Recombinant Clotting Factors: Dangerous (*Useless, Costly*)

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Surgery Grand Rounds
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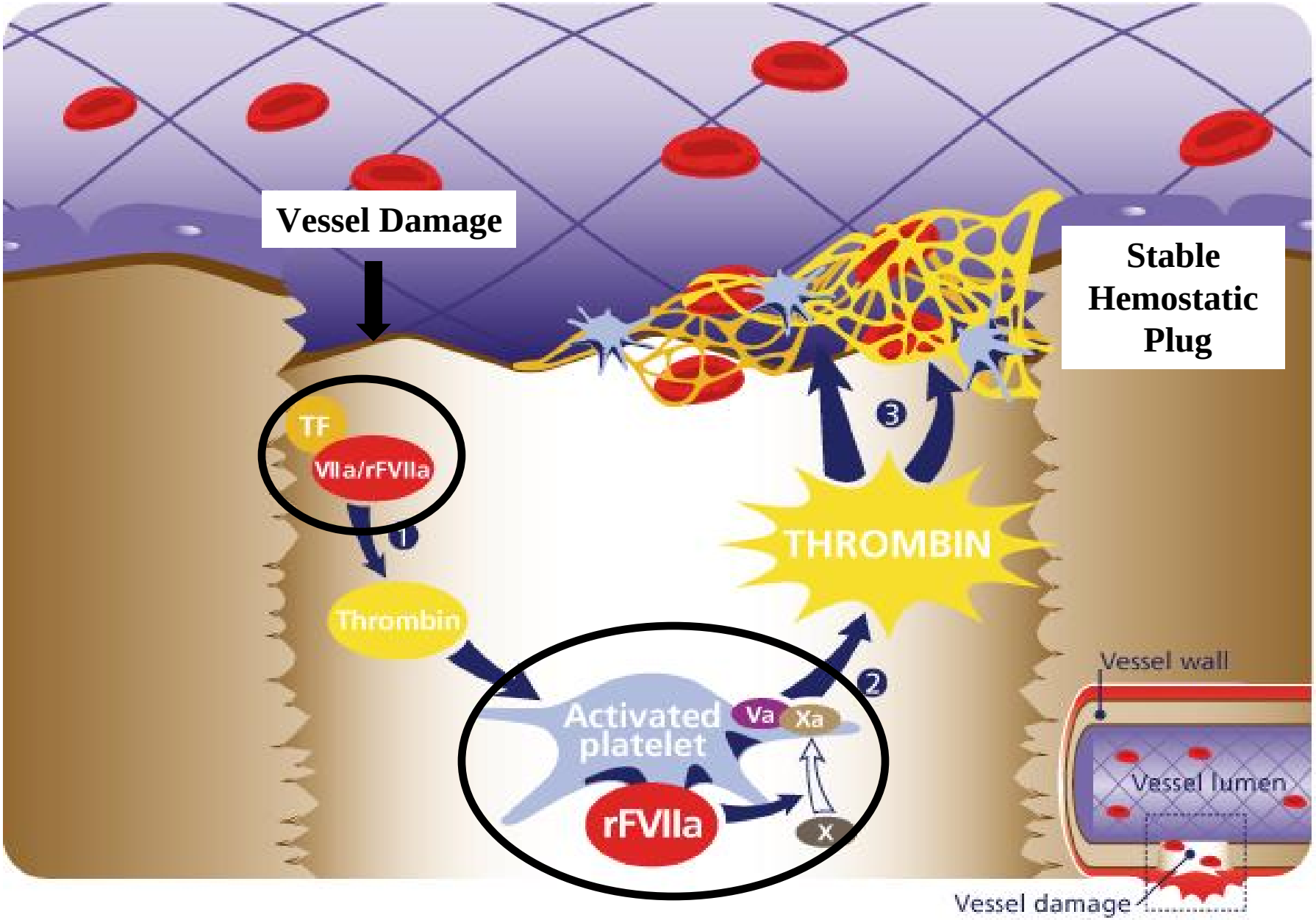
Outline

- Introduction
- Data (*Useless*)
  - Trauma
  - Cardiothoracic
  - Hepatobiliary/Liver transplantation
  - Neurosurgery
  - Orthopedics
- Cost Analysis (*Costly*)
- Dangers (*Harmful*)
- Conclusions

Mechanism of Action



Data

Trauma:
Historical Perspective/Timeline

1990

- **Factor VIIa in the Treatment of Hemophilia**
- Hedner U. *Blood Coagul Fibrinolysis*

1999

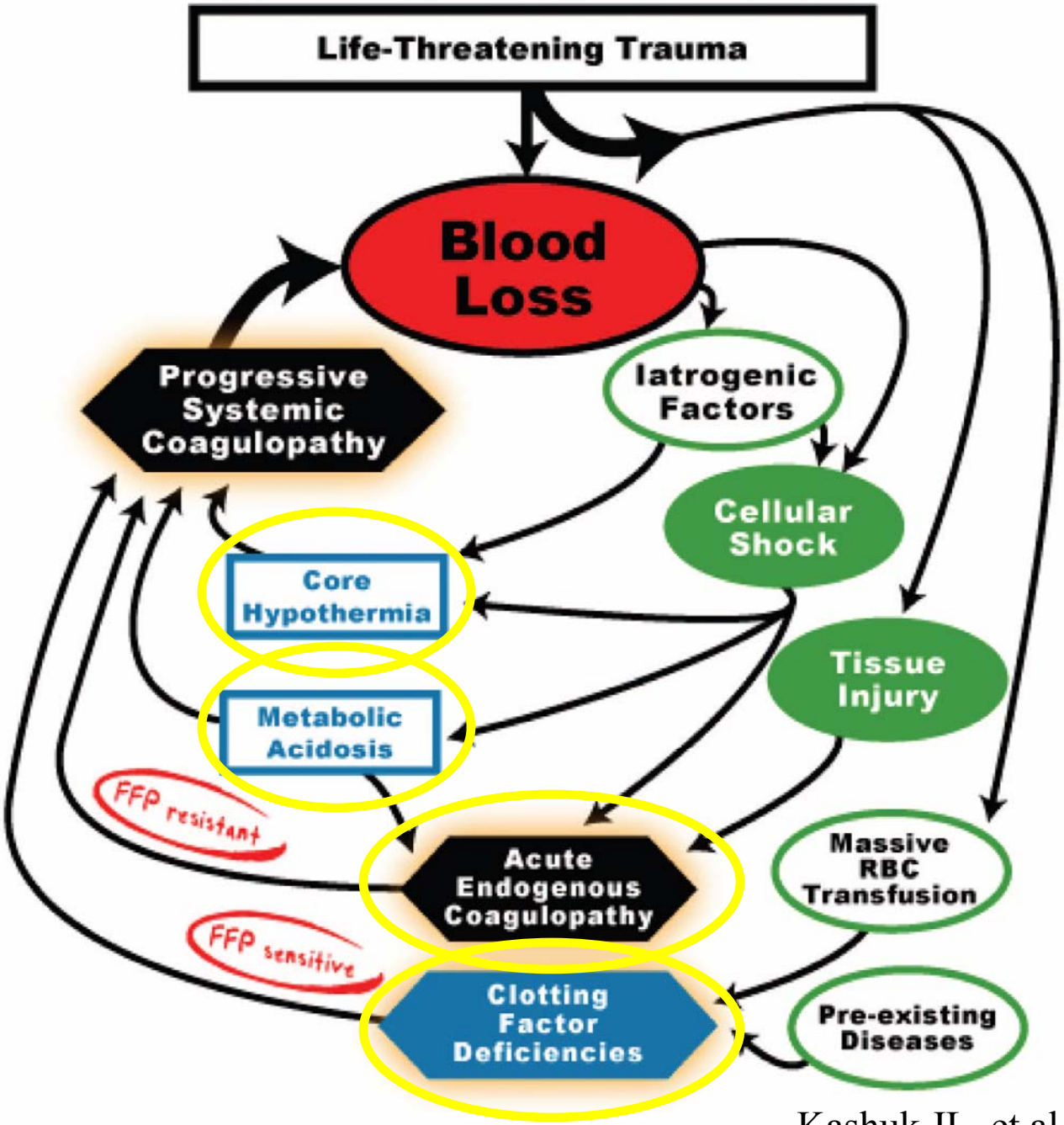
- **Treatment of Traumatic Bleeding with Recombinant Factor VIIa**
- Kenet G et al. *Lancet*

2005

- **Recombinant Factor VIIA as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials**
- Boffard KD et al. *J Trauma*

2010

- **Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage**
- Hauser CJ et al. *J Trauma*



Kashuk JL et al. *J Trauma* 2008

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

- Blunt trauma-rFVIIa ↓ RBC by 2.6 units ($p = 0.03$)
- Penetrating trauma-rFVIIa ↓ RBC by 1 unit ($p = 0.10$)

Table 2 Total RBC Transfusions (Units) During 48 Hours After First Dose of Trial Drug

	Placebo		rFVIIa		Estimated RBC reduction with 90% CI*	p†
	N	Median (range)	N	Median (range)		
Blunt		N = 74		N = 69		
Alive at 48 h	59	7.5 (0–35)	52	7.0 (0–29)	2.6 [0.7;4.6]	0.02
All patients	72	7.2 (0–35)	64	7.8 (0–48)	2.0◊ [0.0;4.6]	0.07◊
Penetrating		N = 64		N = 70		
Alive at 48 h	52	4.2 (0–41)	57	3.9 (0–30)	1.0 [0.0;2.6]	0.10
All patients	61	4.8 (0–41)	69	4.0 (0–37)	0.2◊ [−0.9;2.4]	0.24◊

Boffard KD et al. *J Trauma* 2005

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Table 3 Adverse Events and Clinical Outcomes

	Blunt trauma			Penetrating trauma		
	Placebo (N = 74)	rFVIIa (N = 69)		Placebo (N = 64)	rFVIIa (N = 70)	
Serious adverse events						
Patients with events	49 (66%)	44 (64%)		36 (56%)	36 (51%)	
Number of events	109	91		76	57	
Thromboembolic adverse events						
Patients with events	3 (4%)	2 (3%)		3 (5%)	4 (6%)	
Number of events	3	2		3	4	
48-hour mortality	13 (18%)	13 (19%)	p = 1.00	10 (16%)	12 (17%)	p = 1.00
30-day mortality	22 (30%)	17 (25%)	p = 0.58	18 (28%)	17 (24%)	p = 0.69
Patients with critical complications within 30 days						
ARDS	12 (16%)	3 (4%)	p = 0.03	5 (8%)	4 (6%)	p = 0.74
MOF	9 (12%)	5 (7%)	p = 0.41	7 (11%)	2 (3%)	p = 0.09
Patients with ARDS, MOF or death	31 (42%)	20 (29%)	p = 0.16	22 (34%)	20 (29%)	p = 0.57
Ventilator-free days* (median and range)	13 (0–29)	17 (0–29)	p = 0.43	20 (0–29)	25 (0–29)	p = 0.21
ICU-free days* (median and range)	8 (0–29)	12 (0–29)	p = 0.31	18 (0–29)	23 (0–29)	p = 0.34

MOF, Multiple organ failure; ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit.
* Within 30 days of trial product treatment.

Boffard KD et al. *J Trauma* 2005

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

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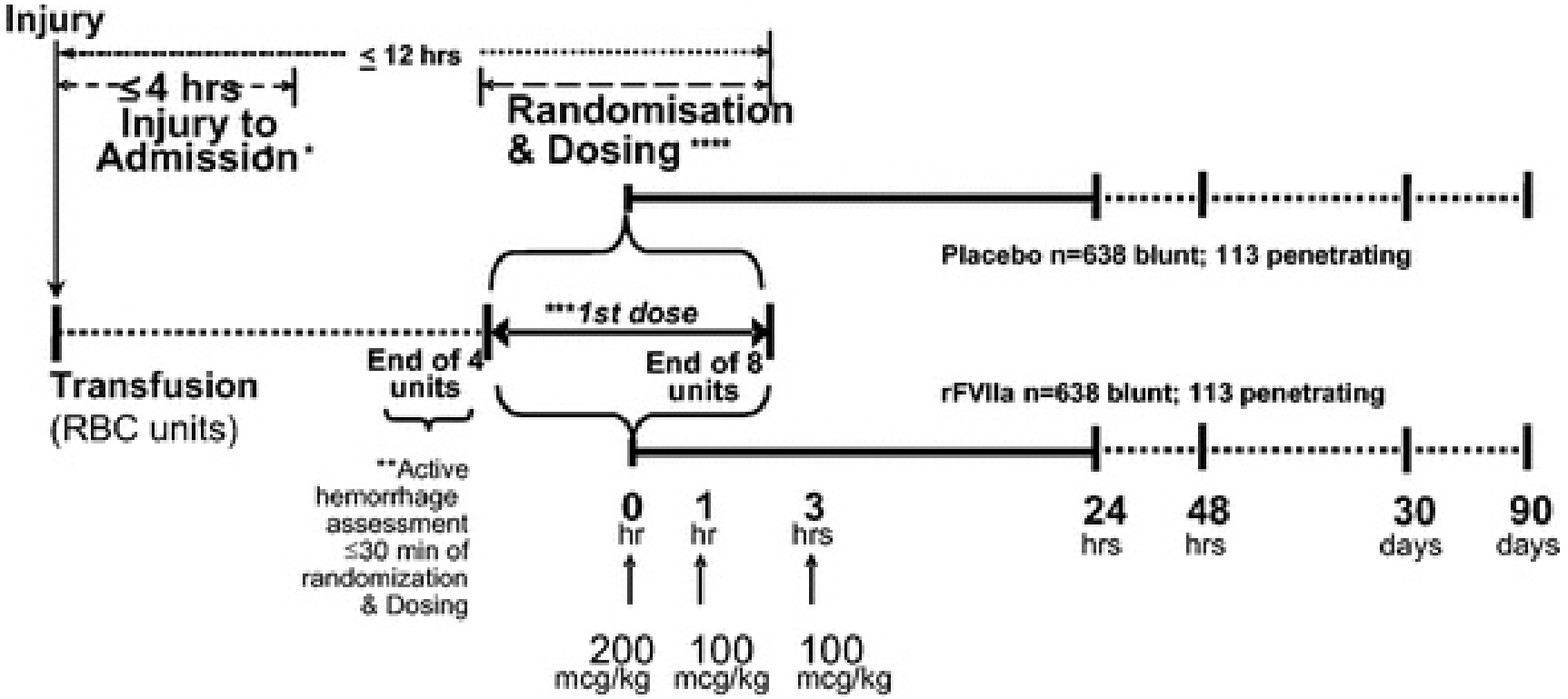
Supported by Novo Nordisk A/S, Bagsvaerd, Denmark. Drs. K. Boffard and B. Riou received consultancy fees and lecture sponsorships from Novo Nordisk. Drs. S. Rizoli, and Y. Kluger received consultancy fees from Novo Nordisk. Mads Axelsen is a former employee of Novo Nordisk.

Boffard KD et al. *J Trauma* 2005

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

Carl J. Hauser, MD, Kenneth Boffard, MD, Richard Dutton, MD, Gordon R. Bernard, MD, Martin A. Croce, MD, John B. Holcomb, MD, Ari Leppaniemi, MD, Michael Parr, MD, Jean-Louis Vincent, MD, PhD, Bartholomew J. Tortella, MD, MBA, Jeannett Dimaits, MD, and Bertil Boudlon, MD; for the CONTROL Study Group



Hauser CJ et al. *J Trauma* 2010

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

TABLE 2. Clinical Outcomes (30-d ITT Analysis)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 218)	Placebo (n = 242)	*p*	rFVIIa (n = 44)	Placebo (n = 38)	*p*
30-d mortality, n (%)	24 (11.0)	26 (10.7)	0.93† 0.37‡	8 (18.2)	5 (13.2)	0.40
Durable morbidity*, n (%)	19 (8.7)	23 (9.5)	0.75	1 (2.3)	0	1.00
Days alive and free from ventilator/RRT through day 30, mean ± SD	17.2 ± 10.3	16.4 ± 10.3	0.31	21.2 ± 11.1	21.9 ± 10.0	0.73
Days alive and free of ICU through day 30	13.7 ± 10.4	12.9 ± 9.9	0.32	18.7 ± 11.2	19.5 ± 10.6	0.65
MOF through day 30§, n (%)	98 (45.0)	129 (53.3)	0.06	10 (22.7)	9 (23.7)	0.90
Days alive and free from MOF through day 30§, mean ± SD	24.6 ± 9.7	24.4 ± 9.4	0.66	24.1 ± 11.6	25.4 ± 10.2	0.45
SOF through day 30, n (%)	214 (98.2)	235 (97.1)	0.49	40 (90.9)	35 (92.1)	0.91
Days alive and free from SOF through day 30, mean ± SD	19.9 ± 8.9	19.5 ± 8.6	0.53	21.9 ± 11.1	23.1 ± 9.8	0.50
Days alive and free of hospital through day 30	4.0 ± 6.9	3.5 ± 6.4	0.39	13.2 ± 10.4	11.3 ± 9.1	0.71

Hauser CJ et al. *J Trauma* 2010

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

TABLE 3. Transfusion Requirements (ITT Population)

	Blunt Trauma					Penetrating Trauma				
	rFVIIa (n = 221)		Placebo (n = 247)			rFVIIa (n = 46)		Placebo (n = 40)		
	N*	Mean ± SD	N*	Mean ± SD	$p^{\dagger}$	N*	Mean ± SD	N*	Mean ± SD	$p^{\dagger}$
Units administered from dosing to 24 h										
Allogeneic transfusions	198	17.1 ± 26.8	228	20.7 ± 25.7	0.03	39	11.2 ± 15.0	35	16.8 ± 19.3	0.09
RBC	184	6.9 ± 10.4	222	8.1 ± 10.9	0.04	37	4.5 ± 7.3	33	6.2 ± 6.5	0.11
FFP	160	4.7 ± 6.4	188	6.9 ± 8.6	<0.001	29	3.8 ± 6.0	33	5.7 ± 6.4	0.04
Platelets	112	3.3 ± 8.4	117	3.4 ± 7.0	0.84	15	1.6 ± 3.7	21	2.5 ± 4.1	0.08
Fibrinogen concentrate	28	1.5 ± 6.7	28	1.3 ± 4.7	0.68	1	0.1 ± 0.4	1	0.4 ± 2.7	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.3 ± 4.3	0.66	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Units administered from dosing to 48 h										
Allogeneic transfusions	201	19.0 ± 27.1	231	23.5 ± 28.0	0.04	39	12.2 ± 15.7	37	18.4 ± 20.7	0.06
RBC	191	7.8 ± 10.6	228	9.1 ± 11.3	0.04	39	5.0 ± 7.4	35	6.8 ± 6.9	0.11
FFP	166	5.3 ± 6.7	195	8.0 ± 10.1	0.001	29	4.0 ± 6.2	33	6.5 ± 7.6	0.02
Platelets	117	3.7 ± 8.6	124	3.9 ± 7.8	0.95	16	1.9 ± 3.9	21	2.7 ± 4.1	0.12
Fibrinogen concentrate	29	1.5 ± 6.7	28	1.3 ± 4.8	0.59	1	0.1	1	0.4	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.4 ± 4.5	0.64	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Patients requiring massive RBC transfusion (≥10 units of RBC) from injury to 24-h postdose, n (%)[‡]	111 (50.2)		134 (54.3)		0.38	14 (30.4)		21 (52.5)		0.04

Hauser CJ et al. *J Trauma* 2010

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

TABLE 4. Adverse Events Through Day 90 (Safety Population)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 224)	Placebo (n = 250)	*p*	rFVIIa (n = 46)	Placebo (n = 40)	*p*
Serious adverse events						
Patients with events, n (%)	147 (65.6)	177 (70.8)	0.23	18 (39.1)	20 (50.0)	0.31
Number of events	348	390		35	44	
Average number of events per patient	2.4	2.2		1.9	2.2	
MESIs*						
Patients with events, n (%)	89 (39.7)	100 (40.0)	0.95	13 (28.3)	10 (25.0)	0.73
Number of events	133	160		17	17	
Sepsis*						
Patients with events	33 (14.7)	45 (18.0)	0.34	4 (8.7)	2 (5.0)	0.69†
Number of events	34	45		4	2	
All fatalities*						
Patients with events	30 (13.4)	33 (13.2)	0.95	9 (19.6)	5 (12.5)	0.38
Number of events	30	33		9	5	
MOF*						
Patients with events	10 (4.5)	17 (6.8)	0.27	1 (2.2)	1 (2.5)	1.00†
Number of events	10	18		1	1	
ARDS*						
Patients with events	8 (3.6)	18 (7.2)	0.08	0	3 (7.5)	0.10†
Number of events	8	19			3	
DIC*						
Patients with events	6 (2.7)	10 (4.0)	0.43	1 (2.2)	1 (2.5)	1.00†
Number of events	6	10		1	1	
Thrombotic AEs*						
Patients with events, n (%)	36 (16.1)	33 (13.2)	0.38	2 (4.3)	4 (10.0)	0.41†
Number of events	45	35		2	5	
Arterial thrombotic AEs, no. events	16	11	0.20	2	1	1.00†
Venous TEs, no. events	29	24	0.25	0	4	0.04†

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Dr. Jeannett Dimsits and Dr. Bartholomew Tortella are employees of Novo Nordisk. Dr. Carl J. Hauser received consulting fees from Novo Nordisk and grant support from NIH/NIGMS. Dr. Kenneth Boffard received consulting fees from Novo Nordisk. Dr. Richard Dutton received consulting fees from Novo Nordisk and grant support from Octapharma and the Department of Defense. Dr. Gordon R. Bernard received consulting fees and grant support from Novo Nordisk. Dr. Martin A. Croce received consulting fees from Novo Nordisk and grant support from Wyeth and EISAI. Dr. John B. Holcomb received consulting fees from Novo Nordisk and HEMCON. Dr. Ari Leppaniemi received consulting fees from Novo Nordisk. Dr. Michael Parr received consulting fees, lecture fees from Novo Nordisk, and grant support from Novo Nordisk and PPD. Dr. Jean-Louis Vincent received consulting fees and grant support from Novo Nordisk. Dr. Bertil Bouillon received consulting fees and lecture fees from Novo Nordisk. Dr. G. Howard received compensation as an independent consultant.

The sponsor was responsible for providing clinical trial supplies, preparing the study protocol, data management, statistical analysis, and preparing the clinical trial report. Anders Rosholm, PhD, is an employee of Novo Nordisk and assisted with the statistical analyses. Jen Faleska, PhD, and Charlotte Yap, MSc, are employees of Novo Nordisk and provided editorial assistance.

Cardiothoracic Surgery

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

Henry Ekert[a], Christian Brizard[b], Robert Eyers[c], Andrew Cochrane[b] and Robert Henning[d]

Table 1 Time from reversal of heparin with protamine sulphate to chest closure in the intention-to-treat (ITT) and full per-protocol groups

	Recombinant activated factor VII		Placebo		
Time (min)	ITT ($n = 40$)	Per protocol ($n = 23$)	ITT ($n = 35$)[a]	Per protocol ($n = 18$)	Significance
Mean (SE)	98.825 (27.27)	62.391 (5.62)	55.314 (29.15)	57.056 (6.36)	ITT, $P = 0.0263$.
95% confidence interval	44.485; 153.16	51.02; 73.765	−2.777; 113.41	44.199; 69.912	Per protocol, $P = 0.0515$

Ekert H et al. *Blood Coagul Fibrinolysis* 2006

Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study

P. Diprose[1], M. J. Herbertson[1†], D. O'Shaughnessy[2] and R. S. Gill[1*†]

Table 7 Postoperative events. Data are median (IQR) unless stated otherwise. MI, myocardial Infarction. *One patient in placebo group who died excluded from the dataset. †Using Kruskal–Wallis ANOVA. ‡Using Fisher exact test

	Placebo group (n=10)	rFVIIa group (n=9)	P-value
Vent time (h)*	13.5 (6.1–18.5)	6.1 (4.7–18.5)	0.501†
ICU stay (days)*	1 (1–4)	2.5 (1–3.5)	0.434†
Hospital stay (days)*	8 (8–14)	11.5 (8.8–19.8)	0.410†
Postoperative stroke	1	1	1‡
Postoperative MI	1	1	1‡
Death	1	0	1‡

Diprose P et al. *Br J Anaesth* 2005

Hepatobiliary Surgery/ Liver Transplantation

Recombinant Factor VIIa for Upper Gastrointestinal Bleeding in Patients With Cirrhosis: A Randomized, Double-Blind Trial

JAIME BOSCH,* DOMINIQUE THABUT,† FLEMMING BENDTSEN,§ GENNARO D'AMICO,‖ AGUSTÍN ALBILLOS,¶ JUAN GONZÁLEZ ABRALDES,* SOEREN FABRICIUS,# ELISABETH ERHARDTSEN,# ROBERTO DE FRANCHIS** on behalf of the European Study Group on rFVIIa in UGI Haemorrhage

Table 3. Results of Therapy

	Placebo N = 121	rFVIIa N = 121	*P* value
Failure on composite end point	Failures/scored patients[a]		
All patients (primary end point)	19/119 (16%)	16/118 (14%)	0.72
Variceal bleeders	16/80 (20%)	8/78 (10%)	0.12
Variceal bleeders Child-Pugh B–C[b]	15/64 (23%)	5/62 (8%)	0.03
Failure to control bleeding within 24 hours			
All patients	10/119 (8%)	6/120 (5%)	0.31
Variceal bleeders	8/80 (10%)	2/78 (3%)	0.10
Variceal bleeders Child-Pugh B–C[b]	7/63 (11%)	0/62 (0%)	0.01
Failure to prevent rebleeding (24 h–day 5)			
All patients	10/116 (9%)	9/116 (8%)	1.00
Variceal bleeders	9/77 (12%)	5/77 (6%)	0.40
Variceal bleeders Child-Pugh B–C[b]	8/61 (13%)	3/62 (5%)	0.13
Mortality			
Deaths within 5 days	4/119 (3%)	7/118 (6%)	0.38
Deaths within 42 days	11/120 (9%)	16/116 (14%)	0.31
Red blood cell requirements (units; mean ± SD)			
Within 24 hours	0.7 ± 1.2	0.9 ± 1.8	0.51
Within 5 days	1.3 ± 1.9	1.5 ± 3.7	0.73
Active bleeding at first endoscopy			
All patients	45/121 (37%)	47/119 (39%)	0.79
Variceal bleeders	33/82 (40%)	33/79 (42%)	0.87

Bosch J et al. *Gastroenterology* 2004

Recombinant Coagulation Factor VIIa in Major Liver Resection

A Randomized, Placebo-controlled, Double-blind Clinical Trial

J. Peter A. Lodge, M.D., F.R.C.S., Sven Jonas, M.D.,† Elie Oussoultzoglou, M.D.,‡ Massimo Malagó, M.D.,§ Christian Jayr, M.D.,‖ Daniel Cherqui, M.D.,# Matthias Anthuber, M.D.,** Darius F. Mirza, M.S., F.R.C.S.,†† Luce Kuhlman, M.D.,‡‡ Wolf-Otto Bechstein, M.D.,§§ Juan Carlos Meneu Díaz, M.D.,‖‖ Jack Tartiere, M.D.,## Daniel Eyraud, M.D.,*** Marianne Fridberg, M.Sc.,††† Elisabeth Erhardtsen, D.V.M.,‡‡‡ Oliver Mimoz, M.D.§§§*

Table 3. Adverse Events

	Placebo		20 μg/kg rFVIIa		80 μg/kg rFVIIa	
	n (%)	E	n (%)	E	n (%)	E
No. of dosed patients	68		66		66	
Adverse events	54 (79%)	161	55 (83%)	173	49 (74%)	153
Serious adverse events	9 (13%)	10	11 (17%)	13	7 (11%)	11
Thromboembolic adverse events	3 (4.4%)	3	3 (4.6%)	3	3 (4.6%)	3
Bleeding complications*	12 (18%)	13	15 (23%)	16	10 (15%)	12
Deaths	3		4		0	

Lodge JP et al. *Anesthesiology* 2005

Safety and Efficacy of a Single Bolus Administration of Recombinant Factor VIIa in Liver Transplantation Due to Chronic Liver Disease

Raymond M. Planinsic,[1] Jan van der Meer,[2] Giuliano Testa,[3] Luis Grande,[4] Angel Candela,[5] Robert J. Porte,[6] R. Mark Ghobrial,[7] Helena Isoniemi,[8] Peter Billeskov Schelde,[9] Elisabeth Erhardtsen,[9] Goran Klintmalm,[10] and Sukru Emre[11]

Table 2. Transfusion Requirements*

	Placebo (n = 19)	rFVIIa 20 μg/kg (n = 18)	rFVIIa 40 μg/kg (n = 23)	rFVIIa 80 μg/kg (n = 22)
Total RBC, U (interquartile range)	11.1 (7.0-17.0)	10.0 (3.0-18.0)	13.0 (7.0-24.0)	10.0 (3.2-21.0)
Allogeneic RBC, U (interquartile range)	8.0 (6.0-15.0)	8.5 (3.0-18.0)	13.0 (6.0-22.0)	7.0 (2.0-17.0)
Autologous RBC, U (interquartile range)	0.9 (0.0-4.3)	0.0 (0.0-4.5)	0.9 (0.0-3.5)	0.0 (0.0-3.7)
Total FFP, U (interquartile range)	11.0 (6.0-32.0)	8.5 (0.0-41.0)	15.5 (8.8-24.0)	6.0 (2.0-23.0)
PC, U (interquartile range)	4.0 (1.0-10.0)	5.5 (0.0-11.0)	9.0 (0.0-19.0)	1.5 (0.0-8.0)

rFVIIa, activated recombinant factor VII; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.
All values in median.
*No significant difference ($P > .05$) in transfusion requirements between study groups.

Planinsic RM et al. *Liver Transpl* 2005

Neurosurgery/ Orthopedics/ Urology

Reversal of Coagulopathy in Critically Ill Patients With Traumatic Brain Injury: Recombinant Factor VIIa is More Cost-Effective Than Plasma

Deborah M. Stein, MD, MPH, Richard P. Dutton, MD, MBA, Mary E. Kramer, RN, and Thomas M. Scalea, MD

Table 2 Outcomes of All Patients

	No rFVIIa (n = 111)		rFVIIa (n = 68)		*p*
	Mean	±	Mean	±	
LOS (d)	11.7	13.9	11.8	10.1	0.976
ICU-LOS (d)	8.5	14.2	10	10.2	0.465
Discharge GCS	13.2	2.6	11.9	2.6	0.006
Discharge RLAS	5.9	2.0	5.2	2.0	0.036
	n	%	n	%	*p*
Mortality	21*	18.9	18†	26.5	0.517
Thromboembolic complications	18	16.2	13	19.1	0.233

Stein DM et al. *J Trauma* 2009

Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial

Philip W Friederich, Christiaan P Henny, Embert J Messelink, Mark G Geerdink, Tymen Keller, Karl-Heinz Kurth, Harry R Büller, Marcel Levi

	Placebo (n=12)	Recombinant factor VIIa			
		20 µg/kg (n=8)	p*	40 µg/kg (n=16)	p*
Units of packed red cells	1·5 (0·4)	0·6 (0·3)	0·047	0 (0)	0·0003
Number (%) of patients needing any transfusion	7 (58%)	3 (38%)	0·651	(0%)	0·001
Duration of operation (min)	180 (16)	126 (21)	0·035	120 (15)	0·014
Length of hospital stay (days)	12 (1·7)	13 (1·3)	0·662	11 (0·7)	0·350

Data are mean (SD), unless otherwise indicated. *Versus placebo.

Table 2: **Transfusion requirements, duration of operation, and hospital admission in the three study groups**

Friederich PW et al. *Lancet* 2003

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[†‡]

R. Raobaikady[1], J. Redman, J. A. S. Ball[2], G. Maloney[3] and R. M. Grounds*

	rFVIIa (n=24)	Placebo (n=24)	P-value
Measured blood loss using method described by Jansen *et al.*[14]			
Total perioperative* blood loss (ml)	2070 (431–6774)	1535 (714–7057)	0.79
Intraoperative (ml)	1598 (331–6574)	1188 (514–6657)	0.57
Postoperative (ml)	240 (0–1210)	370 (80–650)	0.022
Calculated blood loss using method described by Rosencher *et al.*[15]			
Total perioperative* blood loss (ml)	2146 (143–6936)	2787 (328–15224)	0.50
Total perioperative blood transfusion requirement (ml)	289 (42–2365)	706 (53–7138)	0.33
Salvaged RBC[†] (ml)	194 (0–935)	171 (47–676)	0.90
Allogeneic RBC (U)	0 (0–4)	2 (0–16)	0.34
Number of patients transfused with allogeneic blood components[‡]	11 (46%)	16 (67%)	0.24
Total perioperative crystalloid fluid infusion (ml)	7250 (4000–11 000)	7340 (1625–15 000)	0.78
Intraoperative (ml)	3000 (1020–5500)	2950 (1000–5000)	0.15
Postoperative (ml)	4000 (1000–8500)	4500 (625–10 000)	0.67
Total perioperative colloid fluid infusion (ml)	1500 (0–5750)	1500 (0–9500)	0.77
Intraoperative (ml)	1000 (0–4500)	1000 (0–3000)	0.85
Postoperative (ml)	500 (0–2700)	125 (0–6500)	0.50
Operating time (min)	177 (103–320)	189 (115–360)	0.58
Time in ICU after surgery (h)	13.2 (1.6–69.0)	15.5 (1.5–143.3)	0.98
Time in hospital (days)	18 (8–40)	14 (8–69)	0.26
Number of patients returned to operating theatre	1[¶]	1[¶]	
Adverse events[+]	1	1	

Raobaikady R et al. *Br J Anaesth* 2005

Cost

Efficacy and Safety of Recombinant Activated Factor VII in Major Surgical Procedures

Systematic Review and Meta-analysis of Randomized Clinical Trials

Marco Ranucci, MD; Giuseppe Isgrò, MD; Giorgio Soro, MD; Daniela Conti, MD; Barbara De Toffol, MD

rFactor VIIa

- 90 μg/kg = $5,000
- 200, 100, 100 = 400 μg/kg
  $20,000

PRBC

- 1 U PRBC = $350

CONTROL TRIAL COST

- Blunt
  - rFactor VIIa 17 ± 27 U
    $5,950 ± 9,450 (+$20,000)
  - Placebo 21 ± 26 U
    $7,350 ± 9,100
- Penetrating
  - rFactor VIIa 11 ± 15
    $3,850 ± 5,250 (+$20,000)
  - Placebo 17 ± 19
    $5,950 ± 6,650

Cost-benefit ratio is favorable only if each transfused patient is expected to receive 40 units of blood product!!!

Ranucci M et al. *Arch Surg* 2008

Dangers

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Kathryn A. O'Connell, MD, PhD
Jennifer J. Wood, PhD, MPH
Robert P. Wise, MD, MPH
Jay N. Lozier, MD, PhD
M. Miles Braun, MD, MPH

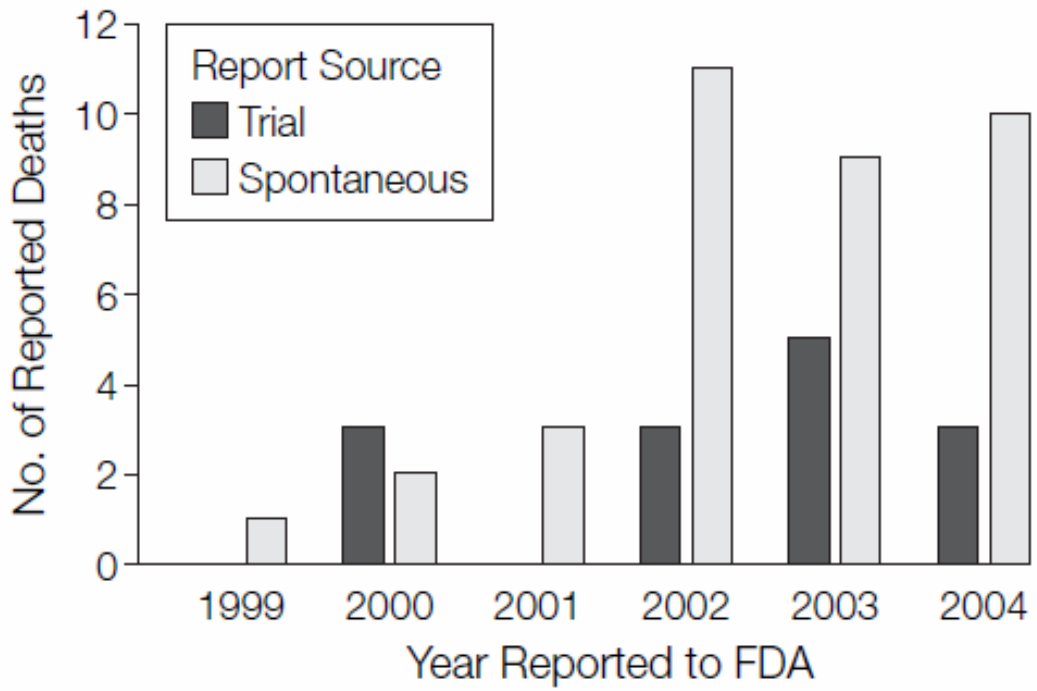
Table 2. Number of Thromboembolic Events Reported With Use of rFVIIa by Site and Report Source*

Site	No. of Reports (%)		
	Trial	Spontaneous	Total
Arterial	37 (20.2)	62 (33.9)	**99 (54.1)**
Non-ICH cerebrovascular accident	13 (7.1)	26 (14.2)	**39 (21.3)**
Acute myocardial infarction	12 (6.5)	22 (12.0)	**34 (18.6)**
Other arterial thromboembolism†	12 (6.5)	14 (7.6)	**26 (14.2)**
Venous	28 (15.3)	46 (25.1)	**74 (40.4)**
Venous other than pulmonary embolus‡	18 (9.8)	24 (13.1)	**42 (22.9)**
Pulmonary embolus	10 (5.5)	22 (12.0)	**32 (17.5)**
Device occluded§	1 (0.5)	9 (4.9)	**10 (5.5)**
Total	**66 (36.1)**	**117 (63.9)**	**183 (100)**

O'Connell KA et al. *JAMA* 2006

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Figure 4. Number of Reported Deaths Among Patients Administered Recombinant Human Coagulation Factor VIIa With a Thromboembolic Event by Year and Source



O'Connell KA et al. *JAMA* 2006

Thromboembolic Complications Associated With Factor VIIa Administration

G. O. Rhys Thomas, MD, Richard P. Dutton, MD, MBA, Bethany Hemlock, MPH, Deborah M. Stein, MD, MPH, Mary Hyder, MD, Roger Shere-Wolfe, MD, John R. Hess, MD, MPH, and Thomas M. Scalea, MD

Table 1 Patients Receiving FVIIa Therapy in the Shock Trauma Center, 2001–2006

Indication	Number	Percentage
Acute hemorrhagic shock	142	50
Traumatic brain injury	100	35
Reversal of warfarin therapy	36	13
Other	7	2
Total	285	100

Rhys Thomas GO et al. *J Trauma* 2007

Thromboembolic Complications Associated With Factor VIIa Administration

- 285 treated with Factor VIIa
- 27 with thromboembolic complication (9.5%)
  - 14/27 (52%) died, (5%)
  - 9/27 (33%) ischemic bowel, (3%)
  - 5/27 (19%) cerebrovascular accident, (2%)
  - 3/27 (11%) pulmonary embolus, (1%)
  - 3/27 (11%) deep vein thrombosis, (1%)

Rhys Thomas GO et al. *J Trauma* 2007

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

N ENGL J MED 363;19 NEJM.ORG NOVEMBER 4, 2010

Table 2. Odds Ratios for Thromboembolic Events.

Thromboembolic Event	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

Levi M et al. *NEJM* 2010

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

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Table 3. Arterial Thromboembolic Events with a Rate Greater Than 0.5%.

Variable	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)			
All arterial thromboembolic events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Coronary events	76 (2.9)	17 (1.1)	2.39 (1.39–4.09)	0.002
Acute coronary syndromes	57 (2.2)	11 (0.7)		
Increased troponin level	19 (0.7)	6 (0.4)		
Cerebrovascular events	45 (1.7)	20 (1.3)	1.27 (0.74–2.17)	0.39
Cerebral infarction	44 (1.7)	19 (1.2)		
Hemiparesis†	1 (<0.1)	1(<0.1)		

Levi M et al. *NEJM* 2010

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

Table 4. All Arterial Thromboembolic Events, According to Age.

Age Group	rFVIIa	Placebo	Odds Ratio (95% CI)*	P Value†
	no./total no. (%)‡			
<18 yr	1/70 (1.4)	1/51 (2.0)		
18–64 yr	73/1764 (4.1)	34/1107 (3.1)	1.36 (0.89–2.08)	0.15
≥65 yr	67/742 (9.0)	14/372 (3.8)	2.43 (1.34–4.41)	0.003
65–74 yr	33/427 (7.7)	8/225 (3.6)	2.12 (0.95–4.71)	0.07
≥75 yr	34/315 (10.8)	6/147 (4.1)	3.02 (1.22–7.48)	0.02

Levi M et al. *NEJM* 2010

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Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

ABSTRACT

BACKGROUND

The use of recombinant activated factor VII (rFVIIa) on an off-label basis to treat life-threatening bleeding has been associated with a perceived increased risk of thromboembolic complications. However, data from placebo-controlled trials are needed to properly assess the thromboembolic risk. To address this issue, we evaluated the rate of thromboembolic events in all published randomized, placebo-controlled trials of rFVIIa used on an off-label basis.

METHODS

We analyzed data from 35 randomized clinical trials (26 studies involving patients and 9 studies involving healthy volunteers) to determine the frequency of thromboembolic events. The data were pooled with the use of random-effects models to calculate the odds ratios and 95% confidence intervals.

RESULTS

Among 4468 subjects (4119 patients and 349 healthy volunteers), 498 had thromboembolic events (11.1%). Rates of arterial thromboembolic events among all 4468 subjects were higher among those who received rFVIIa than among those who received placebo (5.5% vs. 3.2%, P=0.003). Rates of venous thromboembolic events were similar among subjects who received rFVIIa and those who received placebo (5.3% vs. 5.7%). Among subjects who received rFVIIa, 2.9% had coronary arterial thromboembolic events, as compared w
(P=0.002). Rates of arterial thromboeml
who received rFVIIa than among subjects
those who were 65 years of age or older
especially high among subjects 75 years c

CONCLUSIONS

In a large and comprehensive cohort of per
treatment with high doses of rFVIIa on a
risk of arterial but not venous thromboen
(Funded by Novo Nordisk.)

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CONCLUSIONS

In a large and comprehensive cohort of persons in placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly. (Funded by Novo Nordisk.)

Levi M et al. *NEJM* 2010

Conclusions

- rFactor VIIa failed to: (*Useless*)
  - improve mortality (6/6 trials)
  - decrease transfusions (blunt ↓ 4 U, penetrating ↓ 5 U)
  - shorten hospital stay (4/4 trials)

- $$$$
  ($26,000 vs $7,000) (*Costly*)

- Harmful
  (*Dangerous*)
  (increased # thromboembolic events)