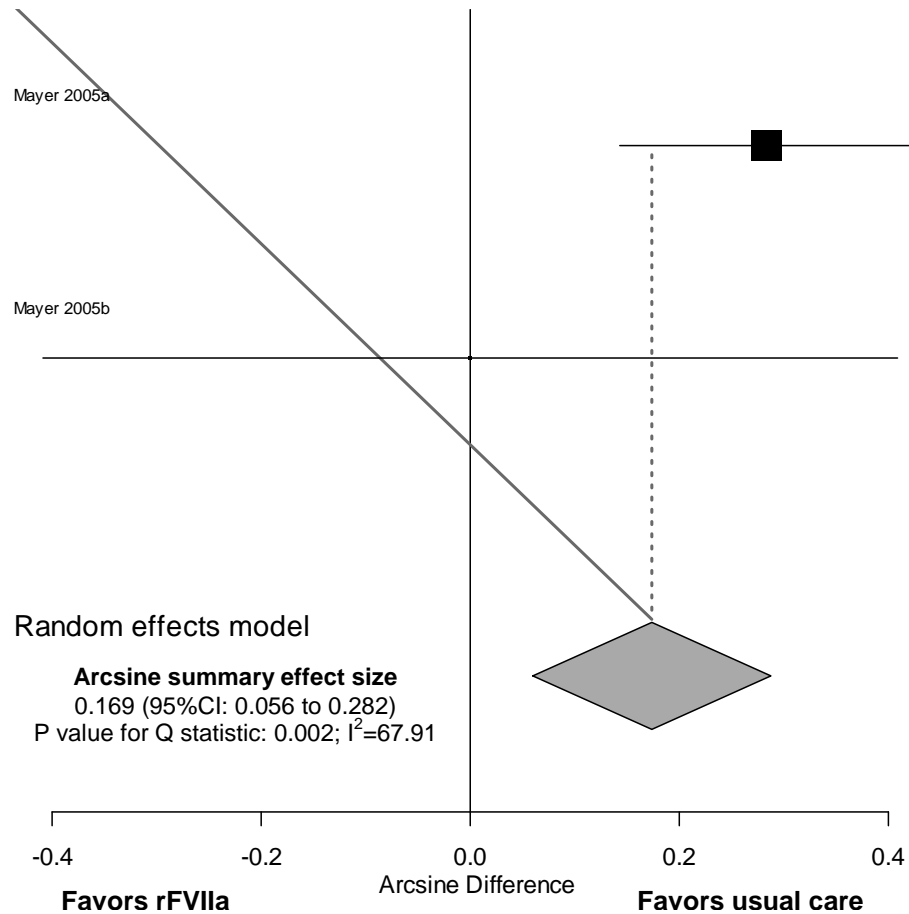


Favors rFVIIa Favors usual care Favors rFVIIa Favors usual care

Article	Arterial TE events/total patients (low dose)		Arterial TE events/total patients (medium dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	6/108	0/96	2/92	0/96
Mayer 2005b	3/18	0/11	0/6	0/11
Mayer 2006	0/24	1/8	0/8	1/8
Mayer 2008	15/265	12/263	27/293	12/263

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

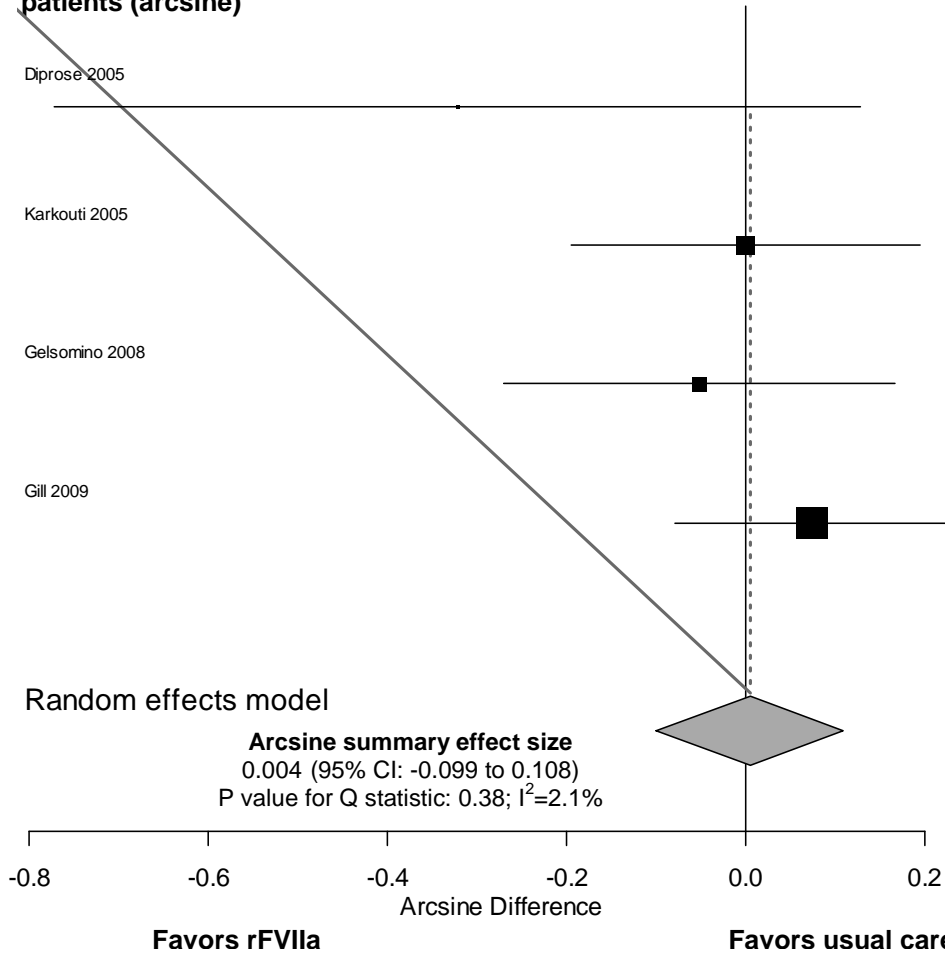
Appendix Figure 9. Arterial thromboembolic events in ICH (high rFVIIa dose, arcsine)



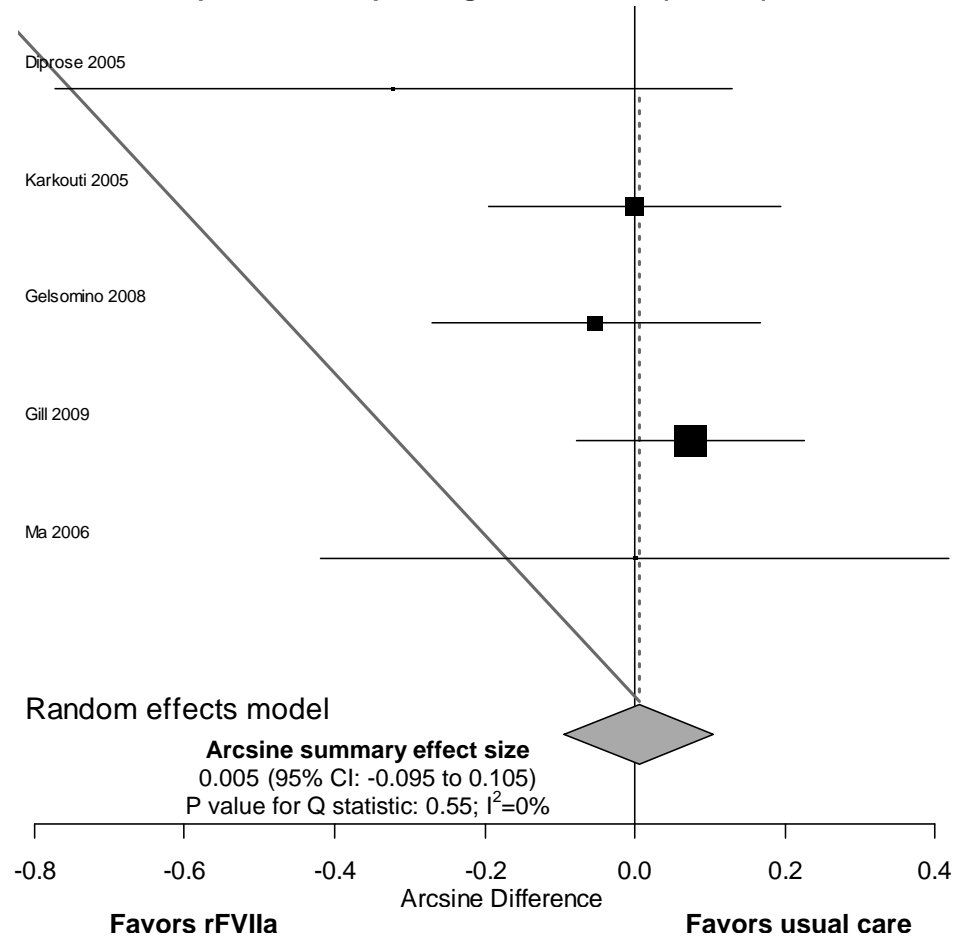
Article	Arterial TE events/Total patients (high dose)	
	rFVIIa	Control
Mayer 2005a	8/103	0/96
Mayer 2005b	0/12	0/11

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

Appendix Figure 10. Mortality in adult cardiac patients (arcsine)



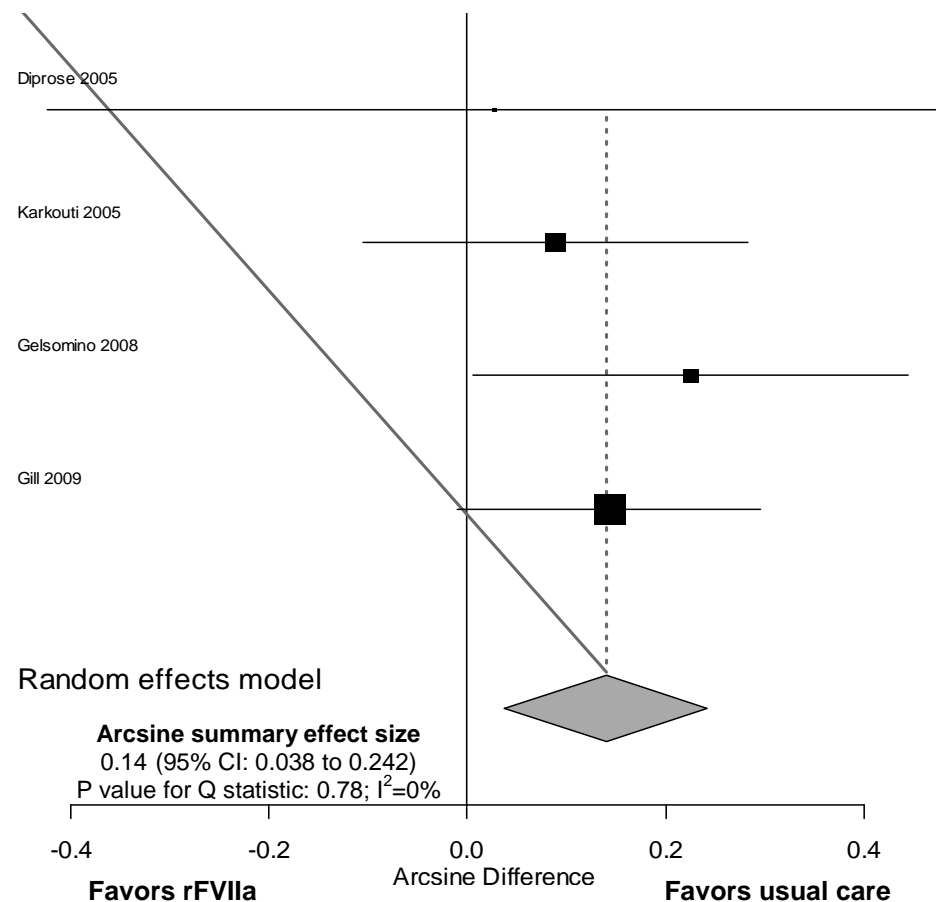
Appendix Figure 11. Sensitivity analysis for mortality in adult cardiac patients incorporating Chinese RCT (arcsine)



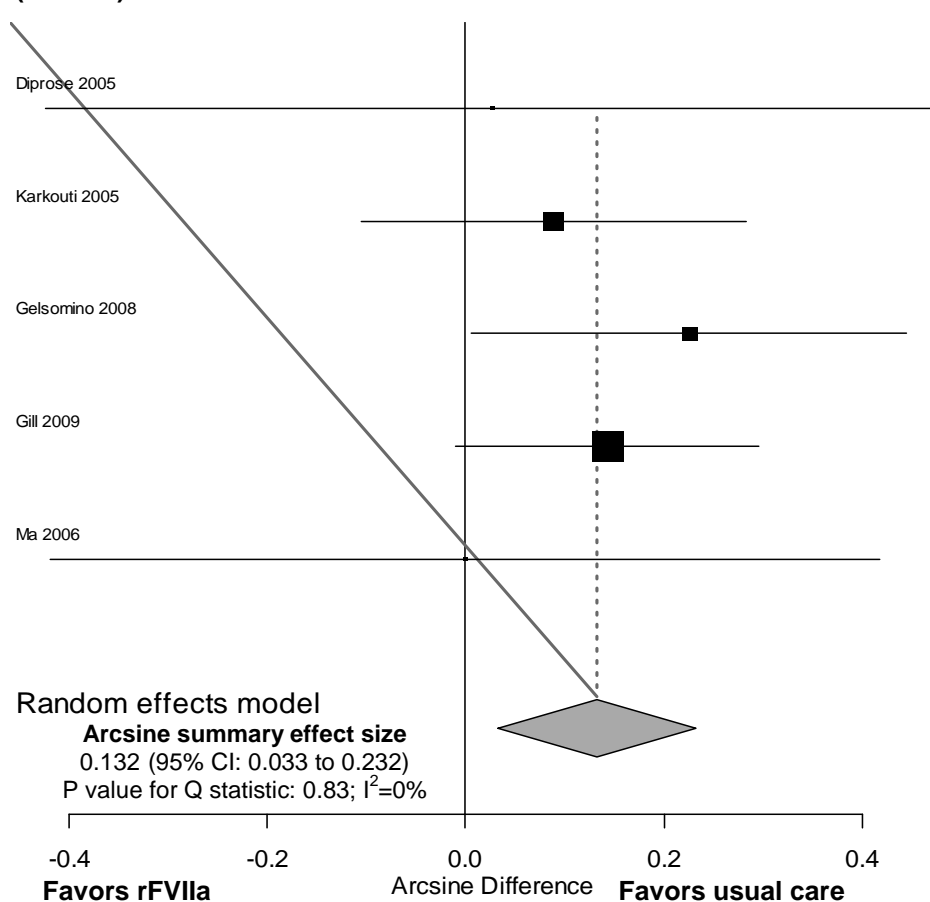
Article	Deaths/Total Patients	
	rFVIIa	Control
Diprose 2005	0/9	1/10
Karkouti 2005	7/51	7/51
Gelsomino 2006	2/40	3/40
Gill 2009	10/103	4/69
Ma 2006	0/11	0/11

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

Appendix Figure 12. All thromboembolic events in adult cardiac patients (arcsine)



Appendix Figure 13. Sensitivity analysis for all thromboembolic events in adult cardiac patients incorporating Chinese RCT (arcsine)



Article	TE Events/Total Patients	
	rFVIIa	Control
Diprose 2005	2/9	2/10
Karkouti 2005	8/51	5/51
Gelsomino 2006	2/40	0/40
Gill 2009	7/103	1/69
Ma 2006	0/11	0/11

Comparison across studies of mean arcsine differences for rFVIIa patients versus usual care. Individual study point estimates of mean arcsine differences are represented by a box or a tick mark, with the box size proportional to the inverse of the variance. The 95% CI around these points estimates are represented by horizontal lines. The point estimate for the arcsine difference pooled across the multiple studies is represented by a dotted vertical line and its 95%CI by a diamond.

Appendix D. Peer Reviewers

Jay Lozier, M.D., Ph.D., National Institutes of Health Clinical Center, Bethesda, MD

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Rochelle Fu, Methodologist/statistician from SRC

Maureane Hoffman, M.D., Ph.D., Durham VA Medical Center, Durham, NC

Stefan Mayer

Bertil Glader, M.D., Ph.D., Lucile Packard Children's Hospital, Stanford, CA.

Per Falk, MD, PhD, Associate Professor, Vice President, Clinical Development, Medical & Regulatory Affairs, Novo Nordisk, Inc.

Appendix E. Study Abstraction Forms

Level 1. (Screening Title and Abstract) Abstraction Form

1. Does this article discuss the use of recombinant factor VIIa in vivo in humans who do not have hemophilia?
(choose one)

No, is NOT on recombinant factor VIIa

No, is on recombinant factor VIIa but is ...: ***(do not check this circle, choose from an option below)***

...in patients who have hemophilia (congenital or acquired)

...in other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)

...is used in humans in vivo, but is NOT used as a therapy or for clinically relevant outcomes

...in animals or in vitro (in culture, molecular, or laboratory studies only)

Yes

Can't tell

Exclude for other reason(s), specify

2. Is in a foreign language

Yes

No

3. For an article that will NOT proceed to full review, is the article still possibly of interest to the research?

Yes

No

Level 2. (Full Text Article Screening) Abstraction Form

1. Is the focus/study population any of the following?

Is NOT on rFVIIa

Patients who have hemophilia A or B or factor VII deficiency (congenital or acquired)

Other populations with congenital or chronic acquired bleeding or clotting disorders (e.g., Glanzmann's)

In vivo in humans, but rFVIIa is NOT used as a therapy or for clinically relevant outcomes

Animals or in vitro (in culture, molecular, or laboratory studies)

2. What is/are the indication(s) for giving rFVIIa? (Check all that apply.)

Intracranial bleeding

Bleeding secondary to trauma

Liver transplant, operative bleeding (whether to prevent or treat)

Cardiac surgery, operative bleeding (whether to prevent or treat)

Prostatectomy, operative bleeding (whether to prevent or treat)

Other indication(s), specify:

Can't tell

3. Is this a secondary report of an already published article (e.g., is on the same study, but with longer follow-up or on a different outcome variable)?

Yes, and specify ref ID# here, if found:

4. What type of article is this?

RCT/ Quasi-RCT (If quasi-RCT, specify why)

Observational study: includes cohort, cross-sectional, case-control and other study types (but NOT case series or report)

Case series or case report

All other (For an article that addresses a KQ1 INDICATION ONLY and is a type of article not mentioned above, check this box only and then skip to question 5. For an article that addresses a KQ2-4 INDICATION ONLY and is a type of article not mentioned above, do NOT check this box; instead check the relevant box immediately below. For an articles that addresses BOTH KQ1 AND KQ2-4 INDICATIONS and is a type of article not mentioned above, check the box here AND the relevant box immediately below.)

...Meta-analysis or systematic review

...Other type of research, specify type:

...In-progress research without results (e.g., RCT methodology paper)

...Guideline or consensus statement

...Can't tell

... All other not covered above (ie, non-research, such as letter, editorial or unsystematic review)

5. Do you think this article will need to be cloned for the next level of extraction?

Yes, it reports on two or more separate RCTS, quasi-RCTS, or observational studies (but is NOT a meta-analysis or review)

Yes, it has more than one intervention arm

Yes, for other reasons, specify:

6. For an article that will NOT otherwise proceed to full review (ie, those above that are NOT RCTS, observational studies, or case series/reports), is there any special reason why it should undergo further review (e.g., there is a study embedded in a letter to editor)?

Yes, specify why:

7. For an article that will not otherwise proceed to full review, does this article contain important information not otherwise captured on this form?

Yes, specify:

8. Do you have any other comments?

Yes

Level 3. Full Text Data Abstraction Form (Study Information and Quality Assessment)

1. Should this article undergo full text review at Level 3?

Yes

No

2. Where did the study take place? (check all that apply)

U.S., specify city, state

U.S. military warzone

Outside of the U.S., specify country or region

Not reported or unclear

3. What was the source of funding for the entire study (check all that apply)

Novo Nordisk®

Other Industry

Government

Foundation

Other

None

Not applicable (e.g. case report or registry)

Not reported or unclear

4. Did Novo Nordisk support any other aspect of this study (such as registry, personnel)? For personnel, specify the nature of the relationship/support with Novo Nordisk in the appropriate text box(es)

Statistician

Other Author(s)

Member of the “study group,” “research team,” or similar designation (and NOT an author on the byline of the paper)

Registry

Other, specify

5. Was the number of enrolling centers reported?

1 center

>1 center

Not reported or unclear

Not applicable (e.g. case report or registry)

6. When did the study take place? Specify as a range in months and years, if given. Leave blank, if unclear.

--

7. Is this a registry study?

Yes

If this is CASE REPORT/SERIES or REGISTRY study (e.g. any non-comparative study), STOP HERE.

8. What was the maximum length of consistent follow-up (ie, follow-up performed/attempted to be performed for all patients)?

Number of days (or specify other unit (e.g., hours), if different than days)

Not reported or Unclear

Not applicable (e.g. a retrospective study)

9. Was informed consent obtained? (check all that apply)

Obtained from patient or legal representative (e.g., parents for minors)

Determined to not be required by relevant IRB, Ethics Committee, or equivalent

Not obtained for other reason, specify

Not reported or Unclear

Not applicable (e.g. most retrospective studies)

10. Was Institutional Review Board approval (or equivalent) obtained?

Yes

Was determined to not be required, give brief explanation

Not reported or unclear

If this is NOT a RCT/QUASI-RCT, SKIP to Q#13.

11. Were **providers** blinded to intervention/treatment allocation (as best you can tell from the description in the article)?

Yes (e.g., article describes placebo injections of identical volume and appearance to treatment injection being given at the same time during treatment)

Partially (e.g., article describes “blinded” treatment and placebo injections but does not provide any other information)

No

Not reported or unclear

12. Were **patients** blinded to intervention/treatment allocation (as best you can tell from the description in the article)?

Yes (e.g., article describes placebo injections of identical volume and appearance to treatment injection being given at the same time during treatment)

Partially (e.g., article describes “blinded” treatment and placebo injections but does not provide any other information)

No

Not reported or unclear

13. Were **outcomes assessors** blinded to intervention/treatment allocation (as best you can tell from the description in the article)?

Yes

Partially (e.g., article states that assessors had no access to patient names or identifying information)

No

Not reported or unclear

14. Did the study assess the success of blinding in any way?

Yes, specify

15. Were any of the following explicitly defined a priori? NOTE: Must be EXPLICITLY defined in the methods section as chosen/performed at the outset of the study to qualify as being defined as a priori. Refer to L3 GUIDELINES for term codes.

Primary outcome(s), specify:

Secondary outcome(s)

Thromboembolic harms and/or mortality outcome(s), specify:

Other harms outcome(s), specify:

Sample size calculation

Statistical analyses

16. Were the data collected prospectively for this study?
 Yes, all data were collected prospectively
 Partially, data were collected both prospectively and retrospectively
 No
 Not reported or unclear
 Not applicable (e.g. retrospective case control study)

17. Were any of the following built into the study design? (check all that apply)
 Interim analyses
 Stopping rules

18. Are you concerned that statistical tests were applied or reported inappropriately? If so, explain why.
 Yes, runs multiple analyses without correction (e.g. Bonferroni correction)
 Other, explain

19. Were multivariate analyses performed to control for confounding factors?
 Yes

20. **FOR COMPARATIVE OBSERVATIONAL STUDIES ONLY (RCTs skip to 21).** Did the study make any attempt to match the control group with the intervention group?
 Yes, describe
 No
 Not Necessary, explain

21. Are you concerned about the potential introduction of bias or lack of generalizability of the study? If so, select all potential problem areas that apply and specify reason. REFER to L3 GUIDELINES for instructions and codes.
 Control and intervention groups were not appropriately matched at baseline (e.g. significantly different demographic or comorbidities between the two groups at baseline, REFER to L3 GUIDELINES), specify
 Control and intervention groups received differential treatment(s), besides rFVIIa
 Differential follow-up time between the control and intervention group, specify
 Problem with withdrawals, loss to follow-up, or other missing data, specify
 Other reason, specify

For RCTs/QUASI-RCTs, skip to Q24

COMPARATIVE OBSERVATIONAL STUDIES

22. Was the control group contemporaneous or historical?
 Contemporaneous
 Historical

23. **FOR COMPARATIVE OBSERVATIONAL STUDIES, THIS IS THE LAST QUESTION ON THIS FORM.** Do you have any other comments?
 Yes

RCTs/QUASI-RCTs

24. If the unit of randomization was not the patient, specify the unit here.

Other, specify

25. Was the method of sequence generation for randomization specified? If so, do you have any concerns (explain concerns in text box)?

Yes, was specified, and I have NO CONCERNS

Yes, was specified, but I HAVE CONCERNS, describe

No, was not specified

26. Was the method of allocation concealment described and appropriate?

Yes, it was both described and appropriate (e.g. opaque, sealed envelope)

It was described but was NOT appropriate (e.g., patient name but no other identifying information removed from chart)

No, it was not described

Not applicable

27. If unit of analysis differed from unit of treatment allocation (e.g., providers were randomized, but analyses were of patient outcomes), did authors acknowledge this issue and make appropriate adjustments or conduct sensitivity analyses?

Yes

No

Not applicable (unit of analysis did not differ from unit of treatment allocation)

28. Were analyses performed according to intention-to-treat?

Yes, explicitly stated

Yes, can be inferred (e.g., article states all patients received assigned treatment and follow-up data are available for all patients)

No

Not reported or unclear

29. Skip this question if analyses **were** performed according to intention-to-treat. But, if analyses were NOT performed according to intention-to-treat, give the following information (check all that apply):

Sensitivity analyses were performed

An explanation for why analyses were not performed according to intention-to-treat was given and is summarized here:

30. **FOR RCTs/quasi-RCTs, THIS IS THE LAST QUESTION ON THIS FORM.** Do you have any other comments?

Yes

Level 4. Full Text Article Data Abstraction Form for Intracranial Hemorrhage Studies

INTRACRANIAL HEMORRHAGE

1. Is this a RCT/Quasi-RCT that reports data on intracranial hemorrhage? **If no, STOP ABSTRACTION**

Yes

No

2. Is this a quasi-RCT? If yes, briefly describe details.

Yes, describe

3. List the number of subjects in each group below

	N Intervention	N Control	Comments
Subjects randomized/baseline			
Subjects receiving assigned therapy			
Subjects lost to follow-up or withdrawn			

4. Briefly describe inclusion/exclusion criteria. If any of the inclusion/exclusion criteria related to recent ischemic/thrombotic/embolic events, also check the tick box indicating that:

Brief description

Yes, at least one exclusion/inclusion criterion related to ischemic/thrombotic/embolic events

5. Was a standard of care defined? (e.g., special transfusion protocols or care by the same cardiac surgery team)

Yes, briefly describe

No

6. rFVIIa Dose Information

rFVIIa Dose	Dose Units (e.g. mg or ug/kg)	Uniform, Mean, or Median Dose? (Use codes U, MN, MD)	SD (or Range or IQR), if applicable	Number of rFVIIa doses	Comments (e.g. specify if variance is range or IQR)

7. Time/Location of rFVIIa administration

Before or at onset of surgery

During surgery, or after, but while still in OR

Postoperatively (e.g. in ICU), but prior to any reoperation

Return from reoperation for bleeding

All other, describe

Not reported or Unclear

Patient demographics and other information

Basic Demographic

8. If different than number of subjects randomized to each group, specify the number of patients with reported demographic data:

N Intervention	N Control	Comments

Variable	N (or Mean or Median) Intervention	SD (or Range or IQR) Intervention	N (or Mean or Median) Control	SD (or Range or IQR) Control	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
9. Age					
10. Gender					
11. Admission INR					
12. Hematoma volume on baseline head CT					
13. Time of rFVIIa administration in relation to time of <i>bleed onset</i>					
14. Time of rFVIIa administration in relation to time of baseline head CT					
15. Systolic blood pressure					
16. Other demographic 1, specify					
17. Other demographic 2, specify					
18. Other demographic 3, specify					
19. Other demographic 4, specify					
20. Other demographic 5, specify					

Baseline categorical variables

21. If different than number of subjects randomized to each group, specify the number of patients with reported baseline data:

N Intervention	N Control	Comments

Variable	N Intervention	N Control	Comments (e.g. specify other variable)
22. Presence of intraventricular hemorrhage on baseline head CT			
23. History of thrombotic/embolic events, specify			
24. Other comorbidity 1, specify			
25. Other comorbidity 2, specify			
26. Other comorbidity 3, specify			
27. Other comorbidity 4, specify			
28. Other comorbidity 5, specify			

Results

29. If different than the number of subjects randomized to each group, specify the number of patients with reported results data:

N Intervention	N Control	Comments

Continuous variable

Event	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Time Frame	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
30. Change in hematoma volume from baseline head CT						
31. Other result 1, specify						
32. Other result 2, specify						
33. Other result 3, specify						
34. Other result 4, specify						
35. Other result 5, specify						
36. Other result 6, specify						
37. Other result 7, specify						
38. Other result 8, specify						

Categorical variables

Event	N Intervention	N Control	Comments (e.g. specify other variable)
39. Mortality			
40. Functional status/disability			
41. Other result 9, specify			
42. Other result 10, specify			
43. Other result 11, specify			
44. Other result 12, specify			
45. Other result 13, specify			
46. Other result 14, specify			
47. Other result 15, specify			
48. Other result 16, specify			

Harm information

49. Were harms measured?

No. If checked here, stop abstraction

50. How were harms identified?

Prospectively, describe

Retrospectively, describe

Both prospectively and retrospectively

Not reported or Unclear

51. Did the study specifically attempt to make the determination that harms were secondary to rFVIIa administration?

Yes, specify how

--

52. If harms were adjudicated in any way, specify how.

Blinded panel

Other

--

53. If different than the number of subjects randomized to each group, specify the number of patients with reported harms data:

N Intervention	N Control	Comments

Undifferentiated Thromboembolic Harms (i.e. without further delineation)

	Total events (n)	N Intervention	N Control	Comments
54. All thromboembolic events				

Arterial Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
55. All arterial thromboembolic events (without further delineation)				
56. Myocardial Infarction				
57. Stroke				
58. Mesenteric thrombosis				
59. Renal infarct				
60. Other arterial thromboembolic event, specify type in comments box				

Venous Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
61. All venous thromboembolic events (without further delineation)				
62. Pulmonary embolism				
63. Deep vein thrombosis				
64. Mesenteric vein thrombosis				
65. Portal vein thrombosis				
66. Thrombosis in right-side chamber of heart				
67. Other venous thromboembolic event, specify type in comments box				

Instrument-related Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
68. All instrument-related thromboembolic events (without further delineation)				
69. ECMO-related thromboembolic events				
70. Arterial line clot				
71. Venous line clot				
72. Other instrument-related thromboembolic event, specify type in comments box				

Other NON-thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
73. Multi-organ failure				
74. Cardiogenic shock/need for balloon pump				
75. Respiratory failure/ARDS				
76. Renal failure				
77. Sepsis				
78. DIC				
79. Other event #1, specify				

80. Other event #2, specify				
81. Other event #3, specify				
82. Other event #4, specify				
83. Other event #5, specify				

84. Do you have any other comments? Please use this space to describe any relevant information that could not be collected on this form.

Level 4. Full Text Article Data Abstraction Form for Traumatic Bleeding Studies

TRAUMA

1. Is this a RCT/Quasi-RCT that reports data on trauma? **If no, STOP ABSTRACTION**

Yes

No

2. Is this a quasi-RCT? If yes, briefly describe details.

Yes, describe

3. List the number of subjects in each group below

	N Intervention	N Control	Comments
Subjects randomized			
Subjects receiving assigned therapy			
Subjects lost to follow-up or withdrawn			

4. Briefly describe inclusion/exclusion criteria. If any of the inclusion/exclusion criteria related to recent ischemic/thrombotic/embolic events, also check the tick box indicating that.

Brief description

Yes, at least one exclusion/inclusion criterion related to ischemic/thrombotic/embolic events

5. Was a standard of care defined? (e.g., special transfusion protocols or care by the same cardiac surgery team)

Yes, briefly describe

No

6. **What types of trauma are included in this arm of the study?**

Blunt trauma

Penetrating trauma

Traumatic brain injury

Other, specify

7. **rFVIIa Dose Information**

rFVIIa Dose	Dose Units (e.g. mg or ug/kg)	Uniform, Mean, or Median Dose? (use codes U, MN, MD)	SD (or Range or IQR), if applicable	Number of rFVIIa doses	Comments (e.g. specify if variance is range or IQR)

8. Describe the timing and location of rFVIIa administration below:

Patient demographics and other information

Basic demographic information

9. If different than number of subjects randomized to each group, specify the number of patients with reported demographic data:

N Intervention	N Control	Comments

Variable	N (or Mean or Median) Intervention	SD (or Range or IQR) Intervention	N (or Mean or Median) Control	SD (or Range or IQR) Control	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
10. Age					
11. Male sex (n)					
12. Weight (or BMI or body surface area, specify units)					
13. Injury Severity Score (ISS)					
14. Other demographic 1, specify					
15. Other demographic 2, specify					
16. Other demographic 3, specify					

Baseline categorical variables

17. If different than the number of subjects randomized to each group, specify the number of patients with reported baseline data:

N Intervention	N Control	Comments

Variable	N Intervention	N Control	Comments (e.g. specify other variable)
18. Acidosis			
19. Abnormal INR			
20. Other comorbidity 1, specify			
21. Other comorbidity 2, specify			
22. Other comorbidity 3, specify			

Results

23. If different than the number of subjects randomized to each group, specify the number of patients with reported results data:

N Intervention	N Control	Comments

Continuous variable

Event	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Time Frame	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
24. RBCs transfused in 24h (packed units)						
25. FFP transfused						
26. ICU time (days)						
27. Change in intracranial hematoma volume (mL)						
28. Other result 1, specify						
29. Other result 2, specify						

Categorical variable

Event	N Intervention	N Control	Comments (e.g. specify other variable)
30. Mortality within 24h			
31. Mortality within 30d			
32. Number of patients requiring transfusions, specify			
33. Need for return to OR/surgical re-exploration			
34. Other result 3, specify			
35. Other result 4, specify			

Harm information

36. Were harms measured?

No. If checked here, STOP abstraction

37. How were harms identified?

Prospectively, describe

Retrospectively, describe

Both prospectively and retrospectively

Not reported or Unclear

38. Did the study specifically attempt to make the determination that harms were secondary to rFVIIa administration?

Yes, specify how

--

39. If harms were adjudicated in any way, specify how.

Blinded panel

Other

--

40. If different than the number of subjects randomized to each group, specify the number of patients with reported harms data:

N Intervention	N Control	Comments

Undifferentiated Thromboembolic Harms (i.e. *without further delineation*)

	Total events (n)	N Intervention	N Control	Comments
41. All thromboembolic events				

Arterial Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
42. All arterial thromboembolic events (<i>without further delineation</i>)				
43. Myocardial Infarction				
44. Stroke				
45. Mesenteric thrombosis				
46. Renal infarct				
47. Other arterial thromboembolic event, specify type in comments box				

Venous Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
48. All venous thromboembolic events (without further delineation)				
49. Pulmonary embolism				
50. Deep vein thrombosis				
51. Mesenteric vein thrombosis				
52. Portal vein thrombosis				
53. Thrombosis in right-side chamber of heart				
54. Other venous thromboembolic event, specify type in comments box				

Instrument-related Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
55. All instrument-related thromboembolic events (without further delineation)				
56. ECMO-related thromboembolic events				
57. Arterial line clot				
58. Venous line clot				
59. Other instrument-related event, specify type in comments box				

Other NON-thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
60. Multi-organ failure				
61. Cardiogenic shock/requirement for balloon pump				
62. Respiratory failure/ARDS				
63. Renal failure				
64. Sepsis				
65. DIC				
66. Other event #1, specify				
67. Other event #2, specify				
68. Other event #3, specify				
69. Other event #4, specify				
70. Other event #5, specify				

71. Do you have any other comments? Please use this space to describe any relevant information that could not be collected on this form.

--

Level 4. Full Text Article Data Abstraction Form for Liver Transplantation Studies

LIVER TRANSPLANT

1. Is this a RCT/Quasi-RCT that reports data on liver transplant? **If no, STOP ABSTRACTION.**

Yes

No

2. Is this a quasi-RCT? If yes, briefly describe details.

Yes, describe

3. List the number of subjects in each group below

	N Intervention	N Control	Comments
Subjects randomized/baseline			
Subjects receiving assigned therapy			
Subjects lost to follow-up or withdrawn			

4. Briefly describe inclusion/exclusion criteria. If any of the inclusion/exclusion criteria related to recent ischemic/thrombotic/embolic events, also check the tick box indicating that:

Brief description

Yes, at least one exclusion/inclusion criterion related to ischemic/thrombotic/embolic events

5. Was a standard of care defined? (e.g., special transfusion protocols)

Yes, briefly describe

No

6. Special type(s) of surgery performed (check all that apply)

Multiorgan transplantation, specify

Other, specify

7. rFVIIa Dose Information

Be sure to indicate in the comments box whether administration of rFVIIa was for preventive or emergent reasons

rFVIIa Dose	Dose Units (e.g. mg or ug/kg)	Uniform, Mean, or Median Dose? (Use codes U, MN, MD)	SD (or Range or IQR), if applicable	Number of rFVIIa doses	Comments (e.g. specify if variance is range or IQR)

8. Time/Location of rFVIIa administration

Before or at onset of surgery

During surgery, or after, but while still in OR

Postoperatively (e.g. in ICU), but prior to any reoperation

Return from reoperation for bleeding

All other, describe
 Not reported or Unclear

Patient demographics and other information

Basic Demographic

9. If different than number of subjects randomized to each group, specify the number of patients with reported demographic data:

N Intervention	N Control	Comments

Variable	N (or Mean or Median) Intervention	SD (or Range or IQR) Intervention	N (or Mean or Median) Control	SD (or Range or IQR) Control	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
10. Age					
11. Gender					
12. Weight (or BMI or body surface area; specify units)					
13. Meld score (or Child Pugh classification)					
14. INR					
15. Warm ischemia at time of donor liver					
16. Cold ischemia at time of donor liver					
17. Other demographic 1, specify					
18. Other demographic 2, specify					
19. Other demographic 3, specify					
20. Other demographic 4, specify					

Baseline categorical variables

Variable	N Intervention	N Control	Comments (e.g. specify other variable)
21. Emergency surgery (e.g. fulminant liver failure)			
22. Prior liver transplantation of other major liver surgery			
23. Presence of multiorgan failure			
24. History of thrombotic/embolic event, specify			
25. Diabetes			
26. Renal failure			
27. CHF			
28. COPD			
29. Hypertension			
30. Other comorbidity 1, specify			
31. Other comorbidity 2, specify			
32. Other comorbidity 3, specify			

Results

33. If different than the number of subjects randomized to each group, specify the number of patients with reported results data:

N Intervention	N Control	Comments

Continuous variable

Event	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Time Frame	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
34. RBCs transfused (packed units)						
35. FFP transfused						
36. Blood loss (or chest tube drainage) (mLs)						
37. OR time (hours)						
38. Other result 1, specify						
39. Other result 2, specify						

Categorical variables

Event	N Intervention	N Control	Comments (e.g. specify other variable)
40. In-hospital mortality, specify			
41. Number of patients requiring transfusion, specify			
42. Need for re-operation or re-transplantation			
43. Other result 3, specify			
44. Other result 4, specify			

Harm information

45. Were harms measured?

No. If checked here, stop abstraction

46. Was there an explicit follow up time set for determination of harms?

Yes, describe

47. How were harms identified?

Prospectively, describe

Retrospectively, describe

Both prospectively and retrospectively

Not reported or Unclear

48. Did the study specifically attempt to make the determination that harms were secondary to rFVIIa administration?

Yes, specify how

49. If harms were adjudicated in any way, specify how.

Blinded panel

Other

50. If different than the number of subjects randomized to each group, specify the number of patients with reported harms data:

N Intervention	N Control	Comments

Undifferentiated Thromboembolic Harms (i.e. without further delineation)

	Total events (n)	N Intervention	N Control	Comments
51. All thromboembolic events				

Arterial Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
52. All arterial thromboembolic events (without further delineation)				
53. Myocardial Infarction				
54. Stroke				
55. Mesenteric thrombosis				
56. Renal infarct				
57. Other arterial thromboembolic event, specify type in comments box				

Venous Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
58. All venous thromboembolic events (without further delineation)				
59. Pulmonary embolism				
60. Deep vein thrombosis				
61. Mesenteric vein thrombosis				
62. Portal vein thrombosis				
63. Thrombosis in right-side chamber of heart				
64. Other venous thromboembolic event, specify type in comments box				

Instrument-related Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
65. All instrument-related thromboembolic events (without further delineation)				
66. ECMO-related thromboembolic events				
67. Arterial line clot				
68. Venous line clot				
69. Other instrument-related thromboembolic event, specify type in comments box				

Other NON-thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
70. Multi-organ failure				
71. Cardiogenic shock/need for balloon pump				
72. Respiratory failure/ARDS				
73. Renal failure				
74. Sepsis				
75. DIC				

76. Other event #1, specify				
77. Other event #2, specify				
78. Other event #3, specify				
79. Other event #4, specify				
80. Other event #5, specify				

81. Do you have any other comments? Please use this space to describe any relevant information that could not be collected on this form.

Level 4. Full Text Article Data Abstraction Form for Cardiac Surgery Studies

CARDIAC SURGERY

1. Is this a RCT/Quasi-RCT that reports data on cardiac surgery? **If no, STOP ABSTRACTION**

Yes

No

2. Is this a quasi-RCT? If yes, briefly describe details.

Yes, describe

3. List the number of subjects in each group below

	N Intervention	N Control	Comments
Subjects randomized			
Subjects receiving assigned therapy			
Subjects lost to follow-up or withdrawn			

4. Briefly describe inclusion/exclusion criteria. If any of the inclusion/exclusion criteria related to recent ischemic/thrombotic/embolic events, also check the tick box indicating that.

Brief description

Yes, at least one exclusion/inclusion criterion related to ischemic/thrombotic/embolic events

5. Was a standard of care defined? (e.g., special transfusion protocols or care by the same cardiac surgery team)

Yes, briefly describe

No

6. **Type (s) of surgery performed (for adults) (check all that apply)**

Multiple surgeries

CABG

Cardiac transplantation

Single valve repair/replacement

Any aortic

All Other, specify

No cardiac surgery for adults

7. **Type (s) of surgery performed (for child) (check all that apply)**

Reoperation (any type)

Correction of congenital heart disease

All other, specify

No surgery performed in child

8. **rFVIIa Dose Information**

rFVIIa Dose	Dose Units (e.g. mg or ug/kg)	Uniform, Mean, or Median Dose? (use codes U, MN, MD)	SD (or Range or IQR), if applicable	Number of rFVIIa doses	Comments (e.g. specify if variance is range or IQR)

- 9. Time/Location of rFVIIa administration
- Before or at onset of surgery
- During surgery, or after, but while still in OR
- Postoperatively (e.g. in ICU), but prior to any reoperation
- Return from reoperation for bleeding
- All other, describe
- Not reported or Unclear

Patient demographics and other information

Basic demographic information

10. If different than number of subjects randomized to each group, specify the number of patients with reported demographic/baseline data:

N Intervention	N Control	Comments

Variable	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
11. Age					
12. Gender					
13. Weight (or BMI or body surface area, specify units)					
14. Other demographic 1, specify					
15. Other demographic 2, specify					
16. Other demographic 3, specify					
17. Other demographic 4, specify					

Baseline categorical variables

Variable	N Intervention	N Control	Comments (e.g. specify other variable)
18. Emergency surgery			
19. Previous cardiac surgery			
20. History of thrombotic/embolic events, specify			
21. Diabetes			
22. Renal failure			
23. CHF			
24. COPD			
25. Hypertension			
26. Other comorbidity 1, specify			
27. Other comorbidity 2, specify			
28. Other comorbidity 3, specify			

Results

29. If different than the number of subjects randomized to each group, specify the number of patients with reported results data:

N Intervention	N Control	Comments

Continuous variable

Event	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Time Frame	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
30. RBCs transfused in 24h (packed units)						
31. FFP transfused						
32. Blood loss (or chest tube drainage) (mLs)						
33. OR time (hours)						
34. Other result 1, specify						
35. Other result 2, specify						
36. Other result 3, specify						
37. Other result 4, specify						
38. Other result 5, specify						
39. Other result 6, specify						

Results categorical variables

Event	N Intervention	N Control	Comments (e.g. specify other variable)
40. In-hospital mortality			
41. Need for return to OR/surgical re-exploration			
42. Number of patients requiring transfusions, specify further			
43. Other result 7, specify			
44. Other result 8, specify			
45. Other result 9, specify			
46. Other result 10, specify			
47. Other result 11, specify			
48. Other result 12, specify			

Harm information

49. Were harms measured?

No. If checked here, STOP abstraction

50. Was there an explicit follow up time for determination of harms?

Yes, describe

51. How were harms identified?

Prospectively, describe

Retrospectively, describe

Both prospectively and retrospectively

Not reported or Unclear

52. Did the study specifically attempt to make the determination that harms were secondary to rFVIIa administration?

Yes, specify how

53. If harms were adjudicated in any way, specify how.

Blinded panel

Other

54. If different than the number of subjects randomized to each group, specify the number of patients with reported harms data:

N Intervention	N Control	Comments

Undifferentiated Thromboembolic Harms (i.e. without further delineation)

	Total events (n)	N Intervention	N Control	Comments
55. All thromboembolic events				

Arterial Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
56. All arterial thromboembolic events (without further delineation)				
57. Myocardial Infarction				
58. Stroke				
59. Mesenteric thrombosis				
60. Renal infarct				
61. Other arterial thromboembolic event, specify type in comments box				

Venous Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
62. All venous thromboembolic events (without further delineation)				
63. Pulmonary embolism				
64. Deep vein thrombosis				
65. Mesenteric vein thrombosis				
66. Portal vein thrombosis				
67. Thrombosis in right-side chamber of heart				
68. Other venous thromboembolic event, specify type in comments box				

Instrument-related Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
69. All instrument-related thromboembolic events (without further delineation)				
70. ECMO-related thromboembolic events				
71. Arterial line clot				

72. Venous line clot				
73. Other instrument-related event, specify type in comments box				

Other NON-thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
74. Multi-organ failure				
75. Cardiogenic shock/requirement for balloon pump				
76. Respiratory failure/ARDS				
77. Renal failure				
78. Sepsis				
79. DIC				
80. Other event #1, specify				
81. Other event #2, specify				
82. Other event #3, specify				
83. Other event #4, specify				
84. Other event #5, specify				

85. Do you have any other comments? Please use this space to describe any relevant information that could not be collected on this form.

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Level 4. Full Text Article Data Abstraction Form for Prostatectomy Studies

PROSTATECTOMY

1. Is this a RCT/Quasi-RCT that reports data on prostatectomy? **If no, STOP ABSTRACTION.**

Yes

No

Study characteristics

2. Is this a quasi-RCT? If yes, briefly describe details.

Yes, describe

3. List the number of subjects in each group below

	N Intervention	N Control	Comments
Subjects randomized/baseline			
Subjects receiving assigned therapy			
Subjects lost to follow-up or withdrawn			

4. Briefly describe inclusion/exclusion criteria. If any of the inclusion/exclusion criteria related to recent ischemic/thrombotic/embolic events, also check the tick box indicating that:

Brief description

Yes, at least one exclusion/inclusion criterion related to ischemic/thrombotic/embolic events

5. Was a standard of care defined? (e.g., special transfusion protocols)

Yes, briefly describe

No

6. Type (s) of surgery performed (check all that apply)

Radial retropubic prostatectomy

Millin prostatectomy

All other, specify

7. rFVIIa Dose Information

Indicate in the comments box whether administration of rFVIIa was for preventive or emergent reasons.

rFVIIa Dose	Dose Units (e.g. mg or ug/kg)	Uniform, Mean, or Median Dose? (Use codes U, MN, MD)	SD (or Range or IQR), if applicable	Number of rFVIIa doses	Comments (e.g. specify if variance is range or IQR)

8. Time/Location of rFVIIa administration

Before or at onset of surgery

During surgery, or after, but while still in OR

Postoperatively (e.g. in ICU), but prior to any reoperation

Return from reoperation for bleeding

All other, describe

Not reported or Unclear

Patient demographics and other information***Basic Demographic***

9. If different than number of subjects randomized to each group, specify the number of patients with reported demographic/baseline data:

N Intervention	N Control	Comments

Variable	N (or Mean or Median) Intervention	SD (or Range or IQR) Intervention	N (or Mean or Median) Control	SD (or Range or IQR) Control	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
10. Age					
11. Gender					
12. Weight (or BMI or body surface area; specify units)					
13. Other demographic 1, specify					
14. Other demographic 2, specify					
15. Other demographic 3, specify					
16. Other demographic 4, specify					

Baseline categorical variables

Variable	N Intervention	N Control	Comments (e.g. specify other variable)
17. History of thrombotic/embolic events, specify			
18. Emergency surgery			
19. Diabetes			
20. Renal failure			
21. CHF			
22. COPD			
23. Hypertension			
24. Other comorbidity 1, specify			
25. Other comorbidity 2, specify			
26. Other comorbidity 3, specify			

Results

27. If different than the number of subjects randomized to each group, specify the number of patients with reported results data:

N Intervention	N Control	Comments

Results continuous variable

Event	Mean (or Median) Intervention	SD (or Range or IQR) Intervention	Mean (or Median) Control	SD (or Range or IQR) Control	Time Frame	Comments (e.g. specify other variable, units, mean/med, SD/range/IQR)
28. RBCs transfused (packed units)						
29. FFP transfused						
30. Blood loss (or chest tube drainage) (mLs)						

31. OR time (hours)						
32. Length of hospital stay (days)						
33. Other result 1, specify						
34. Other result 2, specify						

Results categorical variables

Event	N Intervention	N Control	Comments (e.g. specify other variable)
35. In-hospital mortality			
36. Number of patients requiring transfusions, specify			
37. Need for re-operation or re-transplantation			
38. Other result 3, specify			
39. Other result 4, specify			

Harm information

40. Were harms measured?

No. If checked here, stop abstraction

41. Was there an explicit follow up time set for determination of harms

Yes, describe

42. How were harms identified?

Prospectively, describe

Retrospectively, describe

Both prospectively and retrospectively

Not reported or Unclear

43. Did the study specifically attempt to make the determination that harms were secondary to rFVIIa administration?

Yes, specify how

44. If harms were adjudicated in any way, specify how.

Blinded panel

Other

45. If different than the number of subjects randomized to each group, specify the number of patients with reported harms data:

N Intervention	N Control	Comments

Undifferentiated Thromboembolic Harms (i.e. without further delineation)

	Total events (n)	N Intervention	N Control	Comments
46. All thromboembolic events				

Arterial Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
47. All arterial thromboembolic events (without further delineation)				
48. Myocardial Infarction				

49. Stroke				
50. Mesenteric thrombosis				
51. Renal infarct				
52. Other arterial thromboembolic event, specify type in comments box				

Venous Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
53. All venous thromboembolic events (without further delineation)				
54. Pulmonary embolism				
55. Deep vein thrombosis				
56. Mesenteric vein thrombosis				
57. Portal vein thrombosis				
58. Thrombosis in right-side chamber of heart				
59. Other venous thromboembolic event, specify type in comments box				

Instrument-related Thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
60. All instrument-related thromboembolic events (without further delineation)				
61. ECMO-related thromboembolic events				
62. Arterial line clot				
63. Venous line clot				
64. Other instrument-related thromboembolic event, specify type in comments box				

Other NON-thromboembolic Harms

Event	Total Events (n)	N Intervention	N Control	Comments
65. Multi-organ failure				
66. Cardiogenic shock/need for balloon pump				
67. Respiratory failure/ARDS				
68. Renal failure				
69. Sepsis				
70. DIC				
71. Other event #1, specify				
72. Other event #2, specify				
73. Other event #3, specify				
74. Other event #4, specify				
75. Other event #5, specify				

76. Do you have any other comments? Please use this space to describe any relevant information that could not be collected on this form.

Appendix F. Strength of Evidence and Applicability Assessment Forms

Strength of Evidence Assessment form for: * Clinical Domain of: [_____]

* Outcome(s) of: [_____]

Outcome of Interest	Number of Studies	Number of Subjects		Domains Pertaining to Strength of Evidence						Estimated Magnitude of Effect	Effect of rFVIIa Dosage	Overall Strength of Evidence Grade
				RFVIIa	Usual Care	Risk of Bias Domains			Consistency			
		Design	Quality			Summary Risk of Bias*						
1.				RCTs								
				Comp Obs								
2.				RCTs								
				Comp Obs								
3.				RCTs								
				Comp Obs								
4.				RCTs								
				Comp Obs								
5.				RCTs								
				Comp Obs								

RCT, randomized controlled trial; Comp Obs, comparative observational study; SOE, strength of evidence.

*For further details on assigning a summary risk score, see guidance document.