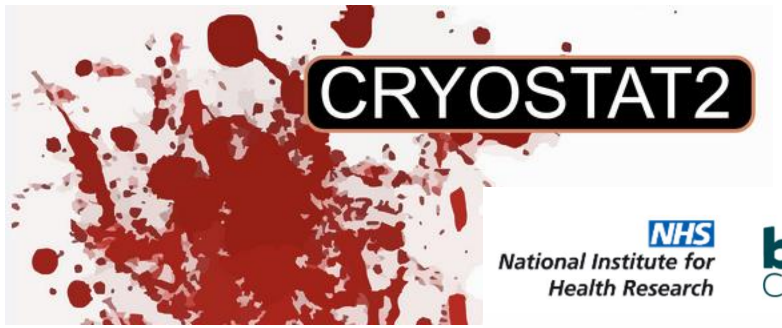
Clinical Trial Up-date:

Cryostat-2 and PROCOAG Trial Results

Marc Maegele
Department for Trauma and Orthopedic Surgery
Cologne Merheim Medical Center (CMMC)
Institute for Research in Operative Medicine (IFOM)
University Witten/Herdecke
Campus Köln-Merheim
E-Mail: Marc.Maegele@t-online.de

2 RCTs in 2023



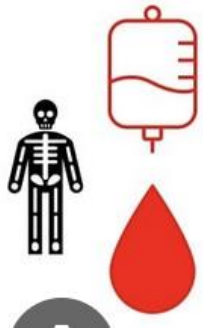
NHS National Institute for Health Research

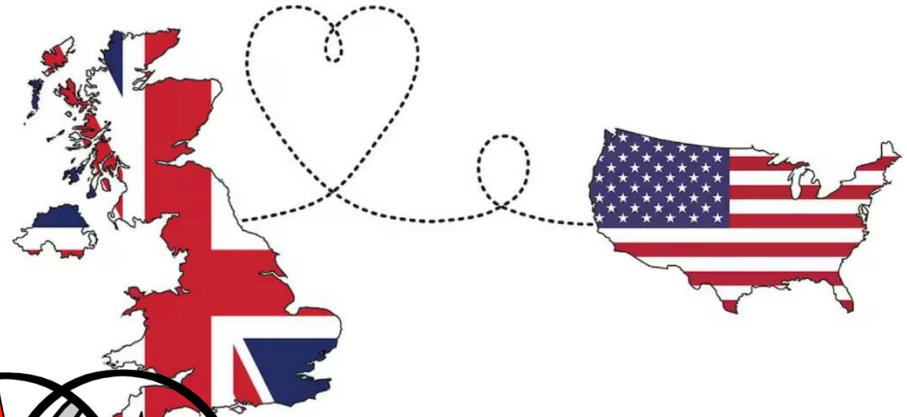
barts CHARITY

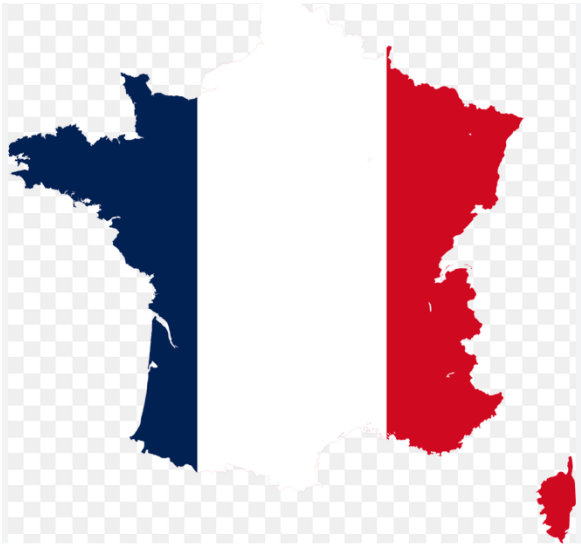
Queen Mary University of London

CENTRE FOR TRAUMA SCIENCES

NHS Blood and Transplant







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Current understanding of hemostatic failure/trauma-induced coagulopathy

Pathophysiology of Trauma-Induced Coagulopathy

Herbert Schöchl[1] Felix C.F. Schmitt[2] Marc Maegele[3,4]

Hamostaseologie 2024;44:31–39.

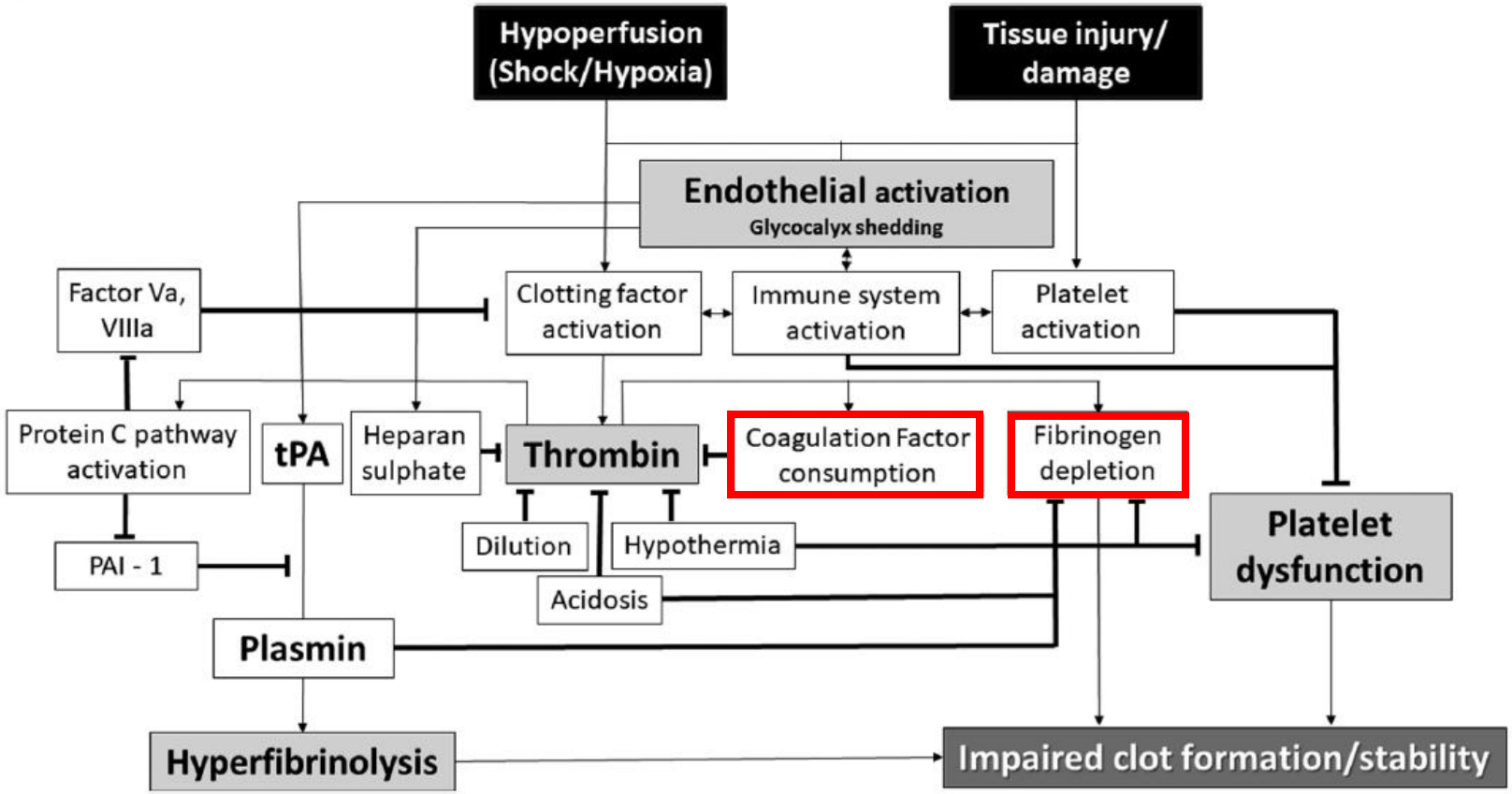

Fig. 1 Schematic overview of potential drivers of trauma-induced coagulopathy. t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1. Activators; inhibitors.

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CRYOSTAT 2

JAMA. doi:10.1001/jama.2023.21019
Published online October 12, 2023.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury
The CRYOSTAT-2 Randomized Clinical Trial

Ross Davenport, PhD; Nicola Curry, MD; Erin E. Fox, PhD; Helen Thomas, MSc; Joanne Lucas, MSc; Amy Evans, MMedSci; Shaminie Shanmugaranjan, BSc; Rupa Sharma, BSc; Alison Deary, MSc; Antoinette Edwards, MA; Laura Green, MD; Charles E. Wade, MD; Jonathan R. Benger, MD; Bryan A. Cotton, MD; Simon J. Stanworth, MD, DPhil; Karim Brohi, MD; for the CRYOSTAT-2 Principal Investigators

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

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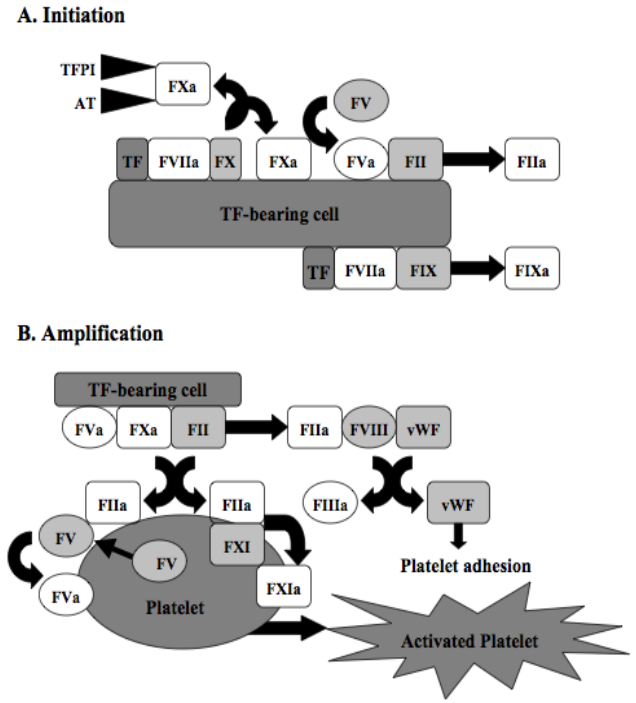
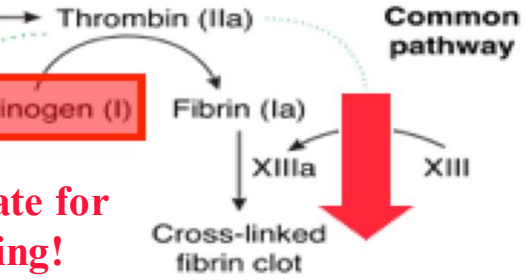
Role of fibrinogen and need for early supplementation

We recommend treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenaemia (viscoelastic sgins of a function fibrinogen deficit or a plasma claus fibrinogen level </= 1.5 g/L) (Grade 1C; unchanged)



Maegele, Textbook of Surgery 2017



Substrate for clotting!

Am J Clin Pathol. 2011 Sep;136(3):364-70. doi: 10.1309/AJCPH16YXJEFSHEO.

Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol.

Chambers LA[1], Chow SJ, Shaffer LE.

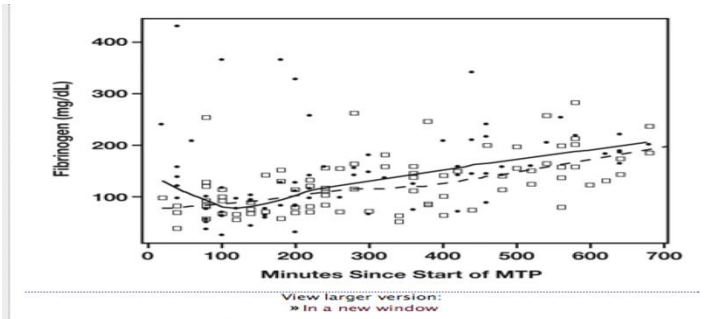
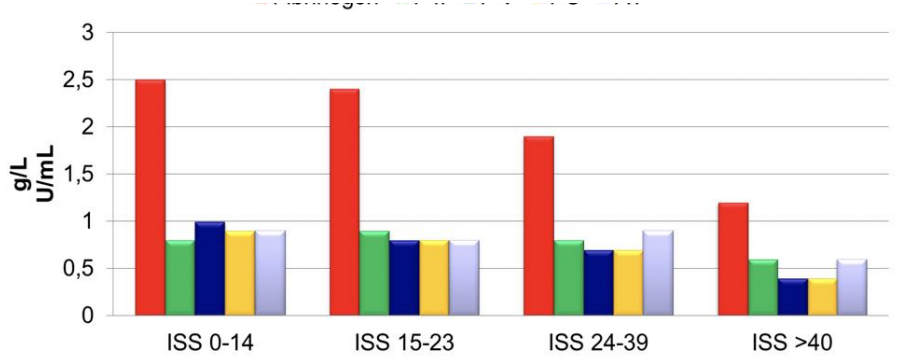


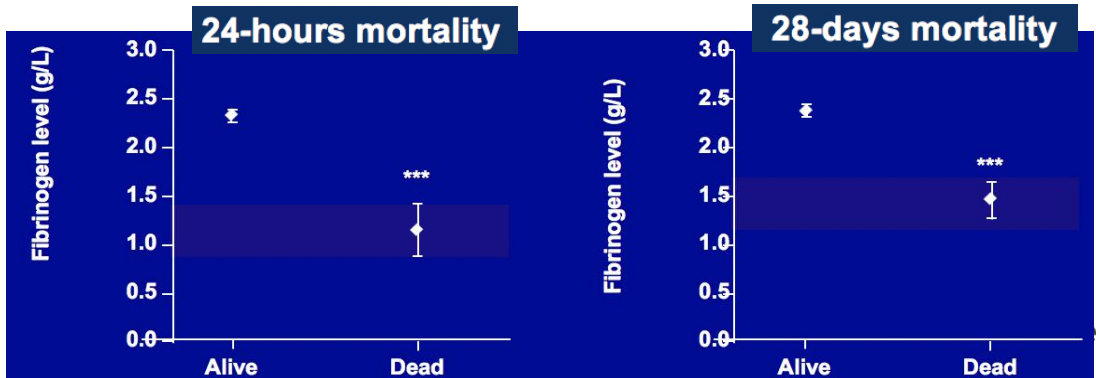
Figure 2

Fibrinogen levels (mg/dL) over time for the 25 patients treated under the original protocol (dots and solid line) and 27 patients treated under the new protocol (boxes and dashed line) who survived at least 12 hours. To convert fibrinogen values to Système International units (µmol/L), multiply by 0.0294. MTP, massive transfusion protocol.



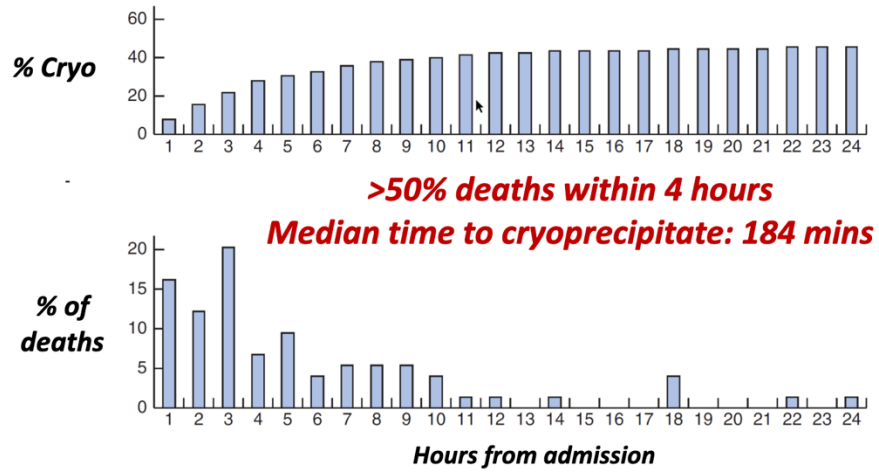
Floccard et al., Injury 2012

Rourke et al., J Thromb Haemost 2012



Rationale for CRYOSTAT 2

UK National Trauma Transfusion Study:



>50% deaths within 4 hours

Median time to cryoprecipitate: 184 mins

CRYOSTAT-1
EARLY CRYOPRECIPITATE IN TRAUMA

Intervention group:

2 pools cryo <90 minutes of admission

Comparator group:

Standard major haemorrhage protocol

	Std MHP (n=20)	*Early Cryo (n=21)*
Received cryo <90 minutes	***29%***	***81%***
Admission fibrinogen (g/dl)	***1.55***	***1.60***
Lowest fibrinogen (g/dl)	***0.60***	***1.81***
Mortality	***28.6%***	***10.0%***

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CRYOSTAT 2: Methods

Inclusion criteria:

Adult patients affected by traumatic injury with
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

Exclusion criteria:

Transferred from another hospital *or*
Trauma team leader deems injury incompatible with life *or*
>3 hours from the time of injury

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CRYOSTAT 2: Methods

Intervention:

3 pools of Cryoprecipitate (6g fibrinogen equivalent)

…as soon as possible (aim to start within 90 minutes)

…in addition to standard local major haemorrhage protocol

Control:

Standard local major haemorrhage protocol

pRBC + FFP in 4 + 4 unit packs with platelets in the second round and then ongoing for 1:1:1 and 2 pools of cryoprecipitate (4g fibrinogen equivalent) and ongoing

Intervention

Patients in both groups received standard treatment according to the local MHP with a balanced, empirical ratio of red blood cells (RBCs) and fresh frozen plasma (FFP). MHPs at participating sites were reviewed by lead trial investigators[14] to ensure consistency.[8,16] Typically, standard MHPs delivered RBC and FFP in 4 + 4 unit packs, with platelet pools transfused with the second and subsequent packs to achieve a 1:1:1 ratio of RBC, FFP, and platelets. Standard protocols also typically include 2 pools of cryoprecipitate (4-g fibrinogen equivalent), added again to the second and subsequent packs. One prehospital helicopter medical service in the UK utilized a combined "RBC and plasma" product and whole blood was available in the US. When transfused, both were recorded as 1 U of RBCs and 1 U of FFP. In the intervention group, patients were to be administered an additional 3 pools of cryoprecipitate (6-g fibrinogen equivalent) as early as possible, with the aim to start within 90 minutes of admission.

CRYOSTAT 2: Methods

Primary Outcome:

28-day all-cause mortality

Secondary Outcomes:

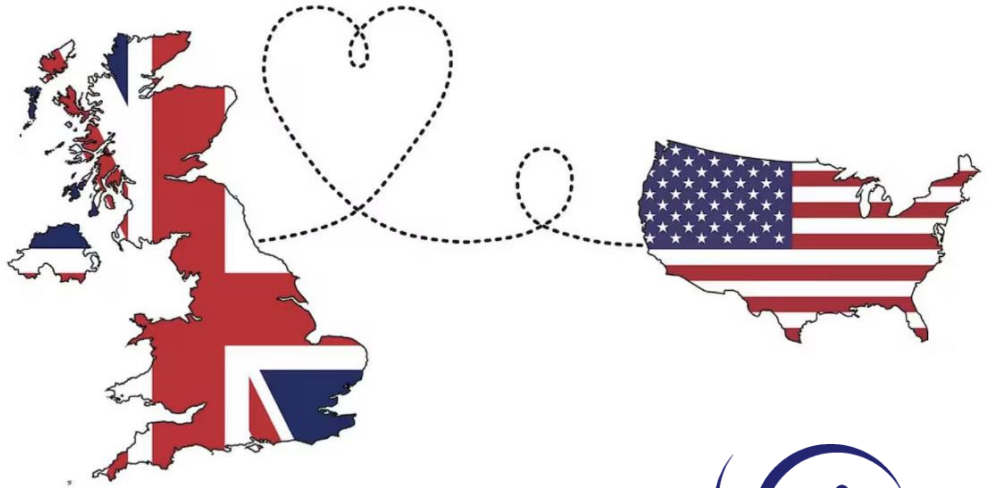
- All-cause mortality at 6 & 24 hours
- Death from bleeding at 6 & 24 hours
- Transfusion requirements at 24 hours
- Mortality at 6 & 12 months
- EQ-5D-5L & GOSE at discharge and 6 months
- Hospital resource use up to discharge or day 28

Randomised, parallel-group
Sealed envelopes at sites

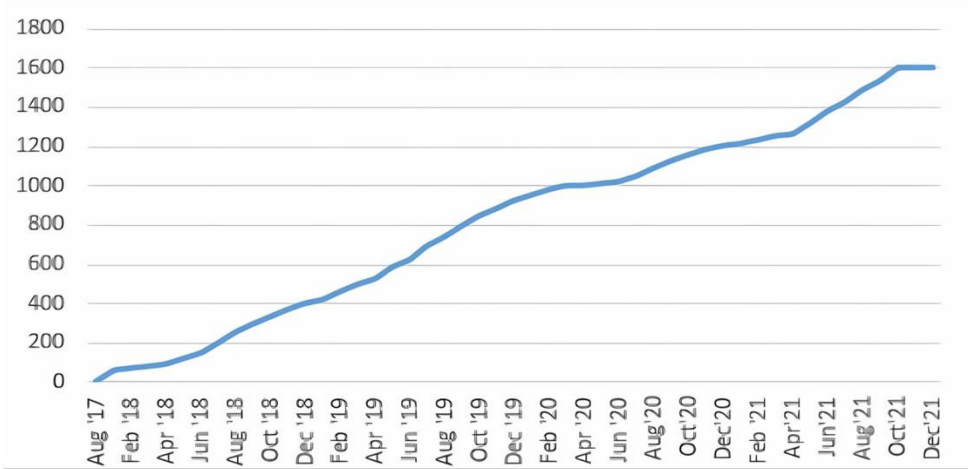
- Varying block size
- Stratified by centre

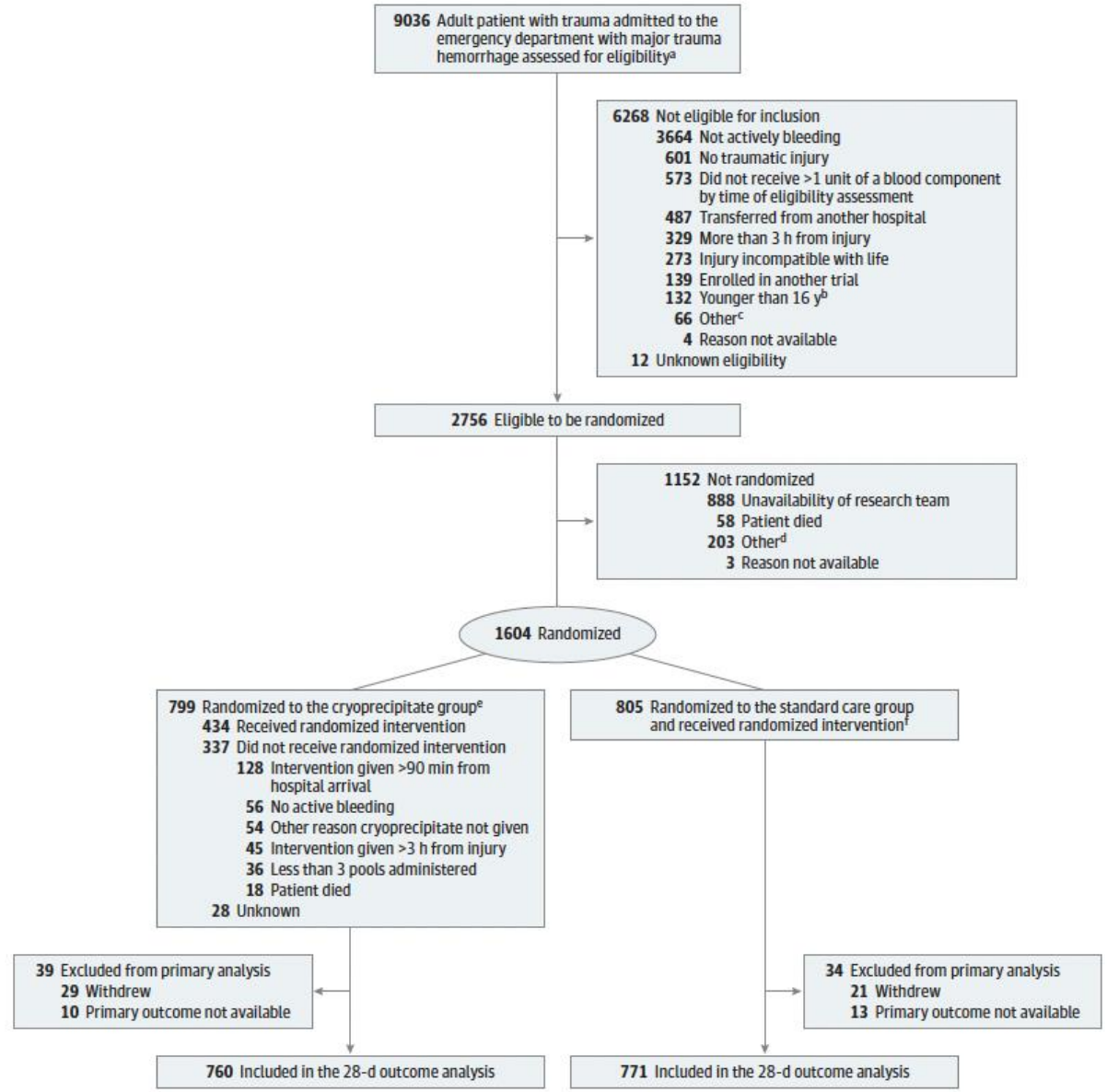
Open label

UK & USA > 26 Major Trauma Centres



CRYOSTAT 2: Recruitment and study flow





CRYOSTAT 2: Patient characteristics

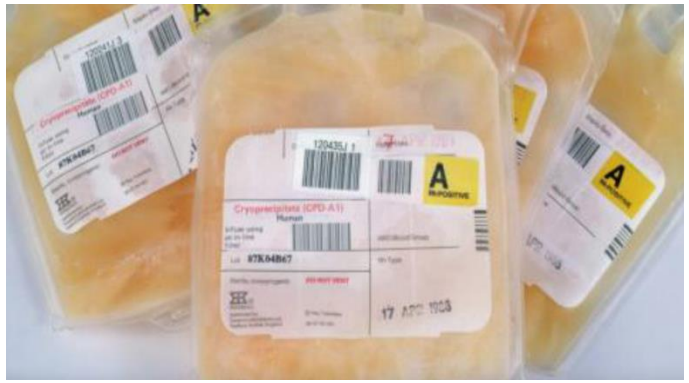


Table 1. Demographic and Injury Characteristics

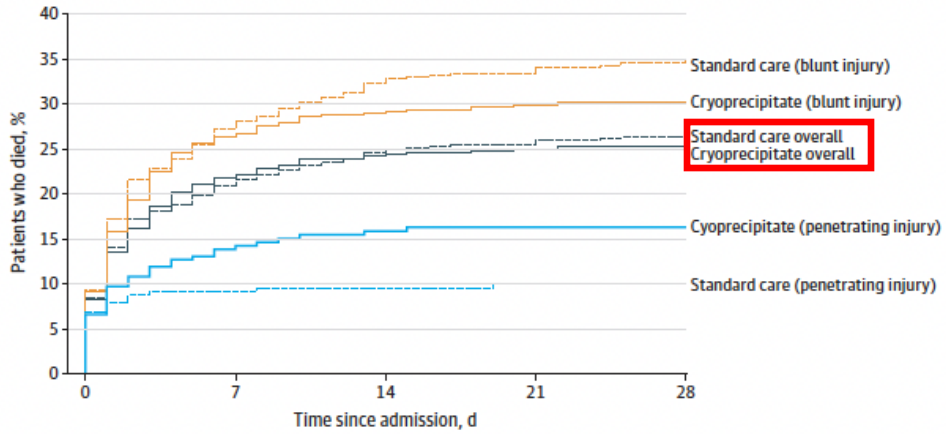
Characteristic	No./total No. (%)	
	Cryoprecipitate group (n = 799)	Standard care group (n = 805)
Participants		
Men	618/785 (79)	633/796 (80)
Women	167/785 (21)	163/796 (20)
Age, median (IQR), y	38 (25-55)	40 (26-55)
Age ≥70 y	71/781 (9)	86/790 (11)
Time from injury to ED arrival, median (IQR), min	75 (55-99)	77 (55-100)
Injuries and physiology on ED arrival		
Blunt injury	495/785 (63)	519/796 (65)
Injury Severity Score, median (IQR)[a]	29 (17-43)	29 (18-43)
Head AIS ≥4[b]	157/665 (24)	191/664 (29)
Systolic blood pressure, median (IQR), mm Hg	102 (84-124)	103 (83-126)
Systolic blood pressure <90 mm Hg	230/724 (32)	250/738 (34)
Heart rate/min, median (IQR)	108 (88-126)	108 (88-127)
In cardiac arrest	12/717 (2)	17/735 (2)
Glasgow Coma Score, median (IQR)[c]	14 (3-15)	13 (3-15)
Prehospital interventions administered		
Red blood cell, median (IQR), U	0 (0-2)	0 (0-2)
Fresh frozen plasma, median (IQR), U	0 (0-1)	0 (0-1)
Crystalloids, median (IQR), mL	0 (0-250)	0 (0-250)
Colloids, median (IQR), mL	0 (0-0)	0 (0-0)
Tranexamic acid	615/783 (79)	639/796 (80)

No differences!

Prehospital care

CRYOSTAT 2: All-cause mortality (primary outcome)

Figure 2. Mortality Overall and by Injury Type



No. of patients at risk					
Cryoprecipitate overall	784	567	532	514	498
Standard care overall	795	569	518	501	479
Cryoprecipitate (blunt injury)	495	348	332	323	310
Standard care (blunt injury)	518	353	320	307	289
Cryoprecipitate (penetrating injury)	289	219	200	191	188
Standard care (penetrating injury)	277	216	198	194	190

The median number of days observed was 28 days for all groups. Mortality at day 28 was analyzed as a binary outcome with odds ratios, 95% CIs, and *P* values reported in the results and in Figure 3.

Primary Outcome: All cause 28-day mortality

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

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CRYOSTAT 2: Secondary outcomes

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

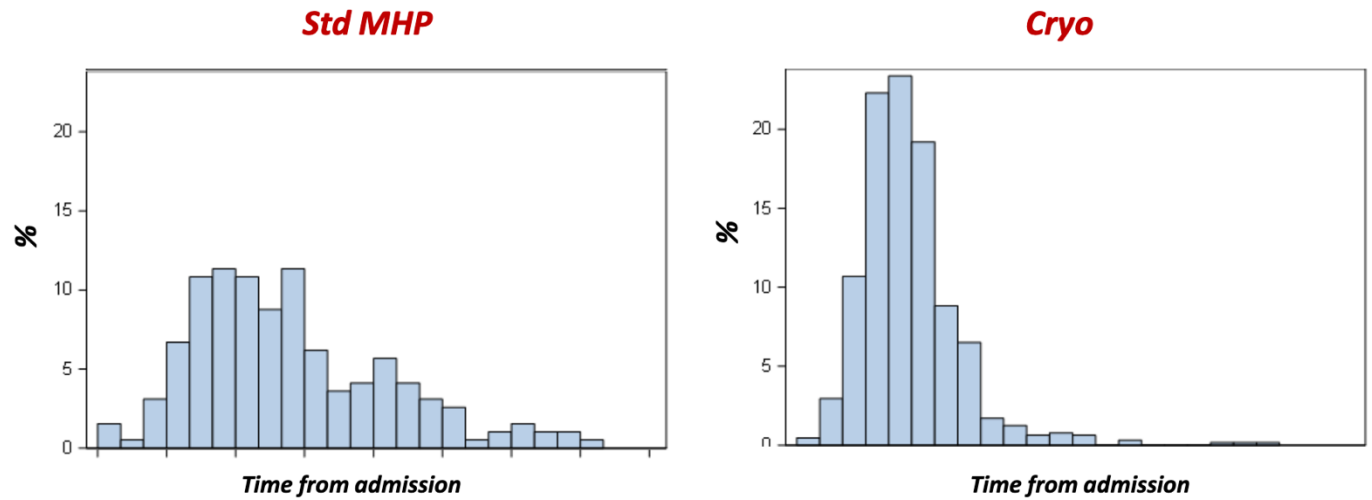
	Std MHP	Early Cryo
RBC units	5 (3-8)	5 (3-9)
FFP	4 (2-8)	4 (2-8)
Platelets	0 (0-1)	0 (0-1)
Cryoprecipitate	0 (0-2)	3 (3-3)
Crystalloid (mls)	1600 (250-3200)	2000 (700-3500)

CRYOSTAT 2: Secondary outcomes

Secondary Outcomes: Complications & Safety

	Std MHP	*Early Cryo*
Thrombotic events		
Venous	***7.1%***	***6.9%***
Arterial	***3.2%***	***3.3%***
Transfusion related events	***0.0%***	***0.4%***

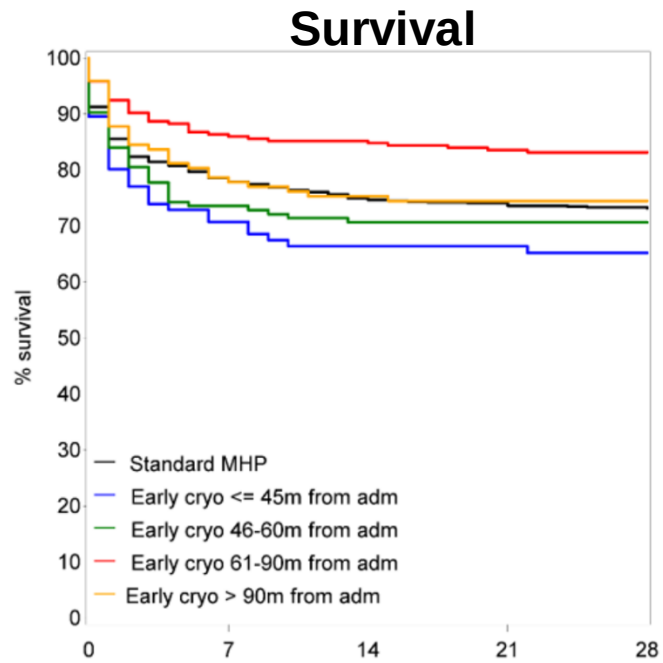
CRYOSTAT 2: Timing of cryoprecipitate and survival



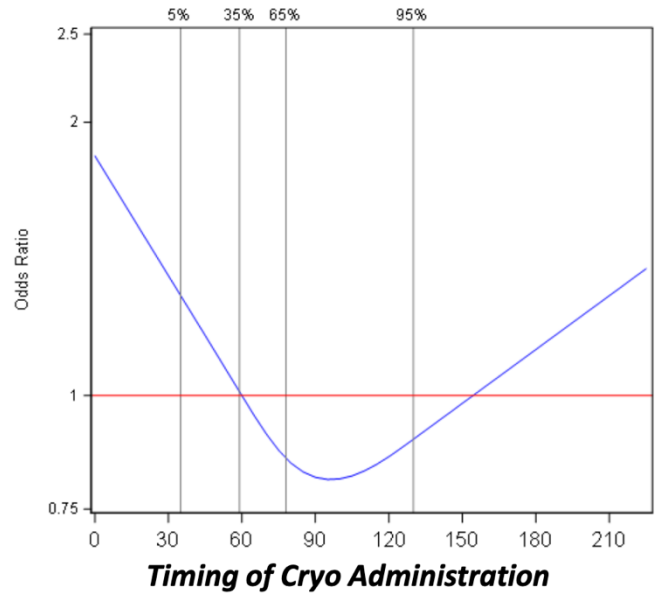
Median time to Cryo: 120 (79-184) vs 68 (53-85) mins

% Cryo within 90 mins: 9% vs 68%

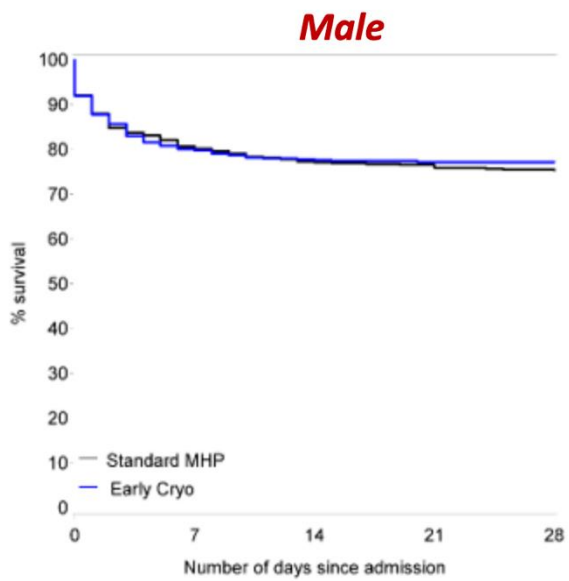
	Std MHP	Cryo <45 mins	Cryo 46-60 mins	Cryo 60-90 mins	Cryo >90 mins
n	***805***	***101***	***147***	***273***	***128***
28-day Mortality	***26.1%***	***34.4%***	***29.2%***	***16.5%***	***25.2%***
OR		***1.29 (0.94-1.77)***	***1.11 (0.84-1.48)***	***0.65 (0.46-0.91)***	***1.00 (0.71-1.41)***

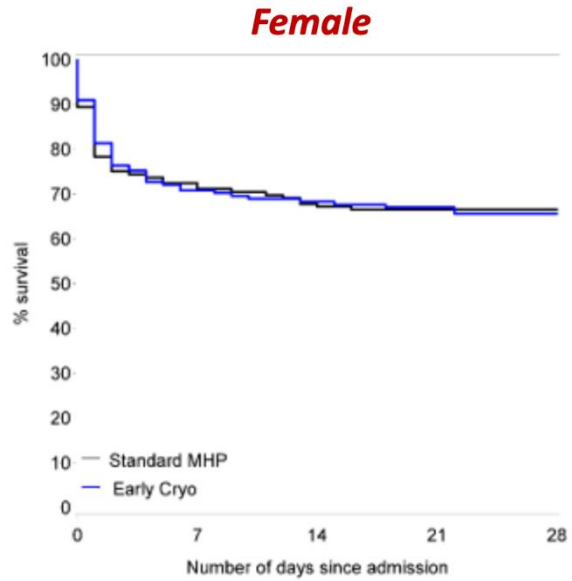


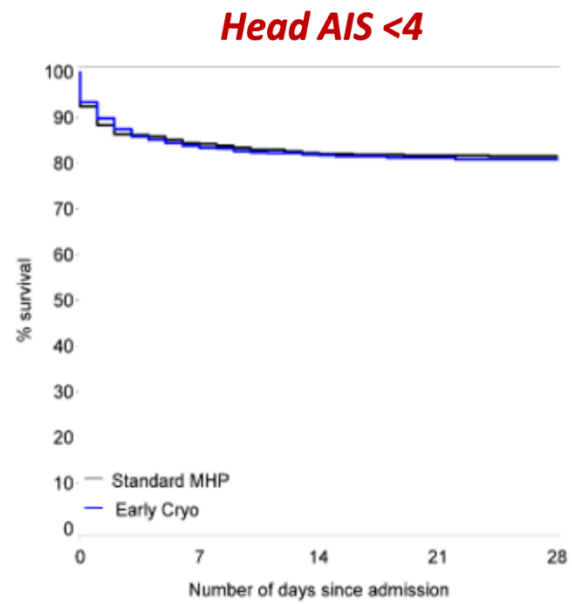
60-90 min

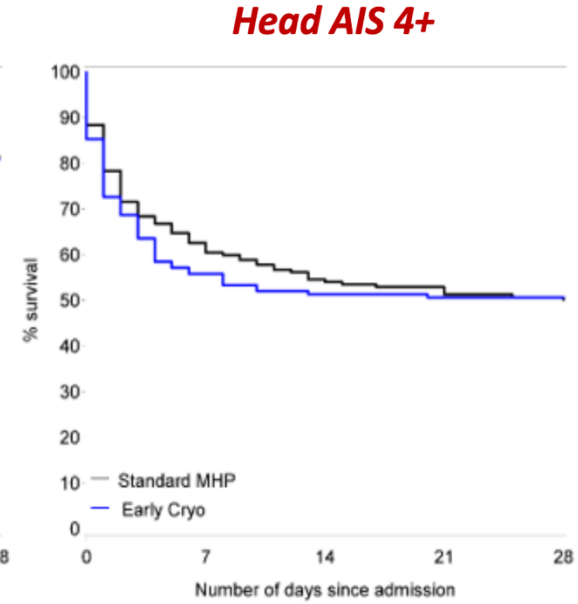


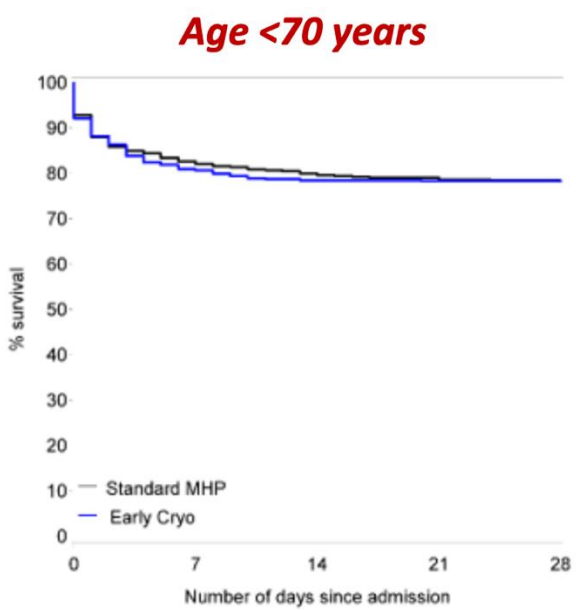
CRYOSTAT 2: Primary outcome by subgroup

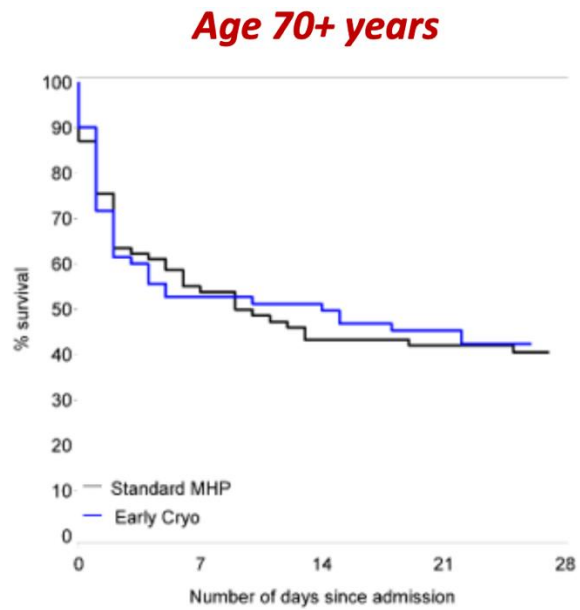


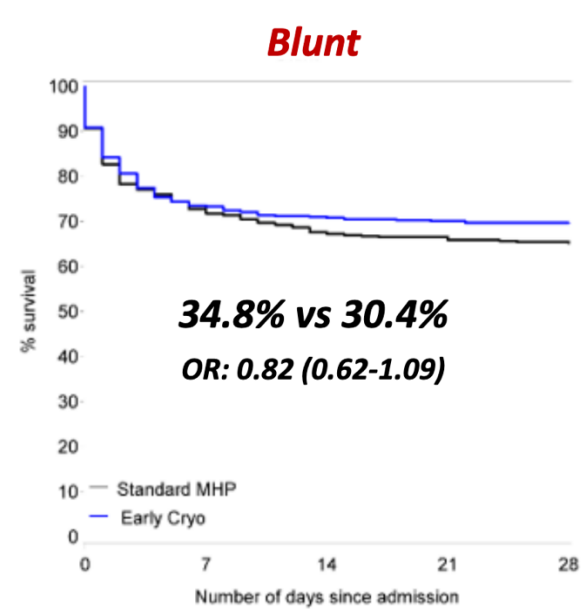


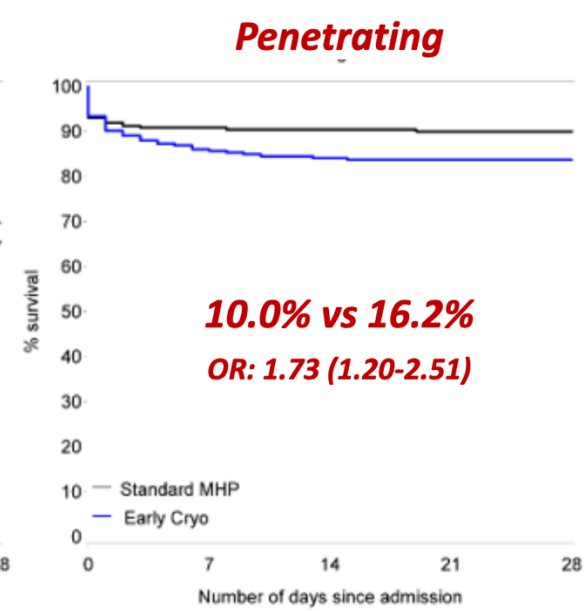












CRYOSTAT 2: Conclusion

CRYOSTAT-2
EARLY CRYOPRECIPITATE IN TRAUMA

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

CRYOSTAT 2: Conclusion

PROCOAG

JAMA. doi:10.1001/jama.2023.4080
Published online March 21, 2023.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion

The PROCOAG Randomized Clinical Trial

Pierre Bouzat, MD, PhD; Jonathan Charbit, MD; Paer-Selim Abback, MD; Delphine Huet-Garrigue, MD; Nathalie Delhaye, MD; Marc Leone, MD, PhD; Guillaume Marcotte, MD; Jean-Stéphane David, MD, PhD; Albrice Levrat, MD; Karim Asehnoune, MD, PhD; Julien Pottecher, MD, PhD; Jacques Duranteau, MD, PhD; Elie Courvalin, MD; Anais Adolle, MSc; Dimitri Sourd, MSc; Jean-Luc Bosson, MD, PhD; Bruno Riou, MD, PhD; Tobias Gauss, MD; Jean-François Payen, MD, PhD; for the PROCOAG Study Group

A randomized controlled trial in adult patients at risk of massive transfusion to test the hypothesis that 4F-PCC administration combined with a ratio-based transfusion is superior to ratio-based transfusion alone in reducing 24-hour blood product consumption

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PROCOAG: Methods

Inclusion criteria:

Adult patients with trauma directly admitted from injury scene to participating center with highest trauma level activation at
RISK of massive transfusion defined as

transfusion of at least 1 unit of pRBC during pre-hospital care or within 1 hour of admission

AND an Assessment of Blood Conssumption Score (ABC)* of at least 2

OR clinical assessment of the attending physician of risk of massive transfusion**

*ABC = 1 point for each, scores above 2 are likely to require massive transfusion
>Penetrating mechanism
>Systolic blood pressure (BP) <90 in emergency department (ED)
>Heart rate (HR) >120 in ED
>Positive Focused Assessment with Sonography for Trauma (FAST)

** Massive transfusion: at least 3 pRBC/1h of admission or at least 10 pRBC within first 24 hours

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PROCOAG: Methods

Exclusion criteria:

Traumatic cardiac arrest before randomization

Patients with catastrophic injuries expected to die within first hour of admission

Secondary admission from a different health care facility

Pre-injury treatment with anticoagulants

Pregnant patients

Known hypersensitivity to 4F-PCC and its analogues

Patients under guardianship

Any inclusion in another trial within past 30 days

Known pre-injury terminal condition

Patients without health insurance (according to French Law)

PROCOAG: Methods

Intervention:

Within 1 hour of admission 4F-PCC at a dose of 25U of factor IX per kg (1 mL/kg). Doses were administered at a speed of 120 mL/h

…in addition to standard local major haemorrhage protocol*

Control (Placebo):
1 mL/kg of normal saline. Doses were administered at a speed of 120 mL/h

… in addition to standard local major haemorrhage protocol*

* Both groups were treated with fluid expansion and early transfusion of blood products with a PRBC:FFP ratio between 1:1 and 2:1. TXA was administered within 3 hours at a loading dose of 1 g followed by 1 g over 8 hours. The source of bleeding was identified and treated as soon as possible. Fibrinogen was administered if measured fibrinogen was low or viscoelastic criteria (VET) showed a functional deficiency. Platelets were transfused to maintain a count higher than $50x10^9$/L.

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PROCOAG: Methods

Primary Outcome:

Total number of all blood product units (RBC, FFP, and platelets) consumed within the first 24 hours after arrival in the trauma bay

Secondary Outcomes:

- Individual blood product units consumed within the first 24 hours
- Time to Prothrombin Time (PT) less than 1.5
- Time to hemorrhage control
- 24-hour and 28-day mortality
- Number of ICU days, ventilator-free days, and hospital-free days through day 28
- Hospitalization status at 28 days
- Glasgow Outcome Scale-Extended score in patients with brain injury seen on computed tomography (CT) on admission (Abbreviated Injury Scale score >2)

Randomised, parallel-group
Sealed envelopes at sites

- Varying block size
- Stratified by centre

France > 12 Major Trauma Centres

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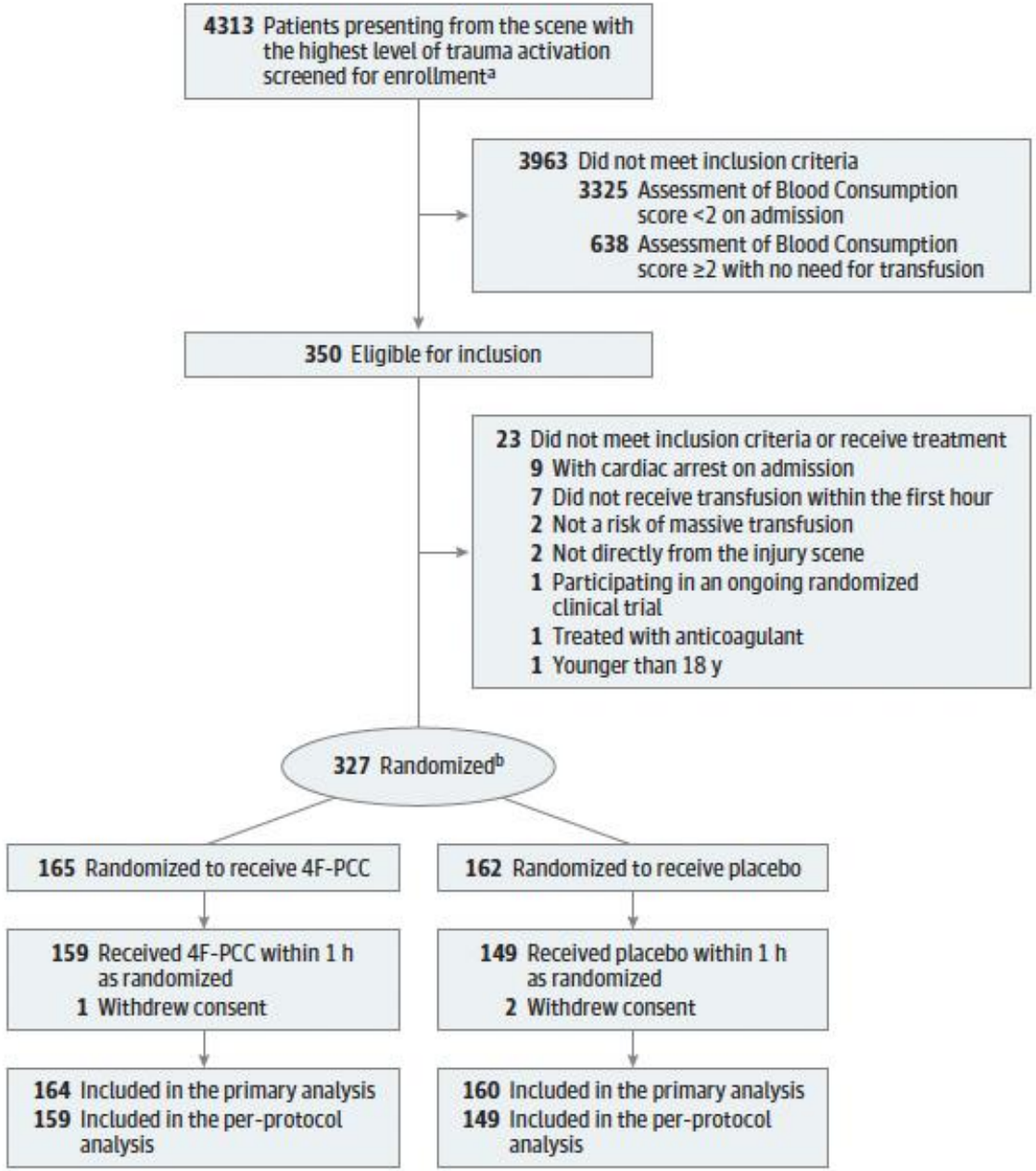
PROCOAG: Study flow



[a] Highest level of trauma activation corresponds to patients with a Glasgow Outcome Scale score less than 9, systolic arterial blood pressure less than 90 mm Hg, and/or acute respiratory distress on arrival at the trauma bay.

[b] Randomization was stratified by center.

PROCOAG: Patient characteristics

Demographics/Prehospital care

Characteristic	Median (IQR) [total No.] 4F-PCC (n = 164)	Placebo (n = 160)
Age, y	39.5 (26-55.5)	39 (27-57)
Sex, No. (%)		
Women	47 (29)	44 (27)
Men	117 (71)	116 (73)
Trauma, No. (%)		
Blunt	135 (82)	125 (78)
Penetrating	29 (18)	35 (22)
Prehospital		
Heart rate, /min	113 (90-131) [151]	114 (90-130) [155]
Systolic arterial blood pressure, mm Hg	101 (80-121) [151]	90 (74-111) [152]
Glasgow Outcome Scale score[a]	14 (9-15) [160]	14 (8-15) [153]
Tranexamic acid infused	125 (76)	138 (86)
Intubated	78 (48)	77 (48)
Time from injury to arrival in the trauma bay, min	105 (80-132) [148]	100 (75-132) [148]

No differences!

Admission

Admission		
Heart rate, /min	119 (95-132) [162]	115 (90-130) [158]
Systolic arterial blood pressure, mm Hg	89 (70-115) [160]	90 (70-110) [156]
Assessment of Blood Consumption score[b]	2 (1-2) [161]	2 (1-2) [147]
Assessment of Blood Consumption score ≥2, No. (%)	84 (52)	78 (53)
Time from arrival to beginning of treatment, min	35 (25-45) [154]	30 (15-50) [150]
Hemoglobin, g/dL[c]	10.5 (8.7-12.0) [160]	9.9 (8.2-11.6) [155]
Lactate, mmol/L[c]	4.5 (2.7-7.1) [132]	4.7 (2.9-7.5) [129]
Platelet count, $\times 10^9$/L	214 (181-266) [132]	204 (150-245) [125]
Fibrinogen, g/L[c]	1.7 (1.2-2.2) [134]	1.8 (1.2-2.2) [128]
Fibrinogen ≤1.5 g/L, No. (%) [No.]	49 (37) [134]	47 (37) [128]
PTr[c,d]	1.3 (1.15-1.51) [142]	1.3 (1.16-1.53) [130]
PTr >1.2, No. (%) [No.]	93 (65) [142]	89 (68) [130]
PTr >1.5, No. (%) [No.]	36 (25) [142]	34 (26) [130]
Thromboelastometry coagulation time, s[c,e]	73 (66-86) [31]	74 (66-95) [34]
Thromboelastometry coagulation time ≥80 s, No. (%) [No.]	11 (35) [31]	13 (38) [34]
AIS Head score >2, No. (%) [No.][f]	55 (35) [156]	50 (34) [149]
ISS[g]	34 (25-50) [156]	38 (29-50) [149]
ISS ≥15, No. (%) [No.]	143 (92) [156]	144 (97) [149]
Revised trauma score[h]	6.8 (5.8-7.6) [160]	6.6 (5.7-7.6) [153]

No differences!

PROCOAG: Patient characteristics (Resuscitation indicators)

	Median (IQR) [total No.]	
	4F-PCC (n = 164)	Placebo (n = 160)
Resuscitation indicators, No. (%)[I]		
Need for hemostasis control procedure (surgical or radiological)	115 (70)	111 (69)
Transfusion of ≥3 U of RBCs within the first hour	67 (42)	60 (38)

	Median (IQR) [total No.]	
Characteristic	4F-PCC (n = 164)	Placebo (n = 160)
Transfusion of ≥10 U of RBCs within the first 24 h	42 (26)	43 (28)
Fibrinogen concentrate treatment	141 (86)	129 (81)
Total dose of fibrinogen concentrate, median (IQR), g	3 (3-7.5)	3 (3-6)
Time from arrival to transfusion of FFP, min	73 (56-105) [122]	91 (59-142) [130]

No differences!

PROCOAG: Total blood product consumption (primary outcome)

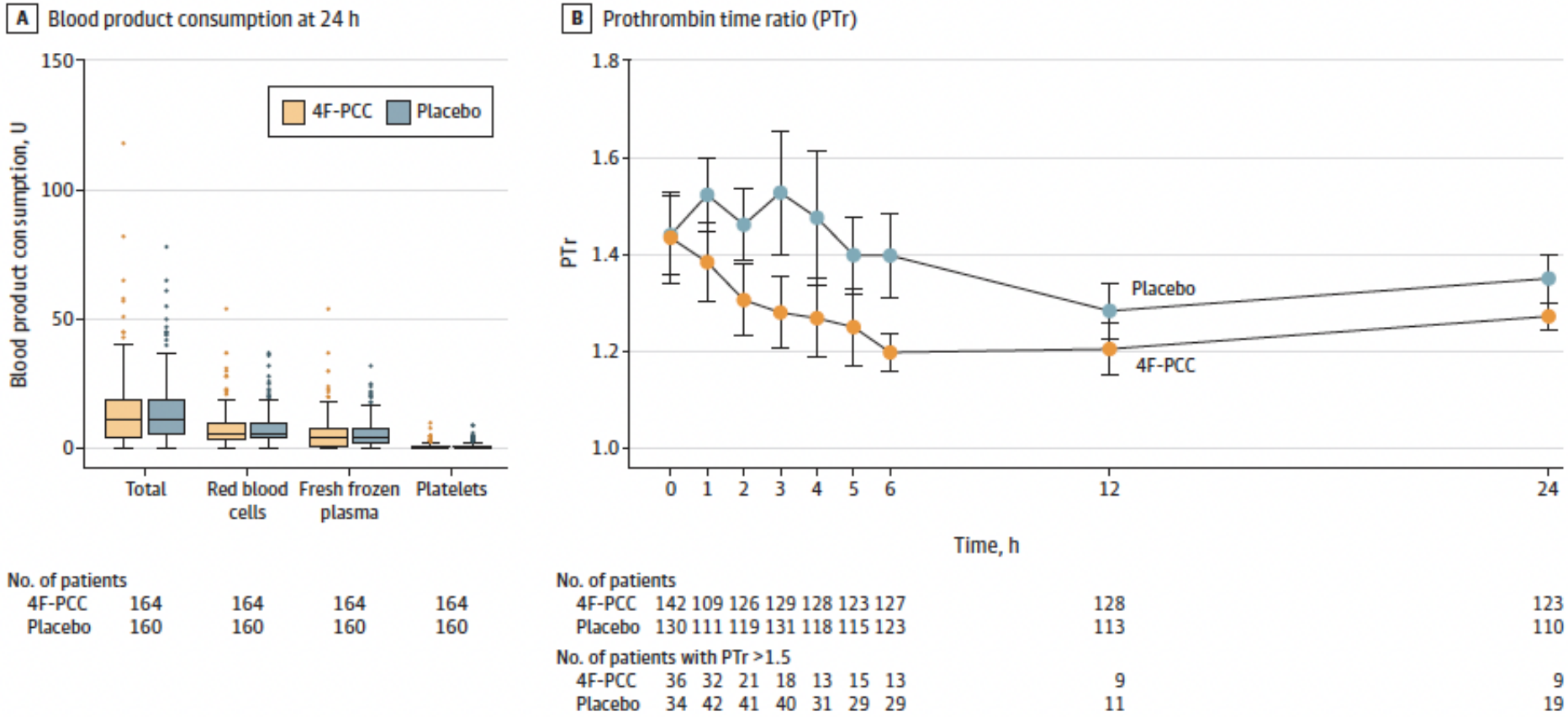
Outcome	No. (%) 4F-PCC (n = 164)	Placebo (n = 160)	Absolute difference (95% CI), %[a]	*P* value[b]
Primary outcome				
Total blood product consumption, median (IQR), U	12 (5 to 19)	11 (6 to 19)	0.2 (−2.99 to 3.33)	.72

Secondary outcomes

Secondary outcomes				
Red blood cell consumption, median (IQR), U[c]	6 (3.5 to 10)	6 (4 to 10)	−0.3 (−1.8 to 1.3)	.93
Fresh frozen plasma consumption, median (IQR), U[d]	4 (1 to 8)	4 (2 to 8)	0.1 (−1.3 to 1.5)	.56
Platelet concentrate consumption, median (IQR), U[e]	1 (0 to 1)	1 (0 to 1)	0.0 (−0.3 to 0.3)	.83
Time to PTr <1.5, median (IQR) [No.], min[f]	0 (0 to 60) [154]	0 (0 to 60) [145]	−8.5 (−48.9 to 32.0)	.86
Mortality				
24-h	18 (11)	20 (13)	−2 (−9 to 5)	.67
28-d	26 (17)	30 (21)	−3 (−12 to 5)	.48
Time to achieve anatomic hemostasis, median (IQR) [No.], min[g]	300 (203 to 423) [131]	288 (210 to 404) [128]	22 (−73.3 to 73.8)	.96
Hospital-free days through day 28, median (IQR)	6.5 (0 to 22.5)	7 (0 to 22)	−0.15 (−1.65 to 1.35)	.78
Ventilator-free days through day 28, median (IQR)	4 (0.5 to 7)	4 (0 to 8)	0.33 (−1.0 to 1.6)	.51
ICU-free days through day 28, median (IQR)	6.5 (0 to 22.5)	7 (0 to 22)	1.22 (−5.93 to 8.37)	.78
Disposition at day 28				
Remained hospitalized	44 (33)	44 (35)	0 (−10 to 10)	.81
Intensive care unit	37 (28)	28 (23)	5 (−5 to 16)	
Home	31 (23)	29 (23)	−3 (−12 to 6)	
Died	26 (17)	30 (21)	−3 (−12 to 5)	
Rehabilitation	19 (14)	22 (18)	−2 (−14 to 9)	
Other	2 (2)	1 (1)	1 (−2 to 3)	
Unknown	5 (3)	6 (4)		
Glasgow Outcome Scale-Extended score, median (IQR) [No.][h]	3 (3 to 4) [36]	3 (3 to 5) [27]	−0.5 (−1.91 to 0.91)	.45

PROCOAG: Secondary outcomes

Figure 2. Transfusion-Related Secondary Outcomes by Treatment Group



- ❖ **No differences in blood product consumption within first 24 hours**
- ❖ **Faster recovery of INR to 1.2 within 6 hours of admission**

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PROCOAG: Secondary outcomes (Complications and safety)

Table 3. Thromboembolic Events by Treatment Group

Thromboembolic event	No. (%) 4F-PCC (n = 164)	No. (%) Placebo (n = 160)	Absolute difference (95% CI), %[a]	Relative risk (95% CI)	*P* value[b]
Patients with at least 1 thromboembolic event, No. (%) [No.]	56 (35) [161]	37 (24) [157]	11 (1 to 21)	1.48 (1.04 to 2.10)	.03
Superficial venous thrombosis	5 (3.1)	1 (0.6)	2 (−1 to 5)		
Deep venous thrombosis	27 (16.8)	23 (14.6)	2 (−6 to 10)		
Pulmonary embolism	20 (12.4)	17 (10.8)	2 (−5 to 9)		
Stroke[c]	2 (1.2)	0	1 (−1 to 3)		
Other[d]	9 (5.6)	5 (3.2)	2 (−2 to 7)		

Abbreviation: 4F-PCC, 4-factor prothrombin complex concentrate.

[a] Absolute differences were not adjusted.

[b] χ^2 test was used for the comparison.

[c] Stroke was diagnosed using cerebral contrast-enhanced computed tomography.

[d] Other includes extremity ischemia (n = 11), thrombosis of venous surgical anastomosis (n = 2), and mesenteric infarction (n = 1). There were no incidents of myocardial infarction in either group.

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PROCOAG: Conclusion

The empiric use of 4F-PCC in patients at risk of massive transfusion was not supported by this RCT as it did not reduce 24-hour blood product consumption and was associated with more thromboembolic events.

Thank you very much!