Managing Coagulopathy in Trauma

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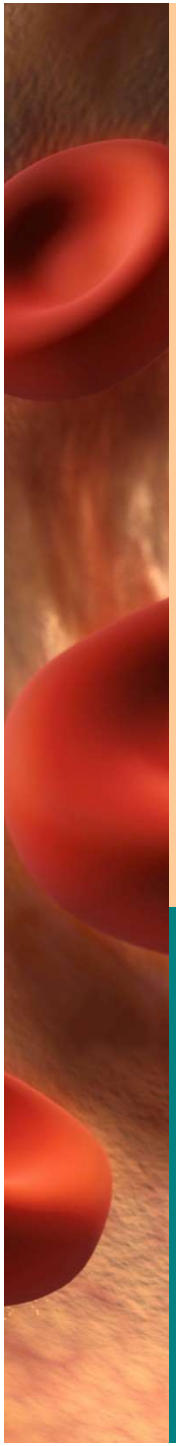
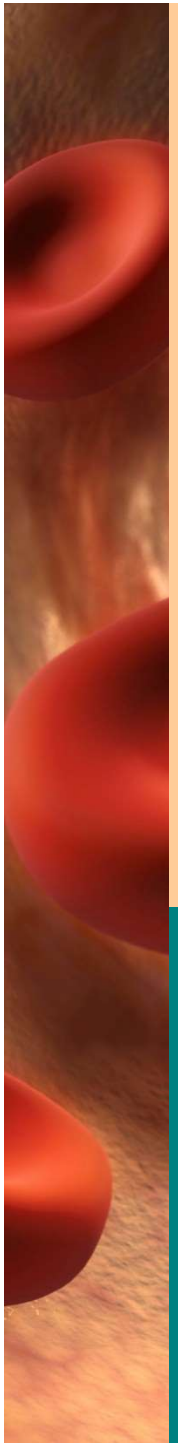
Trauma Medical Director
University of New Mexico School of Medicine



Objectives

- Review reversal strategies for common anticoagulants
- Address Antiplatelet Agents
- Review direct oral anticoagulants and challenges
- Define hemostatic resuscitation
- Review evidence in support of specific strategies



Antithrombotic Agents in Clinical Use

Antiplatelet

- Clopidogrel
- Aspirin
- Ticlopidine
- Dipyridamole
- Prasugrel
- Ticagrelor

- Abciximab
- Eptifibatide
- Tirofiban

Anticoagulant

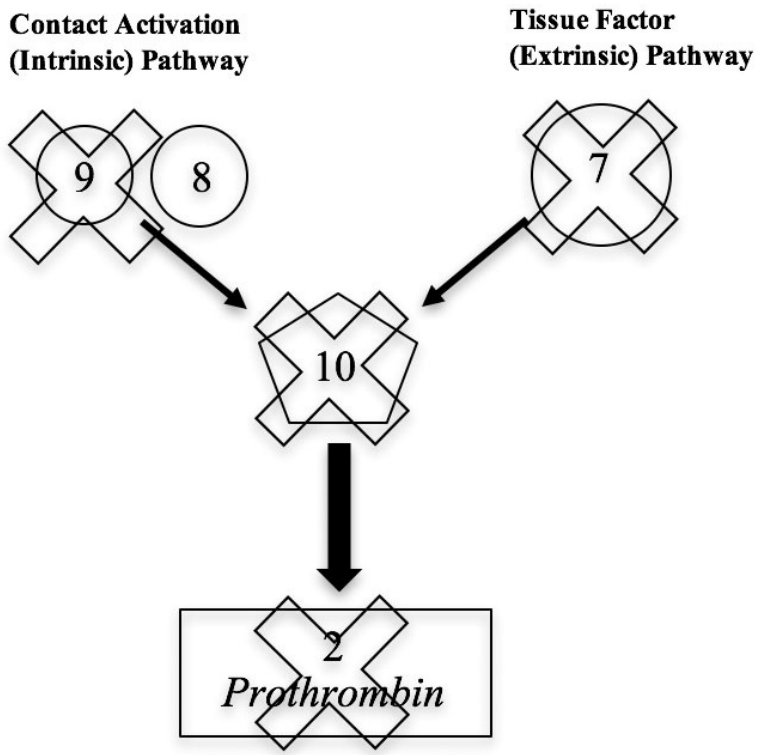
- Warfarin
- Dabigatran
- Rivaroxaban

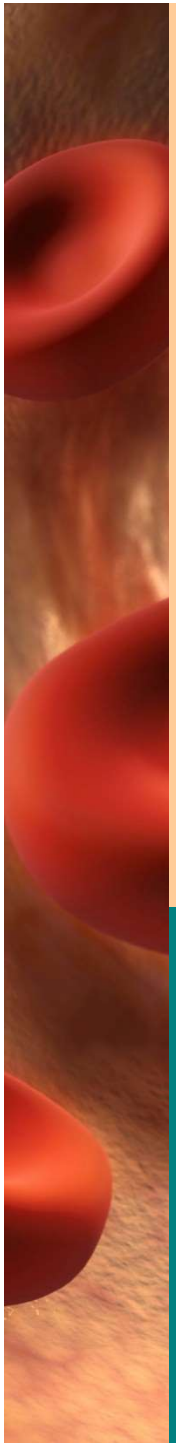
- Heparin
- LMWH (multiple)
- Fondaparinux

- Bivalirudin
- Argatroban
- Lepirudin

VKA: Warfarin (Coumadin)

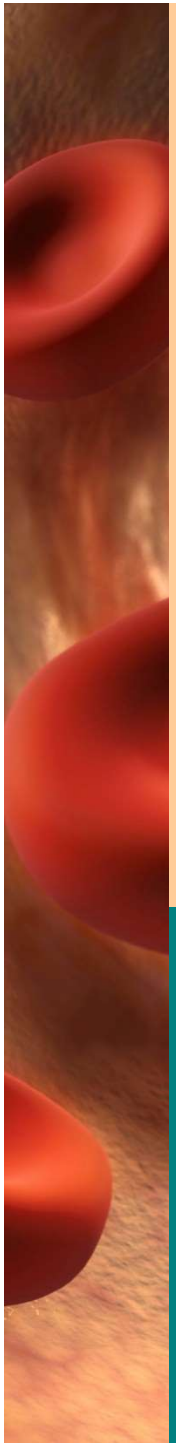
- Inhibits Vit K epoxide reductase
- Inhibits production of factors II, VII, IX, X
- T 1/2 : 36-42 hours
- Monitored using PT/INR





VKA in Trauma

- 3% of patients presenting to a level 1 trauma center
- ~ 3-fold ↑ mortality
- Does INR correction improve mortality?

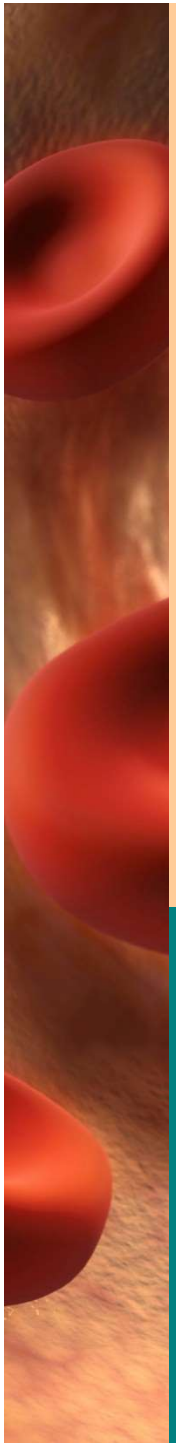


Rapid warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality

Ivascu FA, Howells GA, Junn FS, Bendick PJ, Janczyck RJ

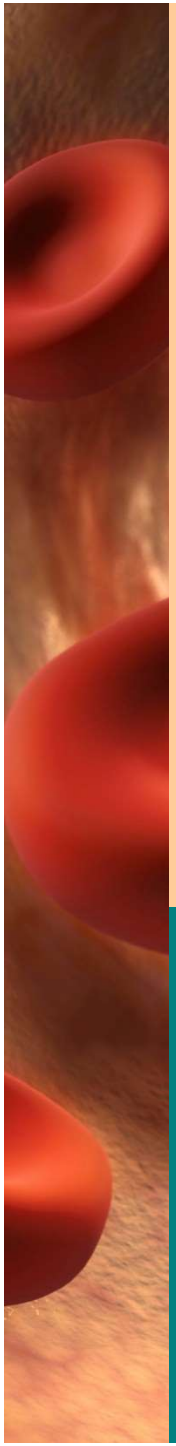
- 48% mortality rate in trauma patients on warfarin sustaining ICH (10% non-anticoag)
- 40% with progression of ICH, despite anticoagulation reversal
- 65% mortality rate
- Mean time to initiate warfarin reversal was 1.9 hours for protocol patients versus 4.3 hours for preprotocol patients- reduced mortality to 10%

***J Trauma*, 2005**



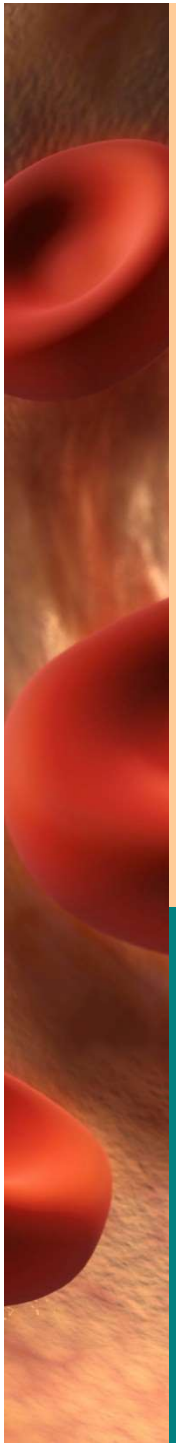
VKA reversal options

- Vitamin K repletion
- Plasma transfusion
- Factor concentrate repletion
  - PCC (prothrombin complex concentrate, factor IX concentrate)



Vitamin K

- All VKA ICH patients should get Vitamin K
- Onset 2-6 hrs, complete response 24 hrs
  - **Vitamin K insufficient on its own**
- IV formulation most rapid, equivalent @ 24 hours
- Anaphylaxis risk of IV formulation- very rare
- UNM Institutional guideline: 10 mg IV



Fresh Frozen Plasma

Advantages

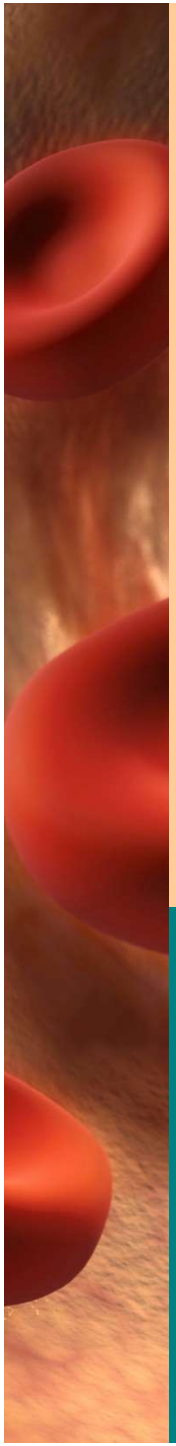
- Historically “Standard of care” in US
- Widely available
- Allows partial reversal
- Contains all coagulation factors, along with fibrinogen and other plasma proteins

Disadvantages

- Thawing
- Compatibility testing

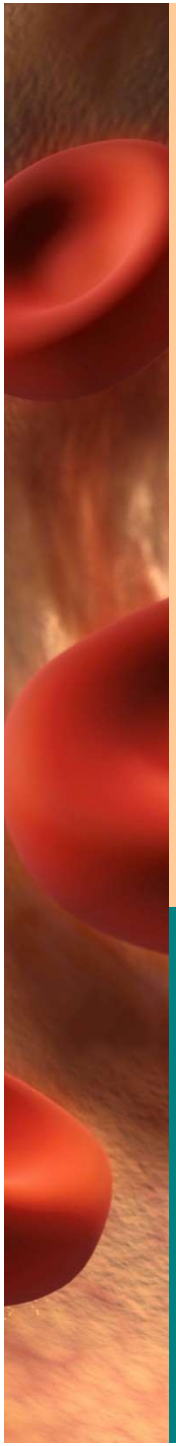
  = DELAYS
- Volume Overload
- TRALI
- factor concentration varies
- Viral transmission: rare

Lee K, et al. *Haemophilia*. 2010;16:949-951
Godier A, et al. *J Thromb Haemost*. 2010;8:2592-2595
Holland L, et al. *Transfusion*. 2009;49:1171-1177
Makris M, et al. *Thromb Haemost*. 1997;77:477-480
Vlaar AP, et al. *Neth J Med*. 2009;67:320-326.



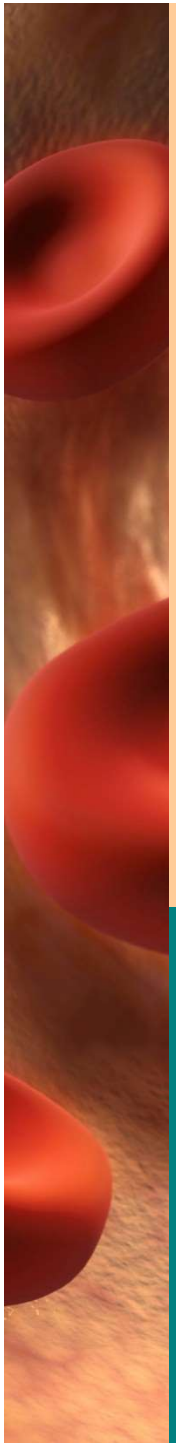
Factor Concentrates

- FEIBA: activated 4- factor concentrate
  - approved for hemophiliacs
- 3 Factor PCC (Bebulin, Profilnine)
  - FDA approved for blood dyscrasias
- **4 Factor PCC (K-Centra, Beriplex)**



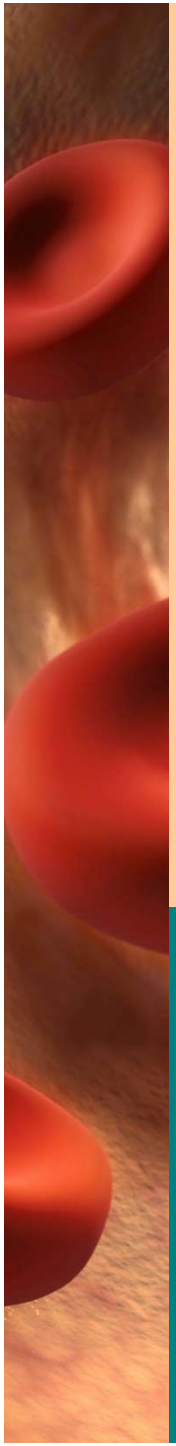
Prothrombin Complex Concentrates

- Concentrate of Factors II, VII, IX, X, Prot C&S, heparin (Factor IX is the workhorse)
- Half Life:
  - **Factor IX~ 24 hrs**, II ~ 60 hrs, X ~ 31 hrs, VII~ 4-6
- Significant complication rate < 1%
- 4-factor concentrate FDA approved for emergent warfarin reversal



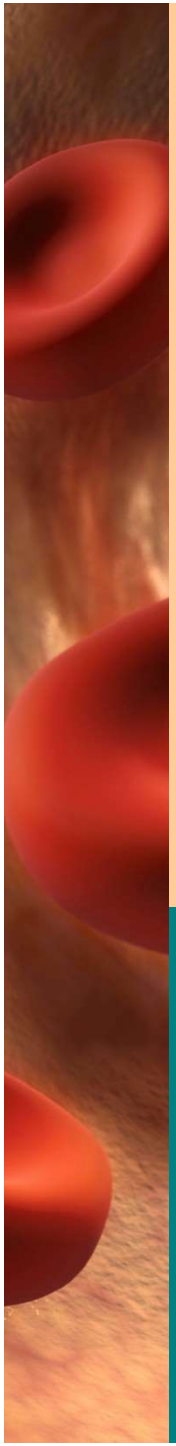
PCC: considerations

- Derived from donor plasma
- Contraindicated if history of HIT
- Dosing:
  - 25 u/kg if INR 2-4
  - 35 u/kg if INR 4-6
  - 50 u/kg if INR >6 (based on weak evidence)



Advantages of PCCs

- More rapid reversal (vs. FFP)
- Longer half-life (vs rFVIIa)
- A balanced replacement of factors
- Better restoration of thrombin generation (vs rFVIIa)
- Better antifibrinolytic activity (vs rFVIIa)
- Acceptable risk profile



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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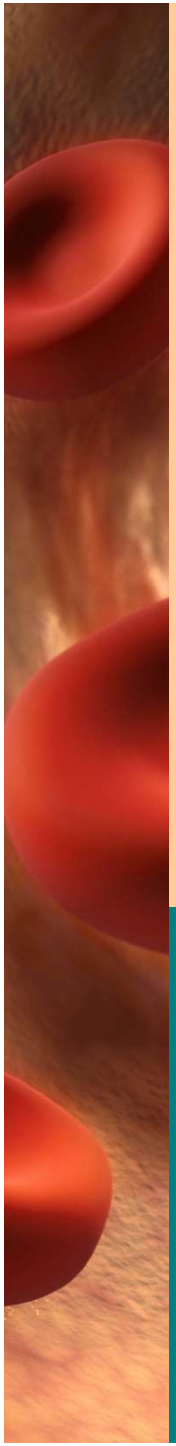
Efficacy and Safety of a Four-Factor Prothrombin Complex Concentrate (4F-PCC) in Patients on Vitamin K Antagonists Presenting with Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study

Ravi Sarode, Truman J. Milling, Jr., Majed A. Refaai, Antoinette Mangione, Astrid Schneider, Billie L. Durn and Joshua N. Goldstein

- PRCT: N= 202 (4F-PCC: 98, FFP:202)
- **Co-Primary endpoints;**
  - Hemostatic Efficacy @ 24 hours;
    - PCC 72.4%, FFP 65.4% (non-inferiority p= 0.0045)
  - INR ≤ 1.3 @ 30 min. post infusion;
    - PCC 62.2%, FFP 9.6% (p< 0.002)



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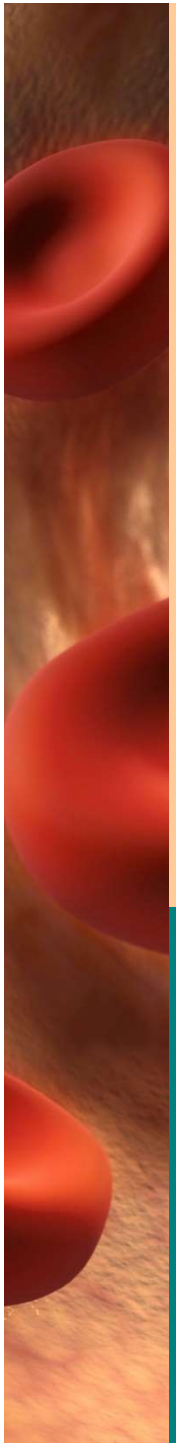
- INR <1.3 @ 24 hrs; PCC 88%, FFP 58%
- Infusion duration: PCC; 17 min, FFP 148 min
- Thromboembolic events: (n=8)7.8% vs (n=7)6.4%, NS
- Adverse events: PCC; 9.7%, FFP; 21.1%



Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

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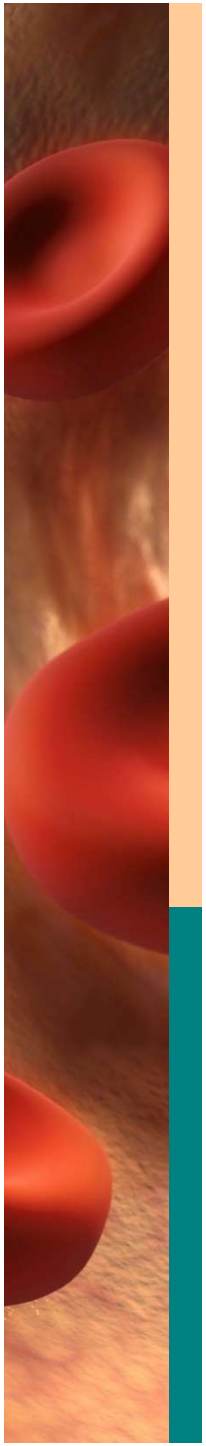
- 23 FFP, 27 PCC
- 2 (9%) vs 18 (67%) reached primary endpoint of INR 1.2 within 3 hours
- 8 (35%) vs 5 (19%) died
- 43 serious adverse events
  - 6 serious adverse events FFP related, 2 PCC related



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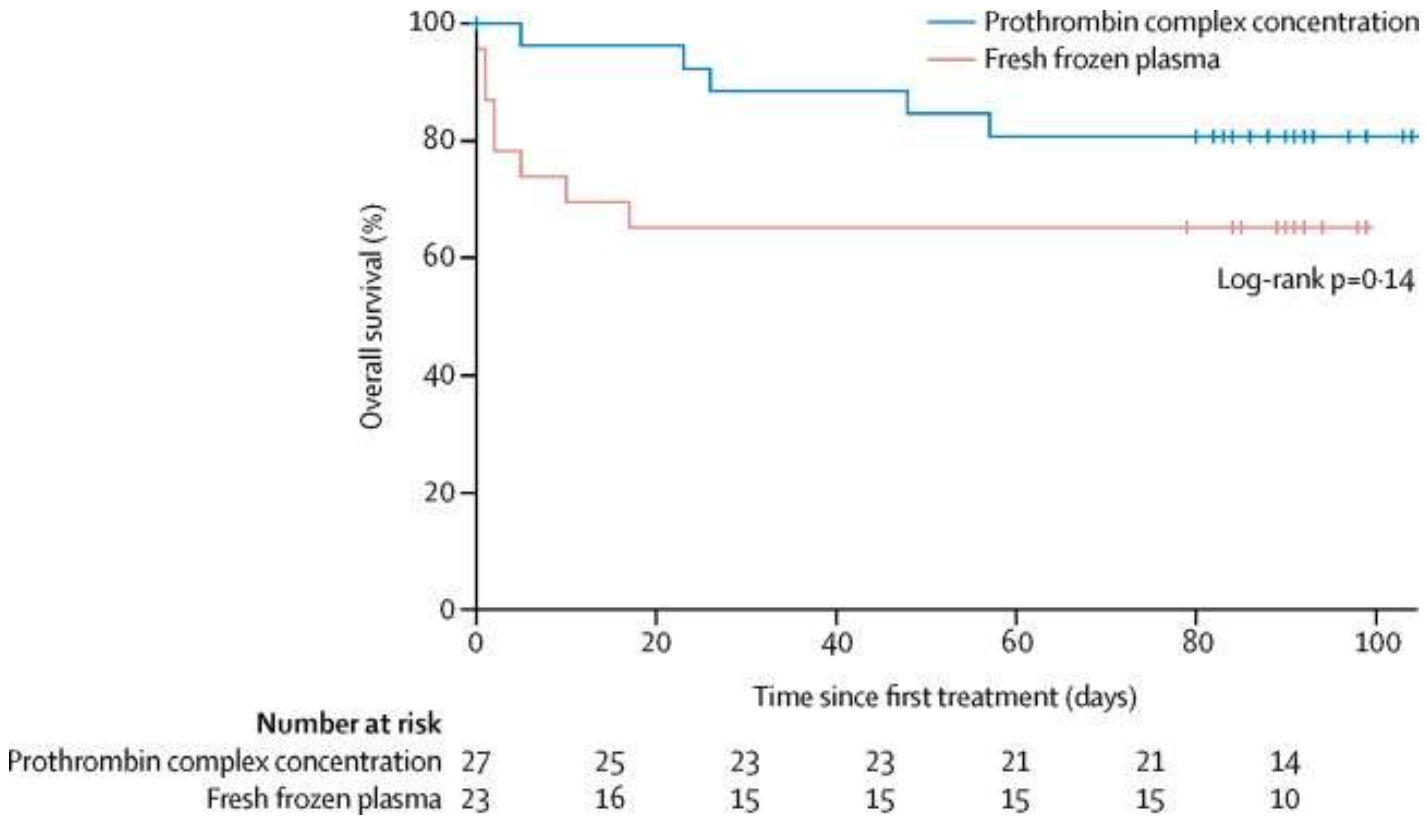
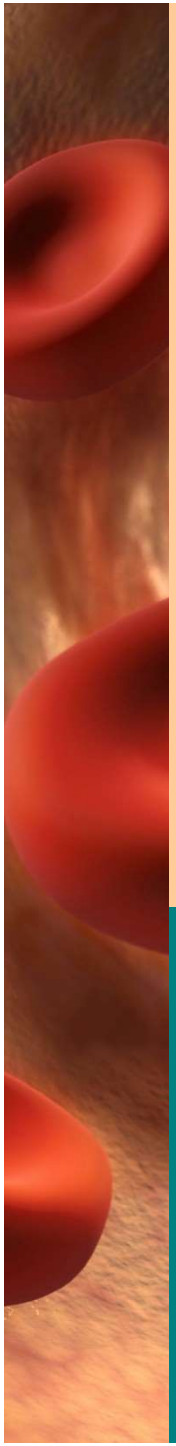




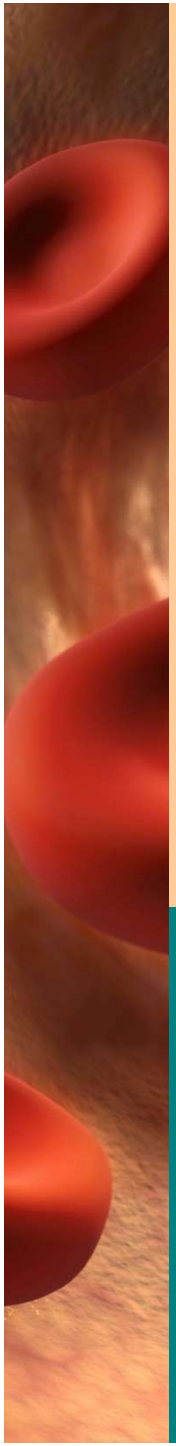
Published Guidelines for Reversal of Warfarin Anticoagulation in Patients With ICH

Society (Year)	Vitamin K	PCC (IU/kg)		Plasma (mL/kg)	rFVIIa
Australian (2013)	IV (5-10 mg)	Preferred (NS)*		Yes (NS)	NS
British Standards (2010)	IV (5-10 mg)	Preferred (50)		NS	NS
EU Stroke (2019)	IV (10 mg)	Preferred (10-50)		Yes (20)	No
ACCP (2018)	IV (10 mg)	Preferred (25-50)		Yes (NS)	NS
AHA (2015)	IV (NS)	Yes (NS)	OR	Yes (10-15)	No
French (2020)	Oral or IV (10 mg)	Preferred (25-50)		Yes (NS)	No

PCC with Vit K preferred by most with improved mortality and faster reversal
AHA acknowledges FFP +vit K mainstay of reversal, but acknowledge PCC may be considered over FFP
NS- not specified

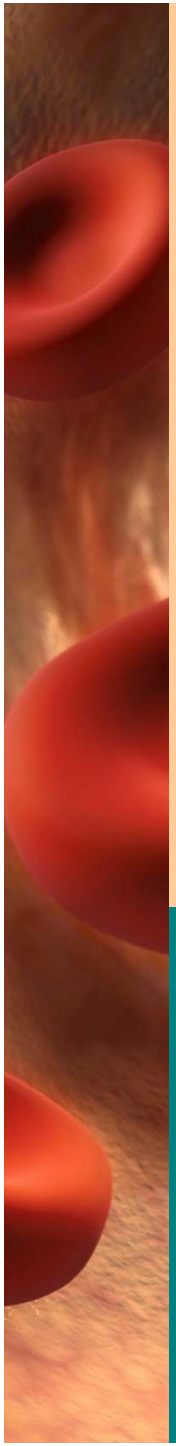
Milling, et all, Am J Emer Med,38. 2020, 1890-1903.

Questions?



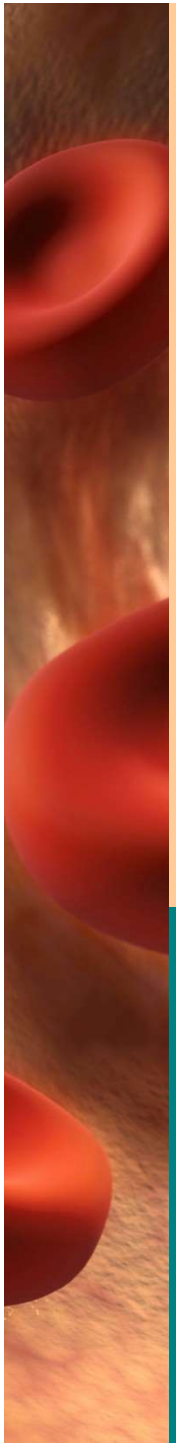
Anti-Platelet Agents

- > 50 million take ASA daily
- ASA + Clopidogrel
  - Increased Efficacy & Bleeding
- Both irreversibly inhibit platelets
- Platelets regenerate 10% day
  - Normal function returns 3-7 days after cessation



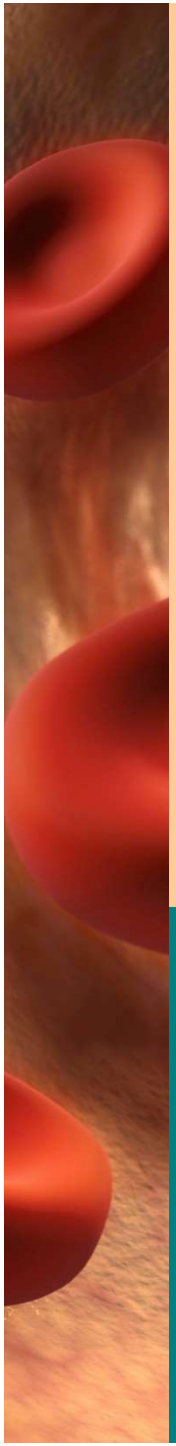
Antiplatelet agents & TBI progression/ outcome

- Question 1: In patients with TBI on prehospital antiplatelet medication, does platelet transfusion improve mortality?
- Question 2: In patients with TBI on prehospital antiplatelet medication, does platelet transfusion reduce hemorrhage progression?
- Question 3: In patients with TBI on prehospital antiplatelet medication, does platelet transfusion reduce the need for neurosurgical intervention?



Does platelet transfusion improve mortality?

- **NO**
  - Ohm C et al. *Effects of antiplatelet agents on outcomes in elderly patients with traumatic intracranial hemorrhage.* J Trauma 2005
  - Ivascu et al. *Predictors of mortality in trauma patients* with intracranial *hemorrhage on preinjury aspirin or clopidogrel.* J Trauma - Inj Infect Crit Care. 2008
  - Washington, et al. *Platelet transfusion: An unnecessary risk for mild traumatic brain injury patients on antiplatelet therapy. J Trauma - Inj Infect Crit Care.* 2011
  - Lee, et al. *Preoperative Low-Dose Aspirin Exposure and Outcomes after Emergency Neurosurgery for Traumatic Intracranial Hemorrhage in Elderly Patients.* Anesth Analg. 2017
  - Holzmacher et al. *Platelet transfusion does not improve outcomes in patients with brain injury on antiplatelet therapy.* Brain Inj. 2018
  - Pelaez, et al. *Not all head injured patients on antiplatelet drugs need platelets: Integrating platelet reactivity testing into platelet transfusion guidelines.* Injury. 2019



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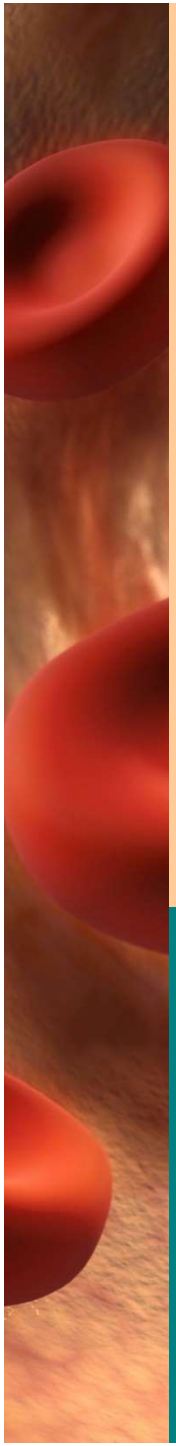
  - Carnevale et al. *Blossoming contusions: Identifying factors contributing to the expansion of traumatic intracerebral hemorrhage.* J Neurosurg. 2018
  - Ogunlade et al. *Efficacy of platelet transfusion in the management of acute subdural hematoma.* Clin Neurol Neurosurg. 2018
  - Pelaez, et al. *Not all head injured patients on antiplatelet drugs need platelets: Integrating platelet reactivity testing into platelet transfusion guidelines.* Injury. 2019



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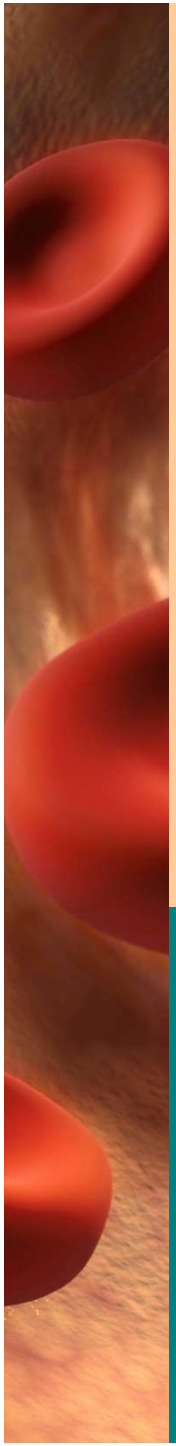
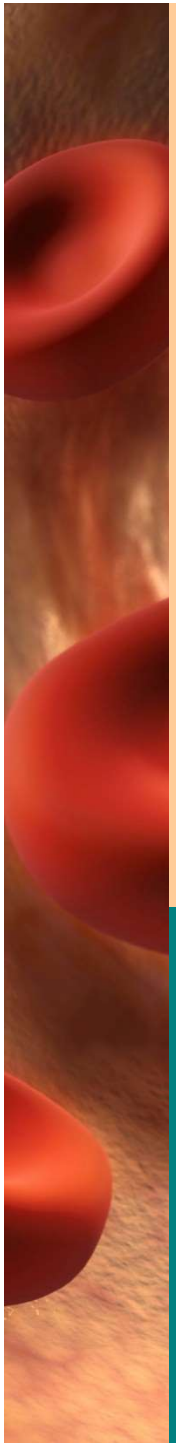
  - Bachelani AM et al. *Assessment of platelet transfusion for reversal of aspirin after TBI*. Surgery 2011
  - Foreman PM et al. *Antiplatelet Medication and Operative Subdural Hematomas: A Retrospective Cohort Study Evaluating Reoperation Rates.* World Neurosurg. 2019



Applications of platelet function testing?

Bachelani AM et al. *Assessment of platelet transfusion for reversal of aspirin after TBI*. Surgery 2011

- Retrospective N = 84
- Documented ASA use = 42%
- VerifyNow ART abnormal = 64%
- Of ASA users 2.4% with normal ART
- Most received platelets with evidence of reversal in only 64%
- No correlation between reported ASA use or abnormal ART and hemorrhage progression or poor outcome



Goal-directed platelet transfusions correct platelet dysfunction and may improve survival in patients with severe traumatic brain injury

Furay E, Daley M, Teixeira PG, Coopwood TB, Aydelotte JD, Malesa N,Tellinghuisen C, Ali S, Brown LH, Brown CVR

- Retrospective, case control
- 35 patients with severe TBI with platelet dysfunction received transfusion
- Compared to 51 historic controls with severe TBI and platelet dysfunction
- Lower mortality (9% vs 35%, p=0.005)

Rapid detection of platelet inhibition and dysfunction in traumatic brain injury

A prospective observational study

Isolated TBI patients N=221

No antiplatelet use (N=111)
Aspirin (N=7a8)
Clopidogrel (N=6)
Aspirin and clopidogrel (N=26)

Platelet function testing

VerifyNow™
Whole Blood Aggregometry

Before and after platelet transfusion (or 6 hours later)

Conclusions

- Poor platelet response highly prevalent in all groups

BUT

- Platelet response DID NOT correlate with outcomes
- Platelet transfusion DID NOT improve platelet function OR outcomes

Alvikas et al. *Journal of Trauma and Acute Care Surgery*. Month 2021 [doi]

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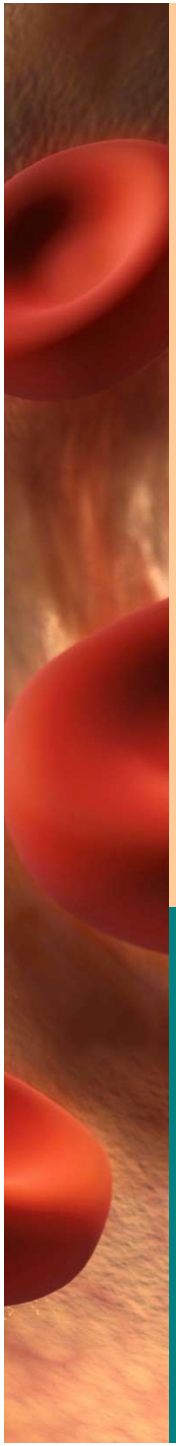
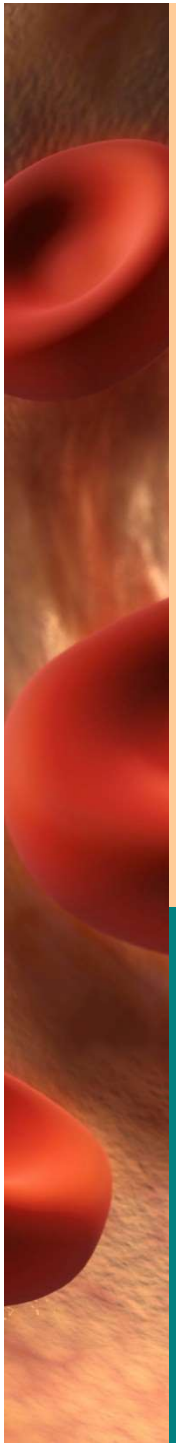
The Journal of Trauma and Acute Care Surgery®



Desmopressin

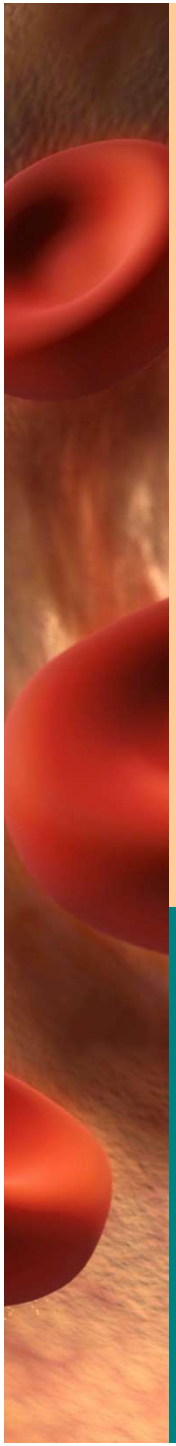
- DDAVP is a synthetic analog to vasopressin
- Increases circulating levels of factor VIII and vWf leading to improved platelet activation
- Used in patients with uremia



The Role of Desmopressin on Hematoma Expansion in Patients with Mild Traumatic Brain Injury Prescribed Pre-injury Antiplatelet Medications

Barletta JF, Abdul-Rahman D, Hall ST, Mangram AJ, Dzandu JK, Frontera JA, Zach

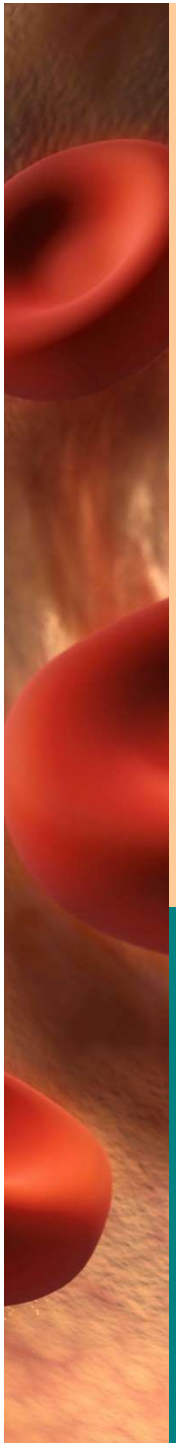
- 202 patients on antiplatelet medications with TBI
  - 158 (78%) received Desmopressin (DDAVP)
  - Dose of 0.3 mcg/kg
  - 69% with SDH, 49% with multicompartment ICH
  - Aspirin most common (75%), followed by dual antiplatelet (13%), and ADP-receptor inhibitors (12%)
- DDAVP associated with lower incidence of expansion with mild TBI (OR 0.259)



Current Management at UNMH

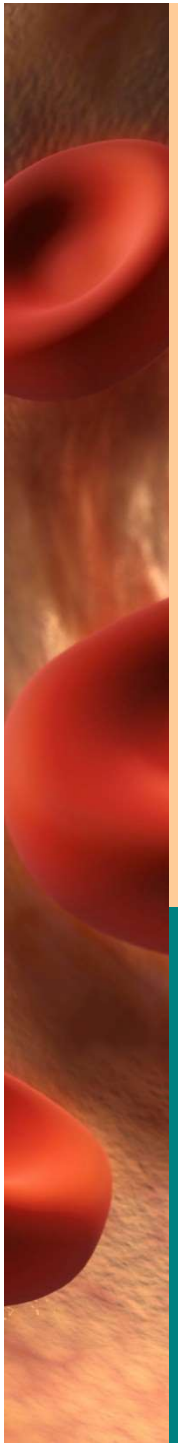
- For those on dual APT (ASA & Clopidogrel)
  - » DDAVP (0.3 mcg/ kg)
  - » platelet transfusion if planning operative intervention
- For those on ASA only
  - » DDAVP (0.3 mcg/kg)
  - » Consider platelet transfusion if planning operative intervention
  - » ART testing
- Be wary of the importance of antiplatelet therapy in some (eg. Coronary stent protection)

Questions?



Direct Oral Anticoagulants (DOACs)

- Direct Thrombin inhibitors: DTIs
  - Dabigatran
- Factor Xa Inhibitors
  - Rivaroxaban, apixaban, edoxaban, betrixaban
- FDA approved indications
  - Stroke prevention in NVAF, DVT and PE, VTE ppx, Prevention in CAD



Dabigatran (Pradaxa)

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

The NEW ENGLAND JOURNAL of MEDICINE

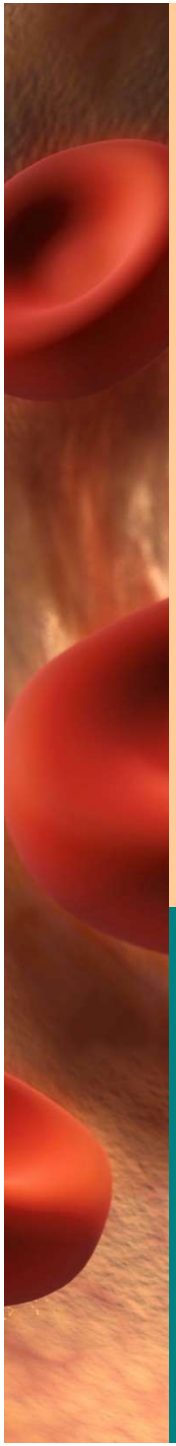
ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group*

- Direct Thrombin Inhibitor (DTI)
- BID Dosing
- No Monitoring
- T1/2: 14 – 16 hrs
- Lower rates of ICH?

- **NO MONITORING**



DTI: Dabigatran

- Elevated PT/ INR, PTT: qualitative markers only
- Thrombin Time (TT): not yet standardized
  - Fibrinogen $\xrightarrow{\text{thrombin}}$ Fibrin

Dabigatran reversal agents

- Vitamin K: NO
- FFP: NO
- PCC: 50 u/kg
- rFVIIa: 100 u/kg
- Hemodialysis: 60% effective/practicality?
- Tincture of Time:
  - T1/2 9-12 hours

PEDIATRIC JOURNAL CLUB: MANAGING DKA IN CHILDREN (EARN 1 CREDIT HOUR OF CME) page 20

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AMA Legal Battle a Victory For Fair Pay From Insurers
Physicians receiving nearly $200M from United-Health Settlement
By Steven J. Stack, MD, AMA Board of Trustees Chair-Elect ▶ page 4

OH HENRY
In Defense of Thought
by Greg Henry, MD

Under Pressure
When an Ophthalmology consult isn't available, an emergency lateral canthotomy could mean the difference between sight and blindness.
See page 8 for a step by step pictorial guide.

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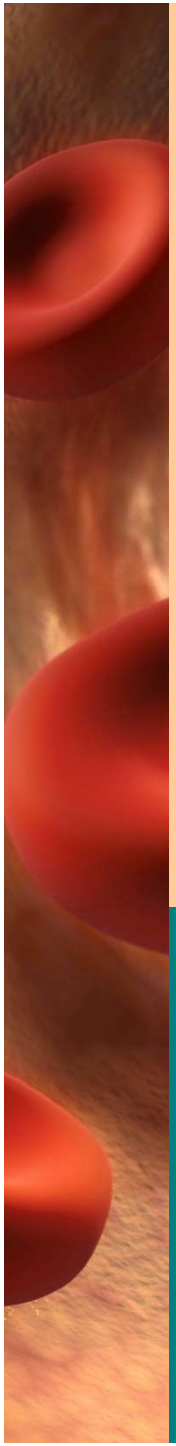
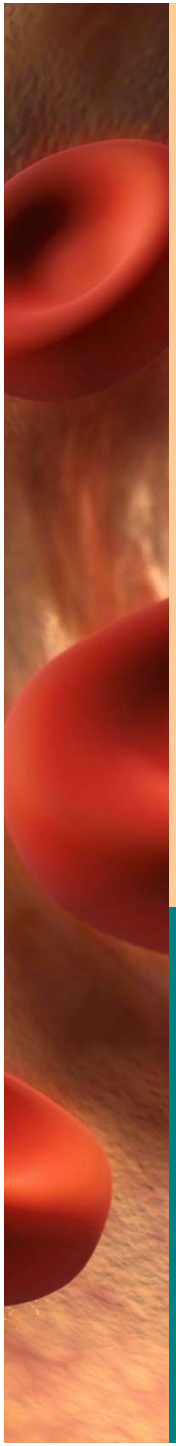


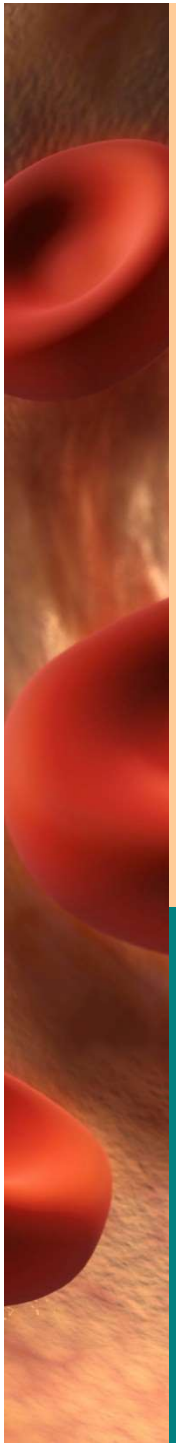
Idarucizumab

- Monoclonal antibody fragment
- Directed at dabigatran
- Binds the thrombin site 350X > thrombin
- NEJM 2017
  - Multicenter, prospective
  - Improved bleeding parameters based on TT or ecarin clotting time
  - Normal hemostasis (93.4%)
  - Low rate of adverse events



Rivaroxaban: Xa inhibitor

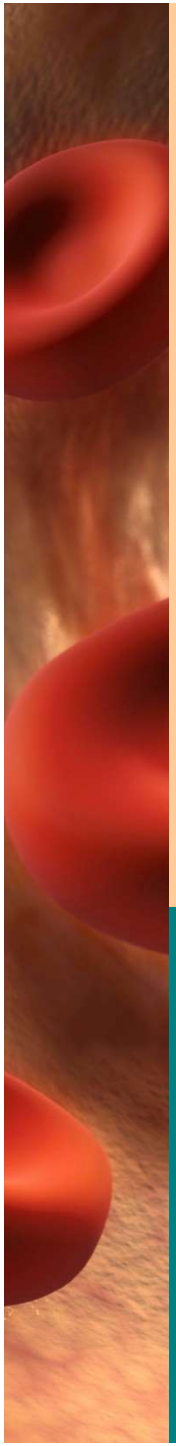
- Approved for VTE prophylaxis after joint replacement, stroke prevention in A-fib and VTE treatment
- No thrombin inhibition (differs from LMWH)
- T1/2: 3 -9 hrs
- No monitoring: *Anti Xa level must be calibrated to local drug specific reference
- Only PCC has been studied at 50 u/ kg
- Andexxa- andexanet alfa, FDA approved reversal agent



Reversal Summary

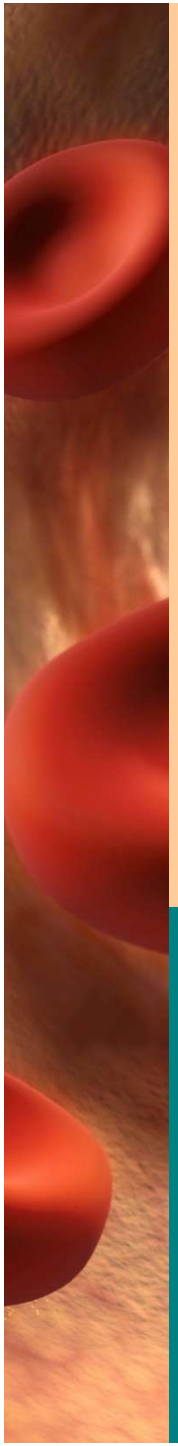
- Coumadin
  - IV vitamin K (10mg) + PCC
    - PCC dose is INR based (25-50 U/kg)
- ASA & Plavix
  - ddAVP 0.3 mcg/kg IV + ? platelets
    - ddAVP alone or no reversal is an option
- DTI (dabigatran)
  - Idarucizumab (2.5-5 g),PCC (50 U/kg), dialysis
- Xa inhibitor (rivaroxaban)
  - PCC (50 U/kg)

Questions?



Trauma Resuscitation

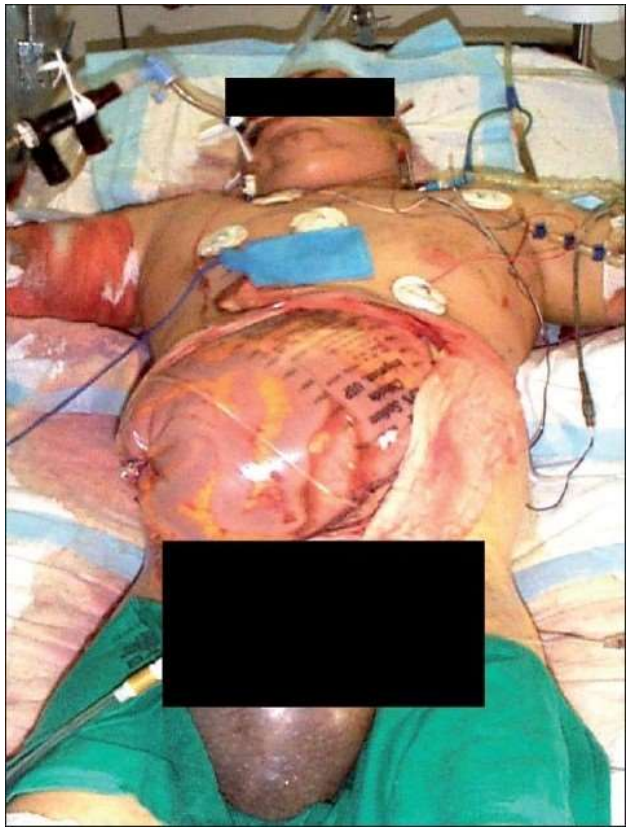
- Leading cause of death in those < 44 years of age
  - ~220,000/yr in US
- Hemorrhage = 30-40% of preventable deaths
- Goal to control bleeding, restore lost blood volume and regain tissue perfusion and organ function



Historical Trauma Resuscitation

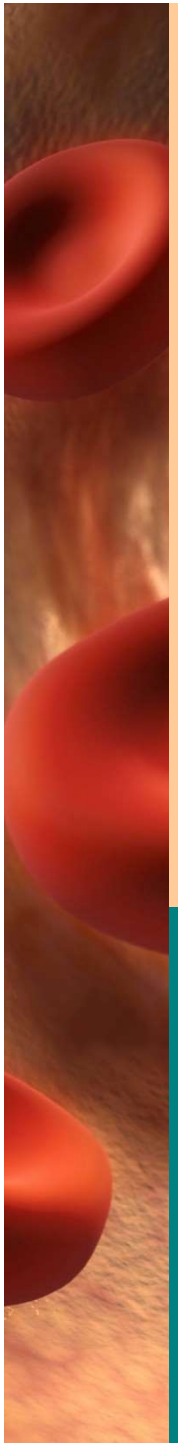
- Fluid boluses used indiscriminately to maintain normal blood pressure
- Blood components given randomly whenever directed by laboratory values

Over-resuscitation



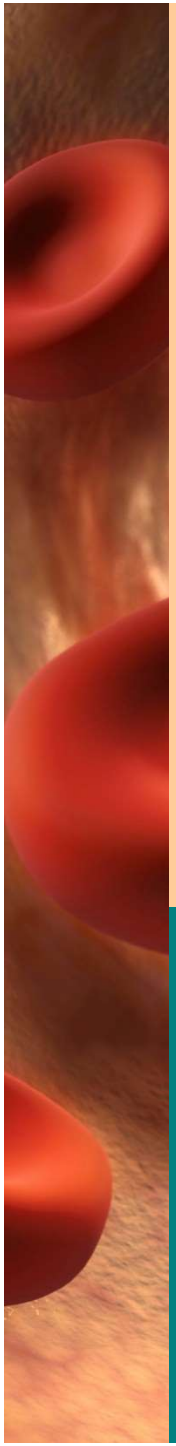
- Abdominal compartment syndrome (ACS), Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Failure (MOF)
- Crystalloid > 1.5 liters in ED independent risk factor for mortality
  - > 70 years old (OR 2.89)
  - Non elderly patients (OR 2.09)
- High volume (> 3 liters), > 70 years OR 8.61

J Trauma, 2011



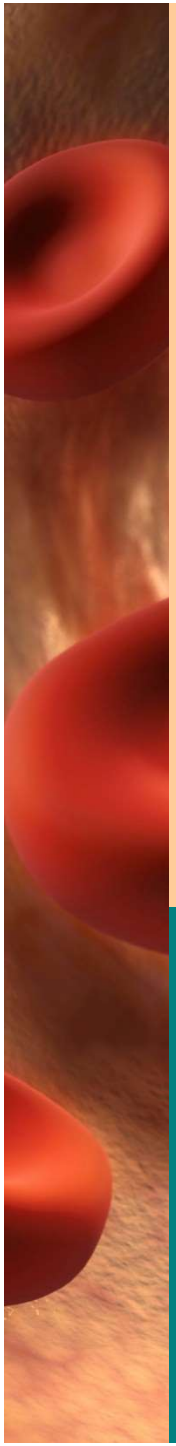
Hemostatic Resuscitation

- Rapid correction of hemostasis-impairing factors
- Balanced combination of blood products
  - Resembling whole blood
  - Avoid dilutional coagulopathy
  - 1:1:1 ratio of platelets, plasma and PRBCs



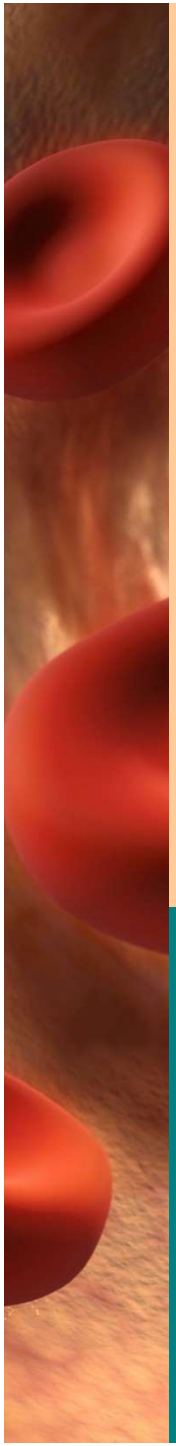
Goals of Hemostatic Resuscitation

- Reverse hypothermia and acidosis
- Limit crystalloid load
- Use blood components in proportion resembling whole blood
- Reverse fibrinolysis associated with massive hemorrhage
- Achieve this balanced ratio within the first 6 hours
  - Hemorrhagic deaths occur within first 2.5 hours



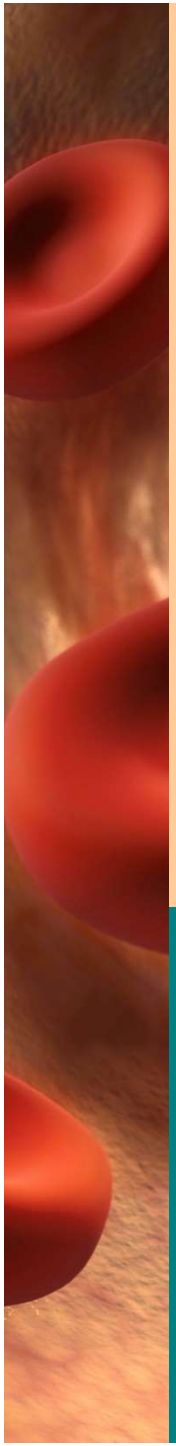
Rationale

- Aggressive resuscitation with crystalloid leads to hemodilution and coagulopathy
- 75% of the crystalloid volume distributes into the extravascular space
- Crystalloids do not contribute to oxygen transport and may actually decrease oxygen-carrying capacity with dilution
- Crystalloids may exacerbate acidosis (NS)



Current Practice

- The 10th edition of the Advanced Trauma Life Support (ATLS) course made content changes related to resuscitation strategies.
  - Removed the phrase, "aggressive resuscitation" and now advocates for *permissive hypotension* before the control of bleeding
  - Suggests less crystalloid use (1 L instead of 2) and early use of plasma and platelets in patients that require massive transfusion or in those with significant anticipated blood loss



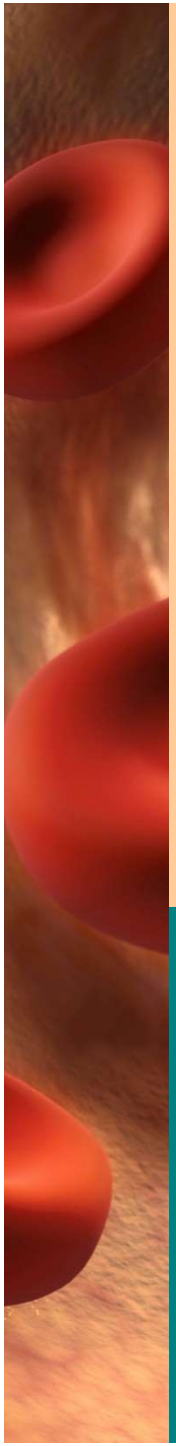
Permissive hypotension

- Target MAP 50-60
- Used until bleeding is controlled surgically
- RCTs showed no difference in mortality, fewer blood products used, decreased coagulopathy

Dutton et al. *J Trauma.* 2002.

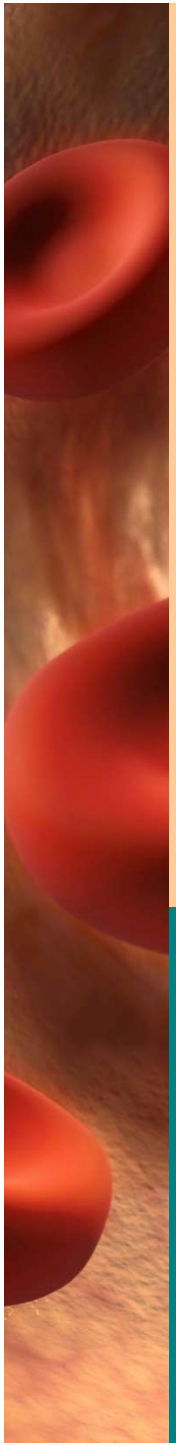
Morrison et al. *J Trauma.* 2011

Schreiber et al. *J Trauma Acute Care Surg.* 2015



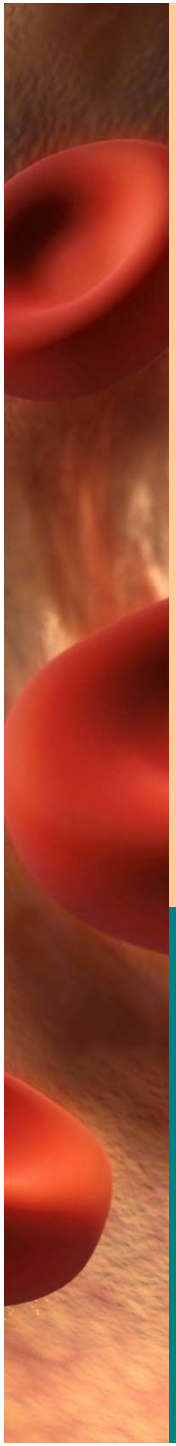
Evidence for specific strategies

- PROMMTT study (*JAMA Surg*, 2013)
  - Multicenter, prospective observational cohort study
  - 905 patients enrolled (transfused ≥ 3 units PRBCs)
    - Mortality of 25% and concentrated in first 6 hours
    - Any transfusion was associated with increased mortality
  - No pattern to transfusion- authors did not direct, merely observed
  - These data suggested an association between earlier and higher ratios of plasma and platelets with a decrease in hospital mortality
    - In patients with substantial bleeding
    - 1:1:1 was superior to 1:1:2



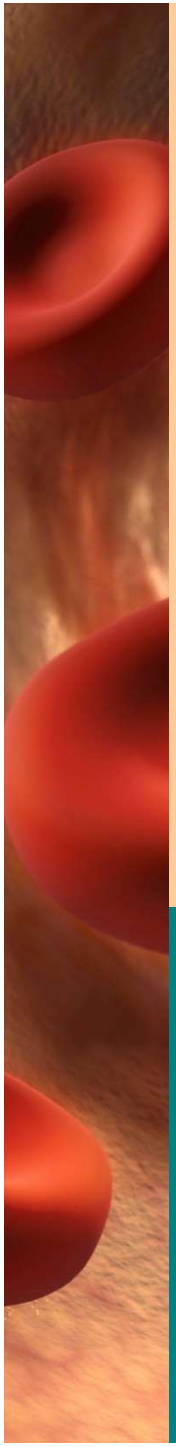
Evidence for specific strategies

- PROMMTT study (*JAMA Surg*, 2013)
  - Must use consistent ratios from the beginning
  - Thawed or liquid plasma was necessary
  - Routine practice of using FFP and platelets in response to lab values was associated with a worse outcome



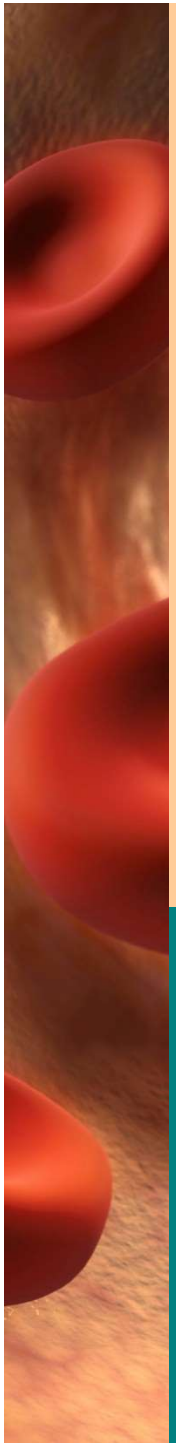
Evidence for specific strategies

- PROPPR trial (*JAMA*, 2015)
  - Multicenter, RCT – 12 sites
  - 680 patients, exception from informed consent
  1. 1:1:1 plasma:platelets: PRBC
  2. 1:1:2 plasma:platelets:PRBC
  - Inclusion criteria
    - Highest activation
    - Age ≥ 15 or ≥ 50 kg
    - Received from scene
    - Received at least 1 unit of any product within first hour or pre-hospital
    - Predicted to receive MTP by an ABC score ≥ 2 or attending surgeon judgement



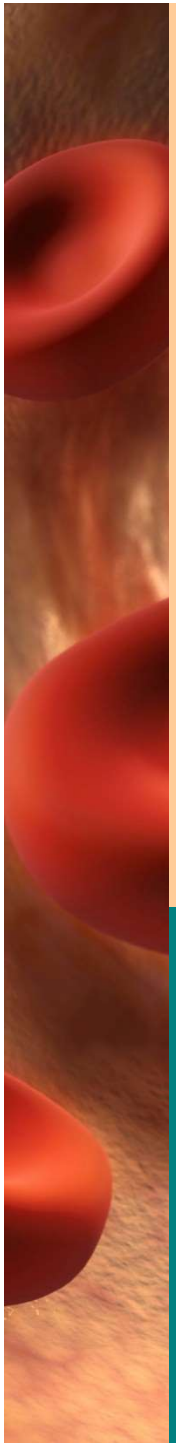
Evidence for specific strategies

- PROPPR trial (*JAMA*,2015)
  - No difference in baseline criteria
  - No difference in mortality
  - FFP:RBC and PLT:RBC ratios were inconsistent for first 24 hrs across centers, within centers and within a single patient's care



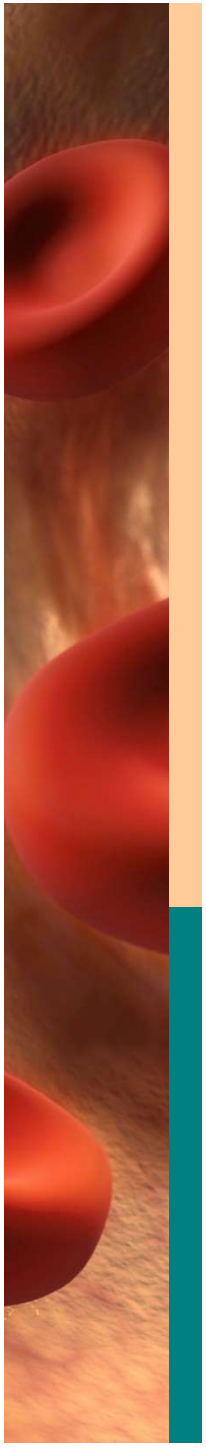
Evidence for specific strategies

- PROPPR trial (*JAMA*,2015)
  - Exsanguination decreased in 1:1:1 group (9.2% vs 14.6%, p=0.03)
  - Hemostasis increased in 1:1:1 group (86% vs 78%, p=0.006)
  - No difference in 23 pre-specified complications
    - > 80% had complication, but this was not different between the two groups
  - Use 1:1:1 at beginning and transition to lab-guided replacement after hemorrhage control achieved



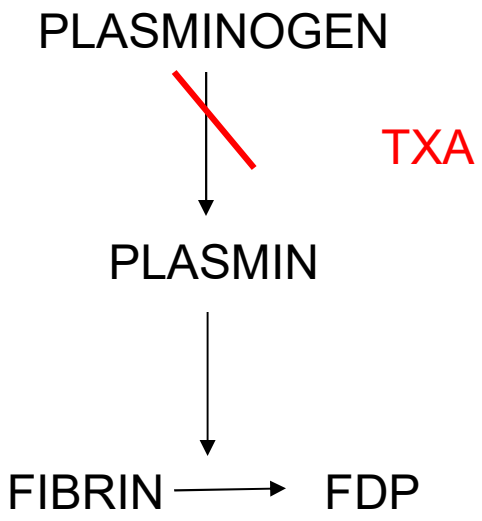
Criticism of PROMMTT and PROPPR

- Survivor bias
  - Patients that live long enough to receive extra blood products (and achieve ratio) are more likely to survive
- Penetrating trauma was highly prevalent (33% in PROMMTT)
- The RCT was underpowered, unblinded, and the majority never achieved the target ratio

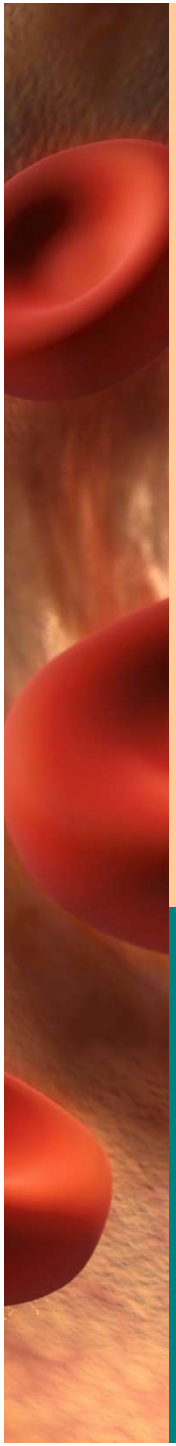


Tranexamic Acid (TXA)

- Cochrane Review: TXA ↓ need for transfusion in elective surgery (RR 0.61 95% CI 0.53-0.7)
- CRASH-2 Trial
  - 20,211 patients, 40 countries
  - ↓ all cause mortality
  - ↓ death due to bleeding
  - NO difference in % transfused
  - NO difference in total transfusion
- Pre-hospital TXA
  - ↓ mortality (HR 0.35, p< 0.001)
  - ↓ volume of transfusion
  - ↓need for MTP



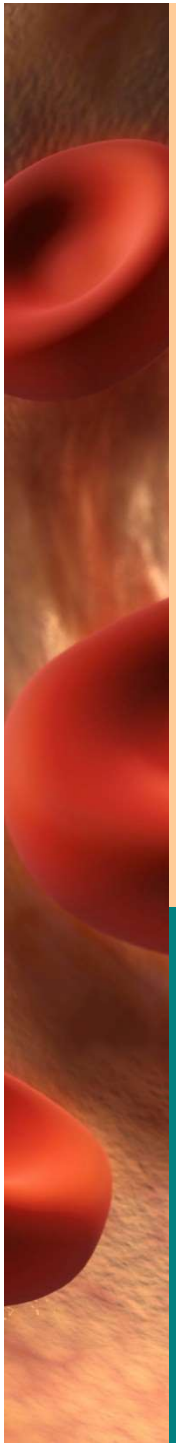
Roberts et al. *Health Techno Assess. 2013*
Shimena et al. *Ann Surg*. 2021



Hypocalcemia

- Calcium is critical for cardiac contractility, vascular tone and CLOTTING
- 59-97% of MTP experience hypocalcemia
- 71% have severe hypoCa+2 (iCa< 0.9) and received more blood products (34 vs 22, p< 0.001)

Giancarellia A et al, *JSR*, 2016
Hall C et al, *Transfusion,* 2021
Moore HB, *JTACS*, 2020



Damage control resuscitation

- Assessment of core temperature
- Limitation of excessive crystalloid use
- Activate the MTP and start with 6 units whole blood in ED
- Tranexamic acid 2 grams IV bolus
- Continue further transfusion in 1:1:1 ratio of FFP, platelets and RBCs
- Prevention and treatment of hypothermia, hypocalcemia, and acidosis (lethal diamond)
- Cryoprecipitate should be given if fibrinogen level < 100
- Hypotensive resuscitation strategies in the absence of neurotrauma
- Rapid control of surgical bleeding

ACUTE CARE SURGERY
UNM

Questions?