

FFP: “Friend or faux pas” in critical care (and trauma)?

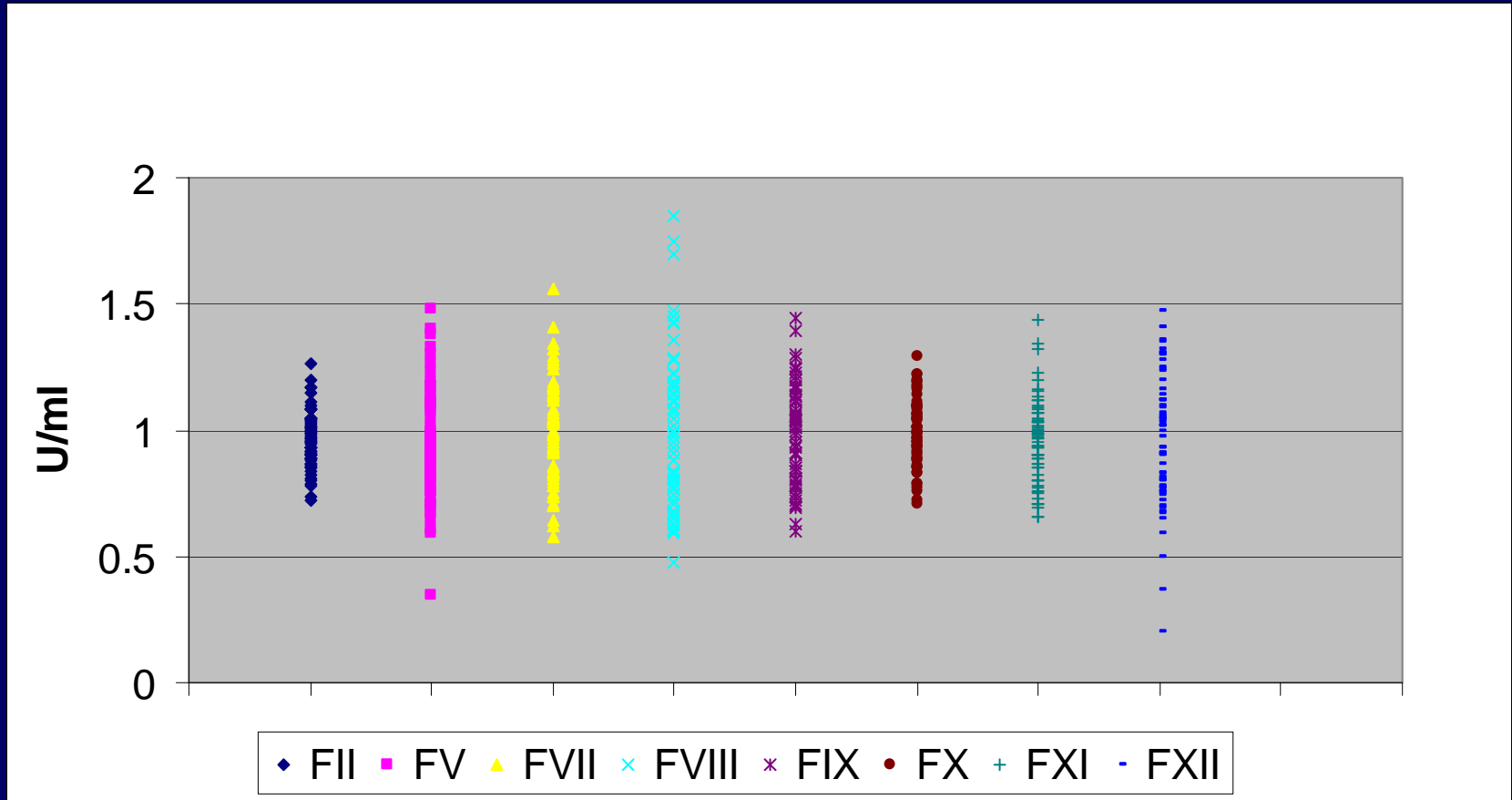
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Themes around the use of FFP in critical care

- Variable but consistent usage
- ‘Coagulopathy’
- High proportion administered as prophylaxis
- Evidence base inadequate but presumably exists because of a plethora of guidelines

What is FFP? Coagulation Factor content

Rebecca Cardigan, CDL, NBS



Many reasons for variable content; clinical implications

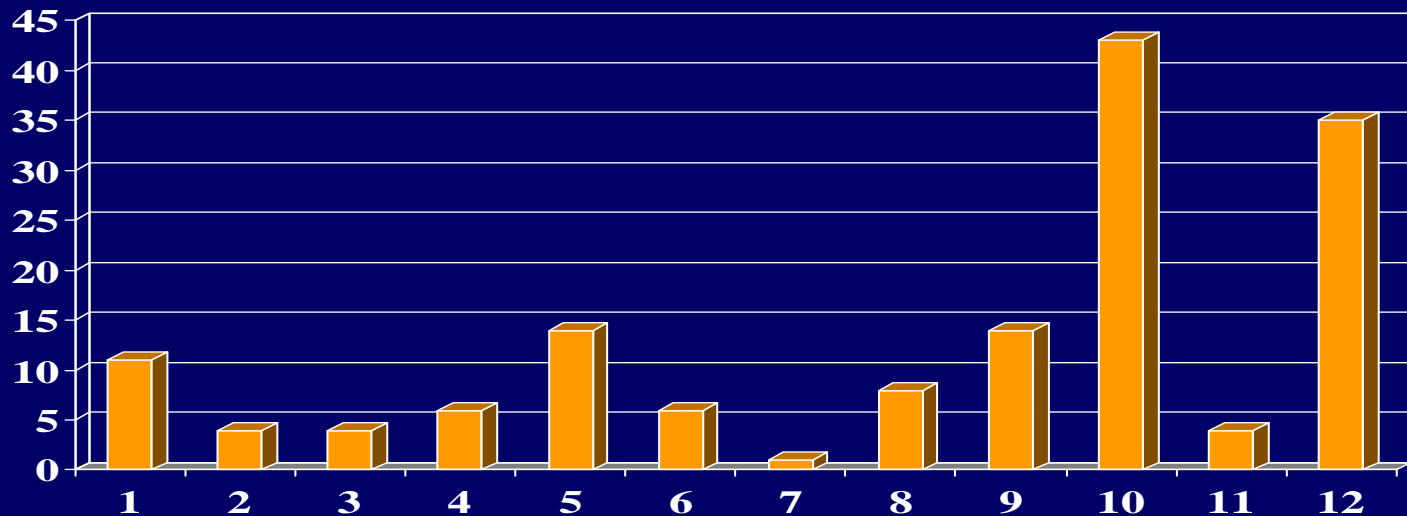
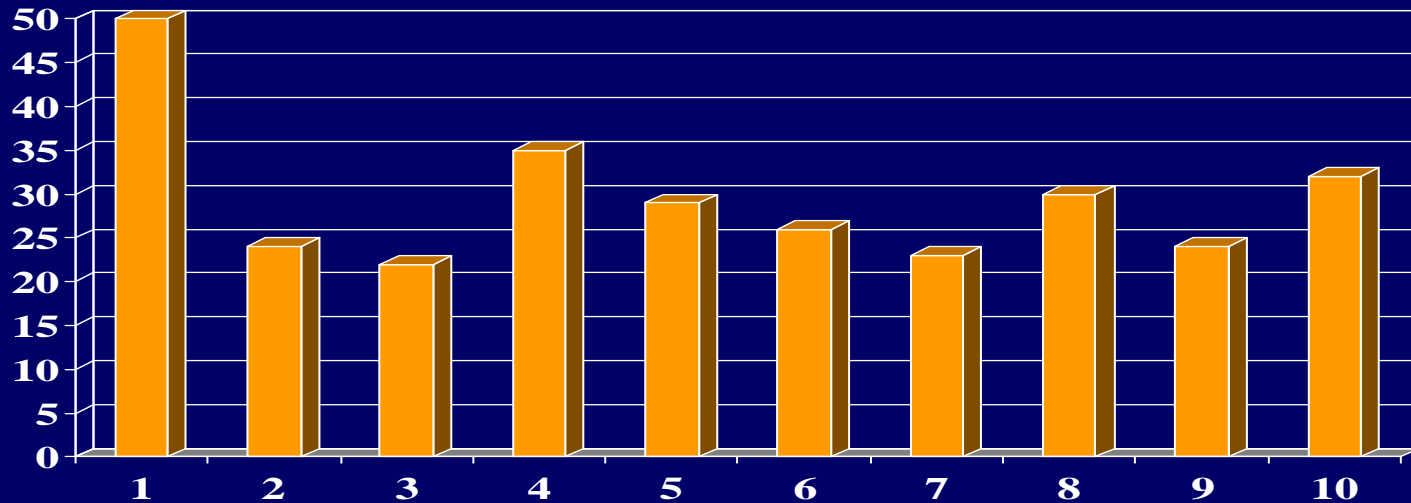
Pathogen inactivated FFP

- 20-30% loss factor VIII in Solvent-detergent FFP
- 15-20% loss factor XI
- 10-15% loss factor XIII, 35% loss PS
- Greater reductions plasmin inhibitors, α_2 -antiplasmin
- Clinical significance uncertain: e.g. thrombosis

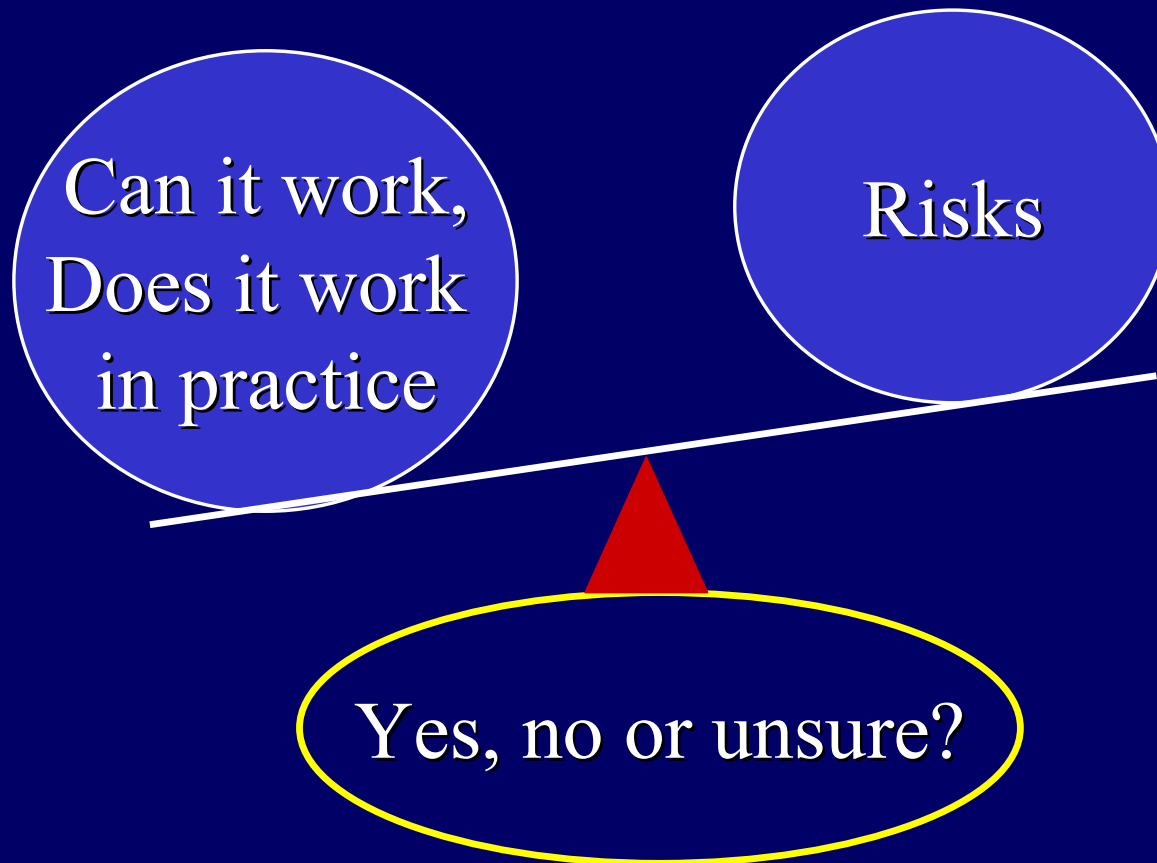
Loss of clotting factor activity— Methylene Blue treatment

- one study indicating changing patterns of demand

Hospital A used 295 units in 10 months, & hospital B used 162 units of FFP



Do presumed benefits of use outweigh finite risk?



“No evidence of effect” or “Evidence of no effect”?

Harm

*Holness; Transfusion Medicine Reviews, 2004;18:184;
& Transfusion 2005, 45: 1048*

Non-infectious as well as infectious risks
FFP most 'high risk' component - SHOT
TA adverse pulmonary sequelae:

-widening our perspective:

- TRALI (acute lung injury)
- TACO (circulatory overload)

Intensive care

Gajic et al, Am J Respir Crit Care Med, 2007

- 2 yr Prospective Cohort Study, Mayo Clinic
- Incidence ALI (standardised) ~8% (74/901)
- Patient and Transfusion (female) risk factors

Dara et al, Crit Care Med, 2005, 33, 2667

- Retrospective Cohort Study of ICU patients
- New Onset ALI more common in FFP transfused group (n=18/44; 18% vs 4%)

TRALI - UK

- Lower incidence
- Different causes
- Options eg Ab screening, use SD plasma, use less plasma, or
- Exclude female donors (2003 NBS)
- SHOT: 36 reports in 2002-3 to 10 reports last year
- One death but FFP not implicated

TACO: Volumes of FP transfusion for changes in coagulation results

Holland and Brooks, Am J Clin Pathol 2006; 126:133-139

Initial INR	Target INR							
	1.3		1.5		1.7		3.0	
	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)
6.0	4.5	64	3.5	50	2.5	36	1.5	21
5.0	4.3	61	3.0	43	2.3	32	1.0	14
4.0	4.0	57	2.5	36	2.0	29	0.5	7
3.0	3.5	50	2.0	29	1.5	21	-	-
2.0	2.5	36	1.5	21	0.5	7	-	-

Relation between PTR and APTT and measured individual coagulation levels

Chowdhury et al. Br J Haematol 2004; 125:69

Table I. PT and aPTT ratios of patients during the study.

	All patients, median (range)	In retrospect FFP not required, median (range)	In retrospect FFP required, median (range)
PT ratio	1.8 (1.4–20)	1.6 (1.4–1.9)	2.2 (1.5–20)
aPTT ratio	1.8 (1.1–10)	1.4 (1.1–2.8)	2.2 (1.2–10)

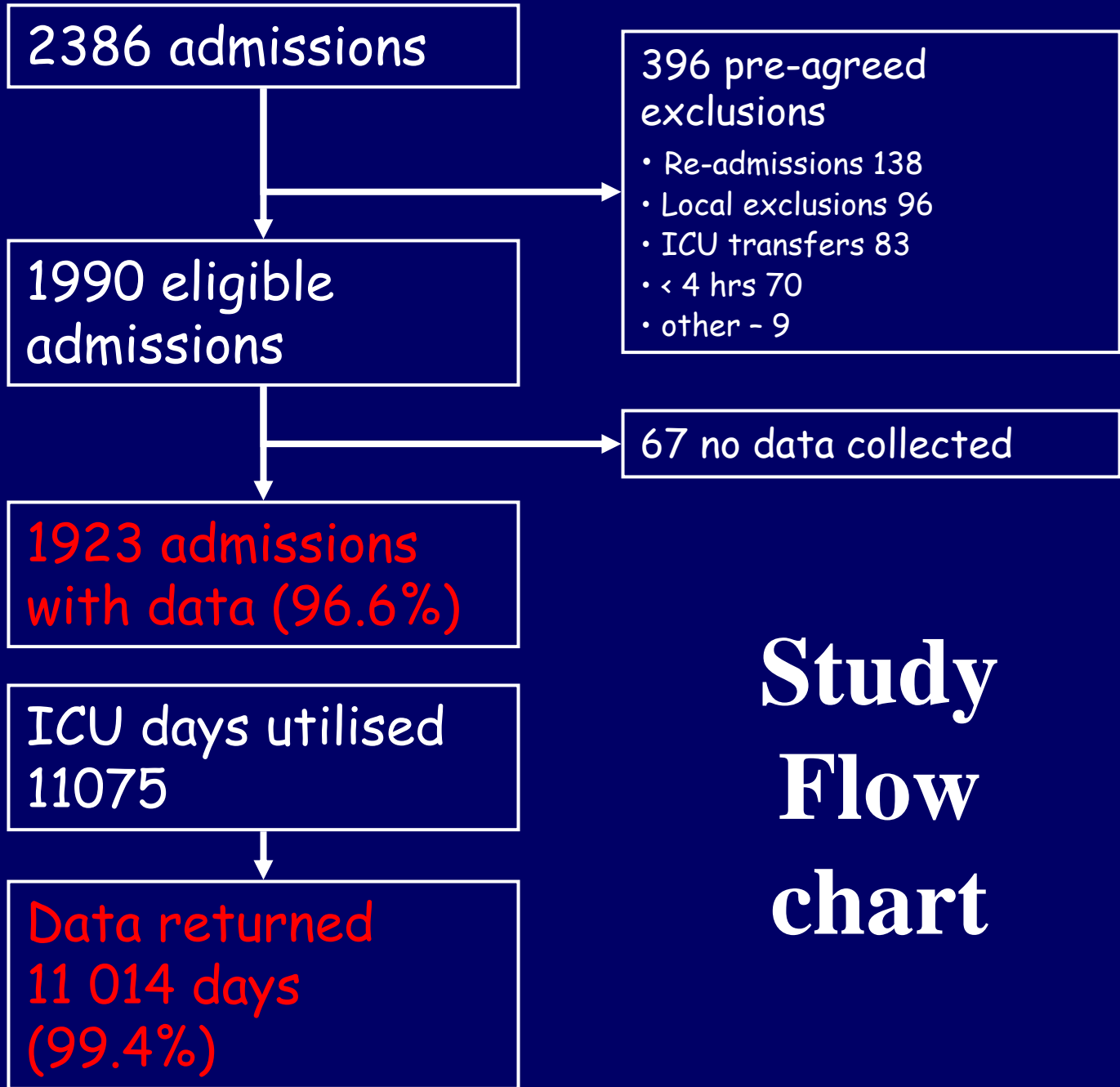
The median and range of the ratio of PT and aPTT, expressed as patient time divided by the mid-point of the normal range, are shown. Patients who, after retrospective analysis of coagulation factor results, had not required FFP are shown separately from those that had.

**Recommended doses of FFP (15mL/kg) did not reliably correct individual factor levels above 30IU/dL
Much higher doses (30mL/kg) were effective**

Understanding current clinical practice in critical care & next steps



Intensive care **S**tudy **O**f
Coagulopathy



Study Flow chart

Type of general ICU admission

	Medical	Surgical	Trauma
All patients	875	908	138
N (%)	(46%)	(47%)	(7%)
Coag.	273	277	25
Patients	(47%)	(48%)	(4%)
N (%)			

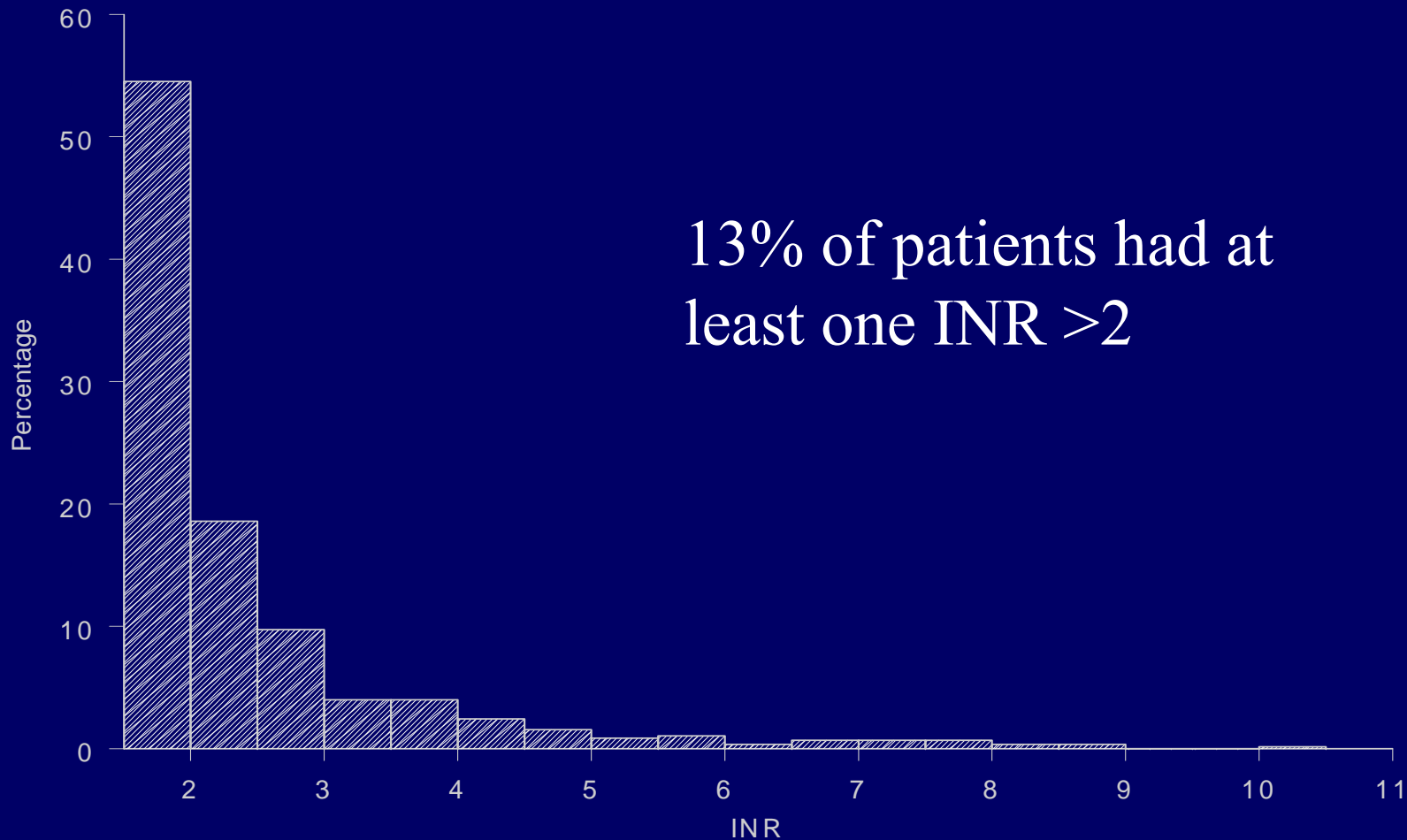
Prevalence of 'coagulopathy' in ICU

Admissions with abnormal coagulation test in ICU N (%)	Worst INR for admissions with abnormal coagulation test in ICU			
	1.6 – 2.5 N (%)	2.6 – 3.5 N (%)	3.6 – 5.0 N (%)	> 5.0 N (%)
576 (30)	421 (73)	79 (14)	46 (8)	30 (5)

30% of all admissions had coagulopathy (INR >1.5) during intensive care admission

Severity of “coagulopathy”

Worst INR for admissions with abnormal coagulation test in ICU



13% of patients had at least one INR >2

FFP transfusion

- 13% of all patients received FFP
- 33% of patient who had coagulopathy received FFP
- 4% of patients with no coagulopathy received FFP

Indications for FFP use

46% of FFP episodes associated with bleeding

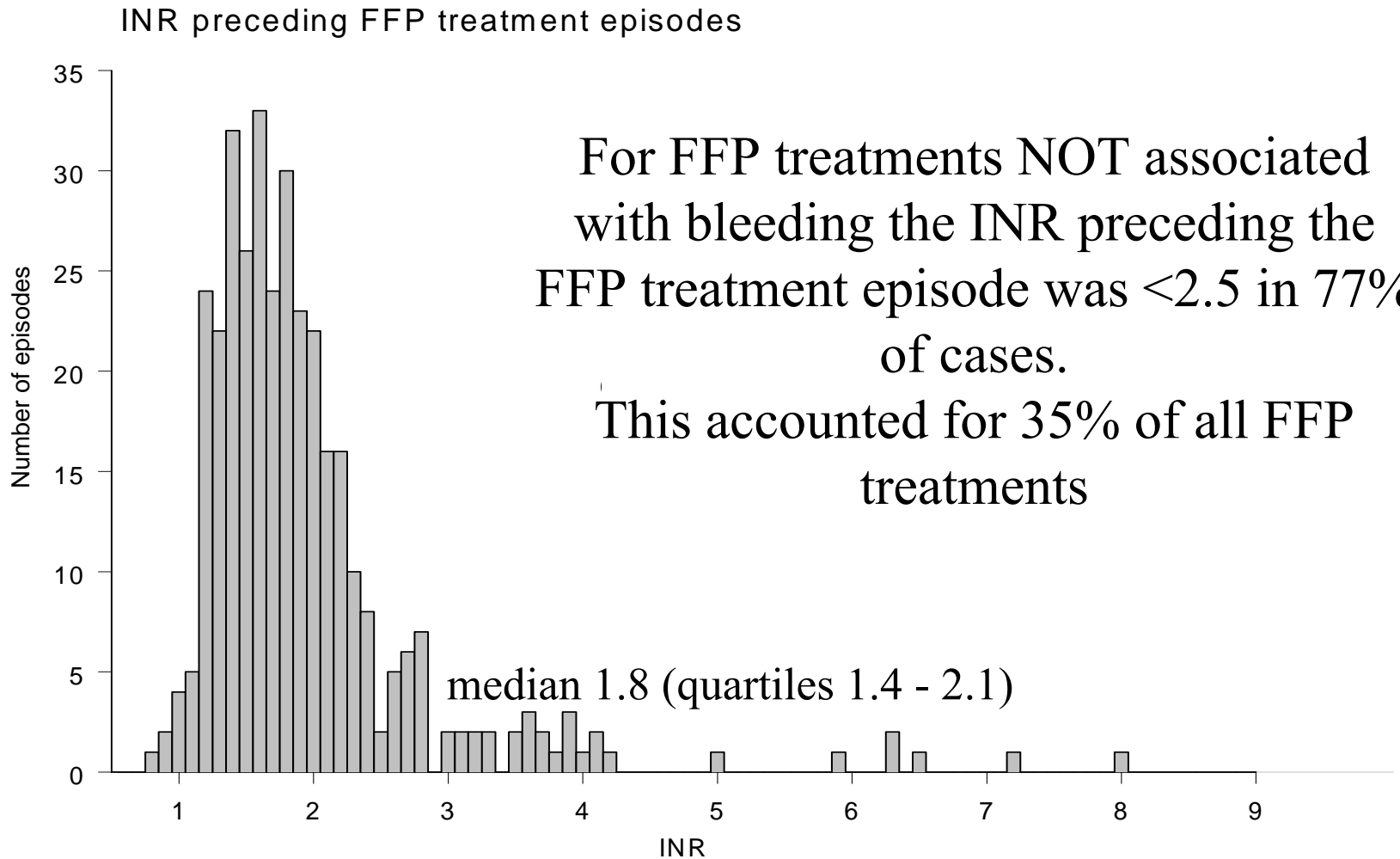
50% of FFP episodes no documented bleeding

15% prior to procedure in absence of bleeding

	Episodes (n = 404)
Reason for episode – N (%)	
Coagulopathy plus bleeding	185 (46)
Coagulopathy without bleeding	138 (34)
Coagulopathy without bleeding, prior to invasive procedure	59 (15)
Other reason	6 (1)
Not known	16 (4)



Intensive Care Study of 'Coagulopathy'



For FFP treatments NOT associated with bleeding the INR preceding the FFP treatment episode was <2.5 in 77% of cases.

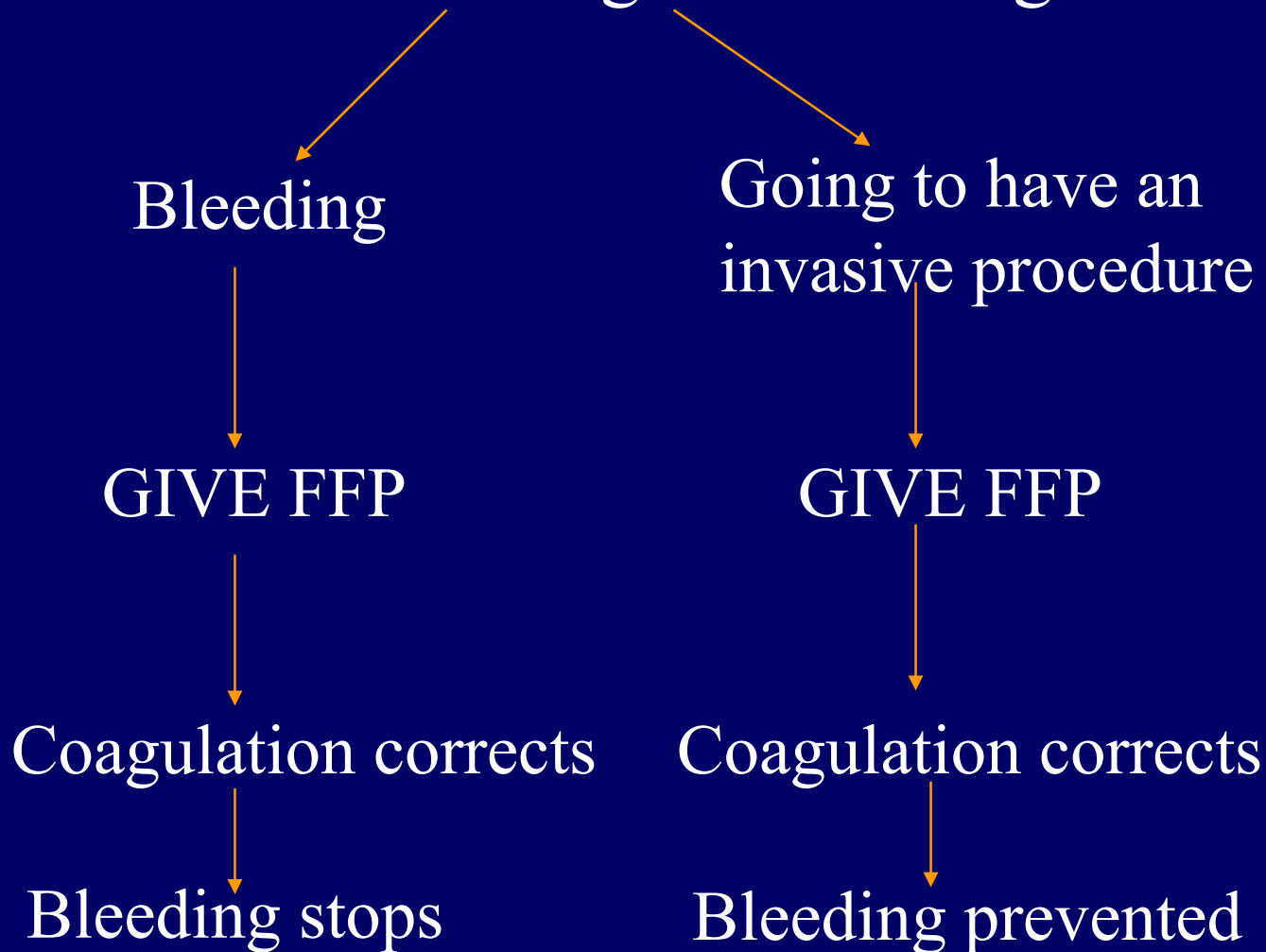
This accounted for 35% of all FFP treatments

Outcomes

- 23% admissions with abnormal coagulation tests had at least one 24 hour period during which clinically significant haemorrhage occurred (defined pragmatically as blood loss ≥ 300 ml or bleeding from critical site e.g. intracranial)
-
- A higher proportion of patients with abnormal coagulation tests died in ICU than those without abnormal coagulation tests (35% vs 12%).

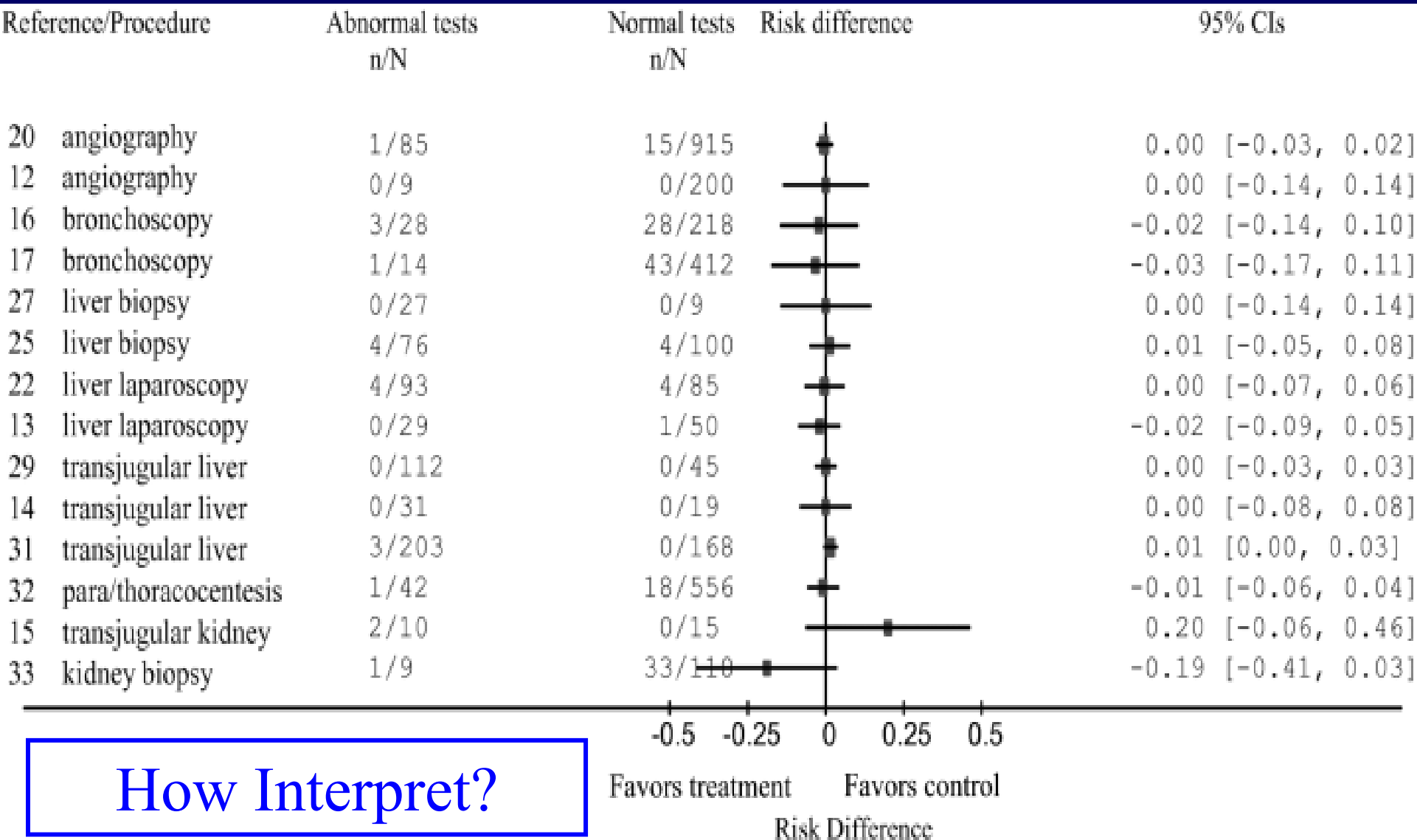
Evidence Base for this practice

Patient with deranged tests coagulation



Studies with 'controls' (normal tests)

Segal and Dzik, Transfusion 2005, 45:1413



How Interpret?

The effect of FFP transfusion in practice

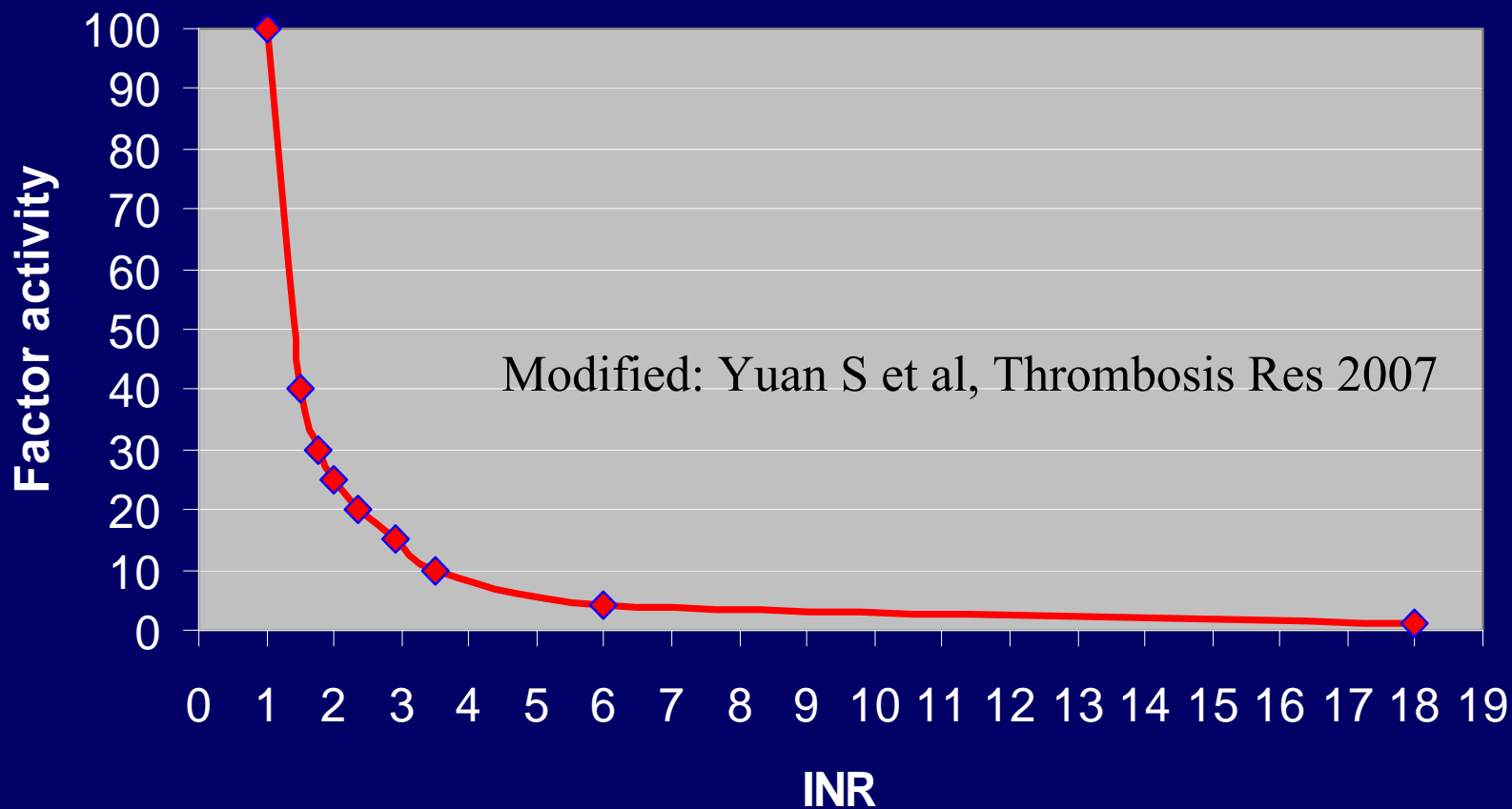
Abdel-Wahab, Transfusion, 2006, 46, 1279

- Prospectively followed hospital patients with pre-transfusion PT 13.1 - 17 secs (INR 1.1 – 1.85)
- 324 plasma units given to 121 patients (first Tx)
- <1% normalised PT and only 15% showed partial correction (median reduction INR 0.07)
- No correlation between PT/INR to estimated bleeding

Chronic Liver disease – *Youssef et al, 2003*

observational studies; : 89% failed to correct PT

Standard coagulation screen tests and the variable effect of plasma on INR & coagulation factor levels



Limitations of INR for other clinical settings

Outcomes & RCTs - Systematic review

Stanworth et al, Brit J of Haematology 2004, 126, 139

- Wide inclusion criteria
- 57 RCTs
- Cover a whole range of clinical settings
- Therapeutic and prophylactic
- Wide range of sample sizes 8 - 261 (per arm)
- Methodological quality - risk of bias & little confidence in the results

Summary about 'general' use

- Coagulopathy is common in adult patients in UK ICUs (period prevalence 30%)
- Some consistency in evidence base = no benefit
 - studies of prophylaxis
 - lack of predictive value for PT/INR and
 - use of FFP to 'correct' standard coagulation tests
- About 50% of FFP treatments still for non-bleeding
- Well-designed clinical studies are needed to inform appropriate use

Evidence for use



Injury-related therapeutic FFP transfusions

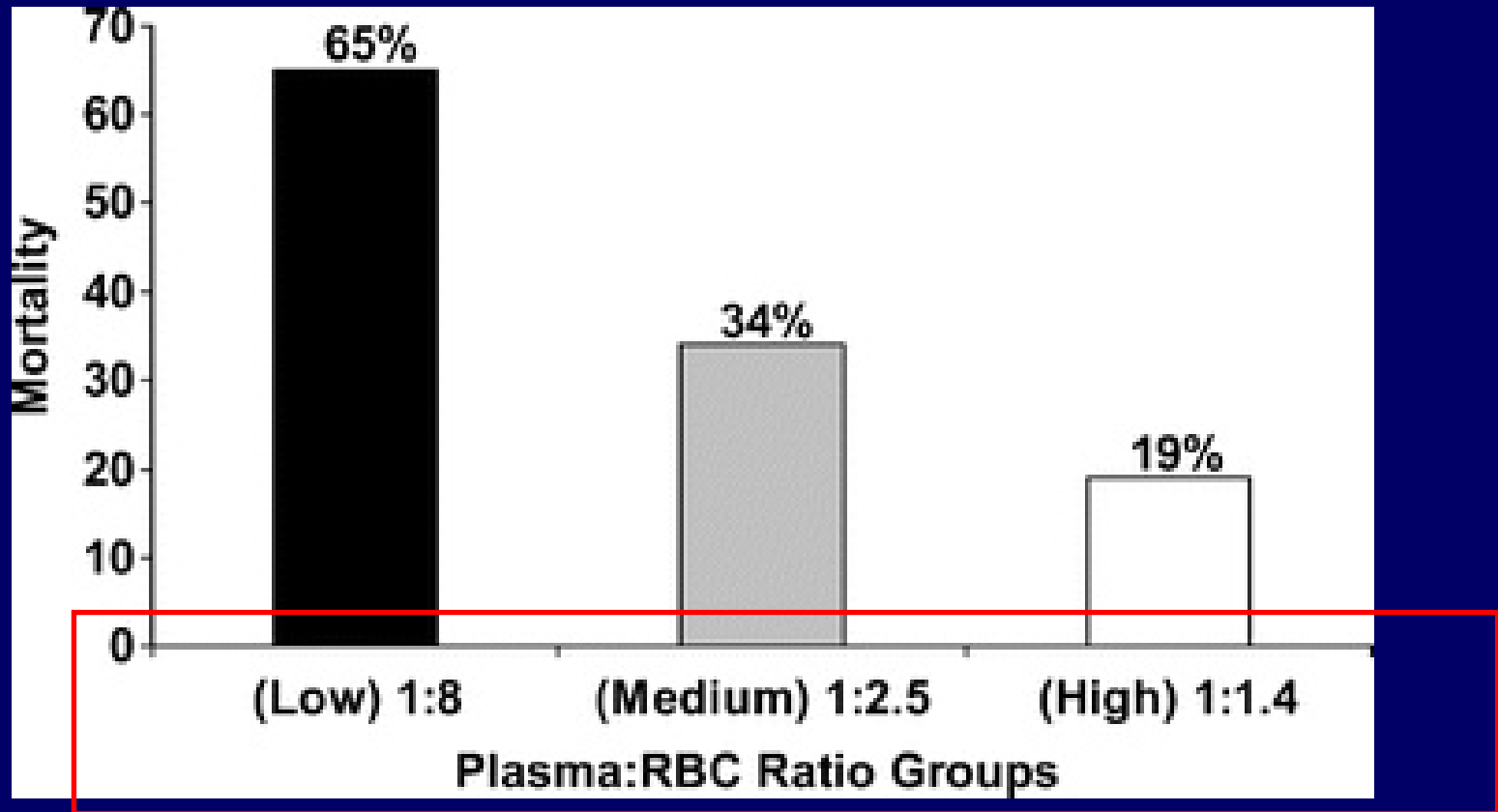
- 91% of injuries warrant no transfusion
- Select group of trauma patients receive massive transfusion
- Control of haemorrhage (diagnostic imaging/ surgical exploration)

Coagulopathy: Limiting Strategies

- Hypotensive resuscitation
- Local modalities (fibrin glue, haemostatic bandage, argon laser, invasive radiology)
- Drugs – Antifibrinolytics, rFVIIa
- Fresh whole blood (higher platelet counts)
- Improved early availability of plasma and/ or fibrinogen/cryoprecipitate (and/or PCC)
- Prompt 1:1:1 resuscitation ratios (RBCs, prethawed universal AB, apheresis platelets)

Evidence from military settings

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



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

Off licence uses of rVIIa: what is driving this use?



Uncontrolled medical bleeding

Critical bleeding in trauma

Bleeding in elective surgery

17 published RCTs –

Cochrane Review: Stanworth et al, 2007

Unlike non-RCTs, rules for appraisal better understood

But Clinical diversity:

- Especially participants
- Nature of intervention
- Outcomes (primary, other) - sizes of effects
- Co-interventions
- Sizes of trials

Prophylactic Studies - results 'Quick read'

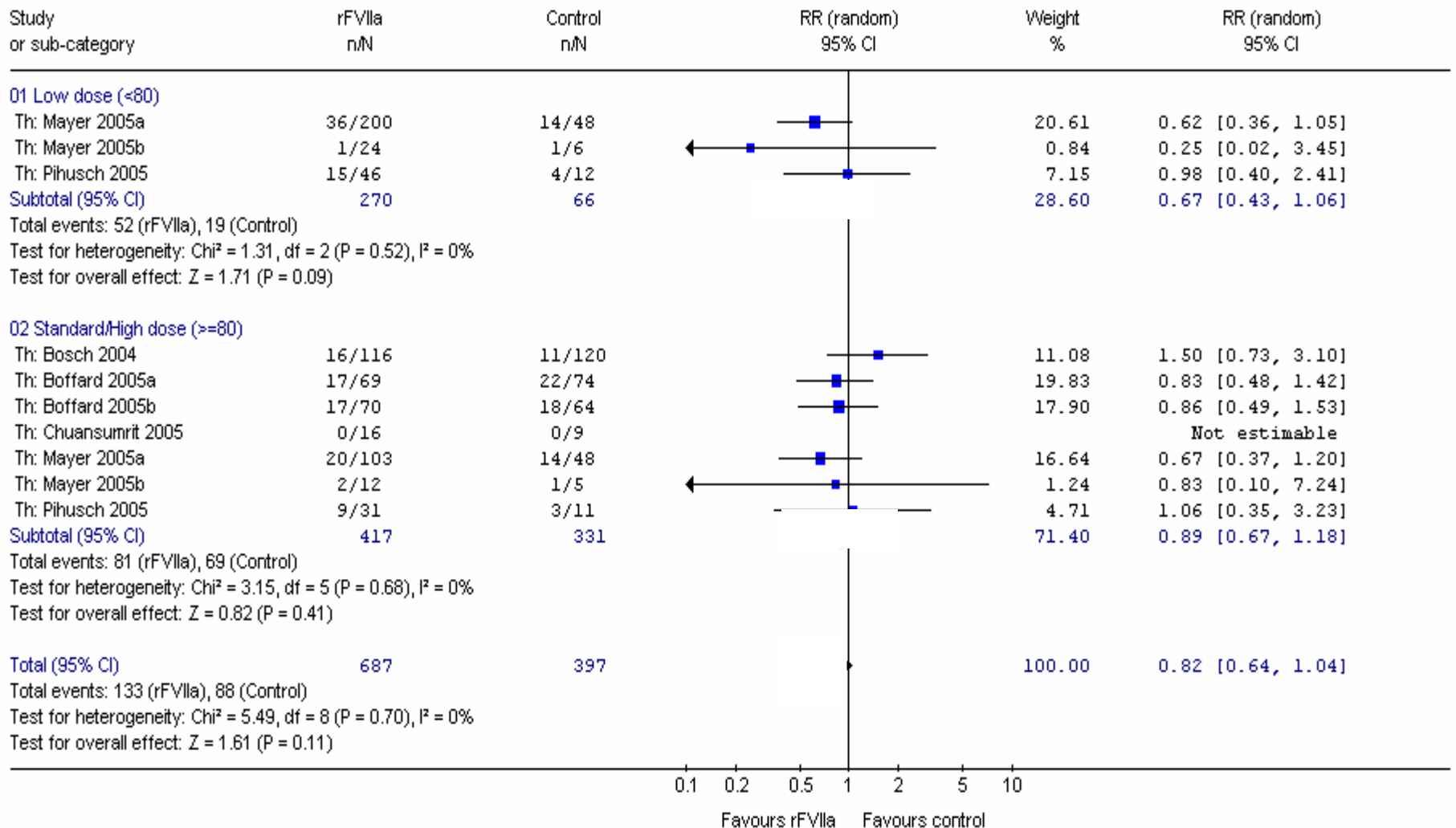
Study	Primary Outcome	Abstract
Friederich	Total operative blood loss	+
	Red cell transfusion requirements	+
Lodge (a)	Red cell transfusion requirements	-
Lodge (b)	Red cell transfusion requirements	-
Planinsic	Red cell transfusion requirements	-
Raobaikady	Total operative blood loss	-
Diprose	Red cell transfusion requirements (proportion of patients transfused)	+
Jeffers	Safety study. Efficacy endpoints were normalisation PT & time hemostasis	
Ekert	Time to chest closure from heparin neutralisation with protamine	-
Shao	Red cell transfusion requirements (proportion of patients transfused)	-

Systematic review - Study Quality

Name /Year	Main Concern
Friederich 2003	Small study size. The high mean blood losses in the control arm appear excessive
Diprose 2005	Small underpowered study. No information to confirm drug allocation was concealed. Differences in baseline characteristics between study arms
Boffard 2005	No detail concerning method of randomisation and whether allocation concealment achieved. Losses to follow-up 13%. Equality of allocation across the 14 centres not assured.

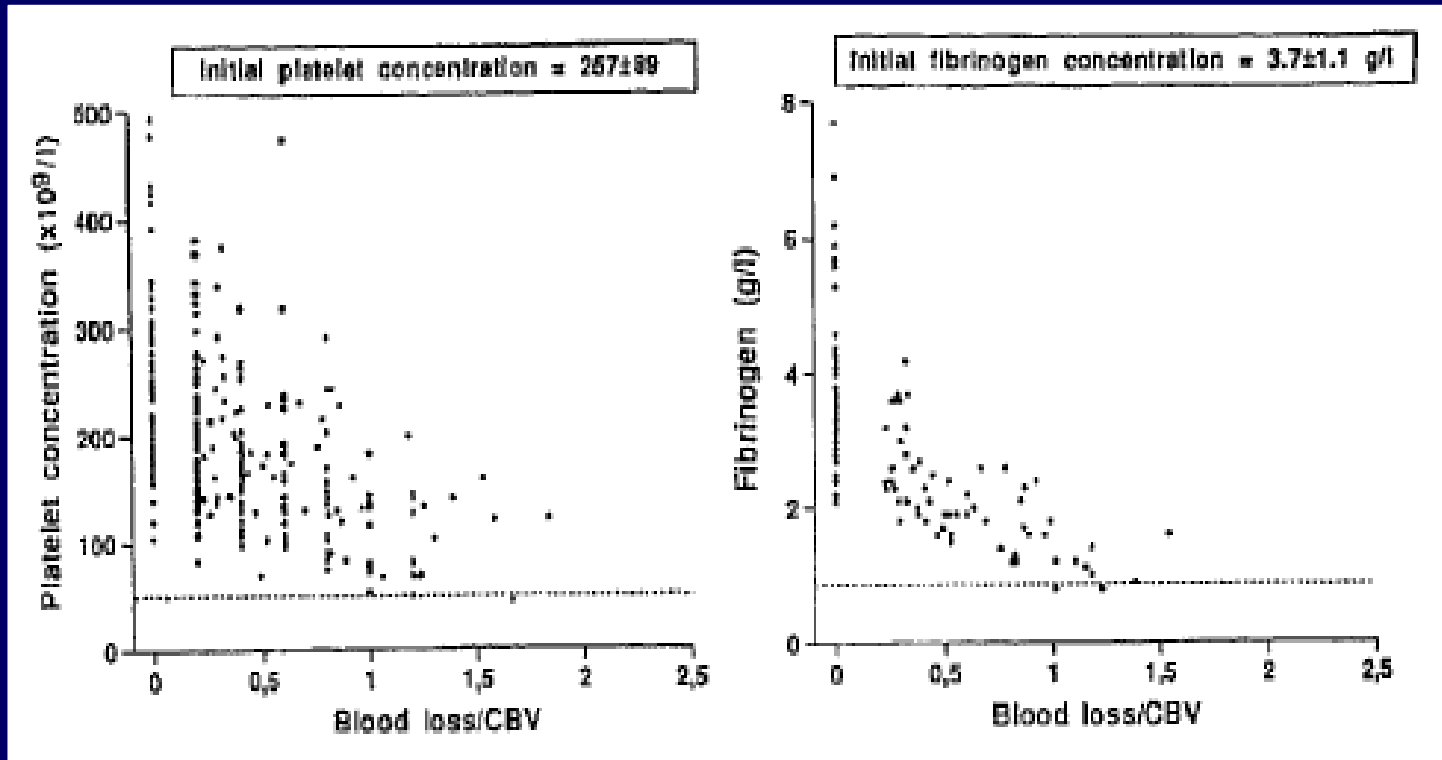
Data across all therapeutic studies, graphical display in a Forest Plot - mortality

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia
 Comparison: 02 rFVIIa used therapeutically vs placebo
 Outcome: 02 Death (with correction for double counting of control groups)



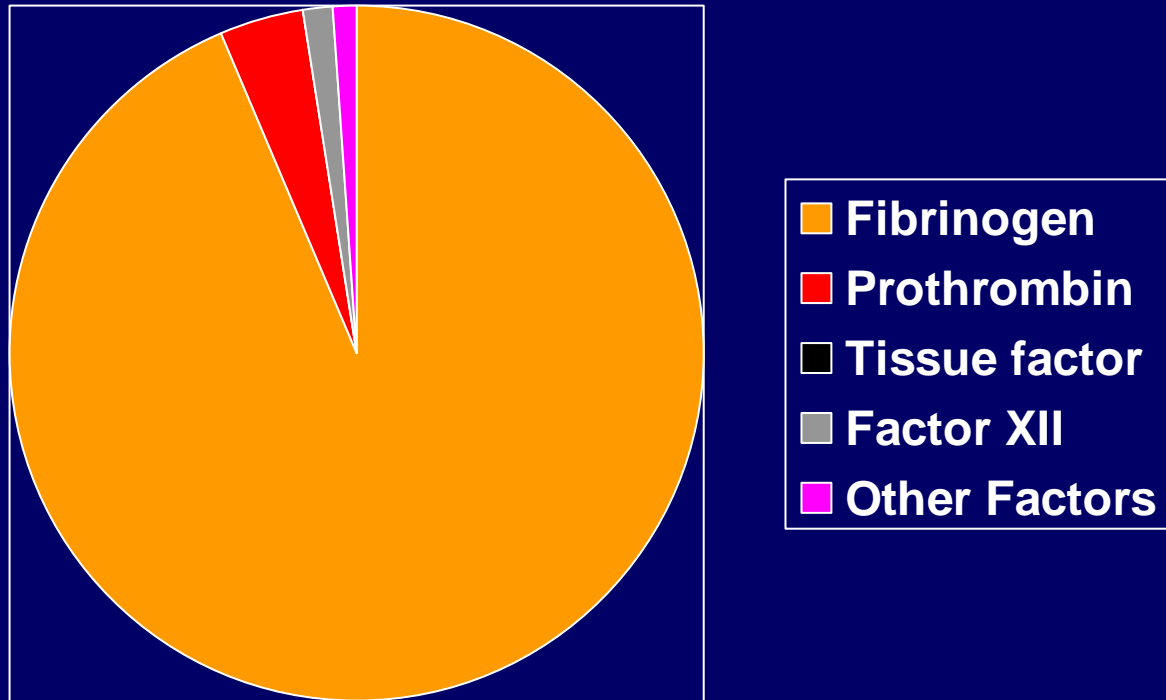
Fibrinogen & major surgical blood loss

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

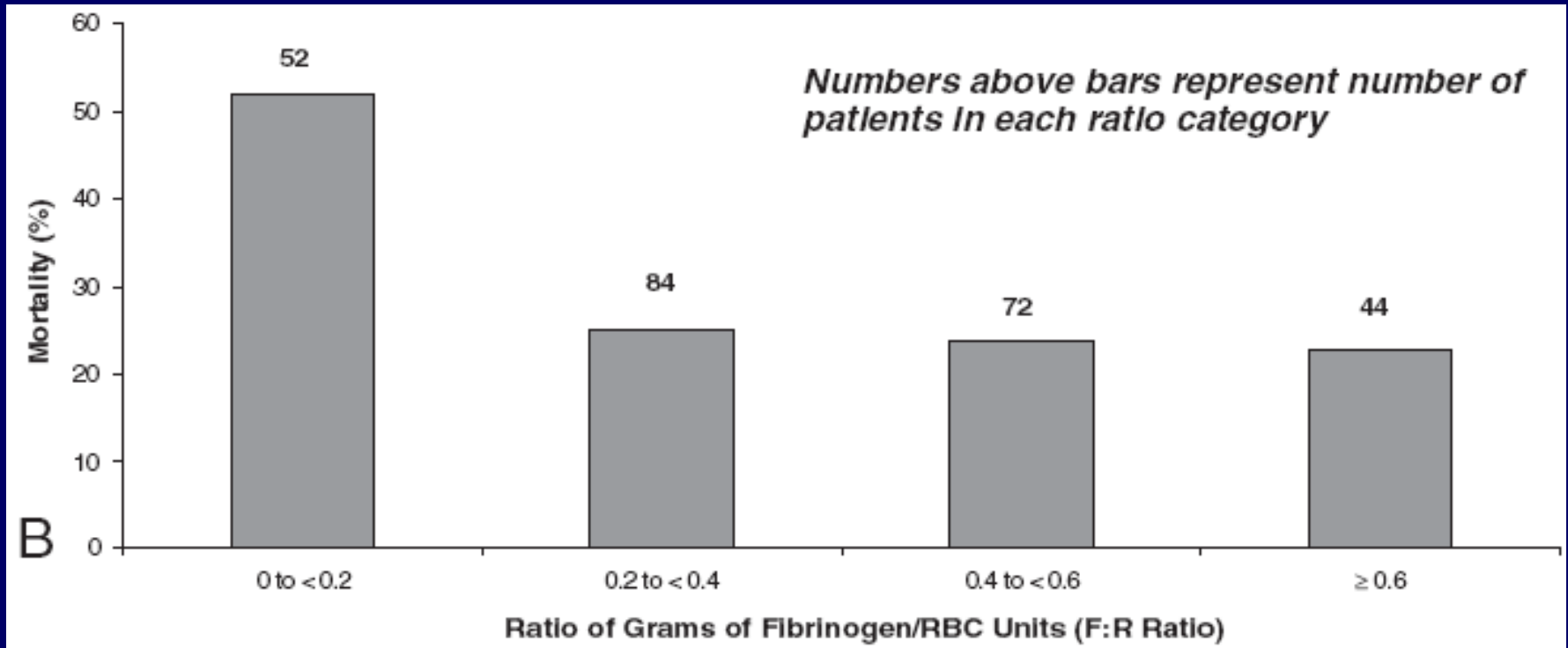


Fibrinogen deficiency developed earlier than other coagulation factors with use of plasma poor RC

Fibrinogen content

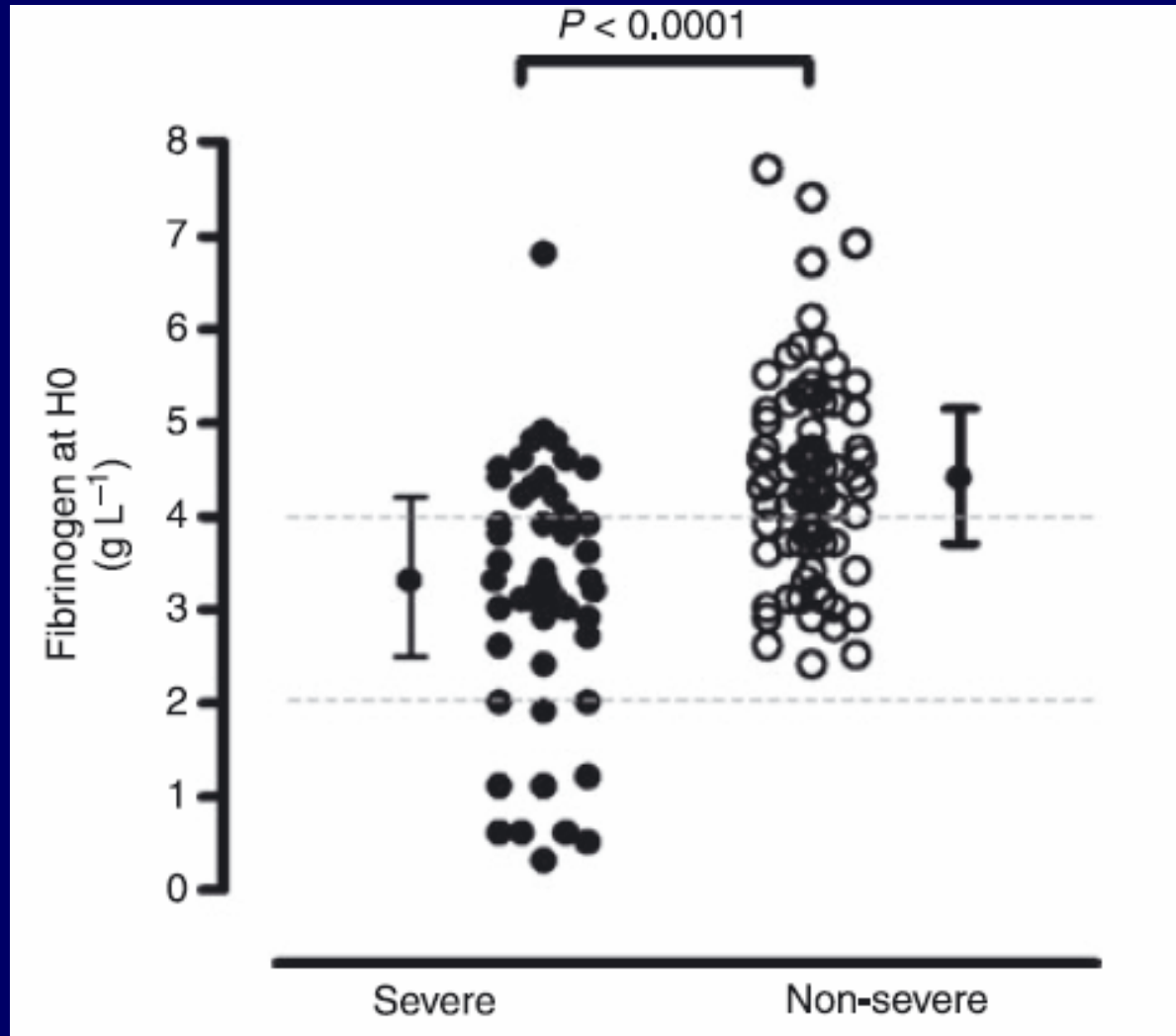


Fibrinogen : Red cell Ratio

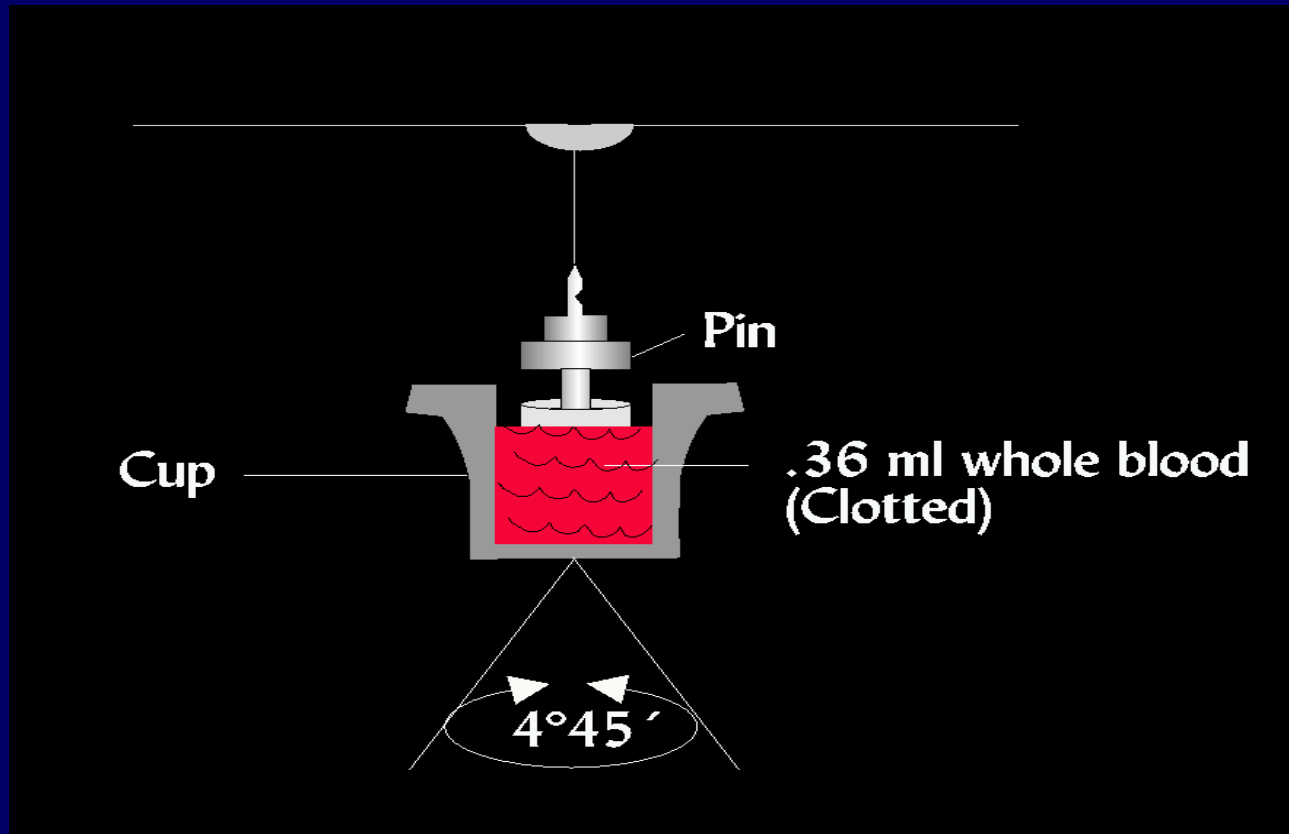


Stinger et al., J Trauma 2008, 64(2), S79-S85

Postpartum haemorrhage Fibrinogen concentration:



Education - TEG® Technology & other new coagulation screening tests



Summary

- The evidence base to guide FFP and cryoprecipitate use is weak
- What do we mean by coagulopathy?
- Distinguishing between evidence of lack of effect and effective use
- eg early massive haemorrhage, particularly trauma related, a 1:1 ratio with RBCs is supported by military experience

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