Diagnosis and treatment of coagulopathies in the bleeding patient: We want it quick and we need it now!

Simon J Stanworth
Consultant Haematologist
Oxford

No conflicts

NHS
Blood and Transplant

Evidence for “Diagnosis and treatment of coagulopathies in the bleeding patient: We want it quick and we need it now!”

Diagnosis - Recognising coagulopathy and bleeding

Treating coagulopathy

- **Blood components – plasma**
- **Sources of fibrinogen**
- **Alternative pro-haemostatic agents and the lessons of rVIIa**

Timely responses

Setting

Bleeding +/- TEST of coagulation

GIVE treatment(s)

TEST improves

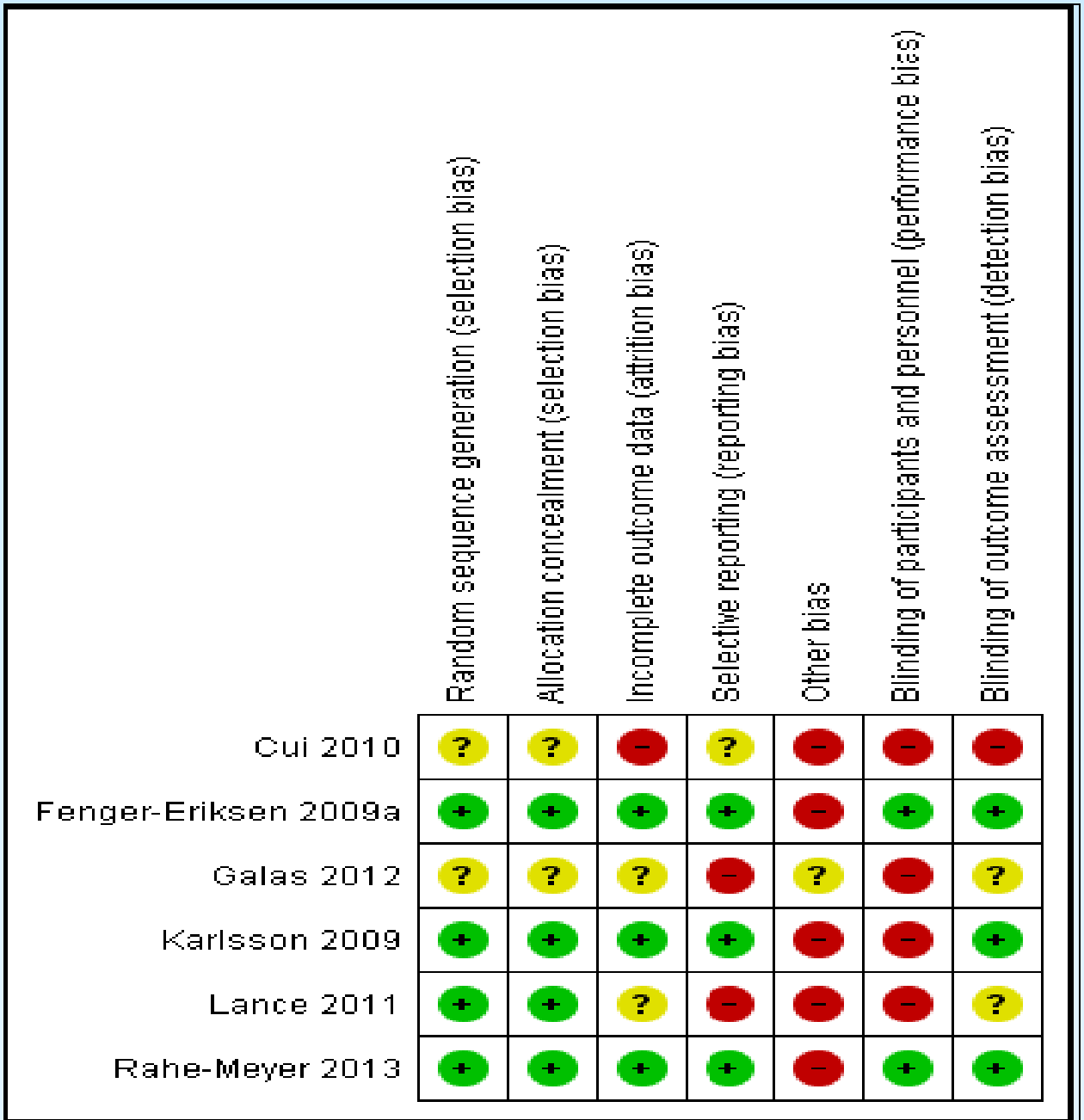
Bleeding stops

Mortality reduction

Methods - Systematic reviews

- Yang L et al. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. Transfusion. 2012
- Whiting P et al. Viscoelastic point of care testing to assist with diagnosis management and monitoring of haemostasis. NICE diagnostics review 2014
- Curry N, et al. Acute management of trauma haemorrhage: a review of RCTs. Crit Care. 2011
- Wikkelso A, et al: Fibrinogen in bleeding patients. Cochrane Database of Systematic Reviews 2013

Quality of trials - Risk of bias



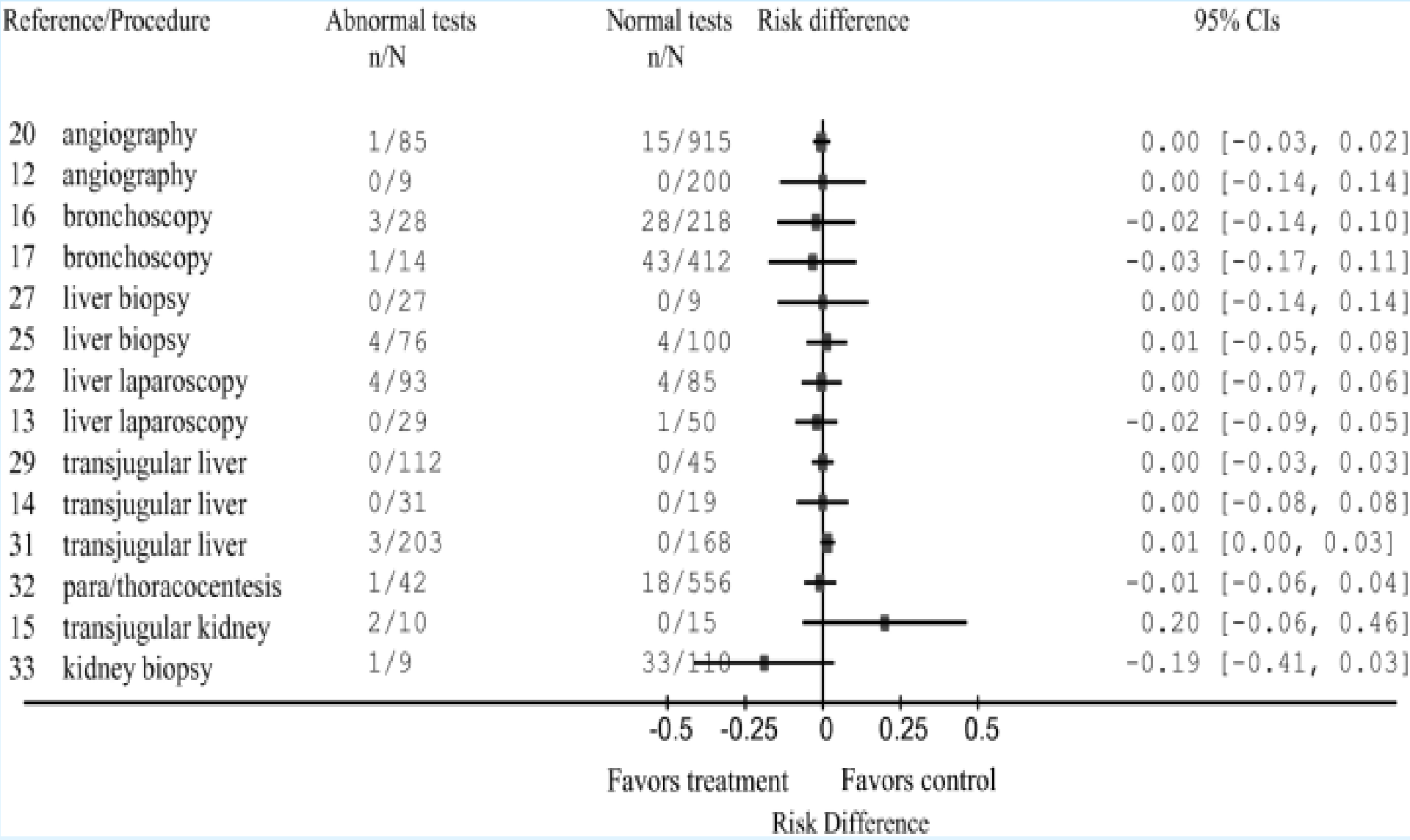
1. What do we mean by coagulopathy?

Laboratory tests

- **PT**
- **INR**
- **APPT**

Studies with ‘controls’ (normal tests)

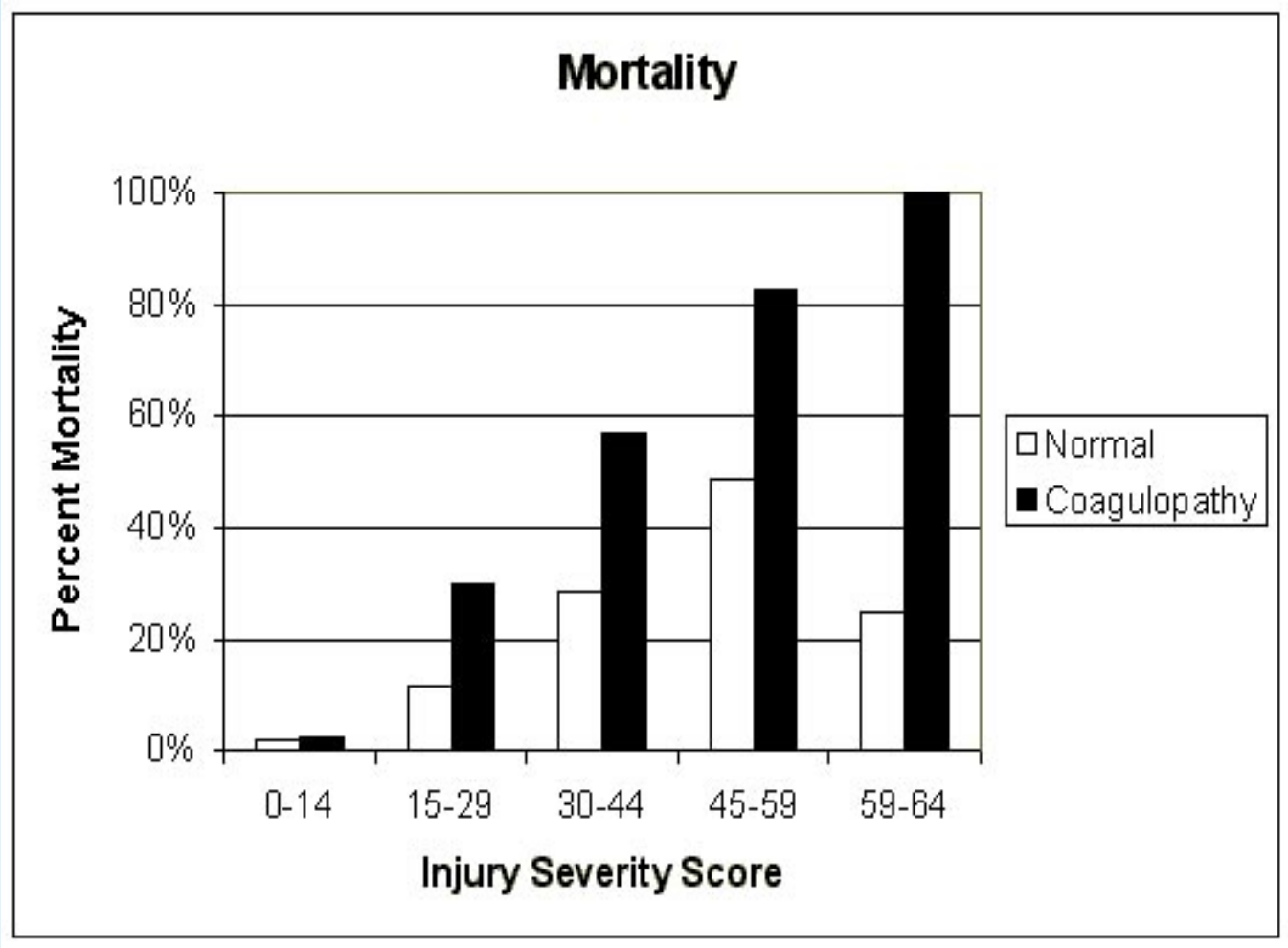
Segal and Dzik, Transfusion 2005, 45:1413



Defined by standard coagulation screen tests

- *In vitro* tests - diagnosis deficiencies of individual factors
- Changes not equally sensitive to all factors or reductions in multiple coagulation factors (sick inpatients).
  Burns et al; Am J Clin Path, 1993
- Not validated in other clinical settings or to predict bleeding
- Normal ranges & thresholds – clinical implications and 'reserve' of levels for haemostasis
- Poor relation between coagulation times & factor depletion

Acute Traumatic 'Coagulopathy'



25% trauma patients

Association with mortality

Predictor of massive transfusion need

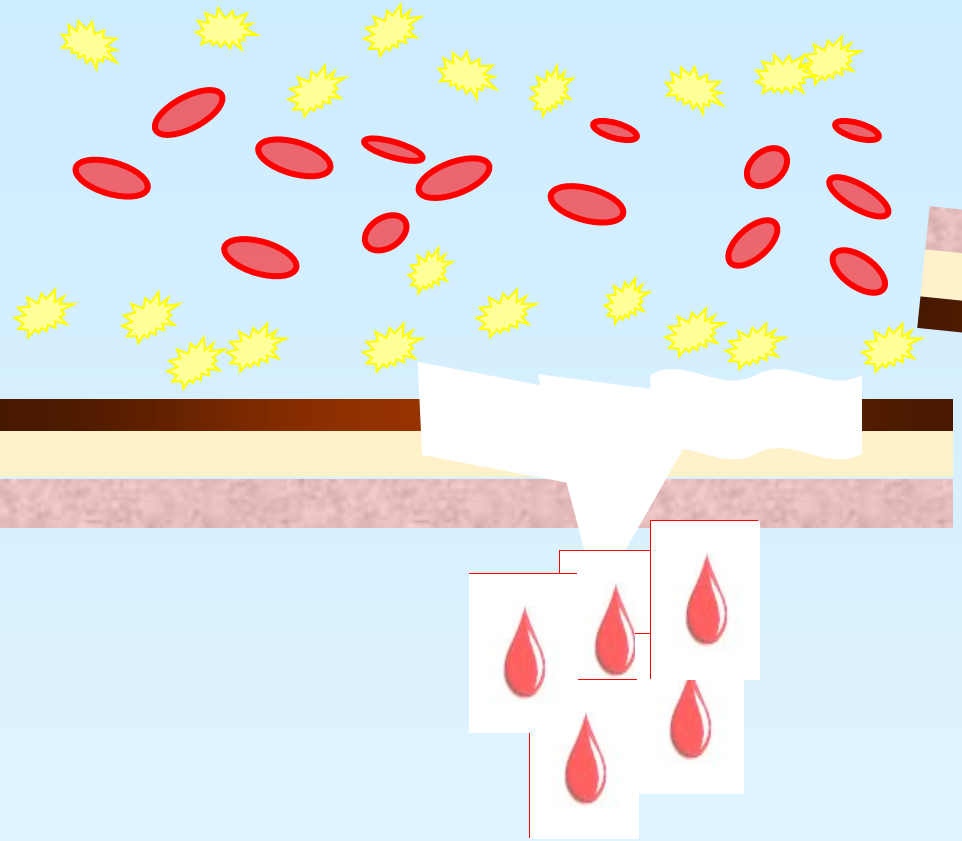
'Unique' clinical entity

Brohi et al

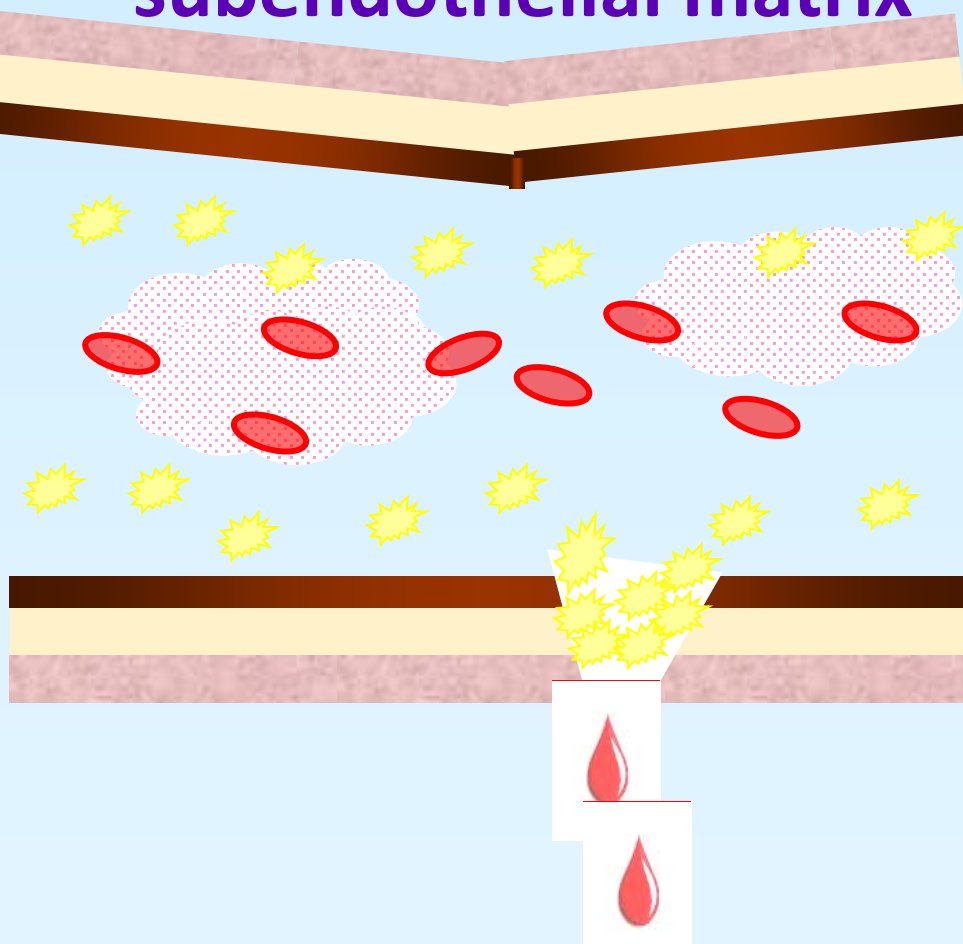
What do the 'experts' use?

Centre	Standard coagulation tests you would use for diagnosis of coagulopathy						If you could only choose one standard test
	INR	PTr	PT	APTT	Fg	Plt	
1	>1.2	>1.2	>1.2ULN		<1.5		PTr >1.2
2	>1.2	>1.2			<1.5		PTr >1.2
3	do not use in acute trauma						N/Applicable
4			>18	>40	<1.5	<100	PT >18
5	>1.2				<1.5	<100	can't, but INR >1.3
6	>1.5		>15	>30	<1	<100	plts <100
7	>1.5		>18	>60	<2	<100	INR >1.5
8	>1.2			>40		<100	Quick < 70%

Injury and exposure of sub-endothelial tissues



Platelet adhesion to collagen in the subendothelial matrix

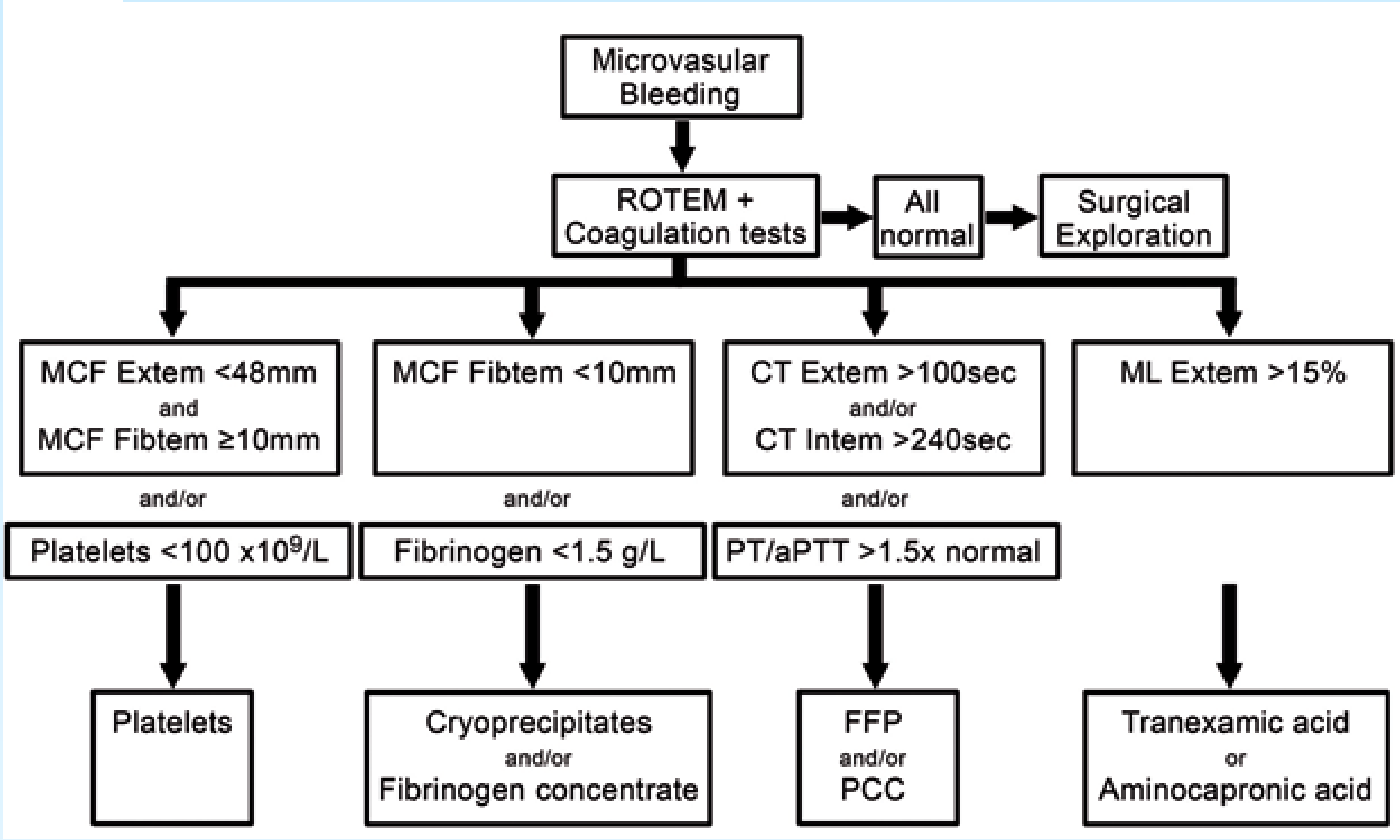


Sample analysis

- Immediate:
  - RoTEM
  - APTT/PT/Fibrinogen

- Alongside other tests
- Early data suggest RoTEM can predict ATC within 5 minutes of patient arrival

TEG/ROTEM guided transfusion resuscitation



Bollinger D, et al. *Transfusion Med Reviews* (in press)

Whiting P et al, NICE diagnostics review 2014

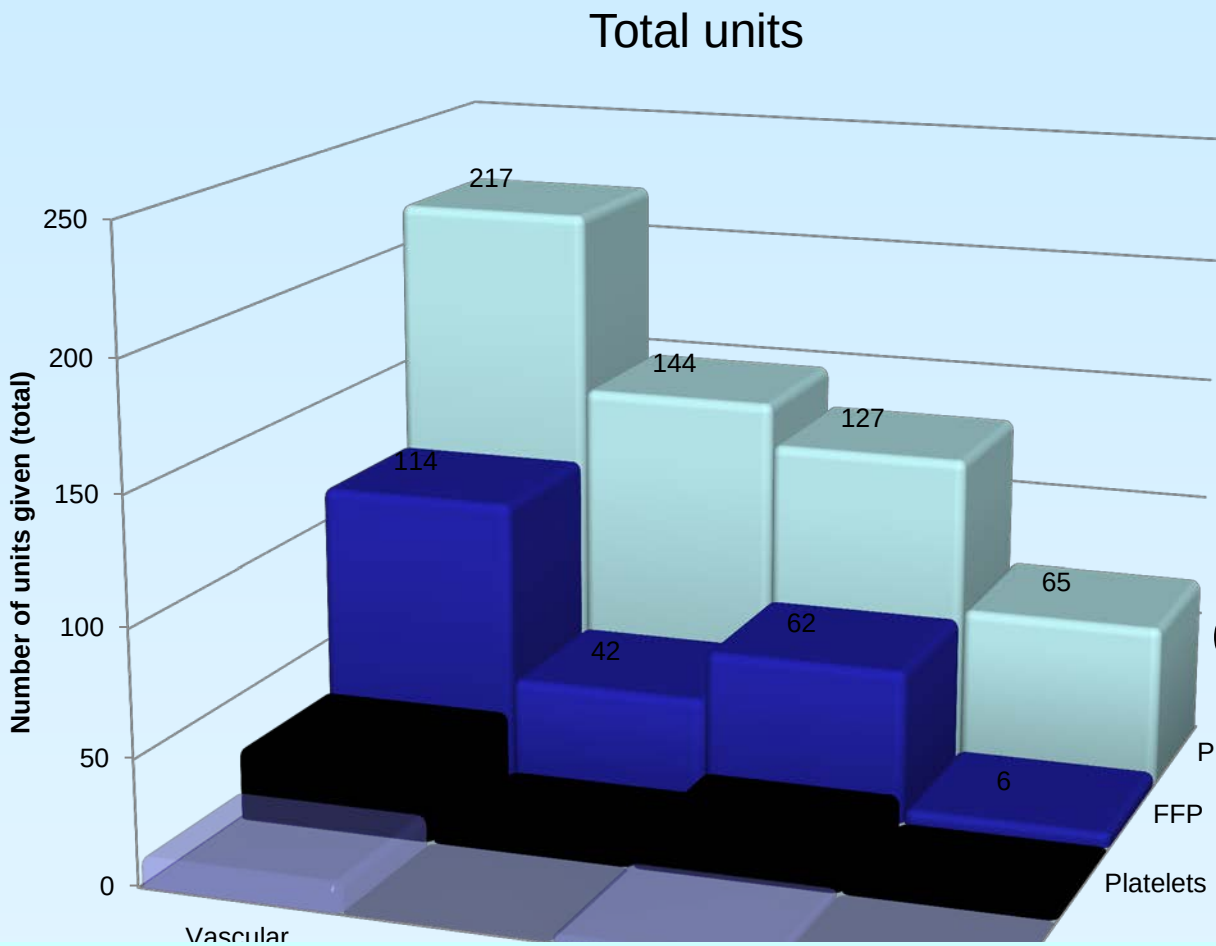
- How clinical outcomes differ among patients tested with viscoelastic testing
- Studies with comparator arms or prediction studies
- Cardiac surgery – 11 RCTs (3 low risk of bias)
  recommended to help detect and monitor
- Trauma – 15 prediction studies
  insufficient evidence to recommend adoption

Nagler et al. Consistency of ROTEM. Thrombosis & Haemostasis 2014

- Comparison within and between analysers
- Reproducibility and time dependent changes
- Large differences in the results of ROTEM parameters and lack of consistency
- Some parameters had higher homogeneity eg MCF

2.
Treating coagulopathy

Clinical Audit: admissions to ED Received ≥4 Units RBC within 24 hours



Red cells
Plasma
Platelets
Cryoprecipitate

Vascular Gastro Trauma Others

Curry N

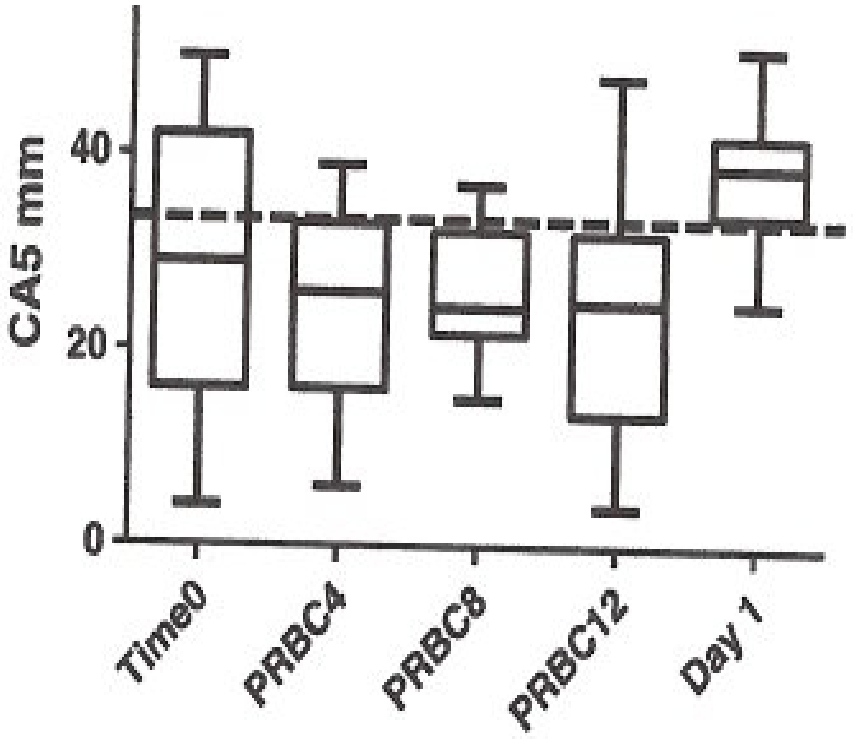
Many changes in resuscitation - how effective?

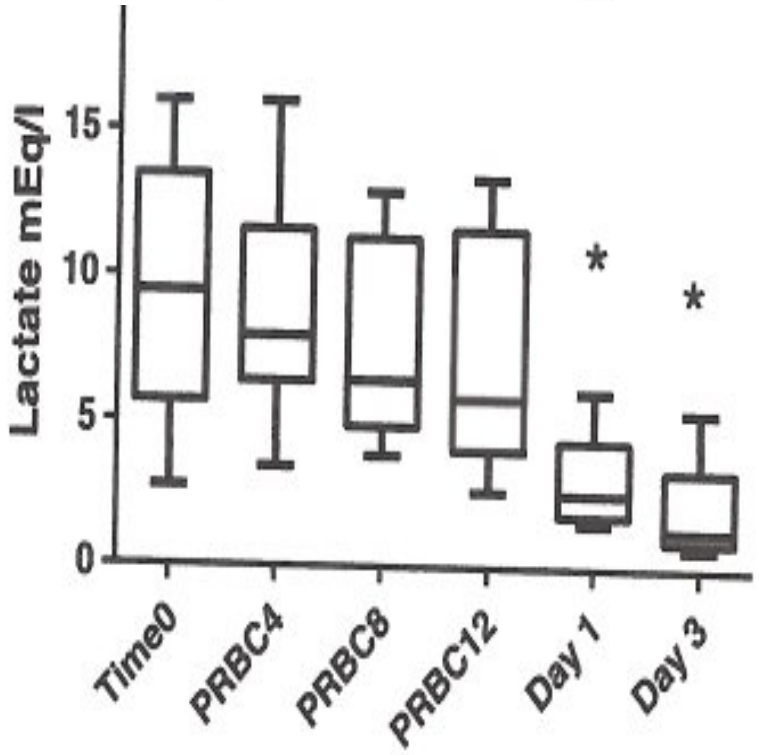
Intervention	Massive haemorrhage management	
	10 years ago	Today
Red blood cells	Often used without other components	Used in conjunction with other blood components
Plasma	Lab-guided	Early formula-based *Viscoelastic tests.*
Platelets Cryoprecipitate	Lab-guided Often given later	Early formula-based approach then lab-guided Higher thresholds
Crystalloids	Often used first	Reduced use

Are we improving outcomes?

Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage

Sirat Khan, MD, Karim Brohi, MD, Manik Chana, MD, Imran Raza, MD, Simon Stanworth, MD, Christine Gaarder, MD, PhD, Ross Davenport, MD, PhD,
***on behalf of* the International Trauma Research Network (INTRN),** *London, United Kingdom*





Limitations e.g. survival

Major Haemorrhage Protocols (civilian trauma)

Patient bleeding / collapses
Ongoing severe bleeding eg: 150 mls/min and Clinical shock
Activate Major Haemorrhage Protocol

Administer Tranexamic Acid – especially in trauma and ideally within 1 hr
(1g bolus followed by 1g infusion over 8 hours)

Call Switchboard on 4444

'Major Haemorrhage, Location, Specialty, Samples being sent with estimated arrival time'
Switchboard will coordinate portering
Consultant involvement essential

Request MHP Pack 1:

Red cells*	**6 units**
FFP	**4 units**

(*Emergency O blood if immediately required, group specific blood, XM blood depending on availability)

Attach wristband to patient
USE SAFE TX system
Take bloods and send to lab:
X-Match, FBC, PT, APTT, fibrinogen, U+E, Ca^{2+}
(2 purple, 1 blue-filled to the line, 1 green)
Near patient testing: ABG, TEG / ROTEM if available

Early use of plasma
What is the optimal ratio?

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

The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

- US Military hospital Iraq 2003 to 2005
- Patients fulfilling definition of massive haemorrhage (>10 red cell units)
- 246 patients (94% penetrating injury)
- Grouped according to plasma to red cell ratio

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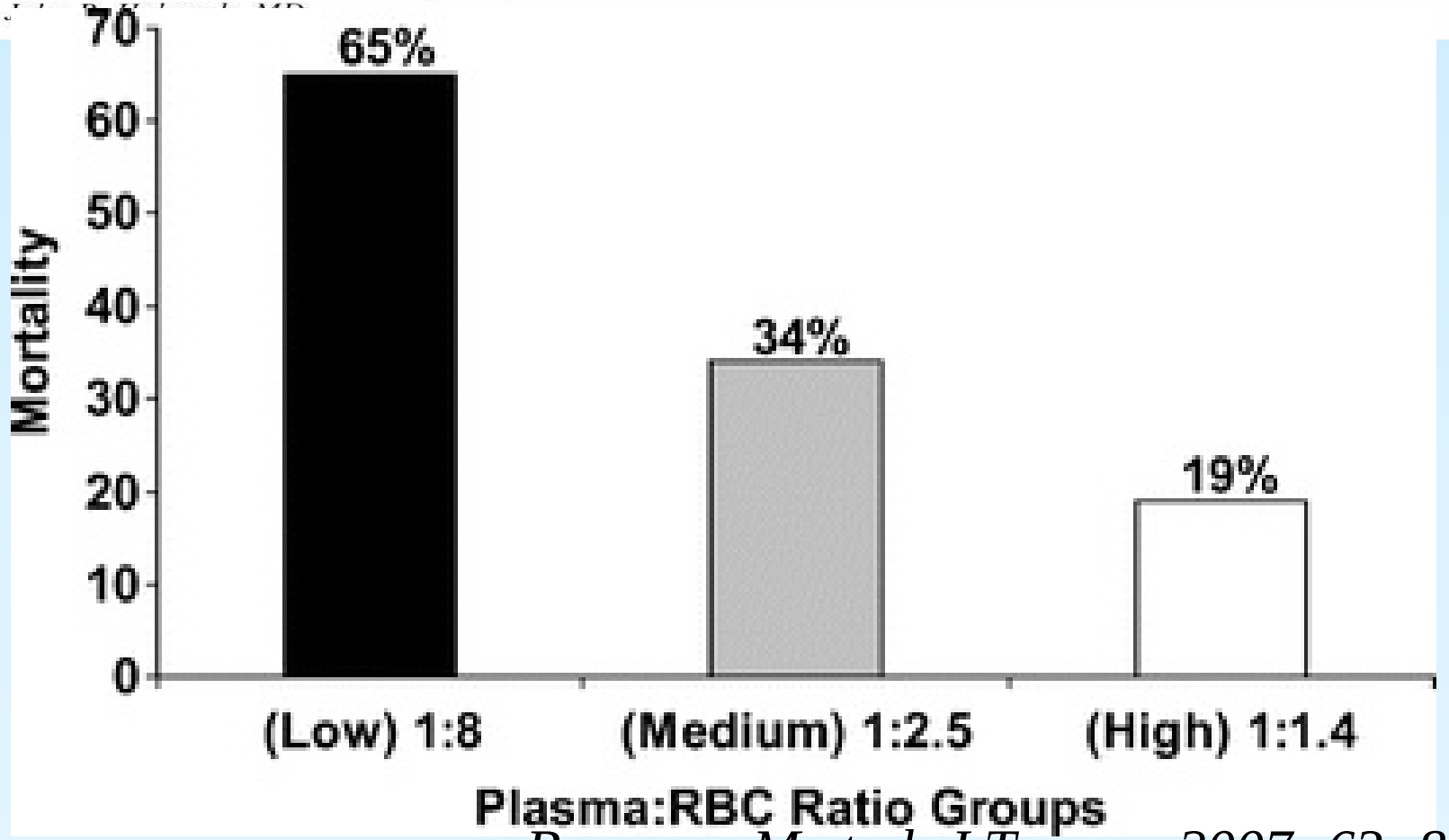


Borgman M et al. J Trauma 2007; 63: 805

Table 1: Descriptive statistics for each plasma to RBC ratio group

Variable Median (IQR)	Low Ratio Group,* n = 31 1:8 (0:12–1:5)	Medium Ratio Group, n = 53 1:2.5 (1:3.0–1:2.3)	High Ratio Group, n = 162 1:1.4 (1:1.7–1:1.2)
ISS†	18 (16–25)	17 (13–25)	18 (16–25)
ISS >25 (%)	23	21	22
AIS score (% 4 or 5)			
Head/neck	16	6	10
Face	0	0	0.6
Thorax§	26[a]	9[ab]	7[b]
Abdomen	26	23	27
Pelvis/extremity	19	23	28
% penetrating trauma	94	92	95
% blunt trauma	6	8	5
INR, n = 212	1.78 (1.00–2.86), n = 21	1.57 (1.31–2.10), n = 42	1.54 (1.30–2.20), n = 149
Hgb,‡ n = 234	9.4 (7.1–11.1), n = 27[a]	10.8 (8.5–12.7), n = 48[ab]	10.9 (9.1–13.1), n = 159[b]
Plt concentration, n = 174	225 (120–281), n = 14	177 (128–241), n = 33	218 (154–278), n = 127

Borgman et al. 2007. J Trauma 63(4)

Survivorship Bias

- In situations where most patients die early in treatment...
- If RBCs are consistently transfused before FFP, then, patients who die early will not survive long enough to receive FFP (RBCs > FFP), whereas those who live longer to receive FFP will have RBC similar to FFP.
- “FFP does not lead to survival; rather survival allows time to receive FFP.”

Other problems

- Retrospective chart review
- Incomplete data collection
- No standard timing for measuring outcomes
- Lack of a standardised massive transfusion protocol...what happens in practice

New RCTs

Full title	Acronym	Trial number	N	Study design Synopsis
Pragmatic, Randomized Optimal Platelets and Plasma Ratios	PROPPR	NCT01545232	580	Randomized single blinded controlled trial comparing ratio of 1 FP: 1 platelet: 1 PRBC to 1FP: 1 platelet: 2 PRBC for massive hemorrhage
Reversal of Trauma Induced Coagulopathy by Coagulation Factor Concentrates or FFP	RETIC	NCT01545635	200	Randomized controlled trial of FP versus factor concentrates for reversal of traumatic coagulopathy
Early Whole Blood in Patients Requiring Transfusion After Major Trauma	N/A	NCT01227005	132	Randomized controlled trial of whole blood and platelets versus blood components (PRBC, platelets and FP) in massive hemorrhage

What is the key ingredient in plasma

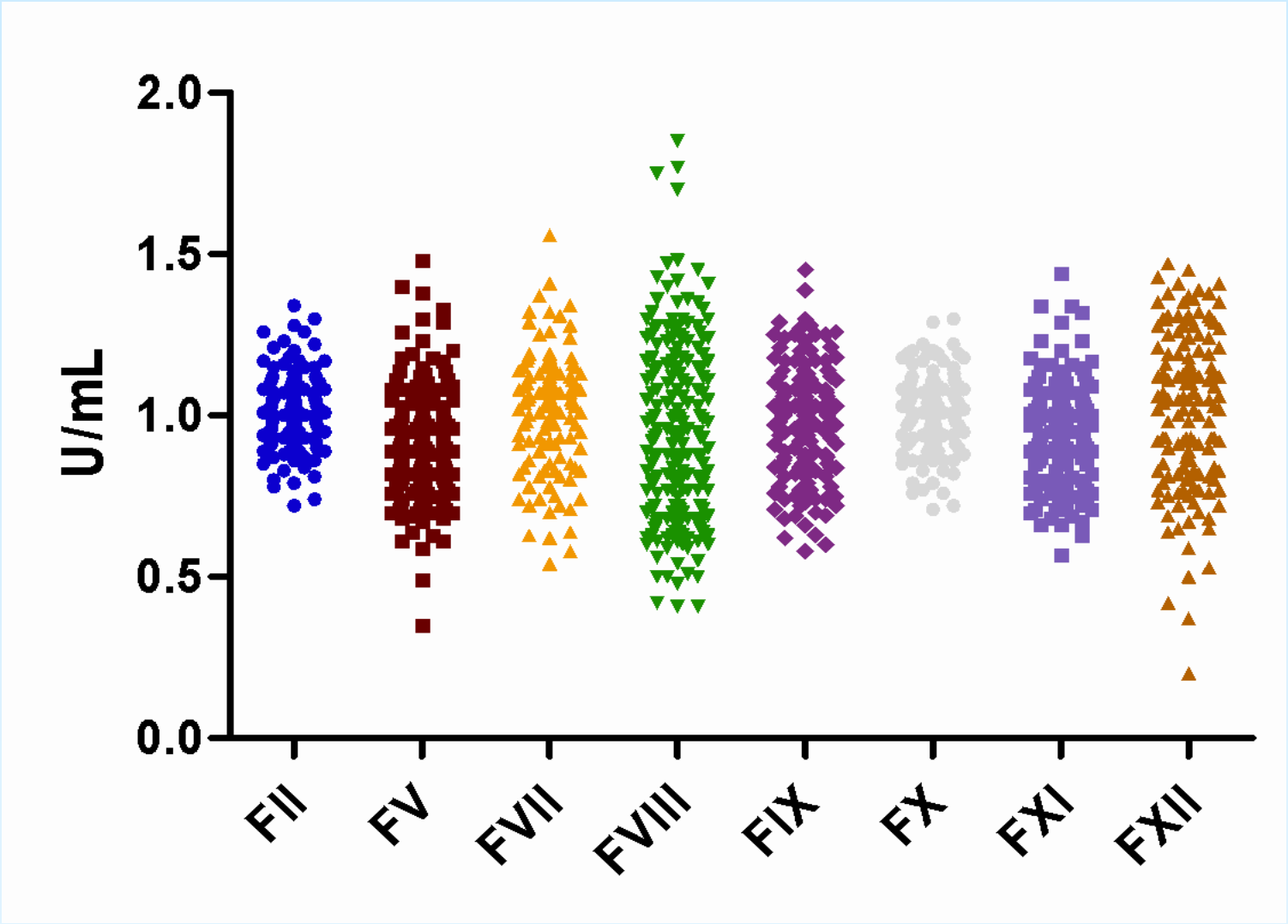
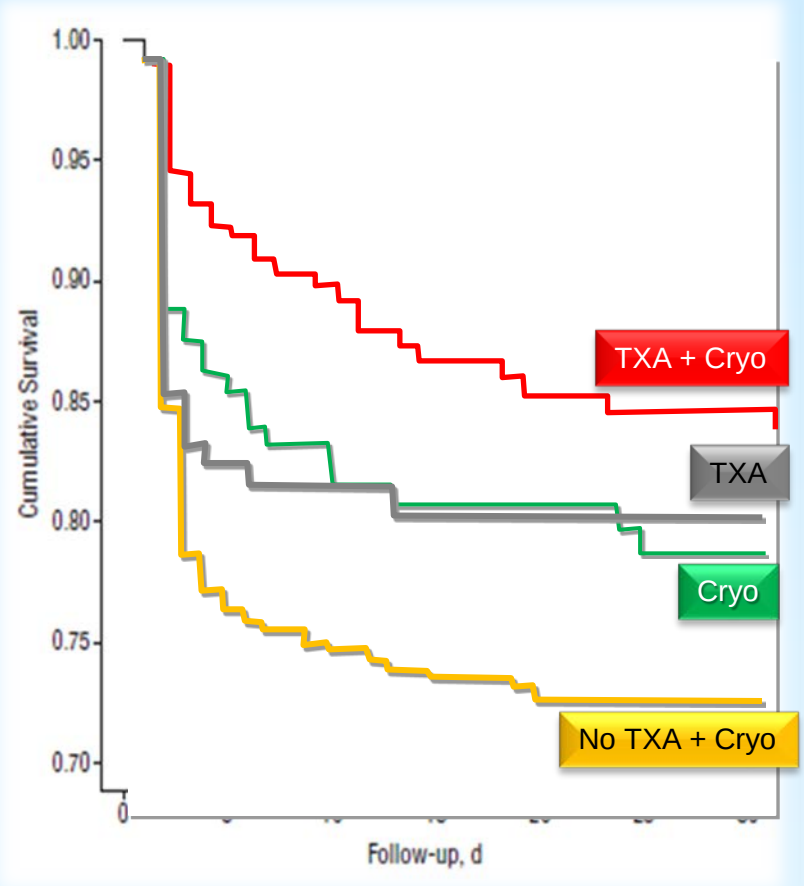


Figure 1 – Coagulation factor concentration in individual units of fresh frozen plasma tested in the Component Development Laboratory of NHS Blood and Transplant.

New research. Sources of fibrinogen MATTERs II study

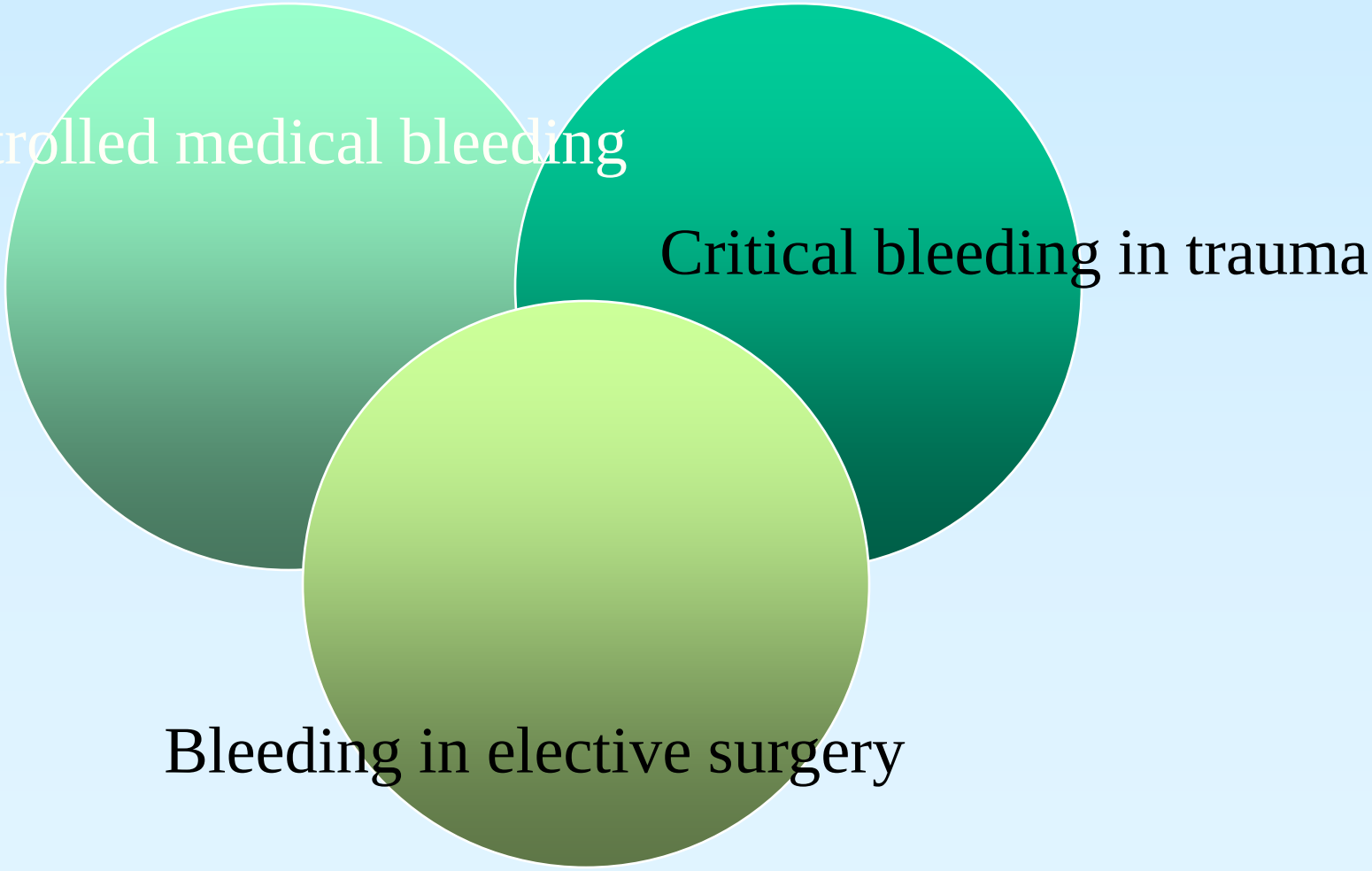
- Retrospective study on prospective data
- Combat casualties
- N=1332
  - TXA: 148
  - Cryo: 168
  - TXA + Cryo: 258
  - No TXA + Cryo: 758



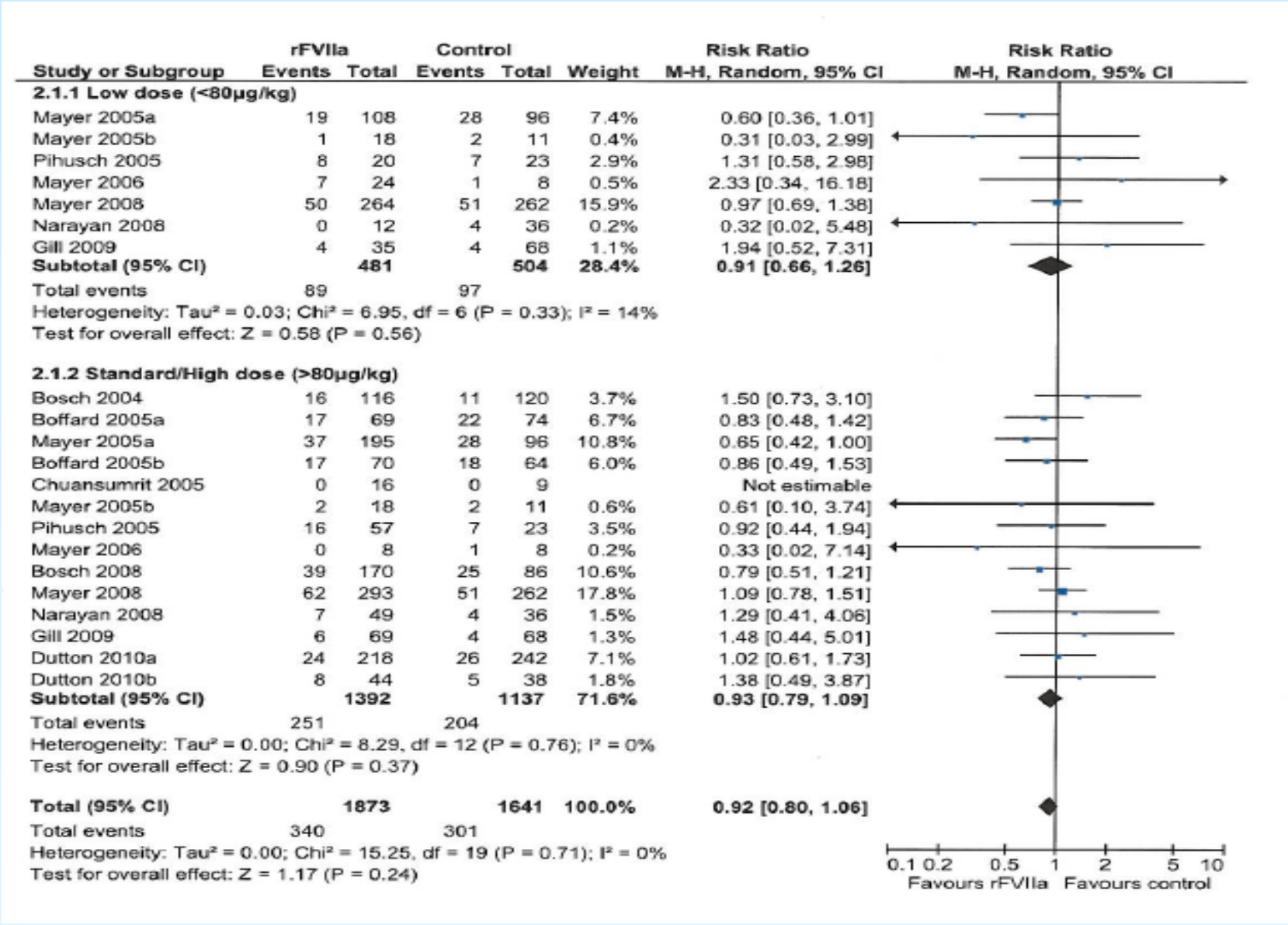
TXA, tranexamic acid

Morrison JJ, *et al.* Jama Surg.2013.764

Which “concentrated factor most studied? Off licence uses of rVIIa



Therapeutic trials – mortality



What are the risks of off-label rFVIIa?

Cochrane Review - All RCTs

Outcome	RCTs	Summary Measure (95% CI)	I^2 (%)
Total TE events	26	RR 1.18 (0.94 to 1.48)	0
Arterial TE events	25	RR 1.45 (1.02 to 2.05)	0
Venous TE events	25	RR 0.92 (0.67 to 1.26)	0

Simpson E et al. Cochrane review 2011.

Cochrane: The use of pro-coagulant haemostatic factors and factor concentrates in the prevention and treatment of bleeding in patients without haemophilia

- Identified trials across all patients settings
- To report whether a pro-coagulant haemostatic product is administered therapeutically or as prophylaxis

More small trials

Fibrinogen
PCC
Factor XIII
Factor IX

Cardiac
Surgery for malignancy
Acute leukaemia
ICH
UC
Premature infants

In total, 7 therapeutic studies that randomised 362 participants (range 20 - 107, average 52); & 12 prophylactic studies that randomised 1032 (range 21 - 479, average 86).

3.
We want it quick?

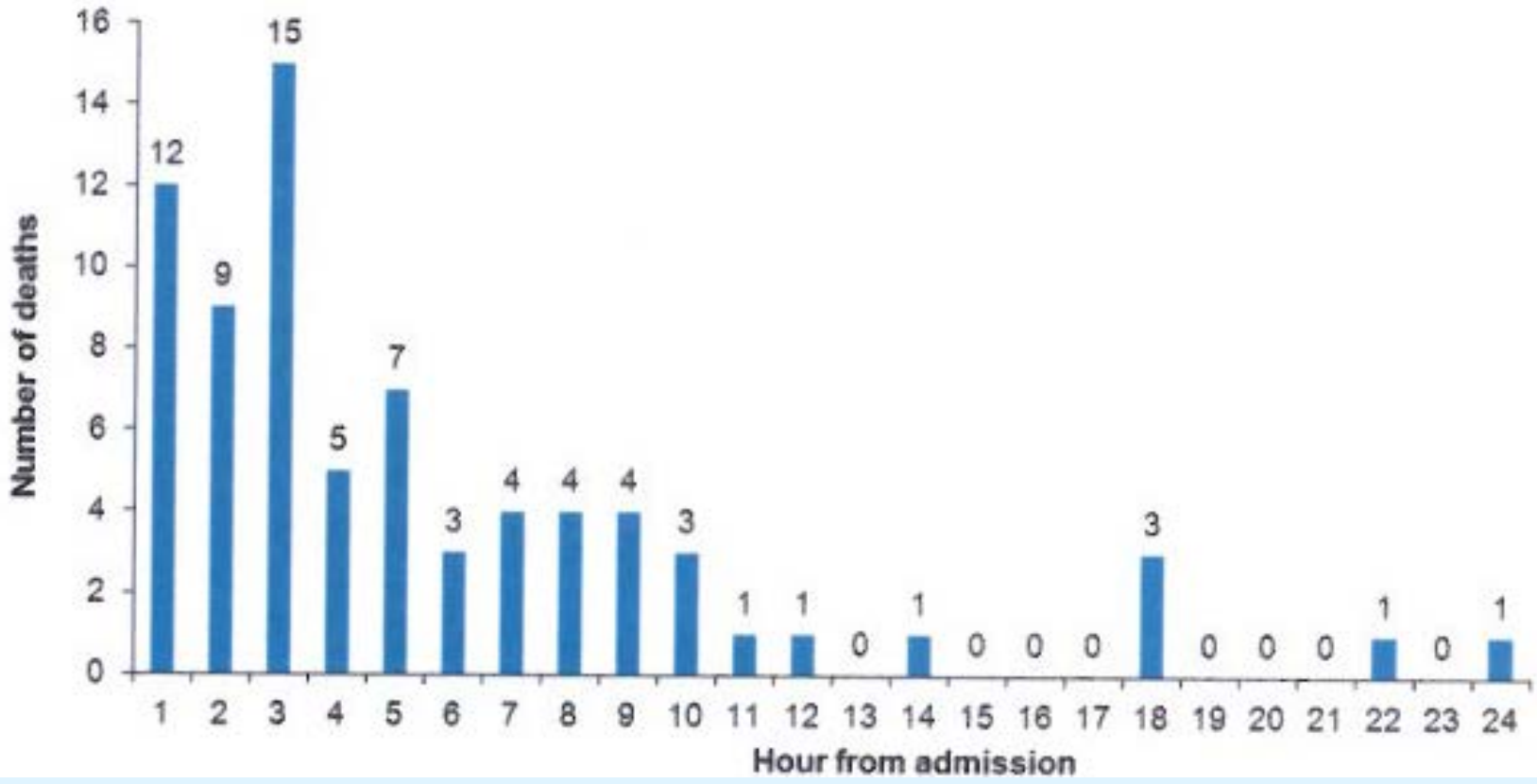
Evidence into practice

Practice: NIHR Trauma study

- 22 hospitals, 2009-11
  - Major trauma centres & trauma units
- N = 12,290
  - 479 major transfusions
  - 146 massive transfusions
- Median times to first Tx:
  - RBC – 30 mins
  - FFP – 80 mins
  - Cryo - 156 mins

Centres across England and Wales

UK Data - NIHR Trauma study
Time of deaths



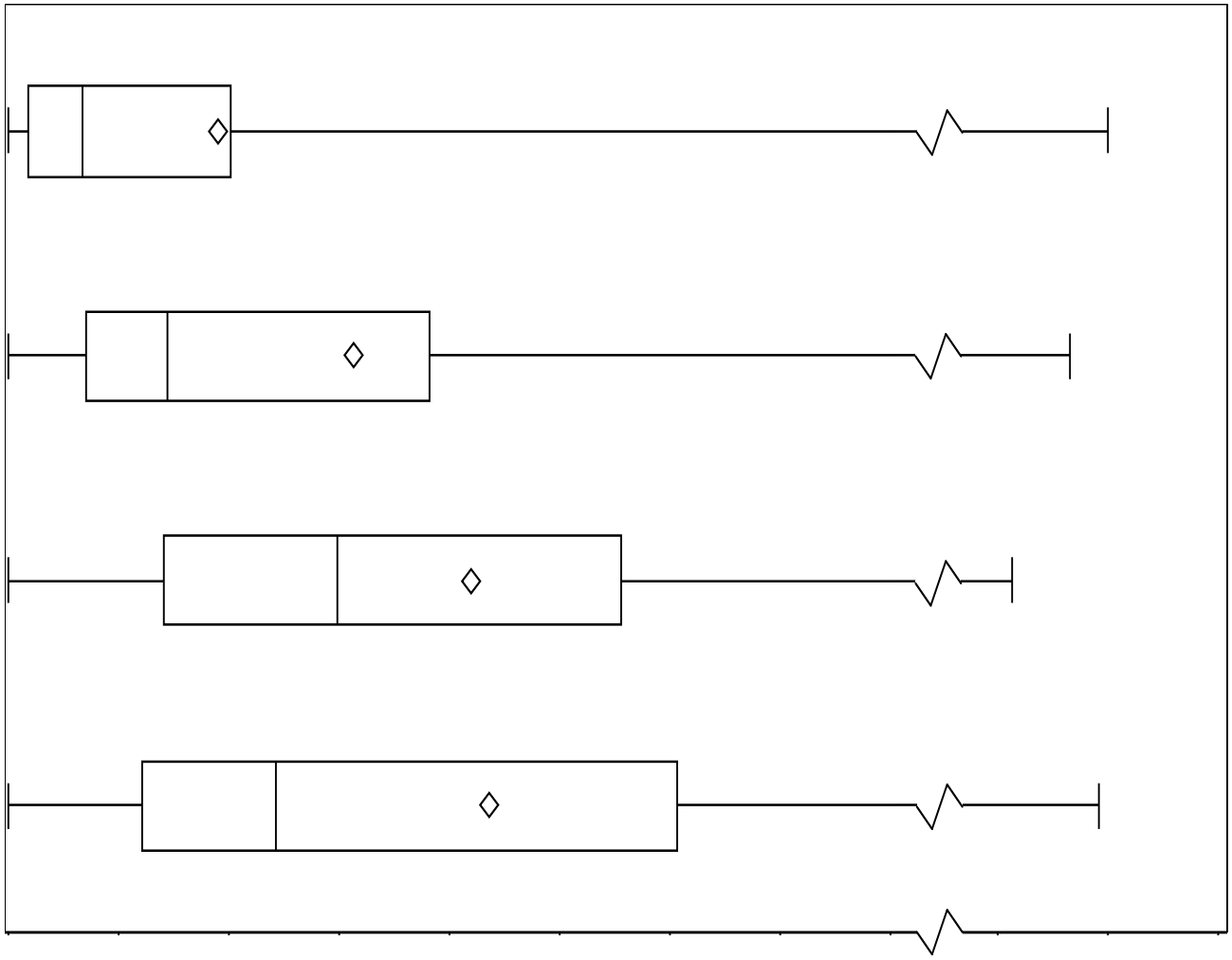
Timely support?

Red cells

Plasma

Cryo

Platelets



Beyond trauma and beyond blood...

- No studies have specifically addressed the use of 1:1:1 blood resuscitation in cardiovascular surgery, upper GI bleeding, burn surgery, liver transplantation, or obstetrical bleeding.

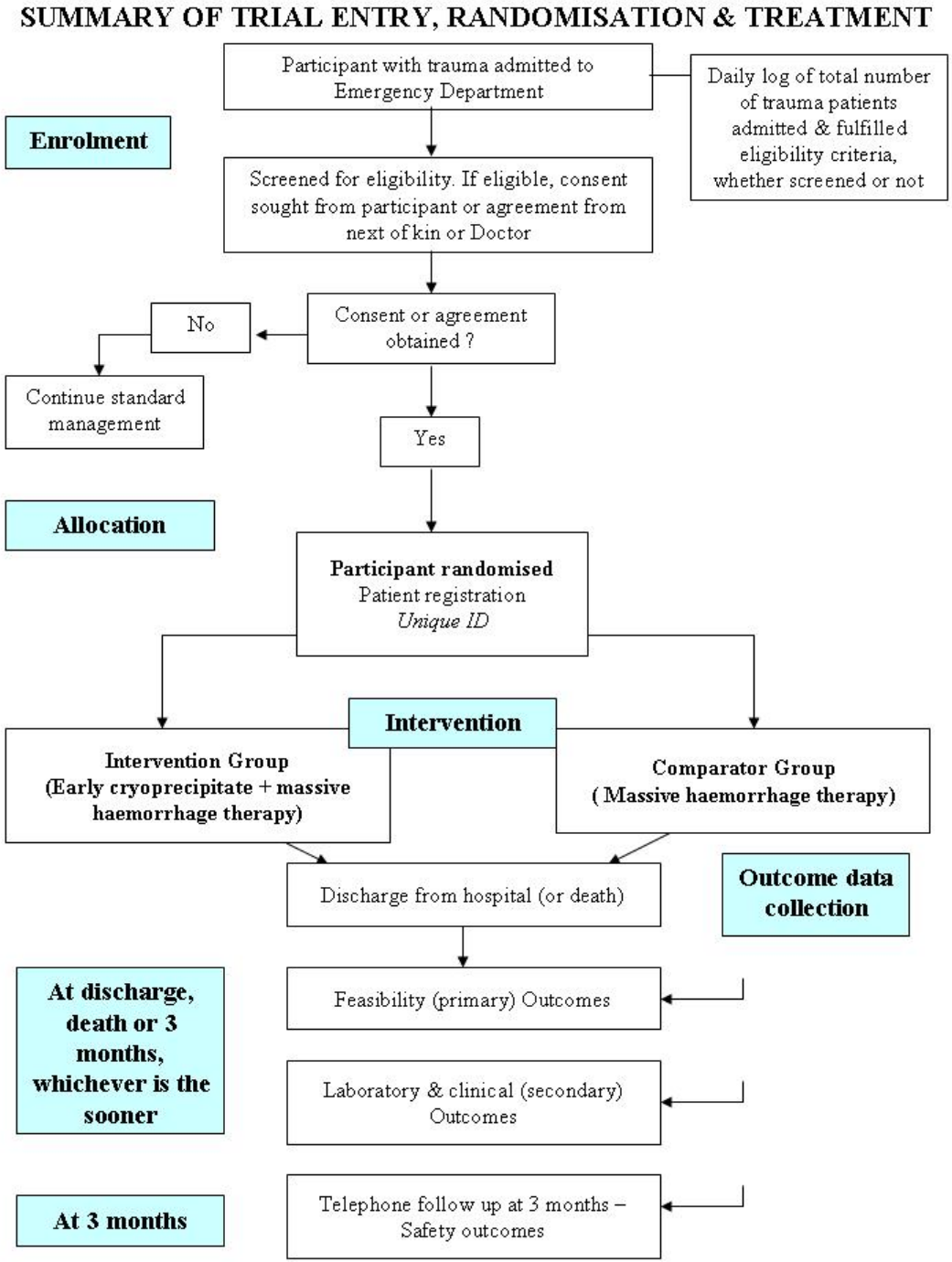
- These often older patients have co-morbidities and clinical features very different from trauma.

Conclusions & Acknowledgements

- Coagulopathy
- Management
- Practice & Timing
- Systematic reviews initiative, NHSBT
- New, relaunched Transfusion Evidence Library:
- www.transfusionevidencelibrary.com

Times to transfusion

	Time in minutes to first transfusion after admission		
	Median	Q1	Q3
All centres			
Red cells	43	12	133
FFP	92.5	44	237.5
Platelets	150	73.5	364.5
Cryoprecipitate	184	84	330



CRYOSTAT

EARLY CRYOPRECIPITATE IN TRAUMA

- **Intervention group:**
  Receive cryoprecipitate within 90 minutes of admission
- **Comparator group:**
  Receive standard massive haemorrhage protocol

Baseline characteristics

	Intervention (n = 22)	Comparator (n = 22)
Age	40	47
Gender	82%	73%
ISS	31	38
Blunt injury	90.9%	72.3%
Admission SBP	84	76
Admission PR	125	113

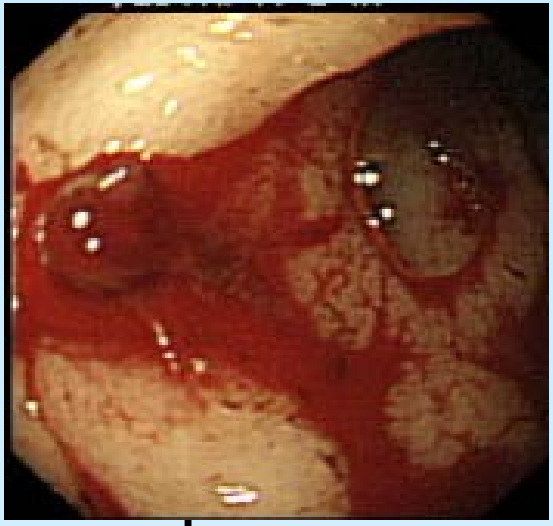
Fibrinogen Levels

	Intervention	Comparator
During active bleeding	2.19 (1.92 – 2.51)	1.28 (1.26 – 1.51)
24 hours	2.97 (2.15 – 3.90)	3.03 (2.43 – 3.26)
7 days	5.66 (5.00 – 7.71)	5.84 (5.45 – 7.00)

Future research implications

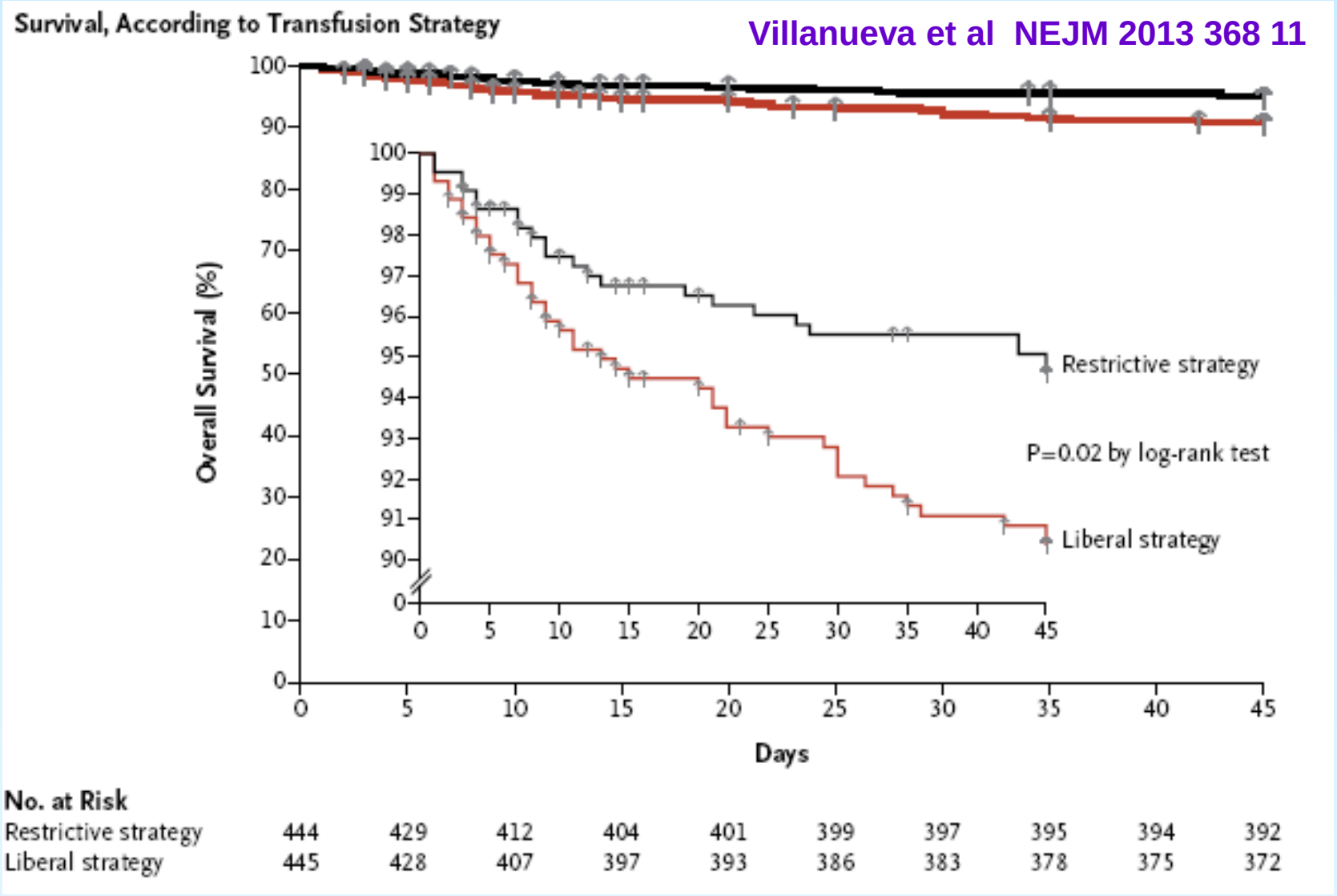
- Next steps might include:
  - Larger trial to assess clinical effects
  - Which intervention?
  - Primary endpoint: mortality

Beyond trauma: E.g. Acute upper gastrointestinal



- Leading cause of admission with haemorrhage
- >70,000 admissions annually in UK
- 25% > 80 years of age with co-morbidity
- 5-10% mortality; little change in rebleeding rates
- Patients with gastro-intestinal bleeding have different clinical features, a greater burden of co-morbidities, and the pathophysiology of haemostatic breakdown differs from trauma

Transfusion strategies for acute upper gastrointestinal bleeding



To quantify the effect of TXA on mortality and morbidity

- **Population:** All adults with significant acute upper or lower gastrointestinal bleeding. The clinician should be substantially uncertain whether or not to use TXA
- **Intervention:** TXA or placebo.
- **Outcome:** Mortality within 28d - overall, cause specific
- **Trial design:** Randomized, double blind
- **Target sample size:** 8,000 adults
- **Where?** 60 UK sites now live. International.

Is TXA safe in AUGIB?

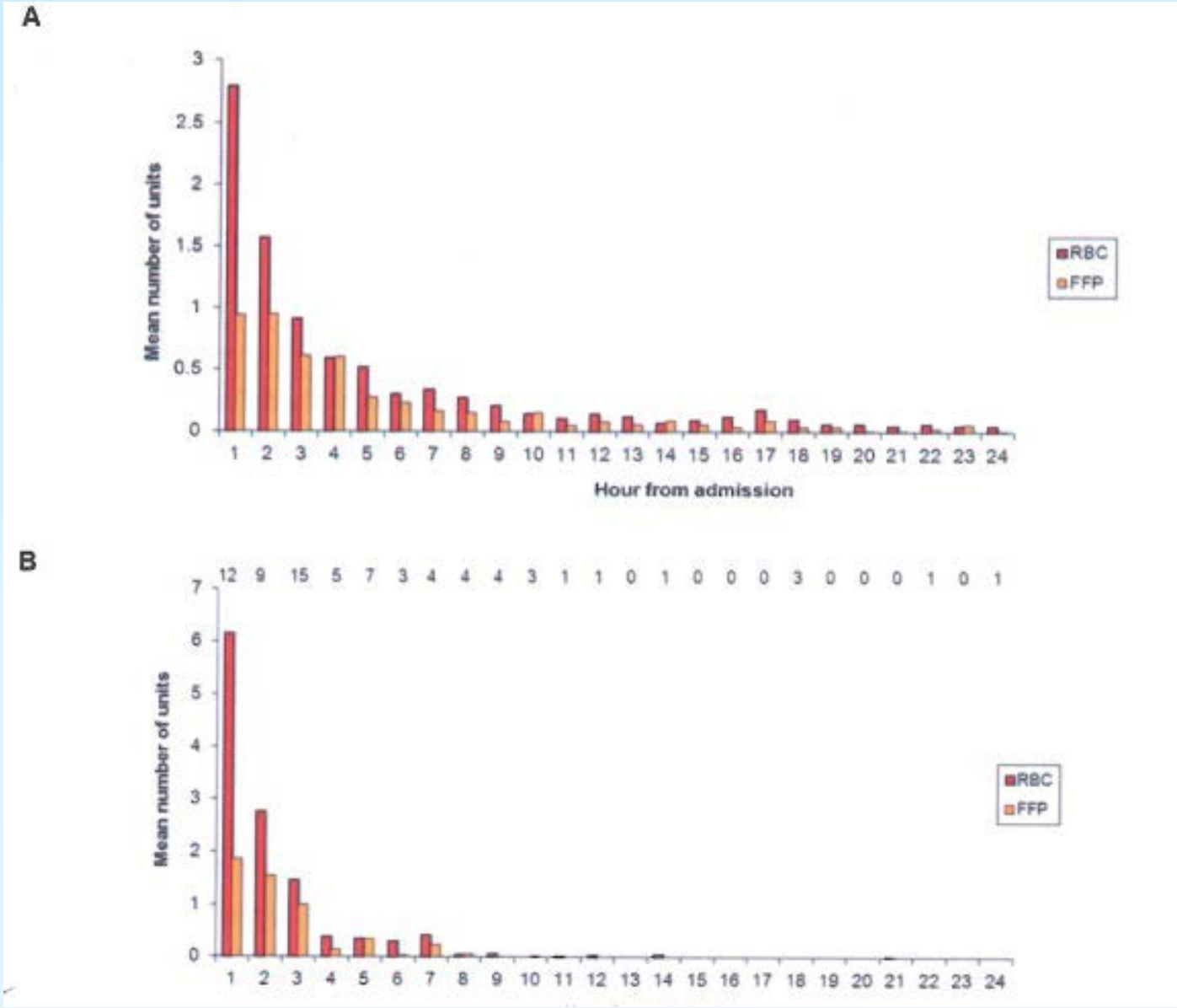
Conclusion

- Transfusion management of patients with major bleeding – update and challenges
- Studies are being undertaken and planned
- Main research gaps are fibrinogen and platelets

Acknowledgments

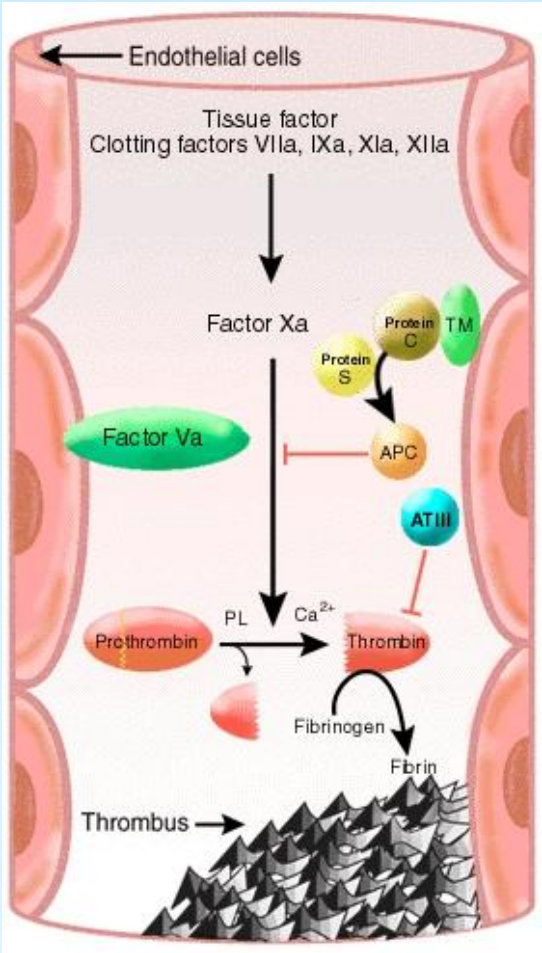
- NIHR PGfAR (Allard, Brohi, Campbell, Curry, Davenport, Eaglestone, Edwards, Glasgow, Hunt, Hyde, Khan, Raza, Rourke, Seeney, Stokes, Woodford)
- INTRN (European network)

Use of red cells and plasma



Fibrinogen in trauma

- Fg the first of all proteins to fall
- Hypothermia: increased Fg breakdown
- Acidosis: reduced Fg production
- Haemodilution:
  - Functional deficiency of Fg – worse with colloids (abnormal polymerisation of Fg)
- Fibrinolysis



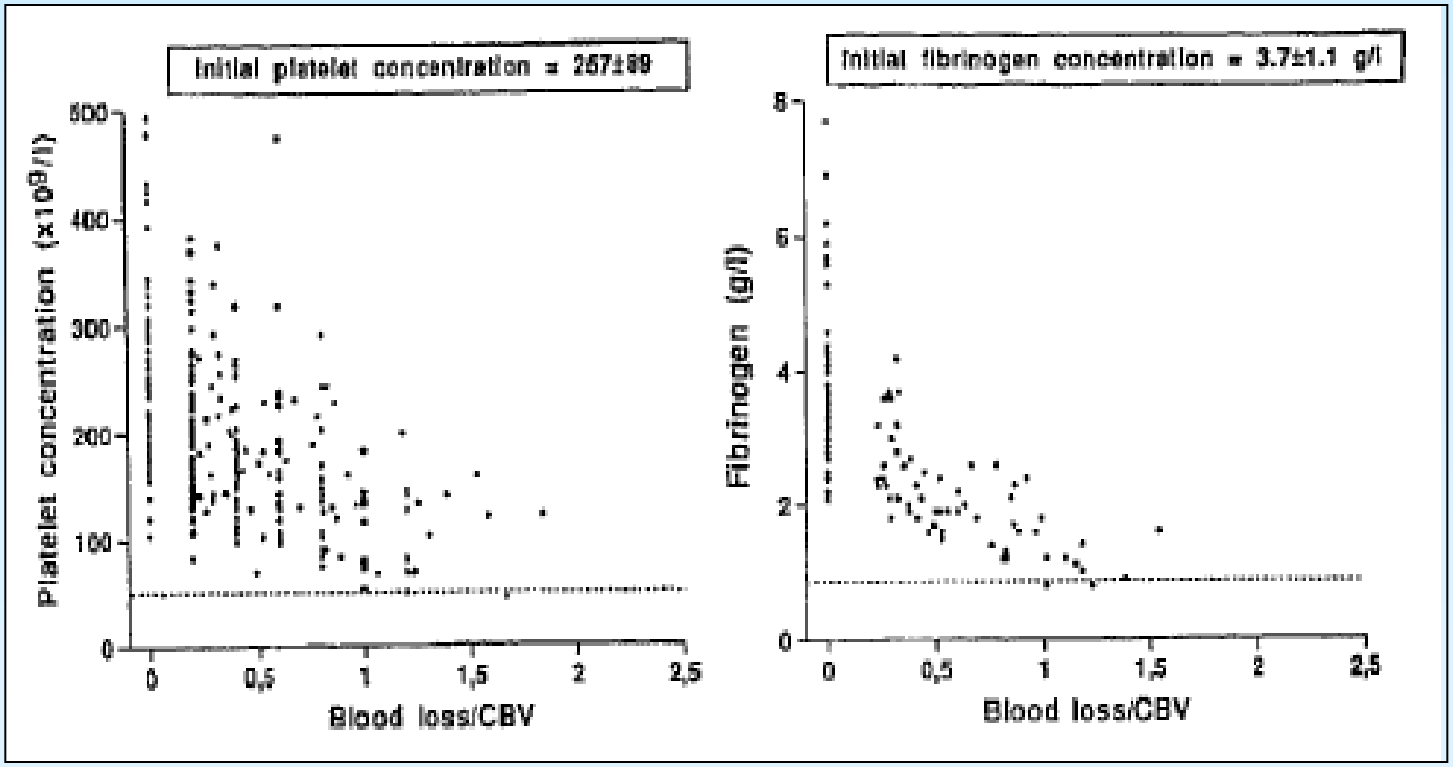
Hiippala, *Anesth Analg*. 1995; **81**

Martini, *Am J Physiol Endocrinol Metab*. 2005; **289**

Fenger-Eriksen, *J Thromb Haemost*. 2009; **7**

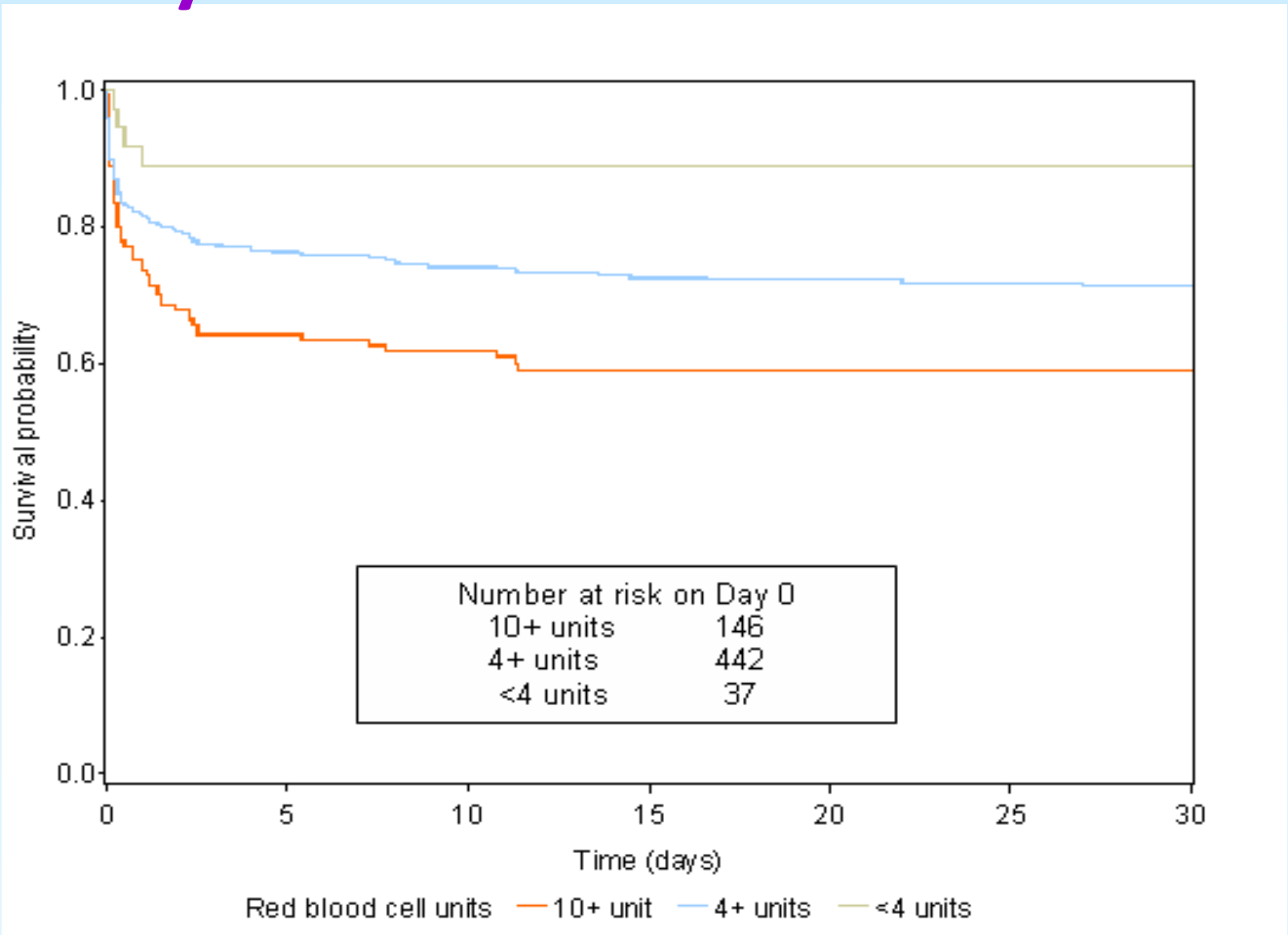
Fibrinogen & major surgical blood loss

Hiippala ST et al., Anesth Analg. 1995 Aug;81(2):360-5



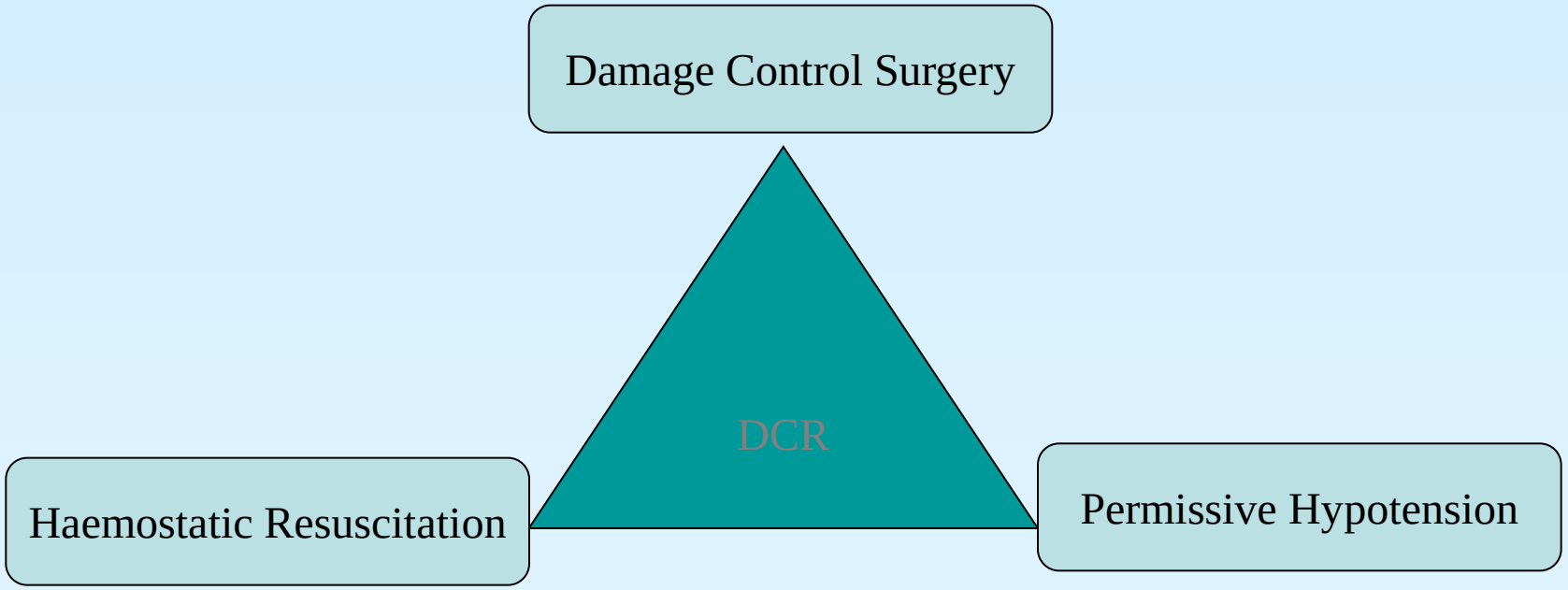
Fibrinogen is major coagulation protein, and deficiency developed earlier than other coagulation factors with use of plasma poor RC

Survival at 30 days post-admission by number RBC units received



Damage Control Resuscitation

– STOP the bleeding:



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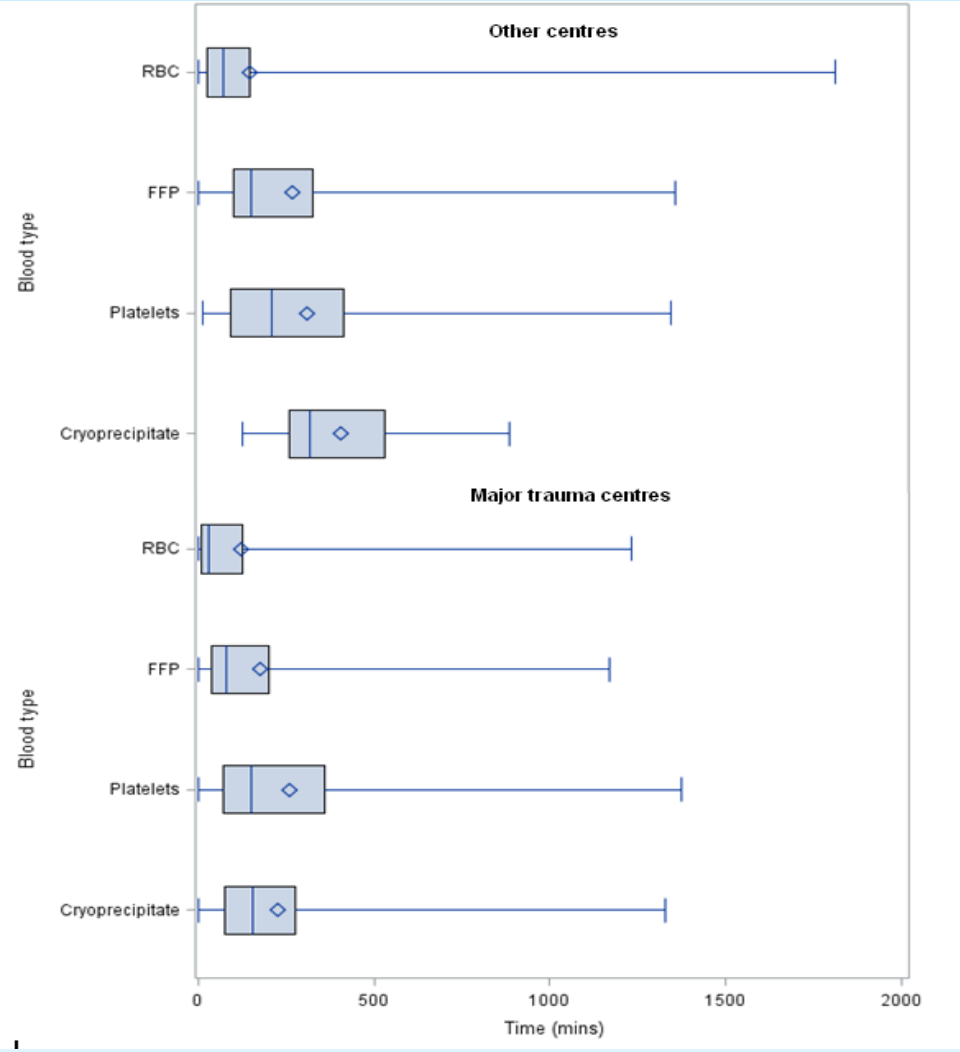
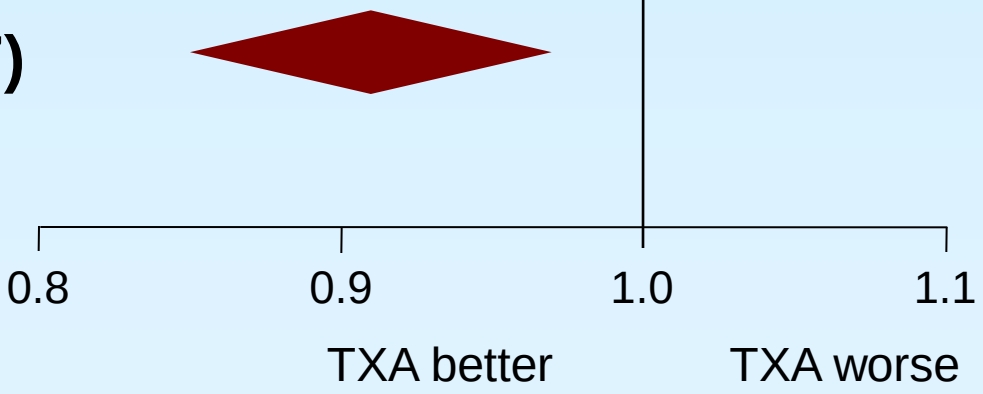


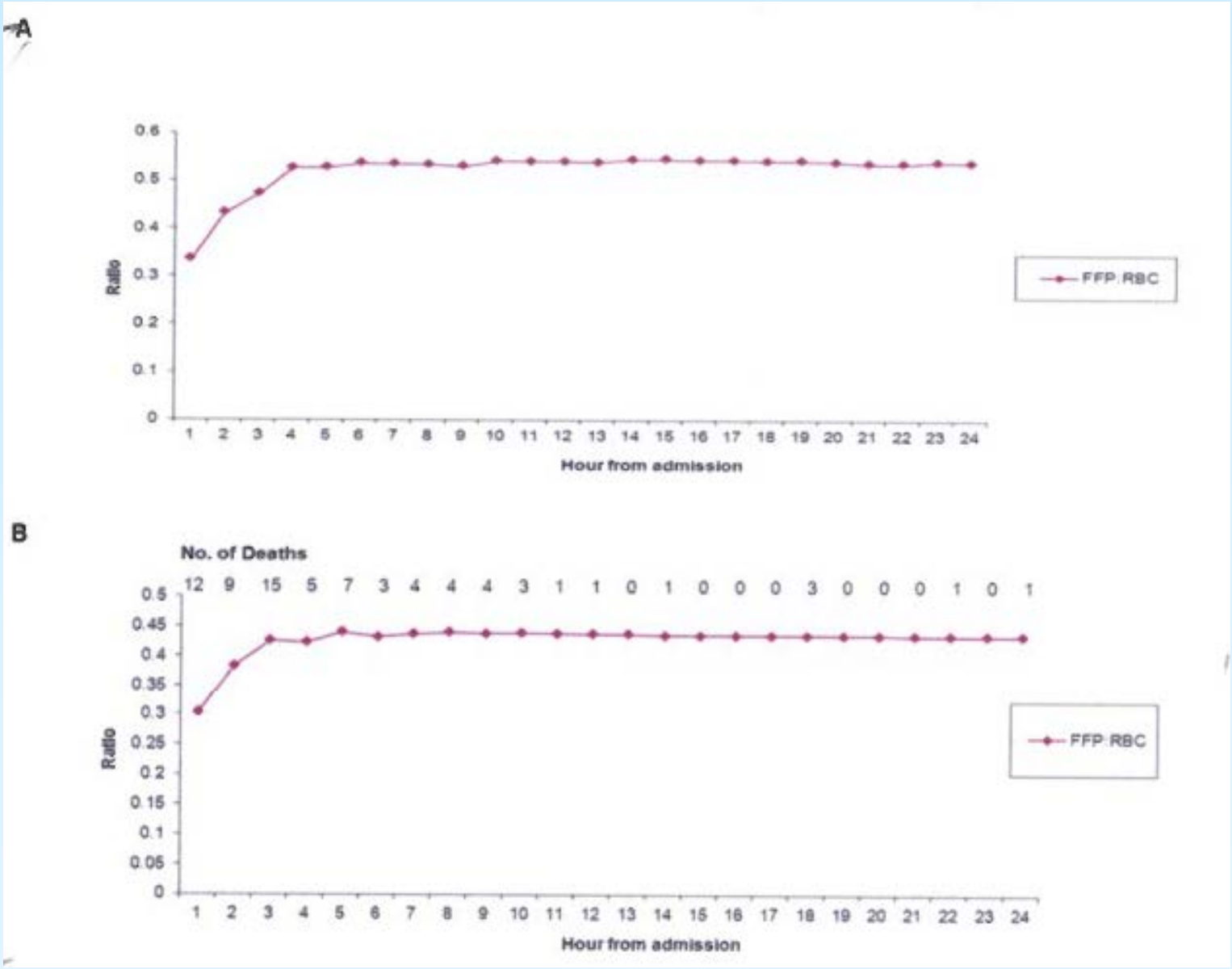
CRASH-2: Any cause of death

TXA	**Placebo**	RR (95% CI)
(n= 10,060)	**(n= 10,067)**	
1,463 (14.5%)	1,613 (16.0%)	
0.91 (0.85–0.97)		

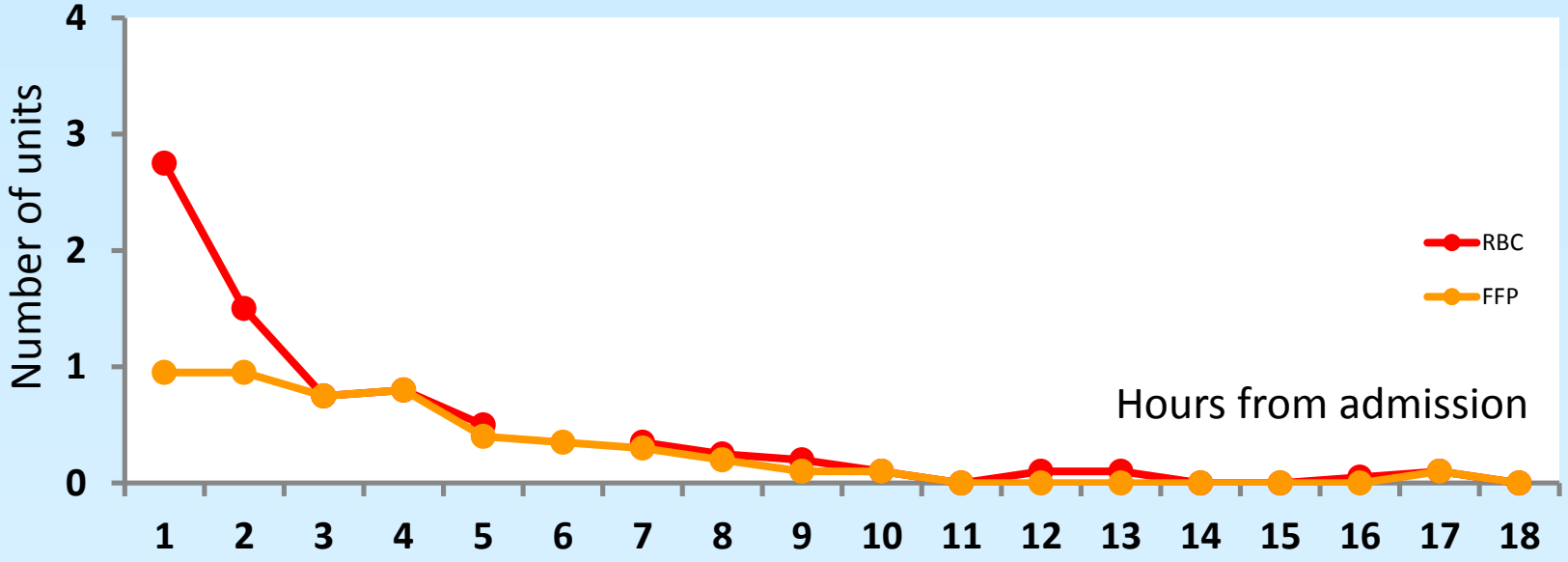


The **CRASH-2** Collaborators. *The Lancet*. 2010; 376(9734):23-32

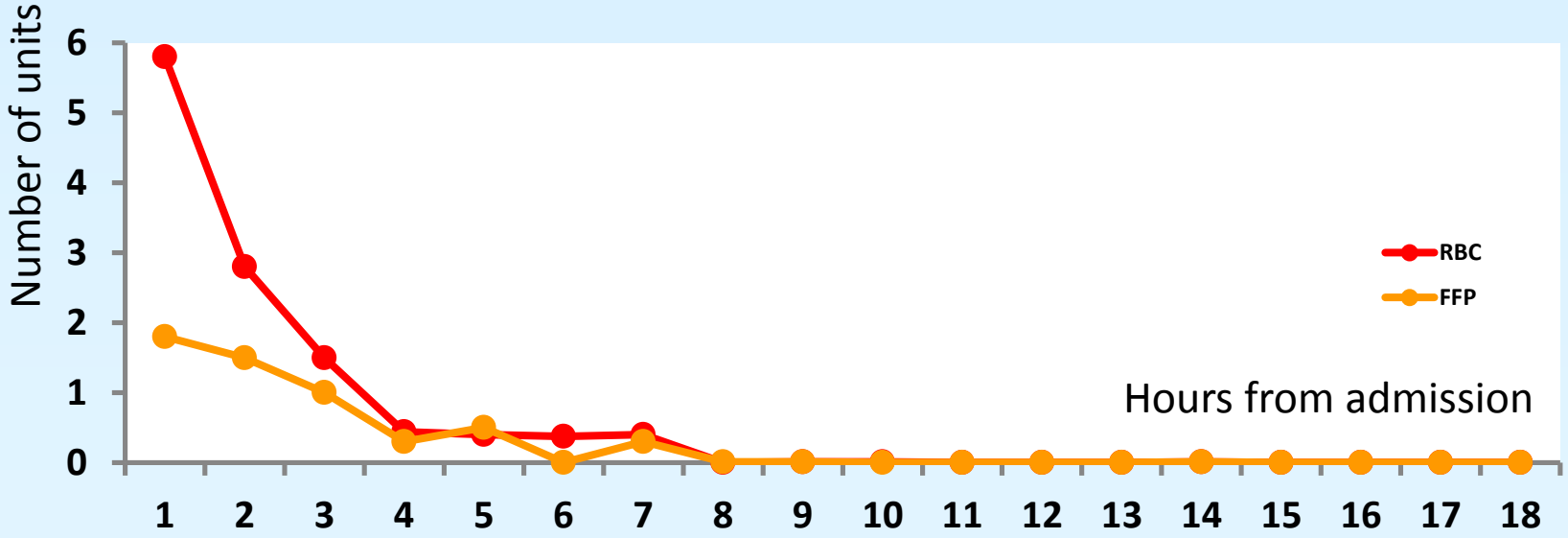
Cumulative Ratio of mean FFP to mean RBC by hour transfused



Mean number of units of RBC and FFP transfused within 24 hours of admission for A) patients who survived (n=356) or B) died (n=78) within that period



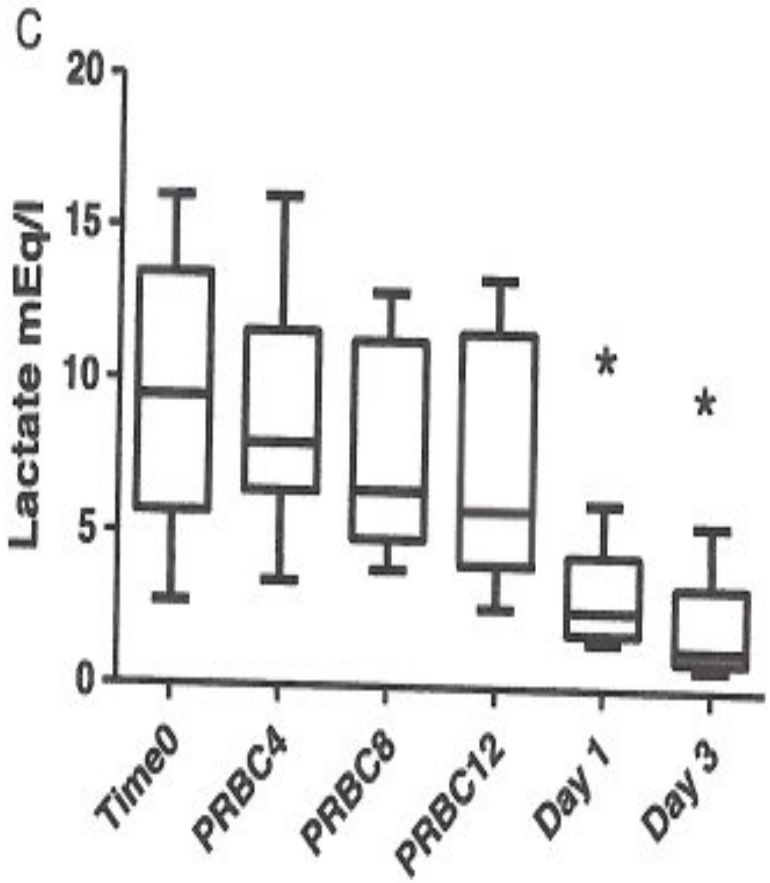
No. of deaths 12 9 15 5 8 3 4 5 4 3 1 2 0 1 0 0 0 3



Summary: Are we improving outcomes?

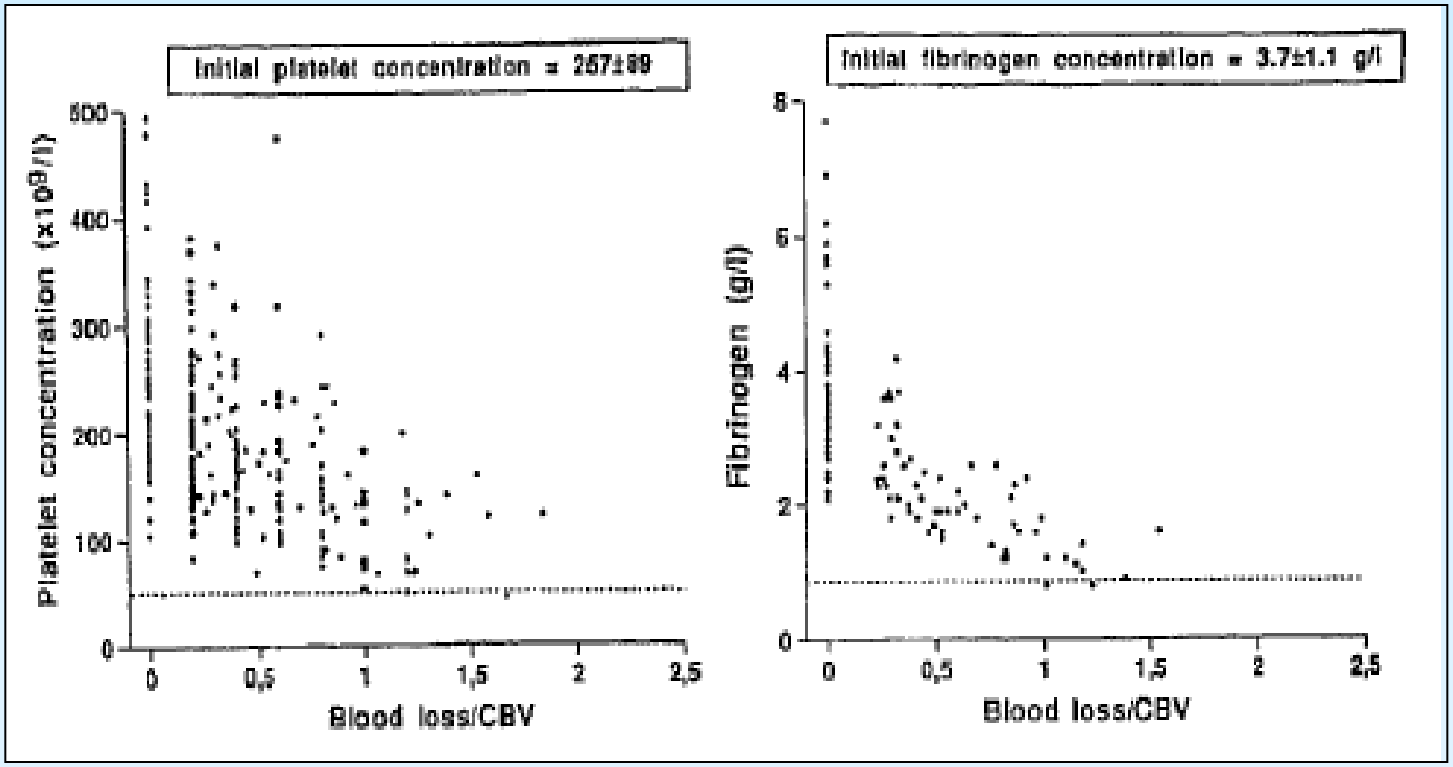
Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage

Sirat Khan, MD, Karim Brohi, MD, Manik Chana, MD, Imran Raza, MD, Simon Stanworth, MD, Christine Gaarder, MD, PhD, Ross Davenport, MD, PhD,
***on behalf of* the International Trauma Research Network (INTRN),** *London, United Kingdom*



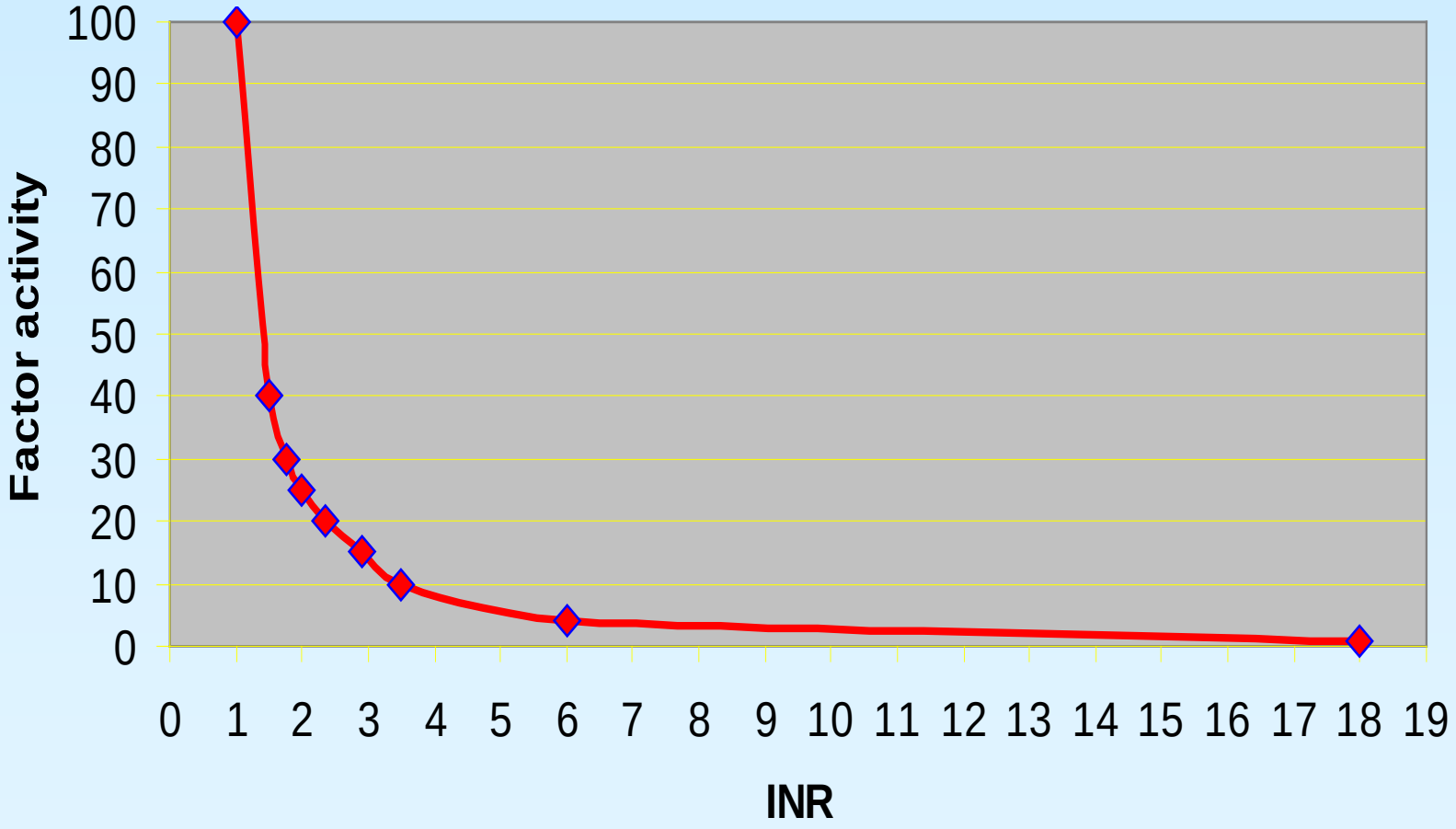
Fibrinogen & major surgical blood loss

Hiippala ST et al., Anesth Analg. 1995 Aug;81(2):360-5



Fibrinogen is major coagulation protein, and deficiency developed earlier than other coagulation factors with use of plasma poor RC

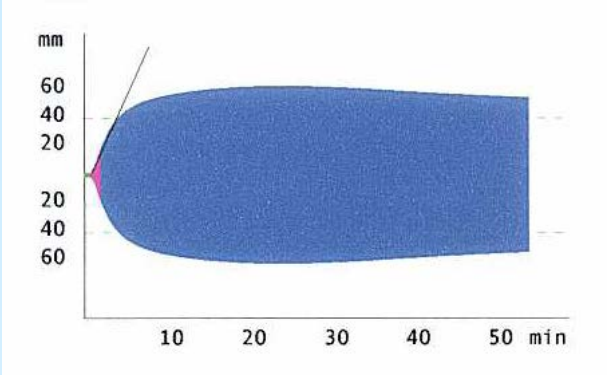
Variable effect of plasma on INR and coagulation factor levels

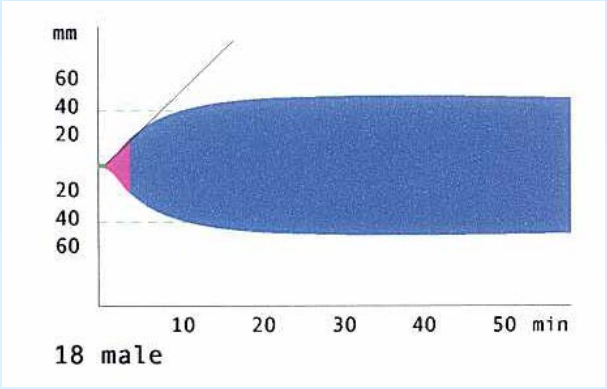


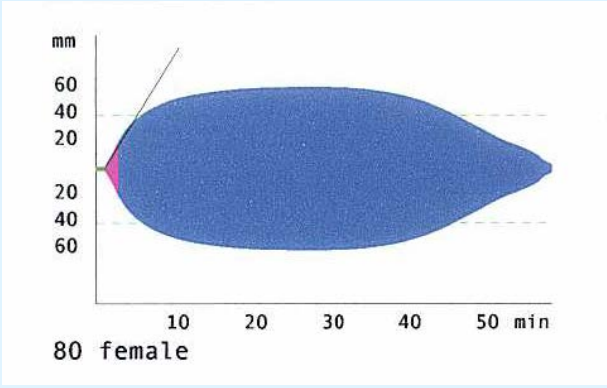
Modified: Yuan S et al, Thrombosis Res 2007

Observational Study – ACIT-2

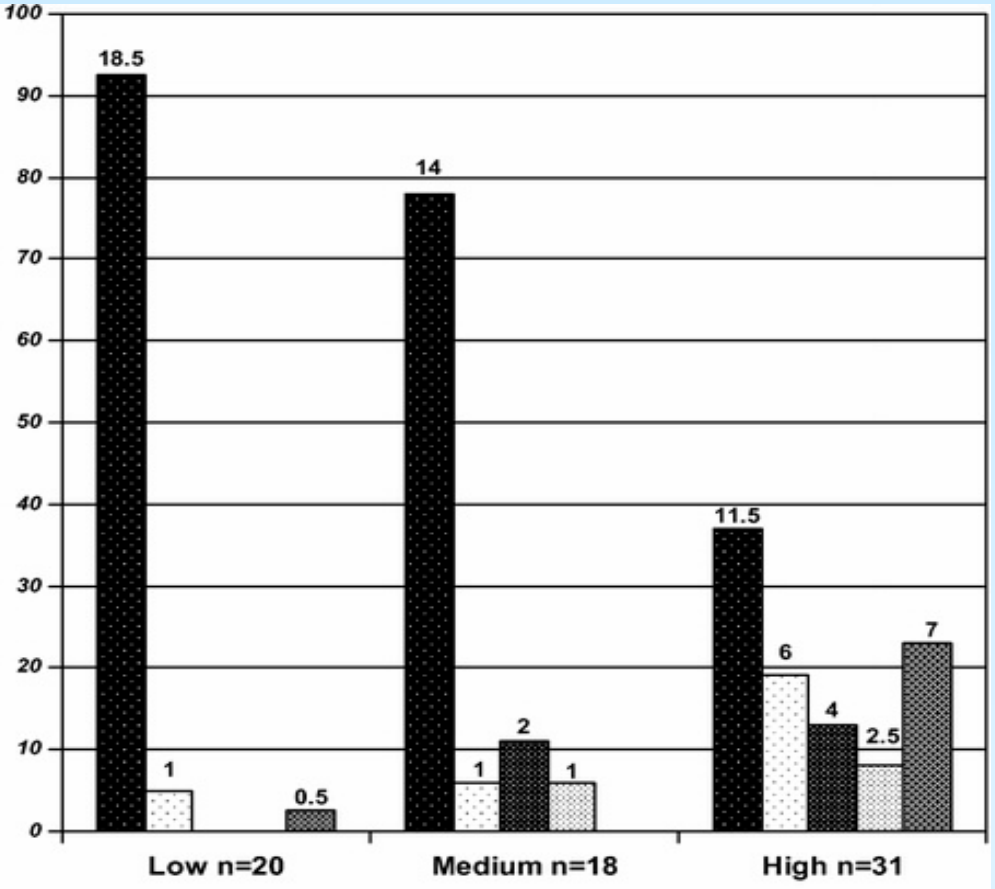
- **Aims 3 & 4 of grant:**
  - **Determine key derangements in coagulation**
  - **Develop a prediction model for massive transfusion**
  - **Understand which blood products are most beneficial**







But...are these groups the same?



Hemorrhage %†	92.5 [a]	78 [a]	37 [b]
Sepsis %	5	6	19
MOF %	0	11	13
Airway/Breathing %	0	6	8
CNS %	2.5	0	23
Time to death (hrs)[2*]	2 (1 – 4) [a]	4 (2-16) [b]	38 (4 – 155) [c]

Other studies of FFP to RBC ratios

Author	'n'	Benefit (HR)	Correction for bias
Duchesne,2008	135	18.9 (6.3-56.4)	No
Gunter, 2008	259	1.8 (1.0-3.1)	No
Holcomb,2008	466	60% vs 40%	Excluded 1 death in 30'
Kashuk, 2008	133	U-shaped	No
Maegele,2008	713	76% vs 54%	Excluded pre-ICU deaths
Sperry,2008	415	2.1 (1.3-3.3)	No
Teixeira, 2009	383	3.5 (2.5-4.8)	No
Zink, 2009	452	74% vs 45%	No
Snyder. 2009	134	1.2 (0.7-2.1)	Time-dependent covariate
Magnotti,2011	103	1.8 (0.9-3.6)	Time-dependent covariate

	FFP	Cryo	FgC
Source	Single donor or pooled plasma	Pooled plasma	Pooled plasma
Volume to deliver 2g	~1 litre	~150-200ml	100ml
Standardisation	No	No	Yes
Viral inactivation	Standard FFP- No	No	Yes – pasteurisation 60°C for 20 hrs; & Fg adsorption/precipitation removes virus
Storage	-30°C Requires thawing	-30°C Requires thawing	Room temperature
Adverse effects	TRALI, TACO, ARDS, TTI	TRALI, TTI	TTI, Thrombosis
Cost of 2g equivalent dose	£400	£190	£800

Trauma studies using FgC

Reference	Study	No	Median dose FgC	Groups	Outcomes
Schochl, 2011	Retrospective, 2 databases	80 vs. 601	6g FgC 1200 IU PCC 6U FFP	FgC +/- PCC vs. FFP	Signif. reduction of RBC, Plt use No difference in mortality
Nienaber, 2011	Retrospective, 2 databases	18 vs. 18	4g FgC 1200 IU PCC 10U FFP	FgC +/- PCC vs. FFP	No difference in mortality ↓MOF with FgC group
Schochl, 2010	Retrospective, Single centre	131	7g FgC 2400IU PCC 10U FFP		↓mortality compared to TRISS
Schochl, 2010	Case report	1	12g FgC		Survived
Schochl, 2010	Case report	1	13g FgC 400IU PCC		Survived
Brenni, 2009	Case report	1	16g FgC 1g TXA		Survived

Cardiac trials – all prophylaxis

Intervention	Patient	Number Trials
Fibrinogen	CABG Cardiac surgery	2
PCC	Cardiac surgery, on warfarin	1
Factor XIII	CABG Myocardial revascularisation	2

Sherliker, L