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Safety of Aprotinin in Congenital Heart Operations: Results from a Large Multicenter Database

Sara K. Pasquali, MD, Matthew Hall, PhD, Jennifer S. Li, MD, MHS,
Eric D. Peterson, MD, MPH, James Jaggers, MD, Andrew J. Lodge, MD,
Jeffrey P. Jacobs, MD, Marshall L. Jacobs, MD, and Samir S. Shah, MD, MSCE

Divisions of Pediatric Cardiology, Cardiothoracic Surgery, and Cardiology in the Departments of Pediatrics, Surgery, and Medicine, Duke University Medical Center, and Duke Clinical Research Institute, Durham, North Carolina; Child Health Corporation of America, Shawnee Mission, Kansas; Division of Thoracic and Cardiovascular Surgery, The Congenital Heart Institute of Florida, All Children's Hospital and Children's Hospital of Tampa, University of South Florida College of Medicine, St. Petersburg and Tampa, Florida; Department of Pediatric and Congenital Heart Surgery, Cleveland Clinic, Cleveland, Ohio; and Division of Infectious Disease, Department of Pediatrics, and Center for Clinical Epidemiology and Biostatistics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Background. Aprotinin was used frequently in children undergoing congenital heart operations with the aim of reducing bleeding, until it was taken off the market after adult studies reported increased renal failure and death. We evaluated the safety of aprotinin in a large multicenter cohort of children undergoing congenital heart operations.

Methods. The Pediatric Health Information Systems Database was used to evaluate aprotinin in children (aged 0 to 18 years) undergoing congenital heart operations at 35 children's hospitals from 2003 to 2007. Propensity scores were constructed to account for potential confounders of age, sex, race, prematurity, genetic syndrome, type of operation (Risk Adjustment in Congenital Heart Surgery-1 category), center, and center volume. Multivariable analysis, adjusting for propensity score and individual covariates was performed to evaluate in-hospital mortality, postoperative renal failure requiring dialysis, and length of stay. Subanalysis was performed in the high-risk cohort undergoing reoperation.

Results. The study included 30,372 patients (56% male) who were a median age of 7 months (interquartile range, 36 days to 3.2 years). Overall, 44% received aprotinin. Multivariable analysis found no difference in postoperative mortality (odds ratio, 1.00; 95% confidence interval [CI], 0.99 to 1.01), dialysis (odds ratio, 1.00; 95% CI, 0.99 to 1.01), or length of stay (least square mean difference, -0.44 days; 95% CI, -1.01 to 0.13) between aprotinin recipients and nonrecipients. No difference was found in mortality or dialysis in patients undergoing reoperation. Aprotinin recipients in the reoperation subgroup had significantly reduced length of stay (least square mean difference, -2.05 days; 95% CI -3.29 to -0.81).

Conclusions. These data suggest aprotinin is not associated with increased mortality or dialysis in children undergoing congenital heart operations and that further evaluation of aprotinin in this population could be undertaken without undue risk.

(Ann Thorac Surg 2010;90:14–21)

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Aprotinin, an antifibrinolytic agent, was often used in children undergoing congenital heart operations with the aim of reducing intraoperative and postoperative bleeding [1, 2]. Aprotinin also has antiinflammatory properties that may be beneficial in attenuating the inflammatory response associated with cardiopulmonary bypass [3–5]. In 2007, however, aprotinin was taken off the market after studies reported increased mortality and renal failure in adults [5, 6]. As a result, aprotinin was also no longer

available to children undergoing congenital heart operations who are more prone to bleeding during and after cardiac operations than adults [7]. Small single-center studies have suggested that aprotinin may not be associated with adverse outcomes in children [8, 9]. Guzzetta and colleagues [8] evaluated 200 neonates undergoing congenital heart operations and found no difference in mortality or renal failure in aprotinin recipients and nonrecipients.

Thus, given the potential benefits and perhaps more favorable safety profile compared with adults, there is

Accepted for publication Feb 24, 2010.

Address correspondence to Dr Pasquali, Division of Cardiology, Department of Pediatrics, Duke University Medical Center, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715; e-mail: sara.pasquali@duke.edu

Dr Jeffrey P. Jacobs discloses that he has a financial relationship with CardioAccess.

interest in further study of aprotinin in children. Because studies to date have been limited in scope and size, a more comprehensive analysis of safety outcomes associated with aprotinin is necessary to determine whether further prospective study could be undertaken without undue risk.

The primary objective of this study was to evaluate safety outcomes associated with aprotinin in a large multicenter cohort of children undergoing congenital heart operations. Also performed was a subanalysis by Risk Adjustment in Congenital Heart Surgery, version 1 (RACHS-1) category and in those undergoing reoperation.

Material and Methods

The Children's Hospital of Philadelphia Committees for the Protection of Human Subjects approved this study with a waiver of informed consent.

Data Source

Data for this multicenter retrospective cohort study were obtained from the Pediatric Health Information Systems Database, which contains resource utilization data from 39 freestanding, tertiary care children's hospitals affiliated with the Child Health Corporation of America (Shawnee Mission, KS). Hospitals participating in the Pediatric Health Information Systems Database, which account for 20% of all tertiary care children's hospitals, provide discharge data, including patient demographics, diagnoses, and procedures. Billing data are also available detailing medications, imaging studies, laboratory tests, and supplies charged to each patient. Data quality and reliability are assured through a joint effort between Child Health Corporation of America and participating hospitals, including bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports.

Study Population

The study excluded 2 centers with an average annual congenital heart surgery volume of fewer than 50 cases per year and 2 centers with wide deviation from other centers in their practice pattern regarding postoperative dialysis, a key outcome measure (likely related to routine use of peritoneal dialysis in postoperative management of fluid status in certain patient groups). Thus, 35 centers were included in the analysis. The study included children aged 18 years old or younger discharged from these centers between January 1, 2003, and December 31, 2007, who underwent congenital heart operations classified in any of the RACHS-1 categories [10]. The RACHS-1 method has been used extensively in risk stratification of patients undergoing congenital heart operations, as previously described [10, 11]. The study excluded patients who did not require cardiopulmonary bypass (*International Classification of Diseases, Ninth Revision* [ICD-9] procedure code 39.61) in conjunction with their operation and those who received any other antifibrinolytic therapy (aminocaproic acid or tranexamic acid).

Data Collection and Study Definitions

Aprotinin recipients were defined as those who received aprotinin on the day of operation. Other variables collected included patient age, sex, race/ethnicity, weight (for neonates), prematurity (ICD-9 codes 765.0×–765.3×), or any type of genetic syndrome or chromosomal abnormality (ICD-9 diagnosis codes 758.0–758.9, 553.3, 756.6–756.7, 759.7–759.9), and primary payer (private insurance, government insurance, other). Center characteristics collected included region and average annual congenital heart surgery volume (only operations included in the RACHS-1 categories) during the study period.

Outcome Measures

The primary outcome was in-hospital mortality. Secondary outcomes included total and intensive care unit length of stay and postoperative renal failure requiring peritoneal or hemodialysis (ICD-9 codes 39.95 or 54.98).

Statistical Analysis

Study variables were summarized using frequencies and percentages for categorical variables and median and interquartile range for continuous variables. Patient and center characteristics and unadjusted outcomes were compared between aprotinin recipients and nonrecipients using χ^2 and Wilcoxon rank sum tests. Similar to previous studies, we combined RACHS-1 categories 5 and 6 for analysis due to the small number of patients in RACHS-1 category 5 [11]. Stratified analysis was performed to evaluate whether the effect of aprotinin on outcome varied by RACHS-1 risk category. The distribution of aprotinin use by center was evaluated and compared with center average annual volume of RACHS-1 classified operations using the Spearman correlation.

Propensity scores were then constructed using multivariable logistic regression to estimate the likelihood a patient would receive aprotinin given an observed set of baseline confounders [12]. Variables entered into the model included age, sex, race/ethnicity, prematurity, genetic syndrome, RACHS-1 category, center, and average annual center volume. Patient weight (for neonates) was initially considered but was not included in the final model because it was highly collinear with prematurity. The model's C statistic was 0.78.

Multivariable analysis was performed to evaluate outcomes independently associated with aprotinin, adjusting for propensity score, each individual covariate, and within-center clustering. Adjusting for both the propensity score and individual covariates in modeling has been termed "doubly robust" in that if either the propensity score adjustment or the confounding variable adjustment is correct, the final estimate of the effect should be correct [13]. For dichotomous outcome variables, modeling consisted of logistic regression using the method of generalized estimating equations. For continuous outcome variables, mixed-effect models were used, treating center as a random effect. Analyses were performed both for the overall cohort and stratified by RACHS-1 category. Odds ratios and 95% confidence intervals are reported for the

generalized estimating equations models, and difference in least square means and 95% confidence intervals comparing aprotinin recipients and nonrecipients from the mixed-effects models.

Finally, a subanalysis was performed in the subset of the cohort undergoing reoperation. This analysis was restricted to 24 centers that had submitted data annually to the Pediatric Health Information Systems Database

since 1999. Patients undergoing reoperation were defined as those who had undergone previous RACHS-1–classified congenital heart operations from 1999 to 2007 at the same institution. Adjusted and adjusted analyses were performed in this subpopulation, as outlined above.

All analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC). We used the conservative Bonferroni correction to account for multiple compari-

Table 1. Patient and Center Characteristics

Variable ^a	Overall	No Aprotinin	Aprotinin	<i>p</i> Value
Patients	30372	17041 (56.1)	13331 (43.9)	
Sex				
Male	16918 (55.7)	9347 (54.85)	7571 (56.8)	<0.001
Age				
≤30 d	6944 (22.9)	3985 (23.4)	2959 (22.2)	<0.001
31 d–1 y	10919 (36.0)	6401 (37.6)	4518 (33.9)	
2–5 y	7861 (25.9)	4329 (25.4)	3532 (26.5)	
6–12 y	2684 (8.8)	1390 (8.2)	1294 (9.7)	
>12 y	1964 (6.5)	936 (5.5)	1028 (7.8)	
Median (IQR), y	0.6 (0.1, 3.2)	0.5 (0.1, 3)	0.7 (0.2, 3.6)	<0.001
Race				
Non-Hispanic white	15539 (53.7)	8568 (53.3)	6971 (54.3)	<0.001
Non-Hispanic black	3761 (13.0)	2165 (13.5)	1596 (12.4)	
Hispanic	5469 (18.9)	2866 (17.8)	2603 (20.3)	
Asian	925 (3.2)	551 (3.4)	374 (2.9)	
Other	3226 (11.2)	1940 (12.1)	1286 (10.0)	
RACHS-1 level				
1	2575 (8.5)	1878 (11.0)	697 (5.2)	<0.001
2	11059 (36.4)	6330 (37.2)	4729 (35.5)	
3	11945 (39.3)	6360 (37.3)	5585 (41.9)	
4	3211 (10.6)	1650 (9.7)	1561 (11.7)	
5/6	1582 (5.2)	823 (4.8)	759 (5.7)	
Genetic abnormality				
Yes	4594 (15.1)	2713 (15.9)	1881 (14.1)	<0.001
Prematurity ^b				
Yes	1321 (4.4)	786 (4.6)	535 (4.0)	0.03
No	5789 (19.1)	3258 (19.1)	2531 (19.0)	
Not applicable	23262 (76.6)	12997 (76.3)	10265 (77.0)	
Payor				
Government	12423 (40.9)	6711 (39.4)	5712 (42.9)	<0.001
Private	11267 (37.1)	6412 (37.6)	4855 (36.4)	
Other	6674 (22.0)	3915 (23.0)	2759 (20.7)	
Center census group				
Northeast	4255 (14.0)	3067 (18.0)	1188 (8.9)	<0.001
South	9662 (31.8)	5419 (31.8)	4243 (31.8)	
North central	8750 (28.8)	4161 (24.4)	4589 (34.4)	
West	7705 (25.4)	4394 (25.8)	3311 (24.8)	
Center volume				
<150	1947 (6.4)	1282 (7.5)	665 (5.0)	<0.001
150–250	14503 (47.8)	7306 (42.9)	7197 (54.0)	
251–350	4797 (15.8)	2353 (13.8)	2444 (18.3)	
>350	9125 (30.0)	6100 (35.8)	3025 (22.7)	

^a Data are presented as number (%) unless otherwise indicated; ^b In neonates only.

IQR = interquartile range; RACHS-1 = Risk Adjustment in Congenital Heart Surgery, version 1.

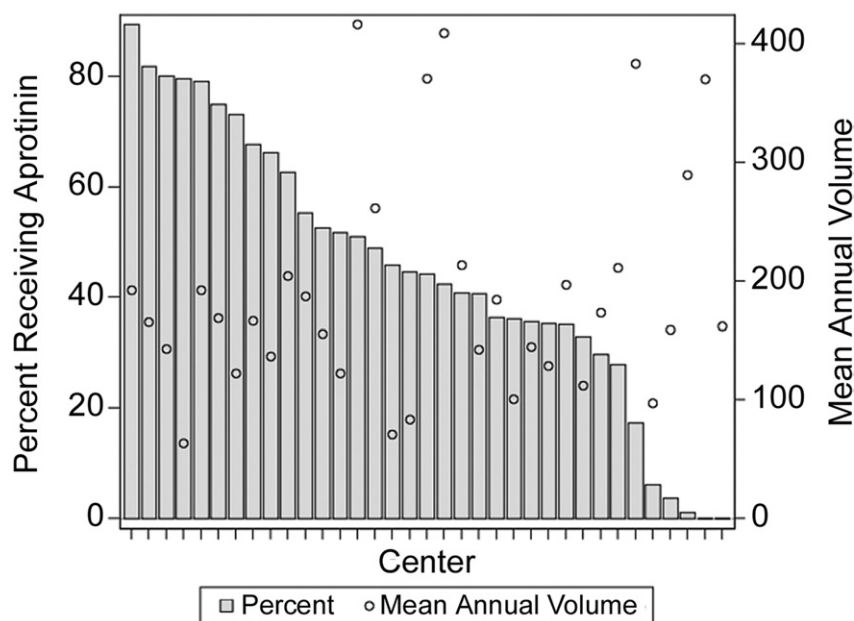


Fig 1. Distribution of aprotinin use is shown by center (bar). The average annual volume of congenital heart operations is also shown (circle).

sons. Thus, a value of $p < 0.01$ was considered statistically significant.

Results

Patient Characteristics and Aprotinin Use

The study included 30,372 patients from 35 centers (Table 1), of which 56% were male and median age was 7 months (interquartile range, 36 days to 3.2 years). Of these, 13,331 patients (44%) received aprotinin. Receipt of aprotinin was associated with older age, higher RACHS-1 category, government insurance, and being treated at a center in the North Central United States. Those with a genetic syndrome or abnormality were less likely to receive aprotinin. Aprotinin use by center varied with a range of 0% to 89% of patients per center receiving aprotinin (Fig 1). There was not a significant linear correlation between center volume and use of aprotinin ($p = 0.2$).

Outcomes

Unadjusted outcomes are reported in Table 2 (overall) and in the Appendix (stratified by RACHS-1 category).

Table 2. Unadjusted Outcomes

Outcome ^a	Overall	No		<i>p</i> Value
		Aprotinin	Aprotinin	
Mortality	964 (3.2)	532 (3.1)	432 (3.2)	0.558
Dialysis	331 (1.1)	161 (0.9)	170 (1.3)	0.006
Total length of stay, d	7 (4, 16)	7 (4, 16)	8 (4, 16)	<0.001
ICU length of stay, d	3 (1, 7)	3 (1, 7)	3 (1, 8)	<0.001

^a Data are displayed as number (%) for dichotomous variables and median (interquartile range) for continuous variables.

ICU = intensive care unit.

Adjusted outcomes are reported in Table 3. Multivariable analysis revealed no difference in mortality, length of stay, or dialysis among aprotinin recipients and nonrecipients (Table 3A). Results were similar in a stratified analysis by RACHS-1 category (Table 3B).

A subanalysis of 4234 patients undergoing reoperation found no difference in mortality or postoperative dialysis (Table 4). Aprotinin recipients had significantly reduced length of stay.

Comment

In this large multicenter study of aprotinin in the pediatric population, we evaluated the safety of aprotinin in children undergoing congenital heart operations. Contrary to the adverse events associated with aprotinin in adults undergoing cardiac procedures, aprotinin was not associated with increased mortality or dialysis in this large cohort of children.

Historically, most medications used in children have not been adequately studied, and treatment decisions are

Table 3A. Adjusted Outcomes

Outcome	<i>p</i> Value	
	OR (95% CI)	
Mortality	1.00 (0.99 to 1.01)	0.447
Dialysis	1.00 (0.99 to 1.01)	0.975
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−0.44 (−1.01 to 0.13)	0.127
ICU length of stay, d	0.18 (−0.15 to 0.51)	0.291

CI = confidence interval; ICU = intensive care unit, LSM = least square means; OR = odds ratio.

Table 3B. Adjusted Outcomes Stratified by Risk Adjustment in Congenital Heart Surgery (version 1) Categories

RACHS-1 Category		p Value
Category 1	OR (95% CI)	
Mortality	1.01 (0.99 to 1.02)	0.094
Dialysis	1.00 (0.99 to 1.01)	0.868
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−1.09 (−3.30 to 1.13)	0.337
ICU length of stay, d	−0.24 (−1.15 to 0.67)	0.602
Category 2	OR (95% CI)	
Mortality	1.00 (0.99, 1.01)	0.471
Dialysis	1.00 (0.99, 1.01)	0.243
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−0.23 (−1.02 to 0.57)	0.575
ICU length of stay, d	0.25 (−0.14, 0.63)	0.213
Category 3	OR (95% CI)	
Mortality	1.00 (0.99, 1.01)	0.465
Dialysis	1.00 (0.99, 1.01)	0.299
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−0.40 (−1.28 to 0.49)	0.377
ICU length of stay, d	0.18 (−0.35 to 0.71)	0.505
Category 4	OR (95% CI)	
Mortality	0.99 (0.97, 1.01)	0.353
Dialysis	0.99 (0.97, 1.01)	0.335
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−0.66 (−3.08 to 1.76)	0.593
ICU length of stay, d	0.23 (−1.29 to 1.75)	0.769
Category 5/6	OR (95% CI)	
Mortality	0.98 (0.93 to 1.03)	0.476
Dialysis	1.00 (0.97 to 1.03)	0.953
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−1.18 (−4.87, 1.24)	0.244
ICU length of stay, d	−1.78 (−4.03, 0.47)	0.121

CI = confidence interval; ICU = intensive care unit, LSM = least square means; OR = odds ratio; RACHS-1 = Risk Adjustment in Congenital Heart Surgery, version 1.

instead based on extrapolation from adult data, clinical experience, or small observational studies [14]. Inadequate information on drug safety and efficacy may deny children potential therapeutic benefits, place them at risk for adverse events, or result in treatment with ineffective

therapies. A growing body of evidence has highlighted some of the potential pitfalls of this approach; for example, many children with heart failure are treated with carvedilol due to the beneficial effects demonstrated in multiple adult heart failure studies [15]. In a recent randomized trial, however, carvedilol did not improve heart failure outcomes in children and adolescents with symptomatic heart failure [16]. Another study found the optimal dose of clopidogrel in children with a cardiac condition at risk for arterial thrombosis was only one-fifth of what would be given if extrapolating from adult data [17].

In the case of aprotinin, this antifibrinolytic agent was used frequently in children undergoing cardiac operations. Children are more prone to bleeding during and after cardiac interventions than adults as a result of greater dilutional effects associated with the cardiopulmonary bypass circuit due to smaller blood volumes, immaturity of the coagulation system, and association of congenital heart disease with coagulation abnormalities [18, 19]. Intraoperative and postoperative bleeding can be associated with prolonged operative times, hemodynamic instability, reoperation, and need for transfusion of blood products, all of which may be associated with prolonged length of stay and increased mortality risk [20]. Prolonged operative times and length of hospital stay have also been shown to be associated with poor neurodevelopmental outcomes [21, 22]. Although the risk of viral transmission with blood product transfusion is low, there can be other adverse effects such as allergic reaction, augmentation of the proinflammatory state that exists after cardiopulmonary bypass, and allosensitization [7].

Results from our study confirm that aprotinin was used commonly, with nearly half of children undergoing congenital heart operations at 35 United States hospitals receiving aprotinin from 2003 to 2007. Aprotinin was taken off the market in 2007 after the Blood Conservation Using Antifibrinolytics in a Randomized Trial found aprotinin was associated with increased mortality in a randomized study of 2331 adults undergoing cardiac operations [5]. This was primarily related to an increased risk of death from cardiovascular causes. Observational data in adults undergoing cardiac operations also suggested that aprotinin was associated with an increased risk of renal failure requiring dialysis [6]. The mechanism

Table 4. Adjusted Outcomes in Subgroup Undergoing Reoperation

Outcome		p Value
	OR (95% CI)	
Mortality	0.99 (0.98 to 1.01)	0.113
Dialysis	1.00 (0.99 to 1.01)	0.929
	LSM Difference	
	Aprotinin—No Aprotinin	
Total length of stay, d	−2.05 (−3.29 to −0.81)	0.001
ICU length of stay, d	−0.82 (−1.59 to −0.05)	0.037

CI = confidence interval; ICU = intensive care unit, LSM = least square means; OR = odds ratio.

for these adverse events was thought to be related to the thrombotic potential of aprotinin and other renal effects, including interference in normal functioning of the proximal tubule, bradykinin system, and renal artery vasoreactivity [23, 24].

In contrast, recent small single-center studies suggest that the adverse outcomes in adults treated with aprotinin may not occur in pediatric patients. Guzzetta and colleagues [8] evaluated 200 neonates undergoing congenital heart operations in an observational study and found that aprotinin was not significantly associated with postoperative serum creatinine levels or the need for dialysis. Backer and colleagues [9] evaluated a more heterogeneous group of 1251 children and adolescents undergoing congenital heart operations and found that aprotinin was not associated with postoperative renal failure, dialysis, or death compared with historical controls.

These previous studies were limited by small sample size, narrow scope, and the use of historical controls. Our study confirms these results in a large, multicenter, diverse group of patients undergoing congenital heart operations. Interestingly, in addition to these observational studies, there have been several randomized trials of aprotinin in children undergoing congenital heart operations. Evaluation of safety was limited in these small trials, however, and a recent meta-analysis combining results from 12 trials could not assess mortality and renal failure [1].

While the focus of this study was to assess safety outcomes associated with aprotinin, multiple other analyses have evaluated efficacy. Several adult trials have shown that aprotinin is associated with decreased postoperative bleeding and need for transfusion compared with placebo, and importantly, may be more effective than other antifibrinolytic agents [2, 5]. A meta-analysis of 12 pediatric trials found a significant reduction in blood product transfusion associated with aprotinin [1]. However, these trials were limited by important methodologic concerns, including small sample size, heterogeneous patient population, lack of standardized transfusion protocols, and varying doses of aprotinin [1]. In addition, not all pediatric trials have demonstrated a beneficial effect of aprotinin, and some studies have suggested that aprotinin may be of benefit in only certain subgroups [25, 26]. Costello and colleagues [26] found that only the subgroup requiring reoperation had a significant decrease in transfusions associated with aprotinin in a small observational study of patients undergoing congenital heart operations.

Although it was not the objective of this study to evaluate efficacy, we did observe that aprotinin was associated with a significantly reduced length of stay in the subgroup undergoing reoperation, which is likely at the highest risk for bleeding. This effect was not seen in other subgroups evaluated. As opposed to other antifibrinolytic agents, aprotinin has also been shown to have antiinflammatory properties [3, 4]. Previous single-center pediatric series have reported a reduction in inflammatory markers in patients who receive aprotinin as well as a reduction in postoperative myocardial dysfunction and

ionotropic support [27, 28]. These properties, along with the potential effect of aprotinin on bleeding, may have contributed to the decreased length of stay we observed in the subgroup undergoing reoperation in our study.

Limitations

This study is subject to the limitations of any observational investigation, including selection bias and the potential effect of confounders. We performed a propensity analysis to account for patient confounders and adjusted for propensity score as well as individual covariates in our models. It is possible that there may be other measured or unmeasured confounders affecting our analysis.

Our study is also subject to the limitations of the database. The database does not contain information on the dose of aprotinin, volume of blood product transfusion, or postoperative chest tube output or bleeding. We were also unable to assess reoperation due to bleeding. However, these factors were unlikely to have affected our evaluation of safety, the primary objective of this study.

We were also not able to specifically assess outcomes associated with aprotinin in the subgroup requiring deep hypothermic circulatory arrest. Previous adult studies have suggested that the use of aprotinin in patients where circulatory arrest is required during the operation may exacerbate any renal toxicity, whereas other studies have not [29, 30]. The use of circulatory arrest is not captured in the Pediatric Health Information Systems Database; however, many of the operations in RACHS-1 categories 5 and 6 require circulatory arrest, and we did not find any difference in dialysis or postoperative mortality in this subgroup in stratified analysis.

Regarding our analysis of renal failure, the database does not contain laboratory information such as creatinine levels. Thus, we may have underestimated the effect of aprotinin on milder degrees of renal dysfunction not requiring dialysis. In addition, we were limited in our subanalysis of patients undergoing reoperation to evaluating patients undergoing reoperation at the same institution; therefore, we may not have captured all patients undergoing reoperation.

Finally, there are limited data regarding the accuracy of coding of congenital heart operation in administrative data sets. Random coding errors may be mitigated by the use of large data sets and groupings of procedures, as in this study. The similarities between overall outcomes of patients undergoing congenital heart operations in our data set compared with other large clinical data sets support the validity of our data [31].

Conclusions

This large multicenter analysis of aprotinin in the pediatric population shows that contrary to studies of adult patients undergoing cardiac surgery, aprotinin was not associated with increased mortality or renal failure requiring dialysis in children undergoing congenital heart operations. These data suggest further evaluation of aprotinin in this population could be undertaken without undue risk.

Dr Pasquali receives support (KL2 RR024127–02) from the National Center for Research Resources, a component of the National Institutes of Health, and from the American Heart Association Mid-Atlantic Affiliate Clinical Research Program. Dr Shah receives support from the National Institute of Allergy and Infectious Diseases (K01 AI73729) and the Robert Wood Johnson Foundation Physician Faculty Scholar Program. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of National Center for Research Resources, National Institutes of Health, American Heart Association, or Robert Wood Johnson Foundation. The authors had full control of the design of the study, methods used, outcome parameters, analysis of data and production of the written report.

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Appendix

Unadjusted Outcomes Stratified by Risk Adjustment in Congenital Heart Surgery (version 1) Category

RACHS-1 Category	Overall	No Aprotinin	Aprotinin	<i>p</i> Value
Category 1				
Mortality	20 (0.78)	8 (0.4)	12 (1.7)	<0.001
Dialysis	4 (0.2)	2 (0.1)	2 (0.3)	0.302
Total length of stay, d	3 (3, 5)	3 (3, 5)	4 (3, 5)	<0.001
ICU length of stay, d	1 (1, 3)	1 (1, 2)	2 (1, 3)	0.205
Category 2				
Mortality	124 (1.1)	77 (1.2)	47 (1.0)	0.272
Dialysis	33 (0.3)	20 (0.3)	13 (0.3)	0.695
Total length of stay, d	5 (4, 10)	6 (4, 10)	5 (4, 9)	0.250
ICU length of stay, d	3 (1, 5)	3 (1, 5)	3 (1, 5)	0.079
Category 3				
Mortality	318 (2.7)	190 (3.0)	128 (2.3)	0.019
Dialysis	126 (1.1)	60 (0.9)	66 (1.2)	0.203
Total length of stay, d	9 (5, 17)	9 (5, 18)	8 (5, 16)	0.002
ICU length of stay, d	4 (2, 8)	4 (2, 8)	4 (2, 7)	0.014
Category 4				
Mortality	237 (7.4)	118 (7.2)	119 (7.6)	0.609
Dialysis	83 (2.6)	41 (2.5)	42 (2.7)	0.714
Total length of stay, d	15 (9, 28)	16 (9, 28)	15 (8, 28)	0.106
ICU length of stay, d	7 (2, 13)	6 (2, 13)	7 (2, 14)	0.054
Category 5/6				
Mortality	265 (16.8)	139 (16.9)	126 (16.6)	0.878
Dialysis	85 (5.37)	38 (4.62)	47 (6.19)	0.165
ICU length of stay, d	26 (17, 43)	26 (17, 45)	26 (17, 43)	0.455
ICU length of stay, d	13 (6, 24)	13 (6, 25)	13 (6, 24)	0.945

Data are displayed as number (%) for dichotomous variables and median (interquartile range) for continuous variables.

ICU = intensive care unit; RACHS-1 = Risk Adjustment in Congenital Heart Surgery (version 1).