Antifibrinolytic agents in current anaesthetic practice

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Summary. Antifibrinolytic drugs have become almost ubiquitous in their use during major surgery when bleeding is expected or commonplace. Inhibition of the fibrinolytic pathway after tissue injury has been consistently shown to reduce postoperative or traumatic bleeding. There is also some evidence for a reduction of perioperative blood transfusion. However, evidence of complications associated with exaggerated thrombosis also exists, although this appears to be influenced by the choice of the individual agent and the dose administered. There is controversy over the use of the serine protease inhibitor aprotinin, whose license was recently withdrawn but may shortly become available on the market again. In the UK, tranexamic acid, a tissue plasminogen and plasmin inhibitor, is most commonly used, with evidence for benefit in cardiac, orthopaedic, urological, gynaecological, and obstetric surgery. In the USA, α-aminocaproic acid, which also inhibits plasmin, is commonly used. We have reviewed the current literature for this increasingly popular class of drugs to support clinical judgement in daily anaesthetic practice.

Keywords: antifibrinolytic agents; cardiac surgical procedures; hepatectomy; intracranial haemorrhages; liver transplantation; orthopaedics; postoperative haemorrhage; post partum haemorrhage; wounds and injuries.

Bleeding after major surgical interventions and trauma is associated with increased morbidity and mortality. Haemorrhage and subsequent transfusion of red blood cells as well as tissue trauma and surgical techniques like cardiopulmonary bypass (CPB) can lead to significant coagulopathy. Consequently, there is need not only for blood transfusion but also for the substitution of coagulation components. This often requires the use of allogeneic blood products with specific risks like haemolytic and allergic reactions, transfusion related lung injury, bacterial contamination, virus transmission, and blood group mismatch. In addition, postoperative haemorrhage can prompt further unplanned surgical interventions. Both re-exploration and transfusion are associated with an increased incidence of infection, mortality and prolonged length of intensive care and hospital stay.1 2 Ultimately, postoperative haemorrhage not only affects patient outcomes, but also results in significant healthcare costs. This is especially relevant as a steady increase in higher risk cases and more complex surgical procedures are leading to a higher demand for blood products, which cannot always be met by supply. Therefore, a multimodal approach to blood conservation, involving surgical, anaesthetic, and pharmacological considerations, is required to reduce perioperative morbidity and to use the available resources judiciously.3

One target of a modern blood conservation strategy is the fibrinolytic system. Fibrinolysis is a physiological surface-bound process where activated plasminogen removes excess fibrin deposition at the site of vascular injury, which improves localization of the fibrin clot and wound healing. There are at least 50 known cleavage sites in the fibrin molecule leading to the formation of fibrin degradation products and D-dimers. Plasminogen is a single chain serine protease characterized by an active site and five Kringle domains, four of which bind to lysine residues in interacting molecules. Physiological inhibitors of plasminogen are the two serine proteases tissue plasminogen activator (tPA) and urinary plasminogen activator. Physiological inhibition of fibrinolysis occurs as inhibition of plasminogen via plasminogen activator inhibitors (PAI-1 and PAI-2) and active centre inhibition of plasmin via polyspecific serine protease inhibitors such as α-2-antiplasmin.4 5

Activation of the fibrinolytic system can be quantified by laboratory-based assays (e.g. euglobulin lysis time, plasmin-α-2-antiplasmin enzyme-linked immuno sorbent assay, D-dimers) or point-of-care tests (clot lysis in viscoelastic assays, such as TEG and RoTEM). However, laboratory assays may not be used routinely, and bedside tests are not fully validated yet. Most trials have used clinical parameters or empirical treatment.

Therapeutic inhibition of fibrinolysis has been shown to reduce bleeding in various clinical situations associated with activation and dysregulation of the fibrinolytic pathway, including cardiac surgery, trauma, liver surgery, neurosurgery, and obstetric haemorrhage. The agents used in this indication are the serine protease inhibitor aprotinin and the lysine analogues tranexamic acid and α-aminocaproic acid.

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The aim of this review was to assess the role of antifibrinolytic agents as a part of a modern blood conservation strategy for patients at risk of haemorrhage after major cardiac or non-cardiac surgery, trauma, or childbirth. It summarizes the literature of the past decade with specific relevance to daily anaesthetic practice, to support clinical decision-making and to enhance further discussion of the topic. A summary of relevant publications is provided in Tables 1–5.

Aprotinin

For many years, aprotinin, a non-specific serine protease inhibitor extracted from bovine lung, was widely used as an antifibrinolytic agent, and became the most popular such drug. It is thought to act by inhibition of the serine protease plasmin that attaches to the fibrin polymer via lysine residues on the target molecules. The polypeptide aprotinin (molecular weight 6500) is an unspecific Kunitz-type protease inhibitor, targeting the active centre of serine proteases. Besides plasmin it also inhibits trypsin, kallikrein, elastase, urokinase, and thrombin. Therefore, it can interfere with contact factor activation [factor XII (FXII)], fibrinolysis, the renin-angiogen system, and neutrophil activation. As a result, the effects of aprotinin on the coagulation system can be anti-coagulatory because of an inhibition of the intrinsic cascade (FXII and thrombin), and pro-coagulatory because of antifibrinolytic action. Preservation of the glycoprotein I b platelet membrane receptor is also attributed to aprotinin, which may protect platelets against CPB induced activation. 6 7 An anti-inflammatory effect of aprotinin was proposed, based on reduced leucocyte activation and cytokine release (such as tumour-necrosis factor alpha or interleukins) after CPB. 8–12 Animal studies suggest that this reduced inflammatory response could even improve the neurological outcome after cerebral ischaemia during CPB. 13 However, the data remain uncertain, and a meta-analysis could not confirm an anti-inflammatory effect of aprotinin in cardiac surgery. 14

First described in the 1930s, aprotinin was introduced into clinical practice in the 1950 for the treatment of hyperfibrinolytic conditions such as pancreatitis. It became almost ubiquitous in complex cardiac surgery in the early 1990s after an impressive reduction of blood loss was demonstrated in 22 patients undergoing open heart surgery. 15 In adult cardiac surgery, aprotinin was mostly dosed according to the full ‘Hammersmith’ regimen with $2 \times 10^6$ kallikrein inhibitor units (KIU) as a loading dose and $2 \times 10^6$ KIU into the prime solution of the bypass circuit, followed by an infusion of 500 000 KIU h$^{-1}$. 15 The bovine polypeptide aprotinin carries a risk of anaphylactic reactions especially in cases of re-exposure within 6 months. A database analysis of >12 000 cardiac cases demonstrated an incidence of 0.09% (95% CI 0.05–0.16%) for primary exposure and 1.5% (95% CI 0.86–2.6%) for re-exposure. The highest rate of hypersensitivity reactions occurred between Day 4 and Day 30 after first exposure (7.4%, 95% CI 2.4–18.8%). A test dose of $10^6$ KIU at least 10 min before the initial bolus dose is recommended by the manufacturer, but did not prevent severe reactions in this dataset. 16 Aprotinin is metabolized by lysosomal enzymes and excreted renally with a terminal elimination half-life of 5–10 h. For many years, aprotinin seemed to be an almost ideal drug as it reduced postoperative blood loss and transfusion without major side-effects. 17 However, its relative benefit was seriously challenged in 2006 when Mangano and colleagues compared aprotinin with other antifibrinolytic agents and placebo in an observational study of more than 4000 patients undergoing myocardial revascularization. They reported a doubling of risk for renal failure and a 55% increase in perioperative myocardial infarction and heart failure in the aprotinin group. 18 However, this study was controversial as it was retrospective, and may have been subject to multicentre bias.

The era of aprotinin seemed to come to an end with the publication of the BART trial (Blood Conservation Using Anti-fibrinolytics in a Randomized Trial). Marketing was temporarily suspended in November 2007 when the first data became available, and aprotinin was then permanently withdrawn from the market in May 2008. In this large multicentre study, Fergusson and colleagues randomly assigned 2331 high-risk cardiac surgical patients to receive prophylactic aprotinin, e-aminocaproic acid, or tranexamic acid. Even though the risk of bleeding was lowest in the aprotinin group, mortality was increased in patients receiving aprotinin compared with the combined rate for the two lysine analogues [risk ratio (RR) 1.53; 95% CI, 1.06–2.22], which led to early termination of the trial. 19 A recent Cochrane review concluded that, although aprotinin appeared to be more effective in reducing blood loss and the need for blood transfusion, it was associated with higher risk of death. 20 Very recently, the data of the BART trial have been called into question. In addition, Health Canada, published a safety review of aprotinin in September 2011, 21 which concluded that the benefit of using aprotinin in non-complex cardiac surgery might outweigh the risk. After this, aprotinin was made available again in Canada for restricted use in isolated coronary bypass graft surgery. 22 The European Medicines Agency also recommended lifting the suspension of aprotinin in February 2012 after a review of the risks and benefits of antifibrinolytic drugs. 23 Those decisions are based on several further perceived shortcomings of the BART trial. First, only patients with high-risk cardiac surgical procedures (i.e. mitral valve surgery, combined coronary artery bypass graft and valve surgery, surgery on multiple valves, redo, and aortic surgery) were included and data might therefore not be applicable to all cardiac surgical patients and also not to other surgical areas. That might explain the high mortality rates reported compared with other published data. 17 24 Secondly, the trial was not targeting mortality as a primary outcome parameter and was not designed and powered for that endpoint. In addition, because the trial was terminated early, it did not reach the patient number calculated in a power analysis to detect a difference in postoperative bleeding. Finally, there are concerns about a possible underdosing of heparin, as celite activated clotting time is prolonged in the presence of aprotinin.
Table 1  Cardiac surgery: AP, aprotinin; TXA, tranexamic acid; EACA, ε-aminocaproic acid; OPCAB, off-pump coronary artery bypass

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Study population</th>
<th>Main findings</th>
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<tr>
<td>Mangano</td>
<td>2006</td>
<td>4374</td>
<td>Prospective, observational AP was associated with a higher risk of renal, cardiovascular and cerebrovascular events compared with TXA and EACA in cardiac surgery</td>
</tr>
<tr>
<td>Fergusson and colleagues</td>
<td>2008</td>
<td>2331</td>
<td>Double-blinded, multicentre RCT Trend to lower blood loss but higher 30-day mortality in AP group compared with TXA and EACA combined in complex cardiac surgery; trial terminated early</td>
</tr>
<tr>
<td>Henry and colleagues</td>
<td>2011</td>
<td>&gt; 25 000</td>
<td>Cochrane systematic review of 252 RCTs AP, TXA, and EACA reduced blood transfusion with AP being more effective; AP reduced the need for re-operation; higher risk for myocardial infarction and death for AP compared with lysine analogues</td>
</tr>
<tr>
<td>Karkouti and colleagues</td>
<td>2010</td>
<td>15 365</td>
<td>Single-centre, retrospective cohort study Higher risk for acute kidney injury (OR 1.5; 95% CI 1.1–2.1) with AP vs TXA in cardiac surgery; trend towards lower mortality for AP only in high-risk patients (OR 0.6; 95% CI 0.3–1.0)</td>
</tr>
<tr>
<td>Sander and colleagues</td>
<td>2010</td>
<td>893</td>
<td>Retrospective single-centre study Higher blood loss and higher rate of re-thoracotomies in the TXA group; higher rate of ischaemic strokes with AP; higher mortality with TXA in subgroup of open heart procedures</td>
</tr>
<tr>
<td>Later and colleagues</td>
<td>2009</td>
<td>298</td>
<td>Double-blind, randomized, placebo-controlled Both AP and TXA reduced blood loss and transfusion requirements compared with placebo in non-complex cardiac surgery; AP was more effective in reducing blood loss (mean difference 155 ml, 95% CI 60–260)</td>
</tr>
<tr>
<td>Greilich and colleagues</td>
<td>2009</td>
<td>78</td>
<td>Double-blind, randomized, placebo-controlled Both EACA and AP reduced 24 h blood loss after CABG compared with placebo; EACA was non-inferior to AP</td>
</tr>
<tr>
<td>Pasquali and colleagues</td>
<td>2012</td>
<td>22 258</td>
<td>Retrospective database analysis Paediatric surgical patients had a lower rate of bleeding needing surgical intervention (OR 0.42; 95% CI 0.22–0.77) and a lower mortality (OR 0.39; 95% CI 0.21–0.71) with TXA vs AP</td>
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<tr>
<td>Breuer and colleagues</td>
<td>2009</td>
<td>199</td>
<td>Retrospective database analysis Significantly lower blood loss at 6 h but not at 12 and 24 h, and lower blood transfusion and re-thoracotomy rates in paediatric cardiac surgical patients for AP vs TXA</td>
</tr>
<tr>
<td>Shimizu and colleagues</td>
<td>2011</td>
<td>160</td>
<td>Randomized, placebo-controlled trial Blood loss at 24 h was significantly lower for TXA vs placebo in paediatric patients (mean difference − 4.9 (95% CI − 9.7 to − 0.01) ml kg⁻¹) but no difference in blood transfusion rate</td>
</tr>
<tr>
<td>Martin and colleagues</td>
<td>2011</td>
<td>234</td>
<td>Retrospective database analysis No significant difference between TXA and EACA with regard to blood loss, transfusion, or adverse events in paediatric cardiac surgical patients</td>
</tr>
<tr>
<td>Martin and colleagues</td>
<td>2011</td>
<td>235</td>
<td>Retrospective, single-centre database analysis Neonates undergoing cardiac surgery had a significantly higher blood loss with EACA compared with AP; no difference in rate of re-operation or transfusion</td>
</tr>
<tr>
<td>Martin and colleagues</td>
<td>2012</td>
<td>227</td>
<td>Retrospective, single-centre database analysis Infants undergoing cardiac surgery had a significantly higher blood loss with EACA compared with AP but no difference in transfusion rate</td>
</tr>
<tr>
<td>Martin and colleagues</td>
<td>2011</td>
<td>604</td>
<td>Retrospective, single-centre database analysis Significantly lower 24 h blood loss in patients receiving TXA vs EACA (400 vs 500 ml, P=0.015)</td>
</tr>
<tr>
<td>Keyl and colleagues</td>
<td>2011</td>
<td>682</td>
<td>Retrospective, single-centre database analysis Lower risk of 24 h blood loss of &gt; 800 ml with TXA compared with EACA (OR 0.53, 95% CI 0.37–0.77)</td>
</tr>
<tr>
<td>Grant and colleagues</td>
<td>2009</td>
<td>120</td>
<td>Double-blind, randomized, placebo-controlled AP reduced the incidence of major adverse cardiac and cerebrovascular events, but was a predictor for postoperative acute kidney injury in OPCAB surgery</td>
</tr>
<tr>
<td>Desai and colleagues</td>
<td>2009</td>
<td>75</td>
<td>Double-blind, randomized, placebo-controlled AP reduced hypercoagulable state (platelet activation and thrombin generation) and red blood cell transfusion and the rate of thrombotic events (graft failure, myocardial infarction, and stroke) in OPCAB surgery</td>
</tr>
<tr>
<td>Adler and colleagues</td>
<td>2011</td>
<td>544</td>
<td>Systematic review and meta-analysis of eight RCTs TXA reduced the risk of allogeneic blood component transfusion and red cell transfusion in OPCAB surgery</td>
</tr>
<tr>
<td>Wang and colleagues</td>
<td>2012</td>
<td>231</td>
<td>Double-blind, randomized, placebo-controlled TXA led to a significant reduction in 6 and 24 h chest-tube drainage, and a reduced number of patients transfused with red blood cells and fresh frozen plasma in OPCAB surgery</td>
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Tranexamic acid and ε-aminocaproic acid

The synthetic lysine-analogues tranexamic acid and ε-aminocaproic acid were first described in 1957 by Okamoto and are now the most widely used antifibrinolytic drugs. Both act by reversibly blocking the lysine binding sites of plasminogen, thus preventing its activation to plasmin, and therefore stopping the lysis of polymerized fibrin. Both drugs are used intravenously in the perioperative setting but are also readily absorbed from the gastrointestinal tract. Plasma half-life is ~2 h and the drugs are excreted unchanged into the urine, which typically continues for up to 36 h (ε-aminocaproic acid) or >24 h (tranexamic acid). Various dosing regimes have been suggested for tranexamic acid with large variation in the cumulative dose, ranging from 10 mg kg\(^{-1}\) to 10 g as a bolus followed by an infusion of 0–2 g h\(^{-1}\). However, there is little evidence to support a regime exceeding a bolus dose of 10 mg kg\(^{-1}\) followed by an infusion of 1 mg kg\(^{-1}\) h\(^{-1}\). For ε-aminocaproic acid, a loading dose of 50 mg kg\(^{-1}\) combined with an infusion of 25 mg kg\(^{-1}\) h\(^{-1}\) has been suggested to generate constant blood concentrations.

In contrast to aprotinin, for which there is limited data suggesting an increased risk for myocardial infarction, there is so far no data proving a detrimental prothrombotic effect for the lysine analogues. However, in recent years, the occurrence of seizures has been linked to tranexamic acid, particularly when high doses are administered. Accidental intrathecal application has been reported to cause polymyoclonal seizures and in other cases myoclonic seizures combined with intractable ventricular fibrillation. After the replacement of aprotinin by tranexamic acid at their institution, Martin and colleagues performed a retrospective analysis of 1188 consecutive patients, which showed an incidence of fits of 4.6% in patients receiving tranexamic acid vs 1.2% in the aprotinin group (P<0.001). The same authors matched 275 patients out of the

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<tr>
<th>Author</th>
<th>Year</th>
<th>Study population</th>
<th>Main findings</th>
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<tr>
<td>Shakur and colleagues</td>
<td>2010</td>
<td>20 211</td>
<td>Multicentre, double-blind, placebo-controlled RCT</td>
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<td></td>
<td></td>
<td></td>
<td>All-cause mortality and risk of death because of bleeding was significantly reduced in trauma patients with TXA vs placebo; no increased risk of thromboembolic events</td>
</tr>
<tr>
<td>Roberts and colleagues</td>
<td>2011</td>
<td>20 211</td>
<td>Multicentre, double-blind, placebo-controlled RCT; subgroup analysis</td>
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<td></td>
<td></td>
<td></td>
<td>Risk of death is reduced if TXA is given within 3 h after trauma; later administration is associated with increased risk of death</td>
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<tr>
<td>Roberts and colleagues</td>
<td>2011</td>
<td>20 548</td>
<td>Cochrane systematic review of four RCTs</td>
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<td></td>
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<td></td>
<td>TXA reduced the risk of death in bleeding trauma patients; no reliable data for AP in trauma</td>
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<tr>
<td>CRASH-2 collaborators</td>
<td>2011</td>
<td>270</td>
<td>Multicentre double-blind, placebo-controlled RCT, nested into CRASH-2</td>
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<tr>
<td></td>
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<td></td>
<td>Tranexamic acid did not demonstrate a reduction in intracranial haemorrhage growth or mortality in trauma patients with brain injury</td>
</tr>
<tr>
<td>Tzortzopoulou and colleagues</td>
<td>2008</td>
<td>254</td>
<td>Cochrane systematic review of six RCTs</td>
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<td></td>
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<td>Antifibrinolytic drugs reduced the amount of transfused blood (−327 ml; 95% CI −469.04 to −185.78) and the amount of blood loss (−427 ml; 95% CI −602.51 to −250.56) in paediatric scoliosis surgery</td>
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<tr>
<td>Wong and colleagues</td>
<td>2008</td>
<td>151</td>
<td>Double-blinded, placebo-controlled RCT</td>
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<td></td>
<td></td>
<td></td>
<td>Estimated blood loss after spinal fusion in adults was reduced by 25% by TXA; no difference for perioperative transfusion and length of hospital stay</td>
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<tr>
<td>Dhawale and colleagues</td>
<td>2011</td>
<td>84</td>
<td>Retrospective database analysis</td>
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<td></td>
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<td></td>
<td>Reduced estimated blood loss in children undergoing spinal fusion with prophylactic lysine analogues compared with no treatment</td>
</tr>
<tr>
<td>Zufferey and colleagues</td>
<td>2006</td>
<td>2523</td>
<td>Meta-analysis of 43 RCTs</td>
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<td></td>
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<td>AP (OR 0.43; 95% CI 0.28–0.64) and TXA (OR 0.17; 95% CI 0.11–0.24) led to a reduction in blood transfusion in orthopaedic surgery, whereas EACA did not</td>
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<tr>
<td>Kagoma and colleagues</td>
<td>2009</td>
<td>2060</td>
<td>Systematic review of 29 RCTs</td>
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<td></td>
<td></td>
<td></td>
<td>Antifibrinolytic agents are associated with reduced blood transfusion after hip and knee replacement; no increased risk for thromboembolic events with antifibrinolytics</td>
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tranexamic acid group to 329 patients who received ω-aminocaproic acid, and found a relative risk for seizures in the latter cohort of 0.44 (95% CI 0.89–0.22). In paediatric patients at the same institution, there was only a tendency to a higher incidence of seizures for tranexamic acid (3.5%) vs aprotinin (0%) with no statistical significance. Keyl and colleagues published the experience from their institution after moving from tranexamic acid to ω-aminocaproic acid as prophylaxis in cardiac surgery. They also found a significantly higher incidence for seizures in patients who received tranexamic acid, with an odds ratio (OR) of 11.7 (95% CI 2.7–50.1). Multivariate analysis of larger cohorts has also identified tranexamic acid as an independent risk factor for postoperative seizures. In 5958 patients, tranexamic acid had an OR of 7.4 (95% CI 2.8–19.3) and in 8929 a total dose of tranexamic acid of >100 mg kg⁻¹ had an OR of 2.6 (95% CI 1.7–3.8). Even though pulmonary endarterectomy with deep hypothermic circulatory arrest is already associated with a higher rate of neurological complications, tranexamic acid seems to significantly increase the risk of seizures in this patient group compared with aprotinin. Tranexamic acid has been found to be a competitive antagonist of the inhibitory neurotransmitter glycine in mice. It increased the rate of

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<th>Table 3</th>
<th>Liver surgery. AP, aprotinin; TXA, tranexamic acid; EACA, ω-aminocaproic acid</th>
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<td>Porte and colleagues 88</td>
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<td>Dalmau and colleagues 89</td>
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<tr>
<td>Dalmau and colleagues 90</td>
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<td>Molenaar and colleagues 91</td>
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<td>Gurusamy and colleagues 94</td>
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<td>Warnaar and colleagues 95</td>
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<td>Wu and colleagues 98</td>
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<th>Table 4</th>
<th>Obstetrics. AP, aprotinin; TXA, tranexamic acid; EACA, ω-aminocaproic acid</th>
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<td>Author</td>
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<tr>
<td>Gai and colleagues 101</td>
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<td>Ferrer and colleagues 102</td>
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<td>Novikova and colleagues 105</td>
<td>2010</td>
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<td>Ducloy-Bouthors and colleagues 106</td>
<td>2011</td>
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<tr>
<td>Gungorduk and colleagues 107</td>
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seizure-like events in neocortical slices, which was attenuated by isoflurane and propofol. These findings provide a possible mechanism for the association of tranexamic acid and postoperative seizures. In current clinical practice, tranexamic acid is administered at a lower dose than in the above studies for bleeding prophylaxis, and further prospective studies are needed to assess the risk–benefit ratio of such use.

**Cardiac surgery**

Surgical intervention on the cardiovascular system and the use of CPB and hypothermia to facilitate surgery have the potential to cause activation of the fibrinolytic system. In particular, the blood–artificial surface interaction within the bypass circuit leads to activation of thrombin, which can trigger fibrinolysis. As this process is not fully suppressed by heparinization, additional measures are required. Prophylaxis and treatment of hyperfibrinolysis is an important component of the haemostatic management for cardiovascular surgery involving CPB.

After the withdrawal of aprotinin from the market, tranexamic acid and $\varepsilon$-aminocaproic acid are the agents of choice for this indication and are used routinely in most centres worldwide. Both agents are effective in reducing blood loss after cardiac surgery when used prophylactically, which has been demonstrated in recent meta-analyses. The blood sparing effect of the lysine analogues was also shown in the Mangano study and in the BART trial, even though there was a trend towards aprotinin being more efficacious to prevent massive bleeding compared with both lysine analogues combined (RR 0.79; 95% CI 0.61–1.01). However, the BART trial was ultimately not adequately powered to determine the superiority of aprotinin because of early termination.

Retrospective data suggest that tranexamic acid might be slightly less effective than aprotinin in reducing postoperative blood loss, but aprotinin might increase the risk of acute kidney injury. In a randomized, double-blinded trial, later and colleagues found both tranexamic acid and aprotinin to reduce postoperative blood loss significantly compared with placebo. The prophylactic administration of $\varepsilon$-aminocaproic acid was non-inferior to aprotinin for reducing 24 h-chest-tube drainage compared with placebo in a double-blinded randomized controlled trial.

The data are comparable for paediatric cardiac surgical patients. A recent database analysis of 22,258 cases showed that $\varepsilon$-aminocaproic acid and aprotinin were similarly effective, whereas tranexamic acid was associated with lower bleeding and mortality rates. In direct retrospective comparison with tranexamic acid, aprotinin had a lower blood loss at 6 h, a lower red blood cell transfusion and re-thoracotomy rate in cardiac surgical patients weighing < 20 kg. In an open-label randomized placebo-controlled trial, tranexamic acid reduced the 24 h blood loss in paediatric cardiac surgical patients by a mean (95% CI) of $−4.9 \approx 9.7$ to $−0.01 \text{ ml kg}^{-1}$. A database analysis of 234 paediatric patients did not show any significant difference regarding blood loss, transfusion, or other outcome parameters between $\varepsilon$-aminocaproic acid and tranexamic acid. However, the relative risk for seizures was non-significantly higher for tranexamic acid (RR 4.21, 95% CI 0.48–37.11). In the same institution, moving from aprotinin to $\varepsilon$-aminocaproic acid in neonates and infants resulted in a higher blood loss but no difference in any other outcome parameter, including transfusion requirements and re-operation.

Comparing the two lysine analogues directly, tranexamic acid seems to reduce blood loss more effectively than $\varepsilon$-aminocaproic acid, but only retrospective data are available to support this. Therefore, a recommendation to use one of the lysine analogues in preference to the other cannot be made based on the existing literature. The choice of drug might be more influenced by availability in specific countries and concerns about side-effects rather than efficacy in reducing postoperative bleeding.

Off-pump coronary artery bypass (OPCAB) surgery is felt to be less invasive with regard to coagulation compared with surgery with CPB. However, ~30% of patients undergoing OPCAB surgery receive allogeneic blood products, and

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<th>Neurosurgery. AP, aprotinin; TXA, tranexamic acid; EACA, $\varepsilon$-aminocaproic acid</th>
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<td>Author</td>
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<td>Roos and colleagues</td>
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might benefit from antifibrinolytic prophylaxis. On the other hand, a hypercoagulable state has been suggested during OPCAB surgery, which could lead to an increase in thromboembolic events, such as myocardial infarction, stroke and reduced graft patency, and could be augmented by antifibrinolytics. A randomized placebo-controlled trial in 120 OPCAB patients has shown that modified full-dose aprotinin reduced the incidence of major adverse cardiac or cerebrovascular events (12 vs 34%, \( P=0.01 \)), but was an independent predictor of postoperative acute kidney injury (45.8 vs 24.6%, \( P=0.03 \)). Being a non-specific serine protease inhibitor, aprotinin might prevent both coagulopathy, and hypercoagulable state during OPCAB surgery. This has been suggested by a smaller randomized placebo-controlled trial, which showed less platelet activation and thrombin generation, but also a reduced number of red blood cell transfusion (0.39 vs 0.66, \( P<0.04 \)) and a lower combined rate of thrombotic events (5.4 vs 29.7%, \( P<0.05 \)) in aprotinin treated patients. This theoretically ideal combination of properties would however warrant further assessment in larger trials, especially in view of the continuing discussion about safety of aprotinin.

For tranexamic acid, a meta-analysis of eight randomized controlled trials calculated reduced risks for overall allogeneic blood component transfusion (RR 0.47, 95% CI 0.33–0.66) and for red cell transfusion (RR 0.51, 95% CI 0.36–0.66) and a reduced number of blood component transfusion (5.4 vs 29.7%, \( P<0.05 \)) in aprotinin treated patients. This theoretically ideal combination of properties would however warrant further assessment in larger trials, especially in view of the continuing discussion about safety of aprotinin.

Trauma

Approximately one-third of all severely injured patients are coagulopathic on arrival in hospital, and mortality in trauma patients increases 4-fold if acute traumatic coagulopathy is present. Pathogenesis depends on various factors, such as haemodilution, shock, tissue injury, inflammation, hypothermia, and acidosis. Endothelial injury and ischaemia initiate both, the coagulation system, via collagen and tissue factor, and the fibrinolytic system by releasing tPA. In the presence of major trauma and shock, an imbalance of the two systems can occur and may lead to a generalized hyperfibrinolytic state. The availability of point-of-care tests, like thromboelastography, has raised awareness for this condition in recent years, and trauma patients have been treated successfully after identifying hyperfibrinolysis with the help of viscoelastic tests.

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial was a very large, multinational and multicentre trial, during which 20 211 adult patients with significant bleeding after trauma were randomly assigned to receive tranexamic acid (1 g bolus + 1 g infusion \( >8 \) h) or placebo within 8 h of trauma. All-cause mortality was significantly lower in the treatment group (RR 0.91; 95% CI 0.85–0.97, \( P=0.0035 \)). There was also significantly less bleeding with no increase in thromboembolic events in the tranexamic acid group. A later analysis of the mortality because of bleeding, as opposed to overall mortality, revealed that there was a significant reduction of death because of bleeding only if tranexamic acid was started within 3 h after trauma. In fact, later administration was associated with significantly increased risk of death because of bleeding compared with placebo (RR 1.44, 95% CI 1.12–1.84; \( P=0.004 \)). Inclusion criteria for this trial were generous, and based only on basic clinical assessment and uncertainty about the benefit of antifibrinolytic treatment in the individual patient. Therefore, a large proportion of patients may have been included who would not have fulfilled laboratory criteria for acute traumatic coagulopathy or even hyperfibrinolysis. However, there was no increase in thromboembolic events in the tranexamic acid group. Considering the complexity of factors affecting outcome in trauma and the great variety in type of trauma and management of the patients enrolled, it is remarkable that CRASH-2 was able to demonstrate a survival benefit with respect to a single, relatively simple intervention. The most recent Cochrane review on antifibrinolytic drugs in trauma found a risk-reduction for death after acute traumatic injury...
of 10% (RR=0.90, 95% CI 0.85–0.97; P=0.0035). However, the conclusions are largely based on the CRASH-2 data. Only four trials were included in total, with just one further trial studying tranexamic acid. The two other studies, investigating aprotinin, provided insufficient data.

As a by-product of the main trial, the CRASH-2 investigators conducted a randomized controlled study in a subset of trauma patients, investigating tranexamic acid in traumatic brain injury. Two hundred and seventy patients with traumatic brain injury in addition to fulfilling the inclusion criteria for the main trial were randomized into a tranexamic acid and in a placebo group. They underwent computed tomography of the head before randomization and 24–48 h later, and the increase of total intracranial haemorrhage was the primary outcome. The growth of haemorrhage was reduced by 3.8 ml (95% CI 11.5–3.9, P=0.33) in the tranexamic acid group and the adjusted OR for death was 0.47 (95% CI 0.21–1.04, P=0.06). The number of new ischaemic lesions was lower in the tranexamic acid group (adjusted OR 0.51, 95% CI 0.18–1.44, P=0.2). As none of the results reached statistical significance the authors rightly conclude that neither benefit nor harmful effects can be excluded based on their data. The study design however makes it difficult to judge on tranexamic acid in traumatic brain injury because all patients enrolled also had significant (extracranial) haemorrhage leading to hypotension and possible coagulopathy. This is likely to impact heavily on overall outcome and on intracranial pathology, both haemorrhagic and ischaemic. Currently, the CRASH-3 trial (ISRCTN15088122) is recruiting patients with traumatic brain injury and no significant extracranial haemorrhage to investi-
gate the effect of tranexamic acid in isolated brain injury.

In conclusion, the existing evidence, based on one large multicentre randomized controlled trial, strongly supports the use of tranexamic acid in bleeding trauma patients as a cost-effective empirical treatment with a good risk–benefit ratio, even without evidence of on-going hyperfibrinolysis. A multidisciplinary European guideline for the management of bleeding after major trauma also recommends the use of antifibrinolytic agents, ideally combined with monitoring of fibrinolytic activity by thromboelastometry.

Orthopaedic surgery

Major orthopaedic operations are often associated with significant blood loss and provide a challenge for the anaesthetists with regard to fluid, transfusion, and coagulation management. Extensive tissue trauma and major fluid shifts can lead to coagulopathy with pathophysiologic changes similar to trauma patients. The role of antifibrinolytic agents has been investigated especially for extensive spinal surgery, but also for joint replacements.

A Cochrane review of antifibrinolytic therapy in paediatric scoliosis surgery identified six randomized trials, each comparing one antifibrinolytic agent vs placebo, including a total of 254 patients. The amount of blood loss and the amount of transfused blood was significantly reduced in the treatment groups. No adverse events were recorded in the patients treated.

Wong and colleagues studied the prophylactic effect of tranexamic acid in spinal surgery, when used according to the dosing regimen suggested by Horrow and colleagues for cardiac surgery. A total of 151 patients from three centres in Toronto, undergoing instrumented spinal fusion, were randomly assigned to receive a bolus of 10 mg kg$^{-1}$ tranexamic acid followed by an infusion of 1 mg kg$^{-1}$ or placebo. Tranexamic acid reduced the estimated perioperative blood loss by 25%. However, there was no significant difference in perioperative transfusion requirements or length of hospital stay, but also no significant difference in vascular occlusive events. In the treatment group, there was one case of myocardial infarction compared with one deep vein thrombosis in the placebo group. A retrospective review of 84 children undergoing spinal fusion surgery showed that treatment with either tranexamic acid or e-aminocaproic acid reduced the estimated blood loss compared with no treatment.

Considering the potential of reducing blood loss, antifibrinolytic prophylaxis can be safely used as part of the blood conservation strategy in spinal surgery. However, current data do not demonstrate a benefit for outcome variables like exposure to blood transfusion or length of hospital stay. It is also not yet clear which antifibrinolytic agent is most effective. A comparison of the efficacy of tranexamic acid vs e-aminocaproic acid in reducing blood loss in corrective spinal surgery is currently underway.

A meta-analysis published in 2006 addressed the question whether antifibrinolytic agents are able to reduce allogeneic blood transfusion in orthopaedic surgery. Forty-three randomized trials studying aprotinin, tranexamic acid or e-aminocaproic acid in a wide variety of major orthopaedic procedures were analysed. Aprotinin and tranexamic acid led to a reduction of allogeneic blood transfusion, while e-aminocaproic acid did not. Unfortunately, there was not sufficient data available for a safety assessment.

A similar meta-analysis looked exclusively at hip and knee arthroplasties. The authors included 29 randomized trials, which had enrolled ~2000 patients in total, demonstrating a considerable heterogenic picture regarding choice of drug, dosing and timing of administration. However, all three agents were associated with a significant reduction in total blood loss when analysed for type of surgery and for type of antifibrinolytic agent. In contrast to the data for spinal surgery, this meta-analysis also showed a reduction for the need of blood transfusion. The pooled RR was 0.52 (95% CI, 0.42–0.64), the RR for patients undergoing total hip replacement 0.42 (95% CI, 0.30–0.58) and 0.13 (95% CI, 0.08–0.20) for total knee arthroplasty, respectively. There was no increased risk for thromboembolic events.

Based on these meta-analyses, antifibrinolytic agents have the potential to reduce the amount of allogeneic transfusions required in hip and knee replacement surgery, probably without increasing the risk of venous thromboembolism.
Liver surgery

Transfusion and coagulation management during hepatectomy or liver transplantation is often highly demanding and coagulopathy is usually multifactorial. Liver failure is associated with a reduced synthesis of both clotting factors and procoagulants and inhibitors of coagulation. Also, clearance of tPA may be reduced, shifting the balance towards fibrinolysis. Therefore, the patient can acquire bleeding complications attributable to a lack of clotting factors, a hyperfibrinolytic state, or both. Likewise, the opposite could be the case: thrombotic events attributable to a dysfunctional fibrinolytic system. All these phenomena are much more pronounced during the anhepatic phase of liver transplantation. Complicating factors are major blood loss with subsequent haemodilution, transfusion, and platelet dysfunction.

Hyperfibrinolysis is a major contributor to coagulation defects in patients undergoing liver surgery. Around 30% of patients admitted to hospital with liver cirrhosis demonstrate increased fibrinolysis, determined by a shortened euglobulin lysis time. In fact, more than three-quarters of patients undergoing liver transplantation develop hyperfibrinolysis at some point during the procedure. Therefore, prophylactic antifibrinolytic treatment could be beneficial in this high-risk patient population. However, a possible prothrombotic effect of antifibrinolytic agents could lead to an increased rate of thromboses within the transplanted organ with subsequent graft failure.

Aprotinin has been shown to reduce blood loss and transfusion requirements effectively in liver transplantation. A randomized, double-blind, placebo-controlled multicentre trial (EMSALT) demonstrated a reduction in blood loss by 44–60% (depending on the aprotinin dose) and reduction of transfusion requirements by 20–37% in 137 patients. There was no significant difference in the rate of thromboembolic events. However, the low rate of only four events in total (two in the high-dose aprotinin group and two in the placebo group) precludes safety assessment. Dalmau and colleagues studied the lysine analogues in 132 patients undergoing liver transplantation. In a randomized, double-blinded fashion, patients were assigned to receive tranexamic acid, epsilon-aminocaproic acid, or placebo. Interestingly, there was only a trend to a lower percentage of patients developing fibrinolysis (measured by TEG) for the tranexamic acid group during dissection, and for both agents after reperfusion. Nevertheless, there was an advantage in the tranexamic group with less red blood cell transfusions intra-operatively (P=0.023) and more patients without any blood transfusion (P=0.016). But there was no significant difference for the first 24 h period and also no significant effect in the epsilon-aminocaproic acid group. Notably, none of the patients receiving prophylactic tranexamic acid needed treatment for clinical fibrinolysis as opposed to six and seven patients, respectively, in the other groups (P=0.021). Regarding safety, there was no significant difference in thrombosis between the groups, but also only a small overall number of events. The same group compared prophylaxis with tranexamic acid and aprotinin in 127 liver transplantations and found no intergroup difference with regard to transfusion requirements, thromboembolic events, and mortality.

Most other studies performed in liver transplantations have investigated aprotinin and tranexamic acid. A meta-analysis of 23 trials between 1993 and 2005 found only the mentioned trial by Dalmau and colleagues including epsilon-aminocaproic acid as well. This meta-analysis concluded that both tranexamic acid and aprotinin reduced blood transfusion without evidence for an increased risk of graft thrombosis. The authors stated that the use of epsilon-aminocaproic acid could not be recommended, because of limited evidence.

A recently published cohort study comparing the use of aprotinin and tranexamic acid in 400 liver transplantations found no difference in blood loss, transfusion, and 1-year survival. Ickx and colleagues randomly assigned 51 cirrhotic patients to receive open-labelled aprotinin or tranexamic acid during liver transplantation. Again, there was no difference between the two drugs with regard to blood loss and transfusion. However, a recent Cochrane review of ‘methods to decrease blood loss and transfusion requirements for liver transplantation’ came to the conclusion that overall evidence in that area is relatively poor mainly because of the high risk of bias in most of the studies. In order to assess the safety of using antifibrinolytic therapy Warnaar and colleagues have reviewed 1492 patients, of which 907 received and 585 did not receive aprotinin during liver transplantation. A propensity score-matched analysis did not show a higher risk for hepatic artery thrombosis in the aprotinin group (OR 1.00; 95% CI 0.50–2.01), but a non-significant trend to more venous thromboembolic events (OR 2.95; 95% CI 0.54–16.23).

Overall, tranexamic acid seems to be the agent of choice in liver transplantation, being equally efficacious as the currently unavailable aprotinin. As opposed to a blind prophylaxis with antifibrinolitics in liver transplantation a goal directed therapy, by using thrombelastometry to assess fibrinolysis, has been suggested. So far, however, there is no evidence for improved outcomes with this approach.

The impact on bleeding and transfusion of fibrinolysis in liver resection is certainly much less compared with transplantation. Hence, antifibrinolytic agents are not routinely indicated as prophylactic therapy. Aiming for a ‘transfusion-free hepatectomy’ Wu and colleagues compared prophylactic tranexamic acid vs placebo in 217 patients undergoing liver tumour resections in a randomized, double-blind fashion. Blood loss was significantly lower in the tranexamic acid group (P=0.0001) and none of the patients required blood transfusion as opposed to 17 in the placebo group (P<0.0001). Tumour size and the transection area also increased the transfusion risk. This study suggests that there might be a benefit of using antifibrinolytic prophylaxis especially in patients undergoing more complex hepatectomies. However, there is certainly not enough evidence for a general recommendation.

Obstetrics

Worldwide, haemorrhage is one of the main causes for perinatal maternal mortality, mainly attributed to limited
access to medical care in developing countries. But, even in the UK, 0.39 fatal peri-partum haemorrhages occur per 100 000 maternities. The incidence of major obstetric bleeding is of course much higher, ~3.7 per 1000 births in the UK, and usually requires a high level of medical care to limit maternal morbidity. Besides the medical and surgical treatment of the cause of bleeding, coagulopathy, because of consumption of clotting factors, haemodilution, and activation of the fibrinolytic system, requires meticulous attention. In an attempt to reduce the need for red blood cell transfusion and allogeneic blood products, tranexamic acid has been used and studied in post-partum haemorrhage after both vaginal delivery and Caesarean sections.

In a single-centre, randomized, open-label study, Gai and colleagues found a significant reduction of bleeding within 2 h of Caesarean section with prophylactic tranexamic acid. However, there was no difference in bleeding during surgery itself, and no report about transfusion frequency in both groups. In addition, the change of haemoglobin concentration was not significantly different in both groups. Therefore, the clinical relevance of these findings remains uncertain. A systematic review of antifibrinolytic agents in post-partum haemorrhage in 2009 discovered only two further trials to evaluate the existing evidence. Two of those studies included patients after Caesarean section, and one study patients after vaginal delivery. The pooled relative risk for post-partum haemorrhage, as defined by the investigator, was 0.44 (95% CI 0.31–0.64). There were no thrombotic events in one study and no report of thrombotic events in the other two, making risk assessment impossible. The authors of this review rightly concluded that all three studies were of poor methodological quality. As a result, a high level of uncertainty remains. A Cochrane review in 2010 of tranexamic acid in post-partum haemorrhage, included only two of the above-mentioned trials and confirmed the poor state of the evidence.

The situation was considerably enlightened by the EXADELI trial (EXAcyll in the treatment of DELivery haemorrhage). This French study was conducted in eight centres and recruited 154 women with a post-partum haemorrhage of >800 ml within 2 h of vaginal delivery. Patients were randomized to receive tranexamic acid (4 g in 1 h followed by 1 g h<sup>−1</sup>) or no treatment, in an open-label fashion. In this well-conducted study, median blood loss during 6 h after enrolment was significantly lower in the treatment group (173 ml vs 221 ml, P<0.041). With antifibrinolytic treatment, haemorrhage could be controlled in 93% of cases with uterotonic drugs alone as opposed to 79% in the control group (P=0.016). This resulted in a shorter duration of bleeding (P=0.004) and a significantly lower number of patients decreasing their haemoglobin >4 g d<sup>−1</sup> (P=0.02). This study did not attempt to answer the question whether antifibrinolytic drugs can prevent post-partum haemorrhage, as only women with significant bleeding were included, and it was not powered to show a mortality benefit. However, indicators for maternal morbidity were improved by tranexamic acid administration. The treatment group received a significantly lower total number of red blood cell transfusions (P<0.001) and procoagulant treatment with fresh frozen plasma or fibrinogen (P=0.001). There was also a trend to a reduced need for invasive surgical procedures. Even though this was not statistically significant, none of the patients underwent hysterectomy or uterine artery ligature as opposed to two patients in the control group. The study was not powered to assess safety; there were two cases of deep vein thrombosis in the treatment and one in the control group. Despite the lack of blinding and the fact that it was not powered for mortality and complications, this is the first high-quality trial supporting the use of tranexamic acid in the setting of post-partum haemorrhage after vaginal delivery. There is clearly a need for further investigations regarding safety and dosing, as this trial used a relatively high-dose regimen in contrast to the doses routinely used in other indications. Gungorduk and colleagues performed a randomized, double-blind and placebo-controlled trial studying prophylactic tranexamic acid before elective Caesarean section in 660 patients. The mean estimated blood loss was significantly lower and the risk for massive blood loss was significantly higher in the placebo group (RR 2.7; 95% CI 1.1–6.3). The reduction in blood transfusion did not reach clinical significance, but exposure to additional uterotonic agents was higher in the placebo group (RR 1.7; 95% CI 1.1–2.6). One weakness of this study was that blood loss was not measured but instead estimated using pre- and 48 h postoperative haematocrit values.

The WOMAN trial (World Maternal Antifibrinolytic) is currently attempting to further assess the role of antifibrinolytic therapy in post-partum haemorrhage. This randomized and double-blinded trial started recruitment worldwide in 2009 in a design similar to the CRASH-2 trial in trauma. The trial has recruited >4000 women to date and is aiming for a total of 15 000. This data set should be able to elucidate the impact of tranexamic acid on mortality and morbidity of post-partum haemorrhage and possible complications. Furthermore, it includes developing countries, where the need for a pragmatic and cost-effective treatment of post-partum haemorrhage is greatest.

At present, the evidence for antifibrinolytics in obstetrics is limited. The EXADELI trial suggests a benefit of tranexamic acid in ongoing post-partum haemorrhage after vaginal delivery. There may also be a reduction in blood loss by prophylactic administration of tranexamic acid after Caesarean section.

### Neurosurgery

In neurosurgical patients massive bleeding and transfusion, with the previously mentioned detrimental effect on the coagulation and fibrinolytic system, are a rare event. However, even small amounts of intracranial blood carry a high risk of morbidity and mortality. Managing the coagulation therefore is primarily focused on the prevention of any haemorrhage within the cranial cavity, and the therapeutic target is improvement of clot stability rather than pathological hyperfibrinolysis.

Antifibrinolytic agents have been used to prevent rebleeding in patients presenting with aneurysmal subarachnoid haemorrhage. The risk of rebleeding within the first 24 h after the
Initial insult have been reported to be as high as 9–17%, and are associated with a remarkable increase in mortality.\textsuperscript{109} \textsuperscript{110} The other major complication after subarachnoid haemorrhage is ischaemia because of cerebral arterial vasospasm. An additional thrombotic event, a possible side-effect of any procoagulant therapy, could be disastrous. Hence, the use of antifibrinolytics, before definitive surgical or interventional treatment of the aneurysm, remains controversial.

A Cochrane review on this topic included nine studies published between 1973 and 2000 and found that even though antifibrinolytic therapy reduced the rebleeding risk, there was an increase in poor outcome because of cerebral ischaemia.\textsuperscript{111} The authors concluded that there were no data to support the use of antifibrinolytics in subarachnoid haemorrhage. It is of interest that eight of those nine trials were published before 1990 and might not represent modern clinical practice. Specifically, the use of calcium antagonists and triple-H-therapy for the prophylaxis of vasospasm was not used, which might account for the higher number of ischaemic events. However, even the study using prophylaxis only showed a reduction in re-bleeding (RR 0.58; 95% CI, 0.42–0.80) with the same rate of ischaemic events but failed to demonstrate a beneficial effect on outcome measured on the Glasgow outcome scale (RR 1.10; 95% CI, 0.91–1.34).\textsuperscript{112}

More favourable for the use of antifibrinolytics in subarachnoid haemorrhage is a study conducted in three university hospitals in Sweden in the late 1990s, which was not included in the Cochrane review.\textsuperscript{113} Hillman and colleagues randomized 596 patients with verified subarachnoid haemorrhage to receive tranexamic acid (1 g every 6 h) or no treatment. The first dose was given in the referring hospital and therapy was discontinued after the aneurysm was secured. Prophylaxis was started early and only given for a short period of time, as 70% of aneurysms had been treated within 24 h of hospital admission. One limiting factor of this study is the unblinded design. In the tranexamic acid group, the number of patients who re-bleed within the first 24 h was significantly lower (2.4 vs 10.8%, \(P=0.01\)). Interestingly, the vast majority of re-haemorrhages occurred within the first 8 h (30 of 33), which supports the strategy of early tranexamic acid prophylaxis. With respect to outcome, the study demonstrated only non-significant trends to a decrease in mortality (16.3 vs 12.9%) and an increase in favourable outcome (Glasgow outcome score 4 or 5: 70.5 vs 74.8%) in the tranexamic acid group. Larger patient cohorts are therefore necessary to confirm this in adequately powered trials. Notably, ischaemic events and clinical signs for vasospasm were not more prevalent in patients who received tranexamic acid.

The impact of the implementation of a similar protocol with \(\text{\textepsilon}\)-amino-o-caproic acid at Columbia University New York was analysed by Starke and colleagues.\textsuperscript{114} Starting in May 2003, all patients diagnosed with subarachnoid haemorrhage were supposed to receive a loading dose (4 g) followed by an infusion of 1 g h\textsuperscript{-1}. The data of 248 patients were analysed, 73 of those received \(\text{\textepsilon}\)-amino-o-caproic acid. The rebleeding rate was significantly lower in treated patients (2.7 vs 11.4%, \(P=0.02\)) with a hazard ratio of 0.23 (\(P=0.05\)). Again, there was only a non-significant trend to increased favourable outcomes. The rate of cerebral ischaemic events was not altered but there was a notable 8-fold increase in lower extremity deep vein thrombosis (\(P=0.003\)).

Another cohort of 356 patients with subarachnoid haemorrhage, who were all treated with \(\text{\textepsilon}\)-amino-o-caproic acid on admission to the neuro-intensive care unit, were reviewed retrospectively by Harrigan and colleagues.\textsuperscript{115} The re-bleeding rate was even lower than in the treatment groups of the two above-mentioned studies. More importantly, the rate of ischaemic complications compared favourably to previous published data in similar patients and did not indicate a higher risk in patients treated with \(\text{\textepsilon}\)-amino-o-caproic acid.

In summary, the existing data suggest that there is a place for antifibrinolytic therapy as prophylaxis for early re-bleeding in subarachnoid haemorrhage with no increased risk of ischaemic events. A benefit for survival and favourable outcome is likely but not yet proved.

\section*{Conclusion}

Antifibrinolytic prophylaxis is widely used in cardiac and non-cardiac surgery with the aim of reducing the risk of blood loss and transfusion. For cardiac surgical procedures involving CPB, current literature shows that antifibrinolytic agents are associated with reduced perioperative blood loss and transfusion requirements, with aprotinin being the most effective agent in that respect. However, there remains conflicting evidence about an increased risk of cardio- and cerebrovascular events, renal dysfunction and possibly mortality for aprotinin in cardiac surgery and a conclusive appraisal is not yet possible. Based on retrospective data only, an association of high-dose tranexamic acid with postoperative seizures has been suggested. A low-dose strategy seems to be equally effective and is therefore advisable.

The available evidence for antifibrinolytic therapy in traumatic haemorrhage is currently largely based on only one high-quality randomized controlled trial, which found a reduced mortality with early administration of tranexamic acid. For orthopaedic surgery, it has been shown that antifibrinolytic treatment is associated with reduced blood loss but not with reduced blood transfusion, and current data do not indicate an increased risk for thromboembolic complications. There is good evidence for a reduction in transfusion requirements in liver transplantation for both aprotinin and tranexamic acid with no indication for an increase in thrombotic complications. The currently available data for the prevention of post-partum haemorrhage with antifibrinolytics are limited attributable to poor methodological quality of most of the recent trials. Treatment of established post-partum haemorrhage with tranexamic acid has been shown to reduce blood loss, transfusion and improve control of the bleeding in one open-label randomized controlled trial. The evidence for the prevention of early rebleeding after subarachnoid haemorrhage has moved in favour of antifibrinolytic drugs over the past decade. In contrast to data from the 1990s recent studies do not show an increase in cerebral ischaemic events with antifibrinolytic
Declaration of interest

None declared.

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