Department of Surgery
Grand Rounds / RSS Session
University of Colorado Denver School of Medicine

Presenter Financial Disclosure

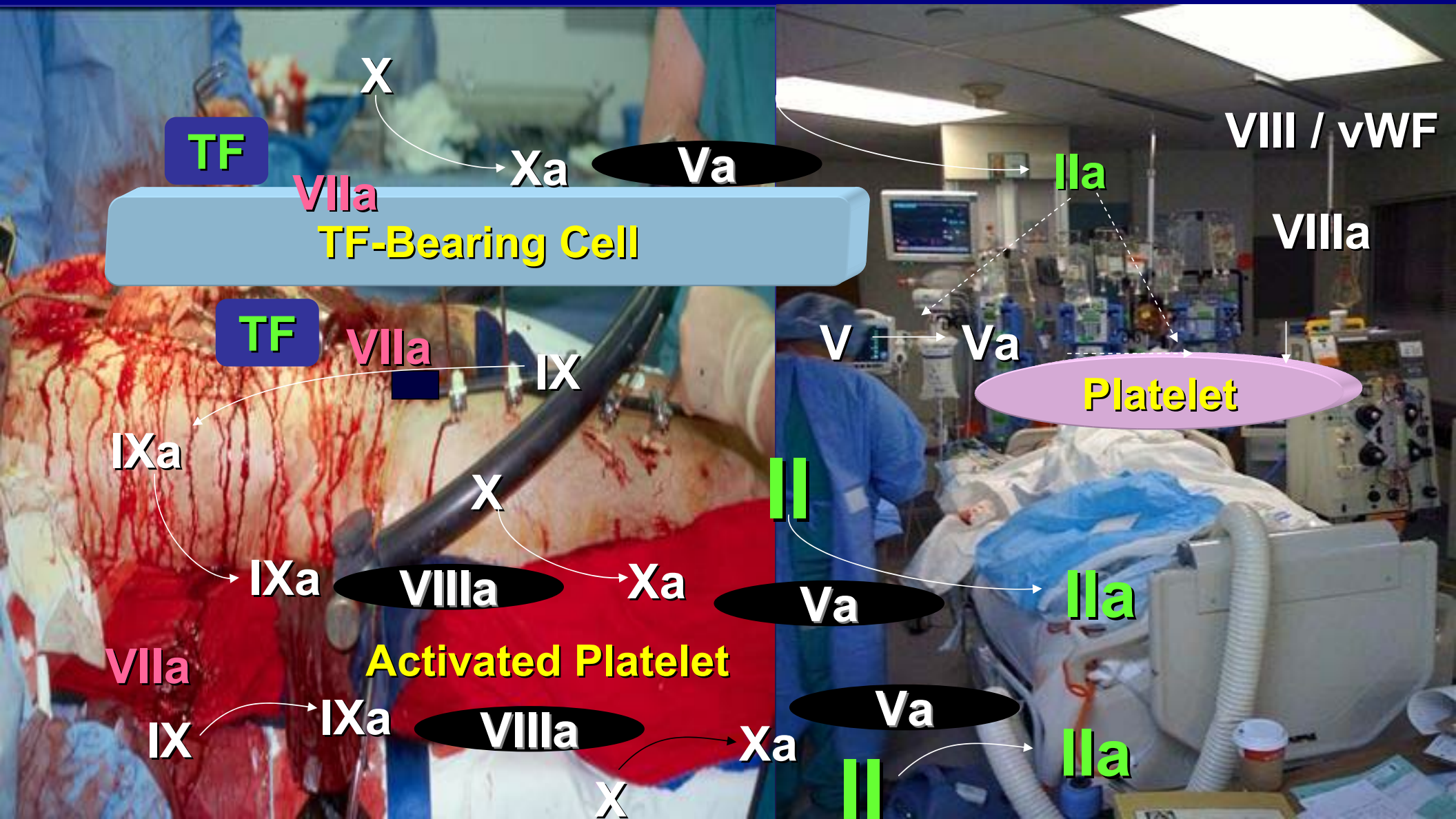
Ernest E Moore, MD
Bruce M Rockwell Distinguished Chair of Trauma
Denver Health Medical Center
Professor and Vice Chairman of Surgery
University of Colorado Denver

"Controversies in Postinjury Hemostasis"

I do not have any relevant financial relationships with any commercial interests to report.

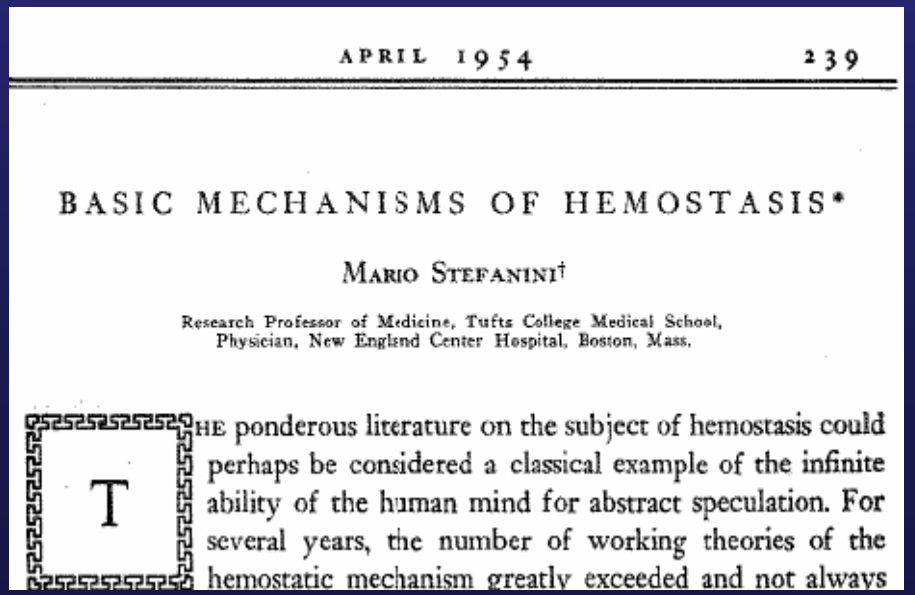
I do not intend to reference off-label/unapproved uses of products or devices in this presentation.

Controversies in Postinjury Hemostasis



" Orderly Ignorance to Confused Enlightenment "

The ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanism greatly exceeded and not always respected the confirmed experimental facts. In recent years, however, the revived interest in this field has led to an accumulation of new findings which has been almost too rapid for their orderly incorporation into a logical working pattern. As a result, we have rapidly gone from a state of "orderly ignorance" to one of "confused enlightenment."



APRIL 1954 239

BASIC MECHANISMS OF HEMOSTASIS*

MARIO STEFANINI†

Research Professor of Medicine, Tufts College Medical School,
Physician, New England Center Hospital, Boston, Mass.

THE ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanism greatly exceeded and not always

Postinjury Hemostasis : Controversies

1. **Acute Coagulopathy of Trauma**
   - Endothelial TM + Thrombin = Activated PC
   - Tissue Factor / Thrombin = DIC + Fibrinolysis

2. **Pre-emptive Blood Components**
   - ? PLT : FFP : RBC

3. **Goal Directed Therapy**
   - ? Coagulation Assessment

Qualitative Platelet Dysfunction : ? PLT Transfusion

> 10 U WB		Stefanini, et al	Clin Res Proc	1954
	Korea	Scott, et al	Blood	1954
> 20 U WB	Vietnam	Miller, et al	Ann Surg	1971
> 15 U MWB		Counts, et al	Ann Surg	1979

Fatal Hepatic Hemorrhage After Trauma

Steven C. Elerding MD, Ernest E. Moore, MD and G. E. Aragon MD

The characteristic picture was uncontrollable hepatic hemorrhage and diffuse bleeding from all exposed surfaces. Only 11 patients (39%) received fresh frozen plasma. In only eight patients (29%) were arterial blood gases measured; the average pH was 7.11. Core temperature was obtained in only six patients (21 percent); the average temperature was 32.2°C.

Am J Surg 1979; 138: 883-8.

ACIDOSIS-INDUCED COAGULOPATHY

Ernest L. Dunn, MD, Ernest E. Moore, MD, Diane J. Breslich, MD, and William B. Galloway, MD

Thirteen adult mongrel dogs (15-20 kg) were anesthetized with pentobarbital (25 mg/kg) and placed in a volume respirator. Thermodilution cardiac outputs, pulmonary artery pressures, and systemic arterial pressures were recorded hourly. Metabolic acidosis was induced by slowly infusing sterile 0.15N hydrochloric acid into the inferior vena cava over 4 hours.

Surg Forum 1979; 30:471-3.

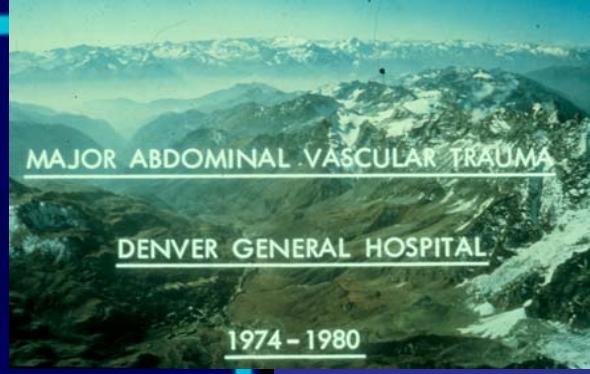
Hypothermia-Induced Coagulopathy

David Bar-Or, MD, Ernest E Moore, MD, John A Marx, MD, and Jim T Good, MD

At lower body temperatures a bleeding diathesis is observed. This phenomenon was studied in 8 adult mongrel dog who were anesthetized and mechanically ventilated. Hypothermia was induced by surface cooling (submersion in ice water) and coagulation studies were performed at 37, 34, 32, 30 and 28°C.

"THE BLOODY VICIOUS CYCLE"

Major Abdominal Vascular Trauma



Hemorrhage

Cellular Shock

Acidosis

Hypothermia

Coagulopathy

AAST 1981
J. Trauma 1982

Presumptive Fresh Frozen Plasma

0022-5282/82/2208-0672$02.00/0
THE JOURNAL OF TRAUMA

Vol. 22, No. 8
Printed in U.S.A.

Major Abdominal Vascular Trauma—A Unified Approach

JEFFRY L. KASHUK, M.D., ERNEST E. MOORE, M.D., J. SCOTT MILLIKAN, M.D., AND JOHN B. MOORE, M.D.

Although coagulation studies were often poorly documented, indirect evidence of inadequate factor replacement was obtained by calculating the ratio of bank blood to unit of fresh frozen plasma (FFP) given. A consistent deviation from the commonly accepted ratio of 4–5:1 was evident, increasing to 8:1 in nonsurvivors and 9:1 in those where an overt coagulopathy was documented.

factor replacement is certainly involved. We believe fresh frozen plasma should be administered with the first four units of bank blood in the hypotensive patient, as well as

J Trauma 1982

Staged Laparotomy : Global Objective

"Abort laparotomy … establish intra-abdominal pack tamponade … complete the surgical procedure once coagulation has returned to an acceptable level."

H H Stone et al
Ann Surg 1983

Damage Control Surgery : Patient Selection

0022-5282/82/2208-0672$02.00/0
THE JOURNAL OF TRAUMA
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Vol. 22, No. 8
Printed in U.S.A.

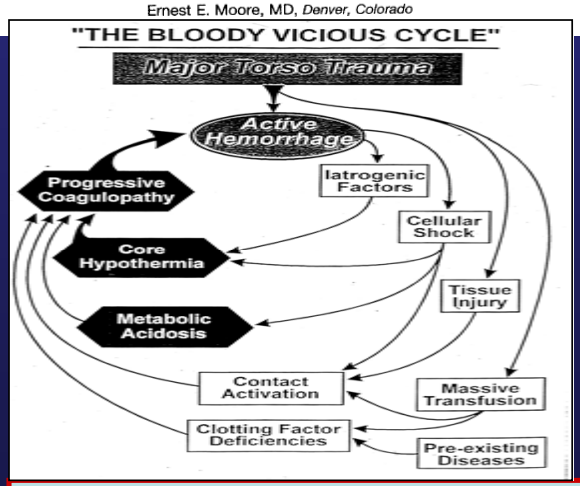
Major Abdominal Vascular Trauma—A Unified Approach

JEFFRY L. KASHUK, M.D., ERNEST E. MOORE, M.D., J. SCOTT MILLIKAN, M.D., AND JOHN B. MOORE, M.D.

Hypothermia, Acidosis, and Coagulopathy

Staged Laparotomy for the Hypothermia, Acidosis, and Coagulopathy Syndrome

Ernest E. Moore, MD, *Denver, Colorado*



Tissue Injury and Cellular Shock

1079-6061/97/4205-0857$03.0000
The Journal of Trauma: Injury, Infection, and Critical Care
Copyright © 1997 by Williams & Wilkins
Vol. 42, No. 5
Printed in the U.S.A.

Predicting Life-Threatening Coagulopathy in the Massively Transfused Trauma Patient: Hypothermia and Acidoses Revisited

Ned Cosgriff, MD, Ernest E. Moore, MD, Angela Sauaia, MD, Mary Kenny-Moynihan, MD, Jon M. Burch, MD, and Ben Galloway, MD

MODEL : Indication for Damage Control

pH < 7.1
Temp < 34 º
ISS > 25
SBP < 70 mm Hg

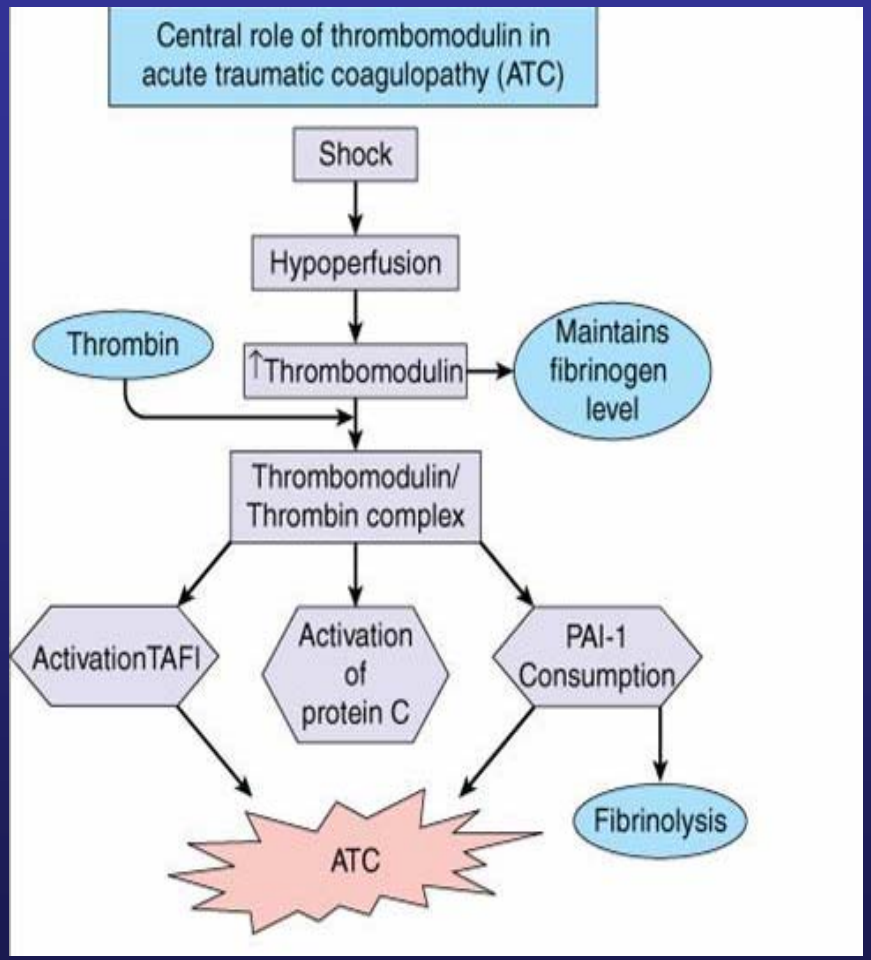
Coagulation Factor Deficiency : ? FFP Transfusion

- Pre-emptive FFP: RBC = 1:4 DGH ... J Trauma 1982

- Canine hemorrhage shock Lucas, et al Ann Surg 1985
  (no benefit of presumptive FFP)
- Pre-emptive FFP: RBC = 1:5 Wilson, et al J Trauma 1987
- FFP after > 10 RBC Lucas, et al J Trauma 1989

- Pre-emptive FFP:RBC = 1:1 DGH ... Ann Surg 2001

Acute Coagulopathy of Trauma



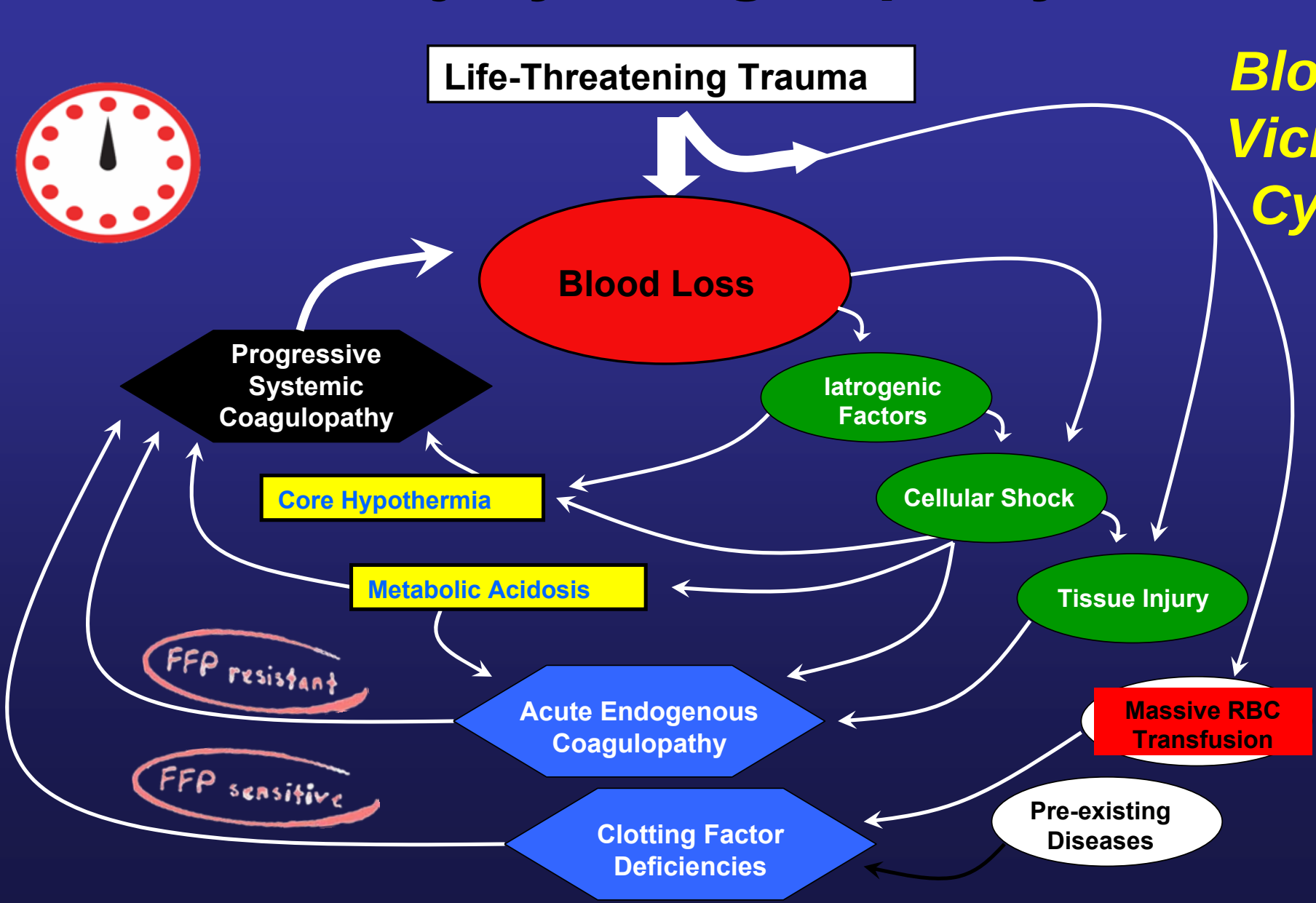
San Francisco General
208 Trauma Activation

Sampling < 10 min

BD > 6mEq/L = 27% ACS

Brohi, Cohen, et al
Ann Surg 2007

Postinjury Coagulopathy

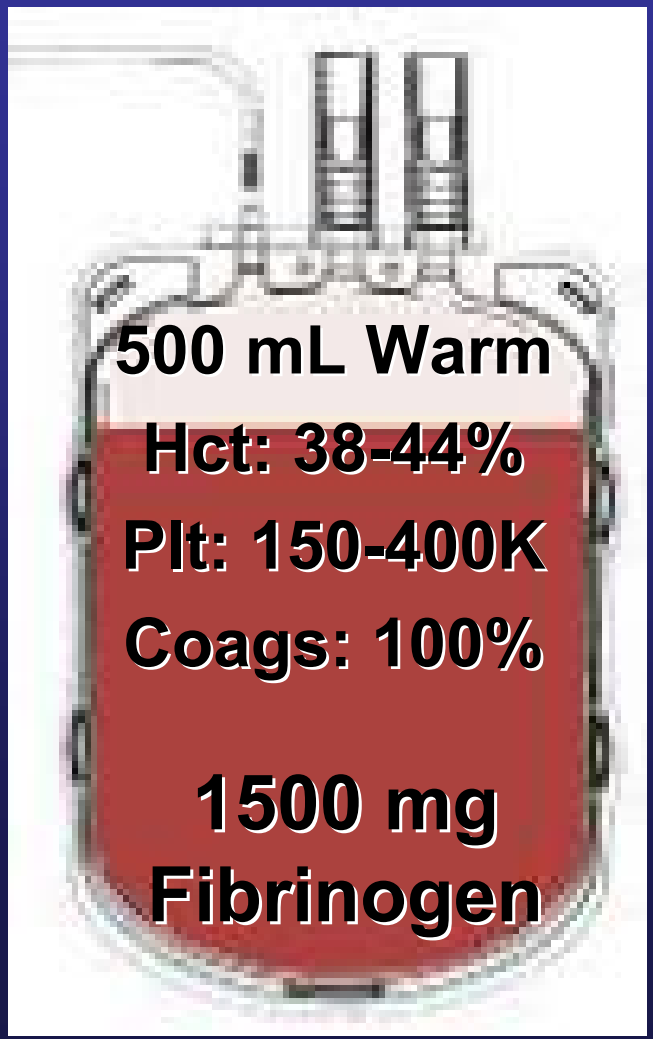


Military Strategy = Replace Lost Blood

Component Therapy :

1U PRBC + 6U PLT + 1U FFP + 10 pk Cryo

- *Hct 29%*
- *Plt 87K*
- *Coag Factor Activity 65%*
- *750 mg Fibrinogen*



Armand & Hess, Transfusion Med. Rev., 2003

Institute of Surgical Research
Brooke Army Medical Center
Fort Sam Houston, Texas

Postinjury Life-Threatening Coagulopathy

1:1:1 … FFP:PLT:RBC

UNCLASS ALARACT
SUBJECT: OPTIMAL RESUSCITATION OF SEVERELY INJURED SOLDIERS

1. COMBAT RESUSCITATION DATA ANALYZED BY THE US ARMY INSTITUTE OF SURGICAL RESEARCH (USAISR) DEMONSTRATE THAT CASUALTIES WHO RECEIVE MORE THAN 10 UNITS OF PACKED RED BLOOD CELLS (PRBCS) IN A 24-HOUR PERIOD (MASSIVE TRANSFUSION) HAVE A PROFOUND SURVIVAL BENEFIT WHEN THE PLASMA (FFP) TO PRBC TRANSFUSION RATIO IS 1:1. CASUALTIES WHO RECEIVE LESS FFP (1 UNIT FFP TO 4 UNITS PRBCS, OR LESS) HAVE AN OVERALL MORTALITY OF 65%, WHILE THOSE WHO RECEIVE A 1:1 RATIO HAVE AN OVERALL MORTALITY OF 20% (P< 0.001).

2. SEVERELY INJURED CASUALTIES SHOULD HAVE THE 1:1 RATIO INITIATED AS EARLY AFTER INJURY AS POSSIBLE. TRANSFUSIONS MUST BE ACCOMPLISHED ACCORDING TO GUIDELINES ESTABLISHED BY THE CENTCOM BLOOD PROGRAM MANAGER. THE CURRENT APPROVED CENTCOM CLINICAL PRACTICE GUIDELINE FOR DAMAGE CONTROL RESUSCITATION AND TRANSFUSION IS POSTED ON THE JOINT PATIENT TRACKING APPLICATION (JPTA) WEBSITE:

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

Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma

John B. Holcomb, MD, FACS, Don Jenkins, MD, FACS, Peter Rhee, MD, FACS, Jay Johannigman, MD, FS, FACS, Peter Mahoney, FRCA, RAMC, Sumeru Mehta, MD, E. Darrin Cox, MD, FACS, Michael J. Gehrke, MD, Greg J. Beilman, MD, FACS, Martin Schreiber, MD, FACS, Stephen F. Flaherty, MD, FACS, Kurt W. Grathwold, MD, Phillip C. Spinella, MD, Jeremy G. Perkins, MD, Alec C. Beekley, MD, FACS, Neil R. McMullin, MD, Myung S. Park, MD, FACS, Ernest A. Gonzalez, MD, FACS, Charles E. Wade, PhD, Michael A. Dubick, PhD, C. William Schwab, MD, FACS, Fred A. Moore, MD, FACS, Howard R. Champion, FRCS, David B. Hoyt, MD, FACS, and John R. Hess, MD, MPH, FACP

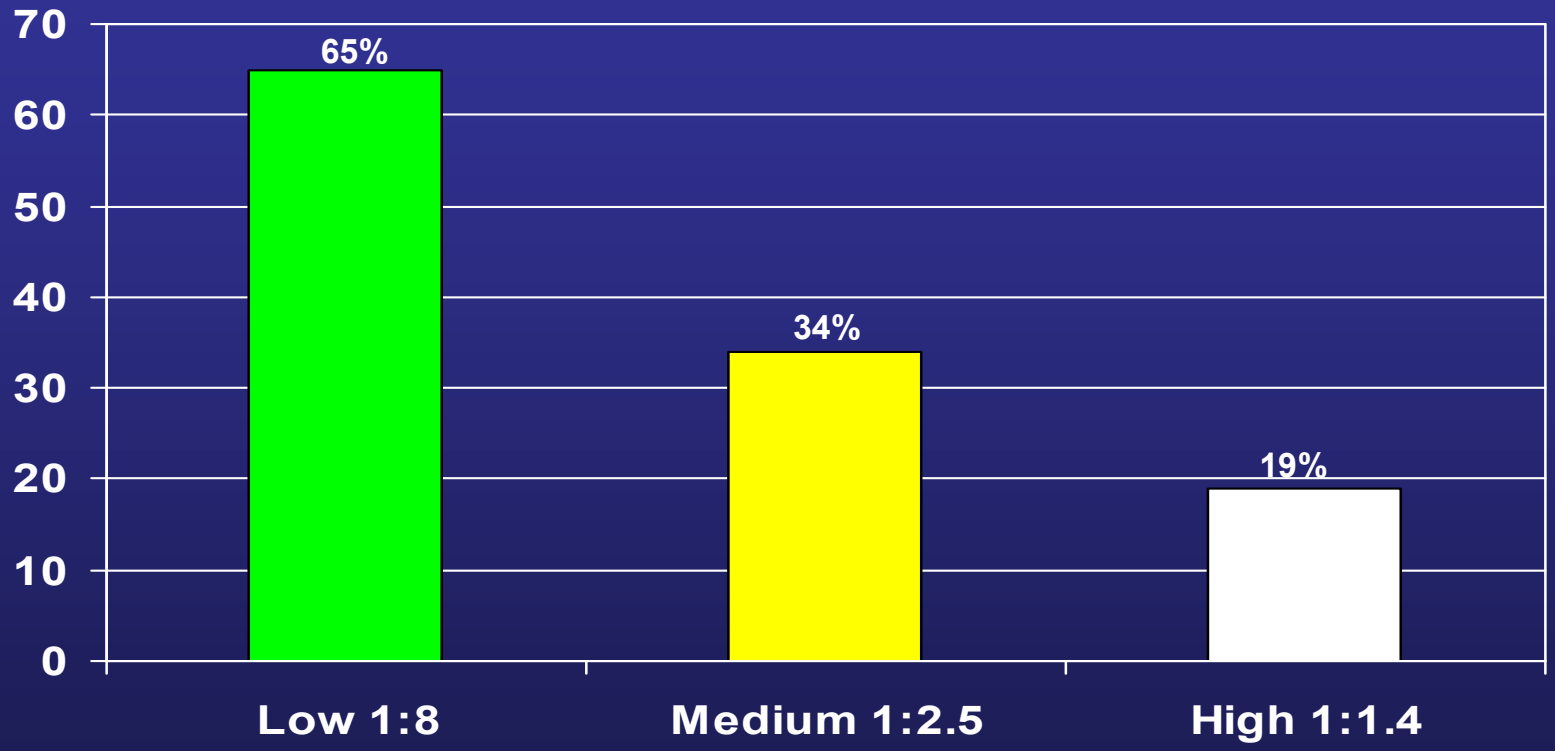
Platelet Transfusion

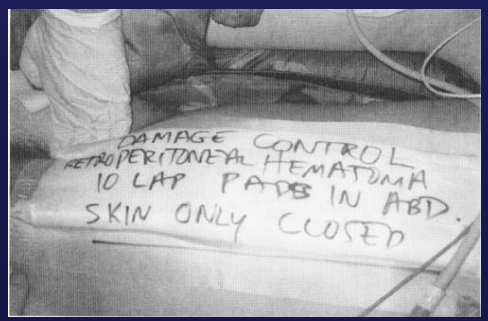
- WB Derived Single Unit = 5.5 X 10^{10}
  (50 ml ; 40 = Plasma)
  Recipient = > 10, 000

- Apheresis Platelets = 3.0 X 10^{11} (300 = Plasma)
  Recipient = > 60,000 ($ 575)

- 1 : 1 : 1 = 0.2 : 1.1 : 1
  (PLT : FFP : RBC)

FFP : RBC Ratio – Military Experience

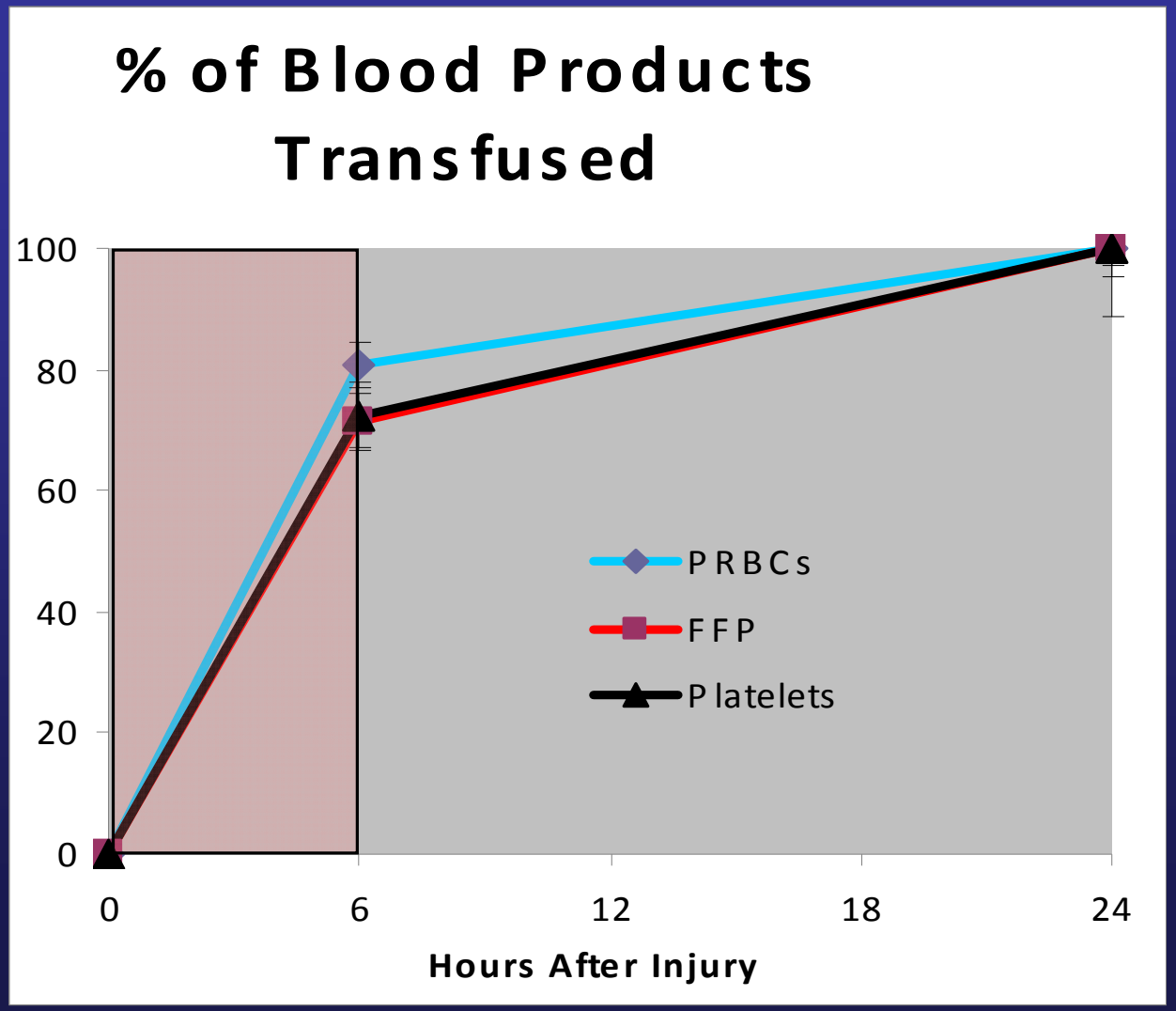




Borgman et al
Brooke Army Medical Center
J Trauma 2007

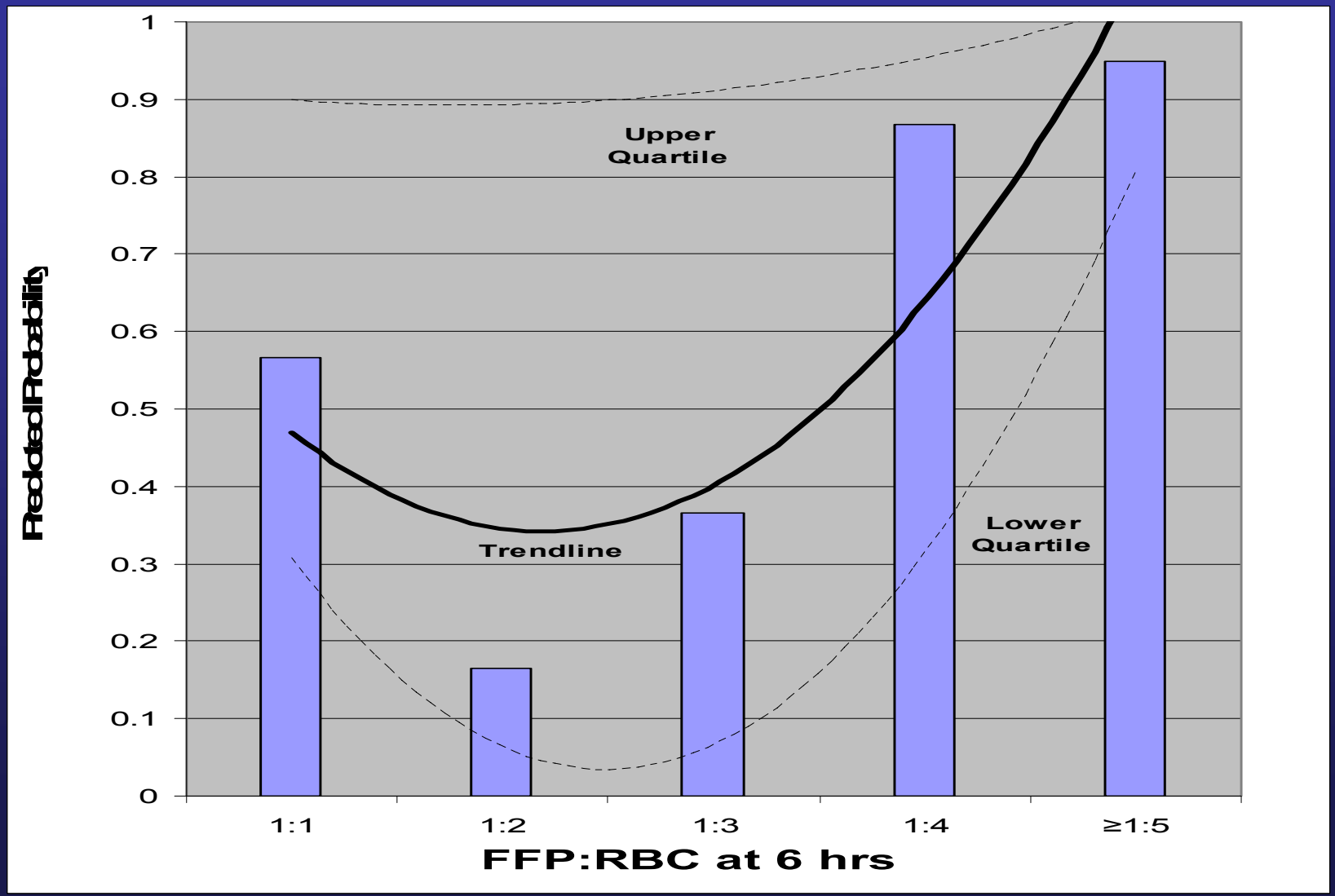
Postinjury Massive Transfusion : First 6 Hours

Massive Transfusion
>10 Units RBC / *6 Hrs*



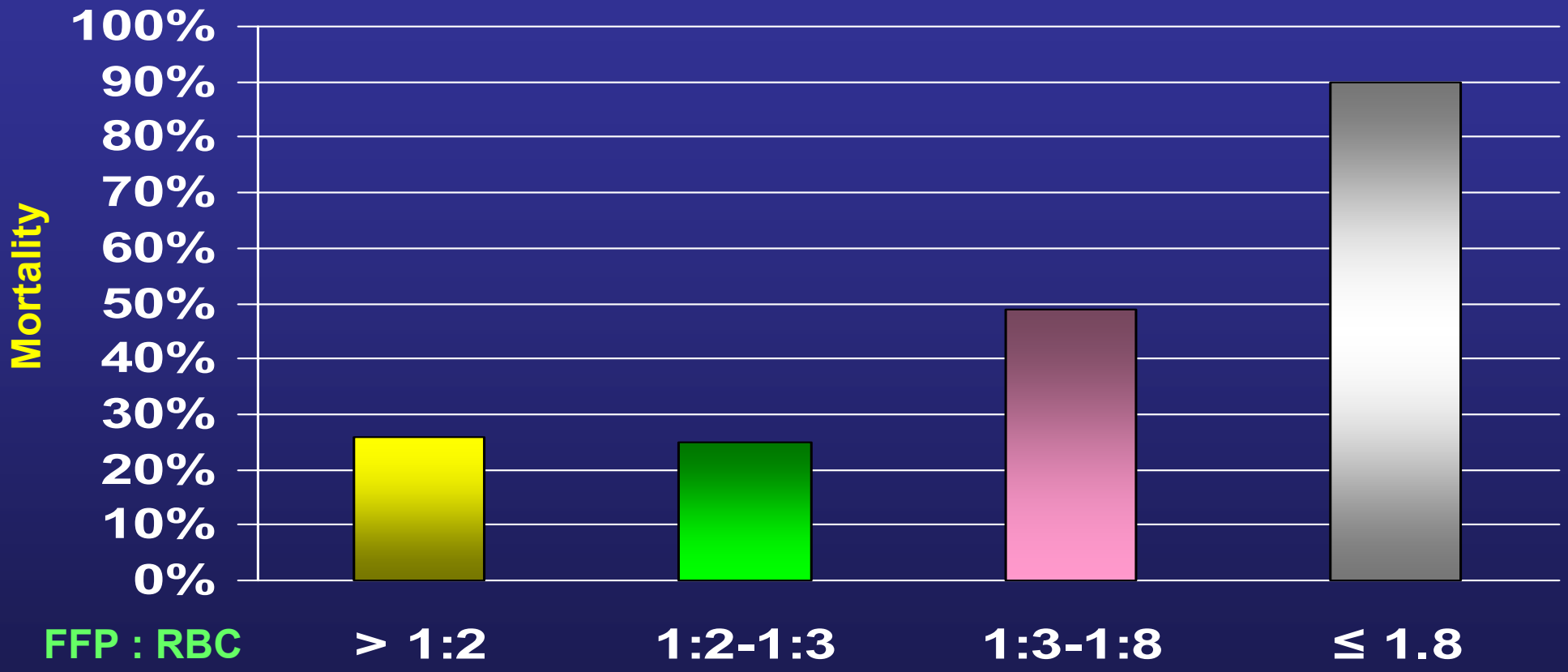
AAST / J Trauma 2008

FFP : RBC Ratio – Civilian Experience



AAST / J Trauma 2008

Civilian Trauma … Massive Transfusion



n = 383 (Head Injury Excluded)

Teixera et al

J Trauma 2009

US Military – FFP:RBC

Mar 2003 - Feb 2006 Pre 1:1 = 1: 2.0

Mar 2006 - Sept 2008 1:1 Policy = 1: 1.2

- Similar cohorts
- No difference in Mortality

Simmons et al
J Trauma 2010

Massive Transfusion Analyses : Issues

1) No Coagulation Functional Response

2) Analysis over 24 hr versus 6 hr

3) Selection Bias / Product Availability

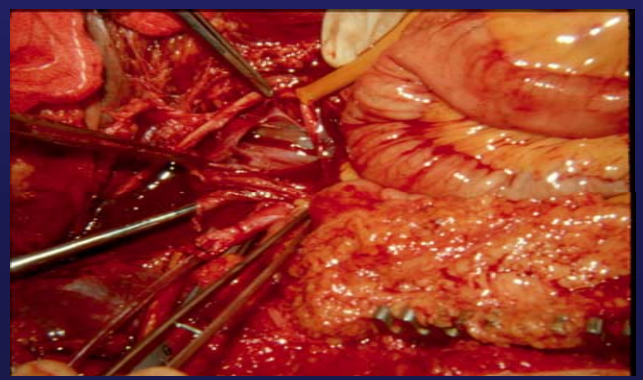
4) Variability in Bioactivity of Blood Products

5) Differences in Injury Patterns

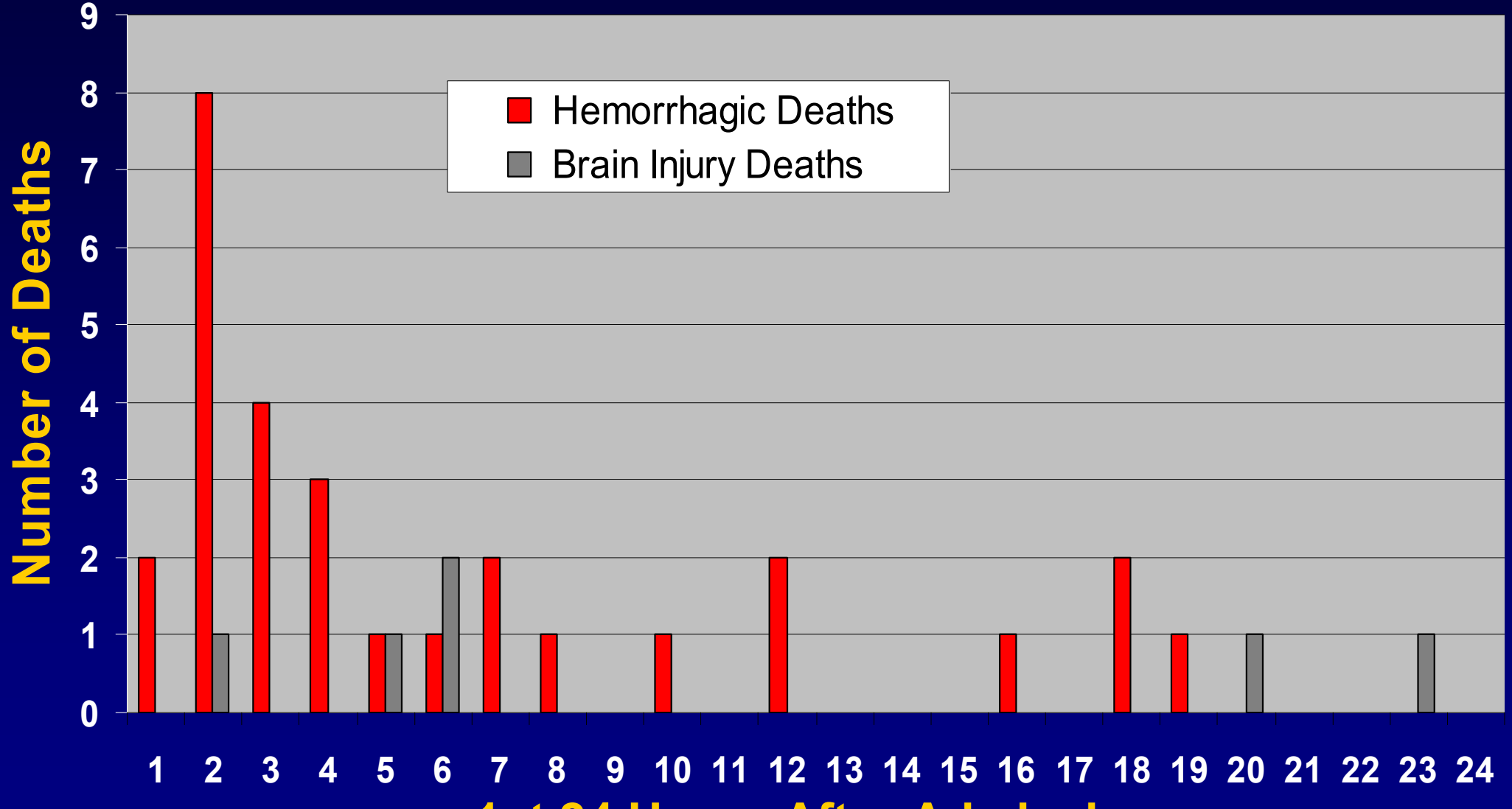
Postinjury Coagulopathy : Scientific Basis

↑ PLT: FFP : RBC →→ →→ ↓ Mortality

??? ↓ Coagulopathy



Death from Hemorrhage Occurs Within the First 6 Hours



66 % within 6 Hr

J Trauma 2007

FFP : RBC >>> Selection Bias

	1 - 1.5 hr	2 - 3 hr	3 - 4 hr	24 hr
< 1:2	8 / 108	9 / 95	13 / 91	43 / 74
≥ 1:2	0 / 13	0 / 34	2 / 39	24 / 60

Snyder et al

J Trauma 2009

Are they dying because they are bleeding or bleeding because they are dying ?

Ben Galloway, MD 1976

"The Clinical Efficacy of FFP is Largely Unproven"

Journal List > Crit Care > v.11(1); 2007

Crit Care. 2007; 11(1): R17.
Published online 2007 February 13. doi: 10.1186/cc5686.

Management of bleeding following major trauma: a European guideline

Donat R Spahn,[1] Vladimir Cerny,[2] Timothy J Coats,[3] Jacques Duranteau,[4] Enrique Ferr

[1]Department of Anesthesiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland
[2]Charles University in Prague, Faculty of Medicine in Hradec Králové, Department of Anaesthesiology and Intensive Care Medici
[3]Leicester Royal Infirmary, Accident and Emergency Department, Infirmary Square, Leicester LE1 5WW, UK
[4]Department of Anaesthesia and Intensive Care, University of Paris XI Faculté de Médecine Paris-Sud, 63 rue Gabriel Péri, 9427
[5]Department of Emergency and Critical Care Medicine, University Hospital Virgen de las Nieves, ctra de Jaén s/n, 18013 Granac
[6]Department of Anaesthesia and Intensive Care, Ospedale Maggiore, Largo Nigrisoli 2, 40100 Bologna, Italy
[7]Department of Orthopaedic Surgery, Denver Health Medical Center, University of Colorado Medical School, 777 Bannock Stree
[8]Departments of Haematology, Pathology and Rheumatology, Guy's & St Thomas' Foundation Trust, Lambeth Palace Road, Lor
[9]Department of Traumatology, General and Teaching Hospital Celje, 3000 Celje, Slovenia
[10]Institute for Research in Operative Medicine, University of Witten/Herdecke, Ostmerheimerstrasse 200, 51109 Köln (Merheim),
[11]Department of Anaesthesia and Intensive Care, Université René Descartes Paris 5, AP-HP, Hopital Cochin, 27 rue du Fbg Sai
[12]Department of Surgery and Trauma, Karolinska University Hospital, 171 76 Solna, Sweden
[13]Ludwig-Boltzmann-Institute for Experimental and Clinical Traumatology, Donaueschingenstrasse 13, 1200 Vienna, Austria
[14]Department of Intensive Care, Erasme Hospital, University of Brussels, Belgium, route de Lennik 808, 1070 Brussels, Belgium
[15]Department of Anaesthesiology, University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen, Germany

✉Corresponding author.
Donat R Spahn: donat.spahn@usz.ch ; Vladimir Cerny: cernyvla@fnhk.cz ; Timothy J Coats: tc61@le.ac.uk ; Jacques Durantea

Received November 8, 2006; Revisions requested December 21, 2006; Revised January 8, 2007; Accepted February 13, 2007.

The Risk of ALI / ARDS is Higher with FFP and Platelets than RBCs

Chest. 2007 May;131(5):1308-14. Epub 2007 Mar 30.

Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medica patients.

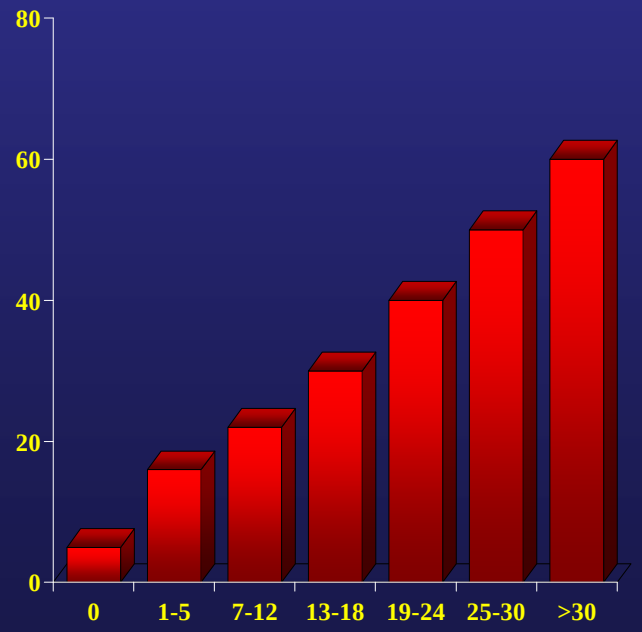
Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O.

Department of Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

BACKGROUND: Transfusion has long been identified as a risk factor for acute lung injury (ALI)/ARDS. No study formally evaluated the transfusion of specific blood products as a risk factor for ALI/ARDS in critically ill medical p METHOD: In this single-center retrospective cohort study, 841 consecutive critically ill patients were studied for th development of ALI/ARDS. Patients who received blood product transfusions were compared with those who did univariate and multivariate propensity analyses. RESULTS: Two hundred ninety-eight patients (35%) received blo transfusions. Transfused patients were older (mean [+/- SD] age, 67 +/- 17 years vs 62 +/- 19 years; $p < 0.001$) a higher acute physiologic and chronic health evaluation (APACHE) III scores (74 +/- 32 vs 58 +/- 23; $p < 0.001$) th who had not received transfusions. ALI/ARDS developed more commonly (25% vs 18%; $p = 0.025$) in patients ex to transfusion. Seventeen patients received massive RBC transfusions (ie, > 10 U of blood transfused within 24 h whom 13 also received fresh-frozen plasma (FFP) and 11 received platelet transfusions. When adjusted for the probability of transfusion and other ALI/ARDS risk factors, any transfusion was associated with the development ALI/ARDS (odds ratio [OR], 2.14; 95% confidence interval [CI], 1.24 to 3.75). Among those patients receiving indi blood products, ALI/ARDS was more likely to develop in patients who received FFP transfusions (OR, 2.48; 95% to 4.74) and platelet transfusions (OR, 3.89; 95% CI, 1.36 to 11.52) than in those who received only RBC transfu (OR, 1.39; 95% CI, 0.79 to 2.43). CONCLUSION: Transfusion is associated with an increased risk of the develop ALI/ARDS in critically ill medical patients. The risk is higher with transfusions of plasma-rich blood products, FFP, platelets, than with RBCs.

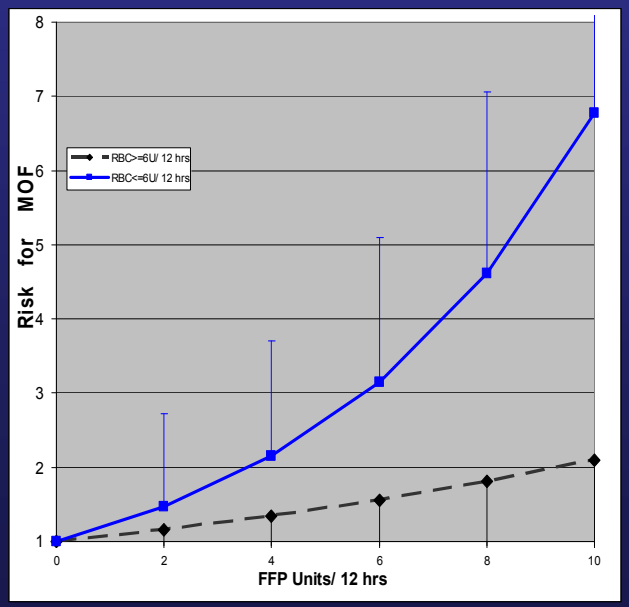
Fresh Frozen Plasma : Adverse Effects

Packed Red Blood Cells : MOF



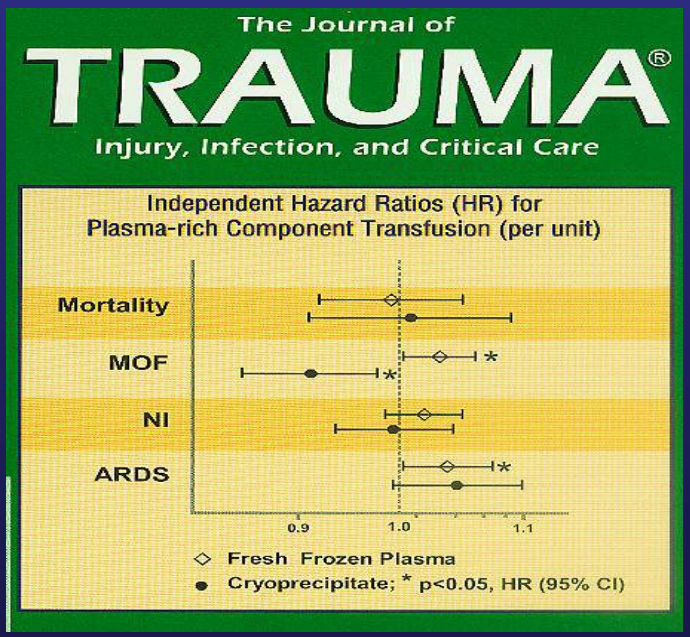
Arch Surg 1997

Fresh Frozen Plasma : MOF



Arch Surg 2010

Fresh Frozen Plasma : MOF



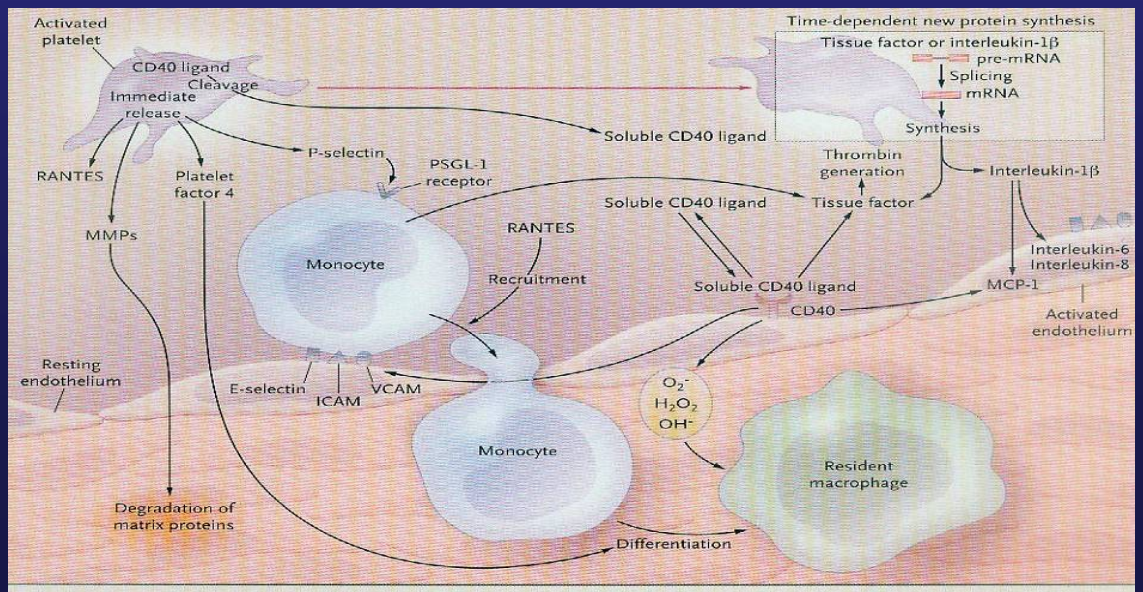
J Trauma 2009

Physiologic Changes with Storage

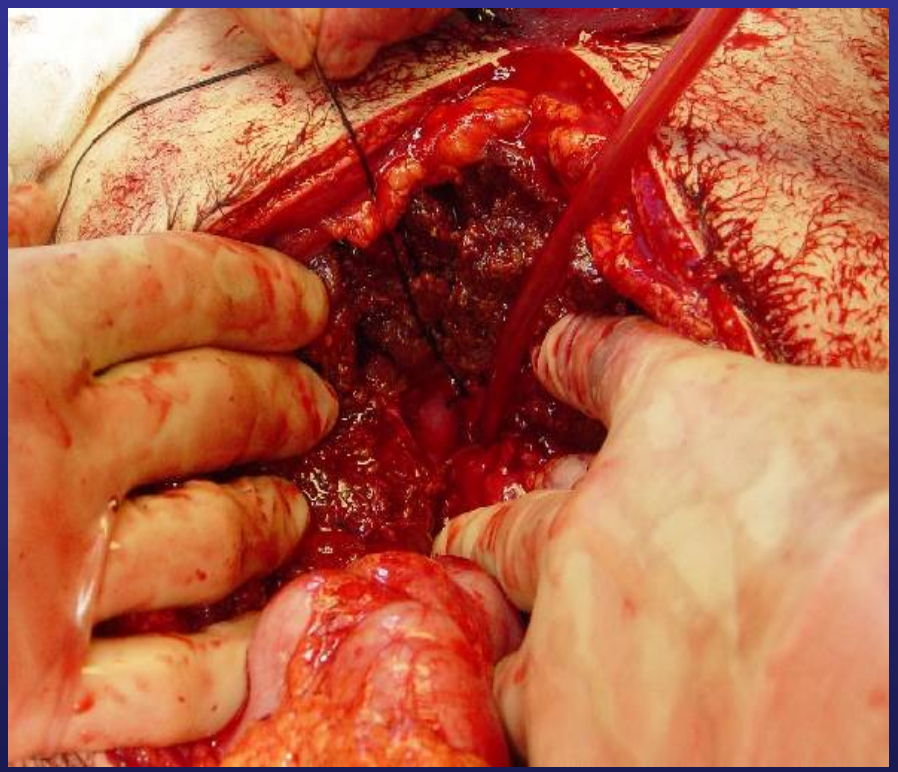
- RBC
- FFP
- PLT

↓ Coagulation

↑ Inflammation



Trauma : Recombinant Factor VIIa



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

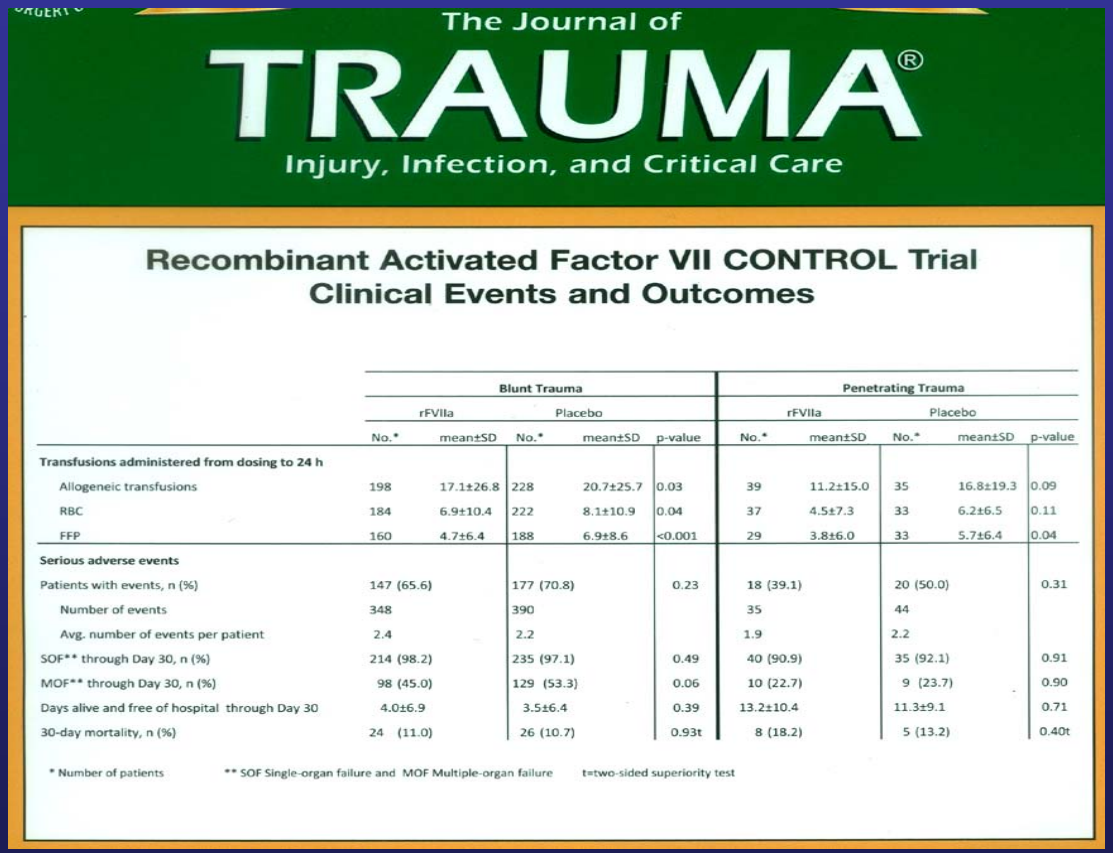
Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

- No Difference in Mortality
- Decreased PRBC … Blunt Trauma
- Decreased ARDS … Blunt Trauma
- Safe (~ 3% Complication Rate)

Boffard et al
J Trauma 2005

CONTROL Trial : RCT / 150 Hospitals / 26 Countries



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

Recombinant Activated Factor VII CONTROL Trial
Clinical Events and Outcomes

	Blunt Trauma					Penetrating Trauma				
	rFVIIa		Placebo			rFVIIa		Placebo		
	No.*	mean±SD	No.*	mean±SD	p-value	No.*	mean±SD	No.*	mean±SD	p-value
Transfusions administered from dosing to 24 h										
Allogeneic transfusions	198	17.1±26.8	228	20.7±25.7	0.03	39	11.2±15.0	35	16.8±19.3	0.09
RBC	184	6.9±10.4	222	8.1±10.9	0.04	37	4.5±7.3	33	6.2±6.5	0.11
FFP	160	4.7±6.4	188	6.9±8.6	<0.001	29	3.8±6.0	33	5.7±6.4	0.04
Serious adverse events										
Patients with events, n (%)	147 (65.6)		177 (70.8)		0.23	18 (39.1)		20 (50.0)		0.31
Number of events	348		390			35		44		
Avg. number of events per patient	2.4		2.2			1.9		2.2		
SOF** through Day 30, n (%)	214 (98.2)		235 (97.1)		0.49	40 (90.9)		35 (92.1)		0.91
MOF** through Day 30, n (%)	98 (45.0)		129 (53.3)		0.06	10 (22.7)		9 (23.7)		0.90
Days alive and free of hospital through Day 30	4.0±6.9		3.5±6.4		0.39	13.2±10.4		11.3±9.1		0.71
30-day mortality, n (%)	24 (11.0)		26 (10.7)		0.93t	8 (18.2)		5 (13.2)		0.40t

* Number of patients ** SOF Single-organ failure and MOF Multiple-organ failure t=two-sided superiority test

- No Difference in Mortality
- Decreased Blood Products
- No Safety Issues

Hauser et al
J Trauma 2010

US Military – Recombinant Factor VIIa

- Combat Casualites (n=2050) 2003 – 2009
- 25% Received FVIIa ; Propensity Scoring Match

- No Difference in Mortality
- No Safety Issues

Wade et al
J Trauma 2010

Role of Postinjury Fibrinolytics

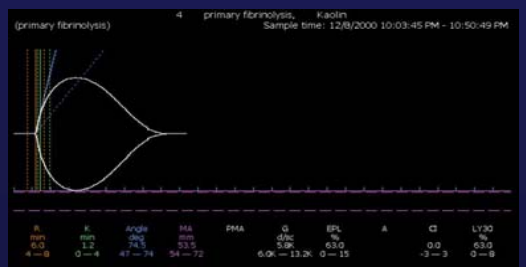
- *Inclusion : Massive Transfusion Protocol*
- *Massive - Moderate – Minor / 6 Hr*

  >10u 5-10u <5u
- **Thrombelastogram**
- *Logistic Regression Models:*

  Risk Stratification for Fibrinolysis

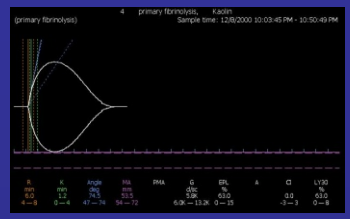
Shipment*#	pRBC	Plasma	Plateletpheresis	Pooled Cryo
1	4	2		
2#	4	2	1	10
3	4	2		
4	4	2	1	10

Each shipment can include the option of "doubling up" (e.g. 8 pRBC + 4 Plasma) as determined by the MTP ordering M.D.
Shipment >4 determined by lab values and TEG results



Ann Surg 2010

Postinjury Fibrinolysis



61 ED RBC

Transient Fibrinolysis
n = 28 (46%)

Primary Fibrinolysis (PF)
n = 11 (18%)

No Fibrinolysis
n = 22 (36%)

Conventional measures associated with PF:

- Higher ISS (p=0.06)
- Increased RBC's (p=0.002)
- Depressed Fibrinogen@ 1 hour (p=0.0005)
- Increased Base Deficit/ Lactate (p=0.0001)

r-TEG findings associated with PF

- *ACT*
- *K time*
- *MA (Maximum Amplitude)*
- *G value (Clot Strength)*
- *ALL p<0.0001*

Timing of Fibrinolysis

Primary: 58 minutes (IQR 18.2-95.9)

Transient: 104 minutes (IQR 13.0-1200)

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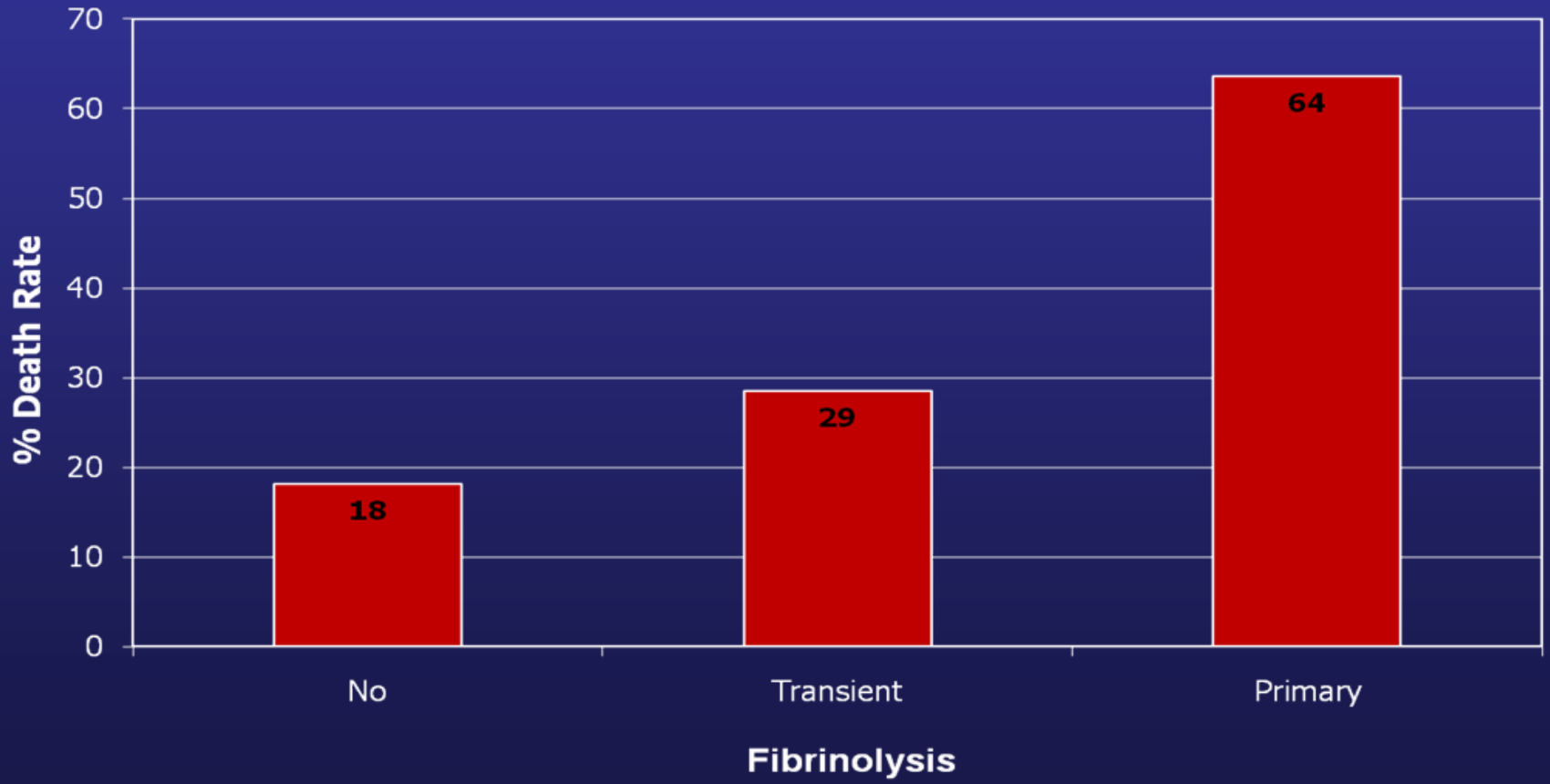
Mortality Associated with Fibrinolysis



p=0.02

Ann Surg 2010

CRASH-2 Trial : RCT / 274 Hospitals / 40 Countries

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

Summary

Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Published Online June 15, 2010
DOI:10.1016/S0140-6736(10)60835-5

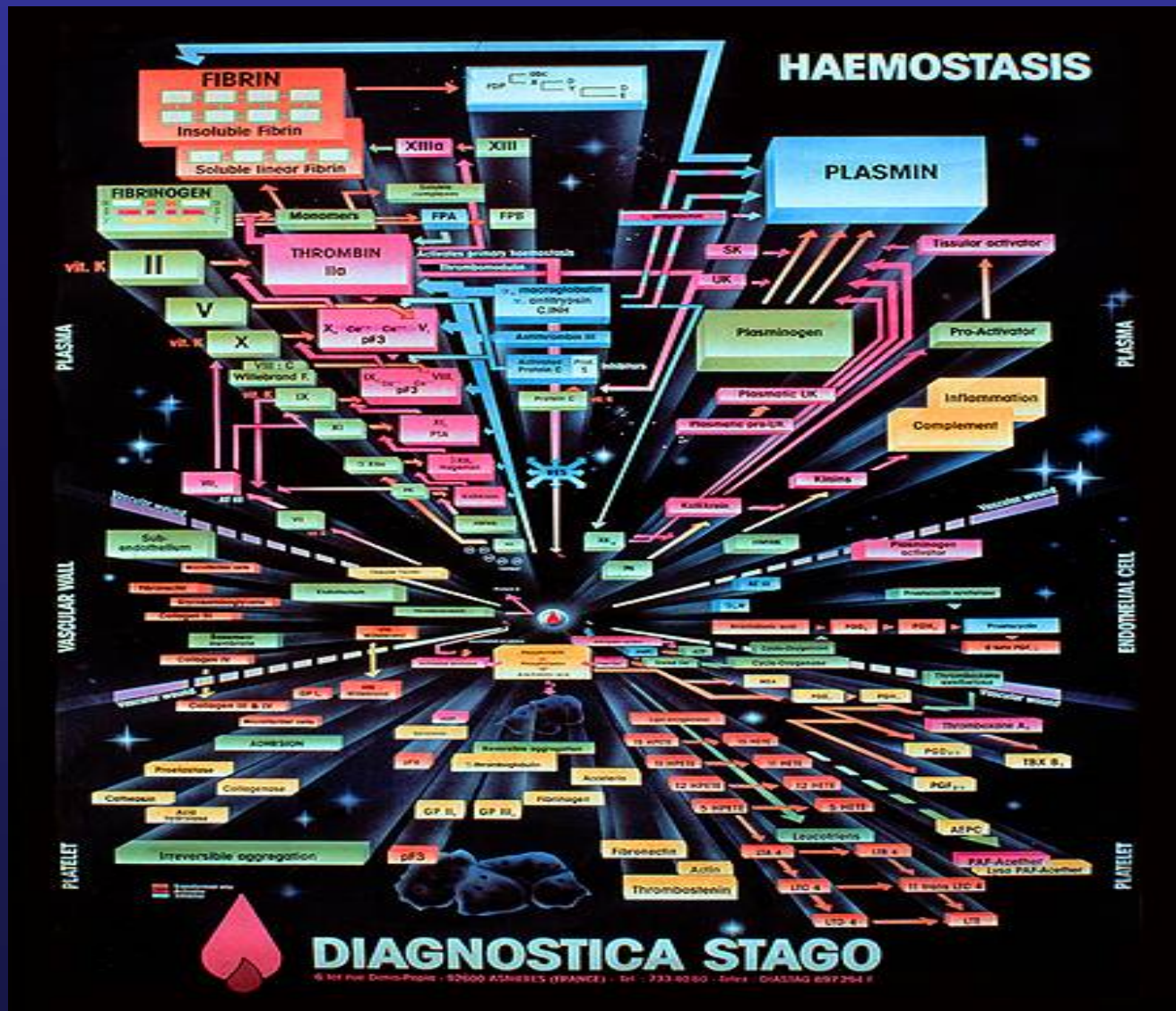
20,211 Adult : SBP < 90 or HR > 110, within 8 Hr

- **Mortality 14.5% vs 16.0% (p<.0035)**
- **No safety issues**

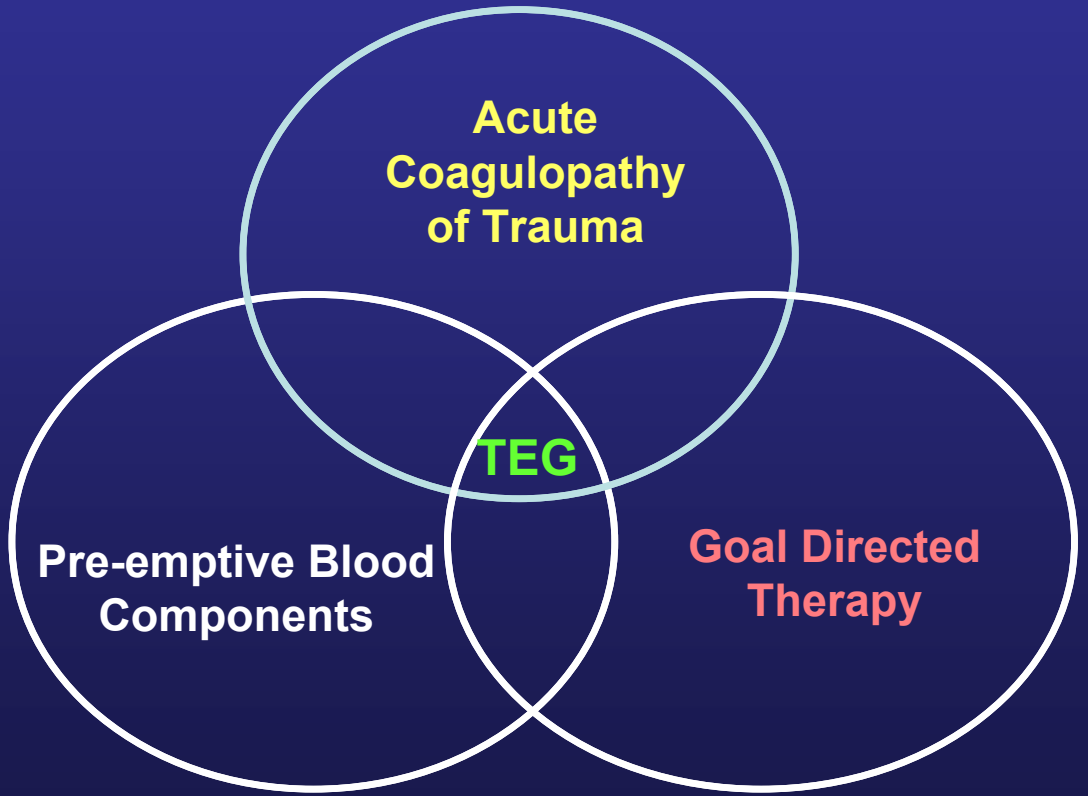
Lancet 2010

In Search of the Scientific Basis for Postinjury Coagulopathy….

The Hemostasis Process



Thrombelastography : ? Answers

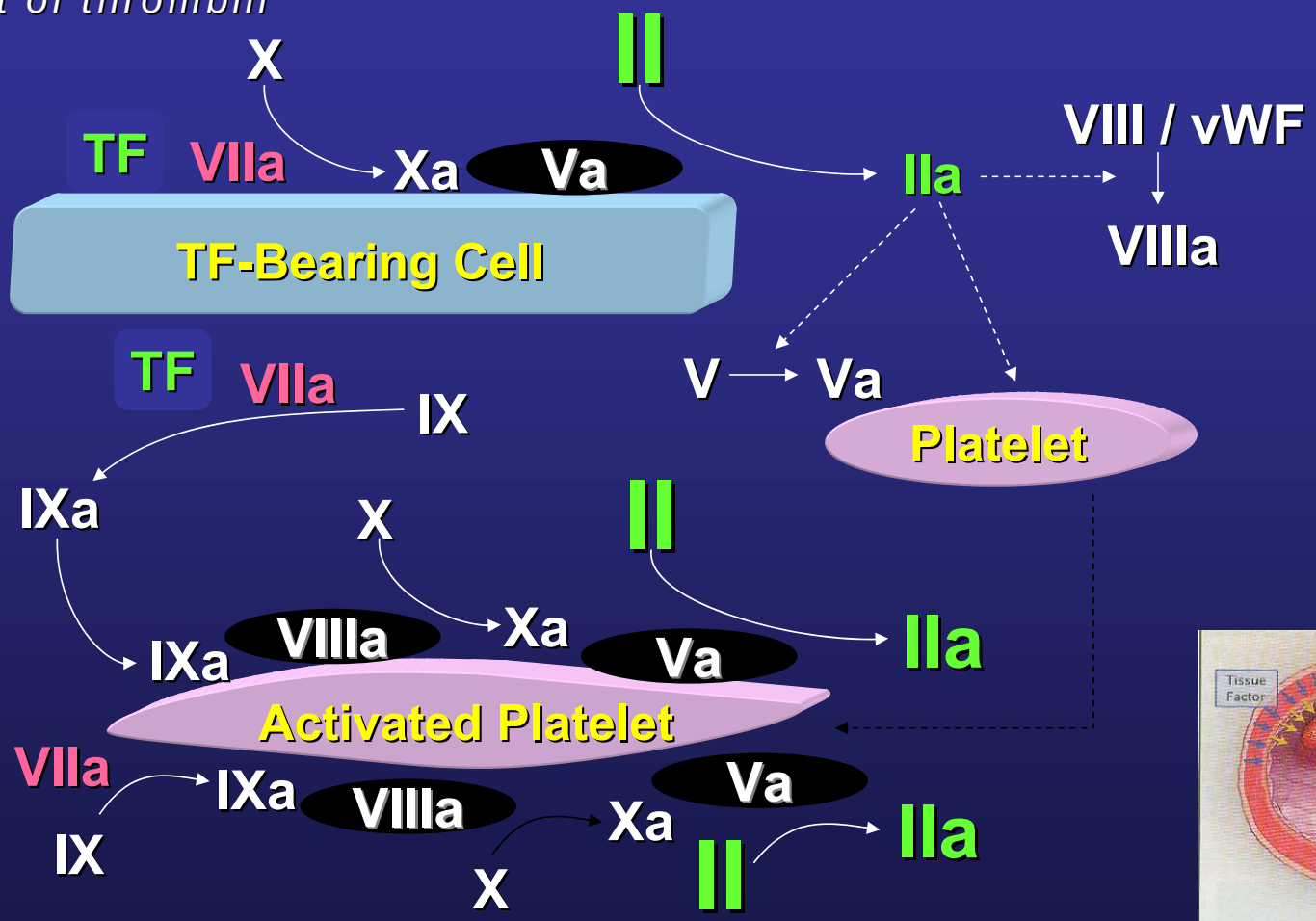


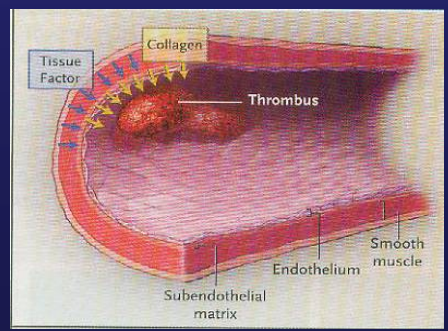
1) Initiation

Endothelial damage
Tissue Factor exposed
TF / VIIa complex
Small amount of thrombin

2) Amplification *Thrombin activates platelets*

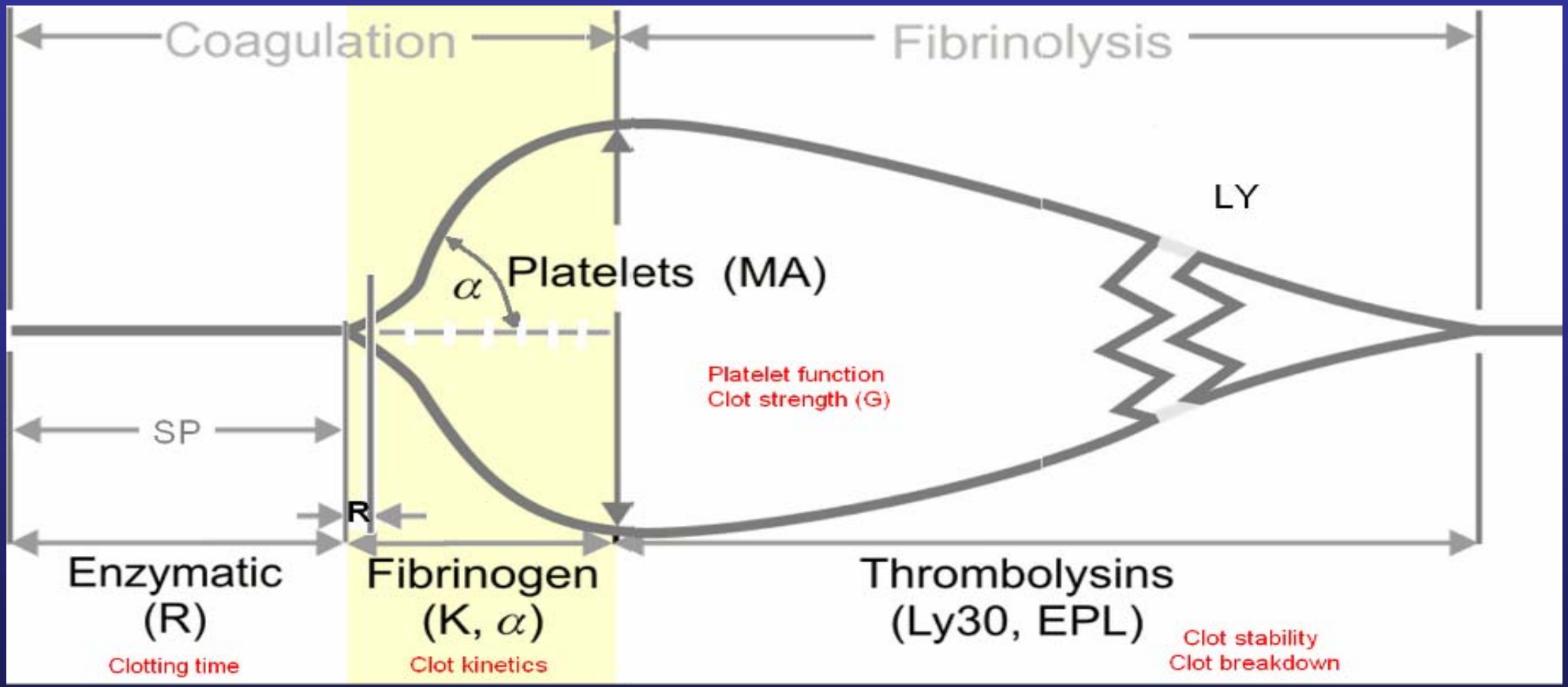
3) Propagation *Tenase and prothrombinase complexes*
= rapid thrombin burst





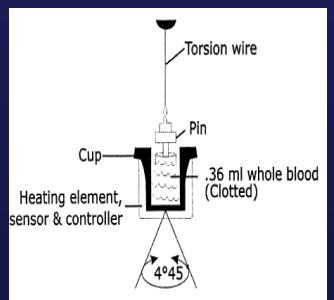
Hoffman M, et al.
Blood Coagul Fibrinolysis. 1998

Rapid Thrombelastography



Amplilute (mm)

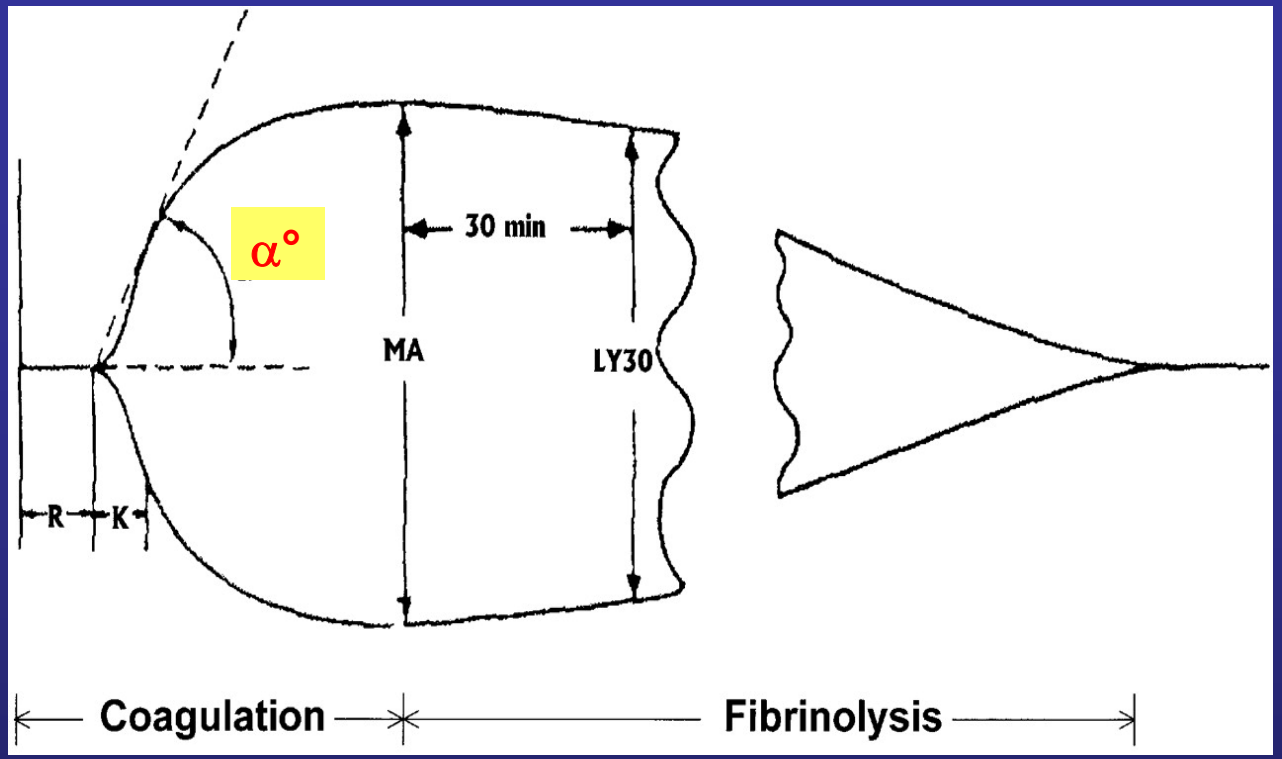
Time (min)



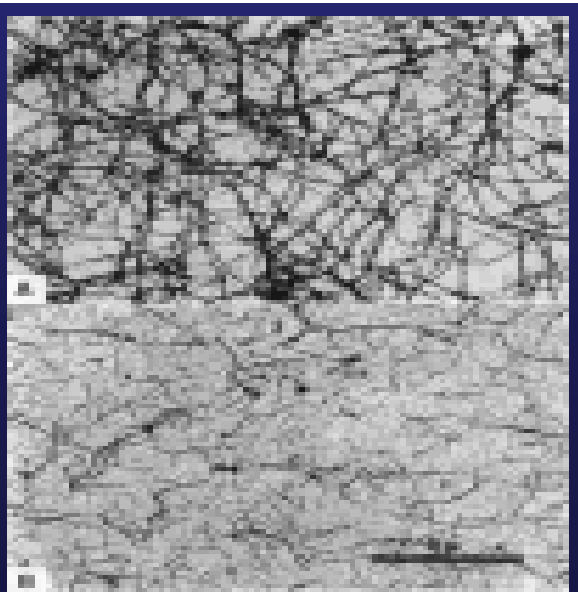
Tissue Factor ... Uncitrated Whole Blood

Angle (α) < 54 °

Rate of clot growth … fibrin build-up and cross-linking

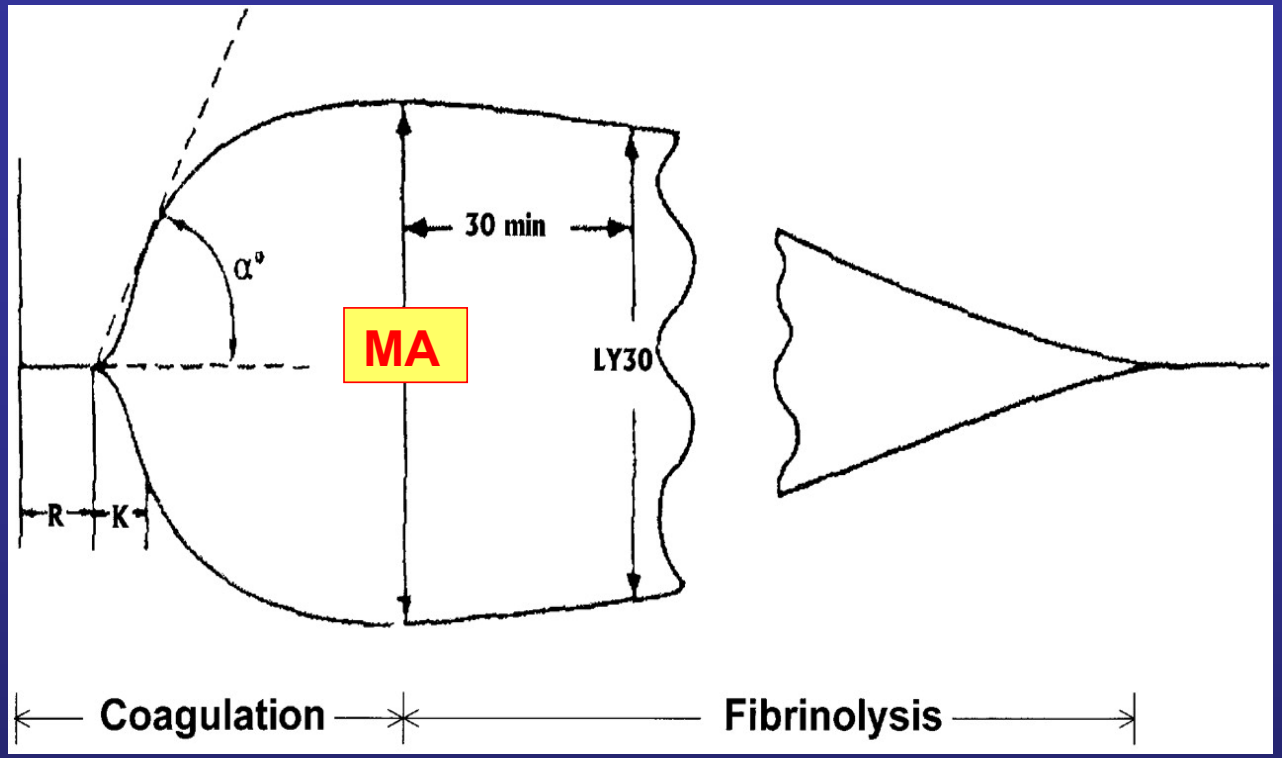


10 units pooled cryoprecipitate or 1 unit / 5 kg
~ 30-50 mg/dL increase in fibrinogen



MA < 50 mm

Strength / stiffness of the developed clot contributed mainly by platelets



1 unit apheresed platelets or 1 random donor equivalent /10 kg
~ 30,000-50,000/μL increase in platelet

Pattern Recognition

Thrombelastrograph

Normal

R;K;MA;Angle = Normal

D.I.C.

Stage 1
Hypercoagulable state with secondary fibrinolysis

Stage 2
Hypocoagulable state

Platelet Dysfunction

Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged
Angle ~ Normal
MA = Very Decreased

Anticoagulants/hemophilia

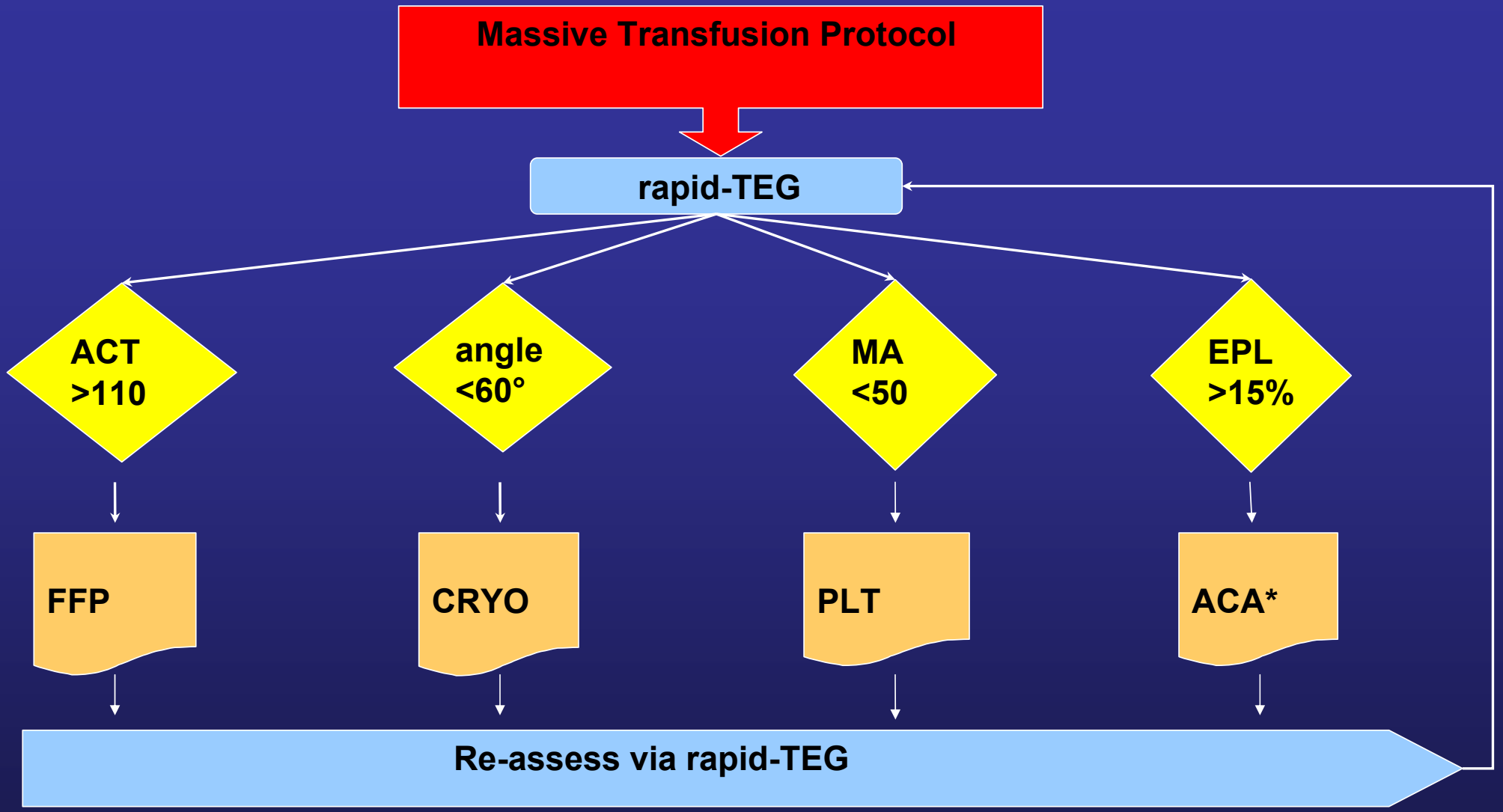
Factor Deficiency
R;K = Prolonged;
MA;Angle = Decreased

Fibrinolysis (UK, SK or t-PA)

Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5%
Ly60 > 15.0%

Hypercoagulability

R;K = Decreased;
MA; Angle = Increased



FFP = fresh frozen plasma; CRYO = cryopercipitate; PLT = apheresis platelets;
ACA = aminocaproicacid * 5 grams in 250 ml infused over 1 hr

Thromboelastography : ED Assessment

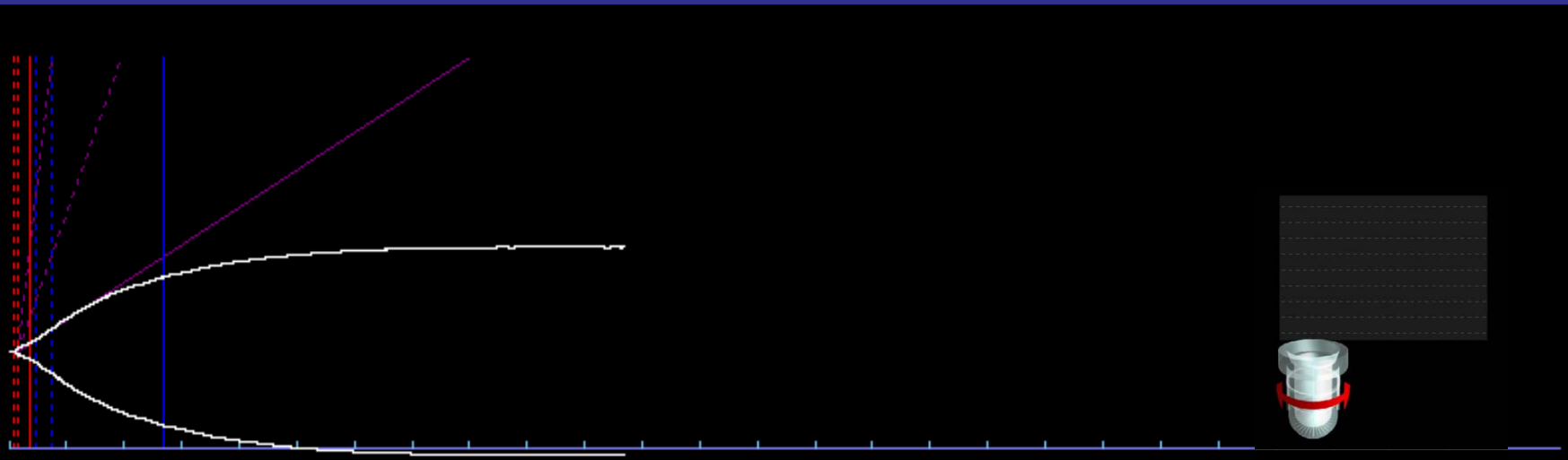
GSW : Right Middle & Lower Lobes / Grade IV Right Liver

G = 1.8 (> 5.3)
Global Clot

ACT = 205 (< 110)
Coagulation Factors

K = 700 (< 120)
Fibrinogen

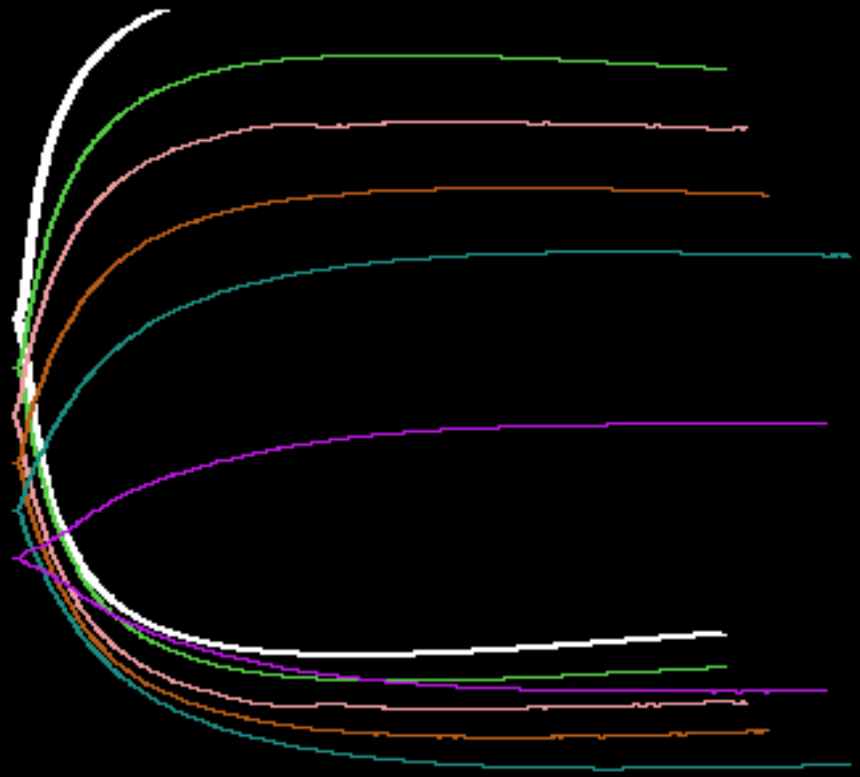
MA = 26 (< 72)
Platelets



TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30	A
sec	sec	sec	sec	deg	mm	d/sc	%	%	mm
206.0	45.0	100.0	700.0	27.0	26.2	1.8K	0.0	0.0	28.2
78 — 110	0 — 60	17 — 40	30 — 120	66 — 82	54 — 72	5.3K — 12.4K	0 — 8	0 — 8	50 — 80

Thromboelastography : OR Resuscitation

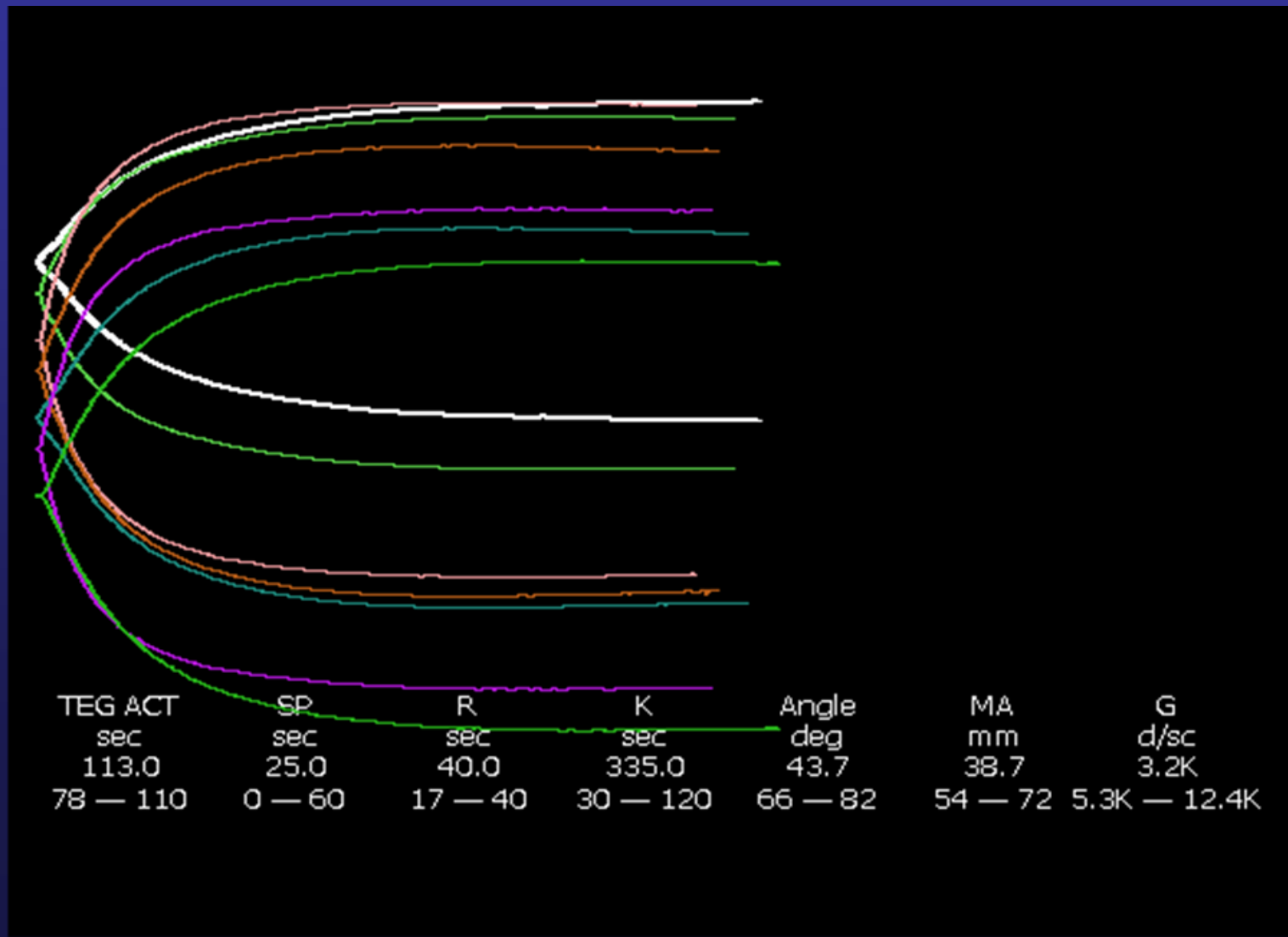
GSW: Right Middle & Lower Lobes / Grade IV Right Liver



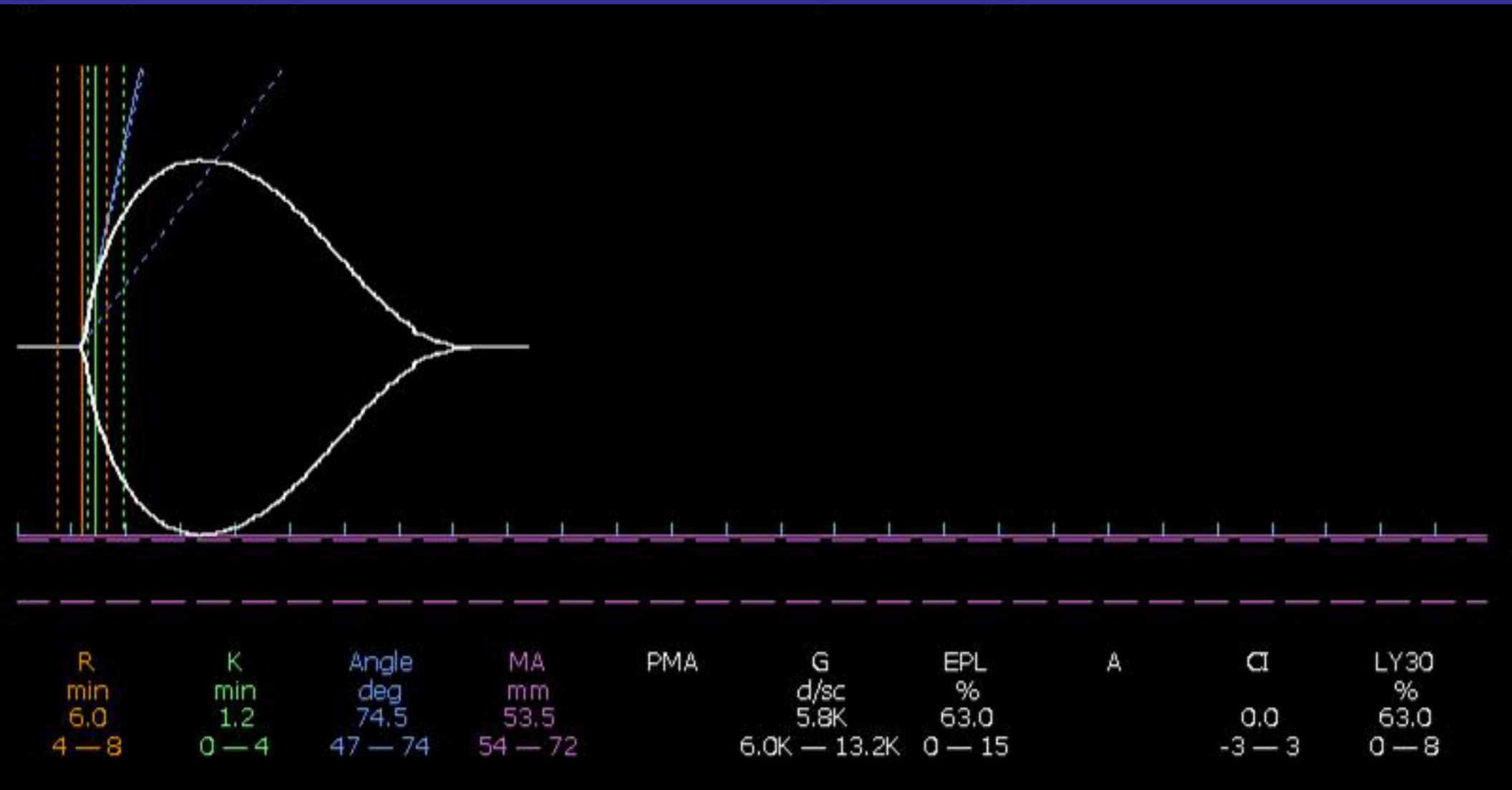
TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30	A
sec	sec	sec	sec	deg	mm	d/sc	%	%	mm
113.0	30.0	40.0	50.0	79.4	70.4	11.9K	1.8	1.8	66.3
78 — 110	0 — 60	17 — 40	30 — 120	66 — 82	54 — 72	5.3K — 12.4K	0 — 8	0 — 8	50 — 80

Trauma Transfer : 9 RBC / 4 FFP

- G = 3.2 (>5.3)
  Clot strength
- ACT = 113 (>110)
  Enzymatic
- K = 335 (<120)
  Fibrinogen
- MA = 38 (>54)
  Platelets



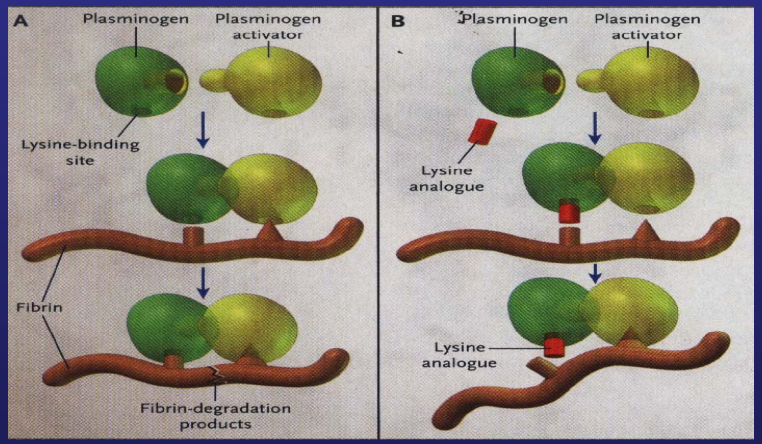
ED Thoracotomy : SW LV … Prehospital CPR 11 min



R	K	Angle	MA	PMA	G	EPL	A	CI	LY30
min	min	deg	mm		d/sc	%			%
6.0	1.2	74.5	53.5		5.8K	63.0		0.0	63.0
4 — 8	0 — 4	47 — 74	54 — 72		6.0K — 13.2K	0 — 15		-3 — 3	0 — 8

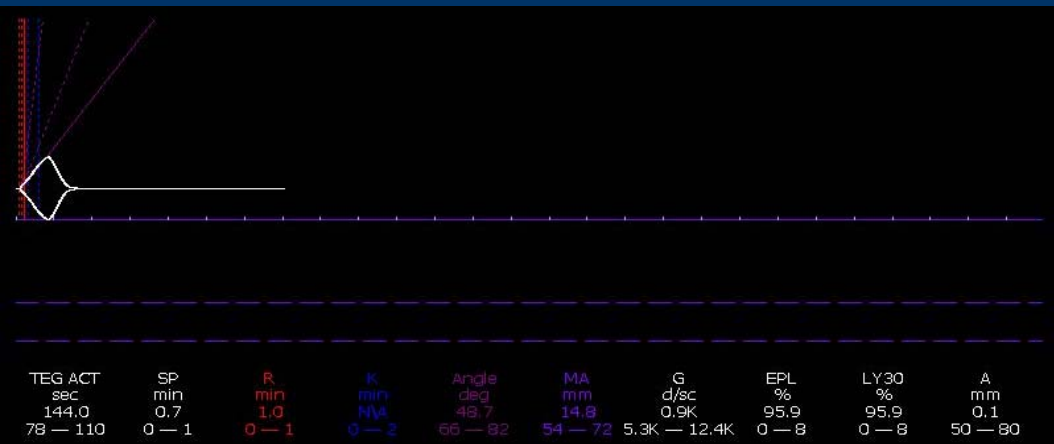
Antifibrinolytic Agents

- **Aminocaproic Acid** … lysine binding site plasminogen
- **Tranexamic Acid** … lysine binding site (10 X)

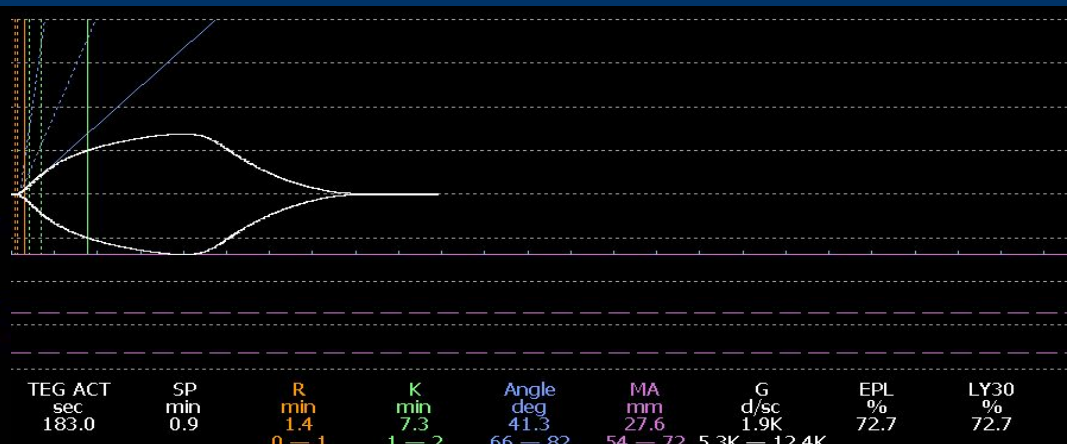


- **Aprotinin** … directly inhibits plasmin (thrombotic complications)

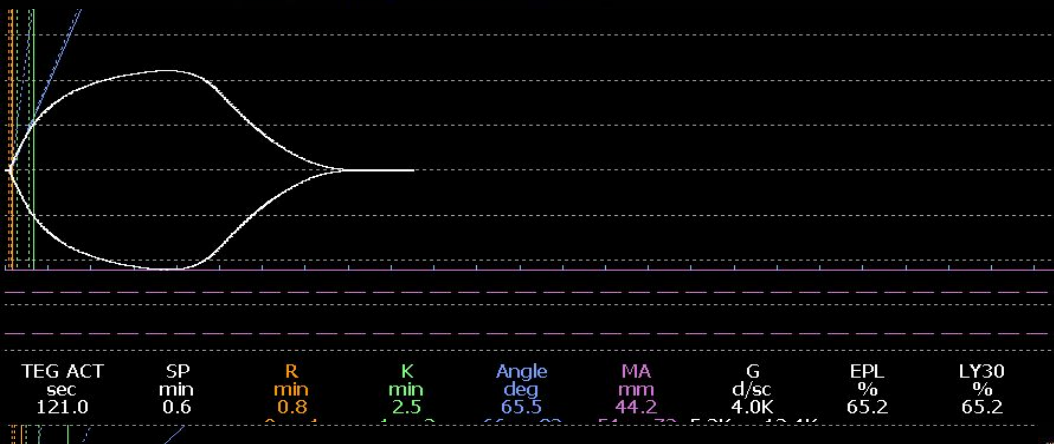
Postinjury Fibrinolysis : S/P MVC



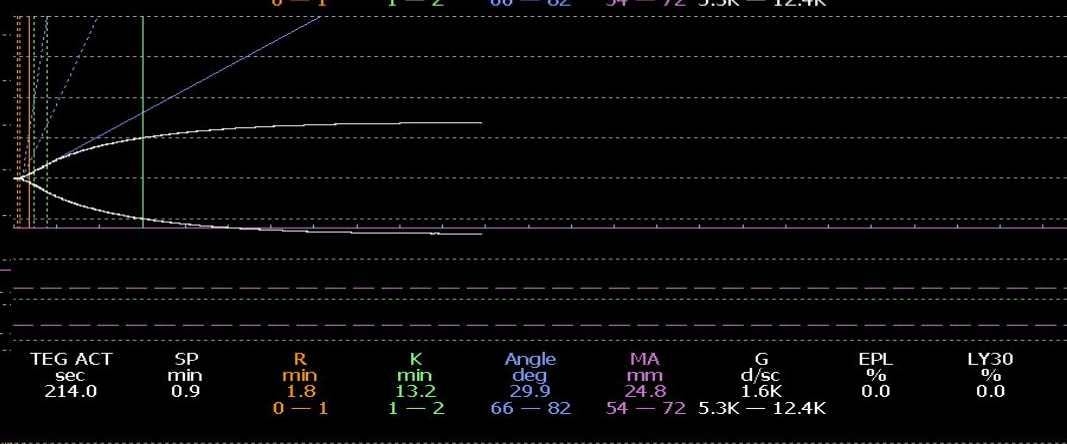
TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30	A
sec	min	min	min	deg	mm	d/sc	%	%	mm
144.0	0.7	1.0	NVA	48.7	14.8	0.9K	95.9	95.9	0.1
78 — 110	0 — 1	0 — 1	0 — 2	66 — 82	54 — 72	5.3K — 12.4K	0 — 8	0 — 8	50 — 80



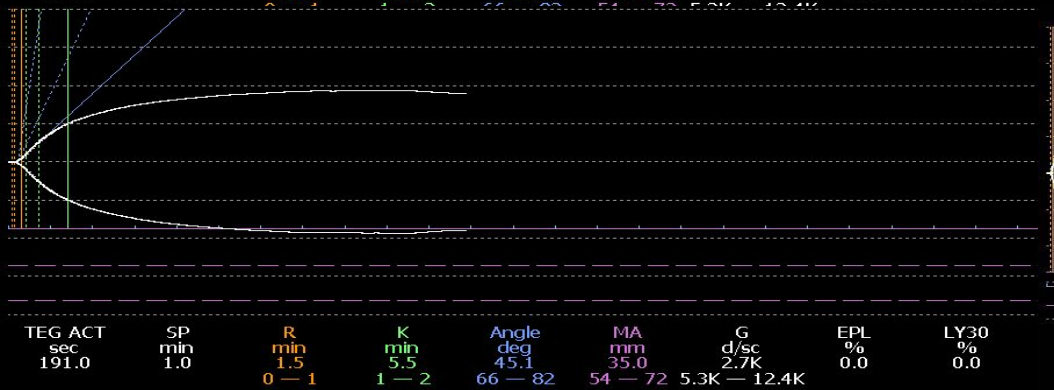
TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30
sec	min	min	min	deg	mm	d/sc	%	%
183.0	0.9	1.4	7.3	41.3	27.6	1.9K	72.7	72.7
		0 — 1	1 — 2	66 — 82	54 — 72	5.3K — 12.4K		



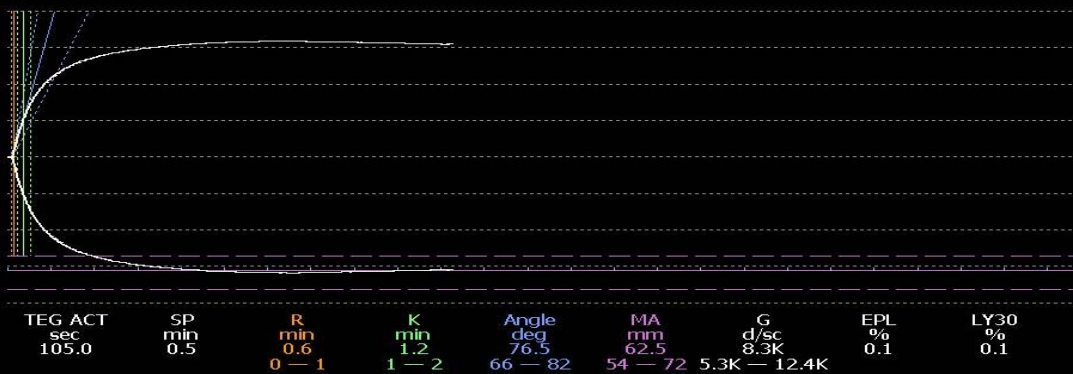
TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30
sec	min	min	min	deg	mm	d/sc	%	%
121.0	0.6	0.8	2.5	65.5	44.2	4.0K	65.2	65.2



TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30
sec	min	min	min	deg	mm	d/sc	%	%
214.0	0.9	1.8	13.2	29.9	24.8	1.6K	0.0	0.0
		0 — 1	1 — 2	66 — 82	54 — 72	5.3K — 12.4K		



TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30
sec	min	min	min	deg	mm	d/sc	%	%
191.0	1.0	1.5	5.5	45.1	35.0	2.7K	0.0	0.0
		0 — 1	1 — 2	66 — 82	54 — 72	5.3K — 12.4K		



TEG ACT	SP	R	K	Angle	MA	G	EPL	LY30
sec	min	min	min	deg	mm	d/sc	%	%
105.0	0.5	0.6	1.2	76.5	62.5	8.3K	0.1	0.1
		0 — 1	1 — 2	66 — 82	54 — 72	5.3K — 12.4K		

Sum : More Unknown than Known

1. Pathogenesis of Postinjury Coagulopathy

~ 1/3 Requiring MT / 6 hr Arrive with ACT… Activated PC

Hypothermia, Acidosis, Dilution, Consumption, Fibrinolysis, etc

2. Pre-emptive Therapy

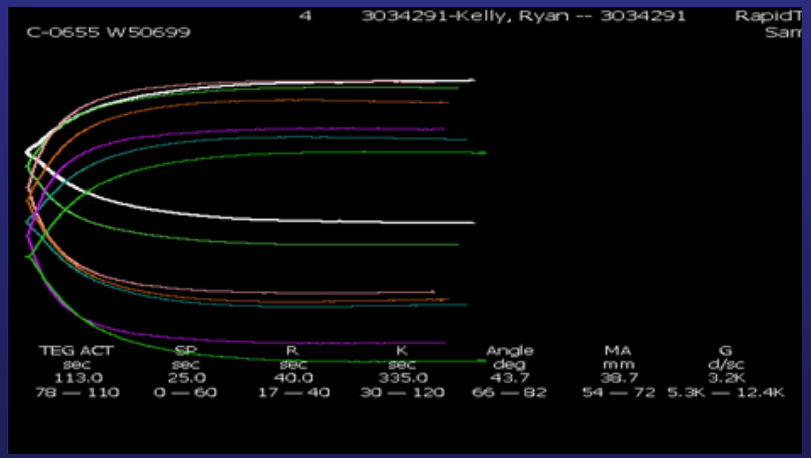
FFP : RBC Ratio = 1:2

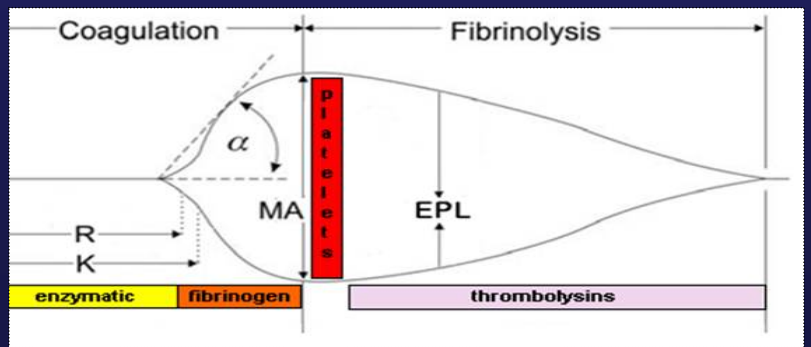
Antifibrinolytics … Selective

Platelets, Fibrinogen

3. Goal Directed Management

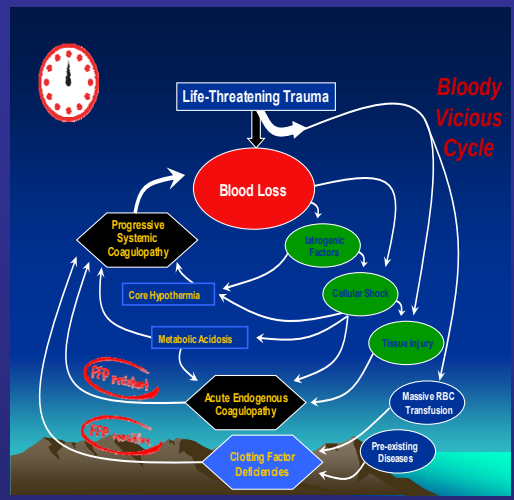
Thrombelastography

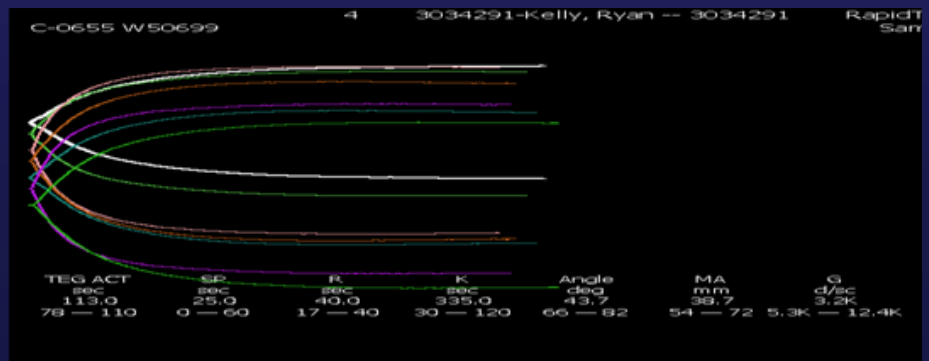


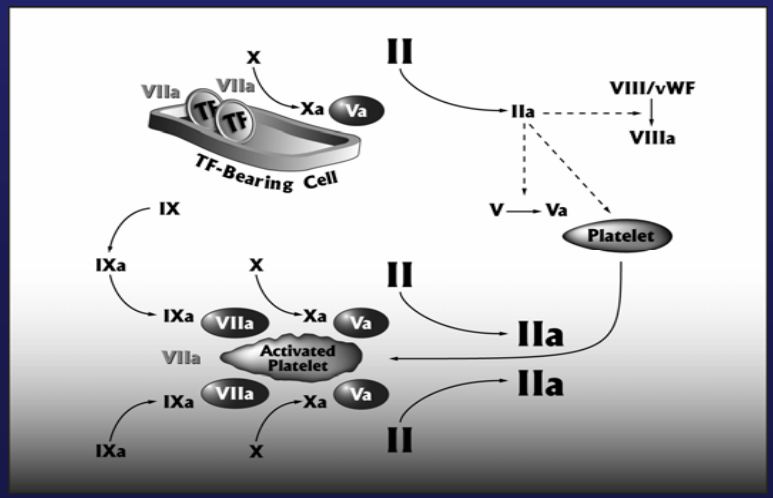


Postinjury Hemostasis : Our Protocol

- **Correct Shock … ASAP !!!**
- **Prevent Hypothermia**
- **Avoid Hypocalcemia**
- **Pre - emptive FFP : RBC = 1 : 2**
- **Pre - emptive Apheresis PLT / Cryo**
  if > 4 RBC 1st 30 min
- **Goal - directed via rTEG**







Thank you !!!

Qualitative Platelet Dysfunction : ? PLT Transfusion

> 10 U WB	Stefanini, et al	Clin Res Proc	1954
Korea WB	Scott, et al	Blood	1954
> 20 U WB Vietnam	Miller, et al	Ann Surg	1971
> 15 U MWB	Counts, et al	Ann Surg	1979
> 10 U RBC	Lucas, et al	Surgery	1985

(no evidence for presumptive PLT)

> 12 U / 12 hr RBC Reed, et al Ann Surg 1986

(no benefit of presumptive PLT)

Coagulation Factor Deficiency : ? FFP Transfusion

- Pre-emptive FFP: RBC = 1:4 DGH ... J Trauma 1982
- Canine hemorrhage shock Lucas, et al Ann Surg 1985
  (no benefit of presumptive FFP)
- Pre-emptive FFP: RBC = 1:5 Wilson, et al J Trauma 1987
- FFP after > 10 RBC Lucas, et al J Trauma 1989
- Pre-emptive FFP:RBC = 1:1 DGH ... Ann Surg 2001
  PLT:RBC = 5:5 (pelvic fracture hemorrhage)
- Pre-emptive FFP:RBC = 1:1 Holcomb et al J Trauma 2007
  (
  (Iraq)
- Pre-emptive PLT:FFP:RBC =1:1:1 Holcomb et al Ann Surg 2008
  (Civilian)

Postinjury Hemostasis with Massive Transfusion

Qualitative Platelet Dysfunction : ? PLT Transfusion

> 10 U WB	Stefanini, et al Clin Res Proc	1954
Korea WB	Scott, et al Blood	1954
> 20 U WB Vietnam	Miller, et al Ann Surg	1971
> 15 U MWB	Counts, et al Ann Surg	1979
> 10 U RBC	Lucas, et al Surgery	1985
	(no evidence for presumptive PLT)	
> 12 U / 12 hr RBC	Reed, et al Ann Surg	1986
	(no benefit of presumptive PLT)	

Coagulation Factor Deficiency : ? FFP Transfusion

Pre-emptive FFP: RBC = 1:4	DGH ... J Trauma	1982
Canine hemorrhage shock	Lucas, et al Ann Surg	1985
	(no benefit of presumptive FFP)	
Pre-emptive FFP: RBC = 1:5	Wilson, et al J Trauma	1987
FFP after > 10 RBC	Lucas, et al J Trauma	1989
Pre-emptive FFP:RBC = 1:1	DGH ... Ann Surg	2001
PLT:RBC = 5:5	(pelvic fracture hemorrhage guidelines)	
Pre-emptive FFP:RBC = 1:1	Holcomb et al J Trauma (Iraq)	2007
Pre-emptive PLT:FFP:RBC =1:1:1	Holcomb et al Ann Surg (Civilian)	2008

Civilian Trauma – Massive Transfusion

FFP : RBC ≥ 1:2	PLT : RBC ≥ 1:2		Mortality
FFP	PLT	=	29%
FFP	-	=	48%
-	PLT	=	34%
-	-	=	59%

n = 466 (10% Head)

Holcomb et al

Ann Surg 2008

Blood Component Expenses

L – RBC	=	$ 225
FFP	=	$ 70
PLT aph	=	$ 575

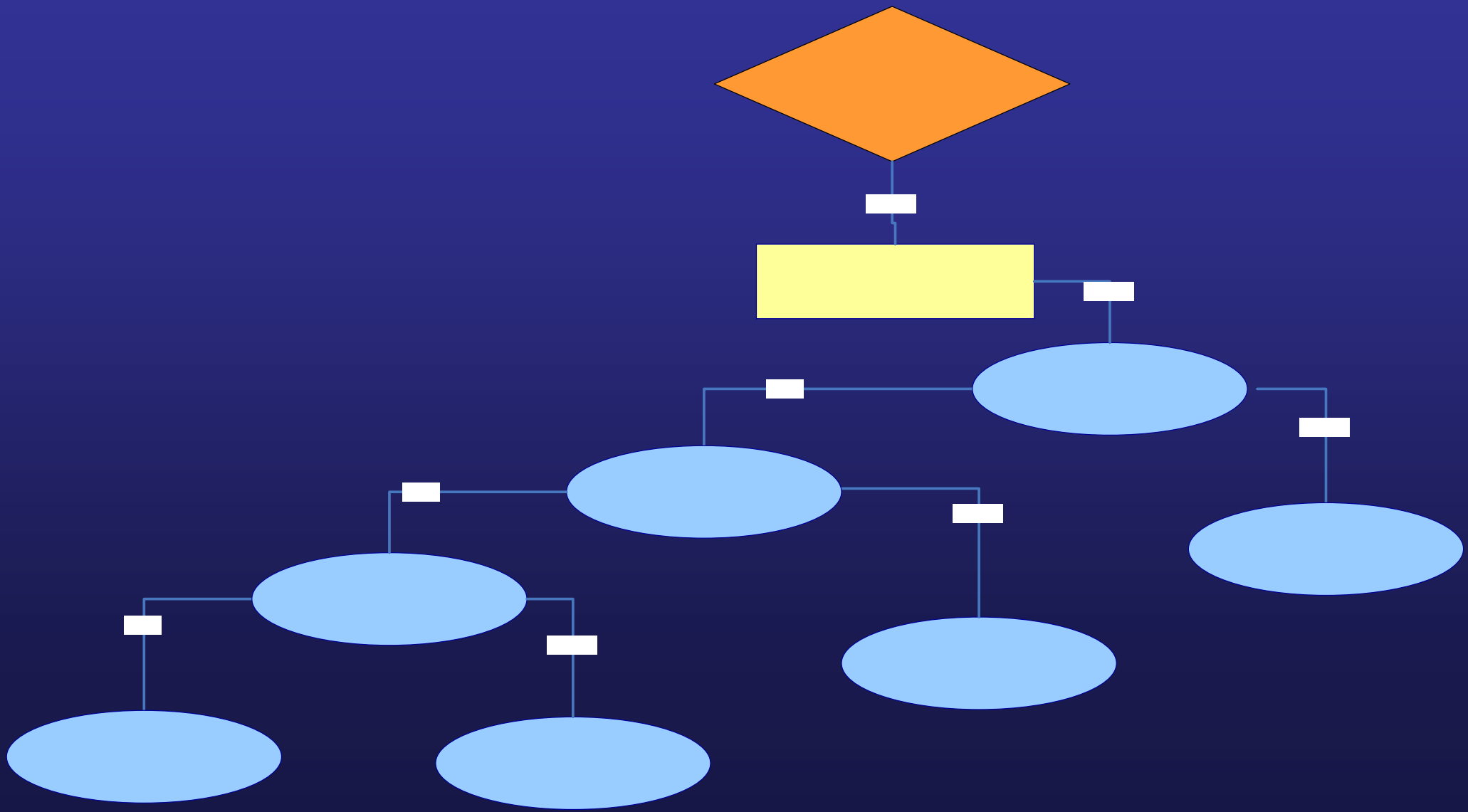
Recombinant Factor VIIa : Coagulopathy

FDA Approved – Hemophiliac VIII / IX Inhibitors

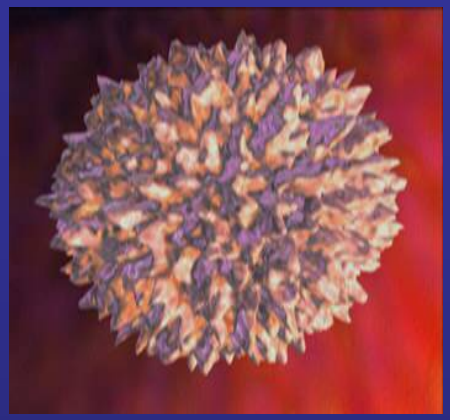
Multiple Trauma Series : Randomized Trial x 2

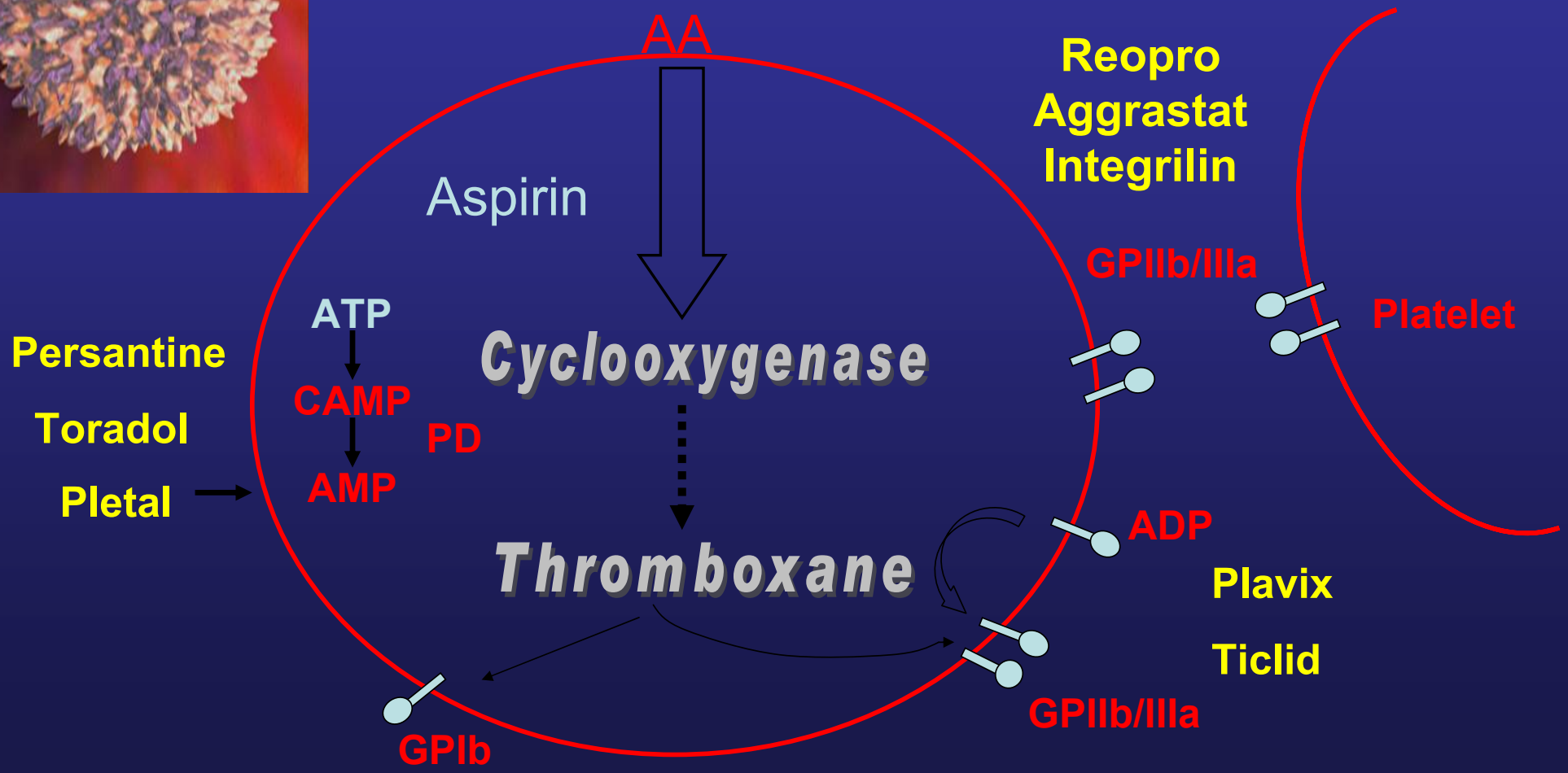
Off – label Use : ? Indication
? Dose
? Risk / Benefit

Postinjury Coagulopathy

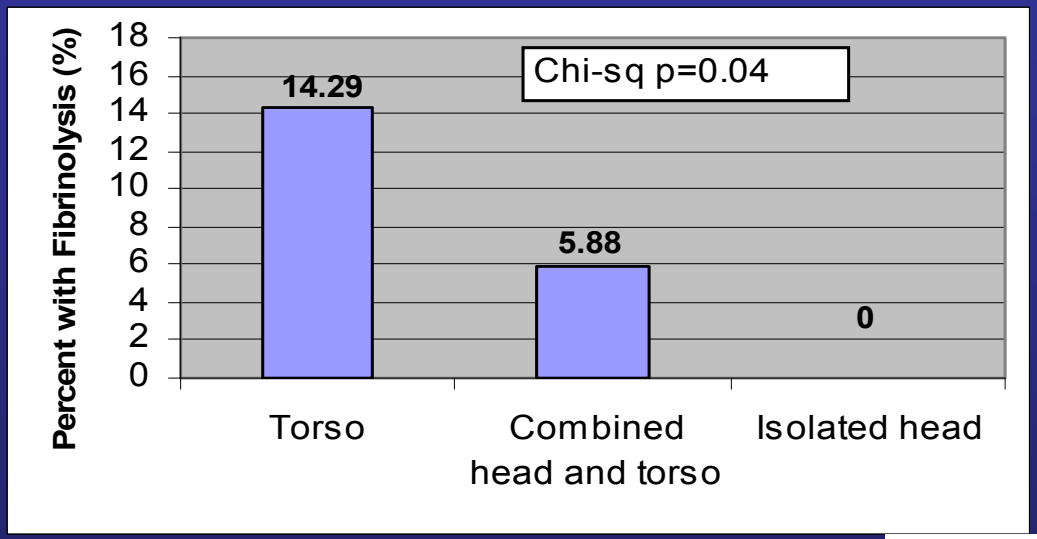


Pharmacologic Control of Thrombus Formation



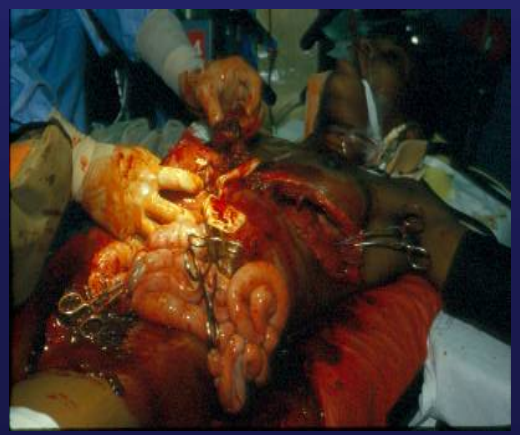


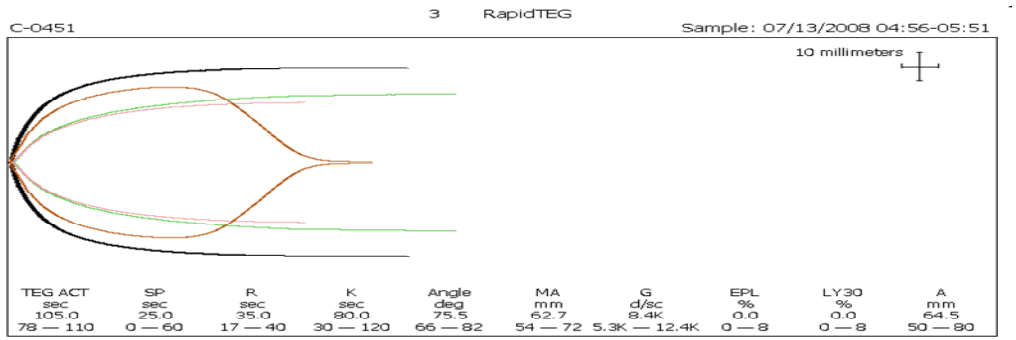
Postinjury Fibrinolysis



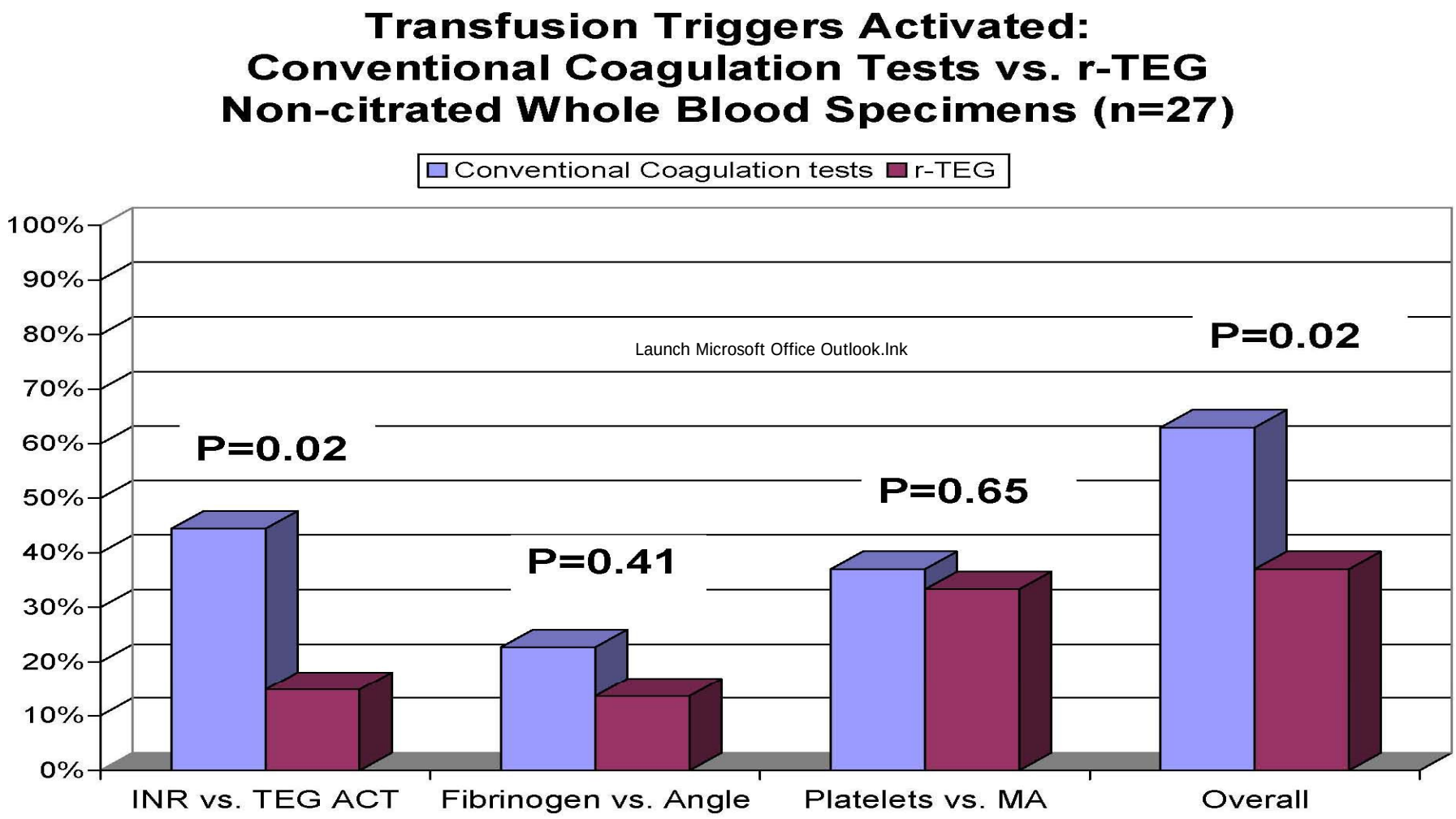
Profound Shock

(Not Brain Tissue)





POC Rapid Thrombelastography

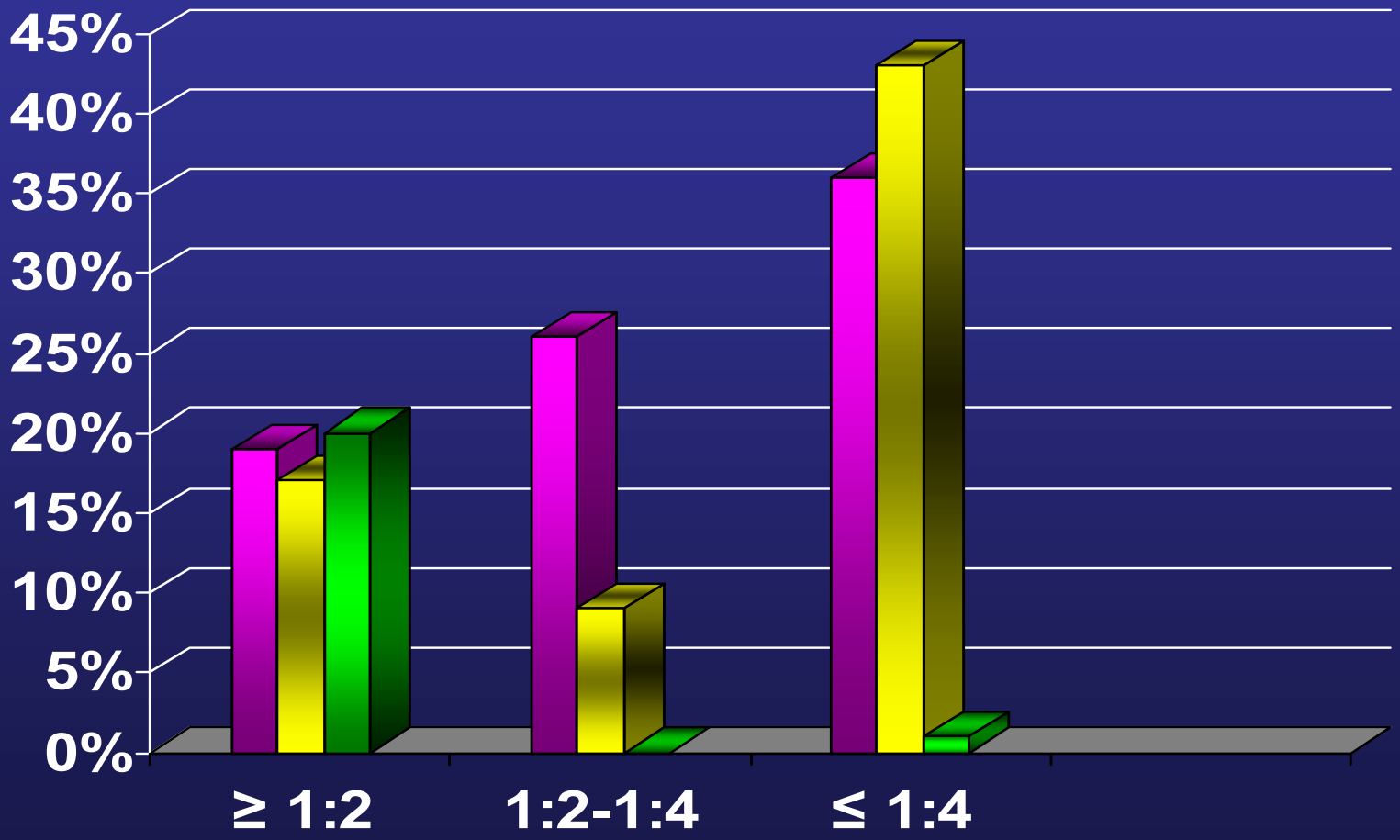


POC Rapid Thromboelastography

Pre TEG	(n = 68)	Post TEG
-13	ED : BD	-15
1.6	ED : INR	1.8
18.0	RBC / 6 hr	17.2
6.8	FFP / 6 hr	6.5
65%	Mortality	29%
21%	Coagulopathy	3%

AAST 2009

Combat Injury Mechanism … FFP : RBC



Mace et al
JACS 2009

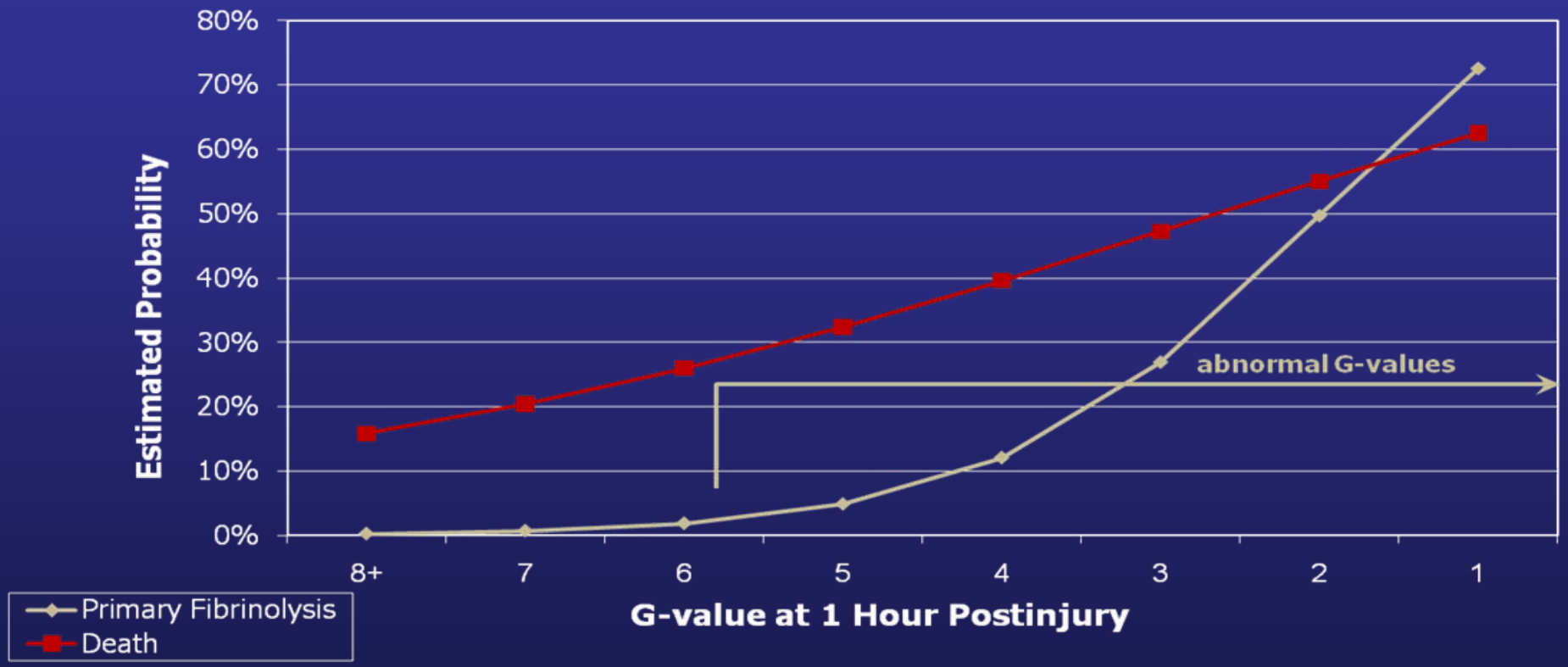
POSTINJURY FIBRINOLYSIS

61 Acute Injury / ED RBC

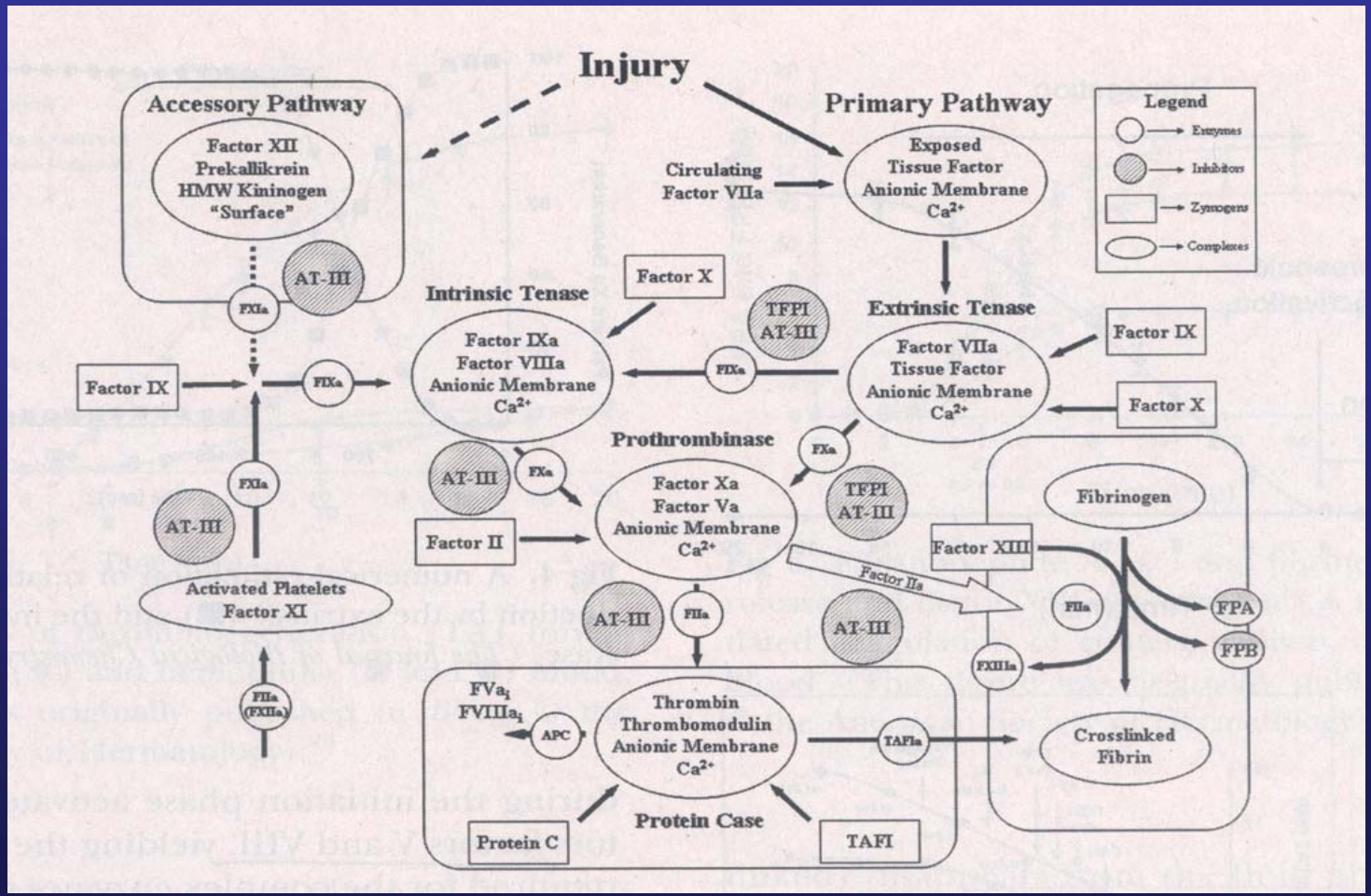
	Massive	Moderate	Minimal
	>10u /6hrs N=32 (52%)	5-10u / 6hrs N=15 (25%)	<5u / 6hrs N=14 (23%)
Mortality →	53%	7%	7%

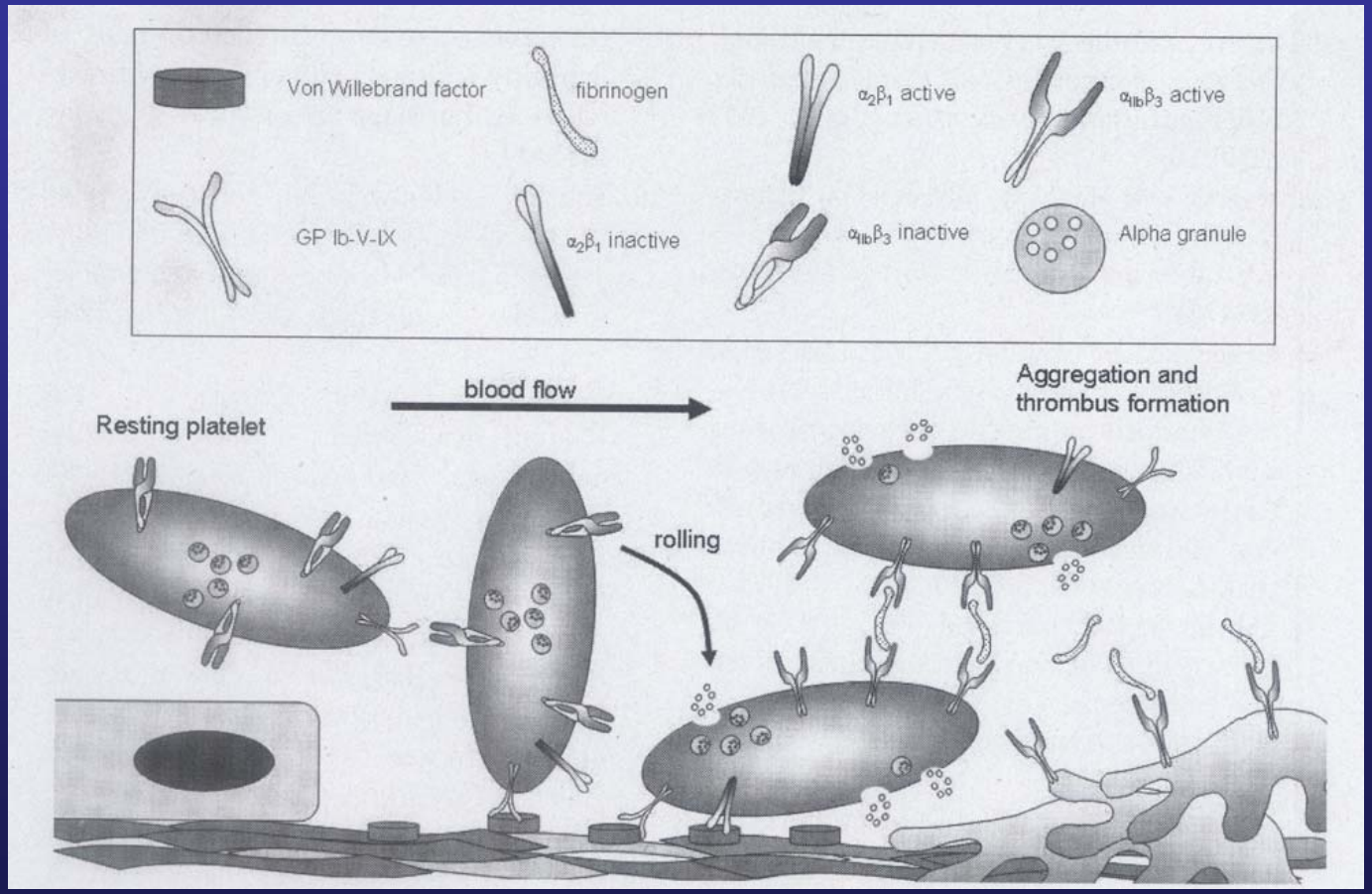
Ann Surg 2010

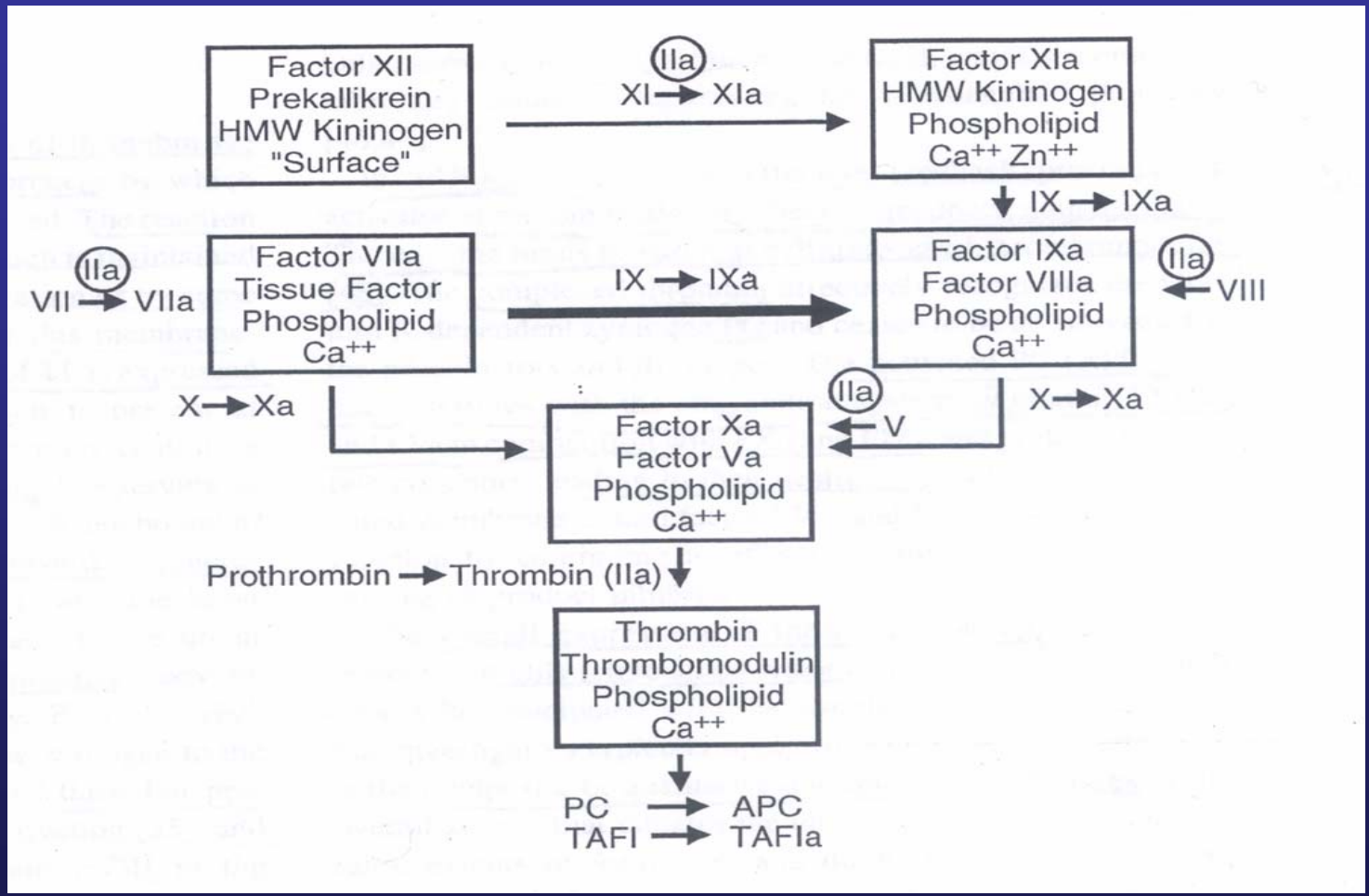
Estimated Probability of Primary Fibrinolysis and Death by G value at 1 hour Postinjury



For every one unit drop in G value (clot strength) by one hour, risk of PF increases by 30% and death by >10%


Injury
Accessory Pathway
Factor XII
Prekallikrein
HMW Kininogen
"Surface"
AT-III
FXIIa
Factor IX
FIXa
FXIIa
AT-III
Activated Platelets
Factor XI
FIIa
(FXIIa)
Primary Pathway
Circulating
Factor VIIa
Exposed
Tissue Factor
Anionic Membrane
Ca2+
Legend
Enzymes
Inhibitors
Zymogens
Complexes
Intrinsic Tenase
Factor X
Factor IXa
Factor VIIIa
Anionic Membrane
Ca2+
TFPI
AT-III
FIXa
Extrinsic Tenase
Factor IX
Factor VIIa
Tissue Factor
Anionic Membrane
Ca2+
Factor X
Prothrombinase
FXa
AT-III
FXa
Factor II
Factor Xa
Factor Va
Anionic Membrane
Ca2+
TFPI
AT-III
Factor IIa
AT-III
FIIa
AT-III
Fibrinogen
Factor XIII
FIIa
FPA
FPB
FXIIIa
FVai
FVIIIai
APC
Thrombin
Thrombomodulin
Anionic Membrane
Ca2+
TAFIa
Crosslinked
Fibrin
Protein Case
Protein C
TAFI


Von Willebrand factor
fibrinogen
$\alpha_2\beta_1$ active
$\alpha_{IIb}\beta_3$ active
GP Ib-V-IX
$\alpha_2\beta_1$ inactive
$\alpha_{IIb}\beta_3$ inactive
Alpha granule
blood flow
Resting platelet
rolling
Aggregation and thrombus formation


Factor XII
Prekallikrein
HMW Kininogen
"Surface"
IIa
XI → XIa
Factor XIa
HMW Kininogen
Phospholipid
Ca++ Zn++
IX → IXa
Factor VIIa
Tissue Factor
Phospholipid
Ca++
IIa
VII → VIIa
IX → IXa
Factor IXa
Factor VIIIa
Phospholipid
Ca++
IIa
VIII
X → Xa
IIa
V
X → Xa
Factor Xa
Factor Va
Phospholipid
Ca++
Prothrombin → Thrombin (IIa)
Thrombin
Thrombomodulin
Phospholipid
Ca++
PC → APC
TAFI → TAFIa