Skilful surgery combined with blood-saving methods and careful management of blood coagulation will all help reduce unnecessary blood loss and transfusion requirements. Excessive surgical bleeding causes hypovolaemia, haemodynamic instability, anaemia and reduced oxygen delivery to tissues, with a subsequent increase in postoperative morbidity and mortality. The role of anaesthetists in managing surgical blood loss has increased greatly in the last decade. Position of the patient during surgery and the provision of a hypotensive anaesthetic regimen were once considered the most important contributions of the anaesthetist to decreasing blood loss. Now, several pharmacological haemostatic agents are being used by anaesthetists as blood-saving agents.

After a brief discussion of the physiology of haemostasis, this article will review the evidence for the role of such agents in reducing perioperative blood loss and transfusion requirements.

**Keywords:** blood, factor VIIa; blood, haemostasis; blood, loss; polypeptides, aprotinin

Skilful surgery combined with blood saving methods and careful management of blood coagulation will all help reduce unnecessary blood loss and transfusion requirements. Excessive surgical bleeding causes hypovolaemia, haemodynamic instability, anaemia and reduced oxygen delivery to tissues, with a subsequent increase in postoperative morbidity and mortality. Adverse effects of allogeneic blood transfusion include transmission of infectious diseases, immunosuppression, transfusion-related acute lung injury, transfusion reactions and graft-vs-host reactions. The cost implication for blood transfusion is also significant and includes the direct blood transfusion costs as well as indirect costs originating from additional treatments and prolonged hospitalization. In a study conducted in the USA, avoiding allogeneic transfusions reduced total treatment costs in abdominal surgery by approximately $5000 per patient.

The role of anaesthetists in managing surgical blood loss has grown greatly in the last decade. Intraoperative blood loss varies according to the anaesthetic agent used and with the type of anaesthesia. Simple elevation of the surgical site may reduce blood loss, but may risk embolism in regions with non-collapsing veins. Maintaining normothermia reduces blood loss, because of the deleterious effects of hypothermia on platelet function. Blood coagulation can also be compromised by fluid replacement and profound haemodilution. Moderate crystalloid substitution accelerates rather than inhibits blood coagulation; however, with advanced crystalloid haemodilution blood coagulation may become compromised. The use of colloids may also compromise coagulation, hydroxyethyl starch more than gelatin and serum albumin. A combination of generous amounts of crystalloids with some colloids may be optimal to maintain blood coagulation and avoid blood loss as resulting from coagulopathy. Controlled hypotension has been used to decrease surgical blood loss. The limited efficacy of this technique may be related to the fact that relatively low blood pressures are commonly tolerated in routine anaesthesia; thus, a further decrease in mean arterial pressure to approximately 50 mm Hg may only offer limited benefit.

Some surgical procedures may be associated with excessive blood loss and/or deranged haemostasis in patients without pre-existing haemostatic abnormalities (cardiopulmonary bypass, orthotopic liver transplantation, prostatic surgery and some orthopaedic procedures). Moreover, we are increasingly confronted with subgroups of patients who refuse blood transfusion or who are likely to lose more blood in the perioperative period (e.g. patients on antiplatelet agents or anticoagulants, patients with hepatic cirrhosis, and those with chronic renal failure). Several pharmacological haemostatic agents are currently being used by anaesthetists as blood-saving agents in such circumstances.

After a brief discussion of the physiology of haemostasis, we will review the evidence for the role of such agents in reducing perioperative blood loss and transfusion requirements.
Physiology of haemostasis in surgery and trauma

Haemostasis depends on a successful balance between the coagulation, complement and fibrinolytic pathways, with complex interactions between plasma proteins, platelets, blood flow and viscosity, and the endothelium. Formation of the primary haemostatic plug at the site of a damaged vessel is the first event in the control of bleeding. Von Willebrand factor binds to the exposed subendothelium, exposing multiple intrinsic binding sites for a specific platelet membrane structure termed GPIb. This is followed by platelet activation, adhesion and generation of a platelet plug. Platelets adhering at the site of injury are exposed to several activating stimuli, which enhance the initial adhesion and allow other platelets to accrete on those already attached. Activation of platelets by thrombin, ADP and von Willebrand factor–GPIb progresses through several metabolic pathways to induce spreading of the platelets over the damaged surface.

Coagulation cascade

Coagulation involves the laying down of a strong fibrin mesh through the primary platelet plug and is brought about by the action of a sequence of pro-enzymes and cofactors that work in concert to generate the final enzyme, thrombin. Thrombin then directly cleaves fibrinogen to produce fibrin (Fig. 1). The enzymes involved in blood coagulation belong to a family of proteases known as serine proteases, a class of enzymes with a common mechanism of enzymatic action that requires the catalytic triad of serine, aspartic acid and histidine within the active site.

Injury to the arterial or venous wall exposes perivascular, tissue factor-expressing cells to blood. Tissue factor (TF) is a cellular receptor for activated factor VII (factor VIIa) and factor VII. It is expressed constitutively in most non-vascular cells and can be induced in monocytes, endothelial cells, smooth muscle cells, circulating monocytes, tissue macrophages and fibroblasts. Factor VIIa, found in small amounts in normal plasma, binds to exposed TF. Once bound to TF, factor VIIa can catalyse the activation of factor VII, which also binds to exposed TF. The factor VIIa–TF complex then activates factors IX and X in the presence of Ca$^{2+}$, leading to the generation of factors IXa and Xa respectively. Activation of factor X through the above mechanism is referred to as the extrinsic pathway.

The intrinsic pathway is initiated by activation of factor XII by kallikrein on foreign surfaces or damaged endothelium, and is facilitated by kininogen. The active form of factor XII, factor XIIa, catalyses the conversion of factor XI to its active form, factor XIa. In the presence of Ca$^{2+}$, factor XIa activates factor IX to its active form, factor IXa. Factor IXa binds to the cofactor factor VIIIa bound on membrane surfaces in the presence of calcium ions to generate a complex with enzymatic activity known as ‘tenase’, a nickname for the enzymatic activity that acts on factor X.

Activation of factor X to factor Xa by the extrinsic or intrinsic pathways is the start of the common pathway of coagulation. The latter pathway is thought to be of little significance in vivo since patients with factor XII, prekallikrein or kininogen deficiency have no bleeding disorders. These proteins are not required for haemostasis. However, they may play a role in fibrinolysis and in fibrin formation during inflammation and wound healing. When factor Xa is generated, it complexes with factor Va, phospholipid and calcium to form the prothrombinase complex, which converts prothrombin to its active form, thrombin. The generated

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**Fig 1** The coagulation cascade. *A small quantity of activated factor VII is physiologically present in the plasma and is responsible for the initial binding with tissue factor (TF). Ca$^{2+}$, calcium ion; PF3, platelet factor-3; HMWK, high molecular weight kininogen.*
thrombin: (i) cleaves fibrinogen, releasing fibrin; (ii) activates factor XIII, responsible for cross-linking the fibrin polymer, rendering it resistant to fibrinolysis; (iii) activates factors V and VIII, generating factors Va and VIIIa, which are cofactors for factors Xa and IXa; and (iv) is a potent platelet-aggregating agent.

Activation of the coagulation cascade triggers several physiological pathways that tend to counteract and limit the spread of coagulation to the area of injury.

**Antithrombin**

Antithrombin inhibits thrombin, factor Xa and other activated clotting factors, but these reactions are slow in the absence of heparin. With heparin, however, the rate of inhibition is accelerated 1000-fold. Although heparin is not normally found in the blood, vascular endothelium is rich in heparan sulphate. Most of the heparan sulphate is located on the non-luminal surface of the endothelium and is exposed only when the vessel lining is damaged.

**Protein C pathway**

In addition to inactivation by antithrombin, thrombin is also inhibited by binding thrombomodulin, a thrombin receptor found on the endothelium. Once bound to thrombomodulin, thrombin undergoes a conformational change at its active site that converts it from a procoagulant enzyme into a potent activator of protein C. Activated protein C serves as an anticoagulant by proteolytically degrading and inactivating factors Va and VIIIa, thereby blocking thrombin generation.

**Tissue factor pathway inhibitor**

Inhibition of the factor VIIa–TF complex is affected by tissue factor pathway inhibitor (TFPI), the majority of which is bound to endothelium. Tissue factor pathway inhibitor first complexes and inactivates factor Xa and then the TFPI–factor Xa complex inactivates factor VIIa within the factor VIIa–TF complex.

**Fibrinolytic system**

Designed to remove intravascular fibrin, thereby restoring blood flow, fibrinolysis is initiated by plasminogen activators that convert plasminogen to plasmin. Plasmin degrades fibrin into soluble fibrin degradation products. It inactivates factors Va and VIIIa, amplifies its own generation, disrupts platelet function and degrades matrix proteins. Human plasminogen harbours within its structure specific lysine-binding sites that mediate the binding of plasminogen to fibrin and play a crucial role in the regulation of fibrinolysis. Regulation and control of the fibrinolytic system is mediated by specific molecular interactions among its main components, and by controlled synthesis and release of plasminogen activators and plasminogen activator inhibitors, primarily from endothelial cells (Fig. 2). Enzymes of the fibrinolytic system are serine proteases, whereas the inhibitors of the fibrinolytic system are grouped into the serpin (serine proteinase inhibitor) superfamily.

Two immunologically distinct physiological plasminogen activators have been identified in blood: tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Tissue-type plasminogen activator, which is synthesized and secreted by endothelial cells, mediates intravascular plasminogen activation and is primarily involved in the dissolution of fibrin in the circulation. In contrast, u-PA binds to specific cellular receptors, resulting in enhanced activation of cell-bound plasminogen, and is primarily involved in tissue remodelling and repair. The fibrinolytic system can be inhibited at two levels. Plasminogen activator inhibitors, the most important of which is endothelial cell-derived type 1 plasminogen activator inhibitor (PAI-1), block t-PA and u-PA, whereas α2-antiplasmin inhibits plasmin. Although α2-antiplasmin rapidly complexes and inactivates free plasmin, fibrin-bound plasmin is relatively protected from inactivation, so that fibrinolysis can occur despite physiological levels of this inhibitor.

A limited number of pharmacological agents have been in use for correction of haemostatic defects in the perioperative period. The lack of clear insight into the pathogenesis of perioperative bleeding as well as its multifactorial origins has hampered the development of specific and new haemostatic agents and added more confusion and ambiguity to the mechanisms of action and clinical applications of currently available agents.

**Vasopressin analogues**

**Desmopressin**

Desmopressin acetate, 1-desamino-8-D-arginine vasoressin (DDAVP), is a synthetic vasopressin analogue. It is pharmacologically altered from naturally occurring vasoressin by deamination of hemicysteine at position 1 and...
substitution of D-arginine for L-arginine at position 8. These changes virtually eliminate vasopressor (V₁ receptor agonist) activity, and enhance the antidiuretic (V₂ receptor agonist) action. It also prolongs the duration of action from 2–6 h to 6–24 h by increasing resistance to enzymatic cleavage.³⁹ Desmopressin is also more potent than arginine vasopressin in stimulating the endothelial release of factor VIII and von Willebrand factor into the plasma (V₂ receptor-mediated effect), where they form a complex with platelets and enhance their ability to aggregate.³⁹ This effect, which mimics replacement therapy with blood products, forms the rationale for the use of desmopressin in the treatment of patients with mild haemophilia A and type I von Willebrand’s disease, who have spontaneous bleeding or are scheduled to undergo surgery.¹¹³

For haemophilia A, von Willebrand’s disease, uraemic thrombocytopeny, and when used perioperatively, desmopressin is given in a dose of 0.3 μg kg⁻¹ and infused slowly because of the risk of acute hypotension.³⁹ Plasma concentrations of factor VIII and von Willebrand factor are approximately doubled or quadrupled, reaching a peak 30–60 min after i.v. infusion.⁸⁴ These doses can be repeated as clinically necessary at intervals of 12 to 24 h, but tachyphylaxis may occur after three or four doses.⁹² After i.v. injection, desmopressin has a distribution half-life of 7–8 min and an elimination half-life of 2.5–4.4 h.⁶²

Desmopressin shortens the bleeding time in a variety of congenital platelet function defects. The ability to shorten the bleeding time in these patients is unpredictable and must be assessed individually in each patient.¹¹⁸ Desmopressin can shorten the prolonged bleeding time in patients with hepatic cirrhosis and in chronic uraemia,⁹¹ despite the fact that von Willebrand factor and factor VIII are within normal levels. It is therefore used to prevent haemorrhage after biopsies or minor surgical procedures or to control acute bleeding in such patients.¹²⁸ Patients with prolonged bleeding time secondary to antiplatelet drugs (aspirin or ticlopidine) may also benefit from the effect of desmopressin as it promptly normalizes primary haemostasis and shortens the bleeding time in most of these patients.¹²⁸

**Desmopressin in cardiac surgery**

Cardiac surgery is one of the classic situations in which there is a call for blood-saving measures. Factors contributing to the relatively large blood losses include the size of the surgical wound, the exposure of blood to artificial surfaces in the extracorporeal circuit, enzymatic and mechanical injury to platelets and coagulation factors, and hyperfibrinolysis during and after cardiopulmonary bypass. In the mid-1980s, there was considerable interest in the haemostatic effect of desmopressin in patients undergoing cardiopulmonary bypass. However, the initial promise suggested by preliminary studies was never confirmed by larger trials. In 1995, Cattaneo and colleagues¹⁷ published a meta-analysis of 17 randomized, double blind, placebo-controlled trials which included 1171 patients undergoing cardiac surgery; 579 of them were treated with desmopressin and 592 with placebo. Desmopressin significantly reduced postoperative blood loss by 9% but had no significant effect on transfusion requirements. In a subanalysis of trials in which the mean blood loss in placebo-treated patients fell in the upper third of distribution of blood loss, desmopressin significantly decreased postoperative blood loss by 34%. In 1997, Laupacis and Ferguson²⁷ published another meta-analysis showing that desmopressin was ineffective in reducing blood loss in cardiac surgery. The primary outcome was the proportion of patients who received at least one perioperative allogeneic red cell transfusion. The most recent meta-analysis of randomized controlled trials studying the role of desmopressin in cardiac surgery was performed by Levi and colleagues⁸⁶ in 1999, in which the use of desmopressin resulted in a small decrease in perioperative blood loss but was not associated with a beneficial effect on other clinical outcomes (mortality, repeat thoracotomy, proportion of patients receiving transfusion). Moreover, desmopressin was associated with a 2.4-fold increase in the risk of myocardial infarction. Therefore, the routine use of desmopressin in uncomplicated cardiac operations in patients without pre-existing bleeding disorders cannot be recommended. However, its use may be beneficial in subgroups of patients with an increased risk of bleeding. In an attempt to identify a group of patients that might benefit from desmopressin therapy, Mongan and Hosking¹⁰⁰ used postoperative thromboelastography to stratify patients according to haemostatic function. They found that desmopressin reduced blood loss and transfusion needs in patients with low maximal amplitudes (<50 mm), but no decrease in blood loss occurred in those patients with a maximal amplitude >50 mm. Despotis and colleagues²¹ used a new point-of-care test (hemoSTATUS) to identify patients at risk of excessive bleeding during cardiac surgery. Patients with abnormal hemoSTATUS results after discontinuation of cardiopulmonary bypass were randomly assigned desmopressin or placebo. Patients who received desmopressin had less blood loss, required less transfusion of red blood cells, platelets and fresh-frozen plasma, and had less total blood-donor exposures. It should be noted, however, that in another study values derived from the hemoSTATUS system did not correlate with mediastinal chest tube drainage after cardiopulmonary bypass, which cast some doubt on the strategy used by Despotis and colleagues.³⁸

Desmopressin has also been useful in treating patients with aspirin-induced platelet dysfunction undergoing cardiopulmonary bypass surgery; randomized trials have shown decreased blood loss and transfusion requirements.²⁷¹⁴¹

**Desmopressin in non-cardiac surgery**

There are few clinical trials evaluating the use of prophylactic desmopressin in reducing bleeding in non-cardiac surgery. There have been two studies evaluating the use of desmopressin in patients having spinal fusion surgery. Kobrinsky and colleagues⁷² reported a beneficial effect in
terms of blood loss and transfusion requirements, while Guay and colleagues found no benefit. Three trials showed no significant differences in blood loss or transfusion requirements when desmopressin was used in elective total hip/knee arthroplasty. In aortoiliac surgery, Lethagen and colleagues reported a small difference in blood loss with desmopressin, although this difference was not statistically significant. However, a subgroup analysis showed that in patients with a basal von Willebrand factor antigen concentration <150 IU dl⁻¹, when treated with desmopressin bled significantly less than those given placebo. Another more recent randomized, double-blind, placebo-controlled study found no benefit in elective aortic surgery when desmopressin (20 μg i.v.) was given at the time of aortic clamp placement. The overall evidence therefore does not support a beneficial effect of desmopressin in haemostatically normal patients undergoing elective non-cardiac surgical procedures.

**Adverse effects**

Adverse effects of desmopressin include mild facial flushing, headache, palpitations and hypotension. Other adverse effects are the result of the potent antidiuretic action of this agent, and include water retention, hyponatraemia and seizures. Desmopressin should also be used with caution during pregnancy, as it may induce premature labour.

Desmopressin promotes the release into plasma of tissue-type plasminogen activator, resulting in a short-lived generation of plasmin, which is promptly neutralized by circulating antiplasmin; no fibrinolytic activation occurs in vitro. Accordingly, inhibiting fibrinolysis when desmopressin is administered is not usually needed.

One of the concerns that has not been substantiated to date is the ability of desmopressin to induce a potentially prothrombotic state through enhanced platelet aggregation and increased factor VIII activity. A recent meta-analysis of 12 randomized controlled trials using DDAVP in cardiac surgery reported an incidence of myocardial infarction of 4.4% in the DDAVP-treated group vs 1.6% in the placebo-treated group (odds ratio=2.07; 95% confidence interval 0.74–5.85; \( P = 0.19 \)).

Antifibrinolytics

Antifibrinolytic agents in current use include the naturally occurring serine protease inhibitor aprotinin, the synthetic protease inhibitor nafamostat and the synthetic lysine analogues aminocaproic acid and tranexamic acid. Antifibrinolytic drugs should ideally be used only in those situations in which hyperfibrinolysis can be detected. Typical surgical procedures which may be associated with hyperfibrinolysis are operations requiring cardiopulmonary bypass, orthotopic liver transplantation, and some urological and orthopaedic operations. However, antifibrinolytics have also been widely and successfully used in surgical procedures not associated with hyperfibrinolysis.

Plasmin, the final enzyme in the fibrinolytic pathway, is a serine protease. It is not surprising, therefore, that inhibitors of serine proteases possess antifibrinolytic properties. They do so by forming reversible enzyme–inhibitor complexes with plasmin and other serine proteases. It is important to note that coagulation enzymes are serine proteases and therefore serine protease inhibitors will possess anticoagulation in addition to antifibrinolytic properties.

Lysine analogues reversibly bind to the lysine-binding site on plasminogen, thereby inhibiting the conversion of plasminogen into plasmin on the surface of fibrin (Fig. 3). They also prevent plasmin degradation of platelet glycoprotein Ib receptors. Lysine analogues can potentially enhance haemostasis when bleeding is associated with primary fibrinolysis (hyperplasminaemia). They should not, however, be used in disseminated intravascular coagulation (DIC) as this may increase intravascular thrombosis, unless low-dose heparin is given concomitantly. The reason is that lysine analogues inhibit both circulating plasmin and fibrin-bound plasmin and therefore interfere with the dissolution of clots in

**Fig 3** Mechanism of action of lysine analogues. On the left, EACA or tranexamic acid (lysine analogues) blocks the lysine-binding site on plasminogen, which is essential for binding to fibrin, and thereby prevents the activation of plasminogen on the surface of fibrin. Binding of lysine analogues to plasminogen prevents the breakdown of fibrin, even though plasmin is generated (lower left).
small blood vessels, further aggravating the condition. This is at variance with aprotinin, which inhibits circulating plasmin and spares fibrin-bound plasmin. Additionally, clinical studies indicate that antifibrinolytic amino acids are haemostatically effective even when bleeding is not associated with overt laboratory signs of hyperfibrinolysis. Both drugs have been widely used to prevent or treat bleeding during tooth extraction in haemophilia and some other coagulation disorders. They are used in the management of recurrent epistaxis, upper gastrointestinal bleeding and primary menorrhagia. Moreover, tranexamic acid appears to reduce the frequency of attacks of hereditary and non-hereditary angioneurotic oedema. Epsilon-aminocaproic acid and tranexamic acid have been used in the past to reduce the incidence of rebleeding in subarachnoid haemorrhage; however, this is not currently adopted because both drugs may induce vasospasm and ischaemic stroke.

**Epsilon-aminocaproic acid**

Epsilon-aminocaproic acid (6-aminohexanoic acid; EACA) is a competitive inhibitor of plasminogen activation and inhibits plasmin to a lesser extent (at higher doses). It has been used in various doses and regimens in patients undergoing surgery. In general, the recommended dose is 150 mg kg\(^{-1}\) as an i.v. bolus before surgery, followed by an infusion of 15 mg kg\(^{-1}\) h\(^{-1}\) during the operation. EACA is largely eliminated unchanged by renal excretion and about 35% undergoes hepatic metabolism to the metabolite adipic acid, which also appears in the urine. The renal clearance (116 ml min\(^{-1}\)) approximates endogenous creatinine clearance, and total body clearance is 169 ml min\(^{-1}\). The terminal elimination half-life for aminocaproic acid is 1 to 2 h.

**EACA in cardiac surgery**

Several trials have studied the prophylactic administration of this drug in patients undergoing cardiopulmonary bypass. In most of these studies, aminocaproic acid was compared with either tranexamic acid or aprotinin. Only a few studies have compared aminocaproic acid directly with placebo. The observed efficacy of aminocaproic acid varied somewhat from study to study, which may be explained by differences in dosage and time of administration. There are four meta-analyses of EACA in cardiac surgery. Levi and colleagues and Fremen and colleagues included EACA and tranexamic acid under the same treatment group (lysine analogues), and concluded that prophylactic administration of lysine analogues led to a significant reduction in postoperative bleeding (30–40%), without increasing the incidence of thromboembolic complications. Munoz and colleagues compared the results of five studies in which EACA was used during cardiac surgery with 52 studies in which aprotinin was used. The authors concluded that the two antifibrinolytic agents appear to have similar efficacies, and that the considerably less expensive EACA may be preferred to aprotinin for reducing haemorrhage with cardiac surgery. However, we should interpret the results of the latter study cautiously because the five EACA studies were in patients undergoing primary surgery, whereas more than 50% of the aprotinin trials were in patients undergoing complex or repeat surgery. In one meta-analysis, aminocaproic acid was not found to have a statistically significant effect on the proportion of patients requiring transfusion. However, there were only three EACA trials among the 60 trials included in the analysis. The poor evaluation of EACA in cardiac surgery and the lack of an adequate number of large randomized controlled trials make it difficult to support the use of EACA in this particular surgical setting.

**EACA in non-cardiac surgery**

In patients undergoing orthotopic liver transplantation, Kang and colleagues described a beneficial effect of low-dose aminocaproic acid (1 g, single infusion). On the other hand, in a large double-blind trial in which EACA and tranexamic acid were compared with placebo, no significant difference in transfusion requirements was found between the EACA and the placebo group. However, administration of the study medication was discontinued at reperfusion of the new liver, and a possible therapeutic effect could have been missed because hyperfibrinolytic bleeding is mainly seen after graft reperfusion. Very low dose EACA (single infusions of 300 mg) is still widely used to treat severe bleeding in liver transplantation; however, there are no randomized trials confirming the efficacy of EACA in this setting.

Primary hyperfibrinolysis may occur in patients undergoing prostatic surgery as a result of the release of plasminogen activators from the prostatic tissue. High levels of plasminogen activators can also be found in urine; this contributes to dissolution of haemostatic clots and haematuria. In a clinical trial involving patients who had undergone prostatectomy, EACA was effective in controlling postoperative haematuria compared with placebo, and its use was not accompanied by significant complications. The drug is not known to reduce the need for transfusion or to decrease mortality after uncomplicated prostatectomy, and therefore is not given routinely.

Although EACA has also been used in patients undergoing other types of surgery, there are not enough data from prospective studies to support the wider application of this agent. In a recently published Cochrane systematic review of the use of antifibrinolytics in elective surgery, the results suggested that EACA might be as effective as other antifibrinolytics. However, the reviewers could not endorse this finding as they were able to include only four trials of EACA (208 patients) compared with 61 trials of aprotinin (7027 patients) and 18 trials of tranexamic acid (1342 patients).

**Adverse effects**

The most common acute side-effect with EACA is hypotension that is usually associated with rapid i.v. administration. Other reported adverse effects are occasionally encountered
Tranexamic acid

Tranexamic acid (trans-4-aminomethyl-cyclohexane carboxylic acid) is a competitive inhibitor of plasminogen activation and, at much higher concentrations, a non-competitive inhibitor of plasmin. Its actions are similar to those of aminocaproic acid, but tranexamic acid is about 10 times more potent in vitro, with higher and more sustained antifibrinolytic activity. Tranexamic acid is usually given as a bolus dose of 10–15 mg kg⁻¹ i.v. before surgery. In cardiac surgery, this is followed by 1 mg kg⁻¹ h⁻¹ for 5–8 h. However, a wide range of dosage regimens has been used in different surgical procedures. Only a small fraction of administered tranexamic acid is metabolized; most is excreted unchanged by the kidney. The dose must be substantially decreased in renal impairment. Pharmacokinetic studies have revealed that tranexamic acid has a volume of distribution of 9–12 litres and an elimination half-life of about 2 h.

There are a number of clinical studies that attest to its effectiveness in decreasing blood loss and transfusion requirement after cardiopulmonary bypass. There is also some evidence that it may be effective in other surgical procedures.

Tranexamic acid in cardiac surgery

Prophylactic administration of lysine analogues has been shown to reduce bleeding after cardiopulmonary bypass by 30–40%. In a recent meta-analysis of 12 trials in patients undergoing cardiopulmonary bypass, tranexamic acid treatment was associated with a reduction in perioperative blood loss and allogenic blood transfusion requirements. The timing of administration of tranexamic acid in relation to the onset of cardiopulmonary bypass seems to be crucial for its beneficial effect. Brown and colleagues showed that tranexamic acid was less effective when given after commencement of bypass. Casati and colleagues compared tranexamic acid with high-dose aprotinin in primary elective cardiac operations. The authors concluded that tranexamic acid and aprotinin show similar clinical effects on bleeding and allogeneic transfusion. Because tranexamic acid is about 100 times cheaper than aprotinin, the authors recommend that its use would be preferable in this setting. Mongan and colleagues reported similar results in a similar patient population. However, there seems to be no proof of a reduction in the operative mortality risk when tranexamic acid is used in patients undergoing cardiac surgery, an effect that has been reported with aprotinin. The use of tranexamic acid in adult and paediatric patients undergoing repeat cardiac surgery was associated with significant reduction in blood loss and transfusion requirements in two studies. On the other hand, Kovesi and Royston thought that the evidence for the use of tranexamic acid in repeat cardiac surgery is neither powerful nor consistent. Tranexamic acid might also be effective in reducing blood loss and the need for allogeneic blood products in patients undergoing off-pump coronary surgery and in those undergoing elective thoracic aortic surgery. The use of tranexamic acid in cardiac surgery is not associated with an increased risk of postoperative myocardial infarction. Wells pooled data from 10 randomized trials that have commented on adverse events, including thrombosis. The incidence of myocardial infarction in tranexamic acid-treated patients was 0.36% compared with 1.5% in the placebo group. However, the end-points used for detection of myocardial infarction varied among the different studies and may not always have been adequate. Current evidence suggests that tranexamic acid can safely and effectively reduce blood loss and allogeneic transfusion in patients undergoing cardiac surgery. It is as effective as aprotinin in the setting of primary cardiac surgery and is far more cost-effective. The evidence for its use in patients on aspirin and those undergoing repeat operations is, however, not compelling.

Tranexamic acid in non-cardiac surgery

There have been several double-blind trials in patients undergoing total knee arthroplasty in which prophylactic administration of tranexamic acid significantly reduced total blood loss by up to 50% and decreased transfusion requirements without increasing the risk of thromboembolic manifestations. Benoni and colleagues found no benefit from administering tranexamic acid after the release of the tourniquet and stated that for optimum efficacy tranexamic acid should be administered prophylactically at an earlier stage. Tanaka and colleagues found that two injections of tranexamic acid, one given before surgery and one on deflation of the tourniquet, was the optimal technique. In patients undergoing total hip replacement, Ekback and colleagues and Benoni and colleagues independently reported a reduction in intraoperative blood loss when tranexamic acid was given prophylactically. However, when tranexamic acid was given at the end of the operation, it did not reduce postoperative blood loss in hip arthroplasty. In spite of its effectiveness, tranexamic acid cannot be recommended for every patient undergoing joint replacement; it...
should be considered for patients in whom large blood losses are predicted or for those who refuse blood transfusion.

Tranexamic acid has also been used in the setting of orthotopic liver transplantation. In a small randomized, placebo-controlled study, it was shown that prophylactic infusion of low-dose tranexamic acid (2 mg kg$^{-1}$ h$^{-1}$) reduced fibrinolysis but not transfusion requirements during orthotopic liver transplantation. On the other hand, Boylan and colleagues and Dalmau and colleagues independently examined the effect of high-dose tranexamic acid (10–40 mg kg$^{-1}$ h$^{-1}$) in primary orthotopic liver transplantation; both groups reported a significant reduction in intraoperative blood loss and transfusion requirements. The use of tranexamic acid in prostatic surgery is not very well studied, although it has been reported that prolonged oral administration of tranexamic acid (1 g three times daily orally for 3 weeks) may reduce the incidence of secondary bleeding and the number of readmissions for haemorrhagic complications after prostatic surgery.

**Adverse effects**

Gastrointestinal side-effects, such as nausea, diarrhoea and abdominal cramping, have been reported primarily with oral forms of tranexamic acid but were not reported with i.v. administration. Rapid i.v. administration of tranexamic acid may, however, cause hypotension and should therefore be administered slowly as an infusion. As with aminocaproic acid, the major concern with tranexamic acid is the potential for increasing the perioperative risk of thromboembolic complications (arterial thrombosis, myocardial infarction and pulmonary embolism). However, apart from anecdotes and case reports, there is no clear-cut evidence that tranexamic acid is associated with an increased risk of thromboembolic complications. With respect to renal toxicity from the use of tranexamic acid, there is little to suggest concern. However, in one study a group of patients were given tranexamic acid (1 g three times daily orally for 3 weeks) may reduce the incidence of secondary bleeding and was associated with a tendency to renal dysfunction.

**Nafamostat**

In 1981, Fujii and Hitomi first reported the use of nafamostat mesilate as a synthetic protease inhibitor. It inhibits thrombin, factors Xa and XIIa, kallikrein, plasmin and complement factors (C1r, C1s). As such, it works as an antifibrinolytic, anticoagulant and anti-inflammatory agent. Moreover, it has also been shown to preserve platelet function during cardiopulmonary bypass. Clinically, it has been used in the treatment of disseminated intravascular coagulation and acute pancreatitis. It has also been investigated as an anticoagulant in extracorporeal circuits and as a haemostatic agent in cardiac surgery. Several studies conducted in Japan reported a significant reduction in postoperative blood loss when nafamostat was used in cardiac surgery. Moreover, in a controlled study of 22 patients undergoing hepatic resection for hepatocellular carcinoma, there was a significant reduction in fibrinolytic activity together with a reduced blood transfusion rate in patients who were treated with nafamostat.

**Aprotinin**

Aprotinin is a naturally occurring 58-residue polypeptide derived from bovine lung with a molecular weight of 6512 Da. It is a powerful inhibitor of plasmin, trypsin, chymotrypsin, kallikrein, thrombin and activated protein C, through the formation of reversible enzyme–inhibitor complexes. The enzymatic activity of aprotinin is generally expressed in kallikrein inactivator units (KIU), with 1 KIU defined as the amount of aprotinin that decreases the activity of two biological kallikrein units by 50%. The mechanisms by which aprotinin exert its haemostatic effects are not fully understood. Studies of perioperative haemostasis have shown that plasma markers of fibrinolytic activity, such as D-dimers, are suppressed during the use of aprotinin. This led to the conclusion that aprotinin reduces perioperative bleeding by acting as a powerful antifibrinolytic. It inhibits circulating plasmin without interfering with fibrin-bound plasmin, and therefore it does not prevent the dissolution of clots in small blood vessels, an effect that is not observed with antifibrinolytic lysine analogues. At higher doses, aprotinin also inhibits kallikrein and thus the intrinsic pathway of coagulation with a subsequent reduction in contact-factor-dependent fibrinolysis and bradykinin production. Plasma concentrations of 125 KIU ml$^{-1}$ are usually needed to inhibit plasmin, whereas concentrations of 300–500 KIU ml$^{-1}$ are needed to inhibit kallikrein.

There is controversy in the literature regarding the effects of aprotinin on platelets. Initial studies in patients undergoing cardiac surgery suggested that aprotinin protects platelets against the initial effect of cardiopulmonary bypass. This has been challenged recently by other studies suggesting that aprotinin does not influence platelet function. The currently held view is that the haemostatic effect of aprotinin is exerted mainly through inhibition of plasmin. Although aprotinin does not directly affect platelet adhesion or aggregation, it may indirectly protect platelets through the inhibition of various platelet agonists produced during cardiopulmonary bypass, including plasmin.

In addition to its haemostatic properties, aprotinin has multiple actions that may suppress the inflammatory response, particularly at higher dosages. By inhibiting kallikrein, aprotinin blocks the conversion of kininogen to the inflammatory mediator bradykinin. It also inhibits the activation of C1 of the complement system, attenuates the release of TNF-α, interleukin (IL)-6 and IL-8, inhibits endogenous cytokine-induced nitric oxide synthase induction, decreases bypass-induced leucocyte activation and inhibits monocyte and granulocyte adhesion molecule up-regulation.
Aprotinin has been used in different dose administration regimens, the most common being a loading dose of 2 million KIU followed by continuous infusion of 500,000 KIU h⁻¹.¹²₅ In cardiac surgery, an additional 2 million KIU is added to the bypass pump prime.³⁹ After i.v. injection, rapid redistribution of aprotinin occurs into the extracellular space, leading to a rapid initial decrease in plasma concentration. It is metabolized in the proximal renal tubules and eliminated in a biphasic pattern: a rapid-phase half-life of approximately 40 min and a slower phase half-life of 7 h.¹¹₃

Aprotinin in cardiac surgery

It was the anti-inflammatory properties of aprotinin that first prompted its use in cardiac surgery but, coincidentally, the initial studies showed a significant reduction in blood loss and transfusion requirements.¹²³ Subsequently, multiple well-designed double-blind trials have demonstrated the effectiveness of aprotinin in patients undergoing procedures requiring cardiopulmonary bypass.⁵ ⁴⁹ ⁸¹ Aprotinin has been of particular benefit in operations characterized by large blood losses, such as those in patients taking aspirin,¹₂₆ in patients with endocarditis,¹⁵₀ and in patients undergoing re-operation¹⁴⁴ or heart transplantation.¹₁⁵ Moreover, aprotinin significantly reduces blood loss in patients undergoing off-pump coronary artery bypass surgery.³³ There are four recent meta-analyses, each of which confirms the efficacy of aprotinin in reducing blood loss and the need for blood transfusion without increasing the risk of myocardial infarction.⁵⁰ ⁷₈ ⁸₆ ¹⁰³ The use of aprotinin was also associated with a two-fold reduction in mortality, an effect that was not shared by other antifibrinolytics.⁸⁶ In a multicentre, double-blind placebo-controlled trial, Levy and colleagues⁸⁷ studied the effect of three different regimens of aprotinin in patients undergoing coronary artery bypass graft surgery. Patients were randomly assigned to either high-dose aprotinin (2×10⁶ KIU loading dose, 2×10⁵ KIU added to the circuit prime, and a continuous infusion of 5×10⁵ KIU h⁻¹ during surgery); low-dose aprotinin (1×10⁶ KIU loading dose, 1×10⁵ KIU added to the circuit prime, and a continuous infusion of 2.5×10⁵ KIU h⁻¹ during surgery); and a pump-prime only regimen (2×10⁶ KIU aprotinin added to circuit prime). The percentage of patients requiring donor blood transfusions in the high- and low-dose aprotinin groups was reduced, whereas pump-prime-only aprotinin had no effect. The efficacy of different low-dose aprotinin regimens has also been reported by other research groups,⁵³ ⁶⁹ but there has been a lack of consistency in the literature regarding the efficacy of prime-only aprotinin regimens.⁵⁷ ¹₃₁

In contrast to low-dose aprotinin, high-dose aprotinin has an anticoagulant activity and decreases thrombin generation, which does not seem to interfere with its haemostatic activity.²⁴ Interestingly, a recent meta-analysis reported a lower incidence of stroke in patients receiving high dose aprotinin.¹⁰⁵ and Lemmer and colleagues suggested that pump-prime-only regimens are possibly associated with more frequent myocardial infarctions.⁸⁰ In clinical studies, high-dose aprotinin reduces post-bypass myocardial ischaemia and myocyte damage,¹⁵⁹ and hospital length of stay in high-risk patients.⁷⁷ In addition to its haemostatic effect, aprotinin decreases experimental bypass-induced and cytokine-induced bronchial inflammation,¹¹ and attenuated lung reperfusion injury following bypass in one small clinical study.¹¹⁷ It seems, however, that aprotinin in doses currently used to reduce blood loss has no significant influence on the systemic inflammatory response during moderate hypothermic cardiopulmonary bypass.¹³⁴

Although not overwhelming, evidence favours the use of aprotinin over other antifibrinolytics as a haemostatic agent in cardiac surgery. It is the most extensively studied antifibrinolytic in this setting. It has consistently been reported to reduce blood loss and transfusion requirements. It is the only antifibrinolytic that has been associated with reduced mortality, a reduced incidence of strokes and shorter hospital stay. Moreover, there are suggestions that its use might be associated with reduced myocardial reperfusion injury and post-bypass inflammatory response. It should, however, be noted that aprotinin is the least cost-effective antifibrinolytic. Some argue that the routine use of aprotinin in all patients should be discouraged because many cardiac surgical procedures are not associated with the need for blood transfusion. This would also avoid the unnecessary risk of sensitization as well as other adverse effects.

Aprotinin in non-cardiac surgery

In major thoracic surgery, blood loss can be a serious problem. This is particularly noticed in surgery for inflammatory pulmonary disease, decortication procedures and re-thoracotomies for recurrent tumours. Kyriss and colleagues⁷⁷ and Bedirhan and colleagues³ independently reported a significant reduction in perioperative transfusion requirements and postoperative bleeding when aprotinin was used during major thoracic surgery. This was not accompanied by increased thromboembolic complications. Available data suggest that aprotinin may be also beneficial in reducing blood loss in lung transplant recipients.⁷⁰ High-dose aprotinin has been used almost routinely in Europe to reduce blood loss in orthotopic liver transplantation, the first experience dating back to 1989.¹⁰⁸ Recently, two placebo-controlled trials have shown beyond doubt that aprotinin reduces blood transfusion requirements during orthotopic liver transplantation by 30–40% compared with placebo.³⁶ ¹¹⁴ Moreover, there is emerging evidence that aprotinin might have a stabilizing effect on haemodynamics after reperfusion of the new liver.⁵⁸ This is probably attributable to its antikallikrein activity, blocking activation of the contact system and the subsequent release of vasodilating substances, such as bradykinin.

In major orthopaedic surgery, several controlled trials have shown that aprotinin significantly reduces the transfusion requirement compared with placebo. This is of particular benefit in spine surgery, revision or bilateral hip surgery, total knee arthroplasty, pelvic surgery and surgery for
infectious or neoplastic bone diseases. In one of these studies, the authors suggested that a much higher dose of aprotinin (4×10^6 KIU initial dose followed by 1×10^6 KIU h⁻¹) might be required to obtain a significant blood-sparing effect in this group of patients. None of these trials has reported an increased incidence of postoperative deep venous thrombosis or pulmonary embolism associated with aprotinin. Recently, Palmer and colleagues studied the efficacy of prophylactic high-dose aprotinin in reducing intraoperative blood loss in neurosurgery in 100 patients enrolled in a randomized, double-blind, placebo-controlled trial. There was a significant reduction in intraoperative blood loss in the aprotinin group and aprotinin treatment was not associated with an increased risk of thrombotic events, even though patients did not receive prophylactic anticoagulation therapy in the postoperative period.

**Adverse effects**

Administration of aprotinin introduces a foreign polypeptide into the systemic circulation; it is therefore not surprising that hypersensitivity reactions may occur. These reactions range from mild skin flushing to severe anaphylaxis and circulatory shock. Most of the published case reports of severe anaphylactic reactions with aprotinin occurred in patients with a history of being exposed to the drug. Dietrich and colleagues evaluated 121 patients undergoing repeat cardiac surgery who were re-exposed to aprotinin. Preoperative anti-aprotinin IgG and IgE antibodies were detected in 18 and nine patients respectively. Three patients out of the 121 (2.5%) experienced an anaphylactic reaction after aprotinin exposure, followed by full recovery; these patients had re-exposure intervals of less than 6 months and the highest preoperative IgG concentrations of all patients. The authors concluded that quantitative detection of anti-aprotinin IgE and IgG lacks specificity for predictive purposes; however, quantitation of anti-aprotinin IgG may identify patients at risk of developing an anaphylactic reaction to aprotinin re-exposure. It has been estimated that on first-time exposure risk of anaphylaxis is less than 0.5%. This increases to 4–5% in those re-exposed within 200 days and drops to 1–2% in those re-exposed after more than 200 days. Pretreatment with corticosteroids and antihistamines seems to have limited effect in preventing such reactions. Several randomized studies in patients undergoing cardiac surgery or orthotopic liver transplantation surgery have shown no adverse effects of aprotinin on postoperative renal function. However, other studies reported a trend towards a mild to moderate increase in postoperative serum creatinine; this was not associated with clinically important adverse outcome (e.g. need for dialysis or irreversible renal failure).

Aprotinin, being extracted from bovine lungs, has been recently withdrawn in Italy because of concerns that it might transmit the agent responsible for bovine spongiform encephalopathy and new-variant Creutzfeldt–Jakob disease. The manufacturers of aprotinin state that the bovine lungs used to extract aprotinin were collected in geographical areas in which no cases of transmissible spongiform encephalopathy had been recorded, and there is no evidence that any patients with the disorder have received aprotinin.

**Conjugated oestrogens**

Conjugated oestrogens, like desmopressin, shorten prolonged bleeding times and reduce or stop bleeding in patients with uraemia. The effect of conjugated oestrogens on the bleeding time is more prolonged (10–15 days) than that of
Conjugated oestrogens (e.g. Premarin, Wyeth-Ayerst Laboratories, Philadelphia, PA, USA), given i.v. at a cumulative dose of 3 mg kg$^{-1}$ (0.6 mg kg$^{-1}$ daily for 4–5 consecutive days), have been reported to considerably shorten the bleeding time, by 50%, for at least two weeks in uraemic patients. A daily oral dose of 50 mg shortened the bleeding time after an average of 7 days of treatment.  

The mechanism of the effect of conjugated oestrogens on the bleeding time in patients with uraemia is unknown. However, there is evidence that they increase levels of von Willebrand factor and factors VII and XII. They may also increase levels of physiological inhibitors of coagulation, such as antithrombin. In patients with chronic renal insufficiency, recombinant erythropoietin causes a dose-dependent increase in haematocrit, which is paralleled by a pronounced shortening of the bleeding time and improvement of platelet adhesion. The routine use of erythropoietin in chronic renal insufficiency has therefore limited the scope for the use of haemostatic drugs such as desmopressin and conjugated oestrogens.

Very few trials have been conducted to determine the efficacy of oestrogens in reducing blood loss during surgery. In one randomized, placebo-controlled trial in patients undergoing orthotopic liver transplantation, conjugated oestrogens significantly reduced transfusion and coagulation factor requirements. In another study, the use of conjugated oestrogens was associated with a 37% reduction in postoperative bleeding after paediatric scoliosis surgery.

Conjugated oestrogens are well tolerated and side-effects are negligible or absent. Since no more than five to seven daily doses are recommended, adverse effects due to oestrogenic hormonal activity are usually avoided. However, in a case report by Litwack and Horrow, the authors thought that the use of conjugated oestrogens might have contributed to the development of fatal occlusion of all saphenous vein grafts after coronary artery bypass grafting. In general, the role of conjugated oestrogens in perioperative haemostasis is limited and at best not well investigated.

Recombinant activated factor VII

Recombinant factor VIIa (rFVIIa) was originally developed for the treatment of bleeding complications in haemophilia patients with inhibitors against factors VIII or IX. In this group of patients, surgery has always been a challenge as it may result in life-threatening bleeding that is difficult to manage by usual measures. Studies have shown that surgery in patients with high-titre inhibitors against factor VIII or IX can be performed safely using rFVIIa. Therapeutic effects of rFVIIa begin at doses up to 10 times higher than physiological concentrations of endogenous factor VII. It is therefore used as a pharmacological intervention rather than a mere replacement of a deficient coagulation factor. Recombinant factor VIIa acts by enhancing the natural coagulation pathway through the formation of tissue factor–factor VIIa complex at the site of endothelial damage. This strictly localized effect is what makes rFVIIa different from other haemostatic agents and almost eliminates all undesirable side-effects. Moreover, studies have shown that rFVIIa, when given in supraphysiological dosage, can bind to the phospholipid membranes of activated platelets where it activates factor X independent of the tissue factor pathway, leading to a massive rise in thrombin generation at the platelet surface. High-dose rFVIIa can therefore compensate for a lack of factor VIII or factor IX through what has been described as a bypass effect, which explains its efficacy in treating patients with haemophilia with inhibitors. This may also explain the effectiveness of rFVIIa in treatment of bleeding episodes in patients with platelet function disorders.

Because of its a short half-life (2.7 h), rFVIIa has to be given as 2-hourly boluses or as a continuous infusion. Which of these regimens is better is still a matter of debate. Some studies have shown that continuous infusions result in a satisfactory haemostatic response. However, others have reported that continuous infusions can be ineffective. Despite these conflicting results, rFVIIa can be administered by continuous infusion as long as levels of factor VII:C of 30–40 IU ml$^{-1}$ are achieved in the immediate postoperative period and levels are maintained above 10 IU ml$^{-1}$ thereafter.

Recombinant factor VIIa is a pan-haemostatic agent and as such can be used in treating bleeding episodes in other disorders of haemostasis, such as factor VII deficiency, quantitative and qualitative platelet disorders, acquired von Willebrand disease, uraemia and liver disease. The use of rFVIIa in patients without pre-existing haemostatic defect is currently under intense investigation. Preliminary results suggest that it can be used safely and effectively to control life-threatening bleeding in surgery and trauma, when all other measures have failed. It can also be used to reduce blood loss and transfusion requirements in elective surgical procedures associated with excessive bleeding. It should be noted, however, that rFVIIa has not been approved for use in any of these applications. The mechanism of action of rFVIIa suggests enhancement of haemostasis limited to the site of injury without systemic activation of the coagulation cascade. Therefore, the use of the drug in trauma patients suffering uncontrolled haemorrhage appears to be rational. Martinowitz and colleagues reported the use of rFVIIa in seven massively bleeding, multi-transfused, and coagulopathic trauma patients after failure of conventional measures to achieve haemostasis. Administration of rFVIIa in a dose range of 120–212 μg kg$^{-1}$ resulted in cessation of the diffuse bleeding, with significant reduction in blood transfusion requirements, and shortening of prothrombin time and activated partial thromboplastin time. The results of this report suggest that rFVIIa may
prove to be of value as an adjunctive haemostatic agent in trauma patients. In other case reports of patients without pre-existing coagulation disorders, who bled profusely during various surgical procedures, the use of rFVIIa was reported to stop bleeding very efficiently.56,102

Recombinant factor VIIa has also been investigated in the elective settings of cardiac, prostatic and liver transplant surgery. Al-Douri and colleagues2 evaluated the role of rFVIIa in five patients (one child aged 2.5 yr and four adults) undergoing surgical procedures including arterial switch, closure of atrial septal defect, and mitral valve replacement with tricuspid valve repair. Haemostasis was achieved with a single dose (30 μg kg⁻¹) of rFVIIa. The authors concluded that rFVIIa represents an effective and well-tolerated treatment for serious bleeding episodes both during cardiac surgery and postoperatively.

A recently reported pilot study in six patients undergoing orthotopic liver transplantation showed a significant reduction of blood loss and red cell transfusions in patients treated with a single dose of rFVIIa.25 A limitation of this study was the use a historical control group for comparison. Moreover, a recently performed placebo-controlled randomized, controlled trial using single-dose rFVIIa (20, 40 or 80 μg kg⁻¹) in liver transplantation did not confirm the previous findings.111 In both trials, rFVIIa was not associated with an increased risk of thromboembolic complications, in particular hepatic artery thrombosis. Friederich and colleagues42 reported the use of rFVIIa in patients undergoing transabdominal prostatectomy. Before surgery, a single dose of rFVIIa (20 or 40 μg kg⁻¹) was given and compared with placebo. A significant reduction of blood loss of 45%, was seen in patients treated with rFVIIa, with no adverse effects noted. This study is of major importance as it is the first randomized controlled trial to indicate that surgical blood loss can be reduced in individuals with normal haemostatic function by the use of a single dose of rFVIIa.

It is clear that rFVIIa is a novel haemostatic agent that has the potential to reduce perioperative blood loss in patients with or without preoperative haemostatic abnormality. Results of currently ongoing large trials are awaited before wider application of rFVIIa is considered.

**Adverse effects**

A major concern when using activated coagulation factors such as rFVIIa is the possible induction of DIC or thromboembolism. However, in the many studies performed so far, rFVIIa was not associated with systemic activation of the coagulation cascade. An analysis of nearly 2000 patients treated with rFVIIa showed neither venous nor arterial thromboembolic events.122 Between July 1996 and August 2000 more than 140 000 single doses of rFVIIa were administered: seven myocardial infarctions have been reported, all in patients with predisposing risk factors; four cases of cerebral ischaemia; four cases of pulmonary embolism; and three cases of venous thromboembolism in other parts of the body.116

The use of rFVIIa in sepsis is potentially hazardous; this is because tissue factor is inducible in monocytes by toxins risking intravascular clot formation. However, the application of active site inhibited FVIIa in a sepsis model in baboons blocked tissue factor and reduced intravascular fibrin deposition and secondary organ failure.158

**Conclusions**

Control of intraoperative blood loss requires contribution from both the surgeon and anaesthetist. Meticulous surgical haemostasis, proper positioning, control of blood pressure, judicious fluid replacement, maintenance of normothermia and correction of clotting factor deficiencies are the basic components of surgical field haemostasis. Such measures will suffice in most patients. Systemic pharmacological haemostatic agents may be of additional benefit in surgical settings associated with excessive surgical bleeding and/or hyperfibrinolysis, in patients with borderline or mild haemostatic defects, or in those who refuse blood transfusion (Table 1). Antifibrinolytics are the most extensively studied haemostatic agents in the perioperative period. Most of the studies have focused on their use in patients undergoing cardiopulmonary bypass. Aprotinin is the antifibrinolytic agent that has the best evidence supporting its use. Its efficacy and safety have been evaluated more extensively. It consistently reduces blood loss and transfusion requirements, and it is the only antifibrinolytic agent that has been associated with reduced mortality, a decreased incidence of stroke, and shortened hospital stay. There are suggestions that its use might be associated with reduced myocardial reperfusion injury and post-bypass inflammatory response. The lysine analogues aminocaproic acid and tranexamic acid are probably as effective as aprotinin in reducing blood loss during cardiac surgery. However, they are poorly evaluated and data supporting their use are rather scarce. This is unfortunate because they have a good safety profile and are significantly cheaper than aprotinin. In non-cardiac surgery, there is some evidence to support the use of antifibrinolytic drugs in patients undergoing orthotopic liver transplantation, and in major orthopaedic, vascular and thoracic surgery.

Recombinant FVIIa is a novel and potent haemostatic agent that has been used for the prevention or treatment
Preliminary results suggest that it can be used safely and effectively to control life-threatening bleeding in surgery and trauma, when all other measures have failed. It can also be used to reduce blood loss in elective surgical procedures associated with excessive bleeding.

The only antifibrinolytic that has been associated with reduced mortality, reduced incidence of strokes and shorter hospital stay. Has been effective in reducing bleeding in major thoracic surgery, in major orthopaedic surgery, and orthotopic liver transplantation.

The advantages and disadvantages of the various haemostatic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Desmopressin</td>
<td>Useful in patients with mild haemophilia or type I von Willebrand’s disease undergoing surgery. Can be used to treat or prevent bleeding in patients with congenital or acquired defects of platelet function, chronic liver disease and uraemia. Useful in treating patients with aspirin-induced platelet dysfunction undergoing cardiopulmonary bypass.</td>
<td>Available evidence does not support its use in haemostatically normal patients undergoing elective cardiac or non-cardiac surgical procedures. Reports of increased risk of postoperative myocardial infarction in patients undergoing coronary artery bypass grafting.</td>
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<tr>
<td>Tranexamic acid</td>
<td>Has been consistently reported to reduce transfusion requirements in cardiac surgery. It is of particular benefit in patients taking aspirin, in patients with endocarditis, and in patients undergoing repeat operations, off-pump surgery or heart transplantation.</td>
<td>In cardiac surgery, it has not been effective in reducing blood loss in patients on aspirin and those undergoing repeat operations. Anecdotes suggesting an increased incidence of thromboembolic manifestations associated with its use. Case reports of graft occlusion after cardiopulmonary bypass; other reports suggest an increased incidence of thromboembolic manifestations.</td>
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<tr>
<td>Nafamostat</td>
<td>Effective in reducing bleeding loss when used in orthotopic liver transplantation, and cardiopulmonary bypass procedures.</td>
<td>No experience with its use in the UK, Europe or the USA.</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>Has been consistently reported to reduce transfusion requirements in cardiac surgery. It is of particular benefit in patients taking aspirin, in patients with endocarditis, and in patients undergoing repeat operations, off-pump surgery or heart transplantation.</td>
<td>Hypersensitivity reactions, particularly on re-exposure.</td>
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<tr>
<td>Factor VIIa</td>
<td>Preliminary results suggest that it can be used safely and effectively to control life-threatening bleeding in surgery and trauma, when all other measures have failed. It can also be used to reduce blood loss in elective surgical procedures associated with excessive bleeding.</td>
<td>Has not been approved for use as a haemostatic agent in patients without pre-existing bleeding disorders undergoing elective surgery. More clinical trials are awaited before definitive conclusions can be made about the safety and the exact role of this new drug in surgical patients. Case reports of myocardial infarction, cerebral ischaemia, pulmonary embolism and deep-vein thrombosis.</td>
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