REVIEW ARTICLE

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A Benefit-Risk Review of Systemic Haemostatic Agents

Part 1: In Major Surgery

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Abstract

Systemic haemostatic agents play an important role in the management of blood loss during major surgery where significant blood loss is likely and their use has increased in recent times as a consequence of demand for blood products outstripping supply and the risks associated with transfusions. Their main application is as prophylaxis to reduce bleeding in major surgery, including cardiac and orthopaedic surgery and orthotopic liver transplantation. Aprotinin has been the predominant agent used in this setting; of the other antifibrinolytic agents that have been studied, tranexamic acid is the most effective and ε-aminocaproic acid may also have a role. Eptacog alfa (recombinant factor VIIa) has also shown promise. Tranexamic acid, ε-aminocaproic acid and eptacog alfa are generally well tolerated; however, when considering the methods to reduce or prevent blood loss intra- and postoperatively, the benefits of these agents need to be weighed against the risk of adverse events. Recently, concerns have been raised about the safety of aprotinin after an association between increased renal dysfunction and

mortality was shown in retrospective observational studies and an increase in all-cause mortality with aprotinin relative to tranexamic acid or ε-aminocaproic acid was seen after a pre-planned periodic analysis of the large BART (Blood conservation using Antifibrinolytics in a Randomized Trial) study. The latter finding resulted in the trial being halted, and aprotinin has subsequently been withdrawn from the market pending detailed analysis of efficacy and safety results from the study. Part 1 of this benefit-risk review examines the efficacy and adverse effect profiles of systemic haemostatic agents commonly used in surgery, and provides individual benefit-risk profiles that may assist clinicians in selecting appropriate pharmacological therapy in this setting.

Systemic haemostatic agents prevent or reduce blood loss by either improving primary haemostasis, stimulating fibrin production or inhibiting fibrinolysis.[1,2] These drugs are primarily used intravenously in situations where major blood loss needs to be managed, such as major surgery, trauma or in patients with specific underlying haemostatic defects. Some of these agents (e.g. an oral formulation of the antifibrinolytic agent tranexamic acid and an intranasal formulation of the procoagulant desmopressin) are also of use in other settings, including the management of excessive or heavy menstrual bleeding (see part 2[3] of this review). Part 1 of this benefit-risk review examines the efficacy and adverse effect profiles of systemic haemostatic agents commonly used in major surgery where significant blood loss is likely, and provides individual benefit-risk profiles that may assist clinicians in selecting appropriate pharmacological therapy in this setting.

A literature search for this part and part 2[3] of this review was performed to identify systematic reviews and primary randomized clinical trials. Inclusion of studies was based mainly on the methods section of the trials. Where available, large, well controlled trials with appropriate statistical methodology were preferred, although smaller trials and observational data were included where no large, well controlled trials were available. Databases searched included MEDLINE (1966–May 2007) and EMBASE (1980–May 2007). Additional references were identified from the reference lists of published articles. Key search terms were 'menorrhagia', 'surgery-related bleeding', 'safety', 'tolerability', 'adverse effects', 'efficacy', 'randomised trial', 'clinical trial', 'heavy menstrual bleeding', 'acute upper gastrointestinal bleeding', 'pregnancy-related bleeding', 'conisation of the cervix', 'ocular trauma', 'hereditary angioneurotic oedema', 'subarachnoid haemorrhage', 'antifibrinolytic agents', 'lysine analogues', 'protease inhibitors', 'tranexamic acid', aminocaproic acid', 'EACA', 'aprotinin', 'nafamostat', 'vitamin K', 'procoagulants', 'desmopressin', 'DDAVP', 'recombinant factor VIIa', 'eptacog alfa', 'nonsteroidal anti-inflammatory drugs', 'NSAIDs', 'mefenamic acid', 'hormones', 'combined oral contraceptives', 'oral contraceptives', 'progestogens', 'danazol', 'gonadotropin releasing hormone analogues', 'norethisterone', 'levonorgestrel-intrauterine device', 'LNG-IUS', 'conjugated estrogens', 'carbazochrome', 'ethamsylate', 'batroxobin', 'para-aminomethyl benzoic acid', 'PAMBA', 'thrombosis', 'venous thromboembolism', and 'VTE'.

1. Systemic Haemostatic Agents Used in Major Surgery

Haemostasis is essentially a balance between thrombus formation and thrombus dissolution (fibrinolysis). Historically, bleeding events have been treated with transfusions of blood components, such as platelets, clotting factors or red blood cells.[4] However, in recent times, demand for blood products has outstripped supply.[5] In addition, there are numerous risks associated with blood transfusion (e.g. transfusion-related lung injury, potential for transmitting infection, immunosuppression and subsequent increased postoperative morbidity).[6-8] As a

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Table I. Intravenous dosages of systemic haemostatic agents recommended/used in clinical trials in cardiac surgery patients without haemostatic disorders

Agent	Dosage
Aprotinin	High-dose regimen: loading dose of 2 million KIU at induction of anaesthesia, followed by a maintenance dose of 500 000 KIU/h as a continuous infusion during surgery (total dose ≥5 million KIU) and optional pump priming dose of 2 million KIU. Low-dose regimen: loading dose of 1 million KIU at induction of anaesthesia, followed by a maintenance dose of 250 000 KIU/h during surgery (total dose <5 million KIU) and optional pump priming dose of 1 million KIU[8,17]
Tranexamic acid	Total dose 3–10 g. Administered as a loading dose of 2–7 g at induction of anaesthesia, followed by a maintenance dose of 20–250 mg/h as a continuous infusion during surgery[8]
Nafamostat	2 mg/kg/h as a continuous infusion during surgery[13]
ε-Aminocaproic acid	Total dose: 10–30 g. Administered as a loading dose of 1–15 g at induction of anaesthesia, followed by a maintenance dose of 1–2 g/h as a continuous infusion during surgery[8]
Desmopressin	0.3 μg/kg as a 20-min infusion at initiation of bypass[8,18]
Eptacog alfa (recombinant factor VIIa)	35–90 mg/kg bolus after discontinuation of bypass[19,20]

consequence, systemic haemostatic agents, such as antifibrinolytics and procoagulants, are increasingly being used to limit blood loss in major surgical procedures where significant blood loss is likely, despite sound surgical techniques, (e.g. cardiothoracic, orthopaedic and spinal surgery and orthotopic liver transplantation) and the treatment of patients with specific underlying haemostatic defects.[2,8-16] The recommended dosages of the most frequently used agents are shown in table I.

1.1 Antifibrinolytics

Antifibrinolytic agents, including the lysine analogues tranexamic acid and ε-aminocaproic acid, and the protease inhibitors aprotinin and nafamostat, have been used successfully for several decades to prevent and/or control bleeding in surgical procedures in both patients with normal haemostasis and those with inherited blood disorders.[8,21,22] The benefits and risks of these drugs in these indications are discussed in more detail in subsequent sections.

Lysine analogues act by forming a reversible complex with plasminogen, whereas protease inhibitors inhibit serine proteases such as plasmin, trypsin and kallikrein.[13] Antifibrinolytics are predominantly used in a surgical setting (table II).[13] Until its recent withdrawal from the market pending analysis of the BART (Blood conservation using Antifibrinolytics in a Randomized Trial) study results,[23,24] aprotinin was the only antifibrinolytic agent approved in the US[17] and Europe,[25] where it was indicated for prophylactic systemic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass surgery who are at increased risk for blood loss and transfusion.

1.1.1 Aprotinin

Aprotinin is a polypeptide of bovine origin that inhibits a broad spectrum of plasma serine proteases over a wide range of concentrations. Inhibition of serine proteases by aprotinin results in a reduction in fibrinolysis, thereby aiding haemostasis during surgical procedures.[64] As well as inhibition of fibrinolysis, the prohaemostatic effects of aprotinin are due to several other mechanisms, including stabilization of platelet function.[17] Aprotinin is the only antifibrinolytic agent with Class A Level 1 evidence for reduction of transfusion requirements and prevention of reoperation for excessive bleeding in cardiac surgery.[65]

Multiple randomized clinical trials have clearly established the efficacy of aprotinin in reducing blood loss and transfusion requirements in patients undergoing cardiac surgery (see table II for outcomes in larger, randomized studies), orthotopic liver transplantation and, to a lesser extent, thoracic surgery and orthopaedic surgery.[13,66-73] Low-dose aprotinin has been shown to be as generally effective as high-dose aprotinin.[28] Meta-analyses have

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Table II. Selected clinical trials of the most common systemic haemostatic agents used during cardiac, hepatic or major orthopaedic surgical procedures. Randomized controlled trials (n ≥ 70) published since 1990 were preferred. Mean values are shown

Agent compared (indication)	Main efficacy outcomes	Thrombotic adverse effects
Aprotinin		
Vs placebo, control, tranexamic acid and/or ε-aminocaproic acid (CABG)[26-39]	↓ Post-op drainage loss in first 12–24 h (by 23–62% in uncomplicated surgery, 67% in reoperation), ↓ total haemoglobin loss (by 68%), ↓ no. of pts requiring transfusion (by 42–76%), ↓ no. of units transfused (by 83%) vs placebo or control. Aspirin prior to procedure did not affect efficacy. Low- or high-dose aprotinin regimens generally equally effective. Fewer aprotinin than tranexamic acid or ε-aminocaproic acid recipients required transfusion in one study; similar efficacy to ε-aminocaproic acid or tranexamic acid in others	
Vs placebo (orthopaedic surgery [hip, spine])[40,41]	↓ Blood loss (by 31%), ↓ no. of pts requiring transfusion (by 15–51%), ↓ red blood cell requirements (by 56%)	No ↑ incidence of post-op VTE
Vs placebo or tranexamic acid (hepatic surgery [elective resection, orthotopic transplantation])[42-45]	↓ Blood loss (by 31–45%), ↓ no. of pts transfused (by 20–60%), ↓ units transfused (by 61%) vs placebo. Similar efficacy to tranexamic acid	
Tranexamic acid		
Vs placebo, control, aprotinin, desmopressin, and/or ε-aminocaproic acid (cardiac surgery [CABG, valve replacement or ASD repair])[18,26,27,31,34-37,39,46-50]	↓ Post-op drainage loss (by 20–48%), ↓ no. of pts requiring transfusion (by ≈43%) in first 12–24 h vs placebo or control. More effective than desmopressin. No difference in efficacy vs aprotinin in three studies but less efficacy in two others. No difference in efficacy vs ε-aminocaproic acid	No ↑ incidence of adverse events
Vs placebo, control and/or ε-aminocaproic acid (orthopaedic surgery [knee, hip])[51-55]	↓ Total blood loss (by 25–56%), ↓ no. of pts requiring transfusion (by 50–90%), ↓ no. of units transfused (by 66–95%) vs placebo or control. No difference in efficacy vs ε-aminocaproic acid	No ↑ incidence of post-op VTE
Vs placebo, ε-aminocaproic acid or aprotinin (hepatic surgery [elective resection, orthotopic transplantation])[45,56,57]	↓ Total blood loss (by 50%), no. of pts transfused (0% vs 16% of placebo recipients). ↓ Hospital costs (by 19%), ↓ operation time (by 17%) vs placebo. Similar efficacy to aprotinin, greater efficacy than ε-aminocaproic acid	
ε-aminocaproic acid		
Vs control, placebo, tranexamic acid and/or aprotinin (CABG)[26,33,35,38,58,59]	↓ Post-op drainage loss (by 34%) in first 12–24 h vs control. Similar or less efficacy to aprotinin in ↓ blood loss (no difference in transfusion requirements), similar efficacy to tranexamic acid	
Vs control or tranexamic acid in major orthopaedic surgery[54]	↓ Blood loss by 38%, ↓ no. of pts transfused (by 66%), ↓ units transfused (by 66%) vs control. Similar efficacy to tranexamic acid	No ↑ incidence of post-op VTE
Vs tranexamic acid (hepatic surgery [orthotopic transplantation])[57]	No different to placebo at reducing blood component requirements, whereas tranexamic acid was superior to placebo	
Desmopressin		
Vs placebo or tranexamic acid (various)[18,60-63]	In cardiac surgery, ↓ total drainage loss (by 40%), ↓ transfusion requirements (by 30%), but platelet count ↑; during spinal fusion surgery, ↓ intra-op blood loss (by 33%), ↓ transfusion requirements (by 26%) vs placebo. No effect in hip or knee surgery. Less effective than tranexamic acid	

ASD = atrial septal defect; **CABG** =coronary artery bypass graft; **post-op** = post-operative; **pts** = patients; **VTE** = venous thromboembolism; ↓ indicates reduced; ↑ indicates increased.

indicated that in addition to these benefits, aprotinin decreases mortality in cardiac surgery almost 2-fold and decreases the need for reoperation.[74-76] Although aprotinin is effective in reducing both surgical blood loss and transfusion requirements,[77] it is considerably more costly in terms of acquisition costs[36,38,39,78] and direct and indirect bleeding-related costs than other antifibrinolytics.[36,38]

Aprotinin has been extensively monitored for adverse events in clinical trials and postmarketing databases. Although it is generally well tolerated, hypersensitivity reactions may occur[79-81] and the risk of this occurring appears to increase after repeated use.[10,11,13,82,83] A case of acute respiratory distress syndrome after an infusion of aprotinin because of bleeding following tonsillectomy has been reported.[84]

Aprotinin does not appear to be associated with an increased risk of venous thromboembolism (VTE),[71] although isolated cases of fatal thrombosis and/or VTE after cardiac or thoracoabdominal aortic surgery or orthotopic liver transplantation have been reported.[85-87]

Unlike the lysine analogues tranexamic acid and ε-aminocaproic acid, aprotinin has high affinity for the kidneys, which could potentially affect renal function.[88] In two retrospective observational studies of aprotinin in patients undergoing either primary or complex coronary artery surgery,[89-91] and a large prospective study in patients undergoing liver transplantation,[92] aprotinin was found to be associated with an increased risk of renal dysfunction during the first postoperative week[89,92] or renal failure requiring dialysis in comparison with patients who did not receive antifibrinolytic therapy.[91] In one analysis, aprotinin was also associated with increased mortality.[90] In comparison, neither tranexamic acid and/or ε-aminocaproic acid was associated with an increased risk of renal,[89-91] cardiac or cerebral events or increased mortality.[90,91] Additional unpublished observational data made available to the US FDA also indicated that aprotinin may be associated with an increased risk for death, kidney failure, congestive heart failure or stroke.[93] While these studies point to a possible association between aprotinin and serious end-organ damage, the retrospective analyses may have been influenced by methodological shortcomings (e.g. the presence of a higher baseline risk in patients receiving aprotinin).[65,94,95]

The BART study, a randomized comparison of aprotinin, tranexamic acid and ε-aminocaproic acid in coronary artery bypass surgery in ≈3000 patients at increased risk for blood loss and transfusion, was planned to evaluate the relative efficacy, safety and tolerability of these three antifibrinolytics.[96] Importantly, this trial was halted in October 2007 following results of a planned periodic analysis that showed an increased incidence of all-cause mortality with aprotinin versus tranexamic acid or ε-aminocaproic acid.[24,97] As a result, world-wide marketing of the drug has been withdrawn until the results of the trial have been compiled and analysed and the benefit-risk profile of aprotinin is clarified.[24]

1.1.2 Tranexamic Acid

Tranexamic acid, which has been used in surgical situations since the 1960s, acts by reversibly blocking lysine binding sites on plasminogen molecules, thereby counteracting fibrinolytic activity.[14,21,98] It is available as oral and intravenous formulations: intravenous tranexamic acid is mainly used during major surgery, while the oral aqueous formulation has been used in some situations (e.g. dental surgery).

In clinical trials in patients undergoing cardiac or major orthopaedic surgery (see table II for outcomes in larger, well designed studies), tranexamic acid was effective in reducing total blood loss, the need for transfusion and the quantity of blood product transfused. In studies comparing tranexamic acid and other haemostatic agents, tranexamic acid generally showed similar efficacy to aprotinin or ε-aminocaproic acid. Tranexamic acid also showed greater efficacy than desmopressin. In a study in patients undergoing cardiopulmonary bypass surgery reported by Hekmat et al.,[39] blood loss was significantly higher with tranexamic acid than aprotinin (by 140mL; $p = 0.03$); however there was no significant difference between tranexamic acid and aprotinin in transfusion requirements. Tranexamic

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acid had similar haemostatic effectiveness as aprotinin in a propensity score case-control comparison in patients undergoing high-transfusion-risk cardiac surgery.[89]

Several meta-analyses of trials in cardiac surgery[66,74,99,100] or liver transplantation[73] and a Cochrane review of antifibrinolytic agents[76] have indicated that tranexamic acid is as effective as aprotinin in decreasing blood loss and the need for allogenic blood transfusion. Although, another meta-analysis has suggested that tranexamic acid may be less effective than aprotinin in reducing 24-hour blood loss,[101] the clinical relevance of this result is uncertain, as the incremental difference in blood loss was small and transfusion requirements did not differ between the two drugs. An update of the latter analysis added four trials subsequently published or identified and found no significant difference between aprotinin and tranexamic acid in the proportions of patients transfused and the number of units of red cells transfused.[78]

Tranexamic acid has also been evaluated in other surgical settings; although it is of little value in some (e.g. thyroid surgery),[102] meta-analyses of trials in orthopaedic surgery indicate that the drug reduces the need for allogenic blood transfusion in knee arthroplasty,[103] but data in total hip arthroplasty are inconclusive.[104] Tranexamic acid may be useful in patients undergoing caesarean section[105] and in surgical patients with underlying bleeding disorders,[106,107] but further investigation is required to confirm results of these studies.

The tolerability profile of tranexamic acid is well established (see part 2[3] of this review for discussion of tolerability of tranexamic acid in women with excessive or heavy menstrual bleeding). Adverse events are uncommon and usually manifest as gastrointestinal complaints, such as nausea, vomiting, dyspepsia or diarrhoea. Symptoms usually disappear with dose reduction.[108] Hypersensitivity reactions such as rash occur occasionally,[109,110] and anaphylaxis to tranexamic acid has been reported.[111] Additional, albeit uncommon (<1%) adverse events include change in mood, giddiness, low blood pressure/orthostatic reactions, myalgias, muscle tenderness, skin rash and alteration in colour vision.[108] While the aetiology of tranexamic acid-induced changes in colour vision has not been elucidated, it has been speculated that they could represent a pharmacodynamic effect on one or more of the pigments involved in colour differentiation in the retinal cone cells.[112] The occurrence of central venous stasis retinopathy has also been reported after the use of tranexamic acid.[113]

Despite a theoretical risk of VTE events, there have only been isolated reports of venous or arterial thrombosis or embolism associated with the use of tranexamic acid[21,114-119] and a causal relationship has not been established.[108,120,121] VTE was not reported or suspected during the 8-week follow-up period in >3000 women aged 30–54 years who were treated with intravenous then oral tranexamic acid after laser conisation of the cervix for mild to severe dysplasia or carcinoma *in situ*.[122] Of interest, tranexamic acid did not compromise early venous graft patency in a recent study in patients undergoing coronary artery bypass graft surgery.[48]

1.1.3 Nafamostat

Nafamostat is a broad-spectrum serine protease inhibitor with a mechanism of action similar to that of aprotinin.[13] Most clinical experience with nafamostat has been in Japan. Although the addition of nafamostat to usual treatment significantly inhibits fibrinolysis and reduces blood loss compared with usual treatment alone in open heart surgery[123-126] or hepatic resection,[127] its antifibrinolytic effect is not as great as that of aprotinin.[128]

1.1.4 ε-Aminocaproic Acid

ε-Aminocaproic acid is also a lysine analogue and has a similar mechanism of action to tranexamic acid but is about 7- to 10-fold less potent, thus requiring dose adjustment.[2,82] The largest clinical experience with this agent has been in patients undergoing cardiac surgery and orthotopic liver transplantation (see table II for outcomes in larger, well designed studies).

In clinical trials in patients undergoing cardiac surgery, ε-aminocaproic acid was effective in reducing post-operative blood loss, being as effective as aprotinin according to an earlier meta-analysis[129]

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and a Cochrane review,[76] but less effective than aprotinin according to later meta-analyses,[100,101] although transfusion requirements with either drug did not differ.[101] ε-Aminocaproic acid showed no benefit over placebo in cancer patients undergoing major orthopaedic surgery. [70] The efficacy of the drug in orthotopic liver transplantation has not been proven in randomized, controlled trials.[16]

ε-Aminocaproic acid is generally well tolerated. However, adverse events appear to be more frequent than with tranexamic acid,[82] and include gastrointestinal reactions, oedema, headache, bradycardia and hypotension.[130] It is possible that the higher doses of ε -aminocaproic acid required to achieve a clinical benefit similar to that of tranexamic acid are associated with a higher incidence of gastrointestinal discomfort.[82]

There have been a few reports of myopathies, including rhabdomyolysis (the breakdown of muscle fibres resulting in the release of muscle cell components into the circulation), with ε-aminocaproic acid, some of which were associated with severe muscle weakness.[131] Rhabdomyolysis may be toxic to the kidney, and can result in severe renal dysfunction and even death. It is therefore important to be able to recognize the signs and symptoms of drug-induced rhabdomyolysis to ensure prompt intervention and treatment.

There have been isolated instances of thrombosis associated with ε-aminocaproic acid,[132-135] including two fatal cases following use of the drug in patients undergoing aortic surgery,[133] a nonfatal case in a patient undergoing cardiac surgery[134] and nonfatal cerebral sinus thrombosis in a woman undergoing treatment for heavy menstrual bleeding.[132] Pulmonary embolism and intracardiac thrombus formation have been described in ε-aminocaproic acid recipients undergoing orthotopic liver transplantation.[16]

1.2 Procoagulants

Procoagulant drugs include the synthetic vasopressin analogue desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) and eptacog alpha (recombinant factor VIIa; Novoseven®).[13] These drugs have been mainly used to prevent excessive or heavy bleeding during surgery or to manage spontaneous bleeding episodes in patients with pre-existing bleeding disorders, but have also been evaluated in a variety of settings in patients without coagulation defects, including major surgery. [13]

1.2.1 Desmopressin

Desmopressin, a vasopressin V_2 agonist, acts by causing a rapid, dose-dependent increase in plasma levels of factor VIII and von Willebrand factor in both patients with pre-existing haemostatic disorders, uraemia or drug-induced platelet dysfunction and in normal individuals.[2,13,82] Desmopressin also appears to improve platelet aggregation,[136] as observed in patients with platelet dysfunction.[137] Tissue plasminogen activator (tPA) activity is also increased after intravenous administration of desmopressin, but has not been associated with clinically significant fibrinolysis.[13]

It has principally been used in patients with pre-existing haemostatic disorders such as haemophilia A and von Willebrand's disease to decrease bleeding times and blood loss during surgical procedures, but it has also been studied in the setting of post-operative blood loss with the aim of reducing transfusion requirements in patients undergoing cardiac surgery.[2,13,60,82] Outcomes in larger, well designed studies are shown in table II.

Adverse effects of desmopressin include mild facial flushing, headache, palpitations, and hypotension;[138] these are due to its vasomotor effects. Because of its potent antidiuretic effect, water retention and hyponatraemia may occur.[139-141] Abdominal cramping has also been reported. Since desmopressin can raise baseline levels of factor VIII and von Willebrand factor >300%,[138,142,143] and because there is an association between elevated factor VIII and thrombosis,[144] there has been concern about the widespread use of desmopressin leading to the development of VTE.[145] There has also been several reports of acute myocardial infarction or cerebral thrombosis [2,13,146] or thrombotic events in patients predisposed to thrombus formation[138] associated with desmopressin use. Consequently, desmopressin should be used with caution in pa-

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tients with coronary heart disease and in those with coexisting genetic prothrombotic conditions, such as Factor V Leiden or antiphospholipid antibodies, and/or co-existing acquired prothrombotic conditions, including the postoperative setting, hormone use and smoking.[8,13,147] A recent example is a case of a cerebral arterial thrombosis in a female smoker with mild von Willebrand disease who was also taking a combined estrogen/progestogen oral contraceptive (COC) and who was administered desmopressin to ensure haemostasis during minor plastic surgery.[148]

1.2.2 Eptacog Alfa (Recombinant Factor VIIa)

Eptacog alfa is a vitamin K-dependent glycoprotein structurally similar to human plasma-derived factor VIIa. It acts by enhancing the natural coagulation pathway by two different mechanisms, one tissue factor (TF)-dependent, the other TF-independent.[13,149-151]

Eptacog alfa is used with high rates of efficacy in the management of bleeding episodes and providing haemostasis cover during surgery in patients with congenital haemophilia complicated by inhibition.[152] There have been numerous reports of its ability to correct prolonged INRs (international normalized ratios) and avert or reverse bleeding in patients with warfarin-induced coagulopathy.[153,154] Although eptacog alfa is only indicated for use in patients with underlying haemostatic abnormalities, more recently it has been successfully used off label as a haemostatic agent in trauma and surgery patients, and in those with intracranial haemorrhage without pre-existing coagulopathy.[149,152,155-158] An observational study[19] and a small randomized, placebo-controlled trial[20] suggest that blood loss and transfusion/blood product requirements are reduced with administration of eptacog alfa in patients undergoing cardiac surgery. However, in three randomized trials in patients undergoing orthotopic liver transplantation[159,160] or liver resection,[161] efficacy was not shown with prophylactic use of eptacog alfa.[162]

Eptacog alfa is generally well tolerated, being relatively free of antigenicity, thrombogenicity and viral transmission.[149] Serious adverse events associated with its use (in ≈1% of patients) have included thrombotic events (mainly in patients with predisposing factors such as diabetes mellitus, obesity and cancer), angina, tachycardia, ataxia, acute renal failure, anaphylactic shock and abnormal liver function.[149,152,163] With regard to thrombogenicity, a safety review of 13 clinical trials of eptacog alfa in a variety of indications concluded that there were no significant differences in the incidence of thrombotic adverse events between placebo or eptacog alfa treatment on a trial-by-trial basis or when data were combined.[164] In addition, a recent review by O'Connell et al.[150] of serious thrombotic events reported to the FDA's adverse event reporting system revealed that most events that followed the use of eptacog alfa were for off-label indications. The authors proposed that randomized controlled trials are required to establish the efficacy and safety of eptacog alfa in patients without haemophilia.[150] As might be expected, the presence of additional prothrombotic factors appears to magnify the risk of thrombosis when administered in patients without a pre-existing coagulopathy. [150]

2. Other Agents

2.1 Etamsylate

Etamsylate (ethamsylate) is a synthetic haemostatic agent that acts by increasing platelet adhesiveness and restoration of capillary resistance.[165] It has been used to reduce capillary bleeding in ear, nose and throat surgery, after prostatectomy, and has also been evaluated for its potential to prevent periventricular haemorrhage in preterm infants.[14,166,167] In addition, its use in preterm infants to prevent periventricular haemorrhage has not resulted in improvement of the long-term neurological or neurodevelopmental outcome.[14,166] Etamsylate is well tolerated, with few patients reporting adverse events (mostly nausea, headache and rashes).[14,165]

2.2 Conjugated Estrogens

Conjugated estrogens, which can be administered intravenously, have a variety of effects on the haemostatic system, although their precise mode of

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Table III. Safety profiles of the most frequently used systemic haemostatic agents used in major surgery

Agent	Adverse effect[a]				
	thrombosis	nephrotoxicity	gastrointestinal tract	hypersensitivity reactions	other
Aprotinin	−	+	−	+++	Probable increased all-cause mortality
Tranexamic acid	−	−	+	+	Retinopathy (rarely)
ε-Aminocaproic acid	−	−	+++	−	Rhabdomyolysis (rarely)
Desmopressin	+[b]	−	−	−	Hyponatremia; vasomotor effects
Eptacog alfa (recombinant factor VIIa)	+++	+	+	+	

a Frequency of adverse effects is shown as − indicates none; + indicates low; ++ indicates medium; +++ indicates high.

b Arterial thrombosis in at-risk patients.

action in achieving haemostasis is unknown. Few clinical trials have been conducted to determine the efficacy of conjugated estrogens in reducing blood loss, but shortening of bleeding times in patients with uraemia,[168] management of gastrointestinal bleeding in uraemic patients,[169,170] and reduction of blood transfusion requirements in patients undergoing orthotopic liver transplantation[171] have been reported.

In general, conjugated estrogens are well tolerated and few adverse effects have been reported.[13] However, the thrombotic profile of these agents, which is similar to that seen with COCs (see part 2[3] of this review), is of concern.[13,172]

3. Conclusion

Selection of the most appropriate haemostatic pharmacological agents in patients undergoing major surgical procedures requires not only consideration of the clinical evidence supporting the efficacy of the various agents, but also the available safety data to ensure that the benefits of this approach are not jeopardized by the risks (see table III for a summary of the safety profiles of the most commonly used systemic haemostatic agents). The procoagulant agents, desmopressin and recombinant factor VIIa, are effective in reducing bleeding in patients with pre-existing haemostatic disorders. Eptacog alpha is also effective in reducing blood loss after trauma and surgery in patients without congenital bleeding disorders and is increasingly being used in these settings. Nevertheless, the safety of this agent in off-label indications (especially the risk of thrombosis) has not been established.

Aprotinin and the lysine analogues tranexamic acid and ε-aminocaproic acid are effective haemostatic agents used to prevent major blood loss during surgery. However, recent data indicating that aprotinin use is associated with renal dysfunction, coupled with the decision to halt the BART trial because of increased all-cause mortality with aprotinin relative to tranexamic acid and ε-aminocaproic acid and the subsequent decision to withdraw the drug pending further analysis of the BART study, indicate an uncertain future for aprotinin.

Part 2 of this review[3] considers the efficacy and adverse effect profiles of systemic haemostatic agents commonly used to manage excessive or heavy menstrual bleeding and provide individual benefit-risk profiles that may assist clinicians in selecting appropriate pharmacological therapy in this setting.

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oping a sustained-release form of oral tranexamic acid). Dr Lukes has been an investigator on several trials using tranexamic acid, including the CDC study on heavy periods using tranexamic acid and desmopressin, is a consultant to Xanodyne Pharmaceuticals Inc. (who are pursuing FDA approval for tranexamic acid in the US) and has been a speaker for Daiichi Sankyo Co. Ltd (FIGO 2006). Dr Lukes received a small stipend for contributing to this manuscript.

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