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HEMOSTASIS AFTER TRAUMA (N SAILLANT, SECTION EDITOR)

# Mechanisms of Traumatic Hyperfibrinolysis and Implications for Antifibrinolytic Therapy

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**Abstract**

**Purpose of the Review** To provide an update on the current knowledge of mechanisms that regulate hyperfibrinolysis and implications of recent findings for use of antifibrinolytics.

**Recent Findings** New data demonstrate a role for both platelet and endothelial dysfunction, as well as novel mechanisms for activated protein C in the pathophysiology of hyperfibrinolysis. Although randomized clinical trial data in mature trauma centers is lacking, most analyses support the early use of tranexamic acid in the treatment of all severely injured patients experiencing hemorrhagic shock.

**Summary** Hyperfibrinolysis is a devastating complication of trauma and hemorrhagic shock. Currently available antifibrinolytics are largely considered safe and effective and further research is needed before restricting antifibrinolytic use in the sub-population of patients with fibrinolytic shutdown. Future development of novel therapeutics to reverse hyperfibrinolysis could improve treatment of this hemostatic disorder.

**Keywords** Hyperfibrinolysis · Antifibrinolytic · Tranexamic acid · Hemorrhagic shock · Trauma

## Introduction

Fibrinolysis is a normal hemostatic process which balances clot formation with clot breakdown to prevent occlusive thrombus formation. However, after severe trauma, pathologic hyperfibrinolysis results in prolonged, coagulopathic bleeding, and contributes to poor outcomes in this patient population. Depending on the method and threshold used to define hyperfibrinolysis, the mortality rate for affected patients ranges between 26 and 76% [1•, 2–5]. The ability to identify patients with hyperfibrinolysis has improved with increasing use of viscoelastic tests to monitor hemostasis clinically. A recent multicenter analysis demonstrated that patients who present with hyperfibrinolysis are more severely injured, have worsened indices of shock, require greater volumes of blood transfusion products, and have a 3-fold higher incidence of mortality compared with those patients without hyperfibrinolysis [1•]. This review focuses on the most recent advances in our understanding of the mechanisms that drive hyperfibrinolysis, antifibrinolytics for hyperfibrinolysis reversal, and implications of recent findings on use of antifibrinolytic therapy.

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## Overview of Fibrinolysis Pathway

While the formation of a stable fibrin clot is essential to achieving hemostasis, the dissolution or lysis of fibrin clots is an equally important component of the coagulation system, as it maintains vessel patency and ensures large pieces of fibrin do not disrupt normal processes in circulation. Fibrinolysis is tightly controlled to both modulate the degree of fibrin formation and safeguard timely and appropriate degradation of fibrin. While forces that dictate fibrin clot structure such as fibrinogen levels, thrombin generation, and cellular activity are important determinants of clot strength and susceptibility to degradation [6], fibrinolysis is highly regulated at the proteolytic level by the plasminogen activator (PA) system [7–9]. The PA system is composed of both profibrinolytic serine proteases and antifibrinolytic serine protease inhibitors

which dictate the enzymatic activity of plasmin. Plasmin is generated from the inactive zymogen, plasminogen by either tissue plasminogen activator (tPA) or urokinase plasminogen activator (uPA). As both tPA and plasminogen have high affinity for fibrin, fibrin acts as a co-factor for tPA-mediated plasmin generation through co-localization. Such binding is not necessary for plasminogen activation by uPA. Once produced, plasmin degrades clots by cleaving fibrin cross links to form soluble fragments that are cleared in circulation [7–9].

The generation and activity of plasmin are regulated by several serine protease inhibitors. Plasmin production is downregulated by both plasminogen activator inhibitor type 1 and 2 (PAI-1 and PAI-2) which inhibit tPA and uPA. Plasmin activity is directly inhibited by α2-antiplasmin (α2AP) which binds plasmin only when plasmin is unbound by fibrin. Thus, fibrin protects plasmin from inhibition by α2AP. Finally, although not a serine protease inhibitor, thrombin activatable fibrinolysis inhibitor (TAFI) can downregulate fibrinolysis by removing both C-terminal lysine and arginine residues present on fibrin where plasminogen would normally bind, thus preventing fibrin from acting as a co-factor to accelerate plasmin generation [7–9].

## Mechanisms of Hyperfibrinolysis Following Trauma

While the mechanisms that promote and regulate fibrinolysis described above demonstrate local fibrinolytic activity during normal hemostasis in a largely intact vessel, the presence of major trauma, tissue disruption, and shock can result in a breakdown of fibrinolytic regulation leading to systemic hyperfibrinolysis (Fig. 1). Previous work has shown that susceptibility to fibrinolysis is, in part, dictated by fibrin network density as the more loosely woven a clot is, the easier it is for plasminogen to access and fully occupy fibrin binding sites [6, 10, 11]. Given that many patients experience critically low fibrinogen and other coagulation factor levels which compromises stable clot formation, the substantial amount of plasmin generated following trauma likely overwhelms procoagulant responses. Thus, trauma-induced hyperfibrinolysis leads a scenario in which the rate of clot breakdown outcompetes the rate of clot formation, resulting in exacerbation of bleeding, worsening hemorrhagic shock, and ultimately coagulopathy.

Mechanistically, the presence of hypoperfusion, or shock, appears to be a pre-requisite rather than contributing factor for hyperfibrinolysis [12]. Shock leads to diffuse activation of the vascular endothelium with subsequent release of high levels of tPA into circulation [3–5]. This massive release of tPA is accompanied by depletion or exhaustion of TAFI [13], α2AP [14, 15•], and PAI-1 [4, 5], and thus uninhibited plasmin generation. During hemostasis, local production of PAI-1 primarily comes from endothelial cells and platelets, with platelets degranulating in response to thrombin stimulation to release PAI-1 [16]. The importance of platelet activation to PAI-1 production was recently highlighted by Moore et al who showed that patients demonstrating reduced platelet responsiveness to adenosine diphosphate stimulation were more susceptible to tPA-mediated fibrinolysis [17]. While it is unknown how shock-induced pre-activation or dysfunction of platelets affects PAI-1 release, this work suggests that platelets may play an important role in the pathophysiology of hyperfibrinolysis.

Very recent work has further added to our understanding of the pathophysiology of traumatic hyperfibrinolysis. While previous findings have supported a role for activated protein C (aPC) in trauma-induced coagulopathy [12], recent data confirm that its ability to inhibit PAI-1 makes aPC an important player in the pathophysiology of hyperfibrinolysis. In a very interesting series of human and mouse experiments, Davenport et al showed that generation of aPC was a key mechanism contributing to fibrino(geno)lysis during acute traumatic coagulopathy [18••]. They found that patients experiencing coagulopathy exhibited early increases in aPC levels in conjunction with hyperfibrinolysis (increases PAP and D-dimer levels) and depletion of fibrinogen and PAI-1 in the absence of a reduced capacity to generate thrombin. Further, the authors utilized transgenic mice with a mutated thrombomodulin receptor to demonstrate in a model of trauma and hemorrhagic shock that inhibition of normal capacity to generate aPC results in diminished fibrinolysis, preserved fibrinogen levels, and improved survival. Together, these results suggest that aPC produced in response to hemorrhagic shock acts predominantly as a profibrinolytic rather than anticoagulant factor.

Other recent findings from Ostrowski et al demonstrate an independent association between circulating adrenaline levels and the degree of hyperfibrinolysis on viscoelastic tests [19]. It is unclear if the link between adrenaline and hyperfibrinolysis is causative or if such increased clot breakdown is reflective of the known effects of sympathoadrenal activation on promoting hypocoagulability, and therefore a susceptibility to fibrinolysis. However, such sympathoadrenal activation and subsequent release of catecholamines such as adrenaline could promote endothelial activation and systemic release of tPA into circulation, thus promoting hyperfibrinolysis.

Finally, Banerjee et al demonstrated using a targeted proteomics approach a distinct set of proteins that are reduced in hyperfibrinolysis patients compared to those with normal lysis parameters [15]. These included a number of coagulation proteins, carrier proteins, glycoproteins, and alternate complement pathway proteins. Many of the changes in coagulation protein expression were expected and known to contribute to dysregulation of fibrinolysis, such as reduced α2AP, plasminogen, protein C, protein S, and TAFI. However, loss of factors II, V, XIII, and fibrinogen were noted as unexpected by the authors given the absence of changes in TEG parameters that are influenced by the enzymatic phases of coagulation, such as

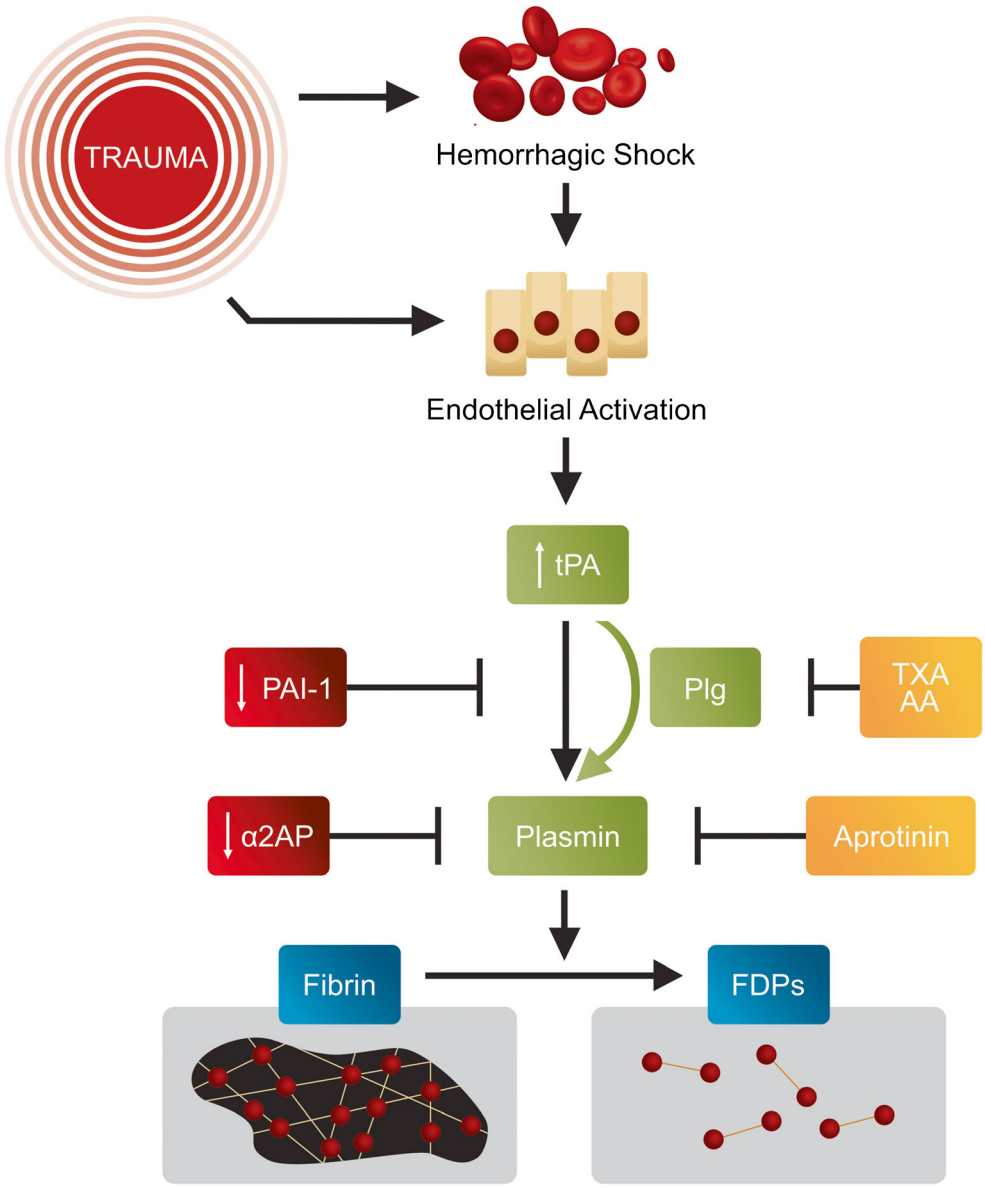


**Fig. 1** Schematic depicting simplified pathophysiology of traumatic hyperfibrinolysis and currently available antifibrinolytic drugs and their targets. Green depicts profibrinolytic proteins; red depicts antifibrinolytic proteins; yellow depicts antifibrinolytic agents. Tissue plasminogen activator (tPA); plasminogen activator inhibitor type 1 (PAI-1); plasminogen (Plg); alpha 2 antiplasmin or plasmin inhibitor (α2AP); tranexamic acid (TXA); epsilon aminocaproic acid (AA); fibrin degradation products (FDPs)

the split point, R times, or alpha angles. These changes likely do make sense given the pathophysiology of hyperfibrinolysis and its contribution to coagulopathy through the sustained attempts by the hemostatic system to form a stable clot in spite of elevated fibrinolysis combined with a higher propensity for hyperfibrinolysis when clot stabilizing factors are critically low, such as FXIII or fibrinogen. The authors suggest the combined use of antifibrinolytics followed by plasma or cryoprecipitate resuscitation would be the best approach to restore circulating levels of these reduced proteins, and thereby slow hyperfibrinolysis [15]. Indeed, this notion is supported by recent data from Kuckelman et al showing in a porcine model of hemorrhagic shock that co-administration of plasma with the antifibrinolytic tranexamic acid (TXA) was superior to TXA alone at reversing trauma-induced coagulopathy [20].

## Tranexamic Acid for Reversal of Hyperfibrinolysis

The most commonly used antifibrinolytic agent available today is TXA. TXA is a synthetic lysine analog that occupies lysine binding sites on plasminogen to inhibit its association with fibrin, making it unavailable for tPA-mediated conversion to plasmin. Use of TXA for treating traumatic hemorrhage was popularized by the success of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial [21]. The CRASH-2 trial enrolled 20,211 patients in 8 countries and randomized them to receive TXA (1-g bolus followed by an additional 1-g infusion over 8 h) or placebo. Patients were included if they were considered to be at high risk of hemorrhage and were within 8 h from their injury. Importantly, the study organizers utilized the uncertainly

principle to guide enrollment, meaning that if the attending physician was uncertain about whether TXA would or would not improve the patient's outcome, they were randomized. If it was clear that the patient would benefit from TXA, they were not enrolled and the drug was administered. Likewise, if there was a clear contraindication for TXA therapy, the patient was not randomized. The authors found a reduction in all-cause mortality among patients who received TXA (14.5% TXA group vs. 16.0% placebo group; $p < 0.01$) and reduction in bleeding deaths (4.9% TXA group vs. 5.7% placebo group; $p < 0.01$), with no apparent increase in thrombotic complications [21]. While a 1.5% reduction in mortality may seem clinically insignificant and likely driven by the large sample size, one must consider that components of the study design such as the highly heterogeneous patient population, diverse hospital standard care procedures, use of TXA in austere environments where other resuscitation fluids may not have been available, and employment of the uncertainly principle all should have reduced the study's ability to detect a difference between treatment groups. Thus, while CRASH-2 did not address which specific patient populations would most benefit from TXA or whether or not such benefits would exist in large urban trauma centers where transport times are short and balanced resuscitation is available, it certainly suggests there is a place for TXA in the treatment of substantial hemorrhage.

This is further supported by several recent observational studies. A retrospective analysis demonstrated that TXA administration was associated with reduced all-cause mortality in patients suffering from hemorrhagic shock [22]. In a multicenter study, Balvers et al showed that among severely injured patients, transfusion of high ratios of plasma and platelets to red blood cells, in conjunction with administration of TXA was associated with improved survival and a reduction in overall blood product administration [23]. The UK and European guidelines recommend empiric use of TXA for all bleeding trauma patients received within 3 h of injury [24], although use of TXA varies greatly among most US trauma centers and is often guided by viscoelastic tests. A retrospective analysis of prospectively collected data from the PROPPR trial compared outcomes among propensity matched patients with hyperfibrinolysis on TEG who did versus did not receive TXA in-hospital [25]. The authors found an improvement in 6-h survival in patients who received TXA, however no differences in either longer term outcomes or hemostasis times. A recent meta-analysis from the subcommittee on practice management guidelines section of (EAST) concluded that while a clear mortality benefit has not been observed with TXA, it is very safe when used within its limitations [26]. This resulted in the committee's conditional recommendation for the early use of TXA as a hemostatic adjunct therapy for in-hospital use in severely injured adult trauma patients.

## Limitations of TXA

There are important limitations to the use of TXA that should be considered. The CRASH-2 trial brought to light the deleterious effects of administering TXA more than 3 h after injury [21]. This finding that TXA has life-saving properties if administered early but detrimental effects if delivered late is an extremely important distinction and has implications for our understanding of both the mechanisms of action of TXA and also limits the clinical use of TXA. Previous work has shown that while TXA inhibits fibrinolysis driven by tPA, it can paradoxically promote uPA-mediated fibrinolysis through a conformational change in plasminogen that makes it more susceptible to activation by uPA [27–29]. Combined, these data could suggest that temporal changes in tPA vs. uPA release following injury could have profound effects on the response to TXA therapy [29]. While the above findings appear to be an important aspect of the pathophysiology of bleeding following traumatic brain injury [30], it remains to be determined if such temporal patterns are apparent in and contribute to the pathophysiology of systemic hyperfibrinolysis and how this affects the effectiveness of TXA.

Among the major concerns surrounding the empiric use of TXA in trauma patients is risks that it could incur for patients experiencing fibrinolytic shutdown (SD). Increased use of viscoelastic tests to identify hyperfibrinolysis clinically as led to the recent identification of three distinct fibrinolysis phenotypes in critically ill patients [31]. These include fibrinolytic SD, physiologic fibrinolysis, and hyperfibrinolysis. SD is by far the most common phenotype and several groups have reported its association with poor outcomes, especially if sustained beyond greater than or equal to seven days beyond the initial injury. The frequency of multi-organ failure as a cause of death among patients with SD has understandably lead to the assumption that TEG SD represents a prothrombotic phenotype resulting in diffuse fibrin deposition and subsequent organ dysfunction. However, data from our lab and others have shed new light on the complexity of the SD phenotype and how we interpret viscoelastic tests in the acutely hemorrhaging patient. Using data from the multicenter PROPPR trial, we evaluated fibrinolysis phenotypes using both TEG and conventional biomarkers (PAP and D-dimer) in conjunction with other coagulation tests to characterize mechanisms of SD among bleeding trauma patients [14]. Using this approach combined with a holistic evaluation of raw velocity and amplitude curves, we found that patients demonstrating fibrinolytic SD by TEG did not exhibit a prothrombotic or antifibrinolytic phenotype. In contrast, these patients exhibited a coagulopathic phenotype characterized by fibrinogen consumption, reduced platelet counts, poor platelet function, coagulation factor depletion, prolonged conventional coagulation assay results, and overall diminished stable clot formation. Importantly, 42% of patients in this population who demonstrated TEG fibrinolytic SD died

of hemorrhage. Similarly, Gomez-Builes found that SD was associated with clotting derangement and increased transfusion requirements [32].

A recent paper by Moore et al describes a sub-phenotype of trauma patients who demonstrate depletion of fibrinolysis inhibitors (DFI) as defined by their sensitivity to tPA challenge on TEG [33]. In an ex vivo model, they show that only those patients with both DFI and hyperfibrinolysis demonstrated increases in clot strength upon treatment with TXA. However, it remains to be seen how this would translate in vivo. A possible explanation for why some patients experience high levels of PAP and D-dimer in the absence of increases in TEG LY30 comes from a recent and elegant study by Gall et al published in *Annals of Surgery* [34••]. They found that patients who presented with low fibrinolysis by viscoelastic tests but high D-dimer levels also exhibited high levels of the cell surface–bound plasminogen receptor, S100A10. This receptor increases local fibrinolysis by co-localizing tPA and plasminogen to catalyze plasmin generation. When shed into circulation, S100A10 can bind free tPA and inhibit *ex vivo* fibrinolysis, resulting in fibrinolysis that is undetectable by viscoelastic tests, however elevated *in vivo*. Addition of S100A10 to healthy donor whole blood resulted in increases in both PAP and D-dimer but a reduction in viscoelastic fibrinolysis, which is inconsistent with the idea that fibrinolysis has occurred and subsequently been shutdown.

In spite of concerns surrounding the use of TXA in patients demonstrating fibrinolytic shutdown, data has shown that upon admission, patients who present with low fibrinolytic activation (low molecular markers of fibrinolysis and low lysis by viscoelastic tests) during active bleeding have the best outcomes [14]. Further, data showing the relative insensitivity of viscoelastic tests for detecting fibrinolytic activation suggest that many hyperfibrinolytic patients are missed by these assays [3, 4]. Thus, withholding antifibrinolytic therapy simply because a patient exhibits hypofibrinolysis by viscoelastic measures is not advisable. Further characterization of the fibrinolytic shutdown phenotype in the future will be necessary to understand the impact of antifibrinolytic therapy on outcomes and inform use of different interventions for this subpopulation.

## Alternative Therapies for Reversal of Hyperfibrinolysis

Aside from TXA, other commonly used antifibrinolytic agents include epsilon aminocaproic acid and aprotinin. Epsilon aminocaproic acid is a synthetic lysine analog similar to TXA but is significantly less potent [35]. It is widely used in most countries that also utilize TXA. Aprotinin is a more non-specific, broad spectrum serine protease inhibitor that can inhibit not only plasmin but also trypsin, kallikrein, and elastase. It is more potent and shown to be more effective at reducing blood loss compared to both TXA and epsilon aminocaproic acid, however was removed from the market due to safety concerns surrounding the risk of anaphylactic adverse reactions [35, 36]. Aprotinin has since been reintroduced for clinical use in Europe under strict guidelines, but is still unavailable for use in the USA.

Several recent studies have demonstrated the effectiveness of blood products for either attenuating hyperfibrinolysis or optimizing TXA's ability to reverse hyperfibrinolysis. Vulliamy et al showed that administration of platelets was associated with a reduction in viscoelastic measures of fibrinolysis, decreased levels of circulating tPA, and increased levels of circulating PAI-1 [37]. Other works has demonstrated that plasma-first resuscitation results in attenuated hyperfibrinolysis [38] and that plasma co-administration improves the effectiveness of TXA in porcine models of hemorrhagic shock [20]. Therefore, when antifibrinolytic drugs are contraindicated, administration of plasma and platelets may be the most therapeutic option.

Given the limited available antifibrinolytics, the identification or development of novel therapeutics for reversal of hyperfibrinolysis is an ongoing need. Although not currently approved for clinical use, several are undergoing preclinical studies (Table 1). A very interesting study from Hijazi et al showed that, in a rodent model of traumatic intracranial hemorrhage, that the catalytically inactive tPA variant, tPA-$S^{481}$, could inhibit both tPA and uPA-mediated plasmin generation [30]. This was associated with a subsequent reduction on hemorrhagic lesion size. Second, the plasmin inhibitor, textilinin, has recently been isolated from snake venom and shown to

**Table 1** Novel antifibrinolytics in pre-clinical development

| Agent | Mechanism of Action | Reference |
|---|---|---|
| tPA-$S^{481}$ | Inhibition of tPA and uPA-mediated plasmin generation | Reference 30: Hijazi et al. *Blood* 2015, 125 (16): 2457–2458 |
| Textilinin | Plasmin inhibitor | Reference 39: Masci et al. *Blood Coagul Fibrinolysis* 2000, 11 (4): 385–393 |
| MDCO-2010 | Serine protease inhibitor | Reference 40: Kim et al. *Anesth Analg* 2012, 115 (2): 244–252 |
| | | Reference 41: Englberger et al. *Anesth Analg* 2014, 119 (1): 16–25 |

reduce blood loss in a murine tail vein bleeding model by approximately 60% [39]. Finally, the synthetic, broad spectrum serine protease inhibitor, MDCO-2010 could be a safer alternative to aprotinin as it inhibits fibrinolysis while sparing unnecessary prolongation of activated clotting times [40]. Initial phase II studies have demonstrated that MDCO-2010 is safe, well-tolerated, and associated with reduced need for transfusions in cardiopulmonary bypass graft patients [41]. Further work will be necessary to determine if any of these novel agents will provide a future alternative to current antifibrinolytics.

## Conclusions

Traumatic hyperfibrinolysis is a multi-faceted and complex pathophysiology secondary to injury and hypoperfusion and involves dysregulation of the plasminogen activator system, circulating cells, and the endothelium. Current data support the use of TXA for hemostatic management and reversal of hyperfibrinolysis, although a study comparing empiric versus viscoelastic test-guided use has yet to be performed. Concerning its limitations, the 3-h treatment window may be related to a longitudinal shift in plasminogen activators; however, this has yet to be definitively reported. Further, although a key argument against empiric use of TXA is the presence of fibrinolytic shutdown, recent findings suggest that further characterization of this phenotype is necessary prior to restricting TXA use in this sub-population. Finally, several novel antifibrinolytic agents in development could overcome limitations of TXA therapy and improve hemostatic management of patients in hemorrhagic shock.

### Compliance with Ethical Standards

**Conflict of Interest** Dr. Jessica C. Cardenas declares that there is no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance


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