

Use of Recombinant Activated Factor VII in Patients Without Hemophilia

A Meta-Analysis of Randomized Control Trials

Cyrus C. Hsia, MD,† Ian H. Chin-Yee, MD,† and Vivian C. McAlister, MB*

Context: Benefits of recombinant activated factor VII (rFVIIa) in hemorrhage may be lost because of thromboembolic events (TAE). **Method:** MEDLINE, EMBASE, BIOSIS, CINAHL, Science Citation Index Expanded, clinicaltrials.gov were searched for placebo controlled trials of rFVIIa in patients without hemophilia. Reports of 22 randomized controlled trials were selected for analysis. Results were pooled using random effects models to calculate the odds ratios (OR) with 95% confidence interval (CI). Subgroup analyses were predetermined.

Results: Among 3184 participants, 478 (15.0%) died and 249 (7.8%) had TAE. Additional blood transfusion was required in 517 (41.2%) of 1256 subjects. Patients receiving rFVIIa were less likely to need additional blood transfusions (OR, 0.54; 95% CI, 0.34–0.86) than patients receiving placebo. Mortality was not increased but may be reduced (OR, 0.88; 95% CI, 0.71–1.09). Reduction in mortality was more likely if rFVIIa was given therapeutically (OR, 0.87; 95% CI, 0.70–1.09) rather than prophylactically (OR, 1.00; 95% CI, 0.37–2.68). Differences in the pooled analysis of TAE were not statistically significant (OR, 1.17; 95% CI, 0.87–1.58) but the incidence of arterial TAE was likely higher in patients receiving rFVIIa (OR, 1.50; 95% CI, 0.93–2.41) although no differences were seen with respect to venous TAE (OR, 0.76; 95% CI, 0.49–1.15).

Conclusions: Use of rFVIIa reduces the need for blood transfusion and it may reduce mortality, especially if the dose of rFVIIa is limited to therapeutic doses of 90 µg/kg. It does not increase the risk of venous thrombosis but it may increase the risk of arterial thrombosis.

(*Ann Surg* 2008;248: 61–68)

In 1983, Hedner and Kisiel first described the ability of human activated factor VII to control hemorrhage in 2 hemophilia A patients with inhibitors.¹ Since then, a recombinant activated factor VII (rFVIIa, NovoSeven, Denmark), which is structurally nearly identical to the plasma-derived protein,² has become the treatment of choice for bleeding in hemophilia patients with inhibitors,³ acquired hemophilia,⁴ rare congenital coagulation factor deficiencies,^{5,6} and inherited platelet disorders.^{7,8}

The molecular mechanisms by which rFVIIa induces hemostasis is incompletely elucidated but it is believed to enhance thrombin generation at the site of injury via tissue factor dependent and independent pathways.^{9,10} The potent hemostatic effects of rFVIIa led to its use in a soldier with uncontrolled bleeding from a rifle injury¹¹ and in a number of case series of other nonhemophilia patients.^{12,13} Reports of randomized clinical trials, conducted in patients without hemophilia, have recently become available.^{14–42} The clinical settings of these trials, which include intracranial hemorrhage (ICH), trauma, gastrointestinal bleeding, cardiac surgery, prostatectomy, stem cell transplantation, orthopedic surgery, liver resection, and liver transplantation, all had a relatively high risk of hemorrhage or death but the sample sizes were insufficient to determine the benefits and risks of rFVIIa. Off-label use of rFVIIa has been increasing⁴³ and at many centers, including our own, the number of nonhemophilia patients exceeds the number of individuals with hemophilia receiving this product although the total amount of rFVIIa used remains greatest in patients with inhibitors and hemophilia.

The beneficial hemostatic effect of rFVIIa in the control of life threatening hemorrhage must be weighed against its procoagulant effect, which may place the recipient at increased risk of thromboembolic adverse events (TAE). A recent review of submissions to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) suggested the risk of TAE and death in nonhemophiliac recipients of rFVIIa to be substantial.² The review concluded that the inherent limitations of passive surveillance as with AERS underscored the requirement for randomized clinical trials.² Unfortunately the impact of the AERS report has been to dampen the enthusiasm required to complete such trials. Previous reviews of rFVIIa did not include recently completed trials and were insufficient to confirm or refute the

From the *Division of General Surgery and †Division of Hematology, University of Western Ontario, London, Ontario, Canada.

Correspondence: Vivian C. McAlister, MD, FRCSC, Department of General Surgery, University of Western Ontario, London Health Sciences Centre, C4-212, University Hospital, London, Ontario, Canada N6A 5A5. E-mail: vmcalist@uwo.ca.

Reprints not available from authors.

Copyright © 2008 by Lippincott Williams & Wilkins

ISSN: 0003-4932/08/24801-0061

DOI: 10.1097/SLA.0b013e318176c4ec

AERS database observation of death in a large proportion of the rFVIIa recipients who suffered a TAE.^{44,45} We performed a meta-analysis of randomized clinical trials that compared rFVIIa to placebo to determine the benefits and harms of rFVIIa in the nonhemophilia population.

METHODS

This review was performed according to guidelines of the Cochrane Collaboration using its program RevMan 4.2,⁴⁶ which conforms to QUORUM standards for the conduct and reporting of meta-analyses of randomized clinical trials.⁴⁷

Data Sources

We identified relevant studies up to November 2007 by searching MEDLINE (1966–2007), EMBASE (1980–2007), BIOSIS (1969–2007), CINAHL (1982–2007), Science Citation Index Expanded (1981–2007), clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials databases. We reviewed the bibliographies of identified articles and reports presented at major scientific meetings and we contacted trial principal investigators and NovoNordisk, the pharmaceutical company that manufactures rFVIIa.

Study Selection

All randomized clinical trials comparing rFVIIa versus placebo, irrespective of participant age, language of study, or publication status, were included. Studies of patients with hemophilia, acquired inhibitors, rare congenital coagulation factor deficiencies, and inherited platelet disorders were excluded. Studies without a placebo control group were also excluded. Short-term trials of rFVIIa in healthy volunteers were not included in the primary analysis but were reviewed for adverse events and used in sensitivity studies of the meta-analysis.

Outcome Measures

We examined the outcomes of all-cause mortality, TAE, and additional red blood cell (RBC) transfusions in each trial. Mortality was recorded as the number of deaths because of any cause during the longest observation period reported in each trial. TAE included all arterial, venous, or otherwise unspecified events likely to be thromboembolic in nature. This was recorded as the number of participants who experienced 1 or more of these events. The number of participants receiving additional RBC transfusions was recorded based on the predetermined criteria for additional transfusion as defined in each study. Previous transfusion with 8 units of blood was a requirement for inclusion in the trauma studies and only the number of patients requiring more than 20 units was reported; this number was included in the additional transfusion data set.¹⁴ If studies reported values for different time points, the number of participants receiving transfusions over the longest observed period was recorded.

Data Extraction

Candidate abstracts were reviewed and appropriate articles were selected for data retrieval. All 3 reviewers independently extracted data from each article using a predefined

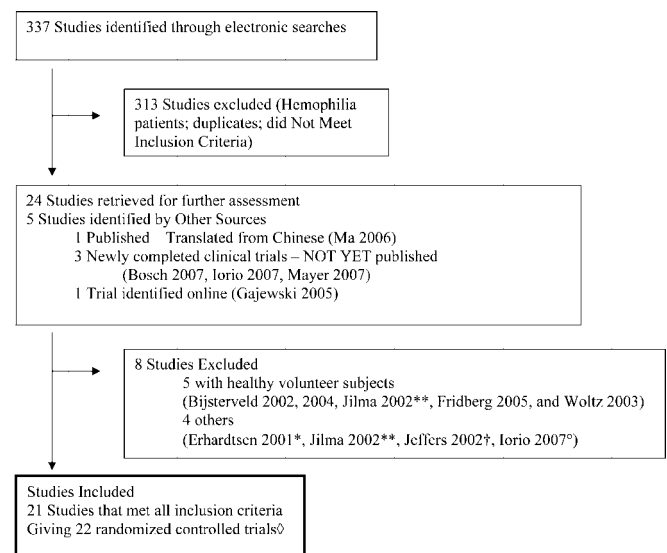
standardized data extraction tool to determine methodological quality, the number of patients randomized, mean duration of follow-up, and outcomes. Any differences were settled by discussion and consensus.

Statistical Analysis

The number of events and number of patients in each of the rFVIIa and placebo arms were used to calculate OR with 95% CI). Meta-analysis was performed using RevMan 4.2, which assigns a weight to each study in the meta-analysis according to its 95% CI.⁴⁶ For assessment of outcomes, a random effects model according to the method of DerSimonian and Laird⁴⁸ was performed. Tests of heterogeneity were calculated using the Mantel-Haenszel method⁴⁹ and the I^2 statistic. Stratified analyses were performed according to: etiology of disease (ICH or not); prophylactic or therapeutic use of rFVIIa; single or multiple doses of rFVIIa; and total dose administered. Choice of subgroups was made a priori, ie, before clinical trials data were obtained.

RESULTS

The electronic search resulted in 337 articles (Fig. 1). We considered 24 articles to be potentially eligible and retrieved the full text versions. Five other articles were found through reviewing bibliographies of articles or reports presented at scientific meetings. Four of the reports were in abstract form only.^{16,21,28,42} These 29 articles were independently reviewed and 21 reports of 22 randomized controlled trials met inclusion criteria. One article included 2 parallel, randomized controlled trials.¹⁴ Eight articles were



Flowchart of study selection that met all inclusion criteria

*Used alternate form of recombinant factor VIIa, FFR+rFVIIa

**Used FFR-rFVIIa and in healthy volunteer subjects

†No placebo group in this trial

‡Control group used activated prothrombin complex concentrates

◊Boffard 2004 study contained two parallel randomized control trial

FIGURE 1. Results of searches for trials of recombinant activated factor VII versus placebo in patients without hemophilia.

TABLE 1. Study Characteristics of Trials of Recombinant Activated Factor VII Versus Placebo in Patients Without Hemophilia

Primary Author Name and Year of Publication	Study Age Eligibility (Yrs)	Setting	Placebo Participants	Placebo Age in Yrs as Mean +/- SD or Median (Range)	rFVIIa Participants	rFVIIa Age in Yrs as Mean +/- SD or Median (Range)	rFVIIa Dosing ($\mu\text{g/kg}$)	I	Study Period
Boffard 2005a ¹⁴	16–65	Blunt trauma	74	35 +/- 13	69	33 +/- 13	400 (200,100,100)	T	30 d
Boffard 2005b ¹⁴	16–65	Penetrating trauma	64	32 +/- 10	70	29 +/- 10	400 (200,100,100)	T	30 d
Bosch 2004 ¹⁵	18–74	GI bleeding, cirrhosis	120	54.2 +/- 10.6	116	52.6 +/- 11.9	800 (100 x 8 doses)	T	42 d
Bosch 2007 ¹⁶	NA	Variceal bleeding, cirrhosis	86	NA	170	NA	300 (200,100) or 600 (200,100 x 5 doses)	T	42 d
Chuansumrit 2005 ¹⁷	<18	Dengue hemorrhagic fever	10	10.5 +/- 3.4	18	9.1 +/- 4.1	100 x 1–2 doses	T	24 h
Diprose 2005 ¹⁸	≥18	Cardiac surgery	10	69.5 (63.5–76.5)*	10	63 (59–66)*	90	P	Initial hospitalization
Ekert 2006 ¹⁹	<1	Cardiac surgery	36	3.9 mo	40	4.0 mo	120 x 1–3 doses	P	42 d
Friederich 2003 ²⁰	18–85	Prostatectomy	12	63 +/- 8.3	8	61 +/- 8.9	20	P	10 d
					16	64 +/- 8.5	40		
Ashrani 2006 ²¹	≥12	Stem cell transplantation	3	44.0 +/- 10.4	4	29.3 +/- 14.4	280 (40 x 7 doses)	T	4 d
					4	18.0 +/- 5.2	560 (80 x 7 doses)		
Lodge 2005a ²²	≥18	Liver transplantation	62	52.3 +/- 11.5	63	53.3 +/- 11.2	180 (60 x 3 doses) [†]	P	Initial hospitalization
					58	52.6 +/- 9.2	360 (120 x 3 doses) [†]		
Lodge 2005b ²³	≥18	Liver resection	68	56.2 +/- 13.3	66	55.5 +/- 13.8	20 (20 x 1 dose) [†]	P	7 d or initial hospitalization
					66	57.9 +/- 11.9	80 (80 x 1 dose) [†]		
Ma 2006 ²⁴	≥18	Cardiac surgery	11	47.5 +/- 10.9	11	50.3 +/- 9.6	40	P	Initial hospitalization
Mayer 2005 ²⁵	≥18	Intracerebral bleed	11	66 +/- 14	6	51 +/- 9	10	T	90 d
					6	68 +/- 22	20		
					6	68 +/- 16	40		
					6	58 +/- 11	80		
					6	64 +/- 14	120		
					6	53 +/- 12	160		
Mayer 2006 ²⁶	≥18	Intracerebral bleed	8	67 +/- 13	8	72 +/- 10	5	T	90 d
					8	60 +/- 15	20		
					8	64 +/- 13	40		
					8	62 +/- 12	80		
Mayer 2005 ²⁷	≥18	Intracerebral bleed	96	68 +/- 12	108	67 +/- 12	40	T	90 d
					92	65 +/- 12	80		
					103	64 +/- 13	160		
Mayer 2007 ²⁸	≥18	Intracerebral bleed	263	65 +/- 14	265	65 +/- 14	20	T	90 d
					293	65 +/- 13	80		
Pihusch 2005 ²⁹	≥12	Stem cell transplantation	23	39 (18–64)	20	36 (20–58)	280 (40 x 7 doses)	T	4 d
					26	38 (20–61)	560 (80 x 7 doses)		
					31	37 (16–57)	1120 (160 x 7 doses)		
Planinsic 2005 ³⁰	≥18	Liver transplantation	19	49.9 +/- 11.0	18	49.4 +/- 13.4	20	P	7 d
					24	49.7 +/- 10.1	40		
					22	51.9 +/- 8.8	80		
Pugliese 2007 ³¹	NA	Liver transplantation	10	54 +/- 12	10	57 +/- 9	40	P	Initial hospitalization
Raobaikady 2005 ³²	18–60	Pelvic/acetabular	24	38 (18–57)	24	44 (18–57)	90	P	30 d
Sachs 2007 ³³	15–70	Spinal fusion surgery	13	56 (17–65)	12	52.5 (18–62)	90 (30 x 3 doses)	T	30 d
					12	56 (17–69)	180 (60 x 3 doses)		
					12	45 (18–63)	360 (120 x 3 doses)		
Shao 2006 ³⁴	>21	Liver resection	81	48.5 (29.5–75.0)	73	52.5 (21.7–76.2)	50 (x1–4 doses)	P	Initial hospitalization
					78	54.1 (22.7–71.6)	100 (x1–4 doses)		
Total 22 trials			1104		2080				

“a” after Boffard 2005 indicates the blunt trauma trial; “b” after Boffard 2005 denotes the penetrating trauma trial.

*Median (interquartile range).

†Majority of participants received this number of doses.

I indicates indication; P, prophylactic; T, therapeutic administration; NA, not applicable or data not available.

excluded (total 252 subjects)^{35–42}; 5 studies were in healthy subjects (96 subjects),^{35–39} 2 trials did not study rFVIIa but used an inactivated form of recombinant factor VIIa, FFR-rFVIIa, instead (74 subjects)^{39–40}; 1 had no placebo group (71 subjects)⁴¹; and 1 used a control group that received activated prothrombin complex concentrates (11 subjects).⁴² Additional information in 4 studies was kindly provided by the investigators or by NovoNordisk.^{16,21,28,42} Further, 1 article was written originally in Chinese and translated.²⁴

Study Quality/Characteristics

All included studies were randomized double-blinded placebo-controlled trials. Allocation appeared to be properly randomized and adequately concealed in all of the studies. Most of the 22 clinical trials were conducted in adults but some included children (Table 1). A total of 3184 subjects were studied in a wide variety of clinical settings. Four trials were conducted in patients with ICH,^{25–28} 1 article with 2 parallel trials in trauma,¹⁴ 2 in upper gastrointestinal bleeding,^{15,16} 3 in cardiac surgery,^{18,19,24} 3 in liver transplantation,^{22,30,31} 2 in liver resection,^{23,34} 2 in orthopedic surgery,^{32,33} 1 in prostatectomy,²⁰ 2 in stem cell transplantation,^{21,29} and 1 trial in dengue hemorrhage fever subjects.¹⁷ In 10 trials, rFVIIa was administered prophylactically^{18–20,23–24,30–32, 34} and in 12 trials it was given therapeutically based on the indications of each trial.^{14–17,21,25–29,33} Unit doses of rFVIIa from 5 µg/kg to 200 µg/kg were administered 1 or more times so that the total dose of rFVIIa ranged from 5 µg/kg to 1120 µg/kg. Study period as determined by the longest intended follow-up, monitoring, or intervention reported for the studies ranged from 6 hours to 90 days (Table 1).

Study Outcomes

Of the total 3184 subjects studied in the 22 trials, 2080 patients received rFVIIa, 1104 received placebo with a total of 478 (15.0%) deaths, and 249 (7.8%) TAE. Additional

blood transfusion was required in 517 (41.2%) of 1256 subjects in studies that reported participant transfusion data.

The overall number of patients receiving additional RBC transfusions was significantly less in the rFVIIa group 292 (39.9%) versus the placebo group 225 (42.9%), (OR, 0.54; 95% CI, 0.34–0.86, Fig. 2). Tests of statistical heterogeneity were positive (I² = 49.5%). The amount of blood transfused was not reported sufficiently or in a manner that permitted pooled analysis. Tests of statistical heterogeneity were negative (I² = 0) with respect to mortality and TAE. Mortality was 14.8% (307 subjects) in the rFVIIa group and 15.5% (171 subjects) in the placebo group (OR, 0.88; 95% CI, 0.71–1.09; Fig. 2). The cause of death was not sufficiently well reported for meta-analysis.

TAE occurred in 8.6% (178 subjects) of the rFVIIa group and in 6.4% (71 subjects) of the placebo group (OR, 1.17; 95% CI, 0.87–1.58; Fig. 3). TAE were classified as arterial (stroke, myocardial infarction, arterial embolism), as venous (deep vein thrombosis, pulmonary embolism) or unspecified. Comparison of rFVIIa to placebo according to TAE type revealed a possible increase in arterial TAE (OR, 1.50; 95% CI, 0.93–2.41) whereas no differences were seen with respect to venous TAE (OR, 0.76; 95% CI, 0.49–1.15). A statistically significant increase in the rate of myocardial infarction was seen in the rFVIIa group but the rates of deep vein thrombosis or pulmonary embolism were similar in both groups (Table 2).

Stratified analyses, performed according to underlying disease (ICH or not), indication (prophylactic versus therapeutic), number of doses of rFVIIa and total dose administered are presented in Table 3. The number of patients requiring transfusion was significantly reduced if the dose of rFVIIa ≤90 µg/kg (OR, 0.42; 95% CI, 0.19–0.93) but not if the dose exceeded 90 µg/kg (OR, 0.62; 95% CI, 0.34–1.14). The reduction in transfusion rates was statistically significant if rFVIIa was administered once (OR, 0.33; 95% CI, 0.11–0.96)

Review: Recombinant activated factor VII for the control of hemorrhage in patients without hemophilia
 Comparison: 01 Recombinant activated factor VII versus placebo
 Outcome: 03 Patients receiving additional red cell transfusion

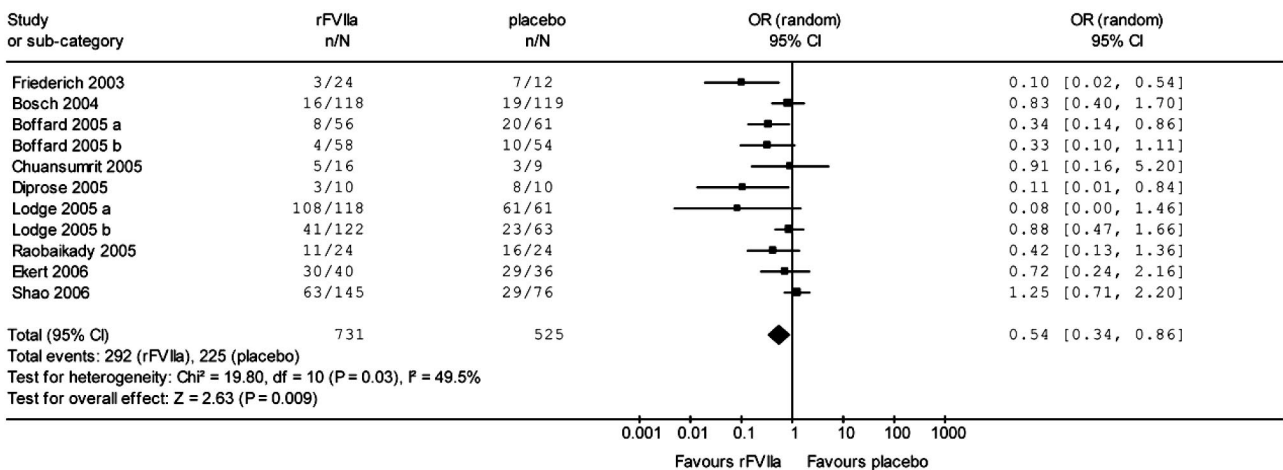


FIGURE 2. Effect of recombinant activated Factor VII compared with placebo on the requirement for additional red blood cell transfusion.

Review: Recombinant activated factor VII for the control of hemorrhage in patients without hemophilia
 Comparison: 01 Recombinant activated factor VII versus placebo
 Outcome: 01 Mortality

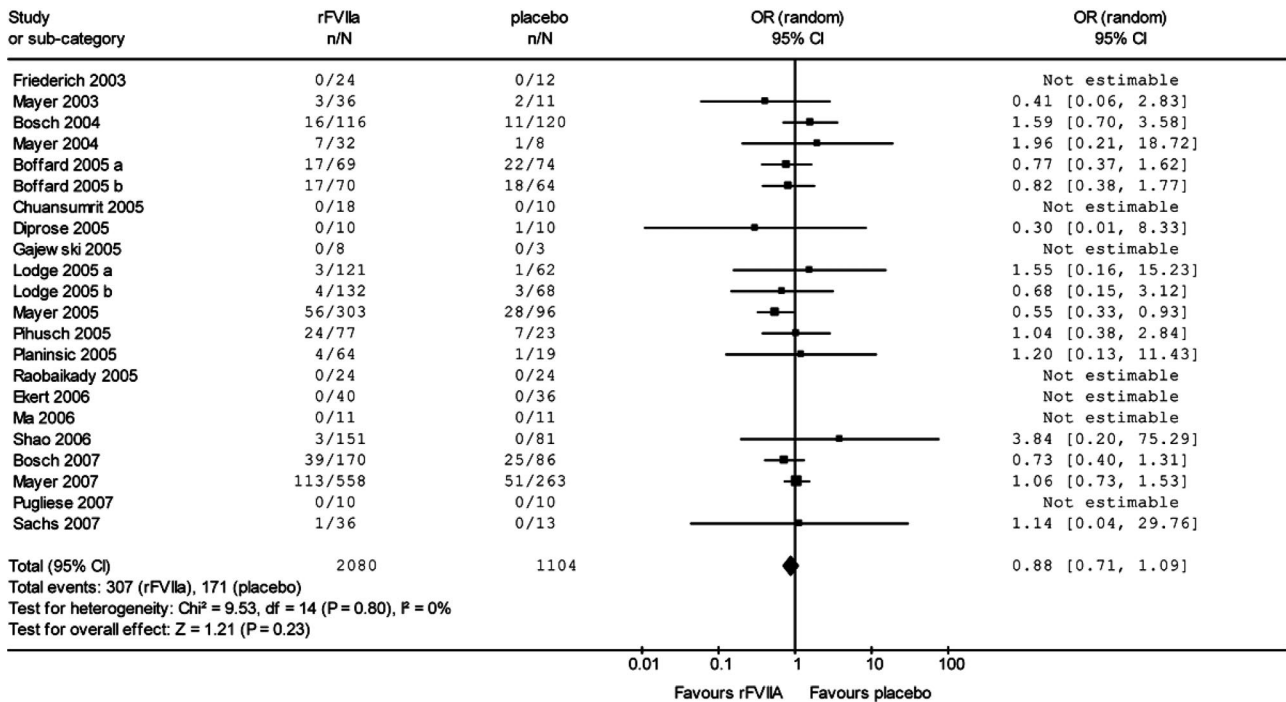


FIGURE 3. Effect of recombinant activated Factor VII compared with placebo on mortality in nonhemophilic patients with hemorrhage.

TABLE 2. Thromboembolic Events in Clinical Trials of Recombinant Activated Factor VII (rFVIIa)

	rFVIIa	Placebo	Fisher Exact Test (2-Tailed)
Arterial thromboembolism—all events	93 (4.5%)	22 (2.0%)	$P < 0.01$
Stroke or transient ischemic attack	29 (1.4%)	9 (0.8%)	$P = 0.17$
Myocardial infarction or ischemia	58 (2.8%)	11 (1.0%)	$P < 0.01$
Arterial thromboembolism—not specified	6 (0.3%)	2 (0.2%)	$P = 0.72$
Venous thromboembolism—all events	65 (3.1%)	43 (3.9%)	$P = 0.25$
Deep vein thrombosis	5 (0.2%)	5 (0.5%)	$P = 0.33$
Pulmonary embolism	4 (0.2%)	3 (0.3%)	$P = 0.70$
Venous thromboembolism—not specified	56 (2.6%)	35 (3.2%)	$P = 0.43$
Thromboembolic events—arterial or venous not specified	20 (1.0%)	6 (0.5%)	$P = 0.30$

but not if administered more often (OR, 0.66; 95% CI, 0.39–1.09). The reduction in transfusion rate was statistically significant if rFVIIa was administered either therapeutically (OR, 0.54; 95% CI, 0.34–0.86) or prophylactically (OR, 0.50; 95% CI, 0.25–0.99). Mortality was more likely to be reduced in the rFVIIa group if it was administered therapeutically (OR, 0.87; 95% CI, 0.70–1.09) versus prophylactically (OR, 1.00; 95% CI, 0.37–2.68) but it was not changed if the dose of rFVIIa was $\leq 90 \mu\text{g/kg}$ (OR, 0.86; 95% CI, 0.64–1.15) versus $>90 \mu\text{g/kg}$ (OR, 0.84; 95% CI, 0.63–1.13).

Sensitivity studies were performed by repeating the meta-analysis using all of the randomized trials including short-term trials of rFVIIa in healthy volunteers. No TAE or other adverse events were reported in the healthy volunteer trials and inclusion of these trials did not alter the outcomes reported above. Inclusion of data from the trauma trials in the additional transfusion data set did not alter outcome when compared with meta-analysis without these data.

DISCUSSION

Recombinant production of the activated form of a human blood clotting factor that can bypass certain deficiencies in coagulation is a remarkable achievement. Recombinant activated factor VII has been licensed for use in hemophilia on the basis of its use in a series of 61 patients with hemophilia A or B and inhibitors undergoing surgery.⁵⁰ Placebo-controlled trials have not been possible in this setting because of a lack of equipoise. However the mechanism of action of rFVIIa is not restricted to patients with hemophilia. The availability of rFVIIa for hemophilia has allowed the tentative extension of its use to patients without hemophilia.⁴³ Concern has been raised about the use of rFVIIa in individuals without hemophilia because it may put patients at considerable risk of thrombosis and death.² Others have suggested that rFVIIa may allow for the inappropriate rescue of patients who might otherwise have died of hemorrhage such

TABLE 3. Subgroup Meta-Analyses: Odds Ratio (95% Confidence Interval) of Outcomes Comparing Recombinant Activated Factor VII to Placebo

	No. Patients Receiving rFVIIa	Mortality	Thromboembolic Events	Additional RBC Transfusion
Stratification—intracerebral hemorrhage trials and all other trials				
Intracerebral hemorrhage trials	929	0.79 (0.48–1.31)	1.25 (0.74–2.12)	Not applicable
Other trials	1151	0.91 (0.71–1.09)	1.11 (0.72–1.71)	0.54 (0.34–0.86)
Stratification according to total dose of recombinant activated FVII				
≤90 μg/kg	1141	0.86 (0.64–1.15)	1.21 (0.83–1.75)	0.42 (0.19–0.93)
>90 μg/kg	939	0.84 (0.63–1.13)	1.25 (0.78–2.01)	0.62 (0.34–1.14)
Stratification according to indication for recombinant activated FVII				
Therapeutic	1493	0.87 (0.70–1.09)	1.13 (0.81–1.59)	0.54 (0.34–0.86)
Prophylactic	587	1.00 (0.37–2.68)	1.33 (0.71–2.49)	0.50 (0.25–0.99)
Stratification according to no. recombinant activated FVII doses given				
Single dose	1204	0.84 (0.63–1.12)	1.20 (0.83–1.74)	0.33 (0.11–0.96)
Multiple doses	876	0.88 (0.71–1.09)	1.13 (0.69–1.86)	0.66 (0.39–1.09)

Review: Recombinant activated factor VII for the control of hemorrhage in patients without hemophilia
 Comparison: 01 Recombinant activated factor VII versus placebo
 Outcome: 02 Patients thromboembolic events

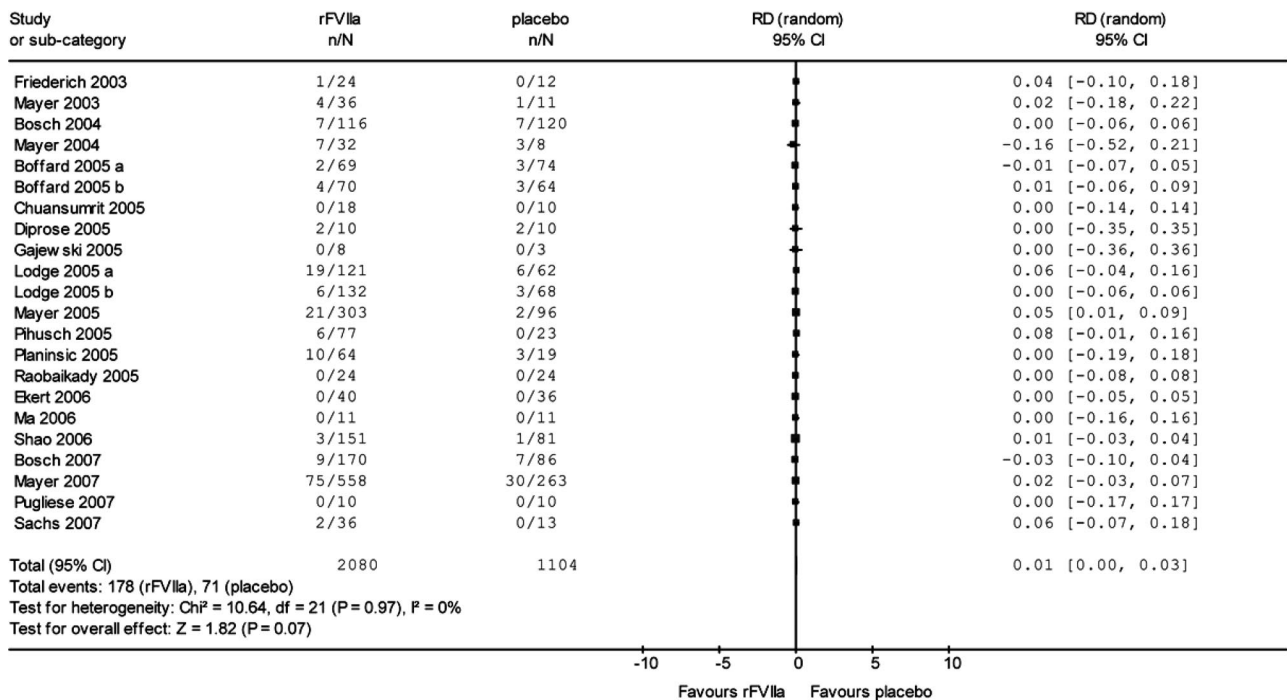


FIGURE 4. Effect of recombinant activated Factor VII compared with placebo on the absolute risk difference of thromboembolic events in nonhemophilic patients with hemorrhage.

as brain-injured survivors of ICH.⁵¹ These concerns have dampened enthusiasm for rFVIIa outside of hemophilia.

The current meta-analysis extends the observations of previous reviews by an additional 9 trials with 1300 patients.^{44,45} It demonstrates that rFVIIa has been subjected to a large number of randomized placebo-controlled trials in a wide variety of clinical situations where nonhemophilic patients were at a high risk of death or injury from hemorrhage. Combined analysis of the trials of rFVIIa can be summarized as showing rFVIIa to be a predictable and potent

promoter of hemostasis that reduces the requirement for transfusion in patients suffering hemorrhage. No advantage appears to be gained by increasing the dose rFVIIa over 90 μg/kg, which is the dose usually given to patients with hemophilia.

This meta-analysis does not exclude the suspicion of the FDA AERS review that rFVIIa is associated with an increased risk of TAE. Thromboembolism and death occurred in both the placebo arm as well as the rFVIIa arm of the trials studied. The absolute risk increase, if it exists,

appears to be approximately 1% (95% CI, 0%-3%; Fig. 4) and confined to arterial thromboembolism. Adverse event reporting is an important method to monitor safety of a product but as noted by the AERS reviewers, registries should not be used to set policy. The AERS review suggested that patients suffering TAE were likely to die, implying an increased risk of death in patients without hemophilia who receive rFVIIa. In none of the subgroups studied here was the risk of death increased by the use of rFVIIa. Although rFVIIa may increase the risk of arterial thromboembolism, it does not increase the mortality rate and it may reduce it. The accumulated evidence from case reports and series of "off-label" usage of rFVIIa provide anecdotal evidence of potential life saving properties of this agent when used in significant life-threatening scenarios.^{11,13} The therapeutic window for rFVIIa is confined by its ability to reduce hemorrhage on one hand and its potential to increase arterial thromboembolism on the other. A wide variety of rFVIIa doses and administration protocols were used in the trials reviewed here. Single use of lower doses of rFVIIa to treat hemorrhage appears to be at least as effective as multiple administrations of large doses to prevent hemorrhage and would be less likely to increase arterial thromboembolism.

Patients with trauma or undergoing surgery were more likely to benefit from rFVIIa than patients with ICH. Initial enthusiasm for rFVIIa after the first large ICH trial was dampened by disappointing results in the second. The discrepancy between the 2 ICH trials was actually because of better survival in the placebo group of 2007 study compared with that of the 2005 study (81% and 71% respectively, Fig. 2).^{27,28}

The evidence from this meta-analysis is not sufficient to endorse unrestricted use of rFVIIa in nonhemophilic patients with hemorrhage. However, it may counter the nihilism that greeted the AERS report and endorse its conclusion, which was that rFVIIa should continue to be tested in nonhemophilic patients. We hope it will inform the design of trials so that the use of this potent agent may be refined. This meta-analysis suggests that one-time therapeutic use of rFVIIa at conventional doses, in patients at high risk of persistent hemorrhage despite standard care, is a strategy to be tested conclusively. Our results indicate that such trials should stratify participants according to their premorbid risk of stroke or myocardial infarction, aim to demonstrate a relative reduction in mortality of 10%-15% and have a sample size of at least 4000 patients if the baseline rate of death is approximately 15% as in this meta-analysis.

REFERENCES

- Hedner U, Kisiel W. Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. *J Clin Invest.* 1983;71:1836-1841.
- O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA.* 2006;295:293-298.
- Hedner U. Treatment of patients with factor VIII and factor IX inhibitors with special focus on the use of recombinant factor VIIa. *Thromb Haemost.* 1999;82:531-539.
- Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired hemophilia with recombinant factor VIIa: a multicentre study. *J Thromb Haemost.* 1997;78:1463-1547.
- Mariani G, Testa MG, Di Paolantonio T, et al. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sang.* 1999;77:131-136.
- Poon MC. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol.* 2001;8:312-318.
- Poon MC, d'Orion R. Recombinant activated factor VII (NovoSeven) treatment of platelet-related bleeding disorders. International registry on recombinant factor VIIa and congenital platelet disorders group. *Blood Coagul Fibrinolysis.* 2000;11:S55-S68.
- Poon MC, d'Orion R, Hann I, et al. Use of recombinant factor VIIa (NovoSeven) in patients with Glanzmann thrombasthenia. *Semin Hematol.* 2001;38:21-25.
- Lisman T, De Groot PHG. Mechanism of action of recombinant factor VIIa. *J Thromb Haemost.* 2003;1:1138-1139.
- Cate H, Bauer KA, Levi M, et al. The activation of factor X and prothrombin by recombinant factor VIIa in vivo is mediated by tissue factor. *J Clin Invest.* 1993;92:1207-1212.
- Kenet G, Walden R, Eldad A, et al. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet.* 1999;354:9193.
- Stein DM, Dutton RP, O'Connor J, et al. Determinants of futility of administration of recombinant factor VIIa in trauma. *J Trauma.* 2005;59:609-615.
- Dutton RP, Hess JR, Scalea TM. Recombinant factor VIIa for control of hemorrhage: early experience in critically ill trauma patients. *J Clin Anesth.* 2003;15:184-188.
- Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma.* 2005;59:8-18.
- Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology.* 2004;127:1123-1130.
- Bosch J, Thabut D, Albillos A, et al. On behalf of the International Study Group on rFVIIa in variceal bleeding. Recombinant factor VIIa (rFVIIa) for active variceal bleeding in patients with advanced cirrhosis: a multi-center randomised double-blind placebo-controlled trial. (Data presented at the 42nd Annual Meeting of the European Association for the Study of the Liver, April 11-15, 2007).
- Chuansumrit A, Wangruangsatid S, Lektrakul Y, et al. Control of bleeding in children with dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. *Blood Coagul Fibrinolysis.* 2005;16:549-555.
- Diprose P, Herbertson MJ, O'Shaughnessy D, et al. Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *Br J Anaesth.* 2005;95:596-602.
- Ekert H, Brizard C, Eyers R, et al. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. *Blood Coagul Fibrinolysis.* 2006;17:389-395.
- Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet.* 2003;361:201-205.
- Ashrani AA, Gabriel DA, Gajewski JL, et al. Pilot study to test the efficacy and safety of activated recombinant factor VII (NovoSeven) in the treatment of refractory hemorrhagic cystitis following high-dose chemotherapy. *Bone Marrow Transplant* 2006;38:825-8. (also see www.clinicalstudyresults.org/documents/company-study_1230_0.pdf)
- Lodge JPA, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transplantation.* 2005;11:973-979.
- Lodge JPA, Jonas S, Oussoultzoglou E, et al. Recombinant coagulation factor VIIa in major liver resection. *Anesthesiology.* 2005;102:269-275.
- Ma B, Wang Z-N, Zhang B-R, et al. Effects of recombinant activated factor VIIa on early recovery after artificial heart valve replacement and cardiopulmonary bypass. *Acad J Sec Mil Med Univ.* 2006;27:1110-1113.

25. Mayer SA, Brun NC, Broderick J, et al; Europe/AustralAsia NovoSeven ICH trial investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74–79.
26. Mayer SA, Brun NC, Broderick J, et al. United States NovoSeven ICH trial investigators. Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care*. 2006;4:206–214.
27. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII intracerebral hemorrhage trial investigators: recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785.
28. Mayer SA, Brun NC, Broderick J, et al. Randomized, placebo-controlled, double-blind phase III study to assess rFVIIa efficacy in acute cerebral hemorrhage: The FAST trial. Presented to XVI European Stroke Conference, Glasgow, UK. May 29–June 1, 2007.
29. Pihusch M, Bacigalupo A, Szer J, et al. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. *J Thromb Haemost*. 2005;3:1935–1944.
30. Planinsic RM, Meer JVD, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transplantation*. 2005;11:895–900.
31. Pugliese F, Ruberto F, Summonti D, et al. Activated recombinant factor VII in orthotopic liver transplantation. *Transplant Proc*. 2007;39:1883–1885.
32. Raobaikady R, Redman J, Ball JAS, et al. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis or pelvis and acetabulum: a double-blind, randomized, placebo-controlled trial. *Br J Anaesth*. 2005;94:586–591.
33. Sachs B, Delacy D, Green J, et al. Recombinant activated factor VII in spinal surgery: a multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial. *Spine*. 2007;32:2285–2293.
34. Shao Y-F, Yang J-M, Chau G-Y, et al. Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Am J Surg*. 2006;191:245–249.
35. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of Recombinant Factor VIIa to Reverse the Anticoagulant Effect of the Pentasaccharide Fondaparinux in Healthy Volunteers. *Circulation*. 2002;106:2550–2554.
36. Bijsterveld NR, Vink R, van Aken BE, et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol*. 2004;124:653–658.
37. Fridberg MJ, Hedner U, Roberts HR, et al. A study of the pharmacokinetics and safety of recombinant activated factor VII in healthy Caucasian and Japanese subjects. *Blood Coagul Fibrinolysis*. 2005;16:259–266.
38. Wolzt M, Levi M, Sarich TC, et al. Effect of recombinant factor VIIa on melagatran-induced inhibition of thrombin generation and platelet activation in healthy volunteers. *Thromb Haemost*. 2004;91:1090–1096.
39. Jilma B, Marsik C, Mayr F, et al. Pharmacodynamics of active site-inhibited factor VIIa in endotoxin-induced coagulation in humans. *Clin Pharmacol Ther*. 2002;72:403–410.
40. Erhardtsen E, Nilsson P, Johannessen M, et al. Pharmacokinetics and safety of FFR-rFVIIa after single doses in healthy subjects. *J Clin Pharmacol*. 2001;41:880–885.
41. Jeffers L, Chalasani N, Balart L, et al. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology*. 2002;123:118–126.
42. Iorio A, Marchesini E, Falco A, et al. Randomised, open, prospective, multicenter pilot study to evaluate the efficacy and safety of activated recombinant Factor VIIa (Novoseven) in acute intracerebral haemorrhage in patients treated with oral anticoagulant or antiplatelet agents. ClinicalTrials.gov Identifier: NCT00222625.
43. Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion*. 2002;42:114–124.
44. Levi M, Peters M, Büller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med*. 2005;33:883–890.
45. Stanworth SJ, Birchall J, Doree CJ, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev*. 2007;2:CD005011.
46. RevMan Analysis 4. 2 for Windows. 2003 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.
47. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet*. 1999;354:1896–1900.
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
49. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.
50. European Medicines Agency. Public Assessment Report: Initial scientific discussion for the approval of Novoseven. 1996 <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Novoseven/072995en6.pdf> (accessed November 27, 2007).
51. Greenberg SM. Is “compassionate use” compassionate?: rFVIIa for intracerebral hemorrhage. *Neurology*. 2006;67:934–935.