



## Current status of antifibrinolytics in cardiopulmonary bypass and elective deep hypothermic circulatory arrest

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### **Bleeding after cardiopulmonary bypass**

Cardiopulmonary bypass (CPB) alters the hemostatic balance and predisposes cardiac surgery patients to an increased risk of microvascular bleeding. Bleeding and the need for transfusion are among the most common complications of cardiac surgery. In fact, until recently, blood transfusions seemed to be required for about 50% of all cardiac surgery patients [1]. Currently, CPB accounts for 10% to 20% of the transfusions performed in the United States [2,3]. Transfusion, however, exposes patients to added risks such as infectious disease transmission [4], transfusion reactions [5], graft-versus-host disease [6], transfusion-induced lung injury [7], and decreased resistance to postoperative infection [8,9]. Transfusion increases the risk of infection by 35% to 300% and increases the risk of pneumonia in coronary artery bypass (CABG) patients by 5% per unit transfused [10]. The primary purported benefit of transfusion, increased oxygen carrying capacity, has not been definitively proven.

Excessive postoperative bleeding may necessitate surgical reexploration, increasing morbidity, and mortality. Postoperatively, the risk of excessive bleeding is 11% [11], and 5% to 7% of patients lose more than 2 L of blood in the first 24 hours after CPB [12]. Reexploration for hemorrhage is required in 3.6% to 4.2% of patients [13], and mortality rates range from 10% to 22% [14]. Bleeding and reexploration consume hospital resources by increasing the operative time and blood-product usage, and the need for mechanical ventilation, intensive care, and longer hospitalization [15,16]. Reexploration also increases

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the rates of renal failure, sepsis, and atrial arrhythmia [13]. Less than half of re-explored patients have a surgical cause for bleeding [15]. It is these patients who might have benefited from prophylactic antifibrinolytic drugs.

Because of the substantial cost, limited blood supply, multiple risks, and lack of proven benefit, health care professionals are now avoiding transfusion by accepting moderate anemia and using blood-saving techniques. In addition, concern about allogeneic blood safety has led to methods intended to minimize perioperative transfusion. Multiple nonpharmacologic blood-saving methods are available for use during CPB, but they are beyond the scope of this article. Instead of using complex blood salvaging techniques, the most effective approach is to avoid blood loss from the beginning [17]. Pharmacologic therapies accomplish this goal. One of these techniques is prophylactic antifibrinolytic therapy. Antifibrinolytic drugs prevent primary fibrinolysis and preserve platelet function by preventing platelet activation. The efficacy of these drugs as prophylactic hemostatic agents in cardiac surgery patients has been validated in numerous studies [3,18–26]. The most widely administered antifibrinolytic drugs are the synthetic lysine analogs (epsilon-aminocaproic acid [EACA] and tranexamic acid [TXA]) and the nonspecific serine protease inhibitor aprotinin [24].

This article briefly reviews the pathophysiology of bleeding after CPB. It then reviews the current status, efficacy, and safety of antifibrinolytic drugs and discusses the use of these agents in patients undergoing routine CPB and elective DHCA.

### **Pathophysiology of excessive bleeding after cardiopulmonary bypass**

The pathophysiology of bleeding after CPB is complex, involving hypothermia, hemodilution, activation of coagulation, endothelial cell and tissue injury [2], foreign-surface contact [2], consumption of clotting factors [27], platelet activation [28], platelet dysfunction [29], and hyperfibrinolysis [30]. These factors are all interrelated and variable from one individual to another; in combination, they lead to a homeostatic imbalance between coagulation and fibrinolysis.

#### *Activation of hemostasis*

During CPB, the hemostatic system is activated by way of multiple pathways, including the intrinsic and extrinsic coagulation cascades [31,32]. Contact with the foreign surface of the CPB circuit results in contact-phase activation of factor XII, prekallikrein, and high-molecular-weight kininogen, thus initiating the intrinsic pathway [33]. Simultaneously, surgical trauma, exposure of raw tissue surfaces to air, generation of factor VIIa (through endothelial cell activation) [34], and reinfusion of pericardial blood result in tissue-factor activation of the extrinsic pathway [35–37]. These pathways converge, leading to the generation of thrombin [35]. Controversy exists about which system provides a more common, or a greater, insult. Recent studies suggest that the extrinsic system may

lead to the greatest activation of the hemostatic system. Despite adequate heparinization, thrombin is still generated before, during, and after CPB [38,39]. Thrombin activates hemostasis, platelets, and endothelial cells, leading to the release of vasoactive substances and other mediators of hemostasis, fibrinolysis, and inflammation [33,34].

### *Activation of fibrinolysis*

Fibrinolysis is activated by several mechanisms, including the production of thrombin, release of tissue plasminogen activator (t-PA) by vascular endothelium, and activation of the intrinsic coagulation pathway [40–42]. The release of t-PA from endothelium can be caused by thrombin [43], epinephrine, bradykinin, factor Xa, factor XII [34], hypothermia [44,45], or CPB alone [46]. The largest surges in t-PA release occur on initiation of CPB and after infusion of protamine [39,47]. Concentrations of plasminogen activator rise rapidly during CPB, while levels of plasminogen activator inhibitor (PAI-1) slowly increase and peak during the postoperative period [48]. Individual variability is high, for t-PA production and PAI-1 release. The genetic characteristics of these proteins are complex, but known polymorphisms exist and have been correlated with early myocardial infarction (MI) [49,50]. Elevations or exaggerated surges of PAI-1 may be related to elevated cytokine and inflammatory activity. This patient-to-patient variability is just now being investigated.

The release of plasma-derived urokinase, as a direct consequence of contact-phase activation by way of activated Hageman factor and kallikrein, also contributes to fibrinolysis by causing further t-PA release and direct fibrinolysis [51]. Serine proteases cleave plasminogen to form plasmin. Plasmin splits fibrinogen and fibrin at specific sites to form fibrin degradation products and D-dimers (Fig. 1).

Fibrin breakdown is a normal hematologic activity that remodels formed clots and removes thrombus as the endothelium heals. The fibrin formation and lysis that occur during CPB are usually mild and self-limited. Excessive fibrinolysis is occasionally seen however, and it can contribute to excessive bleeding.

### *Role of platelets*

The increased plasmin and fibrin degradation products produced during CPB have deleterious effects on platelets [52]. Activation of the fibrinolytic system contributes to platelet dysfunction. Fibrinolysis affects platelet membrane receptors, causing platelet activation and granule release [53].

When hemostasis and fibrinolysis are both activated, a consumptive process ensues that is mediated by thrombin and plasmin. Thrombin mediates the conversion of fibrinogen to fibrin monomers, initiates fibrinolysis by mediating the release of t-PA, and activates factors V, VIII, and XIII, and platelets. Thrombin activates protein C in combination with thrombomodulin on the endothelial surface, consuming previously generated, activated factors V and VIII.

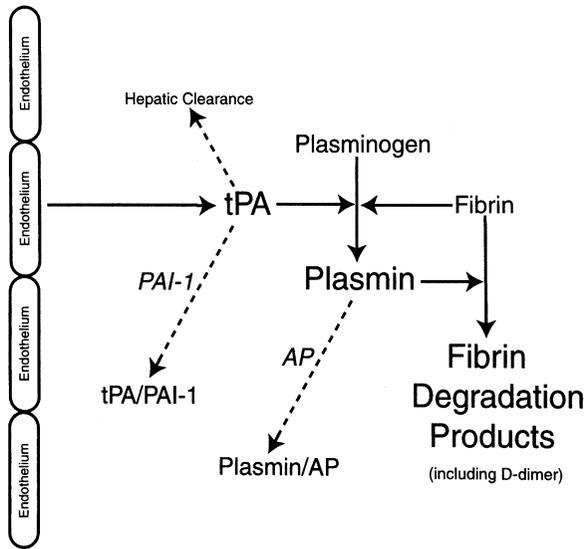


Fig. 1. Overview of the fibrinolytic system. TPA, tissue plasminogen activator, PAI-1, plasminogen activator inhibitor 1; AP antiplasmin (From Chandler W. The fibrinolytic response during cardiopulmonary bypass: Pro or anticoagulant? In: The relationship between coagulation, inflammation and endothelium. Baltimore: Lippincott Williams & Wilkins; 2000. p. 147–68; with permission).

Thrombin down-regulates hemostasis by releasing tissue factor pathway inhibitor; this agent inhibits the extrinsic pathway and stimulates the release of t-PA, which cleaves plasminogen to plasmin. Plasmin cleaves fibrinogen and fibrin monomers to fibrin degradation products and cleaves cross-linked fibrin polymers to D-dimers. Plasmin inactivates factors V and VIII and inhibits the glycoprotein receptors of platelets. Therefore, it is important to attenuate the exaggerated effects of both thrombin and plasmin [54].

Antifibrinolytic therapy can minimize the platelet defect mediated by plasmin and fibrin degradation products [55,56]. Antifibrinolytic agents protect platelet function by inhibiting the proteolytic degradation of glycoprotein platelet surface receptors Ib and IIb/IIIa, allowing platelet function to be preserved after CPB [57,58].

### Use of antifibrinolytic agents during routine cardiopulmonary bypass

Discovery of the usefulness of antifibrinolytic drugs followed the development of CPB during the 1950s and 1960s, because at the time CPB devices that were not optimally biocompatible resulted in severe bleeding related to hyperfibrinolysis. Recently, outcome-based evidence has revealed the effectiveness and safety of these drugs, leading to their increased use during routine low-risk cardiac operations [22].

For example, in a recent meta-analysis, Levi and coauthors [22] examined all randomized, controlled trials undertaken to test the most common strategies used for preserving hemostatic function after CPB. These authors looked for outcome measures of the efficacy and safety of antifibrinolytic agents. The analysis included 72 trials (involving 8409 patients) that used either the lysine analogs or aprotinin and that reported at least one clinically relevant outcome measure (mortality, reexploration, transfusion, or perioperative MI). Compared with placebo, aprotinin decreased the mortality almost twofold (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.34–0.90). Both agents also decreased the need for reexploration (aprotinin: OR, 0.37; 95% CI, 0.25–0.55) (lysine analogs: OR, 0.44; 95% CI, 0.22–0.90) and significantly decreased the number of blood transfusions required. Neither patient group had an increased rate of MI, although the lysine analog studies, either individually or combined, were not prospectively designed to examine MI as an outcome. A separate analysis in patients undergoing complicated cardiac surgery showed similar results [22].

### *Lysine analogues*

EACA and TXA are synthetic agents that competitively inhibit plasmin by adhering to the lysine-binding sites of plasminogen and plasmin, where they interfere with plasmin's ability to digest fibrinogen, fibrin, and platelet glycoprotein receptors. Lysine analogs minimize the increase in primary fibrinolysis that occurs during CPB [20,59]. They reduce blood loss and transfusion requirements in cardiac surgery patients [20,24,25,27,60–67]. Effective inhibition of fibrinolysis necessitates an intravenous loading dose of 100 to 150 mg/kg of EACA or 10 mg/kg of TXA, followed by a constant infusion at one-tenth of the loading dose each hour [68]. However, the best dosage has not been agreed on. These drugs are concentrated and cleared in the kidney, so a dosing adjustment seems warranted in patients with an elevated creatinine level [69]. Pharmacokinetic studies have shown that a bolus of EACA (but not of TXA) should be readministered on institution of CPB [70,71].

Initial investigations of the synthetic antifibrinolytic agents lacked blinding, randomization, and control groups and failed to show significant efficacy [72,73]. More recent investigations documented a savings in blood loss as well as the amount of blood transfused [20,63,65,74]. Lysine analogs are clearly effective, but, compared with placebo, they yielded only a modest (25%) reduction in blood loss and transfusion in the meta-analysis of randomized, controlled trials published by Despotis and coworkers [54].

### *Epsilon-aminocaproic acid*

Epsilon-aminocaproic acid (EACA) (Amicar; Amgen, Inc., Thousand Oaks, CA) was used in the early days of heart surgery, but the perceived risk of microvascular thrombosis later caused its use to be restricted [75–77]. When reports of the successful use of high-dose aprotinin became available in the late 1980s, interest in the use of synthetic antifibrinolytic agents was renewed.

Many investigators have assessed the efficacy of EACA [62,64,78,79]. In studying 40 patients undergoing primary coronary artery bypass grafting (CABG), Daily and associates [62] demonstrated that, compared with a control group, the patients who received a 30-g dose of EACA had decreased blood loss and transfusion. In a retrospective analysis by Jordan and colleagues [64], EACA usage reduced the percentage of patients who received red blood cells by 53%, the number of units used per patient by 57%, the percentage of patients who received platelets by 66%, and the number of platelet units administered per patient by 68%. Also, the EACA patients had a reduced operative time after being weaned from CPB, as well as fewer re-explorations.

In a meta-analysis using transfusion as the outcome variable, Laupacis and Fergusson [21] found that EACA had no significant effect on the proportion of patients transfused despite an odds ratio considerably less than 1.0 (OR, 0.20; 95% CI, 0.04–1.12). The authors attributed this lack of significance to the fact that the analysis included only three randomized, controlled studies (including 118 patients) and to the use of different dosages.

Another recent meta-analysis, by Munoz and coworkers [24], who examined EACA and aprotinin use in cardiac surgery, included nine trials of EACA, which reduced blood loss by 35%. Compared with placebo recipients, the EACA group had 61% fewer transfusions (mean reduction, 0.74 U) and was only 32% as likely to need blood (OR, 0.32; 95% CI, 0.15–0.69;  $P = 0.004$ ). The authors concluded that, despite large differences in the dosage ranges among the studies, EACA, which is substantially less expensive than aprotinin, is just as effective. They found little evidence of thrombosis-related complications, including stroke and MI, in either group. On the contrary, both groups tended to have a considerable reduction in the risk of postoperative stroke, although this finding did not reach significance.

In a randomized, double-blind, placebo-controlled study, Slaughter and associates [27] demonstrated that EACA decreased fibrinolysis 3 hours after CPB (50% reduction in D-dimer concentration;  $P < 0.005$ ) and decreased bleeding (35% reduction compared with placebo;  $P < 0.05$ ), but there were no intergroup differences in the perioperative generation of thrombin or fibrin. These results suggest that there is at least a potential for a perioperative hypercoagulable or prothrombotic state in EACA recipients who are genetically predisposed to this condition. Although clinical trials have failed to show definitive evidence that EACA therapy can lead to thrombosis, there are numerous reports of this complication in the literature [80–82].

In randomized clinical trials comparing EACA to aprotinin, two studies found no differences in postoperative transfusion rates despite reduced blood loss in the aprotinin group [83,84]. Furthermore, in an efficacy and cost-effectiveness study involving patients undergoing repeat cardiac operations, Bennett-Guerrero and coworkers [19] compared EACA to aprotinin therapy and found no intergroup difference in allogeneic blood use despite the fact that aprotinin was more efficacious in reducing blood loss. The authors concluded that EACA is the more cost-effective agent.

### *Tranexamic acid*

Tranexamic acid (TXA) (Cyklokapron; Pharmacia Corporation, Peapack, New Jersey) is a synthetic lysine analog that is similar to EACA but ten times more potent [68]. The mechanism of action of TXA is similar to that of EACA. The usual dose for CPB patients is 1.5 to 10.0 g intravenously. Despite a variability in dosage, there is little doubt that the 10-g dosage scheme is efficacious (Table 1)

In a meta-analysis of drugs used to minimize perioperative blood loss that included 12 studies, Laupacis and Fergusson [21] found that TXA significantly decreased the proportion of cardiac surgical patients transfused (OR, 0.50; 95% CI, 0.34–0.76;  $P = 0.0009$ ). It had no effect on perioperative MI or reexploration, but these variables were not prospectively evaluated.

In repeat operations, TXA is of particular benefit. Shore-Lesserson and coauthors [25] demonstrated that TXA decreased blood loss and reduced transfusion by 33% in patients undergoing repeat cardiac surgery.

The timing of TXA therapy has been examined by several authors. In a study by Horrow and colleagues [85], TXA given before the initiation of CPB decreased chest-tube drainage by 30% during the first 12 hours postoperatively and decreased the transfusion rate from 41% to 22%. Large doses were not beneficial. Administration of TXA after CPB or bleeding becomes established is a controversial practice that could lead to prothrombotic complications [59]. In a study by Casati and colleagues [92] involving both high- and low-risk patients in whom TXA therapy was continued for 12 hours after CPB, this approach had no advantage over placebo in reducing the incidence of bleeding. In a randomized, placebo-controlled, double-blind study by Brown and coworkers [90], TXA decreased bleeding and transfusion in patients undergoing primary CABG when this agent was administered before and during, but not after, CPB.

The literature contains multiple studies that compare the efficacy of TXA to that of aprotinin. In a randomized, double-blind study of 150 patients undergoing primary CABG, Mongan and associates [3] showed that TXA and aprotinin were equally effective in reducing blood loss, the incidence of transfusion, and the amount of blood products transfused. In two more recent, larger trials, Casati and colleagues [60,61] demonstrated that TXA was as effective as aprotinin in reducing blood loss in low-risk patients.

In a randomized trial comparing TXA and aprotinin therapy in high-risk patients, Nuttall and coauthors [91] found that TXA, used with the “platelet-sparing” acute normovolemic hemodilution technique, was similar to aprotinin with respect to reduced blood loss and transfusion requirements. In another study involving high-risk, repeat, multiple valve, combined, or aortic arch procedures [93], 80 patients were prospectively randomized to receive TXA or aprotinin. There were no intergroup differences in complications (including stroke, MI, or death), blood loss, or blood transfused. Aprotinin however, negated the usual effect of CPB duration on chest-tube blood loss, but TXA did not.

TXA treatment results in very few side effects, but few safety data are available from large, prospective, placebo-controlled, double-blind studies. However, there is no evidence that TXA has a thrombogenic effect in noncardiac patients

Table 1  
Summary of studies comparing treatment with TXA versus placebo or untreated controls

Author	Type of surgery (TXA/control)	Dose of TXA	% Receiving donor blood TXA	% Receiving donor blood control	Mean transfusion requirement (units) TXA	Mean transfusion requirement (units) control	Mean total blood loss TXA	Mean total blood loss control
Horrow, 1995 [85]	CABG or valves (n = 21/27)	10 mg/kg then 1mg/kg/h for 12h	29	29	NA	NA	365 g for 12h	552 g for 12h
Horrow, 1991 [74]	CABG or valves (n = 37/34)	10 mg/kg then 1mg/kg/h for 12h	32	36	NA	NA	328 g for 12h*	462 g for 12h
Horrow, 1990 [20]	CABG or valves (n = 18/20)	10 mg/kg then 1mg/kg/h for 10h	NA	NA	1.1	0.9	496 mL for 12h*	750 ml for 12h
DePeppo, 1995 [84]	CABG or valves (n = 15/15)	10 mg/kg then 1mg/kg/h for 10h	7	20	0.07	0.4	534 mL for 24h	724ml for 24h
Specken-brink, 1995 [86]	Primary CABG (n = 15/15)	10 mg/kg then 1 mg/kg/h up to 1g	NA	NA	2.9	3.1	352 mL for 6h*	674 mL for 6h
Blauhut, 1994 [87]	Primary CABG (n = 15/14)	10 mg/kg then 1 mg/kg/h for 10h	47	60	0.8	1.6	403 mL for 24h	453 mL for 24h

Corbeau, 1995 [88]	Primary CABG (n = 41/20)	30 mg/kg in 2 doses	37	60	0.8	1.7	1015 mL for 48h*	1416ml for 48h
Katsaros, 1996 [89]	CABG or valves (n = 104/106)	10 g	11*	25	0.2*	0.5	474 ml for 24h*	906ml for 24h
Karski, 1995 [65]	CABG or valves (n = 49/48)	10 g	40	40	0.8	0.8	640 mL for 24h*	980ml for 24h
Rousou, 1995 [67]	Primary CABG (n = 206/209)	10 g	NA	NA	0.7*	1.3	804 mL for 24h*	1114ml for 24h
Shore-Lesserson, 1996 [25]	Repeat CABG or valve, (n = 17/13)	20 mg/kg then 2 mg/kg/h until end	59*	92	—	—	649ml for 24h*	923ml for 24h
Brown, 1997 [90]	Primary CABG (n = 30/30)	15 mg/kg then 1 mg/kg/h for 5h	27*	66	0.5*	5	710ml for 24h*	1202ml for 24 h
Nuttall, 2000 [91]	Repeat CABG or valve (n = 45/43)	10 mg/kg then 1 mg/kg/h until ICU	33	48	—	—	700ml for 24h*	950ml for 24h
Mongan, 1998 [3]	Primary CABG (n = 75/30)	15 mg/kg then 2 mg/kg/h for 6h + 1g pump prime	25*	66	0*	4.5	700ml for 24h*	1200ml for 24h

CABG, coronary artery bypass grafting; TXA, tranexamic acid

\* Results significant  $P < 0.05$  compared to placebo or control (*Data from* Schumann F: Hemostatic Restoration during Cardiopulmonary Bypass. In: Pifarre R, editor. New anticoagulants for the cardiovascular patient. Philadelphia: Hanley & Belfus, Inc.; 1997. p. 453–69.)

predisposed to thrombosis [94]. Most accounts of thrombosis come from individual case reports [95].

### *Aprotinin*

Aprotinin (Trasylol; Bayer Corporation, Pittsburgh, PA) is a protein serine protease inhibitor derived from bovine lung. This substance is the most potent antifibrinolytic agent known and is used in laboratory medicine to stop fibrinolysis *in vitro* [34]. The dosage for adults is 2 million kallikrein inactivator units (KIU) intravenously for both the patient and the bypass pump, followed by 500,000 KIU/h [96]. Aprotinin has a much longer elimination half-life (7 hours) than either of the synthetic antifibrinolytics. It effectively decreases blood loss during cardiac surgery and preserves platelet function after CPB [3,18,19,21–23, 60,61,96–102,].

### *Mechanism of action*

The mechanism of action of aprotinin is complex but is becoming progressively better understood. This agent has anti-inflammatory and anticoagulant properties that preserve hemostasis by inhibiting the contact pathway and possibly the tissue-factor pathway [103]. Aprotinin reversibly complexes with the active serine site in various proteases, including trypsin, plasmin, and kallikrein [104]. It inhibits factor XIIa, activation of complement, and kallikrein-mediated conversion of plasminogen to plasmin [54,104]. As a plasmin inhibitor, aprotinin diminishes fibrinolysis and the increase in D-dimer levels seen in CPB patients [48,98,99]. It decreases thrombin generation and fibrinolysis during CPB [98,105].

The hemostatic mechanism of aprotinin may be better explained by its ability to preserve platelet glycoprotein receptors Ib and IIb/IIIa or to block a plasmin-mediated platelet defect [56–58,106,107]. Aprotinin preserves platelet function and integrity by inhibiting proteolytic alterations in von Willebrand factor and on platelet glycoprotein Ib and IIb/IIIa receptors [108,109]. It also attenuates the inhibition of platelet function by heparin and decreases thrombin-mediated platelet consumption by inhibiting the PAR1 (protease-activated) receptor [33,102,110].

Aprotinin protects platelets from desensitization by thrombin generated during CPB, increasing the number of platelets available to participate in wound hemostasis [111]. With respect to platelets, aprotinin is antithrombotic because it selectively blocks the major thrombin receptor (PAR1) but not other receptors of platelet activation, such as collagen, adenosine diphosphate (ADP), or epinephrine. The selective targeting of PAR1 protects platelets from unwanted activation by thrombin generated during CPB while allowing platelets to participate in the formation of hemostatic plugs at wound and suture sites where collagen, ADP, and epinephrine are expressed [111,112]. Aprotinin inhibits proteolytic activation of platelets, but platelets can still be activated by nonproteolytic mechanisms [113].

Aprotinin also inhibits factor XIIa by 20% and factor IXa by more than 50%, resulting in heparin-like activity. Some investigators have reported decreased rates of thrombotic complications, presumably because of this antithrombotic tendency. For example, aprotinin recipients undergoing total hip arthroplasty had a decreased incidence of deep venous thrombosis and other thrombotic complications [114,115]. Therefore, aprotinin is described as both antithrombotic and hemostatic.

### *Efficacy*

The clinical efficacy of aprotinin has been extensively studied ever since the drug was originally developed as a trypsin inhibitor for the treatment of acute pancreatitis. Aprotinin costs significantly more than any other fibrinolytic agent and some blood-salvage strategies [116].

Because aprotinin therapy is expensive, research has focused primarily on the drug's efficacy and side effects to justify its use, particularly in lower-risk patients.

Although some early reports and clinical studies in the 1970s and 1980s showed that aprotinin reduced blood loss in heart surgery patients, it was not until 1987 that a new interest in the hemostatic properties of aprotinin arose. At Hammersmith Hospital in London, Royston and Bidstrup [117,118], using a novel high-dose scheme, evaluated the effect of aprotinin on complement activation in patients undergoing open heart surgery. Although the drug did not affect the levels of C3a and C4a, it reduced blood loss and transfusion by 50%.

In an attempt to achieve better results at less cost, many investigators undertook original studies using only moderate amounts of aprotinin (half of the Hammersmith dose), but these studies showed no decreased blood loss. However, most studies showed that “full” or high-dose aprotinin decreases blood loss and transfusion more effectively [18,111,119,120]. High-dose aprotinin decreases blood loss by 29% to 50% (Table 2) [56,98,117,118].

In a parallel, double-blind, placebo-controlled, multicenter study of primary elective CABG, Lemmer and coworkers [101] demonstrated that full-dose, half-dose, and “pump-prime-only” dosing regimens of aprotinin all reduced the amount of transfused blood products by 50% compared with placebo. Further, in a meta-analysis of all available studies up to 1997 [21], aprotinin was shown to decrease transfusion by an average of 1.4 units per patient (OR, 0.31; 95% CI, 0.25–0.39;  $P < 0.0001$ ). This effect was achieved regardless of type of surgery (primary or reoperation), aspirin use, aprotinin dosage, or transfusion trigger. The aprotinin recipients needed fewer reexplorations (OR, 0.44; 95% CI, 0.27–0.73;  $P = 0.001$ ), had a decreased incidence of stroke, and had a nonsignificantly increased incidence of MI.

Despotis and colleagues [54] reviewed four well-controlled, double-blind, randomized, US multicenter clinical trials that documented improved outcomes in aprotinin users compared with placebo recipients. The authors showed an overall 50% decrease in blood loss, a 50% to 90% decrease in donor exposures, and a 40% to 60% decrease in the reexploration rate. In another study, by Lemmer and associates [101], involving patients undergoing primary CABG, aprotinin reduced the rate of early reoperation from 7.3% to 1.1%.

Table 2  
Summary of randomized, double blind trials comparing full dose aprotinin to placebo

Author	Type of surgery	% Receiving donor blood aprotinin	% Receiving donor blood placebo	Mean transfusion requirement (units) aprotinin	Mean transfusion requirement (units) placebo	Mean total blood loss (ml) aprotinin	Mean total blood loss(mL) placebo
Bidstrup, 1989 [97]	Primary CABG (n = 80)	20	95	0.3	2.0	309	573
Bidstrup, 1993 [121]	Primary CABG (n = 96)	20	49	NA	NA	390	620
Bidstrup, 1995 [122]	Primary CABG (n = 60)	23	57	NA	NA	195	504
Murkin, 1994 [123]	Primary CABG or valves (n = 55)	57	87	1.6	4.3	720	1485
Dietrich, 1990 [99]	Primary CABG (n = 20)	37	75	1.7	3.2	739	1442
Harder, 1991 [124]	Primary CABG (n = 80)	32	57	NA	NA	559	911
Fraedrich, 1989 [125]	Primary CABG (n = 80)	42	68	1.8	2.8	652	1204
Dementjeva, 1995 [126]	Primary CABG (n = 100)	22	56	NA	NA	392	690

Swart, 1994 [127]	Primary CABG or valves (n = 100)	68	86	1.8	2.8	506	783
Casas, 1995 [128]	Primary CABG or valves (n = 99)	26	56	0.7	1.8	195	489
Lemmer, 1994 [129]	Primary CABG (n = 151)	38	52	1.1	2.2	855	1503
Lemmer, 1994 [129]	Repeat CABG (n = 65)	30	72	0.4	3.3	1255	1979
Cosgrove, 1992 [130]	Repeat CABG (n = 115)	46	79	NA	NA	720	1121
Minami, 1993 [131]	Repeat CABG (n = 49)	28	52	NA	NA	441	772
Levy, 1995 [34]	Repeat CABG (n = 145)	54	75	1.6	3.4	900	1700
Alderman, 1998 [18]	Primary CABG (n = 401)	38	54	0.8	1.6	664	1168

CABG, coronary artery bypass grafting.

(Data from Schumann F. Hemostatic restoration during cardiopulmonary bypass. In: Pifarre R, editor. New anticoagulants for the cardiovascular patient. Philadelphia: Hanley & Belfus, Inc.; 1997. p.453–69.)

The efficacy of aprotinin has been especially well documented for high-risk patients or those undergoing complex procedures. Royston and coauthors [117] demonstrated that aprotinin recipients undergoing repeat operations had a decrease in blood loss. In aspirin-treated patients, aprotinin reduces blood loss and transfusion to the same degree as in non-aspirin patients undergoing primary [123] or repeat CABG [23,130]. In a multicenter, double-blind, placebo-controlled trial in repeat CABG patients [23], aprotinin decreased blood loss and transfusion in both the high- and low-dose groups without increasing the incidence of MI; the aprotinin recipients also had a lower incidence of reexploration and stroke. Overall, aprotinin therapy seemed to offer a consistent, significant, and clinically relevant reduction in blood loss and transfusion requirements [17].

#### *Clinical safety/graft patency*

Aprotinin is the only agent that has been approved by the US Food and Drug Administration (FDA) to reduce bleeding in cardiac surgery patients [34]. The clinical safety of aprotinin has been confirmed extensively throughout the literature. The drug has very few side effects and is remarkably well tolerated, even in the highest doses [68,132]. High-dose aprotinin seems to induce a reversible microproteinuria related to a transient, isolated defect of tubular protein absorption [133], but it has no effect on the serum creatinine level or the incidence of adverse renal events [134]. Aprotinin can safely be administered to patients with renal failure [135].

Very rarely (in <1 per 1000 patients), aprotinin can trigger anaphylaxis [98,136]. With repeat exposure, the incidence of anaphylaxis is as high as 5% [137], but it decreases if the interval between the initial and subsequent dose is greater than 3 months [138]. Prophylactic antihistamines reduce the severity and incidence of these reactions [139]. Complications reported in the literature include histamine-mediated cardiovascular collapse, heparin resistance, potentiation of muscle relaxants, and renal toxicity [18,130]. Despite several case reports of renal dysfunction, minimal renal effects have been observed in animal experiments and controlled clinical studies [34].

Concerns have been raised regarding thrombotic complications with aprotinin. There have been some case reports of clot formation on catheters [140], thromboembolic complications [141], and decreased graft patency [130,142] in CABG patients. Investigators studying graft patency rates in aprotinin recipients, however, have consistently been confounded by the aprotinin dosage, imaging modality, time interval for patency assessment, heparin dosage, aspirin dosage, distal vessel quality, saphenous vein graft (SVG) quality, and SVG preservation techniques. For example, in a placebo-controlled study in redo CABG patients, Cosgrove and coworkers [130] demonstrated that aprotinin decreased bleeding and transfusion with no difference in mortality but with a (nonsignificant) increase in the incidence of Q-wave MI. The authors concluded that aprotinin may increase the risk of SVG thrombosis in redo CABG patients. The authors' conclusion was based on post mortem examination of graft closures; although the

incidence of MI was numerically higher in the group receiving aprotinin, no denominator was disclosed, and no significance was shown.

High-dose aprotinin prolongs the celite-activated clotting time (ACT), leading to decreased heparin doses [143]. Before this effect on the celite-ACT was recognized, many reports and clinical studies cited an increased incidence of thrombotic complications, graft closure, and MI [121,130]. In their study, Cosgrove and associates [130] used celite-ACT values and gave less heparin, which probably influenced their results. Therefore, in the presence of aprotinin, heparin activity must be monitored with kaolin-ACT, high-dose thrombin time, blood heparin levels by protamine titration, or an empiric dosing scheme [144–146]. Some clinicians recommend giving a total heparin dose of as much as 600 to 700 U/kg.

To perform a definitive prospective, randomized trial of vein graft patency, Alderman and colleagues [18] participated in the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial in 1995. Eight hundred seventy patients undergoing primary CABG were randomized to receive high-dose aprotinin or placebo treatment, followed by early coronary angiography to evaluate SVG patency. In the aprotinin recipients, blood loss was reduced by 43%, transfusion by 49%, and reexploration by 47%. Occlusion of the SVG was observed in 15.4% of the aprotinin-treated patients compared with 10.9% of the placebo group ( $P = 0.03$ ). However, in a subanalysis of the US patients only, the occlusion rates were similar (9.4% aprotinin versus 9.5% placebo). The authors attributed the dramatic difference in occlusion rates (aprotinin: non-US 23% versus US 9.4%; placebo: non-US 12.4% versus US 9.5%) to differences in gender prevalence, to vein harvesting and preservation techniques, to the prevalence of aspirin therapy, and (most important) to small distal anastomotic sites. Aprotinin had no effects on MI or mortality. In following up the IMAGE trial patients, a survey showed no difference in survival or morbidity at a mean of 4 years postoperatively [147].

Subsequently, many studies showed no early SVG occlusion once the effect of aprotinin on the celite-ACT was recognized and alternate methods of measuring the heparin effect were used [100,129,148,149]. Further investigations reported no increased thrombosis or graft closure in placebo-controlled, blinded, randomized trials when graft patency was determined by magnetic resonance imaging, computed tomography, or angiography [34,111,150].

### **Use of antifibrinolytic agents in elective deep hypothermic circulatory arrest**

The use of DHCA during cardi thoracic surgery is associated with an increased risk of perioperative blood loss and renal dysfunction. The coagulopathy induced by hypothermia and circulatory stasis is complex and multifactorial in origin. In brief, hypothermia induces kinetic slowing of coagulation, kinin and kallikrein activation, platelet dysfunction, and fibrinolysis [151]. Furthermore, blood stasis causes a thrombin-induced increase in activated protein C, which

results in further anticoagulation and fibrinolysis by way of endothelial release of t-PA [152].

Use of antifibrinolytic agents to preserve hemostasis would seem to be of greatest benefit in DHCA patients. However, concern over the possibility of thrombotic complications in the setting of blood stasis has caused a controversy to surround the use of antifibrinolytics, particularly aprotinin. Although all of the antifibrinolytic agents have been used for DHCA, none has received as much attention as aprotinin in the literature. Therefore, this section focuses on the use of aprotinin in DHCA.

Early experience raised alarms about the hazards of aprotinin use in DHCA. Excessive mortality, renal failure, and complications were reported in clinical series in which the adequacy of heparinization was questionable. To date, there has been very little evidence from prospective, randomized trials that aprotinin is unusually hazardous. However, mostly because of the lack of well-controlled studies, investigators have also failed to prove that its use offers a definitive benefit.

Some authors have speculated that unproven prothrombotic effects of aprotinin are uniquely expressed under the conditions of stasis and hypothermia that distinguish DHCA from routine CPB alone [153,154]. Aprotinin may attenuate the role of activated protein C in maintaining the fluidity of blood during periods of stasis. This has led to the concern that aprotinin may potentiate thrombosis, especially in the presence of inadequate heparinization [151]. As a serine protease inhibitor, however, aprotinin would also decrease kinin/kallikrein activation directly and would prevent platelet dysfunction by protecting glycoprotein receptors and inhibiting fibrinolysis. These effects would make aprotinin attractive in the setting of DHCA.

Clinical investigations comparing aprotinin recipients with control patients have focused on neurologic outcome, renal dysfunction, and mortality. Most of the thrombotic complications associated with the use of aprotinin during DHCA were described in the early 1990s and may have been the consequence of inadequate heparinization, when it was not clear how to adjust the dose of heparin. The earliest studies were extremely alarming and led to warnings about the use of aprotinin in the product brochure of aprotinin. In an uncontrolled series studied by Sundt and coauthors [26], the aprotinin patients had 30% greater mortality, 60% greater renal dysfunction, and a 25% greater need for dialysis than the control patients. However, the aprotinin group received substantially less heparin than the control group (27,850 versus 40,250 U). In a retrospective study, Westaby [155] found increased coagulation abnormalities, increased reexploration for bleeding, and increased thrombosis-related mortality in aprotinin-treated patients. Both of these studies were completed before 1995, when it was recognized that aprotinin prolongs the celite-ACT. Thus, the complications of these initial studies were attributed to inadequate heparinization.

Current recommendations include higher heparin dosing, keeping the celite-ACT at > 750 seconds, or using kaolin-ACT measurements. Studies using these criteria have shown no difference in mortality, neurologic defects, renal dysfunction, or renal failure in aprotinin versus placebo recipients [156,157]. The first

positive results were reported by Goldstein and associates [158], who, in a retrospective study, found that aprotinin-treated patients had a significantly lower incidence of postoperative transfusion, although they had the same chest-tube output as control patients. Okita and coworkers [159], who described a consecutive series of 112 partially randomized patients, reported decreased blood loss and transfusion in recipients of low-dose aprotinin.

In a randomized, controlled study, Ehrlich and coauthors [156] compared low-dose aprotinin to placebo in DHCA patients undergoing surgery of the thoracic aorta. Compared with the control group, the aprotinin group had less blood loss and transfusion, and no effect on renal function. In a more recent retrospective review of a similar series of patients, Seigne and coworkers [160] found that low-dose aprotinin decreased blood transfusion and had no deleterious renal or myocardial effects. Similarly, in a recent retrospective study, Mora-Mangano and colleagues [151] demonstrated that aprotinin did not increase renal dysfunction, although it also had no effect on blood loss or reexploration. Predictors of postoperative renal dysfunction included transfusion of more than 5 units of blood, low urine output in the operating room, lack of dopamine use, a perioperative hematocrit of <21%, and low urine output in the ICU [151].

In a prospective study concerning the effect of heparin dosage in patients undergoing DHCA with aprotinin, Okita and associates [159] determined that those who received additional heparin, regardless of their ACT, had better platelet preservation and less severe activation of the coagulation system than did patients who received heparin only when their ACT decreased to <500 seconds. Overall, recent studies seem to indicate that aprotinin is not unusually hazardous in DHCA patients as long as adequate heparinization is used; however, the benefits of aprotinin are unclear.

Before this controversy is resolved, further prospective, randomized, placebo-controlled, double-blind studies must be performed on a much larger scale. Based on the most recent studies, however, there seems to be no convincing evidence that aprotinin should be withheld from patients undergoing cardiac surgery with DHCA.

## Summary and future considerations

During cardiac surgery, CPB increases thrombin levels, which augments t-PA and plasmin formation, leading to an increase in fibrinolytic activity. Future therapies may be directed against increased hemostatic and inflammatory activation. The result should be less thrombin formation, better hemostasis, and less blood loss. To this end, numerous strategies have been developed and are being tested. For instance, the process of heparin dosing and protamine reversal are being reexamined. Furthermore, administration of recombinant antithrombin III, which enhances the antithrombotic properties of heparin, has decreased thrombin formation and fibrinolytic activity [161,162]. Also, development of other antithrombins and heparin analogs—such as argatroban, bivalirudin, dermatin sulfate, pentasac-

charide, and recombinant hirudin—is ongoing. The short half-life and potent antithrombotic activity of some of these agents could prove quite useful during CPB. Lastly, other agents such as recombinant activated factor VIIa are being used in cardiac surgery for patients with refractory bleeding [54,163].

The potential for severe bleeding after cardiac surgery and CPB remains a major problem. Current pharmacologic approaches to attenuating the activation of the hemostatic system and preventing fibrinolysis are limited. Antifibrinolytic agents result in decreased consumption of clotting factors and better preservation of platelet function. Prophylactic administration of agents with antifibrinolytic, anticoagulant, and antiinflammatory properties could decrease operative time, blood loss, transfusion, and reexploration, thereby improving patient outcomes and potentially reducing overall health care costs.

The choice of which agent to use in specific patient groups remains controversial, institutionally variable, and somewhat polarized. History shows all three agents to be safe, yet the literature contains individual case reports of thrombotic events. Further research into individual genetic variability among patients may someday elucidate the cause of these rare events. Although antifibrinolytic agents may increase patient safety during cardiac surgery, further investigation into their use is essential.

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