

Trauma haemorrhage from trials to clinical practice

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Global burden of injury



60% of preventable injury related deaths are due to bleeding

Major haemorrhage

UK trauma study:

22 hospitals, n = 12,290

- 50% of deaths in first 3 hrs
- Mortality: 16% at 24h

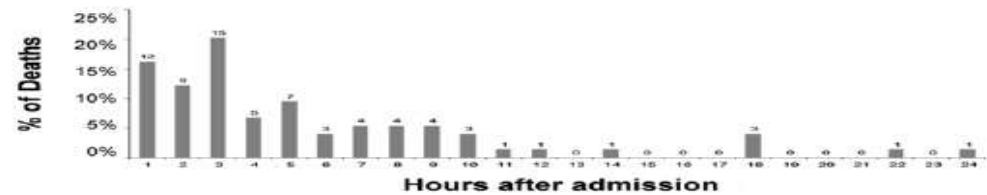
WOMAN study:

N = 20,021

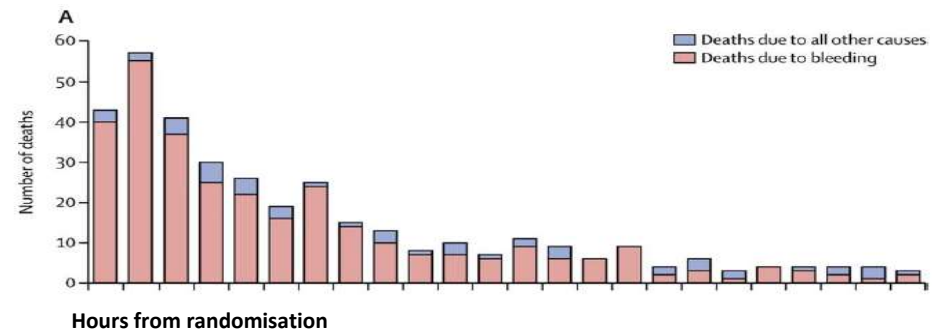
Similar pattern to deaths

- 9% within 1 hour
- 77% in first 24 hr

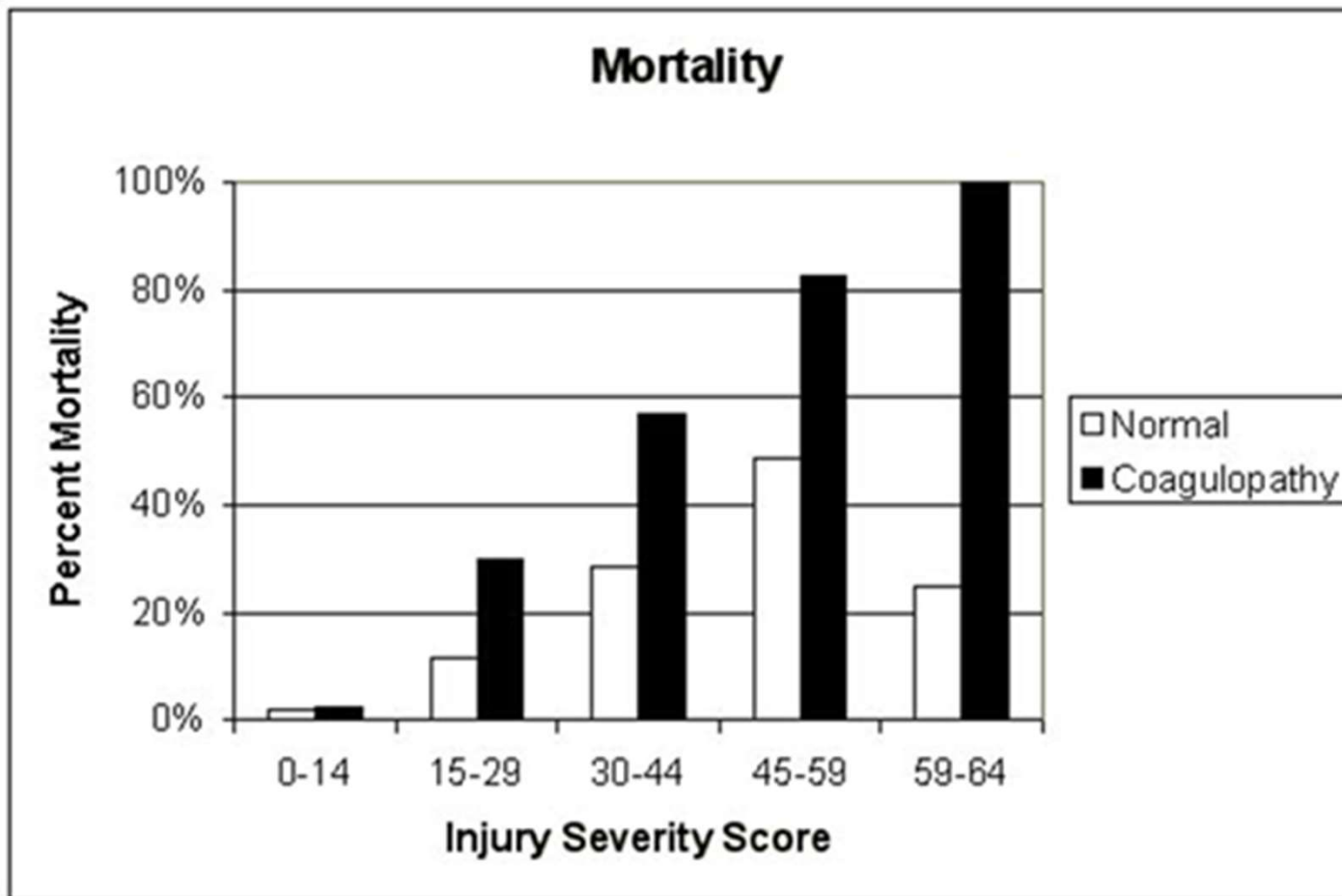
Trauma:



Obstetric:

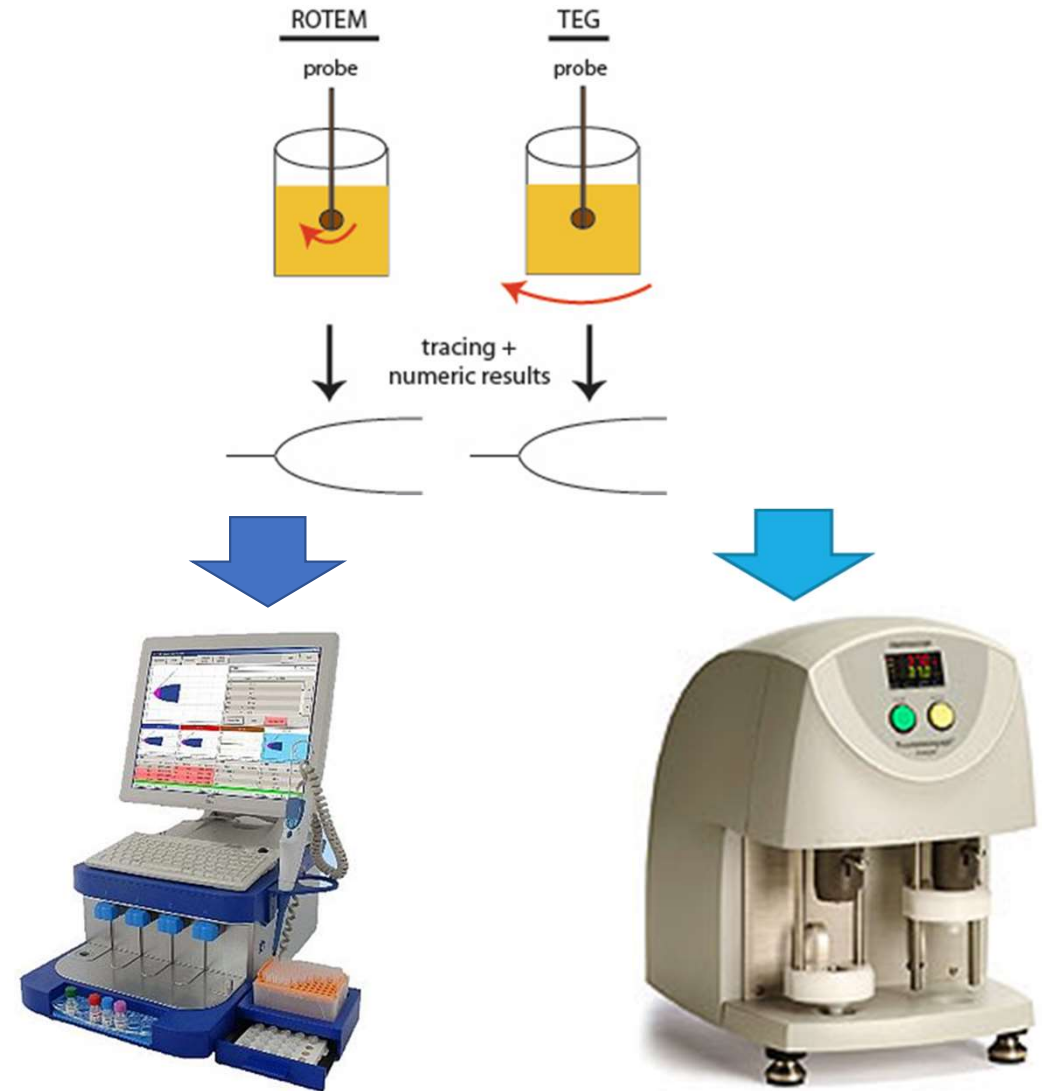
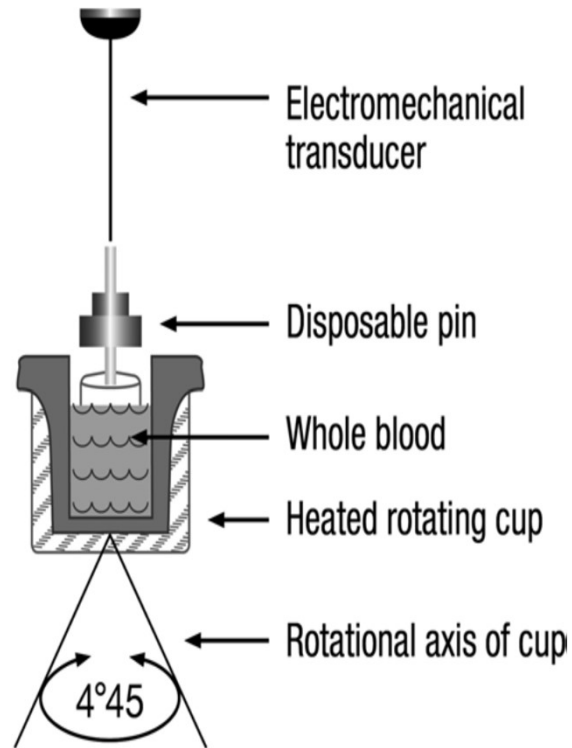


Trauma coagulopathy and mortality

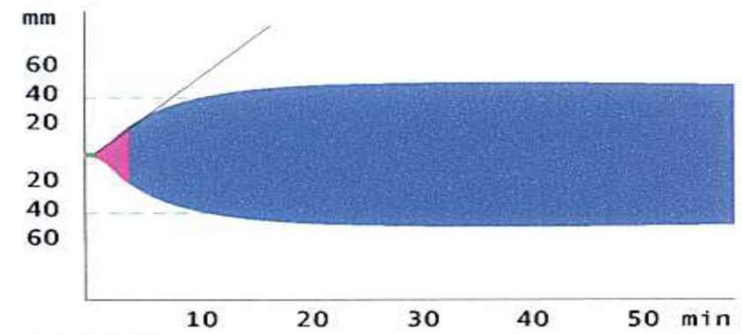
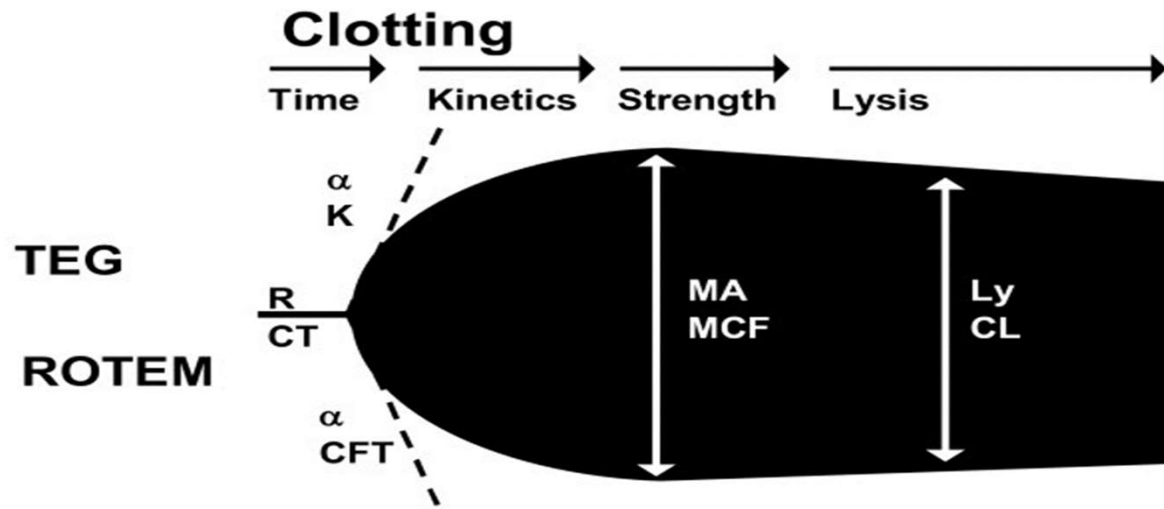


Diagnosis of traumatic coagulopathy

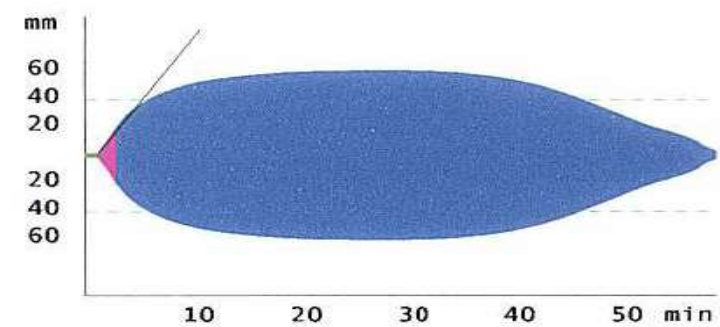
VHA methods



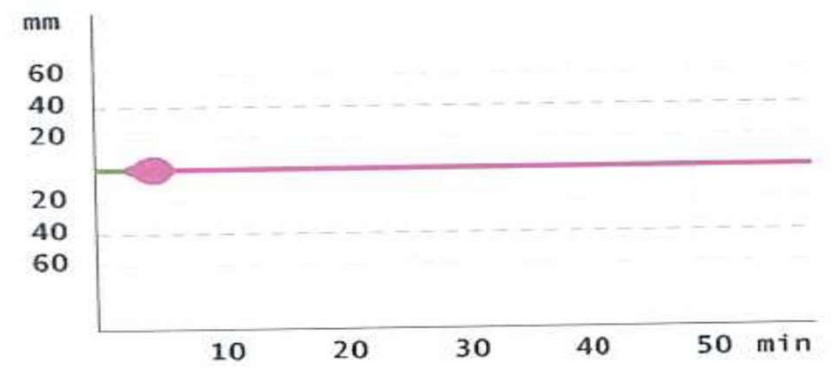
TEG and ROTEM



18 male



80 female



ROTEM

FIBRINOGEN

If FIBTEM CA5 < 10 mm

Give additional 4g equivalent of fibrinogen
(as cryoprecipitate or concentrate)

PLATELETS

If (EXTEM CA5 – FIBTEM CA5) < 30 mm

Give 1 additional pool of platelets

PLASMA

If EXTEM CA5 > 40 mm **AND** EXTEM CT > 80 s

Give 4 additional units of plasma

TRANEXAMIC ACID

If EXTEM LI30 < 85 %

Give additional 1g tranexamic acid

TEG

FIBRINOGEN

If FF TEG MA < 20 mm

Give additional 4g equivalent of fibrinogen
(as cryoprecipitate or concentrate)

PLATELETS

If (rTEG MA – FF TEG MA) < 45 mm

Give 1 additional pool of platelets

PLASMA

If rTEG MA > 65 mm **AND** rTEG ACT > 120 s

Give 4 additional units of plasma

TRANEXAMIC ACID

If rTEG LY30 > 10 %

Give additional 1g tranexamic acid

CCT

FIBRINOGEN

If Fibrinogen < 2 g/L

Give additional 4g equivalent of fibrinogen
(as cryoprecipitate or concentrate)

PLATELETS

If platelets < 100 x 10⁹ /L

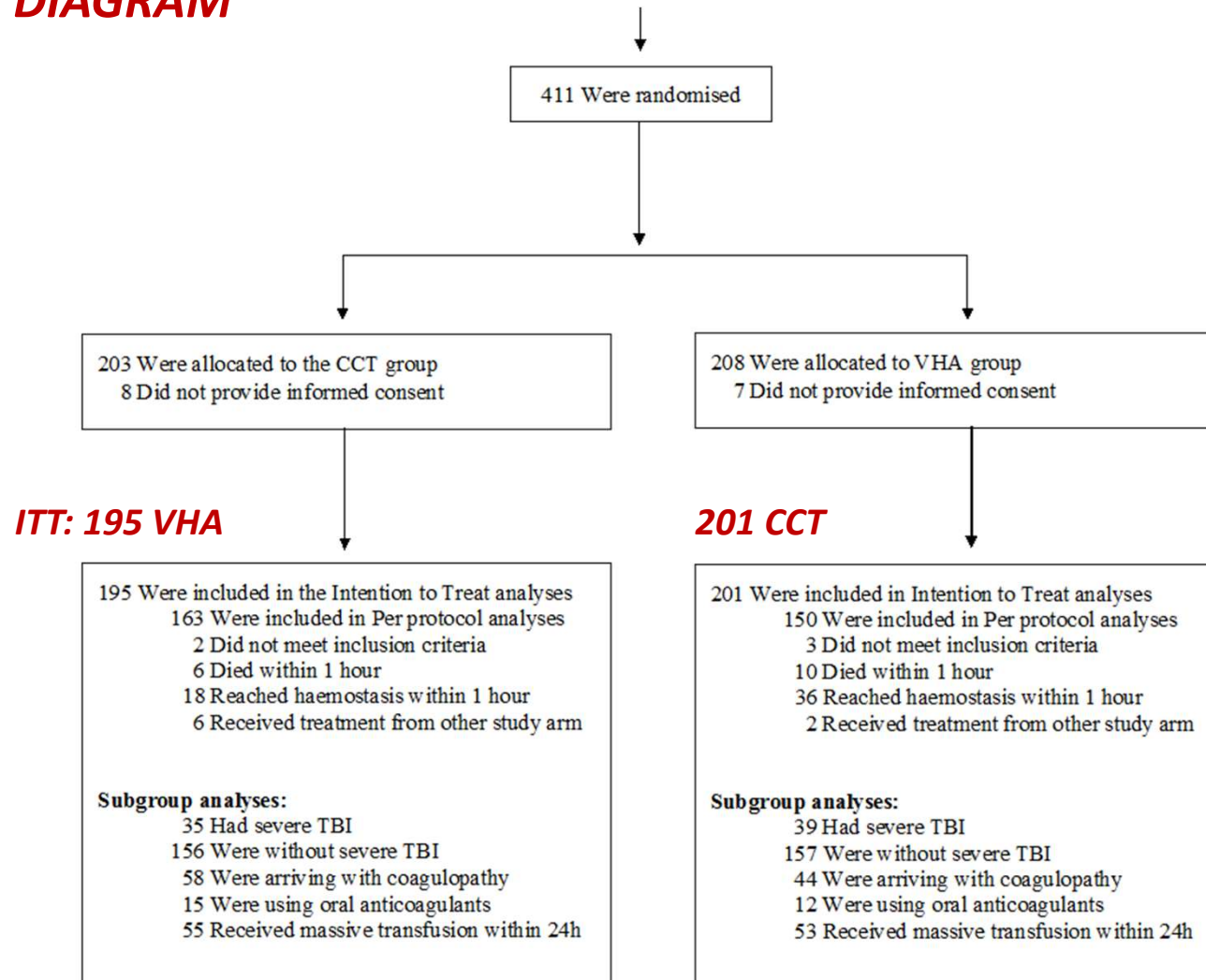
Give 1 additional pool of platelets

PLASMA

If INR > 1.2 **AND** Fibrinogen ≥ 2 g/L

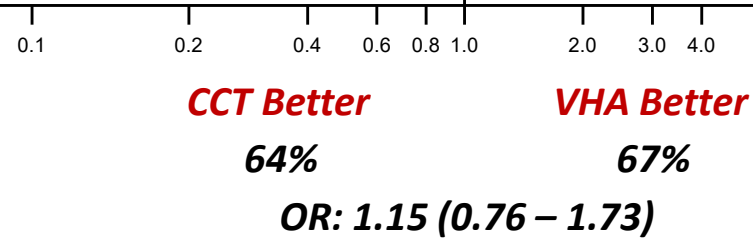
Give 4 additional units of plasma

ITACTIC FLOW DIAGRAM



PRIMARY OUTCOME: At 24 hours, alive & free of massive transfusion

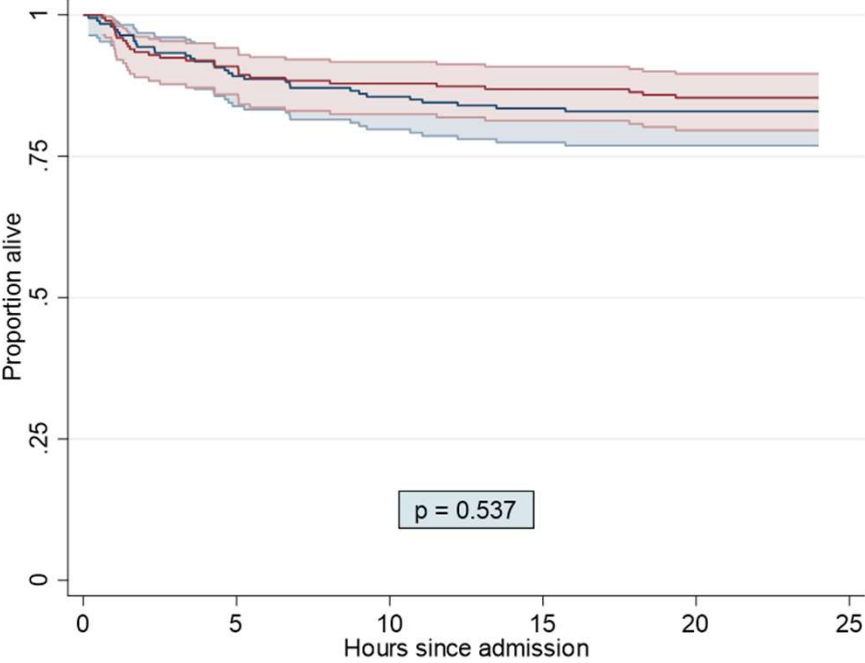
Subgroup	No. patients	No. alive and free of MT (%) - CCT	No. alive and free of MT (%) - VHA	Odds Ratio (95% CI)	p-value interaction
PTr > 1.2 at baseline					0.872
Yes	102	30/58 (52)	25/44 (57)	1.23 (0.56, 2.69)	
No	254	88/123 (72)	97/131 (74)	1.13 (0.65, 1.97)	
Severe TBI					0.148
Yes	74	16/35 (46)	25/39 (64)	2.12 (0.84, 5.34)	
No	313	106/156 (68)	106/157 (68)	0.98 (0.61, 1.57)	
Prior oral anticoagulants					0.268
Yes	27	10/15 (67)	6/12 (50)	0.50 (0.11, 2.28)	
No	363	112/177 (63)	127/186 (68)	1.25 (0.81, 1.93)	
Per Protocol	313	105/163 (64)	96/150 (64)	0.98 (0.62, 1.56)	
Overall (all patients)	396	125/195 (64)	135/201 (67)	1.15 (0.76, 1.73)	



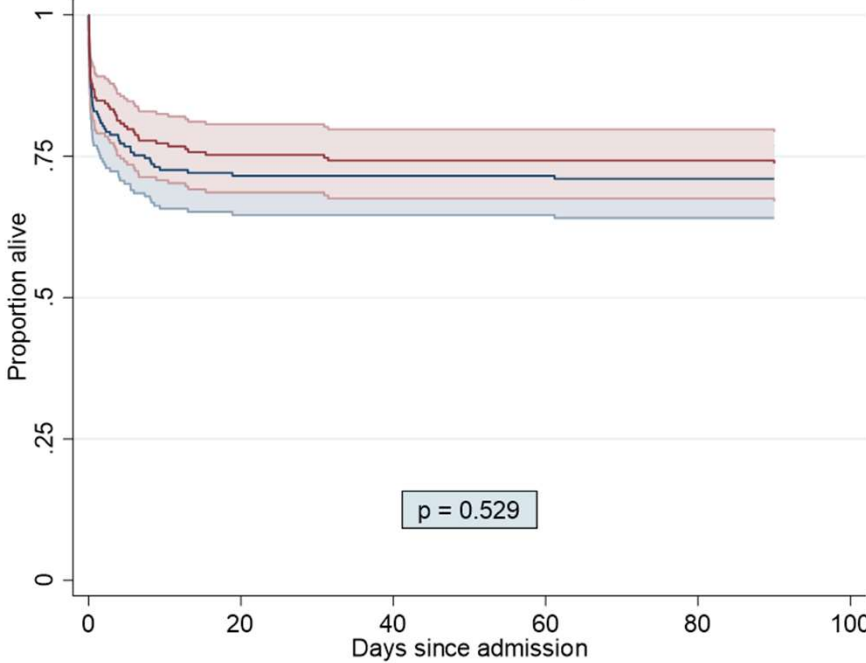
ITACTIC SURVIVAL

28-day Mortality
CCT: 28% VHA: 25%
OR: 0.84 (0.54 – 1.31)

At 24 Hours



At 90 Days



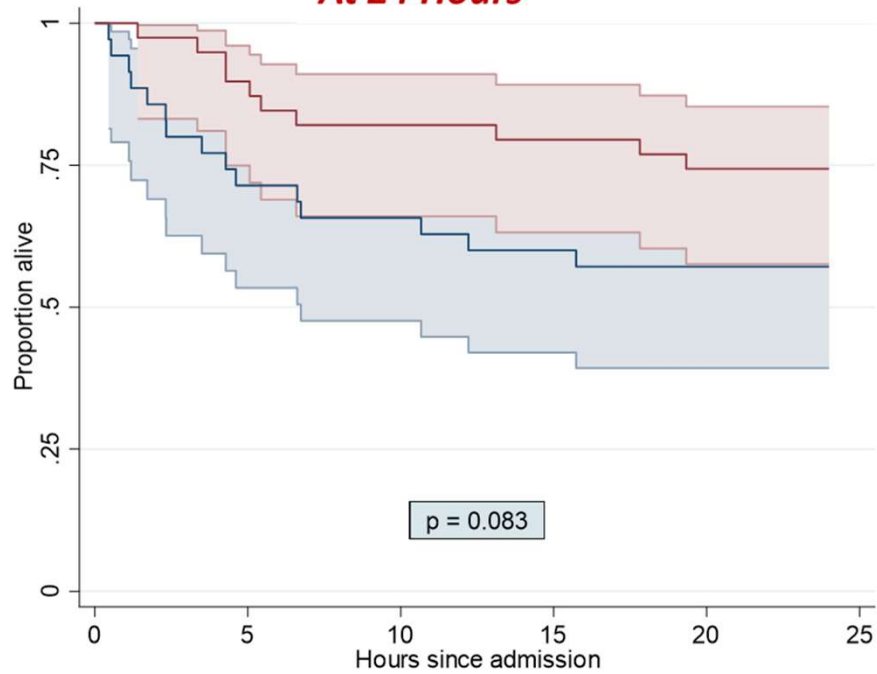
TBI SURVIVAL

28-day Mortality

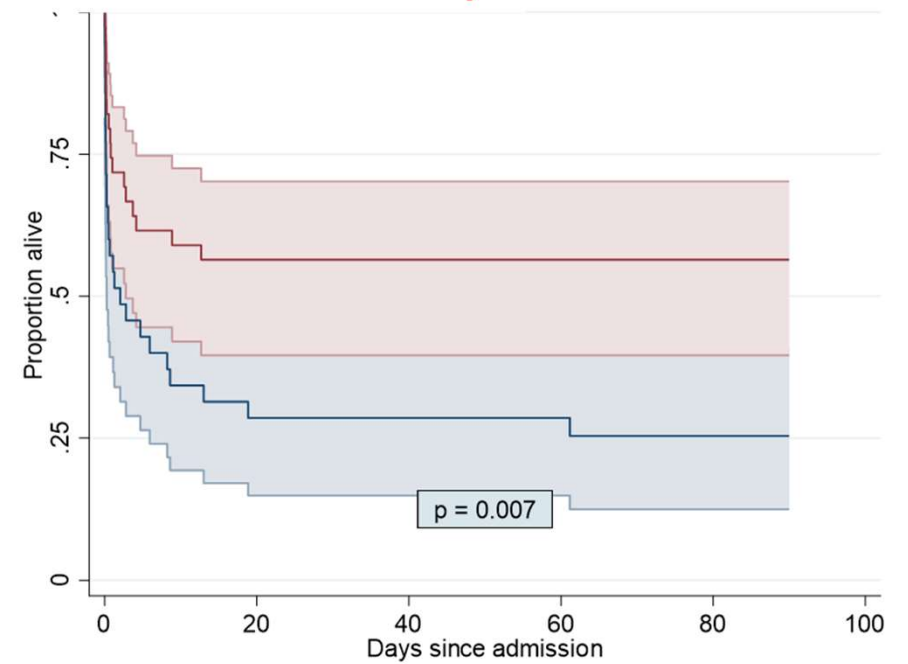
CCT: 74% VHA: 44%

OR: 0.28 (0.10 – 0.74); Adjusted OR: 0.16 (0.03 – 0.90)

At 24 Hours



At 90 Days



How do we interpret these results?

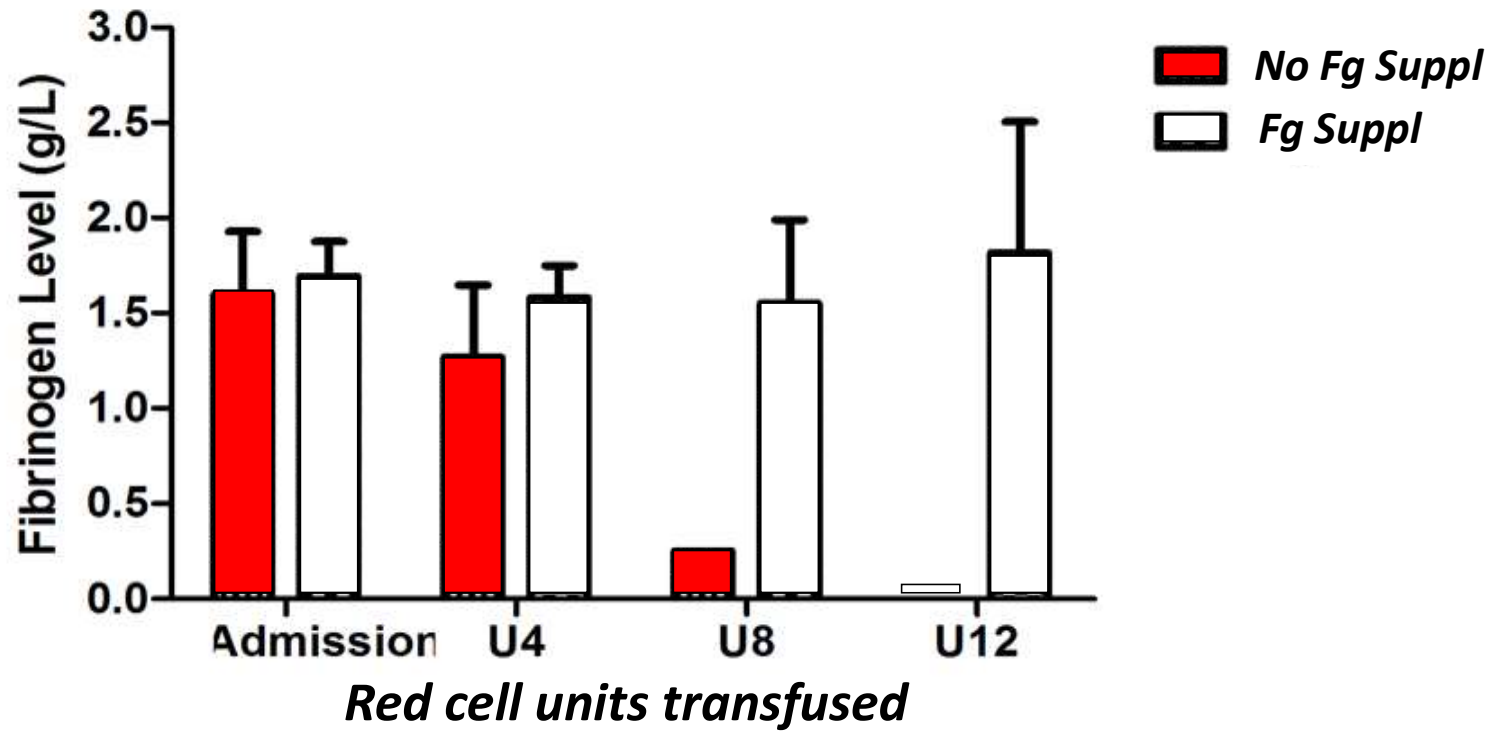
CRYOSTAT-2

EARLY CRYOPRECIPITATE IN TRAUMA

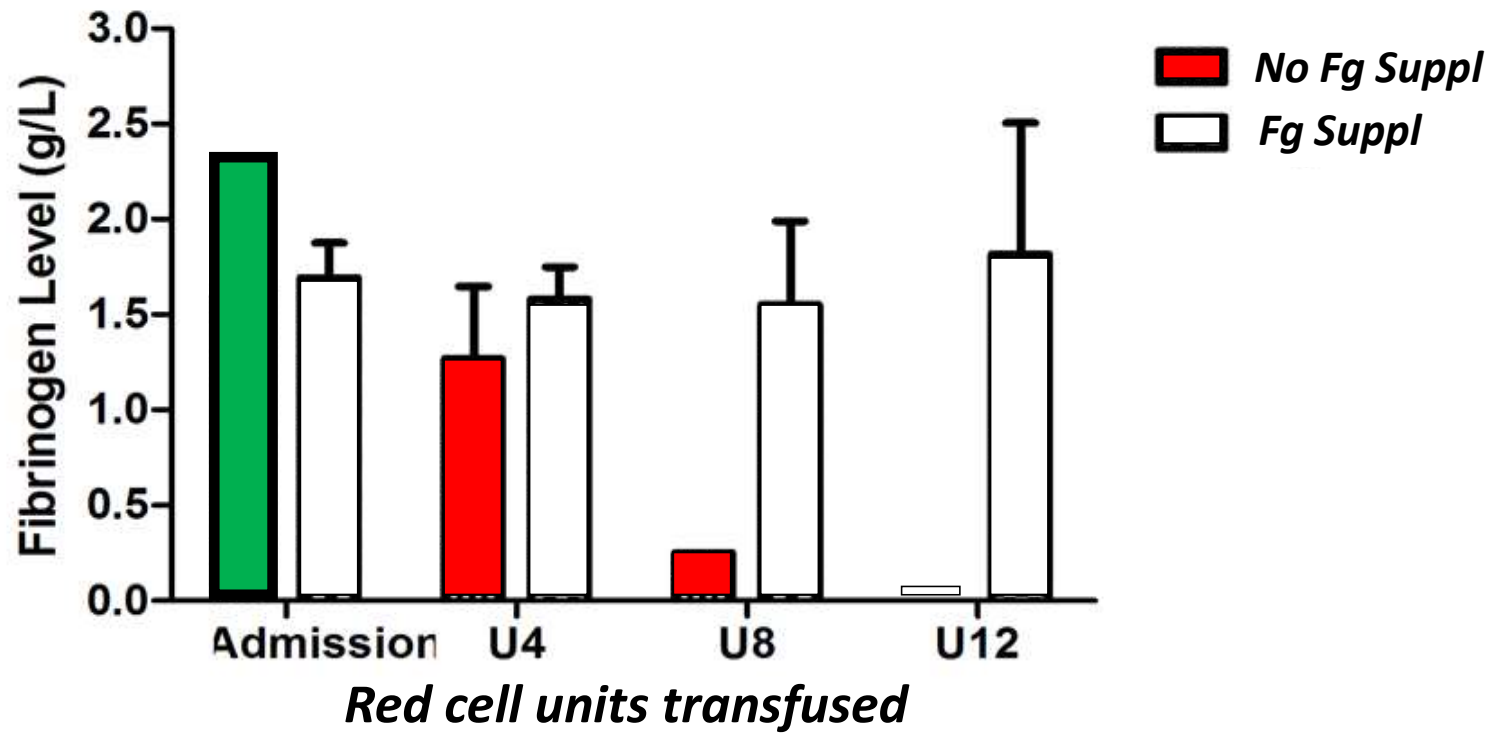
on behalf of the CRYOSTAT-2 team



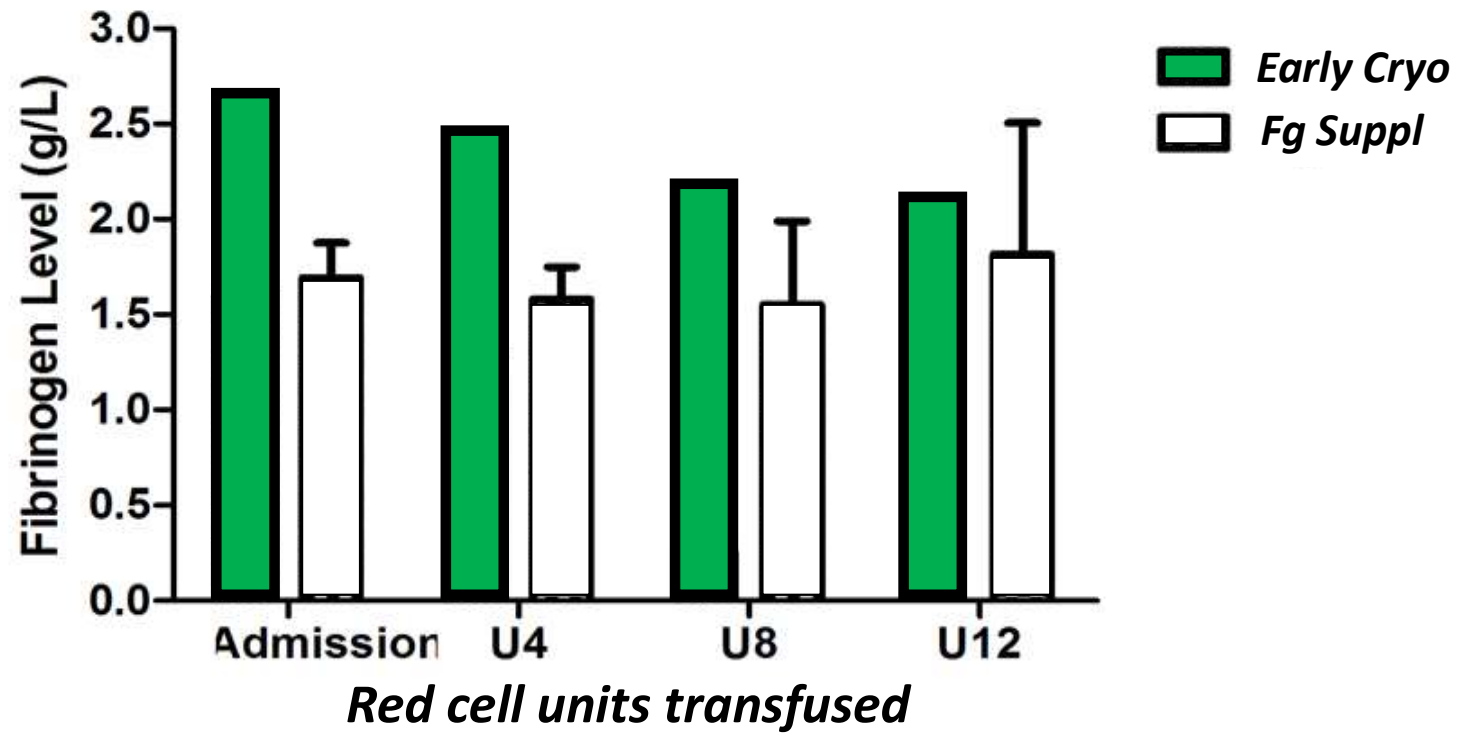
CRYOSTAT-2 TRIAL ETHOS:



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CRYOSTAT-2

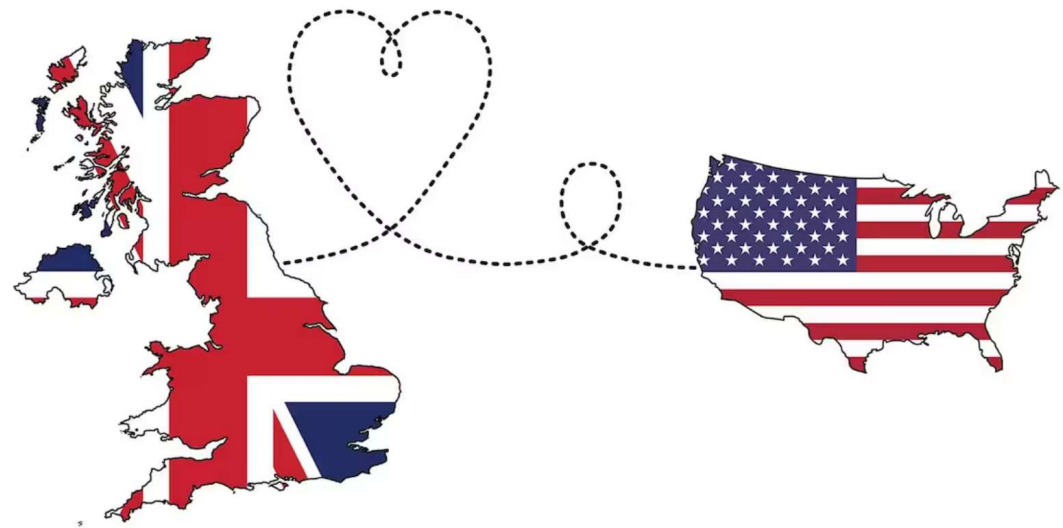
EARLY CRYOPRECIPITATE IN TRAUMA

*A randomised controlled trial
in adult patients with major trauma haemorrhage
to evaluate the effects of early, empiric, administration of
3 pools of cryoprecipitate on mortality*

CRYOSTAT-2 METHODS:

***Randomised, parallel-group
Open label***

***UK & USA
26 Major Trauma Centres***

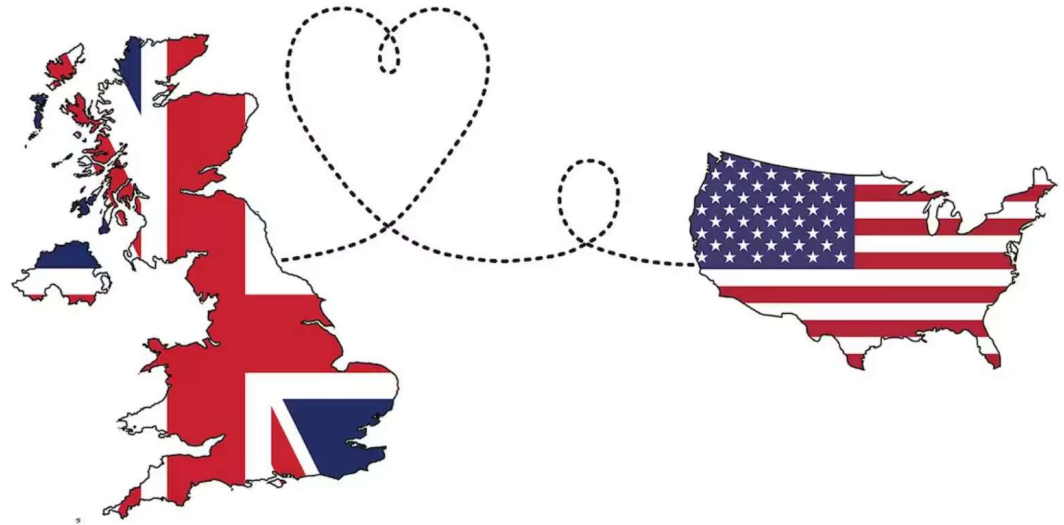


CRYOSTAT-2 METHODS:

- *Adults with traumatic injury*
- *Suspected on-going active haemorrhage*

AND has activated the local major haemorrhage protocol

AND has started or received at least one unit of any blood component

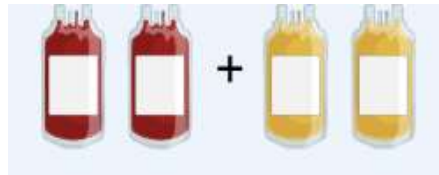
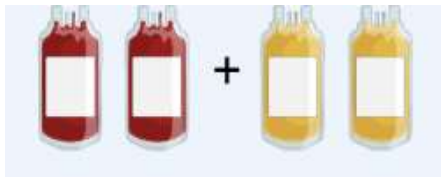


CRYOSTAT-2 METHODS:

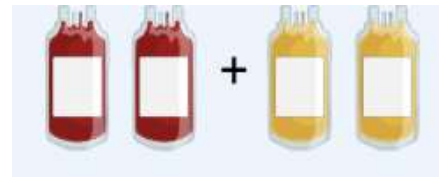
Intervention:



PLUS



Control:





CRYOSTAT-2 METHODS:

Primary Outcome: 28-day all-cause mortality

Secondary Outcomes:

- ***All-cause mortality at 6 & 24 hours***
- ***Death from bleeding at 6 & 24 hours***
- ***Transfusion requirements @ 24 hours***

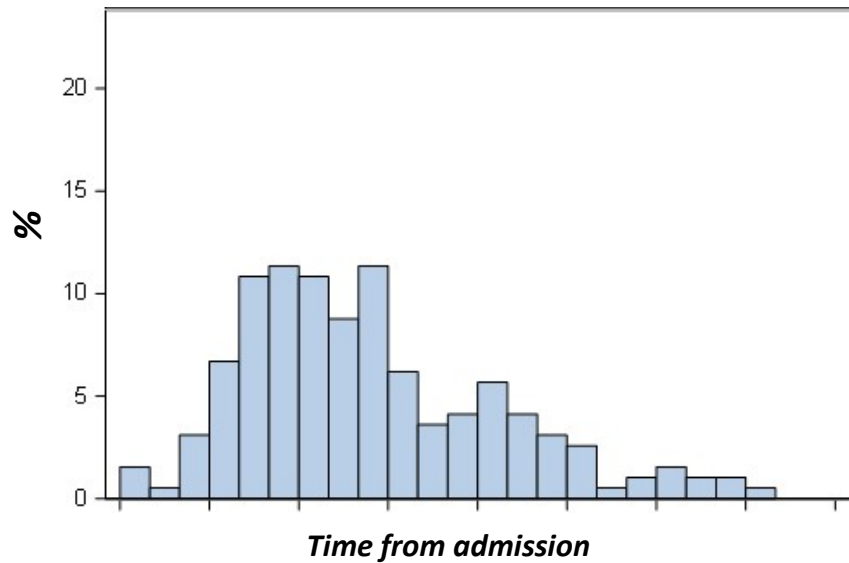
- ***Mortality at 6 & 12 months***
- ***EQ-5D-5L & GOSE at discharge and 6 months***
- ***Hospital resource use up to discharge or day 28***

Patient characteristics

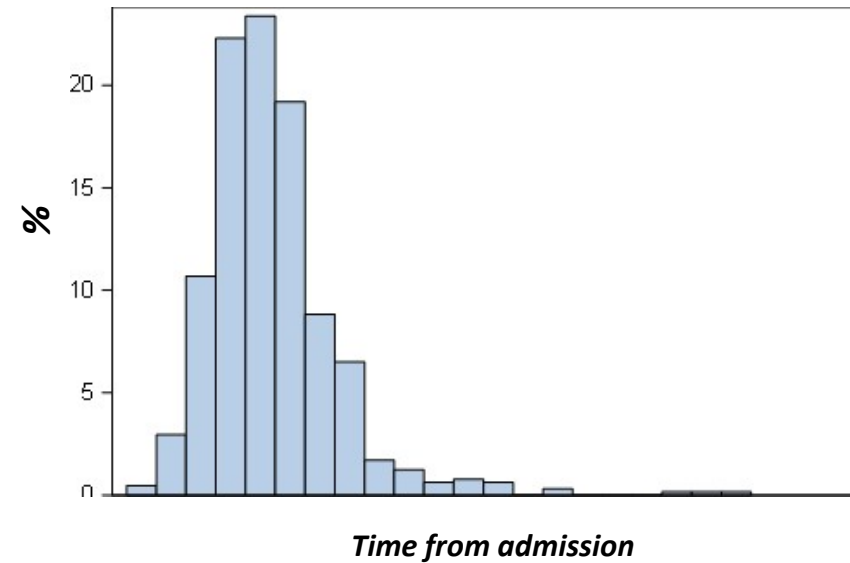
	<i>Std MHP</i> <i>(n=805)</i>	<i>Early Cryo</i> <i>(n=799)</i>
<i>Male</i>	<i>80%</i>	<i>79%</i>
<i>Age (years)</i>	<i>40 (26-55)</i>	<i>38 (25-55)</i>
<i>Time from injury to ED (mins)</i>	<i>77 (55-100)</i>	<i>75 (55-99)</i>
<i>Penetrating injury</i>	<i>35%</i>	<i>37%</i>
<i>Injury Severity score</i>	<i>29 (18-43)</i>	<i>29 (17-43)</i>
<i>Systolic blood pressure (mm Hg)</i>	<i>103 (83-126)</i>	<i>102 (84-124)</i>
<i>Glasgow Coma Scale score</i>	<i>13 (3-15)</i>	<i>14 (3-15)</i>

Timing of Cryoprecipitate

Std MHP



Cryo



Median time to Cryo: 120 (79-184) vs 68 (53-85) mins

% Cryo within 90 mins: 9% vs 68%

Primary Outcome: All cause 28-day mortality

	<i>Std MHP</i>	<i>Early Cryo</i>
<i>28-day Mortality</i>	26.1%	25.3%
		OR: 0.96 (0.75-1.23)
<i>Missing primary outcome</i>	4.2%	4.9%

Secondary Outcomes: 6 & 24 hr Mortality

	Std MHP	Early Cryo	
6-hr mortality	8.6%	7.1%	0.82 (0.61 – 1.15)
24-hr mortality	12.2%	11.2%	0.91 (0.63 – 1.31)
6-hr deaths from bleeding	4.4%	4.1%	0.93 (0.54 – 1.58)
24-hr deaths from bleeding	4.9%	5.5%	1.13 (0.62 – 2.05)
Time to death from bleeding (mins)	86 (40-205)	191 (81-445)	

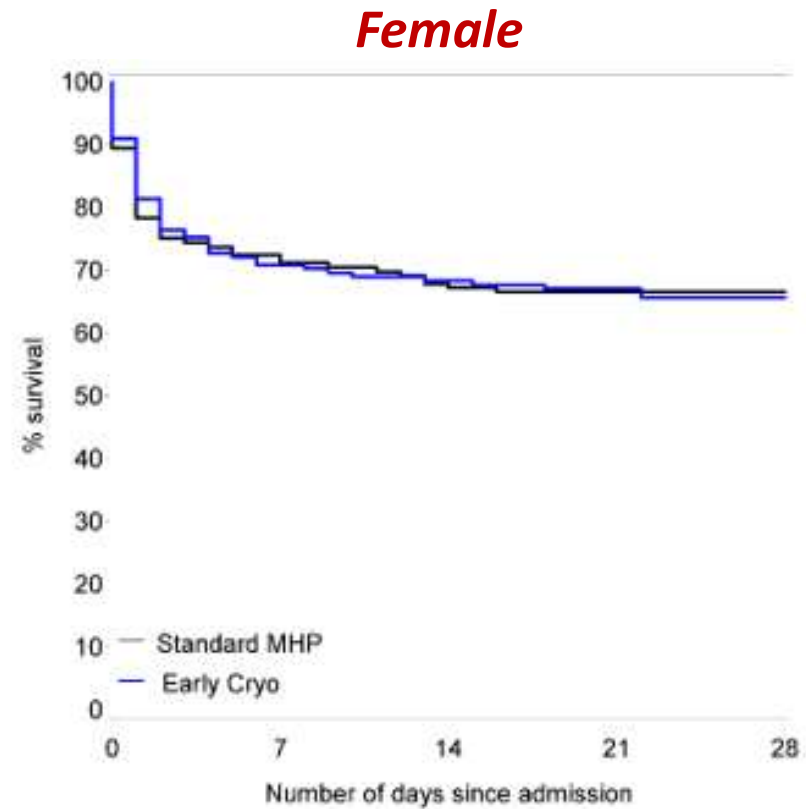
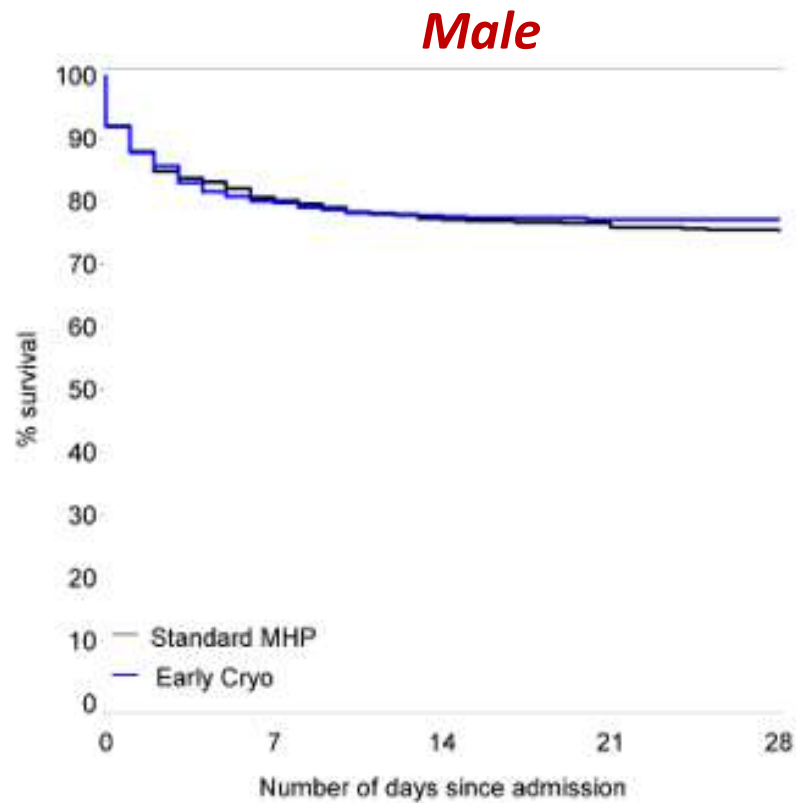
***Secondary Outcomes: Transfusion requirements
Injury to 24 hours***

	<i>Std MHP</i>	<i>Early Cryo</i>
<i>RBC units</i>	<i>5 (3-8)</i>	<i>5 (3-9)</i>
<i>FFP</i>	<i>4 (2-8)</i>	<i>4 (2-8)</i>
<i>Platelets</i>	<i>0 (0-1)</i>	<i>0 (0-1)</i>
<i>Cryoprecipitate</i>	<i>0 (0-2)</i>	<i>3 (3-3)</i>
<i>Crystalloid (mls)</i>	<i>1600 (250-3200)</i>	<i>2000 (700-3500)</i>

Secondary Outcomes: Complications & Safety

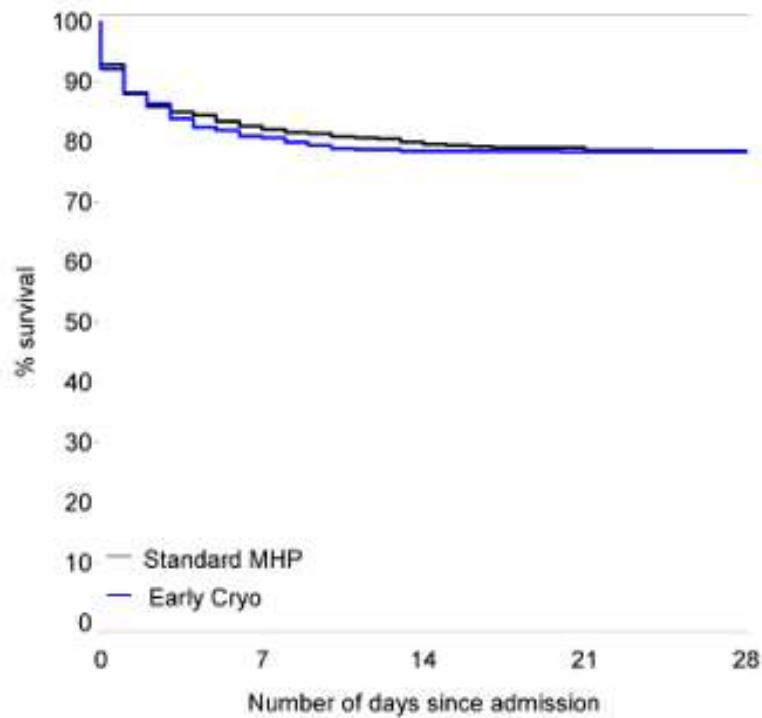
	<i>Std MHP</i>	<i>Early Cryo</i>
<hr/>		
<i>Thrombotic events</i>		
<i>Venous</i>	7.1%	6.9%
<i>Arterial</i>	3.2%	3.3%
 <i>Transfusion related events</i>	 0.0%	 0.4%

Primary Outcome by Subgroup

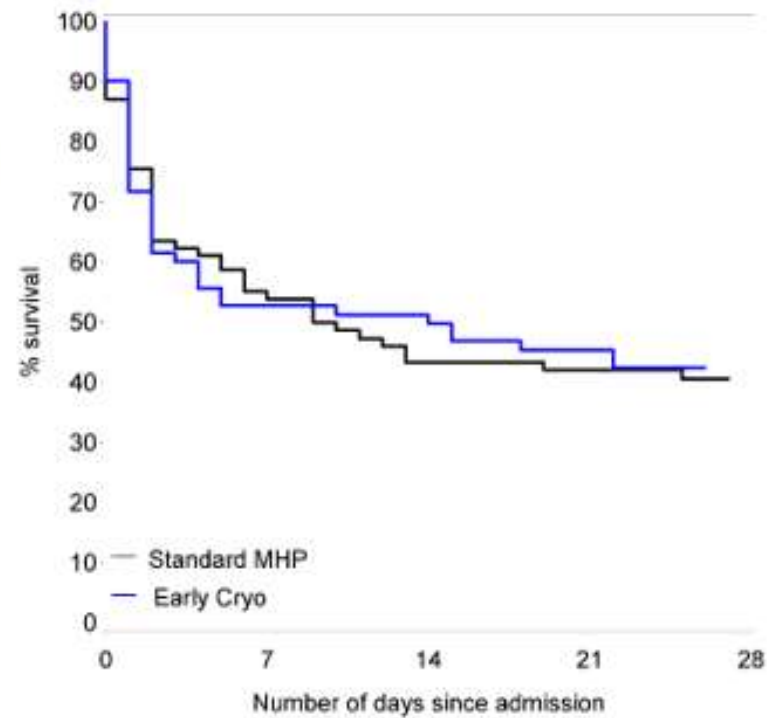


Primary Outcome by Subgroup: Age

Age <70 years

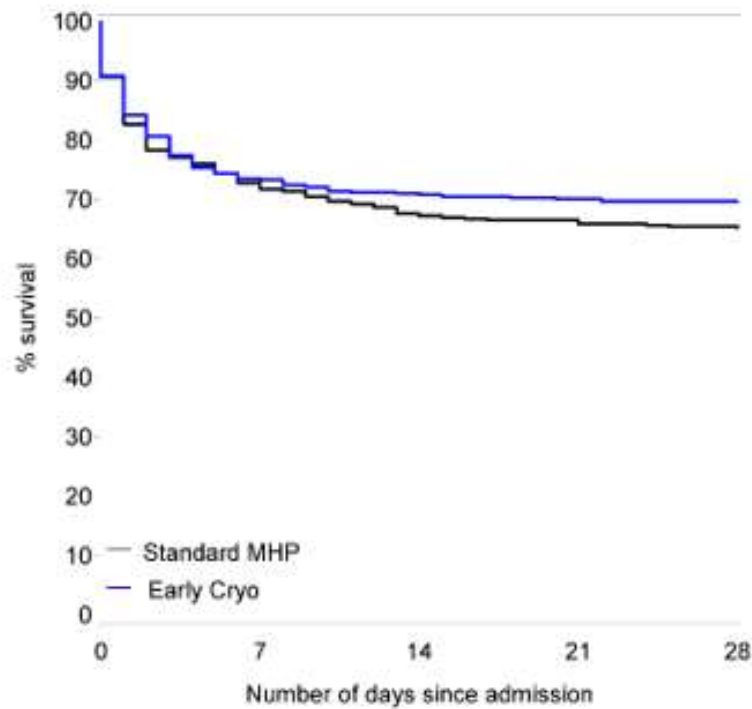


Age 70+ years

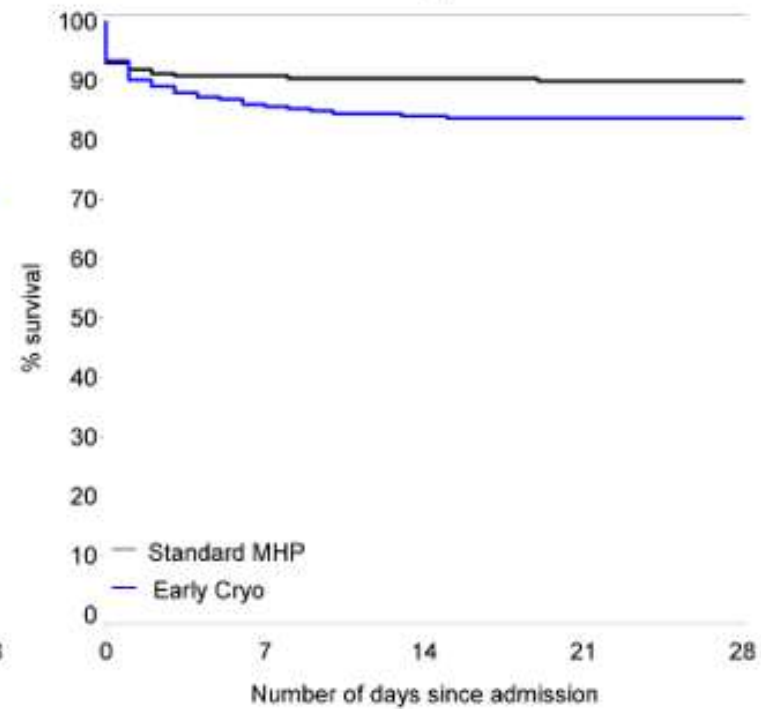


Primary Outcome by Subgroup: Mechanism

Blunt

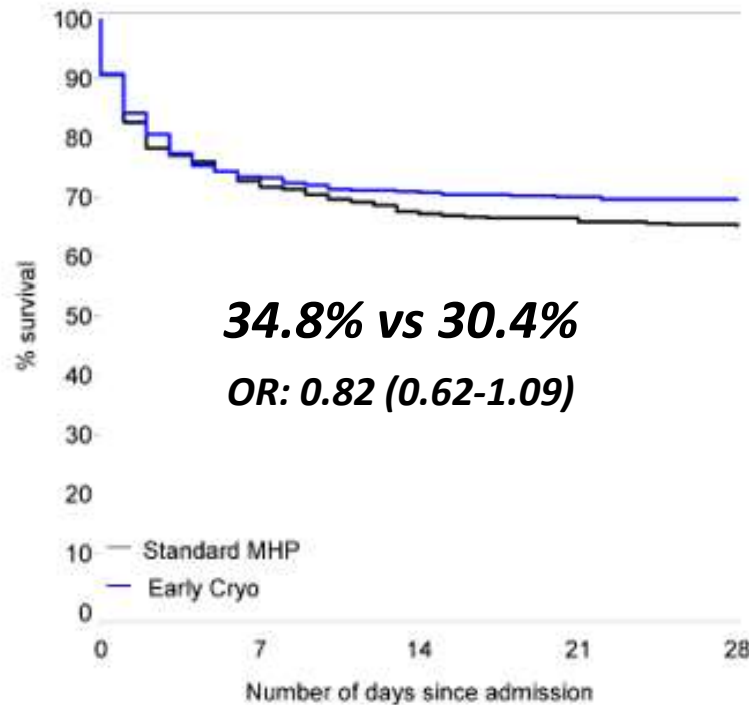


Penetrating

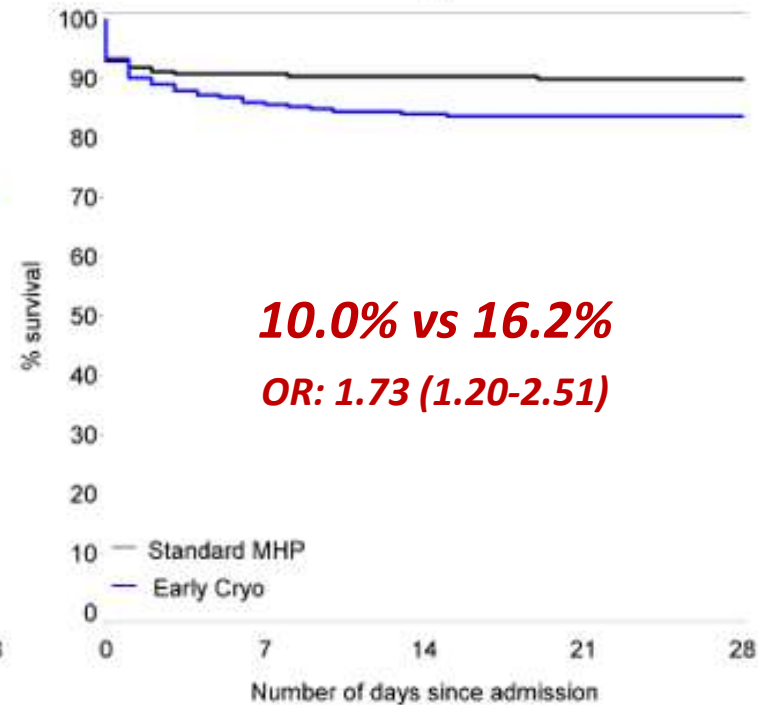


Primary Outcome by Subgroup: Mechanism

Blunt



Penetrating





CRYOSTAT-2

EARLY CRYOPRECIPITATE IN TRAUMA

*Early, empiric, administration of
high-dose cryoprecipitate
did not improve 28-day mortality
in severe trauma haemorrhage*



Where is the optimal place for fibrinogen replacement in major bleeding

Conclusions

- Empiric therapy of fibrinogen replacement is not supported
- Different response according to MOI
- Future work:
 - Individualising therapy
 - Adjuncts to transfusion?

CRYOSTAT-2
EARLY CRYOPRECIPITATE IN TRAUMA

INTRN

**MAJOR
TRAUMA**



FIBRINOGEN EARLY IN
FEISTY
SEVERE TRAUMA STUDY

 UNIVERSITY OF
ABERDEEN

 UNIVERSITY OF
OXFORD

NHS
Oxford University Hospitals
NHS Foundation Trust

 Queen Mary
University of London

CENTRE FOR
TRAUMA
SCIENCES 

NHS
Blood and Transplant

NHS
*National Institute for
Health Research*

barts 
CHARITY