Hyperkalemia and treatment with RAAS-inhibitors during acute heart failure hospitalizations and their association with mortality

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Word count: 4618 words

Abstract

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

Background: Hyperkalemia is a potential complication of RAASi. For patients with HF, fear of hyperkalemia may lead to failure to deliver guideline-recommended doses of RAASi.

Methods: Serum potassium concentrations were measured daily from baseline (<24h of admission) until discharge or day 7 in 1,589 patients enrolled in the PROTECT trial. Incident hyperkalemia was defined as at least one 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/day 7 (p<0.001). Patients developing incident hyperkalemia (n=564; 35%) were more often on mineralocorticoid antagonists (MRAs) 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 (HR 1.73; 95%CI 1.15–2.60), regardless of incident hyperkalemia ($P_{interaction}$>0.1). Patients with incident hyperkalemia, who were discharged on the same or an increased dose of MRAs (HR 0.52; 95%CI 0.32–0.85) or ACEi/ARB (HR 0.47; 95%CI 0.29–0.77) 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 ACEi/ARB during acute HF hospitalization had better 180-day survival.

Keywords:

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

List of abbreviations

ACEi – Angiotensin-Converting Enzyme-Inhibitors

ARB – Angiotensin Receptor Blockers

BNP – Brain Natriuretic Peptide

eGFR – estimated Glomerular Filtration Rate

HF – Heart Failure

HFpEF – Heart Failure with preserved Ejection Fraction

MRAs – Mineralocorticoid Receptor Antagonist

RAASi – Renin Angiotensin Aldosterone System-Inhibitors

Introduction

The treatment of heart failure requires the use of a variety of agents that may cause both hypo and hyperkalemia and both may be associated with a higher mortality in some clinical settings.(1–5)

Hospitalizations for worsening heart failure 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 inhibitors (RAASi), which may cause hyperkalemia.(6) Accordingly, guidelines recommend close monitoring of serum potassium during hospitalizations for HF and that RAASi, both angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEi/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 ACEi/ARB in patients with chronic HF.(10) Similarly, among patients with chronic HF, hyperkalemia is associated with underuse of mineralocorticoid receptor antagonists (MRAs).(11, 12) However, data on the association between incident hyperkalemia and up- or down-titration of RAASi during hospitalization for acute HF are scant.

Therefore, we investigated the relationship between hyperkalemia and adjustment of the dose of RAASi in patients hospitalized with acute HF and subsequent clinical outcome.

Methods

Study design and population

Patients enrolled in the PROTECT trial (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), who had measurements of serum potassium 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 supplementary 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, 20–80 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 who had a serum potassium ≥3.5 mEq/L (or 3.0-3.5 mEq/L if potassium was given intravenously), were enrolled within 24 hours 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, i.e. hypokalemia (<3.5 mEq/L) and hyperkalemia (>5.0 mEq/L).(15) Serum potassium concentrations were measured daily from baseline (<24 hours) 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 of 3.5–5.0 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 developing both hypo- and hyperkalemia during hospitalization (n=34) were excluded for this analysis.

A change in serum potassium was defined as difference of ≥0.2 mEq/L between day 1 and discharge or day 7. Worsening renal function (WRF) was defined as a creatinine change until day 7 (from baseline) ≥0.3 mg/dL in accordance with an earlier study originating from the PROTECT cohort.(16) Changes in cardiovascular treatment were stratified into four categories, i.e. treated neither at admission or discharge, dose 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 for cardiovascular or renal causes or all-cause mortality through 60 days was a secondary outcome of interest.

Statistical analysis

For baseline characteristics, means ± standard deviations, medians (interquartile ranges), or numbers with percentages 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 between groups were tested using the one-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 in doubt, normality was tested via the Kolmogorov-Smirnov test. To achieve normal distribution for further analysis, skewed variables were log-transformed.

Intergroup differences related to changes in doses of ACEi/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 ACEi/ARB and MRA up- or down-titration were corrected for the probability of obtaining this specific therapy. For this correction we used inverse probability weighting (IPW) with the probability to be up-titrated for either ACEi/ARB or MRAs.(17) We performed IPW by doing logistic LASSO penalization analysis using all 69 variables averaged over 5 imputation sets for both ACEi/ARB and MRA separately. We defined successful treatment as those who were able to be up-titrated or remained constant doses of either ACEi/ARB or MRA. 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 <0.1 were used in multivariable 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 ACEi/ARB or MRA was tested using logistic regression models as well. In addition, we created a robust multivariable model including clinically relevant confounders.

Cox proportional hazard models were used to test the effects of up- or down-titration of ACEi/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 (oral dose/2 + IV 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 two-sided p-value <0.05 was considered statistically significant. Stata SE15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC) 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%). Out of these, 28 patients (5%) had hyperkalemia at only one day of hospitalization. In total, 34 patients (2%) had episodes of both hypo- and hyperkalemia. Only for frequency analyses, we narrowed the definition of incident hyperkalemia to >5.5 mEq/L (moderate hyperkalemia) or >6.0 mEq/L (severe hyperkalemia). Then 226 (14%) and 87 (5%) patients were classified as incident hyperkalemia, respectively.

Patients with incident hyperkalemia were younger, with fewer signs of congestion, a higher heart rate, and a lower prevalence of atrial fibrillation/flutter ($P<0.05$ for all) but had similar renal function (eGFR) to other patient groups. However, WRF 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 more often on MRAs (53%) and ACEi/ARB (78%) prior to hospitalization compared to patients with incident hypokalemia or who had a ‘normal potassium’ (35% and 44% for MRAs, and 68% and 77% for ACEi/ARB, respectively) (table 1). In a multivariable 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 BUN (supplementary table 2).

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 (supplementary table 3).

Changes in cardiovascular treatment

For patients with incident hyperkalemia, MRAs were more often down-titrated (15%) compared to patients whose potassium remained in the normal range (9%) or with incident hypokalemia (8%) (figure 1 and supplementary table 4). After correcting 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 (univariable P<0.1), this association remained significant (OR 1.81; 95%CI 1.27–2.58, p=0.001 and OR 1.89; 95%CI 1.32–2.72, p=0.001, respectively). In sensitivity analyses using IPW, this association was not attenuated (OR 1.88; 95%CI 1.30–2.73, p=0.001). Doses of ACEi/ARB were not decreased more frequently in patients with incident hyperkalemia compared to patients with normal potassium concentrations throughout or those with incident hypokalemia (P=0.296). Patients with incident hypokalemia were less often treated with MRA or ACEi/ARB during hospitalization (figure 1). However, after multivariable adjustment this was no longer significant for either therapies class (P=0.061 and P=0.380 respectively). Difference at baseline between subgroups of treatment change for ACEi/ARB and MRA are listed in supplementary tables 5 and 6 respectively.

In univariable analysis, the number of days with hyperkalemia was not associated with ACEi/ARB down-titration (OR: 1.06 (0.89–1.27), p=0.517) (table 3). However, the number of instances that hyperkalemia occurred was associated with down-titration of MRAs (OR: 1.26 (1.09–1.47), p=0.003). This association remained significant after correction for variables with a univariable association with MRA down-titration (OR: 1.23 (1.04–1.44), p=0.014) or after robust correction for various clinical confounders (OR: 1.41 (1.02–1.97), p=0.040).

When tested on a continuous scale, baseline serum potassium was not associated with ACEi/ARB down-titration (table 3). Yet, it was positively associated with MRA down-titration (OR: 1.45 (1.10-1.91), p=0.008) in univariable analysis. However, this effect was no longer significant after correction for clinical confounders (OR: 1.51 (0.87-2.62), p=0.139).

Incident potassium disturbances, RAAS-I therapy, and outcome

Overall, 269 (17%) patients 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 (supplementary 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 (HR 1.14 (1.00–1.30), p=0.049).

Compared to constant doses, down-titration or absence of ACEi/ARB at baseline and discharge/day 7 was associated with a higher 180-day mortality on both unadjusted and adjusted analyses (table 2). Furthermore, when using IPW, the associations persisted (HR 2.56; 95%CI 1.83–3.60, p<0.001, respectively). A similar pattern was observed for MRA down-titration during hospitalization. Also for MRAs, IPW did not attenuate this association (HR 1.67; 95%CI 1.11–2.49, 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 RAASi and a favorable outcome. Patients with incident hyperkalemia and constant doses or increasing doses of MRA had a lower mortality (HR 0.58; 95%CI 0.37–0.91) 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 0.32–0.85). Similarly, patients with incident hyperkalemia and constant or increasing doses of ACEi/ARB had a lower mortality (HR 0.46; 95%CI 0.28–0.75). This association was not attenuated in an IPW analysis (HR 0.47; 95%CI 0.29–0.77). No interaction was observed between incident hyperkalemia and up-titration of ACEi/ARB or MRAs during hospitalization for either all-cause mortality at 180 days or the secondary composite outcome ($P_{interaction}$>0.1 for all). Additionally, when tested in potassium sub-groups, patients with incident hyperkalemia and ACEi/ARB down-titration had a worse 180-day prognosis compared to patients with stable ACEi-/ARBdoses. This was not seen for MRA (supplementary table 9).

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 RAASi. Patients who developed hyperkalemia fared better if the doses of MRA or ACEi/ARB were held constant or increased.

We are unaware of any other trial of hospital admission for HF with such a high density of measurements of serum potassium. More than half of patients in this analysis developed either hypo- or hyperkalemia during hospital admission. Hyperkalemia was most prevalent occurring in 35% of patients at least once, while 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 14% and 5% of patients, respectively. Many clinical trials of heart failure, especially involving RAASi, excluded patients with a baseline serum potassium >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 Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, 14.6% of patients hospitalized with worsening heart failure 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 trials (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), 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 RAASi are more likely to develop hyperkalemia.(21–24) The fact that we did not find similar associations with *incident* hyperkalemia suggests that changes in RAASi may be of overriding importance during hospitalization for acute HF. However, within the 'incident hyperkalemia' group, patients who were down-titrated with ACEi/ARB or MRAs, 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 ACEi/ARB or MRAs (supplementary tables 5 and 6). The greater incidence of hyperkalemia in younger people in our study may reflect greater efforts and success in treating them with MRA. Hypokalemia was strongly associated with not being treated with an MRA. In addition, by using a multi-day method of in-hospital monitoring, our 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 (supplementary table 8). Similar to previous reports, incident hypo- or hyperkalemia during hospitalization was not associated either with mortality or our 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 to be associated with less successful up-titration of ACEi/ARB and underuse of MRA.(10, 12) Unfortunately, no specific data on up- or down-titration of MRA therapy was available in this chronic HF cohort. Additionally, real-world data of the SCREAM study (Stockholm CREAtinine Measurements) 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 ACEi/ARB, are 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 might 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 3.0–3.5 could only be included in case potassium was supplemented parentally. However, no data is available regarding the dose supplements. 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). Since an earlier study by Liu et al. indicated that the effect of Rolofylline on mortality is similar throughout the spectrum of baseline serum potassium concentrations, we do not expect this finding to be of major impact on our results.(31) Besides, treatment with Rolofylline had no impact on our multivariable outcome models. Changes in RAASi were recorded between baseline and day 7, whereas serum potassium concentrations were measured daily. We did not record why investigators changed doses of RAASi, which will have been influenced by patients' symptoms and signs, blood pressure and renal function. Additionally, since changes in RAASi 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 RAASi use might be distorted, compared to clinical practice, by the close monitoring of patients and their serum potassium. 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. We only included patients with five or more measurements of serum potassium which effectively excluded early deaths. Of 47 (3%) patients who died within 7 days of enrollment, 14 (30%) patients showed a serum potassium concentration >5.0mEq/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-patient prognosis (UK National HF Audit on ~30,000 patients).

Conclusion

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 indicate that patients still benefit from constant doses or up-titration of MRAs and/or ACEi/ARB despite incident hyperkalemia in a clinical setting.

Clinical Perspectives: 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 patients with incident hyperkalemia, who were discharged on the same or an increased dose of MRAs and/or ACEi/ARB had a lower 180-day mortality.

Translational Outlook: This study provides data for associations between incident hyperkalemia and RAASi to tailor this therapy in patients hospitalized for acute HF. These data may also support the design of trials to, for example, explore the serum potassium concentration at which RAASi 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 RAASi but if this strategy leads to reductions in morbidity and mortality.

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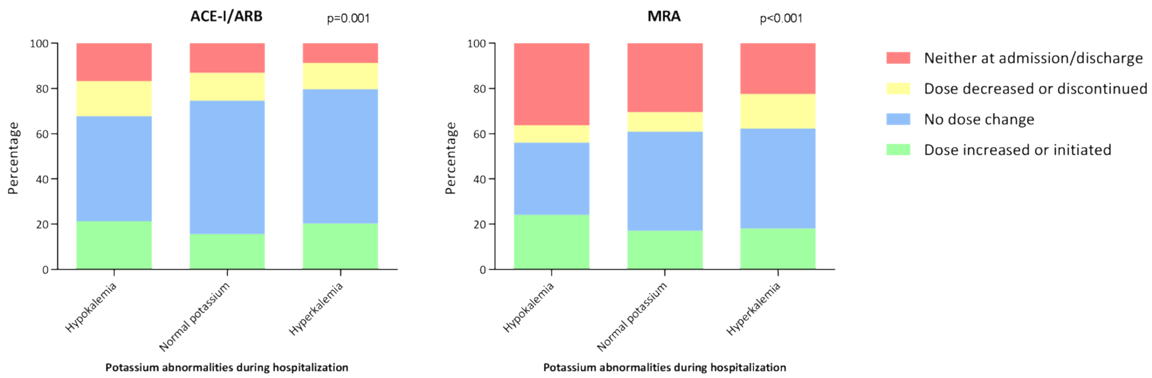
Figure 1. Stacked bar charts depicting changes in cardiovascular therapy between admission and discharge for ACEi/ARB (p=0.001) and MRA (p<0.001). Stratified by developing incident hypokalemia, normal potassium concentrations throughout hospitalization, and incident hyperkalemia during hospitalization, p-value for overall intergroup differences.



429 *Table 1.* Baseline characteristics, stratified by incident hypokalemia, always normal potassium, and incident hyperkalemia during hospitalization until discharge or day 7.

Variables	Level	Total cohort (n=1589)	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	N.A.
Age, years		70.0 ± 11.4	70.5 ± 12.5	70.7 ± 11.1	68.8 ± 11.2	0.007
Male sex		1060 (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 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, mmHg		124.8 ± 17.5	125.2 ± 19.6	124.7 ± 17.3	124.7 ± 16.8	0.93
Heart rate, b.p.m.		80.6 ± 15.5	80.1 ± 16.2	79.7 ± 15.2	81.9 ± 15.6	0.034
Signs & symptoms:						
Orthopnea		1349 (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 & 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
History of:						
Hospitalization for HF 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		1268 (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
Cardiovascular treatment:						
Beta-blockers		1219 (76.7%)	204 (77.0%)	590 (77.6%)	425 (75.4%)	0.62
ACEi/ARB		1202 (75.6%)	181 (68.3%)	583 (76.7%)	438 (77.7%)	0.009
MRA		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
Laboratory:						
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 (x10^9/L)		217 (175, 271)	205 (163, 251)	215 (173, 269)	226 (180, 284)	0.002
White blood cells (x10^9/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 given as proportions, means (±SD) or medians (IQR)

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, BNP = Brain Natriuretic Peptide, b.p.m. = beats per minute, BUN = Blood Urea Nitrogen, COPD = Chronic Obstructive Pulmonary Disease, eGFR = estimated Glomerular Filtration Rate, HFpEF = Heart Failure with preserved Ejection Fraction, IV= intravenous, JVP = Jugular Venous Pressure, MRA = Mineralocorticoid Receptor Antagonists, NYHA = New York Heart Association, Systolic BP = Systolic Blood Pressure.

Table 2. Cox proportional hazard regression for mortality risk at 180 days after change in cardiovascular treatment during hospitalization.

Change in cardiovascular treatment	**Univariable**	**Model 1[$]**	**PROTECT Risk Engine***
ACEi/ARB			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
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 at randomization	2.58 (1.84 – 3.62), <0.001	1.89 (1.35 – 2.62), <0.001	1.85 (1.28 – 2.65), 0.001
MRA			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
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 at randomization	1.31 (0.95 – 1.80), 0.095	1.12 (0.82 – 1.51), 0.479	1.15 (0.82 – 1.61), 0.408

HR, Hazard Ratio; CI, Confidence Interval

[$] 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

Table 3. The association between the magnitude of hyperkalemia (defined as the number of days hyperkalemia occurred (1 to 7 days)) or patients' serum potassium concentrations at baseline (on a continuous scale) and treatment down-titration.

Down-titration	Univariable	Model 1$	Model 2*
ACEi/ARB	OR (CI), p	OR (CI), p	OR (CI), p
Number of days with hyperkalemia	1.06 (0.89 – 1.27), 0.517	N.A.	N.A.
Baseline serum potassium, per 1 mEq/L	1.02 (0.78 – 1.33), 0.879	N.A.	N.A.
MRA	OR (CI), p	OR (CI), p	OR (CI), p
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

$ Model 1: Corrected for heart rate, logarithm of eGFR, history of hyperlipidemia, history of smoking, NYHA-class, treatment with beta-blockers, and treatment with MRAs (in ACEi/ARB) or treatment with ACEi/ARB (in MRA)

* Model 2: Corrected for age, sex, BMI, logarithm of eGFR, NYHA-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 ACEi/ARB, treatment with Rolofylline, edema & raised jugular venous pressure, intravenous dose of loop diuretics, serum sodium concentrations, serum BNP concentrations, and serum hemoglobin concentration.