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Hyperkalemia and Treatment With RAAS Inhibitors During Acute Heart Failure Hospitalizations and Their Association With Mortality

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ABSTRACT

OBJECTIVES This study investigated associations between incident hyperkalemia during acute heart failure (HF) hospitalizations and changes in renin-angiotensin-aldosterone system (RAAS) inhibitors.

BACKGROUND Hyperkalemia is a potential complication of RAAS inhibitors. For patients with HF, fear of hyperkalemia may lead to failure to deliver guideline-recommended doses of RAAS inhibitors.

METHODS Serum potassium concentrations were measured daily from baseline (<24 h after admission) until discharge or day 7 in 1,589 patients enrolled in the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial. Incident hyperkalemia was defined as at least 1 episode of potassium >5.0 mEq/l. The primary outcome was all-cause mortality at 180 days.

RESULTS Overall, serum potassium concentrations increased from 4.3 ± 0.6 mEq/l at baseline to 4.5 ± 0.6 mEq/l at discharge or day 7 ($p < 0.001$). Patients developing incident hyperkalemia (n = 564; 35%) were more often taking mineralocorticoid antagonists (MRAs) therapy prior to hospitalization and were more likely to have them down-titrated during hospitalization, independent of confounders. Incident hyperkalemia was not associated with adverse outcomes. Yet, down-titration of MRAs during hospitalization was independently associated with 180-day mortality (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.15 to 2.60), regardless of incident hyperkalemia ($p_{interaction} > 0.10$). Patients with incident hyperkalemia who were discharged with the same or increased dose of MRAs (HR: 0.52; 95% CI: 0.32 to 0.85) or angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) (HR: 0.47; 95% CI: 0.29 to 0.77) had a lower 180-day mortality.

CONCLUSIONS Incident hyperkalemia is common in patients hospitalized for acute HF and is not associated with adverse outcomes. Incident hyperkalemia is associated with down-titration of MRAs, but patients who maintained or increased their dose of MRAs and/or ACE inhibitors/ARB during acute HF hospitalization had better 180-day survival. (J Am Coll Cardiol HF 2019;7:970–9) © 2019 by the American College of Cardiology Foundation.

The treatment of heart failure (HF) requires a variety of agents that may cause both hypokalemia and hyperkalemia, and both conditions may be associated with a higher mortality in some clinical settings (1-5).

Hospitalizations for worsening HF is often associated with intensification of diuretic therapy that may cause hypokalemia and initiation or adjustment of the dose of life-saving therapies including renin-angiotensin-aldosterone system (RAAS) inhibitors,

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which may cause hyperkalemia (6). Accordingly, guidelines recommend that serum potassium concentrations are closely monitored during hospitalizations for HF and that RAAS inhibitors, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRAs), should be avoided or down-titrated if serum potassium exceeds 5.0 mEq/l (7–9).

Higher serum potassium concentrations are associated with less successful up-titration of ACE inhibitors/ARB in patients with chronic HF (10). Similarly, among patients with chronic HF, hyperkalemia is associated with underuse of MRAs (11,12). However, data for the association between incident hyperkalemia and up- or down-titration of RAAS inhibitors during hospitalization for acute HF are scant.

Therefore, this study investigated the relationship between incident hyperkalemia and adjustment of the dose of RAAS inhibitors in patients hospitalized with acute HF and subsequent clinical outcomes.

METHODS

STUDY DESIGN AND POPULATION. Patients enrolled in the PROTECT (Placebo-Controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial whose serum potassium was measured on at least 5 days during their index hospital admission were included in this analysis. Differences in clinical characteristics between patients included and excluded using these criteria are shown in Online Table 1. Detailed descriptions of the design, implementation, and results have been reported elsewhere (13,14). In short, patients with pre-existing HF, mild or moderate renal impairment (estimated creatinine clearance: 20 to 80 ml/min), increased plasma concentrations of brain natriuretic peptides, and breathlessness at rest or minimal exertion associated with symptoms and signs of volume overload requiring intravenous diuretic therapy and whose serum potassium was ≥3.5 mEq/l (or 3.0 to 3.5 mEq/l if potassium was given parenterally) were enrolled within 24 h of admission and randomized to rolofylline (a selective A_1 adenosine receptor antagonist) or placebo.

DEFINITIONS AND STUDY ENDPOINTS. Serum concentrations of potassium were classified according to clinical reference ranges, that is, hypokalemia (<3.5 mEq/l) and hyperkalemia (>5.0 mEq/l) (15). Serum potassium concentrations were measured daily from baseline (<24 h) until discharge or until day 7. Patients were classified as "incident hypokalemia" if they developed hypokalemia at some point (≥1 time) during hospitalization but no hyperkalemia. The "normal potassium" group was defined as having a serum potassium concentration of 3.5 to 5.0 mEq/l for all measurements until discharge or day 7. Patients who developed hyperkalemia during hospitalization (once or more) but never had hypokalemia were classified as "incident hyperkalemia." Patients who developed both hypo- and hyperkalemia during hospitalization (n = 34) were excluded from this analysis.

A change in serum potassium was defined as a difference of ≥0.2 mEq/l between day 1 and discharge or day 7. Worsening renal function was defined as a creatinine change until day 7 (from baseline) of ≥0.3 mg/dl in accordance with an earlier study originating from the PROTECT cohort (16). Changes in cardiovascular treatment were divided into 4 categories, as follows: treated neither at admission nor at discharge; dose was decreased or discontinued (down-titration); no dose change; or dose increased or initiated (up-titration). All-cause mortality at 180 days was the primary outcome for this analysis, and the composite of rehospitalization

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blockers

BNP = brain natriuretic peptide

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

MRA = mineralocorticoid receptor antagonist

RAAS = renin angiotensin aldosterone system

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for cardiovascular or renal causes or all-cause mortality through 60 days was a secondary outcome of interest.

STATISTICAL ANALYSIS. For baseline characteristics, mean ± SD, median (interquartile range), or number (percentage) were used as appropriate. Characteristics were stratified by the various clinical ranges (incident hypokalemia, normal potassium throughout hospitalization, incident hyperkalemia) until discharge or day 7. Differences among groups were tested using 1-way analysis of variance (ANOVA), chi-square test, or Kruskal-Wallis test as appropriate. To test all variables for normality, histograms or Q-Q plots were used. If doubt was raised, normality was tested using the Kolmogorov-Smirnov test. To achieve normal distribution for further analysis, skewed variables were log-transformed.

Intergroup differences related to changes in doses of ACE inhibitors/ARB and MRAs during hospitalization were depicted using stacked bar charts and tested using chi-square tests. To correct for treatment indication bias, analyses related to the effect of ACE inhibitors/ARB and MRA up- or down-titration were corrected for the probability of obtaining this specific therapy. For this correction, an inverse probability weighting (IPW) was used with the probability of up-titration for either ACE inhibitors/ARB or MRAs (17). IPW was performed by logistic LASSO (Least Absolute Shrinkage and Selection Operator) penalization analysis using all 69 variables averaged over 5 imputation sets for both ACE inhibitors/ARB and MRAs separately. Successful treatment was defined as patients who were able to be up-titrated or whose doses remained constant for either ACE inhibitors/ARB or MRAs. The derived weights were used in the subsequent survival analysis.

The association of clinical variables with incident hypo- and hyperkalemia was tested using logistic regression analyses. All variables with a univariate association <0.10 were used in multivariate models. Similar logistic regression models were used to test the predictive value of incident hyperkalemia on dose changes in cardiovascular treatment. The effect of baseline serum potassium concentrations (on a continuous scale) or the number of days hyperkalemia occurred on down-titration of ACE inhibitors/ARB or MRAs was tested using logistic regression models as well. In addition, a robust multivariate model was created including clinically relevant confounders.

Cox proportional hazard models were used to test the effects of up- or down-titration of ACE inhibitors/ARB and MRAs on outcome, adjusting for age, sex, logarithm of estimated glomerular filtration rate (eGFR), and logarithm of total diuretic dosage of loop diuretics (intravenous dose and one-half of the oral dose until day 7 or discharge) (model 1) and for the PROTECT Risk Engine (18). This model includes 8 variables measured at baseline; age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum albumin, creatinine, sodium, and urea concentrations. Interaction analyses were performed to investigate the interaction for outcome between changes in cardiovascular treatment during hospitalization and potassium abnormalities. The effect of incident dyskalemia on outcome was depicted using Kaplan Meier curves and tested in multivariate analysis using Cox proportional hazard models correcting for model 1 or the PROTECT Risk Engine (18).

A 2-sided p value <0.05 was considered statistically significant. Stata SE15 version 15 software (StataCorp, College Station, Texas) was used for statistical analyses.

RESULTS

BASELINE CHARACTERISTICS. Overall, serum potassium concentrations increased from 4.3 ± 0.6 mEq/l at baseline to 4.5 ± 0.6 mEq/l at discharge or day 7 ($p < 0.001$). The average potassium change during hospitalization was 0.22 ± 0.68 mEq/l. Incident hypokalemia occurred in 265 patients (17%) and incident hyperkalemia in 564 patients (35%). Of those, 264 patients (47%) had hyperkalemia on only 1 day of hospitalization (Online Table 2). In total, 34 patients (2%) had episodes of both hypo- and hyperkalemia. For frequency analyses only, the definition of incident hyperkalemia was narrowed to ≥5.5 mEq/l (moderate hyperkalemia) or >6.0 mEq/l (severe hyperkalemia). Then, 268 patients (17%) and 87 patients (5%) were classified as incident hyperkalemia, respectively.

Patients with incident hyperkalemia were younger, had fewer signs of congestion and a higher heart rate and a lower prevalence of atrial fibrillation/flutter ($p < 0.05$ for all), but they had renal functions (estimated glomerular filtration rate [eGFR]) similar to those of other patient groups. However, worsening renal function until day 7 was observed more frequently in the groups with incident dyskalemia (25% for incident hypokalemia, 17% for normokalemia, and 26% for incident hyperkalemia; $p < 0.001$). Patients who developed incident hyperkalemia were those more often taking MRAs (53%) and ACE inhibitors/ARB (78%) prior to hospitalization than patients with incident hypokalemia or who had a "normal potassium" level (35% and 44% for MRAs, and 68% and 77% for ACE inhibitors/ARB,

TABLE 1 Baseline Characteristics Stratified By Incident Hypokalemia, Always Normal Potassium, and Incident Hyperkalemia During Hospitalization Until Discharge or Day 7

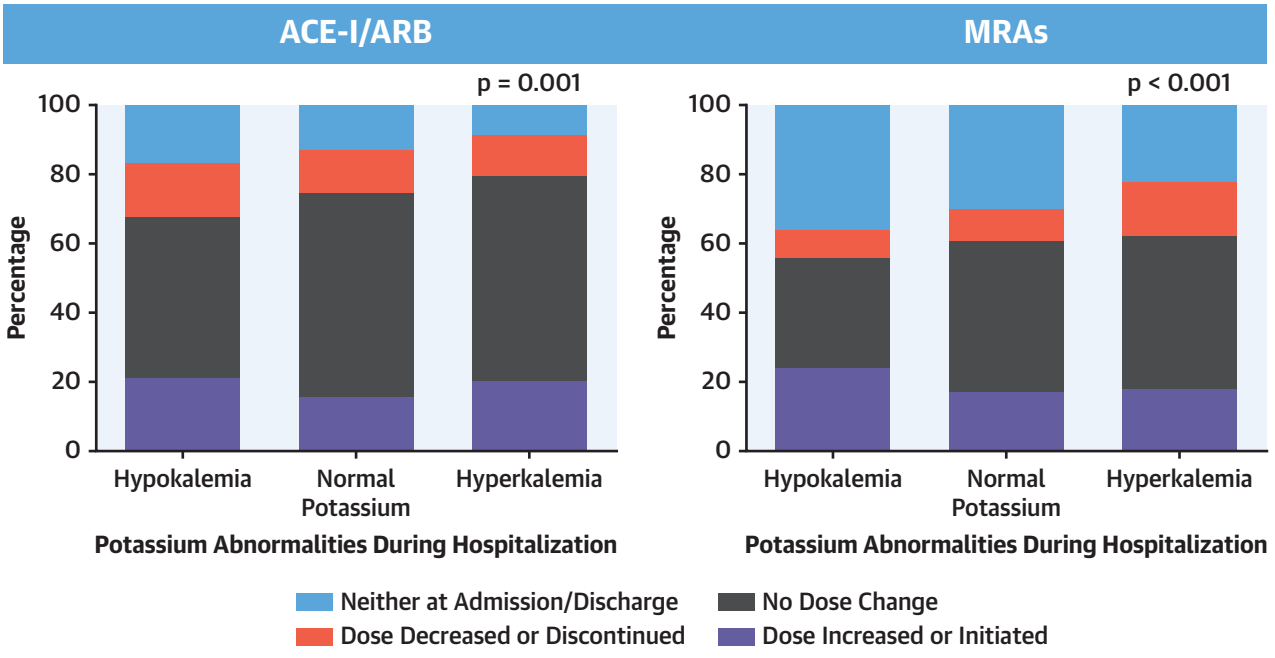
	Total Cohort (N = 1,589)	Hypokalemia ≥1 (n = 265)	No Abnormalities (n = 760)	Hyperkalemia ≥1 (n = 564)	p Value
Demographics					
Potassium, mEq/l	4.3 ± 0.6	3.7 ± 0.5	4.2 ± 0.4	4.7 ± 0.6	NA
Age, yrs	70.0 ± 11.4	70.5 ± 12.5	70.7 ± 11.1	68.8 ± 11.2	0.007
Males	1,060 (66.7)	165 (62.3)	527 (69.3)	368 (65.2)	0.072
BMI, kg/m^2	28.7 ± 6.1	28.6 ± 6.4	29.1 ± 6.3	28.3 ± 5.6	0.074
eGFR, ml/min/1.73 m^2	48.6 ± 19.3	48.4 ± 18.8	49.1 ± 18.6	47.9 ± 20.4	0.53
NYHA functional class					0.17
I/II	249 (16.5)	47 (18.8)	122 (16.9)	80 (15.0)	
III	751 (49.8)	122 (48.8)	375 (51.9)	254 (47.6)	
IV	507 (33.7)	81 (34.4)	226 (31.3)	200 (37.5)	
Systolic BP, mm Hg	124.8 ± 17.5	125.2 ± 19.6	124.7 ± 17.3	124.7 ± 16.8	0.93
Heart rate, beats/min	80.6 ± 15.5	80.1 ± 16.2	79.7 ± 15.2	81.9 ± 15.6	0.034
Orthopnea	1,349 (85.7)	219 (83.9)	659 (87.6)	471 (83.8)	0.10
Angina pectoris	383 (24.1)	61 (23.0)	159 (20.9)	163 (28.9)	0.003
Edema and raised JVP	433 (30.3)	92 (37.6)	202 (29.8)	139 (27.5)	0.018
Rales	165 (10.4)	30 (11.3)	69 (9.1)	66 (11.7)	0.27
Hospitalization for HF in the previous year	802 (50.5)	138 (52.1)	382 (50.3)	282 (50.0)	0.85
Myocardial infarction	794 (50.1)	121 (45.7)	384 (50.7)	289 (51.3)	0.28
Hypertension	1,268 (79.8)	201 (75.8)	619 (81.4)	448 (79.4)	0.14
Hyperlipidemia	777 (48.9)	134 (50.6)	397 (52.2)	246 (43.6)	0.007
Current smoker	317 (20.0)	50 (18.9)	169 (22.3)	98 (17.4)	0.080
COPD or asthma	309 (19.5)	51 (19.2)	148 (19.5)	110 (19.5)	0.99
Diabetes mellitus	723 (45.5)	116 (43.8)	342 (45.0)	265 (47.0)	0.64
Atrial fibrillation/flutter	857 (54.2)	143 (54.2)	423 (55.8)	291 (52.1)	0.040
Beta-blockers	1,219 (76.7)	204 (77.0)	590 (77.6)	425 (75.4)	0.62
ACE inhibitors/ARB	1,202 (75.6)	181 (68.3)	583 (76.7)	438 (77.7)	0.009
MRAs	726 (45.7)	93 (35.1)	337 (44.3)	296 (52.5)	<0.001
Digoxin	476 (30.0)	70 (26.4)	236 (31.1)	170 (30.1)	0.36
IV loop diuretic dose administered on day 1	80 (40–140)	100 (60–180)	80 (40–150)	80 (40–120)	<0.001
Oral dosage loop diuretic administered on day 1	40 (25–60)	40 (20–80)	40 (25–60)	40 (25–60)	0.32
Treated with rolofylline (study drug)	1,052 (66.2)	187 (70.6)	480 (63.2)	385 (68.3)	0.039
BNP, pg/ml	452 (258–830)	581 (324–981)	393 (243–751)	461 (263–826)	<0.001
Albumin, g/dl	3.8 ± 0.4	3.8 ± 0.5	3.9 ± 0.4	3.9 ± 0.4	0.039
Bicarbonate, mEq/l	24.0 ± 3.8	25.3 ± 3.9	24.1 ± 3.6	23.2 ± 38	<0.001
Chloride, mEq/l	101.1 ± 4.9	99.8 ± 5.5	101.2 ± 4.6	101.6 ± 5.0	<0.001
Sodium, mEq/l	139.5 ± 4.1	139.8 ± 4.5	139.6 ± 3.9	139.3 ± 4.2	0.17
Urea (BUN), mg/dl	29 (22–40)	29 (21–40)	28 (22–39)	31 (23–42)	0.028
Uric acid, mg/dl	9.0 ± 2.6	9.4 ± 2.8	8.9 ± 2.5	9.0 ± 2.5	0.032
Serum glucose, mg/dl	126 (103–163)	132 (106–159)	126 (103–164)	123 (99–166)	0.46
Hemoglobin, g/dl	12.7 ± 2.0	12.6 ± 2.0	12.7 ± 1.9	12.9 ± 2.0	0.14
Platelets, ×10^9 cells/l	217 (175–271)	205 (163–251)	215 (173–269)	226 (180–284)	0.002
White blood cells, ×10^9 cells/l	7.5 (6.1–9.3)	7.3 (5.8–9.3)	7.4 (6.0–9.3)	7.7 (6.3–9.2)	0.16
Total cholesterol, mg/dl	148 ± 45	139 ± 45	146 ± 44	154 ± 46	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; IQR = interquartile range; IV = intravenous; JVP = jugular venous pressure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

respectively) (Table 1). In a multivariate analysis, patients with incident hyperkalemia were younger, more often treated with MRAs, and received lower doses of loop diuretics during hospitalization. In addition, hyperkalemic episodes were associated with lower serum sodium concentrations, a higher platelet count, and higher serum concentrations of chloride and blood urea nitrogen (Online Table 3).

CENTRAL ILLUSTRATION **Changes in Cardiovascular Therapy Between Admission and Discharge for ACE Inhibitor/ARB and MRAs**



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"Neither at admission/discharge (no use)" in **blue**; "Dose decreased or discontinued" in **red**; "No dose change" in **gray**; "Dose increased or initiated" in **purple**. Stacked bar charts depicting changes in cardiovascular therapy between admission and discharge for ACE inhibitor/ARB ($p = 0.001$) and MRA ($p < 0.001$). Stratified by development of incident hypokalemia; normal potassium concentrations throughout hospitalization; and incident hyperkalemia during hospitalizations; p value for overall intergroup differences. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid antagonist.

Independent predictors of incident hypokalemia were lower serum concentrations of chloride, higher serum concentrations of bicarbonate and BNP, higher doses of loop diuretics, and not receiving MRAs at baseline (Online Table 4).

CHANGES IN CARDIOVASCULAR TREATMENT. For patients with incident hyperkalemia, MRAs were more often down-titrated (15%) than in patients whose potassium remained in the normal range (9%) or with incident hypokalemia (8%) (**Central Illustration**, Online Table 5). After corrections were made for confounders (i.e., age, sex, eGFR, and total doses of loop diuretics until day 7 or discharge) or correction for all variables with a univariate association with MRA down-titration (univariate $p < 0.10$), this association remained significant (odds ratio [OR]: 1.81; 95% confidence interval [CI]: 1.27 to 2.58; $p = 0.001$ and OR: 1.89; 95% CI: 1.32 to 2.72, $p = 0.001$, respectively). In sensitivity analyses using IPW, this association was not attenuated (OR: 1.88; 95% CI: 1.30 to 2.73; $p = 0.001$). Doses of ACE inhibitors/ARB were not decreased more frequently in patients with incident hyperkalemia than in patients with normal potassium concentrations throughout or those with incident hypokalemia ($p = 0.296$). Patients with incident hypokalemia were less often treated with MRAs or ACE inhibitors/ARB during hospitalization (**Central Illustration**). However, after multivariate adjustment, this was no longer significant for either therapy class ($p = 0.061$ and $p = 0.380$, respectively). Differences at baseline among subgroups of treatment change for ACE inhibitors/ARB and MRAs are listed in Online Tables 6 and 7, respectively.

In univariate analysis, the number of days with hyperkalemia was not associated with ACE inhibitors/ARB down-titration (OR: 1.06; 95% CI: 0.89 to 1.27; $p = 0.517$) (**Table 2**). However, the number of instances that hyperkalemia occurred was associated with down-titration of MRAs (OR: 1.26; 95% CI: 1.09 to 1.47, $p = 0.003$). This association remained significant after correction for variables with a univariate association with MRA down-titration (OR: 1.23;

TABLE 2 Association Between the Magnitude of Hyperkalemia and Patients' Serum Potassium Concentrations at Baseline and Treatment Down-Titration*

Down-Titration	Univariate OR (95% CI), p Value	Model 1 OR (95% CI), p Value†	Model 2 OR (95% CI), p Value‡
ACE Inhibitor/ARB			
Number of days with hyperkalemia	1.06 (0.89–1.27), 0.517	NA	NA
Baseline serum potassium, per 1 mEq/l	1.02 (0.78–1.33), 0.879	NA	NA
MRAs			
Number of days with hyperkalemia	1.26 (1.09–1.47), 0.003	1.23 (1.04–1.44), 0.014	1.41 (1.02–1.97), 0.040
Baseline serum potassium, per 1 mEq/l	1.45 (1.10–1.91), 0.008	1.35 (1.01–1.80), 0.043	1.51 (0.87–2.62), 0.139

*Data show the association between the magnitude of hyperkalemia (defined as the number of days hyperkalemia occurred [1 to 7 days]) and patients' serum potassium concentrations at baseline (on a continuous scale) and treatment down-titration. †Model 1: corrected for heart rate, logarithm of eGFR, history of hyperlipidemia, history of smoking, NYHA functional class, treatment with beta-blockers, and treatment with MRAs (in ACE inhibitor/ARB) or treatment with ACE inhibitor/ARB (in MRAs). ‡Model 2: corrected for age, sex, BMI, logarithm of eGFR, NYHA functional class, left ventricular ejection fraction, systolic blood pressure, history of COPD, history of diabetes mellitus, history of atrial fibrillation, treatment with beta-blockers, treatment with ACE inhibitor/ARB, treatment with rolofylline, edema and raised jugular venous pressure, intravenous dose of loop diuretics, serum sodium concentrations, serum BNP concentrations, and serum hemoglobin concentration.

BMI = body mass index; OR = odds ratio; other abbreviations as in Tables 1 and 2.

95% CI: 1.04 to 1.44; p = 0.014) or after robust correction for various clinical confounders (OR: 1.41; 95% CI: 1.02 to 1.97; p = 0.040).

When tested on a continuous scale, baseline serum potassium was not associated with ACE inhibitors/ARB down-titration (Table 2). Yet, it was positively associated with MRA down-titration (OR: 1.45; 95% CI: 1.10 to 1.91; p = 0.008) in univariate analysis. However, this effect was no longer significant after correction for clinical confounders (OR: 1.51; 95% CI: 0.87 to 2.62; p = 0.139).

INCIDENT POTASSIUM DISTURBANCES, RAAS INHIBITOR THERAPY, AND OUTCOME. Overall, 269 patients (17%) died within 180 days, and 434 patients (27%) experienced the composite secondary outcome. No association was observed between incident hypo- or hyperkalemia and either outcome or the composite outcome (Online Figure 1), even when hyperkalemia was defined as ≥5.5 mEq/l. However, the number of days a patient suffered from hyperkalemia was associated with 180-day mortality, even after correction for the PROTECT Risk Engine (hazard ratio [HR]: 1.14; 95% CI: 1.00 to 1.30; p = 0.049).

Compared to constant doses, down-titration or absence of ACE inhibitors/ARB at baseline and discharge at day 7 were associated with a higher 180-day mortality on both unadjusted and adjusted analyses (Table 3). Furthermore, when IPW was used, the associations persisted (HR: 2.56; 95% CI: 1.83 to 3.60; p < 0.001). A similar pattern was observed for MRA down-titration during hospitalization. Also for patients taking MRAs, IPW did not attenuate this association (HR: 1.67; 95% CI: 1.11 to 2.49; p = 0.013). Additional correction for treatment with the study drug (rolofylline) or placebo had no impact on outcomes.

Incident hyperkalemia had no impact on the association between RAAS inhibitors and a favorable outcome. Patients with incident hyperkalemia and constant doses or increasing doses of MRAs had a lower mortality (HR: 0.58; 95% CI: 0.37 to 0.91) compared to patients who did not receive an MRA or who had doses reduced. Additional IPW analysis did not attenuate this beneficial effect (HR: 0.52; 95% CI: 0.32 to 0.85). Similarly, patients with incident hyperkalemia and constant or increasing doses of ACE inhibitors/ARB had a lower mortality (HR: 0.46; 95% CI: 0.28 to 0.75). This association was not attenuated in an IPW analysis (HR: 0.47; 95% CI: 0.29 to 0.77). No interaction was observed between incident hyperkalemia and up-titration of ACE inhibitors/ARB or MRAs during hospitalization for either all-cause mortality at 180 days or the secondary composite outcome ($p_{interaction}$ >0.10 for all). Additionally, when tested in potassium sub-groups, patients with incident hyperkalemia and ACE inhibitors/ARB down-titration had a worse 180-day prognosis compared to patients with stable ACE inhibitors/ARB doses. This was not seen for MRAs (Online Table 8).

DISCUSSION

This analysis shows that patients hospitalized for acute HF often develop hyperkalemia, and if they do, they are more likely to have doses of MRAs reduced or stopped. Although incident hyperkalemia was not directly associated with longer-term outcomes, incident hyperkalemia was associated with lower use of RAAS inhibitors. Patients who developed hyperkalemia fared better if the doses of MRA or ACE inhibitors/ARB were held constant or increased.

TABLE 3 Cox Proportional Hazard Regression for Mortality Risk at 180 Days After Change in Cardiovascular Treatment During Hospitalization

Change in Cardiovascular Treatment	Univariate HR (95% CI), p Value	Model 1 HR (95% CI), p Value*	PROTECT Risk Engine HR (95% CI), p Value†
ACE inhibitor/ARB			
No dose change (Reference)			
Dose increased or initiated	1.03 (0.69–1.52), 0.895	1.01 (0.70–1.48), 0.940	1.02 (0.68–1.52), 0.939
Dose decreased or discontinued	2.12 (1.49–3.02), <0.001	1.97 (1.40–2.75), <0.001	1.68 (1.17–2.42), 0.005
Subject taking neither currently nor randomly	2.58 (1.84–3.62), <0.001	1.89 (1.35–2.62), <0.001	1.85 (1.28–2.65), 0.001
MRAs			
No dose change (Reference)			
Dose increased or initiated	1.21 (0.83–1.74), 0.322	1.14 (0.80–1.63), 0.472	1.11 (0.76–1.61), 0.595
Dose decreased or discontinued	1.66 (1.11–2.49), 0.013	1.57 (1.06–2.33), 0.026	1.73 (1.15–2.60), 0.008
Subject taking neither currently nor randomly	1.31 (0.95–1.80), 0.095	1.12 (0.82–1.51), 0.479	1.15 (0.82–1.61), 0.408

*Model 1: Corrected for age, sex, logarithm of eGFR, and logarithm of total dose of loop diuretics until day 7 or discharge (IV + oral/2). †Corrected for PROTECT Risk Engine: age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum urea, creatinine, sodium, and albumin concentrations.

CI = confidence interval; HR = hazard ratio; IV = intravenous; PROTECT = Placebo-Controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; other abbreviations as in Table 1.

We are unaware of any other trial of hospital admission for HF with such a high density of measurements of serum potassium. More than one-half of the patients in this analysis developed either hypo- or hyperkalemia during hospital admission. Hyperkalemia was most prevalent in 35% of patients at least once, whereas 17% of patients experienced hypokalemia at least once during hospitalization. Incident serum potassium ≥5.5 mEq/l or >6.0 mEq/l was seen in 17% and 5% of patients, respectively. Many clinical trials of HF, especially involving RAAS inhibitors, excluded patients with a baseline serum potassium concentration of >5.0 mEq/l, which was designed to reduce the risk of developing severe hyperkalemia (19,20). Earlier reports from the PROTECT trial reported that 6% of acute HF patients had hyperkalemia at baseline (21). In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial, 14.6% of patients hospitalized with worsening HF had hyperkalemia at discharge (22). In a recent study, exploring the effect of long-term monitoring of serum potassium after hospitalizations for acute HF, 5.6% of patients developed hyperkalemia post-discharge (4).

Patients at risk for developing hyperkalemia during hospitalization were more often treated with MRAs prior to hospitalization, in keeping with the results of the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study, which showed that patients treated with MRAs developed hyperkalemia more often during follow-up (20,23). Many trials of HF have shown that older patients with diabetes and renal dysfunction treated with RAAS inhibitors were more likely to develop hyperkalemia (21–24). The fact that similar associations with incident hyperkalemia were not found in this study suggests that changes in RAAS inhibitors may be of overriding importance during hospitalization for acute HF. However, within the "incident hyperkalemia" group, those patients whose ACE inhibitors/ARB or MRAs dosage were down-titrated more frequently had a history of diabetes mellitus and showed a worse renal function compared to patients with incident hyperkalemia and stable doses or up-titration of ACE inhibitors/ARB or MRAs (Online Tables 5 and 6). The greater incidence of hyperkalemia in younger people in the present study may reflect greater efforts and successes in treating them with MRAs. Hypokalemia was strongly associated with not being treated with an MRA. In addition, by using a multi-day method of in-hospital monitoring, findings from the present study indicated that patients with a higher severity of hyperkalemia (defined as more days with serum potassium concentrations above 5.0 mEq/l), were more likely to be down-titrated with MRAs.

In this study, a mortality rate of 17% was seen after a follow-up period of 180 days. For the combined outcome of all-cause mortality and cardiovascular or renal rehospitalization at 60 days an incidence rate of 27% was seen (Online Table 9). Similar to previous reports, incident hypokalemia or hyperkalemia during hospitalization was not associated either with mortality or the secondary

composite outcome (21–23,25). However, incident hyperkalemia was strongly associated with down-titration of MRA therapy which was, in turn, associated with a worse prognosis. A previous report from the Swedish HF registry indicated that hyperkalemia was not related to underuse of MRAs (26). In contrast, analyses of the BIOSTAT-CHF cohort, including patients with chronic HF, indicated hyperkalemia was associated with less successful up-titration of ACE inhibitors/ARB and underuse of MRAs (10,12). Unfortunately, no specific data for up- or down-titration of MRA therapy were available in this chronic HF cohort. Additionally, real-world data of the SCREAM (Stockholm CREAtinine Measurements) study indicated hyperkalemia to be common after MRA initiation yet with frequent therapy interruption as a consequence, especially among participants with chronic kidney disease (11).

Our results indicated higher survival rates, after up-titration or constant doses of either MRAs or ACE inhibitors/ARB, were also seen in patients with incident hyperkalemia. This indicates that hyperkalemia at times of intense cardiovascular treatment might not attenuate the beneficial effects of these therapeutic agents, which is in accordance to earlier findings from a post hoc analysis of the EMPHASIS-HF trial regarding chronic HFrEF patients (27). This may be of additional interest, taking the novel therapeutics to lower serum potassium concentrations into account (28,29).

STUDY LIMITATIONS. The PROTECT trial did not include patients with serum potassium concentrations below 3.0 mEq/l. Patients with serum potassium concentrations between 3.0 and 3.5 mEq/l could only be included in case potassium was supplemented parenterally. However, no data were available regarding the supplement doses. In patients with chronic HF, oral potassium supplements did not affect mortality (30). The associations highlighted in this paper need to be considered in the light of a clinical trial setting. For instance, the proportion of patients treated with the study drug (rolofylline) was not equally distributed between potassium subgroups ($p = 0.039$). Because an earlier study by Liu et al. (31) indicated that the effect of rolofylline on mortality is similar throughout the spectrum of baseline serum potassium concentrations, this finding was not expected to have a major impact on the present results. Additionally, treatment with rolofylline had no impact on the present multivariate outcome models. Changes in RAAS inhibitors were recorded between baseline and day 7, whereas serum potassium concentrations were measured daily. We did not record why investigators changed doses of RAAS inhibitors, which will have been influenced by patients' symptoms and signs, blood pressure, and renal function. Additionally, because changes in RAAS inhibitors were only recorded within this specific time window, the effects of dose adjustments after day 7 might have affected outcomes. The incidence of hyperkalemia and its effect on the use of RAAS inhibitors may be distorted, compared to clinical practice, by the close monitoring of patients and their serum potassium levels. In clinical practice, serum potassium will usually be measured less often, which may mean that hyperkalemia is often missed but is more severe when it eventually is detected. We included only patients with 5 or more measurements of serum potassium, which effectively excluded early deaths. Of 47 patients (3%) who died within 7 days of enrollment, 14 patients (30%) showed a serum potassium concentration >5.0 mEq/l at some point during hospitalization. Serum potassium concentrations may fluctuate markedly in the acute setting and may not reflect post-discharge measurements. This could account for the dissociation between in-patient measurements of potassium and long-term outcome that we observed. Other reports suggest that hypo- and hyperkalemia are strongly related to in-hospital prognosis (United Kingdom National HF audit of ~30,000 patients) (32).

CONCLUSIONS

Incident hyperkalemia is common during hospitalization for acute HF but is not associated with a worse post-discharge prognosis. However, incident hyperkalemia is associated with underuse of MRAs, which is associated with an increased risk of mortality at 180 days. Survival analyses indicated that patients still benefit from constant doses or up-titration of MRAs and/or ACE inhibitors/ARB, despite incident hyperkalemia, in a clinical setting.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Even though incident hyperkalemia is common during hospitalization for acute HF, it does not result in impaired prognosis. However, it is associated with down-titration of MRAs, which is associated with worse outcomes. The authors reported that the patients with incident hyperkalemia who were discharged with the same or an increased dose of MRAs and/or ACE inhibitors/ARB had a lower 180-day mortality.

TRANSLATIONAL OUTLOOK: This study provides data for associations between incident hyperkalemia and RAAS inhibitors to tailor this therapy in patients hospitalized for acute HF. These data may also support the design of trials, for example, to explore the serum potassium concentration at which RAAS inhibitor doses should be reduced, should be reconsidered. The effect of treatments designed to manage hyperkalemia should be assessed not only to determine if they can increase the proportion of patients achieving target doses of RAAS inhibitors but whether this strategy leads to reductions in morbidity and mortality.

REFERENCES

1. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004;351:585–92.

2. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543–51.

3. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care 2015;21:S212–20.

4. Núñez J, Bayés-Genís A, Zannad F, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. Circulation 2018;137:1320–30.

5. Aldahl M, Jensen A-SC, Davidsen L, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J 2017;38:2890–6.

6. Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergenc. Eur J Heart Fail 2015;17:544–58.

7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. Eur J Heart Fail 2016;18:891–975.

8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

9. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother 2018;4:180–8.

10. Beusekamp JC, Tromp J, van der Wal HH, et al. Potassium and the use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF. Eur J Heart Fail 2018;20:923–30.

11. Trevisan M, de Deco P, Xu H, et al. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. Eur J Heart Fail 2018;20:1217–26.

12. Ferreira JP, Rossignol P, Machu J-L, et al. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. Eur J Heart Fail 2017;19:1284–93.

13. Weatherley BD, Cotter G, Dittrich HC, et al. Design and rationale of the PROTECT study: a placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect. J Card Fail 2010;16:25–35.

14. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419–28.

15. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? J Am Coll Cardiol 2004;43:155–61.

16. Metra M, Cotter G, Senger S, et al. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion. Circ Heart Fail 2018;11:233–7.

17. Wal WM van der, Geskus RB. ipw: an R package for inverse probability weighting. J Stat Softw 2011;43:1–23.

18. Cleland JG, Chiswell K, Teerlink JR, et al. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the placebo-controlled randomized study of the selective a1 adenosine receptor antagonist rolofylline for patients hospitalized. Circ Heart Fail 2014;7:76–87.

19. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.

20. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

21. Tromp J, Maaten JM Ter, Damman K, et al. Serum potassium levels and outcome in acute heart failure (data from the PROTECT and COACH trials). Am J Cardiol 2017;119:290–6.

22. Khan SS, Campia U, Chioncel O, et al. Changes in serum potassium levels during hospitalization in patients with worsening heart failure and reduced ejection fraction (from the EVEREST trial). Am J Cardiol 2015;115:790–6.

23. Rossignol P, Dobre D, McMurray JJ, et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from. Circ Heart Fail 2014;7:51–8.

24. Desai AS, Swedberg K, McMurray JJ, et al. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM program. J Am Coll Cardiol 2007;50:1959–66.

25. Weisberg LS. Management of severe hyperkalemia. Crit Care Med 2008;36:3246–51.

26. Savarese G, Carrero J-J, Pitt B, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. Eur J Heart Fail 2018;20:1326–34.

27. Eschalier R, McMurray JJ, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol 2013;62:1585–93.

28. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 2011;32:820–8.

29. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. Eur J Heart Fail 2015;17:1050–6.

30. Ekundayo OJ, Adamopoulos C, Ahmed MI, et al. Oral potassium supplement use and outcomes in chronic heart failure: a propensity-matched study. Int J Cardiol 2010;141:167–74.

31. Liu LCY, Valente MAE, Postmus D, et al. Identifying subpopulations with distinct response to treatment using plasma biomarkers in acute heart failure: results from the PROTECT trial: differential response in acute heart failure. Cardiovasc Drugs Ther 2017;31:281–93.

32. National Cardiac Audit Programme (NCAP). National Heart Failure Audit: 2016/17 Summary Report. Available at: https://www.nicor.org.uk/wp-content/uploads/2018/11/Heart-Failure-Summary-Report-2016-17.pdf. Accessed September 5, 2019.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.