

# Long-term Prognosis of Acute Kidney Injury After Acute Myocardial Infarction

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**Background:** Acute kidney injury (AKI) is a common complication during hospitalization and is an accepted risk factor for in-hospital mortality. However, the association of severity of AKI with the long-term risk of death is not well defined.

**Methods:** To examine the independent effect of the severity of AKI on long-term risk of death following acute myocardial infarction (AMI), we performed an observational study of 147 007 elderly Medicare patients admitted for AMI from January 1994 through February 1996 as a part of the Cooperative Cardiovascular Project. We evaluated the association between AKI and all-cause mortality. We defined AKI as absolute changes in serum creatinine level, categorized as none (creatinine level increase,  $\leq 0.2$  mg/dL), mild (0.3-0.4 mg/dL increase), moderate (0.5-0.9 mg/dL increase), and severe ( $\geq 1.0$  mg/dL increase).

**Results:** Overall, 19.4% of the patients had AKI, including 7.1% with mild AKI, 7.1% with moderate AKI, and

5.2% with severe AKI. Less than 10% of patients who had severe AKI were alive at 10 years compared with 12.2%, 21.1%, and 31.7% patients with moderate, mild, and no AKI, respectively. The adjusted hazard ratio for death for in-hospital survivors at 10 years was 1.15 (95% confidence interval [CI], 1.12-1.18) for mild AKI, 1.23 (95% CI, 1.20-1.26) for moderate AKI, and 1.33 (95% CI, 1.28-1.38) for severe AKI. Similar results were obtained in several secondary analyses that included inpatient mortality, excluded mortality in the first 3 years, and stratified by some specified high-risk groups. Moderate or severe AKI were comparable in strength with other known correlates of cardiovascular mortality.

**Conclusions:** Acute kidney injury has an independent and graded association with long-term mortality. These results should stimulate additional mechanistic and interventional studies and plans for follow-up of patients with AKI after discharge.

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**A**CUTE KIDNEY INJURY (AKI; previously known as acute renal failure) is a common complication in hospitalized patients, and its incidence has risen substantially over the past 15 years.<sup>1-3</sup> As a conservative estimate, roughly 17 million admissions annually in the United States are complicated by AKI, resulting in over \$10 billion in costs to the health care system.<sup>4</sup> In high-risk patients, such as those hospitalized with acute myocardial infarction (AMI), congestive heart failure (CHF), sepsis, and those undergoing cardiac surgery, the incidence of AKI is high, ranging from 10% to 25%.<sup>5-10</sup> Several studies have demonstrated that AKI is associated with a marked increase in in-hospital mortality.<sup>6-12</sup> Furthermore, recent studies suggest that even small changes in serum creatinine level (as small as a 0.25 mg/dL change) are associated with increased

short-term mortality.<sup>4,8-10,13,14</sup> (To convert creatinine to micromoles per liter, multiply by 88.4.)

Although AKI is a common complication in the hospital and has an impact on morbidity, mortality, and resource utilization, several important questions remain unanswered. For example, the relationship between AKI and long-term outcomes remains unclear. Understanding the impact of AKI on long-term outcomes will have a marked impact on treatment and risk stratification during hospitalization and will assist with guiding follow-up care after discharge. More importantly, it is also unknown if AKI determined by smaller changes in creatinine level, which in most cases represent short-lived and clinically reversible episodes of AKI, is associated with an elevated risk for long-term mortality. It may be possible that after a "reversible" episode of AKI, the increased risk of death dis-

sipates after a certain length of time. Alternatively, AKI may serve as a pathogenic factor in the development of other renal sequelae, such as proteinuria, hypertension, and chronic kidney disease (CKD), which will compound cardiovascular risk over time. Furthermore, it is unclear if the severity of AKI has a graded association with the long-term risk of mortality and what the relative importance of AKI is in the presence of other known long-term prognostic markers of AMI.

Thus, we sought to assess the association between the presence and severity of AKI and the hazards for death over 10 years in a large cohort of patients who were hospitalized with AMI. Furthermore, we sought to determine the value of AKI as an independent predictor of long-term death compared with other demographic and clinical variables in a national sample of Medicare beneficiaries for whom long-term follow-up data are available.

## METHODS

### PATIENTS

The Cooperative Cardiovascular Project (CCP), a Centers for Medicare and Medicaid Services project developed to improve the quality of care provided to Medicare beneficiaries hospitalized with AMI,<sup>15</sup> included a sample (N=234 769) of fee-for-service patients hospitalized with a principal discharge diagnosis code of AMI (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 410*) at 4834 hospitals from January 1994 through February 1996.

We excluded patients younger than 65 years (n=17 593) and those in whom a clinical diagnosis of AMI was not confirmed (n=31 186). Patients who transferred into a hospital (n=42 278) were excluded because we could not ascertain their clinical characteristics at initial admission. We also excluded patients with a terminal illness (documentation of anticipated life expectancy of <6 months) or metastatic cancer (n=3932) because of competing mortality risk and because the focus of their treatment may not have been targeted toward improved survival. Patients whose records could not be linked to data obtained from the American Hospital Association (n=2363) or from the American Medical Association (n=6796) were also excluded. We also excluded patients who were undergoing chronic peritoneal or hemodialysis (ascertained by ICD-9 procedure codes 5498 and 3995, respectively; n=3058) because it is impossible to diagnose AKI in this population. Patients with missing or invalid values of baseline creatinine or peak serum creatinine level (n=15 708) were also excluded. The total number of patients meeting at least 1 of these exclusion criteria was 93 784, leaving 147 007 patients eligible for analysis.

### STUDY VARIABLES

Trained nurses and medical records technicians abstracted medical records using an automated system designed to provide for standardization of abstraction of data. Strategies to decrease abstraction errors and variability included standardized training sessions, online data definitions, and range checks.

### DEPENDENT VARIABLE

We ascertained death within 10 years after admission by supplementing information on vital status in the CCP with data from the death master file of the Social Security Administration.<sup>16</sup>

Time to death was defined as days from the day of admission to the day of death and censored at 10 years' follow-up.

## INDEPENDENT VARIABLES

### Definition of AKI

The principle exposure variable was AKI defined as an absolute difference of at least 0.3 mg/dL in the peak and admission serum creatinine values during the hospitalization. The cutoff for AKI was chosen to be 0.3 mg/dL because there are several studies demonstrating that this degree of change has an impact on outcomes<sup>4,9,14</sup> and because this is the new definition for AKI proposed by the Acute Kidney Injury Network.<sup>17</sup> We classified AKI into 3 categories—mild, moderate, and severe—based on differences in serum creatinine values of 0.3 to 0.4 mg/dL, 0.5 to 1.0 mg/dL, and greater than 1.0 mg/dL, respectively.

### Other Independent Variables

Because the severity of AKI and the presence of coexisting illnesses influence the survival after AMI, we adjusted for the following predictive variables<sup>18-21</sup> and clinically relevant factors: demographics (age, sex, race, admission status), clinical presentation (Killip class at the time of admission, left ventricular ejection fraction [LVEF], systolic blood pressure, heart rate, respiratory rate, anatomical site of the AMI, Q-wave myocardial infarction, ST-segment elevation myocardial infarction), medical history (AMI, CHF, current smoking status, hypertension, diabetes mellitus, stroke, peripheral vascular disease), comorbidities (mobility, urinary incontinence, dementia, chronic obstructive pulmonary disease, liver disease, infection with human immunodeficiency virus or other immunologic compromise, a serum albumin level <3 g/dL, white blood cell count >13 000/ $\mu$ L, and a hematocrit of <30%), and in-hospital events and procedures such as coronary angiography and percutaneous coronary intervention. (To convert serum albumin to grams per liter, multiply by 10. To convert white blood cell count to  $\times 10^9$ /L, multiply by 0.001. To convert hematocrit to a proportion of 1.0, multiply by 0.01.) We also considered several nonclinical factors: characteristics of the hospitals, according to the American Hospital Association 1994 survey<sup>22</sup> of hospitals (teaching status, ownership, and availability of on-site facilities for cardiac procedures); characteristics of the physicians, according to the American Medical Association Physician master file (specialty, sex, decade of graduation, country of medical school, employment type, and type of training [osteopathic or allopathic]); and hospital AMI volume derived from the CCP data. We derived the severity of CKD based on estimated glomerular filtration rate (eGFR), which was classified into stages of CKD as suggested by the National Kidney Foundation classification.<sup>23</sup> Baseline eGFR was estimated from the modification of diet in renal disease equation using the serum creatinine level on admission.<sup>24</sup>

### STATISTICAL ANALYSIS

Patterns and differences in patient, hospital, and physician characteristics and mortality in whole and stratified by the severity of AKI were assessed by  $\chi^2$  tests for categorical variables and analysis of variance for continuous variables. We used Cox proportional hazards regression models to assess the relative risks of the severity of AKI on death. The tests for proportionality of hazards [along with the plotted log cumulative hazards by  $\ln(t)$ ] were not significant on formal testing (see **Table 1** for P values), thereby suggesting that the hazards were proportional for

**Table 1. Baseline and Clinical Characteristics Based on Severity of AKI**

Description	No AKI (n = 118 462)	Mild AKI (n = 10 406)	Moderate AKI (n = 10 482)	Severe AKI (n = 7657)	P Value
<b>Demographics</b>					
Age, mean (SD), y	76.3 (7.4)	77.5 (7.4)	78.3 (7.4)	78.2 (7.4)	<.001
Female, %	49.3	50.1	51.4	48.5	<.001
Nonwhite race, %	8.8	10.9	11.4	11.8	<.001
Admission status, %					<.001
Home	83.4	82.1	82.8	83.0	
SNF/ECF/LCF	5.4	6.3	7.0	7.0	
Outpatients	9.0	9.0	7.5	7.4	
Others	2.2	2.6	2.7	2.6	
<b>Clinical presentation</b>					
Killip class, %					<.001
1	54.5	38.3	30.5	27.4	
2	12.2	11.4	11.1	10.1	
3	31.4	47.7	54.5	55.0	
4	1.9	2.6	3.9	6.5	
LVEF, %					<.001
≥55	10.8	9.3	7.0	5.9	
40-54	28.8	29.4	25.2	23.3	
20-39	18.6	29.0	30.5	32.6	
<20	2.4	4.7	6.2	7.4	
SBP, mean (SD), mm Hg	145 (33)	147 (33)	144 (35)	140 (36)	<.001
Heart rate, mean (SD)	87 (25)	9 (25)	93 (26)	93 (26)	<.001
Respiratory rate, mean (SD)	22 (6)	23 (7)	24 (8)	24 (8)	<.001
Anterior infarction, %	44.9	50.8	52.5	54.9	<.001
Q-wave infarction, %	59.7	57.6	59.0	60.4	<.001
ST segment elevation infarction, %	29.3	28.4	28.4	28.3	.03
<b>Medical history, %</b>					
Hypertension	60.4	66.3	68.7	68.6	<.001
Diabetes mellitus	29.4	34.0	37.7	40.7	<.001
Prior myocardial infarction	30.6	33.2	34.8	36.1	<.001
Prior heart failure	19.9	27.9	33.5	35.4	<.001
Current smoker	14.8	13.8	13.4	13.6	<.001
Cerebrovascular disease	13.3	16.2	17.4	18.9	<.001
Peripheral vascular disease	9.4	12.8	14.5	15.9	<.001
<b>Comorbid conditions</b>					
Dementia	5.9	6.4	7.2	7.6	<.001
Albumin level <3 g/dL	3.9	5.0	6.6	7.8	<.001
Hematocrit <30%	3.6	5.0	6.5	8.1	<.001
WBC >13 000/μL	20.7	26.2	32.2	36.3	<.001
Liver disease	0.3	0.5	0.5	0.7	.001
Chronic obstructive pulmonary disease	19.7	22.5	23.2	24.3	<.001
HIV or other immunocompromised status	1.2	1.2	1.2	1.3	.57
Urinary incontinence	6.6	8.1	9.4	9.3	<.001
Chronic kidney disease, GFR, mL/min/m <sup>2</sup>					<.001
<30	7.4	7.1	16.0	27.0	
≥30 to <60	45.0	49.1	53.1	53.6	
≥60	47.6	43.8	30.8	19.4	

(continued)

the duration of follow-up. We examined sequentially whether differences in the survival of AKI categories persisted after adjustment for differences in the characteristics of the patients, the physicians, and the hospitals through a series of multivariate regression models. In the final adjustment model of survival analysis, we selected important factors with the biggest point estimates, which reflected the worse effect of factors on mortality at the 10-year follow-up. This examined the strength of association of AKI severities in relation to other variables.

We verified the results among different subgroups determined by age, sex, race, lower LVEF, Killip class, diabetes mellitus, CKD, anemia, hospital teaching status, and hospital loca-

tion as urban vs rural. For the model analyses in subgroups, the corresponding variable or variables related to the subgroups were removed from the list of adjusting variables. We also confirmed the accuracy and reliability of results by using alternate definitions of AKI as the exposure variable. First, we analyzed the association between outcomes and AKI defined as a percentage change in peak serum creatinine level from baseline creatinine level (no AKI, <10% change; mild AKI, 10%-24% change; moderate AKI, 25%-49% change; severe AKI, ≥50% change). In addition, we analyzed the association between outcomes and AKI as defined by the RIFLE classification system<sup>25</sup> for increase in serum creatinine level (R, 50% increase; I, 100% increase; and F, 200%). Because there were substantial deaths dur-

**Table 1. Baseline and Clinical Characteristics Based on Severity of AKI (cont)**

Description	No AKI (n = 118 462)	Mild AKI (n = 10 406)	Moderate AKI (n = 10 482)	Severe AKI (n = 7657)	P Value
Physician characteristics					
Age, mean (SD), y	47 (9.0)	47 (9.0)	47 (9.1)	47 (8.7)	.14
Years in practice, mean (SD)	21 (9.2)	21 (9.2)	21 (9.3)	21 (9.0)	.27
Physician specialty, %					<.001
Cardiology	26.3	26.4	25.5	27.1	
Medicine subspecialty	8.9	9.6	10.0	10.0	
Internal medicine	21.8	22.1	22.1	21.9	
Family practice	14.8	11.9	12.5	11.6	
Physician practice type, %					<.001
Solo practice	28.4	26.8	27.4	26.1	
Joint practice	8.3	7.7	7.9	7.9	
Group practice	35.8	36.0	35.4	36.6	
Medical school affiliated	1.5	2.4	2.1	2.1	
Hospital characteristics, %					
Level of cardiac care facilities					<.001
CABG available	33.8	44.2	43.2	46.9	
Catheterization available	23.6	22.8	22.3	21.2	
No invasive facilities	42.6	33.0	34.5	32.0	
Ownership					<.001
Public	13.3	11.4	11.7	11.3	
Not-for-profit	76.2	77.9	78.0	77.9	
For-profit	10.6	10.7	10.3	10.8	
Teaching status					<.001
COTH hospital	9.8	15.7	15.3	14.6	
Residency/fellowship program affiliated	20.8	25.0	24.5	25.8	
Nonteaching hospital	69.3	59.3	60.1	59.6	
Urban location	76.0	84.0	83.6	84.9	<.001
Hospital events including on arrival					
Cerebrovascular accident	2.3	3.7	5.1	6.0	<.001
Shock	5.6	8.5	14.8	27.9	<.001
Limitation of resuscitation	14.3	20.1	30.8	47.5	<.001
Congestive heart failure	42.7	66.1	76.8	82.7	<.001
Hospital procedures					
PTCA	9.9	10.8	8.9	11.4	<.001
CABG	4.2	10.2	9.5	10.1	<.001
Cardiac catheterization	28.7	34.1	28.0	28.7	<.001

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass graft surgery; COTH, Council of Teaching Hospitals; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; SNF/ECF/LCF, skilled nursing facility, extended care facility, long-term care facility; WBC, white blood cell count.

SI conversion factors: To convert serum albumin to grams per liter, multiply by 10; white blood cell count to  $\times 10^9/L$ , multiply by 0.001; hematocrit to a proportion of 1.0, multiply by 0.01.

ing hospitalization and the survival curves separated early, we performed all Cox proportional hazards regression models after excluding patients who died in-hospital from the cohort. We also performed sensitivity analyses to confirm the long-term prognostic value of AKI if all deaths within 3 years of AMI were excluded. All the analyses were performed using SAS statistical software (version 9.1; SAS Inc, Cary, North Carolina), and dummy variables, which indicated missing values of different variables, were included in the model analyses.

## RESULTS

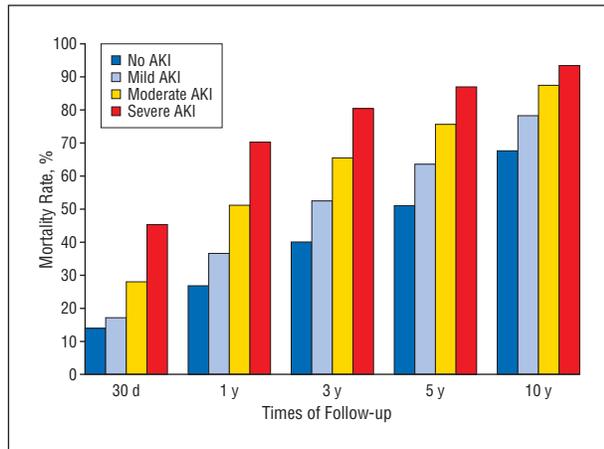
### BASELINE CHARACTERISTICS

Our study cohort consisted of 147 007 patients, of whom 10 406 (7.1%) had mild AKI, 10 482 (7.1%) had moderate AKI, and 7657 (5.2%) had severe AKI during their hospitalization for AMI (Table 1). Patients with increasing severity of AKI were more likely to have LVEF, higher

Killip class, anterior wall AMI and Q-wave AMI, lower albumin level, hematocrit less than 30%, and higher white blood cell count on presentation compared with patients with no AKI (Table 1). When classified according to National Kidney Foundation stages, patients with severe AKI had a higher likelihood of stage 3 and stage 4-5 CKD. Severe AKI was also associated with complications such as CHF, shock, and cerebrovascular accident during hospitalization.

### CRUDE MORTALITY AND ADJUSTED SURVIVAL RATES

**Figure 1** demonstrates the association between the severity of AKI and the mortality rates at 30 days and 1, 3, 5, and 10 years of follow-up after AMI. At all the time points of follow-up, the crude mortality rates were higher among higher class of AKI severity ( $P < .001$ ). The dif-



**Figure 1.** Crude mortality risks by severity of acute kidney injury (AKI). The bar graph representing crude mortality risks at various times of follow-up (30 days and 1, 3, 5, and 10 years) by severity of AKI (none, mild, moderate, and severe). At 10 years' follow-up, the crude mortality rates were 68.3% for patients without AKI, 78.9% for mild AKI, 87.8% for moderate AKI, and 93.5% for severe AKI.

ferences in unadjusted survival rates were apparent within 30 days of admission and persisted with up to 10 years of follow-up ( $P < .001$ ) (**Figure 2A**).

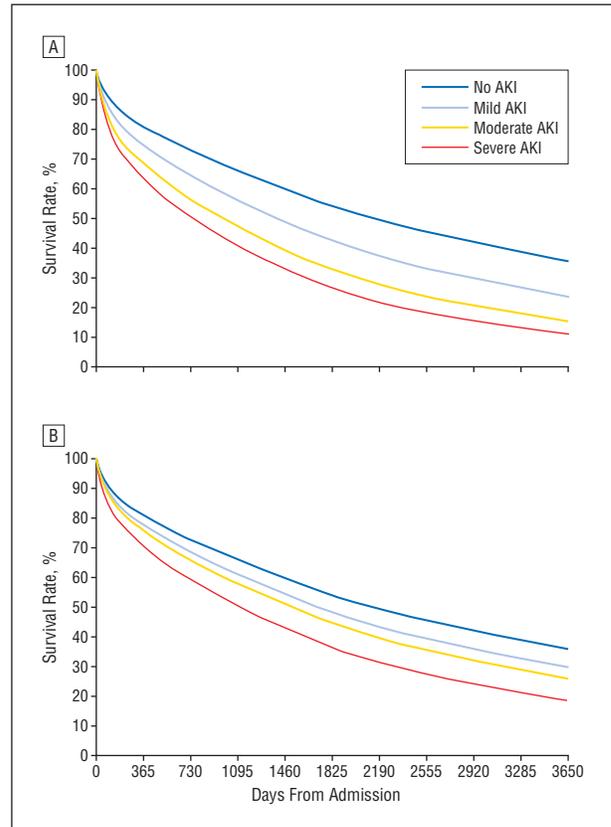
Compared with patients without AKI, patients with increasing severity of AKI had higher adjusted hazard ratios (HRs) of mortality at 10-year follow-up (**Table 2**), even after exclusion of all patients who died in-hospital. After these exclusions and all adjustments for covariates, compared with those with no AKI, the risk of posthospitalization mortality was increased by 15% (95% confidence interval [CI], 12%-18%) with mild AKI, by 23% (95% CI, 20%-26%) with moderate AKI, and by 33% (95% CI, 28%-38%) with severe AKI.

**Figure 3** demonstrates the variables that were associated with mortality during the 10-year follow-up (patients who died during their hospital stay were excluded). Based on the strength of association by point estimates, moderate and severe AKI were among the top variables predictive of poor outcomes. Excluding patients who were identified as "do not resuscitate" and had cardiogenic shock during hospitalization, AKI categories had comparable or stronger association with long-term mortality, as seen with other known variables, such as LVEF, diabetes mellitus, CKD, and anemia.

## SECONDARY ANALYSES

### Alternate Definitions of AKI

The graded relationships described between AKI, as defined by percentage changes in serum creatinine level, and long-term death were validated via unadjusted (Figure 2B) and adjusted analyses (Table 2). The results were similar when the RIFLE classification<sup>25</sup> system was used to define AKI in our secondary analyses (data not shown). The HRs for our primary analysis were numerically identical when we adjusted for baseline renal function via serum creatinine as a continuous variable rather than the categorical variable of CKD stage.



**Figure 2.** Unadjusted survival curves for patients following acute myocardial infarction with different severities of acute kidney injury (AKI) (in-hospital deaths were excluded). A, The survival of patients when AKI was defined as absolute changes in serum creatinine level (no AKI,  $< 0.3$  mg/dL change; mild AKI, 0.3 to 0.4-mg/dL change; moderate AKI, 0.5 to 1.0-mg/dL change; severe AKI,  $> 1.0$ -mg/dL change). B, The survival of patients when AKI was defined by percentage changes in baseline serum creatinine level (no AKI,  $< 10\%$  change; mild AKI, 10%-24% change; moderate AKI, 25%-49% change; severe AKI,  $\geq 50\%$  change). (To convert creatinine to micromoles per liter, multiply by 88.4.)

### Exclusion of Deaths Within 3 Years of Admission

When we excluded those patients who died within 3 years of admission from the cohort, the gradient of risk across the severities of AKI was attenuated, although the association between all severities of AKI and long-term death still remained significant (see Table 2 for CIs).

### Stratified Models

The mortality risks associated with worsening class of AKI were consistently elevated in strata of several high-risk subgroups such as age, diabetes mellitus, CKD, levels of LVEF, Killip class, in-hospital coronary artery bypass graft procedure or percutaneous coronary intervention, and anemia. However, there was some evidence of effect modification. Specifically, there was evidence of interaction by CKD on the association between AKI and long-term death, such that the fully adjusted HRs were greatest in those without prior CKD (HRs: 1.15, 1.24, and 1.32 for mild, moderate, and severe AKI, respectively) and were lower in those with stage 3 CKD (1.16, 1.24, and 1.40,

**Table 2. Multivariate Cox Proportional-Hazards Models of Mortality Examining HRs Associated With Severity of AKI Compared With Patients Without AKI**

Type of Analysis	HR (95% CI)		
	Mild AKI	Moderate AKI	Severe AKI
AKI by absolute change in creatinine level			
Unadjusted (excluding in-hospital deaths)	1.40 (1.36-1.43)	1.81 (1.77-1.86)	2.16 (2.09-2.24)
Multivariate-adjusted (excluding in-hospital deaths) <sup>a</sup>	1.15 (1.12-1.18)	1.23 (1.20-1.26)	1.33 (1.28-1.38)
Multivariate-adjusted (excluding all deaths within 3 y of AKI) <sup>a</sup>	1.10 (1.06-1.14)	1.19 (1.14-1.25)	1.22 (1.14-1.30)
AKI by percentage change in creatinine level			
Unadjusted (excluding in-hospital deaths)	1.19 (1.16-1.21)	1.31 (1.28-1.34)	1.64 (1.60-1.68)
Multivariate-adjusted (excluding in-hospital deaths) <sup>a</sup>	1.10 (1.08-1.12)	1.16 (1.14-1.19)	1.32 (1.28-1.35)
Multivariate-adjusted (excluding all deaths within 3 y of AKI) <sup>a</sup>	1.09 (1.06-1.13)	1.13 (1.10-1.17)	1.21 (1.16-1.27)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Adjusted for all of the variables listed in Table 1.

respectively) and lowest in those with stage 4-5 CKD (1.08, 1.11, and 1.15, respectively). Moreover, the relationship between all severities of AKI and the prespecified covariates demonstrated significantly increased HRs in all strata except for those with mild AKI and CKD stage 4-5 (HR, 1.08; 95% CI, 0.98-1.18), mild AKI and LVEF of less than 20% (HR, 1.09; 95% CI, 0.97-1.22), mild AKI and coronary artery bypass graft (HR, 1.07; 95% CI, 0.97-1.19), and mild AKI and moderate AKI and anemia (HR, 1.11; 95% CI, 0.99-1.24 and HR, 1.10; 95% CI, 0.99-1.22, respectively).

#### COMMENT

We demonstrate that AKI is a common complication in AMI that is associated with notable short- and long-term mortality. Even after consideration and elimination of the short-term effect of AKI on in-hospital mortality, there is a strong independent graded relationship between severity of AKI and long-term mortality at all time points of follow-up for up to at least 10 years following AMI. After adjustment for a comprehensive set of covariates, mild AKI was associated with a 15% increased risk of death, moderate AKI with a 23% increased risk, and severe AKI with a 33% increased risk at 10 years. Moreover, the relationship of AKI with mortality is comparable with several other common indicators of risk in AMI. Severe AKI conferred a high relative risk following AMI, similar to the risk associated with classic post-MI predictors such as history of CHF, reduced LVEF, diabetes mellitus, anemia, and CKD. Our results also further strengthen the argument that even minimal changes in serum creatinine level are prognostically important.

The results of our data were consistent across a number of definitions of AKI, including percentage change in creatinine level (which accounts for baseline creatinine level) and the RIFLE definition<sup>25</sup> of AKI. In addition, our results were consistent when deaths within 3 years were eliminated from analyses. Finally, although the risk dissipated somewhat in patients with advanced CKD, virtually all severities of AKI portended a worse prognosis across different severities of CKD.

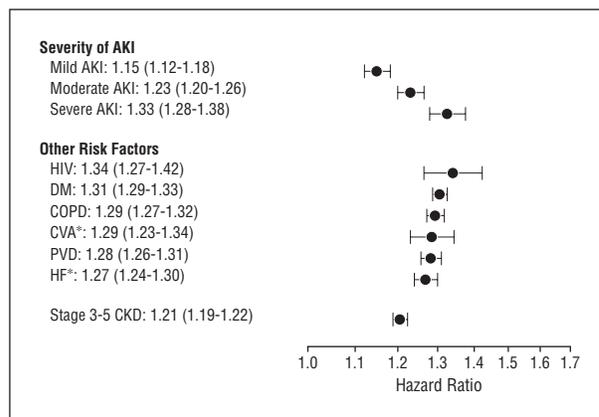
Several studies have demonstrated that baseline renal dysfunction or CKD is associated with poor outcomes during short- and intermediate-term follow-up after AMI<sup>26-30</sup> or acute coronary syndromes.<sup>31-33</sup> Our results demonstrate that dynamic changes in renal function (ie, AKI) during admission for AMI provide more prognostic information than baseline renal function alone.

A few studies have recently attempted to assess the association between AKI and long-term mortality following AMI. Goldberg et al<sup>34</sup> demonstrated that changes in creatinine level of at least 0.5 mg/dL following AMI was associated with a marked increase in 1-year mortality. Jose et al<sup>35</sup> demonstrated that a change in serum creatinine level greater than 0.3 mg/dL within 2 weeks after AMI was associated with an increased risk of cardiovascular morbidity and mortality at 42 months of follow-up.

Our study adds to the findings of these prior studies in several ways. First, we demonstrate elevated risks at a more distant time point (10 years) from the initial event. In fact, less than 10% of patients who had severe AKI were alive at 10 years compared with 12%, 21%, and 32% of patients who were alive and classified as having moderate, mild, and no AKI, respectively. Thus, we demonstrate that the small "bumps" in serum creatinine level do not just signify a short-term risk but are associated with long-term premature death. Second, the worsening mortality with increasing severity of AKI was maintained in several different high-risk subgroups that were examined, such as CKD and coronary artery bypass graft procedure. Third, the previous studies examined the association with a rise in creatinine level above a certain threshold but did not classify patients on the basis of the magnitude of the increase in serum creatinine level. Our data provide further insight by demonstrating the graded risk associated with various severities of AKI. Thus, a change in serum creatinine level of 0.3 to 0.4 mg/dL, one that many would consider minor, provides prognostic information both in the short term and long term. Finally, based on our point estimates, our data also show that AKI is a stronger predictor of long-term death than static measurements of renal function (CKD).

Even patients with mild and moderate AKI, which in most cases is short lived and clinically reversible renal failure, had an elevated risk of death after hospitalization that did not dissipate over time. These findings are novel and do not support the conventional teaching that AKI in its mild form is inconsequential. What are the possible mechanisms for AKI leading to an increased long-term risk of death? After an episode of AKI, it is probable that there is failure to resolve renal structure and function adequately.<sup>36-38</sup> Through a multitude of inflammatory and fibrotic signaling pathways, this residual kidney damage experienced during the acute insult can lead to progressive structural kidney damage, which then predisposes the patient to worsening hypertension, proteinuria, and declining glomerular filtration rate,<sup>39-41</sup> which are all well-known risk factors for cardiac disease.<sup>42-44</sup> Furthermore, kidney damage in patients with established cardiac disease (eg, those who have experienced AMI) may worsen cardiovascular status because of problems excreting sodium and problems with erythropoiesis, which can result in worsening congestive heart failure. However, even though we controlled for several important covariates, because this is an observational study, it is possible that the presence of AKI may merely be a marker for an uncaptured amount of cardiac or vascular dysfunction (residual confounding).

Our study has several other limitations. We had a comprehensive database with a multitude of demographic, physiologic, clinical, and hospital variables that we adjusted for in our multivariate analyses. However, as with all observational studies, it is possible that unmeasured confounders may have influenced our point estimates. Specifically, we are missing data on cardiac status at discharge, postdischarge serum creatinine level, quantification of proteinuria, and need for renal replacement therapy either acutely or chronically. The data may also suffer from ascertainment bias. Sicker patients are more likely to have longer hospitalizations and thus undergo more blood work and assessment of renal function, increasing the probability of detecting a change in serum creatinine level. We had to exclude a fair number of patients from our analysis because they were transferred in from another hospital (we were unable to capture admission variables) or because of missing or invalid baseline or peak serum creatinine values. However, we were still left with more than 140 000 patients for our analysis; thus, to our knowledge this is the largest study of long-term outcomes of AKI ever published. We also did not have information on medications and therefore could not test for interaction between AKI and therapies, such as angiotensin-converting enzyme inhibitors. We did not have information on the etiology of AKI or urine output and therefore could not further stratify our definitions of AKI (eg, prerenal vs intrinsic AKI, oliguric vs nonoliguric AKI). In addition, this analysis was performed using data from patients who were hospitalized from 1994 through 1996. Certainly, the treatment of AMI has improved over the past 10 years, with the use of stents (bare and drug eluting) in percutaneous coronary intervention, the widespread use of dual antiplatelet inhibition, the more prevalent use of antagonists of the renin-angiotensin-aldosterone system following AMI, and im-



**Figure 3.** Adjusted hazard ratios (HRs) (95% confidence intervals) for long-term mortality after acute myocardial infarction for severity of acute kidney injury (AKI) in comparison with other known risk factors. Severe AKI (serum creatinine level increase,  $\geq 1.0$  mg/dL) possesses the strongest adjusted odds ratio for death at 10 years compared with other classic risk factors for death following AMI. The asterisks indicate cerebrovascular (CVA) and heart failure (HF) during index hospitalization. CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; DM, diabetes mellitus; PVD, peripheral vascular disease. (To convert creatinine to micromoles per liter, multiply by 88.4.)

proved strategies to reduce radiocontrast-induced nephropathy. However, the age of the cohort is what has allowed us to provide data on 10-year outcomes. Finally, it is unclear if these findings from our study can be extrapolated to other settings and types of patients with AKI (eg, those who are younger or without AMI).

In conclusion, our findings highlight the clinical and public health importance of AKI. In regard to the scientific field, much work remains to be done. It is unclear what role newer serum and urinary biomarkers for AKI will play in terms of early diagnosis and risk stratification of AKI.<sup>45,46</sup> We also need to understand the predictors of AKI, specifically, the current procedural and pharmacologic interventions for therapy of AMI, that may be helpful to the heart but harm the kidney. Furthermore, research into the mechanistic link between AKI and poor outcomes must be performed, and future trials should address the types of therapies that can be applied to these patients to ameliorate or abolish the risk of death following AKI. Finally, given the increased risk of long-term death following AKI, patients with AKI should be closely monitored in the months to years after discharge for the potential development of CKD and related complications.

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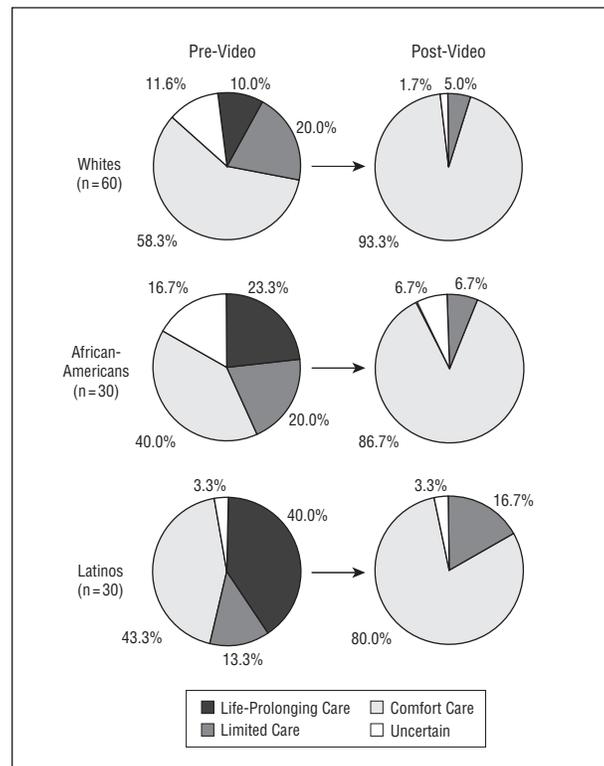
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### Correction

**Errors in Figure.** In the Original Investigation titled “Using Video Images of Dementia in Advance Care Planning” by Volandes et al, published in the April 23, 2007, issue of the *Archives* (2007; 167[8]:828-833), errors occurred in **Figure 3** on page 831. In the pie charts printed in Figure 3, the portions of the post-video pie charts that were shaded to represent life-prolonging care should have been shaded to represent limited care. The corrected figure is reprinted here.



**Figure 3.** Patient preferences, based on race/ethnicity, for level of medical care, before ( $P=.04$ ) and after ( $P=.16$ ) watching video.