Massive transfusion protocols
is the expense justified?

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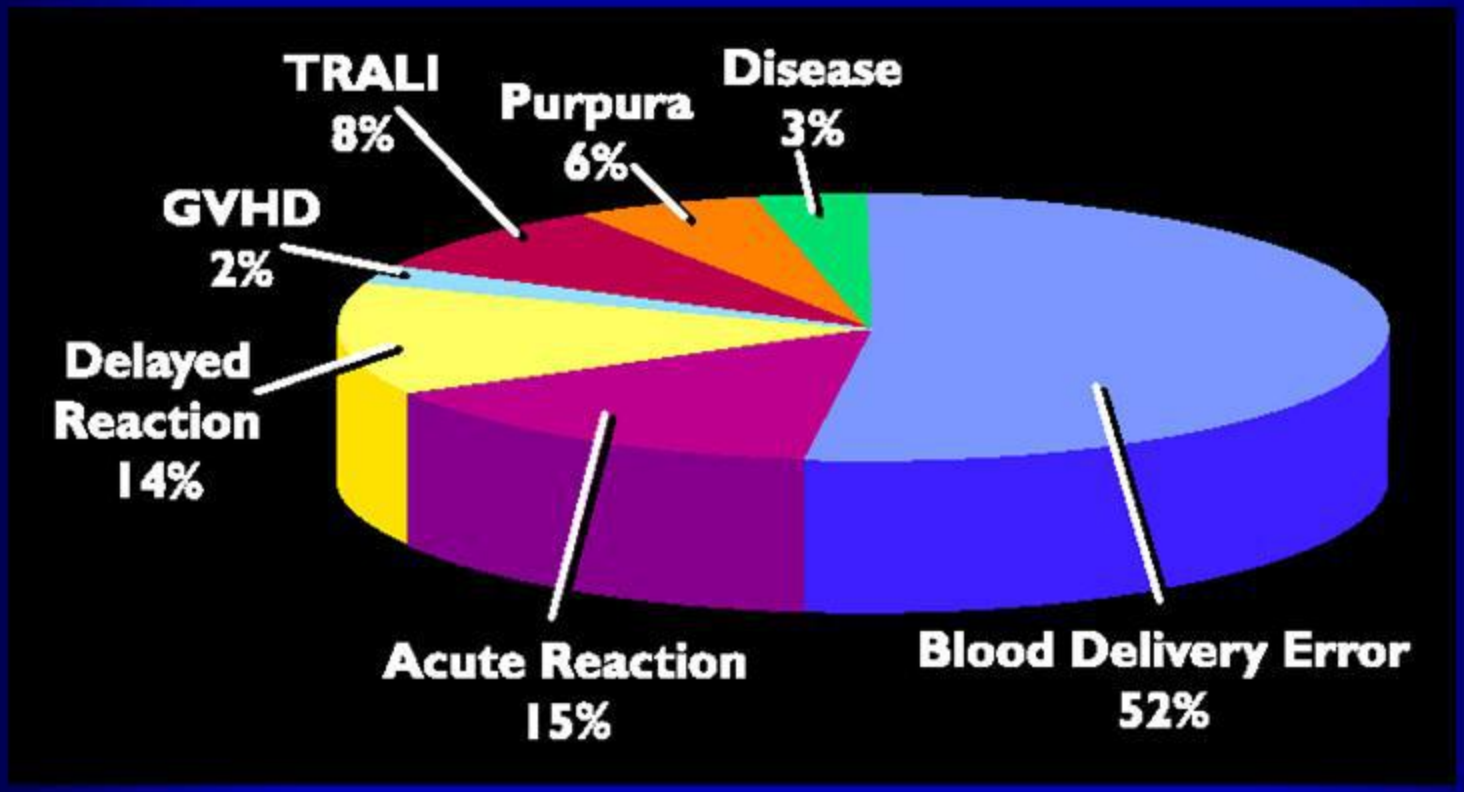
Blood Use - USA

- 13 million units collected, <5% outdated
- 10-12 million units transfused
- 4 million recipients
- 2/3 for surgery
- One-third emergency
- Type O blood - 200,000 units
- 35 transfusion-related deaths from blood incompatibility or infection

Complications of transfusion



52% (191/366) "wrong blood to patient"

only 1/14,000 units in USA

Reduction in transfusion

- Abdominal infection post injury. Only injury severity and number of units transfused and not the presence of colonic injury determined outcome.

  Kirton, J Trauma 2000.

- Transfusions increase incidence of Ventilator Aquired Pneumonia (VAP). Administration of 1-2 units doubles the VAP rate

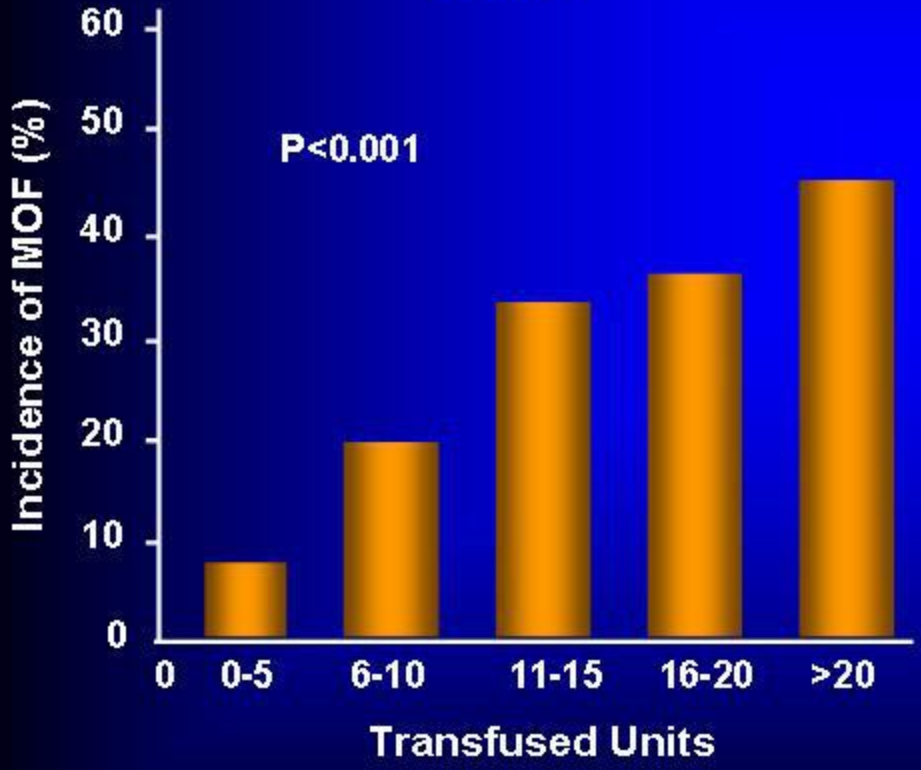
  Schorr CCM 2004; Taylor CCM 2002; Tang Ann Surg 2001

- Transfusion trigger should be a haemoglobin of 70

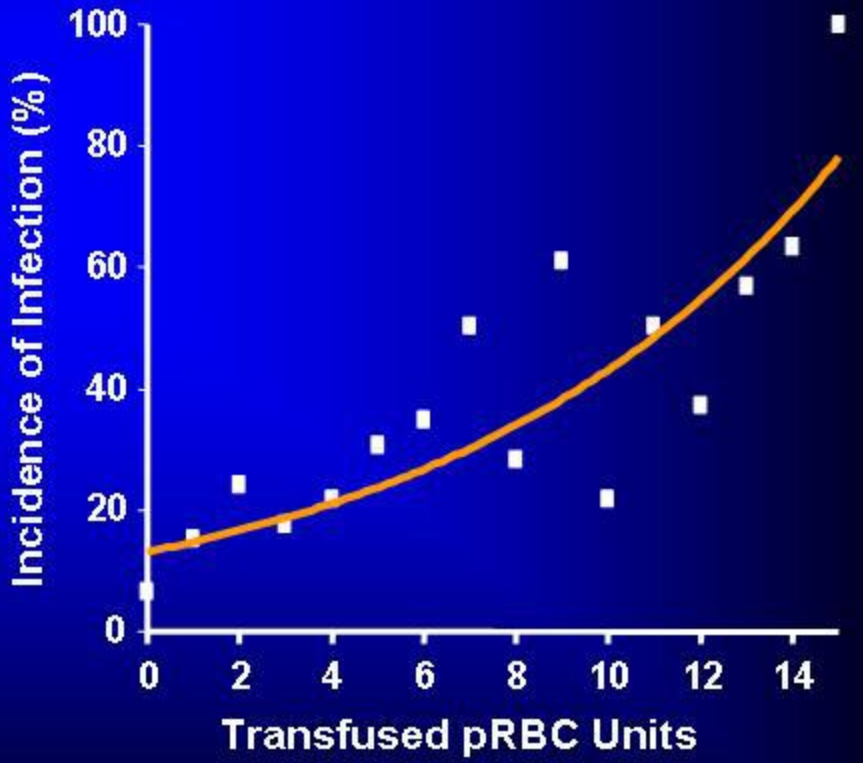
  Hebert NEJM

Impact of transfusion on complications following trauma

Relationship between units of transfused blood in the first 12h and the incidence of MOF[1]



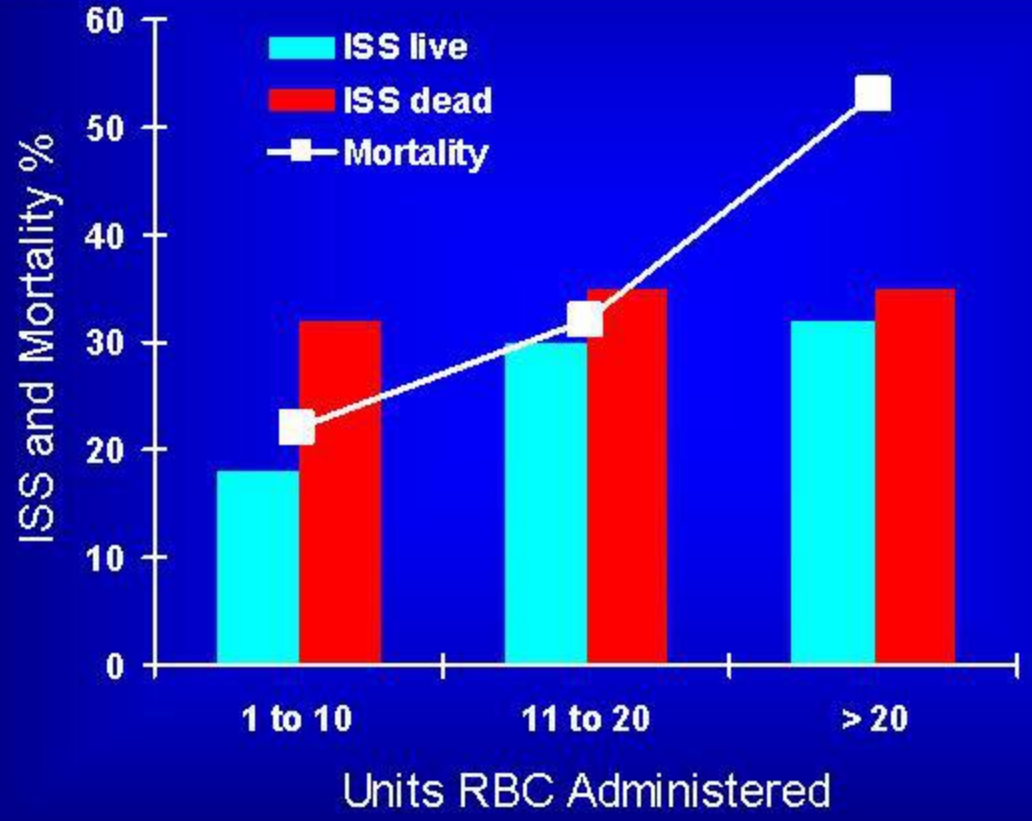
Association between 0-15 units of pRBCs and infection rate[2]



1. Malone DL et al. J Trauma 2003; 898-905.

2. Claridge JA et al. Am Surg 2000;68:566-72.

Blood transfusion requirement has a greater predictability of mortality than ISS



ISS and mortality as a function of the number of RBCs given. The increase in mortality with greater transfusion was highly significant ($p=10^{-6}$). ISS was significant only for the 1-10 units group ($p=10^{-13}$)

Como JJ et al. Transfusion 2004; 44: 809-813

Deployment of Blood
Logistically Costly, Most Discarded

US Armed Forces Blood Program

Bowersox JC, Hess JR. *Artif Cells Blood Subst Immob Biotech.* 1994;22:145-157.

Benefits of transfusion

- Red cell transfusions are used to increase oxygen carrying capacity
- Augment O_2 delivery

Oxygen delivery = Cardiac output x Oxygen content

Many contemporary transfusion practices have no evidence base

Blood: Problems and risks

- Requires donors and cross-matching
- Limited shelf life (up to 42 days)
- Dysfunctional oxygen delivery
- Complications
  - Incompatibility reactions
  - Transmits infection
  - Immunomodulation
  - Metabolic consequences

Transfusion incompatibility

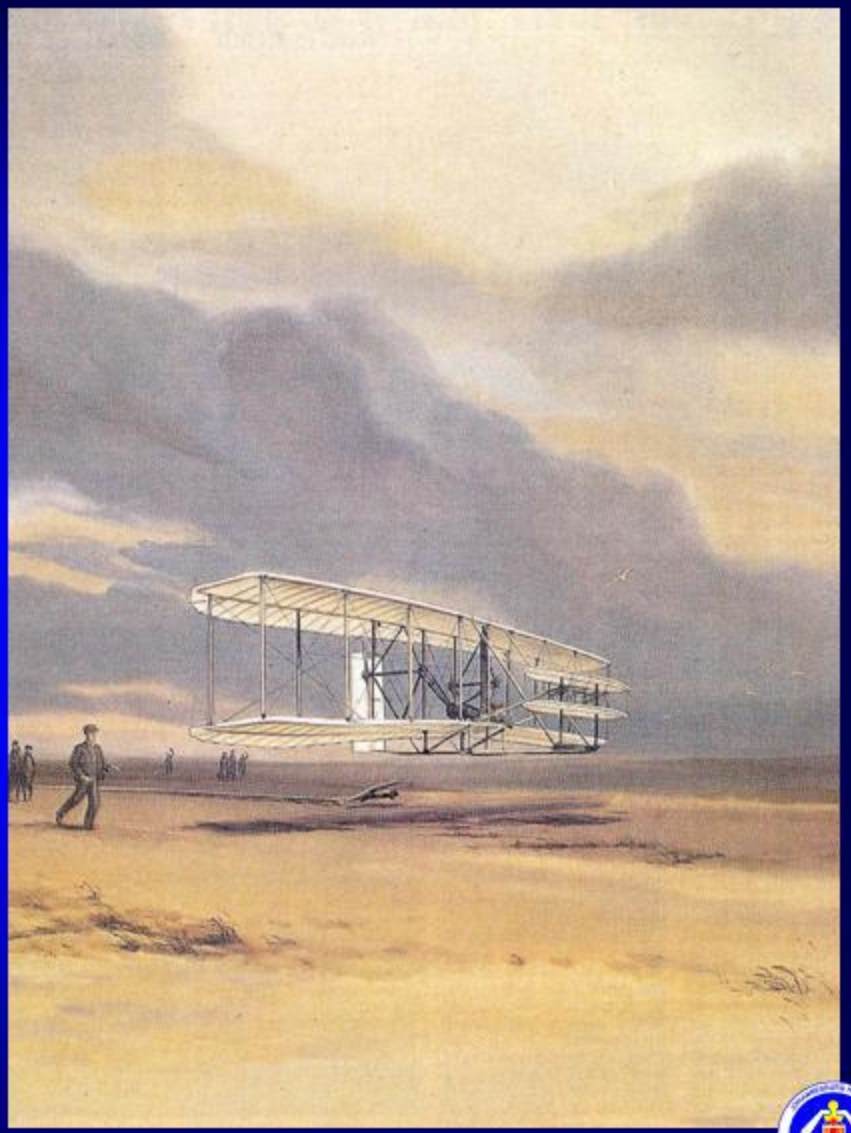
- **Major incompatibility**
  - ABO and previously sensitized
  - Cold autoantibodies
  - Intravascular haemolysis
  - Significant morbidity and mortality

Hospital staff error in 75% of cases

I confess that in 1901 I said to my brother Orville that man would not fly for 50 years…..

Ever since, I have distrusted myself and avoided all predictions

Wilbur Wright 1903



Transmission of infection

- **Donor disease transmission**
  - Hepatitis
  - HIV
  - Herpes, CMV and EBV
  - CJD
  - Malaria, Spirochetes

23 organisms known to be transmissible by blood transfusion

Immunomodulation

- Disrupts recipient immune function
- Down-regulates cellular immune response
- Critically ill patients
- Colonic cancer: Transfusion worsens prognosis

Microaggregates: Buffy coat

- ARDS
- Reticulo Endothelial System (RES) blockade
- Antigenic stimulation
- Stimulates acute phase response
- Clogging of microcirculation

Metabolic abnormalities

- Electrolytes and glucose
- Hypocalcaemia
- Acidosis
- Hypothermia
- Coagulopathy
  - Hypothermia
  - Dilution
  - Consumption of clotting factors

Disseminated intravascular coagulopathy (DIC)

Initiation of coagulation

Release of pro and anti- coagulants:

- Thrombin
- Plasmin

- **Ongoing bleeding**
- **Endothelial dysfunction**
- **Microvascular coagulation**

Management of red cell transfusion

- Hb and Haematocrit may be unreliable
- Look for clinical evidence of hypoxia
- Aim for Hb 80 – 100 g/L following haemorrhage control
- Use warmed PRBC only

Blood transfusion is like marriage…

It should not be entered upon lightly, unadvisedly or wantonly…

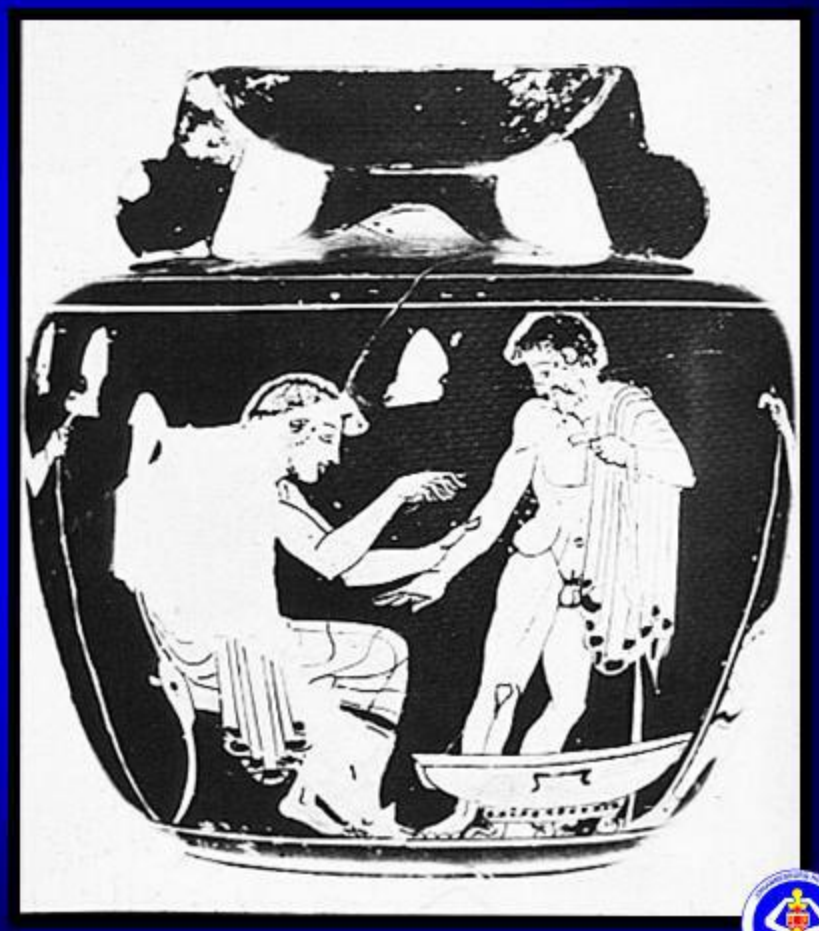
or more often than is absolutely necessary."

R.W. Beal 1976

History of transfusion

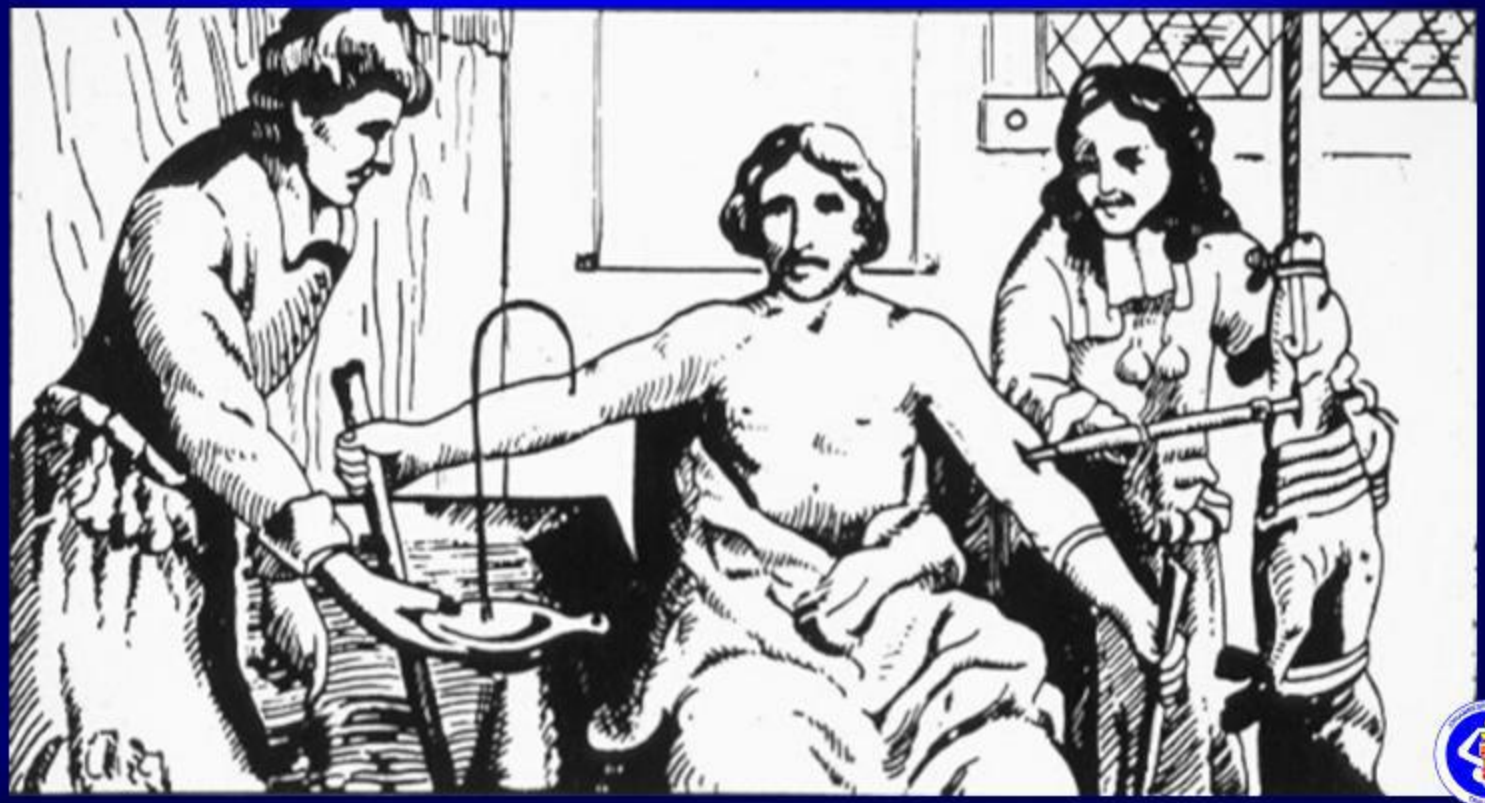
1628 William Harvey human circulation

1656 Christopher Wren infused fluids (ale, wine, drugs) into dogs



1667: First animal transfusion

Denis (Paris) and Lower (London)

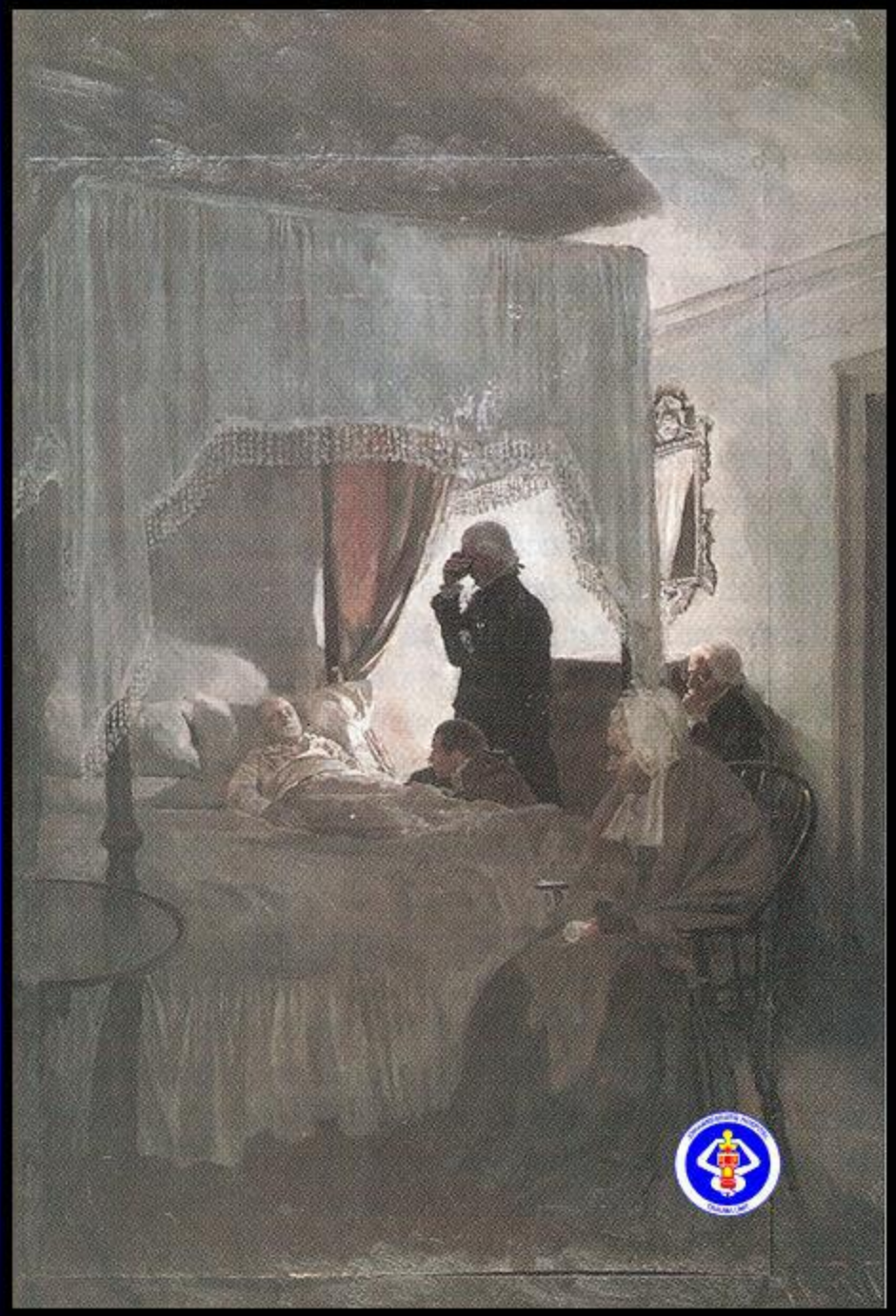


1799

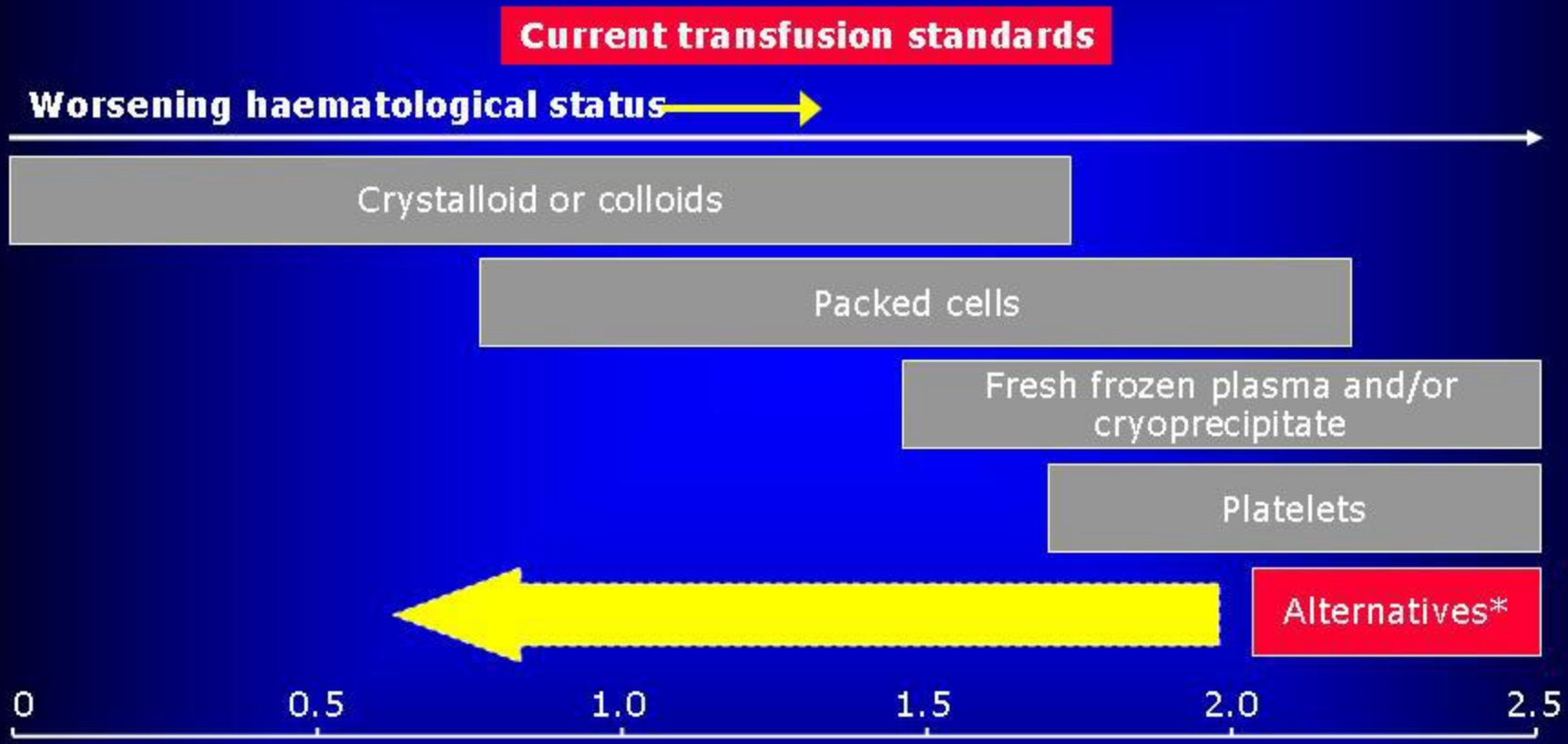
George Washington:

...dead of *sore* throat

Doctors removed
2365cc Blood/**12h**



Traditional transfusion strategy Alternatives



* PCCs, fresh whole blood, rFVIIa

Source: Hardy et al. Can J Anesth 2004; 51:293-310

So load your patient wisely!

Autologous blood transfusion

- Accepted for thoracic injuries
- Controversial if abdominal source
- Filtered “re-hung”
- MAXIMUM 1500 ml before DIC

- Cell salvage preferred

Intraoperative blood salvage

- Cell Saver
- No cross match
- No disease the patient hasn't already got
- No transfusion reaction
- BUT
- Depletion of clotting factors
- Can precipitate DIC
- Hollow viscus injury issue

Platelets

- First abnormality to develop in the
- trauma patient is thrombocytopaenia

- Platelets ineffective during
- acidosis
- hypothermia
- renal failure

Clotting factors

- Clinical versus laboratory diagnosis
- Consider prophylaxis after 2nd unit of blood
- Consider monitoring with thromboelastogram (TEG)

Fresh Frozen Plasma (FFP)

- Clotting factors same as whole blood
- Cryoprecipitate / Fibrinogen
- Smaller volume for same amount of factor
- Higher fibrinogen level

Massive transfusion: Definition

- Blood transfusion > 10 units

or

- Exchange of circulating blood volume in 24 hours

or

- 50% of predicted blood volume lost in three hours
- Based on 70 mL / Kg

Lippincott Williams & Wilkins
a Wolters Kluwer business

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The Journal of

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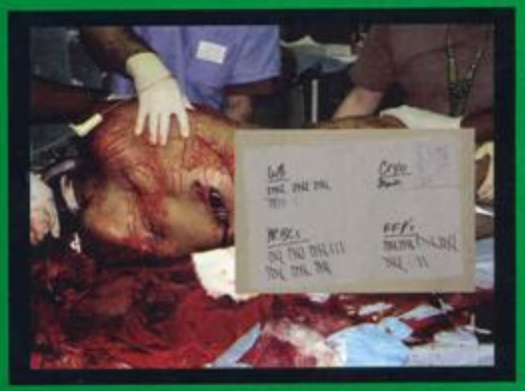
Injury, Infection, and Critical Care



Early Massive Trauma Transfusion:

Current State of the Art

American Association for the Surgery of Trauma

Eastern Association for the Surgery of Trauma

Trauma Association of Canada/L'Association Canadienne de Traumatologie

Western Trauma Association

Full Text
OVID

www.jtrauma.com

Impact of Hemorrhage on Trauma Outcome: An Overview of Epidemiology, Clinical Presentations, and Therapeutic Considerations

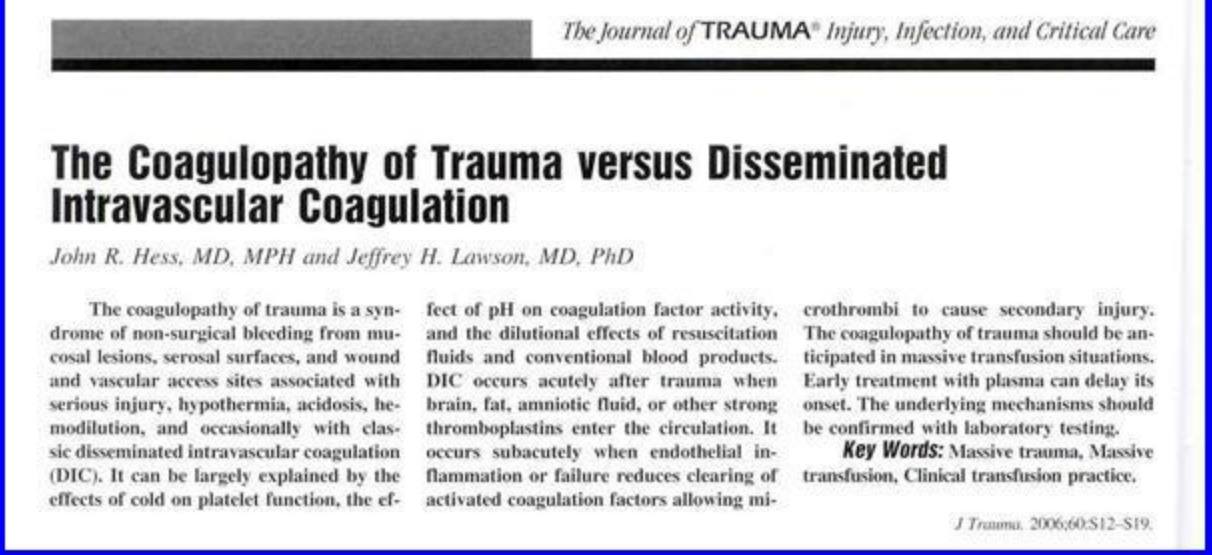
David S. Kauvar, MD, Rolf Lefering, PhD, and Charles E. Wade, PhD

The world-wide impact of traumatic injury and associated hemorrhage on human health and well-being cannot be overstated. Twelve percent of the global disease burden is the result of violence or accidental injury. Hemorrhage is responsible for 30 to 40% of trauma mortality, and of these deaths, 33 to 56% occur during the pre-hospital period. Among those who reach care, early mortality is caused by continued hemorrhage, coagulopathy, and incomplete resuscitation. The techniques of early care, including blood transfusion, may underlie late mortality and long-term morbidity. While the volume of blood lost cannot be measured, physiologic and chemical measures and the number of units of blood given are readily recorded and analyzed. Improvements in early hemorrhage control and resuscitation and the prevention and aggressive treatment of coagulopathy appear to have the greatest potential to improve outcomes in severely injured trauma patients.

Key Words: Trauma, Hemorrhage, Epidemiology, Shock, Mortality, Multiple organ failure, Coagulopathy.

J Trauma 59(6)(S):S1–S11

- **Haemorrhage is responsible for 30-40% of trauma mortality**
  - Pre-hospital
  - Coagulopathy



The Journal of TRAUMA® Injury, Infection, and Critical Care

The Coagulopathy of Trauma versus Disseminated Intravascular Coagulation

John R. Hess, MD, MPH and Jeffrey H. Lawson, MD, PhD

The coagulopathy of trauma is a syndrome of non-surgical bleeding from mucosal lesions, serosal surfaces, and wound and vascular access sites associated with serious injury, hypothermia, acidosis, hemodilution, and occasionally with classic disseminated intravascular coagulation (DIC). It can be largely explained by the effects of cold on platelet function, the effect of pH on coagulation factor activity, and the dilutional effects of resuscitation fluids and conventional blood products. DIC occurs acutely after trauma when brain, fat, amniotic fluid, or other strong thromboplastins enter the circulation. It occurs subacutely when endothelial inflammation or failure reduces clearing of activated coagulation factors allowing microthrombi to cause secondary injury. The coagulopathy of trauma should be anticipated in massive transfusion situations. Early treatment with plasma can delay its onset. The underlying mechanisms should be confirmed with laboratory testing.

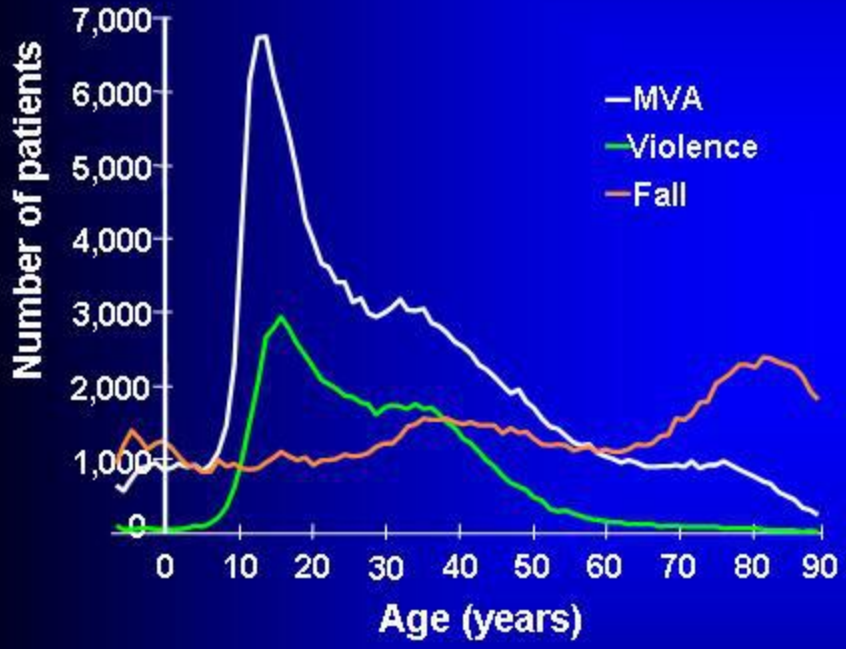
Key Words: Massive trauma, Massive transfusion, Clinical transfusion practice.

J Trauma. 2006;60:S12–S19.

- Coagulopathy that occurs after all surgical bleeding has been controlled
  - Dilution
  - Consumption of clotting factors
  - Hypothermia

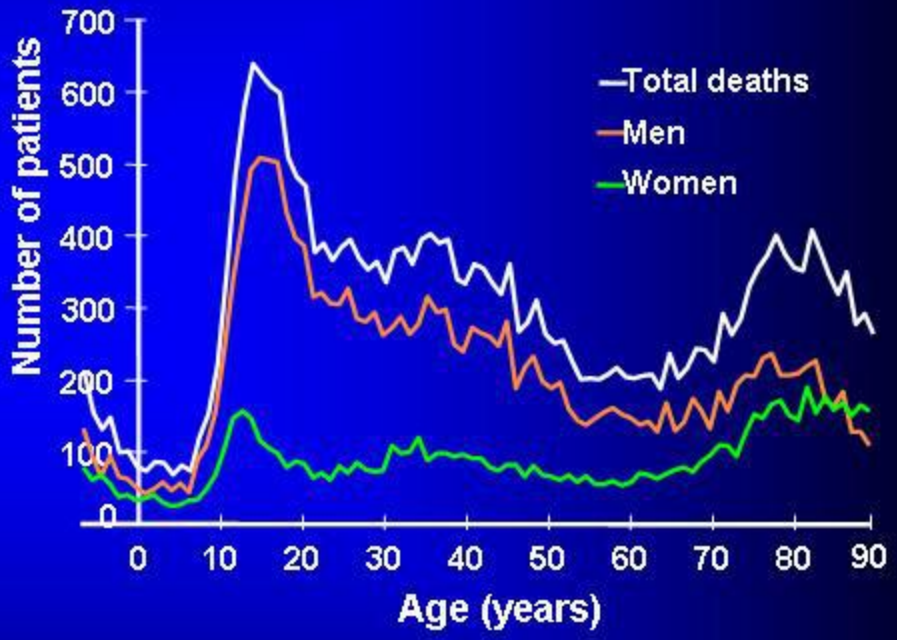
Epidemiology of trauma

Trauma is a disease of the young



n=453,806 (US data from 1997–2002)

Most trauma deaths occur in young males



n=27,052 (US data from 1997–2002)

The Journal of TRAUMA® Injury, Infection, and Critical Care

Indications for Early Red Blood Cell Transfusion

Richard P. Dutton, MD, MBA and Jeffrey L. Carson, MD

J Trauma. 2006;60:S35–S40.

- To improve oxygen delivery
- Myocardial ischaemia develops at an Hb of < 50 g/L
- Best measured with serum lactate

The Journal of TRAUMA® *Injury, Infection, and Critical Care*

Cumulative Risks of Early Fresh Frozen Plasma, Cryoprecipitate and Platelet Transfusion in Europe

Rut Norda, MD, Elsa Tynell, MD, and Olof Åkerblom, MD, PhD

- Non haemolytic transfusion reactions
- Congestive cardiac failure
- Sepsis
- TRALI
- Post transfusion purpura
- Viral transmission
- Anaphylaxix
- Citrate toxicity
- Allo-immunisation

The Journal of TRAUMA® Injury, Infection, and Critical Care

The Clinical Benefits of the Leukoreduction of Blood Products

M. A. Blajchman, MD, FRCP(C)

Many adverse events associated with the transfusion of allogeneic blood products have been shown to be related to the presence of allogeneic leukocytes in the blood product transfused. Until recently little attention has been paid to the leukocytes present in various blood components, however, over the past two decades it has been shown that the removal of such "passenger" leukocytes is associated with improved clinical outcomes. These include: the reduction in the incidence and severity of febrile transfusion reactions; reducing the CMV transfusion transmission risk; reducing the risk of alloimmune platelet refractoriness; the possible avoidance of vCJD transmission; as well as reducing the risk of mortality and organ dysfunction in cardiac surgery patients, and possibly in other categories of patients.

Key Words: Blood transfusion, Adverse events, Transfusion-related immunomodulation, TRIM, Transfusion-associated infections, Transfusion-associated mortality, Organ dysfunction, Blood products.

J Trauma. 2006;60:S83–S90.

- Reduction in incidence and severity of febrile reactions
- Reducing CMV transmission risk
- Reducing alloimmune platelet refractoriness
- Avoidance of vCJD transmission
- Reduction in MODS

Blood components

- Packed red cells
- Plasma
- Clotting factors
- Platelets

The United States has discovered this mix is called "Whole Blood"

The Journal of TRAUMA® Injury, Infection, and Critical Care

The Use of Fresh Whole Blood in Massive Transfusion

Thomas B. Repine, MD, Jeremy G. Perkins, MD, David S. Kauvar, MD, and Lorne Blackborne, MD

Background: Most indications for whole blood transfusion are now well managed exclusively with blood component therapy, yet the use of fresh whole blood for resuscitating combat casualties has persisted in the U.S. military.

Methods: Published descriptions of whole blood use in military and civilian settings were compared with use of whole blood at the 31st Combat Support Hospital (31st CSH) stationed in Baghdad in 2004–2005.

Findings: Concerns about logistics, safety, and relative efficacy of whole blood versus component therapy have argued against the use of whole blood in most settings. However, military physicians have observed some distinct advantages in fresh warm whole blood over component therapy during the massive resuscitation of acidotic, hypothermic, and coagulopathic trauma patients. In this critical role, fresh whole blood was eventually incorporated as an adjunct into a novel whole-blood-based massive transfusion protocol.

Conclusions: Under extreme and austere circumstances, the risk:benefit ratio of whole blood transfusion favors its use. Fresh whole blood may, at times, be advantageous even when conventional component therapy is available.

Key Words: Fresh whole blood, Massive transfusion, Trauma, Combat casualty care, Blood banking, Walking blood bank.

J Trauma. 2006;60:S59–S69.

- Under extreme and austere circumstances, the risk:benefit ratio of whole blood favours its use.
- Fresh whole blood may be advantageous even when conventional component therapy is available

The Journal of TRAUMA® Injury, Infection, and Critical Care

Indications for Early Fresh Frozen Plasma, Cryoprecipitate, and Platelet Transfusion in Trauma

Lloyd Ketchum, MD, John R. Hess, MD, MPH and Seppo Hiippala, MD

- Plasma coagulation concentrations rapidly drop to <40% of normal in trauma
- This occurs before 10 U have been transfused
- Associated with a precipitate drop in platelets to < 50 000

Transfusion guidelines

- Use packed red cells (PRBC)
- Use leucodepleted blood if massive transfusion expected
- Use cross-matched blood if available

Emergency blood

Baseline bloods

- FBC and Platelets
- PT, aPTT, INR
- Fibrinogen
- D-dimer

- Repeat after every 6 Units

Blood bank to issue…

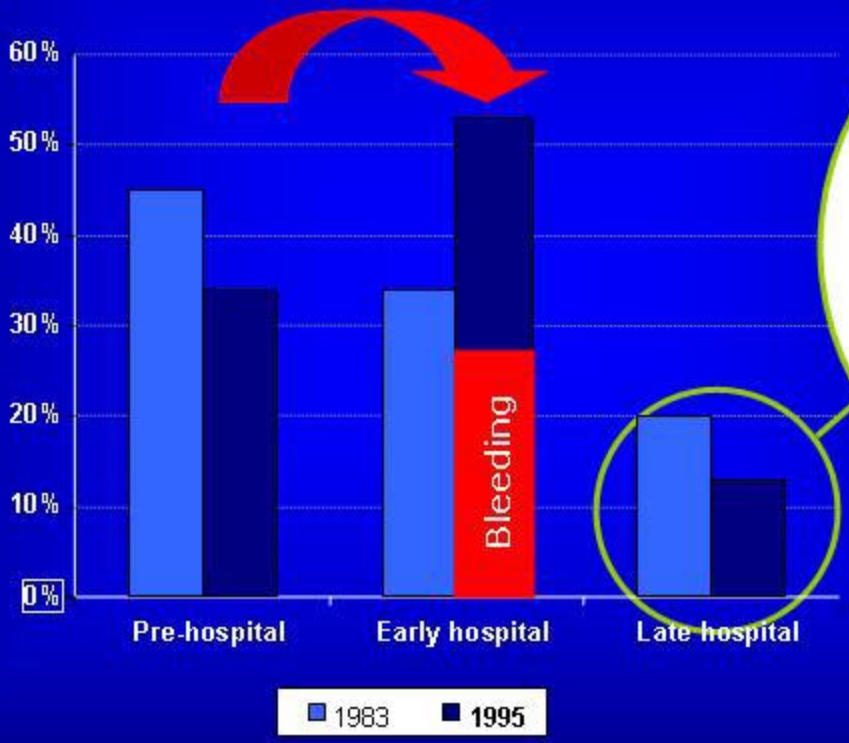
- 6 Units PRBC
- 6 Units FFP
- 1 Apheresis Platelet Unit / 6 Units platelets

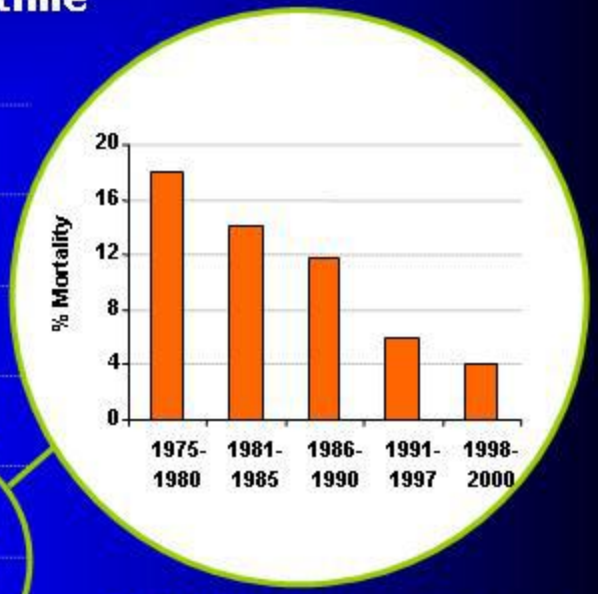
Mortality dynamics have changed

More efficacious EMS has shifted pre-hospital to early hospital death

Today most deaths occurs within 12 hours upon arrival at hospital

Change of Mortality distribution over time





Late death due to post surgical complications is declining

Sources: Trunkey DD, Sci Am, 149: 28-35, 1983, Sauaia A, J Trauma, 38:185-193, 1995, Annual Report Klinik für unfallschirugie, Univärsitsklinikum Essen

Administration

- Micro-aggregate filters not advised
- 1:1 Blood:FFP
- 1 Unit of platelets per 6 Units
- Then repeat bloods

Additional…

- 4 Units FFP if PT or aPTT > 1.5 N
- 10 Units cryo if Fibrinogen < 1 gm / mL
- 10% CaCl if above are required
- Give additional unit of platelets if count <70 000 in presence of ongoing bleeding

Blood conservation

- Return all unused packs to blood bank within 6 hours

Endpoints

- No active bleeding
- No further need for red cells
- Temperature > 35° C
- Ph> 7.3
- Fibrinogen < 1.5 gm / L
- Clotting better than 1.5 normal
- Hb 80-100 gm / L

Massive transfusion protocol

- Return physiology to normal
  - Temperature
  - pH (Acidosis)
  - Check laboratory values
- After two units of transfused blood…
  - For every subsequent unit of blood transfused
    - FFP: 1 Unit (± 2 ml/Kg)
    - Platelets: 1 unit (or 1 aphoresis Mega unit / 10 Units)
    - Cryoprecipitate / fibrinogen: 1 unit (non-responders)

If expected,
initiate massive transfusion protocol

Adjuncts to bleeding control

- Topical
  - Interventional radiology
  - Zeolite mineral powder
  - Chitosan
  - Dry fibrin sealant dressings (DFSD)
- Systemic
  - Aprotinin
  - Desmopressin
  - Tranexamic acid
  - rFVII

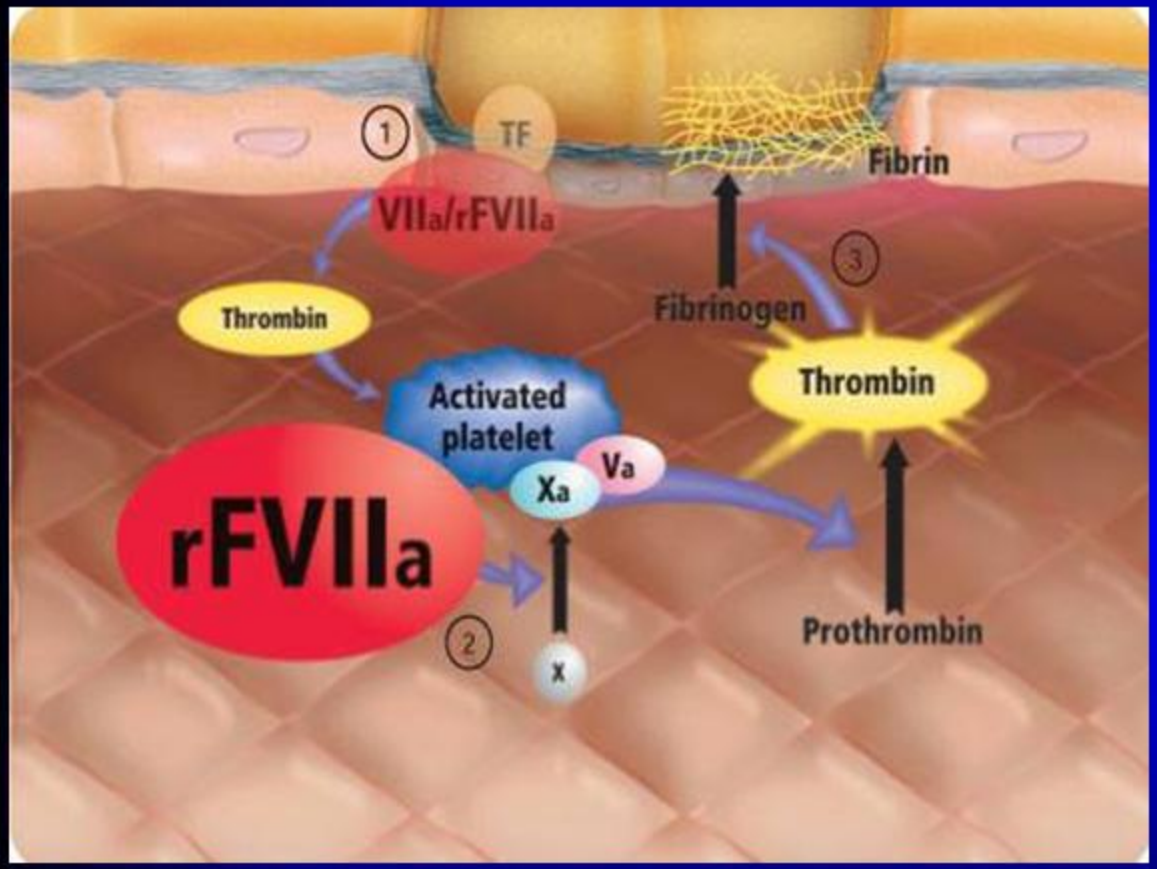
Recombinant factor VIIa

- Not a drug of last resort
  - Less effective if pH < 7.2
  - If other clotting factors left
  - If platelet count low
- Should probably be given after administration of ± 6 units

What is rFVIIa?

- Structure
- Mechanism of action
- Potential uses
  - Coagulopathic patients
  - Severe trauma

rFVIIa Optimizes Localized Hemostasis

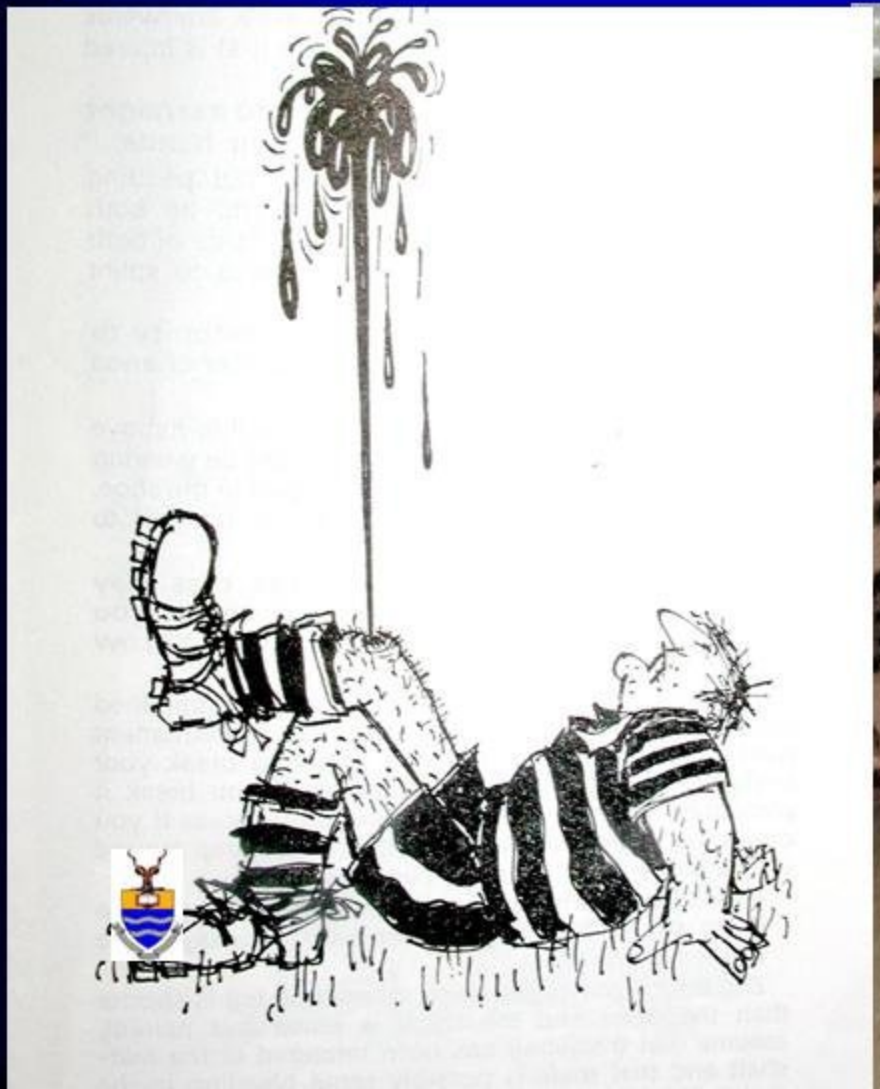


1. rFVIIa works at the site of vascular injury, where TF is expressed and activated platelets are found
2. In pharmacological doses, rFVIIa binds directly to the surface of activated platelets
3. rFVIIa enhances localized thrombin generation and fibrin clot formation, producing a stable clot

Picture modified with permission

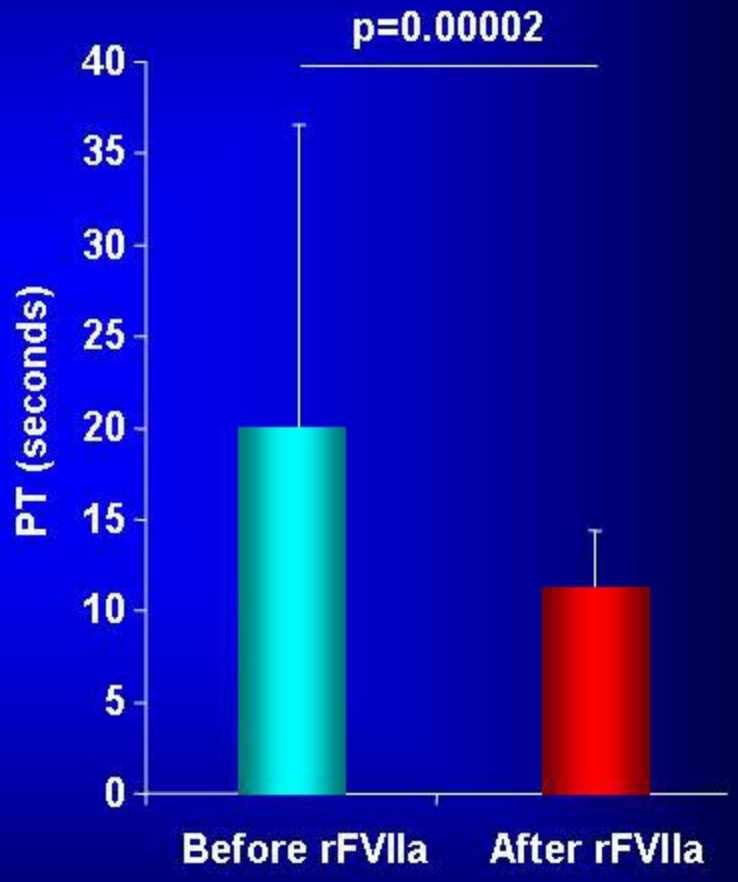
Hoffman, M., Monroe D.M. *Thromb Haemost*. 2001;85:958-965.

Commonest mortality is from bleeding



rFVIIa successfully corrected acquired coagulopathy

- Case series of 81 patients with acute coagulopathy unresponsive to component therapy:
  - 46 cases of acute traumatic haemorrhage
- Prothrombin time visibly decreased in 78/78 cases after rFVIIa dose
- 61/81 patients were classed as responders to rFVIIa.
  - 34/61 responders survived to discharge
- No evidence of thrombus formation remote from the site of bleeding



Effect of a single median rFVIIa dose of 100 µg/kg (80–144 µg/kg)

Dutton RP et al. J Trauma 2004;57:709-19

Trial Background

- rFVIIa approved for patients with haemophilia and inhibitors
- Many anecdotal reports of its use in trauma.
  Therefore real need for a controlled trial
- Trauma trials are significantly complex
- Few placebo controlled trials
- Regulatory issues resulted in non-US study
- 32 centers in 8 countries

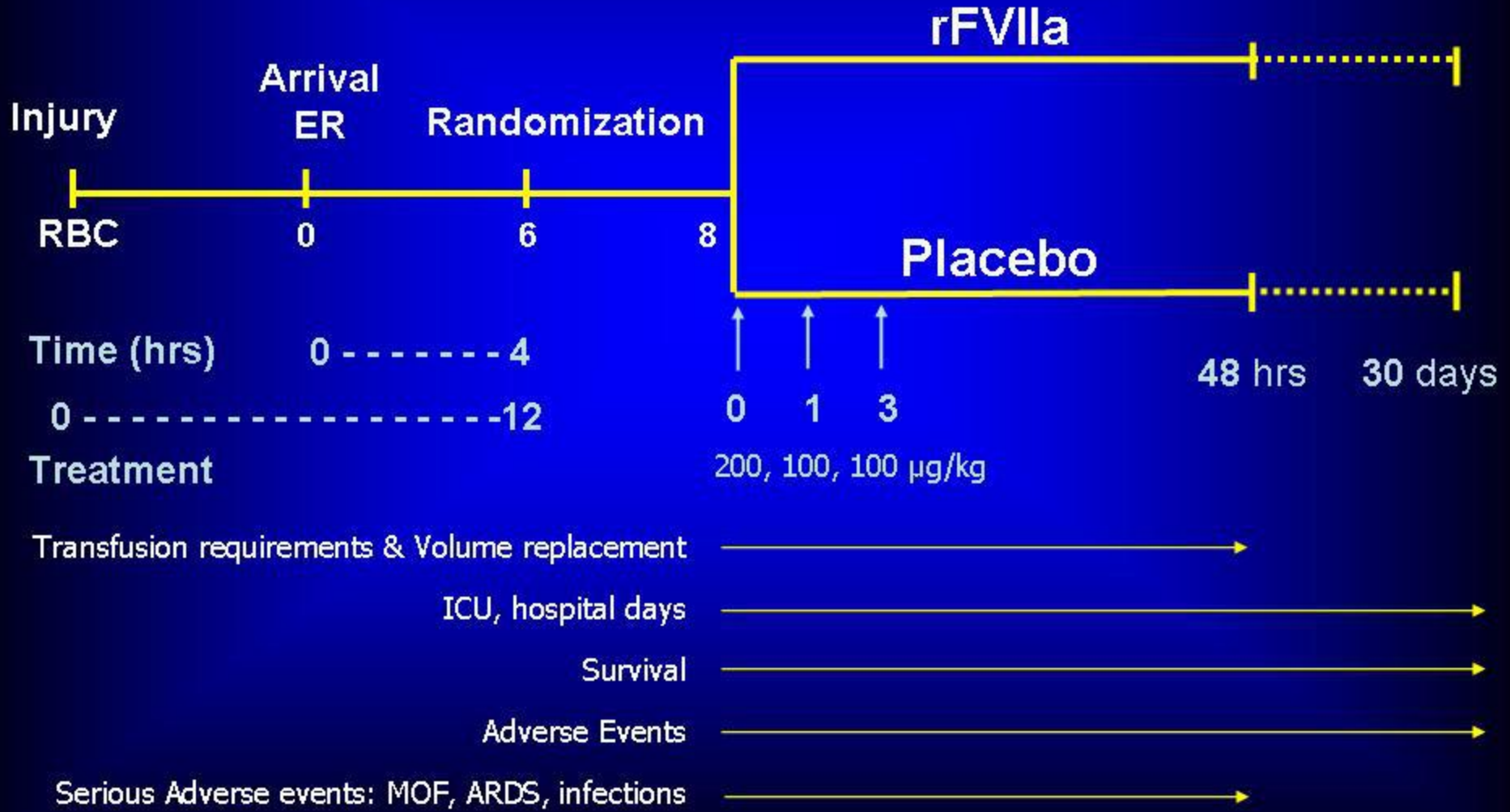
Trial Objective and Design

- Objective:
  - To evaluate the safety and efficacy of rFVIIa given as an adjunct to standard therapy in the treatment of hemorrhage in trauma patients
- Design:
  - Prospective, multi-center, randomized, double-blind, parallel-group, placebo-controlled
  - Patients were randomized to one of two protocols based on whether the trauma was blunt or penetrating
- Safety:
  - Data Safety Monitoring Board

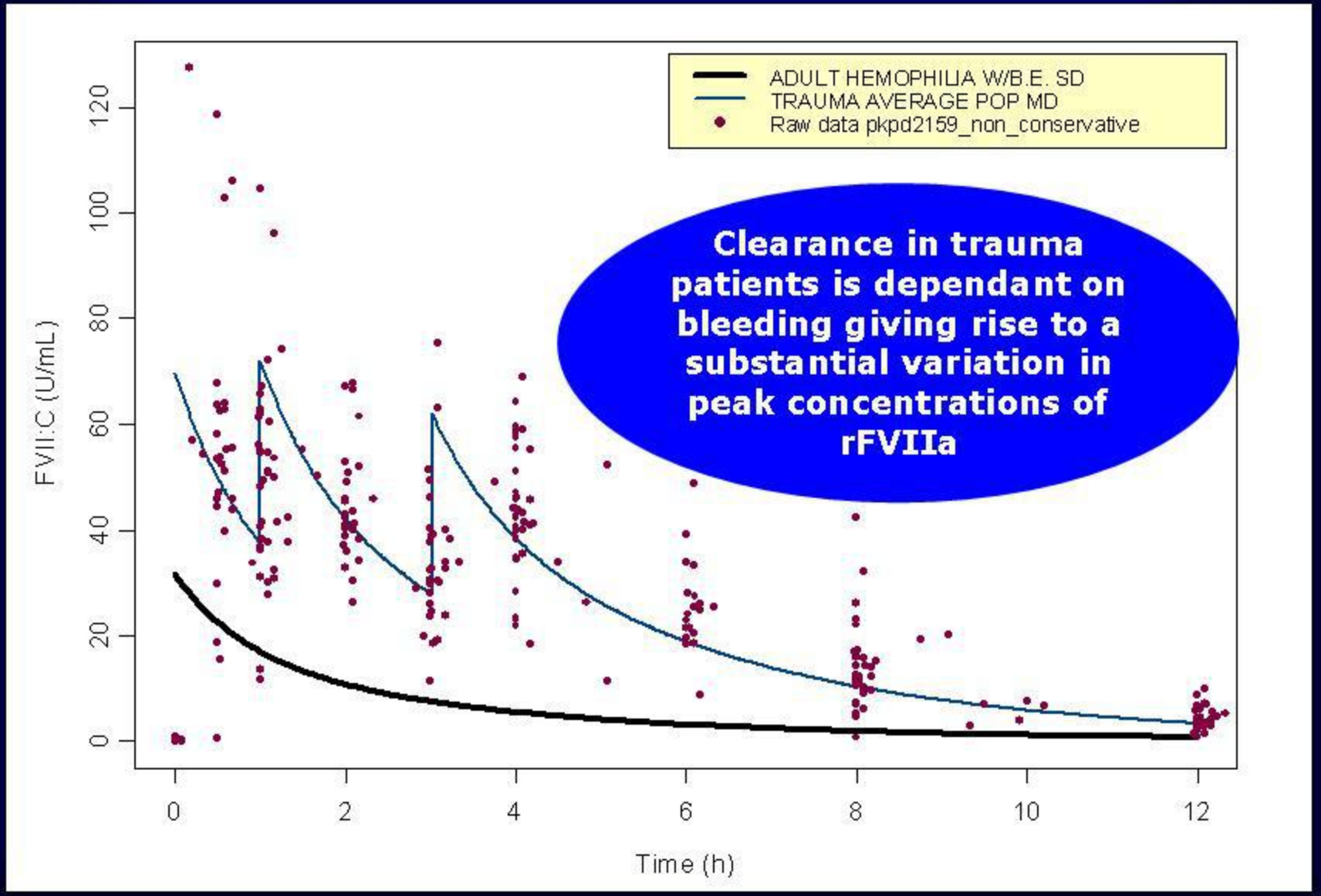
Entry Criteria

- Inclusion criteria
  - Injury due to blunt and/or penetrating trauma
  - Received 6 units of RBC within 4 hours of admission
  - Received 8 units of RBC prior to dosing
- Exclusion criteria
  - GCS < 8 or gunshot wound to the head
  - Severe acidosis pH < 7.0 or a base deficit > 15 mEq/L
  - Injury sustained > 12 h before randomization

Trial Design: Two studies – one protocol



Rationale for dose



Primary endpoint

- Total number of units of RBCs transfused in the first 48 hours after the initial dose of trial product

  Transfusion was used as an endpoint for assessment of hemostatic effect

Secondary endpoints

- Hospitalization
  - Time on Ventilator
  - Time in ICU
  - Time in hospital
- Adverse events
  - (including thromboembolic events)
- Predefined complications (ARDS, MOF)
- 30-day survival

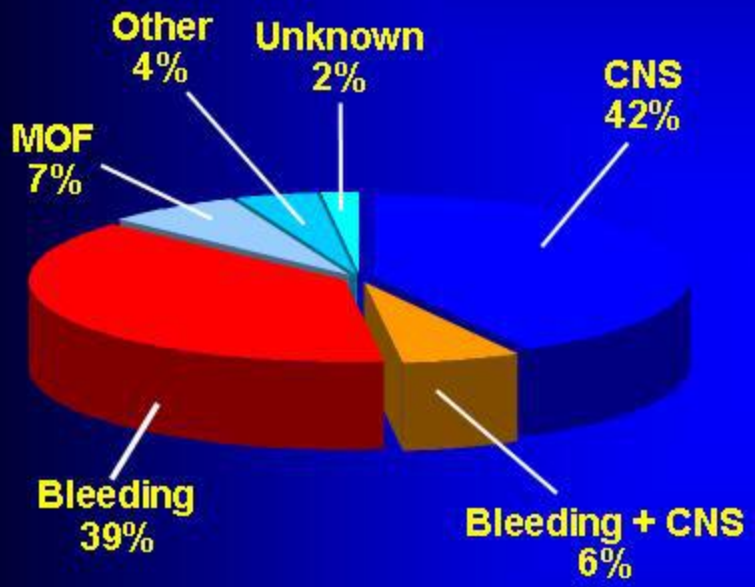
Baseline Characteristics (277 patients)

Mean (± SD)	BLUNT		PENETRATING	
	Placebo ***n=74***	*rFVIIa* ***n=69***	*Placebo* ***n=64***	*rFVIIa* ***n=70***
Age (years)	*35 (13)*	*33 (13)*	*32 (10.42)*	*29 (10.27)*
Male n (%)	*52 (70%)*	*48 (70%)*	*60 (94%)*	*66 (94%)*
ISS score	*32 (13)*	*33 (13)*	*26 (11)*	*26 (15)*

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

Blunt	Placebo N	Placebo Median (range)	rFVIIa n	rFVIIa Median (range)	Est. RBC reduction*	*p*
All patients†	72	7.2 (0–35)	64	7.8 (0–48)	2.00	0.07
Excluding 48h mortality	59	7.5 (0–35)	52	7.0 (0–29)	2.60	0.02

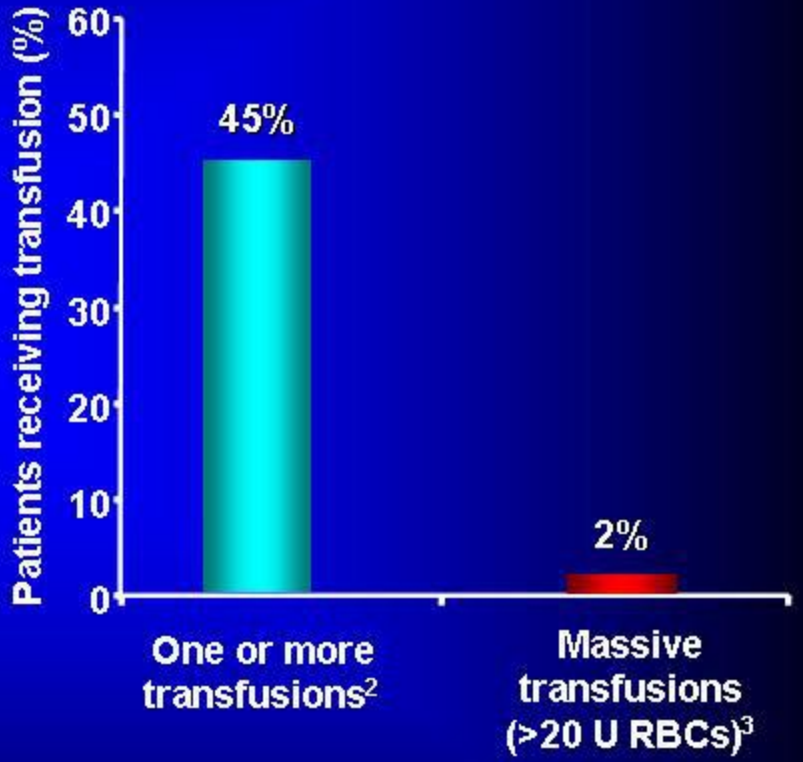
Bleeding is a major cause of death in trauma [1]



N=289

Patients dying in hospital within 48 hours

Many trauma patients require blood transfusions [2]



6-15% are in shock

1. Sauaia A et al. J Trauma 1995;38:185-93

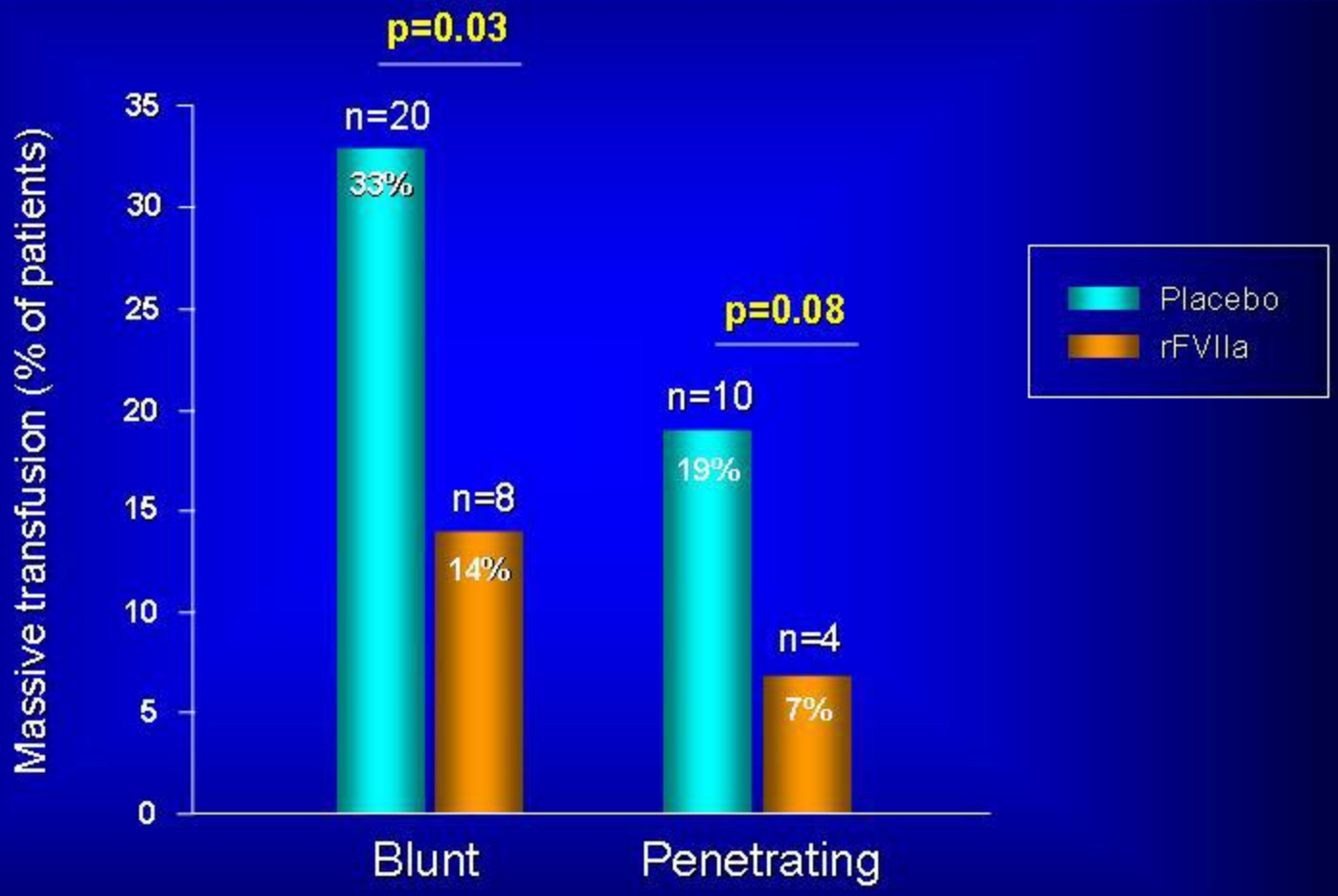
2. Annual Report German Trauma Register 2002

3. Wudel, JH et al. J Trauma 1991;31:1-7

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

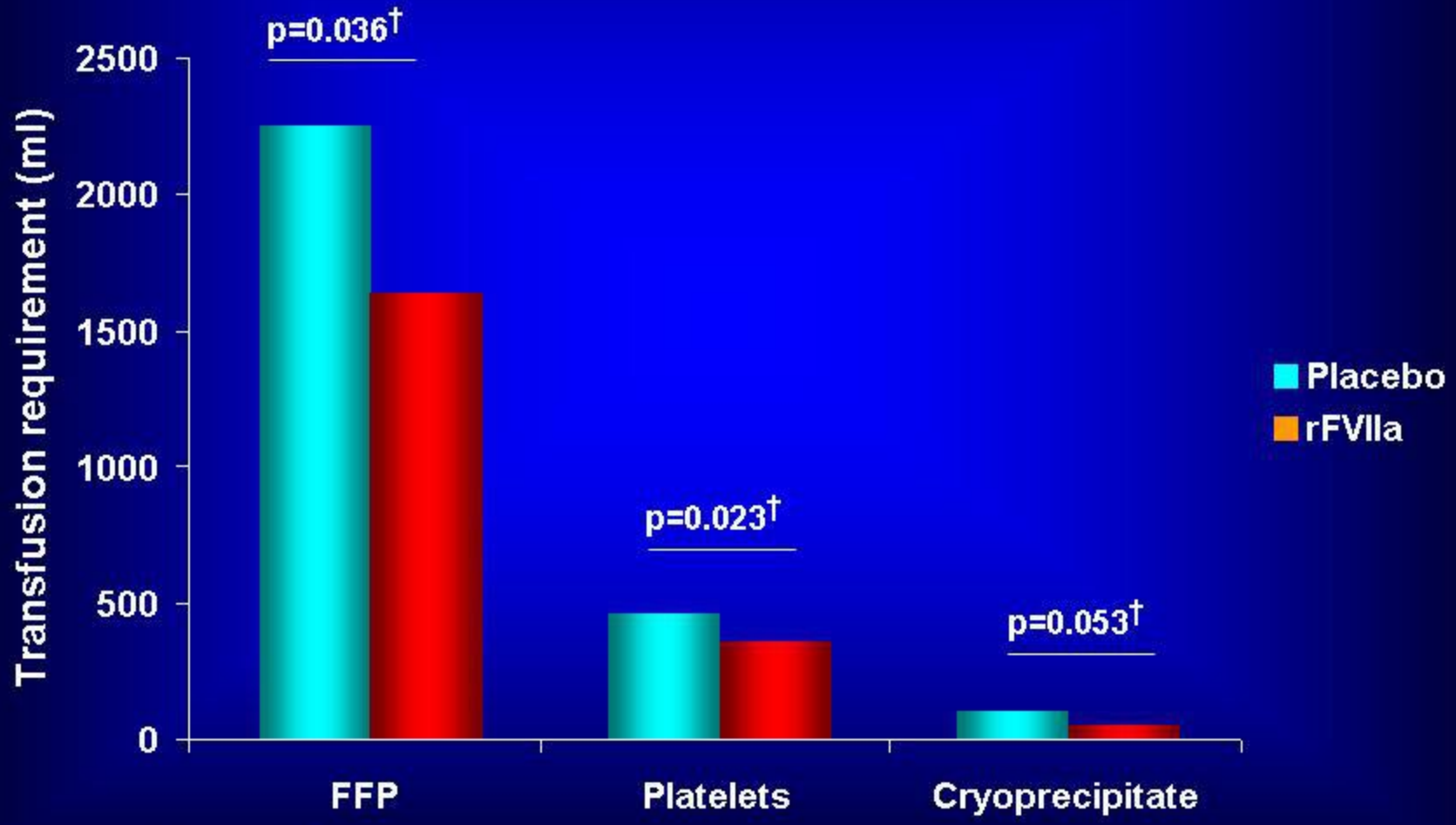
Penetrating	Placebo n	Placebo Median (range)	rFVIIa n	rFVIIa Median (range)	Est. RBC reduction*	*p*
All patients†	61	4.8 (0–41)	69	4.0 (0–37)	0.20	0.24
Excluding 48h mortality	52	4.2 (0–41)	57	3.9 (0–30)	1.00	0.10

>20 unit* Transfusion requirement in the first 48 Hours



* >12 units after trial drug initiation in addition to ≥8 units before trial drug initiation. Patients alive at 48 hours.

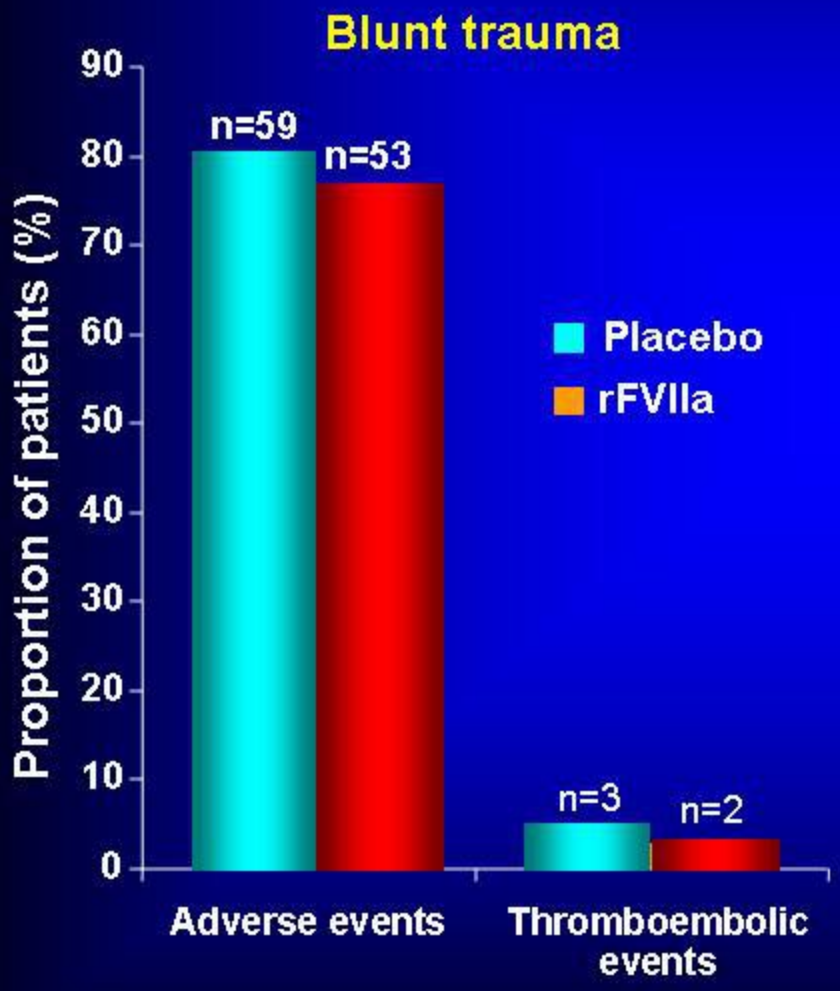
FFP, platelet and cryoprecipitate requirements within 48 hours

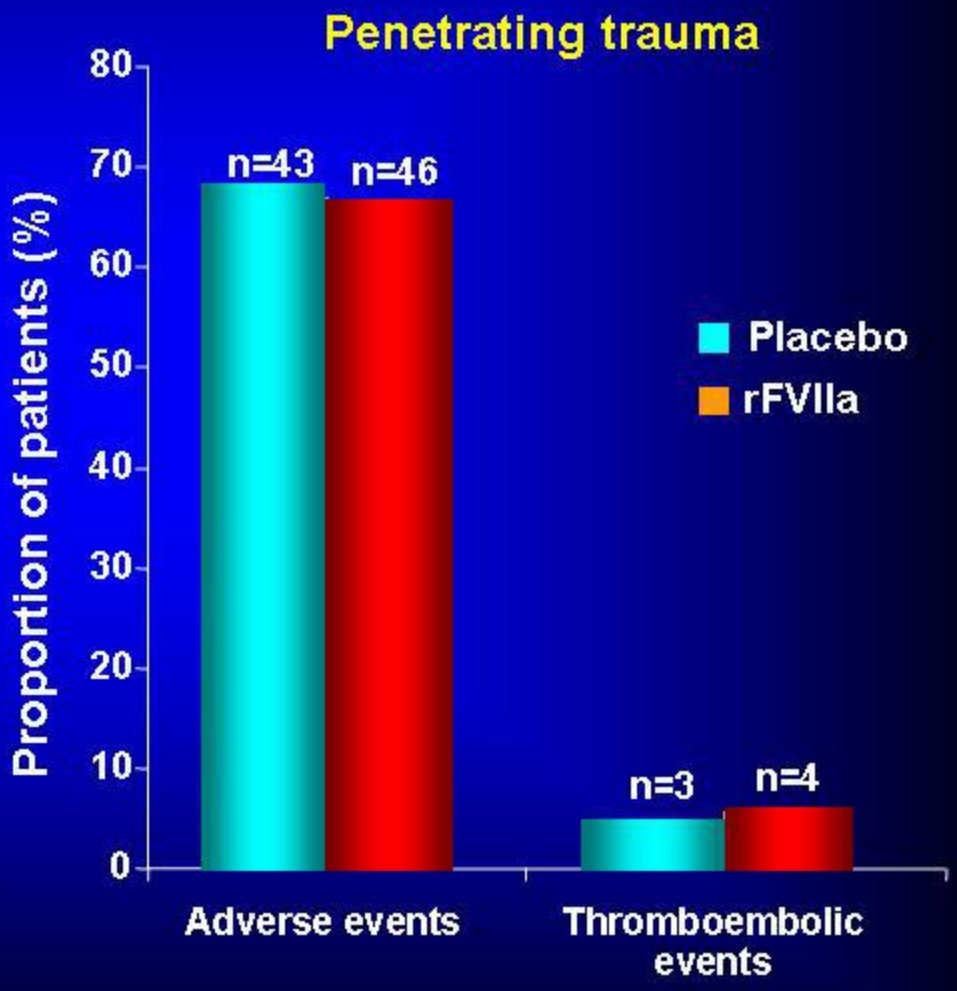


*Patients surviving >48 hours

†p-value for the two-sided Wilcoxon-Mann-Whitney test

Incidence of adverse and thromboembolic events



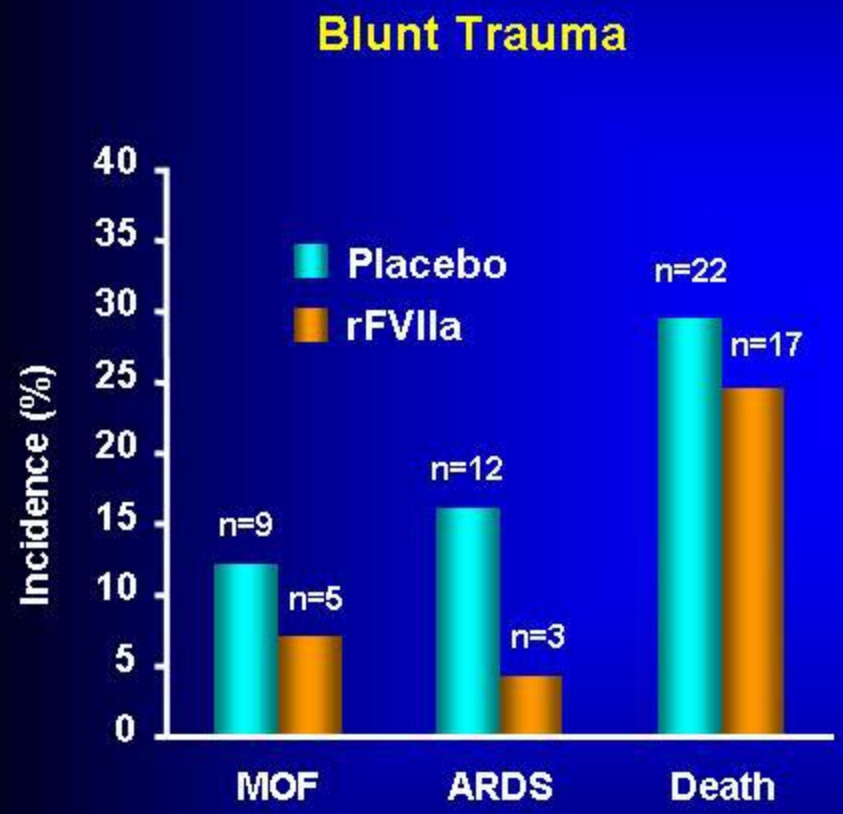


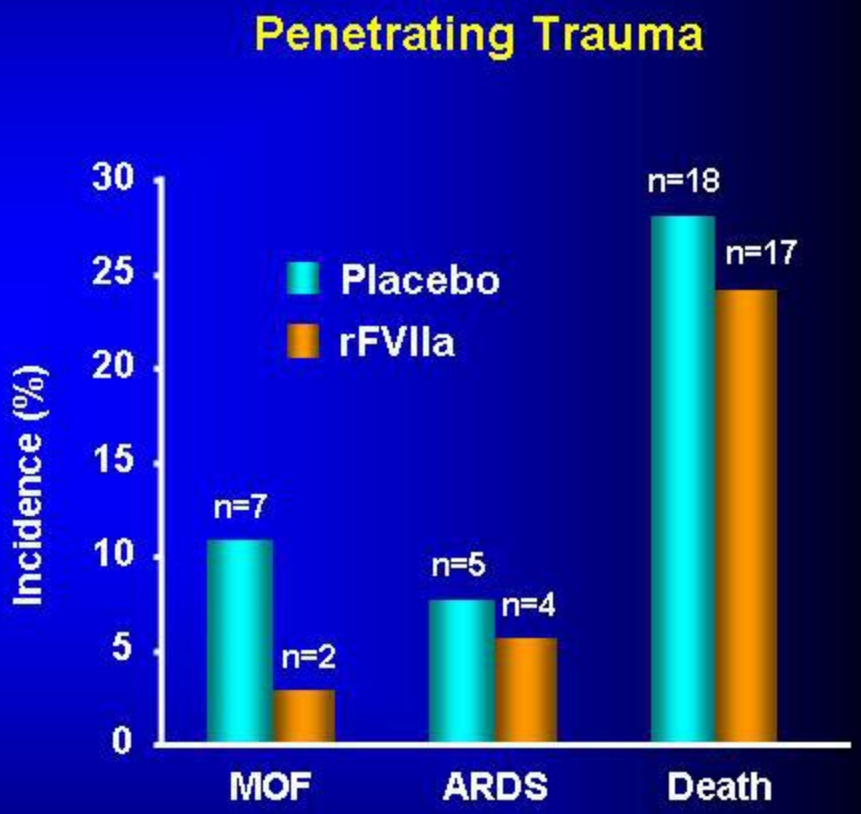
Secondary Endpoints at Day 30

	Median (range)			
	Blunt trauma		Penetrating trauma	
	Placebo (N = 74)	rFVIIa (N = 69)	Placebo (N = 64)	rFVIIa (N = 70)
ICU-free days *	8 (0-29)	13 (0-30)	19 (0-30)	23 (0-30)
Ventilator-free days *	14 (0-30)	17 (0-30)	21 (0-30)	26 (0-30)

***No statistical significance was observed for any of the groups**

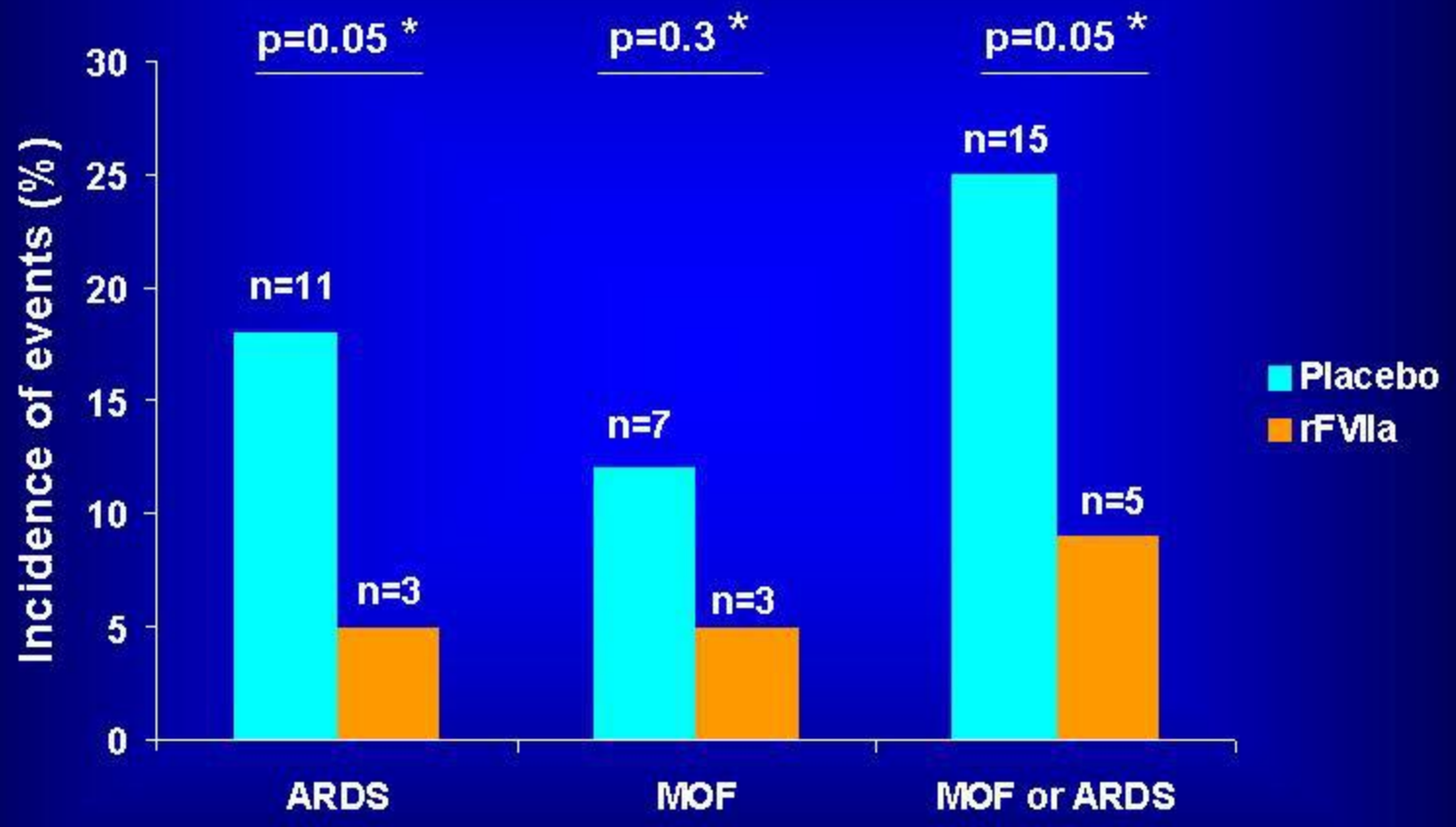
Incidence of MOF, ARDS, and death through 30 days





Predefined critical endpoints: multiple organ failure (MOF), acute respiratory distress syndrome (ARDS) and death

Reports of ARDS and MOF within 30 days - Blunt trauma†



† Patients alive at 48 hours

*p-value for two-sided Fisher's exact test

Conclusion

Patient Safety

- No safety issues were identified
- No increase in the incidence of thromboembolic events
- No increase of MOF or ARDS in either trauma group with rFVIIa vs placebo
- Trends:
  - More ventilator-free days
  - More ICU-free days

Risks to benefit

- rFVIIa is an effective adjunctive treatment for blunt or penetrating trauma patients in situations where major bleeding has been controlled by surgical or other interventions.
- There is no significant effect on hospital mortality rate
- A significant response is seen in blunt trauma and similar effects can be expected in penetrating trauma in cases of extensive tissue destruction, e.g. following high-velocity gunshot or close-range shotgun wounds
- The benefits of increased bleeding control – reduced RBC transfusion need for massive transfusion translated into a lower risk of developing single or multiple organ failure, especially ARDS

Risk to benefit

- For optimal effect, first dose of rFVIIa should be given at or immediately after initial surgical attempt to control the major bleeding sites
- Patients who are unlikely to benefit from the drug
  - Patients at low risk of residual or recurrent bleeding and who are not coagulopathic
  - Patients in whom extensive bleeding cannot be surgically controlled, and whose state of physiological derangement is extremely advanced at time of surgical intervention

Haemorrhage control

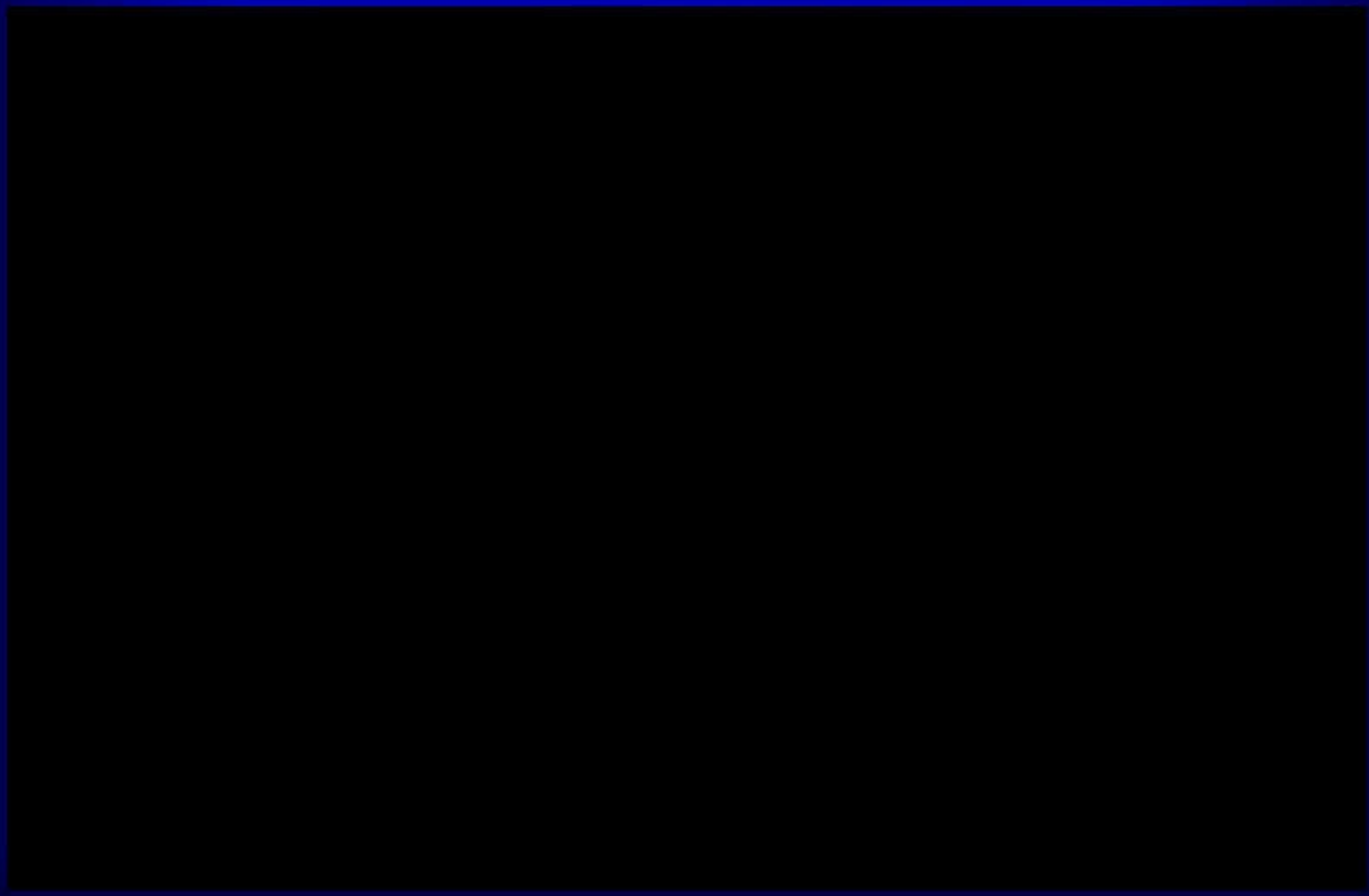
Controlling the bleeding and maintaining blood volume are the primary concerns in trauma management

The treatment of bleeding is to stop the bleeding

We don’t know…

- What is the correct dose?
- What is the correct dose interval?
- What are the correct indications?
- What is the correct cost of the drug?
- What is the reduced burden on society?

So….is the expense justified



We do know…

- **Use may not yet be justified**
  - Too early
  - Too expensive
  - Best benefits have yet to be proven

But properly used will be a major adjunct in the care of the bleeding patient

Summary

- Blood and clotting factors are life saving
- Associated with serious complications
- Rational use is a clinical decision
- Develop a massive transfusion protocol

Thank you


APRIL 19, 2004
SPECIAL REPORT
TIME
REBELLION IN IRAQ: A STATE OF SIEGE
LIVING MANDELA'S DREAM
SOUTH AFRICA
Ten years after apartheid
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uth African life
Matshiqi. "The Mandela era created the delusion of a rainbow nation, which masked a lot of the problems between black and white people in this country."
As he has aged, Mandela's mortality has become more apparent. He grows tired more easily. He can be short tempered. His doctors insist he rest more often, which he does by spending time with his grandkids or his third wife, Graça Machel, widow of a beloved Mozambican leader, Samora Machel. When German Chancellor Gerhard Schröder visited South Africa last January, Mandela stood him up, preferring to extend his vacation with Machel on the Indian Ocean resort island of Mauritius. "We've put him on a pedestal and expect him to behave in a certain way," says granddaughter Ndileka Mandela, who met her grandfather for the first time at 16, when she visited him in prison on Robben Island. "He can be very harsh,

Haemorrhage

- Circulating blood volume is maintained by
  - Replacing lost blood using volume expanders and red blood cells
  - Preventing further blood loss through surgery AND an effective coagulation process
- However
  - Transfusion increases the risk of complications following trauma
  - Coagulation process may be compromised (coagulopathy)