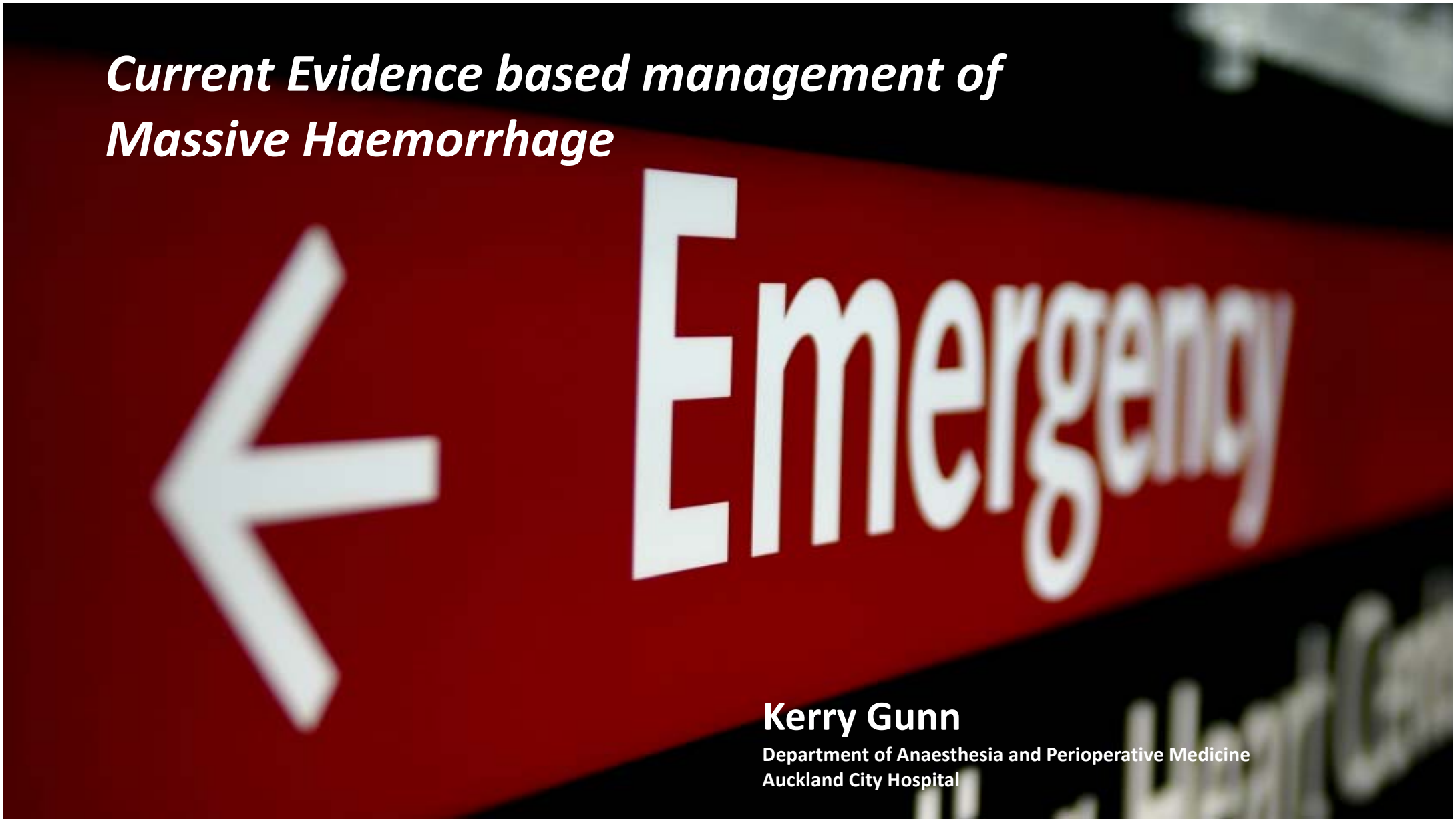
Current Evidence based management of Massive Haemorrhage



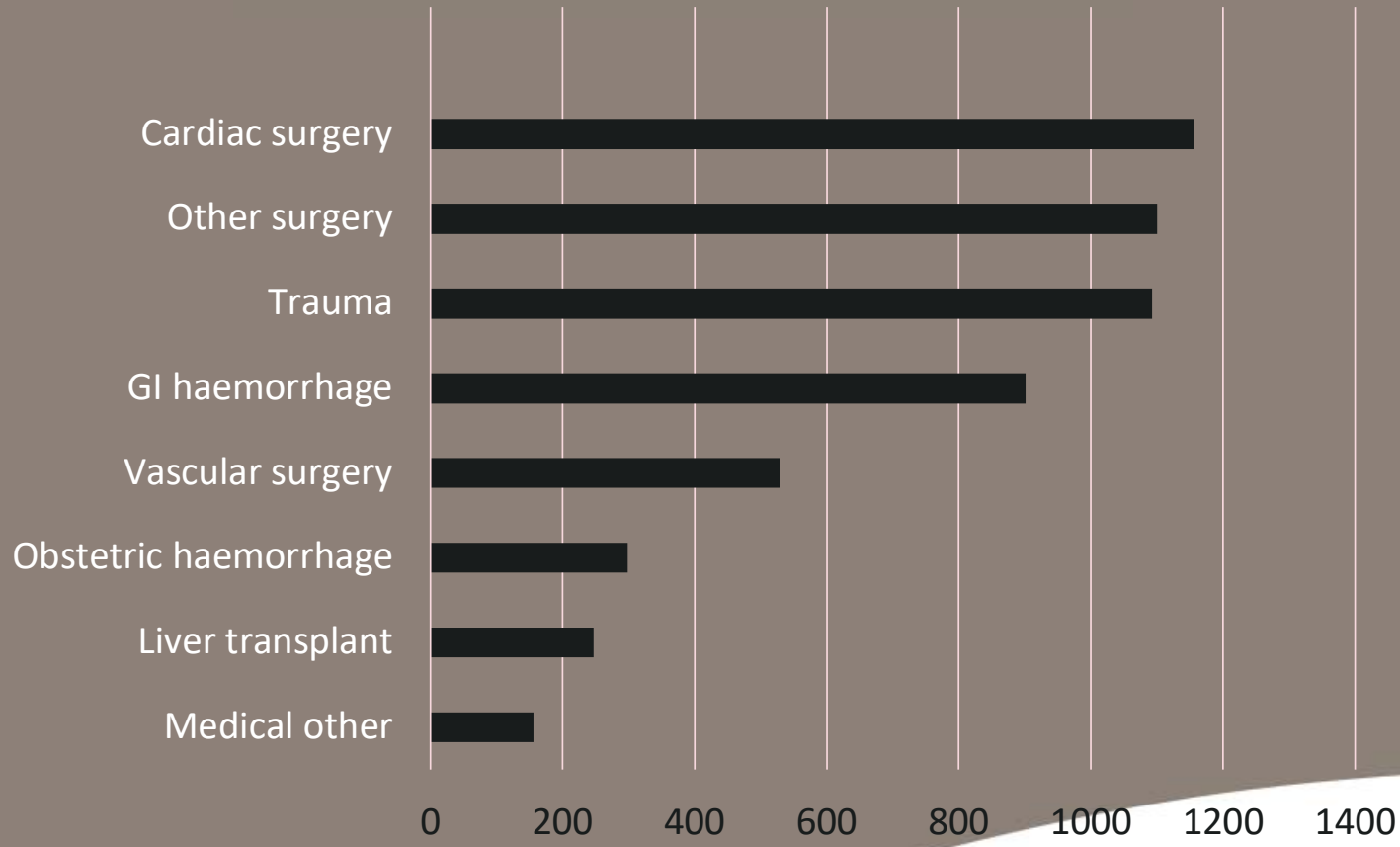
Kerry Gunn
Department of Anaesthesia and Perioperative Medicine
Auckland City Hospital

Summary

- A small proportion (4%) need an aggressive approach to transfusion
- Systems that include plasma and platelets improve outcome
- The key component in plasma is fibrinogen
- The challenge is to develop systems that deliver fibrinogen rapidly enough to the ones that need it and leave the others without it

- TEG improves decision-making and reduces waste

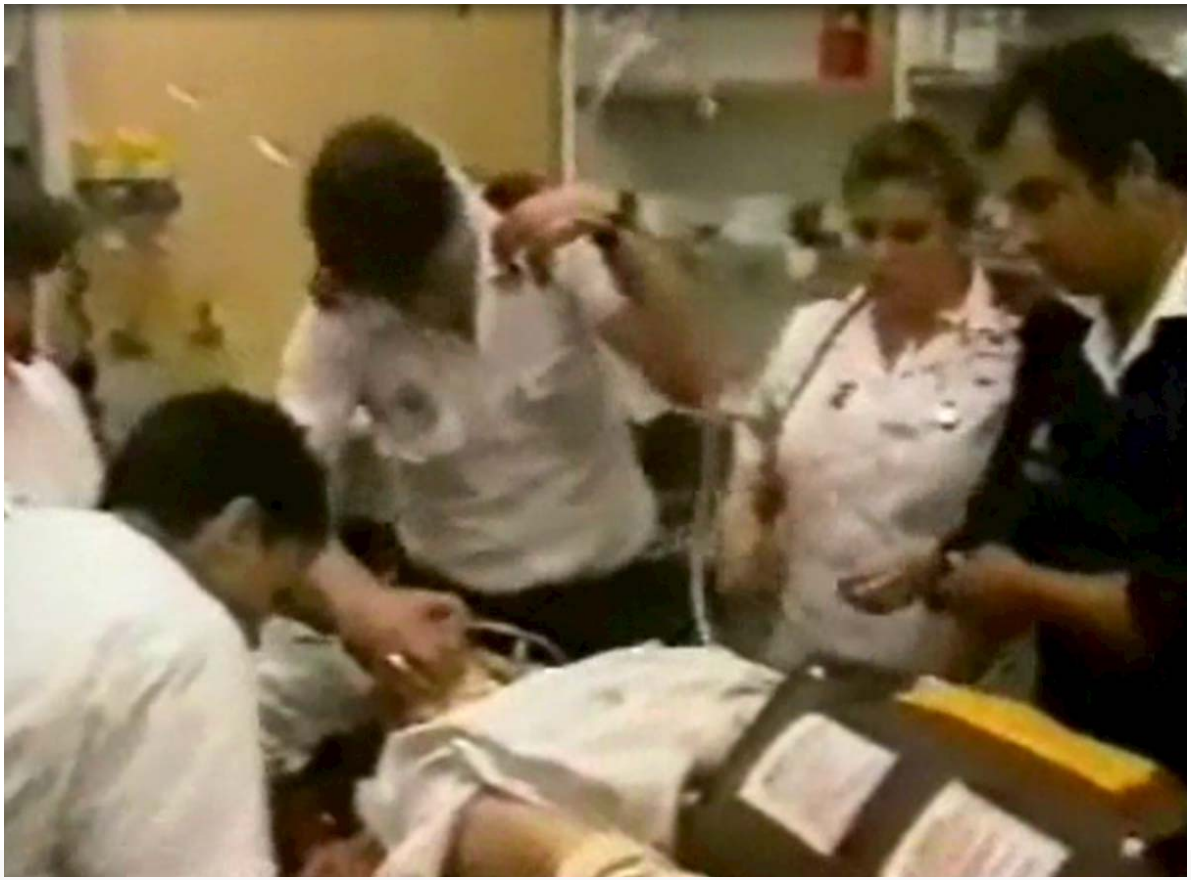
MT Bleeding Context
>5600 MT cases, 25 hospitals



massive transfusion registry

Mortality after trauma was high

- Trauma presentations to Auckland Hospital resus room in 1983
- 602 patients of whom 223 subsequently shown to have major trauma.
- Mortality 60/223 (26.9%)



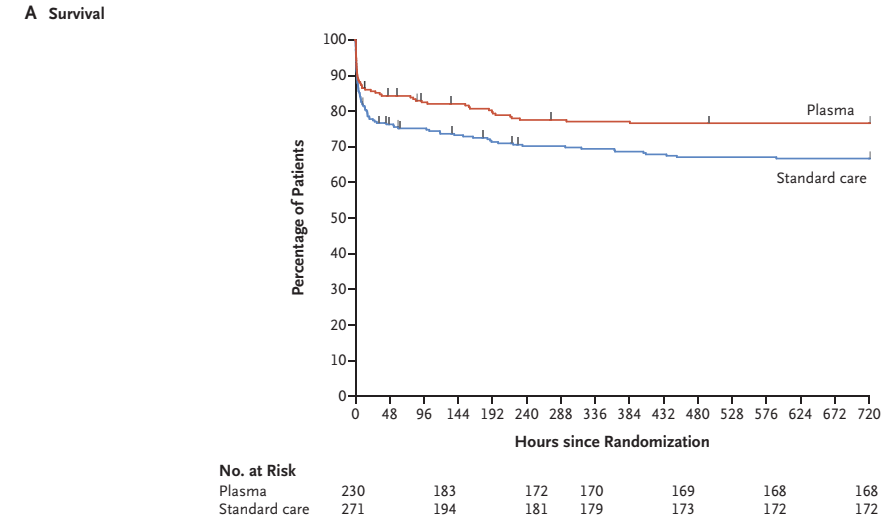
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

CONCORD performance improvement

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*



ORIGINAL ARTICLE

ONLINE FIRST

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

John B. Holcomb, MD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Mitchell J. Cohen, MD; Martin A. Schreiber, MD; Louis H. Alarcon, MD; Yu Bai, MD, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Bryan A. Cotton, MD, MPH; Nena Matijevic, PhD; Peter Muskat, MD; John G. Myers, MD; Herb A. Phelan, MD, MSCS; Christopher E. White, MD; Jiajie Zhang, PhD; Mohammad H. Rahbar, PhD; for the PROMMTT Study Group

- 10 US Trauma centres
- 906 patients > 3 units pRBC (of 35,000 admissions)
- Within first 24 hrs mortality from bleeding reduced 3-4 times with 1:1 ratio
- NO difference in outcome after 24hrs

Arch Surg. Published online October 15, 2012.
doi:10.1001/2013.jamasurg.387

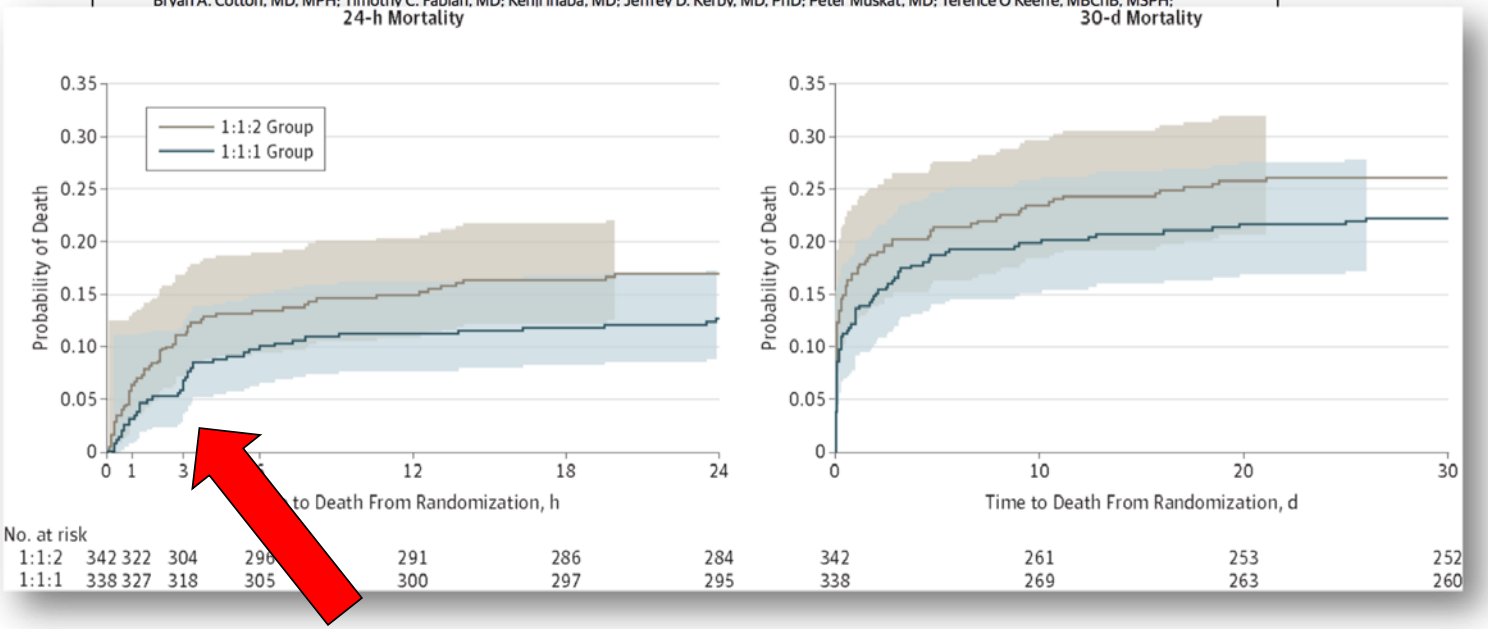
Research

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;



JAMA. 2015;313(5):471-482. doi:10.1001/jama.2015.12

Table 2 Multivariable logistic regression analysis for patients alive and free from massive transfusion within 24 h

	Odds ratio	*P*
Age	1·00 (0·98, 1·01)	0·768
Injury Severity Score	0·98 (0·95, 1·00)	0·071
Heart rate	1·01 (1·00, 1·02)	0·055
Systolic blood pressure	1·00 (0·99, 1·01)	0·929
Haemoglobin level	1·11 (0·95, 1·30)	0·186
AIS score (head) ≥ 3	0·53 (0·27, 1·04)	0·065
Total amount of blood products used	0·81 (0·77, 0·85)	< 0·001
High ratio of plasma to RBCs	2·07 (1·03, 4·13)	0·040
High ratio of platelets to RBCs	2·67 (1·24, 5·77)	0·012
Use of tranexamic acid	2·71 (1·29, 5·71)	0·009
Use of fibrinogen products	1·45 (0·60, 3·49)	0·409

Values in parentheses are 95 per cent confidence intervals. Patients were clustered within each hospital. AIS, Abbreviated Injury Scale; RBC, red blood cell.

Table 3 Multivariable logistic regression analysis for correction of coagulopathy within 24 h

	Odds ratio	*P*
Age	1·03 (1·01, 1·05)	0·001
Fluids per 100 ml in 24 h	0·98 (0·97, 0·99)	0·001
High ratio of plasma to RBCs	0·89 (0·45, 1·78)	0·747
High ratio of platelets to RBCs	0·63 (0·32, 1·26)	0·194
Use of tranexamic acid	1·64 (0·82, 3·29)	0·165
Use of fibrinogen products	1·61 (0·74, 3·54)	0·233

Values in parentheses are 95 per cent confidence intervals. Patients were clustered within each hospital. RBC, red blood cell.

The ‘revised” MTP

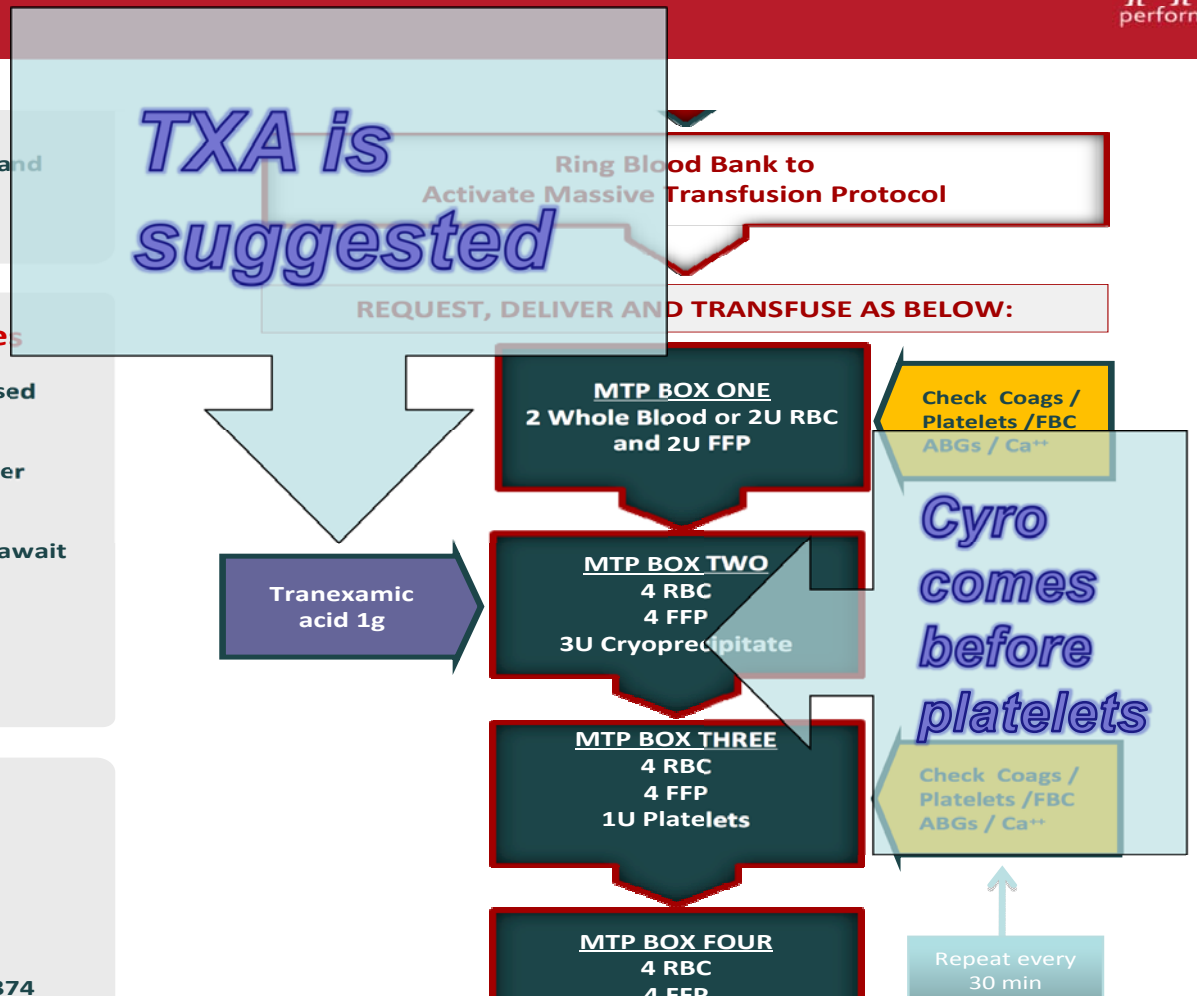
- Call for each box as required
- Make a decision to cease MTP and contact Blood Bank

Blood Bank Responsibilities

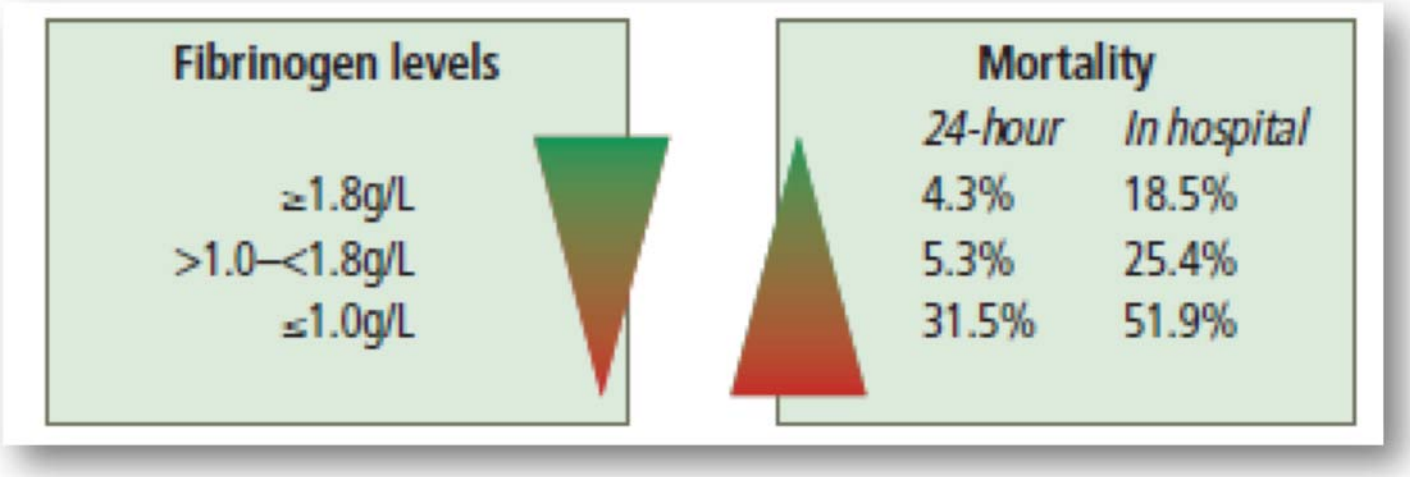
- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box One
- Thaw next box in advance and await request
- Ensure supply of platelets

Contacts

- Blood Bank - Ext 24015
- Coagulation Lab - Ext 7572
- Level 8 Anaesthetist - 021 496 374



Does mortality drop with Fibrinogen concentrate?



Schöchl H, et al. Scand J Trauma Resusc Emerg Med 2012;20:15–25

ADHB Adult Code Crimson MTP

Team Leader Responsibilities

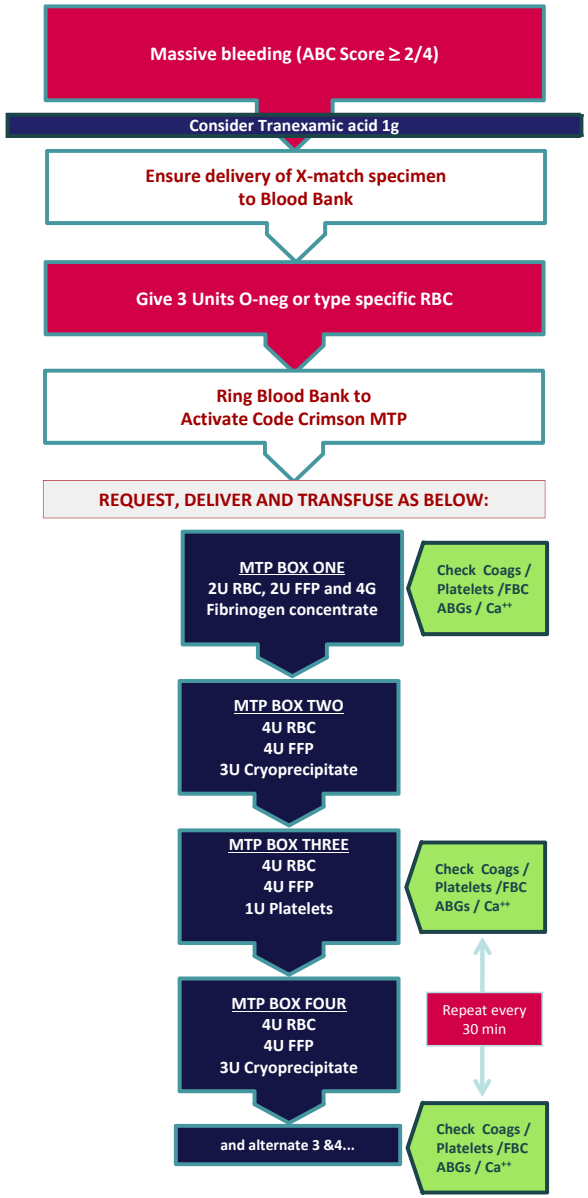
- Team leader should be a trauma team member
- Notify Coag Lab and send Coag requests on the Labplus Urgent form (orange border)
- Activate protocol by ringing Blood Bank (ext 24015) and say "I am activating the "Code Crimson MTP"
- Call for each box as required
- Make a decision to cease MTP and contact Blood Bank

Blood Bank Responsibilities

- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box Four
- Thaw next box in advance and await request
- Ensure supply of platelets

Additional treatment thresholds

- if PR >1.5 or APTT >40 consider additional 4 units FFP
- if fibrinogen <1g/L consider additional 3U Cryoprecipitate
- if platelets <75 x10^9/L consider additional one pack platelets
- if ionized Ca++ <1mmol/L give 10mls Calcium



SOURCES OF FIBRINOGEN

	Fibrinogen Content	Thaw Time Delay	Factors Present	Implications
FFP	1.6G/L	30 min. + Transport	Fibrinogen (I) II, VII, IX, X, XII [V & VIII 65% (N)]	Weak TACO TRALI immunomodulation
Cryoprecipitate	1.3G/150ml	30 min. + Transport	Fibrinogen (I) vWF, VIII XIII fibronectin	Availability no viral inactivation
Fibrinogen Concentrate	1.0G/50ml	NIL	Fibrinogen (I)	Cost 20% greater than cryoprecipitate

Focus on reducing bleeding not transfusion

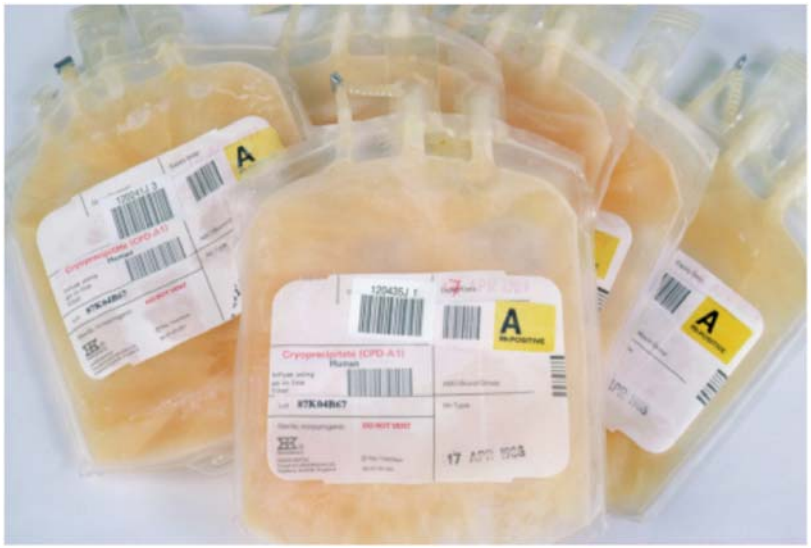
Society of Cardiovascular Anesthesiologists

Cardiovascular Anesthesiology Section Editor: **Charles W. Hogue, Jr.**
Perioperative Echocardiography and Cardiovascular Education Section Editor: **Martin J. London**
Hemostasis and Transfusion Medicine Section Editor: **Jerrold H. Levy**
REVIEW ARTICLE

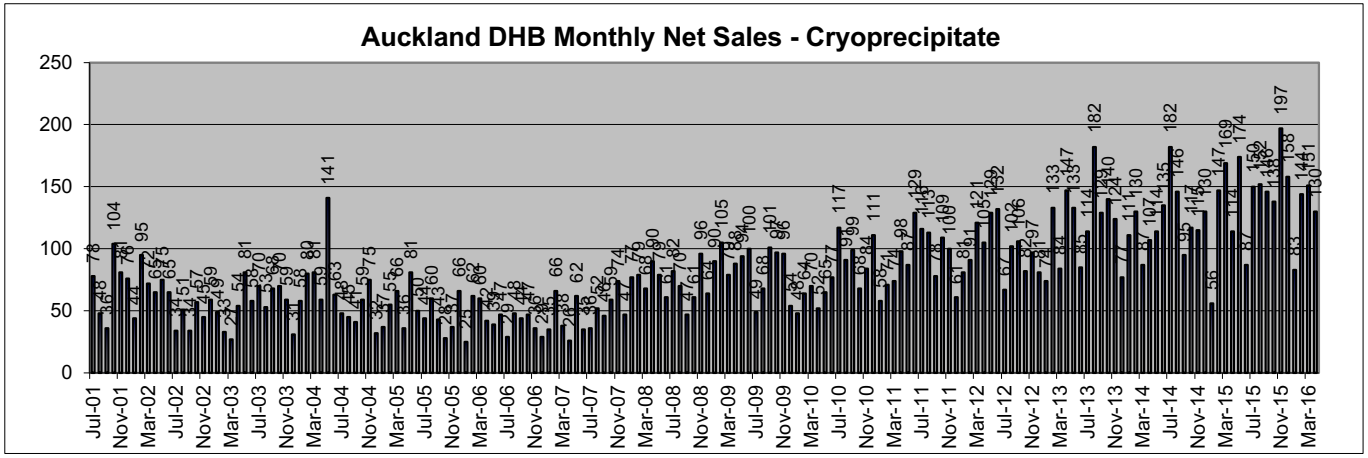
CME

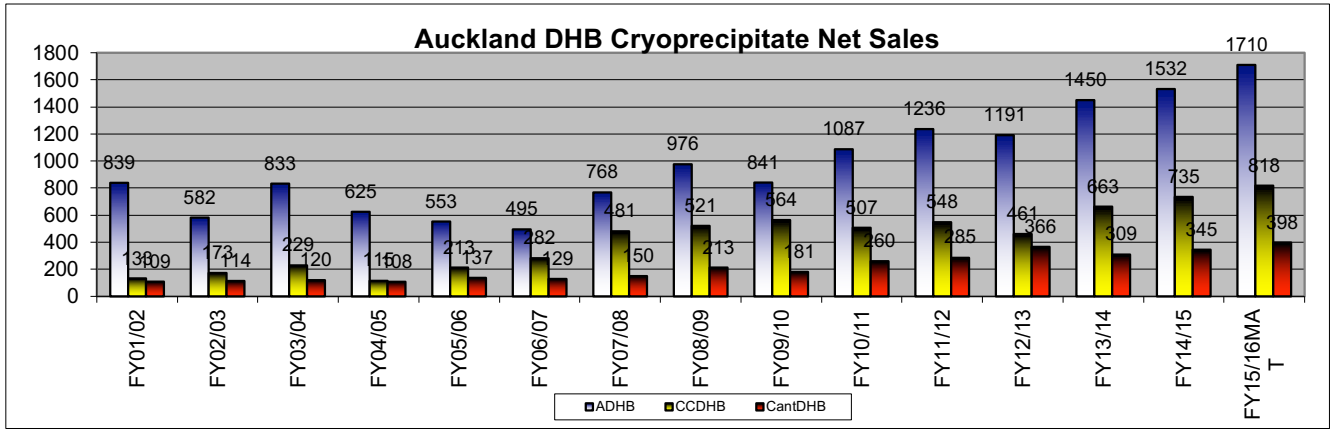
Fibrinogen and Hemostasis: A Primary Hemostatic Target for the Management of Acquired Bleeding

Jerrold H. Levy, MD, FAHA, Fania Szlam, MMSc, Kenichi A. Tanaka, MD, and Roman M. Sniecienski, MD



Cyro use (ADHB)






RiaSTAP
Human Fibrinogen, Powder for Injection
Intravenous Injection Only
1 g
Manufactured by CSL Behring GmbH
35041 Marburg Germany
Distributed and sponsored in Australia
by CSL Limited
189 – 209 Camp Road
Broadmeadows Vic 3047 Australia
Customer Service 1800 063 892
to hang pull here
Aquasonic
100

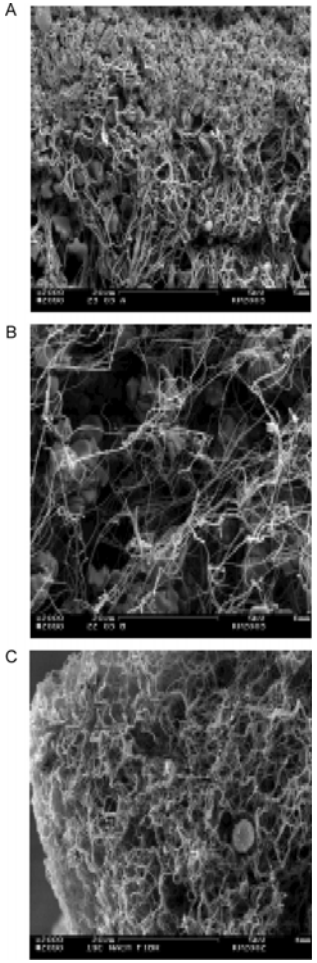
Electron microscopic scan of a ×2000 magnified blood clot.

- fibTEM >10mm
- Fibrinogen > 1.5-2.0 g/L

undiluted

65% haemodiluted

Post fibrinogen administration

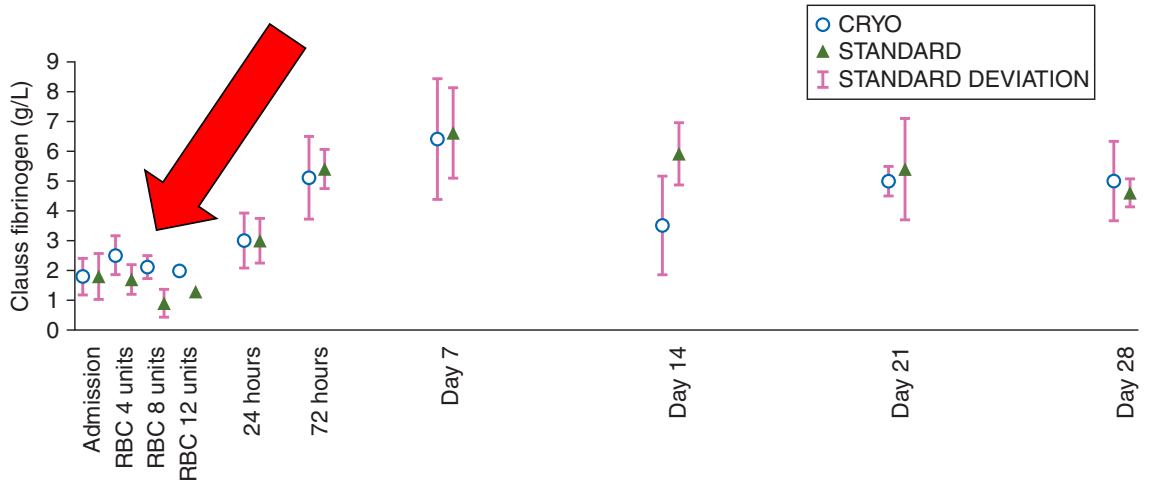


Fries D , Martini W Z Br. J. Anaesth. 2010;105:116-121

ARTICLE

Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial

N. Curry[1,*], C. Rourke[2], R. Davenport[2], S. Beer[1], L. Pankhurst[3], A. Deary[3],



N in CRYO	13	6	3	1	16	15	13	6	5	7
N in STANDARD	15	5	2	1	15	12	10	9	7	8

Fig 2 Comparison of Mean Fibrinogen Concentrations (Standard Deviation) between Study Arms for the Duration of the Trial. Changes of Clauss fibrinogen concentrations were compared using a two way ANOVA with repeated measures for patients in each arm of the trial. No evidence of a difference between changes in mean Clauss fibrinogen concentrations at 24 h and 72 h and the arm of the trial.

RESEARCH Open Access

Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial

Nicola Curry[1,2*], Claire Foley[3], Henna Wong[1,2,4], Ana Mora[3], Elinor Curnow[3], Agne Zarankaite[3], Renate Hodge[3], Valerie Hopkins[3], Alison Deary[3], James Ray[5], Phil Moss[6], Matthew J. Reed[7], Suzanne Kellett[8], Ross Davenport[9] and Simon Stanworth[1,2,4,10]

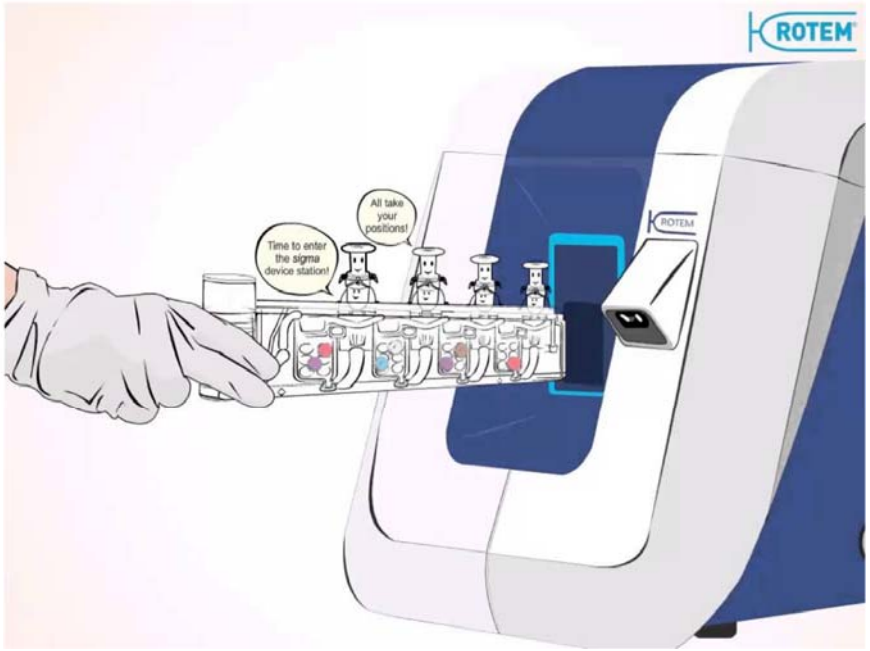
Table 2 Fibrinogen levels over time, by treatment arm

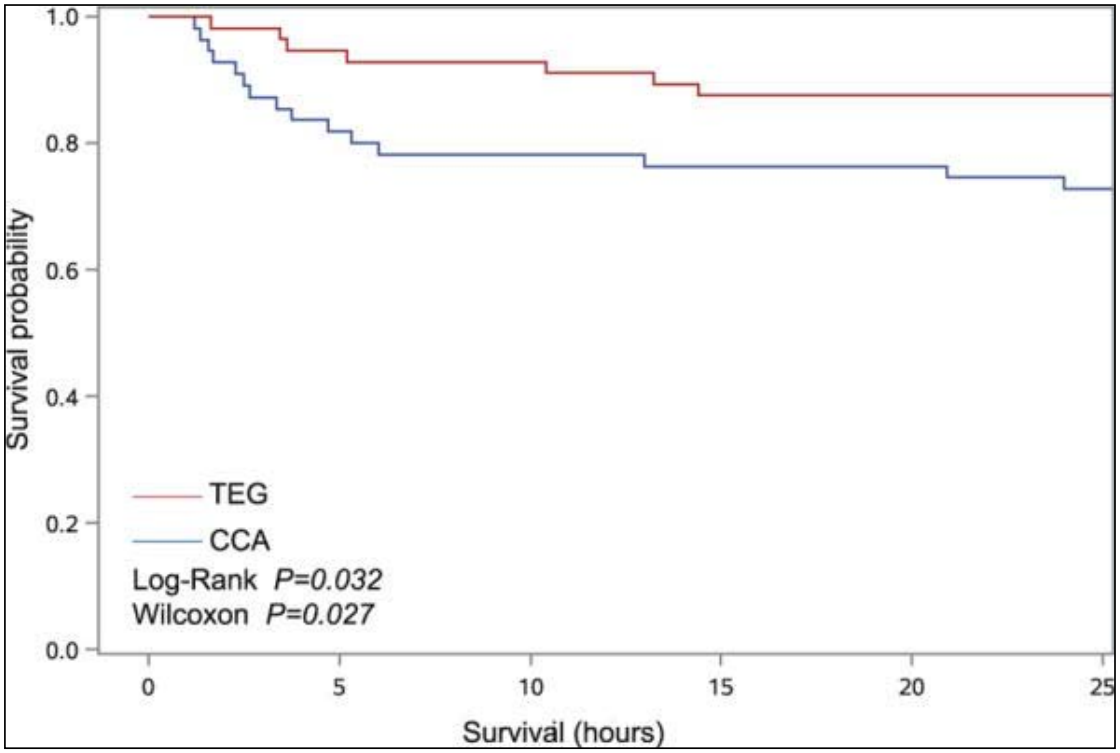
Outcome	Fibrinogen concentrate arm ($n = 24$)	Placebo arm ($n = 24$)	Overall ($n = 48$)	p Value
Fibrinogen, mean (SD)				
At admission	1.6 (0.7)	2.1 (0.9)	1.9 (0.8)	n/a
At 2 h from admission during first active haemorrhage[a]	2.8 (1.3)	1.8 (0.6)	2.3 (1.1)	< 0.0001
7 days from admission	6.7 (1.8)	7.5 (1.9)	7.1 (1.9)	0.2843

[a]*P* value adjusted for value at admission

Curry *et al. Critical Care* (2018) 22:164
https://doi.org/10.1186/s13054-018-2086-x


HAEMONETICS
TEG 6s


ROTEM
All take your positions!
Time to enter the sigma device station!
ROTEM



RANDOMIZED CONTROLLED TRIAL

Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

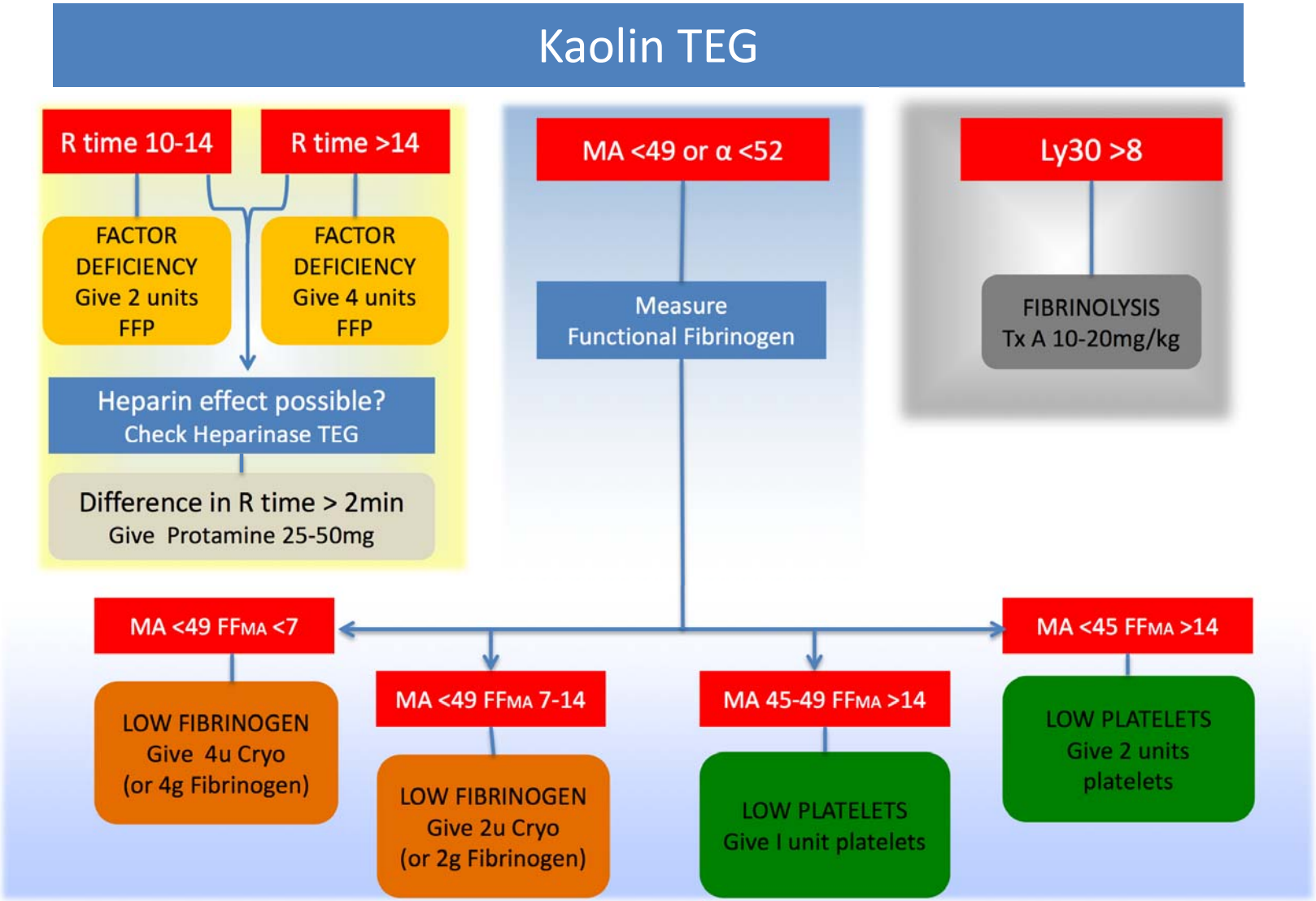
A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays

Eduardo Gonzalez, MD, Ernest E. Moore, MD,*† Hunter B. Moore, MD,* Michael P. Chapman, MD,* Theresa L. Chin, MD,* Arsen Ghasabyan, MPH,* Max V. Wohlauer, MD,* Carlton C. Barnett, MD,*† Denis D. Bensard, MD,*† Walter L. Biffl, MD,*† Clay C. Burlew, MD,*† Jeffrey L. Johnson, MD,*† Fredric M. Pieracci, MD, MPH,*† Gregory J. Jurkovich, MD,*† Anirban Banerjee, PhD,* Christopher C. Silliman, MD, PhD,*‡§ and Angela Sauaia, MD, PhD*¶*

FIGURE 1 . Kaplan-Meier estimates of survival by randomization group for patients analyzed as intention-to-treat. Survival in the TEG group was significantly higher than the CCA group (log-rank P = 0.0324, Wilcoxon P = 0.0275).


Patient ID: HUX8660
Amplitude (mm)
100
80
60
40
20
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
Time (min)
TEG-ACT R K ANGLE MA LY30 FLEV
8/1/2017 1:51 PM CM Citrated K,KH,RT,FF TEG 6s
Add Note
CK 10.7 3.4 55.0 --- ---
CRT 144.0 1.0 1.6 68.6 52.6 ---
CKH 10.4 1.7 69.5 ---
CFF 22.9 417.9

TEG ALGORITHM FOR MANAGEMENT OF BLEEDING PATIENTS



Trauma flowsheet in the Gold Coast

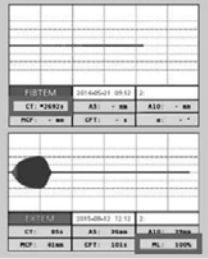
CRITICAL BLEEDING ROTEM TRANSFUSION ALGORITHM

GOLD COAST UNIVERSITY HOSPITAL

Physiological Targets: Temp >36°C pH >7.2 iCa >1 mmol/L Hb>70g/L

STEP 1: HYPERFIBRINOLYSIS

1



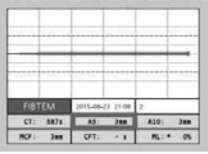
FIBTEM CT > 600 sec
AND
EXTEM A5 < 35 mm
→ TXA 1g + FIB CONC 4g

OR

ML% > 5%
→ TXA 1g

STEP 2: FIBRINOGEN

2



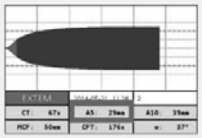
FIBTEM A5 ≤ 8 mm
→ FIB CONC 1g/25Kg BW

OR

FIBTEM A5 ≤ 10 mm
→ CRYO 1 Unit/5Kg BW

STEP 3: PLATELETS

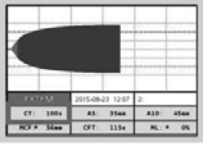
3



FIBTEM A5 > 10 mm
AND
EXTEM A5 ≤ 35 mm
→ PLATELETS 1 dose

STEP 4: FACTORS

4



FIBTEM A5 > 10 mm
AND
EXTEM CT ≥ 90 sec
→ PCC 10 IU/Kg
OR
FFP 2-4 Units

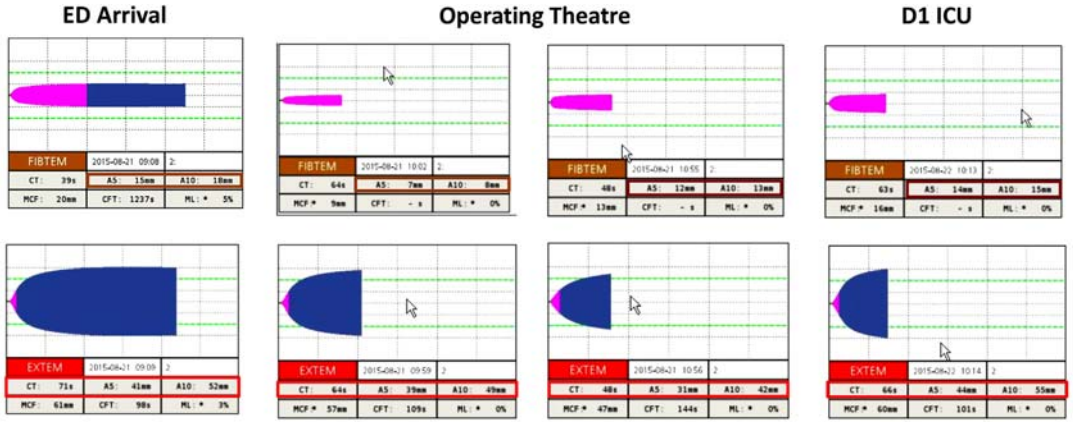
STEP 5: TARGETS

5

FIBTEM A10 > 15 mm AND EXTEM A10 > 45 mm AND EXTEM CT < 80 sec

ALWAYS repeat ROTEM tests 10 mins after treatment

Version 4.0 February 2016



Rotational thromboelastometry significantly optimizes transfusion practices for damage control resuscitation in combat casualties

Nicolas J. Prat, MD, PhD, Andrew D. Meyer, MD, Nichole K. Ingalls, MD, Julie Trichereau, MS, Joseph J. DuBose, MD, *and* **Andrew P. Cap, MD, PhD**, *San Antonio, Texas*

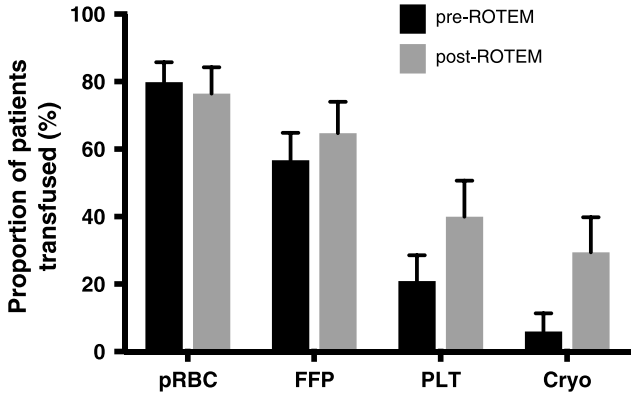


Figure 1. Percentage of transfused patients receiving 1+ unit of each product pre- and post-ROTEM. Data represented in percentage of total patients who received a transfusion over the pre- and post-3 month study period, n = 134 and n = 85, respectively.

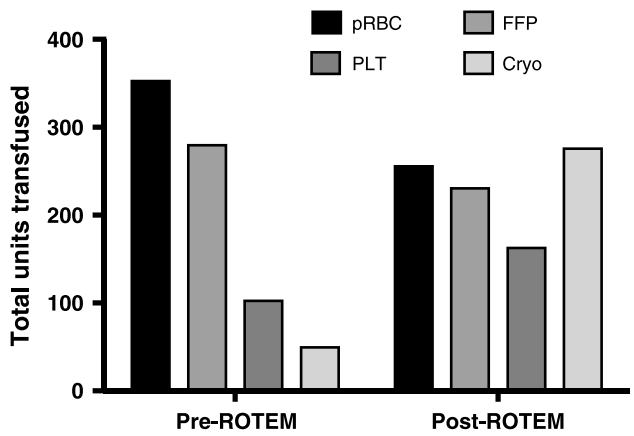


Figure 2. Total blood products (units) transfused in the pre- and post-ROTEM periods. Data represented as mean ± SD.

J Trauma Acute Care Surg
Volume 83, Number 3

Does changing from 1:1 to TEG guided change product use?

Patient history	Perform point-of-care and laboratory coagulation assays
1. Medication • Platelet inhibition • Heparin • Oral anticoagulation (vitamin-K antagonists, Xa or IIa inhibitors) 2. Available laboratory values 3. Past medical history (e.g.): • HIT • Von Willebrand disease • Liver disease	1. **ROTEM®** (EXTEM, INTEM, FIBTEM, APTEM), HEPTEM in case of heparin use 2. Laboratory coagulation • Anti-Xa (screening for heparin and Xa inhibitors) • TT (screening for dabigatran) • PT (screening for vitamin-K antagonists or factor deficiency), CoaguChek® • Factor V (liver failure or factor deficiency) • Factor XIII (factor deficiency) 3. Impedance aggregometry in case of platelet inhibition
Patient physiology (target values)	**Management**
Normothermia (≥ 35.0° C) Normocalcaemia (Ca^{2+} ≥ 1.15 mmol.l^{-1}) Normal acid-base status (pH > 7.2) Haematocrit (0.21-0.24) Permissive hypotension -MAP 55-65 mmHg prior to surgical / interventional source control -MAP 80-90 mmHg in case of TBI	Active warming Calcium i.v. Fluid resuscitation with balanced crystalloid solution. Gelatin may be considered RBC transfusion Permissive hypovolaemia / hypotension Vasopressors combined with volaemia correction
Detect low fibrinogen	**Management**
FIBTEM ≤ 7 mm	**Fibrinogen** 2-4 g i.v. (after 6 g of Fibrinogen, administer factor XIII, 15 U.kg^{-1} i.v.)
Detect fibrinolysis	**Management**
EXTEM / INTEM: Clot lysis after MCF and **APTEM**: normal = Hyperfibrinolysis	**Tranexamic acid** • Bolus: 15 mg.kg^{-1} i.v. (consider empiric use) • Consider continuous infusion 1 – 2 mg.kg^{-1}.h^{-1}
Ongoing bleeding	**Management**
Factor XIII activity < 60% **Platelet count/function** • **EXTEM / INTEM MCF < 40 mm** • **Platelet count** ≤ 50.000.μl^{-1} (≤ 100.000.μl^{-1} in cardiac surgery or TBI) • **Platelet function (Impedance aggregometry)** INR > 2.3 (Quick`s value < 30%) Factor V activity < 20%	Factor XIII 15 U.kg^{-1} i.v. Platelet concentrate Consider desmopressin 0.3 µg.kg^{-1} (max 16 µg) in case of aspirin (like) platelet dysfunction Four-factor prothrombin complex concentrate (slow continuous infusion of small repeated doses – e.g. 500 IU) FFP (2-4 units)
Detect heparin	**Antagonise heparin**
INTEM (CT/CFT) or ACT prolonged and **HEPTEM or heparinase-ACT** normal	**Protamine** (1:1) to antagonise heparin
Special circumstances	**Consider**
Seek haematologist advice	rFVIIa 60 mcg kg^{-1} von Willebrand factor concentrate Idarucizumab

Table 3 Administration of allogeneic blood products, coagulation factors and resuscitation fluids in the two cohorts (2005–2007 and 2012–2014). Values are number (proportion) and mean (SD).

	2005–2007 n = 323	2012–2014 n = 408	p value
RBC; units			
In ED	3.3 (6.3)	1.1 (3.9)	< 0.001
First 24 h	4.8 (7.8)	1.9 (6.1)	< 0.001
FFP; units			
In ED	2.4 (5.0)	0.3 (1.6)	< 0.001
First 24 h	3.4 (6.9)	1.0 (3.8)	< 0.001
Platelets; units			
In ED	0.2 (0.7)	0.1 (0.2)	0.40
First 24 h	0.3 (1.2)	0.3 (0.5)	0.68
FFP:RBC ratio			
In ED	0.6 (0.6)	0.1 (0.2)	< 0.001
First 24 h	0.6 (1.0)	0.4 (0.5)	< 0.001
Fibrinogen			
Administered	126 (39%)	135 (33%)	0.10
Dose; g	2.0 (3.3)	1.8 (4.0)	0.056
Prothrombin complex concentrate (four-factor)			
Administered	14 (4.3%)	37 (9%)	0.013
Dose; IU	46 (230)	116 (510)	0.013
Tranexamic acid	3 (0.9%)	203 (50%)	< 0.001
Factor XIII concentrate			
Administered	–	52 (13%)	< 0.001
Dose; IU	–	228 (714)	
Desmopressin	1 (0.3%)	4 (0.9%)	0.39
Recombinant coagulation factor VII a	10 (3.1%)	–	< 0.001
Crystalloid; ml	2836 (2473)	2672 (3094)	0.001
Colloid (starch); ml	1062 (1037)	36 (207)	< 0.001
Colloid (gelatin); ml	77 (402)	527 (1228)	< 0.001

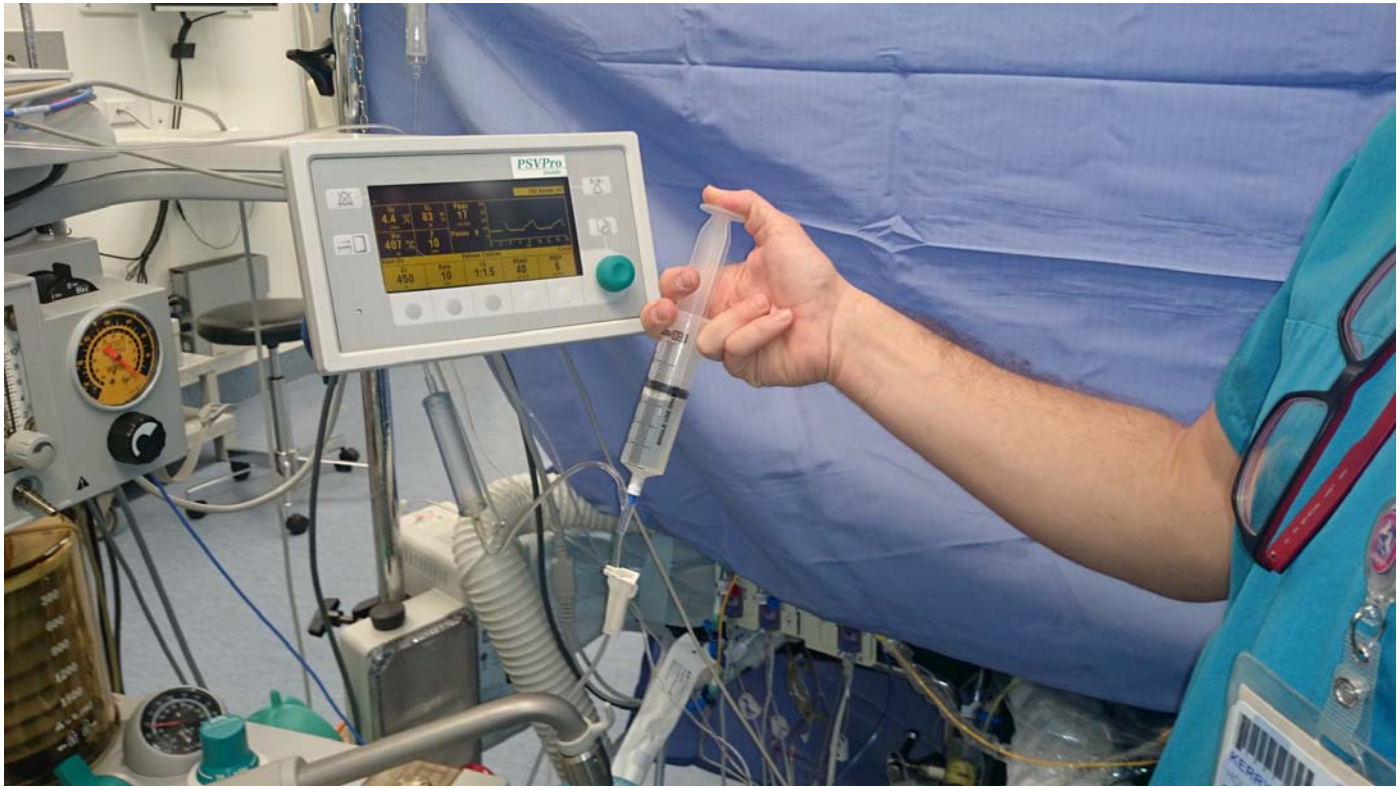
A p value of < 0.01 was considered significant.
RBC, red blood cells; FFP, fresh frozen plasma; ED, emergency department.

Anaesthesia. 2017 May 23. doi: 10.1111/anae.13920.

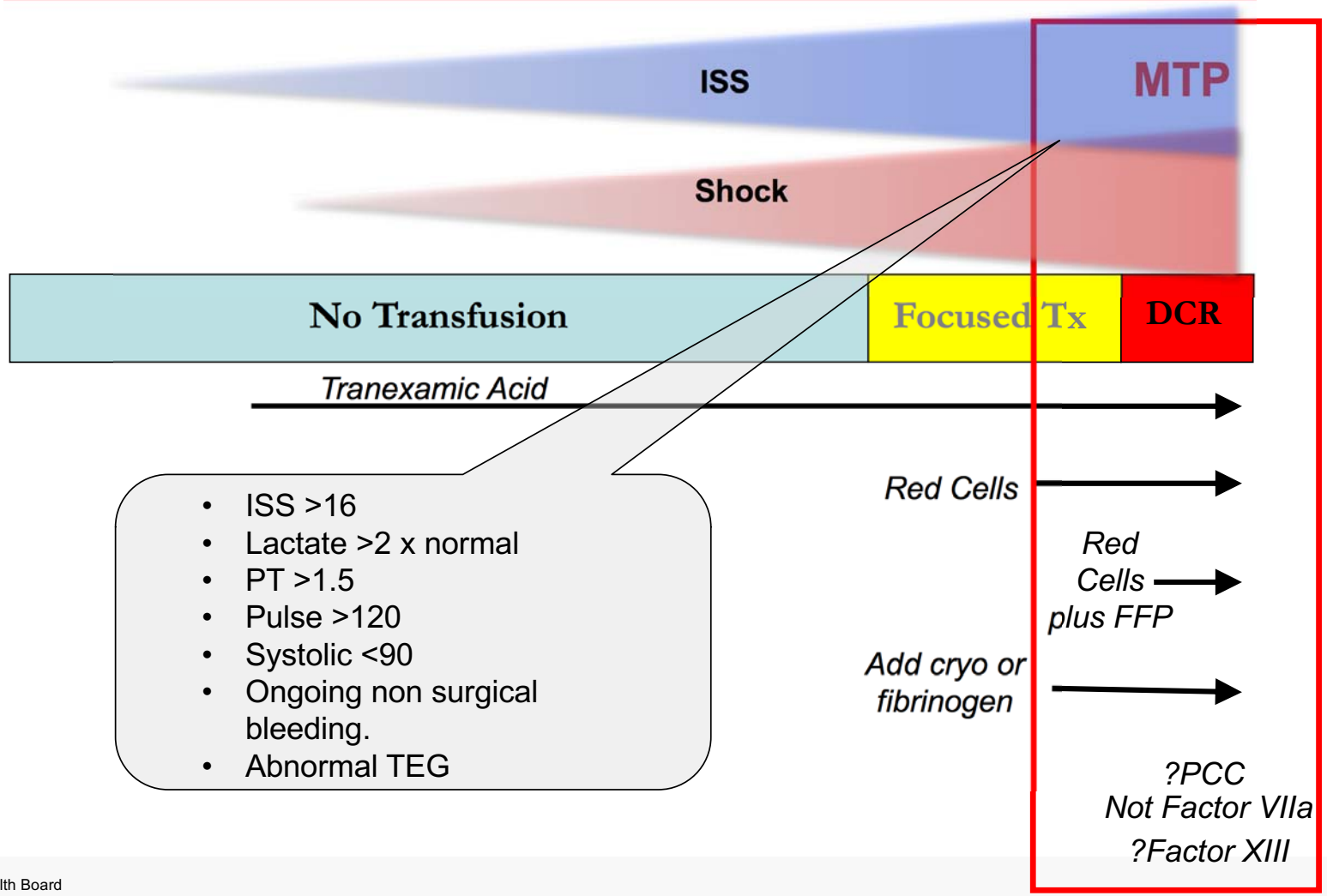

ROTEM
MULTIPLATE


NaCl
G-10
G-10
G-10
8.4%
M 15
1 g
Haemocomplettan® P
1 g
Haemocomplettan® P
1 g
Haemocomplettan® P
1 g
Fibrinogen
Haemocomplettan® P
Baxter
Prothromplex TOTAL
Baxter

FC Administration



Administer RiaSTAP® at room temperature by slow intravenous injection at a rate not exceeding 5 mL per minute.


ISS
MTP
Shock
No Transfusion
Focused Tx
DCR
Tranexamic Acid
Red Cells
Red Cells plus FFP
Add cryo or fibrinogen
?PCC
Not Factor VIIa
?Factor XIII
• ISS >16
• Lactate >2 x normal
• PT >1.5
• Pulse >120
• Systolic <90
• Ongoing non surgical bleeding.
• Abnormal TEG