

Massive obstetric haemorrhage: new strategies for monitoring and managing haemostasis

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Disclosures

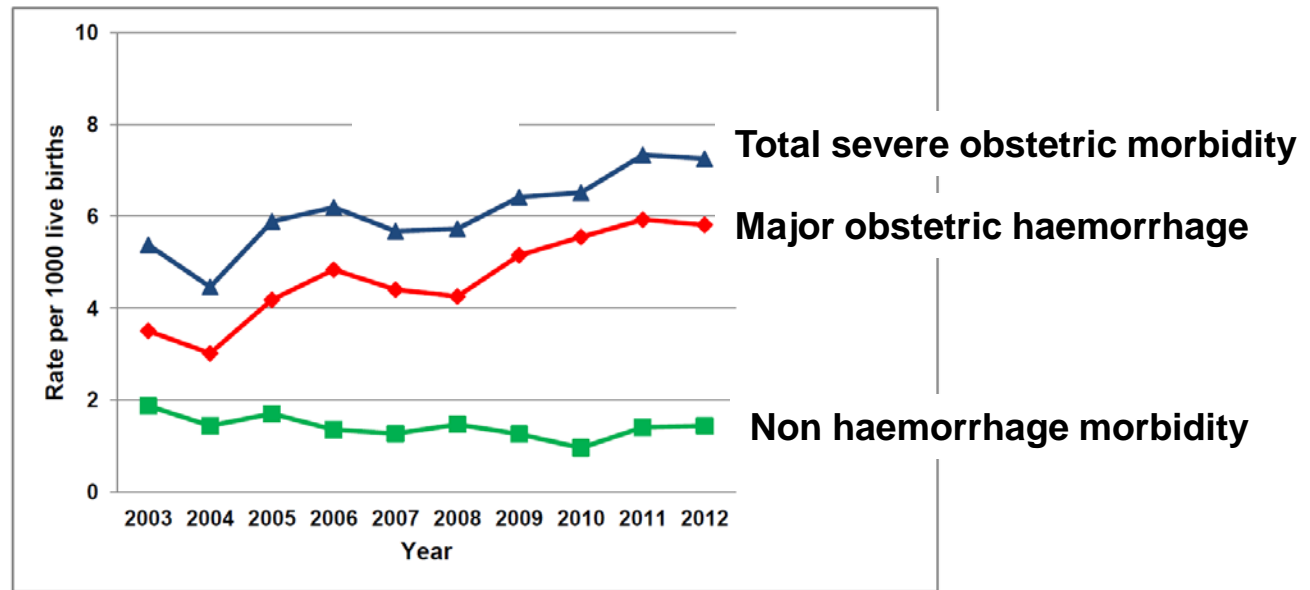
Research Support	CSL Behring and TEM International
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Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	CSL Behring
Scientific Advisory Board	CSL Behring

Presentation includes discussion of the following off-label use of a drug:
Fibrinogen concentrate

Incidence of massive PPH

Massive obstetric haemorrhage¹

- >2500 mL blood loss
- ≥ 5 units RBC
- FFP



Obstetric bleeding caused by:

1. Physical: atony, genital tract trauma, surgery, retain products
2. Haemostatic impairment

Arresting bleeding

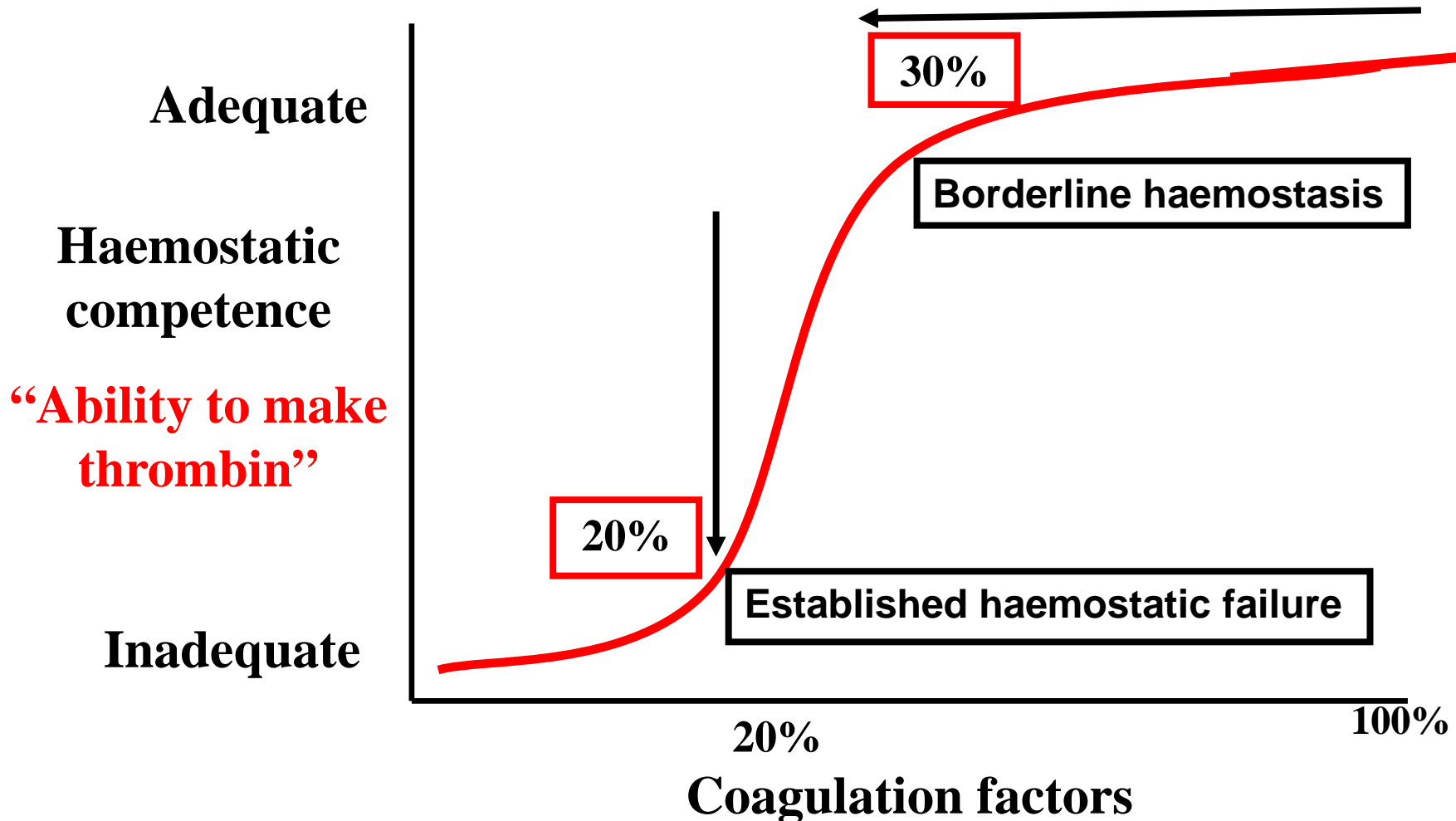
**Clotting factors generate
thrombin**

>30% is sufficient

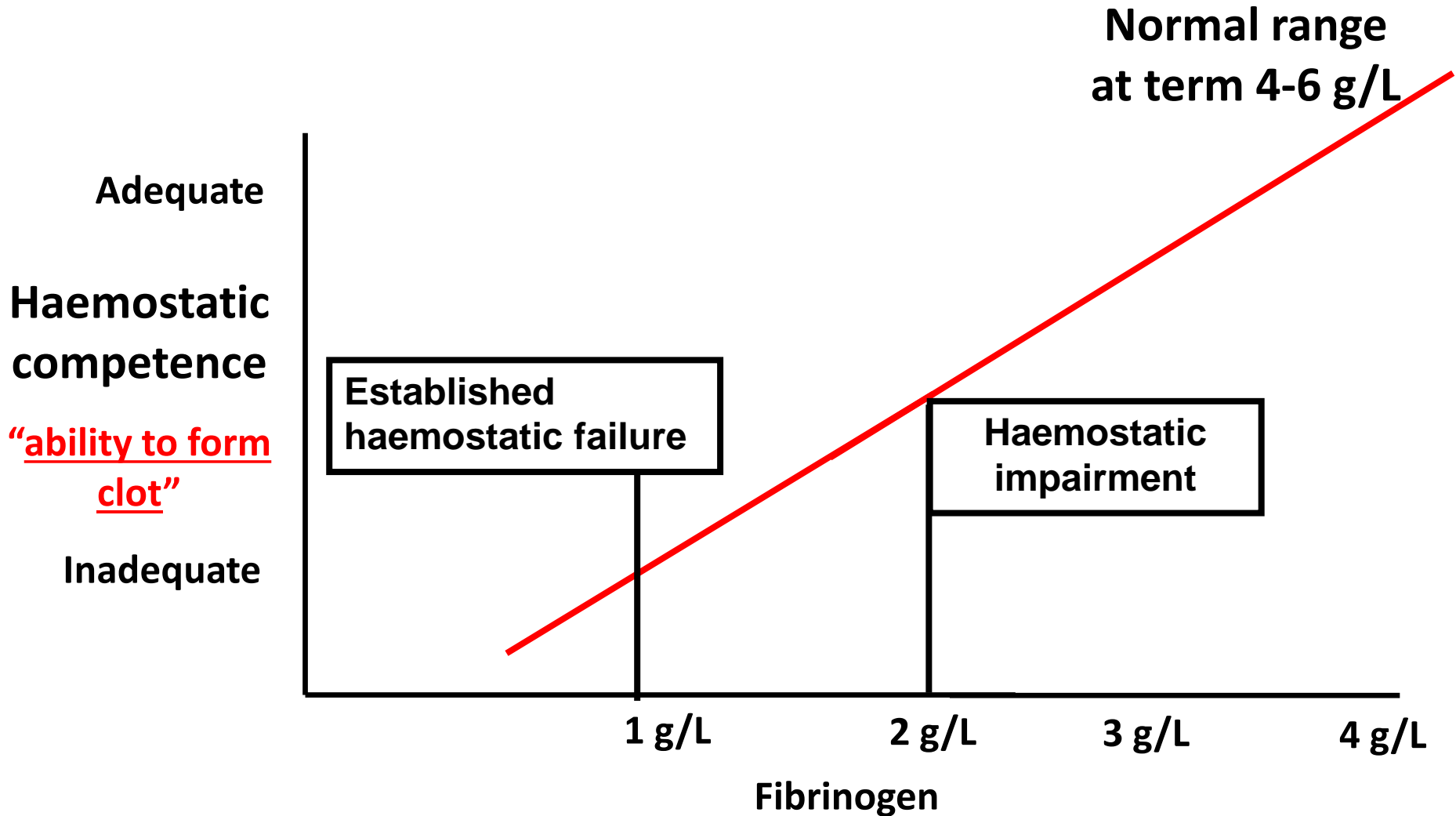
20% is insufficient

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Haemostasis and depletion of clotting factors



Haemostatic impairment: Fibrinogen during PPH



Haemostatic impairment and obstetric haemorrhage

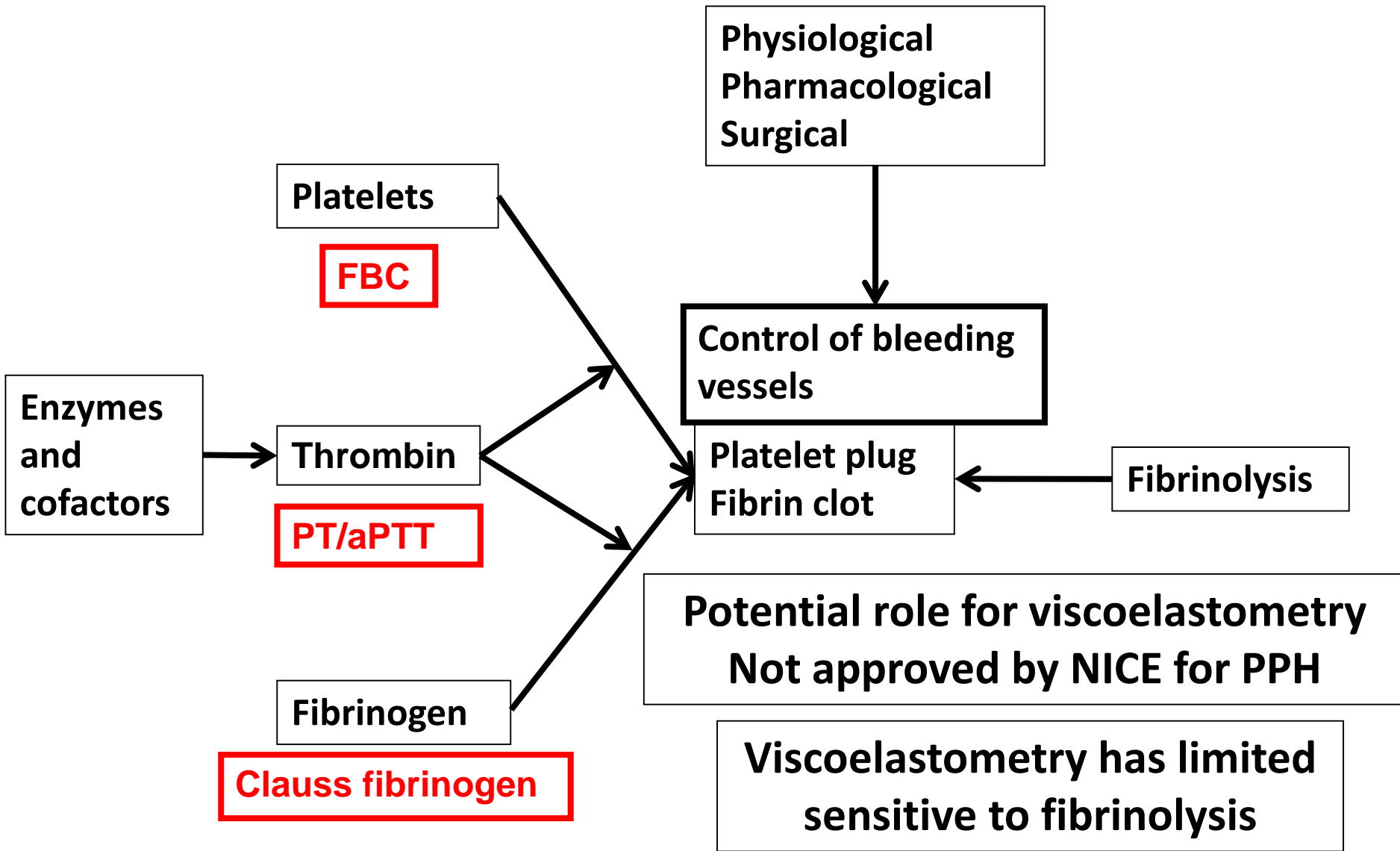
Obstetric complication	Mechanism of haemostatic compromise		
	Dilutional	Consumption localised to uterus	DIC
Trauma			
Surgery			
Atony			
Placental abruption			
Placenta praevia/accreta			
Amniotic fluid embolus			

Haemostatic impairment differs dependent on cause

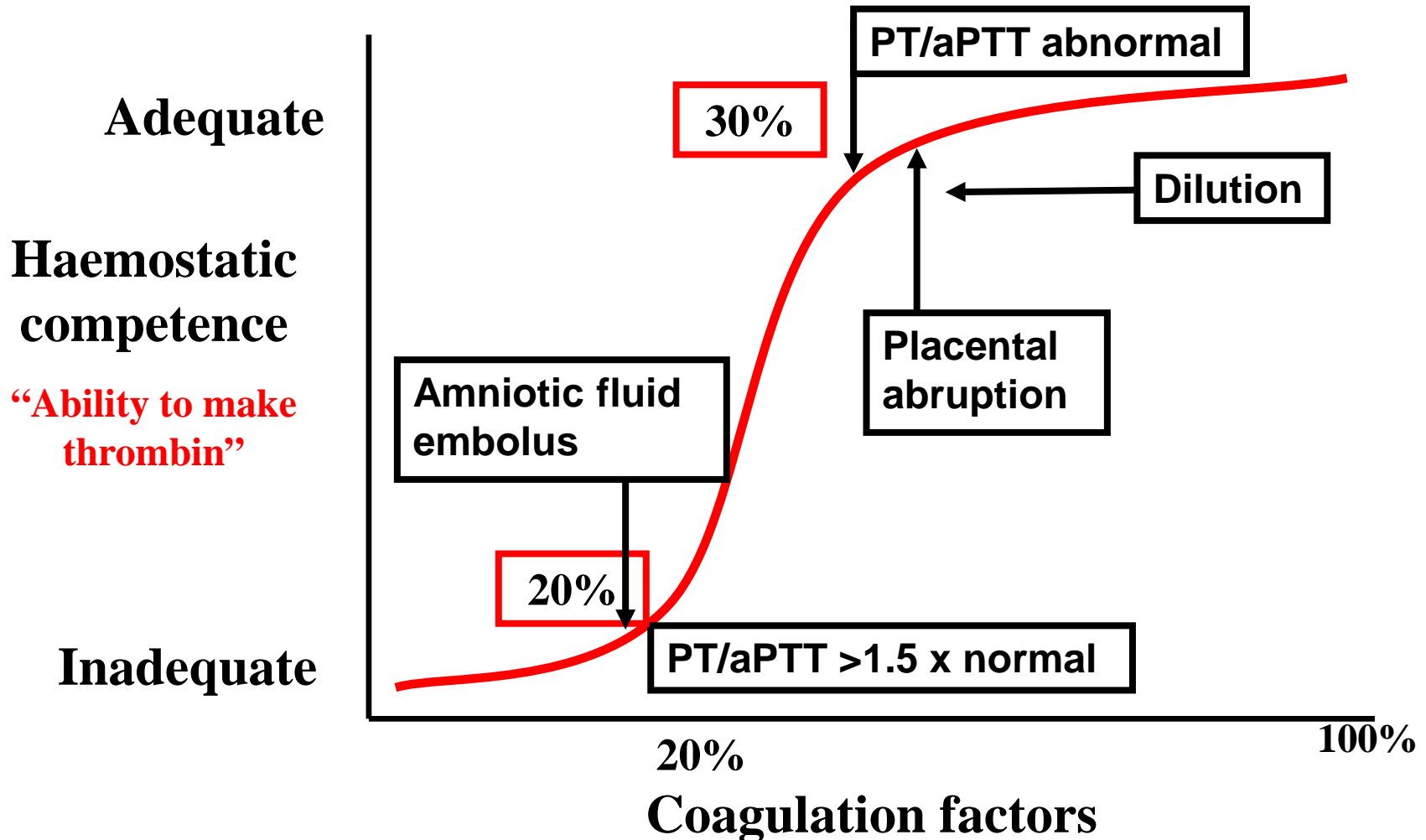
Obstetric complication	Mechanism of haemostatic compromise		
	Dilutional	Consumption localised to uterus	DIC
Trauma	++	+/-	-
Surgery	++	+/-	-
Atony	++	++	-
Placental abruption	+	+++	+
Placenta praevia/accreta	++	++	+ (infection)
Amniotic fluid embolus	+	+	++++

+ Fibrinolysis

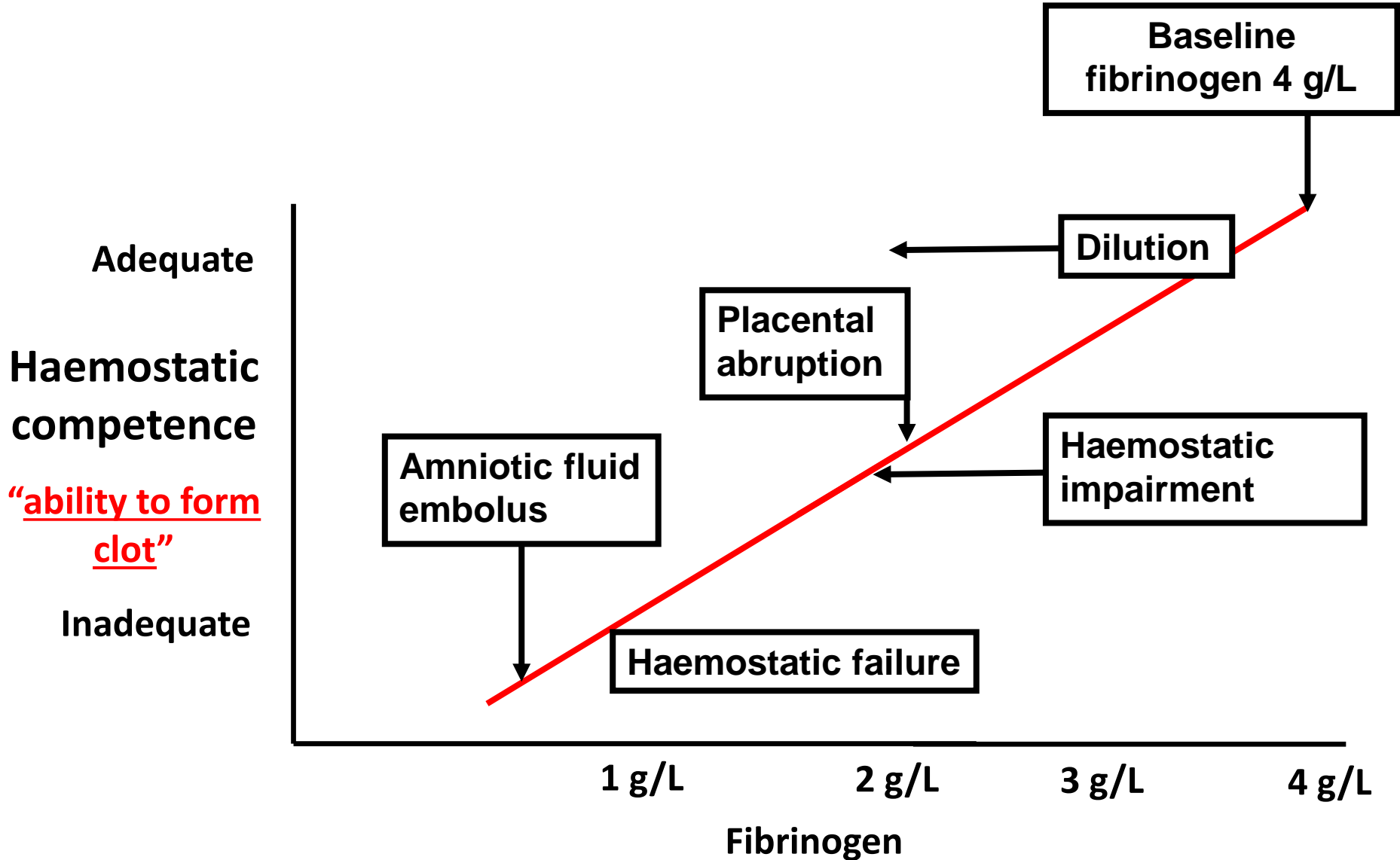
Monitoring haemostasis



Haemostatic impairment: Depletion of clotting factors



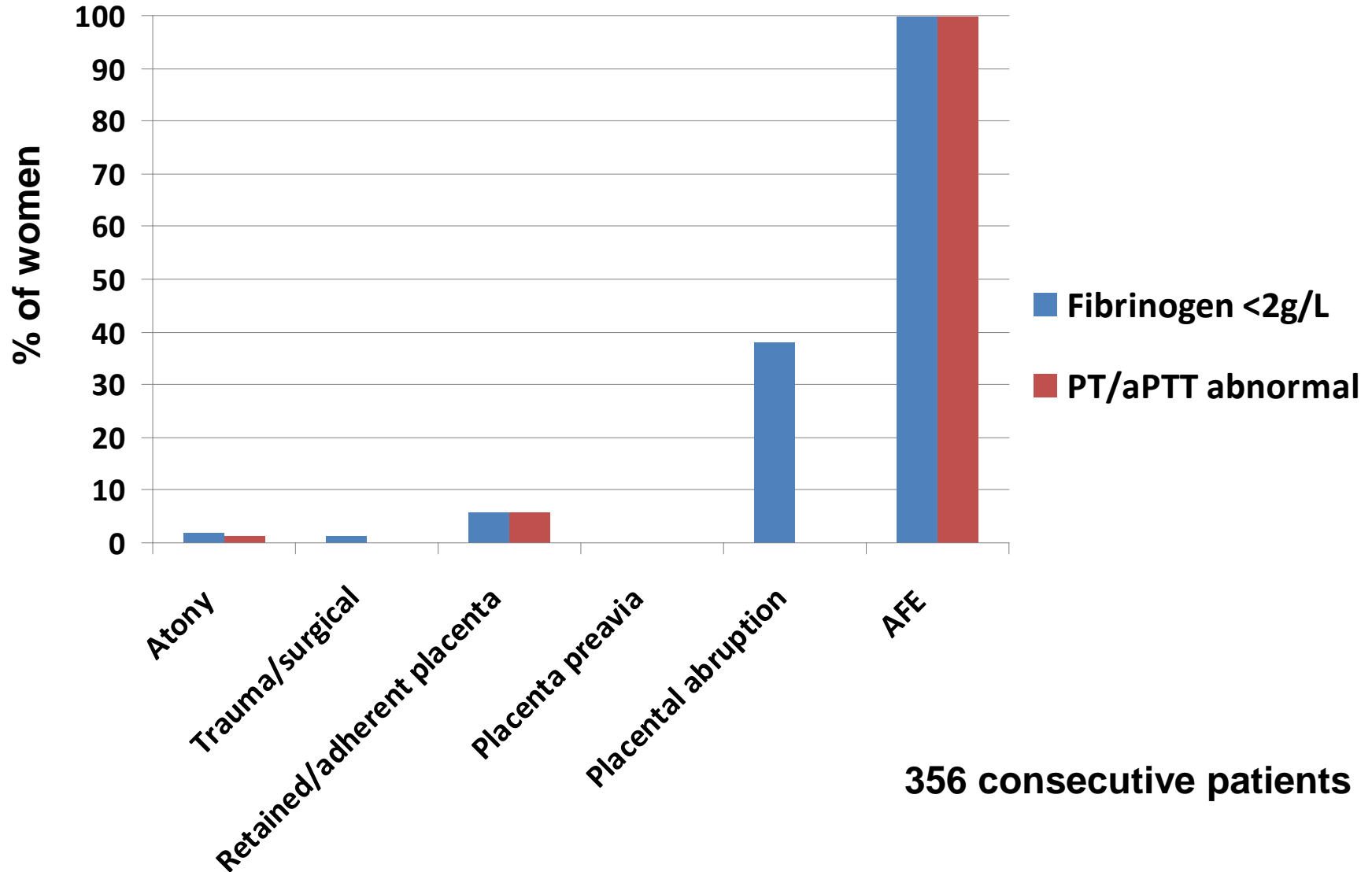
Haemostatic impairment: Fibrinogen



Shock packs for PPH

- **Recent interest in 1:1 RBC:FFP replacement in massive haemorrhage after trauma**
- **Potential role in PPH?**
 - **Some centres advocate 1:1 replacement after 1 – 1.5 L blood loss**
 - **Most women will have normal or enhanced haemostasis**
 - **Early FFP may not improve coagulation**

Coagulation after 1-2L PPH



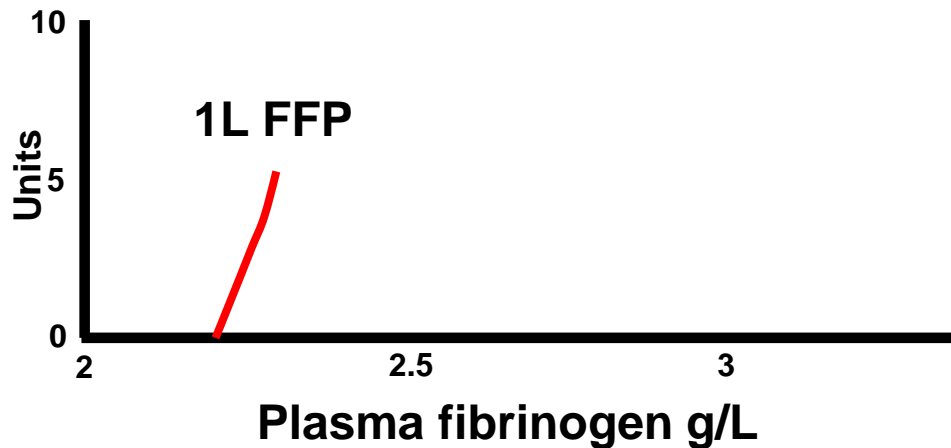
356 consecutive patients

Implications of early empirical FFP replacement during PPH

FFP contains about 2.5 g/L fibrinogen

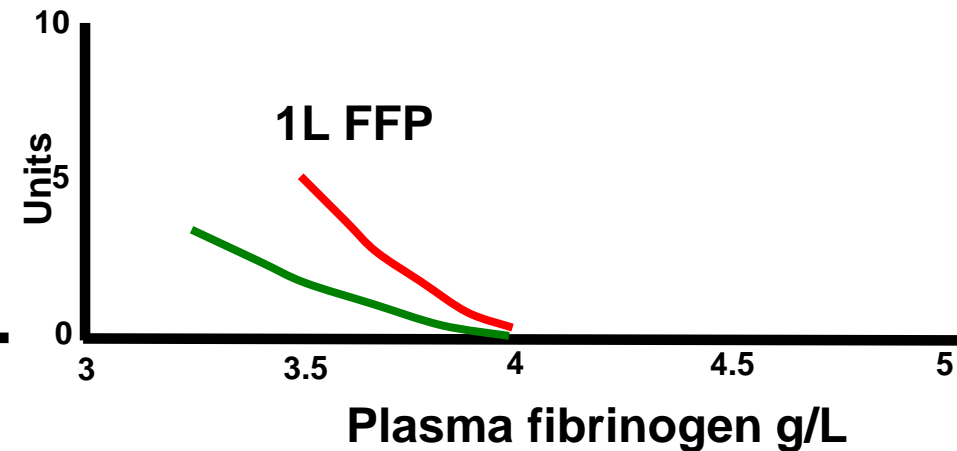
Abruption

Fibrinogen 2.2 g/L



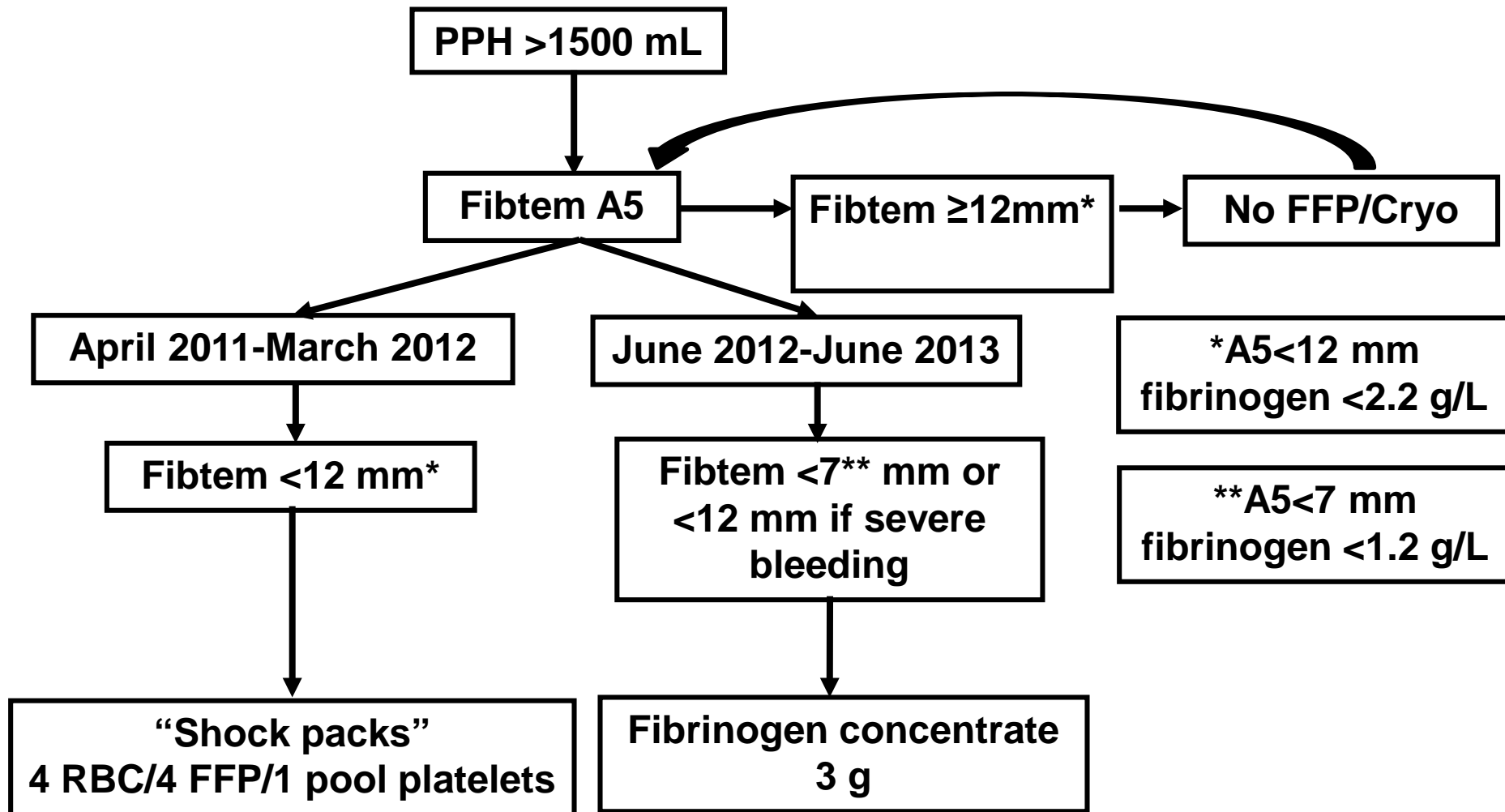
Trauma/surgical bleed/atony

Fibrinogen 4 g/L



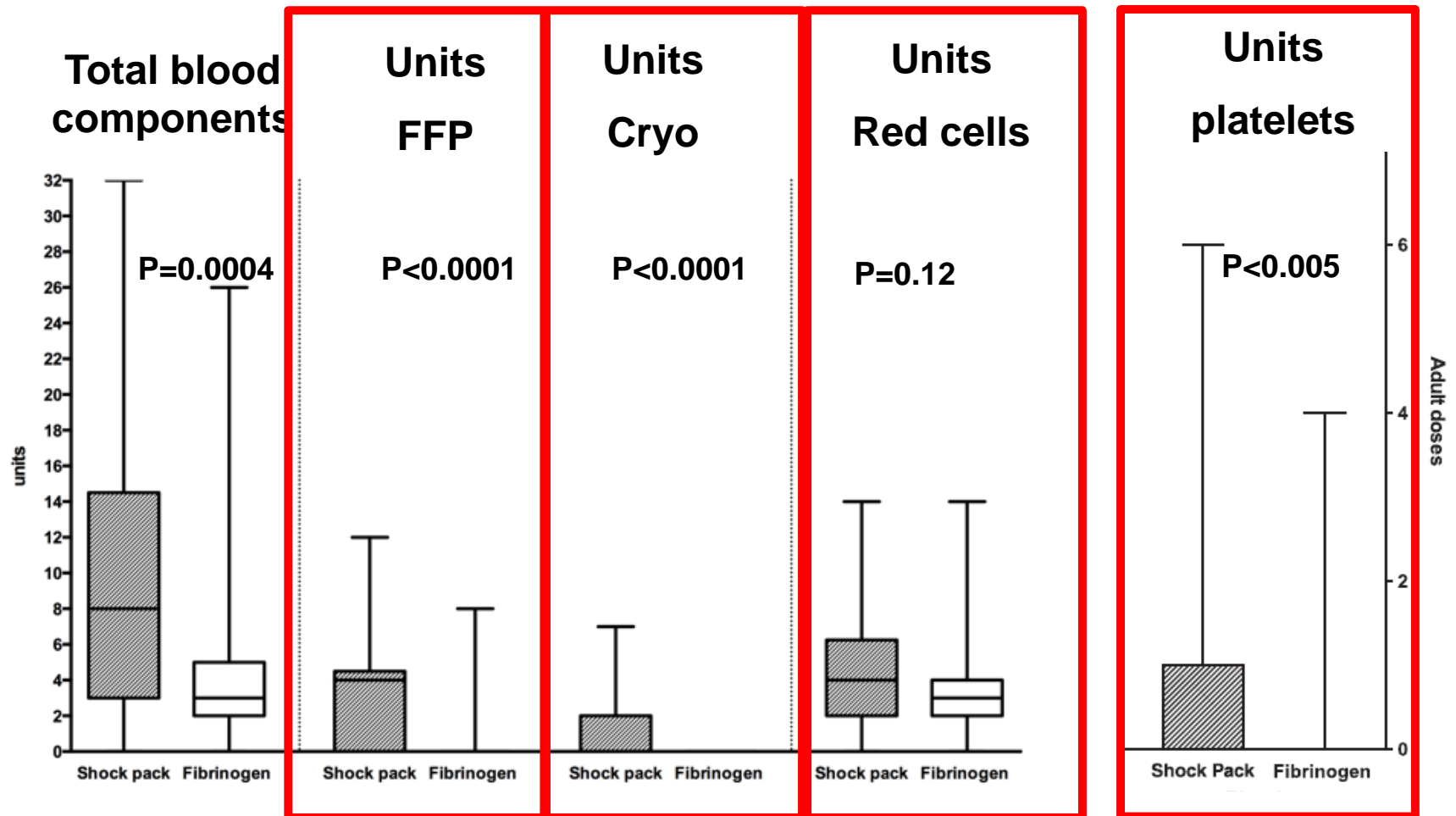
Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in Major Obstetric Haemorrhage

S. Mallaiah, P. Barclay, I. Harrod, C. Chevannes and A. Bhalla: Anaesthesia 70:166-175, 2015



Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in Major Obstetric Haemorrhage

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Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in Major Obstetric Haemorrhage: Follow up report

S. Mallaiah, P. Barclay, I. Harrod, C. Chevannes and A. Bhalla: Anaesthesia 70:760, 2015

	Shock packs N=42	Fibrinogen conc N=107	P value
% requiring >6 units RBC	29%	12%	0.02
% TACO	10%	0%	0.004
% ICU admission	10%	1%	0.02
Postpartum hysterectomy	14%	5%	0.08
Red cell transfusion Med (IQR)	4 (2-6)	3 (1-4)	0.03

Rotem monitored shock packs appears to be inferior to Rotem guided fibrinogen replacement

Unmonitored shock packs unlikely to be optimum treatment for PPH

Retrospective, observational, not randomised, not blinded

Clauss fibrinogen and progression of PPH

	n	Progression to severe PPH	Non progression to severe PPH
		Fibrinogen g/L	
Charbit: median (IQR)	129	3.3 (2.5–4.2)	4.4 (3.7–5.1)
Cortet: mean (SD)	738	3.4 (0.9)	4.2 (1.2)
de Lloyd: mean (SD)	240	3.1 (1.0)	4.4 (1.1)

Clauss fibrinogen is a useful biomarker for progression of PPH

Laboratory Clauss fibrinogen usually takes too long to be clinically useful

Is point of care testing an option?



blood

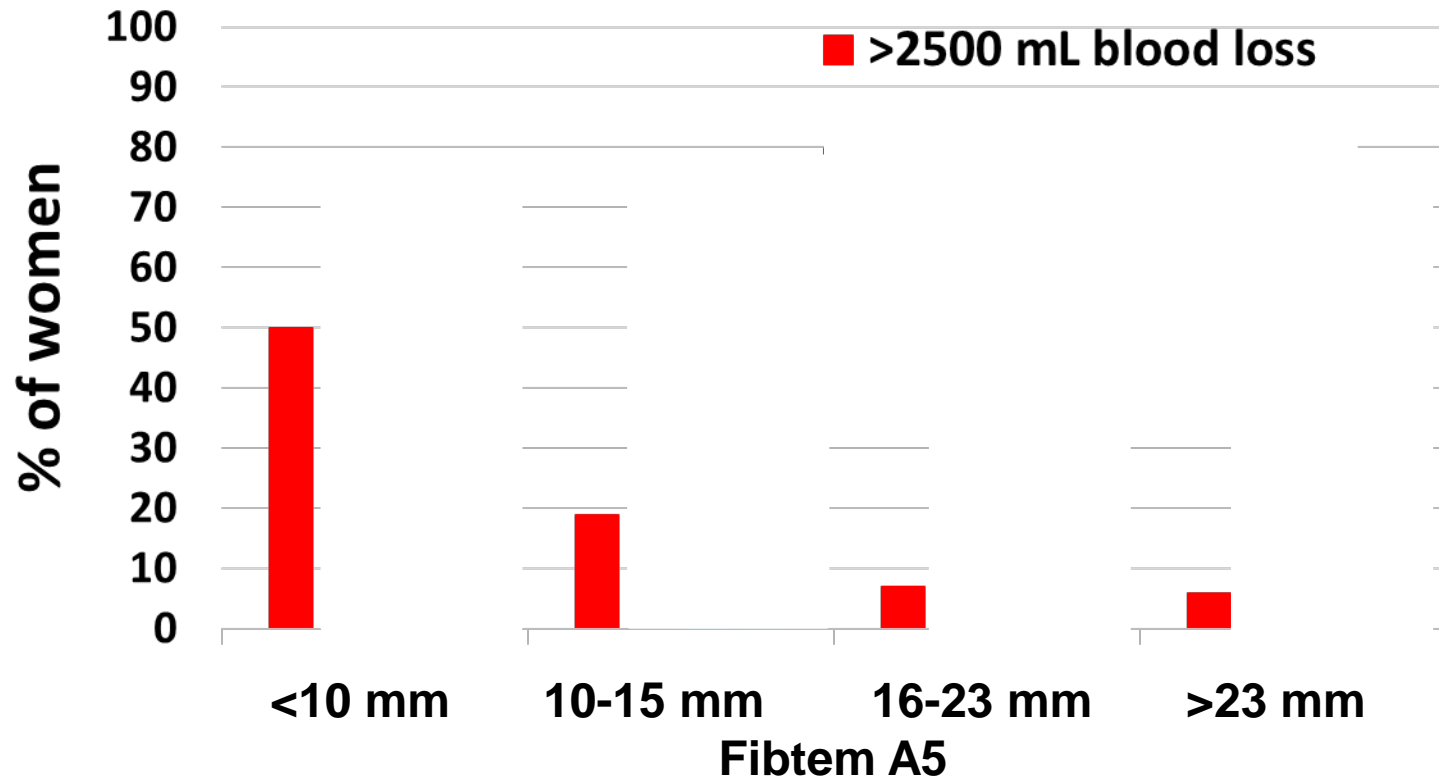
Obstetric Bleeding Study 1: OBS1

Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study

Peter W. Collins,^{1,2} Graeme Lilley,³ Daniel Bruynseels,³ David Burkett-St. Laurent,³ Rebecca Cannings-John,⁴ Elizabeth Precious,¹ Vincent Hamlyn,³ Julia Sanders,^{4,5} Raza Alikhan,¹ Rachel Rayment,¹ Alexandra Rees,⁵ Abigail Kaye,⁵ Judith E. Hall,^{2,3} Shantini Paranjothy,⁶ Andrew Weeks,⁷ and Rachel E. Collis³ **Blood 124:1727-1736, 2014**

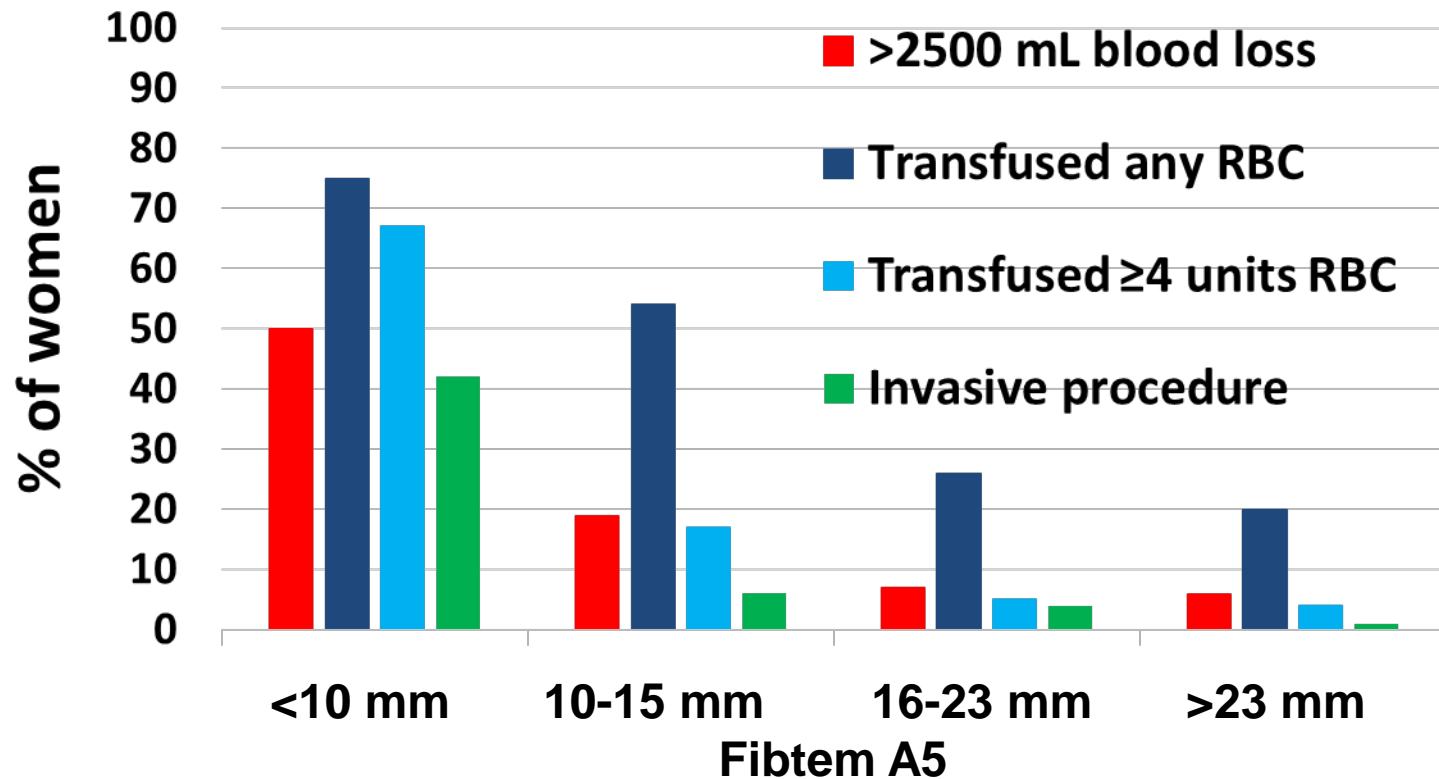
- **6187 deliveries in the 12 months**
- **346 consecutive women experiencing PPH recruited**
 - **1000-1500 mL**
 - **No exclusions**
- **Women recruited at pre-defined time early during PPH**
 - **Before transfusion or interventions**
- **Clauss fibrinogen and Fibtetm measured**
 - **Outcomes recorded**

Outcome of PPH dependent on early Fibtem A5 level: OBS1



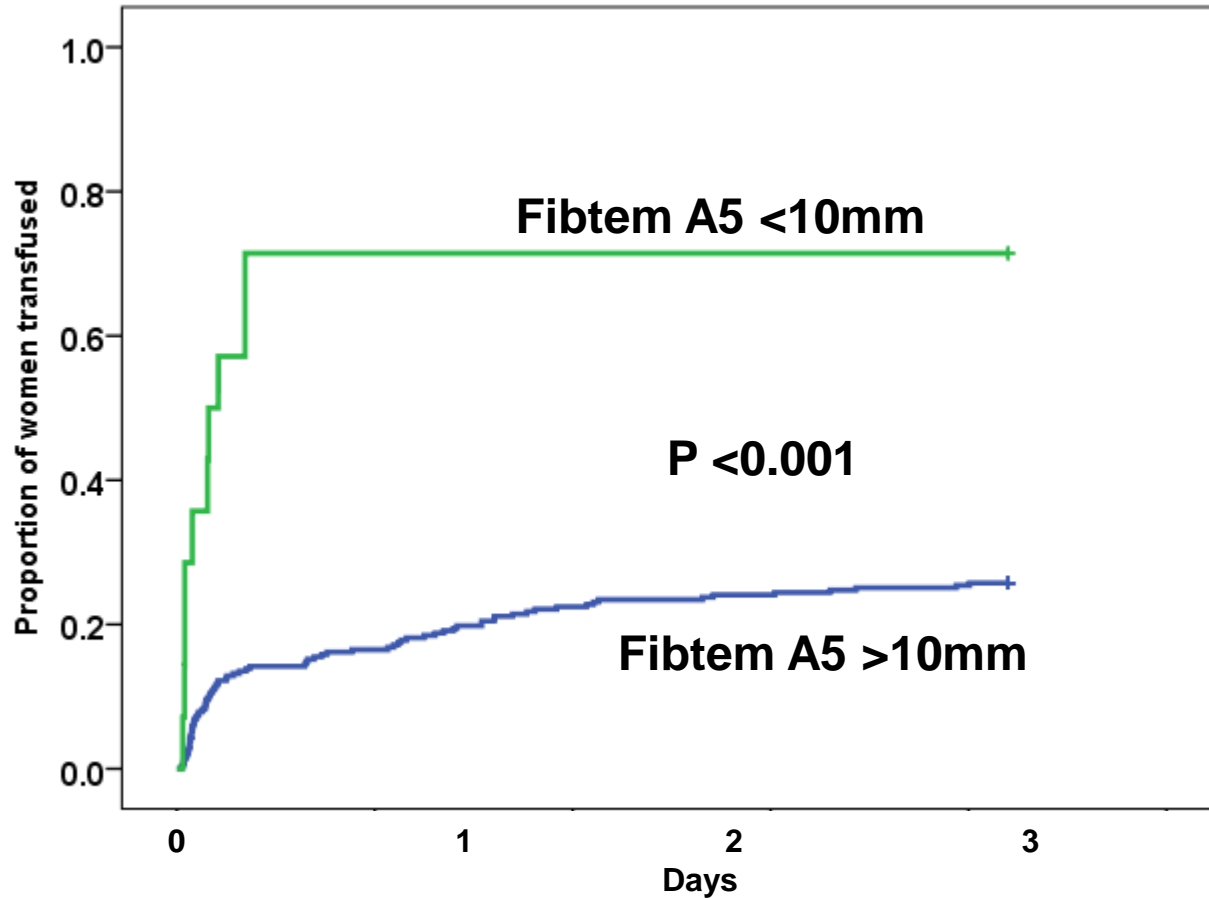
Fibtem A5 taken after 1000-1500 mL and before any transfusion

Outcome of PPH dependent on early Fibtem A5 level: OBS1



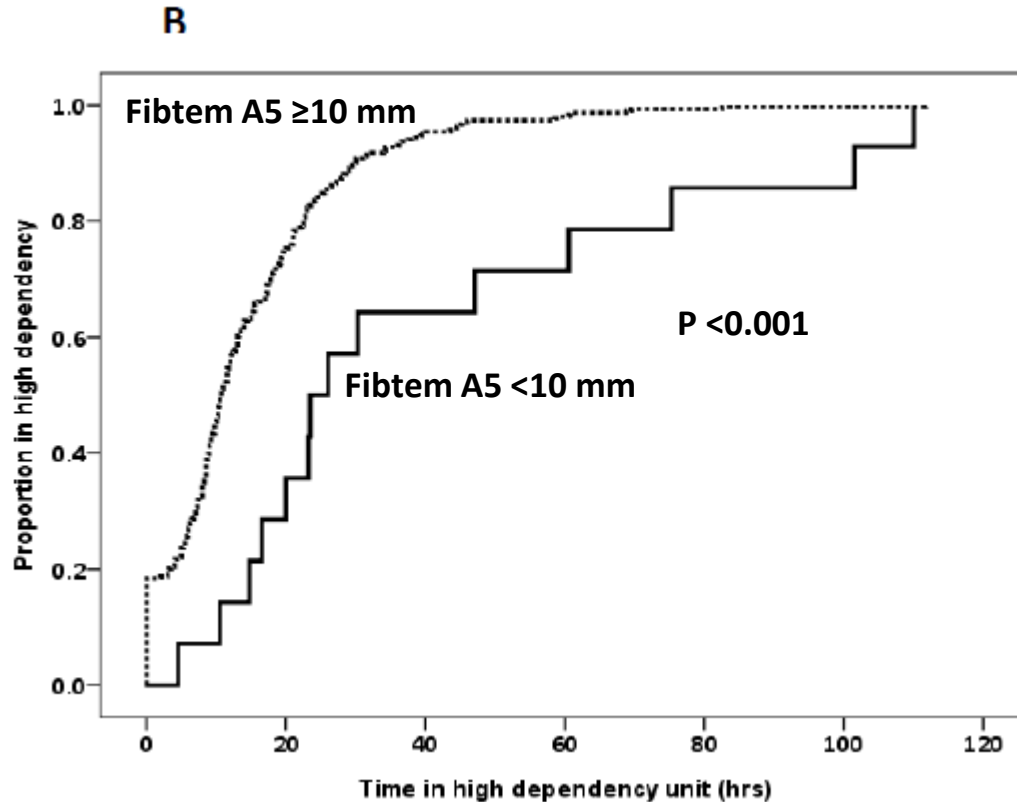
Fibtem A5 taken after 1000-1500 mL and before any transfusion

Time to first blood transfusion: OBS1



Fibtem A5 <10 mm roughly equal to fibrinogen <2 g/L

Time on high dependency unit: OBS1



Median 95% CI

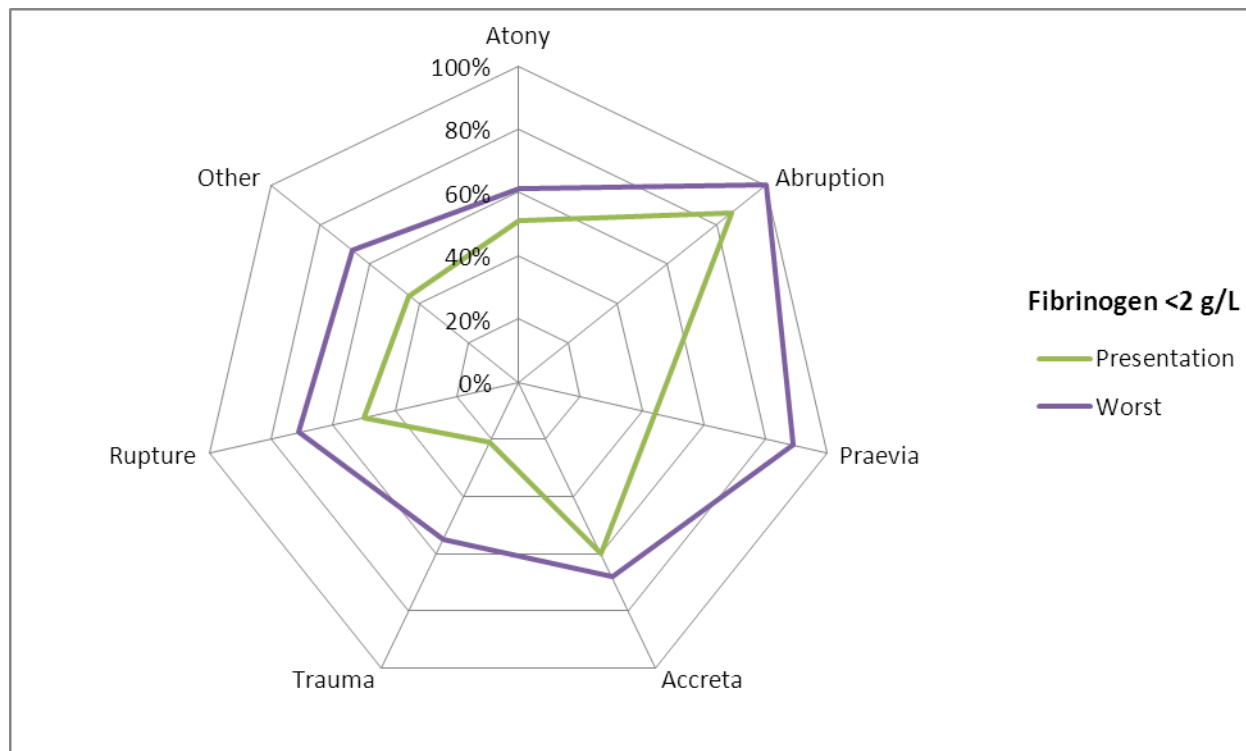
Fibtem A5 < 10 mm: 23.5 (18.4-28.5) hrs

Fibtem A5 ≥ 10 mm: 10.8 (9.7-11.8) hrs

Fibtem A5 < 10 mm roughly equal to fibrinogen < 2 g/L

Fibrinogen and massive transfusion

- **UK Obstetric Surveillance System (UKOSS)**
 - All women in UK requiring ≥ 8 units red cells reported
 - Incidence 2.3 (95% CI 1.9-2.6)/10 000 deliveries

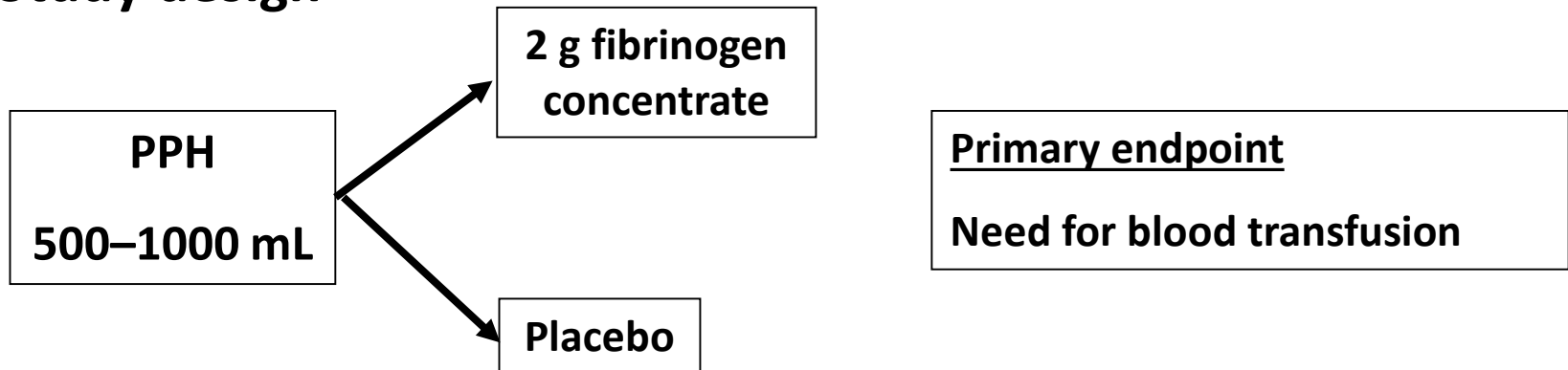


Would correcting fibrinogen early reduce bleeding?

Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial

A. J. Wikkelsø^{1*}, H. M. Edwards², A. Afshari³, J. Stensballe⁴, J. Langhoff-Roos⁵, C. Albrechtsen³, K. Ekelund³, G. Hanke³, E. L. Secher³, H. F. Sharif⁵, L. M. Pedersen⁶, A. Troelstrup⁶, J. Lauenborg⁷, A. U. Mitchell¹, L. Fuhrmann¹, J. Svare², M. G. Madsen⁸, B. Bødker⁹, A. M. Møller¹ and FIB-PPH trial group

Study design



No monitoring of fibrinogen level before infusion

Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial

A. J. Wikkelso

Outcome	Fibrinogen (123)	Placebo (121)	Relative risk (95% CI)	P value
Need for red cell transfusion	25 (20.3%)	26 (21.5%)	0.95 (0.58-1.54)	0.88
Blood loss after study drug	1700 (1500-2000)	1700 (1400-2000)		0.37

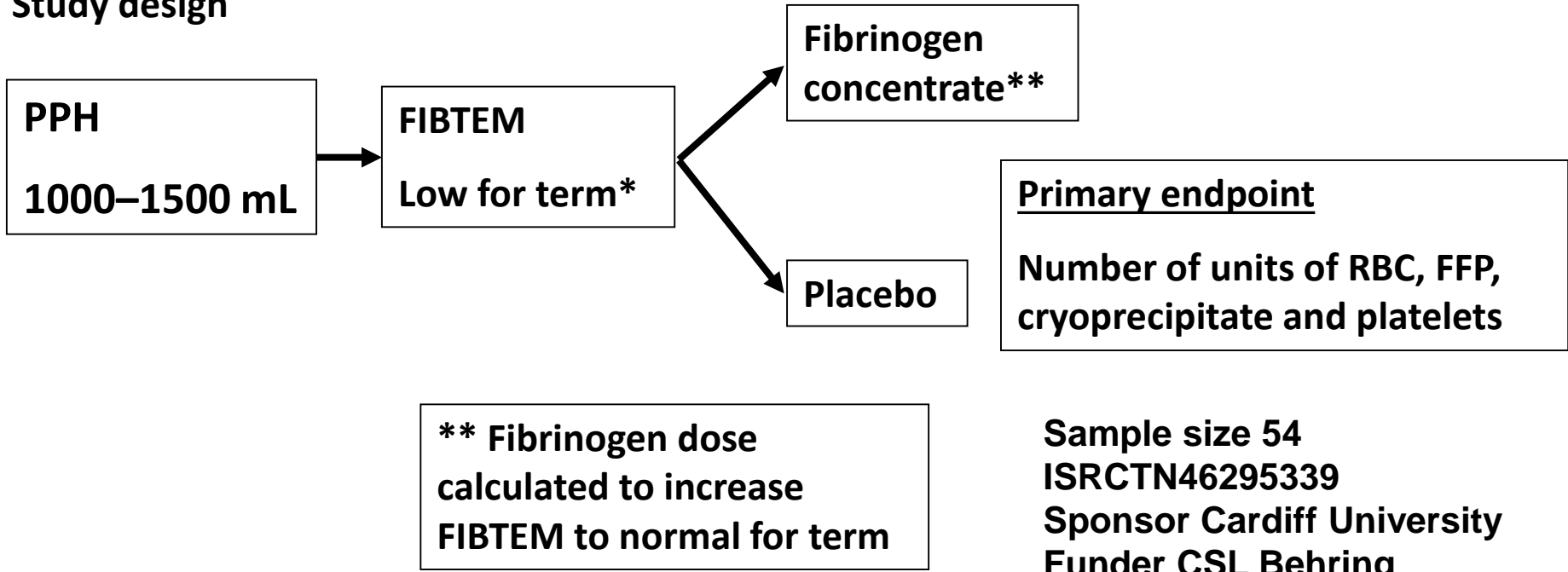
Baseline characteristic	Fibrinogen (123)	Placebo (121)
Fibrinogen (g/L) Mean (SD)	4.5 (1.1)	4.5 (1.3)
Fibrinogen < 2g/L N (%)	1 (0.8)	4 (3.3)



Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage:

A multicentre, prospective, double blind randomised control trial

Study design



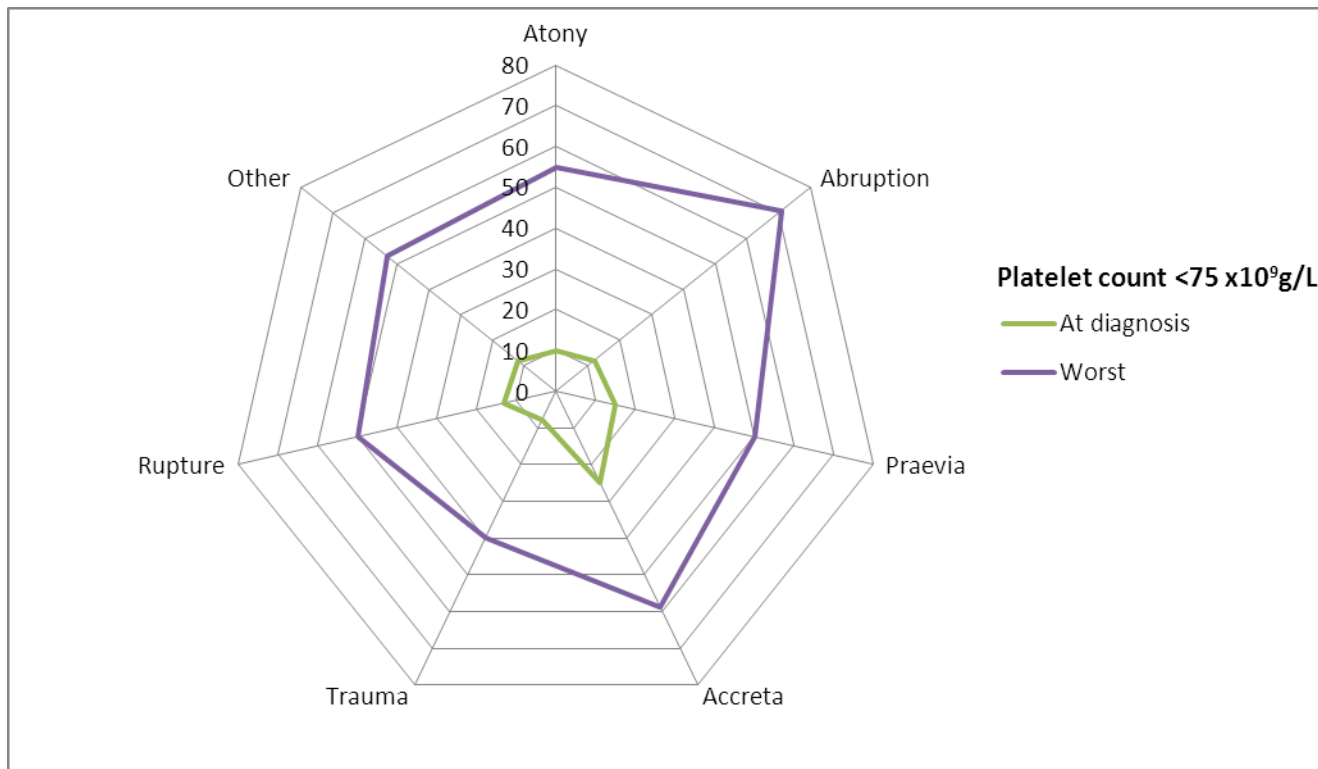
* Fibrinogen <16 mm

** Dose adjusted to given increment to above 23 mm

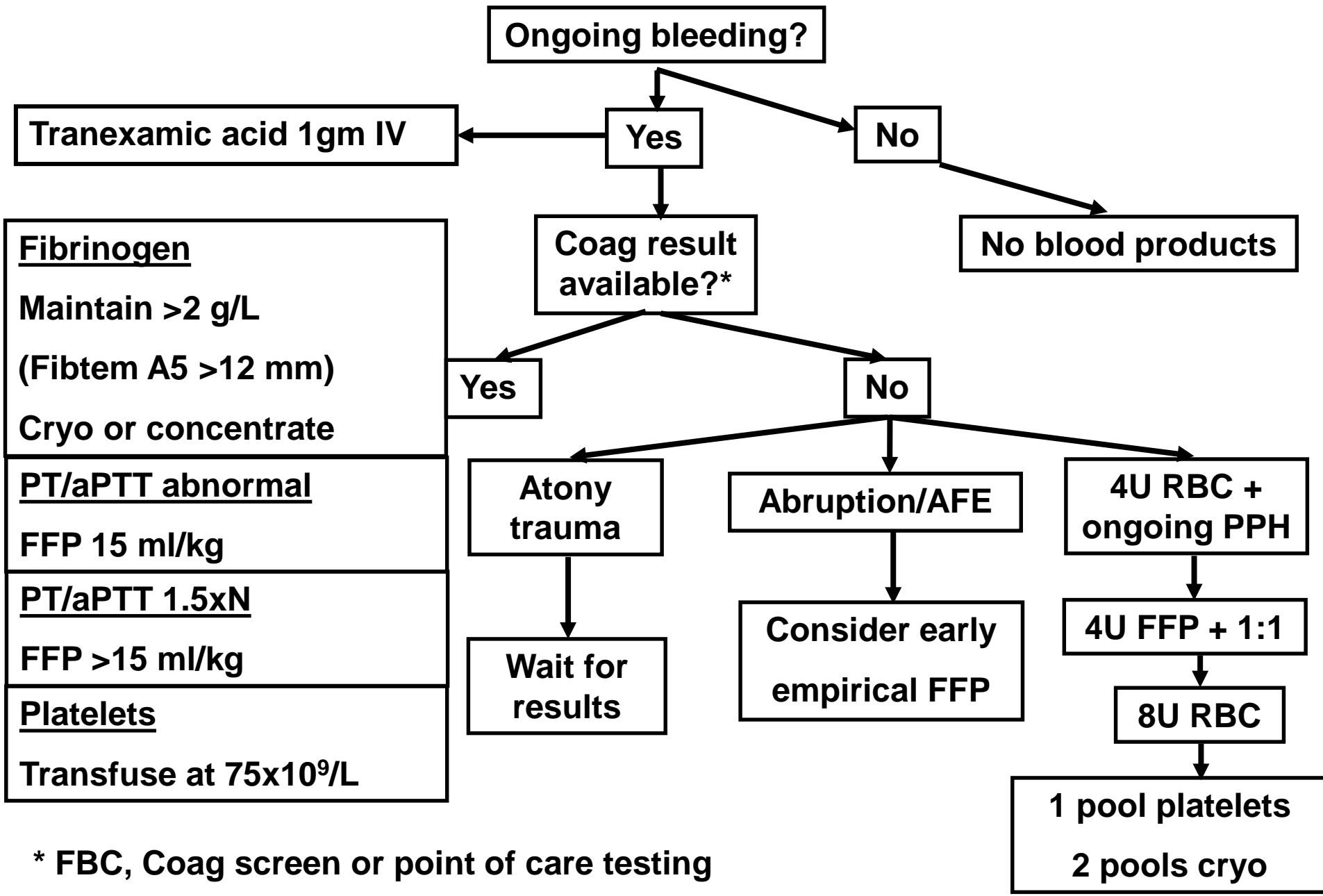


Platelets and massive transfusion

- Platelet recommended when $< 75 \times 10^9/L$
- UK Obstetric Surveillance System (UKOSS)
 - All women in UK requiring ≥ 8 units red cells reported



Revised RCOG algorithm: under consultation

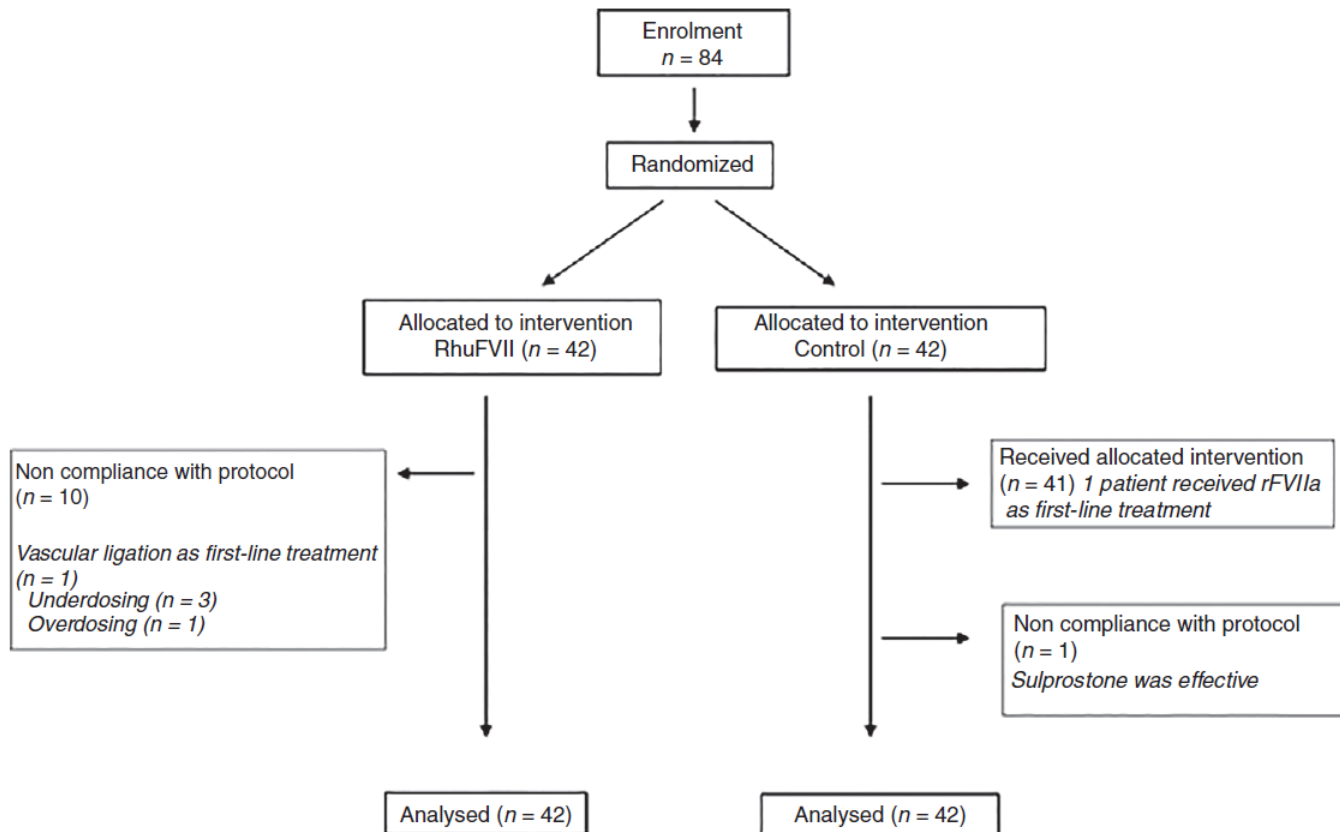


Thank you

Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial

G. LAVIGNE-LISSALDE,^{*†} A. G. AYA,[‡] F. J. MERCIER,[§] S. ROGER-CHRISTOPH,[¶] C. CHAULEUR,^{**}
E. MORAU,^{††} A. S. DUCLOY-BOUTHORS,^{‡‡} A. MIGNON,^{§§} M. RAUCOULES,^{¶¶} A. BONGAIN,^{***}
F. BOEHLEN,^{†††} P. DE MOERLOOSE,^{†††} S. BOUVET,^{‡‡‡} P. FABBRO-PERAY^{‡‡‡} and J.-C. GRIS^{*†}

Journal of Thrombosis and Haemostasis, 13: 520–529 2015



Success
No need for invasive procedures

Open label

Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial

Table 3 Efficacy outcomes

Outcomes	Standard arm (N = 42) n (%)	Intervention arm (N = 42) n (%)	Absolute difference [95% CI]	Relative risk [95% CI]	Mean NNT	P
Primary efficacy outcome	39 (93)	22 (52)	41% [18; 63]	0.56 [0.42; 0.76]	2.6	< 0.0001
Arterial embolization	24 (57)	12 (29)	28% [-4; 61]	0.5 [0.29; 0.86]	3.5	0.0082
Arterial ligation	12 (29)	9 (21)	8% [-30; 44]	0.75 [0.35; 1.59]	14	0.45
Peripartum hysterectomy	8 (19)	3 (7)	12% [-28; 52]	0.38 [0.11; 1.32]	8.4	0.11
Others*	6 (14)	4 (10)	4% [-36; 44]	0.67 [0.20; 2.19]	25	0.50
B-lynch sutures, Bakri Balloon and variants with hemostatic intention						

	Standard arm Med (IQR)	rFVIIa Med (IQR)
Red cells	2 (0-4)	2 (0-4)
% receiving RBC	67	45
FFP	0 (0-4)	0 (0-3)
% receiving FFP	48	45
% receiving platelets	31	26

Total bleed volume not measured