The changing face of massive transfusion

HAABB, Kansas City, 18 April 2018

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Disclosure Statement

- Patent rights and stock ownership in gel-e Life Sciences, a maker of bioabsorbable hemostatic bandages

- Royalties from Army and U Maryland on patents licenses related to AS-7 RBC storage system

- Royalties for writing the chapter on ‘Massive Transfusion” in UpToDate.

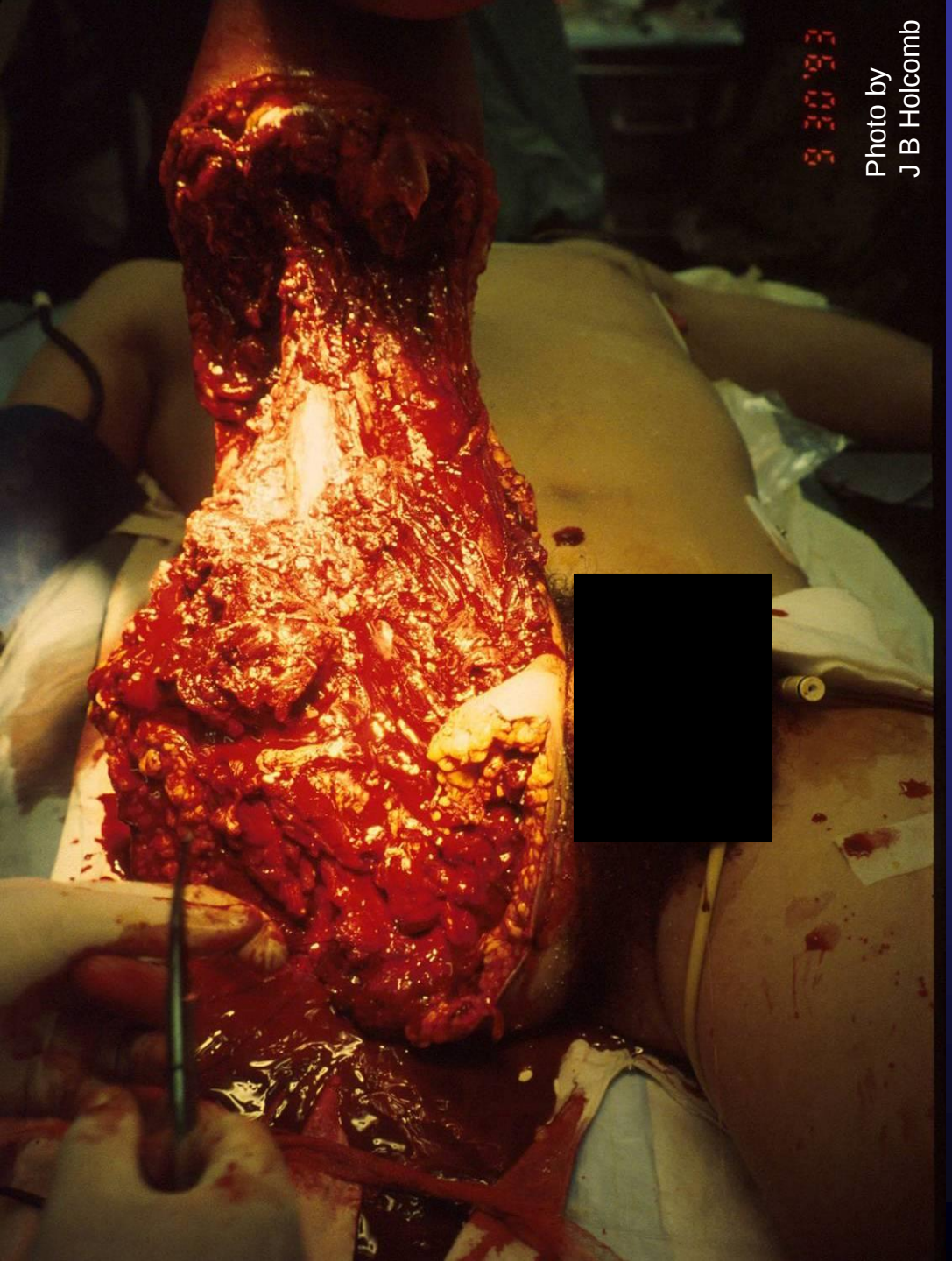
Objectives

- Review the causes of coagulopathy in trauma patients
- Describe the limits of crystalloid fluid and blood product resuscitation
- Describe the PROPRR trial, published in JAMA 2015; 313(5):483-494.
-

Massive transfusion – the old way

- Start 2 large bore IVs
- Resuscitate with crystalloid volume expanders, 2 L initially, more for low BP
- Add RBCs to maintain oxygen transport
- Add plasma to keep PT and PTT less than 1.5 x normal
- Add platelets to keep count > 50 K/mcL
- Add fibrinogen to keep > 100 mg/dL

ATLS Manual, ACS COT

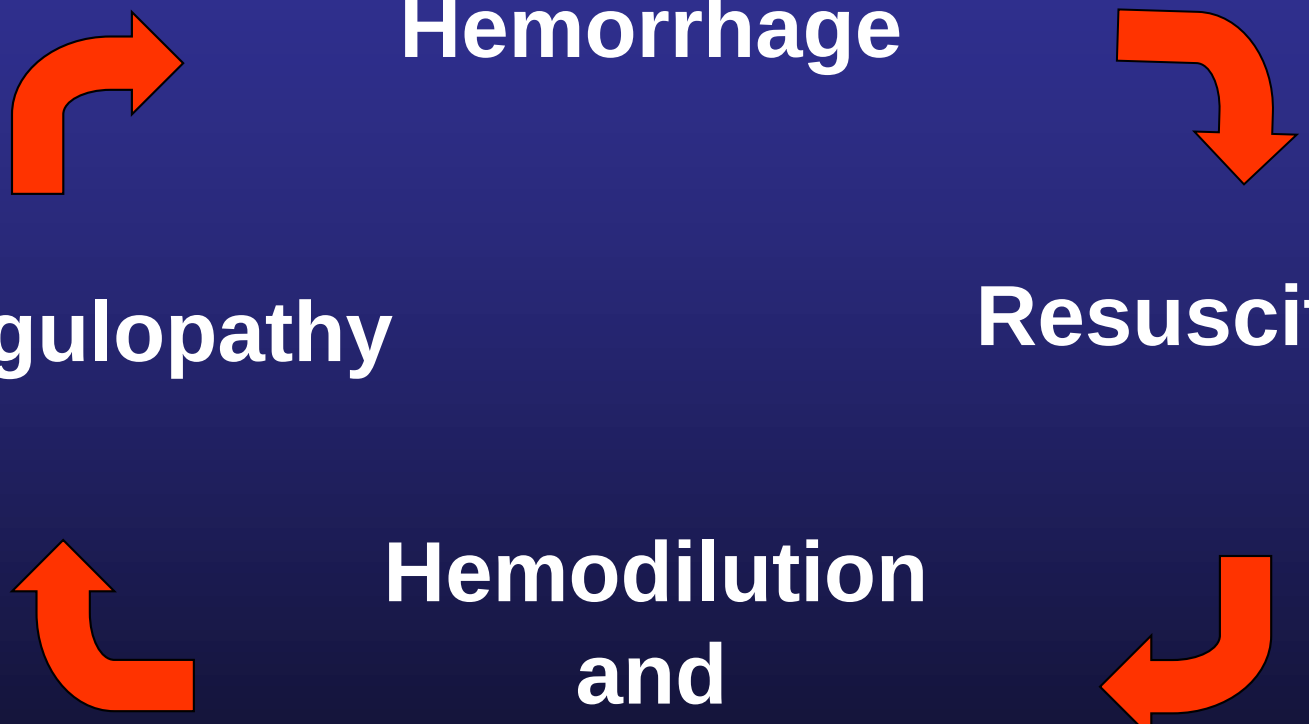


Mogadishu
30 Sep 1993

A soldier is bitten by a great white shark

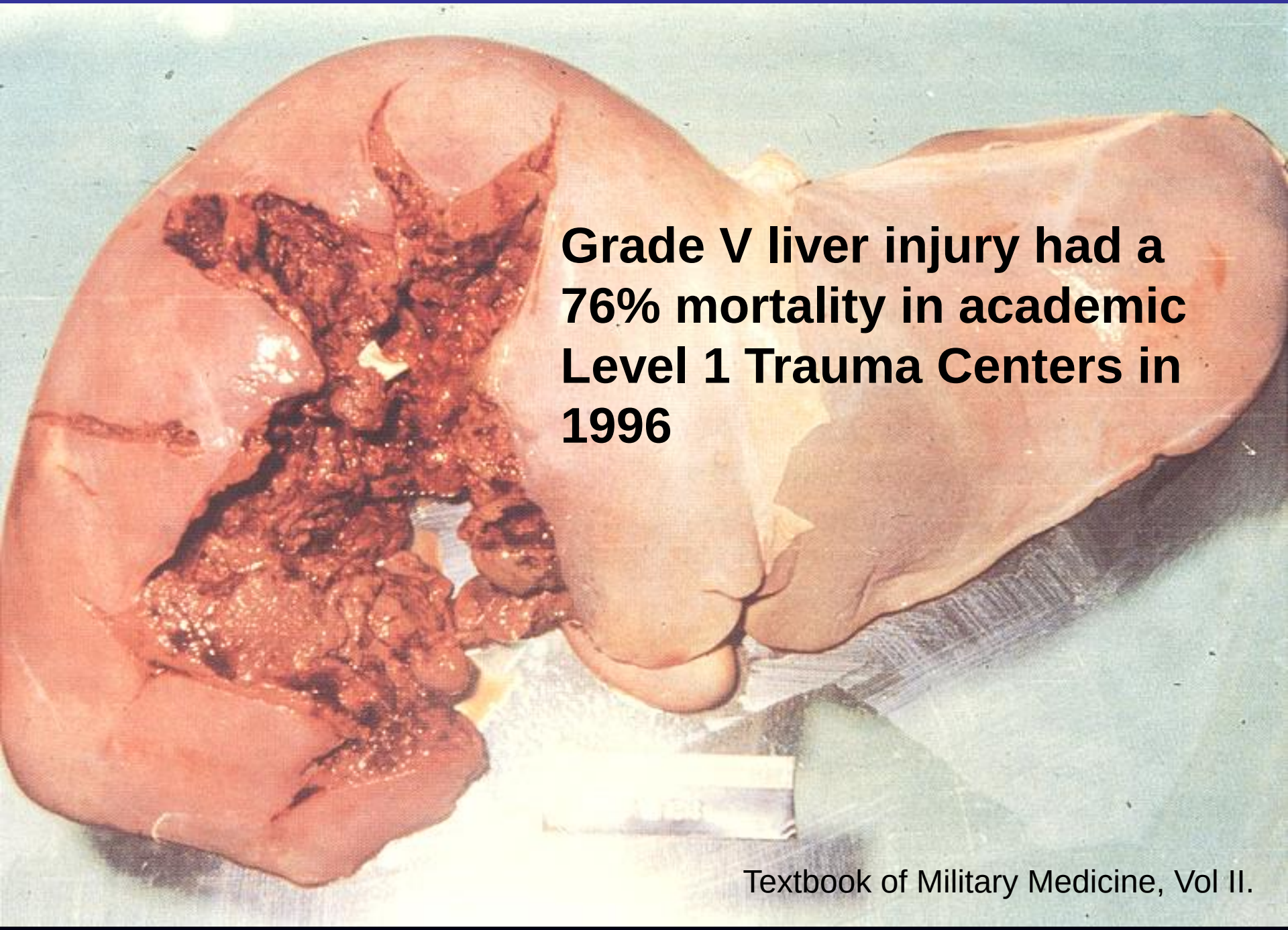
He used all 50 U of RBC they had

“Bloody Vicious Cycle”



The human coagulation system is slow and weak

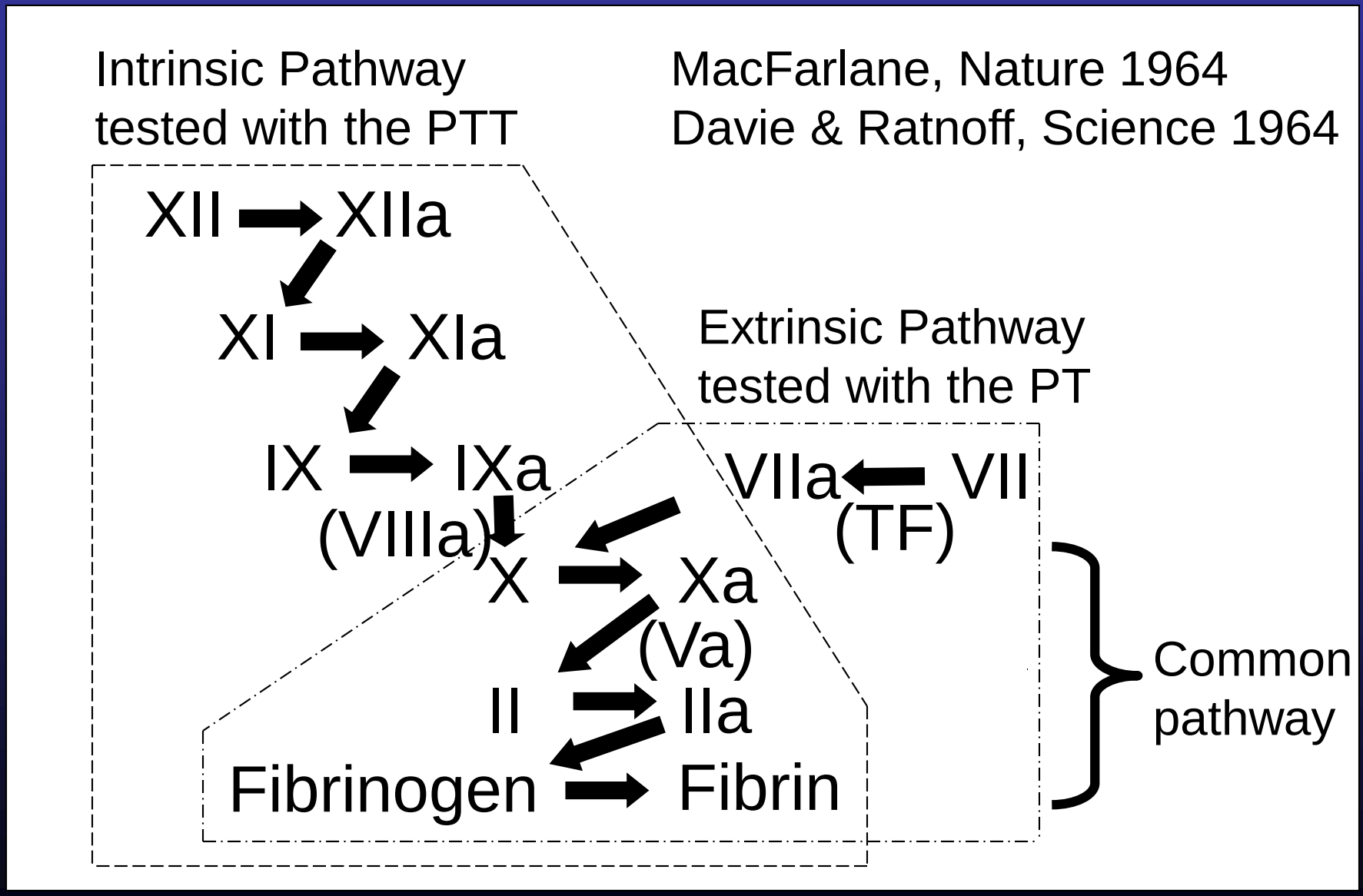
- Clotting takes time (2-10 minutes in the best of circumstances)
- Clots are physically weak
- There is limited clotting material to work with (even in the whole body)
  - 10 grams of fibrinogen total
  - 15 mL of platelets total in normal individuals


Grade V liver injury had a 76% mortality in academic Level 1 Trauma Centers in 1996
Textbook of Military Medicine, Vol II.

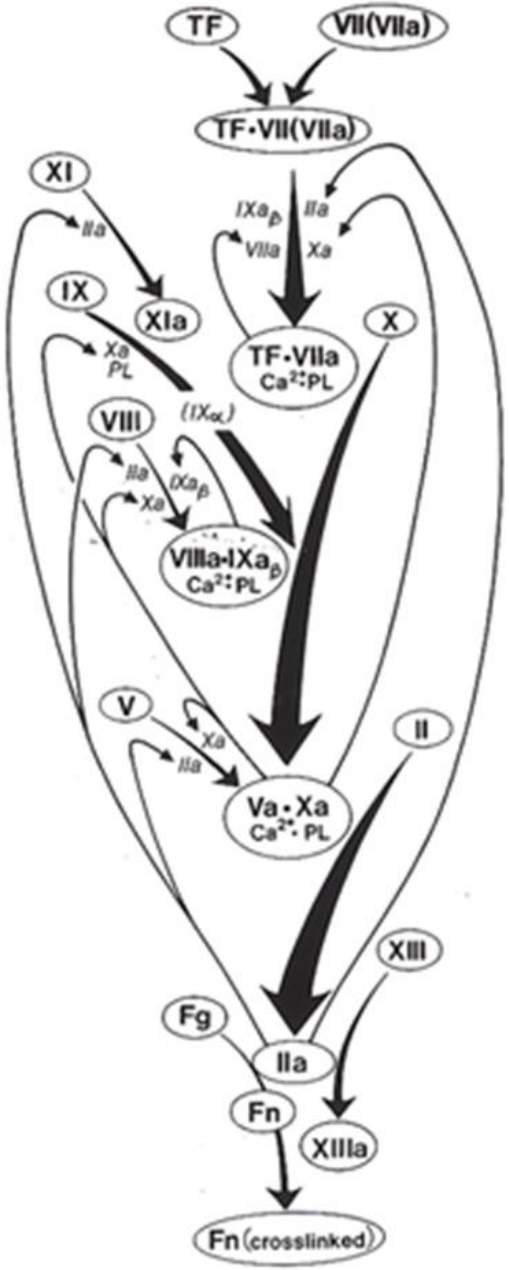
Human blood clotting is weak because it has to be!

- Ten times more people die from clotting than from bleeding (heart attacks, strokes, pulmonary embolii, etc).
- Moderate bleeding is an uncommon event, but clotting is a continuous threat.
- The body evolved to deal with bruising and minor to moderate bleeding.

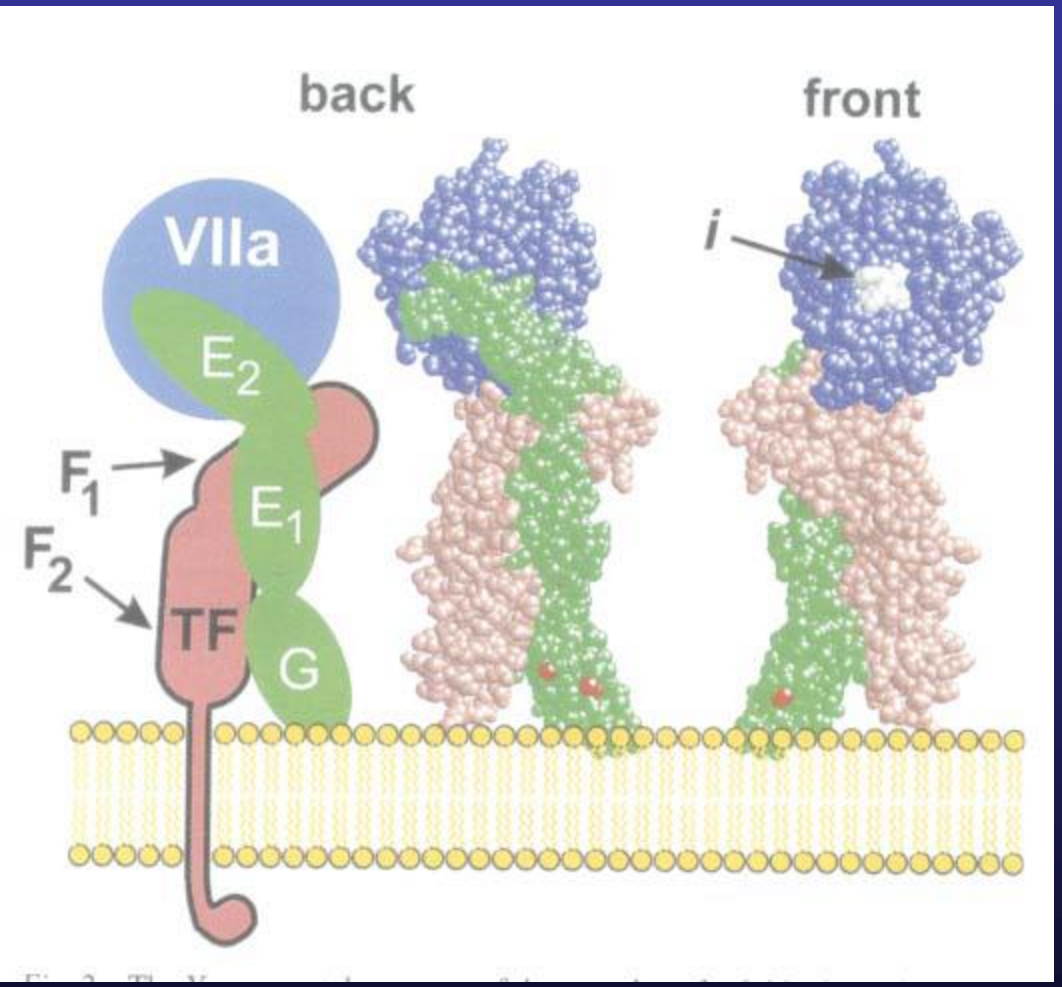
The Classic Coagulation Cascade



Kinetically the coagulation system looks like the extrinsic pathway with many feed-back loops.



Factor VII and Tissue Factor

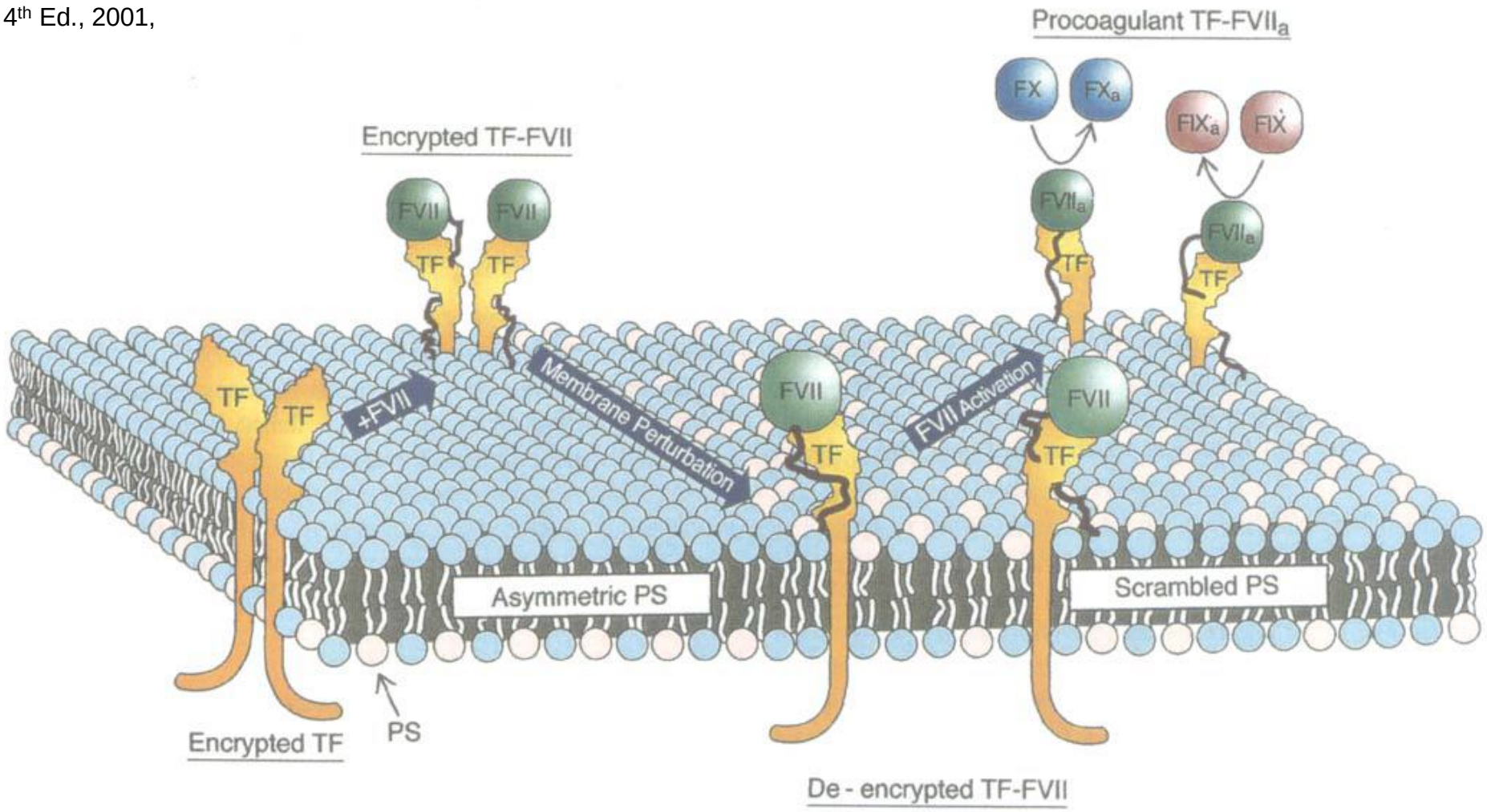


In the resting state, 1% of FVII is in the active or VIIa form. It is more active when bound to TF and even more active when the two are bound on an activated cell surface.

Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001, p780

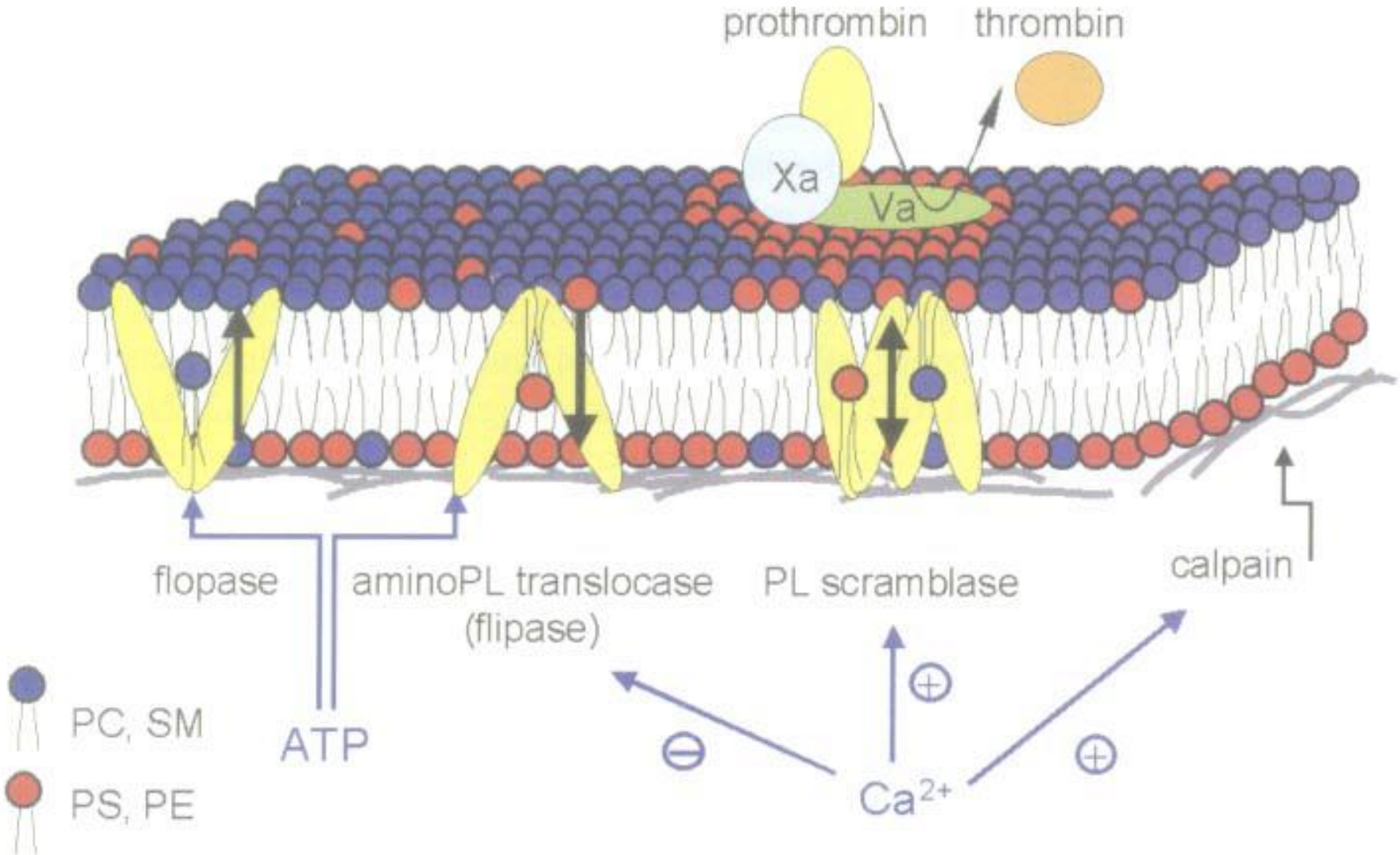
Activation of tissue factor (TF) and Factor VII on the cell surface

Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001,

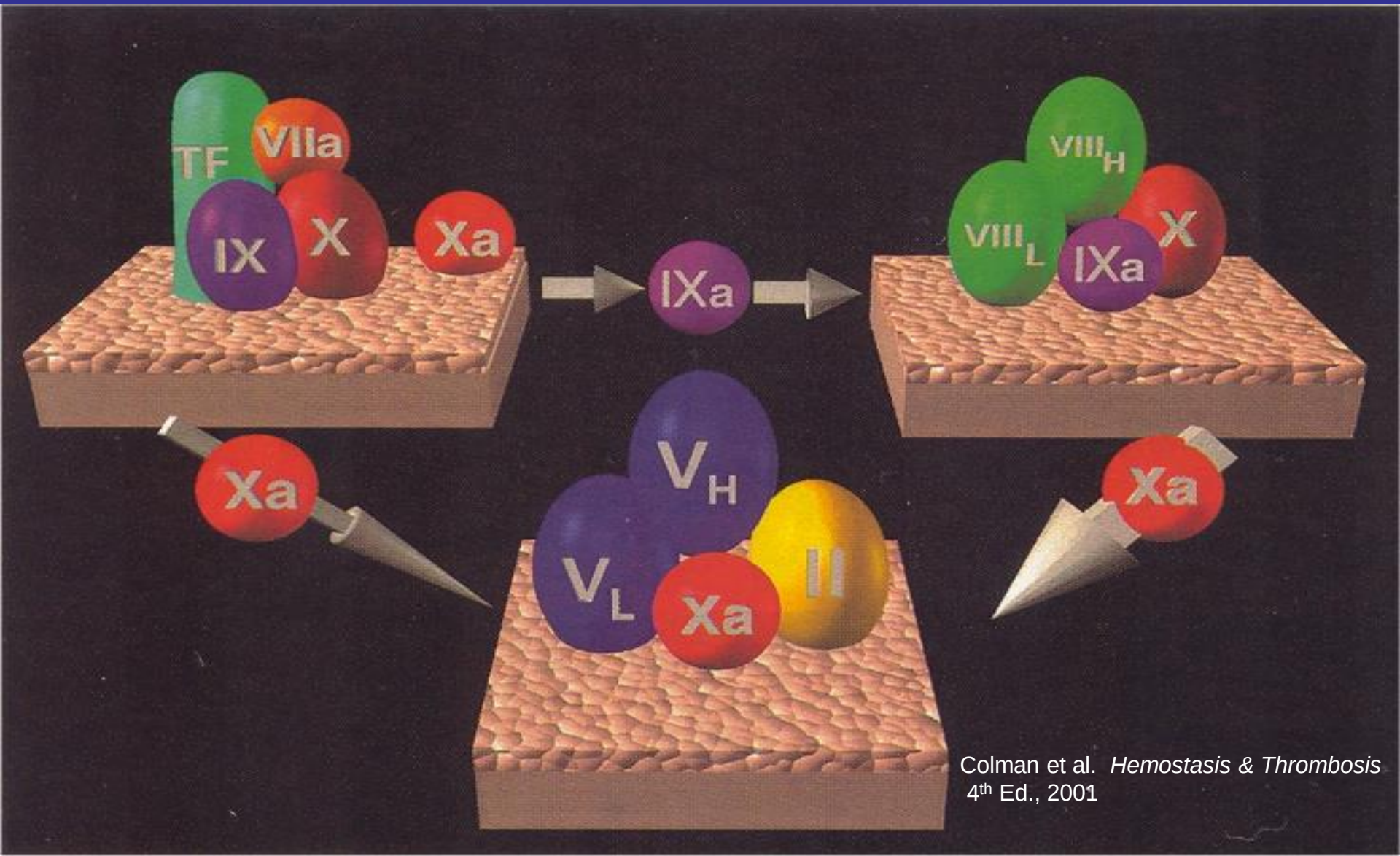


PS scrambling produces negatively charged "rafts" which bind Ca^{++} and vitamin K dependent factors

Colman et al. *Hemostasis & Thrombosis*
4th Ed., 2001



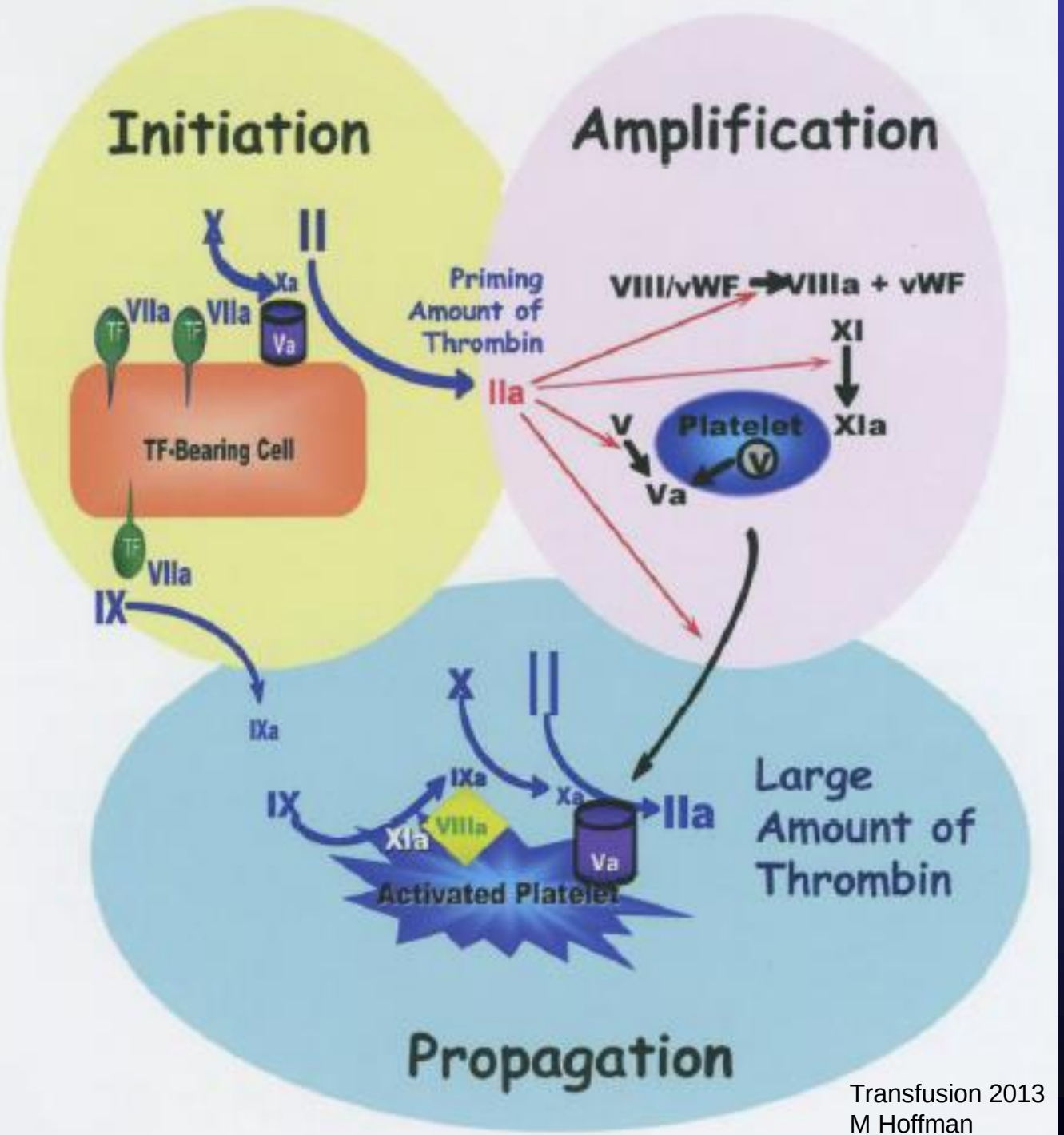
On activated surfaces the complexes are more active than the free enzymes



Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001

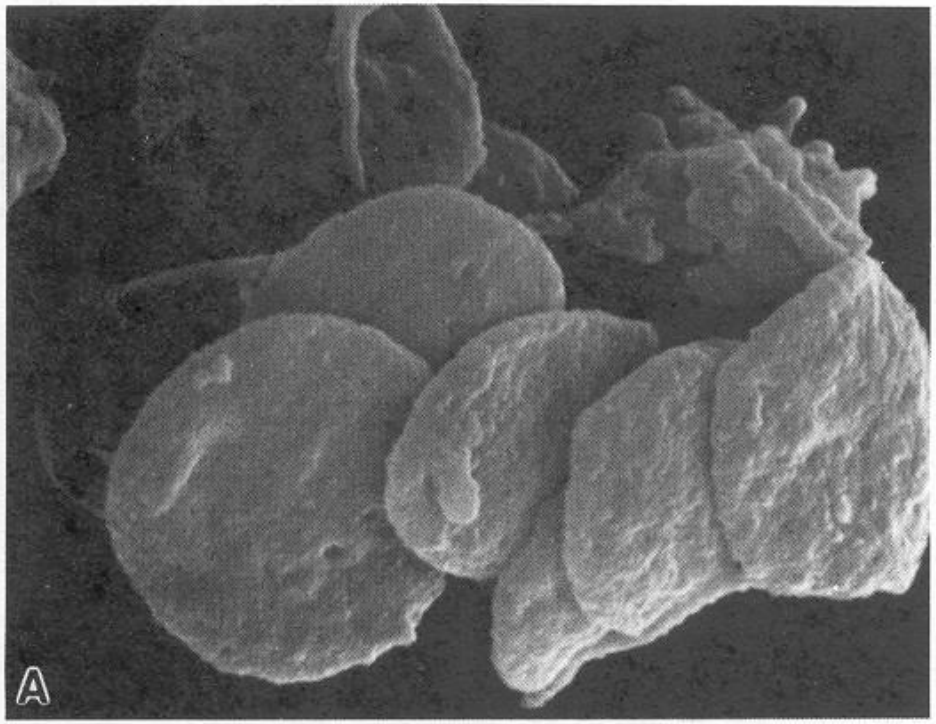
Modern cell-based model of plasma coagulation

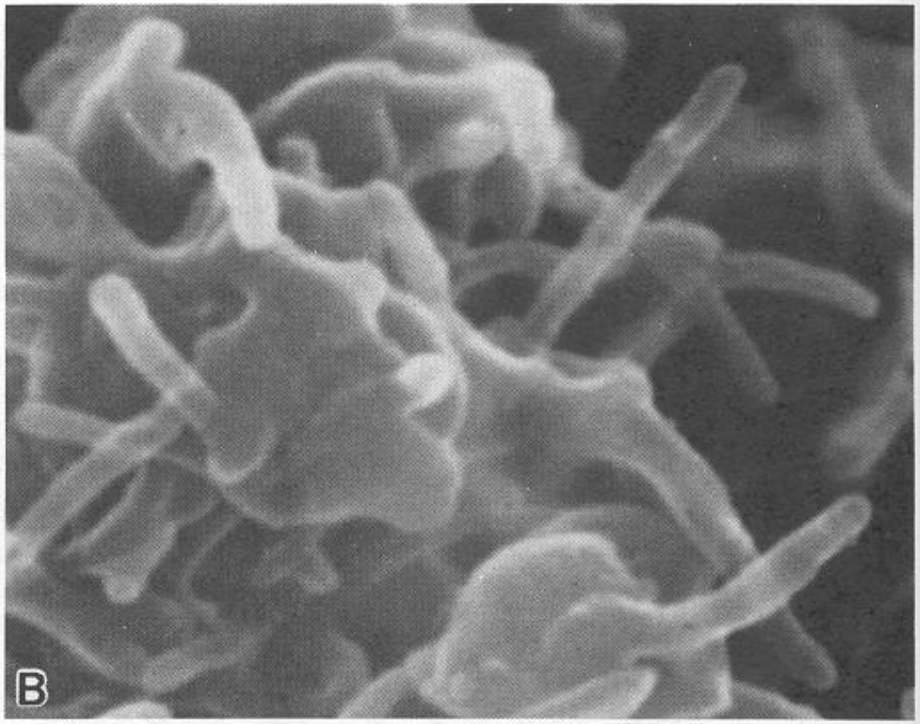
Thrombin activates
- factors I, V, VIII, XI, & XIII
- platelets
- TAFI



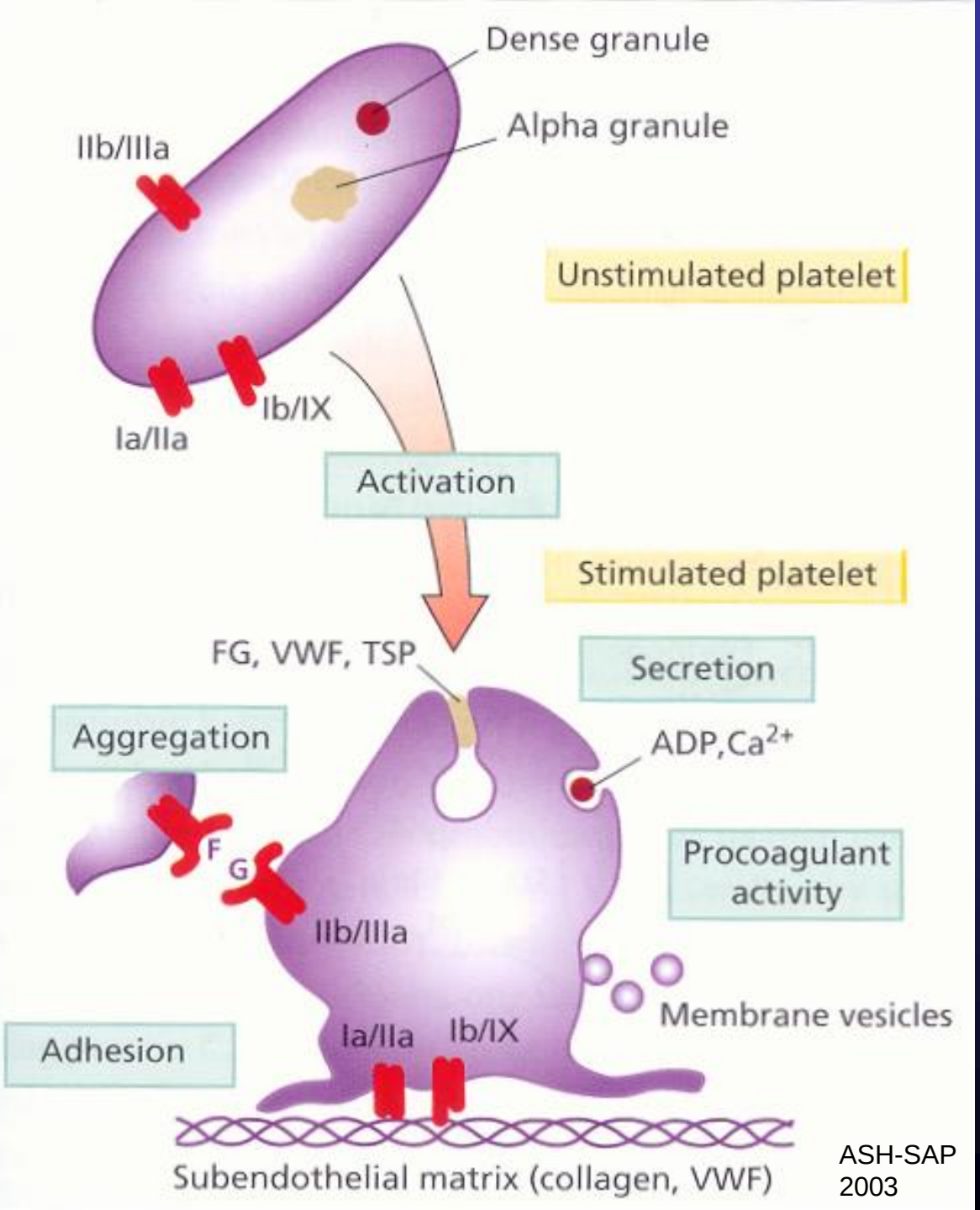
Transfusion 2013
M Hoffman

Platelet activation





Hoffman et al. *Hematology,* 1991, page 1162

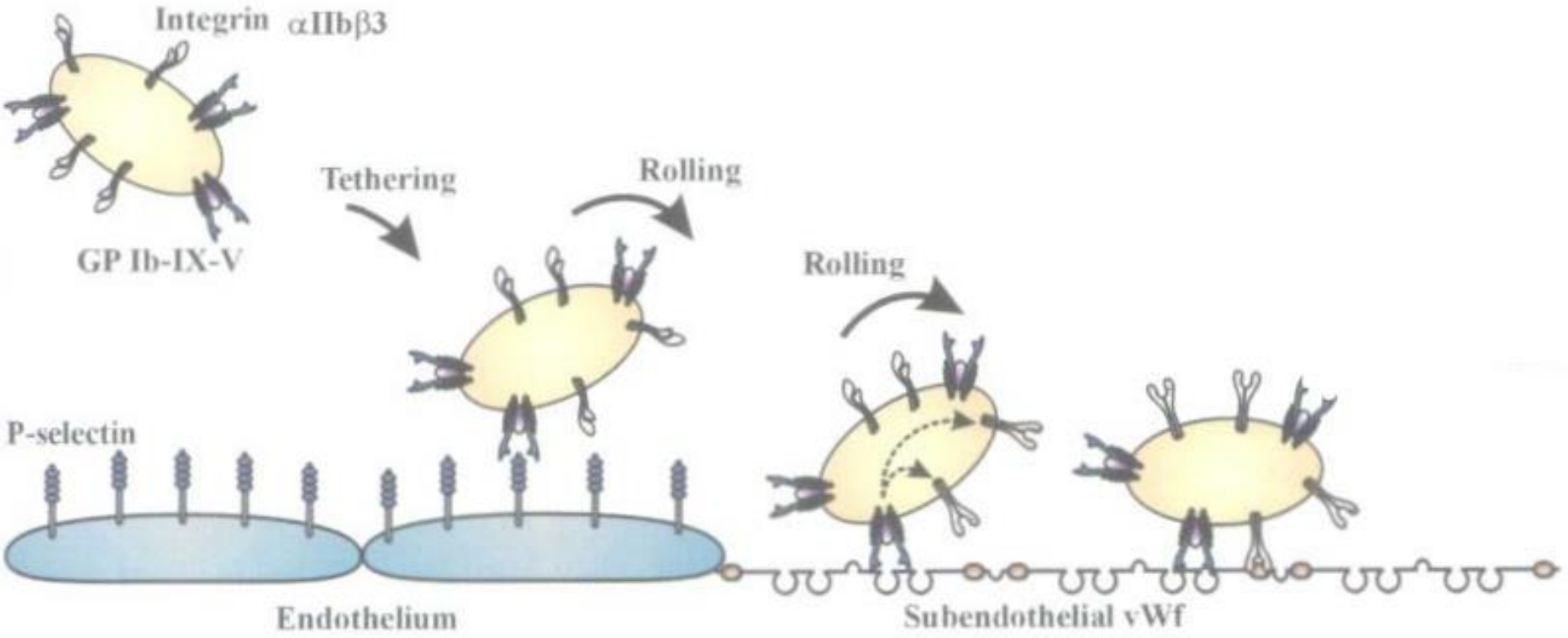


Platelets adhere, activate, secrete and aggregate.

Adherence and activation are coupled by vWF pulling on GPIb-IX. Activation, secretion, and aggregation are coupled by Ca^{++} signaling

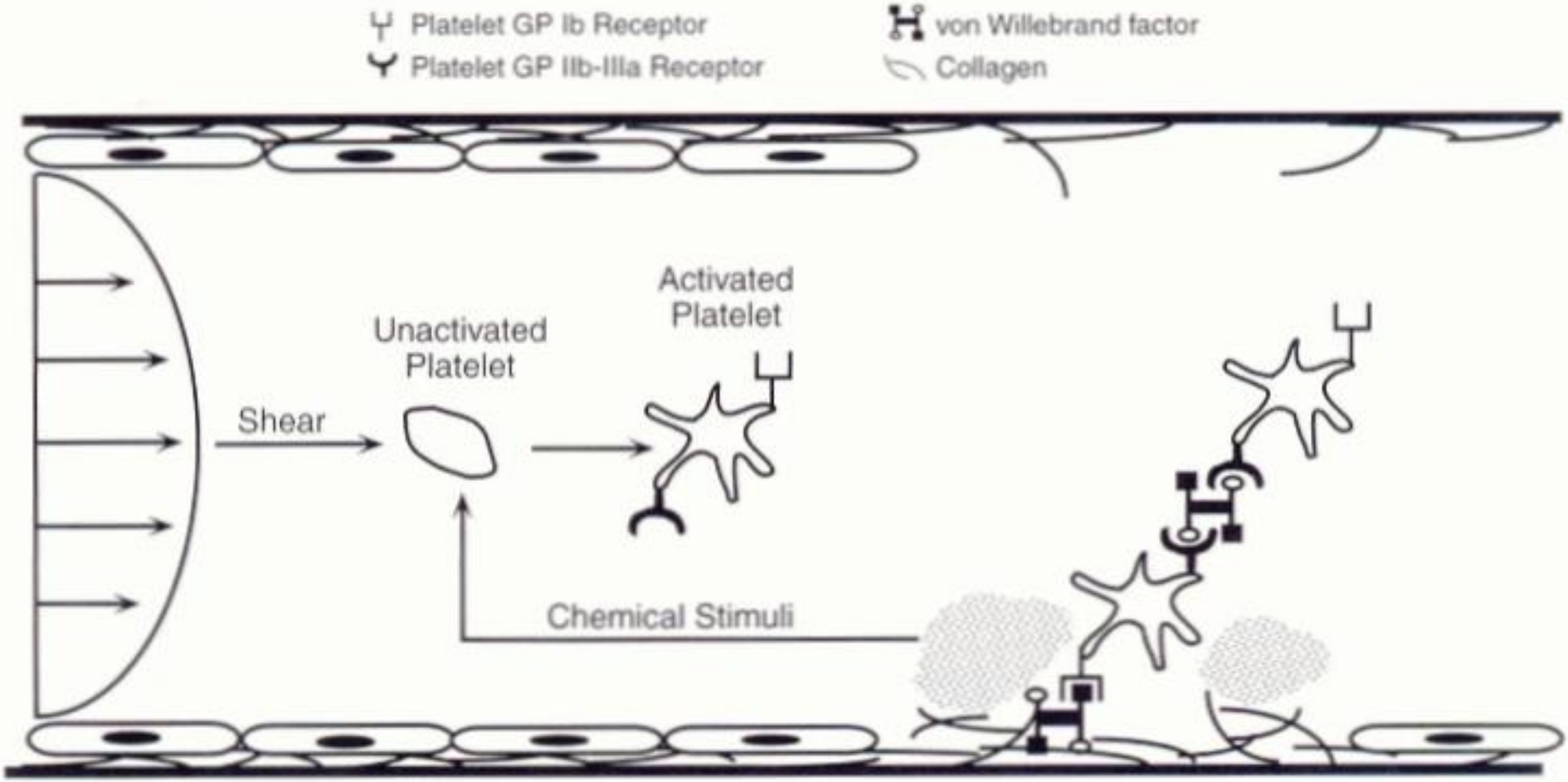
ASH-SAP 2003

The critical role of vWF in platelet adhesion

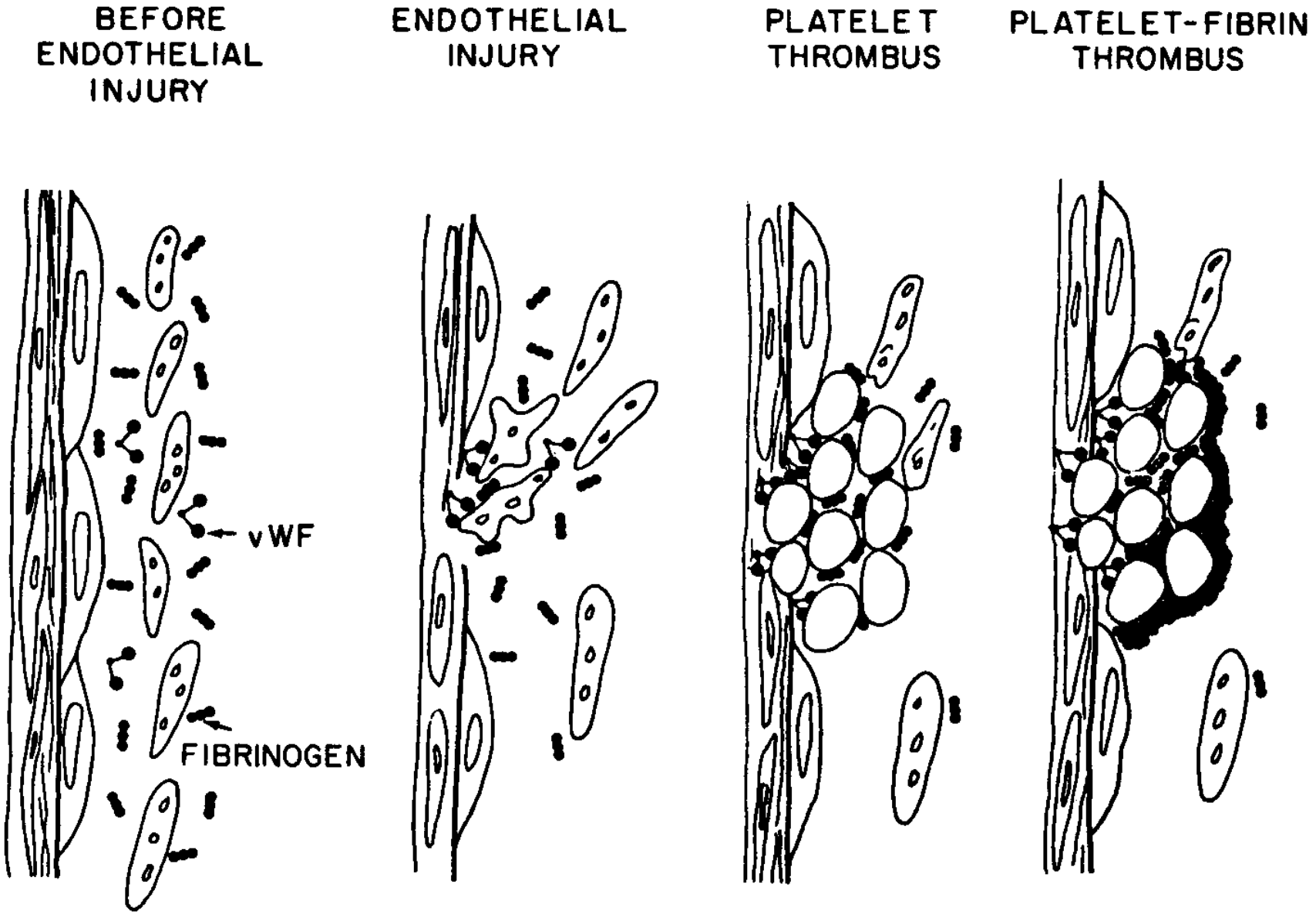


Berndt et al. Thromb Haemostas 2001, 86:178-188

Platelet recruitment and aggregation



Colman et al. *Hemostasis & Thrombosis* 4th Ed., 2001, p632

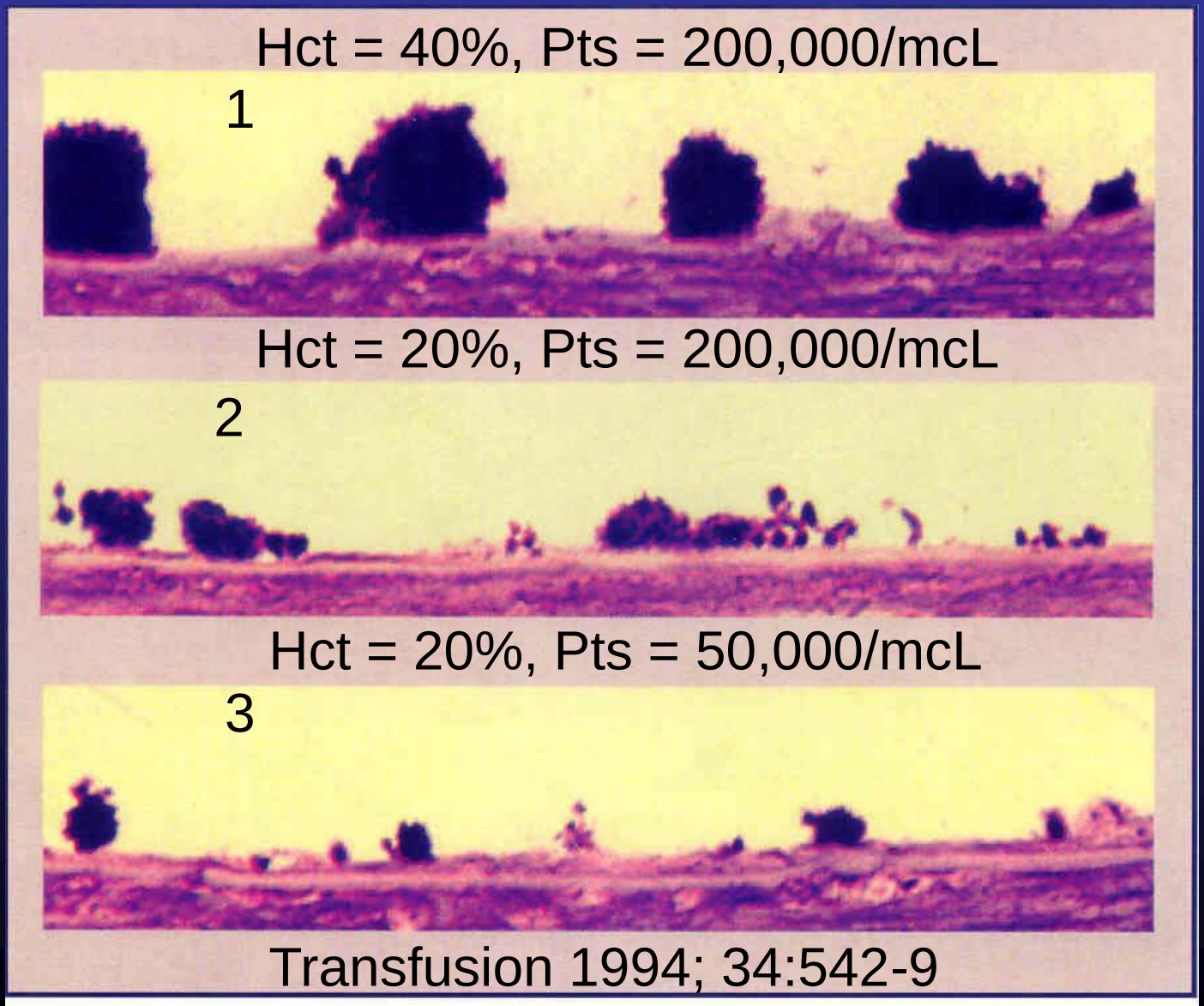


Colman et al. *Hemostasis & Thrombosis, 4th Ed.*, 2001, p647

Two roles of platelets in hemostasis

- Form multicellular aggregates, linked by fibrinogen, to create a physical barrier that limits blood loss.
- Accelerate the rate at which coagulation proteins are activated to facilitate thrombin generation and fibrin strand formation.
- Both roles are necessary for normal hemostasis.

Effect of hematocrit on platelet deposition on damaged arterial segments



Causes of Coagulopathy in the Massively Injured

- Loss
- Dilution
- Hypothermia
- Acidosis

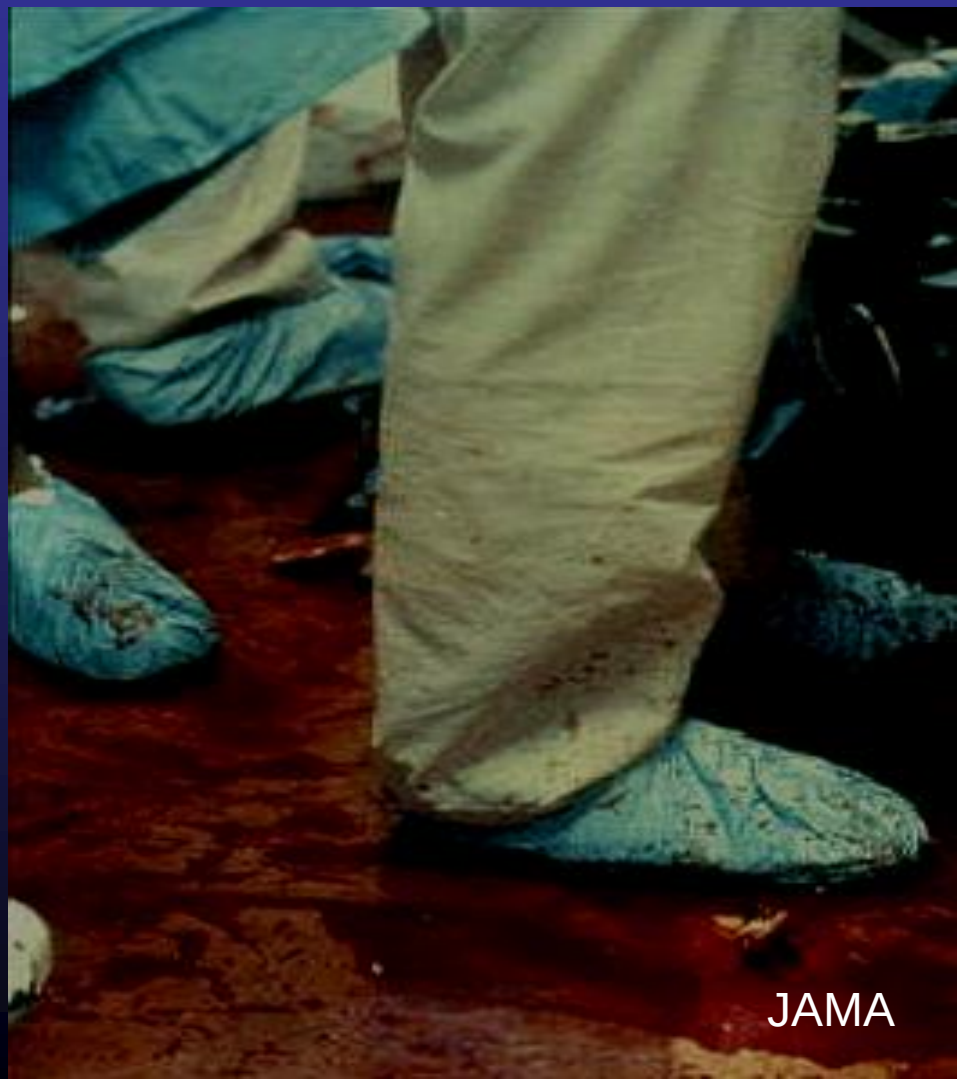
Coagulopathy of Trauma

- Consumption
- Fibrinolysis

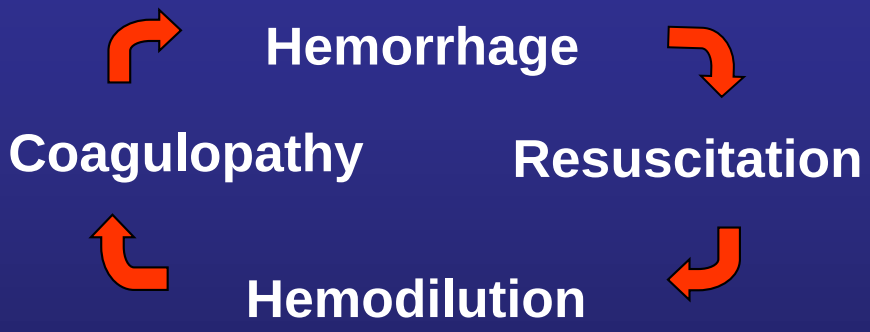
DIC

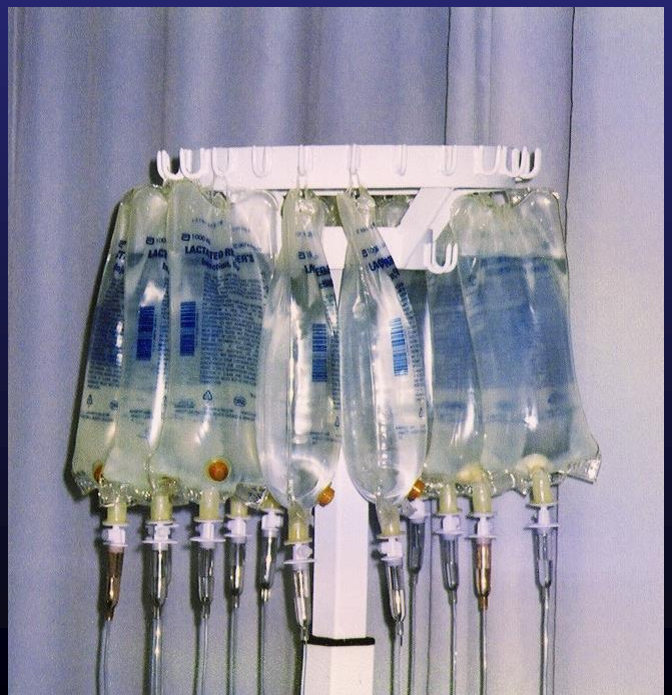
Effect of Blood Loss on the Coagulopathy of Trauma

- A healthy adult has only 10 g of fibrinogen and 15 mL of platelets.
- Amounts lost in shed blood can only be replaced quickly with blood components.

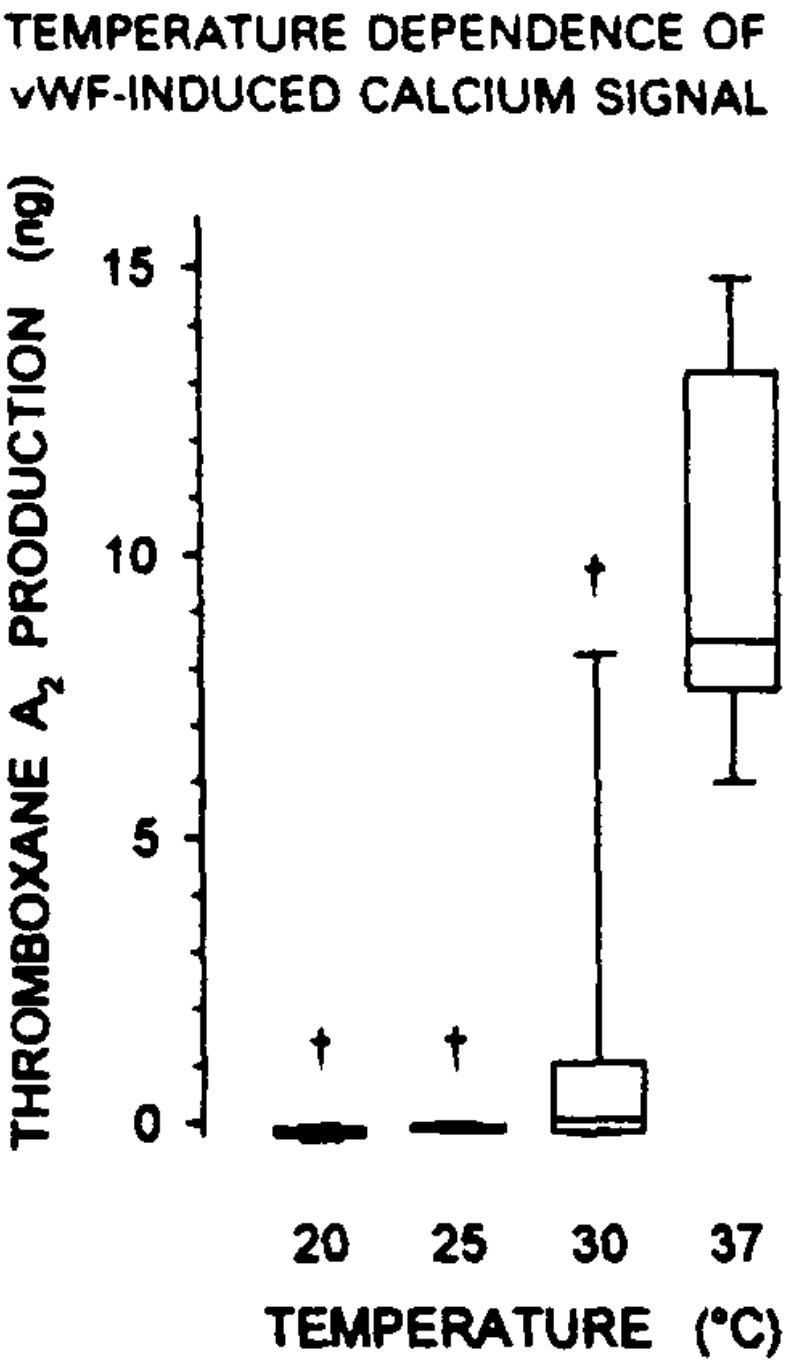


Causes of Dilution in the Massively Injured





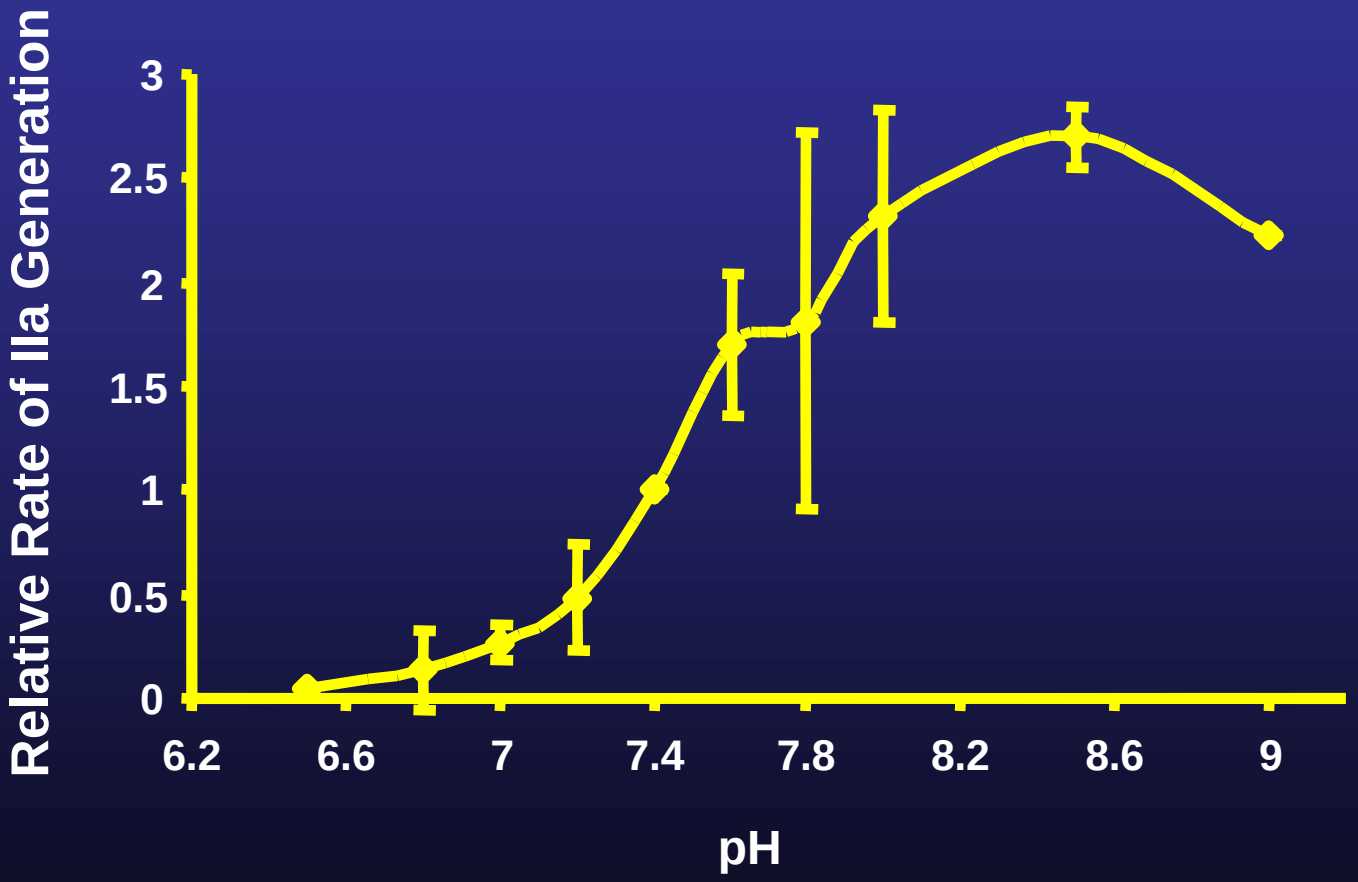
- Movement of interstitial fluid into the intravascular space with reduced BP
- Administration of resuscitation fluids
- Administration of IV fluids as carriers for drugs
- Administration of blood components



Platelet activation by the vWF pathway is gone in 50% of individuals at 30°C and profoundly reduced in 75%

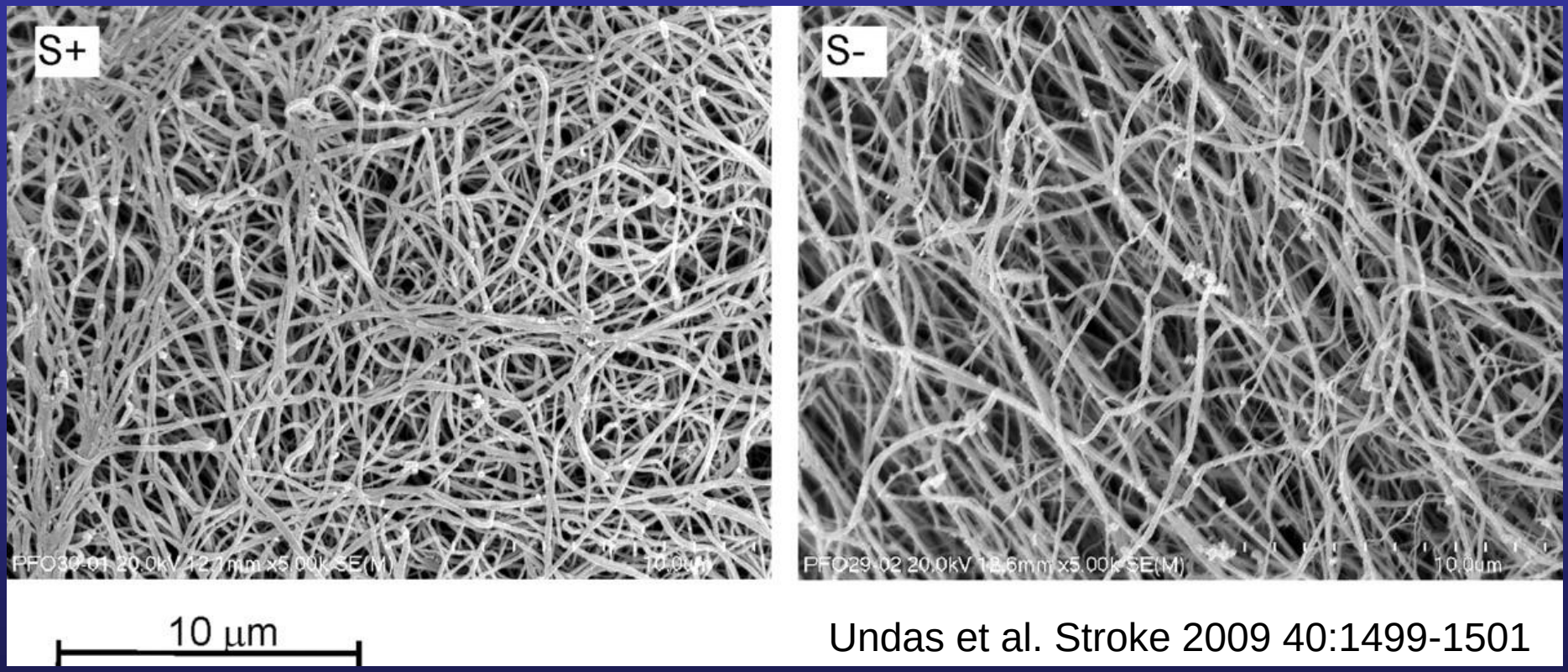
Kermode et al. Blood 1999; 94:199-207

Effect of pH on FXa/Va Activity



Meng et al, J Trauma 2003; 55:886-91

Poor fibrin deposition in trauma patients



Undas et al. Stroke 2009 40:1499-1501

Good thrombin burst leads to

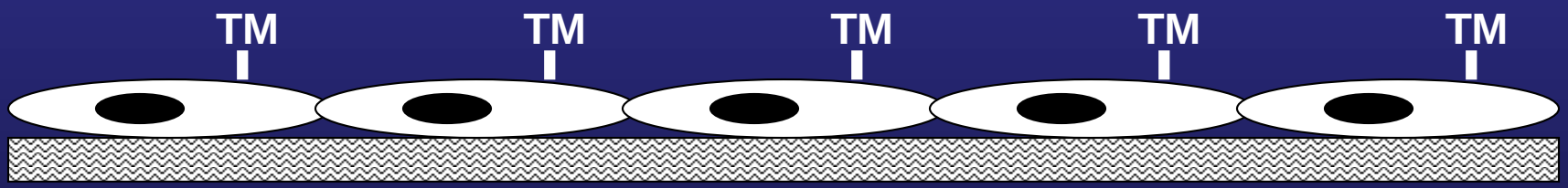
1. Thick fibrin strands with low surface to volume ratio
2. High concentrations of Thrombin Activated Fibrinolysis Inhibitor (TAFI)

Poor thrombin burst leads to

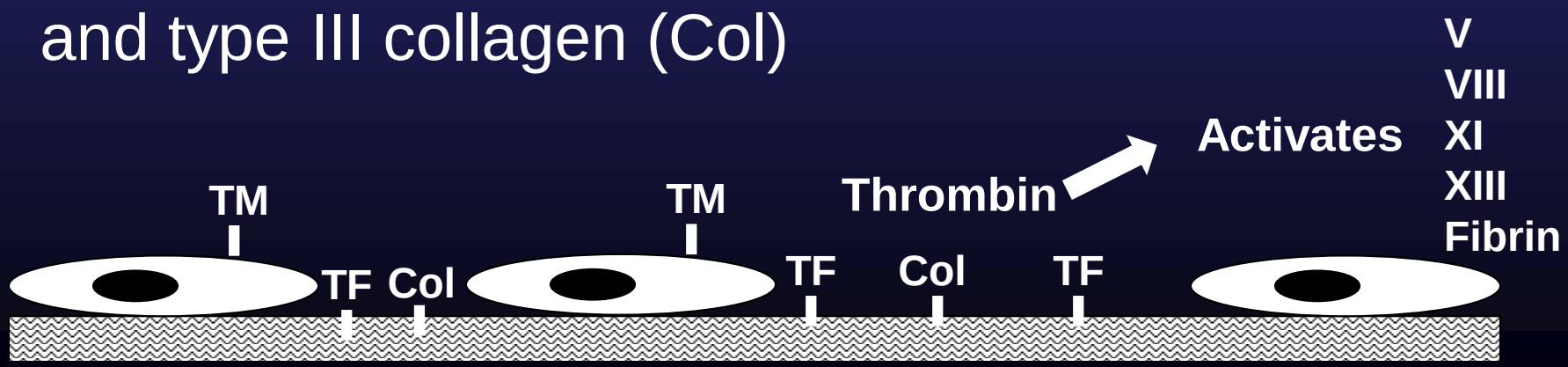
- Thin fibrin strands with high surface to volume ratio
- Low concentrations of the Thrombin Activated Fibrinolysis Inhibitor (TAFI)

Massive injury leads to the rapid activation of coagulation factors

- You have only small amounts of coagulation factors in your body.
- Normal endothelium prevents their activation

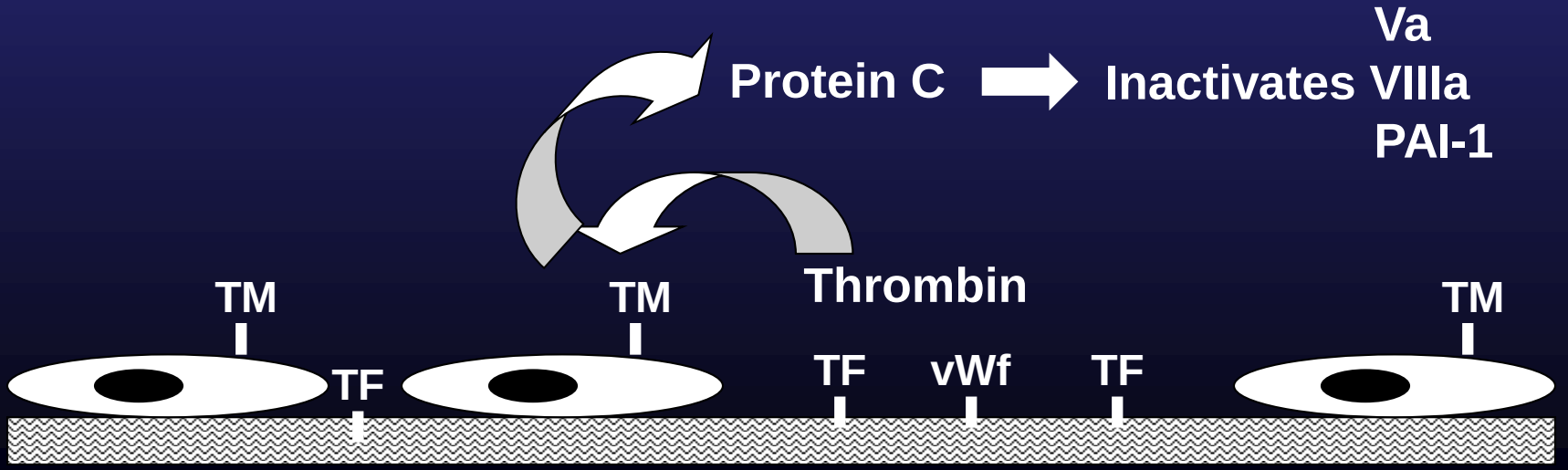


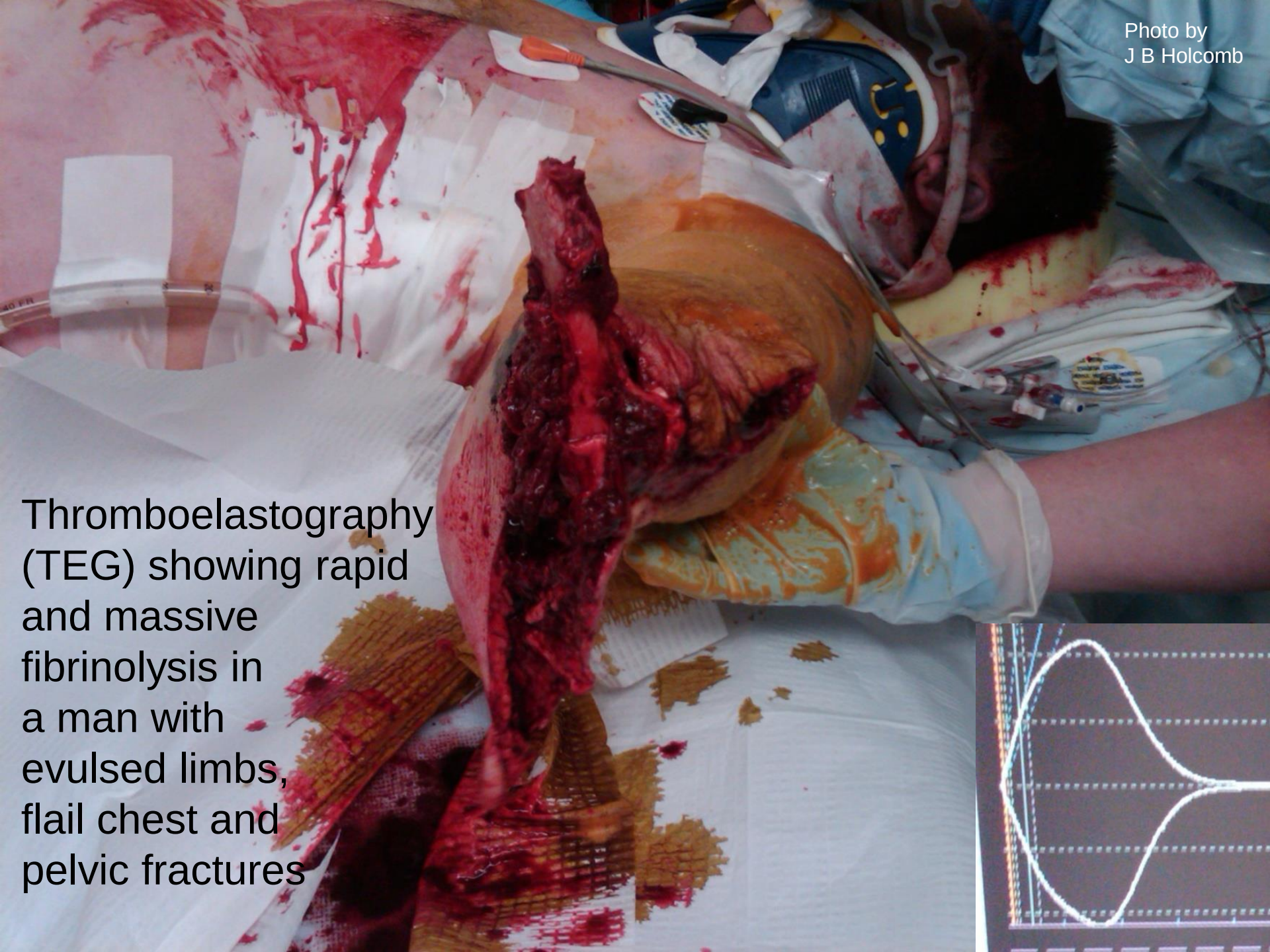
- Damaged endothelium exposes tissue factor (TF) and type III collagen (Col)



Massive injury leads to coagulation factor consumption and fibrinolysis

- Thrombin made in the presence of normal endothelium reacts with thrombomodulin to activate Protein C with inactivates Plasminogen Activator Inhibitor (PAI-1). Uninhibited plasminogen activator (tPA) leads to massive plasmin activation and fibrinolysis





Thromboelastography (TEG) showing rapid and massive fibrinolysis in a man with evulsed limbs, flail chest and pelvic fractures

Probability of Life-Threatening Coagulopathy *Increases* with Shock and Hypothermia

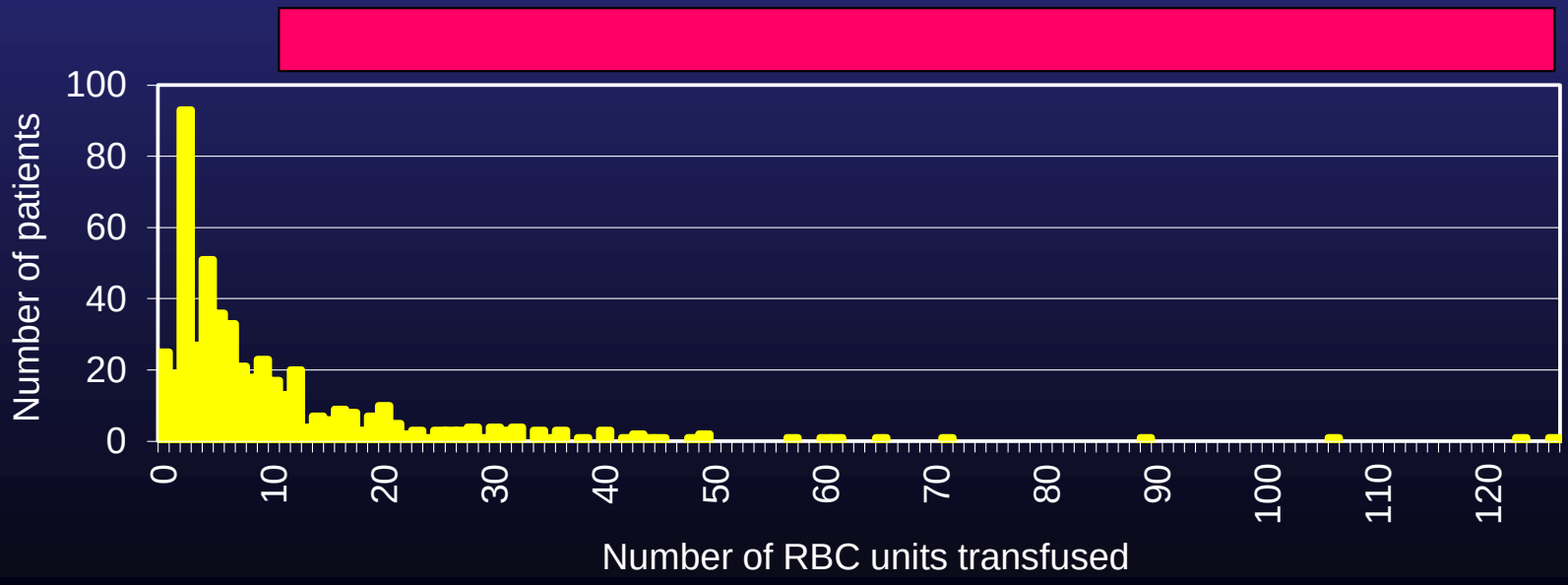
Clinical Status	Conditional Probability of Developing Coagulopathy
No risk factor	1%
ISS > 25	10%
ISS > 25 + SBP < 70 mm Hg	39%
ISS > 25 + pH < 7.1	58%
ISS > 25 + temperature < 34°C	49%
ISS > 25 + SBP < 70 mm Hg + temperature < 34°C	85%
ISS > 25 + SBP < 70 mm Hg + temperature < 34°C + pH < 7.1	98%

SBP, systolic blood pressure.

Cosgriff N et al. *J Trauma.* 1997;42:857-861.

RBC Units Used at STC in 2000

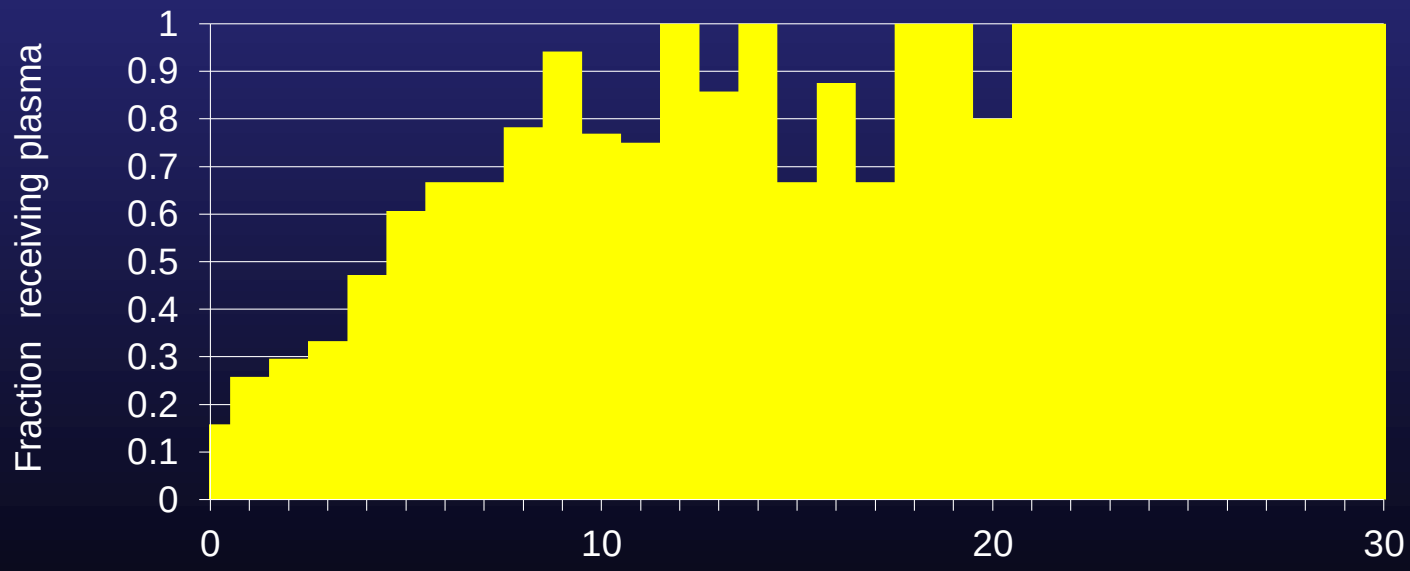
- Only 8% of admissions used RBCs
- 5649 direct admissions received 5219 U RBC
- 3772 RBC units (72% of the total) were given to the 144 patients who received more than 10 U RBC
- These patients had a mean ISS of 32 (lived, ISS = 30; died, ISS = 35) and a 38% mortality



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

Plasma Units Used at STC in 2000

- Among 490 patients receiving 5219 U RBC, 309 used 5226 U plasma T
- The fraction receiving plasma reaches 95% at 10 U of RBC
- In all subgroups, the ratio of plasma units to RBC units was essentially one

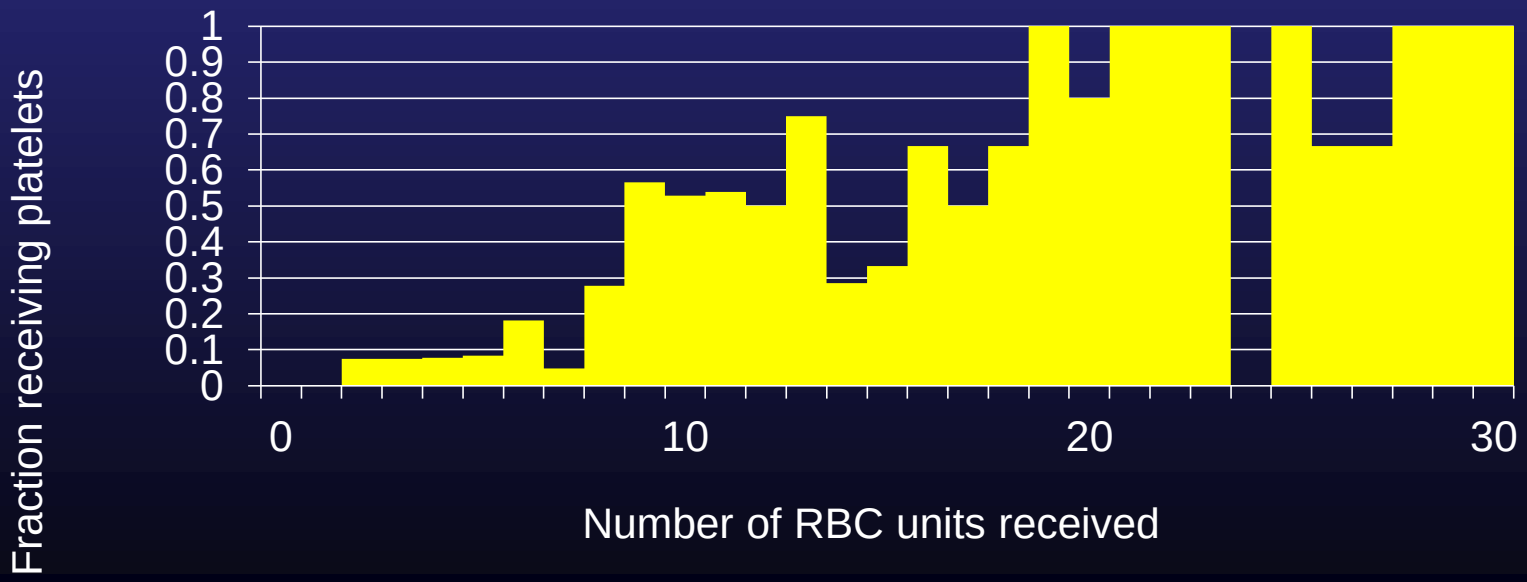


Como JJ et al.

Transfusion 2004; 44:809-813

Platelet Units Used at STC in 2000

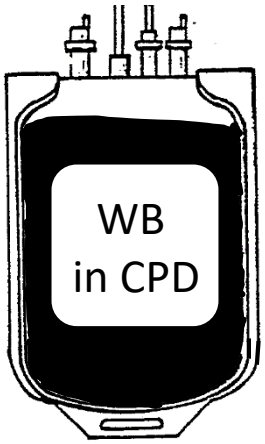
- Among 490 patients receiving 5311 U RBC, 154 received Plts
- The fraction receiving Plts reaches 75% at 10 U and 95% at 20 U of RBC
- The 756 random donor and 356 apheresis units are equivalent to 2892 U of Plts



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

Whole blood or the 3 conventional blood components made from it

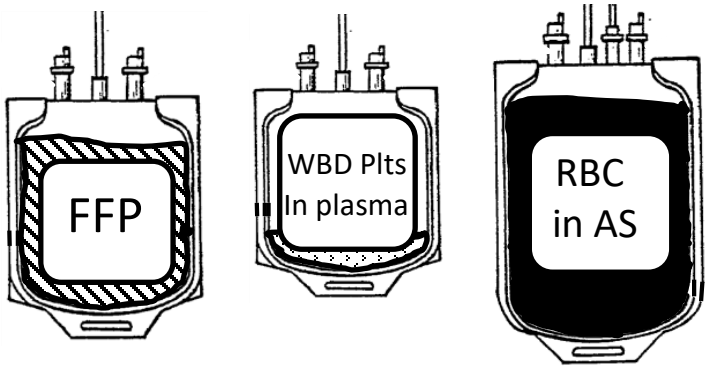
Whole Blood



200 mL RBC
300 mL plasma
125 x 10^9 plts @
212 plts/µL
70 mL anticoagulant

80% plasma 212k plts, Hct 35%
(INR 1.1, PTT 36, circ plts 100-142K)

1:1:1



65% plasma, 90K plts, Hct 29%
(**INR** 1.31, PTT 42, circ plts 63K)

Both units from a donor with a 40% Hct and Plt count of 250,000/µL

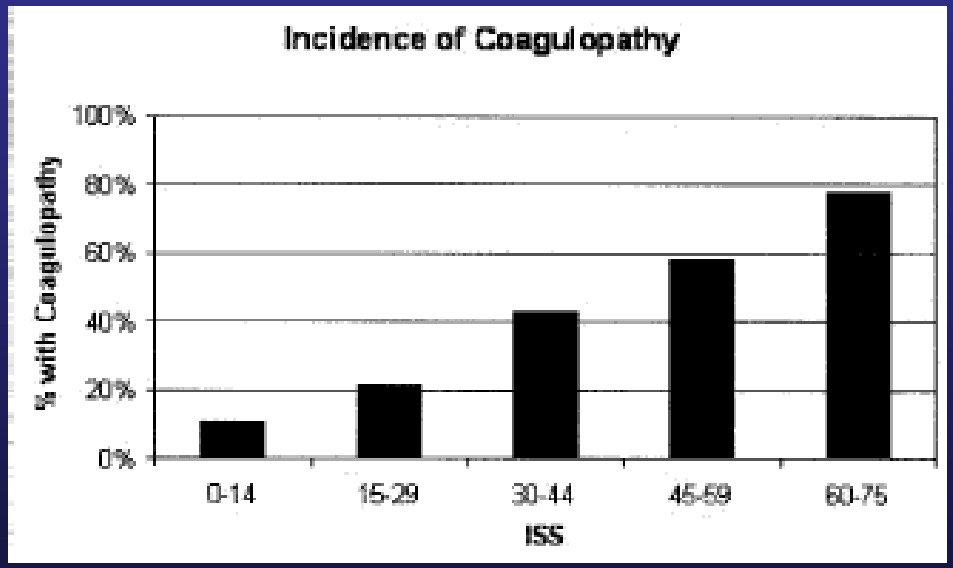
Armand and Hess, Transfus Med Rev 2003; Kornblith et al. J Trauma 2014

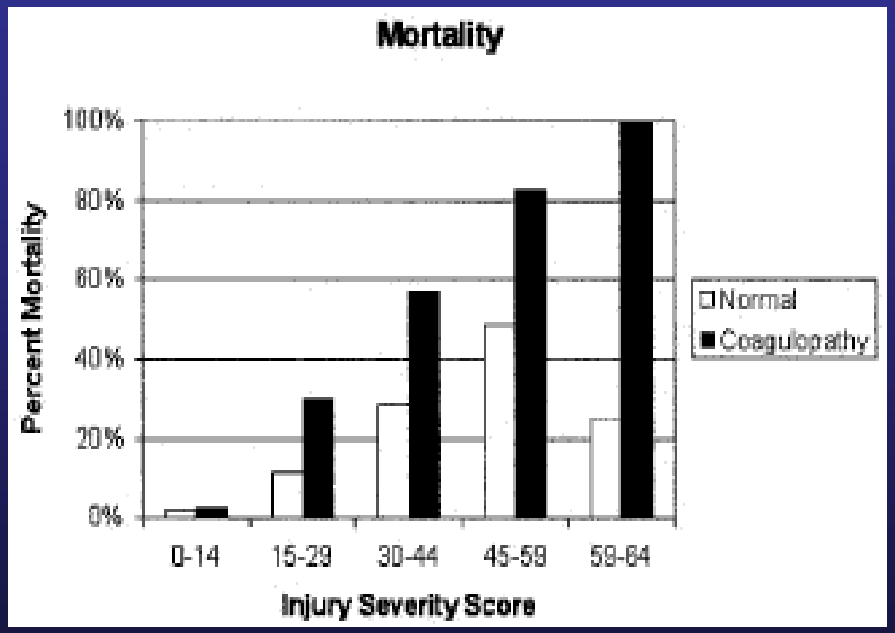
The Journal of TRAUMA® Injury, Infection, and Critical Care

Acute Traumatic Coagulopathy

J Trauma, 2003.

Karim Brohi, BSc, FRCS, FRCA, Jasmin Singh, MB, BS, BSc, Mischa Heron, MRCP, FFAEM, and Timothy Coats, MD, FRCS, FFAEM





- Derangements in coagulation occur rapidly after trauma even after adjusting for ISS
- By the time of arrival at the ED, 1/3 of trauma patients had a coagulopathy associated with a poor outcome

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

J Trauma, 2003.

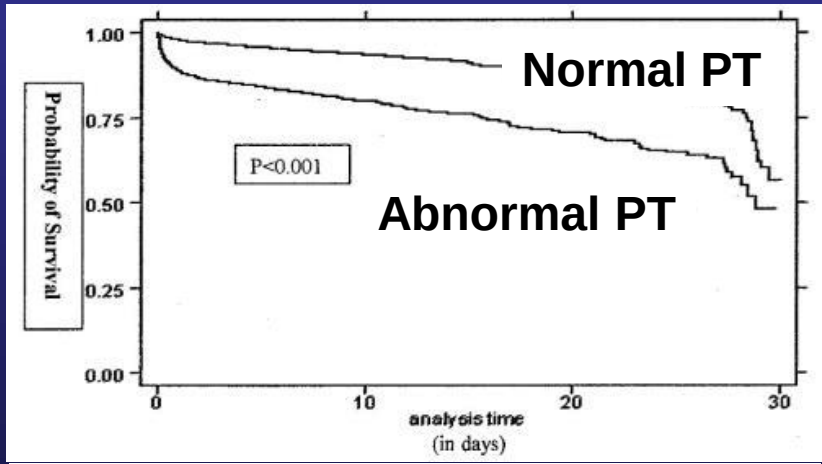
Early Coagulopathy Predicts Mortality in Trauma

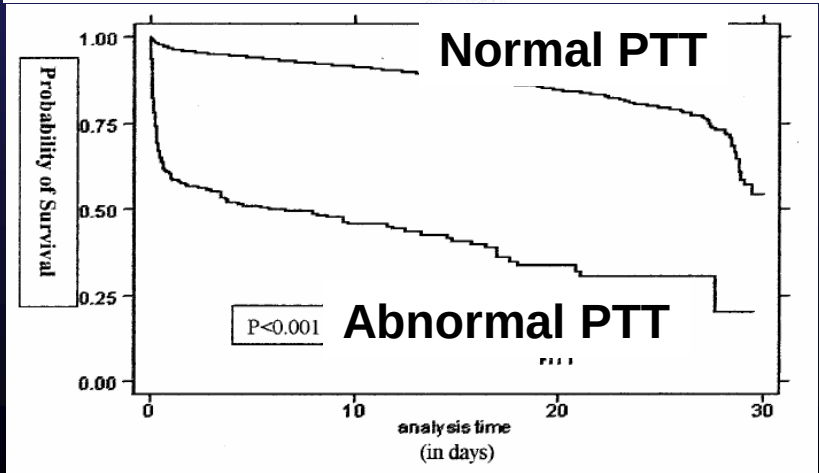
Jana B. A. MacLeod, MD, MSc, Mauricio Lynn, MD, Mark G. McKenney, MD, Stephen M. Cohn, MD, and Mary Murtha, RN

In 20,000 direct admissions to the U. Miami trauma center:

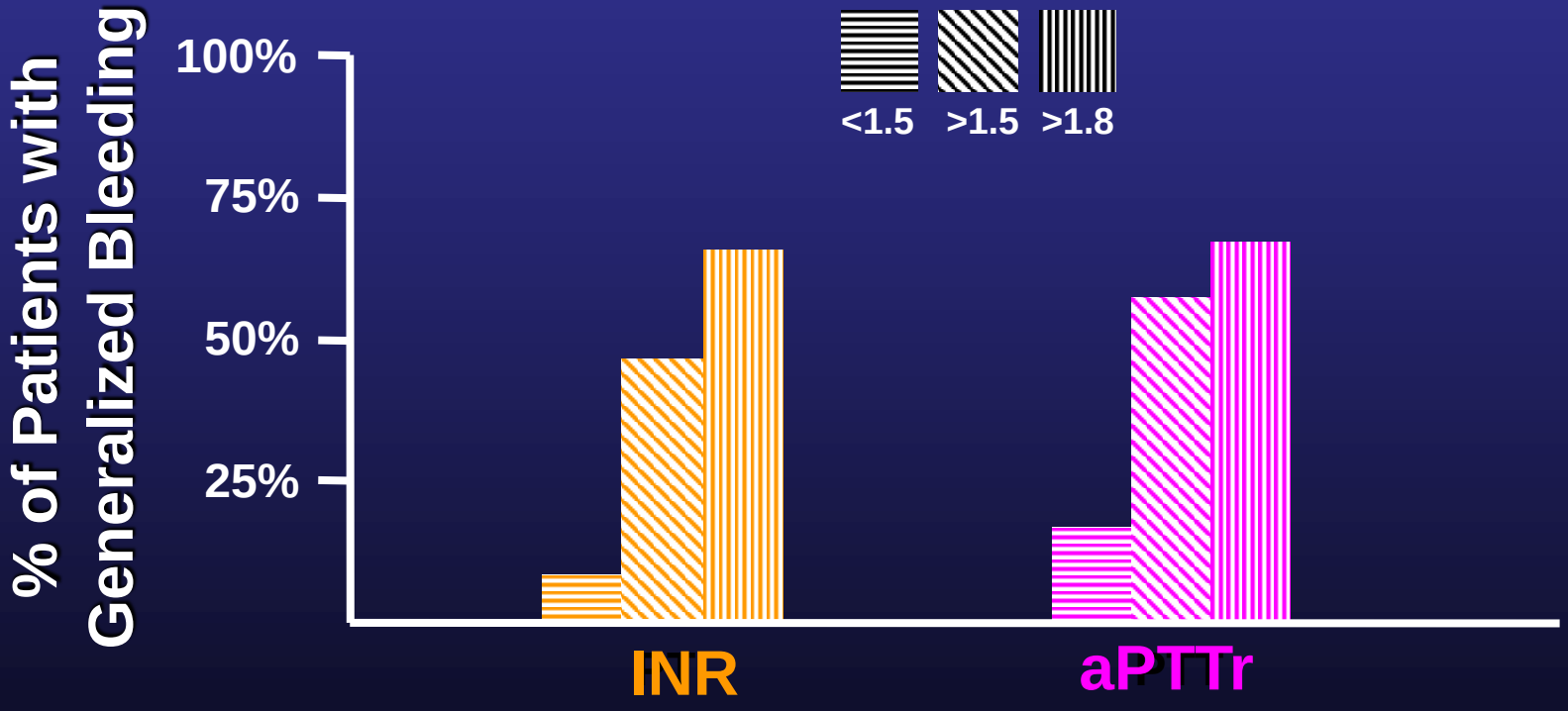
- An abnormal PT was common (28%) and predicted a 35% excess mortality

- An abnormal PTT was uncommon (8%) but predicted a 426% excess mortality



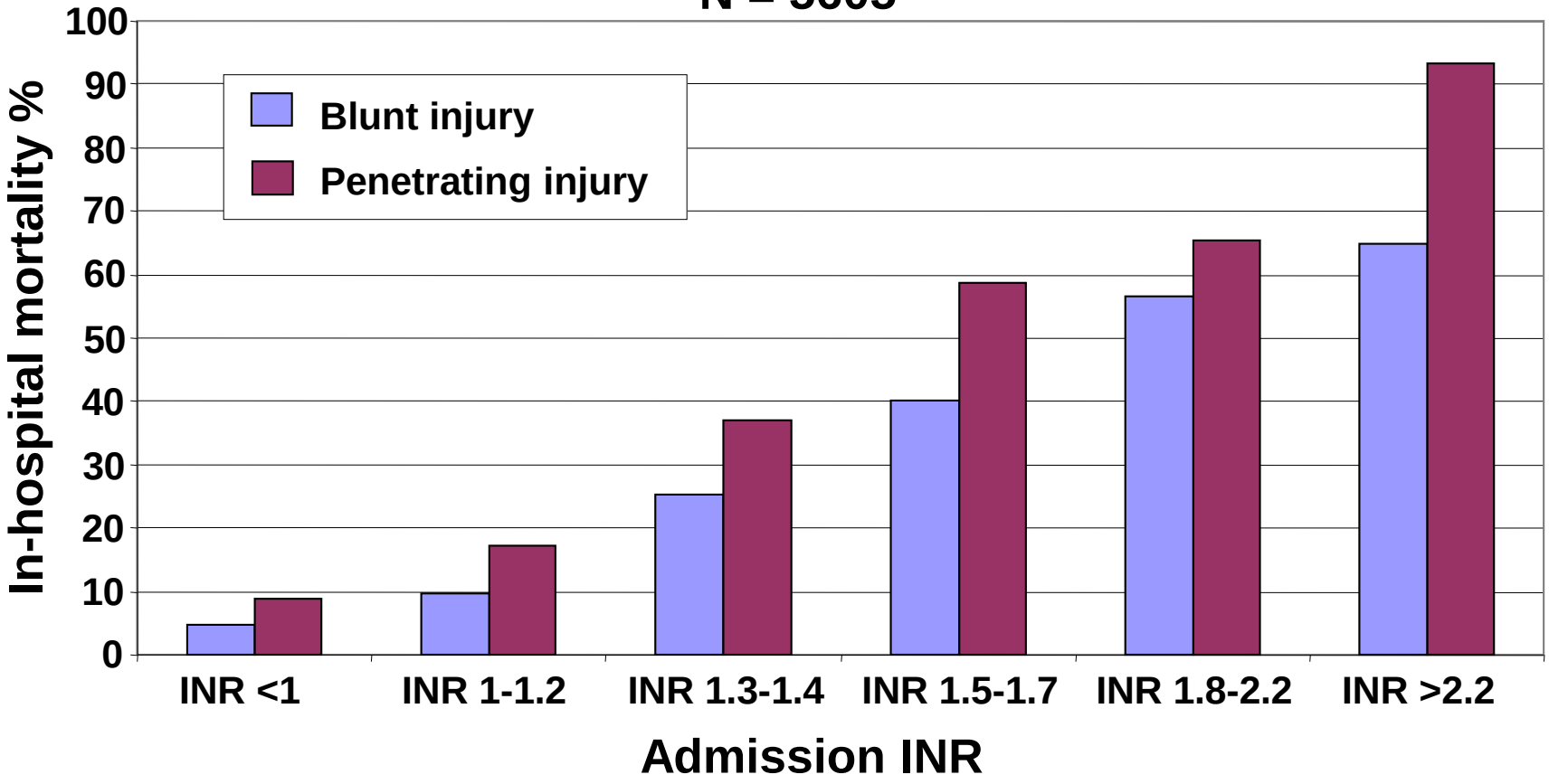


Effect of a prolonged PT or PTT on the frequency of pathologic bleeding in trauma and massive hemorrhage



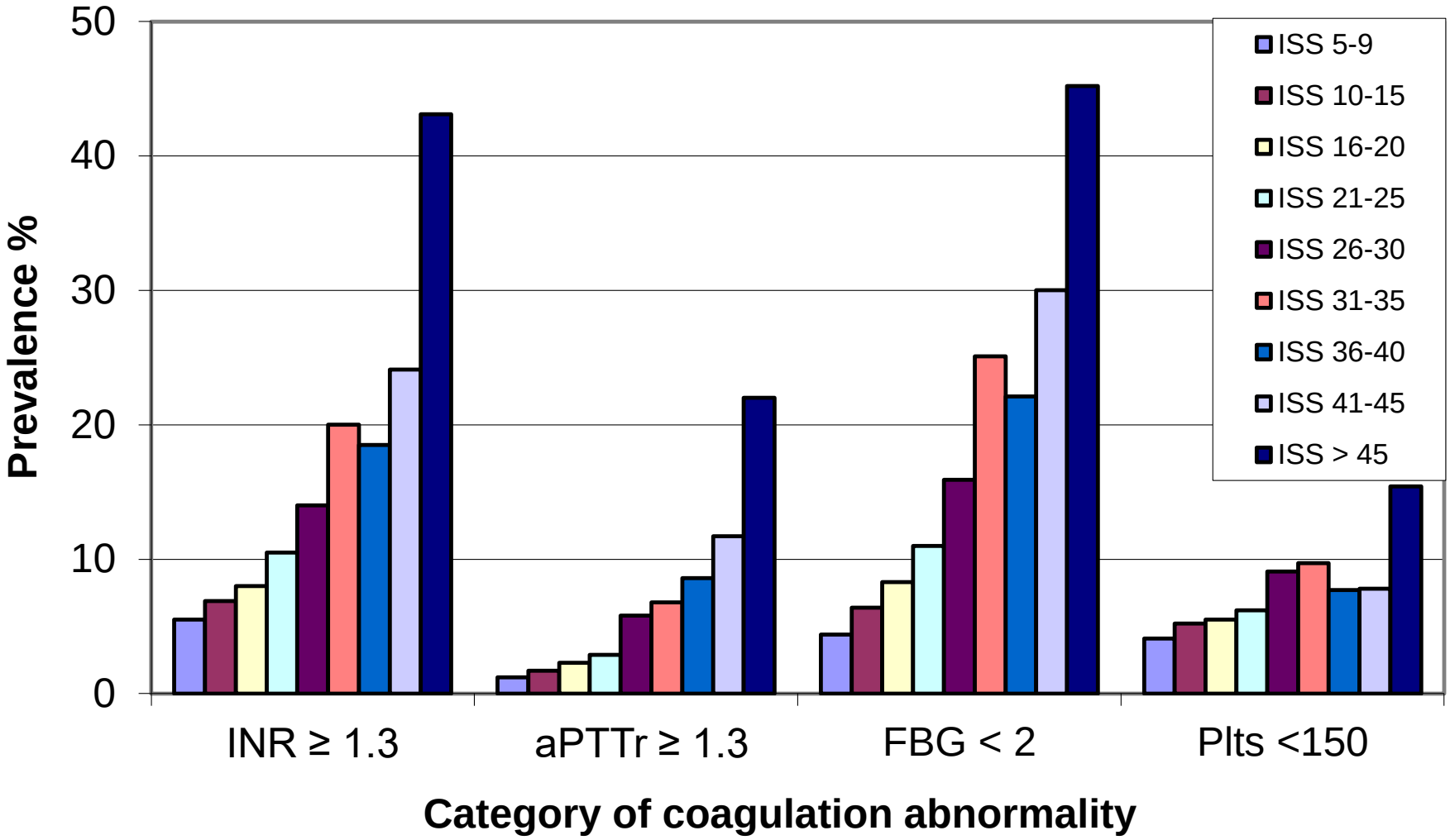
From Counts RB *et al. Ann Surg* 1979;190:91-9.

Admission INR and mechanism of injury in trauma patients admitted directly from the scene of injury with ISS > 15 as predictors of in-hospital mortality at U Maryland Cowley Shock-Trauma Center 2000-2006 N = 5605



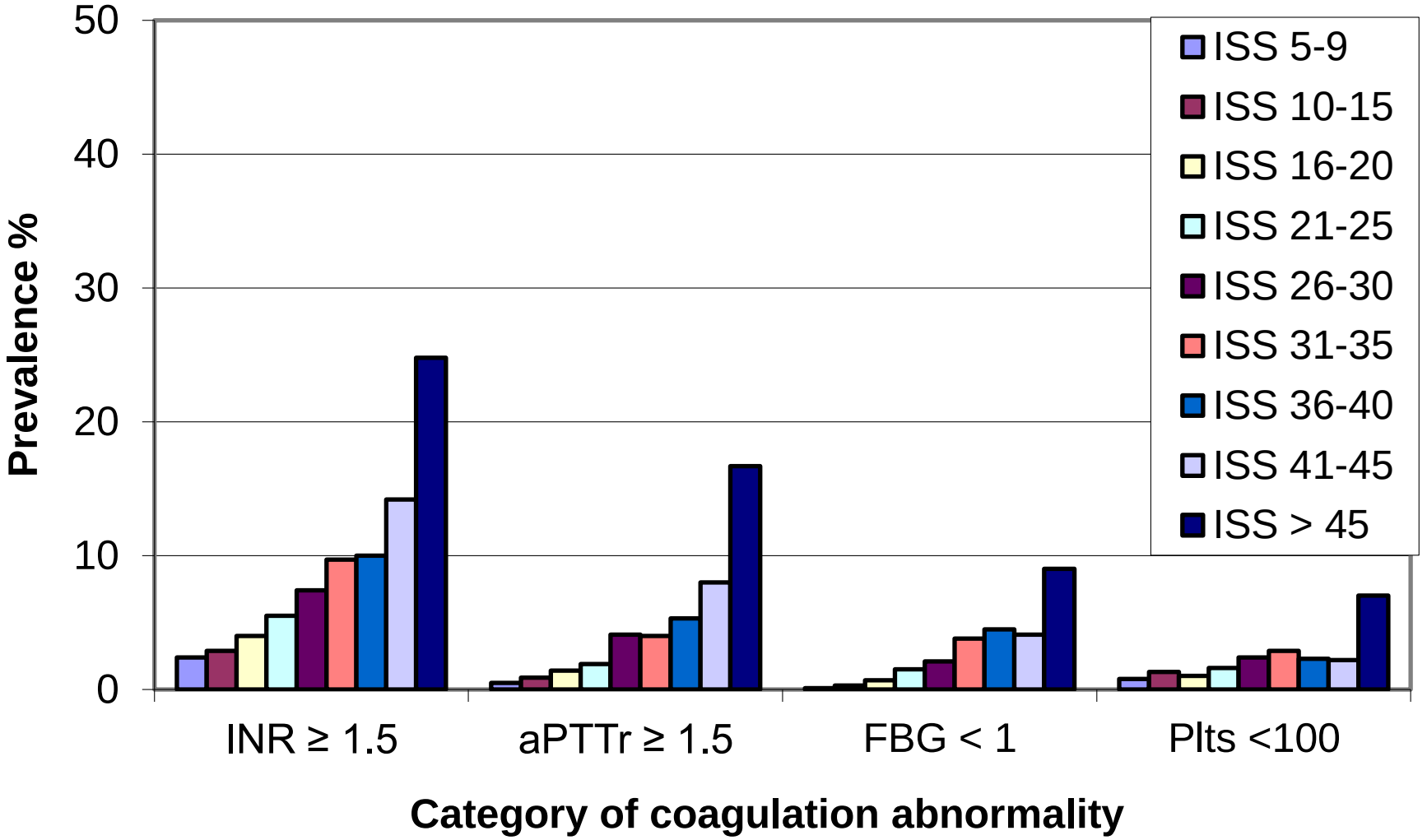
Hess et al. Transfusion 2009; 49:34-39.

Prevalence of abnormal admission coagulation tests in a trauma center population, n = 15,782



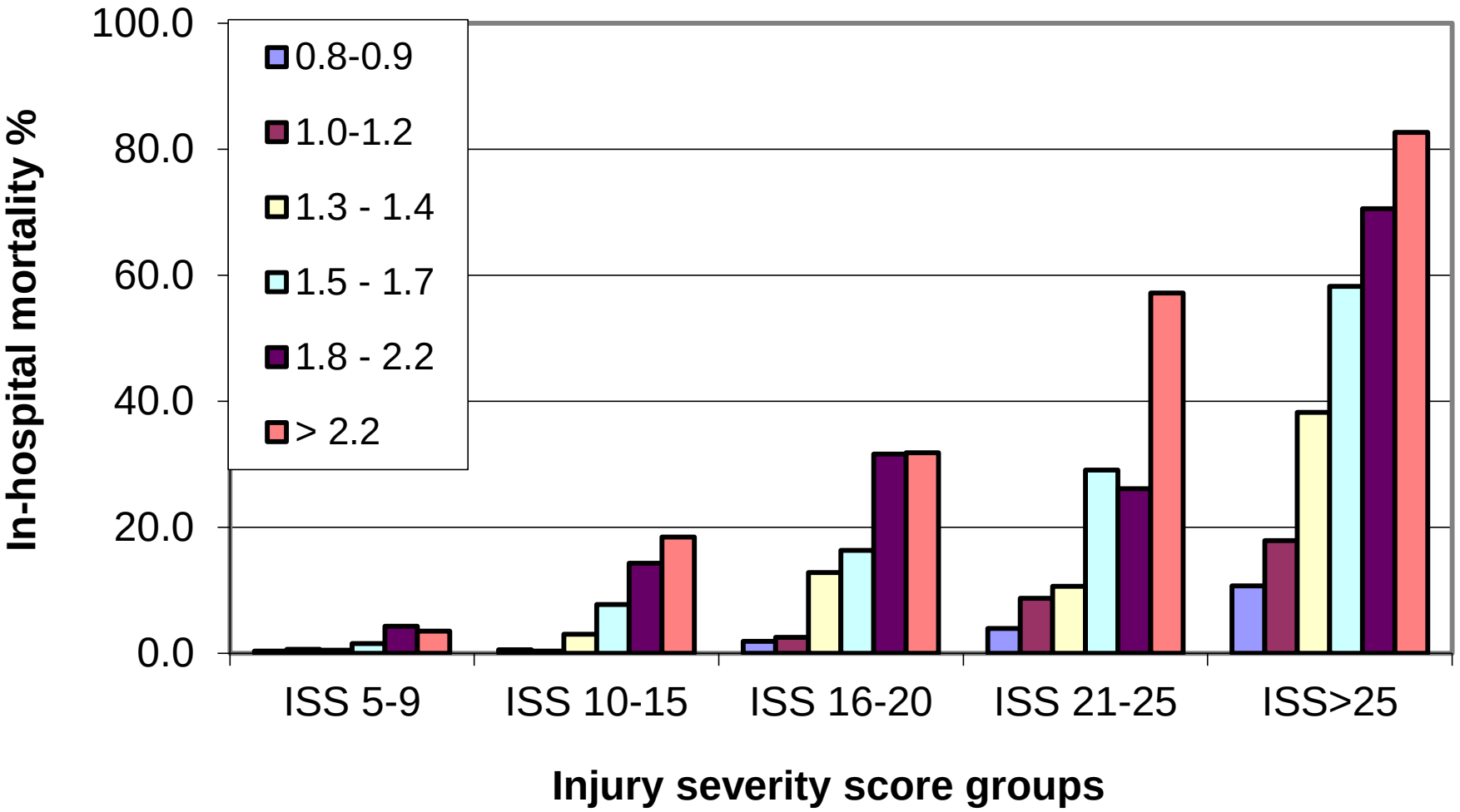
Hess et al. Transfusion 2009; 49:34-39.

Prevalence of coagulopathy based on admission laboratory tests of coagulation



Hess et al. Transfusion 2009; 49:34-39.

Interaction of injury severity and admission INR on in-hospital mortality



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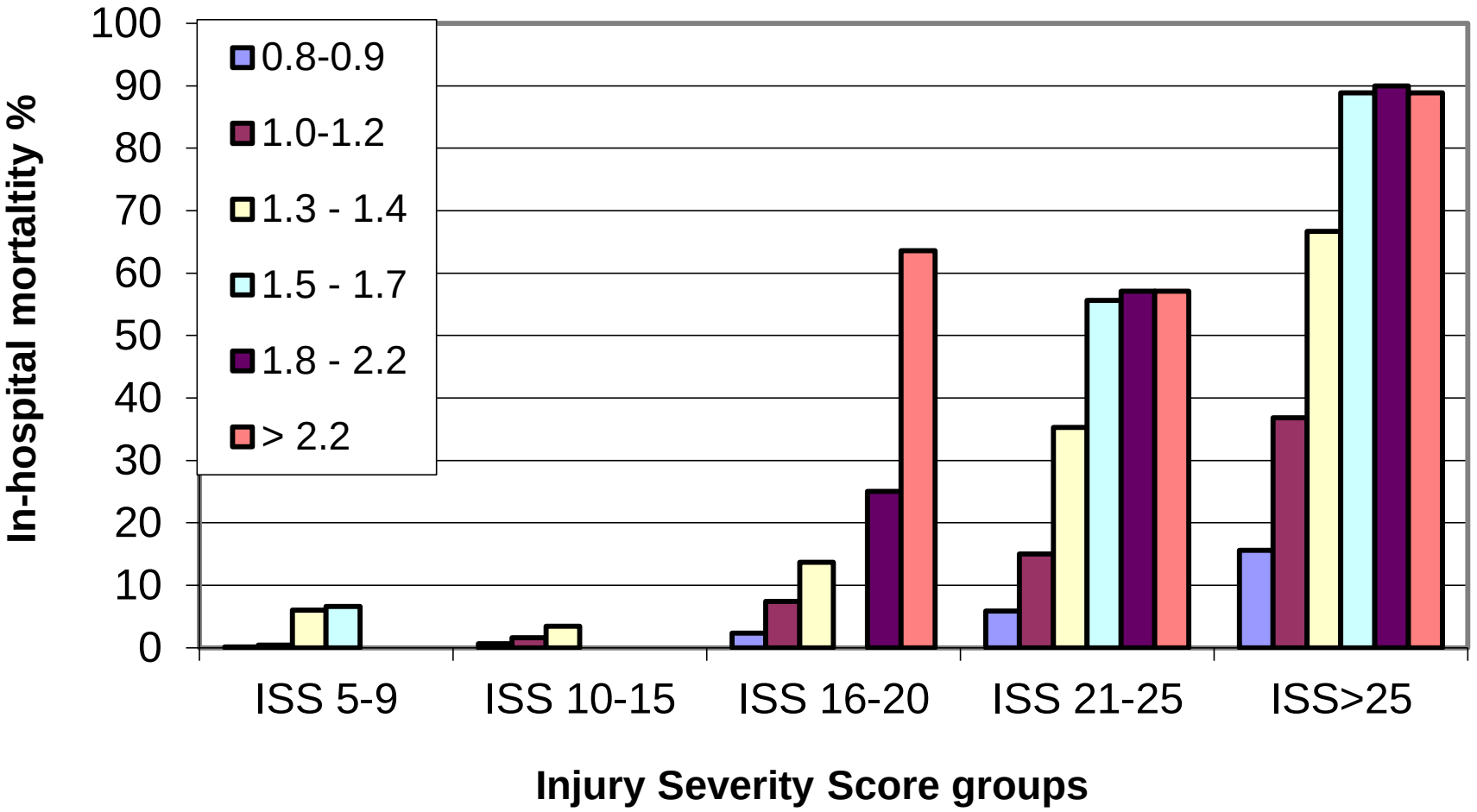
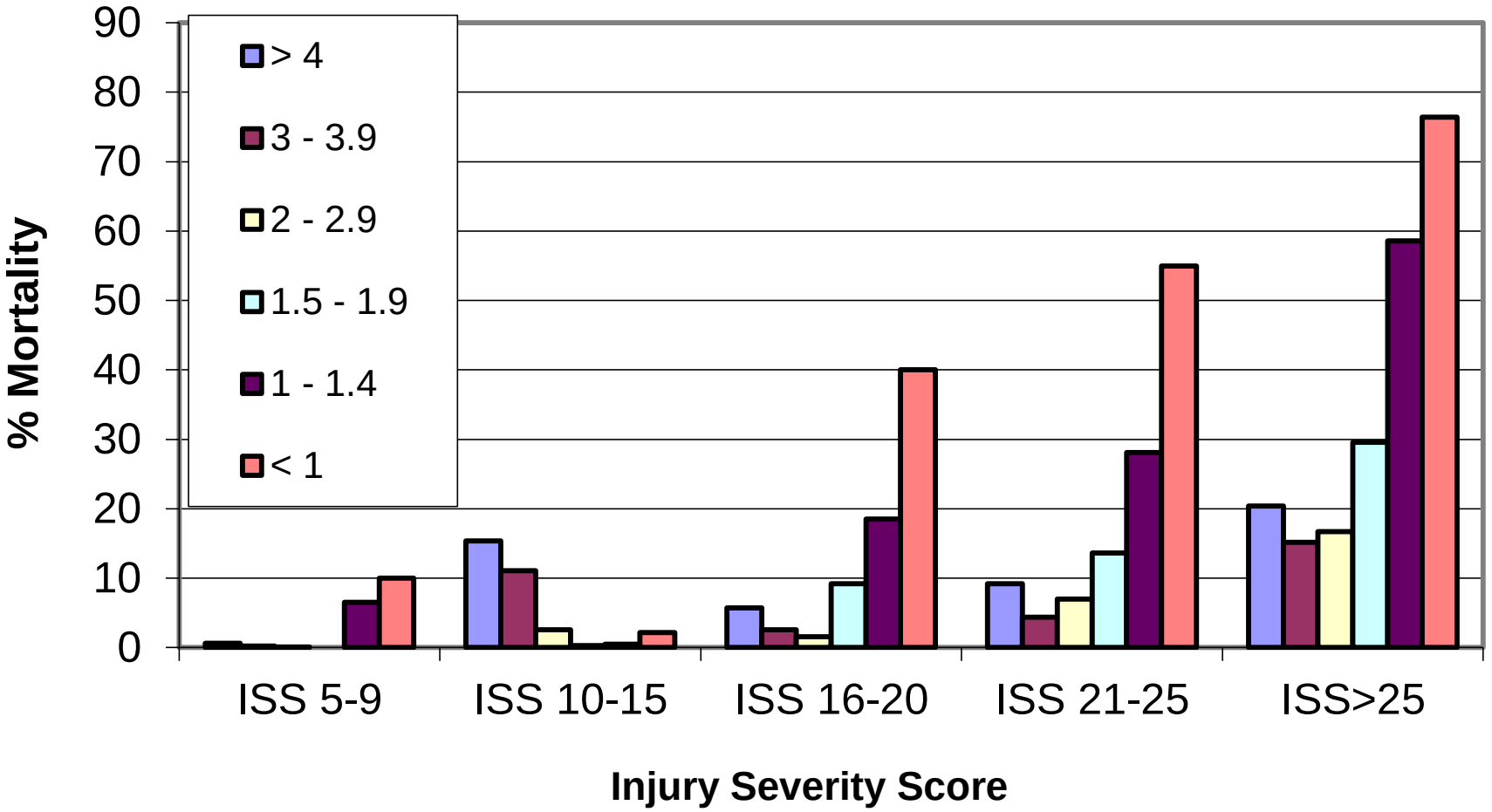
Interaction of ISS and admission aPTTr on in-hospital mortality in a trauma population



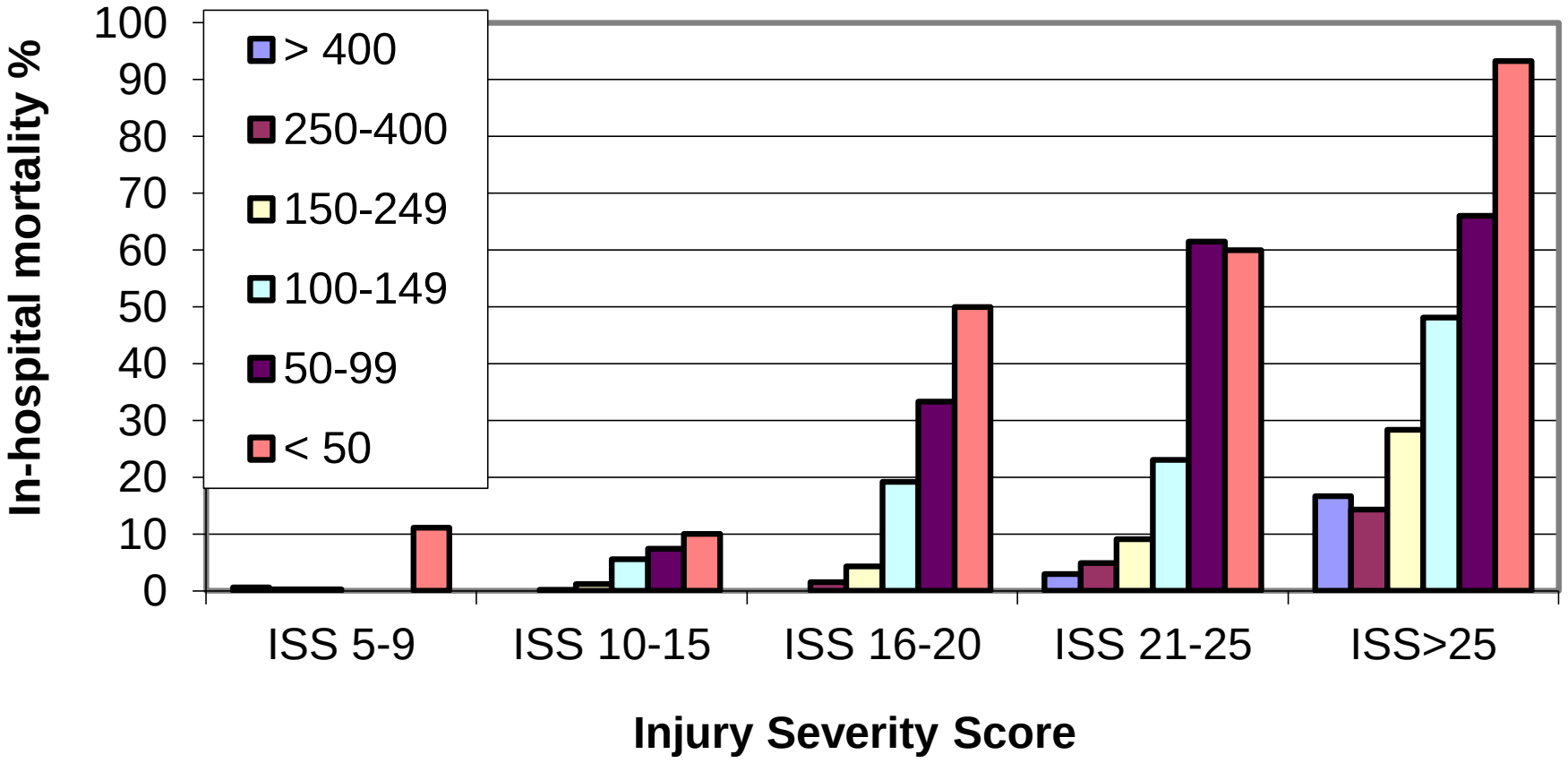
Hess et al. Transfusion 2009; 49:34-39.

Interaction of injury severity and admission fibrinogen on in-hospital mortality



Hess et al. Transfusion 2009; 49:34-39.

Interaction of ISS with admission platelet count on in-hospital mortality



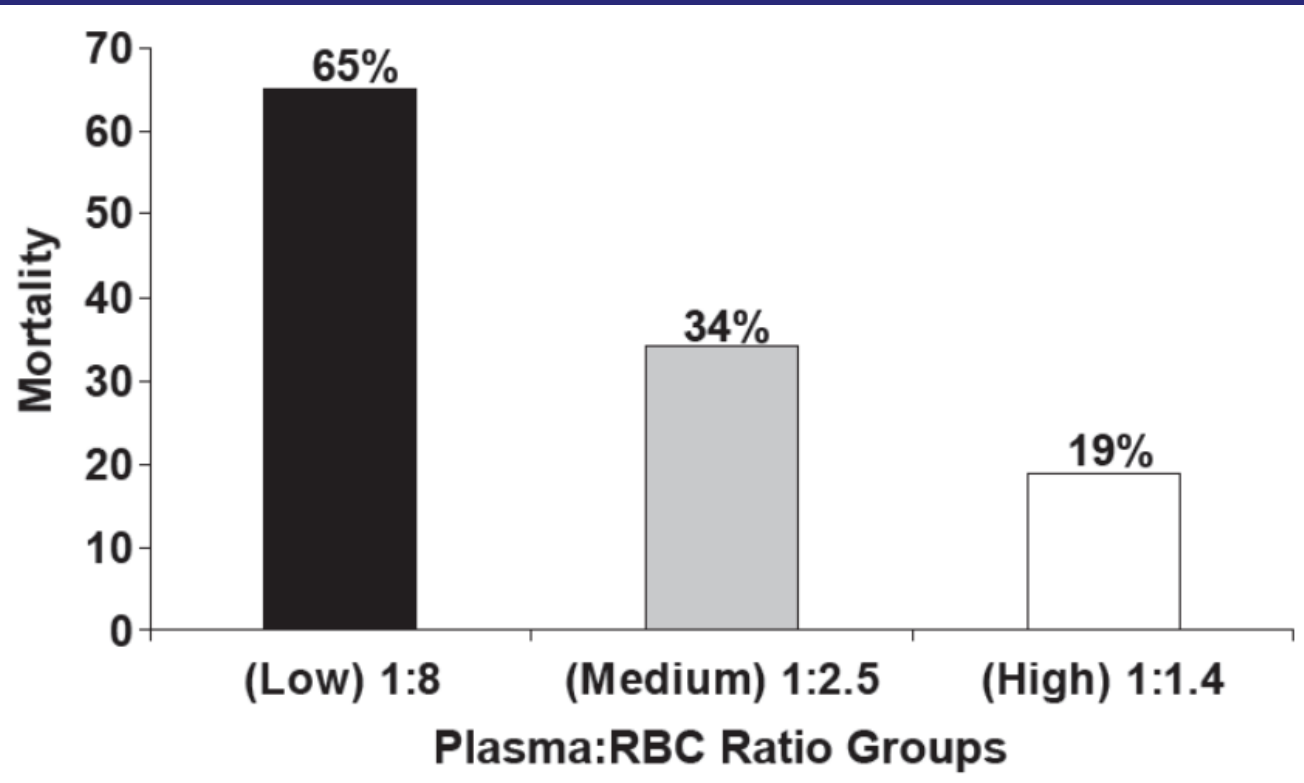
Hess et al. Transfusion 2009; 49:34-39.

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

J Trauma 2007 Nov; 63:805-813

The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD



- 252 patients receiving >10 U of RBC in 24 hours.
- Mortality by plasma:RBC unit ratio

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

Early Massive Trauma Transfusion:

Current State of the Art

Volume 60 ▪ Number 7 ▪ June 2006
Supplement

A symposium held at the U.S. Army Institute of Surgical Research, 26-27 May 2005
John Holcomb and John Hess, Co-chairs and Editors

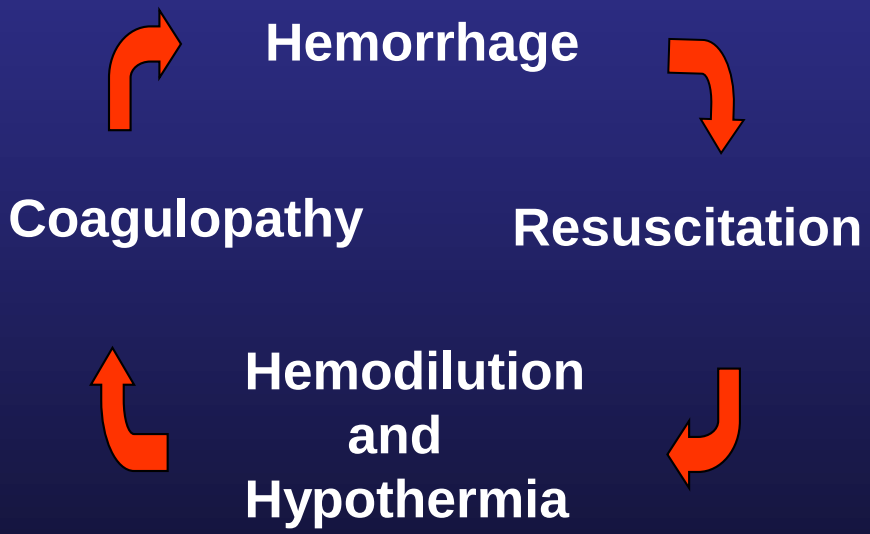
The Journal of TRAUMA® Injury, Infection, and Critical Care

Massive Transfusion Practices Around the Globe and a Suggestion for a Common Massive Transfusion Protocol

Debra L. Malone, MD, LTC USAF, SGRS, John R. Hess, MD, MPH, and Abe Fingerhut, MD

- Reviewed massive transfusion protocols from well-developed trauma systems in Seattle, Houston, Helsinki, Sydney, and Baltimore.
- This group then presented a massive transfusion protocol based on the best data from their review.
  - 1:1:1

Breaking the "Bloody Vicious Cycle"



- Control hemorrhage
- Use best possible resuscitation products
- Prevent hypothermia
- Prevent hemodilution
- Treat coagulopathy

Special Commentary

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

Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma

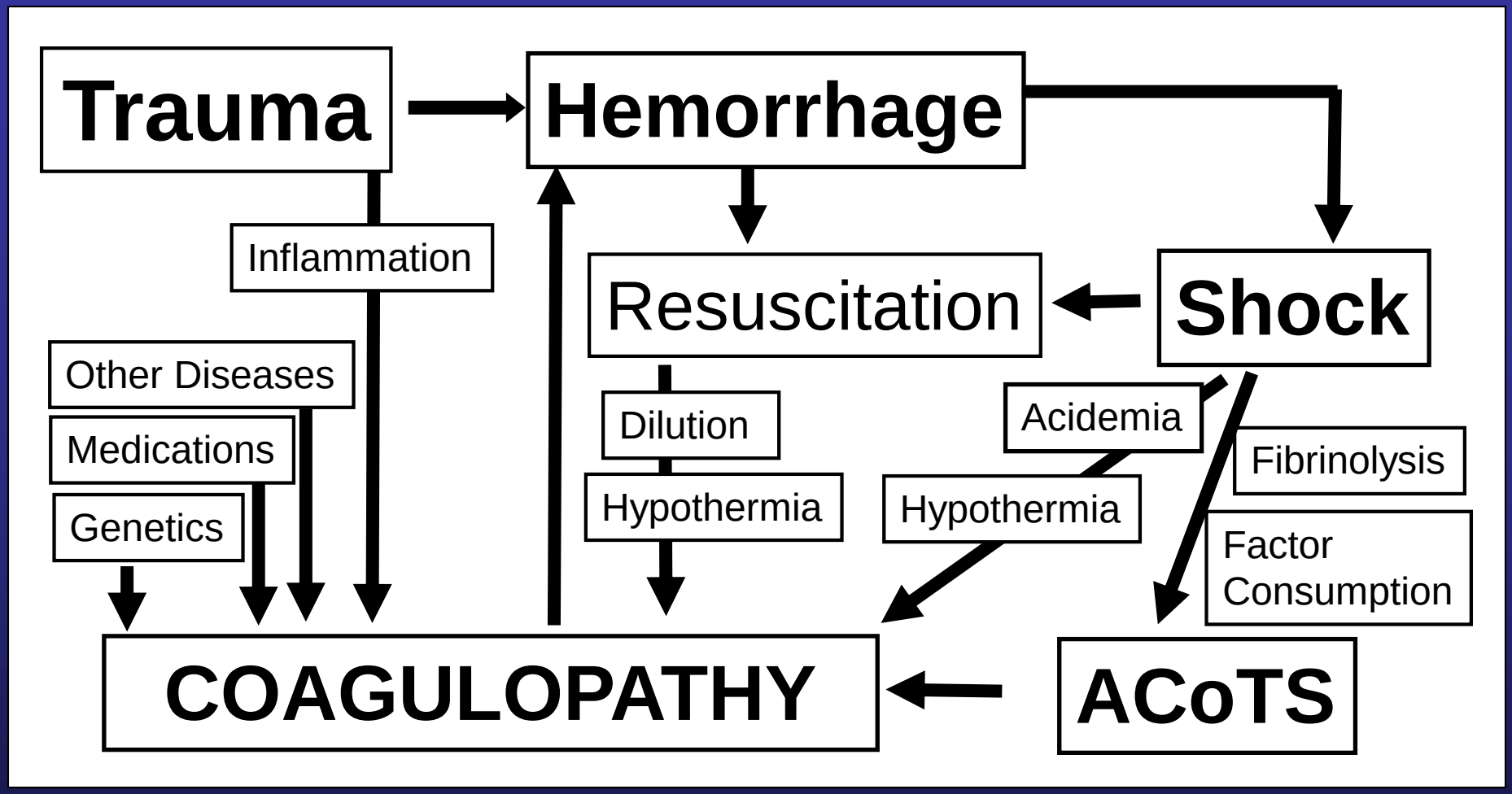
John B. Holcomb, MD, FACS, Don Jenkins, MD, FACS, Peter Rhee, MD, FACS, Jay Johannigman, MD, FS, FACS, Peter Mahoney, FRCA, RAMC, Sumeru Mehta, MD, E. Darrin Cox, MD, FACS, Michael J. Gehrke, MD, Greg J. Beilman, MD, FACS, Martin Schreiber, MD, FACS, Stephen F. Flaherty, MD, FACS, Kurt W. Grathwohl, 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

J Trauma. 2007;62:307–310.

- Resuscitation with a 1:1:1 ratio of RBCs, plasma, and platelets is the recommendation of the Army Surgeon General and his Trauma Consultant.

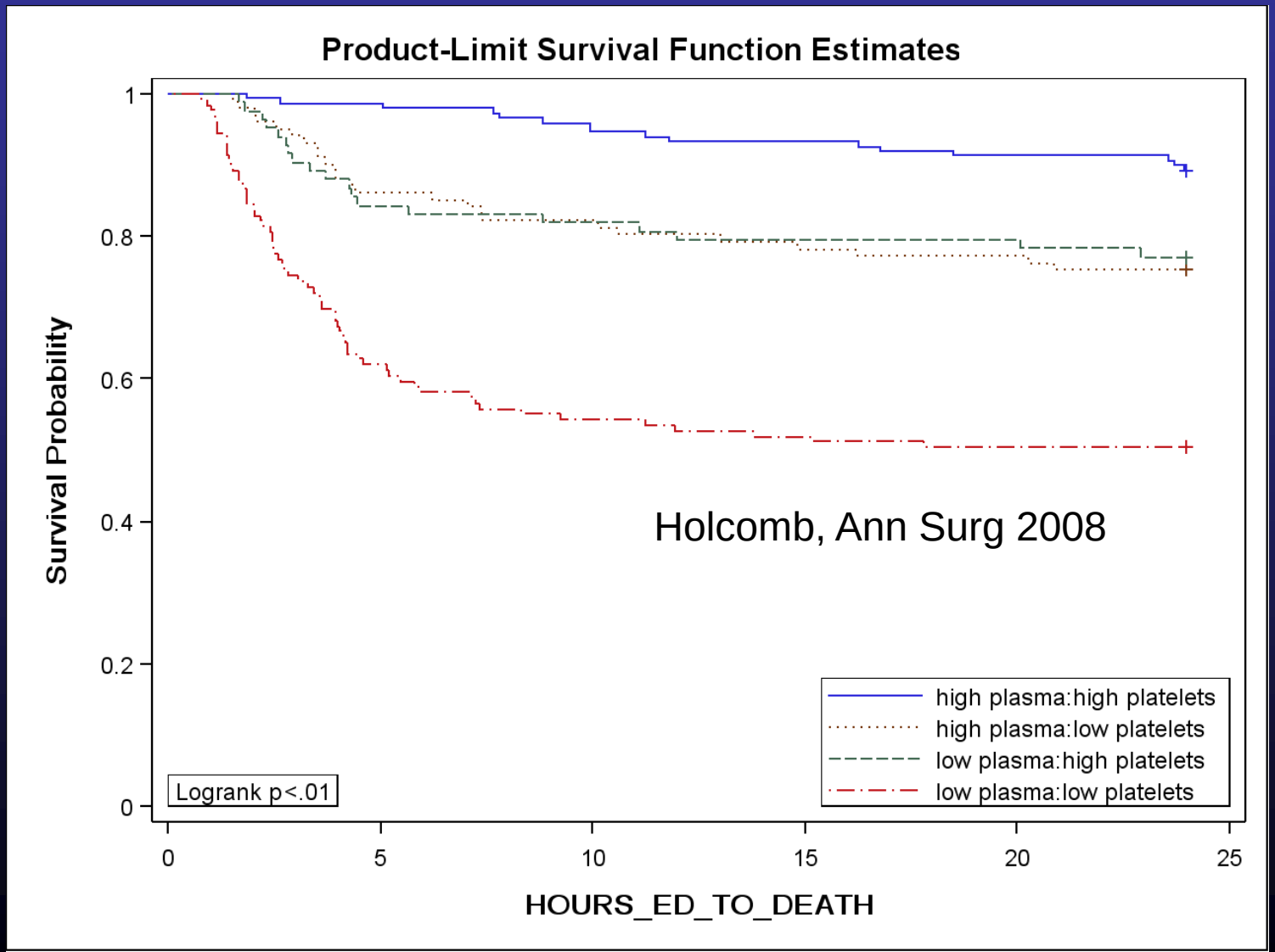
J Trauma, 2007.

EICBT April 2007

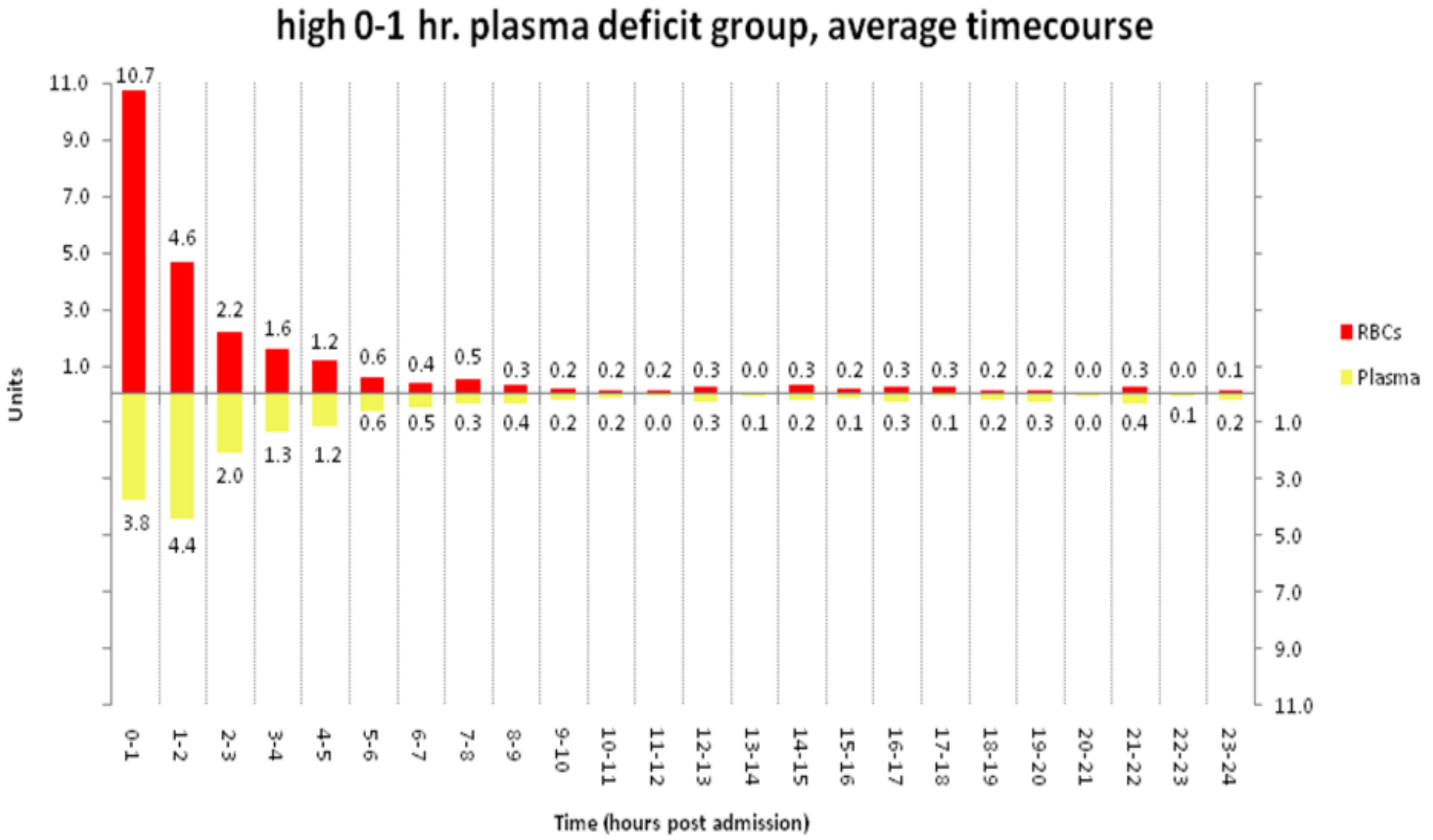


Pathophysiologic mechanisms leading to coagulopathy following injury. Hess et al. J Trauma 2008; 65:748

24 hr mortality of 466 massively transfused trauma patients seen in 2006 at 16 academic trauma centers by units of plasma to units of RBC ratio

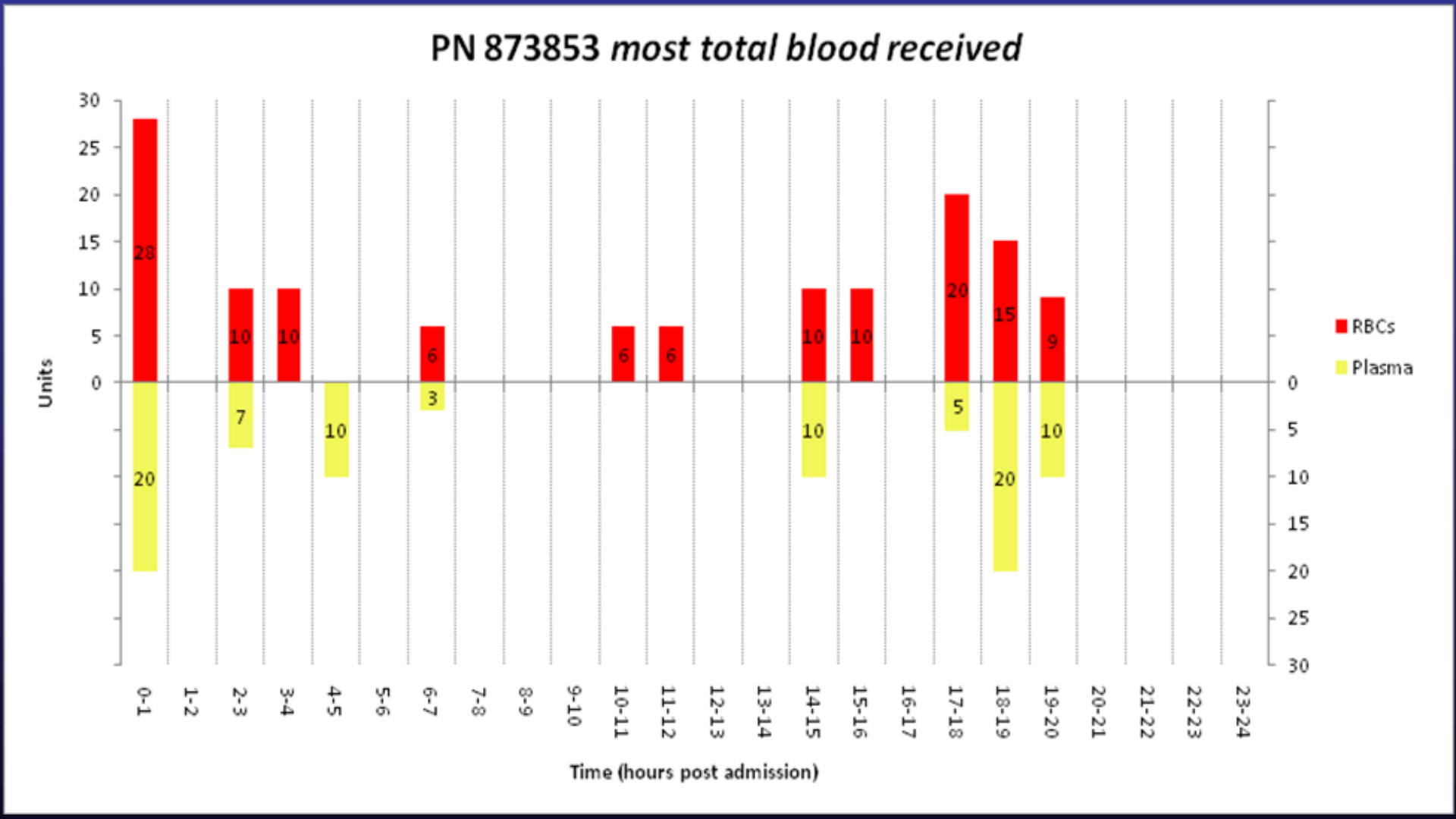


Hourly red cell and plasma use in n=125 high deficit patients



De Biasi et al, Transfusion 2011; 51:1925-32

50 yo man involved in collision of 2 cement trucks received 229 blood components 129 RBC & 95 plasma



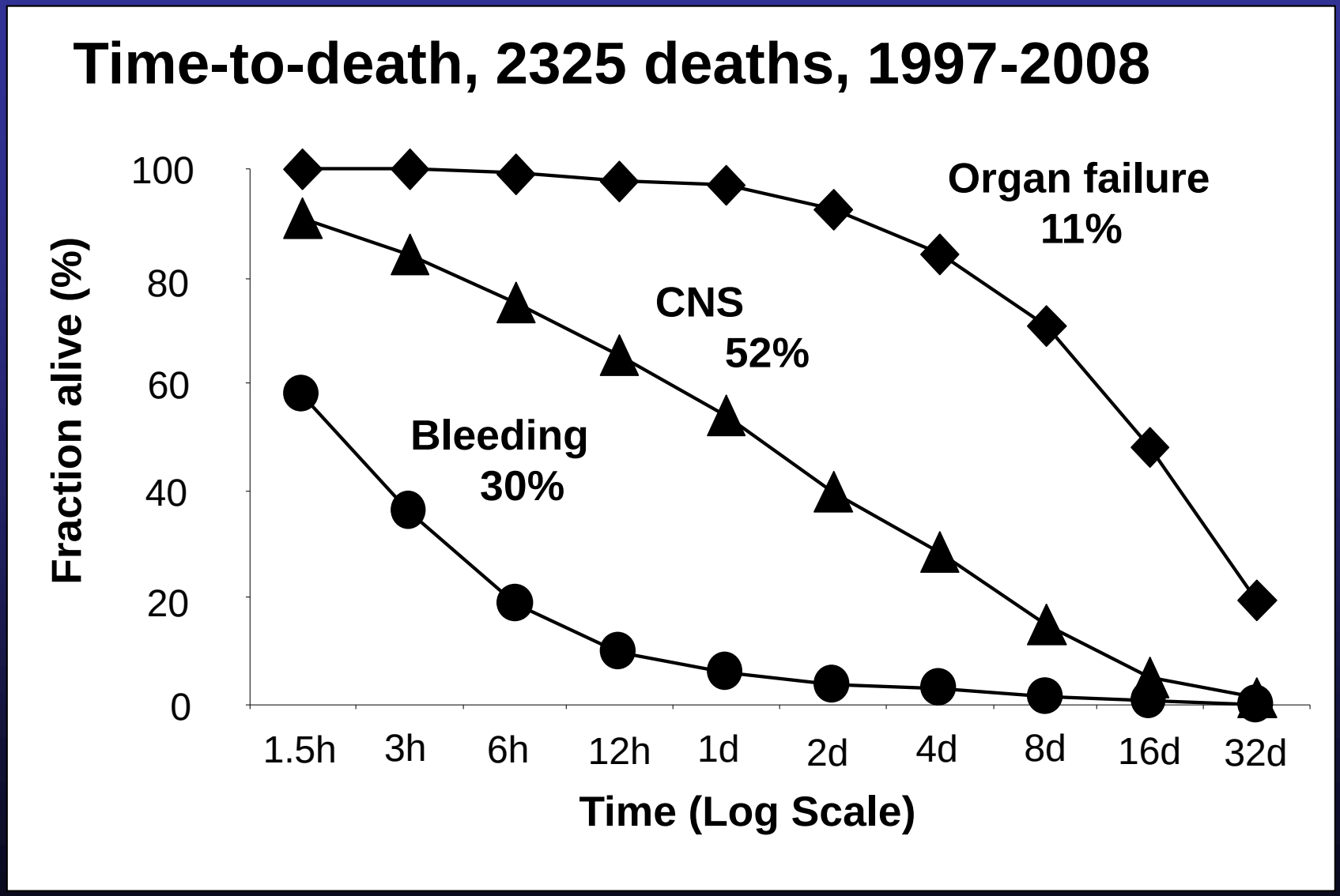
De Biasi et al, Transfusion 2011; 51:1925-32

Making blood available quickly in emergencies

The blood bank refrigerator in the trauma receiving unit

- In the Trauma Center
  - 10 units of O Pos RBC
  - 2 units O Neg RBC
  - 6 U AB thawed plasma
  - 1 U apheresis platelets
- In the Blood Bank
  - 600 more U RBC
  - A, B, & O thawed plasma
  - Apheresis platelets
  - Pre-pooled 6 U cryo

Review of deaths in 68,454 admissions



Dutton et al. J Trauma 2010; 69:260-269.

COMMENTARY

Giving plasma at a 1:1 ratio with red cells in resuscitation: who might benefit?

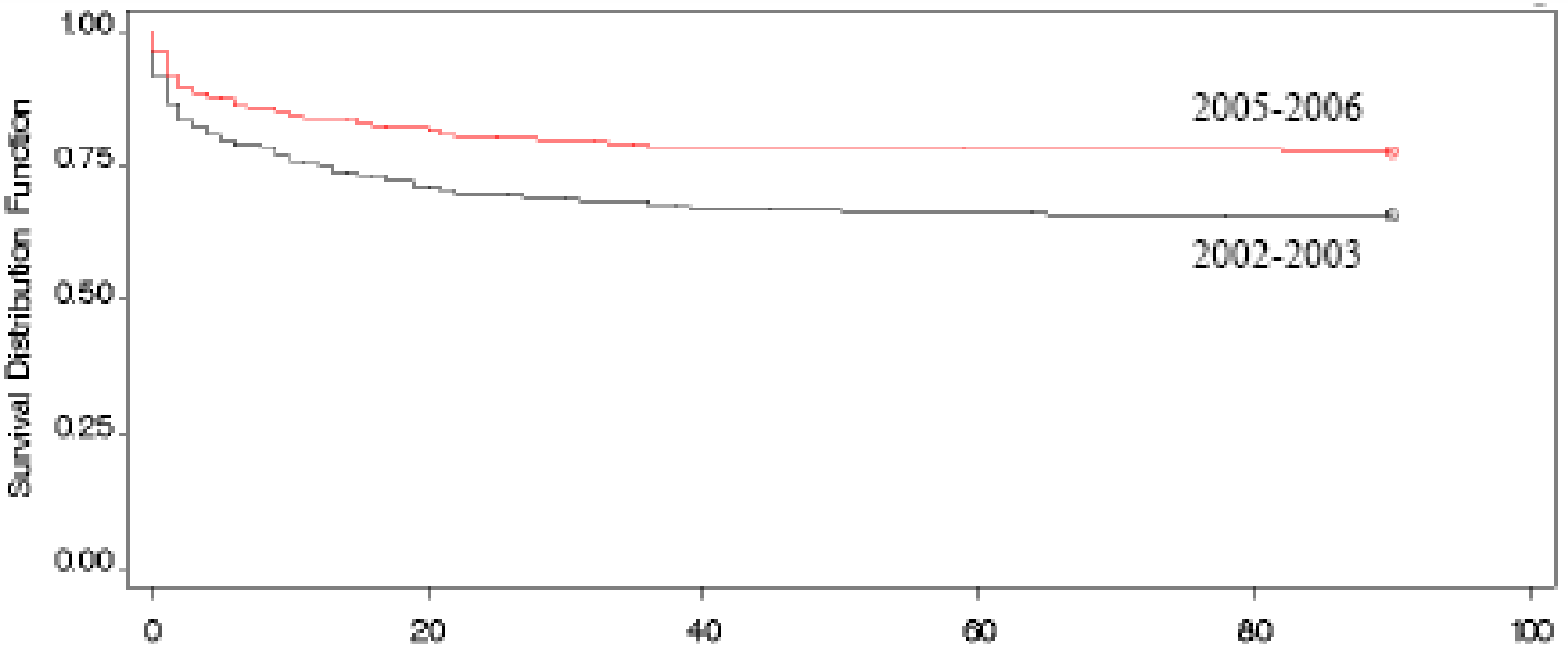
John R. Hess, Richard B. Dutton, John B. Holcomb, and Thomas M. Scalea

- Patients who are:
  - critically injured
  - actively bleeding
  - will go on to be massively transfused
- 2-5% of all injured patients

Transfusion 2008

Benefit of giving more plasma and platelets to massively transfused patients

Figure 1. Kaplan-Meier curve for 90-day survival



Number at risk

2005-2006	442	385	362	352	347	345	345	344	343	343
2002-2003	390	308	281	267	257	255	255	255	255	255

Log-rank, p<0.0001

Par Johansson, J Stensballe. Vox Sang 2009; 96:111-118.

The Netherlands Experience with Frozen −80°C Red Cells, Plasma and Platelets in Combat Casualty Care

J Badloe, F Noorman. *Ministry of Defense, Military Blood Bank, Leiden, Netherlands*

ISBT Abstract 2012

"In … massively transfused patients survival improved from 44% (N = 16) to 84% (N = 32) after the introduction of the new "1:1 transfusion policy" in Nov 2007."

Damage Control Resuscitation Reduces Resuscitation Volumes and Improves Survival in 390 Damage Control Laparotomy Patients

Bryan A Cotton, MD*, et al. **Ann Surg. 2011; 254:598-605**

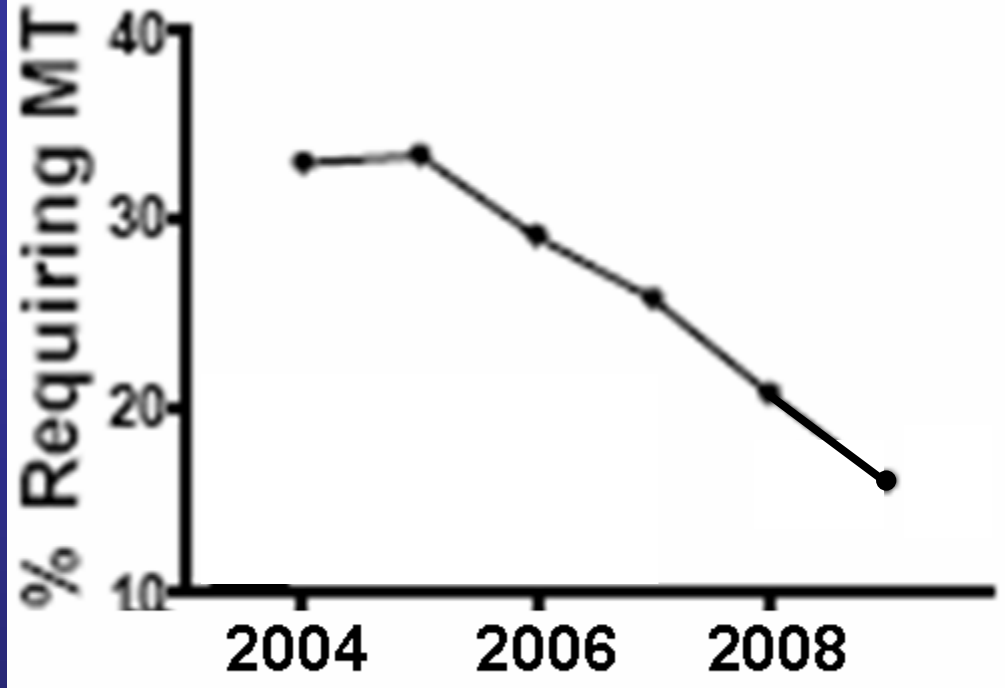
METHODS: A retrospective review of all emergent trauma laparotomies between 01/2004-08/2010 was performed.

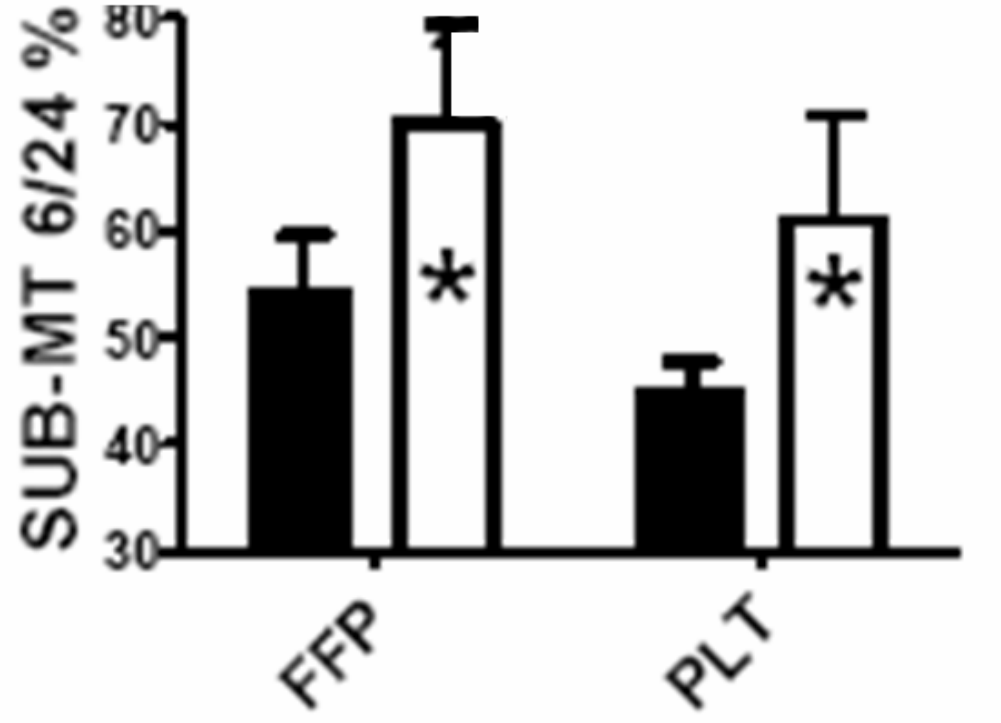
RESULTS: 390 (32%) underwent DCL. Of these, 282 were pre-DCR and 108 were DCR. Groups were similar in demographics, injury severity, arrival vitals and laboratory values. DCR patients received less crystalloids (median 14L vs. 5L), RBC (13U vs. 7U), plasma (11U vs. 8U) and platelets (6U vs. 0U) by 24-hr; all $p<0.05$. 24-hour and 30-day survival was higher in DCR (88% vs. 97%, $p=0.006$ and 76% vs. 86%, $p=0.03$).

Changes in Massive Transfusion over Time: An early shift in the right direction?

Kautza et al. J Trauma 2012 (Glue Grant, NIH)

With earlier administration of FFP and Plts, Massive transfusion has decreased.





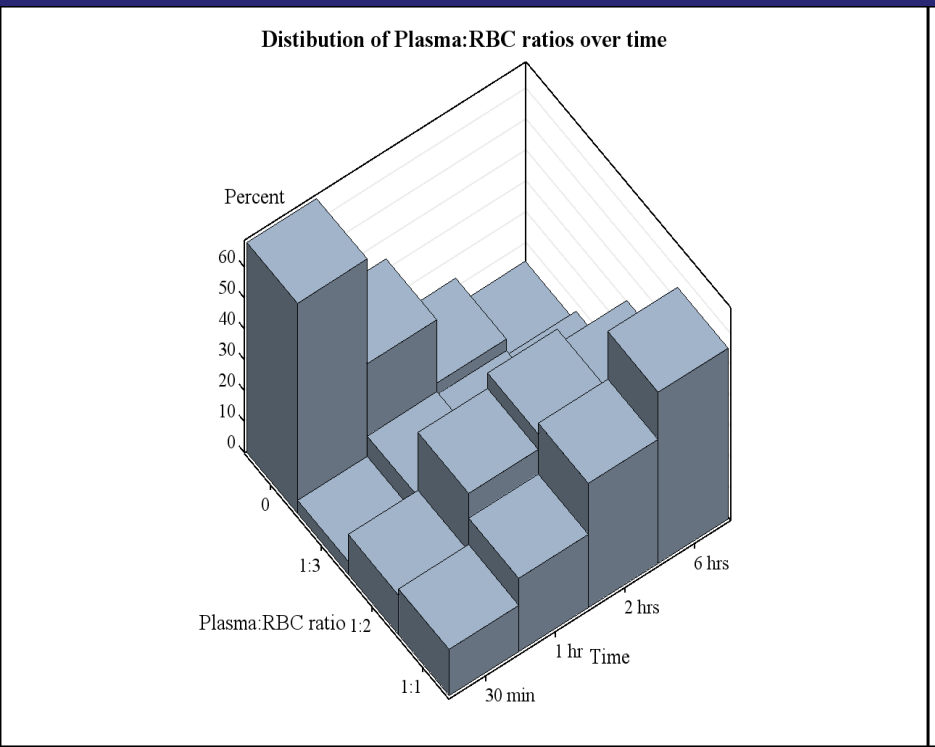
Damage Control Resuscitation

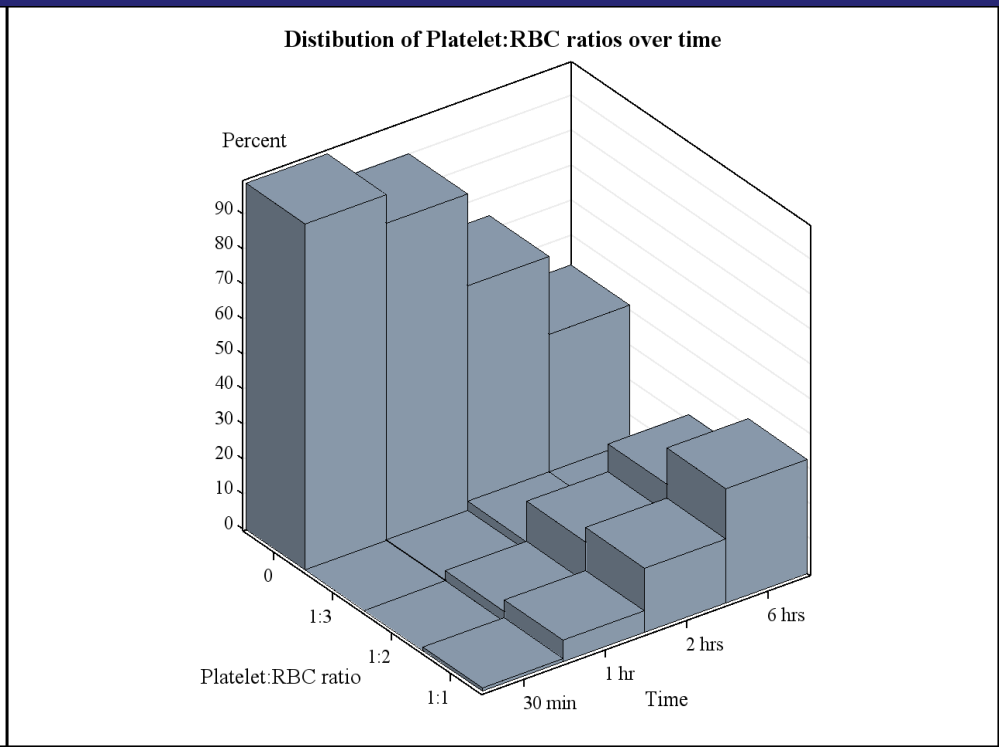
- Restrict crystalloids and permit moderate hypotension during prompt evaluation and initial damage control surgery.
- Resuscitate active hemorrhage with 1:1:1 plasma, platelets, and red cells.
- Supplement with additional cryoprecipitate and platelets based on early lab studies.

PROMMTT

PROSPECTIVE OBSERVATIONAL MULTICENTER MASSIVE TRANSFUSION STUDY

We are slow at issuing plasma and slower with platelets. Making time to issue a QI measure improves performance





PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

NIH/Army 12 site randomized trial of 1:1:1 vs 2:1:1 (RBC:plasma:platelets)

RBC	Plas	Plt	Composition of blood given
1	1	1	Hct 29, Plas 65%, Plts 88K
2	1	1	Hct 40, Plas 52%, Plts 55K

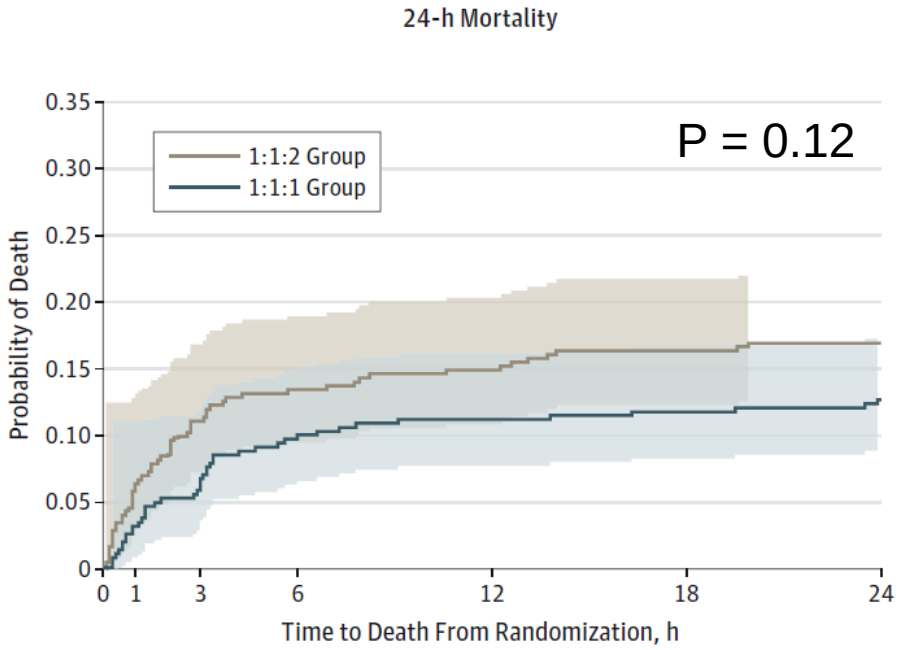
Original Investigation

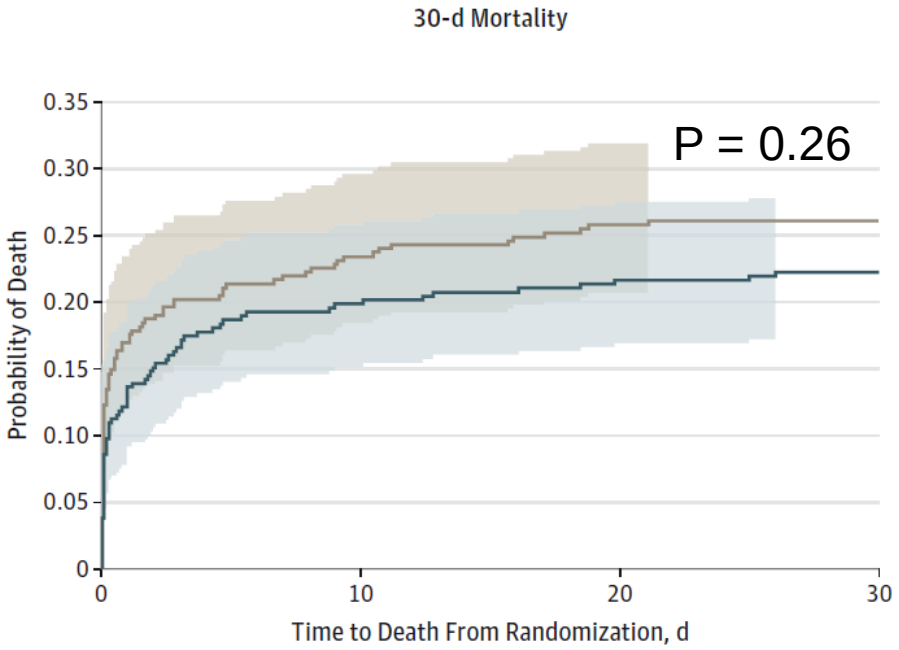
Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma

The PROPPR Randomized Clinical Trial

JAMA 2015: 313:471-482

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

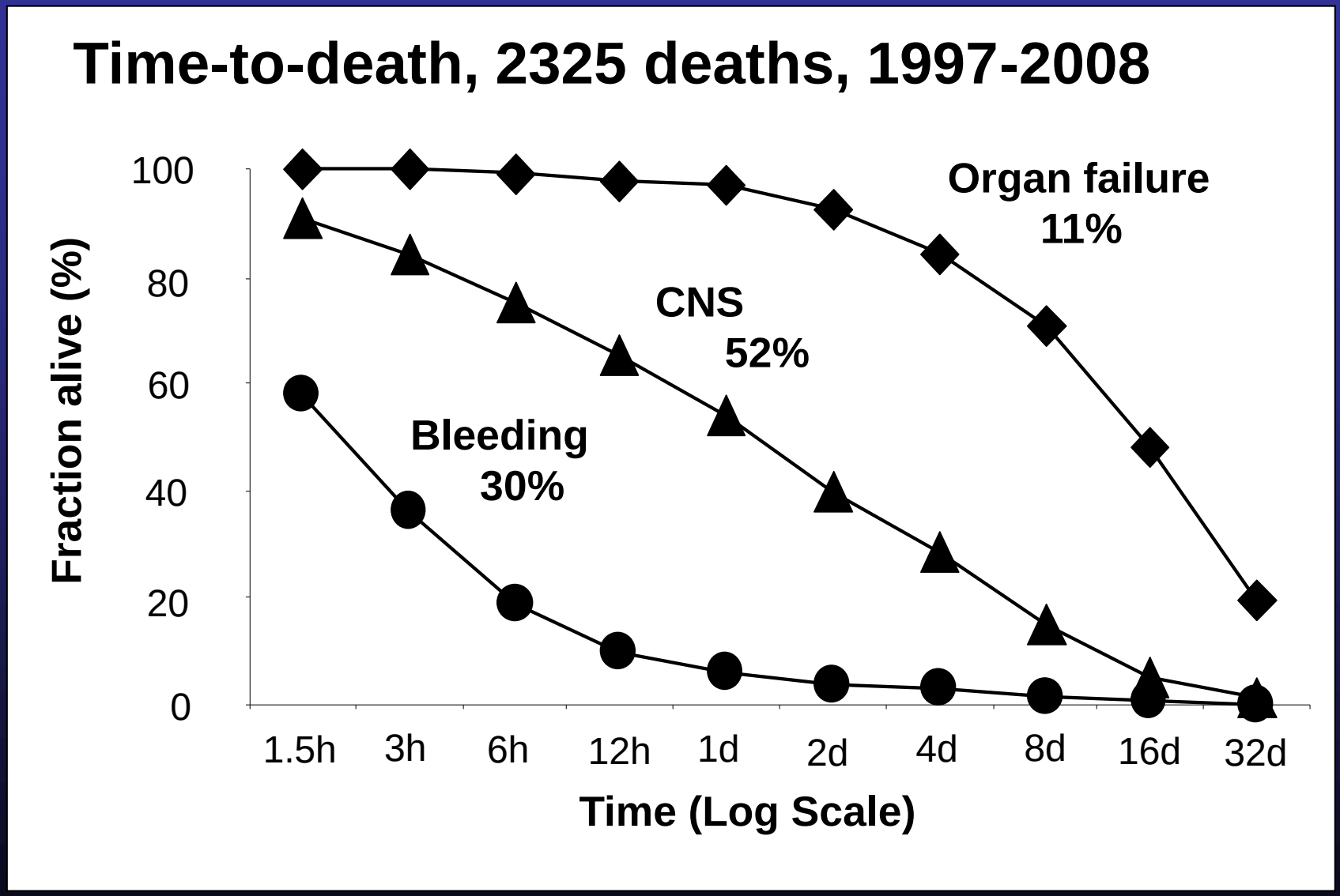




No. at risk

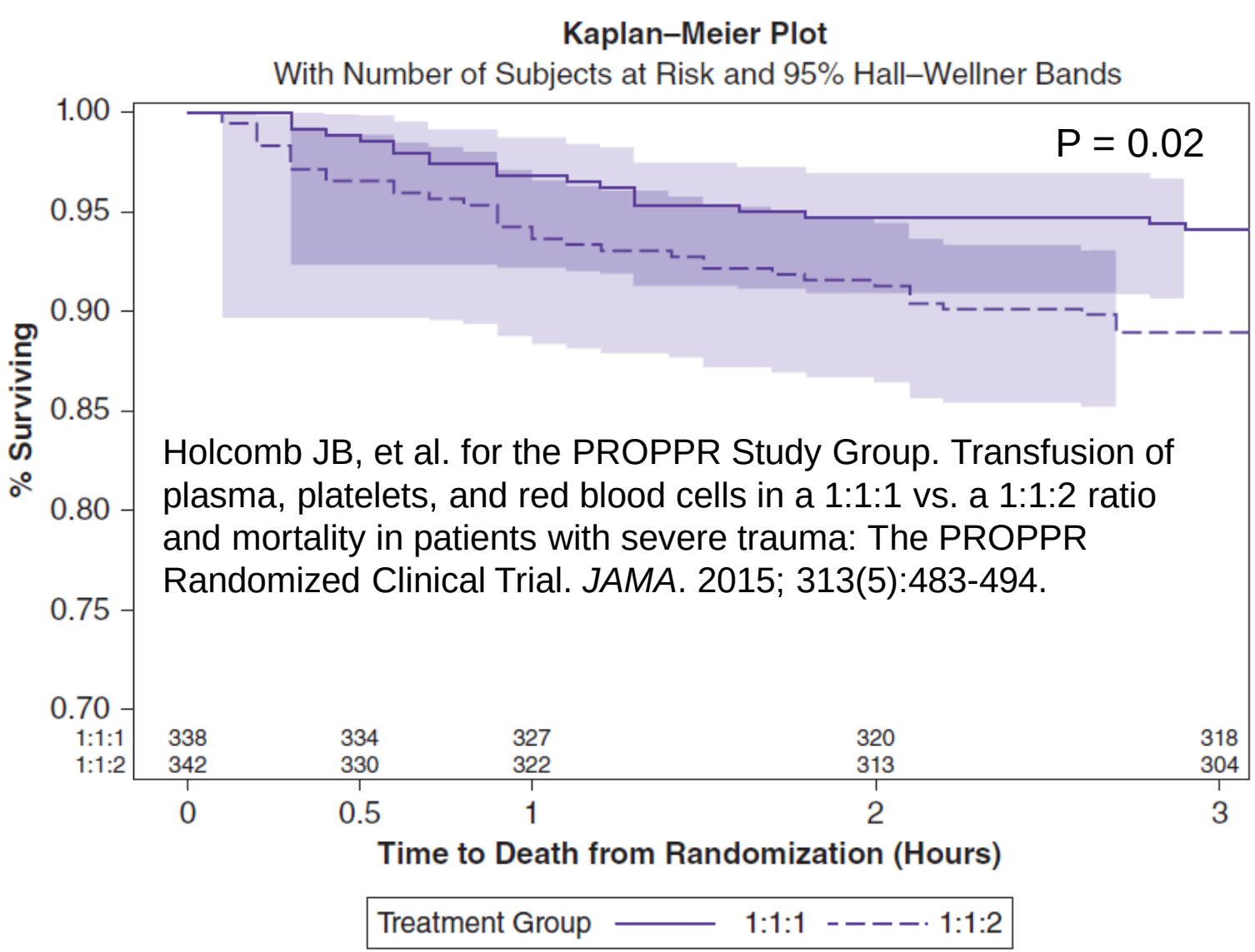
1:1:2	342	322	304	296	291	286	284	342	261	253	252
1:1:1	338	327	318	305	300	297	295	338	269	263	260

Review of deaths in 68,454 admissions



Dutton et al. J Trauma 2010; 69:260-269.

Balanced resuscitation saves lives

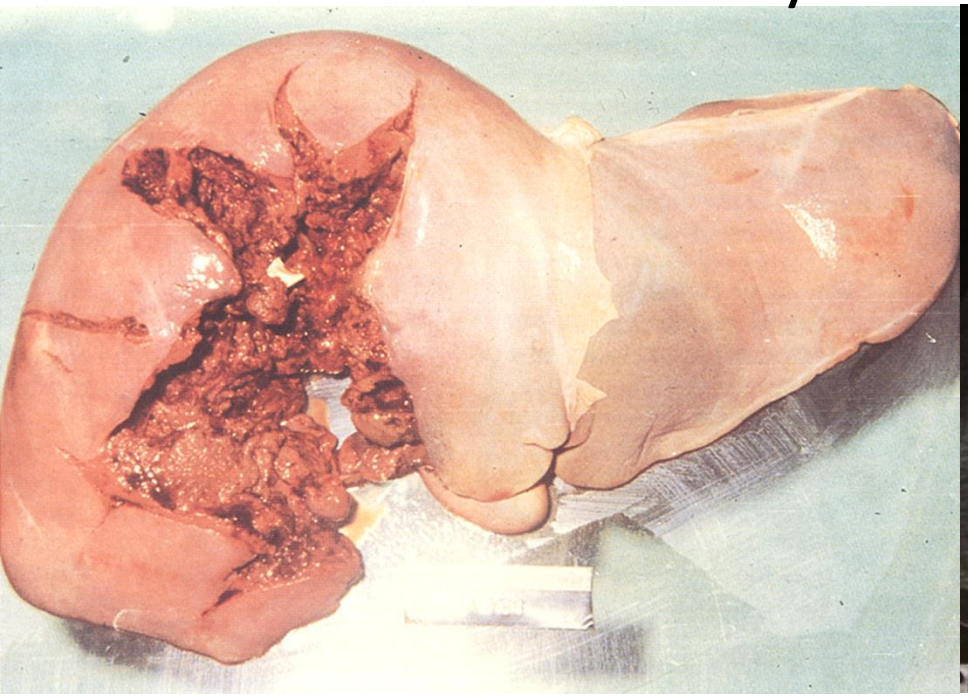


Holcomb JB, et al. for the PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs. a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR Randomized Clinical Trial. *JAMA*. 2015; 313(5):483-494.

Better Hemorrhage Control

Grade V liver injury

1990 - 76% mortality



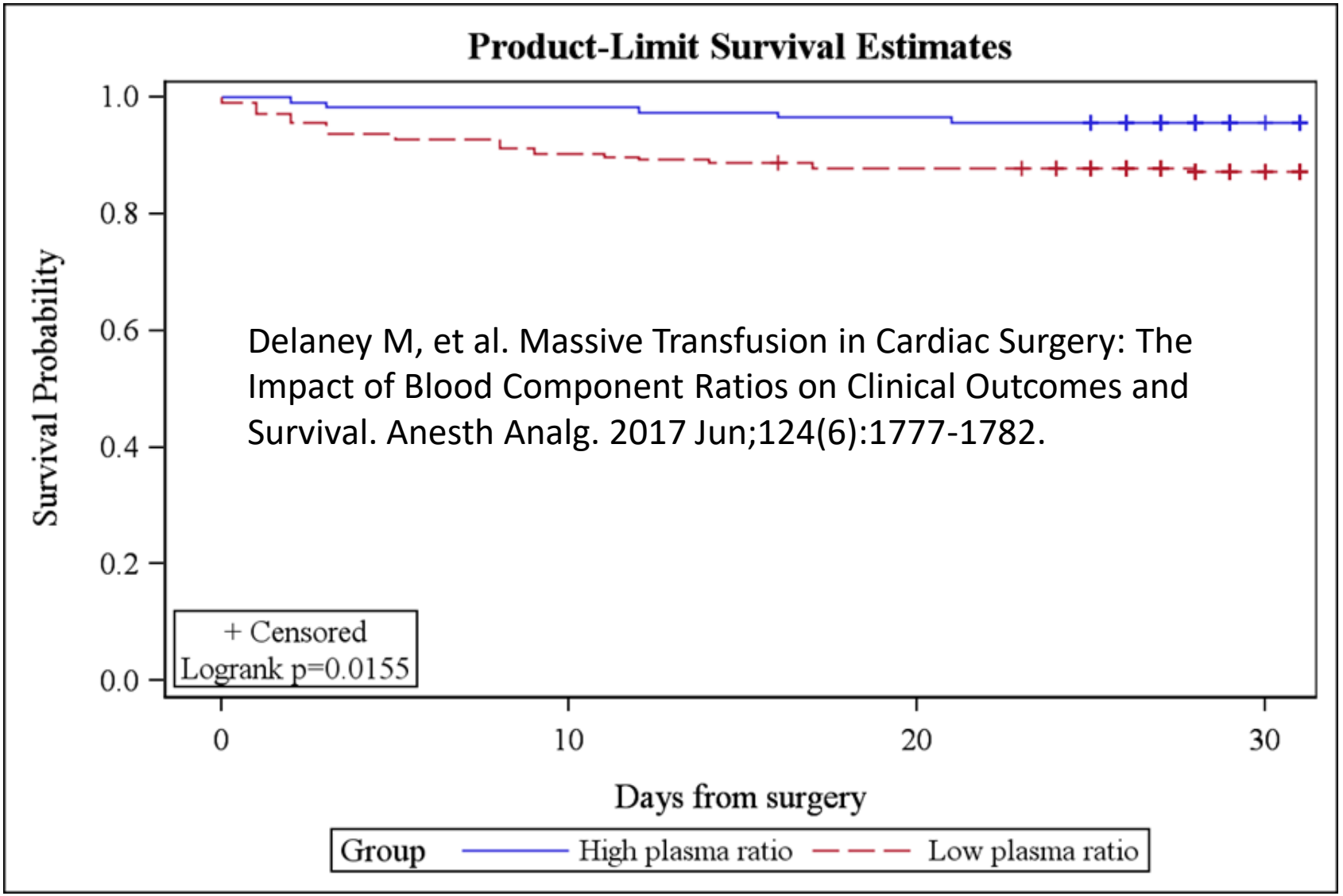
2015 - 6% mortality

Damage control surgery
Saline/RBC resuscitation
Survivors - open wounds

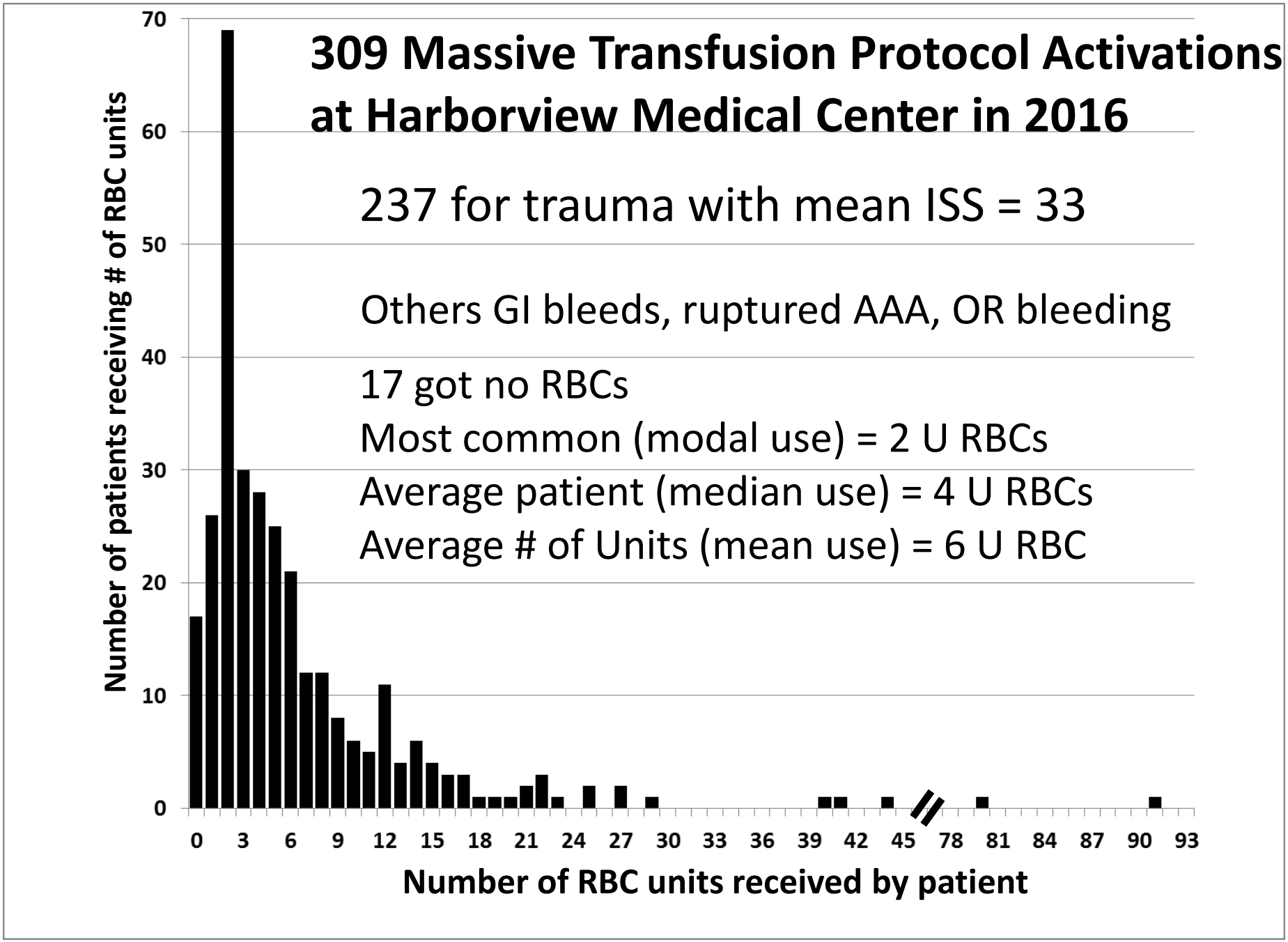
Damage control resuscitation
Hypotensive management
68% non-operative control

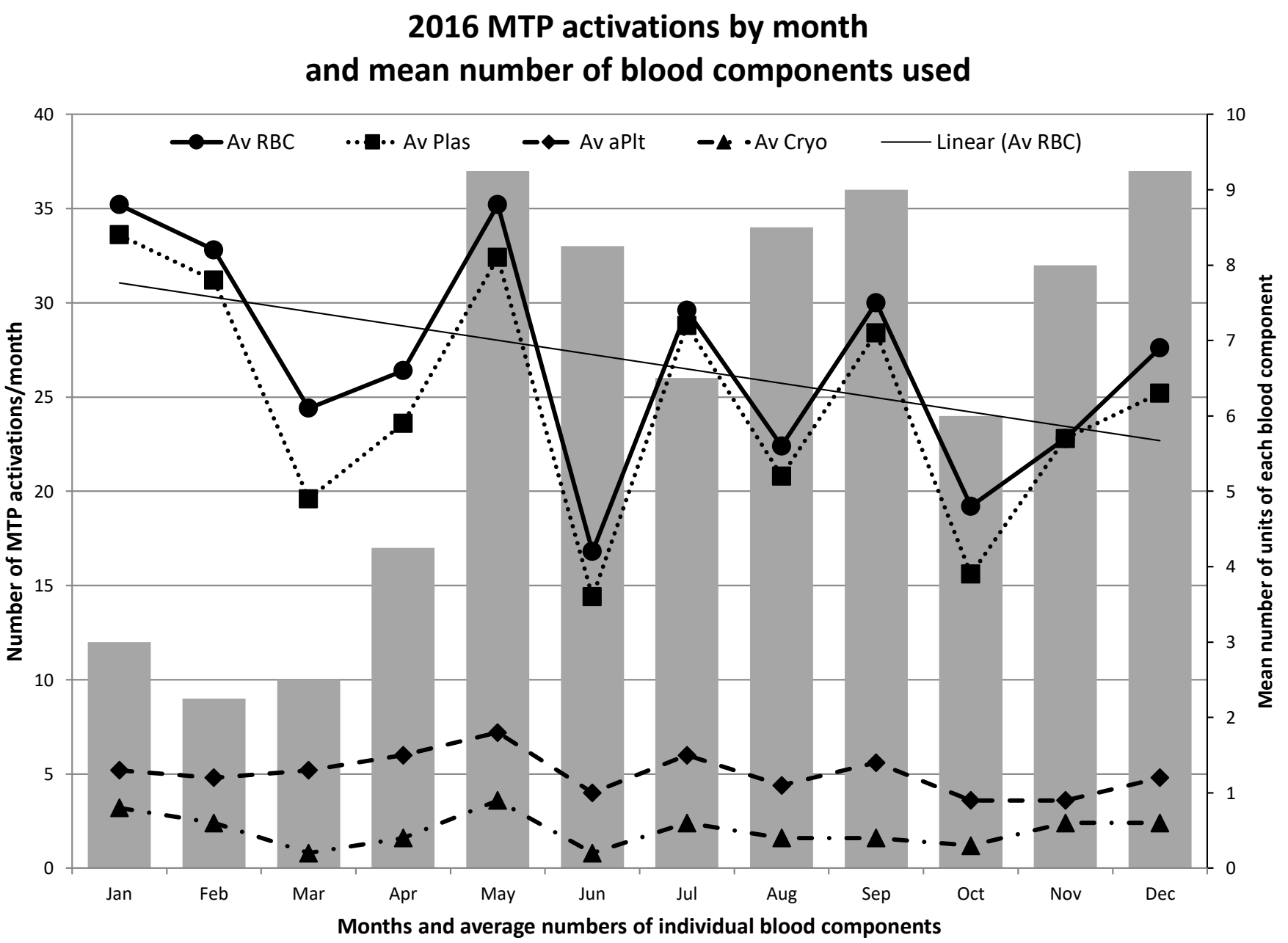
Survival in the RECESS study

among patients receiving ≥ 6 RBCs & ≥8 total blood products

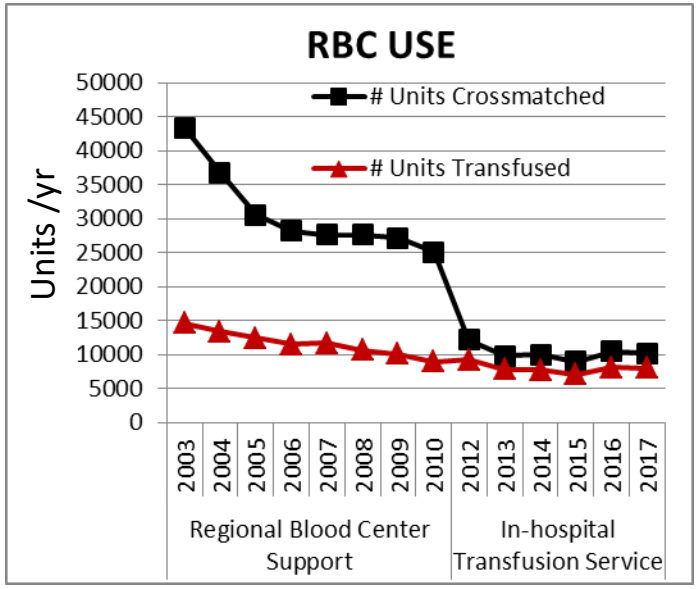


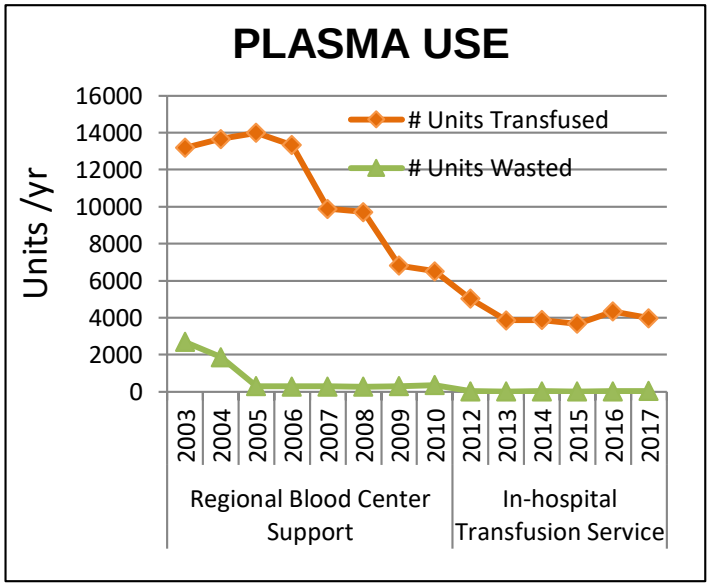
Delaney M, et al. Massive Transfusion in Cardiac Surgery: The Impact of Blood Component Ratios on Clinical Outcomes and Survival. Anesth Analg. 2017 Jun;124(6):1777-1782.

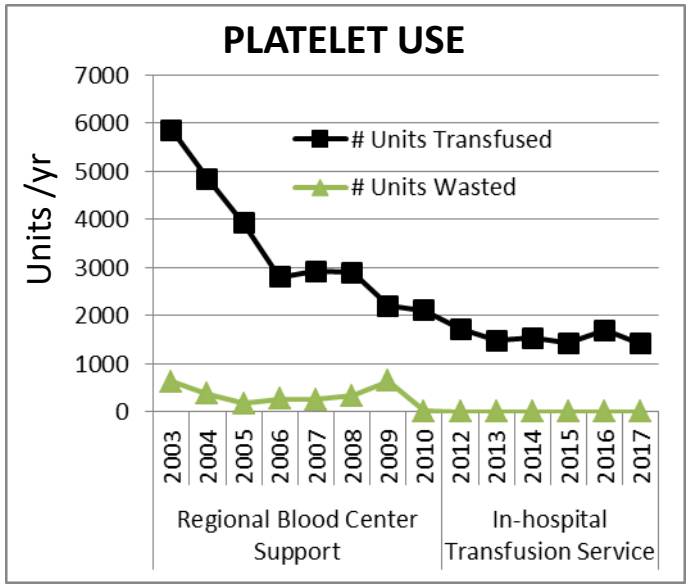

309 Massive Transfusion Protocol Activations at Harborview Medical Center in 2016
237 for trauma with mean ISS = 33
Others GI bleeds, ruptured AAA, OR bleeding
17 got no RBCs
Most common (modal use) = 2 U RBCs
Average patient (median use) = 4 U RBCs
Average # of Units (mean use) = 6 U RBC
Number of patients receiving # of RBC units
0
10
20
30
40
50
60
70
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 78 81 84 87 90 93
Number of RBC units received by patient

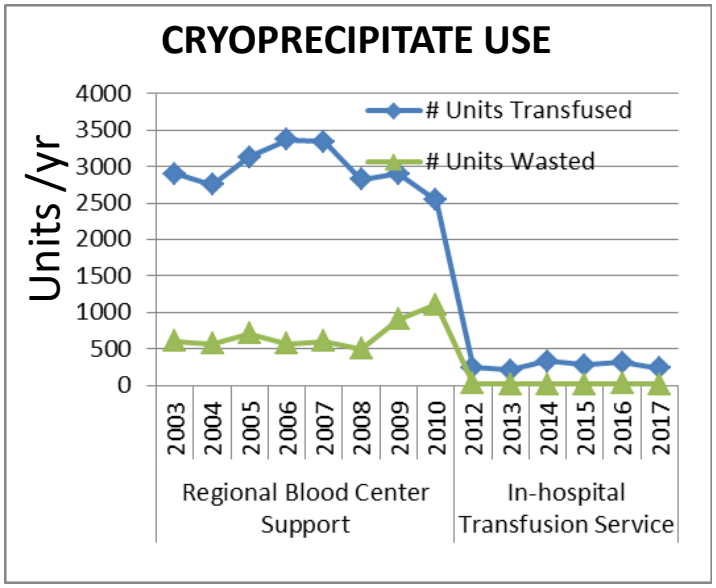

2016 MTP activations by month
and mean number of blood components used
Av RBC
Av Plas
Av aPlt
Av Cryo
Linear (Av RBC)
Number of MTP activations/month
Mean number of units of each blood component
0
5
10
15
20
25
30
35
40
0
1
2
3
4
5
6
7
8
9
10
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Months and average numbers of individual blood components

Blood Product Use at Harborview, 2003-2017









Conclusions

- In the recent past, crystalloid resuscitation led to an epidemic of iatrogenic coagulopathy in injured patients.
- Giving plasma and platelets earlier appears to have improved outcome and reduced blood use.
- Randomized clinical trials, such as the NIH PROPRR study, will improve our understanding.

Thanks to many individuals in Baltimore and Baghdad

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

And the PROPPR trial team: US Army, NHLBI, NIGMS, CIHS, FDA, 12 university level 1 trauma centers and over 250 individuals. The data are still coming out.

Thank you
hessj3@uw.edu

Cover, Blood Cells