

The Complex Mechanism and Treatment of Massive traumatic bleeding



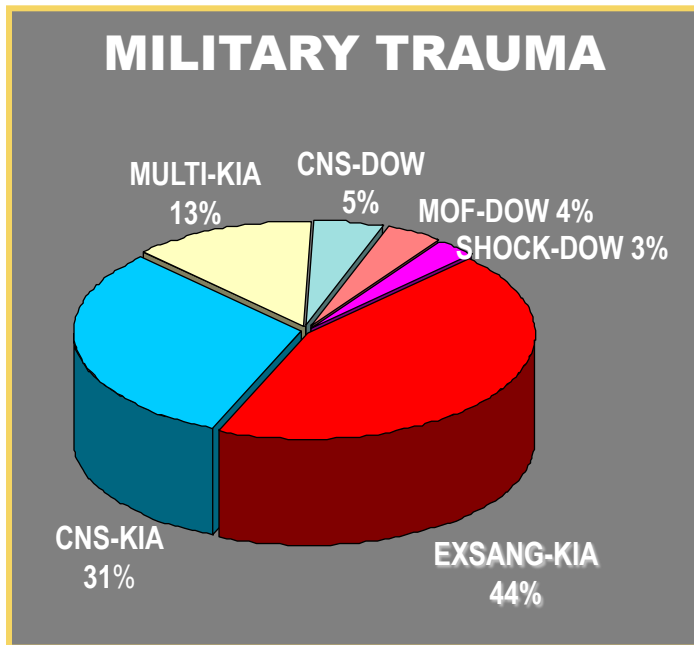
Uri Martinowitz MD

Institute of Thrombosis Hemostasis and The National Hemophilia Center, Sheba medical Center, Tel Hashomer,

Member, Hemorrhage Control Steering Committee , The U.S. Army Medical Research and Materiel Command USAMARC, The Combat Casualty Care Research Program CCRP

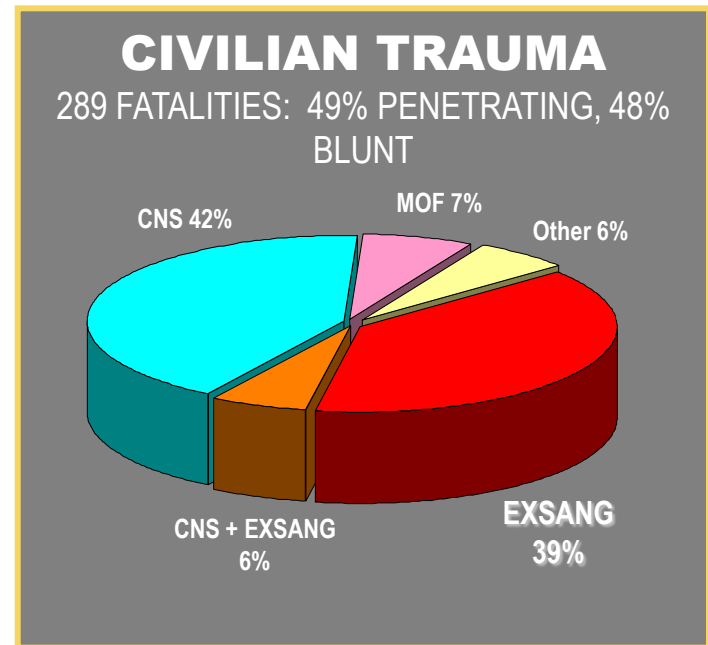
Trauma Is the leading cause of death in the young

Hemorrhage is a major cause of death in trauma



KIA – killed in action; DOW – died of wound; MOF – multiple organ failure.

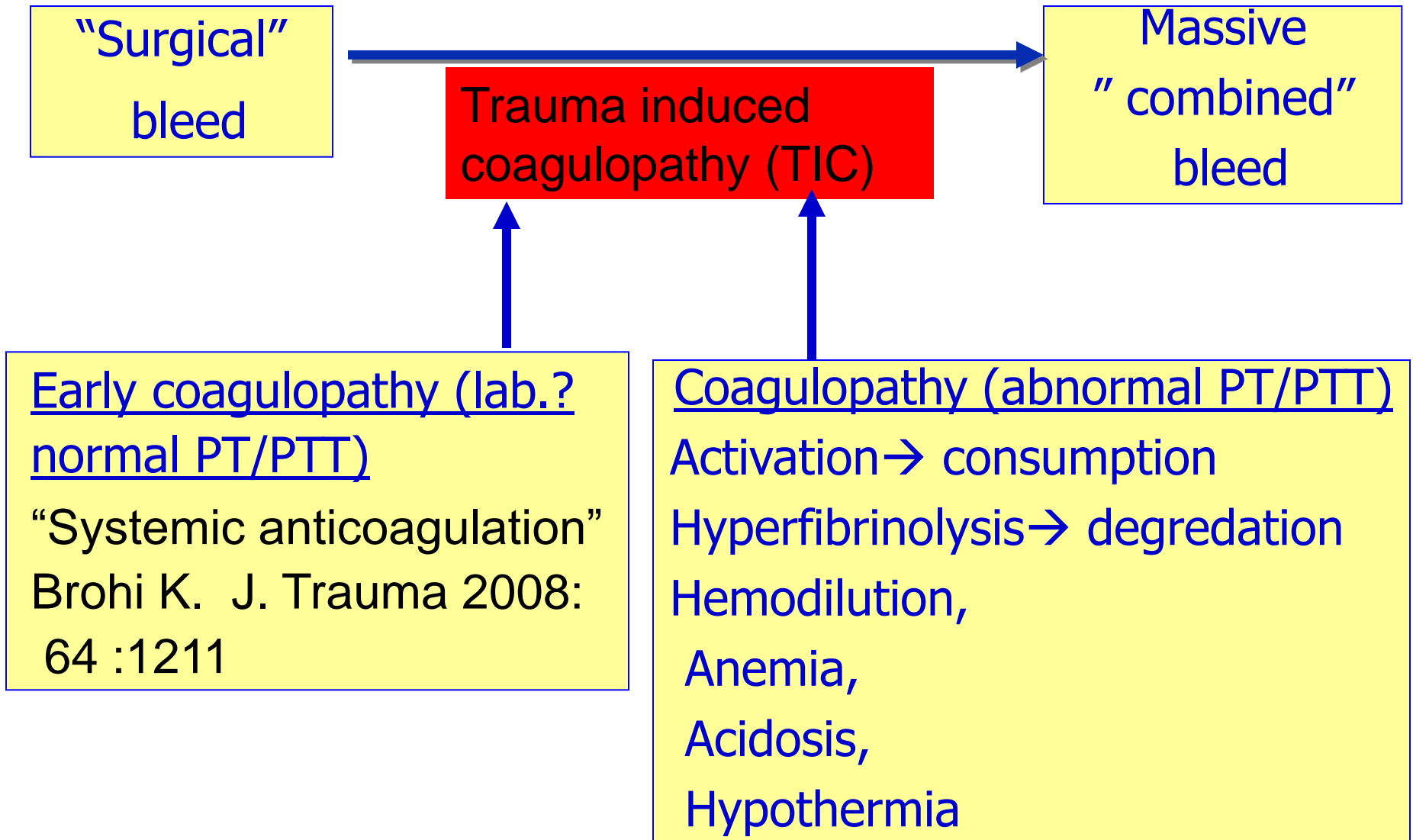
WDMET Vietnam war 1967–1969; 8000 CASUALTIES.



Sauaia A et al. *J Trauma*. 1995; 38:185-193.

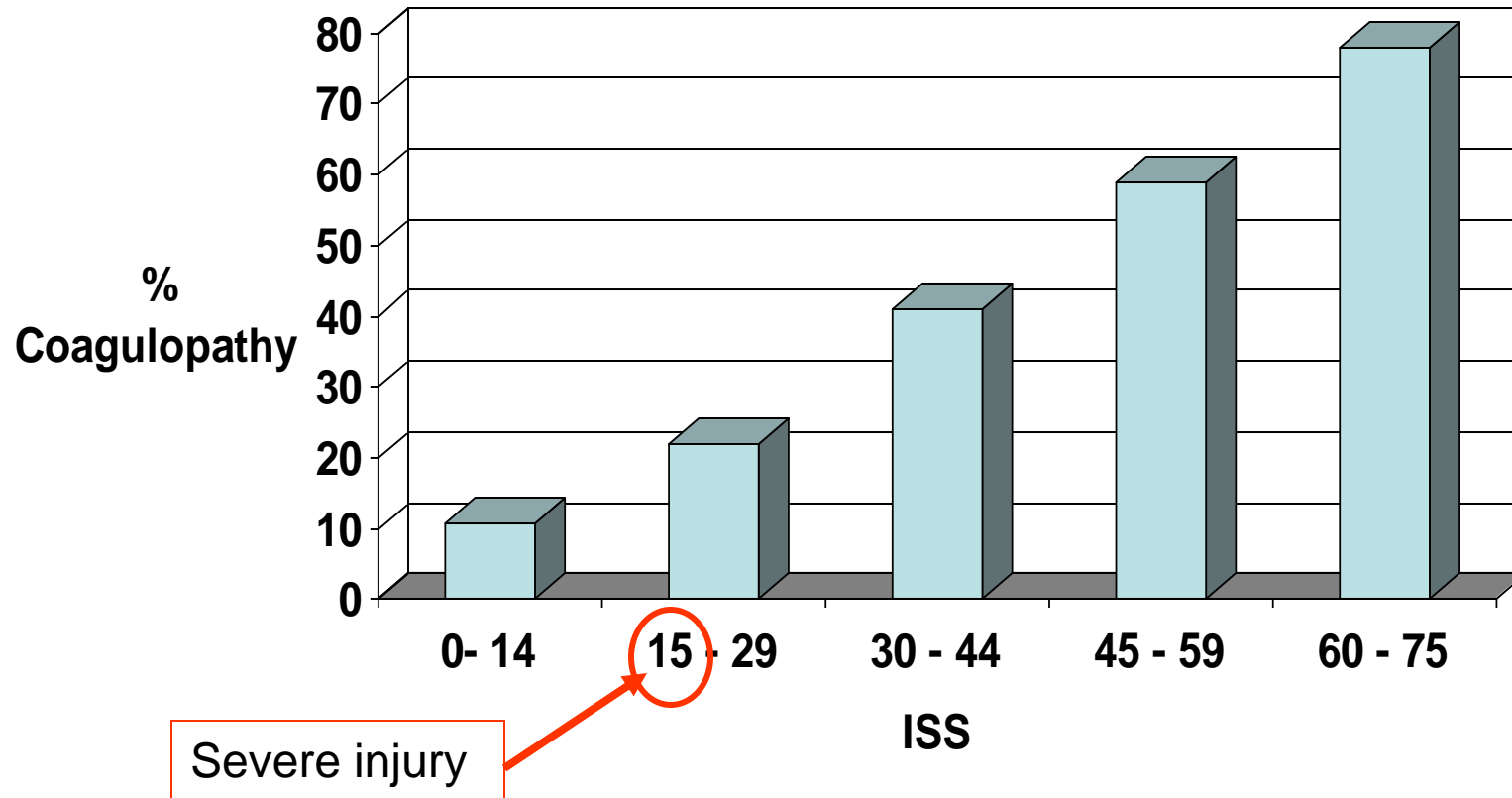
140,000 deaths/year in the US

Massive Hemorrhage in Trauma (and “controlled” trauma.)



Incidence of coagulopathy correlates with ISS (ISS-injury Severity score) in civilian trauma patients

Brohi K: J. Trauma (2003) 55:1127



(Kaufman CR, J. trauma 1997, Cosgriff N. J. Trauma 1997)

Definition of coagulopathy varies :INR>1.2-1.6 ; PTT>35-60

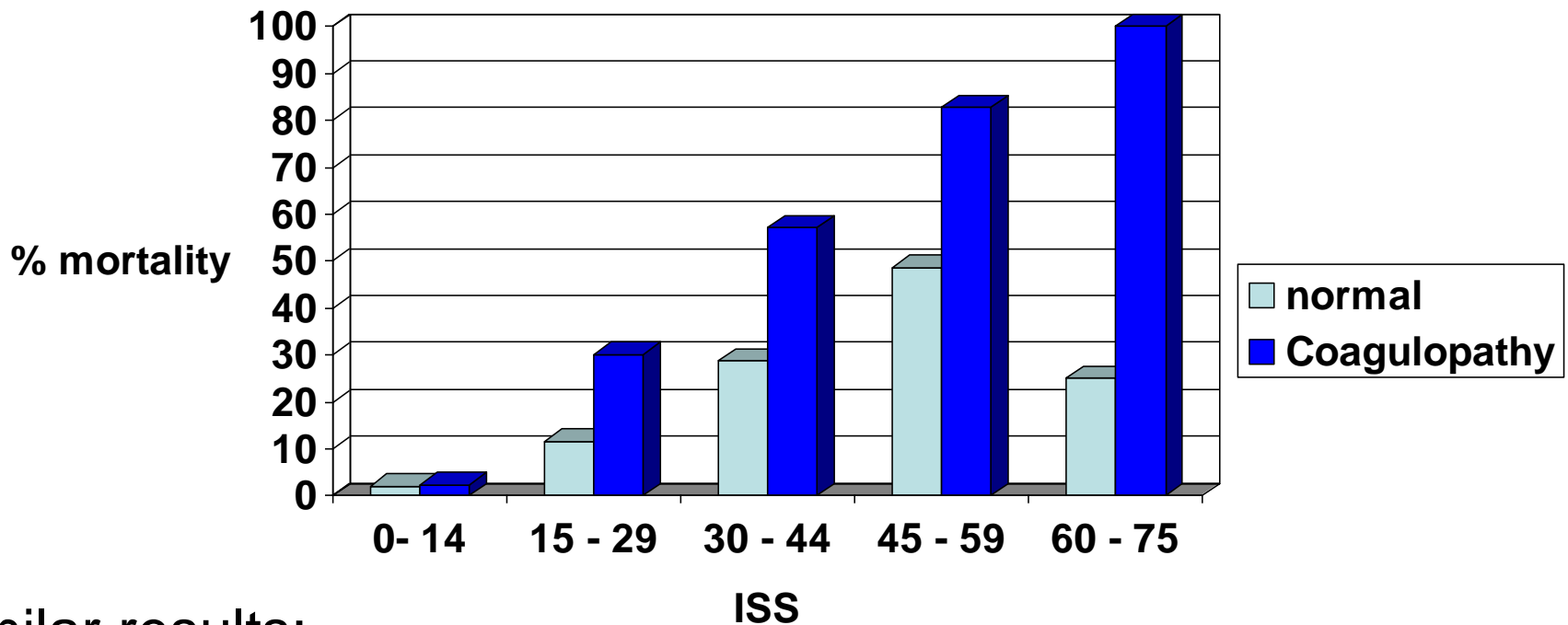
Incidence of coagulopathy varies :10-70% (most 25-35%)

Coagulopathy is associated with increased mortality in civil trauma

4-6 times beyond expected from the injury severity

Brohi K: J. Trauma (2003) 55:1127

(n=1088)



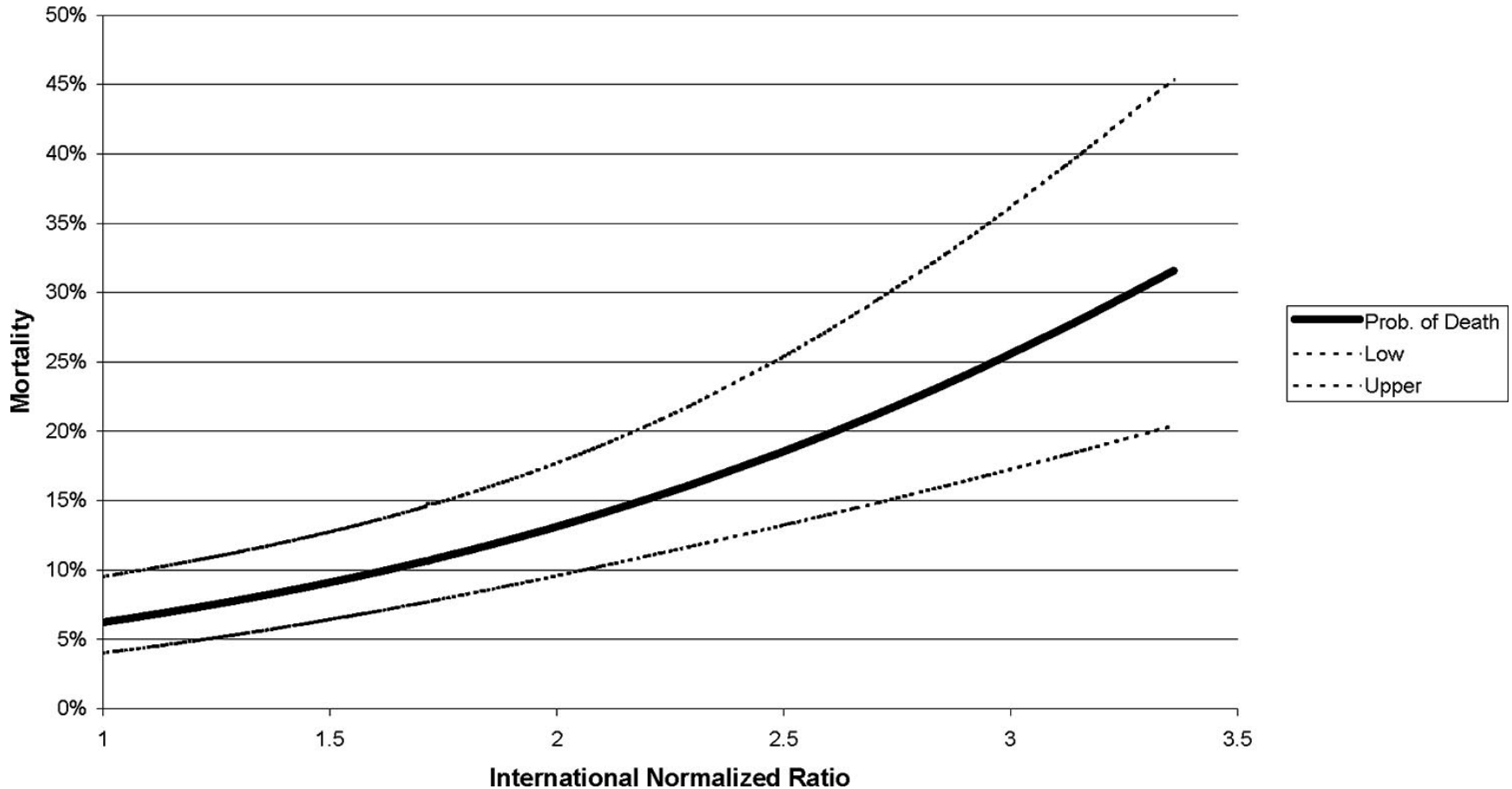
Similar results:

❑ The German Trauma Registry (n=8724); Maegele M. Injury 2007 38:29

❑ US Army in Iraq. Niles S. J. Trauma. 2008;64:1459.

Early Coagulopathy of Trauma in Combat Casualties

The trend of INR associated with mortality with 95% CI by univariate analysis



Traumatic induced coagulopathy (TIC ≠ DIC)

- **Activation → consumption** of factors and platelets
- **Hyperfibrinolysis** (clinical) by tissue damage
→ **degredation** of factors and platelets
- **Dilution** by fluids and massive transfusions
- **Anemia** blood loss and dilution → platelets dysfunction
- **Fibrinogen reduction** (consumtion,degredation) and polimerization defects (coloids,Gelatins)
- **Acidosis**
- **Hypothermia**

Early Traumatic induced coagulopathy

- Blood loss → **hypoperfusion** (no coagulopathy in BD < 6 regardless of ISS*) →
- **Activation of anticoagulation and fibrinolysis via** thrombin activation of Prot. C pathway, leading to early **“systemic anticoagulation”**
(by lab markers - Prot.C, Soluble Thrombomodulin, PTF₁₊₂, PAI 1, tPA, TAFI, D-Dimers, FVII, Fib.)

Dangerous theory-limiting hemostatic treatments

Brohi K. J. Trauma 2008; 64 :1211

Brohi K. Ann. surg. 2007;245:812

Brohi K. Curr. Opin.Crit.Care 2007;13:680

Hess J. J.Trauma 2008;65;748 EICBT

Parr M. J.Trauma 2008;65;766 EICBT

- **DIC definition:** ... intravascular activation of coagulation with loss of localization ...” Fletcher B. et. al. *Thromb Haemost* 2001;86:1327-30
- “Hemostatic activity in trauma is **confined to the area of injury**. Only occasionally, control mechanisms fail to restrict the hemostatic process to the area of injury” *Gando S. . 2001*
- **Activation in the acute phase of trauma is mainly extravascular. No intravascular coagulation** in animal trauma models even after rFVIIa
- *U. Martinowitz J Trauma 2001; M. Schreiber J Trauma 2001 ;M. Lynn J trauma 2002; HG Klemcke J Trauma 2005; D. Fries 2006;2007*

ISTH DIC SSC 2005

...After extensive discussion by Dr. Uri Martinowitz, Nielsen and others, consensus was reached on ... subsets of patients where algorithm... requires modification:

...use of the algorithm in trauma patients be limited to at least 24 hours following injury so that high scores on the algorithm indicating “DIC” do not serve to preclude therapies for life-threatening hemorrhage such as rVIIa (Which ...traditionally has been said to be contraindicated in DIC).

Alterations of hemostasis in trauma

COAGULATION	ANTICOAGULANTS	FIBRINOLYSIS
Fibrinogen ↓	AT ↓	tPA ↑
FV ↓	Prot.C: Ag.+Ac ↓	plasminogen ↓
FII ↓	TFPI ↓	α2-antiplasmin ↓
aPTT / PT ↑	Soluble thrombo-modulin ↑	PAP complex ↑
TF ↑		PAI 1 Ag.+Ac ↑
FPA ↑		FPB ↑
d-Dimer ↑		d-Dimer ↑
TAT ↑		
PLT (counts & function) ↓	Platelets: activation ↑ (P selectin, microparticles, PAC 1 binding) Function +/-	Hypercoagulation Hypocoagulation

Hypothermia

Platelets

■ Thrombocytopenia

- Sequestration in liver and spleen

Villalobos T: J Clin Invest (1958) 37:1

■ Platelet dysfunction

- Adhesion and aggregation

Kermode J: Blood (1999) 94:199

Coagulation factors

■ Reduction of the enzymatic activity

- not impaired > 33 °C

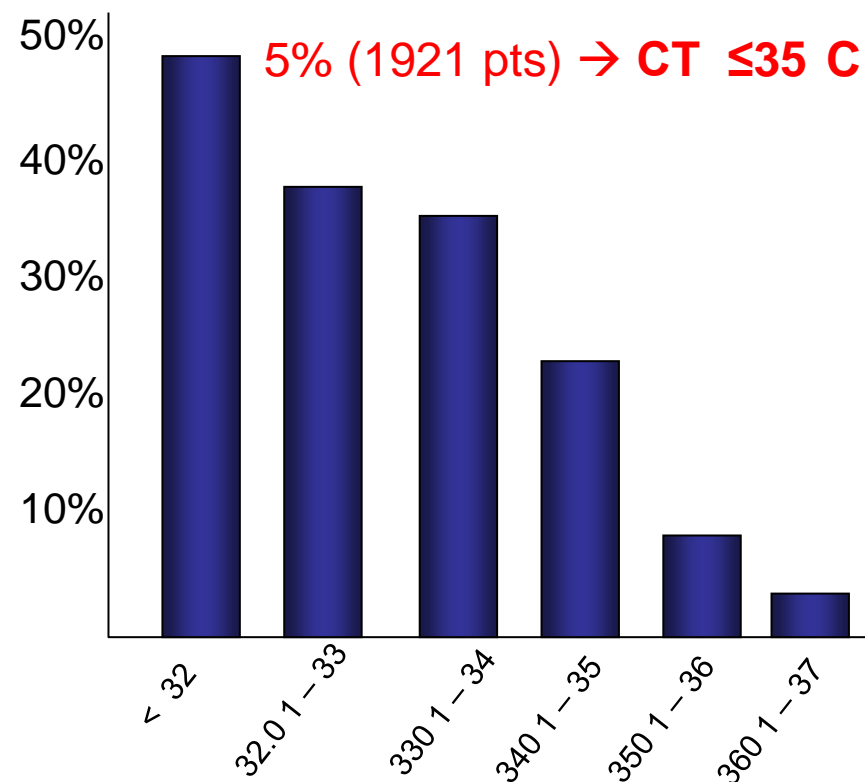
■ Increased fibrinolytic activity

- PAI 1 reduced
- α 2-Antiplasmin reduced → hyperfibrinolysis

Wolberg A: J Trauma (2004) 56:1221

Hypothermia and outcome in major trauma

Mortality in %



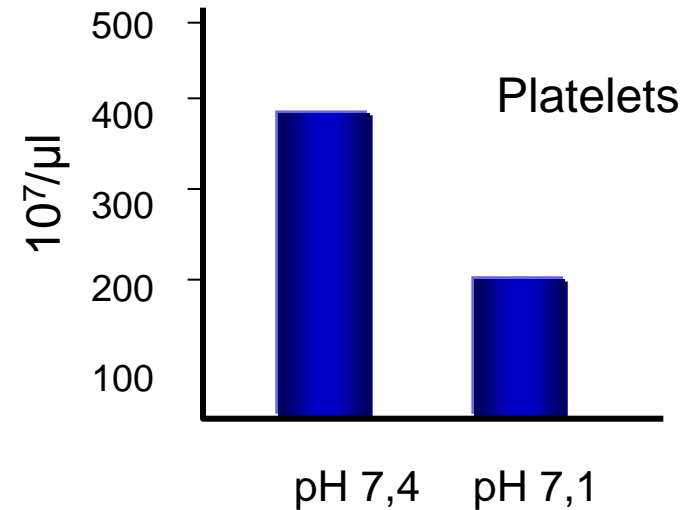
Wang H: Crit Care Med 2005;33:1296

Acidosis compromises coagulation

Platelets

- Thrombocytopenia
- Platelet dysfunction

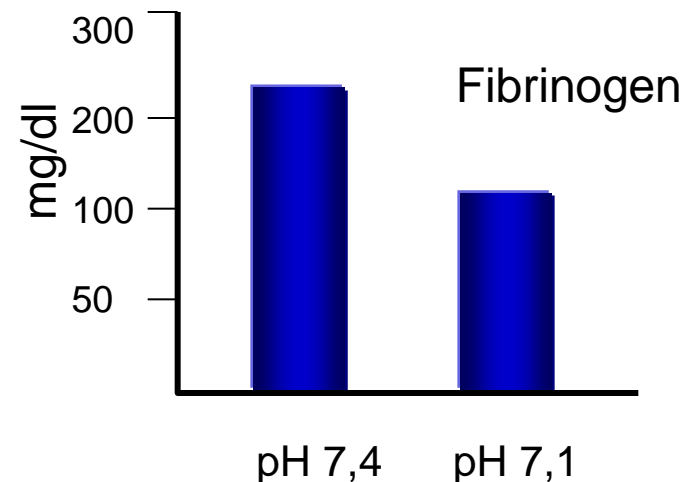
Marumo M: Thromb Res (2001) 104:353



Coagulation factors

- Reduce fibrinogen and
- Decreased clot firmness ↓

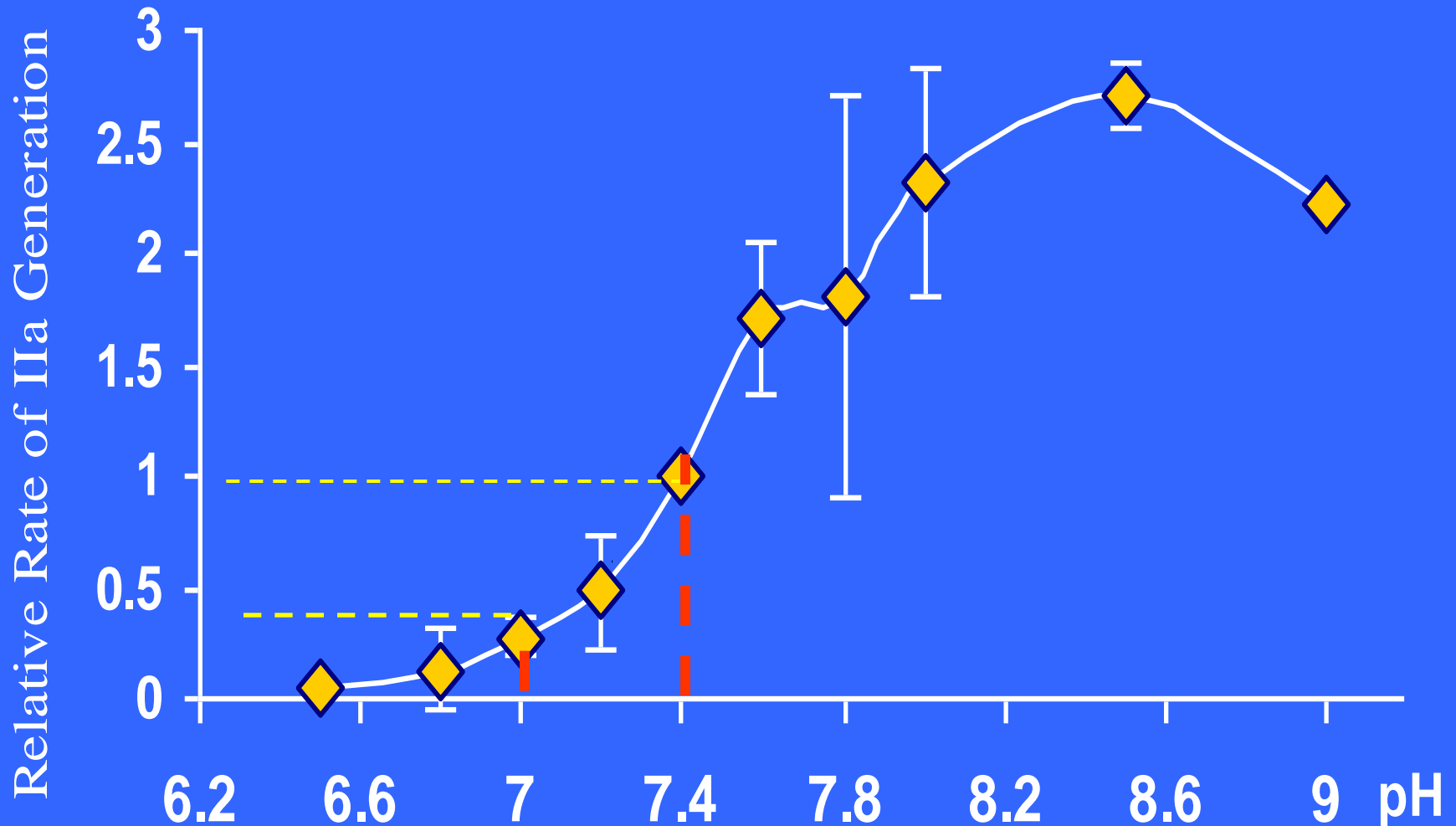
Engstrom M: J. Trauma (2006) 61:624



Martini W: J Trauma (2006) 61: 99

Acidosis compromises coagulation

Effect of pH on Thrombin Generation on phospholipid vesicles



Inhibition of 70% at pH 7.0 as compared to 7.4

Anemia-RBC and platelets interactions

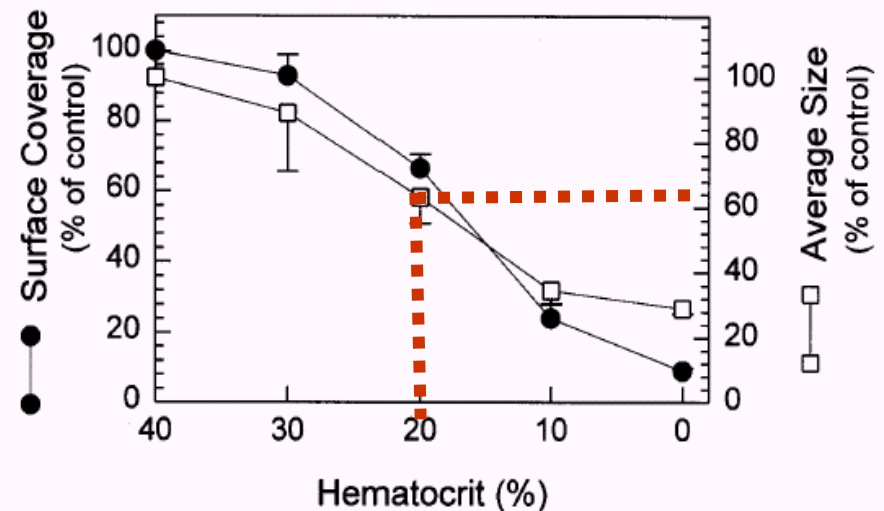
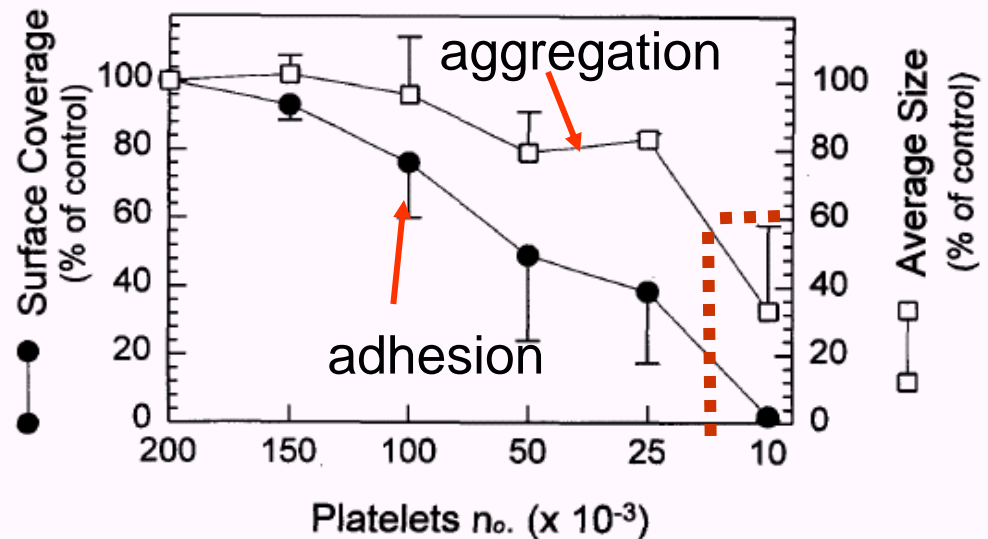
Hct = 40%, PLTs = 200,000/mcL



Hct = 20%, PLTs = 200,000/mcL



Hct = 20%, PLTs = 50,000/mcL



Transfusion 1994; 34:542-9

D. Varon. Thromb. research 1997;85:4:283

Anemia compromises coagulation

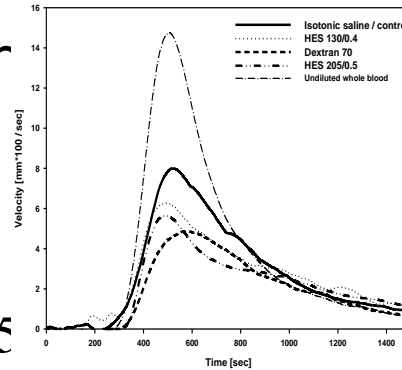
- Anemic patients tend to bleed more in surgery
- Ht 35 vs. 31 at end of CPB =blood loss X4-5
- Patients with bleeding diathesis (uremia, Glanzmans' , irradiation colitis, angiodisplasia etc.) bleed less with correction of Hb (EPO).
- Apart from oxygen carrier -RBC transfusion is an important hemostatic treatment !.
- In massive bleedings the goal is to achieve Ht 30-35,Hb 10-11.

Hemodilution and effects of fluids on coagulation

Interfere with measurement - **"false" high levels of fibrinogen**

Impairs fibrin polymerization

Impaired Platelet function

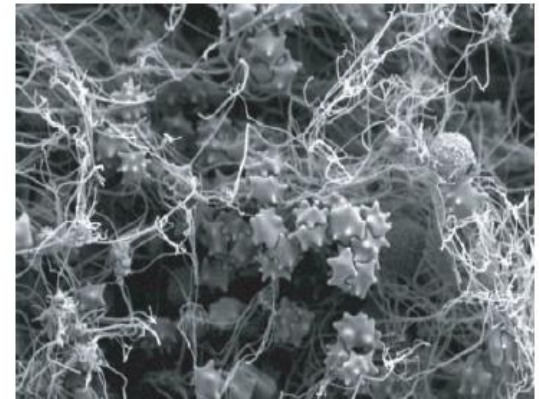


Hiippala ;Blood Coagul Fibrinolysis 1995

Trieb J, T&H 1997; Jamnicki M, Anesthesia. 1999



Undiluted blood clot



65% dilution with gelatin

May explain increased bleeding at
fibrinogen levels above 2 g/L

Blome M et al., Thromb Haemost 2005;93:1101-

Contribution to acidosis

Saline 0.9% pH 4.5 – 7

Ringer Lactate pH 6 - 7.5

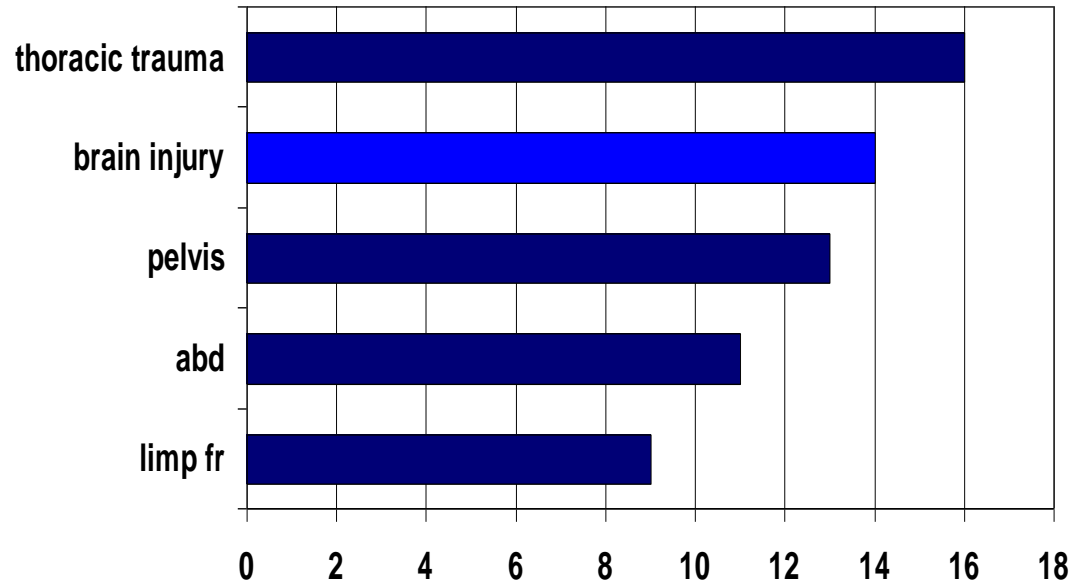
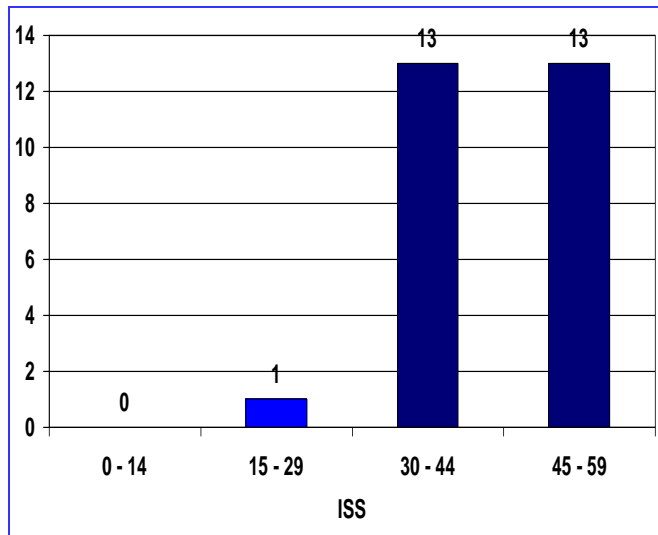
Prough DS &, Anesthesiol. 1999

Fries D, Br J Anaesth. 2005

Hyperfibrinolysis in Trauma

- Underestimated (no routine tests)
- Common in severe trauma (ROTEM) ~20% ISS>15
Vorweg .with permissionon
- Common in hypoperfusion (BD>6) (Lab results)

K. Brohi J. Trauma 2008



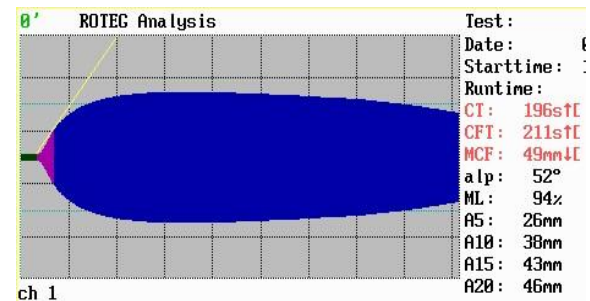
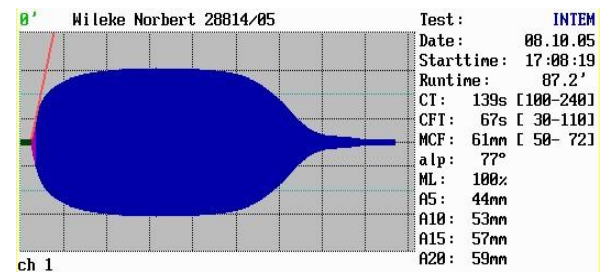
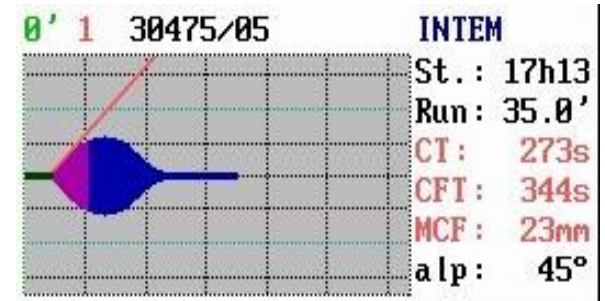
Hyperfibrinolysis according to organ

H. Schochl with permission 2007

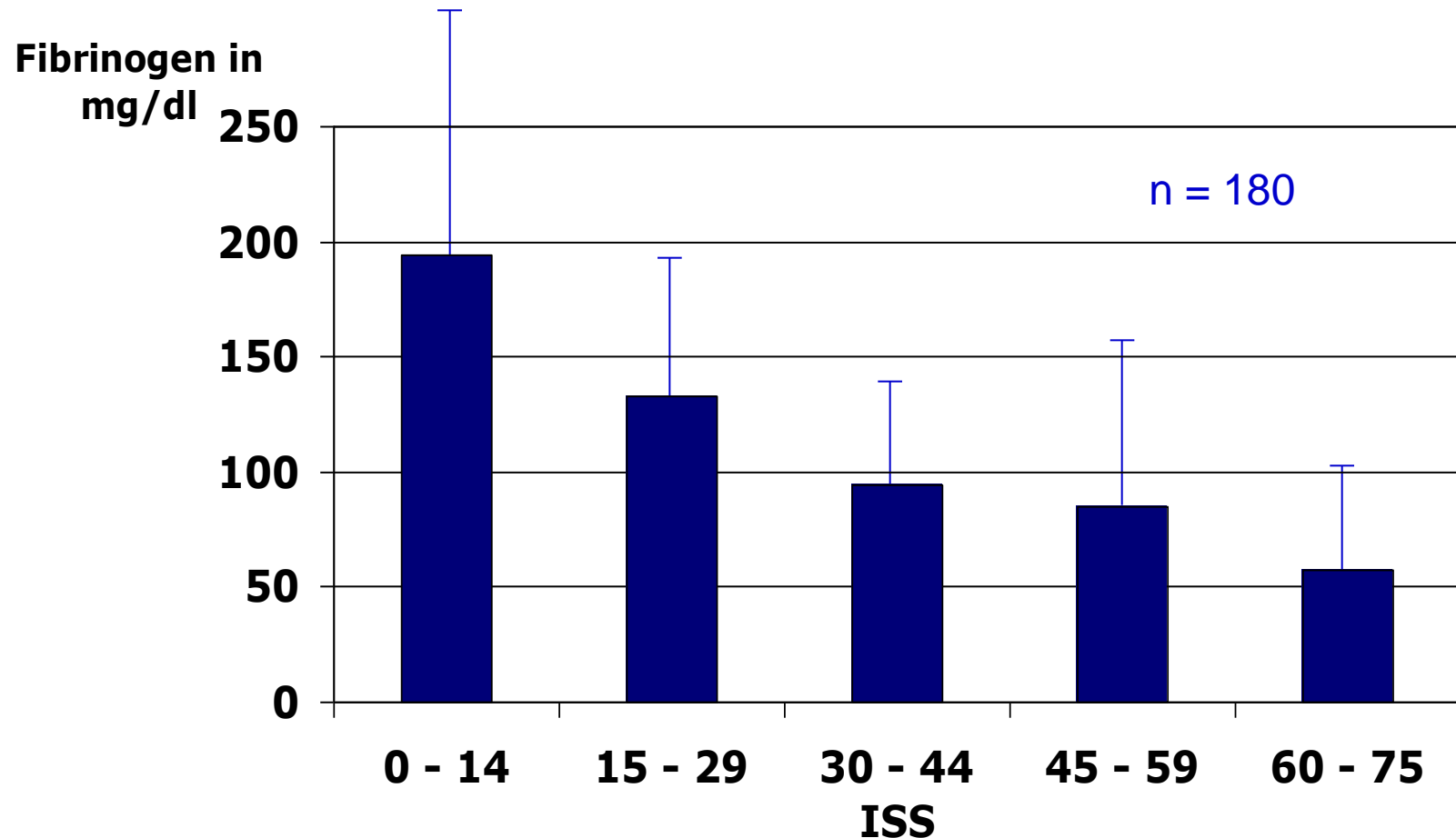
High mortality (84%); increases with severity of fibrinolysis

Thromboelastography

- **Complete lysis < 30min**
 - ER: 11
 - ICU: 3
 - Survivor: 0
- **Complete lysis 30 – 60 min**
 - ER: 3
 - ICU: 4
 - Survivor: 0
- **Complete lysis > 60 min**
 - EM: 0
 - ICU: 5
 - Survivor: 5



Fibrinogen level on admission to ER



Coagulopathy is underestimated - we only see the tip of the iceberg

Lag time of 45-60 min. to results

Consumption

fibrinolysis

Hemodilution

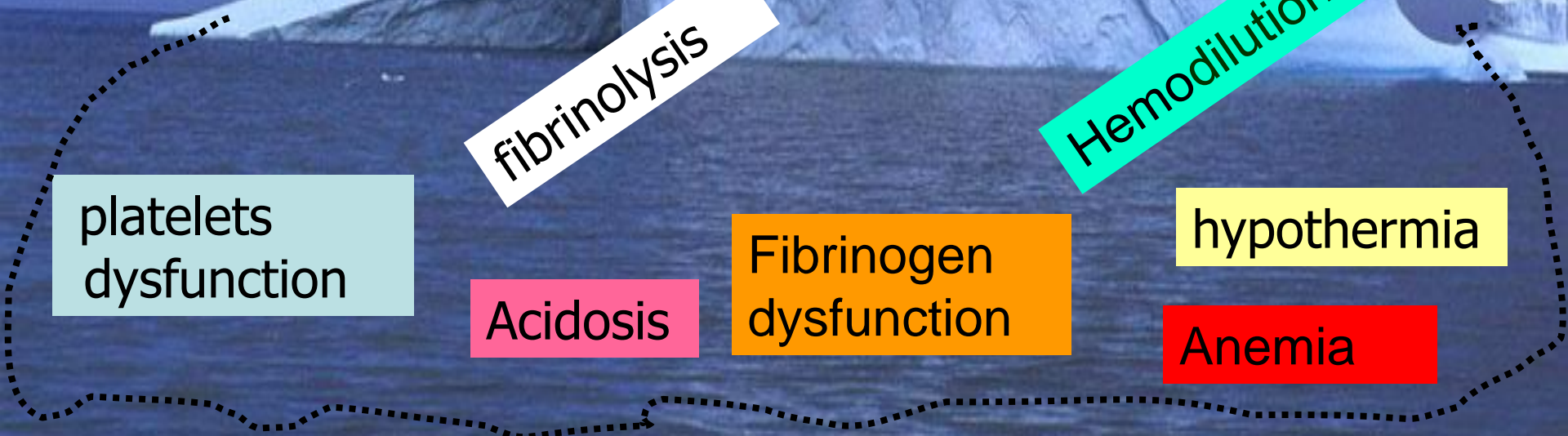
platelets
dysfunction

Acidosis

Fibrinogen
dysfunction

hypothermia

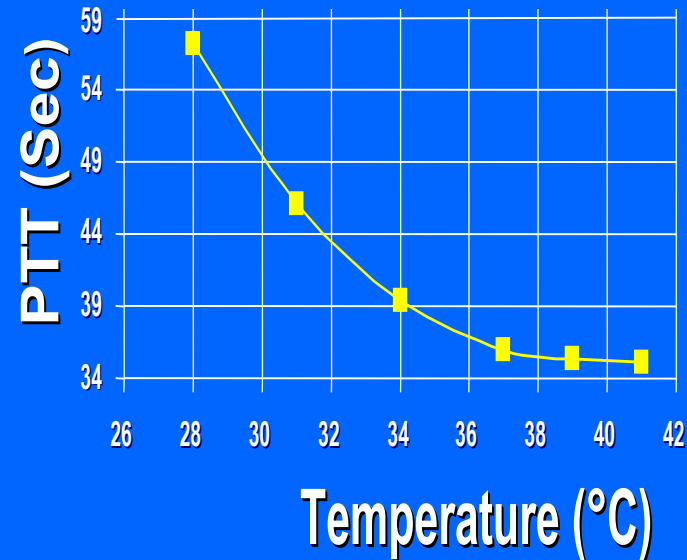
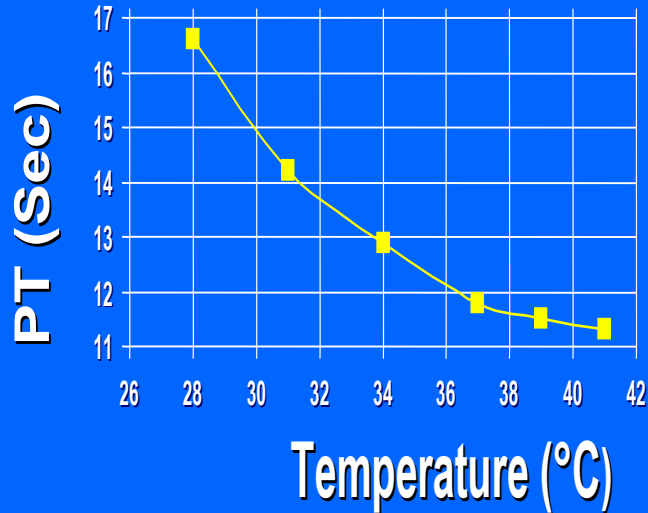
Anemia



Hypothermic coagulopathy is underestimated

Coagulation tests are performed in test tubes at 37 C

Effect of temp. on PT and PTT

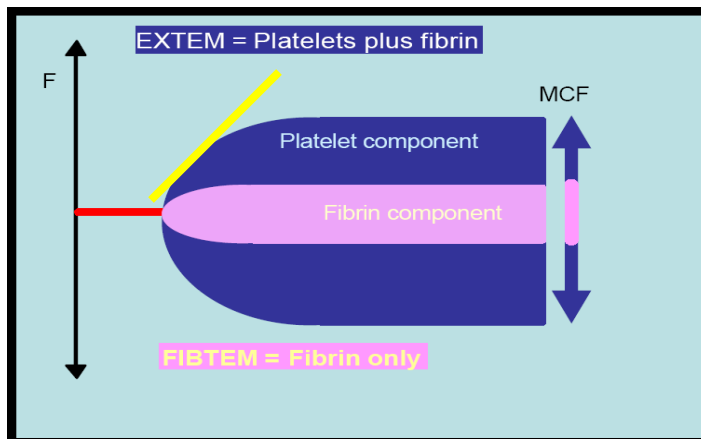
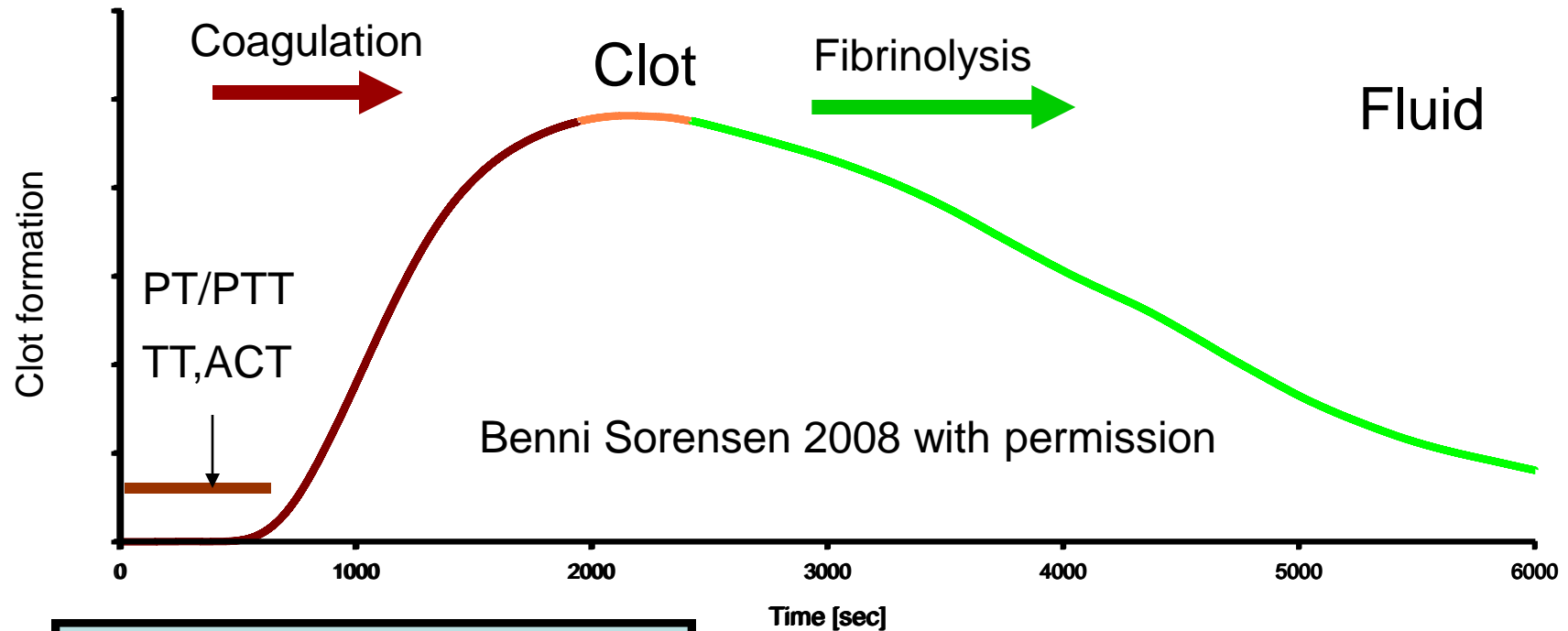


Rohrer MJ, Crit Care Med 1992.

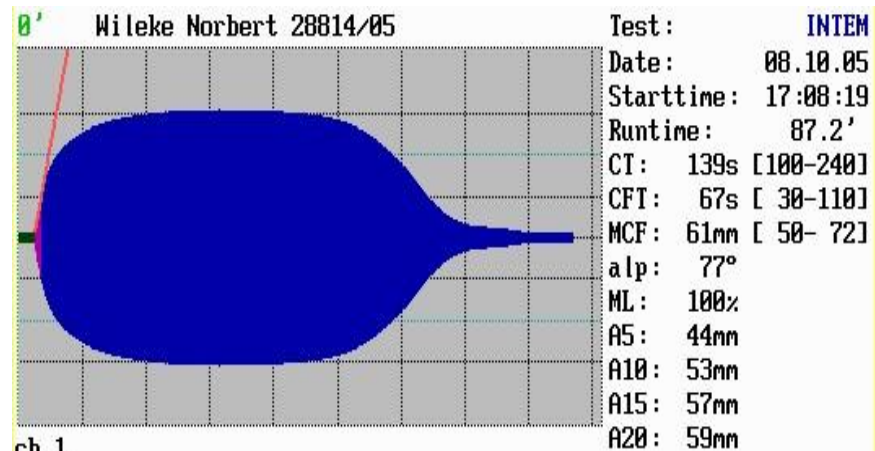
Coagulation process is taking place on cell membranes in body temperature of the patient

Standard coagulation test are of limited value they only detect initiation of clot formation

Fluid



Time [sec]



treatment of massive traumatic bleeding

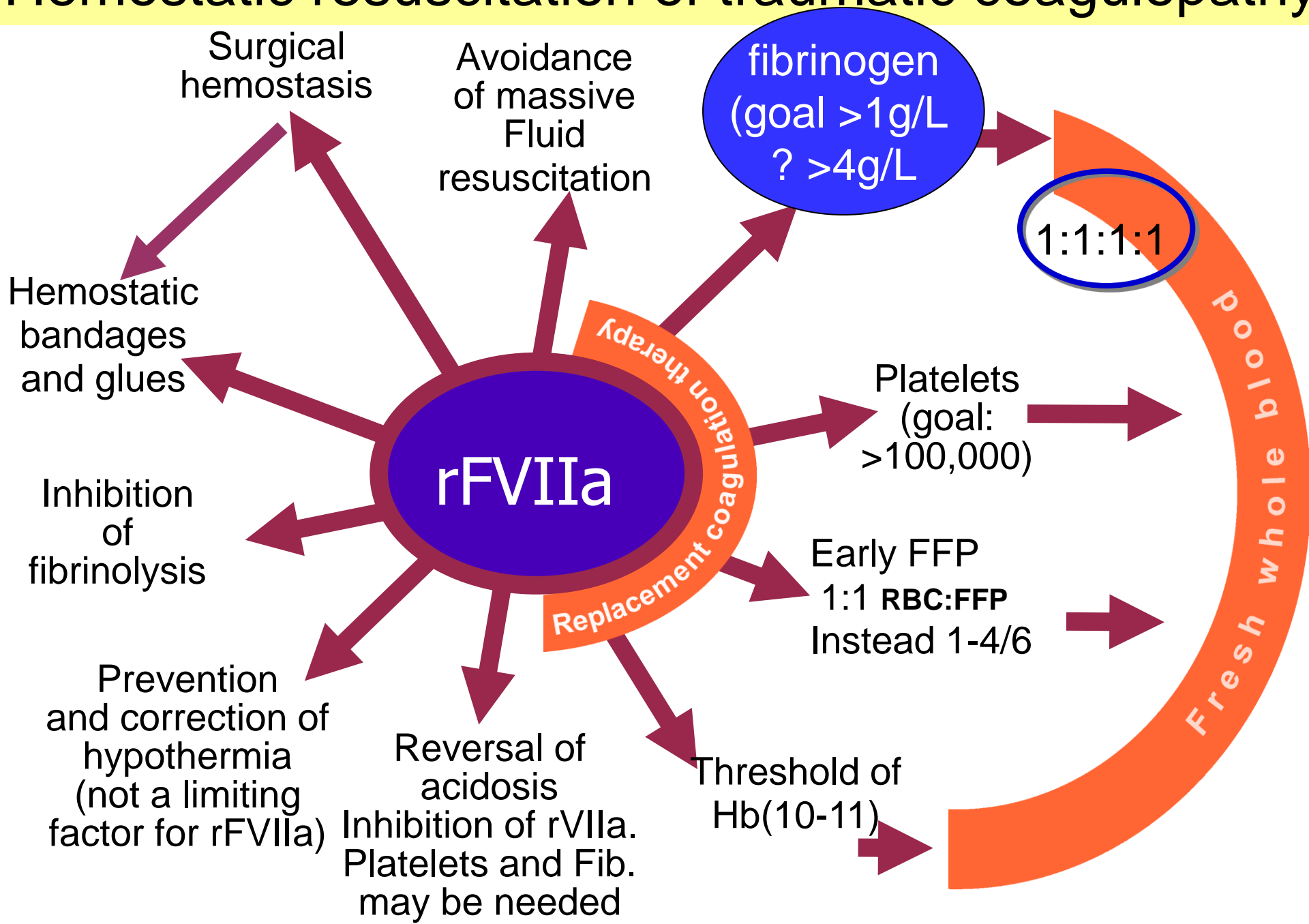
Role of blood bank: from provider to partner

Pär I. Johansson, Transfusion 2007 Aug. 47:176-181s



Early hemostatic resuscitation

Hemostatic resuscitation of traumatic coagulopathy



The blood bank: from provider to partner in massively bleeding patients

Pär I. Johansson, Transfusion 2007 Aug. 47:176-181s (

- Monitoring blood products delivery
- Contacting (consulting) clinicians in case of imbalanced transfusion
- Early FFP (1:1 PRBC: FFP) & PLT
- Massive transfusion packages (5PRBC+5FFP+2PLT)
- Thawed FFP available for immediate delivery
- Real time monitoring of coagulation by TEG

The blood bank: from provider to partner in treatment of massively bleeding patients

Pär I. Johansson, Transfusion 2007 Aug. 47:176-181s

Results in rAAA vs. historical controls (55 : 93)

(prospective randomized study rejected by IRB)

- Suboptimal transfused patients from 10 to 3%:

PLT 155 $10^9/L$ vs. 69 $10^9/L$; $p < 0.001$

APTT 39" vs. 44"; $p < 0.001$,

- Significant **decrease (50%)** in transfusions
- Significant **increase (66% vs. 44%) 30-days survival**
(9% hyperfibrinolysis in TEG)

Pro-hemostatic agents:

Extra-vascular (surgical):

Fibrin glues

New hemostatic polymers

Intravascular -

Fibrinolytic inhibitors

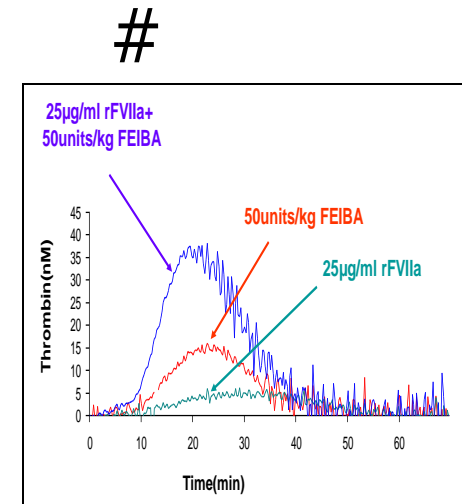
Coagulation factors: cryo, FFP, platelets, **PRBC**

Coagulation concentrates: fibrinogen

FXIII ,PCC, APCC

~~DDAVP ...~~

Injury-specific agents: rFVIIa & mutants, Xa-PL,
pdVIIa-Xa ,mutants rFVIIa, combinations#

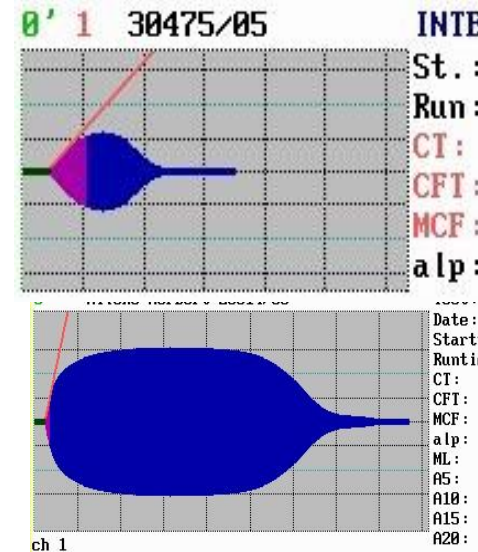


Fibrinolytic inhibitors

- Antifibrinolytic therapy in massive bleeding may prevent coagulopathy and platelets dysfunction.
- Lysine analogs have high safety

Evidence (RCT, meta-analysis, systematic reviews) for reduction of blood loss/ requirements:

- Cardiac surgery (+mortality and redo.) Vaylsteke A. BMC Anesthes.. 2006
- Liver operations Wu C.C. Ann. Surg.2006
- Orthopedic surgery Niskanen RO Acta Orth. 2005; Orpen NM Knee 2006
- No evidence in trauma



- Practice Guidelines of ASA ; Anesthesiology July 2006

Antifibrinolytic therapy ...**may be used** for reducing ... blood transfused for patients at high risk of excessive bleeding

- European Guideline: Crit. Care ;Span et al 2007

Antifibrinolytic therapy **should be considered** in bleeding trauma patients. Tranexamic acid(TXA) 10-15mg/kg followed by 1-2mg/kg/h **Grade 2 C**

- **Dose of 50-100mg/Kg TXA** are used in cardiac surgery for many years with 70% reduction of blood requirements ;Katsaros D.; Ann. Thorac.Surg. 1996;61;1131-5

Traditional trigger for fibrinogen has been
<1.0 g/L

Various studies indicate that in certain conditions the
critical level have to be higher e.g. > 1.5 g/L and
even 4g/L

Hellstrøm P et al., Thromb Res 2002;; Freis D et al JTH 2006

Thorenton B. Unpublished (ISTH SSC 2006) ;Fries D. JTH 2007

•Mean pre partum fibrinogen 4.8g/L; Simon L BJA 1997

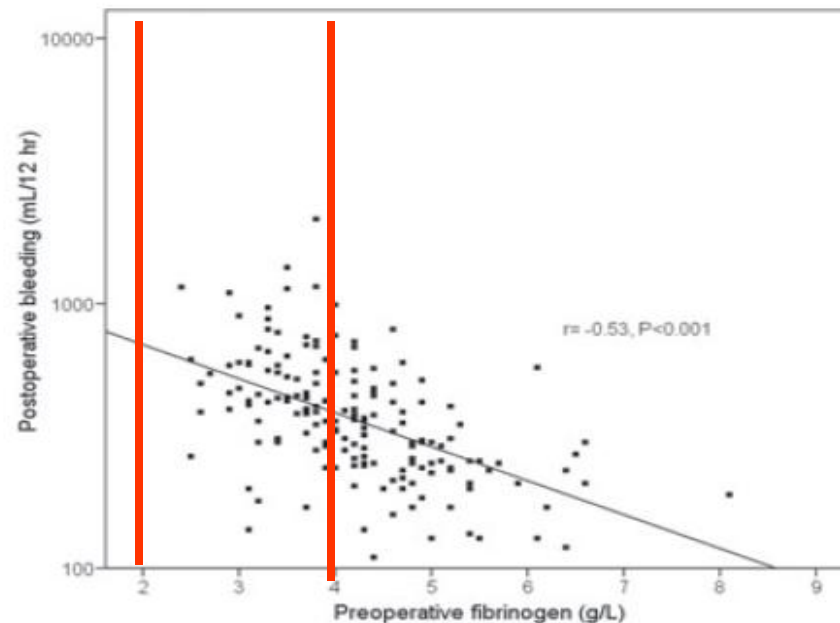
Fibrinogen level is a predictor of severity of PPH

≥ 4g/L negative predictive value 79% [68- 89%], 2 = 2g/L
positive predictive value of 100%[71-100%].

B. Charbit JTH 2006

Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study

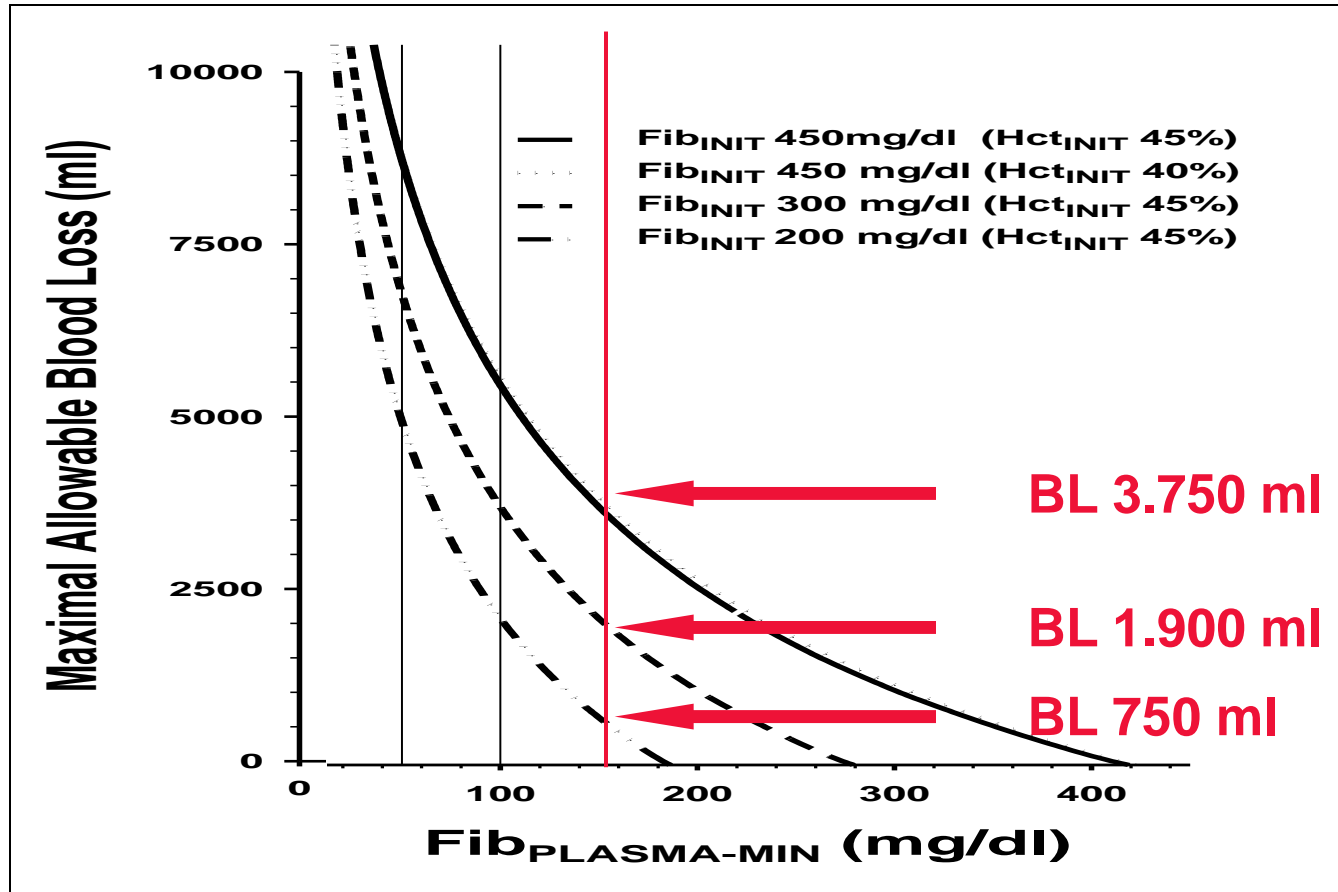
.Karlsson M. Transfusion. 2008 Oct;48(10):2152-8.



- Preoperative Fibrinogen is unrelated risk factor for postoperative bleeding and transfusions. preoperative fibrinogen concentration (even within the normal range) is a limiting factor for postoperative hemostasis after CABG.

Critical blood loss - fibrinogen baseline concentration

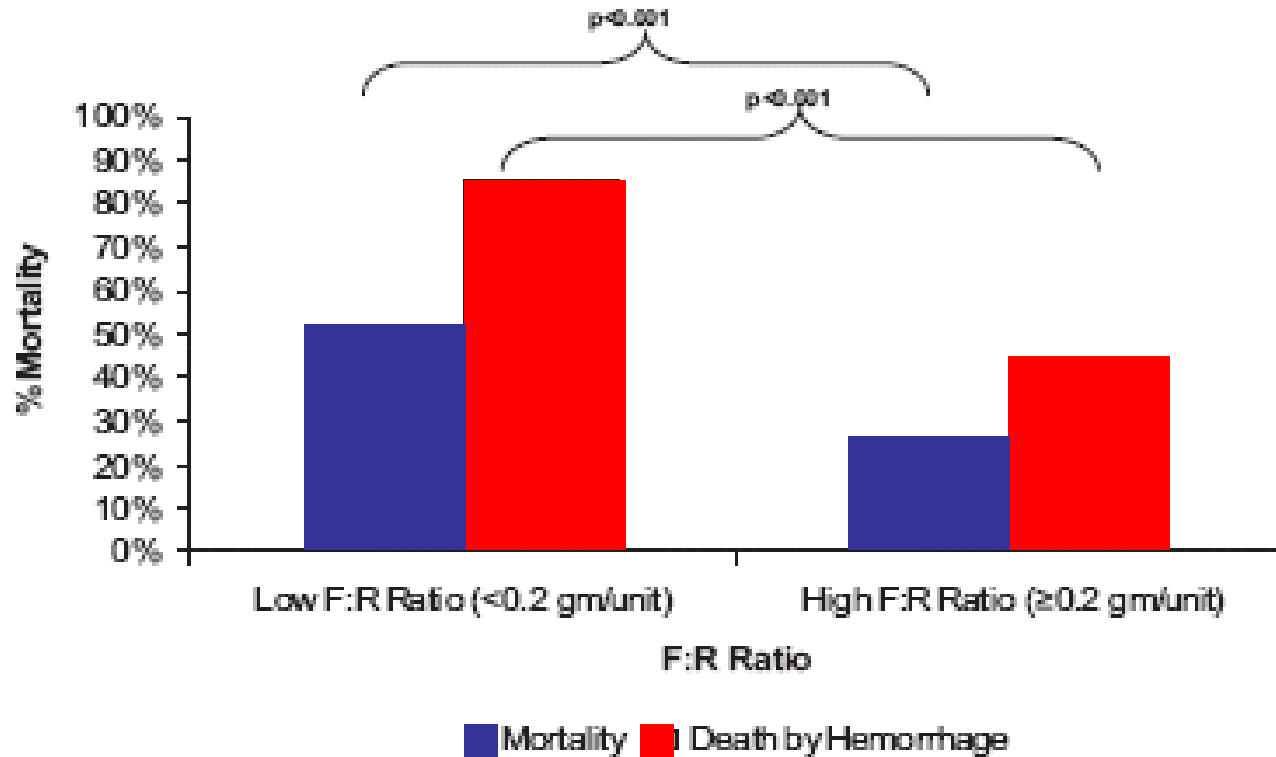
Singbartl K et al. Anest&Analg 2003



FI \geq 150 mg/dl: 750 ml -3.750 ml

Critical FI levels may be reached before the need of RBC's!!!

mortality versus fibrinogen-to-red cell (F:R) ratio



Retrospective chart review of 252 patients at a U.S. Army combat support hospital who received massive transfusion (>10 units of RBCs in 24 hours).

Stinger H. et.al J Trauma. 2008;64:S79 –S85.

Fibrinogen substitution in pis with liver injury & thrombocytopenia

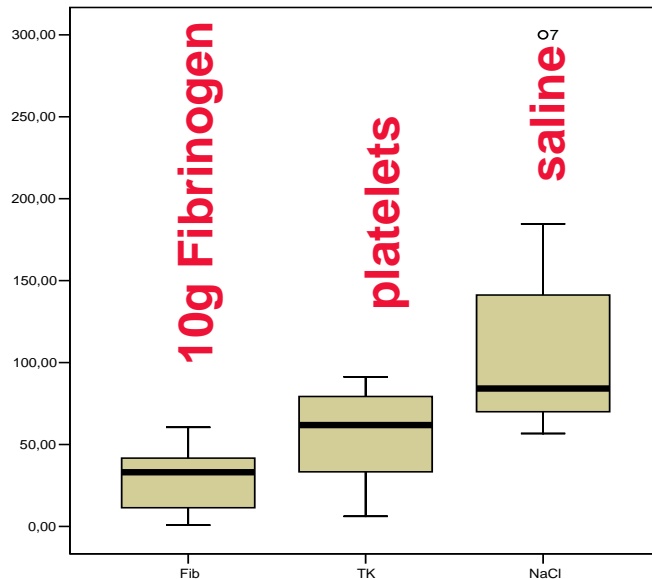
Group A: thrombocytopenia and *saline*

Group B: thrombocytopenia and *fibrinogen*

Group C: thrombocytopenia and *1-2 platelet concentrates*

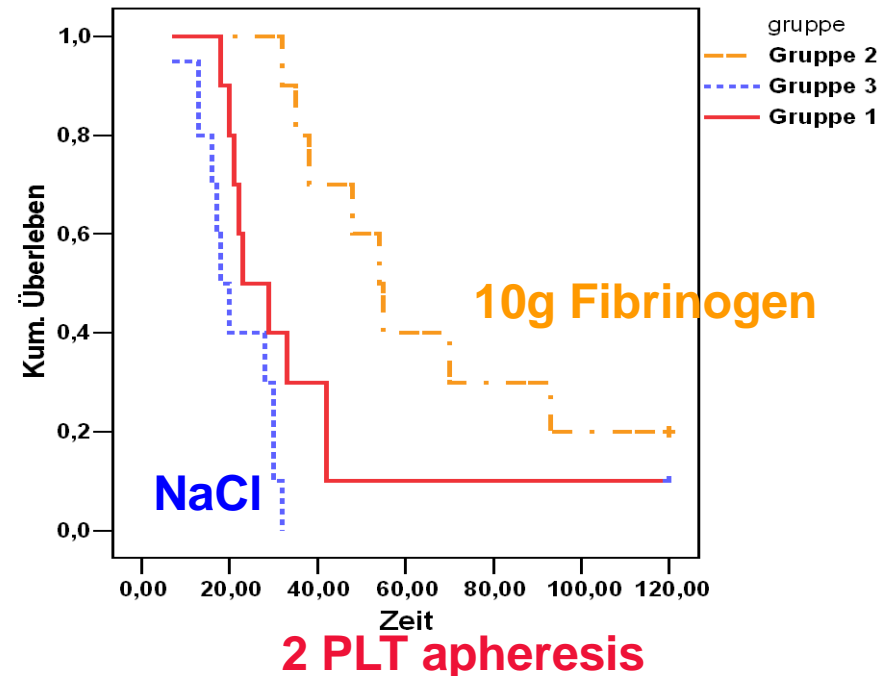
Improvement of Rotem

blood loss dynamics



Freis D et al JTH 2007

Kaplan Meier analysis



Recombinant Activated Factor VII for Adjunctive Hemorrhage Control in Trauma

Uri Martinowitz, MD, Gili Kenet, MD, Eran Segal, MD, Jacob Luboshitz, MD, Al Jorgen Ingerslev, MD, and Mauricio Lynn, MD

Background: Recombinant activated factor VII (rFVIIa) was approved for treatment of hemorrhages in patients with hemophilia who develop inhibitors to factors VIII or IX. Conditions with increased thromboembolic risk, including trauma with or without disseminated intravascular coagulation, were considered a contraindication for the drug. The mechanism of

multitransfused (median, 40 units [range, 25–49 units] of packed cells), coagulopathic trauma patients were treated with rFVIIa (median, 120 $\mu\text{g/kg}$ [range, 120–212 $\mu\text{g/kg}$]) after failure of conventional measures to achieve hemostasis.

Results: Administration of rFVIIa resulted in cessation of the diffuse bleed, with significant decrease of blood require-

onds (respec from to 23.7 0.05). reason throm C sugges

1999: Exsanguinating Soldier with penetrating abdominal Injury: Immediate cessation of the bleeding, Full recovery .

Kenet G. et al The Lancet 1999; 334:1879



J Trauma. 2001;51:431–439.

17 severe trauma cases .Martinowitz U. et al ;Can. Anesthes.

2002

- rFVIIa significantly Improves clotting assays and stops /reduces massive bleeding in **hypothermic** critically ill trauma patients.
- Reduced effect to rFVIIa in **Acidosis**

Martinowitz U. et al ;Can. Anesthes. 2002

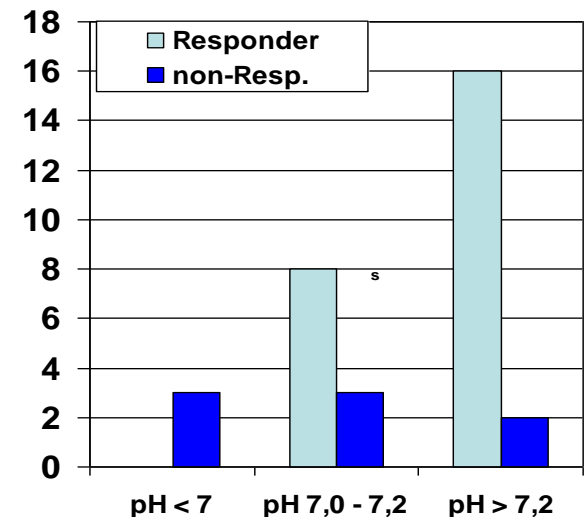
Martinowitz U. et al; J. Thromb. Haemost. 2005

- Similar results in an animal trauma model of hypothermic Pigs.

U. Martinowitz et al J. Trauma 2001/I

- **In vitro data** supporting the clinical observation.

Meng ZH et al J.trauma 2003



Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding

U. Martinowitz^{3,4,8} and M. Michaelson^{1,2}

On behalf of the Israeli Multidisciplinary rFVIIa Task Force:

The National Trauma Advisory Board¹, the Societies of Trauma², Hematology³, Thrombosis and Hemostasis⁴, Anesthesiology⁵, Transfusion Medicine⁶, Neurosurgery⁷, Israeli Defense Forces (IDF)⁸, Israel National Center for Trauma and Emergency Medicine Research⁹, The Ministry of Health¹⁰, The National Blood Services¹¹, and the United States Army¹²; [JTH Apr.2005](#)

- Indications and contraindications
- Definitions of massive bleeding
- Replacement therapy before rFVIIa
- Definition of failure of appropriate treatment
- Timing of administration
- Precondition to administration (pH,Fib,PLT)
- Doses, repeated doses and monitoring

Preconditions for rFVIIa: based on case series of exsanguinating patients (n=36) and literature

- Fibrinogen: > 0,5 preferably $\geq 1\text{g/l}$ (too low. 4- 5g/L?)
- Plt: > $50 \times 10^9/\mu\text{l}$ preferably $\geq 100 \times 10^9$
- pH: > 7.1 (current > 7.2, preferably 7.4 and even higher)
- Hb > 10
- Hypothermia: not relevant for rFVIIa (but should be avoided/treated)
- Fibrinolysis: TXA 2gr . (preferably higher in massive bleed , 4-5 gr IV push, repeat as required)

Dose:

- 90 – 120 $\mu\text{g/kg}$ over 2 – 5 min
- Repeat within 15 min if hemostasis is not achieved

The Israeli guidelines ; Martinowitz U: J Thromb Haemost. (2005)

Control of massive bleeding by rFVIIa without surgical intervention

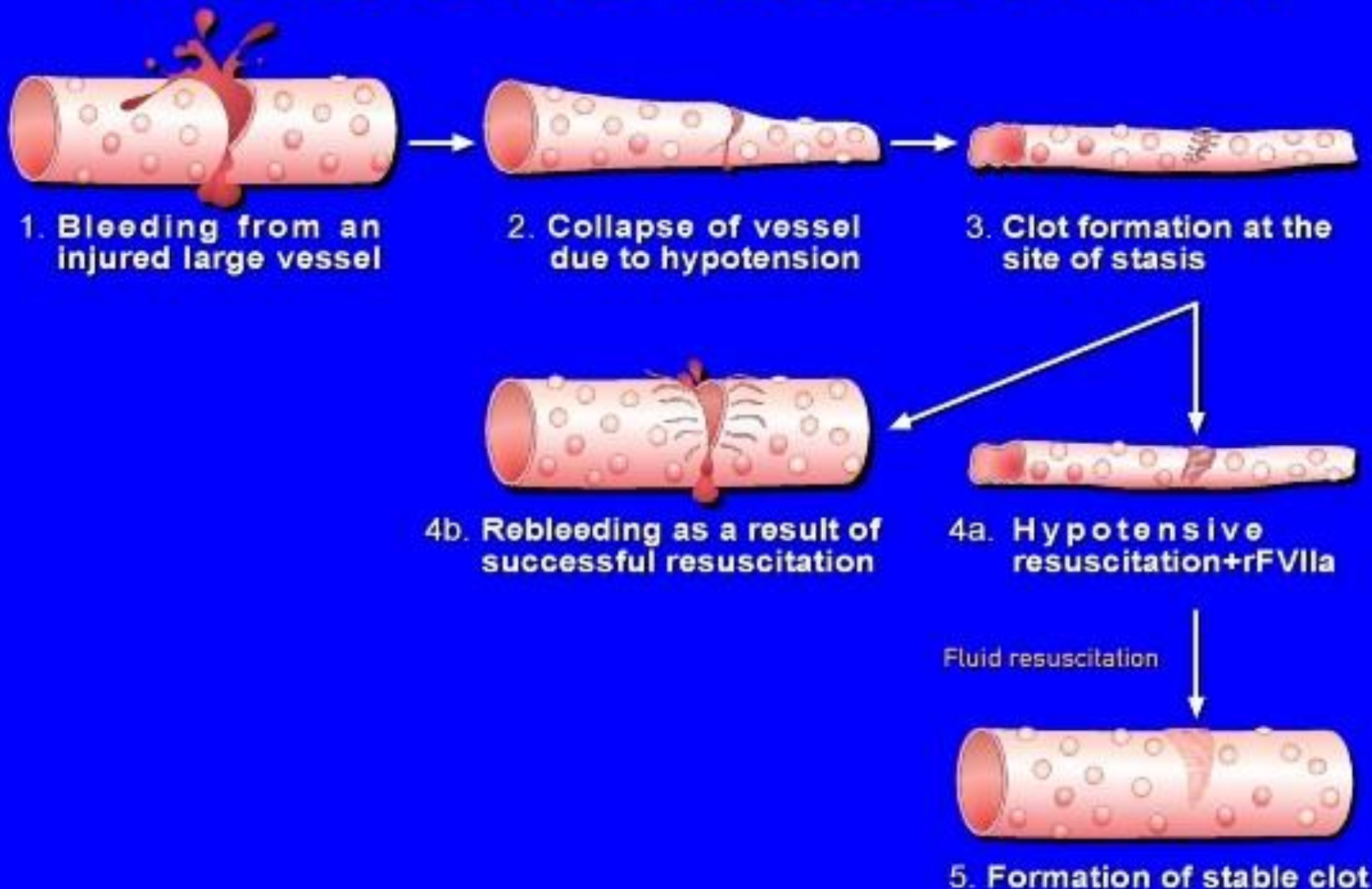
19 y.o female with multi-trauma: Comminuted pelvic#, pneumothorax, retroperitoneal and pelvic hematoma, TBI

☹ Shock, hypothermia, acidosis, coagulopathy

☹ Massive bleeding. Failure of emobilization. Inevitable exsanguination .

😊 rFVIIa (262 µg/kg)→ Immediate hemodynamic stabilization, bleeding ceased, fully recovered

MECHANISM OF HEMOSTASIS OF INJURED LARGE VESSELS BY rFVIIa

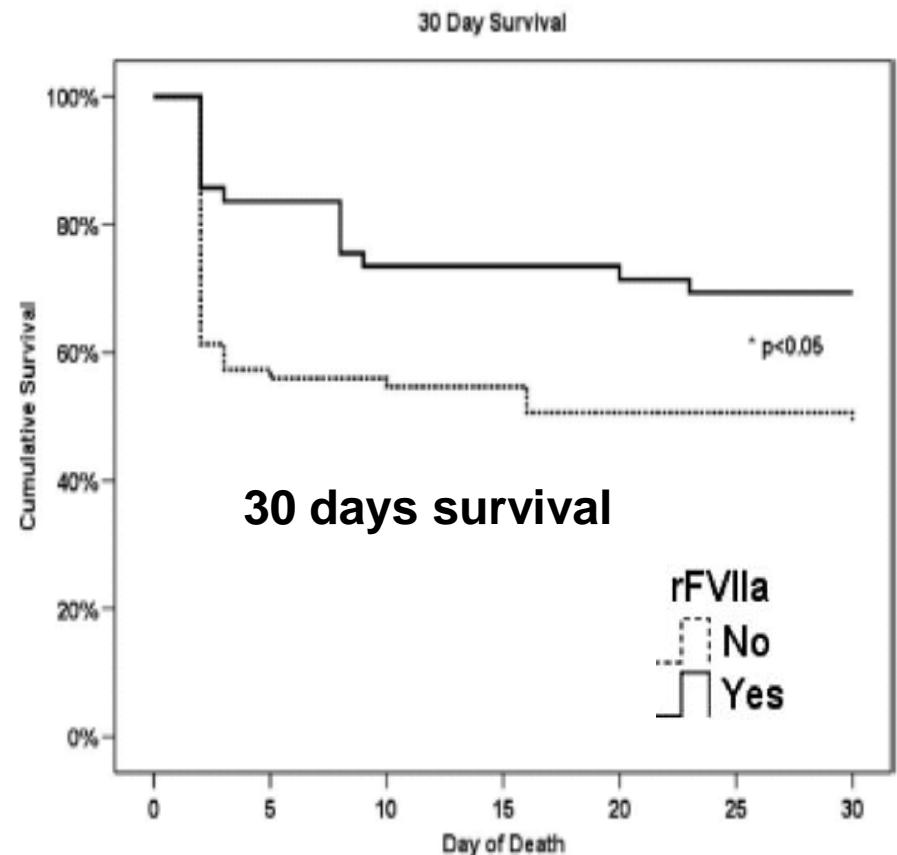
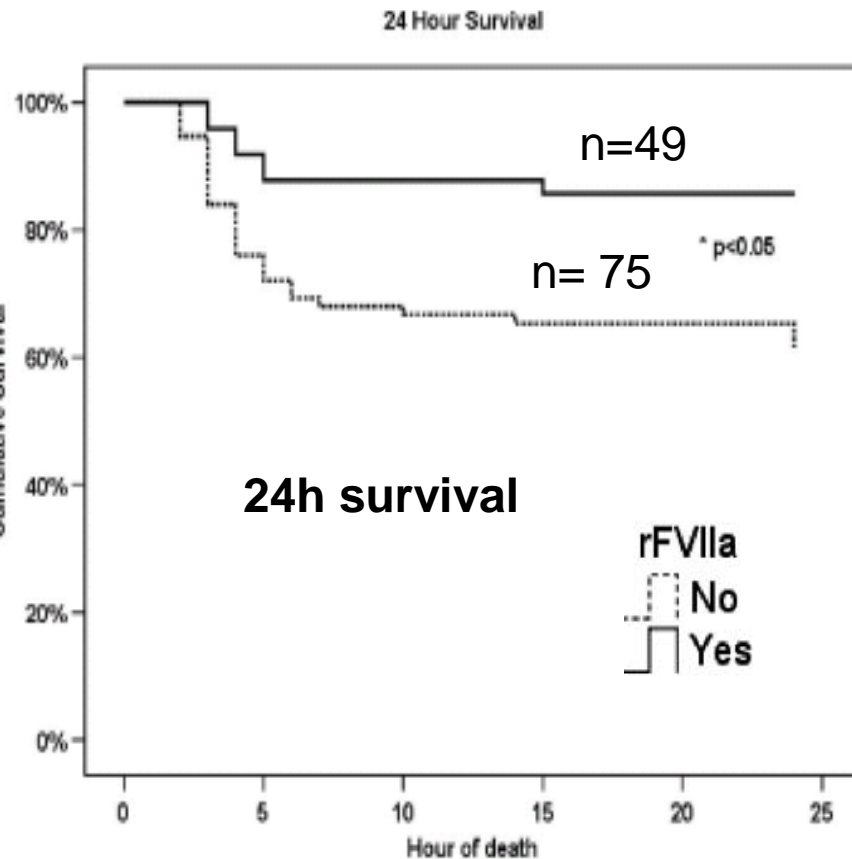


The Effect of Recombinant Activated Factor VII on Mortality in Combat-Related Casualties With Severe Trauma and Massive Transfusion

J Trauma. 2008;64:286–294.

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Daniel F. McLaughlin, MD, Sarah E. Niles, MD, MPH, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, Jose Salinas, PhD, Sumeru Mehta, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Retrospective :Severe trauma (ISS >15) Massive transfusions>24 un/24h
Less blood products ,significantly reduced mortality in rFVIIa
Similar severe thromboembolic events



rFVIIa in trauma and surgery

Despite numerous publications including 17 RCTs the use of rFVIIa remained controversial.

Practice Guidelines of ASA ; Anesthesiology July 2006

European guidelines ; Span D. crit. Care 2007

British Guidelines ; BJH 2006

When traditional well tested options... have been exhausted, rFVIIa should be considered

Hemostasis in the pre-hospital

- Early rFVIIa treatment is rational (beneficial)
- EB data will never exist for pre hospital settings
- Extrapolation from in-hospital trials
- Retrospective pre hospital data (Iraq)
- Extrapolation from pre hospital animal models

rFVIIa without resuscitation:
Decreased mortality p*
Prolongation of survival (2h)
Jeroukhimov I. J Trauma. 2002; 53 (6)

rFVIIa + permissive resusc.:
Decreased mortality p*
Prolongation of survival (6 h)
Sapsford W, J Trauma. 2007;62(4):868

Conclusion

- Coagulopathy is common in major trauma, its severity correlates with bleeding and mortality
- Hypothermia , acidosis, hemodilution are important confounders of the coagulation process
- Hyperfibrinolysis is underestimated
- Fibrinogen depletes early in severe trauma
- Standard coagulation test are of limited value
- Thrombelastography could be helpful in detecting coagulopathy and monitor treatment

Alterations of hemostasis in trauma

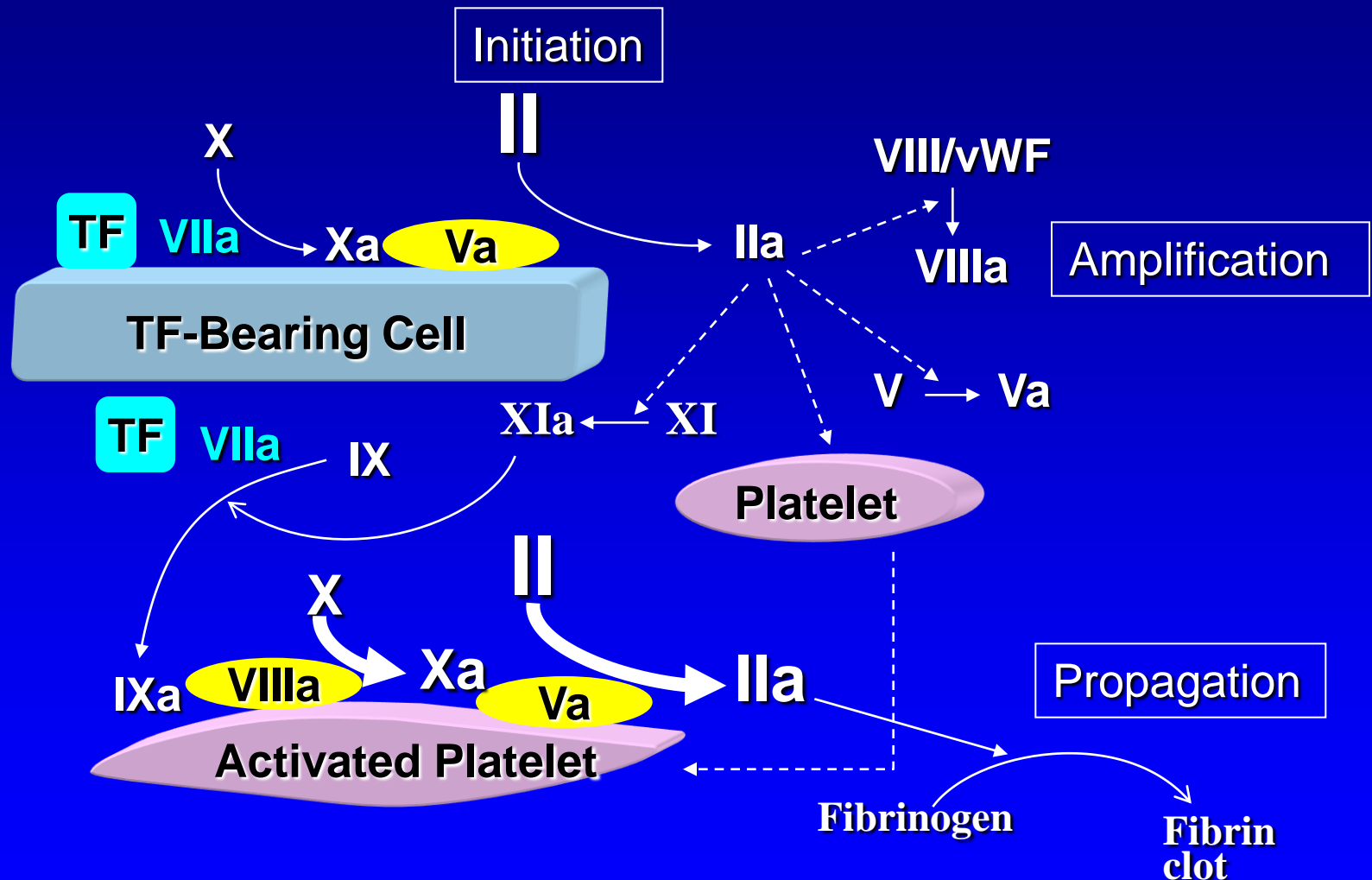
COAGULATION	ANTICOAGULANTS	FIBRINOLYSIS
Fibrinogen ↓	AT ↓	tPA ↑
FV ↓	Prot.C: Ag.+Ac ↓	plasminogen ↓
FII ↓	TFPI ↓	α2-antiplasmin ↓
aPTT / PT ↑	Soluble thrombo-modulin ↑	PAP complex ↑
TF ↑		PAI 1 Ag.+Ac ↑
FPA ↑		FPB ↑
d-Dimer ↑		d-Dimer ↑
TAT ↑		
PLT (counts & function) ↓	Platelets: activation ↑ (P selectin, microparticles, PAC 1 binding) Function +/-	Hypercoagulation Hypocoagulation

coagulation tests fail to detect most of the coagulopathy

- Performed at 37 C
- Do not detect platelets dysfunction, effects of acidosis, anemia and hyperfibrinolysis
- Do not reflect in vivo coagulation (on membranes)
- Lag time of 45-60 min. to results!

Every trauma patient with acidosis, hypothermia ,massive hemodilution ,/transfusions, massive diffuse bleeding= should be considered as coagulopathic

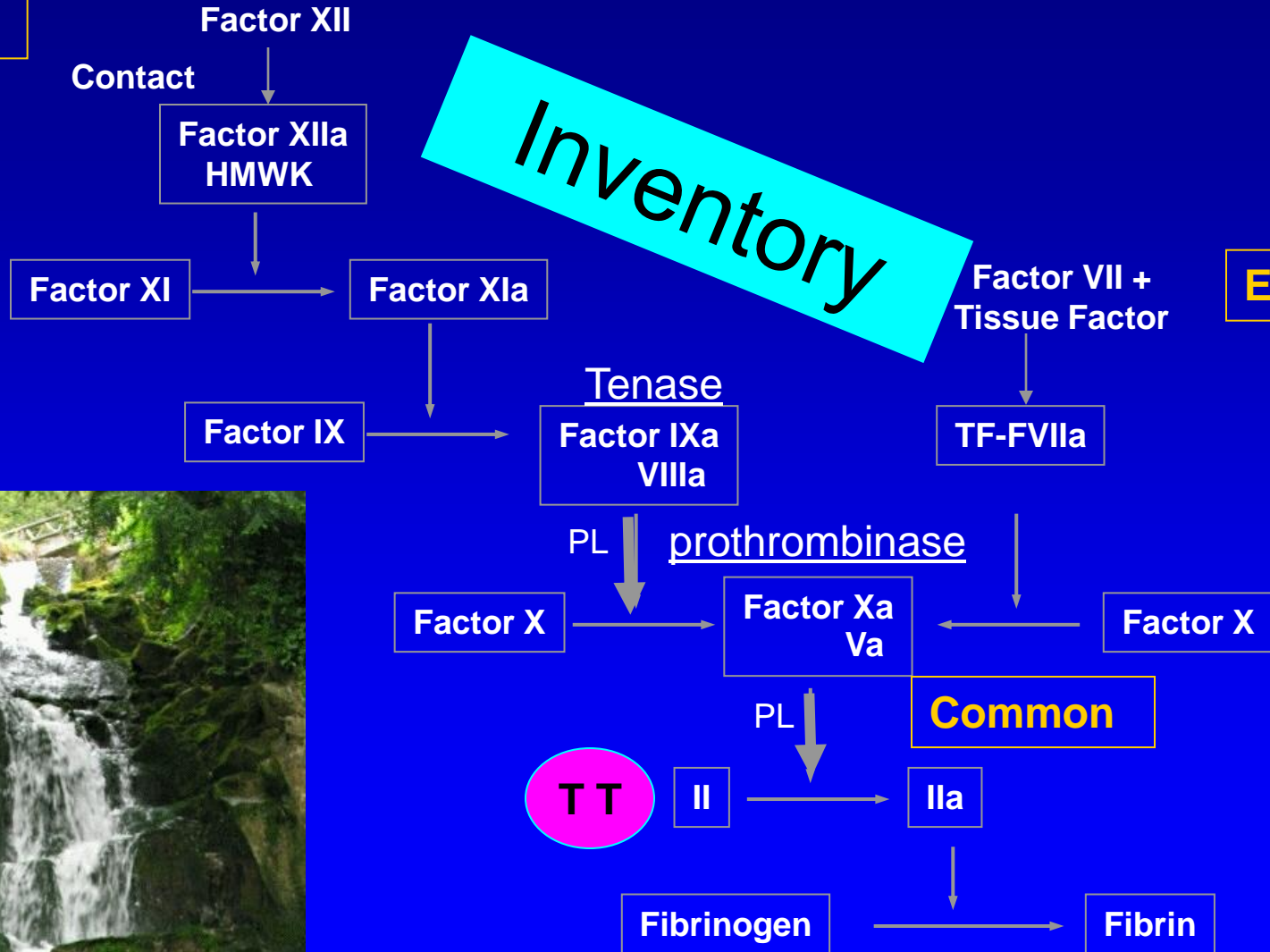
A Cell-Based Model of Normal Hemostasis: Hemostasis Takes Place on Two Cell Surfaces: TF-Bearing Cells and Platelets



Traditional Coagulation Cascade

aPTT

Intrinsic



PT

Extrinsic

TT

II

Common

IIa

Fibrinogen

Fibrin

The Sequence of Hemostasis

A real time image using intra-vital Microscopy

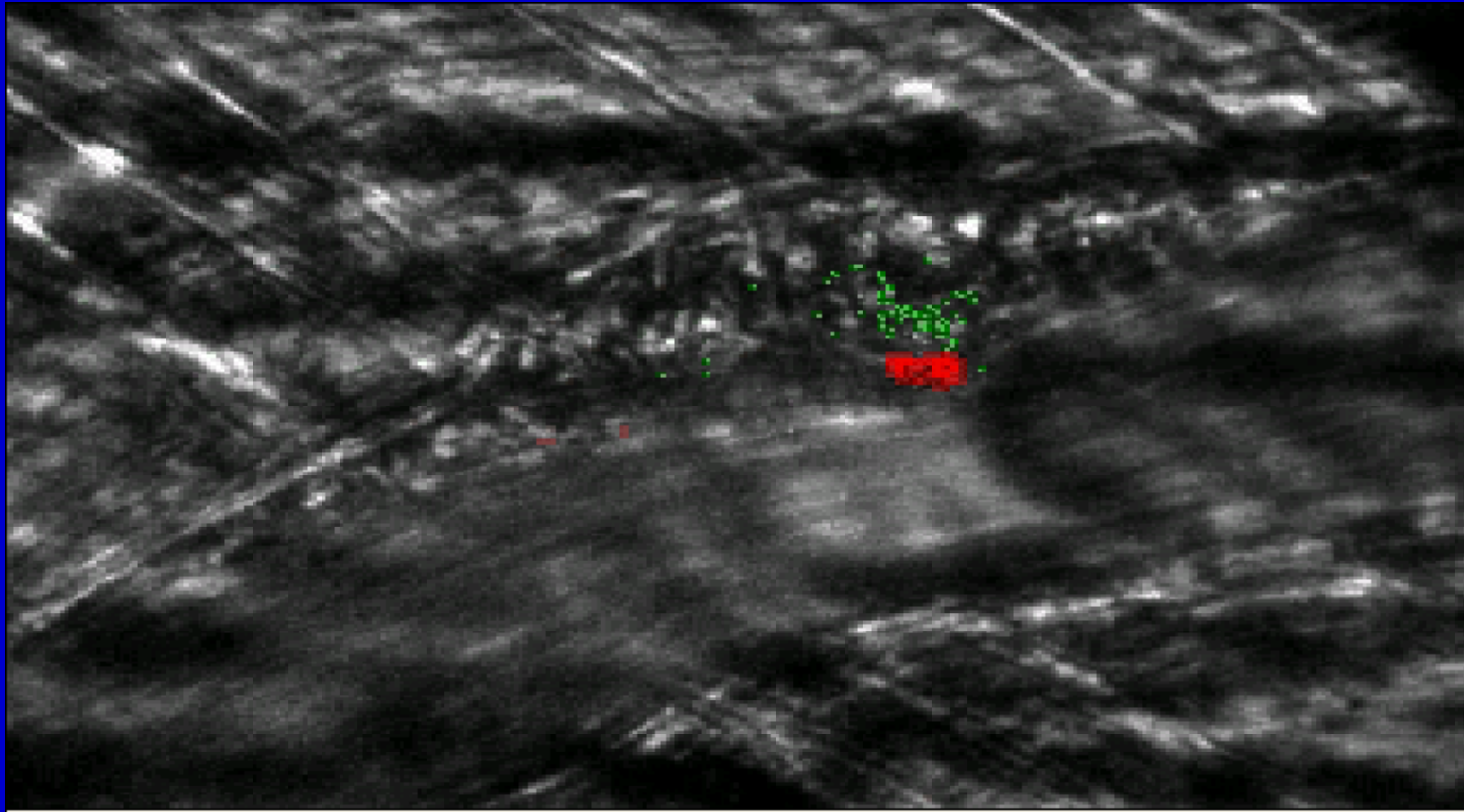
Falati S. Nat. Med. 2002; 8: 1175-1181

In the capillary circulation

RED: Platelets

GREEN: TF

BLUE: Fibrin



jth33fsm2.avi

Coagulopathy in massive
bleeding -are we totally lost?

Not if er followed
informative signs

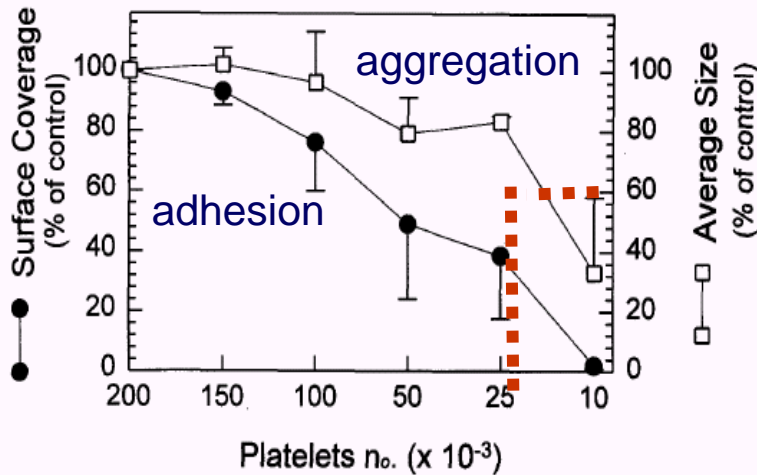
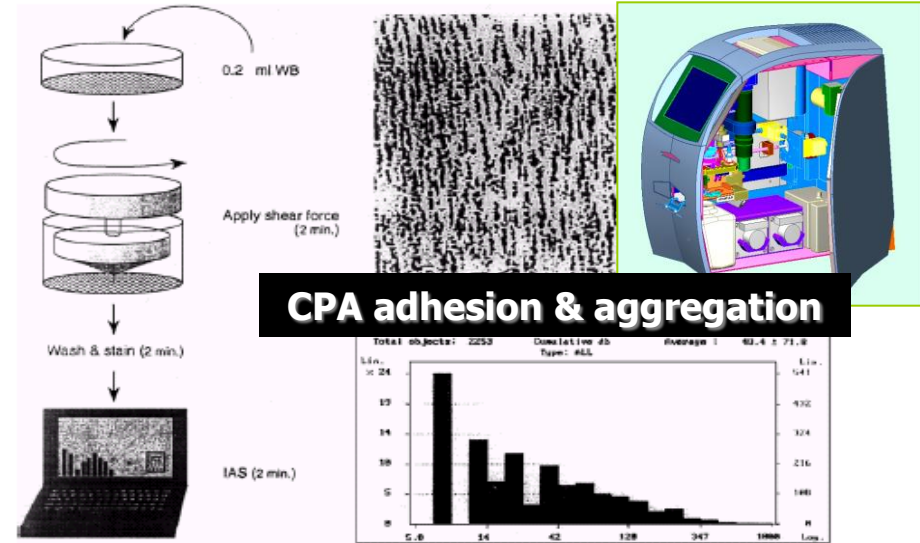
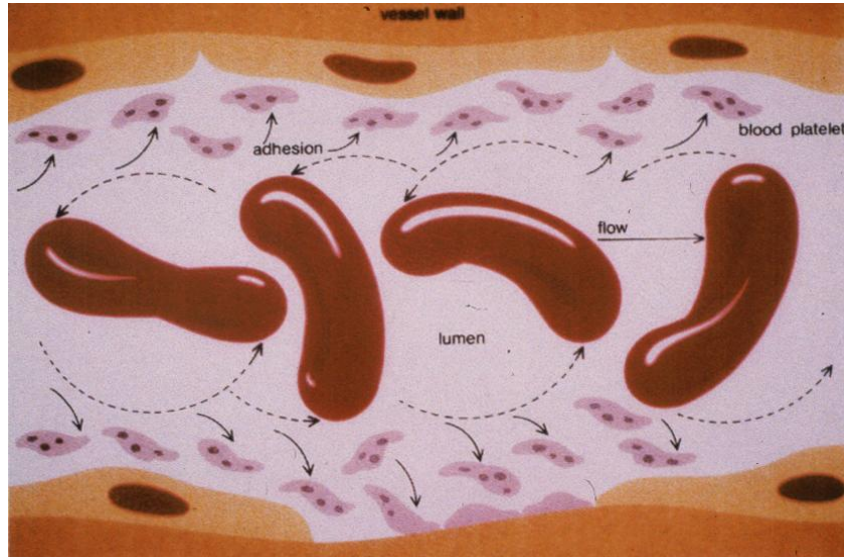


TEG - Thromboelastogram

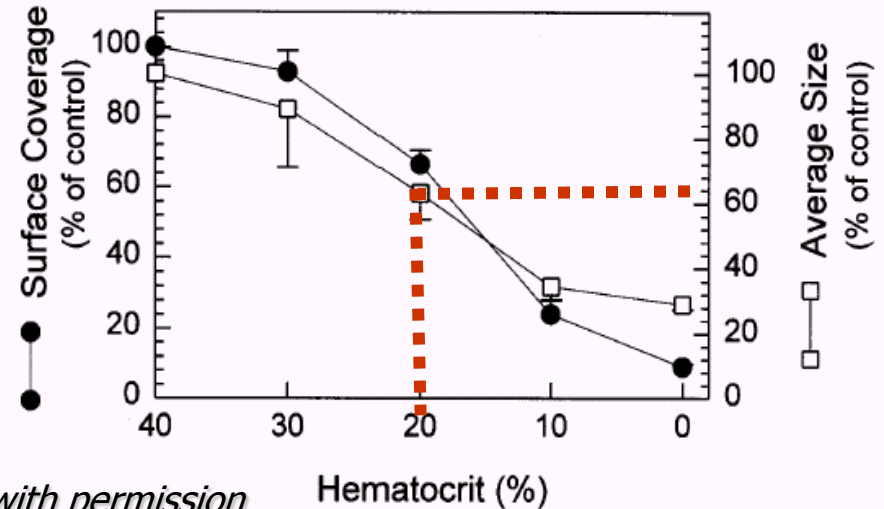
ROTEM - Rotating TEG



Anemia compromises coagulation

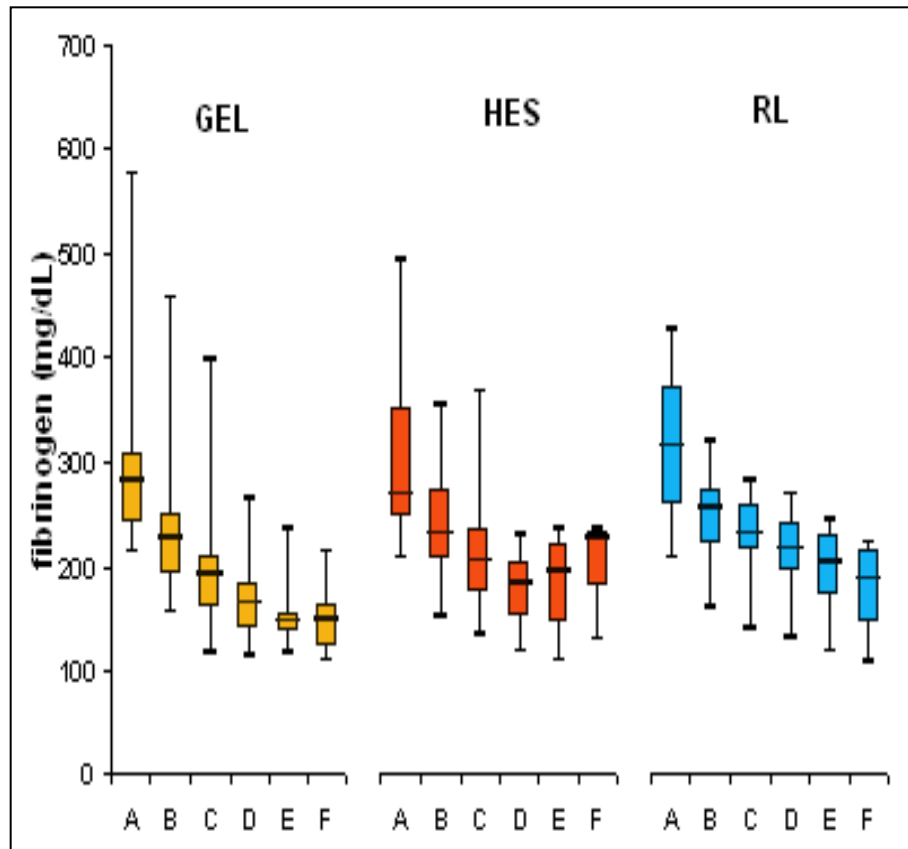


D. Varon et al .1997 with permission

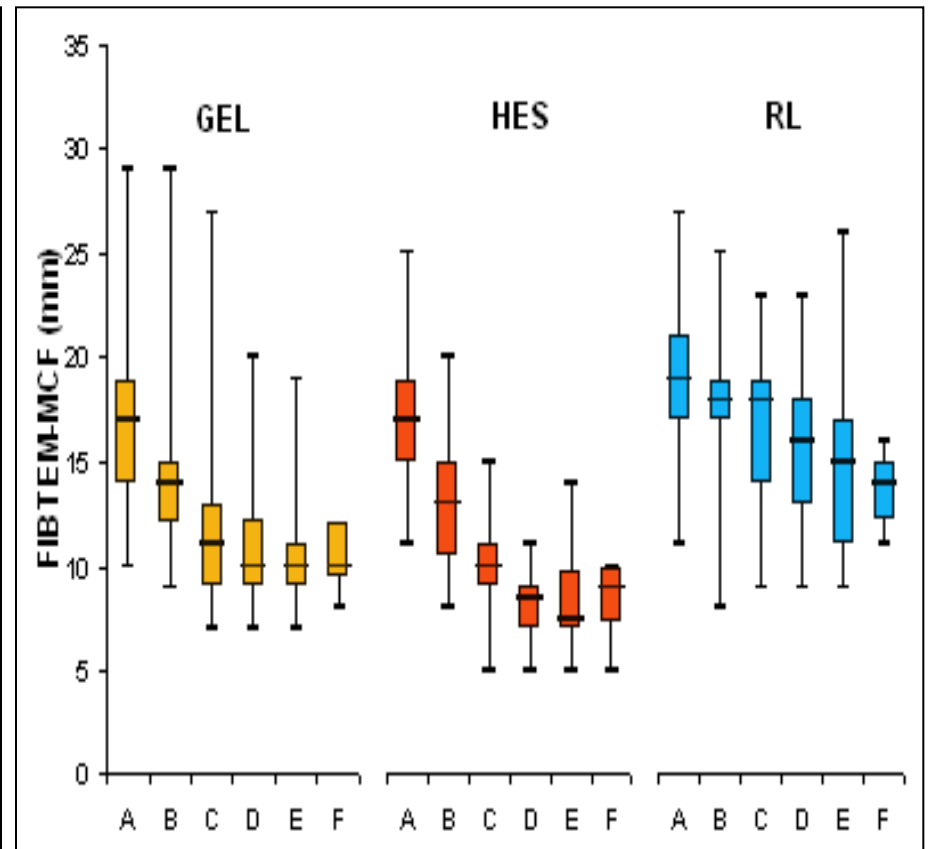


ROTEM® versus standard coagulation analysis

Klaus derived Fibrinogen

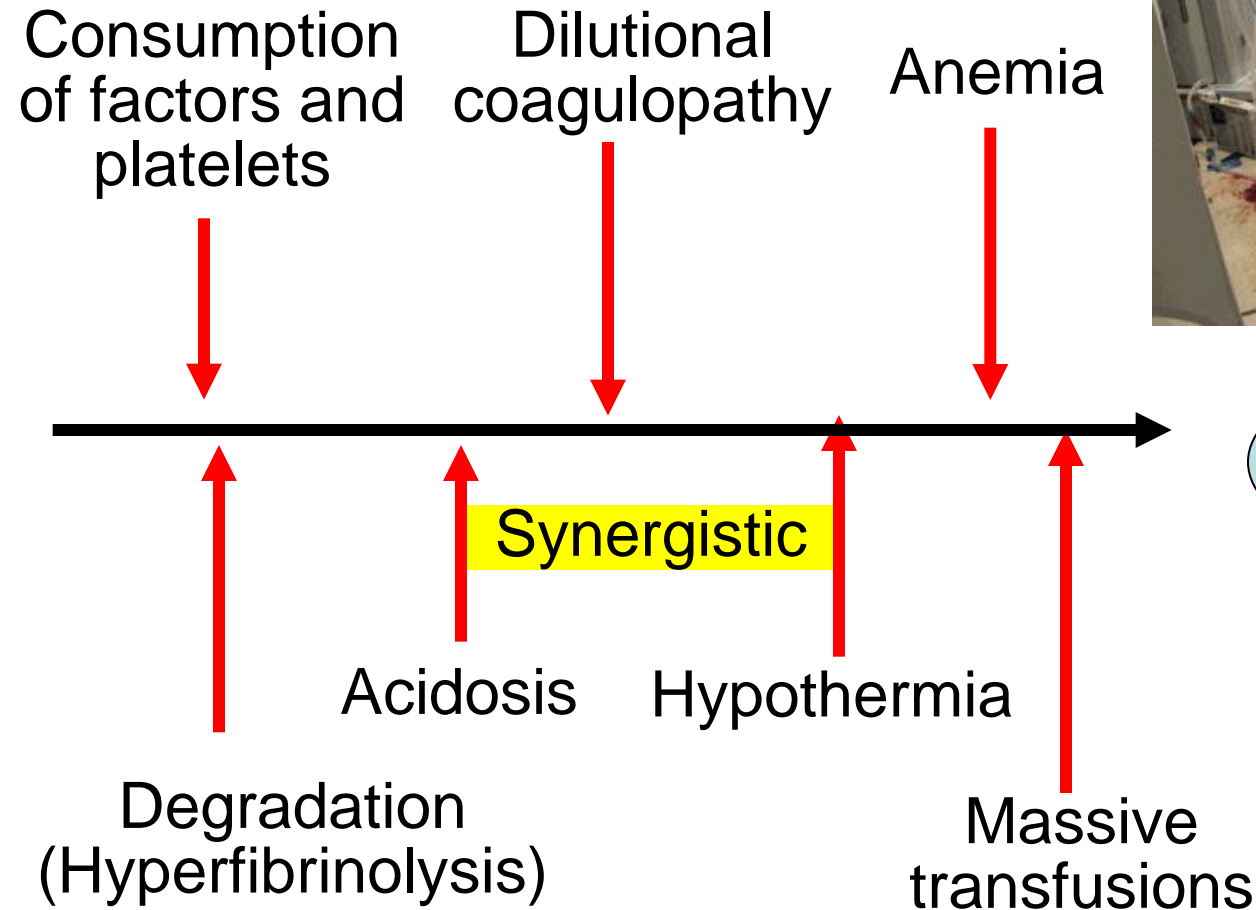


Fibrin polymerisation (FibTEM)



Fries D. With permission

Factors that compromise coagulation in trauma patients



**Multi-factorial
Coagulopathy**



Part 2: Hematological management of massive bleeding



הרופא הישראלי הציל את יו"ר האופוזיציה בהודו

מנהיג האופוזיציה נורה בבומביי ונפצע אנוש ■ הרופאים שנאבקו על חייו כמעט החליטו להרים ידיים ■ רק הוראות מדויקות שקיבלו בטלפון מהפרופ' אורי מרטינוביץ' הוציאו אותו מכלל סכנה

את מצבו בחדר הניתוח – אך ללא הצלחה. על אף שקיבל כ־40 מנות דם ואת התרופה נובו סכן, לא הצליחו הרופאים להשתלט על הדימום מפגי עות הירי.

דקות לפני שהחליטו להרים ידיים, הציע הרופא המרדים בחדר ניתוח להתקשר לפרופ' אורי מרטינוביץ', מנהל המרכז הארצי להמופיליה במר"כ הרפואי שיבא בתל-השומר. המרדים הכיר את פרופ' מרטינוביץ' לאתר ששמע את אחת מהרצאותיו בחדרו. רק אז הסתבר לצוות רופאים ההודי שלא מספיק לתת את "תרופת הפיגועים" – צריך גם לדעת מתי ואיך לתת אותה.

פרופ' מרטינוביץ' הדריך את הרופאים שלב אחר שלב, הסביר טלפונים כיצד ובאיזה סדר הם צריכים לתקן את המרדים הנחוצים לשיפור מעריכת הקרישה ואיך להכין את מערכת הקרישה לקבלת התרופה נובו סכן (הידועה גם בשם פקטור 7). לאחר כמה שעות הוא קיבל טלפון נוסף מבית החולים בבומביי, הפעם כדי לבשר לו שהפצוע הפסיק לדמם והועבר ליחידה לטיפול נמרץ.

התרופה נובו סכן, שמכונה בישראל גם "תרופת הפלא", אכן יכר לה לעשות פלאים – אבל רק כאשר נותנים אותה בזמן הנכון, ולא חר הכנה נאותה של הפצועים והקוקים לה. פרופ' מרטינוביץ' היה הרופא הראשון שגילה כי התרופה, שיועדה בתחילה רק לתולי המור פיליה, יכולה לסייע גם לפצועי טראומה.

"מה שקורה בפציעות האלה", הסביר פרופ' מרטינוביץ', "הוא שמתחיל דימום מכלי הדם שנפגעו, שהופך עם קריסת מערכת הקרישה לדימום מופשט מכל כלי דם קטן. הדימום המופשט ממסך בעצם את כלי הדם הפגועים, שבהם צריך לטפל על ידי תפרי זה כיורוגית". לדבריו, הטיפול בפצוע כזה מורכב ודורש צוות רב מקצועי ומיומן: "כמו בתזמורת, אם אחד מזייף, הלכה הסימפוניה. הבעיה היא שהרבה פעמים נותנים את התרופה בתזמון לא נכון, וללא הכנה, ואז זה לא עובד".

מאת הילה אלרואי דהרב

חייו של מנהיג האופוזיציה בחדרו, שנורה שלושם ונפצע קשה מאוד, ניצלו הודות לסיוע של רופא ישראלי ותרופה המכונה "תרופת הפיגועים".

פראמור מהאג'אן, יו"ר האופוזיציה בחדרו, נורה ביום שבת בבומביי. שלושה כדורים פילחו לו את הכתף, הלכלב והמעי, והוא הועבר במצב קריטי לבית החולים. הרופאים בבית החולים בבומביי ניסו במשך שעות לייצב



קיבל 40 מנות דם. יו"ר האופוזיציה מהאג'אן. משמאל: פרופ' מרטינוביץ' צילום: א.פ.

הבנק הבינלאומי

פנימי הבנק הבינלאומי יהיו סגורים היום בשעות אחרי-הצהריים עקב סכסוך עבודה הנוגע לבונוסים לעובדים.

יו"ר ועד העובדים, חנוך ליכנה, החליט לסגור את הסניפים בתום תקופת הצינון של סכסוך עבודה שהוכרז בעקבות אי-תשלום הבונוסים. הוועד דורש לקבל בונוסים עבור שנת 2004, בעוד שהנהלה טוענת כי שיעורי התשואה שהשיג הבנק בשנה זו אינם מצדיקים את תשלום הבונוסים. ועד העובדים טוען כי הנהלת הבנק אינה מקיימת משא ומתן בתום לב, ומאיים בהחרפת הצעדים. רוברת הבנק מסרה בתגובה כי טענות הוועד אינן נכונות, וכי בכל מקרה תעשה ההנהלה את כל המאמצים כדי למור עד את הנוק שייגרם ללקוחות.

יהודה שרונה

נסיעה יקרה

מחירי הדלק צפויים לעלות בחודש הבא ב־5 אחוז

מחירי הדלק צפויים לעלות בתחילת חודש מאי בשיעור של כ־5 אחוז בממוצע, כך מעריכים במשרד התשתיות.

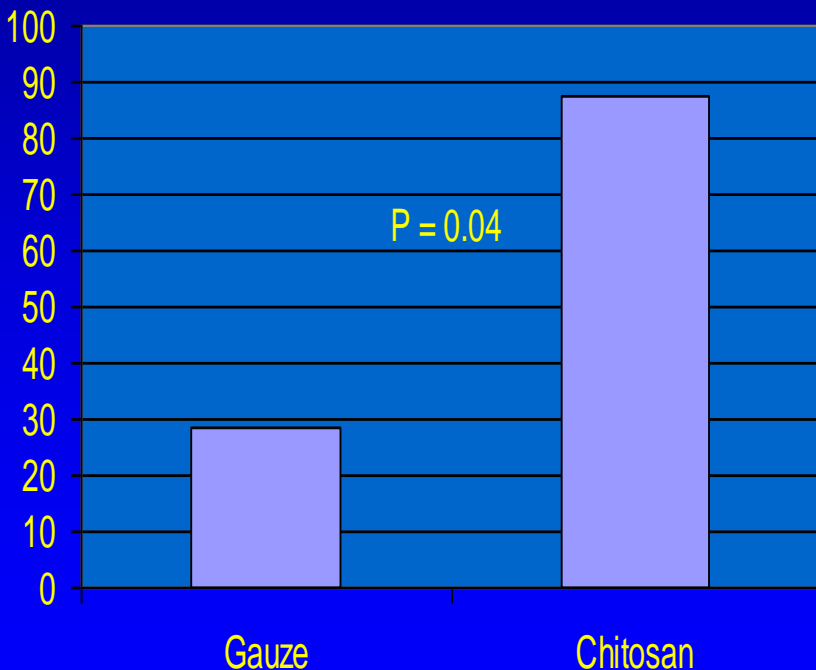
מחירו של ליטר בנזין מסוג 95 אוקטן עומד כיום על 5.90 שקל בתדלוק עצמי ו־6.01 בתדלוק בשירות מלא. במידה ולא יהיו שינויים מהותיים, מחירי הבנזין בתחנות צפויים להתייקר בכ־30 עד 40 אגורות לליטר, לרמה של כ־6.30 שקל. לפי ההערכות שאר מוצרי הדלק יתייקרו בשיעור הדומה של בין 6 ל־8 אחוזים. מועצת המובילים המייצגת את נהגי המשאיות כבר הודיעה אתמול, כי תדרוש לייקר את מחירי ההובלה בעקבות העלייה במחירים. יו"ר מועצת המובילים גבי נהרש ציין כי בתוך חודשים בלבד התייקרה עלות הפעלת משאית בכ־4 אחוז.

ליאור ברון

Local hemostatic agents : Chitosan in GV liver injury

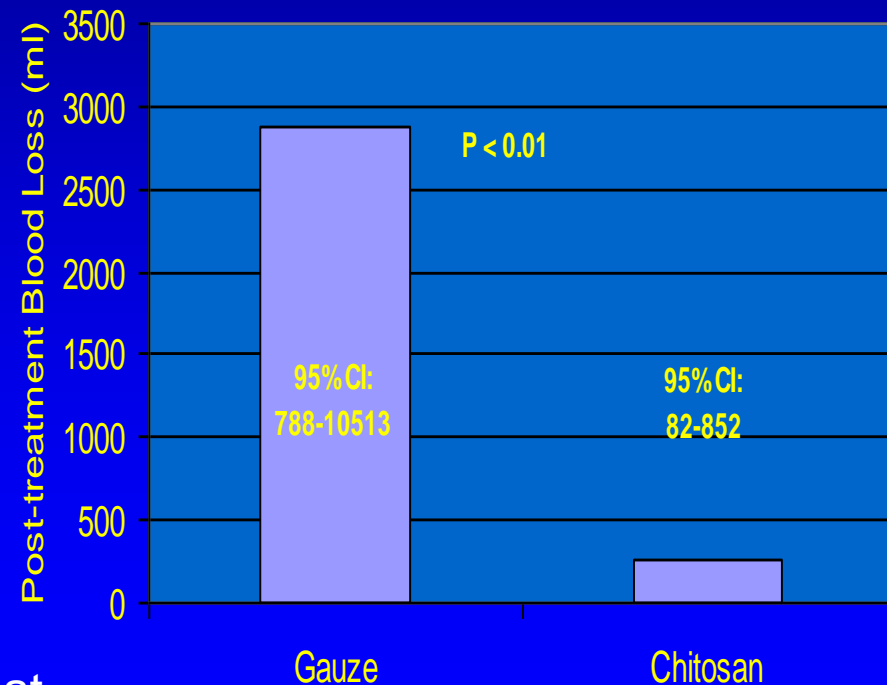


Survival



FDA approved. New absorbable format

Blood Loss



Damage control hemostatic resuscitation: directly addressing the early coagulopathy of trauma

- Resuscitation limited to keep BP at 90 mm
- Intravascular volume restoration by PRBC and thawed plasma as a primary resuscitation fluid (1:1)
- rFVIIa is occasionally used along with the early RBC and as required throughout the resuscitation

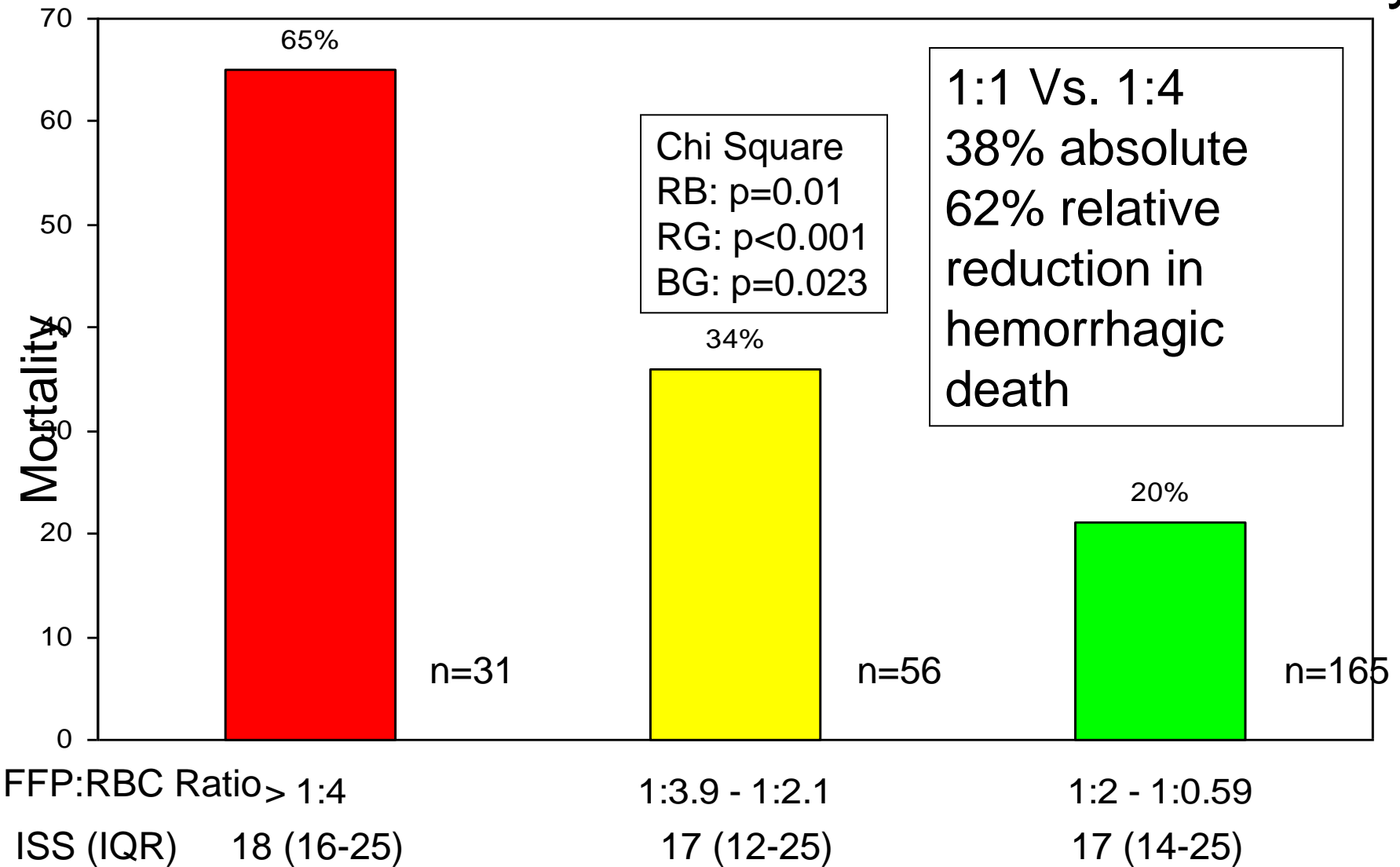
Hocomb J. Et al. J. Trauma 2007 Feb;62(2):307-10.

US Army experience in Iraq

Damage control hemostatic resuscitation:

- Blood bank is activated for massive transfusion protocol
- Crystalloids use is minimized as a drug carrier
- Patients treated in this fashion almost always :
 - arrive in the ICU warm, euvolemic, and non-acidotic
 - a normal INR and minimal edema.
 - The lethal triad is absent.
 - Easily ventilated and more quickly extubated

Effect of FFP:RBC ratio on overall mortality



Thawed FFP is available at all times. Dry FFP in development

Spinella P. US Army data from Iraq ,Dec. 2006 unpublished. With permission

FFP in massive bleeding

PRBC	FFP	Ref ./comments
10	1	1
4-6	1	2-5 ;The common practice until today
3	2	6; computer simulation (10 PRBC:8Plt)
2	1-2	7,8
1	1	9 -12
1	1-1.5	13; mathematical model of hemodilution
According PT, PTT		14; the latest ASA recommendations

1.usc.edu.hsc/medicine/surgery 2004 ;2. Stern SA ,Trauma management ,Mosby 2001 ; 3. Montenegro LM ;in Complications of anesthesia Saunders 1994 ;4.Waldspurger R; Massive transfusions in trauma ;AACN clin.1999
5.Turner DAB; jn Textbook of Anesthesia Churchill Livingstone 2001 ;6.Hishberg A; J trauma 2003 7.Murphy WG; Crit Care Med.1993 ; 8. Harvey MP; Med. J. Aust. 1995 ; 9. Hewson JA Crit. Care .Med 1985 ; 10.Valsaf SN J. trauma 2002
11.Armand R. Trasfus. Med. Rev.2003 12.Malone DL J. Trauma 2006
13.Ho MA; J. Can. Chir.2005 14.Practice guidelines ASA Anesthes. 2006

FFP in massive bleeding Practice Guidelines of ASA

,Anesthesiology 2006

- When PT X1.5 or INR >2 or PTT X2
Dose: 10-15ml/kg
- (Dose for reversal of warfarin : 5-8ml/kg)
- Restores factors level to ~30%* in excessive bleeding of > 1 blood volume (calculated from hemodilution)

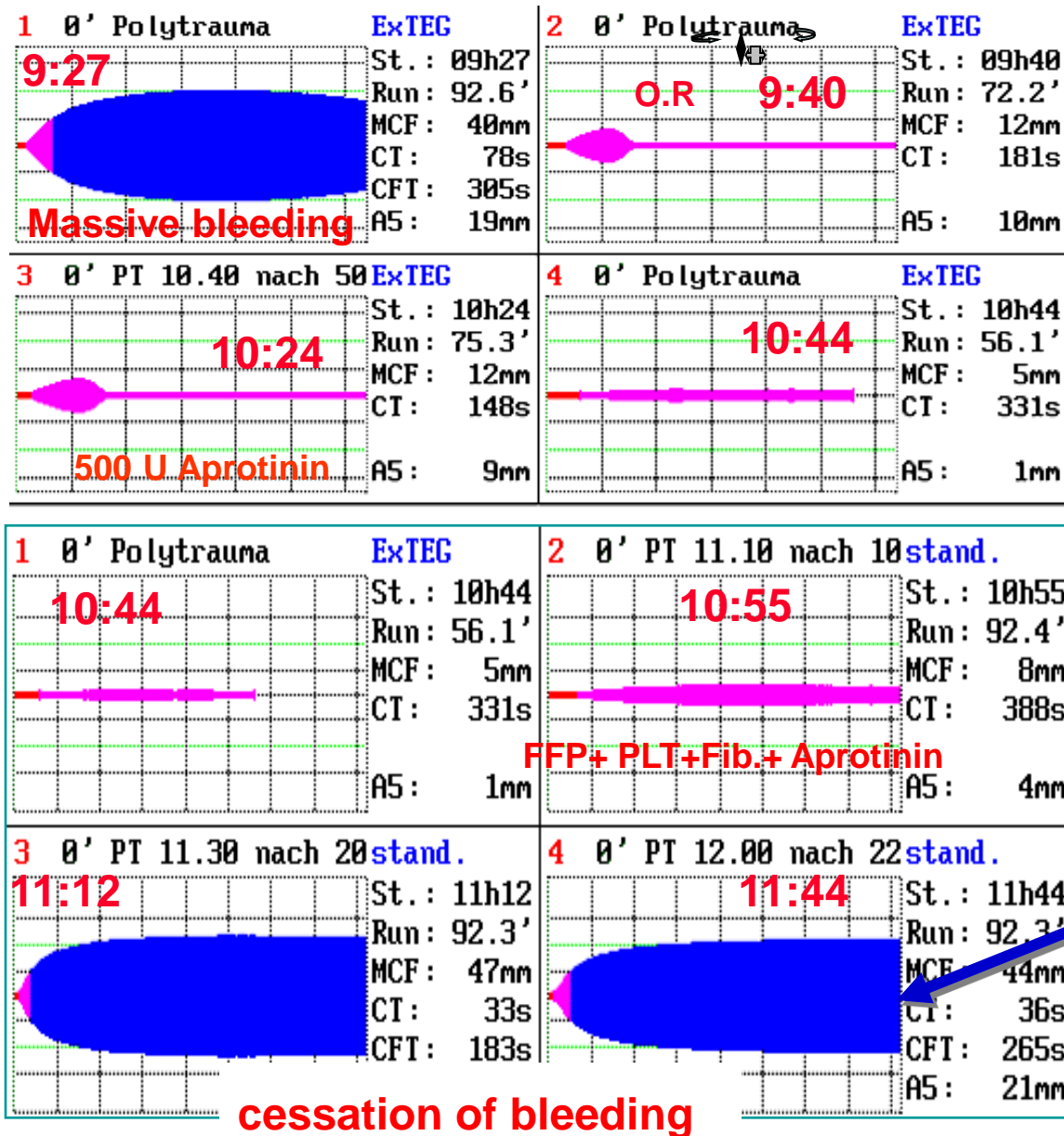
Warning ☹️ * Non hemostatic level for surgery even for most single factor deficiencies !!!

☹️ In massive bleeding -coagulopathy should be **prevented rather than treated**, levels of factors should be >50% ,fibrinogen probably > 2g/L ,and >4g/L in PPH.

Transfusion threshold in massive bleeding

- **Blood increases morbidity and mortality!**
- However, Hb < 11 is associated with need for massive transfusion and increased mortality in patients with severe traumatic injuries Carrico CJ, Acad Emer Med. 2002
- Hb < 11 is an independent predictor for mortality in massively bleeding patients in Iraq
Holcomb J.J Trauma. 2007 Feb;62(2):307-10
- US Army recommendation: Threshold Hb for blood transfusion **in massively bleeding patients is 11**
- **Not to be confused with ICU or stable surgical patients where Hb 7-10 is sufficient .**

Fibrinolytic inhibitors in multitrauma



Should blood pH be corrected? (hemostatic considerations)

Does Bicarbonate Correct Coagulation Function Impaired by Acidosis i

No

Does not reverse TAT, fibrinogen and platelets in HCl acidosis in pigs(Martini)

Yes

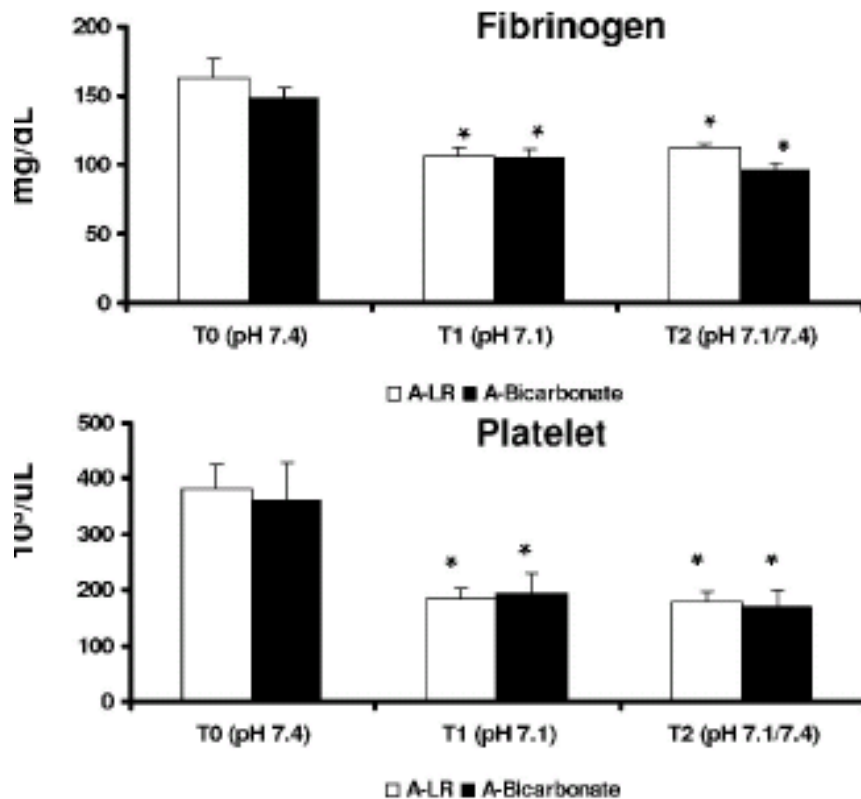


Fig. 2. Changes in fibrinogen concentration and platelet count during acidosis induction (T1) and bicarbonate neutralization (T2).
*p < 0.05, compared with T0.

HCl acidosis in swine does not reflect lactic acidosis
Correction of lactic acidosis in trauma patients restores the response to endogenous and exogenous rFVIIa.

Replacement of platelets and fibrinogen is usually given in such bleeding patients

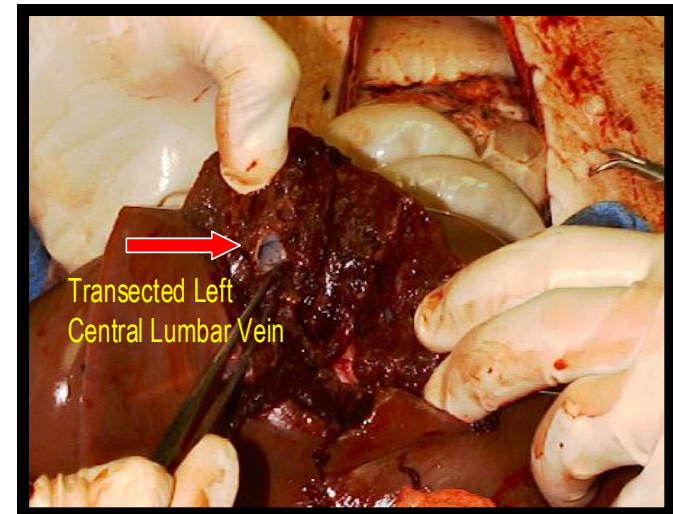
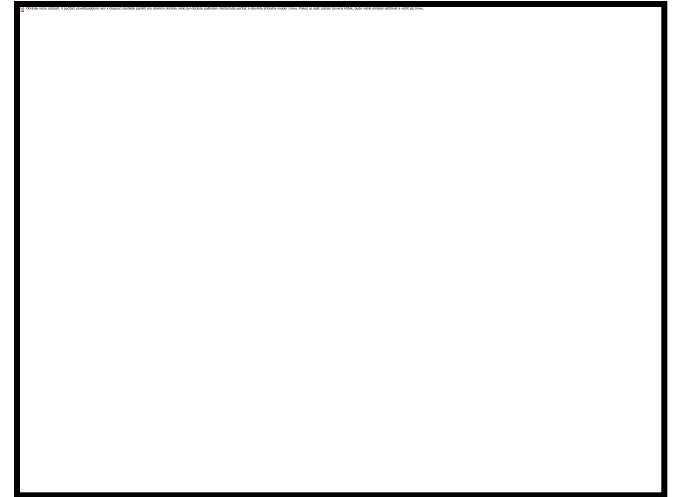
Our rational for the use of rFVIIa in massive bleeding ,based on 4-5 years experience in hemophilia and related disorders:

- **Compartmentalized** mechanism of action -at the site of TF exposure (site of injury)
- **bypasses** various coagulation and platelets defects
- **"super-clot"** formation (theoretical_-Via TAFI), stronger and more resistant against Fibrinolysis.
- **High Safety Profile** in Hemophilia (understanding that traumatic coagulopathy is more profound)

1999: The IDF/US armies joint study

Safety and efficacy of rFVIIa in grade V liver injury in hemodiluted (60% HES) hypothermic pigs.

- Normalization of PT / PTT(p*)
- Decrease 46% blood loss (p*)
- No DIC or signs of TE even high dose after rFVIIA
(supported later by many similar studies: Lynn /Schreiber/ Klemke)



Case series:Off-label use of rFVIIa in Trauma and Surgery

Study	n	Indications	Hemos.	Surv.
Martinowitz U J Trauma 2001	9	trauma	7/9	6/9
Martinowitz Can J Anesth.2002	19	Trauma	79%	69%
Martinowitz U. JTH 2005	36	Trauma	75%	61%
Clark AD Vox Sang.2004	10	Surgery = 9; Trauma = 1 ("last ditch")	60%	30%
O'Connell Transfusion 03	40	Medical = 15; Surgery = 25	80%	42%
Dutton RP J. Trauma 2004	81	Trauma= 46; TBI=20; anticoa.= 9;Other = 6 .Comparison to "matched" controls	80%	42%
Dutton RP(in press)	162	Trauma=94;TBI=37;Warfarin= 23; Other =8	82%	45%
Eikelboom. B.coag.fib.2003.	21	Trauma=3;surgery=15;medical=3	85%	76%
Geeraedts LMG .Injury 05	8	Trauma	100%	62%
Harrison TD J .trauma 2005	29	Trauma (vs.72 historical controls- 40mcg/kg same mortality;	NA	60%
Zaman-khan A. Am.J.Surg.2005	13	Trauma=3; Surgery =7;medical 3	NA	53%
MacLaren R (Mult-icenter) Transfusion 2005	119 196	Prevention of bleeding. Tx of bleeding .Trauma=30; Surg.=127;	52%	81%

Cessation/ reduction in bleeding 80-90%, survival 30-76%

rFVIIa: Summary of label uses

- ☐ Trauma, Trauma non RCT,
- ☐ ICH and TBI
- ☐ Upper GI bleeding*
- ☐ Liver transplantation*
- ☐ Liver resection*
- ☐ Esophageal varicose*
- ☐ Liver biopsy
- ☐ Reversal of:
 - ☐ vit. K antagonists
 - ☐ Anti PLT (GPIIb/IIIa)
 - ☐ Xa and IIa inhibitors

- ☐ Surgery: abdominal , thoracic
Cardiac ,cardiac high risk* ,
prostatectomy* , scoliosis* ,pelvic
fratures* , neurosurgery.

- ☐ ECMO

- ☐ Post Partum Hemorrhage

- ☐ Pulmonary hemorrhage
(blast, BMT, uremia)

- ☐ Dengue fever (DIC)

- Variability hemostasis /survival

- Positive RCT

- Failed in RCT* (all prophylactic)

- Described

Prophylactic administration *

Early Versus Late Recombinant Factor VIIa in Combat Trauma Patients Requiring Massive Transfusion

Jeremy G. Perkins, MD, Martin A. Schreiber, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

J Trauma. 2007;62:1095–1101.

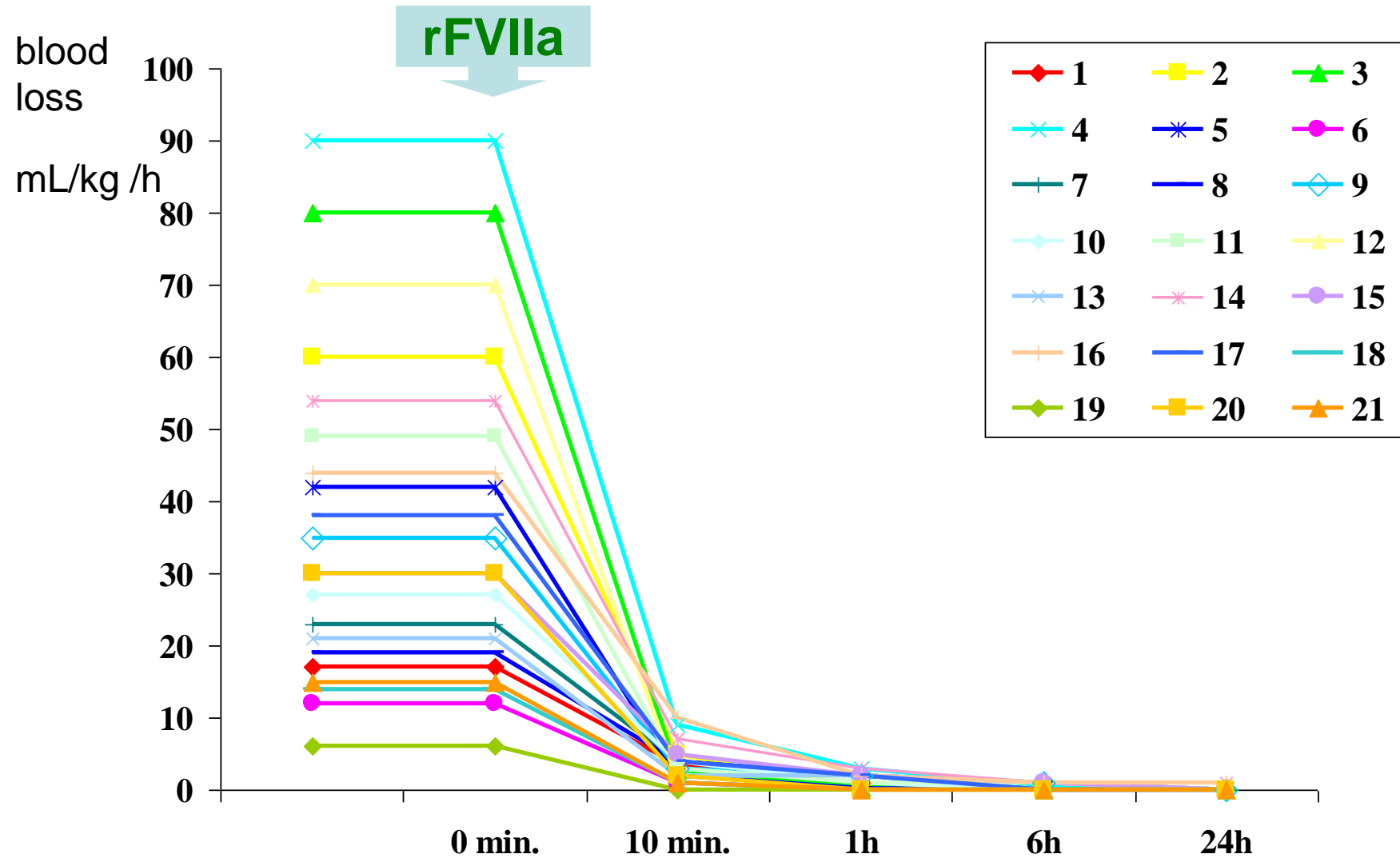
Definition :Early<8 units; Late>8 units. (Early 5.7u late 14u p*)

Results: 5,334 patients 90% penetrating, .365 (6.8%) massive transfusion. (>10 units). Of these, 117 (32%) received rFVIIa. 61 complete records: 17 early ,44 late..

The early rFVIIa group required 20% Less blood during the first 24h (20.6 vs. 25.7, p 0.048)

No difference in: late mortality (33.3% vs. 34.2%,),
ARDS (5.9 vs. 6.8%,),
infection (5.9% vs.9.1%,),
thrombotic events (0%vs. 2.3%)

Haemostatic effect of rFVIIa in surgical and trauma patients



The need for protocols/recommendations

- Many reports including controlled trials in various indications suggest efficacy and safety.
- Dichotomy in many reports between hi hemostatic response (70-100%) and variable survival (30-80%) suggest that selection of **indications, patients, timing and preconditions (as pH, Plt, Fib etc)** are mandatory. “last ditch use does not improve survival”(R. Dutton).

Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding

U. Martinowitz^{3,4,8} and M. Michaelson^{1,2}

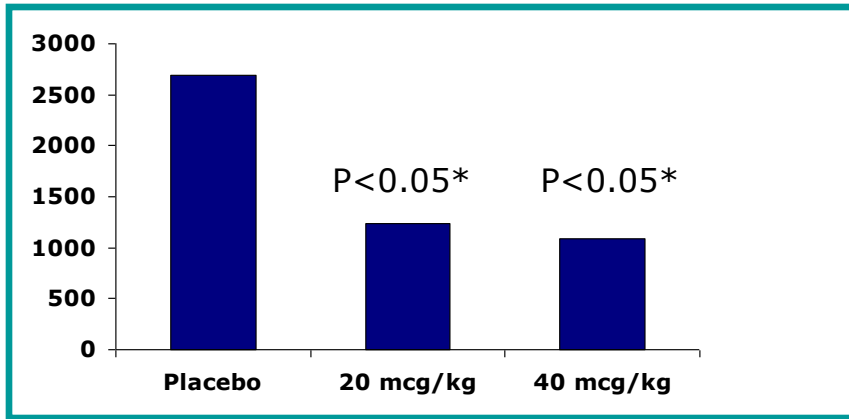
On behalf of the Israeli Multidisciplinary rFVIIa Task Force:

The National Trauma Advisory Board¹, the Societies of Trauma², Hematology³, Thrombosis and Hemostasis⁴, Anesthesiology⁵, Transfusion Medicine⁶, Neurosurgery⁷, Israeli Defense Forces (IDF)⁸, Israel National Center for Trauma and Emergency Medicine Research⁹, The Ministry of Health¹⁰, The National Blood Services¹¹, and the United States Army¹²; **JTH Apr.2005**

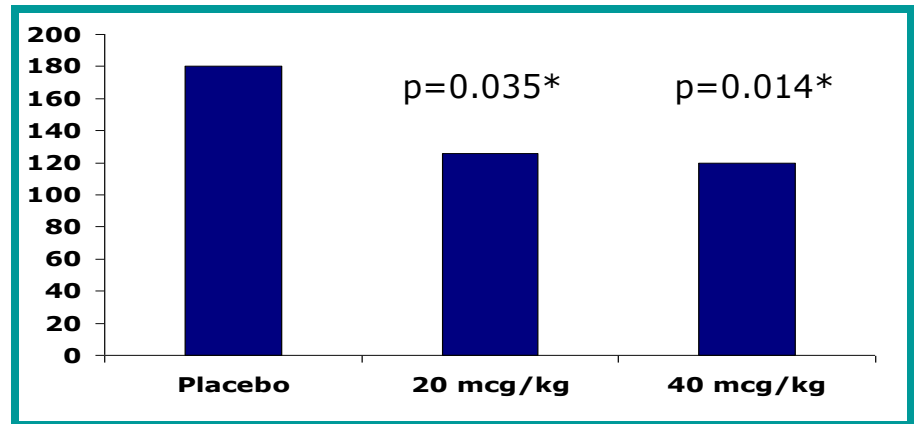
- Indications and contraindications
- Definitions of massive bleeding
- Replacement therapy before rFVIIa
- Definition of failure of appropriate treatment
- Timing of administration
- Precondition to administration (pH, Fib, PLT)
- Doses, repeated doses and monitoring

RCT: rFVIIa reduces blood loss and blood requirements in trans-abdominal retropubic prostatectomy. No safety issues observed

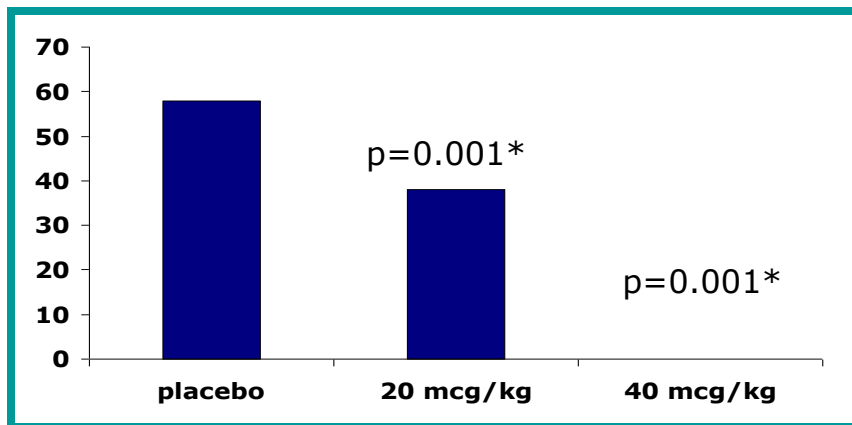
Median peri-operative blood loss



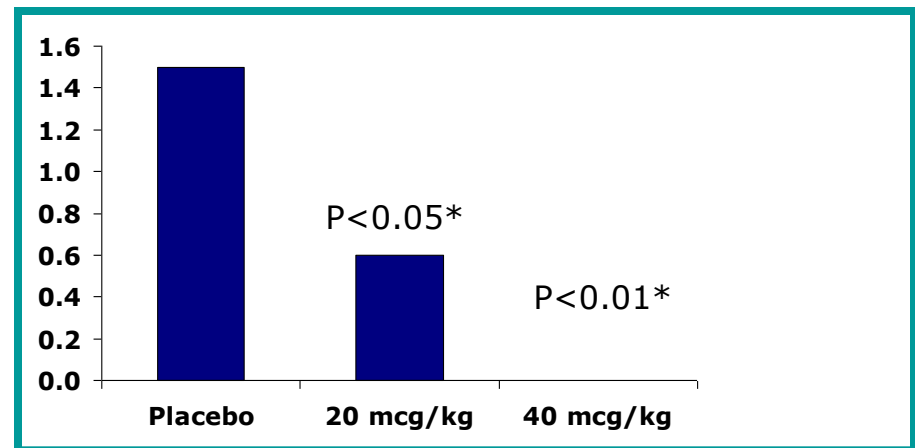
Duration of surgery (min)



percentage of patients requiring transfusion



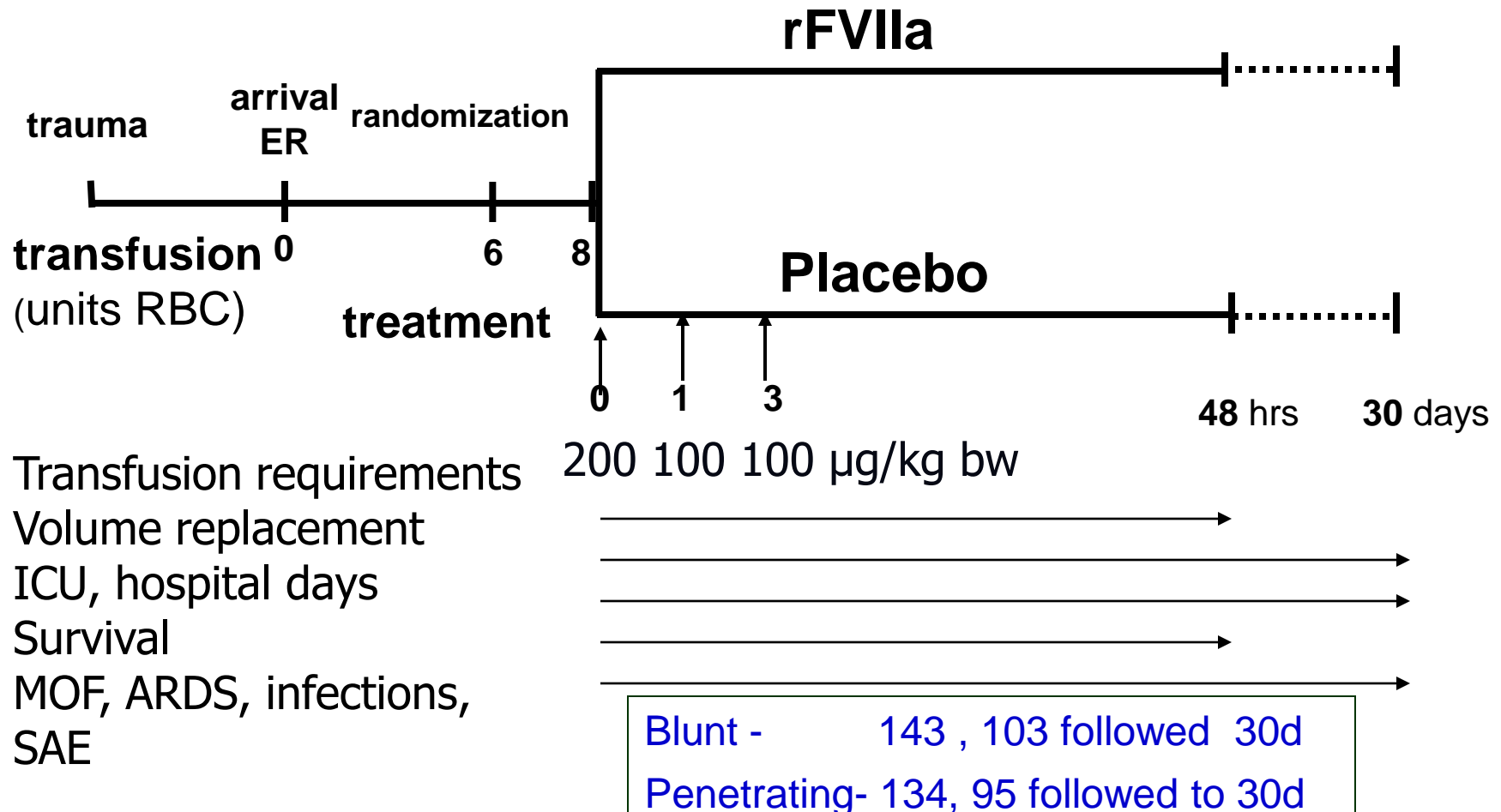
Transfusion requirements (RBC units)



The rFVIIa multicenter trauma trial

2 parallel studies blunt and penetrating trauma .

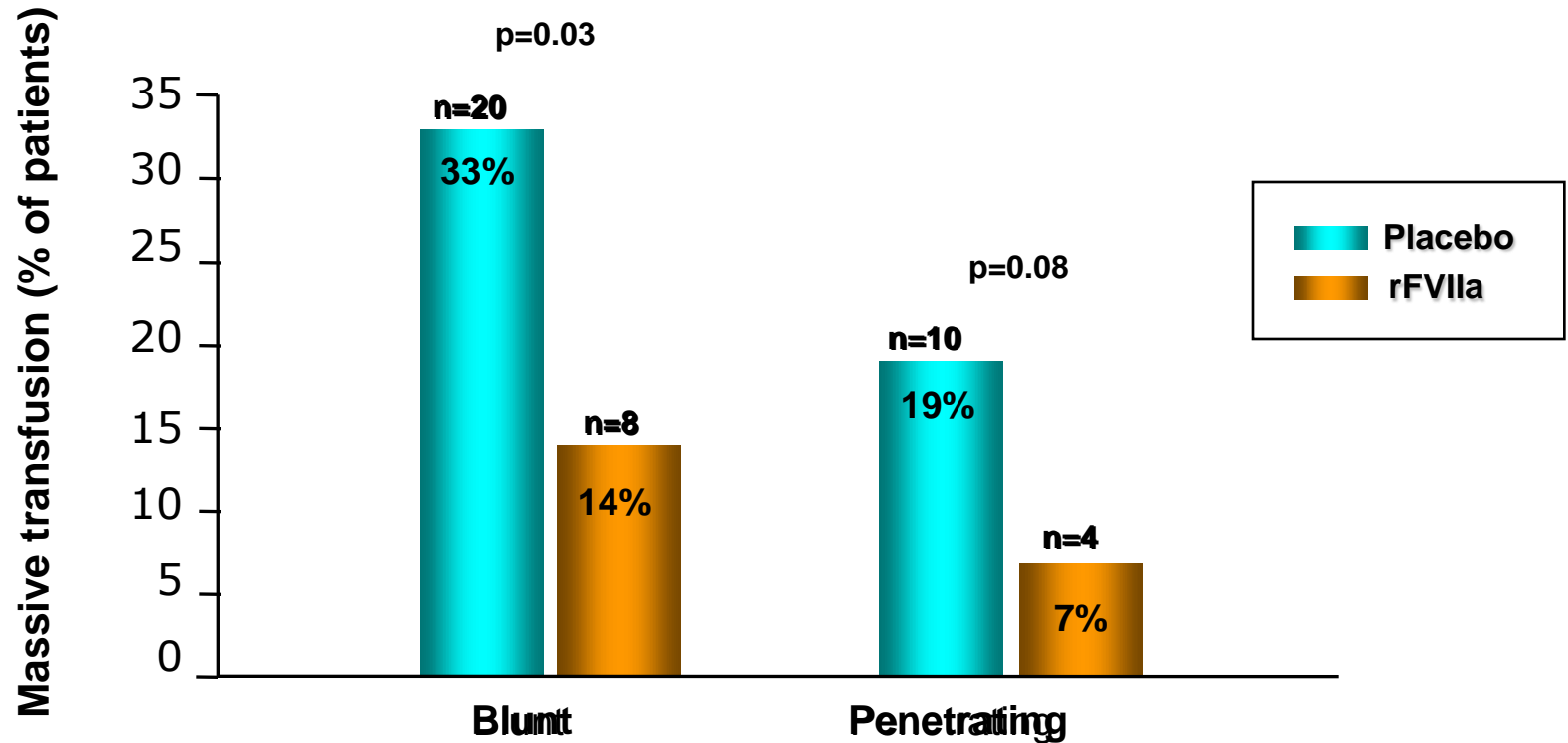
A safety study.



Results

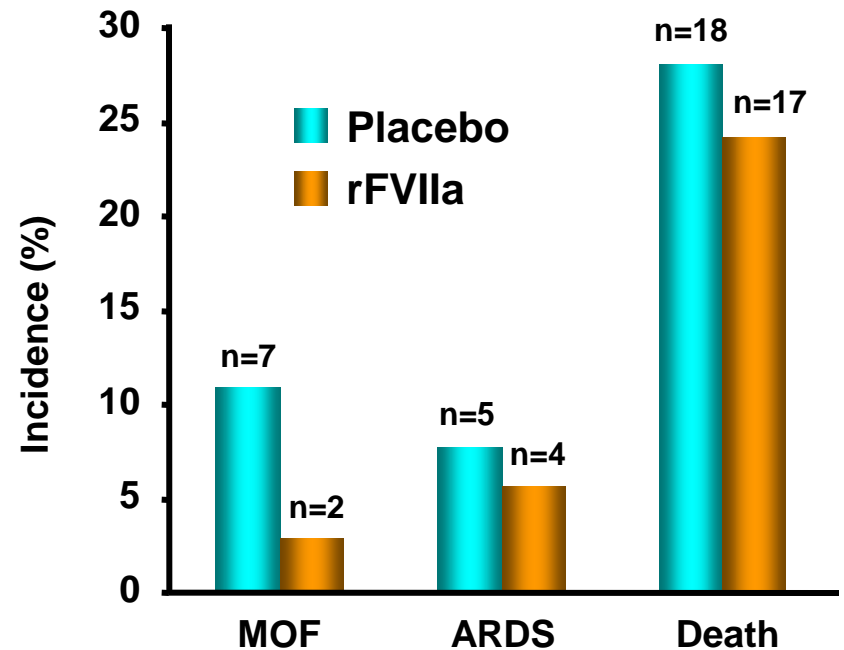
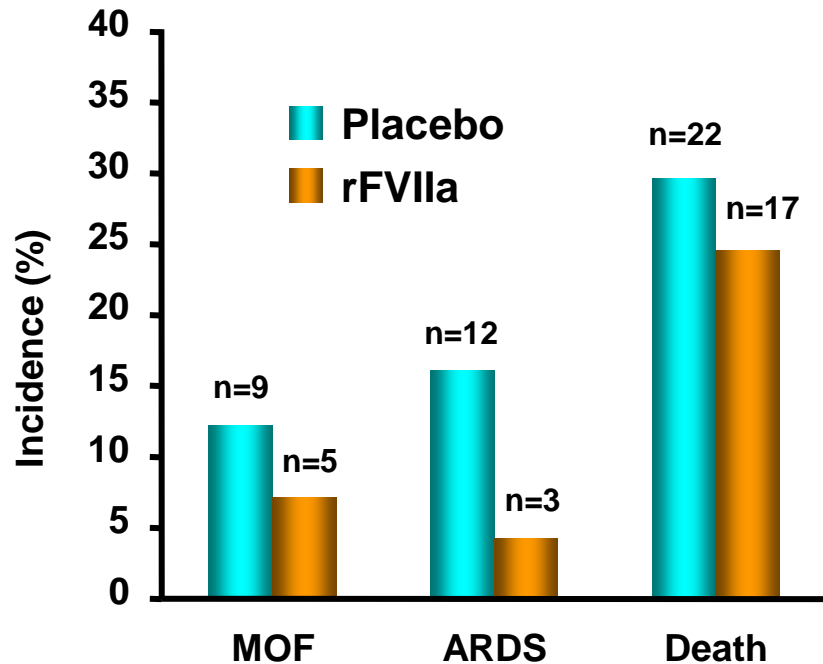
- ☹ Significant reduction of PRBC in blunt trauma
(2.6¹ and 3.5² in coagulopathic subgroup)
- ☹ Significant reduction (50%) in FFP and PLT.
- ☹ Not clinically relevant due to cost of rFVIIa
- 😊 May become cost benefit if real cost analysis
from UK of 2300 Euro/1 PRBC is correct.
- 😊 No increase in SAE^{1,2} including TBI³

😊 Significant reduction (14% vs 33%) in massive transfusions (>20 PC in 48h) in blunt trauma



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

😊 Significant reduction in MOF/ARDS- 20%vs.3% In blunt trauma



Safety of rFVIIa in hemodynamically unstable polytrauma patients with traumatic brain injury: *post hoc* analysis of 30 patients from a prospective, randomized, placebo-controlled, double-blind clinical trial

Yoram Kluger¹, Bruno Riou², Rolf Rossaint³, Sandro B Rizoli⁴, Kenneth David Boffard⁵, Philip Iau Tsau Choong⁶, Brian Warren⁷ and Michael Tillinger⁸ Crit Care. 2007;11(4):R85

- ❖ A *post hoc* analysis of the trauma trial for patients participating in the study who were diagnosed later as having also TBI (13 placebo and 17 rFVIIa)

No significant differences in patients with

polytrauma +TBI in:

Mortality

Ventilator free days

ICU free days,

Thromboembolic AE

Other SAE

☹️😊 The reduction of blood requirements of 2.6¹
and 3.5² May become clinically important
and cost benefit if the next 2 slides are real

Effect of Duration of PRBC Storage on Complications after Cardiac Surgery

Median storage 11 vs. 20 days, average 2 units/patient

- ☹ Higher in-hospital mortality (2.8% vs. 1.7%, $P = 0.004$)
- ☹ Ventilation beyond 72 hours (9.7% vs. 5.6%, $P < 0.001$)
- ☹ Renal failure (2.7% vs. 1.6%, $P = 0.003$),
- ☹ Sepsis (4.0% vs. 2.8%, $P = 0.01$).
- ☹ Composite complications (25.9% vs. 22.4%, $P = 0.001$).

☹️At 1 year, mortality remained significantly less in patients given newer blood (7.4% vs. 11%, $P < 0.001$).

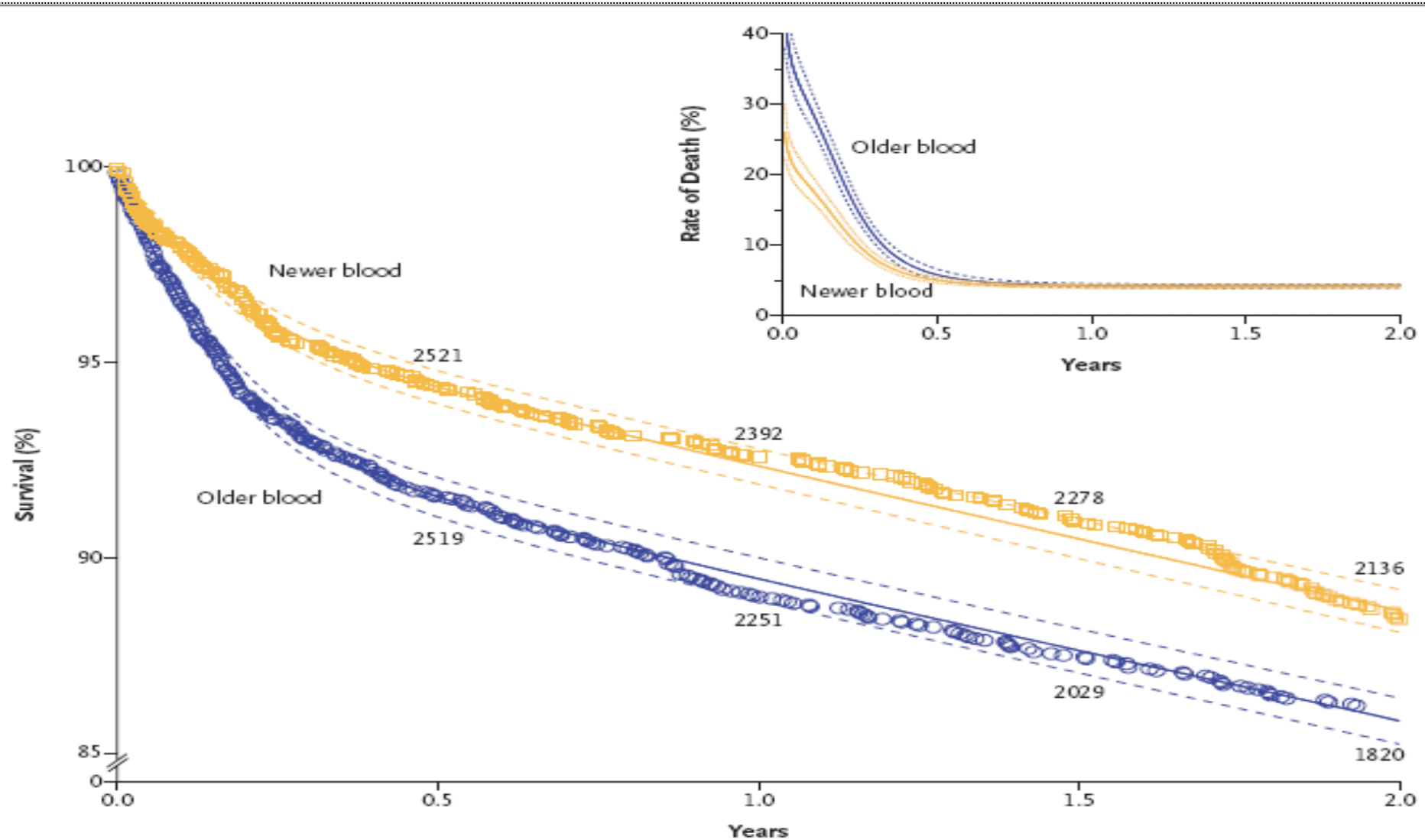


Figure 3. Kaplan–Meier Estimates of Survival and Death.

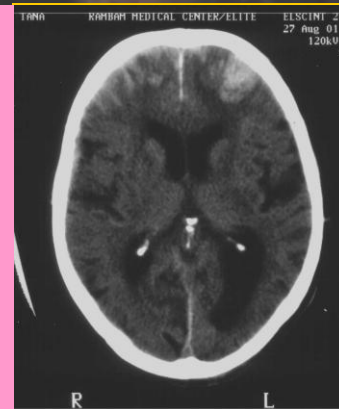
The curves show data from 2872 patients who were given exclusively newer blood (stored for 14 days or less) and

Efficacy and safety of rFVIIa in ICH



50% of lesions increase in size after the initial impact *J. Neurosurgery, Jan. 2002*

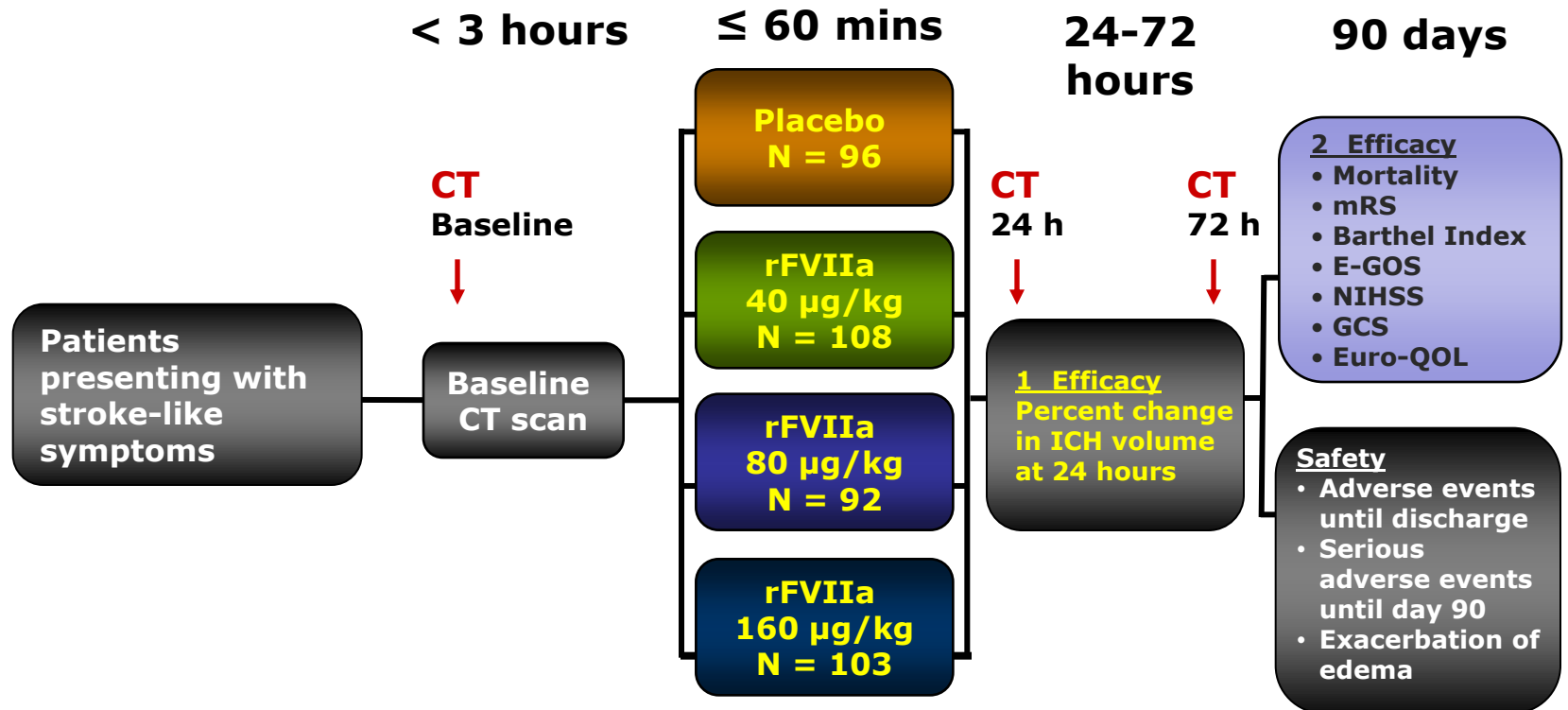
Here size matters :it is the most important predictor for outcome



24 hours

Study design (phase IIb)

400 patients randomized

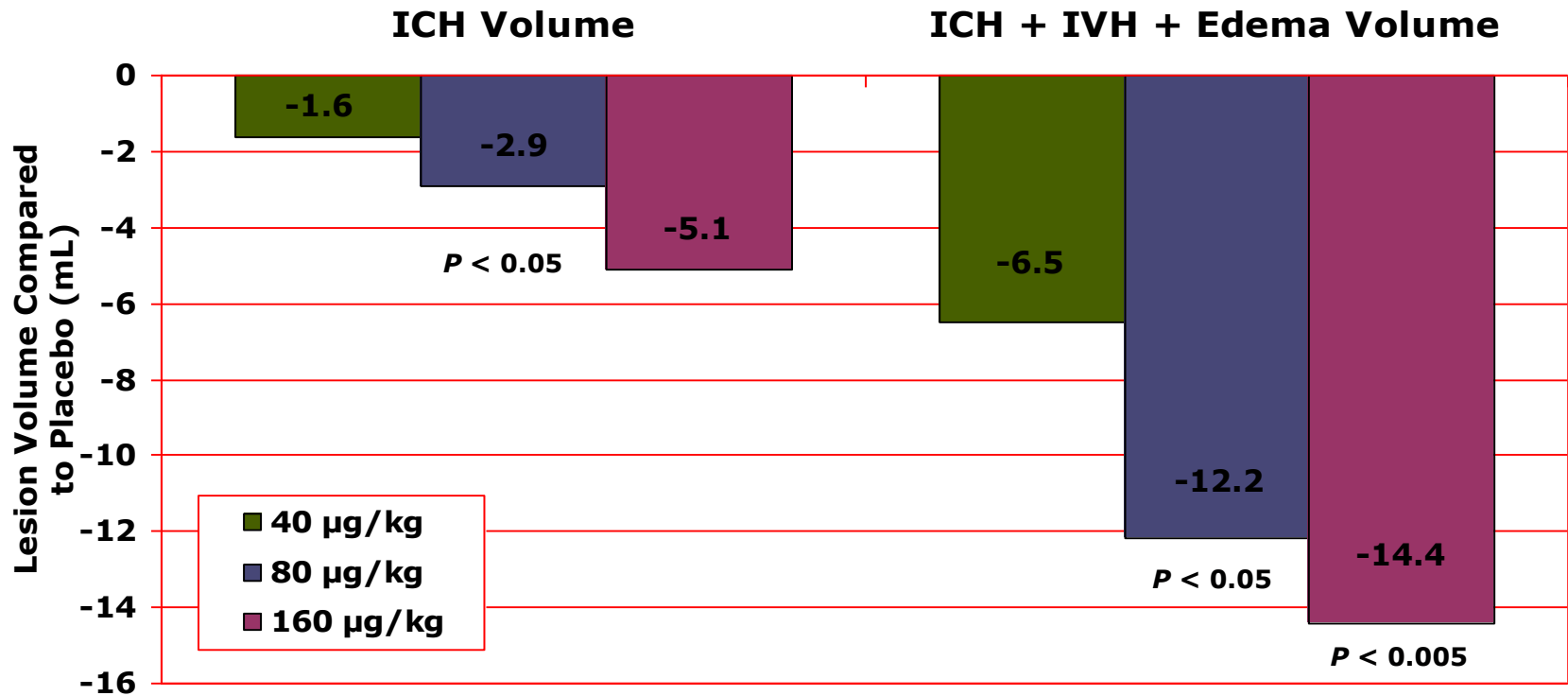


Mayer SA et al. *N Engl J Med*. 2005;352:777-785.

Results

Reduced hematoma growth in a dose- dependent fashion at 72h (52% reduction all groups vs. placebo $p<0.01$)

Mean Difference from Placebo



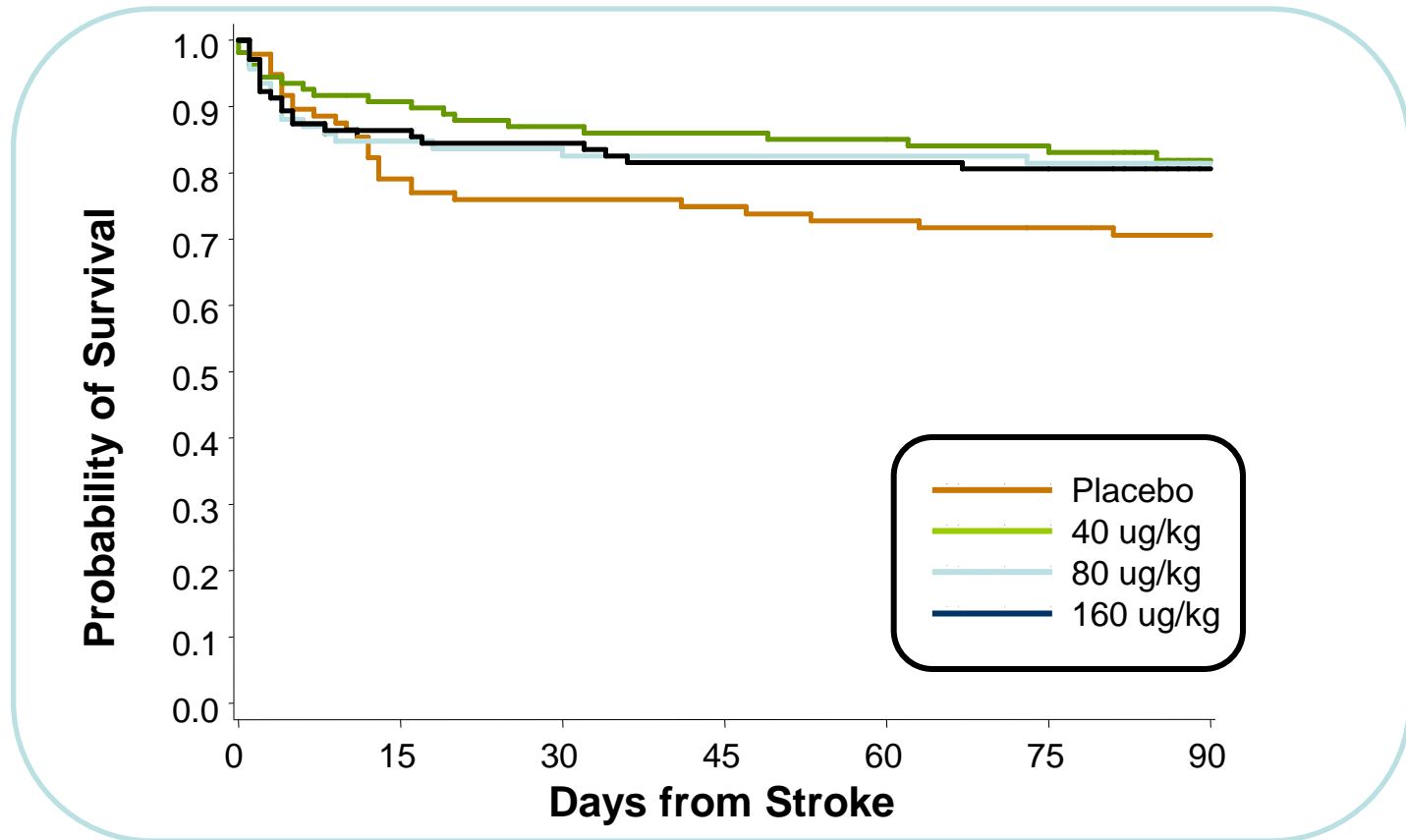
Reduced mortality at 90 days:29%
to 18% (RR 38%) $p=0.02$

Placebo	40 µg/kg	80 µg/kg	160 µg/kg	Combined rFVIIa	<i>P Value</i>
29%	18%	18%	19%	18%	0.025*
RR	38%	38%	34%	38%	

*Combined rFVIIa vs placebo
Chi-square test; $P = 0.02$ [*NEJM* value]

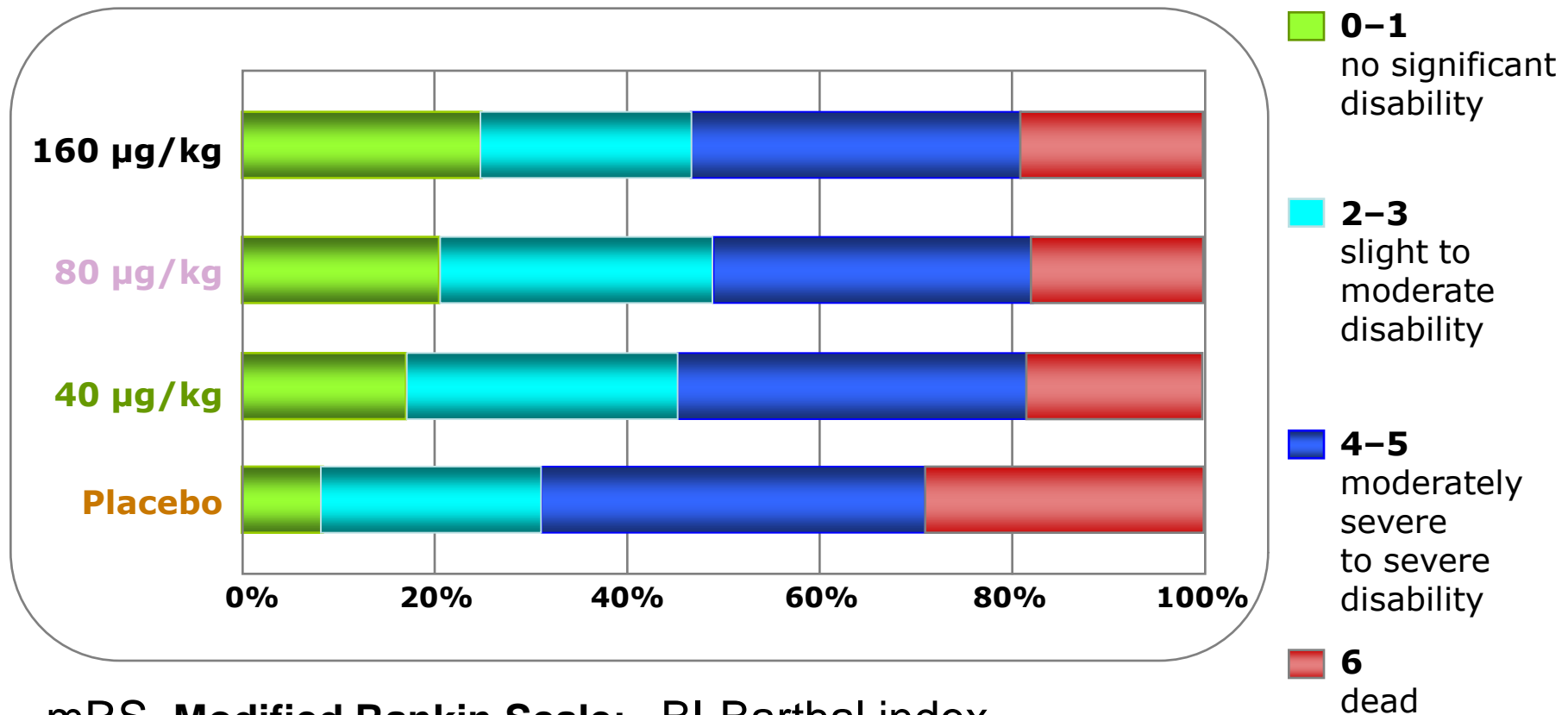
Mayer SA et al. *N Engl J Med*. 2005;352:777-785.

Survival: Kaplan-Meier Curves



Mayer SA et al. *N Engl J Med.*
2005;352:777-785.

Improves global functional outcome (mRS and BI) at 90 days: general shift to the left



mRS- Modified Rankin Scale; BI-Barthal index

Mayer SA et al. *N Engl J Med.* 2005;352:777-785.

Thromboembolic SAEs

Placebo	40 µg/kg	80 µg/kg	160 µg/kg	<i>P</i> <i>Value*</i>
2%	6%	4%	10%	0.12

- **Arterial thromboembolic** SAEs occurred significantly ($P = 0.01$) more frequently with rFVIIa treatment (5%) than with placebo (0%). There was no difference in Thromboembolic SAEs that were fatal or disabling (2%

rFVIIa multicenter ICH phase III

- Similar protocol , 3 doses: placebo, 20µg/kg and 80µg/kg . 820 patients.
- Reduction in hematoma and edema volume as in phase IIb
- No clinical benefit at 90 days
- Safety profile consistent with phase IIb :small increase in cerebral and myocardial ischemia
- Failure due to Imbalances in disease severity

Phase III rFVIIa in ICH, Possible reasons for failure to achieve clinical endpoint: more severe disease in rFVIIa groups (presence of IVH)

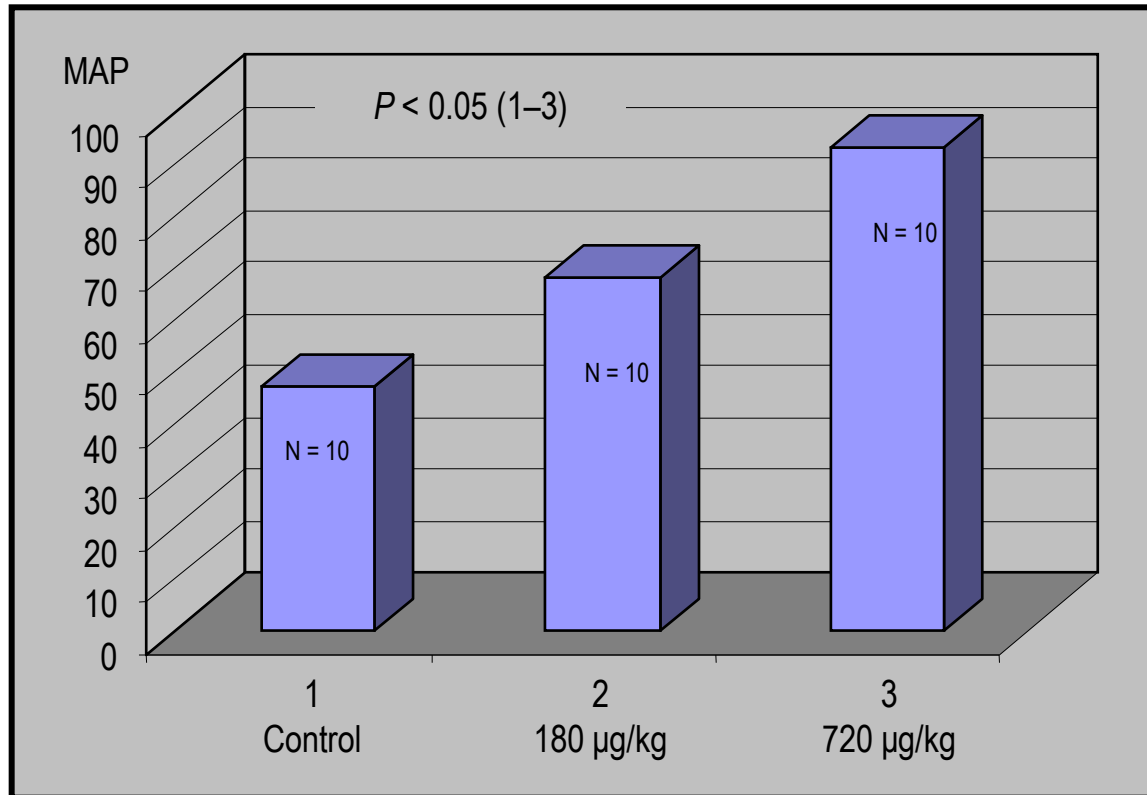
	Placebo n=263	20 µg/kg n=265	80 µg/kg n=293
Male	63%	61%	61%
Age (years)	65 ± 14	65 ± 14	65 ± 13
Caucasian	67%	72%	69%
GCS (median)	14	13	13
GCS 6-8	3%	6%	6%
ICH Volume (mL)	22 ± 25	24 ± 26	23 ± 26
Lobar location	20%	22%	20%
LVH on ECG	23%	31%	30%
MAP (mm Hg)	125 ± 19	126 ± 21	127 ± 23
Presence of IVH	29%	35%	41%

Interpretation of clinician to the company's announcement on no interest in ICH indication

- We are not bound to the company commercial interests or any other interest
- Phase IIb study was well controlled & reliable ,
- Its results showed marked and significant improved outcome
- There is no alternative treatment
- We believe that rFVIIa should be given to patient population as in IIb (with low risk TE)
- But we are now under a higher threat of litigation by patients due to the company's announcement...

Evidence from animal models

2 mm Aortic Laceration in pigs: Rebleed MAP

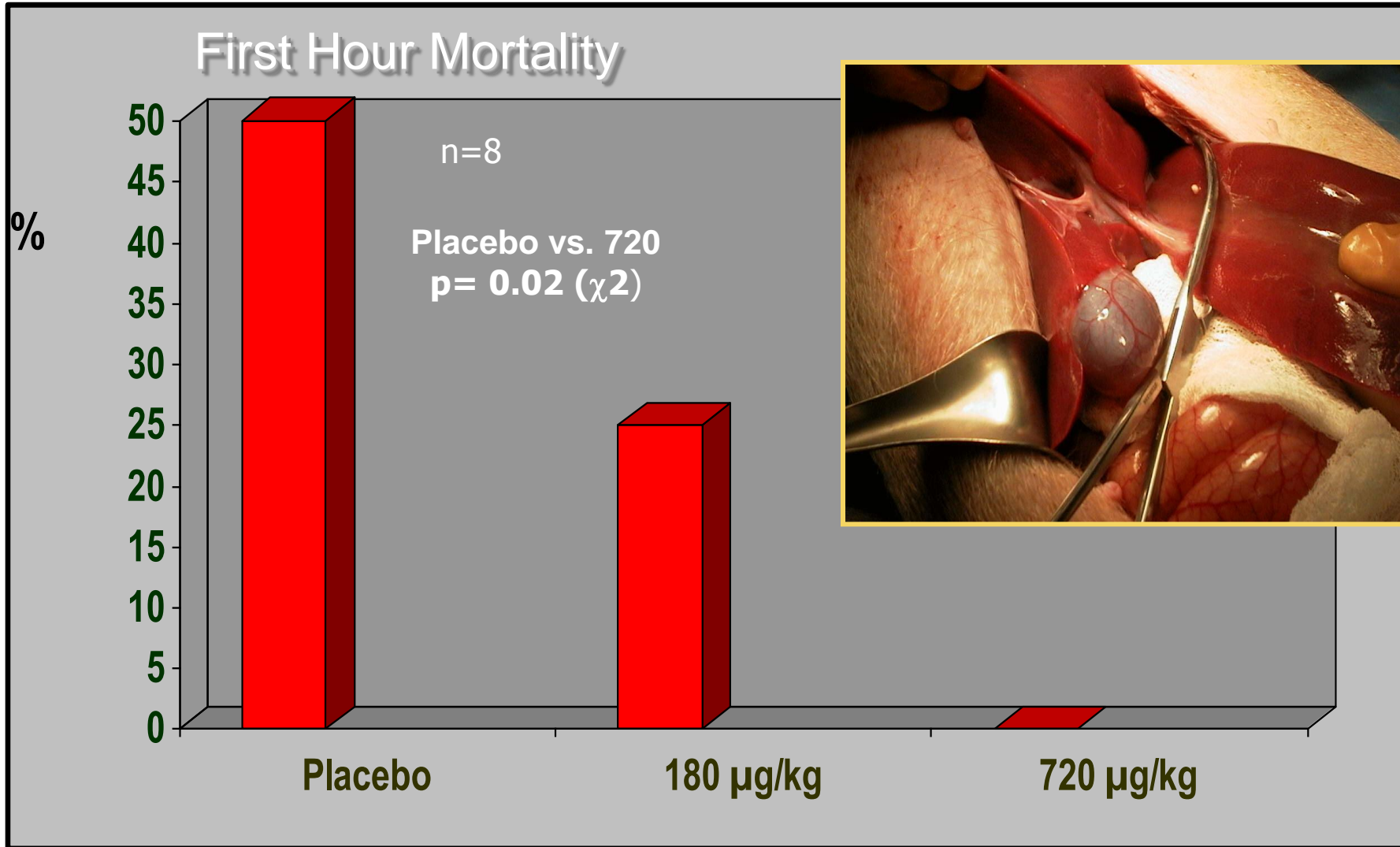


rFVIIa increases “popping of the clot” pressure in porcine uncontrolled aortic hemorrhage

Sondeen J. et al. Shock. 2004 Aug;22(2):163-8

Evidence from animal models

rFVIIa in pre-hospital model of liver laceration



Time From Injury to Death: Prolongation of the “golden hour”

Time (min SD)

8 3 min

Placebo

17 6 min

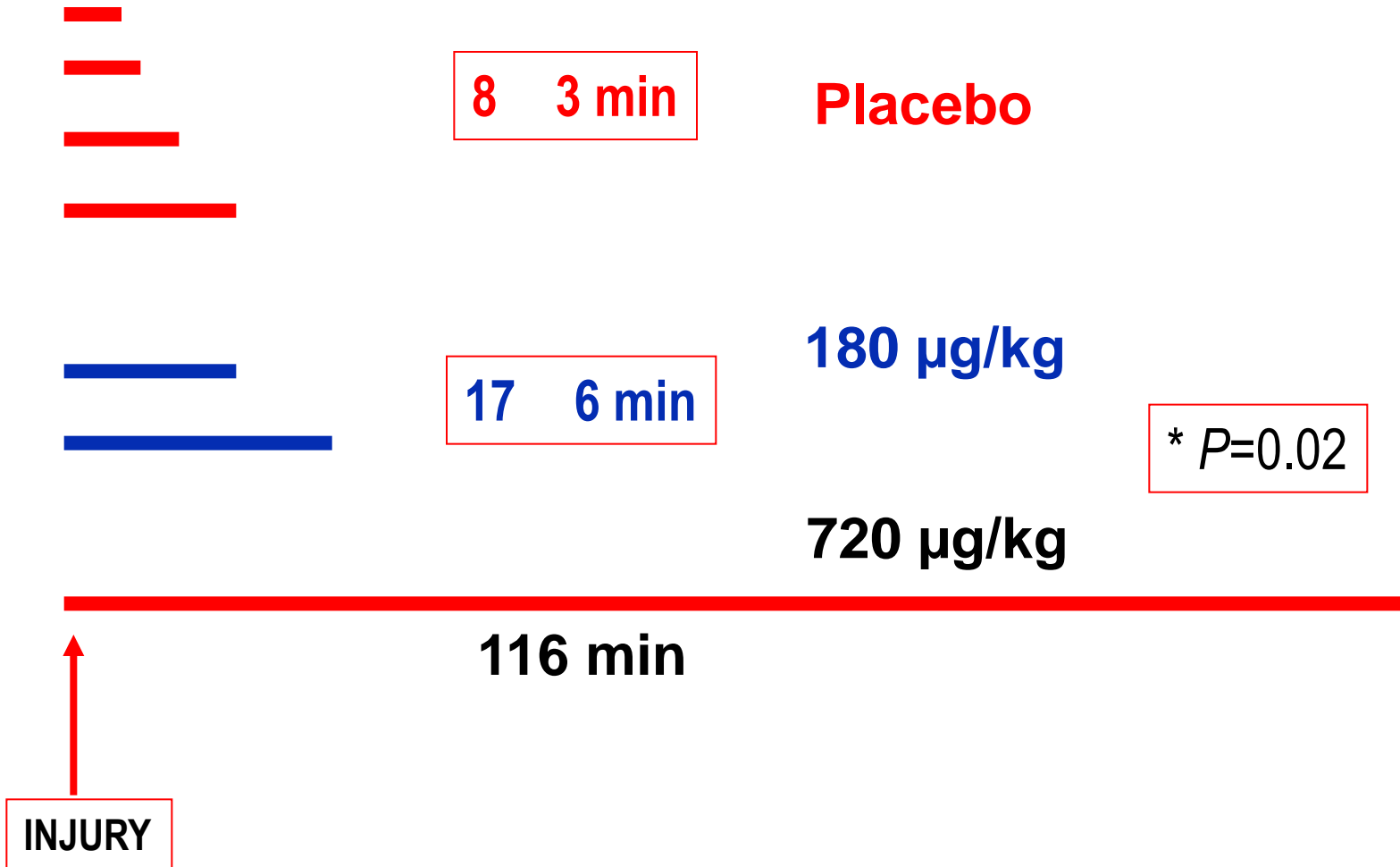
180 µg/kg

720 µg/kg

* $P=0.02$

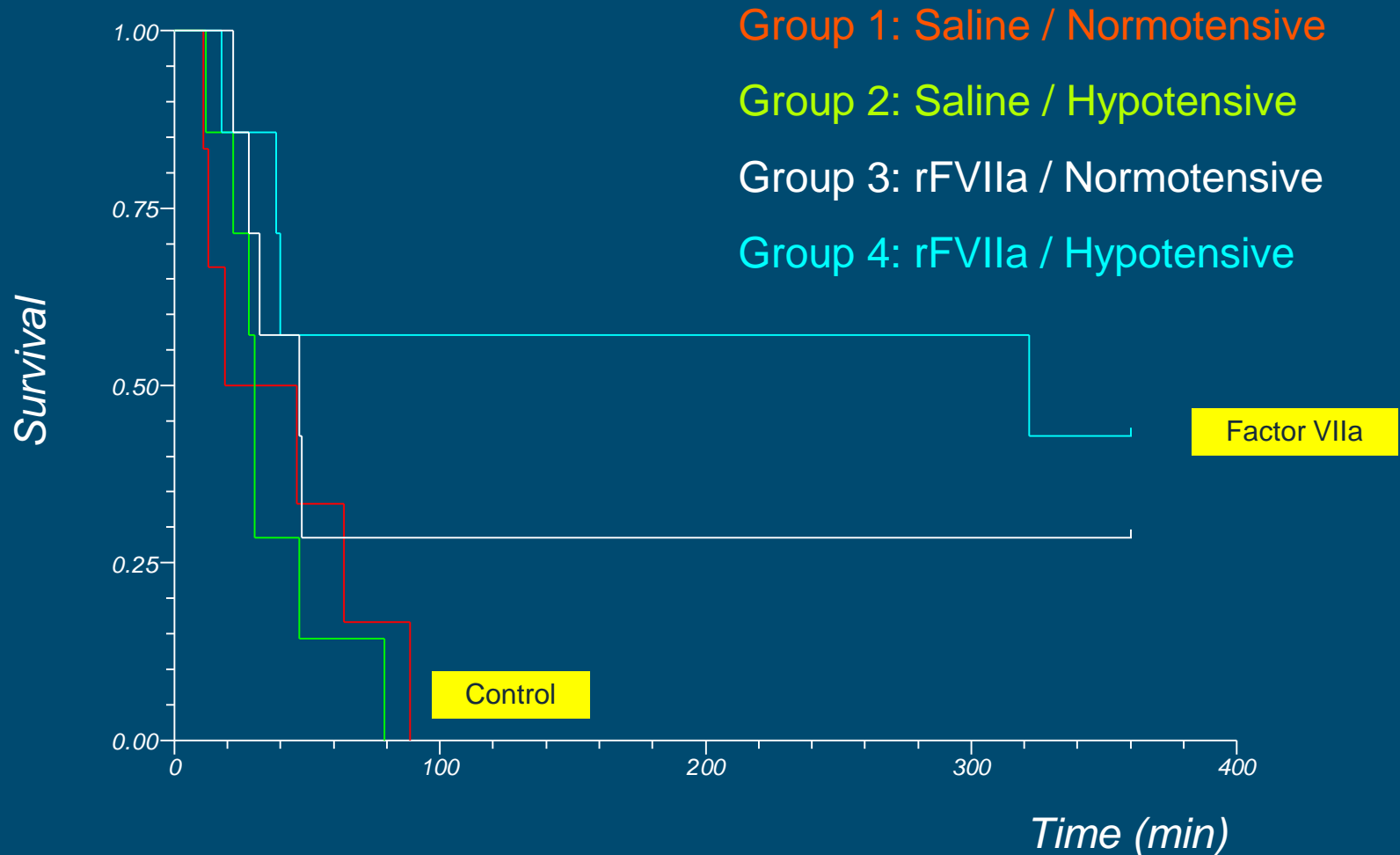
116 min

INJURY



Evidence from animal models

Severe uncontrolled haemorrhage from aortotomy- Survival



Hemostatic and Neuroprotective Effects of hrFVIIa Therapy after Traumatic Brain Injury in Pigs

TBI was induced using a double injury model resulting in both **diffuse axonal injury (DAI)** and **cerebral contusion**:▪

Diffuse axonal injury (DAI) was induced using non-impact rotational acceleration

Within 30 minutes of rotational acceleration injury, a **cerebral contusion injury** was induced with a vacuum pulse generator and 1 atmosphere of negative pressure for two seconds.

Zhang J. et. Al. Experimental Neurology 2008

Fig 2: Comparison of contusion expansion (MRI)

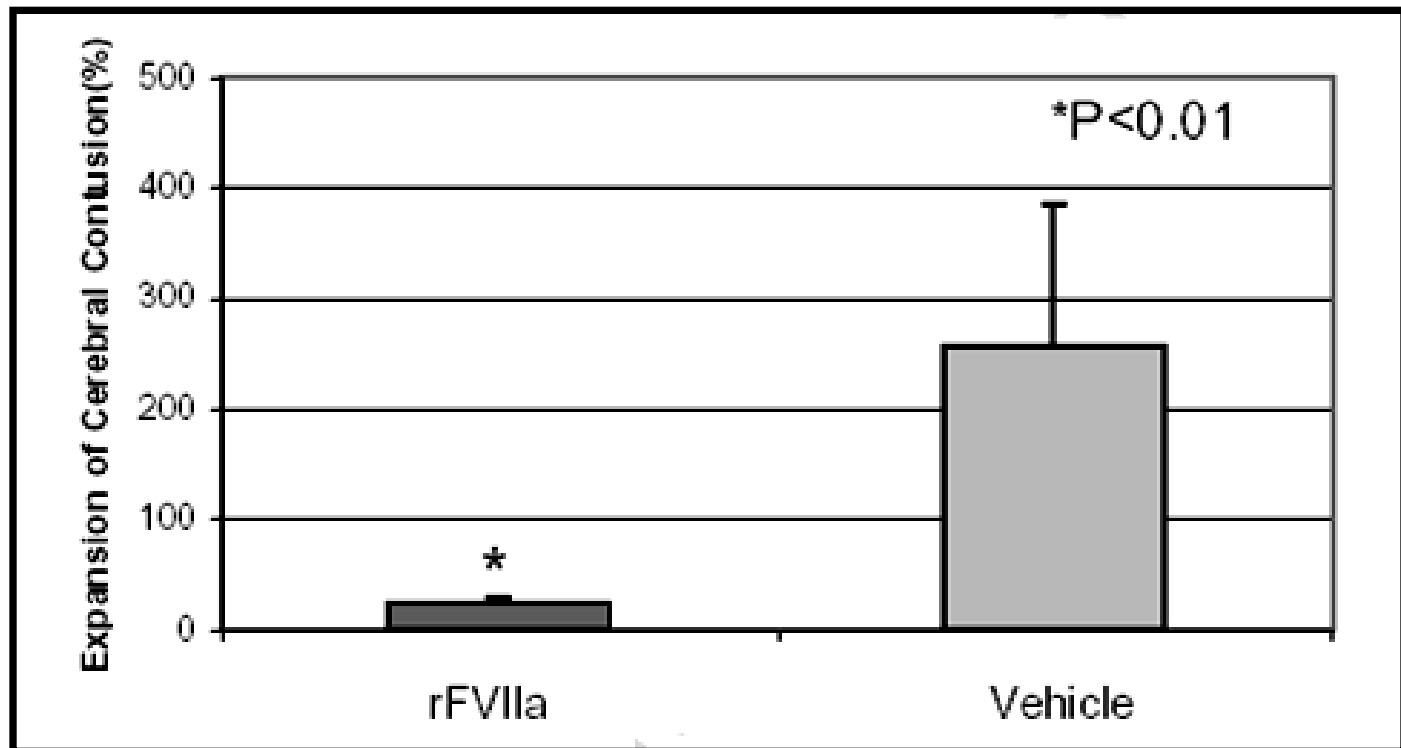
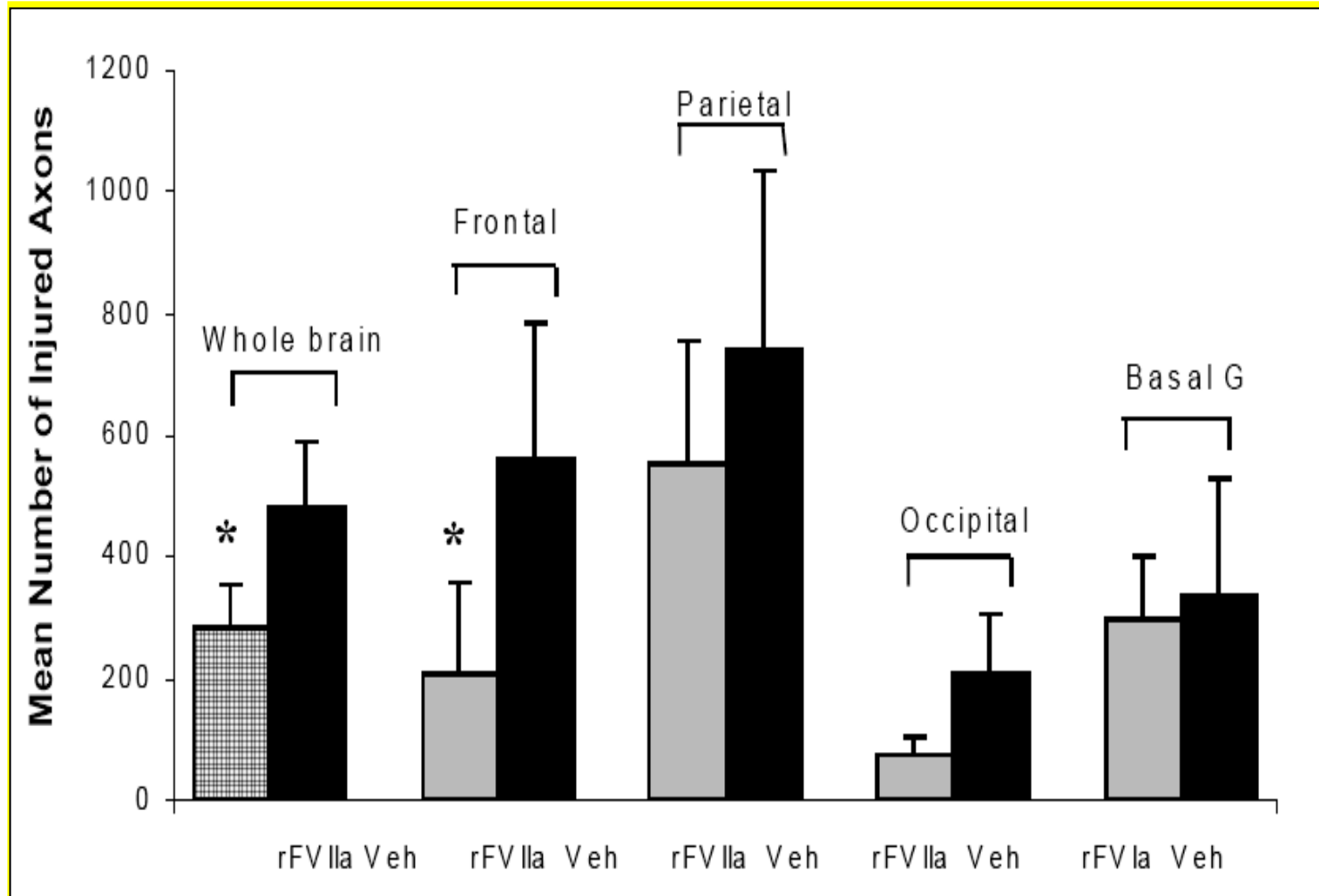
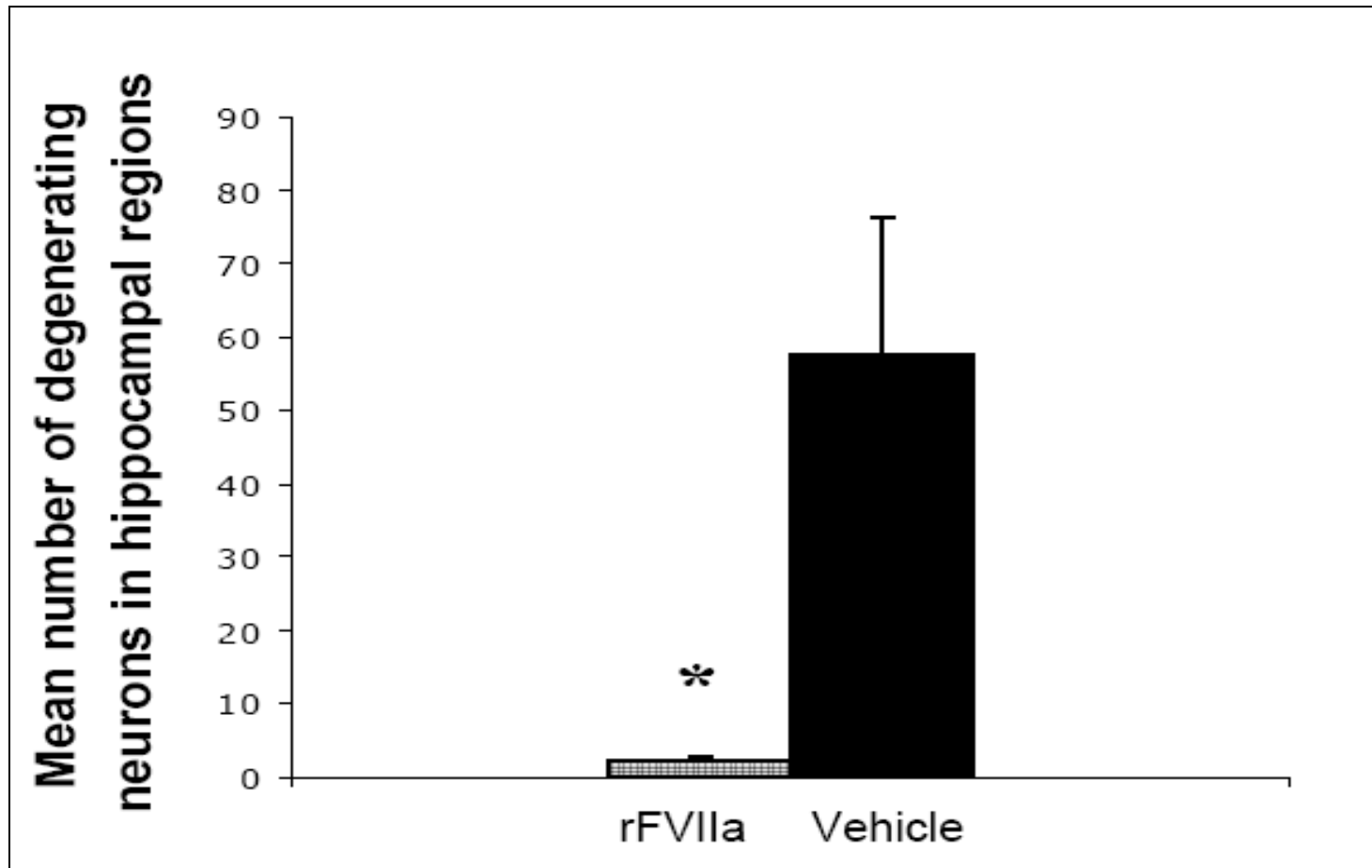


Fig 8: Comparison of contusion expansion (MRI)



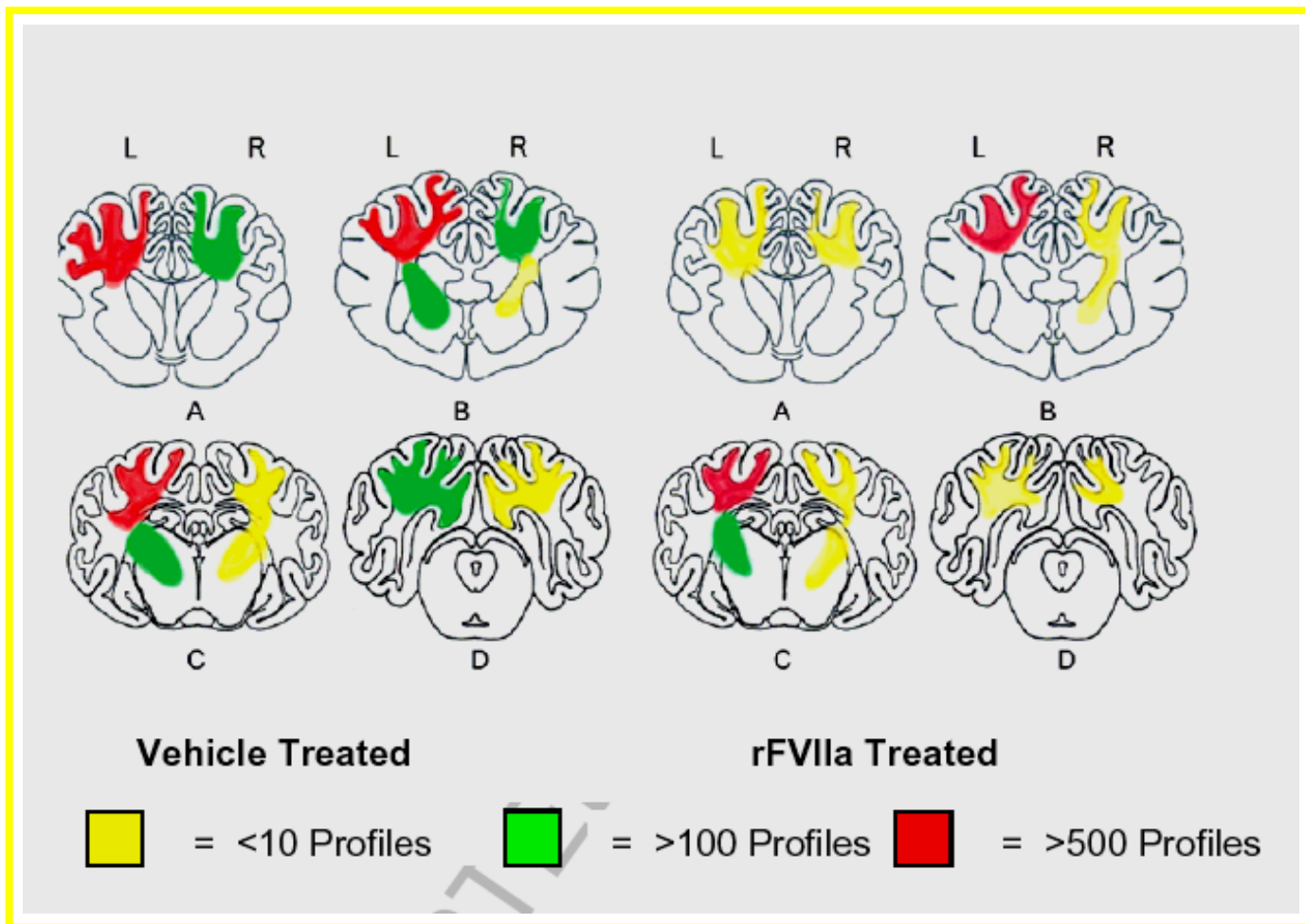
Zhang J. et. Al. Experimental Neurology 2008

* A significant difference between two groups was observed with $p < 0.01$.



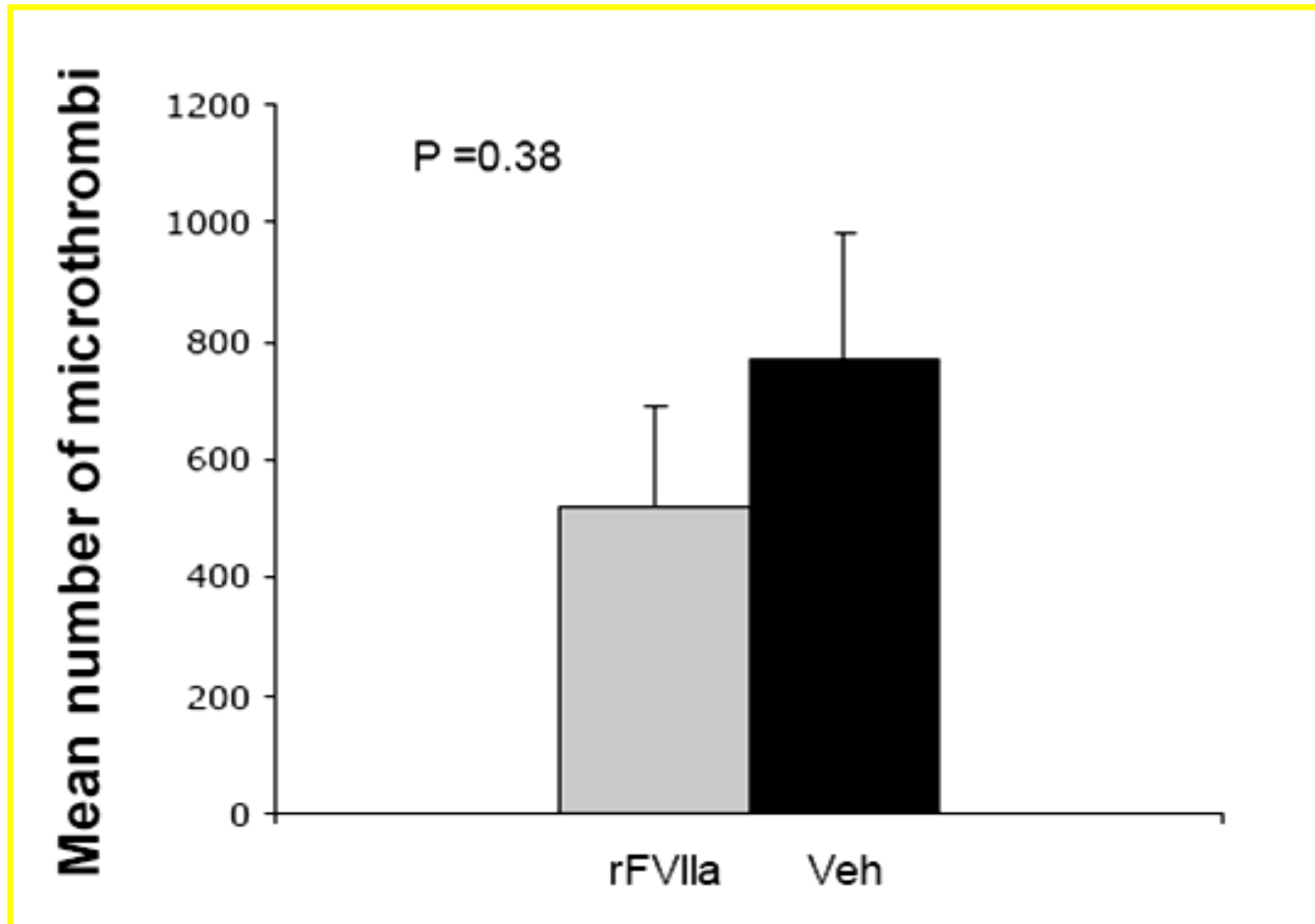
Zhang J. et. Al. Experimental Neurology 2008

Fig 7: Schematic representation of the distribution and severity of **axonal pathology** in various coronal planes of the brain at 3 days post-injury. In all animals the **contusion injury was performed on the left side**.



Zhang J. et. Al. Experimental Neurology 2008

Fig 10: Total number of **microclots**



Whole brain analysis with H&E staining

Safety of rFVIIa

- No more thromboembolism or MODS /ARDS in 1700 surgical patients (pooled randomized trials)
company report
- No more thromboembolism in the multicenter trauma trial. Less ARDS and MOF
Boffard J Trauma 2005
- SAE in 1-2% of recipients of rFVIIa. Such patients are prone for thromboembolic complication due to their underlying condition
Levi M. Crit.Care.Med 2005
- Low risk in young and healthy

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Kathryn A. O'Connell, MD, PhD

Jennifer J. Wood, PhD, MPH

Context The US Food and Drug Administration (FDA) licensed recombinant human coagulation factor VIIa (rFVIIa) on March 25, 1999, for bleeding in patients with he-

- Spontaneous and company reported SAE to FDA over 5 years -185 thromboembolic events
- ☹ Useless report: number without denominator ,can be any incidence .
- ☺ The right perspective: Over 10,000,000 uses during this period (company report) mostly in patients with high risk of thromboembolism.

The Rate of Thromboembolic Events

Publication	# of patients	rFVIIa	Coagulopathy	TE AEs
NovoSeven Trauma Study group	rFVIIa – 139 Placebo – 138	400 µg/Kg within 3 hours		4% (6 patients in each group)*
Subgroup Analysis	rFVIIa – 60 Placebo – 76		Transfusion requirement	rFVIIa 3% Placebo 4%
13 Novo trials Open label & Dose exploratory trial	rFVIIa -748 Placebo - 43	5-320 µg/Kg	AC, Cirrhosis UGIB, Liver Transplant & Trauma	rFVIIa 6% Placebo 5.3% OR – 1.17

*12 TE-AEs - 6 Placebo (2 PE, 3 DVT, MVT, CVA)

6 rFVIIa (2 DVT, 1 Arterial limb, CVA)

Thank you for your participation, I hope it was useful



rFVIIa and Warfarin Overdose

❖ 13 Patients on chronic Warfarin

With INR > 10 in High-Risk (n=5)

Or clinical hemorrhage (n=4)

Or invasive procedures (n=4)

rFVIIa 90-15 μ g/Kg corrected INR

No AE were noted

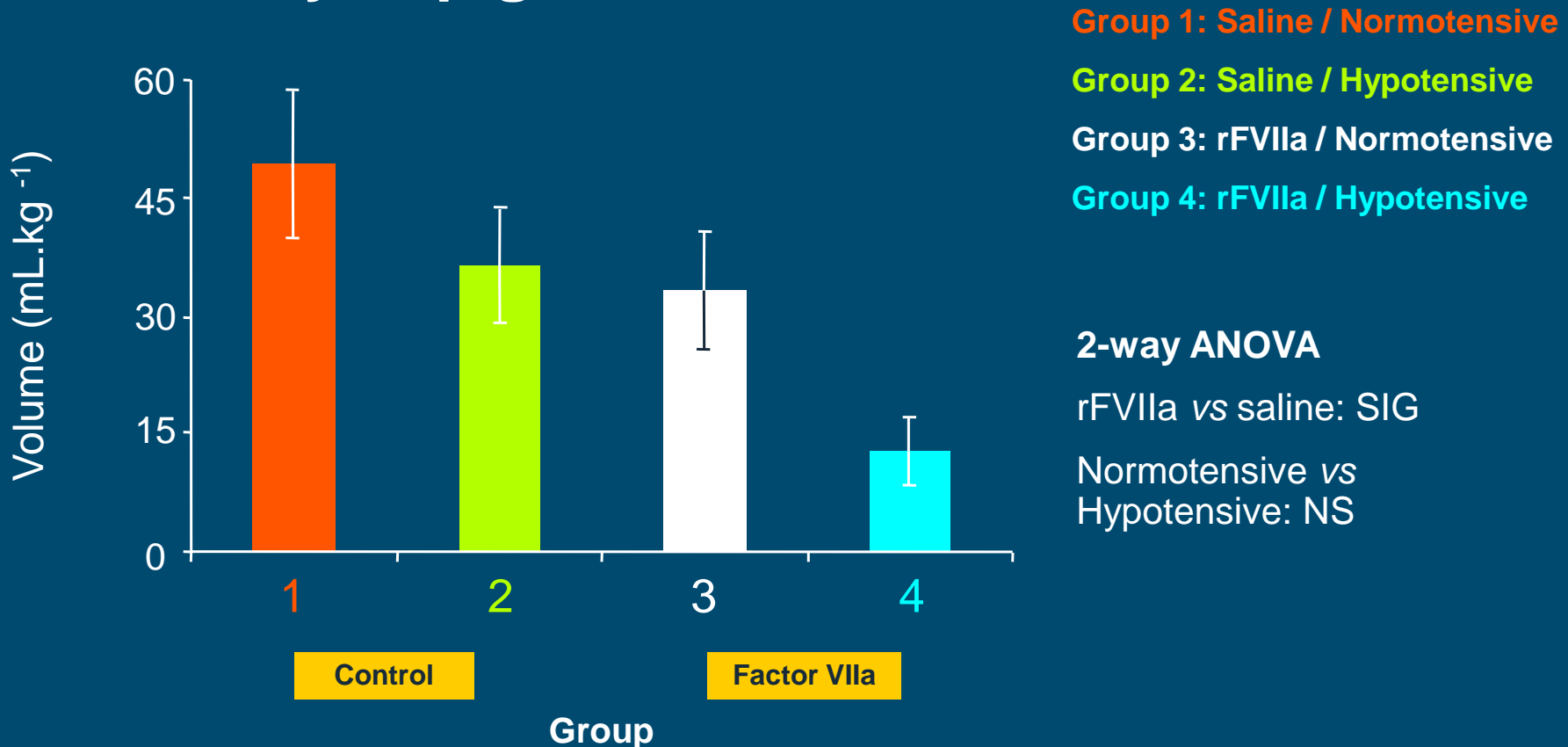
rFVIIa for Reversal of Xa inhibitors

- Fondaparinux (FP) is a selective FXa Inhibitor
- No antidote
- RCT study in 16 Healthy Males :
 - S.C 10mg FP + 90 μ g/Kg rFVIIa (n=8)
 - FP + Placebo (n=4)
 - rFVIIa + Placebo (n=4)

rFVIIa normalized thrombin generation for 2-6 h

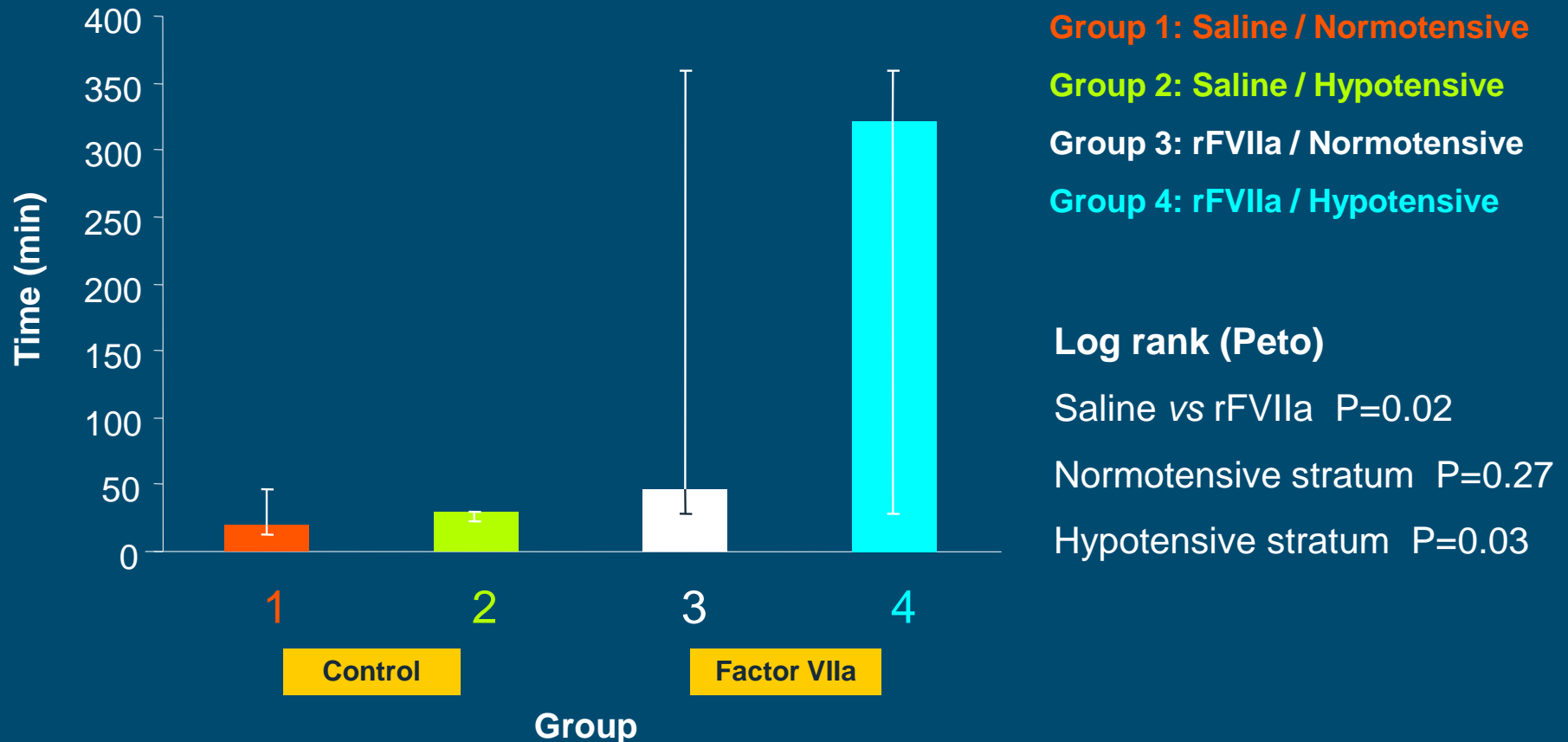
Evidence from animal models

Severe uncontrolled haemorrhage from aortotomy in pigs- Intra-abdominal blood loss



Evidence from animal models

Survival time: Prolongation of the golden hour to 6h



Hypothermia –bypassing Hemostatic activity of rFVIIa

- rFVIIa significantly Improves clotting assays and stops /reduces massive bleeding in hypothermic critically ill trauma patients.

Martinowitz U. et al ;Can. Anesthes. 2002

Martinowitz U. et al; J. Thromb. Haemost. 2005

- Similar results in an animal trauma model of hypothermic Pigs.

U. Martinowitz et al J. Trauma 2001/1

- In vitro data supporting the clinical observation.

Meng ZH et al J.trauma 2003

US Army Hemostatic Resuscitation Clinical Practice Guidelines:

Identify patients at risk for massive transfusion early

- 5 triggers to identify this patient category
- **Temp < 96**
- **SBP < 90**
- **Hb < 11**
- **Base deficit > 6**
- **INR > 1.5**

Acidosis: Effects on Platelets

- Prolongs capillary bleeding time in swine ³¹
- Reduces whole blood clotting response to collagen
- Reduces aggregation-epinephrine,ADP,collagen ^{38, 39}
- Inhibits platelet extracellular calcium influx ^{40, 41}
- In vivo acidosis increased platelet activation and circulating aggregates, decreasing platelet counts ⁴²

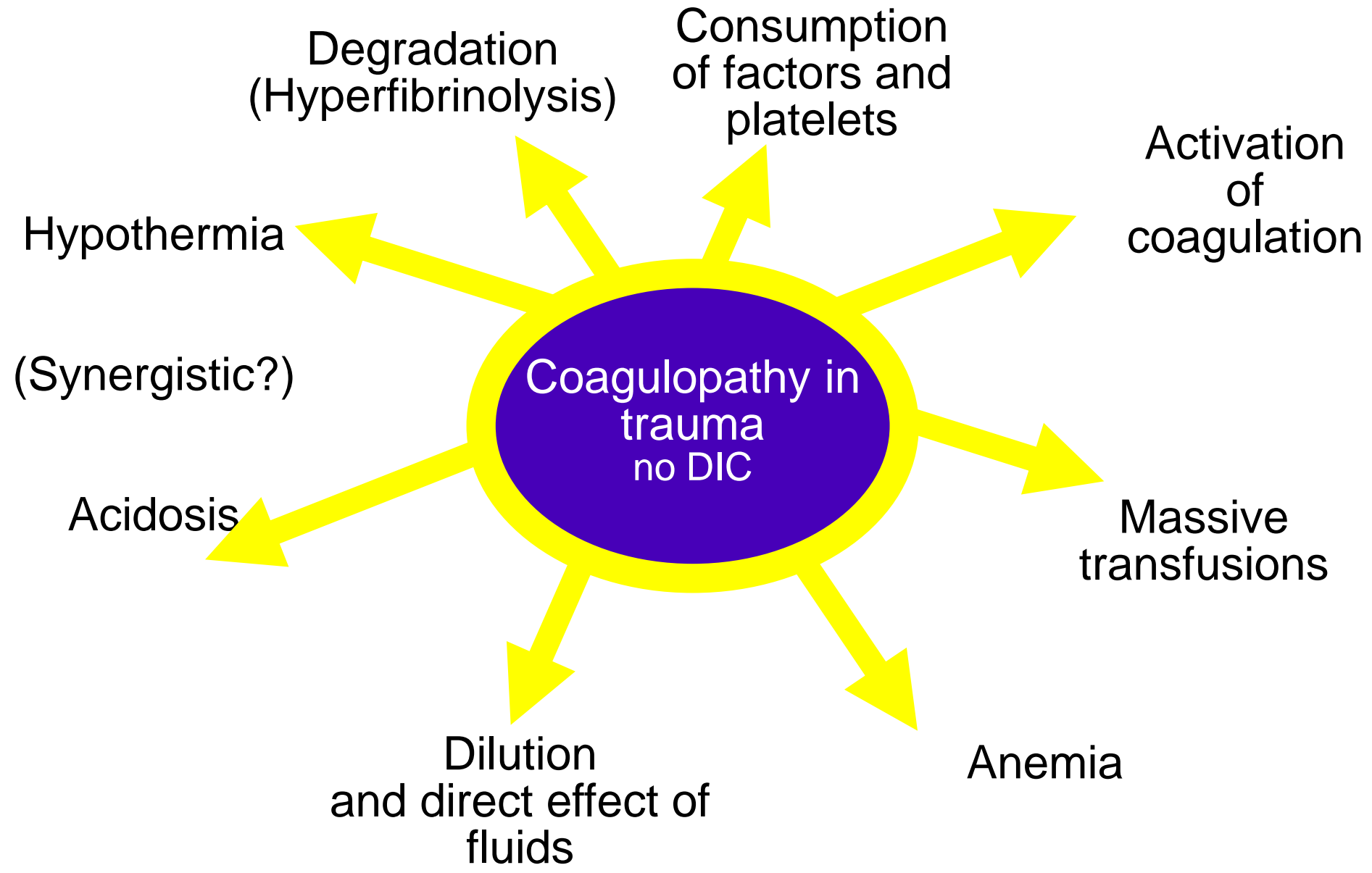
Hypothermia in trauma

- prone to hypothermia
- 66% presented with $BT < 36\text{ }^{\circ}\text{C}$
- 80% of nonsurvivors had $BT < 34\text{ }^{\circ}\text{C}$
- 2,4 fold increase in blood loss when BT was $33,8\text{ }^{\circ}\text{C} + 0,5\text{ }^{\circ}\text{C}$ compared to $36,1\text{ }^{\circ}\text{C} + 0,7\text{ }^{\circ}\text{C}$

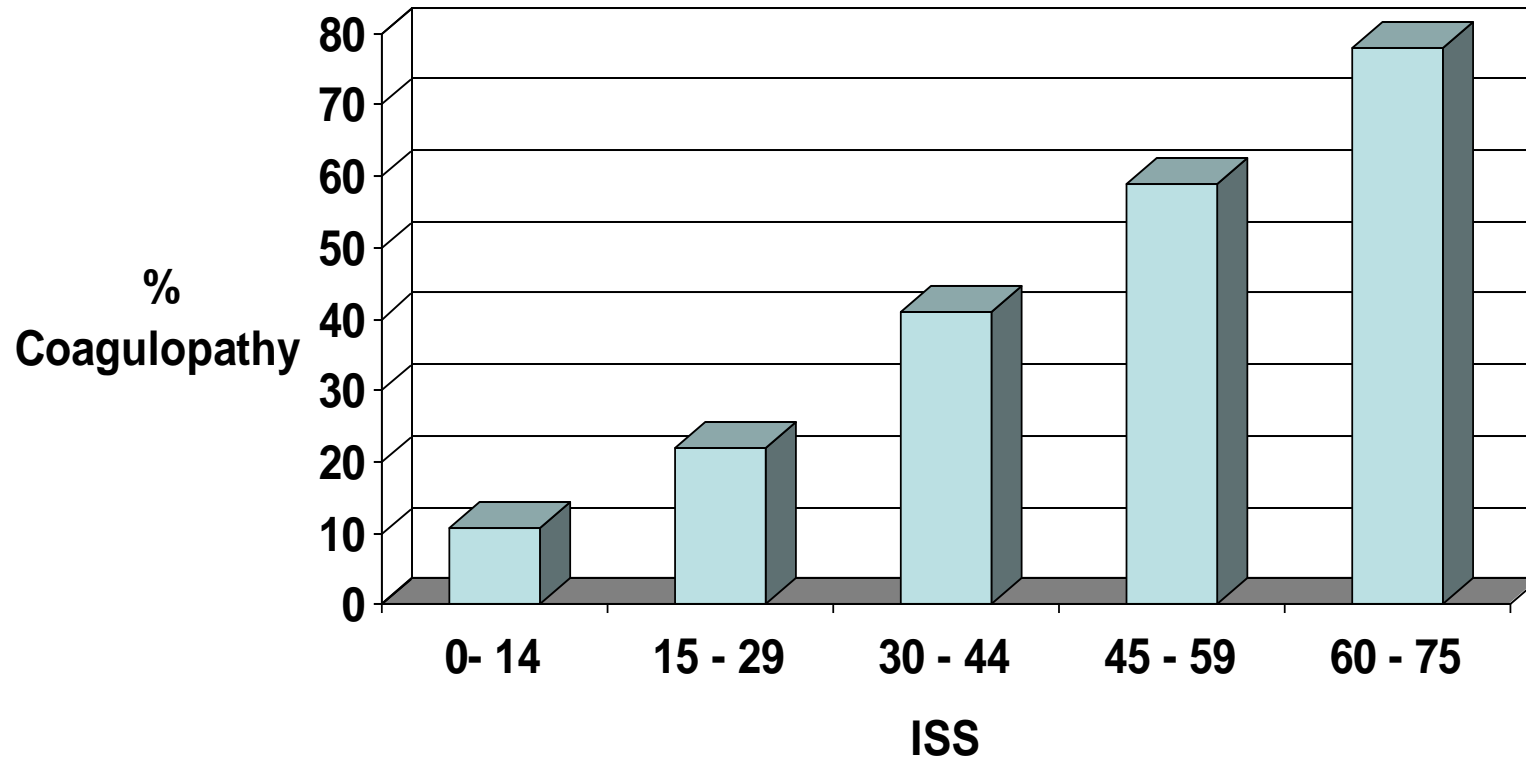
Hypothermia in trauma

- 5% (1921 pts) $\leq 35^{\circ}\text{C}$
- increased mortality
 - for the full cohort
 - (OR 3,03; 95% CI 2,62–3,51)
 - group with brain injury
 - (OR 2,21; CI 1,62–3,03)
- independent
 - age
 - ISS and mechanism of injury
 - route of temperature measurement

The complex coagulopathy in trauma



Severity of coagulopathy correlates with severity of trauma



Brohi K: J. Trauma (2003) 55:1127

(Kaufman CR, J. trauma 1997, Cosgriff N. J. Trauma 1997)

Interpretational considerations

Thrombelastography

- Temperature

- Hypothermia decreased fibrinogen synthesis from the control value of 2.6 ± 0.4 to 1.2 ± 0.2 mg kg⁽⁻¹⁾ h⁽⁻¹⁾ ($P < .05$), with no effect on fibrinogen breakdown.
- Thrombin generation at the initiation phase was delayed by hypothermia, but there were no changes at the propagation phase.
- In thromboelastography measurements, ***the initial clotting time (R time) was prolonged*** from the baseline value of 2.01 ± 0.12 to 4.20 ± 0.24 minutes

The blood bank: from provider to partner in treatment of massively bleeding patients

Pär I. Johansson, Transfusion 2007 Aug. 47:176-181s

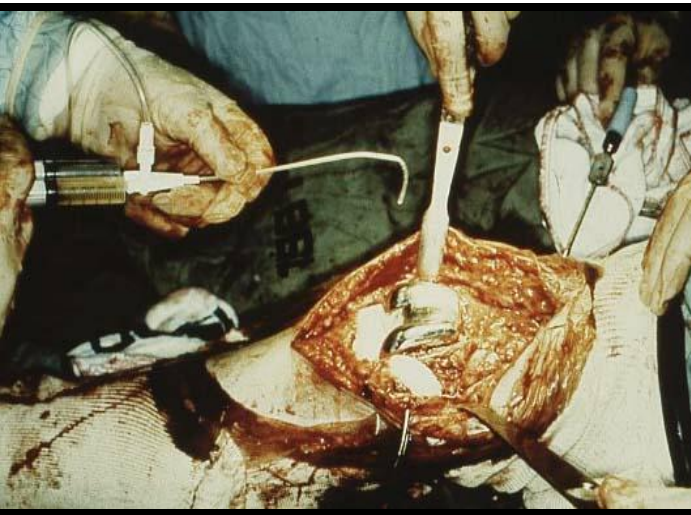
Introduction of central TEG in blood bank for “clinically relevant bleeding” according the clinicians:

- Hyperfibrinolysis as major cause of bleeding 9%
 - Hypocoagulation 26%
 - Hypercoagulation (Short R? artifact?) 45%
 - Not specified (normal?) 20%
-
- 35 patients with continuing post op bleeding- TEG was normal and 34 had redo with identification of surgical bleed

Treatment Of Massive bleeding:

Local hemostatics

Fibrin adhesives



Fibrin bandage



Quick Clot



Chitosan
bandage, Hemcon

Chitosan:

- decreased blood loss
- decreased fluid use
- induced hemostasis
- increased survival



Fibrin foam

High Dose Fibrinogen

- Reverses in vitro dilutional coagulopathy (TEG & EM)
- Controls haemorrhage in dilutional coagulopathy of porcine trauma model
- Reduces haemorrhage and mortality from liver injury in swine with severe thrombocytopenia (30,000) better than platelets .(replacement for platelets?)

Fenger-Eriksen C et al., Br J Anaesth. 2005 Mar;94(3):324-9

Fries D et al., Br J Anaesth. 2005 Aug;95(2):172-7.

Fries D et al., Anesth Analg. 2006 Feb;102(2):347-51.

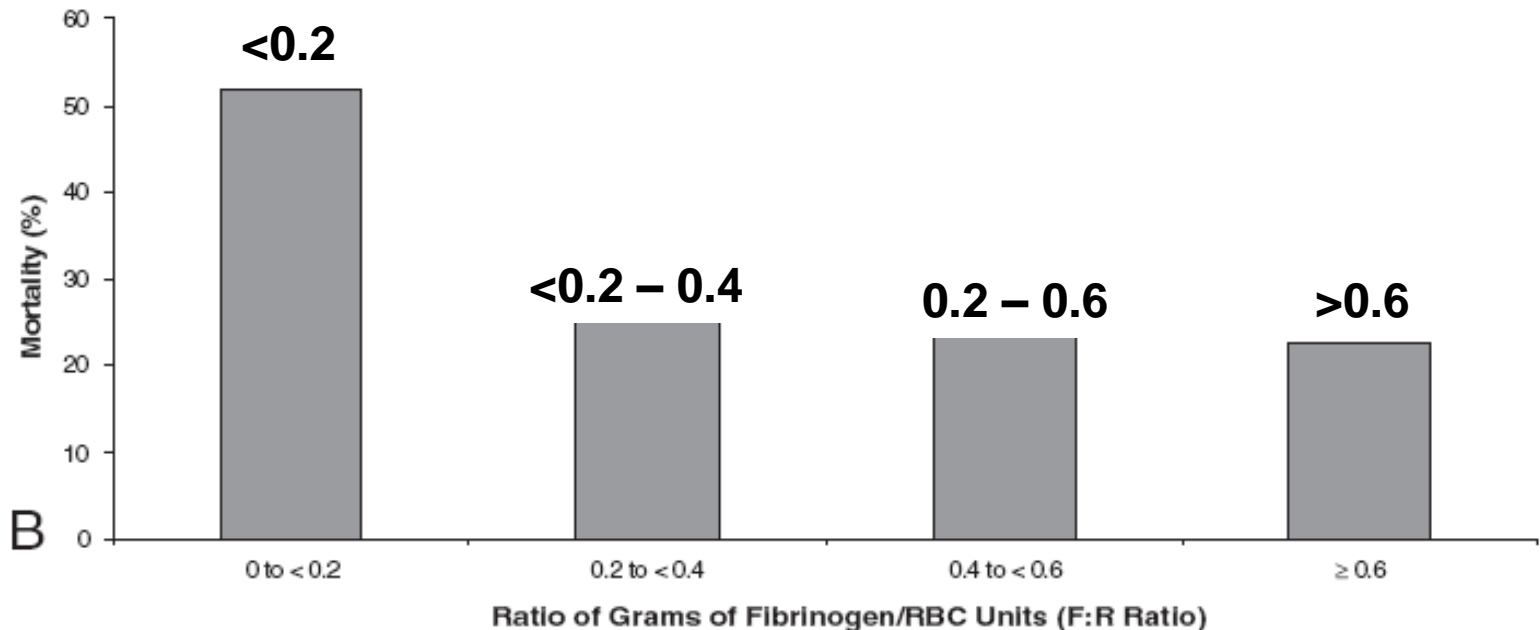
Lang T. et al Hanover University ; Unpublished

Freis D et al JTH 2006 ; Martinowitz U. Unpublished

The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusions at an Army Combat Support Hospital

Harry K. Stinger, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Jose Salinas, PhD, Wenjun Z. Martini, PhD, John R. Hess, MD, Michael A. Dubick, PhD, Clayton D. Simon, MD, Alec C. Beekley, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC

Fibrinogen (g) : transfused red blood cell concentrates



Harry K. Stinger *J Trauma*. 2008;64:S79 –S85

Fibrinogen:

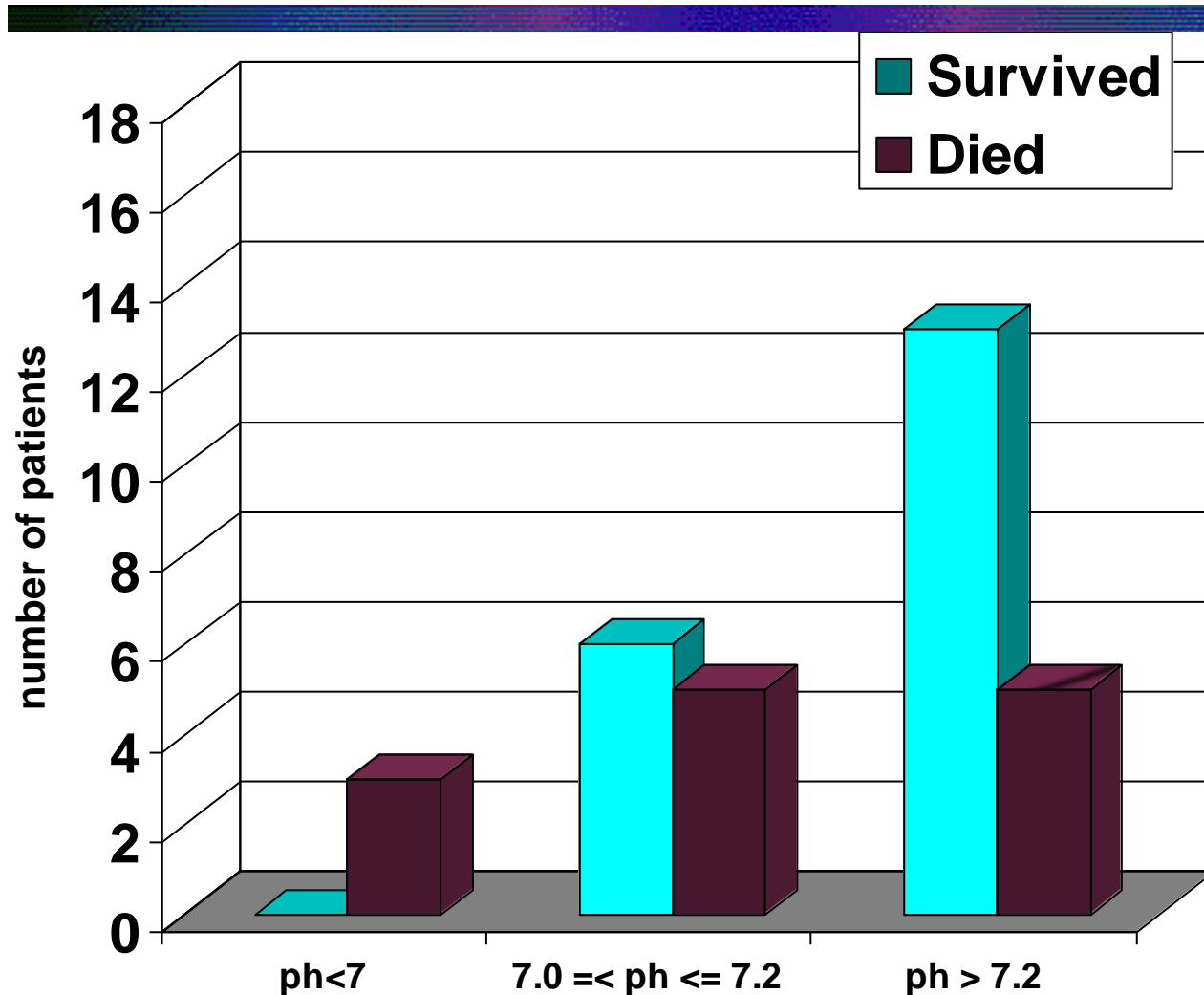
- Traditional trigger for fibrinogen has been <1.0 g/L

Practice Guidelines of ASA ;Anesthesiology July 2006:

- Cryoprecipitate is rarely indicated in concentration $>150\text{mg/d}(1.5\text{gr/L})$
- Usually indicated at concentrations of $0.8-1.0$ g/L when excessive microvascular bleeding continues or in such bleeding when fibrinogen concentration can not be measured

Acidosis and Survival

Overall 22/36 (61%) survived



Chi square test for pH levels in survivors and non-survivors was of borderline significance ($p = 0.06$)

Hypothermia

- ❑ Associated with a significant risk of death in trauma
(100% in temp. below 32 c) *(Danzel DF 1987, Jurkovich GJ 1987, Peng RY 1999)*
- ❑ Slowing of coagulation enzymes *(Krause KR. 2000;; Rohrer MJ. 1992; Patt A. 1988 Wolberg AS 2004 in press)*
- ❑ Impaired PLT function *(Valeri CR 1987. Wolberg AS 2004 in press)*
- ❑ Increased fibrinolysis, endothelial injury *(Kirkpatrick AW. et al. 1999)*

Trauma Patients	* Duke North Carolina (n=44)
PRC	33 14
FFP	9 5
Cryoprecipitate	25 12
Platelets	8 6
Total units	75 22
pH	7.13 0.14
Hb	6.7 2.7
Exsanguinations	13/44 (29.5%)
Other mortality	12/44 (27.2%)
Survival	43%

Transfusion cost per
patient 11,743\$

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

Patients selection

- Indication :Any patient suffering massive, uncontrolled bleeding that hasn't respond to conventional surgical measures and appropriate blood components.
- Contraindication: Unsalvageable patients.
- Relative contraindications: PE,DVT,MI,CVA within 6m. Evaluate Risk/benefit for each patient .
- TBI is not a contraindication

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

Definition of massive hemorrhage

- One blood volume within 24h (10 PC for 70kg patient)
- 50% blood volume within 3h
- Bleeding rate ≥ 150 ml/kg
- Bleeding rate ≥ 1.5 ml/kg/min. ≥ 20 min.

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

Definition of Failure of appropriate treatment

Hemorrhage continues despite:

- All conventional/accessible surgical treatments
- Replacement with: FFP- 5-10 ml/kg (4-6 un For 70 kg)
Cryo.-1-2 un/10kg (10-15 un For 70 kg)
Platelets- 1-2 un/10kg (10-15 un For 70 kg)
- Correction of acidosis (minimum pH > 7.1)
- Warming
- (Fibrinolytic inhibitors?)

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

- Timing for rFVIIa :After $\geq 8-10$ PC
- Preconditions:
Fibrinogen > 50 mg/dl (preferably ≥ 100 mg/dl)
Platelets $> 50,000$ (preferably $\geq 100,000$)
- If the above can not be monitored in real time:
Give replacement therapy before rFVIIa as specified in the "replacement therapy" item.
- Acidosis must be corrected $> \text{pH } 7.1$ before rFVIIa
- Low temperature is not a limiting factor for rFVIIa.
But temp. should be restored to as normal as possible

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

Administration

- Administration of rFVIIa should be combined with surgical hemostasis:
If packing was carried out- consider unpacking just prior to rFVIIa
- Product information (package 1.2;2.4;4.8 mg storage 2-8°C, stability in solution 2-8 °C -24h)
- Initial dose-100mcg/kg iv 2-5 min. (should be 120)
- The arrest of coagulopathic bleeding together with the hemodynamic improvement that follows-may expose surgical bleeding sites. If given outside OR-"second look" should be considered.

The Israeli guidelines for the use of rFVIIa (NovoSeven®) in uncontrolled bleeding

- Repeated doses :The same dose should be repeated if hemostasis is not achieved within 15-20 min. If the response remains inadequate-consider to repeat the replacement therapy +Ca + bicarbonate before the third dose . (up to 5 repeated doses were given)
- Monitoring: No lab. method to monitor the effect. Watch the cessation of hemorrhage and hemodynamic stabilization. Typically-there should be shortening of PT below normal range.

Aging of stored blood :>14-16 days

- RBC aggregation ¹
- Decreased 2,3 DPG ²
- Acidosis
- Increased inflammatory mediators ³
- TRALI ⁴
- Pneumonia ⁵
- Splanchnic ischemia ⁶
- MOF ⁷
- Mortality ^{8,9}

1 Hovav. Transfusion 1999 39(3) 277-81

2 Marik, P.E. JAMA. 1993. **269**(23): p. 3024-9

3 Silliman, C.C. J Lab Clin Med, 1994. **124**(5): p. 684-94

4 Silliman CC.

5 Offner PJ, Arch Surg 2002;137:711-71

6 Marik PE. JAMA. 1993; 269(23): 3024-29

7 Zallen. Am J Surg. 1999; 178:570-72

8 Purdy FR. Can J Anaesth. 1997; 44:1256-61

9 Basran. Anesth Analg, 2006. **103**(1): p. 15-20

5294 Units transfused at 31st CSH :Age at delivery 27 days ,age at transfusion 33 days +/- 6 days

US Army data, Maj. P.C. Spinella

Duration of Red-Cell Storage (>14d) Complications after Cardiac Surgery

CG Koch et al . N Engl J Med 2008;358:1229-39.

Median storage 11 days vs. 20 days (older blood)

- ❖ Higher in-hospital mortality (2.8% vs. 1.7%, $P = 0.004$),
- ❖ Longer intubation beyond 72 hours (9.7% vs. 5.6%, $P < 0.001$),
- ❖ renal failure (2.7% vs. 1.6%, $P = 0.003$),
- ❖ sepsis or septicemia (4.0% vs. 2.8%, $P = 0.01$).
- ❖ More composite complications (25.9% vs. 22.4%, $P = 0.001$).
- ❖ At 1 year, mortality remained significantly less in patients given newer blood (7.4% vs. 11.0%, $P < 0.001$).

Early Versus Late Recombinant Factor VIIa in Combat Trauma Patients Requiring Massive Transfusion

Jeremy G. Perkins, MD, Martin A. Schreiber, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

J Trauma. 2007;62:1095–1101.

Definition :Early<8 units; Late>8 units. (Early 5.7u late 14u p*)

Results: 5,334 patients 90% penetrating, .365 (6.8%) massive transfusion. (>10 units). Of these, 117 (32%) received rFVIIa. 61 complete records: 17 early ,44 late. Equal patients data.

The early rFVIIa group required 20% Less blood during the first 24h (20.6 vs. 25.7, p 0.048)

No difference in: late mortality (33.3% vs. 34.2%,)
ARDS (5.9 vs. 6.8%,),
infection (5.9% vs.9.1%,),
thrombotic events (0%vs. 2.3%)

Component Therapy vs Fresh Whole Blood



1U PRBC + 1U PLT + 1U FFP + 1U Cryo

660 COLD mL

- Hct 29%
- Plt 87K
- Coag activity 65%
- 750 mg fibrinogen
- pH<7

•Armand & Hess, Transfusion Med. Rev., 2003



FWB:

500 mL Warm

Hct: 38-50%

Plt: 150-400K

Coags: 100%

Fibrinogen 1500 mg

pH normal

Liver resection

- 204 non cirrhotic patients randomized for rFVIIa 20,80mcg/kg (1-2 doses) vs. placebo

	placebo	20	80	p
% transfused	41	37	25	0.09
Intraop. bleeding (ml)	1422 1270	1372 1300	1073 990	0.07
intaop. decrease in Ht.	-6.4	-6.7	-3.3	0.04

No difference in blood loss and requirements . Significant overall effect of $p=0.04$. rFVIIa ... **No safety issues**

Lodge

JP, Anesthesiol. 2005

Comment: reduction of 400/1400ml is clinically important ,although it only reached a trend for statistical significance probably due to the large variability in blood loss

Prophylactic administration of rFVIIa in patients with normal coagulation undergoing surgical procedures with high perioperative blood loss

😊 Scoliosis: 26 patients , vs. 26 historical controls:

Significant reduction in blood loss and requirement

Kolban Eur. Spine J. 2005

😞 Surgery for pelvic fracture: Placebo-controlled, 48 patients. No difference in blood loss and requirements

Raobaikady R. Br. J. Anaesth. 2005

😊 No safety issues in all studies

Cardiovascular

- Bleeding reduced from 640ml/h to 100ml/h

Halkos ME. Ann. Thor. Surg. 2005

- Randomized, 20 patients.

8/10 placebo required 105 blood units while
2/10 rFVIIa required 13 units p*

Diprose B.J. Anest. 2005

- Cardiovascular: Last resource use of rFVIIa in 24 pt. vs. historical controls-not effective

Von Heymann crit care med 2005

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Kathryn A. O'Connell, MD, PhD

Jennifer J. Wood, PhD, MPH

Context The US Food and Drug Administration (FDA) licensed recombinant human coagulation factor VIIa (rFVIIa) on March 25, 1999, for bleeding in patients with he-

- Spontaneous and company reported SAE to FDA over 5 years -185 thromboembolic events
- Weakness of report: Lamp of cases . Incidence? benefit /risk ratio? Misleading. The right perspective: Over 10,000,000 uses during this period (company report) mostly in patients with high risk of thromboembolism.

Probable right atrial thrombus immediately after rFVIIa...

Pang G, Donaldson A. Br J Anaesth. 2007 May 23; [Epub ahead of print]

Hematoma Size is the most important predictor for patient outcome in ICH

Broderick, et al, *Stroke*. 1993;24:987]



- mortality of 'ping pong' size hematoma :
app. **40%**
- Mortality on 'golf ball' size hematoma:
app. **70%**

rFVIIa for Liver Transplantation

182 pts: placebo vs. 60 vs. 120ug/kg multiple doses(q2 during surgery).No effect on blood loss/ requirements.

Lodge JP, Liver transpl.2005

83 pts: placebo vs. 20 ,40, 80ug/kg :rFVIIa did not reduce blood loss ; Planiinsic RM ,Liver transp.2005

Conclusion :r FVIIa does not decrease blood loss or blood requirements in OTL .No safety issues.

😊 28 high risk patients treated with single dose rFVIIa vs. 61 low risk patients (control): No difference in blood loss and requirements. Can rFVIIa converts high risk patients to low risk?

Kalicinski P. Pediatr. Transpl. 2005

Can rFVIIa reduce bleeding if combined with hypotensive resuscitation? Will it decrease bleeding in high risk patients?

Prophylactic administration of rFVIIa in patients with normal coagulation undergoing surgical procedures with high perioperative blood loss

☺ TUP: Placebo-controlled, 36 patients .Significant decreased blood loss and transfusions in 40 ug/kg group.

Friederich. Lancet. 2003

☺ Partial Hepatectomy: Placebo-controlled ,204 patients .Trend towards decrease transfusions in 80 ug/kg group (40% reduction)

Lodge. Anesthes. 2005

☺ Cardiac surgery: Placebo-controlled ,20 patients. Significant decreased blood requirements

8/10 placebo vs. 2/10 rFVIIa patients required 105 vs. 13 blood units ,

Diprose B.J. Anest. 2005

rFVIIa: UGI Bleeding in Cirrhosis

RCT: 245 pts, placebo vs 100ug/kg q3, 8 doses, All pts received endoscopic and supportive care

	rVIIa (121)	Placebo (121)	P-value
hemostasis	86%	84%	P=0.72
Death d 5	6%	3%	P=0.38
Death d 42	14%	9%	P=0.31

Conclusions: No safety issues. Although no overall effect of rFVIIa ,exploratory analyses in Childs Class B/C cirrhotic patients showed decrease in number who failed to control variceal bleeding.

Bosch et al. Gastroenterology. 2004; 127: 1123.

Comments: Inappropriate indication? Should be given only to gain time before transplantation?

Aging of stored blood :>14-16 days

- RBC aggregation ¹
- Decreased 2,3 DPG ²
- Acidosis
- Increased inflammatory mediators ³
- TRALI ⁴
- Pneumonia ⁵
- Splanchnic ischemia ⁶
- MOF ⁷
- Mortality ^{8,9}

1 Hovav. Transfusion 1999 39(3) 277-81

2 Marik, P.E. JAMA. 1993. **269**(23): p. 3024-9

3 Silliman, C.C. J Lab Clin Med, 1994. **124**(5): p. 684-94

4 Silliman CC.

5 Offner PJ, Arch Surg 2002;137:711-71

6 Marik PE. JAMA. 1993; 269(23): 3024-29

7 Zallen. Am J Surg. 1999; 178:570-72

8 Purdy FR. Can J Anaesth. 1997; 44:1256-61

9 Basran. Anesth Analg, 2006. **103**(1): p. 15-20

Primary Analysis

Conclusions



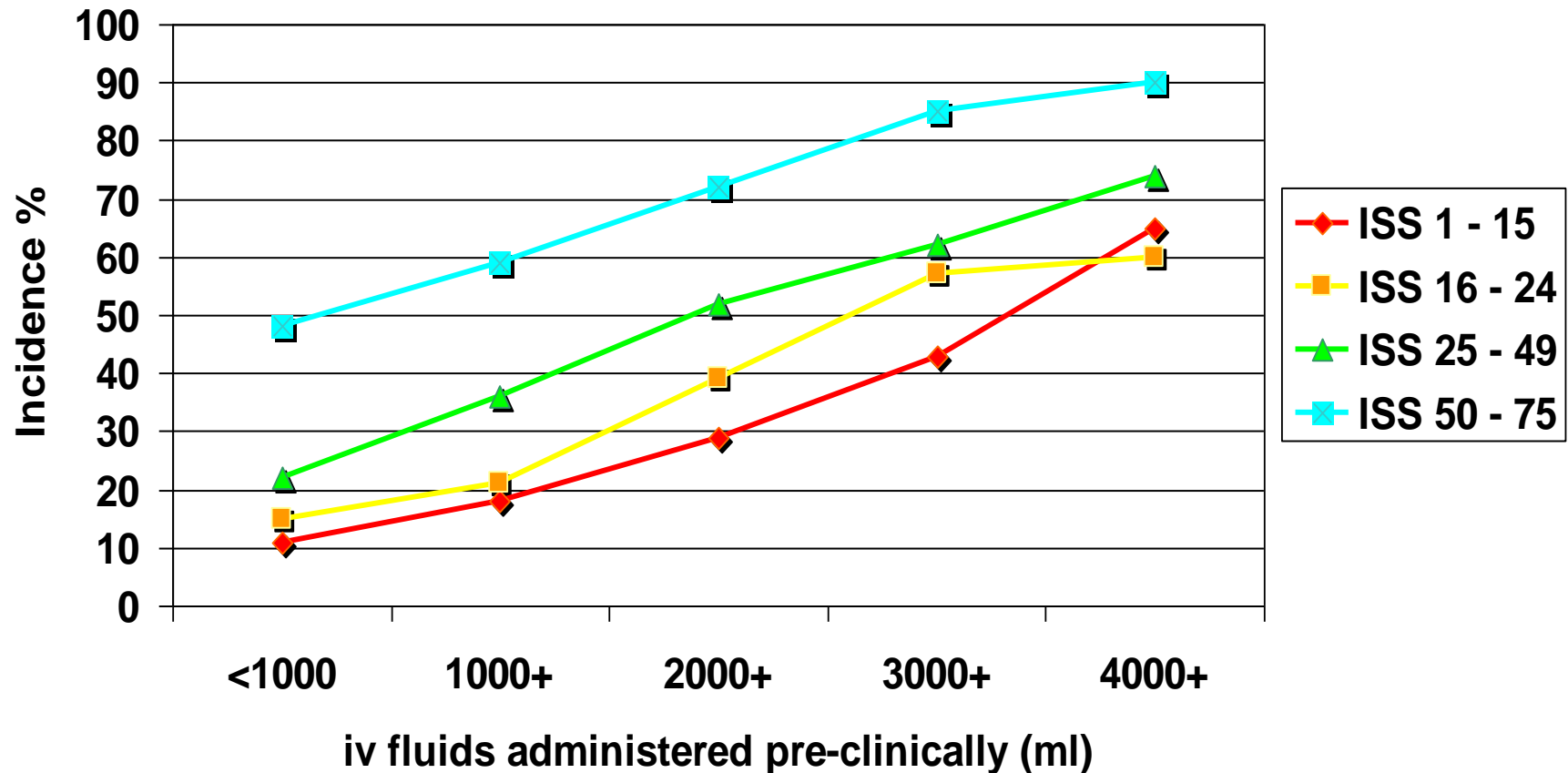
- **Significant dose-related reduction in hematoma growth**
 - Earlier treatment results in less growth
 - Confirms phase 2 data
- **No effect on clinical endpoints identified as primary (mRS) or secondary (mortality) at 90 days**
 - Imbalances in baseline disease severity noted
- **Safety profile consistent with phase 2b data**
 - Small increase in cerebral and myocardial ischemic events
 - No difference in the frequency of DVT or PE

US Army Hemostatic Resuscitation Clinical Practice Guidelines:

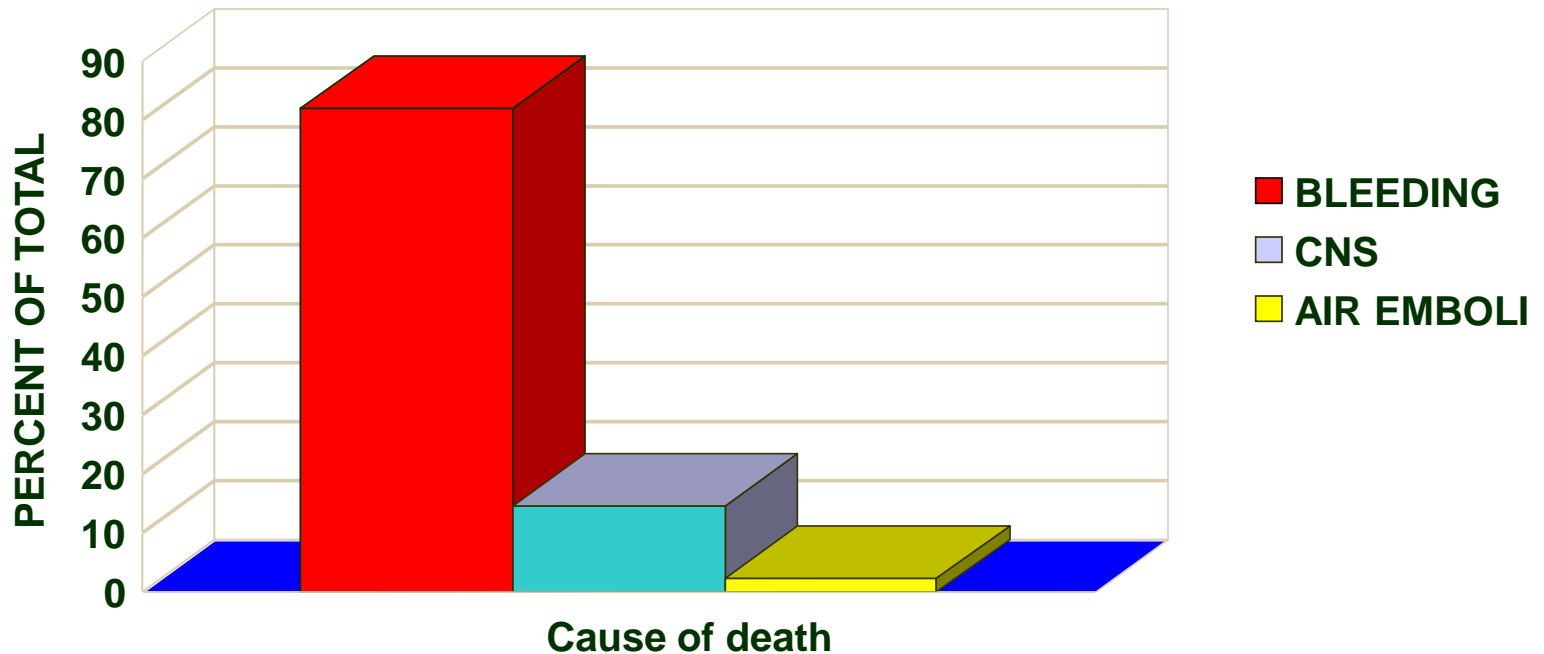
Identify patients at risk for massive transfusion early

- 5 triggers to identify this patient category
- **Temp < 96**
- **SBP < 90**
- **Hb < 11**
- **Base deficit > 6**
- **INR > 1.5**

Hemodilution :Incidence of coagulopathy acording to ISS and pre hospital fluids

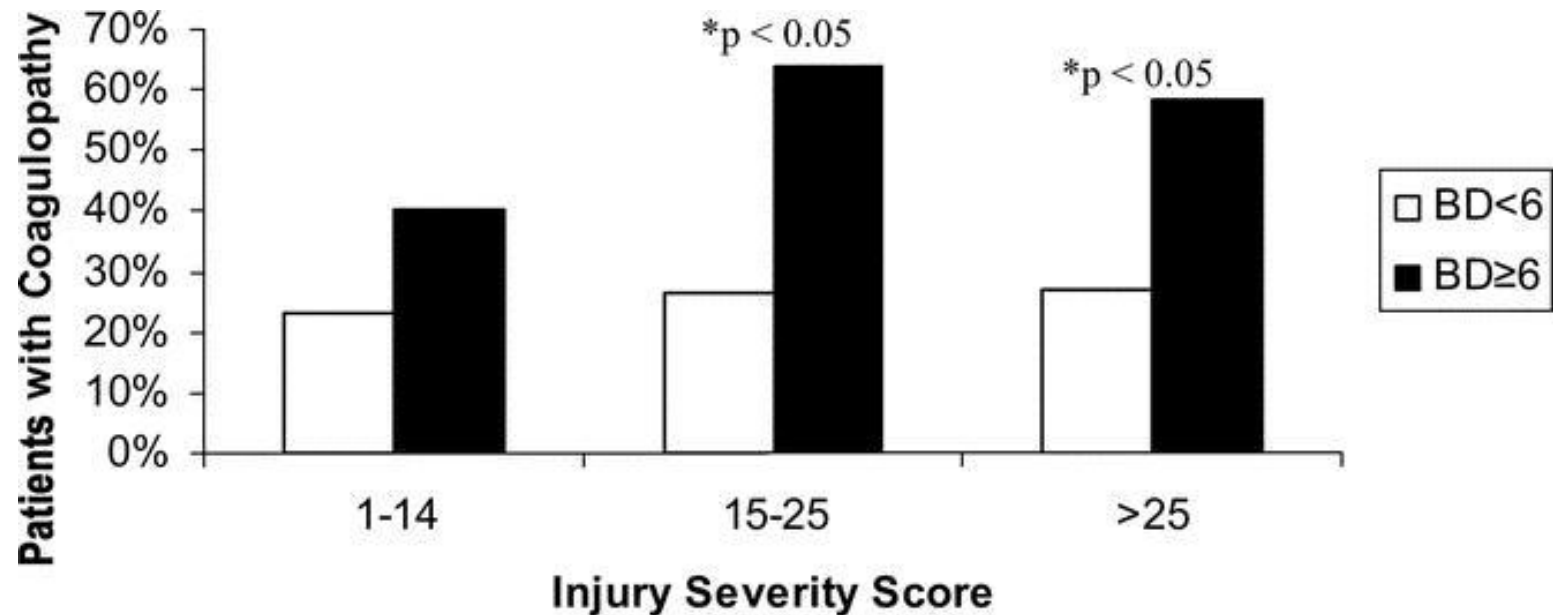


Death among civilian trauma patients in the operating Room

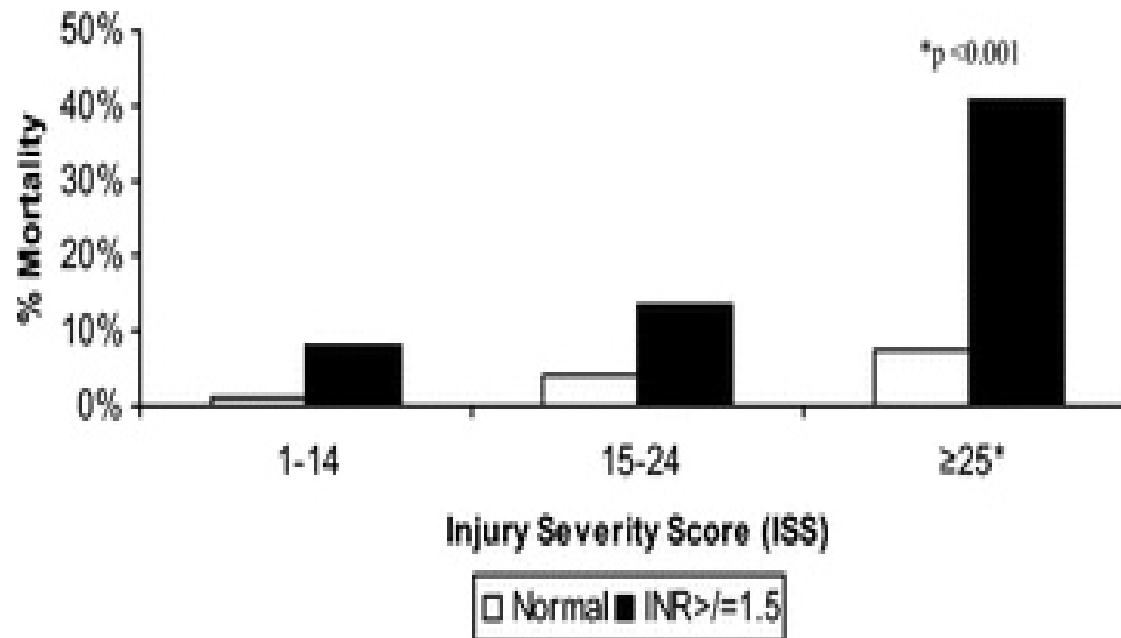


Hoyt DB et al. J Trauma. 1994;37:426–432.

Prevalence of coagulopathy by ISS and BD

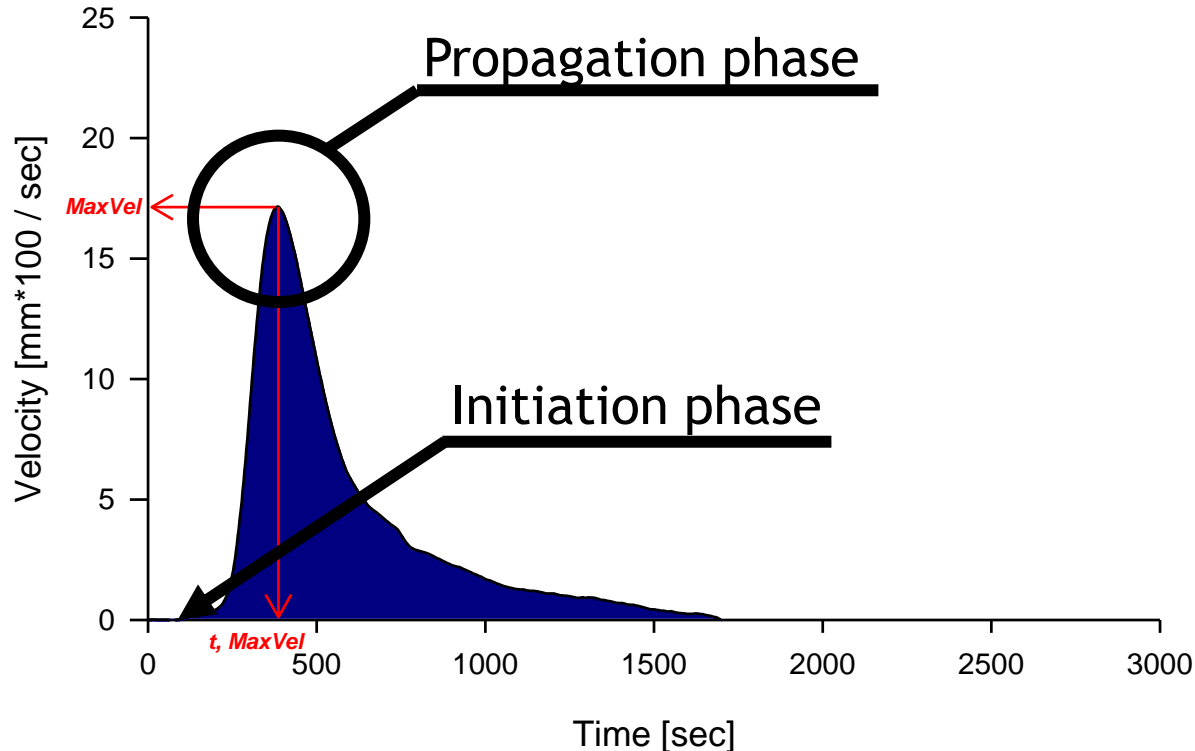


Coagulopathy across ISS categories increases the risk of mortality in combat casualties



Rotem/TEG -Continuous whole blood coagulation test -Thrombelastography

Velocity Profile



The Effect of Recombinant Activated Factor VII on Mortality in Combat-Related Casualties With Severe Trauma and Massive Transfusion

J Trauma. 2008;64:286 –294.

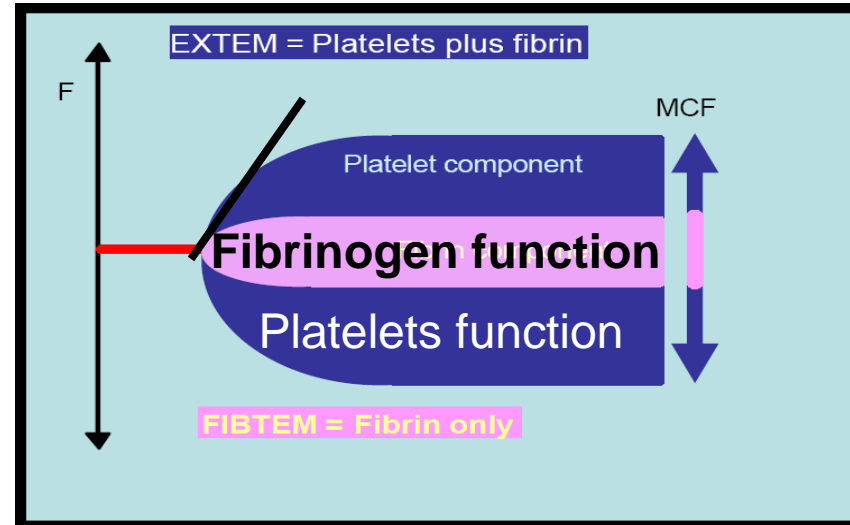
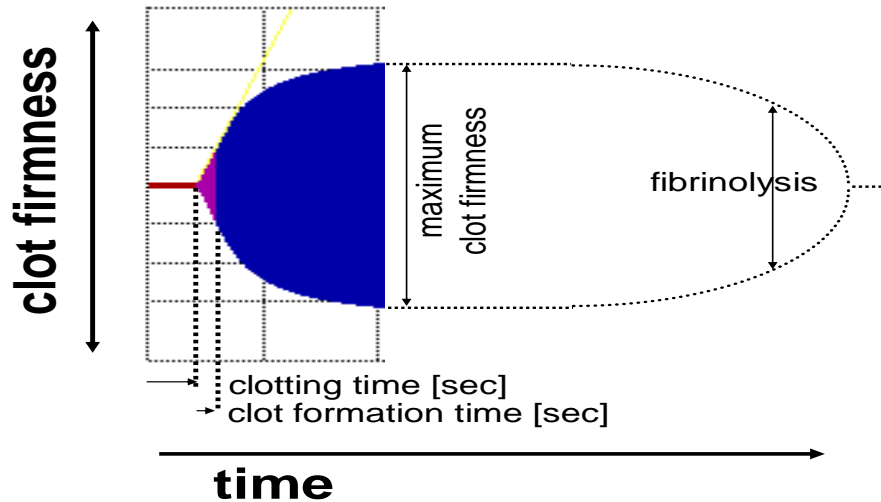
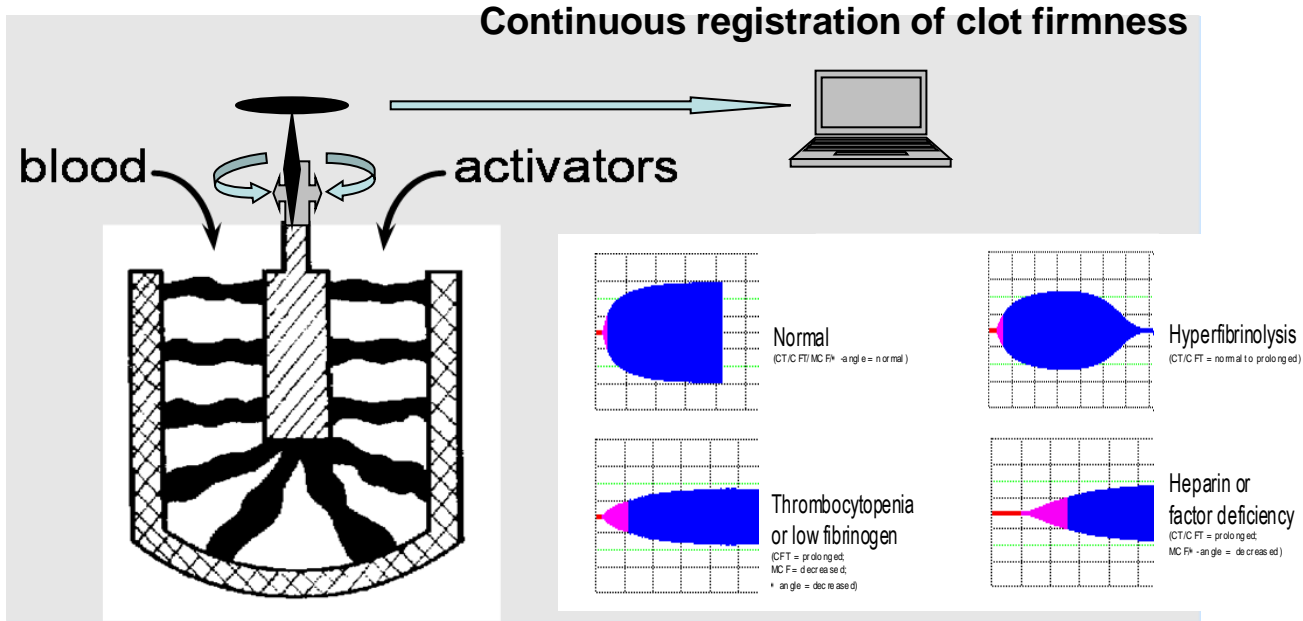
Philip C. Spinella, MD, Jeremy G. Perkins, MD, Daniel F. McLaughlin, MD, Sarah E. Niles, MD, MPH, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, Jose Salinas, PhD, Sumeru Mehta, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Retrospective review of combat casualty patients with:

- Severe trauma (**ISS >15**)
- Massive transfusion: **RBCs >10** units/24h
- Admitted to combat support hospital in Baghdad, December 2003 to October 2005.

Comparison between patients who received rFVIIa and did not receive rFVIIa

Thromboelastography -real time clot analysis



sequence of critical of clotting factor concentrations :

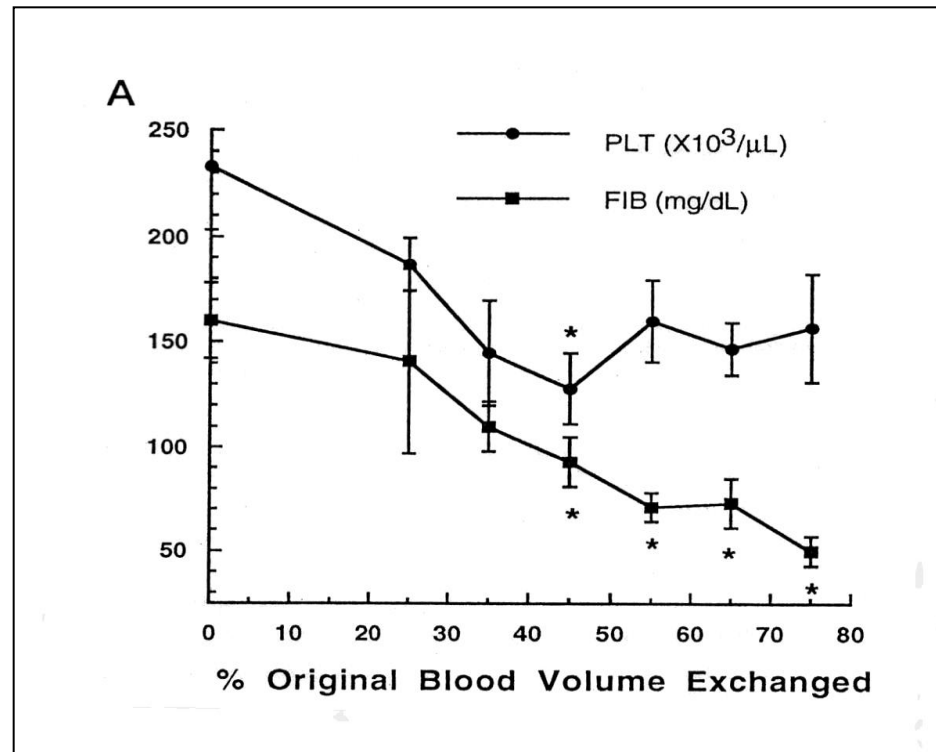
1. Fibrinogen (<1g/L)
2. Prothrombin (20%)
3. Factor V (25%)
4. Factor VII (20%)
5. Platelets (50.000)

Urologic and abdominal surgical interventions (n=60) with an estimated blood loss of $\geq 20\%$ of the total blood volume

Increased bleeding tendency: administration of FFP and platelets

Regression analysis with log. transformation

Fibrinogen (FIB) and platelets (PLT) in patients, undergoing normovolemic hemodilution during huge spine surgery



McLoughlin TM et al. Anesth&Analg 1996

risk 6.4-fold increased :

Gerlach 2002 Factor XIII < 60%

risk 12-fold increased :

additional fibrinogen level < 1.5g/L

risk 9.0-fold increased :

platelets < 150x10⁹/L and F XIII < 60%

... to develop bleeding complication ...

Variable	Preoperative		Postoperative		95% CI	
	No Hematoma	Hematoma	No Hematoma	Hematoma	Preoperative	Postoperative
Factor XIII, %	113.7±27.3	97.89±25.0*	93.5±24.4	71.4±20.6†	7.03/24.5	14.2/29.8
Fibrinogen, g/L	3.43±1.17	2.92±1.22*	2.53±0.99	2.07±0.93†	0.12/0.91	0.14/0.78
Platelet count, ×10 ⁹ /L	241.9±76.2	222.4±79.8	185.6±68.3	150.5±53.7†	-6.0/44.98	12.7/57.5
PT, %	95.3±45.1	91.2±19.5	76.4±12.6	71.7±11.6‡	-10.3/18.56	0.59/8.8
PTT, s	33.2±6.6	33.1±7.6	37.5±15.4	37.1±9.1	2.26/2.26	-4.45/5.30

* $P < 0.01$ vs no hematoma (preoperative).

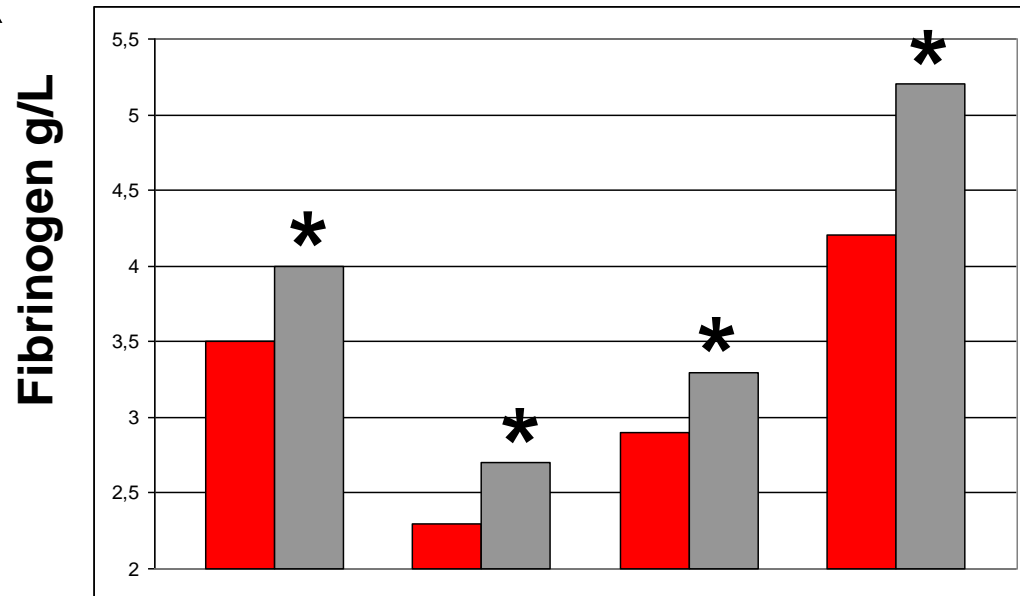
† $P < 0.01$ vs no hematoma (postoperative).

‡ $P < 0.05$ vs no hematoma (postoperative).

Relationship between FXIIIa, fibrinogen and postoperative bleeding in CABG

Blomee M et al. Thromb Haemost 2005

- blood loss during and after CABG n = 98 ;no difference in FXIIIa

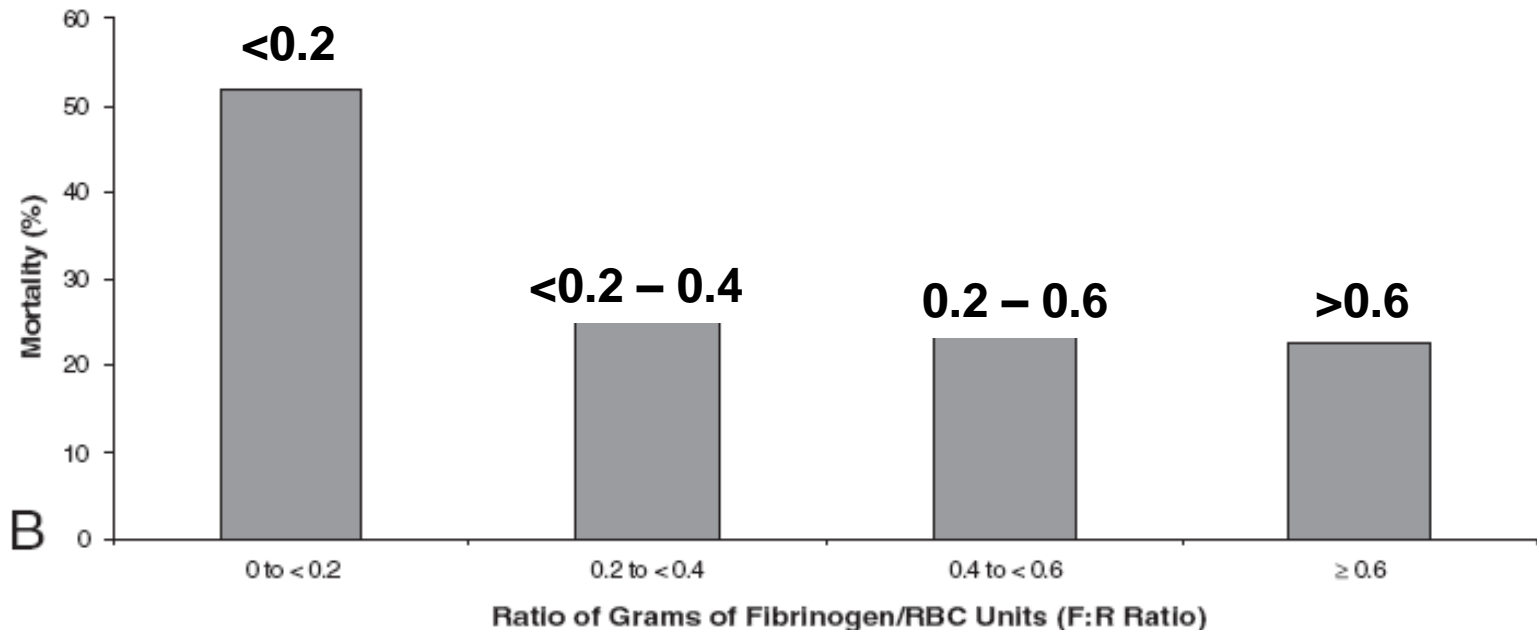


The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusions at an Army Combat Support Hospital

Harry K. Stinger, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Jose Salinas, PhD, Wenjun Z. Martini, PhD, John R. Hess, MD, Michael A. Dubick, PhD, Clayton D. Simon, MD, Alec C. Beekley, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC

Retrospective analysis including about 250 patients undergoing massive transfusion

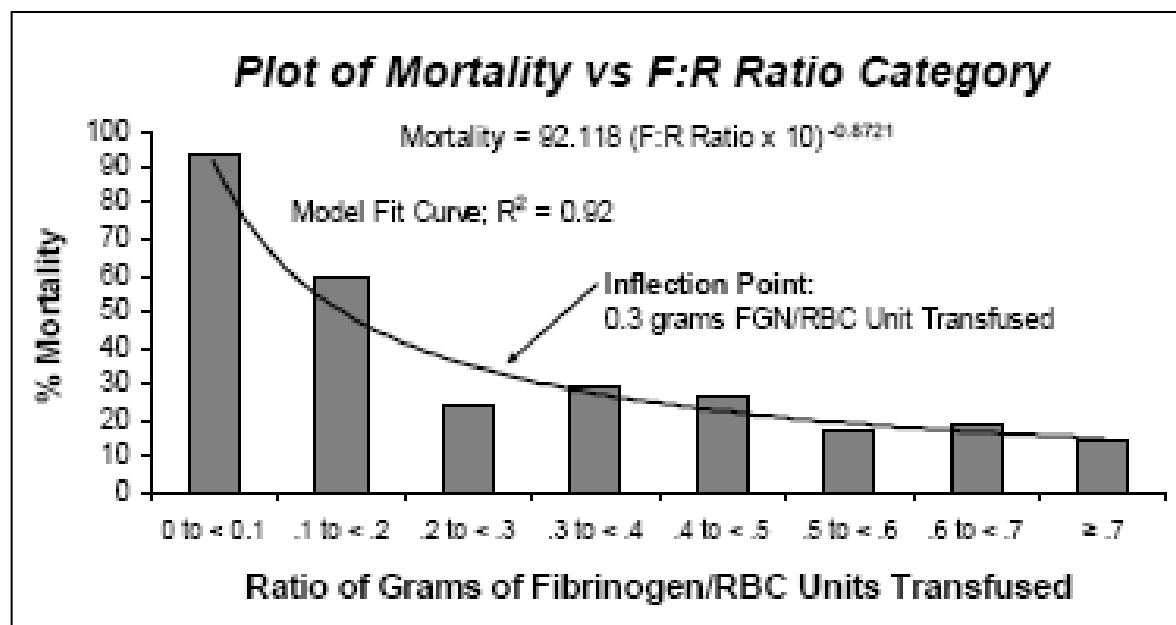
Fibrinogen (g) : transfused red blood cell concentrates



Early Fibrinogen Reduces Mortality in Combat Casualties Requiring Massive Transfusion

Harry K. Stinger, MD¹, Jeremy G. Perkins, MD², Philip C. Spinella, MD³, Jose Salinas, PhD⁴, Wenjun Z. Martini, PhD⁴, Clayton D. Simon, MD¹, John R. Hess, MD⁵, Dietmar Fries, MD⁶, Kurt W. Grathwohl, MD¹, Michael A. Dubick, PhD⁴, Steven E. Wolf, MD⁴, Charles E. Wade, PhD⁴, John B. Holcomb, MD⁴

Retrospective data analysis a time period of about 3 years including more than 450 combat casualties



publication in process

update

Effect of Hct on platelet deposition on damaged arterial segments

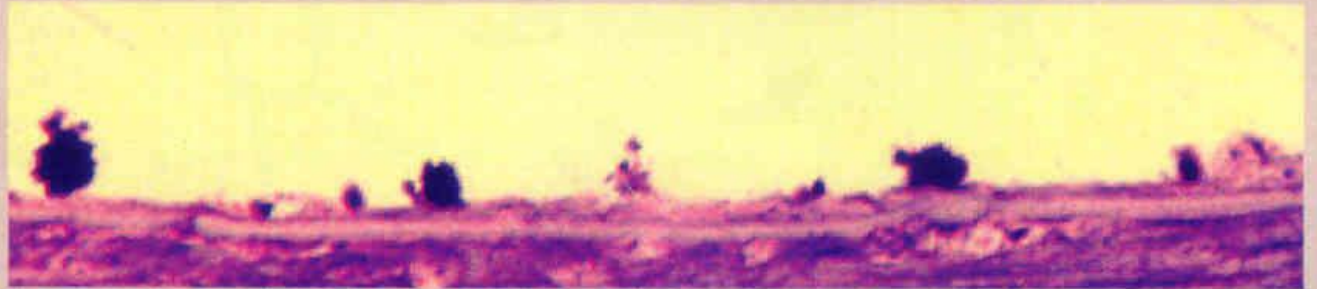
Normal



Anemia

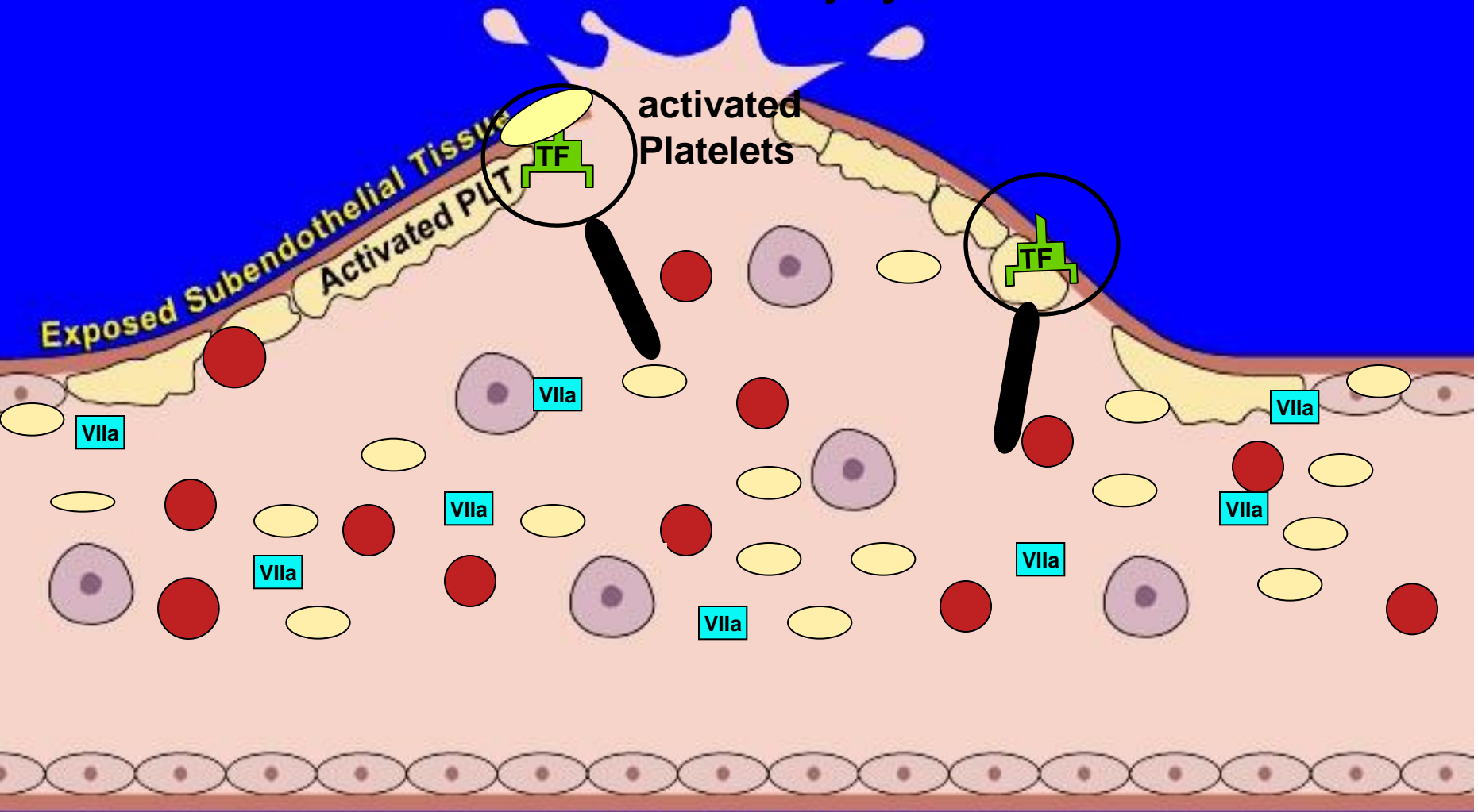


Anemia +
thrombocytopenia



Injury site specific hemostatic agents

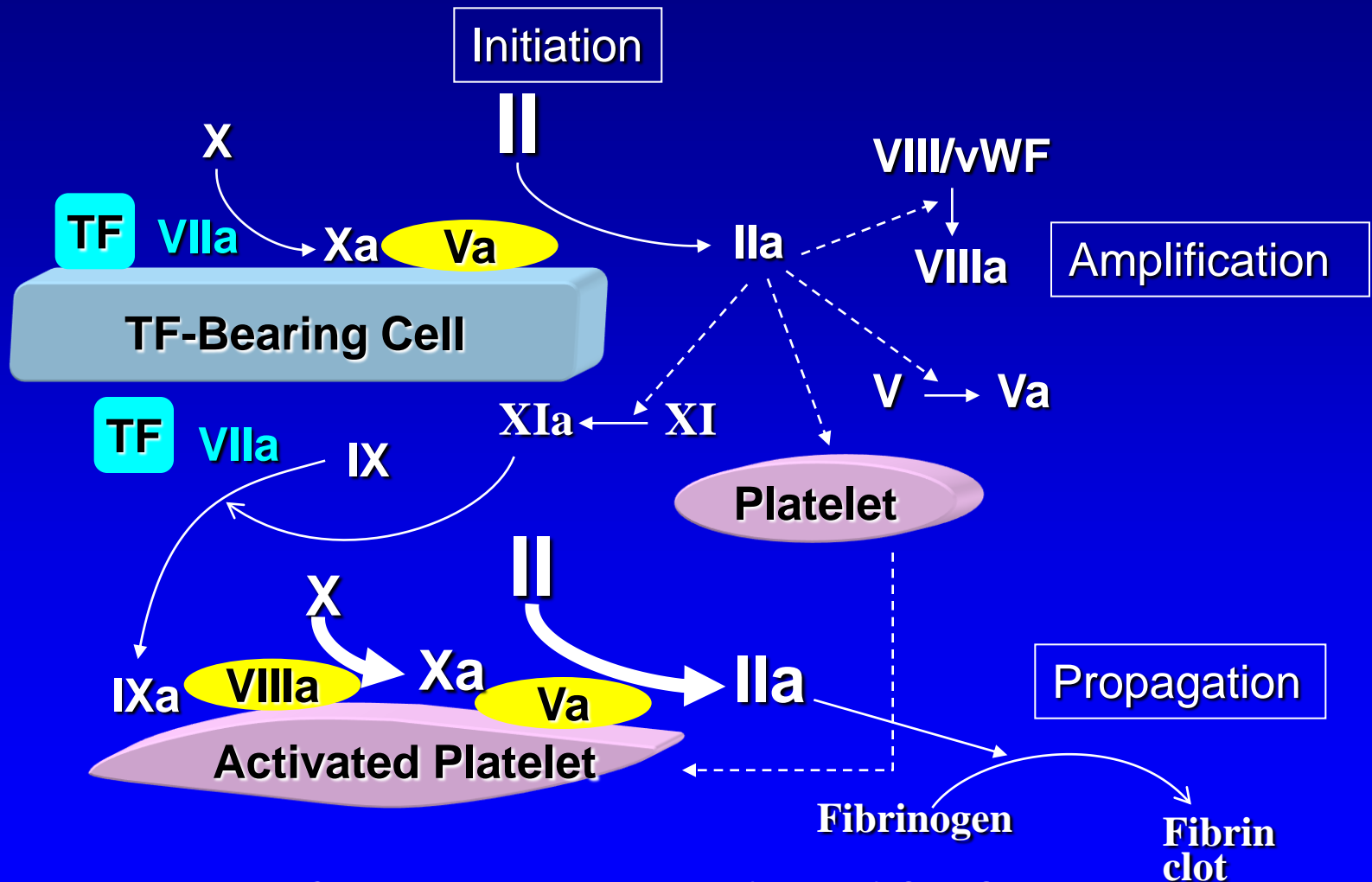
Site of Vascular Injury



Routine coagulation assays do not reflect the in vivo coagulation occurring on cell membranes

Uri Martinowitz

A Cell-Based Model of Normal Hemostasis: Hemostasis Takes Place on Two Cell Surfaces: TF-Bearing Cells and Platelets

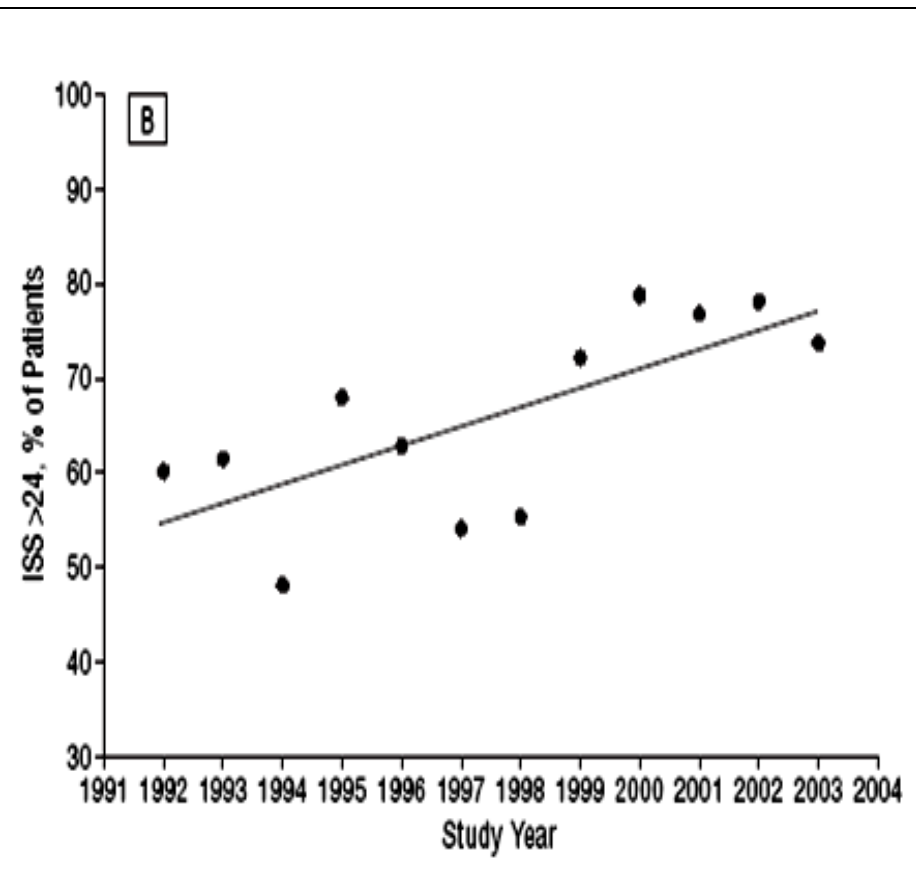


Hoffman M, et al. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S61-S65.

Increase in the severity of trauma patients

Severity of civilian multi-trauma patients

Multi-dimensional trauma victims of urban terror



The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage.

Charbit et al. J Thromb Haemost 2007

OBJECTIVE:

... to determine whether changes in hemostasis during the course of PPH are predictive ...

CONCLUSION:

FI was the only marker to predict **severe bleeding in PPH** ...

positive predictive value of **FI < 2g/L: 100%**

negative predictive value of **FI > 4g/L: 76%**

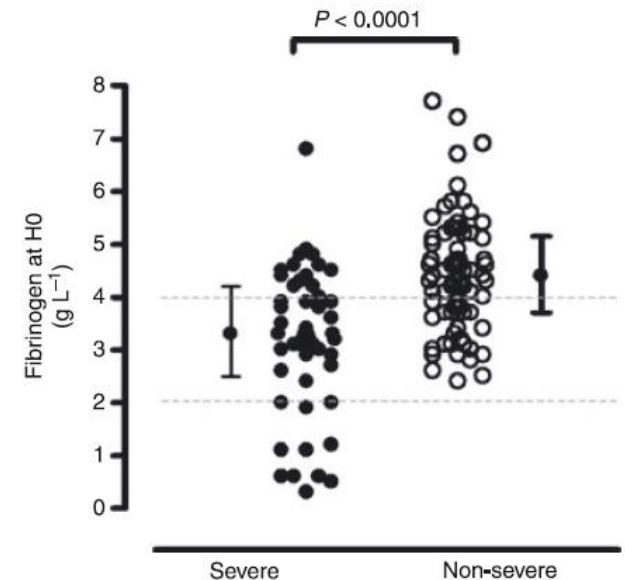


Fig. 2. Individual fibrinogen plasma concentrations at H0 in women with severe (●) or non-severe (○) postpartum hemorrhage. Mean \pm SD values are reported for both groups.