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Comparative Effectiveness Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications

Veronica Yank, M.D.^{1,2,3}, C. Vaughan Tuohy, B.S.⁴, Aaron C. Logan, M.D., Ph.D.⁵, Dena M. Bravata, M.D., M.S.^{6,7}, Kristan Staudenmayer, M.D., M.S.⁸, Robin Eisenhut, B.A.⁹, Vandana Sundaram, M.P.H.⁶, Donal McMahon, M.Sc., Ph.D.¹⁰, Ingram Olkin, Ph.D.¹⁰, Kathryn M. McDonald, M.M.⁶, Douglas K. Owens, M.D., M.S.^{11,6}, and Randall S. Stafford, M.D., Ph.D.^{1,2}

¹Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, Stanford School of Medicine

²Division of General Internal Medicine, Department of Medicine, Stanford School of Medicine

³Palo Alto Medical Foundation Research Institute

⁴University of Pennsylvania School of Medicine

⁵Divisions of Hematology and Blood and Marrow Transplantation, Department of Medicine, Stanford School of Medicine

Address for Reprint Requests: Veronica Yank, M.D., Stanford Prevention Research Center, Stanford University, Medical School Office Building X312, 251 Campus Drive, Stanford, CA 94304-5411, vyank@stanford.edu.

Current Mailing Addresses for All Authors

Veronica Yank, M.D., Stanford Prevention Research Center, Stanford University, Medical School Office Building X312, 251 Campus Drive, Stanford, CA 94304-5411

C. Vaughan Tuohy, B.S., 433 S 45th St, Philadelphia, PA

Aaron C. Logan, M.D., Ph.D., Division of Blood and Marrow Transplantation, Stanford University School of Medicine, 269 West Campus Drive, CCSR 2200, Stanford, CA 94305

Dena M. Bravata, M.D., M.S., Castlight Health, 685 Market Street #300, San Francisco, CA 94105

Kristan Staudenmayer, M.D., M.S., 300 Pasteur Drive, H3980, Stanford, CA 94305

Robin Eisenhut, B.A., 1027 Amarillo Ave, Palo Alto, CA 94303

Vandana Sundaram, M.P.H., Center for Health Policy/Center for Primary Care and Outcomes Research, Stanford University, 117 Encina Commons, Stanford, CA 94305-6019

Donal McMahon, M.Sc., Ph.D., Apt 8 Summerfield, Irishtown Rd, Dublin 4, Ireland

Ingram Olkin, Ph.D., 950 Lathrop Place, Stanford, CA 94305

Kathryn M. McDonald, M.M., Center for Health Policy/Center for Primary Care and Outcomes Research, Stanford University, 117 Encina Commons, Stanford, CA 94305-6019

Douglas K. Owens, M.D., M.S., Center for Health Policy/Center for Primary Care and Outcomes Research, Stanford University, 117 Encina Commons, Stanford, CA 94305-6019

Randall S. Stafford, M.D., Ph.D., Stanford Prevention Research Center, Stanford University, Medical School Office Building X312, 251 Campus Drive, Stanford, CA 94304-5411

Potential Conflicts of Interest

Dr. Stafford reports a consulting relationship with Mylan Pharmaceuticals. Over the past five years, he reports past honoraria from Bayer, and past grant funding from Procter and Gamble, Bayer, Merck and Company, SmithKlineGlaxo, Toyo Shinyaku, and Wako Chemical USA. Dr. Owens has a consulting relationship with Sanofi-Aventis. Drs. Yank, Logan, Bravata, Staudenmayer, McMahon, and Olkin, Mr. Tuohy, and Ms. Eisenhut, Ms. Sundaram, and Ms. McDonald have no disclosures.

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⁶Center for Primary Care and Outcomes Research, Department of Medicine, Stanford School of Medicine

⁷Castlight Health, San Francisco

⁸Division of General Surgery, Department of Surgery, Stanford School of Medicine

⁹Stanford University School of Medicine

¹⁰Department of Statistics, Stanford University

¹¹VA Palo Alto Healthcare System, Palo Alto, CA

Abstract

Background—Recombinant Factor VIIa (rFVIIa), a hemostatic agent approved for hemophilia, is increasingly used for off-label indications.

Purpose—To evaluate benefits and harms of rFVIIa use for five off-label, in-hospital indications: intracranial hemorrhage, cardiac surgery, trauma, liver transplantation, and prostatectomy.

Data Sources—Ten databases (including PubMed, EMBASE, and Cochrane Library) queried from the advent of each through December 2010. English language articles were analyzed.

Study Selection—Two reviewers independently screened titles and abstracts to identify clinical use of rFVIIa for the selected indications and identified all randomized controlled trials (RCTs) and observational studies for full-text review.

Data Extraction—Two reviewers independently assessed study characteristics and rated study quality and indication-wide strength of evidence.

Data Synthesis—Inclusion criteria were met by 17 RCTs, 33 comparative observational studies, and 23 non-comparative observational studies. Identified comparators were limited to placebo (RCTs) or usual care (observational studies). For intracerebral hemorrhage, mortality was not improved with FVIIa use across a range of rFVIIa doses. Arterial thromboembolism was increased with rFVIIa for medium-dose (risk difference 0.03 [0.01, 0.06]) and high-dose use (0.06 [0.01, 0.11]). For adult cardiac surgery, there was no mortality difference, but an increased risk of thromboembolism (0.05 [0.01, 0.10]) with rFVIIa. For body trauma, there were no differences in mortality or thromboembolism, but a reduced risk of acute respiratory distress syndrome (−0.05 [−0.02, −0.08]). Mortality and thromboembolism were consistently higher in observational studies compared to RCTs.

Limitations—The amount and strength of evidence was low for the majority of outcomes and indications. Publication bias could not be excluded.

Conclusion—Limited available evidence for five off-label indications indicates no mortality reduction with rFVIIa use. For some indications, rFVIIa increases thromboembolism.

Primary Funding Source—Agency for Healthcare Research and Quality

Recombinant activated factor VII (rFVIIa) is an expensive and potent procoagulant. Intravenous use of rFVIIa was approved by the U.S. Food and Drug Administration (FDA)

in 1999 for patients with Hemophilia A or B and antibody inhibitors against standard factor replacements. Recently its use has expanded beyond these approved indications to encompass a wide range of in-hospital off-label applications.

Off-label drug use refers to any application that deviates from FDA approved use. The FDA drug approval process mandates that randomized clinical trials demonstrate efficacy and safety. Once approval is given, however, physicians are free to use the drug for other indications. While off-label use is legal and allows for rapid adoption of some therapies, the available evidence supporting it usually falls short of the rigor that accompanies FDA review. While the resulting uncertainty may be acceptable, concerns increase when off-label use is applied to conditions that are clinically distinct from approved indications or it is frequent, costly, or associated with important side-effects or harms.

Increasing off-label use of rFVIIa for hospitalized patients has occurred despite concerns regarding efficacy and safety, including evidence suggesting an increased rate of thromboembolic events (1–5). Our comparative effectiveness review evaluates the benefits and harms of in-hospital off-label rFVIIa use in adults for the selected indications of intracranial hemorrhage, cardiac surgery, trauma, liver transplantation, and prostatectomy.

METHODS

The full report was commissioned by the Agency for Healthcare Research and Quality (AHRQ) and is available, including the search strategies and detailed evidence tables, at its website (6). We developed and followed standardized protocols for data searches, extraction, quality assessments, and syntheses.

Data Sources and Searches

Searches—In collaboration with a research librarian, we developed individualized search strategies for seven bibliographic databases from inception through December 31, 2010: PubMed, EMBASE, Cochrane Library, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, and BIOSIS (Appendix Search Strings). We contacted experts and reviewed bibliographies of identified systematic reviews, files supplied by the manufacturer, and the manufacturer website. A librarian expert on “grey literature” (sources other than published materials indexed in bibliographic databases) searched regulatory sites, clinical trial registries, conference proceedings, and grant and federally funded research sites and contacted authors of abstracts to determine whether full reports had been subsequently published.

Inclusion criteria—We sought studies that compared the use of rFVIIa with alternative therapies, placebo, or usual care for hospitalized patients with five off-label indications: intracranial hemorrhage, cardiac surgery, trauma, liver transplantation, and prostatectomy. For inclusion, studies had to address direct or surrogate clinical outcomes. We did not contact authors regarding results that were not reported in their publications. We excluded studies published only as abstracts and studies of human factor VIIa or modified recombinant forms under development, rFVIIa use for on-label indications, rFVIIa applied to patients substantially similar to those for whom on-label indications are approved (e.g.,

Glanzmann's thrombasthenia), and studies whose outcome measures (e.g., drug half-life) are not relevant to efficacy, effectiveness, or safety. Lastly, we reviewed the English language abstracts and references of studies published in non-English languages. Among these, we identified two small comparative studies likely eligible for effectiveness review (RCT of cardiac surgery (11 rFVIIa patients) (7) and comparative cohort study of brain trauma (7 rFVIIa patients) (8)) and six case series reports (range from 16 to 35 patients) (9–14) likely eligible for harms analyses, if we had the capacity to perform full text review. The RCT was used for sensitivity testing, with comparable results to those reported here. Other non-English language articles were excluded from further review based on a lack of capacity for translation and the determination that such exclusions were unlikely to bias our findings because those identified were few in number and enrolled very few patients.

Study Selection—Two reviewers independently screened titles and abstracts to identify clinical use of rFVIIa for the selected indications and identified all RCTs and observational studies for full-text review. For the effectiveness analyses, we included RCTs and comparative observational studies. We reviewed all RCTs in detail, whereas we only reviewed in detail those comparative observational studies of fair or good quality. We used poor quality comparative observational studies for qualitative sensitivity analyses. Multiple articles reporting on the same patient population were included only once.

While non-comparative studies are a less reliable source of evidence than comparative studies, they may report infrequent events not identified in RCTs (15). Given concerns about the possibility of clinically significant harms, we included registries and cohorts with at least 15 total patients in the harms analyses. We selected 15 patients as the minimum threshold because the risk of bias (e.g., selective reporting) is likely increased in smaller reports. We also included the treatment arms of all comparative studies in the harms analyses.

Data Extraction and Quality Assessment

Two reviewers independently rated study quality and indication-wide strength of evidence and abstracted study characteristics using pre-tested electronic forms. Study quality and indication-wide strength of evidence were evaluated using well established criteria (16–25) and a predefined systematic approach described further in the AHRQ report (6). The quality criteria were specific to the study type and were used to assign each study a quality score from the ordinal scale of “poor, fair, or good” using qualitative determinations rather than numerical scores. For RCTs, essential quality elements included appropriate randomization, allocation concealment, blinding and absence of differential follow-up. For observational studies, essential quality elements included appropriate methods to generate comparability of groups and control for confounding, appropriate blinding, and absence of differential follow-up. Studies that failed to achieve (or did not adequately report) these elements were assigned a quality score of “poor.” Those that achieved these partially or fully were felt to have a lower risk of bias and were assigned quality scores of “fair” or “good” respectively. Strength of evidence (low, moderate, high, or insufficient) was determined similarly (17). Five types of data were abstracted from each included study: study design, population evaluated, rFVIIa dosing and administration, outcomes assessed, and study funding. Disagreements were resolved by discussion and, when necessary, review by a third author.

Data Synthesis and Analysis

We summarized mortality, thromboembolism, and other outcome rates for included studies. We considered studies eligible for meta-analysis if they were good or fair quality RCTs or good quality observational studies and had similar interventions and patient populations. We performed meta-analyses when there were at least two studies of fair or better quality, including at least one of good quality.

The intracranial hemorrhage RCTs had multiple intervention arms in which varying doses of rFVIIa were compared with a single control arm. For these we used a least square fixed effects model, a standard meta-analytic methodology for synthesizing studies of this design. (see Gleser-Olkin model) (26–28) We performed meta-analyses using both fixed effects and random effects models for sensitivity testing. We calculated standardized mean differences for percent hematoma expansion, the only continuous variable analyzed. For dichotomous outcomes, we calculated two effect size metrics: risk differences and arcsine standardized mean differences (29). Results from these metrics were consistent. For ease of interpretation and because outcome rates were similar across studies (such that disadvantages of the risk difference metric were minimized), only risk differences are reported here. We performed meta-analytic calculations with the R statistics package (Version 2.11.1) using a modified “meta” package (by Guido Schwarzer, sc@imbi.uni-freiburg.de, version 1.6-0). While we performed assessments of heterogeneity using the Q and I² statistics, we expected these to be non-significant if there were too few studies included in each meta-analytic calculation. In that case, differences in findings between the fixed and random effects analyses were expected to highlight the presence of heterogeneity, if present.

Because the literature suggested a dose response relationship between rFVIIa and certain outcomes, particularly arterial thromboembolism, and the intracranial hemorrhage RCTs reported outcomes separately for multiple rFVIIa doses and arterial versus venous thromboemboli, we chose *a priori* to analyze these data according to low, medium, and high treatment doses (less than or equal to 40 µg/kg, greater than 40 but less than 120 µg/kg, and greater than or equal to 120 µg/kg) and arterial versus venous thromboembolic outcomes. Dose-response analyses were not possible for other indications because there were too few patients at specific dosages, dosages were unclear, or outcomes were not reported by dosage.

Role of Funding Source

Primary funding for the project was provided by the Agency for Healthcare Research and Quality (AHRQ), with additional support from the National Heart, Lung, and Blood Institute and the Palo Alto Medical Foundation Research Institute. While AHRQ formulated the initial study questions, the funding sources otherwise had no role in the design and conduct of this study or in the collection, management, analysis, or interpretation of the data. AHRQ reviewed the manuscript but did not assist in its preparation.

RESULTS

Our searches identified 6191 potentially relevant articles of which 62 articles reporting on 64 studies met inclusion criteria (Figure 1). Of these, 27 studies (16 RCTs (30–43), 10

comparative observational studies (44–53) are included in the comparative effectiveness review (Table). Most had small to moderate sample sizes (for rFVIIa patients, mean 80; median 44; range 6 to 573). There was great variability in doses of rFVIIa administered (range 5 to 400 µg/kg). Thirty-eight additional studies (16 poor quality comparative (54–69) and 22 non-comparative (70–91) observational studies) were included in the harms analyses. Overall, no studies compared rFVIIa to predecessor products that might be considered alternatives for some indications (e.g., activated prothrombin complex concentrates). Instead, the RCTs examined rFVIIa versus “placebo plus usual care” and the comparative observational studies compared it to “usual care.” There were few fair or good quality studies within any indication (Table)(6). RCTs were generally of better quality than comparative observational studies: only 13% (2 of 16) of RCTs (41–42) were of poor quality, whereas 59% (16 of 27) of the comparative observational studies (54–69) were poor quality. All observational studies that were determined to be poor quality lacked appropriate methods to generate comparability of groups or control for confounding. The small number of studies for any given indication precluded the use of funnel plots or other approaches for evaluation of publication bias. The manufacturer of rFVIIa, Novo Nordisk (Bagsværd, Denmark), sponsored the majority of RCTs.

Effectiveness Review Outcomes

The Table summarizes the key characteristics of the studies providing comparative effectiveness outcome data, along with their quality, strength of evidence, and conclusions. While Figure 2 summarizes the individual studies’ mortality and thromboembolic event risk differences, few of these studies were powered to distinguish important differences between treatment groups for these direct endpoints. Instead they used indirect endpoints (e.g., transfusions requirements) as primary outcomes. For all indications, qualitative sensitivity analyses suggest that poor quality comparative observational studies (those not reviewed in depth in the effectiveness review but included in the harms analysis (Appendix Tables 1–12)) had results consistent with those reported below for the RCTs and higher quality observational studies (6). In the sections that follow, we present the benefits and harms associated with use of rVIIa by specific indication. In all cases where meta-analyses were performed, the results of the fixed effects and random effects models were virtually identical and were in agreement on all determinations of significant findings versus non-significant ones (i.e., those that “crossed the null”), indicating the presence of little heterogeneity among included studies. We report results from the fixed effects models below. Unless otherwise noted, the low strength of evidence critically limits our ability to draw conclusions regarding the comparative effectiveness of rVIIa and usual care.

Intracranial Hemorrhage—Identified RCTs only examined intracerebral hemorrhage (ICH), rather than other forms of intracranial hemorrhage (e.g., subdural hematoma). Four RCTs (30–33) and one comparative observational study (44) examined the use of rFVIIa in 968 intervention patients (Table). Notably, whereas all of the RCTs that examined ICH excluded patients on oral anticoagulation therapy, all of the patients in the one comparative observational study that met inclusion criteria were taking oral anticoagulants—half of whom had ICH and the other half, subdural hematomas. Because of this clinical heterogeneity compared to RCT patients, the observational study data were not included in

meta-analyses. The meta-analyses found no evidence of rFVIIa effect at any dosing level on mortality (Figure 3, Appendix Tables 1–3) or on poor functional outcome (as measured by the modified Rankin scale) (risk difference for low dose -0.02 [95% CI -0.09 to 0.05]; medium -0.03 [-0.10 to 0.04]; high -0.04 [-0.15 to 0.08]) compared with usual care. However, there was an increased rate of arterial thromboembolism with rFVIIa for the medium- and high-dose groups (Figure 3). rFVIIa use significantly decreased relative hematoma expansion at all doses (standardized mean difference for low dose -0.15 [95% CI -0.29 to 0.00]; medium -0.24 [-0.39 to -0.10]; high -0.33 [-0.58 to -0.09]). On statistical testing, there was no evidence of dose effect for any endpoint, including mortality and arterial thromboembolism (6). Thus, moderate strength of evidence suggests that the use of rFVIIa for ICH patients not on oral anticoagulation therapy yields no significant benefit for mortality or functional outcome, but is associated with an increased risk of arterial thromboembolism.

Cardiac Surgery—Two RCTs (34–35) and four comparative observational studies (45–48) of 251 adult cardiac surgery patients receiving rFVIIa met inclusion criteria, of which the two RCTs and two observational studies (45–46) were of high enough quality for meta-analysis. One RCT assessed prophylactic rFVIIa use—at the conclusion of complex, non-coronary artery bypass grafting surgeries (34); the other studies all evaluated treatment use for post-operative bleeding. However, the timing and context of rFVIIa administration was similar for all studies, because bleeding is common after complex, non-coronary artery bypass grafting surgery and rFVIIa was given after termination of cardiopulmonary bypass in all cases. Thus, we considered it appropriate to combine these studies. In meta-analyses, we found no effect of rFVIIa on mortality compared to usual care, but an increased risk of thromboembolism (Figure 3, Appendix Table 4). RBC transfusion requirements were possibly reduced with rFVIIa, but the trend was only apparent across higher quality studies (Appendix Table 5). Results regarding ICU length of stay were not consistent. In summary, 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, but rFVIIa use increases the risk of thromboembolism.

Body Trauma—Four RCTs (published in two papers that each report on one blunt and one penetrating trauma trial in the same paper) (36–37) and three comparative observational studies (49–51) assessed 746 patients who received rFVIIa. Two RCTs (36) censored patients who died within 48 hours of injury for analyses of transfusion requirements—a critical limitation of this literature—but report for all patients on the endpoints of mortality, thromboembolic events, and acute respiratory distress syndrome (ARDS). In meta-analyses of the four RCTs, we found no effect of rFVIIa on mortality or thromboembolism but a significant reduction in ARDS (Figure 3, Appendix Table 6). Recombinant FVIIa reduced transfusion requirements in all four RCTs when all patients were included in the analysis (i.e. including previously censored patients), but the decrease was significant in only one (37) (Appendix Table 7). The observational studies did not report usable comparative data on this outcome. Overall, available evidence of moderate strength identifies no increased risk of thromboembolic events, a reduced risk of ARDS, but no difference in mortality.

Brain Trauma—One RCT (38) and one comparative observational study (52) evaluated 79 patients who had traumatic brain injury and received rFVIIa. The observational study included patients on oral anticoagulation therapy, while the RCT excluded them and also patients for whom neurosurgery was planned. We found no effect of rFVIIa on mortality or thromboembolic events (risk differences (rFVIIa minus usual care) for mortality, 0 in the RCT and -0.2 in the observational study; thromboembolic events, 0.07 and 0.05) (Figure 2, Appendix Table 8). Additionally, rFVIIa use did not influence hematoma growth but was associated with a reduction in time to neurosurgical intervention (i.e., by more quickly normalizing the INR) in the observational study, the one study that evaluated this outcome. In summary, current evidence of low strength is too limited to compare the harms and benefits of rFVIIa.

Liver Transplantation—Four RCTs (39–42) and one comparative observational study (53) evaluated 215 patients with Child’s class B or C cirrhosis who received prophylactic rFVIIa upon initiation of liver transplantation. On systematic review, we found no effect of rFVIIa on mortality or thromboembolism (risk difference range (rFVIIa minus usual care) for mortality, 0 to 0.01; thromboembolic events, -0.03 to 0.17) (Figure 2, Appendix Table 9). There was a trend across studies toward reduced RBC transfusion requirements with prophylaxis, but neither operating room time nor ICU length of stay were reduced (Appendix Table 10). Thus, available evidence of low strength is too limited to compare the harms and benefits of rFVIIa.

Prostatectomy—There was one RCT on prophylactic use of rFVIIa in 24 patients undergoing retropubic prostatectomy for prostate cancer or benign prostatic hypertrophy (92) (providing an insufficient strength of evidence for all outcomes). Mortality and thromboembolic events could not be evaluated due to limited events (no deaths, one thromboembolic event). RBC transfusion requirements and operating room time were significantly decreased with rFVIIa use. (Appendix Tables 11–12)

Evaluation of Harms: Data from RCTs Versus Comparative and Non-Comparative Observational Studies

Unadjusted mortality rates among rFVIIa patients ranged widely from 0 to 0.87 (median 0.17), and thromboembolism rates varied from 0 to 0.39 (median 0.09) (6). In general, mortality rates were lowest in RCTs and highest in observational studies, but the relationship between study type and thromboembolism rate was less clear (Figure 4). RCTs of ICH—which had the longest follow-up and most completely described ascertainment of harms—had mortality and thromboembolic event rates only slightly different than those from observational studies. The discrepancy between harms reported in RCTs versus observational studies was greater for other indications. There was no apparent correlation between rFVIIa dose and harms outcomes (6), which is similar to our effectiveness review finding for ICH of no dose effect. Nor was there an apparent relationship between age and harms outcomes (6), although it is notable that ages tended to cluster for a given indication which may have made any relationship difficult to ascertain. Finally, there was no observable pattern between the likelihood of mortality and thromboembolism (6), which is

similar to the effectiveness review findings for certain indications (ICH and cardiac surgery) of no effect of rFVIIa on mortality despite an associated increase in thromboembolic events.

DISCUSSION

Available evidence indicates that in-hospital, off-label use of rFVIIa does not reduce mortality for any indication. In contrast, use of rFVIIa increases the rate of thromboembolic events in intracranial hemorrhage and cardiac surgery. Of the indications studied, the benefit-to-risk ratio may be most favorable for body trauma because rFVIIa use in this population is associated with a reduced risk of ARDS, although this finding must be placed in the context of no accompanying reduction in mortality. In addition, the strength of evidence is low or moderate for all outcomes, which precludes definitive conclusions. The harms analyses raise additional concerns by noting that mortality rates among rFVIIa patients are generally greater in observational studies—in which patient groups more closely reflect unselected patient populations—compared to RCTs. Our analysis of data from non-federal U.S. hospitals found that 97% of off-label in-hospital uses of rFVIIa were off label, with the majority for ICH, cardiac surgery, and trauma indications (93). This increasingly frequent use of off-label rFVIIa is occurring despite its expense (at least \$10,000 for a single 90 µg/kg dose in a 70 kg patient)(94), lack of mortality benefit, and growing evidence of associated harms.

Our systematic review in some cases extends the findings of previous reviews by incorporating data from comparative observational studies in the effectiveness review, assessing the impact of dosing level when possible, and assessing harms across different study types known to have varying degrees of generalizability to real-world populations. We are able to provide indication-specific findings for disparate clinical applications, as well as an overview of use that identifies outcome patterns across indications, such as an increase in thromboembolism for some. Prior reviews that pooled data for multiple indications identified no mortality benefit with off-label rFVIIa use (2, 95–100) and several noted a nonsignificant increase in thromboembolism (2, 96) (98–100) or, more recently, a significant increase(5), but none could provide indication-specific guidance. Regarding specific indications, a Cochrane review of ICH and hemostatic drug therapies, overwhelmingly rFVIIa, noted no mortality reduction but a nonsignificant increase in thromboembolism (3), while a more recent review by Yuan and colleagues had the same findings as ours regarding a significantly increased risk of arterial thromboembolism without any attendant benefits for mortality or functional outcome(101). A meta-analysis of cardiac surgery observed no effect on mortality and a nonsignificant increase in perioperative stroke(4). For body trauma, three systematic reviews concluded that rFVIIa did not decrease mortality (102–104). For brain trauma, a recent Cochrane review by Perel and colleagues identified few studies and no mortality benefit(105). Other reviews were more supportive of rFVIIa, describing it as a “promising” therapy (106) or one that might reasonably be used as rescue therapy(107–108), but did not perform meta-analyses. Specific to harms analyses, O’Connell and colleagues evaluated data from the FDA’s Adverse Event Reporting System to document serious thromboembolic events following off-label rFVIIa use(1).

Our analysis has several limitations. The heterogeneity of included studies prevented us from pooling data across clinical indications. Second, we found no studies comparing rFVIIa to predecessor products, only to placebo or usual care. Comparisons to usual care may be particularly susceptible to bias from site-to-site variations or advances in clinical care over time. Third, we excluded non-English language articles, albeit only two were comparative studies with very few patients. Fourth, we used quality criteria to determine which observational studies were assessed in detail in the effectiveness review, such that others may have come to different determinations. Nonetheless, these criteria were applied systematically, and qualitative sensitivity testing found that the poor quality studies had similar findings to their better quality counterparts. Fifth, two of the body trauma RCTs (36) experienced withdrawal of consent by patients who had been enrolled under protocols with emergency exceptions to informed consent, but because no information was provided on their treatment arms, we were unable to assess for differential withdrawal. Sixth, the manufacturer of rFVIIa, Novo Nordisk, played a substantial role in sponsoring, designing, directing, analyzing, and publishing much of the RCT evidence. While this circumstance might be expected and does not equate with biased research, it does require special care in evaluating the possibility of bias. Next, we cannot exclude the possibility of selective reporting or publication bias, because the small number of available studies prevents their formal assessments (e.g., using funnel plots). Finally, we found that available studies employed usual care as the comparator and relied heavily on indirect outcomes, both of which may yield more favorable findings than other design options, such as those that use an active comparator or direct outcomes.

In conclusion, off-label use of rFVIIa for ICH and cardiac surgery does not reduce mortality but does increase the risk of thromboembolism. For body trauma, there was no increased risk of thromboembolism and a reduced risk of ARDS, but no difference in mortality. For the remaining indications, the available evidence was too limited to perform meta-analyses. Thus, limited evidence on off-label rFVIIa use for five indications detects no mortality benefit but for some indications an increase in thromboembolism.

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Figure 1.
Literature search and study inclusion or exclusion

Figure 2.

Mortality and thromboembolic event risk differences (rFVIIa minus usual care) for indications with at least two comparative studies included in the effectiveness review. Figure includes indications with two or more comparative studies included in the effectiveness review: ICH (30–33, 44), cardiac surgery (34–35, 45–48), body trauma (36–37, 49–51), brain trauma (38, 52), and liver transplantation (39–42, 53). 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. ICH outcomes here reflect total thromboembolic events, as compared to the arterial thromboembolic events assessed in meta-analyses. For cardiac surgery, there are three study

circles that overlay each other at the zero abscissa for mortality risk and there are two that similarly overlay each other for thromboembolic risk. TE=thromboembolic.

Mortality

Thromboembolic Events

Acute Respiratory Distress Syndrome

Figure 3.

Meta-analysis of off-label rFVIIa use for ICH and adult cardiac surgery in RCTs and good quality observational studies

For ICH, all studies are RCTs (30–33), meta-analyses are performed according to dosing category (low, medium, and high), and analyses of thromboembolic events are for arterial events only. For cardiac surgery, the studies by Diprose (34) and Gill (35) are RCTs, while those by Karkouti (45) and Gelsomino (46) are observational studies, and the meta-analyses of thromboembolic events evaluate all events (both arterial and venous). For body trauma, all studies are RCTs (36–37), and the meta-analyses of thromboembolic events evaluate all events.

Figure 4.

Harms analysis: weighted mortality and thromboembolic events by indication in all RCTs and observational studies

Harms analyses include rFVIIa patients from registries and cohorts (non-comparative observational studies (Non Comp Obs)) with at least 15 patients comparative (ICH (70–72), cardiac surgery (73–83), body trauma (84–87), brain trauma (88–89), and liver transplantation (90–91), as well as patients from the treatment arms of all RCTs (30–43) and comparative observational studies (Comp Obs) (44–69) regardless of quality. For liver transplantation, the reported RCT rate of thromboembolism is an underestimate, because one RCT (40) did not report venous events by arm (treatment versus placebo) and so the events could not be tallied. For studies with overlapping data sets (e.g., the same registry patients being evaluated in a non-comparative study and a comparative observational study), we used the most complete data set for the outcome of interest.

Table

Studies assessed in depth in effectiveness review,* outcomes, strength of evidence,** and conclusions

Study Characteristics		Total Number of Patients		Outcome	Strength of Evidence	Range of Effect Sizes [†] Risk per Time Period (unless otherwise stated)		Conclusions
RCT: n OBS: n	n with Quality	rFVIIa	Usual Care			rFVIIa	Usual Care	Use of rFVIIa versus Usual Care Was Associated With
Intracranial Hemorrhage								
RCT: 4 OBS: 1	2 Good (30, 33) 2 Fair (31–32) 1 Fair (44)	968	384	Mortality	Moderate	0.08–0.22	0.13–0.29	No effect on mortality (Figure 3)
				Arterial TE Events	Moderate	0.04–0.11	0–0.13	Increased rate of arterial TE events (Figure 3)
				Poor Functional Status [#]	Moderate	0.44–0.53	0.46–0.69	No effect on poor functional status
				Percent Hematoma Expansion	Moderate	4–79	11–29	Decrease in percent hematoma expansion
Cardiac Surgery								
RCT: 2 OBS: 4	1 Good (35) 1 Fair (34) 2 Good (45–46) 2 Fair (47–48)	251	216	Mortality	Low	0–0.33	0.06–0.33	No effect on mortality (Figure 3)
				TE Events	Moderate	0–0.22	0–0.20	Increased rate of TE events (Figure 3)
				RBCs Transfused (units)	Low	0–9.1	2–17	Possible reduction in RBC transfusion requirements
				ICU Length of Stay (days)	Low	2.5–14	1–18.5	Unclear impact on ICU length of stay
Body Trauma								
RCT: 4 OBS: 3	2 Good (37) 2 Fair (36) 3 Fair (49–51)	746	900	Mortality	Moderate	0.07–0.31	0–0.51	No effect on mortality (Figure 3)
				TE Events	Moderate	0.03–0.20	0–0.14	No effect on TE event rate (Figure 3)
				ARDS	Moderate	0–0.06	0.04–0.16	Decrease in rate of ARDS (Figure 3)
				RBCs Transfused (units)	Moderate	5.0–16.0	6.8–14.0	Unclear impact on RBC transfusion requirements
Brain Trauma								
RCT: 1 OBS: 1	1 Fair (38) 1 Fair (52)	79	53	Mortality	Low	0.12–0.33	0.11–0.53	No effect on mortality
				TE Events	Low	0.15–0.22	0.08–0.18	No effect TE event rate

Study Characteristics		Total Number of Patients		Outcome	Strength of Evidence	Range of Effect Sizes [†] Risk per Time Period (unless otherwise stated)		Conclusions
RCT: n OBS: n	n with Quality	rFVIIa	Usual Care			rFVIIa	Usual Care	
				Absolute Hematoma Expansion (mL)	Low	7.0	10.4	Use of rFVIIa versus Usual Care Was Associated With No decrease in hematoma growth
Liver Transplantation								
RCT: 4 OBS: 1	2 Fair (39–40) 2 Poor (41–42) 1 Fair (53)	215	117	Mortality	Low	0–0.08	0–0.02	No effect on mortality
				TE Events	Low	0–0.22	0–0.16	No effect on TE event rate
				RBCs Transfused (units)	Low	1.2–13.0	2.3–11.1	Possible reduction in RBC transfusion requirements
				Operating Room Time (min)	Low	268–554	432–598	No reduction in operating room time
				ICU Length of Stay (days)	Low	3.0–4.8	3.0–5.2	No reduction in intensive care unit length of stay
Prostatectomy								
RCT: 1	1 Fair (92)	24	12	Mortality	Insufficient	0	0	Cannot comment due to limited events
				TE Events	Insufficient	0–0.13	0	Cannot comment due to limited events
				RBCs Transfused (units)	Insufficient	0–0.6	1.5	Reduction in RBC transfusion requirements
				Operating Room Time (min)	Insufficient	120–126	180	Reduction in operating room time

RCT=randomized controlled trial. OBS=comparative observational study. TE=thromboembolic. RBC=red blood cell. ARDS=acute respiratory distress syndrome. OR=operating room. ICU=intensive care unit.

* The effectiveness review evaluates in depth all RCTs (30–43) and fair or better quality comparative observational studies (44–53).

** 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.”

[†] 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.

[#] Poor functional status is defined as a modified Rankin Scale (mRS) score of 4–6.