The risks associated with aprotinin use: a retrospective study of cardiac cases in Nova Scotia

Les risques associés à l'utilisation d'aprotinine: une étude rétrospective des cas de chirurgie cardiaque en Nouvelle-Écosse

Robert E. G. Riddell, MD · Karen J. Buth, MSc ·
John A. Sullivan, MD

Received: 16 May 2011 / Accepted: 5 October 2012 / Published online: 7 November 2012
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Abstract

Purpose *In light of the concerns about the safety of aprotinin, we wanted to determine if aprotinin use during cardiac surgery was associated with an increased risk of mortality and morbidity compared with the use of tranexamic acid (TXA). We hypothesized that use of aprotinin is associated with a higher risk of adverse outcomes than use of TXA in our patient population.*

Methods *In this retrospective study at a single surgical centre, we examined primary in-hospital outcomes of postoperative mortality, new acute renal failure, and perioperative blood transfusion, and we also investigated secondary outcomes of stroke, infection, and prolonged stay in the intensive care unit (ICU). The effect of the type of antifibrinolytic on outcome was evaluated for aprotinin cases matched 1:1 with TXA cases using propensity score.*

Results *This study included 3,340 patients who received antifibrinolytics during cardiac surgery (376 patients received aprotinin and 2,964 patients received TXA).*

Patients who received aprotinin were more often elderly and female; they were more commonly presented with congestive heart failure, atrial fibrillation, renal failure, and lower hemoglobin, and they underwent complex and/or urgent surgery. In the matched sample, in-hospital mortality was significantly higher in the aprotinin group (10.9%) compared with the TXA group (5.9%), and ICU stay >72 hr was significantly increased in the aprotinin group (30.0%) compared with the TXA group (21.7%). There was no significant difference in blood product administration between the two groups.

Conclusions *Aprotinin was associated with an increased risk of in-hospital mortality and morbidity following cardiac surgery, and aprotinin was not associated with a decrease in blood product requirements. Continued use of aprotinin in cardiac surgery should follow careful consideration, weighing the demonstrated risks and potential advantages compared with other TXA.*

Résumé

Objectif *Étant donné les inquiétudes concernant l'innocuité de l'aprotinine, nous avons voulu déterminer si l'utilisation d'aprotinine pendant une chirurgie cardiaque était associée à un risque accru de mortalité et de morbidité par rapport à l'utilisation d'acide tranexamique (TXA). Nous avons émis l'hypothèse que l'utilisation d'aprotinine était associée à un risque plus élevé de pronostics défavorables que l'utilisation de TXA dans notre population de patients.*

Méthode *Dans cette étude rétrospective dans un seul centre chirurgical, nous avons examiné les résultats primaires à l'hôpital de mortalité postopératoire, de nouvelle insuffisance rénale aiguë et de transfusion sanguine périopératoire. Nous avons également étudié les résultats secondaires suivants: accident vasculaire*

R. E. G. Riddell, MD
Division of Cardiac Surgery, Dalhousie University,
Halifax, NS, Canada

K. J. Buth, MSc
Division of Cardiac Surgery, Maritime Heart Center,
Halifax, NS, Canada

J. A. Sullivan, MD
Divisions of Cardiac and Vascular Surgery,
Maritime Heart Center, Halifax, NS, Canada

R. E. G. Riddell, MD (✉)
c/o Dr. J. Sullivan, Division of Cardiac Surgery,
New Halifax Infirmary, 1796 Summer St. Rm 2269,
Halifax, NS B3H 3A7, Canada
e-mail: robriddell@gmail.com

cérébral, infection et séjour prolongé à l'unité des soins intensifs (USI). L'effet du type d'antifibrinolytique sur le devenir a été évalué pour les cas d'aprotinine appariés dans un ratio 1:1 aux cas de TXA à l'aide d'un score de propension.

Résultats Cette étude a inclus 3340 patients ayant reçu des antifibrinolytiques pendant une chirurgie cardiaque (376 patients ont reçu de l'aprotinine et 2964 du TXA). Les patients ayant reçu de l'aprotinine étaient plus souvent âgés et de sexe féminin; ces patients ont davantage manifesté d'insuffisance cardiaque congestive, de fibrillation auriculaire, d'insuffisance rénale, ainsi que de niveaux d'hémoglobine plus bas, et ils ont subi des chirurgies complexes et/ou urgentes. Dans l'échantillon apparié, la mortalité hospitalière était significativement plus élevée dans le groupe aprotinine (10,9 %) que dans le groupe TXA (5,9 %), et la probabilité d'un séjour à l'USI > 72 h était significativement accrue dans le groupe aprotinine (30,0 %) par rapport au groupe TXA (21,7 %). Aucune différence significative n'a été observée entre les deux groupes concernant l'administration de produits sanguins.

Conclusion L'aprotinine a été associée à un risque accru de mortalité et de morbidité hospitalières suite à une chirurgie cardiaque, et l'aprotinine n'a pas été associée à une réduction des besoins en produits sanguins. Nous concluons que, comparativement à l'aprotinine, le TXA est un antifibrinolytique plus sécuritaire et tout aussi efficace lorsqu'il est utilisé pendant une chirurgie cardiaque.

Introduction

Bleeding continues to be a major concern in contemporary cardiac surgery. Increased morbidity and mortality are known to be associated with perioperative hemorrhage and with the blood transfusions used to treat them.^{1,2} Antifibrinolytics are used to reduce blood loss during cardiac surgery. Two main categories of antifibrinolytics are serine protease inhibitors, such as aprotinin, and lysine analogues, such as tranexamic acid (TXA) and aminocaproic acid (ACA).

Studies directly comparing the efficacy and safety of aprotinin with that of TXA are conflicting and much controversy exists.³⁻⁹ Numerous studies outlined purported risks of aprotinin use compared with both placebo and the lysine analogues.^{9,10} The focus of this retrospective analysis is on elucidation of the safety and efficacy of aprotinin compared with TXA in cardiac surgery.

Compared with the lysine analogues, aprotinin has previously been associated with greater efficacy, decreased mortality, decreased prevalence of reoperation for

bleeding, decreased prevalence of stroke in patients receiving coronary artery bypass grafts (CABG), and decreased cognitive dysfunction immediately after CABG.^{9,10} Reported safety concerns with aprotinin primarily include mortality,^{5,8,9,11,12} renal failure,^{6,12-14} renal dysfunction,^{3,15,16} and stroke,^{13,15,17} and, to a lesser extent, myocardial infarction.¹³ In May 2008, the results of a randomized control trial, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), provided the most convincing evidence for the adverse outcomes associated with the use of aprotinin.⁸ In November 2007, the BART trial was halted after the Data Safety Monitoring Board noted an increase in mortality for patients in the aprotinin treatment arm compared with patients who received either ACA or TXA. After the BART trial was halted, federal health agencies in Canada, Europe, and the USA suspended aprotinin marketing. The USA Federal Drug Administration removed aprotinin from hospital stocks shortly after the BART trial was published in 2008.

Lysine analogues have been used extensively in cardiac surgery in the USA, Canada, and Europe. At best, tranexamic acid has been shown to be equally as effective as aprotinin at reducing blood loss, and, at worst, it is moderately less effective.^{3-6,8,9,13} Tranexamic acid is more commonly used in low- to medium-risk cardiac cases, presumably due to its lower cost and relatively few reported adverse effects. The majority of studies comparing TXA with aprotinin have shown that TXA is as safe or safer than aprotinin^{6,13}; however, one study has shown that TXA is associated with a higher incidence of seizures, atrial fibrillation, and renal failure when compared with aprotinin.¹¹ This shows our incomplete understanding of antifibrinolytics, specifically, their safety and adverse effect profiles. It also outlines the need for caution in administering any of the antifibrinolytics regardless of the type of surgery or patient profile.

The aim of this study is to compare the short-term in-hospital outcomes of patients who received aprotinin vs those who received TXA. Our hypothesis is that aprotinin is associated with a higher risk of adverse outcomes than TXA in our patient population. On September 11, 2011, Health Canada lifted the ban on aprotinin marketing. They now authorize aprotinin use in CABG surgery with cardiopulmonary bypass stating that the benefits outweigh the risks when used as authorized.^A Given this recent decision by Health Canada, the results of our study in a Canadian institution are an important addition to the current literature.

^A Health Canada Information Update. Available from URL: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_124-eng.php (accessed January 2012).

Methods

Ethics

This retrospective observational study was fully approved by the institutional Research Ethics Board in March 2008, and the requirement to obtain informed consent was waived under Section 2.1c of the Tri-Council Policy Statement. All personal identifiers were removed prior to data analysis to ensure patient anonymity and confidentiality.

Data source and variable selection

Preoperative clinical characteristics, intraoperative variables, and postoperative outcomes were obtained from the Maritime Heart Center Cardiac Surgery Registry, a computerized clinical database housed at the Queen Elizabeth II Health Science Center (QEII HSC) in Halifax, Nova Scotia. This registry includes detailed clinical data prospectively collected on all adult cardiac surgery cases performed at the QEII HSC from 1995 to present. Trained abstractors collect data, and a database administrator maintains the database. The registry captures 100% of cardiac surgeries performed at this institution and is validated annually by a random audit of patient charts.

Preoperative covariates included age, sex, body mass index (with cut-points based on the World Health Organization classification), renal failure (serum creatinine [sCr] $>176 \mu\text{mol}\cdot\text{L}^{-1}$) peripheral vascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, congestive heart failure, atrial fibrillation, hemoglobin, hypertension, smoking history, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), antiplatelet therapy, anticoagulation, type of procedure, and urgency of surgery. Urgency was defined as either urgent (requiring surgery within 24 hr) or emergent (requiring immediate surgery without delay).

The in-hospital outcomes were selected on the basis of clinical relevance and included short-term post-procedural events occurring during the same admission as cardiac surgery. Primary outcomes were in-hospital mortality, acute renal failure (sCr $\geq 200 \mu\text{mol}\cdot\text{L}^{-1}$ and a 50% increase in sCr from preoperative levels), and blood product requirement (red blood cells, fresh frozen plasma, platelets, or cryoprecipitate). Blood loss was not directly quantified in the database; therefore, blood product requirement was examined in order to compare the efficacy of the two antifibrinolytics. Secondary outcomes included postoperative stroke, sepsis and/or deep sternal wound infection, reoperation for bleeding, and a prolonged stay (> 72 hr) in the intensive care unit (ICU). Cardiopulmonary bypass time, aortic cross-clamp time, and requirement for inotropic support leaving the operating room were also reported.

Patient selection

This retrospective study included all adult patients who received an antifibrinolytic while undergoing any cardiac surgical procedure at the QEII HSC in Halifax, Nova Scotia from March 2003 to December 2007. During this time period, data were available on antifibrinolytic use. The QEII HSC is the sole tertiary care centre in Nova Scotia providing cardiac surgical care for a population base of more than one million people along with frequent referrals from the three other Atlantic Provinces. The scope of the clinical activity in cardiac surgery at the QEII HSC comprises approximately 1,100 adult procedures per year.

Cardiac surgical procedures were predominantly valve, isolated CABG, or valve plus CABG. Patients were excluded from the study if they did not receive an antifibrinolytic, if they received more than one antifibrinolytic during the same procedure or during a different procedure during the same admission, or if they received ACA. Aminocaproic acid is not commonly used at our institution, and therefore it was not studied. Patients who had previous cardiac surgery were also excluded. The remaining patients were divided into two groups: those who received aprotinin and those who received TXA.

Antifibrinolytic use

Selection of antifibrinolytics in the cardiac surgery setting at the QEII HSC was not standardized and thus at the discretion of the individual surgeons and anesthesiologists. Patients who received aprotinin received one full standardized dose (defined as a 2 million KIU [280 mg; 200 mL] loading dose) intravenously, a 2 million KIU (280 mg; 200 mL) into pump prime volume, and $500,000 \text{ KIU}\cdot\text{hr}^{-1}$ ($70 \text{ mg}\cdot\text{hr}^{-1}$; $50 \text{ mL}\cdot\text{hr}^{-1}$) intravenously during the operation. Tranexamic acid dosage was not standardized; however, a $1 \text{ mg}\cdot\text{kg}^{-1}$ load and a $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ infusion were commonly used.

Statistical analysis

A non-parsimonious propensity score model was developed to calculate the predicted probability of receiving aprotinin vs receiving TXA. Candidate variables for model building were those associated with the antifibrinolytic group as well as those associated with the primary outcomes in the study. Variance inflation factor was used to assess multicollinearity. The propensity score model included age, sex, body mass index, renal failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, congestive heart failure, atrial fibrillation, hemoglobin, hypertension, smoking history, ACE inhibitor, ARB, antiplatelet therapy, anticoagulation, surgeon, procedure

type and urgency of surgery, and it also included the interaction terms surgeon*procedure type and age*sex. To satisfy the assumption of linearity, age was transformed as age squared and hemoglobin was transformed as a cubic spline function. A mirrored histogram plot of the logit of the propensity scores shows the overlap between the two antifibrinolytic groups before matching (Figure).

Aprotinin cases were matched 1:1 with TXA cases on the logit of the propensity score using caliper matching without replacement; the caliper width was defined as 0.2 of the standard deviation of the logit of the propensity score.¹⁸ Standardized differences were reported for preoperative characteristics of the two antifibrinolytic groups before matching. In the matched sample, standardized differences were used to assess covariate balance between antifibrinolytic groups. There is no clear consensus on the magnitude of the standardized difference that represents imbalance, although values of 0.1 and 0.2 have been used as a threshold value.¹⁹

To account for the matched nature of the sample, McNemar's test was used to assess the statistical significance of treatment effect on dichotomous outcomes.²⁰ The effect of aprotinin vs TXA was estimated as the difference in proportion of outcome events in the two groups in the matched sample.²⁰ The confidence interval for the difference in proportions was calculated using the score interval method with continuity correction.²¹ The confidence interval for difference in proportions was calculated using WinPepi 11.24. All other statistical analysis was performed using SAS® 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

From March 2003 to December 2007, 5,390 cardiac surgery cases were performed at the QEII HSC, and 1,652 of

those either did not receive an antifibrinolytic or did not have antifibrinolytic use recorded. Forty-nine cases received ACA, 27 cases received more than one type of antifibrinolytic, and 322 cases had previous cardiac surgery. The remaining 3,340 cases were included in the study; 376 received aprotinin and 2,964 received TXA.

In the sample before matching, there were many large standardized differences (absolute value > 0.2) in preoperative clinical characteristics between the two groups (Table 1), indicating that the two groups were not comparable.

The standard deviation of the logit of the propensity score was 0.9377. The caliper width, defined as 0.2 of the standard deviation of the logit of the propensity score, was 0.1875. One-to-one caliper matching of aprotinin cases with TXA cases without replacement resulted in 358 matched pairs. Therefore, 95.2% of the aprotinin cases were included in the matched sample. For the 18 aprotinin cases that remained unmatched, the median logit of the propensity score was 0.60 and the interquartile range (IQR) was 0.44–0.81.

Preoperative clinical characteristics of aprotinin and TXA cases in the matched sample are shown in Table 2. The standardized differences between the matched samples are substantially smaller than those between the unmatched samples and all are ≤ 0.10 . This indicates that the propensity score model was adequately specified and covariates were well-balanced between antifibrinolytic groups in the matched sample. Covariate balance was confirmed for the subset of the matched sample in which the measurement of acute renal failure was available. In this subset, there were 340 matched pairs, and the absolute standardized differences ranged from 0.000 to 0.114.

Primary and secondary in-hospital outcomes are reported in Table 3. Mortality and prolonged ICU stay were significantly higher in the aprotinin group compared with

Figure Mirrored histogram plot of the logit of the propensity scores

Table 1 The preoperative clinical characteristics of TXA and aprotinin groups in the sample before matching

Preoperative Characteristic	TXA <i>n</i> = 2,964	Aprotinin <i>n</i> = 376	Standardized difference
Age (yr), <i>n</i> (SD)	65.2 (11.3)	66.0 (13.0)	0.066
Female	738 (24.9)	120 (31.9)	0.157
Body mass index (kg·m ⁻²), <i>n</i> (SD)	29.1 (5.4)	27.6 (4.9)	-0.294
Renal failure	143 (4.8)	42 (11.2)	0.238
Peripheral vascular disease	469 (15.8)	73 (19.4)	0.095
Cerebrovascular disease	383 (12.9)	58 (15.4)	0.072
Diabetes	1,048 (35.4)	111 (29.5)	-0.126
Chronic obstructive pulmonary disease	444 (15.0)	74 (19.7)	0.124
Congestive heart failure	579 (19.5)	107 (28.5)	0.212
Atrial fibrillation	353 (11.9)	72 (19.2)	0.200
ACE inhibitor	1,619 (54.6)	174 (46.3)	-0.167
ARB	282 (9.5)	30 (8.0)	-0.053
Antiplatelet	2,488 (83.9)	266 (70.7)	-0.319
Anticoagulation	957 (32.3)	147 (39.1)	0.142
Hemoglobin (g·L ⁻¹), <i>n</i> (SD)	134.1 (17.6)	126.4 (20.8)	-0.397
Hypertension	2,158 (72.8)	248 (66.0)	-0.148
Smoking history	2,091 (70.6)	248 (66.0)	-0.0968
Procedure other than isolated CABG	859 (29.0)	228 (60.6)	0.670
Urgent/emergent surgery	328 (11.1)	113 (30.0)	0.483

Continuous variables are presented as mean (standard deviation); dichotomous variables are presented as *n* (%). SD = standard deviation; TXA = tranexamic acid; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting

the TXA group. The most common cause of death in both groups was cardiac followed by neurologic and pulmonary causes. Prevalence of acute renal failure, stroke, and infection was also higher among patients receiving aprotinin, but the difference between the two groups did not reach statistical significance. There was no significant difference in blood product requirement or reoperation for bleeding between the two groups.

Cardiopulmonary bypass time, reported as median and IQR, was similar in the aprotinin and TXA groups: 131 [100-180] min and 126 [96-167] min, respectively. Aortic cross-clamp time, reported as median and IQR, was also similar in the aprotinin and TXA groups: 85 [63-120] min and 84 [64-110] min, respectively. Inotropic support leaving the operating room was required in 146 (41%) of aprotinin cases and 142 (40%) of TXA cases.

The prevalence of each major type of blood product administered was compared between the two groups (Table 4). The use of red blood cells, fresh frozen plasma,

Table 2 The preoperative clinical characteristics of TXA and aprotinin groups in the matched sample

Preoperative characteristic	TXA <i>n</i> = 358	Aprotinin <i>n</i> = 358	Standardized difference
Age (yr), <i>n</i> (SD)	66.2 (12.8)	66.1 (12.9)	-0.004
Female	112 (31.3)	112 (31.3)	0.000
Body mass index (kg·m ⁻²), <i>n</i> (SD)	27.9 (5.7)	27.8 (4.8)	-0.021
Renal failure	38 (10.6)	36 (10.1)	-0.016
Peripheral vascular disease	64 (17.9)	67 (18.7)	0.021
Cerebrovascular disease	57 (15.9)	52 (14.5)	-0.039
Diabetes	123 (34.4)	106 (29.6)	-0.103
Chronic obstructive pulmonary disease	73 (20.4)	70 (19.6)	-0.020
Congestive heart failure	100 (27.9)	96 (26.8)	-0.025
Atrial fibrillation	61 (17.0)	66 (18.4)	0.037
ACE inhibitor	175 (48.9)	169 (47.2)	-0.034
ARB	31 (8.7)	29 (8.1)	-0.022
Antiplatelet	267 (74.6)	256 (71.5)	-0.070
Anticoagulation	138 (38.6)	138 (38.6)	0.000
Hemoglobin (g·L ⁻¹), <i>n</i> (SD)	127.4 (20.2)	127.1 (20.4)	-0.015
Hypertension	253 (70.7)	242 (67.6)	-0.067
Smoking history	231 (64.5)	235 (65.6)	0.023
Procedure other than isolated CABG	202 (56.4)	211 (58.9)	0.051
Urgent/emergent surgery	95 (26.5)	95 (26.5)	0.000

Continuous variables are presented as mean (standard deviation); dichotomous variables are presented as *n* (%). SD = standard deviation; TXA = tranexamic acid; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting

platelets, and cryoprecipitate was higher in the aprotinin group. Information regarding dose was unavailable.

Discussion

Numerous studies have compared the risks and benefits of antifibrinolytics. The majority of studies have suggested that aprotinin is the most effective antifibrinolytic for preventing blood loss. Presumably this has led to its preferred use in higher-risk surgeries and for sicker patients.^{22,23} Our results showed that preoperative morbidities and higher-risk more urgent surgeries were more prevalent in the aprotinin group. Surgeons and anesthesiologists preferred aprotinin over TXA for preventing blood loss in high-risk cases. We addressed this selection bias by excluding cases with previous cardiac surgery and by matching aprotinin and TXA patients on their propensity for receiving aprotinin.

Table 3 In-hospital outcomes in the matched sample

Outcome	TXA <i>n</i> = 358	Aprotinin <i>n</i> = 358	Difference Aprotinin - TXA (95% CI)	McNemar's test <i>P</i> value
Mortality	21 (5.9)	39 (10.9)	5.0 (1.1 to 9.1)	0.01
Acute renal failure*	30 (8.8)	38 (11.2)	2.4 (−2.1 to 6.9)	0.29
Blood transfusion	163 (45.5)	185 (51.7)	6.2 (−0.6 to 12.8)	0.07
Stroke	18 (5.0)	21 (5.9)	0.9 (−2.6 to 4.3)	0.74
Sepsis and/or DSWI	16 (4.5)	24 (6.7)	2.2 (−1.3 to 5.8)	0.27
Reoperation for bleeding	23 (6.4)	21 (5.9)	−0.5 (−3.2 to 4.3)	0.88
ICU stay > 72 hr	77 (21.7)	107 (30.0)	8.3 (2.6 to 14.8)	0.005

TXA = tranexamic acid; DSWI = deep sternal wound infection; ICU = intensive care unit; CI = confidence interval. Dichotomous variables are presented as *n* (%). *Acute renal failure data were available for 340 matched pairs

Table 4 Type of blood product transfused in the matched sample

Blood Product	TXA <i>n</i> = 358	Aprotinin <i>n</i> = 358
Red blood cells	158 (44.1)	171 (47.8)
Fresh frozen plasma	59 (16.5)	87 (24.3)
Platelets	51 (14.2)	71 (19.8)
Cryoprecipitates	16 (4.5)	29 (8.1)

TXA = tranexamic acid. Dichotomous variables are presented as *n* (%)

Several recent studies have reported increased mortality associated with aprotinin compared with the other two antifibrinolytics, TXA and ACA.^{5,8,24} In fact, in the BART trial, the higher mortality rate in the aprotinin group precipitated the halt of the trial before its completion. Our study compared aprotinin with TXA by looking at three major outcomes: mortality, acute renal failure, and perioperative blood transfusion.

Our finding that mortality in the aprotinin group was almost double that of the TXA group is consistent with the increased mortality reported in these recent trials. Renal failure was one of the first reported concerns related to aprotinin safety, with studies dating back over a decade. A recent study actually found that TXA had a greater association with renal failure compared with aprotinin, while aprotinin had a greater association with renal dysfunction.¹¹ In our study, acute renal failure occurred more often in the aprotinin group compared with the TXA group, although the magnitude of the difference was small. This is consistent with the majority of recent studies.^{6,13} We found

that ICU stay > 72 hr, which is a surrogate outcome for postoperative morbidity, was significantly higher in the aprotinin group. Our findings raise concern about aprotinin use in other surgical specialties, such as pediatric, thoracic, and orthopedic surgery.^{25–27}

In our study, aprotinin was not associated with decreased blood product requirement. This finding is inconsistent with the majority of studies, which find that aprotinin is, in varying degrees, more effective than TXA for reducing blood loss during cardiac surgery.^{3–5}

A limitation of our study is that blood product dosage and blood loss data were unavailable. Preventing blood loss is beneficial, and there is an increasing body of evidence that adverse outcomes are associated with exposure to allogeneic blood transfusions. Red blood cell transfusion in cardiac surgery patients is strongly associated with poor outcomes, including short- and long-term mortality, renal failure, and increased resource utilization.^{28,29} If aprotinin is in fact more effective at reducing blood loss than TXA, we would expect to see a reduction in morbidity and mortality associated with the reduction in blood product use. Another factor that makes blood transfusion difficult to assess in a nonrandomized trial is the absence of consistent transfusion criteria, which introduces selection bias. This issue is not specific to our centre but is a well-documented problem across the USA and Canada.³⁰

In observational studies, confounding occurs when patients receiving one treatment differ systematically from patients receiving an alternate treatment. Propensity score analysis was used in this study to reduce the impact of confounding when estimating the effect of aprotinin vs TXA. Balance diagnostics showed that the propensity score model was adequately specified. Using propensity scores obtained from this model, we employed a caliper matching method that has been shown to minimize the bias due to measured confounders,²⁰ and 95.2% of the aprotinin cases were included in the matched sample. Nevertheless, one of the underlying principles of propensity score methodology is the assumption that all variables that affect treatment assignment and outcome have been measured. In any observational study there may be unmeasured confounders. Achieving balance on the measured baseline characteristics does not ensure balance on unmeasured variables. For the reasons outlined above, we acknowledge that residual confounding may exist and contribute bias to the estimates of treatment effect.

The results of a single-centre study may lack external validity; however, our institution is unique in that our patients represent a much broader population base than most other single centres. The Maritime Heart Center is the sole tertiary cardiac care provider in a relatively large geographic area (55,300 km²) serving a population base of nearly one million people in Nova Scotia alone, with frequent referrals from the other Atlantic Provinces.

Some researchers suggest that aprotinin is safe depending on patient comorbidities and the surgery type and severity, but even they do not agree on the details and conditions.^{6,9,11,31,32} Aprotinin is not available in the USA. Health Canada has recently lifted the ban and approved aprotinin when used as authorized in CABG surgery. Surgeons and anesthesiologists in Canada need to be aware of the risks of both aprotinin use and TXA use and contrast these risks with the benefits of each.

Conclusion

Results of our retrospective observational study showed that aprotinin was associated with an increased risk of in-hospital mortality and morbidity in cardiac surgery cases. Furthermore, blood product requirement was not reduced in the aprotinin group compared with TXA. Continued use of aprotinin in cardiac surgery should follow careful consideration, weighing the demonstrated risks and potential advantages compared with other antifibrinolytics.

Conflict of interest None declared.

References

1. Dacey LJ, Munoz JJ, Baribeau YR, et al. Reexploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. Northern New England Cardiovascular Disease Study Group. *Arch Surg* 1998; 133: 442-7.
2. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007; 4: CD001886.
3. Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46: 327-38.
4. 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.
5. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *CMAJ* 2009; 180: 183-93.
6. Umscheid CA, Kohl BA, Williams K. Antifibrinolytic use in adult cardiac surgery. *Curr Opin Hematol* 2007; 14: 455-67.
7. Dietrich W, Spannagl M, Boehm J, et al. Tranexamic acid and aprotinin in primary cardiac operations: an analysis of 220 cardiac surgical patients treated with tranexamic acid or aprotinin. *Anesth Analg* 2008; 107: 1469-78.
8. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 358: 2319-31.
9. Later AFL, Maas JJ, Engbers FH, et al. Tranexamic acid and aprotinin in low- and intermediate-risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial. *Eur J Cardiothorac Surg* 2009; 36: 322-9.
10. 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.
11. Martin K, Wiesner G, Breuer T, Lange R, Tassani P. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. *Anesth Analg* 2008; 107: 1783-90.
12. Olenchok SA Jr, Lee PH, Yehoshua T, Murphy SA, Symes J, Tolis G Jr. Impact of aprotinin on adverse clinical outcomes and mortality up to 12 years in a registry of 3,337 patients. *Ann Thorac Surg* 2008; 86: 560-7.
13. Mangano DT, Tudor IC. Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354: 353-65.
14. Furnary AP, Wu Y, Hiratzka LF, Grunkemeier GL, Page US 3rd. Aprotinin does not increase the risk of renal failure in cardiac surgery patients. *Circulation* 2007; 116(11 Suppl): I127-33.
15. Coleman CI, Rigali VT, Hammond J, Kluger J, Jeleniowski KW, White CM. Evaluating the safety implications of aprotinin use: the Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS). *J Thorac Cardiovasc Surg* 2007; 133: 1547-52.
16. Dietrich W, Busley R, Boulesteix AL. Effects of aprotinin dosage on renal function: an analysis of 8,548 cardiac surgical patients treated with different dosages of aprotinin. *Anesthesiology* 2008; 108: 189-98.
17. Royston D, Levy JH, Fitch J, et al. Full-dose aprotinin use in coronary artery bypass graft surgery: an analysis of perioperative pharmacotherapy and patient outcomes. *Anesth Analg* 2006; 103: 1082-8.
18. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; 10: 150-61.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083-107.
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46: 399-424.
21. Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. *Stat Med* 1998; 17: 2635-50.
22. Royston D, Taylor KM, Bidstrup BP, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987; 330: 1289-91.
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. 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.
25. Baldus CR, Bridwell KH, Lenke LG, Okubadejo GO. Can we safely reduce blood loss during lumbar pedicle subtraction osteotomy procedures using tranexamic acid or aprotinin? A comparative study with controls. *Spine (Phila Pa 1976)* 2010; 35: 235-9.
26. Ferreira CA, Vicente WV, Evora PR, et al. Assessment of aprotinin in the reduction of inflammatory systemic response in children undergoing surgery with cardiopulmonary bypass. *Rev Bras Cir Cardiovasc* 2010; 25: 85-98.
27. Herrington CS, Prekker ME, Arrington AK, et al. A randomized, placebo-controlled trial of aprotinin to reduce primary graft

- dysfunction following lung transplantation. *Clin Transplant* 2011; 25: 90-6.
28. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; 116: 2544-52.
29. Surgenor SD, Kramer RS, Olmstead EM, et al. Northern New England Cardiovascular Disease Study Group. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. *Anesth Analg* 2009; 108: 1741-6.
30. Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010; 304: 1568-75.
31. Sodha NR, Boodhwani M, Sellke FW. Is there still a role for aprotinin in cardiac surgery? *Drug Saf* 2007; 30: 731-40.
32. Karkouti K, Wijeyesundera DN, Yau TM, McCluskey SA, Tait G, Beattie WS. The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery. *Anesth Analg* 2010; 110: 21-9.