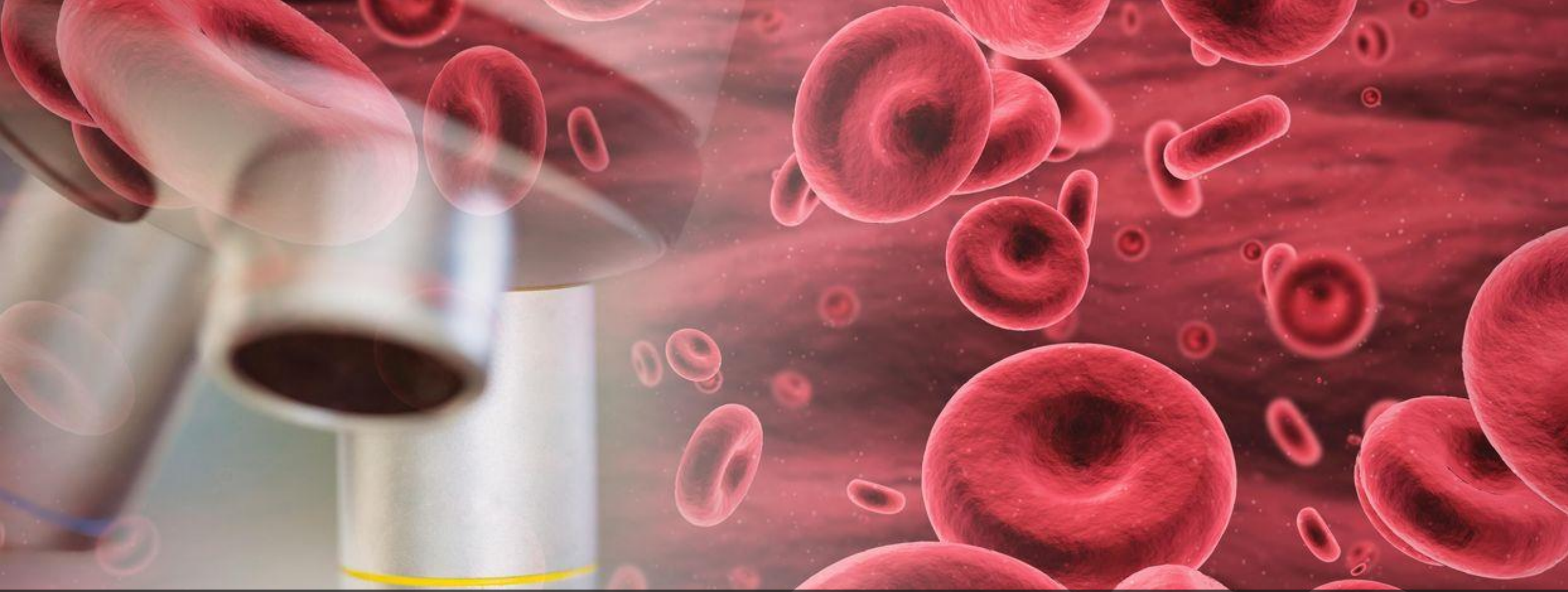
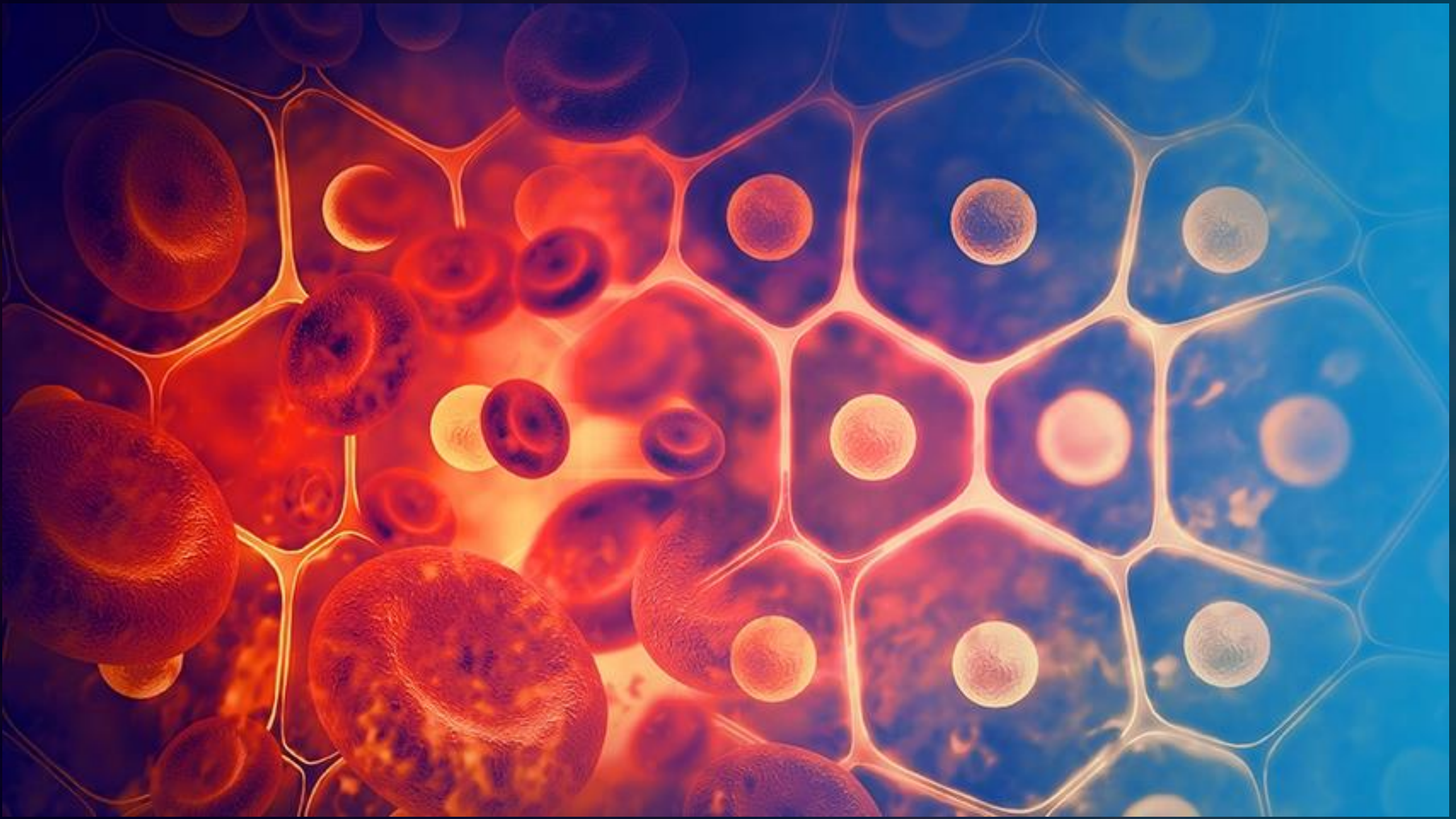


# Prothrombin Complex Concentrate (PCC) in Trauma

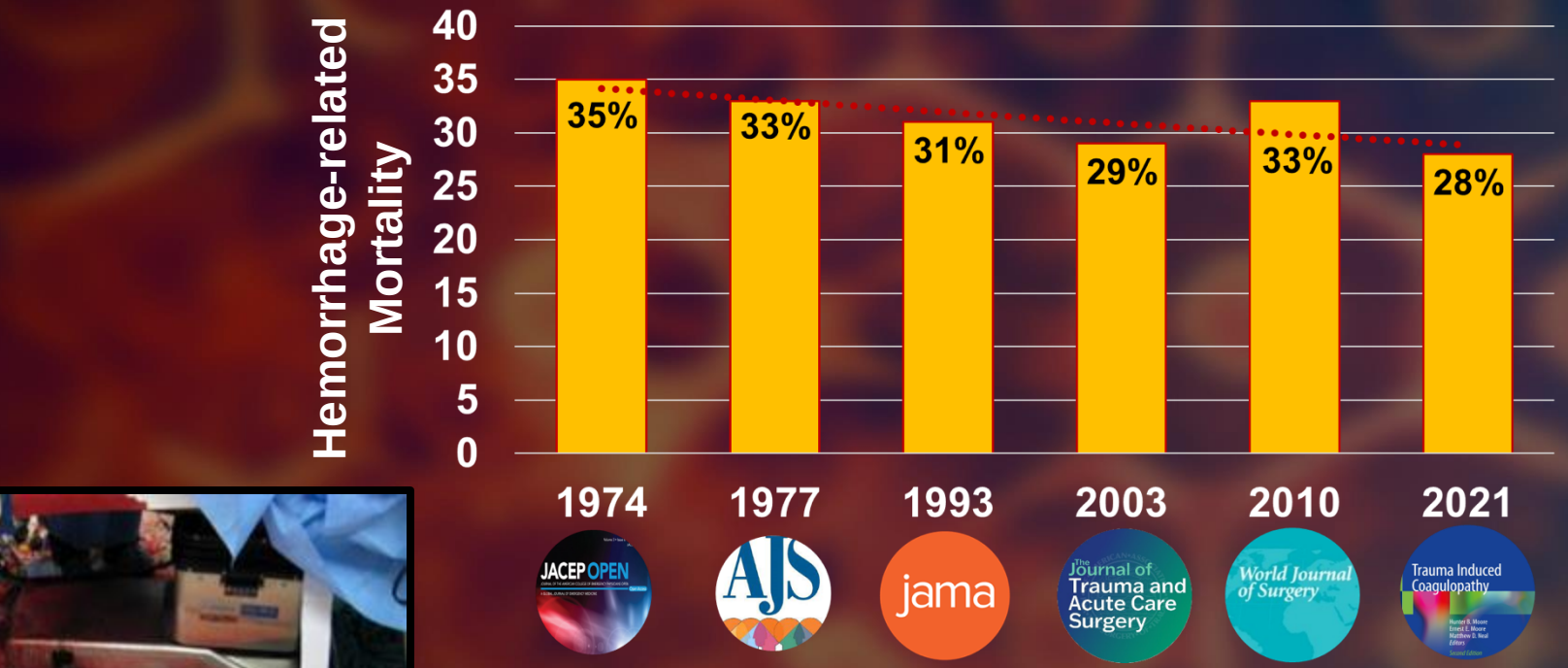

**Bellal Joseph, MD, FACS**

**Professor & Chief of Trauma and Acute Care Surgery**

**The University of Arizona, Tucson, AZ**

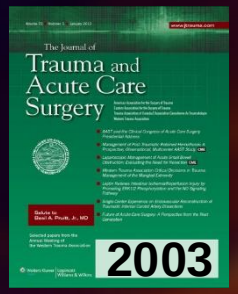


# Trauma patients continue to exsanguinate



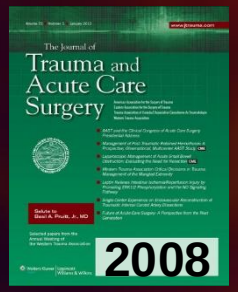

**WHY?**

# Coagulopathy of Trauma




## Early Coagulopathy Predicts Mortality in Trauma

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




## The Coagulopathy of Trauma: A Review of Mechanisms

Hess, John R. MD, MPH, FACP, FAAAS; Brohi, Karim MD; Dutton, Richard P. MD, MBA; Hauser, Carl J. MD, FACS, FCCM; Holcomb, John B. MD, FACS; Kluger, Yoram MD; Mackway-Jones, Kevin MD, FRCP, FRCS, FCEM; Parr, Michael J. MB, BS, FRCP, FRCA, FANZCA, FJFICM; Rizoli, Sandro B. MD, PhD, FRCSC; Yukioka, Tetsuo MD; Hoyt, David B. MD, FACS; Bouillon, Bertil MD

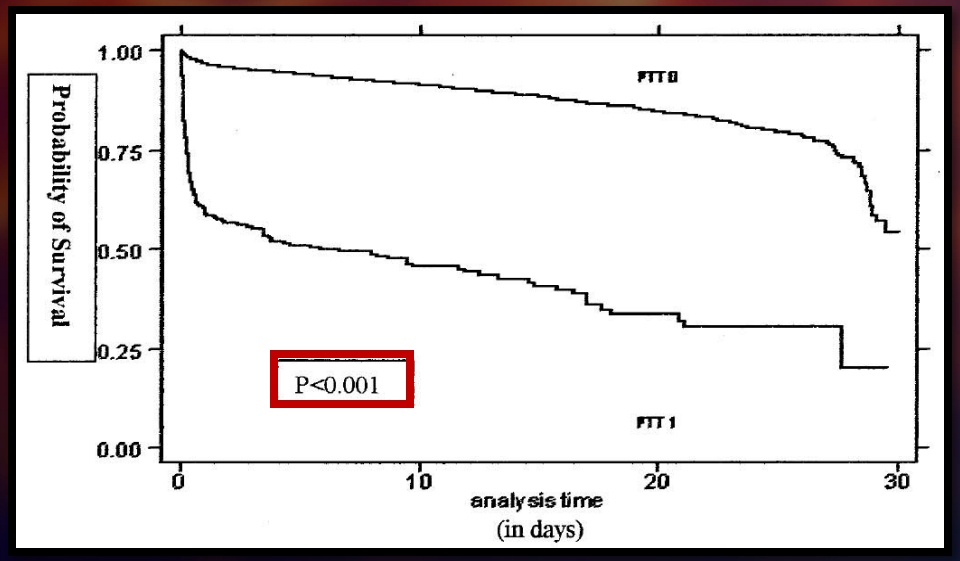
2021

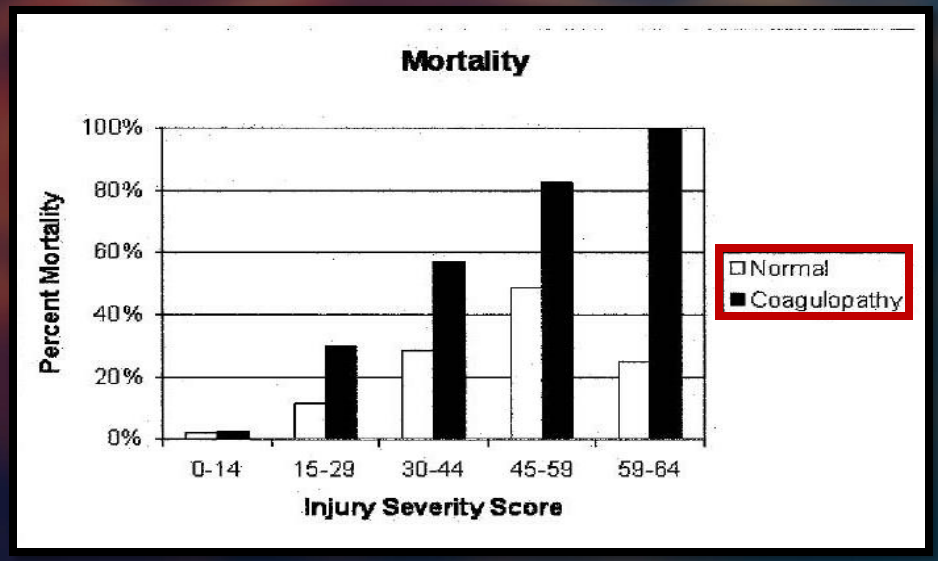
## Trauma-induced coagulopathy

Ernest E. Moore, Hunter B. Moore, Lucy Z. Kornblith, Matthew D. Neal, Maureane Hoffman, Nicola J. Mutch, Herbert Schöchl, Beverley J. Hunt & Angela Sauaia

# Coagulopathy of Trauma

- ¼ of all trauma patients
- Raises mortality **×5**
- Major cause of **preventable** trauma death in **first 24 hrs**



# Coagulopathy of Trauma


Moore, Ernest E., et al. "Trauma-induced coagulopathy." Nature Reviews Disease Primers 7.1 (2021): 1-23.

# Principles of Damage-Control Resuscitation

## Hemorrhagic Shock

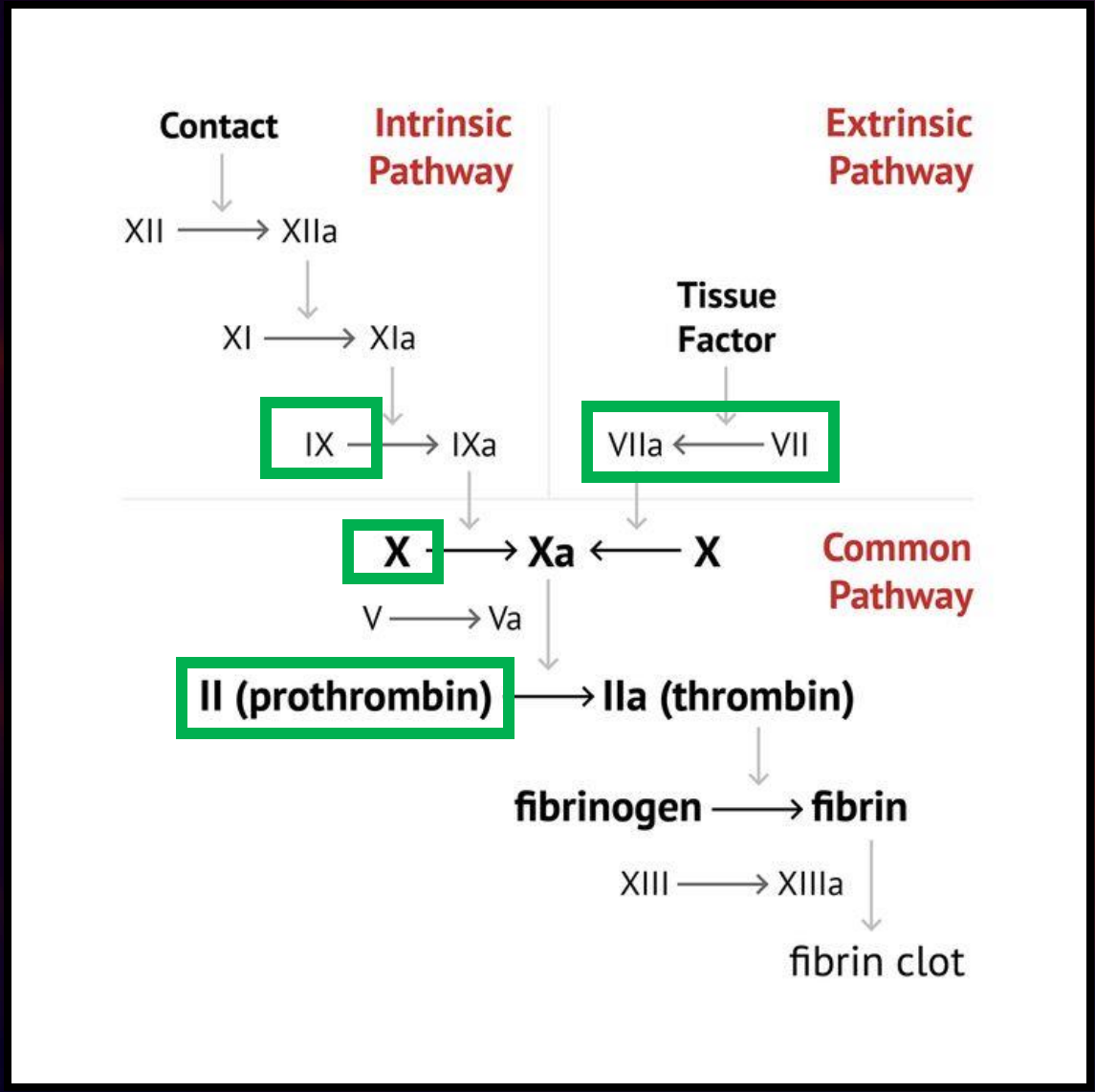
Jeremy W. Cannon, M.D.


**Table 3. Principles of Damage-Control Resuscitation.**

| |
|---|
| Avoid or correct hypothermia |
| Apply direct pressure or a tourniquet proximal to sites of hemorrhage in the extremities; pack junctional wounds with hemostatic dressings |
| Delay fluid administration until the time of definitive hemostasis in selected patients (those with penetrating trauma to the torso and short prehospital transport times) |
| Minimize crystalloid infusions (<3 liters in the first 6 hr) |
| Use a massive-transfusion protocol to ensure that sufficient blood products are rapidly available |
| Avoid delays in definitive surgical, endoscopic, or angiographic hemostasis |
| Minimize imbalances in plasma, platelet, and red-cell transfusions in order to optimize hemostasis |
| Obtain functional laboratory measures of coagulation (e.g., by means of thromboelastography or rotational thromboelastometry) to guide the transition from empirical transfusions to targeted therapy |
| Selectively administer pharmacologic adjuncts to reverse any anticoagulant medications and to address persistent coagulopathy |

- Permissive hypotension
- Limited crystalloids
- Early hemorrhage control
- Hemostatic resuscitation
- **Pharmacologic adjuncts (PCC)**

# Factor Replacement




PCC

| Trade name | Factor II | Factor VII | Factor IX | Factor X |
|---|---|---|---|---|
| 3-factor products | | | | |
| Bebulin[a] | 100 | <5 | 100 | 100 |
| Preconativ | 83.3 | – | 100 | 83.3 |
| Proplex-T | 50 | 400 | 100 | 50 |
| Prothrombinex-HT | 100 | Low | 100 | 100 |
| Profilnine SD[a] | 150 | 35 | 100 | 100 |
| 4-factor products | | | | |
| Beriplex (Kcentra[a]) | 106.9 | 55.1 | 100 | 141.4 |
| Cofact | 56–140 | 28–80 | 100 | 56–140 |
| Kaskadil | 148 | 40 | 100 | 160 |
| Octaplex | 50–129 | 50–129 | 100 | 50–129 |

[a] Indicates FDA approval in US

[b] indicates IU per 1 unit factor IX

# Evolution of the use of PCC

JAMA
The Journal of the American Medical Association

1969

## Prothrombin Concentrates in Treatment of Christmas Disease and Allied Disorders

*Francis A. Breen, Jr., MD, and James L. Tullis, MD*


1969

ORIGINAL ARTICLE ARCHIVE

## Treatment of Hemophilia B with a New Clotting-Factor Concentrate

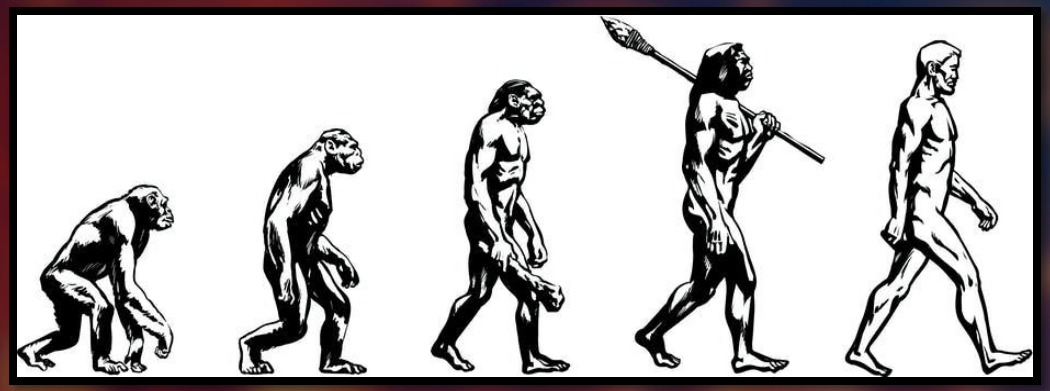
M. SilvijA Hoag, M.D., Frederick F. Johnson, Ph.D., Jean A. Robinson, Ph.D., and Paul M. Aggeler, M.D.

ORIGINAL ARTICLE ARCHIVE

## Evaluation of a New Concentrate for the Treatment of Factor IX Deficiency

Gerald S. Gilchrist, M.B., B.Ch., D.C.H., Henry Ekert, M.B., M.R.A.C.P., Edward Shanbrom, M.D., and Denman Hammond, M.D.

# Evolution of the use of PCC



2008

Present

Hemophilia

Reversal of Vitamin K Antagonists

Trauma-induced Coagulopathy

Holbrook, Anne, et al. "Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines." Chest 141.2 (2012): e152S-e184S.

# PCC Indications

- **Approved indications for PCC in the US**
  - Reversal of major bleeding caused by **vitamin K antagonists (warfarin)**

- **Off-label use**
  - Life-threatening bleeding associated with non-vitamin K antagonist anticoagulants (Direct oral anticoagulants)
  - **Trauma-induced coagulopathy**

# PCC vs FFP

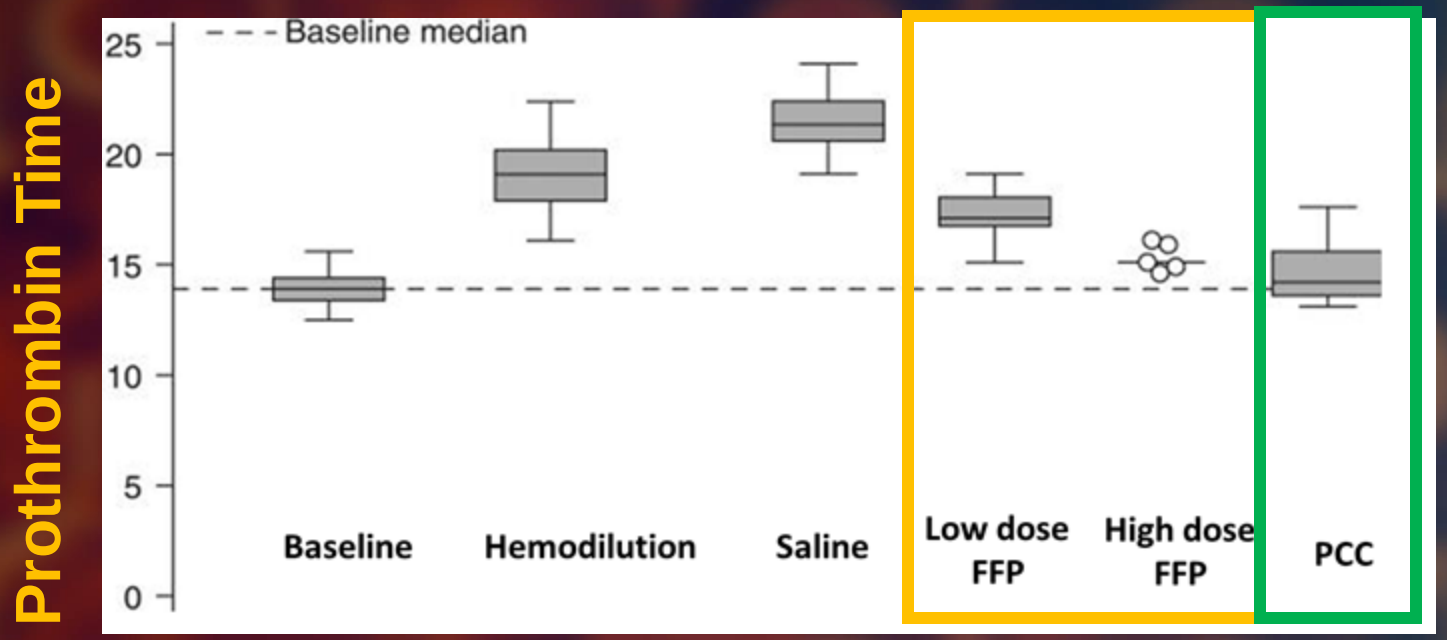
# PCC vs. FFP vs. Saline

## Prothrombin Complex Concentrate Vs. Fresh Frozen Plasma For Reversal of Dilutional Coagulopathy In A Porcine Trauma Model

G. Dickneite and I. Pragst


- **47** male Pigs
- TIC by **hemodilution** and **trauma**
- Animals were randomized into
  - **PCC** (25 IU/kg)
  - **Low /High dose FFP** (15/40 ml/kg)
  - **Saline** (15 ml/kg)
- **Outcomes:** - Coagulation profile
  - Time to hemostasis

# PCC vs. FFP vs. Saline

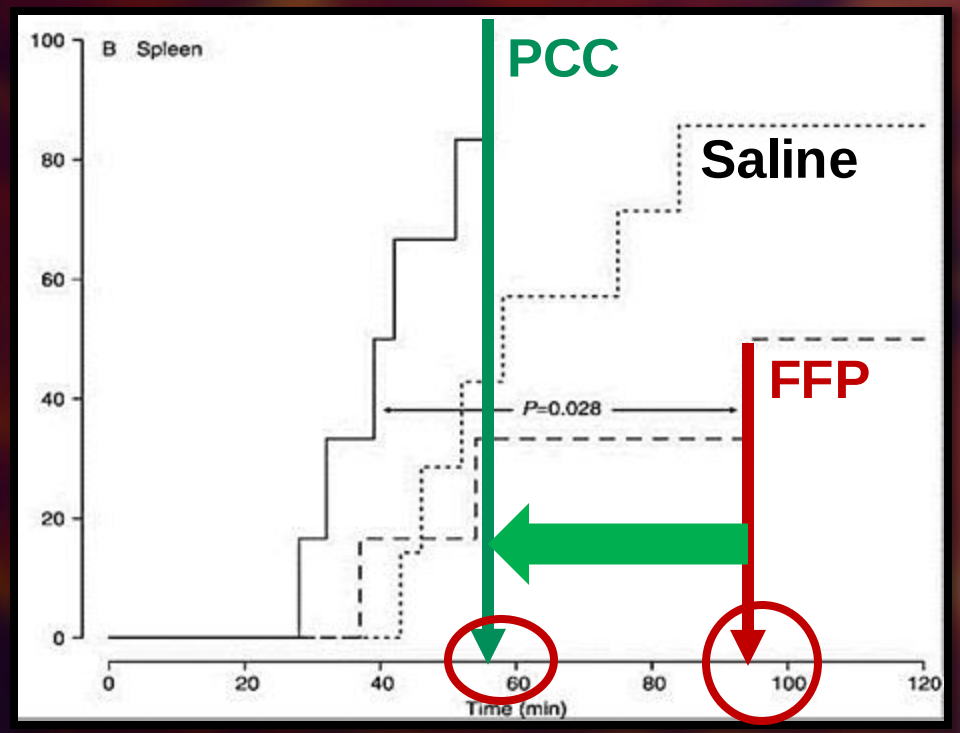



FFP → PT did not normalize

PCC → PT returned to baseline

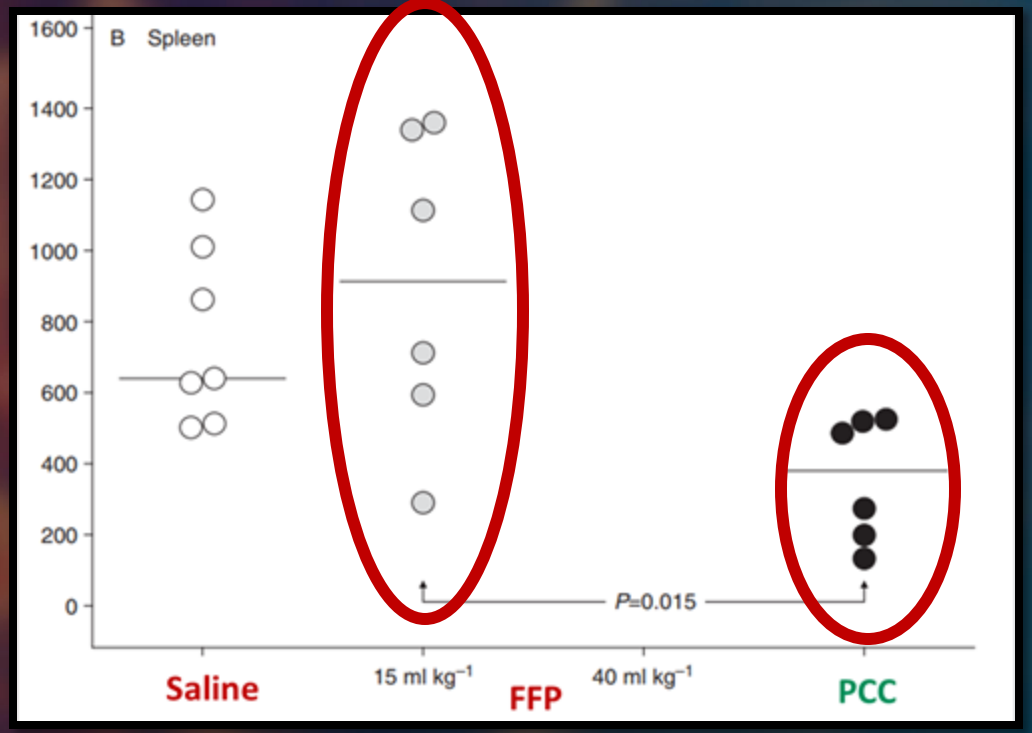
# PCC vs. FFP vs. Saline

## Time to hemostasis




Time to Hemostasis

## Blood loss (mL)




Blood Loss

# Benefits of PCC

- PCC can be used **more rapidly** than FFP
  - **No thawing**
  - **No blood group** testing & matching required
  - **Low risk** for transfusion-related adverse events
- PCC reduces the risk of transfusion-related acute lung injury (**TRALI**)
- PCC is **more effective** than FFP in rapidly reducing the INR

FFP, fresh frozen plasma; INR, international normalised ratio; PCC, prothrombin complex concentrate.

Schulman S, Bijsterveld NR. *Transfus Med Rev* 2007; **21**: 37–48; Huttner HB, *et al. Stroke* 2006; **37**: 1465–70; Vigué B, *et al. Intensive Care Med* 2007; **33**: 721–5; Levy JH, *et al. Anesthesiology* 2008; **109**: 918–26.

# Concerns

**Consumptive Coagulopathy**

**VTE complications**

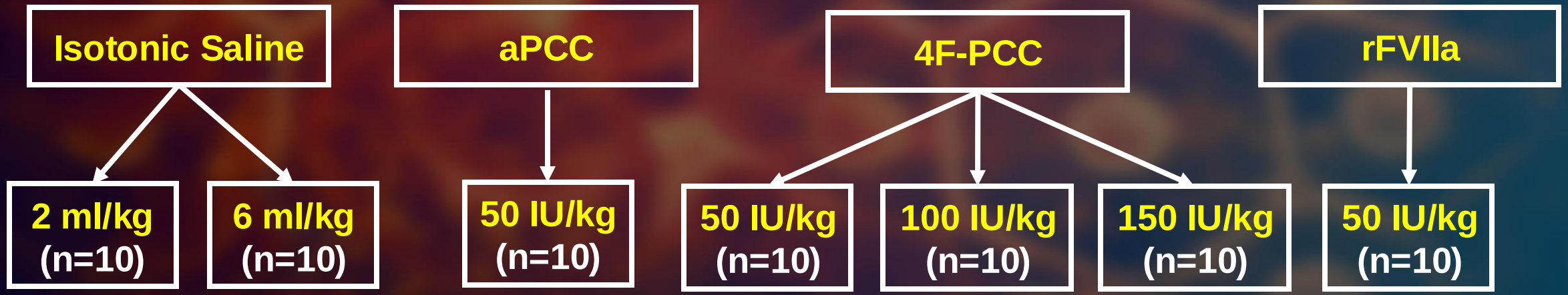
# Evaluation of the prothrombotic potential of 4F-PCC in animal models

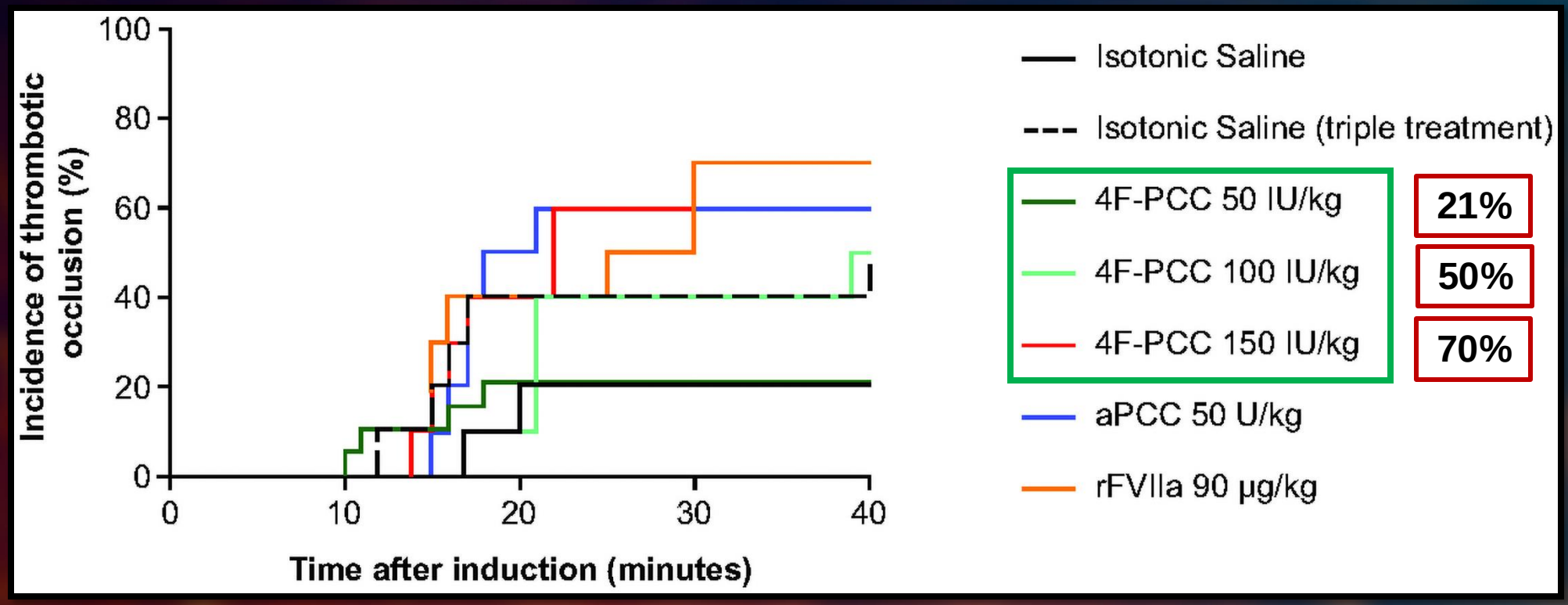
Subhajit Ghosh ,Wilfred Krege ,Baerbel Doerr ,Marcel Mischnik ,Ingo Pragst ,Gerhard Dickneite ,Eva Herzog

PLOS ONE

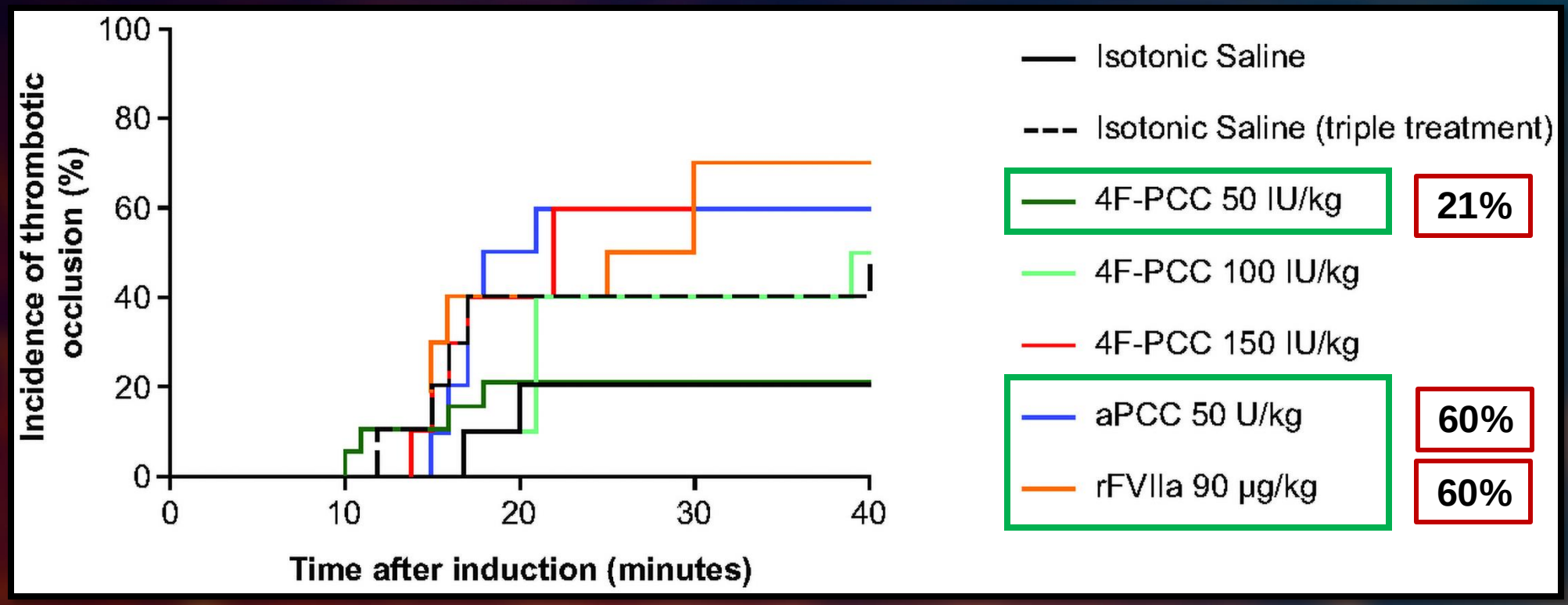
2021

- **70** female rats (9-12 weeks old)
- **Arterial thrombosis** was **induced** by **ferric chloride (FeCl3)**
- To identify the incidence of **thrombus occlusion** and **time to occlusion**






- 4F-PCC demonstrated a **dose-dependent increase** in thrombosis incidence



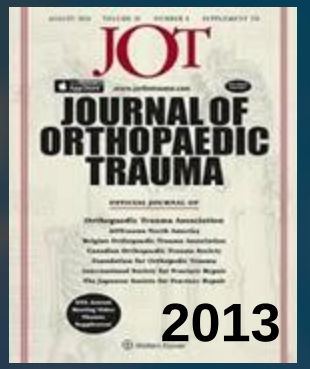

- 4F-PCC demonstrated a **dose-dependent increase** in thrombosis incidence
- The incidence of **thrombotic occlusion** was **lower** in **4F-PCC 50 IU/kg** compared with aPCC 50 U/kg or rFVIIa 90 U/kg

**(21% vs. 60% vs. 60%)**

# PCC vs. FFP

## Assessing the Efficacy of Prothrombin Complex Concentrate in Multiply Injured Patients With High-Energy Pelvic and Extremity Fractures

Bellal Joseph, MD, Mazhar Khalil, MD, Caitlyn Harrison, MD, Tianyi Swartz, MS, Narong Kulvatunyou, MD, Ansab A. Haider, MD, Tahereh O. Jokar, MD, David Burk, MD, Ali Mahmoud, BS, Rifat Latifi, MD, and Peter Rhee, MD




- **2-years** retrospective study
- **81** trauma patients with **INR>1.5** & **lower extremity Fracture**
- PSM 1:2

**3F-PCC (n=27)** **Vs.** **FFP (n=54)**

- ↓ **Time to Surgery** (324min vs. 702min)
- ↓ **Time to INR Correction** (285min vs. 490min)
- ↓ **Transfusion requirements**
- ↔ **VTE** (4% vs. 5%)

# PCC vs. FFP

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


2017

- Single-center, RCT at a Level I TC (**2012-2016**)
- **100** adult (18-80 yrs) pts were randomized into:

**coagulation factor concentrates (CFC)**
**[FC or 4F-PCC]**
**(n=52)**


**Vs.**

**FFP**
**(n=48)**

**The available sample size appears sufficient to make some conclusions that**

**first-line CFC is superior to FFP**

**Rescue Therapy**

(**52**% vs. **4**%)

(aOR: **25.34**, p<0.0001)

**MOF**

(**66**% vs. **50**%)

(aOR: **1.92**, p=0.015)

# PCC as an adjunct to FFP

# 3F-PCC + FFP

## Prothrombin Complex Concentrate Versus Fresh-Frozen Plasma for Reversal of Coagulopathy of Trauma: Is There a Difference?

Bellal Joseph • Hassan Aziz • Viraj Pandit • Daniel Hays • Narong Kulvatunyou • Zeeshan Yousuf • Andrew Tang • Terence O'Keeffe • Donald Green • Randall S. Friese • Peter Rhee


- **2-years** (2011-2012) retrospective study
- Patients with **TIC** (INR≥1.5 & no anticoagulants)
- PSM 1:3

**3F-PCC + FFP (n=63)** **Vs.** **FFP (n=189)**

- ↓ **In-hospital Mortality** (**23**% vs. **28**%)
- ↓ **Time to INR Correction** (**394**min vs. **1050**min)
- ↓ **Transfusion requirements**
- ↔ **DVT** (**1.6**% vs. **1.1**%)

**4-factor PCC:**

- Higher concentration of **factor VII**
- Risk of **VTE Complications**?

Kcentra®,
Receives F
Warfarin R
Undergoing Surgery

New Kcentra Label Includes Urgent Reversal
Surgery Setting



**3-factor** PCC

**4-factor** PCC

# 4F-PCC + FFP

## The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: A propensity matched analysis

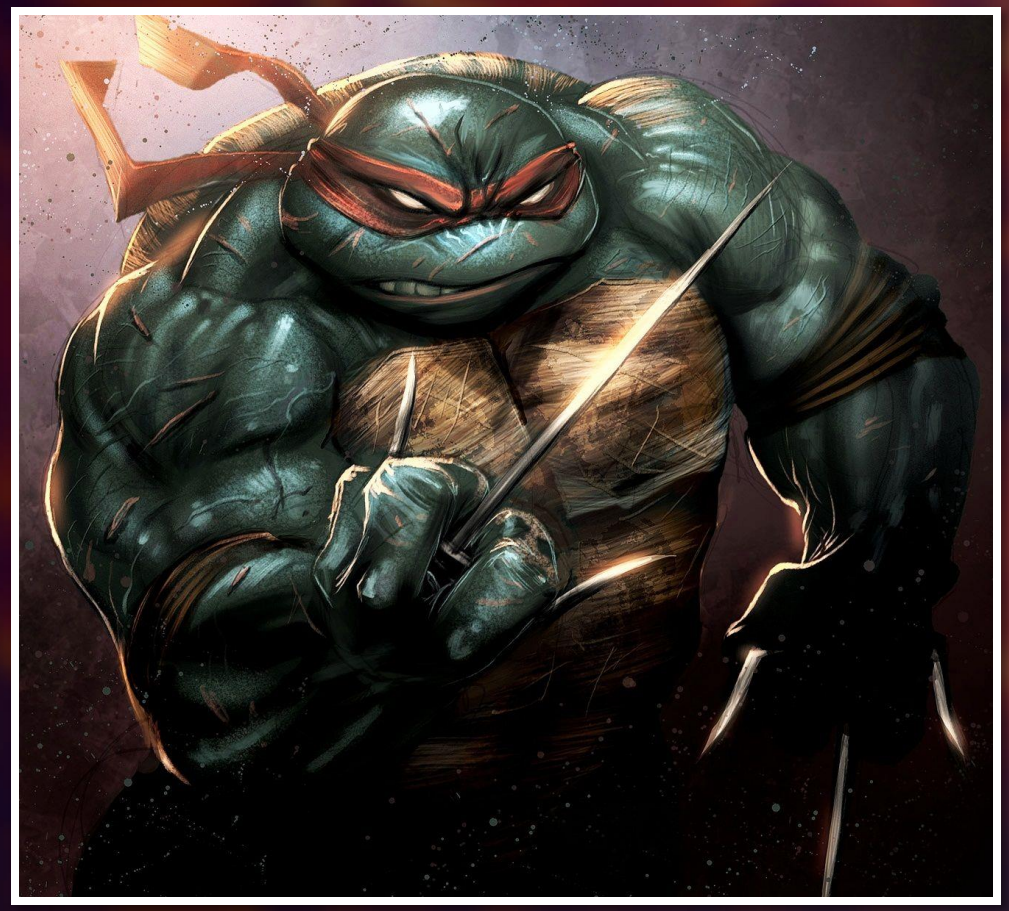
Jehan, Faisal MD; Aziz, Hassan MD; O'Keeffe, Terence MD; Khan, Muhammad MD; Zakaria, El Rasheid MD; Hamidi, Mohammad MD; Zeeshan, Muhammad MD; Kulvatunyou, Narong MD; Joseph, Bellal MD


- **2-years** (2015-2016) study at our Level I trauma center
- Patients with **TIC** (INR≥1.5 & no anticoagulants)
- **PSM 1:2**

**4F-PCC+FFP (n=63)** **Vs.** **FFP (n=189)**

- ↓ **In-hospital Mortality** (25% vs. 33%)
- ↓ **Time to INR Correction** (373min vs. 955min)
- ↓ **Transfusion requirements**
- ↔ **VTE Complications** (2.5% vs. 1.5%)

# 4F-PCC



VS

# 3F-PCC

# 4-Factor vs. 3-Factor

## 3-Factor Vs. 4-Factor PCC in Coagulopathy of Trauma: Four is Better Than Three

Zeeshan M, Hamidi M, Kulvatunyou N, Jehan F, O'Keeffe T, Khan M, Rashdan L, Tang A, Zakaria ER, Joseph B


- **5-year** retrospective analysis at our Level I trauma center
- Patients with **TIC** (INR≥1.5 & no anticoagulants)
- **PSM 1:1**

**4F-PCC + FFP (n=125)** **Vs.** **3F-PCC + FFP (n=125)**

- ↓ **Time to INR Correction** (365min vs. 428min)
- ↓ **Transfusion requirements**
- ↔ **In-hospital Mortality** (26% vs. 28%)
- ↔ **In-Hospital Costs** ($60,838 vs. $61,425)

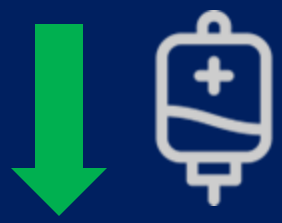
# Are These Studies Powered Enough to Detect VTE?

# Nationwide Use of PCC + FFP

## 4-Factor Prothrombin Complex Concentrate is associated with Improved Survival in Trauma Related Hemorrhage: A Nationwide Propensity Matched Analysis

Muhammad Zeeshan, MD, Mohammad Hamidi, MD, Ara J. Feinstein, MD, Lynn Gries, MD, Faisal Jehan, MD, Joseph Sakran, MD, MPH, Ashley Northcutt, MD, Terence O'Keeffe, MD1, Narong Kulvatunyou, MD, Bellal Joseph, MD

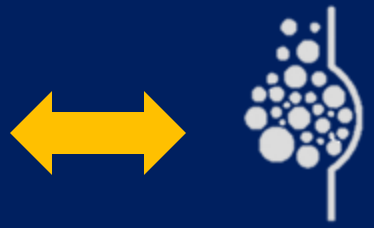

## PCC + FFP vs. FFP



**pRBC & FFP Requirements**

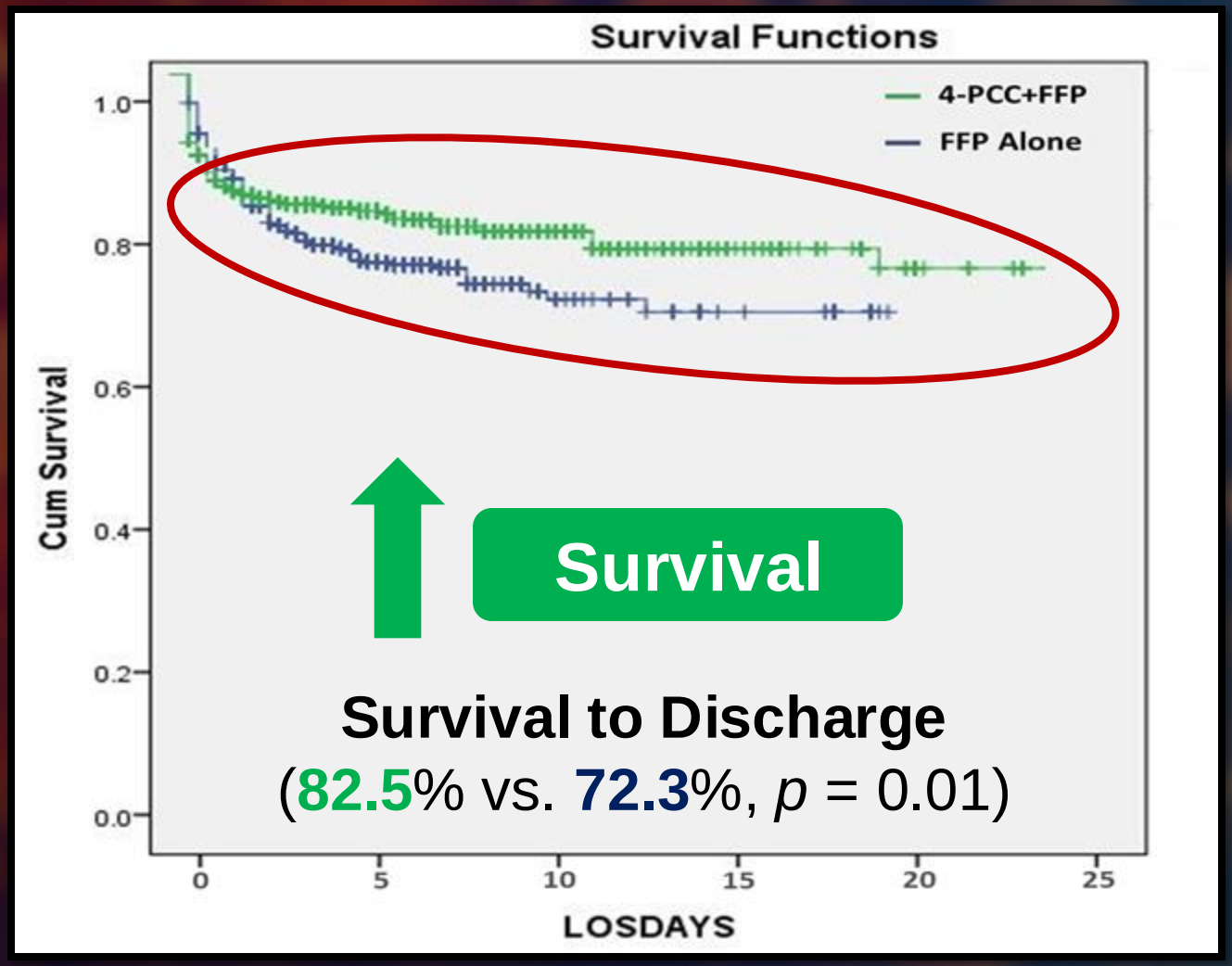
**AKI**
**2.1% vs 7.3%**

**ARDS**
**1.3% *vs* 4.7%**



**VTE**
**4.7% vs. 7.2%**

# Nationwide Use of PCC + FFP



# WB and PCC


DO NOT VENT


NDC 63833-386-02
500 U Range
Prothrombin Complex
Concentrate (Human)
Kcentra®
For Intravenous Administration Only
℞ only
CSL Behring


WHY NOT BOTH?

# WB + 4F-PCC vs. WB

**Four-factor prothrombin complex concentrate in adjunct to whole blood in trauma-related hemorrhage: Does whole blood replace the need for factors?**

Khurrum, Muhammad MD; Ditillo, Michael DO; Obaid, Omar MD; Anand, Tanya MD; Nelson, Adam MD; Chehab, Mohamad MD; Kitts, Daniel James MS; Douglas, Molly MD; Bible, Letitia MD; Joseph, Bellal MD, FACS


- A 3-year (2015–2017) analysi **WB + PCC**

↓ **pRBC**

**(8 U vs. 10 U)**

↓ **FFP**

**(6 U vs. 8 U)**

↓ **AKI**

**(4% vs. 12%)**

↓ **ICU LOS**

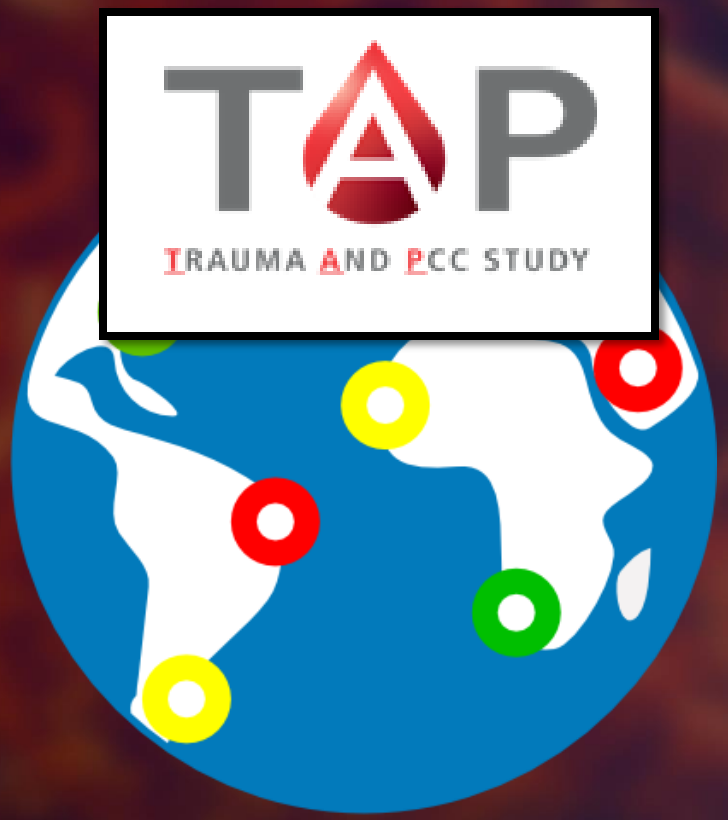
**(5 d vs. 8 d)**

## 10+ Years of Research

- Retrospective
- Not Randomized
- Generalizability?

**We Need Prospective Randomized Clinical Trials**

# Randomized Clinical Trials




# Trauma and 4-Factor Prothrombin Complex Concentrate (TAP) Trial


TAP
TRAUMA AND PCC STUDY

UAB

- Up to **8000 patients**
- About **120 trauma centers**

  **(at least 3 countries)**
- The **second-largest** trauma trial ever conducted

ClinicalTrials.gov

Phase 3

# Evaluation of BE1116 in Patients With Traumatic Injury and Acute Major Bleeding to Improve Survival ( TAP Study )

## Study Design

| | |
|---|---|
| Study Type : | Interventional (Clinical Trial) |
| Estimated Enrollment : | 8000 participants |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignment |
| Masking: | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |
| Primary Purpose: | Treatment |

Available at: https://clinicaltrials.gov/ct2/show/NCT05568888?cond=trauma+an+pcc&draw=2&rank=2

ClinicalTrials.gov

## Inclusion Criteria

- Estimated age **≥ 15 yrs**
- Estimated **weight > 50 kg**
- **RABT score ≥ 2**
- **MTP** activation

## Exclusion Criteria

- **CPR for ≥ 5 mins** before enrollment
- **Isolated** TBI
- **Isolated burns** >20% TBSA
- **Known anticoagulation** treatment
- **History of VTE** within past 3 months

Available at: https://clinicaltrials.gov/ct2/show/NCT05568888?cond=trauma+an+pcc&draw=2&rank=2

## Primary Outcome

- **6-hr** Mortality

## Secondary Outcomes

- **24-hr** Mortality
- **30-day** Mortality
- Need for **hemostasis control procedure**
- BE1116 serious adverse events (**SAEs**)
- Thromboembolic events (**TEEs**)
- **ARDS & AKI**
- Multiple Organ Failure (**MOF**)

jama


# The PROCOAG RCT

## Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion

Pierre Bouzat, MD, PhD; Jonathan Charbit, MD; Paer-Selim Abback, MD; Delphine Huet-Garrigue, MD;& the PROCOAG Study Group

JAMA
The Journal of the American Medical Association
2023

- **Double-blind**, **randomized**, **placebo-controlled** superiority Trial
- **12** French designated **level I trauma centers**
- **324 patients analyzed (164 KANOKAD (4F-PCC) vs. 160 Placebo)**
- **Primary outcome: 24-hr Blood Product Requirements**
- **Secondary outcome: 24-hr & 28-d Mortality**

**4F-PCC (n=164)** Vs. **Placebo (n=160)**

**24-hr Blood Product Requirements (median, 12 U vs. 11 U)**

**Mortality**
**24-hr: 11% vs 13%**
**48-hr: 17% vs 21%**

- **Mortality** in the **4F-PCC arm** was **lower**, however, **not statistically significant**
  - The study was **underpowered** to detect a significant difference in mortality

| 4F-PCC (n=164) | Vs. | Placebo (n=160) |
|---|---|---|

- This included **SVTs** → **Not clinically significant** and not usually included in analyses
  - **Higher VTE** and **Lower Mortality** in **4F-PCC arm** → **Survival Bias?**

# Other Limitations:

- The primary outcome of **24-hour blood product** use is a **less patient-centered outcome** than others such as mortality
- Multiple **confounding factors** are not taken into consideration:

| Confounding Factors | 4F-PCC | Placebo |
|---|---|---|
| TXA Infused (%) | 76 | 86 |
| TXA dosage, median [IQR], g | 3 [3-6] | 3 [3-7.5] |
| Median time from Injury to beginning of treatment, min | 140 | 130 |
| Time to FFP, min | 73 | 91 |
| Time to Achieve Hemostasis, median, min | 300 | 288 |

PRO COAG

- **Underpowered** (n=324)
  - Primary Endpoint:

**24-hr Blood Transfusion**

**(Non-patient centered)**

TAP

TRAUMA AND PCC STUDY

- **Up to 8000 pts**
  - Primary Endpoint:

**6-hr Mortality**

**(Patient-Centered)**

PRO COAG

- **12 TC in France**

European guidelines emphasize viscoelastic testing/fibrinogen

TAP
TRAUMA AND PCC STUDY

- **Global Study**

(At least 3 countries)

PRO COAG

- **Frequentist** Approach

- 4F-PCC (**KANOKAD**)

TAP

TRAUMA AND PCC STUDY

- **Bayesian** Approach

- 4F-PCC (**Kcentra/Beriplex**)

- **Kcentra/Beriplex** contains **higher levels** of **anti-coagulant factors** than **Kanokad**

| | Kanokad (1,000 units) | Kcentra/Beriplex (1,000 units) |
|---|---|---|
| **Protein C** | 444-1560 | 840-1640 |
| **Protein S** | 40-320 | 480-1360 |
| **Heparin** | 0 | 16-80 |
| **Anti-thrombin III** | 0 | 8-60 |

- There is a continued need for a **large, definitive trial**, with **patient-centered outcomes** – which is what **TAP** is.

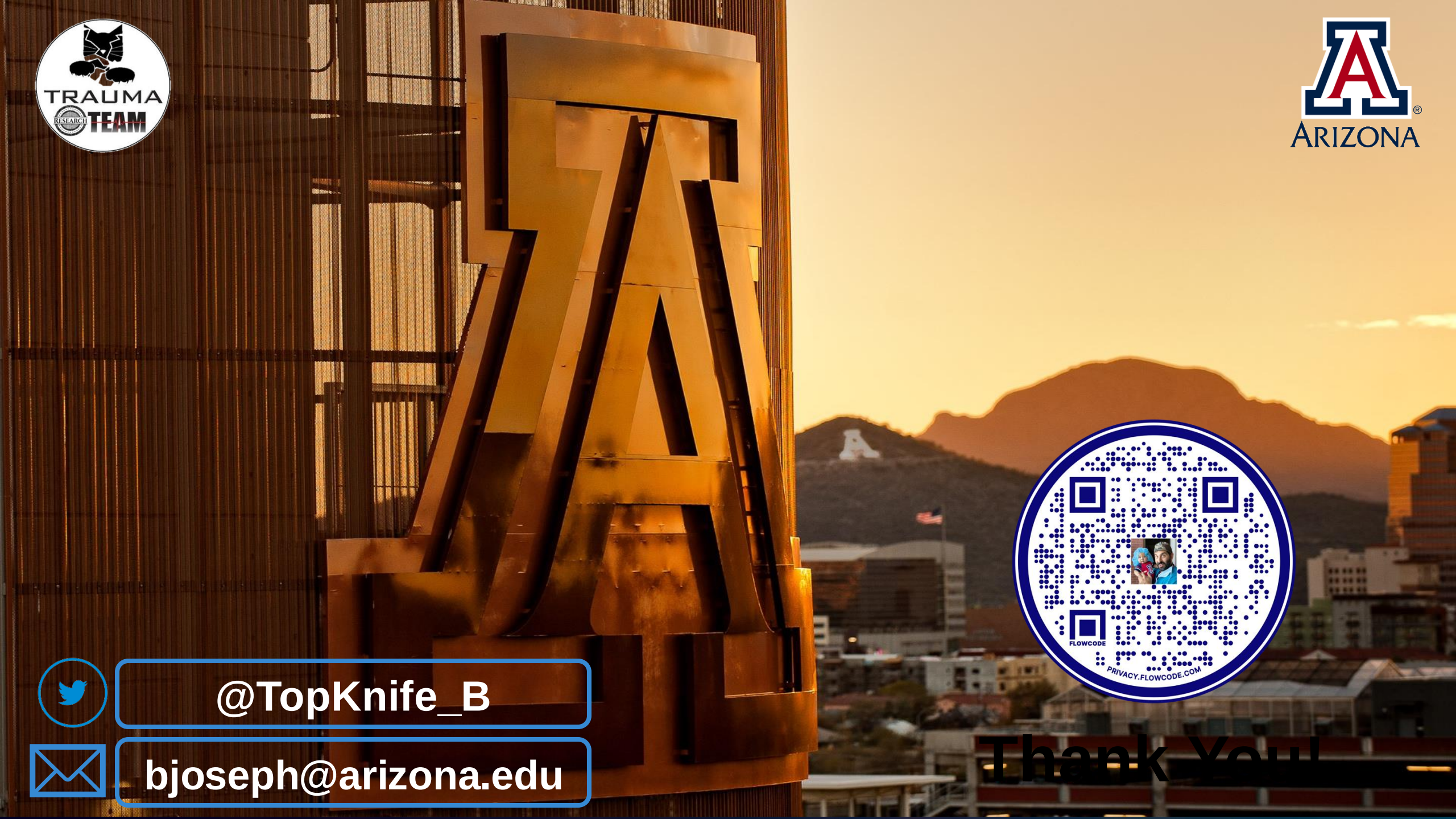
# It All Comes Down to This

**Time to INR Correction is Faster with PCC**

**4-PCC+FFP effectively treats Acquired CoT**

**4-PCC-based Resus Reduces Overall Transfusion Needs**

# The Role of PCC in Resuscitation of Patients with Hemorrhagic Shock Yet to be Defined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Thank You!