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

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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 trauma\(^2\), 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 hyperfibrinolysis\(^3\), early fibrinogen depletion and platelet dysfunction\(^4\) 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 formation\(^5\), 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 therapy\(^7\) 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 lacking\(^2\) 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-\(\alpha_2\)-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 (α2AP) which inhibits plasmin. PAI-1 is found
within two distinct pools within the blood - plasma and platelets. Circulating levels of PAI-1 are relatively low in comparison to the rich source within platelet α-granules. Platelet-rich thrombi are resistant to tPA-mediated fibrinolysis, 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 configuration, subsequent research has discovered that platelets actually retain high levels of active PAI-1, capable of complexing and inactivating the plasminogen activators. Moore et al. 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. Platelets are additionally a source of α2AP, thrombin activatable fibrinolysis inhibitor (TAFI) and factor XIII, 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. 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.

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.\textsuperscript{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.\textsuperscript{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)\textsuperscript{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.\textsuperscript{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.\textsuperscript{35,36} A biphasic response has similarly been described in the fibrinolytic system\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40,44,45} PAI-1 rather than TAFI appears to exert greater control over the fibrinolytic state after trauma.\textsuperscript{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.\textsuperscript{46,47} Primary and secondary fibrin(ogen)olysis are considered to be pathologically activated following trauma in response to shock-induced endothelial tPA release\textsuperscript{46,48,49} and DIC respectively.\textsuperscript{47} Activation of neutrophil elastase-mediated fibrinolytic pathways is additionally believed to contribute to the hyperfibrinolytic state.\textsuperscript{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.\textsuperscript{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\textsuperscript{52,53} and similarly increasing levels of tissue injury will initiate fibrinolysis\textsuperscript{3}, evidenced on ROTEM by shortened lysis onset time (20\% lysis of maximum clot firmness).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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)\textsuperscript{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.\textsuperscript{58} Excessive fibrin degradation may be indicated by raised D-dimer levels; however, elevated levels are encountered in most patients following injury\textsuperscript{1} and are strongly correlated to injury severity\textsuperscript{3}. Kutcher et al.\textsuperscript{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.\textsuperscript{1,3,39,54,60–62} Measurement of tPA and PAP complex levels in combination with fibrinolytic inhibitor levels (PAI-1, α2AP, 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. 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). 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 ATC and are superior to conventional clotting tests (e.g. Prothrombin Time) in predicting the need for massive transfusion in trauma. 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. However, the latest National Institute for Health and Care Excellence (NICE)
guideline on the management of major trauma\textsuperscript{69} 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.\textsuperscript{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.\textsuperscript{71,72} For these reasons European and UK guidelines\textsuperscript{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).\textsuperscript{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\textsuperscript{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. 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. reported hyperfibrinolysis to be uncommon but highly lethal. Chapman et al. 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 ≥ 3%.

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 activation, through rapid inhibition of free tPA by PAI-1 following blood draw. Using a composite measure of PAP and VHA on admission to ED we have shown fibrinolytic activation following severe trauma to be extremely common. Patients without VHA hyperfibrinolysis (ML < 15%) were categorized as ‘normal’ fibrinolytic activity if PAP < 1500 µg/L and ‘moderate’ fibrinolytic activity if PAP > 1500 µg/L. Patients with PAP > 1500 µg/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 α2AP 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 ≤ 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 hours\textsuperscript{92} and more likely to require a massive transfusion\textsuperscript{44}, with increased risk of multi-organ failure (MOF) and longer critical care and hospital stay.\textsuperscript{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.\textsuperscript{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 mmHg\textsuperscript{93}, and was confirmed in a single center retrospective UK study\textsuperscript{94} 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.\textsuperscript{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 VHA\textsuperscript{70} and in the context of clinical trial data to support empiric
antifibrinolytic therapy in suspected trauma hemorrhage\textsuperscript{93}, 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 plasma\textsuperscript{96} (a source of α2AP) and platelets may further dampen fibrinolytic activation\textsuperscript{97} 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 fibrin\textsuperscript{98} and at higher concentrations is a non-competitive inhibitor of plasmin.\textsuperscript{99,100} First described over five decades ago\textsuperscript{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.\textsuperscript{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)\textsuperscript{104}, non-traumatic gastrointestinal (Hemorrhage Alleviation with Tranexamic acid – Intestinal system; HALT-IT)\textsuperscript{105} and postpartum hemorrhage (World Maternal Antifibrinolytic Trial; WOMAN)\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 lives\textsuperscript{109} and be highly cost-effective.\textsuperscript{110,111}

TXA for the management of combat injury and hemorrhage was evaluated in the retrospective MATTERs\textsuperscript{95} and MATTERs II studies.\textsuperscript{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 action94,117,118 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. 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. 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. 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 potent and has not been shown to be associated with reduced transfusion requirements in elective surgery. 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. However, due to methodological deficiencies with this study the conclusions were called into question and the European Medicines Agency have since lifted the suspension. 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%, with increasing age an important clinical predictor. 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; 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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### Table 1 - Summary of studies of hyperfibrinolysis in trauma

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition of hyperfibrinolysis used</th>
<th>Number of patients studied</th>
<th>% patients with hyperfibrinolysis</th>
<th>Mortality - with hyperfibrinolysis (%)</th>
<th>Mortality - without hyperfibrinolysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROTEM studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>ECLT &lt; 90 minutes (and MCF ≤ 18 mm)</td>
<td>87</td>
<td>6%</td>
<td>100%</td>
<td>11%</td>
</tr>
<tr>
<td>2009</td>
<td>EXTEM ML = 100%</td>
<td>33</td>
<td>100%</td>
<td>88%</td>
<td>n/a</td>
</tr>
<tr>
<td>2011</td>
<td>EXTEM ML &gt; 15%</td>
<td>(552)</td>
<td>13 patients</td>
<td>77%</td>
<td>33%</td>
</tr>
<tr>
<td>2011</td>
<td>EXTEM ML &gt; 15%</td>
<td>334</td>
<td>7%</td>
<td>57%</td>
<td>11%</td>
</tr>
<tr>
<td>2012</td>
<td>EFI &gt; 10%</td>
<td>115</td>
<td>20%</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>TEG studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>LY60 &gt; 15%</td>
<td>161</td>
<td>2%</td>
<td>67%</td>
<td>8%</td>
</tr>
<tr>
<td>2010</td>
<td>EPL &gt; 15%</td>
<td>61</td>
<td>18%</td>
<td>64%</td>
<td>24%</td>
</tr>
<tr>
<td>2012</td>
<td>LY30 &gt; 7.5%</td>
<td>1996</td>
<td>2%</td>
<td>76%</td>
<td>10%</td>
</tr>
<tr>
<td>2012</td>
<td>EPL &gt; 15%</td>
<td>118</td>
<td>11%</td>
<td>92%</td>
<td>10%</td>
</tr>
<tr>
<td>2013</td>
<td>LY30 ≥ 3%</td>
<td>73</td>
<td>15%</td>
<td>64%</td>
<td>18%</td>
</tr>
<tr>
<td>2014</td>
<td>LY30 ≥ 3%</td>
<td>1625</td>
<td>11%</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>2014</td>
<td>LY30 ≥ 3%</td>
<td>180</td>
<td>18%</td>
<td>44%</td>
<td>n/a</td>
</tr>
<tr>
<td>2016</td>
<td>LY30 ≥ 3%</td>
<td>2540</td>
<td>18%</td>
<td>34%</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Biomarker studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>PAP &gt;1500 µg/L AND EXTEM ML &lt; 15% (moderate)</td>
<td>303</td>
<td>Moderate 57%</td>
<td>Moderate 12.1%</td>
<td>1%</td>
</tr>
<tr>
<td>2013</td>
<td>PAP &gt;1500 µg/L AND EXTEM ML &gt; 15% (severe)</td>
<td>Moderate 5%</td>
<td>Severe 40%</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>PAP 1500 – 20000 µg/L (moderate)</td>
<td>163</td>
<td>Moderate 45%</td>
<td>Moderate 25%</td>
<td>4.1%</td>
</tr>
<tr>
<td>2014</td>
<td>PAP &gt;20000 µg/L (severe)</td>
<td>Severe 10%</td>
<td>Severe 31%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 – APTEM 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

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