Prognostic significance of serum potassium in patients hospitalized for acute heart failure

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Abstract

Aim We investigated the prognostic significance of serum potassium abnormalities at discharge in patients hospitalized for acute heart failure (AHF).

Methods and results In a retrospective analysis, we included 926 patients hospitalized for AHF, stratified by serum potassium levels at discharge as hypokalaemia (<3.5 mEq/L), normokalaemia (3.5–5.0 mEq/L), and hyperkalaemia (>5.0 mEq/L). The primary endpoint was all-cause death at 1 year since hospital discharge. At discharge, 40 patients had hypokalaemia (4.3%), 840 normokalaemia (90.7%), and 46 hyperkalaemia (5.0%). Patients with hyperkalaemia at discharge were more frequently men, had more signs of congestion, and lower LVEF while patients with hypokalaemia were more likely to be women with HFpEF. Treatment with ACEi/ARBs and MRAs ≥50% of target dose at discharge was similar across groups. One year all-cause death occurred in 10% of the patients with hypokalaemia, 13.9% of those with normokalaemia, and 30.4% of those with hyperkalaemia (P = 0.006). After adjustment for covariates, including renal function, background treatment, and baseline potassium level, hyperkalaemia resulted an independent predictor of the primary endpoint (HR 1.96, 95% IC [1.01–3.82]; P = 0.048).

Conclusions In patients with AHF, the presence of hyperkalaemia at discharge is an independent predictor of 1 year all-cause death.

Keywords Acute heart failure; Serum potassium; Hyperkalaemia; Outcomes

Introduction

Acute heart failure (AHF) is associated with high morbidity and mortality rates after discharge.1,2 Among predictors of outcomes, dyskalaemia is emerging as an important contributor.3–8 Several factors may contribute to dyskalaemia in patients with heart failure (HF), including treatment with diuretics, renin-angiotensin-aldosterone system (RAAs) inhibitors, potassium supplements, and co-morbidities, in particular renal dysfunction.9 In studies conducted in patients with chronic heart failure, the frequency of potassium disturbances is high, with hyperkalaemia which may be present in 15–20% of patients4,6 and hypokalaemia in about 20% of patients.10 On the contrary, the rate of hypokalaemia or hyperkalaemia at discharge for AHF seems to be lower, approaching 3.6% and 5.6%, respectively.11 The relationship between dyskalaemia and outcomes is still a matter of debate, and findings from previously published studies are somewhat conflicting, finding in some cases a U-shaped relationship between serum potassium disturbances and prognosis or failing to show a sustained prognostic significance in adjusted models.8,11,12

Another aspect that should be taken into account is the link between serum potassium and treatment prescription dosing. In fact, the use of target doses of RAAs inhibitors has been associated with better outcomes after discharge,
Despite only a minority of patients is able to tolerate doses >50% of target. In this context, hyperkalaemia represents one of the main reasons of not optimal dosing of these drugs with possible detrimental effects on patients’ outcomes.

The aim of this study is to evaluate the prognostic implications of dyskalaemia at discharge in patients hospitalized for AHF and its relationship with treatment prescription and dosing.

Methods

Study population

In this study, we included a retrospective cohort of 1021 patients hospitalized for AHF from 2003 to 2019 in the Cardiology Ward of Spedali Civili of Brescia, Italy. The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by local institutional board.

Inclusion criteria were signs and symptoms of AHF with the need of intravenous diuretic treatment and NYHA class III/IV at admission. Patients with the following characteristics were excluded: evidence at admission of acute coronary syndrome, cardiogenic shock and/or signs of hypoperfusion, HF due to significant arrhythmias, myocarditis, cardiac tamponade, aortic dissection, dyspnoea due to not cardiovascular causes; presence of valvular heart disease (including moderate to severe aortic or mitral valve stenosis, severe aortic regurgitation, severe primary mitral regurgitation), restrictive, hypertrophic or systemic illness-related cardiomyopathy.

Data regarding medical history were recorded at admission. Clinical congestion was evaluated at admission and at discharge and incorporated in a congestion score ranging from 0 (no congestion) to 3 points (high congestion) based on the presence or not (yes = 1 point, no = 0) of peripheral oedema, pulmonary rales, and jugular vein distension.

Laboratory tests were performed at admission and at discharge. NT-proBNP was measured at discharge using Elecsys assay (Roche Diagnostics, Inc., Monza-Milano, Italy). Estimated glomerular filtration rate (eGFR) was calculated with the simplified Modification of Diet in Renal Disease (MDRD) equation based on serum creatinine value. Echocardiography was performed during hospitalization according to international guidelines, and left ventricular ejection fraction (LVEF) was calculated using the Simpson’s biplane method.

Data regarding follow-up were collected from hospital records, telephone contact with the patient or family member, or with the general practitioner. The follow-up duration was from discharge to 1 year. The primary endpoint was all-cause death at 1 year. The secondary endpoints were HF rehospitalizations and the composite of all-cause death and HF hospitalization at 1 year. The adjudication of outcomes was performed by two independent investigators (V. C. and T. D.), and in case of discordance, the case was discussed within the study staff.

Statistical analysis

Data were presented stratified by serum potassium levels at discharge classified into three categories: hypokalaemia (<3.5 mEq/L), normokalaemia (3.5–5.0 mEq/L), and hyperkalaemia (>5.0 mEq/L). Continuous variables were shown as mean and standard deviation, skewed variables as median and interquartile range (IQR), and dichotomous variables as count and percentage. Comparisons between groups were made, respectively, using ANOVA test for means, Kruskal–Wallis test for medians, and χ² test (or Fisher’s exact test whenever appropriate) for proportions.

Survival was analysed by Kaplan–Meier method, and differences between serum potassium categories investigated by the log-rank test.

A multivariable Cox regression model was used to estimate the effect of serum potassium level on mortality adjusted for clinically relevant confounders including age, sex, systolic blood pressure, history of heart failure, haemoglobin, serum potassium level at baseline, estimated glomerular filtration rate, LVEF, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists. The hazard ratios (HRs), 95% confidence intervals (CIs), and P-values from a Wald test were reported. As sensitivity analysis, we also applied an automatic stepwise selection method considering general characteristics, medical history, laboratory findings during hospitalization and therapies at discharge, to identify the best possible combination of covariates to adjust for in our final model. We excluded variables with more than 20% of missing values and used a significance level of α = 0.05.

A two-tailed P-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Of a total of 1021 patients admitted for AHF, we excluded 28 deceased during index hospitalization and 67 for missing information regarding potassium levels at discharge, resulting in a study population of 926 patients (Figure 1). No relevant differences in clinically relevant confounders emerged between excluded and included subjects (Supporting Information Table S1). At admission, a total of 122 (13.2%) patients had hypokalaemia, 752 normokalaemia (81.2%), and 52 hyperkalaemia (5.6%). The mean change of serum potassium during the hospitalization was 0.1 ± 0.6 mEq/L. At discharge, 40 patients had hypokalaemia (4.3%), 840 normokalaemia
(90.7%), and 46 hyperkalaemia (5.0%). Distribution of blood potassium at discharge is shown in Figure 2. Mean potassium at discharge in the three groups was 3.3 ± 0.2 mEq/L, 4.2 ± 0.4 mEq/L, and 5.3 ± 0.2 mEq/L, respectively. Patients with hyperkalaemia at discharge were more frequently men and had a lower BMI compared with the others. No differences were recorded regarding vital signs. The presence of signs of congestion (evaluated as the proportion of patients with a congestion score ≥2) was numerically lower in hypokalaemia patients, whereas it was higher in hyperkalaemic group compared with patients with normal potassium levels at discharge (hypokalaemia 2.5% vs. normokalaemia 10.6% vs. hyperkalaemia 17.4%; P = 0.077). The median LVEF was markedly different across groups ranging from 37% (28.5–50) in hypokalaemia group to 33.5% (25–47.3) in normokalaemia and to 24% (20–35) in hyperkalaemia (P < 0.001). Medical history showed a significantly higher prevalence of HF and chronic kidney disease in hyperkalaemia group with rates of 87% and 58.7%, respectively. No significant differences were found regarding other cardiac and non-cardiac co-morbidities. Patients with hyperkalaemia at discharge had higher values of serum potassium at baseline compared with other groups (hypokalaemia 3.8 ± 0.6 mEq/L vs. normokalaemia 4.1 ± 0.6 mEq/L vs. hyperkalaemia 4.5 ± 0.8 mEq/L; P < 0.001). No other significant differences were observed in laboratory tests at discharge, except for higher value of aspartate transaminase (AST) in patients with hyperkalaemia. Kidney function tended to be more impaired in the patients with hyperkalaemia (Table 1).

Treatment with guideline directed therapy was better implemented in the hyperkalaemia group, with a high proportion of patients receiving ACEi/ARBs and MRAs at admission which was maintained and even slightly increased at discharge. In

Figure 1 Flow-diagram of the study population.

Legend: K: potassium, HF: heart failure.
hypokalaemic patients the rate of prescription of ACEi/ARBs and MRAs was quite low at admission but significantly increased at discharge, especially MRAs which passed from 45% to 77.5% of patients. No differences were found regarding treatment with diuretics both as cumulative dose in the first 24 h of hospitalization and as dose at discharge. To note patients with hyperkalaemia received more frequently low-dose dopamine during hospitalization (Table 2).

Figure 2 Distribution of the blood potassium at discharge in the study population.

Table 1 Demographic and clinical characteristics of the study population at discharge according to blood potassium levels: hypokalaemia (K+ < 3.5 mEq/L), normokalaemia (3.5 ≤ K+ ≤ 5.0 mEq/L), and hyperkalaemia (K+ > 5.0 mEq/L)

|                      | Hypokalaemia (N = 40) | Normokalaemia (N = 840) | Hyperkalaemia (N = 46) | P-value |
|----------------------|-----------------------|-------------------------|------------------------|---------|
| General characteristics |                       |                         |                        |         |
| Age (years)          | 73.4 ± 10.7           | 70.8 ± 11.4             | 69.1 ± 11.7            | 0.208   |
| Sex (male)           | 21 (52.5)             | 595 (70.8)              | 36 (78.3)              | 0.022   |
| Body mass index (kg/m²) | 25.7 ± 5.2          | 25.9 ± 5.0              | 23.4 ± 4.3             | 0.011   |
| Weight loss (kg)     | 3.2 ± 5.1             | 3.4 ± 4.0               | 3.5 ± 5.2              | 0.924   |
| Systolic blood pressure (mmHg) | 114 ± 16        | 115 ± 18                | 111 ± 14               | 0.417   |
| Heart rate (b.p.m.)  | 73 ± 15               | 69 ± 11                 | 69 ± 13                | 0.097   |
| Congestion score ≥ 2 | 1 (2.5)               | 89 (10.6)               | 8 (17.4)               | 0.077   |
| LVEF (%)             | 37.0 (28.5–50.0)      | 33.5 (25.0–47.3)        | 24.0 (20.0–35.0)       | <0.001  |
| HFrEF                | 20 (51.3)             | 521 (62.6)              | 37 (82.2)              | 0.009   |
| HFmrEF               | 7 (17.9)              | 113 (13.6)              | 3 (6.7)                | 0.291   |
| HFpEF                | 12 (30.8)             | 198 (23.8)              | 5 (11.1)               | 0.081   |
| Medical history      |                       |                         |                        |         |
| Heart failure        | 29 (72.5)             | 576 (68.6)              | 40 (87.0)              | 0.028   |
| Diabetes             | 18 (45.0)             | 292 (34.8)              | 12 (26.1)              | 0.185   |
| Atrial fibrillation  | 18 (45.0)             | 375 (44.6)              | 21 (45.7)              | 0.990   |
| Hypertension         | 30 (75.0)             | 505 (60.1)              | 24 (52.2)              | 0.087   |
| Ischaemic heart disease | 13 (32.5)           | 310 (36.9)              | 16 (34.8)              | 0.823   |
| Chronic obstructive pulmonary disease | 6 (15.0)   | 182 (21.7)              | 12 (26.1)              | 0.454   |
| Chronic kidney disease (eGFR < 60 mL/min/1.73 m²) | 14 (35.0) | 328 (39.0)              | 27 (58.7)              | 0.024   |
| Laboratory           |                       |                         |                        |         |
| Baseline serum potassium (mEq/L) | 3.8 ± 0.6   | 4.1 ± 0.6               | 4.5 ± 0.8              | <0.001  |
| Haemoglobin (g/dL)   | 11.5 ± 1.7            | 11.8 ± 1.8              | 11.9 ± 2.1             | 0.511   |
| Serum creatinine (mg/dL) | 1.1–1.7      | 1.1–1.9                 | 1.6 (1.2–2.1)          | 0.072   |
| eGFR (mL/min/1.73 m²) | 47 (32–71)         | 49 (35–68)              | 44 (27–60)             | 0.203   |
| Bilirubin (mg/dL)    | 0.9 ± 0.5             | 0.8 ± 0.6               | 0.9 ± 0.5              | 0.999   |
| Serum sodium (mEq/L) | 140 ± 5             | 139 ± 4                 | 140 ± 4                | 0.442   |
| Aspartate transaminase (U/L) | 25 (17–28)  | 23 (18–32)              | 29 (22–40)             | 0.030   |
| Alanine transaminase (U/L) | 30 (19–35)  | 32 (23–44)              | 38 (29–50)             | 0.117   |

N = 926 with non-missing information. Data shown as mean ± standard deviation, median (IQR), or count (%).

eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with midrange ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.
The length of stay in hospital was similar across groups. One year all-cause mortality was significantly higher in patients with hyperkalaemia (hypokalaemia 10% vs. normokalaemia 13.9% vs. hyperkalaemia 30.4%; \( P = 0.006 \)) (Table 3, Figure 3). On the contrary, no significant differences were found regarding the composite endpoint of all-cause death and HF hospitalization at 1 year (Table 3, Figure 4). Similar results were also obtained using only CV deaths in the composite endpoint and censoring subjects who died for other causes. At unadjusted Cox regression analysis, only the presence of hyperkalaemia at discharge was associated with mortality while hypokalaemia was not significant. In the adjusted model including LVEF, renal function, treatment with ACEi/ARBs and MRAs, and baseline potassium level, hyperkalaemia resulted an independent predictor of 1 year mortality (HR 1.96, 95% IC [1.01–3.82]; \( P = 0.048 \)) (Table 4). The covariates selected by the stepwise selection among a set of 27 were age, systolic blood pressure, eGFR, treatment with ACEi/ARBs at discharge, and heart rate. The adjusted effect of hyperkalaemia on the risk of 1 year mortality was similar (HR 2.08, 95% IC [1.04–4.17]; \( P = 0.039 \)).

**Discussion**

The present study showed that frequency of potassium disturbances at discharge in patients with AHF is relatively low; however, the presence of hyperkalaemia is associated with a significative worse prognosis with a higher all-cause mortality. The present study showed that frequency of potassium disturbances at discharge in patients with AHF is relatively low; however, the presence of hyperkalaemia is associated with a significative worse prognosis with a higher all-cause mortality. The present study showed that frequency of potassium disturbances at discharge in patients with AHF is relatively low; however, the presence of hyperkalaemia is associated with a significative worse prognosis with a higher all-cause mortality.

### Table 2 Medical therapy before hospitalization, during hospitalization and after discharge according to blood potassium levels: hypokalaemia (K+ < 3.5 mEq/L), normokalaemia (3.5 ≤ K+ ≤ 5.0 mEq/L), and hyperkalaemia (K+ > 5.0 mEq/L)

| Therapy before hospitalization | Hypokalaemia (N = 40) | Normokalaemia (N = 840) | Hyperkalaemia (N = 46) | \( P \)-value |
|------------------------------|-----------------------|-------------------------|-----------------------|------------|
| ACEi/ARBs                    | 40                    | 20 (50.0)               | 840                   | 560 (66.7) | 46 38 (82.6) | 0.006 |
| \( \geq 50\% \) target dose ACEi/ARBs | 19                    | 13 (68.4)               | 515                   | 311 (60.4) | 24 24 (68.6) | 0.507 |
| MRAs                         | 40                    | 18 (45.0)               | 840                   | 376 (44.8) | 46 33 (71.7) | 0.002 |
| \( \geq 50\% \) target dose MRAs | 18                    | 15 (83.3)               | 376                   | 343 (91.2) | 33 33 (100.0) | 0.050 |
| Beta-blockers                | 40                    | 26 (65.0)               | 840                   | 517 (61.5) | 46 34 (73.9) | 0.227 |
| Furosemide                   | 40                    | 35 (87.5)               | 840                   | 703 (83.7) | 46 42 (91.3) | 0.326 |
| Furosemide dose (mg)         | 32                    | 75 (48–175)             | 601                   | 50 (25–125) | 41 75 (50–150) | 0.126 |

| Therapy during hospitalization | Furosemide 24 h dose (mg) | Hypokalaemia (N = 40) | Normokalaemia (N = 840) | Hyperkalaemia (N = 46) | \( P \)-value |
|-------------------------------|---------------------------|-----------------------|-------------------------|-----------------------|------------|
| 40                            | 203 (60–426)              | 823                   | 165 (60–375)            | 46 220 (85–488) | 0.626 |
| Nitrets                       | 40                        | 7 (17.5)              | 840                   | 251 (29.9) | 46 10 (21.7) | 0.131 |
| Low-dose dopamine             | 40                        | 2 (5.0)               | 840                   | 116 (13.8) | 46 15 (32.6) | <0.001 |
| Inotropes                     | 40                        | 4 (10.0)              | 840                   | 62 (7.4) | 46 4 (8.7) | 0.674 |

| Therapy at discharge          | ACEi/ARBs                | 40                    | 23 (57.5)               | 840                   | 626 (74.5) | 46 40 (87.0) | 0.007 |
|                               | \( \geq 50\% \) target dose ACEi/ARBs | 19                    | 13 (68.4)               | 575                   | 327 (56.9) | 37 23 (62.2) | 0.509 |
|                               | MRAse                    | 40                    | 31 (77.5)               | 840                   | 564 (67.1) | 36 34 (97.2) | 0.685 |
|                               | \( \geq 50\% \) target dose MRAs | 31                    | 29 (93.6)               | 840                   | 522 (92.6) | 36 35 (97.2) | 0.822 |
|                               | Beta-blockers            | 40                    | 31 (77.5)               | 840                   | 668 (79.5) | 46 35 (76.1) | 0.822 |
|                               | Furosemide               | 40                    | 39 (97.5)               | 840                   | 800 (95.2) | 46 46 (100.0) | 0.392 |
|                               | Furosemide dose (mg)     | 39                    | 75 (50–230)             | 800                   | 75 (50–230) | 46 100 (50–175) | 0.243 |

Data shown as median (IQR) or count (%).

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

### Table 3 Hospital length of stay and outcomes according to blood potassium levels: hypokalaemia (K + <3.5 mEq/L), normokalaemia (3.5 ≤ K+ ≤5.0 mEq/L), and hyperkalaemia (K+ > 5.0 mEq/L)

| Hospital length of stay (days) | Hypokalaemia (N = 40) | Normokalaemia (N = 840) | Hyperkalaemia (N = 46) | \( P \)-value |
|-------------------------------|-----------------------|-------------------------|-----------------------|------------|
| \( 1 \) year death (%)        | 40                    | 10 (5–15)               | 840                   | 10 (6–15) | 46 12 (7–22) | 0.173 |
| CV death                      | 40                    | 3 (2.5)                 | 840                   | 103 (91.4) | 46 14 (41.1) | 0.006 |
| Non-CV death                  | 40                    | 1 (6.7)                 | 840                   | 14 (93.3) | 46 0 (0) | 0.091 |
| 1 year hospitalization for HF (%) | 40                    | 18 (45.0)               | 840                   | 278 (33.1) | 46 20 (43.5) | 0.117 |
| 1 year death or hospitalization for HF (%) | 40                    | 18 (45.0)               | 840                   | 327 (38.9) | 46 24 (52.2) | 0.161 |

Data shown as median (IQR) or count (%).

CV, cardiovascular; HF, heart failure.

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mortality at 1 year. In addition, we did not observe a lower prescription of ACEi/ARBs and/or MRA in hyperkalaemic patients further confirming the independent detrimental effect on outcomes of hyperkalaemia.

Serum potassium disturbances are an expected complication during the treatment of both acute and chronic heart failure and may be related to several factors including co-morbidities and treatment. Despite the frequency of potassium imbalance may reach high rates in chronic heart failure patients where hypo- and hyperkalaemia may be present in up to 20% of patients, the frequency of patients presenting abnormal levels of serum potassium at discharge is limited in the acute setting, with reported data of about 4–7% for hypokalaemia and 5–9% for hyperkalaemia. In this study, a total of 18.8% of patients had potassium abnormalities at admission, but at discharge, most patients had potassium levels in normal range with a total of 9.3% patients with hypokalaemia or hyperkalaemia (4.3% and 5.0%, respectively). Considering that all the patients received intravenous furosemide for the treatment of AHF, a reduction of serum potassium would be expected in this setting. However, we found only a slight average increase of potassium during the hospitalization as previously reported in other studies. Khan et al. have related this increase to the prescription of ACEi/ARBs and MRA during the hospital course. In fact, as we observed, there were no significant differences in the prescription of such drugs, and the adherence was incremented also in hyperkalaemic patients.

Our findings showed a clearly different clinical profile in patients with hypokalaemia or hyperkalaemia. Indeed, in the group of patients with hypokalaemia, we observed a significant higher proportion of women.
reported in other studies,\textsuperscript{5,7,17} and in particular Beusekamp\textit{et al.} in a model of logistic regression have identified the female gender as one of the factors associated with hypokalaemia.\textsuperscript{5} There was also a significant different stratification of patients according to LVEF. Although the majority of patients in our study cohort had HfREF, there was a higher proportion of patients with HFpEF in hypokalaemia group whereas more than 80% of patients had HfREF in hyperkalaemia group. This clearly affected the prescription of drugs as ACEI/ARBs and MRA which was lower in hypokalaemia group, even if an effective implementation was observed during the hospitalization. Patients with hyperkalaemia at discharge showed a markedly increased risk at baseline, with a significantly lower LVEF, more signs of congestion, and history of previous hospitalization for heart failure and chronic kidney disease. Despite a lower prescription of RAAs inhibitors could be expected in this group, our study showed higher prescription rates compared to patients with low or normal serum potassium levels, likely because most of patients included in this group had discharge potassium values between 5–5.5 mEq/L with only four cases of patients with higher potassium (values range 5.5–5.8 mEq/L).

There are multiple mechanisms underlying the development of potassium disturbances in AHF.\textsuperscript{5} Intense diuretic treatment is frequently associated with reduction in potassium levels. On the other hand, worsening renal function, even transitory due to underfilling status, leads to significant decrease of glomerular filtration rate which in turn might result in increased potassium levels. Pre-existing renal dysfunction is a possible determinant of the direction of potassium levels oscillation during AHF treatment. In addition, hyperkalaemia is one of most common cause of no or low dose prescription of ACEI/ARBs and/or MRA,\textsuperscript{18,19} drugs with well-known beneficial effects on outcomes also in the acute setting as being demonstrated in several recent studies,\textsuperscript{13,20} although, as stated previously, we did non observe a lower prescription of ACEI/ARBs or MRA in patients with hyperkalaemia.

Table 4  Univariable and multivariable Cox regression models for 1 year mortality

| Potassium at discharge | Univariable | Multivariable |
|------------------------|-------------|--------------|
| Hyperkalaemia vs. normokalaemia | 2.38 (1.37–4.14) | 1.96 (1.01–3.82) |
| Hypokalaemia vs. normokalaemia | 1.14 (1.05–1.25) | 1.12 (1.01–1.25) |
| Age (years) | 0.72 (0.27–1.95) | 0.71 (0.26–1.97) |
| Sex | 0.002 | 0.001 |
| Systolic blood pressure (mmHg) | 0.002 | 0.001 |
| LVEF (%) | 0.09 (0.97–1.00) | 0.99 (0.97–1.00) |
| Heart failure | 2.15 (1.37–3.36) | 1.65 (1.02–2.66) |
| Baseline serum potassium (mEq/L) | 1.23 (0.93–1.63) | 0.99 (0.74–1.33) |
| Haemoglobin (g/dL) | 0.86 (0.77–0.95) | 0.95 (0.85–1.07) |
| eGFR (mL/min/1.73 m\(^3\)) | 0.79 (0.73–0.86) | 0.88 (0.79–0.97) |
| ACEI/ARBs at discharge | 0.46 (0.33–0.65) | 0.54 (0.36–0.81) |
| MRAs at discharge | 0.85 (0.6–1.21) | 0.76 (0.50–1.14) |

ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists.

Several recent studies have reported a U-shaped relationship between potassium disturbances and prognosis.\textsuperscript{5,11} Our study failed to demonstrate a link between hypokalaemia and all-cause mortality at 1 year. It may be possible that patients discharged with hypokalaemia were prescribed with potassium supplements and as demonstrated in literature the negative prognostic effect of this condition disappears when hypokalaemia is corrected.\textsuperscript{5,11}

Our analysis underscores the importance of monitoring serum potassium levels in patients with AHF and the need to promptly address hypokalaemia and hyperkalaemia as a therapeutic goal in this condition. To date, there is no clear indication regarding the management of hypokalaemia due to the lack of \textit{ad hoc} trials. On the contrary, new therapeutic options have recently become available for patients with hyperkalaemia. Patiromer and sodium zirconium cyclosilicate are potassium binders which can increase its gastrointestinal secretion.\textsuperscript{21–25} Both drugs are currently approved for the clinical use in Europe and USA for their effectiveness in reducing serum potassium in patients with HF treated with RAAs inhibitors and the Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND) trial is recruiting patients to assess the efficacy of patiromer to reduce the time to cardiovascular mortality and hospitalization and the proportion of subjects on ≥50% of guideline-recommended target dose of RAAs inhibitors (NCT03888066). Unfortunately, a similar trial, the Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure (PRIORITIZE HF) (NCT03532009), has been prematurely stopped due to the SARS-CoV2 pandemic.

**Limitation**

Our study has some limitations to be disclosed. This is an observational study that can identify associations but not prove any cause/effect relationships; residual confounding
unmeasured variables may be present. In addition, this is a single-centre analysis based on a relatively small sample size, and thus, generalizability of the results is limited, although the monocentric design has the advantage to warrant a more standard approach to the decision-making process regarding therapeutic management.

The present work was based on a single serum potassium measurement at the time of discharge, and no data are available regarding possible changes over time. However, the aim of the study was to identify patients who are at higher risk of events after discharge and may benefit of the introduction of potassium binders. Similarly, we did not collect information regarding therapy modification during follow-up.

In our study, we did not recognize a significant prognostic effect of hypokalaemia, despite this was reported in several other studies. As above mentioned, patients with hypokalaemia are usually discharged on potassium supplements, and the correction of hypokalaemia is demonstrated to be associated with a prognosis similar to those with normal potassium levels at the time of discharge. However, data regarding the prescription of potassium supplements were not routinely collected, and this may be a reason of the lack of prognostic significance of hypokalaemia in our study. On the other hand, we reported that patients who had hyperkalaemia at discharge received more frequently treatments with RAAs inhibitors although a lower use could be expected. To note, as shown in Figure 2, a large majority of patients with hyperkalaemia had values between 5–5.5 mEq/L with only four patients with severe hyperkalaemia at discharge.

Our study numerosity in hypokalaemia and hyperkalaemia groups was too small to draw meaningful conclusion about sub-groups analysis. In particular, a comparison between patients with reduced or mid-range LVEF versus preserved LVEF would be of great interest. To note, an interaction between the LVEF groups and kalaemia categories was conducted showing no significant differences in terms of all-cause mortality in these categories (heterogeneity test P-value = 0.934). However, as stated earlier, our study only shows an absence of interaction in this dataset, and a definitive conclusion should be tested in larger cohorts.

Finally, we considered as endpoint all-cause mortality. We did not analyse specific cause of mortality including sudden cardiac death due to the limited sample size especially in hypokalaemia and hyperkalaemia that would prevent to draw solid conclusions.

Conclusion

In patients discharged for AHF, the presence of hyperkalaemia is associated with a higher risk profile including lower LVEF. To date, in our study, no difference in prescription and dosing of RAAs inhibitors at discharge was observed in patients with serum potassium disturbances. The presence of hyperkalaemia resulted independently associated with 1 year all-cause death, while hypokalaemia was not associated with worse outcomes. Further studies are needed to ascertain if patients with hyperkalaemia may benefit from treatment with novel potassium binders to improve adherence to background treatment and long-term outcomes.

Conflict of interest

V.C. received consulting honoraria from CVie Therapeutics Limited and Windtree Therapeutics. M.M. reports personal consulting honoraria from Bayer, Novartis, Fresenius, Servier, and Windtree. Therapeutics for participation to advisory board meetings and executive committees of clinical trials. All other authors declare no conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison between the 67 patients excluded due to missing potassium values at discharge and the 926 patients included in the analysis.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 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 of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18: 991–975.

2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel
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3. Ferreira JP, Claggett BL, Liu J, Desai AS, McMurray JJV, Mebazaa A, Mindham D, Gardner RS, Gilard M, Heymans S, Savarese G, DeVore AD, Carrero JJ, Dahlström U, Anker SD, Lainscak M, Hernandez AF, Pitt B, Lund LH. Association between potassium level and outcomes in heart failure with reduced ejection fraction: a cohort study from the Swedish Heart Failure Registry. Eur J Heart Fail. 2020; 22: 1390–1398.

9. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Dahlström U, Hendriksen JH, Bakris GL, Weir MR, Zannad F. Abnormalities of Potassium in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75: 2836–2850.

12. Hoss S, Elizur Y, Luria D, Keren A, Lotan R, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro M, Park JJ, Ishihara S, AlHabib KF, Maggioni AP, Anker SD, Dahlström U, Filippatos G, van der Harst P, Hillege HH, Anker SD, Kosiborod M, Lund LH, Voors AA, van der Meer P. Potassium and the use of renin-angiotensin-aldosterone system mineralocorticoid receptor antagonists. Changes in serum potassium levels during hospitalization of patients with worsening heart failure and reduced ejection fraction (from the EVEREST trial). Am J Cardiol. 2015; 115: 790–796.

17. GREAT (Global Research on Acute Conditions Team) Network and INI-CRCT (Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists) network, Legrand M, Ludes PO, Massy Z, Rossignol P, Pareja N, Park JJ, Ishihara S, AlHabib KF, Maggioni A, Miro O, Sato N, Cohen-Solal A, Fairman E, Lassus J, Harjopila VP, Mueller C, Peacock FW, Choi DJ, Plaisance P, Spinari J, Josiporod M, Mebazaa A, Gayet E. Association between hypo- and hyperkalemia and outcome in acute heart failure patients: the role of medications. Clin Res Cardiol. 2018; 107: 214–221.

CHF. Eur J Heart Fail. 2018; 20: 923–930.

15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer FT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography, Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2015; 18: 1440–1463.

ESC Heart Failure 2022; 9: 2357–2366
DOI: 10.1002/ehf2.13925
20. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, Spinar J, Müller C, Harjola VP, Lassus J, Miró Ò, Maggioni AP, AlHabib KF, Choi DJ, Park JJ, Zhang Y, Zhang J, Januzzi JL Jr, Kajimoto K, Cohen-Solal A, Mebazaa A, on behalf of the GREAT Network. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. *Eur J Heart Fail*. 2018; 20: 345–354.

21. Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia: current data and opportunities for the future. *Hypertension*. 2015; 66: 731–738.

22. Zannad F, Rossignol P, Stough WG, Epstein M, Alonso Garcia MA, Bakris GL, Butler J, Kosiborod M, Berman L, Mebazaa A, Rasmussen HS, Ruilope LM, Stockbridge N, Thompson A, Wittes J, Pitt B. New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: Considerations for trial design and regulatory approval. *Int J Cardiol*. 2016; 216: 46–51.

23. Pitt B, Rossignol P. Potassium lowering agents: Recommendations for physician and patient education, treatment reappraisal, and serial monitoring of potassium in patients with chronic hyperkalemia. *Pharmacol Res*. 2017; 118: 2–4.

24. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, on behalf of the PEARL-HF Investigators. 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: 820–828.

25. Anker SD, Kosiborod M, Zannad F, Piña IL, McCullough PA, Filippatos G, van der Meer P, Ponikowski P, Rasmussen HS, Lavin PT, Singh B, Yang A, Deedwania P. 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: 1050–1056.