

Evolution of Massive Transfusion Strategies



Kerry Gunn

Department of Anaesthesia and Perioperative Medicine
Auckland City Hospital

- ❑ Honorarium for Novo Nordisk to Chair Meetings

- ❑ A **small** proportion (4%) need an **aggressive** approach to transfusion
- ❑ Systems that include plasma (FFP) and platelets improve outcome
- ❑ The key component in plasma is **fibrinogen**
- ❑ The challenge is to develop **systems** that deliver fibrinogen rapidly enough to these patients
- ❑ The place of **Tranexamic Acid** in Trauma is evolving

- ❑ Unless we include POC monitoring of coagulopathy we risk replacing exsanguination with thrombosis

10 units RBC
in 4 hrs

No Transfusion

Focused Tx

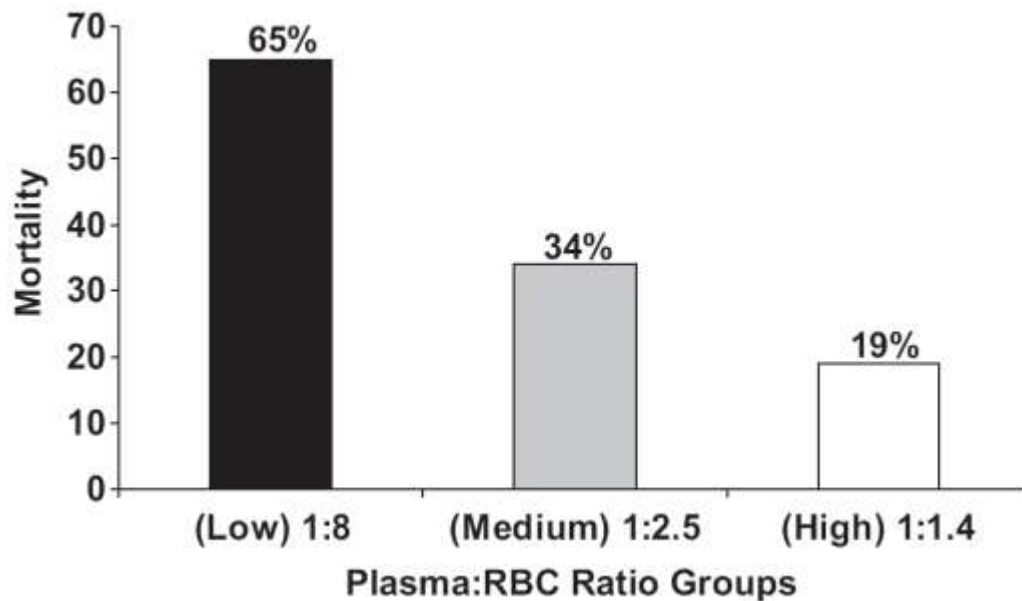
DCR

10 units RBC in
24 hrs



The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD



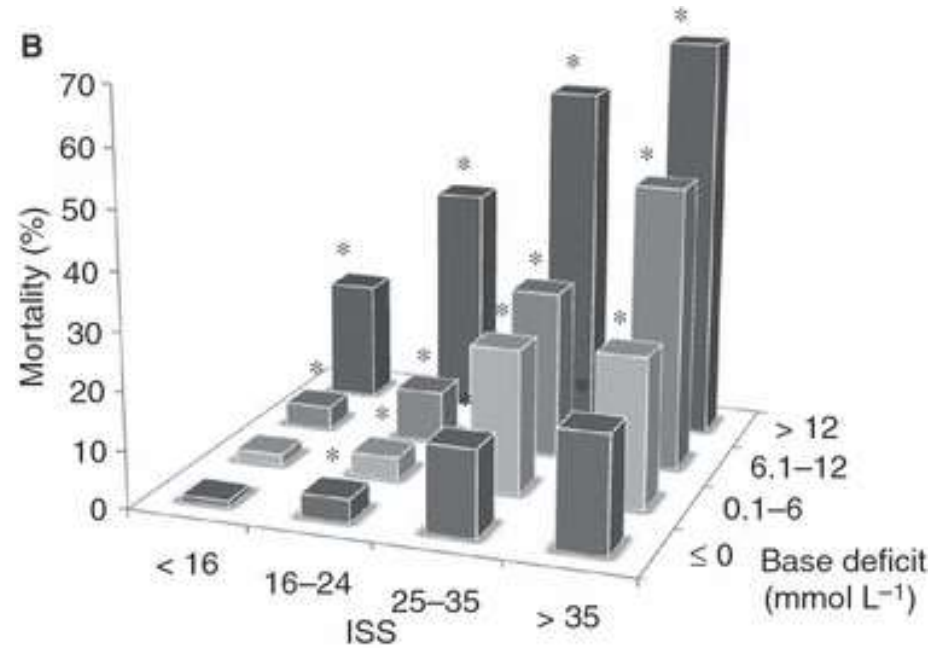
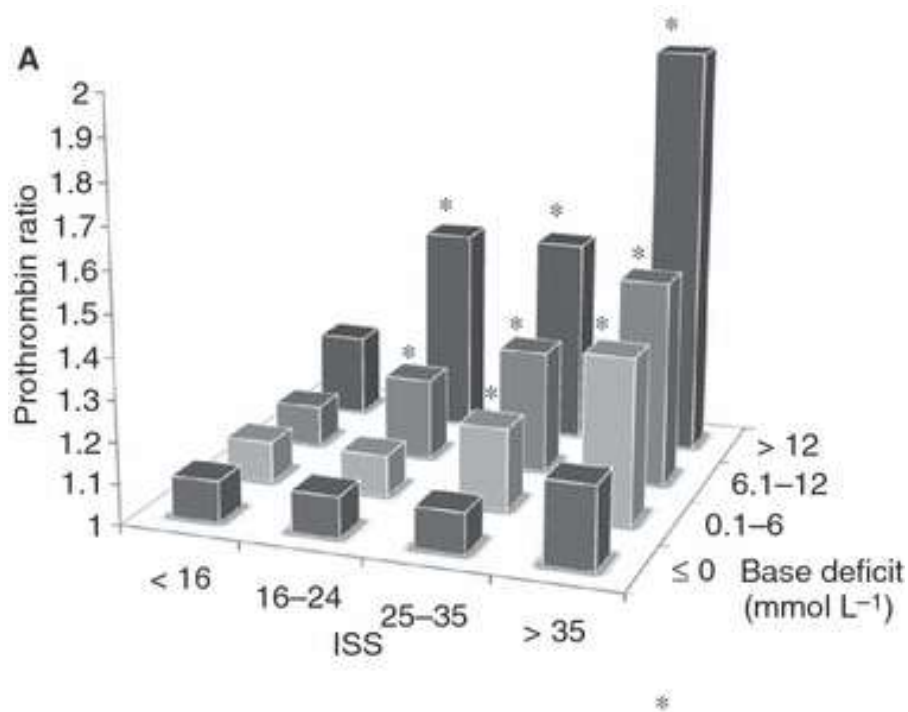
ORIGINAL ARTICLE

Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations

D. FRITH,^{*} J. C. GOSLINGS,[†] C. GAARDER,[‡] M. MAEGELE,[§] M. J. COHEN,[¶] S. ALLARD,^{**}
P. I. JOHANSSON,^{††} S. STANWORTH,^{‡‡} C. THIEMERMANN^{§§} and K. BROHI^{*}

**Trauma Clinical Academic Unit, The Royal London Hospital, Bart's & The London School of Medicine & Dentistry, Queen Mary University London, UK; †Trauma Unit Department of Surgery, Academic Medical Center, University of Amsterdam, Meibergdreef, Amsterdam, the Netherlands; ‡Trauma Unit, Oslo University Hospital, Ullevål, Oslo, Norway; §Department of Trauma and Orthopedic Surgery, Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie/German Trauma Society (TR-DGU), University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Cologne, Germany; ¶Department of Surgery, University of California, San Francisco, CA, USA; **Department of Haematology, Royal London Hospital, Bart's & The London School of Medicine & Dentistry, Queen Mary University London, UK; ††Capital Region Blood Bank, Section for Transfusion Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ‡‡National Health Service Blood & Transplant and Oxford Radcliffe Hospitals, John Radcliffe Hospital, Headington, Oxford, UK; and §§William Harvey Research Institute, Bart's & The London School of Medicine & Dentistry, Queen Mary University, London, UK*

Acute Traumatic Coagulopathy





**The coagulopathy is related to
SHOCK plus
TISSUE INJURY.**

ADHB Adult Massive Transfusion Protocol (MTP)

Massive bleeding with either shock or abnormal coagulopathy

Ensure delivery of X-match specimen to Blood Bank

Give 3 Units O-neg or type specific RBC

Ring Blood Bank to Activate Massive Transfusion Protocol

REQUEST, DELIVER AND TRANSFUSE AS BELOW:

TXA 1G

MTP BOX ONE
2 Whole Blood or 2U RBC and 2U FFP

Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

MTP BOX TWO
4 RBC
4 FFP
1 adult Platelets

MTP BOX THREE
4 RBC
4 FFP
+ 3U Cryoprecipitate

Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

rVIIa
90 mcg/kg
if indicated

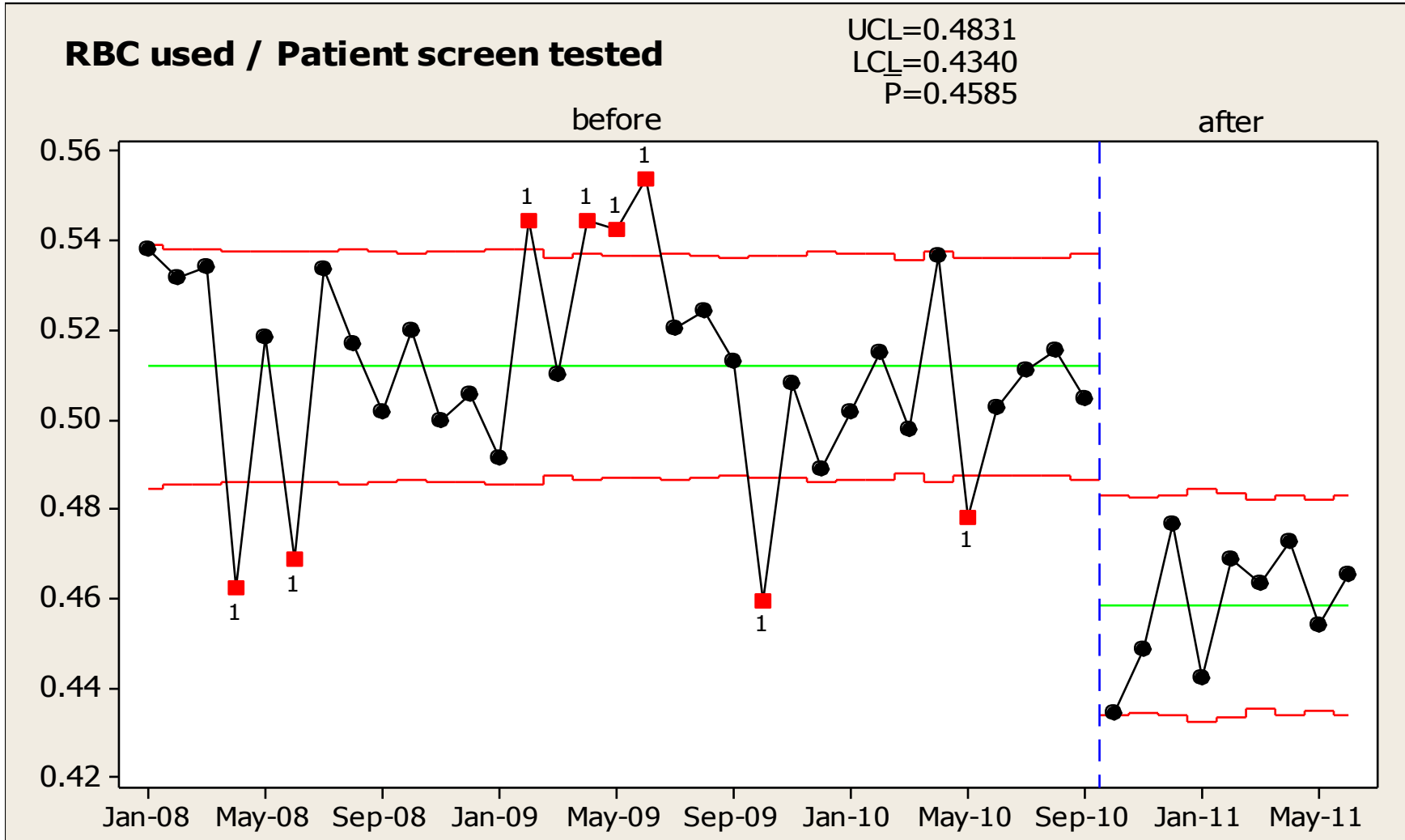
MTP BOX FOUR
4 RBC
4 FFP
1 adult Platelets

Repeat every
30 min

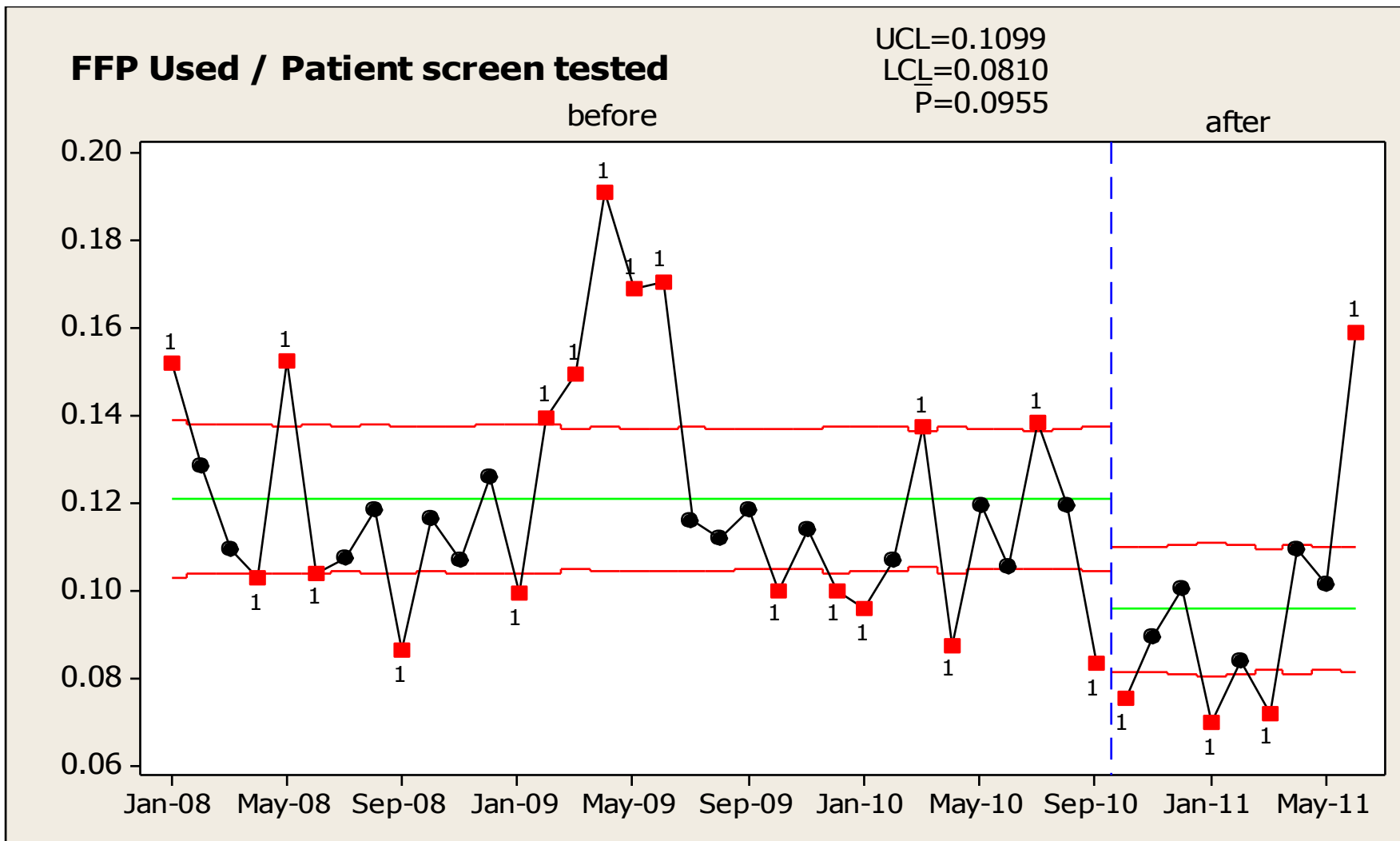
and alternate 3 &4...

Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

Use of red cells in ADHB



Use of FFP in ADHB



Initiating the Massive Transfusion Protocol

	ABC¹	TASH²	McLauchlin³
ED pulse	> 120	> 120	> 105
Systolic BP	< 90	< 100	< 110
BE		-2 to -10	
pH			< 7.2
Hb		7 - 12	< 9.6
FAST	+	+	
Male		+	
Penetrating	+		
Unstable pelvic # or femoral #		+	

1. *J Trauma* 2009;66: 346-3522. *J Trauma* 2006;60:1228-1236

3 *J Trauma* 2008: 64 S57-S63

ADHB Adult Massive Transfusion Protocol (MTP)

Massive bleeding with either shock or abnormal coagulopathy

Ensure delivery of X-match specimen to Blood Bank

Give 3 Units O-neg or type specific RBC

Ring Blood Bank to Activate Massive Transfusion Protocol

REQUEST, DELIVER AND TRANSFUSE AS BELOW:

TXA 1G

MTP BOX ONE
2 Whole Blood or 2U RBC and 2U FFP

Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

MTP BOX TWO
4 RBC
4 FFP
1 adult Platelets

MTP BOX THREE
4 RBC
4 FFP
+ 3U Cryoprecipitate

Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

MTP BOX FOUR
4 RBC
4 FFP
1 adult Platelets

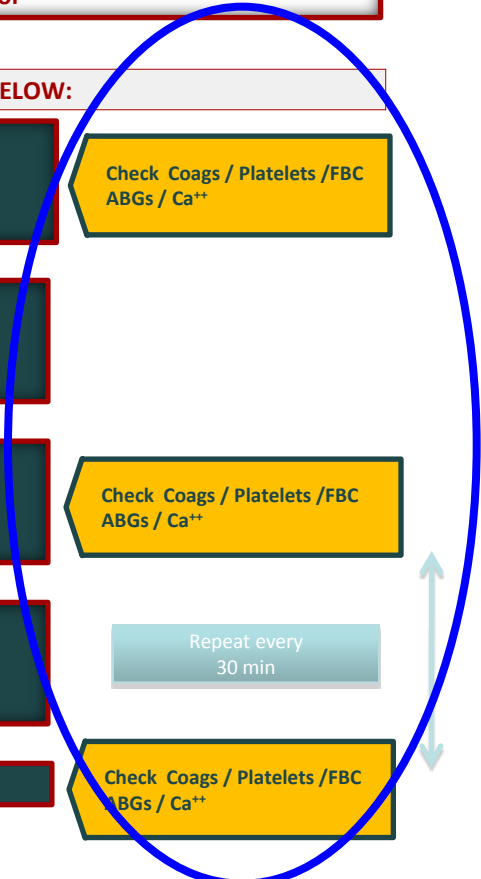
Repeat every
30 min

and alternate 3 &4...

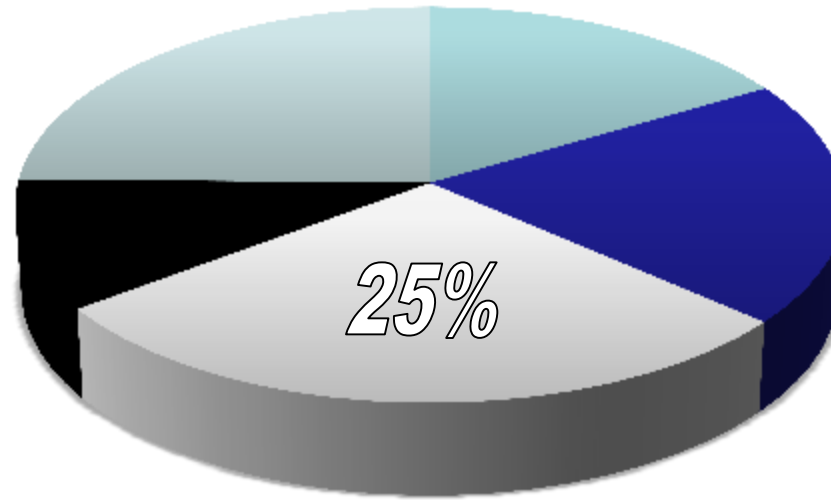
Check Coags / Platelets /FBC
ABGs / Ca⁺⁺

rVIIa
90 mcg/kg
if indicated

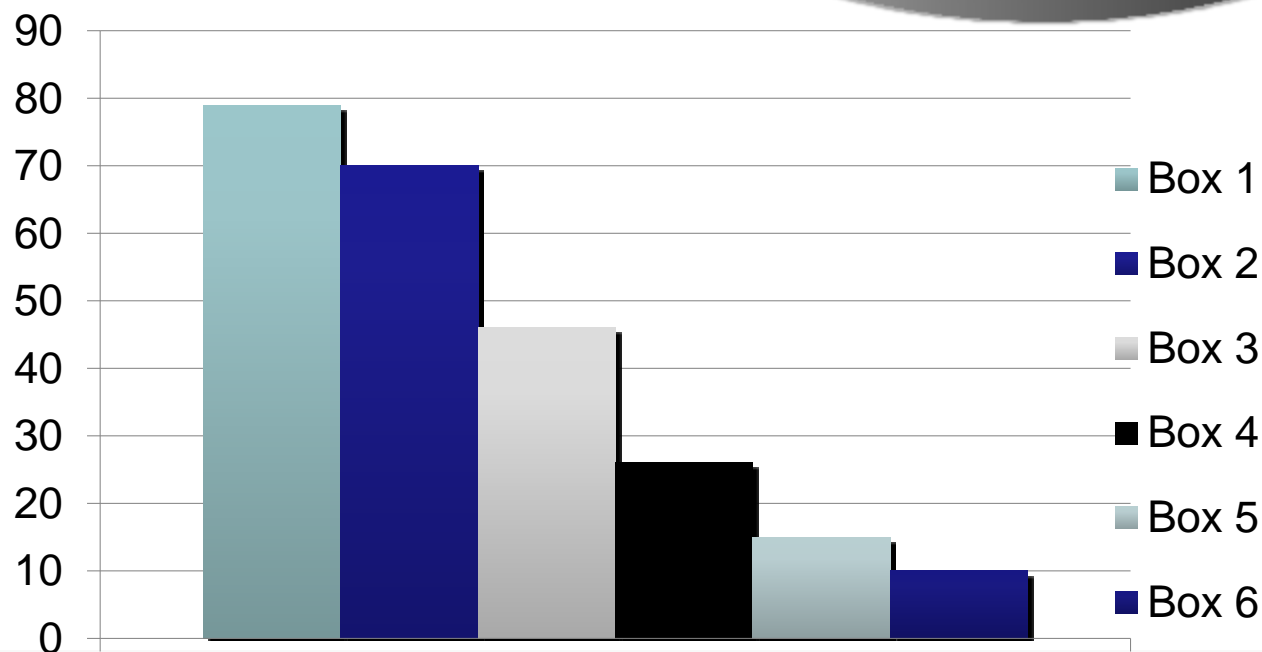
*Ratio of protocol 1:1
Ratio of delivery 1:1.4*



MTP: 86 activations

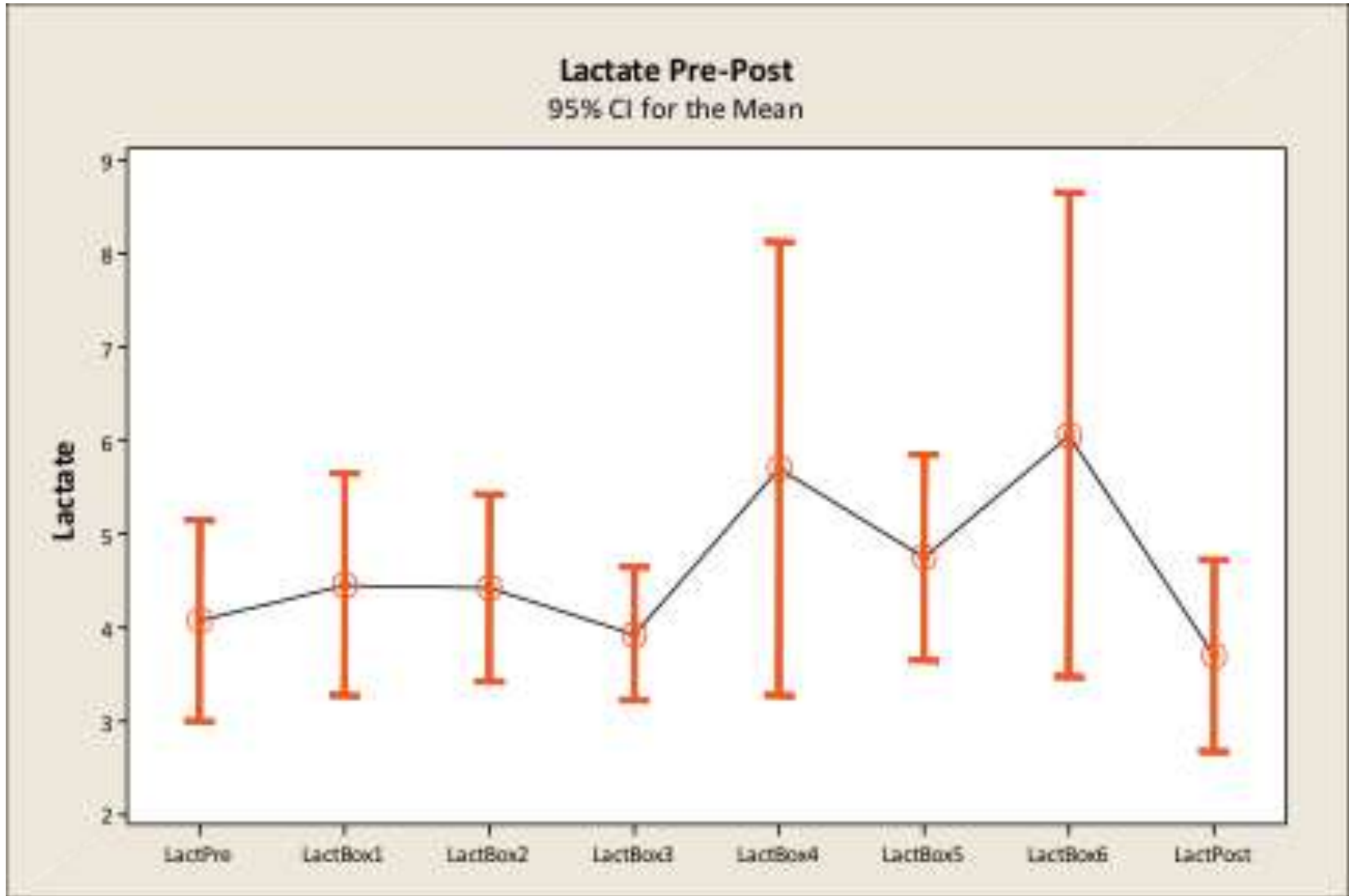


- Surgical
- Medical
- Obstetrics
- Vascular
- Trauma

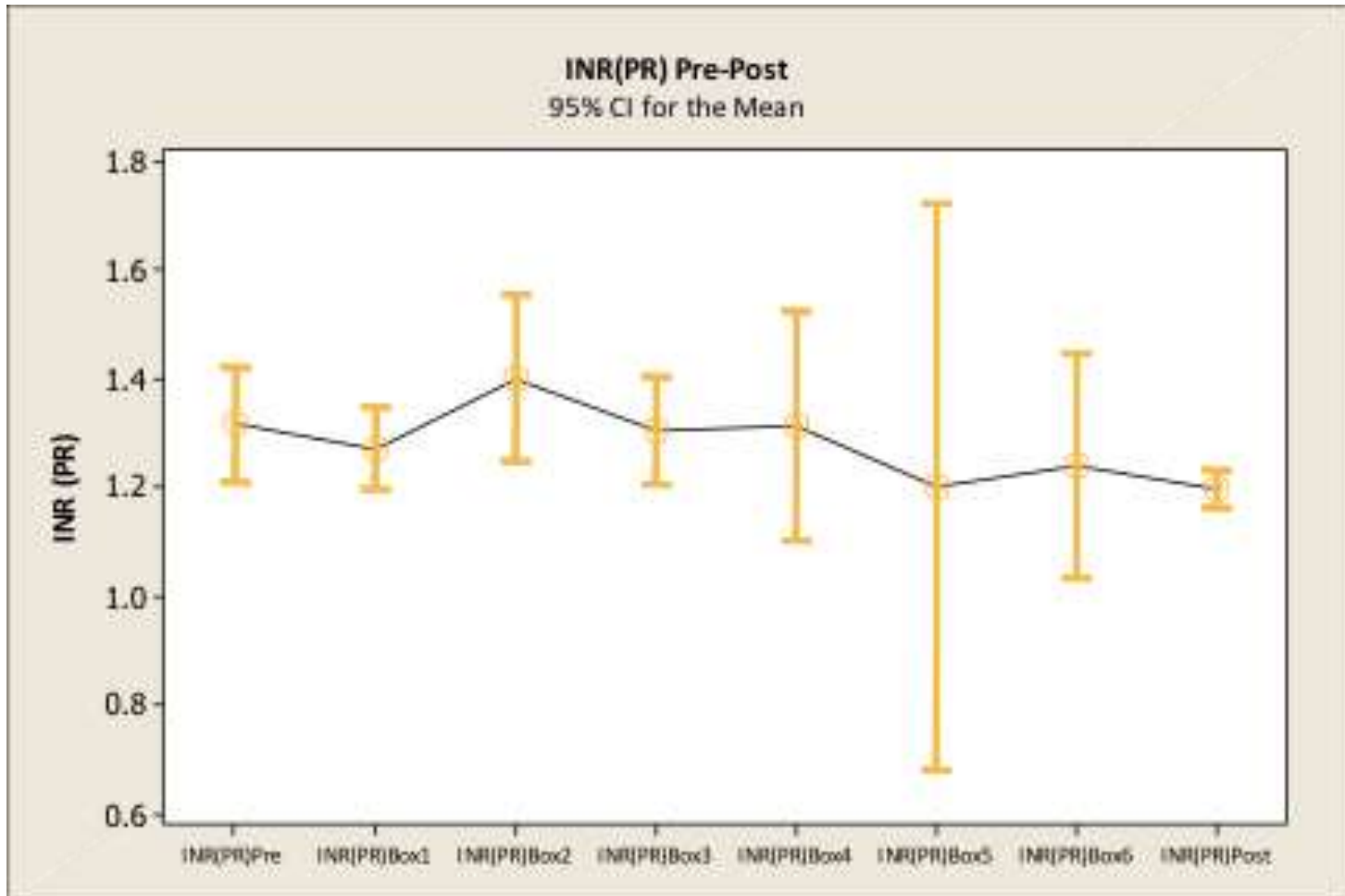


- Box 1
- Box 2
- Box 3
- Box 4
- Box 5
- Box 6

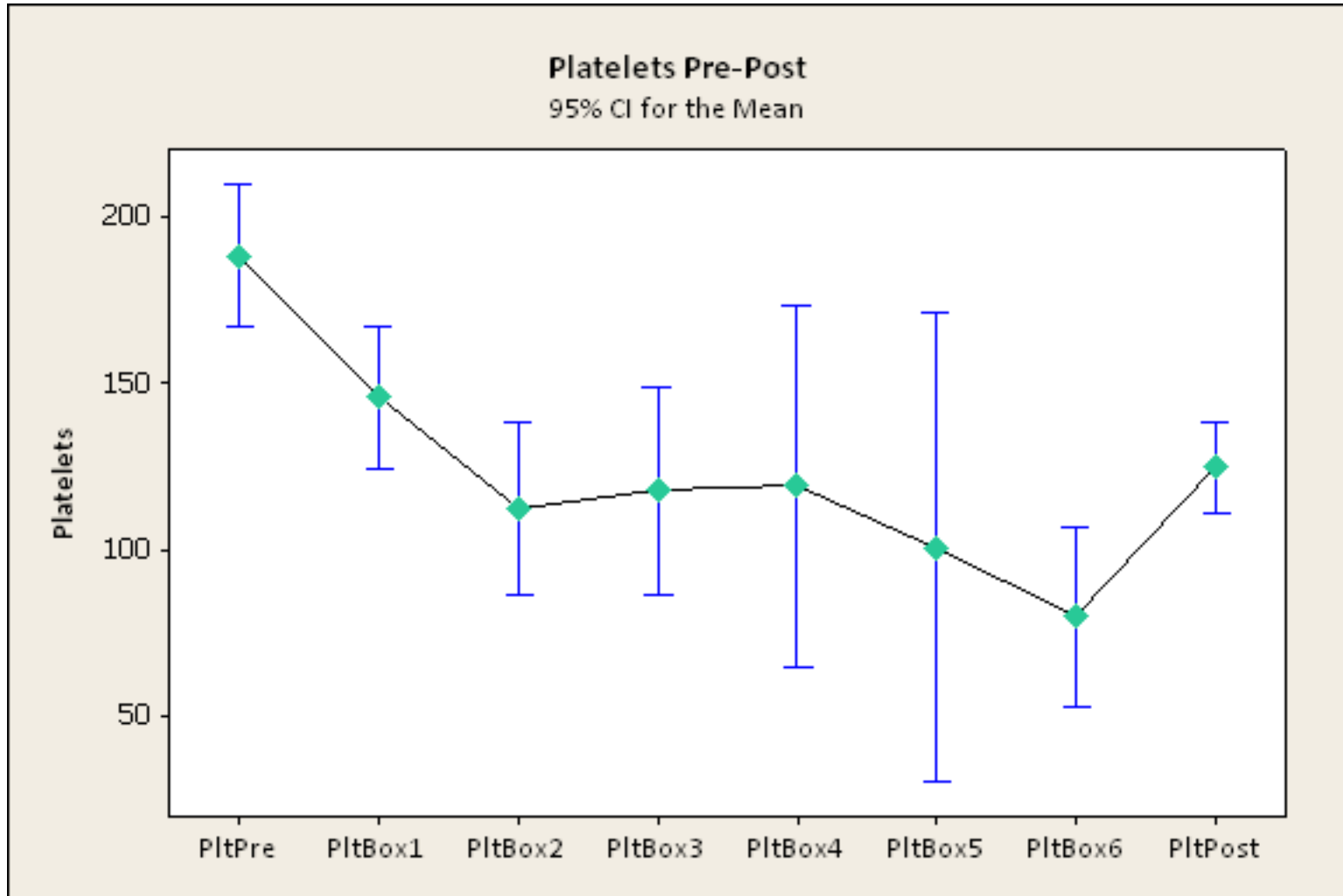
Auckland MTP : Lactate



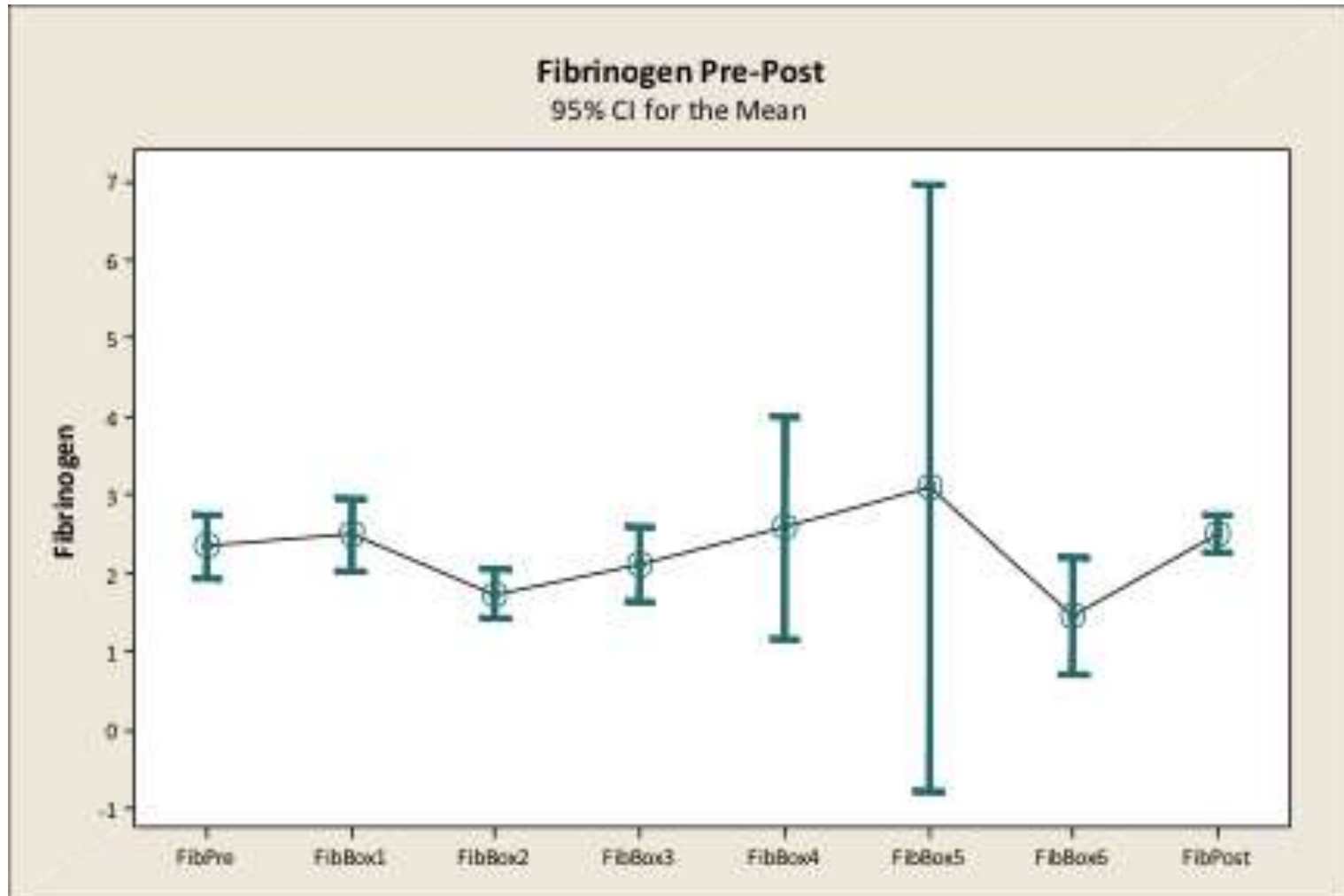
Auckland MTP: INR



Auckland MTP Audit



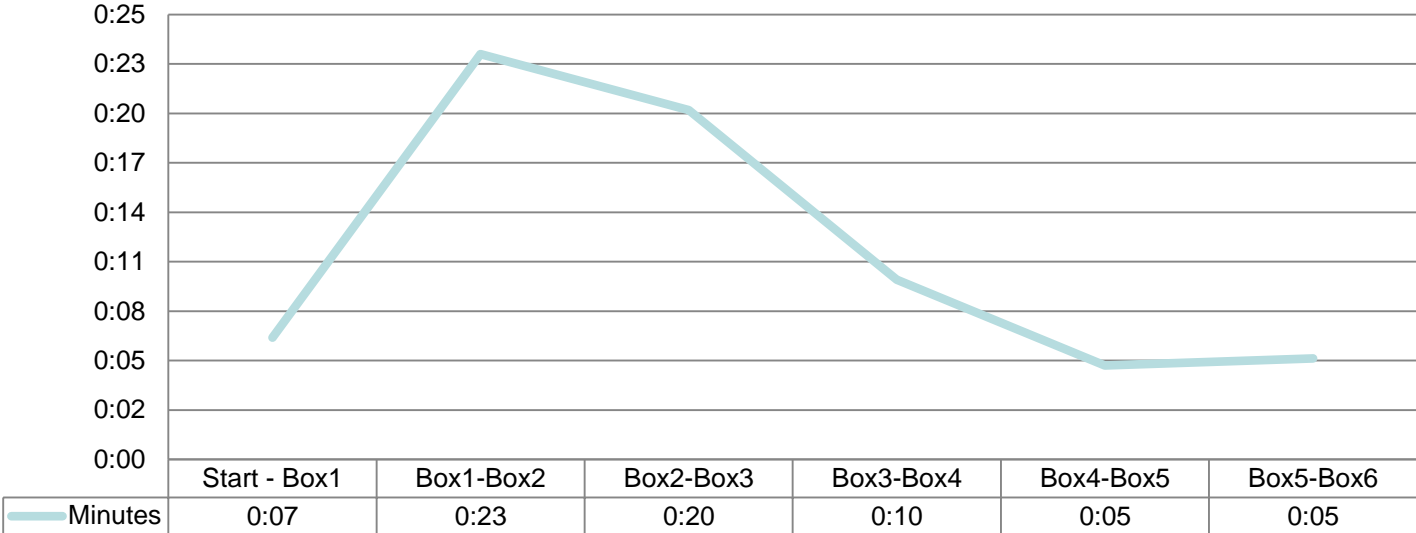
Auckland MTP : fibrinogen



Response time in Auckland to MTP activation



Mean - Minutes between events/boxes





- ❑ Trauma Outcomes Group
 - ❑ Prospective but not randomised data
- ❑ 22 Level 1 units
 - ❑ 2213 patients
 - ❑ 645 received >10U

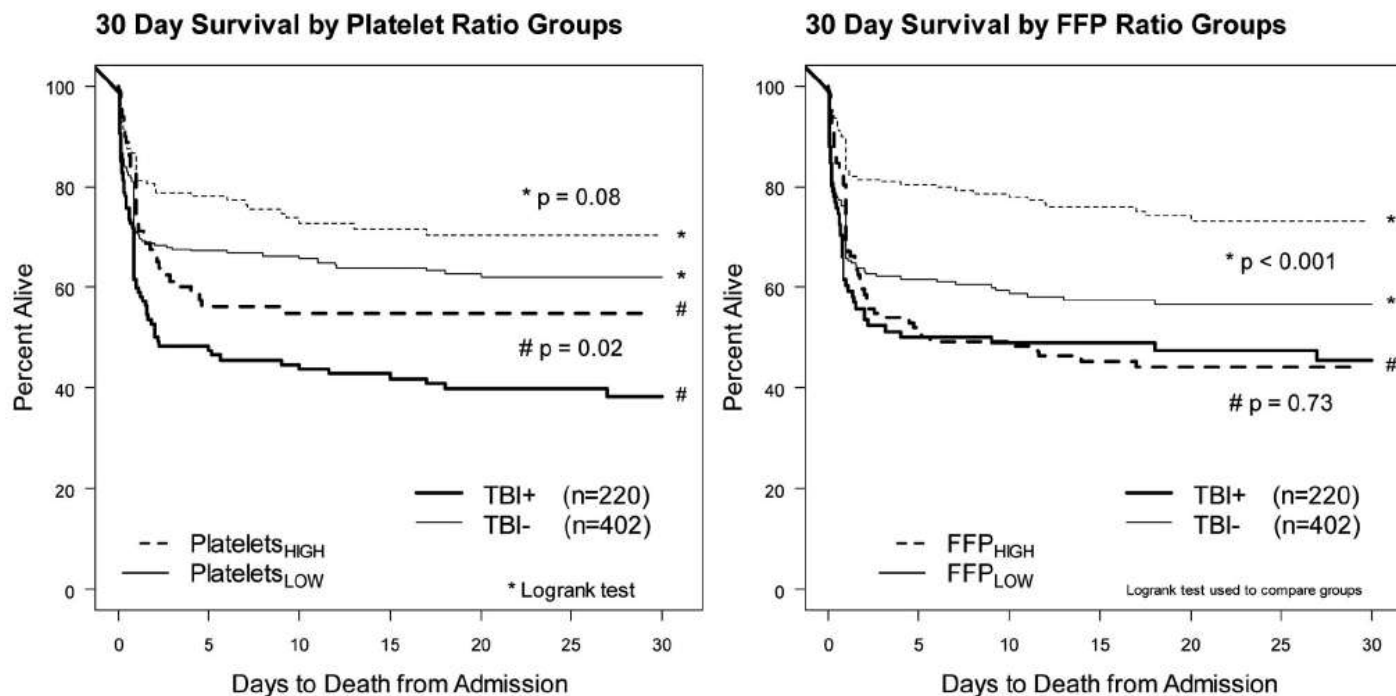
ORIGINAL ARTICLE

High Ratios of Plasma and Platelets to Packed Red Blood Cells Do Not Affect Mortality in Nonmassively Transfused Patients

Chitra N. Sambasivan, MD, Nicholas R. Kunio, MD, Prakash V. Nair, MS, Karen A. Zink, MD, Joel E. Michalek, PhD, John B. Holcomb, MD, Martin A. Schreiber, MD, and the Trauma Outcomes Group

ORIGINAL ARTICLE

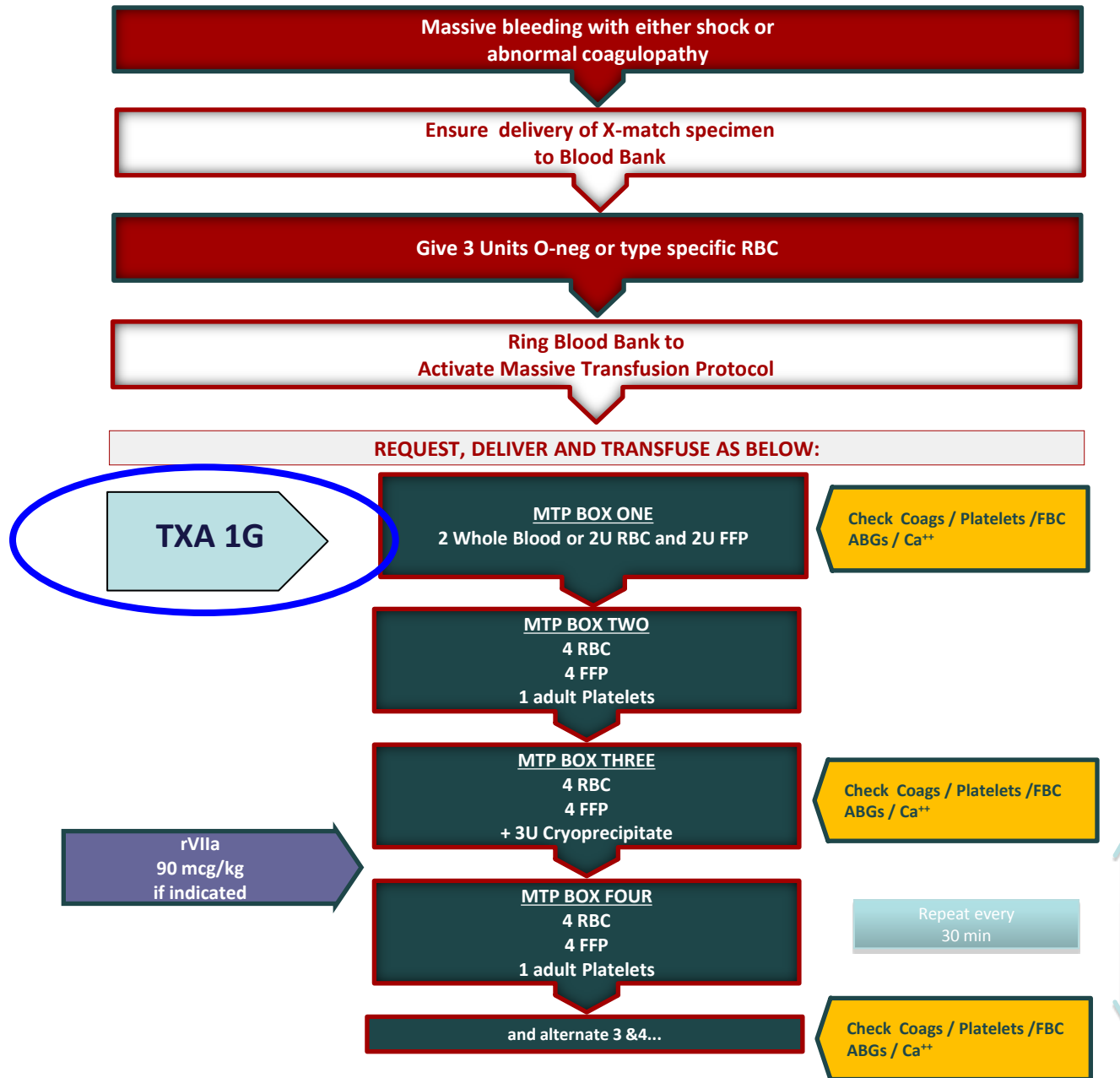
The Association of Blood Component Use Ratios With the Survival of Massively Transfused Trauma Patients With and Without Severe



Abbreviations: Platelets_{High}, Platelet:RBC \geq 1:2, Platelets_{low}, Platelet:RBC < 1:2; FFP_{High}, FFP:RBC \geq 1:2, FFP_{low}, FFP:RBC < 1:2; TBI+, Head Abbreviated Injury Score \geq 3; TBI-, Head Abbreviated Injury Score < 3; min

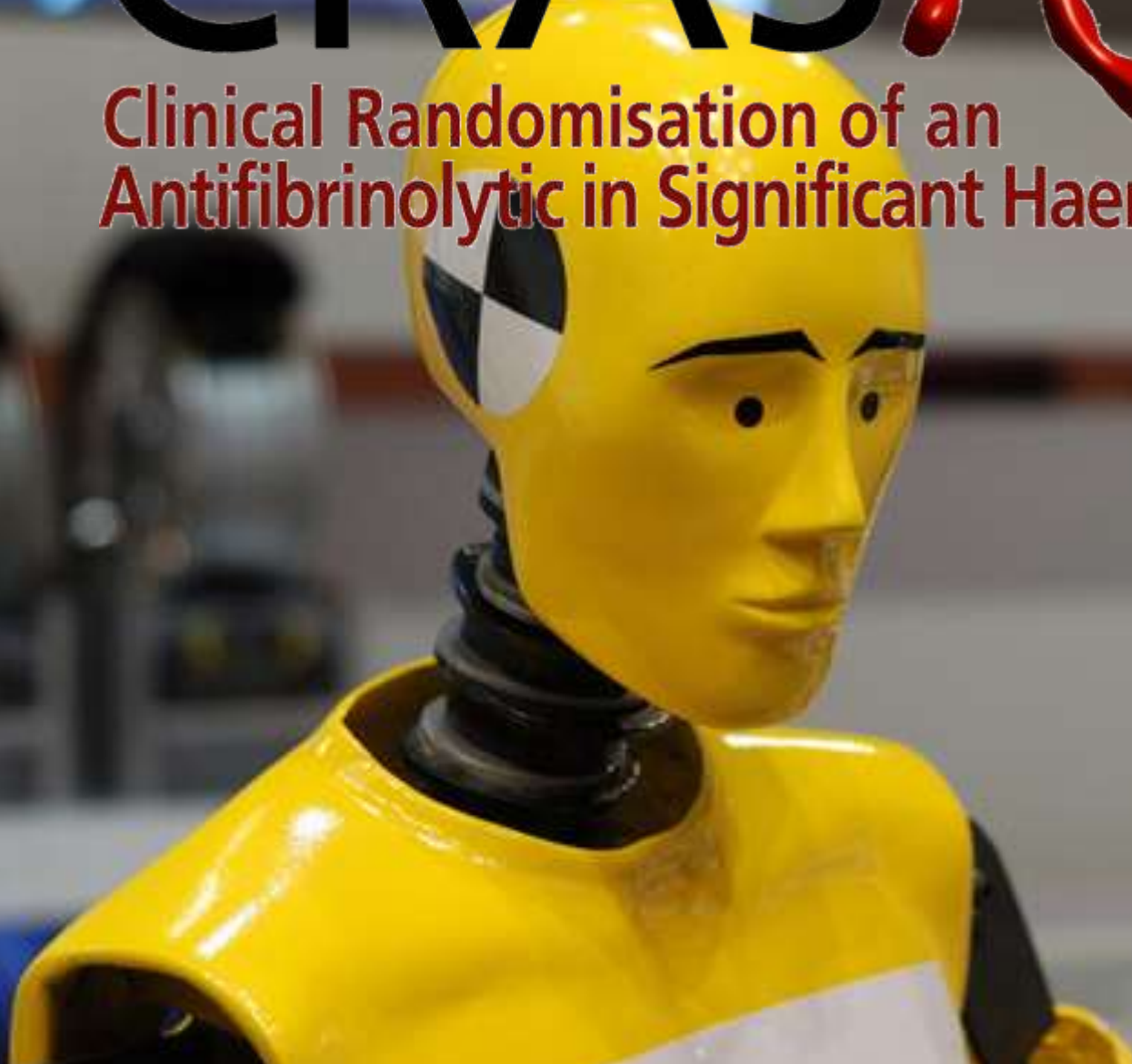
Figure 3. Kaplan-Meier curves for the \geq 10 units RBC in 24-hour groups.

ADHB Adult Massive Transfusion Protocol (MTP)



CRAASH₂

Clinical Randomisation of an
Antifibrinolytic in Significant Haemorrhage





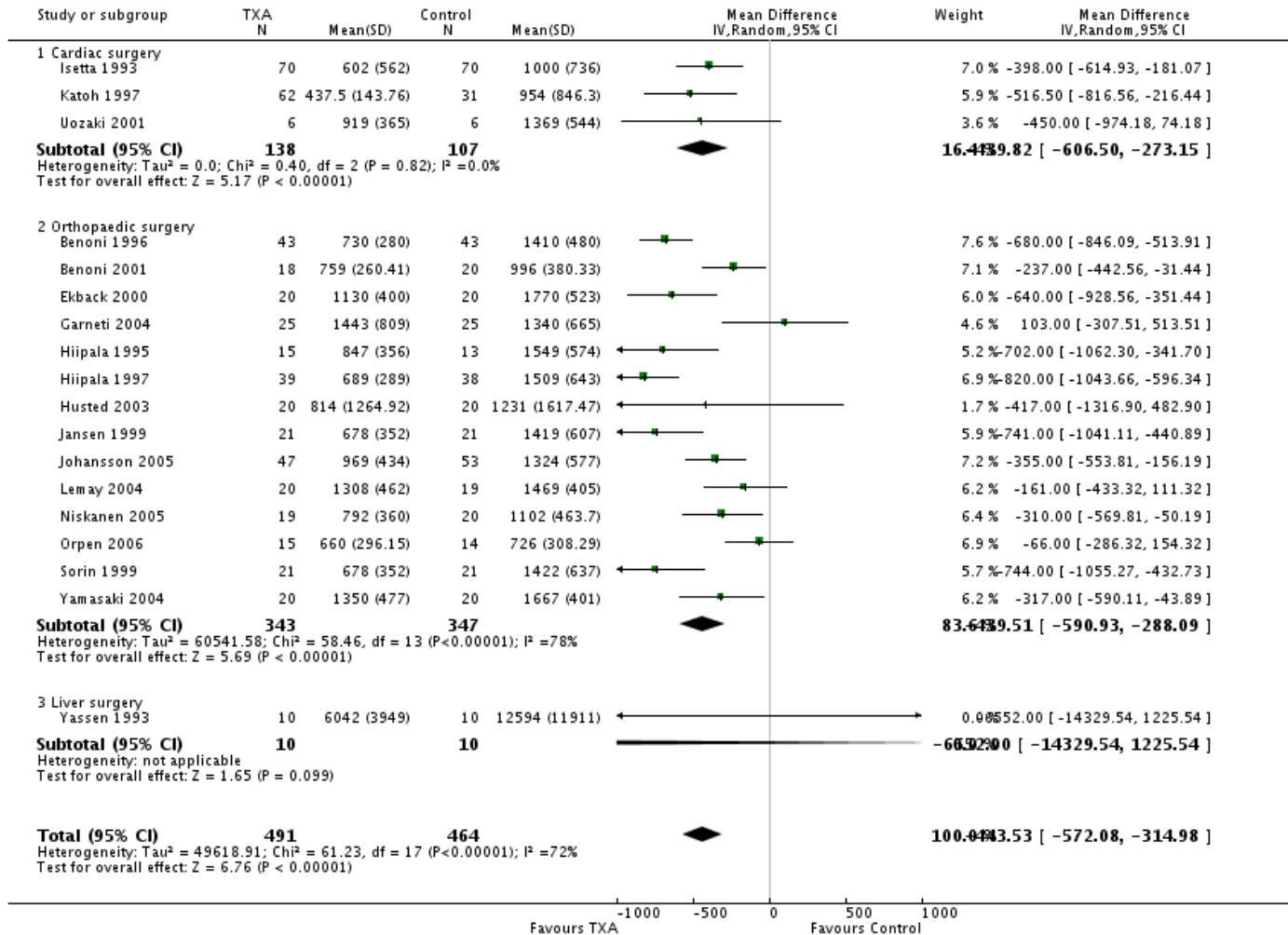
5 ml = 500 mg
Cyklokapron®
100 mg/ml
Tranexamic acid
for intravenous
injection or infusion
Do not store above 25°C
Protect from freezing



CYKLOKAPRON®
100 mg/ml
TRANEXAMIC ACID
Pfizer
5 ml = 500 mg
E.g. intravenous injection

TXA in elective surgery: metaanalysis

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion
 Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss)
 Outcome: 11 Blood loss - Total



Henry DA et al., Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2007



Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

274 hospitals in 40 countries

20,211 patients

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trials Register DOH-27-0607-1919.

Death at 4 weeks

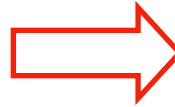
Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035). The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077).

Results

	Tranexamic acid (n=10060)	Placebo (n=10067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14.5%)	1613 (16.0%)	0.91 (0.85-0.97)	0.0035
Bleeding	489 (4.9%)	574 (5.7%)	0.85 (0.76-0.96)	0.0077
Vascular occlusion*	33 (0.3%)	48 (0.5%)	0.69 (0.44-1.07)	0.096
Multiorgan failure	209 (2.1%)	233 (2.3%)	0.90 (0.75-1.08)	0.25
Head injury	603 (6.0%)	621 (6.2%)	0.97 (0.87-1.08)	0.60
Other causes	129 (1.3%)	137 (1.4%)	0.94 (0.74-1.20)	0.63

- 15% reduction in haemorrhagic death
- NN to avoid one hospital death 68
- Vascular occlusive events not increased

Male



2/3 blunt

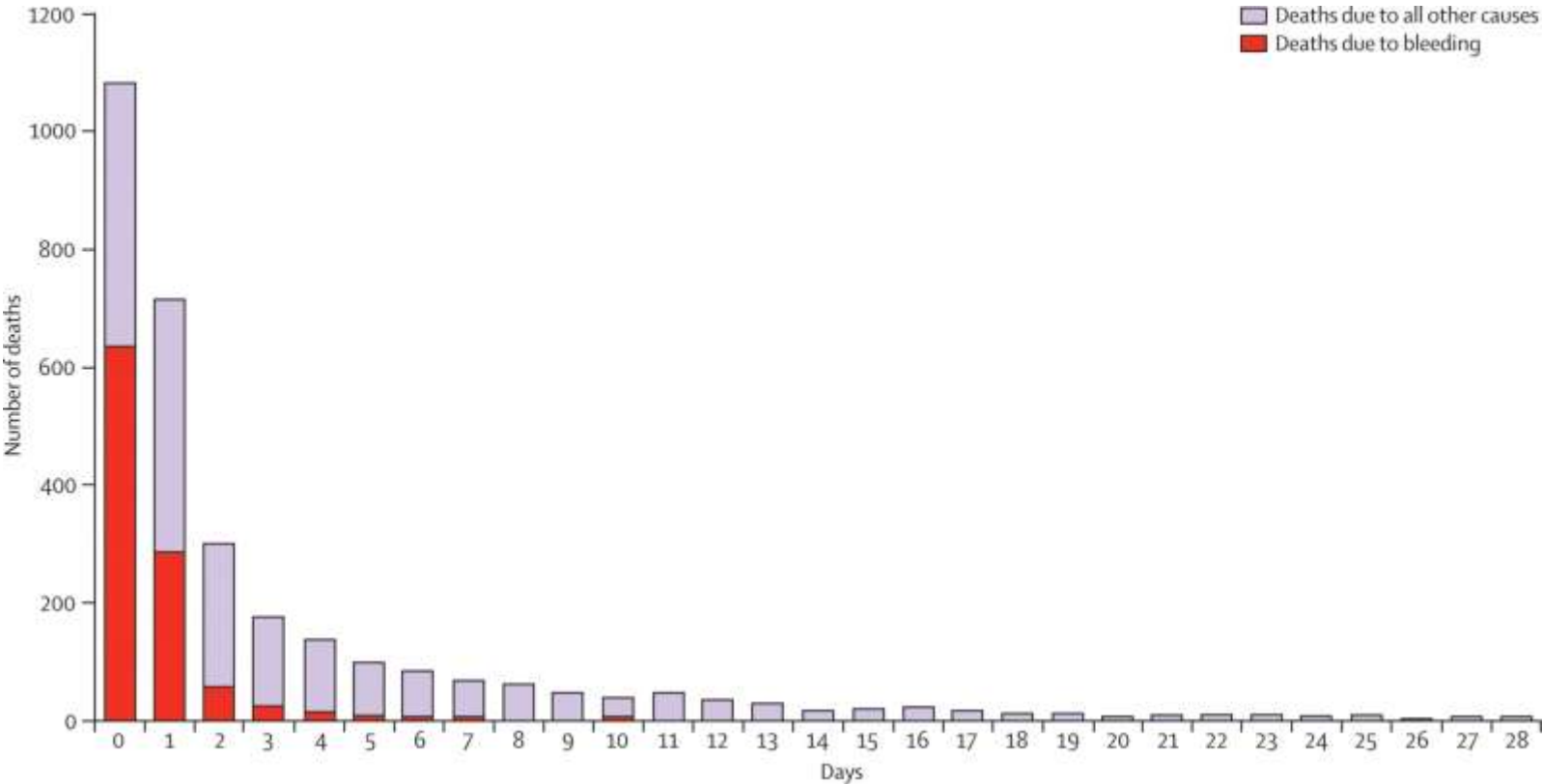


Head injuries



	Tranexamic acid (n=10 093)	Placebo (n=10 114)
Sex		
Men	8439 (83.6%)	8496 (84.0%)
Women	1654 (16.4%)	1617 (16.0%)
Not known	0	1 (0.01%)
Age (years)		
Mean (SD)	34.6 (14.1)	34.5 (14.4)
<25*	2783 (27.6%)	2855 (28.2%)
25-34	3012 (29.8%)	3081 (30.5%)
35-44	1975 (19.6%)	1841 (18.2%)
>44	2321 (23.0%)	2335 (23.1%)
Not known	2 (0.02%)	2 (0.02%)
Time since injury (h)		
Mean (SD)	2.8 (2.2)	2.9 (2.6)
≤1	3756 (37.2%)	3722 (36.8%)
>1-≤3	3045 (30.2%)	3006 (29.7%)
>3†	3287 (32.6%)	3380 (33.4%)
Not known	5 (0.05%)	6 (0.06%)
Type of injury		
Blunt‡	6812 (67.5%)	6843 (67.7%)
Penetrating	3281 (32.5%)	3271 (32.3%)
Systolic blood pressure (mm Hg)		
≤75	1566 (15.5%)	1608 (15.9%)
76-89	1615 (16.0%)	1697 (16.8%)
≥90	6901 (68.4%)	6791 (67.1%)
Not known	11 (0.11%)	18 (0.18%)
Respiratory rate (per min)		
<10	160 (1.6%)	149 (1.5%)
10-29	8355 (82.8%)	8436 (83.4%)
>29	1491 (14.8%)	1429 (14.1%)
Not known	87 (0.86%)	100 (0.99%)
Central capillary refill time (s)		
≤2	3432 (34.0%)	3406 (33.7%)
3-4	4665 (46.2%)	4722 (46.7%)
>4	1699 (16.8%)	1672 (16.5%)
Not known	297 (2.9%)	314 (3.1%)
Heart rate (beats per min)		
<77	875 (8.7%)	871 (8.6%)
77-91	1727 (17.1%)	1770 (17.5%)
92-107	2556 (25.3%)	2546 (25.2%)
>107	4872 (48.3%)	4853 (48.0%)
Not known	63 (0.62%)	74 (0.73%)
Glasgow Coma Score (total)		
Severe (3-8)	1799 (17.8%)	1839 (18.2%)
Moderate (9-12)	1353 (13.4%)	1351 (13.4%)
Mild (13-15)	6934 (68.7%)	6908 (68.3%)
Not known	7 (0.07%)	16 (0.16%)
Any protocol violation	39 (0.4%)	39 (0.4%)

Mortality per day after injury



About 2 %

	Tranexamic acid (n=10 060)	Placebo (n= 10 067)	RR (95% CI)	p value
Vascular occlusive events*				
Any vascular occlusive event	168 (1.7%)	201 (2.0%)	0.84 (0.68–1.02)	0.084
Myocardial infarction	35 (0.3%)	55 (0.5%)	0.64 (0.42–0.97)	0.035
Stroke	57 (0.6%)	66 (0.7%)	0.86 (0.61–1.23)	0.42
Pulmonary embolism	72 (0.7%)	71 (0.7%)	1.01 (0.73–1.41)	0.93
Deep vein thrombosis	40 (0.4%)	41 (0.4%)	0.98 (0.63–1.51)	0.91
Need for transfusion and surgery				
Blood product transfused	5067 (50.4%)	5160 (51.3%)	0.98 (0.96–1.01)	0.21
Any surgery	4814 (47.9%)	4836 (48.0%)	1.00 (0.97–1.03)	0.79
Neurosurgery	1040 (10.3%)	1059 (10.5%)	0.98 (0.91–1.07)	0.67
Chest surgery	1518 (15.1%)	1525 (15.1%)	1.00 (0.93–1.06)	0.91
Abdominal surgery	2487 (24.7%)	2555 (25.4%)	0.97 (0.93–1.02)	0.28
Pelvic surgery	683 (6.8%)	648 (6.4%)	1.05 (0.95–1.17)	0.31
Median (IQR) units of blood product transfused†	3 (2–6)	3 (2–6)	..	0.59‡
Dependency				
No symptoms	1483 (14.7%)	1334 (13.3%)	1.11 (1.04–1.19)	0.0023
Minor symptoms	3054 (30.4%)	3061 (30.4%)	1.00 (0.96–1.04)	0.94
Some restriction	2016 (20.0%)	2069 (20.6%)	0.97 (0.92–1.03)	0.36
Dependent (not requiring constant attention)	1294 (12.9%)	1273 (12.6%)	1.02 (0.95–1.09)	0.63
Fully dependent	696 (6.9%)	676 (6.7%)	1.03 (0.93–1.14)	0.57
Alive (disability status not known)	54 (0.5%)	41 (0.4%)		
Dead	1463 (14.5%)	1613 (16.0%)	0.91 (0.85–0.97)	0.0035

Data are number (%), unless otherwise indicated. Counts are for numbers of patients with at least one such event. RR=relative risk. *Includes both fatal and non-fatal events.

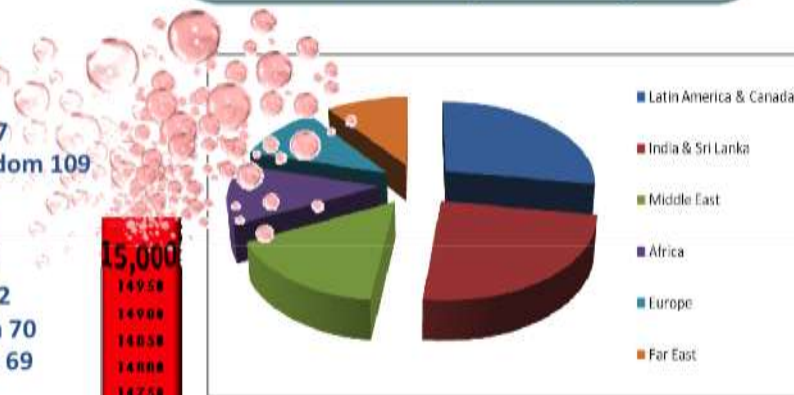
†Transfused patients only. ‡Analysis used logarithmic transformation of mean units of blood products transfused.

Table 3: Vascular occlusive events, need for transfusion and surgery, and level of dependency

OVER 15,000 PATIENTS RANDOMISED!

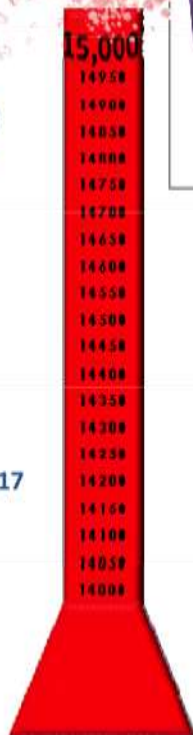
- India 3,579
- Colombia 1,991
- Egypt 1,762
- Nigeria 1,460
- Georgia 1,220
- Ecuador 949
- Indonesia 661
- Thailand 656
- Cuba 478
- Iraq 392
- Mexico 368
- Peru 278
- Malaysia 137
- United Kingdom 109
- Iran 105
- Albania 103
- Sri Lanka 88
- Cameroon 72
- Saudi Arabia 70
- South Africa 69
- Ghana 54
- Italy 52
- Argentina 45
- Belgium 44
- China 44
- Zambia 43
- Tanzania 41
- Slovakia 31
- Tunisia 25
- Czech Republic 17
- El Salvador 16
- Spain 15
- Australia 12
- Japan 9
- Canada 2
- Singapore 2
- Serbia 1

A huge thank you to all our collaborators who have contributed to this total. We are on the home run – less than 5,000 to go!



TOP RECRUITERS

- Hospital Universitario San Vicente de Paul, Colombia
- Mataria Teaching Hospital, Egypt
- Hospital Luis Vernaza, Ecuador
- Suez Canal University, Egypt
- Tbilisi State University Clinical Hospital 'I Javakhishvili', Georgia
- National Hospital Abuja, Nigeria
- Medical Trust Hospital Kochi, India



What's good



- Large
- Mortality endpoint
- Well constructed
- Safely profile confirmed
- Makes sense
- Huge implications for “third world”

...and us?

What's confusing?



- ❑ What is this group of patients and is 16% mortality OK?
- ❑ Who should we give it to here?
- ❑ Where is its place with an MTP and factor VIIa?

