A comparison before and after aprotinin was suspended in cardiac surgery: Different results in the real world from a single cardiac center in China

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Objective: Use of aprotinin has been suspended in cardiac surgery since recent studies reported its risks associated with mortality and other adverse events. This study was to investigate the safety and efficacy of aprotinin through a comparison before and after aprotinin was suspended in cardiac surgery.

Methods: We designed a case-control study in two groups of patients who underwent cardiac surgery just before and after aprotinin was suspended in China. The aprotinin group (n = 1699) was defined as operations performed from June 19, 2007, to December 18, 2007, when aprotinin was used in all the patients. The control group (n = 2225) was defined as operations performed from December 19, 2007, to June 18, 2008, when aprotinin was not used. We compared early postoperative outcomes between the two groups.

Results: The aprotinin group had less postoperative blood loss, transfusion requirement, and reoperation for bleeding. Application of aprotinin did not increase the risk of in-hospital mortality (0.5% vs 1.0%; $P = .08$) and other major adverse outcome events, including renal, cardiac, neurologic, and pulmonary complications. The aprotinin group had a shorter mechanical ventilation time ($P = .04$), a lower rate of delayed mechanical ventilation time ($P = .04$), and a higher arterial oxygen tension/inspired oxygen fraction ratio in arterial blood gas analysis ($P < .001$). Multivariable logistic regression analysis confirmed findings from univariate analysis. After propensity adjustment for the baseline characteristics, we obtained similar results.

Conclusions: Use of aprotinin in cardiac surgery could reduce blood loss and transfusion requirement significantly and showed a protective effect on the lungs, but it did not increase the risk of mortality or major complications.

Aprotinin, a serine protease inhibitor, has been widely used in cardiac surgery for more than 10 years, since it was first approved by the US Food and Drug Administration for use in high-risk patients requiring coronary artery surgery in 1993. The main purpose of aprotinin is to reduce blood loss and limit inflammatory responses after cardiopulmonary bypass (CPB). Many studies¹⁻⁸ have proved the safety and efficacy of aprotinin in patients undergoing cardiac surgery. Therefore, application of aprotinin had been a therapeutic routine in many cardiac centers. However, Mangano and

associates^{9,10} found the use of aprotinin in patients undergoing coronary artery bypass grafting (CABG) to be associated with higher mortality and increased risk of renal, cerebral, and cardiac adverse events in both short-term and long-term studies. These findings and conclusions resulted in controversies in aprotinin use in cardiac surgery all over the world. Several large-scale retrospective studies focused on the safety concerns of aprotinin and yielded different results.¹¹⁻¹⁶ The prospective randomized controlled multicenter study named BART¹⁷ (the Blood Conservation Using Antifibrinolytics in a Randomized Trial) compared aprotinin with two other antifibrinolytics in patients undergoing high-risk cardiac surgery. The aprotinin group had higher 30-day mortality than the other two groups and the study's recommendation was to "preclude its use in patients undergoing high-risk cardiac surgery." As a result of the BART, the US Food and Drug Administration suspended the use of aprotinin in cardiac surgery on November 5, 2007. Subsequently, the State Food and Drug Administration of China suspended its use in cardiac surgery on December 19, 2008.

However, several issues or concerns have to be addressed for the clinical safety of aprotinin. First, most of the enrolled patients in these studies were white. Ethnic differences exist in blood coagulation function and fibrinolysis^{18,19} and in responses to special drugs such as warfarin.^{20,21} Does

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The study was funded by Key Projects in the National Science & Technology Pillar Program during the Eleventh Five-year Plan Period (2006BAI01A09) and Key Projects of Beijing Municipal Science & Technology Commission (D0906004040391).

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Received for publication Dec 4, 2008; revisions received Feb 18, 2009; accepted for publication March 9, 2009; available ahead of print April 27, 2009.

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J Thorac Cardiovasc Surg 2009;138:897-903

0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2009.03.021

Abbreviations and Acronyms

BART	= Blood Conservation Using Antifibrinolytics in a Randomized Trial
CABG	= coronary artery bypass grafting
CI	= confidence intervals
CPB	= cardiopulmonary bypass
ICU	= intensive care unit
KIU	= kallikrein international units
PaO ₂ /FIO ₂	= arterial oxygen tension/inspired oxygen fraction ratio

aprotinin have the same effect and safety concerns in Asian populations as in white patients? Second, a relatively lower dosage of aprotinin was given in Chinese cardiac surgery than that used in the aforementioned studies. Does a low dose of aprotinin have fewer safety concerns in cardiac surgery and can the optimal (safe and effective) dosage of aprotinin be found? Third, the pivotal BART study focused on a special cohort of patients who underwent high-risk cardiac surgery, and its conclusion was to stop the use of aprotinin in high-risk cardiac surgery. Is this recommendation valid in low-risk cardiac surgery or in the whole body of patients undergoing cardiac surgery? Fourth, aprotinin is superior to other antifibrinolytics in reducing blood loss after surgery.^{9,17} The suspension or permanent withdrawal of aprotinin will lead to increased transfusion requirements and concomitant complications. Do patients benefit more or less after the suspension of aprotinin in cardiac surgery?

To address these questions, we performed an observational study in a single cardiac center in China to evaluate the safety and efficacy of aprotinin in cardiac surgery in the Chinese population.

METHODS**Study Design**

We conducted an observational study based on a policy change in cardiac surgery: the use of aprotinin in cardiac surgery was suspended in China on December 19, 2007. We defined two groups of patients who underwent cardiac surgery during equal periods before and after that date. The aprotinin group (n = 1699) was defined as consecutive adult patients undergoing open cardiac surgery from June 19, 2007, to December 18, 2007, during which period aprotinin was used in all patients. The control group (n = 2225) was defined as consecutive adult patients undergoing open cardiac surgery from December 19, 2007, to June 18, 2008, during which aprotinin was not used and no other antifibrinolytic medications were given. This study was performed in the Department of Cardiovascular Surgery, Fuwai Hospital, Beijing, which is the largest cardiac center in China, with more than 7000 cardiovascular surgical operations performed per year. During the study period, the surgical team did not change, the proportions of every type of operations were almost same, and the perioperative management followed the same protocol in the two groups. Clinical baseline characteristics and postoperative outcomes were collected throughout hospitalization materials. The study was approved by the ethics committee of Fuwai Hospital.

Study Population

All the enrolled patients were at least 18 years of age and underwent open-thorax cardiac surgical procedures with CPB. The cardiac surgical procedures included the following: CABG, valve replacement or repair, surgery for congenital heart disease, surgery of the aorta, and other cardiac surgical procedures. Patients who required urgent procedures, repeat cardiac surgery, or combined cardiac surgical procedures were also considered eligible. Infrequent procedures such as heart transplantation and procedures without CPB were excluded. We excluded 2389 pediatric patients with congenital heart disease (who are younger than 18 years and for whom aprotinin is not routinely used according to the protocol in our center) and 728 operations without CPB.

Administration of Aprotinin

In the Cardiac Surgery Department of Fuwai Hospital, the maximum effective regimen of aprotinin was not given. For patients in the aprotinin group, a test dose of 10,000 kallikrein international units (KIU) of aprotinin was administered during a 30-minute period after the insertion of a central venous line and induction of anesthesia. In the absence of an anaphylactic reaction, the loading dose (1 million–3 million KIU) was given by the anesthetist. An additional dose of 2 million KIU was added to the CPB circuit. The total dosage of aprotinin was 3 to 5 million KIU, with a mean dosage of 3.7 ± 1.2 million KIU. For patients in the control group, neither aprotinin nor other antifibrinolytic medications were given during the operation.

Outcomes and Definition

Primary outcomes were blood loss, transfusion requirement, and reoperation for bleeding. *Blood loss* was defined as the blood lost from chest tubes in the first 24 hours and the second 24 hours after the operation. *Transfusion requirement* included the amount of red cells and plasma. *Reoperations for bleeding* were designated as those resulting from massive bleeding or cardiac tamponade within 24 hours after the operation.

Secondary outcomes included in-hospital mortality and major adverse events. *In-hospital mortality* was defined as death from any cause after the operation during hospitalization. *Renal dysfunction* required a postoperative serum creatinine level of at least $177 \mu\text{mol/L}$ with an increase over preoperative baseline levels of at least $62 \mu\text{mol/L}$. The serum creatinine value selected for analysis was the peak value after the operation. *Renal failure* was defined as renal dysfunction requiring dialysis owing to prolonged oliguria or anuria. Neurologic complications included new-onset stroke, coma, and encephalopathy. *Stroke* was defined as a history of central neurologic deficit persisting more than 24 hours. *Coma* was defined as unresponsive coma lasting more than 24 hours. *Encephalopathy* was defined as reversible neurologic deficit (recovery within 72 hours of onset). *Low cardiac output syndrome* was defined as a cardiac index lower than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and the postoperative need for left ventricular assist device, intra-aortic balloon pump (IABP), and inotropic support. Pulmonary complications included delayed mechanical ventilation time (>24 hours), reintubation owing to respiratory failure, and serious pneumonia, which was diagnosed by sputum culture and radiographic findings.

Tertiary outcomes included the length of intensive care unit (ICU) stay, total mechanical ventilation time, and arterial oxygen tension/inspired oxygen fraction (PaO₂/FIO₂) ratio in the blood gas analysis 24 hours after the operation.

Subgroup Analysis

In addition, we divided the patients into subgroups according age, sex, type of procedure, and risk level to investigate whether aprotinin was an independent risk factor of mortality, reoperation for bleeding, and composite complications. The cut point of age subgroup was 65 years old. The *high-risk subgroup* in our study was defined as patients undergoing aortic surgery and repeated surgical procedures, and the *low-risk subgroup* included all the primary procedures except aortic surgery.

Statistical Analysis

Data of clinical baseline characteristics and postoperative outcomes were compared statistically. The Student *t* test and χ^2 test were used to analyze continuous variables and categorical variables, respectively, in univariate analyses; means and standard deviations were used for continuous variables and frequencies for categorical variables. Multivariable logistic regression analyses were used to examine whether use of aprotinin was independently related to defined postoperative outcomes. Fifteen risk predictors were assessed for association with outcomes by stepwise methods. Besides aprotinin, predictors studied included age, weight, sex, emergency operation, left ventricular ejection fraction, preoperative atrial fibrillation, history of myocardial infarction, prior open cardiothoracic operations, history of cerebral adverse events, hypertension, diabetes metabolism, history of heart failure, CPB time, aortic crossclamp time, and preoperative serum creatinine level. All outcomes of interest were as follows: reoperation owing to bleeding, in-hospital mortality, renal dysfunction, renal failure necessitating dialysis, low cardiac output syndrome, intra-aortic balloon pumping after the operation, new-onset neurologic complications, delayed mechanical ventilation time, serious lung infection, and repeat intubation owing to respiratory failure. Selection bias not controlled by multivariable regression was assessed with a propensity-adjustment method. Using logistic regression modeling, we calculated propensity scores for the use of aprotinin (vs control), including 15 treatment-selection covariates. Multivariable regression was performed with and without propensity scores as a variable and yielded similar results.

All analyses were performed with SPSS statistical software (version 11.0; SPSS, Inc, Chicago, Ill).

RESULTS

The clinical baseline characteristics of the two groups are shown in Table 1. The study comprised 3924 patients, 1699 patients in the aprotinin group and 2225 patients in the control group. The proportion of every type of operation was similar between the two groups (Figure 1). The control group had more patients having an emergency operation (2.5% vs 1.6%; *P* = .05) and more patients with preoperative atrial fibrillation (18.7% vs 16.1%; *P* = .03). There was no significant difference between the two groups in other preoperative and operative characteristics (Table 1).

Blood Loss and Transfusion (Figure 2)

Blood loss in the control group was higher than that in the aprotinin group for both the first 24 hours (628.1 ± 378.2 mL vs 402.5 ± 267.3 mL; *P* < .001) and the second 24 hours (246.4 ± 231.7 mL vs 212.8 ± 209.8 ; *P* < .001). Similarly, the transfusion requirement for red cells (3.2 ± 5.6 units vs 2.6 ± 5.8 units; *P* = .002) and plasma (400.5 ± 724.2 mL vs 317.0 ± 746.0 mL; *P* < .001) was significantly higher in the control group. The rate of reoperation for bleeding was higher in the control group (3.7% vs 2.0%; *P* = .002) (Table 2). Multivariate regression analysis revealed that aprotinin was an independent predictor of reoperation for bleeding after adjustment of effects from other covariates (*P* = .002; relative risk, 0.51; 95% confidence intervals [CI], 0.34–0.78). After propensity score adjustment, multivariate regression analysis continued to demonstrate a significant association between the use of aprotinin and a decreased risk of reoperation for bleeding (Table 3).

TABLE 1. Preoperative baseline characteristics of the patients

Characteristic	Aprotinin group (n = 1699)	Control group (n = 2225)	P value (2-tailed)
Age	47.8 ± 17.2	48.0 ± 16.0	.64
Weight	63.6 ± 13.0	64.4 ± 13.4	.08
Male/female	1033/666	1314/911	.27
Hypertension	452 (26.6%)	587 (26.4%)	.88
Diabetes mellitus	164 (9.7%)	252 (11.3%)	.09
Creatinine (μmol/L)	80.3 ± 30.6	79.9 ± 29.2	.65
History of renal failure	19 (1.1%)	15 (0.7%)	.14
Cerebrovascular events	47 (2.8%)	86 (3.9%)	.06
Myocardial infarction	208 (12.2%)	300 (13.5%)	.25
Congestive heart failure	275 (16.2%)	410 (18.4%)	.07
Atrial fibrillation	273 (16.1%)	416 (18.7%)	.03*
LVEF (%)	60.4 ± 8.7	60.2 ± 8.3	.55
Emergency status	27 (1.6%)	56 (2.5%)	.05*
Repeat procedure	67 (3.9%)	65 (2.9%)	.08
CPB time (min)	108.8 ± 51.0	110.2 ± 49.9	.38
Aortic crossclamp time (min)	72.6 ± 36.3	71.2 ± 32.4	.21
CABG	535 (31.5%)	735 (33.0%)	.31
Valve disease	511 (30.1%)	636 (28.6%)	.31
CHD	397 (23.4%)	473 (21.3%)	.12
Aortic disease	115 (6.8%)	164 (7.4%)	.47
Other disease	141 (8.3%)	217 (9.8%)	.12

LVEF, Left ventricular ejection fraction; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; CHD, congenital heart disease. The Student *t* test was used to analyze continuous variables and χ^2 test was used for categorical variables.

*Statistical significance was set at *P* < .05.

Mortality and Other Outcome Events

A total of 32 (0.8%) patients died during hospitalization after surgery. The in-hospital mortality was 0.5% in the aprotinin group as compared with 1.0% in the control group (*P* = .08; Table 2). Results of the multivariate regression analyses showed that aprotinin was not independently associated with in-hospital death (*P* = .14; relative risk, 0.55; 95% CI, 0.24–1.22) (Table 3). However, the aprotinin group had a lower rate of delayed mechanical ventilation time than the control group (8.8% vs 10.7%; *P* = .04). All rates of other adverse outcome events, including renal dysfunction, renal failure necessitating dialysis, new-onset neurologic complications, low cardiac output syndrome, serious pneumonia, reintubation owing to respiratory failure, and composite complications, were similar in the two groups. Both univariate analysis and multivariate logistic regression analysis obtained consistent results (Tables 2 and 3). Multivariate logistic regression analysis with or without propensity score adjustment yielded identical results (Table 3).

Length of ICU Stay

There was no significant difference in the mean length of stay in the ICU between the aprotinin group and the control group (55.8 ± 84.4 hours vs 53.8 ± 77.4 hours; *P* = .44) (Table 2).

FIGURE 1. Comparison of every type of procedure in the two groups. CABG, Coronary artery bypass grafting; CHD, congenital heart disease.

Mechanical Ventilation Time

The mean mechanical ventilation time after operation in the aprotinin group was significantly shorter than that in the control group (18.9 ± 45.0 hours vs 22.2 ± 53.6 hours; $P = .04$) (Table 2).

Blood Gas Analysis

Arterial blood gas was regularly analyzed 24 hours after the operation. The aprotinin group had a higher $\text{PaO}_2/\text{FiO}_2$ ratio than the control group (535.2 ± 221.2 vs 505.8 ± 214.8 ; $P < .001$) (Table 2).

FIGURE 2. Comparison of the postoperative blood loss and transfusion. Red blood cell (RBC) transfusion: 1 unit = 150 mL.

Subgroup Analysis

Subgroup analysis showed that the use of aprotinin did not increase in-hospital mortality and composite complications. Furthermore, in the male, old-age, and low-risk subgroups, aprotinin was associated with a lower mortality. However, the suspension of aprotinin significantly increased the rate of reoperation for bleeding in the subgroups of young-age, male, low-risk, and CABG (Table 4).

DISCUSSION

According to our findings, the use of aprotinin in cardiac surgery could significantly reduce blood loss and transfusion

TABLE 2. Comparison of perioperative outcomes

Perioperative outcomes	Aprotinin group (n = 1699)	Control group (n = 2225)	P value (2-tailed)
Blood loss (mL)			
First 24 hours	402.5 ± 267.3	628.1 ± 378.2	<.001*
Second 24 hours	212.8 ± 209.8	246.4 ± 231.7	<.001*
Blood transfusion			
Plasma (mL)	317.0 ± 746.0	400.5 ± 724.2	<.001*
Red cells (unit)	2.6 ± 5.8	3.2 ± 5.6	.002*
Reoperation for bleeding	34 (2.0%)	83 (3.7%)	.002*
In-hospital mortality	9 (0.5%)	23 (1.0%)	.08
Renal failure			
Renal failure requiring dialysis	21 (1.2%)	22 (1.0%)	.46
Renal dysfunction	28 (1.6%)	23 (1.0%)	.09
LCOS	327 (19.2%)	467 (21.0%)	.18
IABP after operation	13 (0.6%)	22 (1.0%)	.46
Neurologic complications	38 (2.2%)	47 (2.1%)	.79
Pulmonary complications			
Delayed mechanical ventilation time	149 (8.8%)	239 (10.7%)	.04*
Reintubation	10 (0.6%)	23 (1.0%)	.13
Serious lung infection	16 (0.9%)	19 (0.9%)	.77
Composite complications	394 (23.2%)	534 (24.0%)	.55
Length of ICU stay (h)	55.8 ± 84.4	53.8 ± 74.4	.44
Mechanical ventilation time (h)	18.9 ± 45.0	22.2 ± 53.6	.04*
$\text{PaO}_2/\text{FiO}_2$ ratio	535.2 ± 221.2	505.8 ± 214.8	<.001*

LCOS, Low cardiac output syndrome; IABP, intra-aortic balloon pump; ICU, intensive care unit; $\text{PaO}_2/\text{FiO}_2$, arterial oxygen tension/inspired oxygen fraction. The Student *t* test was used to analyze continuous variables, and the χ^2 test was used for categorical variables. *Statistical significance was set at $P < .05$.

TABLE 3. Propensity-adjusted effect of aprotinin on perioperative outcome events in logistic regression model

Perioperative outcome events	Without propensity score		With propensity score	
	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)
Reoperation for bleeding	.002*	0.51 (0.34–0.78)	.002*	0.51 (0.34–0.78)
In-hospital mortality	.14	0.55 (0.24–1.22)	.12	0.52 (0.23–1.17)
Renal failure requiring dialysis	.58	1.20 (0.64–2.25)	.63	1.17 (0.62–2.20)
Renal dysfunction	.10	1.60 (0.91–2.80)	.13	1.56 (0.88–2.74)
LCOS	.42	0.93 (0.79–1.11)	.44	0.94 (0.79–1.11)
IABP after operation	.27	0.66 (0.32–1.37)	.32	0.69 (0.34–1.43)
Neurologic complications	.76	1.07 (0.68–1.68)	.80	1.06 (0.68–1.67)
Delayed mechanical ventilation time	.02*	0.75 (0.60–0.95)	.01*	0.75 (0.59–0.94)
Reintubation	.08	0.50 (0.23–1.10)	.07	0.48 (0.22–1.07)
Serious lung infection	.69	1.15 (0.58–2.30)	.74	1.13 (0.56–2.25)
Composite complications	.95	1.00 (0.85–1.17)	.94	0.99 (0.85–1.17)

CI, Confidence intervals; LCOS, low cardiac output syndrome; IABP, intra-aortic balloon pump. *Statistical significance was set at $P < .05$.

requirement and have a protective effect on the lungs, without increasing the risk of mortality or major complications. This was an observational study conducted in a single cardiac center of China, and it was not supported by a business sponsor. This study was initiated by a policy change of suspending the use of aprotinin in patients undergoing cardiac surgery on December 19, 2007. By that cut point, we obtained two naturally well-matched groups in a relatively short period. Thus, the selection bias for patient recruitment between the two groups would be low, although the study was not a prospective randomized control trial. Therefore, our study provided a unique opportunity to demonstrate the effect of aprotinin in cardiac surgery practice.

The mechanisms of aprotinin have been elucidated in many studies.²²⁻²⁴ Through its inhibition of multiple mediators (eg, kallikrein, plasmin), aprotinin attenuates inflammatory responses, fibrinolysis, and thrombin generation. As a result, it can protect the organs and reduce bleeding after cardiac sur-

gery. In the present study, blood loss, transfusion requirement, and rate of reoperation for bleeding after the operation were significantly increased after the suspension of aprotinin. Our results showed that aprotinin was effective in reducing bleeding in cardiac surgery, which was the same effect reported in most prior studies.^{1,3,9,13,14,25} As to the safety of aprotinin in cardiac surgery, Chinese patients as this sample from the Asian population were investigated to study whether the adverse effects mentioned by the previous articles would develop after administration of aprotinin in cardiac surgery. Our results illustrated that the use of aprotinin did not increase the risk of in-hospital mortality and other major complications. Of particular note, mortality in the aprotinin group (0.5%) was lower than that in the control group (1.0%), although the difference did not reach statistical significance ($P = .08$).

In the present study, the use of aprotinin was effective in reducing blood loss, and it did not create more safety concerns than those in the control group. These results were notably different

TABLE 4. Multivariate logistic regression analysis of effect of aprotinin in various major subgroups

Major subgroups	In-hospital mortality		Composite complications		Reoperation for bleeding	
	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)
Age						
≥65 y (n = 630)	.04*	0.21 (0.05–0.93)	1.00	1.00 (0.70–1.43)	.08	0.48 (0.21–1.10)
<65 y (n = 3294)	.25	0.57 (0.21–1.50)	1.00	1.00 (0.84–1.19)	.01*	0.56 (0.35–0.89)
Sex						
Male (n = 2347)	.04*	0.34 (0.12–0.95)	.70	1.04 (0.85–1.27)	.003*	0.47 (0.29–0.77)
Female (n = 1577)	.71	0.78 (0.21–2.89)	.75	0.96 (0.75–1.23)	.39	0.72 (0.34–1.52)
Risk level						
High risk (n = 399)	.78	0.83 (0.23–3.06)	.83	1.05 (0.66–1.69)	.93	1.04 (0.47–2.28)
Low risk (n = 3525)	.05*	0.36 (0.13–0.99)	.94	0.99 (0.84–1.17)	<.001*	0.42 (0.26–0.68)
Procedures						
CABG (n = 1270)	.052	0.12 (0.01–1.02)	.66	1.07 (0.80–1.41)	.006*	0.36 (0.17–0.75)
Valve (n = 1147)	.12	0.25 (0.04–1.45)	.27	0.86 (0.66–1.12)	.07	0.45 (0.19–1.07)
CHD (n = 870)	.91	1.11 (0.17–7.23)	.45	0.86 (0.59–1.26)	.43	0.64 (0.21–1.95)
Aortic (n = 279)	.72	1.43 (0.20–10.33)	.85	0.95 (0.72–1.43)	.84	0.90 (0.34–2.40)
Others (n = 358)	.54	0.54 (0.08–3.86)	.15	1.47 (0.87–2.48)	.62	1.38 (0.39–4.94)

CABG, Coronary artery bypass grafting; CHD, congenital heart disease; CI, confidence intervals; high risk, including aortic surgical procedures and repeated procedures; low risk, including all the primary procedures except the aortic operation. *Statistically significant difference.

from findings of recent studies opposing the use of aprotinin in cardiac surgery. The possible reasons were as follows: First, racial difference may partially lead to different results. In the prior studies, most of the enrolled patients were white, whereas all the patients enrolled in the present study were Chinese (Asian). It has been reported that there are racial or ethnic differences in the blood coagulation function and fibrinolysis system^{18,19} and differences in responses to special drugs such as warfarin.^{20,21} Until now, there have been no large-scale studies about aprotinin available in the Asian population. A different response to aprotinin may exist between white and Asian populations. Second, a lower dose of aprotinin may cause fewer safety concerns. In Chinese cardiac surgery, aprotinin was given at a relatively lower dosage than the maximum effective regimens. In the previous studies, a low dose of aprotinin was effective in reducing blood loss,^{3,25} and Mangano, Tudor, and Dietzel⁹ reported that a high dose of aprotinin was associated with an increased mortality and morbidity. There might be an optimal dose range of aprotinin that will be safe and effective in cardiac surgery. Third, the BART study focused on a special cohort of patients who underwent high-risk surgery. Whether aprotinin has the same clinical impact on all patients undergoing cardiac surgery has not been proved. In this study, most of the patients were at low risk. Low-risk patients might benefit from aprotinin without major safety concerns. In view of these uncertainties of aprotinin, further studies are warranted in different races, operations, and dosages before a final decision is made about whether to continue or discontinue the use of aprotinin in cardiac surgery.

The shorter mechanical ventilation time and higher $\text{PaO}_2/\text{FiO}_2$ ratio in blood gas analysis indicated better respiratory function in the aprotinin group in this study. It has been reported that aprotinin could decrease lung edema in cardiac surgery.^{24,26} In this study, aprotinin might protect the lungs through reducing inflammatory responses from damage after CPB, and less blood transfusion in the aprotinin group might also be beneficial to the lungs.

Among 399 patients in the high-risk subgroup, the use of aprotinin was not associated with an increase of mortality, composite complications, and reoperation for bleeding. Although in the low-risk subgroup ($n = 3525$) aprotinin decreased mortality ($P = .05$; odds ratio, 0.36; 95% CI, 0.13–0.99) and the rate of reoperation for bleeding ($P < .001$; odds ratio, 0.42; 95% CI, 0.26–0.68), it was not associated with composite complications ($P = .94$; odds ratio, 0.99; 95% CI, 0.84–1.17). Therefore, this indicated that its use in low-risk patients was safe and effective.

The present study does have some limitations. First, it was a retrospective observational study in a single center, and its patient allocation was based on a policy change. However, there was no significant difference in most of the preoperative characteristics. Second, although all the patients underwent surgical procedures within the restricted consecutive 12 months, a time-related selection bias might exist between the two groups. Third, all the enrolled patients were Chinese,

and the results may be relevant and applicable only in the Chinese or Asian population.

In conclusion, in this observational cohort study of Chinese patients, use of aprotinin in cardiac surgery could significantly reduce blood loss and transfusion requirement and have a protective effect on the lungs, without increasing the risk of mortality or major complications. Should aprotinin be totally suspended or replaced in cardiac surgery in a precipitous manner? Further large well-designed and well-constructed randomized controlled trials in different races, dosages, and cardiac operations will be required to give a definitive answer to this question.

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