Fibrinogen / Tranexamsyre

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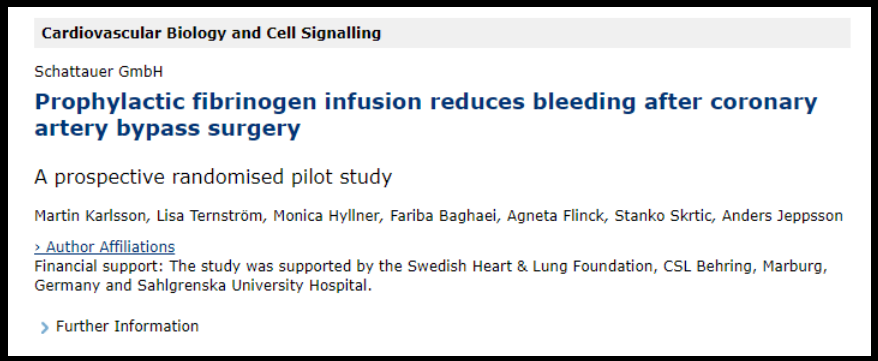
Disclosures

- CSL Behring
- LFB
- Novo Nordisk
- TEM International
- Nycomed

Fibrinogen koncentrat til blødende patienter 2009



Cardiovascular Biology and Cell Signalling

Schattauer GmbH

Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery

A prospective randomised pilot study

Martin Karlsson, Lisa Ternström, Monica Hyllner, Fariba Baghaei, Agneta Flinck, Stanko Skrtic, Anders Jeppsson

› Author Affiliations

Financial support: The study was supported by the Swedish Heart & Lung Foundation, CSL Behring, Marburg, Germany and Sahlgrenska University Hospital.

› Further Information

Journal of Thrombosis and Haemostasis, 7: 795–802 DOI: 10.1111/j.1538-7836.2009.03331.x

ORIGINAL ARTICLE

Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial

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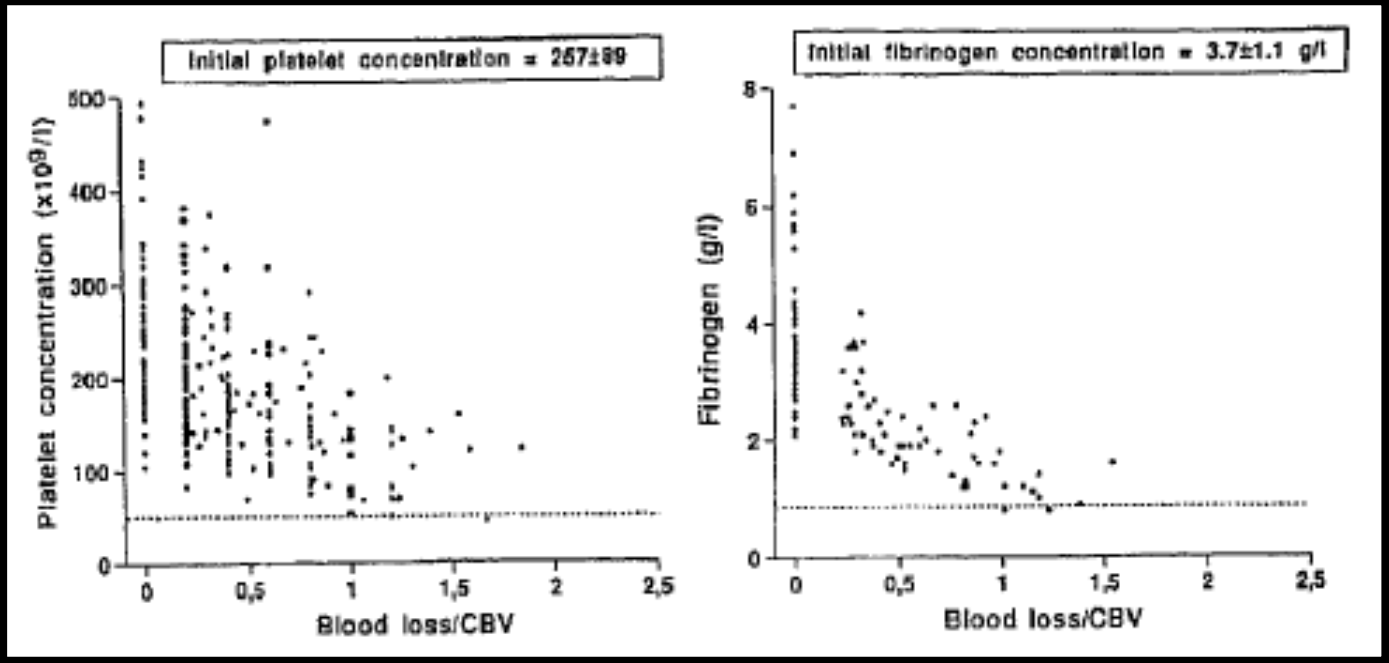
Erhvervet fibrinogen mangel
- 1995



60 blødende patienter (abdominal/urologisk kirurgi)
Fibrinogen mangel udvikles tidligere end mangel på thrombocytter eller øvrige koagulations faktorer under blødning

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

Erhvervet fibrinogen mangel

Cystektomi - 2010

	Baseline	30% Blodtab	Absolute Decrease
Haematocrite	0.43 ± 0.03	0.29 ± 0.02	- 32 ± 5
P-fibrinogen (µmol/L)	9.5 ± 1.9	5.1 ± 0.8*	- 44 ± 4.4**
F-II:C U/ml	1,25 ± 0,2	0,68 ± 0,1*	- 44 ± 6**
F-VII:C U/ml	1,07 ± 0,2	0,73 ± 0,2*	- 31 ± 7
FVIII:C U/ml	1.45 ± 0.6	0.88 ± 0.4*	- 39 ± 16
FX:C U/ml	1,19 ± 0,2	0,73 ± 0,2*	- 39 ± 6**
FIX:C U/ml	1.22 ± 0.26	0.89 ± 0.16*	- 27.5 ± 6.6**
FXIII:C U/ml	1,26 ± 0,2	0,71 ± 0,1*	- 43 ± 6**
vWF;Ristocitin co-factor U/ml	1.51 ± 0.60	1.02 ± 0.38*	- 30 ± 14

N=20 in each group. *significantly different from baseline value. **relative decrease significantly different from expected decrease. Data presented as mean ± standard deviation.

J Thromb Haemost. 2009 Jul;7(7):1099-105.

Erhvervet fibrinogen mangel
Obstetrik - 2011

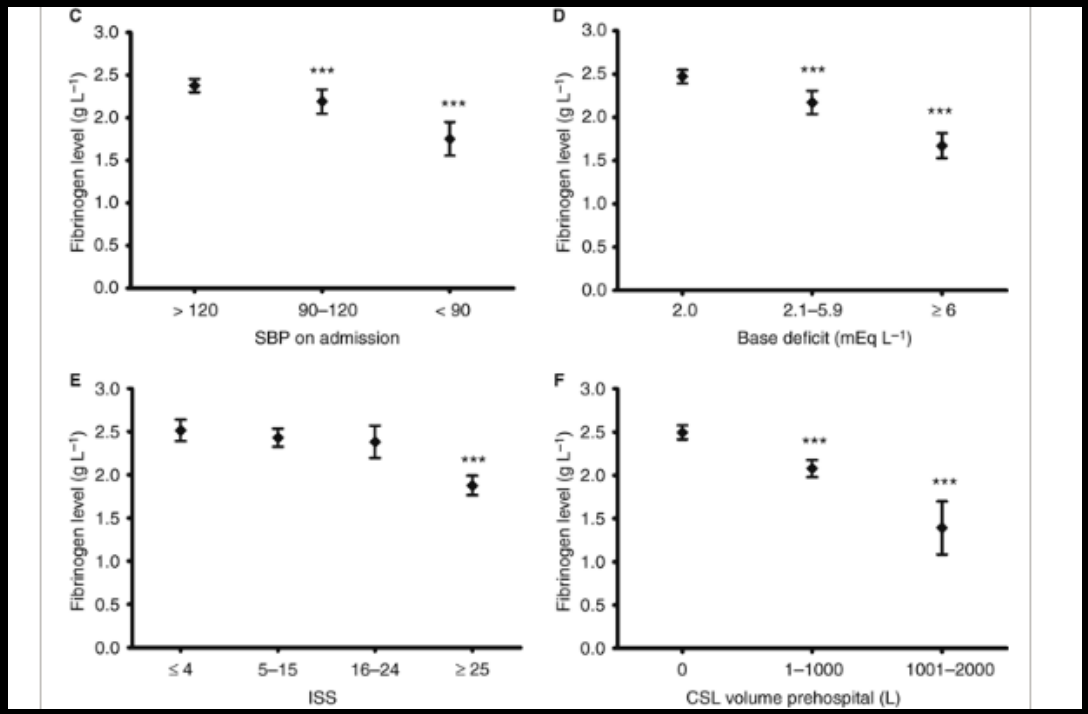
- Fibrinogen levels predicts bleeding during postpartum bleeding:
  - Fibrinogen levels <2 g/l
  - Positive predictive value for bleeding at 100%

  - Fibrinogen levels >4 g/l
  - Negative predictive value for bleeding at 79%

Charbit B, Mandelbrot L, Samain E, et al. J Thromb Haemost 2007; 5: 266–73

Traume
Fibrinogen levels

- 517 prospektivt co-horte traumepatienter



- Cryoprecipitate associated with improved survival
- Lavt fibrinogen independent associated with injury severity score og shock

Brohi K et al. Volume10, Issue7 July 2012 Pages 1342-1351

Introduktion
Erhvervet fibrinogen mangel

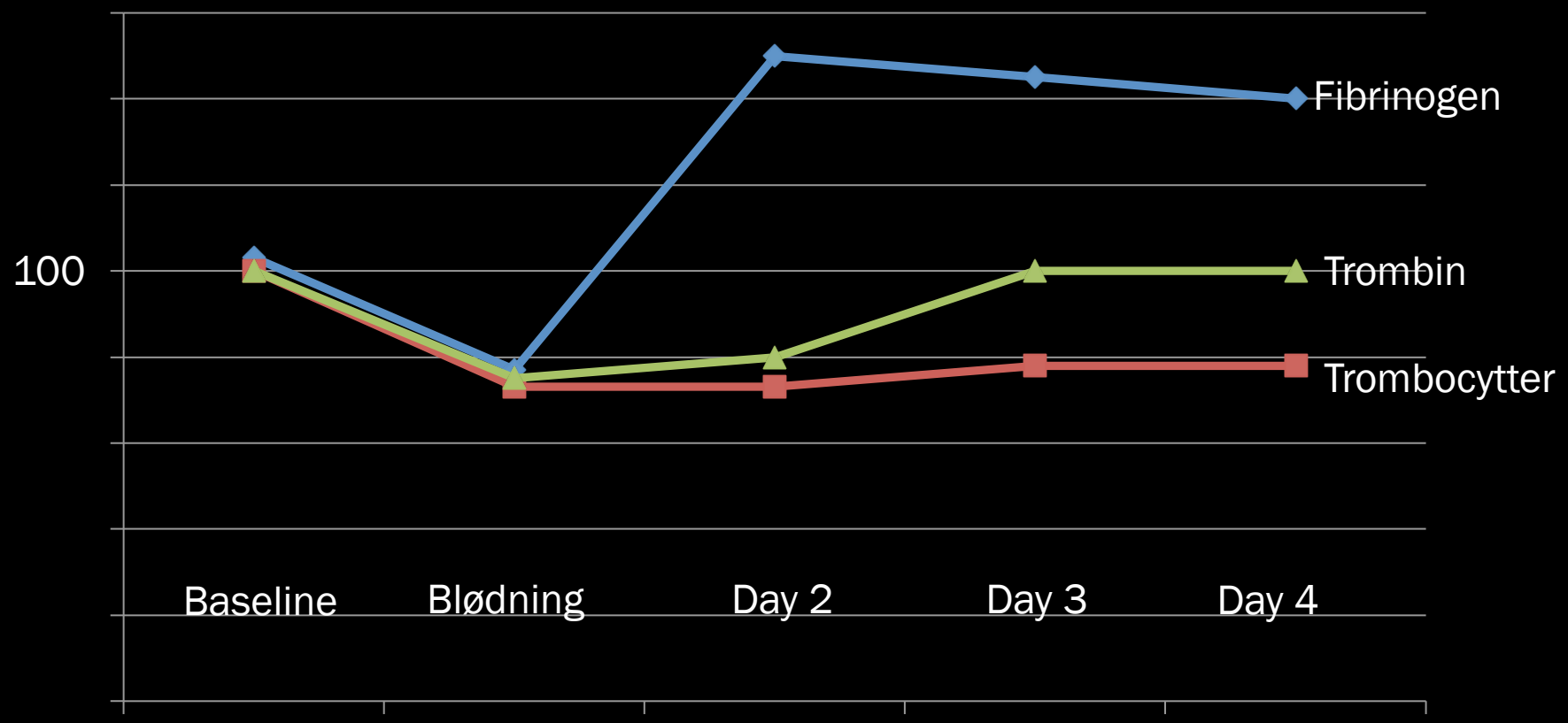
- Tab / forbrug
- Fortynding

- Specifik påvirkning af fibrinogen skyldes;
  1) Hyperfibrinolyse

  2) Væske resuscitation med kolloid plasma ekspander medfører dysfunktionel fibrinogen

  3) Acidose øger nedbrydning af fibrinogen

Recovery af koagulations faktorer efter blødning



Martini WZ et al. J Trauma; In press

Fibrinogen
Substitutions behandling ved blødning

- *"weak evidence supports the use of fibrinogen concentrate in bleeding patients"*
  - » *Wikkelsø et al Cochrane Database Syst Rev. 2013 Aug 29;(8):CD008864*

- Efficacy and Safety of Fibrinogen Concentrate in Surgical Patients: A Meta-Analysis of Randomized Controlled Trials
  - » J Cardiothorac Vasc Anesth. 2016 Oct;30(5):1196-204.
  - 14 RCT
  - Reduceret blødning / transfusionsbehov
  - Trend mod reduceret mortalitet

Fibrinogen administration til blødende patienter – Major aorta kirurgi

- RCT – Placebo (N=31) vs ROTEM guided individualised administration of fibrinogen concentrate (N=29)

Median dose of 8g

- Primary endpoint:
  - Number of units of allogeneic blood components within 24 hours after infusion
  - Fibrinogen: median=2 vs Placebo: median=13, p<0.0001

No safety concerns

- Secondary endpoint
  - Number of patients with total avoidance of allogeneic blood components
  - Fibrinogen: 44.8% vs Placebo: 0%, p<0.0001

Rahe-Meyer N et al.,

OXFORD JOURNALS BJA: British Journal of Anaesthesia

Br J Anaesth. 2016 Jul; 117(1): 41–51.
Published online 2016 Jun 9. doi: 10.1093/bja/aew169

PMCID: PMC4913420
PMID: 27317703

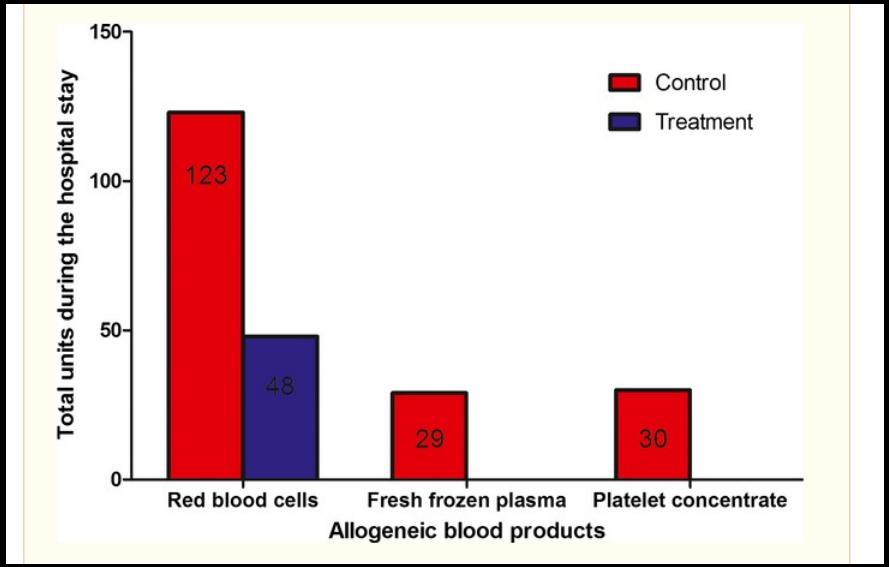
Randomized evaluation of fibrinogen *vs* placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy

- Multicenter RCT 519 patienter
- Aortakirurgi på CPB +/- cardiac procedures
- Fibrinogen vs placebo
- Primary endpoint: allogenic blood transfusion

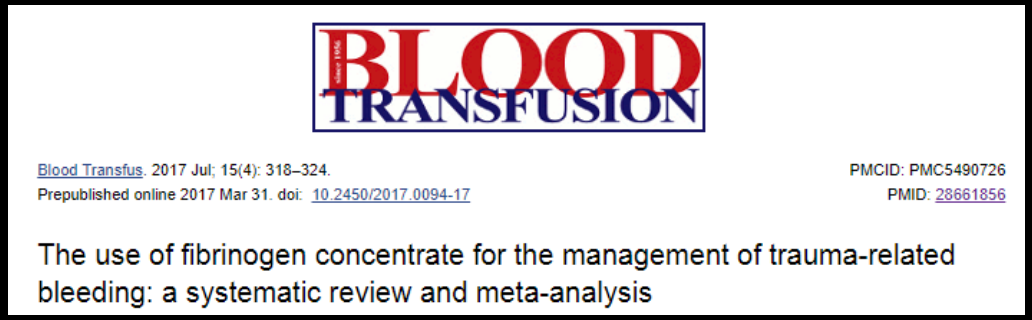
Parameter	FCH (*n*=78)	Placebo (*n*=74)	*P*-value
Primary end point			
Total number of units of allogeneic blood product during first 24 h after study medication			
Median (IQR)	5.0 (2.0–11.0)	3.0 (0.0–7.0)	0.026
Secondary end points			
Number of patients with total avoidance of allogeneic blood product 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

Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery.

- 116 pt, single center: Complex cardiac surgery operation + CPB
- Fibrinogen (FIBTEM 22 mm) vs placebo
- Primary endpoint:



Ranucci M, J Am Heart Assoc. 2015 Jun 2;4(6):e002066.

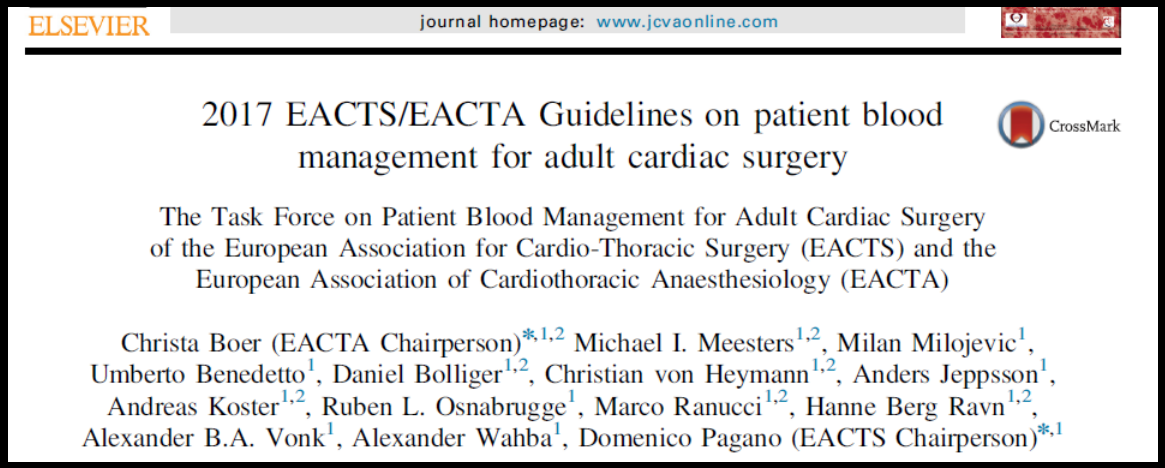


BLOOD TRANSFUSION

Blood Transfus. 2017 Jul; 15(4): 318–324.
Prepublished online 2017 Mar 31. doi: 10.2450/2017.0094-17
PMCID: PMC5490726
PMID: 28661856

The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis

- Review – 1650 traumepatienter
  - 6 retrospektive + 1 prospektivt
  - *"no beneficial effect of fibrinogen concentrate in the setting of severe trauma"*
  - *"poor quality of data retrieved"*



ELSEVIER journal homepage: www.jcvaonline.com

2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery

CrossMark

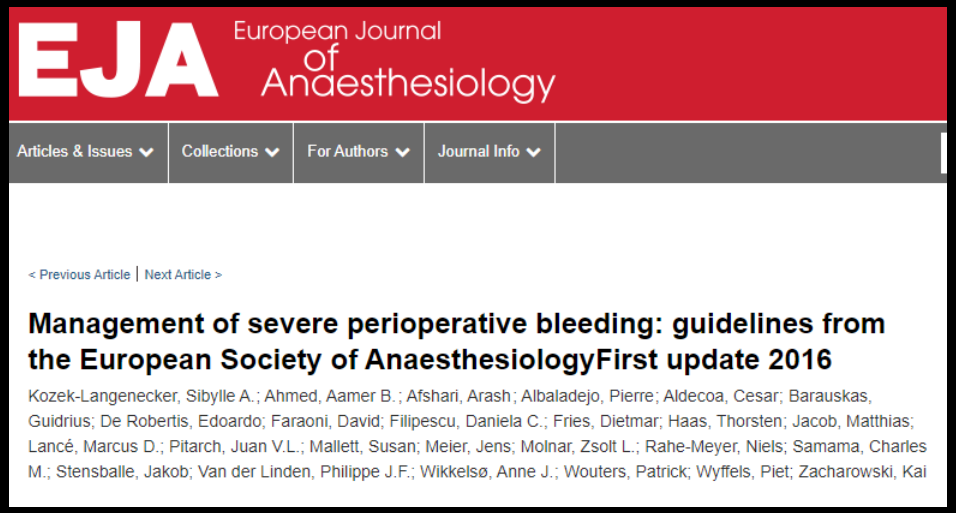
The Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA)

Christa Boer (EACTA Chairperson)*[,1,2] Michael I. Meesters[1,2], Milan Milojevic[1], Umberto Benedetto[1], Daniel Bolliger[1,2], Christian von Heymann[1,2], Anders Jeppsson[1], Andreas Koster[1,2], Ruben L. Osnabrugge[1], Marco Ranucci[1,2], Hanne Berg Ravn[1,2], Alexander B.A. Vonk[1], Alexander Wahba[1], Domenico Pagano (EACTS Chairperson)*[,1]

Thoraxkirurgi

”In the bleeding patient with a low fibrinogen level (below1.5 g/l), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions”.

IIb



Perioperativ blødning

"We recommend treatment of hypofibrinogenaemia in bleeding patients". 1C

"We suggest an initial fibrinogen concentrate dose of 25 to 50mgkg1". 2C

Postpartum blødning

A plasma fibrinogen level of greater than 2 g/l should be maintained during ongoing PPH. [*New 2016*]

Grade of recommendation: C

Timing og rette dosering

- Kun fibrinogen substitution ved verificeret mangel
- OG
- Aktuelt blødnings problem

Fibrinogen
Substitutions behandling

Br J Anaesth. 2015 Jan 13. pii: aeu444. [Epub ahead of print]

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

Wikkelsø AJ[1], Edwards HM[2], Afshari A[3], Stensballe J[4], Langhoff-Roos J[5], Albrechtsen C[3], Ekelund K[3], Hanke G[3], Secher EL[3], Sharif HF[5], Pedersen LM[6], Troelstrup A[6], Lauenborg J[7], Mitchell AU[8], Fuhrmann L[8], Svare J[2], Madsen MG[9], Bødker B[10], Møller AM; FIB-PPH trial group.

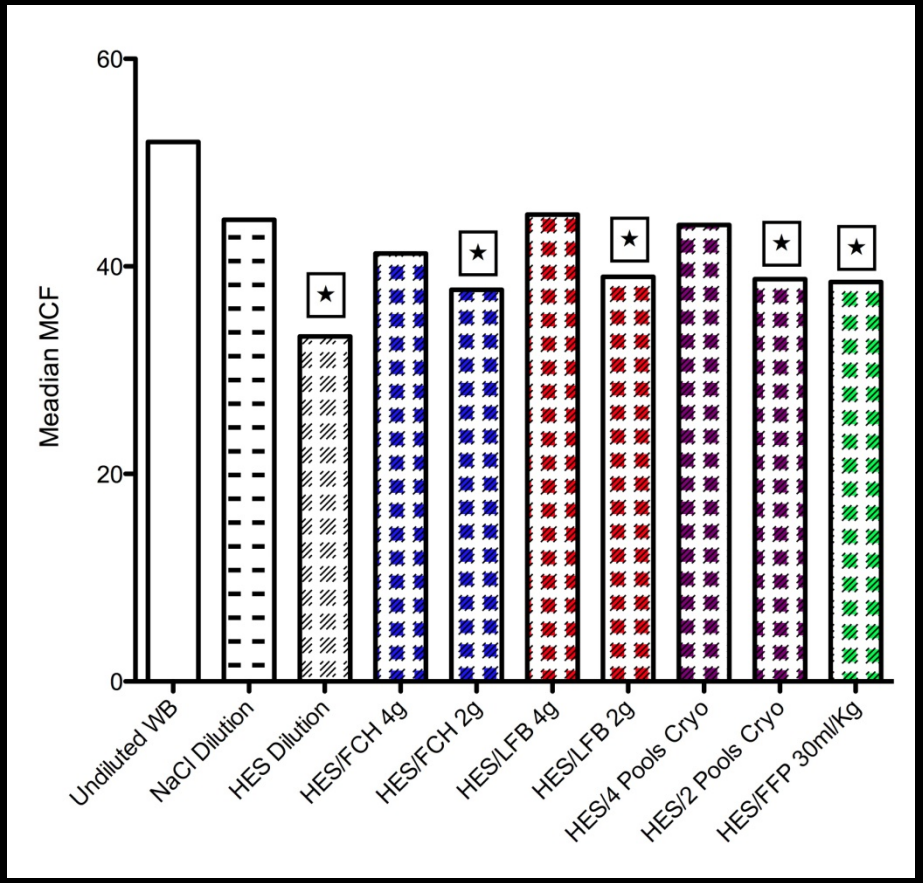
Author information

- 249 kvinder med PPH randomiseret til 2 g fibrinogen vs placebo
- Primary endpoint; Transfusion – ingen forskel

- 2.2% of patients had a level of fibrinogen <2 g/L
- 46 patients not included due to massive bleeding

Fibrinogen kilder

- Fortyndings koagulopati–
  Hæmostatisk effekt af forskellige fibrinogen kilder



Tranexamsyre

Hyperfibrinolyse
CRASH II trial

- 10 096 patienter: Tranexamsyre
- 10 115 patienter: Placebo

Administreret tidligt <3 timer

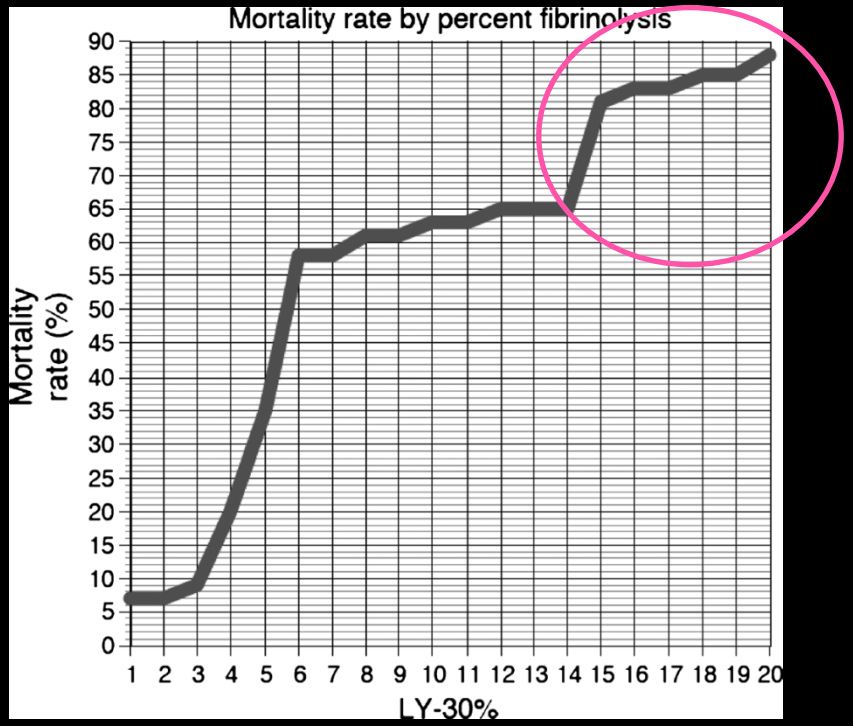
- All-cause mortality
  - Tranexamsyre : 1463 [14.5%]
  - Placebo: 1613 [16.0%]
  - Relative risk 0.91, 95% CI 0.85-0.97; p=0.0035.

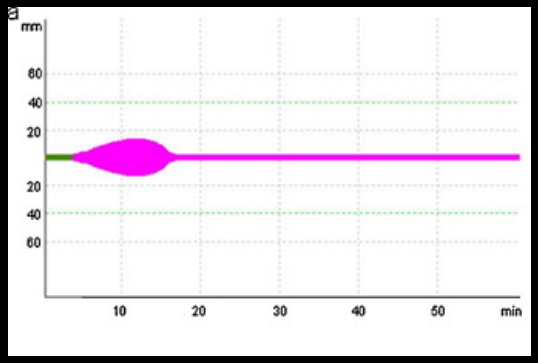
- Død på grund af blødning
  - Tranexamsyre 489 [4.9%]
  - Placebo 574 [5.7%]
  - Relative risk 0.85, 95% CI 0.76-0.96; p=0.0077

CRASH-II trial (Lancet. 2010 Jul 3;376(9734):23-32)

Hyperfibrinolysis

Diagnose

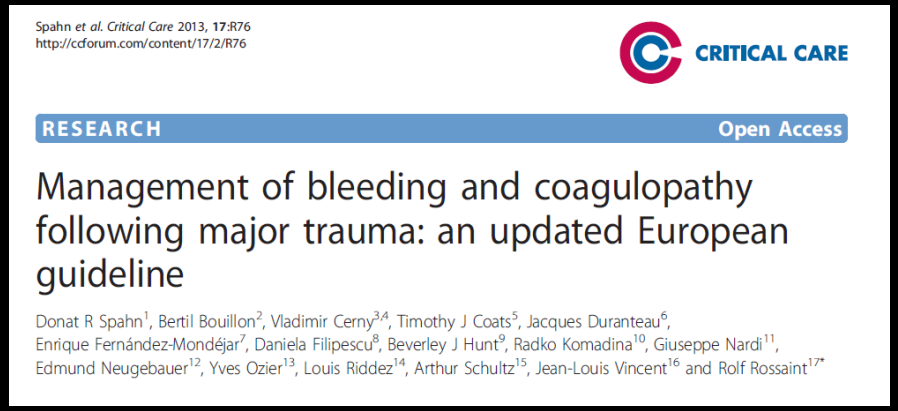




Tranexamsyre

- Rutinemæssigt administration

- Hofte/knæ/rygkirurgi (2a)
- Hjertekirurgi (1c)
- Traume (1a)
- Postpartum blødning (2c)
- Kraniofacial kirurgi
- (GI blødning)



Spahn *et al. Critical Care* 2013, **17**:R76
http://ccforum.com/content/17/2/R76

CRITICAL CARE

RESEARCH Open Access

Management of bleeding and coagulopathy following major trauma: an updated European guideline

Donat R Spahn[1], Bertil Bouillon[2], Vladimir Cerny[3,4], Timothy J Coats[5], Jacques Duranteau[6], Enrique Fernández-Mondéjar[7], Daniela Filipescu[8], Beverley J Hunt[9], Radko Komadina[10], Giuseppe Nardi[11], Edmund Neugebauer[12], Yves Ozier[13], Louis Riddez[14], Arthur Schultz[15], Jean-Louis Vincent[16] and Rolf Rossaint[17*]

Pabinger I et al Wien Klin Wochenschr. 2017; 129(9): 303–316.

Bivirkninger

- Diarre, kvalme, opkast
- Hypotension/dizziness (for hurtig administration)
- Anafylaksi
- Synsforstyrrelser
- Kramper

Kontra-indikationer

- Svær nyreinsufficiens
- Krampetendens
- Diseminated intravascular coagulation uden betydelig blødning
- Aktiv trombotisk sygdom (venetrombose, lungeemboli, arteriel trombose og cerebral trombose)
- Blødning i øvre urin veje (clot risiko)

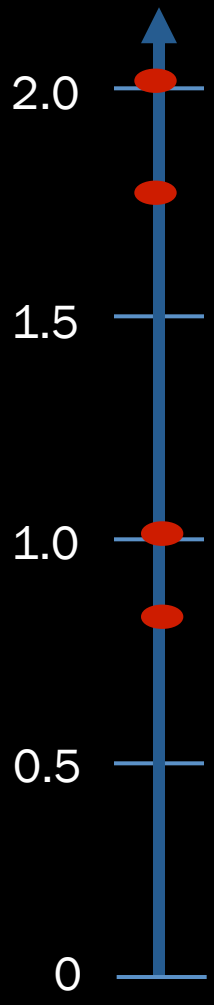
Konklusion

- Fibrinogen niveau falder hurtigt ved større blødning

- Fibrinogen behandling
  - IKKE profylaktisk
  - Kun ved påvist lavt niveau (?) + pågående blødning

- Tranexamsyre
  - Til “næsten” alle blødende patienter
  - Bivirkninger / kontraindikationer

Hvilket fibrinogen niveau



Austrian Society of Anaesthesiology, Task Force Coagulation
http://www.oegari.at

Management of bleeding following major trauma; an updated European guideline
Spahn et al. Crit Care. 2010;14(2):R52.

Fibrinogen concentrate – a potential universal haemostatic agent
Fenger-Eriksen et al. Expert Opin Ther 2009 Oct;9:1325-33

Management of bleeding following major trauma; European guideline
Spahn et al. Crit Care 2007; 11(1) R17

Practice guidelines for perioperative blood transfusion and adjuvant therapies
ASA Anesthesiology 2006; 105:198-208