Are platelets necessary in box 1 of a major haemorrhage pack for trauma?

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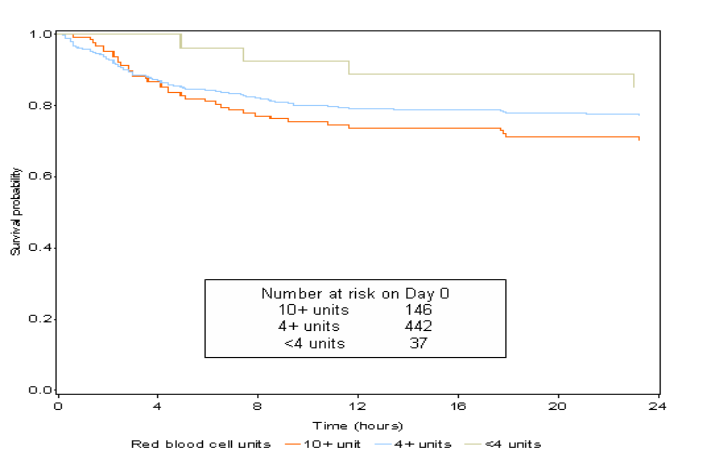
SPOTLIGHT ON PLATELETS,
BIRMINGHAM NOVEMBER 2015

Trauma haemorrhage in UK

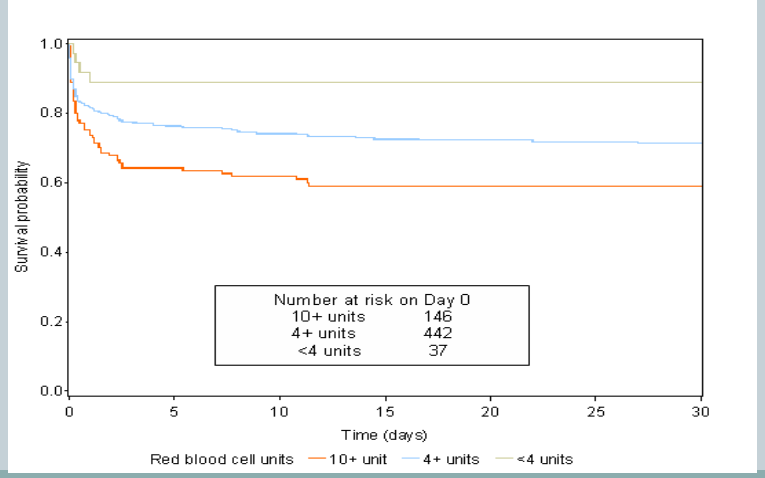
- Trauma 30-40% patients deaths from haemorrhage

	Incidence	Annual UK Cost	Annual UK mortality
Trauma	13 per 100,000	£168 million	~10,000

24 hour mortality



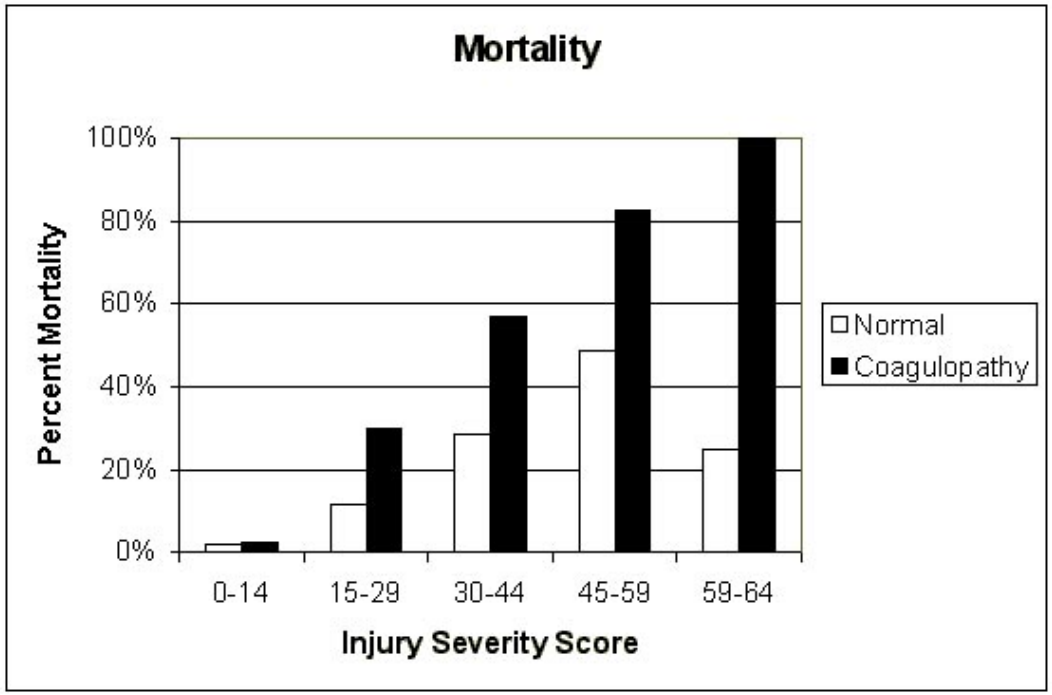
30 day mortality



Why is haemostasis important?

- 25% trauma patients have coagulopathy
- Haemorrhagic deaths are often in first 6 hours
- Predictor of massive transfusion need

- Risk of death is x3-4 higher
- Cause of death:
  - Early: bleeding
  - Late: all other causes (MOF, ALI, etc)



PROPPR study

Research

Original Investigation

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

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

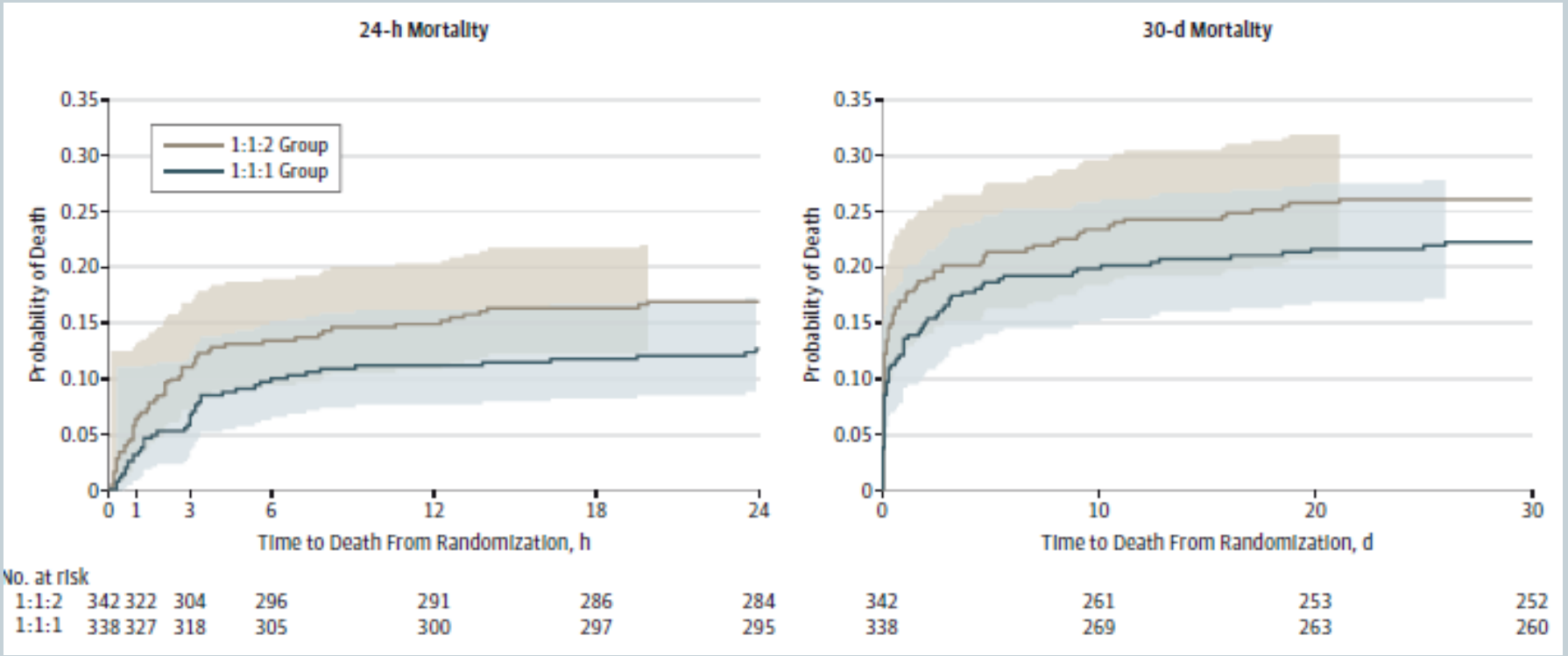
PROPPR study

- 12 level trauma centres in US
- 680 patients (338 vs. 342)
- Adults with trauma predicted to need a MT (10 or more RBC in 24h)
- Primary outcome: 24hr + 30 day mortality – powered to see a 10% difference

		Container 1	Container 2
Group 1[a]	Platelets	1	1
1:1:1	Plasma	6	6
	RBCs	6	6
Group 2[b]	Platelets	0	1
1:1:2	Plasma	3	3
	RBCs	6	6

[a] Group 1: Platelets first, then alternate RBCs and Plasma, as clinically required.
[b] Group 2: Platelets first (if available), then alternate 2 RBCs and 1 Plasma, as clinically required.
The container cycles were repeated until hemostasis was achieved and resuscitation completed.

PROPPR



No differences between overall 24h (12.7% vs. 17%) and 30 day mortality (22.4% vs. 26.1%)

Reduction in death from exsanguination: 9.2% vs. 14.6% (p = 0.03)

PROPPR

- More patients achieved anatomic haemostasis:
  - 86.1% vs. 78.1% (p = 0.006)
- Median no. blood components given during 1st haemorrhage:
  - 16units vs. 15 units
- There were no differences in ARDS, MOF, VTE and transfusion events

What evidence did the PROPPR team have prior to study start?

FFP:RBC RATIOS

PLT:RBC RATIOS

Evidence for FFP:RBC ratios

Study (2007-2011)	N	% blunt	MT definition	Coagulation Pre	Coagulation Post	Ratio ↓ mortality
Borgman	246	6	≥10U/24 hr	INR 1.63	NR	1:1.4
Duschesne	135	42	≥10U/24 hr	NR	NR	1:1
Gunter	259	46	>10U/24 hr	NR	NR	>2:3
Holcomb	466	65	≥10U/24 hr	INR 1.6	NR	1:2
Kashuk	133	NR	>10U/6 hr	INR 1.4	Max ↓ 1:1- 1:2	1:2-1:3
Maegele	713	92	>10U by ITU	APTT 53s	NR	1:1
Scalea	250	85	≥10U/24 hr	NR	NR	No
Sperry	415	100	>8U/12 hr	INR 1.82	NR	≥1:1.5
Snyder	134	40	≥10U/24 hr	INR 1.6-1.9	NR	No
Teixeira	383	NR	≥10U/24 hr	NR	NR	≥1:3
Zink	466	65	≥10U/24 hr	INR 1.3-1.5	NR	≥1:1
Shaz	214	54	>10U/24 hr	NR	NR	≥1:2
Davenport	50	88	≥10U/24 hr	PT 12	Max ↓ 1:2-3:4	N/A
Magnotti	103	63	≥10U/24 hr	INR 1.6-2.4	NR	No

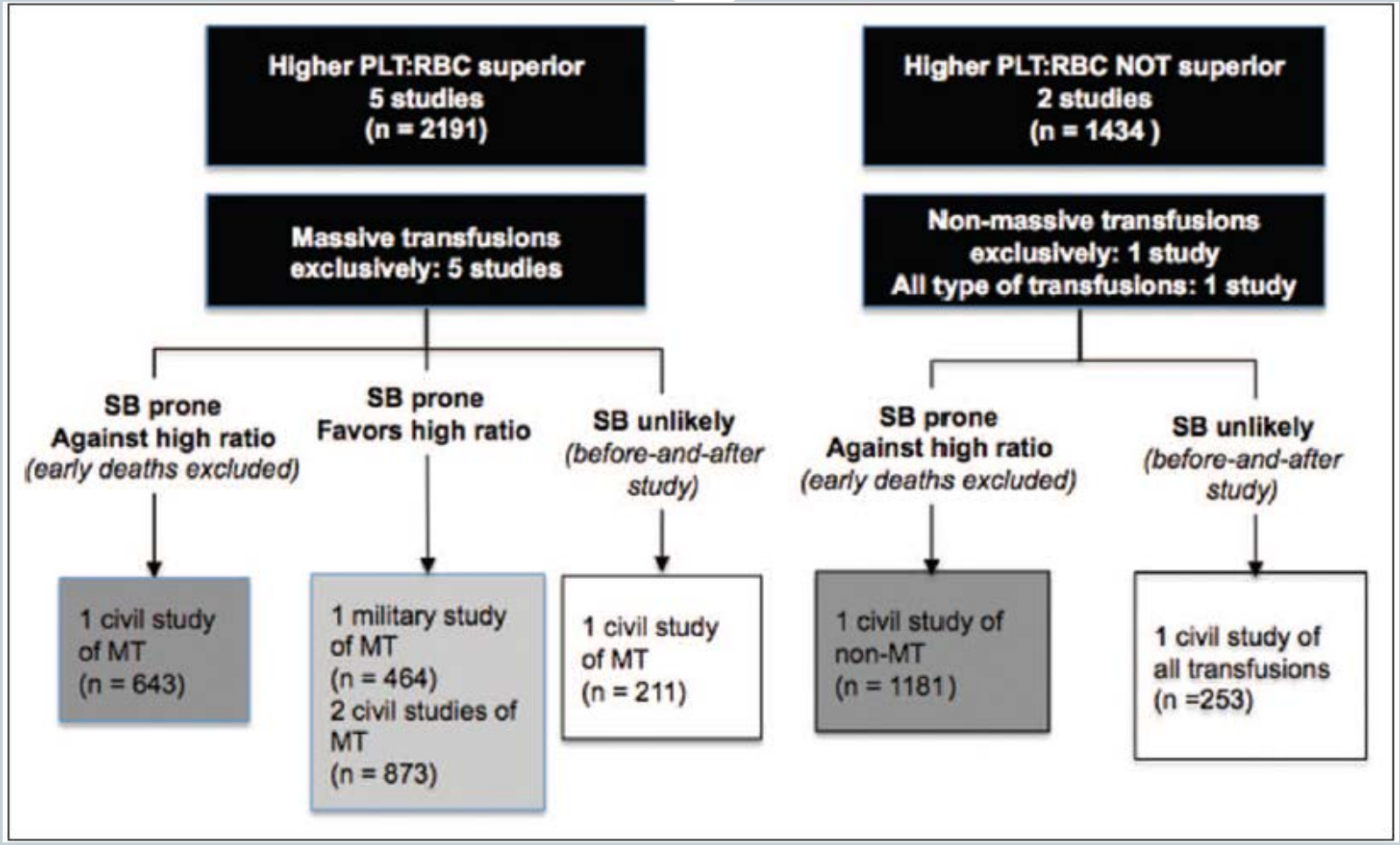
Evidence for plt:RBC ratios

Study	n	setting	Plt count	Other blood products used	Author statement
Holcomb, 2011	643	Civilian, MT	192-216	FFP, rVIIa	NS difference
Sambasivan, 2011	1181	Civilian, non-MT	198-245	FFP	NS difference
Perkins, 2009	464	Military, MT	255-261	FFP, cryo, rVIIa	Improved mortality
Inaba, 2010	657	Civilian, MT	NR	FFP, cryo	Improved mortality
Shaz, 2010	216	Civilian, MT	NR	FFP	Improved mortality
*Dirks, 2010	253	Civilian, all bleeding	186-190	FFP	NR
*Cotton, 2008	211	Civilian, MT	NR	FFP	NS difference
*Del Junco, 2013 (PROMMT)	619	Civilian, MT	NR	FFP	Insufficent data to show early plts improve mortality, Most pts had plts tx after 3 hours (see UK data)

* - minimal survival bias

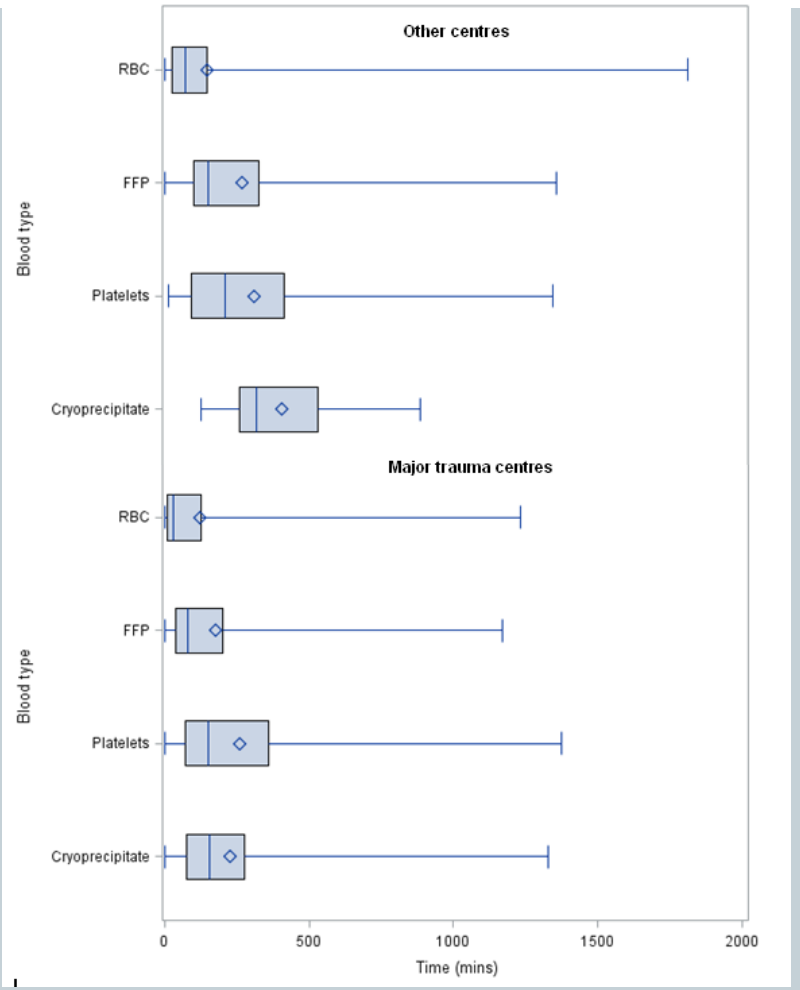
Hallet et al, Crit Care Med 2013

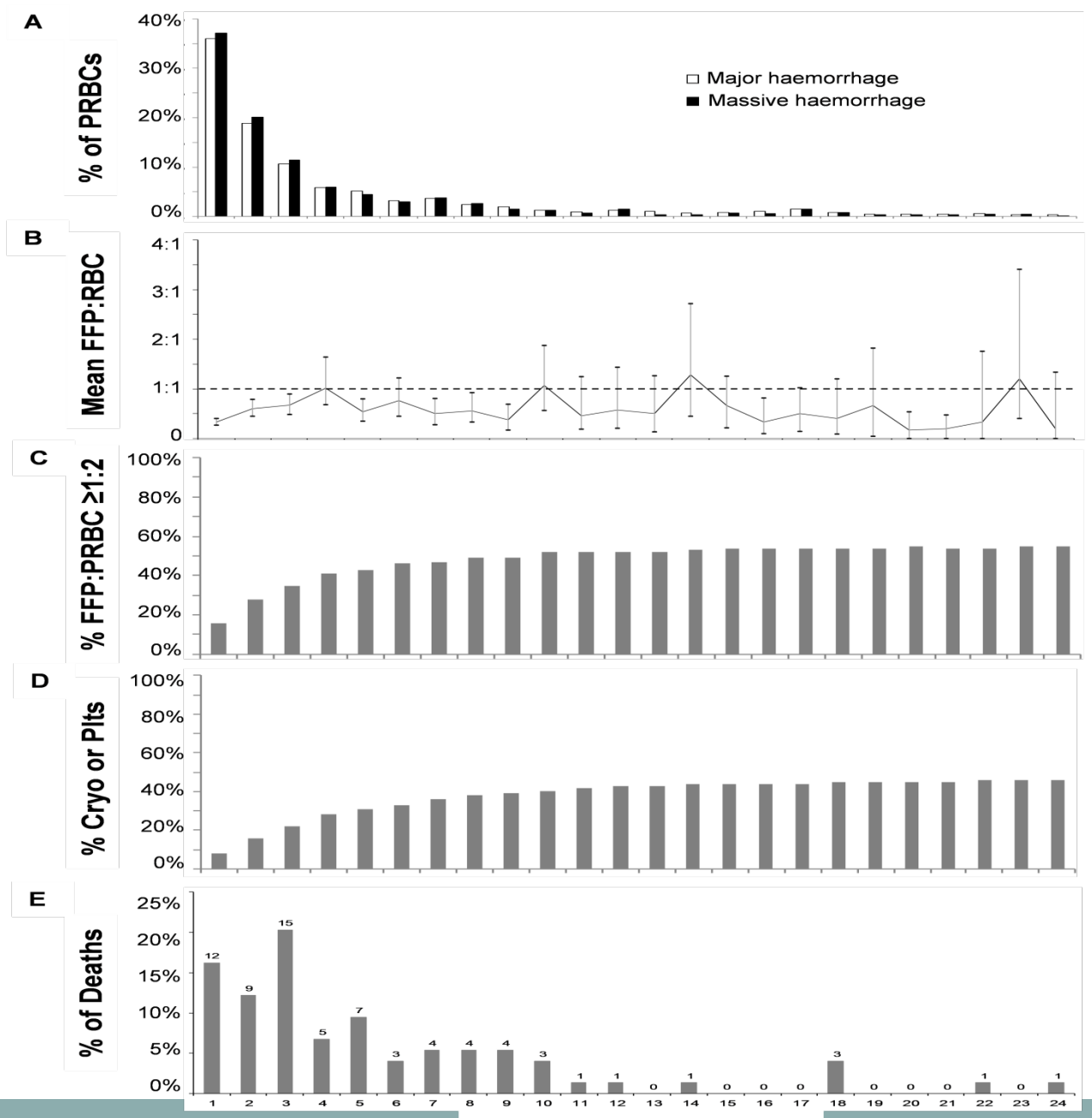
Outcomes according to survival bias



UK NIHR Trauma study

- 22 hospitals, between 2009-2011
  - Major trauma centres & trauma units
- N = 12,290
  - 479 major transfusions
  - 146 massive transfusions
- Median times to first Tx:
  - RBC – 43 mins (30 mins)
  - FFP – 93 mins (80 mins)
  - **Plts – 144 mins (120 mins)**
  - Cryo - 184 mins (156 mins)
- **19.2% pts with MT did not get any plts in first 24 h**
- Mortality: 16% at 24h, 25% at 28 d, 32% at 1 year

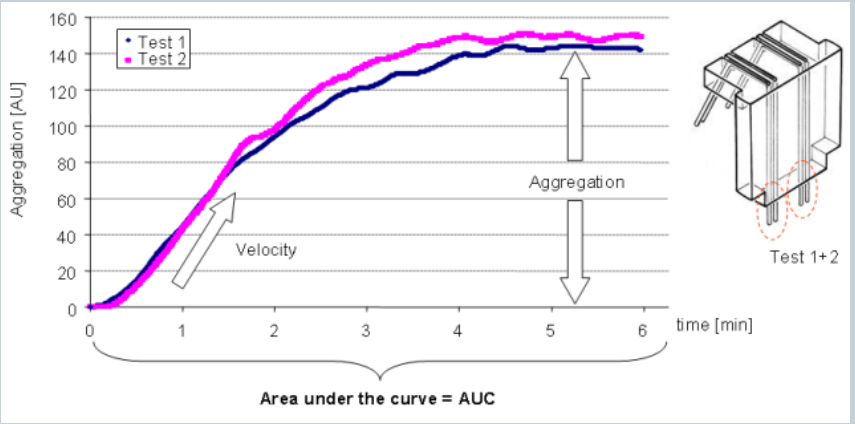




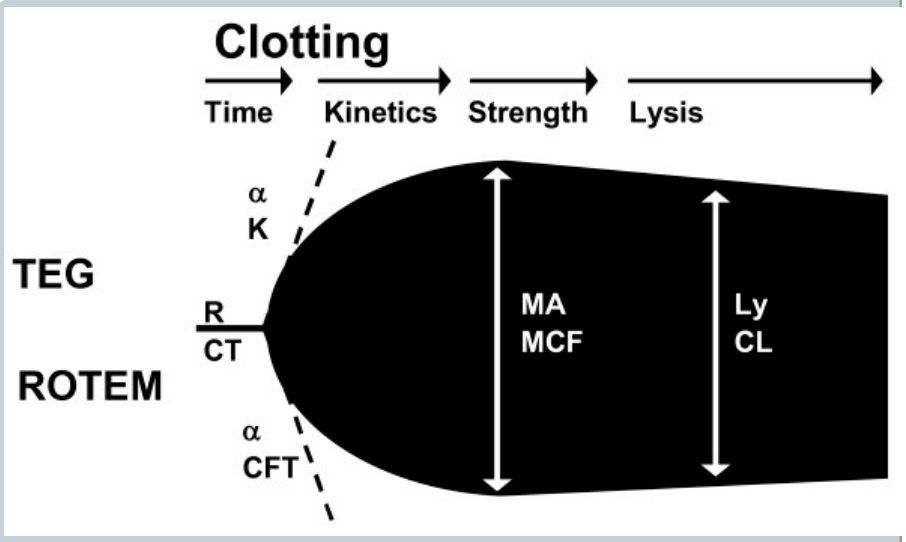
> 50% of deaths occur in first 3 hrs, with < 10% after 10 h

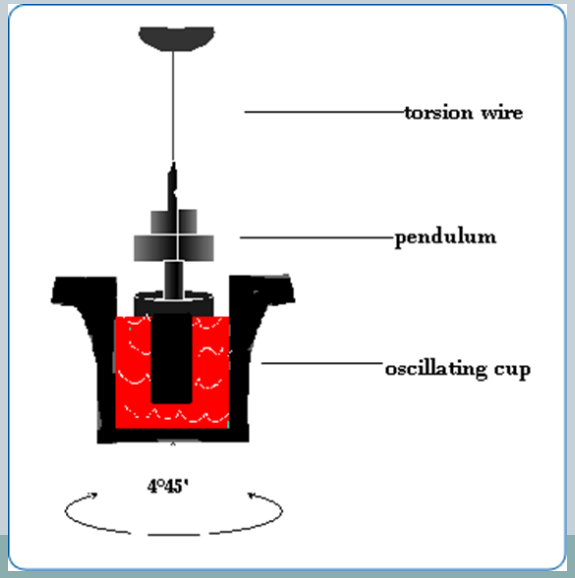
Platelet POC tests

- Platelet mapping/ Multiplate:
  - Several studies: reduced ADP activated platelet function
  - Correlates with transfusion need
- Solomon *et al*, 2011:
  - Multiplate: ADP reduced in non-survivors
  - ROTEM: platelet component ↓



Platelet testing





How to determine if platelets should be given?

'Plt contribution' to the MA/MCF as well as the speed of development of a stable clot

Platelet role in TIC

Kutcher et al:

- 101 trauma patients
- Impedance aggregometry to characterise platelet dysfunction in trauma patients on arrival to ED
- 45.5% showed decreased platelet aggregation in response to:
  - ADP, thrombin receptor-activating peptide, arachidonic acid (AA), and/or collagen.
- 10-fold increase in mortality in patients having any one of these platelet aggregation deficits
- Admission AA and collagen responsiveness were sensitive and specific predictors of mortality.

Solomon et al:

- 163 trauma patients
- Multiple electrode aggregometry testing showed minor changes in plt response were associated with mortality (reduction in ADP response found in non-survivors)
- The platelet contribution to clot firmness using (ROTEM) was significantly decreased in nonsurvivors

Wohlauer et al:

- Platelet Mapping: found a pronounced inhibition of clot strength when activated with ADP and AA in 51 trauma patients sampled within 30 minutes of injury

Kutcher et al, *J Trauma Acute Care Surg* 2012; 73: 13-9.
Solomon et al, *Thromb Haemost* 2011; 106: 322-30.
Wohlauer et al, *J Am Coll Surg* 2012; 21: 739-46.

VHA Guiding treatment

Reference	Study Type	No	TEG or ROTEM	Treatment Algorithm	Outcomes
Johansson 2009	Retrospective cohort, historical control	442 390	TEG	↑R - FFP α<52 – FFP or Fg MA<46 – plts Ly30>8% - TA	DCR + TEG improved survival by 11%
Kashuk 2011	Prospective Historical control	34 34	r-TEG	G < 5.0 and: ↑R > 110sec - FFP α <66 – cryo MA <54 - plts	Mortality fell from 65 % to 29% Conducting an RCT
Schochl 2010	Retrospective	131	ROTEM	FgC: if FIBTEM MCF <10mm PCC: if EXTEM CT >1.5x ULN	Signif. reduction in mortality compared to expected mortality (p=0.03)
Schochl 2011	Retrospective 2 databases	80 601	ROTEM	As above Nil	Reduction of blood exposure No difference in death

iTACTIC trial

- Since platelet count is slow to fall
  - CCT/FBC do not differentiate platelet dysfunction
  - Might POC testing provide a better means of guiding transfusion when compared to CCT
- Large European RCT in 6 major trauma centres
- Aiming: 392 patients
- Primary endpoint: proportion of subjects alive and free from MT at 24h
- Powered to see a 13% reduction in primary outcome in VHA group

iTACTIC trial

- **1:1:1** - 1 RBC : 1 FFP/Octaplas : 1 Platelets
- **TXA** - 1g iv + 1g iv 8 hours infusion, if < 3 hours post injury.
  - If 1g administered prehospital, add 1g iv 8 hours infusion

CCT arm Algorithm

If lab INR/poc INR > 1.2

Give 4 units FFP/Octaplas

If Fibrinogen < 1.5 g/L

Give 2 pool Cryo OR 4 gm Fibrinogen concentrate

If Fibrinogen < 1.0 g/L

Give 3 pools Cryo OR 6 gm Fibrinogen concentrate

If platelet count < 100 x 10^9/L

Give 1 pool platelets

VHA Algorithm ROTEM ®

If FIBTEM CA5 < 10mm

Give 2 pools Cryo OR 4 gm Fibrinogen concentrate

If FIBTEM CA5 < 10mm AND EXTEM CA5 < 30mm

Give 3 pools Cryo OR 6 gm Fibrinogen concentrate

If EXTEM CA5 < 40mm AND FIBTEM CA5 > 10mm

Give 1 pool platelets

If EXTEM CT > 80 secs

Give 4 units FFP/Octaplas

If EXTEM Li30 < 97%

Give 1gm TXA

Is there an alternative?

- Fibrinogen is a key coagulation protein
- Low Fg levels are associated with poorer outcomes
- NHSBT has led the way in trauma Fg replacement trials
- CRYOSTAT
- E-FIT

CRYOSTAT
EARLY CRYOPRECIPITATE IN TRAUMA

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NHS National Institute for Health Research