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Aprotinin

An Update of its Pharmacology and Therapeutic Use in Open Heart Surgery and Coronary Artery Bypass Surgery

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Data Selection

Sources: Medical literature published in any language since 1966 on aprotinin, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'aprotinin', 'aprotinin-solution', 'Bayer-A-128', 'Bayer-A128', 'Riker-52G', 'RP-9921', 'heart-surgery' and 'coronary-bypass'. Medline and EMBASE search terms were 'aprotinin', 'aprotinin-solution', 'Bayer-A-128', 'Bayer-A128', 'Riker-52G', 'RP-9921', 'heart-surgery' and 'coronary-bypass'. Searches were last updated 18 December 1998.

Selection: Studies in patients undergoing open heart surgery or coronary artery bypass graft surgery with cardiopulmonary bypass who received aprotinin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Aprotinin, heart surgery, coronary artery bypass graft surgery, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Cardiopulmonary bypass (CPB) is associated with defective haemostasis which results in bleeding and the requirement for allogenic blood product transfusions in many patients undergoing open heart surgery (OHS) and/or coronary artery bypass graft surgery (CABG) with CPB. Conservation of blood has become a priority during surgery because of shortages of donor blood, the risks associated with the use of allogenic blood products and the costs of these products.

Aprotinin is a serine protease inhibitor isolated from bovine lung tissue which acts in a number of interrelated ways to provide an antifibrinolytic effect, inhibit contact activation, reduce platelet dysfunction and attenuate the inflammatory response to CPB. It is used to reduce blood loss and transfusion requirements in patients with a risk of haemorrhage and has clear advantages over placebo or no treatment.

High dose aprotinin significantly reduces postoperative blood loss compared with aminocaproic acid and desmopressin, and decreases transfusion requirements compared with desmopressin. Results are less consistent with tranexamic acid: high dose aprotinin either reduces blood loss significantly more than, or to an equivalent level to, tranexamic acid. A variety of other lower aprotinin dosage regimens consistently result in similar reductions in blood loss to aminocaproic acid or tranexamic acid.

Data from clinical trials indicate that aprotinin is generally well tolerated, and the adverse events seen are those expected in patients undergoing OHS and/or CABG with CPB. Hypersensitivity reactions occur in <0.1 to 0.6% of patients receiving aprotinin for the first time. The results of original reports indicating that aprotinin therapy may increase myocardial infarction rates or mortality have not been supported by more recent studies specifically designed to investigate this outcome. However, a tendency to early vein graft occlusion with aprotinin has been shown and care with anticoagulation and vessel grafts is required. No comparative tolerability data between aprotinin and the lysine analogues, aminocaproic acid and tranexamic acid, are available.

Conclusion: Comparative tolerability and cost-effectiveness data for aprotinin and the lysine analogues are required to more fully assess their individual roles in reducing blood loss and transfusion requirements in patients undergoing CPB during OHS and/or CABG. However, clinical evidence to date supports the use of aprotinin over its competitors in patients at high risk of haemorrhage, in those for whom transfusion is unavailable or in patients who refuse allogenic transfusions.

Pharmacodynamic Properties

Aprotinin is a serine protease inhibitor which dose-dependently inhibits human trypsin, plasmin and kallikrein. In patients undergoing cardiopulmonary bypass (CPB), aprotinin has been shown to prevent plasmin-mediated fibrinolysis and inhibit the contact activation system via kallikrein inhibition, preserve platelet surface adhesive receptor glycoprotein (GP)Ib function and attenuate heparin-induced platelet dysfunction, and display anti-inflammatory and antioxidant effects. The antifibrinolytic effects of high dose aprotinin (see Dosage and Administration summary), as measured by reductions in D-dimer levels, are less than those of tranexamic acid, similar to those of aminocaproic acid and superior to those of desmopressin. Aprotinin has anti-inflammatory effects equivalent to methylprednisolone (1g before CPB) in patients undergoing CPB.

Pharmacokinetic Properties

Aprotinin cannot be administered orally because of gastric inactivation. Mean plasma aprotinin concentrations reported previously were 37 to 47 mg/L at the beginning of CPB and 26 to 27 mg/L at the end of CPB after administration of high dose aprotinin (see Dosage and Administration summary). These concentrations are adequate to suppress plasmin throughout the procedure. As well, a more recent trial found high dose aprotinin produced concentrations needed to inhibit kallikrein throughout surgery.

After intravenous administration, aprotinin is rapidly distributed into the extracellular compartment, and plasma aprotinin concentrations then decrease biphasically. Distribution and elimination half-lives are 0.32 to 0.50 hours and 5.25 and 8.28 hours for the 2 phases, respectively.

Aprotinin is filtered by the glomeruli but then actively reabsorbed by the proximal tubules and gradually metabolised in the kidney. Approximately 25 to 40% of a single intravenous dose of ^{131}I-labelled aprotinin was measured in the urine of healthy volunteers within 48 hours of administration. Aprotinin clearance was substantially reduced, and the elimination half-life and area under the plasma concentration-time curve increased in 2 patients with chronic renal impairment who received 140mg by intravenous infusion over 30 minutes. However, renal impairment did not affect peak plasma aprotinin concentrations or distribution half-life.

Therapeutic Use

The clinical efficacy of aprotinin has been evaluated in patients undergoing open heart surgery (OHS) and/or coronary artery bypass graft surgery (CABG), including those undergoing repeat sternotomy and those receiving aspirin. It has been compared with untreated controls and placebo as well as the lysine analogues tranexamic acid and aminocaproic acid, and the vasopressin analogue desmopressin.

An evaluation of comparative efficacy is difficult because dosage regimens of all active treatments vary between studies. However, high dose aprotinin (see Dosage and Administration summary) significantly reduces postoperative blood loss compared with aminocaproic acid and desmopressin, and decreases transfusion requirements compared with desmopressin. Results are less consistent in comparisons with tranexamic acid: high dose aprotinin reduced blood loss significantly more than tranexamic acid in some studies and to equivalent levels in others. A variety of other lower dose aprotinin regimens consistently result in similar reductions in blood loss to aminocaproic acid or tranexamic acid.

In patients undergoing CPB during OHS, no significant difference in the reduction in postoperative blood loss or transfusion requirements could be shown between high dose and low dose (50% of the high dose using the same protocol)

regimens. Aprotinin 280mg [2×10^6 kallikrein inactivator units (KIU)] added to the pump priming fluid of the CPB circuit has usually been shown to decrease blood loss and transfusion requirements significantly more than placebo, although in a study in patients undergoing repeat CABG, no difference was seen.

While some studies using a variety of dosage regimens in paediatric patients undergoing OHS with CPB have shown significant reductions in blood loss and/or transfusion requirements, others have failed to demonstrate any advantage of aprotinin over no treatment. However, results available so far indicate that aprotinin may be beneficial in children undergoing repeat or very complicated OHS.

A recent meta-analysis suggests that high dose aprotinin, but not low dose or pump prime only aprotinin, significantly reduces the incidence of stroke in patients undergoing CPB.

Although no cost-effectiveness studies have been conducted for aprotinin, studies examining the effect on costs of aprotinin suggest that low dose aprotinin (50% of the high dose regimen) is cost saving compared with no treatment, aminocaproic acid and various anti-inflammatory strategies. In contrast, high dose aprotinin has been shown to increase costs compared with aminocaproic acid. However, neither study comparing the costs of aprotinin and aminocaproic acid included critical care or hospitalisation costs.

Tolerability

Aprotinin is generally well tolerated in clinical trials. Adverse events reported are generally consistent with those expected in patients undergoing CPB during OHS and/or CABG. Unfortunately, there are scant comparative tolerability data for aprotinin and aminocaproic acid, tranexamic acid or desmopressin. Aprotinin appears to be well tolerated in paediatric patients.

Some concerns remain regarding graft patency and myocardial infarction (MI) rates and allergic reactions. The trend toward a higher incidence of MI and mortality seen in some earlier trials has not been confirmed by further investigations specifically designed to investigate this outcome. However, a recent large multicentre prospective study in patients undergoing primary CABG showed that high dose aprotinin increased the probability of early vein graft occlusion, particularly in patients with high risk factors. Surgical procedures used at different sites in this study may also have contributed to this effect and indicate that care with anticoagulation and vessel grafts is required when using aprotinin.

The reported incidence of hypersensitivity reactions in clinical trials in patients receiving mainly high dose aprotinin ranges from <0.1 to 0.6%. Most of the patients in these trials received aprotinin for the first time and it has been shown that reactions are more likely to occur in patients with prior exposure to aprotinin. Indeed, a retrospective analysis in 240 patients re-exposed to aprotinin a mean of 344 days after first exposure reported 7 allergic reactions (2.8%).

Increases in serum creatinine levels of ≥44 μmol/L (0.5 mg/dl) above preoperative levels were more common in patients receiving aprotinin than those not receiving aprotinin in some but not all studies. However, these elevations in serum creatinine levels were generally small, and levels returned to baseline and did not predispose patients to renal dysfunction.

Drug Interactions

Aprotinin alters the results of coagulation assays that depend on contact activation, i.e. it prolongs the activated partial thromboplastin time and activated clotting time (ACT). Consequently, the previously recognised ACT value of >400 to >450 seconds may not reflect adequate heparinisation in patients receiving aprotinin. There is general agreement that heparin dosage should not be decreased during

aprotinin administration, and current recommendations are to maintain the celite ACT at >750 seconds or the kaolin ACT at >480 seconds, or to use a fixed dose heparin regimen or to maintain heparin concentrations at $\geq 2.7 \times 10^3$ IU/L using heparin/protamine titration.

Dosage and Administration

Aprotinin is administered intravenously through a central line. The high dose regimen is a loading dose of aprotinin 280mg (2×10^6 KIU) administered as an infusion over 20 to 30 minutes after the induction of anaesthesia followed by an infusion of aprotinin 70 mg/h (5×10^5 KIU/h) that is then maintained throughout surgery. In addition, this regimen includes aprotinin 280mg added to the pump priming fluid of the CPB circuit.

A variety of lower dose regimens have been investigated but the most common are a standard low dose regimen of 50% of the high dose regimen using the same protocol or aprotinin 280mg in the pump prime only.

An intravenous test dose of aprotinin 1.4mg or 1ml is recommended at least 10 minutes before the loading dose in patients with known previous exposure to aprotinin, or in patients for whom this information is not available, because of the risk of anaphylactic reactions.

1. Introduction

Aprotinin is a serine protease inhibitor isolated from bovine lung tissue that has specific affinity for kallikrein and plasmin. As such, it is used as a pharmacological agent to reduce perioperative blood loss and transfusion requirements in patients undergoing surgery with a risk of haemorrhage. The pharmacology and therapeutic efficacy of aprotinin in reducing blood loss associated with cardiac surgery was reviewed in *Drugs* in 1995.[1] This review updates the therapeutic use of aprotinin in open heart surgery (OHS) and coronary artery bypass surgery (CABG) with cardiopulmonary bypass (CPB) in the light of recent clinical results.

1.1 Haemostasis During and After Cardiopulmonary Bypass

An overview of defective haemostasis associated with extracorporeal circulation was provided in the previous review.[1] In general, loss of vascular integrity, thrombocytopenia, defects in platelet function, a hyperfibrinolytic state and coagulation defects are all factors which may contribute to the defective haemostasis observed during CPB. In addition, the extrinsic coagulation pathway is activated when blood vessels are cut during OHS.[2] Many of these changes in coagulation and fibrinolysis are controlled by serine protease inhibitors.

Briefly, haemodilution with crystalloids and/or colloids decreases the concentration of coagulation factors and platelets, and moderate hypothermia under which surgery is carried out decreases enzymatic activity and stimulates platelet activity.[1] Blood cells and platelets (and their receptors) are damaged, and coagulation factors are denatured by mechanical trauma, high shear stress and turbulence in the CPB circuit. Contact activation during exposure to the CPB circuit results in activation of the coagulation, fibrinolytic, kinin, angiotensin and complement systems (fig. 1; see previous review for further details).[1] Activation of the intrinsic coagulation pathway results in increased kallikrein and subsequent plasmin activity, which leads to fibrinolysis. Plasma proteins, including fibrinogen, adsorbing onto the surface of the CPB circuit promote platelet aggregation.

Finally, contact activation of the complement system results in a generalised inflammatory response. In its more serious form, this whole body inflammatory response or postperfusion syndrome is manifest as bleeding, pulmonary dysfunction, renal dysfunction and increased susceptibility to infection.[3-6]

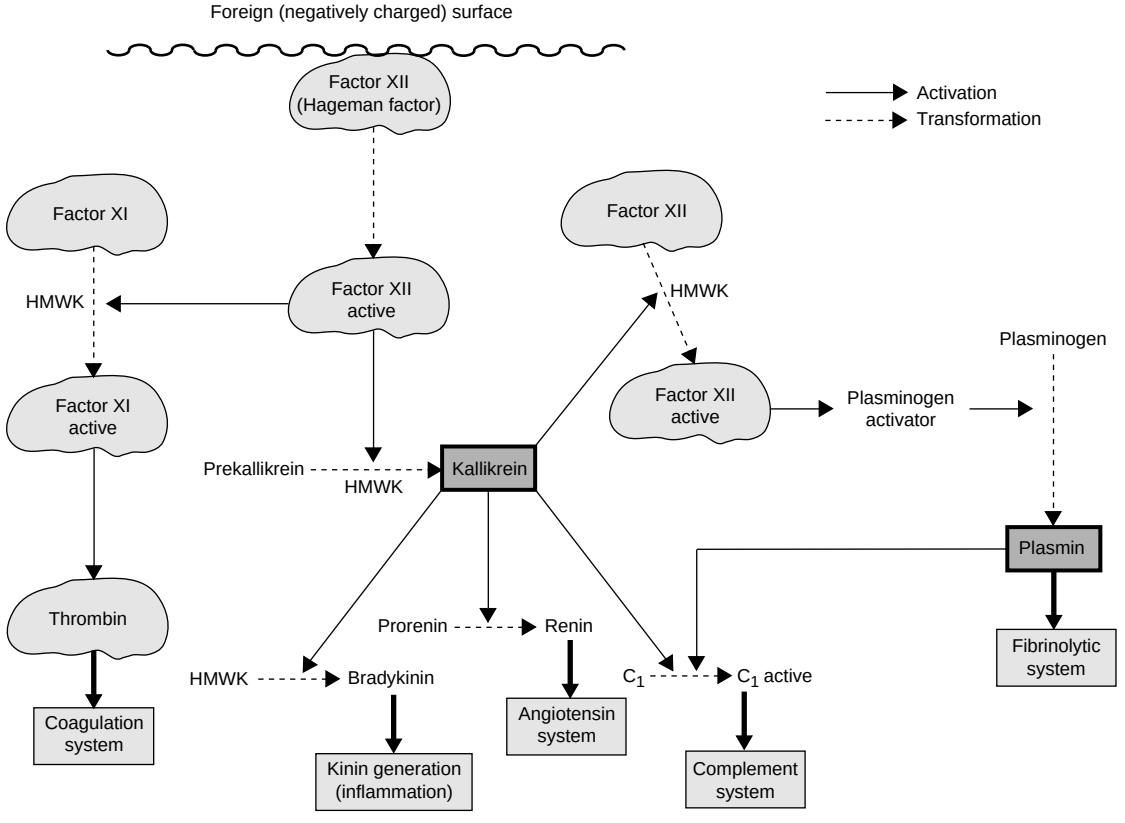

Fig. 1. A schematic diagram showing the roles of kallikrein and plasmin as mediators in the coagulation, fibrinolytic, kinin, angiotensin and complement systems following activation at a foreign surface (from Davis and Whittington[1]). **C_1** = complement 1; **HMWK** = high molecular weight kininogen.

1.2 Aprotinin Dosage Regimens During Cardiopulmonary Bypass

Amounts of aprotinin are expressed primarily in milligrams throughout this review (1mg = 0.15 μmol). The biological activity of aprotinin can be expressed as kallikrein inactivator (or inhibitor) units [KIU (1mg = 7143 KIU)].[1] Aprotinin is administered in a variety of dosage regimens, the more standard of which are:

- high dose aprotinin = 280mg (2×10^6 KIU) intravenously after the induction of anaesthesia but before sternotomy followed by 70 mg/h (5×10^5 KIU/h) by intravenous infusion for the duration of surgery plus aprotinin 280mg added to the pump priming fluid of the CPB circuit
- low dose aprotinin = half the high dose regimen (unless otherwise stated), i.e. 140mg (1×10^6 KIU) intravenously followed by 35 mg/h (2.5×10^5 KIU/h) by intravenous infusion plus aprotinin 140mg added to the pump priming fluid of the CPB circuit
- pump prime only = aprotinin 280mg (unless otherwise stated) in the pump priming fluid of the CPB circuit only.

The aim of the high dose regimen is to achieve plasma aprotinin concentrations necessary to inhibit kallikrein and plasmin. The rationale for the low dose regimen is to achieve comparable efficacy to the high dose regimen while reducing drug costs and possibly the risk of some adverse events.

The use of the low dose regimen does not inhibit kallikrein (based on calculated values) and, thus, does not prevent the formation of bradykinin and activated complement (fig. 1). Therefore, the full anti-inflammatory effect of aprotinin is achieved only with the high dose regimen. Aprotinin in the pump priming fluid is designed to protect platelets during the initial phase of CPB.[1,7-9]

2. Pharmacodynamic Properties

Aprotinin dose-dependently inhibits a number of proteases, including human trypsin, plasmin, plasma kallikrein and tissue kallikreins, by forming reversible enzyme-inhibitor complexes.[1,10] These proteases perform important functions in the kallikrein-kininogen-kinin, complement, coagulation and fibrinolytic systems (see section 1 and fig. 1).[10] Despite a large amount of research, the mechanism of action by which aprotinin prevents coagulopathy and blood loss during CPB has not yet been fully elucidated. There is evidence for several possible mechanisms, which are probably interrelated and dosage specific. Aprotinin inhibits the contact-coagulation system via kallikrein inhibition, inhibits protein C, attenuates plasmin-induced fibrinolysis and preserves platelet receptor function.[10] It has also displayed anti-inflammatory effects.[11]

The effects of aprotinin on the hyperfibrinolytic state, platelet dysfunction and inflammatory reaction induced by CPB are discussed in more detail in the following sections. Specifically, recent randomised studies comparing these effects of aprotinin with those of other agents used to reduce blood loss during CPB are evaluated. In these studies blood was drawn from patients undergoing CPB before, during and up to 24 hours after surgery and the various markers of pharmacological effect were then measured.

2.1 Effects on Fibrinolysis

Clinical evidence suggests that direct inhibition of plasmin is the major mechanism of the antifibrinolytic effects of aprotinin, while inhibition of the contact activation system via kallikrein inhibition is involved to a lesser extent (reviewed by Davis and Whittington[1] and Dobkowski and Murkin[10]). Recent randomised controlled studies in patients undergoing CPB have confirmed previous evidence[1] that, compared with placebo or no treatment, aprotinin reduces the formation of fibrin degradation products (D-dimers), increases α_2-antiplasmin and plasminogen activator inhibitor (PAI) activity and attenuates the release of tissue plasminogen activator (t-PA) from endothelial cells, thus confirming its antifibrinolytic activity.[12-18]

The comparative effects of the high dose aprotinin regimen (section 1.2) and tranexamic acid on D-dimer levels in blinded studies appear to depend on the dose of tranexamic acid used. The increase in D-dimer levels seen in untreated patients undergoing CPB was significantly attenuated in patients receiving high dose aprotinin or tranexamic acid (10 mg/kg then 1 mg/kg/h; total 20 mg/kg) in 1 study ($p < 0.05$) with no significant difference between treatments.[12] However, compared with high dose aprotinin, D-dimer levels were significantly lower with tranexamic acid 10 mg/kg then 3 mg/kg/h[19] or tranexamic acid 20 mg/kg then 8 mg/kg/h.[20] In other blinded studies, high dose aprotinin had an effect on D-dimer levels similar to that of aminocaproic acid 80 mg/kg then 30 mg/kg/h[19] and superior to that of desmopressin 0.3 to 0.4 μg/kg.[21]

In contrast to comparative results for D-dimer levels, both α_2-antiplasmin and PAI activity were significantly greater in patients receiving high dose aprotinin than in those receiving tranexamic acid (10 mg/kg then 1 mg/kg/h; total 20 mg/kg) or no treatment in a study of 43 patients undergoing CPB.[12] These differences in the antifibrinolytic effects of aprotinin and tranexamic acid probably reflect their different mechanisms of action.[10,12]

Aprotinin inhibits serine proteases in a dose-dependent manner,[10] and so it is of interest to note the antifibrinolytic effects of different dosage regimens. A low dose regimen of aprotinin 4 mg/kg (3×10^4 KIU/kg) in the pump prime and 1 mg/kg/h (0.75×10^4 KIU/kg/h) intravenously during surgery significantly attenuated the rise in D-dimer

levels compared with no treatment in 2 separate studies (1 unblinded).[13,16] However, pump prime only aprotinin 70, 140 or 280mg did not have any significant effect on D-dimer levels compared with placebo or no treatment in 3 double-blind studies.[13,22,23] The activity of both α_2-antiplasmin and PAI-1 were significantly higher with both this low dose regimen and pump prime only aprotinin 140mg compared with no treatment.[13]

2.2 Effects on Platelet Dysfunction

Aprotinin prevents the prolongation of bleeding time that occurs after CPB, indicating that it preserves platelet function.[1,10] Suggested mechanisms by which aprotinin may preserve platelet function and numbers are:

- reduction of thrombin generation
- preservation of platelet surface adhesive receptor glycoprotein (GP)Ib function
- reduction of thromboxane A_2 release from platelets
- prevention of heparin-induced platelet dysfunction.[1]

While some more recent studies have confirmed these various effects of aprotinin on platelet function,[12,17,19,20,23-27] others have failed to show specific effects.[28-30]

In studies comparing the effects of high dose aprotinin and tranexamic acid 20 mg/kg on platelet function, both agents significantly reduced bleeding time,[12,20] and preserved platelet aggregation in response to adenosine diphosphate (ADP)[12] and ristocetin,[20] with no difference between agents.

2.3 Effects on Inflammatory Responses

Many of the inflammatory cascades activated by CPB are enzyme mediated and involve serine proteases (reviewed by Murkin[31] and Royston[11]). Serine protease inhibitors have the potential to ameliorate the inflammatory response to CPB by regulating cytokine release and leucocyte activation.[11,31] Several prospective, randomised, and in most instances blinded, studies with untreated control groups have confirmed an anti-inflammatory effect for aprotinin in patients undergoing CPB,[32-39] while others have shown no such effect.[40,41] It should be noted that one of these latter studies was in paediatric patients and used a nonstandard low dose aprotinin regimen of 2.8 mg/kg (2×10^4 KIU/kg)[40] and the other used pump prime only aprotinin 280mg,[41] whereas the studies showing a positive effect for aprotinin all, except one,[39] used either the standard high dose or low dose aprotinin regimens (see section 1.2).

In a series of *in vivo* and *ex vivo* studies using blood from patients undergoing CPB, high dose aprotinin was shown to:

- enhance the endogenous release of the anti-inflammatory cytokine interleukin (IL)-10 in response to CPB[33]
- increase plasma levels of the anti-inflammatory cytokine inhibitor IL-1 receptor antagonist (IL-1ra) to a greater extent than in untreated controls at 24 hours after CPB[37]
- reduce production of the pro-inflammatory cytokine IL-8 in bronchial alveolar lavage fluid and accumulation of neutrophils in the airways of patients after CPB.[34]

Aprotinin had similar anti-inflammatory effects to methylprednisolone 1g in patients undergoing CPB. Both agents attenuated CPB-induced systemic tumour necrosis factor (TNF)-α release and neutrophil integrin CD11b up-regulation (low dose aprotinin),[36,38] and reduced CPB-induced IL-6 release (high dose but not low dose aprotinin).[32,35]

Aprotinin has shown antioxidant effects in adult[42] and paediatric patients[43] and in *in vitro* studies.[44-46] In the comparative studies available, aprotinin but not aminocaproic acid[46] or tranexamic acid[47] attenuated cytokine-induced increases in nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) expression in murine bronchial epithelial cells *in vitro*. Both endogenous NO and iNOS have been implicated in the pathophysiology of a variety of conditions (including circulatory shock,[48] systemic inflammatory response syndrome,[49] myocardial reperfusion injury,[47] heart failure[50] and cardiac allogenic graft rejection[51]) which may occur after OHS and/or CABG with CPB.

3. Overview of Pharmacokinetic Properties

Since the last review was published in *Drugs*, very few new data on the pharmacokinetics of aprotinin have become available. Therefore, an overview of the pharmacokinetic profile of aprotinin is presented here with new data from 1 clinical study[52] and from 2 patients with renal impairment.[53]

Aprotinin cannot be administered orally because of gastric inactivation.[3] When administered by intravenous infusion, aprotinin displays a dose-proportional plasma pharmacokinetic profile over the dose range 70 to 280mg. After administration of a single 30-minute intravenous dose of aprotinin 70 to 280mg to patients awaiting cardiac surgery or to female patients undergoing primary elective abdominal hysterectomy, mean maximum plasma concentrations (C_{max}) ranged from 8.4 to 59.6 mg/L (60 to 425.7×10^3 KIU/L).[1]

The plasma concentration of aprotinin required to inhibit kallikrein has been reported as 28 to 35 mg/L (200 to 250×10^3 KIU/L) and that needed to inhibit plasmin as 7 to 17 mg/L (50 to 125×10^3 KIU/L).[1,3,7,52] In clinical studies reported in detail previously,[1] administration of high dose aprotinin resulted in mean plasma drug concentrations of 37 to 47 mg/L at the beginning of CPB and 26 to 27 mg/L at the end of CPB.

In a more recent study in 14 patients receiving high dose aprotinin while undergoing CPB during CABG and/or heart valve replacement (HVR) surgery, aprotinin concentrations were ≥25 mg/L (1.79×10^5 KIU/L) throughout CPB (table I).[52] The aprotinin infusion was continued for only 4 hours in this study although no operations were completed within this time (mean 6, range 4.2 to 8 hours). However, in a separate trial, the high dose regimen produced the higher plasma drug concentrations needed to inhibit kallikrein (>28 mg/L) throughout the surgical period (6 hours).[54]

These results indicate that with high dose aprotinin the plasma drug concentrations required to inhibit plasmin are achieved during the entire bypass period and concentrations needed to inhibit kallikrein may also be achieved during this time. However, more pharmacokinetic studies are still required to clarify the apparent inconsistency of the results of previous studies investigating standard low dose aprotinin in which linear pharmacokinetic properties were not always displayed.[1]

Table I. Plasma aprotinin concentrations in 14 patients undergoing cardiopulmonary bypass (CPB) during open heart or coronary artery bypass graft surgery who received aprotinin 280mg intravenously after the induction of anaesthesia followed by 70 mg/h for 4 hours plus 280mg added to the pump priming fluid of the CPB circuit[52]

Time of sample	Plasma aprotinin concentration in mg/L (KIU/L)
30 min after start of aprotinin administration	33 (2.34×10^5)
30 min after start of CPB	32 (2.29×10^5)
90 min after start of CPB	26 (1.84×10^5)
End of CPB	25 (1.79×10^5)

KIU = kallikrein inactivator (inhibitor) units.

Aprotinin is rapidly distributed into the extracellular compartment after intravenous administration. Plasma drug concentrations decrease biphasically, with distribution and elimination half-lives of 0.32 to 0.50 hours and 5.25 to 8.28 hours for the 2 phases, respectively. Animal studies have shown that aprotinin is primarily accumulated within the proximal tubular epithelial cells of the kidneys. After undergoing glomerular filtration, aprotinin is actively reabsorbed by the proximal tubules, stored in phagolysosomes and then gradually metabolised by lysosomal enzymes in the kidney. Approximately 25 to 40% of a single intravenous dose of ^{131}I-labelled aprotinin was found in the urine of healthy volunteers within the first 48 hours. However, the total urinary excretion of unchanged drug is low (range 1.1 to 8.7%), but appears to increase slightly when the infused dose is increased.[1]

In female patients undergoing hysterectomy, no significant differences in the mean values obtained for C_{max} or area under the plasma concentration-time curve (AUC) were noted between younger (<60 years) and older (>60 years) women.[55,56]

The pharmacokinetics of aprotinin 140mg by intravenous infusion over 30 minutes in 2 patients with chronic renal dysfunction undergoing elective

hysterectomy have been examined.[53] There was a substantial decrease in aprotinin clearance leading to an increase in the elimination half-life and the AUC of aprotinin in these patients. C_{max} and the distribution half-life of the drug were not affected by renal impairment. There are no reports of the potential effects of hepatic impairment on the pharmacokinetic profile of aprotinin.

4. Therapeutic Use

Although aprotinin has been used in a number of surgical indications where significant blood loss can be expected, this section focuses on the areas where aprotinin is most widely used, i.e. in CABG or OHS (mainly HVR) using CPB. At the time of the previous review,[1] aprotinin had previously shown efficacy in placebo-controlled trials in patients undergoing CPB (see section 4.2).[1] Data from trials comparing the efficacy of aprotinin with other antifibrinolytic agents in patients undergoing OHS and/or CABG are now available and are the focus of this section.

In addition, the question of an optimal dosage regimen remained unanswered at the time of the last review. Recent trials which have examined the different dosage regimens are reviewed and the results discussed in detail. Finally, information on the use of aprotinin in paediatric patients undergoing OHS is updated.

4.1 Study Design

Patients about to undergo CABG or OHS were anaesthetised in a standard manner before being given heparin 300 to 400 IU/kg or 3 to 4 mg/kg as a starting dose. In the majority of studies cited in this review heparin was then administered to maintain an activated clotting time (ACT) with celite of >750 seconds or with kaolin of >450 to >480 seconds during CPB, or using a fixed dosage regimen (generally 50 mg/h) or to maintain heparin blood concentrations at 2.7×10^3 IU/L using heparin/protamine titration. In contrast, in the majority of studies cited in the previous review, heparin was administered to maintain the celite ACT at >400 to >450 seconds (see section 6 for discussion on heparin administration with aprotinin). Heparin activity was reversed by protamine at the end of bypass. A membrane oxygenator was used in most studies, although a few used a bubble oxygenator. Patients were cooled to between 30 to 32°C during CPB. In general, patients received a transfusion when haemoglobin levels fell to <80 g/L or haematocrit value to <30%.

The aprotinin regimens used in these studies, unless otherwise stated, are those outlined in section 1.2. The high dose regimen was aprotinin 280mg (2×10^6 KIU) intravenously after the induction of anaesthesia followed by 70 mg/h (5×10^5 KIU) by intravenous infusion for the duration of the operation. Aprotinin 280mg was also added to the pump priming fluid of the CPB circuit. The standard low dose regimen usually followed the same protocol with all doses reduced by half. In addition, some trials used a regimen involving only the addition of aprotinin to the CPB pump priming fluid (pump prime only).

It should be noted that the majority of these studies included fewer than 100 patients in each treatment group and are, therefore, susceptible to type II statistical error.

4.1.1 Clinical End-Points

The primary outcome measures in these studies were blood loss and use of blood products. Generally, postoperative blood loss (volume of loss from chest drains over 8 to 24 hours) was measured, although some studies also measured intraoperative loss into swabs or sponges or through suction. Blood products used postoperatively were usually allogenic transfusion of whole blood or packed red blood cells (PRC), although some studies also measured the use of fresh frozen plasma (FFP) and platelets.

Blood loss and use of blood products are clinically and economically significant end-points. Reducing perioperative blood loss can result in shorter surgery time and can decrease time in the intensive care unit (ICU) as well as the risk of rescue surgery to control bleeding. This generally leads to short term functional benefits for the patient as well as the decreased theatre and hospital

Table II. Risks associated with transfusion of allogenic blood and blood products[10]

ABO/rhesus incompatibility
Sepsis
Alloimmunisation resulting in an acute haemolytic reaction
Febrile reactions
Immunosuppression (with increased risk of infection and/or graft rejection)
Viral transmission: hepatitis B or C, HIV, HTLV
Coagulopathy

HTLV = human T-cell lymphotropic virus

costs related to a shorter stay. Transfusion of allogenic blood and blood products is associated with the risk of several complications (table II), and decreasing transfusion requirements reduces these risks. In addition, the costs (some long term) involved in managing these complications are reduced or avoided, as are the direct costs involved in providing blood products.[1,10,57,58]

4.2 Effects on Blood Loss and Transfusion Requirements

Previously reviewed data from patients undergoing cardiac surgery[1] indicate that compared with placebo, high dose aprotinin significantly reduces postoperative blood loss (by 35 to 81%) and allogenic transfusion requirements (by 35 to 97%) and markedly increases the percentage of patients who do not require allogenic transfusions (by 40 to 88%). Significant reductions in blood loss and transfusion requirements, and increases in the number of patients who do not require transfusions, were also reported at that time in patients undergoing primary CABG who received low dose or pump prime only aprotinin compared with placebo or no treatment.

Subsequently, the efficacy of the standard high dose and low dose aprotinin regimens has been compared with placebo (with no direct comparison between aprotinin regimens) in 3 trials involving a total of 1088 patients undergoing either primary or repeat surgery. The results of these studies, showing that both regimens significantly improve study outcomes, are summarised in table III.[59-61] Two of these trials also included standard pump prime only aprotinin 280mg, which was superior to placebo in the trial by Lemmer et al.[60] in patients undergoing primary surgery but not in the smaller trial by Levy et al.[61] in patients undergoing repeat surgery.

Alternative low dose regimens of aprotinin 140mg infused over 20 minutes prior to CPB plus 140mg in the pump prime[62] and aprotinin 70mg in the pump prime[22] have also shown significant reductions in mean 24-hour postoperative blood loss compared with placebo.

Lemmer et al.[60] (table III) performed a subanalysis of their results and compared patients considered at high risk of haemorrhage (n = 496; 97% because they were taking aspirin) with those not considered at high risk of bleeding (n = 148). In the low risk group, the mean total number of blood products required in the aprotinin-treated patients (at any dosage) was not significantly different from that of placebo-treated patients. However, mean total blood product exposures per patient, number of patients requiring transfusion of any blood product and the mean number of PRC units used were all significantly reduced by aprotinin (at all dosages) compared with placebo in patients at high risk of haemorrhage.[60]

4.2.1 High Dose Aprotinin

The antifibrinolytic efficacy of high dose aprotinin in patients undergoing CABG and/or HVR surgery has been compared with that of the lysine analogues tranexamic acid and aminocaproic acid in several studies and with that of the vasopressin analogue desmopressin in a single trial. Results from these prospective, randomised, controlled, and in most instances double-blind, studies are summarised in table IV.

Two studies which included a total of >150 patients have each compared aprotinin with aminocaproic acid, tranexamic acid and no treatment.[19,65] High dose aprotinin significantly reduced postoperative blood loss compared with both aminocaproic acid and tranexamic acid.[19,65] Reductions in total 24-hour postoperative blood loss compared with controls were 52 and 63% with aprotinin, 30 and 37% with aminocaproic acid, and 26 and 9%

Table III. Efficacy of high dose (HD), low dose (LD) and pump prime only (PP) aprotinin (APR) compared with placebo (PL) in patients undergoing cardiopulmonary bypass during coronary artery bypass graft (CABG) or heart valve replacement (HVR) surgery. Summary of results of prospective, randomised, double-blind studies published since the previous review on APR in *Drugs*.[1]

Reference	Surgical procedure	Treatment regimen (no. of patients)	Mean 24-hour postoperative blood loss (ml)	Mean no. PRC units per patient (% patients requiring transfusion)	Comparative efficacy
D'Ambra et al.[58]	Primary HVR	HD (65)	296*** (8h)	2 (63)	HD, LD > PL
		LD (62)	368*** (8h)	1.9 (52)	
		PL (64)	568 (8h)	1.3 (48)	
Lemmer et al.[59]	Primary CABG	HD (160)	786***	0.8*** (34***)	HD, LD, PP > PL
		LD (168)	811***	0.9***(37***)	
		PP (159)	899***	0.9*** (35***)	
		PL (157)	1286	1.8 (55)	
Levy et al.[60]	Repeat CABG	HD (61)	900**	1.6* (54**)	HD, LD > PL; PP ≡ PL
		LD (59)	1040*	1.6** (53**)	
		PP (68)	1420	2.5 (74)	
		PL (65)	1700	3.4 (85)	
Ray et al.[61]	HVR	HD (50)	1.7[b]***	(19)	HD, LD > PL
		LD[c] (50)	3.0[b]*	(35)	
		PL (50)	6.9[b]	(40)	
Speekenbrink et al.[22]	Primary CABG	HD[d] (38)	504**	1.6 (29)	HD, PP > PL
		PP[d] (37)	662*	2.0 (24)	
		PL (37)	1068	2.9 (22)	

a HD = APR 280mg (2×10^6 KIU) intravenously after the induction of anaesthesia but before sternotomy followed by 70 mg/h (5×10^5 KIU) by intravenous infusion for the duration of surgery plus APR 280mg (2×10^6 KIU) added to the pump priming fluid of the CPB circuit. Unless otherwise stated, LD = APR 140mg (1×10^6 KIU) intravenously followed by 35 mg/h (2.5×10^5 KIU) by intravenous infusion plus APR 140mg (1×10^6 KIU) added to the pump priming fluid of the CPB circuit. PP = APR 280mg in the pump priming fluid.

b Median haemoglobin loss (g) in patients with normal preoperative platelet function.

c 140mg infused intravenously over 20min prior to bypass plus 140mg in the pump priming fluid.

d Pump priming dose only 70mg not 280mg.

KIU = kallikrein inactivator units; **PRC** = packed red blood cells; **>** indicates greater clinical efficacy than; ≡ indicates equivalent clinical efficacy to; * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ *vs* placebo.

with tranexamic acid.[19,65] Use of blood products (PRCs, FFP and platelets) was significantly decreased with the high dose aprotinin regimen compared with tranexamic acid (8 versus 50% of patients) but not aminocaproic acid (17%) in the study by Menichetti et al.[19] There were no significant differences between active treatment groups in the units of allogenic blood required or the percentage of patients requiring transfusion in the study by Penta de Peppo et al.[65]

In direct one-on-one comparisons, the high dose aprotinin regimen reduced blood loss to a significantly greater extent than desmopressin[21] and to a similar extent to tranexamic acid (table IV).[20,66,67] Blood loss with aprotinin was significantly lower in repeat surgery[63] but equivalent in primary CABG when compared with aminocaproic acid.[64] Aprotinin reduced the percentage of patients requiring PRC transfusion compared with desmopressin (26 *vs* 66%),[21] but there were no significant differences in the use of blood products between aprotinin and aminocaproic acid or tranexamic acid in these studies.[20,64,67] Interestingly, in a subgroup analysis of patients undergoing repeat sternotomy, the number of mean units of PRC transfused per patient in the 24 hours after surgery was significantly lower with aprotinin (1.25) than tranexamic acid (3.86; $p < 0.05$).[67]

An important secondary outcome to reduced blood loss is a reduction in the incidence of reoperations to control bleeding (surgical or diffuse/oozing). A recent, but as yet unpublished, meta-

Table IV. Comparative efficacy of high dose aprotinin[a] (APR) *versus* desmopressin (DES), aminocaproic acid (ACA) and/or tranexamic acid (TRA) in patients undergoing cardiopulmonary bypass (CPB) during coronary artery bypass graft (CABG), heart valve replacement (HVR) or other complex open heart surgery (OHS). Summary of prospective, randomised, double-blind (unless stated otherwise) comparative studies

Reference (surgical procedure)	Treatment regimen	No. of patients	Mean 24-hour postoperative blood loss (ml)	Total blood products [units] (% patients requiring blood products)	Comparative efficacy
Casas et al.[21] (HVR, CABG or both)	APR	48	195**††	0.7[c] (26**††)	APR > DES, PL
	DES 0.3-0.4 μg/kg[b]	50	400	1.6[c] (66)	
	PL	51	489	1.8[c] (56)	
Bennett-Guerrero et al.[62] (repeat HVR or CABG)	APR	99	511†	2[c]	APR > ACA
	ACA 150 mg/kg then 30 mg/kg/h	105	655	3[c]	
Eberle et al.[63] (primary CABG)	APR	20	391** (12h)	175ml[c] (45)	APR ≡ ACA > CTR
	ACA 10g then 2.5 g/h plus 10g in priming fluid	20	582** (12h)	225ml[c] (60)	
	CTR	20	1091 (12h)	100ml (10[d])	
Penta de Peppo et al.[64][e] (HVR or CABG)	APR	15	344*†‡	0[f] (0)	APR > ACA, TRA, CTR; ACA > CTR
	ACA 10g then 2 g/h for 5h	15	509*	8[f] (20)	
	TRA 10 mg/kg then 1 mg/kg/h for 10h	15	534	1[f] (7)	
	CTR	15	724	6[f] (20)	
Menichetti et al.[19][g] (CABG)	APR	24	298*†‡	(8)*‡	APR > ACA > TRA > CTR
	ACA 80 mg/kg then 30 mg/kg/h plus 80 mg/kg in priming fluid	24	512*‡	(17)*‡	
	TRA 10 mg/kg then 3 mg/kg/h plus 10 mg/kg in priming fluid	24	737*	(50)	
	CTR[h]	24	811	(75)	
Boughenou et al.[20] (HVR)	APR	17	523	4.7[c]	APR ≡ TRA
	TRA 20 mg/kg then 8 mg/kg	18	438	2.5[c]	
Mongan et al.[65] (primary CABG)	APR	75	567[i]	0 (27)	APR ≡ TRA
	TRA 15 mg/kg then 2 mg/kg/h	75	680[i]	0 (25)	
Wong et al.[66][j] (OHS)	APR	30	391 (12h)	2.10[c]	APR ≡ TRA
	TRA 10g	29	331 (12h)	2.68[c]	

a High dose = APR 280mg (2×10^6 KIU) intravenously after the induction of anaesthesia but before sternotomy followed by 70 mg/h (5×10^5 KIU) by intravenous infusion for the duration of surgery plus aprotinin 280mg (2×10^6 KIU) added to the pump priming fluid of the CPB circuit.
b Administered 15min after protamine administration.
c Packed red blood cells.
d 90% of patients received autologous retransfusion.
e Not blinded.
f Allogenic blood transfusion.
g Active treatment groups blinded.
h Methodology does not clearly state whether this group received placebo or no treatment.
i Mean value for patients without excessive blood loss, i.e. <1L.
j Published as an abstract.

CTR = untreated control group; **KIU** = kallikrein inactivator units; **PL** = placebo; **>** indicates greater clinical efficacy than; ≡ indicates equivalent clinical efficacy; * $p < 0.05$, ** $p < 0.001$ *vs* placebo or control; † $p < 0.05$ *vs* aminocaproic acid; †† $p < 0.05$ *vs* desmopressin; ‡ $p < 0.05$ *vs* tranexamic acid.

analysis of 28 randomised clinical trials of high dose aprotinin (n = 1618) versus placebo (n = 1611) reported reoperation rates of 3.17% for aprotinin and 6.44% with placebo [relative risk 0.49; 95% confidence interval (CI) 0.35-0.69].[68]

4.2.2 Low Dose Aprotinin

Unfortunately, no published studies have compared the standard low dose aprotinin regimen (section 1.2) and other antifibrinolytic agents. Table V summarises the results of prospective, randomised, double-blind studies that compared various other nonstandard low dose regimens or pump prime only aprotinin with aminocaproic acid or tranexamic acid.

Low dose regimens of aprotinin [140mg (1×10^6 KIU) plus 140mg in the CPB pump priming fluid] and tranexamic acid (2.5g plus 2.5g in the pump prime) both provided significant reductions in blood loss and blood product requirements compared with no treatment, with no difference in either end-point between these 2 agents.[71] In contrast, pump prime only aprotinin (280mg) and tranexamic acid (10g) regimens failed to show any significant improvement in the former end-point compared with no treatment in a small study reported as an abstract (table V).[70]

In the only comparative trial to include patients taking aspirin within 48 hours of surgery, a low-dose aprotinin regimen [28mg (2×10^5 KIU) then 28 mg/h], tranexamic acid (10 mg/kg then 1 mg/kg/h) and aminocaproic acid (5g then 1 g/h) all significantly reduced both blood loss and the use of blood products (PRCs, FFP and platelets) compared with no treatment (table V).[69] Patients in this study were undergoing primary ≥3-vessel CABG with no repeat surgery patients included.

4.2.3 High Dose versus Low Dose Aprotinin

Both the high dose and the low dose regimens of aprotinin are superior to placebo. However, in terms of reducing transfusion requirements or

Table V. Comparative efficacy of nonstandard aprotinin (APR) low dosage regimens versus aminocaproic acid (ACA) and/or tranexamic acid (TRA) in patients undergoing cardiopulmonary bypass during coronary artery bypass graft (CABG), heart valve replacement (HVR) or other complex open heart surgery (OHS). Summary of prospective, randomised, double-blind (unless otherwise stated) comparative studies

Reference (surgical procedure)	Treatment regimen	No. of patients	Mean 24-hour postoperative blood loss (ml)	Total blood products [units] (% patients requiring blood products)	Comparative efficacy
Landymore et al.[68]a,b (primary CABG)	APR 28mg then 28 mg/h	48	515**	0.5*	APR, ACA, TRA > CTR
	TRA 10 mg/kg then 1 mg/kg/h	56	535**	0.38**	
	ACA 5g then 1 g/h	44	543*	0.32*	
	CTR	50	798	1.7	
Gilron et al.[69]c (repeat CABG)	APR 280mg in priming fluid	9	1817[d]		APR ≡ TRA, PL
	TRA 10g	9	1655[d]		
	PL	9	1940[d]		
Pugh & Wielogorski[70]e (HVR, CABG, or both)	APR 140mg plus 140mg in priming fluid	21	230*	420ml[f]*	APR ≡ TRA
	TRA 2.5g plus 2.5g in priming fluid	22	375*	600ml[f]*	
	CTR	23	615	1050ml[f]	

a Active treatment groups blinded.

b Aspirin permitted.

c Published as an abstract.

d Total perioperative blood loss.

e Anaesthetist and perfusionist aware of group allocation.

f Allogenic blood transfusion.

CTR = untreated control group; **PL** = placebo; **>** indicates greater clinical efficacy than; ≡ indicates equivalent clinical efficacy; * $p < 0.05$, ** $p < 0.001$ *vs* CTR.

blood loss, no significant benefit of one regimen over the other has consistently been shown.

Two randomised double-blind studies have directly compared high dose and low dose aprotinin in a total of 220 patients undergoing CPB during primary OHS.[72,73] No significant difference between groups in mean 24-hour postoperative blood losses was shown in either study (537 *vs* 611ml and 502 *vs* 530ml for high dose *vs* low dose groups). A statistically significant difference in postoperative blood loss between the 2 regimens was seen in the study by Gschossmann et al.[72] between 6 and 12 hours after surgery [70ml with high dose *vs* 110ml with low dose ($p = 0.003$)]. 61% of high dose recipients ($n = 50$) and 46% of low dose recipients ($n = 50$) did not require a blood transfusion in the study by Weber et al.[73]

The high dose regimen has been shown to be superior to the pump prime only regimen. Dietrich et al.[74] recently directly compared high dose with pump prime only (section 1.2) aprotinin in 230 patients undergoing either primary or repeat OHS. Both perioperative blood loss and the mean volume of allogenic blood transfused were significantly lower with the high dose regimen compared with pump prime only [665 *vs* 877ml ($p < 0.05$) and 1.3 *vs* 1.9 units ($p < 0.05$), respectively]. In addition, 57% of high dose recipients did not require allogenic blood transfusion compared with 43% of pump prime only recipients.[74]

4.2.4 Paediatric Open Heart Surgery

At the time of the last review,[1] 5 comparative studies had examined the clinical role of aprotinin in paediatric OHS. Of these, some showed significant reductions in blood loss and blood transfusion requirements, while others failed to demonstrate any advantage of aprotinin over no treatment.[1,29] Since then, 5 further prospective studies have attempted to clarify the clinical role of aprotinin in children undergoing OHS. The results of these studies are summarised in table VI.[58,75-78]

Two studies were unable to show any statistically significant difference between aprotinin-treated and untreated patients in terms of standard outcomes such as blood loss and the need for transfusions.[58,76] However, an extremely low dose of aprotinin was used in the study by Davies et al. (table VI).[58] Two studies (one double-blind and one nonblind) which showed a significant decrease in the number of patients requiring blood products with aprotinin compared with placebo or untreated control groups included only patients undergoing repeat surgery.[75,77] Another nonblind study reported no significant benefit with aprotinin over no treatment in patients undergoing primary surgery for ventricular septal defects or tetralogy of Fallot, but a significant decrease in blood loss and transfusion requirements in children undergoing more complex primary surgery for transposition of the great arteries.[78]

Overall, the difficulty of drawing conclusions regarding the use of aprotinin in paediatric cardiac surgery remains because these more recent studies still have small patient numbers and a heterogeneous mix of study designs, surgical procedures and dosage regimens. The results available so far indicate that aprotinin may be beneficial in children at high risk, i.e. undergoing repeat sternotomy or very complex procedures. However, further investigation is required to confirm this and define a paediatric dosage regimen.

4.3 Pharmacoeconomic Evaluations

Although no cost-effectiveness studies have been conducted for aprotinin, studies have been published which have examined the effect on costs of using aprotinin compared with no treatment,[75,77,79-82] aminocaproic acid[63,83,84] and various anti-inflammatory strategies.[85]

The effect on costs of the use of low dose aprotinin compared with no treatment has been examined in 97 patients (of which 46 were historical controls) undergoing first time repeat CABG (i.e. their second CABG) in a retrospective study.[79] All costs were viewed from the perspective of the acute care hospital as provider, and included costs for drug acquisition, blood products and critical care and hospitalisation. Costs were expressed in 1995 US dollars.

Table VI. Efficacy of aprotinin (APR) in paediatric patients undergoing cardiopulmonary bypass during open heart surgery. Summary of prospective, randomised, double-blind (unless otherwise stated) studies published since the previous review of aprotinin in *Drugs*[1]

Reference (type of surgery)	Treatment regimen	No. of patients	Mean 24h postoperative blood loss (ml/kg)	Total blood products [units] (% patients requiring transfusion)	Comparative efficacy
Carrel et al.[77] (primary)[a,b,c]	APR 7 mg/kg then 2.8 mg/kg/h plus 7mg in priming fluid	20	47*	53 ml/kg/24h*	APR (either regimen) > CTR
	APR 7mg in priming fluid	18	52	66 ml/kg/24h**	
	CTR	18	55	75 ml/kg/24h	
Davies[57] (primary and reoperative)	APR 0.02 mg/m^2 then 0.008 mg/m^2/h plus 0.033 mg/m^2 in priming fluid[d]	19	23.6	47.2 ml/kg/24h	APR ≡ PL
	PL	23	28.6	48.3 ml/kg/24h	
D'Errico[74] (reoperative)	APR 240 mg/m^2 then 56 mg/m^2/h plus 240 mg/m^2 in priming fluid	19	27	(53**[e])	APR (either regimen) > PL
	APR 120 mg/m^2 then 28 mg/m^2/h plus 120 mg/m^2 in priming fluid	18	35	(89**[e])	
	PL	20	44	(95[e])	
Gomar[75]b,f (primary)	APR 240 mg/m^2 then 50 mg/m^2/h plus 50 mg/m^2 in priming fluid	12	6.9	39[e] ml/kg	APR ≡ CTR
	CTR	13	10.0	43[e] ml/kg	
Miller et al.[76]b (reoperative)	APR 56 mg/kg then 28 mg/kg/h plus 56mg in priming fluid	15	36	(47†)	APR (either regimen) > CTR
	APR 28 mg/kg then 14 mg/kg/h plus 28mg in priming fluid	15	31.6	(47†)	
	CTR	15	28.9	(80)	

a Results for subgroup of patients undergoing surgery for transposition of the great arteries.

b Nonblind.

c Nonrandomised.

d Dosage for children with a body surface area of ≤ 1.16m^2 (140 KIU/m^2 then 56 KIU/m^2/h plus 240 KIU/m^2). Dosage for children with a body surface area > 1.16m^2 was 0.035 mg/m^2 (250 KIU/m^2) then 0.01 mg/m^2/h (70 KIU/m^2/h) plus 0.04 mg/m^2 (280 KIU/m^2) in the pump priming dose.

e Packed red blood cells.

f Published as an abstract.

CTR = untreated control; **PL** = placebo; **>** indicates greater clinical efficacy than; ≡ indicates equivalent clinical efficacy to; * $p < 0.05$ *vs* priming fluid only aprotinin and CTR; ** $p < 0.05$ *vs* CTR or PL; † $p < 0.05$ *vs* CTR for use of fresh frozen plasma or platelets.

The approximate cost saving per patient receiving aprotinin was $US1516, as a result of savings on blood products of $US878 and length of stay (0.3 days in critical care and 1.9 days in hospital) of $US1088, with the cost of aprotinin being $US450. In a prospective nonblind 3-way comparison between high dose, low dose and no aprotinin in patients undergoing CPB during OHS and/or CABG, total costs for drug acquisition and transfusion were significantly reduced in patients receiving low dose (n = 31) but not high dose (n = 50) aprotinin compared with those for no treatment (n = 52).[80]

Two prospective, randomised studies in paediatric patients undergoing repeat OHS with CPB showed a cost saving with aprotinin compared with no treatment or placebo when patient hospital charges for drug acquisition, blood products and

time in the operating room, ICU and hospital were considered (aprotinin dosage regimens used in both studies are detailed in table VI).[75,77] The currency year was not stated in either study. In the analysis by Miller et al.,[77] total patient charges were $US12 598 in the no treatment group compared with $US12 189 with the low dose aprotinin regimen used and $US9880 with the high dose aprotinin regimen used. Total patient charges in the study by D'Errico et al.[75] were $US8893, $US5006 and $US5319, respectively, with placebo and the low dose and high dose aprotinin regimens used.

Although high dose aprotinin (4-hour infusion) was significantly more effective than aminocaproic acid (150 mg/kg then 30/mg/kg/h for 4 hours) in decreasing blood loss and requirement for platelet transfusions in patients undergoing repeat OHS in the study by Bennett-Guerrero et al.[63] (see table IV), median overall bleeding-related costs were lower for aminocaproic acid ($US1088; currency year not stated) than for aprotinin ($US1813; p = 0.0001). Costs to the hospital included in this study were those of drug acquisition, blood products, infectious complications and operating room time but not ICU or hospitalisation.

In contrast, when Van Norman et al.[83] retrospectively examined the charts of 81 patients who had undergone repeat or complex OHS, they found that costs related to transfusions, operating room use and anaesthesia service were $US298 less per patient with low dose aprotinin ($US1992) than aminocaproic acid 5 to 10g then 1g/h ($US2290) [currency year not stated].

An interesting prospective randomised study by Gott et al.[85] compared low dose aprotinin, a leucocyte depletion strategy (by filtration) and the use of heparin-bonded circuitry with no treatment in 400 patients undergoing primary or repeat OHS and/or CABG. All 4 groups received methylprednisolone 250mg 30 to 60 minutes before CPB. Patients were stratified preoperatively into low risk (<5% predicted mortality), medium risk (5 to 15%) and high risk (>15%) based on cardiac anatomy and function, priority and type of surgery, comorbidities, age and body surface area. In high risk patients, aprotinin reduced the length of hospital stay by up to 10 days (p = 0.02) and hospital charges by $US6000 to $US48 000 [currency year not stated] compared with all other groups (p = 0.0007).

4.4 Stroke in Patients Undergoing Cardiopulmonary Bypass

A recent meta-analysis of US studies evaluating aprotinin in CABG and HVR surgery (primary and repeat) showed a significant reduction in the frequency and incidence of stroke in patients receiving high dose aprotinin compared with placebo (7 of 955 = 0.7% versus 19 of 949 = 2%; p = 0.032).[86] The incidence of stroke with low dose or pump prime only aprotinin was not significantly different from that with placebo (low dose: 3 of 410 = 0.7%, p = 0.17; pump prime: 3 of 245 = 1.6%, p = 0.6). The normal expected rate of stroke in patients undergoing cardiac surgery is ≥2%, and it is thought that the embolic and inflammatory effects of CPB (see section 1) may contribute to the occurrence of stroke in these patients.[86] Although careful interpretation of these results is required, further investigation of the effects of aprotinin on stroke is clearly warranted.

5. Tolerability

Aprotinin is generally well tolerated at the dosages used to reduce blood loss and transfusion requirements in patients undergoing CPB during OHS and/or CABG. Previous data[1] indicate that adverse events with aprotinin are generally consistent with those associated with such surgery. Specifically, no significant differences in the type or incidence of adverse events between aprotinin and placebo or no treatment were seen in a meta-analysis of 4 studies (n = 886),[87] a multicentre UK study (n = 671)[88] and a single-centre German study (n = 1784).[89]

Unfortunately, the majority of studies comparing the efficacy of aprotinin with that of other fibrinolytic agents discussed in section 4 did not report tolerability data.[19,65,67,69-71,90] Casas et

al.[21] reported that no adverse drug reactions occurred in patients receiving high dose aprotinin, desmopressin or placebo. One aprotinin and 2 desmopressin recipients required re-exploration for bleeding, and a thromboembolic event occurred in 3 patients, 1 from each treatment group.

In studies involving paediatric patients there were no episodes of anaphylaxis or adverse events likely to be drug related, and no differences in renal function or overall complications between aprotinin and placebo recipients were reported.[58,75,77,78]

Comparisons of the tolerability of high dose, low dose and pump prime only aprotinin with placebo have been made with variable results in terms of myocardial infarction (MI) rates and the incidence of renal dysfunction (see sections 5.1 and 5.2).[59-61] No statistically significant difference in the overall incidence of postoperative cardiovascular complications occurred between regimens in 2 studies.[59,61]

The following sections update data concerning the controversy that still exists (reviewed previously[1]) regarding the possible increased risk of graft occlusion and MI, hypersensitivity reactions and renal dysfunction in aprotinin recipients.

5.1 Graft Patency and Myocardial Infarction

Some concern continues regarding the thrombotic potential of aprotinin because of its haemostatic properties. Inadequate heparinisation of patients in the older trials may have contributed to these concerns (see section 6).

The previous review[1] described 3 randomised, double-blind placebo-controlled studies specifically designed to investigate graft patency in patients undergoing CABG with CPB. The study by Bidstrup et al.[91] showed no difference in patency rates between aprotinin and placebo, whereas Lemmer et al.[92] showed a trend toward more occlusions with aprotinin, and the small study by Laub et al.[93] showed a significant difference in patency rates in favour of placebo.[1] However, it has since been noted that the results of Laub et al. were included as 1 of 5 centres in the study by Lemmer et al.[92] and are the cause of the trend towards decreased patency rates with aprotinin in the latter study.[8,94] The results from the other 4 centres show no difference in graft patency between aprotinin and placebo (reviewed by Royston).[8]

In a subsequent study by Lass et al.,[95] graft patency was measured by coronary angiography between 18 and 35 days after CABG in 44 patients receiving high dose aprotinin and 35 patients receiving placebo. Patent grafts were seen in 32 aprotinin recipients (73%) and 25 placebo recipients (71%) in this prospective, randomised, double-blind trial.

More recently, a similarly designed study reported by Alderman et al.[96] measured graft patency angiographically a mean of 10.8 days after primary CABG in 879 patients from 13 international centres receiving high dose aprotinin or placebo. In patients with angiographically assessable grafts, ≥1 occluded saphenous vein graft was seen in 15.4% of 363 patients receiving aprotinin compared with 10.9% of 340 patients receiving placebo, which resulted in an overall relative risk (RR) of 1.5 for aprotinin [90% confidence interval (CI) 1.1-2.1; $p = 0.03$].

However, it is important to note the significant differences in the occlusion rates between the 10 US centres (54% of patients) and the 3 European centres (46% of patients) with occlusion rates in the US of 9.4 and 9.5%, respectively, for aprotinin and placebo (RR 1.0; 90% CI 0.5-1.8; $p = 0.72$) and in Europe of 23 and 12.4%, respectively (RR 2.1; 90% CI 1.3-2.9; $p = 0.01$). Graft occlusion rates in the European centres were higher during the first enrolment tercile and decreased subsequent to changes to surgical procedures, in particular, heparinisation and graft vessel treatment. In addition, patients enrolled at the European sites had more risk factors for graft occlusion than those enrolled at the US sites (see also section 7). Very low occlusion rates were seen in internal thoracic artery grafts with no significant difference between treatment groups (aprotinin 1.8% *vs* placebo 1%; $p = 0.32$).

The results of some studies that have investigated the incidence of myocardial infarction (MI) and mortality with aprotinin have generated con-

cerns that it may increase the risk of these outcomes compared with placebo when the low dose or pump prime only regimens are used. In 754 patients undergoing primary CABG, Lemmer et al.[60] found a significantly higher incidence of definite, probable or possible MI [as measured by electrocardiogram (ECG) and serum cardiac enzyme concentrations] in patients receiving pump prime only aprotinin (16%) compared with placebo (9%; p = 0.045). In contrast, Levy et al.[61] found no significant difference in the incidence of definite, probable or possible MI (criteria included ECG, cardiac enzymes and autopsy results) between high dose, low dose or pump prime only aprotinin and placebo in 287 patients undergoing repeat CABG. No significant difference between aprotinin (any dose) and placebo was seen in either of these studies for definite MI, or definite or probable MI.

Following on from these studies,[60,61] Smith and Muhlbaier[97] analysed pooled data from 6 US studies (2 unpublished) and reported an incidence of definite, probable or possible MI in patients receiving pump prime only aprotinin (n = 245) of 17.6% compared with 14.8% in placebo recipients (n = 861). Mortality rates in this analysis for aprotinin versus placebo were 2.7 and 2.8% for high dose (n = 860), 5.4 and 3.8% for low dose (n = 317), and 2.9 and 3.2% for pump prime only aprotinin. Although none of these results were statistically significant, on the basis of the trend, the authors concluded that adequate safety documentation was only available for the high dose regimen and further investigations were required for the other regimens.

Subsequently, a meta-analysis of data on all CABG patients (n = 4399) from placebo-controlled clinical trials has been completed (but is not yet published or subject to peer review) to investigate mortality and the risk of MI with aprotinin compared with placebo.[98] The mortality rate for high dose aprotinin was 2.9% in 481 patients compared with 4% in 472 patients receiving low dose aprotinin, giving an odds ratio of 1.41 (95% CI 0.69-2.88; p = 0.34). No significant difference in the incidence of definite, probable or possible MI compared with placebo was seen, with rates of 13.3 *vs* 13.1% for high dose, 17.8 *vs* 15.1% for low dose and 17.9 *vs* 15.1% for pump prime only aprotinin. In addition, in the study by Alderman et al.,[96] high dose aprotinin had no significant effect compared with placebo on MI rates (2.9 *vs* 3.8%) or mortality (1.4 *vs* 1.6%).

5.2 Hypersensitivity Reactions

Administration of aprotinin has been associated with hypersensitivity reactions, ranging from mild skin rashes and urticaria to anaphylaxis and, rarely, death. This is to be expected with a nonhuman protein, and specific prescribing recommendations are detailed in section 7. Aprotinin-specific immunoglobulin (Ig) G antibodies have been reported in 26 to 47% of patients after first exposure.[1] Although the contribution of these antibodies to an allergic reaction to aprotinin has not been confirmed, one study has shown that they can persist for 4 years in 39% of these patients.[99] The method of measuring antibody levels may be important, however: in a recent German study[100] 26 of 56 (46.4%) patients developed IgG antibodies to aprotinin as determined by Western Blot but only 14 (26.8%) as detected using enzyme-linked immunosorbent assay (ELISA).

At the time of the previous review,[1] the reported incidence of hypersensitivity reactions in clinical trials in patients receiving mainly high dose aprotinin ranged from 0.3 to 0.6%.[1] Most of these patients had received aprotinin for the first time. In addition, a meta-analysis of US controlled clinical trials in patients with no prior exposure to aprotinin (n = 2285) reported an incidence of hypersensitivity or anaphylactic reactions of ≤0.1% in both aprotinin and placebo recipients.[101]

However, reactions are more likely to occur in patients with prior exposure to aprotinin.[1] A retrospective analysis which included 240 patients re-exposed to aprotinin (total re-exposures 248) a mean of 344 days after first exposure revealed 7 adverse hypersensitivity reactions (2.8%).[102] Two patients reacted to the test dose (1 mild and 1 severe

reaction) and received no further aprotinin. In total, 1 reaction was rated as doubtful by the investigators, 2 mild (no intervention), 1 moderate (restoration of circulation within 15 minutes with vasopressors) and 3 severe (longer-lasting circulatory depression and instability despite the use of vasopressors). An interval between exposures of <6 months resulted in a significantly higher incidence of hypersensitivity reactions than in patients with a longer interval (4.5% of 111 compared with 1.5% of 137; $p < 0.05$). It should be noted that pretreatment with histamine H_1/H_2 receptor antagonists (antihistamine) was administered to 141 patients, corticosteroids to 140 patients and both agents to 83 patients in this study.

There are few published case reports of anaphylactic reactions associated with aprotinin therapy. Eight case reports have been published since 1984, with 5 recorded as serious.[103-109]

5.3 Renal Dysfunction

There is concern regarding the potential for aprotinin to cause renal dysfunction because it is selectively taken up by and accumulates in the renal tubules (see section 3). Aprotinin appears to reversibly overload the tubular reabsorption mechanisms.[110] Significant increases in indices of renal tubular overload and dysfunction have been demonstrated in aprotinin-treated patients compared with placebo recipients, but these were not associated with differences in serum creatinine levels.[1,110,111]

Clinical experience reviewed previously[1] indicates that aprotinin has minimal adverse effects on renal function in patients undergoing cardiac surgery. In some studies aprotinin had no effect on renal function; in others it was associated with transient or reversible elevations in serum creatinine levels of ≥44 μmol/L (0.5 mg/dl).[1]

Subsequent studies have shown similar results. In 2 studies, there were no significant differences in the incidence of patients having peak elevations in serum creatinine levels of ≥44 μmol/L (0.5 mg/dl) over baseline levels in 897 patients receiving high dose, low dose or pump prime only aprotinin or placebo.[60,61] In another study, increases in serum creatinine levels of ≥44 μmol/L (0.5 mg/dl) were seen in 30, 14 and 8% of patients receiving aprotinin high dose (n = 71) or low dose (n = 70), or placebo (n = 71) [p = 0.003 aprotinin versus placebo].[59] However, elevated creatinine levels did not appear to predispose patients to renal dysfunction in this study.

6. Drug Interactions

At the time of the last review[1] there were very few reports of clinically significant drug interactions with aprotinin, and, except for heparin, this continues to be the case. Heparinisation is essential during CPB to provide continuous anticoagulation and thus prevent thrombotic complications and/or possible bleeding secondary to the depletion of coagulation factors. Previously, following administration of standard loading doses of heparin, fixed-dosage heparin was administered to maintain the ACT, as measured by the celite surface activation method (celite ACT), at >400 to >450 seconds during CPB. However, aprotinin prolongs both activated partial thromboplastin time and celite ACT, which is consistent with its known ability to inhibit the contact activation of the intrinsic clotting cascade (see section 2). Therefore, the previously recognised ACT value of >400 to >450 seconds may not reflect adequate heparinisation in the presence of aprotinin, with a resultant increased risk of thrombotic complications (section 5.1).

There is general agreement that the heparin dosage should not be decreased during aprotinin administration, i.e. aprotinin is not heparin sparing. Current recommendations are:

- to maintain the celite ACT at >750 seconds
- to use kaolin as the contact activator (kaolin ACT), as kaolin ACT appears to be unaffected by aprotinin (kaolin ACT should be maintained at >480 seconds)
- to use a fixed heparin dose regimen with a total starting dose (patient and priming fluid) of ≥350 IU/kg with additional heparin based on patient weight and the duration of CPB
- or heparin/protamine titration to maintain heparin concentrations $\geq 2.7 \times 10^3$ IU/L.[1,8,10,101,112]

A further potential option that has been successfully used is monitoring serum heparin concentrations (using the Hepcon® heparin monitoring system, Medtronic HemoTec).[60]

In a study of 9 patients with previously untreated hypertension, aprotinin 280mg intravenously over 2 hours blocked the acute hypotensive effect of captopril. Aprotinin has been shown to inhibit the activity of thrombolytic agents both in animal models and *in vitro*.[1]

7. Dosage and Administration

High, low and pump prime fluid only doses of aprotinin have been used to reduce perioperative bleeding and transfusion requirements in patients undergoing CPB during OHS or CABG. Aprotinin is administered intravenously (except when only added to the pump priming fluid) and this should be through a central line.

The high dose regimen is a loading dose of aprotinin 280mg (2×10^6 KIU) administered as an intravenous infusion over 20 to 30 minutes after induction of anaesthesia but before sternotomy. An infusion of aprotinin 70 mg/h (5×10^5 KIU/h) is then maintained throughout surgery. In addition, aprotinin 280mg is added to the pump priming fluid of the CPB circuit by replacing an aliquot of the priming fluid before CPB is initiated. Clinical trials have investigated a number of lower dose regimens. The most common of these is a standard low dose regimen which is 50% of the high dose regimen using the same protocol, or a pump prime only regimen comprising aprotinin 280mg in the pump priming fluid of the CPB circuit (see section 1.2).

As yet, specific dosage recommendations for paediatric patients undergoing CPB during OHS are not available. A range of dosage regimens that are effective and well tolerated in this population is listed in table VI.

It is advised that an intravenous test dose of aprotinin 1.4mg[1,101] or 1ml[10] be administered at least 10 minutes before the loading dose to patients with known or suspected previous exposure to aprotinin because of the risk of anaphylactic reactions. It has also been recommended that some form of testing for sensitisation be carried out before surgery in these patients.[10] However, skin tests are not a reliable indicator of pre-existing antibodies against aprotinin.[99,113] The intravenous administration of a histamine H_1 receptor antagonist (antihistamine) 15 minutes before initiation of aprotinin may prevent or mitigate serious anaphylactic reactions; however, standard emergency treatments for anaphylactic reactions should be readily available.[1,101]

Aprotinin is manufactured using bovine lungs from countries with no known cases of bovine spongiform encephalitis (BSE) and the manufacturing process follows recommendations and regulations for the minimisation of BSE transmission via medicinal products.[114-116] A recent investigation of the aprotinin manufacturing process showed an overall reduction of the infectious agent of greater than 18 $\log_{10}$, indicating a very high capacity of the process for the inactivation/removal of the BSE agent, if present.[117]

8. Place of Aprotinin in Patient Management

Diffuse intra- and/or post-operative bleeding occurs in many patients undergoing CPB despite proper surgical technique, and blood transfusions are often required. In addition, some patients are at greater risk of perioperative bleeding than others and are more likely to require transfusions. Risk factors for perioperative bleeding include:

- repeat surgery through a previous median sternotomy
- procedures requiring a prolonged time on CPB
- presence of a coagulopathy (not always apparent before surgery)
- presence of sepsis or endocarditis
- preoperative antiplatelet or anticoagulant therapy, e.g. aspirin, NSAIDs, warfarin
- dialysis-dependent renal failure.[1,3,10,118]

An estimated 20% of all allogenic blood transfusions in the US are associated with cardiac surgery.[119] Conservation of blood has become a priority during surgery because of shortages of donor

blood, the risks associated with allogenic blood or blood product transfusion (see table II), and the cost of transfusion products.[5,6,10] A variety of methods intended to minimise perioperative allogenic transfusions have therefore been developed.[5,10,120,121] These include the following:

- preoperative autologous donation either during the month before or immediately before surgery
- intra- and post-operative blood cell salvage, using the Cell Saver (a centrifugal cell washing system), haemofiltration or autotransfusion
- normovolaemic haemodilution
- reducing heparin use, i.e. a lower dose may be more appropriate when using membrane oxygenators or heparin coated circuits
- the use of drugs intended to either minimise blood loss, such as aprotinin, or stimulate red blood cell production, such as erythropoietin.

Pharmaceutical methods to minimise blood loss are used either in conjunction with some or all of the methods of blood conservation listed above, or as a way of avoiding some of the more complicated and time-consuming of these methods.[122] Drugs currently employed to reduce blood loss and transfusion requirements in patients undergoing CPB during OHS and/or CABG include the naturally occurring serine protease inhibitor aprotinin, the synthetic lysine analogues aminocaproic acid and tranexamic acid, and the synthetic vasopressin analogue desmopressin. Aminocaproic acid and tranexamic acid both inhibit plasminogen/plasmin binding to fibrin and partially preserve platelet ADP content after CPB. Tranexamic acid is ≥7 times more potent, on a molar basis, than aminocaproic acid.[10,57] Desmopressin shortens bleeding time by inducing the release of the procoagulant factor VIII (von Willebrand factor) from the endothelium.[10,57]

Aprotinin has been shown to significantly reduce postoperative blood loss and allogenic transfusion requirements, and to decrease the number of patients requiring allogenic transfusions, compared with placebo or no treatment in large, randomised, double-blind, controlled studies.[1] Both the lysine analogues have also been shown to decrease perioperative blood loss and the percentage of patients requiring transfusions compared with placebo in smaller numbers of similarly well designed studies.[10] However, the results of 2 separate meta-analyses of randomised trials investigating the efficacy of aprotinin, tranexamic acid, aminocaproic acid and desmopressin show that desmopressin is not effective in reducing transfusion requirements in patients undergoing CPB during cardiac surgery.[121,123]

High dose aprotinin (defined in sections 1.2 and 7) reduced blood loss significantly more than aminocaproic acid but has shown no statistically significant advantage over this agent in terms of transfusion requirements in the studies reviewed in this paper. High dose aprotinin was superior to tranexamic acid in some studies and equivalent in others. However, conclusions regarding efficacy between high dose aprotinin and tranexamic acid are difficult to make because of the range of dosage regimens of tranexamic acid used in these studies. A large well designed study comparing high dose aprotinin and a standard dosage of tranexamic acid which included longer term patient outcomes (i.e. length of stay and/or complications during surgery or hospitalisation) and/or mortality as end-points would indeed be useful.

Nonstandard low dose regimens of aprotinin appear to have similar efficacy to aminocaproic acid and tranexamic acid as regards blood loss. Unfortunately, there are no studies directly comparing the standard low dose aprotinin regimen or pump prime only regimen with either lysine analogue.

As a serine protease inhibitor, aprotinin acts in a number of interrelated ways to provide an antifibrinolytic effect (by inhibition of plasmin), reduce platelet dysfunction and attenuate the inflammatory response to CPB. In contrast, the lysine analogues act solely as antifibrinolytics by binding to plasminogen so that plasmin is unable to bind to fibrin, thus preventing its degradation.[112] Several commentators have speculated on the clinical significance of the anti-inflammatory properties of aprotinin, particularly its potential to decrease the severity and/or incidence of CPB-induced compli-

cations other than bleeding, such as organ ischaemia and CNS sequelae.[10,31,57] Recent evidence indicating that high dose aprotinin may reduce the incidence of cerebrovascular complications seen in patients undergoing cardiac surgery[86] is particularly interesting and warrants further investigation.

Concerns have been expressed regarding allergic reactions after re-exposure to aprotinin, possible aprotinin-induced renal dysfunction and increased graft occlusion and MI rates. Serum creatinine levels increase in most patients during and after CPB, and aprotinin administration has been associated with further transient increases. These changes have not been associated with serious or long term renal dysfunction. IgG antibodies to aprotinin are formed in a significant number of patients; allergic adverse reactions have been reported in a small percentage of patients and are more likely in those re-exposed to aprotinin. Standard precautions (see section 7) should limit the occurrence and severity of these reactions.

A thrombotic potential, as evidenced by early graft occlusion or MI, has been attributed to aprotinin. However, although its mechanism of action has not been clearly defined, there is no *in vitro* or *in vivo* evidence of a prothrombotic effect for aprotinin.[124] It has been variously suggested that study design faults, poor target vessel quality, unusual graft preservation techniques, and/or inadequate heparinisation may have contributed to the original reports indicating that aprotinin therapy may increase graft occlusion rates.[8,93,94,124]

Several studies that specifically examined graft patency or the incidence of MI after aprotinin therapy did not show a statistically significant increase in either end-point with high dose aprotinin compared with placebo or no treatment.[8-10,59-61,94,97,98] However, as the incidence of these end-points is low, it is the study by Alderman et al.[96] that is pivotal because it was designed with a sufficient sample size to investigate angiographically whether high dose aprotinin has any adverse effect on graft patency in primary CABG surgery. This study concluded that aprotinin did not have any effect on MI or mortality but that it increased the probability of early vein graft occlusion, particularly in patients with high risk factors (female gender, small and poor distal vein quality, lack of preoperative aspirin therapy, low protamine dose and possibly use of aprotinin-treated blood as excised vein perfusate). After adjustment for these risk factors the aprotinin versus placebo RR decreased from 1.5 to 1.05 (90% CI 0.6 to 1.8). The disparate results from the US and European centres (section 5.1) indicate that although aprotinin may have exacerbated graft occlusion in patients with high risk factors, surgical procedure (particularly anticoagulation and handling of the vein grafts) may have contributed to this effect.

This study, currently being discussed by the medical community, adds to the debate regarding the most beneficial surgical practices and accompanying laboratory monitoring parameters when using aprotinin in various patient groups. A very useful outcome of this discussion would be a set of clear guidelines, such as the US guidelines for laboratory monitoring of anticoagulation during CABG with aprotinin[101] which, if followed, would minimise the risk of premature graft occlusion with aprotinin.

Unfortunately, there are no comparative tolerability data for aprotinin and aminocaproic acid or tranexamic acid. In addition, neither of these lysine analogues has been the focus of any large scale clinical trials documenting tolerability as well as efficacy.[10,112] Aminocaproic acid and, to a lesser extent, tranexamic acid have been associated with minor adverse events such as nausea, diarrhoea and orthostatic symptoms, and more serious but rarely reported cases of myonecrosis. Hypersensitivity reactions are not a problem with these synthetic agents. However, whether the use of these agents results in increased rates of graft occlusion or MI is not known. Although there are several published case reports of thrombosis associated with tranexamic acid or aminocaproic acid, there have been no studies specifically aimed at assessing graft patency in patients receiving either lysine analogue.[57,112]

A clear role for aprotinin in paediatric patients undergoing open heart surgery with CPB is still not

apparent. Well designed studies in this patient group have failed to consistently demonstrate a benefit.[58,75-78] However, the drug may be of value in patients undergoing repeat operations and in other patients at high risk of haemorrhage, and further study in these patient groups is warranted.[58,75,77,78]

Pharmacoeconomic evaluations of the use of aprotinin in patients undergoing cardiac surgery are limited to simple cost analyses. Standard low dose aprotinin provided significant cost savings compared with other anti-inflammatory strategies in high risk patients in 1 prospective study and with no treatment in 1 retrospective study when costs for drug acquisition, blood products, the operating room, critical care and hospitalisation were included. Low dose aprotinin was also cost saving compared with aminocaproic acid in high risk patients in 1 retrospective study and with no treatment in 1 prospective study when only costs relating to factors including drug acquisition, blood products and operating room were included. However, in 2 prospective studies, high dose aprotinin increased costs compared with either aminocaproic acid or no treatment when costs relating to drug acquisition, blood products and operating room use were considered. Several aprotinin dosage regimens have been shown to save costs compared with no treatment or placebo in paediatric patients. Unfortunately, the effect on costs of the use of tranexamic acid compared with aprotinin has not been examined.

All direct costs of treatment, including acquisition cost of drug and blood products, length of stay in the operating room, intensive care and hospital ward, the need for surgical re-exploration, and the costs associated with the treatment of transfusion- or drug-related adverse events, need to be considered in evaluating the true health economic value of aprotinin. The comparatively high acquisition cost of aprotinin (1996 US dollar value >$US1000 for high dose aprotinin compared with $US40 and $US32, respectively, for aminocaproic acid 12g and tranexamic acid 20g)[112] is significant. Despite the proven effectiveness of aprotinin, cost factors are likely to deter many health providers from using the drug in the absence of complete pharmacoeconomic analyses comparing its cost effectiveness with that of the lysine analogues.

Aprotinin is clearly the most well studied agent currently available for preventing haemorrhage in patients undergoing CPB during CABG and/or OHS, and its efficacy compared with placebo or no treatment is established. It also has a full safety database according to GCP (good clinical practice) standards available. In comparison, there are far fewer data on the efficacy and tolerability of either aminocaproic acid or tranexamic acid. Aprotinin has shown some advantages over these agents in well designed studies, but this is inconsistent and not always demonstrated for the important outcome of transfusion requirements. Furthermore, the issues of thrombotic potential and cost effectiveness remain unresolved not only for aprotinin but also for its competitors. On balance, the standard low dose regimen of aprotinin appears to be as effective as high dose aprotinin in reducing blood loss and transfusion requirements. However, the pump prime only dose is not consistently effective and there is evidence linking its use to higher MI rates. A predicted tolerability advantage for low dose over high dose aprotinin has not been shown, and although studies to date indicate that this regimen may have some economic advantage over the high dose regimen, the evidence for this is not conclusive.

In conclusion, comparative tolerability and cost-effectiveness data for aprotinin and the lysine analogues are required to more fully assess their individual roles in reducing blood loss and transfusion requirements in patients undergoing CPB during OHS and/or CABG. However, clinical evidence to date supports the use of aprotinin, either the standard high dose or low dose regimen, in preference to its competitors in patients at high risk of haemorrhage, in those for whom transfusion is unavailable or in patients who refuse allogenic transfusions.

References

1. Davis R, Whittington R. Aprotinin: a review of its pharmacology and therapeutic efficacy in reducing blood loss associated with cardiac surgery. Drugs 1995 Jun; 49: 954-83

2. Boisclair MD, Lane DA, Philippou H, et al. Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood 1993 Dec 1; 82 (11): 3350-7
3. Robert S, Wagner BKJ, Boulanger M, et al. Aprotinin. Ann Pharmacother 1996; 30 (4): 372-80+407-8
4. Pakalnis R, O'Hara IB, Campbell FW. Prevention and treatment of post-cardiopulmonary bypass bleeding. Curr Opin Anaesth 1995; 8 (1): 49-55
5. John LCH, Deverall PB. Current methods to reduce the adverse haematological consequences of cardiopulmonary bypass. Br J Clin Pract 1996; 50 (4): 203-6
6. McCarthy MW, Coley KC. Aprotinin for prophylaxis of blood loss. Ann Pharmacother 1994 Nov; 28: 1246-8
7. Levy JH, Bailey JM, Salmenperä M. Pharmacokinetics of aprotinin in preoperative cardiac surgical patients. Anesthesiology 1994 May; 80: 1013-8
8. Royston D. Aprotinin in patients having coronary artery bypass graft surgery. Curr Opin Cardiol 1995; 10 (6): 591-6
9. Royston D. Aprotinin therapy [editorial]. Br J Anaesth 1994 Dec; 73: 734-7
10. Dobkowski WB, Murkin JM. A risk-benefit assessment of aprotinin in cardiac surgical procedures. Drug Saf 1998 Jan; 18: 21-41
11. Royston D. Preventing the inflammatory response to open-heart surgery: the role of aprotinin and other protease inhibitors. Int J Cardiol 1996 Apr 26; 53 Suppl: S11-37
12. Blauhut B, Harringer W, Bettelheim P, et al. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994 Dec; 108: 1083-91
13. Hayashida N, Isomura T, Sato T, et al. Effects of minimal-dose aprotinin on coronary artery bypass grafting. J Thorac Cardiovasc Surg 1997 Aug; 114: 261-9
14. Ray MJ, Marsh NA. Aprotinin reduces blood loss after cardiopulmonary bypass by direct inhibition of plasmin. Thromb Haemost 1997 Sep; 78: 1021-6
15. Lu H, Du Buit C, Soria J, et al. Postoperative hemostasis and fibrinolysis in patients undergoing cardiopulmonary bypass with or without aprotinin therapy. Thromb Haemost 1994 Sep; 72: 438-43
16. Mastroroberto P, Chello M, Zofrea S, et al. Suppressed fibrinolysis after administration of low-dose aprotinin: reduced level of plasmin-alpha(2)-plasmin inhibitor complexes and postoperative blood loss. Eur J Cardiothorac Surg 1995 Mar; 9: 143-5
17. Spannagl M, Dietrich W, Beck A, et al. High dose aprotinin reduces prothrombin and fibrinogen conversion in patients undergoing extracorporeal circulation for myocardial revascularization. Thromb Haemost 1994 Jul; 72: 159-60
18. Dietrich W, Dilthey G, Spannagl M, et al. Influence of high-dose aprotinin on anticoagulation, heparin requirement, and celite- and kaolin-activated clotting time in heparin-pretreated patients undergoing open-heart surgery. Anesthesiology 1995 Oct; 83: 679-89
19. Menichetti A, Tritapepe L, Ruvolo G, et al. Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: aprotinin vs tranexamic acid vs epsilon aminocaproic acid. J Cardiovasc Surg 1996; 37 (4): 401-7
20. Boughenou F, Madi-Jebara S, Massonnet-Castel S, et al. Fibrinolytic inhibitors and the prevention of bleeding in cardiac valvular surgery: comparison of tranexamic acid and high dose aprotinin [in French]. Arch Mal Coeur Vaiss 1995 Mar; 88: 363-70
21. Casas JI, Zuazujausoro I, Mateo J, et al. Aprotinin versus desmopressin for patients undergoing operations with cardiopulmonary bypass: a double-blind placebo-controlled study. J Thorac Cardiovasc Surg 1995 Oct; 110: 1107-17
22. Speekenbrink RGH, Wildevuur CRH, Sturk A, et al. Low-dose and high-dose aprotinin improve hemostasis in coronary operations. J Thorac Cardiovasc Surg 1996 Aug; 112: 523-30
23. Rossi M, Storti S, Martinelli L, et al. A pump-prime aprotinin dose in cardiac surgery: appraisal of its effects on the hemostatic system. J Cardiothorac Vasc Anesth 1997 Dec; 11: 835-9
24. Christensen U, Schiodt J. Effects of aprotonin on coagulation and fibrinolysis enzymes. Fibrinolysis Proteolysis 1997 Jul; 11: 209-14
25. Primack C, Walenga JM, Koza MJ, et al. Aprotinin modulation of platelet activation in patients undergoing cardiopulmonary bypass operations. Ann Thorac Surg 1996 Apr; 61: 1188-93
26. Ammar T, Sarier K, Vela-Cantos F. The effects of aprotinin and tranexamic acid on the platelet membrane GPIB receptor [abstract 60]. Anesth Analg 1997 Feb; 84 Suppl.
27. Kanbak G, Inal M, Alatas O, et al. Effect of high-dose aprotinin on plasma levels during cardiopulmonary bypass. Turk J Med Sci 1997; 27 (2): 175-7
28. Wahba A, Black G, Koksch V, et al. Aprotinin has no effect on platelet activation and adhesion during cardiopulmonary bypass. Thromb Haemost 1996 May; 75: 844-8
29. Boldt J, Zickmann B, Schindler E, et al. Influence of aprotinin on the thrombomodulin protein C system in pediatric cardiac operations. J Thorac Cardiovasc Surg 1994 May; 107: 1215-21
30. Wahba A, Philip A, Bauer MF, et al. The blood saving potential of vortex versus roller pump with and without aprotinin. Perfusion 1995; 10 (5): 333-41
31. Murkin JM. Cardiopulmonary bypass and the inflammatory response: a role for serine protease inhibitors? J Cardiothorac Vasc Anesth 1997; 11 (2) Suppl. 1: 19-23
32. Diego RP, Mihalakakos PJ, Hexum TD, et al. Methylprednisolone and full-dose aprotinin reduce reperfusion injury after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997 Feb; 11: 29-31
33. Hill GE, Diego RP, Stammers AH, et al. Aprotinin enhances the endogenous release of interleukin-l0 after cardiac operation. Ann Thorac Surg 1998 Jan; 65: 66-9
34. Hill GE, Pohorecki R, Alonso A, et al. Aprotinin reduces interleukin-8 production and lung neutrophil accumulation after cardiopulmonary bypass. Anesth Analg 1996 Oct; 83: 696-700
35. Mihalakakos P, Hofmann S, Hill GE. Steroids and full dose aprotinin, not half dose, reduce the possibility of reperfusion injury following CPB in humans [abstract]. Anesthesiology 1996 Sep; 85 Suppl.: abstr.128
36. Ruggeroli AC, Carruthers RG, Pohorecki R, et al. Cardiopulmonary bypass-induced inflammation: steroids *vs* aprotinin [abstract]. Anesthesiology 1995 Sep; 83 Suppl: abstr.83
37. Tran T, Pohorecki R, Hofmann S, et al. The effect of aprotinin on anti-inflammatory cytokines following CPB [abstract]. Anesthesiology 1997 Sep; 87 Suppl.: Abstr.96
38. Hill GE, Alonso A, Spurzem JR, et al. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans. J Thorac Cardiovasc Surg 1995 Dec; 110: 1658-62
39. Alonso A, Galbraith TA, Spurzem JR, et al. The effect of 'pump prime only' aprotinin on neutrophil CD11b upregulation during and following cardiopulmonary bypass in humans [abstract]. Chest 1996 Oct; 110 Suppl.: 204S
40. Seghaye MC, Duchateau J, Grabitz RG, et al. Influence of low-dose aprotinin on the inflammatory reaction due to cardiopulmonary bypass in children. Ann Thorac Surg 1996 Apr; 61: 1205-11

41. Ashraf S, Tian Y, Cowan D, et al. Low-dose aprotinin modifies hemostasis but not proinflammatory cytokine release. Ann Thorac Surg 1997 Jan; 63: 68-73
42. Rao PS, Palazzo RS, Bocchieri KA, et al. Aprotinin protects against myocardial and oxidant formation and endothelial cell damage during open heart surgery. Ann N Y Acad Sci 1996; 793: 514-6
43. Broche VF, Suàrez AR, Olembe E, et al. Aprotinin effects related to oxidative stress in cardiosurgery with mechanical cardiorespiratory support (CMCS). Ann N Y Acad Sci 1996; 793: 521-4
44. Buchele S, Roberts T, Newland M, et al. Mechanism of aprotinin-induced reduction of airway nitric oxide during CPB [abstract]. Anesthesiology 1996 Sep; 85 Suppl.: abstr.129
45. Bruda NL, Hurlbert BJ, Hill GE. Aprotinin reduces nitric oxide production in vitro and vivo in a dose dependent manner [abstract]. Anesthesiology 1996 Sep; 85 Suppl.: abstr.130
46. Hill GE, Taylor JA, Robbins RA. Differing effects of aprotinin and -aminocaproic acid on cytokine-induced inducible nitric oxide synthase expression. Ann Thorac Surg 1997; 63 (1): 74-7
47. Hill GE, Robbins RA. Aprotinin but not tranexamic acid inhibits cytokine-induced inducible nitric oxide synthase expression. Anesth Analg 1997 Jun; 84: 1198-202
48. Szabó C, Southan GJ, Thiemermann C. Beneficial effects and improved survival in rodent models of septic shock with S-methylisothiourea sulfate, a potent and selective inhibitor of inducible nitric oxide synthase. Proc Natl Acad Sci U S A 1994 Dec; 91: 12472-6
49. Ungureanu-Longrois D, Balligand JL, Kelly RA, et al. Myocardial contractile dysfunction in the systemic inflammatory response syndrome: role of a cytokine-inducible nitric oxide synthase in cardiac myocytes. J Mol Cell Cardiol 1995 Jan; 27 (1): 155-67
50. Haywood GA, Tsao PS, Von der Leyen HE, et al. Expression of inducible nitric oxide synthase in human heart failure. Circulation 1996; 93: 1087-94
51. Szabolcs M, Michler RE, Yang X, et al. Apoptosis of cardiac myocytes during cardiac allograft rejection: relation to induction of nitric oxide synthase. Circulation 1996; 94: 1665-73
52. Bennett-Guerrero E, Sorohan JG, Howell ST, et al. Maintenance of therapeutic plasma aprotinin levels during prolonged cardiopulmonary bypass using a large-dose regimen. Anesth Analg 1996 Dec; 83: 1189-92
53. Müller FO, Schall R, Hundt HKL, et al. Pharmacokinetics of aprotinin in two patients with chronic renal impairment. Br J Clin Pharmacol 1996 Jun; 41: 619-20
54. Royston D, Cardigan R, Mackie I, et al. Comparison of plasma aprotinin concentrations using weight related and fixed dose regimen [abstract no. A 273]. Anesthesiology 1998 Sep; 89 (3A) Suppl.
55. Schall R, Groenewoud G, Hundt HKL, et al. Pharmacokinetic profile of aprotinin (Trasylol Rm) in female patients undergoing primary elective hysterectomy. Drug Invest 1992; 4 (4): 292-9
56. Schall R, Müller FO, Hundt HKL, et al. Pharmacokinetic profile of high doses of aprotinin in patients undergoing primary elective hysterectomy: a meta-analysis of two clinical trials. Drug Invest 1994 Apr; 7: 200-8
57. Royston D. Blood-sparing drugs: aprotinin, tranexamic acid, and -aminocaproic acid. Int Anesthesiol Clin 1995 Winter; 33: 155-79
58. Davies MJ, Allen A, Kort H, et al. Prospective, randomized, double-blind study of high-dose aprotinin in pediatric cardiac operations. Ann Thorac Surg 1997 Feb; 63: 497-503
59. D'Ambra MN, Akins CW, Blackstone EH, et al. Aprotinin in primary valve replacement and reconstruction: a multicenter, double-blind, placebo-controlled trial. J Thorac Cardiovasc Surg 1996; 112 (4): 1081-9
60. Lemmer Jr JH, Dilling EW, Morton JR, et al. Aprotinin for primary coronary artery bypass grafting: a multicenter trial of three dose regimens. Ann Thorac Surg 1996 Dec; 62: 1659-68
61. Levy JH, Pifarre R, Schaff HV, et al. A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. Circulation 1995 Oct 15; 92: 2236-44
62. Ray MJ, O'Brien MF, Hawson GAT. A comparison of the relative efficiency of high and low dose aprotinin in their reduction of blood loss after cardiopulmonary bypass surgery [abstract]. Thromb Haemost 1997 Jun Suppl.: 441
63. Bennett-Guerrero E, Sorohan JG, Gurevich ML, et al. Cost-benefit and efficacy of aprotinin compared with aminocaproic acid in patients having repeated cardiac operations: a randomised, blinded clinical trial. Anesthesiology 1997 Dec; 87: 1373-80
64. Eberle B, Mayer E, Hafner G, et al. High-dose aminocaproic acid versus aprotinin:antifibrinolytic efficacy in first-time coronary operations. Ann Thorac Surg 1998; 65: 667-73
65. Penta de Peppo AP, Pierri MD, Scafuri A, et al. Intraoperative antifibrinolysis and blood-saving techniques in cardiac surgery: prospective trial of 3 antifibrinolytic drugs. Tex Heart Inst J 1995; 22 (3): 231-6
66. Mongan PD, Brown RS, Thwaites BK. Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularisation. Anesth Analg 1998; 87: 258-65
67. Wong BI, McLean RF, Fremes SE, et al. Aprotinin & tranexamic acid for complex open-heart surgery [abstract]. Anesth Analg 1995 Apr; 80 Suppl.: SCA-13
68. Bayer Corporation.. Trasylol: pooled analysis of relative risk of re-operations in patients undergoing CABG - a comparison of full Trasylol dose to placebo. Data on file, 1997
69. Landymore RW, Murphy JT, Lummis H, et al. The use of low-dose aprotinin, -aminocaproic acid or tranexamic acid for prevention of mediastinal bleeding in patients receiving aspirin before coronary artery bypass operations. Eur J Cardiothorac Surg 1997 Apr; 11: 798-800
70. Gilron I, Ralley FE, DeVarennes B, et al. Coronary reoperation with aprotinin, tranexamic acid or placebo: effects on blood loss, outcome and cost [abstract]. Can J Anaesth 1995 May; 42 (Pt 2): A3
71. Pugh SC, Wielogorski AK. A comparison of the effects of tranexamic acid and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 1995 Jun; 9: 240-4
72. Gschossmann J, Pracki P, Struck E. Efficacy of aprotinin in different doses and autologous blood transfusions in cardiac surgery. Cardiovasc Surg 1994 Dec; 2: 716-9
73. Weber C, Kalmar P, Pokar H. Safety and efficacy of aprotinin in open heart surgery: dose comparison study of full *vs* half Hammersmith-dosage [abstract]. Anesth Analg 1995 Apr; 80 Suppl.: SCA-117
74. Dietrich W, Schöpf K, Spannagl M, et al. Influence of high- and low-dose aprotinin on activation of hemostasis in open heart operations. Ann Thorac Surg 1998; 65: 70-8
75. D'Errico CC, Shayevitz JR, Martindale SJ, et al. The efficacy and cost of aprotinin in children undergoing reoperative open heart surgery. Anesth Analg 1996 Dec; 83: 1193-9

76. Gomar C, del Pozo D, Fita G, et al. Aprotinin in paediatric cardiac surgery: blood loss and use of blood products [abstract]. Br J Anaesth 1995 Jun; 74 Suppl. 2: 33
77. Miller BE, Tosone SR, Tam VKH, et al. Hematologic and economic impact of aprotinin in reoperative pediatric cardiac operations. Ann Thorac Surg 1998; 66: 535-41
78. Carrel TP, Schwanda M, Vogt PR, et al. Aprotinin in pediatric cardiac operations: a benefit in complex malformations and with high-dose regimen only. Ann Thorac Surg 1998; 66: 153-8
79. Able ME, Tilly DA. The effect on costs of the use of half-dose aprotinin for first time reoperative coronary artery bypass patients. Clin Ther 1998; 20 (3): 581-91
80. Lazzara RR, Kidwell FE, Kraemer MF, et al. Reduction in costs, blood products, and operating time in patients undergoing open heart surgery. Arch Surg 1997 Aug; 132: 858-61
81. Sun GE, Hatton RC, Lockwood A, et al. Clinical outcomes and costs of cardiothoracic surgery before and after the availability of aprotinin. Hosp Pharm 1997; 32 (2): 203-9
82. Lathi KG, Hariawala M, Fotouhi F, et al. Economics of aprotinin in cardiac surgery [abstract]. Anesth Analg 1995 Apr; 80 Suppl.: SCA119
83. Van Norman G, Lu J, Spiess B, et al. Aprotinin versus aminocaproic acid in moderate-to-high-risk cardiac surgery: relative efficacy and costs. Anesth Analg 1995 Apr; 80 Suppl.: SCA-19
84. Viravan K, Eto K. Evaluation of the efficacy and the cost-effectiveness of aprotinin versus epsilon-aminocaproic acid in blood conservation in cardiac surgery [abstract]. Int Pharm Abstr 1995 Nov 15; 32: 2340
85. Gott JP, Cooper WA, Schmidt Jr FE, et al. Modifying risk for extracorporeal circulation: trial of four antiinflammatory strategies. Ann Thorac Surg 1998; 66: 747-54
86. Levy JH, Ramsay JG, Murkin J. Aprotinin reduces the incidence of strokes following cardiac surgery [abstract]. Circulation 1996 Oct 15; 94 Suppl.: I-535
87. Bayer Corporation. Aprotinin prescribing information. West Haven, Connecticut, USA
88. Bidstrup BP, Harrison J, Royston D, et al. Aprotinin therapy in cardiac operations: a report on use in 41 cardiac centers in the United Kingdom. Ann Thorac Surg 1993 Apr; 55: 971-6
89. Dietrich W, Barankay A, Hahnel C, et al. High-dose aprotinin in cardiac surgery: three years' experience in 1,784 patients. J Cardiothorac Vasc Anesth 1992 Jun; 6: 324-7
90. Eberle B, Mayer E, Hafner G, et al. A randomized prospective trial of aprotinin vs. aminocaproic acid: which agent is more effective in suppressing cardiopulmonary bypass-induced fibrinolysis and postoperative chest drainage? [abstract]. Anesthesiology 1995 Sep; 83 Suppl: abstr.110
91. Bidstrup BP, Underwood SR, Sapsford RN, et al. Effect of aprotinin (Trasylol) on aorta-coronary bypass graft patency. J Thorac Cardiovasc Surg 1993 Jan; 105: 147-52
92. Lemmer Jr JH, Stanford W, Bonney SL, et al. Aprotinin for coronary bypass operations: Efficacy, safety, and influence on early saphenous vein graft patency: a multicenter, randomized, double-blind, placebo-controlled study. J Thorac Cardiovasc Surg 1994; 107: 543-53
93. Laub GW, Riebman JB, Chen C, et al. The impact of aprotinin on coronary artery bypass graft patency. Chest 1994 Nov; 106: 1370-5
94. Ray MJ, Marsh NA, Mengerson K. A brief review of studies evaluating the adverse effects of aprotinin therapy in aorto-coronary bypass surgery. Thromb Haemost 1997 May; 77: 1038-40
95. Lass M, Simic O, Ostermeyer J. Re-graft patency and clinical efficacy of aprotinin in elective bypass surgery. Cardiovascular Surgery 1997; 5 (6): 604-7
96. Alderman EL, Levy JH, Rich JB, et al. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. J Thorac Cardiovasc Surg 1998; 116: 716-30
97. Smith PK, Muhlbaier LH. Aprotinin: safe and effective only with the full-dose regimen. Ann Thorac Surg 1996; 62 (6): 1575-7
98. Bayer Corporation.. Analysis on mortality and risk of myocardial infarction. Data on file, 1998
99. Weipert J, Meisner H, Jochum M, et al. Long-term follow-up of aprotinin-specific immunoglobulin G antibodies after cardiac operations. J Thorac Cardiovasc Surg 1997; 114 (4): 676-8
100. Pfannschmidt J, Steeg D, Jugert F. Routine intraoperative application of high-dose aprotinin in open heart surgery in adults: antibody formation after first exposure. Curr Med Res Opin 1995; 13 (5): 282-4
101. Bayer Corporation. Trasylol R prescribing information. West Haven, Connecticut, USA
102. Dietrich W, Späth P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. J Thorac Cardiovasc Surg 1997 Jan; 113: 194-201
103. Diefenbach C, Abel M, Limpers B, et al. Fatal anaphylactic shock after aprotinin reexposure in cardiac surgery. Anesth Analg 1995 Apr; 80: 830-1
104. Cottineau C, Moreau X, Druet M, et al. Anaphylactic shock during use of high-dose aprotinin in cardiac surgery. Ann Fr Anesth Reanim 1993 Jan 1; 12: 590-3
105. Dewachter P, Mouton C, Masson C, et al. Anaphylactic reaction to aprotinin during cardiac surgery. Anaesthesia 1993 Dec 1; 48: 1110-1
106. Schulze K, Graeter T, Schaps D, et al. Severe anaphylactic shock due to repeated application of aprotinin in patients following intrathoracic aortic replacement. Eur J Cardiothorac Surg 1993 Aug 1; 7: 495-6
107. Wuthrich B, Schmid P, Schmid ER, et al. IgE-mediated anaphylactic reaction to aprotinin during anaesthesia. Lancet 1992 Jul 18; 340: 173-4
108. Schuler TM, Frosch PJ, Arza D, et al. Allergie vom Soforttyp. Anaphylaktishce reaktion auf Aprotinin. Munch Med Wochenschr 1987 Nov; 129: 816-7
109. La-Ferla GA, Murray WR. Case report. BMJ 1984 Nov 3; 289: 1176
110. Feindt PR, Walcher S, Volkmer I, et al. Effects of high dose aprotinin on renal function in aortocoronary bypass grafting. Ann Thorac Surg 1995 Oct; 60: 1076-80
111. Fraedrich G, Neukamm K, Schneider T, et al. Safety and risk/benefit assessment of aprotinin in primary CABG. In: Friedel N, Hetzer R, Royston D, editors. Blood use in cardiac surgery. New York: Springer-Verlag, 1991: 221-31
112. Barrons RW, Jahr JS. A review of post-cardiopulmonary bypass bleeding, aminocaproic acid, tranexamic acid, and aprotinin. Am J Ther 1996 Dec; 3: 821-38
113. Ruskowski H, Joos A, Kiefer H, et al. Untersuchungen zur Antigenitat von Trasylol in der Offenen Herzchirurgie. J Thorac Cardiovasc Surg 1993; 41: 86
114. Stadler PJW, Hübner GE, Koch R-C, et al. Application of safety measures in the production of Trasylol concerning bovine spongiform encephalopathy. J Biotechnol Healthcare 1996; 3 (1): 61-9

115. Hubner GE, Koch R-C, Sprenger KBG, et al. Examination of the biological safety of a drug derived from mammalian organs. Arzneimittel Forschung 1996; 46 (1): 657-61
116. Goelker CF, Whiteman MD, Gugel KH, et al. Reduction of the infectivity of scrapie agent as a model for BSE in the manufacturing process of Trasylol. Biologicals 1996; 24: 103-11
117. Goelker CF, Whiteman MD, Gugel KH, et al. Reduction of the infectivity of scrapie agent as a model for BSE in the manufacturing process of TrasylolR. Biologicals 1996; 24 (2): 103-11
118. Lemmer Jr JH, Metzdorff MT, Krause AH, et al. Aprotinin use in patients with dialysis-dependent renal failure undergoing cardiac operations. J Thorac Cardiovasc Surg 1996 Jul; 112: 192-4
119. Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Anesthesiology 1998; 88: 327-33
120. Cooley DA. Conservation of blood during cardiovascular surgery. Am J Surg 1995 Dec; 170 (6A Suppl): 53S-9S
121. Laupacis A, Fergusson D, International Study of Peri-operative Transfusion (ISPOT) Investigators. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. Anesth Analg 1997 Dec; 85: 1258-67
122. Hardy J-F, Bélisle S. Natural and synthetic antifibrinolytics: inert, poisonous or therapeutic agents? Can J Anaesth 1997 Sep; 44: 913-5
123. Fremes SE, Wong BI, Lee E, et al. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. Ann Thorac Surg 1994; 58 (6): 1580-8
124. Royston D. Coagulation in cardiac surgery. Adv Card Surg 1996; 8: 19-45

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