Serum Potassium Levels and Outcome in Acute Heart Failure (Data from the PROTECT and COACH Trials)

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Serum potassium is routinely measured at admission for acute heart failure (AHF), but information on association with clinical variables and prognosis is limited. Potassium measurements at admission were available in 1,867 patients with AHF in the original cohort of 2,033 patients included in the Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion trial. Patients were grouped according to low potassium (<3.5 mEq/l), normal potassium (3.5 to 5.0 mEq/l), and high potassium (>5.0 mEq/l) levels. Results were verified in a validation cohort of 1,023 patients. Mean age of patients was 71 ± 11 years, and 66% were men. Low potassium was present in 115 patients (6%), normal potassium in 1,576 (84%), and high potassium in 176 (9%). Potassium levels increased during hospitalization (0.18 ± 0.69 mEq/l). Patients with high potassium more often used angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists before admission, had impaired baseline renal function and a better diuretic response ($p = 0.005$), independent of mineralocorticoid receptor antagonist usage. During 180-day follow-up, a total of 330 patients (18%) died. Potassium levels at admission showed a univariate linear association with mortality (hazard ratio [log] 2.36, 95% confidence interval 1.07 to 5.23; $p = 0.034$) but not after multivariate adjustment. Changes of potassium levels during hospitalization or potassium levels at discharge were not associated with outcome after multivariate analysis. Results in the validation cohort were similar to the index cohort. In conclusion, high potassium levels at admission are associated with an impaired renal function but a better diuretic response. Changes in potassium levels are common, and overall levels increase during hospitalization. In conclusion, potassium levels at admission or its change during hospitalization are not associated with mortality after multivariate adjustment. **(Am J Cardiol 2017;119:290−296)**

Serum potassium is routinely measured during hospitalization for acute heart failure (AHF), and heart failure (HF) guidelines recommend daily assessment of potassium during treatment with intravenous loop diuretics.[1] Potassium levels at admission are associated with loop diuretic therapy and intensive neurohormonal activation.[2−5] In chronic HF, low serum potassium levels were found to be associated with increased mortality.[4,6] However, a recent study in an AHF population with a reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <35%) showed no association between potassium levels at admission or a change in potassium during hospitalization and clinical outcome.[7] Nonetheless, this study only focused on a HFrEF population, and no information was available on diuretics and diuretic response, which can confound findings.[8] Data on the clinical importance of potassium in patients with AHF with both reduced and preserved ejection fraction are absent.[7,9] Current guidelines recommend to keep potassium levels from 4.5 to 5.5 mmol/l; however, recommendations for AHF are lacking.[1,3] Therefore, in the present study, we

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investigated the association between serum potassium levels at admission, changes during hospitalization, and the association with clinical characteristics and mortality.

Methods

The study population was a subcohort of the Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial of which results and study design have been published previously.[10,11] In brief, the PROTECT trial investigated the role of the selective A1 adenosine receptor antagonist rolofylline on treatment effect, defined as a trichotomous end point of failure, unchanged, and success. The study originally included 2,033 patients with a history of HF admitted with AHF. Potassium measurements were available in 1,867 patients at admission. In the PROTECT trial, patients with serum potassium levels below <3.0 mEq/l were excluded, and patients with serum potassium levels from 3.0 to 3.5 mEq/l were allowed if parental supplemental potassium was administered.

Results of survival analysis were verified in a validation cohort in the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure (COACH) of which design and results have been published before.[12,13] In brief, the COACH trial studied the effects of additional basic and intensive nurse-led support on the combined end point of death and HF hospitalization of 1,023 patients with HF who were admitted for AHF. The results of this trial were neutral. Potassium levels were available in 999 patients at admission and 1,023 patients at discharge. Patients in this trial were included independent of potassium levels. Estimated glomerular filtration rate (eGFR) was based on the simplified Modification of Diet in Renal Disease formula, and HF with a preserved ejection fraction was defined as having a LVEF >45%.[14]

For baseline characteristics, potassium levels were divided into 3 groups based on cut-off values of <3.5, 3.5 to 5.0, and >5.0 mEq/l (low, normal, and high).[4] Hypokalemia was defined as a potassium level <3.5 mEq/l and hyperkalemia as a potassium level >5.5 mEq/l. In the PROTECT trial, discharge potassium was defined as potassium levels at day 7 after admission or at discharge, whichever came first. In the COACH trial, potassium was measured around discharge. The change in potassium levels during hospitalization was determined as the difference between potassium levels at admission and discharge. The primary end point for this substudy of the PROTECT trial was all-cause mortality at 180 days. The primary end point used for this substudy of the COACH trial was all-cause mortality at 3 years. Continuous variables are presented as means ± standard deviations or medians with interquartile ranges. Categorical variables are presented as numbers with percentages. Intergroup differences were analyzed using the Kruskal−Wallis 1-way analysis of variance, the 1-way analysis of variance, or the chi-square test where appropriate.

For further analysis, potassium variables were log-transformed to achieve normal distribution as this provided the best fit in this population despite expectations of a U-shaped relation. Survival differences between low, normal, and high potassium are graphically depicted using Kaplan−Meier curves. Differences are tested using the log-rank test. Survival analysis is performed using Cox regression analysis. Model fit was tested using multifractional polynomials. In addition, goodness of fit was tested using the Grønnesby and Borgan variation of the Hosmer−Lemeshow test.

Multivariate correction was done in the index cohort with an established risk engine for this population which includes 8 variables measured at admission, namely age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum sodium, urea, creatinine, and albumin levels.[15] In the validation cohort, the COACH risk engine was used for multivariate correction. The COACH risk engine includes gender; age; pulse pressure; diastolic blood pressure; a history of stroke, diabetes, peripheral vascular disease, and myocardial infarction; estimated glomerular filtration rate; previous HF hospitalizations; sodium; LVEF; and levels of N-terminal pro-b-type natriuretic peptide.[16]

All tests were performed 2 sided, and a p value of <0.05 was considered significant. All statistical analyses were performed using STATA version 11.0 (StataCorp LP, College station, Texas).

Results

Table 1 provides the baseline characteristics of the main study population. Baseline characteristics of the validation cohort are presented in Supplementary Table 1. Of patients enrolled in the PROTECT trial, 115 patients (6%) had low, 1,576 (84%) had normal, and 176 (9%) had high potassium levels. Hyperkalemia (>5.5 mEq/l) at baseline was present in 54 patients (1%). Overall, potassium levels increased during hospitalization (0.18 ± 0.69), yet 566 patients (34%) experience a decrease in potassium levels. In a total of 909 patients (55%), the potassium level increased during hospitalization, and only 100 patients (6%) had no change in potassium levels (defined as no change at all). Higher potassium levels at admission were associated with higher rates of diabetes, more previous usage of angiotensin-converting enzyme (ACE) inhibition and mineralocorticoid receptor antagonists (MRA), and a lower eGFR. Plasma BNP levels were similar Treatment with MRAs was most often changed during hospitalization (Figure 1). The association between baseline serum potassium levels, randomized treatment, and clinical outcomes is presented in Table 2. Diuretic response expressed as kilograms of weight loss per 40 mg of furosemide was lower for patients with low potassium from admission to day 4 after admission ($p = 0.005$, Table 2). When examining tertiles of diuretic response, patients with higher potassium were more often in the higher tertile (p value for trend = 0.002, Figure 2). Also, when correcting for previous MRA usage (β −0.089, $p < 0.001$) or a change in MRA usage during hospitalization (β −0.085, $p = 0.001$), potassium levels at admission remained associated with diuretic response. Serum potassium levels were not associated with the trichotomous primary end point of the PROTECT study ($p = 0.800$, Table 2).

Patients with high and low levels of potassium had higher mortality rates within the first 7 days compared to patients with normal potassium levels. Multifractional

Table 1
Baseline characteristics (PROTECT)

Variable	Serum Potassium (mEq/L)			p- value
	3.0-3.4 (n=115)	3.5-5.0 (n=1576)	>5.0 (n=176)	
Potassium levels at admission (mEq/L)	3.3 (3.2, 3.4)	4.2 (3.9, 4.5)	5.3 (5.2, 5.7)	NA
Treatment allocation (% rolofylline)	76 (66%)	1051 (67%)	119 (68%)	0.959
Age (Years)	69 ± 11	70 ± 12	69 ± 10	0.310
Men	74 (64%)	1055 (66%)	117 (67%)	0.850
Left ventricular ejection fraction	30 (20, 45)	30 (22, 40)	29 (20, 40)	0.910
Heart failure with a preserved ejection fraction	10 (18%)	113 (15%)	11 (13%)	0.740
NYHA class				0.660
I/II	23 (21%)	267 (18%)	26 (15%)	
III	54 (50%)	763 (51%)	84 (49%)	
IV	32 (29%)	463 (31%)	60 (35%)	
Body mass index (kg/m2)	29 ± 7	29 ± 6	29 ± 6	0.930
Systolic blood pressure (mmHg)	125 ± 19	124 ± 18	124 ± 17	0.880
Diastolic blood pressure (mmHg)	74 ± 12	74 ± 12	74 ± 12	0.990
Coronary Heart Disease	86 (75%)	1083 (69%)	126 (72%)	0.330
Hypertension	82 (71%)	1260 (80%)	138 (78%)	0.084
Diabetes mellitus	51 (44%)	697 (44%)	97 (55%)	**0.023**
Atrial Fibrillation	66 (57%)	859 (55%)	83 (47%)	0.130
Chronic obstructive pulmonary disease	31 (27%)	301 (19%)	37 (21%)	0.120
Potassium day 7 (mEq/L)	4.1 (3.8, 4.4)	4.5 (4.1, 4.9)	4.9 (4.4, 5.2)	**<0.001**
Creatinine (mg/dL)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.7 (1.3, 2.2)	**<0.001**
eGFR (mL/min/1.73m^2)	48 ± 17	46 ± 20	37 ± 17	**<0.001**
BUN (mg/dL)	26 (20, 36)	29 (22, 40)	38 (28, 50)	**<0.001**
Sodium (mEq/L)	141 (138, 143)	140 (137, 142)	143 (142, 141)	**<0.001**
BNP (pg/mL)	495 (267, 885)	456 (258, 805)	426 (233, 826)	0.678
Orthopnea	94 (83%)	1311 (84%)	147 (85%)	0.950
Rales	13 (11%)	150 (10%)	19 (11%)	0.740
Edema	39 (34%)	414 (26%)	53 (30%)	0.130
Increased jugular venous pressure	42 (40%)	568 (40%)	69 (46%)	0.350
Prior medication use				
ACE-inhibitors	57 (50%)	967 (64%)	128 (73%)	**<0.001**
Angiotensin receptor blocker	21 (18%)	254 (16%)	16 (9%)	**0.037**
Beta-blockers	86 (75%)	1212 (77%)	133 (76%)	0.810
Calcium-channel blockers	15 (13%)	210 (13%)	28 (16%)	0.630
Digoxin	35 (30%)	444 (28%)	48 (27%)	0.840
Mineralocorticoid receptor antagonist	43 (37%)	672 (43%)	104 (59%)	**<0.001**

p-values below the significance threshold of 0.05 are indicated in bold.

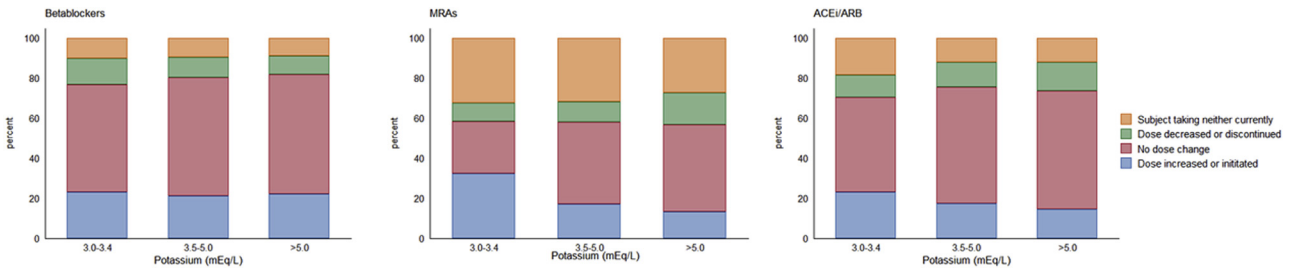

Figure 1. Stacked bar graphs showing changes in medication dosage for ACE inhibitors/angiotensin II receptor blockers (ARB), β blockers, and aldosterone receptor blockers stratified according to low (3.0 to 3.4), normal (3.5 to 5.0), and high potassium (>5.0) in PROTECT. p Value for difference is 0.942 for β blockers, 0.183 for ACEi/ARB, and <0.001 for aldosterone receptor blockers.

polynomials showed that the relation between serum potassium levels and outcome was linear. Serum potassium levels at admission showed a univariably significant association with 180-day all-cause mortality in PROTECT (Figure 3, Table 3). When corrected for age and gender, predictive power was maintained. When adding eGFR to the model, predictive power was lost. When correcting for the variables included in the PROTECT risk engine, serum potassium was not a significant predictor of mortality.

A change in serum potassium levels (defined as the difference between admission and discharge or day 7, whichever came first) was associated with mortality, but not after multivariate analysis. Potassium levels at discharge or day 7 were not associated with all-cause mortality (Table 3).

Table 2
Treatment and clinical outcomes (PROTECT)

Variable	Serum Potassium (mEq/L)			p-value
	3.0-3.4(n=115)	3.5-5.0 (n=1576)	>5.0 (n=176)	
Change of weight from day 1-4 weight loss (kg)	-2.1 (-4, -.9)	-2.2 (-4.1, -1)	-2.7 (-4.4, -1.4)	0.170
IV loop diuretics total dose (mg)				
Day 1	100 (60, 175)	80 (40, 140)	80 (40, 120)	**0.013**
Day 7	110 (60, 165)	100 (60, 200)	120 (60, 160)	0.950
Average daily IV dose day1-day7	51 (23, 97)	37 (17, 79)	40.0 (20, 73)	**0.035**
Oral loop diuretics dose (mg)				
Day 1	80 (40, 120)	40 (40, 80)	40 (40, 80)	**0.006**
Day 7	80 (40, 120)	60 (40, 80)	40 (40, 80)	**0.001**
Total diuretic dose (mg)				
Day 1	120 (60, 180)	80 (60, 160)	80 (51, 140)	**0.014**
Day 7	40 (20, 80)	40 (20, 7)	35 (20, 61)	**0.030**
Weight loss per 40mg furosemide (kg)	-.34 (-.71, -.10)	-.38 (-.80, -.13)	-.48 (-.98, -.21)	**0.005**
Trichotomous outcome				0.800
Failure	28 (24%)	346 (22%)	41 (23%)	
Unchanged	43 (37%)	588 (37%)	71 (40%)	
Success	44 (38%)	642 (41%)	64 (36%)	
Persistent renal impairment	24 (21%)	220 (14%)	30 (17%)	0.083
Worsening of heart failure	11 (10%)	178 (11%)	20 (11%)	0.406
Death	3 (2.6%)	24 (1.5%)	8 (4.6%)	**0.016**
Increase in creatinine	19 (17%)	192 (12%)	21 (12%)	0.346
Failure hemofiltration	2 (1.7%)	8 (0.5%)	2 (1.1%)	0.308
Death; cardiovascular; renal rehospitalization at 60 days	33 (29%)	456 (29%)	50 (28.4%)	0.990
Death; heart failure rehospitalization at 60 days	27 (24%)	340 (22%)	41 (23.3%)	0.793
Death; rehospitalization at 60 days	37 (32%)	538 (34%)	55 (31.3%)	0.700

p-values below the significance threshold of 0.05 are indicated in bold.

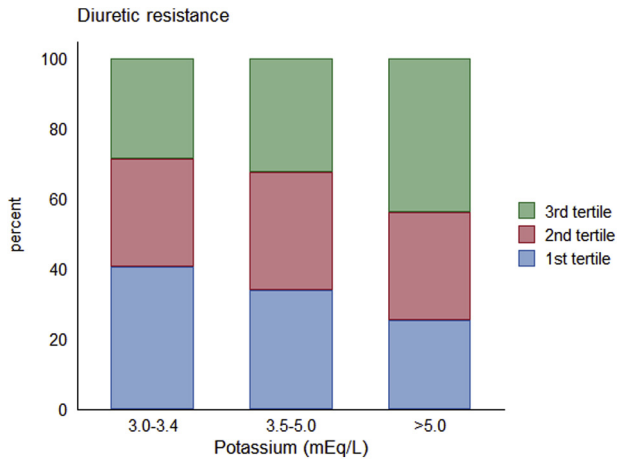

Figure 2. Stacked bar graphs showing tertiles of diuretic response according to low (3.0 to 3.4), normal (3.5 to 5.0), and high potassium (>5.0) in PROTECT. p Value for trend is 0.002.

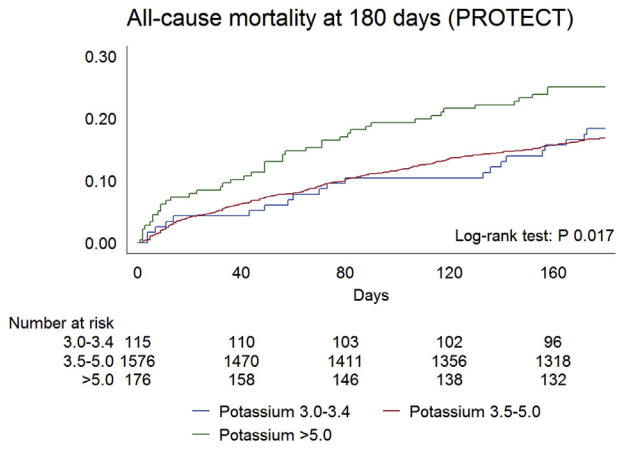

Figure 3. Kaplan–Meier curves stratified according to low (3.0 to 3.4), normal (3.5 to 5.0), and high potassium (>5.0) in PROTECT.

When looking at differential predictive value in subgroups, no significant interactions were found for age, gender, eGFR, a history of myocardial infarction, diabetes, hypertension, atrial fibrillation, or HF status (Supplementary Figure 1, available online). In the COACH cohort, 67 patients (6.7%) had hypokalemia (<3.5 mEq/l), and 33 patients (3.3%) had hyperkalemia (>5.5 mEq/l) at baseline. Serum potassium was associated with 3-year all-cause mortality in univariate analysis (Figure 4, Table 3) even when corrected for age and gender. After adjusting for eGFR, potassium was no longer associated with clinical outcome, as well as when adjustment was performed for the variables included in the COACH risk engine. Change of potassium levels between admission and discharge was not associated with outcome. Potassium levels at discharge were significantly associated with outcome in univariate analysis. However, significance was lost in multivariate analysis (Table 3).

Discussion

In the present study, we evaluated serum potassium levels and their association with outcome in a heterogeneous

Table 3
Cox regression

	PROTECT (HR; 95%CI; p-value)	COACH (HR; 95%CI; p-value)
Admission		
Univariable	2.36 (1.07-5.23) **0.034**	3.57 (1.84-6.93) **<0.001**
Model 1	2.54 (1.13-5.70) **0.023**	2.99 (1.52-5.86) **0.002**
Model 2	1.63 (0.72-3.67) 0.237	1.58 (0.80-3.10) 0.186
Model 3	1.36 (0.61-3.07) 0.453	1.35 (0.49-3.72) 0.563
Change*		
Univariable	0.82 (0.68-0.98) **0.028**	0.89 (0.78-1.03) 0.118
Model 1	0.83 (0.69-0.99) **0.041**	0.92 (0.80-1.06) 0.263
Model 2	0.87 (0.73-1.05) 0.156	0.90 (0.79-1.04) 0.148
Model 3	0.98 (0.82-1.17) 0.815	0.89 (0.71-1.12) 0.313
Discharge†		
Univariable	0.74 (0.30-1.81) 0.503	**2.50 (1.10-5.66) 0.028**
Model 1	0.84 (0.34-2.12) 0.724	**2.40 (1.07-5.41) 0.034**
Model 2	0.79 (0.32-1.98) 0.617	1.29 (0.57-2.94) 0.537
Model 3	1.02 (0.41-2.54) 0.960	0.63 (0.18-2.25) 0.480

Model 1: corrected for age and sex, Model 2: corrected for age, sex and eGFR, Model 3: corrected for the PROTECT 8-variable risk model in PROTECT and the COACH risk model in COACH.

p-values below the significance threshold of 0.05 are indicated in bold.

* Between admission and day of discharge in COACH, between admission and day 7 or day of discharge if day of discharge is before day 7 in PROTECT.

† Day of discharge in COACH, day 7 or day or day of discharge if day of discharge is before day 7 in PROTECT.

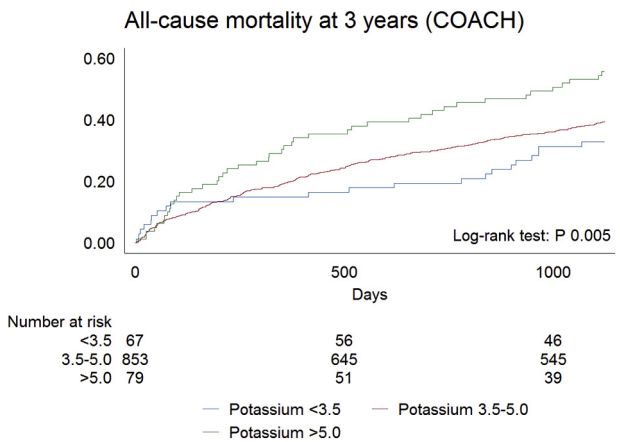

Figure 4. Kaplan−Meier curves stratified according to low (<3.5), normal (3.5 to 5.0), and high potassium (>5.0) in COACH.

population with AHF in 2 independent patient cohorts. In both cohorts, patients with higher serum potassium levels had worse outcomes; however, this association was not independent of established risk factors, in particular renal function. These results were confirmed in an unbiased and independent cohort.

Our study shows that overall potassium levels increase during hospitalization and that changes in potassium levels are common during hospitalization for AHF. However, with intensive diuretic treatment, one would expect overall potassium levels to reduce during hospitalization as potassium is excreted together with sodium by the transporter on which loop diuretics act.[8,17] In the Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan (EVEREST) study, a mild increase of potassium levels between admission and discharge was found in the overall population.[7] This can potentially be explained by the treatment choices that were based on potassium levels, in which patients with lower potassium would be less intensively treated with diuretics and given potassium supplementation. Interestingly, eGFR was lower in patients with a decrease in potassium levels between admission and discharge in the same cohort. Indeed, also in our study, eGFR was lower in patients with higher potassium levels. This can potentially be explained by that high potassium levels in this cohort reflect a worse renal function, a finding which has been described previously.[18,19]

Conversely, patients with higher serum potassium were found to have a better diuretic response in this cohort. One reason could be that diuretic response is not dependent on kidney function alone as suggested by earlier evidence.[20,21] Previous studies reported on the relation between potassium and diuretic response.[22,23] In the first study, an improved diuretic response was found in patients with higher levels of potassium at admission. In the second study, low potassium was one of the strongest predictors of a poor diuretic response in multivariate analysis. In addition, potassium supplementation was suggested to improve survival when given together with diuretic therapy.[24] Based on these findings, potassium might be a target for therapy to improve diuretic response through targeting patients with low potassium levels with supplementation. However, management choices confound these findings. Indeed, also in this cohort, patients with low levels of potassium were less often treated with ACE inhibition. This suggest that patients who are unable to be uptitrated to guideline-directed medication dosages due to either too high or too low potassium levels might have a worse diuretic response. However, no data are available on the interaction between guideline-directed treatment and diuretic response, and this would require further study.

So far, contradicting data concerning the predictive value of potassium in different HF populations have been published.[4] In chronic HF, a substudy from the Randomized Aldactone Evaluation Study trial found that an increase in potassium levels after spironolactone treatment was not associated with an increase in mortality.[25,26] Also, in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, hyperkalemia did not interfere with the survival benefit of the study drug.[27] In patients with acute HF with reduced ejection fraction, no independent predictive value of potassium was found, which is confirmed by this study for both patients with a reduced and preserved ejection fraction.[7] Of note, a positive univariate association was found in this study between potassium levels at admission and all-cause mortality. However, predictive value was attenuated when corrected for renal function in multivariate analysis. This suggests that potassium levels at admission and during hospitalization for AHF reflect clinical associations and do not have an independent effect on mortality.[9,28] Following, potassium levels at admission and changes during hospitalization can be considered to be a surrogate marker, reflecting clinical characteristics such as renal function and diabetes.[7]

This is a post hoc analysis of 2 randomized controlled trials, which could have induced selection bias. Furthermore, the PROTECT trial excluded patients with potassium levels <3.5 mEq/l, where patients with levels of potassium from 3.0 to 3.4 mEq/l were allowed if parental supplemental potassium was administered. However, no such limitations were present in COACH. Unfortunately, no information was available on potassium supplementation in both the PROTECT and COACH cohorts. However in a different study, no effect of potassium supplementation on all-cause mortality was found, suggesting that its effects as a confounder are limited.[29] In addition, no information was available on usage of thiazide diuretics. Furthermore, potassium levels at admission for AHF might inform treatment management decisions, influencing outcomes.

Disclosures

Dr. Cleland was on the Steering Committee for the PROTECT trial, served on the advisory board for MSD, and received payments for both. Dr. O'Connor is a consultant to Merck & Co., Inc. Dr. Ponikowski has received honoraria from Merck & Co., Inc. Drs. Davison and Cotter are employees of Momentum Research Inc., which was contracted to perform work on the project by Merck & Co., Inc. Dr. Metra has received honoraria and reimbursements from NovaCardia, sponsors of the study, and Merck & Co., Inc. Dr. Givertz has received institutional research support and served on a scientific advisory board for Merck & Co., Inc. Dr. Teerlink has received research funds and consulting fees from Merck & Co., Inc. Dr. Bloomfield is an employee of Merck & Co., Inc. Dr. Dittrich served as a consultant to Merck & Co., Inc. Dr. Voors has received speaker and consultancy fees from Merck & Co., Inc. All other authors have reported that they have no conflict of interest to declare.

Supplementary Data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.amjcard.2016.09.038.

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