Tranexamic Acid for Acute Hemorrhage: A Narrative Review of Landmark Studies and a Critical Reappraisal of Its Use Over the Last Decade

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The publication of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 (CRASH-2) study and its intense dissemination prompted a renaissance for the use of the antifibrinolytic agent tranexamic acid (TXA) in acute trauma hemorrhage. Subsequent studies led to its widespread use as a therapeutic as well as prophylactic agent across different clinical scenarios involving bleeding, such as trauma, postpartum, and orthopedic surgery. However, results from the existing studies are confounded by methodological and statistical ambiguities and are open to varied interpretations. Substantial knowledge gaps remain on dosing, pharmacokinetics, mechanism of action, and clinical applications for TXA. The risk for potential thromboembolic complications with the use of TXA must be balanced against its clinical benefits. The present article aims to provide a critical reappraisal of TXA use over the last decade and a "thought exercise" in the potential downsides of TXA. A more selective and individualized use of TXA, guided by extended and functional coagulation assays, is advocated in the context of the evolving concept of precision medicine. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

AKI = acute kidney injury; **aOR** = adjusted odds ratio; **aPC** = activated protein C; **BP_{syst}** = systolic blood pressure; **BW** = body weight; **Cal-PAT** = California Prehospital Antifibrinolytic Therapy; **CI** = confidence interval; **CRASH-2** = Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2; **DVT** = deep vein thrombosis; **EACA** = ε-aminocaproic acid; **ENT** = ear/nose/throat; **fSD** = fibrinolytic shutdown; **GABA** = γ-aminobutyric acid; **HR** = hazard rate; **IDF** = Israel Defense Forces; **ISS** = injury severity score; **Ly30** = lysis after 30 minutes; **MATTERs** = Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study; **MOF** = multiorgan failure; **NHS** = National Health Services; **NMDA** = *N*-Methyl-D-aspartic acid; **NNT** = number needed to treat; **OR** = odds ratio; **PAI 1/2** = plasminogen activator inhibitor 1 (endothelium) and 2 (placenta); **PAP** = plasmin–antiplasmin; **pat.** = patients; **PATCH** = Prehospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage; **PE** = pulmonary embolism; **PPH** = postpartum hemorrhage; **pRBC** = packed red blood cells; **RCT** = randomized controlled trial; **RR** = relative risk; **SHR** = subdistribution hazard ratio; **TAFI** = thrombin activatable fibrinolysis inhibitor; **TBI** = traumatic brain injury; **TIC** = trauma-induced coagulopathy; **tPA** = tissue plasminogen activator; **Tpx** = transplantation; **TXA** = tranexamic acid; **uPA** = urokinase-type plasminogen activator; **VHA** = viscoelastic hemostatic assays; **VTE** = venous thromboembolism; **WHO** = World Health Organization; **WOMAN** = World Maternal Antifibrinolytic

For the last decade, tranexamic acid (TXA) has been one of the most reported pharmaceutical agents in the literature. A query in PubMed using the isolated term "tranexamic acid" for the time window between January 2010 and March 2019 returned over 2700 items. While TXA has been around for years, its clinical use increased exponentially from a decade ago following the publication of several studies, with one involving >20,000 patients.[1] In parallel to this reemergence, concerns about potential side effects were raised and continued to be raised in more recent years.[2–6] In our opinion, a rather noncritical interpretation of the study results and a common misunderstanding of TXA as an antihemorrhagic (instead of antifibrinolytic) agent have misled some colleagues to promote indiscriminate use of TXA in a range of therapeutical and increasingly also prophylactic scenarios. Here, we aim to provide a critical reappraisal of TXA clinical use, a "thought exercise" in the potential downsides of TXA, based on publications that might sensitize the readers for a more cautious approach.

TXA: THE PHARMACEUTICAL AGENT

TXA is the transform of 4-(aminomethyl) cyclohexanecarboxylic acid. As ε-aminocaproic acid (EACA), the synthetic compound is a lysine analog, but with approximately 10 times more potency as compared to EACA with respect to its inhibiting effect on fibrinolysis.[7] While the compound is also approved for topical and oral applications, this

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article focuses only on its intravenous use. As shown in Figure 1, TXA acts via competitive blocking of the lysine binding sites on plasminogen. Plasminogen has 5 binding sites for TXA, 1 with high and the remaining with lower affinity.[13] TXA inhibits plasminogen (the proenzyme) binding to plasmin (ie, blocking activation of plasmin), and it also inhibits the binding of plasmin (the active form) to fibrin (ie, blocking fibrinolysis). Hence, the mechanism of action is to stabilize existing clots rather than promoting new clot formation.[14] This is an important distinction, as it emphasizes that TXA is an antifibrinolytic and not an antihemorrhagic agent.

In addition, TXA reduces the plasmin-mediated release of vasoactive peptides, such as bradykinin and histamine. Direct inhibition of plasmin seen with higher concentrations of TXA may reduce the proinflammatory action of plasmin on the complement system, leading to a net anti-inflammatory effect.[15] As implied here, plasminogen and plasmin play many various roles in inflammation, angiogenesis, chemotaxis, tissue remodeling, and wound healing, many of which could be affected by TXA.[13] TXA is thought to have protective effects on the endothelium, and it is shown to render beneficial modulation of inflammation and other responses following ischemia and reperfusion.[16–18] Yet, the precise mechanisms by which TXA exerts its beneficial effects in the context of hemorrhage remain largely unknown.[16]

Peak plasma concentrations of TXA are obtained rapidly after short intravenous infusion, and plasma concentrations thereafter decline in a multiexponential manner. TXA diffuses quickly into the synovia and other tissues and is distributed throughout all tissues.[7,19] Around 10% of the plasma concentration can be found in the cerebrospinal fluid and 1% in mother's milk.[7,19] TXA is eliminated unchanged via glomerular filtration and excreted in the urine within 2 to 3 hours after administration.[7,19] The antifibrinolytic effects of TXA may last up to 7 or 8 hours. After 24 hours, about 90% of a single intravenous application is eliminated.[7,19]

The antifibrinolytic effects of TXA were first published in the 1960s.[20,21] For a long time, its primary intravenous use was confined to cardiac surgery, with its use peaking after the withdrawal of aprotinin in 2008. Since then, the use of TXA has expanded to the treatment of hemorrhagic conditions in a variety of settings, including trauma, obstetrics, cardiac surgery, liver surgery, and orthopedic surgery. TXA is contraindicated in patients with hypersensitivity, severe renal impairment, history of convulsions, and active intravascular clotting.[7,19,22] The proof of concept for TXA in settings where hyperfibrinolysis is the underlying pathology was through the demonstration that TXA

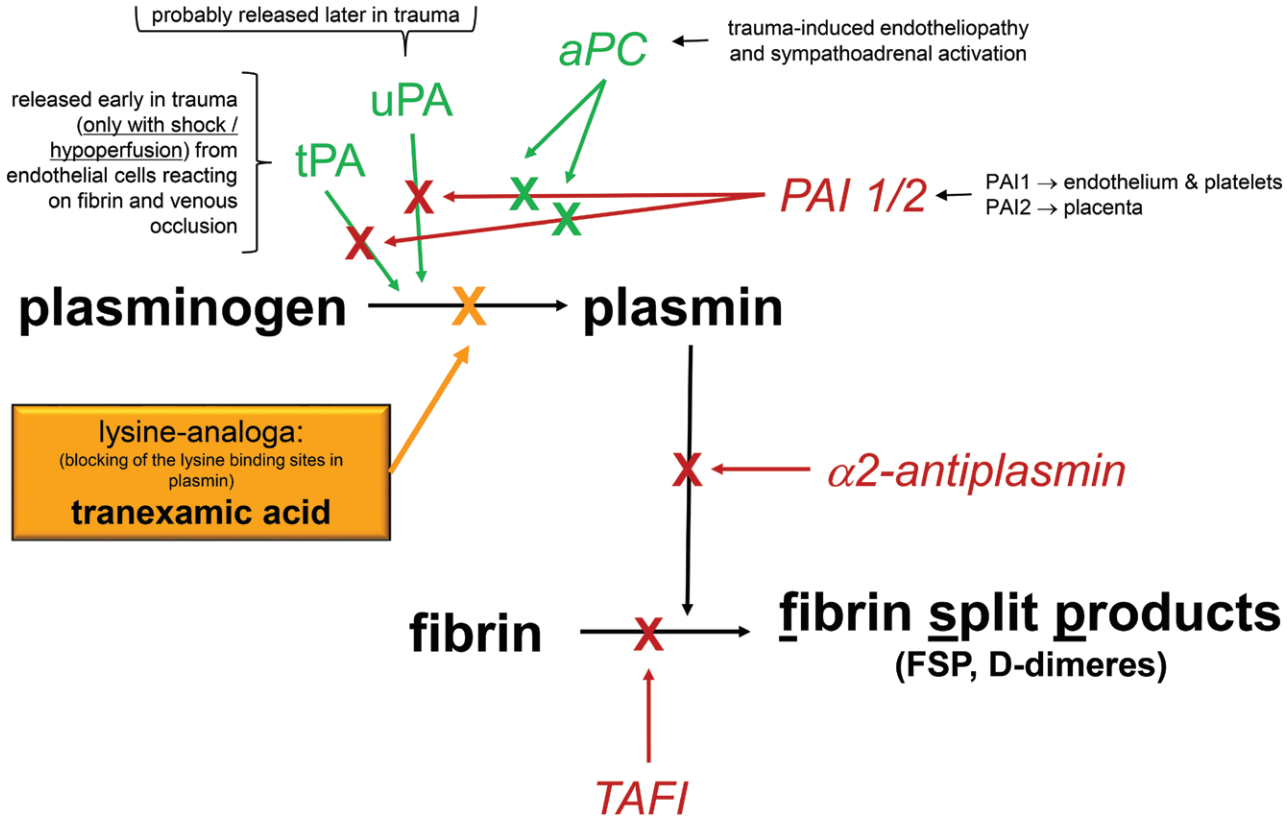

Figure 1. Mechanism of action of TXA. Profibrinolytic effects are in green, and antifibrinolytic effects are in red. The predominant mediator of postinjury hyperfibrinolysis appears to be tPA released from ischemic endothelium. PAI-1 binding of circulating tPA appears to be a major mechanism for the postinjury shutdown.[8,9] In the presence of high uPA, TXA might increase plasminogen-mediated fibrinolysis and bleeding.[10,11] aPC indicates activated protein C; PAI 1/2, plasminogen activator inhibitor 1 (endothelium) and 2 (placenta); TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator; TXA, tranexamic acid; uPA, urokinase-type plasminogen activator. Modified from Lier and Maegele, Blutungsmanagement: tranexamsäure in der präklinik. Pro und kontra [Coagulation management: prehospital tranexamic acid. Pro and contra]. *Notfall+Rettungsmedizin*, 2018, with permission.[12]

attenuates fibrinolysis-induced early increases in D-dimers and plasmin–antiplasmin (PAP) complexes, and this has been shown for trauma and postpartum hemorrhage (PPH) among others.[23–25]

Seizures following the application of TXA are a rare complication but are published in a range of different settings including neurosurgery, orthopedic surgery, obstetrics, and ear/nose/throat (ENT) surgery.[6] The most recent meta-analysis conducted in the most common clinical setting, ie, cardiac surgery with extracorporeal circulation, found a cumulative incidence rate of TXA-associated seizures of 2.7%, with an odds ratio (OR) of seizure of 5.39 (95% confidence interval [CI], 3.29–8.85; $P < .001$).[26] The possible mechanisms involved are multifactorial and include a dose-dependent reduction of γ-aminobutyric acid (GABA) type A receptor–dependent signal transmission,[27] a quick and reversible block of *N*-methyl-D-aspartic acid (NMDA) receptors, and a right shift of the glycine concentration–response curve of NMDA-dependent currents.[28] The incidence rate of TXA-associated seizures increases with increasing dosing levels of TXA.[26,27]

THE CHRONOLOGY

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 Study

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 (CRASH-2) trial has triggered awareness and interest in TXA among colleagues of various specialities.[1] Adult trauma patients (20,211) with or at risk of significant bleeding in 274 hospitals across 40 countries were randomly assigned within 8 hours of injury to either TXA (loading dose 1 g over 10 minutes then infusion of 1 g over 8 hours, n = 10,060) or matching placebo (saline, n = 10,067). TXA reduced all-cause mortality within 28 days (absolute reduction = 1.5%; number needed to treat [NNT] 67) and death due to bleeding (absolute reduction = 0.8%; NNT = 119). The positive effects of TXA were most pronounced in a small subgroup of patients (478 patients in TXA and 562 in the placebo arm) with shock, that is, systolic blood pressure ≤75 mm Hg (Table 1). However, the administration of TXA was neither associated with a reduced transfusion of blood products nor did the study report on any specific laboratory test results for coagulation or clinical information regarding shock and injury severity. The study was mainly conducted in developing countries with limited access to standard trauma care, and the patient inclusion into the study was performed according to what was called "uncertainty" principle, that is, "when the responsible doctor was substantially uncertain as to whether or not to treat with this agent, these patients were eligible for randomization.[1]"

In the following year and out of 3076 total deaths, the same authors published a subanalysis of the 1063 bleeding-related deaths observed in CRASH-2.[29] The early application of TXA within 1 hour after trauma was associated with the largest survival benefit (absolute reduction = 2.4%, NTT = 41). The administration of TXA between 1 and 3 hours also reduced the risk of death due to bleeding (absolute reduction = 1.3%, NTT = 77; Table 1), while TXA given after 3 hours increased the risk of death due to bleeding (144/3272 [4.4%] vs 103/3362 [3.1%]; relative risk [RR] = 1.44 [95% CI, 1.12–1.84]; $P = .004$). When these data were extrapolated, it was assumed that TXA could potentially save between 70,000 and 100,000 lives each year worldwide, and following a petition by the CRASH-2 authors in 2012,[31] TXA was accepted to the World Health Organization (WHO) list of "Essential Medicines."[32,33]

Military Application of TXA in Trauma Emergency Resuscitation Study and Other Follow-up Studies

The beneficial effects of TXA reported from the CRASH-2 trial triggered a series of follow-up studies, conducted specifically in bleeding scenarios and patients in shock requiring massive transfusion in both military and civilian settings. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study (MATTERs) retrospectively analyzed 896 wounded soldiers who had received ≥1 unit of packed red blood cells (pRBCs).[34] This study specifically addressed some of the shortcomings of CRASH-2, as it focused on severely injured patients who were treated in an advanced military medical setting, reported laboratory testing results to determine coagulopathy, and excluded the "uncertainty" principle for inclusion due to its design.[4] The use of TXA was associated with a significant survival benefit (17.4% vs 23.9%; $P = .03$; absolute reduction = 6.5%; NNT = 15; for those receiving massive transfusion [≥10 pRBC/24 h] 14.4% vs 28.1%; $P = .004$; absolute reduction = 13.7%; NTT = 7) and less coagulopathy ($P = .003$). Similarly, the Israel Defense Forces (IDF), which are also responsible for civilian trauma care in their national setting, concluded from their experience with TXA that

Table 1. Main Results of CRASH-2,[1] CRASH-2 Follow-up,[29] and WOMAN[30]

CRASH-2
Any cause of death (28 d): TXA 1463 (14.5%) vs placebo 1613 (16.0%); RR = 0.91 (95% CI, 0.85–0.97[a]); $P = .0035$
Bleeding: TXA 489 (4.9%) vs 574 (5.7%); RR = 0.85 (95% CI, 0.76–0.96[a]); $P = .0077$
Patient in shock (BP_{syst} ≤75 mm Hg): TXA 478 of 1562 pat. (30.6%) versus 562 of 1599 pat. (35.1%); RR = 0.87; 95% CI (0.76–0.99[a])
CRASH-2 follow-up
TXA within 1 h after trauma: TXA 198 of 3747 pat. (5.3%) versus placebo 286 of 3704 pat. (7.7%); RR = 0.68 (95% CI, 0.57–0.82); $P < .0001$
TXA 1–3 h after trauma: TXA 147 of 3037 pat. (4.8%) versus placebo 184 of 2996 pat. (6.1%); RR = 0.79 (95% CI, 0.64–0.97[a]); $P = .03$
WOMAN
Death due to bleeding: TXA 155 (1.5%) versus placebo 191 (1.9%); RR = 0.81 (95% CI, 0.65–1.0[a]); $P = .045$
Death if TXA within 3 h: TXA 89 (1.2%) versus placebo 127 (1.7%); RR = 0.69 (95% CI, 0.52–0.91[a]); $P = .008$
Laparotomy to control bleeding: TXA 82 (0.8%) versus placebo 127 (1.3%); RR = 0.64 (95% CI, 0.49–0.85); $P = .002$

Abbreviations: BP_{syst}, systolic blood pressure; CI, confidence interval; CRASH-2, Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2; pat., patients; RR, relative risk; TXA, tranexamic acid; WOMAN, World Maternal Antifibrinolytic.

[a]The "no effect" occurs when the CIs of RRs approaches 1.0, indicating reduced clinical relevance despite statistical significant differences denoted by a low *P* value.[10] In terms of statistics, the reported differences might be marginal at best[10,80] (for details, see "Statistics").

"there is likely a benefit in the civilian sector as well" for this agent.[35] In their prospective data collection from severely injured trauma patients, Cole et al[36] further addressed the indications for TXA. While its use was not independently associated with any changes in outcome in the overall or nonshocked cohorts of patients, in patients with shock (injury severity score [ISS] >15 and base deficit ≥6 mEq/L), TXA was independently associated with a reduction in multiorgan failure (MOF; OR = 0.27 [95% CI, 0.10–0.73]; P = .01) and reduced adjusted all-cause mortality (OR = 0.16 [95% CI, 0.03–0.86]; P = .03).

Since 2015, several multidisciplinary guidelines developed on both sides of the Atlantic[37–40] recommend the use of TXA to patients with "excessive bleeding" or those who are "bleeding or at risk of significant hemorrhage as soon as possible and within 3 hours of injury," respectively, with the dosing regimen adopted from the CRASH-2 trial.

The World Maternal Antifibrinolytic Study in PPH

The World Maternal Antifibrinolytic (WOMAN) trial, which was conducted with a similar protocol as CRASH-2 but in PPH, confirmed the survival benefit observed for TXA in CRASH-2 in the obstetric context.[30] A similarly small but statistically significant reduction was found for death due to bleeding in patients who received TXA (based on the published data, the NNT was 250), especially if TXA was administered within 3 hours of delivery (NNT = 200), and in those undergoing laparotomy to control bleeding (NNT = 200; Table 1).

In both trials, CRASH-2 and WOMAN, the administration of TXA beyond 3 hours of trauma or delivery was associated with an increase in mortality compared to placebo. When the cohorts from both studies were combined in a meta-analysis totaling 40,138 patients with acute severe bleeding from trauma and PPH, TXA was shown to significantly increase overall survival from bleeding (OR = 1.20 [95% CI, 1.08–1.33]; P = .001).[41] Immediate treatment improved survival by >70% (OR = 1.72 [95% CI, 1.42–2.10]; P < .0001), and thereafter, the survival benefit decreased by 10% for every 15 minutes of treatment delay until the 3-hour window had elapsed. After the 3-hour window, no beneficial effect with TXA was observed.

Prehospital Administration of TXA

The first trial to assess and demonstrate a positive effect of TXA when given early and during the prehospital phase of care to trauma patients with signs of hemorrhagic shock was the California Prehospital Antifibrinolytic Therapy (Cal-PAT) trial.[42] This trial was conducted as a prospective, multicenter, observational, and nonrandomized cohort. The result showed a statistically significant decrease in 28-day mortality in favor of early TXA use (3.6% vs 8.3%; absolute mortality reduction = 4.7%; OR = 0.41 [95% CI, 0.21–0.8]; NTT = 21). The strongest effect was a statistically significant decrease in mortality at 28 days observed in patients requiring massive transfusion with >10 units of blood products (n = 70; 8.5% vs 23.2%; absolute mortality reduction = 14.7%; OR = 0.31 [95% CI, 0.11–0.84]; NTT = 7) and for ISS >16 (n = 170; 6% vs 14.5%; absolute mortality reduction = 8.5%; OR = 0.37 [95% CI, 0.17–0.80]; NTT = 12).

The Prehospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage (PATCH) study is currently recruiting trauma patients in Australia and New Zealand to confirm the results from CRASH-2 in the context of more developed countries with rapid access to standard trauma care including bleeding management and blood products.[43] The extension of this study to Germany is currently under consideration and is anticipated to accelerate recruitment. Table 2 summarizes the chronology of the landmark TXA studies published to date. Besides these studies listed, a range of small- to medium-sized publications conducted in different clinical settings has been published following CRASH-2.

THE CRITIQUE

The publication of the results from the CRASH-2 trial in 2010 was well received around the world and echoed positively in many subsequent publications. Along with further scientific evaluation, a publicity campaign was launched by the National Health Services (NHS), which promoted a liberal use of TXA in every trauma patient.[4,44] While TXA has been adopted and is still recommended with a strong level of recommendation by major multidisciplinary European guidelines,[38–40] a slightly divergent view on the clinical use of TXA has emerged in the United States, as well as Australia and New Zealand.[4,10,45,46]

Pharmacokinetics

There are almost no published pharmacokinetic studies for TXA apart from the setting of cardiac surgery, and the dosing regimens currently being used remain largely empirical.[13,14] In the CRASH-2 trial, a loading dose of 1 g of TXA

Table 2. The Chronology of TXA Landmark Studies

Year	Title	Main Result
2010	CRASH-2[1]	TXA recommended for all trauma patients
2011	CRASH-2 follow-up[29]	time dependency of TXA effect
2012		TXA accepted in the WHO list of "Essential Medicines"
	MATTERs[34]	TXA especially effective for those requiring massive transfusion
2014	Israel Defense Forces[35]	"likely benefit in the civilian sector"
2015	Cole et al[36]	TXA effective only for "severely injured shocked patients"
2016		limitation of TXA indication on patients with "severe hemorrhage"
2017	WOMAN[30]	TXA effective in postpartum hemorrhage
2018	Gayet-Ageron et al[41]	survival benefit with TXA decreased by 10% for every 15 min of treatment delay until 3 h
	Cal-PAT[42]	the prehospital application of TXA is effective

Abbreviations: Cal-PAT, California Prehospital Antifibrinolytic Therapy; MATTERs, Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study; TXA, tranexamic acid; WHO, World Health Organization; WOMAN, World Maternal Antifibrinolytic.

infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours, or matching placebo (0.9% saline) was used; in the WOMAN trial, there was the option for a second 1-g bolus if bleeding continued. In the absence of other experiences, the CRASH-2 dosing regimen is currently being recommended by most multidisciplinary and international guidelines[38–40] and is used in nearly every perioperative setting (except cardiac surgery) for almost every patient irrespective of body weight (BW). Perioperatively, only 1 g is recommended.[47]

In the following, some data with respect to the pharmacology of TXA are presented. Unfortunately, none of these concentrations are based on any formal in vivo dose–response studies, and the corresponding therapeutic margin for TXA and its minimal therapeutic dose to inhibit fibrinolysis remain largely unknown.[48] A systematic review published in 2019 identified 20 in vitro studies and 1 in vivo trial that artificially stimulated fibrinolysis with tissue plasminogen activator (tPA) and measured fibrinolysis using a range of viscoelastic, optical density, or immunological assays.[49] Tissue hypoxia and ischemia induced by hemorrhagic shock increased the release of tPA from endothelial Weibel-Palade bodies, and tPA seems to be responsible for hyperfibrinolysis in severely injured trauma patients.[50–52] It is released early after trauma while urokinase-type plasminogen activator (uPA) is released with temporal delay,[13] but the nature of the plasminogen activator (tPA versus uPA) may impact on the efficacy of TXA: the required plasma concentrations are ≈20 µg/mL for tPA- and ≈150 µg/mL for uPA-induced fibrinolysis.[13] Steady-state concentrations of ≈20 µg/mL are obtained by a 10-mg/kg BW loading dose, followed by a 5-mg/kg/h infusion.[53] The minimum in vitro concentration of TXA to completely inhibit fibrinolysis has been reported at 6.54 µg/mL (95% CI, 5.19–7.91 µg/mL) for neonatal plasma and 17.5 µg/mL (95% CI, 14.59–20.41 µg/mL) for adult plasma.[54] A plasma concentration of 6.3 µg/mL is supposed to be achieved with a loading dose of ≈10 mg/kg BW, and a concentration of 20 µg/mL is expected to be achieved with a loading dose of 30 mg/kg BW.[16] In a porcine model of hemorrhagic trauma, hypovolemia had minimal impact on the distribution of TXA but significantly decreased its clearance. In the setting of ongoing hemorrhage, blood loss may become a significant route of drug elimination.[55]

As an analog to the essential amino acid lysine, TXA may be involved in a variety of functions, such as protein synthesis, metabolic signaling events, protein–protein interactions, and posttranslational modifications in immunity and inflammation, among others. However, it remains largely unknown how TXA affects these important functions.[10] It is known that the lysine binding sites of inhibitory glycine and GABA type A receptors are involved in the induction of seizures following TXA application.[56] In addition, TXA is eliminated through the kidneys, and, as such, a dose adjustment to reflect glomerular function deterioration is recommended,[7,14,19,22] although this is very rarely done in clinical practice.

Pathophysiology of Traumatic Coagulopathy

The outcome of civilian trauma patients treated with TXA in developed trauma settings and centers does not follow the outcome reported in the CRASH-2 or MATTERs trials.[57,58] Neither the CRASH-2 nor the WOMAN trials recorded a reduction in transfusion rates or volumes in patients treated with TXA.

Hemostatic derangements in the context of trauma, also referred to as trauma-induced coagulopathy (TIC), were initially perceived as a primarily hyperfibrinolytic entity, supporting TXA as the logical therapeutic intervention.[59–61] On the other hand, 3 different phenotypes of fibrinolytic responses of the body to massive trauma have been described: hyperfibrinolysis, physiologic fibrinolysis, and hypofibrinolysis (also referred to as "fibrinolytic shutdown [fSD]"),[62] with a distribution to each phenotype of approximately 20%, 20%, and 60%, respectively (Figure 2).[8,62,65,70] The hyperfibrinolytic phenotype is found in patients with life-threatening and profuse bleeding with a high risk of exsanguination within the first hours following trauma. In contrast, hypocoagulable patients display a high percentage of mortality due to traumatic brain injury (TBI) and septic, thrombotic, or organ failure.[71] While every surviving hyperfibrinolytic patient switches to a hypofibrinolytic, prothrombotic state within 24 hours, the switch from a hypofibrinolytic to a hyperfibrinolytic phenotype is rarely encountered.[65] The concept of fSD is not new and was identified as a potential driver of irreversible shock after hemorrhage by Hardaway and Johnson[72] already back in 1963.[8] The potential mechanisms that are discussed around fSD may include platelet activation, resulting in early increased levels of plasminogen activator inhibitor 1 (PAI-1) acutely after injury or low tPA activity from impaired generation after injury.[8,9] An increased risk for fSD among severely injured trauma patients receiving TXA has been described (RR = 1.65 [95% CI, 11.10–1.64]; P = .004).[70] Thus, the nondiscriminative and liberal administration of an antifibrinolytic agent to a patient population that could be largely in a hypofibrinolytic state does not seem to be physiologically or pharmacologically sound and would potentially expose patients to a higher risk for thromboembolic complications (eg, see Table 4). Viscoelastic hemostatic assays (VHAs) are not highly sensitive for fibrinolytic activation, but they are currently the only tests able to diagnose hyperfibrinolysis early in a clinically useful time frame for trauma resuscitation,[73,74] and "before we can validate the efficacy of TXA to inhibit fibrinolytic activation, an assay capable of detecting fibrinolytic activation with good sensitivity and specificity needs to be found.[75]"

Statistics

The American Statistical Association has issued a statement on the appropriate use and interpretation of statistical parameters to clarify frequently observed and yet ongoing uncertainties around null hypothesis testing and potential misinterpretation of P values and CIs.[76] Recently, there have been suggestions that P values and null hypothesis testing should be restricted or even banned from the medical literature.[77,78] Notably, P values provide no information on the magnitude or the importance of an effect, as statistical significance does not necessarily imply clinical significance.[79]

Table 1 summarizes the statistical analyses of CRASH-2,[1] the CRASH-2 follow-up,[29] and the WOMAN trial.[30] The "no effect" occurs when the CIs of RRs approach 1.0, indicating reduced clinical relevance despite statistically

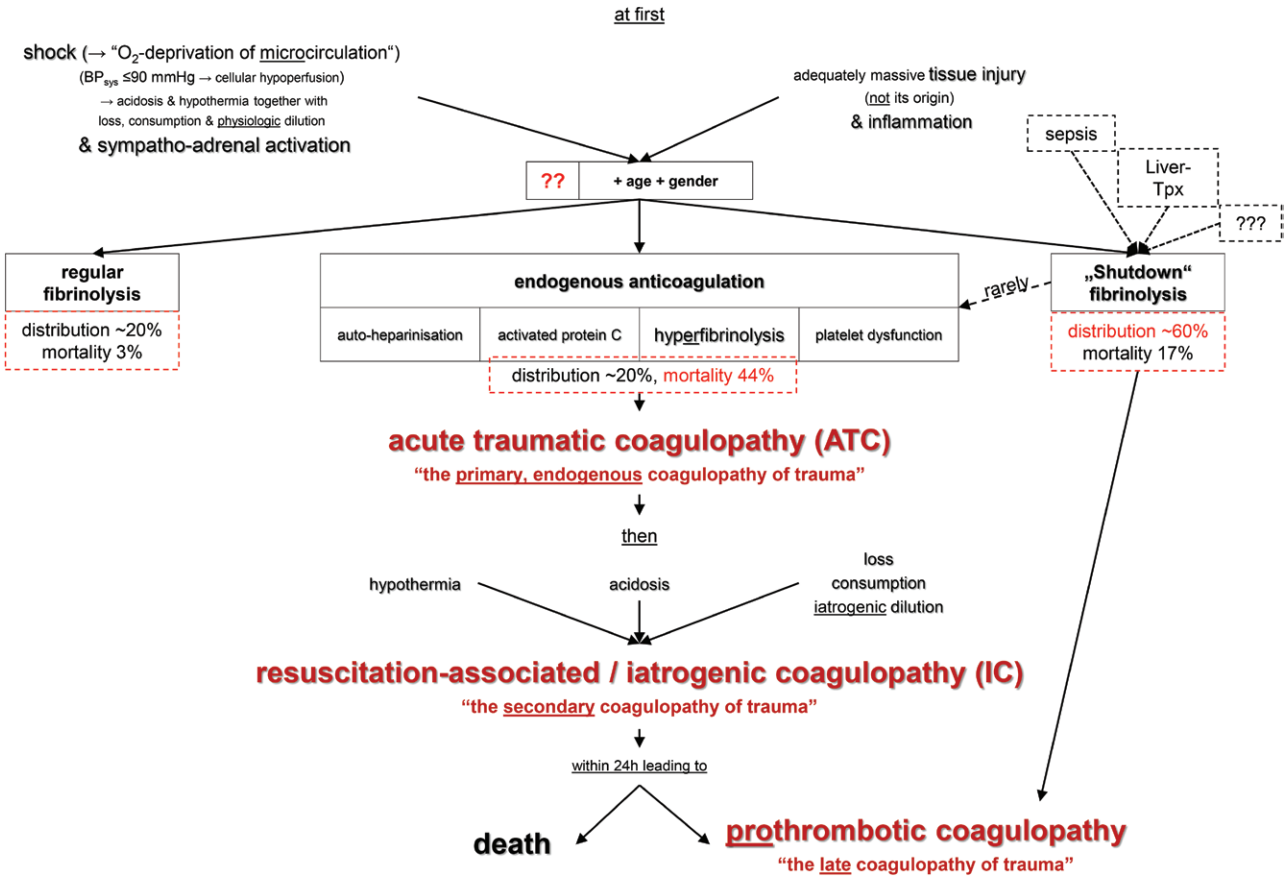

Figure 2. Current understanding of the pathophysiology of traumatic coagulation disturbances. Increasingly, cellular hypoxia, that is, the disturbed microcellular oxygen demand, is regarded as the primary driver of traumatic coagulation disturbances.[9] Together with unknown variables, age- and gender-related differences in energy metabolism and oxidative stress modify the reaction.[63] The acute traumatic coagulopathy is a primary distinct entity, and the endotheliopathy of trauma occurs within minutes of injury.[64] The secondary iatrogenic coagulopathy worsens the primary one. Approximately 70% of major trauma patients who present with shutdown remain in this phenotype up to 120 hours postinjury. Within 24 hours, patients presenting with hyperfibinolysis die or transition into the prothrombotic phenotype.[65] Early mortality is highest with the hyperfibrinolytic phenotype and associated with exsanguination; persistent shutdown at 24 hours is associated with elevated late mortality due to organ failure.[17,62,65,66] Neither cellular hypoxia nor fibrinolytic shutdown is specific to multiple trauma: shutdown can also be found in sepsis,[67] liver transplantation,[68] or other perioperative settings.[69] BP_{syst} indicates systolic blood pressure; Tpx, transplantation. Modified from Lier and Maegele, Blutungsmanagement: tranexamsäure in der präklinik. Pro und kontra [Coagulation management: prehospital tranexamic acid. Pro and contra]. *Notfall+Rettungsmedizin*, 2018, with permission.[12]

significant differences denoted by a low *P* value.[10] As outlined in Table 1, the upper CI limit of most results is very close to or includes the null value of 1.[80] In terms of statistics, the reported differences might be marginal at best.[10,80] As the *P* value is strongly affected by sample size,[78–80] these small differences may become statistically significant when the sample size is large enough but irrespective of clinical relevance.[10,80–82] In the WOMAN trial, the initially planned sample size was changed and increased during the recruitment from 15,000 to >20,000 subjects.

Patients and physicians are more influenced by RR ratios rather than by absolute risk ratios.[81] The presented studies on the use of TXA are examples of the frequent but potentially misleading mixture of absolute and relative effects. In the WOMAN trial,[30] TXA use was associated with an absolute reduction of 0.40% but a relative reduction of 21.06% in mortality due to bleeding. If TXA was administered within 3 hours, the absolute mortality reduction was 0.50% versus a relative reduction of 29.42%. Lastly, in those patients undergoing laparotomies for bleeding control, TXA was associated with an absolute reduction in mortality of 0.50% versus a relative reduction of 38.47%. Based on the same data, one could either conclude that "1 in 200 women can be saved" (absolute reduction = 0.5%) or "1 in 3 women can be saved" (relative reduction = 33.0%). The latter was published on website of the WOMAN trial.[83] The CRASH-2 follow-up study reported an absolute reduction of mortality of 2.5% in patients with time to TXA treatment ≤1 hour (7.7% for placebo vs 5.3% for TXA).[29] The authors stated TXA will reduce "the risk of … death due to bleeding by about 30%.[84]" Both absolute and RRs have clear values and should be considered. Nevertheless, in this context, the dropping of the adjective "relative" might imply a larger effect than what the actual one is. Table 3 shows these differences for the CRASH-2 and WOMAN trials.

In a pooled analysis from the CRASH-2 and WOMAN trials, the survival benefit decrease by 10% for every 15-minute delay of treatment.[41] The title of this pooled analysis article referred to "acute severe hemorrhage." In the CRASH-2 trial, only 50.4% of the patients received a

Table 3. Reported Absolute and Relative Reductions of Mortality With TXA Treatment in CRASH-2,[1] CRASH-2 Follow-up,[29] and WOMAN[30]

Trial	Absolute Reduction (%)	Relative Reduction (%)
CRASH-2		
Any cause of death	1.5 (14.5 vs 16.0)	9.38
Death due to bleeding	1.8 (4.9 vs 5.7)	14.04
Death in patients in shock (BP_{syst} ≤75 mm Hg)	4.5 (30.6 vs 35.1)	12.83
CRASH-2 follow-up		
TXA started within 1 h after trauma	2.4 (5.3 vs 7.7)	31.17
TXA started in 1–3 h after trauma	1.3 (4.8 vs 6.1)	21.32
WOMAN		
Death due to bleeding	0.4 (1.5 vs 1.9)	21.06
Death if TXA started within 3 h	0.5 (1.2 vs 1.7)	29.42
Death in patients undergoing laparotomy to control bleeding	0.5 (0.8 vs 1.3)	38.47

Abbreviations: BP_{syst}, systolic blood pressure; CRASH-2, Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2; TXA, tranexamic acid; WOMAN, World Maternal Antifibrinolytic.

blood transfusion, and those transfused received a median of 3 (2–6) pRBC units[1]; in the WOMAN trial, 54% of the patients received a transfusion, but only 20% had a blood loss >1500 mL.[30] As such, a much smaller subgroup of these 2 studies (around 3000 patients in total) had "severe hemorrhage," and, as *P* values are strongly affected by the size of a study,[78–80] statistical analysis and results may be different.

Thromboembolic Complications

In 1963, the empiric administration of TXA was advocated for liver transplantation,[85] but 6 years later, this practice was questioned due to increased mortality from venous thromboembolism.[62,86] From the 20,211 patients in the CRASH-2 study, a total of 369 vascular (venous or arterial) occlusive events (myocardial infarction, stroke, pulmonary embolism [PE], deep vein thrombosis [DVT]) were reported: 168 in the TXA group versus 201 in the placebo group.[1] This study collected only "expected complications of the trial treatment [but] adverse events that were serious, unexpected, and suspected to be related to the study treatment were reported separately.[1]" The CRASH-2 authors stated that they were unable "…to exclude the possibility of some increase in risk" and that they "…might have under-reported the frequency of these events.[1]" The critique that thromboembolic complications were very rarely reported because "they were not actively sought in many of the participating hospitals" was brought up early in the discussion around the trial results of CRASH-2 and by multiple authors.[5,43] In the MATTERs, with TXA treatment, a 9-fold increase for PE (0.3% without vs 2.7% with TXA) and a 12-fold higher rate for DVT (0.2% without vs 2.4% with TXA) were noted. This increase may be considered against the background of a higher magnitude of injury sustained in the TXA group,[34] but the possibility that this increase in thromboembolic complications might be caused by TXA has also been indicated by others.[5,9,43,87,88] In a prospective cohort study by Cole et al,[36] a 4-fold increase in thromboembolic events was observed in hemorrhagic shocked patients treated with TXA (8% in TXA vs 2% in no-TXA cohorts; $P < .01$), and this was specifically assessed and "confirmed by either ultra-sound scan (DVT) and/or computed tomographic pulmonary angiography (PE).[36]" During pregnancy and postpartum, DVT is generally far more common than PE, with 4–5 cases of DVT encountered per each case of PE.[89,90] In the WOMAN trial, a DVT rate of 0.03% in TXA arm versus 0.07% in the placebo arm and a PE rate of 0.2% in both arms were recorded.[30] A PE rate as much as almost 1 magnitude higher than the DVT rate in the same population is quite unexpected and surprising and may raise concerns with the accuracy of detecting, diagnosing, and reporting these important and relevant complications. As in our view and those of others,[5,43] neither the CRASH-2 nor the WOMAN trial has sufficiently assessed thromboembolism in their respective cohorts (see above), both publications may not be selected to provide strong evidence against a possible effect of TXA on increased vascular occlusive events. Concerning perioperative use, a recent meta-analysis of Yates et al[6] including 268 randomized controlled trials (RCTs) concluded that "72% of perioperative TXA RCTs excluded patients with major comorbidities and that 59% of RCTs excluded patients with a history of thromboembolic events," and "there were wide CIs around the risk of a venous thromboembolism (VTE), meaning that the possibility of increased VTE rates in patients with a previous history of thrombotic events cannot be confidently excluded, and there is insufficient evidence on TXA safety in these patients to make definitive recommendations for use of antifibrinolytic therapy." The statement that TXA does not cause thromboembolic effects is not a proven fact but is rather based on "moderate quality evidence,"[6,75] and there is "a need for additional investigation…before strong recommendations can be made.[6]"

Table 4 provides an overview of prospective and retrospective studies conducted in the setting of both civilian and military trauma, which reported on the potential thromboembolic effects of TXA. The administration of TXA was associated with reduced mortality in some[34,36,91] and increased mortality in others,[2,92,94,95] while no effect on mortality was reported by 1 trial.[93] In most of these studies, the TXA cohort was more severely injured, but those cohorts are quite similar to the trauma patients currently being considered as candidates for TXA administration according to the updated recommendations.[38–40] The data presented in Table 4 suggest a correlation and not necessarily a causality. There may be a range of confounding factors for the generation of both venous and arterial thrombotic occlusions, for example, transfusion of pRBCs, plasma, or platelets. The considerable rate of complications with TXA may shadow its benefits if all patients would receive the agent indiscriminately. A recent systematic review and meta-analysis of observational studies on the use of TXA in trauma reported a pooled RR for venous thromboembolism of 1.61 (95% CI, 0.86–3.01).[87] Another publication included 19 studies and 13 studies in the systematic review and meta-analyses, respectively.[5] The pooled incidence of in-hospital thrombotic events (9 studies, 1656 patients) was 5.9% (95% CI, 33.3%–8.5% vs 2.0% [95% CI, 11.8%–2.3%] in the CRASH-2 trial). When combining the data from these meta-analyses[5,87] with the >8200 patients from the studies listed in Table 4, the application of TXA to trauma patients

Table 4. Trials in the Trauma Setting Which Have Reported on Side Effects of TXA

Source	Setting	n	Result	Note
Morrison et al[34]	Retrospective, military observational study; 293 soldiers (ISS = 25) received TXA (mean, 2.3 g within 1 h after injury); ≥1 pRBC	896	Positive: in TXA group reduced mortality (17.4% vs 23.9%; *P* = .03) Negative: 9-fold increased rate for PE and 12-fold increased rate for DVT	TXA group more severely injured
Swendsen et al[91]	Retrospective, civil cohort; 52 pat. with TXA (initially 1 g within 3 h after injury) versus 74 pat. without TXA	126	Positive: complete group: TXA with reduced mortality (5.8% vs 17.6%; *P* = .05) hypotensive group: TXA with reduced 24-h mortality (4.3% vs 19.1%; *P* = .03) Negative: complete group: increased rate for DVT/PE (11.5% vs 0; *P* = .004) and AKI (25% vs 11%; *P* = .02); hypotensive group: increased rate for DVT/PE (12% vs 0%; *P* = .012) and trend toward increased AKI (28% vs 15%; *P* = .12)	Complete group: TXA more severely injured (ISS = 27 vs 20) Hypotensive group: comparable ISS
Valle et al[2]	Retrospective, civil observational study trauma patients requiring an emergency operation and/or transfusion (1 g bolus, followed by 1 g/8 h); of these 150 shocked pat. (ISS = 28; 97% transfusion; TXA within 97 min after injury) propensity matched compared with 150 pat. without TXA	1217	Negative: TXA group with increased mortality (27% vs 17%; *P* = .024); for >2 L pRBC mortality 49% vs 24% (*P* = .0065)	
Cole et al[36]	Prospective, civil cohort; 160 pat. received TXA within 3 h after injury	365	Positive: multivariate analysis: TXA independently associated with reduced MOF (OR = 0.27; CI, 00.10–0.73; *P* = .01) and protective for mortality (OR = 0.16; CI, 00.03–0.86; *P* = .03) Negative: shocked pat. (n = 128): TXA 4× increase in thromboembolism (8% vs 2%; *P* < .01)	TXA group more severely injured (ISS = 33 vs 29)
Harvin et al[92]	Retrospective, civil analysis of trauma pat. with Ly30 ≥3%; 98 pat. received TXA	1032	Negative: unadjusted in TXA group higher in-hospital mortality (40% vs 17%, *P* < .001); multivariate analysis: TXA independent predictor for 24-h mortality (OR = 1.92; CI, 11.05–3.25; *P* = .035)	TXA group more severely injured (ISS = 29 vs 14)
Howard et al[93]	Retrospective, military observational study; 3773 soldiers (≥1 pRBC) with subgroups (massive transfusion [n = 784] and propensity matched [n = 1030])	3773	Negative: univariate and multivariate analyses of the total sample no statistically significant association between TXA use and mortality. Use of TXA associated with increased risk of PE in the total sample (HR = 2.82; CI, 22.08–3.81; *P* < .001) and in massive transfusion sample (HR = 3.64; CI, 11.96–6.78; *P* = 0.003). Use of TXA associated with increased risk of DVT in the total sample (HR = 2.00; CI, 11.21–3.30; *P* = .02)	TXA group more severely injured
Johnston et al[94]	Retrospective, military analysis, of these 173 massive transfusions and 139 TXA-pat.	455	Negative: TXA group with increased rate for thromboembolism (34.5% vs 6.8%; *P* < .001). Univariate analysis: TXA independent risk factor for venous thromboembolism (OR = 2.58; CI, 11.20–5.56; *P* = .02)	TXA group more severely injured (ISS 27 vs 15; *P* < .001)
Myers et al[95]	Retrospective, civil, single-center study; analysis of 21,931 pat. between 2012 and 2016, 189 matched pairs	378	Negative: TXA associated with >3-fold increase in the odds of VTE (aOR = 3.3; 95% CI, 11.3–9.1; *P* = 0.02). TXA not significantly associated with survival (aOR = 0.86; 95% CI, 00.23–3.25; *P* = .83). Risk of VTE remained elevated in the TXA cohort despite accounting for mortality (SHR = 2.42; 95% CI, 11.11–5.29; *P* = .03)	TXA group more severely injured (ISS = 16 vs 14; *P* = .19)
Total		8242		

Abbreviations: AKI, acute kidney injury; aOR, adjusted odds ratio; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard rate; ISS, injury severity score; Ly30, lysis after 30 minutes; MOF, multiorgan failure; OR, odds ratio; pat., patients; PE, pulmonary embolism; pRBC, packed red blood cell; SHR, subdistribution hazard ratio; TXA, tranexamic acid; VTE, venous thromboembolism.

may pose a certain risk for possible thromboembolic complications.

CONCLUSIONS

The antifibrinolytic pharmaceutical TXA is widely available, inexpensive, heat stable, and cost-effective in its proper indications.[49] The agent is highly effective in treating hyperfibrinolysis and represents an essential component in the context of comprehensive blood management strategies and for severe hemorrhage as an antifibrinolytic and not an antihemorrhagic agent.[12] However, and despite its widespread use, substantial knowledge gaps remain regarding its dosing, kinetics, mechanism of action, clinical application, and safety. In particular, its potential thromboembolic side effects may raise concerns with its indiscriminate use. While the data generally support the beneficial effects of TXA (in certain populations), as with any other medical treatment, benefits must always be weighed against potential risks and side effects, which underscores the need for a more rational discussion around its more selective use in various clinical entities and patient populations.

According to the current evidence, the individualized and selective[36,70,96] indication for TXA is the treatment of severe life-threatening hemorrhage, best used before the onset of shock, within 3 hours of trauma or delivery, and if bleeding cannot be stopped by other interventional measures (eg, compression and/or tourniquet). Advanced functional hemostatic testing assays (eg, viscoelastic testing) may help with detecting hyperfibrinolysis and promoting a more guided administration of TXA in the clinical setting.[11] In the absence of these assays, in cases of traumatic injury or perioperative ongoing bleeding with a blood loss of 1000–1500 mL, with expected hyperfibrinolysis, 1 g (15–20 mg/kg BW) of TXA might be given slowly over 10 minutes intravenously.[12]

"There are no magic bullets when it comes to drugs for stopping bleeding.[97]" TXA is a valuable component within our arsenal to treat severe and life-threatening bleeds in different clinical scenarios but needs to be included into multimodal concepts and algorithms with its use within defined indications. Ubiquitous, generous, liberal, and indiscriminate application following outdated "one-size/dose-fits-all" concepts is not reasonable and not supported by the data currently available.[10,14] As stated by the authors of the WOMAN trial, "TXA should not replace another effective intervention" and "results do not support the prophylactic use of tranexamic acid."[98] Potential adverse effects also need to be considered for the prophylactic use of TXA in settings of elective and emergency surgeries,[10] and its prophylactic use might sometimes (eg, in the setting of arthroplasty)[22] be off-label. ■

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REFERENCES

1. Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. 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.
2. Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg*. 2014;76:1373–1378.
3. Mitra B, Mazur S, Cameron PA, et al; PATCH-Trauma Study Investigators. Tranexamic acid for trauma: filling the 'GAP' in evidence. *Emerg Med Australas*. 2014;26:194–197.
4. Binz S, McCollester J, Thomas S, et al. CRASH-2 study of tranexamic acid to treat bleeding in trauma patients: a controversy fueled by science and social media. *J Blood Transfus*. 2015;2015:874920.
5. Benipal S, Santamarina JL, Vo L, Nishijima DK. Mortality and thrombosis in injured adults receiving tranexamic acid in the post-CRASH-2 era. *West J Emerg Med*. 2019;20:443–453.
6. Yates J, Perelman I, Khair S, et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. *Transfusion*. 2019;59:806–824.
7. Electronic medicines compendium (eMC). Cyklokapron injection - summary of product characteristics (SmPC). Available at: https://www.medicines.org.uk/emc/product/1077/smpc/. Accessed May 29, 2019.
8. Moore HB, Moore EE, Huebner BR, et al. Fibrinolysis shutdown is associated with a fivefold increase in mortality in trauma patients lacking hypersensitivity to tissue plasminogen activator. *J Trauma Acute Care Surg*. 2017;83:1014–1022.
9. 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(suppl 2):S110–S114.
10. Dobson GP, Doma K, Letson HL. Clinical relevance of a p value: does tranexamic acid save lives after trauma or postpartum hemorrhage? *J Trauma Acute Care Surg*. 2018;84:532–536.
11. Gall LS, Brohi K, Davenport RA. Diagnosis and treatment of hyperfibrinolysis in trauma (a European perspective). *Semin Thromb Hemost*. 2017;43:224–234.
12. Lier H, Maegele M. Blutungsmanagement: tranexamsäure in der präklinik. Pro und kontra [Coagulation management: prehospital tranexamic acid. Pro and contra]. *Notfall+Rettungsmedizin*. 2018 [Epub ahead of print].
13. Grassin-Delyle S, Theusinger OM, Albrecht R, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. *Anaesthesia*. 2018;73:719–729.
14. Goobie SM, Frank SM. Tranexamic acid: what is known and unknown, and where do we go from here? *Anesthesiology*. 2017;127:405–407.
15. Amara U, Flierl MA, Rittirsch D, et al. Molecular intercommunication between the complement and coagulation systems. *J Immunol*. 2010;185:5628–5636.
16. Diebel LN, Martin JV, Liberati DM. Early tranexamic acid administration ameliorates the endotheliopathy of trauma and shock in an *in vitro* model. *J Trauma Acute Care Surg*. 2017;82:1080–1086.
17. Dries DJ. The tranexamic acid conundrum. *Air Med J*. 2018;37:151–153.
18. Teng Y, Feng C, Liu Y, Jin H, Gao Y, Li T. Anti-inflammatory effect of tranexamic acid against trauma-hemorrhagic shock-induced acute lung injury in rats. *Exp Anim*. 2018;67:313–320.

19. Rote Liste Fachinformation (German SmPC). Cyklokapron. Available at: https://www.fachinfo.de/suche/fi/008797. Accessed February 2, 2018.
20. Okamoto S, Okamoto U. Amino-methyl-cyclohexane-carboxylic acid: amcha. *Keio J Med*. 1962;11:105-115.
21. 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;13:177–185.
22. Prescribers' Digital Reference (PDR). Tranexamic acid. Available at: https://www.pdr.net/drug-summary/Cyklokapron-tranexamic-acid-1885. Accessed March 5, 2019.
23. Stein P, Studt JD, Albrecht R, et al. The impact of prehospital tranexamic acid on blood coagulation in trauma patients. *Anesth Analg*. 2018;126:522–529.
24. Ducloy-Bouthors AS, Duhamel A, Kipnis E, et al. Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial. *Br J Anaesth*. 2016;116:641–648.
25. Shakur-Still H, Roberts I, Fawole B, et al. Effect of tranexamic acid on coagulation and fibrinolysis in women with postpartum haemorrhage (WOMAN-ETAC): a single-centre, randomised, double-blind, placebo-controlled trial. *Wellcome Open Res*. 2018;3:100.
26. Lin Z, Xiaoyi Z. Tranexamic acid-associated seizures: a meta-analysis. *Seizure*. 2016;36:70–73.
27. Irl H, Kratzer S, Schwerin S, et al. Tranexamic acid impairs hippocampal synaptic transmission mediated by gamma aminobutyric acid receptor type A. *Eur J Pharmacol*. 2017;815:49–55.
28. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol*. 2016;79:18–26.
29. Roberts I, Shakur H, Afolabi A, et al; CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377:1096–1101, 1101 e1091-1092.
30. WOAMN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389:2105–2116.
31. World Health Organisation (WHO). Tranexamic acid (Inclusion) -- adults. Available at: http://www.who.int/selection_medicines/committees/expert/18/applications/tranexamic/en/. Accessed February 9, 2018.
32. 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.
33. World Health Organisation (WHO). Summary of the report of the 18th meeting of the WHO expert committee on the selection and use of essential medicines. Available at: http://www.who.int/selection_medicines/committees/expert/18/en/. Accessed February 9, 2018.
34. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg*. 2012;147:113–119.
35. Lipsky AM, Abramovich A, Nadler R, et al. Tranexamic acid in the prehospital setting: Israel Defense Forces' initial experience. *Injury*. 2014;45:66–70.
36. 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;261:390–394.
37. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. *Anesthesiology*. 2015;122:241–275.
38. 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.
39. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care*. 2019;23:98.
40. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol*. 2017;34:332–395.
41. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron FX, Roberts I; Antifibrinolytic Trials Collaboration. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet*. 2018;391:125–132.
42. Neeki MM, Dong F, Toy J, et al. Tranexamic acid in civilian trauma care in the California prehospital antifibrinolytic therapy study. *West J Emerg Med*. 2018;19:977–986.
43. Gruen RL, Jacobs IG, Reade MC; PATCH-Trauma study. Trauma and tranexamic acid. *Med J Aust*. 2013;199:310–311.
44. Barking & Dagenham Community Choir. Give tranexamic acid. Available at: https://www.youtube.com/watch?v=scOQIKGUd_c. Accessed March 09, 2019.
45. Pusateri AE, Weiskopf RB, Bebarta V, et al; US DoD Hemorrhage and Resuscitation Research and Development Steering Committee. Tranexamic acid and trauma: current status and knowledge gaps with recommended research priorities. *Shock*. 2013;39:121–126.
46. Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg*. 2013;74:1575–1586.
47. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg*. 2013;100:1271–1279.
48. Goobie SM. Tranexamic acid: still far to go. *Br J Anaesth*. 2017;118:293–295.
49. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. *Blood Coagul Fibrinolysis*. 2019;30:1–10.
50. 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;41:514–521.
51. 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*. 2016;80:16–23.
52. Lowenstein CJ, Morrell CN, Yamakuchi M. Regulation of weibel-palade body exocytosis. *Trends Cardiovasc Med*. 2005;15:302–308.
53. Goobie SM, Meier PM, Sethna NF, et al. Population pharmacokinetics of tranexamic acid in paediatric patients undergoing craniosynostosis surgery. *Clin Pharmacokinet*. 2013;52:267–276.
54. Yee BE, Wissler RN, Zanghi CN, Feng C, Eaton MP. The effective concentration of tranexamic acid for inhibition of fibrinolysis in neonatal plasma in vitro. *Anesth Analg*. 2013;117:767–772.
55. Derickson MJ, McClellan JM, Marko ST, et al. The effects of hemorrhage on the pharmacokinetics of tranexamic acid in a swine model. *J Trauma Acute Care Surg*. 2018;85:S44–S48.
56. Kratzer S, Irl H, Mattusch C, et al. Tranexamic acid impairs γ-aminobutyric acid receptor type A-mediated synaptic transmission in the murine amygdala: a potential mechanism for drug-induced seizures? *Anesthesiology*. 2014;120:639–649.
57. Cornelius BG, McCarty K, Hylan K, et al. Tranexamic acid: promise or panacea: the impact of air medical administration of tranexamic acid on morbidity, mortality, and length of stay. *Adv Emerg Nurs J*. 2018;40:27–35.
58. Boutonnet M, Abback P, Le Saché F, et al; Traumabase Group. Tranexamic acid in severe trauma patients managed in a mature trauma care system. *J Trauma Acute Care Surg*. 2018;84:S54–S62.
59. 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.

60. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev*. 2009;23:231–240.
61. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54:1127–1130.
62. 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;77:811–817.
63. Lusczek ER, Myers C, Popovsky K, Mulier K, Beilman G, Sawyer R. Plasma metabolomics pilot study suggests age and sex-based differences in the metabolic response to traumatic injury. *Injury*. 2018;49:2178–2185.
64. Naumann DN, Hazeldine J, Davies DJ, et al. Endotheliopathy of trauma is an on-scene phenomenon, and is associated with multiple organ dysfunction syndrome: a prospective observational study. *Shock*. 2018;49:420–428.
65. Roberts DJ, Kalkwarf KJ, Moore HB, et al. Time course and outcomes associated with transient versus persistent fibrinolytic phenotypes after injury: a nested, prospective, multicenter cohort study. *J Trauma Acute Care Surg*. 2019;86:206–213.
66. Taylor JR 3rd, Fox EE, Holcomb JB, et al; PROPPR Study Group. The hyperfibrinolytic phenotype is the most lethal and resource intense presentation of fibrinolysis in massive transfusion patients. *J Trauma Acute Care Surg*. 2018;84:25–30.
67. Schmitt FCF, Manolov V, Morgenstern J, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. *Ann Intensive Care*. 2019;9:19.
68. Nicolau-Raducu R, Beduschi T, Vianna R, et al. Fibrinolysis shutdown is associated with thrombotic and hemorrhagic complications and poorer outcomes after liver transplantation. *Liver Transpl*. 2019;25:380–387.
69. Raveh Y, Souki F, Livingstone J, et al. Fibrinolytic shutdown is associated with intraoperative thrombosis and hemorrhage during visceral transplant. *Semin Cardiothorac Vasc Anesth*. 2019 May 8 [Epub ahead of print].
70. Meizoso JP, Dudaryk R, Mulder MB, et al. Increased risk of fibrinolysis shutdown among severely injured trauma patients receiving tranexamic acid. *J Trauma Acute Care Surg*. 2018;84:426–432.
71. Moore HB, Moore EE, Liras IN, et al. Targeting resuscitation to normalization of coagulating status: hyper and hypocoagulability after severe injury are both associated with increased mortality. *Am J Surg*. 2017;214:1041–1045.
72. Hardaway RM, Johnson DG. Influence of fibrinolysin on shock. *JAMA*. 1963;183:597–599.
73. Inaba K, Rizoli S, Veigas PV, 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;78:1220-1229.
74. Gall LS, Davenport RA. Fibrinolysis and antifibrinolytic treatment in the trauma patient. *Curr Opin Anaesthesiol*. 2018;31:227–233.
75. Goobie SM, Faraoni D. Tranexamic acid and perioperative bleeding in children: what do we still need to know? *Curr Opin Anaesthesiol*. 2019;32:343–352.
76. Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. *Am Stat*. 2016;70:129–133.
77. Trafimow D, Marks M. Editorial. *Basic Appl Soc Psych*. 2015;37:1–2.
78. Marino MJ. How often should we expect to be wrong? Statistical power, P values, and the expected prevalence of false discoveries. *Biochem Pharmacol*. 2018;151:226–233.
79. Schober P, Bossers SM, Schwarte LA. Statistical significance versus clinical importance of observed effect sizes: what do P values and confidence intervals really represent? *Anesth Analg*. 2018;126:1068–1072.
80. Letson H, Dobson G, Dennis A, et al. WOMAN trial: letters to the editor. *Lancet*. 2017;390:1581–1584.
81. Houle TT, Stump DA. Statistical significance versus clinical significance. *Semin Cardiothorac Vasc Anesth*. 2008;12:5–6.
82. Mascha EJ, Vetter TR. Significance, errors, power, and sample size: the blocking and tackling of statistics. *Anesth Analg*. 2018;126:691–698.
83. World Maternal Antifibrinolytic (WOMAN) Trial. WOMAN. Available at: http://womantrial.lshtm.ac.uk/. Accessed November 26, 2017.
84. Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care*. 2014;18:685.
85. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963;117:659–676.
86. Groth CG, Pechet L, Starzl TE. Coagulation during and after orthotopic transplantation of the human liver. *Arch Surg*. 1969;98:31–34.
87. Nishida T, Kinoshita T, Yamakawa K. Tranexamic acid and trauma-induced coagulopathy. *J Intensive Care*. 2017;5:5.
88. Moore HB, Moore EE, Huebner BR, et al. Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis. *J Surg Res*. 2017;220:438–443.
89. Blanco-Molina A, Rota LL, Di Micco P, et al; RIETE Investigators. Venous thromboembolism during pregnancy, postpartum or during contraceptive use. *Thromb Haemost*. 2010;103:306–311.
90. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*. 2006;194:1311–1315.
91. Swendsen H, Galante J, Bateni G, Scherer L, Scherer C. Tranexamic acid use in trauma: effective but not without consequences. *J Trauma Treat*. 2013;2:179.
92. Harvin JA, Peirce CA, Mims MM, et al. The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. *J Trauma Acute Care Surg*. 2015;78:905–909.
93. Howard JT, Stockinger ZT, Cap AP, Bailey JA, Gross KR. Military use of tranexamic acid in combat trauma: does it matter? *J Trauma Acute Care Surg*. 2017;83:579–588.
94. Johnston LR, Rodriguez CJ, Elster EA, Bradley MJ. Evaluation of military use of tranexamic acid and associated thromboembolic events. *JAMA Surg*. 2018;153:169–175.
95. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86:20–27.
96. Napolitano LM. Prehospital tranexamic acid: what is the current evidence? *Trauma Surg Acute Care Open*. 2017;2:e000056.
97. Schreiber ME; Current Practice of Medicine for Severe Bleeding. *Product Development Program for Interventions in Severe Bleeding Due to Trauma or Other Causes 2010*. Bethesda, MD: National Institutes of Health, U.S. Food and Drug Administration; 2010.
98. Shakur H, Roberts I. Authors' reply. *Lancet*. 2017;390:1584.