

Hemostasis Management: Systemic Agents

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Predator, 1987

Dutch (Arnold
Schwarzenegger) to Jesse
Ventura:

“You are bleeding!”

Jesse Ventura to Arnold:

“I ain't got time to bleed”

SURGICAL PATIENTS: RISKS FOR BLEEDING

- Repeat procedures
- Jehovah's Witnesses
- Aortic surgery
- Dialysis patient
- Endocarditis/active infections
- Preexisting anticoagulants
- Liver disease
- Patients receiving clopidogrel

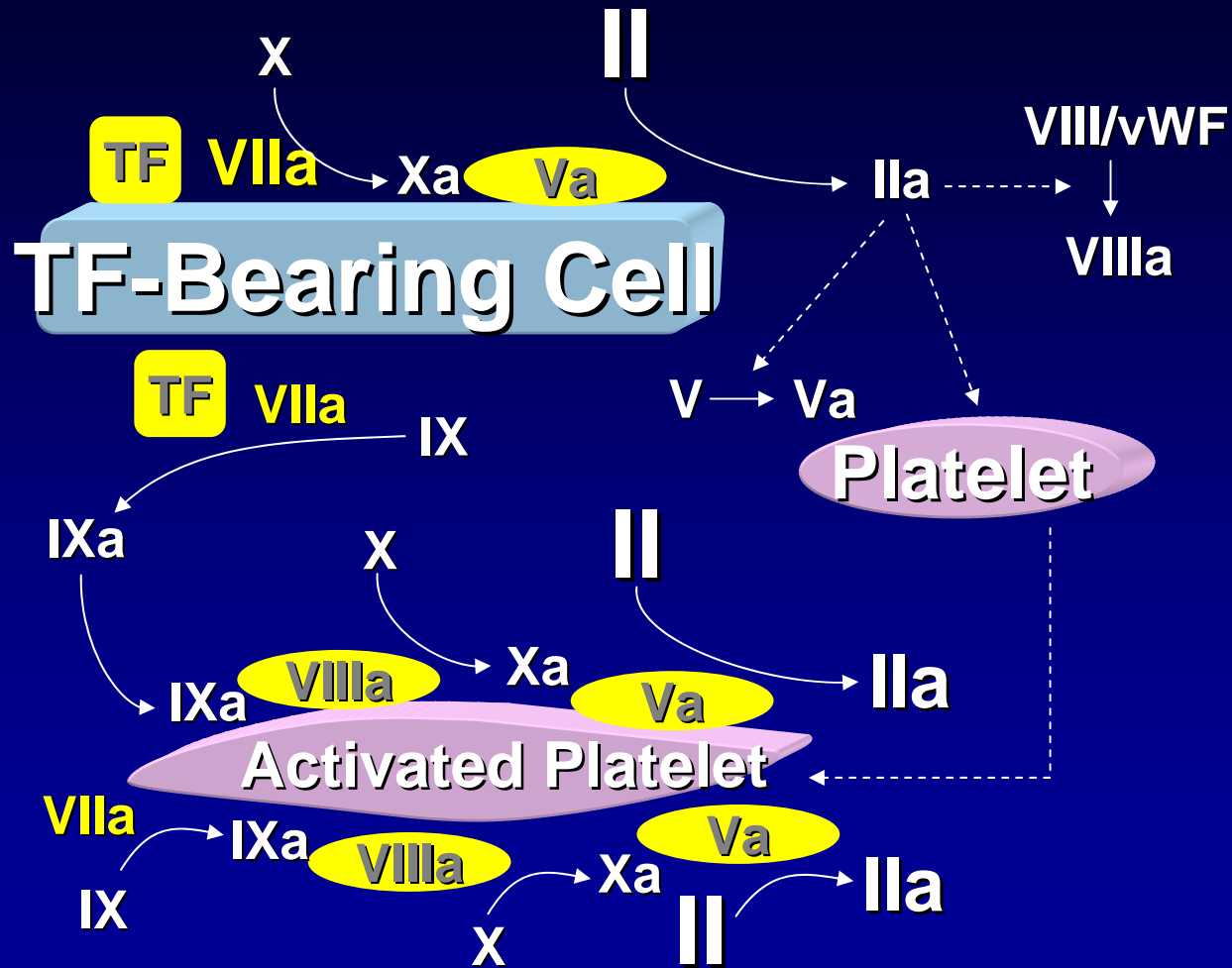
HEMOSTASIS

The stoppage of bleeding, hemorrhage, or blood flow through a blood vessel or body part.

COMPONENTS OF HEMOSTASIS

- **Vasculature**
- **Coagulation proteins**
- **Platelets**

Normal Hemostasis



Hoffman M et al. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S61-S65.

PROHEMOSTATIC AGENTS

- Aprotinin
- Lysine analogs
- Protamine
- Desmopressin
- Recombinant Factor VIIa (rFVIIa)
- Topical hemostatic agents
- Factor concentrates

APROTININ

1. Levy JH, Bailey JM, Salmenpera M. Pharmacokinetics of aprotinin in preoperative cardiac surgical patients. *Anesthesiology* 1994;80:1013-8.
2. Levy JH, Pifarre R, Schaff HV, et al: A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. *Circulation* 1995;92:2236-2244.
3. D'Ambra MN et al: Aprotinin in primary valve replacement and reconstruction: a multicenter, double-blind, placebo-controlled trial. *J Thorac Cardiovasc Surg* 1996;112:1081-9.
4. Alderman EL, Levy JH, Rich JB, et al: Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. *J Thorac Cardiovasc Surg*. 1998;116:716-30.

APROTININ

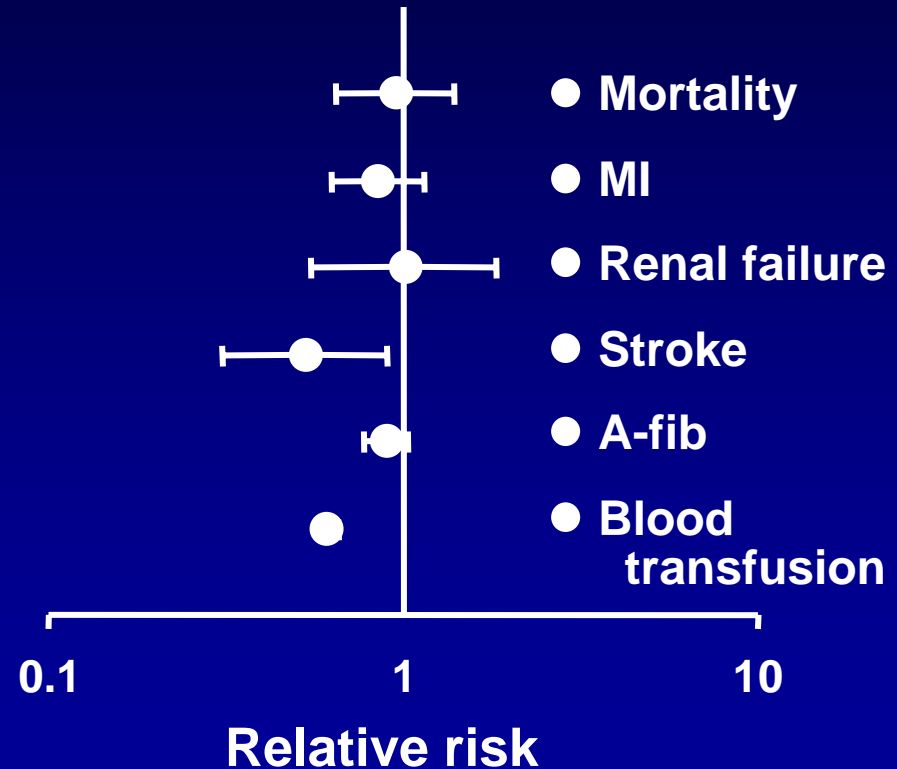
1. Miller BE et al: Hematologic and economic impact of aprotinin in reoperative pediatric cardiac operations. *Ann Thorac Surg.* 1998;66:535-40; discussion 541.
2. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg.* 2001;71:745-54.
3. Morris CD, Vega JD, Levy JH, et al: Warfarin therapy does not increase bleeding in patients undergoing heart transplantation. *Ann Thorac Surg.* 2001;72:714-8.

Meta-Analyses of Safety and Efficacy of Aprotinin in CABG Surgery

- Quantitative overview to evaluate clinical outcomes of aprotinin in CABG

- MEDLINE, EMBASE and PHARMLINE (1988-2001) and reference lists of CABG studies
 - random allocation of treatment
 - placebo control
 - enrollment of only CABG pts
 - non-combined use with another experimental medication or device
 - prophylactic and continuous intra-operative use

- **Data from 35 CABG trials (n = 3,879)**



CABG, coronary artery bypass graft.

Sedrakyan:J Thorac Cardiovasc Surg 2004;128:442.

LYSINE ANALOGS:
Epsilon-aminocaproic
acid (EACA) and
Tranexamic acid (TA)

EACA/Tranexamic acid

- Often small numbers, variable design, ?Tx criteria, ?Factor reduction
- Most EACA/TA studies with lower risk patients
- Meta analyses need to be cautiously interpreted
- Low costs have been a major driving factor for lysine analog use

Kikura, Levy, Tanaka: A double-blind, placebo-controlled trial of epsilon-aminocaproic acid for reducing blood loss in coronary artery bypass grafting surgery. J Am Coll Surg 2006;202:216-22

- 100 pts in a D,PC,R study to receive EACA (100 mg/kg before incision, 1 g/hour infusion until chest closure, 10 g in CPB circuit) vs placebo.
- Postop CT drainage EACA 649 (261) vs 940 (626) mL; $P = 0.003$).
- No differences RBC Tx: EACA 24% v 18% placebo, $P = 0.62$ or units Tx (EACA 2.2 (0.8) v 1.9 (0.8 U), $P = 0.29$).
- EACA did not reduce risk of RBC Tx compared with placebo (odds ratio: 1.2, 95% confidence interval; 0.4 to 3.2, $P = 0.63$).
- EACA reduced postop CT drainage volume by 30% but did not reduce need for allogeneic Tx.

PROTAMINE

PROTAMINE

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

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

PATIENTS AT RISK FOR PROTAMINE REACTIONS

- NPH-insulin diabetics
- ? Fish allergy
- ? Prior vasectomy
- ? Prior exposure

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

Vasopressin Receptors

- **V1a**: vasoconstriction
- **V1b**: adenohypophysis which stimulates release of ACTH
- **V2**: Smooth muscle vasodilation, and increase vWF (desmopressin - AVP analog with V2-specificity)

Levi: Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999;354(9194):1940.

- Meta-analysis of all randomized controlled trials of aprotinin, lysine analogues and desmopressin.
- 72 trials (8409 pts) were included.
- Aprotinin decreased mortality almost two-fold
- Both decreased the frequency of surgical re-exploration and allogeneic blood Tx.
- Desmopressin resulted in a 2.4-fold increase in the risk of MI, a small decrease in periop blood loss, but NO beneficial effects on other clinical outcomes.

Recombinant Factor VIIa (rFVIIa)

rFVIIa Mechanism of Action

- Recombinant human coagulation factor VIIa
- rFVIIa increases TF occupancy
- rFVIIa in pharmacologic doses binds to activated platelets
- rFVIIa provides FX activation independent of Tissue Factor (TF)
- Improves platelet function

REPORTS OF rFVIIa Use: Surgery

- van Buuren HR: Successful surgery using rFVIIa for recurrent, idiopathic nonulcer duodenal bleeding in a patient with Glanzmann's thrombasthenia. *Digestive Diseases & Sciences*. 47:2134-6, 2002.
- Svartholm E et al: Treatment of bleeding in severe necrotizing pancreatitis with rFVIIa. *Anesthesiology* 96:1528, 2002.
- Slappendel R et al: Use of rFVIIa to reduce postop bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. *Anesthesiology* 96:1525, 2002.
- Tobias JD. Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. *Anesthesiology* 96:1522, 2002.
- Chuansumrit A et al: The use of rFVIIa to control bleeding in a preterm infant undergoing exploratory laparotomy. *Pediatrics* 110(1 Pt 1):169-71, 2002.

REPORTS OF rFVIIa Use: Cardiac Surgery

- Hendriks HG: An effective treatment of severe intractable bleeding after valve repair by one single dose of rFVIIa. *Anesth Analg* 93:287, 2001.
- Tanaka KA et al: Treatment of excessive bleeding in Jehovah's Witnesses following cardiac surgery rFVIIa. *Anesthesiology* 2003;98:1513
- Stratmann G: Use of rFVIIa as a rescue treatment for intractable bleeding following repeat aortic arch repair. *Ann Thorac Surg* 2003 76: 2094
- Halkos ME et al: Early experience with activated rFVII for intractable hemorrhage after cardiovascular surgery. *Ann Thorac Surg* 2005;79(4):1303-6.
- Diprose P: Activated rFVII after CPB reduces allogeneic Tx in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *Br J Anaesth* 2005;95:596-602

Mechanism of Action: rFVIIa

- Friederich PW et al: Ability of rFVIIa to generate thrombin during inhibition of TF in human subjects. *Circulation*;103:2555,2001.
- Hoffman M et al: Platelet-dependent action of high-dose factor VIIa. *Blood*;100:364,2002.
- Bijsterveld NR et al: Ability of rFVIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation*:106;2550, 2002.
- Gallistl S et al: rFVIIa does not induce hypercoagulability in vitro. *Thromb Haemostasis*;81:245, 1999.
- Pike AC et al: Structure of human FVIIa implications for the triggering of blood coagulation. *PNAS of the US*:96:8925, 1999.

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

O'Connell KA et al

JAMA 2006; 295:293-298

Thromboembolic Adverse Events (TBE)

- 431 adverse event reports, 3/99-12/04
- 168 reports described 185 TBE
- In 36 (72%) of 50 reported deaths, TBE was probable cause
- 52% TBE occurred within 24 hrs of last rFVIIa dose
- 38% noted concomitant use of other hemostatic agents

Levy, Fingerhut, Brott T et al: Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile. *Transfusion* 2006;46: 919-33.

- Critical safety data obtained from 13 Novo Nordisk-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 were found between placebo-treated and rFVIIa-treated patients for thrombotic AEs, either on an individual trial basis or for these trial populations combined ($P = 0.57$).

Rescue Therapy with rFVIIa 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 (ie, platelets, FFP, cryo, desmopressin)
- 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;44:1325-1331.

Summary

- Aprotinin is a broad-spectrum protease inhibitor that reduces bleeding and need for allogeneic transfusions
- Lysine analogs have variable effects on reducing bleeding and there are no safety data
- Protamine does not reverse LMWHs.
- DDAVP has minimal effects on bleeding
- rFVIIa is a novel, off-label approach for refractory surgical bleeding
- Allogeneic blood exposure may pose risks and alternative agents need to be developed.

BleedingWeb.com