Hypochloremia, Diuretic Resistance, and Outcome in Patients with Acute Heart Failure

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Abstract

Background

Chloride plays a role in renal salt sensing, neurohormonal activation and regulation of diuretic targets, and hypochloremia predicts mortality in acute heart failure (AHF). AHF therapies such as diuretics alter chloride homeostasis. We studied the association between (changes in) chloride levels and diuretic responsiveness, decongestion, and mortality in patients with AHF.

Methods and results

Patients hospitalized for AHF in the PROTECT trial (n=2033) with serum chloride levels within 24 hours of admission and 14 days later were studied. Hypochloremia was defined as chloride < 96 mEq/L.

Median baseline chloride was 101.0 [97.0-104.0] mEq/L. Low baseline chloride was associated with high bicarbonate, poor diuretic response, less hemoconcentration, and more worsening heart failure (all *P*<0.01). Newly developed hypochloremia at day 14 was common and associated with a decline in renal function, and increase in blood urea nitrogen (*P*<0.01). Baseline chloride was not significantly associated with mortality after multivariable adjustment, however day 14 chloride was strongly and independently associated with 180-day mortality (HR per SD decrease: 1.33 [1.17-1.50], *P*<0.001). Hypochloremia at baseline that resolved was not associated with mortality (p=0.55), but new or persistent hypochloremia at day 14 was associated with increased mortality (HR: 3.11 [2.17-4.46, *P*<0.001].

Conclusions

Hypochloremia at AHF hospital admission was strongly associated with impaired decongestion. New or persistent hypochloremia 14 days later was independently associated with reduced survival, whereas hypochloremia that resolved by day 14 was not.

Abbreviations

BUN	Blood Urea Nitrogen
eGFR	Estimated Glomerular Filtration Rate
PROTECT	Placebo-controlled Randomized Study of the Selective A1 antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function

Introduction

During hospitalization for acute heart failure, renal function and electrolytes are usually closely monitored, as diuretics are known to affect both. Guidelines recommend daily monitoring of blood urea nitrogen (BUN), creatinine, potassium, and sodium during intravenous diuretic therapy.[1-3] Interestingly, chloride is not mentioned in this list and similarly research studies investigating the role of chloride are scarce, even though chloride, and not sodium, has a predominant role in renal salt sensing mechanisms.[4,5] Also, tubular glomerular feedback and renin release have been shown to be primarily driven by chloride rather than sodium.[6] Chloride is a critical regulator of sodium transporter pathways through phosphorylation of a family of serine-threonine kinases.[7,8]

Recently, two studies demonstrated a strong, independent association between hypochloremia and an increased risk of mortality in both acute and chronic heart failure.[9,10] Both of these studies demonstrated that the prognostic value of chloride was greater than that of sodium. Given the influence of chloride on the targets of diuretic therapy, we sought to determine if hypochloremia is associated with reduced diuretic response and decongestion. Reciprocally given the effect of diuretics on chloride homeostasis, we furthermore aimed to evaluate changes in serum chloride and the prognostic significance of these changes.

Methods

Study design and procedures

The study population and design of the Placebo-controlled Randomized Study of the Selective A1 antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal

Function (PROTECT) study has been described in detail previously.[11] The PROTECT study was a large, multicenter, phase III randomized clinical trial, that enrolled 2,033 patients hospitalized for acute heart failure with mild to moderate renal dysfunction. The local ethics committed at each participating center approved the trial, and all patients provided written informed consent. The primary endpoint of treatment success, failure, or no change was neutral, and no effect was seen on 180-day mortality.

At baseline signs and symptoms of heart failure were assessed. Standard laboratory assessments were performed at baseline, day 7, and day 14. Diuretic response was defined as weight change on day 4 per 40 mg of intravenous furosemide (or equivalent doses) administered from baseline to day 3.[12] Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation. Hemoconcentration was defined as an increase in hemoglobin from baseline to day 4. Worsening renal function was defined as an increase ≥ 0.3 mg/dL from baseline to day 7 or 14, and a percentage change > 25%. The endpoint selected for this analysis was 180-day mortality.

Chloride

Chloride at baseline was available in 1960 patients (96%), at day 7 in 1814 patients (89%), and at day 14 in 1783 patients (88%). Hypochloremia was defined as a serum chloride concentration ≤ 96 mmol/L.[13] Chloride was missing due to death at 7 and 14 days in 86 patients (4%). Performing the primary analyses in the subgroup of patients without missing chloride data (n=1649) yielded similar results (data not shown).

Statistical analysis

The analyses were performed in the intention to treat population. Continuous variables are presented as mean ± standard deviation or median with [interquartile range] when appropriate. Categorical values are presented as frequencies and percentages. A linear trend

was statistically tested over quintiles of diuretic response, after checking for non-linear trends. Correlation coefficients presented are Spearman's. Uni- and multivariable linear regression analysis was performed with transformed values when necessary. Transformations were checked using multifractional polynomials. Multivariable explanatory regression models, including all univariable variables with a p-value < 0.10, were constructed via backward elimination. Cox proportional hazard regression analysis and Kaplan Meier survival estimates were performed to investigate the association of chloride with the selected endpoints. Multivariable models were corrected for study treatment and clinical covariates from a previously published model developed in PROTECT.[14] The added value of chloride for estimating the risk of mortality was assessed by examining gain in Harrell's C-index (a measure of model discrimination, higher values are better), using likelihood ratio tests for nested survival models, and assessment of continuous net reclassification improvement (NRI, a category-independent measure quantifying the degree of improvement in model-based risk estimates obtained by adding a marker to a model). A P-value <0.1 for interactions, and a two tailed P value < 0.05 was considered statistically significant. Analyses were performed using R: a Language and Environment for Statistical Computing, version 3.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline chloride and clinical characteristics

Median admission chloride was 101.0 [97.0-104.0] mEq/L and baseline characteristics per quintile of chloride are presented in table 1. Lower chloride levels were associated with younger age, lower ejection fraction and lower systolic and diastolic blood pressure (all *P*<0.03). In addition, lower chloride was associated with lower sodium, higher BUN, higher

bicarbonate, and higher hemoglobin (*P*<0.001). Interestingly, eGFR, creatinine, and (NT-pro) BNP were not different over quintiles of chloride.

Response to decongestive therapy:

Across quintiles of chloride, a lower chloride was associated with poorer diuretic response (kg weight loss per 40mg furosemide, Table 2). Furthermore, there was less weight change, higher diuretic doses, and more frequent requirement for adjuvant thiazide diuretics or inotropes during hospitalization in patients with hypochloremia (table 2, all *P*<0.01). In addition, low chloride was strongly associated to a lower rate of improvement in intravascular volume as indicated by a 20% absolute difference in the rate of hemoconcentration across quintiles of chloride (Table 2). Chloride remained significantly associated with diuretic response, even after correction for sodium and bicarbonate levels in addition to potential baseline and in hospital confounders (p<0.001). There was no significant difference in the incidence of worsening renal function over quintiles of chloride. Odds ratios for markers of poor decongestion and hypochloremia are shown in figure 1.

Chloride levels and outcome

In univariable Cox regression analysis, lower baseline chloride was associated with a higher risk of 180-day mortality (HR per SD decrease: 1.35 [1.22-1.49], *P*<0.001), however, after adjusting for baseline sodium, baseline chloride was no longer predictive of mortality (*P*=0.163) whereas sodium remained significantly associated (*P*<0.001). Notably, upon multivariable adjustment for baseline characteristics, neither baseline sodium nor chloride remained associated with outcome (Table 3). Addition of baseline chloride to a multivariable model containing sodium resulted in no improvement in model performance (*P*=0.627, Supplementary table 1).

Lower chloride levels at day 7 and day 14 were associated with a higher risk of 180-day mortality in both univariable and multivariable models, whereas day 7 and day 14 sodium levels were not predictive (table 3). Figure 2 shows the adjusted hazard ratios for sodium and chloride at different time points.

Addition of day 7 or 14 chloride to a multivariable model that included sodium at the same time point, significantly, though modestly improved the c-statistic (from 0.72 to 0.73; *P*<0.001, for both day 7 and day 14 chloride), and NRI (*P*<0.01, supplementary table 1). There was no significant interaction between sodium and chloride at any time point. A significant interaction between day 14 chloride and day 14 bicarbonate was observed where the risk associated with lower chloride was greater in patients with higher levels of bicarbonate. However this did not reduce the predictive value of day 14 chloride on 180-day mortality (supplementary table 2).

Change in chloride levels

On average, chloride levels in the overall population were stable over time (supplementary figure 1), and median chloride at baseline day 7 and day 14 were respectively 101.0 [97.0-104.0] mEq/L, 100 [96.0-103.0] mEq/L, and 101.0 [97.0-104.0] mEq/L. However, there were important individual changes in chloride levels, which explains the modest correlations between baseline and day 7 or day 14 chloride levels (r=0.60, *P*<0.001 and r=0.57, *P*<0.001). Comparing patients with hypochloremia at baseline and 14 days (Table 4) we find that 45% of patients with hypochloremia at day 1 no longer had hypochloremia by 14 days, and 59% of hypochloremia at day 14 was newly developed (figure 3). The majority of baseline and treatment related parameters were remarkably similar between patients whose hypochloremia was stable, improved, or worsened (table 4). The most notable difference we found in terms of clinical characteristics between these groups was a significant increase in BUN from day 1 to day 14, and a decrease in eGFR in patients with who developed new

hypochloremia at day 14 (table 4). There was no significant difference in changes in sodium or bicarbonate. Additionally, rolofylline administration was not associated with changes in chloride levels (*P*=0.782).

Change in chloride and outcomes:

A decrease in chloride from baseline to either day 7 or day 14 were both associated with an increased risk of 180-day mortality irrespective of baseline sodium and baseline chloride levels (supplementary table 3). However, the change seemed to be less important than the ultimate level of chloride achieved since after adjustment for day 14 chloride levels the change was no longer significant (supplementary Table 3). Patients with hypochloremia at baseline that persisted to day 14, and patients that newly developed hypochloremia by day 14 had 2-3 fold increase in the rate of mortality compared to patients without hypochloremia (HR: 3.11 [2.17-4.46], *P*<0.001, compared to patients with no hypochloremia at day 1 and day 14). Remarkably, as shown in table 4 the risk of 180-day mortality for patients with baseline hypochloremia whose chloride returned to normal by day 14 was comparable to patients who never had hypochloremia (HR: 1.19 [0.67-2.09], *P*=0.550, compared to patients with no hypochloremia at day 1 and day 14). Sensitivity analyses did not identify baseline or treatment related factors that could explain which patients with hypochloremia at day 14 were at higher risk for adverse outcomes (data not shown) or the reasons for improvement or worsening in serum chloride with treatment. Notably, a multivariable linear regression analysis (including all variables in table 1, and decongestion parameters from table 2) explained only 11% of the variance in change in chloride from baseline to day 14 (supplementary table 4).

Discussion

The principle findings of this study are that a low serum chloride is associated with a lower diuretic response, less decongestion, and increased mortality. We found that significant changes in serum chloride were very common during the treatment of AHF with approximately half of hypochloremic patients either resolving or developing new hypochloremia. Importantly, baseline hypochloremia that normalized during admission was not associated with adverse outcomes, whereas new or persistent hypochloremia was associated with 2-3 fold increased risk of mortality. Given the important role for chloride in neurohormonal and sodium homeostatic pathways, these associations might suggest that modulation of serum chloride may possibly improve diuretic response and potentially outcomes in patients with acute heart failure.

Chloride and response to therapy

Chloride has a great number of functions in the body, and deregulation of chloride results in a wide range of abnormalities. [15,16] Chloride has an important role in salt sensing, and seems to be the main driver in the kidneys ability to sense volume overload, as chloride containing solutions, but not non-chloride containing sodium solutions, elicited a response from the kidney. [4,5] Chloride has also been shown to reduce renin release, in contrast to non-chloride containing sodium salts which do not affect renin levels. [6] The role of chloride in regulation and response to volume retention in acute heart failure, is therefore of great interest as both fluid regulation and renin-angiotensin-aldosterone activation are deregulated in this setting.

Recent evidence suggests an association between chloride and diuretic targets. Several studies showed that sensing of hypochloride by WNKs (with no lysine K) causes upregulation of the sodium-potassium-chloride cotransporter (NKKC2). [7,8] Binding of chloride to the active site of WNK inhibits autophosphorylation and therefore decreases the availability of both NKCC2 and NCC and consequently reduces renal salt reabsorption. Both

the activity of loop diuretics, the most common therapy in acute heart failure that is prescribed to over 90% of all acute heart failure patients, and thiazide diuretics appear to be regulated by chloride.

In this study, we found a consistent association between lower baseline chloride levels and poor decongestion. We assessed multiple markers of decongestion, such as diuretic response, hemoconcentration, and physician assessed worsening heart failure, and found large difference of these parameters across the quintiles of chloride. We especially observed a remarkable difference in hemoconcentration, which was 20% more prevalent in the highest chloride quintile, compared to the lowest quintile. However, this study is observational and does not allow to assume a causative relationship. It may nonetheless be speculated that repletion of chloride might decrease fluid overload and subsequently improve decongestion, as evidence suggest a direct effect of chloride on reducing salt reabsorption through regulation of sodium transporters. In this scenario chloride itself would be one of the drivers of fluid overload and poor response to therapies. On the other hand chloride depletion could also be a result of therapy and hence be a sign of a more severe heart failure patient. Either mechanistic studies, or interventional chloride studies may be warranted to distinguish between these two possible scenarios.

Chloride levels over time and association with outcome

Despite overall stable levels of chloride over time in our entire study population, we observed great individual variation in chloride levels at different time points, and modest correlations between chloride levels at different time points. The shift in and out of hypochloremia might be a consequence of treatment, as loop diuretics block the NKCC2 in the kidney and generally cause a disproportionate excretion of chloride compared to sodium.[17] As such it is likely that hypochloremia at day 7, and day 14 may at least in part be diuretic treatment induced. In this study we found a greater predictive value of outcome for

day 7 and day 14 chloride, compared to baseline chloride. Interestingly, baseline hypochloremia was free from adverse prognostic significance as long as it resolved with treatment, whereas new or persistent hypochloremia was associated with 2-3 fold increase risk of mortality. The possibility that treatment induced changes in chloride are important is further supported by our finding that patients with higher levels of bicarbonate, which is retained by the body in response to chloride wasting, [18] have a higher risk of adverse outcome for any given decrease in chloride, compared to patients with normal bicarbonate levels. The increased impaired outcome associated with new-onset or persistent hypochloremia, compared to resolved baseline hypochloremia suggests that chloride is not just a marker of risk, as this would generate a greater risk associated with baseline hypochloremia, even when it resolved. Conversely our results show that new onset or persistent hypocholoremia carries greater prognostic significance.

Finally, we also found that a decrease in chloride levels over time was independently predictive of adverse outcome. Significance of the change in chloride was however lost after correction for the chloride level achieved at day 7 or day 14, indicating that the final value of chloride achieved contains more prognostic information than the change itself. A multivariable regression analysis for the change in chloride did not find important factors that could explain this change. More speculative, another explanation could be that the resultant chloride after a massive challenge to chloride homeostasis from treatment for acute heart failure is what makes the difference, rather than the change itself. Additional validation of our findings is required, however based on these results prospective studies investigating either chloride sparing therapies, or chloride replacement may be considered.

Limitations

This study is a post hoc analysis of a randomized controlled trial with all limitations as such. Additionally, we did not have long-term follow-up chloride data available and were

not able to study whether restoration of chloride levels attenuated the increased risk of adverse outcome over time.

Conclusion

Low baseline chloride was strongly associated with markers of poor decongestion. Hypochloremia after hospitalization for AHF, but not at baseline was strongly associated with mortality, suggesting the resultant chloride level carries greatest prognostic importance.

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Figure legends

Figure 1: Odds ratios for hypochloremia and markers of poor decongestion

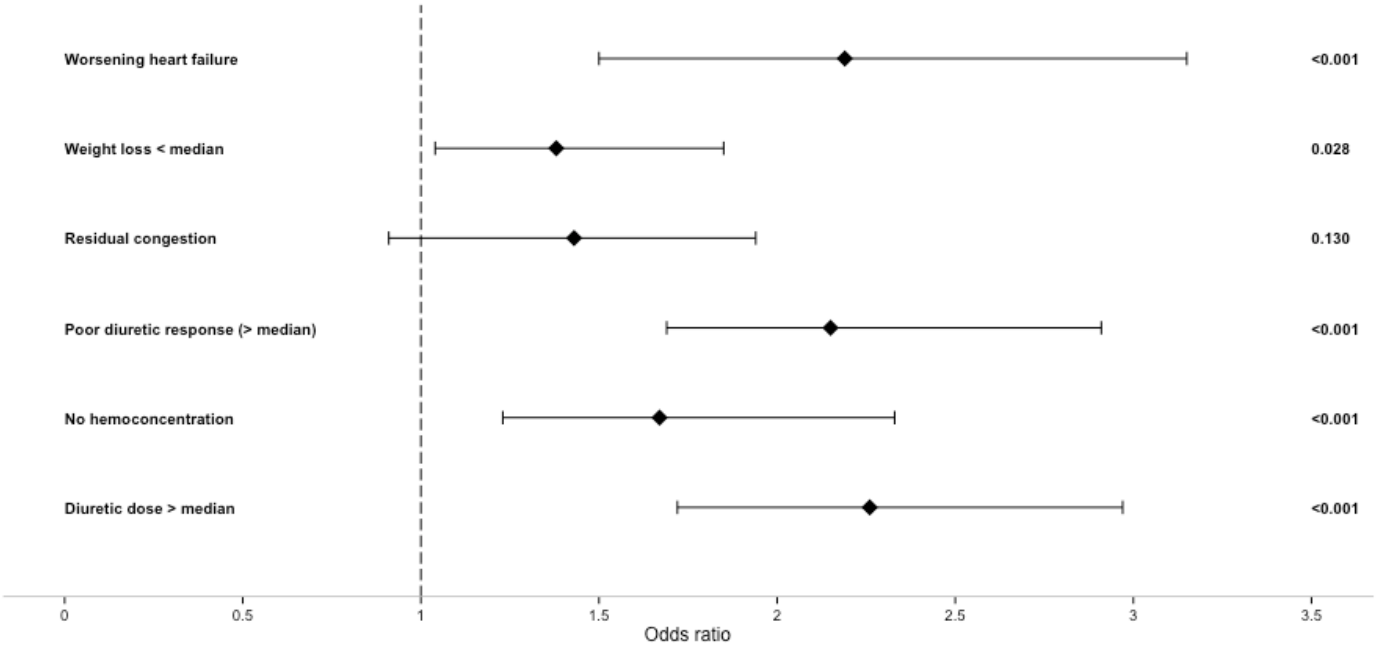


Figure 2: Adjusted hazard ratios 180-day mortality for different time points of sodium and chloride

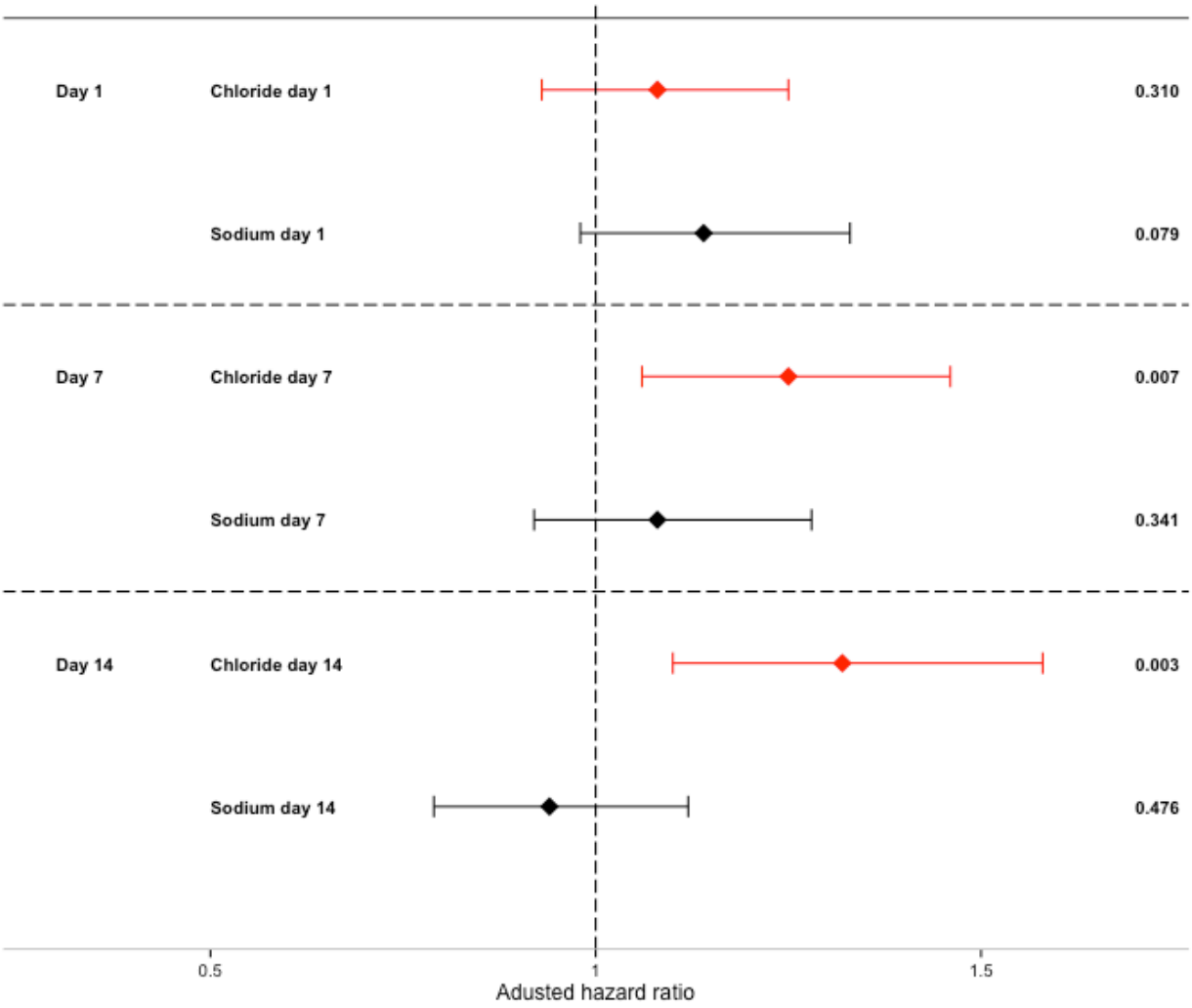


Figure 3: Percentages of hypochloremia on day 1 or day 14, or both

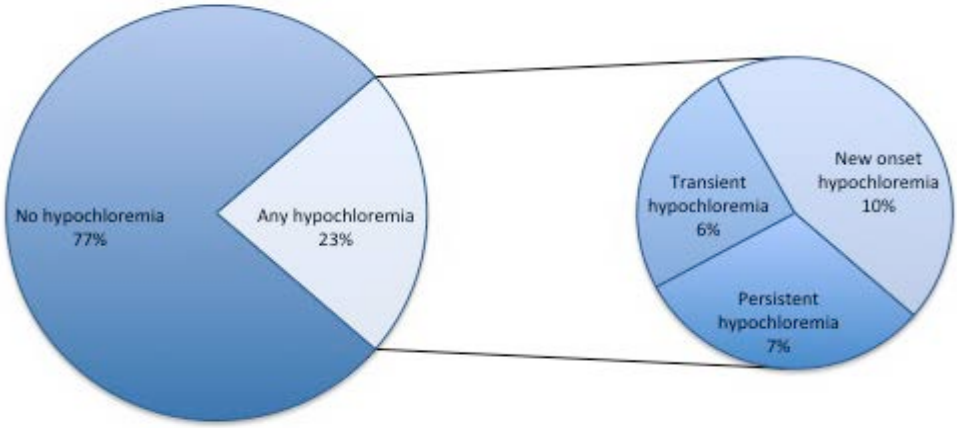


Table 1: Clinical characteristics per quintile of baseline chloride

	Q1	Q2	Q3	Q4	Q5	P for trend
N =	431	430	346	452	301	
Chloride (mEq/L)	95.0 [92.0-96.0]	99.0 [98.0-100.0]	101.0 [101.0-102.0]	104.0 [103.0-105.0]	107.0 [106.0-109.0]	
Demographics						
Sex (% Male (n))	64.5 (278)	68.1 (293)	68.5 (237)	65.9 (298)	67.1 (202)	0.683
Age (years)	68.8±12.3	70.4±11.9	69.5±12.2	71.1±10.9	71±10.2	**0.009**
LVEF (%)	31.3±14.4	31±12.9	32.9±12.5	32.8±11.9	33.8±12.5	**0.025**
Systolic Blood Pressure (mmHg)	117.5±17.4	121.8±16.9	125.9±16.8	128±17.3	130.7±16.5	**<0.001**
Diastolic Blood Pressure (mmHg)	70.2±12.4	73±11.2	74.8±11.2	75.3±11.5	77.1±11.6	**<0.001**
Heart Rate (beats/min)	79.6±16.5	80±15.5	79.5±13.5	81.6±15.9	80±15.1	0.330
Rolofylline administration (%(n))	64 (276)	69.5 (299)	64.7 (224)	69.9 (316)	65.1 (196)	0.576
Medical History						
Hypertension (%(n))	71.2 (307)	77.4 (333)	80.1 (277)	82.1 (371)	88.4 (266)	**<0.001**
PCI (%(n))	26.9 (115)	30.5 (130)	27.6 (94)	22.5 (101)	21.4 (64)	**0.009**
CABG (%(n))	27.6 (118)	23.5 (100)	20.9 (71)	17.7 (80)	15.7 (47)	**<0.001**
NYHA Class (%(n))						**<0.001**
I-II	16.7 (72)	16.7 (72)	15.9 (55)	19.2 (87)	15.6 (47)	
III	49.4 (213)	48.4 (208)	52.3 (181)	45.4 (205)	46.2 (139)	
IV	28.5 (123)	28.1 (121)	25.7 (89)	31.2 (141)	35.2 (106)	
ICD therapy (%(n))	24.4 (105)	18.6 (80)	15.3 (53)	10 (45)	9.3 (28)	**<0.001**
Prior Medication Use						
ACE inhibitors or ARB (%(n))	71.5 (308)	77 (331)	76.6 (265)	78.9 (356)	73.8 (222)	0.200
Beta blockers (%(n))	79.4 (342)	79.5 (342)	73.7 (255)	74.5 (336)	75.1 (226)	**0.035**
Mineralocorticoid Receptor Antagonists (%(n))	49.2 (212)	46.3 (199)	42.2 (146)	42.1 (190)	39.9 (120)	**0.004**
Calcium Antagonists (%(n))	8.8 (38)	12.3 (53)	13.6 (47)	15.1 (68)	19 (57)	**<0.001**
Laboratory Values						
Creatinine (mg/dL)	1.4 [1.2-1.8]	1.4 [1.1-1.7]	1.4 [1.1-1.7]	1.4 [1.1-1.7]	1.4 [1.1-1.9]	0.329
eGFR (ml/min/1.73m^2)	47.2 [36.3-61.4]	49.1 [37.9-63]	50.8 [37.3-64.9]	49.4 [37.3-64.2]	47.9 [35.6-65.3]	0.326
Blood Urea Nitrogen (mg/dL)	33 [24-48]	30 [22-40]	28 [21-38]	28 [22-39]	28 [22-39]	**<0.001**
Sodium (mmol/L)	135 [133-138]	138 [136-141]	140 [138-142]	141 [140-143]	143 [141-145]	**<0.001**
Potassium (mmol/L)	4.2 [3.8-	4.2 [3.8-	4.2 [3.9-	4.2 [3.9-	4.4 [4-4.8]	**<0.00**

	4.6]	4.6]	4.6]	4.6]		**1**
Bicarbonate (mEq/L)	25 [22-28]	24 [22-27]	24 [22-26]	23 [21-26]	22 [20-25]	**<0.001**
Hemoglobin (g/dL)	12.8±2.1	12.8±2	12.8±1.9	12.7±1.8	12.2±2	**<0.001**
NT-proBNP (pg/mL)	3000 [3000-4726]	3000 [3000-3294]	3000 [3000-3947.8]	3000 [3000-3847.8]	3000 [3000-3153]	0.330
BNP (mg/dL)	1300 [834-2078]	1310 [838.6-2215]	1237 [764-2318.2]	1220.9 [920-2260]	1153.5 [765.8-2241]	0.894

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BNP: brain natriuretic peptide; CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; ICD: implantable cardiac defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York heart association; NT-proBNP: n-terminal pro BNP; PCI: percutaneous coronary intervention

Table 2: Clinical, rehospitalization, and mortality outcomes per quintile of baseline chloride

Variable	Q1	Q2	Q3	Q4	Q5	P for trend
N =	431	430	346	452	301	
Clinical Outcomes						
Diuretic Response (kg/40 mg furosemide)	-0.24 [-0.52--0.06]	-0.31 [-0.70--0.10]	-0.44 [-0.83--0.25]	-0.50 [-0.93--0.25]	-0.48 [-0.94--0.23]	**<0.001**
Weight change day 1 - 4 (kg)	-2.5±3.2	-2.6±2.8	-2.9±3	-3.2±3	-2.9±2.7	**0.009**
Total diuretic dose, day 1 - 3 (mg)	320 [180-580]	260.2 [180-429.5]	220 [140-360]	200 [120-329.9]	180 [120-306.6]	**<0.001**
Total IV diuretic dose through day 7 (mg)	400 [160-918]	320 [160-615]	241.6 [120-440]	240 [120-460]	210 [113.2-420]	**<0.001**
In-hospital thiazide diuretic use	24.6 (106)	19.8 (85)	15 (52)	15 (68)	15 (45)	**<0.001**
Inotropics (%(n))	11.4 (49)	8.8 (38)	6.1 (21)	3.1 (14)	4.7 (14)	**<0.001**
Residual Congestion on day 7 (%(n))	70.4 (129)	61.2 (122)	51.6 (79)	53.3 (105)	56.6 (90)	0.071
Hemoconcentration on day 4 (%(n))	50 (143)	58.5 (165)	58.3 (144)	62.2 (199)	69.3 (147)	**<0.001**
WRF (≥0.3 mg/dL, and >25% increase in creatinine from baseline), day 7	9.6 (40)	7.7 (32)	8.3 (28)	8.9 (39)	11.6 (34)	0.412
WRF (≥0.3 mg/dL, and >25% increase in creatinine from baseline), day 14	9.5 (39)	8.5 (35)	12.5 (42)	10.6 (46)	13.7 (40)	0.052
Treatment failure due to Worsening Heart Failure (%(n))	15.1 (64)	10.3 (44)	9 (31)	6.5 (29)	6.6 (20)	**<0.001**
180-day mortality (%(n))	25.5 (110)	20 (86)	15 (52)	11.9 (54)	13 (39)	**<0.001**

Abbreviations: IV: intravenous; WRF: worsening renal function

Table 3: Cox regression analysis for baseline, day 7, and day 14 chloride

	180-day mortality			
	Univariable		**Multivariable***	
	HR [CI]	P-value	HR [CI]	P-value
Chloride day 1 (per SD decrease)	1.35 [1.22-1.49]	<.001	1.08 [0.93-1.25]	0.310
Sodium day 1 (per SD decrease)	1.40 [1.28-1.55]	<.001	1.14 [0.98-1.33]	0.079
Chloride day 7 (per SD decrease)	1.51 [1.36-1.68]	<.001	1.25 [1.06-1.46]	0.007
Sodium day 7 (per SD decrease)	1.48 [1.33-1.65]	<.001	1.08 [0.92-1.28]	0.341
Chloride day 14 (per SD decrease)	1.61 [1.44-1.80]	<.001	1.32 [1.10-1.58]	0.003
Sodium day 14 (per SD decrease)	1.47 [1.32-1.63]	<.001	0.94 [0.79-1.12]	0.476

*** Corrected for age, previous HF hospitalization, edema, SBP, log BUN, log creatinine, albumin, rolofylline treatment, and sodium or chloride**

Abbreviations: BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio; SBP: systolic blood pressure; SD: standard deviation

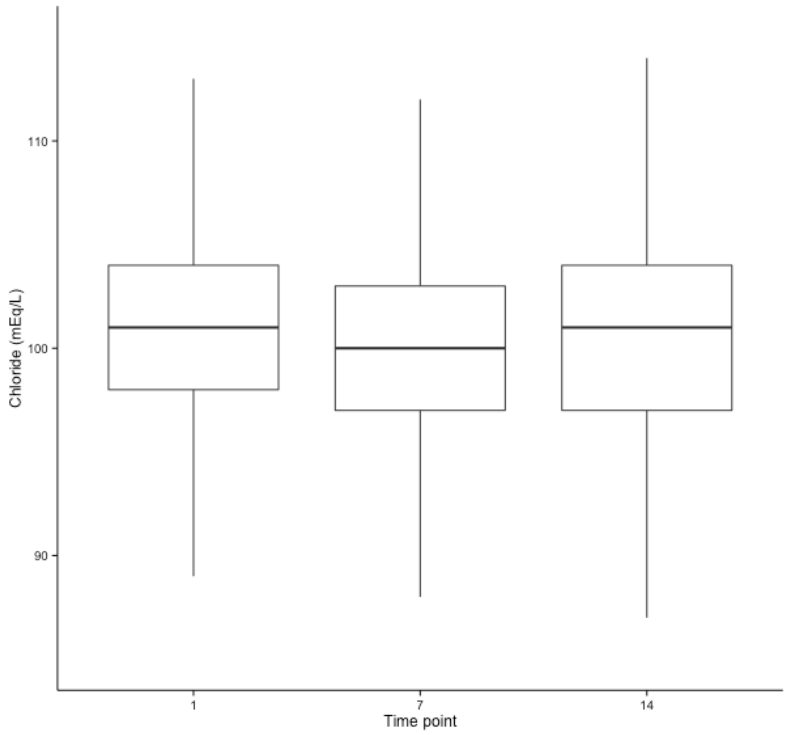
Table 4: Clinical characteristics per group with hypochloremia at baseline and/or day 14

Variable	HypoCl day 1 & 14	HypoCl day 1	HypoCl day 14	No HypoCl	P for trend
N =	122	98	177	1346	
Demographics					
Sex (% Male)	71.3 (87)	62.2 (61)	67.2 (119)	66.6 (896)	0.607
Age (years)	66.1±11.7	69.4±13.5	71.2±11.5	70.1±11.4	**<0.001**
LVEF (%)	28.1±14	34.2±16.6	30.8±13.1	32.4±12.4	0.085
Systolic Blood Pressure (mmHg)	112.7±17.2	120.6±18.4	119.5±17.5	126.4±16.9	**<0.001**
Diastolic Blood Pressure (mmHg)	68±11	71.7±13.4	70.9±11.2	75±11.6	**<0.001**
Rolofylline administration (%)	62.3 (76)	72.4 (71)	67.8 (120)	66.9 (900)	0.782
Medical History					
Hypertension (%)	68 (83)	73.5 (72)	74.6 (132)	81.2 (1093)	**<0.001**
PCI (%)	25.6 (31)	20.6 (20)	33.7 (59)	25.2 (336)	0.854
CABG (%)	36.9 (45)	19.4 (19)	24.6 (43)	19.6 (262)	**<0.001**
NYHA Class					**<0.001**
I-II	18 (22)	19.4 (19)	19.2 (34)	16.3 (220)	
III	45.9 (56)	44.9 (44)	49.7 (88)	48.5 (653)	
IV	32 (39)	29.6 (29)	20.9 (37)	31 (417)	
ICD therapy (%)	34.4 (42)	13.3 (13)	24.3 (43)	13.5 (182)	**<0.001**
Laboratory Values					
Creatinine (mg/dL)	1.5 [1.2-1.9]	1.3 [1.1-1.7]	1.4 [1.2-1.8]	1.4 [1.1-1.8]	0.161
eGFR (ml/min/1.73m^2)	46.5 [36.2-58.2]	52.3 [38.4-63.9]	47.2 [34.9-62.8]	50.4 [37.5-64.8]	**0.044**
Blood Urea Nitrogen (mg/dL)	39 [26-50.8]	28.5 [21-48.8]	30 [23-45]	28 [21-38]	**<0.001**
Sodium (mmol/L)	133 [130.2-136]	135 [132-138]	139 [137-141]	141 [138-143]	**<0.001**
Potassium (mmol/L)	4.2 [3.8-4.6]	4.3 [3.9-4.6]	4.1 [3.8-4.5]	4.2 [3.9-4.7]	0.422
Bicarbonate (mEq/L)	25 [22-29]	26 [23-29]	24 [21-27]	24 [21-26]	**<0.001**
Hemoglobin (g/dL)	12.7±2.1	13.2±2.2	12.5±1.8	12.7±1.9	0.163
NT-proBNP (pg/mL)	3000 [3000-5177]	3000 [2971-3000]	3000 [3000-4952]	3000 [3000-3622]	**0.003**
BNP (mg/dL)	1196.5 [833-1607.5]	1507.5 [1027.2-2145.2]	1430 [907.5-2390.8]	1215.5 [780.4-2217.4]	0.325
Delta Sodium (day 14 – day 1)	-2 [-4-1]	2.5 [0-6]	-5 [-7--2]	0 [-3-2]	**<0.001**
Delta Chloride (day 14 – day 1)	-1 [-3-1.8]	5.5 [4-9]	-7 [-10--5]	0 [0302]	**<0.001**
Delta Potassium (day 14 –	0.3 [-0.1-	0.4 [-0.1-0.8]	0.3 [-0.2-	0.4 [0-0.8]	0.369

day 1)	0.8]		0.8]		
Delta Bicarbonate (day 14 – day 1)	-1 [-3-3]	-2 [-4-1]	1 [-2-4]	0 [-2-3]	**0.004**
Delta Creatinine (day 14 – day 1)	0 [-0.2-0.3]	-0.1 [-0.2-0.1]	0.2 [-0.1-0.5]	0 [-0.2-0.2]	0.055
Delta Blood Urea Nitrogen (day 14 – day 1)	2.5 [-5-10.8]	-2[-9-5]	12 [2-25]	3 [-3-11]	**<0.001**
Delta eGFR (day 14 – day 1)	0 [-7.8-9.5]	2.4 [-2.4-10.2]	-6.5 [-15-1.8]	0 [-7.8-7.1]	**0.003**
Clinical Outcomes					
Diuretic Response day 4 (kg/40 mg furosemide)	-0.20 [-0.39-0.04]	-0.31 [-0.67--0.08]	-0.20 [-0.44--0.05]	-0.44 [-0.89--0.20]	**<0.001**
Total diuretic dose, day 1 - 3 (mg)	412.5 [240-800]	260 [144.2-541.9]	310 [200-560]	215.1 [140-360]	**<0.001**
In-hospital thiazide diuretic use	29.5 (36)	26.5 (26)	32.8 (58)	15.4 (207)	**<0.001**
Metolazone use	18 (22)	8.2 (8)	11.3 (20)	2.7 (37)	**<0.001**
180-day mortality (%)	30.3 (37)	13.3 (13)	25.4 (45)	11.2 (151)	**<0.001**

Abbreviations: BNP: brain natriuretic peptide; CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; ICD: implantable cardiac defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York heart association; NT-proBNP: n-terminal pro BNP; PCI: percutaneous coronary intervention

Supplementary figure 1: Chloride levels over time



Supplementary table 1: Gain in C-index, and NRI in survival models 180-day mortality

	C-index	Gain in C-index	P-value	NRI	P-value
Base model*	0.72				
Add baseline chloride	0.72	0.0%	0.982	-0.05	0.627
Add day 7 chloride	0.73	1.6%	<0.001	0.29	<0.001
Add day 14 chloride	0.73	1.8%	<0.001	0.26	0.008

*** Base model includes age, previous HF hospitalization, edema, SBP, log BUN, log creatinine, albumin, rolofylline treatment, and sodium**

Abbreviations: BUN: blood urea nitrogen; HF: heart failure; SBP: systolic blood pressure

Supplementary table 2: Cox regression analysis day 14 chloride (per SD decrease) per tertile of bicarbonate

	180-day mortality			
	Univariable		**Multivariable***	
	HR [CI]	P-value	HR [CI]	P-value
Bicarbonate tertile 1 21 [20-23]	1.57 [1.32-1.87]	<.001	1.36 [1.10-1.68]	0.004
Bicarbonate tertile 2 25 [24-26]	1.69 [1.38-2.05]	<.001	1.45 [1.13-1.85]	0.003
Bicarbonate tertile 3 28 [27-30]	1.91 [1.52-2.39]	<.001	1.48 [1.14-1.91]	0.003

*** Adjusted for age, previous HF hospitalization, edema, SBP, log BUN, log creatinine, albumin, rolofylline treatment, and sodium**

Abbreviations: BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio; SBP: systolic blood pressure; SD: standard deviation

Supplementary table 3: Cox regression analysis 180-day mortality delta chloride

	180-day mortality			
	Multivariable*		**Multivariable* + day 7 or 14 chloride**	
	HR [CI]	P-value	HR [CI]	P-value
Chloride day 7-1 (per SD decrease)	1.26 [1.12-1.41]	<.001[§]	1.16 [0.99-1.37]	0.072
Chloride day 14-1 (per SD decrease)	1.31 [1.16-1.47]	<.001[§]	1.18 [0.98-1.41]	0.075

*** Corrected for age, previous HF hospitalization, edema, SBP, baseline sodium, log BUN, log creatinine, albumin and rolofylline treatment**
$ remains significant after addition of baseline chloride to the mv model

Abbreviations: BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio; SBP: systolic blood pressure; SD: standard deviation

Supplementary table 4: multivariable linear regression model delta chloride day 14 – day 1

Variable	Beta Coeff	95% CI	T value	p-value
Sodium per SD	-1.410	-1.64--1.18	-12.156	<0.001
Bicarbonate per SD	0.887	0.65-1.19	7.742	<0.001
Total cholesterol per SD	0.688	0.47-0.91	6.164	<0.001
Orthopnea	1.272	0.14-2.40	2.072	0.028

r^2=0.107