Early Postoperative Outcomes and Blood Product Utilization in Adult Cardiac Surgery
The Post-Aprotinin Era

Stacia M. DeSantis, PhD; J. Matthew Toole, MD; John M. Kratz, MD; Walter E. Uber, PharmD; Margaret J. Wheat, RPh; Martha R. Stroud, MS; John S. Ikonomidis, MD, PhD; Francis G. Spinale, MD, PhD

Background—Aprotinin was a commonly used pharmacological agent for homeostasis in cardiac surgery but was discontinued, resulting in the extensive use of lysine analogues. This study tested the hypothesis that early postoperative adverse events and blood product utilization would affect in this post-aprotinin era.

Methods and Results—Adult patients (n=781) undergoing coronary artery bypass, valve replacement, or both from November 1, 2005, to October 31, 2008, at a single institution were included. Multiple logistic regression modeling and propensity scoring were performed on 29 preoperative and intraoperative variables in patients receiving aprotinin (n=325) or lysine analogues (n=456). The propensity-adjusted relative risk (RR) for the intraoperative use of packed red blood cells (RR, 0.75; 95% confidence interval [CI], 0.57 to 0.99), fresh frozen plasma (RR, 0.37; 95% CI, 0.21 to 0.64), and cryoprecipitate (RR:0.06; 95% CI, 0.02 to 0.22) were lower in the aprotinin versus lysine analog group (all \( P<0.05 \)). The risk for mortality (RR, 0.53; 95% CI, 0.16 to 1.79) and neurological events (RR, 0.87; 95% CI, 0.35 to 2.18) remained similar between groups, whereas a trend for reduced risk for renal dysfunction was observed in the aprotinin group.

Conclusions—In the post-aprotinin era, with the exclusive use of lysine analogues, the relative risk of early postoperative outcomes such as mortality and renal dysfunction have not improved, but the risk for the intraoperative use of blood products has increased. Thus, improvements in early postoperative outcomes have not been realized with the discontinued use of aprotinin, but rather increased blood product use has occurred with the attendant costs and risks inherent with this strategy. (Circulation. 2011;124[suppl 1]:S62–S69.)

Key Words: aprotinin ■ cardiac surgery ■ blood products ■ bleeding ■ postoperative outcomes

Cardiac surgery and cardiopulmonary bypass (CPB) can cause excessive bleeding and potential postoperative complications. The serine protease inhibitor aprotinin was commonly used in this clinical context as the only Food and Drug Administration–approved pharmacological agent to minimize blood loss.\(^1\)\(^–\)\(^5\) However, retrospective studies suggested that aprotinin may have postoperative consequences with respect to renal dysfunction and mortality, and that these adverse events may be dose dependent.\(^3\)\(^–\)\(^6\)\(^–\)\(^10\) One prospective study, the Blood Conservation using Antifibrinolytics Trial (BART), which used a high dose aprotinin protocol in patients undergoing cardiac surgery, was terminated early because of concerns regarding increased mortality with aprotinin.\(^11\) However, there were a number of potential confounding issues in these past studies which included but were not limited to patient selection bias, use of off-pump procedures versus CPB, variability in the empirical dosing strategy of aprotinin, and preoperative medication profiles, which can make the interpretation on outcomes difficult. While a continued subject of debate,\(^12\)\(^–\)\(^19\) the concerns regarding potential adverse events led to the voluntary withdrawal and discontinuation of aprotinin in November 2007, with the exception of its availability for compassionate use. As a result, tranexamic acid and epsilon aminocaproic acid, which are generically termed lysine analogues, have now become the most common pharmacological treatment option for antifibrinolytic therapy after cardiac surgery, particularly in patients requiring CPB.\(^3\)\(^,\)\(^11\)\(^–\)\(^19\) Unlike aprotinin, lysine analogues have not been approved as a pharmacological approach to address post–cardiac surgery–related bleeding. Furthermore, it remains unknown whether and to what degree adverse events and blood product utilization have been significantly

From the Department of Biostatistics and Epidemiology (S.M.D.), the Department of Pharmacy Services (W.E.U., M.J.W.), and the Division of Cardiothoracic Surgery (J.M.T., J.M.K., M.R.S., J.S.I., F.G.S.), Medical University of South Carolina and Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, SC.

Presented at the 2010 American Heart Association meeting in Chicago, IL, November 12–16, 2010.

Correspondence to Francis G. Spinale, MD, PhD, Division of Cardiothoracic Surgery, Medical University of South Carolina, 114 Doughty St, Charleston, SC 29403. E-mail wilburnm@musc.edu

© 2011 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.110.002543
affected with the exclusive use of these lysine analogues when compared to the “aprotinin era” when potential confounding variables are taken into consideration. The present study tested the central hypothesis that following adjustment for preoperative covariates and/or through propensity scoring, improved blood product utilization and early postoperative outcomes have not been realized in this post-aprotinin era.

Methods
The overall objective of this study was to perform a retrospective, single-center analysis with respect to early postoperative outcomes and blood product utilization in the aprotinin era (November 2005 to October 2007), in which there was uniformity in the aprotinin dosing protocols at this single center, to the post-aprotinin era (November 2007 to October 2008), in which only lysine analogues, using consistent dosing protocols, were utilized. Moreover, the present study addressed potential confounding factors such as preoperative medication profiles, patient status, and intraoperative variables—all of which have been shown previously to independently influence early postoperative outcomes, particularly in the context of evaluating the effects of antifibrinolics.⁵,¹⁰,¹２⁻¹⁹

Patients
A retrospective chart review of all patients undergoing cardiac surgery was conducted from October 2005 to October 2008 at the Medical University of South Carolina (MUSC). All patients older than 21 years of age who underwent the following cardiac surgical procedures requiring cardiopulmonary bypass (CPB) were included in the construction of the database: coronary revascularization with or without concomitant valve replacement/repair, isolated valve replacement/repair, and heart transplantation. Less frequent procedures that required CPB, such as congenital heart surgery and left ventricular assist devices, were not included in this analysis. This data collection process and analysis was reviewed and approved by the MUSC Institutional Review Board (HR 18816). Standardized doses of the antifibrinolics were used: Aprotinin (TrasyloL, Bayer, Westhaven, CT), 2 million KIU loading dose followed by 0.5 million KIU/h infusion during CPB; Tranexamic acid (Cyklokapron, Pfizer, NY, NY), 15 to 30 mg/kg loading dose followed by 4 to 16 mg/kg per hour infusion during CPB; Epsilon aminocaproic acid (Amicar, Hospira, Lake Forest, IL), 150 mg/kg loading dose followed by 25 mg/kg per hour infusion during CPB. Five cardiothoracic surgeons participated in these cases and remained constant throughout the data collection interval.

Sources of Data Collection
The master list for all patients that could be included in this retrospective study was first identified by use of the computerized database that exists within the Division of Cardiothoracic Surgery, MUSC, which is maintained following the Society of Thoracic Surgeons format. For the purposes of capturing blood product utilization, a merged dataset was obtained by using the MUSC Surgeons format. Following this merging, the database was stripped of all patient identification and combined to form the master database. We have utilized this approach previously to examine the effects of set-point pretreatment in patients undergoing cardiac surgery.⁵⁰ During the study interval, standardized set points had been established in terms of administration of packed red blood cells, fresh frozen plasma, and cryoprecipitate in the perioperative period. First, clinically significant bleeding was defined as >300 mL of chest tube output within 1 hour, or >400 mL of chest tube output in any 2-hour interval, or >100 mL per hour of output on 2 occasions after the first 2 hours. Second, if the threshold for clinically significant bleeding was met, then a prespecified age-dependent set-point for hematocrit was used to determine packed red blood cell administration (∼<70 years old, then a hematocrit of <23%; >70 years old, then a hematocrit of <27%). Third, if the platelet count was <75 000 or there was recent history of platelet antagonist therapy or an elevated prothrombin time, then platelet transfusion would be considered. Fourth, if the above criteria were met and the fibrinogen levels were <150 mg/dL, then transfusion of fresh frozen plasma would be considered. The clinical decision for utilization of recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk, Princeton, NJ) was based on encountering significant, nonsurgical intraoperative bleeding or postoperative bleeding refractory to conventional treatments.

Variables Measured
Demographic variables included: patient age, sex, body surface area, and smoking status. Comorbidities considered included diabetes, hypertension, coagulation disorders, reoperation, chronic renal/liver disease, and preoperative medication profiles (including aspirin). The composite risk score, EuroSCORE, was computed for each patient.²¹ The preoperative medication profiles were carefully scrutinized for angiotensin-converting enzyme (ACE) inhibitors because it has been shown previously to be a significant covariate when considering postoperative renal function in the context of antifibrinolytic therapy.¹³ Operative variables included procedure type, cardiopulmonary bypass time, cross-clamp time, total operative time, intubation time, and length of hospital stay. Blood product utilization was broken out by units of packed red blood cells, units of fresh frozen plasma, units of platelets, cryoprecipitate, and rFVIIa administration. Blood product utilization was dichotomized into blood products utilized in the first 24 hours and those utilized more than 24 hours after the initial procedure and until discharge. The exception to this was rFVIIa, in which the number of patients receiving rFVIIa over the entire admission-discharge period was recorded. Postoperative outcome variables included major adverse cardiac and cerebrovascular events, repeat surgery for hemorrhage or cardiac tamponade, renal failure defined as >2.0 mg/dL, increase in creatinine and/or the need for dialysis treatment, and respiratory failure defined as ventilatory support for more than 48 hours.

Statistical Analysis
In this analysis, 325 patients were included in the aprotinin group; for the lysine analogues, 250 patients received aminocaproic acid and 206 patients received tranexamic acid. For the purposes of this study, and to provide a robust means for adjusting for potential confounding variables, the lysine analogues were combined and simply identified as the lysine analog group (n=456 combined). Baseline demographic variables for patients assigned to the aprotinin versus lysine analog groups were compared using χ² tests for categorical variables. Nonparametric Wilcoxon rank sum test was used to compare the groups on continuous variables.

A stepwise approach for analyzing the blood product and other postoperative outcomes was utilized. First, an unadjusted analysis with group as the only predictor was performed. Second, a covariate-adjusted analysis in which group and the covariates found to be significant confounders were included in a logistic regression model with aprotinin or lysine analog group as the outcome, and insignificant predictors were removed using a backwards elimination algorithm setting of α=0.15 in univariate analysis were included in a logistic regression model with aprotinin or lysine analog group as the outcome, and insignificant predictors were removed using a backwards elimination algorithm setting of α=0.05. Propensity scores were then generated from the logistic regression model, and aprotinin and lysine analog subjects were matched 1:1, using a greedy matching algorithm that matches the nearest available pair with a specified maximum caliber of 0.¹² A total of 434 subjects were able to be matched through the use of this algorithm. For unmatched analyses, the association between aprotinin and number of units of intraoperative or postoperative blood product utilized was assessed using Poisson regression, with the number of blood products as the outcome and group as the exposure of interest.
Matched analyses of blood product utilization were performed using a generalized estimating equations (GEE)-based Poisson regression approach to account for the correlation induced by matching. The resulting parameter estimates are interpreted as the “relative risk of one additional unit of blood product usage in aprotinin versus lysine analog group.” All Poisson regression results are presented in terms of a relative risk (RR) and 95% confidence interval (CI). For all unmatched analyses, binary postoperative outcomes were analyzed using logistic regression models with a binary indicator of the event as the outcome and aprotinin as the exposure of interest. Matched analyses of binary outcomes were performed using a GEE-based logistic regression approach to account for the correlation induced by matching. For rare outcomes (which included all binary outcomes except for prolonged ventilator usage), odds ratios can be interpreted as approximate relative risks. Therefore, results are presented as relative risks and 95% CIs.

Finally, length of stay outcomes were considered as time to event data. Correspondingly, these were analyzed using the Cox proportional hazards models for unmatched data, and the Wei, Lin, and Weissfeld pseudo-likelihood approach for matched data. This approach is similar to GEE estimation and uses a robust sandwich estimate of the covariance matrix. Results are presented as hazard ratios (HR, which may be interpreted as relative risks) and 95% CIs. A 2-sided α-level of 0.05 indicated significance. Similarly, in adjusted analyses, 95% CIs excluding 1 indicate significance at the 0.05 α-level. All analyses were performed in SAS Version 9.2 (SAS Institute, Cary, NC).

Results

Patient Demographics and Preoperative and Intraoperative Variables

Baseline and intraoperative characteristics of the patients in the aprotinin and lysine analog groups are presented in Table 1. Patients were slightly older (63 versus 61 years, P=0.04), with a greater incidence of hypercholesterolemia (61.8% versus 51.3%, P=0.003) and diabetes (44.7% versus 24.9%, P<0.0001) in the lysine analog versus the aprotinin group. There was a higher percentage of aprotinin versus lysine analog patients with valve replacement/repair (41.9% versus 27.2%, P<0.0001). Left ventricular (LV) ejection fraction was lower (47.5% versus 52.1%, P<0.0001), and the percentage of patients with a positive smoking history was higher (29.4% versus 23.3%, P=0.0004) in the aprotinin versus lysine analog group. Preoperative use of ACE inhibitors, diuretics, positive inotropic agents, and aspirin was significantly higher in the aprotinin group, consistent with LV dysfunction and symptomatic heart failure. The aprotinin group had significantly higher EuroSCORE than the lysine analog group (7.0 versus 5.3, P<0.0001). With respect to interoperative variables, both cross-clamp time (92.1 versus 79.7 minutes, P<0.0001) and cardiopulmonary bypass time (144.6 versus 111.4 minutes, P<0.0001) were higher in the aprotinin versus the lysine analog group. Thus, in the aprotinin group, the incidence of preexisting LV dysfunction was higher, and the duration and complexity of the surgical procedures was greater. These preoperative and intraoperative differences between the aprotinin and lysine analog groups underscores the rationale and purpose for utilizing covariate-adjusted and propensity score analysis.

Unadjusted Comparisons of Blood Product Utilization and Postoperative Outcomes

Table 2 presents early postoperative outcomes that were defined as those that occurred during the initial admission and discharge period. These values reflect the unadjusted, unmatched results for the aprotinin and lysine analog groups. In the early intraoperative/postoperative time point, the average number of red blood cell units was higher in the aprotinin

Table 1. Preoperative Demographics and Intraoperative Variables in Patients Receiving Aprotinin or Lysine Analouges

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin (n = 325)</th>
<th>Lysine Analouges* (n = 456)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient history profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>47.5</td>
<td>52.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.0 ± 0.26</td>
<td>2.0 ± 0.24</td>
<td>0.92</td>
</tr>
<tr>
<td>Age</td>
<td>61.2 ± 15.2</td>
<td>63.3 ± 13.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>63.2</td>
<td>64.4</td>
<td>0.74</td>
</tr>
<tr>
<td>Current smoker, Y, %</td>
<td>29.4</td>
<td>23.3</td>
<td>0.0004</td>
</tr>
<tr>
<td>Diabetes, Y, %</td>
<td>24.9</td>
<td>44.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypercholesterolemia, Y, %</td>
<td>51.3</td>
<td>61.8</td>
<td>0.003</td>
</tr>
<tr>
<td>History of renal failure, Y, %</td>
<td>7.7</td>
<td>5.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, Y, %</td>
<td>12.2</td>
<td>15.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Peripheral vascular disease, Y, %</td>
<td>12.5</td>
<td>12.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Cerebrovascular disease, Y, %</td>
<td>12.2</td>
<td>13.0</td>
<td>0.74</td>
</tr>
<tr>
<td>Previous myocardial infarction, Y, %</td>
<td>20.8</td>
<td>23.1</td>
<td>0.43</td>
</tr>
<tr>
<td>EuroScore, mean (SD)</td>
<td>7.0 (3.3)</td>
<td>5.3 (3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative cardiac medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers, Y, %</td>
<td>61.4</td>
<td>66.1</td>
<td>0.17</td>
</tr>
<tr>
<td>ACE inhibitors, Y, %</td>
<td>40.7</td>
<td>16.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nitrates, Y, %</td>
<td>7.4</td>
<td>9.9</td>
<td>0.22</td>
</tr>
<tr>
<td>Antiarrhythmics, Y, %</td>
<td>11.9</td>
<td>8.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Antiplatelet, Y, %</td>
<td>3.6</td>
<td>5.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Diuretic, Y, %</td>
<td>19.0</td>
<td>6.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inotropes, Y, %</td>
<td>7.1</td>
<td>2.2</td>
<td>0.0006</td>
</tr>
<tr>
<td>Steroids, Y, %</td>
<td>5.3</td>
<td>5.2</td>
<td>0.92</td>
</tr>
<tr>
<td>Aspirin, Y, %</td>
<td>47.5</td>
<td>27.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticoagulant, Y, %</td>
<td>42.1</td>
<td>57.9</td>
<td>0.73</td>
</tr>
<tr>
<td>Procedure type</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG, %</td>
<td>41.2</td>
<td>65.8</td>
<td></td>
</tr>
<tr>
<td>Valve, %</td>
<td>41.9</td>
<td>27.2</td>
<td></td>
</tr>
<tr>
<td>Transplant/other, %</td>
<td>16.9</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Intraoperative/postoperative profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>144.6 ± 63.0</td>
<td>111.4 ± 53.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>92.1 ± 34.9*</td>
<td>79.7 ± 39.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total length of stay, d</td>
<td>9 [6–12]</td>
<td>8 [5–12]</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative length of stay, d</td>
<td>7 [5–10]</td>
<td>6 [5–9]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; BSA, body surface area; and CABG, coronary artery bypass graft.

*Lysine analogues: tranexamic acid or aminocaproic acid. Values are presented as mean ±SD or percentages. Length of stay is presented as median [interquartile range]. P values are computed from t tests (with Satterthwaite approximation) for mean values, χ² for frequencies, and Wilcoxon rank sum for length of stay.
group. In the late postoperative period, the average number of units of fresh frozen plasma and cryoprecipitate was higher in the aprotinin group. With respect to unadjusted postoperative outcomes, the percentage of patients requiring reoperation for bleeding and the incidence of transient neurological events and the requirement for renal dialysis appeared higher in the aprotinin group.

Adjusted Comparisons of Blood Product Utilization and Postoperative Outcomes

In light of the significant differences in preoperative cardiac disease states and comorbidities, aprotinin and lysine analog groups were not well matched, as multivariable logistic regression modeling allowed for the identification of group designation (ie, aprotinin versus lysine analog). Variables that were predictive for group designation included EuroSCORE, CBP time, surgery type (ie, valve replacement/repair versus CABG alone), presence or absence of diabetes, and the preoperative use of ACE inhibition, diuretics, or aspirin (goodness-of-fit statistic; C-statistic=0.77). As a result, these variables were utilized in the covariate-adjusted analyses presented in Table 3.

The unadjusted and covariate-adjusted relative risks and 95% CIs for blood product utilization resulting from Poisson regression are presented in Table 3. The unadjusted risk for intraoperative administration of packed red blood cells and intraoperative platelets was higher in the aprotinin group, and the unadjusted risk for the use of all blood products (with the
exception of rFVIIa) in the late postoperative period was higher. However, in covariate-adjusted analysis, the risk for utilization of specific blood products in the intraoperative period was significantly lower in the aprotinin group. Specifically, as shown in Table 3, the covariate-adjusted risk for the use of fresh frozen plasma and cryoprecipitate was significantly lower in the intraoperative period. However, the covariate-adjusted risk for the use of fresh frozen plasma in the later postoperative period remained higher in the aprotinin group. In contrast, the covariate-adjusted risk for the use of rFVIIa in the entire intraoperative and postoperative period was substantially lower in the aprotinin group.

The unadjusted and covariate-adjusted relative risks and 95% CIs for early postoperative outcomes are also presented in Table 3. The unadjusted risk for reoperation due to bleeding, transient neurological events, and the need for dialysis was all higher in the aprotinin group. The unadjusted risk for any neurological event (whether transient or permanent) was higher in the aprotinin group. The unadjusted risk for a prolonged length of hospital stay was also higher in the aprotinin group. However, when adjusted for the aforementioned preoperative and intraoperative covariates, the risk for all early postoperative events in the aprotinin group was similar to that of the lysine analog group (ie, the relative risk was not significantly different from 1).

Past studies have provided evidence that covariate adjustment does not sufficiently match patients on underlying prognostic indicators. Accordingly, a propensity-adjusted analysis to determine a more unbiased relative risk of blood product utilization and postoperative adverse events was performed. In this approach, the patients were matched on the propensity score generated by the above-mentioned covariates that significantly predicted group membership, which yielded a final matched data set of 434 patients. The results from this approach for blood product utilization are shown in Figure 1. The propensity-adjusted risk for early (<24 hours) utilization of packed red blood cells (RR, 0.75; 95% CI, 0.57 to 0.99), fresh frozen plasma (RR, 0.37; 95% CI, 0.21 to 0.64), and cryoprecipitate (RR, 0.06; 95% CI, 0.02 to 0.22) was significantly lower in the aprotinin group versus the lysine analog group. In the late (>24 hours) postoperative period, the relative risk of blood product utilization was not significantly different from 1, with 1 notable exception; the propensity-adjusted risk for the use of rFVIIa was significantly lower in the aprotinin group (RR, 0.21; 95% CI, 0.08 to 0.51). The propensity-adjusted relative risks for postoperative adverse events after propensity-adjusted analyses are shown in Figure 2. Most of these relative risks were less than 1, and none were significantly different from 1, indicating a similar risk of these outcomes in the aprotinin and lysine analog groups. Finally, the propensity-adjusted total length of stay (HR, 1.06; 95% CI, 0.88 to 1.30) and postoperative length of stay (HR, 1.08; 95% CI, 0.88 to 1.32) were not significantly different between the 2 groups.

Discussion

Management of early perioperative bleeding is a basic objective in cardiac surgery, as it is a fundamental determinant of postoperative outcomes. Although past studies have provided evidence that aprotinin reduced perioperative blood loss, concerns regarding potential adverse events resulted in the removal of aprotinin from routine clinical use. This resulted in the lysine analogues becoming the primary means of antifibrinolytic therapy in the context of cardiac surgery. However, whether and to what degree this “post-aprotinin era” has yielded improvements in early postoperative outcomes, and whether blood product utilization has been affected, remain to be fully examined. The unique findings from the present study were 3-fold. First, preoperative comorbidities such as reduced LV systolic function and use of antifibrinolytic therapy in the context of cardiac surgery. Overall, the propensity-adjusted analysis failed to identify any risk reduction in significant perioperative adverse events in the post-aprotinin era. Indeed, there was a trend for a reduction in the risk of respiratory in the aprotinin group (P=0.06). Although the propensity-adjusted risk of renal failure was reduced in the aprotinin group, this was not significant (P=0.13). MACCE indicates major adverse cardiac and cerebrovascular events.
cardiovascular medications were more likely in the aprotinin group, as was the complexity of the cardiac procedure. These findings suggest that in the post-aprotinin era, lysine analogues are not being utilized to the same degree in high-risk patients. Second, using propensity scoring, the risk for intraoperative/perioperative use of blood products such as fresh frozen plasma and cryoprecipitate was lower in the aprotinin era patients, as was the overall risk for the use of rFVIIa. Third, the adjusted risk for perioperative renal dysfunction has not improved with the exclusive availability of lysine analogues. These new findings suggest that this post-aprotinin era has resulted in a higher risk for the use of refined and recombinant blood products with the potential attendant costs and risks inherent with this strategy and improvements in postoperative adverse events have not been realized. The majority of past studies that compared the relative effects of aprotinin or lysine analog administration were performed when both agents were available. These past retrospective studies underscored the importance of considering confounding variables in the analysis, which may prevent interpretation of the effects of these antifibrinolytic agents with respect to early postoperative outcomes. Previous studies identified that preoperative variables such as cardiovascular status, diabetes, preexisting renal dysfunction, and the complexity of the procedure (combined CABG/valve replacement) may directly influence the outcome response variables. In addition, other studies demonstrated that the preoperative use of ACE inhibitors, the use of CPB, and the duration of the CPB time could independently influence postoperative outcomes such as renal dysfunction, neurological events, and mortality. Finally, the effects of aprotinin may be dependent on the dosing strategy used, as several studies reporting detrimental findings with respect to postoperative outcomes did not use a standardized dosing procedure. The present study built on past observations by considering all of these potentially confounding variables in the analysis of patients requiring CPB who received a uniform antifibrinolytic dosing strategy at a single institution. Moreover, the present study examined blood product utilization and postoperative events, using established set-points for transfusions and over an interval of time in which the cardiac surgeons performing the cardiac procedures were consistent. Finally, this study is the first to perform a quantitative analysis of blood product utilization and early adverse events in the “post-aprotinin era,” whereby only lysine analogues were available for antifibrinolytic therapy. There were several important differences in the patient demographics between the aprotinin and lysine analog groups. Specifically, there was a higher incidence of LV dysfunction requiring cardiovascular medications than in the lysine analog group. There are several possible explanations for this observation. First, aprotinin administration was routinely considered for relatively high-risk patients, such as those with preexisting LV dysfunction, whereas the off-label use of lysine analogues is not. Thus, in the post-aprotinin era, it is possible that patients with preexisting LV dysfunction are not routinely considered for administration of lysine analogues. One of the notable differences between the present study and past retrospective studies regarding aprotinin was the relative risk for postoperative renal failure. In a study by Furnary et al., an analysis of a cardiac surgery database revealed that the unadjusted risk for renal failure was higher with aprotinin, but when adjusted for the number of red blood cell transfusions, the independent effects of aprotinin in the risk model for renal failure was attenuated. This underscores the importance of inclusion of independent covariates when assessing the relative risk. However, this past registry analysis was performed when selection bias between aprotinin and lysine analogues may have been operative, did not directly compare the adjusted risk of renal failure between aprotinin and lysine analogues, and did not utilize propensity matching. The present study evaluated the relative risk for renal failure as that of a clinically significant rise in postoperative creatinine levels, a need for postoperative dialysis, or a combination of these events. The present study as well as past reports have identified that preoperative use of ACE inhibitors is an independent contributory variable for the risk of postoperative renal dysfunction. Propensity-adjusted analysis suggested that the risk for renal dysfunction was actually increased by 85% in the post-aprotinin era with the use of lysine analogues. These new findings build on the results from past registry findings. This study examined an interval of time when aprotinin was the pharmacological agent of choice for antifibrinolytic therapy to an interval of time when this serine protease had been withdrawn. One of the deciding factors for the withdrawal of aprotinin was the initial adverse events reported in the prospective study BART. The BART study was terminated early due to the fact that an interim analysis demonstrated a higher relative risk for 30-day mortality in the aprotinin group when compared with the lysine analog groups. However, the BART study used a prespecified definition for massive bleeding, and in the interim analysis, the risk for massive bleeding appeared to be reduced with aprotinin when compared with lysine analogues. However, the BART study was not designed to evaluate the relative risk of blood product utilization in the early and late postoperative periods. In the present study, and consistent with the BART study, the unadjusted risk for reoperation due to excessive bleeding was higher in the aprotinin group. This risk was reduced with the introduction of confounding variables such as preoperative functional status and CPB times, indicating that aprotinin was utilized in more complex cases in which an inherent risk for postoperative bleeding was higher. However, one unique finding from the present study was that despite the higher incidence of comorbidities, surgical complexity, and as a consequence increased reoperation for bleeding, the propensity-adjusted risk for intraoperative blood product utilization in the aprotinin group was substantially reduced when compared with lysine analogues. These findings suggest that aprotinin reduced the risk for receiving intraoperative blood products such as packed red blood cells, fresh frozen plasma, and cryoprecipitate, independent of the incidence of significant postoperative bleeding.
Limitations and Summary

There are a number of limitations to the present study that must be recognized. First, this is a retrospective study, and the inherent limitations of this approach have been discussed in the preceding sections. Second, this was a single-center study, and, in relative terms, the sample size was small. However, the single-center approach limited the variability that can occur with multicenter studies, in which the antifibrinolytic formulations and dosing regimens can differ as well as increase the procedure variability by increasing the number of cardiac surgeons. Third, the present study combined the lysine analogues together to provide a more robust comparison to the aprotinin era patients. Although this approach has been commonly used previously,\textsuperscript{2,11} it prevents comparison between the lysine analogues.

There are also limitations to covariate-adjusted and propensity-adjusted analysis approaches. Propensity matching invariably reduces sample size because patients are closely matched on confounding variables; however, uniform results were obtained whether covariate adjustment or propensity matching were used. The analysis was predicated on comparisons between aprotinin and lysine analogues in terms of the primary outcomes of blood product utilization and renal failure, and a robust statistical power was achieved for this purpose. However, the present study probably was underpowered in terms of identifying significant differences in postoperative outcomes such as mortality and neurological events. Using the observed incidence in the propensity-matched samples for the outcomes of mortality (aprotinin: 2.3\% versus lysine analogues: 4.7\%\textsuperscript{2}) and neurological events (aprotinin: 4.7\% versus lysine analogues: 5.1\%), a conditional power calculation was computed for these two outcomes,\textsuperscript{27,28} An observed incidence within the aprotinin group of at least 7.6\% for mortality (assuming a continual rate of 4.7\% in the lysine analog group) and at least a 6.4\% incidence in neurological outcomes (assuming a continual rate of 5.1\% in the lysine analog group) would have been required. Given the observed incidence of these outcomes in the present study as well as in past reports,\textsuperscript{4,11} it follows that an extremely large sample size would be required and ultimately would yield conclusions similar to those of the present study.

Nevertheless, the unique findings from the present study suggest that the withdrawal of aprotinin has not yielded an improvement in postoperative outcomes such as a reduced incidence of renal failure, which would have been anticipated based on past retrospective studies.\textsuperscript{5–8,11} Moreover, the relative risk for the use of refined blood products such as cryoprecipitate and rFVIIa has increased significantly in this post-aprotinin era. Indeed, a recent study has identified that increased use of rFVIIa can increase the risk of arterial thrombotic events.\textsuperscript{29} Thus, while remaining speculative, the risk of higher utilization of rFVIIa in this post-aprotinin era may in turn contribute to adverse postoperative outcomes such as neurological events. Excessive postoperative bleeding and the management of fibrinolysis remain contemporary problems confronting the cardiac surgeon.\textsuperscript{19,30} In light of the fact that increased blood product utilization holds inherent risks and costs, the findings from the present study underscore the need for improvements in pharmacological strategies that modulate the fibrinolytic cascade after cardiac surgery.

Sources of Funding

This study was supported by National Institutes of Health grant HL-59165 and a Merit Award from the Veterans’ Affairs Health Administration.

Disclosures

None.

References

Early Postoperative Outcomes and Blood Product Utilization in Adult Cardiac Surgery:
The Post-Aprotinin Era
Stacia M. DeSantis, J. Matthew Toole, John M. Kratz, Walter E. Uber, Margaret J. Wheat,
Martha R. Stroud, John S. Ikonomidis and Francis G. Spinale

Circulation. 2011;124:S62-S69
doi: 10.1161/CIRCULATIONAHA.110.002543
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/124/11_suppl_1/S62

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/