



NARRATIVE REVIEW

Clinical use of tranexamic acid: evidences and controversies

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Abstract Tranexamic acid (TXA) significantly reduces blood loss in a wide range of surgical procedures and improves survival rates in obstetric and trauma patients with severe bleeding. Although it mainly acts as a fibrinolysis inhibitor, it also has an anti-inflammatory effect, and may help attenuate the systemic inflammatory response syndrome found in some cardiac surgery patients. However, the administration of high doses of TXA has been associated with seizures and other adverse effects that increase the cost of care, and the administration of TXA to reduce perioperative bleeding needs to be standardized.

Tranexamic acid is generally well tolerated, and most adverse reactions are considered mild or moderate. Severe events are rare in clinical trials, and literature reviews have shown tranexamic acid to be safe in several different surgical procedures. However, after many years of experience with TXA in various fields, such as orthopedic surgery, clinicians are now querying whether the dosage, route and interval of administration currently used and the methods used to control and analyze the antifibrinolytic mechanism of TXA are really optimal. These issues need to be evaluated and reviewed using the latest evidence to improve the safety and effectiveness of TXA in treating intracranial hemorrhage and bleeding in procedures such as liver transplantation, and cardiac, trauma and obstetric surgery.

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Introduction

Fibrinolysis is a process that remodels and degrades blood clots to restore vascular permeability. The fibrinolytic cascade starts simultaneously with hemostasis, and the clot forms when platelets bind to fibrinogen to form thrombin. This in turn will produce a fibrin mesh (clot retraction mediated by platelet integrin alpha II beta 3) that is stabilized by factor XIII and protected from fibrinolysis by plasminogen activator inhibitors (PAI-1), thrombin mediated fibrinolysis activation inhibitors (TAFI), and antiplasmin (alpha2-AP). These are found in the nucleus of the clot in a higher proportion than fibrinolytic components (plasminogen activators, urokinase-type plasminogen activator (u-PA), tissue-type plasminogen activator (t-PA), and the plasminogen substrate itself). However, the proportion of profibrinolytic factors is higher around the fibrin mesh, and they will therefore remodel the clot and ensure the permeability of the vessel, particularly in medium to small-caliber arteries. In patients with impaired hemostasis (bleeding or thrombosis), fibrinolysis may be overactivated, leading to bleeding.^{1,2}

Tranexamic acid is a molecular analog of lysine that inhibits fibrinolysis by preventing the binding of plasminogen to fibrin.² Its preventive use has been studied in different surgical procedures, and it has proven effectiveness in reducing intraoperative bleeding. It is recommended in surgeries with an expected blood loss of more than 500 mL.³

TXA administration reduces mortality in bleeding trauma patients and in postpartum hemorrhage.^{4,5} There is also evidence for TXA in other scenarios, such as cardiovascular surgery, patients with liver disease undergoing invasive surgery or procedures with risk of bleeding, and patients with acute hemorrhagic pathology; however, further studies are required before it can be routinely indicated. In vascular and urologic surgery, the use of TXA is still under investigation, although some randomized evidence in favor has already been published.^{6,7}

In this narrative review of the latest scientific evidence and expert opinions, we address the issues surrounding the use of TXA in clinical situations in which it is recommended.

Methods

This narrative review is based on a bibliographic search carried out in the PubMed National Library for case-control studies, clinical practice guidelines and consensus documents published between 2000 and June 2020.

We used the Jadad scale to classify the case-control studies included in this review and select those that are most relevant for all patient populations and clinical settings. Jadad is a 5-point quality scale ranging from 0 (poor) to 5 (rigorous) based on 3 criteria: patient randomization, blinding, and case dropouts.⁸ The studies are summarized in tables.

The initial manuscripts were selected by the authors (MJC, LC, PG, MK, EM, AS) and were then reviewed for inclusion by 2 of the authors, (MJC, AS), who eliminated articles with a score of 3 or lower on the Jadad Scale (poor quality).

This review does not aim to discuss all possible issues surrounding the use of TXA; instead, we focus on practical issues of efficacy and safety reported in each clinical con-

text reviewed: orthopedic surgery and traumatology, liver disease and liver transplant, cardiac surgery, polytrauma patients, obstetric patients, and subarachnoid hemorrhage.

Discussion

Main concerns about tranexamic acid in orthopedic surgery and traumatology

i. Efficacy and safety of TXA in orthopedic surgery

TXA reduces transfusion rates by 25% in procedures such as primary knee⁹ and hip¹⁰ arthroplasty (Table 1). However, the latest efficacy reviews (Table 1), especially those related to thromboembolic events and renal complications, do not report safety outcomes.

Because individual comorbidities such as ischemic heart disease, history of stroke, peripheral vascular disease, thromboembolic disease, or vascular stent are not commonly reported, the meta-analysis of Fillingham et al.,¹¹ which included 78 randomized clinical trials, used an American Society of Anesthesiologists (ASA) physical status of III or greater as a proxy for the presence of comorbidities associated with an elevated risk of a thromboembolic event. Study populations in which more than 50% of patients were ASA III or higher were compared with populations in which more than 50% were ASA I or II. Because of limitations in the inclusion and exclusion criteria in randomized clinical trials (RCT), meta-regression was performed using ASA status as a proxy for patients at higher risk for arterial and venous thromboembolic events. The authors found that the administration of TXA did not increase the risk of thromboembolic disease in patients undergoing arthroplasty surgery, but the level of evidence is moderate.^{11,12} The same authors published a clinical practice guideline in which they concluded that the effect of TXA was independent of the method of administration, the number of doses, the use of single or multiple doses, or administration before or after the incision. They also observed that 92% of the studies used a history of a thromboembolic event as the exclusion criterion, and noted that there is a paucity of randomized clinical trials on the risk of adverse effects of intravenous, topical and oral TXA in patients with a known history of VTE, MI, CVA, TIA, and/or vascular stenting, that no clinical trials have investigated specific risk factors, and that there is a paucity of randomized clinical trials on the risk of arterial thromboembolism. Taking these results into account, the authors' decision to consider TXA safe in this setting appears questionable.¹³

The Premier Perspective database, which includes 510 US hospitals, is based on notifications of total hip or knee arthroplasty in 872,416 patients from 2006 to 2012.¹⁴ When stratifying according to age and comorbidity index, patients treated with TXA (compared to those not treated) presented a lower rate of thrombotic complications (0.6% vs 0.8%), acute renal failure (1.2% vs 1.6%), and combined complications (1.9% vs 2.6%). In another review,¹⁵ the risk of venous thromboembolism was analyzed by reviewing 73 randomized controlled trials with 4,174 patients and 2,779 controls. The incidence of venous thromboembolism was

Table 1 Tranexamic acid in orthopedic surgery: meta-analysis.

Author (year)	Patients	Dosage	Blood loss	Transfusion risk	Adverse effects	
Type of study			Mean of difference (IC 95%)	RR (IC 95%)		
Knee arthroplasty						
Fillingham et al. ⁹	67 studies				Not described in article.	
2018	> 9000 patients				In a safety meta-analysis (Fillingham YA, ^{11,13} 2018) TXA was only evaluated in primary knee arthroplasty	
Meta-analysis		IV High doses ($\geq 20 \text{ mg.kg}^{-1} \text{ o } > 1 \text{ g}$) vs control	-283,06 (-353,6; -219,7)	0,21 (0,15- 0,27)		
		IV low doses vs control	-272,29 (-397,42; -155,83)	0,35 (0,22-0,51)		
		Topical (> 1,5 g) vs control	-329,4 (-426,63; -240,21)	0,26 (0,15-0,4)		
		Topical (< 1,5 g) vs control	-266,32 (-341,69; -200,0)	0,25 (0,17 - 0,35)		
Hip arthroplasty						
Fillingham et al. ¹⁰			16 RCT	31 RCT	Not described in article.	
2018			1668 patients	2545 patients	In a safety meta-analysis (Fillingham YA, ^{11,13} 2018) ATX was only evaluated in primary hip arthroplasty	
Meta-analysis		IV high doses ($\geq 20 \text{ mg.kg}^{-1} \text{ o } > 1 \text{ g}$) vs control	-332,54 (-430,22; -250,28)	0,28 (0,2-0,38)		
		IV low doses vs control	-313,72 (-414,95; -218,21)	0,37 (0,26-0,5)		
		Topical (> 1,5 g) vs control	-296,66 (-392,97; -200,82)	0,29 (0,17-0,47)		
		Topical (< 1,5 g) vs control	-363,75 (-733,03; -295,16) (NS)	0,29 (0,12-0,58)		
Author (year)	Patients	Dosage	Intraoperative blood loss Mean of difference (IC 95%)	Total blood loss Mean of difference (IC 95%)	Transfusion risk RR (IC 95%)	Adverse effects
Spine surgery						
Lu VM ²³	6 RCT	10-30 mg.kg ⁻¹ initial bolus and	-124,11 (-207,15; -41,06)	-229,76 (-331,46; -128,06)	0,56 (0,29; 1,07)	4 patients with mild kidney function impairment
2018	937 patients	1 a 2 mg.kg ⁻¹ .h ⁻¹ perfusion				1 pulmonary embolism
Meta-analysis						1 deep venous thrombosis

IV, intravenous.

not significantly different from that of the controls (2.1% vs 2.0%).

ii. Dosage, timing and route of administration of TXA in orthopedic surgery

The meta-analysis by Fillingham et al.^{9,10} stratified TXA according to dosage, and considered $> 1 \text{ g}$ or $\geq 20 \text{ mg.kg}^{-1}$ for IV administration to be a high dose (the general dose is 15 mg.kg^{-1} body weight). (Table 1).

With regard to the timing of TXA administration to achieve maximum efficacy, the study by Tanaka et al.¹⁶ concluded that in knee arthroplasty, 1 g of IV TXA administered preoperatively followed by a second dose (1 g) after removal of the hemostasis tourniquet significantly reduced blood loss without increasing the risk of thromboembolic complications. In primary hip arthroplasty, Imai et al.¹⁷ recommend 1 g of IV TXA 10 minutes before surgery followed by a second dose 6 hours thereafter as an effective strategy for reducing blood loss. In general, IV administration of TXA is recommended before the surgical incision, but this recommendation has a moderate level of evidence because the studies that support it are inconclusive.^{9,10,18–20}

In spinal surgery, the most frequently used doses are 10 to 30 mg.kg^{-1} as a loading dose prior to the surgical incision, followed by 1 to $2 \text{ mg.kg}^{-1}.\text{h}^{-1}$ during surgery^{21–23} (Table 1).

There are very few pharmacokinetic studies in TXA outside the setting of cardiac surgery, and the dosing regimens currently used are largely empirical. 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.²⁴

Results obtained from *in vitro* experiments may not accurately predict the effect *in vivo*. Picetti et al.²⁵ analyzed 21 pharmacodynamics studies of which 20 were *in vitro* and one was *in vivo*, and determined the drug plasma levels capable of reducing the activity of tissue plasminogen activator by 80% *in vitro* (10 mg.mL^{-1}), although other studies have not been able to verify these findings.²⁶ In the studies by Fillingham et al.,^{9,10,18} topical, IV, and oral formulations of TXA were all superior to placebo in terms of reduced blood loss and transfusion risk, while no formulation was clearly superior when compared to each other. The use of repeated doses of oral, IV, topical TXA and higher doses of IV TXA did not significantly reduce blood loss or the risk of transfusion.

Topical administration of TXA may currently be considered as an alternative to the IV route in patients in whom the level of thrombotic risk is unknown, as it has the advantage of minimal systemic absorption and therefore less risk of complications.¹² Its effectiveness in reducing bleeding and transfusion is similar or slightly inferior than IV administration, but in the absence of thrombotic risk factors, IV administration is reasonable to achieve effective and reproducible plasma levels. However, it should be borne in mind that TXA has a dose-dependent cytotoxicity that affects wound re-epithelialization and can induce cell shedding. Therefore, bolus administration of topical TXA should not exceed a concentration of 5 to 10 mg.mL^{-1} and a concentration of TXA of 25 to 50 mg.mL^{-1} is recommended when

moistening a surgical wound (the usual concentration in the vial is 100 mg.mL^{-1}).²⁷

iii. Tranexamic acid and hip fracture

Although elderly patients can be candidates for primary hip arthroplasty, their clinical profile differs from other orthopedic patients. Efficacy and risk of complications is more uncertain than with elective orthopedic surgery, so the indication for TXA in hip fracture must be individualized. In a recent meta-analysis that included a total of 892 patients from 11 clinical studies, intravenous TXA reduced the risk of transfusion by 46%, with no increase in the risk of thromboembolic events; however, the quality of evidence is low.²⁸

Various authors recommend taking an individualized, cautious approach when using TXA in this scenario.²⁹ Table 2 summarizes the different studies published on TXA in patients with hip fractures.

iv. Main recommendations for the use of TXA in orthopedic surgery

- Preoperative administration of TXA in primary hip and knee arthroplasty surgery is effective and safe.
- Topical administration of TXA is recommended as an alternative to intravenous (IV) TXA in orthopedic surgery patients in whom thrombotic risk data are unavailable.
- The indication of TXA in hip fracture should be individualized.

Tranexamic acid in patient with liver disease and liver transplantation

i. Efficacy and safety of TXA in liver disease and liver transplantation

Although patients with impaired liver function can present thrombocytopenia and a deficiency of factors produced in the liver (mainly V, VII, X, and fibrinogen), their ability to form thrombin is maintained by a high von Willebrand factor and factor VIII ratio. This, together with a low plasma concentration of natural anticoagulants (proteins C and S and antithrombin III), causes resistance to thrombomodulin that results in hypercoagulation and portal thrombosis, especially in patients with greater liver involvement (Child C and ascites). In this context, 2 situations can occur: hypofibrinolysis with an increase in PAI-1 and TAFI, especially in patients with hepatic decompensation due to infection/inflammation; and hyperfibrinolysis in patients with advanced but not decompensated liver involvement, probably due to low TAFI levels.³⁰

In general, hyperfibrinolysis is usually found in patients scheduled for liver transplantation (LT); therefore, the profile of the patient awaiting LT differs slightly from that of the cirrhotic patient with inflammatory decompensation, and widely from that of the septic patient (with and without liver disease), who mainly presents hypofibrinolysis and a prothrombotic phenotype. However, despite clear signs of fibrinolysis on laboratory tests, the presence of clinical fibrinolysis (cause of bleeding) is rare.^{31,32}

The detection of hyperfibrinolysis by laboratory tests has variable sensitivity and specificity, depending on the test

Table 2 Tranexamic acid in patients with hip fracture.²⁸

Author (year)	RCT	Intervention: doses TXA	N patients (TXA vs Control)	Blood loss mL (SD mL) (TXA vs Control)	% Transfusion (TXA vs Control)	Adverse effects	Jadad ⁷
Sadeghi 2007	Yes	15 mg.kg ⁻¹ IV bolus	32	960 (284)	37	No reported	3
Zufferey 2010	Yes	15 mg.kg ⁻¹ preoperatively IV bolus and repeat at 3 hours later	57	1484 (374)	57	16% vascular adverse effects at 6 weeks in TXA group and 6% in placebo group	3
Vijay 2013	Yes	500 mg preoperatively IV bolus + infusion 1 mg.kg ⁻¹ .h ⁻¹ during surgery until end	53	975 (741) ^a	42		
Emara 2014	Yes	- 1- 10 mg.kg ⁻¹ bolus preop + continuous infusion of 500 mg in 250 mL of SS with an infusion of 80 mL.h ⁻¹ until the end of surgery.	45	1178 (912) ^a	60	6 patients in TXA IV group (five cases of DVT and one case of stroke) versus 1 patient with DVT in the control group and no case in the topic TXA group	3
Lee 2015	NO	- 1.5 g TXA in 100 mL SS - SS topic	IV 20	91 ^b (17,6)	40		
Kang 2016	Yes	1 g IV bolus preoperatively	Topic 20 Control 20	640 (25)	5	There were no differences in mortality between both groups at 30 and 90 days.	3
Tengberg 2016	Yes	3 g in 100 mL SS topic through surgical deep drainage	84	625 (35)	5		
Baruah 2016	NO	1 g IV bolus preop + IV infusion 3 g in 24 h	40	1100 (30)	35	No reported	3
Watts 2017	Yes	15 mg.kg ⁻¹ bolus IV 15 minutes before surgery	30	No reported	6		
		2 doses of 15 mg.kg ⁻¹ in 100 mL SS IV prior to the incision and another at the end of the surgery	69	1526.6 (1012.7)	81.8	90-day mortality was 27,2% in the TXA group compared to 10,2% (n = 4) in placebo group	4
			39	2100,4 (1152,6)	84.6		
			30	408,97 (106,35)	90	No reported	
			30	676,67 (87,88)	100		
			69	902	17		
			69	1205	26	There were no differences in mortality between both groups at 30 and 90 days	4

RCT, Randomized control trial; SS, saline serum; SD, standard deviation; TXA, Tranexamic acid; IV, intravenous.

^a Median (Interquartile Range).

^b Deep drainage volumen.

^c Only patients with hip fracture.

used and the population studied, and it is difficult to make comparisons given the heterogeneity of the patient populations included in the studies published so far. The reference test is euglobulin clot lysis time (ECLT), or alternatively the clot ratio at 60 minutes. In ECLT, clot lysis measured by viscoelastic techniques has excellent specificity but low sensitivity, with Rotem's FIBTEM obtaining the best result.³¹

During LT, between 50% and 70% of patients present hyperfibrinolysis during the anhepatic phase and reperfusion of the liver graft, presenting a profile characterized by elevated t-PA and low PAI-1 in the initial phases (hepatectomy and anhepatic), with a hatching of the t-PA in graft reperfusion that is attenuated and compensated by the sudden increase in PAI-1 at the end of the procedure. TAFI, plasminogen and alpha2-APE are maintained at low levels throughout the procedure.³²

The main cause of massive bleeding in LT is hyperfibrinolysis, especially during graft reperfusion. This is associated with graft dysfunction and enhanced by the transfusion of prothrombotic factors (plasma, prothrombin complex) that stimulate hyperfibrinolysis and tissular hypoperfusion. Therefore, the prediction of hyperfibrinolysis is closely linked to the prediction of intraoperative bleeding. Hyperfibrinolysis in the reperfusion phase of liver transplantation is often a transient, self-limiting situation that resolves within 15 to 20 minutes. Despite the lack of clear evidence of an increased risk of hypercoagulability associated with the use of antifibrinolytics during LT, a significant number of case reports have described dramatic thrombotic events that are most likely associated with the administration of this class of drug. As a result, routine prophylactic administration of antifibrinolytics in patients undergoing LT cannot currently be recommended. Antifibrinolytic therapy (EACA or TXA) should only be considered in LT recipients with significant bleeding when hyperfibrinolysis is either suspected or confirmed by VET.³⁰ Steib et al.³³ determined that a maximum amplitude of less than 35 mm in the thromboelastogram was predictive of hyperfibrinolysis and bleeding. More recently, A10FIBTEM < 8 mm and A10EXTEM < 35 mm have been found to predict intraoperative bleeding.^{34,35}

Liver transplantation invariably involves hypofibrinogenemia, so correction of fibrinolysis with active bleeding involves the administration of fibrinogen or cryoprecipitate at the same time as treatment with antifibrinolytic drugs.³⁶ In our personal experience, intraoperative hyperfibrinolysis should be corrected with a TXA bolus of 1 to 2 g IV and fibrinogen with 2 to 4 g IV if A10EXTEM is < 15 mm or clotting time on FIBTEM is > 300 seconds. This dosage regimen is similar to that proposed by other authors.³⁰

Given the uncertainty of whether prophylaxis with antifibrinolytics should be performed in patients with severely impaired liver function in surgical procedures or during liver transplantation, no clear recommendation can be made. Even if hyperfibrinolysis is a cause of bleeding, systematic intraoperative administration of antifibrinolytics is not recommended due to the risk of thrombosis, especially of the hepatic artery. Aprotinin was withdrawn from the market due to a tendency towards thrombosis and possible renal failure. Few randomized, double-blind studies have compared TXA prophylaxis with placebo; however, as different doses are used, a meta-analysis cannot be performed. Boylan used high doses,³⁷ Dalmau moderate doses,³⁸

and both demonstrated an important reduction in blood transfusion. In a comparative study in liver transplantation, antifibrinolytics, TXA and aprotinin showed the same efficacy when given prophylactically.³⁹ Regarding safety, a series of patients receiving prophylactic TXA did not show an increase in thrombotic phenomena relative to other series or to a group of untreated patients.⁴⁰ In contrast, venous thrombosis was higher in patients treated with aprotinin; however, after adjusting for risk, no differences were observed.⁴¹

ii. Main recommendations for the use of TXA in liver disease and liver transplantation.

- Although patients with impaired liver function may present coagulation factor deficiency, this status may be compensated, so it is important to evaluate a possible tendency towards hypercoagulation.
- The hemostatic profile of the liver transplant candidate is slightly different from that of the cirrhotic patient with inflammatory decompensation. Hyperfibrinolysis is detected in a higher proportion in patients scheduled for liver transplantation.
- Systematic antifibrinolytic prophylaxis cannot be recommended in patients with severe impairment of liver function or during liver transplantation.

Tranexamic acid in cardiac surgery, according to patient and type of surgery: special concerns

i. Patient and type of surgery: special concerns

Cardiac surgery (CS) is one of the specialties with the highest bleeding risk. The causes of coagulopathy after cardiopulmonary bypass (CPB) are multifactorial. Hemodilution and exposure to CPB circuits cause platelet destruction and thrombin generation, which increase fibrinolytic activity.⁴²⁻⁴⁴ Furthermore, hypothermia and the administration of heparin and protamine also influence perioperative bleeding if the dosage is not correct. As fibrinolysis is an important cause of bleeding, antifibrinolytic drugs have been shown to be effective in reducing bleeding and the need for transfusion, and their use is now a Class I recommendation (level of evidence A) by the American Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists.⁴⁵

TXA is indicated in all CS with and without CPB. It has been most widely studied in the context of coronary artery bypass surgery, although it has also been investigated in valve and ascending aortic surgery (Table 3).^{42,46} Cardiac surgery patients have been one of the most widely studied populations in the context of TXA use, and the largest study, published by Myles et al.,⁴² did not detect any TXA-induced thromboembolic complications.

ii. Dosage and interval of administration of TXA in cardiac surgery

Table 4 summarizes chronologically the different TXA regimens in CS.^{42,47,48} In the study by Sigaut et al.,⁴⁸ 2 groups of patients receiving a TXA dose greater than 50 mg.kg⁻¹ and a lower dose were compared. No differences were found in the mortality, blood transfusion, and reinterventions to control bleeding.

Table 3 Tranexamic acid in cardiac surgery.

Author, year, Level of evidence (Jadad [®])	Patients and intervention groups	Objectives & Results	Comments
Myles PS et al. ⁴² (2017) RCT	4631 adults' patients bypass coronary surgery - 2320 Placebo - 2311 TXA.	Objective 1 ^o : Mortality and thrombotic complications during the first 30 days ($p = 0.22$): [●]386(16. 7%) Placebo [●]420 (18.1%) TXA	Well-designed study with a very good sample size High doses (to 1 mL.kg ⁻¹ and 0,5 mL.kg ⁻¹ , according to Table S8 of the Supplemental material of Myles study 100 mg.kg ⁻¹), significantly reduces bleeding ($p = 0,026$) and number of units transfused of blood products ($p = 0.017$)
Jadad 4	Initially 100 mg.kg ⁻¹ more than 30 min post anaesthesia induction After, 50 mg.kg ⁻¹ due to the high incidence of seizures	Objective 2 ^o : Total number of blood products transfused during hospitalization ($p < 0.001$). [●]7994 Placebo [●]4331 TXA Re-intervention for major bleeding or cardiac tamponade ($p = 0.001$): [●]2.8% Placebo [●]1.4% TXA Seizures ($p = 0.002$) [●]0.1% Placebo [●]0.7% TXA	The incidence of seizures is low in both groups.
Sigaut et al. ⁴⁸ (2014) RCT	569 Adult's patients Coronary by-pass surgery - 284 low doses TXA	Objective 1 ^o : Incidence of transfusion up to 7 postoperative days ($p = 0.3$) [●]180 low doses TXA [●]170 high doses TXA	Well-designed study with correct size No differences in mortality or transfusion rate
Jadad 5 (level 1b)	10 mg.kg ⁻¹ bolus + 1 mg.kg ⁻¹ .h ⁻¹ + 1 mg.kg ⁻¹ priming OP - 285 high doses TXA 30 mg.kg ⁻¹ bolus + 16 mg.kg ⁻¹ .h ⁻¹ + 2 mg.kg ⁻¹ priming OP	Objective 2 ^o : Blood products transfusion ($p = 0.02$) [●]4.1 ± 0.39 low doses TXA [●]2.5 ± 0.38 high doses TXA Blood loss first 24h (mL) ($p = 0,01$) [●]820 ± 50.7 low doses TXA [●]590 ± 50.4 high doses TXA Re-surgical for bleeding ($p = 0.03$) [●]17 low doses TXA [●]14 high doses TXA Seizures ($p = 0.7$) [●]2 low doses TXA	Significant differences in blood loss, blood products transfused, and re-interventions for bleeding control Incidence of seizures also low compared to other series reporting 3-7% of seizures

Table 3 (Continued)

Author, year, Level of evidence (Jadad [®])	Patients and intervention groups	Objectives & Results	Comments
Kuiper et al. ⁴⁷ (2019)	355 Adults Cardiac surgery	[●]4 high doses TXA Mortality from day 0 to day 28 ($p = 0.2$) [●]14 low doses TXA [●]8 high doses TXA 1st Objective: Blood loss the day of the surgery ($p < 0.001$)	
Observational, prospective open cohort database	- 204 blood products administration of and haemostatic medication according to medical criteria	[●]890 mL. Medical criteria	
Jadad 5	- 151 blood products administration of and ROTEM-guided haemostatic medication	[●]565 mL. Guided by ROTEM	
		Use red blood cell transfusion and haemostatic medication. Decreased absolute risk of: [●]17% by red blood cell transfusion ($p = 0.024$)	
		[●]12% for fresh frozen plasma ($p = 0.019$)	
		[●]12% for fresh frozen plasma ($p = 0.019$)	
		[●]4% by platelet transfusion ($p = 0.582$)	
		In general, more TXA was administered but not more fibrinogen 2nd Objective: Re-surgical intervention for bleeding and mortality [●]No statistically significant difference	
		In hospital stay [●]A mean of 4 days was reduced ($p < 0.001$)	
		Economic costs [●]€4.8 million (\$5.6 million) per year for the authors' hospital with about 1,000 procedures annually.	

RCT, Randomized control trial; OP, On-Pump coronary artery bypass surgery.

Table 4 Dosage regimens of tranexamic acid in cardiac surgery.

Author	Year	Loading dose	Maintenance dose	Dose in on-pump	Plasmatic concentration
Horrow et al., ⁴⁹ (1995)	1995	10 mg.kg ⁻¹	1 mg.kg ⁻¹ .h ⁻¹	No	
Fiechtner et al., ⁵⁰ (2001)	2001	10 mg.kg ⁻¹	1 mg.kg ⁻¹ .h ⁻¹	-	14-54 mg.L ⁻¹
Dowd et al., ⁵¹ (2002)	2002	12,5 mg.kg ⁻¹	6,5 mg.kg ⁻¹ .h ⁻¹	1 mg.kg ⁻¹	52 mg.L ⁻¹
Dowd et al., ⁵¹ (2002)	2002	30 mg.kg ⁻¹	16 mg.kg ⁻¹ .h ⁻¹	2 mg.kg ⁻¹	125 mg.L ⁻¹
Fergusson (BART) et al., ⁵² (2008)	2008	30 mg.kg ⁻¹	16 mg.kg ⁻¹ .h ⁻¹	2 mg.kg ⁻¹	-
Sevilla Document (Leal-Noval et al., 2013) ⁵³	2013	30 mg.kg ⁻¹	16 mg.kg ⁻¹ .h ⁻¹	2 mg.kg ⁻¹	-

Seizures in adult patients after CS are an independent predictor of permanent neurological damage and increase mortality by up to 29%.⁵⁴ The 2 main risk factors are open heart surgery, and especially advanced age. This latter could be due to the presence of vascular microembolisms that can cross the blood-brain barrier and can in themselves be epileptogenic. The TXA molecule, meanwhile, inhibits GABA-A receptors of the hippocampus and glycine receptors, causing an increase in neuronal excitability.⁵⁵⁻⁵⁷

The recommended TXA doses according to CS transfusion risk scales such as the Acta-Port Score^{58,59} are:

1. Low risk of bleeding (Acta Port Score ≤ 19 with a transfusion prediction of between 5% and 69%): TXA bolus of 10 mg.kg⁻¹ prior to sternotomy + 1 mg.kg⁻¹.h⁻¹ perfusion throughout surgery. In this case, the dose is not adjusted for kidney failure.
2. High risk of bleeding (Acta Port Score ≥ 20 with a transfusion prediction of between 73% and 95%): TXA bolus of 30 mg.kg⁻¹ prior to sternotomy + 10 mg.kg⁻¹.h⁻¹ perfusion throughout surgery. The dose is adjusted according to glomerular filtrate levels (adapted from Jerath et al.⁶⁰): ≥ 60 (mL.min⁻¹/1.73 m²) - 10 (mg.kg⁻¹.h⁻¹); 30-60 (mL.min⁻¹/1.73 m²) - 5 (mg.kg⁻¹.h⁻¹); < 30 (mL.min⁻¹/1.73 m²) or dialysis - 3 (mg.kg⁻¹.h⁻¹).

iii. Main recommendations for the use of TXA in cardiac surgery

- Antifibrinolytic drugs have been shown to be extremely beneficial in cardiac surgery with CPB and are now recommended with a high level of evidence.
- TXA administration at doses higher than 50 mg.kg⁻¹ has failed to demonstrate a decrease in mortality, bleeding, or transfusion risk; instead, there is an increased risk of seizures.
- TXA is not generally considered necessary in CPB priming, but it is recommended to adjust the dose based on renal function, according to the serum creatinine level of each patient.

Tranexamic acid in the polytrauma patient: important questions

The CRASH-2 study, which showed a 14.5% reduction in 28-day mortality in the TXA group compared to 16% in the placebo group, has impacted TXA use in trauma patients.⁴ A subsequent analysis derived from this study showed that patients treated with TXA within 1 hour of trauma had a 5.3% risk of mortality from bleeding compared to 7.7% in the placebo group. However, the risk of mortality from bleeding increased in patients treated more than 3 hours after the injury (4.4% vs 3.1%) (Table 5).¹²

Since publication of this study, many guidelines and scientific societies strongly recommend the administration of TXA. Early administration, at least within the first 3 hours of the trauma, is recommended.⁶¹

Despite its impact, the CRASH-2 study has important limitations that need to be considered: selection bias; the inclusion criteria make it impossible to determine the homogeneity of cohorts; there are no data on injury severity scores, presence of shock (lactate, base deficit) or fibrinolysis at admission; TXA did not reduce bleeding, and only 50% of study patients received blood transfusion; and there are no data on the number of cases requiring massive transfusion (MT) or the number of MT protocols used by the different hospitals.⁶²

i. Is there evidence for starting administration of tranexamic acid in the out-of-hospital setting?

The CRASH study⁴ is so far the only study providing a high degree of evidence for out-of-hospital administration. Stein et al.⁶³ performed a prospective study in 70 patients to evaluate changes in coagulation from on-scene administration of 1 g TXA to hospital admission. Patients treated with TXA showed higher FIBTEM (14 ± 5 vs. 11 ± 3.5; $p = 0.010$) and EXTEM (61 ± 6 vs. 50 ± 8; $p < 0.001$) values compared to the control group. The increase in D-dimer was significantly greater in the control group, indicating greater fibrinogen degradation (Table 5).

The prospective, multicenter Cal-PAT study⁶⁴ in 362 patients treated with prehospital TXA compared with 362 patients in a historical group showed a decrease in 28-day

Table 5 Tranexamic acid in polytraumatic patient.

Author (year)	Patients	Groups/Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad ⁵
Moore et al., ⁷⁶ (2016)	Age ≥ 18	3 Fibrinolysis phenotypes:	2540	- Define FL types	HF (34%)	-	GCS of 3 in the SD and HF group may be a bias in mortality	(Not describe missing) No clinical trial
Descriptive	ISS > 15	- HF		- Define FL type predictors	SD (22%)			
Multicentric		- Phy		- FL relationship with mortality	Phy (14%)			
2 Centres Raza et al., ⁷⁸ (2013)	Trauma	- SD - PAP ≤ 1500+LM < 15% normal	288/325	-Prevalence and severity of FL	p < 0,0001 Normal = 100	-		(Describe missing) No clinical trial
	Age > 15	- - PAP > 1500+LM < 15% moderate (PAP only)		-Sensitivity of ROTEM to detect FL	PAP only = 165			
Prospective Observational Cohorts	Trauma Activation	- - PAP > 1500+LM > 15% severe		-Association FL/ Tissue injury	Severe = 15			
		- - PAP ≤ 1500+LM > 15% TEG only			TEG only = 8			
CRASH-2 ⁴ (2010)	Adult trauma (SAP < 90 mmHg and/or HR > 110) or bleeding risk at 8 h post-trauma	TXA Group	20211	Effect of early administration of TXA on survival, thrombotic lesions, and transfusion	Mortality TXA 14,5% vs 16 %; p 0.0035 RR 0.91 Vascular event TXA 1.7% vs 2 %; p 0.085	Any vascular occlusion (1.7% vs 2%; p = 0.084)	Lack of description of ISS and injuries of both groups	5
		Placebo Group						
Prospective RCT Multicentric								

RCT, randomized control trial; FL, Fibrinolysis; HF, Hiperfibrinolisis; SD, *South Down* Fibrinolysis; PHY, Fibrinolysis physiological; GCS, Glasgow Coma Score; PAP, Plasmine anti-plasmine complex; LM, Lysis maxima; TEG, Thromboelastography; ISS, *Injury Severity Score*; SAP, Systolic arterial pressure; HR, heart rate.

mortality (3.66 vs. 8.3%). The difference in mortality was greatest in severely injured patients with ISS > 15 (6% vs. 15.5%).

These studies support prehospital administration of TXA, despite their design limitations. The randomized double-blind STAAMP study,⁶⁵ which evaluates the effect of prehospital TXA on 30-day mortality did not result in a significantly lower 30-day mortality, but it was safe and did not result in a higher incidence of thrombotic complications or adverse events.

ii. Should all multiple trauma patients receive TXA?

Which trauma patients benefit the most from TXA treatment?

The first question is probably: in which kind of trauma is TXA indicated? Should it be limited to severely bleeding, coagulopathic patients with hemodynamic compromise/shock? Or should the cyclist with an isolated tibial fracture also be included? Despite an increasing number of studies recommending liberal use, current guidelines recommend using TXA only for severe bleeding or in patients who are bleeding or at risk of significant hemorrhage that is (or at least might be) due to hyperfibrinolysis.⁶⁶ This raises the second question: Is TXA safe? There is growing concern about the possibility of thromboembolic complications.²⁴ In the military setting, TXA administration is an independent risk factor for VTE.^{67–70} Additionally, statistical analysis ambiguities (more specifically, the interpretation of statistical tests), especially the upper limits of the confidence intervals in almost every study published by the *London School of Hygiene & Tropical Medicine*, may confound study findings.²⁴ The authors are aware of this problem. The results of CRASH-2, CRASH-3 and WOMAN were not reproducible in a modern hospital setting in developed countries with a high socioeconomic status.^{71–74}

Nevertheless, 25% of patients present acute traumatic coagulopathy (ACT) on arrival at the hospital,⁷⁵ and the presence of fibrinolysis is also an aggravating factor for mortality.⁷⁵

Moore et al.,⁷⁶ differentiated 3 phenotypes using thromboelastography in a study of 2,540 patients. Hyperfibrinolysis appeared in 18% of patients, and was associated with the highest mortality rate (34%), hypofibrinolysis was present in the 46% of patients and was associated with the second highest mortality rate (22%), and physiological fibrinolysis, found in 36% of patients, was associated with a 14% death rate. The authors⁷⁷ believe that an imbalance between the plasminogen activator inhibitor (PAI-I) and activator (tPA) could be the cause of hypofibrinolysis, and they question the use of TXA in these patients, suggesting that patients should be treated on the basis of thromboelastographic results, although more evidence is required (Table 5).⁷⁸

Despite the progress in fibrinolysis phenotype diagnosing, empirical treatment with TXA within the first 3 hours after trauma is still recommended in mature trauma systems. Especially in patients with significant hemorrhage and systolic blood pressure less than 90 mmHg or heart rate higher than 110 beats /minute or who require any transfusion.⁴

iii. What is the ideal dosage and interval of TXA in trauma patients?

Grassin-Delyle et al.,⁷⁹ in a pharmacokinetic study in 73 trauma patients who received 1 g of intravenous TXA before

arrival at the hospital, found that the plasma concentration on arrival at the hospital was 28.7 (21.85–38.5 [8.7–89.0]) $\mu\text{g}\cdot\text{mL}^{-1}$ and less than 20 $\mu\text{g}\cdot\text{mL}^{-1}$ (the lowest target concentration) in 21% of patients. The TAMPITI study⁸⁰ randomizes patients to receive placebo or 2 single IV boluses of TXA (4 g or 2 g), and the STAAMP⁶⁵ trial studies the effect of pre-hospital infusion of TXA, evaluating doses higher than 4 $\text{mg}\cdot\text{kg}^{-1}$ in patients requiring transfusion.

iv. Is monitoring essential after TXA administration in trauma patients?

According to Moore et al.,⁸¹ the empirical administration of TXA warrants careful evaluation, and the authors support its use within 2 hours of injury in severe trauma patients with a pattern of thromboelastogram-documented hyperfibrinolysis. When evaluating clot formation with thromboelastography, platelet-induced clot retraction may be interpreted as a false positive for hyperfibrinolysis, so some authors suggest measuring a sample in parallel with TXA to rule this out.⁸²

v. Main recommendations for the use of TXA in trauma.

- In trauma patients with high suspicion of bleeding, TXA administration is recommended in the first 3 hours after the injury.
- Current evidence is limited to a recommendation of out-of-hospital administration of TXA.
- The ideal dosage and interval of administration of TXA in these patients has yet to be defined.

Tranexamic acid in the obstetric patient

Postpartum hemorrhage (PPH) is still the obstetric emergency with the highest maternal mortality. The overall incidence of PPH is estimated at between 6% to 11%, and that of severe PPH is between 1% and 3%.⁸³ According to the latest consensus guidelines published by NATA (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis), PPH is defined as blood loss of more than 500 mL in the first 24 hours, and severe PPH as blood loss of over 1000 mL.⁸³

Up to 75% of PPH cases are caused by uterine atony,⁸⁴ which is why the use of uterotonics is recommended as the first line of treatment, with a 1A level of evidence.⁸³ However, only 6.4% of PPH-related deaths are due to uterine atony,⁸⁴ suggesting that other causes and treatments should be considered.

During placental delivery, degradation of fibrinogen and fibrin occurs together with an increase in the activation of plasminogen activators and fibrin degradation products due to activation of the fibrinolytic system, which is why TXA may be useful in cases of PPH that are not associated with uterine atony.^{84,85}

i. Current evidence on the use of TXA in the obstetric patient.

A recent meta-analysis⁸⁴ analyzing the efficacy of pre-incident TXA in caesarean section and the use of TXA after vaginal delivery, with uterotonic co-administration, showed a decrease in the incidence of bleeding, blood transfusion and additional medical interventions. Administration of prophylactic TXA for vaginal delivery also reduced bleeding.⁸⁶

Table 6 Tranexamic acid in obstetrics' patients.

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad ⁵
Novikova N ⁸⁴	Healthy women with low risk of bleeding by caesarean section or childbirth	Evaluates 12 RCT.	N: 3285	To determine the effectiveness and safety of TXA in preventing PPH compared to placebo, no treatment, or uterotonics	Decrease incidence of bleeding greater than 400-500 mL in vaginal delivery.	Nausea and vomiting were more frequent in TXA group.	Using the GRADE criteria, the risk of bias was assessed as moderate	
(2015)		9: Efficacy of pre incisional TXA in caesarean sections 3: Efficacy of TXA after vaginal delivery.	Caesarea's: 2453 Deliveries: 832		Decrease bleeding more than 1000 mL in caesarean sections. Decrease bleeding, blood transfusion, and additional medical interventions.	Serious adverse effects could not be assessed by sample size		
Meta-analysis and Systematic review		In all RCTs, TXA was associated with uterotonics and compared with placebo or no treatment.						
Mirghafourvand M ⁸⁶	Pregnant women with a single foetus at low risk of PPH	TXA group: 1 g of after delivery	N: 120	To assess the effect of TXA on postpartum vaginal bleeding in low risk of postpartum haemorrhage women	Bleeding as measured was significantly less in the TXA group.	2 cases had nausea and vomiting in TXA group and none in the control group, but the study is not powerful to assess adverse effects.	The size of the study is one of its biggest biases.	3
(2015)		Control: Placebo	TXA: 60 Control: 60			No thrombotic events.		
RCT double-blind								

Table 6 (Continued)

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad ⁵
Sujata N ⁸⁷ (2016) RCT	Women undergoing elective or urgent caesarean section with high risk of PPH	TXA group: 10 mg.kg ⁻¹ Control: Saline Serum Both administered 10 minutes before the incision.	N: 60 TXA: 30 Control: 30	To assess the effect of TXA in patients undergoing caesarean section with a high risk of PPH	TXA group required significantly less additional uterotonics.	TXA was safe for both and was not associated with a greater number of thrombogenic events, but the power of the study was insufficient to analyse the adverse effects.	The risk of bias is high because the study was not double-blind.	
WOMAN ⁵ (2017) RCT multi-centre, double blind	Women > 16 years old with clinical diagnosis of PPH after caesarean section or vaginal delivery	TXA group: 1 g, and a possible second dose after 30 minutes if bleeding was ongoing. Control: Placebo.	N: 20.021 TXA: 10,036 Control: 9,985	To determine the effects of TXA on mortality, hysterectomy, and other complications in women with PPH	TXA did not decrease mortality from any cause or the incidence of hysterectomy. TXA decreased mortality from bleeding in patients who were administered in the first 3 hours postpartum. The TXA also significantly reduced the incidence of laparotomies to control bleeding.	There were no significant differences regarding the incidence of thromboembolic events, organ failure, or sepsis.	Regarding hysterectomy, in many cases the decision to perform a hysterectomy was already made before administering the drug. Regarding mortality, in some cases it was so early after randomization that it should not be associated with AT use.	5

Table 6 (Continued)

Author (year) Type of study	Patients	Groups /Intervention	n	Objective	Results	Adverse effects	Comments, Bias	Jadad ⁵
Brenner A (Brenner et al., 2018)	WOMAN's study patients randomized in the first 3 hours postpartum.	TXA group: 1 g and a possible second dose after 30 minutes if bleeding was ongoing. Control: Placebo.	N: 14,923 TXA: 7,518 Control: 7,405	To determine the effects of TXA on mortality and hysterectomy in women with PPH	TXA showed a significant decrease in death from bleeding, but not from hysterectomy.	No evaluated	This sub-analysis tries to avoid the biases discussed in the WOMAN study, but it has important statistical limitations.	5
WOMAN sub- analysis	Excluding hysterectomies and early deaths							
Sentilhes L ⁸⁸ (2018)	Women in labour with vaginal delivery of a single expected child without increased risk of bleeding or thrombosis	TXA group: 1 g of TXA after delivery Control: Placebo	N: 3,891 TXA: 1,945 Control: 1,946	To know if the administration of prophylacti- cally TXA in addition to oxytocin after delivery reduces the incidence of PPH	TXA decreased bleeding \geq 500 mL, but not significantly ($p = 0,07$) TXA decreased significantly bleeding > 500 mL, clinically significant PPH, and the use of additional uterotonics.	TXA was associated with an increased incidence of nausea and vomiting, but not increase the incidence of thromboembolic events at 3 months.	The importance of the difference between \geq 500 mL and > 500 mL remains to be defined.	5
RCT multi- centre, double blind								

RCT, Randomized control trial; TXA, Tranexamic acid; PPH, Postpartum Haemorrhage.

TXA after caesarean section with PPH risk reduced the need for uterotonics (Table 6).⁸⁷

The WOMAN trial,⁵ published in 2017, evaluated the efficacy of administration of TXA vs placebo in 20,021 patients with a clinical diagnosis of PPH. TXA reduced mortality from bleeding, but not all-cause mortality. However, as in other types of patients, mortality due to bleeding was reduced when the drug was administered within the first 3 hours postpartum, but not when it was administered after this window.⁵ Hysterectomy was not reduced with TXA; however, many hysterectomies were indicated at the time PPH was diagnosed, so TXA did not affect this decision - a study weakness acknowledged by the authors.⁵ In a recent study carried out in 15 French hospitals,⁸⁸ the administration of 1 g of TXA in the immediate postpartum period together with oxytocin decreased clinically significant PPH and the use of additional uterotonics (Table 6).⁸⁸

Based on the foregoing evidence, after the administration of uterotonics and following diagnosis of PPH, the administration of 1 g IV TXA is recommended within the first 3 hours of delivery, repeating the dose after 30 minutes if necessary. This recommendation has a 1B level of evidence.⁸³

However, in the case of caesarean section, the NATA consensus guidelines advise against the routine use of tranexamic acid to prevent PPH, reserving its use for cases of antepartum bleeding and in women at increased risk of PPH, and recommend administering TXA at doses of 0.5 to 1 g in addition to oxytocin in patients with high risk of PPH.⁸³ Despite the decrease in the incidence of bleeding greater than 500 mL after vaginal delivery shown in the study by Sentilhes et al.,⁸⁸ the prophylactic use of TXA in vaginal delivery is not currently recommended. In severe PPH, the NATA guidelines recommend goal-guided replacement using laboratory results or viscoelastic techniques (Table 6).⁸³

ii. Main recommendations for the use of TXA in the obstetric patient.

- The use of prophylactic TXA in vaginal delivery is not currently recommended.
- TXA may be useful in postpartum hemorrhage (PPH) situations that are not associated with uterine atony.
- Once PPH has been diagnosed. After administration of uterotonics, 1 g of IV TXA is recommended within the first 3 hours of delivery, repeating the dose after 30 minutes if necessary. This recommendation has a high level of evidence.

Tranexamic acid in subarachnoid hemorrhage: evidence and controversies

Subarachnoid hemorrhage due to aneurysmal rupture occurs in relatively young patients (mean age 55 years).^{89–91} A frequent complication of patients with SAH is rebleeding of the aneurysm itself, which occurs in the first 3 to 6 hours after SAH, and is the main cause of mortality and morbidity.^{92–94} Early interventional treatment through coiling and/or clipping of the aneurysm fails to prevent most rebleeding that occurs in the early stages. Therefore, early medical treatment with antifibrinolytics could be indicated in these patients. However, although studies performed so far report

a reduction in rebleeding, TXA did not improve morbidity and mortality, and the benefit of TXA in late cerebral ischemia is controversial.^{89,91,93}

These studies, it should be noted, are heterogeneous in terms of drug, medication, dose, and final objectives.⁹⁵ The results of the ultra-early, short-term administration study are still pending.⁹⁶

In view of the foregoing, routine administration of TXA is not indicated except in selected cases, and the best dosage and interval remain unclear.⁹²

The most important studies performed in patients with intracranial hemorrhage - TICH-2⁹⁷ and CRASH-3⁹⁸ - show that functional status 90 days after intracerebral hemorrhage did not differ significantly between patients receiving TXA and those receiving placebo, despite a reduction in early deaths and serious adverse events. Treatment within 3 hours of injury reduces head injury-related death. TXA should be administered as soon as possible after injury. The CRASH-3⁹⁸ study reports that TXA is safe in patients with TBI.

i. Current evidence and controversies on the use of TXA in subarachnoid hemorrhage.

The current recommendations of the Neurocritical Care Society's Multidisciplinary Consensus Conference on management of SAH are⁹⁰:

- 1) Early, short course with antifibrinolytic therapy before definitive treatment of the aneurysm (begun at the time of diagnosis and continued up to the point at which the aneurysm is secured, or at 72 hours post-ictus, whichever is shorter) (weak recommendation).
- 2) Do not start treatment 48 h after the event or extend it for more than 3 days when the risk of rebleeding has already decreased (Strong recommendation).

In addition, the authors suggest avoiding the use of antifibrinolytic therapy in patients with high thromboembolic risk, and closely monitoring for possible thromboembolic complications.

However, the authors of the 2013 European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage point out that there is currently no medical treatment that improves outcomes by reducing rebleeding (class 1, level A evidence), and further studies with ultra-early and short-term administration of TXA are needed.^{95,96}

Considering all these data, and despite the different approaches put forward in the studies analyzed,^{89,91,93} we believe that early treatment of the aneurysm either by endovascular technique (coiling) or by clipping is currently the treatment of choice and the mainstay of management in patients with subarachnoid hemorrhage due to aneurysmal rupture. However, rebleeding in the first few hours is a risk factor associated with high mortality. Starting treatment with TXA at the time of diagnosis and continuing it for the first 24 hours at most, or until the aneurysm is secured early, could provide protection against rebleeding, and prevent the ischemic complications associated with longer treatments.

ii. Main recommendations for the use of TXA in subarachnoid hemorrhage.

- A frequent complication of patients with subarachnoid hemorrhage (SAH) is rebleeding of the aneurysm itself. This occurs in the first 3 to 6 hours after SAH, and is the main cause of mortality and morbidity.
- Routine administration of TXA in SAH is not indicated, except in selected cases. The ideal dosage and interval is not clear.
- The recommendation of early treatment with TXA for the first 72 hours, before definitive treatment of the aneurysm, is weak.

Conclusion

We agree that the use of TXA provides benefits to improve patient outcomes during major bleeding. But, more quantitative studies are needed to evaluate the prophylactic use of TXA, optimal drug dosage, administration time as well as relevant safety aspects. Strong trials and subsequent meta-analyses of such studies remain the pinnacle of reliable evidence. However, in the absence of such evidence, the anesthesiologist must evaluate the results reported in retrospective cohort studies with expert opinions of less scientific evidence. Still, we must use the full range of reliable, reproducible, and peer-reviewed data to increase our knowledge.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Holcomb JB. Multidisciplinary approach to the challenge of hemostasis. *Anesth Analg*. 2010;110:354–64.
- Tengborn L, Blombäck M, Berntorp E. Tranexamic acid - An old drug still going strong and making a revival. *Thromb Res*. 2015;135:231–42.
- Lloyd TD, Neal-Smith G, Fennelly J, et al. Peri-operative administration of tranexamic acid in lower limb arthroplasty: a multicentre, prospective cohort study. *Anaesthesia*. 2020;75:1050–8.
- CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23–32.
- Shakur H, Roberts I, Fawole B, et al. 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;389:2105–16.
- Monaco F, Nardelli P, Pasin L, et al. Tranexamic acid in open aortic aneurysm surgery. A randomised clinical trial. *Br J Anaesth*. 2019;124:35–43.
- Mina SH, Garcia-Perdomo HA. Effectiveness of tranexamic acid for decreasing bleeding in prostate surgery: a systematic review and meta-analysis. *Cent European J Urol*. 2018;71:72–7.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
- Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. *J Arthroplasty*. 2018;33, 3090–8.e1.
- Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis. *J Arthroplasty*. 2018;33, 3083–9.e4.
- Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis. *J Arthroplasty*. 2018;33, 3070–82.e1.
- Sheng Xu, Chen Jerry Yongqiang, Zheng Qishi, et al. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: A systematic review and network meta-analysis. *Thromb Res*. 2019;176:61–6.
- Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic Acid Use in Total Joint Arthroplasty: The Clinical Practice Guidelines Endorsed by the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. *J Arthroplasty*. 2018;33: 3065–9.
- Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*. 2014;349:g4829.
- Franchini M, Mengoli C, Marietta M, et al. Safety of intravenous tranexamic acid in patients undergoing major orthopaedic surgery: a meta-analysis of randomised controlled trials. *Blood Transfus*. 2018;16:36–43.
- Tanaka N, Sakahashi H, Sato E, et al. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. *J Bone Joint Surg Br*. 2001;83:702–5.
- Imai N, Dohmae Y, Suda K, et al. Tranexamic Acid for Reduction of Blood Loss During Total Hip Arthroplasty. *J Arthroplasty*. 2012;27:1838–43.
- Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic acid in total joint arthroplasty: the endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. *Reg Anesth Pain Med*. 2019;44:7–11.
- Saravanan R, Venkatraman R, Karthik K, et al. Efficacy of different doses and timing of tranexamic acid in major orthopedic surgeries: a randomized trial. *Rev Bras Anesthesiol*. 2020;70:311–7.
- Souza Neto E, Usandizaga G. Comparison of two doses of intrarticular tranexamic acid on postoperative bleeding in total knee arthroplasty: a randomized clinical trial. *Rev Bras Anesthesiol*. 2020;70:318–24.
- Colomina MJ, Koo M, Basora M, et al. Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial. *Br J Anaesth*. 2017;118:380–90.
- Mosaad AA, Abd-MH, Abd-elazeem EM, et al. A Comparative Study between Prophylactic High Dose of Tranexamic Acid and Low Doses Tranexamic Acid in Reducing Perioperative Blood Loss in Spine Surgery. *J Clin Anesth*. 2017;1:1–4.
- Lu VM, Ho Y-T, Nambiar M, et al. The Perioperative Efficacy and Safety of Antifibrinolytics in Adult Spinal Fusion Surgery. *Spine*. 2018;43:E949–58.
- Lier H, Maegele M, Shander A. Tranexamic Acid for Acute Hemorrhage: A Narrative Review of Landmark Studies and a Critical Reappraisal of Its Use Over the Last Decade. *Anesth Analg*. 2019;129:1574–84.
- Picetti R, Shakur-Still H, Medcalf RL, et al. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. *Blood Coagul Fibrinolysis*. 2019;30:1–10.
- Yang QJ, Kluger M, Goryński K, et al. Comparing early liver graft function from heart beating and living-donors: A pilot study aiming to identify new biomarkers of liver injury. *Biopharm Drug Dispos*. 2017;38:326–39.

27. Eikebrokk TA, Vassmyr BS, Ausen K, et al. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. *BJS Open*. 2019;3:840–51.
28. Xiao C, Zhang S, Long N, et al. Is intravenous tranexamic acid effective and safe during hip fracture surgery? An updated meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg*. 2019;139:893–902.
29. Heidet M. Tranexamic acid for acute traumatic hemorrhage in emergency medicine: why not, but... *Eur J Emerg Med*. 2020;27:85–6.
30. Rouillet S, Labrousche S, Mouton C, et al. Lysis Timer: a new sensitive tool to diagnose hyperfibrinolysis in liver transplantation. *J Clin Pathol*. 2019;72:58–65.
31. Abuelkasem E, Lu S, Tanaka K, et al. Comparison between thrombelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation. *Br J Anaesth*. 2016;116:507–12.
32. Bezinover D, Dirkmann D, Findlay J. Perioperative Coagulation Management in Liver Transplant Recipients. *Transplantation*. 2018;102:578–92.
33. Steib A, Gengenwin N, Freys G, et al. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. *Br J Anaesth*. 1994;73:645–8.
34. Blasi A, Sabate A, Beltran J, et al. Correlation between plasma fibrinogen and FIBTEM thromboelastometry during liver transplantation: a comprehensive assessment. *Vox Sang*. 2017;112:788–95.
35. Sabate A, Blasi A, Costa M, et al. Assessment of rotational thromboelastometry for the prediction of red blood cell requirements in orthotopic liver transplantation. *Minerva Anesthesiol*. 2018;84:447–54.
36. Sabate A, Gutierrez R, Beltran J, et al. Impact of Preemptive Fibrinogen Concentrate on Transfusion Requirements in Liver Transplantation: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Am J Transplant*. 2016;16:2421–9.
37. Boylan JF, Klinck JR, Sandler AN, et al. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. *Anesthesiology*. 1996;85:1043–8, discussion 30A-31A.
38. Dalmau A, Sabaté A, Koo M, et al. Prophylactic use of Tranexamic Acid and Incidence of Arterial Thrombosis in Liver Transplantation. *Anesth Analg*. 2001;93:516.
39. Dalmau A, Sabaté A, Koo M, et al. The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: A comparative study. *Liver Transplant*. 2004;10:279–84.
40. Dalmau A, Sabaté A, Acosta F, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg*. 2000;91:29–34.
41. Warnaar N, Mallett SV, Klinck JR, et al. Aprotinin and the risk of thrombotic complications after liver transplantation: a retrospective analysis of 1492 patients. *Liver Transpl*. 2009;15:747–53.
42. Myles PS, Smith JA, Forbes A, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med*. 2017;376:136–48.
43. Yang QJ, Jerath A, Bies RR, et al. Pharmacokinetic modeling of tranexamic acid for patients undergoing cardiac surgery with normal renal function and model simulations for patients with renal impairment. *Biopharm Drug Dispos*. 2015;36:294–307.
44. Gerstein NS, Brierley JK, Windsor J, et al. Antifibrinolytic Agents in Cardiac and Noncardiac Surgery: A Comprehensive Overview and Update. *J Cardiothorac Vasc Anesth*. 2017;31:2183–205.
45. Society of Thoracic Surgeons Blood Conservation Guideline Task Force VA, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91:944–82.
46. Koster A, Faraoni D, Levy JH. Antifibrinolytic Therapy for Cardiac Surgery. *Anesthesiology*. 2015;123:214–21.
47. Kuiper GJAJM, van Egmond LT, Henskens YMC, et al. Shifts of Transfusion Demand in Cardiac Surgery After Implementation of Rotational Thromboelastometry-Guided Transfusion Protocols: Analysis of the HEROES-CS (HEmostasis Registry of patiEnts in Cardiac Surgery) Observational, Prospective Open Cohort Datab. *J Cardiothorac Vasc Anesth*. 2019;33:307–17.
48. Sigaut S, Tremey B, Ouattara A, et al. Comparison of Two Doses of Tranexamic Acid in Adults Undergoing Cardiac Surgery with Cardiopulmonary Bypass. *Anesthesiology*. 2014;120:590–600.
49. Horrow JC, Van Riper DF, Strong MD, et al. The dose-response relationship of tranexamic acid. *Anesthesiology*. 1995;82:383–92.
50. Fiechtner BK, Nuttall GA, Johnson ME, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg*. 2001;92:1131–6.
51. Dowd NP, Karski JM, Cheng DC, et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. *Anesthesiology*. 2002;97:390–9.
52. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358:2319–31.
53. Leal-Noval SR, Muñoz M, Asuero M, et al. The 2013 Seville Consensus Document on alternatives to allogenic blood transfusion. An update on the Seville Document. *Med Intensiva*. 2013;37:259–68.
54. Goldstone AB, Bronster DJ, Anyanwu AC, et al. Predictors and outcomes of seizures after cardiac surgery: a multivariable analysis of 2,578 patients. *Ann Thorac Surg*. 2011;91:514–8.
55. Sharma V, Katznelson R, Jerath A, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. *Anaesthesia*. 2014;69:124–30.
56. Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. *Can J Anaesth*. 2012;59:6–13.
57. Takagi H, Ando T, Umemoto T. All-Literature Investigation of Cardiovascular Evidence (ALICE) group. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. *J Cardiovasc Surg*. 2017;58:633–41.
58. Klein AA, Collier T, Yeates J, et al. The ACTA PORT-score for predicting perioperative risk of blood transfusion for adult cardiac surgery. *Br J Anaesth*. 2017;119:394–401.
59. PORT score for PeriOperative Risk of blood Transfusion in cardiac surgery by ACTA. Available at: https://qxmd.com/calculate/calculator_436/PORT-score-for-PeriOperative-Risk-of-blood-Transfusion-in-cardiac-surgery-by-ACTA. [accessed 20 June 2020].
60. Jerath A, Yang QJ, Pang KS, et al. Tranexamic Acid Dosing for Cardiac Surgical Patients With Chronic Renal Dysfunction. *Anesth Analg*. 2018;127:1323–32.
61. 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.
62. Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg*. 2013;74:1575–86.
63. Stein P, Studt J-D, Albrecht R, et al. The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients. *Anesth Analg*. 2018;126:522–9.
64. Neeki M, Dong F, Toy J, et al. Tranexamic Acid in Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study. *West J Emerg Med*. 2018;19:977–86.
65. Guyette FX, Brown JB, Zenati MS, STAAMP Study Group. Tranexamic Acid During Prehospital Transport in Patients at Risk for

- Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. *JAMA Surg.* 2020;156:11–20.
66. Lier H, Shander A. Tranexamic acid: the king is dead, long live the king! *Br J Anaesth.* 2020;124:659–62.
 67. Walker PF, Schobel S, Caruso JD, et al. Trauma Embolic Scoring System in military trauma: a sensitive predictor of venous thromboembolism. *Trauma Surg Acute Care Open.* 2019;4:e000367.
 68. Howard JT, Stockinger ZT, Cap AP, et al. Military use of tranexamic acid in combat trauma: Does it matter? *J Trauma Acute Care Surg.* 2017;83:579–88.
 69. Johnston LR, Rodriguez CJ, Elster EA, et al. Evaluation of Military Use of Tranexamic Acid and Associated Thromboembolic Events. *JAMA Surg.* 2018;153:169–75.
 70. Adair KE, Patrick JD, Kliber EJ, et al. TXA (Tranexamic Acid) Risk Evaluation in Combat Casualties (TRECC). *Trauma Surg Acute Care Open.* 2020;5:e000353.
 71. Benipal S, Santamarina JL, Vo L, et al. Mortality and Thrombosis in Injured Adults Receiving Tranexamic Acid in the Post-CRASH-2 Era. *West J Emerg Med.* 2019;20:443–53.
 72. Gillissen A, Henriquez D, van den Akker T, et al. The effect of tranexamic acid on blood loss and maternal outcome in the treatment of persistent postpartum hemorrhage: A nationwide retrospective cohort study. *PLoS One.* 2017;12, e0187555.
 73. Boutonnet M, Abback P, Le Saché F, et al. Tranexamic acid in severe trauma patients managed in a mature trauma care system. *J Trauma Acute Care Surg.* 2018;84:S54–62.
 74. Hu W, Xin Y, Chen X, et al. Tranexamic Acid in Cerebral Hemorrhage: A Meta-Analysis and Systematic Review. *CNS Drugs.* 2019;33:327–36.
 75. Bonet A, Madrazo Z, Koo M, et al. Thromboelastometric Profile and Acute Coagulopathy of the Polytraumatized Patient: Clinical and Prognostic Implications. *Cir Esp.* 2018;96:41–8.
 76. Moore HB, Moore EE, Liras IN, et al. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multi-center Evaluation of 2,540 Severely Injured Patients. *J Am Coll Surg.* 2016;222:347–55.
 77. Moore EE, Moore HB, Gonzalez E, et al. Postinjury fibrinolysis shutdown. *J Trauma Acute Care Surg.* 2015;78:S65–9.
 78. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost.* 2013;11:307–14.
 79. 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;73:719–29.
 80. Spinella PC, Thomas KA, Turnbull IR, TAMPITI Investigators. The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI): A Randomized, Double-Blind, Placebo-Controlled, Single-Center Trial. *Front Immunol.* 2020;11:2085.
 81. Moore EE, Moore HB, Gonzalez E, et al. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. *Transfusion.* 2016;56:S110–4.
 82. Longstaff C. Measuring fibrinolysis: from research to routine diagnostic assays. *J Thromb Haemost.* 2018;16:652–62.
 83. Muñoz M, Stensballe J, Ducloy-Bouthors A-S, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. *Blood Transfus.* 2019;17:112–36.
 84. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev.* 2015:CD007872.
 85. 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;116:641–8.
 86. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, et al. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. *Aust N Z J Obstet Gynaecol.* 2015;55:53–8.
 87. Sujata N, Tobin R, Kaur R, et al. Randomized controlled trial of tranexamic acid among parturients at increased risk for postpartum hemorrhage undergoing cesarean delivery. *Int J Gynaecol Obstet.* 2016;133:312–5.
 88. Sentilhes L, Winer N, Azria E, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med.* 2018;379:731–42.
 89. Levy JH, Koster A, Quinones QJ, et al. Antifibrinolytic Therapy and Perioperative Considerations. *Anesthesiology.* 2018;128:657–70.
 90. Le Roux P, Menon DK, Citerio G. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Neurocritical Care.* 2014;21:S1–26.
 91. Starke RM, Kim GH, Fernandez A, et al. Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. *Stroke.* 2008;39.
 92. Germans MR, Post R, Coert BA, et al. Ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA): study protocol for a randomized controlled trial. *Trials.* 2013;14:143.
 93. Harrigan MR, Rajneesh KF, Ardelt AA, et al. Short-term antifibrinolytic therapy before early aneurysm treatment in subarachnoid hemorrhage: effects on rehemorrhage, cerebral ischemia, and hydrocephalus. *Neurosurgery.* 2010;67:935–9, discussion 939–940.
 94. Hillman J, Fridriksson S, Nilsson O, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg.* 2002;97:771–8.
 95. Anker-Møller T, Trolborg A, Sunde N, et al. Evidence for the Use of Tranexamic Acid in Subarachnoid and Subdural Hemorrhage: A Systematic Review. *Semin Thromb Hemost.* 2017;43:750–8.
 96. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis.* 2013;35:93–112.
 97. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet.* 2018;391:2107–15.
 98. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet.* 2019;394:1713–23.