# Hematologic Aspects of Obstetrical Hemorrhage

Thomas Coyle MD

# Aims

- Coagulopathy in PPH
- Standard transfusion therapy of PPH
- Massive transfusion therapy of PPH
- Adjunct medications and supportive care

# Coagulopathy in PPH

One quarter of patients PPH have coagulopathy

- Dilutional
- Localized consumption in placenta
- Disseminated intravascular coagulation
- Preexisting coagulopathy

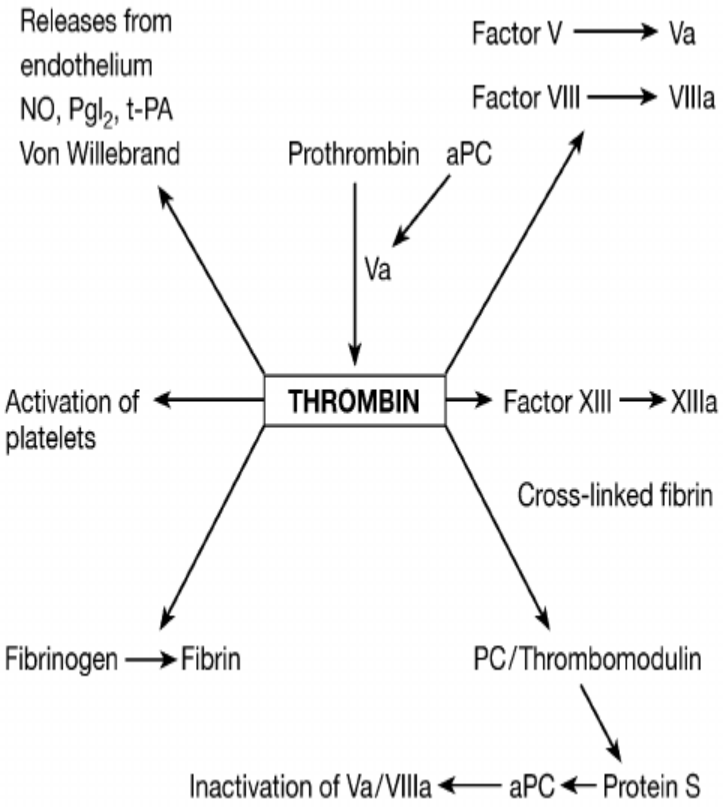
Atony, tissue trauma – coagulopathy unlikely initially dilutional coagulopathy with advanced

Severe abruption - localized consumption

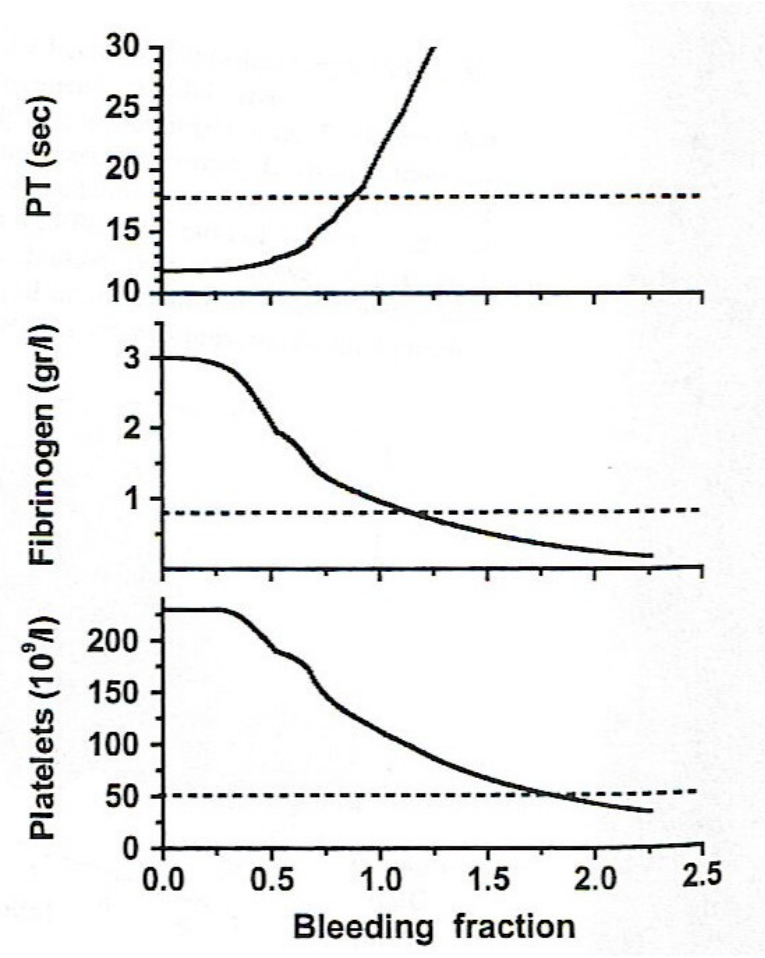
Amniotic fluid embolism - severe DIC

# Overview of DIC

- Activation of thrombin
- Consumption of platelets and factors
- Bleeding
- Activation of plasmin
- Fibrinolysis
- PAI-1 inhibition of fibrinolysis
- Microvascular thrombosis and ischemi
- Organ dysfunction
- Macrovascular thrombosis

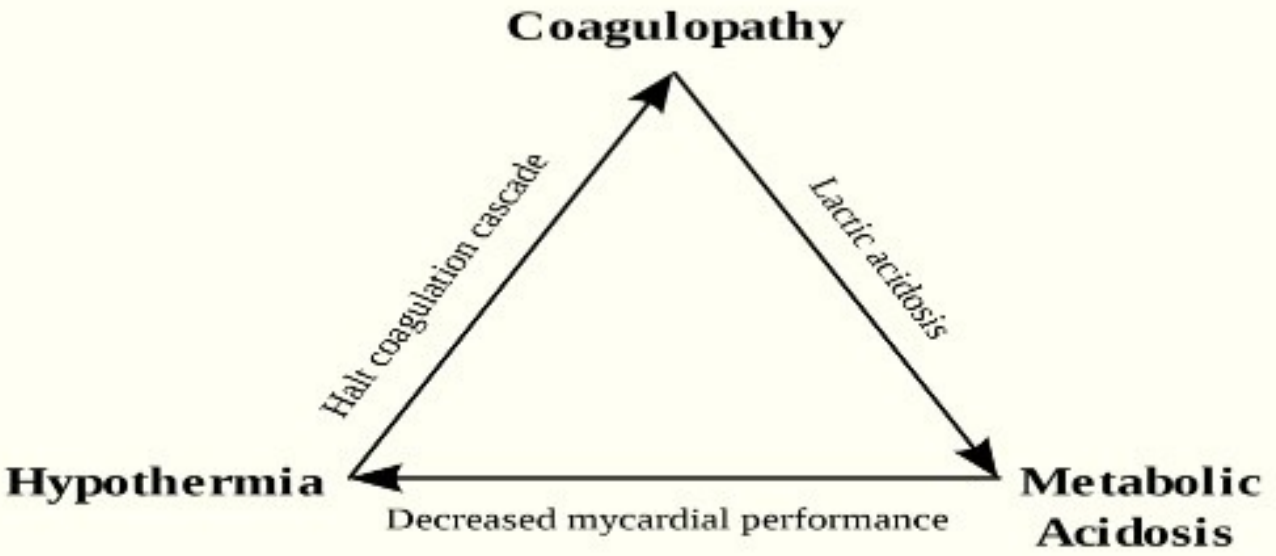


# Dilutional Coagulopathy Computer Simulation




Hirshberg A Trauma 54:454, 2003

# The Lethal Triad



# Assessment of Coagulopathy

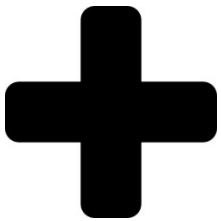
- Clinical
- Standard labs
- Thromboelastography



CBC
Platelets
PT
PTT
Fibrinogen
K
i CA

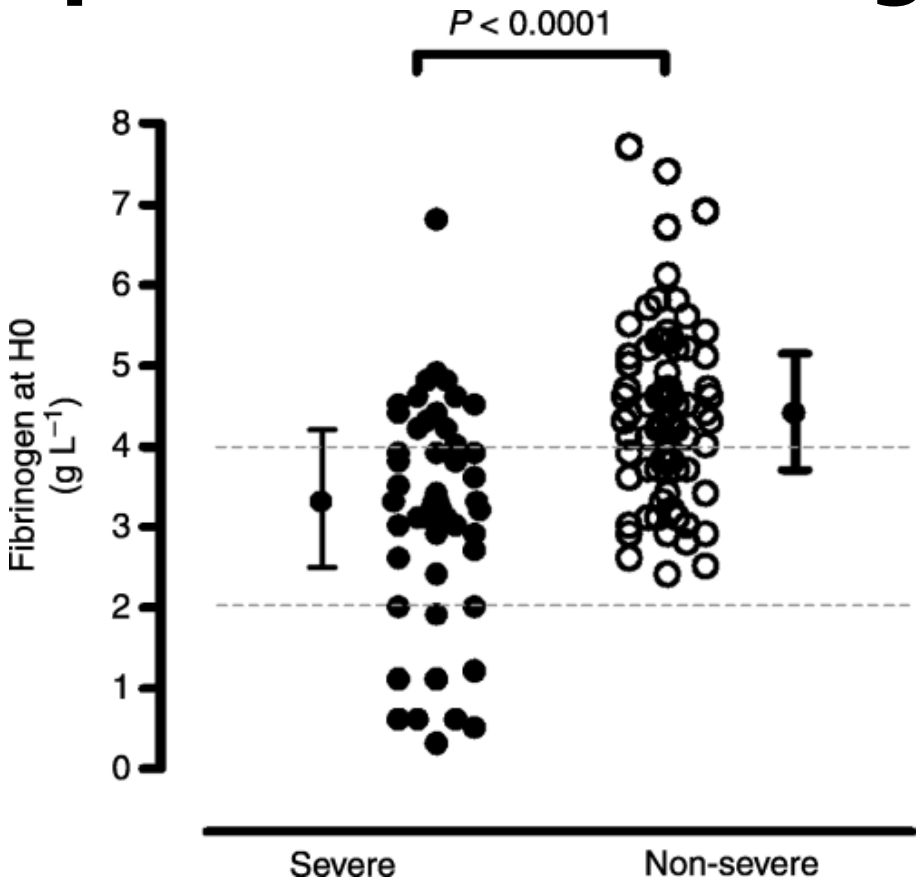
T & S





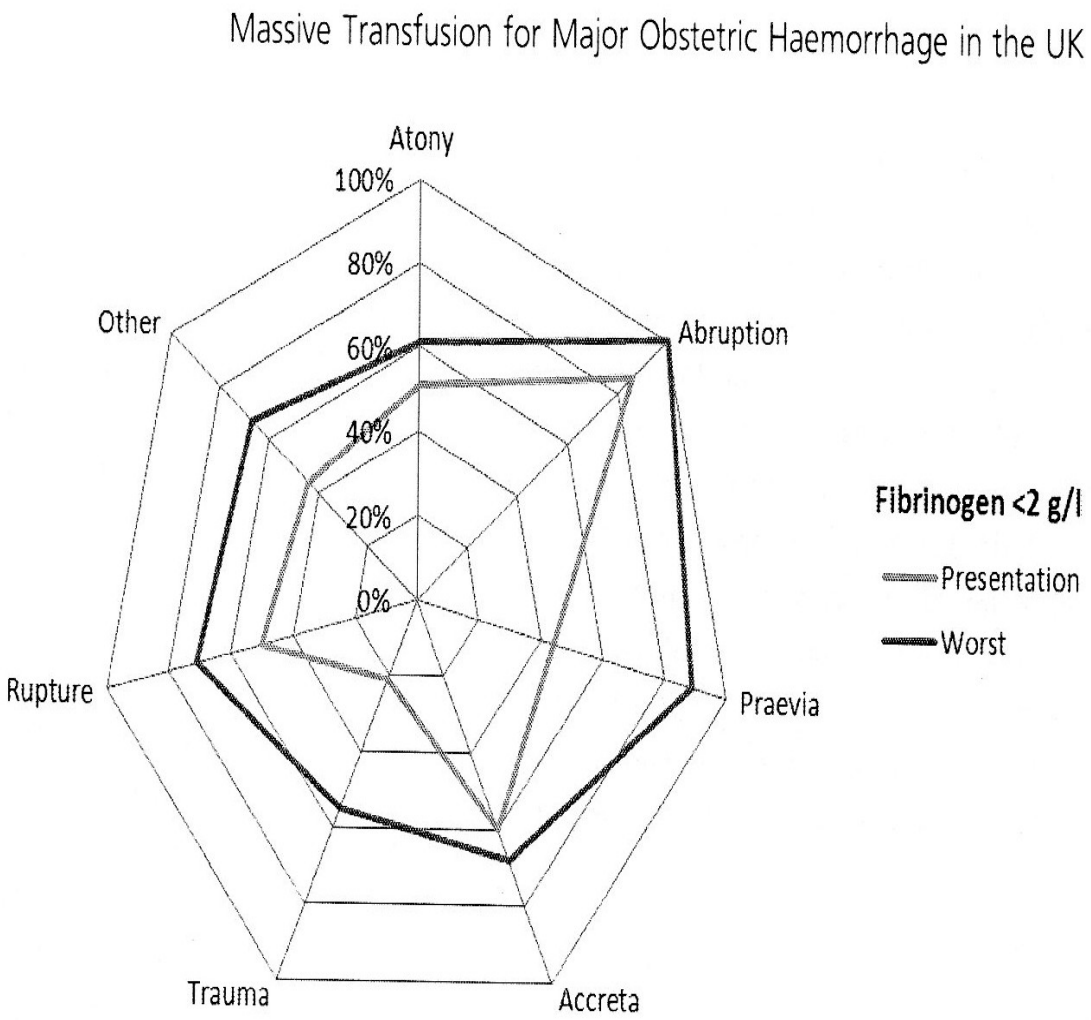


# The decrease of fibrinogen is an early predictor of the severity of postpartum hemorhage



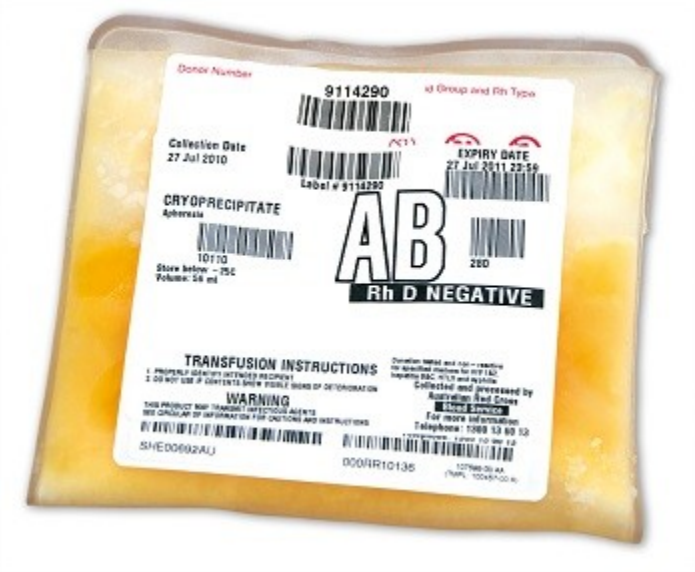

Charabit H et al

**Journal of Thrombosis and Haemostasis**
Volume 5, Issue 2, pages 266-273, 22 JAN 2007 DOI: 10.1111/j.1538-7836.2007.02297.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02297.x/full#f2




Green L et al  Brit J Haem 172: 616, 2016

# Cryoprecipitate

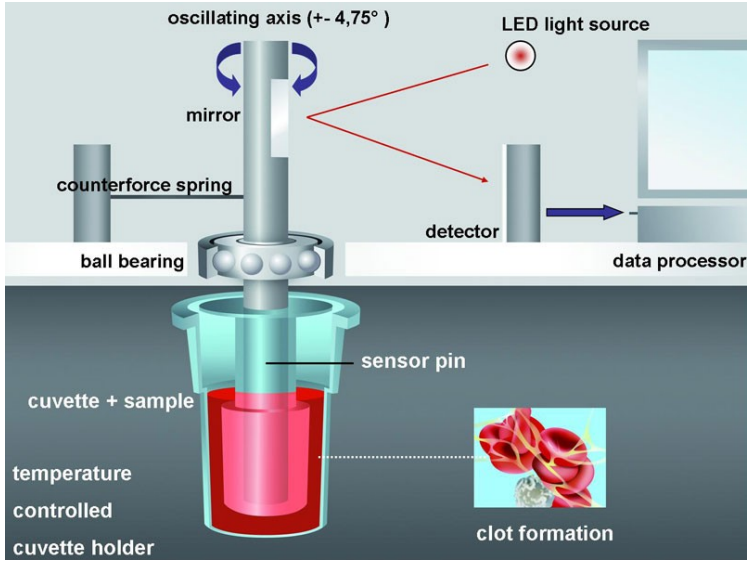


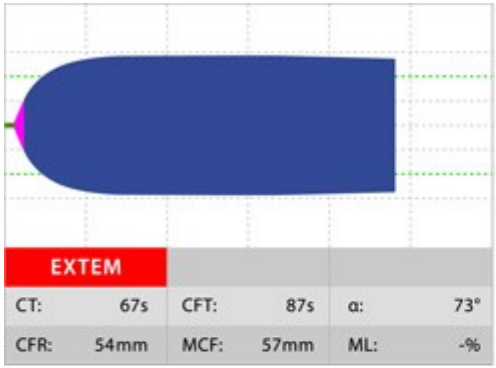

Each unit manufactured from a unit of FFP

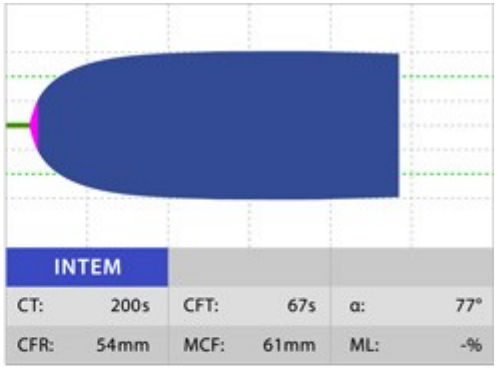
Contains 150 mg Fibrinogen and 100 units F8 and VwF

5 units pooled

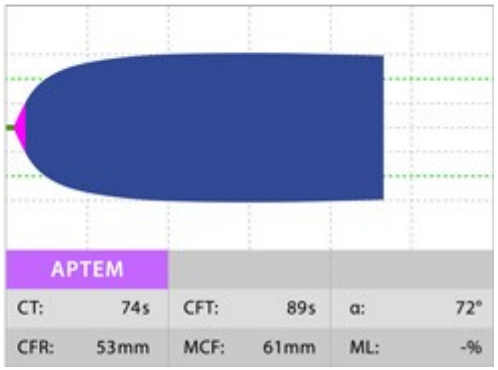
Usual dose is 2 pools which will generally raise fibrinogen  by 1 gm/dl.


oscillating axis (+- 4,75° )
LED light source
mirror
counterforce spring
detector
ball bearing
data processor
sensor pin
cuvette + sample
temperature
controlled
cuvette holder
clot formation

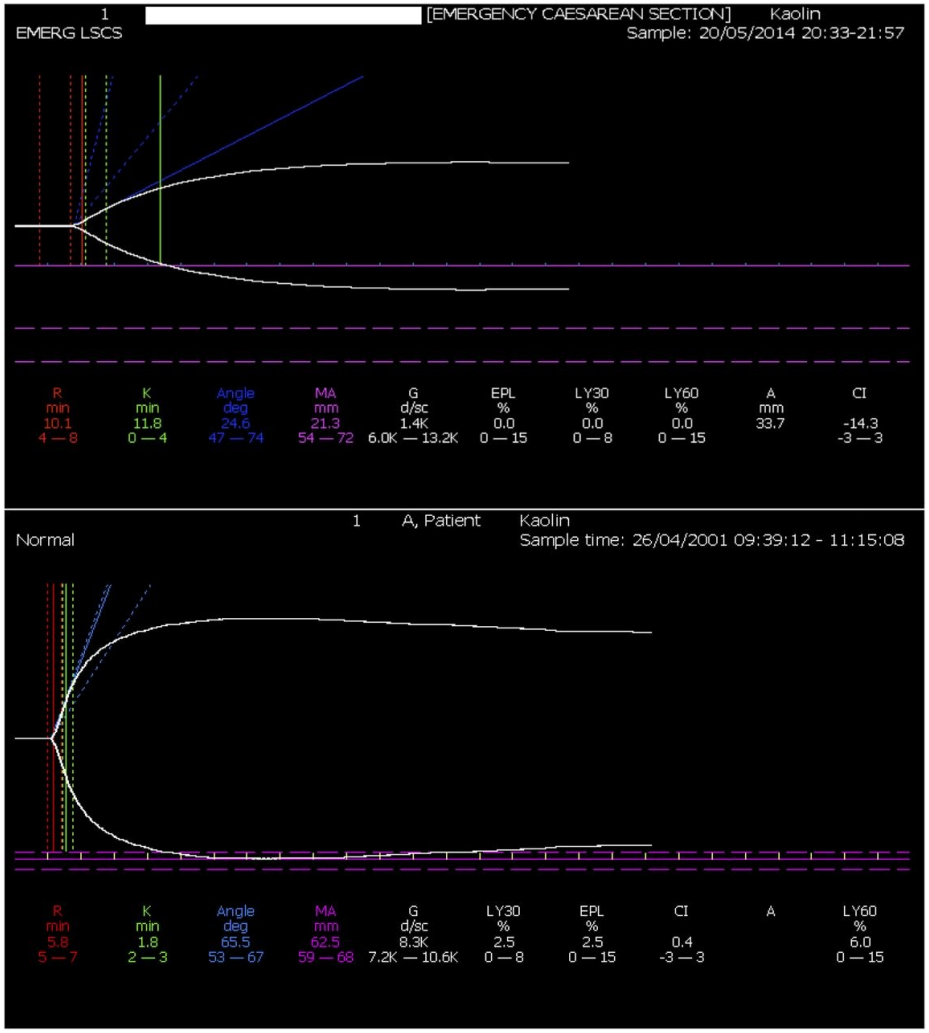

EXTEM
CT: 67s
CFT: 87s
α: 73°
CFR: 54mm
MCF: 57mm
ML: -%


INTEM
CT: 200s
CFT: 67s
α: 77°
CFR: 54mm
MCF: 61mm
ML: -%


FIBTEM
CT: 66s
CFT: -s
α: 57°
CFR: 9mm
MCF: 10mm
ML: -%


APTEM
CT: 74s
CFT: 89s
α: 72°
CFR: 53mm
MCF: 61mm
ML: -%

**TEG trace 40 minutes into surgery, showing severely prolonged R and K times and reduced α angle and maximum amplitude (MA).**




**Sue Pavord, and Helena Maybury Blood 2015;125:2759-2770**

©2015 by American Society of Hematology

# Transfusion in PPH



Hulse M et al Transfusion, 2017

# I got this !



# Classes of hemorrhagic shock

| | Class I | Class II | Class III | Class IV |
|---|---|---|---|---|
| Blood loss (mL) | Up to 750 | 750–1500 | 1500–2000 | >2000 |
| Blood loss (% of blood volume) | Up to 15% | 15%–30% | 30%–40% | >40% |
| Pulse rate | <100 | 100–120 | 120–140 | >140 |
| Blood pressure (mm Hg) | Normal | Normal | Decreased | Decreased |
| Pulse pressure (mm Hg) | Normal | Decreased | Decreased | Decreased |
| Respiratory rate | 14–20 | 20–30 | 30–40 | >35 |
| Urine output (mL/h) | >30 | 20–30 | 5–15 | Negligible |
| Mental status | Slightly anxious | Mildly anxious | Anxious, confused | Confused, Lethargic |
| Fluid | Crystalloid | Crystalloid | Crystalloid + | Crystalloid + |

*From* Advanced Trauma Life Support (ATLS) student course manual. 9th edition. Chicago (IL): American College of Surgeons; 2012

# Mortality in patients with low post op HgB who decline transfusion for religious reasons

| Postoperative HgB (g/dL) | Total study population | 30-day in-hospital mortality* | No cardiovascular disease (n = 230) | | Cardiovascular disease (n = 70) | |
|---|---|---|---|---|---|---|
| | | | Number | 30-day in-hospital mortality, n (%) | Number | 30-day in-hospital mortality* |
| 1.1-2.0 | 7 | 7 (100) | 5 | 5 (100) | 2 | 2 (100) |
| 2.1-3.0 | 24 | 13 (54.2) | 19 | 10 (52.6) | 5 | 3 (60.0) |
| 3.1-4.0 | 28 | 7 (25.0) | 20 | 2 (10.0) | 8 | 5 (62.5) |
| 4.1-5.0 | 32 | 11 (34.4) | 20 | 4 (20.0) | 12 | 7 (58.3) |
| 5.1-6.0 | 54 | 5 (9.3) | 40 | 3 (7.5) | 14 | 2 (14.3) |
| 6.1-7.0 | 56 | 5 (8.9) | 44 | 5 (11.4) | 12 | 0 (0) |
| 7.1-8.0 | 99 | 0 (0) | 82 | 0 (0) | 17 | 0 (0) |

•*Results reported as number (%).

Carson JL et al Transfusion 42:812,

# Simple Transfusion of PRBC and crystalloids

- ATLS class III
- Trigger HgB 7 with target HgB 8 – 10
- Majority of patients with PPH from atony or tissue trauma will not be coagulopathic early in hemorrhage.



Hemoglobin 7 to try and maintain between 8 and 10

Fibrinogen > 2 gms/dl

Platelets >50,000

PT < 1.5 control

# TEG Directed Transfusion Protocol

## Treatment targets:

| | |
|---|---|
| R time | <6 min |
| K time | <3 min |
| α angle | >50° |
| MA | >57 mm |

## Response to TEG results

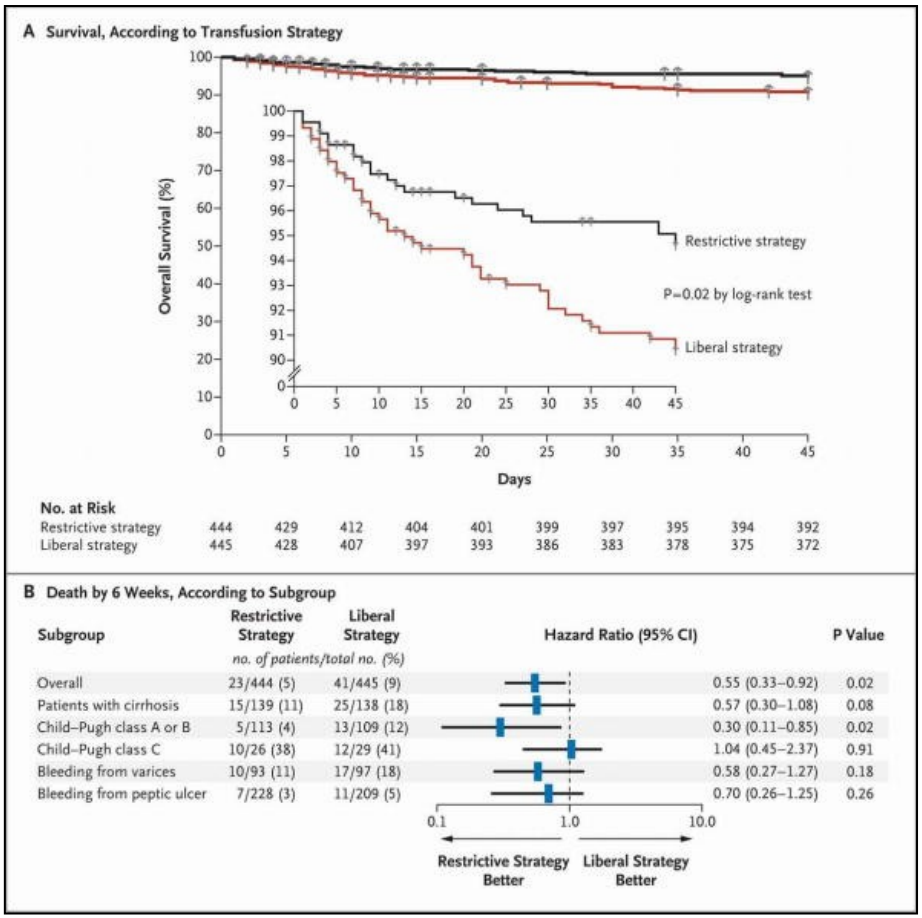
| | | |
|---|---|---|
| R time | 6-8 m | 2 FFP |
| R time | >8 m | 4 FFP & 2 Cryo |
| α angle | <50° | 2 Cryo |
| MA | 50-57mm | 1 Plts |
| MA | <50mm | 2 Plts & 2 Cryo |

Pavord Blood 2014

**Transfusion strategies for acute upper gastrointestinal bleeding.**

Villanueva C; Colomo A; Bosch A; Concepcion M; Hernandez-Gea V; Aracil C; Graupera I; Poca M; Alvarez-Urturi C; Gordillo J; Guarner-Argente C; Santalo M; Muniz E; Guarner C

New England Journal of Medicine. 368(1):11-21, 2013 Jan 03.
DOI: 10.1056/NEJMoa1211801



TRIM

ABO mismatch

TACO

West Nile Virus

TRALI

ZIKA

Delayed type hemolytic reactions

BACTERIAL CONTAMINATION

# Houston, we have a problem



# Massive Transfusion Protocol Indications

Predicted blood loss:  6 units in 3 hours or 10 units/24 hours

ATLS class 4

Consider from initiation when

- Amniotic Fluid Embolism
- Severe abruption
- Delayed recognition
- Preexisting or present coagulopathy (preeclampsia, HELLP, acute fatty liver)
- Fibrinogen below 200

# MTP Advantages/Disadvantages

**Advantages**

- Prevention of dilutional coagulopathy
- In the massively bleeding patient less total blood used because of earlier control of hemostasis
- Observational studies suggest survival benefit in trauma
- Less third spacing, renal damage and abdominal compartment syndrome

**Disadvantages**

- Increased pulmonary toxicity: TACO, TRALI
- Unnecessary exposure of some patients to plasma and platelets
- Wastage/cost
- No controlled trials and survivor bias in observational trials



# MTP

- 6 units in 3 hours or 10 in 24 hours
- Do not use unless necessary – Taco/ARDS/Trali
- Lead physician calls and ends
- Dedicated communicator to blood bank who follows patient throughout spectrum
- Single tech blood bank
- Runner
- Place order in epic
- Send stat type and screen

# MTP

- Blood bank sends a pack containing one dose of platelets, 6 prbc and 6 ffp
- You should and must ask for cryo in addition (in epic order set).
- Transfuse cryo and platelets first then alternate prbc and ffp
- FFP may arrive later 20 min to thaw.  Catch up
- Type specific or Type O neg prbc and AB plasma till type known
- Red cells and FFP in cooler, platelets at room temp
- Communicator keeps BB informed of needs for next round
- Stop MTP promptly when bleeding stopped, return unused units

Original Investigation

# Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma
## The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

Table 3. Adjudicated Cause of Death by Treatment Group and Period From Randomization

| | First 24 Hours | | | 30 Days | | |
|---|---|---|---|---|---|---|
| | No. (%) | | | No. (%) | | |
| | 1:1:1 Group (n = 338) | 1:1:2 Group (n = 342) | Difference (95% CI),%[a] | 1:1:1 Group (n = 335) | 1:1:2 Group (n = 341) | Difference (95% CI), %[a] |
| Total No. of deaths | 43 | 58 | | 75 | 89 | |
| Cause of death[b] | | | | | | |
| Exsanguination | 31 (9.2) | 50 (14.6) | −5.4 (−10.4 to −0.5) | 36 (10.7) | 50 (14.7) | −3.9 (−9.1 to 1.2) |
| Traumatic brain injury | 11 (3.3) | 12 (3.5) | −0.3 (−3.2 to 2.7) | 27 (8.1) | 35 (10.3) | −2.2 (−6.7 to 2.2) |
| Respiratory, pulmonary contusion, or tension pneumothorax | 3 (0.9) | 1 (0.3) | 0.6 (−0.9 to 2.4) | 5 (1.5) | 2 (0.6) | 0.9 (−0.8 to 3.0) |
| Sepsis | 0 | 0 | 0 (−1.1 to 1.1) | 1 (0.3) | 2 (0.6) | −0.3 (−1.9 to 1.2) |
| Multiple organ failure | 0 | 0 | 0 (−1.1 to 1.1) | 10 (3.0) | 8 (2.3) | 0.6 (−2.0 to 3.4) |
| Type of cardiovascular event | | | | | | |
| Stroke | 0 | 1 (0.3) | −0.3 (−1.7 to 0.9) | 2 (0.6) | 1 (0.3) | 0.3 (−1.1 to 1.9) |
| Myocardial infarction | 1 (0.3) | 1 (0.3) | 0 (−1.4 to 1.4) | 1 (0.3) | 2 (0.6) | −0.3 (−1.9 to 1.2) |
| Pulmonary embolism | 0 | 1 (0.3) | −0.3 (−1.7 to 0.9) | 0 | 1 (0.3) | −0.3 (−1.7 to 0.9) |
| Transfusion-related fatality | 0 | 0 | 0 (−1.1 to 1.1) | 1 (0.3) | 0 | 0.3 (−0.8 to 1.7) |

[a] Calculated using exact unconditional methods based on the Farrington-Manning score statistic.

[b] A patient may have had more than 1 cause of death.




Transfuse 4 units of PRBC first
If bleeding continues 4 units of FFP
Then alternate 1:1 RBC:FFP till 8
Once 8 units prbc given, give additionally 2 five packs of cryoprecipitate and platelets unless platelet count > 75,000
Then follow MTP

ISTH Collins P et al J of Thromb Haemos 14:205,2015



Ca + - 1 g Ca gluconate for iCa <1.1 or q 4 – 6 units of PRBC

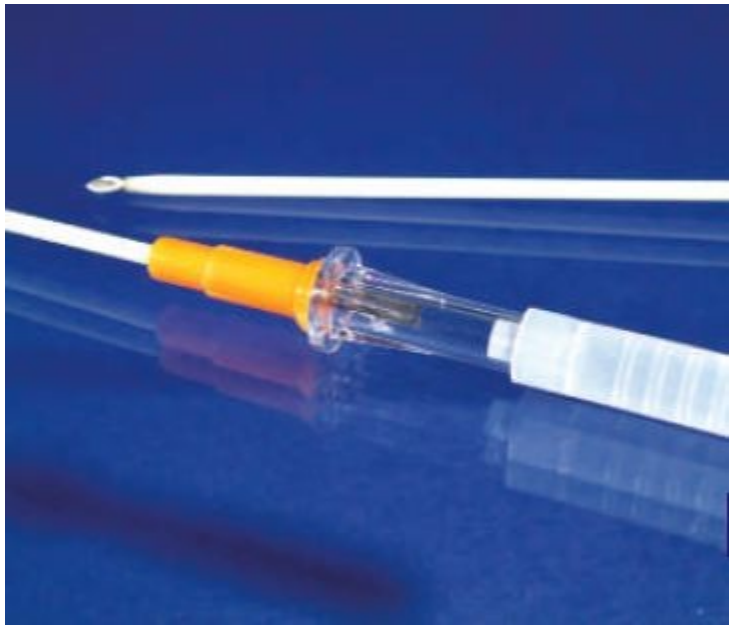


K + - Insulin and D50





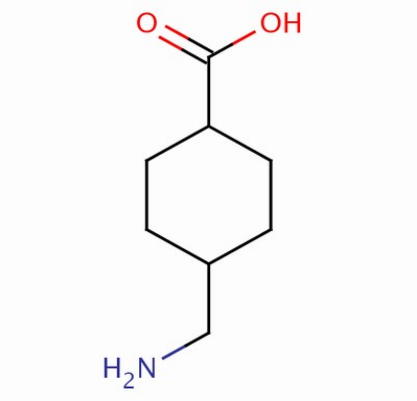




# Cell Saver



# Tranexamic acid




Lysine analog which competes for lysine binding sites on plasminogen preventing interaction with fibrin and preventing activation of fibrinolysis

Decreased M&M in major trauma. (Crash-2 trial collaborators, Lancet 376:23, 2010)

Decreased transfusion and blood loss in orthopedic surgery (Lin Z Orthopedics 39:119, 2016)

Decreased transfusion and blood loss in cardiothoracic surgery (Hutton B et al BMJ 345, 2012)

No increase in thromboembolic events

TXA is cheap !!! $ 10-18 a dose.

Ducloy-Bouthors *et al. Critical Care* 2011, **15**:R117
http://ccforum.com/content/15/2/R117

CRITICAL CARE

RESEARCH Open Access

# High-dose tranexamic acid reduces blood loss in postpartum haemorrhage

Anne-Sophie Ducloy-Bouthors[1*], Brigitte Jude[2,3], Alain Duhamel[4,5], Françoise Broisin[6], Cyril Huissoud[7], Hawa Keita-Meyer[8,9], Laurent Mandelbrot[9,10], Nadia Tillouche[11], Sylvie Fontaine[11], Françoise Le Goueff[12], Sandrine Depret-Mosser[13], Benoit Vallet[1,14], for The EXADELI Study Group[15] and Sophie Susen[2,3]

72 women 4 gm loading dose followed by 1 gm hr. vs standard care

Randomized not placebo controlled or blinded

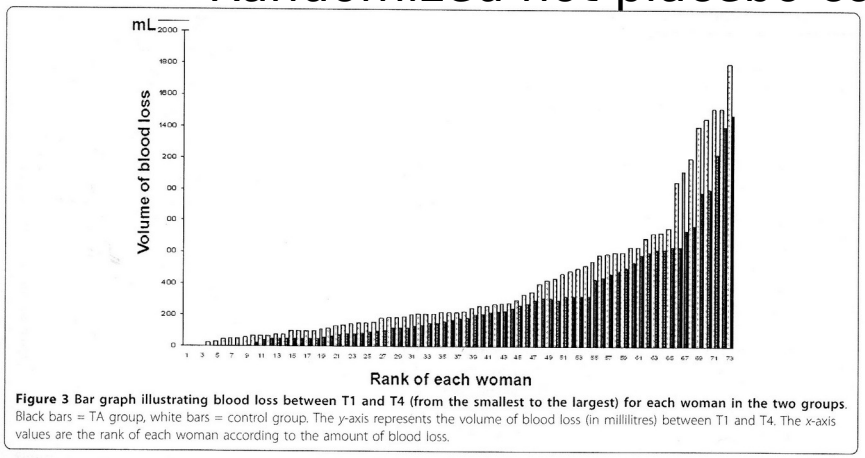



**Figure 3 Bar graph illustrating blood loss between T1 and T4 (from the smallest to the largest) for each woman in the two groups.** Black bars = TA group, white bars = control group. The *y*-axis represents the volume of blood loss (in millilitres) between T1 and T4. The *x*-axis values are the rank of each woman according to the amount of blood loss.

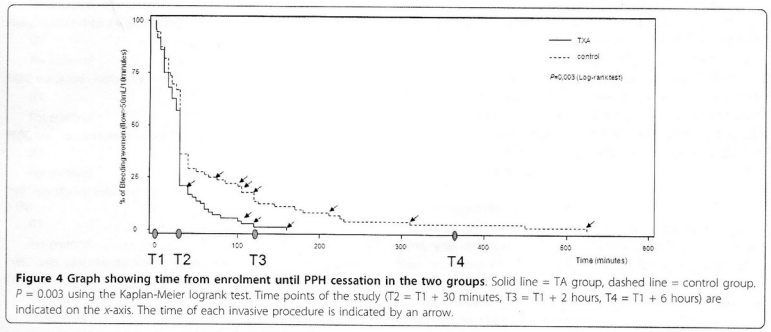



**Figure 4 Graph showing time from enrolment until PPH cessation in the two groups.** Solid line = TA group, dashed line = control group. *P* = 0.003 using the Kaplan-Meier logrank test. Time points of the study (T2 = T1 + 30 minutes, T3 = T1 + 2 hours, T4 = T1 + 6 hours) are indicated on the *x*-axis. The time of each invasive procedure is indicated by an arrow.

# Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

*WOMAN Trial Collaborators**

Multinational mostly resource poor

PPH 500 ml vaginal or 1000 ml if CS

10051 randomized to receive TXA 1 gram ivss (may repeat x 1) vs 10009 placebo plus standard care

The lancet 2017

# Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

*WOMAN Trial Collaborators**

| | Tranexamic acid group (n=10 036) | Placebo group (n=9985) | RR (95% CI) | p value (two-sided) |
|---|---|---|---|---|
| Bleeding | 155 (1·5%) | 191 (1·9 %) | 0·81 (0·65–1·00) | 0·045 |
| Pulmonary embolism | 10 (0·1%) | 11 (0·1) | 0·90 (0·38–2·13) | 0·82 |
| Organ failure | 25 (0·3%) | 18 (0·2%) | 1·38 (0·75–2·53) | 0·29 |
| Sepsis | 15 (0·2%) | 8 (0·1%) | 1·87 (0·79–4·40) | 0·15 |
| Eclampsia | 2 (0·02%) | 8 (0·1%) | 0·25 (0·05–1·17) | 0·057 |
| Other | 20 (0·2%) | 20 (0·2%) | 0·99 (0·54–1·85) | 0·99 |
| Any cause of death | 227 (2·3%) | 256 (2·6%) | 0·88 (0·74–1·05) | 0·16 |

Data are n (%), unless otherwise indicated. RR=risk ratio.

***Table 2:*** Effect of tranexamic acid on maternal death

# Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

*WOMAN Trial Collaborators**

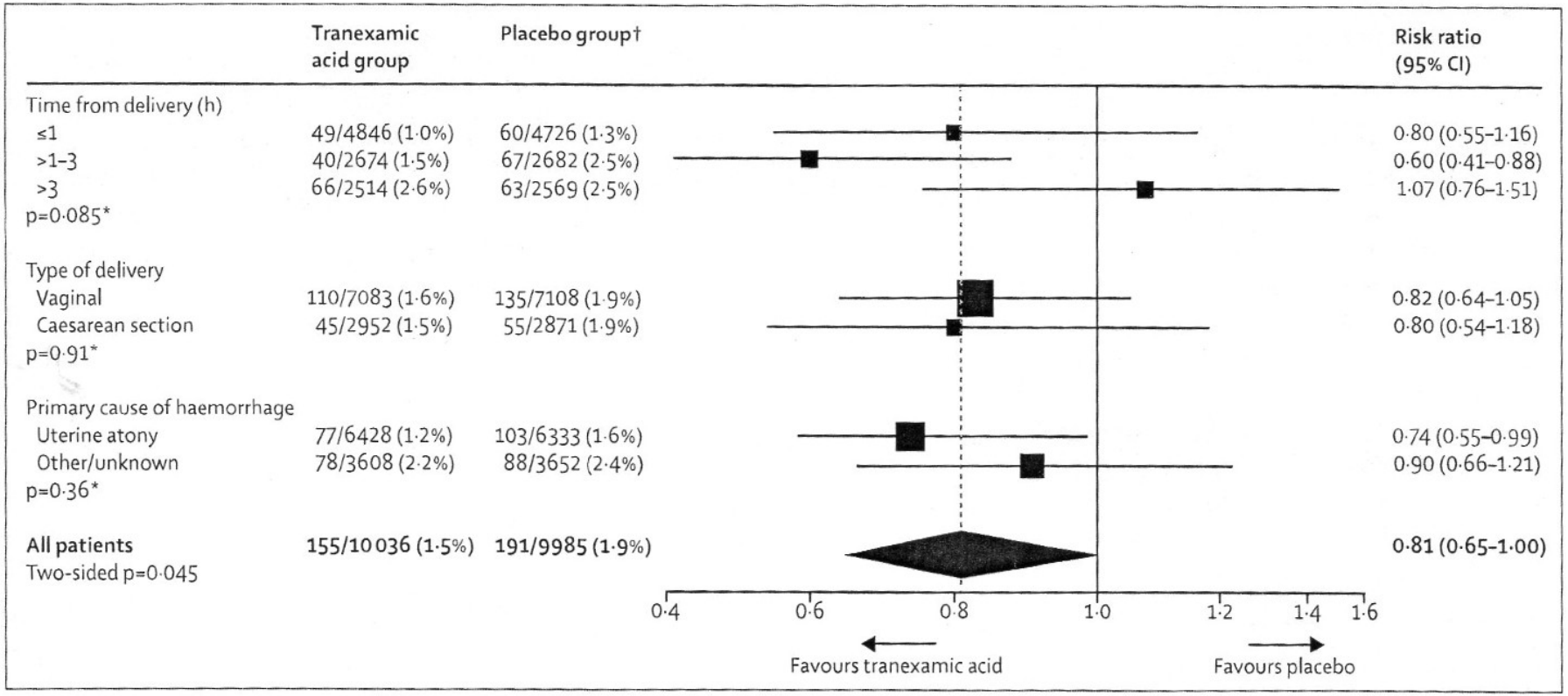



*Figure 3:* **Death from bleeding by subgroup**

*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

*Journal of Thrombosis and Haemostasis*, **13**: 520–529 DOI: 10.1111/jth.12844

ORIGINAL ARTICLE

# 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*†

Randomized controlled trial in PPH unresponsive to uterotonics

42 patients received a single infusion of rFVIIa vs 42 control

Need for second line intervention decreased by 1 in 3 but thromboembolic events increased by about 1 in 20 in rFVIIa group

No effect on mortality

**Safety of Recombinant Activated Factor VII in Randomized Clinical Trials**

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

N Engl J Med 2010; 363:1791-1800
November 4, 2010DOI:
10.1056/NEJMoa1006221

**Table 2. Odds Ratios for Thromboembolic Events.**

| Thromboembolic Event | rFVIIa (N=2583) | Placebo (N=1536) | Odds Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| | *number (percent)*† | | | |
| All events | 264 (10.2) | 134 (8.7) | 1.17 (0.94–1.47) | 0.16 |
| Arterial events | 141 (5.5) | 49 (3.2) | 1.68 (1.20–2.36) | 0.003 |
| Venous events | 137 (5.3) | 88 (5.7) | 0.93 (0.70–1.23) | 0.61 |

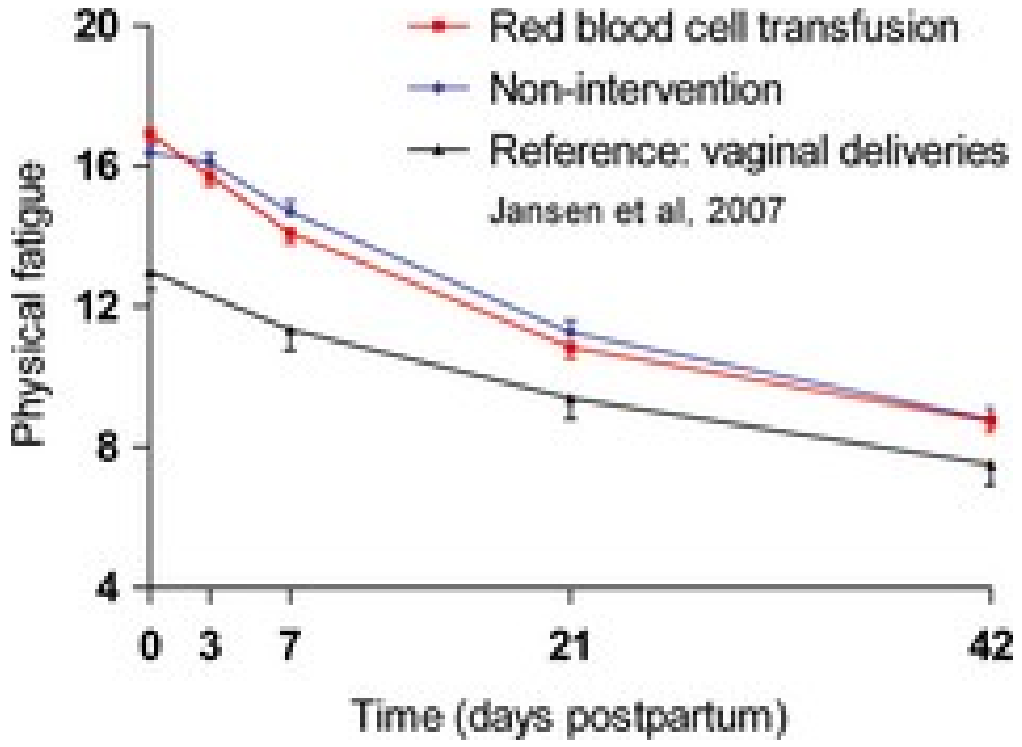
* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received the assigned study drug.

# Recombinant FVIIa

- Consider for refractory bleeding
- Platelets and Fibrinogen corrected to target ranges prior to rFVIIa
- Optimal dose unknown but likely 60 mcg/Kg
- May repeat once after 20-30 minutes
- If two doses are ineffective further doses unlikely to help.
- Expensive  $1 per mcg

Collins P J Thromb Haemostasis 14:205, 2015

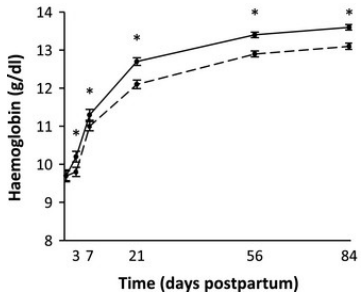
# Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial

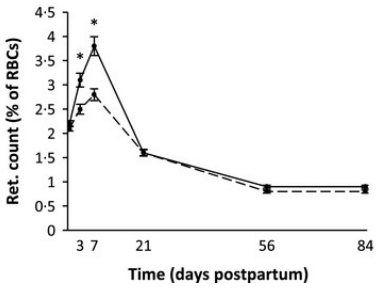


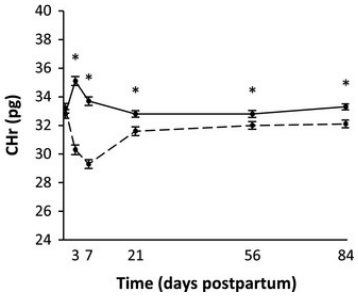

**BJOG: An International Journal of Obstetrics & Gynaecology**
Volume 121, Issue 8, pages 1005-1014, 10 JAN 2014 DOI: 10.1111/1471-0528.12531
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.12531/full#bjo12531-fig-0002

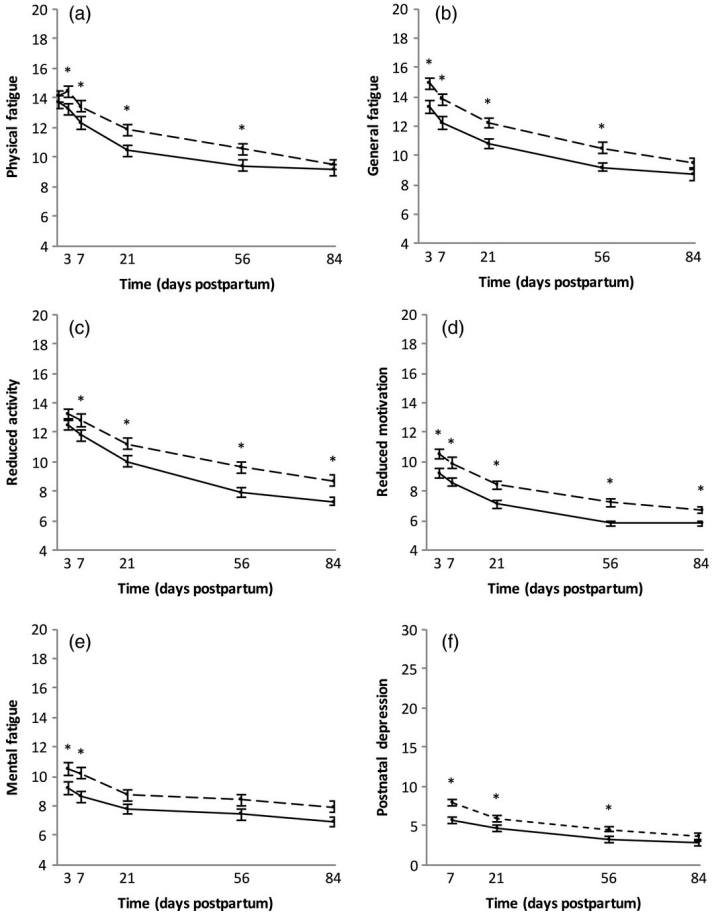
# Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial

Randomized study of iv iron 97 pt.
vs oral iron 99 pt. following PPH




**Vox Sanguinis**
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http://onlinelibrary.wiley.com/doi/10.1111/vox.12477/full#vox12477-fig-0002

# DVT prophylaxis

Patients with PPH have increased risk of VTE (Tapper et al Obstet & Gyn 123:987, 2014)

Pharmacological DVT prophylaxis should be started when PPH is controlled. (Pavod and Maybury Blood 125:2759, 2015)

# Summary

- Assess coagulopathy; clinical, coag  profile & TEG
- Treat hypofibrinogenemia with cryo
- Controlled hemorrhage restrictive transfusion Hgb trigger of 7 with aim to maintain 8-10
- Uncontrolled hemorrhage – MTP
  - 6 units 3 hour or 10 units in 24
  - Late recognition
  - Coagulopathy
  - AFE, severe abruption
  - Hypofibrinogenemia
  - ACS stage IV shock

- TXA 1 gm ivss in first 3 hours
- rFVIIA consider only as salvage.
- Iron and dvt prophy