Trends in the Incidence of Acute Kidney Injury in Patients Hospitalized With Acute Myocardial Infarction

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Background: Acute kidney injury (AKI) is common in patients with acute myocardial infarction (AMI) and is associated with permanent renal impairment and death. Although guidelines increasingly emphasize AKI prevention, whether increased awareness has translated into reduced AKI rates is unclear.

Methods: Among 33,249 consecutive hospitalizations in 31,532 unselected patients with AMI across 56 US centers from Cerner Corporation’s HealthFacts database, we examined the temporal trends in AKI incidence from 2000 to 2008. Acute kidney injury was defined as an absolute increase in creatinine level of at least 0.3 mg/dL or a relative increase of at least 50% during hospitalization.

Results: From 2000 to 2008, the mean age of patients increased (from 66.5 to 68.6 years), as did the known AKI risk factors, including chronic kidney disease, cardiogenic shock, diabetes mellitus, heart failure, coronary angiography, and percutaneous coronary intervention. Despite this, AKI incidence declined from 26.6% in 2000 to 19.7% in 2008 (P < .001). After multivariate adjustment, the trend of decreasing AKI rates persisted (4.4% decline per year; P < .001). In addition, in-hospital mortality also declined over time among patients developing AKI, from 19.9% in 2000 to 13.8% in 2008 (P < .003).

Conclusions: In a large national study, AKI incidence in patients hospitalized with AMI declined significantly from 2000 to 2008 despite the aging population and rising prevalence of AKI risk factors. These findings may reflect increased clinician awareness, better risk stratification, or greater use of AKI prevention efforts during this time period.

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See Invited Commentary at end of article

A CUTE KIDNEY INJURY (AKI) is common in patients hospitalized with an acute myocardial infarction (AMI), developing in 1 in 5 patients.1,2 Development of AKI is associated with adverse long-term outcomes, including development of permanent renal impairment and end-stage renal disease.1,3 Moreover, even minor increases in serum creatinine level are associated with increased in-hospital and long-term mortality,1,2 longer length of stay (LOS) and higher cost.6,8 Owing to its high prevalence and prognostic importance, professional societies and expert groups have increasingly emphasized the importance of AKI prevention and prompt recognition in patients hospitalized with AMI.9,10 Whether these recommendations have translated into lower incidence of AKI over time remains unclear.

Better understanding of temporal trends in AKI incidence would highlight whether recent efforts focused on reducing AKI have been successful, and would inform future AKI prevention initiatives. Accordingly, we analyzed data from the Cerner Corporation’s (Kansas City, Missouri) Health Facts database, a contemporary registry of patients admitted to 56 hospitals across the United States, to define the trends in AKI from 2000 to 2008. This database has an extensive collection of laboratory data, including detailed assessments of renal function, in a large consecutive cohort of patients with AMI. Our goals were to understand the temporal trends in the incidence of AKI and use of AKI prevention strategies among patients hospitalized with AMI. Health Facts provided an ideal opportunity to address these questions, given its detailed information on in-hospital laboratory assessments, as well as medication use.
DATA SOURCE, STUDY POPULATION, AND STUDY DESIGN

We used data from 56 US participating hospitals in Health Facts from January 1, 2000, to December 31, 2008, to identify the time trends in the incidence of AKI among patients with AMI.11,12 The median number of patients per hospital was 219 (interquartile range [IQR], 48-1030), and the median duration of hospitals' participation was 2.9 years (IQR, 1.2-5.3). Hospitals were frequently urban (88.9%), teaching (35.9%), and represented all US regions (Northeast, 38.9%; Midwest, 25.6%; South, 26.9%; and West, 9%) and sizes (bed size: 100-199, 20.9%; 200-299, 23.1%; 300-499, 17.9%; and ≥500 beds, 11.5%). All data were deidentified, and an exemption was provided by the Saint Luke's Hospital institutional review board. The Cerner Corporation provided the data but had no role in study conception, design, analyses, drafting, or review of the manuscript.

Data collected included hospital characteristics, patients' demographics (from medical records and registration data), medical history and comorbidities (using International Classification of Diseases, Ninth Revision [ICD-9] codes), comprehensive laboratory studies (including all creatinine measurements during hospitalization), in-hospital medications, procedures, complications, and in-hospital mortality.11,12 We included patients hospitalized with a primary discharge diagnosis of AMI as determined by ICD-9 codes 410.xx and further confirmed AMI by requiring that patients had at least 1 elevated cardiac biomarker (troponin or creatine kinase-MB) and were not discharged within the first 24 hours (N=38,422) (Figure 1). We excluded patients transferred from other hospitals (full laboratory data may not be available) or from hospice (since goals of hospice care differ from those in the overall population) (n=81). To improve generalizability, we excluded patients from hospitals treating fewer than 20 patients with AMI during the study period (n=76, from 11 hospitals) and patients with LOSs greater than 31 days (n=381). We excluded patients who died within 24 hours of arrival (n=557) because they would not have had sufficient time to develop AKI. Next, we excluded patients receiving hemodialysis (n=1058) because they would have been unable to develop AKI. Finally, patients with fewer than 2 creatinine assessments were also excluded, yielding a final analytic cohort of 31,532 patients with AMI with 33,249 encounters (Figure 1).

AKI DEFINITION

Consistent with prior work,2,13 AKI was defined using Acute Kidney Injury Network (AKIN) study group criteria2,13 as an absolute increase in serum creatinine level of 0.3 mg/dl or more, or a relative increase in serum creatinine level of 50% or more during hospitalization (to convert creatinine to micromoles per liter, multiply by 88.4).

OUTCOMES

The primary outcome of interest was incidence of AKI over time. Additional outcomes included temporal trends in the use of medications that may influence AKI, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, N-acetyl cysteine (NAC), and intravenous sodium bicarbonate during hospitalization.

STATISTICAL ANALYSIS

Primary Analysis

We evaluated the unadjusted trends in baseline characteristics and the incidence of AKI across study years using the Mantel-Haenszel extension of the χ2 test for trend (categorical variables) and the linear test for trend (continuous variables). Since we evaluated temporal trends for AKI, the year of admission was the main predictor variable. Hierarchical multivariate logistic regression models were then constructed, with AKI as the dependent variable, year of admission as the main exposure variable (modeled as continuous variable ranging from year 2000 to 2008), and hospital site as a random effect. Models were adjusted for factors that were previously demonstrated or clinically considered to influence AKI, including age, sex, race/ethnicity, diabetes mellitus, heart failure (HF), cardiogenic shock, Modification of Diet in Renal Disease glomerular filtration rate (GFR) on admission (continuous variable), and cardiac catheterization with or without revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). This model estimated the adjusted probability of AKI per incremental year over the study period (with 2000 as the comparison year). Since the etiology of AKI in patients undergoing cardiac catheterization and their AKI preventative measures may differ from those treated conservatively, we tested whether the temporal trend in AKI was different between these 2 groups by adding an year×cardiac catheterization interaction term to the model.

Controlling for Surveillance Bias

Since the AKI trend could be biased by change in surveillance patterns for AKI, we adjusted the model with 2 variables: the number of creatinine measurements per day, and the median time to AKI diagnosis. In addition, since a decreasing trend in LOS could bias the AKI trends, we adjusted the final model for LOS. Finally, we also adjusted the model for final creatinine measurement at discharge.

Secondary Analyses

To understand if there was a temporal trend in the use of medications that could influence the AKI trend, we developed separate multivariate models with each medication class as the dependent variable and year of admission as the main predictor variable, adjusting for all the covariates as described in the main model. Finally, we studied the variation in the AKI incidence and medications known to influence AKI across the 56 par-
AKI itself was changing over time. To determine the between-hospital variation, we plotted the overall incidence of AKI and the rates of medication use for each hospital and estimated the median odds ratio (MOR), a quantitative measure of this variation.\textsuperscript{16,17} The MOR represents the median of all odds ratios (ORs) when comparing the odds of AKI for all possible pairs of patients with identical characteristics presenting at 2 different randomly chosen hospitals. Finally, we estimated the MOR for development of AKI across the study years to determine if the variation in AKI was changing over time.

**Sensitivity Analyses**

Participating hospitals entered the Health Facts study at different times. To determine whether the AKI trend was disproportionately influenced by hospitals with short duration of participation, potentially biasing the overall trend, we performed sensitivity analyses in which models were compared in hospitals participating less than 5 years vs those participating at least 5 years. It was also conceivable that a declining AKI trend could result from a decline in only mild AKI, whereas severe AKI remained unchanged over time. To address this, we estimated the adjusted trend in severe AKI (defined as doubling of creatinine level) over the study period. To ensure that AKI trends were not influenced by AKI developing many days after admission, we truncated the sample to an LOS of (1) the first 14 days and (2) the first 7 days.

**In-Hospital Mortality Trends Among Those With AKI**

Finally, we evaluated the in-hospital mortality trends among those with AKI. To identify adjusted trends in mortality, we developed a multivariate logistic regression model with in-hospital mortality as the dependent variable. The model included a year × AKI interaction term and adjusted for trends in confounders and practice pattern changes over time as in the main model.

**RESULTS**

**BASELINE CHARACTERISTICS**

Owing to the unselected nature of this database, there was a high prevalence of comorbidities, such as diabetes mellitus, chronic kidney disease, and congestive heart failure. The Table shows the prevalence of patient characteristics over time. Key risk factors for AKI increased significantly from 2000 to 2008, including mean age (66.5 vs 68.6 years), chronic kidney disease (3.9\% vs 12.7\%), cardiogenic shock (4.3\% vs 5.7\%), diabetes mellitus (30.3\% vs 35.1\%), heart failure (29.8\% vs 32.7\%), use of coronary angiography (59.0\% vs 70.0\%), and PCI (32.1\% vs 47.0\%; P < .001 for all comparisons).

**AKI TRENDS**

Overall, the incidence of AKI was 22.5\%. The crude incidence of AKI declined significantly over time from 26.6\% in the year 2000 to 19.7\% in 2008 (P < .001) (Figure 2), representing an absolute difference of 6.9\%. When adjusted for trends in potential confounders and practice pattern changes over time that could bias the AKI trends (surveillance bias), we observed a 4.4\% decline in AKI per year (95\% CI, 2.0\%-6.8\%; P < .001).

**INTERACTION WITH CARDIAC CATHETERIZATION STATUS**

When stratified by cardiac catheterization status, the crude incidence of AKI declined significantly in patients undergoing cardiac catheterization (from 24.6\% in the year 2000 to 16.5\% in 2008; P value for trend < .001). In patients who were treated conservatively, the decrease in the crude AKI rate was much less substantial, and not statistically significant (from 29.4\% in 2000 to 27.0\% in 2008; P value for trend, .66; P value for unadjusted interaction, < .001). After adjustment for hospital site and other confounders, a significant decrease in AKI incidence over time was observed in both groups; however, the magnitude of decline in AKI incidence was more substantial in patients undergoing cardiac catheterization (5.6\% decline in AKI per incremental year [P = .001] vs 3.3\% decline per year among those treated conservatively [P = .01]; P value for interaction, .28).

**SECONDARY ANALYSIS**

The temporal trends in the use of medications potentially related to development of AKI are presented in the Table. While diuretic use decreased over time (from 56.4\% in 2000 to 47.0\% in 2008; P < .001), the use of NAC increased (from 0.6\% in 2000 to 10.6\% in 2008; P < .001) over time. When adjusted for confounders, NAC was the only medication potentially related to AKI that had a statistically significant temporal increase in its use (OR, 1.19; 95\% CI, 1.01-1.40) (Figure 3).

**HOSPITAL VARIATION**

There was a significant variation in the incidence of AKI across hospitals, ranging from 10\% to 32\% (Figure 4). After multivariate adjustment, this substantial variation in AKI incidence across hospitals persisted (adjusted median OR, 1.26); this indicates that 2 patients with identical clinical characteristics would have an average increase of 26\% in their risk of developing AKI simply due to being admitted to different hospitals. We also observed that this MOR remained unchanged over time, with an MOR of 1.22 in the beginning year 2000 and 1.21 in the year 2008. We also observed large variation in the use of medications potentially related to development of AKI: NAC (0\%-38\%), intravenous sodium bicarbonate (0\%-33\%), diuretics (10\%-86\%), ACE-ARB (27\%-87\%), and NSAIDs (0\%-27\%).

**SENSITIVITY ANALYSES**

The adjusted AKI trend among the hospitals participating less than 5 years vs those participating at least 5 years was similar (a 4.30\% decline in AKI per year in hospitals participating < 5 years [P = .04] vs a 4.11\% decline among those participating ≥ 5 years [P = .003]; P value for interaction = .94). When we evaluated adjusted trends in severe AKI (doubling of serum creatinine), we found that severe AKI occurred in only 1176 patients (3.5\%). However, we found a similar, 5.2\% decline in the incidence of severe AKI per year (95\% CI, 1.8\%-8.4\%; P < .001), indicating that even
severe AKI declined significantly over time. When the LOS was limited to a shorter duration, the AKI trend continued to show a decline—a 4.14% decrease (95% CI, 1.53%-6.69%; \(P = .002\)) when LOS was limited to 14 days, and a 5.21% decline (95% CI, 2.28%-8.06%; \(P = .001\)) when LOS was limited to 7 days. Finally, the proportion of patients excluded due to less than 2 creatinine measurements increased over time. To ascertain if selection bias occurred in excluding these patients, we compared this group with the included patients, and we found that the excluded patients were younger and had fewer comorbidities and were thus at lower risk for AKI (data not shown). Inclusion of these patients in the study would have resulted in an even stronger declining AKI trend. Thus, our results may underestimate the true magnitude of AKI decline over time.

### IN-HOSPITAL MORTALITY TRENDS AMONG PATIENTS WITH AKI

We observed declining in-hospital mortality over time among patients with AKI, from 19.9% in 2000 to 13.8% in 2008 (\(P = .003\)). When adjusted for potential confounders, this decrease in hospital mortality among pa-
In this large cohort of patients with AMI, we found that the incidence of AKI has declined over time, despite a concomitant increase in AKI risk factors. This trend persisted after extensive multivariate adjustment, supporting the robustness of these findings. While the magnitude of this decrease in AKI incidence was particularly pronounced in patients undergoing coronary angiography, it was also observed among those treated conservatively. Our findings demonstrate a substantial variability in AKI rates across participating sites, suggesting that hospital-based processes of care may, in part, contribute to the incidence in AKI rates across participating sites, suggesting that hospital-based processes of care may, in part, contribute to the variability in AKI rates across participating sites, suggesting that hospital-based processes of care may, in part, contribute to the variability in AKI rates.

MAJOR FINDINGS AND THEIR IMPLICATIONS

In this large cohort of patients with AMI, we found that the incidence of AKI has declined over time, despite a concomitant increase in AKI risk factors. This trend persisted after extensive multivariate adjustment, supporting the robustness of these findings. While the magnitude of this decrease in AKI incidence was particularly pronounced in patients undergoing coronary angiography, it was also observed among those treated conservatively. Our findings demonstrate a substantial variability in AKI rates across participating sites, suggesting that hospital-based processes of care may, in part, contrib-
ute to AKI incidence and highlighting a potential opportunity for quality improvement. Finally, we also observed a concomitant decrease in in-hospital mortality trend among patients developing AKI, even after multivariate adjustment.

Whether this declining AKI trend reflects enhanced AKI awareness and prevention efforts or better selection of patients for coronary angiography and PCI over time cannot be determined with certainty. However, several of our findings indirectly suggest that better AKI prevention efforts may be playing a role. We observed a greater degree of decline in AKI among patients who underwent cardiac catheterization—the group in which there are more opportunities for AKI prevention (including preprocedural hydration and judicious contrast use). While randomized clinical trials have not demonstrated NAC to be effective in preventing AKI,18 the greater use of NAC over time likely represents a proxy for greater awareness and use of other AKI preventive measures. The American College of Cardiology (ACC)/American Heart Association (AHA)/Society of Coronary Angiography and Intervention (SCAI) guidelines and large observational studies advocate that in-hospital care should focus on detecting and preventing kidney injury.9,10 It is possible that guideline endorsement by the ACC/AHA/SCAI and publication of studies demonstrating adverse outcomes in patients with AKI had an impact on physician behavior.

Despite these improvements, significant opportunities for quality improvement remain. We observed a wide variation across hospitals not only in AKI incidence but also in medications that might influence AKI. These variations potentially reflect differences in hospital-based processes of care and suggest that opportunities may exist for further reductions in AKI.19 Of note, some hospitals had very low AKI rates; better understanding of the practice patterns at these centers may offer valuable insights into effective strategies for AKI prevention that could be then implemented at other institutions.

PRIOR LITERATURE REVIEW

Our data are in contrast with those of prior studies that show a rising incidence of acute renal failure (ARF). However, this rising incidence of AKI was demonstrated in disease conditions other than AMI. Waikar et al20 reported an increasing ARF incidence among hospitalized patients. However, these were older data, from 1988 to 2002, when the prognostic significance of ARF was less recognized and less attention was paid to ARF prevention. Similar reports of a rising ARF incidence have been observed in those undergoing CABG and cardiac surgery, including heart transplantation, a population at a high risk of developing AKI.21,22 Data reported by Xue et al23 from hospitalized, elderly Medicare beneficiaries, with presumably more comorbidities, also showed that ARF incidence was rising when evaluated from 1996 to 2001. The contrast between our data and those of prior observations may stem from differences in patient populations, their underlying disease conditions and comorbidities, different time periods, or differing AKI definitions used; it is also possible that the AKI decline we observed may be due to greater opportunities for AKI prevention in patients with AMI (eg, preprocedural hydration and judicious contrast use) and greater uptake and application of guidelines endorsing AKI preventive efforts.

LIMITATIONS

Several limitations should be considered while interpreting these data. First, we did not have data on intravenous fluid administration other than sodium bicarbonate; neither did we have information on the type and amount of contrast use during coronary angiography. Second, while we examined a large cohort of patients from multiple hospitals in the United States, these results are limited to centers that have an electronic medical record and may not be generalizable to all patients with AMI. Third, creatinine measurements were not obtained in all patients at the same time intervals because we depended on clinical data to detect AKI. However, these data reflect “real-world” clinical practice in an unselected patient cohort and as such may be the best data source to examine...
this issue. Fourth, while our multivariate models adjusted for known predictors of AKI, the possibility of unmeasured confounding affecting our results cannot be eliminated. Finally, no causal inferences about the relation between higher use of renal protective medications and declining AKI trends are possible from these observational data.

In conclusion, AKI incidence in patients with AMI declined from 2000 to 2008, despite an increase in AKI risk factors such as age, diabetes mellitus, cardiogenic shock and HF, potentially reflecting increased clinician awareness, better risk stratification, and AKI prevention efforts during this time period. Nevertheless, the AKI rates remain high, with substantial variability across hospitals. Future prospective studies are needed to better understand the reasons for this variation and define opportunities for further improvement in patient outcomes.

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Acute Kidney Injury

Glimpses Into Epidemiology and Opportunities for Improvement

While acute kidney injury (AKI), a newer term for acute renal failure, has long been recognized as a common and serious complication of hospitalized patients, the study of AKI epidemiology has lagged. An important advance took place with the introduction of consensus AKI definitions by expert panels—first the Risk, Injury, Failure, Loss, and End-stage Renal Disease (RIFLE) criteria by the Acute Dialysis Quality Initiative in 2004, and then the Acute Kidney Injury Network (AKIN) criteria in 2007. These have allowed researchers to examine AKI epidemiology using a common case definition and to overcome one important limitation in the prior literature when cases were defined using different criteria in different studies, rendering it difficult to interpret variations in reported disease incidence. Since then, several studies have characterized AKI incidence...