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The Prognostic Value of Using the Duration of Acute Kidney Injury in Cardiac Surgery: An Example Using Two Antifibrinolytics

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Abstract: Previously, we reported that the addition of duration to the Acute Kidney Injury Network (AKIN) definition of acute kidney injury (AKI) is a marker for more severe kidney injury and predicts long-term mortality. We aimed to evaluate an example of the utility of adding AKI duration to the AKIN definition by comparing the historical use of aprotinin with Amicar. In a single-center observational study, we followed 4987 consecutive patients undergoing cardiac surgery between 2002 and 2007 for postsurgery AKI. Patients with a history of hemodialysis were excluded. Duration of AKI was calculated by the number of days AKI was present as defined by a ≥0.3 (mg/dL) or a ≥50% increase in serum creatinine from baseline or new onset of acute dialysis. Kaplan-Meier and Cox's proportional hazard modeling was conducted to evaluate 5-year mortality. Fifty-three percent of patients received Amicar (n = 2333) and 47% received high-dose aprotinin (n = 2093). Patients receiving aprotinin had evidence of more advanced disease and comorbidity and were more likely to develop AKI and have longer durations of AKI than Amicar ($p < .001$): 7.0 ± 11.5 vs. 3.8 ± 6.0 days ($p < .001$). Nearest-neighbor propensity matching demonstrated aprotinin had significantly worse 5-year mortality compared with Amicar (relative risk [RR] = 2.09, 95% confidence interval [CI] = 1.65–2.65). AKI duration added to the AKIN definition of AKI may provide the necessary sensitivity and specificity for evaluating renal outcomes in clinical trials.
Keywords: acute kidney injury, Amicar, aprotinin, cardiac outcomes, cardiopulmonary bypass. *JECT. 2011;43:227–231*

Small changes in serum creatinine postoperatively in cardiac surgery have not caught the attention of the practicing cardiac surgeon because many of the values return to normal before discharge from the hospital during the index admission. We have shown that the duration of the creatinine rise reflecting acute kidney injury (AKI) has a significant impact on long-term survival (1). To demonstrate the use of using duration of AKI in the postoperative cardiac surgery model, we chose the example of the nephrotoxicity of aprotinin.

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Antifibrinolytic agents have been postulated to be nephrotoxic through acute tubular necrosis or glomerular injury as demonstrated through randomized trials and meta-analyses (2,3). No research to date has investigated the implications of the duration of AKI associated with cardiac surgery among patients who receive antifibrinolytics in the United States. The duration of AKI is a marker for more severe kidney injury and predicts long-term mortality and thus can be a useful measure for evaluating risks and benefits of pharmacological agents, devices, and practice patterns (1). As an example of the usefulness of this tool, we sought to compare the duration of AKI among patients under going cardiac surgery and receiving either Epsilon-aminocaproic acid (Amicar®; Xanodyne Pharmaceuticals, Inc., Newport, KY) or aprotinin (Trasylol®; Bayer Pharmaceuticals Corporation, Wayne, NJ).

MATERIALS AND METHODS

We prospectively followed 4987 patients undergoing cardiac surgery between 2002 and 2007 as an observational study. All patients had daily serum creatinine collection. Patients who had a history of dialysis were excluded from the analysis (n = 70). Of the remaining patients, 4426 patients received either Amicar or aprotinin and were included in the final analysis; thus, there were no patients in this analysis who did not receive either Amicar or aprotinin. The Maine Medical Center Institutional Review Board has approved the use of data for quality improvement and research.

To determine AKI and the duration of AKI, the last preoperative serum creatinine before surgery was compared with each postoperative serum creatinine. AKI was defined as a ≥0.3 (mg/dL) or ≥50% increase in serum creatinine from baseline on each postoperative day (4). Duration of AKI was defined using the number of days AKI was present and grouped by the following: no AKI or AKI for 1–2, 3–6, and ≥7 days as previously described (1). Severity of AKI was classified by Acute Kidney Injury Network (AKIN) staging criteria (4).

Patients were followed during the hospital admission for cardiac surgery until discharge and matched to the Social Security Death Master File for long-term follow-up (5). In-hospital clinical outcomes were summarized by percentages and means (± standard deviation). We used χ^2 tests and tests of trend to test similarities between categories of duration of AKI. Degrees of freedom for the χ^2 tests depended on the number of groups. All clinical outcome variables in Table 1 were tested using the χ^2 test with 1 degree of freedom, except for AKI duration (1), AKIN stages (1), percent changes in peak creatinine (1), and length of stay where the unpaired *t* test was used. Cox's proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) with "no AKI" as the referent, adjusting for age, baseline estimated glomerular filtration rate, left ventricular end diastolic pressure, baseline hematocrit, ejection fraction, vascular disease, left main disease >50%, unstable angina, and emergent procedure resulting from biological plausibility and univariate associations with survival and duration of AKI. Adjusted HRs were reported with 95% confidence intervals and *p* values. Nearest-neighbor propensity matching was used to conduct the analysis among similarly matched patients and risk factors matching on age, prior coronary artery bypass surgery, unstable angina, vascular disease, urgent or emergency surgery, ejection fraction, left ventricular end diastolic pressure, number of diseased vessels, left main disease >50%, use of intra-aortic balloon pump before surgery, and baseline hematocrit. Nearest-neighbor matching matched 2398 patients for AKI comparison and Cox's proportional hazard modeling. All analyses were conducted using Stata release 9.0 software (Stata Corp., College Station, TX) (6).

Table 1. Patient and disease characteristics.

Variables	Amicar (n = 2333)	Aprotinin (n = 2093)	*p* Value
Patient demographics			
Age, mean ± SD	64.1 ± 10.5	68.6 ± 11.1	<.001
Sex (% female)	27.7	32.3	.001
Body mass index, mean ± SD	29.5 ± 5.7	28.9 ± 5.8	<.001
Preoperative characteristics			
Hypertension (%)	66.4	64.9	.304
COPD (%)	10.1	15.1	<.001
Vascular disease (%)	19.1	25.4	<.001
Diabetes (%)	32.4	32.9	.715
Preoperative hematocrit Mean ± SD	40.0 ± 4.8	38.6 ± 5.2	<.001
Preoperative creatinine Mean ± SD (mg/dL)	1.0 ± .4	1.1 ± .5	<.001
Preoperative eGFR Mean ± SD (mL/min/m^2)	82.0 ± 27.0	76.3 ± 26.4	<.001
Preoperative eGFR categories			
≥90 (mL/min/m^2)	35.3	27.6	<.001
60–89	46.3	46.3	
30–59	16.9	23.0	
15–29	1.4	2.7	
<15	.1	.4	
Cardiac profile			
Type of surgery (%)	78.6	59.1	<.001
Coronary artery bypass grafting			
Coronary artery bypass graft/valve	9.3	21.6	
Valve	12.1	19.3	
Surgical priority (%)			
Elective	32.9	25.6	<.001
Urgent	62.3	61.9	
Emergent	4.8	12.5	
Left main disease (≥50% stenosis, %)	23.9	28.0	.002
Unstable angina (%)	61.4	50.0	<.001
Intra-aortic balloon pump (%)	3.9	11.4	<.001
Number of diseased vessels, mean ± SD	2.0 ± 1.1	1.9 ± 1.1	.046
Ejection fraction, mean ± SD	52.9 ± 11.8	49.3 ± 13.7	<.001
LVEDP, mean ± SD (mmHg)	18.3 ± 7.4	20.2 ± 8.3	<.001
Prior coronary artery bypass graft (%)	1.9	11.2	<.001

p value: χ^2 test, test of trend.
SD, standard deviation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEDP, left ventricular end diastolic pressure. Postoperative eGFR calculated from the highest postoperative serum creatinine (mg/dL) using the Modification of Diet in Renal Disease equation.

RESULTS

Fifty-three percent of patients received Amicar (n = 2333) and 47% received high-dose aprotinin (n = 2093) (Table 1). Of the 4426 patients, 1723 (38.9%) of the patients developed AKI during the postcardiac surgery hospitalization: AKI

occurred among 33.7% of patients receiving Amicar and 44.7% among patients receiving aprotinin. Patients receiving aprotinin were more likely to develop longer durations of AKI than Amicar (Figure 1; Table 2, $p < .001$): 7.0 ± 11.5 vs. 3.8 ± 6.0 days ($p < .001$). Aprotinin was also associated with worse in-hospital outcomes over Amicar including 31 patients undergoing postoperative dialysis before discharge compared with one patient in the Amicar treatment group (Table 2). After risk adjustment, 5-year mortality for patients was not significantly different for those receiving aprotinin vs. Amicar overall (relative risk [RR] = 1.28, 95% confidence interval [CI] = 1.00–1.65) and by strata of duration: no AKI (RR = .94; .64–1.38); AKI for 1–2 days (RR = 1.68; .93–3.00); AKI for 3–6 days (RR = 1.32; .66–2.66); and AKI for ≥7 days (RR = 1.45; .78–2.68) (Table 3).

Nearest-neighbor propensity matching demonstrated aprotinin had more patients developing AKI (45% vs. 34%, $p < .001$) and longer durations of AKI for 1–2 days (18% vs. 19%); AKI for 3–6 days (13% vs. 10%); and AKI for ≥7 days (13% vs. 5%). Unlike the adjusted modeling, the propensity-matched patients receiving aprotinin had significantly worse 5-year mortality compared with Amicar (RR = 2.09, 95% CI = 1.65–2.65) (Figure 2; log-rank test $p < .001$). The findings were consistent among each duration category of AKI, because aprotinin was associated with increased risk of 5-year mortality compared with Amicar: AKI for 1–2 days (RR = 2.47; 1.45–4.21); AKI for 3–6 days (RR = 1.90; .98–3.67); and AKI for ≥7 days (RR = 1.56; .88–2.76).

Table 2. Assessment of in-hospital outcomes.

Variables	Amicar (n = 2333)	Aprotinin (n = 2093)	*p* Value
Postoperative clinical outcomes			
Postoperative peak creatinine			
Mean ± SD	1.2 ± 1.1	1.4 ± 1.0	<.001
AKI duration, mean ± SD (days)	3.8 ± 6.0	7.0 ± 11.5	<.001
AKI duration			
No AKI	66.3	55.3	<.001
1–2 days	19.4	18.0	
3–6 days	9.6	13.4	
7+ days	4.8	13.3	
AKIN criteria			
No AKI	66.3	55.3	<.001
Stage 1	28.0	33.3	
Stage 2	4.2	6.9	
Stage 3	1.6	4.5	
Percent change in peak creatinine			
<50%	79.0	69.3	<.001
50–99%	14.2	17.9	
100–199%	5.8	9.6	
≥200%	1.0	3.3	
In-hospital acute dialysis (%)	.04	1.48	<.001
Length of postoperative stay			
Mean ± SD (days)	7.1 ± 7.4	10.1 ± 12.5	<.001
Extubation time mean ± SD (hours)	7.3 ± 8.0	11.0 ± 12.7	<.001
Atrial fibrillation (%)	24.9	34.9	<.001
Intra- or postoperative use of intra-aortic balloon pump (%)	2.0	9.3	<.001
Low-output syndrome (%)	2.8	10.9	<.001
Mediastinitis (%)	1.5	2.4	.023
Return to operating room for bleeding (%)	2.6	3.8	.021
Q-wave myocardial infarction (%)	2.1	4.0	.012
Pneumonia (%)	1.9	4.9	<.001
In-hospital mortality (%)	1.7	7.1	<.001

p value for χ^2 or test of trend.
SD, standard deviation; AKI, acute kidney injury; AKIN: Acute Kidney Injury Network; Renal failure: new onset of acute dialysis during postoperative admission.

DISCUSSION

Aprotonin has been found to be nephrotoxic in several clinical trials and observational studies using AKI definitions that solely used peak changes in serum creatinine. None of these studies examined duration of AKI, which we maintain is an additional important parameter of AKI. Duration of AKI in the setting of cardiac surgery is known to predict short-term and long-term outcomes (1). Our present study provides additional evidence for the known renal toxicity of aprotinin when compared with Amicar by using a novel measure, duration of AKI. This same methodology could easily be applied when comparing other pharmaceuticals or interventions with regard to the incidence and the duration of AKI, recognizing that longer durations have a more profound impact on survival.

The longer duration of AKI may denote more severe kidney injury or delayed recovery of the kidney tubules. In the example of aprotinin, the drug accumulates in the proximal tubule because it is taken up by the megalin receptor pathway after filtration. The accumulation of aprotinin damages the proximal tubule and causes apoptosis

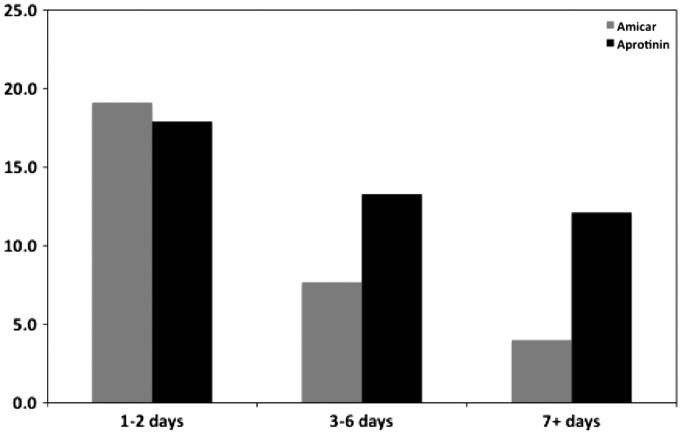

Figure 1. Duration of acute kidney injury (AKI) by antifibrinolytic agent. The percent of patients with AKI is graphed by the duration of kidney injury (1–2, 3–6, and ≥7 days) by type of antifibrinolytic: Amicar (gray bars) or aprotinin (black bars).

Table 3. Assessment of long-term mortality.

Duration of AKI	Model 1 Crude (95% CI)		Model 2 Covariates (95% CI)		Model 3 Propensity (95% CI)	
Aprotinin	2.11	(1.78–2.51)	1.28	(1.00–1.65)	2.09	(1.65–2.65)
Aprotinin by AKI duration						
None	1.49	(1.14–1.94)	0.94	(.64–1.38)	1.35	(.94–1.92)
1–2 days	2.53	(1.72–3.74)	1.68	(.93–3.00)	2.47	(1.45–4.21)
3–6 days	1.94	(1.24–3.04)	1.32	(.66–2.66)	1.90	(.98–3.67)
≥7 days	1.31	(.90–1.92)	1.45	(.78–2.68)	1.56	(.88–2.76)

p value.
95% CI, 95% confidence interval; adjusted hazard ratio from Cox proportional hazard model; Model 1, crude; Model 2, adjusted for age, baseline estimated glomerular filtration rate, left ventricular end diastolic pressure, baseline hematocrit, ejection fraction, vascular disease, left main disease >50%, unstable angina, and emergent procedure; Model 3, nearest-neighbor propensity matched analysis (aprotinin matched on baseline hematocrit, number of diseased vessels, ejection fraction, left ventricular end diastolic pressure, vascular disease, priority of surgery, left main disease >50%, unstable angina, pre-operative intra-aortic balloon pump, and prior coronary artery bypass graft surgery; AKI, acute kidney injury.

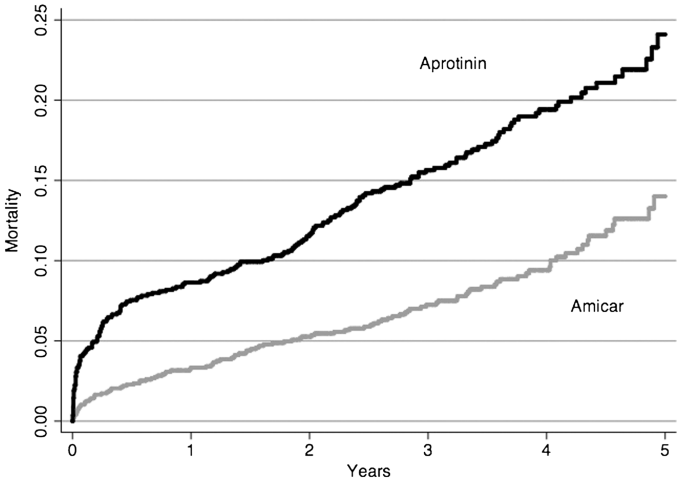

Figure 2. Five-year mortality for propensity matched patients by antifibrinolytic agent. Kaplan Meier plotting 5-year mortality for nearest-neighbor propensity matched patients for Amicar (gray) or aprotinin (black). Log-rank test $p < .001$.

and necrosis of these cells leading to AKI (7–9). The recovery from AKI requires the remaining tubular cells to undergo dedifferentiation, division, and redifferentiation to replace the necrotic cells. If the surrounding cells are impaired with the presence of aprotinin, the processes of recovery may be ineffective or delayed causing a longer duration of AKI.

Aprotonin is not currently available for purchase in the United States. We have used it as an example to demonstrate the usefulness of adding the duration of AKI to the current AKIN definition.

By examining the effects of a drug that is known to be nephrotoxic, this report validates a novel measure of nephrotoxicity, which is the "duration of AKI." Duration of AKI as a new measure has biologic relevance, is sensitive and specific (short and long duration), easy to measure, and is associated with poor short-term and long-term outcomes. Thus, the addition of duration of AKI can provide vital information in regard to risk classification if added to the existing classification systems of AKI. The purpose of this report is to demonstrate the value of enhancing the current AKIN definition with the addition of duration of AKI. In this example, the analysis suggests that one of the antifibrinolytics (Amicar) currently used in cardiac surgery procedures in the United States today has less nephrotoxicity than aprotinin with fewer patients developing AKI as well as shorter durations of AKI, placing the patient on a more favorable survival curve.

In conclusion, by showing that aprotinin is associated with a longer duration of AKI and higher long-term mortality compared with Amicar, we have demonstrated the prognostic use of adding AKI duration to the AKIN definition of AKI. In this example, we showed that in the new era of managing cardiac surgery patients without aprotinin, there will likely be less nephrotoxicity and the duration of AKI will be shorter and long-term survival will likely improve. Adding AKI duration to the AKIN definition in the course of evaluating renal outcomes in clinical trials may provide the necessary sensitivity and specificity for prediction of the likelihood of worse long-term survival.

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