Long-term Risk of Mortality and End-Stage Renal Disease Among the Elderly After Small Increases in Serum Creatinine Level During Hospitalization for Acute Myocardial Infarction

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**Background:** Although small changes in creatinine level during hospitalization have been associated with risk of short-term mortality, associations with posthospitalization end-stage renal disease (ESRD) and long-term mortality are unknown. We assessed the relationship between change in serum creatinine levels up to 3.0 mg/dL and death and ESRD among elderly survivors of hospitalization for acute myocardial infarction.

**Methods:** Retrospective cohort study of a nationally representative sample of Medicare beneficiaries admitted with acute myocardial infarction to nonfederal US hospitals between February 1994 and July 1995. Outcomes were mortality and ESRD through June 2004.

**Results:** The 87,094 eligible patients admitted to 4473 hospitals had a mean age of 77.1 years; for the 43.2% with some creatinine increase, quartiles of increase were 0.1, 0.2, 0.3 to 0.5, and 0.6 to 3.0 mg/dL. Incidence of ESRD and mortality ranged from 2.3 and 139.1 cases per 1000 person-years, respectively, among patients with no increase to 20.0 and 274.9 cases per 1000 person-years in the highest quartile of creatinine increase. Compared with patients without creatinine increase, adjusted hazard ratios by quartile of increase were 1.45, 1.97, 2.36, and 3.26 for ESRD and 1.14, 1.16, 1.26, and 1.39 for mortality, with no 95% confidence intervals overlapping 1.0 for either end point.

**Conclusion:** In a nationally representative sample of elderly patients discharged after hospitalization for acute myocardial infarction, small changes in serum creatinine level during hospitalization were associated with an independent higher risk of ESRD and death.

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The Cooperative Cardiovascular Project (CCP) was a national quality-improvement project to improve the care of patients hospitalized with AMI. The original CCP data set contains 234,754 randomly selected hospital admissions for AMI in 210,981 Medicare beneficiaries from all 50 states hospitalized between February 1994 and July 1995. Patients with an International Classification of Diseases, Ninth Revision, Clinical Modification principal discharge diagnosis code of 410 (AMI) were sampled from 6,684 nonfederal hospitals, composing virtually all acute care hospitals in the United States. Trained abstractors recorded hospital chart data, with extensive data quality monitoring. Patients from the CCP cohort were linked to the US Renal Data System by means of health insurance claim number and beneficiary identification code to identify ESRD. Valid personal identifier numbers (health insurance claim/beneficiary identification code) were available for 94.7% of the CCP patients. Matches were subsequently individually verified on the basis of a 5-point scoring system designed to test validity by using age, sex, and US Renal Data System–verified date of death. Date of death for patients without ESRD was obtained from the Medicare Enrollment Database. Follow-up for ESRD and mortality included the period from the inception of the CCP data collection (February 1994) through June 2004. Our study was approved by the institutional review board of the University of Alabama at Birmingham.

EXCLUSIONS
We based much of our exclusion criteria on previous studies that used the CCP data. We included the first hospitalization for the 210,981 patients in the CCP, and we excluded patients who reached the primary or censoring outcome during hospitalization, including those with a first date of long-term renal replacement therapy during hospitalization (n = 323) and death before hospital discharge (n = 3,408). We further excluded patients for the following reasons: a diagnosis of ESRD before hospital admission (n = 3,106), AMI not confirmed by clinical criteria (n = 26,249), transfer to the index hospital (n = 29,712), transfer from the index hospital within 24 hours of admission (n = 34,759), race other than African American or white (n = 81,878), and age less than 65 years (n = 15,552). Because our focus was the risk associated with change in kidney function among patients not requiring dialysis during hospitalization, we excluded patients who received acute hemodialysis during hospitalization as determined by the International Classification of Diseases, Ninth Revision, Clinical Modification procedure code 3995, shown to have high predictive validity for AKI requiring dialysis, as well as patients in the 99th percentile of increase in serum creatinine level during hospitalization (n = 4176). In addition, we excluded patients with missing or invalid data, as follows: admission or peak serum creatinine level missing or less than 0.1 mg/dL (n = 10,105), missing admission hematocrit (n = 10,115), and inability to identify outcome due to invalid health insurance claim/beneficiary identification code (n = 11,257). Owing to overlap, the total number of patients with any missing data was 24,955. We excluded patients who were not African American or white for 2 main reasons: race/ethnicity is an important confounding variable, and races/ethnicities other than African American or white cannot be classified with reasonable reliability from Medicare administrative data sets.

STUDY VARIABLES
We used the first serum creatinine level collected within 24 hours of hospital admission as the baseline serum creatinine level at the time of hospitalization. Estimated glomerular filtration rate, calculated by means of the abbreviated Modification of Diet in Renal Disease Study equation, was used as a measure of kidney function at admission. We divided patients into the following glomerular filtration rate categories by means of a modification of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative stages of kidney disease: 60 or more, 45 to 59, 30 to 44, 15 to 29, and less than 15 mL/min/1.73 m². To calculate the maximum change in serum creatinine level, we subtracted the starting serum creatinine level from the peak serum creatinine level measured during hospitalization. We classified patients into 5 mutually exclusive categories based on change in serum creatinine level during hospitalization as follows: a decrease or no change in serum creatinine level during admission, or an increase in serum creatinine level of 0.1, 0.2, 0.3 to 0.5, or 0.6 to 3.0 mg/dL. The cutoff points for increase in creatinine level were selected to approximate the quartiles of creatinine change among patients who experienced an increase in serum creatinine level.

We defined anemia as a hematocrit of less than 39% in men and less than 36% in women. We created 4 mutually exclusive levels of hospital technology mix as described previously.

STATISTICAL ANALYSES
We compared patient baseline characteristics across the levels of serum creatinine change with the χ² trend statistic for dichotomous variables and analysis of variance for continuous variables. We used Spearman rank correlation coefficients to test for a trend of higher death and ESRD incidence rates among patients with greater levels of serum creatinine change. To assess the association of change in creatinine with ESRD or mortality, we performed time-to-event analysis with Cox proportional hazards models using serum creatinine change as the primary independent variable and ESRD or mortality as the dependent variable. With ESRD as the end point, patients not developing ESRD were censored at the time of death or the end of follow-up. With mortality as the end point, patients were censored at the time of ESRD or the end of follow-up. In both multivariate regression models, initial adjustment was made for identical risk factors to include common risk factors for competing risks, including baseline patient characteristics, in-hospital and discharge medical treatment, and hospital characteristics; only covariates that retained statistical significance at the P < .05 level were kept in the final models. For regression models, we used a robust sandwich estimate to account for clustering within hospitals. We tested for violations of the proportional hazards assumption and accounted for violations by means of time-dependent covariates and tested for interactions between change in serum creatinine level and demographic characteristics, comorbidities, kidney function, and receipt of percutaneous coronary interventions or coronary artery bypass graft (CABG). In the regression model for the outcome of ESRD, there were no violations of the proportionality of hazards assumption, and, in the regression model for the outcome of mortality, there was a violation of the proportionality assumption for age, which we accounted for by using a time-dependent covariate. To assess the influence of missing data on our results, we imputed values for missing data elements, and the results demonstrated no change in statistical significance or substantive change in point estimates of risk for either end point.

RESULTS
Among the 87,094 patients in the analytic sample discharged from 4,473 hospitals, the mean (SD) change in serum creatinine level was 0.16 (0.35) mg/dL, and 49,502 patients (56.8%) experienced a decrease or no change in serum creatinine level during hospitalization. For the
37,592 patients (43.2%) who experienced an increase in serum creatinine level during hospitalization, the distribution of creatinine increase is shown in Figure 1. Mean (SD) age of the sample was 77.1 (7.5) years. The mean (SD) age among patients who experienced a decrease or no change in serum creatinine level was 76.8 (7.5) years (Table 1) and rose to 78.4 (7.4) years among patients with the greatest change in creatinine level. The proportion of African Americans and patients with diabetes mellitus, hypertension, previous myocardial infarction, history of congestive heart failure, and history of stroke was greatest among patients with larger changes in creatinine level. Patients with the greatest change in serum creatinine level also had worse kidney function at baseline, as reflected by a higher admission serum creatinine level and lower estimated glomerular filtration rate; greater changes in serum creatinine level were also associated with a lower admission hematocrit. Serum creatinine change was associated with more frequent CABG procedures during hospitalization and transfers to the intensive care unit, as well as less frequent percutaneous coronary interventions and thrombolytic therapy. Patients with increases in serum creatinine level were less likely to receive a β-blocker or aspirin at discharge, but more likely to receive an angiotensin-converting enzyme inhibitor and to be treated at hospitals with a higher technology index.

Median follow-up was 4.1 years (interquartile range, 0.6-5.2 years), amounting to 199,263.1 person-years. After 10 years of follow-up, 1.8% and 73.3% of patients developed ESRD and died, respectively, and the incidence rates of ESRD and death were 3.8 and 154.7 cases per 1000 person-years, respectively (Table 2). The incidences of ESRD and mortality were greatest among patients with larger changes in creatinine level; for example, patients with a creatinine increase of 0.6 to 3.0 mg/dL experienced an ESRD and mortality incidence of 20.0 and 274.9 cases per 1000 person-years, respectively.

After adjustment for demographic characteristics, comorbid medical conditions (history of stroke, hypertension, diabetes mellitus, previous myocardial infarction or CABG, and previous or current smoking), and admission characteristics (presence of reduced kidney function and presence of anemia), all levels of serum creatinine increase were independently and significantly associated with a greater ESRD risk, with the greatest risk being among patients with more extreme creatinine changes (Figure 2A and Figure 3A). The adjusted risk of ESRD associated with a creatinine increase of 0.6 to 3.0 mg/dL (vs a decrease or no change) was 3.26 (95% confidence interval [CI], 2.73-3.71). Although there were statistically significant interactions between creatinine change and race (P = .04), age (P < .001), history of hypertension (P = .01), and history of diabetes mellitus (P < .001) with respect to the outcome of ESRD, these interactions did not influence the main findings of greater ESRD risk associated with serum creatinine change.
After adjustment for demographic characteristics, comorbid medical conditions (history of stroke, hypertension, diabetes mellitus, previous myocardial infarction or CABG, and previous or current smoking), admission characteristics (presence of reduced kidney function, presence of anemia, and Acute Physiology and Chronic Health Evaluation II score), in-hospital treatment (receipt of thrombolytic therapy, percutaneous coronary interventions, CABG, and intensive care unit admission), and discharge medications (angiotensin-converting enzyme inhibitor, β-blocker, and aspirin prescription), there was a statistically significant association between all levels of serum creatinine increase and mortality after discharge (Figures 2B and 3B). The adjusted risk of death associated with a serum creatinine change of 0.6 to 3.0 mg/dL (vs a decrease or no change) was 1.39 (95% CI, 1.35-1.43). Although there were statistically significant interactions between creatinine change and age (P < .001), history of hypertension (P = .01), history of diabetes mellitus (P = .04), and presence of reduced kidney function (P = .04) with respect to the outcome of mortality, these interactions did not influence the main findings of the association of creatinine change with mortality.

In univariate and adjusted analyses, receipt of β-blockers and aspirin at the time of discharge was associated with a decreased adjusted risk of mortality (adjusted hazard ratios, 0.74 [95% CI, 0.72-0.75] and 0.83 [95% CI, 0.81-0.84], respectively). There was no statistically significant interaction between medication receipt and change in serum creatinine level with respect to mortality, suggesting that the association between these medications and mortality was comparable regardless of creatinine change during hospitalization.
In a nationally representative sample of Medicare beneficiaries discharged from the hospital after AMI, we have demonstrated an association between small increases in serum creatinine level during hospitalization and subsequent long-term risk of both ESRD and mortality independent of known risk factors. Not only were these risks manifested over 10 years of follow-up, but they were evident for even small increases in serum creatinine level and were present in a dose-response manner.

Although this is, to our knowledge, the first systematic description of creatinine increase and longer-term ESRD and mortality risk in a national study, there has been growing interest in the association between reductions in kidney function during hospitalization and risk of relatively short-term mortality.6,7,27-32 Growing evidence suggests that small changes in creatinine level are associated with higher postdischarge mortality.27,33 Loef et al,33 among patients undergoing cardiac surgery at a single center, demonstrated that patients experiencing a 25% increase in serum creatinine level were 1.63 times more likely to die over an 8-year period. Brown et al,27 in a study involving 8 medical centers, demonstrated a greater risk of death 90 days after discharge, including in-hospital mortality, associated with a 50% creatinine increase during hospitalization for CABG surgery. Our results within a national sample of patients from more than 4000 hospitals support these findings and further demonstrate that incremental changes in serum creatinine level are associated with a greater risk of death over a 10-year period.

Our results also demonstrate that small degrees of creatinine change among elderly patients not requiring dialysis during hospitalization are associated with a higher ESRD risk after discharge. Few data exist, but previous studies suggest that between 1.6% and 16.2% of patients surviving hospital-associated AKI severe enough to require dialysis may develop ESRD.34-36 A recent single-center study in Scotland demonstrated that, even among patients not requiring renal replacement therapy, decreases in kidney function as classified by the RIFLE criteria (risk, hypertension, diabetes mellitus, previous myocardial infarction or coronary artery bypass graft, and previous or current smoking), and admission laboratory values (estimated glomerular filtration rate and presence of anemia), B, HR is adjusted for demographic characteristics (age, sex, race), comorbid conditions (history of stroke, hypertension, diabetes mellitus, previous myocardial infarction or coronary artery bypass graft, and previous or current smoking), admission laboratory values (estimated glomerular filtration rate and presence of anemia), in-hospital treatment (receipt of thrombolytic therapy, percutaneous coronary intervention, coronary artery bypass graft, and intensive care unit admission), and discharge medications (angiotensin-converting enzyme inhibitor, β-blocker, and aspirin prescription). To convert creatinine to micromoles per liter, multiply by 88.4.

Table 2. Unadjusted Incidence Rates of ESRD and Mortality After Hospital Discharge, Cooperative Cardiovascular Project, 1994-2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESRD Incidence Rate per 1000 Person-Years (95% CI)</th>
<th>All-Cause Mortality Incidence Rate per 1000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3.8 (3.6-4.0)</td>
<td>154.7 (153.5-155.9)</td>
</tr>
<tr>
<td>Maximum change in serum creatinine level during hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease or no change</td>
<td>2.3 (1.8-2.8)</td>
<td>139.1 (132.0-146.6)</td>
</tr>
<tr>
<td>Increase in creatinine, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1: 0.1</td>
<td>2.5 (1.8-3.1)</td>
<td>145.5 (137.2-154.3)</td>
</tr>
<tr>
<td>Quartile 2: 0.2</td>
<td>3.6 (2.7-4.9)</td>
<td>157.0 (147.7-166.9)</td>
</tr>
<tr>
<td>Quartile 3: 0.3-0.5</td>
<td>6.3 (4.9-8.1)</td>
<td>193.6 (182.6-205.2)</td>
</tr>
<tr>
<td>Quartile 4: 0.6-3.0</td>
<td>20.0 (18.2-21.9)</td>
<td>274.9 (268.0-281.9)</td>
</tr>
<tr>
<td>Test for trend, P valuea</td>
<td>.004</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

a Spearman rank correlation coefficient.
In our sample, the prescription of patients for close monitoring and aggressive treatment. 

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mortality associated with kidney disease.50,51

in turn, the risk of cardiovascular morbidity and mor-
of kidney disease progression among these patients and,
in kidney function during hospitalization increase the risk 
tients. In addition, as our study demonstrates, these in-
or subclinical pathologic processes within these pa-
atinine level may also reflect unmeasured comorbidities
fined. An inflammatory response and important changes
changes were undertreated.

The reasons for the association between small changes in serum creatinine level and adverse outcomes are ill defined. An inflammatory response and important changes in many physiologic functions and organ systems accompany an acute reduction in kidney function.45-49 Subsequent risk of adverse events, therefore, may be associated with these primary effects of decreases in kidney function. On the other hand, these small increases in creatinine level may also reflect unmeasured comorbidities or subclinical pathologic processes within these patients. In addition, as our study demonstrates, these individuals are at risk of ESRD, and it is possible that changes in kidney function during hospitalization increase the risk of kidney disease progression among these patients and, in turn, the risk of cardiovascular morbidity and mortality associated with kidney disease.50,51

The smallest changes in serum creatinine level described herein are within the range that may be due to chance variation at the individual level or the “critical difference” (CD) of a serum creatinine measurement.29,31

In our study, increases in serum creatinine level were associated with higher risks of both ESRD and death after AMI, but it is important to note that the absolute risk of mortality was far greater than that of ESRD (154.7 vs 3.8 cases per 1000 person-years, respectively), consistent with other studies.41-43 Clinicians caring for elderly patients after AMI should be aware of changes in creatinine level during hospitalization and target these patients for close monitoring and aggressive treatment. In our sample, the prescription of β-blockers and aspirin, consistent with guidelines contemporaneous with the baseline cohort,44 exhibited a protective association with future mortality regardless of creatinine change during hospitalization, but patients with greater creatinine changes were undertreated.

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In our study, the CD for mean admission serum creatinine level likely subserves the range of increase in serum creatinine level for the 2 smallest categories of creatinine change (0.1 and 0.2 mg/dL) and includes a portion of the range for the third-smallest category (0.3-0.5 mg/dL). On the basis of the 1994 College of American Pathology Survey’s summary serum creatinine level coefficients of variation for US hospitals, and a 4% intrindividual coefficient for variation of creatinine level,59 the CD for mean admission serum creatinine level in this sample is estimated at ±0.33 mg/dL for patients in the first 2 groups (0.1 and 0.2 mg/dL) and ±0.36 mg/dL in the third (0.3-0.5 mg/dL). Notably, according to the more recent 2006 College of American Pathology survey,60 these increases in serum creatinine level would still be included within the CD with the use of current methods. Our study therefore describes greater risks of events that, in the aggregate, are associated with changes in serum creatinine level below the detectable threshold of meaningful variation at the individual level by means of current assays, demonstrating the need for more sensitive markers of kidney function and biomarkers of AKI in clinical practice.1

There are notable limitations to our study. First, our study sample was a population of elderly patients with AMI at high risk of adverse events after hospitalization, and our results may not be applicable to younger populations or patients without cardiovascular disease. Further research is necessary to determine whether these results apply to populations with less comorbidity. Second, this was a retrospective observational analysis from which causal inference cannot be derived and which is subject to bias from unmeasured factors. The size and national scope of the data provide a high statistical power, and the ability to provide extensive adjustment given the large

Figure 3. Adjusted Kaplan-Meier curves for end-stage renal disease (ESRD) (A) and all-cause mortality (B) according to maximum level of serum creatinine level increase during hospitalization, Cooperative Cardiovascular Project, 1994 to 2004. A, Adjusted for demographic characteristics (age, sex, and race), comorbid conditions (history of stroke, hypertension, diabetes mellitus, previous myocardial infarction or coronary artery bypass graft, and previous or current smoking), and admission laboratory values (estimated glomerular filtration rate and presence of anemia). B, Adjusted for demographic characteristics (age, sex, and race), comorbid conditions (history of stroke, hypertension, diabetes mellitus, previous myocardial infarction or coronary artery bypass graft, and previous or current smoking), admission laboratory values (estimated glomerular filtration rate and presence of anemia), in-hospital treatment (receipt of thrombolytic therapy, percutaneous coronary intervention, coronary artery bypass graft, and intensive care unit admission), and discharge medications (angiotensin-converting enzyme inhibitor, β-blocker, and aspirin prescription). To convert creatinine to micromoles per liter, multiply by 88.4.

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In a nationally representative sample of Medicare beneficiaries discharged from the hospital after admission for AMI, we have demonstrated an independent association between small changes in serum creatinine level during hospitalization and subsequent risk of mortality and ESRD. These risks were evident in a dose-response manner and were present during 10 years of follow-up. Further research should focus on etiologic mechanisms connecting AKI and risk of adverse events, increasing the sensitivity of current methods of detecting AKI, and improving the care of patients discharged after AMI to reduce long-term mortality and risk of ESRD.

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