

# Review: Recombinant factor VIIa does not differ from placebo for prevention or treatment of bleeding in patients without hemophilia

Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev.* 2007;(2):CD005011.

**Clinical impact ratings:** Hematol/Thrombo ★★★★★☆☆

**QUESTION**

In patients without hemophilia, is recombinant factor (rF) VIIa effective for prevention or treatment of bleeding?

**METHODS**

**Data sources:** MEDLINE, EMBASE/Excerpta Medica, LILACS, Cochrane Injuries Group Specialized Register, Cochrane Central Register of Controlled Trials, National Research Register, NBS Systematic Review Initiative RCT Database, Meta-database of Ongoing Trials, KoreaMed, IndMed, PakMediNet, Cambridge Scientific abstracts, ZETOC, ISI Proceedings (all to March 2006); bibliographies of relevant studies; and experts.

**Study selection and assessment:** Randomized controlled trials (RCTs) that compared rFVIIa with placebo, other treatments, or different doses of rFVIIa in patients of any age who were at risk for blood loss because of surgery or those receiving treatment for medical, surgical, or trauma bleeding. Studies of patients with hemophilia or other hemostatic defects were excluded. Quality assessment of individual studies was based on randomization, allocation concealment, blinding, follow-up, and equal use of cointerventions in groups. 13 placebo-controlled, double-blind RCTs met the selection criteria (1 RCT included children): 6 RCTs (*n* = 724) evaluated prophylactic rFVIIa, and 7 RCTs (*n* = 1214) evaluated therapeutic rFVIIa.

**Outcomes:** Death, bleeding, transfusion, and adverse events.

**MAIN RESULTS**

Meta-analysis showed that prophylactic or therapeutic rFVIIa did not differ from placebo for death, total blood loss (7 RCTs, *n* = 539, weighted mean difference -306 mL, 95% CI -800 to 187), transfusion, or thromboembolic events (Table). Low (< 80

µg/kg) and high (≥ 80 µg/kg) doses of rFVIIa did not differ for bleeding or transfusion.

**CONCLUSION**

Recombinant factor VIIa does not differ from placebo for prevention or treatment of bleeding in patients without hemophilia.

*Source of funding:* No external funding.

*For correspondence:* Dr. S. Stanworth, John Radcliffe Hospital, Oxford, England, UK. E-mail [simon.stanworth@nbs.nhs.uk](mailto:simon.stanworth@nbs.nhs.uk).

**Prophylactic (PROPH) or therapeutic (THER) recombinant factor (rF) VIIa vs placebo (PLAC) in patients without hemophilia\***

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT
		PROPH rFVIIa	PLAC		
Death	9 (723)	2.2%	3.2%	10% (-116 to 63)	Not significant
Transfusion	7 (592)	56%	68%	15% (-1 to 28)	Not significant
				<b>RRI (CI)</b>	<b>NNH</b>
Thromboembolic events	9 (719)	8.0%	7.0%	25% (-24 to 107)	Not significant
		THER rFVIIa	PLAC	RRR (CI)	NNT
Death	10 (1084)	20%	22%	18% (-4 to 36)	Not significant
				<b>RBI (CI)</b>	
Control of bleeding	4 (382)	79%	76%	3.0% (-10 to 19)	Not significant
				<b>RRI (CI)</b>	<b>NNH</b>
Transfusion	1 (25)	25%	11%	125% (-71 to 1619)	Not significant
Thromboembolic events	10 (1220)	5.6%	3.6%	39% (-21 to 145)	Not significant

\*Abbreviations defined in Glossary. Weighted event rates, RRR, RRI, RBI, NNT, NNH, and CI calculated from control event rates and relative risks in article. Results based on a random-effects model.

**COMMENTARY**

The review by Stanworth and colleagues, which evaluates off-label use of rFVIIa to prevent and treat bleeding in patients without hemophilia, has several strengths: an extensive literature search, strict methodological quality assessment of studies, and evaluation of clinically relevant outcomes, such as mortality, blood loss, transfusion requirements, and adverse events (thromboembolism).

Although all included RCTs were double-blind and placebo-controlled, the lack of clarity in randomization, except for 1 study (1), raises questions about their validity. Heterogeneous patient populations were enrolled in both prophylactic RCTs (surgery for pelvic fractures, radical prostatectomy, partial hepatectomy, liver transplant, and coronary bypass) and therapeutic RCTs (bleeding after stem cell transplantation, trauma-related bleeding, upper gastrointestinal bleeding in cirrhosis, Dengue fever in children, and intracerebral hemorrhage [ICH]). The criteria for cointerventions, such as additional hemostatic drugs and transfusions, were also heterogeneous. A favorable effect for rFVIIa compared with placebo was shown in only 1 RCT involving patients with spontaneous ICH, in which the estimate of ongoing bleeding could only be evaluated separately as a reduction in hematoma volume.

Use of rFVIIa led to a nonsignificant increase in arterial thromboembolic events. As history of thrombosis and vaso-occlusive disease were

exclusions, the incidence of thromboembolic complications could be underestimated in clinical practice.

The conclusions of the review may be altered by several ongoing trials. However, a recent RCT (not in the meta-analysis) of rFVIIa in patients with spontaneous ICH did not show a significant effect on mortality or severe disability, thereby supporting the authors' conclusions (2). Until more data are available, the efficacy of rFVIIa outside currently licensed clinical indications (i.e., congenital hemophilia A or B with inhibitors, acquired hemophilia, congenital FVII deficiency, or Glanzmann thrombasthenia) remains to be determined. Clinicians considering off-label use of rFVIIa should be aware of the lack of supporting evidence.

*Benilde Cosmi, MD  
S. Orsola-Malpighi University Hospital  
Bologna, Italy*

**References**

1. Bosch J, Thabut D, Bendtsen F, et al. *Gastroenterology.* 2004;127:1123-30.
2. Steiner T, Mayer SA, Brun NC, et al. Presented at the XXI Congress of the International Society on Thrombosis and Haemostasis. 6-12 July 2007; Geneva, Switzerland.