CURRENT OPINION

Drug Safety 2007; 30 (9): 731-740
0114-5916/07/0009-0731/$44.95/0

Is There Still a Role for Aprotinin in Cardiac Surgery?

Neel R. Sodha,[1] *Munir Boodhwani*[2] and *Frank W. Sellke*[1]

1 Division of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
2 Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Abstract

Cardiac surgery is associated with a systemic inflammatory response and systemic coagulopathy, which can result in significant organ dysfunction and bleeding. Aprotinin, a serine protease inhibitor, can limit systemic inflammation, and has been associated with myocardial, pulmonary and cerebral protection in addition to its proven haemostatic efficacy. Data are currently conflicting regarding the haemostatic efficacy of aprotinin relative to alternative agents including tranexamic acid. Recent studies have demonstrated aprotinin usage is associated with increased rates of thrombotic and renal complications, but these findings are at odds with the majority of studies relating to aprotinin safety to date. The lack of adequately powered, randomised studies evaluating aprotinin and alternative agents limits drawing conclusions about the complete use or disuse of aprotinin presently and requires individualised patient selection based on bleeding risk and co-morbidities for its usage.

Cardiac surgery is associated with a host of deleterious effects on the body as a whole. If the surgery involves the utilisation of cardioplegic arrest and cardiopulmonary bypass (CPB), the myocardium is subject to ischaemia-reperfusion injury[1-3] and a systemic inflammatory response that develops secondary to surgical trauma and blood contact with the artificial surfaces of the CPB circuit.[4-6] This contact with a foreign surface leads to activation of the complement system, the coagulation cascade and the fibrinolytic system, which subsequently culminate in activation of inflammatory leukocytes and platelets.[7] Interestingly, many of these changes have also been reported during cardiac surgery not utilising cardioplegic arrest and CPB, such as during 'off pump' coronary artery bypass grafting (CABG).[8-11] A coagulopathy ensues, resulting from the inflammatory response and platelet dysfunction and destruction secondary to mechanical trauma as well as over-activation of platelets during CPB. These pathological responses can manifest clinically as myocardial dysfunction, systemic hypotension, oedema and bleeding. Although myocardial dysfunction and systemic hypotension are generally managed with adrenergic agonists and pulmonary oedema with supportive mechanical ventilation, excessive bleeding intra- and postoperatively often necessitates transfusion of blood products (packed red blood cells) and platelets to avoid the deleterious consequences of anaemia and the need for re-exploration for bleeding.[12,13] In addition to the risks of blood product transfusion, such as transmission of infectious diseases, transfusion-related acute lung injury and graft versus host reactions, evidence indicates poorer overall outcomes associated with blood and platelet transfusion including stroke, myocardial infarction (MI) and death.[14-16]

Although some degree of this response is unavoidable, one effective therapeutic strategy for ameliorating some of this reaction has been the

usage of aprotinin, which has been shown to improve haemostasis as well as reduce myocardial injury, platelet dysfunction and the systemic inflammatory response to CPB.[7] Despite its therapeutic efficacy, several recent, well publicised reports have invigorated the debate over the safety of aprotinin usage citing increased risks of thrombotic complications (MI, stroke), renal dysfunction and overall increases in mortality.[17,18] Compounding the adverse outcomes in these studies was the lack of demonstrable haemostatic benefit over alternative agents such as ε-aminocaproic acid (EACA) and tranexamic acid, both of which are antifibrinolytics and were not associated with the aforementioned adverse outcomes.[17-19] Although the benefits of aprotinin on haemostasis have been well documented in multiple, randomised, double-blind, placebo-controlled trials,[20-24] these recent reports are at odds with previous investigations in to the usage of aprotinin in cardiac surgery and what was found to be an acceptable safety profile.[25-27]

This article summarises our current understanding of the mechanism of action of aprotinin, the beneficial effects associated with its use, available evidence regarding its efficacy and adverse effects, and our current opinion regarding its appropriate usage in adult cardiac surgery.

1. Haemostatic Mechanism of Action

Aprotinin is a naturally occurring serine protease inhibitor isolated from bovine lung tissue, which forms a reversible enzyme inhibition complex with serine proteases by binding to the proteases in a dose dependent manner. These proteases include plasmin (the final enzyme in the fibrinolytic pathway), trypsin, chymotrypsin, kallikrein, thrombin, activated protein C, elastase and tissue plasminogen activator (tPA).[28,29] Of these proteases, interaction with plasmin and kallikrein are likely to be the most important for haemostasis and the reduction of inflammation. The mechanism of action of aprotinin has yet to be fully elucidated, although current knowledge demonstrates that it is an antifibrinolytic modulator of coagulation, with both haemostatic and antithrombotic properties,[30,31] a modulator of the inflammatory cascade and a platelet protectant.

Studies have demonstrated the effects of aprotinin on haemostasis to be multi-armed. Aprotinin has several interactions with platelets, which augment haemostasis. By preserving platelet receptor function (glycoprotein [GP]Ib, GPIIb/IIIa),[32] it allows for adequate platelet adhesion and aggregation, which is deranged by CPB.[30] The haemostatic and antithrombotic properties of aprotinin are mediated through thrombin, a serine protease, and the protease-activated receptor-1 (PAR1) on human platelets. Thrombin proteolytically cleaves PAR1, exposing a ligand, which results in the intramolecular activation of the receptor and, subsequently, the platelet.[31,33-35] Ferraris et al.[36] have shown that platelet PAR1 is rendered dysfunctional after CPB, and is associated with increased blood loss. By inhibiting thrombin-mediated PAR1 platelet activation during CPB in humans,[37] aprotinin reduces the overwhelming activation and depletion of platelet functionality during CPB, allowing platelets to retain their function for haemostasis.[30,38] Although thrombin-mediated platelet activation is blocked, collagen, adenosine diphosphate (ADP) and adrenaline (epinephrine) are still able to activate platelets via an independent pathway,[31] allowing for haemostasis at the site of surgical wounds.[37] PAR1 activation is also known to result in increased cytokine expression (in endothelial cells),[39] changes in intracellular calcium and the phosphorylation of various enzymes, which may contribute to systemic inflammation, responses that aprotinin may attenuate.[40] The interactions described in this section, of aprotinin, thrombin and PAR1, also provide support for the assertion that aprotinin is not prothrombotic.[30,31,41] Specifically, Poullis et al.[31] have demonstrated that aprotinin inhibits thrombin-mediated platelet aggregation *in vitro*. In a rabbit model of *in vivo* vascular thrombosis, aprotinin was shown to prolong time to thrombosis and decrease the weight of thrombus, in part through inhibition of protease-dependent platelet activation, when compared with placebo.[30] Aprotinin has also been shown during *in vitro* studies to restore the adhesive capacity of dysfunctional platelets after CPB[42] and decrease the heparin-induced inhibition of platelet contractile force.[43]

The interactions of aprotinin with the PAR1 receptor on platelets have also recently been shown to extend to the PAR1 receptor on endothelial cells. In an *in vitro* study utilising human umbilical vein

endothelial cells, pretreatment of the cells with aprotinin significantly reduced PAR1 cleavage and reduced calcium fluxes caused by thrombin. In this study, aprotinin inhibited interleukin (IL)-6 secretion caused by thrombin, demonstrating that endothelial cell activation by thrombin and downstream inflammatory responses can be inhibited by aprotinin *in vitro* through blockade of PAR1, providing a new mechanism to help explain the anti-inflammatory properties of aprotinin observed clinically.[39]

Plasmin, a serine protease that is the final enzyme in the fibrinolytic pathway, is directly inhibited by aprotinin, thereby limiting fibrinolysis. Aprotinin has also been shown to increase levels of α_2-antiplasmin and plasminogen activation inhibitor activity, while decreasing the release of tPA from endothelial cells.[44] Protein C, an endogenous anticoagulant, is also inhibited by aprotinin, contributing to haemostasis.[45] Through its interaction with kallikrein, aprotinin inhibits the intrinsic pathway of coagulation, possibly decreasing overconsumption of coagulation products during CPB.[45]

2. Haemostatic Efficacy

The haemostatic efficacy of aprotinin compared with placebo is well established and has been well documented in both individual randomised trials[20,25,46] and in meta-analyses.[26,27] One of these meta-analyses of aprotinin use during cardiac surgery for CABG (32 studies, n = 3879) analysed randomised, placebo-controlled trials from 1988 to 2001.[26] The analysis found that 40.3% of patients treated with aprotinin required a blood transfusion, compared with 63.3% of patients who did not receive aprotinin, which is a 39% relative risk reduction in transfusion requirement. There were no statistically significant differences in mortality, MI or renal failure. There was a decrease seen in risk for perioperative stroke, and a trend toward decreased postoperative atrial fibrillation, neither of which reached statistical significance.

In addition to the haemostatic efficacy of aprotinin in the setting of CPB-induced coagulopathy, several recent studies have highlighted its role in the setting of antiplatelet therapy. Antiplatelet agents, such as aspirin (acetylsalicylic acid) and clopidogrel, are associated with increased bleeding and the need for blood products in the setting of cardiac surgery and can at times delay the undertaking of surgical intervention over concerns for increased risk of bleeding.[47] Several recent trials have assessed the efficacy of aprotinin in patients receiving antiplatelet therapy for acute coronary syndrome (ACS). Akowuah et al.[48] performed a randomised trial including 49 patients who presented with ACS, where the treatment arm continued aspirin and clopidogrel until the day of CABG, with use of a standard regimen of intraoperative aprotinin. The control arm discontinued antiplatelet therapy 5 days prior to surgery and received placebo intraoperatively. The aprotinin group had significantly less blood loss and chest tube drainage, and also received fewer transfusions of packed red blood cells, with the same rates of re-exploration.[48] Similar results were found in a larger, randomised, double-blind, placebo-controlled trial, in which 75 patients with unstable angina were all given clopidogrel prior to CABG, with the treatment arm receiving aprotinin and the control arm receiving placebo. Again, the aprotinin group had significantly less postoperative bleeding, and received fewer packed red blood cells or platelet transfusions.[49] A smaller retrospective study of 33 patients undergoing CABG (18 aprotinin, 15 no aprotinin) had results consistent with the other studies: less blood loss, transfusion of packed red blood cells and platelets, and reduced need for re-exploration.[50]

3. Systemic Effects

3.1 Pulmonary

Royston and colleagues[21] initially studied aprotinin in cardiac surgery to assess its protection of the lung from CPB-induced injury. Subsequent investigation in this area has shown administration of aprotinin can attenuate CPB-induced as well as cytokine-induced bronchial inflammation, lung reperfusion injury and oxidative injury through preservation of superoxide dismutase levels.[51] When administered in the pulmonary artery during CPB, aprotinin treated groups were found to have better forced expiratory volume in 1 second (FEV_1) and partial pressure of alveolar carbon dioxide ($paCO_2$) levels.[52] The drug has also been shown to reduce leukocyte se-

questration and improve gas exchange post protamine infusion in patients undergoing bypass.[53] Large animal models utilising CPB have found aprotinin usage results in less pulmonary oedema and inflammation; it also limits the elevations in pulmonary vascular resistance commonly seen after cardiopulmonary bypass.[54,55]

3.2 Myocardial

The effects of aprotinin on the myocardium and coronary vasculature are extensive. Given the drugs ability to limit tissue oedema and inflammation, several studies have assessed the role of aprotinin in preventing postoperative atrial fibrillation/atrial flutter. One small trial showed a reduction in the incidence of postoperative atrial fibrillation,[56] but a larger analysis did not.[57] Porcine studies of myocardial ischaemia-reperfusion injury and CPB demonstrated treatment with aprotinin resulted in reduced myocardial infarct size, improved myocardial contractility, decreased incidence of arrhythmia requiring cardioversion, and in a greater degree of endothelial preservation as evidenced by improved coronary microvascular relaxation to endothelial dependent vasorelaxants.[54,58,59] A clinical study involving 80 patients undergoing CABG also demonstrated that treatment with aprotinin versus placebo resulted in less myocardial enzyme leakage postoperatively, suggesting that aprotinin has a protective effect on the myocardium beyond that achieved with blood cardioplegia and systemic hypothermia alone.[60] Royston et al.[61] recently published a study of 1723 patients that showed aprotinin usage was associated with a reduced requirement for cardiovascular support with inotropic drugs, vasopressors and antiarrythmics compared with placebo-treated patients. Although shown to preserve endothelial function in the coronary microcirculation,[54,58,59] early reports using rat aorta raised concern over impaired endothelial dependent vasorelaxation in large arteries with aprotinin usage,[62] but subsequent studies using clinically relevant doses of aprotinin in porcine coronary arteries found aprotinin did not impair endothelial dependent vasorelaxation.[63] As in the lung, myocardial oedema has been shown to be reduced with aprotinin usage in a porcine model of regional cardiac ischaemia and cardiac arrest. This study further revealed increased preservation of cellular junctions and decreased requirements for intravenous fluids to maintain haemodynamic parameters in aprotinin-treated animals.[64]

3.3 Immunological

Administration of a full Hammersmith dose has an improved effect on modulating the inflammatory cascade due to interaction with kallikrein.[65] Low-dose regimens provide similar haemostatic efficacy as that of high-dose regimens; however, studies of inflammatory mediator levels post-bypass with low-dose regimens failed to demonstrate suppression of these inflammatory markers.[66] Inhibition of kallikrein limits the conversion of kininogen to bradykinin, and activation of the complement system and white blood cells. This reduction in bradykinin formation is of clinical relevance in that bradykinin has been shown to mediate tissue oedema by increasing capillary membrane permeability, reducing systemic vascular resistance and cardiac output, and increasing third spacing.[67] With aprotinin treatment, neutrophils display reduced expression of the membrane attack complex and activation of the first component of human complement (C1) is reduced, along with attenuation of the release of tumour necrosis factor-α (TNFα), IL-6, IL-8 and elastase.[59,68] When compared with methylprednisolone, aprotinin demonstrated similar effects on mediators of inflammation.[69] *In vitro* studies of rat neutrophil clusters of differentiation (CD)11b/CD18 and intracellular adhesion molecule (ICAM)-1 have shown hypoxia/re-oxygenation-induced upregulation of these molecules is decreased by administration of aprotinin, thereby possibly limiting neutrophil attachment and transmigration at the endothelial cell.[58,70] These findings are supported by findings of decreased myeloperoxidase activity in the myocardium with aprotinin usage.[58,71]

4. Adverse Effects and Current Controversies

Although these aforementioned effects of aprotinin are generally well accepted, three areas of controversy have recently been highlighted: (i) the incidence of thrombotic complication with aprotinin usage; (ii) the incidence of renal dysfunction with aprotinin usage; and (iii) the haemostatic efficacy of

aprotinin in comparison with the antifibrinolytic lysine analogues EACA and tranexamic acid.

4.1 Incidence of Thrombotic Complications: Myocardial Infarction and Cerebrovascular Events

Renewed concerns regarding thrombotic complications arose in response to the randomised, placebo-controlled IMAGE (International Multicenter Aprotinin Graft Patency Experience) trial in 1998.[20] The trial raised concerns regarding an increased incidence of graft occlusion in aprotinin treated groups, where among 703 patients with assessable saphenous vein grafts, occlusions occurred in 15.4% of aprotinin-treated patients and 10.9% of patients receiving placebo. After adjustment for risk factors associated with vein graft occlusion, the aprotinin versus placebo risk ratio decreased from 1.7 to 1.05 (90% CI 0.6, 1.8). Notably, the incidence of graft occlusion varied widely between sites: at Danish and Israeli sites, where patients had more adverse characteristics, occlusions occurred in 23.0% of aprotinin treated patients and 12.4% of placebo-treated patients versus US sites, where patients had characteristics more favourable for graft patency, occlusions occurred in 9.4% of the aprotinin group and 9.5% of the placebo group, and did not affect the occurrence of MI or mortality. An increased incidence of graft occlusion has not been confirmed in a subsequent analysis.[26]

In 2006, Mangano et al.[17] published the results from an observational propensity score adjusted study that evaluated 4374 patients undergoing CABG who were enrolled in the McSPI (Multicentre study on Perioperative Ischemia) international database. The patients either received no antifibrinolytic treatment (n = 1374), aprotinin (n = 1295), tranexamic acid (n = 822) or EACA (n = 883), with the decision as to treatment made by the treating physicians. Assignment was non-random; therefore, patients in the aprotinin group were at higher risk for adverse events, which was adjusted by a propensity scoring. They found aprotinin was associated with an increased incidence of cardiovascular events by 55% (odds ratio [OR] 1.42; 95% CI 1.09, 1.86) and cerebrovascular events by 181% (OR 2.15; 95% CI 1.14, 4.06).

These results are at odds with the majority of randomised, controlled studies[22,72-76] and meta-analyses[26,27] published to date. The meta-analysis by Sedrakyan et al.[26] of 35 CABG trials (n = 3879) found aprotinin therapy was not associated with increased or decreased incidence of MI (relative risk [RR] 0.85; 95% CI 0.63, 1.14), but was associated with a reduced risk of stroke (RR 0.53; 95% CI 0.31, 0.90), with similar findings in a recent publication by Royston et al.[61] This retrospective analysis of data from 1723 patients enrolled in five prospective, randomised, double-blind, placebo-controlled trials of aprotinin in CABG (961 placebo, 862 aprotinin) found aprotinin-treated patients had a reduced incidence of cerebrovascular outcomes (OR 0.42; 95% CI 0.19, 0.93) and that there was no difference in frequency of death (OR 1.00; 95% CI 0.54, 1.85), or MI (OR 0.92; 95% CI 0.64, 1.31). Henry et al.[27] published similar findings in a Cochrane Systematic Review of 7027 patients (the incidence of stroke was not increased or decreased in the Cochrane review). Karkouti et al.[19] compared the risks associated with aprotinin with those associated with tranexamic acid in 898 patients undergoing high-risk cardiac surgery using propensity scoring to match patients given different treatments and found no difference between overall risk of MI (OR 1.25; 95% CI 0.52, 2.75), stroke (OR 1.15; 95% CI 0.56, 2.40) or death (OR 0.91; 95% CI 0.56, 1.46).

Aside from the effects of aprotinin on the incidence of stroke, there is evidence that aprotinin may in fact be neuroprotective from CPB insult. Porcine studies have demonstrated that aprotinin reduces inflammation and improves neurological outcome after a prolonged period of deep hypothermic circulatory arrest or low-flow CPB.[77,78] A prospective pilot study found that, of patients undergoing elective CABG, those who received aprotinin demonstrated a statistically significant improvement compared with controls on cognitive testing, administered at 4 days and 6 weeks postoperatively in comparison with testing preoperatively.[79] A subsequent study of 40 patients demonstrated a similar finding of reduced neurocognitive impairment in aprotinin-treated patients in the first week after surgery.[80,81] Possible mechanisms for this neuroprotective effect of aprotinin are reduction in kallikrein-induced elevations in bradykinin with resulting re-

duction in cerebral oedema,[82] reduced microembolisation to the cerebral circulation and inhibition of leukocyte extravasation during systemic inflammation,[69,83] or interaction with PAR1.[84,85] Junge et al.[84] have shown thrombin, plasmin and tPA can activate PAR1 signalling in murine brain tissue; furthermore, intracerebroventricular injection of a PAR1 antagonist can reduce infarct volume. A subsequent study investigating the platelet activation that occurs in the setting of cerebrovascular ischaemia, demonstrated platelets in this setting are exhausted and desensitised to thrombin through cleavage of PAR1.[85]

4.2 Incidence of Renal Dysfunction/ Renal Failure

A primary postoperative concern with aprotinin administration has been regarding postoperative renal function, as some studies using high-dose aprotinin versus placebo have demonstrated increases in renal dysfunction in aprotinin treated groups,[86,87] whereas others have found only transient increases in serum creatinine level without a significantly increased risk of irreversible renal failure or the need for dialysis.[26,88] Fauli et al.[89] examined the effects of low- and high-dose aprotinin compared with placebo on renal parameters in 60 patients with normal, baseline renal function undergoing cardiac surgery utilising CPB, and found that both low- and high-dose aprotinin resulted in increased excretion of α_1-microglobulin during CPB, but only high-dose aprotinin was associated with this effect 24 hours after surgery. β-Glucosaminidase excretion remained similar between all three groups, indicating aprotinin is associated with greater renal tubular overload without tubular damage.[89] The 2006 study by Mangano et al.,[17] previously described in section 4.1, demonstrated significant increases in the risk of renal events (OR 2.34; 95% CI 1.27, 4.31) [renal dysfunction: control 2% vs aprotinin 5%; renal failure: control 1% vs aprotinin 5%; $p < 0.01$]. Findings of increased rates of adverse renal events were also seen in the study of high-risk patients undergoing cardiac surgery and receiving aprotinin by Karkouti et al.,[19] where among patients with abnormal renal function at baseline, aprotinin was associated with a significantly increased risk of postoperative renal dysfunction (OR 1.69; 95% CI 1.07, 2.69). Since the drug is excreted renally, high concentrations of aprotinin may cause a reversible overload of the renal tubular re-absorptive mechanism. These effects may also be due to direct toxicity to proximal tubular cells and alterations in intrarenal blood flow through inhibition of renin and kallikrein activity. These alterations in intrarenal blood flow may be responsible for the increased incidence of postoperative acute renal failure in patients who are receiving ACE inhibitors preoperatively.[90]

4.3 Comparative Haemostatic Efficacy

Based on the previously discussed adverse effects under debate, the question arises as to whether equally efficacious alternative therapies are available. The two most commonly used antifibrinolytics in the US aside from aprotinin are EACA and tranexamic acid. Both of these agents were included in the recent reports highlighting risks of aprotinin usage, and were found to be equally efficacious in reducing blood loss, without increased thrombotic complications or renal dysfunction.[17,19] These findings are at odds with other reports that have not shown EACA to consistently reduce bleeding or reduce the need for allogenic blood transfusion,[27,91] or tranexamic acid to be equivalent to aprotinin in terms of reduced transfusion requirement and blood loss.[92] The largest meta-analysis of 2106 patients comparing trials of aprotinin versus the lysine analogues found perioperative blood loss to be significantly greater with tranexamic acid and EACA than with aprotinin: weighted mean differences were 106mL (95% CI 37, 176) and 184mL (95% CI 134, 235), respectively.[93] The pooled RR of receiving an allogenic red blood cell transfusion with tranexamic acid and EACA, compared with aprotinin, were 1.08 (95% CI 0.88, 1.32) and 1.14 (95% CI 0.84, 1.55), respectively. For re-exploration, the Cochrane RR for tranexamic acid versus aprotinin was 0.98 (95% CI 0.51, 1.88). The authors concluded that the data are conflicting regarding the equivalence of lysine analogues and aprotinin in reducing perioperative bleeding, transfusion and the need for re-exploration and "an uncertain basis for replacing aprotinin with the cheaper lysine analogues."[93] These trials generally included patients at low risk for excessive bleeding (patients undergoing primary CABG),

which may have limited their ability to detect differences in efficacy. Notably, the RR for re-exploration with tranexamic acid versus aprotinin calculated in the study[93] was changed in favour of aprotinin when the results of a single small trial[94] (in which all cases of re-exploration occurred in the aprotinin-treated group [tranexamic acid 0/45, aprotinin 6/45]) were excluded from analysis.

5. Discussion

The lack of agreement between recent reports highlighting adverse events with aprotinin usage[17-19] and previously published randomised trials[20-24] may be attributable to the observational design utilised in these studies. Observational studies are limited in their ability to determine causation, but are useful in detecting low-frequency adverse events. In observational studies, the decision to use a certain drug or treatment is made by the treating physician, not by a predetermined method (i.e. randomisation); therefore, there is an inherent bias based on perception of need that can influence outcomes as patients considered to be at higher risk may be given a more risky treatment, as in the case of aprotinin. Some of this bias can be adjusted for by using propensity scoring, which incorporates known confounders and other covariates in to the determination of treatment effects; however, although propensity scoring can reduce bias, it does not eliminate it.[95] Furthermore, not all confounders and clinically important covariates can be measured and, as a result, observational studies, with or without propensity matching, should not be considered an alternative to large, randomised, controlled trials. With regard to aprotinin usage, the decision to use aprotinin was not part of the study protocols; therefore, a bias may exist towards use of aprotinin in high-risk patients, such that the use of the drug may serve as a marker for patients likely to have worse outcomes regardless of the drug. Additional variables that could have influenced outcomes, such as duration of CPB, dosage of aprotinin, platelet transfusions and use of ACE inhibitors, were also not reported and merit further investigation.

Answers to many of the questions raised may arise from the BART (Blood Conservation Using Antifibrinolytics: Randomized Controlled Trial in High-Risk Cardiac Surgery) trial and the US FDA analysis of Bayer's recently submitted data from a privately commissioned observational study of 67 000 patients. The FDA's initial review of the data provided by Bayer has found aprotinin may be associated with "increased risk for death, kidney failure, CHF, and stroke."[96] The ongoing BART investigation (target enrolment of 2970 patients) is the largest triple-blind, randomised controlled trial of antifibrinolytic drugs in high-risk cardiac surgery to determine whether aprotinin is superior to EACA or tranexamic acid in decreasing postoperative bleeding. The pre-specified primary outcome is bleeding and secondary outcomes include organ failure (renal, cardiovascular and cerebrovascular events). The assessment of benefits and risks will be free from confounding by indication, which has been a major criticism of prior observational studies. Interim results presented at the Annual Meeting of the Society of Cardiovascular Anesthesiologists have shown no differences in important clinical outcomes among patients receiving aprotinin, tranexamic acid or EACA.[97]

6. Recommendations

Although aprotinin certainly has beneficial effects on systemic inflammation and haemostasis, the current concerns raised by Mangano et al.,[17,18] Karkouti et al.[19] and the initial review of Bayer's observational study[96] warrant limiting the usage of aprotinin to cases where the risk of bleeding is high. At our institution, these cases include patients on antiplatelet therapy with clopidogrel and significant coagulopathy secondary to hepatic dysfunction or active infection (endocarditis), or prolonged operations such as multiple valve operations, complex aortic surgery and redo cardiac surgery. As with many issues in the care of patients, good clinical judgment is required to optimise care delivery. One should not make blanket judgments because aprotinin should 'always' or 'never' be used. An assessment of the benefits and risks of agents, such as aprotinin, should be undertaken on an individual patient basis.

Acknowledgements

Dr Sodha and Dr Boodhwani have no conflicts of interest that are directly relevant to the content of this article. Dr Sellke is a member of the Speaker's Bureau for Bayer Corpo-

ration. No sources of funding were used to assist in the preparation of this manuscript.

References

1. Ramlawi B, Feng J, Mieno S, et al. Indices of apoptosis activation after blood cardioplegia and cardiopulmonary bypass. Circulation 2006; 114 (1 Suppl.): I257-63
2. Saldanha C, Hearse DJ. Cardioplegia and vascular injury: dissociation of the effects of ischemia from those of the cardioplegic solution. J Thorac Cardiovasc Surg 1994; 108: 279-90
3. Anselmi A, Abbate A, Girola F, et al. Myocardial ischemia, stunning, inflammation, and apoptosis during cardiac surgery: a review of evidence. Eur J Cardiothorac Surg 2004; 25: 304-11
4. Biglioli P, Cannata A, Alamanni F, et al. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. Eur J Cardiothorac Surg 2003; 24: 260-9
5. de Vroege R, te Meerman F, Eijsman L, et al. Induction and detection of disturbed homeostasis in cardiopulmonary bypass. Perfusion 2004; 19: 267-76
6. Pintar T, Collard CD. The systemic inflammatory response to cardiopulmonary bypass. Anesthesiol Clin North America 2003; 21: 453-64
7. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. Ann Thorac Surg 2001; 71: 745-54
8. Gomes WJ, Erlichman MR, Batista-Filho ML, et al. Vasoplegic syndrome after off-pump coronary artery bypass surgery. Eur J Cardiothorac Surg 2003; 23: 165-9
9. Hazama S, Eishi K, Yamachika S, et al. Inflammatory response after coronary revascularization: off-pump versus on-pump (heparin-coated circuits and poly2methoxyethylacrylate-coated circuits). Ann Thorac Cardiovasc Surg 2004; 10: 90-6
10. Lazar HL, Bao Y, Rivers S. Does off-pump revascularization reduce coronary endothelial dysfunction? J Card Surg 2004; 19: 440-3
11. Aljassim O, Karlsson M, Wiklund L, et al. Inflammatory response and platelet activation after off-pump coronary artery bypass surgery. Scand Cardiovasc J 2006; 40: 43-8
12. Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine. First of two parts: blood transfusion. N Engl J Med 1999; 340: 438-47
13. Moulton MJ, Creswell LL, Mackey ME, et al. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996; 111: 1037-46
14. Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. Semin Cardiothorac Vasc Anesth 2004; 8: 267-81
15. Karkouti K, Wijeysundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004; 44: 1453-62
16. Spiess BD, Royston D, Levy JH, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion 2004; 44: 1143-8
17. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-65
18. Mangano DT, Miao Y, Vuylsteke A, et al. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. JAMA 2007; 297: 471-9
19. Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006; 46: 327-38
20. 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
21. Royston D, Bidstrup BP, Taylor KM, et al. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 1987; 2: 1289-91
22. 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: 543-51; discussion 551-3
23. 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; 62 (6): 1659-67; discussion 1667-8
24. 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; 92 (8): 2236-44
25. 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; 55: 971-6
26. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg 2004; 128: 442-8
27. Henry DA, Moxey A, Carless J, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 1999; (4): CD001886
28. Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs. Arzneimittelforschung 1983; 33: 479-94
29. Mahdy AM, Webster NR. Perioperative systemic haemostatic agents. Br J Anaesth 2004; 93: 842-58
30. Khan TA, Bianchi C, Voisine P, et al. Aprotinin inhibits protease-dependent platelet aggregation and thrombosis. Ann Thorac Surg 2005; 79: 1545-50
31. Poullis M, Manning R, Laffan M, et al. The antithrombotic effect of aprotinin: actions mediated via the protease activated receptor 1. J Thorac Cardiovasc Surg 2000; 120: 370-8
32. van Oeveren W, Harder MP, Roozendaal KJ, et al. Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1990; 99: 788-96; discussion 796-7
33. Coughlin SR, Vu TK, Hung DT, et al. Expression cloning and characterization of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. Semin Thromb Hemost 1992; 18: 161-6
34. Coughlin SR, Vu TK, Hung DT, et al. Characterization of a functional thrombin receptor: issues and opportunities. J Clin Invest 1992; 89: 351-5
35. Landis RC, Haskard DO, Taylor KM. New antiinflammatory and platelet-preserving effects of aprotinin. Ann Thorac Surg 2001; 72: S1808-13
36. Ferraris VA, Ferraris SP, Singh A, et al. The platelet thrombin receptor and postoperative bleeding. Ann Thorac Surg 1998; 65: 352-8
37. Day JR, Punjabi PP, Randi AM, et al. Clinical inhibition of the seven-transmembrane thrombin receptor (PAR1) by intravenous aprotinin during cardiothoracic surgery. Circulation 2004; 110: 2597-600
38. Maquelin KN, Nieuwland R, Lentjes EG, et al. Aprotinin administration in the pericardial cavity does not prevent platelet activation. J Thorac Cardiovasc Surg 2000; 120: 552-7
39. Day JR, Taylor KM, Lidington EA, et al. Aprotinin inhibits proinflammatory activation of endothelial cells by thrombin through the protease-activated receptor 1. J Thorac Cardiovasc Surg 2006; 131: 21-7

40. Sellke FW. Organ protection in cardiac surgery. In: Sellke FW, editor. Improving outcomes in open heart surgery. Boston (MA): Interactive Communications, 2005
41. Poston RS, White C, Gu J, et al. Aprotinin shows both hemostatic and antithrombotic effects during off-pump coronary artery bypass grafting. Ann Thorac Surg 2006; 81: 104-10; discussion 110-1
42. Bradfield JF, Bode AP. Aprotinin restores the adhesive capacity of dysfunctional platelets. Thromb Res 2003; 109: 181-8
43. Carr Jr ME, Carr SL, Roa V, et al. Aprotinin counteracts heparin-induced inhibition of platelet contractile force. Thromb Res 2002; 108: 161-8
44. Dietrich W. Reducing thrombin formation during cardiopulmonary bypass: is there a benefit of the additional anticoagulant action of aprotinin? J Cardiovasc Pharmacol 1996; 27 Suppl. 1: S50-7
45. Alston TA. Aprotinin. Int Anesthesiol Clin 2004; 42: 81-91
46. Bidstrup BP, Royston D, Sapsford RN, et al. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 1989; 97: 364-72
47. Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol 2002; 40: 231-7
48. Akowuah E, Shrivastava V, Jamnadas B, et al. Comparison of two strategies for the management of antiplatelet therapy during urgent surgery. Ann Thorac Surg 2005; 80: 149-52
49. van der Linden J, Lindvall G, Sartipy U. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: a double-blind, placebo-controlled, randomized clinical trial. Circulation 2005; 112 (9 Suppl.): I276-80
50. Lindvall G, Sartipy U, van der Linden J. Aprotinin reduces bleeding and blood product use in patients treated with clopidogrel before coronary artery bypass grafting. Ann Thorac Surg 2005; 80: 922-7
51. Nader ND, Davidson BA, Tait AR, et al. Serine antiproteinase administration preserves innate superoxide dismutase levels after acid aspiration and hyperoxia but does not decrease lung injury. Anesth Analg 2005; 101: 213-9
52. Erdogan M, Kalaycioglu S, Iriz E. Protective effect of aprotinin against lung damage in patients undergoing CABG surgery. Acta Cardiol 2005; 60: 367-72
53. Ege T, Arar C, Canbaz S, et al. The importance of aprotinin and pentoxifylline in preventing leukocyte sequestration and lung injury caused by protamine at the end of cardiopulmonary bypass surgery. Thorac Cardiovasc Surg 2004; 52: 10-5
54. Lazar HL, Bao Y, Tanzillo L, et al. Aprotinin decreases ischemic damage during coronary revascularization. J Card Surg 2005; 20: 519-23
55. Yun TJ, Rho JR. Aprotinin attenuates the elevation of pulmonary vascular resistance after cardiopulmonary bypass. J Korean Med Sci 2006; 21: 25-9
56. Olivencia-Yurvati AH, Wallace WE, Wallace N, et al. Intraoperative treatment strategy to reduce the incidence of post-cardiopulmonary bypass atrial fibrillation. Perfusion 2002; (17 Suppl.): 35-9
57. Gillespie EL, Gryskiewicz KA, White CM, et al. Effect of aprotinin on the frequency of postoperative atrial fibrillation or flutter. Am J Health Syst Pharm 2005; 62: 1370-4
58. Khan TA, Bianchi C, Voisine P, et al. Reduction of myocardial reperfusion injury by aprotinin after regional ischemia and cardioplegic arrest. J Thorac Cardiovasc Surg 2004; 128: 602-8
59. Bull DA, Maurer J. Aprotinin and preservation of myocardial function after ischemia-reperfusion injury. Ann Thorac Surg 2003; 75: S735-9
60. Karaca P, Konuralp C, Enc Y, et al. Cardioprotective effect of aprotinin on myocardial ischemia/reperfusion injury during cardiopulmonary bypass. Circ J 2006; 70: 1432-6
61. Royston D, Levy JH, Fitch J, et al. Full-dose aprotinin use in coronary artery bypass graft surgery: an analysis of perioperative pharmacotherapy and patient outcomes. Anesth Analg 2006; 103: 1082-8
62. Ulker S, Cinar MG, Bayraktutan U, et al. Aprotinin impairs endothelium-dependent relaxation in rat aorta and inhibits nitric oxide release from rat coronary endothelial cells. Cardiovasc Res 2001 Jun; 50 (3): 589-96
63. Fischer JH, Steinhoff M. Effects of aprotinin on endothelium-dependent relaxation of large coronary arteries. Eur J Cardiothorac Surg 2005; 28: 801-4
64. Khan TA, Bianchi C, Araujo E, et al. Aprotinin preserves cellular junctions and reduces myocardial edema after regional ischemia and cardioplegic arrest. Circulation 2005; 112 (9 Suppl.): I196-201
65. Wachtfogel YT, Hack CE, Nuijens JH, et al. Selective kallikrein inhibitors alter human neutrophil elastase release during extracorporeal circulation. Am J Physiol 1995 Mar; 268 (3 Pt 2): H1352-7
66. Englberger L, Markart P, Eckstein FS, et al. Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. Eur J Cardiothorac Surg 2002; 22: 545-51
67. Cugno M, Nussberger J, Biglioli P, et al. Increase of bradykinin in plasma of patients undergoing cardiopulmonary bypass: the importance of lung exclusion. Chest 2001; 120: 1776-82
68. Wachtfogel YT, Kucich U, Hack CE, et al. Aprotinin inhibits the contact, neutrophil, and platelet activation systems during simulated extracorporeal perfusion. J Thorac Cardiovasc Surg 1993; 106: 1-9; discussion 9-10
69. Hill GE, Alonso A, Spurzem JR, et al. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans. J Thorac Cardiovasc Surg 1995; 110: 1658-62
70. Pruefer D, Makowski J, Dahm M, et al. Aprotinin inhibits leukocyte-endothelial cell interactions after hemorrhage and reperfusion. Ann Thorac Surg 2003; 75: 210-5; discussion 215-6
71. Harmon D, Lan W, Shorten G. The effect of aprotinin on hypoxia-reoxygenation-induced changes in neutrophil and endothelial function. Eur J Anaesthesiol 2004; 21: 973-9
72. Kalangos A, Tayyareci G, Pretre R, et al. Influence of aprotinin on early graft thrombosis in patients undergoing myocardial revascularization. Eur J Cardiothorac Surg 1994; 8: 651-6
73. Havel M, Grabenwoger F, Schneider J, et al. Aprotinin does not decrease early graft patency after coronary artery bypass grafting despite reducing postoperative bleeding and use of donated blood. J Thorac Cardiovasc Surg 1994; 107: 807-10
74. Lass M, Welz A, Kochs M, et al. Aprotinin in elective primary bypass surgery: graft patency and clinical efficacy. Eur J Cardiothorac Surg 1995; 9: 206-10
75. Wendel HP, Heller W, Michel J, et al. Lower cardiac troponin T levels in patients undergoing cardiopulmonary bypass and receiving high-dose aprotinin therapy indicate reduction of perioperative myocardial damage. J Thorac Cardiovasc Surg 1995; 109: 1164-72
76. Taggart DP, Djapardy V, Naik M, et al. A randomized trial of aprotinin (Trasylol) on blood loss, blood product requirement, and myocardial injury in total arterial grafting. J Thorac Cardiovasc Surg 2003; 126: 1087-94
77. Anttila V, Hagino I, Iwata Y, et al. Aprotinin improves cerebral protection: evidence from a survival porcine model. J Thorac Cardiovasc Surg 2006; 132: 948-53
78. Heikkinen J, Kaakinen T, Dahlbacka S, et al. Aprotinin to improve cerebral outcome after hypothermic circulatory arrest:

a study in a surviving porcine model. Heart Surg Forum 2006; 9: E719-24

79. Harmon DC, Ghori KG, Eustace NP, et al. Aprotinin decreases the incidence of cognitive deficit following CABG and cardiopulmonary bypass: a pilot randomized controlled study. Can J Anaesth 2004; 51: 1002-9
80. Buziashvili YI, Ambat'ello SG, Aleksakhina YA, et al. Influence of cardiopulmonary bypass on the state of cognitive functions in patients with ischemic heart disease. Neurosci Behav Physiol 2006; 36: 107-13
81. Buziashvili YI, Aleksakhina YA, Ambat'ello SG, et al. Use of p300 cognitive evoked potentials in the diagnosis of impairments of higher mental functions after cardiac surgery in conditions of cardiopulmonary bypass. Neurosci Behav Physiol 2006; 36: 115-8
82. Levy JH, Sypniewski E. Aprotinin: a pharmacologic overview. Orthopedics 2004; 27: s653-8
83. Asimakopoulos G, Thompson R, Nourshargh S, et al. An anti-inflammatory property of aprotinin detected at the level of leukocyte extravasation. J Thorac Cardiovasc Surg 2000; 120: 361-9
84. Junge CE, Sugawara T, Mannaioni G, et al. The contribution of protease-activated receptor 1 to neuronal damage caused by transient focal cerebral ischemia. Proc Natl Acad Sci U S A 2003; 100: 13019-24
85. Jurk K, Jahn UR, Van Aken H, et al. Platelets in patients with acute ischemic stroke are exhausted and refractory to thrombin, due to cleavage of the seven-transmembrane thrombin receptor (PAR-1). Thromb Haemost 2004; 91: 334-44
86. 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: 1081-9
87. Feindt PR, Walcher S, Volkmer I, et al. Effects of high-dose aprotinin on renal function in aortocoronary bypass grafting. Ann Thorac Surg 1995; 60: 1076-80
88. Mora Mangano CT, Neville MJ, Hsu PH, et al. Aprotinin, blood loss, and renal dysfunction in deep hypothermic circulatory arrest. Circulation 2001; 104 (12 Suppl. 1): I276-81
89. Fauli A, Gomar C, Campistol JM, et al. Kidney-specific proteins in patients receiving aprotinin at high- and low-dose regimens during coronary artery bypass graft with cardiopulmonary bypass. Eur J Anaesthesiol 2005; 22: 666-71
90. Kincaid EH, Ashburn DA, Hoyle JR, et al. Does the combination of aprotinin and angiotensin-converting enzyme inhibitor cause renal failure after cardiac surgery? Ann Thorac Surg 2005; 80: 1388-93; discussion 1393
91. Kikura M, Levy JH, Tanaka KA, et al. A double-blind, placebo-controlled trial of epsilon-aminocaproic acid for reducing blood loss in coronary artery bypass grafting surgery. J Am Coll Surg 2006; 202: 216-22; quiz A44-5
92. Diprose P, Herbertson MJ, O'Shaughnessy D, et al. Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. Br J Anaesth 2005; 94: 271-8
93. Carless PA, Moxey AJ, Stokes BJ, et al. Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. BMC Cardiovasc Disord 2005; 5: 19
94. Nuttall GA, Oliver WC, Ereth MH, et al. Comparison of blood-conservation strategies in cardiac surgery patients at high risk for bleeding. Anesthesiology 2000; 92: 674-82
95. Byar DP. Problems with using observational databases to compare treatments. Stat Med 1991; 10: 663-6
96. Hiatt WR. Observational studies of drug safety: aprotinin and the absence of transparency. N Engl J Med 2006; 355: 2171-3
97. Mazer D, Fergusson D, Hebert P, et al. Incidence of massive bleeding in a blinded controlled trial of antifibrinolytic drugs [abstract]. Anesth Analg 2006; 102: SCA1-95

Correspondence: Dr *Frank W. Sellke*, Beth Israel Deaconess Medical Center, 110 Francis Street, LMOB 2A, Boston, MA 02215, USA.
E-mail: fsellke@bidmc.harvard.edu