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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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0017

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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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Acknowledgments

We are grateful to the following individuals for their hard work, assistance and contribution to this Comparative Effectiveness Review: Rose Campbell of the Oregon Health Sciences University, Michael Handrigan formerly of AHRQ, Robin Varghese of the University of Western Ontario, and Allison Gienger, Peter Richmond, Noelle Pineda, Rebecca Drieling, and Christine Wijman of Stanford University.

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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
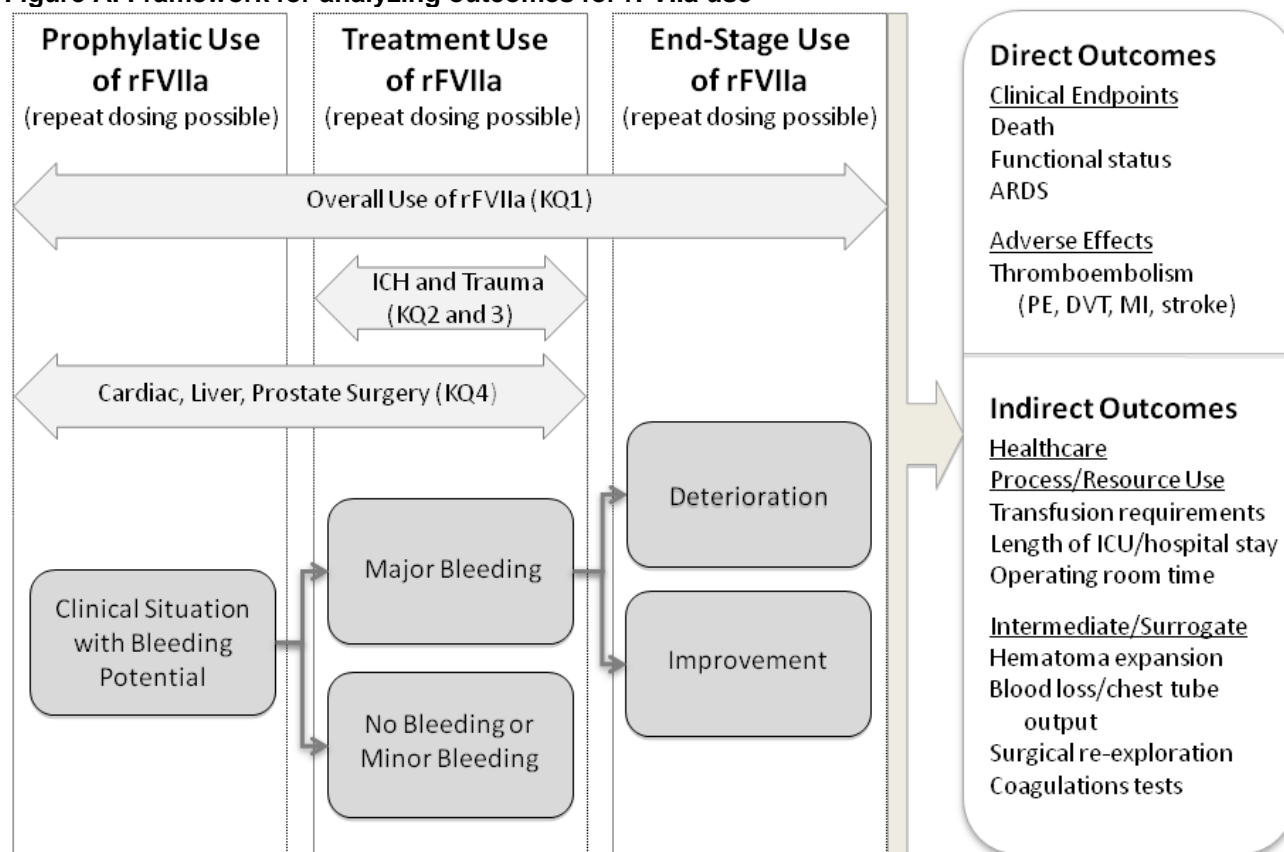
Premier Database Analysis to Assess In-Hospital Use of rFVIIa

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
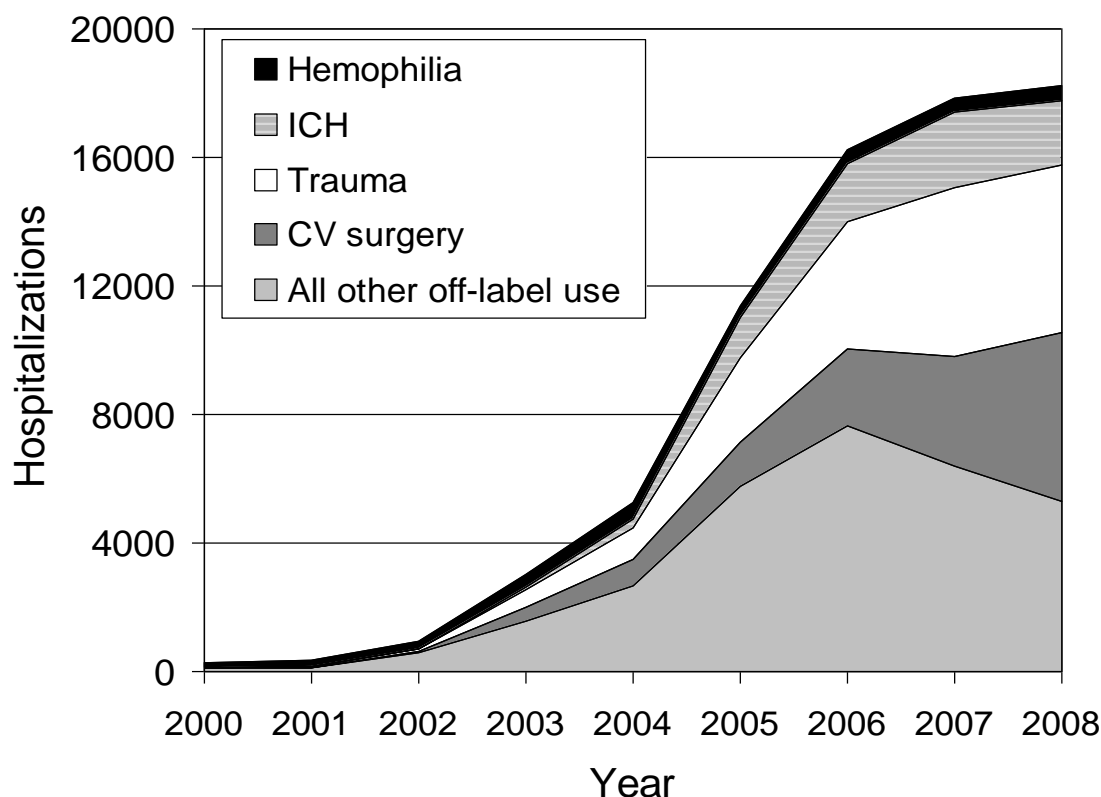
We did not evaluate outpatient rFVIIa use. The majority of use of rFVIIa occurs in the outpatient setting, and the majority of outpatient use is for on-label indications related to hemophilia. According to the Premier database on in-hospital use in the United States, cases of use for the approved hemophilia 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)
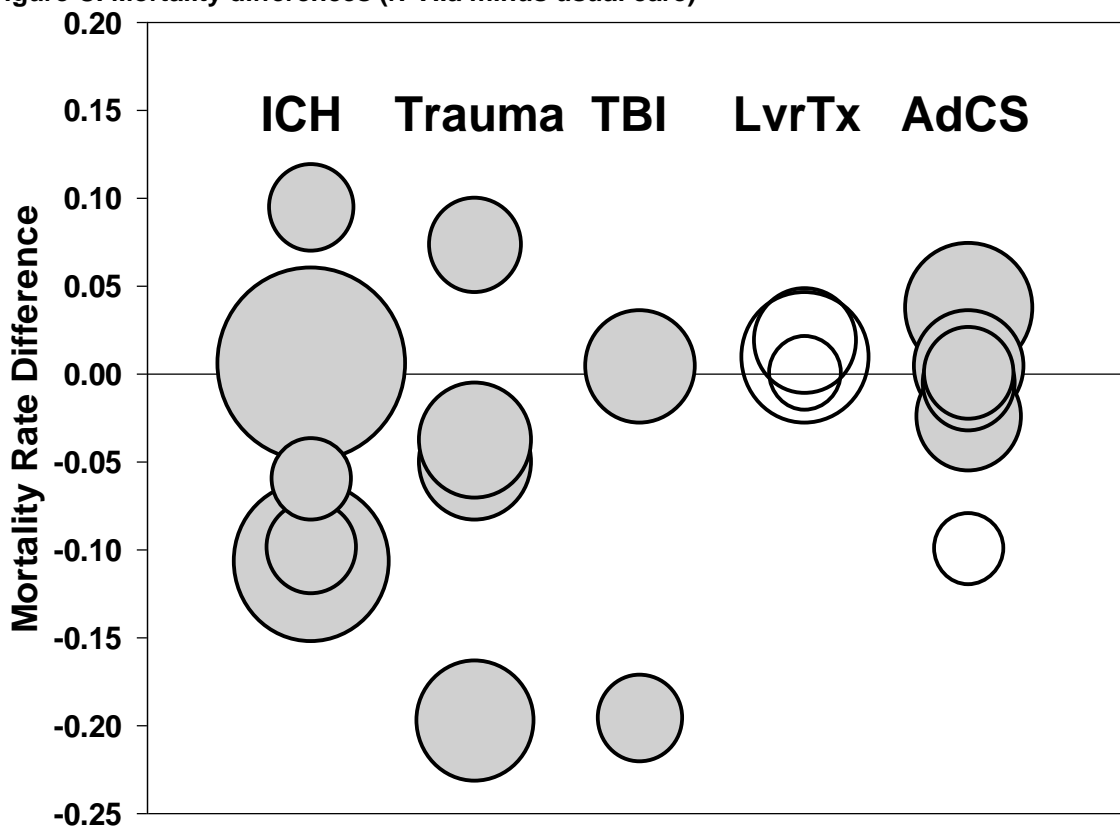
Figure D. Thromboembolic event risk differences (rFVIIa minus usual care)
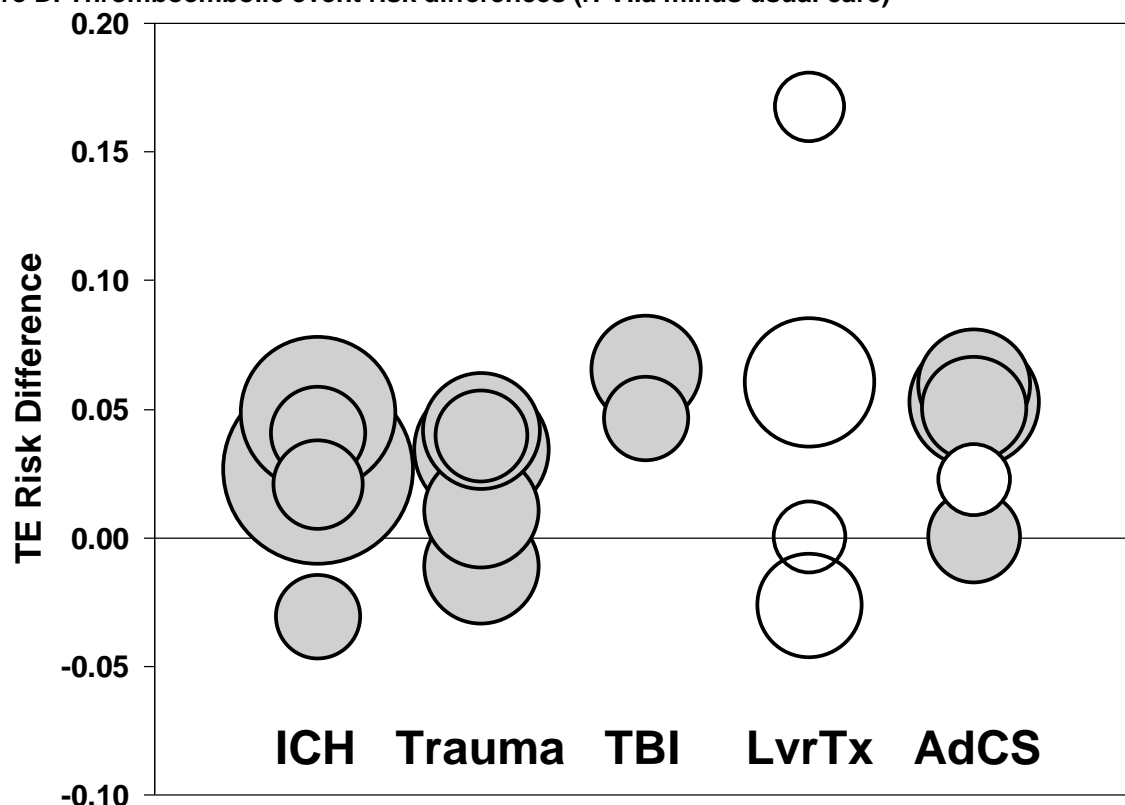
- There was no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 (95 percent CI -0.086 to 0.024), medium-dose group: 0.020 (95 percent CI -0.076 to 0.036), high-dose group: 0.027 (95 percent CI -0.121 to 0.068); *p* value of the *Q* statistic for all risk differences is 0.248) (also 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] and 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: • Intracranial hemorrhage: 0.34 • Body trauma: 0.33 • Brain trauma: 0.33 • Liver transplant-ation: 0.38 • Adult cardiac surgery: 0.23 • Pediatric cardiac surgery: 0.22 • Prostatec-tomy: 0	NA	NA	NA	NA	• 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	• Published studies of rFVIIa are often limited by small study size, inconsistent study quality, use of indirect outcomes, and heterogeneity by dosage and indication.

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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	Units RBCs transfused	Other indirect outcome	
KQ2. Intracranial hemorrhage							
RCT: 4 OBS: 1	rFVIIa: 968 UC: 414	*Moderate* rFVIIa: 0.08-0.22 UC: 0.13-0.29	*Moderate* rFVIIa: 0.04-0.11 UC: 0-0.13	*Poor functional status*[d] *Moderate* rFVIIa: 0.44-0.53 UC: 0.46-0.69	NA	*Percent hematoma expansion* *Moderate* rFVIIa: 4-79 UC: 11-29	Use of rFVIIa compared to usual care, within the ICH subgroup of intracranial hemorrhage • 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 In summary, current evidence of moderate strength suggests that neither benefits nor harms substantially exceed each other
KQ3a. Body trauma							
RCT: 2 OBS: 3	rFVIIa: 267 UC: 429	*Low* rFVIIa: 0.07-0.31 UC: 0-0.51	*Low* rFVIIa: 0.03-0.12 UC: 0-0.08	*ARDS* *Low* rFVIIa: 0.02-0.06 UC: 0.04-0.16	*Low* rFVIIa: 6.9-16.0 UC: 7.7-14.0	NA	Use of rFVIIa compared to usual care • Did not affect mortality or TE event rate • May decrease the rate of ARDS • Had an unclear impact on RBC transfusion requirements In summary, current evidence of low strength suggests the potential for benefit and little evidence of increased harm
KQ3b. Brain trauma							
RCT: 1 OBS: 1	rFVIIa: 79 UC: 53	*Low* rFVIIa: 0.12-0.33 UC: 0.11-0.53	*Low* rFVIIa: 0.15-0.22 UC: 0.08-0.18	NA	NA	*Absolute hematoma expansion (mL)* *Low* rFVIIa: 7.0 UC: 10.4	Use of rFVIIa compared to usual care • 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) In summary, current evidence of low strength is too limited to compare harms and benefits

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

Number of studies	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	Units RBCs transfused	Other indirect outcome	
KQ4a. Liver transplantation							
RCT: 4 OBS: 1	rFVIIa: 215 UC: 117	*Low* rFVIIa: 0-0.08 UC: 0-0.02	*Low* rFVIIa: 0-0.22 UC: 0-0.16	NA	*Low* rFVIIa: 1.2-13.0 UC: 2.3-11.1	*OR time (min)* *Low* rFVIIa: 268-554 UC: 432-598 *ICU LOS (day)* *Low* rFVIIa: 3.0-4.8 UC: 3.0-5.2	Use of rFVIIa compared to usual care • Did not affect mortality or TE event rate • May reduce RBC transfusion requirements • Did not reduce OR time or ICU length of stay In summary, 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	*Low* rFVIIa: 0-0.33 UC: 0.06-0.33	*Moderate* rFVIIa: 0-0.22 UC: 0-0.20	NA	*Low* rFVIIa: 0-9.1 UC: 2-17	*ICU LOS (day)* *Low* rFVIIa: 2.5-14 UC: 1-18.5	Use of rFVIIa compared to usual care • 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 In summary, current evidence of moderate strength (TE event rate outcome) or low strength (all other outcomes) suggests that neither benefits nor harms substantially exceed each other

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	Units RBCs transfused	Other indirect outcome	
KQ4bii. Pediatric cardiac surgery							
RCT: 1 OBS: 0	rFVIIa: 40 UC: 36	Not reported *Insufficient* rFVIIa: 0 UC: 0		NA	*mL RBC transfused* *Insufficient* rFVIIa: 77 UC: 127	*Time to chest closure (min)* *Insufficient* rFVIIa: 98.8 UC: 55.3	The one included study cannot comment on use of rFVIIa compared to usual care on mortality (because these data were not reported) or on TE event rate (because there were limited events). Use of rFVIIa compared to usual care • May reduce RBC transfusion requirements • Was associated with an increase in time to chest closure In summary, current evidence is insufficient for comparing harms and benefits
KQ4c. Prostatectomy							
RCT: 1 OBS: 0	rFVIIa: 24 UC: 12	*Insufficient* rFVIIa: 0 UC: 0	*Insufficient* rFVIIa: 0-0.13 UC: 0	NA	*Insufficient* rFVIIa: 0-0.6 UC: 1.5	*OR time (min)* *Insufficient* rFVIIa: 120-126 UC: 180	The one included study cannot comment on use of rFVIIa compared to usual care on mortality or TE event rate because there were limited events. Use of rFVIIa compared to usual care • Was associated with reduced RBC transfusion requirements and OR time In summary, current evidence is insufficient for comparing harms and benefits

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

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

[b]Strength of evidence is based on scores within four evidence domains (risk of bias, consistency, directness, and precision) and is rated as "low," "moderate," "high," or "insufficient."

[c]Only non-KQ studies are listed here because the studies on Key Questions 2-4 are subsequently reviewed lower in the table.

[d]Poor 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 Hemophlia 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 (EMEA) 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 EMEA 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 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 heterogenous 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

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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
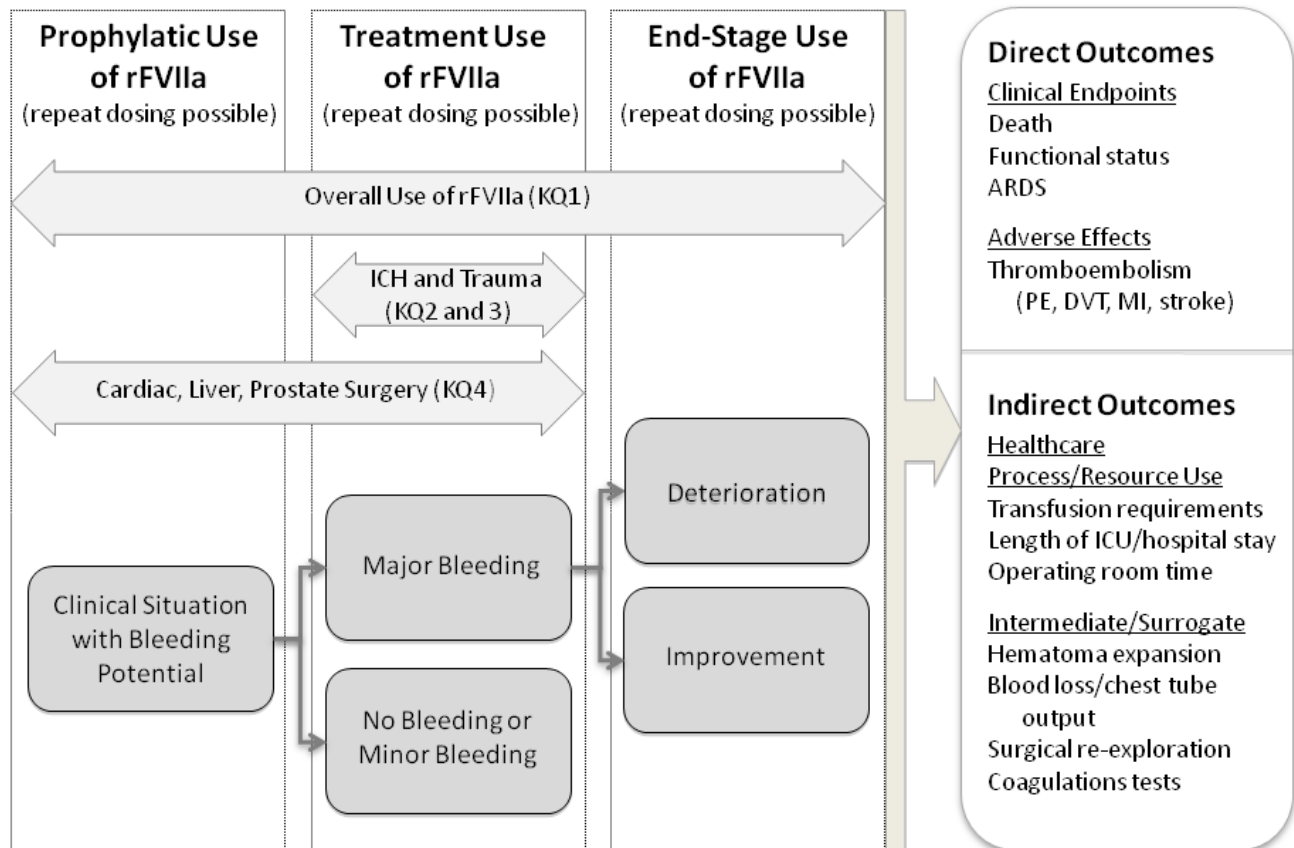
Search Strategy

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

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when added onto "usual care" might vary according 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 generalizeability, 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 latter[68]).

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 exisiting 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 agains 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 assesors** 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 *imprecise* 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	- Eligibility criteria and proportion of screened patients enrolled - Demographic characteristics - Severity or stage of illness - Event rates in treatment and control groups	- 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	- Dose, schedule, and duration of medication	- 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	- Whether comparator is the best available alternative to the treatment under study	- Use of sub-standard alternative therapy	Describe whether comparators reflect best alternative treatment and how this may influence treatment effect size
Outcomes	- Effects of intervention on most important benefits and harms, and how they are defined	- 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	- Range and intensity of follow-up	- 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	- Geographic setting - Clinical setting (e.g. referral center versus community)	- 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 hiearchy.

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:

$$\arcsin difference(p_T, p_C) = \arcsin(\sqrt{p_T}) - \arcsin(\sqrt{p_C})$$

$$\approx \sqrt{p_T} - \sqrt{p_C}$$

We performed formal assessments of heterogeneity using the Q statistic for heterogeneity (and I^2 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 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 methods developed by Olkin et al[82] 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
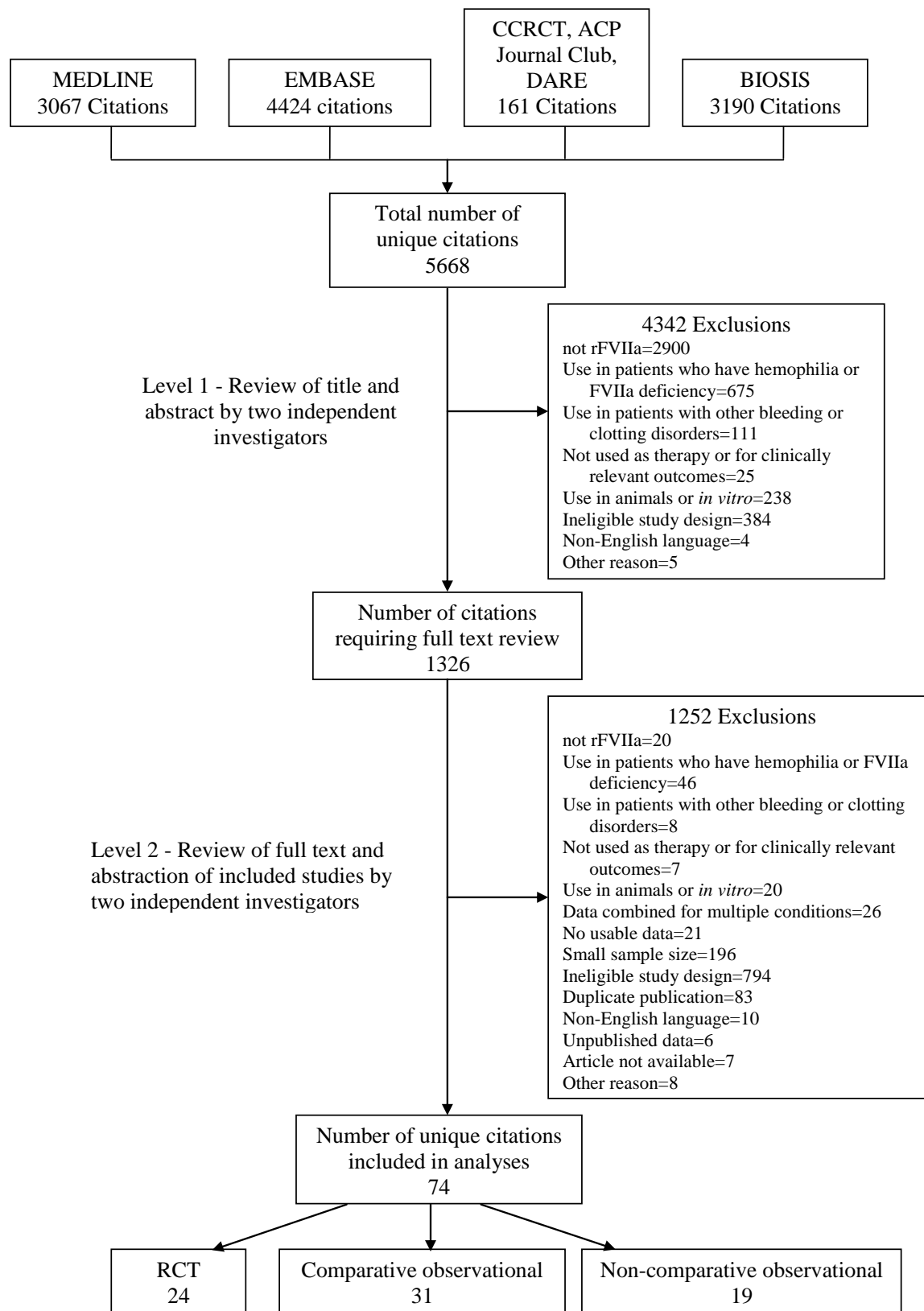
"Small sample size" applies only to non-comparative studies with less than 15 patients. "Duplicate publication" includes studies with overlapping patient populations.

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

Article	Study design	Time period	Country or Region	Setting	Sample size[#] rFVIIa	Sample size[#] UC	Mean age*, years (SD) [Range] rFVIIa	Mean age*, years (SD) [Range] UC	rFVIIa dose, µg/kg	Manufacturer Sponsorship
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]† (also reports on body trauma)	Retrospective non-comparative	6/2001-12/2003	International	Online registry	20	-	7.7 (5.8)	-	Median: 100 Range: 9-393	Funding
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][I]	63[U] [59-66][I]	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][I]	-	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

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

Article	Study design	Time period	Country or Region	Setting	Sample size[#] rFVIIa	Sample size[#] UC	Mean age*, years (SD) [Range] rFVIIa	Mean age*, years (SD) [Range] UC	rFVIIa dose, µg/kg	Manufacturer Sponsorship
(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]|	29[U] [26-30]|	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 2004[100] has multiple control groups. The range of sample sizes is presented.

[#]Jeffers 2002[142] 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.

[U]Median;

[I]IQR;

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	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
Hallevi 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
Kalicinski 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 casess) 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
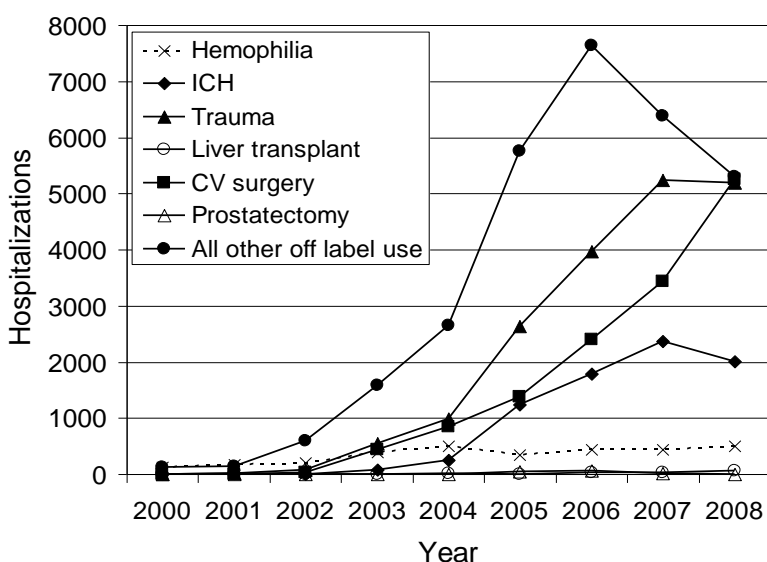
Figure 4. Growth of in-hospital, off-label vs. on-label uses of rFVIIa in Premier database, 2000-2008
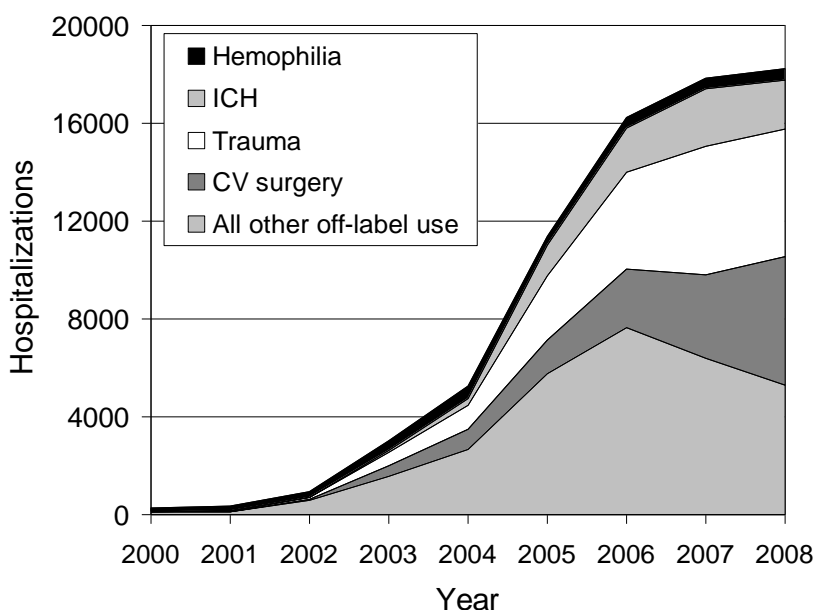
Figures 3 and 4 present similar information. However, "all other" in Figure 4 includes liver transplantation and prostatectomy, as well as all of the other indications.

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.

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

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

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 ug/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 hematopeitic 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

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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 ug/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 ug/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	Outcomes Evaluated Indirect
Kolban 2006[158]	Scoliosis surgery (adolescents) Prophylaxis	Retrospective comparative observational	1 center Szczecin, Poland 2000-2003	Rx: 26 Ucare: 26 Mean dose: 23 ug/kg	Rx: 17 [10-22] Ucare: 16 [12-19]	Mortality Adverse events including TE events	Transfusion requirements†† Blood loss

[U]Median; [I]Interquartile range; †Examples of transfusion requirements were red blood cells and fresh frozen plasma

^Dutton 2004[100] 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 study[89] (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., sudural 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 potiential 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 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 Ilyas[89] 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 al[82] 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 I^2 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 2005a[21] 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 RCT[23] 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 Australia, Europe, Asia, North America 8/2002-3/2004	All Rx: 303 40: 108 80: 92 160: 103 Ucare: 96	Rx: 40: 67 (12) 80: 65 (12) 160: 64 (13) Ucare: 68 (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 Adverse events including TE events Poor functional outcome (mRS 4-6)	Change in hematoma volume
Mayer 2005b[86]	RCT Treatment	14 centers Australia, Europe, Asia 8/2001-10/2002	All Rx: 36 10: 6 20: 6 40: 6 80: 6 120: 6 160: 6 Ucare: 11	Rx: 10: 51 (9) 20: 68 (22) 40: 68 (16) 80: 58 (11) 120: 64 (14) 160: 53 (12) Ucare: 66 (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 -any history of thrombotic disease -previous disability (mRS>2)	Mortality Adverse events including TE events 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 Treatment	Multicenter NR NR	All Rx: 5 80: 2 80+3.5/h CI: 2 80+7.0/h CI: 1 UCare: 5	Rx: NR UCare: 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
Brody 2005[91]†	Retrospective comparative Treatment	1 University hospital USA 3/2002-1/2003	Rx: 12 Mean 4.8 mg SD 2.1 mg UCare 15	Rx: 71 (13) UCare: 77 (7)	Inclusion: -spontaneous warfarin-associated ICH -INR>1.3 Exclusion: NR	Mortality Adverse events including TE events Functional outcome (GCS)	ICU and hospital LOS
Hallevi 2008[92]†	Retrospective comparative Treatment	1 University hospital USA NR	All Rx: 46 40 (on warfarin): NR 80 (not on warfarin): NR UCare: 148	Rx: 60 [38-87] UCare: 58 [40-80]	Inclusion: -spontaneous ICH (could include those on warfarin) Exclusion: -GCS<5 -Recent thromboembolic event	Mortality Adverse events including TE events Functional outcome (mRS)	Change in hematoma volume

†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 2005a[23] 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 of 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^ rFVIIa	Usual care	Mean age (SD) [Range] rFVIIa	Usual care	Mortality rate rFVIIa	Usual care	Sig	Poor functional outcome on mRS* rate rFVIIa	Usual care	Sig
Mayer 2005a[23]	RCT *Treatment*	40 80 160	108 92 103	96	67 (12) 65 (12) 64 (13)	68 (12)	0.176 0.185 0.194	0.292	p=.05 p=.10 p=.11	0.546 0.495 0.544	0.688	p=.02 p=.008 p=.02
	All Patients				-	-	0.185	0.292	p=.02	0.530	0.688	p=.004
Mayer 2005b[86]	RCT *Treatment*	10 20 40 80 120 160	6 6 6 6 6 6	11	51 (9) 68 (22) 68 (16) 58 (11) 64 (14) 53 (12)	66 (14)	0 0 0.167 0 0.167 0.167	0.182	NR	0 0.333 0.667 0.5 0.5 0.667	0.455	NR
	All Patients				-	-	0.083	0.182	NR	0.444	0.455	NR
Mayer 2006[87]	RCT *Treatment*	5 20 40 80	8 8 8 8	8	72 (10) 60 (15) 64 (13) 62 (12)	67 (13)	0.25 0.25 0.375 0	0.125	NR	0.625 0.375 0.625 0.25	0.500	NR
	All Patients				-	-	0.219	0.125	NR	0.469	0.500	NR
Mayer 2008[88]	RCT *Treatment*	20 80	276 297	268	65 (14) 65 (13)	65 (14)	0.181 0.209	0.190	p=.38 p=.75	0.492 0.505	0.466	1.0 [0.6-1.6]# 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 80 120-160	426 403 115	383	-	-	0.181 0.196 0.191	0.214		0.502 0.497 0.548	0.522	
	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

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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 *Treatment*	4.8[&] (2.1)	12	15	71 (13)	77 (7)	0.42	0.13	NR	$	$	NR
Hallevi 2008[92]†	Retrospective comparative *Treatment*	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 2005[23] and Mayer NEJM 2008:[88] 108, 91, 103, and 96 in the 40, 80, 160, and usual care groups, respectively in Mayer NEJM 2005[23], and 264, 293, and 262 in the 20, 80, and usual care groups, respectively in Mayer NEJM 2008[88]

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 2008[88] 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 2008[88] 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 2005[91] 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 *Treatment*	40 80 160	108 92 103	96	67 (12) 65 (12) 64 (13)	68 (12)	0.065 0.043 0.097	0.021	NR	0.056 0.022 0.078	0	NR	0.009 0.022 0.019	0.021	NR
	All Patients						0.069	0.021	p=.12	0.053	0	p=.01	0.017	0.021	NR
Mayer 2005b[86]	RCT *Treatment*	10 20 40 80 120 160	6 6 6 6 6 6	11	51 (9) 68 (22) 68 (16) 58 (11) 64 (14) 53 (12)	66 (14)	0 0.333 0.333 0 0 0	0.091	NR	0 0.167 0.333 0 0 0	0	NR	0 0.167 0 0 0 0	0.091	NR
	All Patients						0.111	0.091	NR	0.083	0	NR	0.028	0.091	NR
Mayer 2006[87]	RCT *Treatment*	5 20 40 80	8 8 8 8	8	72 (10) 60 (15) 64 (13) 62 (12)	67 (13)	0 0.25 0.125 0	0.125	NR	0 0 0 0	0.125	NR	0 0.25 0.125 0	0	NR
	All Patients						0.094	0.125	NR	0	0.125	NR	0.094	0	NR
Mayer 2008^^[88]	RCT *Treatment*	20 80	265 293	263	65 (14) 65 (13)	65 (14)	0.098 0.126	0.087	NR	0.057 0.092	0.046	NR p=.04	0.042 0.034	0.042	NR NR
	All Patients						0.113	0.087	NR	0.075	0.046	NR	0.038	0.042	NR
Unweighted Sum	All RCTs	5-40 80 120-160	415 399 115	378			0.096 0.103 0.087	0.071		0.058 0.072 0.070	0.034		0.039 0.030 0.017	0.037	
	All Patients						0.098	0.071		0.066	0.034		0.032	0.037	
Ilyas 2008[89]	Retrospective comparative *Treatment*	[10-100]	24	30	76.5 (11)	76.4 (12.4)	0.04	0	NR	0.04	0	NR	0	0	NR

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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 *Treatment*	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 *Treatment*	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 *Treatment*	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 2008[88] 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 *Treatment*	40 80 160	108 92 103	96	67 (12) 65 (12) 64 (13)	68 (12)	16 [4-28]* 14 [2-27]* 11 [0-23]*	29 [16-44]*	p=.07 p=.05 p=.02^ All Pts: p=.01^	5.4 [1.7-9.0]* 4.2 [0.3-8.0]* 2.9 [-0.8-6.6]*	8.7 [4.9-12.4]*	p=.13 p=.14 p=.008^ All Pts: p=.01^
Mayer 2005b[86]	RCT *Treatment*	10 20 40 80 120 160	6 6 6 6 6 6	11	51 (9) 68 (22) 68 (16) 58 (11) 64 (14) 53 (12)	66 (14)	"same"	"same"	Not significant	NR	NR	NR
Mayer 2006[87]	RCT *Treatment*	5 20 40 80	8 8 8 8	8	72 (10) 60 (15) 64 (13) 62 (12)	67 (13)	64 (106) 79 (172) 37 (51) 4 (9)	11 (18)	Not significant	13 (19) 10 (21) 1 (2) 1 (2)	2 (4)	Not significant
Mayer 2008[88]	RCT *Treatment*	20 80	276 297	268	65 (14) 65 (13)	65 (14)	18 [13-24] 11 [6-17]	26 [20-32]	p=.09 p=<.001	4.9 [2.9-7.0] 3.7 [1.7-5.7]	7.5 [5.4-9.6]	p=.08 p=.009
Ilyas 2008[89]	Retrospective comparative *Treatment*	[10-100]	24	30	76.5 (11)	76.4 (12.4)	NR	NR	NR	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
Brody 2005[91]†	Retrospective comparative *Treatment*	4.8& (2.1)	12	15	71 (13)	77 (7)	NR	NR	NR	NR	NR	NR
Hallevi 2008[92]†	Retrospective comparative *Treatment*	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 2005a[23];

&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)
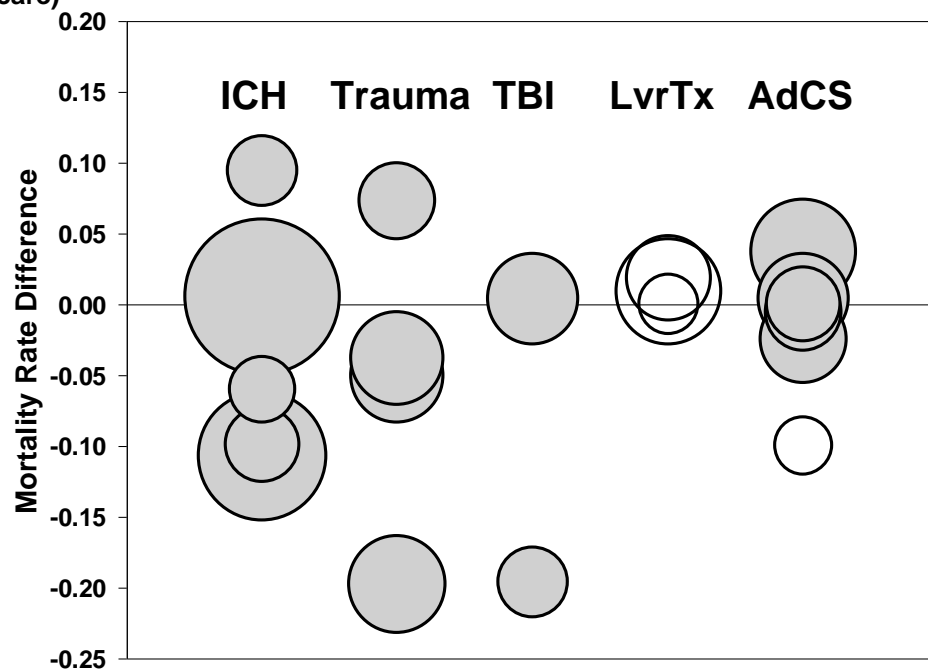
Figure 6. Mean differences in rates of thromboembolic events, by study and rFVIIa indication (rFVIIa minus usual care)
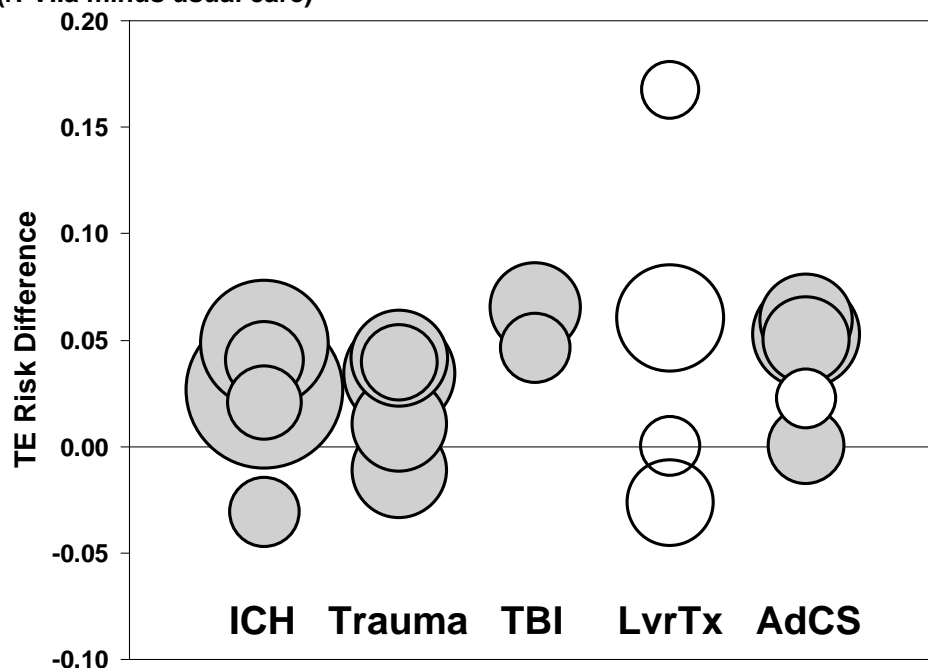
ICH=intracranial hemorrhage here—although in rest of report "ICH" indicates a subset of intracranial hemorrhage, namely intracerebral hemorrhage; Trauma=body trauma; TBI=brain trauma (traumatic brain injury); LvrTx=liver transplantation; AdCS=adult cardiac surgery
The figures show mean differences in 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)

Mayer 2005a

Mayer 2005b

Mayer 2006

Mayer 2008

Random effects model

Risk difference summary effect size
-0.031 (95%CI: -0.086 to 0.024)
P value for Q statistic: 0.248; I^2=22.73

-0.4   -0.2   0.0   0.2   0.4
Risk Difference

Favors rFVIIa   **Favors usual care**

Figure 8. Mortality in ICH (medium rFVIIa dose)

Mayer 2005a

Mayer 2005b

Mayer 2006

Mayer 2008

Random effects model

Risk difference summary effect size
-0.02 (95%CI: -0.076 to 0.036)
P value for Q statistic: 0.248; I^2=22.73

-0.5   -0.4   -0.3   -0.2   -0.1   0.0   0.1
Risk Difference

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

Figure 9. Mortality in ICH (high rFVIIa dose)

Mayer 2005a

Mayer 2005b

Random effects model

Risk difference summary effect size
-0.027 (95%CI: -0.121 to 0.068)
P value for Q statistic: 0.248; I^2=22.73

-0.3   -0.2   -0.1   0.0   0.1   0.2   0.3
Risk Difference
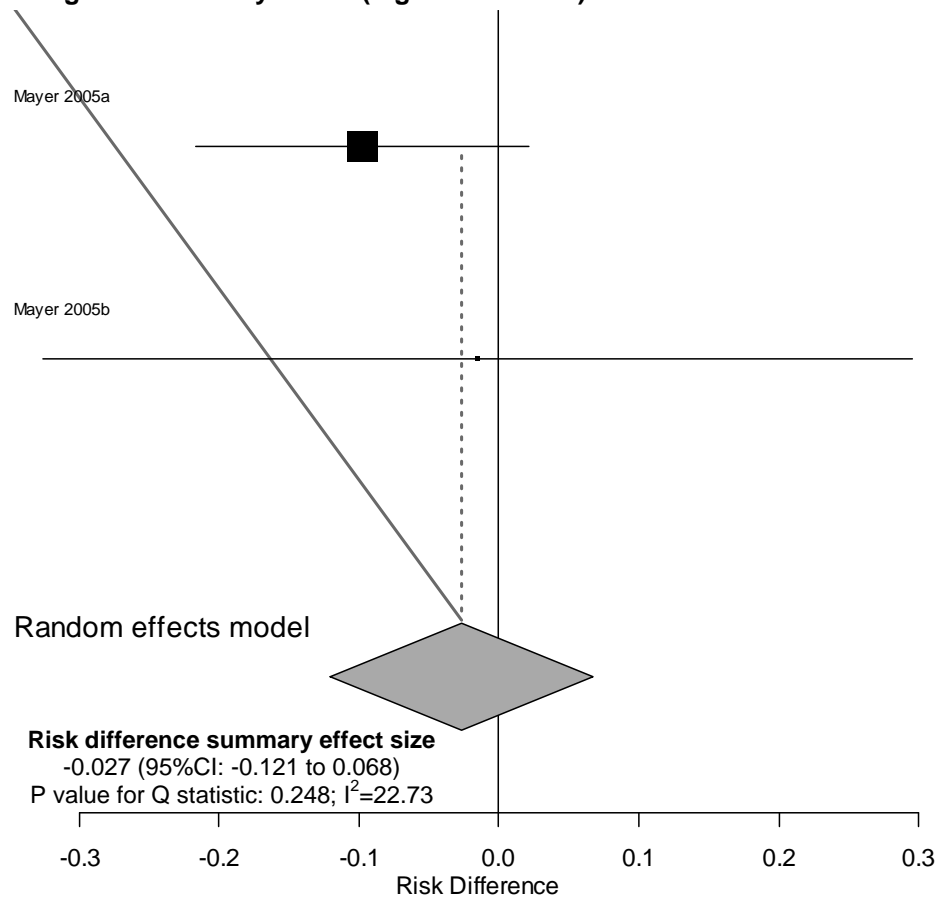
Favors rFVIIa   **Favors usual care**

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)

Mayer 2005a

Mayer 2005b

Mayer 2006

Mayer 2008

Random effects model

Risk difference summary effect size
-0.024 (95%CI: -0.092 to 0.045)
P value for Q statistic: 0.088; I^2=43.53

-0.4   -0.2   0.0   0.2   0.4
Risk Difference
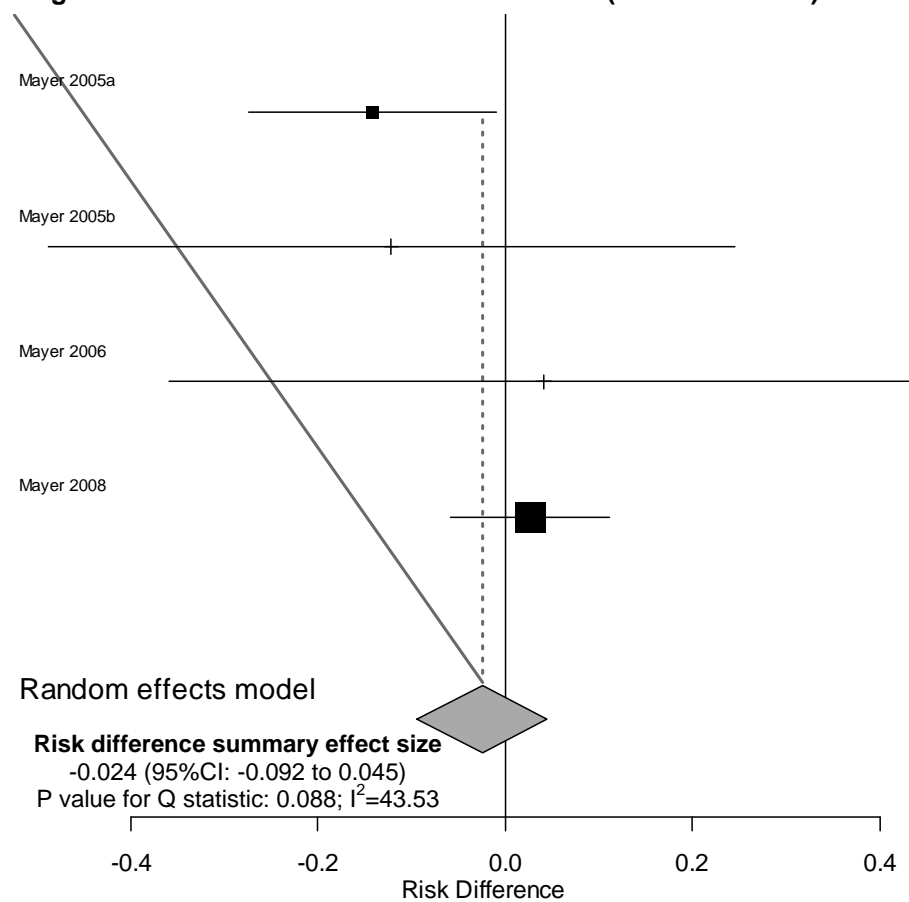
Favors rFVIIa   **Favors usual care**

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

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

Mayer 2005a

Mayer 2005b

Mayer 2006

Mayer 2008

Random effects model

Risk difference summary effect size
-0.029 (95%CI: -0.099 to 0.041)
P value for Q statistic: 0.088; I^2=43.53

-0.6   -0.4   -0.2   0.0   0.2   0.4
Risk Difference

Favors rFVIIa   **Favors usual care**
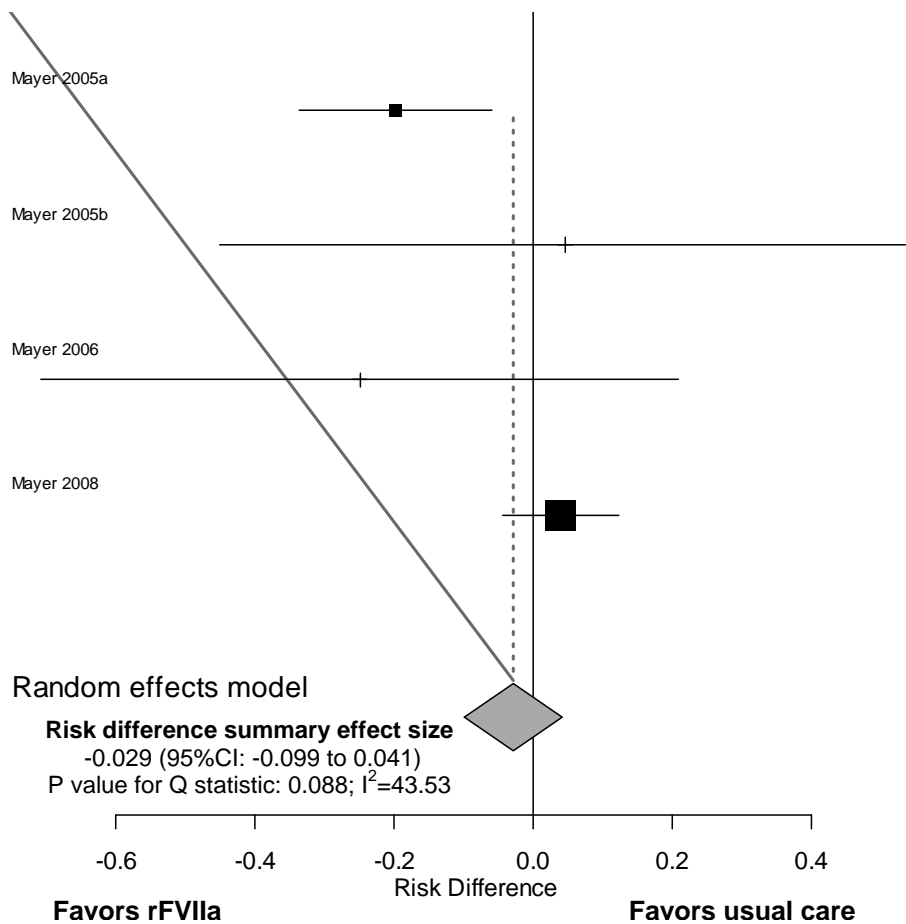
Figure 12. Poor modified Rankin score in ICH (high rFVIIa dose)

Mayer 2005a

Mayer 2005b

Random effects model

Risk difference summary effect size
-0.04 (95%CI: -0.154 to 0.075)
P value for Q statistic: 0.088; I^2=43.53

-0.2   0.0   0.2   0.4
Risk Difference

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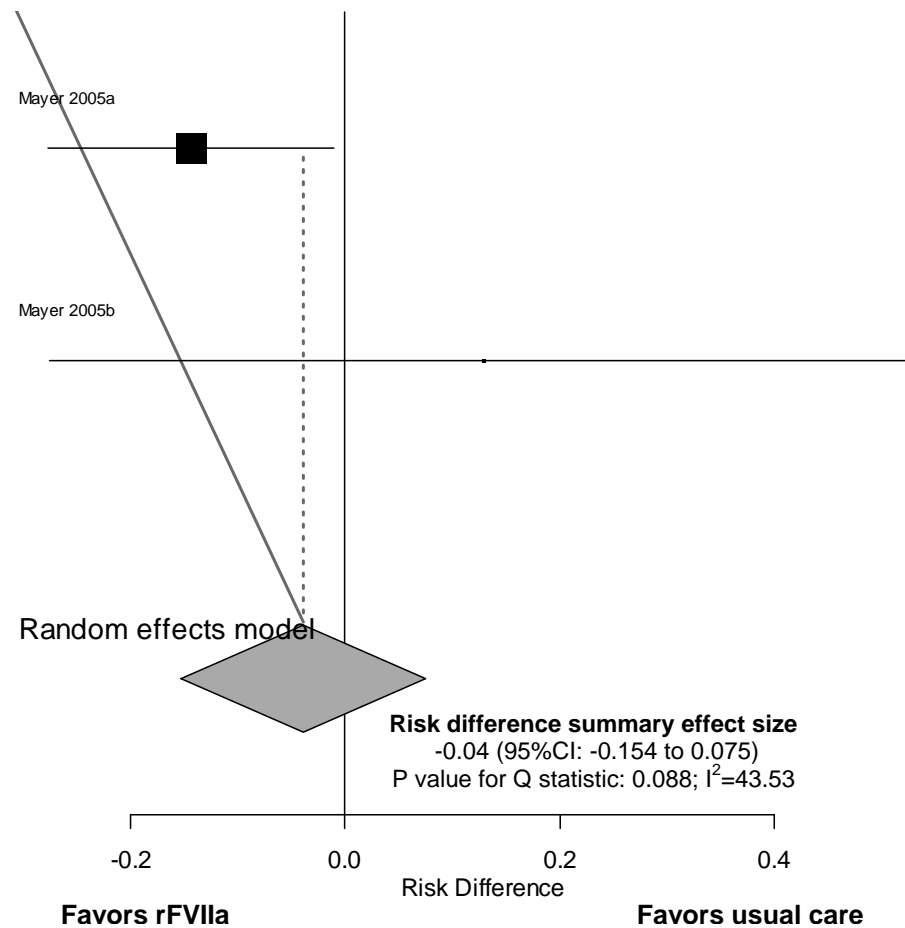
Article	mRS/total patients (medium dose)		mRS/total patients (high dose)	
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	45/91	66/96	56/103	66/96
Mayer 2005b	3/6	5/11	7/12	5/11
Mayer 2006	2/8	4/8	NA	NA
Mayer 2008	148/293	122/262	NA	NA

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Figure 13. Arterial TE events in ICH (low rFVIIa dose)
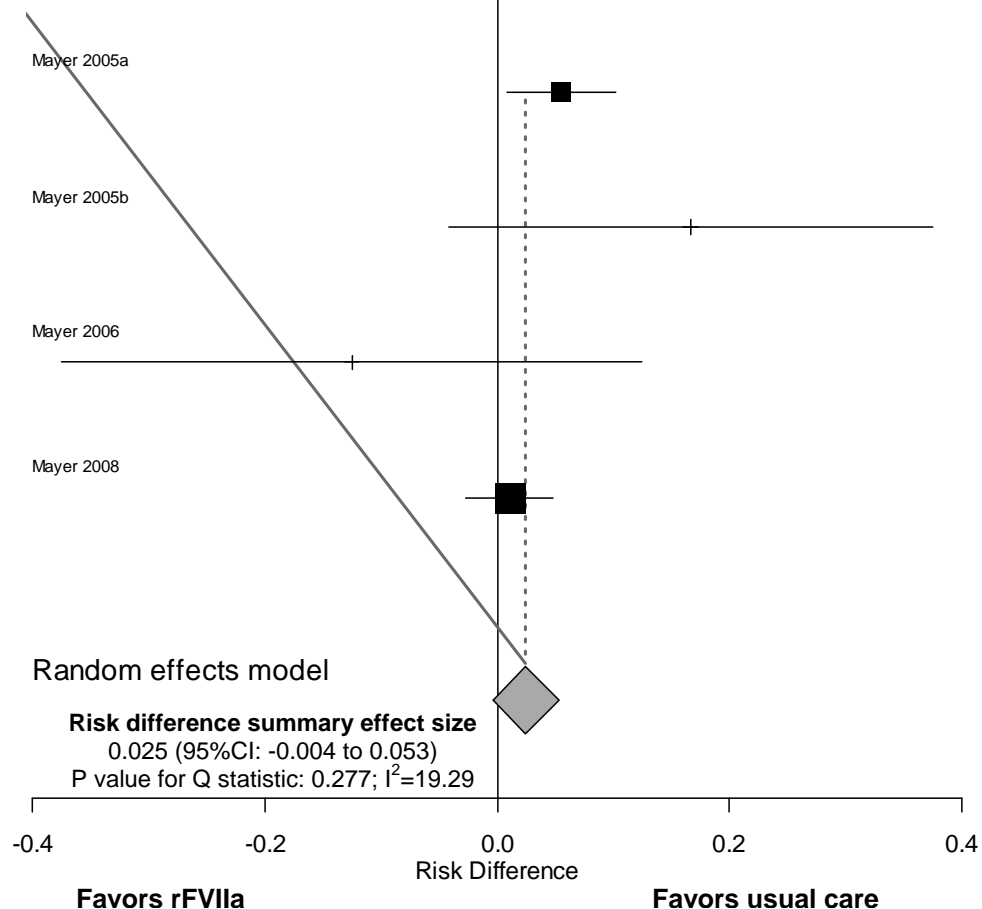
Figure 14. Arterial TE events in ICH (medium rFVIIa dose)

Mayer 2005a

Mayer 2005b

Mayer 2006

Mayer 2008

Random effects model

Risk difference summary effect size
0.025 (95%CI: -0.004 to 0.053)
P value for Q statistic: 0.277; I^2=19.29

-0.4   -0.2   0.0   0.2   0.4
Risk Difference

Favors rFVIIa

Favors usual care

Random effects model

Risk difference summary effect size
0.035 (95%CI: 0.008 to 0.062)
P value for Q statistic: 0.277; I^2=19.29

-0.4   -0.3   -0.2   -0.1   0.0   0.1   0.2
Risk Difference
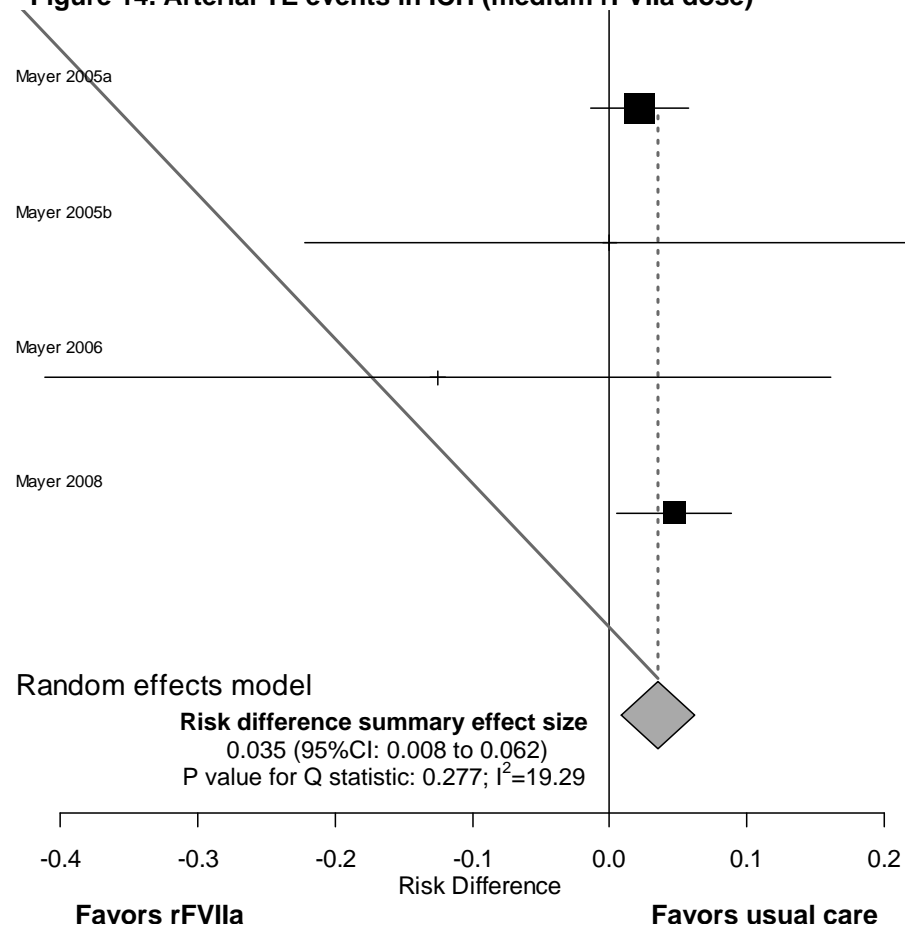
Favors rFVIIa

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

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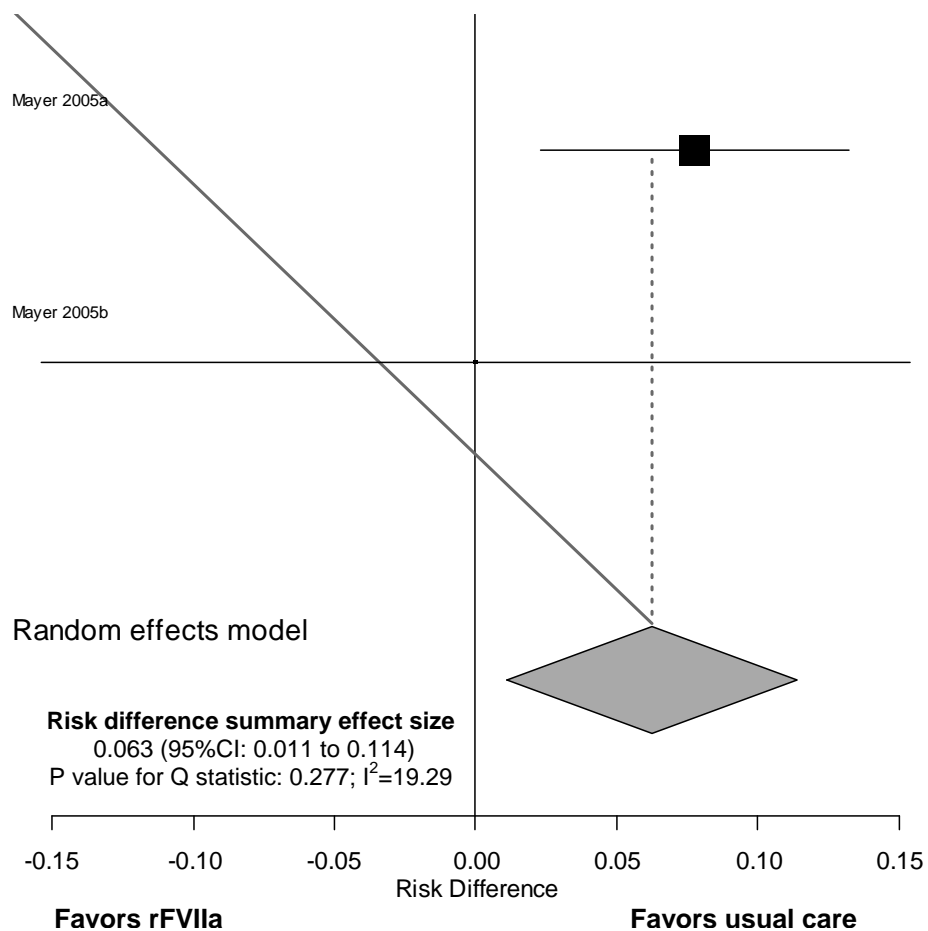
Figure 16. Relative change in hematoma volume for ICH (low rFVIIa dose)

Mayer 2005a

Mayer 2005b

Random effects model

Risk difference summary effect size
0.063 (95%CI: 0.011 to 0.114)
P value for Q statistic: 0.277; I^2=19.29

-0.15   -0.10   -0.05   0.00   0.05   0.10   0.15
Risk Difference

Favors rFVIIa   **Favors usual care**

Mayer 2005a

Mayer 2006

Mayer 2008

Random effects model

Standardized mean difference
-0.157 (95%CI: -0.302 to -0.012)
P value for Q statistic: 0.653; I^2=0

-0.5   0.0   0.5   1.0
Standardized Mean Difference (SMD)

Favors rFVIIa   **Favors usual care**

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

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

Figure17. Relative change in hematoma volume for ICH (medium rFVIIa dose)
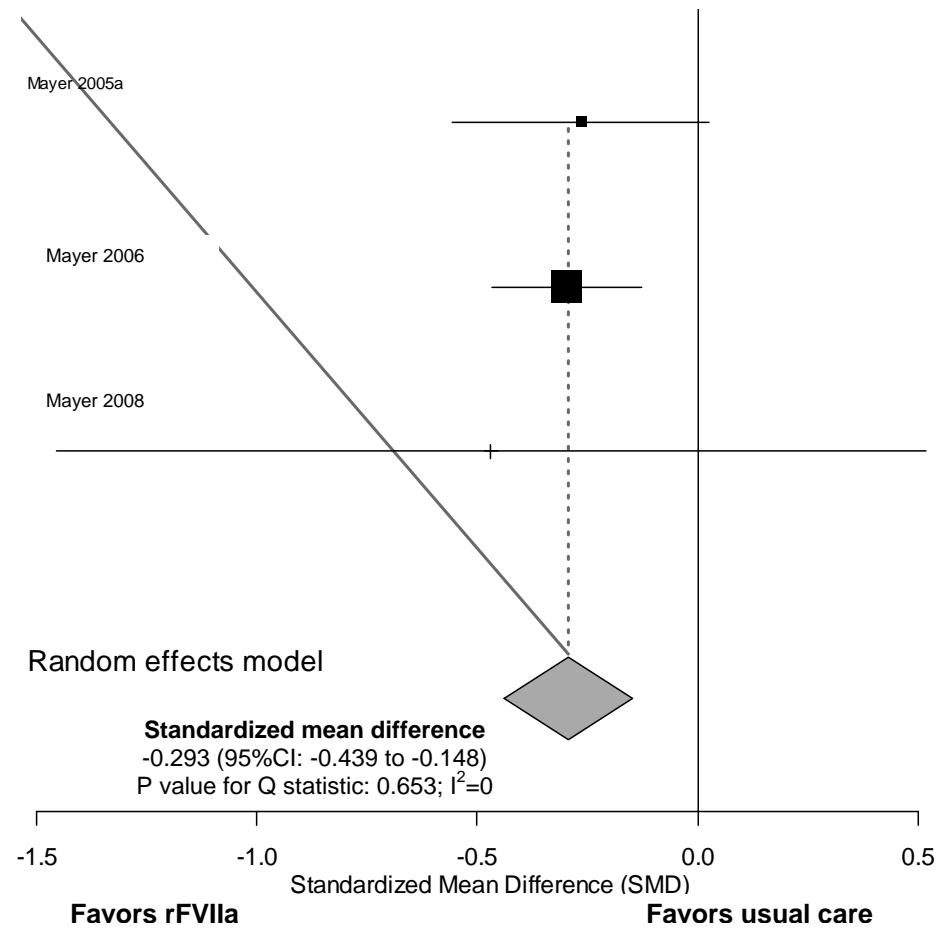
Figure 18. Relative change in hematoma volume for ICH (high rFVIIa dose)

Mayer 2005a

Mayer 2006

Mayer 2008

Random effects model

Standardized mean difference
-0.293 (95%CI: -0.439 to -0.148)
P value for Q statistic: 0.653; I^2=0

-1.5 -1.0 -0.5 0.0 0.5
Standardized Mean Difference (SMD)

Favors rFVIIa   **Favors usual care**

Mayer 2005a

Random effects model

Standardized mean difference
-0.304 (95%CI: -0.549 to -0.06)
P value for Q statistic: 0.653; I^2=0

-0.6 -0.5 -0.4 -0.3 -0.2 -0.1
Standardized Mean Difference (SMD)

Favors rFVIIa   **Favors usual care**

| Article | Mean percent change in hematoma volume/total patients | | | |
| | (medium dose) | | (high dose) | |
	rFVIIa	Control	rFVIIa	Control
Mayer 2005a	14/87	29/94	11/99	29/94
Mayer 2006	4/8	11/8	NA	NA
Mayer 2008	11/285	26/254	NA	NA

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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 2005[23] and Mayer 2008,[88] and 2 patients in Hallevi 2008[92] 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 coagulopthy 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 faciliate 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 studies[97-99] 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 restrospective cohort studies 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 trials[96] and within 24 hours in one of the observational studies[98] 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 heterogeneic 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 study[98] 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 study[97] 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 Theatre 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 µ/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 RCT[178] 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 µg/kg, but the actual drug dose administered was not reported.[98] The Rizoli study[97] 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 µg/kg, which was liberalized over time to higher doses, and that repeat doses were common. The Fox study[99] described the doses of rFVIIa as "typically 90-120 µg/kg." The range of rFVIIa doses administered across studies thus appears to be potentially quite broad (from 17.1 µg/kg to 120 µg/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 Nascimento[181] 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 Dutton[100] 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 Rizoli[97] and Spinella[98] 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 administation. 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 RCT[178] 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 occcured 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 ug/kg after transfusion of eighth unit RBCs, followed by two 100 ug/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 would 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
Rizoli 2006[97a]	Retrospective comparative Treatment	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 ug/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 Treatment	Combat support hospitals in Iraq. Data from Joint Theatre Trauma Registry (JTTR) 4/2006-8/2007	All Rx: 41 Usual care: 12 Dose: "typically" 90-120	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††
Dutton 2004[100]†	Retrospective comparative Treatment	1 University hospital USA 6/2001-12/2003	All Rx: 81 Usual care: 32-449^ Dose: 100 for hemorrhagic shock; 50 for congenital or pharmacologic coagulopathy	Rx: 41 (21) Usual care: NR	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 evidenceof coagulopathy (abnormal PT and PTT) -Patient viability for meaningful longterm survivial as determined by institutional gatekeeper Exclusion: -Lack of patient viability	Mortality Adverse events including TE events	Transfusion requirements†† Hospital LOS
Harrison 2005[101]†	Retrospective comparative Treatment	1 Hospital USA 2/2003-12/2003	All Rx: 29 Usual care: 72 Dose: 60	Rx: 41 (21) Usual care: 42 (22)	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

†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.

CI95% 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 2007[182] was used instead of Spinella 2008[98] in the harms analysis of mortality and TE events. Perkins 2007 is an overlapping non-comparative study with more patients.

^ Dutton 2004[100] 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 *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	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).

& Nascimento2008[181] is an extension of Rizoli 2006[97] with more patients. It also reports data on thromboembolic events not reported in the original publication.

^ Dutton 2004[100] 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 *Treatment*	400	52	59	33 (13)	35 (13)	6.9 (6.2)[&]	10.9 (9.3)[&]	p=.02[&]
Boffard 2005[96] (penetrating arm	RCT *Treatment*	400	57	52	29 (10)	32 (10)	4.5 (5.3)[&]	7.7 (9.9)[&]	p=.10[&]
Rizoli 2006[97]	Retrospective comparative *Treatment*	NR	38	204	36.8 [30.6-43.1][CI]	41.1 [38.1-44.1][CI]	#	#	#
Spinella 2008[98]	Retrospective comparative *Treatment*	120	49	75	NR	NR	16[U] [13-27]	14[U] [11-19]	p=.02
Fox 2009[99]	Retrospective comparative *Treatment*	90-120	41	12	28 (9)	24 (10)	NR	NR	NR
Dutton 2004[100]†	Retrospective comparative *Treatment*	50; 100	81	32-449^	41(21)	NR	^	NR	NR
Harrison 2005[101]†	Retrospective comparative *Treatment*	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; [U]Median.

*The sample size for RBC transfusions is smaller in Boffard 2005[96] because patients who died within the 48-hour observation period for RBC transfusions were excluded.

^ Dutton 2004[100] 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 2005[96]. 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
Population	
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	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
Intervention	
As series of treatment doses of 200, 100 and 100 mcg/kg during treatment for trauma Transfusion protocol in place at most sites	RCT dose is relatively high compared to other studies
Comparator	
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	Other prophylactic hemostatic agents potential comparators, but not used in this setting Usual care has likely changed moderately since the studies were conducted.
Outcomes	
Primary outcomes: RBC transfusion requirements in RCTs (over 48 hours) and patient mortality Secondary outcomes: thromboembolic events, ARDS	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
Timing and intensity of follow-up	
Follow-up for duration of hospitalization, one COBS with 30-day mortality information Detailed protocol for ascertainment of MI and DVT	Longer term outcomes desirable
Setting	
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	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

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 study[189] 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 RCT[106] 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 study[107] 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 at 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
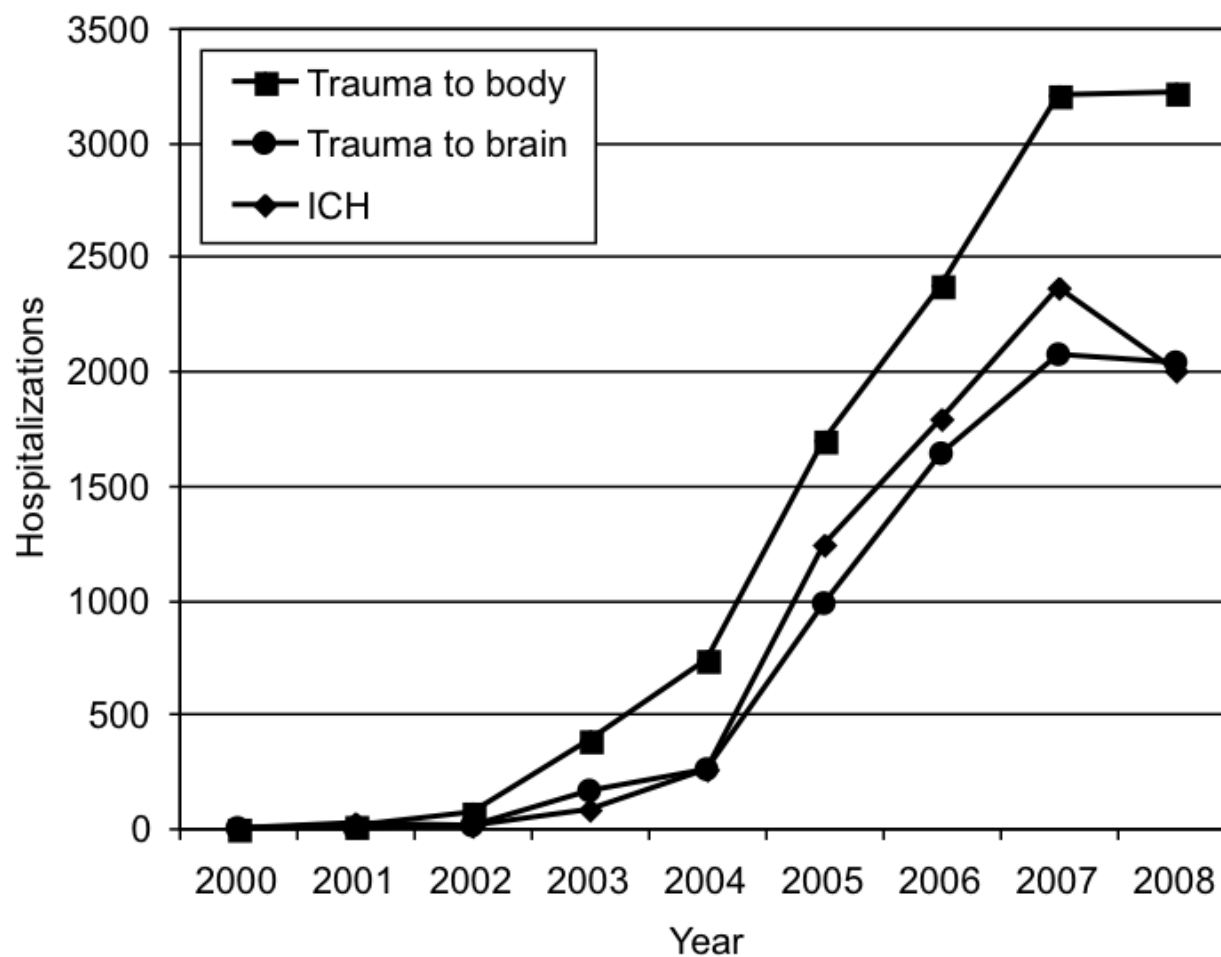
Comparison to Premier Database

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 seconday 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 8/2004-5/2006	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)
Stein 2008[107]	Retrospective comparative Treatment	1 center University of Maryland School of Medicine, Baltimore, MD, USA 7/2002-6/2006	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

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 2008[106] 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 80 120 160 200	12 11 14 12 12	36	All Rx: 51.5 (21.5)	51.4 (19.5)	0 0 0.071 0.167 0.333	0.111	NR	0.167 0.182 0.214 0 0.167	0.083	NR	11.8 (13) 5.0 (5.3) 8.9 (17.7) 3.9 (10.4) 4.9 (13)	10.4 (25)	p=.96 p=.38 p=.96 p=.27 p=.86
	All Patients		61	36	51.5 (21.5)	51.4 (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 (26.9)	44.8 (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 thombosis 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 Planinsic[111] and Lodge[110] both had authors employed by the manufacturer of rFVIIa. The RCTs by Pugliese[112] and Liu[113] reported no

financial ties to the manufacturer. The comparative observational study by Hendriks[114] 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 Pugliese[112] 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, wheres the Liu RCT[113] 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-peratively. 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 RCT[111] 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 RCT[112] 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 RCT[113] 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 study[111] a dose of 20, 40, or 80 µg/kg; in the Pugliese study[112] a dose of 40 µg/kg; and in the Liu study[113] a dose of "70-80 µg/kg."

Comparative observational study. Treated patients in the Hendriks cohort study[114] 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 RCT[113] 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 study[110] 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 study[111] 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 study[112] reported no deaths in either group. The Hendriks cohort study[114] 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 RCT[110] noted 16 percent (19 of 121) in the aggregate rFVIIa group and 10 percent (6 of 61) in the usual care group. The Planinsic RCT[111] 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 Pugliese[112] RCT stated that no thromboembolic events occurred in either group. The Liu RCT[113] only stated that no events occurred in the treatment group, without commenting on the control group. The Hendriks cohort study[114] 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 study[114] 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 Lodge[110] and Planinsic[111] 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.

<u>ICU length of stay (LOS).</u> None of the RCTs reporting on this outcome found a difference between groups in ICU LOS. The Planinsic RCT[111] 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 ug/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]	Inclusion/Exclusion Criteria	Outcomes Evaluated Direct	Outcomes Evaluated Indirect
Liu 2009[113]	RCT Prophylaxis	1 center Guangzhou, China 3/2003-7/2006	All Rx: 14 Ucare: 14 Dose: 70-80 ug/kg	Rx: 51.9 [36-54] Ucare: 47.5 [41-65]	Inclusion: -OLT	TE events	Blood loss Operating time
Hendriks 2001[114]	Prospective comparative Prophylaxis	1 center Netherlands 12/1998-9/1999	All Rx: 6 Ucare: 12 Dose: 80 ug/kg	Rx: 43^U [37-61] Ucare: 48^U [34-63]	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 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.	Adverse events including TE events	Transfusion requirements† † Operating time
De Gasperi 2005[115]†	Retrospective comparative Prophylaxis	1 center Milan, Italy 2/2003	All Rx: 6 Ucare: 6 Dose: 20 ug/kg at the start of surgery. Additional 20 ug/kg 30-40 minutes after reperfusion for significant bleeding.	Rx: 45 (4) Ucare: 47 (9)	Inclusion: -OLT	Mortality	Transfusion requirements† † Blood loss

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]	Inclusion/Exclusion Criteria	Direct	Indirect
						Population Characteristics	**Outcomes Evaluated**
Kalicinski 2005[116]†	Retrospective comparative Prophylaxis	1 center Poland Time period not reported.	All Rx: 28 Ucare: 61 Mean dose: 51.5 ug/kg; Range: 30-100 ug/kg	Rx: 13.2 (4.2) Ucare: 11.3 (5.6)	Inclusion: -OLT from cadaveric donor Exclusion: -patients receiving retransplants or transplants from living related donors	Mortality Adverse events including TE events	Transfusion requirements† † Operating time Hospital and ICU LOS
Niemann 2006[117]†	Retrospective comparative Prophylaxis	1 center University of California, San Francisco, CA, USA 2000-2004	All Rx: 11 Ucare: 11 Mean dose: 58 ug/kg, SD=18 ug/kg	Rx: 48 (15) Ucare: 41 (17)	Inclusion: -OLT in adult patients with MELD score>20 and PT>1.5-2 times normal control Exclusion: -Re-transplantation or combined transplantation -rFVIIa given within 24 hours prior to surgery or given during surgery but >30 minutes from incision	Mortality Adverse events including TE events	Transfusion requirements† † 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-inflammatary 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 *Prophylaxis*	180[#] 360[#]	63 58	62	53.3 (11.2) 52.6 (9.2)	52.3 (11.5)	0.016* 0.034*	0.016*	NR	0.190^ 0.121^	0.097^	NS
Planinsic 2005[111]	RCT *Prophylaxis*	20 40 80	18 24 22	19	49.4 (13.4) 49.7 (10.1) 51.9 (8.8)	49.9 (11)	0.056* 0.083* 0.045*	0.053*	NR	0.222 0.083 0.091	0.158	NR
Pugliese 2007[112]	RCT *Prophylaxis*	40	10	10	NR	NR	0	0	NR	0	0	NR
Liu 2009[113]	RCT *Prophylaxis*	[70-80]	14	14	51.9 [36-54]	47.5 [41-65]	NR	NR	NR	0	NR	NR
Hendriks 2001[114]	Cohort *Prophylaxis*	80	6	12	43[U] [37-61]	48[U] [34-63]	NR	NR	NR	0.167	0	NR
De Gasperi 2005[115]†	Retrospective comparative *Prophylaxis*	[20-40]	6	6	45 (4)	47 (9)	0	0	NR	NR	NR	NR
Kalicinski 2005[116]†	Retrospective comparative *Prophylaxis*	52 [30-100]	28	61	13 (4)	11 (6)	0.071	0.082	NR	0	0.098	NR
Neimann 2006[117]†	Retrospective comparative *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 2005[110] and Planinsic 2005[111] because in each study two additional deaths were not reported by trial arm.

^Lodge 2005[110] reports arterial thromboembolic events only.

[#] The majority of patients in Lodge 2005[110] received 3 doses of either 60 or 120 ug/kg rFVIIa (range: 3-6 dose).

NR=not reported; NS=not significant; [U]Median

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 *Prophylaxis*	180[#] 360[#]	62* 56*	61	53.3 (11.2) 52.6 (9.2)	52.3 (11.5)	7.0[U] [0-76.5][R] 6.3[U] [0-76.4][R]	8.2[U] [1.5-100.0][R]	NS	"same"	"same"	NS	3.5 3.0	3.0	NS
Planinsic 2005[111]	RCT *Prophylaxis*	20 40 80	18 23 22	19	49.4 (13.4) 49.7 (10.1) 51.9 (8.8)	49.9 (11.0)	10.0[U] [3.0-18.0] 13.0[U] [7.0-24.0] 10.0[U] [3.2-21.0]	11.1[U] [7.0-17.0]	NS	"same"	"same"	NS	"same"	"same"	NS
Pugliese 2007[112]	RCT *Prophylaxis*	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 *Prophylaxis*	[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 *Prophylaxis*	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 *Prophylaxis*	[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 *Prophylaxis*	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 *Prophylaxis*	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 2005[110] received 3 doses of either 60 or120 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 2009[113] 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); [R]Denotes range instead of IQR; [U]Median; 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 2005[110] and Planinsic 2005[111]) or that "The mean number of intensive care units days was comparable between studies." (Lodge 2005[110]).

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 |
| | | | | Domains Pertaining to Risk of Bias | | | Consistency | Directness | Precision | | | |
		rFVIIa	Usual Care	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 cohort[212] 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 CAGB.[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 RCT[118] examined prophylactic use, while the Gill RCT[119] 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 RCT[118] 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 RCT[119] 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 RCT[211] 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 study[121] 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 cohort[123] 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 cohort[122] 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 or RBC transfusion requirements, mortality, stroke, and ICU LOS, among others.

Intervention Characteristics

RCTs. In the Diprose RCT[118] 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 RCT[119] 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 RCT[211] 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 cohort[121] 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 cohort[123] 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 cohort[122] 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 I^2 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

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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 RCT[211] 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 RCT[211] 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 RCT[119] 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 Bowman[124] 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 study[120] 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
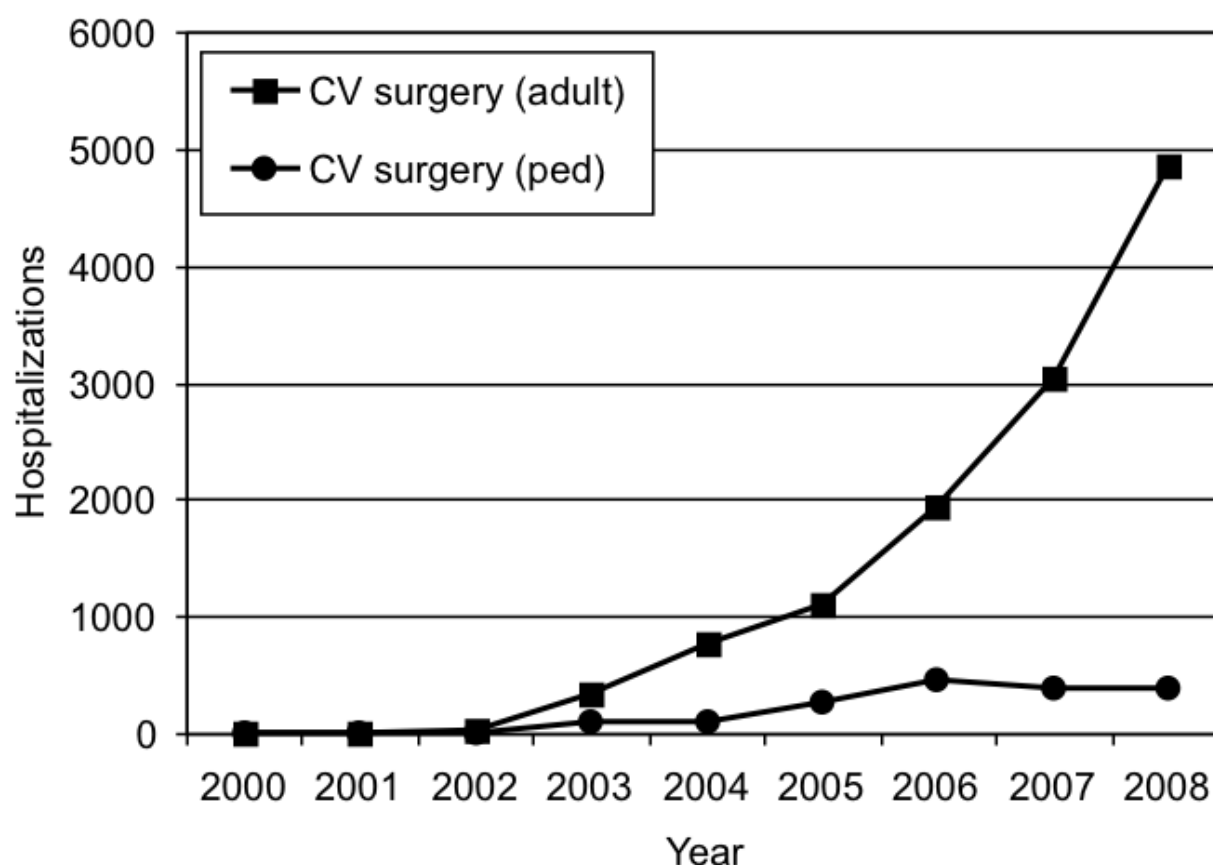
Strength of Evidence

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 Time period not reported.	All Rx: 10 Ucare: 10 Dose: 90 ug/kg	Rx: 69.5[U] [63.5-76.5][I] Ucare: 63[U] [59-66][I]	Inclusion: -scheduled to undergo complex non-coronary cardiac surgery requiring CPB. -over 18 Exclusion: -recent thrombotic disease	Mortality TE events (stroke and MI only)	Transfusion requirements†† Blood loss Hospital and ICU LOS
Gill 2009[119]	RCT Treatment	30 Centers 13 countries 8/2004-11/2007	All Rx: 104 40: 35 80: 69 Ucare: 68	Rx: 40: 68 (12) 80: 63 (16) Ucare: 62 (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 Adverse events including TE events	Transfusion requirements†† Blood loss
Karkouti 2005[120]	Retrospective comparative Treatment	1 Center Toronto, Canada 11/2002-2/2004	All Rx: 51 Ucare: 51 Mean Dose: 62 ug/kg SD: 13 ug/kg	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 Adverse events including TE events	Blood loss 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 Treatment	1 Center Study location not reported. 6/2000-3/2003	All Rx: 24 Ucare: 24 Dose: 60-80 ug/kg with possible second and third doses if blood loss continued at >100 mL/hr.	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 Adverse events including TE events	Transfusion requirements†† Blood loss ICU LOS Need for surgical re-exploration
Tritapepe 2007[122]	Retrospective comparative Treatment	1 Center Rome, Italy 1/2000-3/2006	All Rx: 23 Ucare: 23 Mean dose: 82 ug/kg	Rx: 62.4 (9.4) Ucare: 62.2 (9.1)	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 Adverse events including TE events	Transfusion requirements†† Blood loss ICU LOS
Gelsomino 2008[121]	Retrospective comparative Treatment	1 Center Florence, Italy 9/2005-6/2007	All Rx: 40 Ucare: 40 Median Dose: 18.3 ug/kg, IQR: 9-16 ug/kg	Rx: 70.1 (9.2) Ucare: 75.8 (9.8)	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 Adverse events including TE events	Transfusion requirements†† Blood loss ICU LOS Need for surgical re-exploration

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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.
U Median; I Interquartile 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 *Prophylaxis*	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 *Treatment*	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 *Treatment*	51.1	51	51	56	59	0.137	0.137	NS	0.157	0.098	NR
Gelsomino 2008[121]	Retrospective comparative *Treatment*	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 *Treatment*	89.3	24	24	63.5	63.5	0.333*	0.333*	p=1	0	0	NR
Tritapepe 2007[122]	Retrospective comparative *Treatment*	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 *Treatment*	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 *Treatment*	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 2005[118]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; [U]median
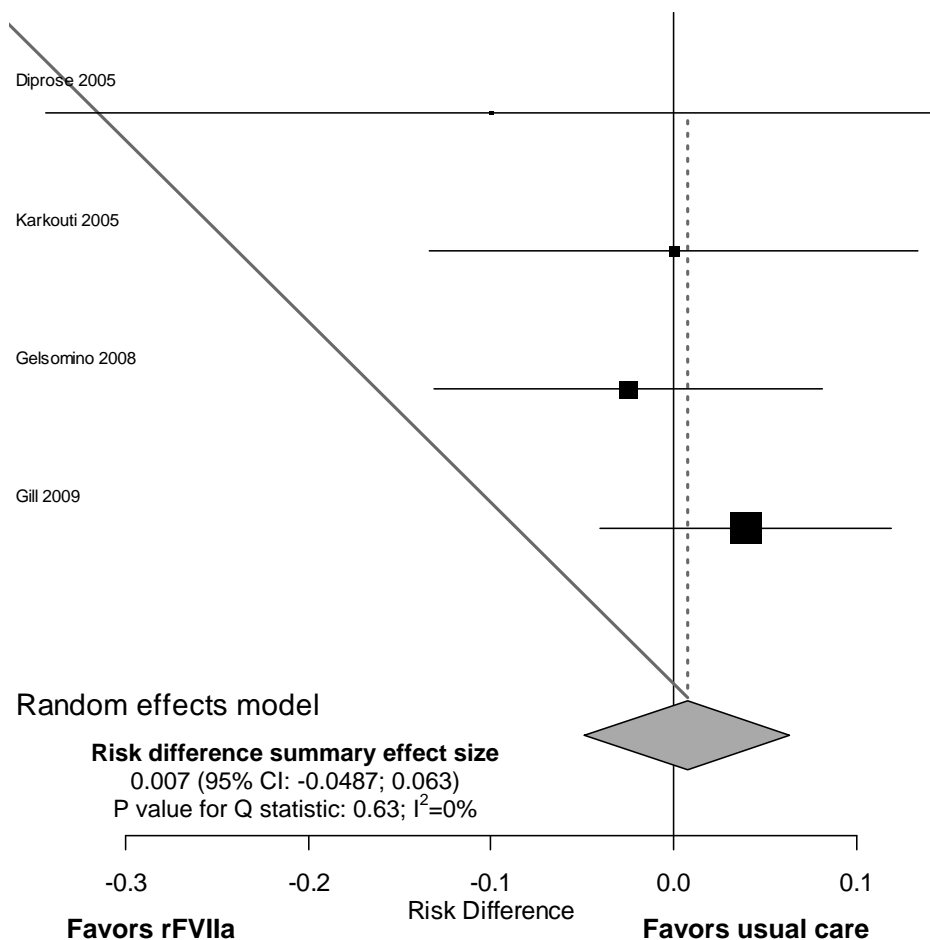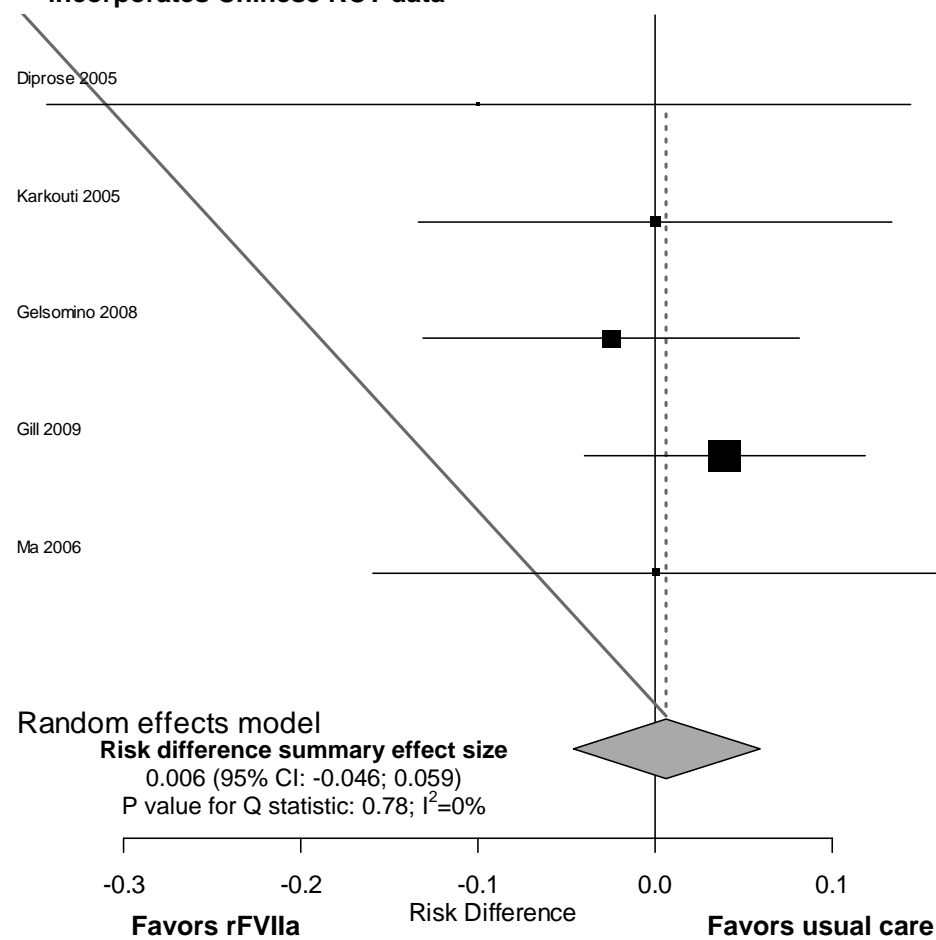
Figure 21. Mortality in adult cardiac surgery

Diprose 2005

Karkouti 2005

Gelsomino 2008

Gill 2009

Random effects model

Risk difference summary effect size
0.007 (95% CI: -0.0487; 0.063)
P value for Q statistic: 0.63; I^2=0%

-0.3   -0.2   -0.1   0.0   0.1
Risk Difference

Favors rFVIIa   **Favors usual care**

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

Diprose 2005

Karkouti 2005

Gelsomino 2008

Gill 2009

Ma 2006

Random effects model

Risk difference summary effect size
0.006 (95% CI: -0.046; 0.059)
P value for Q statistic: 0.78; I^2=0%

-0.3   -0.2   -0.1   0.0   0.1
Risk Difference

Favors rFVIIa   **Favors usual care**

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

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Figure 23. All thromboembolic events in adult cardiac surgery

Diprose 2005

Karkouti 2005

Gelsomino 2008

Gill 2009

Random effects model

Risk difference summary effect size
0.053 (95% CI: 0.01 to 0.096)
P value for Q statistic: 0.99; I^2=0%

-0.2   0.0   0.2   0.4
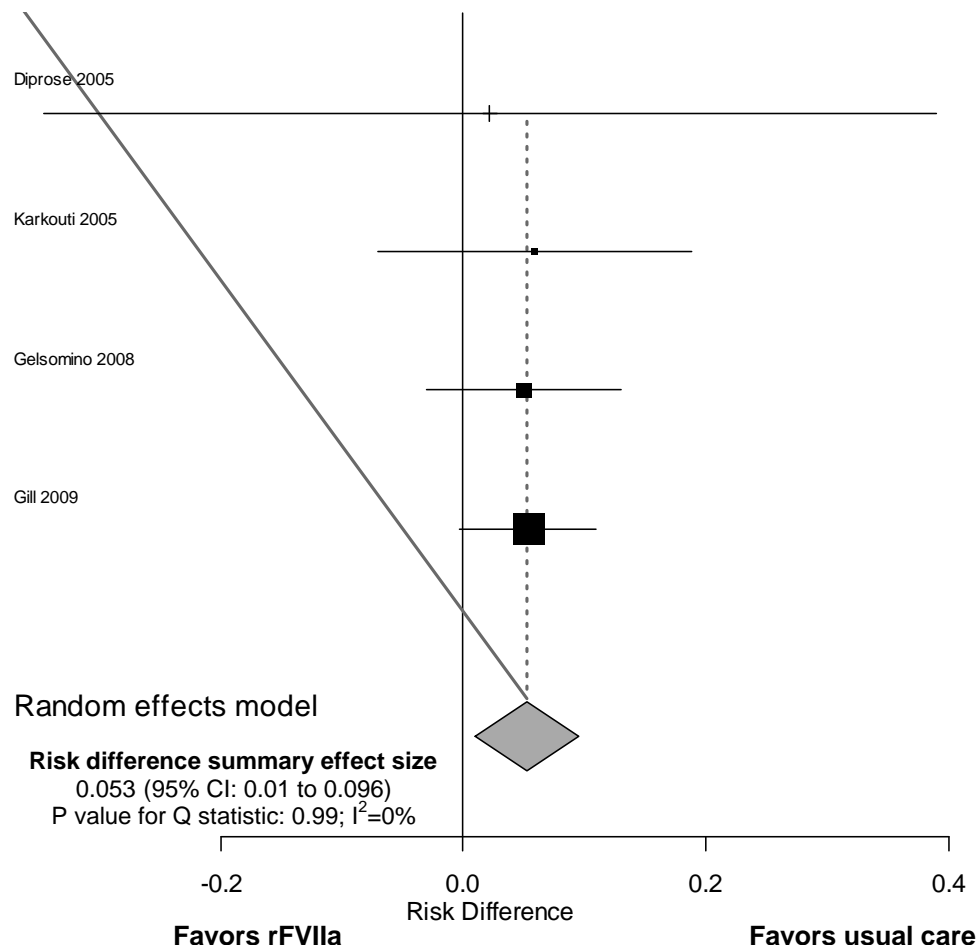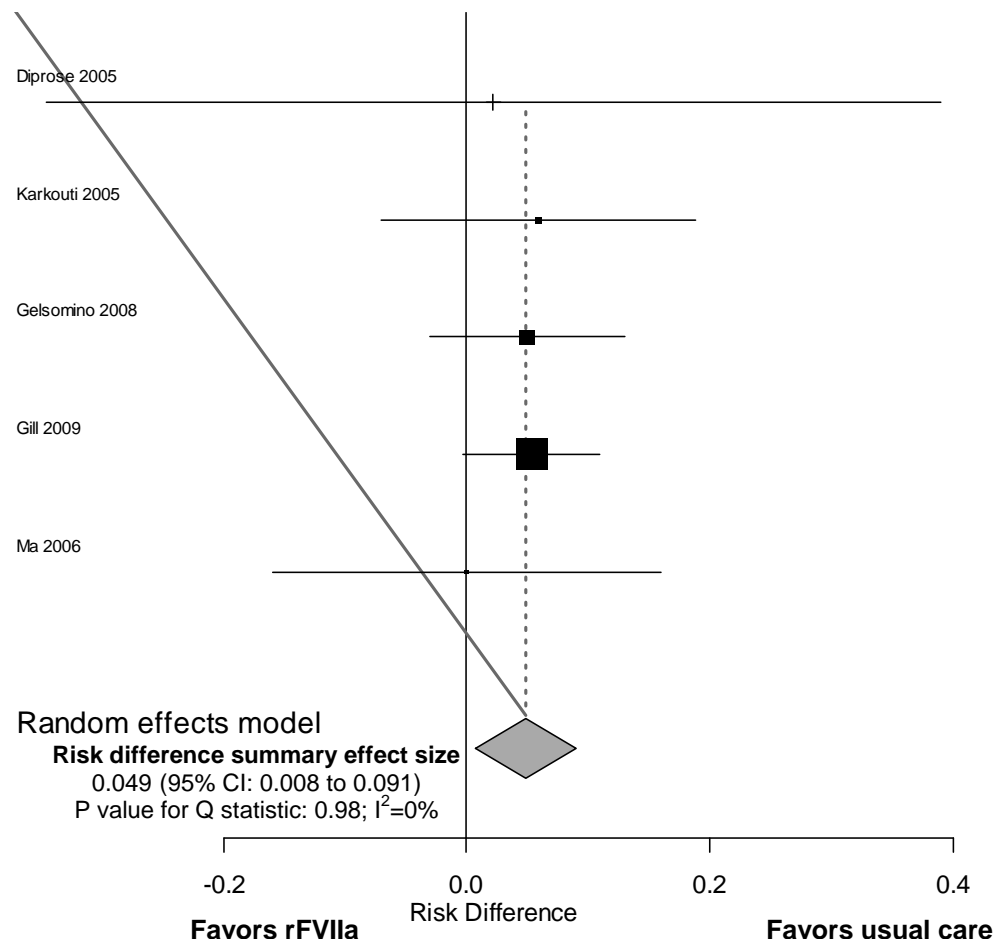Risk Difference

Favors rFVIIa   **Favors usual care**

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

Diprose 2005

Karkouti 2005

Gelsomino 2008

Gill 2009

Ma 2006

Random effects model

Risk difference summary effect size
0.049 (95% CI: 0.008 to 0.091)
P value for Q statistic: 0.98; I^2=0%

-0.2   0.0   0.2   0.4
Risk Difference

Favors rFVIIa   **Favors usual care**

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

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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 *Prophylaxis*	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 *Treatment*	40 80	35 69	68	68 (12) 63 (16)	62 (16)	^	^	^	"no diff"†	"no diff"†	NR
Karkouti 2005[120]	Retrospective comparative *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	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 *Treatment*	100	36	385	58 (15)	NR	3.1$^#$	NR	NR	NR	NR	NR
Trowbridge 2008[125]†	Prospective comparative *Treatment*	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 2005[118] 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 2005[123]

$^#$ Estimated graphically from figure 1 in Bowman 2008[124].

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

NR=not reported;　NS=not significant;

^{U}Denotes median

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

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 uniform[217] 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 Niles[140] 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 ipsalateral 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 Treatment	1 center Iowa City, IO, USA 2004-2006	All Rx: 15 Ucare: 15 Dose not reported	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	

†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

[U]Median

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 *Prophylaxis*	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 *Treatment*	90	9	8	9 years (4)	10 years (3)	NR	NR	NR	NR	NR	NR
Agarwal 2007[138]†	Retrospective comparative *Treatment*	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 *Treatment*	[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	Insufficient
Thrombo-embolic Events	1[137]	40	36	RCT	Poor	High	Unknown	Direct	Imprecise	Unknown	Unknown	Insufficient
Units of WholeBl/ RBCs Tx	1[137]	40	36	RCT	Poor	High	Unknown	Indirect	Imprecise	Weakly Favors rFVIIa	Unknown	Insufficient
Time to Chest closure	1[137]	40	36	RCT	Poor	High	Unknown	Indirect	Imprecise	Increase with rFVIIa	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 RCT[141] 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 RCT[141] 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 Time period not reported.	All Rx: 24 20: 8 40: 16 Ucare: 12	Rx: 20: 61 (8.9) 40: 64 (8.5) Ucare: 63 (8.3)	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 -know 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 Adverse events including TE events	Transfusion requirements (e.g. RBCs, FFP) Blood loss Hospital length of stay Operating time

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 *Prophylaxis*	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 *Prophylaxis*	20 40	8 16	12	61 (8.9) 64 (8.5)	63 (8.3)	0.6 (0.3) 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 study[91] 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 RCT[96] 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 registry[102] 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 study[228] 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 study[107] 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 study[111] 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 Lodge[110] was substantially higher than in the other RCTs,[111-113] and Lodge[110] 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 study[127] included only patients undergoing orthotopic heart transplant or LVAD implantation, and another[122] 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*

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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
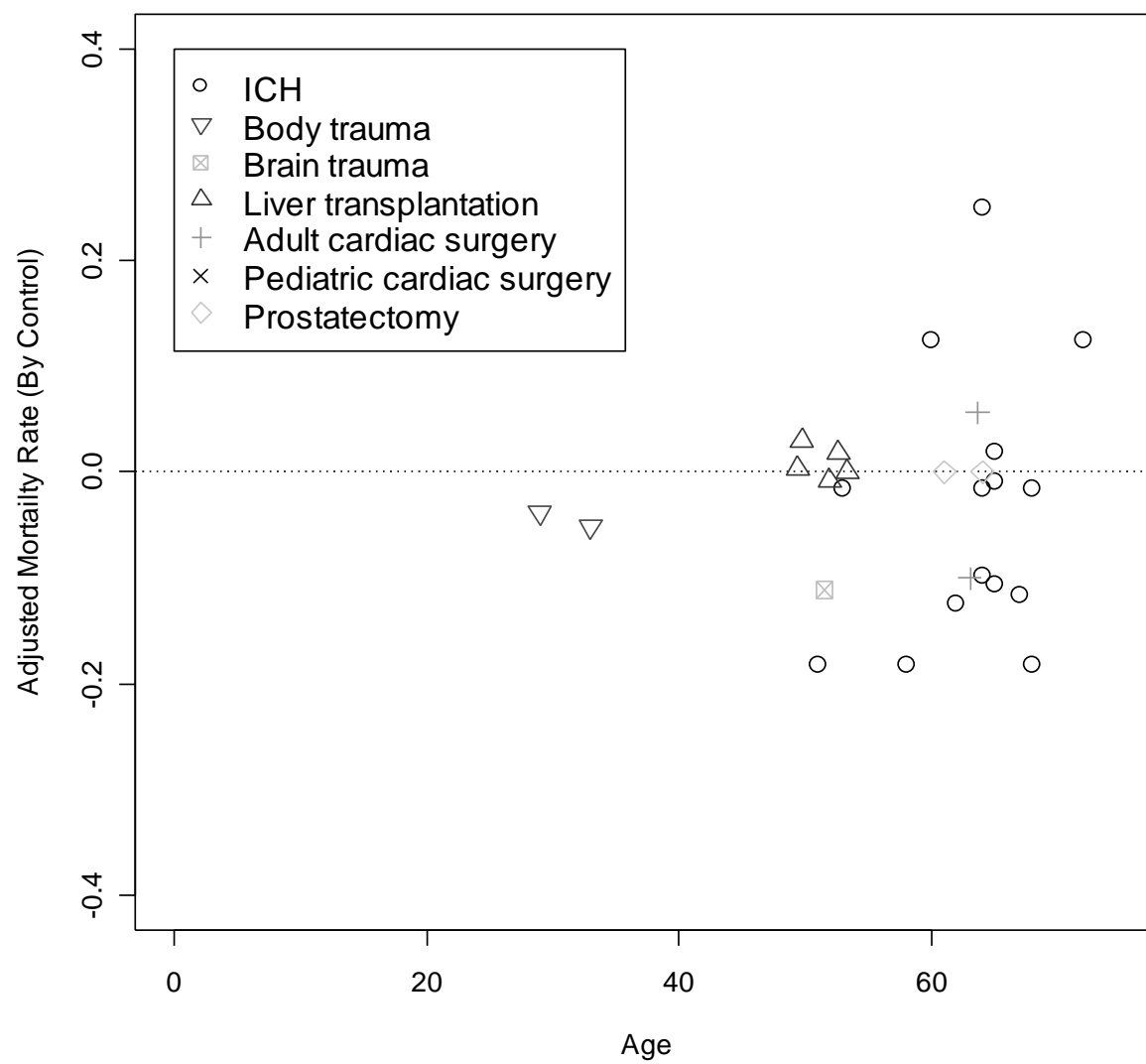
Figure 26. Adjusted all thromboembolic event rate by age from the RCTs
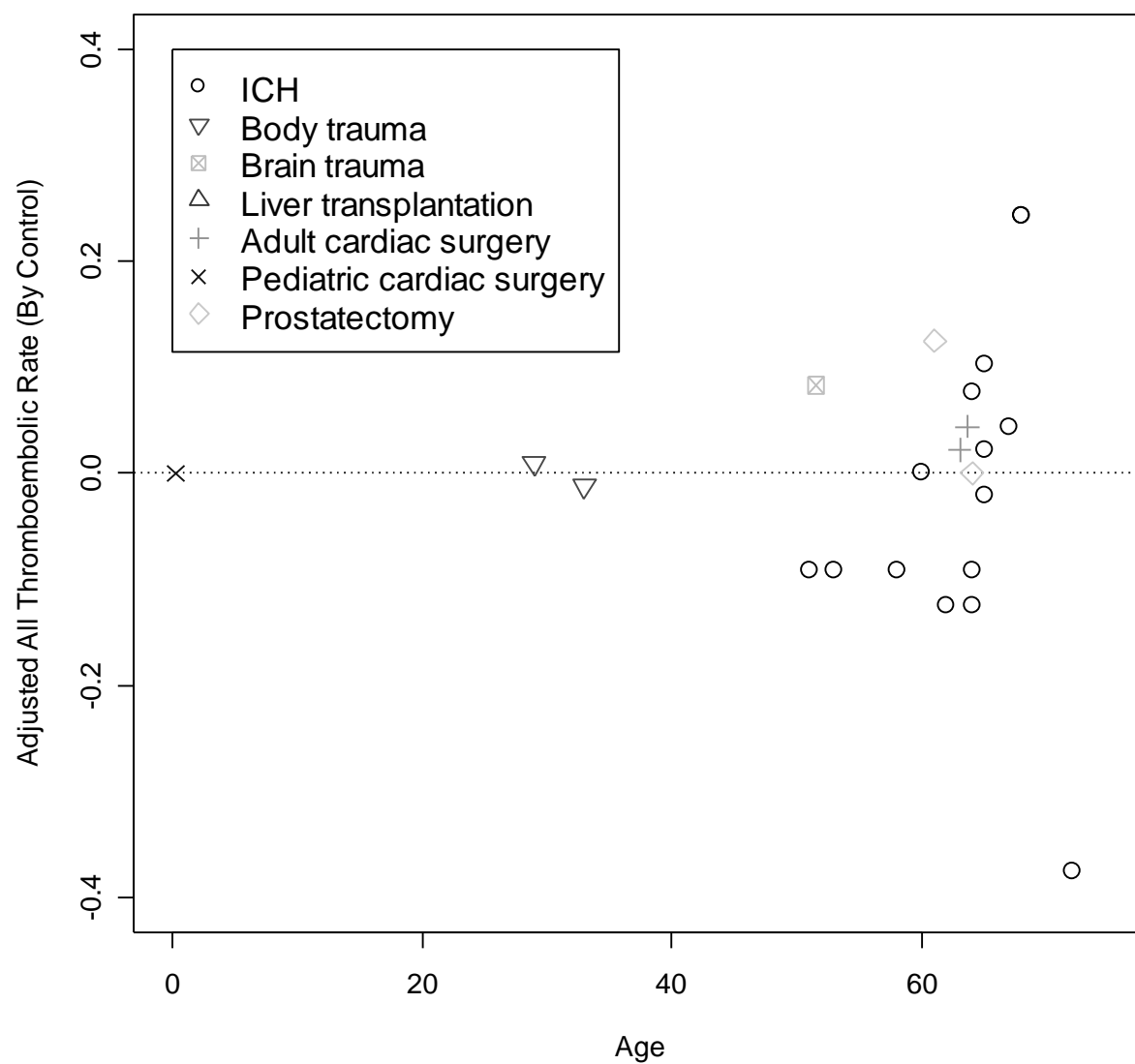
Figure 27. Weighted mean mortality (95 percent CI) by study design for each indication

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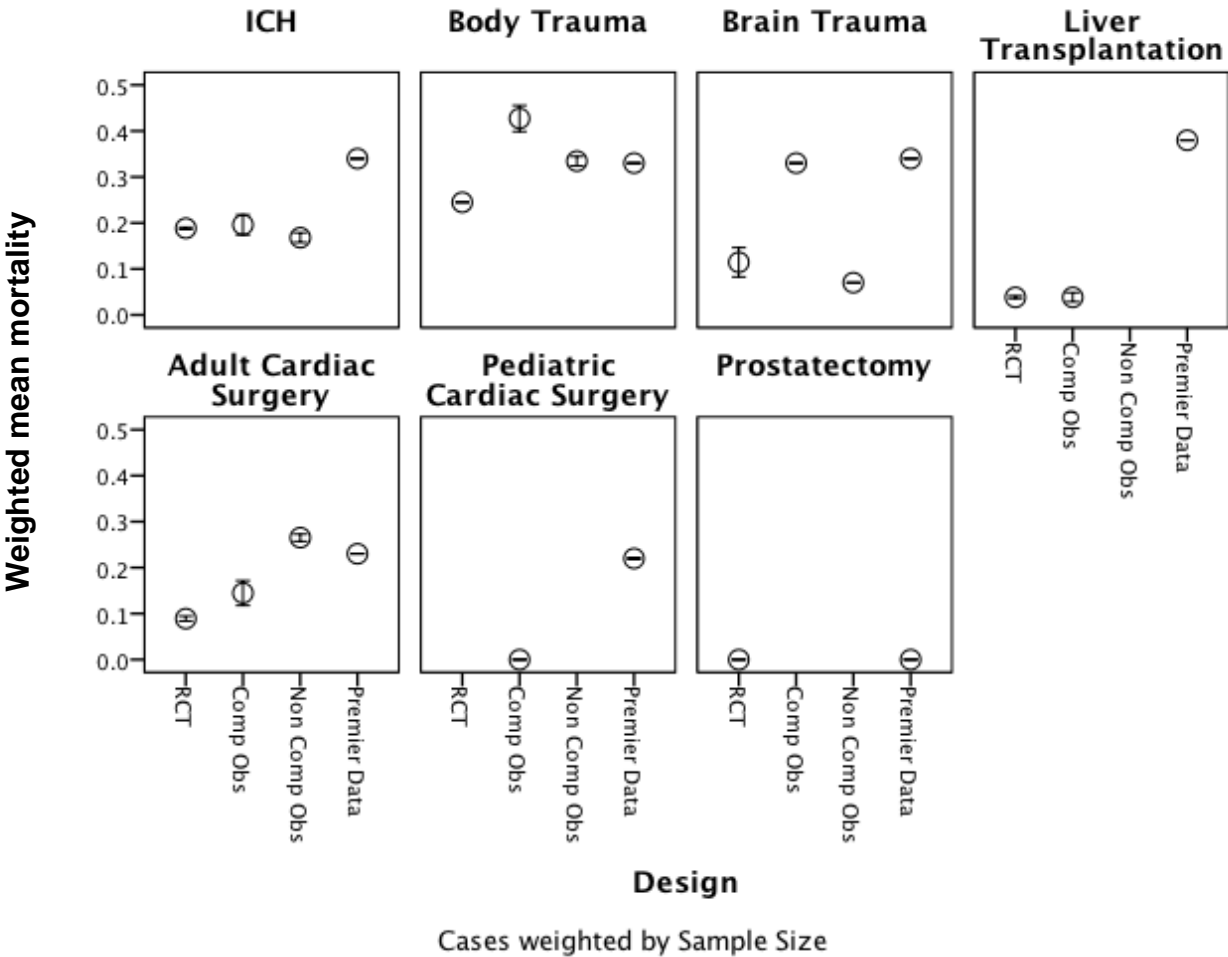
Figure 28. Weighted mean total thromboembolic event rate (95 percent CI) by study design for each indication

Design

Cases weighted by Sample Size
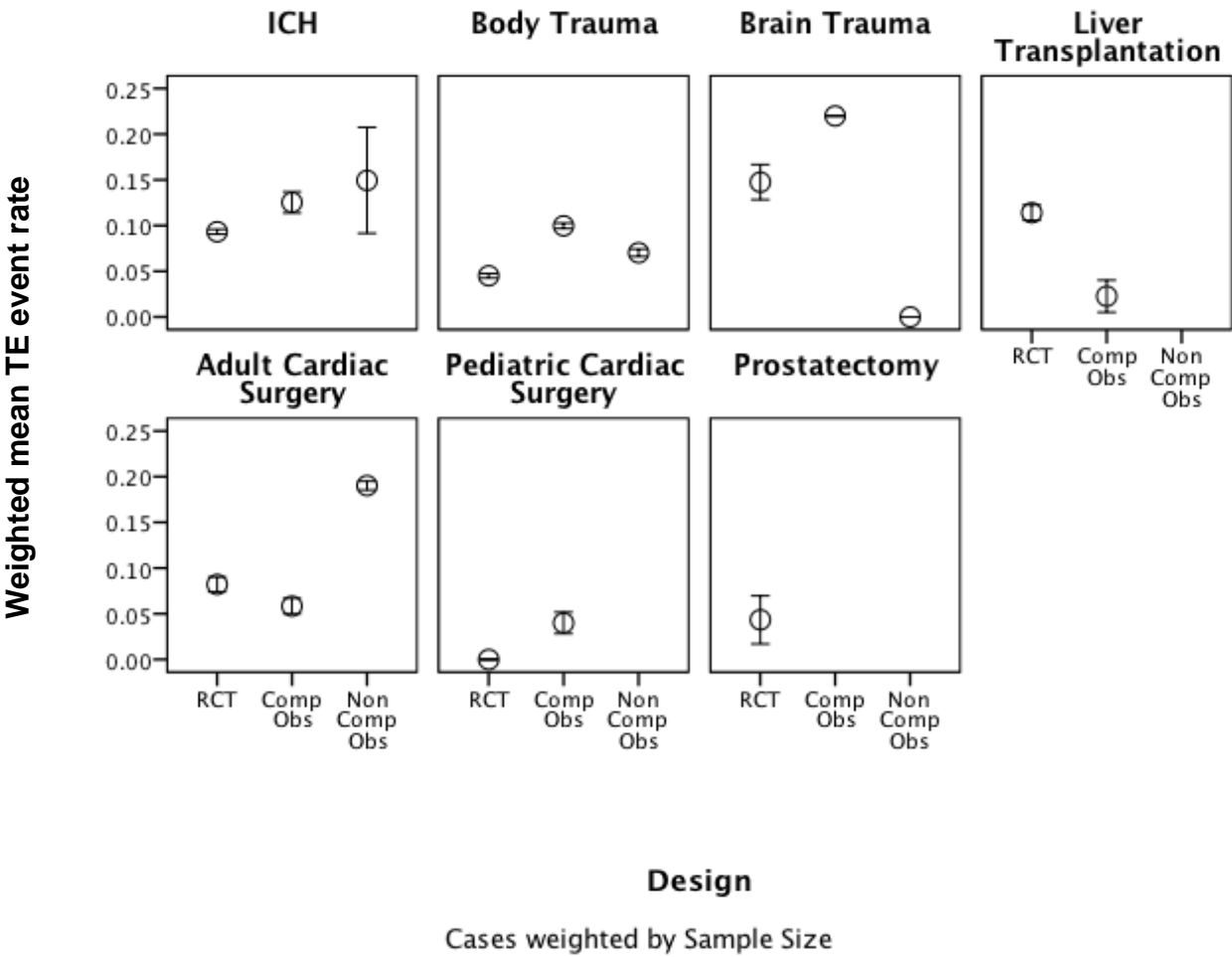
Figure 29. Mortality by mean age per indication
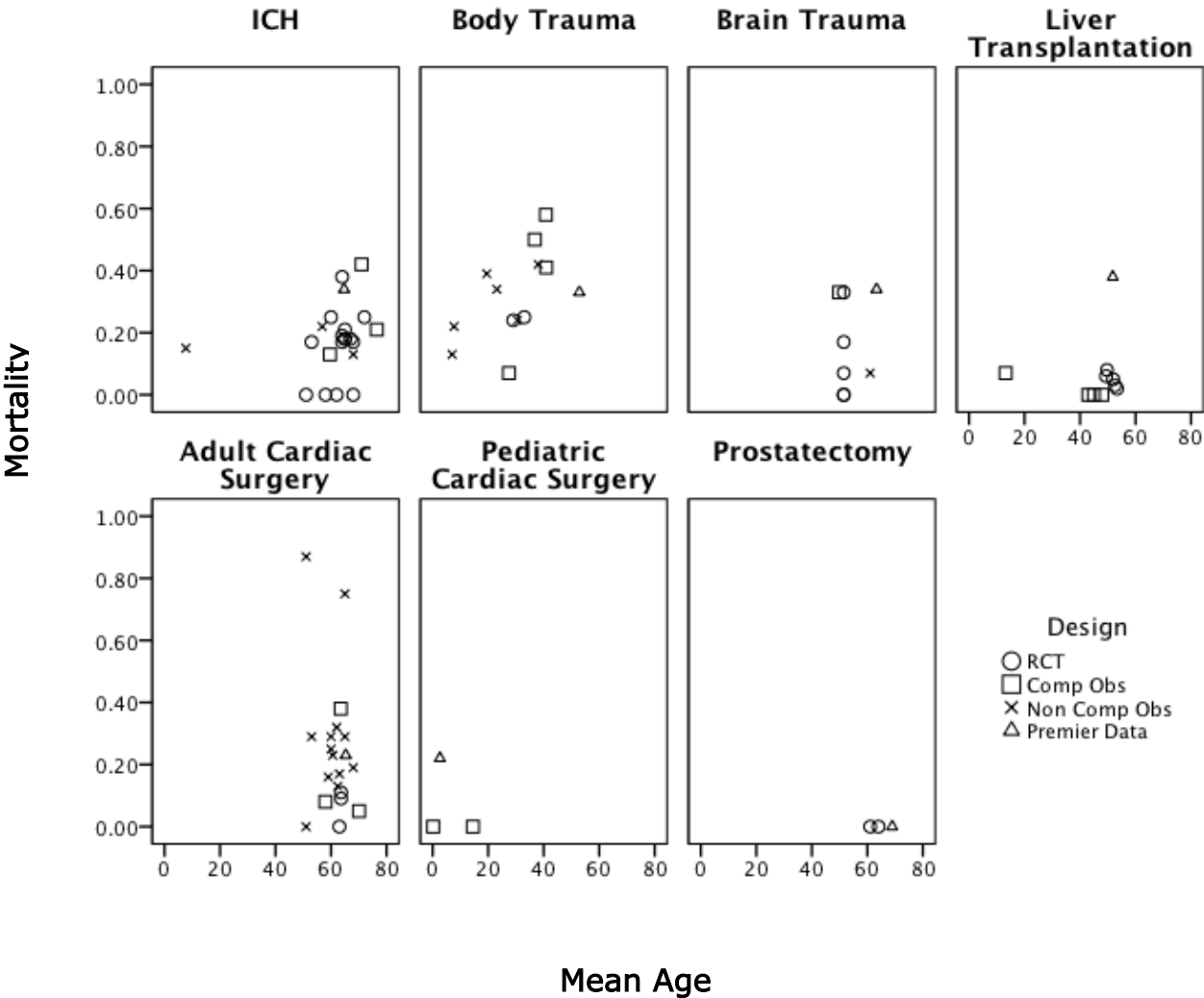
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 30. Mortality by rFVIIa dose per indication
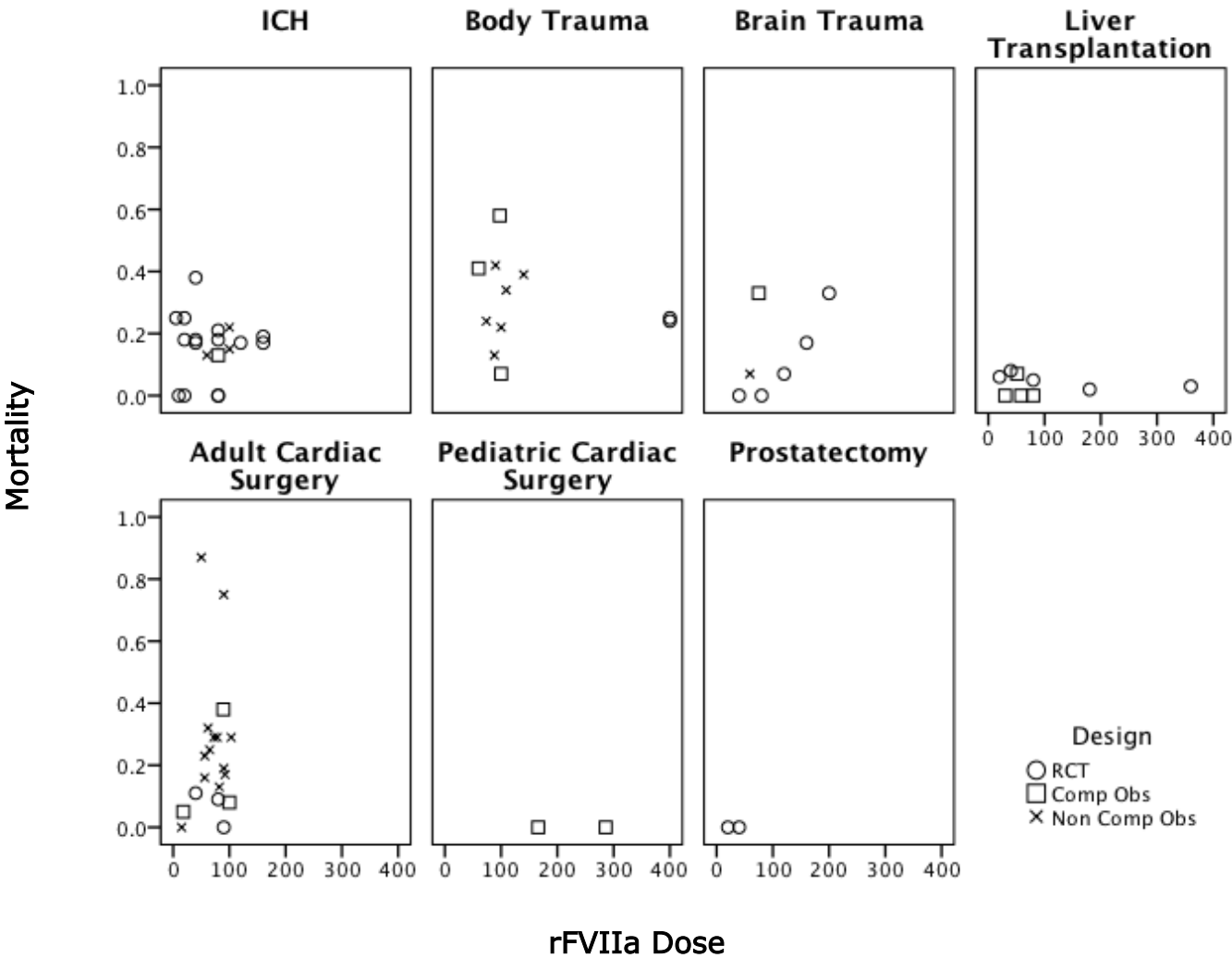
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 31. Thromboembolic events by mean age per indication
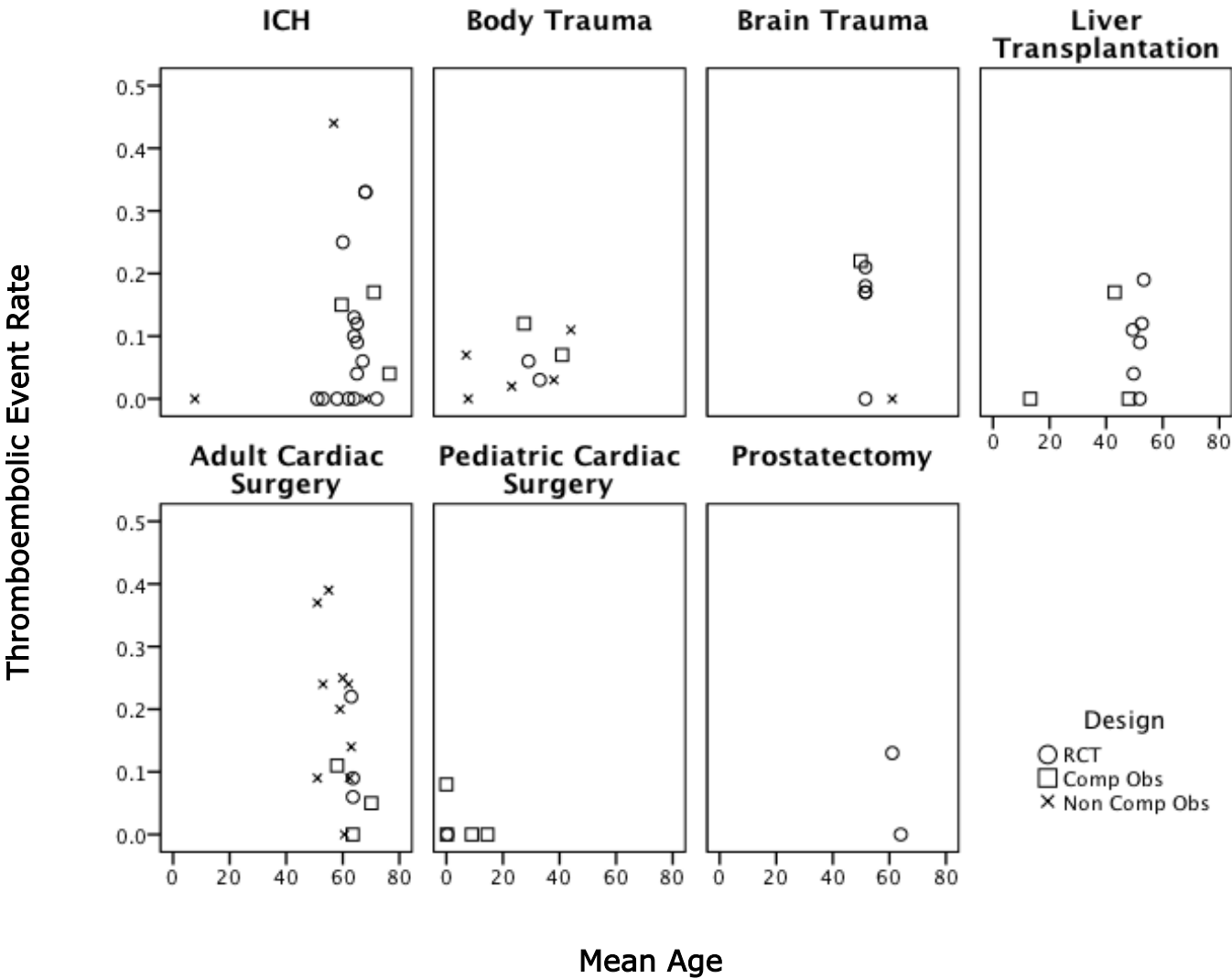
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 32. Thromboembolic events by rFVIIa dose per indication
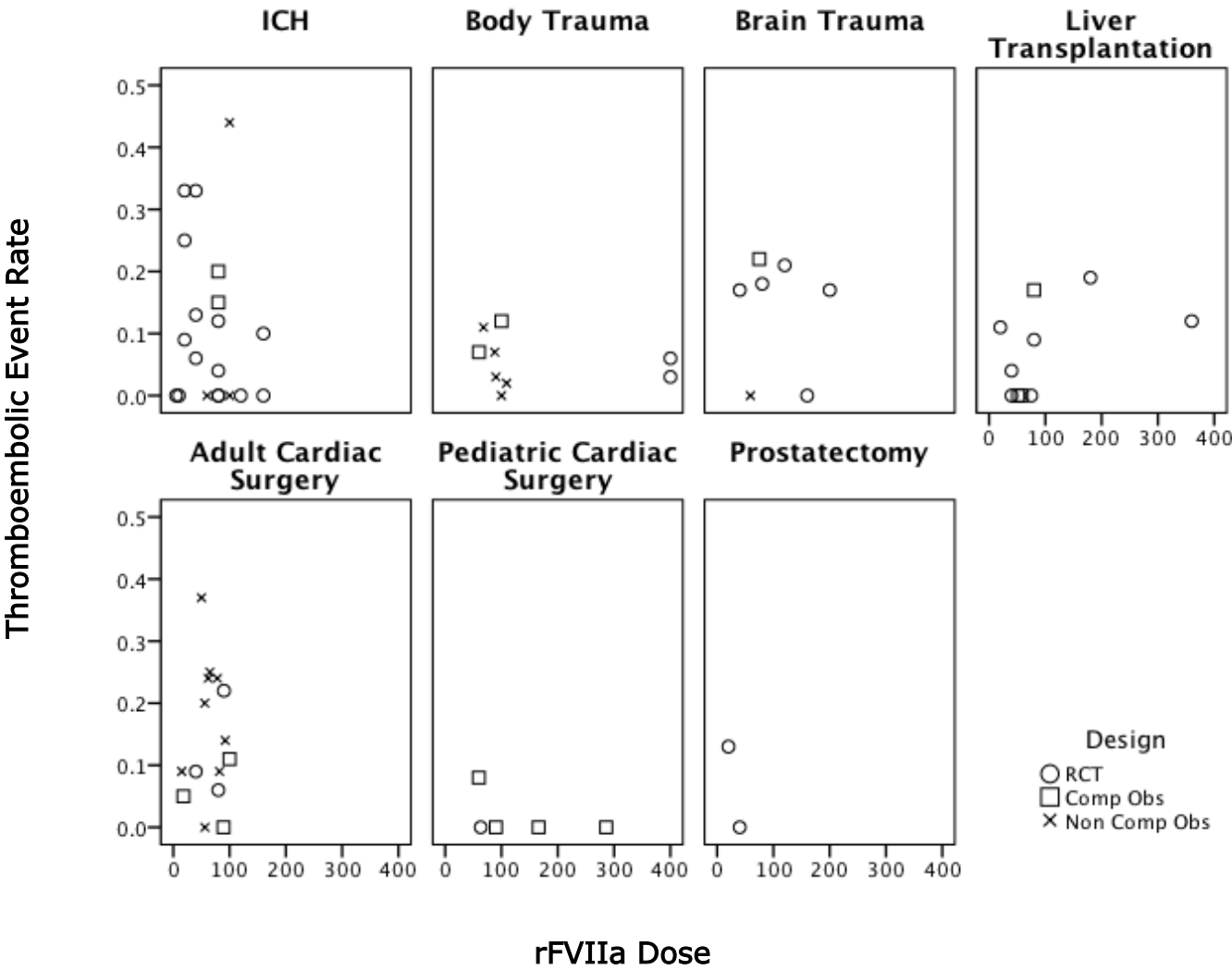
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

Figure 33. Association of mortality and thromboembolic event rate
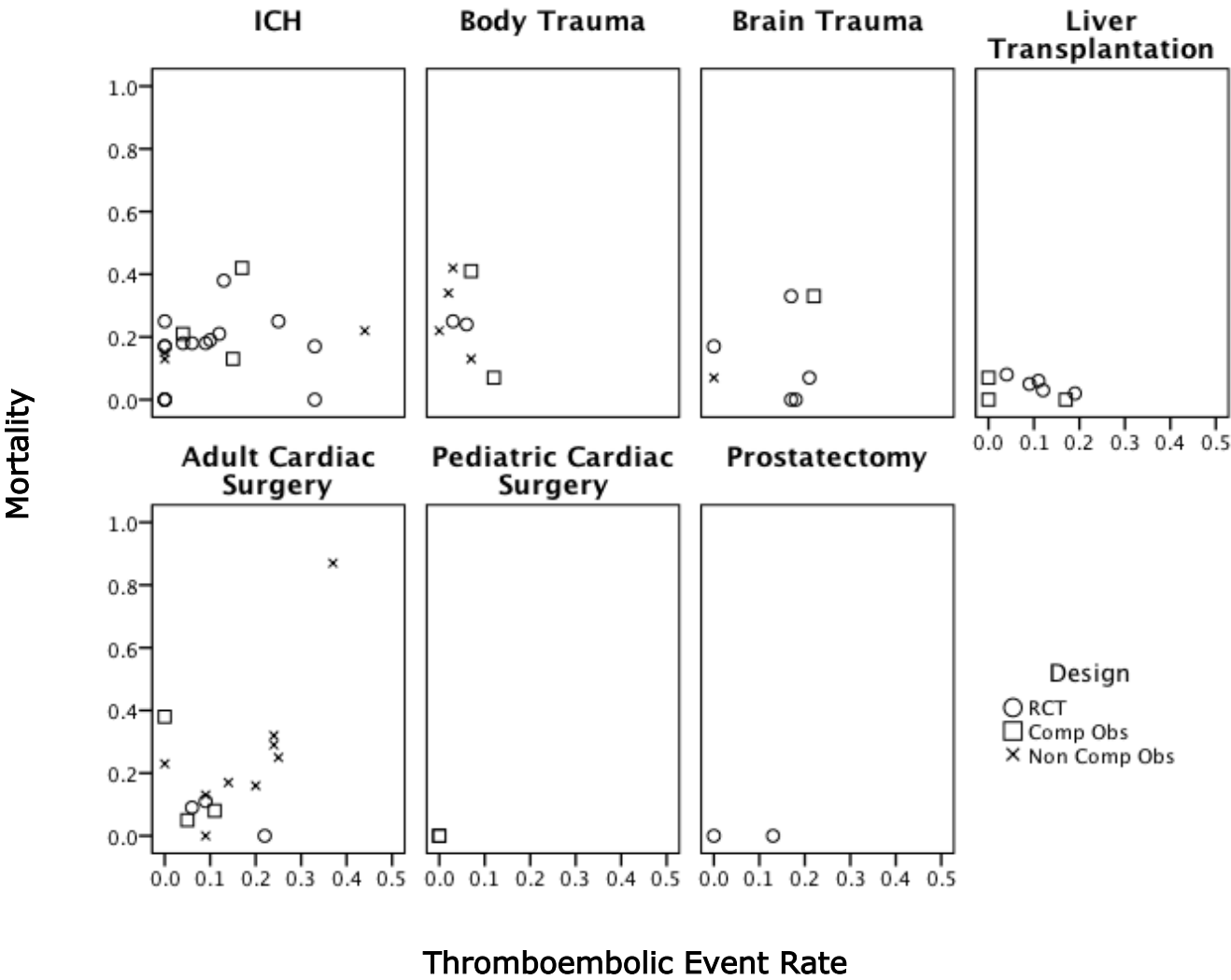
Data points in this figure include only the intervention arms (i.e. rFVIIa patients) from comparative studies. A data point for each dosing arm is presented for RCTs with multiple dosing arms; thus, the number of studies may not equal the number of data points.

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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

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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 Health[231] 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 trial[96] 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 thomboembolism. 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 under-estimate 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 RCT[211] 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 were 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 thrombembolic 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
EMEA	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