

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 29, 2008

VOL. 358 NO. 22

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Ph.D., Paul C. Hébert, M.D., M.H.Sc., C. David Mazer, M.D., Stephen Frenes, M.D., Charles MacAdams, M.D., John M. Murkin, M.D., Kevin Teoh, M.D., M.Sc., Peter C. Duke, M.D., Ramiro Arellano, M.D., M.Sc., Morris A. Blajchman, M.D., Jean S. Bussi eres, M.D., Dany C ot e, M.D., Jacek Karski, M.D., Raymond Martineau, M.D.,* James A. Robblee, M.D., M.B.A., Marc Rodger, M.D., M.Sc., George Wells, Ph.D., Jennifer Clinch, M.A., and Roanda Pretorius, M.Sc., for the BART Investigators†

ABSTRACT

BACKGROUND

Antifibrinolytic agents are commonly used during cardiac surgery to minimize bleeding and to reduce exposure to blood products. We sought to determine whether aprotinin was superior to either tranexamic acid or aminocaproic acid in decreasing massive postoperative bleeding and other clinically important consequences.

METHODS

In this multicenter, blinded trial, we randomly assigned 2331 high-risk cardiac surgical patients to one of three groups: 781 received aprotinin, 770 received tranexamic acid, and 780 received aminocaproic acid. The primary outcome was massive postoperative bleeding. Secondary outcomes included death from any cause at 30 days.

RESULTS

The trial was terminated early because of a higher rate of death in patients receiving aprotinin. A total of 74 patients (9.5%) in the aprotinin group had massive bleeding, as compared with 93 (12.1%) in the tranexamic acid group and 94 (12.1%) in the aminocaproic acid group (relative risk in the aprotinin group for both comparisons, 0.79; 95% confidence interval [CI], 0.59 to 1.05). At 30 days, the rate of death from any cause was 6.0% in the aprotinin group, as compared with 3.9% in the tranexamic acid group (relative risk, 1.55; 95% CI, 0.99 to 2.42) and 4.0% in the aminocaproic acid group (relative risk, 1.52; 95% CI, 0.98 to 2.36). The relative risk of death in the aprotinin group, as compared with that in both groups receiving lysine analogues, was 1.53 (95% CI, 1.06 to 2.22).

CONCLUSIONS

Despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin, as compared with the lysine analogues, precludes its use in high-risk cardiac surgery. (Current Controlled Trials number, ISRCTN15166455.)

From the Ottawa Health Research Institute (D.A.F., P.C.H., M.R., J.C., R.P.), the University of Ottawa (D.A.F., P.C.H., J.A.R., M.R., G.W.), and the University of Ottawa Heart Institute (J.A.R., G.W.) — all in Ottawa; the University of Toronto (C.D.M., S.F., J.K.), Keenan Center/Li Ka Shing Institute, St. Michael's Hospital (C.D.M.), the Sunnybrook Health Science Centre (S.F.), and Toronto General Hospital (J.K.) — all in Toronto; the University of Calgary, the Foothills Medical Centre, and the Libin Cardiovascular Institute of Alberta — all in Calgary, AB (C.M.); the University of Western Ontario, London, ON (J.M.M.); Hamilton Health Sciences Centre (K.T.), McMaster University (K.T., M.A.B.), and the Canadian Blood Services (M.A.B.) — all in Hamilton, ON; the University of Manitoba and the Health Sciences Centre, Winnipeg, MB (P.C.D.); Queen's University, Kingston, ON (R.A.); H opital Laval, Institut Universitaire de Cardiologie et de Pneumologie de l'Universit e Laval, Laval, QC (J.S.B., D.C.); and Institut de Cardiologie de Montr eal, Montreal (R.M.) — all in Canada. Address reprint requests to Dr. H ebert at the Clinical Epidemiology Program, General Campus, Ottawa Health Research Institute, Box 208, 501 Smyth Rd., Ottawa, ON K1H 8L6, Canada, or at paul.hebert@cma.ca.

*Deceased.

†Investigators in the BART study are listed in the Appendix.

This article (10.1056/NEJMoa0802395) was published at www.nejm.org on May 14, 2008.

N Engl J Med 2008;358:2319-31.

Copyright   2008 Massachusetts Medical Society.

EVERY YEAR AN ESTIMATED 1 MILLION TO 1.25 million patients worldwide undergo cardiac surgery, including high-risk procedures such as repeat coronary-artery bypass grafting (CABG), valve replacements, and combined procedures.¹ High-risk procedures present an increased risk of death, massive bleeding, renal failure, and thrombotic complications, as compared with first-time isolated CABG.²⁻⁴ Three antifibrinolytic agents have been used in cardiac surgery to minimize bleeding and reduce the need for transfusion: aprotinin, a naturally occurring serine protease inhibitor, and two lysine analogues, tranexamic acid and aminocaproic acid.⁵

In clinical trials, all three drugs have been shown to be effective in reducing the need for blood transfusion, as compared with placebo.⁵⁻⁸ Similarly, meta-analyses of placebo-controlled trials have suggested that aprotinin saves lives and decreases the risk of stroke and repeat surgery for massive bleeding.^{7,9,10}

However, controversy regarding which drug should be used has resulted in a substantial variation in practice.^{11,12} A recent Cochrane review of 20 head-to-head comparisons of randomized trials suggested that there are still too few data to definitively recommend one drug over another.¹³ There are also substantial differences in cost among the study drugs. The direct pharmacy cost of aprotinin for a 4-hour cardiac procedure has been reported to be more than \$1,400, as compared with less than \$4 for aminocaproic acid.¹⁴ Also, concern regarding the safety of aprotinin has arisen from observational studies showing an association between aprotinin and increased rates of cardiovascular and cerebrovascular complications, renal failure, and short- and long-term mortality.¹⁵⁻¹⁸ A meta-analysis by Brown and colleagues suggested that concern related to the safety of aprotinin was not supported by evidence from previous randomized trials, with the possible exception of an increased risk of perioperative renal insufficiency.¹⁹

Given the limited comparative evidence related to the overall safety and the potential clinical superiority of one of the three agents over the others in reducing the risk of clinically important massive bleeding, we conducted a randomized clinical trial to determine whether aprotinin was superior to tranexamic acid and aminocaproic acid in decreasing the risk of massive postoperative bleeding in patients undergoing high-

risk cardiac surgery. We also sought to determine whether aprotinin was superior to the other two antifibrinolytic drugs in decreasing the risk of life-threatening or fatal postoperative complications.

METHODS

STUDY DESIGN

The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study was a multicenter, blinded, randomized, controlled study comparing three antifibrinolytic agents commonly used in cardiac surgery. We enrolled patients undergoing high-risk cardiac surgery, which was defined as a surgical intervention with an average mortality of at least twice the norm for isolated primary CABG and a risk of repeat surgery exceeding 5%.

The study was approved by the research ethics committee at each participating center and the central coordinating center. Written informed consent was obtained from all patients. The study was designed, conducted, and reported by the executive committee. None of the pharmaceutical companies making the study drugs contributed medications or financial support; none had any role in trial design or in data accrual, analysis, or reporting.

STUDY POPULATION

From August 2002 to October 2007, we recruited patients who were at least 19 years of age from 19 Canadian cardiac surgical units. All the patients were undergoing one of the following high-risk cardiac surgical procedures for which cardiopulmonary bypass was required: repeat cardiac surgery, isolated mitral-valve replacement, combined valve and CABG surgery, multiple valve replacement or repair, and surgery of the ascending aorta or aortic arch. Patients who required either urgent or elective procedures were considered eligible. We excluded patients who were undergoing lower-risk operations, such as isolated primary CABG with or without cardiopulmonary bypass, isolated mitral-valve repair or aortic-valve replacement, and infrequent procedures such as heart transplantation, implantation of a left ventricular assist device, and surgery to repair congenital heart defects (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The screening, eligibility, and enrollment of patients are shown in Figure 1.

STUDY INTERVENTIONS

The research pharmacist at each center randomly assigned patients to receive one of the three antifibrinolytic medications with the use of a voice-activated automated centralized program to confirm eligibility, center status, and characteristics of patients. An independent biostatistician generated the randomization scheme, which consisted of a computer-generated random listing of study-group assignments, stratified according to center and in variable permuted blocks of 6 and 9. Researchers, patients, members of the clinical teams, and members of the data and safety monitoring committee were all unaware of study-group assignments.

The dosage strategy for each study medication was based on the maximum effective regimens used in previous randomized, controlled trials²⁰⁻²³ (Fig. 1 in the Supplementary Appendix). Specifically, for patients in the aprotinin group, a test dose of 40,000 kallikrein international units (KIU) of aprotinin was administered during a 10-minute period after the insertion of a central venous line and induction of anesthesia. In the absence of an anaphylactic reaction, the remainder of the loading dose (1.96 million KIU) was given. Once the loading dose was completed, a maintenance infusion of 500,000 KIU per hour was initiated and maintained during surgery. An additional dose of 2 million KIU was added to the cardiopulmonary-bypass circuit.

For patients in the aminocaproic acid group, a test dose of 200 mg was administered during a 10-minute period after the insertion of a central venous line and induction of anesthesia. In the absence of anaphylaxis, the remainder of the loading dose (9800 mg) was given. Once the loading dose was completed, a maintenance infusion of 2000 mg per hour was initiated and maintained during surgery. No additional medication was added to the bypass circuit.

For patients in the tranexamic acid group, a test dose of 5 ml of the drug, from a total dose of 30 mg per kilogram of body weight that was mixed in 250 ml of normal saline, was administered during a 10-minute period after the insertion of a central venous line and induction of anesthesia. The remainder of the loading dose (30 mg per kilogram) was given in the absence of signs of anaphylaxis. Once the loading dose was completed, a maintenance infusion of 16 mg per kilogram per hour was initiated and main-

tained during surgery. An additional 2 mg per kilogram was added to the bypass circuit.

All maintenance infusions were discontinued on closure of the midline sternotomy. Blinding maneuvers and cointerventions are detailed in the Supplementary Appendix.

STUDY OUTCOMES

Our primary study outcome, massive postoperative bleeding, was a composite outcome of bleeding from chest tubes that exceeded 1.5 liters during any 8-hour period or massive transfusion, which was defined as the administration of more than 10 units of red cells within 24 hours after surgery. As part of the primary outcome, we also included repeat surgery due to hemorrhage or cardiac tamponade starting within the first 24 hours after protamine administration and death from hemorrhage during the 30-day study period.

Secondary outcomes included in-hospital death, death from any cause at 30 days, and life-threatening or serious adverse clinical events. The diagnosis of myocardial infarction was based on the presence of new Q waves in two contiguous electrocardiogram leads or confirmed graft occlusion within the first 30 days after surgery. Stroke was defined as a focal neurologic deficit lasting more than 24 hours. Renal failure was defined as the need for at least one dialysis treatment, a doubling of the baseline serum creatinine level, or a serum creatinine level of more than 150 μmol per liter (1.7 mg per deciliter). Respiratory failure was defined as the need for invasive mechanical ventilation for more than 48 hours. Cardiogenic shock was defined as the need for vasopressors and inotropic agents, a balloon pump, or a ventricular-assist device for more than 48 hours.

Tertiary outcomes included the rate of death in the intensive care unit (ICU) and at hospital discharge, the use of red cells and other blood components, and the length of hospital stay. Patients who were not admitted to an ICU were assigned an ICU length of stay of 0. We defined the length of hospital stay as the discharge date minus the surgery date plus 1 day.

An independent adjudication committee, whose members were unaware of study-group assignment, reviewed all deaths to assign a primary cause of death as well as to determine whether death was associated with hemorrhage, thrombosis, or renal failure. Causes of death were grouped post hoc as cardiac or noncardiac. Cardiac causes

consisted of congestive heart failure, cardiogenic shock, myocardial infarction, and right ventricular failure. Noncardiac causes included hemorrhage, stroke, sepsis or multiorgan failure, and other or unknown causes.

STATISTICAL ANALYSIS

We hypothesized that aprotinin would be superior to both tranexamic acid and aminocaproic acid, the two primary comparisons. We determined that we would need 990 patients per group, or a total of 2970 patients, who were undergoing high-risk cardiac surgery to detect an absolute difference of 3 percentage points (from 6% to 3%) in the incidence of massive postoperative bleeding between patients receiving aprotinin and those receiving each of the other two antifibrinolytic agents, assuming a power of 80% with a two-sided alpha value of less than 0.05 (i.e., an overall two-sided alpha error of less than 0.025 with the use of the Bonferroni correction) and a noncompliance rate of 1%.

In addition to the final analysis, we performed two planned interim analyses of the primary clinical outcome and important safety outcomes when 33% and 66% of patients, respectively, were accrued. We conducted the three sequential analyses with the use of the O'Brien–Fleming spending function.²⁴ The data and safety monitoring committee received the reports of the interim analyses as well as regular reports to assess serious adverse events. At its discretion, the committee could review study-group assignments.

All patients were followed for 6 months. In this study, we report on the first 30 days from the time of randomization. We conducted primary analyses according to the intention-to-treat principle. We assessed baseline characteristics of patients in the three study groups with the use of frequency distributions and univariable descriptive statistics, including measures of central tendency and dispersion.

For our primary analyses, we conducted two pairwise comparisons of the proportion of patients with massive postoperative bleeding (aprotinin vs. tranexamic acid and aprotinin vs. aminocaproic acid) with the use of the chi-square test. We calculated unadjusted relative risks with 95% confidence intervals for each comparison. As a means of correcting for two primary comparisons, we also compared overall massive bleeding and each of its components with the use of 97.5%

Figure 1 (facing page). Enrollment and Outcomes.

In each of the three study groups, patients who were ineligible according to the study protocol because of changes in the surgical procedure or in the patient's condition after randomization were included in the intention-to-treat analysis: 30 in the aprotinin group, 25 in the tranexamic acid group, and 28 in the aminocaproic acid group. CABG denotes coronary-artery bypass grafting, and INR international normalized ratio.

confidence intervals. We used logistic-regression models to further elucidate the measure of effect while adjusting for potentially confounding variables, including operative procedure, age, sex, presence of coexisting illnesses, preoperative use of aspirin, and the risk score of the American Society of Anesthesiologists (ASA), which ranges from 1 (healthy and low risk) to 5 (moribund and high risk).

For the secondary outcomes of death and serious adverse events, we conducted pairwise chi-square tests to ascertain the relation between aprotinin and tranexamic acid and between aprotinin and aminocaproic acid. For analyses with cell sizes of less than 5, we used Fisher's exact test. As with the primary outcome analysis, we calculated unadjusted relative risks of death with 95% confidence intervals for each of the two comparisons, as well as mortality estimates with the use of logistic-regression models to adjust for possibly confounding factors, including operative procedure, age, sex, presence of coexisting illnesses, preoperative use of aspirin, and the ASA risk score. We compared pairwise differences in the time to death between the study groups with the use of log-rank tests. A priori subgroup analyses for our primary outcome and for death included the type of procedure, age, sex, presence of coexisting illnesses, aspirin use, baseline hemoglobin level, and the ASA risk score.

We conducted additional analyses to better understand the influence of cointerventions, compliance, and loss to follow-up on the robustness of the intention-to-treat analysis. These studies included an analysis of primary and secondary outcomes in which only patients who completed the study per the protocol were included, an analysis in which we substituted death from massive hemorrhage with death from any cause at 30 days for the primary outcome, and an analysis in which we assessed death from any cause at 30 days among patients who did and did not meet

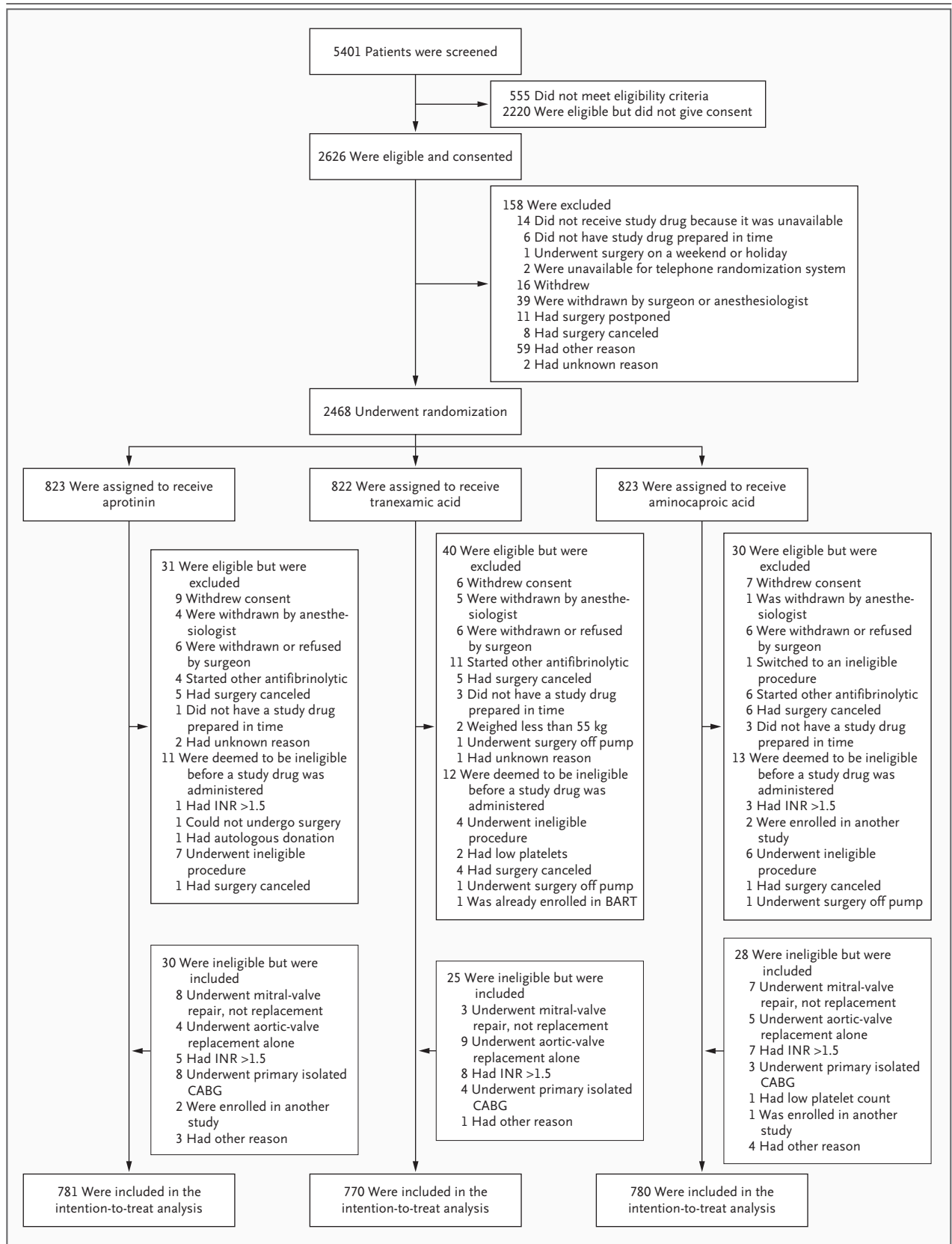


Table 1. Demographic, Clinical, and Surgical Characteristics of the Patients.*

Characteristic	Aprotinin (N=781)	Tranexamic Acid (N=770)	Aminocaproic Acid (N=780)
Demographic			
Age — yr	67.0±10.8	66.9±11.4	66.6±10.8
Male sex — no. (%)	543 (69.5)	562 (73.0)	569 (72.9)
Weight — kg	80.5±17.0	81.5±17.7	82.1±17.3
Height — cm	167.3±16.1	167.8±15.0	168.8±15.0
Clinical			
Coexisting illness — no. (%)			
Disabling stroke	12 (1.5)	17 (2.2)	24 (3.1)
Previous thromboembolism	31 (4.0)	31 (4.0)	31 (4.0)
Severe lung disease	57 (7.3)	40 (5.2)	45 (5.8)
Chronic renal dysfunction	41 (5.2)	58 (7.5)	43 (5.5)
Severe liver disease	1 (0.1)	3 (0.4)	1 (0.1)
Diabetes mellitus	185 (23.7)	180 (23.4)	194 (24.9)
Cancer	79 (10.1)	106 (13.8)	86 (11.0)
Other illness	357 (45.7)	334 (43.4)	329 (42.2)
Previous myocardial infarction — no. (%)	212 (27.1)	228 (29.6)	219 (28.1)
Angina — no./total no. (%)			
Any history	394/781 (50.4)	405/769 (52.7)	396/778 (50.9)
Canadian Cardiovascular Society class [†]			
III	167 (48.0)	150 (44.4)	168 (49.1)
IV	56 (16.1)	63 (18.6)	44 (12.9)
Congestive heart failure — no. (%)			
Any history	313 (40.1)	313 (40.6)	287 (36.8)
New York Heart Association class [‡]			
III	149 (55.4)	152 (57.6)	155 (59.8)
IV	31 (11.5)	32 (12.1)	22 (8.5)
Poor left ventricular function [§]	67 (8.6)	87 (11.3)	76 (9.7)
Surgical			
Type of surgery — no./total no. (%)			
Elective	631/781 (80.8)	618/770 (80.3)	633/779 (81.3)
Urgent	150 (19.2)	151 (19.6)	145 (18.6)
Emergency	0	1 (0.1)	1 (0.1)
Type of procedure — no. (%)			
Repeat CABG	76 (9.7)	94 (12.2)	89 (11.4)
CABG plus other procedure	438 (56.1)	427 (55.5)	417 (53.5)
Other procedure	267 (34.2)	249 (32.3)	274 (35.1)
Duration of surgery — hr	4.2±1.6	4.2±1.6	4.4±1.7

Table 1. (Continued.)

Characteristic	Aprotinin (N = 781)	Tranexamic Acid (N = 770)	Aminocaproic Acid (N = 780)
Total cross-clamp time — hr	1.7±0.7	1.7±0.8	1.8±0.8
Preoperative hemoglobin — no./total no. (%)			
<11.0 g/dl	57/780 (7.3)	49/763 (6.4)	48/776 (6.2)
11.0–14.0 g/dl	385 (49.4)	404 (52.9)	380 (49.0)
>14.0 g/dl	338 (43.3)	310 (40.6)	348 (44.8)
Preoperative drug therapy			
Cardiac therapy — no. (%)			
Digoxin or digitalis	91 (11.7)	79 (10.3)	83 (10.6)
ACE inhibitor	369 (47.2)	355 (46.1)	368 (47.2)
Nitrates	199 (25.5)	205 (26.6)	188 (24.1)
Beta-blocker	397 (50.8)	430 (55.8)	419 (53.7)
Calcium-channel blocker	221 (28.3)	199 (25.8)	211 (27.1)
Diuretic	359 (46.0)	334 (43.4)	316 (40.5)
Other antiarrhythmic agent	78 (10.0)	69 (9.0)	70 (9.0)
Anticoagulant — no. (%)			
Heparin — U/day			
≤10,000	29 (3.7)	19 (2.5)	17 (2.2)
>10,000	84 (10.8)	71 (9.2)	68 (8.7)
Low-molecular-weight	32 (4.1)	44 (5.7)	45 (5.8)
Warfarin	101 (12.9)	96 (12.5)	95 (12.2)
Other anticoagulant	4 (0.5)	6 (0.8)	6 (0.8)
Antiplatelet agent — no./total no. (%)			
Low-dose aspirin			
None	397/770 (51.6)	409/763 (53.6)	399/773 (51.6)
≤325 mg/day	352/770 (45.7)	345/763 (45.2)	357/773 (46.2)
>325 mg/day	20/770 (2.6)	7/763 (0.9)	16/773 (2.1)
Glycoprotein IIa/IIIb receptor inhibitor	3 (0.4)	6 (0.8)	11 (1.4)
Other agent	36 (4.6)	40 (5.2)	26 (3.3)
Thrombolytic agent — no. (%)			
Tissue plasminogen activator	0	1 (0.1)	0
Streptokinase	0	2 (0.3)	0
Other agent	0	1 (0.1)	1 (0.1)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and CABG coronary-artery bypass grafting.

† The percentages of patients in this category were calculated by using the number of patients with a history of angina and congestive heart failure as the denominator: 348 in the aprotinin group, 338 in the tranexamic acid group, and 342 in the aminocaproic acid group.

‡ The percentages of patients in this category were calculated by using the number of patients with New York Heart Association class III or IV as the denominator: 269 in the aprotinin group, 264 in the tranexamic acid group, and 259 in the aminocaproic acid group.

§ Poor left ventricular function was defined as a left ventricular ejection fraction of less than 30%.

our primary outcome of massive bleeding. We report uncorrected P values or 95% confidence intervals.

RESULTS

STUDY POPULATION

Of the 5401 patients who underwent screening, 555 did not meet the eligibility criteria. In addition, 2220 patients or their surgeon or anesthesiologist did not provide consent. Of the 2626 patients for whom consent was obtained, 158 did not undergo randomization (Fig. 1).

Of the 2331 patients who were included in the intention-to-treat analysis, 781 were in the aprotinin group, 770 were in the tranexamic acid group, and 780 were in the aminocaproic acid group. Three patients who were discharged from the hospital before 30 days (two in the aprotinin group and one in the tranexamic acid group) withdrew consent, so we did not know their survival status at 30 days. We did not have any outcome data, except for mortality status, for one patient in the aprotinin group. Sixteen patients received a study drug that differed from their assigned drug. Unblinding occurred for 12 patients in the aprotinin group, 11 in the tranexamic acid group, and 9 in the aminocaproic acid group. The study groups were similar at baseline with respect to all important clinical and demographic characteristics (Table 1).

The study was terminated on October 16, 2007, on the recommendation of the independent data and safety monitoring committee. The committee advised termination because of a strong trend toward higher mortality in the aprotinin group than in the other two groups on the basis of interim data for 2163 patients (see the Supplementary Appendix).

MASSIVE BLEEDING

A total of 261 of 2330 patients (11.2%) met our definition for massive bleeding. Among patients in the aprotinin group, 74 (9.5%) had massive bleeding, as compared with 93 (12.1%) in the tranexamic acid group and 94 (12.1%) in the aminocaproic acid group (relative risk of aprotinin in both comparisons, 0.79; 95% confidence interval [CI], 0.59 to 1.05) (Table 2, and Table 1 in the Supplementary Appendix). The use of 97.5% confidence intervals increased the upper boundary of the interval from 1.05 to 1.09 (Table 2 in the Supplementary Appendix). Adjustment for the effect of important clinical factors did not alter the magnitude of the effect comparing aprotinin with tranexamic acid (adjusted odds ratio, 0.78; 95% CI, 0.56 to 1.08) and aminocaproic acid (adjusted odds ratio, 0.80; 95% CI, 0.58 to 1.11).

The relative risk of massive bleeding among patients receiving aprotinin, as compared with both groups receiving lysine analogues combined, was 0.79 (95% CI, 0.61 to 1.01). The rates of the various components of the composite outcome are listed in Table 2. Multivariable analysis with adjustment for the effect of many variables did not modify crude estimates. Rates of massive bleeding in various major subgroups are presented in Table 3.

DEATH AND OTHER ADVERSE OUTCOMES

A total of 108 of 2331 patients (4.6%) died within 30 days after study randomization. The 30-day rate of death from any cause was 6.0% in the aprotinin group, as compared with 3.9% in the tranexamic acid group (relative risk, 1.55; 95% CI, 0.99 to 2.42) and 4.0% in the aminocaproic acid group (relative risk, 1.52; 95% CI, 0.98 to 2.36) (Table 3, and Table 3 in the Supplementary Appendix). The survival experience is illustrated in

Table 2. The Components of Massive Postoperative Bleeding in the Patients.*

Components	Aprotinin (N = 780)	Tranexamic Acid (N = 770)	Aminocaproic Acid (N = 780)	Aprotinin vs.	
				Tranexamic Acid	Aminocaproic Acid
				relative risk (95% confidence interval)	
Bleeding from chest tubes	41 (5.3)	58 (7.5)	65 (8.3)	0.70 (0.47–1.03)	0.63 (0.43–0.92)
Massive transfusion	16 (2.1)	17 (2.2)	22 (2.8)	0.93 (0.47–1.83)	0.73 (0.38–1.37)
Death due to hemorrhage	11 (1.4)	8 (1.0)	4 (0.5)	1.36 (0.55–3.36)	2.75 (0.88–8.60)
Reoperation for bleeding	43 (5.5)	62 (8.1)	64 (8.2)	0.68 (0.47–1.00)	0.67 (0.46–0.98)
Any massive bleeding	74 (9.5)	93 (12.1)	94 (12.1)	0.79 (0.59–1.05)	0.79 (0.59–1.05)

* Patients could have more than one component.

Table 3. Massive Bleeding and 30-Day Mortality in Major Subgroups of Patients.*

Major Subgroup	Massive Bleeding		30-Day Mortality	
	Aprotinin vs. Tranexamic Acid	Aprotinin vs. Aminocaproic Acid	Aprotinin vs. Tranexamic Acid	Aprotinin vs. Aminocaproic Acid
<i>relative risk (95% CI)</i>				
All patients	0.79 (0.59–1.05)	0.80 (0.60–1.07)	1.55 (0.99–2.42)	1.52 (0.98–2.36)
Sex				
Male	0.85 (0.61–1.19)	0.86 (0.62–1.21)	1.71 (0.95–3.10)	1.34 (0.78–2.31)
Female	0.63 (0.35–1.12)	0.61 (0.35–1.09)	1.27 (0.64–2.51)	1.87 (0.87–4.05)
Age				
<65	0.82 (0.50–1.35)	0.77 (0.47–1.24)	3.42 (1.14–10.26)	1.80 (0.77–4.24)
65 to <75	0.81 (0.51–1.29)	0.86 (0.54–1.37)	1.72 (0.81–3.65)	2.27 (1.00–5.14)
75 to <80	0.77 (0.41–1.44)	0.81 (0.42–1.56)	1.53 (0.56–4.19)	0.83 (0.35–1.97)
≥80	0.56 (0.18–1.77)	0.51 (0.16–1.60)	0.67 (0.26–1.74)	1.22 (0.39–3.78)
Type of procedure				
Repeat CABG	1.03 (0.33–3.25)	0.73 (0.25–2.14)	2.51 (0.78–8.01)	2.37 (0.74–7.57)
CABG plus ≥1 procedure	0.78 (0.53–1.13)	0.84 (0.57–1.23)	1.55 (0.86–2.81)	1.29 (0.73–2.26)
Other	0.74 (0.45–1.20)	0.72 (0.45–1.16)	1.24 (0.53–2.90)	1.76 (0.70–4.40)
Baseline use of aspirin				
None	0.95 (0.61–1.48)	0.93 (0.59–1.44)	1.72 (0.92–3.22)	3.16 (1.44–6.91)
Any	0.68 (0.46–0.99)	0.71 (0.48–1.03)	1.39 (0.73–2.64)	0.96 (0.55–1.69)
Coexisting illness				
None	1.25 (0.74–2.12)	0.88 (0.55–1.41)	4.40 (1.28–15.15)	2.42 (0.94–6.20)
Any	0.64 (0.45–0.91)	0.73 (0.51–1.06)	1.24 (0.76–2.03)	1.30 (0.78–2.15)
Baseline hemoglobin (g/dl)				
<11.0	0.98 (0.38–2.51)	1.12 (0.42–3.01)	2.15 (0.72–6.42)	2.11 (0.70–6.29)
11.0 to 14.0	0.68 (0.46–1.02)	0.75 (0.50–1.14)	1.10 (0.61–1.97)	0.99 (0.56–1.76)
>14.0	0.95 (0.59–1.53)	0.78 (0.50–1.21)	2.76 (1.01–7.50)	3.10 (1.14–8.43)
Baseline ASA score†				
<4	0.74 (0.48–1.15)	0.76 (0.49–1.18)	2.18 (0.95–5.04)	1.58 (0.75–3.36)
≥4	0.87 (0.59–1.30)	0.87 (0.59–1.29)	1.34 (0.78–2.32)	1.61 (0.90–2.87)

* ASA denotes American Society of Anesthesiologists, and CABG coronary-artery bypass grafting.

† The ASA score ranges from 1 to 5, with higher numbers indicating greater risk.

Figure 2. The relative risk of death of patients receiving aprotinin, as compared with the combined rate of 3.9% in the two groups receiving lysine analogues, was 1.53 (95% CI, 1.06 to 2.22) (see the Supplementary Appendix).

Of 2328 patients who were included in the analysis for the cause of death, 25 deaths (3.2%) were attributed to a cardiac cause in the aprotinin group, as compared with 10 (1.3%) in the tranexamic acid group (relative risk, 2.47; 95% CI, 1.19 to 5.10) and 13 (1.7%) in the aminocaproic acid group (relative risk, 1.93; 95% CI, 0.99 to 3.74) (Table 4). Aprotinin was associated with an

increased risk of death from a cardiac cause (relative risk, 2.19; 95% CI, 1.25 to 3.84) when both lysine-analogue groups were combined. Deaths attributed to other causes were similar in the three study groups. All rates of adverse events, including stroke, myocardial infarction, and renal failure and dysfunction, and rates of organ failure were also similar in the three groups (Table 5).

TRANSFUSION OUTCOMES

Overall, 1439 of 2330 patients (61.8%) received at least 1 unit of red cells: 419 of 780 (53.7%) in the aprotinin group, 506 of 770 (65.7%) in the tran-

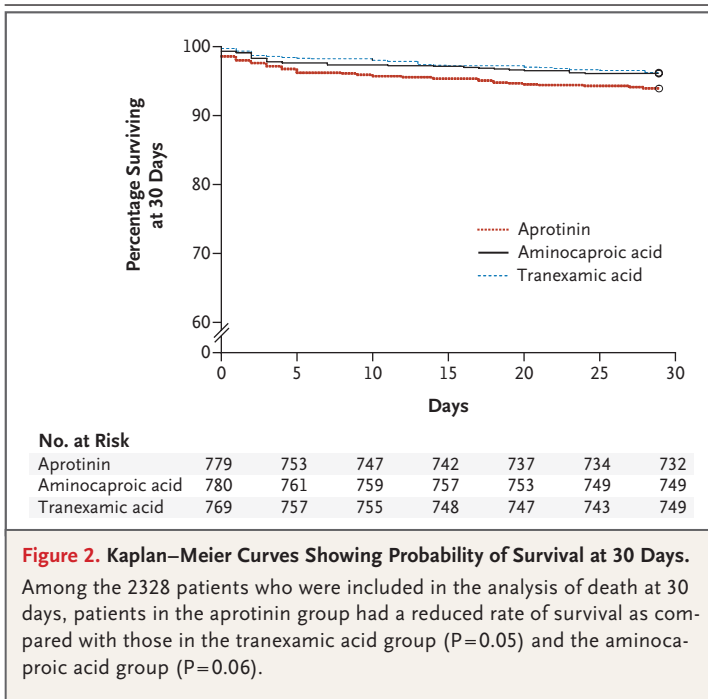


Figure 2. Kaplan–Meier Curves Showing Probability of Survival at 30 Days.

Among the 2328 patients who were included in the analysis of death at 30 days, patients in the aprotinin group had a reduced rate of survival as compared with those in the tranexamic acid group ($P=0.05$) and the aminocaproic acid group ($P=0.06$).

examic acid group, and 514 of 780 (65.9%) in the aminocaproic acid group (Table 4 in the Supplementary Appendix). In the aprotinin group, the relative risk of any red-cell transfusion was 0.82 (95% CI, 0.75 to 0.89) as compared with the tranexamic acid group and 0.81 (95% CI, 0.75 to 0.88) as compared with the aminocaproic acid group. In the aprotinin group, the risk of exposure to other blood products (except platelets) was similar to that in the tranexamic acid group and lower than in the aminocaproic acid group.

LENGTH OF STAY

The median length of stay in the ICU in the aprotinin group was 1.2 days (interquartile range, 0.9 to 3.0), as compared with 1.5 days (interquartile range, 0.9 to 3.0) in the tranexamic acid group ($P=0.16$) and 1.8 days (interquartile range, 0.9 to 3.0) in the aminocaproic acid group ($P=0.02$). The median length of the hospital stay in the aprotinin group was 8.0 days (interquartile range, 7.0 to 12.0), as compared with 8.5 days (interquartile range, 7.0 to 12.0) in the tranexamic acid group ($P=0.22$) and 8.0 days (interquartile range, 7.0 to 12.0) in the aminocaproic acid group ($P=0.17$).

SENSITIVITY ANALYSES

The censoring of data from 16 patients who did not follow the treatment protocol did not appre-

ciably change any of the measures of effect. For the primary outcome, when we substituted death from any cause at 30 days for death from hemorrhage, the relative risk associated with aprotinin increased to 0.93 (95% CI, 0.72 to 1.20) as compared with tranexamic acid and to 0.87 (95% CI, 0.68 to 1.11) as compared with aminocaproic acid. In the comparison between aprotinin and tranexamic acid, the relative risk of death from any cause at 30 days was 1.57 (95% CI, 0.88 to 2.81) among patients who had the primary outcome of massive bleeding and 1.85 (95% CI, 0.98 to 3.50) among those who did not have this primary outcome ($P=0.91$ by the Breslow–Day test for homogeneity of strata). In the comparison between aprotinin and aminocaproic acid, the relative risk of death from any cause at 30 days was 2.82 (95% CI, 1.37 to 5.83) among those who had the primary outcome of massive bleeding and 1.20 (95% CI, 0.69 to 2.08) among those who did not have this primary outcome ($P=0.04$ by the Breslow–Day test for homogeneity of strata).

DISCUSSION

Among patients undergoing high-risk cardiac surgery, we documented an increase of 2 percentage points in the rate of death (from approximately 4% to 6%) among patients receiving aprotinin, as compared with those receiving either tranexamic acid or aminocaproic acid. The observed increase in mortality translates into a number needed to harm of 50 patients. When we compared the combined mortality rates in the lysine-analogue groups with the rate in the aprotinin group, we noted a significant absolute increase of 2.1%, or a relative increase of 54%, in the number of deaths in the aprotinin group.

We conducted a number of additional analyses to better understand how aprotinin may have caused excess deaths. Of the 108 patients who died, the proportion who were believed to have died of cardiogenic shock, right ventricular failure, congestive heart failure, or myocardial infarction was higher in the aprotinin group than in the other two groups. Among the adjudicated deaths, the use of aprotinin was associated with a significant doubling of the risk of death from cardiac causes, as compared with the use of tranexamic acid or aminocaproic acid. Although all the deaths were clinically adjudicated in our trial, without detailed autopsies and coronary angio-

Table 4. Adjudicated Primary Cause of 108 Deaths.

Primary Cause of Death	Overall (N=2328)*	Aprotinin (N=779)	Tranexamic Acid (N=769)		Aminocaproic Acid (N=780)		Aprotinin vs. Tranexamic Acid	Aprotinin vs. Aminocaproic Acid
			<i>no. of events (%)</i>		<i>no. of events (%)</i>			
Cardiac cause of death								
Any	48 (2.1)	25 (3.2)	10 (1.3)		13 (1.7)		2.47 (1.19–5.10)	1.93 (0.99–3.74)
Congestive heart failure	5 (0.2)	1 (0.1)	2 (0.3)		2 (0.3)		0.49 (0.04–5.43)	0.50 (0.05–5.51)
Cardiogenic shock	19 (0.8)	9 (1.2)	3 (0.4)		7 (0.9)		2.96 (0.80–10.90)	1.29 (0.48–3.44)
Myocardial infarction	14 (0.6)	8 (1.0)	3 (0.4)		3 (0.4)		2.63 (0.70–9.89)	2.67 (0.71–10.03)
Right ventricular failure	10 (0.4)	7 (0.9)	2 (0.3)		1 (0.1)		3.46 (0.72–16.58)	7.01 (0.86–56.83)
Noncardiac cause of death								
Any	60 (2.6)	22 (2.8)	20 (2.6)		18 (2.3)		1.09 (0.60–1.97)	1.22 (0.66–2.26)
Hemorrhage	20 (0.9)	8 (1.0)	8 (1.0)		4 (0.5)		0.99 (0.37–2.62)	2.00 (0.61–6.62)
Stroke	10 (0.4)	1 (0.1)	4 (0.5)		5 (0.6)		0.25 (0.03–2.21)	0.20 (0.02–1.71)
Sepsis or multiorgan failure	17 (0.7)	6 (0.8)	5 (0.7)		6 (0.8)		1.18 (0.36–3.87)	1.00 (0.32–3.09)
Other or unknown	13 (0.6)	7 (0.9)	3 (0.4)		3 (0.4)		2.30 (0.60–8.87)	2.34 (0.61–9.00)

* Of the 2331 patients in the intention-to-treat analysis, 3 were not evaluated for cause of death because they withdrew consent and were discharged from the hospital before 30 days (2 in the aprotinin group and 1 in the tranexamic acid group).

Table 5. Major Secondary Outcomes.

Adverse Event	Aprotinin		Tranexamic Acid		Aminocaproic Acid		Aprotinin vs. Tranexamic Acid	Aprotinin vs. Aminocaproic Acid
	<i>no. of patients</i>	<i>events (%)</i>	<i>no. of patients</i>	<i>events (%)</i>	<i>no. of patients</i>	<i>events (%)</i>		
Stroke	759	22 (2.9)	753	28 (3.7)	768	22 (2.9)	0.78 (0.45–1.35)	1.01 (0.57–1.81)
Myocardial infarction	717	33 (4.6)	727	28 (3.9)	735	20 (2.7)	1.19 (0.73–1.95)	1.69 (0.98–2.92)
Deep-vein thrombosis or pulmonary embolism	712	9 (1.3)	718	8 (1.1)	729	7 (1.0)	1.00 (0.99–1.01)	1.00 (0.97–1.01)
Respiratory failure	771	96 (12.5)	769	100 (13.0)	776	98 (12.6)	0.96 (0.74–1.24)	0.99 (0.76–1.28)
Cardiac shock	772	112 (14.5)	769	112 (14.6)	778	119 (15.3)	1.00 (0.78–1.27)	0.95 (0.75–1.20)
Renal failure								
Preexisting condition								
Any	770	129 (16.8)	766	137 (17.9)	774	132 (17.1)	0.94 (0.75–1.17)	0.98 (0.79–1.23)
Doubling of baseline creatinine level	772	49 (6.3)	766	34 (4.4)	773	38 (4.9)	1.43 (0.93–2.19)	1.29 (0.86–1.95)
Postoperative creatinine level >150 μmol/liter	772	119 (15.4)	767	125 (16.3)	775	124 (16.0)	0.95 (0.75–1.19)	0.96 (0.76–1.21)
Postoperative dialysis	773	24 (3.1)	769	24 (3.1)	778	21 (2.7)	0.99 (0.57–1.74)	1.15 (0.65–2.05)
New condition								
Any	770	102 (13.2)	766	97 (12.7)	774	100 (12.9)	1.05 (0.81–1.36)	1.03 (0.79–1.33)
Doubling of baseline creatinine level	772	47 (6.1)	766	31 (4.0)	773	35 (4.5)	1.50 (0.97–2.34)	1.34 (0.88–2.06)
Postoperative creatinine level >150 μmol/liter	772	92 (11.9)	767	86 (11.2)	775	93 (12.0)	1.06 (0.81–1.40)	0.99 (0.76–1.30)
Postoperative dialysis	773	16 (2.1)	769	19 (2.5)	778	11 (1.4)	0.84 (0.43–1.62)	1.46 (0.68–3.13)

grams in all patients we had no means of confirming the primary cause of death.

The complications repeatedly mentioned as a concern in observational studies of aprotinin were renal injury and renal failure.^{15,17} In our study, the use of aprotinin did not significantly increase the risk of renal failure or the need for postoperative renal replacement despite an increase in the proportion of patients who had a doubling of serum creatinine levels. Given the low rates in all three study groups, it is possible that we missed a small increase in the risk of renal dialysis associated with aprotinin. In addition, the adjudication of death did not identify renal failure as contributing to or causing death associated with aprotinin use. A meta-analysis by Brown and colleagues showed a nonsignificant relative risk of renal failure with high-dose aprotinin.¹⁹ As in our study, the authors noted a significant increase in the relative risk of doubling the postoperative serum creatinine levels.

Although aprotinin is potentially more effective than other active agents in controlling hemostasis, we noted only a possible trend suggesting that it decreased massive bleeding, our primary outcome. However, a cautious interpretation of this trend is warranted. When we corrected for multiple comparisons, the upper bounds of the 97.5% confidence intervals included as much as a 9% decrease in massive bleeding with the use

of either tranexamic acid or aminocaproic acid. Also, only repeat surgeries and important blood losses through chest tubes, one of the main indications for surgery, were potentially improved by the use of aprotinin. The two other components of the primary outcome were not improved. Finally, aprotinin did not appear to prevent massive bleeding or save the life of patients who had massive bleeding.

A limitation of our trial was that we included patients who were undergoing high-risk cardiac surgery rather than the approved indication for aprotinin. Therefore, our inferences are primarily limited to high-risk patients. However, the results of subgroup analyses suggest that the adverse effects on mortality associated with aprotinin may also have been present among healthier patients, those under the age of 65 years, and those without coexisting illnesses at the time of surgery.

In summary, despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin as compared with lysine analogues precludes its use in patients undergoing high-risk cardiac surgery.

Supported by the Canadian Institutes of Health Research and the Ontario Ministry of Health and Long Term Care.

Drs. Mazer and Murkin report receiving consulting fees and lecture fees from Bayer, and Dr. Fremes, receiving lecture fees from Bayer. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The Canadian investigators who participated in BART are as follows: **Trial Executive Committee:** P.C. Hébert (cochair), D.A. Fergusson (cochair), C.D. Mazer, S. Fremes, C. MacAdams, J.M. Murkin, K. Teoh, P.C. Duke, R. Arellano, M.A. Blajchman, J.S. Bussi eres, D. C ot e, J. Karski, R. Martineau, J.A. Robblee, M. Rodger, G. Wells, R. Pretorius. **Writing Committee:** D.A. Fergusson (cochair), P.C. H ebert (cochair), C.D. Mazer, S. Fremes, C. MacAdams, J.M. Murkin, K. Teoh, P.C. Duke. **Adjudication Committee:** P.C. H ebert (chair), R. Arellano, A. Denault, S. Fremes, C. MacAdams. **BART Investigators and Steering Committee:** *Centre Hospitalier Universitaire de Sherbrooke-H opital Fleurimont, Sherbrooke, QC:* R. Martin; *Foothills Medical Centre, Calgary, AB:* C. MacAdams; *Ottawa Heart Institute, Ottawa:* J.A. Robblee; *H opital Laval, Laval, QC:* D. C ot e, J. Bussi eres; *Institute de Cardiologie de Montr eal, Montreal:* A. Denault, A. Rochon, R. Martineau; *Kingston General Hospital, Kingston, ON:* J.P. Cain; *London Health Sciences Centre, London, ON:* J.M. Murkin; *Jewish General Hospital, Montreal:* F. B eique; *Capital Health, QEII Health Sciences Centre, Halifax, NS:* R. Arellano, G. Hirsch; *St. Michael's Hospital, Toronto:* C.D. Mazer; *Sudbury Regional Hospital, Sudbury, ON:* S. Mathur; *Sunnybrook Health Sciences Centre, Toronto:* S. Fremes; *Toronto Hospital, Toronto:* J. Karski; *Walter C. McKenzie Health Sciences Centre, Edmonton, AB:* B. Finegan; *Vancouver General Hospital, Vancouver, BC:* D. Ansley; *Victoria Heart Institute Foundation, Victoria, BC:* G.E. Townsend; *Hamilton Health Sciences Centre, Hamilton, ON:* K. Teoh; *Winnipeg Health Sciences Centre, Winnipeg, MB:* P.C. Duke; *St. Boniface Hospital, Winnipeg, MB:* R. Friesen, T.W.R. Lee, R. Hudson. **Data and Safety Monitoring Committee:** A. Laupacis (chair), Toronto; J.F. Hardy, Montreal; C. Pelletier, Montreal; R. Roberts, Hamilton. **Independent Trial Statistician:** J. Clinch. **Site Participating Investigators:** *Centre Hospitalier Universitaire de Sherbrooke-H opital Fleurimont:* D. B erard, S. Coutu,  . de M edicis, D. Greentree, X. Mueller, M. Martin; *Foothills Medical Centre:* D. Seal, A. Maitland, C. Bands, B. Caton, R. Chun, J. Haigh, D. Ha, G. Hopper, R. Kowalewski, W. Mansell, D. Sirounis, T. Tang, J. Appoo, A. Bayes, J. Burgess, P. Fedak, W. Kidd, G. Prystay; *Ottawa Heart Institute:* B. MacDonald, H. Nathan, T. Mesana; *H opital Laval:* M. Beauvais, S. Blackburn, D. Duperey, P. Laflamme, D. Marcotte, A. Martineau, J.-M. Ouellet, F. Parent, S. St.-Onge, A. St. Pierre, J. Villeneuve, M. Rheault; *Institute de Cardiologie de Montr eal:* S. B elisle, R. Blain, J. Taillefer, P. Couture, J. Cogan, G. Hemmings, C. Ayoub, J.-S. Lebon, B. Qizilbash, A. Deschamps, M. Pellerin; *Kingston General Hospital:* R. Arellano, M. Cummings, M. Fleming, R. Henry, B. Milne, J. Parlow, T. Saha, S. Shelley, L. Wang; *London Health Sciences Centre:* D. Bainbridge, R. Novick, N. McKenzie, A. Menkis, M. Quantz, N. Badner, D. Cheng, S. Dain, W. Dobkowski, J. Granton, C. Harle, I. Iglesias, J. Kutt, B. Mezon, F. Ralley, M. St. Amand, R. Teneja, A. Vannelli; *Jewish General Hospital:* J.-F. Morin, Y. Langlois, F. Ma; *Capital Health, QEII Health Sciences Centre:* B. Kent, C. Allen, R. Barker, J. Glenn, K. Hirsch, P. Kolysher, A. Vlatten, I. Rapchuk, R. Hall, C. DiQuinzio, A. Dickliosen, R. Baskett, K. Stewart, J. Sullivan, J.F. Legare, I. Ali, S. O'Blenes, C. Hancock-Friesen, J. Wood, I. Ali; *St. Michael's Hospital:* G. Hare, S. Abrahamson, J. Baker, D. Bonneau, R. Bowry, R. Chen, W. Darrach, J. Dickson, L. Errett, P. Houston, H. Joo, M. Kataoka, S. Lambert, D. Latter, Y. Leclerc, P. Leung, R. Levene, K.

Lin, C. Loffelmann, D. McKnight, J. McLean, V. Naik, W. Noble, C. Tousignant, S. Verma, J. Wassermann; *Sunnybrook Health Sciences Centre*: G. Cohen, G. Christakis, S. O'Blenes, B. Goldman; *Toronto University Health Networks*: G. Djaiani, L. Fedorko, D. Cheng, T. Yau, R. Cusimano, C. Feindel, S. Brister, T. David, V. Rao, H. Scully, A. Ralph-Edwards; *Walter C. McKenzie Health Sciences Centre*: M. Kruger, D. Modry, S. Wang, E. Gelfand, J. Mullen, A. Koshal, D. Ross; *Vancouver General Hospital*: M. Lampa; *Victoria Heart Institute Foundation*: J. Allison, N. Fenje, G. Wollach, S. Willms, M. Van Der Wal, G. Moll, J. Dutton, R.T. Brownlee, J. Ofeish, M. Perchinsky; *Hamilton Health Sciences Centre*: L. Abouzahr, F.V. Chu, I.J. Cybulsky, A. Lamy, L.C. Semelhago; *Winnipeg Health Sciences Centre*: B. Muirhead, R. DeBrouwere, J. Enns, S. Kowalski, D. Maguire, M. Raabe, W. Lindsay; *St. Boniface Hospital*: I. Thomson, D. Peters, S. MacKenzie, J. Scatliff, S. Young, D. Maguire, E. Jacobsohn, J. Enns, J. Zivot, H. Grocott, S. Kowalski, R. DeBrouwere, C. Christodoulou. **Site Coordinators**: *Centre Hospitalier Universitaire de Sherbrooke-Hôpital Fleurimont*: L. Laroche, S. Croteau, V. Gagnon, R. Gagnon; *Foothills Medical Centre*: K. Maier; *Ottawa Heart Institute*: S. Finlay, D. Winch; *Hôpital Laval*: L. Auclair, M.-C. Ferland, H. Dugas, L. Mercier, N. Gagné, M. Doucet, J. Soucy; *Institute de Cardiologie de Montréal*: M. Roy; *Kingston General Hospital*: D. Dumerton Shore, B. Orr; *London Health Sciences Centre*: S. Adams, B. Irwin, S. Squire, E. Pardy; *Jewish General Hospital*: M. Crecca, P. Chamoun; *Halifax Health Sciences Centre*: M. Rossiter, J. McIsaac; *St. Michael's Hospital*: N. Sikich, D. Michaud; *Sudbury Regional Hospital*: B. Gauthier, V. Chrapchynski, K. Vehkala, J. Whissel, R.A. Poirier, F. Gee, C. Dion; *Sunnybrook Health Sciences Centre*: M. Jamil, A. Piekos, M. Vallieres, N. Fountas, J. Vincent; *Toronto Hospital*: Y. Yang, H. Poonawala, J. Carroll; *Walter C. McKenzie Health Sciences Centre*: V. Wilkinson, C. Bryden; *Vancouver General Hospital*: N. Hsu, R. Fox; *Victoria Heart Institute Foundation*: L. Reimer; *Hamilton Health Sciences Centre*: M.H. Blackall; *Winnipeg Health Sciences Centre*: S. Kenny; *St. Boniface Hospital*: G. Darroch, R. Gerstein. **Site Pharmacy Staff**: *Centre Hospitalier Universitaire de Sherbrooke-Hôpital Fleurimont*: S. Cloutier; *Foothills Medical Centre*: J. Herrick, P. Matthes, C. Threinen, A. Kayll-Peters; *Ottawa Heart Institute*: J. Taichman; *Hôpital Laval*: N. Chateauvert, T. Grenier; *Institute de Cardiologie de Montréal*: M. Robitaille, A. Nguyen Raymond; *Kingston General Hospital*: C. Gray; *London Health Sciences Centre*: P. Psutka, M. Alexander; *Jewish General Hospital*: M. Martin, E. Cohen, J. Roy; *Capital Health, QEII Health Sciences Centre*: D. Snow; *St. Michael's Hospital*: L. Parsons, J. Proceviat; *Sudbury Regional Hospital*: L. Gibb; *Sunnybrook Health Sciences Centre*: S. Szick (January 2002–August 2002); D. Baird (August 2002–August 2003); R. Pretorius (August 2003–present). **Research Assistant**: D. Bleskie. **Data Verification and Data Management**: D. Bleskie, M.J. Kabir, C. Bordeleau; M.-L. Tran, M. Rhubab, I. McCue, S. Doucette, J. Coté, S. Domingo, A. Aziz, M. Stassen, D. Vetter, A. Coady. **Site Monitoring and Orientation**: K. Maier, M. Roy, M.-C. Ferland, I. Watpool; **Coordinating Center Secretarial Support**: N. Cleary, E. Nowakowska, L. Roy, L. Webb, T. Routh, C. Piché.

REFERENCES

1. Herbertson M. Recombinant activated factor VII in cardiac surgery. *Blood Coagul Fibrinolysis* 2004;15:Suppl 1:S31-S32.
2. Hardy JF, Perrault J, Tremblay N, Robitaille D, Blain R, Carrier M. The stratification of cardiac surgical procedures according to use of blood products: a retrospective analysis of 1480 cases. *Can J Anaesth* 1991;38:511-7.
3. Machiraju VR. How to avoid problems in redo coronary artery bypass. *J Card Surg* 2002;17:20-5.
4. Lytle BW, Loop FD, Cosgrove DM, et al. Fifteen hundred coronary reoperations: results and determinants of early and late survival. *J Thorac Cardiovasc Surg* 1987; 93:847-59.
5. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997;85:1258-67.
6. Fremes SE, Wong BI, Lee E, et al. Meta-analysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 1994;58:1580-8.
7. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007;4: CD001886.
8. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? *Clin Trials* 2005;2:218-29.
9. Levi M, Cromheecke ME, de Jonge E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;354:1940-7.
10. 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.
11. Fergusson D, Blair A, Henry D, et al. Technologies to minimize blood transfusion in cardiac and orthopedic surgery: results of a practice variation survey in nine countries. *Int J Technol Assess Health Care* 1999;15:717-28. [Erratum, *Int J Technol Assess Health Care* 2000;16:296.]
12. Graham ID, Fergusson D, McAuley L, Laupacis A. The use of technologies to minimize exposure to perioperative allogeneic blood transfusion in elective surgery: a survey of Canadian hospitals. *Int J Technol Assess Health Care* 2000;16: 228-41.
13. Carless PA, Moxey AJ, Stokes BJ, Henry DA. 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.
14. Umscheid CA, Kohl BA, Williams K. Antifibrinolytic use in adult cardiac surgery. *Curr Opin Hematol* 2007;14:455-67.
15. Shaw AD, Stafford-Smith M, White WD, et al. The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med* 2008;358:784-93.
16. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008;358:771-83.
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. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007;115:2801-13.
20. Karski JM, Dowd NP, Joiner R, et al. The effect of three different doses of tranexamic acid on blood loss after cardiac surgery with mild systemic hypothermia (32 degrees C). *J Cardiothorac Vasc Anesth* 1998;12:642-6.
21. Karski JM, Teasdale SJ, Norman P, et al. Prevention of bleeding after cardiopulmonary bypass with high-dose tranexamic acid: double-blind, randomized clinical trial. *J Thorac Cardiovasc Surg* 1995;110: 835-42.
22. Karski JM, Teasdale SJ, Norman PH, Carroll JA, Weisel RD, Glynn MF. Prevention of postbypass bleeding with tranexamic acid and epsilon-aminocaproic acid. *J Cardiothorac Vasc Anesth* 1993;7: 431-5.
23. Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). *J Thorac Cardiovasc Surg* 1989;97:364-72.
24. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.

Copyright © 2008 Massachusetts Medical Society.