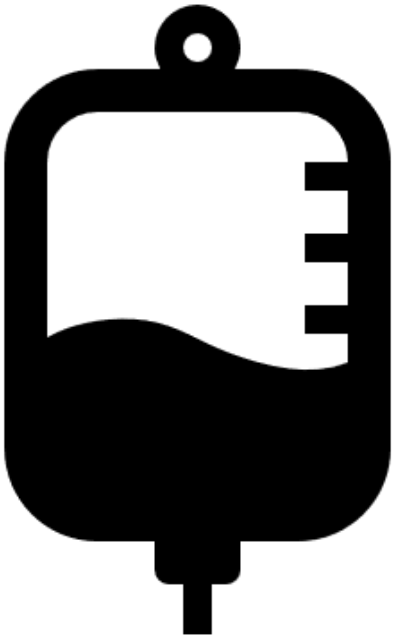
Traumatic Coagulopathy and Tranexamic Acid: A "TEG" of War



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Learning Objectives:

For Pharmacists:

1. Compare the hemostatic pathophysiology of trauma and non-trauma patients
2. Discuss current trauma guideline recommended therapy options for cessation of bleeding
3. Critique evidenced-based literature for the use of tranexamic acid on hemostatic coagulopathy
4. Given a patient case, determine the role of tranexamic acid for bleeding cessation

For Pharmacy Technicians:

1. Compare the hemostatic pathophysiology of trauma and non-trauma patients
2. List current trauma guideline recommended therapy options for cessation of bleeding
3. Recognize the appropriate dose and interval of tranexamic acid used for trauma patients

Normal Hemostatic Pathophysiology

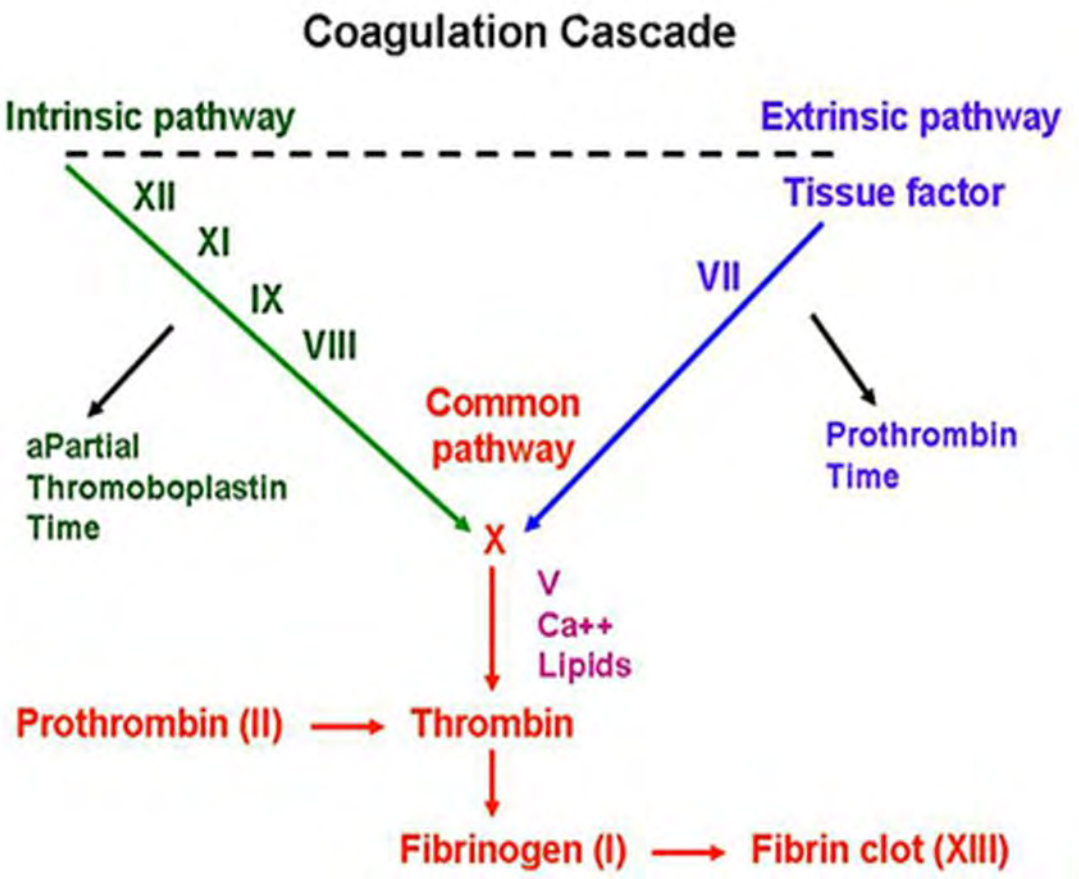
Background

A hemostatic balance that is maintained in the body by complicated interactions between the coagulation and fibrinolytic systems under normal physiology.

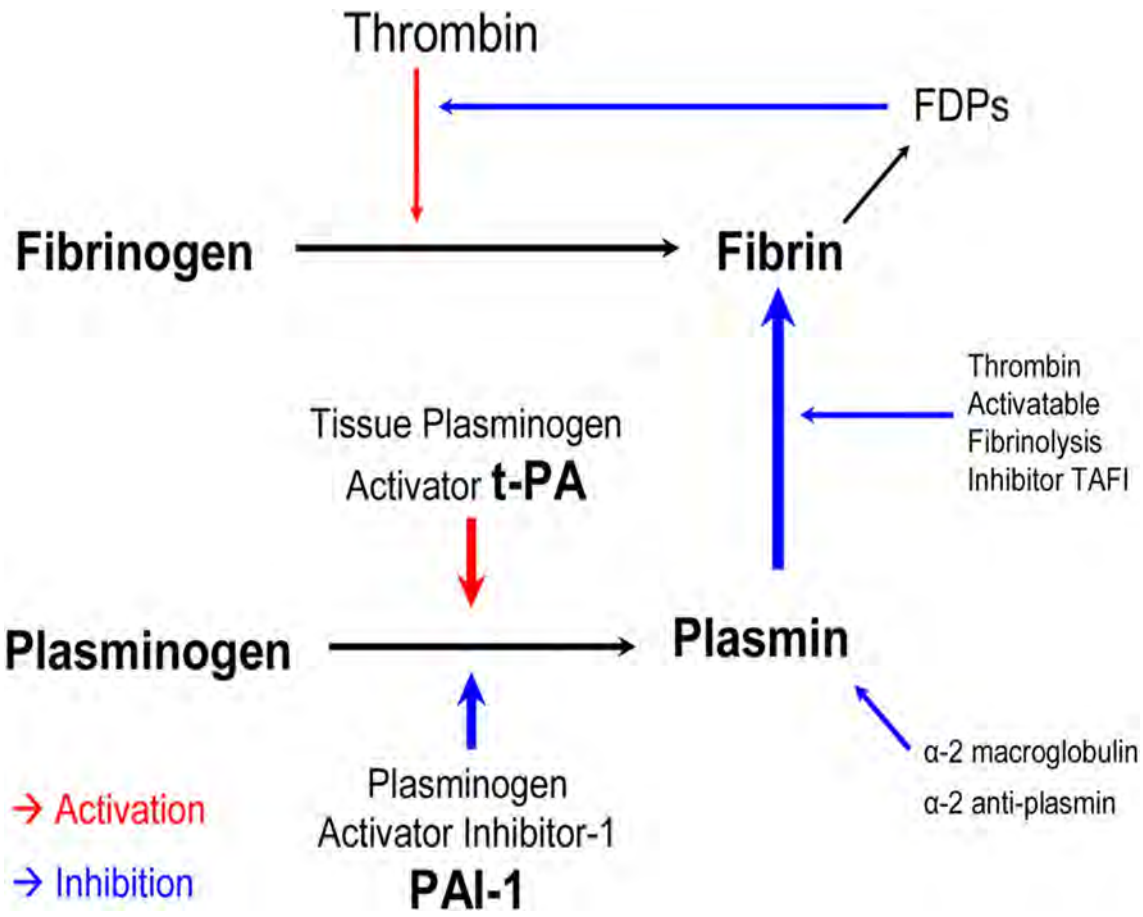
Thrombogenic and antithrombogenic components in the body[1]

Site	Thrombogenic	Antithrombogenic
Vessel Wall	Exposed endothelium	Heparin
	Tissue factor	Thrombomodulin
	Collagen	Tissue plasminogen activator (TPA)
Circulating Elements	Platelets	Antithrombin
	Platelet activating factor	Protein C and Protein S
	Clotting factor	Plasminogen
	Prothrombin	
	Fibrinogen	
	Von Willebrand factor	

Coagulation Cascade



Fibrinolysis



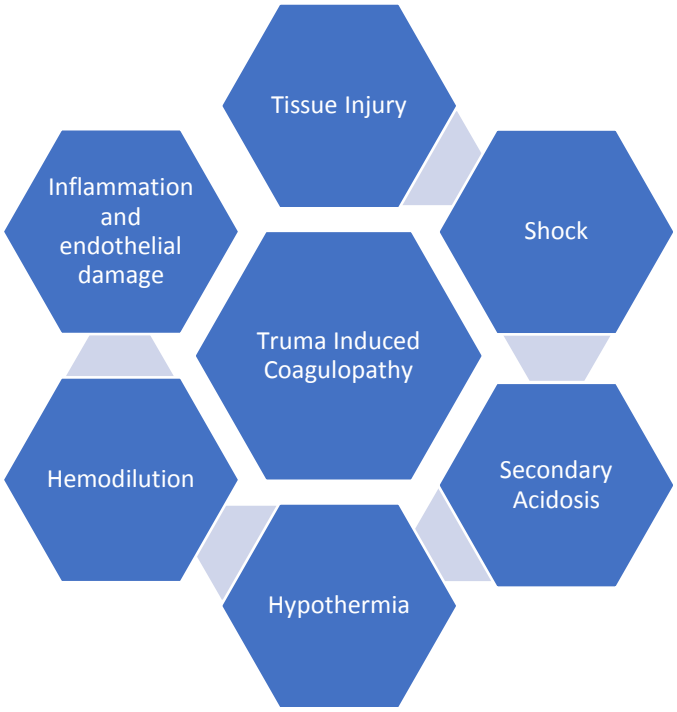
Where does plasmin come from?

Plasminogen → tPA / urokinase → Plasmin

Plasminogen comes from liver and is incorporated into the clot during formation

tPA comes from injured endothelium over a series of days

Trauma Induced Coagulopathy Pathophysiology



Background

A clinical syndrome featuring coagulopathy occurring in the early stage of trauma that is caused by activation of coagulation, fibrinolytic and anti-coagulation pathways.[2]

The balance of the coagulation system also changes rapidly during injury and resuscitation so that the trauma induced coagulopathy phenotype can change over time. The patient's coagulation status can cycle rapidly between an anticoagulant state and a procoagulant state within hours to days.[3]

Key Processess in Trauma Induced Coagulopathy[3]

Natural anticoagulant dysfunction

Platelet dysfunction

Hyperfibrinolysis

Fibrinogen consumption

Trauma Induced Coagulopathy Characteristics[4]

Hemostatic Item	Normal	Trauma Induced Coagulopathy Characteristic
Prothrombin Time	11-12.5 seconds	Prolonged
Fibrinogen	150-400 mg/dL	Low
Antithrombin	0.15-0.2 mg/ml	Low
Fibrinogen degradation products	<10 mcg/mL	Increased
Platelets	150,000-450,000/ml	Decreased
Protein C	65-135 IU/dL	Low

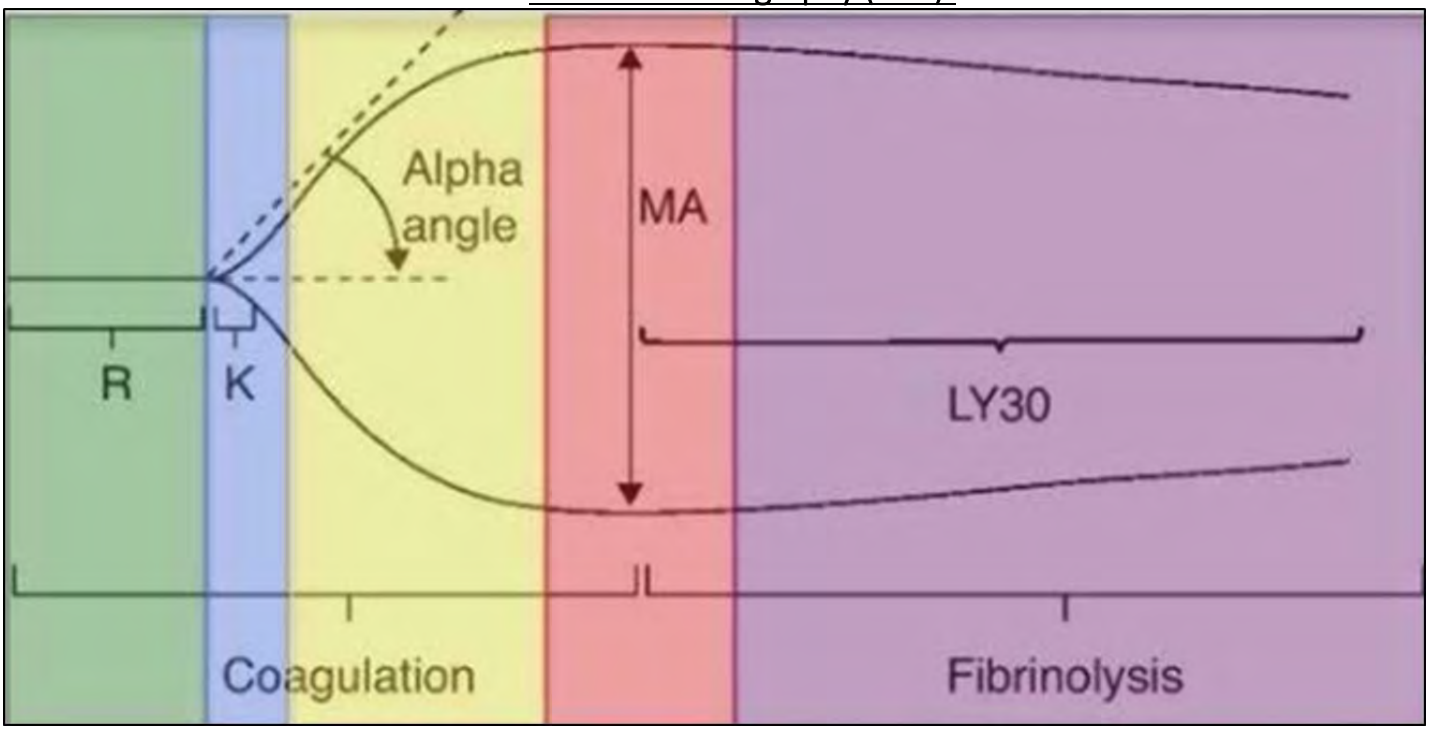
Coagulation Tests[4]

Conventional Test	What it measures	Normal value
Prothrombin time (PT)	Factors II (prothrombin), VII, X Time it takes the blood to clot	11-12.5 seconds
International Normalized Ratio (INR)	Adjusts the PT ratio based on the sensitivity of the thromboplastin used to perform the test	No anticoagulation: 0.8-1.1
Activated Partial Thromboplastin Time (aPTT)	Used to monitor heparin therapy	20-35 second
Platelet counts	International normalized ratio (INR) And platelets	Platelets: 150,000 to 450,000/ ml of blood
Hemoglobin/hematocrit[5]	Protein in the red blood cells that delivers oxygen and volume of red blood cells	Hemoglobin men: 13.5-17. g/dL Hemoglobin women: 12-15.5 g/dL Hematocrit men: 41%-50% Hematocrit women: 36%-48%
Anti-Xa level[6]	Measurement of antithrombin-catalyzed inhibition of factor Xa by unfractionated heparin and direct inhibition of factor Xa by low-molecular weight heparin	Therapeutic ranges dependent on agent

Limitations:

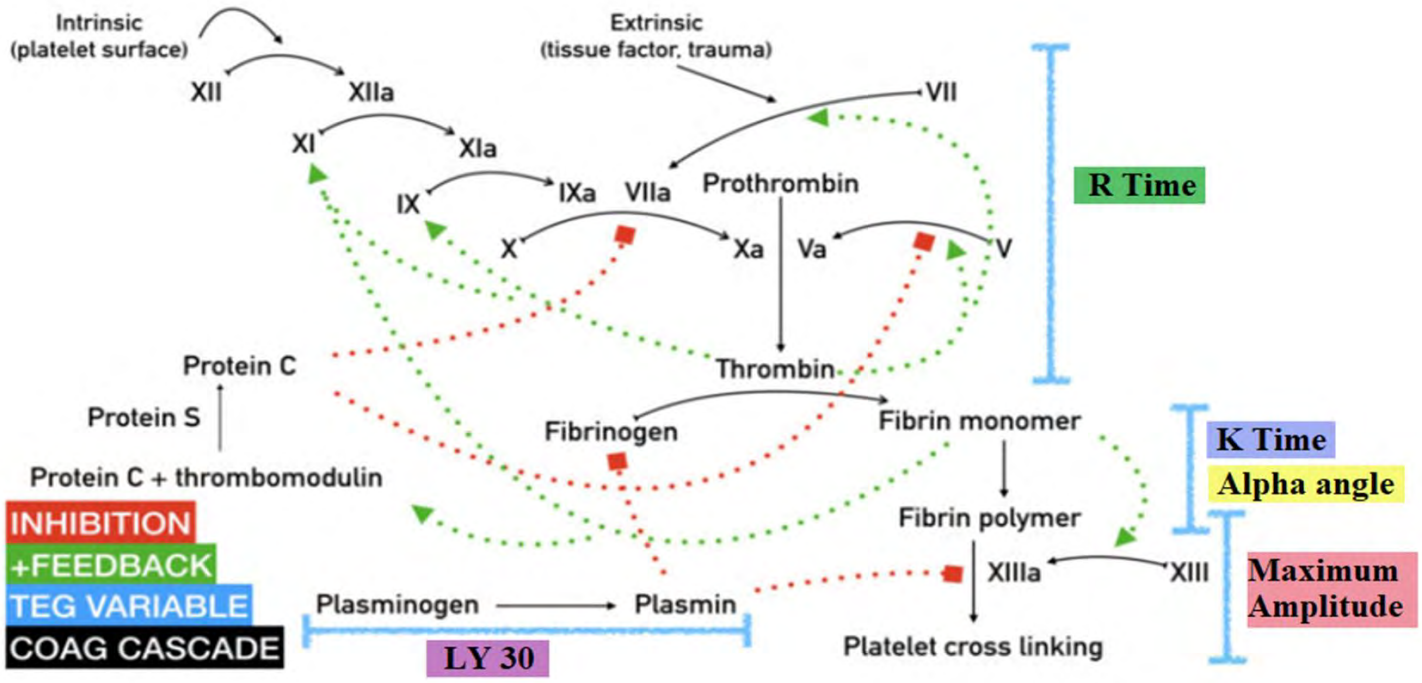
- Fibrinolysis is not well captured by standard assays
- Associated with excessive blood product use
- Cannot provide overall hemostatic function in semi-real time

Thromboelastography (TEG)[7]

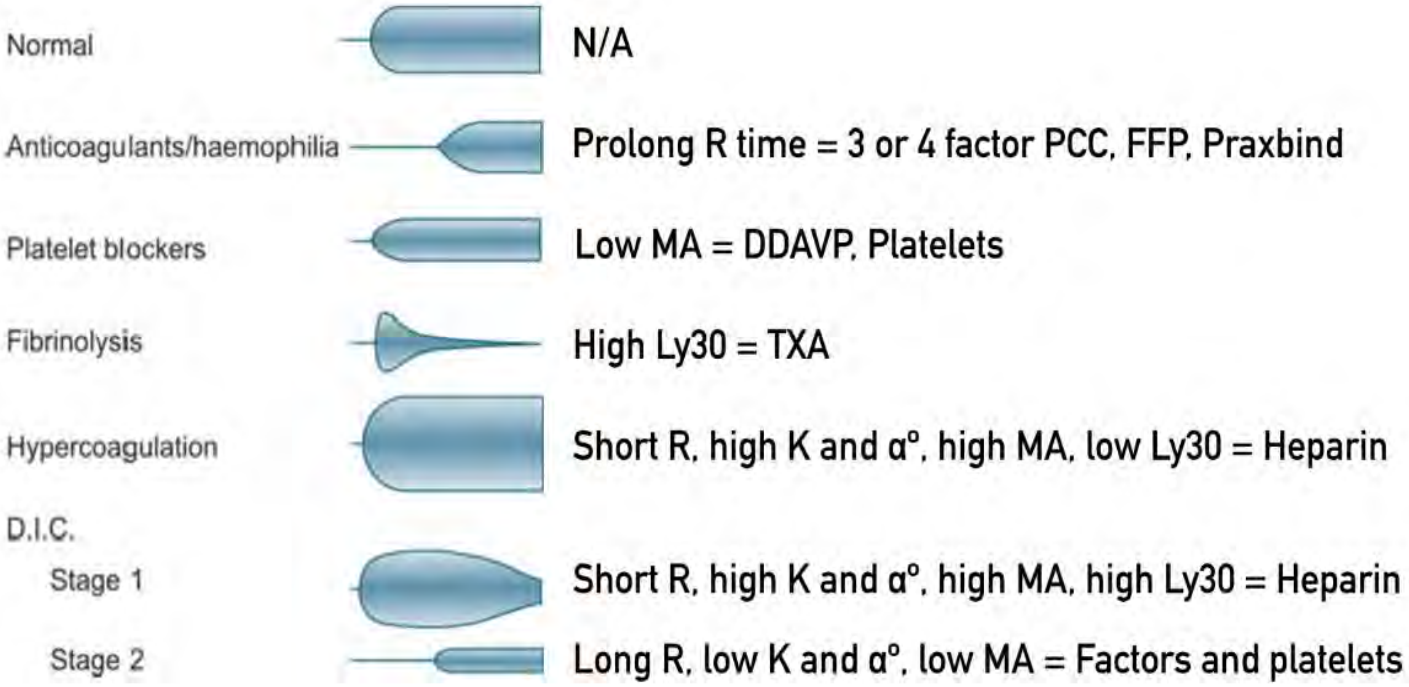


Thromboelastometry (TEG) and rotational thromboelastometry (ROTEM) are tests that measures the viscoelastic properties of whole blood.
These tests provide rapid information on the dynamics of clot development, stabilization, and dissolution (fibrinolysis).

Thromboelastogram (TEG)				
Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 - 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 - 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 - 72 degrees	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 - 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (LY30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 - 8%	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid



http://www.emdocs.net/thromboelastogram-teg-five-minute-primer-emergency-physician/



http://www.emdocs.net/thromboelastogram-teg-five-minute-primer-emergency-physician/

TEG is performed using a citrated sample of whole blood placed into a heated sample cup with calcium chloride, kaolin, and phospholipids. As the sample cup oscillates, formation of a clot results in the generation of rotational forces on a pin suspended from a torsion wire. These forces are transmitted to an electrical transducer, creating a waveform (shown in the figure above).[8]

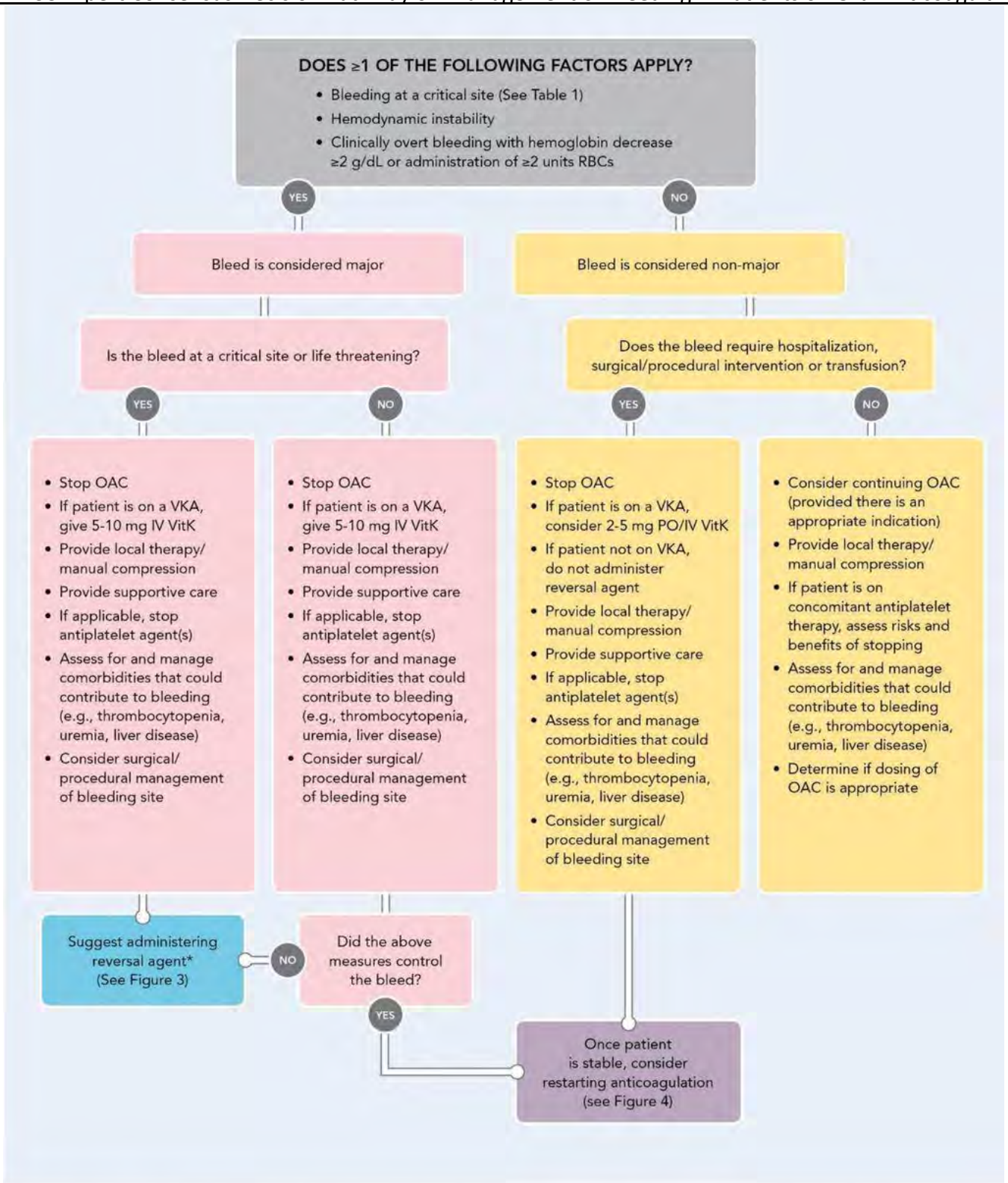
Limitations:

- Difficult to standardize
- Significant variability in TEG/ROTEM results even when repeated on the same sample
- Laboratory-trained personnel maintain the machine and perform testing
- More expensive than standard testing
- Limited/no availability at many hospitals
- Limited provider awareness and training for interpretation

Guideline Directed Management

Eastern Association for the Surgery of Trauma Damage Control Resuscitation in Patients with Severe Traumatic Hemorrhage[9]

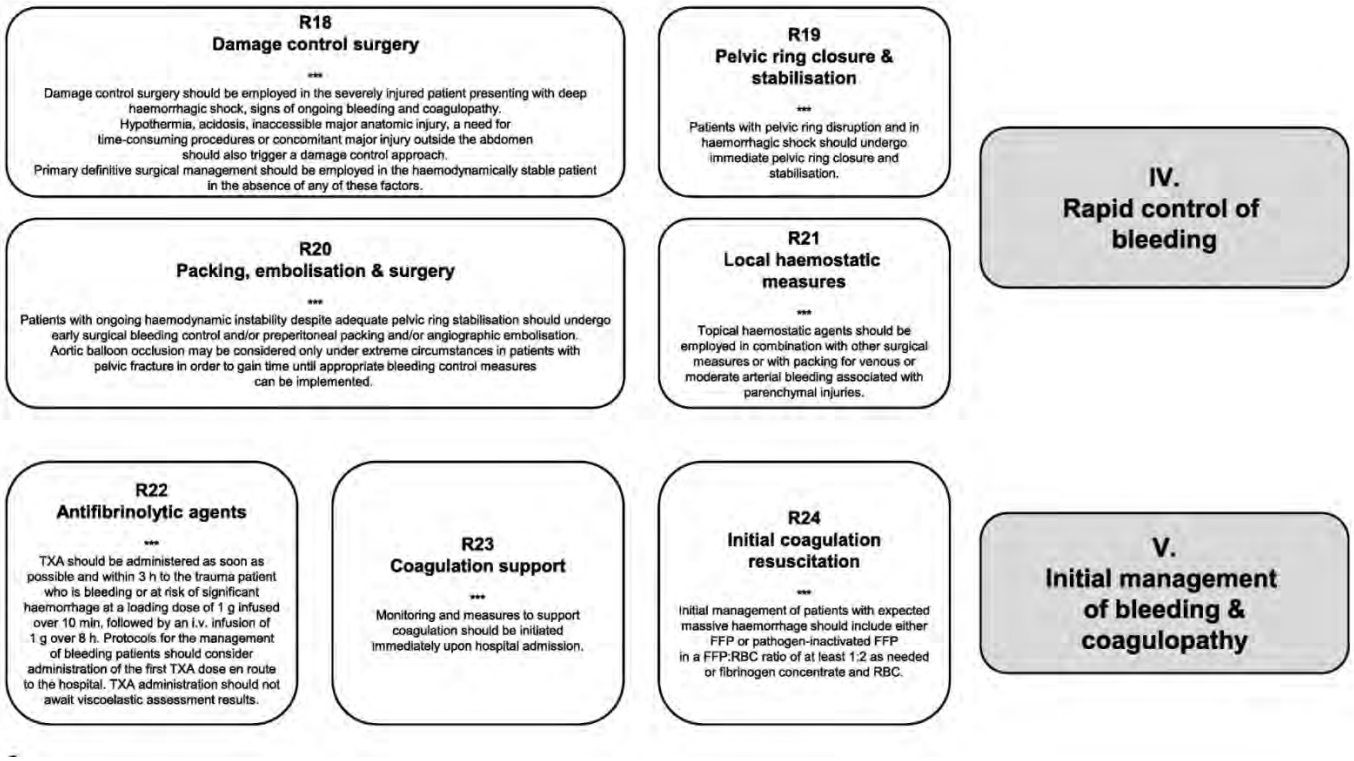
Question	Recommendation
PICO 1	In adult patients with severe trauma, we *recommend* the use of a massive transfusion/damage control resuscitation protocol in comparison to no protocol to reduce mortality.
PICO 2	In adult patients with severe trauma, we *recommend* targeting a high ratio of plasma and platelets to red blood cells as compared to a low ratio to reduce mortality. This is best achieved by transfusing equal amounts of RBC, PLAS, and PLT during the early empiric phase of resuscitation.
PICO 3	In adult patients with severe trauma, we cannot recommend for or against the use of rVIIa as a hemostatic adjunct in comparison to no rVIIa.
PICO 4	In adult patients with severe trauma, we *conditionally recommend* the use of TXA as an in-hospital hemostatic adjunct in comparison to no TXA.



DOAC = direct oral anticoagulant; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; PO = per os "by mouth"; RBCs = red blood cells; VitK = vitamin K; VKA = Vitamin K antagonist

*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

European Guidelines on Management of Major Bleeding[11]



Other Hemostatic Agents[12,13]

Agent	MOA	Admin	Ease of Access	Side Effects	Total Cost for 1 full treatment (AWP)
PCC (Kcentra ®)	Increase levels of inactive factors II, VII, IX, X, protein C & S	IV; 25-50 U/kg Max: 5000 U	Reconstitute before administering	Hypotension, nausea, vomiting, anemia	~$6,000 (80 kg patient)
Phytonadione (Mephyton ®)	Promotes liver synthesis of factors II, VII, IX, X	IV; initial 10 mg as soon as possible with PCC for INR >1.4	Dilute injection; administer using infusion pump. Do not push.	Pain, swelling at injection site, chest pain, dizziness	~$52
Fresh frozen plasma (FFP)	Replaces all clotting factors and plasma proteins	10-30 ml/kg	Stored frozen. Must be thawed and used with 24 hours	Transfusion associated circulatory overload; anaphylaxis	~$220

Cryoprecipitate	Contains fibrinogen, factor VIII, fibronectin, factor XIII, and Vw factor	5-10 U in 50-200 ml for a typical adult	Has to be made using FFP and centrifuge	Infection, volume overload, transfusion rxns	~$144
Tranexamic Acid (Lysteda®)	Displaces plasminogen from fibrin resulting in inhibition of fibrinolysis	1 gram IV bolus over 10 minutes within 3 hours injury followed by 1 gram over 8 hours infusion	Direct IV injection with a max rate of 100 mg/min	HA, thrombosis, abd/back pain, , N/V/D, visual disturbances, anaphylaxis, hypotension	~$75
Desmopressin (DDAVP®)	Increases plasma levels of von Willebrand factor, factor VIII, and t-PA	0.3-0.4 mcg/kg infuse over 15 to 30 minutes	Dilute solution for injection in 50 ml NS for IV infusion	Hyponatremia, hypertension, headache	~$375 (70 kg patient)

Tranexamic Acid[14]: anti-fibrinolytic drug and a synthetic equivalent of the amino acid lysine.

Indications
• Administer less than 3 hours from time of injury • Severe hemorrhagic shock with systolic blood pressure below 90 mmHg • Heart rate above 110 beats per minute • Multi-system trauma with evidence of active hemorrhage • Major pelvic fracture with evidence of active hemorrhage • Solid organ injuries with evidence of active hemorrhage • Traumatic amputations
Contraindications
• Acquired defective color vision • Hypersensitivity to TXA or any of its ingredients • Subarachnoid hemorrhage and/or known isolated head injury • Do not give in conjunction with prothrombin complex concentrate (PCC) • Active intravascular clotting and/or history of thromboembolism • Known history of renal failure
How is it given
• Loading dose bolus: 1 gram TXA + 100 ml normal saline over 10 minutes • Followed by infusion: 1 gram TXA + 250 ml normal saline over 8 hours
Adverse effects
• Anaphylaxis • Thrombosis • Nausea, vomiting, diarrhea • Visual disturbances: blurred vision, changes in color • Hypotension with rapid infusion (rate >100 mg/min)

Controversy: **Rationale for use and mechanism of action of tranexamic acid in trauma population.**

Table 1. CRASH-2 Trial[15]

Citation	Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet*. 2010;376:23-32. doi:10.1016/S0140-6736(10)60835-5.
Objective	To determine the effects of the early administration of a short course of tranexamic acid (TXA) on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients
Methods	
Study Design	• Placebo-controlled, multicenter, international, double blind • Funded by Bupa Foundation, the JP Moulton Charitable Foundation and the Health Technology Assessment program of the National Institute for Health Research
Population	Inclusion • Adult trauma patients with significant hemorrhage (SBP<90 mmHg or HR >110 bpm or both) • Considered to be at risk of significant hemorrhage • Within 8 hours of injury Exclusion • Patient's considered to have a clear contraindication to antifibrinolytic therapy should not be randomized • Patients for whom the responsible doctor considered that there was a clear indication were not randomly assigned
Intervention	When the responsible doctor was substantially uncertain as to whether to treat with this agent, these patients where eligible for randomization Patients were randomly assigned to receive a loading dose of 1 gram of tranexamic acid infused over 10 minutes, followed by an IV infusion of 1 gram over 8 hours or matching placebo (0.9% saline)
Outcomes	• Primary: death in hospital within 4 weeks of injury. Cause of death was described by the following categories (bleeding, vascular occlusion (MI, stroke, PE), multiorgan failure, head injury, and other • Secondary: vascular occlusive events (MI, stroke, PE and DVT), surgical intervention, receipt of blood transfusion and units of blood products transfused. Outcomes were recorded if they occurred while the patient was still in hospital for up to 28 days after randomization
Statistical Analysis	• Intention to treat analyses with a 4 week follow up • Based on Medical Research Council CRASH trial of corticosteroids in head injury, the overall risk of death was 20%. Expected a similar risk of death here. • Current trial was planned to be able to detect a 2% survival benefit. A trial of 20,000 patients was planned which would have an 85% change of achieving a two-sided p value of less than 0.01 and a 95% chance of a two-sided p value of less than 0.05. This was met with a study population of 20,211 patients.
Results	
Baseline Characteristics	**TXA (n=10,093) vs Placebo (10,114)**

Mean time since injury (hours)	SBP <90 (%)	Glasgow Coma Scale 3-8 (%)	Glasgow Coma Scale 13-15 (%)	Blunt Trauma (%)	Mean age (years)

	2.8 vs 2.9	31.5 vs 32.7	17.8 vs 18.2	68.7 vs 68.3	67.5 vs 67.7	34.6 vs 34.5

Outcomes	• Death from any cause 14.5% vs 16%; RR 0.91 95% CI (0.85-0.97) p=0.0035 • Death by bleeding 4.9% vs 5.7%; RR 0.85 95% CI (0.76-0.96) p=0.0077 • No difference in vascular occlusive events 1.7% vs 2%; 0.84 95% CI (0.68-1.02) p=0.084 • Blood transfusion 50.4% vs 51.3%; RR 0.98 95% CI (0.96-1.01) p=0.21	
Author's Conclusions	Tranexamic acid could be given in a wide range of health-care settings and safely reduced the risk of death in bleeding trauma patients in the study. TXA appears most effective when given early after the trauma and should be given only within approximately 3 hours.	
Critique	<u>Strengths</u> • Trial design • Low baseline mortality rate • Pragmatic trial • External validity • Follow-up • No defined inclusion criteria • NNT	<u>Limitations</u> • No mention of similar standards of care throughout clinical centers • No measure of fibrinolytic activity • No data regarding hemorrhagic shock severity • Injury severity score (ISS) unmeasured • RBC transfusion availability (~50% did not get transfused)
Summary	The use of tranexamic acid in the trauma patient with significant bleeding reduces mortality by 1.5% without increasing thromboembolic events.	

Table 2. MATTERs Trial[16]		
Citation	Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg*. 2012;147:113-119. doi:10.1001/archsurg.2011.287.	
Objective	To characterize contemporary use of tranexamic acid in combat injury and to assess the effect of its administration on total blood product use, thromboembolic complications and mortality	
Methods		
Study Design	Retrospective, observational cohort study at a single surgical hospital	
Population	<u>Inclusion</u> • Patients who received at least 1 unit of PRBCs within 24 hours of admission following combat related injury	<u>Exclusion</u> • No receipt of packed red blood cells
Intervention	A standard dosing regimen of tranexamic acid (TXA) consisted of an intravenous bolus of 1 gram, repeated as felt indicated by the managing clinician. Patients who received TXA were assigned to the treatment group and compared with those who did not receive TXA.	
Outcomes	Primary: 24 and 48 hours and in-hospital mortality	

<table>
<tr><td></td><td>Secondary: transfusion requirements and coagulation parameters (prothrombin time and activated partial thromboplastin time), TXA dose, timing of TXA, and incidence of thrombotic events such as deep venous thrombosis or pulmonary thromboembolism.</td></tr>
<tr><td>Statistical Analysis</td><td>Comparison between the TXA and no-TXA groups were performed using a chi squared test and differences in means were assessed using t test or Mann-Whitney rank sum test. Continuous variables were dichotomized using defined cutoff values recorded at the time of admission: Glasgow coma scales score (≤8 vs >8), systolic blood pressure (≤90 vs 90 mm Hg), injury severity score (> 15 vs ≤15), and body region abbreviated injury scores (≥3 vs <3).</td></tr>
<tr><td colspan="2">Results</td></tr>
<tr><td>Baseline Characteristics</td><td>N=896 patients constituted the overall MATTERs study cohort. Of these, 293 (32.7%) received intravenous TXA within 1 hour of injury. In the overall cohort, the TXA group had a lower revised trauma score and a greater percentage of patients presenting with a depressed GCS score and hypotension. In the overall cohort, the rate of PTE and DVT were greater in the TXA group compared with the no-TXA group, but no fatalities attributed to PTE in either cohort.
<table>
<tr><th colspan="6">TXA(n=293) vs No TXA (n=603)</th></tr>
<tr><td>Mean Injury Severity Score (#)</td><td>SBP <90 (%)</td><td>Glasgow Coma Scale ≤8 (%)</td><td>Gunshot Wound (%)</td><td>Explosion (%)</td><td>Mean age (years)</td></tr>
<tr><td>25.5 vs 22.5</td><td>22.8 vs 13.8</td><td>63.3 vs 35.6</td><td>25.3 vs 36.7</td><td>74.7 vs 62.4</td><td>24.9 vs 23.1</td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td>• Overall: absolute reduction in in-hospital mortality for TXA group = 6.5 %; p=0.03
• TXA group: lower 48-hour mortality 11.3% vs 18.9%; p=0.004
• Massive transfusion: absolute reduction in in-hospital mortality for TXA group =13.7%; p=0.004
• Rate of PE greater in TXA group 2.7% vs 0.3%; p=0.001
• Rate of DVT greater in TXA group 2.4% vs 0.2%; p=0.001</td></tr>
<tr><td>Author's Conclusions</td><td>The use of TXA in conjunction with a blood component-based resuscitation following combat injury results in improved measures of coagulopathy and survival</td></tr>
<tr><td>Critique</td><td><u>Strengths</u>
• Confirms findings from the CRASH-2 trial
• No difference in 24-hour mortality
• Included measures of injury severity and coagulation
• All patients required blood transfusion
• The PRBC:FFP ratio in each group is the same
• NNT
<u>Limitations</u>
• Trial design
• Details for VTE cause lacking
• Details of cause and time of death lacking
• Dose
• Guidelines changed half-way through trial
• Rate of PE/DVT higher in TXA group</td></tr>
<tr><td>Summary</td><td>TXA is the most useful in patients that are severely injured and require the most transfusions. After correcting for severity of injury, TXA was not associated with increased risk of DVT or PE.</td></tr>
</table>

<table>
<tr><th colspan="3">Table 3. MATTERs II Trial[17]</th></tr>
<tr><td>Citation</td><td colspan="2">Morrison JJ, Ross JD, Dubose JJ, et al. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II study. JAMA Surg. 2013;148:218-225. doi: 10.1001/jamasurg.2013.764.</td></tr>
<tr><td>Objective</td><td colspan="2">To quantify the impact of fibrinogen containing cryoprecipitate in addition to the antifibrinolytic tranexamic acid on survival in combat injured.</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">Retrospective, cohort study on prospectively gathered injury, injury management, and outcomes data on combat casualties in the US and UK Joint Theater trauma registries</td></tr>
<tr><td>Population</td><td><u>Inclusion</u>
Patients who received at least 1 unit of PRBCs within 24 hours of admission following combat related injury</td><td><u>Exclusion</u>
No receipt of packed red blood cells</td></tr>
<tr><td>Intervention</td><td colspan="2">The study population was divided into 4 cohorts: casualties who received cryoprecipitate but not tranexamic acid, casualties who received tranexamic acid but not cryoprecipitate, casualties who received tranexamic acid and cryoprecipitate, and patients who received neither tranexamic acid nor cryoprecipitate</td></tr>
<tr><td>Outcomes</td><td colspan="2">Primary: mortality defined as death within 30 days of wounding</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">Parameters were compared across the 4 treatment cohorts by analysis of variance for continuous measures and logistic regression for proportions. A pair of propensity scores were used as adjustments in nonordinal polytomous logistic regression for proportions and analysis of covariance for continuous measures as an aid to assess the balance between the groups.</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">N=1,332 patients. The prehospital use of blood products by a physician-led retrieval team was different among groups. Patients in the tranexamic acid/cryoprecipitate group had a lower level of consciousness and were more hypotensive.
<table>
<tr><th></th><th>TXA (n=148)</th><th>Cryo (n=168)</th><th>TXA + Cryo (n=258)</th><th>Neither (n=758)</th><th>P value</th><th>P value*</th></tr>
<tr><td>Mean Age (y)</td><td>24.2</td><td>24.9</td><td>24.7</td><td>23.6</td><td>0.42</td><td>0.61</td></tr>
<tr><td>Male; n(%)</td><td>143 (96.6)</td><td>161 (95.8)</td><td>251 (97.3)</td><td>710 (93.7)</td><td>0.08</td><td>0.57</td></tr>
<tr><td>GSW; n(%)</td><td>48 (32.4)</td><td>41 (24.4)</td><td>42 (16.3)</td><td>281 (37.1)</td><td><0.001</td><td>0.23</td></tr>
<tr><td>GCS ≤8; n(%)</td><td>59 (55.1)</td><td>54 (42.5)</td><td>139 (72)</td><td>180 (3.2)</td><td><0.001</td><td>0.001</td></tr>
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	SBP ≤90 mm Hg; n(%)	19 (14.6)	38 (25.7)	68 (3.6)	146 (21.6)	0.003	0.14

Outcomes	• In-hospital mortality: p= 0.001
	  ○ TXA 18.2%, Cryo 21.4%, TXA + Cryo 11.6%, Neither 23.6%
	• Mean doses of TXA: p= 0.001
	  ○ TXA 1.9 g, TXA + Cryo 2.4 g
	• Mean units of PRBC: p < 0.001
	  ○ TXA 8, Cryo 20.1, TXA + Cryo 22, Neither 5.3	

Author's Conclusions	The administration of cryoprecipitate and tranexamic acid may improve the survival in the seriously injured requiring transfusion.	
Critique	Strengths • Propensity scores • Comparison of relatively heterogeneous subgroups • Number of patients in trial • Potential mortality benefit may extend beyond acute injury • NNT	Limitations • Cryoprecipitate is a complex preparation containing more than fibrinogen alone • No data pertaining to inflammatory markers, organ dysfunction, or cause of death • Reported limited prehospital data • May be unrecognized temporal relationships that remain unadjusted influencing mortality • Doses of TXA used
Summary	The early use of TXA should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage.	

Table 4. CRASH-3 Trial[18]		
Citation	Roberts I, Belli A, Brenner A, et al. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomized, placebo-controlled trial. *Lancet*. 2019;394:1713-1723. doi:10.1016/S0140-6736(19)32233-0.	
Objective	Aimed to quantify the effects of tranexamic acid on head injury-related death, disability, and adverse events in patients with TBI	
Methods		
Study Design	International, multi-center, randomized, placebo-controlled trial	
Population	Inclusion • Adults with traumatic brain injury (TBI) who were within 3 hours of injury, had a Glascow Coma Scale (GCS) of 12 or lower or any intracranial bleeding on CT scan and no major extracranial bleeding were eligible	Exclusion • Patients greater than 8 hours from injury initially • Post amendment, patients greater than 3 hours from injury • No evidence of intracranial bleeding
Intervention	When the responsible doctor was substantially uncertain as to whether to treat with this	

	agent, these patients where eligible for randomization Patients were randomly assigned to receive a loading dose of 1 gram of tranexamic acid infused over 10 minutes, followed by an IV infusion of 1 gram over 8 hours or matching placebo (0.9% saline)
Outcomes	Primary: changed to head injury death in hospital within 28 days of injury for patients treated within 3 hours of injury Secondary: early head injury related death (within 24 hour after injury), all-cause and cause-specific mortality, disability, vascular occlusive events, seizures, complications, neurosurgery, days in intensive care unit, and adverse events within 28 days of randomization
Statistical Analysis	Intention-to-treat analysis. The primary analyses will be presented as relative risks and 95% confidence intervals. Kaplan-Meier estimates for the time to each of the primary and secondary outcomes will also be plotted. A sensitivity analysis was conducted on TBI patients with a GCS of 3 and bilateral un-reactive pupils in an attempt to not bias the treatment effect towards the null.

Results

Baseline Characteristics

TXA (n=4,649) vs Placebo (n=4,553)					
Mean time since injury (hours)	SBP < 90 (%)	Glasgow Coma Scale 3-8 (%)	Glasgow Coma Scale 13-15 (%)	Men (%)	Mean age (years)
1.9 vs 1.9	2 vs 2	40 vs 38	27 vs 28	80 vs 80	41 vs 42

Outcomes

- Overall: 18.5% vs 19.8% RR 0.94 95% CI 0.86-1.02
- Exclude GCS of 3 or bilateral unreactive pupils: TXA (n=3,880) vs Placebo (n=3,757): 12.5% vs 14% RR 0.89 95% CI (0.8-1)
- Overall: vascular occlusive events same 1.6% vs 1.6% RR 0.98 (0.74-1.28)
- GCS 9-15: 5.8% vs 7.5% RR 0.78 95% CI (0.64-0.95)

Author's Conclusions

Administration of tranexamic acid to patients with TBI within 3 hours of injury reduced head-injury related death, with no evidence of adverse effects or complications

Critique

<u>Strengths</u>

- Trial design
- Pragmatic
- Showed TXA is safe in patients with TBI
- One of the largest trials in patients with TBI
- Dose same as CRASH-2
- Pre-planned analysis excluding patients with a GCS of 3 or with

<u>Limitations</u>

- Primary outcome was head injury related death classified by physician
- All-cause mortality was used instead of intracranial bleeding mortality
- No statistically significant results
- 28-day head injury related mortality as endpoint might have biased null
- Estimated sample size to be 10,000 patients with TBI to have 90% power

	bilateral unreactive pupils • Sicker patients compared to CRASH-2	
Summary	Tranexamic acid is safe to use in patients with traumatic brain injury. However, the evidence of providing a true patient-oriented benefit is not strong enough to routinely use tranexamic acid in every patient with isolated traumatic brain injuries.	

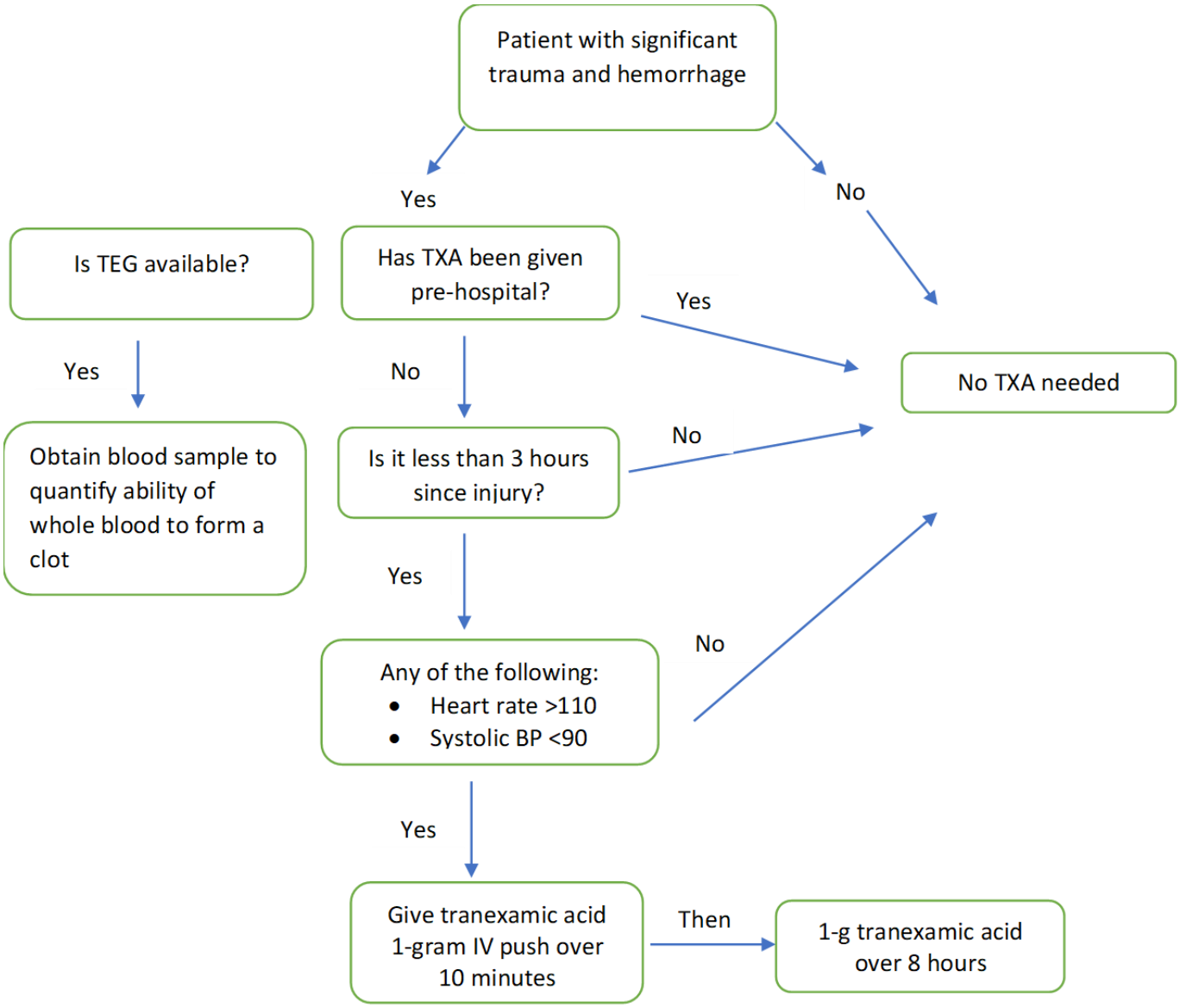
Conclusion and Recommendation

Summary of Literature

	CRASH-2	MATTERs	MATTERs II	CRASH-3
What was the population size?	n= 20,000	N= 900	N=1,300	N=13,000
Did the population represent the typical trauma patient?	Yes	Yes	Yes	Yes
Average Injury Severity Score	N/A	24.8	24.6	N/A
Prospective?	Yes	No	No	Yes
Appropriate use of a validated tool to assess illness severity?	Yes	Yes	Yes	Yes
Follow standard of care?	Yes	Yes	Yes	Yes
Dose of TXA?	1 gram over 10 minutes→ 1 gram over 8 hours infusion	1 gram IV followed by repeat doses	1 gram IV followed by repeat doses	1 gram IV over 10 minutes→ 1 gram IV over 8 hours infusion
Primary outcome?	Death in hospital within 4 weeks of injury	Mortality at 24 hours, 48 hours, and 30 days	In-hospital mortality	Head injury related death in hospital within 28 days
TXA use reduce mortality?	Yes	Yes at 48 hours and in-hospital mortality	No	No
TXA use improve outcomes such as head injury related death?	Yes	N/A	N/A	Yes
TXA use safe?	Yes	Yes	Yes	Yes

Final Recommendation

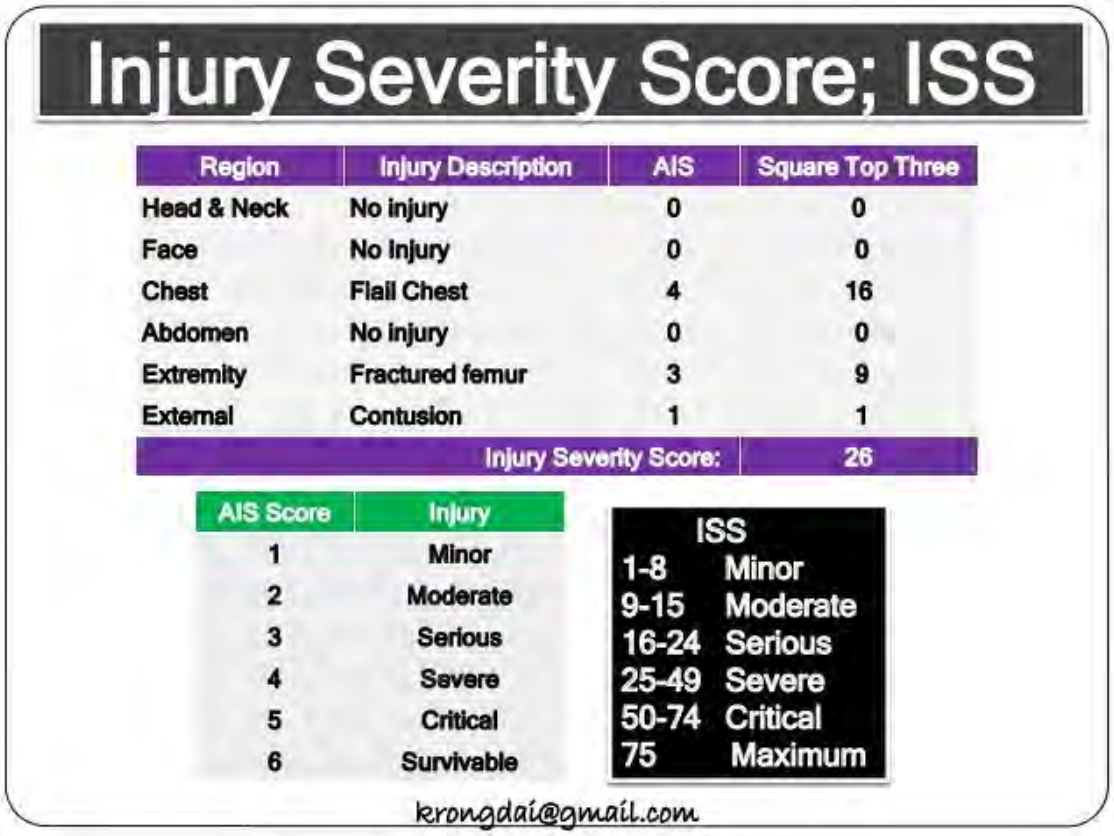
Tranexamic acid is safe and effective for trauma patients with suspected or actual hemorrhage.



Appendix

Glasgow Coma Scale		
Response	Scale	Score
Eye Opening Response	Eyes open spontaneously	4 Points
	Eyes open to verbal command, speech, or shout	3 Points
	Eyes open to pain (not applied to face)	2 Points
	No eye opening	1 Point
Verbal Response	Oriented	5 Points
	Confused conversation, but able to answer questions	4 Points
	Inappropriate responses, words discernible	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
Motor Response	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticate posture	3 Points
	Extensor (rigid) response, decerebrate posture	2 Points
	No motor response	1 Point
Minor Brain Injury = 13-15 points; **Moderate Brain Injury** = 9-12 points; **Severe Brain Injury** = 3-8 points		

https://smhs.gwu.edu/urgentmatters/news/keep-it-simple-acute-gcs-score-binary-decision



https://www.slideshare.net/krongdai/trauma-scoring

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