Use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without hemophilia: a systematic review and meta-analysis

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Abstract

Background: The benefits and risks of off-label use of recombinant factor VIIa in patients without hemophilia are contested. We performed a systematic review to assess the effectiveness and safety of such use.

Methods: We searched electronic databases including MEDLINE, EMBASE and CENTRAL for randomized controlled trials comparing recombinant factor VIIa with placebo in any patient population except those with hemophilia up to January 2010. Eligible articles were assessed for inclusion, data were extracted, and study quality was evaluated. Outcomes included mortality, blood loss, requirements for red blood cell transfusion, number of patients transfused and thromboembolic events.

Results: We identified 26 trials: 14 on off-label prophylactic use of recombinant factor VIIa (n = 1137) and 12 on off-label therapeutic use (n = 2538). In the studies on prophylactic use, we found no significant difference in mortality or thromboembolic events between the treatment and placebo groups. We found modest benefits favouring recombinant factor VIIa in blood loss (weighted mean difference –276 mL, 95% confidence interval [CI] –411 to –141 mL), red blood cell transfusion (weighted mean difference –281 mL, 95% CI –433 to –129 mL) and number of patients transfused (relative risk 0.71, 95% CI 0.50 to 0.99). In the therapeutic trials, we found a nonsignificant decrease in mortality and a nonsignificant increase in thromboembolic events but no difference in control of bleeding or red blood cell transfusion.

Interpretation: Clinically significant benefits of recombinant factor VIIa as a general hemostatic agent in patients without hemophilia remain unproven. Given its potential risks, such use cannot be recommended, and in most cases, it should be restricted to clinical trials.

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Recombinant factor VIIa is a hemostatic agent licensed for the treatment of bleeding in patients with hemophilia who have inhibitors. It is also used off-label for the prevention and treatment of bleeding in patients without hemophilia.

In the Australian and New Zealand Haemostasis Registry, use of recombinant factor VIIa increased to a plateau in 2006, which was maintained through 2008.[1] Because only 1% of the 2700 patients in this registry had a diagnosis of hemophilia, physicians may believe that off-label use of this agent is effective and outweighs the risks. Randomized controlled trials (RCTs) evaluating recombinant factor VIIa have raised concerns about adverse effects, particularly thromboembolic events.[2–7] These concerns have been supported by passive surveillance reports from the US Food and Drug Administration's Adverse Event Reporting System, which suggest an increased risk among unselected patients.[8] In addition, although cost is but one component, at a dose of 80 μg/kg for a 70-kg patient, the approximate cost of 5.6 mg of recombinant factor VIIa would be $6270 in Canada (Chantal Couture, Canadian Blood Services, Ottawa, Ont.: personal communication, 2010) and £2800 in the United Kingdom. By contrast, the current cost of one unit of red blood cells is $419 in Canada (Marcel Leclair, Finance, Canadian Blood Services, Ottawa, Ont.: personal communication, 2010) and £133 in the United Kingdom (Julie Staves, National Health Service Blood and Transplant, Hertfordshire, UK: personal communication, 2010).

We conducted a systematic review and meta-analysis of the effectiveness and risks of recombinant factor VIIa in patients without hemophilia and assessed the implications of these results for future research.

Methods

Literature search

We searched the following bibliographic databases on Jan. 18, 2010: MEDLINE, EMBASE, CENTRAL (*The Cochrane Library* Issue 4,

2009), CINAHL, the UK Blood Transfusion and Tissue Transplantation Services Transfusion Evidence Library, LILACS, KoreaMed, IndMed, PakMediNet, mRCT, ClinicalTrials.gov and the World Health Organization's ICTRP Database (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100408/DC1). The search was not restricted by language, but we included only published, full-text versions of RCTs. We also checked the reference lists of the identified RCTs and recently published systematic reviews.[4,9–13]

Study selection

We included RCTs comparing recombinant factor VIIa with no treatment, an alternative treatment or different doses of recombinant factor VIIa in patients without hemophilia. We excluded RCTs involving patients with congenital bleeding disorders or healthy volunteers. Two of us (Y.L. and S.S.) independently screened all of the citations, including the titles and abstracts, and reviewed the full text of citations considered relevant.

Outcomes

We divided the RCTs into two groups: prophylactic use and therapeutic use. In the prophylactic group, recombinant factor VIIa was given to prevent anticipated bleeding, for example during an operation; in the therapeutic group, the agent was given to treat bleeding that was already established. For the studies of prophylactic use, the outcomes included mortality, total blood loss, use of red blood cell transfusion (measured in millilitres), number of patients receiving transfusions and number of thromboembolic events. Thromboembolic events included any reported arterial event (increased troponin level, myocardial infarction or ischemia, stroke and "other") or venous event (deep vein thrombosis, pulmonary embolus, thrombophlebitis and "other"). For studies of therapeutic use, the same outcomes were used, except control of bleeding was measured instead of total blood loss.

Details on risk of bias (random sequence generation, concealment of allocation, blinding, loss to follow-up and power calculation) were collected. Two of us (Y.L., S.S. or J.B.) independently extracted data using a predesigned form; disagreements were resolved by consensus.

Statistical analysis

The meta-analysis was conducted using the random-effects model, decided a priori, because of the marked clinical heterogeneity. We performed a subgroup analysis in which low-dose therapy was defined as less than 80 μg/kg and standard or high-dose therapy was defined as 80 μg/kg or more. Because there was minimal difference in results between these groups, we present only combined results.

Data were combined using the Mantel–Haenszel method for dichotomous outcomes and inverse variance for continuous outcomes. Pooled estimates were reported as relative risks (RRs) for dichotomous data (e.g., mortality) and weighted mean differences for continuous data (e.g., transfusion requirements). A unit of red blood cells was assumed to be 300 mL. Statistical heterogeneity was examined using the I^2 statistic and visual inspection of graphs. Heterogeneity was explored post hoc using study size (< 50 v. ≥ 50 patients), concealment of allocation (adequate v. unclear or inadequate) and transfusion protocol (present v. absent).

Results

We identified 449 records through the literature search, from which 26 RCTs were included in the final analysis (Figure 1). The report by Boffard and coauthors was considered as two separate trials in blunt and penetrating trauma.[14]

Study and patient characteristics

Of the 26 RCTs, 14 were of the prophylactic use of recombinant factor VIIa, with study samples of 18 to 235 patients (Table 1). (Tables 1–4 can be found at the end of the article.) The clinical settings included cardiopulmonary bypass surgery,[15–18] liver biopsy,[19] hepatic resection,[20,21] liver transplantation,[22–24] traumatic pelvic fracture,[25] spinal surgery,[26] radical prostatectomy[27] and skin excision following burns.[28] Dosing regimens varied from a single dose of 5 μg/kg to multiple doses totalling 360 μg/kg.[22,26] The primary outcomes were predominantly blood loss,[25–27] red blood cell transfusion[16,21–23,27,28] and number of patients receiving allogeneic transfusion.[15,20,21] Protocols for transfusion were reported in 8 of 11 RCTs. The main criterion for excluding patients was prior thromboembolic or vascular disease. Active surveillance for adverse events occurred in five studies.[20–23,27]

Twelve RCTs were of the therapeutic use of recombinant factor VIIa, with sample sizes ranging from 28 to 400 patients (Table 2). The clinical settings included trauma,[14] cirrhosis with upper gastrointestinal bleeding,[29,30] bleeding after cardiac surgery,[31] dengue hemorrhagic fever,[32] bleeding after hematopoietic stem-cell transplant,[33] spontaneous intracranial hemorrhage[3,34–36] and traumatic intracranial hemorrhage.[37] Dosing regimens varied from a single dose of 5 μg/kg[36] to multiple doses totalling 1120 μg/kg.[33] The primary outcomes included control of bleeding,[29,30,32,33,35] transfusion requirements,[14] adverse events[31,34,36,37] and, in one study of intracranial hemorrhage, a clinical com-

bined outcome of severe disability or death.[3] Common exclusion criteria were history of clotting and hemorrhagic diathesis. Transfusion protocols were not required in the studies of intracranial hemorrhage and were described in four of the remaining seven studies; specifically, they were not described in the two trauma studies in which the primary outcome was transfusion requirement.[14]

Study quality

Overall, most of the 26 RCTs had some potential threats to validity (Table 3), primarily because of the lack of detail provided in the report. Sequence generation was adequate in 13 trials, allocation concealment was adequate in 7, and blinding was adequate in 16 studies. A power calculation was performed and the target sample size was achieved in only 10 studies. Most of the studies (8 of the 14 prophylactic trials and all 12 of the therapeutic studies) were either supported by NovoNordisk (the manufacturer of recombinant factor VIIa) or were coauthored by an employee of NovoNordisk.

Outcomes

Prophylactic use

The pooled RR for mortality was 0.82 (95% confidence interval [CI] 0.36 to 1.83; I^2 = 0%). The individual results from the 13 studies that provided mortality data had a 95% CI that included 1.0 (Figure 2). Rates of death in the placebo groups were generally low across all studies, the maximum being 3/9.[28]

Eight studies contributed data on blood loss. The pooled weighted mean difference was −276 mL (276 mL less blood loss in the recombinant factor VIIa arms; 95% CI −411 to −141 mL) (Table 4). This finding is likely to be an overestimate of the effect of recombinant factor VIIa, since four studies reporting no difference could not be incorporated into the pooled analysis because outcomes were not available as means and standard deviations.[16,21,23,25] Also, there was important statistical heterogeneity (I^2 = 78%); when we excluded studies with fewer than 50 patients, the I^2 value was 0%.

Ten studies provided data on the use of red blood cell transfusion. The pooled weighted mean difference between the treatment and control arms was −281 mL (95% CI −433 to −129 mL) (Table 4). This finding is again likely to be an overestimate of the effect of recombinant factor VIIa since three studies reporting no difference could not be incorporated into the pooled analysis because outcomes were not available as means and standard deviations.[16,21,25] There was evidence of significant heterogeneity (I^2 = 63%); when we excluded studies with fewer than 50 patients, the I^2 value was 0%.

Seven studies reported and contributed data on the number of patients who received transfusions. The pooled RR was 0.71 (95% CI 0.50 to 0.99), with marked heterogeneity (I^2 = 61%) (Table 4). The proportion of patients who received transfusions in the control arms ranged from 37%[20] to 100%.[22]

Twelve studies contributed data on thromboembolic events. The pooled RR was 1.38 (95% CI 0.76 to 2.51; I^2 = 0%). The 95% CIs in the individual studies all included 1.0 (Figure 3). Rates of thromboembolic events in the control groups were generally low across the studies, the maximum being 2/10.[15]

Therapeutic use

All 12 studies contributed data on mortality. The pooled RR for overall mortality was 0.90 (95% CI 0.76 to 1.06), with no statistical heterogeneity (I^2 = 0%) (Figure 2). All but one of the studies (the initial efficacy trial in spontaneous intracranial hemorrhage) yielded an RR with a 95% CI that included 1.0.[35] The rates of death in the control groups varied from 0/9[32] to 22/74 (30%).[14]

Nine trials reported on the control of bleeding. Four of them had data suitable for inclusion in

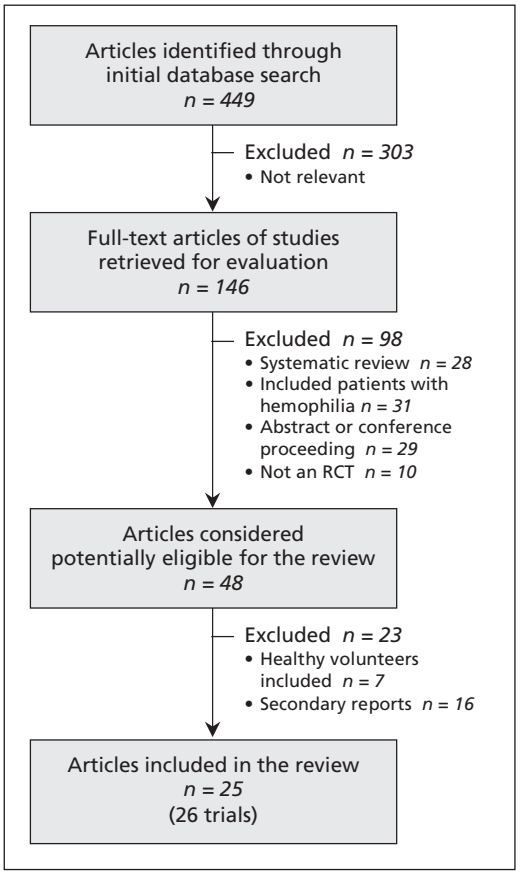


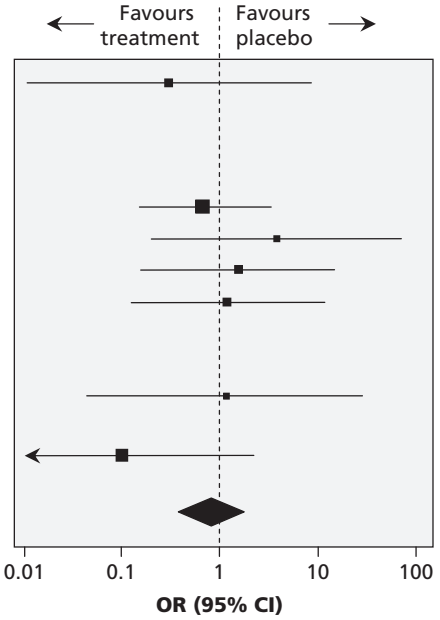
Figure 1: Selection of randomized controlled trials (RCTs).

the pooled analysis.[29,30,32,33] The pooled RR was 1.05 (95% CI 0.97 to 1.14; I^2 = 0%) (Table 4). The five remaining trials were of therapeutic use of recombinant factor VIIa in intracranial hemorrhage; they measured control of bleeding in terms of hematoma growth, which could not be combined quantitatively.[3,34–37] None of the safety trials[34,36,37] showed a significant reduction in their secondary outcomes of growth of volume of hemorrhage. The initial efficacy study reported a statistically significant reduction in the growth of hemorrhage volume with recombinant factor VIIa associated with reduced disability at 90 days;[35] however, the second, larger, efficacy trial[3] found no significant difference between study groups in the primary outcome at 90 days.

Only four studies contributed data on the use of red blood cell transfusion.[29–32] The pooled weighted mean difference was 21 mL (95% CI −108 to 150; I^2 = 0%) (Table 4). The 95% CIs in

Prophylactic use

Study	Treatment *n/N*	Placebo *n/N*	OR (95% CI)
Diprose et al.[15]	0/10	1/10	0.30 (0.01–8.33)
Ekert et al.[16]	0/40	0/36	–*
Ma et al.[17]	0/11	0/11	–*
Essam[18]	0/15	0/15	–*
Lodge et al.[20]	4/132	3/68	0.68 (0.15–3.12)
Shao et al.[21]	3/151	0/81	3.84 (0.20–75.29)
Lodge et al.[22]	3/121	1/62	1.55 (0.16–15.23)
Planinsic et al.[23]	4/64	1/19	1.20 (0.13–11.43)
Pugliese et al.[24]	0/10	0/10	–*
Raobaikady et al.[25]	0/24	0/24	–*
Sachs et al.[26]	1/36	0/13	1.14 (0.04–29.76)
Friederich et al.[27]	0/24	0/12	–*
Johansson et al.[28]	0/9	3/9	0.10 (0.00–2.23)
Overall	15/647	9/370	0.82 (0.36–1.83)



Therapeutic use

Study	Treatment *n/N*	Placebo *n/N*	RR (95% CI)
Mayer et al.[3]	112/557	51/262	1.03 (0.77–1.39)
Boffard et al.[14]	17/69	22/74	0.83 (0.48–1.42)
Boffard et al.[14]	17/70	18/64	0.86 (0.49–1.53)
Bosch et al.[29]	16/116	11/120	1.50 (0.73–3.10)
Bosch et al.[30]	39/170	25/86	0.79 (0.51–1.21)
Gill et al.[31]	10/104	4/68	1.63 (0.53–5.00)
Chuansumrit et al.[32]	0/16	0/9	–*
Pihusch et al.[33]	24/77	7/23	1.02 (0.51–2.07)
Mayer et al.[34]	3/36	2/11	0.46 (0.09–2.40)
Mayer et al.[35]	56/303	28/96	0.63 (0.43–0.94)
Mayer et al.[36]	7/32	1/8	1.75 (0.25–12.26)
Narayan et al.[37]	7/61	4/36	1.03 (0.32–3.29)
Overall	308/1611	173/857	0.90 (0.76–1.06)

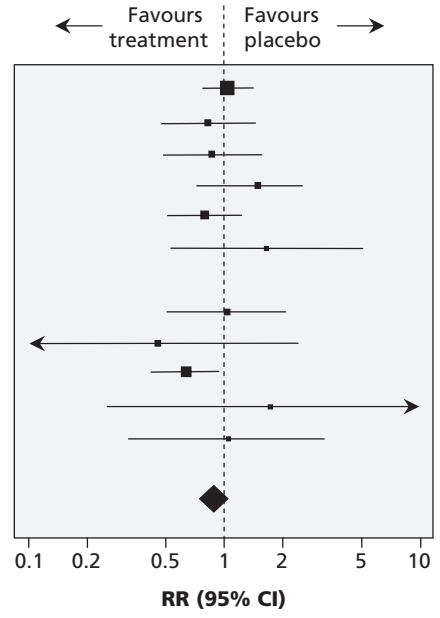


Figure 2: Pooled analysis of mortality data from randomized controlled trials of the prophylactic use (top panel) and therapeutic use (bottom panel) of recombinant factor VIIa in patients without hemophilia. A value below 1.0 indicates a decreased risk of death with recombinant factor VIIa. *Not estimable. CI = confidence interval, OR = odds ratio, RR = risk ratio.

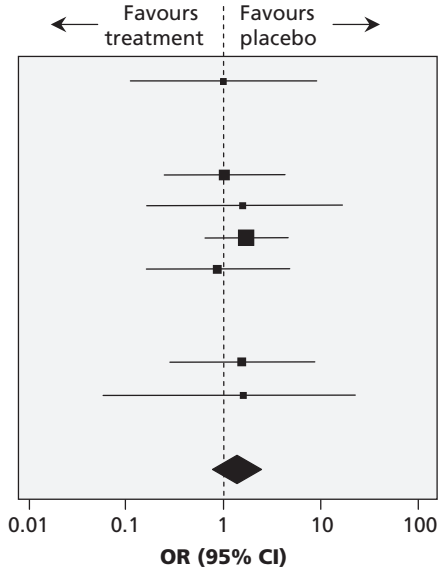
each of the four studies included zero (no difference). Because data from the RCT by Boffard and colleagues[14] were reported as medians and ranges, we could not incorporate them into the pooled analysis. The exclusion of these studies likely did not change the pooled weighted mean difference, because there was no significant difference in the primary outcome of number of units of red blood cells transfused for all patients at 48 hours.

Two of the 12 studies contributed data on the number of patients who received transfusions.[31,32] The pooled RR was 0.81 (95% CI 0.70 to 0.93; I^2 = 0%) (Table 4). For the trial of therapeutic use in the setting of cardiac surgery,[31] we used the number of patients who received transfusions within five days; this outcome favoured recombinant factor VIIa, as compared with the cut-off of 24 hours, which did not show a statistically significant difference between the study groups.

All of the trials of therapeutic use contributed data on thromboembolic events. The pooled RR was 1.18 (95% CI 0.86 to 1.62; I^2 = 0%) (Figure 3). The 95% CIs of the individual studies all included 1.0. Rates of thromboembolic events in the control groups were generally low across all studies, the maximum being 3/8.[36]

Prophylactic use

Study	Treatment *n/N*	Placebo *n/N*	OR (95% CI)
Diprose et al.[15]	2/10	2/10	1.00 (0.11–8.95)
Ekert et al.[16]	0/40	0/36	–*
Ma et al.[17]	0/11	0/11	–*
Lodge et al.[20]	6/132	3/68	1.03 (0.25–4.26)
Shao et al.[21]	3/151	1/81	1.62 (0.17–15.85)
Lodge et al.[22]	19/121	6/62	1.74 (0.66–4.60)
Planinsic et al.[23]	6/64	2/19	0.88 (0.16–4.76)
Pugliese et al.[24]	0/10	0/10	–*
Raobaikady et al.[25]	0/24	0/24	–*
Sachs et al.[26]	8/36	2/13	1.57 (0.29–8.60)
Friederich et al.[27]	1/24	0/12	1.60 (0.06–42.13)
Johansson et al.[28]	0/9	0/9	–*
Overall	45/632	16/355	1.38 (0.76–2.51)



Therapeutic use

Study	Treatment *n/N*	Placebo *n/N*	RR (95% CI)
Mayer et al.[3]	55/558	21/263	1.23 (0.76–2.00)
Boffard et al.[14]	2/69	3/74	0.71 (0.12–4.15)
Boffard et al.[14]	4/70	3/64	1.22 (0.28–5.24)
Bosch et al.[29]	7/121	7/121	1.00 (0.36–2.76)
Bosch et al.[30]	9/176	7/89	0.65 (0.25–1.69)
Gill et al.[31]	7/104	1/68	4.58 (0.58–36.38)
Chuansumrit et al.[32]	0/16	0/9	–*
Pihusch et al.[33]	8/77	0/23	5.23 (0.31–87.34)
Mayer et al.[34]	5/36	1/11	1.53 (0.20–11.73)
Mayer et al.[35]	21/303	2/96	3.33 (0.79–13.93)
Mayer et al.[36]	7/32	3/8	0.58 (0.19–1.77)
Narayan et al.[37]	13/61	5/36	1.53 (0.60–3.95)
Overall	138/1623	53/862	1.18 (0.86–1.62)

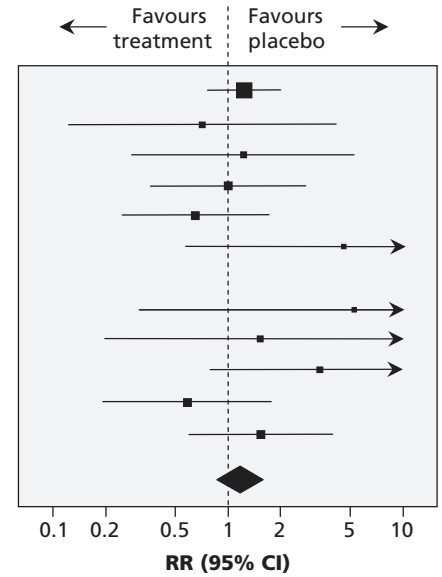


Figure 3: Pooled analysis of data on thromboembolic events from randomized controlled trials of the prophylactic use (top panel) and therapeutic use (bottom panel) of recombinant factor VIIa in patients without hemophilia. A value below 1.0 indicates a decreased risk of thromboembolic event with recombinant factor VIIa. *Not estimable. CI = confidence interval, OR = odds ratio, RR = risk ratio.

Publication bias

Funnel plots for the above outcomes did not show marked asymmetry (data not shown). The funnel plot for number of patients who received transfusions in the prophylactic trials suggested that small studies with an RR greater than 1.0 (favouring placebo) may be missing.

Interpretation

We included 14 RCTs on the prophylactic use ($n = 1137$) and 12 on the therapeutic use ($n = 2538$) of recombinant factor VIIa in patients without hemophilia in our review. This number of trials might be considered to be sufficient for an informative result. However, the results indicated continuing uncertainty about the magnitude of benefits and harms. In the prophylactic studies, only modest benefits favouring recombinant factor VIIa were seen in the outcomes of blood loss, requirements of red blood cell transfusion (equivalent to less than one unit of red blood cells saved) and number of patients receiving transfusions. In the therapeutic studies, there was no clear advantage of recombinant factor VIIa over placebo for the outcomes of mortality, control of bleeding and transfusion requirements. However, for mortality, the 95% CI was close to significance and may be considered clinically important (RR 0.90; 95% CI 0.76 to 1.06). In both groups of trials, there was a trend toward increased thromboembolic events, although most RCTs excluded patients with a history of thromboembolic events. Promising results in earlier therapeutic studies were not replicated in larger trials,[3,30,38] and the risk of bias assessment highlighted frequent problems in randomization, blinding and sample size.

Continued lack of clarity about the overall clinical effectiveness certainly stems from recombinant factor VIIa being genuinely less effective than was originally predicted. The trials in our review were undertaken across diverse clinical settings where different complex hemostatic pathways operate, and the expectation that recombinant factor VIIa would reverse all coagulopathy is inappropriate.[12]

The findings of our review are similar to those of a recent appraisal by Hsia and colleagues.[4] However, we grouped the RCTs by how recombinant factor VIIa was used (prophylactic or therapeutic), because the expectations of benefit and acceptance of risk in these two situations are different. This separation and greater attention to the risk of bias in the included stud ies has emphasized the degree of uncertainty about effectiveness of off-label use of recombinant factor VIIa.

Our review raises challenges for future research assessing hemostatic agents, particularly concerning the choice of outcomes. Blood loss and control of bleeding are difficult to record in a standardized manner. Transfusion protocols should be supplied. The presence of a protocol was shown to decrease the effect of an intervention, as measured by reduction in use of allogeneic blood, compared with studies that had no transfusion protocol.[39–41] In the studies included in our review, transfusion protocols were not always provided, and even less frequently were protocols reported for hemostatically active co-interventions such as plasma and platelet products (Tables 1 and 2). Mortality is the key outcome for therapeutic trials. However, in our review, we found that the baseline risk of death in the control groups ranged from 0% to 30%, with a mean of 20%. If we assumed a baseline risk of 20% and designed a superiority trial with an α level of 0.05 and β level of 0.20 and an expected RR of 0.90 (equivalent to a mortality of 18% in the treatment group), the trial would require about 12 000 patients to detect this difference. The cumulative number of participants evaluated to date in therapeutic trials is less than a quarter of this number.

Limitations

We were not able to obtain additional outcome data from some studies to allow them to be included in the pooled analyses. These studies generally showed no difference between recombinant factor VIIa and placebo; therefore, their inclusion might be expected to move values further toward a no-difference summary estimate. In addition, we included only published full-text articles. Although publication bias was investigated and has been previously explored,[7] it is impossible to completely exclude it.

Conclusion

Clinically significant benefits of recombinant factor VIIa as a general hemostatic agent in patients without hemophilia remain unproven. Our systematic review did not show a consistent benefit of off-label use of recombinant factor VIIa in the therapeutic setting and at best only modest benefits in the prophylactic setting. Given its potential risks, off-label use of this hemostatic agent cannot be recommended, and in most instances, it should be restricted to clinical trials.

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Table 1: Characteristics of randomized controlled trials of the prophylactic use of recombinant factor VIIa in patients without hemophilia (part 1 of 2)

Study	Study population	No. of initial patients (treatment/ control)	Dose of recombinant factor VIIa	Control	Transfusion protocol	Primary outcome	Secondary outcomes
Diprose et al.[15]	Cardiac surgery	20 (10/10)	Single dose of 90 μg/kg after protamine	Saline	Transfusion if hemoglobin < 85 g/L	No. of patients receiving allogeneic transfusion	Blood products transfused; length of stay; adverse events
Ekert et al.[16]	Cardiac surgery (infants)	82 (36/40)	Single dose of 40 μg/kg after protamine; dose repeated up to 2 times if ongoing bleeding	Placebo	Not stated	Time to chest closure after reversal of heparin	Blood loss within 12 h; blood products transfused within 48 h
Ma et al.[17]	Cardiac surgery	22 (11/11)	Single dose of 40 μg/kg after protamine	Placebo	Not stated	No stated primary outcome	Blood loss within 24 h; blood products transfused
Essam[18]	Cardiac surgery	30 (15/15)	Single dose of 90 μg/kg after protamine	No rVIIa	Transfusion if hemoglobin < 70 g/L	No stated primary outcome	Blood loss within 24 h; blood products transfused within 24 h; length of stay
Jeffers et al.[19]	Liver biopsy	66 (66/0)	Single dose of 5, 20, 80 or 120 μg/kg	No control group	Not stated	Time to hemostasis and duration of normal prothrombin time	Adverse events
Lodge et al.[20]	Partial hepatectomy	204 (112/63)	20 or 80 μg/kg; second dose at 5 h if operation ongoing	Placebo	Transfusion if hematocrit < 25% and platelet count $< 30 \times 10^9$/L	No. of patients receiving allogeneic transfusion within 48 h	Blood loss during surgery; red blood cells transfused within 48 h; adverse events
Shao et al.[21]	Partial hepatectomy	235 (145/76)	50 or 100 μg/kg; dose repeated every 2 h until end of surgery (maximum 4 doses)	Placebo	Transfusion if blood loss > 500 mL	No. of patients receiving allogeneic transfusion within 48 h; units of red blood cells transfused within 48 h	Blood loss during surgery; blood products transfused within 48 h; length of stay; adverse events
Lodge et al.[22]	Liver transplantation	209 (121/61)	60 or 120 μg/kg; dose repeated every 2 h until end of surgery	Placebo	Transfusion if hematocrit < 25%, platelet count $< 30 \times 10^9$/L and coagulation ratios > 1.5 × normal	Units of red blood cells transfused within 24 h	Blood products transfused within 24 h; blood loss within 24 h; length of stay; adverse events
Planinsic et al.[23]	Liver transplantation	87 (54/19)	Single dose of 20, 40 or 80 μg/kg	Placebo	Transfusion if hematocrit < 25%, platelet count $< 30 \times 10^9$/L and coagulation ratios > 1.5 × normal	Units of red blood cells transfused within 24 h	Blood products transfused within 24 h; blood loss within 24 h; length of stay; adverse events
Pugliese et al.[24]	Liver transplantation	20 (10/10)	Single dose of 40 μg/kg	Placebo	Transfusion if hemoglobin < 100 g/L and INR > 1.5	No stated primary outcome	Blood products transfused during surgery; blood loss during surgery
Raobaikady et al.[25]	Reconstructive surgery for traumatic pelvic fractures	48 (12/12)	90 μg/kg; second dose at 2 h if ongoing bleeding	Placebo	Transfusion if hemoglobin < 80 g/L, platelet count $< 100 \times 10^9$/L and coagulation ratios > 1.5 × normal	Blood loss within 48 h	Blood products transfused within 48 h; no. of patients receiving allogeneic transfusion within 48 h; length of stay; adverse events within 30 d; duration of surgery

Table 1: Characteristics of randomized controlled trials of the prophylactic use of recombinant factor VIIa in patients without hemophilia (part 2 of 2)

Study	Study population	No. of initial patients (treatment/ control)	Dose of recombinant factor VIIa	Control	Transfusion protocol	Primary outcome	Secondary outcomes
Sachs et al.[26]	Spinal fusion surgery	60 (36/13)	30, 60 or 120 μg/kg; given at dosing trigger and repeated at 2 h and 4 h	Placebo	Transfusion if hemoglobin < 90 g/L, platelet count < 75×10^9/L and coagulation ratios > 1.5 × normal	Adverse events within 30 d; blood loss during surgery	Blood products transfused during surgery; duration of surgery
Friederich et al.[27]	Retropubic prostatectomy	36 (24/12)	Single dose of 20 or 40 μg /kg	Saline	Transfusion if hemoglobin < 80 g/L intraoperatively and < 100 g/L postoperatively	Blood loss within 24 h; blood products transfused	Length of stay; adverse events; duration of surgery
Johansson et al.[28]	Skin excision and grafting	18 (9/9)	40 μg /kg; second dose at 90 min	Placebo	Transfusion if hemoglobin < 100 g/d, platelet count < 80×10^9/L; transfuse fresh frozen plasma in 1:1 ratio to red blood cells for microvascular bleeding	Blood products transfused within 24 h	Length of stay; mortality at 30 d; postoperative complications; duration of surgery

Note: INR = international normalized ratio, rVIIa = recombinant factor VIIa.

Table 2: Characteristics of randomized controlled trials of the therapeutic use of recombinant factor VIIa in patients without hemophilia (part 1 of 2)

Study	Study population	No. of initial patients (treatment/ control)	Dose of recombinant factor VIIa	Control	Transfusion protocol	Primary outcome	Secondary outcomes
Boffard et al.[14]*	Blunt trauma	158 (69/74)	200 μg/kg initially; 100 μg/kg at 1 and 3 h	Placebo	Not stated	Units of red blood cells transfused within 48 h	Blood products transfused within 48 h; mortality at 30 d; length of stay; adverse events within 30 d
Boffard et al.[14]*	Penetrating trauma	143 (70/64)	200 μg/kg initially; 100 μg/kg at 1 and 3 h	Placebo	Not stated	Units of red blood cells transfused within 48 h	Blood products transfused within 48 h; mortality at 30 d; length of stay; adverse events within 30 d
Bosch et al.[29]	Upper gastrointestinal bleeding and cirrhosis	245 (121/121)	100 μg/kg; repeated at 2, 4, 6, 12, 18, 24 and 30 h	Placebo	Transfusion to maintain hematocrit at 25%–30%	Combined outcome of control of bleeding or rebleeding or death at 5 d	Mortality at 5 and 42 d; units of red blood cells transfused within 5 d; length of stay; adverse events within 42 d
Bosch et al.[30]	Upper gastrointestinal bleeding and cirrhosis	265 (170/86)	200 μg/kg; repeated at 2, 8, 14 and 20 h, or repeated only at 2 h	Placebo	Transfusion to maintain hematocrit at 25%–30% and if platelet count < 30×10^9/L	Combined outcome of control of bleeding or rebleeding or death at 5 d	Mortality at 5 and 42 d; units of red blood cells transfused within 5 d; length of stay; adverse events within 42 d

Table 2: Characteristics of randomized controlled trials of the therapeutic use of recombinant factor VIIa in patients without hemophilia (part 2 of 2)

Study	Study population	No. of initial patients (treatment/ control)	Dose of recombinant factor VIIa	Control	Transfusion protocol	Primary outcome	Secondary outcomes
Gill et al.[31]	Post cardiac surgery	179 (104/68)	Single dose of 40 or 80 μg/kg on reaching prespecified bleeding trigger	Placebo	Transfusion if hemoglobin < 80 g/L; if bleeding, transfusion if INR > 1.5, platelet < 75×10^9/L and fibrinogen < 0.7 g/L	Adverse events within 30 d	Blood loss at 4 h, 24 h and 5 d; blood products transfused within 5 d; reoperation within 30 d
Chuansumrit et al.[32]	Dengue hemorrhagic fever (children)	28 (18/10)	100 μg/kg; dose repeated at 30 min if ongoing bleeding	Placebo	Not stated	Change in bleeding at 24 h	Blood products transfused within 24 h; adverse events within 24 h
Pihusch et al.[33]	Post hematopoietic stem-cell transplantation	100 (77/23)	40, 80 or 160 μg/kg; dose repeated every 6 h × 6	Placebo	Transfusion if hemoglobin < 80 g/L and platelet count < 20×10^9/L (< 75×10^9/L in hemorrhagic cystitis or diffuse alveolar hemorrhage)	Change in bleeding at 38 h	Blood products transfused within 96 h; adverse events within 96 h
Mayer et al.[34]	Spontaneous intracranial hemorrhage	48 (36/12)	Single dose of 10, 20, 40, 80, 120 or 160 μg/kg	Placebo	Not stated	Adverse events within 90 d	Change in volume of intracranial hemorrhage at 24 h; neurologic status at 5 d; disability at 90 d; mortality at 90 d
Mayer et al.[35]	Spontaneous intracranial hemorrhage	400 (303/96)	Single dose of 40, 80 or 160 μg/kg	Placebo	Not stated	Change in volume of intracranial hemorrhage at 24 h	Disability at 90 d; mortality at 90 d; adverse events within 90 d
Mayer et al.[36]	Spontaneous intracranial hemorrhage	41 (32/8)	Single dose of 5, 20, 40 or 80 μg/kg	Placebo	Not stated	Adverse events within 90 d	Change in volume of intracranial hemorrhage at 24 h; neurologic status at 5 d; disability at 90 d; mortality at 90 d
Mayer et al.[3]	Spontaneous intracranial hemorrhage	841 (558/263)	Single dose of 20 or 80 μg/kg	Placebo	Not stated	Severe disability or death within 90 d	Change in volume of intracranial hemorrhage at 24 and 72 h; disability at 90 d; adverse events at 90 d
Narayan et al.[37]	Traumatic intracranial hemorrhage	97 (61/36)	Single dose of 40, 80, 120, 160 or 200 μg/kg	Placebo	Not stated	Adverse events within 15 d	Change in volume of intracranial hemorrhage at 24 and 72 h; disability at 15 d

Note: INR = international normalized ratio.
*The report by Boffard and coauthors was considered as two separate trials in blunt and penetrating trauma.

Table 3: Methodologic quality of the included studies of the use of recombinant factor VIIa in patients without hemophilia

Study	Adequate sequence generation	Adequate concealment of allocation	Adequate blinding	Loss to follow-up, %	Power calculation performed	Target sample size achieved
Prophylactic use (14 RCTs)						
Diprose et al.[15]	Yes	ND	Yes	0	Yes	No
Ekert et al.[16]	ND	ND	Yes	1	No	–
Ma et al.[17]	Yes	ND	ND	0	No	–
Essam[18]	ND	ND	ND	0	No	–
Jeffers et al.[19]	Yes	ND	Yes	6	Yes	Not stated
Lodge et al.[20]	Yes	Yes	Yes	9	Yes	Yes
Shao et al.[21]	ND	ND	ND	6	Yes	Not stated
Lodge et al.[22]	ND	ND	ND	13	Yes	Yes
Planinsic et al.[23]	ND	ND	ND	5	Yes	Yes
Pugliese et al.[24]	ND	ND	ND	0	No	–
Raobaikady et al.[25]	Yes	ND	ND	0	Yes	Yes
Sachs et al.[26]	ND	ND	Yes	18	Yes	Yes
Friederich et al.[27]	Yes	Yes	Yes	0	Yes	Not stated
Johansson et al.[28]	Yes	ND	ND	0	No	–
Therapeutic use (12 RCTs)						
Boffard et al.[14] (blunt trauma)*	ND	ND	ND	14	Yes	Yes
Boffard et al.[14] (penetrating trauma)*	ND	ND	ND	9	Yes	Yes
Bosch et al.[29]	Yes	Yes	Yes	3	Yes	Yes
Bosch et al.[30]	Yes	Yes	Yes	3	Yes	No
Gill et al.[31]	Yes	Yes	Yes	0	Yes	No
Chuansumrit et al.[32]	ND	ND	Yes	11	No	–
Pihusch et al.[33]	Yes	Yes	Yes	2	Yes	Yes
Mayer et al.[34]	ND	ND	Yes	2	No	–
Mayer et al.[35]	Yes	Yes	Yes	4	Yes	Not stated
Mayer et al.[36]	ND	ND	Yes	2	No	–
Mayer et al.[3]	Yes	ND	Yes	3	Yes	Yes
Narayan et al.[37]	ND	ND	Yes	0	No	–

Note: ND = insufficient detail provided, RCT = randomized controlled trial.
*The report by Boffard and coauthors was considered as two separate trials in blunt and penetrating trauma.

Table 4: Summary estimates from the pooled analysis of results from randomized controlled trials (RCTs) of the use of recombinant factor VIIa in patients without hemophilia

Outcome	No. of studies	No. of patients	Summary estimate (95% CI)	I^2 value
Prophylactic use (14 RCTs)				
Mortality, RR	13	1017	0.82 (0.36 to 1.83)	0
Blood loss, mL, WMD*	8	505	–276 (–411 to –141)	78
Red blood cell transfusion, mL, WMD*	10	641	–281 (–433 to –129)	63
No. of patients receiving transfusion, RR*	7	765	0.71 (0.50 to 0.99)	61
Thromboembolic event, RR	12	987	1.38 (0.76 to 2.51)	0
Therapeutic use (12 RCTs)				
Mortality, RR	12	2468	0.90 (0.76 to 1.06)	0
Control of bleeding, RR*	4	616	1.05 (0.97 to 1.14)	0
Red blood cell transfusion, mL, WMD*	4	590	21 (–108 to 150)	0
No. of patients receiving transfusion, RR*	2	197	0.81 (0.70 to 0.93)	0
Thromboembolic event, RR	12	2485	1.18 (0.86 to 1.62)	0

Note: CI = confidence interval, RR = relative risk, WMD = weighted mean difference.
*Forest plots of the pooled estimates for these outcomes are shown in Appendix 2 (prophylactic use) and Appendix 3 (therapeutic use); the appendices are available online at www.cmaj.ca/cgi/content/full/cmaj.100408/DC1.