

The Risk-Benefit Profile of Aprotinin Versus Tranexamic Acid in Cardiac Surgery

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BACKGROUND: Aprotinin is superior to other antifibrinolytic drugs for preventing major blood loss after cardiac surgery but may also increase perioperative mortality. It remains unclear whether its risk-benefit profile differs among low-, moderate-, and high-risk cardiac surgical patients.

METHODS: In this retrospective single-center cohort study, we included 15,365 patients who underwent cardiac surgery with cardiopulmonary bypass from 2000 to 2008. Of these, 1017 received aprotinin (6×10^6 U) and 14,358 received tranexamic acid (50–100 mg/kg). Propensity score methods were used to create a matched-pairs cohort ($n = 1544$) that adjusted for important between-group differences. The influence of patients' risk status on aprotinin's association with in-hospital mortality, morbidity, and blood loss was measured.

RESULTS: In the matched set, aprotinin was only associated with increased acute kidney injury ($>50\%$ decrease in estimated glomerular filtration or dialysis; odds ratio 1.5; 95% confidence interval [CI] 1.1–2.1). Patients' risk status significantly influenced the associations of aprotinin with mortality, acute kidney injury, and massive blood loss (transfusion of ≥ 10 U of red blood cells or need for surgical reexploration). Among high-risk patients, the respective odds ratios were 0.6 (CI 0.3–1.0), 1.1 (CI 0.7–1.7), and 0.7 (CI 0.4–1.04), and among low- to moderate-risk patients, they were 1.5 (CI 0.9–2.7), 2.2 (CI 1.4–3.5), and 1.2 (CI 0.9–1.07) (Breslow-Day test for homogeneity of odds ratios between high-risk versus low- to moderate-risk patients: $P < 0.05$ for all 3 outcomes).

CONCLUSIONS: Aprotinin tends to have a better risk-benefit profile than tranexamic acid in high-risk, but not low- to moderate-risk, patients. Its use in high-risk cases may therefore be warranted.

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Impaired hemostasis is a major sequela of cardiac surgery with cardiopulmonary bypass (CPB), because it frequently leads to excessive blood loss and blood product transfusions and is linked to adverse outcomes.¹ Although its causes are multifactorial, a major

contributing factor is excessive fibrinolysis.² To alleviate this complication, physicians often administer drugs that inhibit fibrinolysis. Two types of these drugs are clinically available: lysine analogues (tranexamic acid and ϵ -aminocaproic acid) and serine protease inhibitors (aprotinin).² The lysine analogues act by reversibly binding to the lysine-binding site of plasminogen, thereby preventing its conversion into plasmin, a fibrin-degrading serum protease.³ Aprotinin also attenuates fibrinolysis by inhibiting the action of plasmin,³ but it does this more efficiently by forming reversible enzyme inhibitor complexes.⁴ Unlike the lysine analogues, aprotinin simultaneously inhibits other serine proteases, such as thrombin and kallikrein, thereby enhancing its hemostatic effects and conferring it antiinflammatory effects.^{5,6}

The relative risk-benefit profile of these drugs is controversial. Aprotinin has generally been considered to be clinically superior to the lysine analogues, particularly in complex, high-risk cases in which patients are more likely to develop profound coagulopathy and systemic inflammatory response syndrome.⁷ Recently, however, several observational studies^{8–10} and a randomized trial (Blood Conservation Using Antifibrinolytics in a Randomized Trial [BART])¹¹ have found that patients who receive aprotinin have

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higher morbidity and mortality than those who receive lysine analogues. Largely based on these new findings, the marketing approval for aprotinin was recently withdrawn in Europe and placed under severe restrictions in North America.

Very little of the current data, however, pertains to use in high-risk cases, which is where the benefits of aprotinin are most likely to outweigh its risks. Most studies limited their sample to coronary artery bypass graft (CABG) surgeries, which are generally low- to moderate-risk cases. Even in the BART trial, which aimed specifically to study high-risk cases,¹¹ complex or emergency surgeries were excluded or not enrolled; consequently, the study included predominantly moderate-risk patients. In our previous observational study,¹² we assessed the risk-benefit profile of aprotinin by comparing the outcomes of 449 patients who received aprotinin with 449 propensity score-matched patients who received tranexamic acid at an institution where aprotinin was preferentially used in high-risk cases. Because most high-risk patients at the institution received aprotinin during the study period, however, we were unable to find a suitable match for many of them. Our assessment, therefore, was also limited primarily to low- and moderate-risk patients.

Given the restrictions placed on aprotinin in 2007, we have since been using tranexamic acid in all of our cardiac surgical patients. Thus, we now have data on more high-risk patients who received tranexamic acid but would have previously received aprotinin. This change in practice provided us the opportunity to compare aprotinin with tranexamic acid across a wider spectrum of risk than in our previous study. Our hypothesis was that aprotinin would have a superior risk-benefit profile in higher-risk cardiac surgical cases.

METHODS

Patient Sample

After obtaining institutional ethics board approval, which waived the requirement for informed consent, consecutive patients, aged 18 yr or older, who underwent cardiac surgery with CPB from January 2000 to May 2008 at the Toronto General hospital, were included in this single-center cohort study. Patients who did not receive aprotinin or tranexamic acid and those who participated in the BART trial ($n = 144$) were excluded. For patients who were readmitted for additional operations requiring CPB during the study period, only data from their first admission were used.

Study Setting and Clinical Practice

A full range of adult cardiac surgery procedures is performed at the Toronto General Hospital, which is a quaternary-care teaching hospital affiliated with the University of Toronto. Clinical care during the study period was guided by previously described standardized guidelines.¹²

Until its use was restricted, institutional guidelines recommended that aprotinin (test dose followed by 2×10^6 U over 30 min after induction of anesthesia, 2×10^6 U in the pump prime, and 2×10^6 U infused over 4 h) be used in complex procedures requiring prolonged CPB support, >1 previous sternotomy, or endocarditis. All other patients were to receive 50–100 mg/kg (given over 5–10 min IV after induction of anesthesia) of tranexamic acid, with higher-risk patients receiving the higher dose. After aprotinin use was restricted, this tranexamic acid regimen was used in all patients undergoing CPB procedures.

Anticoagulation during CPB was achieved with heparin to maintain kaolin activated clotting time >480 s.

Data Collection

All perioperative data were prospectively collected in institutional databases, as has been previously described.^{12,13} Full-time research personnel blinded to the details of this study adjudicated all patient outcomes from patients' records. Quality assurance checks of the databases have consistently revealed a missing data rate of <2% and an error rate of <2%. Patients with missing values for variables used in the multivariable analyses were excluded.

Outcomes

Based on existing data, 3 outcomes were of primary interest: in-hospital death, acute kidney injury (based on the RIFLE¹⁴ criteria of >50% decrease in estimated glomerular filtration rate, calculated with the Cockcroft-Gault¹⁵ equation, using preoperative and highest creatinine concentration during the first week after surgery, or the need for initiation of dialysis after surgery), and massive blood loss (transfusion of ≥ 10 U of red blood cells or surgical reexploration).

Other measured outcomes included postoperative acute kidney failure requiring dialysis support, stroke (new persistent neurological deficit with radiological confirmation), myocardial infarction (new electrocardiogram changes plus elevated cardiac enzymes), and serious infections (sepsis or deep sternal infection).

Covariates

Measured perioperative variables that may have influenced aprotinin use or perioperative blood loss were examined. These included preoperative patient characteristics (demographics, important comorbidities, as well as preoperative creatinine, hemoglobin, platelet, and international normalized ratio of prothrombin time), surgery-related variables (surgeon, procedure, urgency, and CPB duration), and patients' large-volume red blood cell transfusion risk score, as determined by a previously validated risk score.¹⁶

Measure of Patients' Risk Status

The Toronto Risk Score regression formula was used to calculate each patient's predicted perioperative risk for major adverse events.¹⁷ This prediction

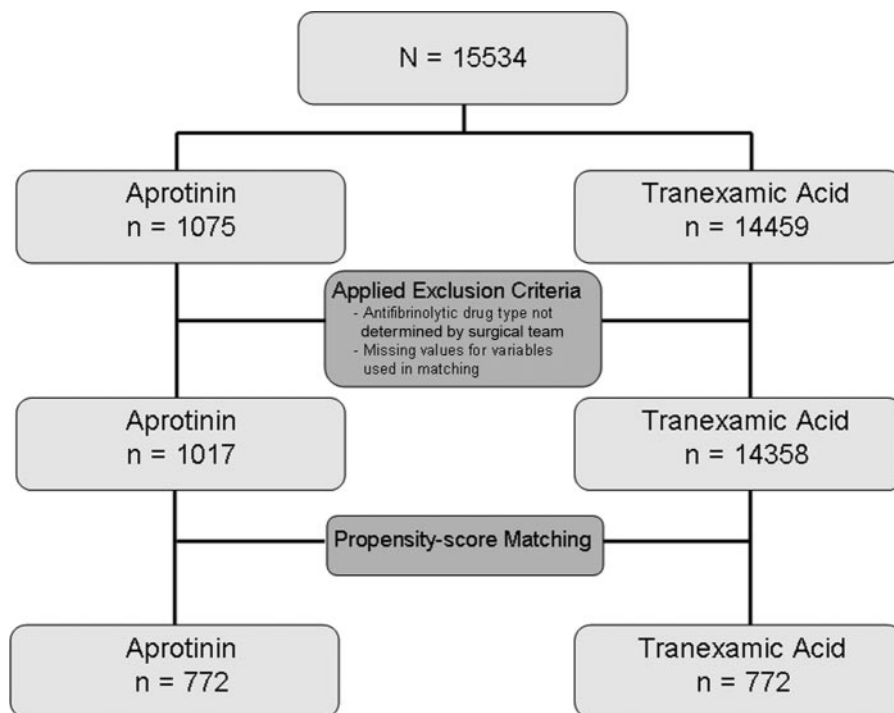


Figure 1. Patient flow diagram.

rule was used instead of better known ones, such as the EURO score,¹⁸ because it was developed (on patients who underwent surgery between 1996 and 2000) and validated (on patients who underwent surgery between 2000 and 2002) at our institution. It should, therefore, be more accurate than other scores for estimating the risk status of patients who undergo cardiac surgery at our institution. Details of the risk score are shown in the Appendix.

Statistical Analyses

Because treatment assignment was not based on random allocation, propensity score methods were used to match patients who received aprotinin to patients who received tranexamic acid.^{19,20} A propensity score for receiving aprotinin was estimated using a multivariable logistic regression model. All measured covariates (except for year of surgery) were considered for inclusion as predictor variables in this model (criteria for inclusion, $P < 0.2$). Each patient who received aprotinin was then matched to a patient who received tranexamic acid based on similar propensity scores (using a 5 → 1 computerized greedy-matching technique).²¹

The matched pairs were then compared on all measured covariates to determine whether the groups were balanced. Groups were considered to be balanced on a covariate if the standardized mean difference, which is the absolute difference of the group means as a percentage of their pooled SD, was $<10\%$.¹⁹ If the model failed to achieve balance for any covariate that was not in the model, the covariate was forced into subsequent models. If balance was not achieved for a covariate that was in the model, the cross-products of that covariate with other clinically related

variables were included in subsequent models. This process was repeated until the propensity score derivation model resulted in matched groups that were balanced on all important covariates.²² The outcomes between these matched pairs were then compared using conditional logistic regression.¹⁹

The influence of patients' perioperative risk status on the relative risk-benefit profile of aprotinin and tranexamic acid was assessed by plotting the cubic spline function curves of the observed rates of mortality, acute kidney injury, and massive blood loss against the predicted risk for major adverse events (as calculated by the Toronto Risk Score regression formula)¹⁷ for matched patients according to type of drug received. The Breslow-Day²³ test for homogeneity of odds ratios was used to determine whether the effects of the drugs differed between high-risk and low- to moderate-risk subgroups.

Statistical analyses were performed using SASTM version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 15,534 patients underwent cardiac surgery with CPB during the study period and received aprotinin or tranexamic acid. After application of the exclusion criteria, 15,365 patients were included in the study, 1017 (6.6%) of whom received aprotinin (Fig. 1). As can be seen in Table 1, there were many important prognostic differences between those who received aprotinin and those who received tranexamic acid. Most notably, aprotinin patients underwent more complex, high-risk surgeries requiring markedly longer CPB support than tranexamic acid patients.

Table 1. Comparisons of Selected Covariates and Outcomes in the Entire Sample and According to Antifibrinolytic Therapy

Variables	Entire sample			Matched patients			Unmatched patients	
	Aprotinin (n = 1017)	TA (n = 14,358)	SMD	Aprotinin (n = 772)	TA (n = 772)	SMD	Aprotinin (n = 245)	TA (n = 13,586)
Age (yr)	55 ± 17	63 ± 12	60%	58 ± 16	58 ± 16	5.3%	48 ± 17	63 ± 12
Female	35% (360)	26% (3762)	21%	35% (269)	38% (295)	7.0%	37% (91)	26% (3467)
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.2	20%	1.9 ± 0.2	1.9 ± 0.3	2.9%	1.9 ± 0.3	1.9 ± 0.2
Hypertension	39% (395)	60% (8555)	43%	42% (325)	45% (351)	6.8%	29% (70)	60% (8204)
Diabetes mellitus (Type I or II)	15% (153)	27% (3943)	28%	16% (121)	16% (127)	2.1%	13% (32)	28% (3816)
Peripheral vascular disease (History of aortoiliac, femoropopliteal, or carotid artery disease)	11% (112)	17% (2382)	15%	12% (92)	12% (96)	1.6%	8% (20)	17% (2286)
Cerebrovascular disease (History of stroke or transient ischemic attacks)	11% (108)	9% (1276)	6%	10% (79)	12% (89)	4.2%	12% (29)	9% (1187)
Atrial fibrillation	17% (177)	7% (962)	41%	17% (131)	15% (119)	4.2%	19% (46)	6% (843)
Left ventricular ejection fraction <40%	24% (243)	18% (2645)	14%	23% (177)	19% (150)	8.6%	27% (66)	18% (2495)
Unstable angina (within 30 d of surgery)	13% (132)	38% (5466)	53%	16% (122)	15% (119)	1.1%	4% (10)	39% (5347)
Recent myocardial infarction (within 30 d of surgery)	2% (18)	5% (709)	15%	2% (17)	2% (14)	2.8%	0.4% (1)	5% (695)
Recent cardiac catheterization (within 2 d of surgery)	29% (293)	7% (1018)	79%	25% (193)	26% (199)	1.8%	41% (100)	6% (819)
Active endocarditis	8% (78)	0.6% (80)	72%	6% (49)	6% (43)	3.3%	12% (29)	0.3% (37)
Preoperative estimated glomerular filtration rate (mL/min)	82 ± 38	81 ± 32	2%	79 ± 35	79 ± 36	0.5%	91 ± 44	81 ± 32
Preoperative hemoglobin concentration (g/dL)	12.8 ± 2.1	13.5 ± 1.6	43%	12.9 ± 2.0	12.9 ± 1.9	1.8%	12.5 ± 2.2	13.6 ± 1.6
Preoperative platelet count (×10 ⁹ /L)	223 ± 78	233 ± 70	14%	223 ± 77	223 ± 78	0.1%	222 ± 82	233 ± 70
Preoperative international normalized ratio of prothrombin time	1.2 ± 0.4	1.1 ± 0.2	61%	1.2 ± 0.4	1.2 ± 0.4	0.4%	1.2 ± 0.4	1.1 ± 0.2
Procedure			121%			4.2%		
Isolated CABG	10% (101)	61% (8721)		13% (100)	12% (94)		0.4% (1)	64% (8627)
Any valve replacement or repair	31% (312)	22% (3104)		35% (268)	33% (257)		18% (44)	21% (2847)
Other procedures	59% (604)	18% (2533)		52% (404)	55% (421)		82% (200)	16% (2112)
Urgent surgery	21% (214)	7% (1074)	49%	20% (151)	19% (148)	1.0%	26% (63)	7% (926)
Redo sternotomy	62% (626)	5% (708)	232%	52% (402)	53% (407)	1.3%	91% (224)	2% (301)
CPB duration (min)	143 ± 59	99 ± 36	118%	134 ± 53	135 ± 59	1.4%	172 ± 67	97 ± 33
Deep hypothermic circulatory arrest	12% (124)	3% (447)	48%	12% (92)	13% (97)	2.0%	13% (32)	3% (350)
Large-volume RBC transfusion risk score ¹⁶	4.4 ± 1.6	1.4 ± 1.1	155%	3.1 ± 1.5	3.1 ± 1.5	1.4%	3.4 ± 1.6	1.5 ± 1.2
Propensity score	0.43 ± 0.3	0.04 ± 0.1	306%	0.33 ± 0.26	0.33 ± 0.26	0.04%	0.74 ± 0.14	0.02 ± 0.05
Predicted risk for major adverse events ^a	0.24 ± 0.15	0.16 ± 0.09	88%	0.23 ± 0.14	0.24 ± 0.15	5.2%	0.26 ± 0.16	0.15 ± 0.08

All data are presented as mean ± sd or percentages (n).

TA = tranexamic acid; SMD = Standard mean difference, which is the absolute mean difference divided by the pooled sd ; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; RBC = red blood cell.

^a As calculated by the Toronto Risk Score prediction rule¹⁷; not included in the propensity-score calculations.

The final estimated propensity score model included 15 main-effects variables (with 41 degrees of freedom) and no interaction variables (*c*-index = 0.93) (Table 2). The model's most predictive variables, as measured by the Wald χ^2 , were the number of previous sternotomies, type of procedure, urgency, endocarditis, and surgeon

(Table 2). Of the 1017 patients who received aprotinin in the entire cohort, 772 (76%) were matched to similar patients who received tranexamic acid (Fig. 1). Covariate balance (standardized mean difference <10%) was achieved for all measured covariates (Table 1). Table 1 also shows the propensity scores and the predicted

Table 2. Propensity Score Model

Variables (classification)	Degrees of freedom	Wald χ^2	P
Age (continuous)	1	6.9	0.009
Cerebrovascular disease (categorical; yes or no)	1	2.9	0.09
Unstable angina (categorical; yes or no)	1	3.6	0.06
Endocarditis (categorical; none, remote, active, or active abscess)	3	44.9	<0.0001
Preoperative dialysis (categorical; yes or no)	1	3.9	0.05
Preoperative intraaortic balloon pump (categorical; yes or no)	1	1.8	0.2
Preoperative hemoglobin concentration (continuous)	1	3.4	0.07
Surgeon (categorical; 13 surgeons)	12	42.2	<0.0001
Procedure (categorical; aortocoronary bypass, valve, or other)	2	73.1	<0.0001
Type of other procedures (categorical; 10 procedures such as heart transplant)	9	22.9	0.006
Urgency (categorical; elective, same hospitalization, urgent, emergent)	3	51.7	<0.0001
Redo sternotomy (categorical; multiple previous, single previous, or no)	2	618	<0.0001
CPB duration (continuous)	1	13.7	0.0002
Deep hypothermic circulatory arrest (categorical; ≤ 15 min, 16–29 min, ≥ 30 min)	2	22	<0.0001
Large-volume RBC transfusion risk score (continuous)	1	18.5	<0.0001

CPB = cardiopulmonary bypass; RBC = red blood cell.

perioperative risk for major adverse events for the entire sample as well as for the matched and unmatched patients. As can be seen, balance was also achieved on these variables.

A suitable match could not be identified for 24% of patients who received aprotinin. Compared with matched aprotinin patients, these patients had markedly higher propensity scores (Table 1). This difference was primarily due to the high (91%) rate of previous sternotomies, with about half having undergone multiple previous sternotomies. Given the importance of this variable in estimating propensity scores (see above), this seems to have been the principal reason for not finding a suitable match for them.

Outcomes

The unadjusted observed adverse event rates were markedly higher in patients who received aprotinin than in those who received tranexamic acid (Table 3). After propensity score matching, however, aprotinin was only associated with increased risk of acute kidney injury (odds ratio 1.5; 95% confidence interval [CI] 1.1–2.1) (Table 3).

The cubic spline function curves of the predicted risk for adverse events versus observed rates of mortality, acute kidney injury, and massive blood loss in the matched group are shown in Figure 2a–c, respectively. As can be seen, there was an important interaction between patients' risk status and the relative risk-benefit profile of the drugs. For mortality and massive blood loss, the risk-benefit profile of aprotinin changed from unfavorable to favorable when the predicted risk for adverse events was approximately 0.3. This risk level corresponded to approximately the 75th percentile in the matched group (and the 90th percentile in the entire study population). A similar pattern was observed for acute kidney injury (as well as for other measured adverse events, the results of which are not shown) but at a markedly higher

Table 3. Outcomes

Outcomes ^a	Entire sample			Matched patients		
	Aprotinin (n = 1017)	TA (n = 14,358)	P	Aprotinin (n = 772)	TA (n = 772)	P*
Death	9% (87)	2% (247)	<0.0001	7.0% (54)	7.4% (57)	0.8
Acute kidney injury	15% (149)	4% (564)	<0.0001	13.5% (104)	9.2% (71)	0.009
Massive blood loss	25% (256)	8% (1077)	<0.0001	21.4% (165)	21.2% (164)	0.9
Other measured outcomes						
Received at least 1 RBC unit	81% (826)	61% (8816)	<0.0001	78% (604)	79% (609)	0.8
Received platelets	60% (613)	19% (2771)	<0.0001	56% (429)	53% (410)	0.3
Received fresh frozen plasma	68% (696)	29% (4226)	<0.0001	65% (498)	65% (501)	0.9
Acute kidney failure requiring dialysis support	7.4% (75)	1.3% (187)	<0.0001	5.6% (43)	3.6% (28)	0.07
Myocardial infarction	3% (26)	2% (275)	0.1	3.0% (23)	2.3% (18)	0.4
Stroke	4% (38)	1% (189)	<0.0001	3.6% (28)	2.3% (18)	0.1
Serious infection	6% (65)	2% (310)	<0.0001	5.7% (44)	4.7% (36)	0.4

TA = tranexamic acid; RBC = red blood cell.

^a See text for definitions.

* Conditional logistic regression used.

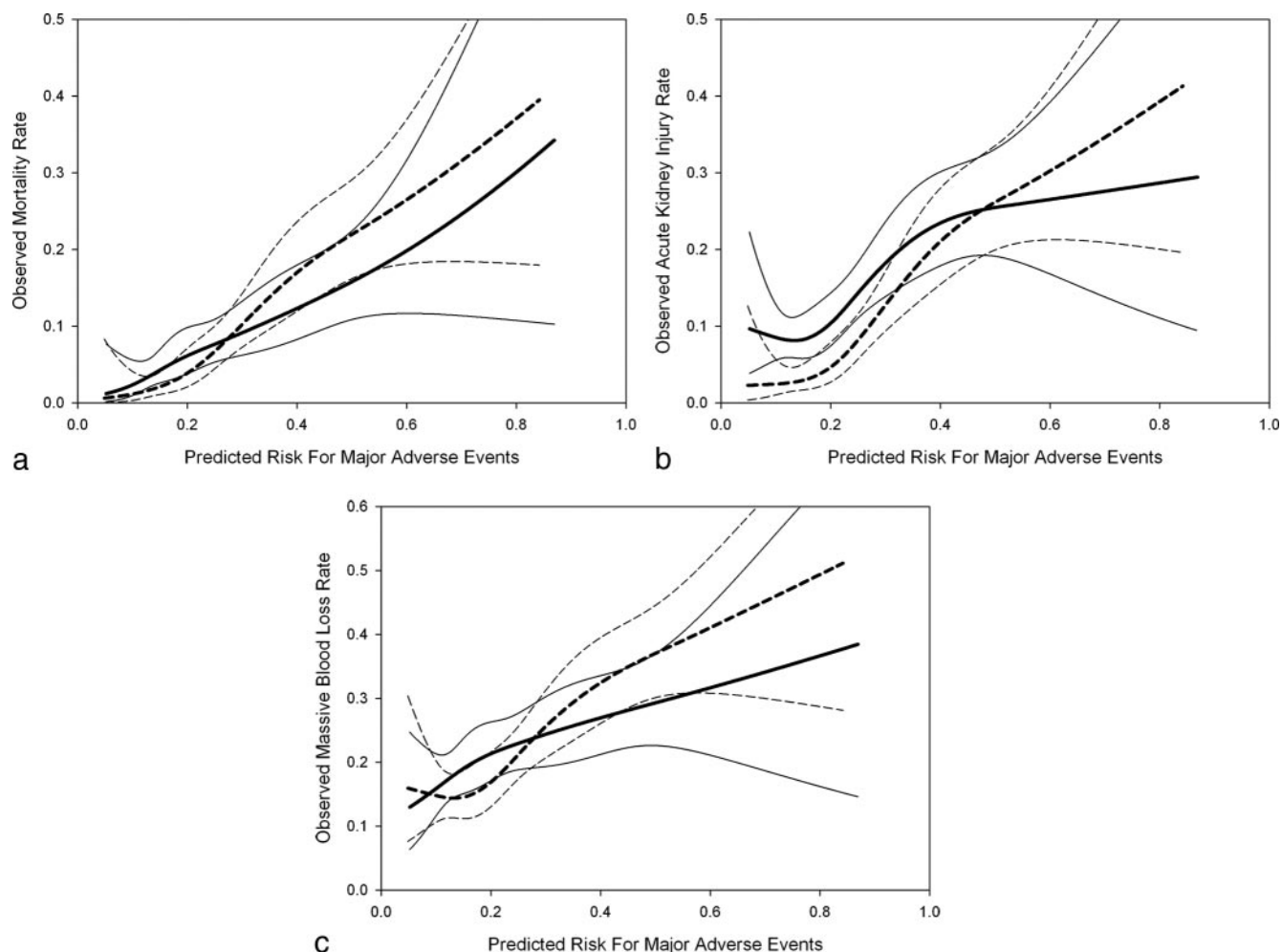


Figure 2. Relationship between patients' predicted adverse event rates, as calculated using the Toronto Risk Score regression formula, and the rates of mortality (a), acute kidney injury (b), and massive blood loss (c) in the matched group. These relationships were modeled using restricted cubic spline functions. Solid lines represent patients who received aprotinin, and dashed lines represent those who received tranexamic acid. Faded lines are the 95% confidence intervals of the relationships.

predicted adverse event rate of approximately 0.5 (which corresponded to the 95th percentile in the matched set and 99th percentile in the entire study population).

Using the predicted risk for major adverse events of 0.3 as the threshold for categorizing patients as high risk, the odds ratio for mortality associated with aprotinin use in the matched group was 0.6 (95% CI 0.3–1.0; $P = 0.05$) in high-risk patients and 1.5 (95% CI 0.9–2.7; $P = 0.1$) in the remaining patients (Fig. 3a; Breslow-Day test, $P = 0.01$), the odds ratio for acute kidney injury was 1.1 (95% CI 0.7–1.7; $P = 0.8$) in high-risk patients and 2.2 (95% CI 1.4–3.5; $P = 0.0006$) in the remaining patients (Fig. 3b; Breslow-Day test, $P = 0.03$), and the odds ratio for massive blood loss was 0.7 (95% CI 0.4–1.04; $P = 0.07$) in high-risk patients and 1.2 (95% CI 0.9–1.7; $P = 0.2$) in the remaining patients (Fig. 3c; Breslow-Day test, $P = 0.02$).

Matched high-risk patients had the following characteristics: 25% had unstable angina, 41% had left

ventricular dysfunction, 25% had peripheral vascular disease, 45% had elevated baseline creatinine concentrations, 54% had 1 or more previous sternotomies, 46% underwent urgent surgery, and 81% underwent complex surgical procedures (i.e., procedures other than isolated CABG or single valve) with an average CPB duration of 143 (SD $\pm$ 57) min.

DISCUSSION

Despite the widespread, long-term use of the anti-fibrinolytic drugs aprotinin and tranexamic acid in cardiac surgery, little is known about their comparative risk-benefit profile, particularly in the setting of complex, high-risk surgeries in which, because of high excessive blood loss and complication rates, differences in their potency and side effect profile can have important prognostic implications.

In this study, we compared the risk-benefit profile of aprotinin and tranexamic acid in cardiac surgery across a wide spectrum of risk, ranging from simple,

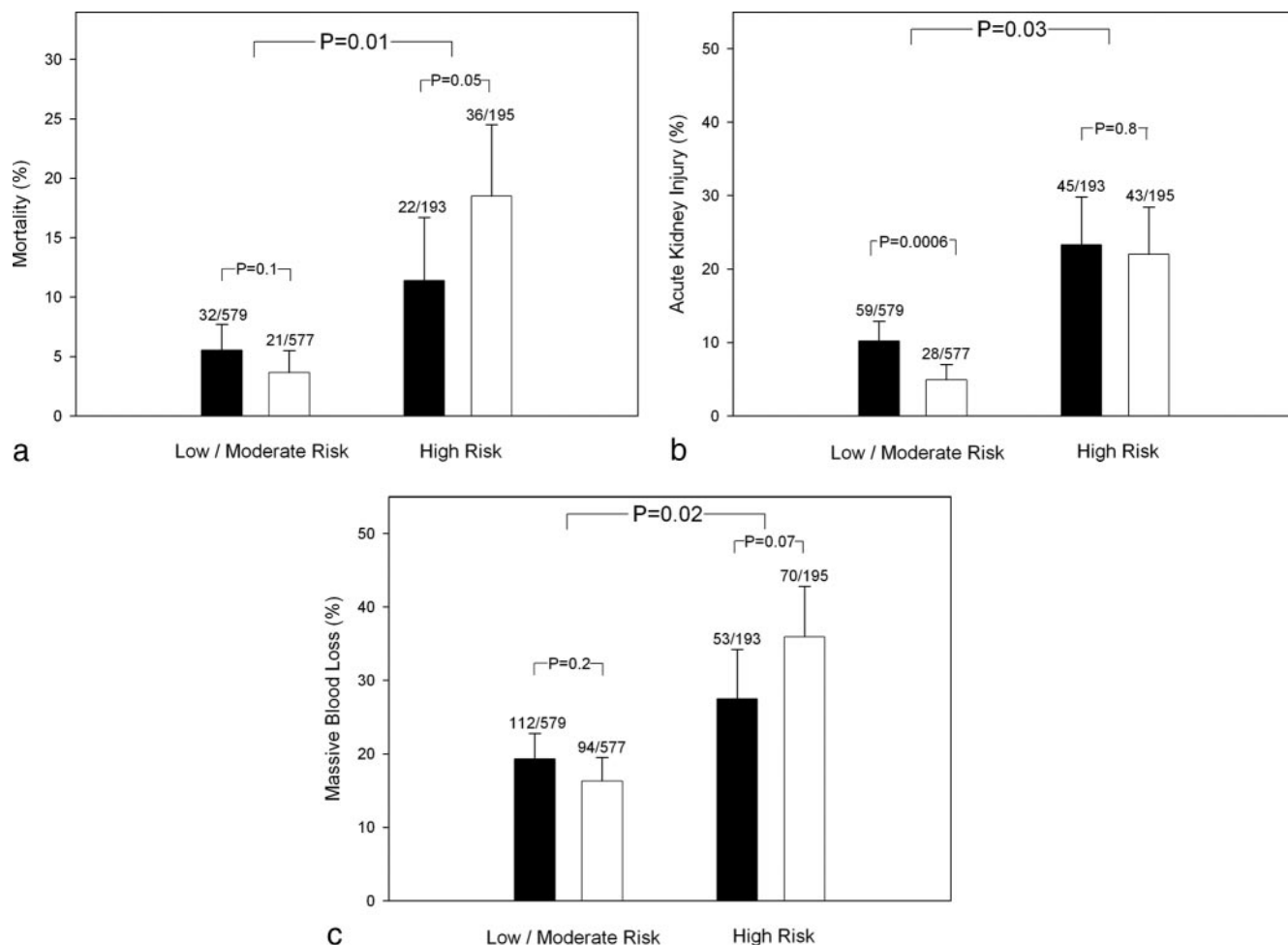


Figure 3. The differential effects of aprotinin versus tranexamic acid on mortality (a), acute kidney injury (b), and massive blood loss (c) relative to patients' risk status in the matched group. Patients whose predicted risk for major adverse events was >0.3 are classified as high risk. Patients who received aprotinin are represented in black, and those who received tranexamic acid in white. Bars are the SD. The χ^2 test was used to compare the rates within each risk category. The Breslow-Day test was used to determine whether drug effects were significantly different between the risk categories.

low-risk surgeries to complex, high-risk surgeries. When we matched patients who received aprotinin to similar patients who received tranexamic acid based on their propensity scores and compared their outcomes at the group level, we found that aprotinin use was associated with increased risk of acute kidney injury but not with any of the other measured adverse outcomes. When we then examined the influence of patients' risk status on measured outcomes, however, we found that high-risk patients had a significantly different response to aprotinin than low- to moderate-risk patients. Specifically, we found that aprotinin tended to be associated with less massive blood loss and lower adverse event rates in patients whose risk status placed them in the top 25th percentile of the matched group (which corresponded to the top 10th percentile of our institution's cardiac surgery population), but it tended to be associated with higher adverse event rates in lower-risk patients.

We measured patients' risk status by a risk score that was developed and validated at our institution

that incorporated several patient- and surgery-related variables. Given that the principal determinants of high risk were the urgency and complexity of surgery, however, our estimates should be externally generalizable. Our findings are also physiologically plausible, because it is in these types of cases that patients frequently develop profound coagulopathy, systemic inflammatory response syndrome, or both.⁷ It is therefore in these types of cases that, compared with tranexamic acid, aprotinin's greater hemostatic and antiinflammatory potency should outweigh its greater proclivity for hypercoagulability, renal dysfunction, and hypersensitivity.²⁴

The clinical implication of our findings is that aprotinin may be the antifibrinolytic of choice and should therefore remain available for clinical use in patients undergoing high-risk cardiac surgery. These are the patients who are undergoing emergency, complex procedures that require prolonged CPB support, and they constitute approximately 10% of the general cardiac surgery population. This finding

is highly relevant because neither the United States Food and Drug Administration nor Health Canada has made a final determination on the status of aprotinin.

Our findings are consistent with most pertinent data. As in our study, a recent comprehensive meta-analytical analysis of randomized clinical trials that were published before the BART trial found that aprotinin is associated with increased risk of acute kidney injury but not with any other adverse events.²⁵ On the other hand, several recent observational studies,^{8–10} as well as the randomized BART trial,¹¹ have found aprotinin to also be associated with higher risks of other adverse events and mortality. For the most part, however, these studies included CABG surgeries, and their analysis was therefore limited to low- to moderate-risk cases. Even in the BART trial, where the objective was to assess aprotinin in high-risk cases, patients undergoing emergency or most types of complex surgery were excluded.¹¹ As a result, the study's sample consisted primarily of low- to moderate-risk cases. When we calculated the risk status of the 144 patients that our institution contributed to the BART trial with the Toronto Risk Score, we found that their median predicted perioperative risk for major adverse events was 0.16 (25th and 75th percentile 0.12; 0.23), which would have placed them in the low- to moderate-risk category of our matched group. It would be surprising if the risk profiles of patients from other centers differed substantially from ours. It seems, therefore, that the results of the BART trial may not be applicable to high-risk cases.

Our study has several limitations. First, because patient allocation was not randomly determined and patients could only be matched based on measured covariates, there may be between-group differences in unmeasured confounders. Because aprotinin was preferentially used in higher-risk cases, we would anticipate unmeasured confounders to bias our results against aprotinin. This, therefore, cannot explain why we found aprotinin to be associated with improved outcomes in high-risk cases. Another possible source of bias relates to changes in clinical practice or case mix that may have occurred during the study period. Although we deliberately did not control for year of surgery to increase the number of matches, we did control for multiple measures of comorbidity, surgical complexity, and the individual surgeon. Moreover, clinical practice at our institution did not undergo major changes during the study period, and the measured outcome rates were relatively constant during the entire study period (results not shown). Thus, the unmeasured temporal influences on our results should be small. Another limitation of this study is that it lacked a placebo control group and, therefore, provides no information on the overall risks and benefits of using antifibrinolytic drugs in cardiac surgery. Finally, given that this was an observational

study, we can only comment on associations and cannot prove causation. Thus, an adequately powered, randomized, comparative clinical trial aimed at patients undergoing high-risk cardiac surgery is needed to verify our findings. The high adverse event rates in this group of patients makes the conduct of such a study quite feasible.

In summary, we conducted a single-center cohort study in which we compared the outcomes of 772 cardiac surgical patients who received aprotinin with 772 propensity score-matched patients who received tranexamic acid from 2000 to 2008. As in previous studies, we found that aprotinin was associated with increased overall risk of acute kidney injury. We also found, however, that the effects of aprotinin were significantly influenced by the patients' risk status, such that it tended to be associated with lower massive blood loss and adverse event rates in high-risk patients, but not in low- to moderate-risk patients. Thus, our findings suggest that the use of aprotinin may be warranted in patients whose risk status, as determined by their comorbidities, surgical acuity, and complexity, places them at approximately the top 10th percentile of the cardiac surgery population. Our findings need to be verified by randomized controlled trials in high-risk cases.

APPENDIX. The Toronto Risk Score¹⁷ for Predicting Major Adverse Events Following Cardiac Surgery

Variable	Regression coefficient	Weight
Age 65–74 yr	0.074	1
Age ≥75 yr	0.226	2
Female sex	0.404	2
Left ventricle ejection fraction 20%–40%	−0.068	2
Left ventricle ejection fraction <20%	0.515	3
Urgent case	−0.312	1
Emergent case	0.846	6
Myocardial infarction within 30 d of surgery	0.353	1
Redo coronary artery bypass surgery	1.106	4
Triple vessel disease	0.286	1
Left main disease	0.312	1
Congestive heart failure	0.326	2
Preoperative creatinine >150 μmol/L	0.718	2
Diabetes (Types I or II)	0.205	1
Peripheral vascular disease	0.296	1
Hypertension	0.142	1
Complex valve surgery (>1 valve or 1 valve plus additional procedures)	0.295	2
Other pathology requiring surgical correction	0.617	2
Constant	−2.595	—

The predicted probability of adverse events is calculated using the formula: Probability = $\Sigma e^{\beta} / (1 + \Sigma e^{\beta})$, where e is the exponent and β is the regression coefficient.

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