Effective Health Care Program

Heart and Blood Vessel Conditions
Off-Label Uses of rFVIIa

Utilization and Clinical Data on In-Hospital, Off-Label Uses of Recombinant Factor VIIa

Key Clinical Issue

Off-label use of recombinant activated factor VII (rFVIIa) in the hospital setting has increased despite limited comparative data on its effectiveness and safety. How is it being used, and what is the evidence of benefits and harms for treated patients?

Background Information

The U.S. Food and Drug Administration has approved rFVIIa for the treatment and prevention of bleeding in patients with hemophilia A or B with inhibitors, acquired hemophilia, or congenital factor VII deficiency. However, in recent years the off-label use of rFVIIa has increased in the hospital setting to prevent or manage uncontrolled bleeding. The most common in-hospital, off-label uses of rFVIIa are for spontaneous intracranial hemorrhage, bleeding secondary to trauma, and cardiac surgery (see Fig. 1 on the reverse).

A note about this Clinician Guide

A systematic review of 74 clinical studies was conducted by independent researchers, funded by AHRQ, to synthesize the evidence on what is known and not known on this clinical issue.

This topic was nominated through a public process. The research questions and the results of the report were subject to expert input, peer review, and public comment.

The results of this review are summarized here for use in your decisionmaking and in discussions with patients. The full report, with references for included and excluded studies, is available at www.effectivehealthcare.ahrq.gov.

Conclusions

For the uses examined, current evidence does not show that off-label use of rFVIIa reduces mortality or improves other direct outcomes. Thromboembolic events are increased by use of rFVIIa to treat spontaneous intracranial hemorrhage and in adult cardiac surgery.

Clinical Bottom Line

In-Hospital, Off-Label Uses for rFVIIa[1]	Evidence on Benefits vs. Usual Care	Evidence on Harms vs. Usual Care
Spontaneous intracranial hemorrhage*	No effect on mortality or functional status. ●●○ Attenuation of hematoma expansion. ●●○	Increased risk for arterial thromboembolic events, particularly at doses >40 µg/kg of patient body weight.† ●●○
Adult cardiac surgery	No effect on mortality, RBC transfusion requirements, or ICU length of stay. ●○○	Increased risk for thromboembolic events when compared to usual care. ●●○
Body trauma*	No consistent effect on mortality. ●○○ Possible reduction in acute respiratory distress syndrome. ●○○	No effect on thromboembolic events. ●○○
Brain trauma	No effect on mortality, Glasgow coma scale, or hematoma volume change. ●○○	No effect on thromboembolic events. ●○○
Liver transplantation*	No effect on mortality, OR time, or ICU length of stay. ●○○ Possible reduction in 24-hr RBC transfusion requirements. ●○○	No effect on thromboembolic events. ●○○

* Current evidence does not provide a connection between improvements in indirect outcomes (e.g., reversal of bleeding) with those of direct outcomes (e.g., mortality). Explanations include: 1) bleeding control by itself is not enough to influence direct outcomes, or 2) the risk of overall harms outweighs the potential benefits from indirect outcomes.

† Even though the effect of treating spontaneous intracranial hemorrhage with rFVIIa at doses ≤40 µg/kg of patient body weight was not statistically different from zero, there may have been insufficient statistical power to detect a difference.

Confidence Scale

High: ●●● There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.
Moderate: ●●○ Findings are supported, but further research could change the conclusions.
Low: ●○○ There are very few studies, or existing studies are flawed.

[1] In January 2010, an FDA-required warning statement regarding the serious thrombotic events associated with the use of rFVIIa (NovoSeven® RT) outside labeled indications was added to the product insert. This warning was similar to that issued in 2005 for the original formulation of rFVIIa (NovoSeven®).

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Additional Details Regarding Increased Risk of Thromboembolic Events* With rFVIIa Use for Spontaneous Intracranial Hemorrhage and Adult Cardiac Surgery

In-Hospital, Off-Label Use of rFVIIa	TE Events/Total Patients (%) rFVIIa	TE Events/Total Patients (%) Usual Care	Risk Difference Summary Effect Size (95% CI)	Estimated Effect on TE Events
Spontaneous intracranial hemorrhage				
Low dose (≤40 µg/kg)	24/415 (5.8)	13/378 (3.4)	0.025 (-0.004 to 0.053)	No effect† ●●○
Medium dose (41–119 µg/kg)	29/399 (7.3)	13/378 (3.4)	0.035 (0.008 to 0.062)	Increase with rFVIIa ●●○
High dose (≥120 µg/kg)	8/115 (7.0)	0/107 (0)	0.063 (0.011 to 0.114)	Increase with rFVIIa ●●○
Adult cardiac surgery‡	19/203 (9.4)	8/170 (4.7)	0.053 (0.01 to 0.096)	Increase with rFVIIa ●●○

* Data for spontaneous intracranial hemorrhage includes only arterial thromboembolic events. Data for adult cardiac surgery includes all reported thromboembolic events as venous and arterial events were not reported separately.

† Even though the effect of treating spontaneous intracranial hemorrhage with rFVIIa at doses ≤40 µg/kg of patient body weight was not statistically different from zero, there may have been insufficient statistical power to detect a difference.

‡ The dose used in cardiac surgery was on the lower end of those studied (17-90 µg/kg) and was typically only given in the form of 1-2 infusions, rather than multiple infusions seen in some of the other indications.

CI = confidence interval; TE = thromboembolic.

Additional Off-Label Uses of rFVIIa Requiring Future Research

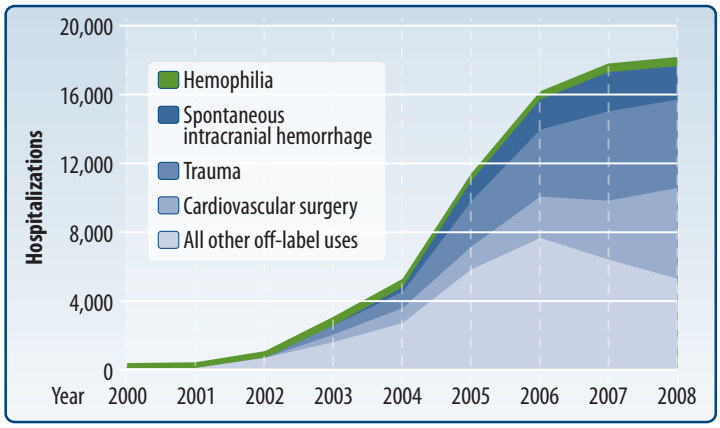
Surgery

- Management of abdominal aortic aneurysm (with and without surgical intervention).
- Pediatric cardiac surgery.
- Surgical procedures beyond cardiac and vascular surgery.
- Vascular surgeries (not related to abdominal aortic aneurysm).

Medical Conditions

- Cancer-related conditions.
- Gastrointestinal bleeding not related to liver disease.
- Hematopoietic stem cell transplantation.
- Liver disease (other than transplantation).
- Neonatal conditions (beyond cardiac surgery).
- Obstetrical conditions.
- Primary clotting disorders (other than hemophilia).
- Pulmonary conditions (e.g., pulmonary hemorrhage and pulmonary transplantation).
- Secondary clotting disorders (e.g., complications of warfarin anticoagulation).

Figure 1. Growth of in-hospital, off-label vs. on-label uses of rFVIIa in Premier database, 2000-2008*



* The unit of analysis was any hospital "case" of rFVIIa use—defined as any application during a patient hospitalization.

Source

The information in this guide is based on *Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care*, Comparative Effectiveness Review No. 21, prepared by the Stanford–UCSF Evidence-based Practice Center under Contract No. 290-02-0017 for the Agency for Healthcare Research and Quality, May 2010. Available at: www.effectivehealthcare.ahrq.gov. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, Texas.

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