New Concepts in the Prevention and Treatment of Bleeding

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### Disclosures for Jerrold H Levy, MD, FAHA, FCCM

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>DoD, ViroPharma</td>
</tr>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Consultant</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
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<td>Honoraria</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>CSL Behring, Baxter, Boehringer-Ingelheim, Johnson&amp;Johnson, Merck, Novo Nordisk</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: Yes
Learning Objectives

• Discuss basic concepts of hemostasis
• Review pathophysiologic mechanisms coagulopathy post surgery and trauma
• Discuss therapeutic approaches to treating bleeding
• Review the critical role of fibrinolysis in bleeding
Dutch (Arnold Schwarzenegger) to Jesse Ventura: 
“You are bleeding!”

Jesse Ventura to Arnold: 
“I ain’t got time to bleed”
HEMOSTASIS
COMPONENTS OF HEMOSTASIS

- Vasculature
- Coagulation proteins
- Platelets
Hemostasis

Subendothelial matrix

Hemostatic plug

Endothelial cell

WBC

Platelets

Fibrin

RBC

WBC
Normal Hemostasis

CLOT FORMATION

- Platelet
- Red Blood Cell
- Fibrin
VASCULAR ENDOTHELium

COAGULOPATHY OF TRAUMA
Types of hyperfibrinolysis

• **A** = fulminant

• **B** = intermediate

• **C** = late

Hyperfibrinolysis Diagnosed by Rotational Thromboelastometry (ROTEM®) Is Associated with Higher Mortality in Patients with Severe Trauma

Oxiver M. Theusinger, MD, Gido A. Wannen, MD, Maximilian Y. Emmert, MD, Adrian B. Rein, MD, Jennifer Enron, MD, Burkhardt Seifert, PhD, Hans-Peter Simmen, MD, Donat R. Spahn, MD, FRCA, and Werner Baulig, MD

(Anesth Analg 2011;113:1003-12)
TEG/ROTEM: summary

- POC testing and transfusion algorithms reduce the need for allogeneic blood.
- TEG/ROTEM are useful tests as part of POC testing, but also have greater importance in trauma.
- Fibrinolysis is a critical aspect of tissue injury and life threatening hemorrhage, but also for predictive outcomes.
- But do we really need to monitor for fibrinolysis vs just treat?
Critical Role of Fibrinolysis in Bleeding

• Hyperfibrinolysis with extensive tissue injury
• Extensive data in cardiac/ortho surgery
• Growing application in trauma
• Liver transplantation / diseases (reduced α2-Antiplasmin)
• Postpartum hemorrhage (local HF in the uterus, placenta has PAI-2)
• Excessive menstrual bleeding
MONITORING COAGULOPATHY
Challenges of **Routine** Coagulation Testing

- **Partial Picture of Coagulation**
  - Plasma tests
  - Does NOT include platelet contribution (approx. 80% of clot strength)
  - Does NOT include fibrinogen

- **Timeliness**
  - Processing required (spinning samples down, etc.)
  - Wait time is variable
  - Results are dated, arrive after treatment
Global Hemostasis Test using whole blood (includes enzymatic, platelets, lysis)

* TEG Analyzer Overview section of the TEG® 5000 User manual
Clinical Evidence Supporting FFP Use: Meta-analysis of 80 RCTs

• Updated analysis of 80 RCTs to July 2011
• Covered prophylactic and therapeutic use of FFP in liver disease, cardiac surgery, warfarin anticoagulation reversal, TTP, plasmapheresis, burns, shock, and head injury

CI = confidence interval; RCTs = randomized controlled trials
Evidence-based Practice Guidelines for Plasma Transfusion

• We suggest that plasma be Tx to trauma patients requiring massive Tx (quality of evidence = moderate).

• We cannot recommend for or against Tx of plasma at a plasma:RBC ratio of ≥1:3 in trauma patients during massive Tx (evidence = low).

• We cannot recommend for or against Tx of plasma for patients undergoing surgery in the absence of massive Tx (evidence = very low).

Roback JS et al; *Transfusion*. 2010;50:1227-1239.
Reducing Risks with Plasma

- SD treated pooled plasma
  - Consistent factor concentrations
  - Lower risk of Ab mediated reaction
- Use prediction tools for MT to discriminate who requires high plasma/PLTs
- TEG/ROTEM Directed Hemostatic Resuscitation
  - Alternative agents
  - Fibrinogen, PCC, rFVIIa, antifibrinolytics
• PI: John Holcomb: DoD/NIH funded/12 centers
• Randomized to high or low FFP:RBC ratios: 1:1:1 vs 1:1:2
• 580 patients over 2 years
• 24 hour and 30 day mortality in massive Tx - >10 U RBCs in first 24 hrs

http://clinicaltrials.gov/show/NCT01545232
PROHEMOSTATIC AGENTS
PHARMACOLOGIC PROHEMOSTATIC AGENTS

• Antifibrinolytics
• Protamine
• DDAVP (desmopressin)
• Recombinant Factor VIIa (rVIIa, NovoSeven)
• Protein concentrates, fibrinogen
• Fibrin glue/topical thrombin
LYSINE ANALOGS: Epsilon aminocaproic acid and tranexamic acid
EACA/Tranexamic acid

- Often small numbers, variable design, ?Tx criteria, ?Factor reduction
- Most data is TA, NOT EACA
- Doses of TXA range from 2 g to 25 g
- Meta analyses need to be cautiously interpreted
- EACA removed from many European markets
- TXA is approved for excessive menstrual bleeding 1.3 g PO TID
- Increasingly used in trauma patients
SEIZURES/TRANEXAMIC ACID

- Yeh HM: Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of TA. Anesthesiology 2003; 98: 270-2
- Furtmuller R: TA, a widely used antifibrinolytic agent, causes convulsions by a GABA antagonistic effect. J Pharmacol Exp Ther 2002; 301: 168-73
GABA

Tranexamic Acid

EACA-Amicar
• 20,211 trauma patients randomized and treated ≤8 hrs of injury: 2 g tranexamic acid (TxA) or placebo
• In hospital mortality ≤4 weeks primary outcome: vascular occlusive events, transfusions, or surgical interventions were secondary outcomes
• All cause mortality = 14.5% TxA (1,463/10,060) vs 16% placebo (1,613/10,067) p=0.0035
• Bleeding related mortality reduced 4.9% vs 5.7% without increases in fatal or nonfatal vascular occlusive events
• No differences in transfusion
CRASH-2

• Benefit when admin within 3 hrs
• No difference in blood transfusions
• TXA effect varied according to time to treatment/
• TXA $\leq 1$ h reduced the risk of mortality
• TXA should be given as early as possible to bleeding trauma patients.
• How does it reduce risk of death??

TISSUE INJURY

- tPA, Urokinase, Kallikrein
- Hemostatic factors
- Bleeding
- Coagulopathy
- Inflammation
- Edema

Plasminogen
- PAI 1, TAFI
- Tranexamic acid, EACA

Prothrombin
- Anticoagulants
- α2-antiplasmin

Fibrinogen

Fibrin

Clot

Thrombin

Fibrinolysis

Endothelium

tPA

Activation

Plasmin

C₁

Lysis

Activation

Monocytes, PMNs

Levy JH: Lancet. 2010 Jun 14
PROTAMINE

- Basic polypeptide isolated from salmon sperm
- 70% arginine, reverses unfractionated heparin not LMWH
- Heparin rebound can occur
- Produces ADRs
- No alternatives available
Excess protamine causes hemostatic dysfunction

Mochizuki: Protamine reversal of heparin affects platelet aggregation and ACT after CPB. Anesth Analg 1998; 87:781-785
ANAPHYLAXIS TO PROTAMINE

• All patients: 0.06% (1/1500)
• NPH diabetics: 0.6-2% (1/50-1/160)

Levy JH: Anesth Analg 1986; 65:739
Levy JH: JTCS 1989; 98:200
PROTAMINE REACTIONS
PATHOPHYSIOLOGY

• IgE antibodies
• IgG antibodies
• Complement activation
• Direct/indirect effects
Desmopressin
(DDAVP)
Vasopressin Receptors

- **V1a**: vasoconstriction
- **V1b**: adenohypophysis which stimulate release of ACTH
- **V2**: Smooth muscle vasodilation, and increase vWF (desmopressin - AVP analog with V2-specificity)
Summary: DDAVP Rx on surgical bleeding with inherited coagulation disorders

- Data includes small numbers, mostly retrospective analyses
- Data includes multimodal approaches
- Antifibrinolytics are used concomitantly and other factor concentrates
- Bleeding depends on types of surgical procedure; superficial vs major vascular/cardiac/neuro
- Monitoring effects, especially with platelet function tests, is limited
Recombinant Factor VIIa (rFVIIa)
rVIIa (NovoSeven®)  
Mechanism of Action  

- NovoSeven® is human rFVIIa  
- rFVIIa increases TF occupancy  
- rFVIIa in pharmacological doses binds to activated platelets  
- rFVIIa provides FX activation independent of Tissue Factor (TF)  
- Improves platelet function
Mechanism of Action of Recombinant Factor VIIa

Thromboembolic Adverse Events (TBE) After Use of Recombinant Human Coagulation Factor VIIa

O’Connell KA et al
JAMA 2006; 295:293-298

- Critical safety data obtained from 13 Novo sponsored clinical trials of rFVIIa in patients with coagulopathy due to anticoagulant therapy, cirrhosis, or severe traumatic injury.
- Thrombotic AEs were reported for 5.3% (23/430) of placebo and 6.0% (45/748) of active treatment.
- No significant differences was found between placebo-treated and rFVIIa-treated patients for thrombotic AEs, either on an individual trial basis or for these trial populations combined (p = 0.57).
Original Article

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
Volume 363(19):1791-1800
November 4, 2010
Study Overview

• We examined the incidence of thromboembolic events associated with off-label use of rFVIIa in patients with bleeding problems.

• Coronary arterial thrombotic events and abnormal clotting among older patients were more common with rFVIIa than with placebo.
## Population and Dose-Group Distribution in Placebo-Controlled Trials of rFVIIa

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>rFVIIa</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient trials</td>
<td>1536</td>
<td>2583</td>
<td>4119 (92.2)</td>
</tr>
<tr>
<td>CNS bleeding (5 studies)</td>
<td>65</td>
<td>423</td>
<td>974</td>
</tr>
<tr>
<td>Liver disease (7 studies)</td>
<td>54</td>
<td>449</td>
<td>795</td>
</tr>
<tr>
<td>Trauma (3 studies)</td>
<td>36.5</td>
<td>428</td>
<td>409</td>
</tr>
<tr>
<td>Cardiac surgery (3 studies)</td>
<td>45.4</td>
<td>114</td>
<td>153</td>
</tr>
<tr>
<td>Traumatic brain injury (1 study)</td>
<td>50.9</td>
<td>36</td>
<td>61</td>
</tr>
<tr>
<td>Spinal surgery (1 study)</td>
<td>46.6</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Others (6 studies)</td>
<td>38.5</td>
<td>73</td>
<td>155</td>
</tr>
<tr>
<td>Healthy volunteer trials (9 studies)</td>
<td>27.2</td>
<td>117</td>
<td>232</td>
</tr>
</tbody>
</table>
### Table 2. Odds Ratios for Thromboembolic Events.

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

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received the assigned study drug.
All Arterial Thromboembolic Events, According to Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>rFVIIa</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)*</th>
<th>P Value†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 yr</td>
<td>1/70 (1.4)</td>
<td>1/51 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 yr</td>
<td>73/1764 (4.1)</td>
<td>34/1107 (3.1)</td>
<td>1.36 (0.89–2.08)</td>
<td>0.15</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>67/742 (9.0)</td>
<td>14/372 (3.8)</td>
<td>2.43 (1.34–4.41)</td>
<td>0.003</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>33/427 (7.7)</td>
<td>8/225 (3.6)</td>
<td>2.12 (0.95–4.71)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>34/315 (10.8)</td>
<td>6/147 (4.1)</td>
<td>3.02 (1.22–7.48)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Odds ratios were calculated by means of logistic regression with adjustment for indication.
† The P value was not calculated for the first age group because there were only two events.
‡ The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received a study drug.
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.
FCard-1610: Patient Randomization

Consented (N=2619)

Reasons for exclusion:
- Did not meet inclusion criteria for bleeding trigger (n=2268)
- Other (n=179)

Randomized (N=179)

Randomized but not dosed (n=7)

Randomized and dosed (n=172)

Placebo (n=68)
40 µg/kg (n=35)
80 µg/kg (n=69)

Gill R: Circulation 2009;120(1):21-7
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>40 µg/kg</th>
<th>80 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>68</td>
<td>35</td>
<td>69</td>
</tr>
<tr>
<td><strong>CABG only</strong></td>
<td>8 (12%)</td>
<td>5 (14%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td><strong>Single valve</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>14 (21%)</td>
<td>5 (14%)</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>MVR</td>
<td>7 (10%)</td>
<td>4 (11%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td><strong>Double procedure</strong></td>
<td>45 (66%)</td>
<td>25 (71%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td><strong>Triple procedure</strong></td>
<td>9 (13%)</td>
<td>3 (9%)</td>
<td>13 (19%)</td>
</tr>
</tbody>
</table>

Gill R: Circulation 2009;120(1):21-7
FCard-1610: Reason to Randomize

- **Bleeding**
  - $\geq 200 \text{ mL/h}$
- Did not require immediate re-operation
- Intention was to manage with blood products

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>40 $\mu$g/kg rFVIIa</th>
<th>80 $\mu$g/kg rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>69</td>
<td>35</td>
<td>68</td>
</tr>
<tr>
<td>Volume of chest drainage (ICU to randomization), mL, mean (SD)</td>
<td>597 (403)</td>
<td>616 (264)</td>
<td>550 (448)</td>
</tr>
</tbody>
</table>

% Patients Requiring Re-operations

Analyses done by chi-square tests.

FCard-1610: Re-operations Due to Bleeding

- Placebo (n=68)
- 40 µg/kg rFVIIa (n=35)
- 80 µg/kg rFVIIa (n=69)

Overall active vs PBO

- $P = 0.0347$
- $P = 0.2089$
- $P = 0.0422$

- n=17/68
- n=5/35
- n=8/69
Median drainage volume (mL) from the cardiothoracic cavity from 15 min after randomization to 4 hours after randomization
Rescue Therapy with rVIIa in the Perioperative Setting: Off label

- Severe (1 L/hr) or life-threatening (CNS) bleeding without surgical source of bleeding
- Marginal response to routine hemostatic therapy (i.e., platelets, FFP, cryo, DDAVP)
- Judicious use with CV disease, DIC or ongoing activation (CPB)
- Consider lower dose (30 mcg/kg)
- Patients with multiple antibodies and platelets/factors not available

Goodnough LT: Transfusion 2004;44(9):1325-31
Fibrinogen
Fibrinogen is the key substrate of thrombin for clot formation.

Fibrinogen Biology

- Soluble glycoprotein made in the liver
- Two sets of α, β, and γ chains
- Facilitates platelet aggregation via GP IIb/IIIa receptors
- Substrate for thrombin
- During fibrin formation, FPA and FPB released
- FXIIIa acts to cross-link fibrin molecules to form insoluble clot

Fibrinogen Receptors on Platelets
Glycoprotein (GP) IIb/IIIa

• Approx. 13,000 copies of fibrinogen receptors are present on a single activated platelet

• Aggregated platelets via fibrinogen provide a catalytic surface for thrombin generation

Hypofibrinogenemia

- Fibrinogen is an acute phase reactant; levels increase as an inflammatory response.
- Normal fibrinogen levels = 200-400 mg/dl; however most algorithms recommend Tx @ 100 mg/dl.
- Fibrinogen corrects TEG, RoTEM abnormalities, and increase clot strength.
- In US, cryoprecipitate is used: CRYO contains also vWF and FXIII.
- Elsewhere fibrinogen concentrates are used.
Cryoprecipitate: proteins per bag

- FVIII, IU/bag: 80 – 100
- vWF, IU/bag: 80 – 100
- Fibrinogen mg/bag: 150 – 250
- FXIII, IU/bag: 50 – 100
- Fibronectin, mg/bag: 50 – 60
How I use fibrinogen replacement therapy in acquired bleeding

by Jerrold H. Levy, and Lawrence T. Goodnough

Blood
Volume 125(9):1387-1393
February 26, 2015
Clinically Important Bleeding?

YES

Consider early tranexamic acid administration:
- 1 g load
- 1 g infusion over 8 hours

Send coagulation tests:
- Fibrinogen level
- Platelet count
- PT/PTT
- INR
- ROTEM®/TEG®

Maintain homeostasis:
- Normothermia
- Normocalcemia
- Normal pH

Fibrinogen level < 1.5-2.0 g/L and/or
FIBTEM A10 < 6-8 mm

YES

Fibrinogen concentrates (25-50 mg/kg)
or
Cryoprecipitate (8-10 units)

Platelet count < 100 10⁳/mm³

YES

Platelet concentrate (8-10 units)

INR > 1.7 and Hypovolemia

YES

FFP (20-30 mL/kg)

YES

Massive transfusion protocol
MANAGING BLEEDING
# PCCs and Factor Replacement Products

<table>
<thead>
<tr>
<th>Vitamin K-dependent coagulation factors</th>
<th>4-Factor PCC*</th>
<th>Plasma</th>
<th>4F-PCC activated (FEIBA))</th>
<th>3-Factor PCC*</th>
<th>rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VII</td>
<td>✓</td>
<td>✓</td>
<td>✓ activated</td>
<td>Low levels²³</td>
<td>✓ activated</td>
</tr>
<tr>
<td>IX</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Protein C</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Factors in PCCs are ~25x more concentrated than the factors in plasma.
†In plasma, total content of factors relative to volume is low; large volumes are required for reversal.

Options for reversing warfarin

- **Coagulation factor concentrates-PCCs** (e.g. KCENTRA® P/N)
  - Contain all clotting factors required in a concentrate
  - Fast application possible
  - Low volume
  - Predictable and measurable effect

- **Recombinant FVIIa**
  - Off label use
  - Dose not established

- **Vitamin K**
  - Available orally or intravenous
  - Readily available and inexpensive
  - Response slow and unpredictable
  - Not appropriate for emergencies

- **Human plasma** (e.g. FFP, 24-hour plasma)
  - Contains factors that are required and some that are not required
  - Risk of fluid overload and viral transmission
  - Longer time required to thaw and transfuse the product
  - Duration of infusion requires patient monitoring
  - May fail to completely reverse anticoagulation

Levy JH: Anesthesiology 2008;109(5):918
Correlation of INR With Factor Levels

Mean Factor Activity Levels vs INR

Adapted with permission from Gulati G et al. Arch Pathol Lab Med. 2011;135:
Summary

• Bleeding is complex and patients bleed due to multiple issues
• Allogeneic blood exposure may pose risks and alternative agents need to be considered.
• Antifibrinolytics have extensive applications in surgical patients.
• Purified and recombinant products are in our future as therapeutic approaches
• Fibrinogen is a critical component to evaluate and treat in a bleeding patient