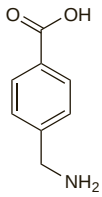
Aminomethylbenzoic Acid

Aminometilbenzoico, ácido; PAMBA. 4-Aminomethylbenzoic acid.

$C_8H_9NO_2$ = 151.2.
CAS — 56-91-7.
ATC — B02AA03.
ATC Vet — QB02AA03.



Profile

Aminomethylbenzoic acid is an antifibrinolytic with actions and uses similar to those of tranexamic acid (p.1080). It is given orally in typical doses of 300 mg to 1 g daily, in 3 or 4 divided doses; it is also given by intramuscular injection, or intravenously by slow injection or infusion.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gumbix†; ***Cz.:*** Gumbix†; Pamba; ***Ger.:*** Gumbix; Pamba.

Ancestim *(USAN, rINN)*

Ancestimum; r-metHuSCF; SCF; Stem Cell Factor. *N*-L-Methionyl-1–165-haematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer.

Анцестим
CAS — 163545-26-4.
ATC — L03AA12.
ATC Vet — QL03AA12.

Adverse Effects and Precautions

Injection site reactions commonly occur with the use of ancestim. Other skin reactions, including pruritus, rash, and urticaria, are less frequent. Systemic hypersensitivity reactions are also common and may be life-threatening. Premedication with antihistamines (both H_1- and H_2-antagonists) and an inhaled beta$_2$ agonist bronchodilator should be used, and the patient observed for at least an hour after ancestim is given. Tachycardia and respiratory symptoms including pharyngitis, dyspnoea, and cough, have also been reported.

Ancestim should not be given in the period from 24 hours before to 24 hours after a dose of cytotoxic chemotherapy or radiotherapy.

Uses and Administration

Ancestim is a recombinant human stem cell factor. It is used with filgrastim (p.1070) to mobilise peripheral blood progenitor cells that are to be collected by apheresis harvest and used for autologous transplantation. The dose of ancestim is 20 micrograms/kg daily by subcutaneous injection; the injections of ancestim and filgrastim must be given at separate sites.

◊ References.

1. Chin-Yee IH, *et al.* Optimising parameters for peripheral blood leukapheresis after r-metHuG-CSF (filgrastim) and r-metHuSCF (ancestim) in patients with multiple myeloma: a temporal analysis of CD34(+) absolute counts and subsets. *Bone Marrow Transplant* 2002; **30:** 851–60.
2. Prosper F, *et al.* Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy. *Leukemia* 2003; **17:** 437–41.
3. To LB, *et al.* Successful mobilization of peripheral blood stem cells after addition of ancestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte colony-stimulating factor) alone or with chemotherapy plus filgrastim. *Bone Marrow Transplant* 2003; **31:** 371–8.
4. da Silva MG, *et al.* Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection. *Bone Marrow Transplant* 2004; **34:** 683–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Stemgen; ***Canad.:*** Stemgen; ***NZ:*** Stemgen.

Antithrombin III *(BAN, rINN)*

Antithrombin III Human; Antithrombine III; Antithrombinum III; Antitrombiini III; Antitrombin III; Antitrombina III; Antitrombina III humana; Antytrombina III; AT-III; Cofactor I de la heparina; Heparin Cofactor; Heparin Cofactor I; Major Antithrombin.

Антитромбин III
CAS — 52014-67-2.
ATC — B01AB02.
ATC Vet — QB01AB02.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Human Antithrombin III Concentrate; Antithrombinum III Humanum Densatum). A preparation of a glycoprotein fraction obtained from human plasma that inactivates thrombin in the presence of an excess of heparin. The plasma is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, distributed into sterile containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or in an atmosphere of inert gas. No antimicrobial preservative is added but a suitable stabiliser (such as albumin) is permitted. When reconstituted in the volume of solvent stated on the label, the resulting solution contains not less than 25 international units of antithrombin III per mL.
A white or almost white, hygroscopic, friable solid or powder. Store in airtight containers. Protect from light.

USP 31 (Antithrombin III Human). A glycoprotein, which is the major inhibitor of thrombin and other activated clotting factors, including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. When reconstituted in the recommended volume of diluent, the pH is between 6.0 and 7.5, and the potency is not less than 25 USP units of antithrombin III per mL.
Store at a temperature of 2° to 8°, excursions permitted up to 25°. Protect from light.

Antithrombin Alfa *(USAN, rINN)*

Antithrombine Alfa; Antithrombinum Alfa; Antitrombina alfa; Human Antithrombin III from the milk of transgenic goats (glycoform alfa); Recombinant Human Antithrombin.

Антитромбин Альфа
CAS — 84720-88-7.

Units

The potency of antithrombin III is expressed in international units and preparations may be assayed using the second International Standard for antithrombin concentrate (1997); each ampoule contains 4.7 international units of functional activity and 5.1 international units of antigenic activity.

One USP unit is described as the amount of antithrombin III that forms a complex with 1 unit of thrombin at 25° in the presence of heparin at a pH of 8.4. Since assays of antithrombin III are carried out at 37°, it is unclear whether USP units and international units are precisely equivalent, but in practice US preparations, like those elsewhere, appear to have their potency defined in international units.

The potency of antithrombin alfa is also expressed in international units.

Adverse Effects and Precautions

Adverse effects of antithrombin III include flushing, headache, dizziness, chest tightness, nausea, a foul taste in the mouth, chills, and cramps. These can be controlled by slowing or stopping the infusion. Allergic reactions occur rarely.

Human plasma-derived antithrombin III preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60°, have reduced the risk of transmitting some viral infections. Antithrombin alfa is produced in the milk of transgenic goats, and should not be used in patients who are hypersensitive to goat proteins or goat milk components.

Uses and Administration

Antithrombin III is a protein in plasma; it is the major endogenous inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII (p.1045), and is the cofactor through which heparin (p.1303) exerts its effect. Genetic and acquired deficiency of antithrombin III occurs and is associated with susceptibility to thromboembolic disorders.

Human plasma-derived antithrombin III is given intravenously to patients with antithrombin III deficiency in the treatment of thromboembolism and for prophylaxis associated with surgical and obstetric procedures. The aim of therapy is to restore plasma-antithrombin III concentrations to at least 80% of normal. The dose, frequency, and duration of therapy are individualised for each patient taking into account the patient's pretreatment concentration and presence of active coagulation. A usual initial dose is about 30 to 50 international units/kg.

Antithrombin alfa is used similarly in the prophylaxis of venous thromboembolism in surgical patients with congenital antithrombin III deficiency. The dose is individualised, but a usual initial dose is about 20 to 25 international units/kg given as an intravenous infusion over 15 minutes, followed by a maintenance infusion of about 4 to 5 international units/kg per hour.

◊ References.

1. Bucur SZ, *et al.* Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion* 1998; **38:** 481–98.
2. Roemisch J, *et al.* Antithrombin: a new look at the actions of a serine protease inhibitor. *Blood Coag Fibrinol* 2002; **13:** 657–70.
3. Konkle BA, *et al.* Use of recombinant human antithrombin in patients with congenital antithrombin deficiency undergoing surgical procedures. *Transfusion* 2003; **43:** 390–4.

Septicaemia. Antithrombin III has been used in septicaemia (p.190) in an attempt to manage the pro-coagulant state that occurs. Initial small studies reported a reduction in mortality[1] but a large controlled study[2] (KyberSept) found that treatment with antithrombin III had no effect on 28-day mortality. A further small observational study and meta-analysis also found no benefit from the use of antithrombin III in septicaemia.[3] These studies had used antithrombin III for less than 7 days, and a small study[4] in surgical patients with septicaemia found that 14 days of treatment with antithrombin III did improve measures of coagulation and fibrinolysis, the changes being most evident in the second week of therapy. However, the study was not large enough to test effects on mortality. Subsequent analysis of data from the KyberSept study appeared to show that 28-day mortality was in fact reduced in patients who had not been given heparin as well as antithrombin III;[5] combined use increased the risk of bleeding and apparently decreased the benefits of treatment with antithrombin III.

1. Eisele B, *et al.* Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; **24:** 663–72.
2. Warren BL, *et al.* KyberSept Trial Study Group. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286:** 1869–78. Correction. *ibid.* 2002; **287:** 192.
3. Messori A, *et al.* Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care* 2002; **6:** 447–51.
4. Hoffmann JN, *et al.* Effect of long-term and high-dose antithrombin supplementation on coagulation and fibrinolysis in patients with severe sepsis. *Crit Care Med* 2004; **32:** 1851–9.
5. Hoffmann JN, *et al.* The KyberSept Investigators. Benefit/risk profile of high-dose antithrombin in patients with severe sepsis treated with and without concomitant heparin. *Thromb Haemost* 2006; **95:** 850–6.

Veno-occlusive disease. There is some evidence[1] from case reports and small studies that antithrombin III may have a beneficial effect on veno-occlusive disease associated with haematopoietic stem cell transplantation (p.1811).

1. Ibrahim RB, *et al.* Anti-thrombin III in the management of hematopoietic stem-cell transplantation–associated toxicity. *Ann Pharmacother* 2004; **38:** 1053–9.

Preparations

Ph. Eur.: Human Antithrombin III Concentrate;
USP 31: Antithrombin III Human.

Proprietary Preparations (details are given in Part 3)
Arg.: Kybernin P; ***Austral.:*** Thrombotrol-VF; ***Austria:*** Atenativ; Kybernin P; Thrombhibin; ***Braz.:*** Kybernin P; ***Canad.:*** Thrombate; ***Cz.:*** Anbinex; ATryn; Kybernin P; ***Denm.:*** Atenativ; ***Fin.:*** Atenativ; ***Fr.:*** Aclotine; ***Ger.:*** Anbinex; AT III; Atenativ; Kybernin; ***Gr.:*** Atenativ; Kybernin P; ***Hung.:*** Atenativ; Kybernin P; ***Indon.:*** Kybernin P; ***Ital.:*** Anbin; Atenativ; Kybernin P; ***Jpn:*** Neuart; ***Mex.:*** Atend; Octatit; ***Neth.:*** Atenativ; ***Norw.:*** Atenativ; ***NZ:*** Thrombotrol-VF; ***Port.:*** Atenativ; ATryn; ***Spain:*** Anbinex; Atenativ; Kybernin P; ***Swed.:*** Atenativ; ***Switz.:*** Atenativ; Kybernin; ***Turk.:*** Kybernin P; ***UK:*** ATryn; ***USA:*** Thrombate III.

Aprotinin *(BAN, USAN, rINN)*

Aprotiniini; Aprotinina; Aprotininas; Aprotinine; Aprotininum; Aprotynina; Bayer A-128; Riker 52G; RP-9921.

Апротинин

CAS — 9087-70-1.
ATC — B02AB01.
ATC Vet — QB02AB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Aprotinin). A polypeptide consisting of 58 amino acids that inhibits the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It contains not less than 3 Ph. Eur. units/mg calculated with reference to the dried substance. An almost white, hygroscopic powder. Soluble in water and in isotonic solutions; practically insoluble in organic solvents. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Aprotinin Concentrated Solution). A solution of aprotinin containing not less than 15 Ph. Eur. units/mL. A clear colourless solution. Store in airtight containers. Protect from light.

USP 31 (Aprotinin). A polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilised powder. Its potency is not less than 3 USP units/mg calculated with reference to the dried substance.

The lyophilised powder should be stored in airtight containers at a temperature between 8° and 15°. Protect from light. The bulk solution should be stored in airtight containers at a temperature not exceeding 25°. Do not allow to freeze.

Incompatibility. Aprotinin is reported to be incompatible with corticosteroids, heparin, tetracyclines, and nutrient solutions containing amino acids or fat emulsions.

Units

The potency of aprotinin is expressed in terms of kallikrein (kallidinogenase) inactivator units (KIU) or of trypsin inactivation (Ph. Eur. units). One KIU is contained in 140 nanograms of aprotinin. One Ph. Eur. and one USP unit is equivalent to about 1800 KIU.

Potency has also been expressed in terms of plasmin inactivation (antiplasmin units).

Adverse Effects and Precautions

Aprotinin is usually well tolerated. Local thrombophlebitis can occur. Adverse effects including bronchospasm, hypotension, cardiac arrhythmias, gastrointestinal disturbances, and skin rashes are considered to be hypersensitivity reactions; anaphylaxis, including fatalities, has occurred. Licensed UK product information warns that the risk of anaphylactic reaction increases when re-exposure occurs within 6 months, but product information in the US extends this warning to contra-indicate the use of aprotinin for 12 months after a previous exposure. A test dose is recommended for all patients and the use of prophylactic histamine antagonists may be considered; a hypersensitivity reaction to the therapeutic dose of aprotinin can still occur even after an uneventful test dose. There have been reports of renal dysfunction and reversible renal failure in patients given aprotinin during open-heart surgery with extracorporeal circulation; the risk may be increased in patients with pre-existing renal impairment or risk factors for altered renal function. For further details of an increased risk of cardiovascular and cerebrovascular events, renal failure, and death in patients undergoing surgery, see Haemorrhagic Disorders under Uses and Administration, below.

Disseminated intravascular coagulation. Fatal disseminated intravascular coagulation has been reported in a patient after the use of intraoperative autotransfusion and aprotinin during surgery.[1] Activation of the clotting system occurs during autotransfusion although this usually causes no systemic adverse effects. While there were other possible causes, it was suggested that aprotinin could have contributed to deposition of fibrin microthrombi in the microvasculature and prevented subsequent fibrinolysis.

1. Milne AA, *et al.* Disseminated intravascular coagulation after aortic aneurysm repair, intraoperative salvage autotransfusion, and aprotinin. *Lancet* 1994; **344:** 470–1.

Effects on coagulation tests. In patients receiving heparin, aprotinin may prolong the activated clotting time when measured by some methods, but this may not represent increased anticoagulation. It has been recommended that an alternative to the activated clotting time should be used to monitor heparin therapy when aprotinin is used concurrently.

It should also be noted that aprotinin injection and heparin injection are pharmaceutically incompatible.

Effects on the respiratory system. Acute respiratory distress syndrome developed in a 24-year-old male 2 hours after the start of an intravenous infusion of aprotinin for bleeding after tonsillectomy.[1] Mechanical ventilation was required for 4 days.

1. Vucicevic Z, Suskovic T. Acute respiratory distress syndrome after aprotinin infusion. *Ann Pharmacother* 1997; **31:** 429–32.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, can occur with the use of aprotinin both on primary and secondary exposure. In a study[1] of 248 re-exposures to aprotinin in 240 patients undergoing cardiac surgery, there were 7 cases of anaphylactic reactions ranging from mild to severe with a higher incidence of reactions occurring in those patients re-exposed within 6 months of the previous dose. A review[2] of 124 reported reactions in 122 patients also found that reactions ranged from mild to severe, and that about half were life-threatening and 11 were fatal. The risk of reaction was greatest with re-exposure to aprotinin as this had been the situation in 80% of the cases, although there were 19 cases associated with the first use of aprotinin. The average risk of anaphylaxis was estimated to be 2.8% in re-exposed patients. Most reactions occurred within 6 months of previous exposure, and the risk was greatest in the first 3 months. Various diagnostic tests have been tried in an attempt to predict hypersensitivity risk. Aprotinin-specific serum-IgG was reported to be detectable in about 50% of patients who had received only one aprotinin treatment, but other tests such as preoperative skin testing were not found to be reliable.

A number of measures have been suggested in order to reduce the risk of hypersensitivity reactions to aprotinin, including the use of an intravenous test dose in all patients, but it must be noted that these also have the potential to trigger a reaction.[1] For patients who have previously received aprotinin it has been recommended that re-exposure should be avoided for at least 6 months,[1,2] that aprotinin-specific antibody screening should be done,[2] and that prophylactic histamine H_1- and H_2-antagonists should be given to ameliorate severe anaphylactic reactions[1] although there are reports of reactions occurring despite antihistamine and corticosteroid prophylaxis.[2] It has also been suggested that in cardiac surgery, aprotinin should only be given when cardiopulmonary bypass is available to assist resuscitation.[1,2]

There have also been rare reports of hypersensitivity reactions on re-exposure to aprotinin used locally as a component of fibrin sealant.[3,4] In one fatal case[4] the previous exposure to fibrin sealant had been 5 years before.

1. Dietrich W, *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: **113:** 194–201.
2. Beierlein W, *et al.* Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; **79:** 741–8.
3. Beierlein W, *et al.* An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; **40:** 302–5.
4. Oswald A-M, *et al.* Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99:** 762–3.

Interactions

Heparin. For comment on the use of aprotinin with heparin, see Effects on Coagulation Tests, above.

Neuromuscular blockers. For reports of apnoea when aprotinin was used with neuromuscular blockers, see p.1904.

Retinoids. Aprotinin should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p.1619).

Pharmacokinetics

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. After intravenous use, it is excreted in the urine as inactive degradation products. The terminal elimination half-life is about 5 to 10 hours.

Renal impairment. The terminal elimination half-life of aprotinin was reported as 13.3 and 14.9 hours, respectively, in two patients with chronic renal impairment given aprotinin by intravenous infusion over 30 minutes.[1] A study[2] of cardiac surgical patients undergoing cardiopulmonary bypass also found that aprotinin clearance was reduced in those with renal impairment. The elimination half-life was about 20 hours in patients with end stage renal disease compared with about 8 hours in those with creatinine clearance greater than 50 mL/min.

1. Müller FO, *et al.* Pharmacokinetics of aprotinin in two patients with chronic renal impairment. *Br J Clin Pharmacol* 1996; **41:** 619–20.
2. O'Connor CJ, *et al.* The impact of renal dysfunction on aprotinin pharmacokinetics during cardiopulmonary bypass. *Anesth Analg* 1999; **89:** 1101–7.

Uses and Administration

Aprotinin is a haemostatic. It is an inhibitor of proteolytic enzymes including chymotrypsin, kallikrein (kallidinogenase), plasmin, and trypsin.

Aprotinin has been used to reduce blood loss and transfusion requirements in patients at increased risk of major blood loss during coronary artery bypass graft surgery with cardiopulmonary bypass. However, the marketing of aprotinin injection has been suspended worldwide because of a possible increased risk of death associated with its use in cardiac surgery (see Haemorrhagic Disorders, below). Nevertheless, it may be available in some countries, such as the USA, using a special access protocol. It has also been used in the treatment of hyperfibrinolytic haemorrhage associated with raised plasma concentrations of plasmin. Aprotinin is applied topically as a component of fibrin glues (p.1069).

It is recommended that because of the risk of hypersensitivity reactions an intravenous test dose of 10 000 KIU should be given to all patients at least 10 minutes before the therapeutic dose. All intravenous doses of aprotinin should be given through a central venous line.

In **coronary artery bypass graft surgery**, the test dose is followed by a loading dose given with the patient in a supine position, after induction of anaesthesia but before incision; 2 000 000 KIU is given intravenously over 20 to 30 minutes. The loading dose is followed by a continuous infusion of 500 000 KIU/hour until the end of the operation. An additional dose of 2 000 000 KIU is added to the prime volume of the extracorporeal circuit. In patients with septic endocarditis, a dose of 3 000 000 KIU is added to the prime volume of the circuit and the continuous infusion may be continued into the early postoperative period. The total amount of aprotinin used is usually no more than 7 000 000 KIU. A regimen using half the dose for loading, maintenance, and to prime the circuit, may be used in low-risk patients.

Haemorrhagic disorders. Aprotinin has been used in the treatment of life-threatening haemorrhage caused by raised plasma concentrations of plasmin. It has also been used in the treatment of severe bleeding arising from overdosage with thrombolytics (see Treatment of Adverse Effects under Streptokinase, p.1404).

Aprotinin has been used to reduce blood loss in patients undergoing surgery, particularly cardiac surgery involving cardiopulmonary bypass. This bypass procedure is complicated by a postperfusion syndrome that includes impairment of haemostasis and pulmonary dysfunction. Contributing factors include ischaemia reperfusion, surgical trauma, endotoxaemia, and blood contact with the artificial surfaces of the bypass apparatus. This syndrome has been interpreted as a 'whole body inflammatory response', and the beneficial effect of aprotinin has been attributed to an attenuation of this response. As well as its inhibitory effect on fibrinolysis, aprotinin is thought to have effects on the complement system, cytokines, neutrophil activation, and platelet function.[1,2] Aprotinin has reduced blood loss and transfusion requirements in patients undergoing both primary and repeat cardiac surgery.[1,3-6] The usual dosage regimen (as given in Uses and Administration, above) and low-dosage regimens (50% of the usual dose) appear to be equally effective, but regimens that use aprotinin only as a pump prime dose appear to be less effective.[1,5]

The safety of aprotinin in cardiac surgery has been questioned, however, because of the results of two observational studies. One analysis[7] of patient outcome after the use of aminocaproic acid, aprotinin, tranexamic acid, or no treatment, found that although the three drugs had reduced blood loss to a similar extent, aprotinin was associated with an increased risk of cardiovascular and cerebrovascular events (myocardial infarction, heart failure, stroke, or encephalopathy) and renal failure. Observational follow-up also found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death in the 5 years after surgery.[8] In another study[9] that compared data from patients who had received either aprotinin or tranexamic acid, there was an increased risk of renal dysfunction associated with aprotinin, particularly in patients with abnormal pre-operative renal function. In response to these studies, the FDA recommended[10] that patients receiving aprotinin should be carefully monitored, and that physicians should consider limiting its use to situations where the clinical benefit of reduced blood loss is essential and outweighs the potential risks. The concerns raised by these studies and the FDA's recommendation prompted further analysis of data relating to the effects of aprotinin. A meta-analysis[5] that included studies in different types of surgery, although the majority were in cardiac surgery, found no increased risk of death, cardiovascular events, or renal failure. However, because the reporting of renal function was lacking for many studies, and therefore a potential for bias, the authors were not confident that a modest increase in risk could be ruled out. Another meta-analysis[11] that was limited to studies in cardiac surgery also found no increased risk of death or cardiovascular events with aprotinin. There was also no increase in the risk of dialysis-dependent renal failure, but high-dose aprotinin did increase the risk of renal dysfunction, compared with placebo. Two large retrospective studies, which attempted to account for confounding variables, were also undertaken in cohorts of patients who had undergone coronary artery bypass graft surgery. One study found that, compared with aminocaproic acid, aprotinin increased the risk of in-hospital death.[12] The other found increased in-patient renal dysfunction, and death at 30 days and 1 year, in patients given aprotinin compared with aminocaproic acid or no antifibrinolytic therapy. Survival estimates also found an association between aprotinin use and reduced survival for up to 10 years after surgery.[13] Preliminary data analysis from a randomised study (BART) also found an increased risk of death with aprotinin, compared with aminocaproic acid or tranexamic acid, and in November 2007, authorities such as the FDA[14] and EMEA[15] recommended that marketing of aprotinin injection be suspended.

Aprotinin has been used to reduce transfusion requirements during liver transplantation, by its effect on intra-operative hyperfibrinolysis.[16,17] However, concerns about an increased risk of thromboembolism in these patients has been raised.[18] A systematic review[19] of 23 studies using antifibrinolytic drugs, 18 of which used aprotinin, found no evidence of an increased risk of thromboembolic complications in liver transplant patients, but noted that the studies were underpowered and that identification