

TITLE PAGE

Diagnosis And Treatment Of Hyperfibrinolysis In Trauma (A European Perspective)

Lewis S Gall MRCS, BMSc (Hons), Karim Brohi FRCS FRCA, Ross A Davenport FRCS, PhD

Mr Lewis S Gall MRCS, BMSc (Hons); Professor Karim Brohi FRCS FRCA; Dr Ross A Davenport
FRCS, PhD

Affiliations

Centre for Trauma Sciences, Blizard Institute, Bart's and the London School of Medicine &
Dentistry, Queen Mary University of London, UK

Corresponding author

Dr Ross A Davenport

Centre for Trauma Sciences, Blizard Institute

Barts and the London School of Medicine & Dentistry

Queen Mary University of London

4 Newark Street, London, E1 2AT, United Kingdom

Phone: 020 737 40723

E-mail: ross.davenport@qmul.ac.uk

E-mail

Lewis Gall lewisgall@nhs.net

Karim Brohi k.brohi@qmul.ac.uk

Abstract

Fibrinolysis activation occurs almost universally after severe trauma. Systemic hyperfibrinolysis is a key component of Acute Traumatic Coagulopathy and associated with poor clinical outcomes, although controversy exists over optimal treatment strategies. The mechanistic drivers and dynamics of fibrinolytic activation in response to injury and trauma resuscitation are currently unclear. Furthermore, therapeutic triggers are compounded by the lack of a sensitive and rapid diagnostic tool, with discrepancy between hyperfibrinolysis diagnosed by viscoelastic hemostatic assays versus biomarkers for fibrinolysis. . ROTEM and TEG appear capable of detecting the severest forms of hyperfibrinolysis but are relatively insensitive to moderate, yet clinically significant fibrinolytic activation. Rapid evaluation of the current status of the fibrinolytic system remains a challenge and therefore the decision whether to administer an antifibrinolytic agent should be based upon available evidence from clinical trials. In line with current European guidelines, we recommend that all bleeding trauma patients, and in particular severely injured patients with evidence of hemorrhagic shock, should receive early empiric tranexamic acid. This review explains our current knowledge of the pathophysiological pathways which induce hyperfibrinolysis in trauma hemorrhage, evaluates the available diagnostic modalities and describes current treatment strategies.

Keywords

Trauma, Fibrinolysis, Hemorrhage, Coagulopathy, Tranexamic Acid

Introduction

Fibrinolysis activation occurs almost universally following severe injury.¹ Physiological fibrinolysis is a proportionate response to increased fibrin generation following tissue trauma², whereas excessive or systemic fibrinolytic activation is inappropriate and potentially lethal. Acute Traumatic Coagulopathy (ATC) is an early and endogenous hemostatic abnormality of which global hypocoagulation, systemic hyperfibrinolysis³, early fibrinogen depletion and platelet dysfunction⁴ are key components. ATC is triggered by massive tissue injury in conjunction with hypoperfusion (shock) in the early phase after major trauma.³ Hyperfibrinolysis, is defined by disproportionately increased fibrinolytic activity with respect to fibrin formation⁵, and is associated with poor clot integrity, excessive bleeding and worse coagulopathy, in addition to increased morbidity and mortality.⁶

Controversy currently exists over patient selection for antifibrinolytic therapy⁷ and is a reflection of our limited understanding of both the mechanism and dynamics of fibrinolytic activation after traumatic injury. Hyperfibrinolysis in trauma has yet to be properly defined with many different arbitrary definitions used in the literature (Table 1). Sensitive diagnostics for a rapid and current assessment of the fibrinolytic system are lacking² despite the increasing use of viscoelastic hemostatic assays (VHA) (e.g. rotational thromboelastometry (ROTEM; Tem International GmbH, Munich, Germany) and thromboelastography (TEG; Haemonetics, Braintree, USA)) to define fibrinolytic activation states. Correlation of lysis parameters with laboratory gold standards of fibrinolysis e.g. plasmin- α 2-antiplasmin complex (PAP) levels has proven difficult to interpret, and therefore

the clinical sequela of acute hyperfibrinolysis and/or early hypofibrinolysis has yet to be accurately described. In particular, the impact of a highly activated (or inhibited) fibrinolytic system on bleeding risk, organ failure and thrombotic complications is unclear.

Understanding the drivers of trauma-induced fibrinolysis, the temporal relationship to injury and resuscitation, as well as optimal treatment strategies are priorities for the trauma research community. The purpose of this review is to explain our current knowledge of the pathophysiological pathways which induce hyperfibrinolysis in trauma hemorrhage, evaluate the available diagnostic modalities and describe current treatment strategies.

Regulation of fibrinolysis

The coagulation and fibrinolytic systems are both activated following trauma and exist in a dynamic equilibrium.^{1,8} Plasmin both degrades fibrin and prevents propagation of the clot distant to the site of injury. Plasminogen may be activated either by tissue-type or urinary-type plasminogen activators (tPA and uPA respectively) or by the contact pathway. tPA is a serine protease produced and secreted primarily by pre-capillary arteriole and post-capillary venule endothelial cells⁹⁻¹¹ and is the primary plasminogen activator in the vasculature. In response to vascular injury or the presence of thrombin, additional stores of tPA from endothelial Weibel-Palade bodies¹² and possibly by poorly characterized other small storage granules¹³ are released.¹⁴

Fibrinolytic activation is tightly controlled by plasminogen activator inhibitor 1 (PAI-1) which principally inhibits tPA and α -2 antiplasmin (α 2AP) which inhibits plasmin. PAI-1 is found

within two distinct pools within the blood - plasma and platelets.¹⁵ Circulating levels of PAI-1 are relatively low in comparison to the rich source within platelet α -granules.¹⁵ Platelet-rich thrombi are resistant to tPA-mediated fibrinolysis¹⁶, however, platelet contribution to plasma levels of PAI-1 and the degree to which platelets modulate trauma-induced hyperfibrinolysis is uncertain. Whilst initial studies suggested that only 10% of platelet PAI-1 was in an active configuration¹⁷⁻¹⁹, subsequent research has discovered that platelets actually retain high levels of active PAI-1^{20,21}, capable of complexing and inactivating the plasminogen activators. Moore *et al.*²² demonstrated that platelet lysate mixed with whole blood *ex vivo*, resulted in a faster clotting time and reduced tPA-mediated fibrinolysis measured by TEG, in accordance with earlier studies describing the anti-fibrinolytic function of platelet PAI-1.^{16,23} Platelets are additionally a source of α 2AP¹⁶, thrombin activatable fibrinolysis inhibitor (TAFI)²⁴ and factor XIII²⁵, all of which promote clot stabilization. Platelet-mediated fibrinolytic inhibition could in theory explain the improved outcomes associated with early transfusion of high ratios of platelets to red blood cells in patients with traumatic hemorrhage.²⁶⁻²⁸ Characterization of the antifibrinolytic capacity of platelets, and the efficacy of platelet transfusions on clot stability following trauma is therefore a research priority. Importantly, recent studies have indicated platelets also contain profibrinolytic properties (outlined in the paper by White in this issue of Seminars in Thrombosis and Hemostasis), which should be considered in such studies.²⁹

The fibrinolytic system in traumatic coagulopathy

ATC is an endogenous process, driven by the combination of endothelial hypoperfusion and tissue injury, with hyperfibrinolysis, hypocoagulation, increased thrombin generation and

early fibrinogen depletion identified as key components.^{3,30} Present in up to 25% of trauma patients, ATC occurs in the first hour after injury, before significant fluid resuscitation or hemodilution has occurred.^{31,32} During resuscitation of the bleeding trauma patient, ATC is compounded by ongoing blood loss and treatment strategies which utilize hypocoagulable fluids e.g. crystalloids, with ensuing hemodilution, hypothermia and acidemia development contributing to a global failure of the coagulation system. Trauma Induced Coagulopathy (TIC)³³ describes collectively the innate component of ATC and all subsequent coagulopathies which develop, typically iatrogenic and related to suboptimal fluid resuscitation or delayed hemorrhage control.³⁴ A temporal switch in coagulation status from the initial hypocoagulability of TIC to a hypercoagulable response occurs over hours to days after major trauma.^{35,36} A biphasic response has similarly been described in the fibrinolytic system^{37,38} with an initial acceleration of clot lysis lasting for several hours after injury, followed by inhibition of fibrinolytic capacity lasting between four to eleven days.³⁹

Activation of the Protein C (PC) pathway has been identified in both clinical human studies and experimental animal models as a potential mediator of hyperfibrinolysis in ATC.⁴⁰⁻⁴³ In addition to its inhibitory effect on thrombin generation, activated protein C in excess binds to and neutralizes PAI-1, resulting in de-repression of shock-mediated tPA release from the endothelium leading to uninhibited activation of fibrinolysis.^{40,44,45} PAI-1 rather than TAFI appears to exert greater control over the fibrinolytic state after trauma.^{1,3} Gando and colleagues alternatively consider traumatic coagulopathy to reflect disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype, characterized by activation of the tissue-factor dependent coagulation pathway, insufficient anticoagulant mechanisms

and increased fibrinolysis.^{46,47} Primary and secondary fibrin(ogen)olysis are considered to be pathologically activated following trauma in response to shock-induced endothelial tPA release^{46,48,49} and DIC respectively.⁴⁷ Activation of neutrophil elastase-mediated fibrinolytic pathways is additionally believed to contribute to the hyperfibrinolytic state.⁵⁰ Subsequently it is proposed that insufficient anticoagulant mechanisms (e.g. low protein C and antithrombin levels) combined with PAI-1-mediated inhibition of fibrinolysis shifts the patient into DIC with a thrombotic phenotype.^{46,47,51}

Central to both hypotheses is the mechanism of shock-induced hyperfibrinolysis. Tissue hypoperfusion in isolation e.g. cardiac arrest, is capable of initiating hyperfibrinolysis^{52,53} and similarly increasing levels of tissue injury will initiate fibrinolysis³, evidenced on ROTEM by shortened lysis onset time (20% lysis of maximum clot firmness).⁵² Sympathoadrenal activation following severe trauma leads to a surge in circulating catecholamines which are hypothesized to contribute to coagulopathy and hyperfibrinolysis by means of endothelial activation and glycocalyx degradation.^{54,55} The combination of both tissue injury and hemorrhagic shock in patients suffering major trauma causes a surge in tPA release from the endothelium driving a massive fibrinolytic response.^{3,51} Almost 90% of severely injured patients defined as Injury Severity Score (ISS) > 15 have PAP levels on admission of at least twice the upper limit of normal.¹ The fibrinolytic response to trauma and shock is a dynamic process which evolves over time and may be exacerbated further by clinical interventions e.g. surgery, resuscitation. When these changes occur, and the specific drivers for any up or down-regulation in the fibrinolytic pathways are not known, in part due to limitations in our ability to measure ongoing fibrinolysis rather than markers of prior activation (e.g. PAP).

Diagnosis of hyperfibrinolysis in trauma

Detection of post-injury changes in the fibrinolytic system in a clinically meaningful timeframe (i.e. to guide therapy) is challenging. Diagnostics currently available to quantify fibrinolysis are laboratory measures of fibrin degradation, measurement of individual proteins of the fibrinolytic system and VHA. The Euglobulin Clot Lysis Time (ECLT)^{56,57} is a validated assessment of overall fibrinolysis *in vivo*, however has little clinical utility in trauma due to the prolonged assay time and loss of plasma inhibitors (i.e. antiplasmin) in the acidification process. A further limitation is that ECLT is performed on diluted platelet poor plasma rather than whole blood and it is not capable of assessing the response to antifibrinolytic therapy since these agents are normally discarded within the supernatant during processing.⁵⁸ Excessive fibrin degradation may be indicated by raised D-dimer levels; however, elevated levels are encountered in most patients following injury¹ and are strongly correlated to injury severity³. Kutcher *et al.*⁵⁹ found that patients with VHA-detectable hyperfibrinolysis have significantly higher D-dimer levels but that as a clinical marker on its own, D-dimer was not predictive of hyperfibrinolysis after adjusting for injury severity and shock.

The fibrinolytic response to trauma is characterized by quantification of specific fibrinolytic proteins and complexes which are primarily measured by ELISA.^{1,3,39,54,60–62} Measurement of tPA and PAP complex levels in combination with fibrinolytic inhibitor levels (PAI-1, α 2AP, TAFI) enables a comprehensive albeit static assessment of the fibrinolytic system, but is confined to the research setting due to the time it takes to process each assay. A functional,

global assay (such as a viscoelastic test or a plasma-based clot lysis assay) may provide better overall evaluation of the status of the fibrinolytic system.⁶³ Any increase in fibrinolytic activation (PAP>1500 µg/L, twice the upper limit of normal) has been shown to be associated with a 12-fold increase in 28-day mortality and greater transfusion requirements compared to those with 'normal' levels of fibrinolytic activity (PAP < 1500 µg/L).¹ However, measurement of circulating levels of PAP or the downstream D-dimer fragment represents recent plasmin generation (and fibrinolysis) but not necessarily the extent of ongoing fibrinolysis. Development of a point-of-care test capable of rapidly quantifying the extent of fibrinolytic activation e.g. PAP or α2AP may assist in guiding therapy although in isolation would still only represent an assessment of prior fibrinolytic activity. However, in combination with a dynamic assay such as a VHA, both rapid and serial read-outs of fibrinolytic biomarker levels have the potential to better determine the degree of ongoing fibrinolysis.

Role of VHA in trauma hemorrhage & diagnosis of hyperfibrinolysis

The major advantage of VHAs over other diagnostics is near patient testing and speed, with provision of a comprehensive assessment of clot formation dynamics including fibrinolysis in whole blood. ROTEM and TEG are capable of rapidly diagnosing ATC⁶⁴⁻⁶⁶ and are superior to conventional clotting tests (e.g. Prothrombin Time) in predicting the need for massive transfusion in trauma.⁶⁷ An international panel of trauma researchers has recommended that VHA use should be considered during the early phases of trauma resuscitation and remains the only test capable of diagnosing hyperfibrinolysis in a clinically relevant timeframe.⁶⁸ However, the latest National Institute for Health and Care Excellence (NICE)

guideline on the management of major trauma⁶⁹ concludes that there is currently insufficient evidence to support the superiority of VHA over standard laboratory coagulation tests to target treatment. A recent Cochrane systematic review has suggested that at present in the setting of trauma, VHA should only be used for research purposes.⁷⁰ Whilst VHA can provide results rapidly, there is a need for randomized clinical trial data to ascertain any superiority over standard laboratory tests as a tool to guide trauma resuscitation.^{71,72} For these reasons European and UK guidelines^{69,73} currently recommend early empiric treatment of hyperfibrinolysis in the bleeding trauma patient rather than waiting for VHA-confirmation of increased fibrinolysis.

Extrapolation of the incidence and outcomes associated with hyperfibrinolysis in trauma from the literature is confounded by a number of methodological issues: (1) inconsistency in threshold definitions for VHA detected hyperfibrinolysis; (2) lack of standardization of VHAs with consequent lab-to-lab variation; (3) wide variation in patient populations; (4) discrepancies in sampling protocols that vary between minutes of injury to 12 hours; and (5) a lack of clarity between VHA versus biomarker diagnosed hyperfibrinolysis.

VHA detected hyperfibrinolysis is reported in 2 – 20% of trauma patients presenting to the Emergency Department (ED) and is associated with mortality rates up to 100% (Table 1).^{59,64,74–80} Hyperfibrinolysis is currently defined by ROTEM as a reduction in maximum clot firmness (MCF) of greater than 15% (ML > 15%), 60 minutes after the onset of clot formation. The continuous ROTEM variable of lysis onset time (LOT) may detect severe hyperfibrinolysis faster^{53,81}, although this has not been validated in trauma patients. Three

distinct temporal patterns of ROTEM-detected hyperfibrinolysis have been described: (1) fulminant lysis described as complete clot lysis (EXTEM ML of 100%) within 30 minutes and associated with the highest mortality; (2) intermediate lysis as that occurring between 30 and 60 minutes; and (3) late lysis occurring beyond 60 minutes.⁷⁵ Defining TEG hyperfibrinolysis according to the manufacturer's recommendation of clot lysis exceeding 7.5%, 30 minutes after maximum clot amplitude (LY30 > 7.5%), Cotton *et al.*⁷⁸ reported hyperfibrinolysis to be uncommon but highly lethal. Chapman *et al.*⁸² subsequently found the lower threshold of 3% to be superior at diagnosing clinically relevant hyperfibrinolysis and predicting both massive transfusion and mortality. Consequently, TEG hyperfibrinolysis is now widely defined as LY30 \geq 3%.⁸³⁻⁸⁵

Is VHA diagnosed fibrinolysis an accurate reflection of the status of the fibrinolytic system?

VHAs accurately identify patients with the highest degree of fibrinolysis, but appears relatively insensitive at detecting lower levels of fibrinolytic activation¹, through rapid inhibition of free tPA by PAI-1 following blood draw.⁸⁶ Using a composite measure of PAP and VHA on admission to ED we have shown fibrinolytic activation following severe trauma to be extremely common.¹ Patients without VHA hyperfibrinolysis (ML < 15%) were categorized as 'normal' fibrinolytic activity if PAP < 1500 μ g/L and 'moderate' fibrinolytic activity if PAP >1500 μ g/L. Patients with PAP > 1500 μ g/L combined with VHA hyperfibrinolysis (ML > 15%) were classified as 'severe'. Whilst only 5% of patients were classified as 'severe', the largest proportion of patients (57%) had 'moderate' fibrinolytic activation which was not detected by ROTEM. PAP levels were closely related to injury severity, with approximately 90% of patients with ISS>15 demonstrating biomarker

confirmed hyperfibrinolysis. In a similar study utilizing PAP and TEG, Cardenas *et al.*⁸⁷ found that 45% of patients had PAP>1500 µg/L with an associated 6-fold increase in overall mortality despite there being no evidence of hyperfibrinolysis on TEG (median LY30 1.1 % (0.2 – 2.4) (Table 1).

Differences in ROTEM and TEG methodology and the reagents used (Table 2) alters the sensitivity to fibrinolysis across platforms and individual assays. Harr *et al.*⁸⁸ reported that functional fibrinogen TEG (FFTEG) and FIBTEM were comparable in their ability to detect fibrinolysis faster than the other VHA assays. KaolinTEG appears superior in its ability to detect fibrinolysis in a dose-dependent manner across various tPA concentrations whereas RapidTEG detects lysis at high concentrations of tPA only. The more powerful clot activation required to generate faster results by RapidTEG, results in a clot more resistant to tPA-induced fibrinolysis which may result in under-diagnosis of hyperfibrinolysis. VHA and biomarkers of fibrinolysis by definition do not measure the same thing, PAP reflects prior activation of fibrinolysis in vivo whereas VHAs quantify coagulation and to some extent fibrinolytic potential. Clarification of the status of the fibrinolytic system and therapeutic requirements of a bleeding trauma patient with grossly elevated PAP or D-dimer levels, but does not meet the diagnostic threshold for VHA hyperfibrinolysis is clearly a research imperative.

The circumstances required for VHA to detect 'severe' hyperfibrinolysis have yet to be confirmed. In one study tPA levels of nearly five times normal and α 2AP levels below 75% of normal were shown to be required before ROTEM hyperfibrinolysis was visualised.¹ We

hypothesize that free tPA within the ROTEM cup is required to generate plasmin and that only in the presence of low antiplasmin levels is there reduced inhibition of newly formed plasmin, resulting in ROTEM-detectable hyperfibrinolysis. Platelet dysfunction may additionally influence the ability of VHA to detect hyperfibrinolysis since impairment of ADP-induced platelet activation following trauma is associated with increased sensitivity to tPA-mediated fibrinolysis.⁸⁹ Alternatively the pattern of biomarker positive fibrinolysis with negative VHA lysis may represent prior excessive lytic activity which has rapidly reverted to normal or hypofibrinolysis during the early phase response to trauma. A further explanation may lie in the relative availability of promoters or inhibitors of fibrinolysis within the VHA with respect to thrombin generation potential since both clot strength and lysis are products of one another.

At the opposite end of the spectrum, it is similarly unclear what the implications of low VHA fibrinolysis are for the trauma patient. Whilst the upper boundary for 'normal' VHA fibrinolysis ($ML \leq 15\%$ ⁹⁰ or $LY30 < 3\%$ ⁸²) is commonly quoted, no lower boundary has been reported and it has recently been suggested that patients with VHA hypofibrinolysis have worse clinical outcomes.^{83,91} Further investigation is required to phenotype VHA hypofibrinolysis to understand whether all patients with this entity are the same. In particular what biomarker patterns are associated with VHA hypofibrinolysis, the mechanisms that drive low fibrinolytic activity, the temporal relationship with injury, shock and resuscitation as well as clinical sequela e.g. mortality, VTE, organ failure. Improvements in the sensitivity of existing VHAs or development of diagnostic tools with greater definition

to identify and characterize trauma patients with hyper or hypofibrinolysis are urgently required.

Who should receive antifibrinolytic treatment?

Patients with TIC are eight times more likely to die within the first 24 hours⁹² and more likely to require a massive transfusion⁴⁴, with increased risk of multi-organ failure (MOF) and longer critical care and hospital stay.⁹² Correct patient selection for treatment of hyperfibrinolysis provides an opportunity to improve upon these poor outcomes but given the lack of a validated diagnostic tool in trauma hemorrhage, the decision of who to treat requires an evidence-based clinical decision. The CRASH-2 trial randomized 20,211 injured patients to receive an antifibrinolytic or placebo based on pragmatic inclusion of all adult trauma patients who were bleeding or were suspected to be bleeding.⁹³ Patients who received empiric dosing of tranexamic acid (TXA) had a lower overall mortality (14.5% vs 16%) and a lower risk of death due to bleeding (4.9% vs 5.7%). Subgroup analysis from CRASH-2 found the greatest survival benefit to be in those patients with a systolic blood pressure less than 75 mmHg⁹³, and was confirmed in a single center retrospective UK study⁹⁴ which additionally reported reduced MOF in shocked patients who received TXA. Similarly antifibrinolytic therapy administered empirically to military casualties with combat associated traumatic hemorrhage was associated with lower in-hospital mortality.⁹⁵ Once again the greatest benefit was observed in patients requiring a massive transfusion with TXA independently associated with survival. Given the current lack of evidence regarding the diagnostic accuracy of VHA⁷⁰ and in the context of clinical trial data to support empiric

antifibrinolytic therapy in suspected trauma hemorrhage⁹³, withholding treatment for VHA confirmed hyperfibrinolysis cannot be recommended.

How should hyperfibrinolysis be treated?

The primary method of targeted reversal of hyperfibrinolysis in trauma is currently with the antifibrinolytic TXA. Important questions remain however over the optimal dosing regime, timing, which patient subgroup derives most benefit and later thrombotic events. Early hemorrhage control and reversal of shock may in theory attenuate fibrinolytic activation through improved endothelial oxygenation and reduced tPA generation. Damage control resuscitation with a balanced transfusion strategy including early fresh frozen plasma⁹⁶ (a source of $\alpha 2AP$) and platelets may further dampen fibrinolytic activation⁹⁷ through increased PAI-1 delivery.

Evidence for the use of Tranexamic Acid in trauma

TXA (trans-4-aminomethylcyclohexane-1-carboxylic acid) is a synthetic analogue of the amino acid lysine. It exerts an antifibrinolytic effect by competitively blocking the lysine binding sites on plasminogen, thereby preventing the interaction of plasmin(ogen) with fibrin⁹⁸ and at higher concentrations is a non-competitive inhibitor of plasmin.^{99,100} First described over five decades ago^{100,101} TXA has found widespread global clinical application in part due to it being readily available, cheap and having a proven safety profile. It is used routinely in the elective surgical setting, including gynecological, orthopedic, cardiac and liver transplant surgery where it has been shown to reduce blood loss and the need for

blood transfusion without increased thromboembolic events.^{102,103} TXA is considered a relatively old pharmacological agent although is currently being evaluated in international clinical trials of traumatic intracranial bleeding (Clinical Randomization of an Antifibrinolytic in Significant Head Injury; CRASH-3)¹⁰⁴, non-traumatic gastrointestinal (Hemorrhage Alleviation with Tranexamic acid – Intestinal system; HALT-IT)¹⁰⁵ and postpartum hemorrhage (World Maternal Antifibrinolytic Trial; WOMAN)¹⁰⁶.

The seminal study of TXA use in trauma hemorrhage (CRASH-2) was the first trial to demonstrate improved survival from bleeding with an antifibrinolytic. TXA was administered as a 1g bolus over 10 minutes followed by a second 1g infusion over eight hours. The beneficial effects of early TXA therapy (bolus dose within 3 hours) in reducing all-cause mortality and death due to bleeding did not vary significantly by baseline risk of death.¹⁰⁷ TXA can therefore be administered safely to all patients with traumatic bleeding with no evidence to suggest it should be reserved only for high risk patients with the most severe hemorrhage.¹⁰⁸ Performed in 40 countries, the CRASH-2 results did not identify any effect of geographical location on the efficacy of TXA on reducing death from bleeding.¹⁰⁹ In fact, countries with the most advanced healthcare systems appeared to derive the greatest relative risk reduction. Hemorrhage is the leading cause of preventable death globally from trauma and empiric use of TXA within three hours of injury, is likely to save many lives¹⁰⁹ and be highly cost-effective.^{110,111}

TXA for the management of combat injury and hemorrhage was evaluated in the retrospective MATTERS⁹⁵ and MATTERS II studies.¹¹² In study of 896 combat casualties, the

MATTERs study concluded that patients receiving TXA (n=293) had a significantly lower overall in-hospital mortality (17.4% vs 23.9%). However, a potential confounding factor is that the TXA cohort received a greater volume of cryoprecipitate. In order to specifically address this, the MATTERs II study examined 1332 patients to investigate the effect of TXA and cryoprecipitate on survival. In-hospital mortality was highest in patients who received neither TXA nor cryoprecipitate (23.6%) and was lowest in patients who received both TXA and cryoprecipitate (11.6%). The individual benefit of TXA and cryoprecipitate therapy was similar; both associated with an odds ratio (OR) of 0.61 and 95% CIs of 0.42 to 0.89 and 0.40 to 0.94 respectively. Combined TXA and cryoprecipitate therapy had an additive rather than a synergistic effect with an OR of 0.34 (95% CI, 0.20 – 0.58). Based upon this body of evidence, NICE⁶⁹, the Cochrane Collaboration¹¹³, the Association of Anesthetists of Great Britain and Ireland (AAGBI)¹¹⁴ and the European “STOP the Bleeding Campaign”^{73,115} recommend that empiric intravenous TXA be given to all trauma patients with active or suspected active hemorrhage as soon as possible and within three hours of injury. In order to achieve early administration, ideally within the first hour, it is recommended that procedures be in place for delivery of the first dose of TXA pre-hospital at the scene of injury.⁷³

The survival benefit from antifibrinolytic therapy is greatest when it is administered early, within the first hour following trauma.¹¹⁶ Whether patients with confirmed (biomarker or VHA diagnosed) hyperfibrinolysis derive additional benefit is not known. Furthermore the precise mechanism by which TXA confers survival benefit is unknown with some evidence to suggest it has anti-inflammatory action^{94,117,118} in addition to its primary anti-fibrinolytic

effects. As a result the relative efficacy of TXA on early bleeding vs late deaths from MOF and sepsis is unclear. Paradoxically, late administration beyond three hours in the CRASH-2 trial was associated with increased risk of death due to bleeding. Possible explanations are that late delivery reflects poorer outcomes associated with delayed trauma care or is secondary to PAI-1-mediated suppression of fibrinolysis with resultant microvascular thromboses.⁴⁶ If hyperfibrinolysis transitions rapidly into a hypofibrinolytic state then further blockade of fibrinolysis with delayed antifibrinolytic therapy has the potential to be harmful although the effects of TXA, or other agents on hypofibrinolysis have yet to be characterized. Recently, a novel hypothesis based on data from a murine model of severe Traumatic Brain Injury (TBI) has been proposed.¹¹⁹ Whilst both tPA and uPA levels in the brain increased following injury, they did so at different rates, with tPA peaking soon after TBI (within three hours) and uPA demonstrating a delayed peak after approximately eight hours. TXA blocks tPA-mediated fibrinolysis, however it actually enhances uPA-mediated fibrinolysis.¹²⁰ The delayed and protracted rise in uPA following injury combined with the ability of TXA to enhance uPA-mediated fibrinolysis provides a potential mechanism for the paradox of increased hemorrhage-related mortality with delayed therapy. Further research to evaluate the importance of uPA-mediated fibrinolysis in non-TBI related trauma is required along with the potential role of therapeutics capable of attenuating both tPA and uPA in bleeding after major injury.

Alternative antifibrinolytic therapy in trauma

The alternate antifibrinolytic agents aprotinin and epsilon aminocaproic acid (EACA) have some unfavorable properties compared to TXA, hence were not selected for clinical trial

evaluation in trauma hemorrhage. Compared with TXA, the synthetic lysine analogue EACA is ten times less potent¹²¹ and has not been shown to be associated with reduced transfusion requirements in elective surgery.¹²² Aprotinin was withdrawn from the market after it was found to be associated with increased mortality in a randomized trial of patients undergoing cardiac surgery.¹²³ However, due to methodological deficiencies with this study the conclusions were called into question and the European Medicines Agency have since lifted the suspension.¹²⁴ Aprotinin is a potent, long acting antifibrinolytic and future clinical trials should be considered to determine the efficacy in trauma hemorrhage as well as any additional benefits over TXA. In the search for an ideal antifibrinolytic to treat hyperfibrinolysis, a greater understanding of the pathophysiology of fibrinolytic pathways in trauma is required to determine optimal pharmacodynamics and how best to monitor the effect of any drug on fibrinolytic activity.

Thrombotic risk of antifibrinolytic therapy in trauma

A principal concern with the use of antifibrinolytics is potentiation of a prothrombotic state, either immediately after trauma during increased thrombin generation, or during the acute phase of recovery from major injury. Without thromboprophylaxis, multi-trauma patients have a baseline risk of hospital-acquired venous thromboembolism (VTE) exceeding 50%¹²⁵, with increasing age an important clinical predictor.¹²⁶ As trauma care advances, more patients survive beyond the initial 24-hours from injury and consequently more patients will be at risk of VTE. Some authors are concerned VTE rates are influenced directly by antifibrinolytic therapy;⁷ however, TXA has been shown to improve survival and is often

administered to those at greatest risk of VTE (e.g. major trauma, shock, critical care utilization and invasive procedures). In the surgical setting, a recent meta-analysis concluded that the risk of thromboembolic events with antifibrinolytic use was uncertain.¹⁰² In a retrospective cohort study of 872,416 patients undergoing total hip or knee arthroplasty in the United States, antifibrinolytic therapy was associated with lower rates of blood transfusion without any increase in VTE.¹²⁷ CRASH-2 represents the largest randomized trial to evaluate antifibrinolytic use in trauma patients and found no increase in clinically significant vascular occlusive events with TXA compared to placebo (1.7% vs. 2.0%). In fact patients who received TXA had a lower incidence of myocardial infarction post-injury.⁹³ Whilst the MATTERS study reported higher unadjusted rates of VTE in patients receiving an antifibrinolytic (TXA vs. No TXA: PE, 2.7% vs. 0.3% and DVT, 2.4% vs. 0.2%), the difference was nonsignificant on multivariate analysis and the investigators attributed the difference to the higher injury burden and degree of shock in the TXA group.⁹⁵

In order to reduce the incidence of VTE in this inherently high-risk group of patients, rather than avoiding early antifibrinolytic therapy, future research should focus on the role of proactive targeted thromboprophylaxis. Development of new methods to monitor fibrinolytic status as the trauma patient transitions from hyperfibrinolysis to a hypofibrinolytic state would permit earlier insertion of retrievable vena cava filters, or use of higher prophylactic doses of anticoagulants. Additionally the role of antiplatelet therapy in prevention of post-traumatic thrombotic events needs greater clarification.

Conclusion

Fibrinolytic activation within the limitations of current assays, is presumed almost universal following trauma. Assessing hyperfibrinolysis through biomarker assays (e.g. PAP) remains the gold standard, and in comparison with VHA demonstrates the insensitivity of ROTEM and TEG for accurate diagnosis of increased fibrinolytic activation. Rapid evaluation of current or active fibrinolysis remains a challenge but whilst our understanding of available diagnostics improves, the decision whether to administer an antifibrinolytic agent should be based upon available evidence from clinical trials. In line with current European guidelines, we recommend that all bleeding trauma patients (both suspected and confirmed), those that require immediate blood transfusion and all severely injured patients with evidence of hemorrhagic shock receive early empiric antifibrinolytic therapy.

Early empiric TXA is associated with a mortality benefit and is the current mainstay of treatment for hyperfibrinolysis in trauma. Which patient subgroups derive greatest benefit from reversal of hyperfibrinolysis, optimal timing, choice of drug and potential for increased thrombotic events with antifibrinolytics should be the focus for future research. Given the advances in pharma engineering since TXA was first described over 50 years ago, it seems unlikely that such an old drug whose mechanism of action in traumatic hemorrhage is unclear will remain the optimal agent to treat trauma patients. Improved understanding of the pathways that drive excessive fibrinolytic activation, including the role of uPA, may lead to the development of novel and more efficacious therapeutics. The fibrinolytic system is highly dynamic, evolving over time following injury and yet studies have on the whole been limited to measurement of fibrinolysis at the point of ED arrival. Future studies should focus on serial sampling to fully characterize the temporal changes that occur in the coagulation

and fibrinolytic systems in response not just to the initial trauma, but over subsequent hours and days following resuscitation, surgery and antifibrinolytic therapy. At present TXA remains the most studied drug in traumatic hemorrhage, with sufficient evidence of efficacy and safety to recommend early empiric administration for the treatment of hyperfibrinolysis.

Acknowledgements

The authors have received support from both Haemonetics and Tem International GmbH in the form of equipment and reagents on an unrestricted basis as part of our ongoing research program.

References

1. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost* 2013;11:307-314
2. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev* 2015;29:17-24
3. Brohi K, Cohen M, Ganter M, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma* 2008;64:1211-7
4. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg* 2012;73:13-9
5. Hunt BJ, Segal H. Hyperfibrinolysis. *J Clin Pathol* 1996;49:958

6. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 2006;60:S3-11
7. Moore EE, Moore HB, Gonzalez E, Sauaia A, Banerjee A, Silliman CC. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. *Transfusion* 2016;56:S110-4
8. Dunbar NM, Chandler WL. Thrombin generation in trauma patients. *Transfusion* 2009;49:2652-60
9. Levin EG, Loskutoff DJ. Cultured bovine endothelial cells produce both urokinase and tissue-type plasminogen activators. *J Cell Biol* 1982;94:631-6
10. Levin EG, Santell L, Osborn KG. The expression of endothelial tissue plasminogen activator in vivo: a function defined by vessel size and anatomic location. *J Cell Sci* 1997;110:139-48
11. Levin EG, del Zoppo GJ. Localization of tissue plasminogen activator in the endothelium of a limited number of vessels. *Am J Pathol* 1994;144:855-61
12. Huber D, Cramer EM, Kaufmann JE, et al. Tissue-type plasminogen activator (t-PA) is stored in Weibel-Palade bodies in human endothelial cells both in vitro and in vivo. *Blood* 2002;99:3637-45
13. Emeis JJ, van den Eijnden-Schrauwen Y, van den Hoogen CM, de Priester W, Westmuckett A, Lupu F. An endothelial storage granule for tissue-type plasminogen activator. *J Cell Biol* 1997;139:245-56
14. Yau JW, Teoh H, Verma S. Endothelial cell control of thrombosis. *BMC Cardiovasc*

Disord 2015;15:130

15. Van De Craen B, Declerck PJ, Gils A. The Biochemistry, Physiology and Pathological roles of PAI-1 and the requirements for PAI-1 inhibition in vivo. *Thromb Res* 2012;130:576-85
16. Fay WP, Eitzman DT, Shapiro AD, Madison EL, Ginsburg D. Platelets inhibit fibrinolysis in vitro by both plasminogen activator inhibitor-1-dependent and -independent mechanisms. *Blood* 1994;83:351-6
17. Declerck PJ, Alessi MC, Verstreken M, Kruithof EK, Juhan-Vague I, Collen D. Measurement of plasminogen activator inhibitor 1 in biologic fluids with a murine monoclonal antibody-based enzyme-linked immunosorbent assay. *Blood* 1988;71:220-5
18. Booth NA, Simpson AJ, Croll A, Bennett B, MacGregor IR. Plasminogen activator inhibitor (PAI-1) in plasma and platelets. *Br J Haematol* 1988;70:327-33
19. Schleef RR, Sinha M, Loskutoff DJ. Immunoradiometric assay to measure the binding of a specific inhibitor to tissue-type plasminogen activator. *J Lab Clin Med* 1985;106:408-15
20. Brogren H, Karlsson L, Andersson M, Wang L, Erlinge D, Jern S. Platelets synthesize large amounts of active plasminogen activator inhibitor 1. *Blood* 2004;104:3943-8
21. Brogren H, Wallmark K, Deinum J, Karlsson L, Jern S. Platelets retain high levels of active plasminogen activator inhibitor 1. *PLoS One* 2011;6:e26762
22. Moore HB, Moore EE, Gonzalez E, et al. Hemolysis exacerbates hyperfibrinolysis, whereas plateletolysis shuts down fibrinolysis: evolving concepts of the spectrum of

- fibrinolysis in response to severe injury. Shock 2015;43:39-46
23. Levi M, Biemond BJ, van Zonneveld AJ, ten Cate JW, Pannekoek H. Inhibition of plasminogen activator inhibitor-1 activity results in promotion of endogenous thrombolysis and inhibition of thrombus extension in models of experimental thrombosis. Circulation 1992;85:305-12
 24. Mosnier LO, Buijtenhuijs P, Marx PF, Meijers JCM, Bouma BN. Identification of thrombin activatable fibrinolysis inhibitor (TAFI) in human platelets. Blood 2003;101:4844-6
 25. Mitchell JL, Lionikiene AS, Fraser SR, Whyte CS, Booth NA, Mutch NJ. Functional factor XIII-A is exposed on the stimulated platelet surface. Blood 2014;124:3982-90
 26. Holcomb JB, Tilley BC, Baraniuk S, et al. 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. JAMA 2015;313:471-82
 27. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248:447-58
 28. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009;197:565-70
 29. *****White. *****White - platelets also contain profibrinolytic properties *****. Semin Thromb Hemost. 2016

30. Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012;10:1342-1351
31. Brohi K, Singh J, Heron M, Coats T. Acute Traumatic Coagulopathy. *J Trauma* 2003;54:1127-1130
32. Floccard B, Rugeri L, Faure A, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury* 2012;43:26-32
33. Davenport R, Khan S. Management of major trauma haemorrhage: treatment priorities and controversies. *Br J Haematol* 2011;155:537-548
34. Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. *Curr Opin Anaesthesiol* 2016;29:212-9
35. Boldt J, Papsdorf M, Rothe A, Kumle B, Piper S. Changes of the hemostatic network in critically ill patients - is there a difference between sepsis, trauma, and neurosurgery patients? *Crit Care Med* 2000;28:445-50
36. Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ. Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma Inj Infect Crit Care* 2005;58:475-481
37. Chakrabarti R, Hocking ED, Fearnley GR. Reaction pattern to three stresses - electroplexy, surgery, and myocardial infarction - of fibrinolysis and plasma fibrinogen. *J Clin Pathol* 1969;22:659-62
38. Gando S. Disseminated intravascular coagulation in trauma patients. *Semin Thromb Hemost* 2001;27:585-92

39. Innes D, Sevitt S. Coagulation and fibrinolysis in injured patients. *J Clin Pathol* 1964;17:1-13
40. Brohi K, Cohen M, Ganter M, Matthay M, Mackersie R, Pittet J-F. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg* 2007;245:812-818
41. Cohen M, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg* 2012;255:379-385
42. Cohen MJ, Kutcher M, Redick B, et al. Clinical and mechanistic drivers of acute traumatic coagulopathy. *J Trauma Acute Care Surg* 2013;75:S40-7
43. Chesebro B, Rahn P, Carles M, et al. Increase in activated protein C mediates acute traumatic coagulopathy in mice. *Shock* 2009;32:659-665
44. Brohi K, Cohen M, Davenport R. Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care* 2007;13:680-685
45. Cohen M, Brohi K, Ganter M, Manley G, Mackersie R, Pittet J-F. Early Coagulopathy After Traumatic Brain Injury: The Role of Hypoperfusion and the Protein C Pathway. *J Trauma Inj Infect Crit Care* 2007;63:1254-1262
46. Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. *Ann Surg* 2011;254:10-9
47. Gando S, Wada H, Thachil J. Differentiating disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype from coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS). *J Thromb Haemost* 2013;11:826-835

48. Kooistra T, Schrauwen Y, Arts J, Emeis JJ. Regulation of endothelial cell t-PA synthesis and release. *Int J Hematol* 1994;59:233-55
49. Bärtsch P, Haeberli A, Hauser K, Gubser A, Straub PW. Fibrinogenolysis in the absence of fibrin formation in severe hypobaric hypoxia. *Aviat Space Environ Med* 1988;59:428-32
50. Hayakawa M, Sawamura A, Gando S, et al. Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. *Surgery* 2011;149:221-230
51. Gando S. Acute coagulopathy of trauma shock and coagulopathy of trauma: a rebuttal. You are now going down the wrong path. *J Trauma* 2009;67:381-3
52. Viersen VA, Greuters S, Korfage AR, et al. Hyperfibrinolysis in out of hospital cardiac arrest is associated with markers of hypoperfusion. *Resuscitation* 2012;83:1451-5
53. Schöchel H, Cadamuro J, Seidl S, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest: results from a prospective observational thromboelastometry study. *Resuscitation* 2013;84:454-9
54. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. High circulating adrenaline levels at admission predict increased mortality after trauma. *J Trauma Acute Care Surg* 2012;72:428-36
55. von Känel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. *Eur J Haematol* 2000;65:357-69
56. Kowalski E, Kopec M, Niewiarowski S. An evaluation of the euglobulin method for the determination of fibrinolysis. *J Clin Pathol* 1959;12:215-8

57. Boudjeltia KZ, Cauchie P, Remacle C, et al. A new device for measurement of fibrin clot lysis: application to the euglobulin clot lysis time. *BMC Biotechnol* 2002;2:8
58. Katz J, Lurie A, Becker D, Metz J. The euglobulin lysis time test: an ineffectual monitor of the therapeutic inhibition of fibrinolysis. *J Clin Pathol* 1970;23:529-32
59. Kutcher ME, Cripps MW, McCreery RC, et al. Criteria for empiric treatment of hyperfibrinolysis after trauma. *J Trauma Acute Care Surg* 2012;73:87-93
60. Chapman MP, Moore EE, Moore HB, et al. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. *J Trauma Acute Care Surg* 2015;80:16-23
61. Ostrowski SR, Sørensen AM, Larsen CF, Johansson PI. Thrombelastography and biomarker profiles in acute coagulopathy of trauma: a prospective study. *Scand J Trauma Resusc Emerg Med* 2011;19:64
62. Cardenas JC, Matijevic N, Baer LA, Holcomb JB, Cotton BA, Wade CE. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. *Shock* 2014;41:514-21
63. Lisman T. Decreased plasma fibrinolytic potential as a risk for venous and arterial thrombosis. *Semin Thromb Hemost* 2016; Epub July 29
64. Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. *Crit Care* 2015;19:97
65. Carroll RC, Craft RM, Langdon RJ, et al. Early evaluation of acute traumatic

- coagulopathy by thrombelastography. *Transl Res* 2009;154:34-9
66. Jeger V, Zimmermann H, Exadaktylos AK. Can RapidTEG accelerate the search for coagulopathies in the patient with multiple injuries? *J Trauma* 2009;66:1253-7
 67. Davenport R, Manson J, Ath H De, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011;39:2652-8
 68. Inaba K, Rizoli S, Veigas P V, et al. 2014 Consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation: Report of the panel. *J Trauma Acute Care Surg* 2015;78:1220-9
 69. National Institute for Health and Care Excellence (NICE). Major trauma: assessment and initial management. Guideline 39. 2016. Available at: www.nice.org.uk/guidance/ng39. Accessed September 11, 2016
 70. Hunt H, Stanworth S, Curry N, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. *Cochrane database Syst Rev* 2015;2:CD010438
 71. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. *Ann Surg* 2016;263:1051-9
 72. TACTIC partners. iTACTIC Trial: Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy. Available at: www.tacticgroup.dk/. Accessed September 11, 2016
 73. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*

2016;20:100

74. Levrat A, Gros A, Rugeri L, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth* 2008;100:792-7
75. Schöch H, Frietsch T, Pavelka M, Jámbor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. *J Trauma* 2009;67:125-31
76. Theusinger OM, Wanner GA, Emmert MY, et al. Hyperfibrinolysis diagnosed by rotational thromboelastometry (ROTEM) is associated with higher mortality in patients with severe trauma. *Anesth Analg* 2011;113:1003-12
77. Tauber H, Innerhofer P, Breitkopf R, et al. Prevalence and impact of abnormal ROTEM(R) assays in severe blunt trauma: results of the "Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study". *Br J Anaesth* 2011;107:378-87
78. Cotton BA, Harvin JA, Kostousouv V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. *J Trauma Acute Care Surg* 2012;73:365-70
79. Ives C, Inaba K, Branco BC, et al. Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. *J Am Coll Surg* 2012;215:496-502
80. Kashuk J, Moore E, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. *Ann Surg* 2010;252:434-42
81. Dekker SE, Viersen VA, Duvekot A, et al. Lysis onset time as diagnostic rotational thromboelastometry parameter for fast detection of hyperfibrinolysis. *Anesthesiology* 2014;121:89-97

82. Chapman MP, Moore EE, Ramos CR, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg* 2013;75:961-7
83. Moore HB, Moore EE, Liras IN, et al. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients. *J Am Coll Surg* 2016;222:347-55
84. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014;77:811-7
85. Pommerening MJ, Goodman MD, Farley DL, et al. Early diagnosis of clinically significant hyperfibrinolysis using thrombelastography velocity curves. *J Am Coll Surg* 2014;219:1157-66
86. Leebeek FWG, Rijken DC. The fibrinolytic status in liver diseases. *Semin Thromb Hemost* 2015;41:474-80
87. Cardenas JC, Matijevic N, Baer LA, Holcomb JB, Cotton BA, Wade CE. Elevated Tissue Plasminogen Activator and Reduced Plasminogen Activator Inhibitor Promote Hyperfibrinolysis in Trauma Patients. *Shock* 2014;41:514-21
88. Harr JN, Moore EE, Chin TL, et al. Viscoelastic hemostatic fibrinogen assays detect fibrinolysis early. *Eur J Trauma Emerg Surg* 2015;41:49-56
89. Moore HB, Moore EE, Chapman MP, et al. Viscoelastic measurements of platelet function, not fibrinogen function, predicts sensitivity to tissue-type plasminogen activator in trauma patients. *J Thromb Haemost* 2015;13:1878-87

90. Lang T, von Depka M. Possibilities and limitations of thrombelastometry/-graphy. *Hämostaseologie* 2006;26:S20-9
91. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown. *J Trauma Acute Care Surg* 2014;77:811-817
92. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury* 2007;38:298-304
93. 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 haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23-32
94. Cole E, Davenport R, Willett K, Brohi K. Tranexamic Acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg* 2015;261:390-4
95. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg* 2012;147:113-9
96. Moore HB, Moore EE, Morton AP, et al. Shock-induced systemic hyperfibrinolysis is attenuated by plasma-first resuscitation. *J Trauma Acute Care Surg* 2015;79:897-904
97. Vulliamy P, Gillespie S, Gall L, Brohi K, Davenport RA. Platelet transfusions reduce fibrinolysis but do not restore platelet function during trauma hemorrhage. *J Trauma Acute Care Surg* (in press)
98. McCormack PL. Tranexamic acid: a review of its use in the treatment of

- hyperfibrinolysis. *Drugs* 2012;72:585-617
99. Dubber AC, Mcnicol GP, Douglas AS, Melander B. Some properties of the antifibrinolytically active isomer of amino-methylcyclohexane carboxylic acid. *Lancet* 1964;284:1317-1319
 100. Verstraete M. *Haemostatic drugs: a critical appraisal*. 1st ed. The Hague: Martinus Nijhoff; 1977:132
 101. Okamoto S, Sato S, Takada Y, Okamoto U. An active stereo-isomer (trans-form) of amcha and its antifibrinolytic (antiplasminic) action in vitro and in vivo. *Keio J Med* 1964;13:177-85
 102. Henry D, Carless P, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011;3:CD001886
 103. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;344:e3054
 104. Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012;13:87
 105. Roberts I, Coats T, Edwards P, et al. HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014;15:450
 106. Shakur H, Elbourne D, Gülmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage:

- an international randomised, double blind placebo controlled trial. *Trials* 2010;11:40
107. Roberts I, Perel P, Prieto-Merino D, et al. Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *BMJ* 2012;345:e5839
 108. Perel P, Prieto-Merino D, Shakur H, Roberts I. Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technol Assess* 2013;17:1-45
 109. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. *BMC Emerg Med* 2012;12:3
 110. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* 2011;6:e18987
 111. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess* 2013;17:1-79
 112. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERS II Study. *JAMA Surg* 2013;148:218-25

113. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev* 2015;5:CD004896
114. Klein AA, Arnold P, Bingham RM, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. *Anaesthesia* 2016;71:829-42
115. Rossaint R, Bouillon B, Cerny V, et al. The STOP the Bleeding Campaign. *Crit Care* 2013;17:136
116. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;377:1096-101
117. Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care* 2007;11:R117
118. Godier A, Roberts I, Hunt BJ. Tranexamic acid: less bleeding and less thrombosis? *Crit Care* 2012;16:135
119. Hijazi N, Abu Fanne R, Abramovitch R, et al. Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice. *Blood*. 2015;125:2558-67
120. Medcalf RL. The traumatic side of fibrinolysis. *Blood* 2015;125:2457-8
121. Faught C, Wells P, Fergusson D, Laupacis A. Adverse effects of methods for minimizing perioperative allogeneic transfusion: A critical review of the literature. *Transfus Med Rev* 1998;12:206-225

122. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology* 2006;105:1034-46
123. Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008;358:2319-31
124. European Medicines Agency. Press release February 17, 2012. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001447.jsp&mid=WC0b01ac058004d5c1. Accessed September 10, 2016
125. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994;331:1601-6
126. Selby R, Geerts W, Ofosu FA, et al. Hypercoagulability after trauma: hemostatic changes and relationship to venous thromboembolism. *Thromb Res* 2009;124:281-7
127. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014;349:g4829

Table 1 - Summary of studies of hyperfibrinolysis in trauma

	Year	Definition of hyperfibrinolysis used	Number of patients studied	% patients with hyperfibrinolysis	Mortality - with hyperfibrinolysis (%)	Mortality - without hyperfibrinolysis (%)	
ROTEM studies							
	Levrat ⁷⁴	2008	ECLT < 90 minutes (and MCF ≤ 18 mm)	87	6%	100%	11%
	Schochl ⁷⁵	2009	EXTEM ML = 100%	33	100%	88%	n/a
	Theusinger ⁷⁶	2011	EXTEM ML > 15%	(552) ^a	13 patients ^b	77%	33%
	Tauber ⁷⁷	2011	EXTEM ML > 15%	334	7%	57%	11%
	Kutcher ⁵⁹	2012	EFI > 10%	115	20%	52%	13%
TEG studies							
	Carroll ⁶⁵	2009	LY60 > 15%	161	2%	67%	8%
	Kashuk ⁸⁰	2010	EPL > 15%	61	18%	64%	24%
	Cotton ⁷⁸	2012	LY30 > 7.5%	1996	2%	76%	10%
	Ives ⁷⁹	2012	EPL > 15%	118	11%	92%	10%
	Chapman ⁸²	2013	LY30 ≥ 3%	73	15%	64%	18%
	Pommerening ⁸⁵	2014	LY30 > 3%	1625	11%	18%	10%
	Moore ⁹¹	2014	LY30 ≥ 3%	180	18%	44%	n/a
	Moore ⁸³	2016	LY30 ≥ 3%	2540	18%	34%	n/a
Biomarker studies							
	Raza ¹	2013	PAP >1500 µg/L AND EXTEM ML < 15% (moderate) PAP >1500 µg/L AND EXTEM ML > 15% (severe)	303	Moderate 57% Severe 5%	Moderate 12.1% Severe 40%	1% ^c
	Cardenas ⁶²	2014	PAP 1500 – 20000 µg/L (moderate) PAP >20000 µg/L (severe)	163	Moderate 45% Severe 10%	Moderate 25% Severe 31%	4.1% ^c

^a Includes trauma and non-trauma patients presenting to the ED

^b Denominator for trauma patients not available

^c No fibrinolysis defined as PAP < 1500 µg/L

ECLT, euglobulin clot lysis time; EPL, estimated percent lysis; EFI, enzymatic fibrinolysis index (EXTEM ML – APTM ML); LY30, clot lysis 30 minutes after maximal amplitude; ML, maximum lysis 60 minutes after the onset of clot formation; n/a, data not available from original publication

Table 2 – Commonly employed VHA assays to measure coagulation and fibrinolysis

VHA Platform	Assay	Reagents used	Description
TEG	KaolinTEG	Re-calcified with calcium chloride and activated with Kaolin	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway
TEG	RapidTEG	Re-calcified then activated with Kaolin and tissue factor (RapidTEG Reagent)	Extrinsic pathway assessment of clot formation, fibrin polymerisation and fibrinolysis with faster results than Kaolin TEG.
TEG	Functional Fibrinogen TEG	Re-calcified then activated with lyophilized tissue factor and a platelet inhibitor that binds to glycoprotein-IIb/IIIa receptors (Functional Fibrinogen Reagent)	Assessment of the fibrinogen contribution to clot formation after blocking platelets
ROTEM	EXTEM	Re-calcified with calcium chloride (star-tem) and activated with thromboplastin (tissue factor) derived from rabbit brain (ex-tem)	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway
ROTEM	FIBTEM	Re-calcified and platelets inhibited with cytochalasin D (fib-tem) and activated with ex-tem	Assessment of the fibrinogen contribution to clot formation after blocking platelets
ROTEM	APTEM	Re-calcified and fibrinolysis inhibited with aprotinin (ap-tem) and activated with ex-tem	Assessment of clot firmness after blocking hyperfibrinolysis with aprotinin