Massive Hemorrhage Protocols: What is the science?

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Transfusion Camp May 2021

Disclosures

- Funding from Canadian Blood Services, Octapharma, and Defense Research and Development Canada for research only

Objectives

1. Understand the pathophysiology of the coagulopathy in different bleeding patients – it's complicated!
2. Learn the science behind the key components of a massive hemorrhage protocol
3. Key things you need to remember for every massively bleeding patient

What are you treating? Why do we do what we do?
What are key things you need to provide to the patient?

“The acute coagulopathy of trauma/shock”

“Shock-induced endotheliopathy”

Pathophysiology of the coagulopathy in bleeding patients

Probably each patient is highly different

Johansson et al. Crit Care 2017;21:25.

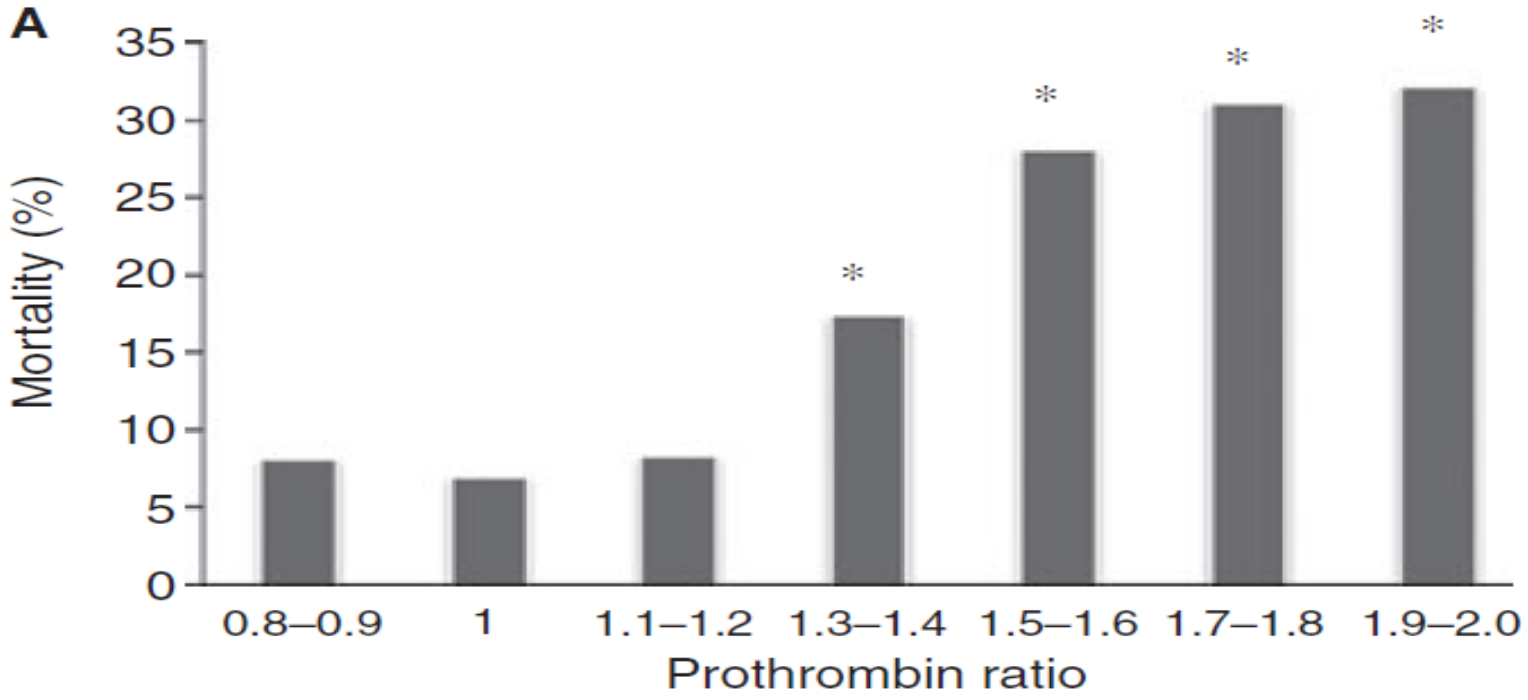
Coagulopathic before resuscitation starts

- Observational study of 1,088 trauma patients
- Defined coagulopathy as:
  - PT>18, aPTT>60, or TT>15
- 24% met this definition on arrival to the trauma room before undergoing dilution from RBCs and crystalloid
- Coagulopathy associated with higher mortality rates
  - 46% with vs. 11% without coagulopathy died ($p<0.001$)
- No association between the amount of fluids and the development of coagulopathy

Brohi K, et al. *J Trauma.* 2003;54(6):1127-1130

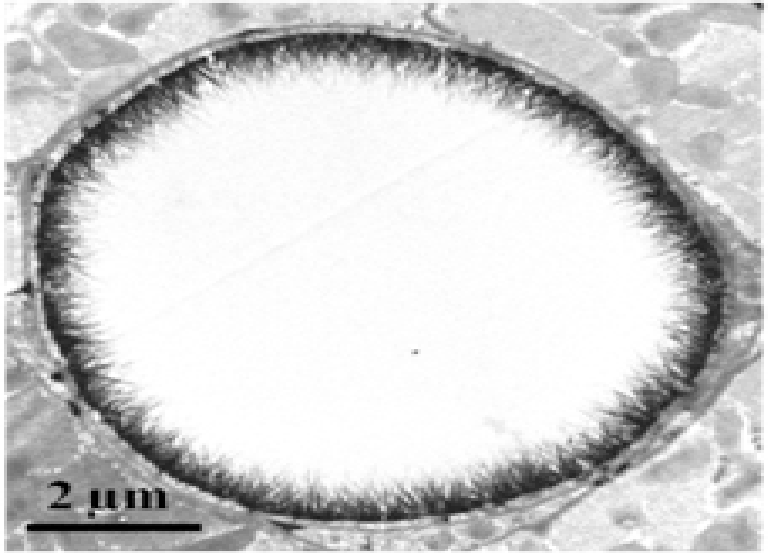
Mortality increases at >1.2

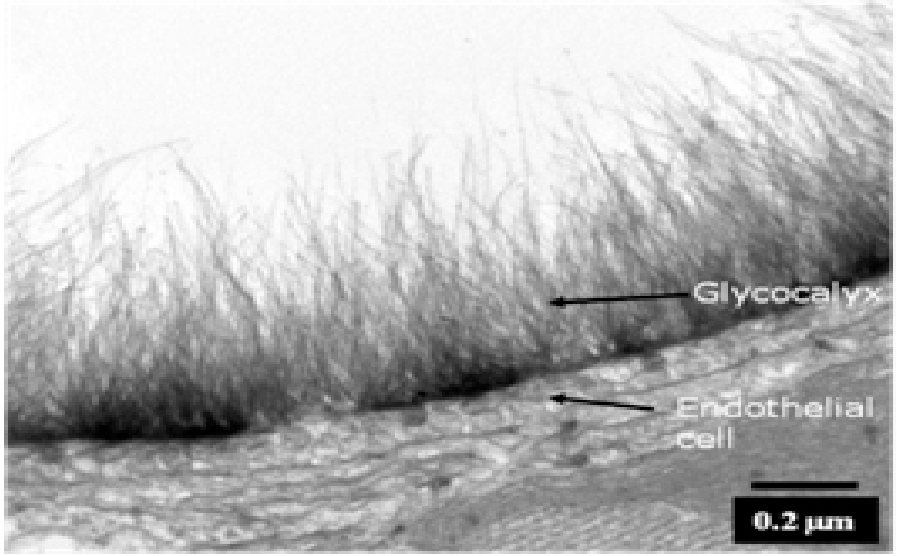
Firth D, et al. J H and T 2010; 8: 1919-25



- **Baseline INR tells you how badly injured your patient is**

Problem #1 - Degradation of the glycocalyx on endothelial cells





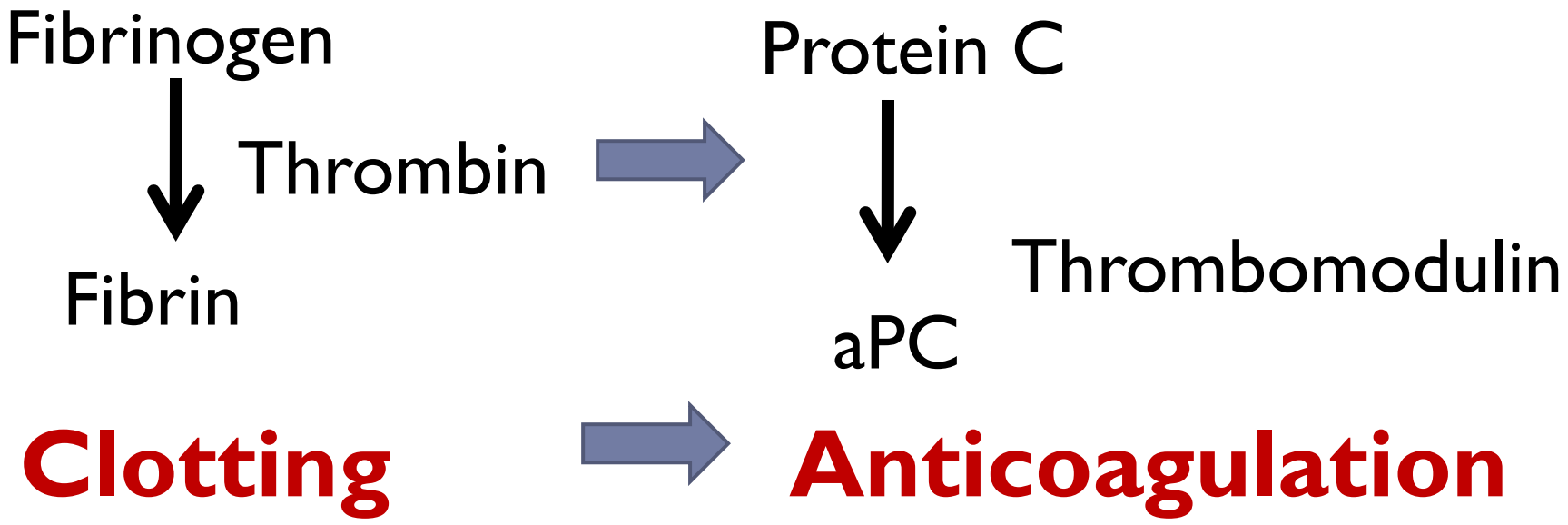
Exposes thrombomodulin

Release of natural heparins from glycocalyx

Johansson et al. Ann Surgery 2011; 254: 194-200

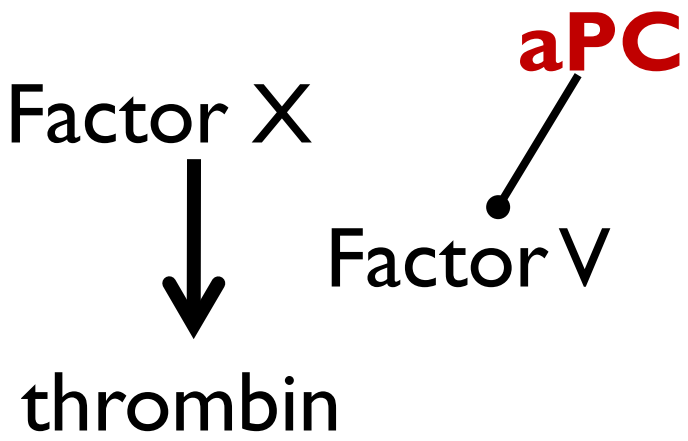
Ostrowski et al. J Trauma Acute Care Surg 2012;73:60-6.

Problem #2: Thrombin is distracted



Brohi et al. J Trauma 2008 May;64(5):1211-7
Floccard et al. Injury 2012 Jan;43(1):26-32.

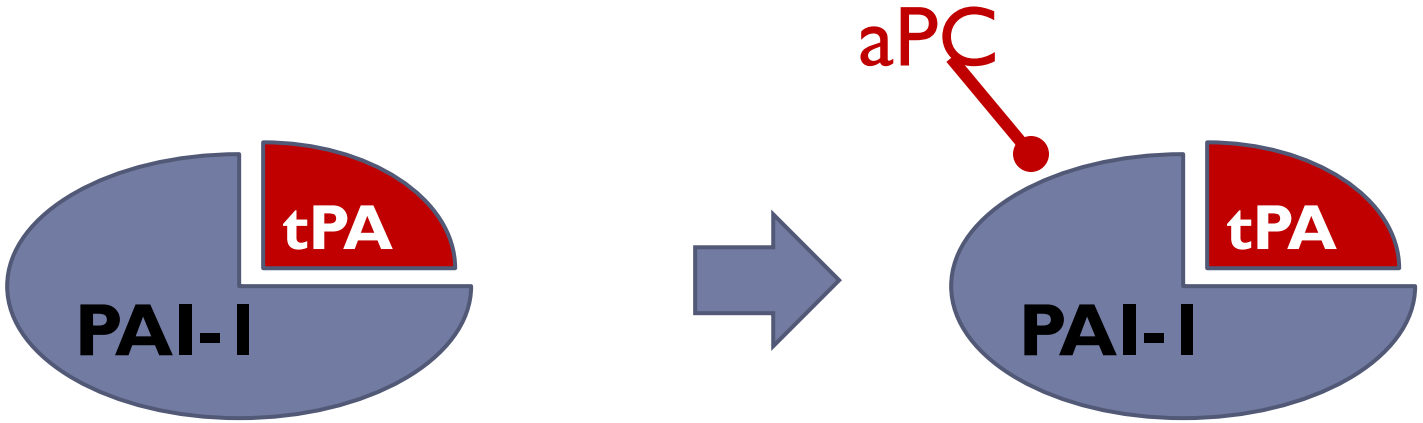
Problem #3: aPC cleaves factor V



Reduced thrombin generation

Jansen et al. J Trauma 201;7:S435-40.

Problem #4: “derepressed” t-PA by degrading plasminogen activator inhibitor

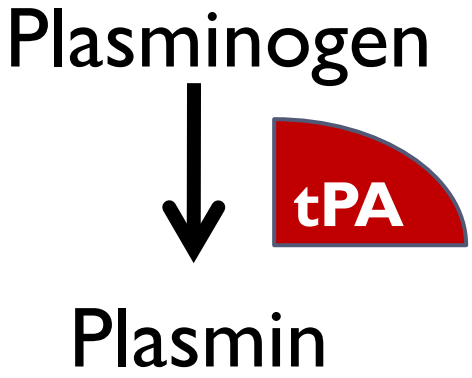


tPA under control

tPA out of control

Brohi et al. J Trauma 2008 ;64(5):1211-7
Floccard et al. Injury 2012;43(1):26-32

Problem #4: t-PA degrades fibrinogen



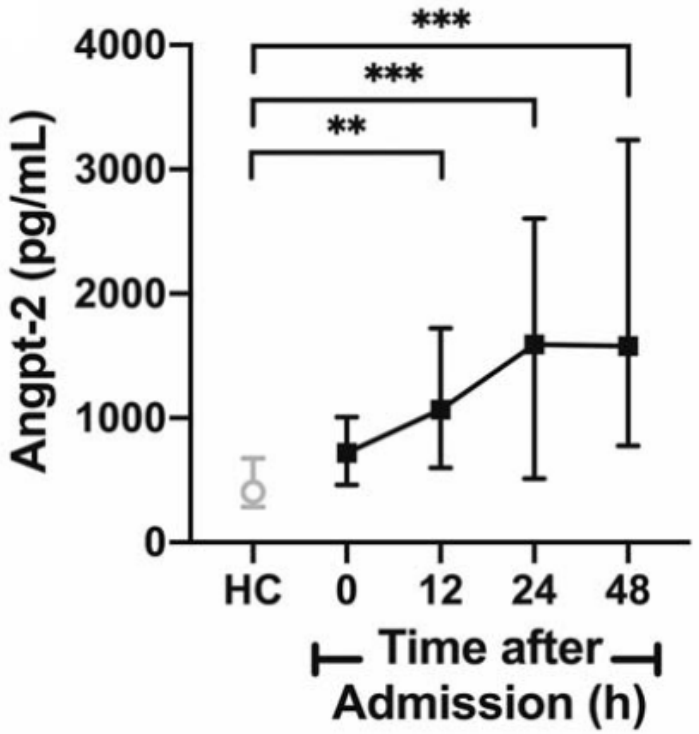
HYPERFIBRINOLYSIS

Fibrin(ogen)olysis

Loss of a protein involved in primary & secondary hemostasis

Problem #5: Endothelial cells activated

Endothelial activation leads to release of angiopoietin-2



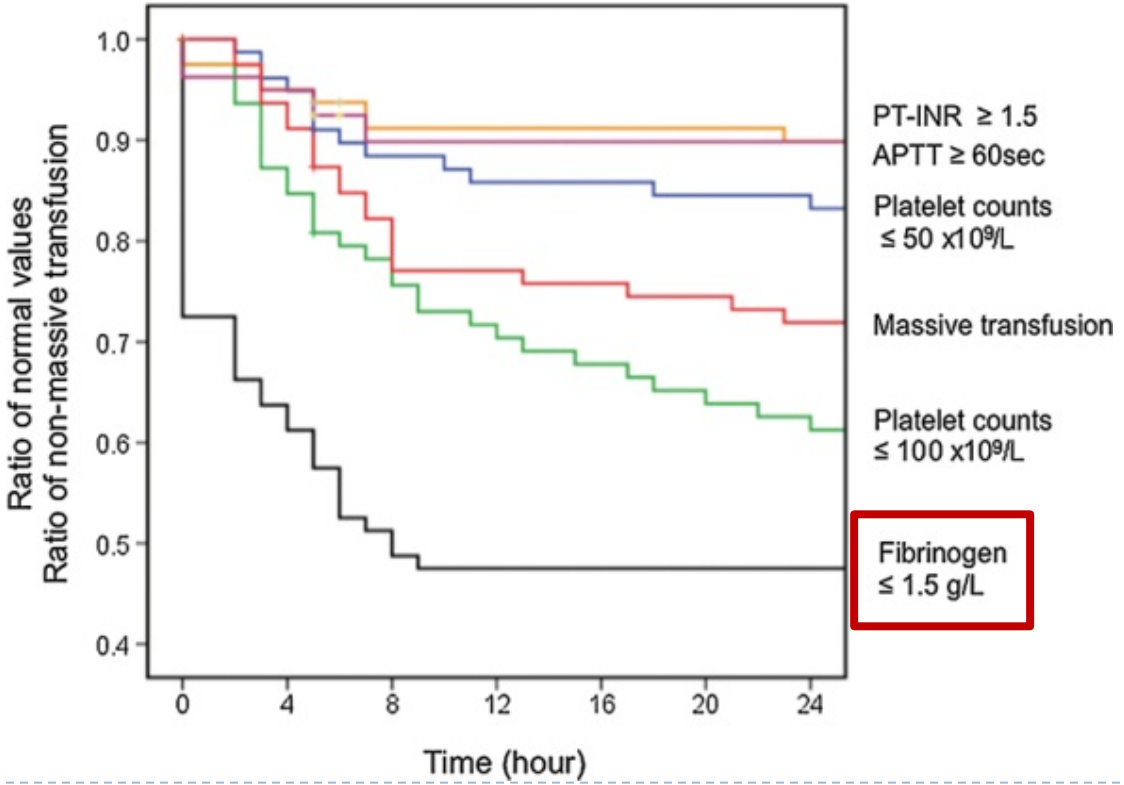
Uhlich RM, Shock. 2020 Dec;54(6):703-709

Before resuscitation starts

- Autoheparinization
- Upregulated thrombomodulin
- Activated protein C
- Depletion of factor V
- Uncontrolled tPA
- Hyperfibrinolysis
- Activated endothelial cells

Other coagulation factors maintained

Time from arrival in ED to critical levels



Gando & Hayakawa 2016

Postpartum hemorrhage – multiple pathologies?

Situation	Coagulation disorder (not confirmed)
PIH/HELLP Syndrome	Similar to DIC (reduced PLTs, fibrinogen, increased D-Dimers)
Amniotic fluid embolism	As above
PPH from atony/laceration	Consumption problem Fibrinogen <2 g/L concerning
Abruption	Consumption problem
Congenital factor deficiency	Single factor (previously undiagnosed; possibly as high as 20%)

GI Bleeds – Coagulopathy uncommon

	Liberal policy (n=533)	Restrictive policy (n=403)
Medications and fluids		
Proton pump inhibitor (pre-endoscopy)	270 (53%)	225 (56%)
Iron (oral or intravenous)‡‡	47 (9%)	43 (11%)
Any intravenous fluids§§	412 (81%)	297 (75%)
Colloid volume in 24 h	0·2 (0·6)	0·1 (0·4)
Crystalloid volume in 24 h	1·6 (1·4)	1·9 (1·7)
Platelets¶¶	13 (2%)	13 (3%)
Fresh frozen plasma¶¶	22 (4%)	24 (6%)
Cryoprecipitate¶¶	1 (<1%)	2 (<1%)

Jairath et al. TRIGGER. Lancet 2015;386(9989):137-44

- The goal of the MHP is to put in place a protocol to ensure massively hemorrhaging patients receive state-of-the-art care to achieve the best possible outcomes
- Uniform, high quality, standardized care

Science behind the MHP

More than just an order for a ratio

T^7

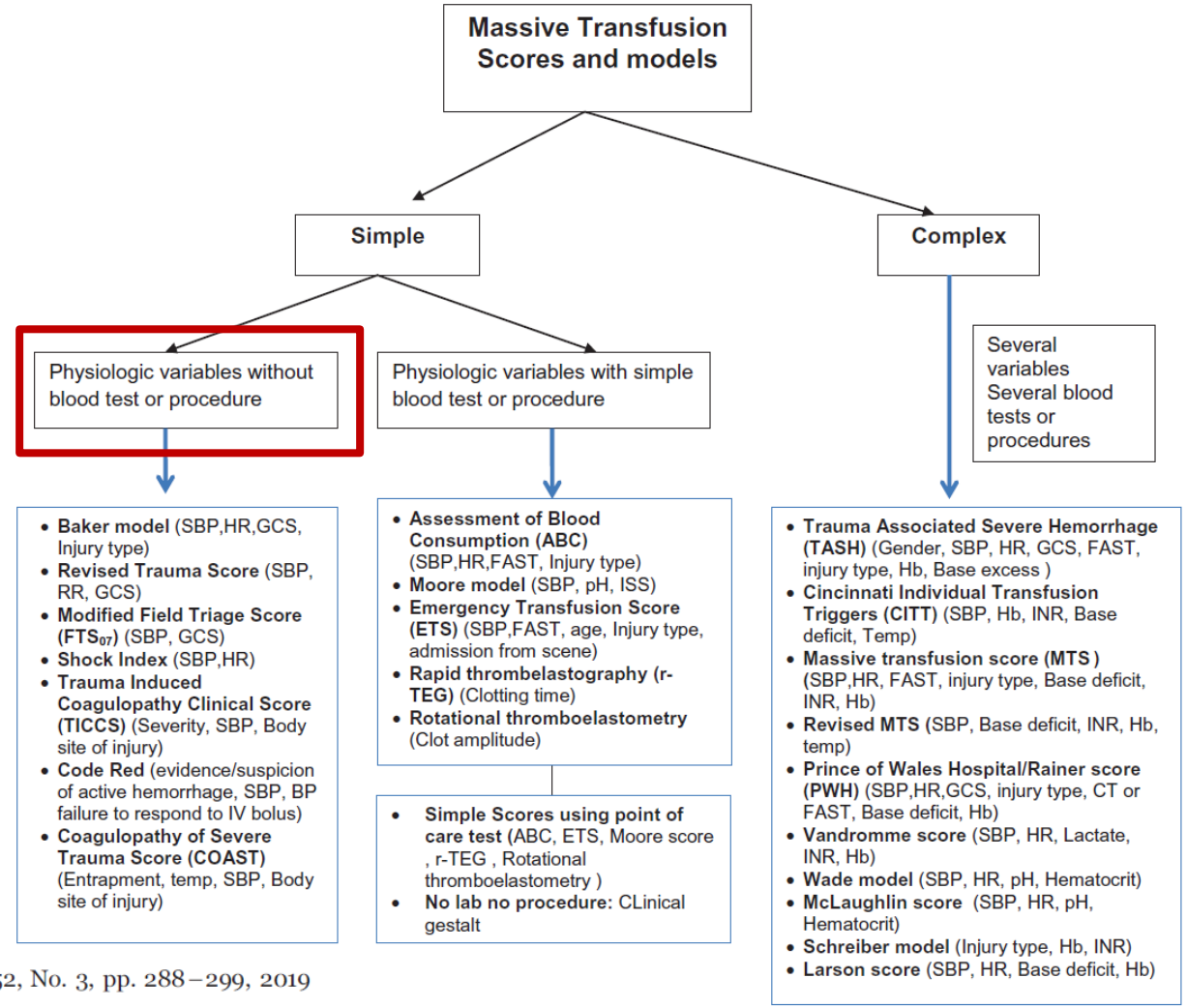
	T
1	**Triggering**
2	Team (and Training)
3	Testing
4	Tranexamic acid
5	Temperature
6	Transfusion
7	Termination

Triggering – Balance under and over activation

- Triage
  - MHP are activated in highly stressful situations
  - There are no "scores" that work well
  - Overtransfusion common (MHPs almost never needed for GI or ENT bleeds)
- Under-triage?
  - Could be catastophic: a patient dying of haemorrhagic shock
- Over-triage?
  - More than 50% of activations = overtriage
  - Put patient at risk of overtransfusion (the risk of rapid blood delivery) of RBCs "because they arrived"
  - TACO and other transfusion complications
  - Blood wastage

Morse BC, et al. American Surg 2012; 78: 679-684.

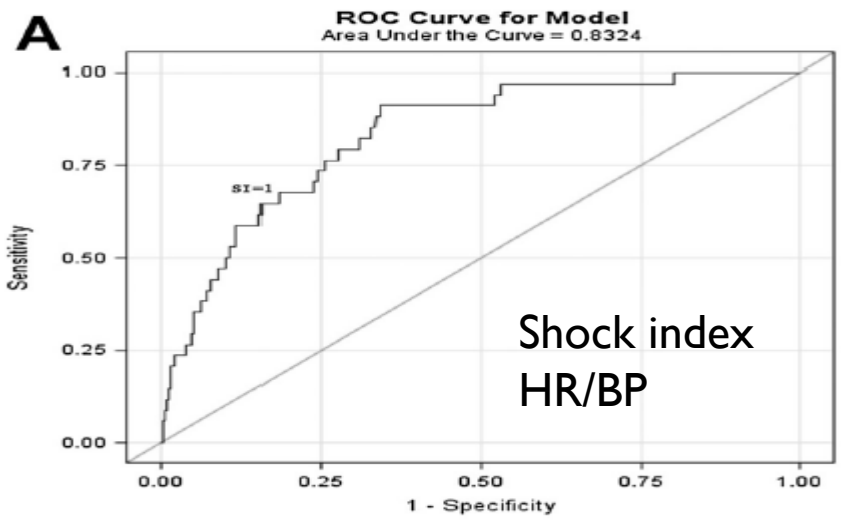
It would be better not to need lab tests



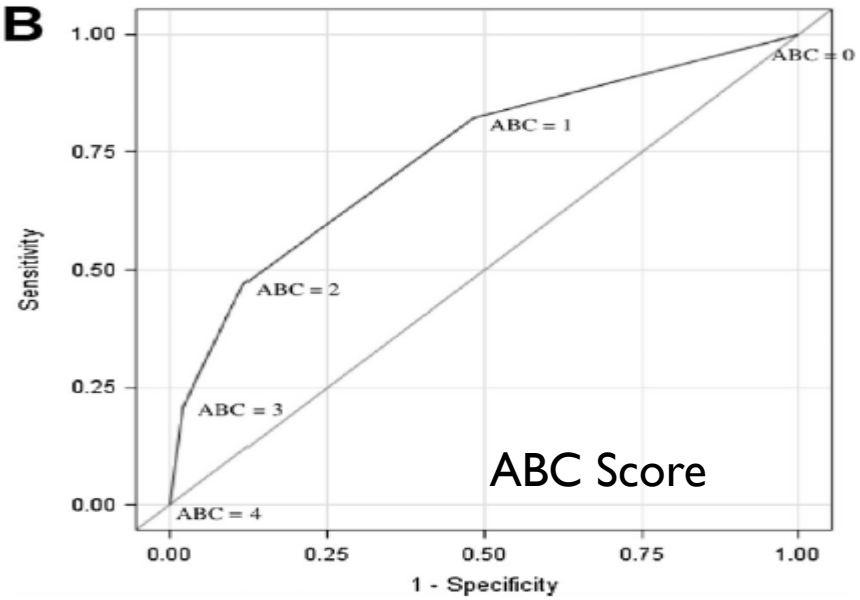
Clinician gestalt is no better either!

SHOCK, Vol. 52, No. 3, pp. 288–299, 2019

Shock Index vs ABC score to predict MT



SI≥1: Sens 68%, Spec 81%



ABC≥2: Sens 47%, Spec 89%

Schroll et al. Injury 2018 Jan;49(1):15-19

Speed to Pack 1

Arrival to activation 9 mins (IQR 3, 20) & activation to delivery of cooler 8 mins (IQR 5, 11)

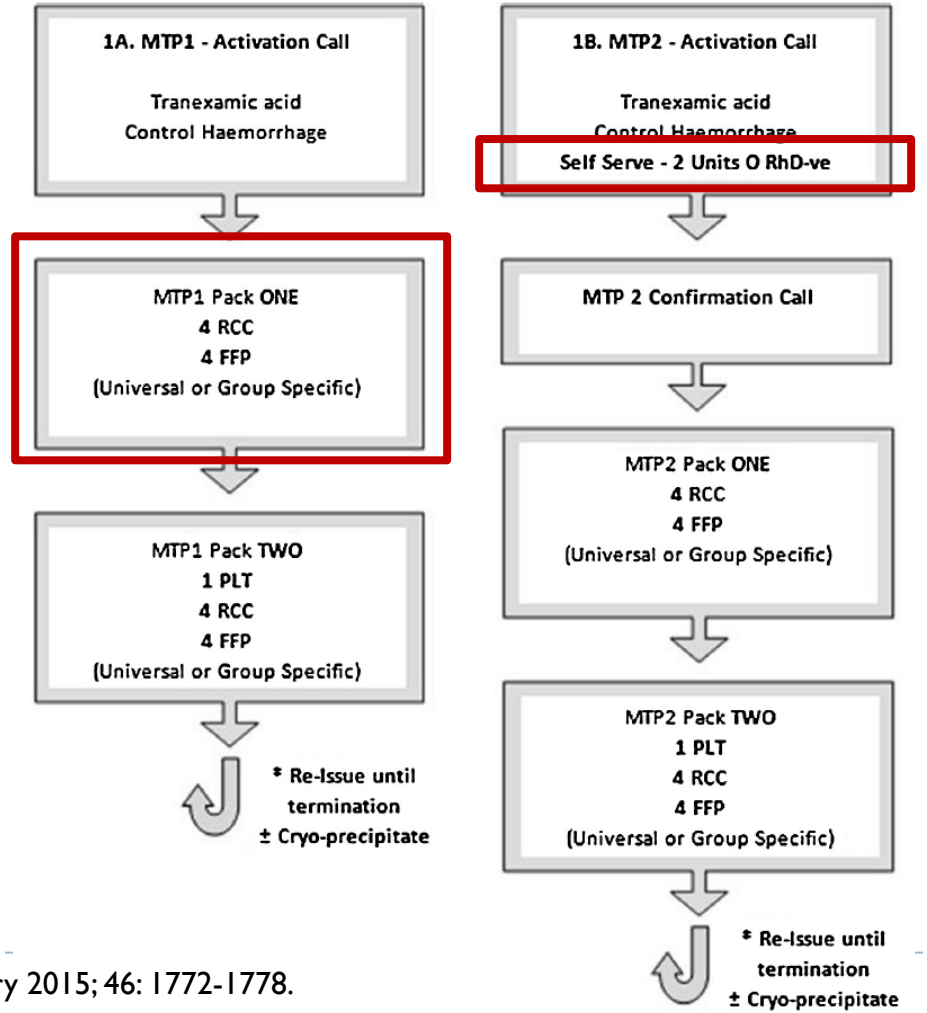
680 patients from PROPPR study = severe traumas

Each minute delay to 1st pack increased risk of death by 5%

Multivariate regression predicting 30-day mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01–1.09	0.016
Anatomic injury severity (ISS)	1.05	1.03–1.06	<0.001
Disturbed arrival physiology (w-RTS)	0.61	0.53–0.69	<0.001
Randomization group (1:1:2)	1.46	0.92–2.29	0.102
Resuscitation Intensity (units)	1.03	0.60–1.44	0.184

J Trauma Acute Care Surg. 2017 July ; 83(1): 19–24.

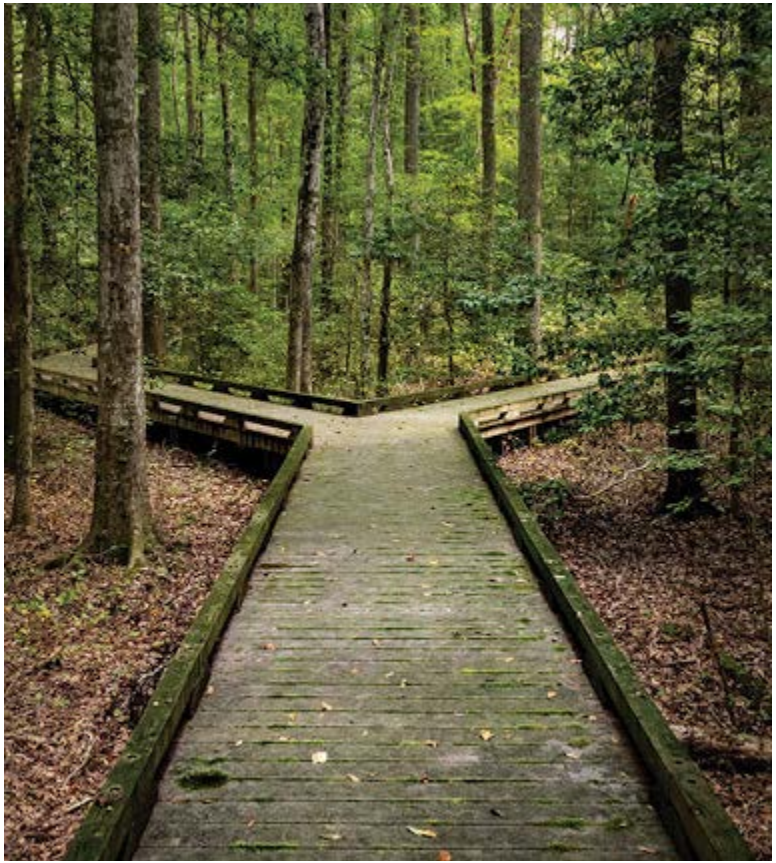


Activation from 24% to 13% of traumas

Plasma wastage

- Boutefnouchet T et al. Injury 2015; 46: 1772-1778.

4 UNITS UNMATCHED RBCs



CODE TRANSFUSION

T^7

	T
1	Triggering
2	**Team**
3	Testing
4	Tranexamic acid
5	Temperature
6	Transfusion
7	Termination

Team training matters

- Simulations have been successfully employed for training in obstetrical hemorrhage, pediatric hemorrhage, and trauma
- A systematic review of 33 studies involving 1,203 residents found simulation was associated with improved provider behavior and patient outcomes.
- A systematic review of 13 studies of trauma team training, both non-technical skills and team-based performance improved
- Improvements from simulation extend to improved outcomes in trauma and cardiac arrest care

T^7

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Two ways to test

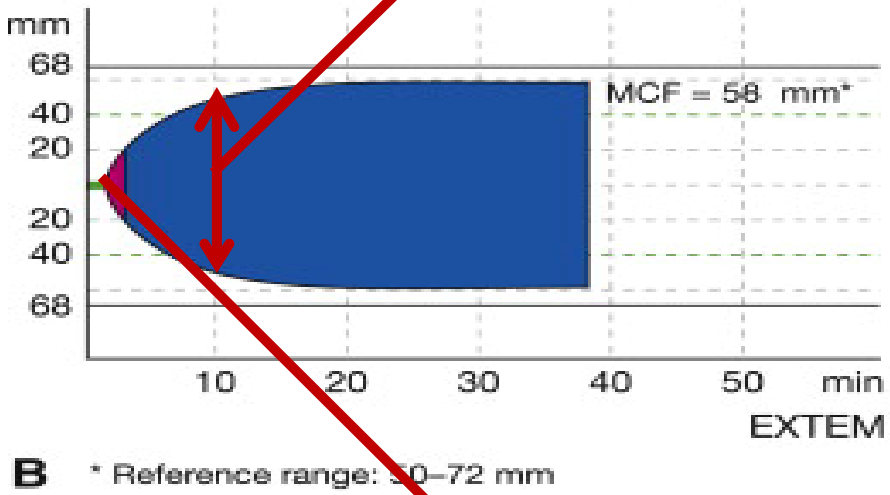
INR, PTT, and fibrinogen done in the laboratory on a centrifuged plasma sample

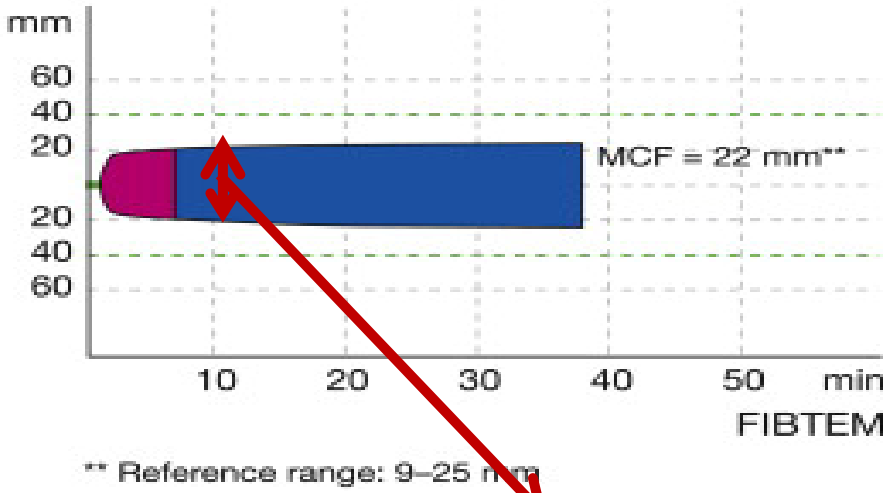
vs.

Viscoelastic testing

ROTEM 101 (TEG is another platform)

MCF<35 give platelets





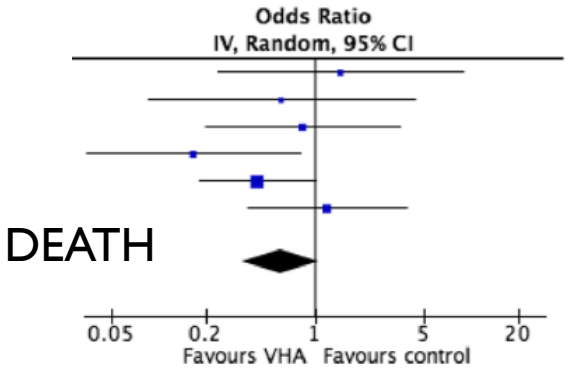
B * Reference range: 50–72 mm

** Reference range: 9–25 mm

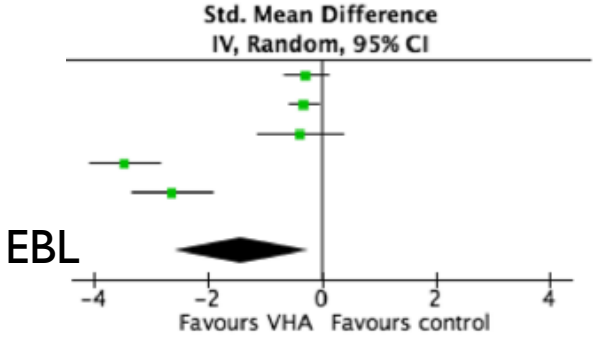
CT>90 give plasma

MCF<8-10 give fibrinogen 4 grams

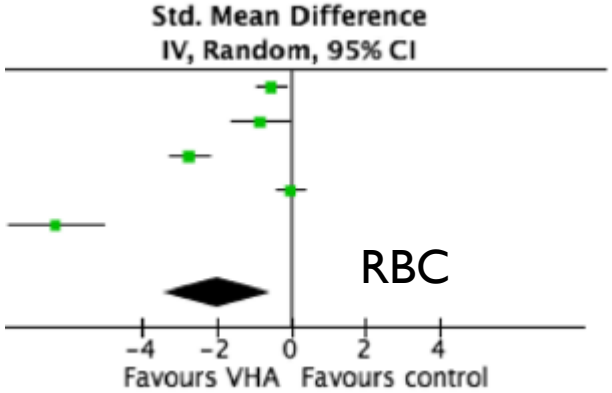
Systematic review – ROTEM/TEG vs. SOC



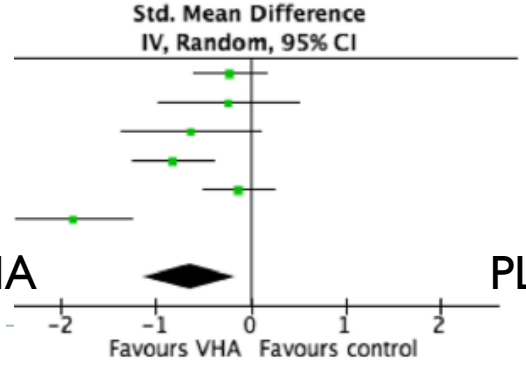
DEATH



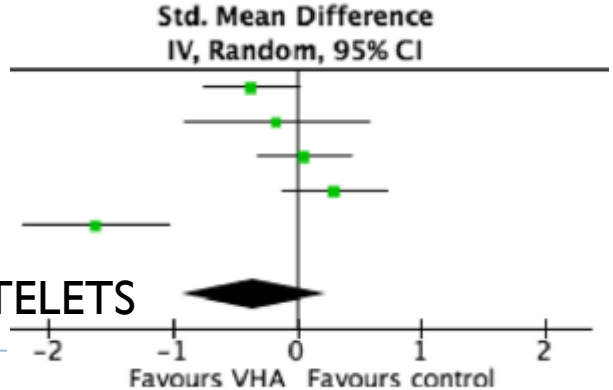
EBL



RBC



PLASMA



PLATELETS

Scand J Trauma Resusc Emerg Med. 2017;25(1):39.

ROTEM impact - Cardiac Surgery-related Hemorrhage Step-wedge cluster RCT (7402 patients)

Outcome	Relative Risk (95% CI)	P-value
Red cell transfusions	**0.91 (0.84, 0.98)**	**0.01**
Platelet transfusions	**0.81 (0.72, 0.91)**	**<0.001**
Plasma transfusions	1.04 (0.91, 1.18)	0.57
Cryoprecipitate or fibrinogen concentrate transfusions	1.19 (0.89, 1.59)	0.24
Major bleeding	**0.86 (0.75, 0.98)**	**0.02**
Major complications	1.01 (0.80, 1.26)	0.97

Karkouti et al. Circulation. 2016;1341152-1162

iTACTIC Trial (n=396) – negative trial

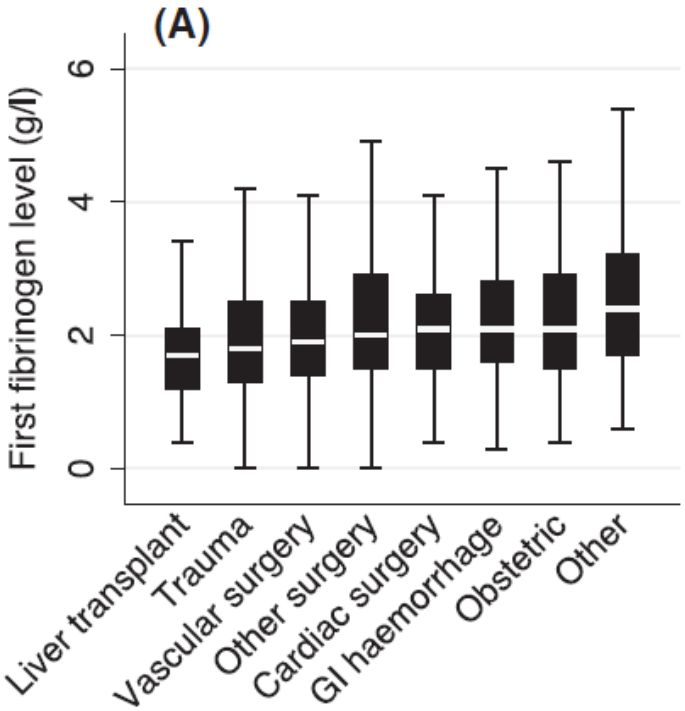
Table 2 Secondary outcomes for the intention-to-treat population

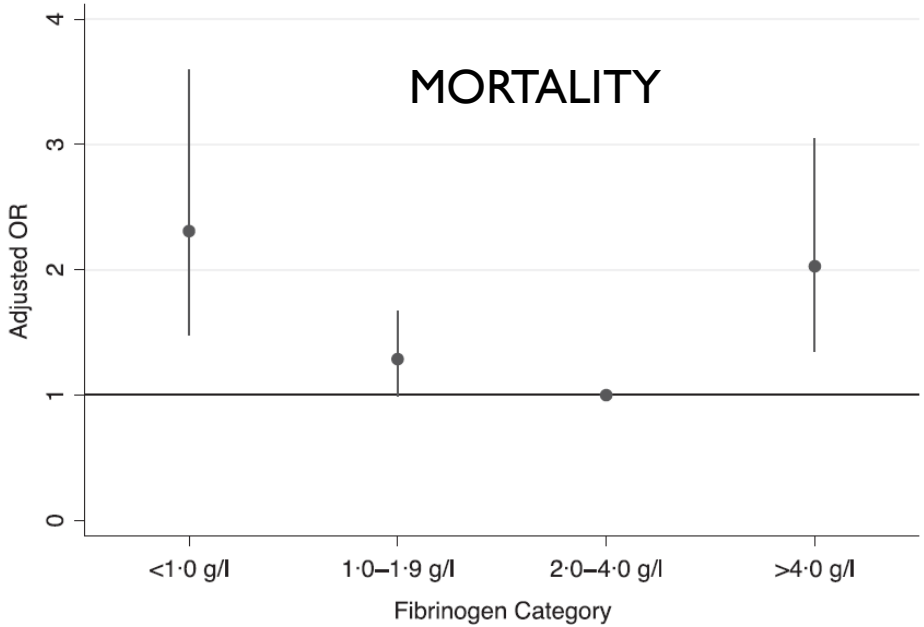
	CCT (*n* = 195)	VHA (*n* = 201)	Odds ratio (95% CI)	*p* value
Mortality at 6 h—no. (%)	22/195 (11%)	22/201 (11%)	0.97 (0.52–1.80)	0.915
Mortality at 24 h—no. (%)	33/195 (17%)	29/201 (14%)	0.83 (0.48–1.42)	0.495
Mortality at 28 days—no. (%)	55/194 (28%)	50/201 (25%)	0.84 (0.54–1.31)	0.435
Mortality at 90 days—no. (%)	56/177 (31%)	53/179 (29%)	0.91 (0.58–1.42)	0.678
Death from exsanguination—no. (%)	17/56 (30%)	13/51 (25%)	0.78 (0.34–1.82)	0.576
Died before haemostasis—no. (%)	24/54 (44%)	19/50 (38%)	0.77 (0.35–1.67)	0.505

Baksaas-Aasen K, Gall LS, Intensive Care Med. 2021 Jan;47(1):49-59.

And very few hospitals have viscoelastic testing at the bedside…

Fibrinogen levels in bleeding patients

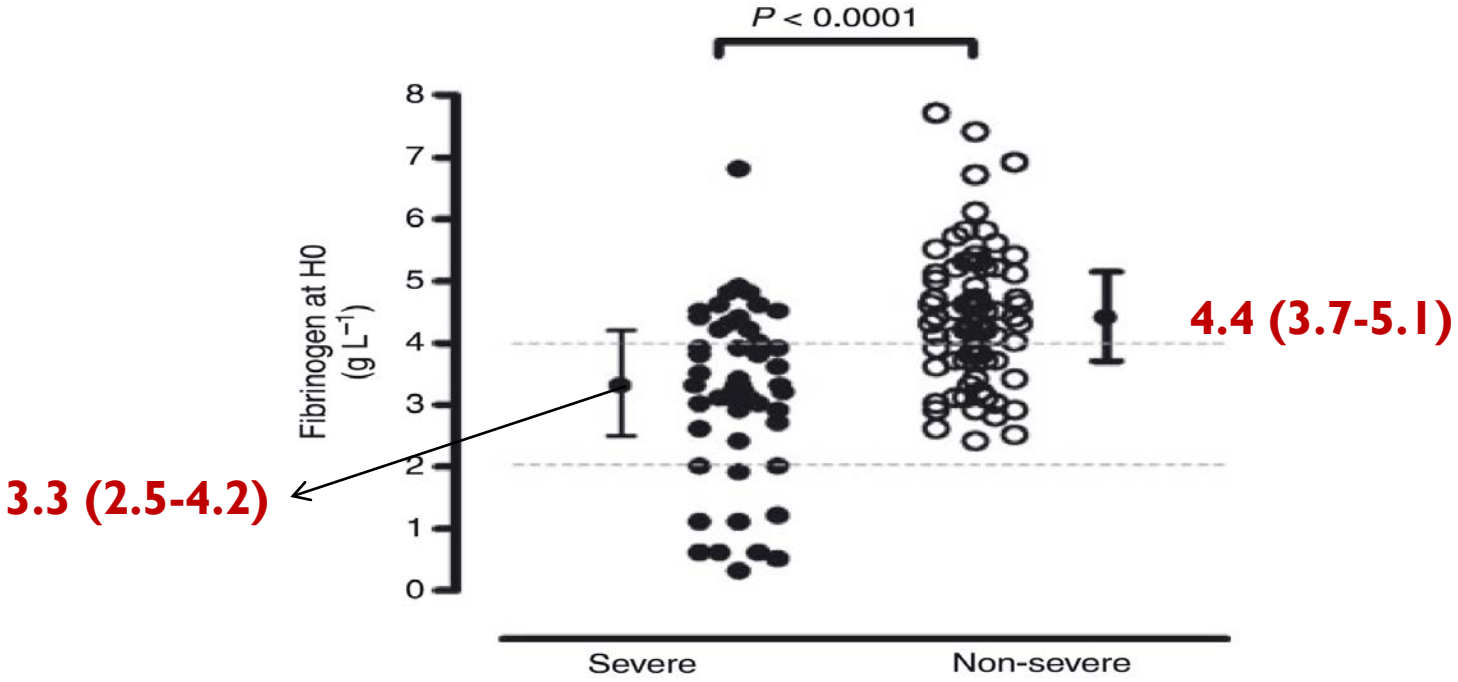




McQuilten ZK, Br J Haematol. 2017 Oct;179(1):131-141.

Fibrinogen<2.0 g/L and PPH

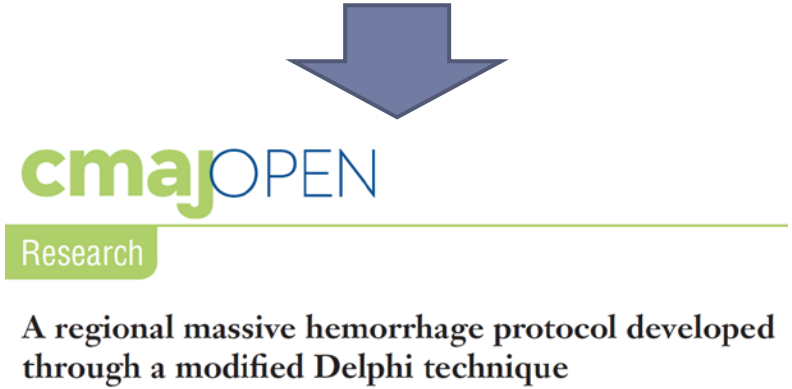
Women without bleeding have fibrinogens between 3.5-6.5



Charbit, et al. JHT 2006; 5: 266-73

Bottom line:

1. If you have access to point of care testing (TEG/ROTEM) – learn how to use it
2. If you don't (and most don't) – keep using standard lab tests
3. Order testing every 1 hour or every 4 RBCs
4. Standard panel = CBC, INR, fibrinogen, calcium, K, (PTT at baseline)



Callum JL, et al, CMAJ Open. 2019 Sep 3;7(3):E546-E561.

23. The protocol should state the minimum laboratory protocol resuscitation targets for transfusion: 1) hemoglobin > 80 g/L (RBC); 2) INR < 1.8 (plasma or prothrombin complex concentrates); 3) fibrinogen > 1.5 g/L (cryoprecipitate or fibrinogen concentrates); 4) platelets > 50 × 10^9/L; 5) ionized calcium > 1.15 mmol/L. Relevant transfusion targets can also be used if viscoelastic testing is performed.

cmajOPEN

Research

A regional massive hemorrhage protocol developed through a modified Delphi technique

Callum JL, et al, CMAJ Open. 2019 Sep 3;7(3):E546-E561.

T^7

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Antifibrinolytics: CRASH-2 trial

Shakur H, et al. *Lancet.* 2010; 376:23-32

- N=20,211 patients randomized to placebo vs. 1+1 gram of tranexamic acid
- sBP<90, HR>110, at risk for significant hemorrhage
- Tranexamic acid reduces death rate overall (OR 0.91) and death from bleeding (OR 0.85)
- Most effective in reducing risk of death from bleeding if given within the first hour from injury (OR 0.68)
- NNT to save 1 life = 1 in 67 (US $500)
- No increase in arterial or venous thromboembolic complications

WOMAN Trial (n=20,060)

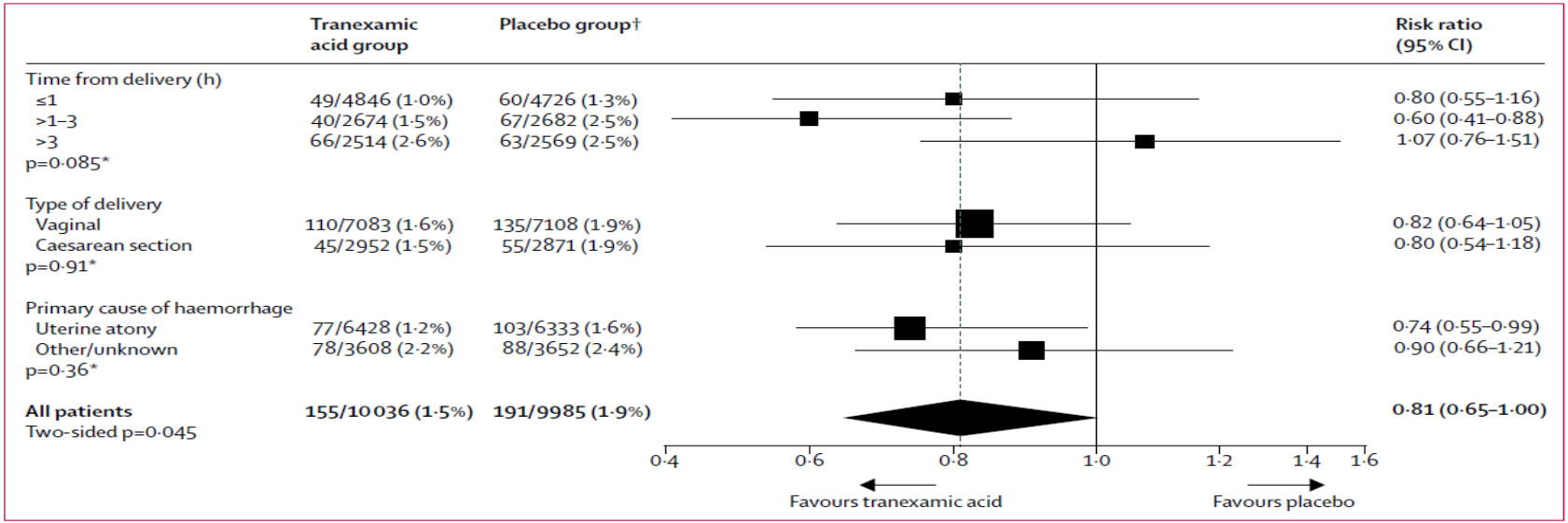


Figure 3: **Death from bleeding by subgroup**
*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

No difference in hysterectomy rates or TE complications

Published online April 26, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30638-4

TXA Delay

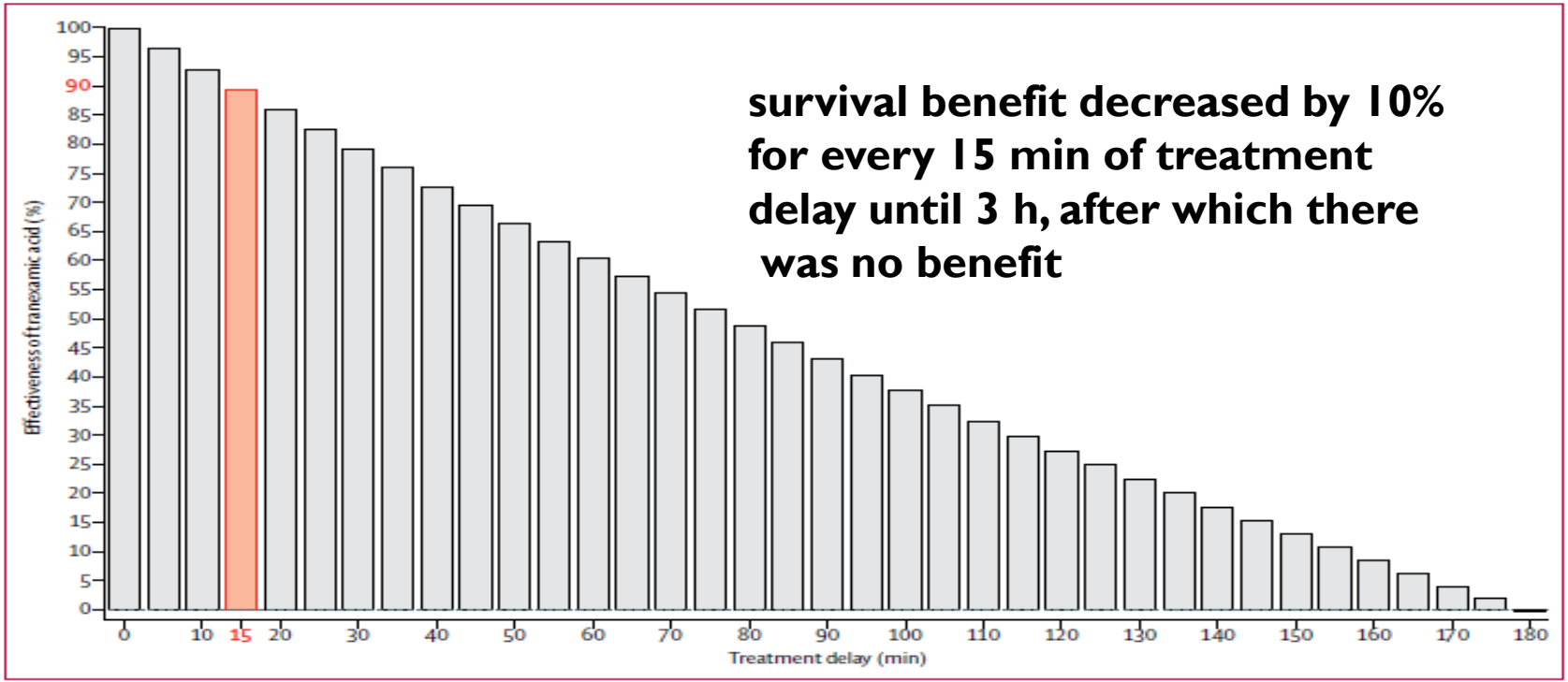
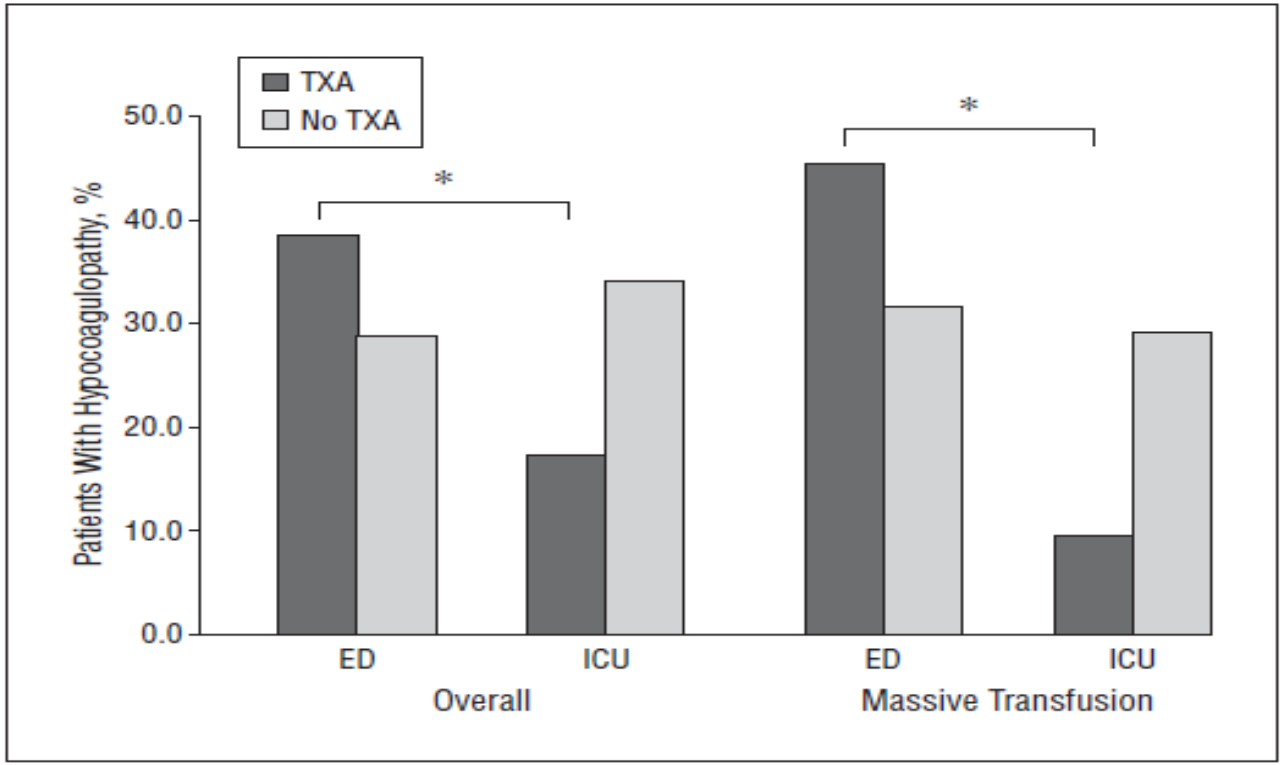


Figure 4: Reduction in effectiveness of tranexamic acid with increasing treatment delay

Lancet 2018; 391: 125–32

TXA improves coagulopathy by ICU



Morrison et al. Arch Surg 2012;147:113-9

HALT-IT

HALT-IT Trial Collaborators. Lancet. 2020 Jun 20;395(10241):1927-1936.

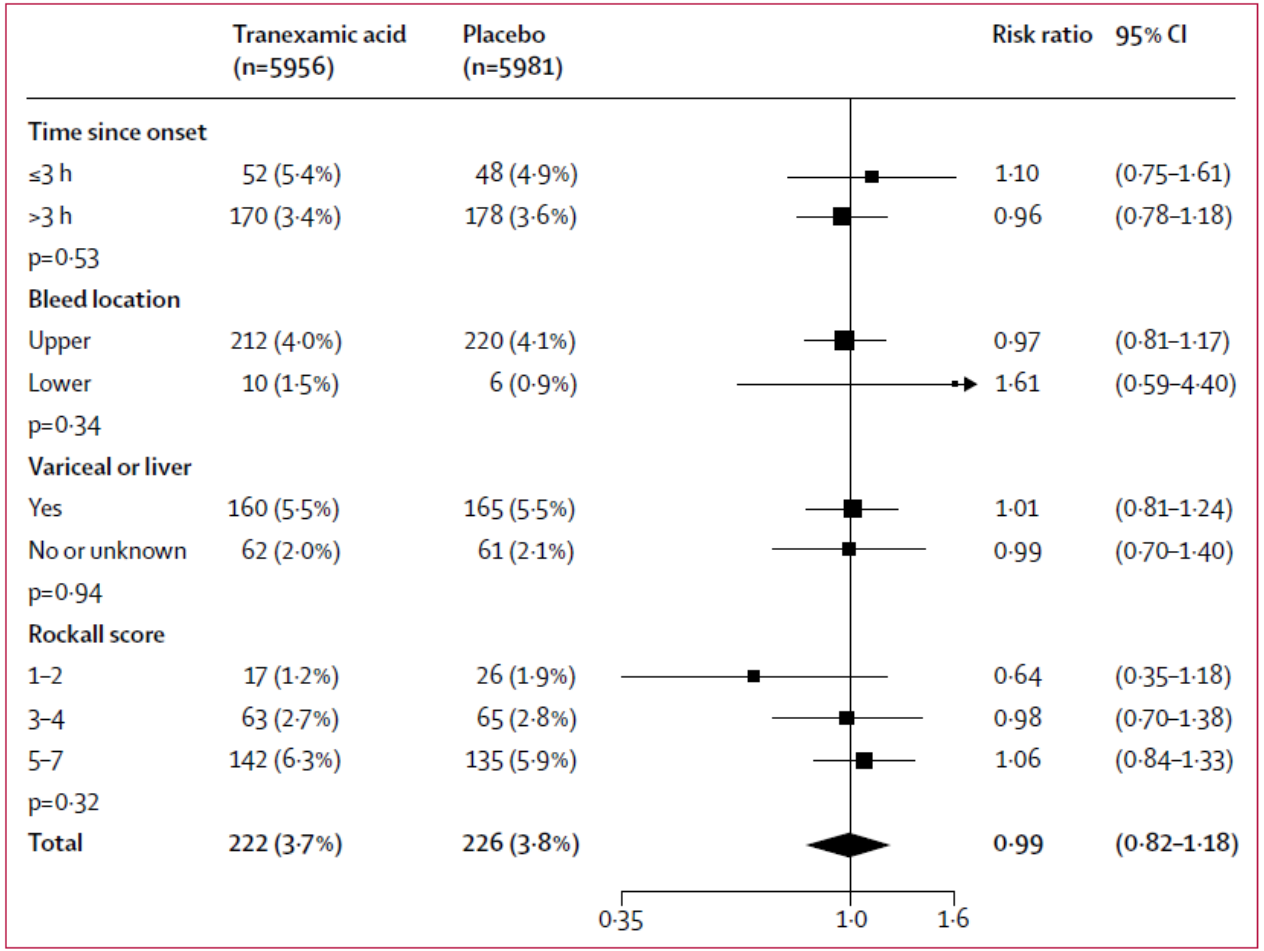


Figure 3: Effect of tranexamic acid on death due to bleeding within 5 days

	Tranexamic acid	Placebo	Outcomes
Complications			
Any thromboembolic event	86/5952 (1·4%)	72/5977 (1·2%)	1·20 (0·88 to 1·64)
Venous events (deep vein thrombosis, pulmonary embolism)	48/5952 (0·8%)	26/5977 (0·4%)	1·85 (1·15 to 2·98)
Deep vein thrombosis	23/5952 (0·4%)	12/5977 (0·2%)	1·92 (0·96 to 3·86)
Pulmonary embolism	28/5952 (0·5%)	16/5977 (0·3%)	1·76 (0·95 to 3·24)
Arterial events (myocardial infarction, stroke)	42/5952 (0·7%)	46/5977 (0·8%)	0·92 (0·60 to 1·39)
Myocardial infarction	24/5952 (0·4%)	28/5977 (0·5%)	0·86 (0·50 to 1·48)
Stroke	19/5952 (0·3%)	18/5977 (0·3%)	1·06 (0·56 to 2·02)
Renal failure	142/5951 (2·4%)	157/5978 (2·6%)	0·91 (0·73 to 1·14)
Liver failure	196/5952 (3·3%)	184/5977 (3·1%)	1·07 (0·88 to 1·30)
Respiratory failure	105/5952 (1·8%)	131/5978 (2·2%)	0·81 (0·62 to 1·04)
Cardiac event	100/5952 (1·7%)	89/5977 (1·5%)	1·13 (0·85 to 1·50)
Sepsis	210/5952 (3·5%)	216/5977 (3·6%)	0·98 (0·81 to 1·18)
Pneumonia	193/5952 (3·2%)	174/5978 (2·9%)	1·11 (0·91 to 1·36)
Seizure	38/5952 (0·6%)	22/5977 (0·4%)	1·73 (1·03 to 2·93)

T^7

	T
1	Triggering
2	Team
3	Testing
4	Tranexamic acid
5	**Temperature**
6	Transfusion
7	Termination

Hypothermia – Prevention & Management

- Minimal number of studies
- Poorly monitored during pre-hospital and pre-OR phase
- Temp <34°C associated with an increase in mortality
- Each 1°C increases blood loss by 16% and risk of transfusion by 22%
- In the pre-hospital phase, trauma patients with minor injury have a fall in temperature with passive warming (blankets), versus a rise with resistive warming blankets AND they are more comfortable on arrival

Reynolds BR, et al. J Trauma Acute Care Surg. 2012; **73**(2): 486-91.
Dirkmann D, et al. Anesth Analg. 2008; **106**(6): 1627-32.
Kober A, et al. Mayo Clin Proc. 2001; **76**(4): 369-75.
Walpoth BH, et al. N Engl J Med. 1997; **337**(21): 1500-5.
Lundgren P, et al. Scand J Trauma Resusc Emerg Med. 2011; **19**: 59.

Temperature

- N=922 Trauma patients surviving to OR
- 70% hypothermic (<36°C)
- How often is temperature monitored at multiple points throughout care:

	EMS	Trauma Room	OR	ICU
% Temp Checked	18%	66%	80%	98%

6%
"warmed"

94%
"warmed"

Alam et al. TAC Meeting 2016

T^7

	T
1	Triggering
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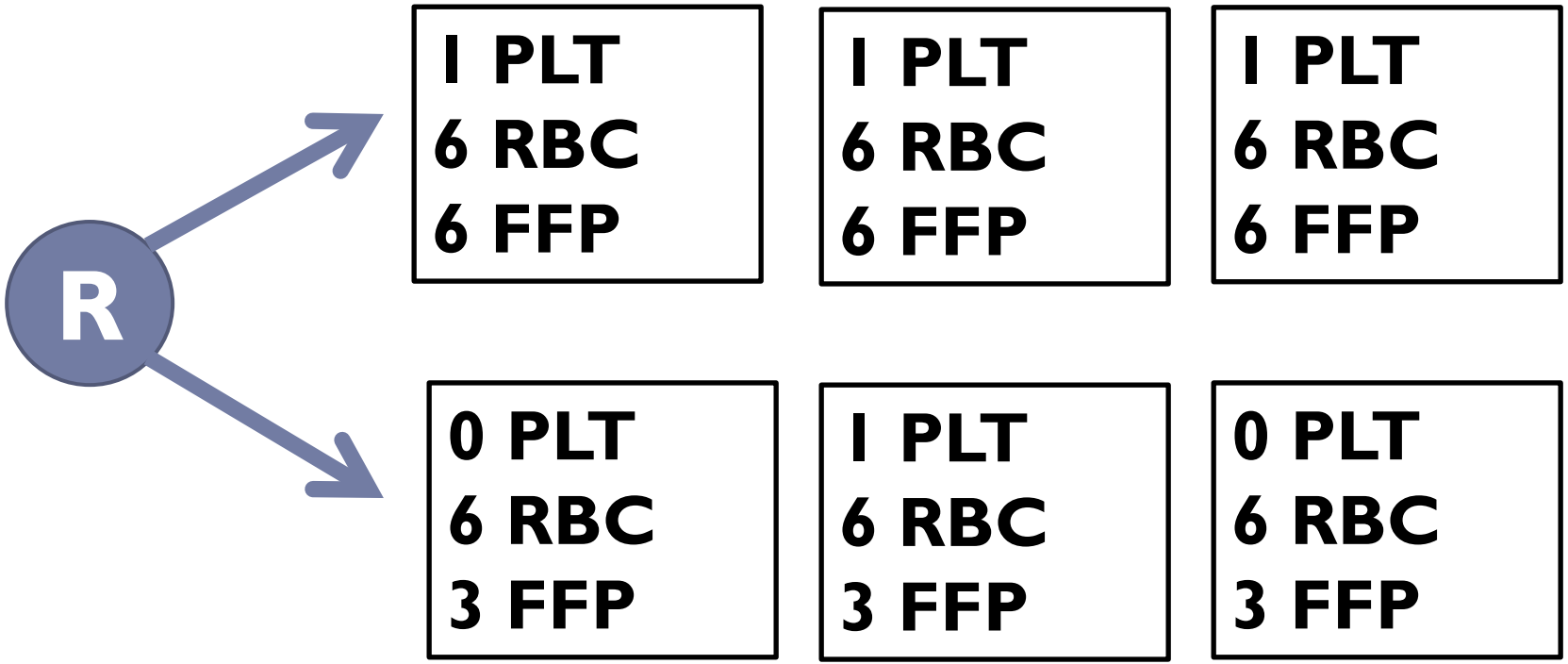
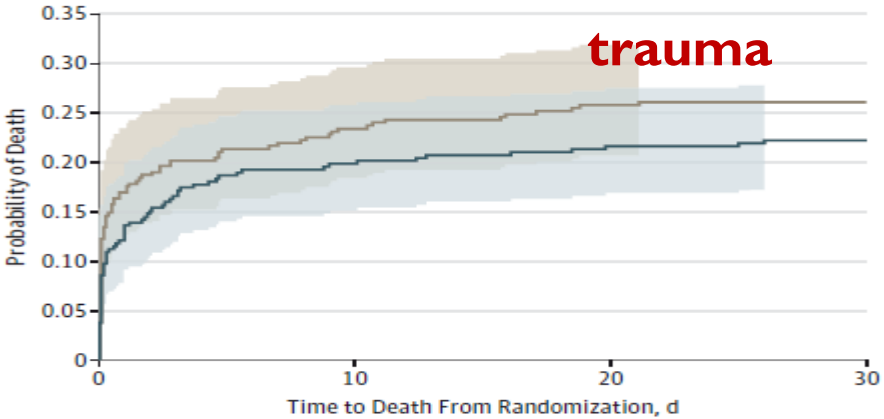
PROPPR 1:1:1 vs. 2:1:1 (blinded until cooler tamper lock cut)



- Primary outcome: 24 hour and 30 day mortality

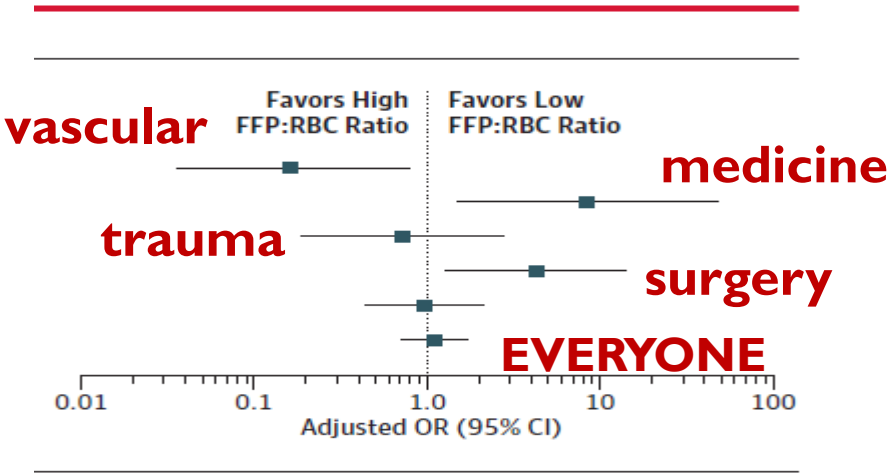
1:1 = 2:1

PROPRR



Holcomb, JAMA 2015; 313: 471-482

JAMA SURG HARVARD



Mesar, JAMA Surg 2017; March 8.

Table 2. Trial Outcomes by Treatment Group

	1:1:1 Group (n = 338)	1:1:2 Group (n = 342)	Difference (95% CI), %	Adjusted RR (95% CI)	*P* Value[a]
24-h Mortality, No. (%)[b]	43 (12.7)	58 (17.0)	−4.2 (−9.6 to 1.1)	0.75 (0.52 to 1.08)	.12
30-d Mortality, No. (%)[b]	75 (22.4)	89 (26.1)	−3.7 (−10.2 to 2.7)	0.86 (0.65 to 1.12)	.26
Achieved hemostasis					
No. (%)	291 (86.1)	267 (78.1)			.006
Anatomic, median (IQR), min[c]	105 (64 to 179)	100 (56 to 181)			.44
Hospital-free days, median (IQR)[c,d]	1 (0 to 17)	0 (0 to 16)			.83
Ventilator-free days[d]					
Total No. of patients	337	340			
Median (IQR)[c]	8 (0 to 16)	7 (0 to 14)			.14
ICU-free days[d]					
Total No. of patients	337	340			
Median (IQR)[c]	5 (0 to 11)	4 (0 to 10)			.10
Incidence of primary surgical procedure	290 (85.8)	284 (83.0)	2.8 (−2.8 to 8.3)		
Disposition at 30 d, No. (%)[e]					
Home	118 (34.9)	105 (30.7)			
Remained hospitalized	82 (24.3)	77 (22.5)			
Other[f]	59 (17.5)	71 (20.8)			.37
Morgue	75 (22.2)	89 (26.0)			
Unknown	4 (1.2)	0			
Glasgow Outcome Scale-Extended score					
Total No. of patients[g]	30	28			
Median (IQR)[c]	4 (3 to 6)	4.5 (3.5 to 7.0)			.11

Not blinded

Bottom line

The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition

Initial coagulation resuscitation

Recommendation 24 In the initial management of patients with expected massive haemorrhage, we recommend one of the two following strategies:

- FFP or pathogen-inactivated FFP in a FFP:RBC ratio of at least 1:2 as needed. (Grade 1C)
- Fibrinogen concentrate and RBC. (Grade 1C)

Spahn *et al. Critical Care* (2019) 23:98
https://doi.org/10.1186/s13054-019-2347-3

cmajOPEN

Research

A regional massive hemorrhage protocol developed through a modified Delphi technique

34. The initial management of the rapidly bleeding patient that precludes the use of laboratory-guided transfusion should begin with immediate red blood cell (RBC) transfusion and then transfusions at an RBC:plasma ratio of 2:1.

CMAJ Open 2019. DOI:10.9778/cmajo.20190042

CRYOSTAT2 – 1289 of 1568 patients

Can PCC replace plasma?

	4F-PCC Group (N=54)	FP Group (N=47)	P-value
Further hemostatic therapy needed (to 4 hrs)	11 (20%)	15 (32%)	0.25
Severe / Massive hemorrhage	11 (21%)	18 (38%)	0.08
24-hr chest tube drainage (median; IQR)	450 (370-630)	700 (470-950)	<0.001
24-hr allogeneic blood component transfusions			
RBC + Platelet + FP (excluding IMP)	8.6 (7.0-10.6)	10.8 (8.6-13.4)	0.15
RBC	2.2 (1.7-2.9)	3.2 (2.5-4.2)	0.05
Platelet	6.2 (5.1-7.6)	7.2 (5.9-8.9)	0.3
FP	0.3 (0.2-0.4)	4.4 (3.6-5.3)	<0.001

Karkouti K, JAMA Netw Open. 2021 Apr 1;4(4):e213936.

T^7 Summary

	T	
1	Triggering	Every 1 min to first RBC = 5% increase in death If in doubt start with 2-4 RBCs
2	Team	Training improves patient care
3	Testing	Viscoelastic point of care testing may be better
4	Tranexamic acid	Every 15 minute delay reduces benefit by 10%
5	Temperature	We don't measure
6	Transfusion	1:1 = 2:1 and PCC vs. Plasma?
7	Termination	We forget (evidence not shown)

Pediatrics – Anything different?

- Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies:
  - Definition: TBV replaced in 24 hours
  - Transfusion complications are more common – hyperkalemia, hypothermia, hypocalcemia
  - Rh-status critical for all female traumas
  - TXA – 10 mg/kg to max adult dose
  - Weight based dosing for all products

J Trauma Acute Care Surg 2019;86:744-754.

Homework –things to ensure you remember

1. Give TXA immediately, but withhold for GI bleeds
2. Don't delay time to RBCs
3. Measure temperature and warm patient
4. Read the MHP when you start at each hospital
5. Measure the fibrinogen

Thank you for your attention

Happy to take questions