I concentrati di fibrinogeno: fra sperimentazione ed evidenze cliniche

Marco Marietta

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board per Novo-Nordisk**
- **Consulenze / Relazioni a congressi per Kedrion, Orphan, Novo-Nordisk**

Come un istante déja-vu, ombra della gioventù,
ci circondava la nebbia…

ORIGINAL ARTICLE

N Engl J Med 2005;352:777-85.

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, M.D., Nikolai C. Brun, M.D., Ph.D., Kamilla Begtrup, M.Sc., Joseph Broderick, M.D., Stephen Davis, M.D., Michael N. Diringer, M.D., Brett E. Skolnick, Ph.D., and Thorsten Steiner, M.D., for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators*

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

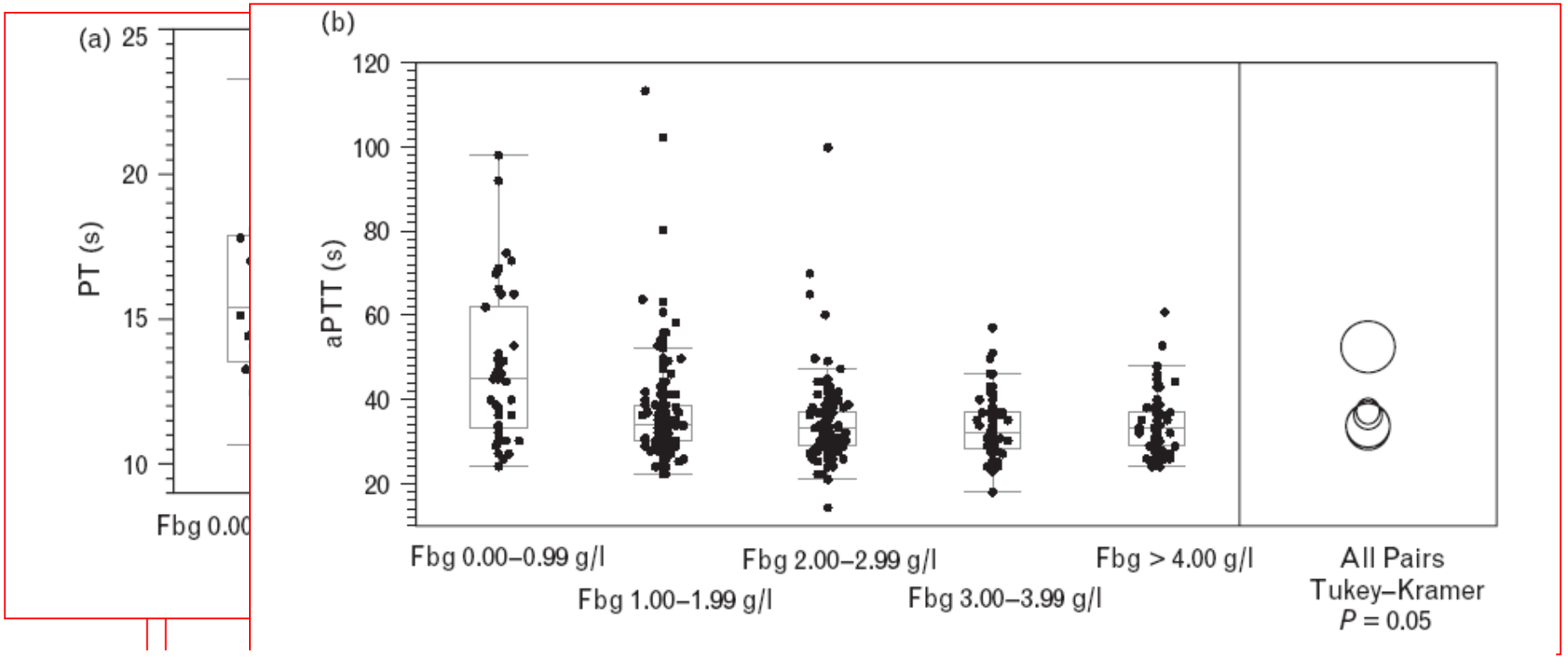
J Trauma. 2005;59:8–18.

Dalla fisiopatologia alla terapia…

Blood Coagulation and Fibrinolysis 2008, 19:765–770

Impact of fibrinogen concentration in severely ill patients on mechanical properties of whole blood clots

Carl-Erik Dempfle[a], Thorsten Kälsch[a], Elif Elmas[a], Nenad Suvajac[a], Thomas Lücke[b], Elke Münch[b] and Martin Borggrefe[a]



Valore di fibrinogeno > 1g/L è una soglia solo per PT/APTT, mentre le proprietà meccaniche del coagulo migliorano in continuo

SHOCK, Vol. 39, No. 1, pp. 45–49, 2013

FUNCTIONAL FIBRINOGEN ASSAY INDICATES THAT FIBRINOGEN IS CRITICAL IN CORRECTING ABNORMAL CLOT STRENGTH FOLLOWING TRAUMA

Jeffrey N. Harr,* Ernest E. Moore,*†‡ Arsen Ghasabyan,†‡ Theresa L. Chin,* Angela Sauaia,*‡ Anirban Banerjee,‡ and Christopher C. Silliman‡§‖

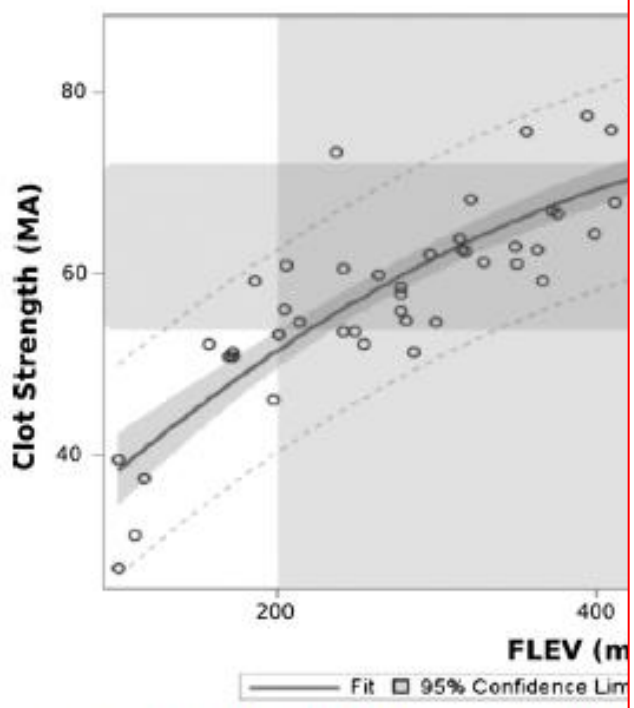


FIG. 3. **Functional fibrinogen level measured clot strength (MA).** $R^2 = 0.80$ parameters appear to be associated with dL. Normal values are shaded.

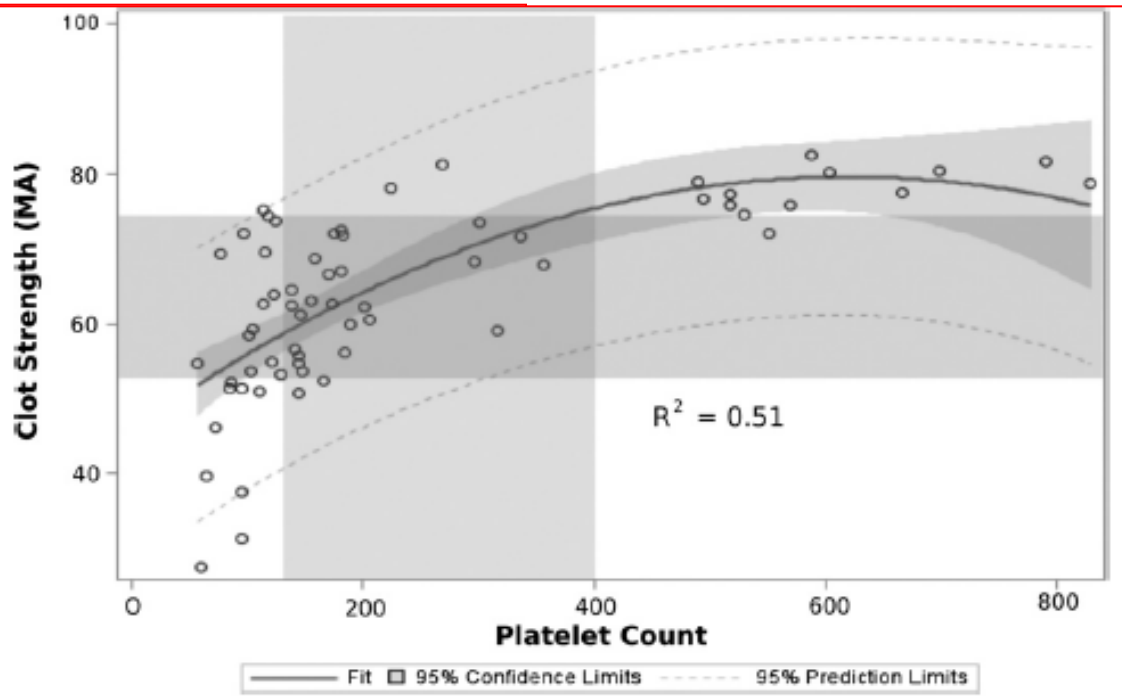


FIG. 4. **Platelet count has a moderate correlation to clot strength (MA).** $R^2 = 0.51$ ($P < 0.0001$). A platelet count greater than 100,000/μL was associated with normal clot strength parameters. An increase in platelet count does not appear to significantly contribute to clot strength at numbers greater than 300,000/μL. Normal values are shaded.

J Thromb Haemost 2007; **5**: 1019–25.

The effect of fibrinogen concentrate on thrombocytopenia

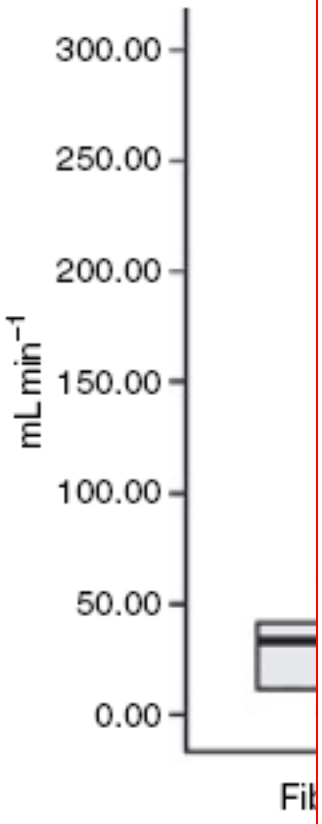


Fig. 3. Rate of blood loss
with fibrinogen, platelets
platelet group, $^{\#}P < 0.05$
$^{\Delta}P < 0.05$ platelet group

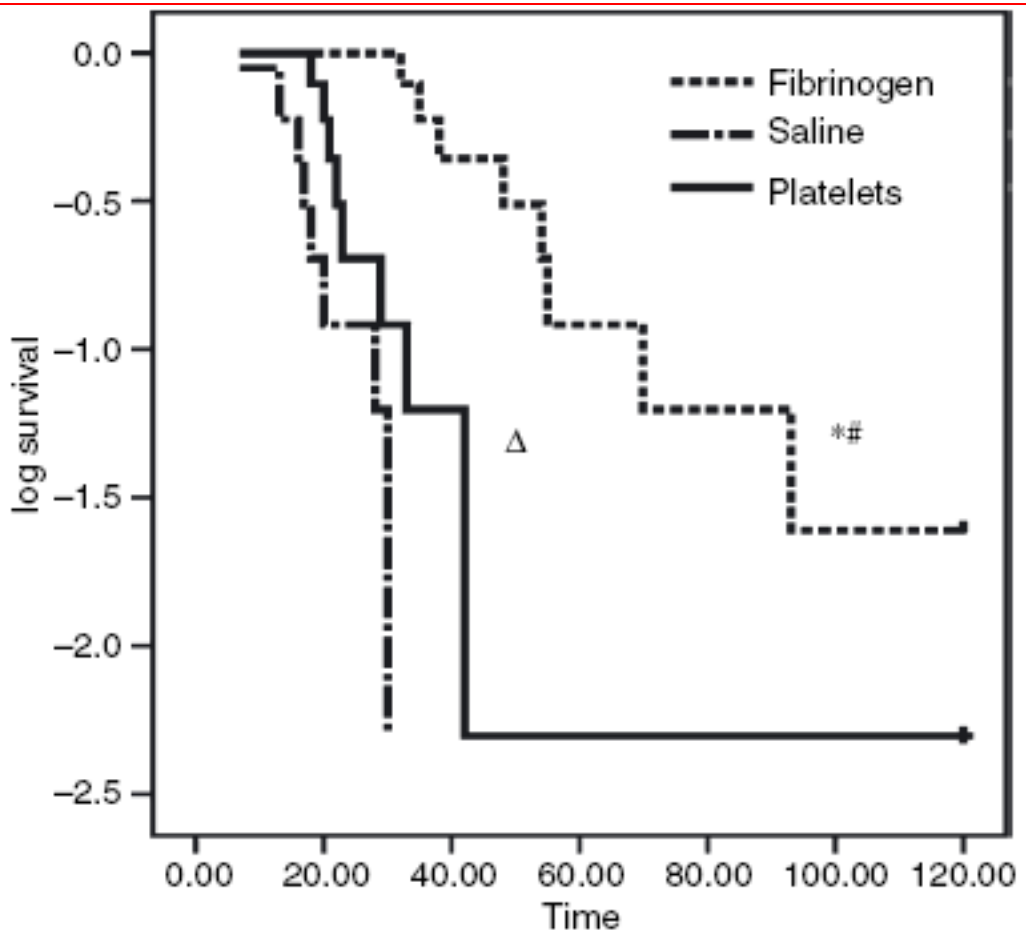


Fig. 4. Kaplan–Meier analysis: survival time (min) after liver injury in animals treated with platelets, fibrinogen or normal saline. $^{*}P < 0.05$ fibrinogen group vs. platelet group, $^{\#}P < 0.05$ fibrinogen group vs. saline group. $^{\Delta}P < 0.05$ platelet group vs. saline group.

British Journal Of Anaesthesia, 117 (5): 576–82 (2016)

Fibrinogen supplementation *ex vivo* increases clot firmness comparable to platelet transfusion in thrombocytopenia†

B. Schenk[1,*], A. K. Lindner[2], B. Treichl[2], M. Bachler[1], M. Hermann[1], O. H. Larsen[3], C. Fenger-Eriksen[3,4], D. Wally[2], H. Tauber[2], C. Velik-Salchner[2] and D. Fries[1]

Patient population

One hundred patients, ages 18–85 years, in clinical need of platelet transfusion (as assessed by the treating physician) were enrolled at the Medical University of Innsbruck, Department of Anaesthesiology and General Intensive Care Medicine, mostly after heart surgery (platelet concentrates were administered only postoperatively after cardiopulmonary bypass). Exclusion criteria were pregnancy, nursing or active participation in another clinical trial.

Table 1 Patient characteristics and selected laboratory data

	Median	Range	N
Age (years)	70	37–86	95
Weight (kg)	79	47–125	95
Height (cm)	173	150–190	95
BMI	27	16–46	95
Visit 1			
Platelet count ($\times 10^9$ litre^{-1})	86	8–216	92
Erythrocytes ($\times 10^{12}$ litre^{-1})	3.0	2.3–4.4	92
Fibrinogen (mg dl^{-1})	194	53–375	88
Visit 2			
Platelet count ($\times 10^9$ litre^{-1})	110	22–291	95
Erythrocytes ($\times 10^{12}$ litre^{-1})	3.2	2.2–5.1	95
Fibrinogen (mg dl^{-1})	212	69–396	88
Visit 3			
Platelet count ($\times 10^9$ litre^{-1})	92	10–240	32
Erythrocytes ($\times 10^{12}$ litre^{-1})	3.1	2.6–3.8	32

British Journal Of Anaesthesia, 117 (5): 576–82 (2016)

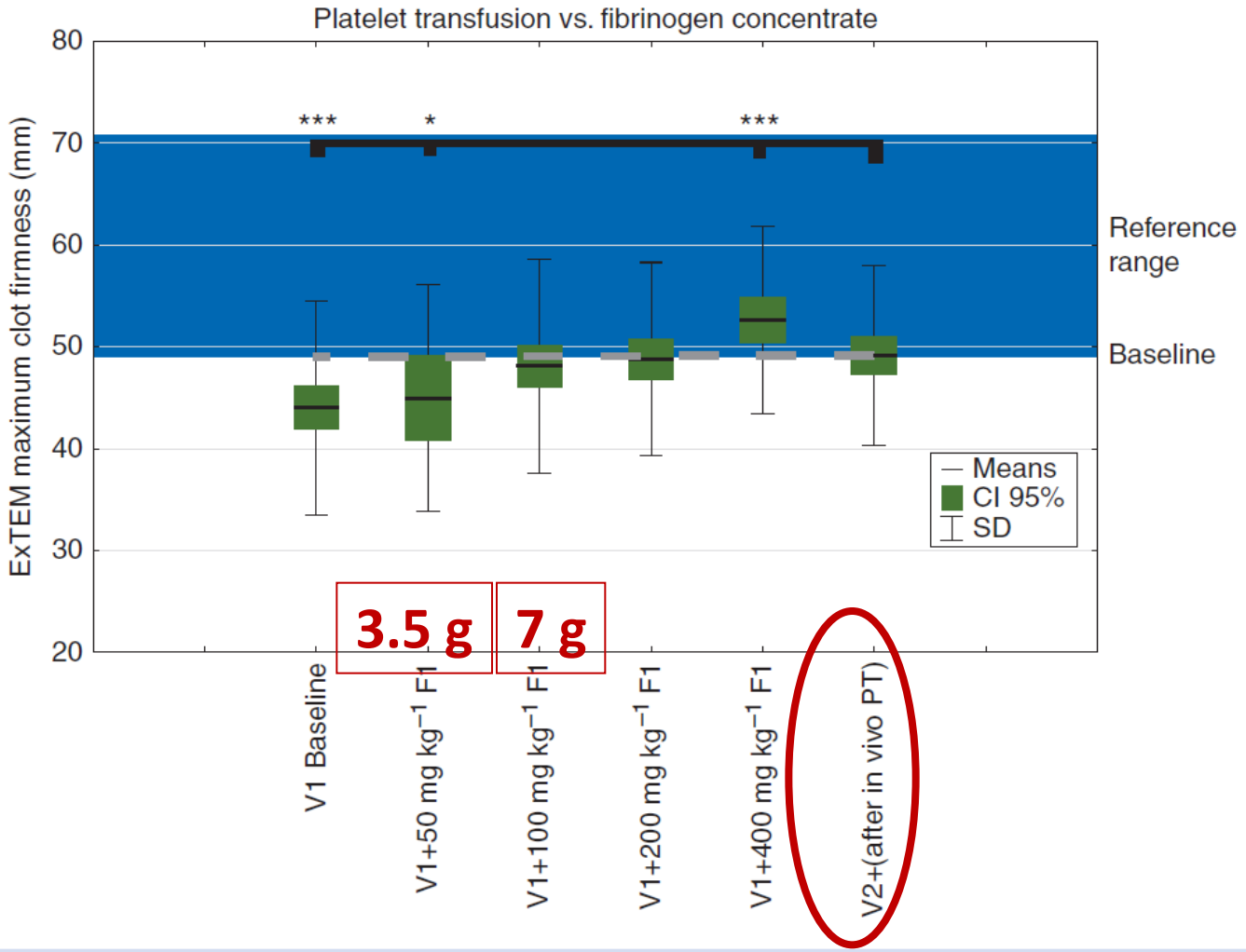


Fig 1 Effect of *ex vivo* fibrinogen supplementation compared with *in vivo* platelet transfusion on EXTEM MCF. EXTEM MCF before (baseline V1) and after platelet transfusion (baseline V2). Samples before PT were spiked with fibrinogen concentrate (equivalent to 50–400 mg kg^{-1} body weight). Blood samples from patients 1 h after PT (V2) were defined as baseline values. Differences from V2 are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Wilcoxon signed-rank test). Data presented as mean (SD). CI, confidence interval.

British Journal of Anaesthesia **117** (5): 548–50 (2016)
doi:10.1093/bja/aew332

Fibrinogen—is it a universal haemostatic agent?

D. Bolliger[1,*] and K. A. Tanaka[2]

[1]Department of Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland, and [2]Department of Anesthesiology, Division of Cardiac Anesthesiology, University of Maryland, Baltimore, MD, USA

- ✓ *Viscoelastic clot strength increases in the presence of anaemia, while anaemia exacerbates microvascular bleeding via reduced platelet margination*
- ✓ *Under anaemic state the effect of fibrinogen on viscoelastic clot strength may be overestimated in vitro, and therefore can not be directly compared with in vivo platelet activity*
- ✓ *30% of patients had been treated with P_2Y_{12} inhibitors before surgery, whose effects are not reflected on thromboelastometry, because thrombin-induced platelet activation sustains the active state of GPIIb/IIIa receptors*

Hagemo *et al. Critical Care* 2014, **18**:R52
http://ccforum.com/content/18/2/R52

CRITICAL CARE

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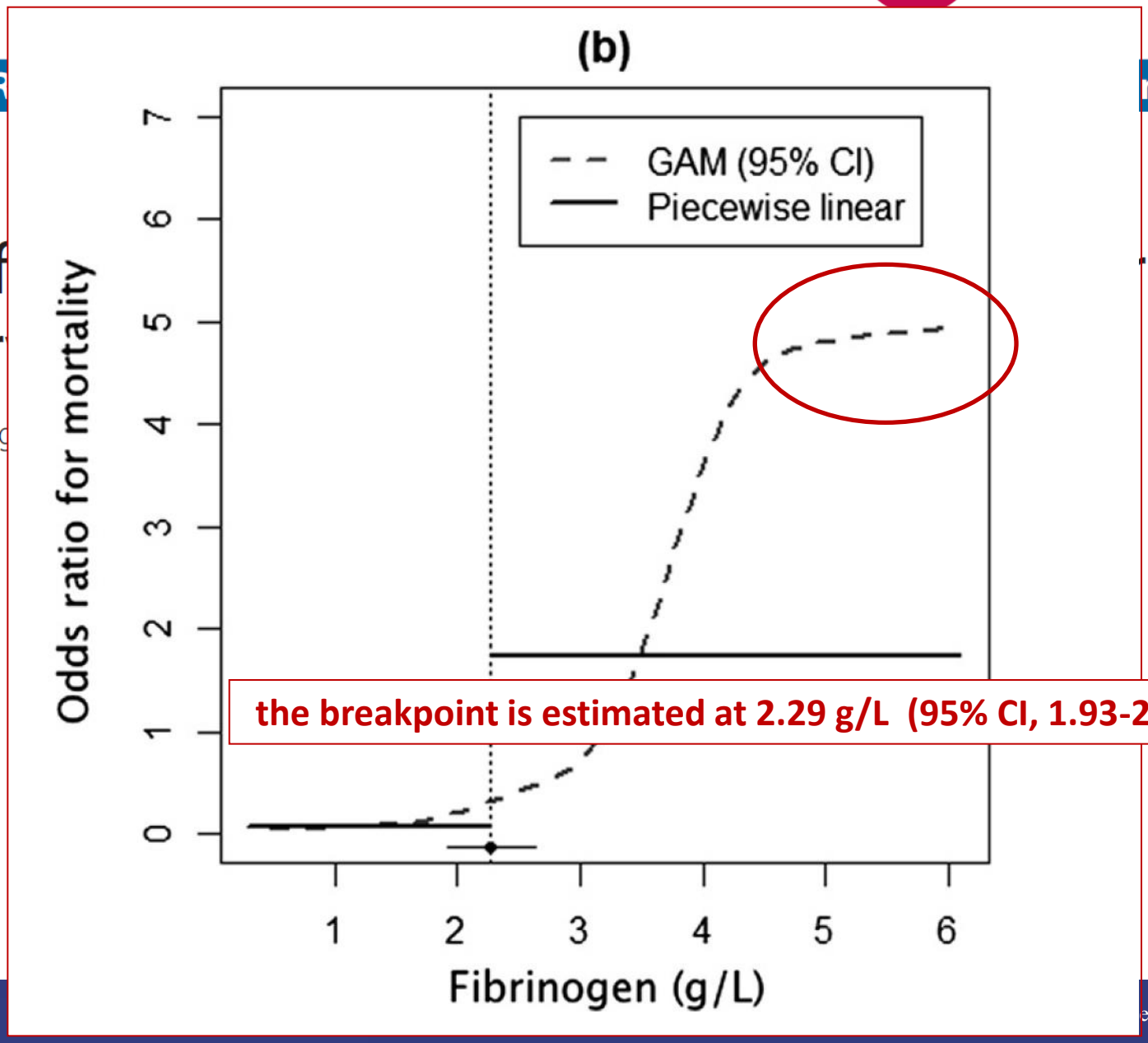


the breakpoint is estimated at 2.29 g/L (95% CI, 1.93-2.64)

Hagemo *et al. Critical Care* 2014, **18**:R52
http://ccforum.com/content/18/2/R52

CRITICAL CARE

RESEARCH Open Access

Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study

Jostein S Hagemo[1,2*], Simon Stanworth[3], Nicole P Juffermans[4,5], Karim Brohi[6], Mitchell Jay Cohen[7],

Table 2 Linear and piecewise linear multiple logistic regression models with 28-day mortality as the dependent variable

	Linear model		Piecewise linear model		
	Odds ratio v	*P* value	Segment	Odds ratio (95% CI)	*P* value
Fibrinogen (g/l)[a]	0.46	< 0.001	Lower	0.08	< 0.001
	(0.31, 0.67)			(0.03, 0.20)	
			Upper	1.77	0.076
				(0.94, 3.32)	
Injury severity score[b]	1.03	0.008	Lower	1.18	< 0.001
	(1.01, 1.05)			(1.10, 1.27)	
			Upper	0.93	0.001
				(0.89, 0.97)	

Journal of Thrombosis and Haemostasis, 5: 266–273

ORIGINAL ARTICLE

The decrease of fibrinogen is an early predictor of the severity of postp

B. CHAR
O. SIBO
M. H. DE
A, ‡¶

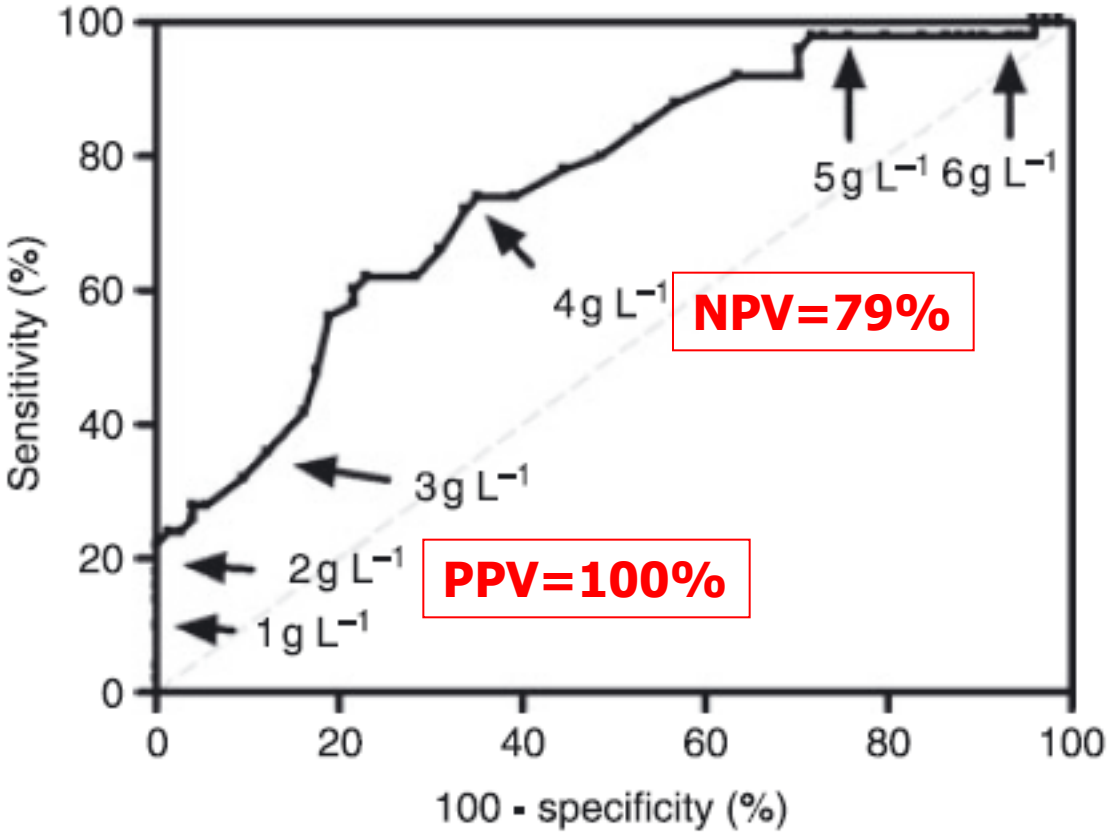


Fig. 3. ROC curve of fibrinogen plasma concentration at H0 for the diagnosis of severe postpartum hemorrhage.

BMJ 2016;355:i6536 doi: 10.1136/bmj.i6536 (Published 9 December 2016)

FEATURE

CHRISTMAS 2016: FOOD FOR THOUGHT

Is caviar a risk factor for being a millionaire?

Anders Huitfeldt argues that the answer depends on your definition of "risk factor" and calls for greater clarity in research

Anders Huitfeldt *postdoctoral scholar*

Dalla fisiopatologia alla terapia…

LA COAGULOPATIA DEL TRAUMA

Rossaint *et al. Critical Care* (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

Fibrinogen and cryoprecipitate

Recommendation 28 **If a concentrate-based strategy is used, we recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/l. (Grade 1C)**

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses must be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. (Grade 2C)

Coagulation management

We recommend treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function. **1C**

We recommend that a plasma fibrinogen concentration $<1.5–2.0\,g\,l^{-1}$ or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution. **1C**

We suggest an initial fibrinogen concentrate dose of $25–50\,mg\,kg^{-1}$. **2C**

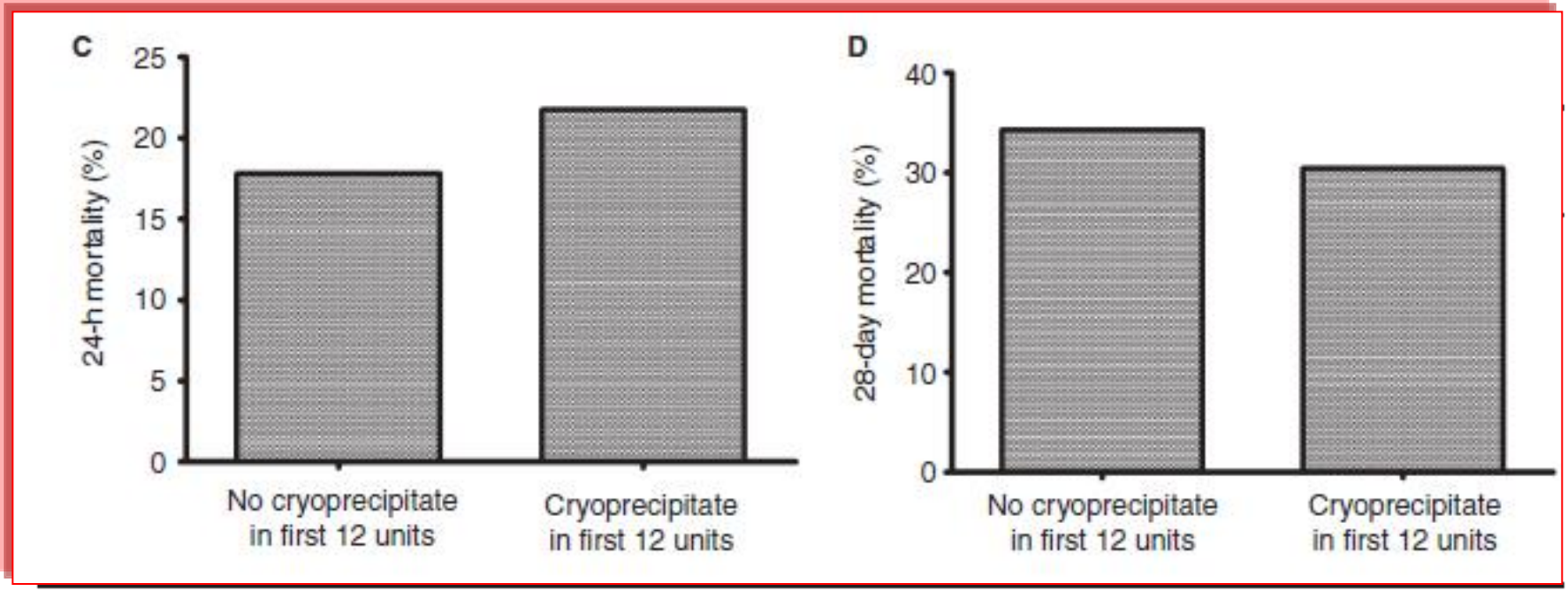
We suggest that the indication for cryoprecipitate is lack of available fibrinogen concentrate for the treatment of bleeding and hypofibrinogenaemia. **2C**

Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes

C. ROURKE,*[1] N. CURRY,†[1] S. KHAN,* R. TAYLOR,† I. RAZA,* R. DAVENPORT,* S. STANWORTH† and K. BROHI*

J Thromb Haemost 2012; **10:** 1342–51.

PROSPETTICO DI COORTE



APTT, activated partial thromboplastin time; CI, confidence interval.

Nardi *et al. Critical Care* (2015) 19:83
DOI 10.1186/s13054-015-0817-9

CRITICAL CARE

RESEARCH Open Access

Trauma-induced coagulopathy: impact of the early coagulation support protocol on blood product consumption, mortality and costs

Table 3 Impact of introduction of early coagulation support protocol on consumption of blood components[a]

		2011	2013	Missing	*P*-value
Patients with ISS >15 and ≥3 U of PRBC		130	96		
Blood components transfused within 24 hr					
PRBC (U)	Mean (SD)	8.09 (6.7)	6.5 (4.8)	–	0.149
	Median (IQR)	5 (6.0)	4 (5.5)		
PTL (U)	Mean (SD)	4.18 (5.9)	2.68 (4.75)	–	0.046
	Median (IQR)	0 (6)	0 (6)		
Plasma (U)	Mean (SD)	8.97 (9.47)	4.21 (4.61)	–	<0.001
	Median (IQR)	6 (8)	4 (6)		
Outcome					
Dead within 24 hr	n (%)	8 (6.15%)	3 (3.12%)	–	0.361
Hospital mortality	n (%)	26 (20.0%)	13 (13.5%)	–	0.218

[a]IQR, Interquartile range; ISS, Injury Severity Score; PRBC, Packed red blood cells; PTL, Platelets; SD, Standard deviation.

BJA

British Journal of Anaesthesia, 117 (6): 775–82 (2016)

doi: 10.1093/bja/aew343
Critical Care

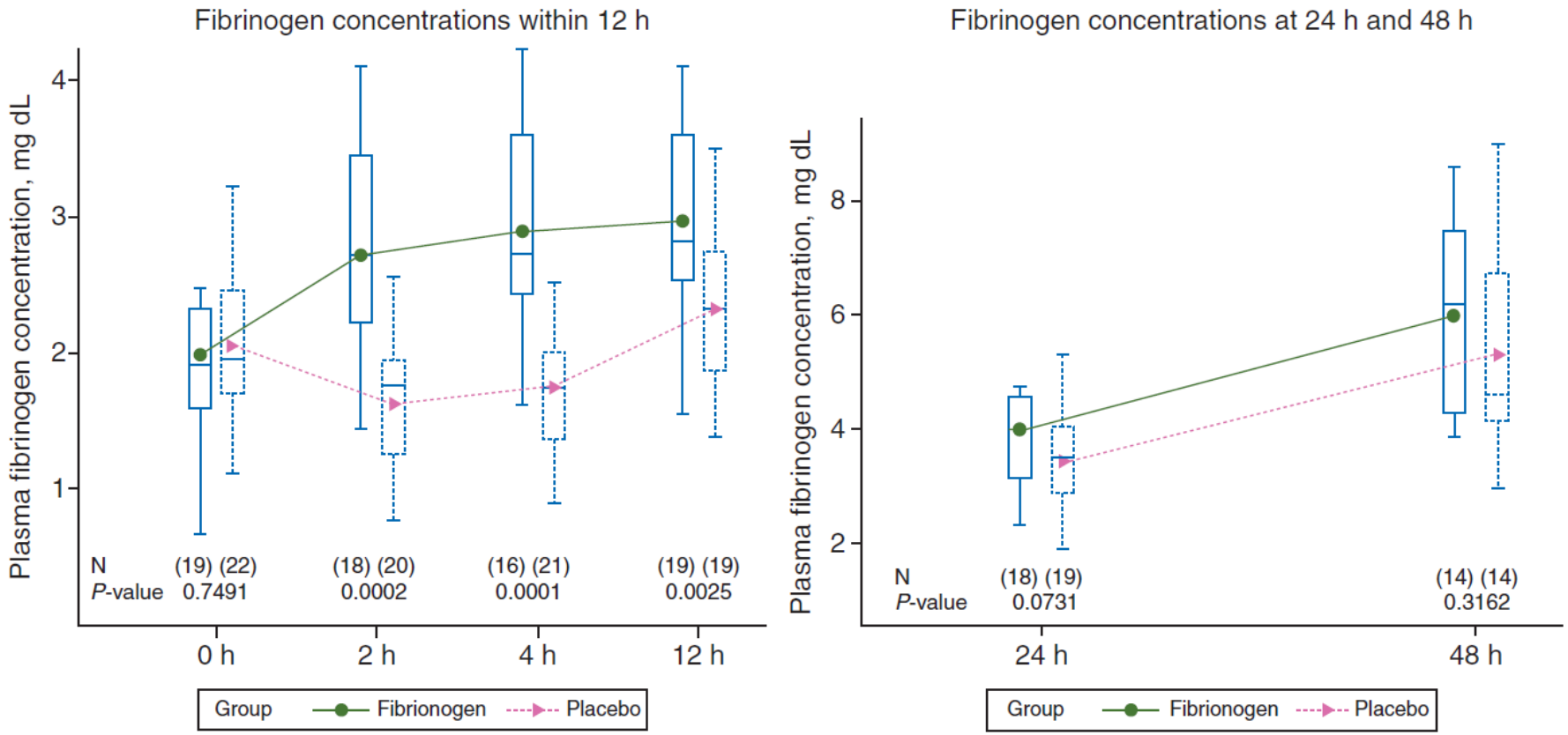


Fig 2 Plasma Fibrinogen Concentrations throughout 48 h of Hospitalization.
Data are presented as means (standard deviation) or median (interquartile ranges)
FC, fibrinogen concentrate

BJA

British Journal of Anaesthesia, 117 (6): 775–82 (2016)

doi: 10.1093/bja/aew343
Critical Care

Table 3 Clinical endpoints. Data are presented as number of positive outcomes over total number of patients assessed per study group, and percentages. Placebo considered reference standard for relative risk calculation. [1]One subject in the FC group died nine days after hospital admission as a result of worsening severe brain injury; in the placebo group, the single death was mostly related to anoxic brain injury after cardiac arrests as a result of initial traumatic bleeding. [2]One study participant was lost to follow-up at day 28. [3]The only death in the trial (in the FC group) that was classified as being mainly as a result of exsanguination occurred in a 61 year-old female with a history of two previous myocardial infarctions. It happened in less than 2 h of hospital arrival after prehospital and in-hospital cardiac arrests after resuscitative efforts were discontinued because of futility. CI, confidence interval; FC, fibrinogen concentrate

	Placebo	FC	Relative Risk	95% CI
All-cause 28-day mortality[1]	1/24 (4.2)	2/20[2] (10)	2.4	−0.2 to 23
Death by exsanguination[3]	0	1/21 (4.8)	NA	NA
Symptomatic Deep Venous Thrombosis	0	0	NA	NA
Deep Venous Thrombosis on Leg Doppler	3/14 (21.4)	2/15 (13.3)	0.62	−0.1 to 3.2
Pulmonary Embolism	1/24 (4.2)	2/21 (9.5)	2.3	−0.2 to 23.4
Myocardial Infarction	0	0	NA	NA
Stroke	0	0	NA	NA
Acute Lung Injury	2/24 (8.3)	0	NA	NA
Acute Respiratory Distress Syndrome	2/24 (8.3)	0	NA	NA
Acute Kidney Injury	2/24 (8.3)	3/21 (14.3)	1.7	−0.3 to 9.3
Multiple Organ Failure	2/24 (8.3)	2/21 (9.5)	1.1	−0.2 to 7.4
Infection	8/24 (33.3)	5/21 (23.8)	0.7	−0.3 to 1.8

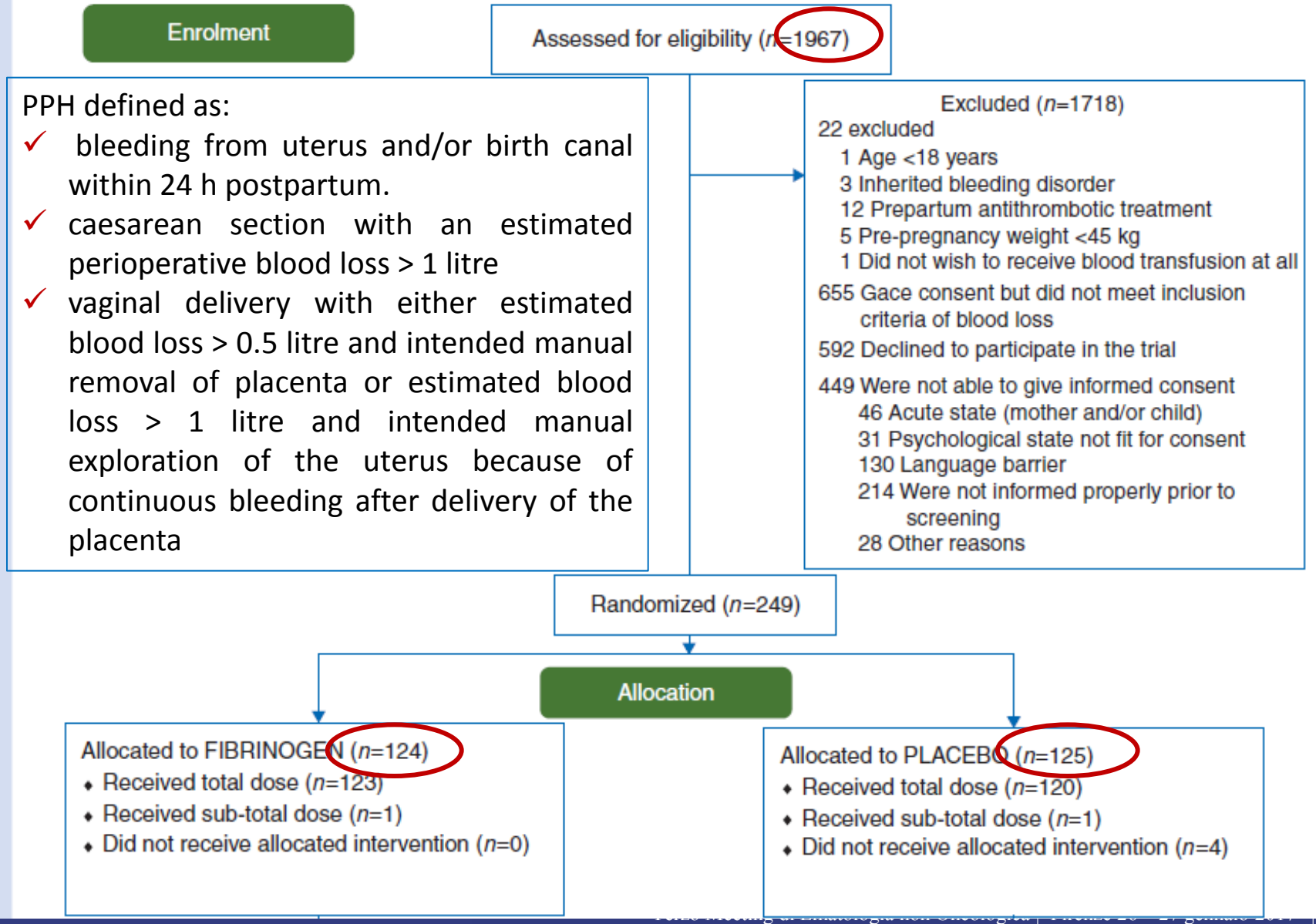
L'EMORRAGIA POST-PARTUM

British Journal of Anaesthesia 114 (4): 623–33 (2015)
Advance Access publication 13 January 2015 · doi:10.1093/bja/aeu444

BJA

PPH defined as:

- ✓ bleeding from uterus and/or birth canal within 24 h postpartum.
- ✓ caesarean section with an estimated perioperative blood loss > 1 litre
- ✓ vaginal delivery with either estimated blood loss > 0.5 litre and intended manual removal of placenta or estimated blood loss > 1 litre and intended manual exploration of the uterus because of continuous bleeding after delivery of the placenta



British Journal of Anaesthesia 114 (4): 623–33 (2015)
Advance Access publication 13 January 2015 · doi:10.1093/bja/aeu444

BJA

Pre-emptive treatment with fibrinogen concentrate for

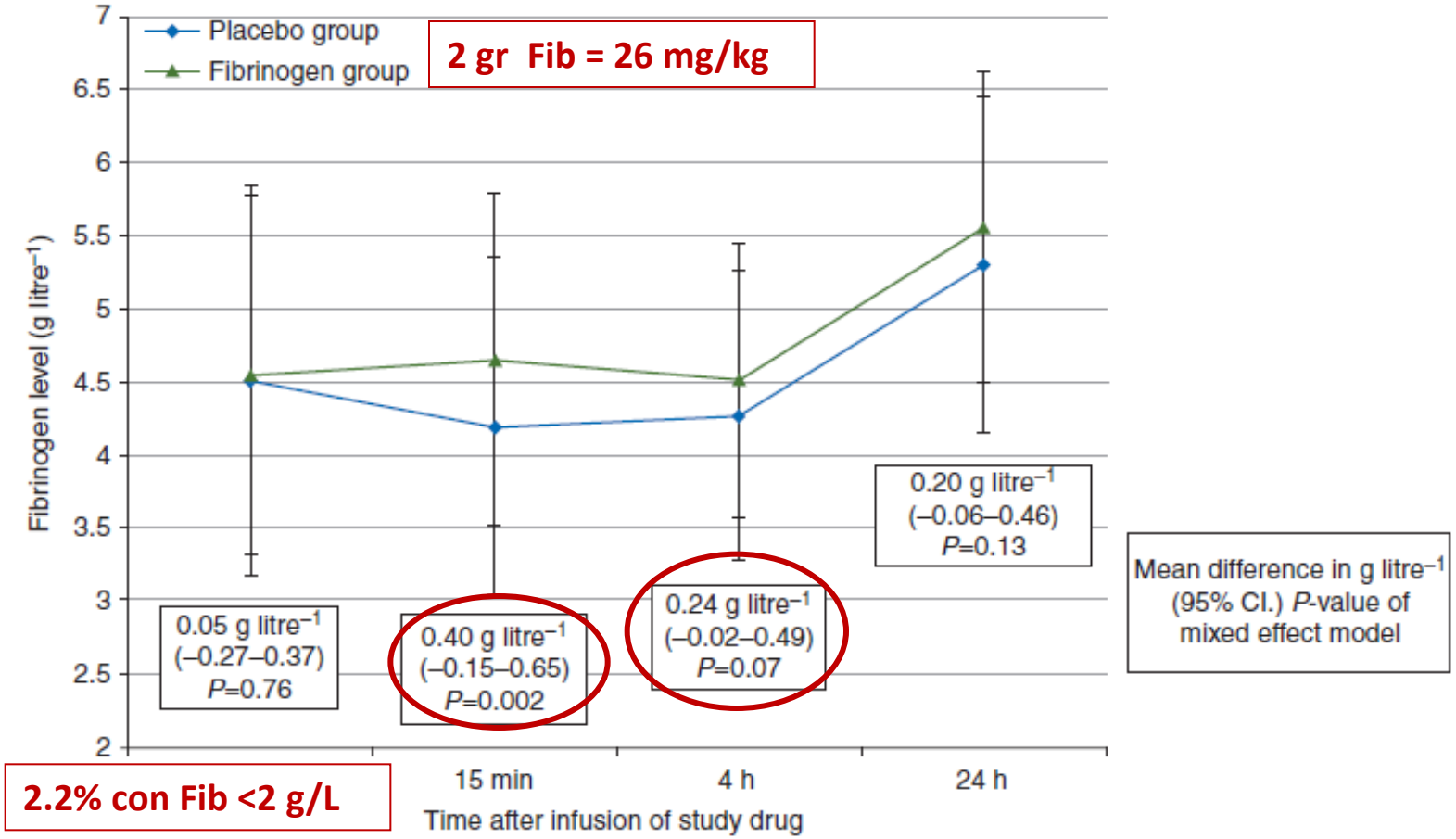


Fig 2 Mean fibrinogen concentrations in placebo and fibrinogen groups from baseline to 24 h after study drug administration, with whiskers indicating standard deviation. Mean difference of the fibrinogen concentration between the fibrinogen and placebo group is given below at each time point from baseline to 24 h after the study drug administration, with 95% confidence interval (CI) given in parenthesis and *P*-value.

British Journal of Anaesthesia **114** (4): 623–33 (2015)
Advance Access publication 13 January 2015 · doi:10.1093/bja/aeu444

BJA

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

A. J. Wikkelsø[1*], H. M. Edwards[2], A. Afshari[3], J. Stensballe[4], J. Langhoff-Roos[5], C. Albrechtsen[3], K. Ekelund[3], G. Hanke[3], E. L. Secher[3], H. F. Sharif[5], L. M. Pedersen[6], A. Troelstrup[6], J. Lauenborg[7], A. U. Mitchell[1], L. Fuhrmann[1], J. Svare[2], M. G. Madsen[8], B. Bødker[9], A. M. Møller[1] and FIB-PPH trial group

Table 2 Primary and secondary outcomes, intention to treat. RBC, red blood cell. Data are presented as the median [IQR] or *n* (%). *One hundred and forty-eight values are missing (61%). †Mean difference with 95% confidence interval (CI; Student's *t*-test). ‡Wilcox rank sum test

Outcome	Fibrinogen (*n*=123)	Placebo (*n*=121)	Relative risk (95% CI)	*P*-value
Primary outcome				
Need for RBC transfusion (during the 6 week period postpartum)	25 (20.3%)	26 (21.5%)	0.95 (0.58–1.54)	0.88
Secondary outcomes				
Estimated blood loss after study drug (ml)	1700 [1500–2000]	1700 [1400–2000]	66 [−78; 210]†	0.37
Need for RBC transfusion (up to 4 h after study drug)	4 (3.3%)	10 (8.3%)	0.39 (0.13–1.22)	0.11
Need for RBC transfusion (up to 24 h after study drug)	14 (11.4%)	19 (15.7%)	0.72 (0.38–1.38)	0.35
Need for RBC transfusion (up to 7 days after study drug)	25 (20.3%)	26 (21.5%)	0.95 (0.58–1.54)	0.88
Total amount of blood transfused	0 [0,0]	0 [0,0]	‡	0.83
Range [min, max]	[0,7]	[0,4]		
Severe PPH*	20 (40.0%)	24 (52.2%)	0.77 (0.49–1.19)	0.31
Death	0 (0.0%)	0 (0.0%)	–	
Haemostatic intervention	0 (0.0%)	0 (0.0%)	–	
Transfusion of ≥4 units of RBCs	8 (6.5%)	3 (2.5%)	2.62 (0.71–9.65)	0.22
Decrease in haemoglobin >40 g litre^{-1}*	20 (40.0%)	24 (52.2%)	0.77 (0.49–1.19)	0.31
Rebleeding	2 (1.6%)	2 (1.7%)	0.98 (0.14–6.87)	1.00
Lowest haemoglobin <58 g litre^{-1}	1 (0.8%)	5 (4.1%)	0.20 (0.02–1.66)	0.12

Anaesthesia 2015, 70, 166–175 doi:10.1111/anae.12859

Orig

Introd
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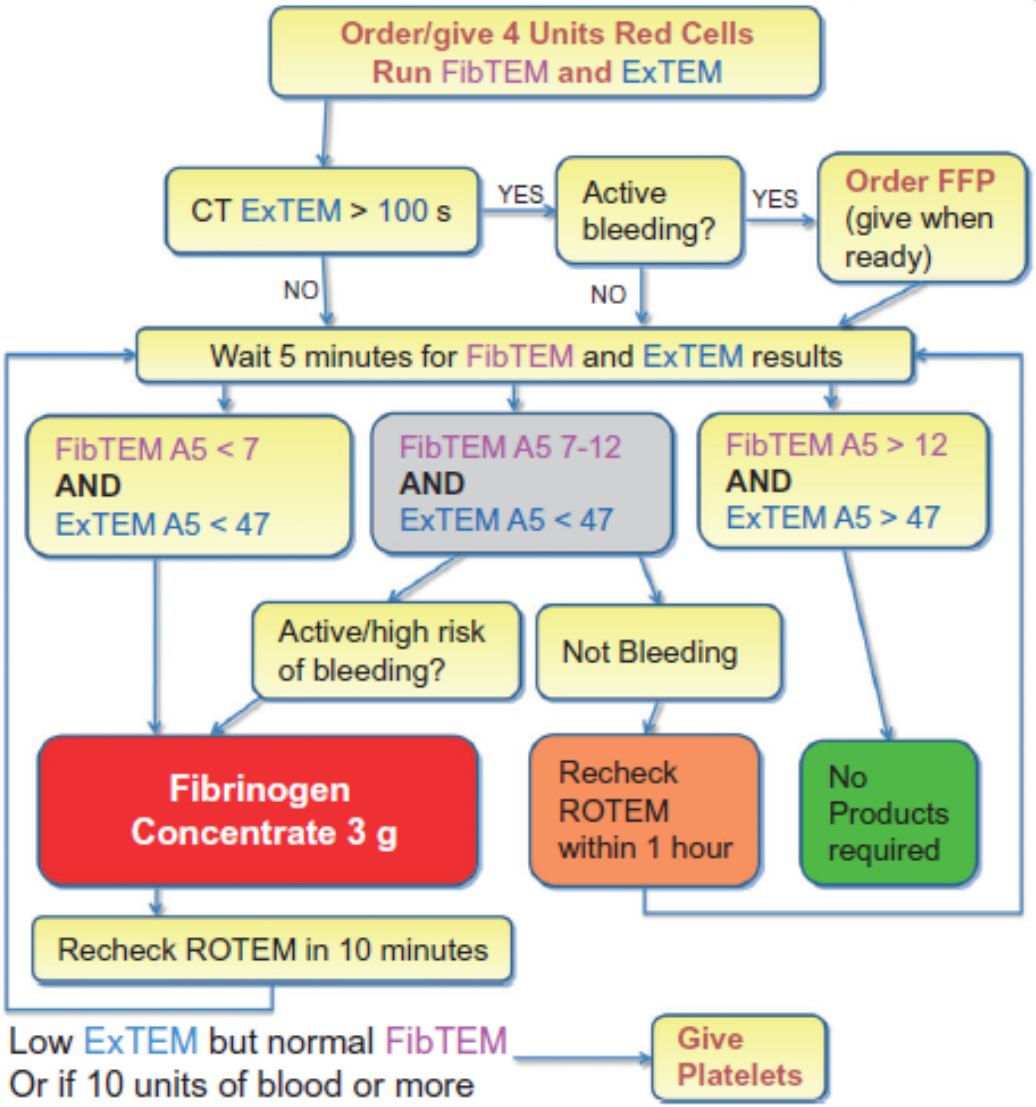
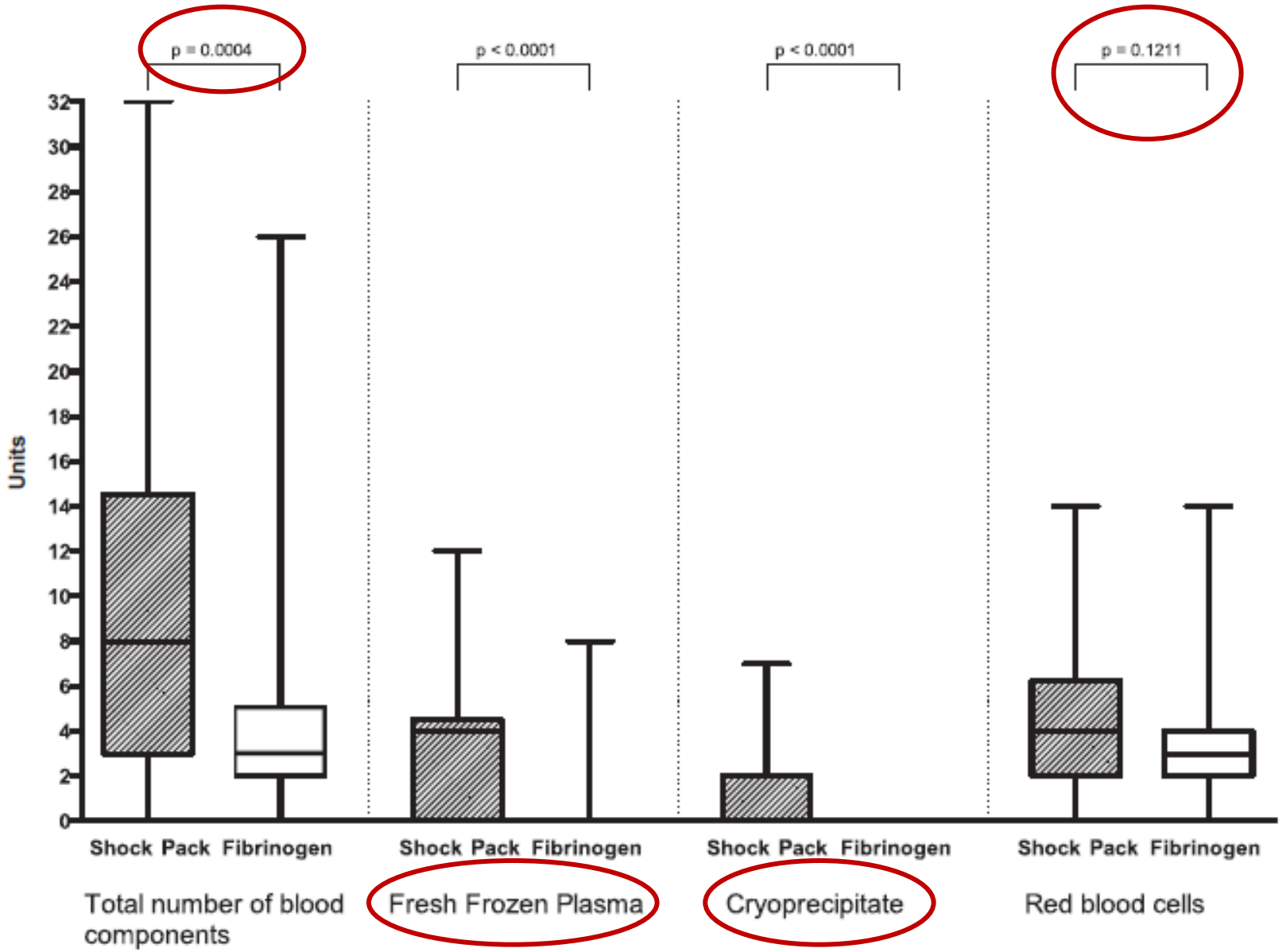
S. Mallaia

Protocol for Massive **Obstetric** Haemorrhage, guided by results from ROTEM

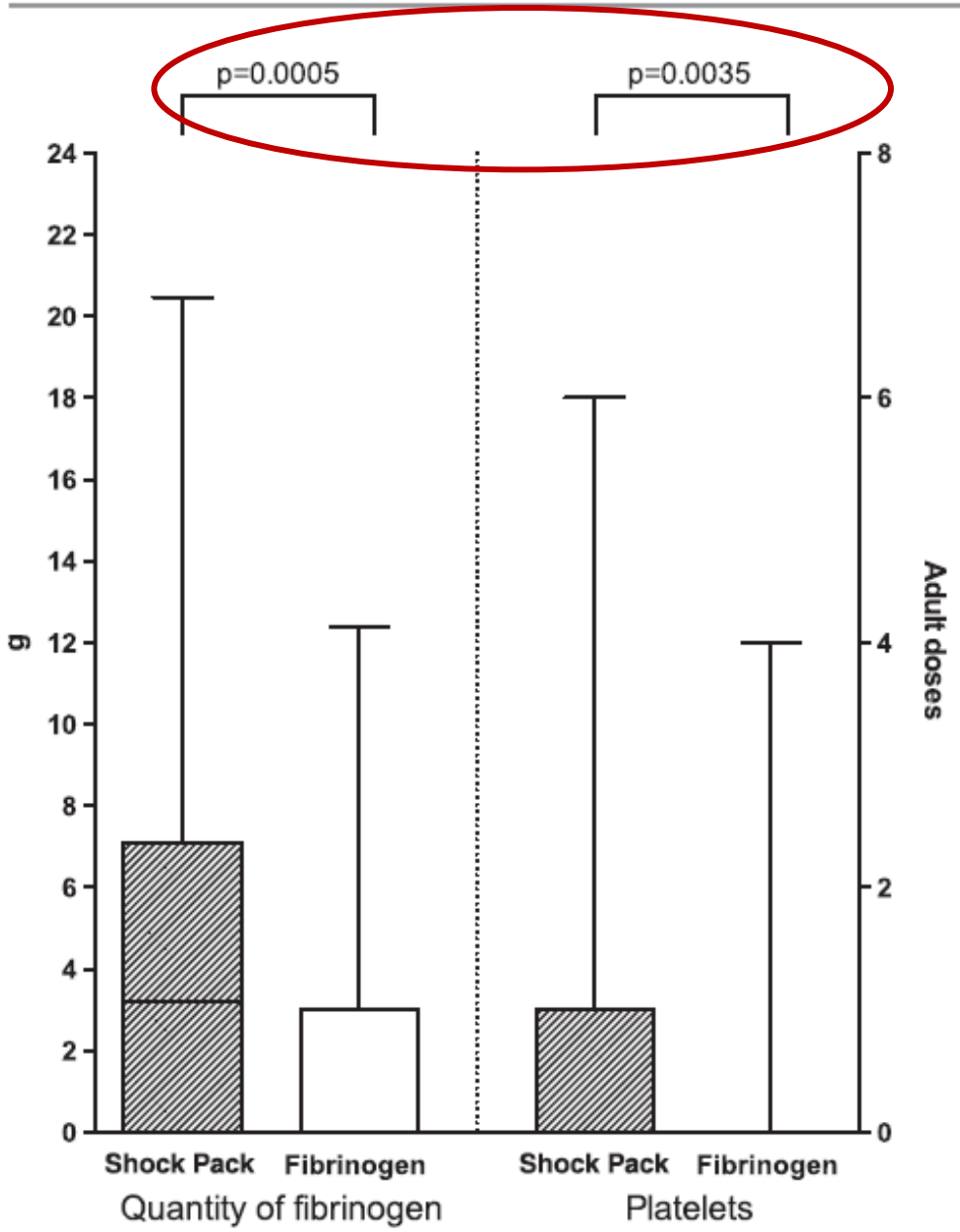
Liverpool Women's



Anaesthesia 2015, 70, 166–175 doi:10.1111/anae.12859



Anaesthesia 2015, 70, 166–175 doi:10.1111/anae.12859



	Shock Pack (n = 42)	Fibrinogen (n = 51)	p value
ICU admission	4 (9%)	1 (2%)	NS
TACO	4 (9%)	0	0.0367
TRALI	0	0	NS
Postpartum hysterectomy	6 (14%)	3 (6%)	NS
Death	0	0	NS

TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

LA CHIRURGIA UROLOGICA

The effect of fibrinogen concentrate on perioperative bleeding in transurethral resection of the prostate: A double blind placebo-controlled and randomized study

Mohammad Soleimani[1] MD, Navid Masoumi[1] MD, Navid Nooraei[2] MD,
Alireza Lashay[1] MD, Mohammad Reza Safarinejad[3] MD

Methods: Sixty men with benign prostatic hyperplasia, who were chosen to undergo TUR-P, entered this prospective randomized double-blind placebo-controlled pilot study. The participants were randomly assigned to two groups: treatment (n=31) and placebo (n=29). They received an infusion of 2 gr fibrinogen concentrate (treatment group) or normal saline (placebo group) before surgery. Data regarding bleeding amount, the operation and complications were recorded and analyzed.

J Thromb Haemost. 2016 Nov 26. doi: 10.1111/jth.13575. [Epub ahead of print]

The effect of fibrinogen concentrate on perioperative bleeding in transurethral resection of the prostate: A double blind placebo-controlled and randomized study

Variables	Fibrinogen (n=31)	95% CI[¶]	Placebo (n=29)	95% CI[¶]	P Value
Operation time (min)	43 (17)	37-49	42 (14)	37-47	0.86
Resected adenoma (gr)	19 (12)	15-23	19 (10)	16-22	0.92
Volume of irrigating fluid (L)	17 (8)	14-20	19 (8)	16-22	0.43
Operation blood loss (mL)	521 (290)	419-623	557 (411)	408-706	0.90
Hemoglobin level 6 hours after the surgery (gr/dL)	12.26 (2)	11.6-13	12.16 (1)	11.8-12.6	0.81
Hemoglobin level 24 hours after the surgery (gr/dL)	11.60 (2)	11.12.2	12.00 (1)	11.6-12.4	0.31
Volume of post-operation irrigating fluid (L)	29 (13)	27.7-20.3	28 (11)	26.8-39.8	0.80
Post-operation blood loss (mL)	291 (270)	196-296	341 (314)	277-405	0.80
Post-operation irrigation time (hr)[¥]	18 (2)	17.3-18.7	18 (3)	17.4-18.6	0.45
First MAP[*] (mmHg)	122 (16)	116-127	117 (16)	116-118	0.30
Last MAP[ƒ] (mmHg)	124 (16)	119-129	119 (14)	114-124	0.21

J Thromb Haemost. 2016 Nov 26. doi: 10.1111/jth.13575. [Epub ahead of print]

LA CARDIOCHIRURGIA

Efficacy and Safety of Fibrinogen Concentrate in Surgical Patients: A Meta-Analysis of Randomized Controlled Trials

First Author	Year of Publication	Journal	Clinical Settings	Timing	Number of Patients	Indication for Fibrinogen Administration	Fibrinogen Dose and Comparator	Control Group Treatment	Risk of Bias
Cui Y[12]	2010	*Artif Organs*	Cardiac surgery for severely cyanotic pediatric patients with complex congenital heart disease	Intraoperatively and postoperatively	40	Thromboelastography	Fg (500-1000 mg), FFP, PLT	FFP, PLT	High
Fenger-Eriksen C[13]	2009	*J Thromb Haemost*	Radical cystectomy for localized bladder cancer	Intraoperatively	21	30% reduction in hematocrit level from baseline	Fg 45 mg/kg	Placebo (isotonic saline, 2.25 mL/kg)	Moderate
Galas FR[14]	2014	*J Thorac Cardiovasc Surg*	Elective cardiac surgery with cardiopulmonary bypass	Intraoperatively	63	Diffuse capillary bleeding and plasma Fg level <1 g/L	Fg 60 mg/kg	Cryoprecipitate 10 mL/kg	Moderate
Jeppsson A[15]	2016	*Br J Anaesth*	Patients scheduled for elective coronary artery bypass graft surgery with plasma Fg level ≤3.8 g/L	Intraoperatively	52	Prophylactically given	Fg 2 g	Placebo (0.9% sodium chloride 100 mL)	Low
Karlsson M[16]	2009	*Thromb Haemost*	Elective coronary artery bypass graft surgery	Preoperatively	20	Plasma Fg level ≤3.8 g/L	Fg 2 g	No treatment	Low
Lancé MD[17]	2012	*Vox Sang*	Major elective surgery (cardiovascular, abdominal, orthopedic)	Intraoperatively and postoperatively	43	Prolonged blood loss >150 mL/h or >1.5 mL/kg for 20 min or acute blood loss >700 mL at once	Fg 2 g and 2 U FFP	4 U FFP	High
Najafi A[18]	2014	*Acta Med Iran*	Total hip arthroplasty surgery	Intraoperatively	30	Prophylactically given	Fg 30 mg/kg	Placebo (100 mL of normal saline were infused within 10 min)	High
Rahe-Meyer N[19]	2013	*Anesthesiology*	Elective thoracic or thoracoabdominal aortic replacement surgery with cardiopulmonary bypass	Intraoperatively	80	5-min bleeding mass of 60-250 g immediately after removal from CPB and completed surgical hemostasis	Fg doses were determined from the MCF of the FIBTEM test*	Placebo (50 mL of 0.9% saline were infused within 5 min)	Low
Rahe-Meyer N[20]	2015	*EACTA 2015 (oral presentation only)*	Elective aortic surgery with cardiopulmonary bypass with or without other cardiac surgery	Intraoperatively	142	5-min bleeding mass of 60-250 g immediately after removal from CPB and completed surgical hemostasis	Fg doses were determined from the MCF of the FIBTEM test*	Placebo (not specified)	High
Ranucci M[21]	2015	*J Am Heart Assoc*	Cardiac surgery with an expected cardiopulmonary bypass duration >90 min and at least one of the following: age >65, nonelective or redo surgery, sCr >1.36 mg/dL	Intraoperatively	116	Prophylactically given	Fg doses were determined from the MCF of the FIBTEM test†	Placebo (0.9% saline)	Low

Study or Subgroup	Fibrinogen Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fenger-Eriksen C (2009)	0	11	0	10		Not estimable
Galas FR (2014)	0	30	0	33		Not estimable
Jeppsson A (2016)	0	26	0	26		Not estimable
Karlsson M (2009)	0	10	0	10		Not estimable
Rahe-Meyer N (2013)	1	38	4	42	25.2%	0.28 (0.03-2.36)
Rahe-Meyer N (2015)	1	74	5	68	34.5%	0.18 (0.02-1.53)
Ranucci M (2015)	1	58	3	58	19.9%	0.33 (0.04-3.11)
Sabate A (2016)	1	51	3	48	20.5%	0.31 (0.03-2.91)
Tanaka KA (2014)	0	10	0	10		Not estimable
Wikkelsø AJ (2015)	0	124	0	125		Not estimable
Total (95% CI)		**432**		**430**	**100.0%**	**0.26 (0.09, 0.78)**
Total events	4		15			

Heterogeneity: chi-square = 0.18, df = 3 (P = 0.98); I^2 = 0%

Test for overall effect: z = 2.41 (P = 0.02)

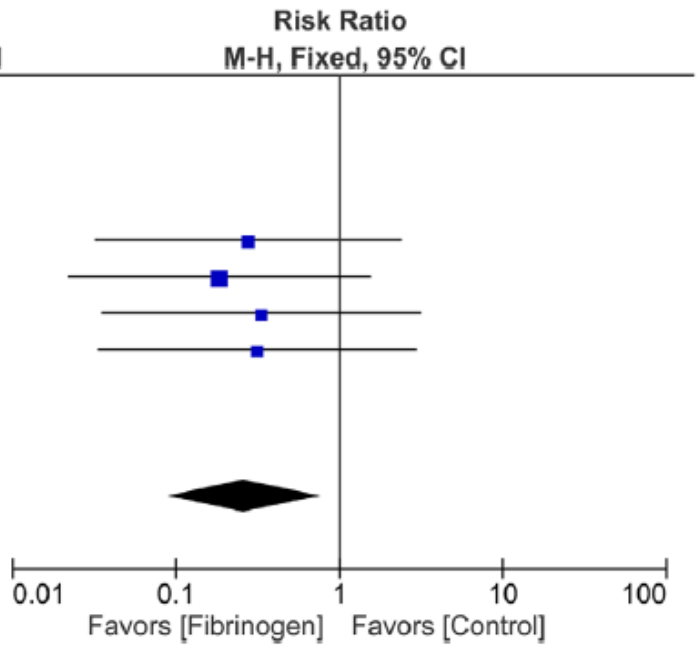


Fig 2. Forest plot for all-cause mortality. Mantel-Haenszel method (M-H).

Journal of Cardiothoracic and Vascular Anesthesia, Vol 30, No 5 (October), 2016: pp 1196–1204

Study or Subgroup	Fibrinogen Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Galas FR (2014)	320	439	30	410	219	33	11.8%	−90.00 (−263.96 to 83.96)
Jeppsson A (2016)	1,103	518	26	1,272	588	26	5.6%	−169.00 (−470.21 to 132.21)
Karlsson M (2009)	565	150	10	830	268	10	10.6%	−265.00 (−455.35 to −74.65)
Najafi A (2014)	976	553	15	1,100	350	15	4.8%	−124.00 (−455.19 to 207.19)
Rahe-Meyer N (2013)	650	611	38	850	674	42	6.2%	−200.00 (−481.58 to 81.58)
Ranucci M (2015)	300	148	58	355	259	58	21.3%	−55.00 (−131.77 to 21.77)
Sadeghi M (2014)	477	143	30	703	179	30	20.7%	−226.00 (−307.98 to −144.02)
Tanaka KA (2014)	925	884	10	1,315	1,713	10	0.4%	−390.00 (−1584.75 to 804.75)
Wikkelsø AJ (2015)	1,700	370	124	1,700	444	125	18.6%	0.00 (−101.49 to 101.49)
Total (95% CI)			**341**			**349**	**100.0%**	**−126.83 (−207.16 to −46.51)**

Heterogeneity: Tau² = 6368.30; chi-square = 17.46, df = 8 (p = 0.03); I^2 = 54%
Test for overall effect: z = 3.09 (p = 0.002)

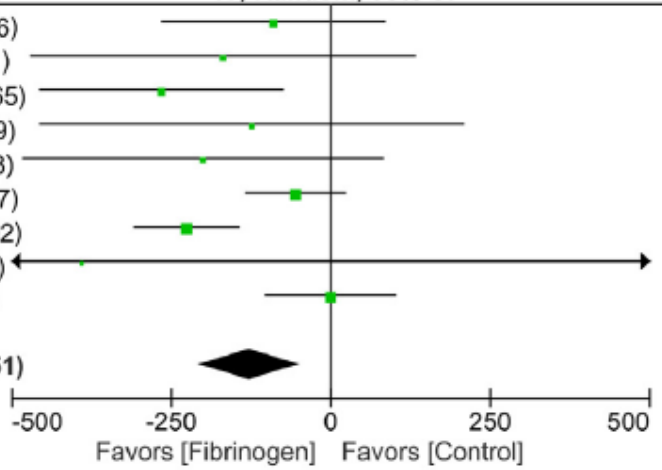


Fig 3. Forest plot for bleeding.

Study or Subgroup	Fibrinogen Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cui Y (2010)	0	1.1	20	1.5	1.7	20	12.2%	−1.50 (−2.39 to −0.61)
Fenger-Eriksen C (2009)	0	1.5	11	1.5	1.5	10	7.4%	−1.50 (−2.78 to −0.22)
Jeppsson A (2016)	0.63	1.17	26	1.33	3.11	26	7.5%	−0.70 (−1.98 to 0.58)
Karlsson M (2009)	2	0.5	10	2	1.7	10	9.3%	0.00 (−1.10 to 1.10)
Najafi A (2014)	0.8	1.01	15	1.06	1.2	15	13.8%	−0.26 (−1.05 to 0.53)
Rahe-Meyer N (2013)	0	2.2	38	2	2.2	42	11.0%	−2.00 (−2.97 to −1.03)
Ranucci M (2015)	0	0.7	58	1	1.5	58	22.0%	−1.00 (−1.43 to −0.57)
Sabate A (2016)	2	4.4	40	3	4.4	41	3.9%	−1.00 (−2.92 to 0.92)
Sadeghi M (2014)	1.5	1.8	30	2	1.5	30	13.0%	−0.50 (−1.34 to 0.34)
Total (95% CI)			**248**			**252**	**100.0%**	**−0.93 (−1.33 to −0.52)**

Heterogeneity: Tau² = 0.15; chi-square = 13.80, df = 8 (p = 0.09); I^2 = 42%
Test for overall effect: z = 4.47 (p < 0.00001)

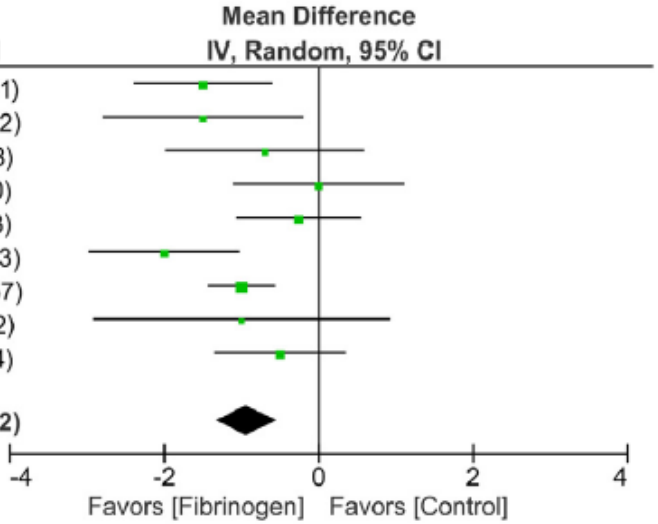


Fig 4. Forest plot for the number of red blood cells units transfused.

Journal of Cardiothoracic and Vascular Anesthesia, Vol ▮, No suppl (▮), 2016: pp ▮▮▮–▮▮▮

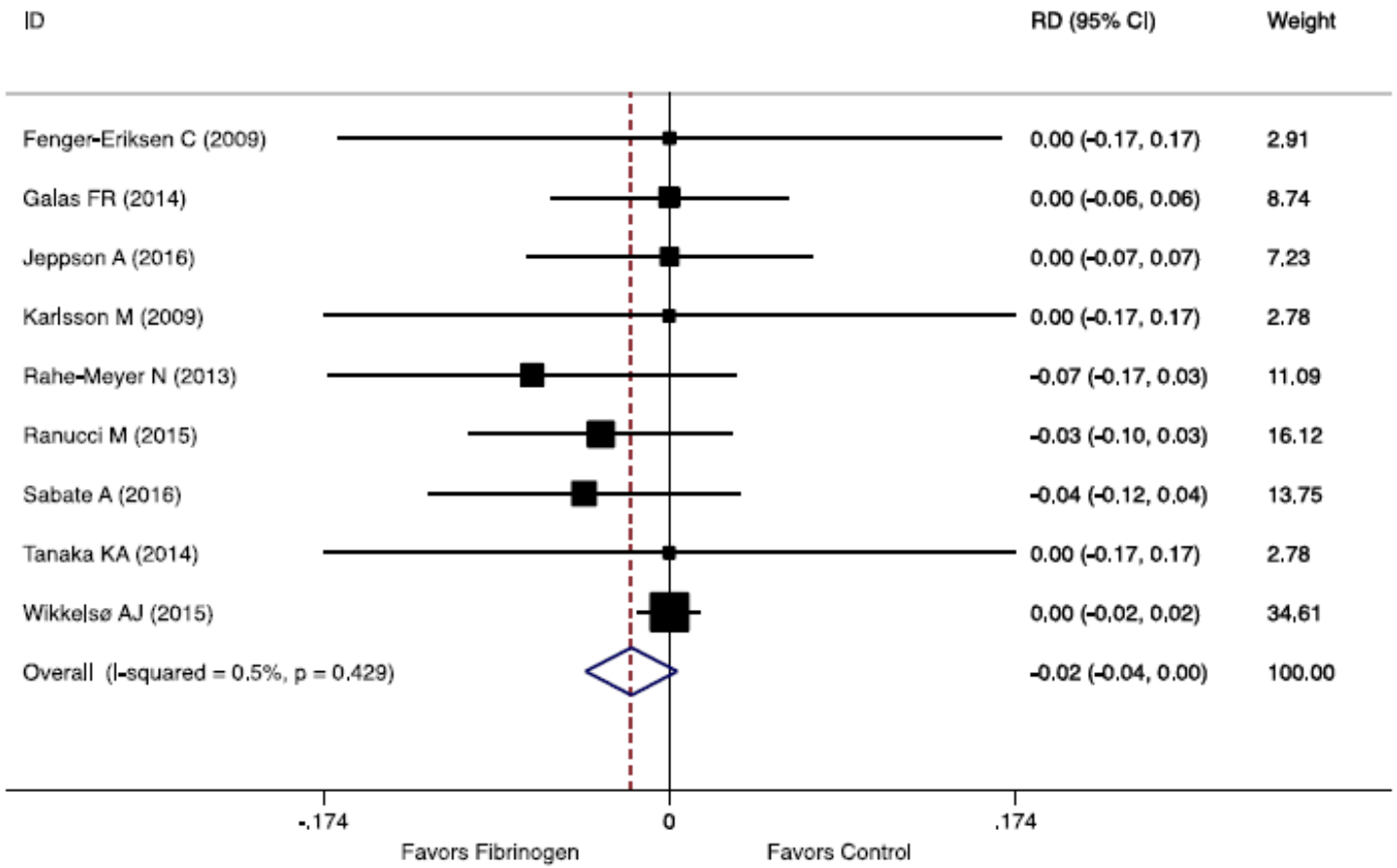


Fig 2. Forest plot for all-cause mortality (risk difference). Risk difference, 9 studies; number of studies combined, 9; fixed-effect model, mean = –0.019 (95% confidence interval = 0.042-0.004); z-score = –1.62; p = 0.104.

FIBRINOGENO in pillole

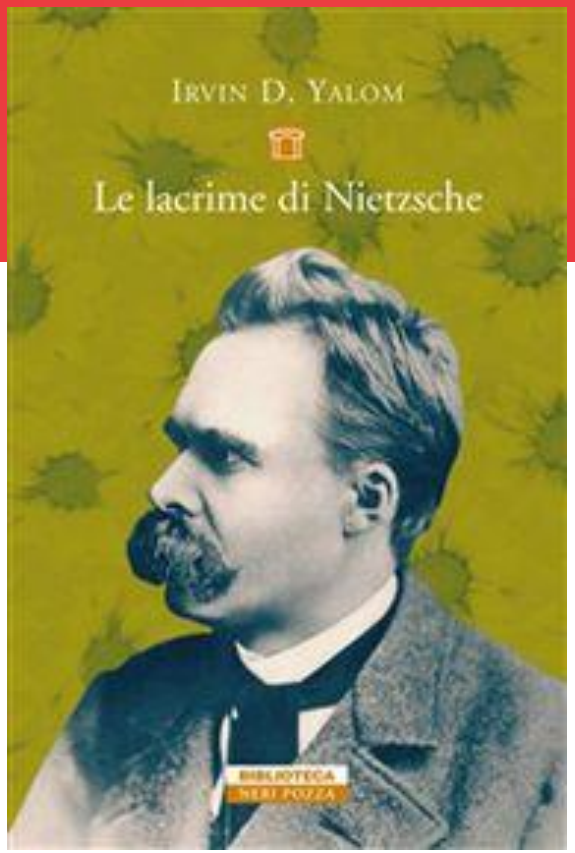
1. Non evidenze solide su end-point forti dell'efficacia della terapia sostitutiva
2. Non chiari i valori target della terapia sostitutiva, ma sembra ragionevole garantire livelli >1.5-2 g/L nelle emorragie critiche
3. Non chiari i dosaggi, né se sia più efficace il crioprecipitato o i concentrati

4.1 Indicazioni terapeutiche

Trattamento di episodi di sanguinamento in pazienti affetti da ipo- o afibrinogenemia congenita con tendenza al sanguinamento.

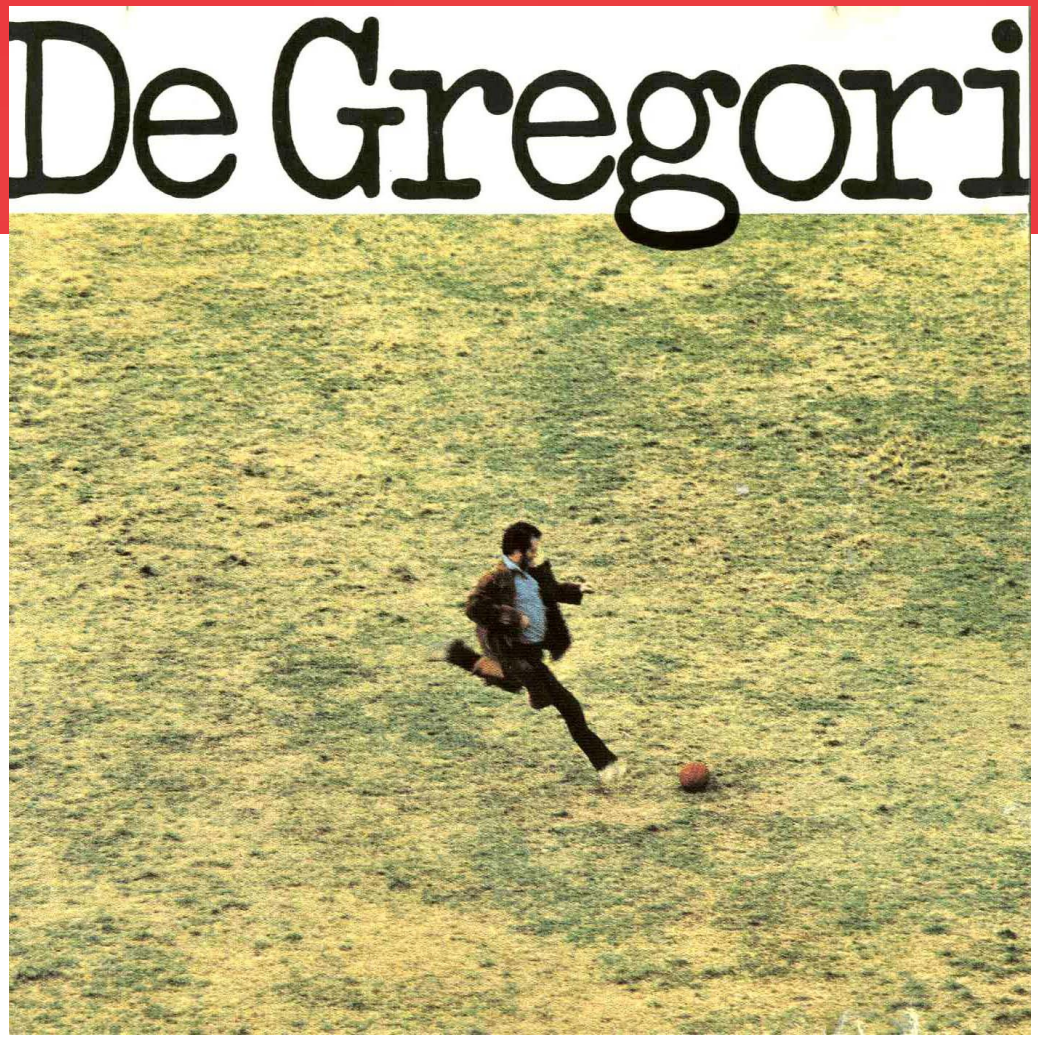
«Come posso ingannarmi in ciò che dico, maledetto pedante? «disse don Chisciotte. « Dimmi, non vedi quel cavaliere che viene verso di noi sopra un cavallo grigio pomellato, che ha in testa un elmo d'oro?»

«Quello ch'io giungo a intravedere», rispose Sancho, «non è altro che un uomo sopra un asino, grigio scuro come il mio, che ha sulla testa qualcosa che luccica».



*Da bambino, una volta qualcuno mi ha definito **"il ragazzo della promessa senza fine"**. Una frase che mi è piaciuta. Me la sono canticchiata migliaia di volte*

«E che cosa ne è stato di questo ragazzo della promessa senza fine?»
«Ah, ecco la domanda! Ci penso spesso. Già, che cosa ne è stato? Ormai so che di promessa non ce n'è più: è stata consumata tutta!»



Il ragazzo si farà anche se ha le spalle strette
quest'altr'anno giocherà con la maglia numero sette…

Accepted for publication in the *Journal of Thrombosis and Haemostasis*
doi: 10.1111/j.1538-7836.2010.04083.x

Received 6 September 2010, accepted 6 September 2010

Debate

What is the appropriate level of fibrinogen to trigger treatment? And what is the optimal dose of fibrinogen?

TITLE : Fibrinogen concentrate for management of bleeding : Against indiscriminate use

AUTHORS : Yves Ozier [1], Beverley J Hunt [2]

Accepted for publication in the *Journal of Thrombosis and Haemostasis*

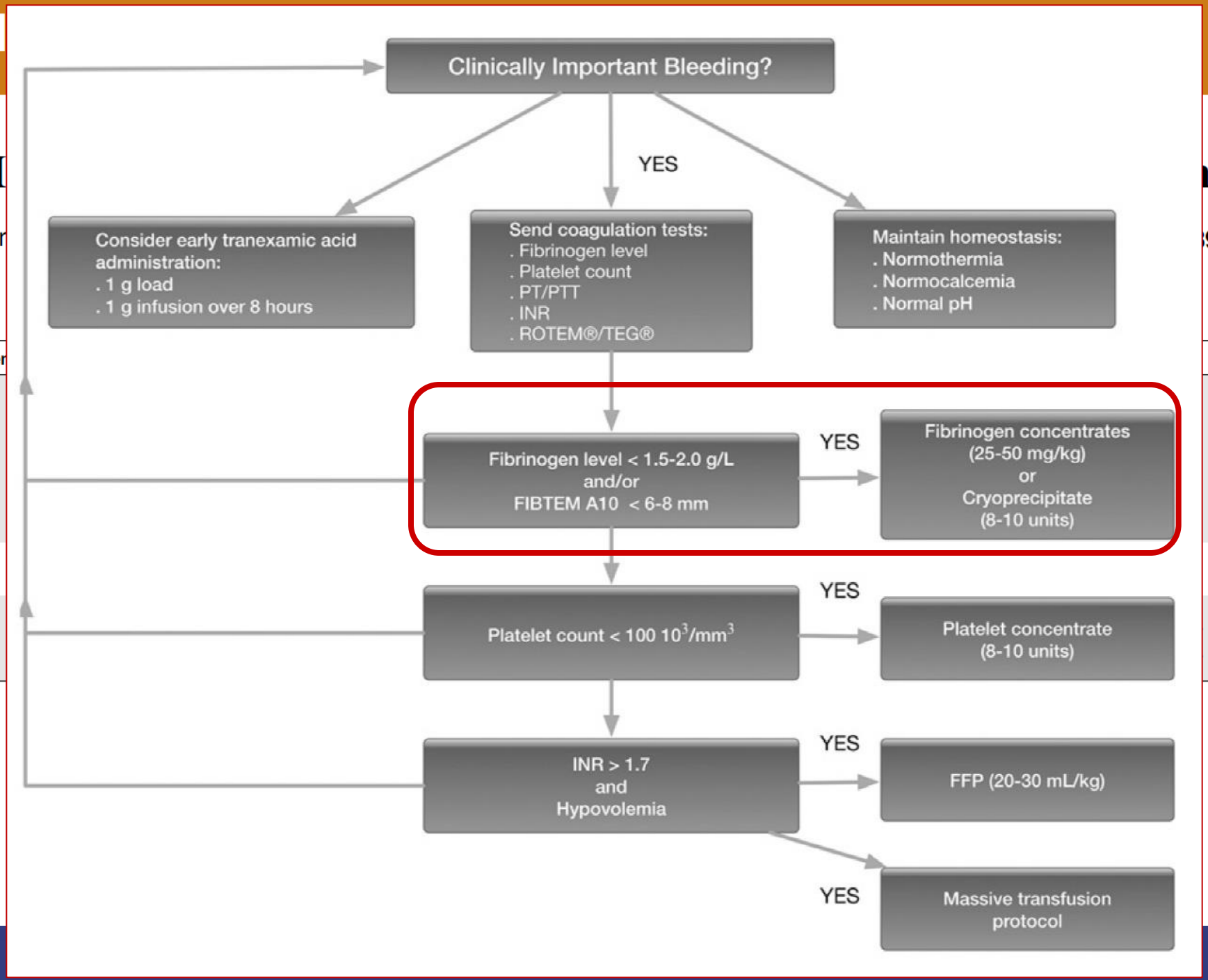
doi: 10.1111/j.1538-7836.2010.04099.x

Received 6 September 2010, accepted 21 September 2010

Debate

Fibrinogen concentrate for management of bleeding

In our opinion the key question for this debate is 'How should we supplement fibrinogen levels?' rather than 'Should we supplement fibrinogen levels?'.

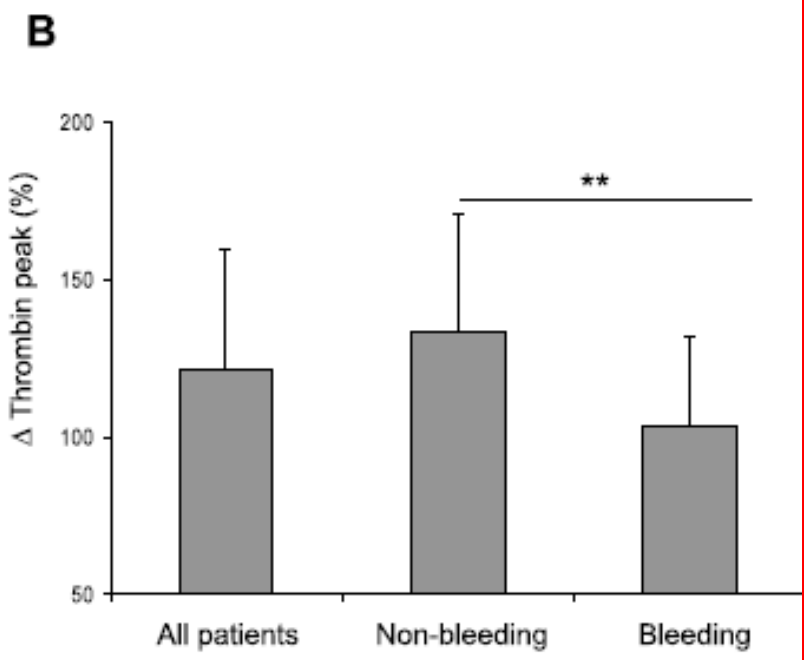

Clinically Important Bleeding?
YES
Consider early tranexamic acid administration:
. 1 g load
. 1 g infusion over 8 hours
Send coagulation tests:
. Fibrinogen level
. Platelet count
. PT/PTT
. INR
. ROTEM®/TEG®
Maintain homeostasis:
. Normothermia
. Normocalcemia
. Normal pH
Fibrinogen level < 1.5-2.0 g/L
and/or
FIBTEM A10 < 6-8 mm
YES
Fibrinogen concentrates
(25-50 mg/kg)
or
Cryoprecipitate
(8-10 units)
Platelet count < 100 10³/mm³
YES
Platelet concentrate
(8-10 units)
INR > 1.7
and
Hypovolemia
YES
FFP (20-30 mL/kg)
YES
Massive transfusion
protocol

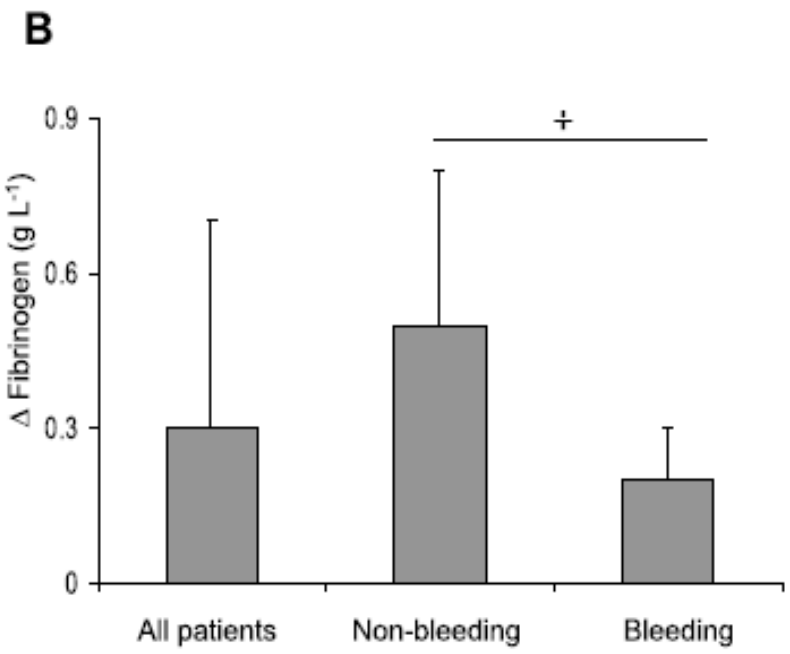
Increased thrombin generation and fibrinogen level after therapeutic plasma transfusion: Relation to bleeding

Saskia E. M. Schols[1,2], Paola E. J. van der Meijden[1], René van Oerle[1,2], Joyce Curvers[3], Johan W. M. Heemskerk[1], Elisabeth C. M. van Pampus[2]

[1]Department of Biochemistry (CARIM), Maastricht University and [2]Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands; [3]Catharina Hospital, Eindhoven, The Netherlands

Thromb Haemost 2008; 99: 64–70





Tutti i gatti sono grigi?

•Quali evidenze?

Autore, anno	TIPO DI STUDIO POPOLAZIONE	TRATTAMENTO	OUTCOME
Schochl, 2010	Retrospettivo 131 paz con trauma	Fibrinogeno in base a ROTEM se non miglioramento CP PCC aggiunto se TAO o ExTEM>1.5 128 solo FIB, 101 anche CCP, 12 PFC, 29 plt	↓ Mortalità osservata vs mortalità attesa TRISS (14% vs 27.8%, p=0.0018)
Schochl, 2011	Retrospettivo 681 paz con trauma	80 paz FIB/PCC (media 6 gr, 1200 PCC) 601 PFC (media 6 UI)	= mortalità = LOS-ICU = unità RBC ↓ paz con RBC/PLT
Gorlinger, 2011	Retrospettivo 3865 paz CC	Confronto prima/dopo algoritmo basato su ROTEM+PCC+FIB	↓ RBC/FFP ↓ MT ↑CP ↓ eventi TE = MORTALITA‘

Injury, Int. J. Care Injured 44 (2013) 209–216

The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma

Petra Innerhofer [a], Isabella Westermann [a], Helmuth Tauber [a], Robert Breitkopf [a], Dietmar Fries [b], Tobias Kastenberger [c], Rene El Attal [c], Alexander Strasak [d], Markus Mittermayr [a,*]

⑩ CF concentrates are used first

Trattamento	Dosi	Indicatore
Fibrinogeno concentrato	25-50 mg/kg	Fibrinogeno <1.50-2 g/L FIBTEM MCF <7 mm
Concentrati Complesso Protrombinico	20-30 UI/kg	PT < 50%, INR >1.5 EXTEM CF > 90s
PFC	20-30 ml/kg	In base ad esperienza del medico INR >1.5, APTT >50s
Concentrati piastrinici	1 U aferesi	Piastrine < 50-100.000/mmc EXTEM MCF > 45 mm

Titolo

Esempio

- Il DNA
  - Struttura
  - Istoni
- L'epigenetica fisiologica
- L'epigenetica patologica
  - Geni oncosoppressori
  - Geni oncogeni

Blood Transfus 2016; 14: 3-7

POSITION PAPER

Coagulopathy and transfusion strategies in trauma. Overwhelmed by literature, supported by weak evidence

Daniele Poole

Unfortunately, in the high concentrations levels, instead, any increase in fibrinogen concentration caused an increased risk of death.

This paradoxical result was replicated for the injury severity score (ISS), with a biphasic effect characterized by increased risk of death with increased scores within ISS low values (i.e. <25.7) and risk reduction as the score increased in the high range of ISS values.

As mentioned earlier, I think it is legitimate not to trust results from models providing paradoxical results.

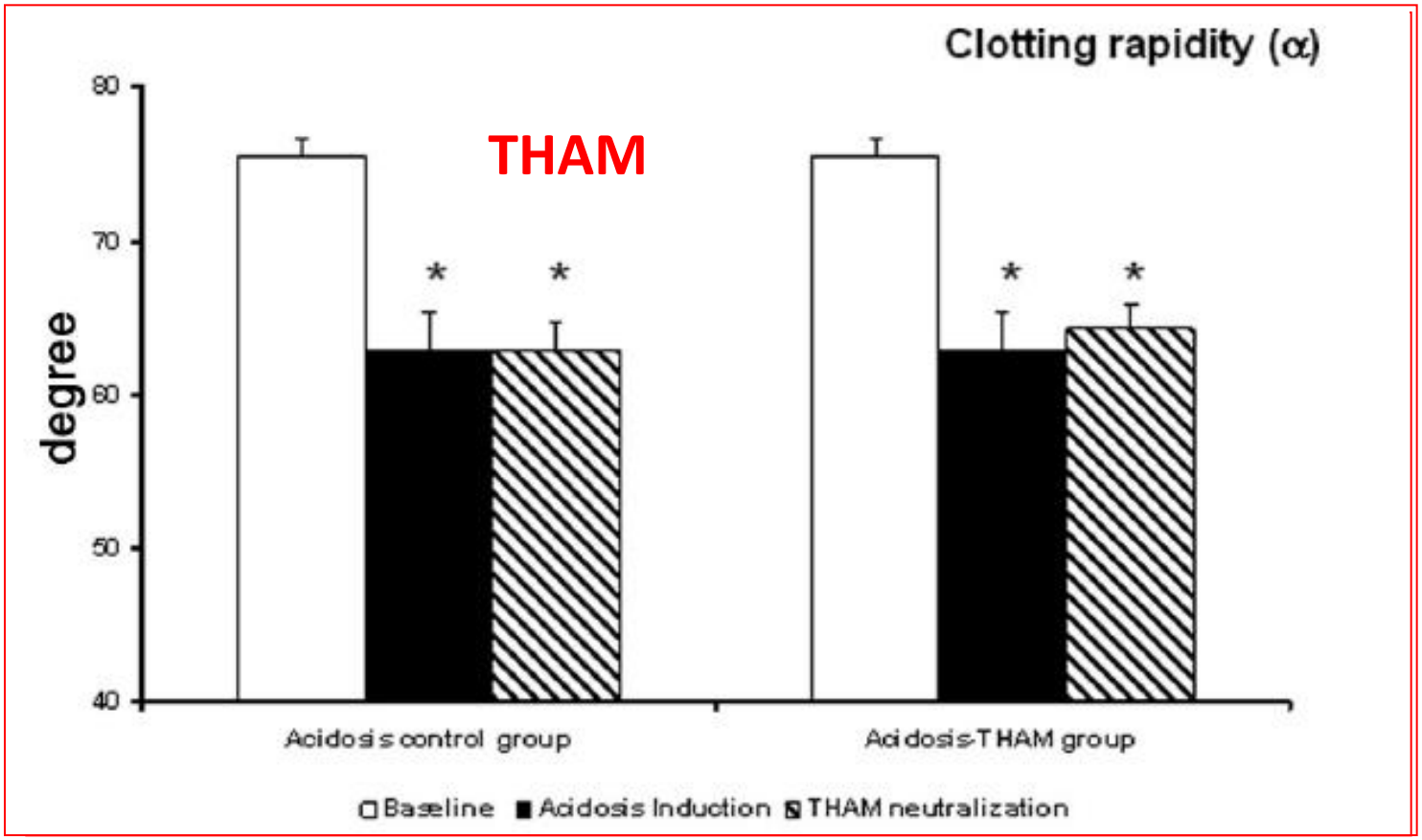
Besides this, for each gram/Litre of fibrinogen increase within low concentrations, mortality decreased by 92%, reasonably an exaggerated result.

Other studies did not seem to provide higher quality evidence.

Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability

(*J Trauma*. 2009;67: 202–209)

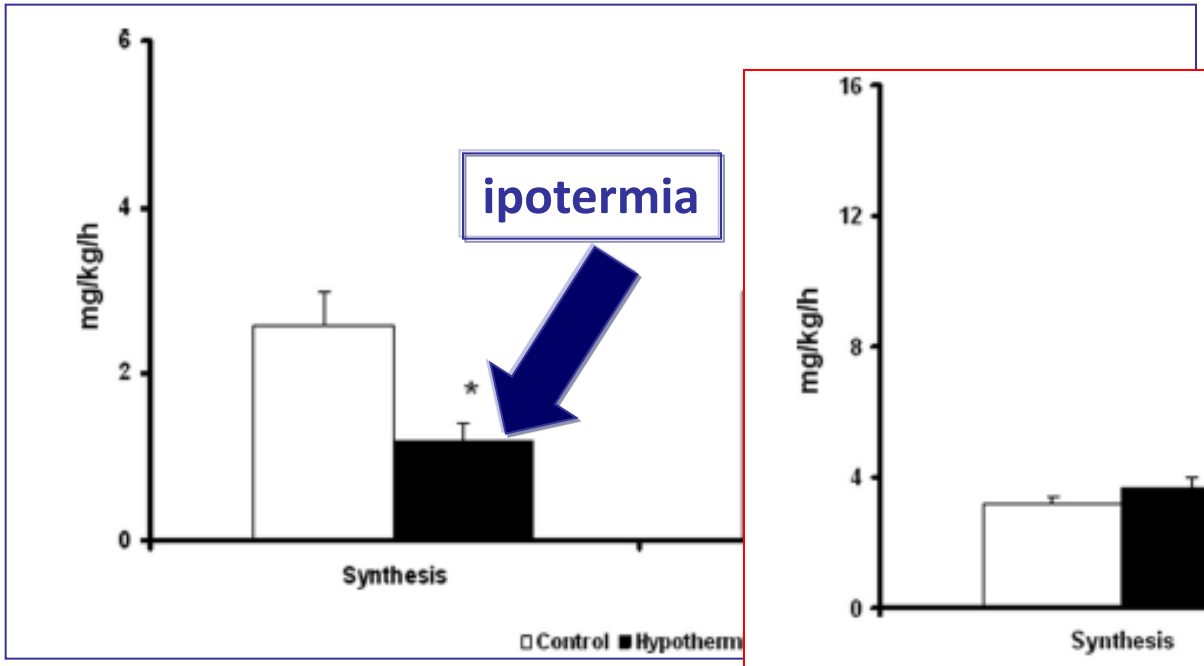
Wenjun Zhou Martini, PhD

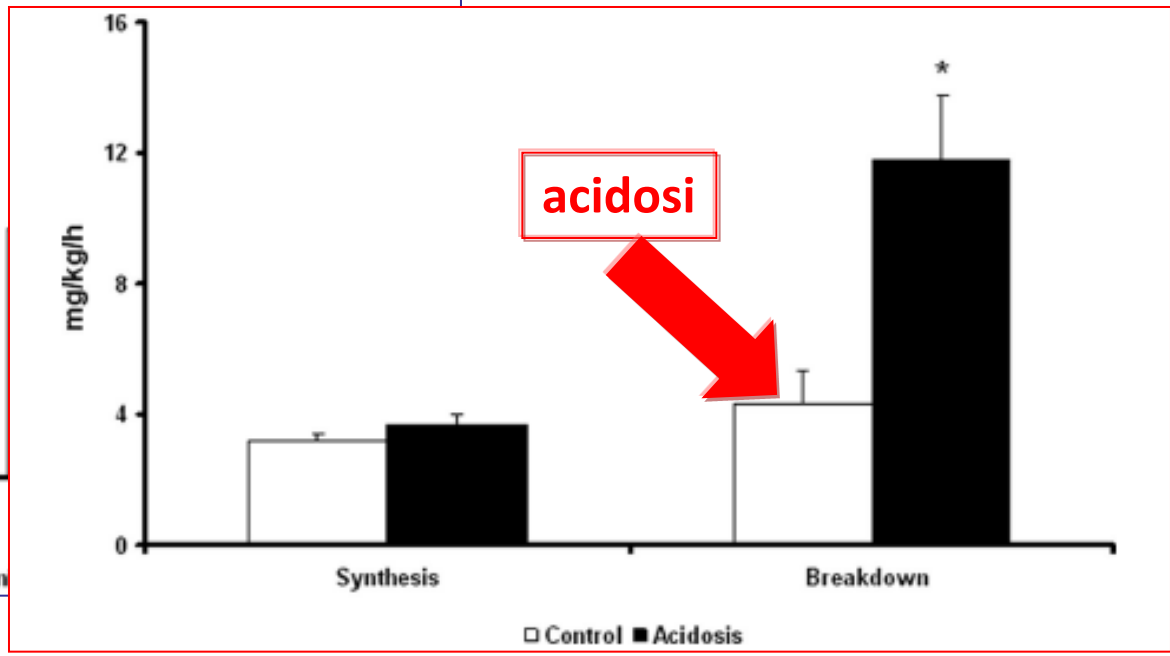


Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability

Wenjun Zhou Martini, PhD

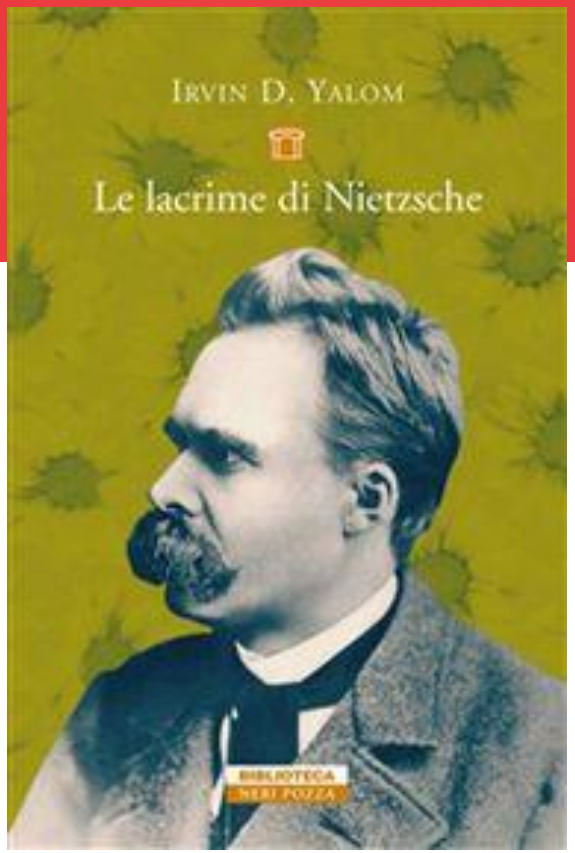
(*J Trauma*. 2009;67: 202–209)





«Come posso i *:? «disse*
don Chisciotte. *verso di*
noi sopra un *un elmo*
d'oro?»
«Quello ch'io g *altro che*
un uomo sopra *ılla testa*
qualcosa che lu

Tutti i gatti sono grigi?



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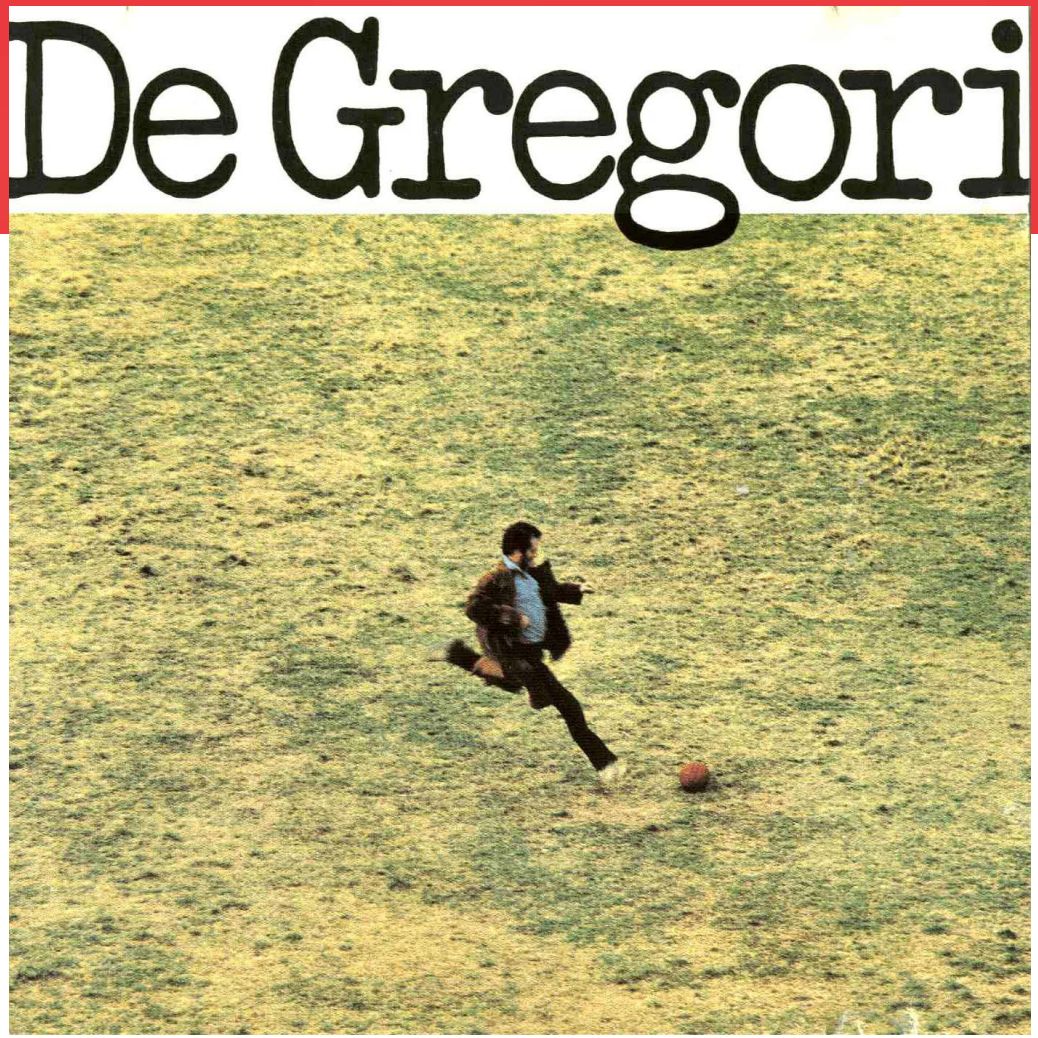

Il ragazzo si farà anche se ha le spalle strette
quest'altr'anno giocherà con la maglia numero sette…

Dalla fisiopatologia alla terapia…

Come un istante déja-vu, ombra della gioventù,
ci circondava la nebbia…

ORIGINAL RESEARCH

(J Am Heart Assoc. 2015;4: e002066

American Heart Association | American Stroke Association.

Randomized, Double-Blinded, Placebo-Controlled Trial of Fibrinogen Concentrate Supplementation After Complex Cardiac Surgery

Marco Ranucci, MD; Ekaterina Baryshnikova, PhD (Biol.); Giulia Beatrice Crapelli, MD; Niels Rahe-Meyer, MD; Lorenzo Menicanti, MD; Alessandro Frigiola, MD; for the Surgical Clinical Outcome REsearch (SCORE) Group*

Fibrinogen concentrate dose (g) =
Target FIBTEM MCF [22mm] - actual FIBTEM MCF [mm] x (bodyweight [kg /140])

After 15 minutes from fibrinogen concentrate (or placebo) administration and in the presence of ongoing microvascular bleeding, a second EXTEM was performed, and in case of a CT longer than 80 seconds, the patients of the study arm were planned to receive 4-factors PCCs (Confidex; CSL Behring, Marburg, Germany) at a dose of 7 U/kg, whereas patients in the control arm received placebo treatment.

(J Am Heart Assoc. 2015;4: e002066

American Heart | American Stroke Association.

Table 3. Effi

Endpoint	P Value
Primary endpo	
Avoidance	
Any prod	0.015
Packed r	0.015
Fresh fro	0.006
Platelet	0.119
Secondary end	
Transfusion	
Packed r	0.010
Fresh fro	0.002
Platelet	0.023
Transfusion	
Packed r	0.224
Postoper	0.042
Massive re	0.496
Surgical rev	0.496

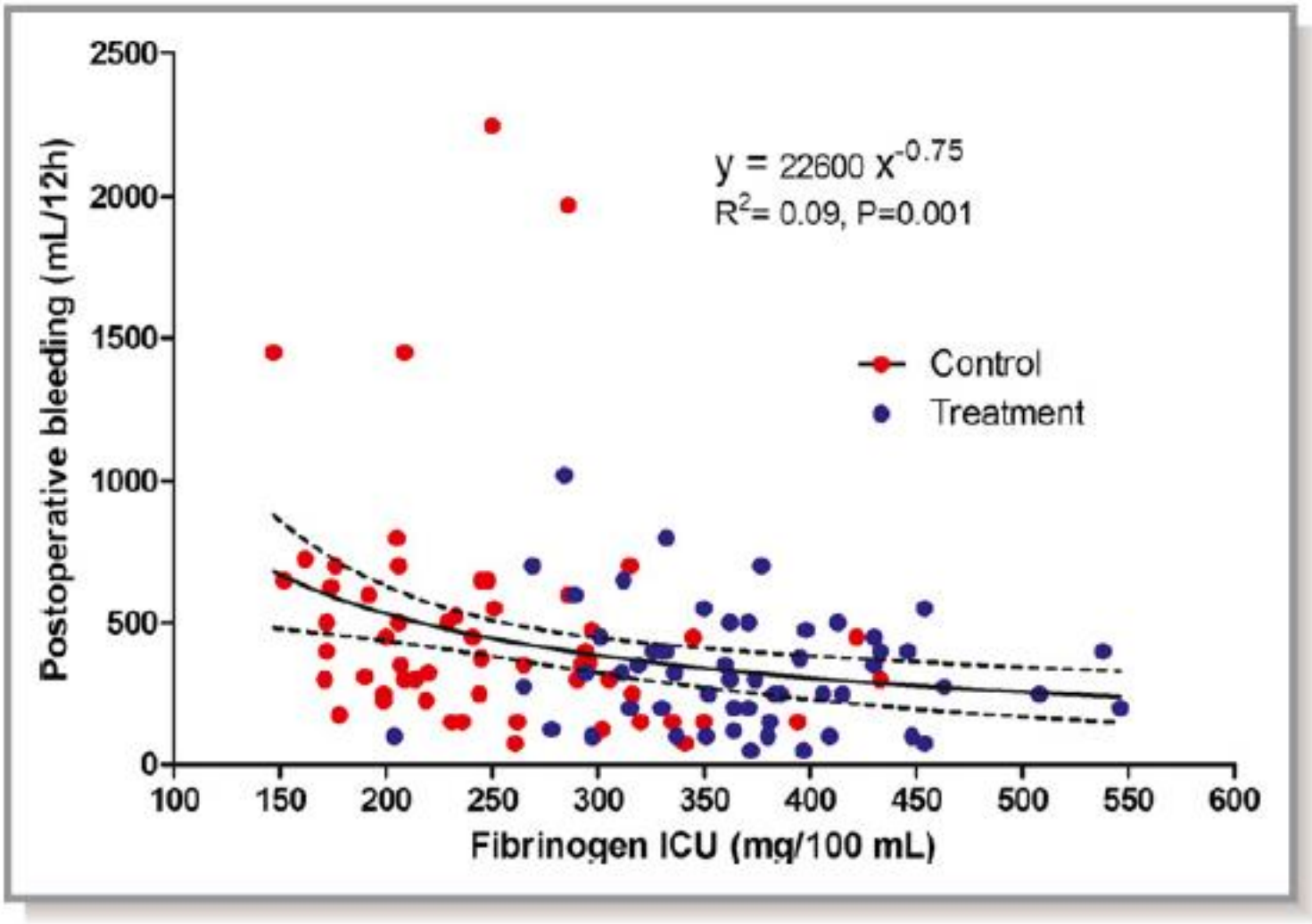

Figure 3. Fibrinogen levels and postoperative bleeding. Dashed lines are 95% confidence interval. ICU indicates intensive care unit.

BJA

British Journal of Anaesthesia, 117 (1): 41–51 (2016)

doi: 10.1093/bja/aew169
Cardiovascular

CARDIOVASCULAR

Randomized evaluation of fibrinogen *vs* placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy

N. Rahe-Meyer[1,*], J. H. Levy[2], C. D. Mazer[3], A. Schramko[4], A. A. Klein[5], R. Brat[6], Y. Okita[7], Y. Ueda[8], D. S. Schmidt[9], R. Ranganath[10] and R. Gill[11]

The dose of FCH was based on FIBTEM maximum clot firmness (MCF) at the end of CPB, targeting a FIBTEM MCF of 22 mm.

BJA

British Journal of Anaesthesia, 117 (1): 41–51 (2016)

doi: 10.1093/bja/aew169
Cardiovascular

Table 2 Efficacy and safety results. AE, adverse event; FCH, human fibrinogen concentrate; FFP, fresh frozen plasma; IQR, interquartile range; TEAE, treatment-emergent adverse event

Parameter	FCH (*n*=78)	Placebo (*n*=74)	P-value
Primary end point			
Total number of units of allogeneic blood product during first 24 h after study medication			
Median (IQR)	5.0 (2.0–11.0)	3.0 (0.0–7.0)	0.026
Secondary end points			
Number of patients with total avoidance of allogeneic blood product transfusion			
n (%)	12 (15.4)	21 (28.4)	0.047
Units of packed red blood cells administered (first 24 h)			
Median (IQR)	1.0 (0.0–3.0)	0.0 (0.0–2.0)	0.101
Units of FFP administered (first 24 h)			
Median (IQR)	4.0 (0.0–6.0)	0.0 (0.0–4.0)	0.017
Units of platelet concentrate administered (first 24 h)			
Median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–1.0)	0.089
Blood loss after administration of study medication: 5 min bleeding mass (g)			
Second 5 min bleeding mass [median (IQR)]	78.0 (55.0–110.0)	72.0 (45.0–96.0)	0.195
Decrease from first 5 min bleeding mass [median (IQR)]	20.0 (3.0–50.0)	19.5 (1.0–42.0)	0.319
Blood loss after administration of study medication: chest tube drainage volume [ml; median (IQR)]			
6 h	260.0 (155.0–410.0)	297.5 (200.0–455.0)	0.241
12 h	405.0 (245.0–600.0)	447.5 (320.0–700.0)	0.137
24 h	590.0 (400.5–839.5)	682.5 (530.0–1050.0)	0.120