Potassium and the use of RAAS inhibitors in Heart Failure with reduced ejection fraction: data from BIOSTAT-CHF

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Abstract

Background: Hyperkalemia is a common comorbidity in patients with heart failure with reduced ejection fraction (HFrEF). Whether it affects the use of RAAS-inhibitors and thereby negatively impacts outcome is unknown. Therefore, we investigated the association between potassium and uptitration of ACE-inhibitor/ARB and its association with outcome.

Methods and results: Out of 2,516 patients from the BIOSTAT-CHF study, potassium levels were available in 1,666 patients with HFrEF. These patients were sub-optimally treated with ACEi/ARB or beta-blockers and were anticipated and encouraged to be uptitrated. Potassium levels were available at inclusion and 9 months. Outcome was a composite of all-cause mortality and HF-hospitalization at 2 years.

Patients were 67±12 years old and 77% was male. At baseline, median serum potassium was 4.2(3.9–4.6) mEq/L. After 9 months, 401 (24.1%) patients were successfully uptitrated with ACEi/ARB. During this period, mean serum potassium increased by 0.16±0.66 mEq/L ($p<0.001$). Baseline potassium was an independent predictor of lower ACEi/ARB dosage achieved (OR 0.70; 95%CI 0.51–0.98). An increase in potassium was not associated with adverse outcomes (HR 1.15; 95%CI 0.86–1.53). No interaction on outcome was found between baseline potassium, potassium increase during uptitration, or potassium at 9 months and increased dosage of ACEi/ARB ($p_{interaction}$ >0.5 for all).

Conclusion: Higher potassium levels are an independent predictor of enduring lower dosages of ACEi/ARB. Higher potassium levels do not attenuate the beneficial effects of ACEi/ARB uptitration.

Keywords*:*

75 Hyperkalemia, guideline-directed medication, heart failure, RAASi, outcome

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List of abbreviations:

ACEi – Angiotensin-Converting Enzyme-Inhibitors

ARBs – Angiotensin Receptor Blockers

BNP – Brain Natriuretic Peptide

COPD – Chronic Obstructive Pulmonary Disease

CRP – C-Reactive Protein

eGFR – estimated Glomerular Filtration Rate

HF – Heart Failure

HFrEF – Heart Failure with reduced Ejection Fraction

LVEF – Left Ventricular Ejection Fraction

MRA – Mineralocorticoid Receptor Antagonist

NT-proBNP – N-terminal prohormone of Brain Natriuretic Peptide

RAASi – Renin Angiotensin Aldosterone System-Inhibitors

Introduction

Heart failure (HF) is associated with high mortality and morbidity (1). Current treatment possibilities for HF patients with a reduced ejection fraction (HFrEF) include ACE-inhibition (ACEi), angiotensin-receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and beta-blockers. These treatments have shown to improve outcomes for patients with HFrEF (2-5). Unfortunately, administration of recommended doses of guideline directed medication is not often achieved (6,7).

In the general population, hyperkalemia is common and may negatively impact administration of adequate dosages of ACEi and ARB (8). Unfortunately, knowledge on this association in patients with HF is absent. Additionally, hyperkalemia is associated with worse outcomes and potassium levels are therefore closely monitored during increase of the doses of inhibitors of the RAAS system in clinical trials (9-12). Both hyperkalemia as well as the effect of hyperkalemia on tolerating higher doses of RAAS inhibitors can severely impede outcomes and interfere with their survival benefit (8,13).

Currently, no data is available on the independent association of potassium levels (or potassium change during treatment) and the achieved dose of ACEi/ARB. Additionally, limited data is available on the interaction between ACEi/ARB and the association between hyperkalemia and clinical outcome in patients with HFrEF (14). Therefore, we studied the association between serum potassium levels and successful uptitration of ACEi/ARB to HF guideline-directed dosages in the BIOSTAT-CHF cohort, which was specially designed to study effects of uptitration (15). Furthermore, we studied the interaction between guideline-directed treatment and hyperkalemia on outcomes.

Methods

Study cohort

For the present study, data from the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), an international, multicenter, prospective, observational study was investigated. Patients received ≤50% of target dosages of ACEi/ARBs and/or beta-blockers at time of inclusion and treating physicians anticipated and encouraged an increase of fraction target dose of ACEi/ARBs and/or beta-blockers to guideline directed levels. Patients were included as in- or outpatients. Potassium was measured at time of inclusion. The first 3 months after inclusion were considered as an active uptitration period, followed by a stabilization period of 6 months. Detailed description of the rationale, design, and implementation of the BIOSTAT-CHF study has been reported elsewhere (15).

For the current study, only HF patients with HFrEF (LVEF<40%) with available potassium levels at baseline were included. Out of 2,516 patients from the original study cohort, 697 patients with a preserved or unknown ejection fraction were excluded. Of the remaining 1,819 patients, serum potassium levels were measured in 1,666 patients. Potassium measurements at 9 months were available in 918 patients (*Supplementary figure 1*).

Definitions and study endpoints

Potassium levels were classified according to clinical reference ranges, i.e. hypokalemia; <3.5 mEq/L, normokalemia; 3.5 - 5.0 mEq/L, and hyperkalemia; >5.0 mEq/L (16). We defined successful uptitration as an increase of beta-blockers and ACEi/ARB if patients obtained over 50%

of the target dose at 9 months of follow-up and the administered dose at 9 months was greater than the dose administered at baseline according to the ESC-guidelines (17). Patients who died between baseline and 9 months (N=203) were excluded from this analysis (supplementary figure 1). Patients receiving equal guideline recommended target doses (i.e. >= 100%) at baseline and 9 months were classified as successfully uptitrated patients. Patients receiving ≤ 50% of the guideline-recommended dose were labeled not successfully uptitrated (*Supplementary figure 2*). In sensitivity analysis, we did not include baseline doses and only tested for administered doses of ACEi/ARBs and beta-blocker at three months (18). The primary endpoint for outcome analyses of this study was a combined endpoint of all-cause mortality and HF related hospitalizations at 2 years. HF related hospitalizations were determined by the enrolling investigator.

Statistical analysis

For baseline characteristics, study results for continuous variables are presented as the mean (± standard deviation), medians (+ interquartile ranges) or numbers with percentages where appropriate. Baseline characteristics were stratified by serum potassium levels in hypokalemia (<3.5 mEq/L), normokalemia (3.5-5.0 mEq/L), and hyperkalemia (>5.0 mEq/L), respectively. An increase or decrease in potassium between baseline and 9 months was determined as more than a 0.1 mEq/L difference between baseline and 9 months. Intergroup differences between more than two groups were tested using the one-way analysis of variance (ANOVA); Kruskal-Wallis test or chi2-test where appropriate. Q-Q plots and histograms were used to visually test all variables

for normality. Normality was tested using the Kolmogorov-Smirnov test, when necessary. For further analyses, skewed variables were log-transformed to achieve normal distribution.

Relationship of potassium levels with successful uptitration between baseline and 9 months was studied using logistic regression. In a stepwise manner, this was corrected for clinically relevant confounders of potassium, which age, sex, eGFR, systolic blood pressure, diabetes mellitus, and ACEi/ARB usage at 9 months (in case of beta-blocker uptitration) or beta-blocker usage at 9 months (in case of ACEi/ARB uptitration). Additionally, we corrected for uptitration models that best predicted successful uptitration rates in this cohort for beta-blockers and ACEi/ARB (18). For beta-blockers, these include age, country of inclusion, diastolic blood pressure, heart rate, and signs of pulmonary congestion. For ACEi/ARB these include sex, BMI, eGFR, alkaline phosphatase, and country of inclusion, as published previously (18). The association between potassium and outcome is depicted using Kaplan-Meier curves for potassium levels at baseline, potassium levels at 9 months and a change of potassium levels between baseline and 9 months. A difference in survival was tested using the log-rank test. To investigate the association with survival of potassium in multivariable analyses, Cox regression analyses were performed correcting for clinically relevant variables, these include age, sex, eGFR, hypertension, diabetes mellitus, and ACEi/ARB or beta-blocker use at 9 months. Interaction analyses were performed to investigate the interaction between successful uptitration and its association with outcome of potassium levels (as a continuous variable).

A two-sided p-value <0.05 was considered statistically significant and 95% CI were presented for all odds ratios. For statistical analyses, Stata MP13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.) was used.

Results

Baseline characteristics

Out of a total of 1,666 patients, 114 patients (6.9%) had potassium levels below 3.5 mEq/L, 1,418 patients (85.1%) had normal potassium levels (i.e. 3.5 to 5.0 mEq/L), and 134 patients (8.0%) had hyperkalemia (above 5.0 mEq/L) at baseline (*table 1*). Only 34 (2%) patients had potassium levels above 5.5 mEq/L. In the overall population, mean age (± SD) was 67 ± 12 years of which 77% were male. Patients with hyperkalemia were more often men, had lower heart rates and less signs of pulmonary congestion and peripheral edema. Estimated GFR was significantly lower in patients with hyperkalemia and patients with high serum potassium were more often on MRA treatment.

A difference in prevalence of hyper- and hypokalemia across Europe is depicted in *figure 1A and 1B*. Hyperkalemia was particularly prevalent in Slovenia (19%), Poland (13%), Serbia (12%) and Greece (11%) (figure 1A). After correction for potential confounders (i.e. renal function, history of diabetes mellitus, history of hypertension, fraction target dose of ACEi/ARB, beta-blocker, and MRA and uptake of diuretics (yes/no) at baseline), rates of hyperkalemia were highest in Slovenia, followed by Poland, Serbia, and Greece (P <0.05 for all). Highest rates of hypokalemia were found in the Netherlands (P<0.05) (*supplementary table 1A and 1B*). Differences in listed characteristics between European countries are displayed in *supplementary table 2*.

During 9 months' follow-up potassium levels increased (0.16 ± 0.66 mEq/L, p<0.001) and 523 (57%) of patients experienced an increase of potassium levels between baseline and 9 months, while 319 (35%) of patients had a decrease in potassium. At 9 months, 21 patients (2.3%) had potassium levels below 3.5 mEq/L, 786 patients (85.4%) had normal potassium levels (i.e. 3.5

to 5.0 mEq/L), and 113 patients (12.3%) were patients with hyperkalemia (above 5.0 mEq/L). Of patients with hypokalemia at baseline, 53.5% also had available data at 9 months. In case of normokalemia and hyperkalemia at baseline, this was 55.6% en 50.7% at 9 months respectively (*supplementary table 3*).

Association of potassium and uptitration of guideline directed medication

After 9 months, uptitration of ACEi/ARB was successful in a total of 401 patients (24.1%). For beta-blockers, successful uptitration was seen in 278 (16.7%) patients (*supplementary figure 2*). Results of logistic regression analyses are shown in *figure 2 and supplementary figure 3*. Higher serum potassium at baseline was associated with lower odds of successful uptitration at 9 months in univariable analyses (OR 0.77; 95%CI 0.62–0.95; p=0.016; per increment of 1.0 mEq/L potassium). Also after correcting for clinically relevant confounders (i.e. age, sex, eGFR, systolic blood pressure, diabetes mellitus, and beta-blocker usage at 9 months), higher potassium levels at baseline showed a significant association with less successful uptitration (OR 0.80; 95%CI 0.64–0.99; p=0.043). When correcting for the previously published uptitration model, higher potassium levels at baseline were still associated with lower odds of successful uptitration (OR 0.70; 95%CI 0.51–0.98; p=0.035). After excluding patients already on ACEi/ARB target dose, potassium remained predictive for successful uptitration when correcting for both the uptitration model (OR 0.52; 95%CI 0.35–0.78; p=0.002) and model 3 (OR 0.66; 95%CI 0.50-0.87; p= 0.003). Further adjustment by MRA uptake at target dose (yes/no) did not change the association between baseline potassium levels and ACEi/ARB uptitration when correcting for the uptitration model (OR 0.54 95%CI 0.35–0.81; p=0.003) as well as for model 3 (OR 0.68; 95%CI 0.51-0.89; p=

0.006). No interaction was observed between potassium and renal function for successful uptitration ($P_{interaction}$ 0.988) suggesting that the association between hyperkalemia and uptitration is similar across the renal function spectrum. In sensitivity analysis, baseline serum potassium was univariable associated with uptitration success of ACEi/ARB (OR 0.81; 95%CI 0.67–0.98; p=0.031). However, this was attenuated after multivariable adjustment (p=0.086). As expected, no association was found between baseline potassium levels and uptitration of beta-blockers. Higher serum potassium levels at 9 months were not associated with successful uptitration of ACEi/ARB or beta-blockers (*supplementary figure 3*). A potassium increase over 9 months was associated with successful uptitration of ACEi/ARB (OR 1.37; 95%CI 1.09-1.72; p= 0.008), but not of beta-blockers.

Potassium and outcome

Results of survival analyses are presented in *figure 3a/b*, *supplementary figure 4,* and *Table 2.* Overall, 627 (37.6%) patients reached the combined endpoint at 2 years. Hypo- and hyperkalemia at baseline or potassium analyzed on a continuous scale were not associated with worse outcomes (*Table 2*). Similarly, a change between potassium levels at baseline and 9 months or potassium levels at 9 months were not significantly related to outcome. When used as a continuous variable, potassium change during 9 months was not associated with outcome (HR 0.98; 95%CI 0.81-1.19; p=0.844). Potassium levels at baseline, a change of potassium during uptitration or potassium levels after uptitration, did not attenuate the beneficial effects of successful uptitration of ACEi/ARBs or beta-blockers ($P_{interaction}$ >0.5 for all).

Discussion

This study shows that low and high serum potassium levels are common among patients with HFrEF. Potassium levels above 5.0 mEq/L were observed in 8% of HFrEF patients across Europe and being particularly prevalent in Eastern Europe and Greece. Furthermore, higher baseline potassium levels were an independent predictor of unsuccessful uptitration of ACEi/ARBs in HFrEF patients. Potassium levels or changes in potassium levels during uptitration were not associated with worse outcomes. Furthermore, a potassium increase during uptitration did not attenuate the beneficial effects of uptitration of ACEi/ARBs. The findings of this study might have implications for clinical practice, suggesting that lowering potassium levels in patients with hyperkalemia might lead to improved guideline directed treatment with ACEi and ARB. These data are important considering the availability of new potassium lowering drugs (19,20).

Our study shows an overall rate of baseline potassium abnormalities of 6.9% and 8.0% for hypo- and hyperkalemia respectively. Our results show a difference in prevalence of potassium abnormalities between European countries, even after rigorous multivariable correction, which might reflect differences in health systems or local practice (18). Our findings are in line with earlier reports from the Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial (6% and 9% respectively) and 6.7% and 3.3% in the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure (COACH) trial (14). Overall, potassium levels increased during uptitration of ACEi/ARB, with 2.3% of patients having hypokalemia and 12.3% of patients having hyperkalemia at 9 months. During 9 months of follow-up, a significant increase of potassium was seen in the majority of patients (57.4%) and can be explained by the actively increased doses of ACEi and

ARB. Unfortunately, the study design did not allow for analysis on early changes (e.g. <1 month) after dose adjustments.

In this study, higher potassium levels at baseline were associated with less uptitration of ACEi/ARB. This suggests that HF patients with hyperkalemia at the start of therapy are at greater risk for lower doses or discontinuation of ACEi/ARB, which impede outcomes (6,18). This is in line with earlier reports from a general patient population where high potassium levels were found to be responsible for a significant proportion of discontinuation or lowering of dosage of ACEi and ARB. Here, discontinuation or lowering of dosages of ACEi/ARB were associated with more adverse outcomes (8). Also in previous results from the BIOSTAT-CHF study, sub-optimal dosages of ACEi/ARB were associated with worse outcomes in HF patients (18). This suggests that lower dosages and/or discontinuation of ACEi/ARB due to high potassium levels severely impede outcomes.

Hypokalemia at baseline or at 9 months was not associated with worse outcomes. This is in line with earlier reports from the COACH, PROTECT and EVEREST trials, where potassium also did not show an independent association with outcome (14,21). Nevertheless, reports on the association of potassium with outcome are mixed. Previous results of post-hoc analyses performed in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial showed that hypokalemia (<4.0 mEq/L) is associated with adverse outcomes and amplified the beneficial effect of eplerenone (22,23). Additionally, a propensity matched study from Ahmed et al. showed that hypokalemia is associated with more adverse outcomes (22). In another sub-analysis of the Digitalis Investigation Group trial, Bowling et al. shows that this was also true for HF patients with CKD and that potassium also predicts a combined endpoint

of all-cause mortality and HF rehospitalizations (24). However, it has been suggested that the association of hypokalemia with adverse outcomes reflect lower usage of MRA or higher diuretic usage and dosage, on which data was often not available in previous reports (22,24-26).

Regardless of its association with outcome, potassium levels did not attenuate the beneficial effects of ACEi/ARB and beta-blockers. Previously, results from the Randomized Aldactone Evaluation Study (RALES) showed that hyperkalemia was associated with higher mortality rates, but did not interfere with the beneficial effects of spironolactone (9). The EMPHASIS-HF trial showed that the favorable effects of eplerenone on outcome did not differ for hyperkalemic compared to normokalemic patients (25). Additionally, a sub-analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial showed that potassium levels also did not interfere with the beneficial effects of Candesartan (27). The findings of the current study confirm results of the post-hoc analysis of the CHARM trial, but also show that potassium levels do not interfere with the beneficial effects of ACEi/ARB uptitration. Previously, Lund et al. discussed the association between ACEi/ARB usage and renal function, indicating that even in HF patients with severe renal insufficiency, administering ACEi/ARB improves outcome (28,29). Nevertheless, it should be noted that potassium levels as well as increases of potassium levels during uptitration took place within the relative “normal” range of potassium levels of 3.0 mEq/L and 5.5 mEq/L. Additionally, our study shows for the first time that potassium increases during uptitration of ACEi and ARBs do not interfere with the beneficial effects of these lifesaving therapies.

Study limitations

This is a post-hoc analysis, which comes with the usual limitations of selection bias. Potassium levels were only measured twice, at baseline and at 9 months of follow-up. A non-repetitive measurement could falsely positive diagnose a HF patient with hyperkalemia. Repeated measurements could correct for this deviation, but were not available. Unfortunately, potassium levels were not monitored after the first 3 months of active uptitration. This would provide additional data on potassium fluctuations over time. Additionally, patients with no potassium measurement at 9 months could have died, suggesting caution in interpreting data on potassium and outcome at 9 months. Furthermore, we did not have any information about potassium supplementation as well as on diuretic dosages, which might interfere with potassium levels.

Conclusion

Potassium abnormalities are prevalent among HF patients. Higher potassium levels are associated with lower rates of successful ACEi/ARB uptitration. Potassium abnormalities are not related to adverse outcomes and do not attenuate the beneficial effects of successful ACEi/ARB uptitration.

Disclosures

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Figure legends

Figure 1. Incidence levels of hyperkalemia (A) and hypokalemia (B) per country

Figure 2. Odds Ratios (95% CI) for successful uptitration of ACEi/ARB depicted for baseline potassium (as continuous variable). Model 1: Corrected for age, sex, and eGFR. Model 2: Corrected model 1, systolic blood pressure, and diabetes mellitus. Model 3: Corrected for model 2 and beta-blocker usage at 9 months. Uptitration Model: Corrected for BIOSTAT-CHF uptitration model Sex, BMI, eGFR, alkaline phosphatase, and country of inclusion

Figure 3. Combined endpoint of all-cause mortality and HF-hospitalization rates stratified by serum potassium levels in mEq/L at baseline (A) and 9 months (B).

Table 1. Baseline characteristics

Values are given as proportions, means (±SD) or medians (IQR)

Variables (proportions %)	Total cohort (n=1,666)	Pot < 3.5 (n=114)	3.5 ≤ Pot ≤ 5.0 (n=1,418)	Pot > 5.0 (n=134)	p-value	Trend
Demographics						
Potassium levels (mEq/L)	4.3 (3.9 – 4.6)	3.2 (3.1 – 3.4)	4.3 (4.0 – 4.5)	5.4 (5.2 – 5.5)	NA	NA
Age (years)	69 (60 – 76)	69 (63 – 76)	68 (59 – 77)	70 (62 – 75)	0.808	0.974
Men	1,275 (77)	69 (61)	1,101 (78)	105 (78)	<0.001	0.002
BMI (kg/m2)	26.9 (24.1 – 30.4)	26.7 (24.2 – 31.4)	26.9 (24.0 – 30.4)	27.0 (24.2 – 30.1)	0.688	0.726
Heart rate (/min)	76 (68 – 90)	80 (70 – 97)	77 (67 – 90)	75 (68 – 90)	0.019	0.020
LVEF (%)	27 ± 7	27 ± 7	27 ± 7	28 ± 7	0.434	0.134
SBP (mmHg)	123 ± 21	126 ± 24	123 ± 21	124 ± 20	0.169	0.903
NYHA class III-IV	557 (38)	30 (32)	484 (39)	43 (38)	0.466	0.476
eGFR (mL/min/1.73 m2)	65.0 ± 24.1	64.2 ± 24.4	65.8 ± 24.0	56.5 ± 23.7	<0.001	0.015
- eGFR < 45 mL/min	347 (21)	23 (20)	280 (20)	44 (33)	0.002	0.009
Signs & symptoms						
Pulmonary congestion	854 (52)	73 (64)	712 (51)	67 (51)	0.035	0.057
Extent of peripheral edema*						
- Not present	595 (44)	21 (23)	511 (44)	63 (52)	<0.001	<0.001
- Above Knee	75 (5)	8 (9)	64 (6)	3 (2)	0.139	0.047
Medical history						
Diabetes mellitus	529 (32)	34 (30)	447 (32)	48 (36)	0.534	0.297
Myocardial infarction	641 (38)	37 (32)	555 (39)	49 (37)	0.330	0.574
Atrial fibrillation	713 (43)	49 (43)	615 (43)	49 (37)	0.314	0.272
Hypertension	976 (59)	71 (62)	826 (58)	79 (59)	0.700	0.632
eGFR <60	747 (45)	52 (46)	614 (43)	81 (61)	0.001	0.012
COPD	288 (17)	21 (18)	237 (17)	30 (22)	0.238	0.352
Laboratory						
Hemoglobin (g/dL)	13.4 ± 1.9	13.0 ± 1.8	13.4 ± 1.9	13.3 ± 1.8	0.069	0.232
Erythrocytes (10e12/L)	4.5 (4.1 – 4.9)	4.4 (4.1 – 4.9)	4.5 (4.1 – 4.9)	4.6 (4.1 – 5.0)	0.817	0.632
Platelets (10e9/L)	214 (173 – 258)	209 (171 – 261)	212 (173 – 257)	228 (187 – 281)	0.019	0.023
NT-proBNP (ng/L)^	4447 (2359 – 8824)	4132 (2621 – 7839)	4402 (2250 – 8522)	5947 (3211 – 11124)	0.068	0.155
CRP (mg/L)	12.9 (5.5 – 26.4)	16.5 (8.2 – 30.4)	12.9 (5.4 – 26.4)	10.2 (4.5 – 19.1)	0.002	0.001
Creatinine (µmol/L)	102 (84 – 127)	99 (77 – 124)	101 (83 – 126)	115 (91 – 150)	<0.001	<0.001
Iron (µmol/L)	8 (5 – 13)	8 (5 – 13)	8 (5 – 13)	9 (6 – 13)	0.080	0.028
Medication						
ACE-I/ARB	1,229 (74)	83 (73)	1,046 (74)	100 (75)	0.949	0.746
Beta-blocker	1,390 (83)	91 (80)	1,190 (84)	109 (81)	0.419	0.822
MRA	920 (55)	52 (46)	783 (55)	85 (63)	0.019	0.005
Diuretics	1,665 (100)	114 (100)	1,417 (100)	134 (100)	0.916	0.975
Digoxin	302 (18)	12 (11)	271 (19)	19 (14)	0.034	0.578

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, BNP = Brain Natriuretic Peptide, COPD = Chronic Obstructive Pulmonary Disease, CRP = C-reactive protein, eGFR = estimated Glomerular Filtration Rate, LVEF = Left Ventricular Ejection Fraction, MRA = Mineralocorticoid Receptor Antagonists, NT-proBNP = N-Terminal prohormone of Brain Natriuretic Peptide, NYHA = New York Heart Association, SBP = Systolic Blood Pressure.

* Extent of peripheral edema was determined in 1,367 patients.

^ Serum NT-proBNP levels were determined in 736 patients.

Table 2. Cox proportional hazard regression model for the analysis of event rates for the combined endpoint (all-cause mortality + HF-hospitalizations) in HF patients stratified by potassium levels on baseline, 9 months, and potassium change.

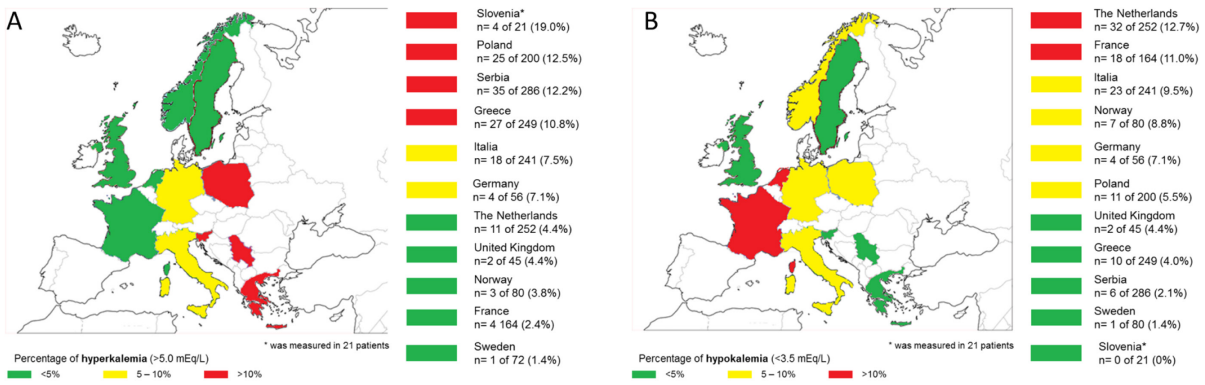
(n of patients ; n of event)	**<3.5 mEq/ L** (114 ; 46)	**3.5-5.0 mEq /L** (1,418 ; 530)	**>5.0 mEq /L** (134 ; 51)
Baseline	HR (CI), p		HR (CI), p
Univariable	1.10 (0.83-1.47) 0.493	ref	1.01 (0.77-1.31) 0.968
Model 1	1.11 (0.83-1.48) 0.493	ref	0.90 (0.69-1.18) 0.448
Model 2	1.12 (0.84-1.50) 0.430	ref	0.88 (0.67-1.15) 0.353
Model 3	1.13 (0.84-1.51) 0.419	ref	0.89 (0.68-1.17) 0.406
9 months	(21 ; 12)	(786 ; 212)	(113 ; 43)
Univariable	1.65 (0.61-4.48) 0.328	ref	1.34 (0.80-2.24) 0.270
Model 1	1.85 (0.68-5.04) 0.231	ref	1.22 (0.72-2.05) 0.466
Model 2	1.75 (0.63-4.81) 0.280	ref	1.19 (0.70-2.01) 0.518
Model 3	1.97 (0.71-5.49) 0.193	ref	1.19 (0.70-2.01) 0.513
Change	**Decrease** (319 ; 103)	**No change** (78 ; 17)	**Increase** (523 ; 146)
Univariable	1.26 (0.96-1.65) 0.101	ref	1.23 (0.93-1.64) 0.148
Model 1	1.25 (0.95-1.65) 0.105	ref	1.17 (0.88-1.56) 0.275
Model 2	1.27 (0.96-1.66) 0.091	ref	1.15 (0.87-1.54) 0.328
Model 3	1.23 (0.94-1.62) 0.135	ref	1.15 (0.86-1.53) 0.341

Model 1: Corrected for age, sex, and eGFR

Model 2: Corrected for age, sex, eGFR, systolic blood pressure, and diabetes mellitus

Model 3: Corrected for the age, sex, eGFR, systolic blood pressure, and diabetes mellitus, ACEi/ARB usage at 9 months, or beta-blocker usage at 9 months

471 Figure 1



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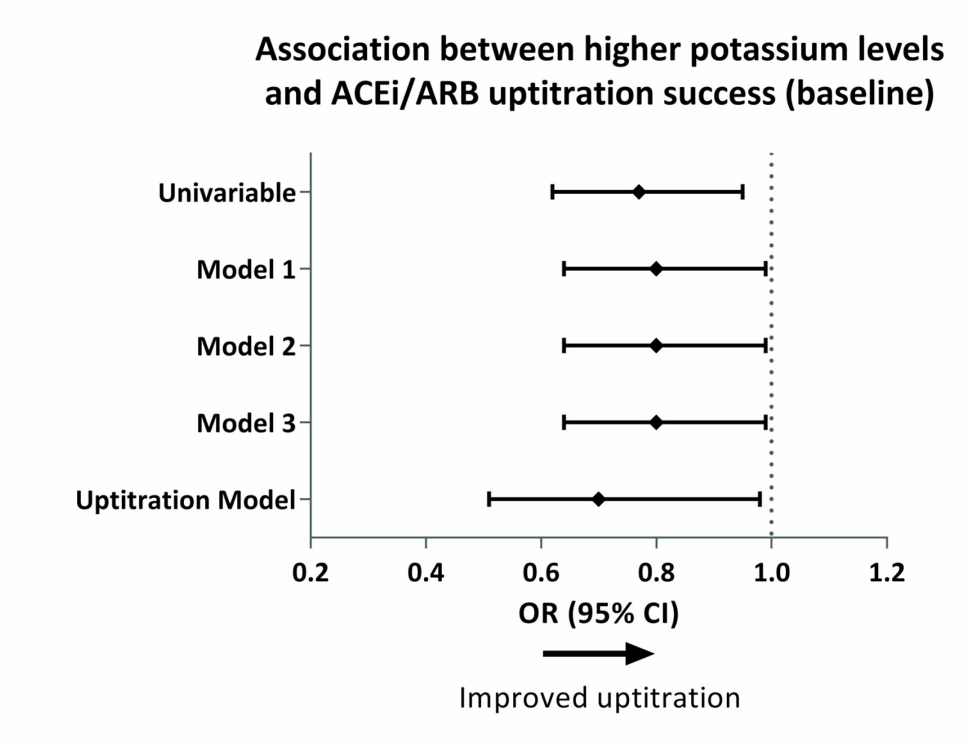
473 Figure 2



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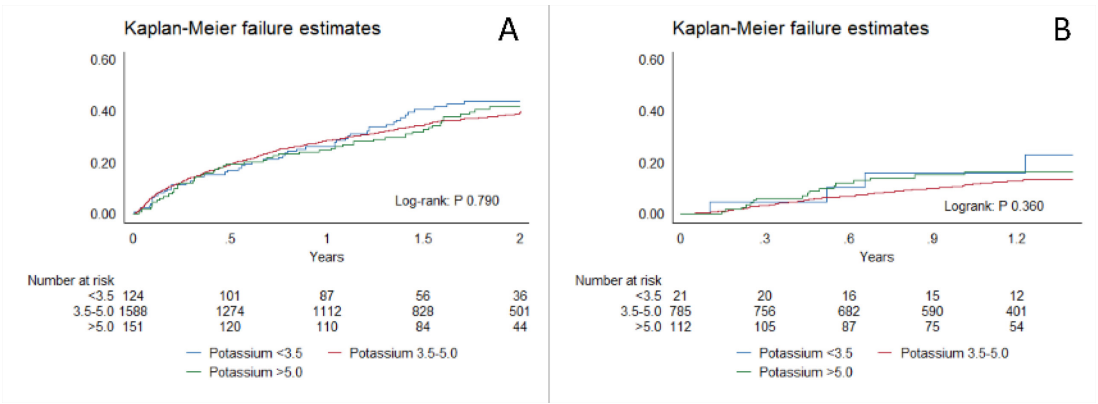
475 Figure 3


Kaplan-Meier failure estimates
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0.60
0.40
0.20
0.00
Log-rank: P 0.790
0
.5
1
1.5
2
Years
Number at risk
<3.5 124 101 87 56 36
3.5-5.0 1588 1274 1112 828 501
>5.0 151 120 110 84 44
Potassium <3.5
Potassium 3.5-5.0
Potassium >5.0
Kaplan-Meier failure estimates
B
0.60
0.40
0.20
0.00
Logrank: P 0.360
0
.3
.6
.9
1.2
Years
Number at risk
<3.5 21 20 16 15 12
3.5-5.0 785 756 682 590 401
>5.0 112 105 87 75 54
Potassium <3.5
Potassium 3.5-5.0
Potassium >5.0

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