Serum Potassium Levels and Mortality in Acute Myocardial Infarction

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Context Clinical practice guidelines recommend maintaining serum potassium levels between 4.0 and 5.0 mEq/L in patients with acute myocardial infarction (AMI). These guidelines are based on small studies that associated low potassium levels with ventricular arrhythmias in the pre–β-blocker and prereperfusion era. Current studies examining the relationship between potassium levels and mortality in AMI patients are lacking.

Objective To determine the relationship between serum potassium levels and in-hospital mortality in AMI patients in the era of β-blocker and reperfusion therapy.

Design, Setting, and Patients Retrospective cohort study using the Cerner Health Facts database, which included 38 689 patients with biomarker-confirmed AMI, admitted to 67 US hospitals between January 1, 2000, and December 31, 2008. All patients had in-hospital serum potassium measurements and were categorized by mean postadmission serum potassium level (<3.0, 3.0-<3.5, 3.5-<4.0, 4.0-<4.5, 4.5-<5.0, 5.0-<5.5, and ≥5.5 mEq/L). Hierarchical logistic regression was used to determine the association between potassium levels and outcomes after adjusting for patient- and hospital-level factors.

Main Outcome Measures All-cause in-hospital mortality and the composite of ventricular fibrillation or cardiac arrest.

Results There was a U-shaped relationship between mean postadmission serum potassium level and in-hospital mortality that persisted after multivariable adjustment. Compared with the reference group of 3.5 to less than 4.0 mEq/L (mortality rate, 4.8%; 95% CI, 4.4%-5.2%), mortality was comparable for mean postadmission potassium of 4.0 to less than 4.5 mEq/L (5.0%; 95% CI, 4.7%-5.3%), multivariable-adjusted odds ratio (OR), 1.19 (95% CI, 1.04-1.36). Mortality was twice as great for potassium of 4.5 to less than 5.0 mEq/L (10.0%; 95% CI, 9.1%-10.9%; multivariable-adjusted OR, 1.99; 95% CI, 1.68-2.36), and even greater for higher potassium strata. Similarly, mortality rates were higher for potassium levels of less than 3.5 mEq/L. In contrast, rates of ventricular fibrillation or cardiac arrest were higher only among patients with potassium levels of less than 3.0 mEq/L and at levels of 5.0 mEq/L or greater.

Conclusion Among inpatients with AMI, the lowest mortality was observed in those with postadmission serum potassium levels between 3.5 and <4.5 mEq/L compared with those who had higher or lower potassium levels.

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POTASSIUM HOMEOSTASIS IS CRITICAL to prevent adverse events in patients with cardiovascular disease. Several studies have demonstrated a relationship between low serum potassium levels, usually less than 3.5 mEq/L, and the risk of ventricular arrhythmias in patients with acute myocardial infarction (AMI).[1-7] On the basis of these studies, experts and professional societies have recommended maintaining potassium levels between 4.0 and 5.0 mEq/L,[8,9] or even 4.5 to 5.5 mEq/L,[10] in AMI patients. However, most prior studies were conducted before the routine use of β-blockers, reperfusion therapy, and early invasive management in eligible patients with AMI. In addition, these studies were small (usually <1000 patients), which precluded a robust assessment of the relationship between potassium levels and mortality. Furthermore, most of these studies focused on the outcome of postinfarction ventricular arrhythmias, which occur much less frequently in the current AMI treatment era. Therefore, there is a lack of current, adequately powered studies that define the optimal range of serum potassium levels with respect to mortality and other important clinical outcomes in patients with AMI.

For editorial comment see p 195.

To address this critical knowledge gap, we analyzed data from Cerner Health Facts, a database of patients hospitalized with AMI in the United States between 2000-2008. Our objectives were (1) to characterize the distribution and trend of serum potassium levels during hospitalization in patients with AMI; (2) to determine the relationship between serum potassium levels and in-hospital mortality; and (3) to evaluate the rela-

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tionship between potassium levels and ventricular arrhythmias or cardiac arrest in patients with AMI.

METHODS

Data Source and Study Cohort

The data source for this investigation was the Cerner Corporation's Health Facts AMI database. This database includes 67 US hospitals with 39 759 consecutive patients with AMI hospitalized between January 1, 2000, and December 31, 2008. Documentation of AMI required a primary discharge diagnosis of AMI, using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes 410.xx, along with positive cardiac biomarkers. For this analysis, we included 38 689 patients with biomarker-confirmed AMI who also had at least 1 in-hospital serum potassium measurement (eFigure 1 available at http://www.jama.com).

Data in the Health Facts database were obtained from patients' electronic medical records and included demographics (age, sex, and race); medical history, comorbidities, and in-hospital procedures documented by *ICD-9-CM* codes; comprehensive laboratory data (including all in-hospital potassium measurements); pharmacy data; in-hospital mortality; and hospital characteristics. All data were deidentified before being provided to the investigators; therefore, an exemption from review was provided by the Saint Luke's Hospital institutional review board.

The 67 hospitals that contributed data to this analysis had a median duration of participation with the Health Facts database of 2.9 years (interquartile range [IQR], 1.2-5.3 years), and a median of 219 patients with AMI (IQR, 48-1030) per center. These hospitals were comparable in their characteristics to those reported in other national registries[11]: they were most commonly urban (88.5%), were less frequently teaching hospitals (35.9%), represented all geographic regions of the United States (Northeast 38.5%, Midwest 25.6%, South 26.9%, and West 9%), and a broad range of sizes (bed size 1-99, 26.9%; 100-199, 20.5%; 200-299, 23.1%; 300-499, 17.9%; and ≥500 beds, 11.5%).

Inpatient Serum Potassium Measurements and Outcomes

The Health Facts database included all AMI patients' serum potassium levels and their time of measurement relative to hospital admission. The admission (baseline) serum potassium level was defined as the first potassium level obtained during hospitalization. The mean postadmission serum potassium level was defined as the average of all potassium levels measured after the admission level but before hospital discharge. Our primary focus was the relationship between mean postadmission potassium levels and outcomes, because postadmission potassium levels are potentially modifiable during AMI hospitalization and are the subject of guidelines concerning AMI management.[8-10] Additional analyses were also conducted to assess the relationship between admission potassium levels (a nonmodifiable factor in AMI patients) and outcomes. All serum potassium values were measured and reported in mEq/L (1 mEq/L = 1 mmol/L).

The primary outcome for this analysis was in-hospital mortality, as documented in the Health Facts database. Secondary outcomes included the composite of ventricular fibrillation or flutter (documented by *ICD-9-CM* codes 427.4, 427.41, or 427.42) or cardiac arrest (*ICD-9-CM* code 427.5) during hospitalization.

Statistical Analysis

Baseline demographics and clinical characteristics were compared among patients categorized by the following mean postadmission serum potassium levels: less than 3.0, 3.0 to less than 3.5, 3.5 to less than 4.0, 4.0 to less than 4.5, 4.5 to less than 5.0, 5.0 to less than 5.5, and 5.5 or greater mEq/L. Hierarchical logistic regression was then used (with hospital site as a random effect to account for clustering across centers) to assess the independent association between mean postadmission serum potassium levels and mortality, after adjustment for potential patient- and hospital-level confounders.

For multivariable models, factors previously demonstrated to be prognostically significant or thought to be clinically important, and covariates identified in bivariate analyses as predictors of in-hospital mortality were considered.[12,13] The following models were generated sequentially to determine the successive influence of potential confounders on the relationship between mean postadmission serum potassium levels (reference group, 3.5-<4.0 mEq/L) and mortality: (1) unadjusted; (2) adjusted only for age and sex; (3) adjusted for age, sex, and admission glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease equation[14]; and (4) adjusted for age, sex, GFR, and the following covariates: race; baseline comorbidities captured by *ICD-9-CM* codes (diabetes, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia, dialysis); admission potassium level; other laboratory values on admission (glucose, white blood cell count, hematocrit); peak cardiac troponin level (an estimate of infarct size); number of potassium checks per patient; cardiogenic shock and acute respiratory failure on admission (determined by *ICD-9-CM* codes); in-hospital procedures captured by *ICD-9-CM* codes (cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery); acute kidney injury as defined by the Acute Kidney Injury Network[15,16] (an increase in serum creatinine by ≥0.3 mg/dL, or a relative increase in serum creatinine of ≥50%, during hospitalization); length of hospital stay; and medications during hospitalization (fibrinolytic therapy, aspirin, clopidogrel, ticlopidine, β-blockers, angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, bronchodilators, statins, insulin treatment, and oral antihyperglycemic agents).

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Nonlinear trends for all continuous covariates were tested through the use of restricted cubic splines, given the complex relationship between potassium levels and several baseline variables. We then conducted 2 sensitivity analyses to determine the robustness of the mortality models and minimize the possibility of residual confounding. First, patients who died within 24 hours of admission were excluded to reduce possible survivor bias. In a second sensitivity analysis, we analyzed whether the association between mean postadmission potassium level and in-hospital mortality differed among patients who were treated or untreated with potassium supplementation during hospitalization.

Additional analyses were also conducted to determine the relationship between admission serum potassium levels and in-hospital mortality using the same potassium comparison groups: less than 3.0, 3.0 to less than 3.5, 3.5 to less than 4.0 (reference group), 4.0 to less than 4.5, 4.5 to less than 5.0, 5.0 to less than 5.5, and 5.5 or greater mEq/L. As before, the following successive models were generated: unadjusted; adjusted for age and sex; adjusted for age, sex, and admission GFR; and adjusted for age, sex, GFR, plus all other covariates listed previously. Separate multivariable logistic regression models were then constructed (using the same covariates) to determine rates of the composite of ventricular arrhythmias or cardiac arrest (instead of mortality) across strata of mean postadmission potassium levels and admission potassium levels, with the same reference group (3.5 to <4.0 mEq/L).

A 2-sided *P* value of .05 was considered to be statistically significant, and 95% CIs were presented for all odds ratios (ORs). Analyses were conducted with SAS software version 9.2.

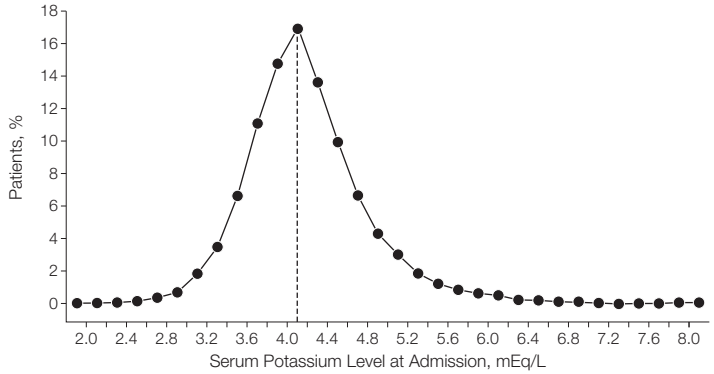
RESULTS

Serum Potassium Levels and Baseline Characteristics

A total of 38 689 patients with biomarker-confirmed AMI had at least 1 serum potassium level measured during hospitalization. Potassium level at admission was measured in 38 689 patients, 37 208 (96.2%) of whom had the admission potassium level measured within the first 24 hours of hospitalization. Additional (postadmission) potassium levels were obtained in 34 026 patients. The mean (SD) number of potassium measurements per patient during hospitalization was 5.9 (SD, 5.9), and the median number of measurements per patient was 4.0 (IQR, 2.0-7.0). The distribution of admission serum potassium levels approximated that of a normal distribution (FIGURE 1), with a mean admission potassium level of 4.2 mEq/L (SD, 0.6 mEq/L), and a median admission potassium level of 4.1 mEq/L (IQR, 3.8-4.4 mEq/L). During hospitalization, potassium values tended to remain fairly constant (FIGURE 2), with a mean postadmission potassium value of 4.2 mEq/L (SD, 0.6 mEq/L), and a median value of 4.1 mEq/L (IQR 3.8-4.5 mEq/L).

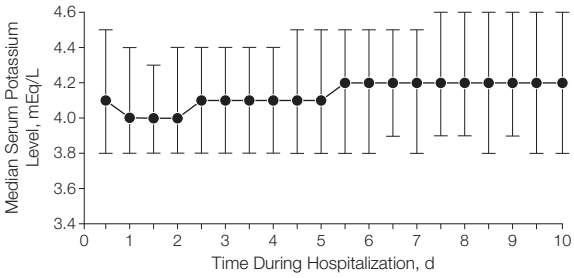
Baseline characteristics of the 34 026 study patients by strata of mean postadmission serum potassium are shown in TABLE 1. The relationship between potassium levels and baseline variables was complex: U-shaped for some variables (age, female sex, glucose level at admission, cardiogenic shock, and acute kidney injury); and inverted U-shaped for other variables (prior myocardial

Figure 1. Distribution of Serum Potassium Levels at Admission in the Overall Population (N=38 689)



Median potassium level at admission was 4.1 mEq/L (vertical dotted line). Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. The first interval includes all serum potassium levels less than 2.0 mEq/L and the last interval includes all that are 8.0 mEq/L or greater.

Figure 2. Trend of Serum Potassium Levels During Hospitalization



Each data point indicates the median and bars indicate the interquartile range of all potassium levels in the overall population that were measured during a half-day (or 12-hour) time period. On the x-axis, each tick mark corresponds to a half-day period of hospitalization. The numbers of patients for each half-day period are: 0.5 d, 34 921; 1.0 d, 17 480; 1.5 d, 14 169; 2.0 d, 14 208; 2.5 d, 11 496; 3.0 d, 11 276; 3.5 d, 8775; 4.0 d, 8614; 4.5 d, 6839; 5.0 d, 6733; 5.5 d, 5421; 6.0 d, 5425; 6.5 d, 4321; 7.0 d, 4411; 7.5 d, 3573; 8.0 d, 3457; 8.5 d, 2861; 9.0 d, 2847; 9.5 d, 2292; and 10.0 d, 2347.

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Table 1. Baseline Characteristics By Mean Postadmission Serum Potassium Level[a]

Baseline Characteristic	Postadmission Serum Potassium Level, Mean, mEq/L							*P* Value
	<3.0	3.0-<3.5	3.5-<4.0	4.0-<4.5	4.5-<5.0	5.0-<5.5	≥5.5	
No. of patients	26	778	11 153	16 536	4442	840	251	
Age, mean (SD), y	73.6 (12.1)	70.3 (13.9)	68.0 (14.3)	68.0 (14.1)	70.7 (13.4)	72.8 (13.6)	74.6 (13.3)	.22
Female, sex	14 (53.8)	438 (56.3)	4995 (44.8)	6277 (38.0)	1825 (41.1)	383 (45.6)	121 (48.2)	<.001
White race	22 (84.6)	639 (82.8)	9555 (86.1)	14 339 (87.2)	3817 (86.4)	699 (83.4)	202 (82.1)	.87
History								
Heart failure	5 (19.2)	285 (36.6)	3578 (32.1)	5101 (30.8)	1684 (37.9)	393 (46.8)	120 (47.8)	<.001
Prior myocardial infarction	1 (3.8)	39 (5.0)	646 (5.8)	961 (5.8)	279 (6.3)	47 (5.6)	5 (2.0)	.90
Dyslipidemia	7 (26.9)	240 (30.8)	4519 (40.5)	6747 (40.8)	1415 (31.9)	184 (21.9)	35 (13.9)	<.001
Current smoking	4 (15.4)	139 (17.9)	2474 (22.2)	4054 (24.5)	777 (17.5)	98 (11.7)	17 (6.8)	<.001
Hypertension	9 (34.6)	462 (59.4)	6200 (55.6)	8882 (53.7)	2483 (55.9)	457 (54.4)	114 (45.4)	.02
Cerebrovascular disease	1 (3.8)	36 (4.6)	462 (4.1)	706 (4.3)	201 (4.5)	33 (3.9)	13 (5.2)	.49
Peripheral vascular disease	0 (0.0)	20 (2.6)	299 (2.7)	423 (2.6)	132 (3.0)	30 (3.6)	4 (1.6)	.36
Dementia	3 (11.5)	25 (3.2)	258 (2.3)	274 (1.7)	74 (1.7)	16 (1.9)	9 (3.6)	.001
COPD	1 (3.8)	88 (11.3)	1424 (12.8)	2273 (13.7)	814 (18.3)	163 (19.4)	43 (17.1)	<.001
Diabetes	8 (30.8)	217 (27.9)	3214 (28.8)	5175 (31.3)	1754 (39.5)	342 (40.8)	76 (30.3)	<.001
Dialysis	0 (0.0)	16 (2.1)	161 (1.4)	310 (1.9)	241 (5.4)	91 (10.8)	36 (14.3)	<.001
Admission laboratory values, mean (SD)								
Potassium, mEq/L	3.8 (0.8)	3.7 (0.6)	3.9 (0.6)	4.2 (0.6)	4.5 (0.7)	4.9 (0.9)	5.4 (1.1)	<.001
Creatinine, mg/dL	1.5 (1.0)	1.4 (1.3)	1.2 (0.8)	1.3 (1.0)	1.8 (1.6)	2.5 (2.2)	3.0 (2.4)	<.001
GFR, mL/min	52.4 (25.1)	60.8 (26.3)	67.5 (25.9)	65.7 (26.0)	53.2 (27.1)	40.8 (25.3)	33.2 (23.8)	<.001
White blood cell count, cells/μL	13.8 (6.4)	11.7 (5.6)	10.9 (6.5)	10.7 (6.7)	11.1 (7.8)	12.0 (11.9)	12.8 (5.9)	.63
Hematocrit, %, mean (SD)	40.9 (6.6)	38.5 (6.2)	39.3 (5.9)	39.5 (6.0)	38.1 (6.3)	37.2 (6.3)	35.8 (6.6)	<.001
Peak troponin, median (IQR), ng/mL	4.4 (0.8-24.9)	5.2 (1.3-18.7)	7.2 (1.8-29.3)	6.6 (1.7-27.0)	5.9 (1.5-21.9)	5.9 (1.4-25.0)	6.9 (1.4-23.8)	<.001
Glucose, mg/dL	227 (141)	179 (97)	165 (86)	164 (85)	174 (98)	182 (97)	186 (105)	.06
No. of potassium checks per patient, median (IQR)	2 (2-4)	4 (3-6)	4 (3-7)	5 (3-8)	5 (3-9)	4 (2-8)	3 (2-5)	<.001
In-hospital procedures								
Coronary angiography	7 (26.9)	385 (49.5)	7301 (65.5)	11 148 (67.4)	2476 (55.7)	341 (40.6)	63 (25.1)	<.001
PCI	4 (15.4)	276 (35.5)	4987 (44.7)	6688 (40.4)	1336 (30.1)	173 (20.6)	44 (17.5)	<.001
CABG surgery	0 (0.0)	15 (1.9)	936 (8.4)	2467 (14.9)	524 (11.8)	35 (4.2)	3 (1.2)	<.001
In-hospital medication use								
Aspirin	16 (61.5)	635 (81.6)	9412 (84.4)	14 410 (87.1)	3833 (86.3)	678 (80.8)	153 (61.0)	.73
Other platelet inhibitors	6 (23.1)	430 (55.3)	6892 (61.8)	10 209 (61.7)	2511 (56.5)	409 (48.7)	78 (31.1)	<.001
Fibrinolytic agents	0 (0.0)	16 (2.1)	363 (3.3)	593 (3.6)	136 (3.1)	34 (4.1)	8 (3.2)	.24
β-Blockers	15 (57.7)	624 (80.2)	9417 (84.4)	14 152 (85.6)	3736 (84.1)	629 (75.0)	134 (53.4)	<.001
Calcium channel blocker	5 (19.2)	204 (26.2)	2555 (22.9)	3924 (23.7)	1233 (27.8)	229 (27.3)	39 (15.5)	<.001
Diuretic	9 (34.6)	399 (51.3)	5410 (48.5)	8018 (48.5)	2461 (55.4)	461 (54.9)	122 (48.6)	<.001
Nitrates	13 (50.0)	528 (67.9)	8139 (73.0)	12 463 (75.4)	3302 (74.3)	584 (69.6)	127 (50.6)	.86
Bronchodilators	6 (23.1)	133 (17.1)	2197 (19.7)	3547 (21.5)	1168 (26.3)	205 (24.4)	56 (22.3)	<.001
ACE inhibitor or ARB	8 (30.8)	435 (55.9)	7109 (63.8)	10 837 (65.5)	2786 (62.7)	386 (46.0)	63 (25.1)	<.001
Statins	7 (26.9)	417 (53.6)	7241 (64.9)	11 112 (67.2)	2826 (63.6)	412 (49.1)	71 (28.3)	<.001
Insulin treatment	9 (34.6)	192 (24.7)	2794 (25.1)	4340 (26.2)	1290 (29.0)	250 (29.8)	72 (28.7)	<.001
Oral antihyperglycemic agents	1 (3.8)	91 (11.7)	1473 (13.2)	2583 (15.6)	832 (18.7)	132 (15.7)	16 (6.4)	<.001
Any potassium supplementation (oral or IV)	23 (88.5)	645 (82.9)	6833 (61.3)	7983 (48.3)	1576 (35.5)	199 (23.7)	30 (12.0)	<.001
In-hospital course								
Hospital length of stay, median (IQR), h	48 (17-70)	89 (55-140)	108 (71-173)	118 (74-198)	125 (75-211)	100 (63-174)	41 (19-88)	<.001
Cardiogenic shock	3 (11.5)	38 (4.9)	558 (5.0)	605 (3.7)	176 (4.0)	59 (7.0)	48 (19.1)	.09
Acute respiratory failure	6 (23.1)	76 (9.8)	964 (8.6)	1004 (6.1)	327 (7.4)	102 (12.1)	58 (23.1)	.77
Acute kidney injury	3 (11.5)	79 (10.2)	818 (7.3)	1453 (8.8)	671 (15.1)	210 (25.0)	87 (34.7)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IQR, interquartile range; IV, intravenous; PCI, percutaneous coronary intervention.
SI Conversion Factors: To convert creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.
[a] Data are reported as No. (%) unless otherwise indicated.

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infarction, dyslipidemia, smoking history, GFR at admission, in-hospital revascularization procedures, and use of several in-hospital medications including aspirin, β-blockers, statins, and ACE-inhibitors). Similar relationships between baseline characteristics and strata of admission potassium levels were observed (eTable 1, available at http://www.jama.com).

Serum Potassium Levels and In-Hospital Mortality

Of the 38 689 study patients, 2679 (6.9%; 95% CI, 6.7%-7.2%) died during hospitalization. There was a U-shaped relationship between in-hospital mortality and mean postadmission potassium level (TABLE 2, FIGURE 3). Compared with the reference group (3.5-<4.0 mEq/L; mortality rate, 4.8%; 95% CI, 4.4%-5.2%), mortality was comparable for patients with a mean postadmission potassium level of 4.0 to less than 4.5 mEq/L (5.0%; 95% CI, 4.7%-5.3%), multivariable adjusted OR, 1.19; 95% CI, 1.04-1.36. Mortality was twice as great for potassium of 4.5 to less than 5.0 mEq/L (10.0%; 95% CI, 9.1%-10.9%) (multivariable adjusted OR, 1.99; 95% CI, 1.68-2.36), and was even greater at higher potassium levels. Similarly, mortality rates were higher for potassium levels of less than 3.5 mEq/L. This U-shaped relationship was only slightly attenuated and persisted after stepwise adjustments for covariates (Table 2). The U-shaped relationship was similar in patients who did or did not receive potassium supplementation during hospitalization (adjusted *P* value for interaction, .18). Similar results were also obtained when restricting analyses to patients still alive at 24 hours (data not shown). The association between admission serum potassium levels and in-hospital mortality was also U shaped but not as pronounced as for mean postadmission serum potassium levels (eTable 2; eFigure 2).

Table 2. In-Hospital Event Rates and Logistic Regression Models for Mortality, and Separately for Ventricular Fibrillation or Cardiac Arrest, by Mean Postadmission Potassium Level

	Postadmission Serum Potassium Level, Mean, mEq/L						
	<3.0	3.0-<3.5	3.5-<4.0	4.0-<4.5	4.5-<5.0	5.0-<5.5	≥5.5
No. of patients	26	778	11 153	16 536	4442	840	251
In-hospital mortality							
No. of deaths	12	89	539	821	442	208	154
Mortality, %	46.2	11.4	4.8	5.0	10.0	24.8	61.4
Mortality, OR (95% CI)							
Model 1: unadjusted	17.0 (7.72-37.6)	2.38 (1.87-3.03)	1 [Reference]	1.06 (0.94-1.18)	2.27 (1.99-2.59)	6.64 (5.53-7.97)	32.7 (24.9-43.1)
Model 2: adjusted for age and sex	16.4 (7.28-37.0)	2.23 (1.75-2.85)	1 [Reference]	1.06 (0.95-1.19)	2.11 (1.85-2.42)	6.01 (4.99-7.25)	30.7 (23.1-40.8)
Model 3: adjusted for age, sex, and GFR at admission	15.2 (6.56-35.2)	2.10 (1.64-2.69)	1 [Reference]	1.00 (0.89-1.12)	1.60 (1.39-1.83)	3.82 (3.15-4.63)	17.4 (13.0-23.3)
Model 4: adjusted for all covariates[a]	8.11 (2.69-24.4)	1.45 (1.06-1.99)	1 [Reference]	1.25 (1.09-1.44)	1.96 (1.64-2.34)	3.27 (2.52-4.24)	6.44 (4.27-9.70)
In-hospital ventricular fibrillation, ventricular flutter, or cardiac arrest							
No. of events[b]	5	49	551	683	180	57	37
Event rate, %	19.2	6.3	4.9	4.1	4.1	6.8	14.7
Events, OR (95% CI)							
Model 1: unadjusted	5.08 (1.90-13.57)	1.30 (0.95-1.76)	1 [Reference]	0.84 (0.75-0.94)	0.85 (0.72-1.02)	1.53 (1.15-2.03)	3.59 (2.50-5.16)
Model 2: adjusted for age and sex	5.42 (2.02-14.57)	1.37 (1.01-1.86)	1 [Reference]	0.82 (0.73-0.93)	0.87 (0.73-1.04)	1.62 (1.22-2.15)	3.96 (2.75-5.69)
Model 3: adjusted for age, sex, and GFR at admission	4.99 (1.84-13.52)	1.31 (0.97-1.79)	1 [Reference]	0.80 (0.71-0.90)	0.78 (0.66-0.93)	1.34 (1.00-1.80)	3.21 (2.21-4.67)
Model 4: adjusted for all covariates[a]	2.31 (0.74-7.24)	1.06 (0.76-1.48)	1 [Reference]	1.03 (0.90-1.17)	1.15 (0.94-1.39)	1.62 (1.16-2.26)	2.65 (1.70-4.13)

Abbreviations: GFR, glomerular filtration rate; OR, odds ratio.

[a] Includes demographics (age, sex, race); comorbidities (diabetes, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia, dialysis); first measurement during hospitalization of the following laboratory values (admission glomerular filtration rate calculated by Modification of Diet in Renal Disease equation, potassium, glucose, white blood cell count, hematocrit); peak troponin level; presence of cardiogenic shock and acute respiratory failure on admission; procedures during hospitalization including cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery; acute kidney injury during hospitalization; medications during hospitalization (fibrinolytic therapy, aspirin, clopidogrel, ticlopidine, β-blockers, angtioensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, nitrates, diuretics, bronchodilators, statins, insulin treatment, oral antihyperglycemic agents); number of serum potassium checks during hospitalization; length of hospital stay; and clustering by hospital site (using hierarchical logistic regression models with random effects introduced for hospital site).

[b] Ratio of events per patient is 1 to 1.

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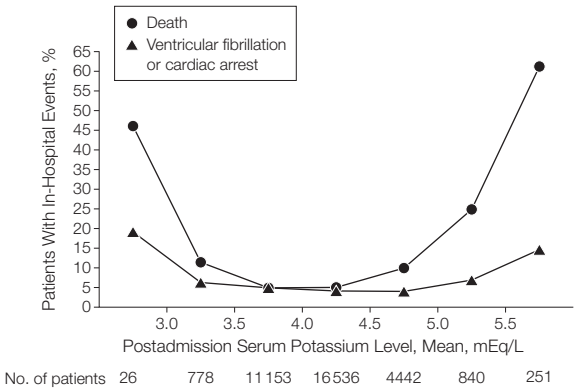
Figure 3. Rates of In-Hospital Mortality and of the Composite of Ventricular Fibrillation or Cardiac Arrest by Mean Postadmission Serum Potassium Level



Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. The first interval includes all serum potassium levels less than 3.0 mEq/L; the last interval includes all levels equal to or greater than 5.5 mEq/L. Numbers of events and event rates are listed in Table 2.

Serum Potassium Levels and Ventricular Arrhythmias or Cardiac Arrest

Of the 38 689 patients with AMI, 1707 (4.4%; 95% CI, 4.2%-4.6%) had an episode of ventricular fibrillation, ventricular flutter, or cardiac arrest during hospitalization. For mean postadmission potassium levels (Table 2; Figure 3), rates of ventricular arrhythmias or cardiac arrest were relatively flat across a wide range of potassium levels (3.0-<5.0 mEq/L), in contrast to mortality rates for which the optimal mean postadmission potassium range was narrower (3.5-<4.5 mEq/L). After adjustment for all covariates (including potassium level at admission), rates of ventricular arrhythmias or cardiac arrest were higher (compared with the reference group, 3.5-<4.0 mEq/L) only for the lowest and highest mean postadmission potassium levels (<3.0 mEq/L and ≥5.0 mEq/L; Table 2). For potassium levels at admission, compared with the reference group of 3.5 to less than 4.0 mEq/L, rates of ventricular arrhythmias or cardiac arrest increased for lower (<3.5 mEq/L) but not for higher potassium levels (eTable 2; eFigure 2).

Power Analysis

We observed a 2-fold greater risk of mortality associated with a mean postadmission potassium level of 4.5 to less than 5.0 mEq/L (mortality rate, 10.0%; 95% CI, 9.1%-10.9%) compared with 3.5 to less than 4.0 mEq/L (mortality rate, 4.8%; 95% CI, 4.4%-5.2%), or compared with 4.0 to less than 4.5 mEq/L (mortality rate, 5.0%; 95% CI, 4.7%-5.3%). Based on the sample size and variation in outcomes observed in this study, we had greater than 99.9% power to detect a 2-fold difference in mortality rates between the lower third (3.5-<4.0 mEq/L) or middle third (4.0-<4.5 mEq/L), compared with the upper third (4.5-<5.0 mEq/L), of the "clinically normal" potassium range of 3.5 to 5.0 mEq/L.

COMMENT

In this retrospective cohort study of patients with AMI, we found a U-shaped relationship between serum potassium levels and in-hospital mortality. The lowest mortality was observed among patients with potassium level between 3.5 and 4.5 mEq/L, with higher mortality rates observed for potassium levels of at least 4.5 mEq/L or less than 3.5 mEq/L. In contrast, rates of ventricular arrhythmias or cardiac arrest were flat in patients with potassium levels between 3.0 and 5.0 mEq/L, and higher rates were observed only for potassium levels of less than 3.0 mEq/L or at least 5.0 mEq/L. Although these associations were observed for potassium levels at admission (a nonmodifiable risk factor) and postadmission mean potassium levels (a modifiable risk factor), the association of mean postadmission potassium levels with mortality remained robust, even after adjusting for potassium level at admission.

This study is among the first that is adequately powered to evaluate the association between the full range of serum potassium levels and mortality following AMI, and suggests that maintaining serum potassium levels between 3.5 and 4.5 mEq/L may be more advisable than the 4.0 to 5.0 mEq/L range currently recommended by practice guidelines in patients with AMI.[8,9]

Outcomes associated with in-hospital potassium levels in patients with AMI have been described previously.[1-6] Most of these studies included fewer than 1000 patients and concluded that low potassium levels (usually <3.5 mEq/L) were associated with higher rates of postinfarction ventricular arrhythmias.[1-6] On the basis of those studies, current AMI guidelines recommend maintaining serum potassium between 4.0 and 5.0 mEq/L,[8,9] and some experts even advise a higher range of 4.5 to 5.5 mEq/L.[10]

However, the studies on which these guidelines were based have significant limitations. First, they focused on postinfarction ventricular arrhythmias, and were underpowered to examine the relationship between potassium levels and mortality. To our knowledge, the largest prior study included 1074 patients with AMI and demonstrated a U-shaped relationship between potassium levels and early postinfarction ventricular fibrillation events, but lacked power to show an association between potassium level and mortality.[17,18] Second, most prior studies were conducted before routine use of β-blockers, reperfusion therapy, and early invasive approaches for patients with AMI.[1,2,4-6] β-Blockers reduce the incidence of postinfarction mortality and sudden cardiac death[19,20]; raise serum po-

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tassium levels (by blocking epinephrine-induced depression of potassium levels through β-receptor stimulation)[21-24]; and suppress hypokalemia-mediated ventricular arrhythmias.[21-24] Third, the rate and prognostic value of ventricular arrhythmias and cardiac arrest following AMI is much lower in the current era of AMI management compared with 20 years ago.[25-27] Therefore, the old AMI studies on which current potassium guidelines are based may no longer apply to contemporarily managed patients with AMI.

This study should be considered in the context of several potential limitations. The relationship between potassium levels and mortality was U shaped, whereas the rate of ventricular fibrillation or cardiac arrest was relatively flat across a wide range of mean postadmission potassium levels, except for extreme values (<3.0 and ≥5.0 mEq/L). In our opinion, this discrepancy between the steeper increase in mortality rates and the less steep increase in rates of ventricular fibrillation or cardiac arrest at the extremes of potassium levels may represent a bias in the coding of ventricular arrhythmia and cardiac arrest events in hospitalized patients. Although hypokalemia has traditionally been associated with heightened ventricular excitability and an increased risk of ventricular arrhythmias, hyperkalemia has been associated with reduced ventricular excitability, with other causes of cardiac arrest occurring more frequently, including complete heart block and sinus arrest.[28,29] It is possible that these nonshockable rhythms associated with hyperkalemia (while still potentially fatal) may be less likely to be coded as cardiac arrest than rhythms of ventricular origin. Indeed, the inaccuracy of cardiac arrest diagnosis codes among patients who die during hospitalization has been previously reported.[30] To overcome this limitation, we designated our primary outcome in this study to be mortality, which is unbiased and of much greater clinical significance than ventricular arrhythmias in the current AMI treatment era.

Our study was observational, and despite the use of robust methods and hierarchical modeling with statistical adjustment, there is a possibility of residual confounding, or that the relationship between potassium level and clinical events may represent reverse causation. In particular, the large ORs for mortality at the extremes of potassium levels (<3.0 and ≥5.5) are based on a small number of events (Table 2), may be affected by outliers, and may represent high illness severity rather than a causal relationship. Large trials that randomize patients with AMI to different potassium targets would be necessary to definitively establish the optimal range for maintaining serum potassium levels in patients with AMI, but such trials are unlikely to be undertaken given the high cost and extensive regulatory procedures required for their conduct. Until such trials are conducted, our findings suggest that overly aggressive repletion of potassium levels (which is often automated through the implementation of hospital order sets) may not be advisable in patients with AMI (particularly in those with levels between 3.5 and 3.9 mEq/L), as potassium levels of at least 4.5 mEq/L are associated with harm.

Our study applies only to patients with AMI and may not extrapolate to patients with other cardiac conditions, including heart failure. Recent analyses from a trial of highly selected heart failure patients suggest that potassium levels of less than 4.0 mEq/L are associated with higher mortality,[31,32] but β-blockers (which alter potassium levels and mortality rates in heart failure patients) were not used in that study.[33] Studies such as ours should be replicated in the heart failure population.

In conclusion, our large study of patients with AMI challenges current clinical practice guidelines that endorse maintaining serum potassium levels between 4.0 and 5.0 mEq/L. These guidelines are based on small, older studies that focused only on ventricular arrhythmias (and not mortality) and were conducted before the routine use of β-blockers, reperfusion therapy, and early invasive management in AMI patients. Our data suggest that the optimal range of serum potassium levels in AMI patients may be between 3.5 and 4.5 mEq/L and that potassium levels of greater than 4.5 mEq/L are associated with increased mortality and should probably be avoided.

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Study concept and design: Goyal, Kosiborod.
Acquisition of the data: Spertus, Kosiborod.
Analysis and interpretation of the data: Goyal, Spertus, Gosch, Venkitachalam, Jones, Van den Berghe, Kosiborod.
Drafting of the manuscript: Goyal.
Critical revision of the manuscript for important intellectual content: Goyal, Spertus, Gosch, Venkitachalam, Jones, Van den Berghe, Kosiborod.
Statistical analysis: Gosch, Jones.
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Administrative, technical, or material support: Spertus, Kosiborod.
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Online-Only Material: eTable 1 and eTable 2 and eFigure 1 and eFigure 2 are available at http://www.jama.com.

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