Factor-Based Resuscitation for Traumatic Hemorrhage in Civilian and Military Settings

Matthew Martin, MD, FACS

Los Angeles County + USC Medical Center

Professor of Surgery, USC and USUHS


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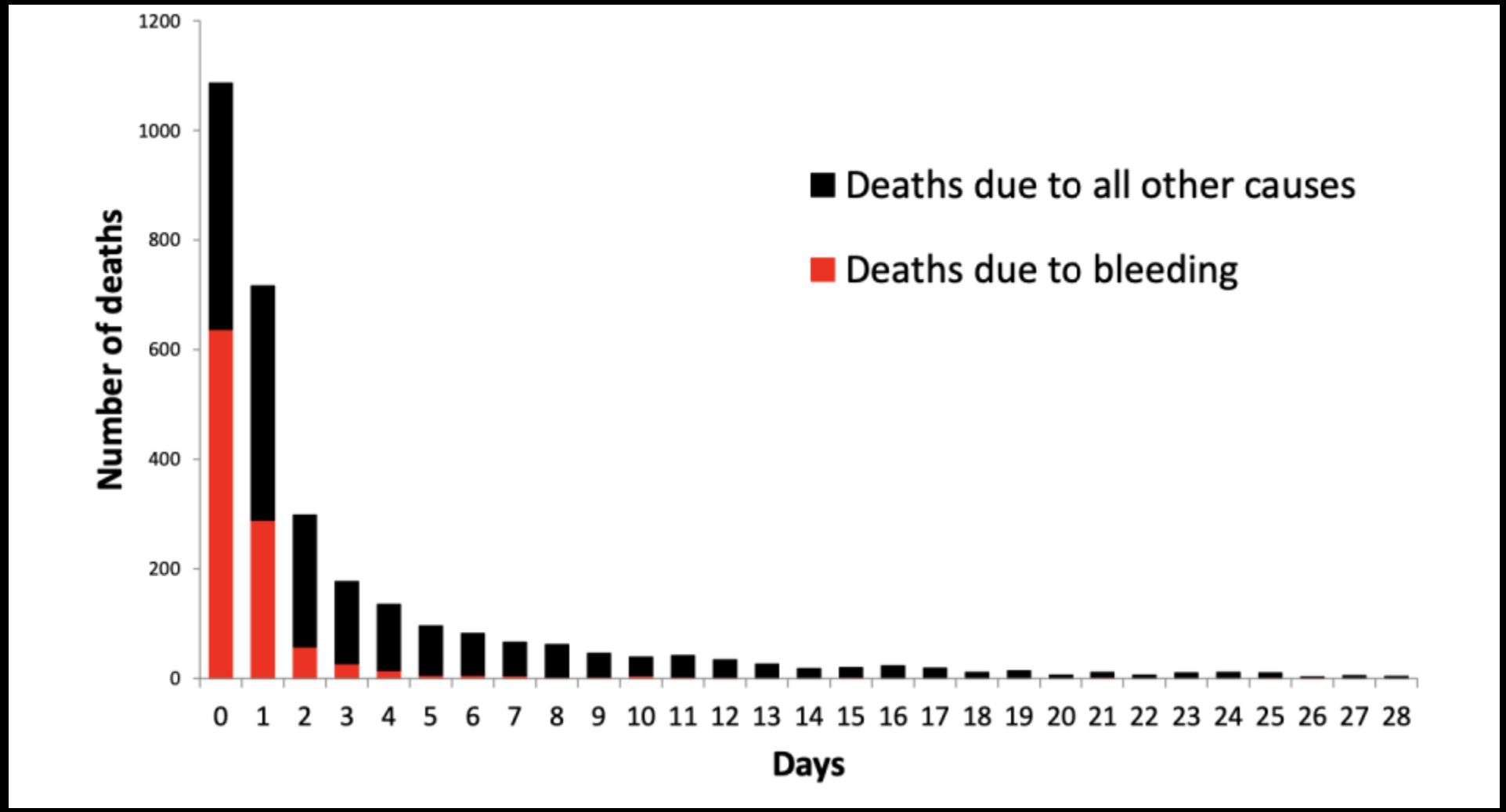
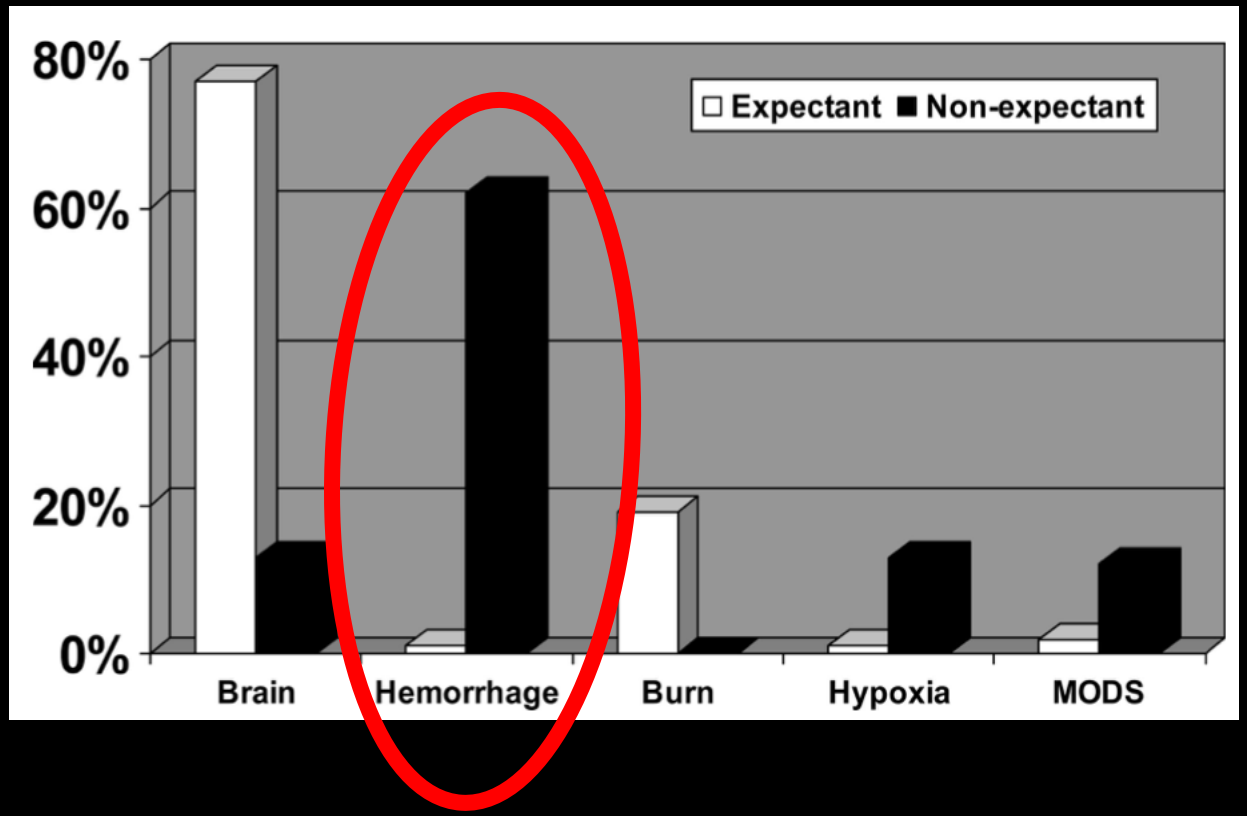
Bleeding Deaths

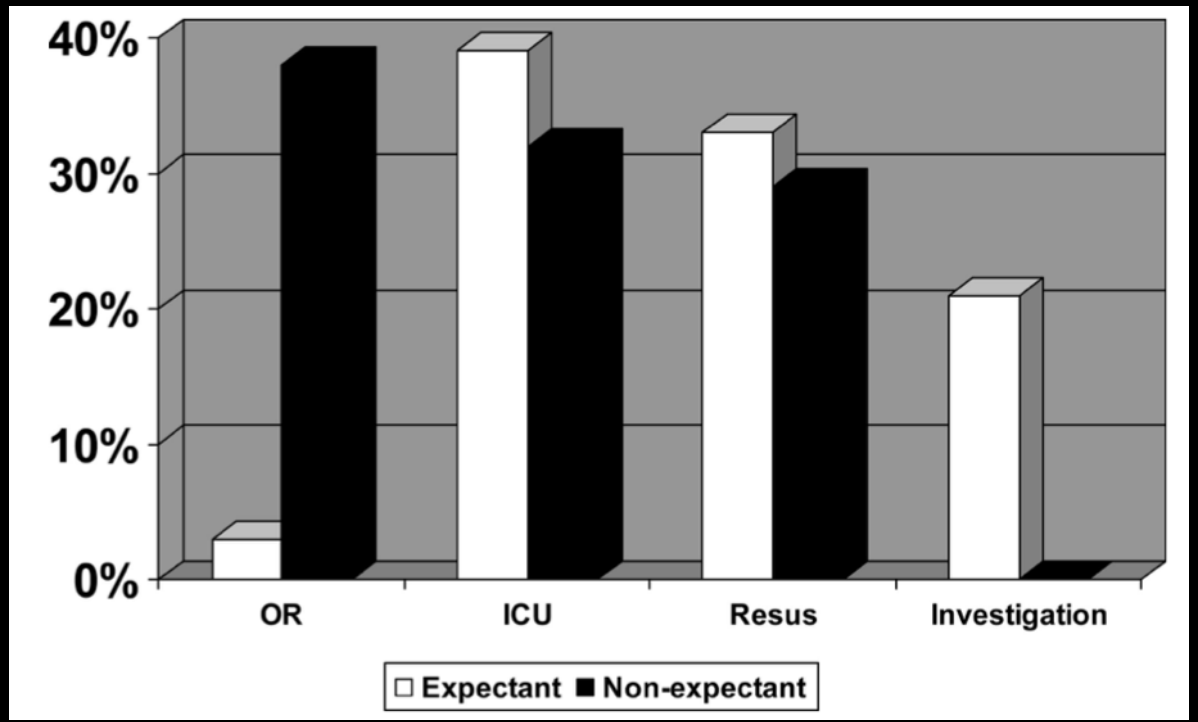


The Journal of **TRAUMA®** *Injury, Infection, and Critical Care*

An Analysis of In-Hospital Deaths at a Modern Combat Support Hospital

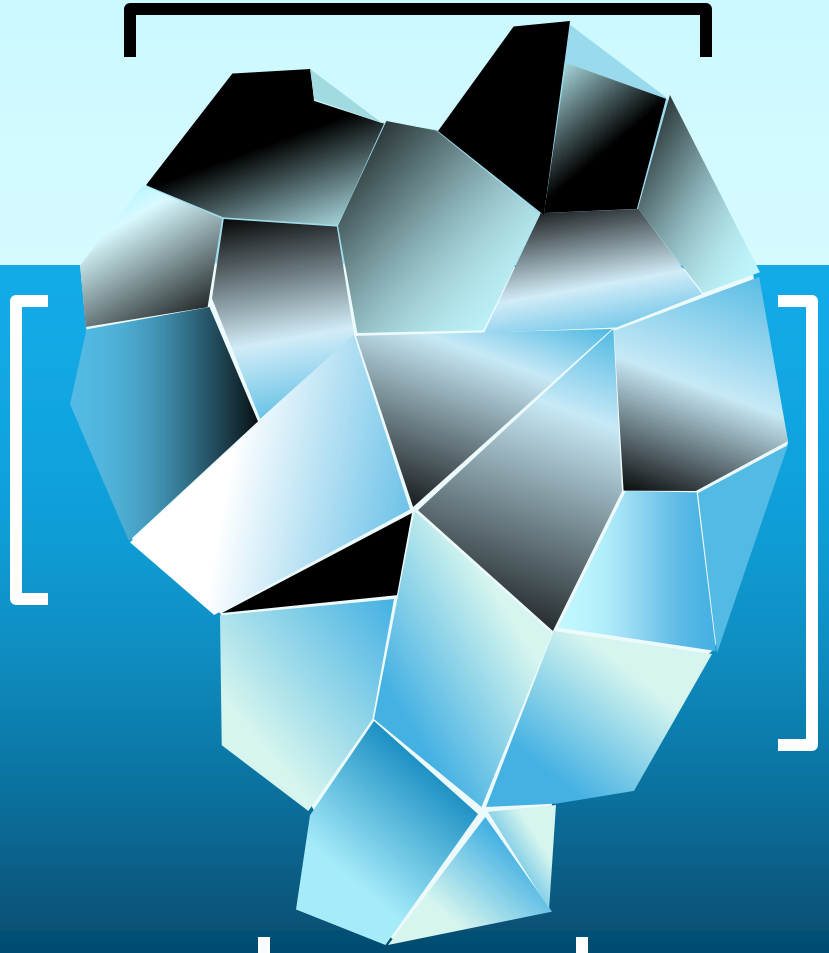
LTC Matthew Martin, MD, MAJ John Oh, MD, MAJ Heather Currier, MD, LTC Nigel Tai, FRCS, LTC Alec Beekley, MD, CPT Matthew Eckert, MD, and COL John Holcomb, MD





Outcomes Iceberg

Post-Injury Deaths



Complications
Near-misses
Mis-diagnoses

Iatrogenia
Delay Dx
Delay Tx

Long-term disability
Late Deaths

ATLS Classes of Hemorrhagic Shock

Class of haemorrhagic shock				
	I	II	III	IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	> 2000
Blood loss (% blood volume)	Up to 15	15–30	30–40	> 40
Pulse rate (per minute)	< 100	100–120	120–140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	> 35
Urine output (mL/hour)	> 30	20–30	5–15	Negligible
Central nervous system/ mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

4 Classes of Hemorrhage for the Surgeon

Alexander A. Artemiev

1. "Why did I get involved in this operation?"
2. "Why did I become a surgeon?"
3. "Why did I become a doctor?“
4. "Why was I born?"

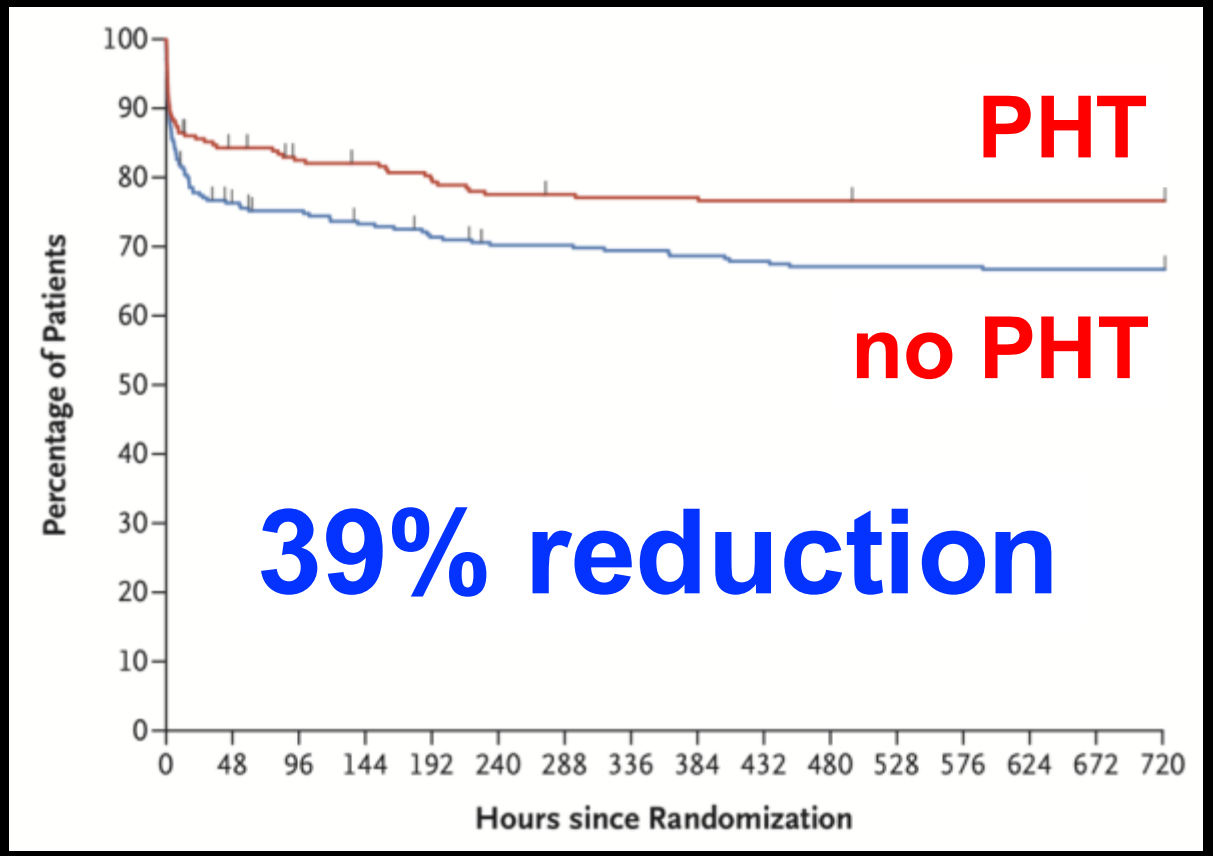
JAMA | Original Investigation

Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival

Stacy A. Shackelford, MD; Deborah J. del Junco, PhD; Nicole Powell-Dunford, MD; Edward L. Mazuchowski, MD, PhD; Jeffrey T. Howard, PhD; Russ S. Kotwal, MD, MPH; Jennifer Gurney, MD; Frank K. Butler Jr, MD; Kirby Gross, MD; Zsolt T. Stockinger, MD

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*



- Interaction with PRBCs
- Benefit with either product

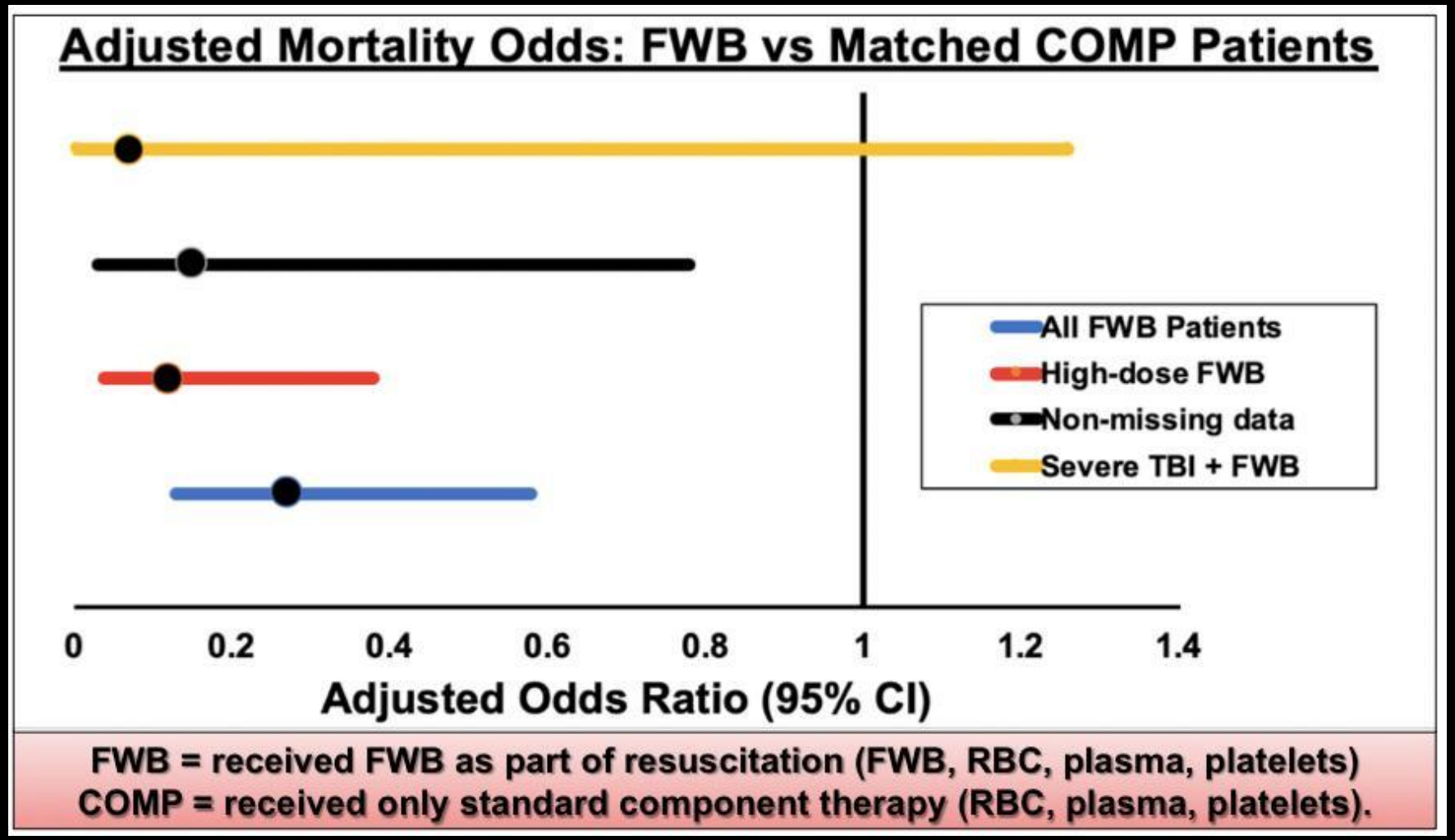
The NEW ENGLAND JOURNAL of MEDICINE

JULY 26, 2018 VOL. 379 NO. 4

Whole blood at the tip of the spear: A retrospective cohort analysis of warm fresh whole blood resuscitation versus component therapy in severely injured combat casualties

Surgery
Volume 171, Issue 2, February 2022, Pages 518-525

Jennifer M. Gurney, MD, FACS[a,b,c,*], Amanda M. Staudt, PhD[d], Deborah J. del Junco, PhD[b], Stacy A. Shackelford, MD, FACS[b,c], Elizabeth A. Mann-Salinas, PhD[a,b], Andrew P. Cap, PhD, MD[a,c], Philip C. Spinella, MD[e], Matthew J. Martin, MD, FACS[c,f]

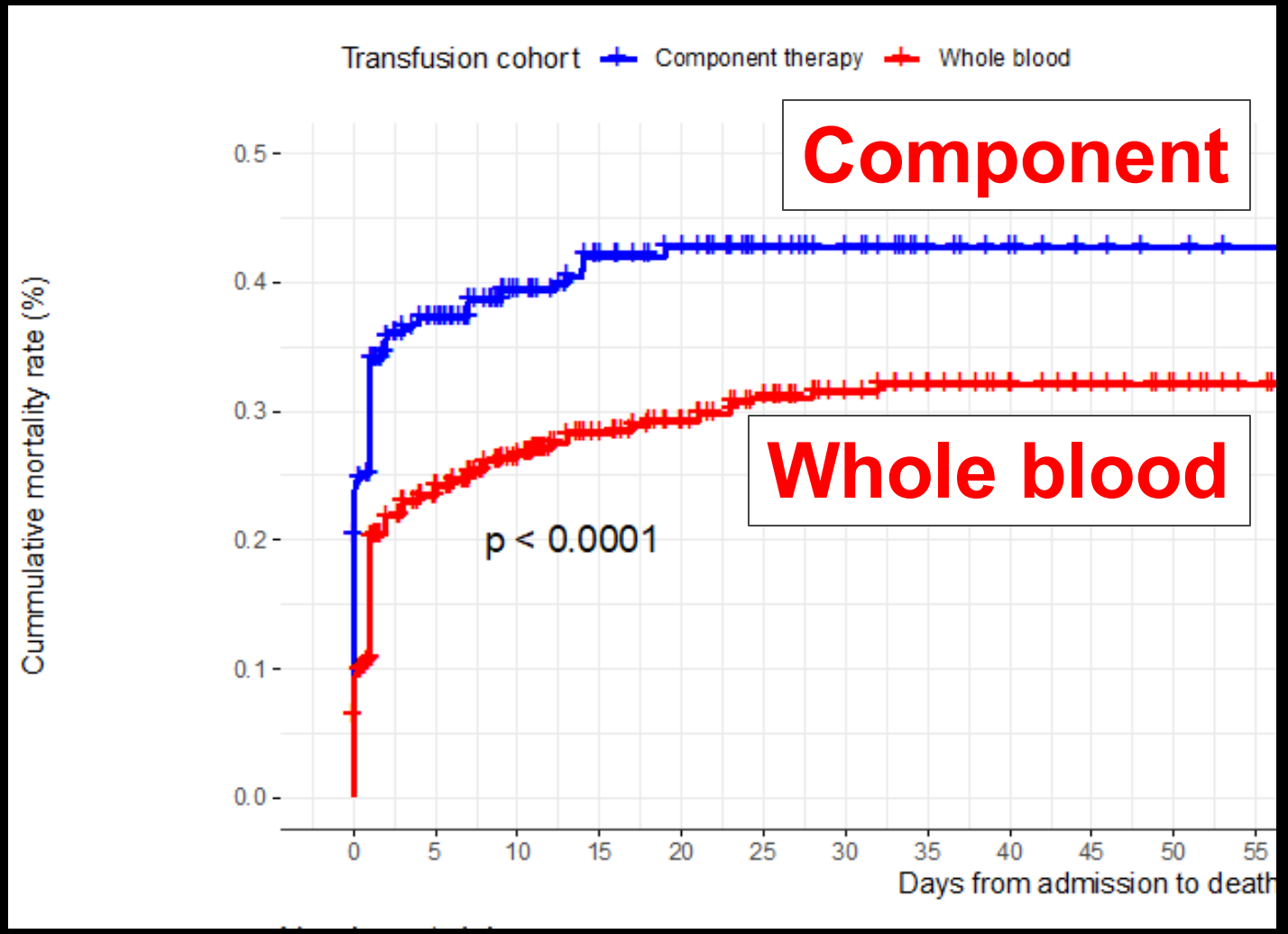


Warm Fresh Whole Blood

prehospital?
civilian?

Civilian LTOWB

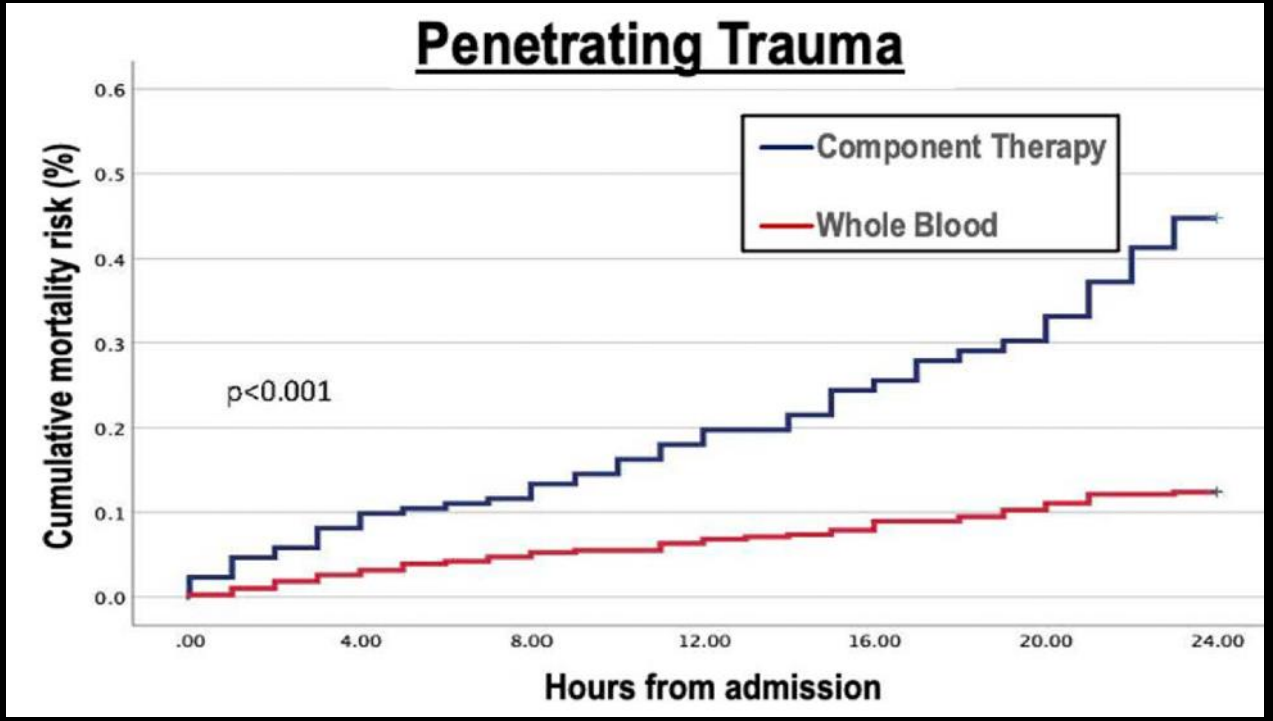
- Multicenter
- Prospective observational

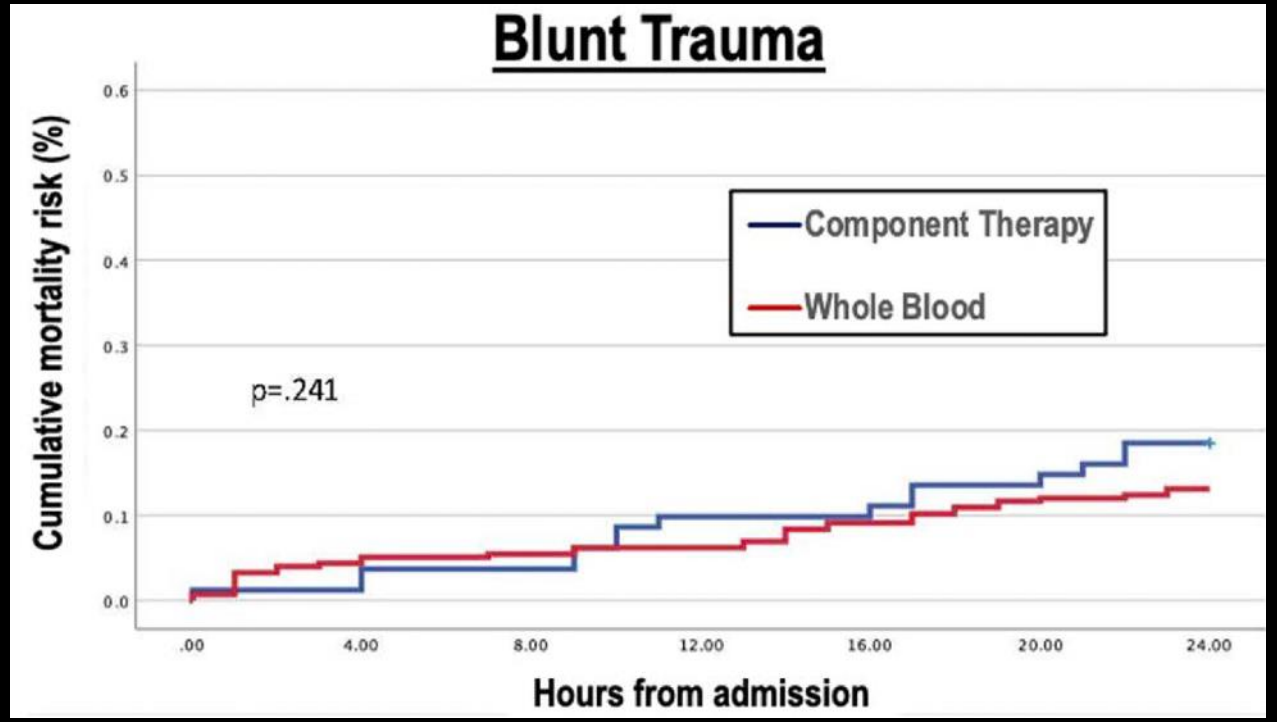


The Journal of Trauma and Acute Care Surgery

Mechanism matters: Differential benefits of cold-stored whole blood for trauma resuscitation from a prospective multicenter study

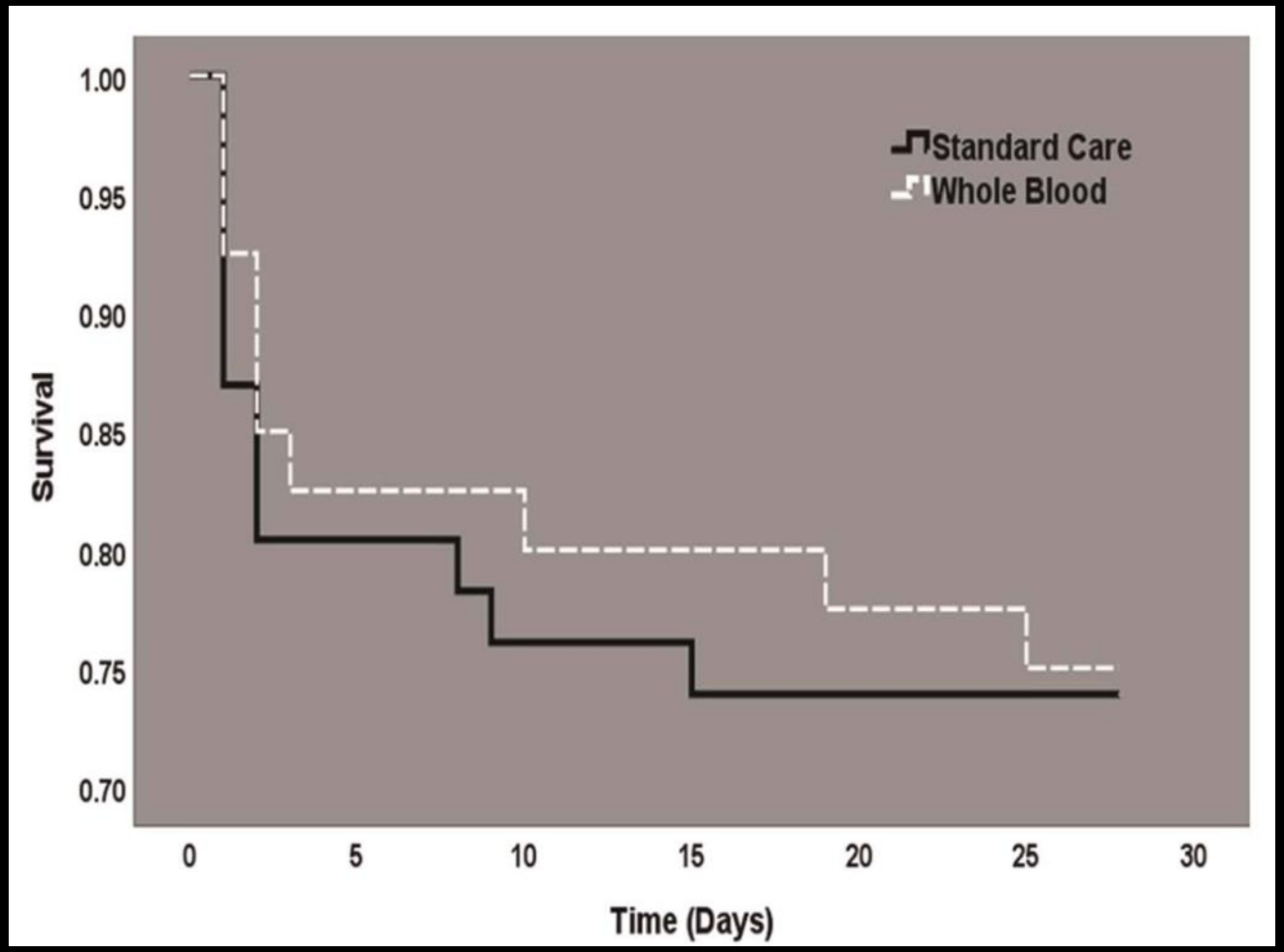
Joshua Dilday, DO, Shea Gallagher, MD, MBA, Kazuhide Matsushima, MD, Morgan Schellenberg, MD, Kenji Inaba, MD, Joshua P. Hazelton, DO, John Oh, MD, Jennifer Gurney, MD, Matthew Martin, MD, *and* **the EAST Whole Blood Multicenter Collaborative**, *Milwaukee, Wisconsin*





Prehospital low titer group O whole blood is feasible and safe: Results of a prospective randomized pilot trial (PPOWER Trial)

Frank X. Guyette, MD, MPH, Mazen Zenati, MD, PhD, Darrell J. Triulzi, MD, Mark H. Yazer, MD, Hunter Skroczky, BS, Barbara J. Early, BSN, Peter W. Adams, BS, Joshua B. Brown, MD, MCS, Louis Alarcon, MD, Matthew D. Neal, MD, Raquel M. Forsythe, MD, Brian S. Zuckerbraun, MD, Andrew B. Peitzman, MD, Timothy R. Billiar, MD, *and* Jason L. Sperry, MD, MPH, *Pittsburgh, Pennsylvania*



- Small pilot study (N=86)
  - all HEMS transport
- PH WB vs SOC
- No outcome differences

J Trauma Acute Care Surg
Volume 92, Number 5

Original article

Rational and design of the T-STORHM Study: A prospective randomized trial comparing fresh whole blood to blood components for acutely bleeding trauma patients

citation
Whole
cts
IAL AT UAB

LiTES

Linking Investigations in Trauma and Emergency Services

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

LiTES

Linking Investigations in Trauma and Emergency Services

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

ELSEVIER

Injury

Volume 56, Issue 5, May 2025, 112173

Transfusion of modified whole blood versus blood components therapy in patients with severe trauma: Randomized controlled trial protocol (WEBSTER trial)

Alberto F García [a b e], Yaset Caicedo [c f], Andrés Gempeler [c], Liliana Vallecilla [c], Carmenza Macia [d], Claudia Orlas [l], María Isabel Fernández [c], Paula Lancheros-Ramírez [c], Marcela Quintero [d], Edna Hernández [d], Sandra Vargas [d], Laura Cardenas-Perez [d], Fredy Ariza [g], Virginia Zarama [h], Sandra Carvajal [h], Einar Billefals [g], Álvaro Sánchez [i], Marisol Badiel [k], Fernando Rosso [j], Marcela Granados [b]...Carlos A Ordoñez [a b e]

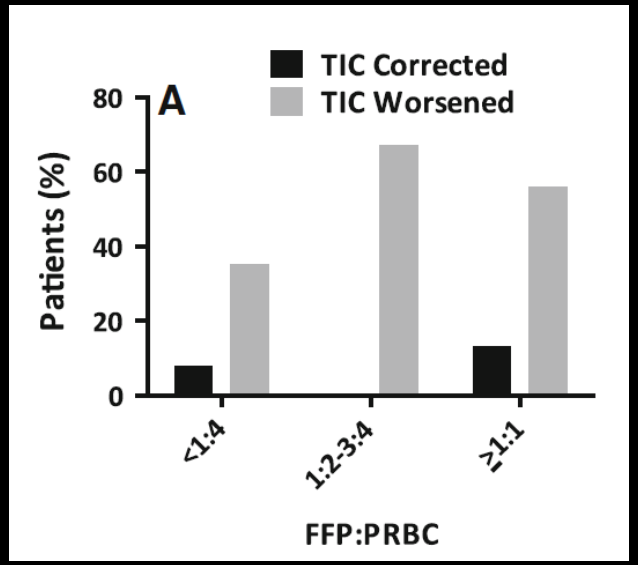
Factor Concentrates?

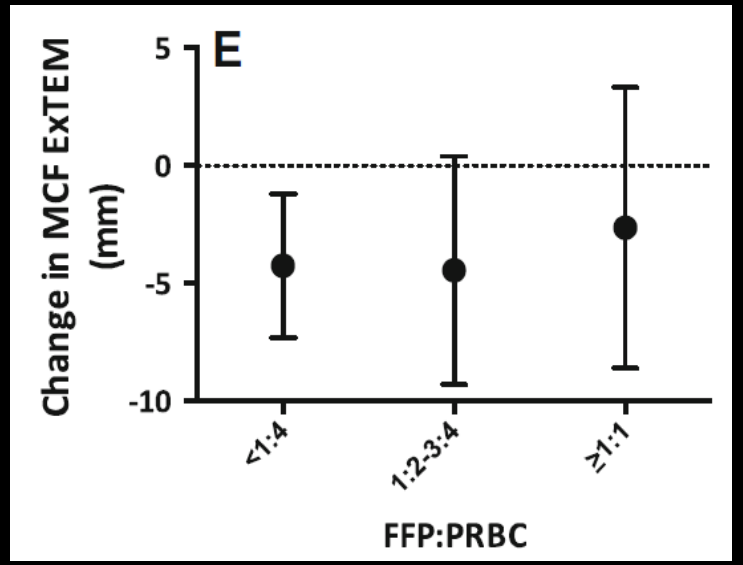
Is DCR the Optimal Approach?

Sirat Khan
Ross Davenport
Imran Raza
Simon Glasgow
Henry D. De'Ath
Pär I. Johansson
Nicola Curry
Simon Stanworth
Christine Gaarder
Karim Brohi

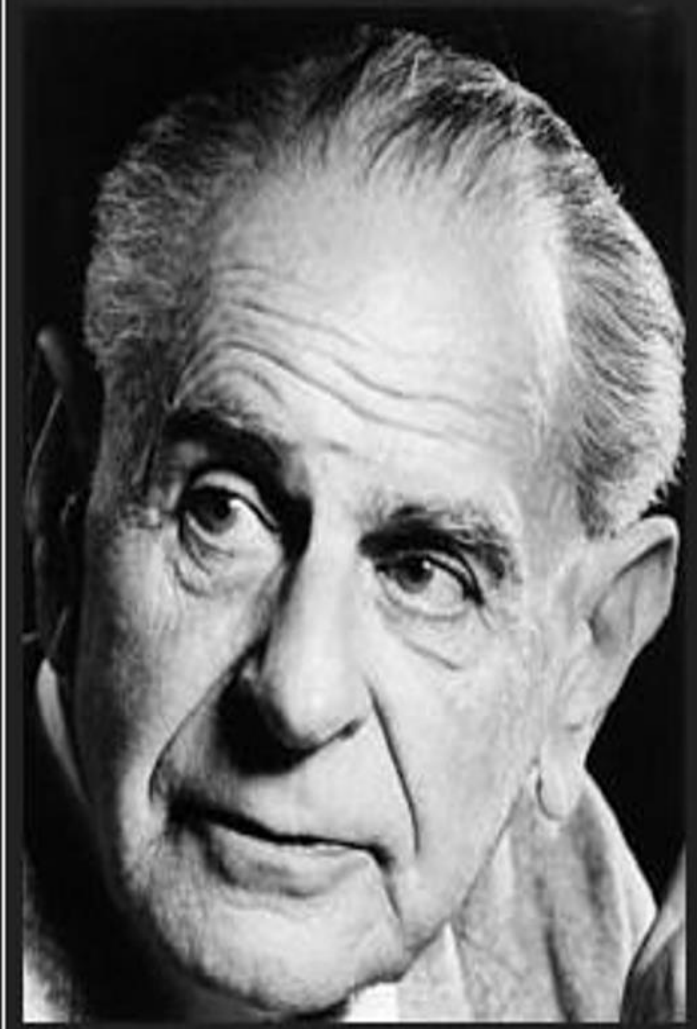
Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage

- International, multicenter, prospective





"Plasma largely ineffective in standard doses"



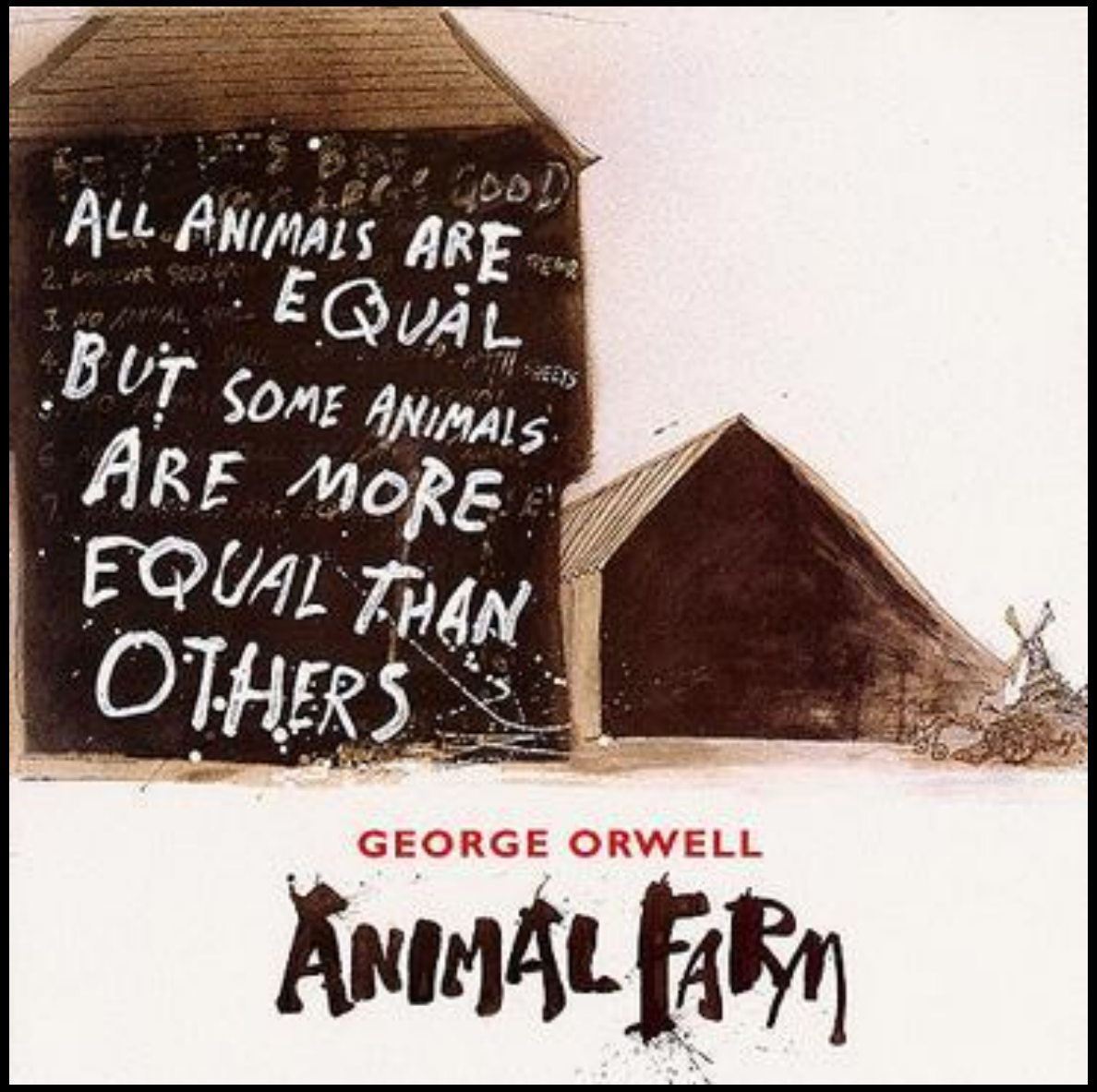
Science may be described as the art of systematic over-simplification.

(Karl Popper)

What is REALLY going on?

- Blood loss, factor loss
- Hemoconcentration and/or dilution
- FACTOR CONSUMPTION
  - select clotting factors
  - fibrinogen
- Resuscitation
- Endotype response
- Variable & dynamic

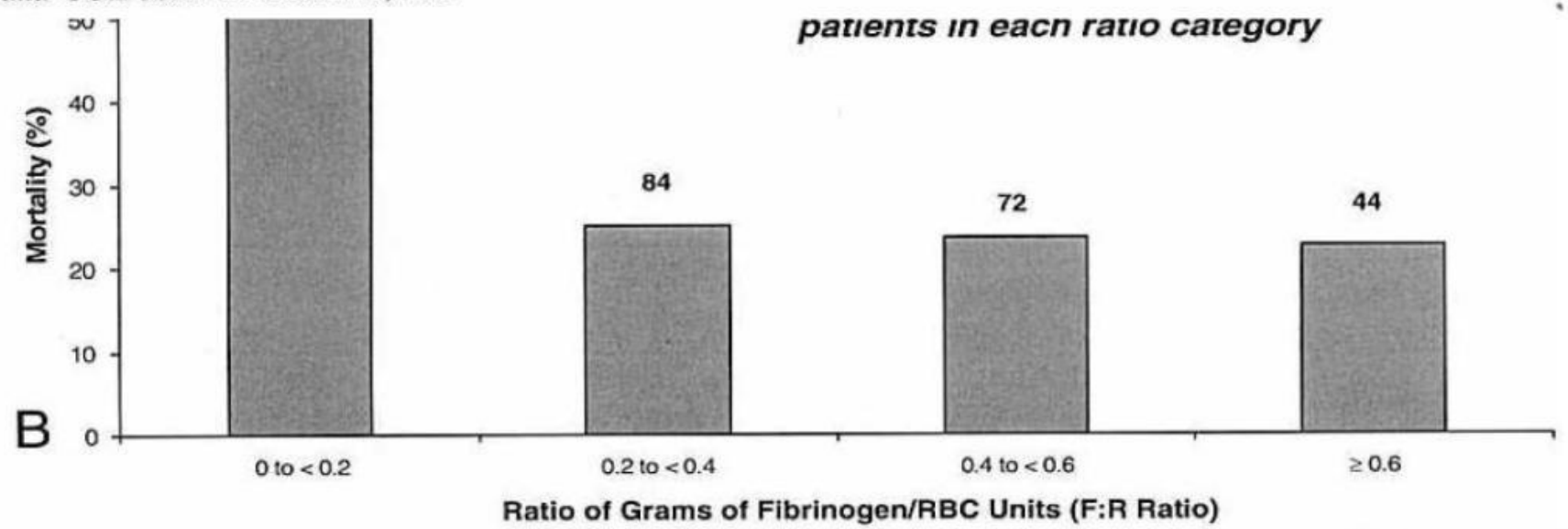
Some Factors More Important



It's the Fibrinogen!

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

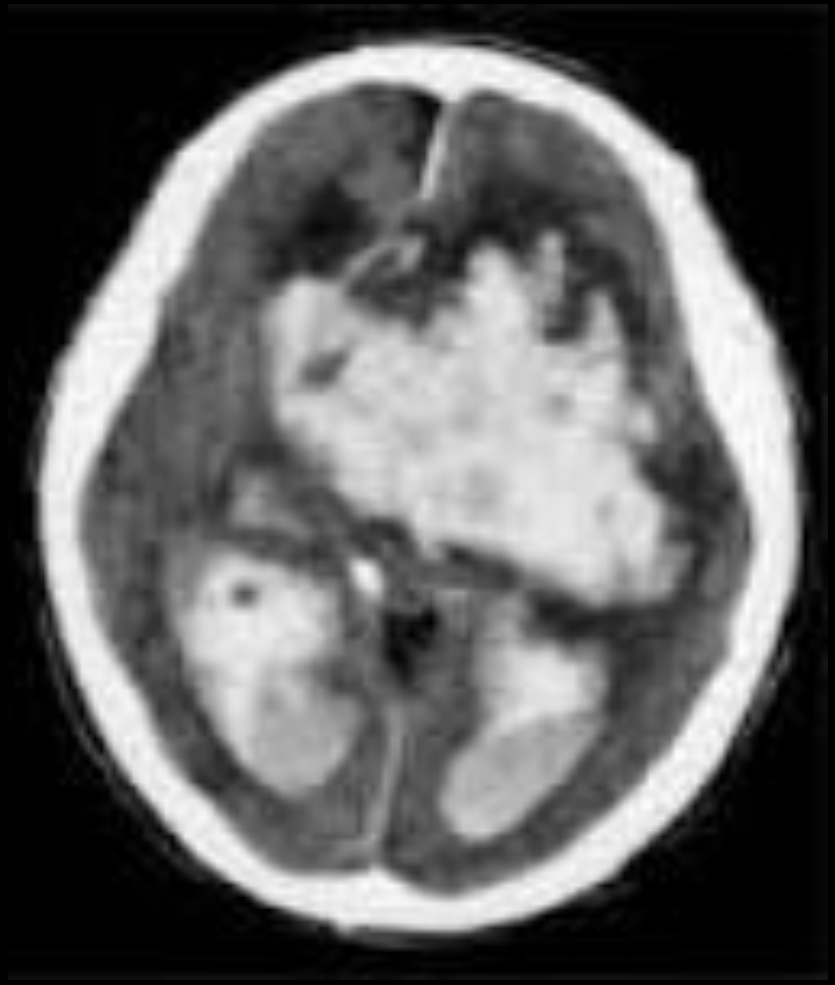
Harry K. Stinger, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Jose Salinas, PhD, Wenjun Z. Martini, PhD, John R. Hess, MD, Michael A. Dubick, PhD, Clayton D. Simon, MD, Alec C. Beekley, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC



*J Trauma 2007; **64**(Supp2)*

And Clotting Factor Deficiency

PCC reversal 15 minutes



FFP reversal 8 hours

Your Patient is Bleeding!

- Fibrinogen critically low and coagulopathic. What do you want to do?
- A. Give FFP – about 2-3 liters
- B. Give 10 units cryo (in an hour)

Your Patient is Bleeding!

- Fibrinogen critically low and coagulopathic. What do you want to do?
- A. Give FFP – about 2-3 liters
- B. Give 10 units cryo (in an hour)
- C. Give these now

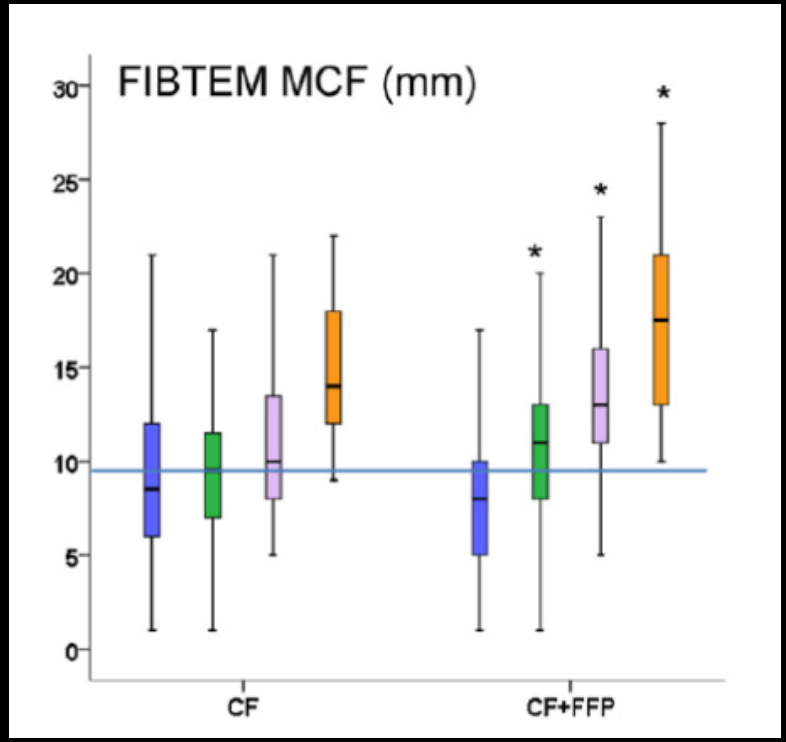
But can you only give FCs??

The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma

Petra Innerhofer [a], Isabella Westermann [a], Helmuth Tauber [a], Robert Breitkopf [a], Dietmar Fries [b], Tobias Kastenberger [c], Rene El Attal [c], Alexander Strasak [d], Markus Mittermayr [a,*]

[a] Clinic of Anaesthesiology and Intensive Care Medicine, Innsbruck Medical University, Innsbruck, Austria
[b] Clinic of General and Surgical Intensive Care Medicine, Innsbruck Medical University, Innsbruck, Austria
[c] Clinic of Trauma Surgery and Sports Medicine, Innsbruck Medical University, Innsbruck, Austria
[d] Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria

- Factor Conc vs FFP
- Same clot strength
- BUT……
  - Less RBCs (2 vs 9 units)
  - Lower sepsis and MOF

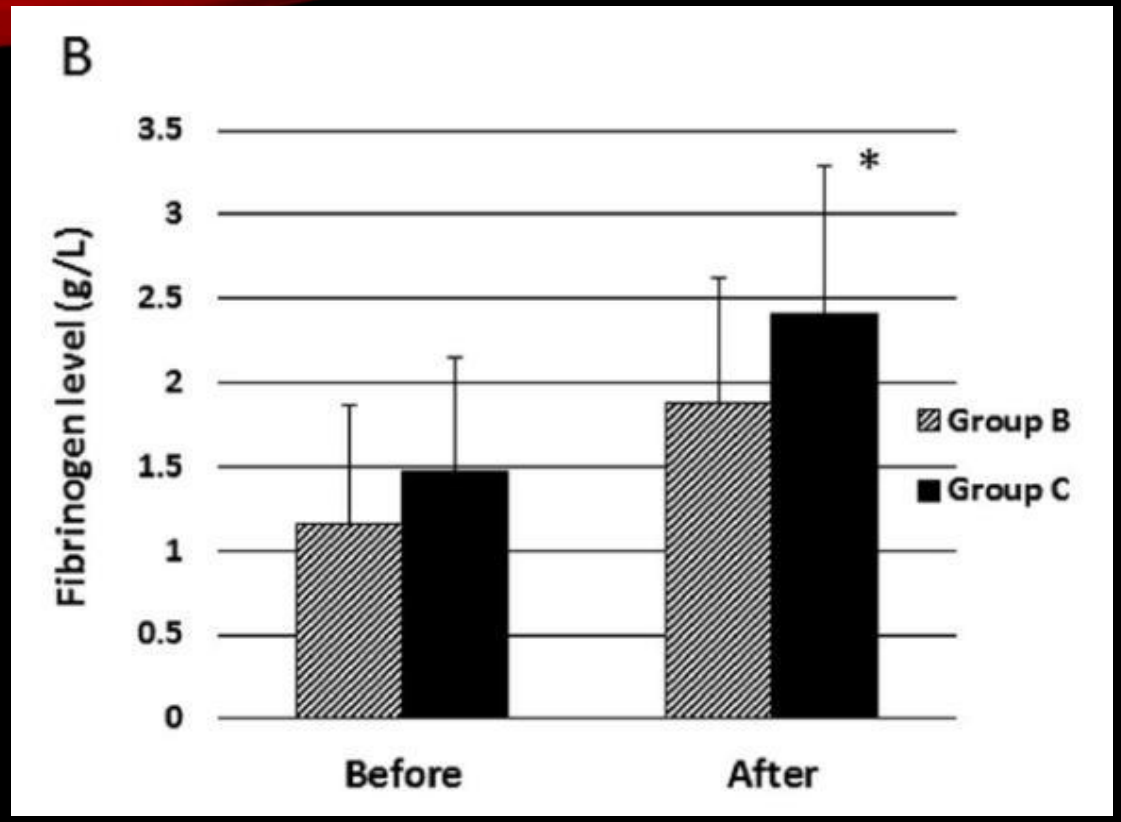


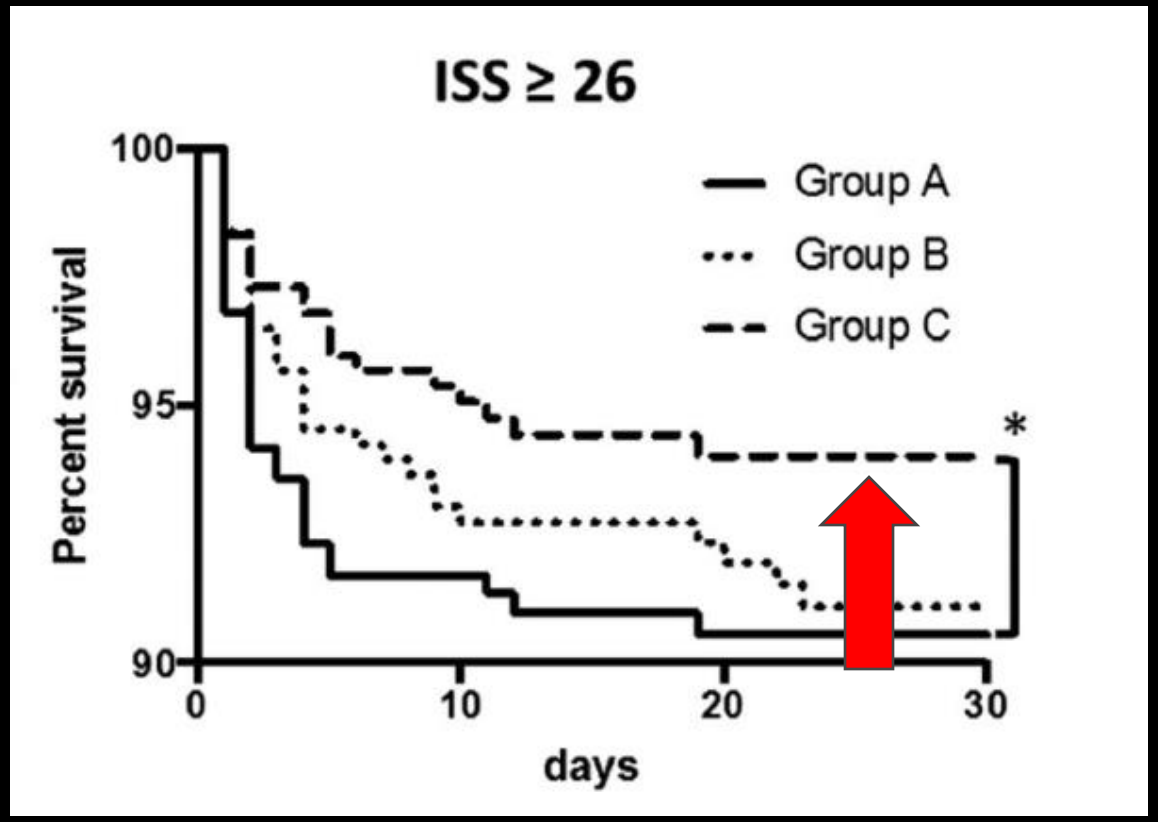
The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion

Ulrike Nienaber [a], Petra Innerhofer [b,*], Isabella Westermann [b], Herbert Schöchl [c], Rene Attal [d], Robert Breitkopf [b], Marc Maegele [a,e]

- 36 patients, all severely injured
- Factor concentrate only group
  - 3 units PRBC vs 13
  - Sepsis 17% versus 33%
  - MOF 17% versus 61%

Give empirically or guided?





Pre-emptive administration of fibrinogen concentrate contributes to improved prognosis in patients with severe trauma

Koji Yamamoto,[1] Atsushi Yamaguchi,[2] Makoto Sawano,[2] Masaki Matsuda,[2] Masahiro Anan,[1] Koichi Inokuchi,[2] Satoru Sugiyama[2]

CRYOSTAT-2
EARLY CRYOPRECIPITATE IN TRAUMA

What About Cryo??

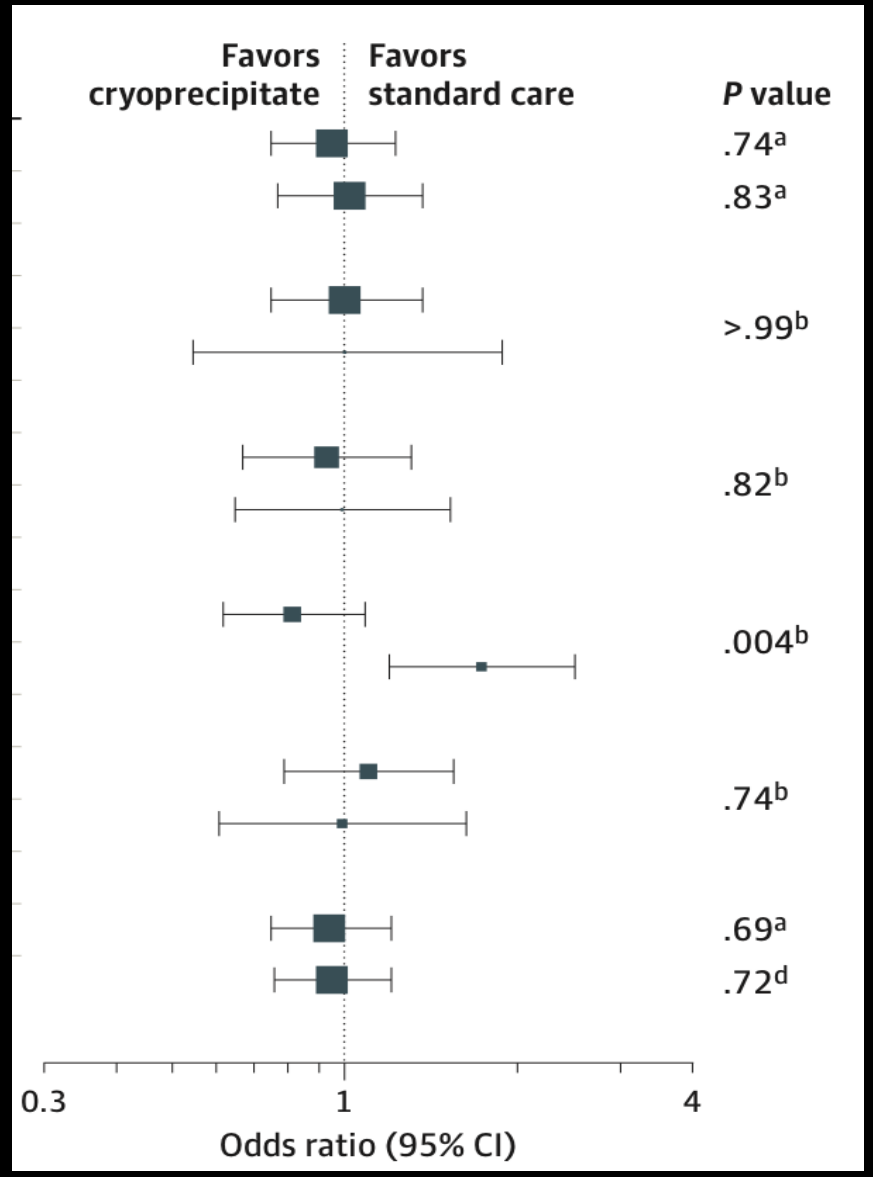
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury

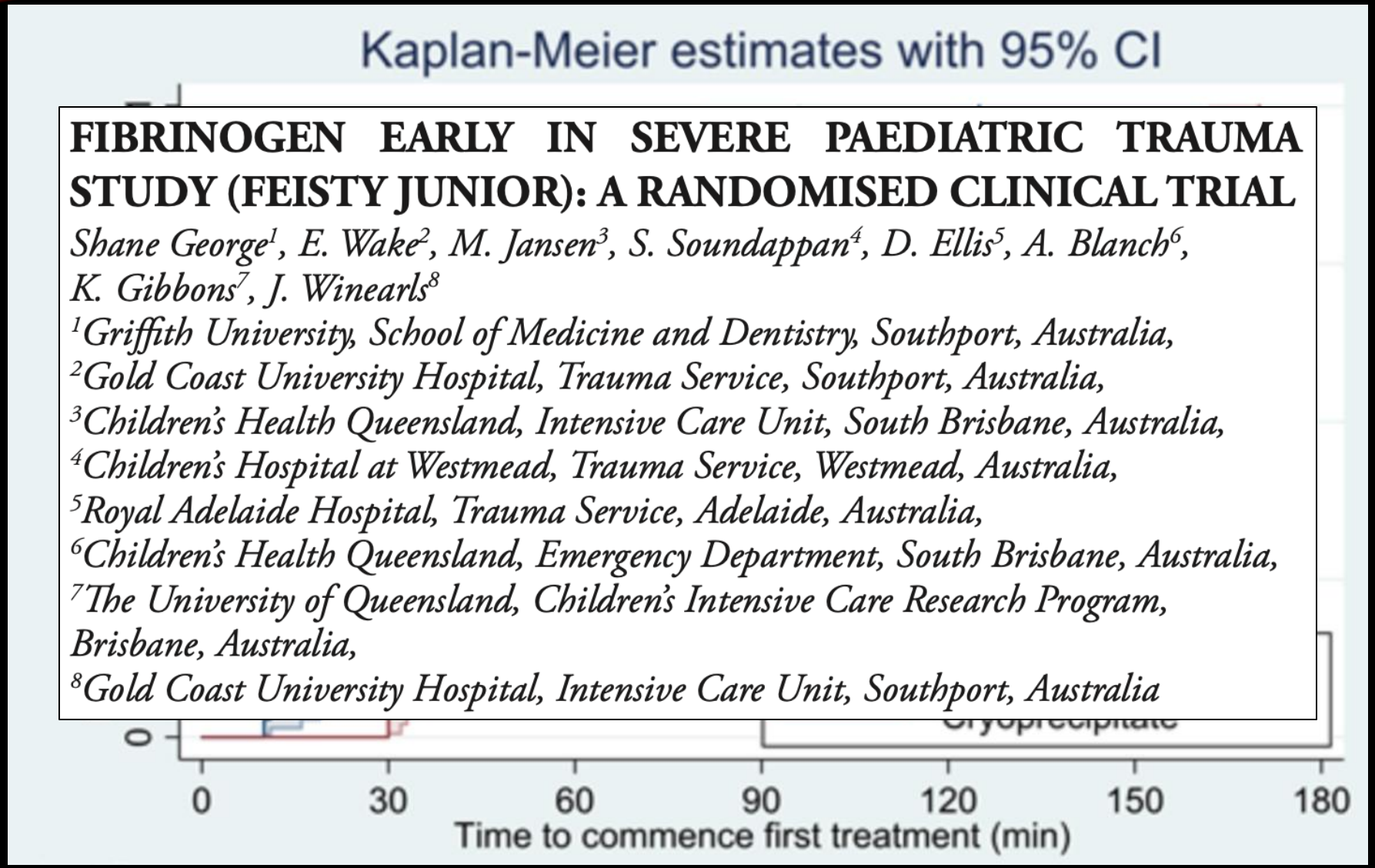
The CRYOSTAT-2 Randomized Clinical Trial

Ross Davenport, PhD; Nicola Curry, MD; Erin E. Fox, PhD; Helen Thomas, MSc; Joanne Lucas, MSc; Amy Evans, MMedSci; Shaminie Shanmugaranjan, BSc; Rupa Sharma, BSc; Alison Deary, MSc; Antoinette Edwards, MA; Laura Green, MD; Charles E. Wade, MD; Jonathan R. Benger, MD; Bryan A. Cotton, MD; Simon J. Stanworth, MD, DPhil; Karim Brohi, MD; for the CRYOSTAT-2 Principal Investigators

- Median time to cryo – 60 minutes
- 15% took > 90 mins
- Raised fibrinogen
- No impact on outcomes



FEISTY - Fibrinogen Early In Severe Trauma Study: Fibrinogen Concentrate Vs. Cryoprecipitate In Severe Traumatic Haemorrhage: A Pilot Randomised Controlled Trial



FIBRINOGEN EARLY IN SEVERE PAEDIATRIC TRAUMA STUDY (FEISTY JUNIOR): A RANDOMISED CLINICAL TRIAL

Shane George[1], E. Wake[2], M. Jansen[3], S. Soundappan[4], D. Ellis[5], A. Blanch[6], K. Gibbons[7], J. Winearls[8]

[1]Griffith University, School of Medicine and Dentistry, Southport, Australia,
[2]Gold Coast University Hospital, Trauma Service, Southport, Australia,
[3]Children's Health Queensland, Intensive Care Unit, South Brisbane, Australia,
[4]Children's Hospital at Westmead, Trauma Service, Westmead, Australia,
[5]Royal Adelaide Hospital, Trauma Service, Adelaide, Australia,
[6]Children's Health Queensland, Emergency Department, South Brisbane, Australia,
[7]The University of Queensland, Children's Intensive Care Research Program, Brisbane, Australia,
[8]Gold Coast University Hospital, Intensive Care Unit, Southport, Australia

Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial

Nicola Curry[1,2*], Claire Foley[3], Henna Wong[1,2,4], Ana Mora[3], Elinor Curnow[3], Agne Zarankaite[3], Renate Hodge[3], Valerie Hopkins[3], Alison Deary[3], James Ray[5], Phil Moss[6], Matthew J. Reed[7], Suzanne Kellett[8], Ross Davenport[9] and Simon Stanworth[1,2,4,10]

Curry *et al. Critical Care* (2018) 22:164

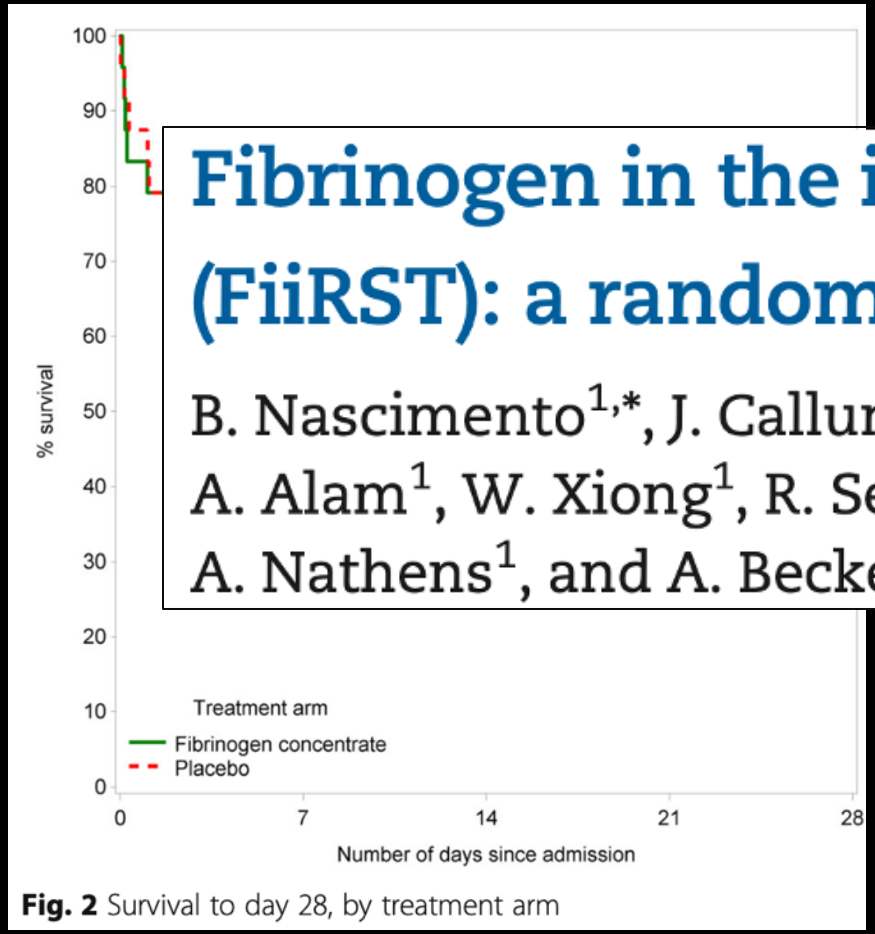


Fig. 2 Survival to day 28, by treatment arm

- **No outcome benefit**

Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial

B. Nascimento[1,*], J. Callum[1], H. Tien[1], H. Peng[2], S. Rizoli[3], P. Karanicolas[1], A. Alam[1], W. Xiong[1], R. Selby[1], A-M. Garzon[1]. C. Colavecchia[1]. R. Howald[1], A. Nathens[1], and A. Beckett[4]

British Journal of Anaesthesia, 117 (6): 775–82 (2016)

in

45 minutes

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

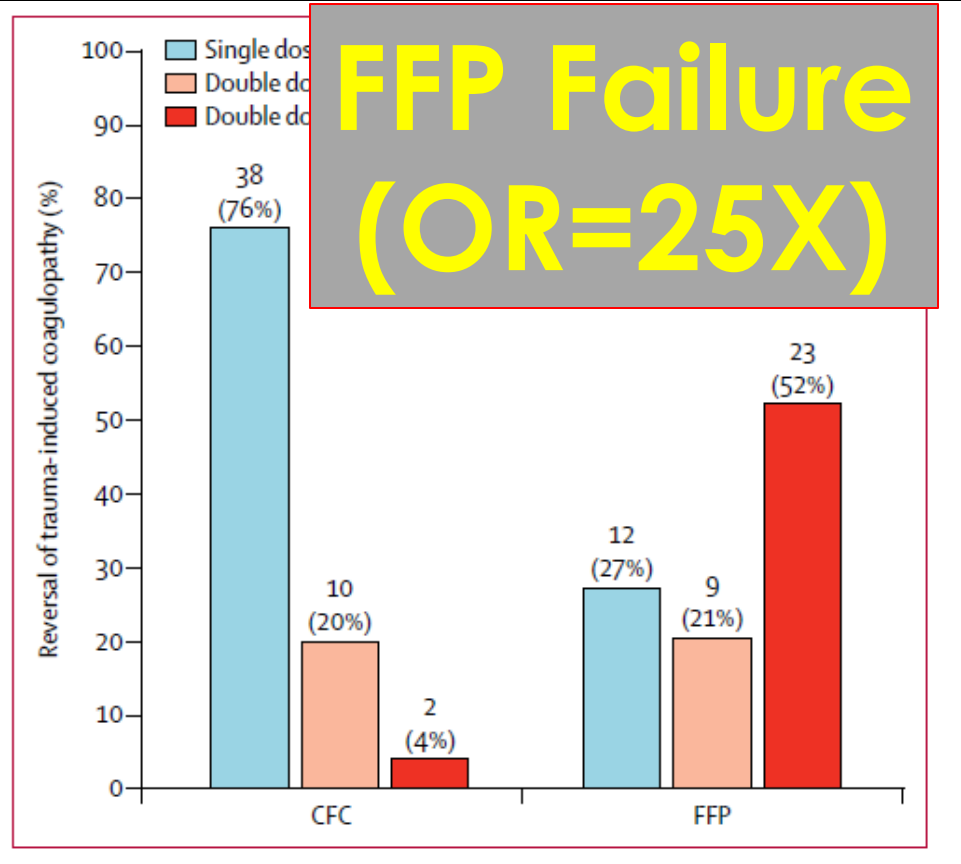
Petra Innerhofer, Dietmar Fries, Markus Mittermayr, Nicole Innerhofer, Daniel von Langen, Tobias Hell, Gottfried Gruber, Stefan Schmid, Barbara Friesenecker, Ingo H Lorenz, Mathias Ströhle, Verena Rastner, Susanne Trübsbach, Helmut Raab, Benedikt Treml, Dieter Wally, Benjamin Treichl, Agnes Mayr, Christof Kranewitter, Elgar Oswald

- **ISS > 15 and coagulopathy on ROTEM**
- **Randomized 100 pts to DCR vs CFCs**

	CFC (n=50)	FFP (n=44)
Age (years)	42·5 (27·3 to 50·5)	42·5 (24 to 56)
Sex		
Female	12 (24%)	12 (27%)
Male	38 (76%)	32 (73%)
BMI (kg/m²)	24·69 (23·44 to 26·31)	24·01 (22·84 to 25·73)
Time to emergency department (min)	61·5 (40·0 to 89·8)	56·5 (43·8 to 85·0)
ISS	35 (29 to 42)	30 (24 to 45)

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

Petra Innerhofer, Dietmar Fries, Markus Mittermayr, Nicole Innerhofer, Daniel von Langen, Tobias Hell, Gottfried Gruber, Stefan Schmid, Barbara Friesenecker, Ingo H Lorenz, Mathias Ströhle, Verena Rastner, Susanne Trübsbach, Helmut Raab, Benedikt Treml, Dieter Wally, Benjamin Treichl, Agnes Mayr, Christof Kranewitter, Elgar Oswald



FFP Failure (OR=25X)

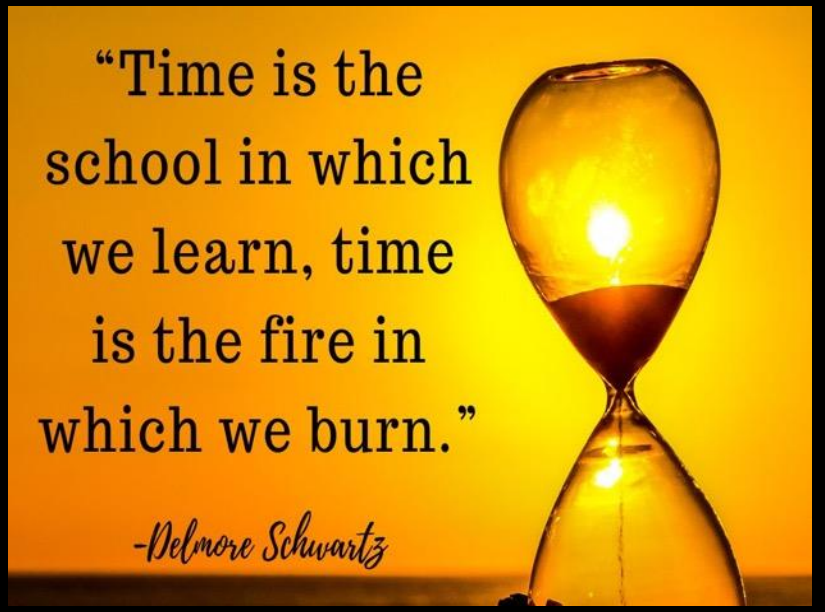
- Massive transfusion
- CFC = 12%
- FFP = 30%

Why is Plasma so bad at raising fibrinogen levels?

- Low fibrinogen content
- NOT standardized – can be variable
  - as opposed to factor concentrates!

also

- Dilutes existing/added fibrinogen



British Journal of Anaesthesia 113 (4): 585–95 (2014)
Advance Access publication 26 July 2014 · doi:10.1093/bja/aeu086

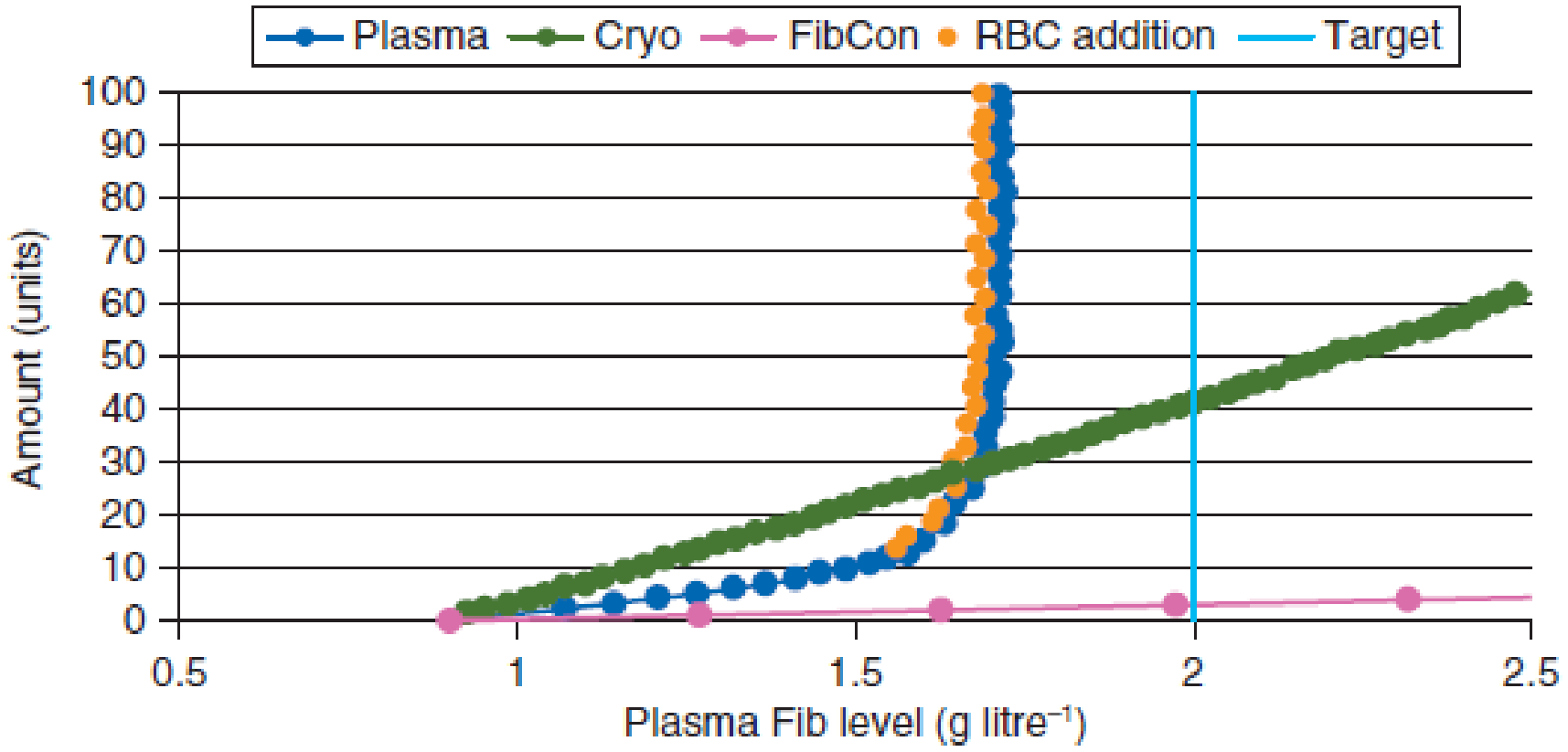
BJA

CARDIOVASCULAR

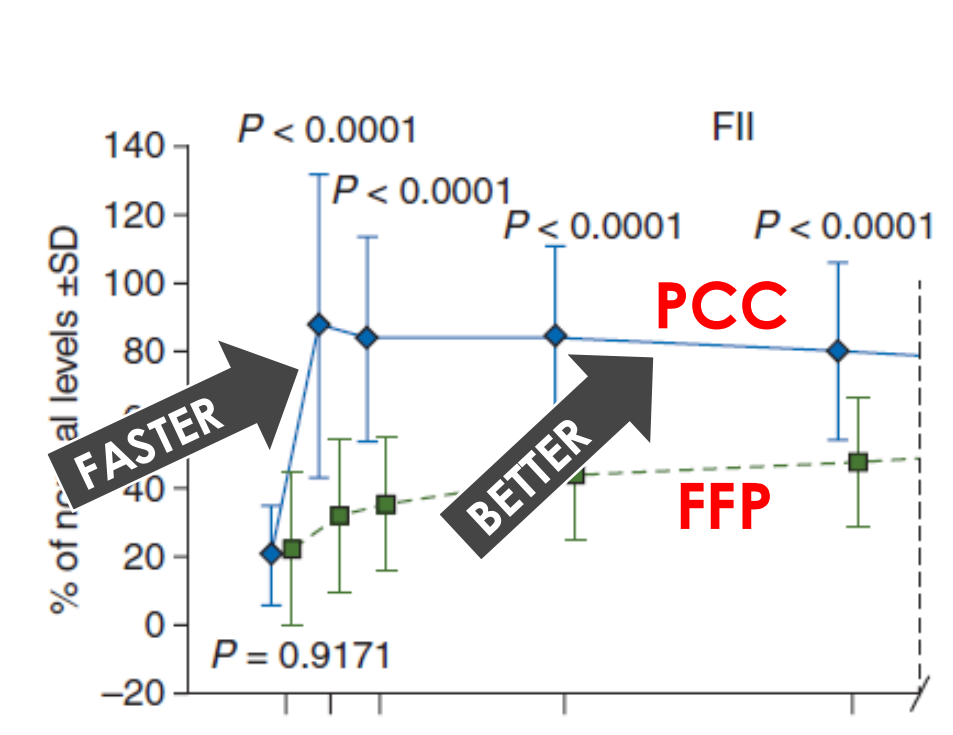
Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate

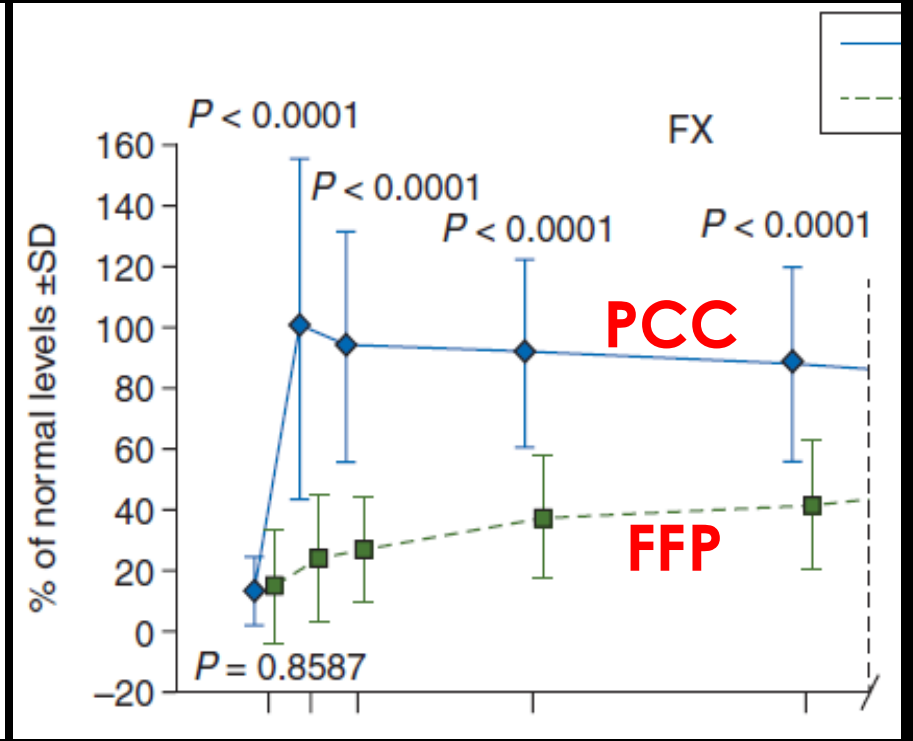
P. W. Collins[1*], C. Solomon[2,3], K. Sutor[4], D. Crispin[4], G. Hochleitner[5], S. Rizoli[6], H. Schöchl[7,8], M. Schreiber[9] and M. Ranucci[10]

Fib level graph



What About PCC vs FFP?





British Journal of Anaesthesia **111** (S1): i35–i49 (2013)
doi:10.1093/bja/aet380

BJA

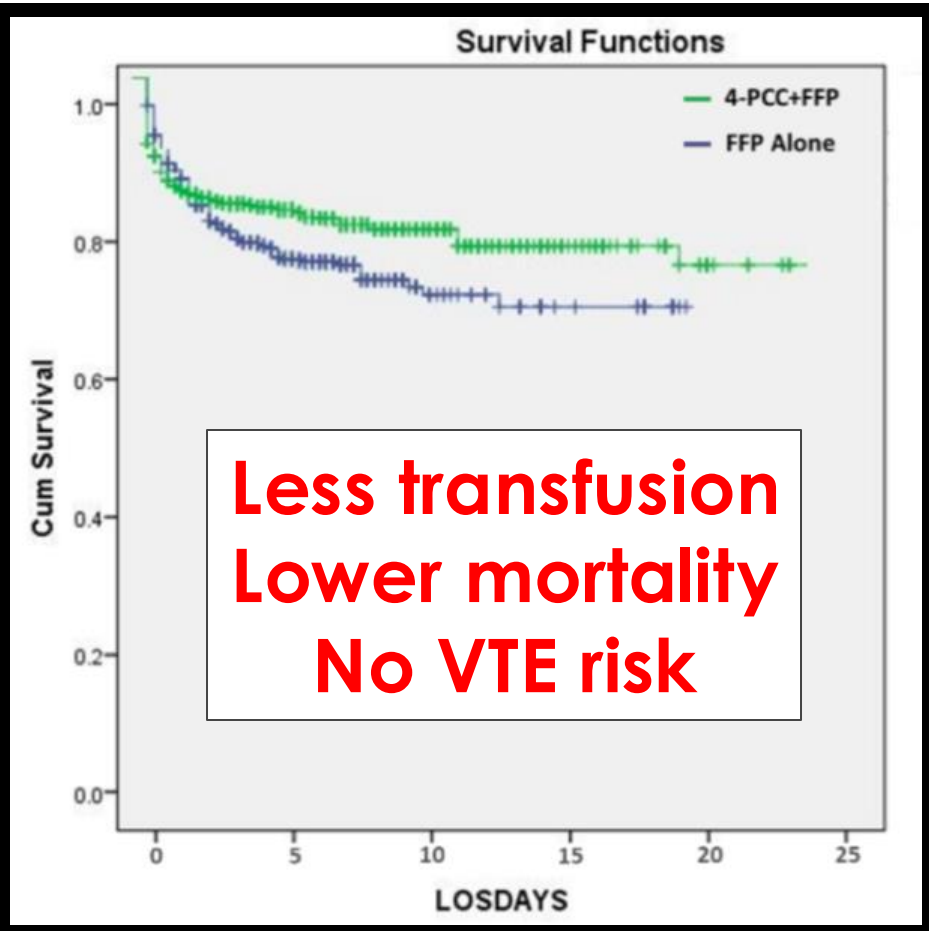
Perioperative factor concentrate therapy

K. A. Tanaka[1]*, S. Esper[1] and D. Bolliger[2]

4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE IMPROVES SURVIVAL IN TRAUMA: A NATIONWIDE PROPENSITY MATCHED ANALYSIS

Muhammad Zeeshan MD, Mohammad Hamidi MD, Lynn Gries Muhammad Khan MD, Ara J. Feinstein* MD, Joseph Sakran* MD,MPH, Terence O'Keeffe* MD, Narong Kulvatunyou* MD, Bellal Joseph* MD, University of Arizona - Tucson

Invited Discussant: Matthew Martin, MD



Prothrombin Complex Concentrates (PCC)

JAMA | Original Investigation |

Efficacy and Safety (…hrombin Complex Concentra… of Massive Transfus… The PROCOAG Rand…

Pierre Bouzat, MD, PhD; Jonathan Charb… D; Marc Leone, MD, PhD; Guillaume Marcotte, MD; Jean-Stéphane… r, MD, PhD; Jacques Duranteau, MD, PhD; Elie Courv… Riou, MD, PhD; Tobias Gauss, MD; Jean-François Payen, …

- …n
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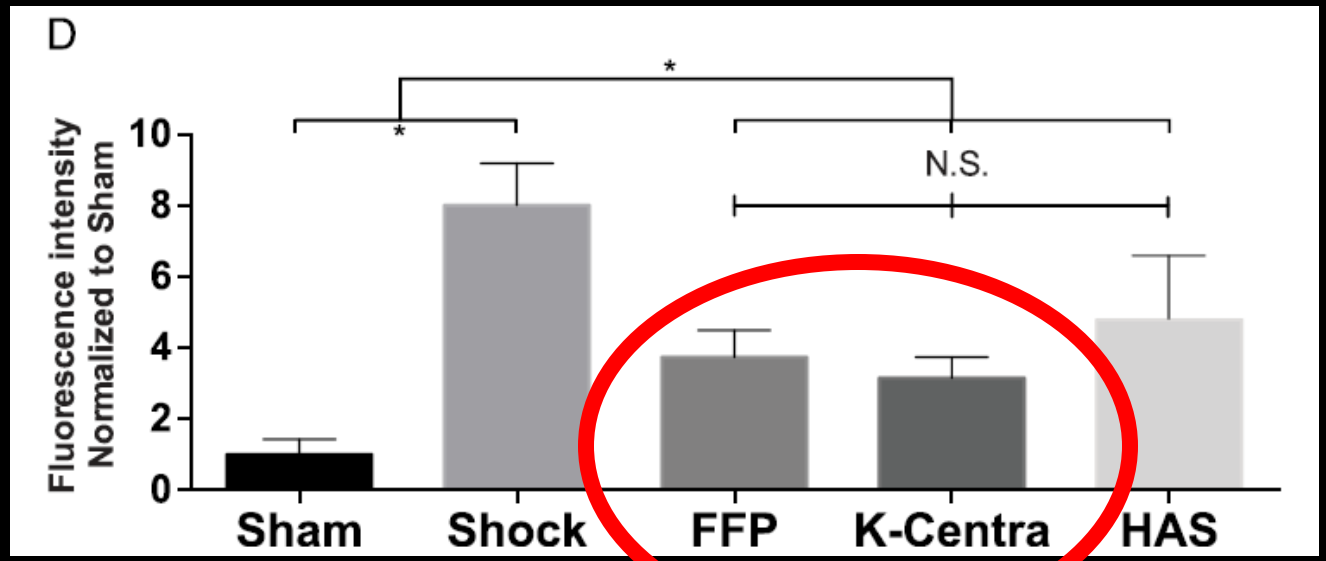
TAP Trial Termination

CSL Behring has made the difficult decision to end the Trauma and Prothrombin Complex Concentrate (TAP) Trial of Kcentra® (BE1116_3006), for trauma patients with major bleeding. The trial began in early 2023 and was originally scheduled to last until 2026.

But….the endothelium??

Modulating the endotheliopathy of trauma: Factor concentrate versus fresh frozen plasma

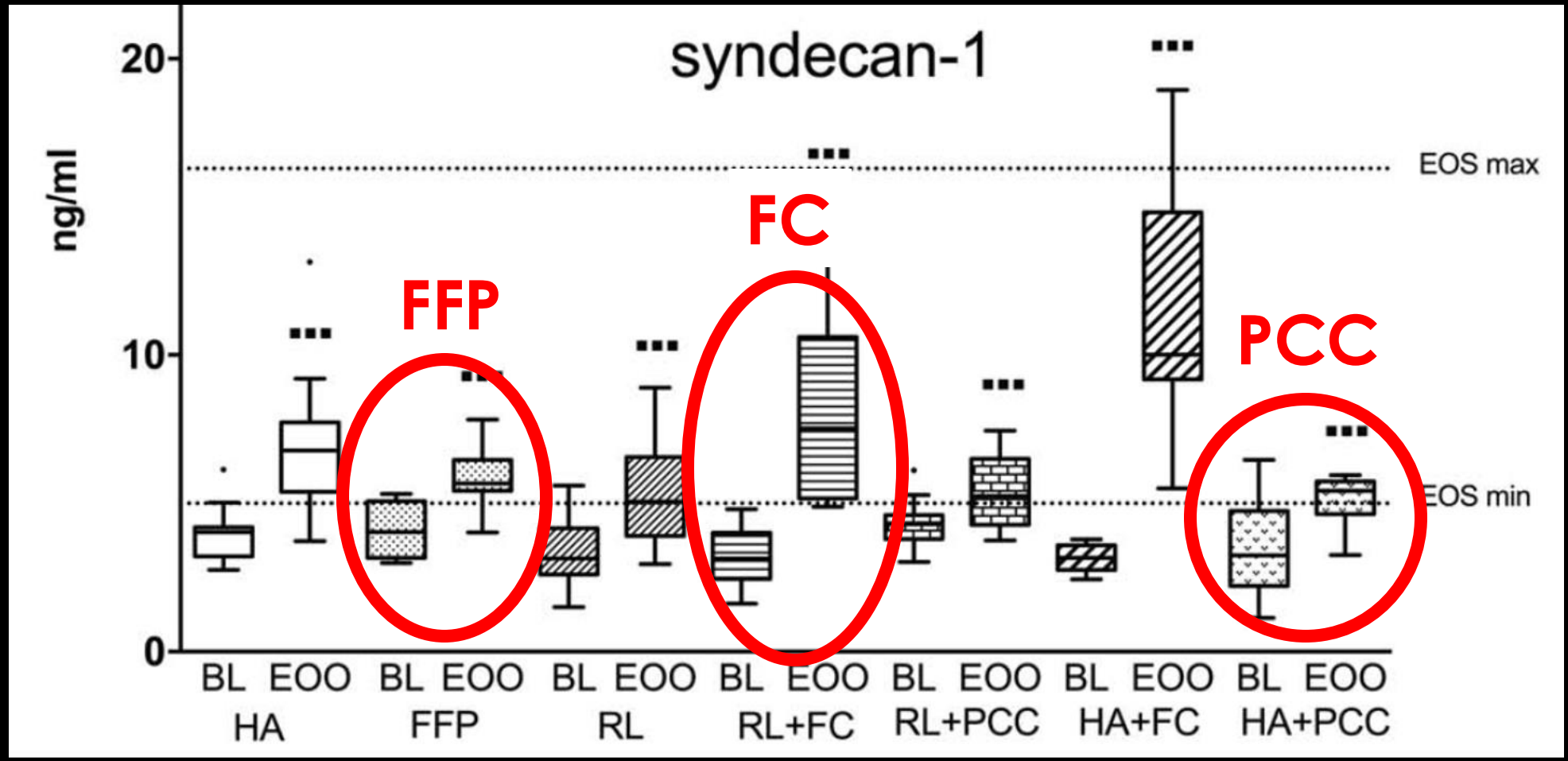
Shibani Pati, MD, PhD, Daniel R. Potter, PhD, Gyulnar Baimukanova, MD, PhD, David H. Farrel, MD, John B. Holcomb, MD, *and* Martin A. Schreiber, MD, *San Francisco, California*



What about fibrinogen concentrate??

EFFECT OF COAGULATION FACTOR CONCENTRATES ON MARKERS OF ENDOTHELIAL CELL DAMAGE IN EXPERIMENTAL HEMORRHAGIC SHOCK

Nikolaus Hofmann,*† Johannes Zipperle,* Florian Brettner,‡ Mohammad Jafarmadar,* Mostafa Ashmwe,* Claudia Keibl,* Martin Ponschab,* Ulrike Kipman,§ Arian Bahrami,*|| Heinz Redl,* Soheyl Bahrami,* Valentin Fuhrmann,¶ and Herbert Schöchl***



SHOCK, Vol. 52, No. 5, pp. 497–505, 2019

Other Adjuncts: Vasopressors??

Fill the Tank!!!

Traumatic Shock: The Reality

- Often polytrauma and multifactorial
- Assume hemorrhage, but may or may not be
- Acidosis, electrolytes (Ca++, K+)
- Vasoplegia, cardiomyopathy
- Endocrine/paracrine deficiencies

JAMA Surgery | Original Investigation

Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock

A Randomized Clinical Trial

JAMA Surg. Published online August 28, 2019. doi:https://doi-org.offcampus.lib.washington.edu/10.1001/jamasurg.2019.2884

Carrie A. Sims, MD, PhD; Daniel Holena, MD; Patrick Kim, MD; Jose Pascual, MD, PhD; Brian Smith, MD; Neils Martin, MD; Mark Seamon, MD; Adam Shiroff, MD; Shariq Raza, MD; Lewis Kaplan, MD; Elena Grill, BS; Nicole Zimmerman, MS; Christopher Mason, MD; Benjamin Abella, MD, MPhil; Patrick Reilly, MD

- 100 patients, randomized to AVP vs placebo
  - at least 6 U blood
- Vasopressin bolus + infusion (4U + 0.04 U/min)
  - continued for 48 hours
- Balanced resuscitation until hemorrhage control

Main Outcomes/Findings

- Vasopressin administration
  - decreased blood products (1.7L vs 3.0L)
  - increased urine output
  - improved fluid balance

- No difference in complication rates, LOS, or mortality
- No adverse events in VP group

Key Points

- No benefit of empiric FCs as an “add-on”
- FCs can clearly be utilized to reduce blood products
- FCs can replace blood products in select scenarios
- Large variability in protocols, goals, and metrics
- Fibrinogen concentrate optimal for rapid replacement

- “Equivalent” clinical outcomes and “No benefit…”
- Settings: rural, austere, military, MASCAL, disaster


What do we Want?
EVIDENCE BASED SCIENCE
When do we Want It?
AFTER PEER REVIEW

THANK YOU!