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Antifibrinolytic Therapy for Cardiac Surgery

An Update

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IN cardiac surgery, antifibrinolytic agents, including aprotinin and lysine analogs (ε-aminocaproic acid [EACA] and tranexamic acid [TXA]), have been extensively studied, and they decrease hemostatic activation, reduce bleeding, and decrease allogeneic blood product transfusions (table 1). This beneficial effect is important in the context of high-risk cardiac surgery, defined as complex surgeries including redo sternotomy, multiple valves replacement, ascending aorta or aortic arch procedures, or emergency surgery where the risk for major bleeding, massive blood product transfusion, and increased postoperative complications is important.[1] In the 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines, antifibrinolytic agents were strongly recommended (level of recommendation A) to be a part of the blood conservation approach.[2] After the marketing suspension of aprotinin in 2007, additional pharmacologic agents were further evaluated in clinical studies including ecallantide and MDCO-2010, while additional pharmacokinetic and safety data of other antifibrinolytic agents have been reported. We review the most recent developments in "antifibrinolytic therapy" in the context of cardiac surgery.

Aprotinin

Aprotinin is a serine protease inhibitor that structurally resembles tissue factor pathway inhibitor and inhibits multiple proteases including plasmin, kallikrein, trypsin, and activated factor XII. Since 2005, observational data with retrospective propensity-matched studies reported an increased incidence of adverse effects associated with the administration of aprotinin during cardiac surgery (table 2).[1,3–7] In the following months, an intense, sometimes emotional, debate regarding the validity of the reported data and the safety profile of aprotinin ensued. In 2007, preliminary data from the Blood conservation using Antifibrinolytics in a Randomized Trial (BART) study,[8] a prospective study performed in high-risk patients undergoing cardiac surgery, initially reported an increased mortality associated with aprotinin (6% 30-day mortality for aprotinin) compared with lysine analogs (3.9% for TXA and 4% for EACA), which was followed by a Food and Drug Administration (FDA) warning. In November 2007, following requests of German health authorities and the FDA, Bayer Healthcare (Leverkusen, Germany) announced the withdrawal of aprotinin from the market. Later, the European Medicines Agency (EMA), FDA's European counterpart, reported the opinion of a committee including experts in this field that reported a number of problems with the way the BART study was conducted, which cast doubt on the previous conclusions. Indeed, some major issues were highlighted: (1) the imbalances in the way blood-thinning medicines such as heparin were used, (2) inappropriate monitoring of the use of these drugs, and (3) unnecessary exclusion of patients from the initial analysis.* The Committee found that the BART study results were not replicated in other

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* Available at: http://www.ema.europa.eu/ema/pages/news_and_events/news/2012/02/news_detail_001447.jsp (Ref: EMA/CHMP/119704/2012). Accessed February 17, 2012.

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studies and that the overall data available showed that aprotinin's benefits are greater than its risks in restricted indication. In September 2011 Health Canada† and in February 2012 the EMA‡ lifted the suspension of aprotinin from the market. However, it was stated that aprotinin should only be given during the primary coronary artery bypass grafting (CABG) surgery and should be avoided in patients with preoperative renal dysfunction due to increased risks of postoperative renal failure and requirement for renal replacement therapy. In July 2012, Bayer Healthcare announced that all rights on aprotinin were transferred to the Nordic Group (Boston, Massachusetts).§ Recently, the BART investigators published an article that outlines their points of disagreement with criticisms published about the BART study and conclusions drawn by Health Canada.[9]

Although different meta-analyses have been recently published, they all include data from the BART study, an important concern based on EMA and other findings.[10,11] Walkden *et al.*[7] recently performed a case–control study of two cohorts that include more than 3,000 patients undergoing cardiac surgery in a single tertiary center. After adjustment for different baseline risk factors, the withdrawal of aprotinin was associated with a significant increase in 30-day mortality in the high-risk group (defined as complex surgeries including redo sternotomy, multiple valve replacement, ascending aorta or aortic arch procedures, or emergency surgery). In addition, more bleeding and transfusion requirements, higher incidences of surgical reexploration, and renal failure were noted. These observations regarding bleeding and transfusions were more relevant in a subgroup of high-risk patients. However, results obtained from case–control studies should be interpreted with caution considering the increased risk of bias associated with this study design.

Ecallantide

Ecallantide (previously DX-88) is a recombinant peptide that is a potent inhibitor of plasma kallikrein and is indicated for treatment of hereditary angioedema. After successful completion of a dose-ranging study for the use of DX-88 in cardiac surgical patients with low bleeding risk (CONSERV-1 trial), the highest of the evaluated doses was used in the CONSERV-2 trial (0.13 mg/kg over 5 min followed by a 0.14 mg kg^{-1} h^{-1} continuous infusion).[12] This study, performed in high-risk patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), compared blood loss and blood product utilization in patients randomized to receive

Table 1. Antifibrinolytic Agents: Drugs Description, Doses, and Mechanisms of Action

Drugs	Composition	Mechanism of Action	Elimination	Pharmacodynamics	Suggested Dosing in Adults	Approval
Aprotinin	Protein, isolated from bovine lung tissue	Protease inhibitor; reversibly complexes with the active sites of plasmin, kallikrein, and trypsin; inhibition of fibrinolysis, activated factor XIIa, thrombin-induced platelet activation, and inflammatory response	Predominantly proteolysis, <10% renal	Initial plasma half-life 150 min and terminal half-life 10 h	1. "Full dose": 2×10^6 KIU bolus patient, 2×10^6 KIU bolus CPB, continuous infusion of 5×10^5 KIU. 2. "Half dose": 1×10^6 KIU bolus patient, 1×10^6 KIU bolus CPB, continuous infusion of 2.5×10^5 KIU	Suspended since 2008; suspension lifted in Canada in 2011 and Europe in 2012; In the United States still suspended
Tranexamic acid	Synthetic lysine analog	Antifibrinolytic; competitive inhibition of the activation of plasminogen to plasmin	Renal	Plasma half-life 3 h	1. "High dose": 30 mg/kg bolus patient, 2 mg/kg CPB, and continuous infusion of 16 mg/kg; 2. "Low dose": 10 mg/kg bolus patient, 1–2 mg CPB, and continuous infusion of 1 mg/kg	United States, Canada, Europe
ε-Aminocaproic acid	Synthetic lysine analog	Antifibrinolytic: competitive inhibition of the activation of plasminogen to plasmin	Renal	Plasma half-life 2 h	100 mg/kg bolus patient, 5 mg/kg CPB, and continuous infusion of 30 mg/kg	United States, Canada

CPB = cardiopulmonary bypass; KIU = Kallikrein International Unit.

† Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/res/eapgce_trasylol-eng.php. Accessed September 21, 2011.

‡ Available at: http://www.ema.europa.eu/ema/pages/news_and_events/news/2012/02/news_detail_001447.jsp (Ref: EMA/CHMP/119704/2012). Accessed February 17, 2012.

§ Available at: http://www.nordicpharmagroup.com/art-4-4-39-european-commission-approved-reinstatement-of-aprotinintrasylol-marketing-authorisation-in-european-union.html. Accessed February 17, 2012.

Table 2. Summary of Studies That Assessed the Safety of Aprotinin

Authors	Year	Design	Aprotinin (n)	Control (n)	Death	Kidney Dysfunction	Kidney Failure
Karkouti *et al*.[2]	2006	Case–control propensity	449	TXA: 449	NS	↑	NS
Mangano *et al*.[3]	2006	Observational propensity	1,295	TXA: 822; EACA: 823	↑	↑	↑
Schneeweiss *et al*.[4]	2008	Retrospective	33,517	EACA: 44,682	↑	NS	NS
Shaw *et al*.[5]	2008	Retrospective	1,343	EACA: 6,776	↑	↑	↑
Fergusson *et al*.[8]	2008	RCT	781	TXA: 770; EACA: 780	↑*	NS	NS
Karkouti *et al*.[6]	2010	Retrospective propensity	1,017	TXA: 1,544	NS	NS	↑†
Walkden *et al*.[7]	2013	Case–control propensity	1,754	TXA: 1,754	NS	↓‡	↓‡

↑ is increased with aprotinin; ↓ is increased in control.

* $P = 0.05$ for aprotinin *vs*. TXA and $P = 0.06$ for EACA. † Aprotinin significantly increased the incidence of acute kidney injury in low-risk and intermediate-risk patients ($P = 0.006$), and no difference observed in high-risk patients ($P = 0.8$). ‡ Difference observed in the whole population, but no difference when considering only high-risk patients.

EACA = ε-aminocaproic acid; NS = not statistically significant; RCT = randomized controlled trial; TXA = tranexamic acid.

either ecallantide or two different TXA doses. The study had to be terminated prematurely due to an increased mortality observed in the ecallantide arm. In addition, ecallantide was less effective for reducing postoperative blood loss and blood product transfusion requirement.

MDCO(CU)-2010

The serine proteinase inhibitor MDCO-2010 (previously CU-2010) is a synthetic molecule that actively inhibits plasmin, plasma kallikrein, coagulation factors such as factor Xa and factor XIa, and activated protein C. *In vitro*, the drug was as effective as aprotinin inhibiting fibrinolysis and 10-fold more potent than TXA.[13] MDCO-2010 was recently studied in a phase II-b clinical trial performed in patients undergoing CABG surgery with CPB to assess pharmacokinetics and effects on coagulation, chest tube drainage, and transfusion requirements.[14] Increasing MDCO-2010 doses (n = 24) were compared with placebo (n = 8) and reported a predictable pharmacokinetic profile with a significant reduction in transfusion rates in the MDCO-2010 arms, a reduction of blood loss in the groups that received the three highest doses, and acceptable initial safety results. However, the subsequent multicenter study (ClinicalTrials.gov NCT01530399) was terminated prematurely in October 2012 after inclusion of 44 of the 90 patients planned due to an increased number of serious adverse events in the treatment groups. The characteristics and the causes of the safety issues and any potential link to the study drug are still under investigation.[14]

Lysine Analogs: TXA and EACA

Lysine analogs including TXA and EACA are the most extensively used antifibrinolytic agents. Data on the pharmacokinetics and safety issues have significantly evolved since the withdrawal of aprotinin from marketing and will be summarized as follows.

Tranexamic Acid

Pharmacodynamics. Although the pharmacokinetic properties of TXA have been previously reported in cardiac surgery, the "optimal" plasma concentration that should be targeted to maximally inhibit fibrinolysis is not known, and dosing strategies vary widely. On the basis of the initial investigations from the 1970s, two basic target concentrations have been advocated. A lower concentration of approximately 10 to 20 μg/ml, which is thought to inhibit approximately 80% of fibrinolysis, and a high concentration of approximately 100 μg/ml, which should completely inhibit fibrinolysis.[15] In a recent *in vitro* investigation, hyperfibrinolysis was induced by addition of high-dose tissue-type plasminogen activator to both cord blood obtained from full-term cesarean sections and healthy adults. The degree of fibrinolysis was measured by using TEG® (Hemostasis System; Haemoscope Corporation, USA).[16] In this study, the TXA concentration to effectively inhibit fibrinolysis was 6.54 μg/ml (95% CI, 5.19 to 7.91 μg/ml) for neonatal blood and 17.5 μg/ml (95% CI, 14.6 to 20.5 μg/ml) for adult blood.

When interpreting TXA studies, extensive dosing variability is reported among trials. Different established target concentrations in adults were translated into a low-dose TXA protocol, corresponding to a 10-mg/kg loading dose (a loading dose of 1 to 2 mg/kg into the CPB prime) and 1 mg kg^{-1} h^{-1} infusion during surgery, and a high-dose protocol (as used in the BART study[8]) with a 30 mg/kg loading dose, 2 mg/kg into the CPB prime, and constant infusion of 16 mg kg^{-1} h^{-1} during surgery.[15] However, two recent investigations[17,18] demonstrated that these protocols resulted, in most patients, in plasma concentrations that largely exceeded the target plasma concentrations at steady state: with 28 to 55 μg/ml in the "Low-dose" group and 114 to 209 μg/ml in the "high-dose" groups (fig. 1).[18]

By using a TXA concentration of 20 μg/ml as the target dose, Grassin-Delyle *et al*.[19] used a complex pharmacokinetic modeling to calculate a dosing regimen for TXA in small children undergoing cardiac surgery (fig. 1). According

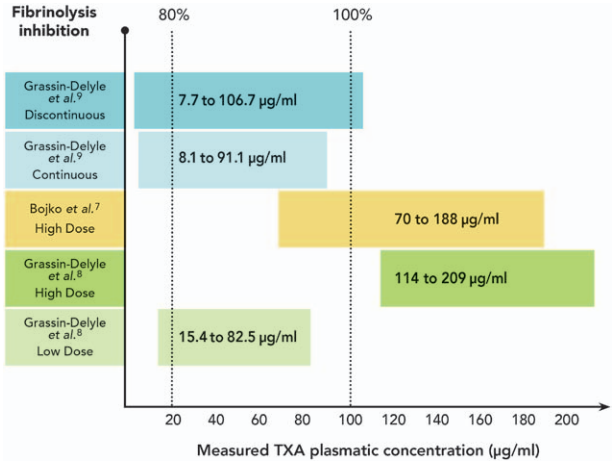

Fig. 1. Tranexamic acid (TXA) plasma concentration measured after administration of different dose schemes in adults and pediatrics. High dose: 30 mg/kg loading dose, 2 mg/kg in cardiopulmonary bypass (CPB), and 16 mg kg^{-1} h^{-1}. Low dose: 10 mg/kg loading dose, 1 mg/kg in CPB, and 1 mg kg^{-1} h^{-1}. Continuous: 10 mg/kg loading dose, 10 mg/kg in CPB, and 1 mg kg^{-1} h^{-1}. Discontinuous: 10 mg/kg loading dose, 10 mg/kg in CPB, and 10 mg/kg at the end of CPB.

to this model, a bolus of 6.4 mg/kg followed by a continuous infusion of 2.0 to 3.1 mg kg^{-1} h^{-1} would result in stable effective TXA concentrations throughout surgery.

Inhibition of Fibrinolysis during Cardiac Surgery. However, the determination of the target concentration and assessment of complete inhibition of fibrinolysis are largely dependent on the assays used, and an *in vitro* test system might not completely reflect *in vivo* occurrences during cardiac surgery. A recent preliminary randomized controlled study compared the effects of the high-dose (30 mg/kg followed by 16 mg kg^{-1} h^{-1}) *versus* a modified low-dose TXA (5 mg/kg followed by 5 mg kg^{-1} h^{-1}) regimen to placebo on fibrinolysis by using TEG® (Hemostasis System; Haemoscope Corporation) and D-dimer measurements.[20] The lysis rate measured at 30 min on TEG® did not reveal any significant difference between the three groups throughout the different time points of measurement. However, the D-dimer levels in the placebo group increased continuously during the procedure, whereas D-dimer generation was completely inhibited in both treatment groups. In a recent study performed in children undergoing cardiac surgery who received a TXA loading dose of 10 mg/kg followed by a continuous infusion of 10 mg kg^{-1} h^{-1}, usually defined as the lower dose scheme in children,[21] the addition of extremely high tissue-type plasminogen activator concentrations *in vitro* (1,535 units/ml) was not associated with any fibrinolytic activation when measured on rotational thromboelastometry (ROTEM®; Tem International GmbH, Germany) parameters.[22] These results confirmed that the use of what we currently considered as low-dose protocols is associated with a powerful inhibition of fibrinolysis.

Dosing Protocols and Clinical Efficacy. Although recent evidence suggested that the lower dose scheme could be used to effectively inhibit fibrinolysis activation, the clinical efficacy of these low-dose protocols in terms of reduction of blood loss and transfusion requirements remains to be demonstrated. Sigaut *et al.* recently randomized 600 patients undergoing cardiac surgery with CPB to receive either a high-dose (30 mg/kg loading dose, 2 mg/kg in CPB, and 16 mg kg^{-1} h^{-1}) or a low-dose (10 mg/kg loading dose, 1 mg/kg in CPB, and 1 mg kg^{-1} h^{-1}) TXA protocol. Interestingly, the authors stratified patients between two groups corresponding to high (defined as patients receiving a dual antiplatelet at any time within 5 days of surgery, repeat coronary artery bypass graft, repeat valve surgery, combined coronary artery bypass graft and valve surgery, multiple valve surgery, surgery of the aorta, intracardiac tumor ablation, and surgery for endocarditis) or low bleeding risks (all the others).[15] Although there was no difference in transfusions until day 7 between the two TXA doses in the general population, less reexploration for bleeding was observed in the high-risk subgroup that received a high TXA dose. In addition, the percentage of patients transfused with fresh-frozen plasma and platelet concentrates as well as the total number of these components transfused decreased in the same high-dose group.

In a nonrandomized, single-center registry that included approximately 1,200 patients, Waldow *et al.*[23] assessed the clinical efficacy of three different TXA dose regimens (1 g bolus, 5 g bolus, and 3 g bolus + 15 mg kg^{-1} h^{-1} infusion during the aortic cross-clamping). Patients and procedural characteristics were comparable, postoperative blood loss did not differ between groups, and no difference in the incidence of myocardial infarction, stroke, and 30-day mortality was noted.

Although derived from trauma, another bleeding context, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial randomized more than 20,000 traumatized patients to received either TXA or placebo appears to be remarkable in the context of TXA dose and clinical efficacy.[24] Although there are clear differences between the controlled scenario of cardiac surgery and the rather uncontrolled condition of trauma, some similarities are noteworthy, such as the large (surgical) trauma with massive release of tissue factor, the hemodilution, and the hypothermia. In the CRASH-2 patients with massive bleeding or risk of massive bleeding due to major trauma, the administration of TXA (1-g loading dose followed by an infusion of 1 g over 8 h) was associated with a significant reduction in mortality due to hemorrhage (relative risk, 0.85; 95% CI, 0.76 to 0.96; $P = 0.007$). This large study first reported that early administration of a low TXA dose, which is comparable with the low-dose TXA protocol in cardiac surgery, reduced mortality from 16 to 14.5%.

Safety

Convulsive Seizures. In 2010, two Canadian cardiac centers reported an increased incidence in clinical seizures after the

Table 3. TXA: Seizures and All-cause Mortality

	TXA Dose	Patients (n)	Seizures			Mortality		
			Control (%)	TXA (%)	*P* Value	Control (%)	TXA (%)	*P* Value
Sander *et al.*[26]	50 mg/kg bolus; 50 mg/kg CPB	Total = 893; TXA = 336; Aprot = 557	0.9	2.7	0.05	6.9	8.6	0.34
		Open: Heart = 320, TXA = 105, Aprot=215	1.9	6.7	0.04	7.5	16.2	0.02
Koster *et al.*[27]	1 g bolus/0.5 g CPB/infusion 0.2 g/h	Total: N = 4,883, TXA = 1,029, Aprot = 3,854	1.2	1.8	0.32	1.1	1.5	0.446
		Open: Heart = 2,779, TXA = 636, Aprot = 2,143	1.3	3.0	0.04	1.7	5.7	<0.001
Makhija *et al.*[28]	10 mg/kg bolus/infusion 1 mg kg^{-1} h^{-1}	TXA = 31, EACA = 30	3.3	10	0.19	0.0	6.4	0.49
Martin *et al.*[29]	2 g bolus/2 g CPB/ Infusion 0.5 g/h	TXA = 275, EACA = 329	3.3	7.6	0.019	5.0	4.7	0.899
Martin *et al.*[30]	50 mg/kg boluses before and after CPB; 100 mg/100 ml CPB prime	TXA = 114, EACA = 120	0.8	3.5	0.203	3.3	2.6	0.999

Aprot = aprotinin; CPB = cardiopulmonary bypass; EACA = ε-aminocaproic acid; TXA = tranexamic acid.

change from aprotinin to TXA although the dosing of TXA varied largely among patients (61 to 259 mg/kg).[25] Advanced age and open-heart procedures were found as risk factors. These results were confirmed in two retrospective studies that showed an increased incidence of clinical seizures associated with the use of TXA, which was more pronounced in patients undergoing open-heart procedures (table 3).[26,27] In a recent study that compared 31 patients who received TXA (10 mg/kg followed by 1 mg kg^{-1} h^{-1}) with 30 patients who received EACA (50 mg/kg followed 25 mg kg^{-1} h^{-1}) during thoracic aortic surgery, the risk of seizure was not significantly increased with TXA compared with EACA (relative risk, 0.49; 95% CI, 0.09 to 2.73).[28] However, in another study including 604 patients, Martin *et al.*[29] reported that TXA (2 g, 0.5 g/h, and 2 g in CPB) significantly increased the incidence of seizures (7.6%) compared with EACA (10 g, 2.5 g/h, and 10 g) (3.3%, $P = 0.019$). These results were not confirmed in children undergoing cardiac surgery in another study that compared 114 children undergoing cardiac surgery that received TXA (50 mg/kg, 100 mg/ml in CPB, and 50 mg/kg at the end of CPB) with 120 that received EACA (75 mg/kg, 75 mg/ml in CPB, and 75 mg/kg at the end of CPB), children exposed to TXA had a increased incidence of seizure, but relative risk was not statistically significant (relative risk, 4.21; 95% CI, 0.48 to 37.11).[30]

Although the underlying mechanisms are not fully elucidated, Kratzer *et al.*[31] suggested that TXA enhances neuronal excitation by antagonizing inhibitory γ-aminobutyric acid (GABA) neurotransmission. Lecker *et al.*[32] showed that TXA inhibits neural glycine receptors, whereas inhibition of the inhibiting neurotransmitter glycine is an established cause of seizures.

Viewing the similarities in the chemical structures of TXA, GABA, and glycine, it is conceivable that an interaction of TXA with both GABA and glycine receptors contributes to the increase in clinical seizures (fig. 2) observed when TXA is given. However, viewing the chemical structure of EACA and its close similarity to GABA and glycine as well, it is noteworthy that it has not been reported to produce neurological side effects (fig. 2). The authors also showed that isoflurane and, to a lesser extend, propofol are able to reverse the TXA effect on the glycine receptor.[32] Interestingly, the TXA peak concentration observed in the cerebral spinal fluid was reached approximately 5 h after the plasma peak concentration. These pharmacokinetic properties might explain the 7- to 8-h delay reported in a large retrospective study between TXA administration and the development of clinical seizures after cardiac surgery.[33] However, it is interesting to note that TXA is also approved for excessive menstrual bleeding at a dose of approximately 4 g/day for 5 days of therapy, with a favorable safety and efficacy profile.[34] Therefore, although biochemical mechanisms may well explain the association between TXA and seizures, the special population of cardiac surgical patients and particularly the condition of CPB (with possible interactions with the blood–brain barrier) might also have a large impact on this observation.

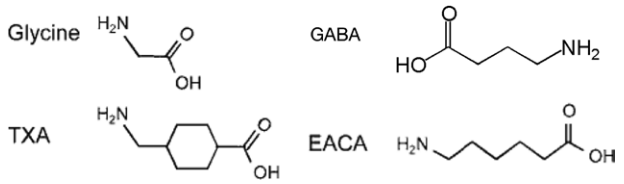

Fig. 2. Chemical structure of antifibrinolytics, γ-aminobutyric acid (GABA), and glycine. EACA = ε-aminocaproic acid; TXA = tranexamic acid. Adapted, with permission of American Society for Clinical Investigation, from Lecker *et al*. J Clin Invest 2012; 122:4654–66[32]; permission conveyed through Copyright Clearance Center, Inc. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Despite the potential relation between TXA and seizures, the clinical impact of TXA-induced clinical seizures is difficult to determine. In a large retrospective clinical study performed in patients who underwent cardiac surgery with CPB without TXA, the incidence of seizures was 1% and associated with a five-fold increase in mortality.[35] A large retrospective study including more than 11,500 cardiac surgical patients including patients who have received TXA (30 mg/kg, followed by a 16 mg kg^{-1} h^{-1}, with 2 mg/kg added to the CPB circuit prime) reported a 0.9% incidence of clinical seizures associated with a 2.5 times higher in-hospital mortality in those patients.[33] Again, apart from patient's age and morbidity, complexity of surgical procedures, and condition of the aorta, TXA administration was a strong independent predictor of seizures. However, the exact relation between TXA-induced seizures and increased mortality is not clear. Understanding the current molecular mechanism of TXA-associated clinical seizures, it seems unlikely that the temporary receptor malfunction leads to a structural brain damage, multiorgan failure, and death. It is more likely that regional or topical cerebral hypoperfusion and tissue injury, which may mirror other tissue/end-organ damage, results in a regional/topical disturbance of the blood–brain barrier and greater susceptibility toward the effects of TXA. A recently published 1-yr follow-up of three patients who presented seizures after TXA treatment without experiencing any persisting neurological disturbance might support this hypothesis.[36]

Mortality. Although the clinical consequences of TXA-associated clinical seizures remain to be elucidated, the two- to three-fold increased mortality in patients undergoing open-heart procedures who received TXA should be interpreted carefully (table 3).[26,27] The retrospective data for these investigations and the huge intercenter variability on complication's rates limit the significance of the observation. However, these studies included a relatively large number of patients, but further well-designed prospective trials are urgently needed.

ε-Aminocaproic Acid. ε-Aminocaproic acid is a lysine analog used in cardiac surgery, mostly in the United States. However, pharmacokinetic data are sparse, and only limited data about safety and efficacy, obtained mostly from small clinical trials, are available. In 2006, Kikura *et al.*[37] randomized 100 patients to receive either EACA or the same infusion of normal saline. In the EACA group, patients received 100 mg/kg EACA as a loading dose over 20 to 30 min after endotracheal intubation, followed by a continuous infusion of 1 g/h during surgery, and 10 g as a loading dose given into the CPB circuit prime solution. The placebo group received identically appearing normal saline. The authors concluded that prophylactic administration of EACA reduced postoperative blood loss volume by 30% but did not significantly reduce perioperative blood product administration. In a small randomized, double-blinded, placebo-controlled, and noninferiority trial including 78 patients undergoing primary CABG, Greilich *et al.*[38] compared a loading dose of 100 mg/kg EACA and 5 g for the CPB prime followed by a continuous infusion of 30 mg kg^{-1} h^{-1} with a full "Hammersmith" aprotinin dose and placebo. They observed a significant reduction in D-dimer concentrations and 24-h chest tube drainage in the treatment groups, whereas no difference between aprotinin and EACA was noted. In one small prospective trial performed in 64 patients undergoing aortic surgery, and one only retrospective study including 604 patients undergoing a variety of different cardiac procedures, the safety profile of EACA was compared with TXA.[28,29] In both studies, the incidence of postoperative renal dysfunction was significantly increased in patients receiving EACA.

In pediatric patients, Sarupria *et al.*[39] compared two dosing EACA protocols with placebo in 120 patients undergoing correction of the Tetralogy of Fallot. The discontinuous protocol consisted in a three 100 mg/kg boluses: one after induction of anesthesia, one at CPB initiation, and the last one after protamine infusion. The continuous protocol was based on a 75 mg/kg EACA bolus after induction of anesthesia followed by a 75-mg kg^{-1} h^{-1} continuous infusion until chest closure. Both treatment arms were effective in reducing the postoperative bleeding and transfusion requirements, whereas continues infusion protocol was most effective in this regard. There were no differences among the three groups in the need for surgical reexploration, incidence of renal failure, neurologic complications, length of intensive care unit stay, and mortality among the three groups. However, the continuous protocol was further associated with a significant reduction in the duration of mechanical ventilation.

Two retrospective studies in infants less than 1 yr old reported an increase in postoperative chest tube drainage after arterial switch operation after the shift from aprotinin to EACA. In one study including 139 infants who received repeated EACA boluses (75 mg/kg bolus before and after CPB and 75 mg/kg per 100 ml of CPB prime),[40] differences in postoperative blood loss were moderate (18 ml/kg per 24 h for aprotinin *vs.* 23 ml/kg per 24 h for EACA) and not associated with an increase in transfusion requirement and surgical reexploration incidences. In the other study, Scott *et al.*[41] compared 77 infants who

received EACA with a 75-mg/kg loading dose for the patient and into the CPB prime followed by a continuous infusion of 75 mg kg^{-1} h^{-1} with children who received aprotinin. The authors reported a significant increase in uncontrolled bleeding in infants treated with EACA, associated with increased incidence of activated factor VII (25 *vs.* 10%) administration, and higher need for surgical reexploration (27 *vs.* 10%).

Summary

"Antifibrinolytic agents" reduce fibrinolysis in cardiac surgery, blood loss, chest tube drainage, and transfusion requirements. Although, the mechanisms of action are complex, and involve various biochemical pathways, they are not completely elucidated and have clinically relevant side effects. Recent studies and drug development evaluating other novel serine protease inhibitors were terminated prematurely due to an increased incidence of adverse events. Although aprotinin will be reintroduced in certain countries, its use will be restricted to limited indications. Before these indications can be extended again to complex surgical procedures, additional safety studies will be needed. Despite the extensive use of EACA in the United States, clinical safety and efficacy data are limited, and there are increased risks for postoperative renal dysfunction after EACA administration. On the basis of the reports for aprotinin and TXA, which have been extensively used for many years before significant side effects were associated with their use, we believe that the safety and efficacy profile of EACA needs further investigation. The relation between TXA dosing and clinical seizures and their impact on clinical outcomes need further investigations. Open-heart procedures may play a role in this regard as the incidence of seizures and an increased mortality had been associated with TXA in this patient population. The large CRASH-2 trial of TXA in trauma patients showed that a low-dose TXA protocol (approximately 2 g in adults) in high-risk patients translated into a reduction of mortality. Because of dose-dependent side effects of TXA, we believe that a low-dose TXA protocol should be preferentially used in cardiac surgery.

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Competing Interests

Dr. Levy serves on a steering committee for Boehringer-Ingelheim (Ingelheim am Rhein, Germany), CSL Behring (King of Prussia, Pennsylvania), and Medicines Company (Parsippany, New Jersey). The other authors declare no competing interests.

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