THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Managing Hemostasis in Trauma
Acute Coagulopathy of Trauma/Shock

NovoSeven®

NovoSeven® Efficacy and Risk

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Death by Trauma: Statistics

- Unintended or intentional injury are the most common cause of death in N Americans age 1–45
  - 93,000/year in the USA (much higher in third world)
- 50% of deaths are caused by severe neurological injury before reaching the hospital
- 20,000 die in hospital of *hemorrhage* within 48 hours
  - 30–35% of blood loss with uncompensated shock is fatal
  - 3–4,000 of hemorrhage deaths are preventable
  - Coagulopathy, failure to achieve hemostasis

Boffard KD, Choog PIT, Kloger Y, et al. The treatment of bleeding is to stop the bleeding! Treatment of trauma-related hemorrhage. On behalf of the NovoSeven Trauma Study Group. Transfusion 2009; 49:240–7S.

Trauma Stats

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CDC: WISQARS*

10 Leading Causes of Death, United States
2007, All Races, Both Sexes

Rank	Age Groups										
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	All Ages
1	Congenital Anomalies 5,785	Unintentional Injury 1,588	Unintentional Injury 960	Unintentional Injury 1,229	Unintentional Injury 15,697	Unintentional Injury 14,977	Unintentional Injury 16,551	Malignant Neoplasms 50,167	Malignant Neoplasms 103,171	Heart Disease 496,095	Heart Disease 616,067
2	Short Gestation 4,897	Congenital Anomalies 646	Malignant Neoplasms 480	Malignant Neoplasms 479	Homicide 5,551	Suicide 5,378	Malignant Neoplasms 13,288	Heart Disease 37,434	Heart Disease 65,927	Malignant Neoplasms 389,730	Malignant Neoplasms 562,875
3	SIDS 2,453	Homicide 396	Congenital Anomalies 196	Homicide 213	Suicide 4,140	Homicide 4,756	Heart Disease 11,839	Unintentional Injury 35,316	Chronic Low Respiratory Disease 12,777	Cerebro-vascular 115,961	Cerebro-vascular 135,952
4	Maternal Pregnancy Comp. 1,783	Malignant Neoplasms 364	Homicide 133	Suicide 160	Malignant Neoplasms 1,653	Malignant Neoplasms 3,463	Suicide 8,722	Liver Disease 8,212	Unintentional Injury 12,193	Chronic Low Respiratory Disease 109,952	Chronic Low Respiratory Disease 127,924
5	Unintentional Injury 1,265	Heart Disease 173	Heart Disease 110	Congenital Anomalies 178	Heart Disease 1,084	Heart Disease 3,223	HIV 3,572	Suicide 7,779	Diabetes Mellitus 11,304	Alzheimer's Disease 73,797	Unintentional Injury 123,706
6	Placenta Cord Membranes 1,135	Influenza & Pneumonia 109	Chronic Low Respiratory Disease 54	Heart Disease 131	Congenital Anomalies 402	HIV 1,991	Homicide 3,052	Cerebro-vascular 8,366	Cerebro-vascular 10,500	Diabetes Mellitus 57,328	Alzheimer's Disease 74,632
7	Bacterial Sepsis 620	Septicemia 78	Influenza & Pneumonia 48	Chronic Low Respiratory Disease 64	Cerebro-vascular 195	Diabetes Mellitus 610	Liver Disease 2,970	Diabetes Mellitus 5,753	Liver Disease 8,004	Influenza & Pneumonia 46,941	Diabetes Mellitus 71,382
8	Respiratory Distress 789	Perinatal Period 70	Benign Neoplasms 41	Influenza & Pneumonia 55	Diabetes Mellitus 168	Cerebro-vascular 609	Cerebro-vascular 2,133	HIV 4,156	Suicide 5,068	Nephritis 38,464	Influenza & Pneumonia 52,717
9	Circulatory System Disease 524	Benign Neoplasms 59	Cerebro-vascular 38	Cerebro-vascular 45	Influenza & Pneumonia 163	Congenital Anomalies 417	Diabetes Mellitus 1,984	Chronic Low Respiratory Disease 4,153	Nephritis 4,440	Unintentional Injury 36,242	Nephritis 46,448
10	Neonatal Hemorrhage 597	Chronic Low Respiratory Disease 57	Septicemia 36	Benign Neoplasms 43	Three Tied 160	Liver Disease 384	Septicemia 910	Viral Hepatitis 2,815	Septicemia 4,231	Septicemia 26,362	Septicemia 34,828

Produced By: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

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24-YO W♂, GSW in ED

A 24-YO white male arrived in the ED with a gunshot wound causing massive abdominal trauma. He had been given three units of Dextran® in transit to achieve fluid resuscitation but was hemorrhaging.

ED personnel ordered and administered four RBC units. Upon the second RBC batch order the transfusion service director recommended one plasma and one pheresis platelet concentrate. After 8 RBCs, 1 plasma, and 1 platelet, still bleeding, labs were:

PT: 20.8 s (Mean of RI 12.9); PTT: 82.5 s (MRI 30.1)
FG: 130 mg/dL (200-400 mg/dL); PLT: 70,000/mcL

Current Typical Approach to ACOTS

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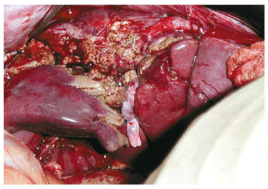
24-YO W♂, GSW in ED

In surgery, major vessels were tied, but the field was obscured by microvascular bleeds. The patient went into shock and expired.



Thanks to Mary Anne Krupsky, Michelle Brown, Birmingham, AL and Jose De Jesus, Tuscaloosa, AL for information on which this case is based.

Current Typical Approach to ACOTS

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American Society of Anesthesiologists Surgical Practice Guidelines: *RBCs*

- Monitor BP, pulse, ABG (pH, O_2 sat), urine output, EKG when feasible
- Monitor physical blood loss
- Transfuse when HGB <6 g/dL in young, healthy patient
- Do not transfuse when HGB >10 g/dL
- Based on acuity and clinical history when HGB 6–10 g/dL
  - O_2 sat, tissue ischemia, bleeding rate, IV volume replacement, evidence for coagulopathy
- Autotransfuse (recovery) when feasible

Current Typical Approach to ACOTS

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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- Assess surgical field for microvascular bleeding
  - Suction canisters, surgical sponges, surgical drains
- Platelet concentrate transfusion
  - No platelets if count is >100,000/mcL
  - "Usually" give platelets if <50,000/mcL, unless…
    - Limited blood loss is anticipated based on type of surgery
    - If thrombocytopenia is due to HIT, ITP, or TTP, where platelets are ineffective
  - From 50–100,000/mcL, use platelets if…
    - Potential of bleeding into confined space such as brain or eye
    - Aspirin, clopidogrel, cardiopulmonary bypass, platelet disorder

Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

Current Typical Approach to ACOTS

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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- Give plasma if microvascular bleeding…
  - And PT >1.5X normal ("normal" is undefined),
  - Or PTT >2X normal,
  - Or when transfused with >1 blood volume (~70 mL/kg),
  - Or need for urgent reversal of warfarin therapy,
  - Or known factor deficiency &concentrate is unavailable,
  - Or heparin resistance (antithrombin deficiency).
- Do not use plasma only to augment volume, use colloid plasma expanders
- Dosage is 10–15 mL plasma/kg to achieve ≥30% factor concentration
  - Or 5–8 mL/kg if only for warfarin reversal

Current Typical Approach to ACOTS

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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- CRYO when there is microvascular bleeding and…
  - Fibrinogen <100 mg/dL or documented deficiency,
  - Or massive transfusions without opportunity to determine fibrinogen level
- CRYO delivers 150–250 mg fibrinogen
- Consider rFVIIa when RBCs, PLTs, plasma and CRYO fail to stop microvascular bleeds

Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006; 105: 198–208.

Current Typical Approach to ACOTS

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Massive Tx requirement is likely in young, healthy combat casualties when…

- Systolic <110 mm Hg
- Pulse >105
- pH <7.25
- HCT <32%
- HGB <10 g/dL
- INR >1.5 (Is INR the correct measure?)

McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma 2008;64:S57–63.
Schreiber MA, Perkins J, Kiraly L, et al. Early predictors of massive transfusion in combat casualties. J Am Coll Surg 2007;205:541–5

Current Typical Approach to ACOTS

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RBC/Plasma 1:1?

- USA hospital in Baghdad Green Zone
  - Retrospective w/o controls but extensive, accurate data
  - Tx >2000 wounded, massively Tx >600 wounded
- Ratio and results
  - Receiving <1 plasma/4 RBCs: 65% mortality
    - Confounding data: soldiers who received >10 RBCs but died before plasma could thaw are counted in this arm
  - Receiving 2 plasma/3 RBCs: 19% mortality
    - Surgeons report less bleeding and edema
  - Now implementing 1:1 plasma/RBC Rx
- Anticipated adverse effects; none recorded
  - Plasma supply, TRALI, anaphylaxis, ARDS, MOF, thrombosis

Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affect mortality in patients receiving massive transfusions in a combat support hospital. J Trauma 2007; 63: 805–13.

Current Typical Approach to ACOTS

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Massive Trauma With Hemorrhagic Shock

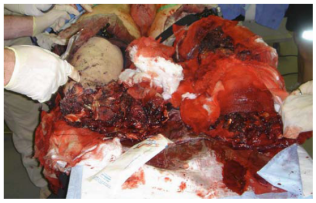
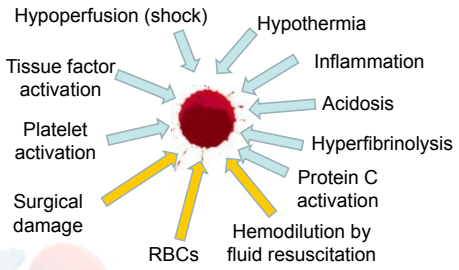


Figure 2. Severely injured patients can present with coagulopathy at the time of hospital admission. This soldier arrived in hemorrhagic shock and required massive transfusion with packed red blood cells (pRBC), coagulation products, and whole blood. Tourniquets were placed on the patient's thighs in the field to minimize blood loss.

Coagulopathy

Acute Coagulopathy of Trauma-Shock (ACOTS)



Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

Coagulopathy
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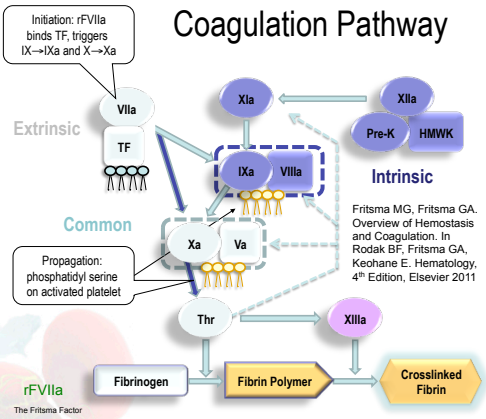
Coagulation Pathway



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

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Probability of Life-threatening Coagulopathy

Condition (n = 58, >10 RBCs)	% Coagulopathy
Injury severity score (ISS) >25 alone	10%
ISS >25 & systolic BP <70 mm Hg	39%
ISS >25 & body temp <34°C	49%
ISS >25 & pH <7.10	58%
ISS >25; SBP <70 mm Hg; body temp <34°C	85%
ISS >25; SBP <70 mm Hg; temp <34°C; pH <7.10	98%
Life-threatening coagulopathy arbitrarily defined as PT and PTT >2X mean of RI Definition of injury severity score; trauma.org	

Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. J Trauma 1997;42:857-862

Coagulopathy
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Injury Severity Score (ISS)

Region	Description (Examples)	Injury Score (1–6)	Highest 3 Squared
Head & neck	Cerebral contusion	3 (Serious)	9
Face	Scratches	1 (Minor)	
Chest	Sucking wound	4 (Severe)	16
Abdomen	Liver contusion Spleen rupture	2 (Moderate) 5 (Critical)	25
Extremity	Fractured femur	3 (Serious)	
External	No injury	0	
Total ISS			50
Maximum is 75. If an injury is assigned a score of 6 (unsurvivable), the ISS is automatically 75. The ISS is the only anatomical scoring system in use and correlates linearly with mortality, morbidity and hospital stay.			

Baker SP, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96

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Coagulopathy in Trauma

ISS & Coagulopathy n = 1088	% Coagulopathy by Lab Assay
Injury severity score (ISS) >15; median 20	57.7%
Injury severity score <15	10.9%
Coagulopathy at Admission	**% Mortality**
Yes (24.4%)	46%
No	10.9%
Overall mortality	19.5%
Coagulopathy defined prior to & independent of fluid replacement as: PT >18s,16.3%; PTT >60s, 24.4%; or thrombin time >15s, 14.2%	

Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54: 1127-30

Coagulopathy
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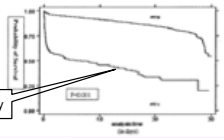
PT and PTT Predict Mortality

- Review of 7638 level I trauma admissions
- Initial PT >14s: 28%
  - 6.3% of patients with PT <14s died
  - 19.3% of patients with PT >14s died
  - Independent mortality increase 35%; OR, 3.6; p <0.0001
    - When controlling for age, ISS, BP, HCT, pH, and head injury
- Initial PTT >34s: 8%
  - Independent mortality increase 326%; OR 7.8; p <0.001

MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39-44.



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Coagulopathy and Shock

- 208 pts, 75% male, level I trauma center
  - 3/03 to 6/04
- Specimens within 10 minutes of arrival
  - PT, PTT
  - Base deficit (BD, metabolic acidosis): measure of shock
- Assays made at conclusion of study
  - Plasminogen activator inhibitor 1 (PAI-1)
  - Prothrombin fragment 1+2 (PF 1+2)
  - Soluble thrombomodulin (TM)
  - Protein C activity (PC)
  - Fibrinogen (FG)
  - D-dimer (DD)

Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion, modulated through the protein C pathway? Ann Surg 2007; 245: 812-8.

Coagulopathy

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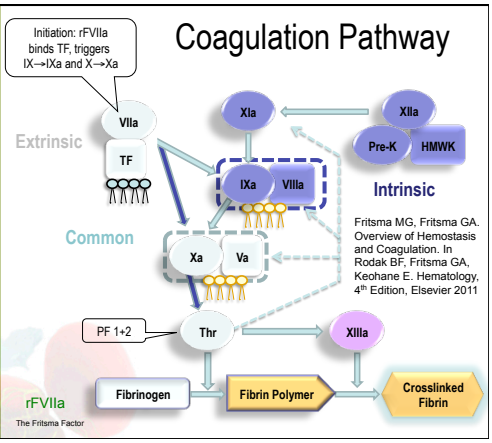
Coagulation Pathway



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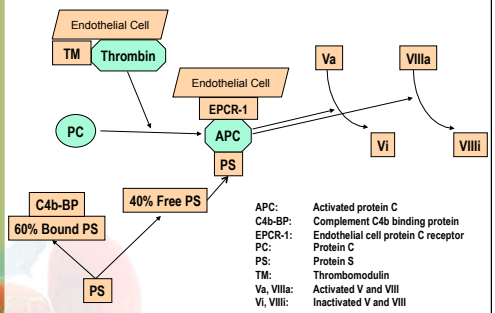
The Protein C Control Pathway



APC: Activated protein C
C4b-BP: Complement C4b binding protein
EPCR-1: Endothelial cell protein C receptor
PC: Protein C
PS: Protein S
TM: Thrombomodulin
Va, VIIIa: Activated V and VIII
Vi, VIIIi: Inactivated V and VIII

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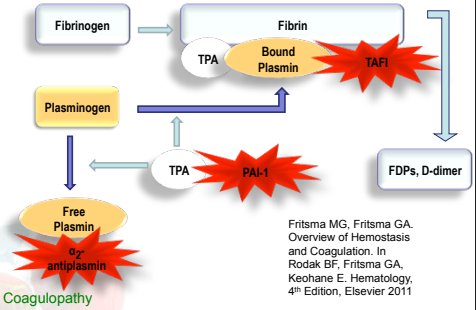
Fibrinolysis



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Coagulopathy

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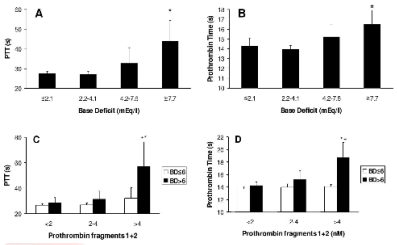
PT, PTT Versus Hypoperfusion (Shock, Surrogate is Base Deficit)



A and B: PT and PTT as a function of BD
C and D: PT and PTT prolonged in BD, PF1+2 baseline

Coagulopathy

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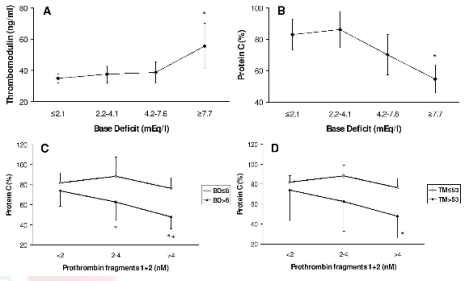
TM and PC Versus BD and PF 1+2



A and B: TM rises and PC drops as a function of BD
C: PC drops as a function of [PF 1+2] only in BD
D: PC drops as a function of [PF 1+2] only in TM rise

Coagulopathy

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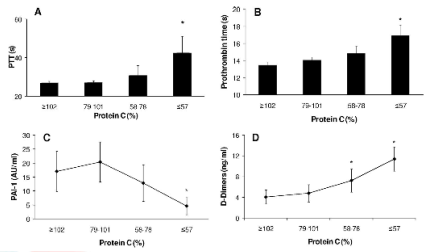
PT, PTT, PAI-1, D-D Versus PC



A and B: PTT and PT prolong as PC drops
C: PAI-1 drops as PC drops
D: D-dimer rises as PC drops

Coagulopathy

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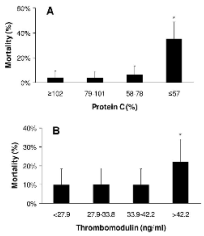
PC, TM Versus Mortality



A: Mortality as PC drops
B: Mortality as TM rises

Coagulopathy

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Conclusions
Early Post-injury Coagulopathy

- Coagulopathy not due to reduced coagulation factors
- Fibrinogen levels normal in all patients
- PT and PTT prolonged only in increased BD (hypoperfusion, shock)
- TM rises and PC falls in increased BD
- Activated PC depletes PAI-1
  - Reduced inhibition of tissue plasminogen activator
  - Key outcome: reduced fibrinolysis

Coagulopathy

Brohi K, Cohen MJ, Ganter MT, et al. Acute Traumatic Coagulopathy: Initiated by hypoperfusion, modulated through the protein C pathway? Ann Surg 2007; 245: 812-8.

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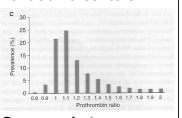
Definition and "Drivers" of ACOTS

- Retrospective cohort study
  - 3646 trauma patients at 5 international trauma centers
- Prothrombin time ratio >1.2
  - Mortality 22.7% Vs. 7.0%, p <0.001
  - RBCs 3.5 Vs. 1.2 units, p <0.001
  - Plasma 2.1 Vs. 0.8 units, p <0.001
- ACOTS defined as PTR >1.2 correlates with ISS and shock
- Confirmed using rat model (not described)



Frith D, Goslings JC, Gaarder C, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010;8: 1919-25.

Coagulopathy

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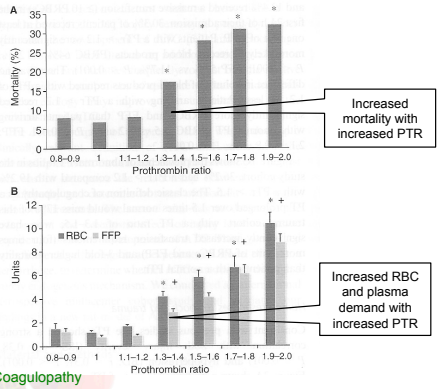

Coagulopathy

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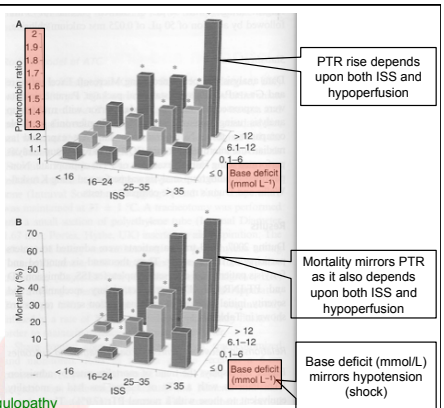

Coagulopathy

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Recombinant Activated Factor VII

- Pre-1980 (and still available)
  - Prothrombin complex concentrates (PCC) extracted from human plasma using Ba_2SO_4 absorption: Proplex®
    - Factors II, VII, IX, and X, once used for IX deficiency patients
  - Activated PCC for FVIII or FIX deficiency with inhibitors
    - FEIBA FH ®
    - Variant efficacy traced to FVIIa activity
- 1980: Extract FVIIa from human plasma
  - Kisiel, Broze
- 1983: Compassionate use in two humans
- 1988: Novo Nordisk®, Bagsvaerd, Denmark, undertook to synthesize rFVIIa
- March 25, 1999: FDA releases NovoSeven® rFVIIa

Kisiel W. Recollections on the discovery of factor VIIa as a novel therapeutic agent for hemophiliacs with inhibitors. J Thromb Haemost 2009;7:1053–6.
Broze GJ, Majerus PW. Purification and properties of human coagulation factor VII. J Biol Chem 1980;255:1242–7.

rFVIIa
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FEIBA FH Dosages

- Activated prothrombin complex concentrate
  - Activated II (thrombin), VII, IX, and X

Indication	Dose
Joint bleeding	50 units/kg every 12 h
Mucous membrane bleeding	50 units/kg every 6 h
Muscle bleeding	100 units/kg every 12 h
To avoid DIC, FEIBA FH dose may not exceed 200 units/kg in 24 hours and infusion rate may not exceed 2 units/kg/minute	
There is no test to monitor FEIBA. The patient's clinical response, e. g., bleeding or hematoma size, is the only guide.	
Cost $0.50/unit, single Rx for a 70 kg patient is $1750	

rFVIIa
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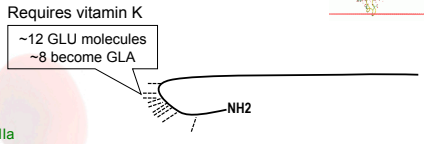
rFVIIa; NovoSeven

- Secreted from baby hamster kidney cells, proteolytically converted to two-chain active form
- Limitation: γ-carboxylation of 2/3 of glutamic acids at carboxy terminus
  - Seems to be enough γ-carboxylated GLUs
  - Requires coexpressed γ-glutamyl carboxylase
  - Requires vitamin K



rFVIIa
The Fritsma Factor 33

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Physiology of rFVIIa & Tissue Factor

- rFVIIa binds TF of injured vessels, activating FX; FXa binds FV; activates II→IIa; generates fibrin
- rFVIIa activates platelets directly through thrombin receptors and triggers primary coagulation even in Glanzmann thrombasthenia
- rFVIIa activates *thrombin activatable fibrinolysis inhibitor* (TAFI), simultaneously reduces fibrinolysis
- rFVIIa hemostatic action is localized by TF
  - FEIBA functions systemically
  - DIC risk is negligible

Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders —a 2006 review. Haemophilia 2006;12:457–72.
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;71:1836–41.

rFVIIa
The Fritsma Factor 34

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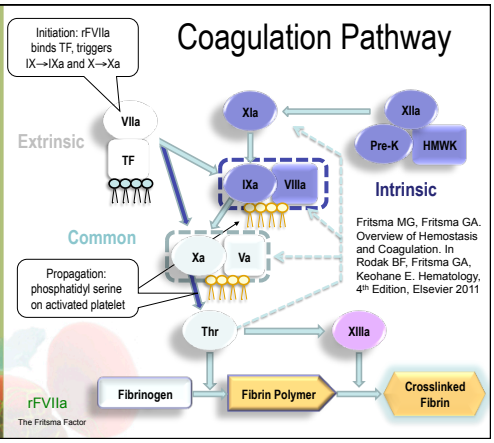
Coagulation Pathway



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

rFVIIa
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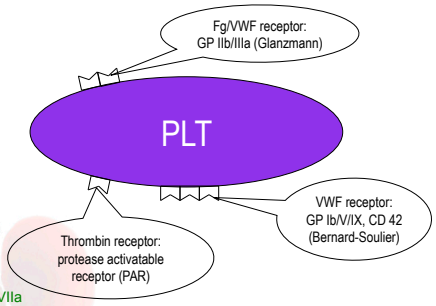
Platelet Receptors (and 50 more)



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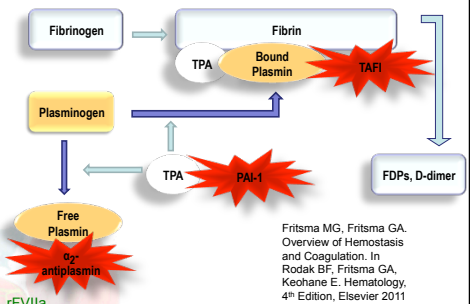
Fibrinolysis



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

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rFVIIa 3/25/99 FDA Indications

- Bleeding episode Rx in hemophilia A or B with inhibitors or in acquired hemophilia
- Bleeding prevention in invasive procedures in hemophilia A or B with inhibitors or acquired hemophilia
- Bleeding Rx in congenital FVII deficiency
- Bleeding prevention in invasive procedures in congenital FVII deficiency

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)
Room Temperature Stable

rFVIIa
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rFVIIa Dosages Cleared by FDA

Cleared Indication	IV Bolus Dose
Hemophilia A or B or acquired hemophilia with inhibitor • Bleeding episode	90 mcg/kg every 2 h until hemostasis is achieved
Hemophilia A or B or acquired hemophilia with inhibitor • Surgery	90 mcg/kg immediately before and every 2 h during surgery
• Post-surgery • minor	90 mcg/kg every 2 h for 48 h, then every 2–6 h until healed
• Post-surgery • major	90 mcg/kg every 2 h for 5 d then every 2 h until healed
Congenital FVII deficiency—bleeding episode or surgery	15–30 mcg/kg every 4–6 h until healed
Acquired hemophilia—bleeding episode or surgery	70–90 mcg/kg every 2–3 h until hemostasis is achieved
Cost $1.00/mcg, single Rx for a 70 kg patient is $6300	

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Off-label Applications for NovoSeven

- Cardiac, thoracic, aortic and spinal surgery; hepatic resection; hysterectomy or post-partum bleeding
- Severe multiple trauma
- Non-traumatic intracranial hemorrhage if <4 hours from onset
- Reversal of antithrombotic (warfarin) overdose

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Off-label Guidelines for NovoSeven

- Evaluate underlying disorder
- Evaluate salvageability of the patient
- Ensure no inherent thrombophilia, prior AMI or stroke
- Exhaust current treatment options
  - RBCs, plasma, PLTs, CRYO
- Document amount of blood products used
- Ensure pH >7.25

Mathew P, Simon TL, Hunt KE, Crookston KP. How we manage requests for recombinant factor VIIa (NovoSeven). Transfusion 2007;47:8–14.

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Generalized Off-label Guidelines for NovoSeven

- Always offer rFVIIa when bleeding continues after conventional Tx therapy
  - RBC, plasma, platelets, and CRYO
  - rFVIIa doesn't work when coagulation factors <30%
  - 40–90 mcg/kg in adults for all emergent scenarios
- Contraindicated in previous thrombosis
  - Stroke: ensure it is intracranial hemorrhage
  - Assume no thrombosis in young trauma victims
- 20–40 mcg/kg in non-emergent warfarin reversal

Personal communication, R. Sarode, MD, Director, Transfusion Medicine and Hemostasis Reference Laboratory, UT Southwestern MC, Dallas, TX

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Warfarin Reversal by rFVIIa

Skolnick BE, Mathews DR, Khutoryansky NM, et al. Exploratory study on the reversal of warfarin with rFVIIa in healthy subjects. Novo Nordisk Inc., Princeton, NJ, United States. Blood, April 12, 2010 e-pub, accessed 5-13-10.

The use of warfarin has a well-known bleeding risk. Recombinant FVIIa is a non-plasma derived, rapid-acting and rapidly infused potential treatment for this condition. This randomized, single-center, placebo-controlled, double-blinded, dose-escalation, exploratory Phase 1 trial assessed the safety and effects of rFVIIa in reversing warfarin-induced changes in bleeding and coagulation parameters, using a punch-biopsy-induced bleeding model in healthy subjects. The effects of warfarin (experiment 1) and rFVIIa (5-80mcg/kg, experiment 2) were evaluated. Outcomes were bleeding duration, blood loss, **coagulation parameters** and safety. Warfarin treatment significantly increased bleeding duration and blood loss from pre-treatment (experiment 1, 12 subjects). **However, these parameters post-rFVIIa treatment were not significantly different from placebo** (experiment 2, 114 subjects). **Mean aPTT, PT and INR were reduced from warfarin-elevated levels**. Recombinant FVIIa (80mcg/kg) significantly reversed warfarin effects on **all thromboelastography parameters,** compared to placebo ($p<0.05$), and **returned the speed of thrombin generation to baseline level**, but did not affect total thrombin generation. There were no thromboembolic or other serious adverse events. In this exploratory trial, the reversal of warfarin effects was observed in the thromboelastography, thrombin generation and clotting assays. However, this reversal did not translate to improvements in the bleeding model parameters evaluated by the punch-biopsy model.

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Acute Care Facility NovoSeven Guide

- Post-cardiac surgery
  - 90–120 mcg/kg, 1–2 doses at 2h intervals, rarely 3
  - Treat to bleeding cessation
- Newborns
  - Split vial into 4–6 aliquots, use all within 24 hours
  - 90–120 mcg/kg at 2h intervals, treat to normalized PT
  - *Not recommended* by Novo Nordisk
- Glanzmann, congenital platelet disorders
  - Often children, dose accordingly
  - Avoids alloimmunization to platelet concentrates
  - 90–120 mcg/kg, 2h intervals, treat to bleeding cessation
- Trauma
  - 90–120 mcg/kg, second at 2h 40–60, rarely 3
- Intracranial hemorrhage
  - 90–120 mcg/kg, 2h intervals, treat to control expansion
  - Observe resolution of neurological symptoms
  - 3.5x odds for serious thromboembolic event

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Off Label Use in Trauma: 2005

- Israeli soldier with bleeding rescued by rFVIIa
- Approved by USA surgeon general for battlefield
- Case reports of efficacy and research protocols by Col. John B. Holcomb, MD
  - Commander of the US Army Institute of Surgical Research, Ft Sam Houston, TX, and Trauma Consultant for The Army Surgeon General

Alten JA, Benner K, Green K, et al. Pediatric off-label use of recombinant factor VIIa. Pediatrics 2009;123:1066–72.
Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 2005;33:883–90.
Tatoulis J, Theodore S, Meswani M, et al. Safe use of recombinant activated factor VIIa for recalcitrant postoperative haemorrhage in cardiac surgery. Interact Cardiovasc Thorac Surg 2009;9:459–62.
Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. J Thromb Haemost 2005;3:640–8.

rFVIIa

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Spinella: Iraq Combat Trauma

- Retrospective case-control study of 124 severe Iraq combat trauma patients
  - ≥10 units RBCs/24h
- Determine if rFVIIa reduces 24 h and 30 d mortality
- Determine association of rFVIIa with severe VTE

One 120 mcg/kg dose	Means	
Transfusion	**75 Controls**	**49 rFVIIa**
RBC (units)	14	16
Plasma (units)	8	10
Fresh whole blood (units)	0	4
Cryo (units)	0	10

Spinella PC, Perkins JG, McLaughlin DF, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. J Trauma 2008; 4: 286–93.

rFVIIa

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Spinella: Mortality Rate in Iraq

All-cause Mortality	75 Controls	49 rFVIIa	P
12 h	25 (33%)	6 (12%)	.008
24 h (cumulative)	26 (35%)	7 (14%)	.01
30 d (cumulative)	38 (51%)	15 (31%)	.03
Thromboembolism	0	2	.15
37 patients died from hemorrhage	29 (78%)	8 (57%)	.12

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Cameron: Blood Products Australia and New Zealand

- Uncontrolled retrospective registry data of 108 patients receiving rFVIIa for trauma
- Two PEs, 1 CVA, 1 DIC

Median Dose 90 mcg/kg	Median Pre-rFVIIa	Median Post-rFVIIa	P
RBCs	16	3	< .001
Plasma	8	1	< .001
PLT	3	0	< .001
CRYO	5	0	< .001
PT/INR	Shortened/reduced		< .001
PTT	Shortened		.004

Cameron P, Phillips L, Balogh Z, et al. The use of recombinant activated factor VII in trauma patients: Experience from the Australian and New Zealand haemostasis registry. Injury 2007; 38: 1030–8.

rFVIIa

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Harrison: General Trauma

- Prospective study of rFVIIa-treated trauma patients matched to historic controls
- Mortality rates 41% in rFVIIa, 40% in controls (NS)
- Thromboemboli in 6.9% of rFVIIa, 19.7% of controls; (P=0.2)

1–2 40 mcg/kg doses	Means (SD not shown)		P
Transfusion	72 Controls	29 Cases	
RBC (units)	22.0	18.3	.036
Plasma (units)	14.1	14.2	NS
PLT (5-pack units)	2.3	1.4	.01
Cryo (5-pack units)	1.5	0.59	.006

Harrison TD, Laskosky J, Jazaeri O, et al. "Low-dose" recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. J Trauma 2005; 59: 150–4.

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Holcomb: Tx Requirements: 48 Hours After First Dose of rFVIIa

	Placebo		rFVIIa		P
	N	Median	N	Median	
RBC (units)	65	6.6	48	2.9	<0.001
Plasma (mL)	54	1400	35	660	0.001
PLT (mL)	62	300	46	50	0.01

- Incidence of MOF or ARDS was 20% for placebo, 3% for rFVIIa, P=.004
- Incidence of thromboembolic events was 4% for placebo and 3% for rFVIIa, P=1.00

Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med 2009;70: 22–5.

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For Patients Alive at 48 Hours

Median RBC Units					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
7.5 (n=72)	7.0 (n=52)	.02*	4.2 (n=52)	3.9 (n=64)	.10

ARDS or Multi-organ Failure					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
49 (66%)	44 (64%)	NS	36 (56%)	36 (51%)	NS

Thromboembolic Events					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
3 (4%)	2 (3%)	NS	3 (5%)	4 (6%)	NS

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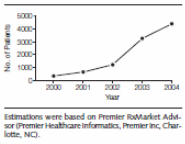
FDA Reports Thromboembolic Events

Divs. of Epidemiology and Hematology collected adverse event data 3/25/99–12/31/04, all US and non-US patients including post-licensure clinical trials

Figure 1. Estimated Number of Patients Treated With Recombinant Human Coagulation Factor VIIa by Year



Estimations were based on Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC).

Table 1. Number of Thromboembolic Event Reports With Use of rFVIIa by Report Source and Reason for Use and Bleeding Status

	No. of Reports (%)	
	Trial (n = 59)	Spontaneous (n = 109)
Reason for use		
Surgery (bleeding or prophylaxis)	27 (46)	48 (44)
Intracranial bleeding	19 (32)	5 (4)
Bleeding, nonsurgical	8 (14)	26 (24)
Trauma, nonsurgical	5 (8)	9 (8)
Hemophilia	0	17 (16)
Unknown*	0	4 (4)
Bleeding status		
Active bleeding	35 (59)	80 (73)
Prophylaxis	24 (41)	22 (20)
Unknown*	0	7 (7)

Abbreviation: rFVIIa, recombinant human coagulation factor VIIa.
*Indicates no information about reason for use or whether patient was bleeding or not.

O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295:293–8.

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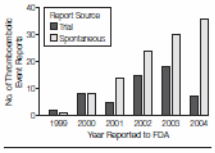
Thrombotic Events and Deaths

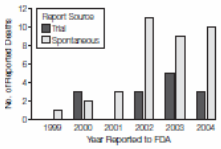
168 reports: 183 thrombotic events, 52 deaths

Figure 3. Number of Thromboembolic Event Reports With Recombinant Human Coagulation Factor VIIa Reported to FDA by Source and Year



FDA indicates US Food and Drug Administration. Some reports had more than 1 thromboembolic event.

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



FDA indicates US Food and Drug Administration.

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Thrombotic Event Sites

Site	Number (%)
Ischemic stroke	39 (21.3%)
Acute myocardial infarction	34 (18.6%)
Peripheral artery occlusion	26 (14.2%)
Deep venous thrombosis	42 (22.9%)
Pulmonary embolus	32 (17.5%)
Occluded line	10 (5.5%)
Total	**183 (100%)**
Patients in 5-y survey	~10,700
Rate of thrombotic events	0.017%

rFVIIa Thrombosis

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London Times, September 17, 2006

"*Wounded Iraq Troops Given Danger Drug*"

"*The Ministry of Defense has been accused of playing 'Russian roulette' with soldiers' lives after it admitted using an unlicensed drug linked to 67 deaths in America. Troops suffering severe injuries in Iraq have been treated with NovoSeven®, a drug licensed only for hemophiliacs.*"

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

rFVIIa Thrombosis

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Subsequent Discussion

Recombinant Factor VIIa and Thromboembolic Events

To the Editor: Dr O'Connell and colleagues[1] reviewed thromboembolic complications of recombinant human coagulation factor VIIa (rFVIIa) as reported to the US Food and Drug Administration (FDA) MEDWATCH database. As with any medication, rFVIIa has both positive and negative effects; therefore, risks and benefits must be considered before administering the drug. In our trauma practice, we cannot know which of our patients with life-threatening hemorrhage are also at risk for ischemic stroke, myocardial infarction, or other thrombotic complications. We are cautious with rFVIIa use in the presence of arterial injury and will not use it in patients undergoing extracorporeal circulatory support. However, some patients have dilutional coagulopathy severe enough to warrant the use of almost any therapy to salvage them from hemorrhagic shock, regardless of risk.[2] A recent randomized, placebo-controlled, double-blind trial of the use of rFVIIa in patients with trauma did not find an increased risk of thromboembolic events.[3] This study, however, excluded patients older than 65 years, who would be most likely to experience adverse thromboembolic events.

Less clear to us is the risk-benefit ratio for off-label rFVIIa use in patients who are not in extremis. One frequent use of rFVIIa is the reversal of warfarin therapy in patients presenting with active bleeding, such as those patients with subdural hematoma. Coagulation may be normalized more rapidly than with traditional administration of plasma, with a decreased risk of fluid overload. It would therefore be helpful to know how many of the reported thromboembolic complications described by O'Connell et al were observed in patients who were taking warfarin analogs or platelet inhibitors before the rFVIIa dose, what proportion of the prophylactic use was in patients with conditions such as cirrhosis that are associated with coagulopathies, and what proportion was in patients with normal coagulation systems.

Finally, the comments on the study of rFVIIa in patients with intracranial hemorrhage[4] were valuable, because this was the first prospective study to suggest a dose-response effect in the thromboembolic complication rate. Understanding the risks of rFVIIa will be enhanced if reports to MedWatch include the dose of drug administered, other procoagulant therapies, underlying pathophysiology, and the timing of complications. Such detail may help in designing future trials of rFVIIa.

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Financial Disclosures: Dr Dutton reported serving as a research design consultant for Novo Nordisk, the manufacturers of rFVIIa. Dr Stein reported that her research is funded by Novo Nordisk. No authors have an ownership position or direct financial interest in Novo Nordisk. No other authors reported financial disclosures.

1. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA*. 2006; 295:293–298.
2. Dutton RP, McCann M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma*. 2004;57:709–719.
3. 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.
4. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785.

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Response by Authors

In Reply: The comments from Dr Dutton and colleagues emphasize the importance of benefit-risk considerations for patients in extremis vs those who are not. Available information from the FDA's database of 168 patients with post-rFVIIa thromboembolic events does not include sufficient detail to respond to all of their questions. However, regarding prophylactic use, the records identify only 1 patient who underwent warfarin reversal. An elderly man with an international normalized ratio of 2.7 received fresh-frozen plasma (6 units) and 2.4 mg of rFVIIa (30 μg/kg) before evacuation of a subdural hematoma, and vitamin K after surgery. Pulmonary embolism was diagnosed 3 days later. Among 46 reports of prophylactic rFVIIa use, 26 specifically mentioned the presence of serious liver disease.

We agree about the importance of reporting serious adverse events to the FDA's MedWatch program and including as complete detail as possible. These anecdotal reports can contribute to the design of needed prospective trials. Clinicians can easily provide reports of adverse events via the online MedWatch reporting system,[1] download the voluntary reporting form and fax it to 1-800-FDA-0178, or call 1-800-FDA-1088 to report by telephone. Alternatively, adverse events can be reported to the product manufacturer, who is then required to report to the FDA.

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Financial Disclosures: None reported.

1. Voluntary reporting by health professionals. US Food and Drug Administration. http://www.fda.gov/medwatch/report/hcp.htm. Accessed March 14, 2006.

rFVIIa Thrombosis

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Novo Nordisk Phase 2 Trial

- Multicenter prospective randomized double-blind placebo-controlled trial evaluated effect of rFVIIa on RBC transfusion requirements in patients with blunt or penetrating trauma
- 277 patients, 143 blunt, 134 penetrating
  - Criteria: required 6 RBC units within 4 hours of admission
- Placebo or rFVIIa at 0 h (200 mcg/kg), 1 h (100 mcg/kg), and 3 h (100 mcg/kg)
- Adverse events: adult respiratory distress syndrome (ARDS), multi-organ failure (MOF) and thromboembolic events (TE)

Bruder E, Howes DW. rFVIIa in trauma: A review and opinion-based guidelines. Trauma 2007; 9: 237–43.

rFVIIa Thrombosis

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rFVIIa Phase III Trial Withdrawal

Hauser CJ, Boffard KD, Dutton RP, et al. Efficacy and safety of recombinant activated factor VII in the management of hemorrhagic shock due to trauma. J Thromb Haemost 20097 (Suppl2):290–1.

Background: Hemorrhage contributes significantly to multiple organ failure (MOF) and death following severe injury. We performed a multicenter, international, placebo controlled Phase III trial to evaluate recombinant activated factor VII (rFVIIa) as an adjunct to standard hemostatic methods in trauma patients presenting in hemorrhagic shock. We assessed the safety of rFVIIa and its efficacy in improving survival, reducing blood loss, and decreasing MOF.
Methods: 573 actively bleeding patients (481 blunt, 92 penetrating), who had received 4–8 units of blood within 12 h of injury and had evidence of ongoing hemorrhagic shock were randomly assigned to receive rFVIIa (200 μg/kg at 0 h, 100 μg/kg at 1 h and 3 h) or placebo. Clinical care was standardized according to evidence-based guidelines. The primary outcome was 30-day mortality. Secondary outcomes included total allogeneic blood product transfusions and the incidence and duration of organ failure. Safety and clinical outcomes were assessed to 90 days.
Results: The study was terminated prematurely after 573 patients (1502 initially planned) because an unexpectedly low mortality rate (~10%) precluded demonstration of efficacy. No difference in 30-day mortality was observed ($P = 0.93$). rFVIIa decreased total blood product use at 48 h compared with placebo in blunt trauma patients (23.5 vs. 19.0 units; $P = 0.04$). There were no differences in the incidence or duration of organ failure ($P = 0.09$). There were no differences in adverse events, including thromboembolic events.
Conclusions: Treatment of blunt trauma patients in hemorrhagic shock with rFVIIa decreased blood product use without an observed increase in thromboembolic complications, but did not demonstrate improvement in organ system failure or mortality.

rFVIIa Thrombosis

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Baltimore Sun, May 16, 2010

Federal agents probing Army's use of trauma drug

Criminal investigation looking at military's use of blood-clotting injections for treating war casualties

May 16, 2010 | By Robert Little, The Baltimore Sun

Sun photo by Monica Lopossay

Federal criminal investigators are exploring the Army's use of a controversial and expensive blood-clotting drug injected into wounded troops in Iraq and Afghanistan.

The drug, called Factor VII, was hailed as a lifesaving breakthrough by military leaders and administered to hundreds of soldiers and Marines earlier in the wars. It has since proved largely ineffective in clinical trials and been the subject of safety warnings by U.S. and European regulators, who say it can cause potentially deadly blood clots.

Within the past several weeks, agents from the Army's Criminal Investigation Command have interviewed scientists and officers at the Army's medical laboratory in San Antonio about Factor VII, according to military sources with knowledge of the investigation. Researchers in San Antonio were among the first to explore Factor VII's role in treating trauma patients and have produced some of the few scientific studies suggesting that the drug saves lives in combat.

The manufacturer, the Danish drug company Novo Nordisk, said it had received a subpoena in January from the Defense Department's inspector general's office. Company officials said they are cooperating with the U.S. attorney's office in Baltimore, which is overseeing the investigation.

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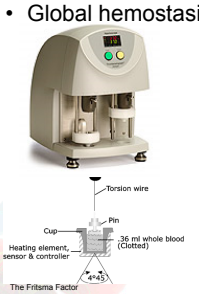
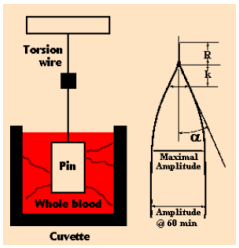
Laboratory Monitoring

- PT, PTT, FG, D-dimer, PLT count
  - Broad assessment, not accurate for dosing
- Global hemostasis: thromboelastograph





The Fritsma Factor 61

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Thromboelastogram

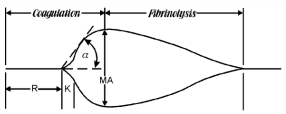
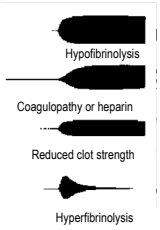


Figure 4. Thromboelastograph (TEG) tracing. The reaction time (R) represents the time to onset of clot formation. K time is a measure of the speed to reach a certain level of clot strength. α angle represents the rate of clot formation. The maximum amplitude (MA) measures the clot strength. Reprinted with permission from Kiraly, J Trauma 2006;61:57–64.



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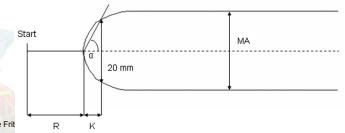
TEG Parameters

Clotting time	R	Interval from when the blood was placed in the analyzer until initial fibrin formation
Clot kinetics	K	Interval to reach a chosen clot strength
	α	Interval to fibrin buildup and cross-linking
Clot strength	MA	Maximum dynamic properties of fibrin and platelet bonding via GP IIb/IIIa
Hemostasis profile	CI	Linear combination of K, K, α, MA and G
Clot stability	LY30	Rate of amplitude reduction 30 m after MA



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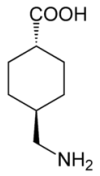
Tranexamic Acid (Cyclokapron) Rx

- Synthetic lysine blocks plasminogen binding sites
  - Cyclohexane carboxylic acid
- Reduces Tx requirements in surgery without change in mortality



CRASH-2 trial collaborators (570). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet 2010; 376: 23-32

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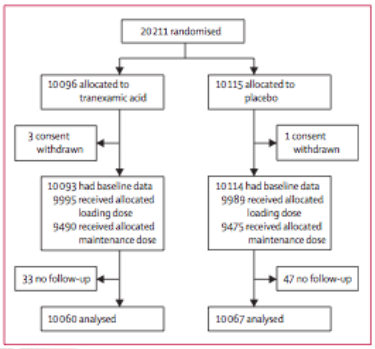
CRASH-2



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Tranexamic Acid Death by Cause

	Tranexamic acid	Placebo	RR	p
	n = 10060	n = 10067		
Any cause of death	1463 (14.5%)	1613 (16%)	0.91	0.0035
Bleeding death	489 (4.9%)	574 (5.7%)	0.85	0.0077
Vascular occlusion death	33 (0.3%)	48 (0.5%)	0.69	0.096
No dependency symptoms	1483 (14.7%)	1334 (13.3%)	1.11	0.0023

- No significant differences:
  - MI, stroke, PE, DVT, blood products, surgery

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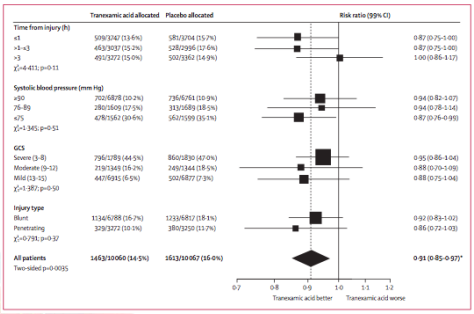
All-cause Mortality by Subgroups



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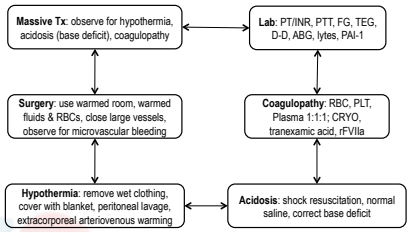
Summary: ACOTS



Modified from: Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: Its pathophysiology and treatment in the injured patient .World J Surg 2007 31: 1055–64