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Cost–Benefit and Efficacy of Aprotinin Compared with ϵ-Aminocaproic Acid in Patients Having Repeated Cardiac Operations

A Randomized, Blinded Clinical Trial

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Background: **Aprotinin and ϵ-aminocaproic acid are routinely used to reduce bleeding during cardiac surgery. The marked difference in average wholesale cost between these two drug therapies (aprotinin, $1,080 *vs.* ϵ-aminocaproic acid, $11) has generated significant controversy regarding their relative efficacies and costs.**

Methods: **In a multicenter, randomized, prospective, blinded trial, patients having repeated cardiac surgery received either a high-dose regimen of aprotinin (total dose, 6×10^6 kallikrein inactivator units) or ϵ-aminocaproic acid (total dose, 270 mg/kg).**

Results: **Two hundred four patients were studied. Overall (data are median [25th–75th percentiles]), aprotinin-treated patients had less postoperative thoracic drainage (511 ml [383–805 ml] *vs.* 655 ml [464–1,045 ml]; $P = 0.016$) and received fewer platelet transfusions (0 [range, 0–1] *vs.* 1 [range, 0–2]; $P = 0.036$). The surgical field was more likely to be considered free of bleeding in aprotinin-treated patients (44% *vs.* 26%; $P = 0.012$). No differences, however, were seen in allogeneic erythrocyte transfusions or in the time required for chest closure. Overall, direct and indirect bleeding-related costs were greater in aprotinin- than in ϵ-aminocaproic acid–treated patients ($1,813 [$1,476–2,605] *vs.* $1,088 [range, $511–2,057]; $P = 0.0001$). This difference in cost per case varied in magnitude among sites but not in direction.**

Conclusions: **Aprotinin was more effective than ϵ-aminocaproic acid at decreasing bleeding and platelet transfusions. ϵ-aminocaproic acid, however, was the more cost-effective therapy over a broad range of estimates for bleeding-related costs in patients undergoing repeated cardiac surgery. A cost-benefit analysis using the lower cost of half-dose aprotinin ($540) still resulted in a significant cost advantage using ϵ-aminocaproic therapy ($P = 0.022$). (Key words: Aprotinin. ϵ-aminocaproic acid. Coagulation. Fibrinolysis. Surgery: cardiac. Complications: bleeding. Cost-benefit analysis.)**

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MORE than 400,000 cardiac operations for myocardial revascularization, valve surgery, or both are performed annually in the United States.[1] Bleeding is a common complication of these procedures and results in prolongation of the operative procedure and increased blood transfusions with their attendant risks and costs.[2–6] Cardiac operations account for approximately 10% of the 11 million units of allogeneic blood transfused annually in the United States.[4,7] Repeated cardiac operations are increasing in number and represent a group particularly at risk for bleeding.[2,3,8–11] Although the cause of periop-

erative bleeding is multifactorial, cardiopulmonary bypass-induced fibrinolytic activity and platelet dysfunction appear to be the most important causes.[2,3] Several kinds of pharmacologic agents are commonly administered to improve hemostasis in these patients. They work by inhibiting fibrinolysis, although other mechanisms, such as preservation of platelet function, may be relevant.[8,12-17]

Aprotinin, a 58 amino acid serine protease inhibitor isolated from bovine lung has been shown to decrease bleeding associated with cardiac surgery.[8-11,18] The average wholesale price of this drug to hospitals in the United States is $1,080 per patient[19] and is of concern to health-care providers and payers. The cost of aprotinin alone may represent more than 5% of the total cost of cardiac catheterization and cardiac surgery.[20] The lysine analog ϵ-aminocaproic acid also decreases bleeding associated with cardiac surgery[12,18,21,22] and has an average wholesale price of $11 per patient.[19]

Approximately 45,000 repeated cardiac operations are performed annually in the United States.[1,23] If there is no or minimal difference in efficacy between these two therapies, significant cost savings would accrue if ϵ-aminocaproic acid were used instead of aprotinin. Therefore we tested the hypothesis that ϵ-aminocaproic acid provides a less costly approach to limit bleeding in patients having repeated cardiac surgery.

Methods

Patient Selection

After institutional review board approval and written informed consent, participants were enrolled at Duke University Medical Center (Durham, NC), the University of Michigan Medical Center (Ann Arbor, MI), and the Fundación Favaloro (Buenos Aires, Argentina) between October 1994 and May 1996. Patients undergoing repeated cardiac operation for either coronary artery bypass graft surgery, valvular heart surgery, or both were included. Exclusion criteria were serum creatinine concentration >2.5 mg/dl; age < 18 yr; history of allergy to aprotinin or to protamine; thrombolytic therapy within 48 h before surgery; evidence of disseminated intravascular coagulation or significant upper urinary tract bleeding; patients undergoing repeated operation *via* a thoracotomy approach; and history of a preexisting coagulation disorder.

Anesthesia and Surgery

After oral methadone and benzodiazepine premedication, venous, radial arterial, and pulmonary arterial catheters were inserted. Induction and maintenance of general anesthesia were accomplished with midazolam hydrochloride and fentanyl citrate by infusion. Patients underwent standard nonpulsatile hypothermic (28-32°C) cardiopulmonary bypass with a membrane oxygenator and hemodilution. Porcine heparin was administered as a bolus of 300 units/kg and supplemented as necessary to maintain a kaolin-activated coagulation time of >450 s during cardiopulmonary bypass. Increased cardiopulmonary bypass pump fluid volume due to cardioplegia and ice used for topical myocardial cooling was removed during cardiopulmonary bypass by ultrafiltration or by use of an erythrocyte-scavenging device. A bladder or rectal temperature of >36°C was required before separation from cardiopulmonary bypass. Heparin was neutralized with 1 mg protamine/100 units heparin. After cardiopulmonary bypass, crystalloid and colloid solutions were administered to optimize intravascular volume, temperature was maintained >36°C by convective warming, and systolic and mean systemic arterial blood pressures were maintained <140 mmHg and 90 mmHg, respectively, using vasoactive agents.

Study Drug

Patients were randomly assigned to a treatment group using a computer-generated schedule and study drug was prepared according to a protocol by the respective hospital pharmacies. Because surgical technique is an important predictor of bleeding, patients were stratified according to surgeon to ensure an even distribution between groups with respect to surgeon. Each patient received a high-dose intravenous regimen of either (1) aprotinin, 2×10^6 kallikrein inactivator units on skin incision, 0.5×10^6 kallikrein inactivator units/h $\times$ 4-h infusion on initiation of cardiopulmonary bypass, and 2×10^6 kallikrein inactivator units added to the cardiopulmonary bypass prime solution; or (2) ϵ-aminocaproic acid, 150 mg/kg on skin incision, 30 mg/kg $\times$ 4-h infusion on initiation of cardiopulmonary bypass, and saline placebo added to the cardiopulmonary bypass prime solution. These high-dose regimens are similar to those used in previous studies.[12,18] Patients received 1 ml study drug in a blinded manner before the loading dose to test for possible allergy.[24] All clinicians and investigators were blinded to the identity of the study drug, and the drugs were administered in equal volumes.

Transfusion Protocol

During and after cardiopulmonary bypass, allogeneic erythrocytes were transfused if the hematocrit concentrations were <0.18 and <0.25, respectively. In the presence of persistent microvascular bleeding, the protocol called for the administration of fresh frozen plasma if the prothrombin time or the activated partial thromboplastin time was more than 50% of control, cryoprecipitate if the plasma fibrinogen concentration was less than 150 mg/dl, and platelets if the platelet count was less than 100,000/μl or if other coagulation values were normal. Blood in the operative field was collected using an erythrocyte scavenging device and readministered.

Clinical Outcomes and Analysis of Cost

The primary efficacy outcome was the volume of thoracic drainage within the first 24 h after operation. Other measures of efficacy included the number of allogeneic blood product transfusions, number of donor exposures, duration of chest closure, and surgical assessment of the "dryness" of the surgical field. One unit of platelets represented 200–250 ml volume and was obtained from either a single donor by plasmapheresis or from the pooling of platelets from six blood donors. Chest closure duration was defined as the time from termination of cardiopulmonary bypass until reapproximation of the sternum.

This study's primary objective was to evaluate the relative bleeding-related costs of these two drug therapies. Costs to the hospital, in contrast to charges to patients, were evaluated. The costs of the drugs were obtained from the *Drug Topics Red Book* average of 1996 wholesale prices.[19] They were $1,080 for 6×10^6 kallikrein inactivator units of aprotinin and $11 for 270 mg/kg of ε-aminocaproic acid (for an average 70-kg patient).[19] The cost of each unit of allogeneic erythrocytes ($151.20) has been reported previously and accounts for several direct and indirect costs, including blood procurement from the American Red Cross, blood testing, hospital costs of infectious complications and transfusion reactions, transfusion service overhead, and transfusion tubing/filters/blood warming coils.[25] This cost is similar to the value ($149.80) used in a study evaluating the cost-effectiveness of autologous blood donations.[26] To the previously reported costs of platelets $541.14, fresh frozen plasma $81.85, and cryoprecipitate $332.18, we added a cost of $3.45 for each donor exposure to account for the hospital cost of infectious complications.[25,27] For example, a dose of cryoprecipitate from 10 donors would have a cost of $34.50 added to it. The cost of operating room time was estimated to be $4.70/min.[28]

Sensitivity analyses were performed to determine how changes in the estimated bleeding-related costs would influence the relative cost-effectiveness of these two drug therapies. In particular, because half-dose aprotinin may be as effective as the full dose used in this study, we also performed a cost-benefit analysis using the lower cost of half-dose aprotinin ($540). The perspective of a health-care institution was used because its costs are most likely to be influenced by these therapies.

Determination of Fibrinolytic Activity

To assess the extent of fibrinolytic activity in the two groups, blood samples were obtained in a subset of patients (n = 82) at Duke University Medical Center immediately before induction of anesthesia, 3 h after termination of cardiopulmonary bypass, and at 8 A.M. on the first postoperative day. Blood samples were collected in citrate-containing vacutainer tubes, centrifuged, and the plasma stored at −20°C until they were assayed for D-dimer concentration using the Dimer Gold assay kit (American Diagnostica, Greenwich, CT; normal, 68.6 ± 14.8 ng/ml). D-dimer is a degradation product of cross-linked fibrin and correlates with fibrinolytic activity.[3,12,29]

Statistical Analysis

Sample size for the study was estimated from previous study findings.[30,31] A study population of 200 patients was estimated to have at least 90% power at $\alpha = 0.05$ (two-tailed) to detect a difference of 250 ml in 24-h thoracic drainage, given an SD of 200 ml. This sample size of 200 patients was also estimated to have at least 90% power at $\alpha = 0.05$ (two-tailed) to detect a difference of one unit in allogeneic erythrocyte transfusions, given an SD of two units.

Groups were compared to ensure similarity with respect to preoperative characteristics. For these and other univariate comparisons including outcome variables other then the primary outcomes, the Pearson chi-square test was used for categorical variables, and the nonparametric Wilcoxon rank-sum test was used for continuous variables. The primary outcomes (thoracic drainage, erythrocyte units transfused, and bleeding-related costs) were non-Gaussian in their distribution. Thus these data were ranked, and a two-way analysis of variance was used on the ranks to test effects of drug, study center, and their interaction. When

Table 1. Preoperative Demographics

	Aprotinin	EACA
No. of patients	99	105
Age (yr)	62 ± 14	63 ± 12
Gender (% male)	67	65
Weight (kg)	76 ± 14	75 ± 14
Preoperative LVEF (%)	52 ± 14	53 ± 16
Hx diabetes* (%)	28	21
Hx myocardial infarction† (%)	45	49
Hx hypertension (%)	55	62
Preoperative aspirin use (%)	53	53
Preoperative heparin use (%)	37	41
Preoperative hematocrit	0.39 ± 0.05	0.39 ± 0.05
Preoperative platelets ($\times 1{,}000 \cdot \mu l^{-1}$)	212 ± 65	213 ± 66
Preoperative PT ratio	1.1 ± 0.2	1.1 ± 0.1
Preoperative PTT (s)	45 ± 26	45 ± 26
Preoperative serum creatinine ($mg \cdot dl^{-1}$)	1.2 ± 0.4	1.1 ± 0.3

Values are mean ± SD where appropriate. There were no significant differences between groups ($P > 0.5$ in every case).

EACA = ϵ-aminocaproic acid; Hx = history of; LVEF = left ventricular ejection fraction, determined from cardiac catheterization data; PT ratio = prothrombin time ratio (PT seconds divided by control value in seconds); PTT = partial thromboplastin time.

* Diabetes mellitus was considered present if a patient required oral hypoglycemic or insulin medication.

† Myocardial infarction was defined as ECG evidence of an old myocardial infarction or previously documented episodes of increased CPK-MB isoenzymes without concurrent ECG changes.

‡ Hypertension was defined as blood pressure greater than 140/90 mmHg documented on at least three occasions or a history of increased blood pressure requiring medication.

appropriate, data are presented as means ± SD. Non-Gaussian data are presented as medians with 25th and 75th percentiles.

Results

Two hundred four patients were enrolled in the study, and all patients were included in the final analysis. The randomization code was broken in four patients because of clinicians' concerns of excessive bleeding in these cases (aprotinin group, two patients; ϵ-aminocaproic acid group, two patients). The statistical significance of outcome results was not affected by including these four patients. Study groups were similar with respect to preoperative demographic factors (table 1) and intraoperative characteristics (table 2).

Table 3 summarizes measures of efficacy. Overall, aprotinin-treated patients had less postoperative thoracic drainage and received fewer platelets. The surgical field was considered "dry" more frequently in aprotinin-treated patients. No differences, however, were seen in allogeneic erythrocyte transfusions or in the time required for chest closure.

Overall median bleeding-related costs, however, were $725 higher in aprotinin-treated patients (median [25th-75th percentiles]: $1,813 [$1,476-2,605] *vs.* $1,088 [$511-2,057]; $P = 0.0001$). This difference in cost varied in magnitude among sites but not in direction: (median) site 1 ($1,745 *vs.* $1,047), site 2 ($1,476 *vs.* $380), and site 3 ($2,327 *vs.* $2,057. Mean total bleeding-related costs were also significantly higher ($796) in the aprotinin-treated patients. Sensitivity analyses showed that the superior cost-effectiveness of ϵ-aminocaproic acid was relatively insensitive to changes in the estimated costs of blood products and operating room time. In fact, a doubling (*i.e.*, a 100% increase) in the estimate for the cost of all blood products and operating room time still resulted in a significant difference ($P = 0.02$) in cost between groups. Sensitivity analyses also showed that ϵ-aminocaproic acid was more cost-effective to a threshold value of $486 for the cost of aprotinin therapy. That is, a cost-benefit analysis using the lower cost of half-dose aprotinin ($540) still

Table 2. Intraoperative Patient Characteristics

	Aprotinin	EACA
First repeat cardiac operation (%)	93	92
Third or subsequent cardiac operation (%)	7	8
CABG procedure only (%)	57	55
Valve procedure only (%)	30	34
Combined CABG + valve procedure (%)	13	11
IMA used (%)	43	40
Grafts per patient	2.7 ± 0.9	2.7 ± 0.9
Total OR heparin dose ($\times 1{,}000$ units)	35 ± 8.6	36 ± 8.3
Total OR protamine dose (mg)	301 ± 97	304 ± 113
CPB time (min)	149 ± 52	145 ± 56
AoXC time (min)	82 ± 35	78 ± 34

Values are mean ± SD where appropriate. There were no significant differences between groups ($P > 0.5$ in every case).

EACA = ϵ-aminocaproic acid; CABG = coronary artery bypass graft; Valve = cardiac valve; IMA = internal mammary artery; Grafts per patient = no. of distal coronary artery bypass grafts per patient having CABG; OR = operating room; CPB = cardiopulmonary bypass; AoXC = aortic cross clamp.

Table 3. Measures of Efficacy

	Aprotinin	EACA	*P*
Thoracic drainage first 24 h postoperatively	511 [383–805]	655 [464–1045]	0.016
Surgeon* considered field "dry" (%)	44	26	0.012
Units of allogeneic RBC	2 [0–4]	3 [1–4]	0.289
Units of platelets	0 [0–1]	1 [0–2]	0.036
Units of fresh frozen plasma	0 [0–2]	1 [0–3]	0.259
Units of cryoprecipitate	0 [0–0]	0 [0–0]	0.422
No. of donor exposures	2 [0–7]	3 [1–13]	0.084
Transfused with ≥5 allogeneic RBC (%)	31	38	0.738
Chest closure† duration (min)	50 [40–69]	54 [42–67]	0.439
Reexploration for bleeding (%)	4	3	0.716
Post-CPB minus preoperative Δ D-dimer (ng/ml)‡	137 [4–352]	155 [−16–262]	0.328
PO day 1 minus preoperative ΔD-dimer (ng/ml)‡	48 [3–275]	44 [−14–210]	0.328

With the exception of proportions all data are expressed as median [25th–75th percentile]. $P > 0.05$ is not significant.

EACA = ϵ-aminocaproic acid; RBC = packed red blood cells; Post-CPB minus preoperative ΔD-dimer = the change in plasma D-dimer concentration from preoperatively through 3 h postcardiopulmonary bypass (a positive number represents an increase from preoperatively); PO day 1 minus preoperative ΔD-dimer = the change in plasma D-dimer concentration from preoperatively as compared with postoperative day 1 (a positive number represents an increase from preoperatively).

* Surgeon assessment of surgical field done following administration of protamine.

† Chest closure was defined as time from separation from cardiopulmonary bypass until closure of median sternotomy.

‡ Samples obtained from a subset of patients (EACA, n = 40; aprotinin, n = 42).

resulted in a significant cost advantage using ϵ-aminocaproic therapy ($P = 0.022$).

Incremental cost-effectiveness ratios could not be calculated because the groups were not different with regard to an outcome that could be translated into quality-adjusted years of life saved.[26] There was no difference between groups in D-dimer levels (table 3), discharge hematocrit concentration, and platelet count or in the change of these values from baseline.

Discussion

Bleeding is a common complication of cardiac surgical procedures. Strategies for reducing allogeneic blood transfusions include the use of pharmacologic agents, reinfusion of shed blood, preoperative donation of autologous blood, and acute normovolemic hemodilution.[2,3] Aprotinin and ϵ-aminocaproic acid are drugs commonly used to decrease bleeding associated with cardiac surgery. Both full-dose ($1,080) and half-dose aprotinin ($540), however, are more costly than ϵ-aminocaproic acid ($11) in the United States. Public concern over the risks of blood transfusions,[32] pressure to reduce health-care costs, and controversy regarding the comparable efficacy of these drugs have generated considerable interest regarding the relative cost-effectiveness of these two therapies.

Table 4 presents a summary of previous studies in which aprotinin therapy was compared to a synthetic antifibrinolytic agent (ϵ-aminocaproic acid or tranexamic acid).[29–31,33–36] These studies are limited by small sample size, lack of blinding, and lack of a cost-effectiveness analysis. Furthermore, most of these studies excluded patients having repeated cardiac surgery, the patient population for which aprotinin is primarily indicated.[37]

The present study compared the efficacy and cost-effectiveness of aprotinin and ϵ-aminocaproic acid in patients undergoing repeated cardiac surgery. Although aprotinin was more efficacious in some respects, the marked difference in cost between these therapies resulted in ϵ-aminocaproic acid being the more cost-effective therapy overall. The increased efficacy of aprotinin was demonstrated by differences in thoracic drainage, platelet transfusions, and by the surgeon's assessment of "dryness" of the surgical field. Allogeneic erythrocyte transfusions were not different between groups, which suggests that the difference in efficacy between these therapies is minimal.

Compared with ϵ-aminocaproic acid, aprotinin did not significantly reduce donor exposures in this trial. Its cost-effectiveness thus could not be expressed as quality-adjusted years of life saved. We instead performed a cost-benefit analysis in which we accounted for the bleeding-related costs of these two therapies; that is, health-care expenditures likely to be influenced by the use of these agents. Cost to the hospital was assessed rather than charges to patients. The costs of blood products and operating room time were included because these resources have been shown to be altered by the use of these agents.[9–11]

Despite more than 20 randomized clinical trials conducted to date,[9–12,18,21,22] no data exist to support the hypothesis that other variables, such as the duration of

Table 4. Summary of Previous Studies

Study	Study Population	No. of Patients Analyzed per Group	Blinded?	Cost-effectiveness Analysis	Total Drug Dose	24 h Thoracic Drainage*	Location
Trinh-Duc *et al.*[33] (1992)	Reoperation = 7% Included aortic surgery	28	No	No	EACA: 20 g Ap: 6×10^6 KIU	No difference	France
Blauhut *et al.*[29] (1994)	Reoperation = 0% Excluded ASA and heparin	14	No	No	TA: 20 mg/kg Ap: 6×10^6 KIU	No difference	Austria, Switzerland
Penta de Peppo *et al.*[34] (1995)	Reoperation = 0%	15	No	No	EACA: 20 g Ap: 6×10^6 KIU	Aprotinin superior	Italy
Speekenbrink *et al.*[31] (1995)	Reoperation = 0% Excluded heparin	15	No	No	TA: 15 mg/kg Ap: 2×10^6 KIU	No difference	The Netherlands
Boughenou *et al.*[36] (1995)	Reoperation = % not specified Excluded ASA	17	Yes	No	TA: 36 mg/kg Ap: 6×10^6 KIU	No difference	France
Pugh *et al.*[35] (1995)	Reoperation = 0%	21	No	No	TA: 5 g Ap: 2×10^6 KIU	No difference	England
Menichetti *et al.*[30] (1996)	Reoperation = 0% Excluded ASA and low Hct	24	No	No	EACA: 310 mg/kg Ap: 6×10^6 KIU	Aprotinin superior	Italy

Reoperation = % of patients undergoing repeat cardiac operation; ASA = patients on aspirin preoperatively; Heparin = patients on heparin preoperatively; Low Hct = patients with preoperative hematocrit <38%; EACA = ϵ-aminocaproic acid; TA = tranexamic acid; Ap = aprotinin; Total drug dose = intraoperative total dose (total aprotinin dose may have been slightly larger in some cases during longer intraoperative duration).

* Allogeneic transfusions no different ($P > 0.05$) between aprotinin and EACA or TA (all studies).

postoperative tracheal intubation, intensive care unit stay, and hospital length are influenced by these hemostatic agents. Of note, these outcomes were not significantly different between groups in our study. The incidences of in-hospital death (5.9%), stroke (3.4%), and myocardial infarction (5.4%) in this study population are consistent with previously reported outcomes in high-risk cardiac surgery patients.[9-11] This study was not designed to have sufficient power to detect a difference between the two groups in these outcome measures.

This study was designed to give a more efficacious agent a favorable chance of showing cost-effectiveness. To this end we selected a patient population (*i.e.*, repeated cardiac surgery) in whom these agents, and in particular aprotinin, have consistently been shown to be highly efficacious.[9-11] In fact, repeated cardiac surgery represents the primary indication for aprotinin therapy.[37] We also included estimated savings related to differences in chest closure duration,[9-11] despite the fact that small decreases in operating room duration are unlikely to result in real cost savings given the semifixed nature of this cost.[28] The time period for the outcome of allogeneic blood product transfusions (*i.e.*, from termination of cardiopulmonary bypass through the first 24 h after operation) was also chosen to enhance detection of a drug effect. In fact, a separate analysis using the time period from initiation of study drug through discharge from the hospital did not change the results of this trial.

Patients received full-dose aprotinin in this trial because this dose has most consistently reduced bleeding in patients undergoing repeated cardiac surgery.[9-11,38-41] Because some studies have shown that half-dose ($540) aprotinin is as efficacious as high-dose aprotinin, we also performed a cost-benefit analysis using the lower cost of half-dose aprotinin ($540). In this sensitivity analysis using the cost of half-dose aprotinin, the significant cost advantage of ϵ-aminocaproic therapy persisted; ϵ-aminocaproic acid therapy would result in lower overall costs down to a threshold value of $486 for the cost of aprotinin therapy.

Greater variability exists for previously reported dosing regimens of ϵ-aminocaproic acid. We used a high-dose regimen for ϵ-aminocaproic acid (270 mg/kg) given the low cost of this drug and the lack of proved serious complications associated with its use. A placebo group may have enhanced the scientific design of this study. However, because both of these therapies have been shown to reduce bleeding complications, we believed that it would be unethical to include a placebo group.

The safety of these agents is similar but not identical. Anaphylaxis, an uncommon (0.3%) but potentially fatal side effect after the use of aprotinin,[24] has not been attributed to the administration of ϵ-aminocaproic acid. Otherwise, the prophylactic administration of these agents has not been proved to result in adverse outcomes. Despite the many patients studied to date,[9-12,18,21,22] there is no evidence that these agents cause renal failure or clinically significant thrombosis.

Aprotinin and ϵ-aminocaproic acid appear to work in part by inhibiting fibrinolysis, although controversy exists regarding other possible mechanisms of action.[8,12-17] Consistent with previous studies, in this trial both therapies prevented the several-fold increase in D-dimer seen when these agents are not used.[12,29] The comparable degree of inhibition of fibrinolysis, reflected in D-dimer concentration combined with the superior efficacy of aprotinin suggests that aprotinin may have additional hemostatic effects, perhaps by preventing cardiopulmonary bypass-associated platelet dysfunction.[14]

In conclusion, aprotinin therapy was more effective than ϵ-aminocaproic acid therapy at reducing bleeding associated with repeated cardiac surgery. Considering overall bleeding-related costs, however, ϵ-aminocaproic acid therapy was more cost-effective than aprotinin therapy. ϵ-aminocaproic acid was also the more cost-effective therapy even assuming the cost of half-dose aprotinin. These data suggest that ϵ-aminocaproic acid therapy provides a less costly approach to limit bleeding in the setting of repeated cardiac surgery.

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