Aprotinin Does Not Increase the Risk of Renal Failure in Cardiac Surgery Patients

Anthony P. Furnary, MD; YingXing Wu, MD; Loren F. Hiratzka, MD; Gary L. Grunkemeier, PhD; U. Scott Page 3rd, MD

Background—Aprotinin is frequently used in high-risk cardiac surgery patients to decrease bleeding complications and transfusions of packed red blood cells (PRBC). Transfusions of PRBC are known to directly increase the risk of new onset postoperative renal failure (ARF) in cardiac surgery patients. A recent highly publicized report implicated aprotinin as an independent causal factor for postoperative renal failure, but ignored the potential confounding affect of numerical PRBC data on ARF. We sought to investigate that claim with an analysis that included all perioperative risk factors for renal failure, including PRBC transfusion data.

Methods and Results—Prospectively collected patient data from 12 centers contributing to the Merged Cardiac Registry, an international multicenter cardiac surgery database, operated on between January 2000 and February 2006 were retrospectively analyzed. A previously published risk model for ARF incorporating 12 variables was used to calculate a baseline ARF risk score for each patient in whom those variables were available (n=15,174). After adding transfused PRBC data 11,198 patients remained for risk-adjusted assessment of ARF in relation to aprotinin use. Risk-adjusted multivariable analyses were carried out with, and without, consideration of transfused PRBC. Aprotinin was used in 24.6% (2757/11,198). The overall incidence of ARF was 1.6% (180/11,198) and was higher in the aprotinin subset (2.6%, 72/2757 versus 1.3%, 108/8441; P<0.001). The incidence of ARF directly and significantly increased with increasing transfusions of PRBC (P<0.001). Risk-adjusted analysis without transfused PRBC in the model suggests that aprotinin significantly impacts ARF (P=0.008; OR=1.5). However, further risk adjustment with the addition of the highly significant transfused PRBC variable (P<0.0001; OR=1.23/transfused PRBC) to the model attenuates the purported independent affect of aprotinin (P=0.231) on ARF.

Conclusions—The increase in renal failure seen in patients who were administered aprotinin was directly related to increased number of transfusions in that high-risk patient population. Aprotinin use does not independently increase the risk of renal failure in cardiac surgery patients.

Key Words: renal failure ■ transfusion ■ cardiac surgery ■ kidney ■ risk factors

Aprotinin (trasylol, Bayer) is an intravenous antifibrinolytic serine protease inhibitor that has been shown in several randomized multicenter trials to reduce the incidence of postoperative bleeding1–4 and transfusion2–7 after cardiac surgery. Aprotinin has been in use in the United States since its FDA approval in 1993 and has been used in Europe since the 1980s.3 In addition to reductions in postoperative bleeding and transfusion, it has been shown to reduce postcardiopulmonary bypass inflammation1,8,9 and reduce the incidence and severity of postoperative cerebrovascular accidents.6,10,11 Because of the multitude of these salutary data, aprotinin has been cited in the STS guidelines for blood conservation12 as a Class I (Level of evidence A) agent for reducing transfusions in high-risk cardiac surgery patients.

A recent nonrandomized multicenter observational analysis13 suggested that aprotinin independently increases the risks of cardiovascular, cerebrovascular, and renal events—which were defined as renal dysfunction or renal failure. In that article renal dysfunction was specifically defined as “a postoperative serum creatinine level of at least 177 mmol per liter with an increase over preoperative baseline levels of at least 62 mmol per liter.” Renal failure was defined as “renal dysfunction requiring dialysis or in-hospital death with evidence at autopsy of acute renal failure.” This nonrandomized retrospective study from 66 centers involving 4374 patients, in whom the use of aprotinin was based solely on surgical judgment, concluded: “continued use of aprotinin is not prudent.”

Subsequent to that publication, a second observational study by Karkouti et al14 suggested that aprotinin increases the risk of renal dysfunction in cardiac surgery patients with elevated preoperative creatinine levels, but does not increase...
the risks of cardiac events, cerebrovascular events, or death. These authors defined renal failure as "a new requirement for dialysis support" and defined acute renal dysfunction as "a greater than 50% increase in creatinine concentration during the first postoperative week to more than 100 μmol per L in women and greater 110 μmol per L in men, or a new requirement for dialysis support."

Because these were nonrandomized observational studies with hotly debated conclusions that have become controversial on an international scale, we sought to corroborate their single mutual finding that aprotinin was independently associated with an increased risk of acute renal failure. Thus in the current set of analyses we focus on the primary end point common to both the previous studies—new onset, dialysis-requiring, acute renal failure (ARF) in the postoperative period.

Methods

These analyses were carried out through a retrospective analysis of a large international multicenter cardiac surgery database—the Merged Cardiac Registry (MCR), Health Data Research, Portland, Ore. This database contains prospectively collected data that is locally verified as validated aprotinin usage information. The 23 105 patients collected prospectively from these centers who underwent operation between January 2000 and February 2006 (the date of publication of the Mangan article13) were evaluated in this study.

A recently published risk model15 for predicting acute dialysis-dependent renal failure (ARF) after cardiac surgery was used to calculate a baseline predicted ARF risk score for all patients. This risk model, which emanated from the Cleveland Clinic Foundation (CCF), includes 12 variables—gender, congestive heart failure, left ventricular ejection fraction <35%, preoperative placement of an intraaortic balloon pump, chronic obstructive pulmonary disease, insulin-requiring diabetes, previous cardiac surgery, surgery type (valve, valve+CABG), and preoperative creatinine (2 categories). This model was used to calculate a baseline ARF risk score (the linear predictor) for each patient in whom those variables were available. A secondary logistic regression model was fitted using the CCF-ARF risk score as the single predictor to get the calibrated predicted risk of ARF.

Only patients who had complete CCF-ARF risk score data were retained in the analysis. In fact every patient from 1 center was excluded at this stage for universal lack of preoperative creatinine data, leaving 11 centers in the data set. The CCF-ARF risk model operating characteristic (ROC) curve analysis revealed that the predictability of the CCF-ARF risk model on our data was excellent, with a c-statistic of 0.82 (95% CI 0.79 to 0.84). This indicates good model discrimination for postoperative ARF and is essentially equivalent to that obtained in the original publication.

Aprotinin was used in 24.6% (2757/11 198) of the patients in the MCR data set. The incidence of aprotinin use varied by institution and increased by year (Figure 1a and 1b). Operative procedures included 8090 isolated CABG (72%), 1692 (15%) isolated valve operations, and 1416 (13%) combined valve/CABG operations. The demographic composition of patients in the study is shown in Table 1.

The CCF-ARF risk model was first validated using the 15 174 patients with all available scoring data. Receiver operating characteristic (ROC) curve analysis revealed that the predictability of the CCF-ARF risk model on our data was excellent, with a c-statistic of 0.82 (95% CI 0.79 to 0.84). This indicates good model discrimination for postoperative ARF and is essentially equivalent to that obtained in the original publication.

Aprotinin was used in 24.6% (2757/11 198) of the patients in the final study population. The incidence of aprotinin use varied by institution and increased by year (Figure 1a and 1b). Operative procedures included 8090 isolated CABG (72%), 1692 (15%) isolated valve operations, and 1416 (13%) combined valve/CABG operations. The demographic composition of patients in the study is shown in Table 1.

The overall incidence of ARF was 1.6% (180/11 198). The incidence of ARF in patients who received aprotinin was twice as high as it was in those who did not receive this drug (2.6% [72/2757] versus 1.3% [108/8441]; P<0.001). However, this univariate comparative outcome is not unusual because examination of the demographic comparison (Table 1) reveals that patients who were selected by their surgeons to receive aprotinin were, preoperatively, at a higher risk for renal failure than those in the nonaprotinin group. Specifically those in the surgeon-selected aprotinin group had higher incidences of CCF-ARF risk model variables such as complex surgery, redo surgery, congestive heart failure, low ejection fraction, chronic obstructive pulmonary disease,

Definitions

Acute renal failure (ARF) is defined as any new onset dialysis-requiring (either continuous renal replacement or intermittent therapy) acute renal failure after cardiac surgery and occurring during the same hospitalization as that surgery. It includes both acute (eventually resolving) and chronic (onset of permanent) renal failure. It excludes patients on preoperative chronic dialysis.

Transfused packed red blood cells are any transfusion of packed red blood cells occurring anytime during hospitalization for the cardiac surgical procedure under study. This variable represents the actual number of PRBC transfused per patient.

Three sequential multivariable analyses were done to determine whether aprotinin had an independent effect on the incidence of ARF. All models incorporated the baseline CCF-ARF risk adjustment calculated for each patient from the Cleveland model. Aprotinin was then added to the model to assess its potential independent effect over and above the predicted CCF-ARF baseline risk. This first of these analyses was carried out without consideration of numerical transfused PRBC data in the model, as was done in the Mangan analysis.13 The second analysis was performed with both numerical PRBC transfusion data and aprotinin in the model. Finally, a third analysis was done on only those patients who received no transfusions during their admission.

Continuous variables are expressed as mean±SD and discrete variables as percentages. Continuous variables for 2 groups were compared using the t test, and comparison of proportions with the Chi-square test. Multivariate analysis to identify independent predictors for ARF was performed using logistic regression. The ability of model discrimination was measured by c-statistic. Comparisons were considered significant when P<0.05. Statistical analyses were performed using SPSS 11.5 (SPSS Inc) and S-PLUS 6.2 (Insightful Corp).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
female gender, and higher average preoperative creatinine. In addition these patients were older and had a higher incidence of previous ARF that had resolved before surgery.

Thus the preoperative CCF-ARF risk model predicts a significantly higher expected incidence of renal failure in the aprotinin population as compared with the nonaprotinin group (2.1% versus 1.2%; P<0.001), which is also what was observed. The observed incidence of ARF for the nonaprotinin group was as expected (O/E ratio=1.3%/1.2%=1.06, P=NS). But the observed incidence was significantly higher than expected in the aprotinin group (O/E ratio=2.6%/2.1%=1.22, P<0.001).

The composite CCF-ARF risk score, incorporating 12 ARF-associated variables, was entered into a multivariable analysis along with aprotinin. (Table 2, Model A) This first model suggests, as did Mangano’s,13 that aprotinin independently increases the odds of ARF by a factor of 1.5 times.

However, aprotinin is not the only perioperative variable capable of potentially inducing renal failure. Interestingly, our data show—as does that of others17—that the number of packed red blood cells transfused in the intra- and postoperative periods directly and significantly increases the incidence of new onset renal failure (Figure 2). This univariate analysis of the influence of increasing PRBC transfusions on ARF demonstrates the significant direct association between increasing PRBC use and increasing incidence of ARF (P<0.0001; OR=1.23 per transfused PRBC used).

It is important then to note that the number of packed cells transfused per patient in the aprotinin group was significantly higher than in the nonaprotinin group (2.1±3.3 versus 1.7±2.9 U transfused PRBC per patient; P<0.001). Again, this is not an unexpected finding as the predicted transfusion requirements of the surgeon-selected aprotinin group were significantly higher than the predicted transfusion requirements of the nonaprotinin group (2.4±1.9 versus 1.6±1.4, P<0.001). This indicates appropriate surgical use of this antifibrinolytic drug.

Despite this difference in predicted risk of transfusion, there were no differences in the percentage of patients transfused in each group (aprotinin: 50.2% 1385/2757; nonaprotinin 48.4% 4084/8441; P=0.09). However, the aprotinin patients received significantly less PRBC than predicted by the Bayesian transfusion risk model (observed transfused PRBC per patient=2.1 U versus expected transfused PRBC per patient=2.4 U; O/E=0.88; P<0.001), thus validating the usefulness of this drug in decreasing transfusion requirements. The nonaprotinin transfusion rate was exactly as predicted by the transfusion model (observed transfused PRBC per patient=1.7 U versus expected transfused PRBC per patient=1.7 U; O/E=1.06; P=NS).

Again using the CCF-ARF risk model for risk-adjusted assessment, a second multivariable analysis to assess the influence of both transfused PRBC and aprotinin on ARF was carried out. When the numerical PRBC transfusion data were added to the baseline model (A), transfused PRBC were found to be an independent risk factor for ARF (Table 2, Model B). More importantly, the addition of the highly significant numerical PRBC transfusion variable to the model

### TABLE 1. Demographics of the Populations

<table>
<thead>
<tr>
<th></th>
<th>Non-Aprotinin (n=8441)</th>
<th>Aprotinin (n=2757)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.7±11.1</td>
<td>67.5±11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female*</td>
<td>28.1%</td>
<td>31.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>28.9±6.3</td>
<td>28.6±5.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>77.8%</td>
<td>55.3%</td>
<td></td>
</tr>
<tr>
<td>Valve</td>
<td>12.4%</td>
<td>23.5%</td>
<td></td>
</tr>
<tr>
<td>CABG+valve*</td>
<td>9.9%</td>
<td>21.1%</td>
<td></td>
</tr>
<tr>
<td>CHF*</td>
<td>18.3%</td>
<td>30.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preop IABP*</td>
<td>3.5%</td>
<td>2.4%</td>
<td>0.193</td>
</tr>
<tr>
<td>EF&lt;35%*</td>
<td>9.6%</td>
<td>10.5%</td>
<td>0.003</td>
</tr>
<tr>
<td>COPD*</td>
<td>13.9%</td>
<td>18.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>36.4%</td>
<td>37.4%</td>
<td>0.361</td>
</tr>
<tr>
<td>Prior open heart surgery*</td>
<td>8.1%</td>
<td>20.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergent surgery*</td>
<td>3.5%</td>
<td>3.9%</td>
<td>0.344</td>
</tr>
<tr>
<td>Preoperative creatinine</td>
<td>1.2±0.7</td>
<td>1.3±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤1.2</td>
<td>65.5%</td>
<td>61.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.2–2.1*</td>
<td>31.8%</td>
<td>32.6%</td>
<td></td>
</tr>
<tr>
<td>≥2.1*</td>
<td>2.7%</td>
<td>5.8%</td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of renal failure</td>
<td>0.9%</td>
<td>2.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.5%</td>
<td>71.1%</td>
<td>0.556</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; EF, left ventricular ejection fraction; COPD, congestive obstructive pulmonary disease.

* variable used in the CCF-ARF risk model.
attenuates the independent affect of aprotinin \( (P=0.231, \text{OR}=1.23, \text{CI}=0.88, 1.74) \) on ARF.

Because aprotinin and PRBC may have been prescribed together in some instances and thus potentially produced statistical collinearity (which inflates the variance estimates), the variance inflation factor (VIF) was calculated for the 3 significant independent risk factors in each of our models. This analysis of collinearity produced VIFs that were close to 1 for PRBC (1.1), aprotinin (1.0), and CCF-ARF (1.2), whereas a value of 10 or greater is considered to be an indication of important collinearity.

ROC analysis of the first 2 ARF models (A & B) presented in Table 2 shows that the c-statistic for the transfused PRBC model (B), without aprotinin in the model (0.91), is higher than that for the model that includes only aprotinin and ignores numerical transfusion data (0.82). This indicates better discrimination for the model with numerical transfusion data in the equation and aprotinin excluded from the equation.

Finally, because of the major impact of numerical transfusion data on the second model, we sought confirmatory evidence of the apparent nonsignificant relationship of aprotinin with ARF in those patients who were never transfused. We therefore repeated these analyses on the nontransfused patient subgroups \( (n=5729) \), in which there were again equal proportions of nontransfused patients (aprotinin: 49.8\% (1372/2757); nonaprotinin 51.6\% (4357/8441); \( P=0.09 \)).

The CCF-ARF predicted risk of ARF was slightly, but not significantly, higher in the nontransfused aprotinin group (1.1\% versus 0.8\%). However, the actual rates of renal failure were significantly lower than predicted in both nontransfused subgroups (aprotinin nontransfused group: observed ARF=0.4\% versus expected ARF=1.1\%; \( O:E=0.33; P<0.001 \)) (nonaprotinin nontransfused group: observed ARF=0.2\% versus expected ARF=0.8\%; \( O:E=0.2; P<0.001 \)). There was no significant difference in the risk-adjusted incidence (\( O/E \) ratio) of renal failure between the nontransfused subgroups. Multivariable analysis of the nontransfused subgroup (Table 2, Model C) found no independent affect of aprotinin on renal failure \( (P=0.654) \) in the nontransfused subpopulation.

## Discussion

Our analyses suggest that the implication of aprotinin as a causal factor for postoperative ARF may have been incorrect and premature. These data show: (1) That aprotinin does not independently increase the risk of postoperative ARF as previously suggested; (2) Increasing use of transfused PRBC is directly and independently related to an increased risk of postoperative ARF; (3) Aprotinin lowers the expected risk of transfusion; (4) The Cleveland Clinic risk model for ARF is validated, but further postoperative ARF risk assessment could be improved with the addition of numerical PRBC transfusion data to the model.

It becomes apparent then, that both the univariate association of and the previously published\(^13\) “independent effect” of aprotinin on the incidence of ARF seems to have been statistically manufactured by more transfusions of PRBC in the aprotinin population. The seeming paradoxical fact that the aprotinin group received more transfused PRBC than the nonaprotinin group is likely attributable to the interaction of several interrelated mitigating factors.

Concerns that aprotinin therapy is associated with increased renal failure are not supported by data from published, randomized, placebo-controlled clinical trials.\(^6\) This study, like the Mangano\(^13\) and Karkouti\(^14\) studies, was a nonrandomized retrospective, observational study in which the use of aprotinin was determined solely by the operating surgeon. Surgeons who use aprotinin outside of a randomized study are more likely to administer this agent to patients at higher risks of bleeding and death and to do so in a nonuniform fashion. This fact is illustrated in Figure 1, which shows the wide variability of aprotinin utilization at the 11 centers in this study. Surgeons are more likely to choose

### Table 2. Risk Models for Renal Failure

<table>
<thead>
<tr>
<th>Model</th>
<th>Model A</th>
<th>Model B</th>
<th>Model C (Nontransfused Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n=15,174 )</td>
<td>( n=11198 )</td>
<td>( n=5729 )</td>
</tr>
<tr>
<td>CCF-ARF</td>
<td>( &lt;0.001 )</td>
<td>( &lt;0.001 )</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>0.008</td>
<td>0.021</td>
<td>0.054</td>
</tr>
<tr>
<td># PRBC</td>
<td>NU</td>
<td>NU</td>
<td>NU</td>
</tr>
<tr>
<td>c-statistic</td>
<td>0.82 (0.79–0.85)</td>
<td>0.91 (0.89–0.93)</td>
<td>0.83 (0.70–0.96)</td>
</tr>
</tbody>
</table>

**CCF-ARF** indicates Cleveland Clinic Foundation Acute Renal Failure Risk score; \#PRBC, variable representing the No. of transfused cells per patient; NU, not used; NA, not applicable.
aprotinin for patients who have intrinsically higher preoperative risks (Table 1), including that of bleeding. This theory was confirmed in our study, as the predicted risk of transfusion in the aprotinin group was significantly higher than that of the nonaprotinin group. This finding is also corroborated by Mangano’s observational data in which the incidence of repeat sternotomy (redo operation) was more than 2 times higher in the aprotinin group (13.9%) than it was in theaminocaproic acid (6.1%) or tranexamic acid (5.1%) groups. Our data further confirm that the number of observed transfusions in these selectively chosen aprotinin patients is indeed higher than that of those who have been selectively excluded from aprotinin use by the operating surgeon.

Thus, in the absence of a randomized study, selective aprotinin use occurs in patients who are at a higher risk for perioperative transfusion and, these selected patients do indeed receive more PRBC than those who are purposely excluded from its use. Furthermore, it follows that if patients who receive aprotinin are transfused with more PRBC than patients who do not receive aprotinin, those who do receive aprotinin will have a higher incidence of ARF because transfusions themselves independently increase the incidence of ARF. However, it is highly important to recognize that this association is only an association and not a causation—that is ARF is not attributable to the use of aprotinin itself. Aprotinin may thus be a surrogate variable associated with other true risk factors such as the number of PRBC transfused.

In reviewing the previous publications on the subject of ARF we came to the realization that this one major risk factor for ARF—the number of packed red blood cells transfused in the perioperative period—had been excluded from the previously published analyses implicating aprotinin as a causal factor. In those analyses transfusions were treated only as a categorical (yes/no) variable with disregard to the to the increasing quantitative effect of transfused PRBC on ARF. Therefore, we retrospectively analyzed our prospectively collected data both with, and without, regard to numerical PRBC transfusion data.

Transfusions of PRBCs have been shown\(^\text{17}\) to increase the risk of ARF. Our study confirms this observation. Transfusions in this study increased the risk of ARF in the postcardiac surgery patient by 1.23 times for every unit of PRBC transfused. In the analysis by Kincaid et al.,\(^\text{17}\) intraoperative transfusions of PRBC were found to significantly increase the risk of nondialysis dependent ARF (defined as a postoperative creatinine greater than 2.0 mg/dL) by 1.04 times per unit of PRBC given. In that study only pre- and intraoperative variables were used, including the number of intraoperative PRBC transfused. Neither an analysis of total PRBC use throughout the patients’ hospitalization nor an analysis of dialysis-requiring ARF was done. Nonetheless, the association between an increasing number of transfused PRBC given intraoperatively and an increasing incidence of nondialysis dependent ARF was established.

The CCF-ARF risk model was also created using only preoperative variables. This was done to develop and validate a risk algorithm that would accurately predict ARF after cardiac surgery. The CCF-ARF risk model thus provided a proven and validated preoperative method of risk adjustment from which we could work to assess the potential independent impact of aprotinin, transfused PRBC, and other perioperative variables on the risk-adjusted incidence of ARF. It is important to note that transfused PRBC—a nonpreoperative variable—was not included in the CCF-ARF analysis. Because transfused PRBC were not incorporated in the baseline model, we found that the addition of this perioperative variable added significantly to the post-hoc predictability of that model.

In the Mangano study transfusions were treated as a categorical (Yes/No) variable with disregard to the actual number of PRBC that were transfused. We believe that this was the fundamental statistical error that lead to the errant conclusion that aprotinin significantly increases the risk of ARF.

Similarly, in the Karkouti\(^\text{14}\) article the propensity analysis was performed only on those patients in the aprotinin group who had a lower number of transfusions because those who received a higher number of transfusions could not be matched to similar patients in the propensity control group. Furthermore, demographic comparison of the analyzed aprotinin population to the propensity selected control group showed that the aprotinin patients received significantly more blood products than the “matched” cohort. We believe that the failure to correct for this imbalance was the fundamental statistical error in that study.

Exclusion of important predictive prognosticators will hamper any statistical analysis, causing it to render the wrong conclusion. This is demonstrated with a sequential analysis of our own data in Figure 3. This figure shows several odds ratios, with 95% confidence intervals, depicting the signifi-
cance of aprotinin in relation to ARF in each of the 4 sequential patient populations and for the 3 multivariate risk models—A, B, and C (Table 2)—we used in this study. Note that the sample sizes given in this figure decrease (from 23,105 to 15,174 to 11,198 to 5,729) as the models become more complex because of missing variables for some of the patients.

The univariate risk of aprotinin, that is before any risk adjustment, for causing renal failure in each of the 4 population sample sets is shown in the gray bars “U0”, “UA”, “UB”, and “UC”. Note that the odds ratios for the univariate analysis of aprotinin in relation to ARF in these subsequent sample populations are all between 2.0 and 2.5 and are not statistically different from that of the original cohort.

The multivariable (risk-adjusted) odds ratios for aprotinin in relation to ARF are shown in black. Bar “MA” represents the odds ratio for aprotinin after CCF-ARF risk adjustment, which did not include PRBC—or “model A” from Table 2. Bar “MB” represents the odds ratio from “model B”—after the additional adjustment was made for numerical transfusion data. Bar “MC” represents the odds ratio from “model C”—after CCF-ARF risk adjustment in just those patients who did not receive any PRBC transfusions.

Note that aprotinin appears to be significant in all sample sets by univariate analysis. It also appears to be significant using the model A (PRBC-excluding) methodology. However, it is only with the addition of the important prognostic numerical PRBC variable that aprotinin is finally seen not to be a true independent predictor of ARF. Further validation of this clarifying concept is provided by the nontransfused subset of patients, which confirms no relationship between aprotinin use and ARF.

Our multicenter study population of 11,198 patients with validated aprotinin usage data is nearly 5 times as large as the Mangano\textsuperscript{13} multicenter study and more than 12 times as large as the Karkouti\textsuperscript{14} propensity-matched comparison. In addition, our analysis of ARF was performed using a risk-adjusted methodology using a precisely described and externally validated model of postoperative ARF. Neither the Mangano\textsuperscript{13} nor the Karkouti\textsuperscript{14} study used any such risk adjustment.

We understand that a cautionary word regarding this analysis, as well as that of the Mangano\textsuperscript{13} and Karkouti\textsuperscript{14} articles, is in order. All 3 studies are observational and retrospective in nature and as such are subject to the limitations of post-hoc analyses. Observational studies such as these may suffer from selection bias (as noted above). Try as we might, no statistical analyses can completely control for selection bias, which we believe was an important confounding factor in the previous 2 studies. Other limitations include the possibility that there are other predictive prognostic variables not included in the data set that are also risk factors for ARF.

The Mangano\textsuperscript{13} and Karkouti\textsuperscript{14} articles have sparked much controversy and stimulated heated debate\textsuperscript{12,18–25} over this topic in the past year. In September 2006 the US Food and Drug Administration convened a public advisory committee meeting to discuss the Mangano\textsuperscript{13} and Karkouti\textsuperscript{14} findings and the safety and overall risk-benefit profile for Trasylol. The FDA thereafter, in December 2006, issued a “new Warning” (http://www.fda.gov/medwatch/safety/2006/safety06.htm#Trasylol) that Trasylol administration increases the risk of renal dysfunction and may increase the need for dialysis in the perioperative period. The data presented herein raise important questions about the validity of that warning, which was based solely on the Mangano\textsuperscript{13} and Karkouti\textsuperscript{14} studies.

Finally, those interested in this hotly contested topic should note that a recent publication from the Mangano group\textsuperscript{26} focused specifically on the perioperative risks that predispose to renal dysfunction/failure. That paper used the exact definition of renal dysfunction/failure and the same patient dataset as were used in the original Mangano publication on Aprotinin.\textsuperscript{13} It is most interesting to note that aprotinin was not listed at all as a potential etiologic factor for ARF in this more recent paper from the same dataset.

### Summary

Aprotinin does not independently increase the risk of postoperative renal failure after cardiac surgery. Rather, increasing packed red blood cell transfusions in the perioperative period are directly and independently related to an increased risk of postoperative renal failure. Aprotinin lowers predicted transfusion requirements. In addition the Cleveland Clinic risk model for renal failure was validated by our data, but further postoperative ARF risk assessment would be enhanced with the addition of numerical transfused PRBC data to the model.

### Conclusion

We conclude that the implication of aprotinin as a causal factor for postoperative renal failure was incorrect and premature. Previously published results were likely faulty because of the absence of both numerical transfusion data and appropriate risk adjustment for other variables predictive of ARF. We believe that all efforts to minimize packed red blood cell transfusion should be undertaken to prevent even higher occurrence rates of ARF. All subsequent analyses of postoperative ARF, whether prospective or retrospective, should take into account the number of transfusions used in the perioperative period, as this is a highly significant risk factor for the ARF outcome end point.

Furthermore, based on the data presented herein, the FDA should reconsider the previously published aprotinin advisory warnings. Although our data suggest aprotinin to be safe in terms of ARF, a dedicated randomized controlled trial would definitively answer this question. Finally, tort lawyers should use caution in this area, as we have provided ample scientific evidence that aprotinin is both safe and effective.

### Disclosures

None.

### References


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