Title

Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance

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Abstract

Background: Low serum chloride is common in patients with chronic heart failure (CHF) and is associated with worse outcomes.

Objectives: We investigated the clinical and prognostic associations, including cause of death associations, of low serum chloride in patients referred to a secondary care clinic with suspected heart failure.

Methods: Patients with echocardiogram and serum chloride were evaluated (n=5613). CHF was defined as signs and symptoms of the disease and **either** left ventricular systolic dysfunction (LVSD) worse than mild: heart failure with reduced ejection fraction (HFREF) **or** LVSD mild or better *and* raised NTproBNP levels (>125 ng/L): heart failure with preserved ejection fraction (HFPEF). Hypochloraemia was defined as greater than 2 standard deviations below the mean in the local normal distribution (<96 mmol/L).

Results: Of the 5613 patients referred, 908 patients did not have CHF, 1988 had HFREF, and 2717 had HFPEF. Compared to patients in Q4 (median chloride 106 mmol/L), patients in Q1 (median 96 mmol/L) had more severe symptoms (38% NYHA III or IV *vs.* 25%, P<0.001) and were more likely to take loop diuretics (79% *vs.* 59%, P<0.001). The annual mortality rate for patients with CHF was 11%. Hypochloraemia was associated with an increased risk of death independent of NTproBNP. Patients in Q1 had a 2-fold increased risk of death compared to patients in Q4 (P<0.001). Sudden death was a common mode of death amongst patients with hypochloraemia.

Conclusions: Hypochloraemia is strongly related to an adverse prognosis and may be a therapeutic target in patients with CHF.

Keywords

Heart failure, chloride, outcome, hypochloraemia, diuretics, prognosis.

Main text

Introduction

Electrolyte abnormalities are common in patients with chronic heart failure (CHF) and may affect treatment decisions and outcome. Hyponatraemia and both hypo- and hyper-kalaemia are adverse prognostic markers that have been therapeutic targets in some recent trials.[1,2] Hyponatraemia is a marker of severe CHF that might prompt consideration of a heart transplant.[3] Until very recently, the possible importance of serum chloride levels in patients with CHF had been overlooked.

Hypochloraemia (<96 mmol/L) is common in patients with CHF and is associated with a higher risk of mortality in patients with acute or chronic heart failure, independent of prognostic markers such as amino-terminal pro-B-type natriuretic peptide (NTproBNP).[4-10] It is not yet clear whether hypochloraemia has a direct pathological effect,[5,8] or is merely a consequence of diuretic therapy,[11] or a marker of congestion and disease severity.[12]

Previous studies of chloride in patients with heart failure have either involved patients admitted with acute heart failure[4] or myocardial infarction[10], or highly selected study populations.[5-7,9] Information on the clinical and prognostic significance of abnormal serum chloride levels in unselected out-patients with heart failure, with either reduced (HFREF) or preserved ejection fraction (HFPEF) are lacking. Importantly, there is little data on the mode of death associated with abnormal chloride levels in patients with heart failure. We therefore

investigated the prevalence and clinical and outcome associations of hyper- and hypochloraemia in a large cohort of ambulatory patients with HFREF or HFPEF.

Methods

Patient population

Between September 2000 and October 2016, consecutive referrals (n=6897) from both primary and secondary care were enrolled at a single secondary care clinic serving a local population of about 500,000 people (The Hull LifeLab). The study conforms to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent.

For the purpose of this analysis, CHF was defined as the presence of signs or symptoms consistent with the diagnosis and **either** left ventricular systolic dysfunction (LVSD) worse than mild, defined as HFREF **or** LVSD absent or at most mild *and* abnormal NT-pro-BNP plasma levels (>125 ng/L), defined as HFPEF.

Hypochloraemia, hyponatraemia and hypokalaemia were defined as greater than 2 standard deviations below the mean electrolyte level in the normal distribution for the local population (<96 mmol/L, <135 mmol/L and <3.5 mmol/L respectively). Hyperchloraemia was defined as greater than two standard deviations above the mean chloride level in the normal distribution for the local population (>105 mmol/L).

Outcomes

Patients were followed up until 16/10/2016. The primary outcomes of interest were all-cause mortality and the composite endpoint of mortality or hospitalisation with heart failure. For each patient who died, the cause of death was adjudicated as detailed in the supplement.

Statistical Analysis

Categorical data are presented as percentages, normally distributed continuous data are presented as mean ± standard deviation (SD) and non-normally distributed variables are presented as median and interquartile range (IQR).

The relationship between chloride and other variables was assessed by Pearson correlation coefficients. Uni- and multi- variable linear regression models were used to identify variables associated with serum chloride. Only variables with $p<0.05$ in univariable analysis were included in the multivariable model. Log-transformed NTproBNP was used.

Patients with CHF were sub-divided as a whole and by phenotype (HFREF or HFPEF) into chloride quartiles and groups depending on the presence of hyponatraemia and / or hypochloraemia: group 1 – hyponatraemia and hypochloraemia, group 2 – normal sodium and hypochloraemia, group 3 – hyponatraemia and normal chloride and group 4 – normal sodium and chloride levels. Chi-squared tests were used to compare categorical variables and one-way analysis of variance (ANOVA) to compare continuous variables across the groups, assumptions of ANOVA (normality or residuals and equal variance) were checked. Kruskal-Wallis tests were used to compare non-normally distributed continuous variables across the quartiles and groups.

Associations between variables and outcome were assessed with Cox regression, proportionality of hazards was checked by residual plotting. Univariable analysis was

conducted using all variables in the dataset and variables with P>0.1 in univariable analysis or with more than 10% missing values (an arbitrary threshold) were not included in the multivariable analyses. Kaplan-Meier curves were used to demonstrate outcome by different groups.

Harrell's C-statistic (area under the receiver-operating characteristic curve) was used to highlight the discrimination of different outcome models with and without chloride. 25-fold cross validation was performed on all variables in the database.

Statistical analysis was carried out using the Stata 14 and SPSS 23 software packages. The two-tailed level of statistical significance was set at $P < 0.05$.

Results

Of the 6897 patients referred to the heart failure service, 5613 had data on echocardiography, NTproBNP and serum chloride at baseline, 908 patients did not have HF and were not included in the analysis. Of the remaining 4705 patients (table 1), 1988 patients had HFREF (supplementary table 1) and 2717 patients had HFPEF (supplementary table 2).

The prevalence of hypochloraemia was 10.7% in patients with heart failure, 12.6 % in patients with HFREF and 9.3% in patients with HFPEF (P<0.001).

By comparison, the prevalence of hyponatraemia was 11.3% amongst all patients with heart failure, 13.1% in patients with HFREF and 10.1% in patients with HFPEF (P=0.002).

The prevalence of dual hypochloraemia and hyponatraemia was 5.9% in all patients, 7.2% in patients with HFREF and 5.0% in patients with HFPEF (P=0.001).

The prevalence of *hyper*chloraemia was 13.2% amongst all patients with heart failure, 11.7% in patients with HFREF and 14.3% patients with HFPEF (P=0.001).

Patient characteristics by serum chloride levels

Median chloride of patients in the first quartile (Q1) was 96 mmol/L (range 76-99 mmol/L) and 106 mmol/L (range 104-117 mmol/L) in the fourth quartile (Q4).

Patients in Q1(including those with hypochloraemia (<96 mmol/L)) were older, more likely to have AF or diabetes and had more severe symptoms and a higher rate of loop diuretic prescription compared to patients in Q2-4 (P<0.001) (table 1). 59% of patients in Q1 who were taking loop diuretic were prescribed doses greater than 80mg of furosemide per day (table 1).

Patients with hypochloraemia had higher NTproBNP than those with normal chloride levels (P<0.001). There was a general trend towards higher NTproBNP amongst patients in Q1 compared to Q2-4; the relationship was significant (P<0.001) but weak (r^2 = 0.021; scatterplot not shown).

By contrast, patients with hyperchloraemia (>105 mmol/L) were less likely to have severe symptoms and signs, had lower NTproBNP and had a lower rate of diuretic prescription than patients with hypochloraemia or low-normal chloride (Q1 and Q2) (P<0.001).

Similar trends were observed across the quartiles in the HFREF and HFPEF subgroups (supplementary tables 1 and 2). Median NTproBNP was higher (1750 ng/L vs. 734 ng/L; P<0.001), and the proportion of patients with NYHA III or IV symptoms (35% vs. 24%; P<0.001) or taking a loop diuretic (75% vs. 54%; P<0.001) was greater amongst patients with

HeFREF compared to patients with HFPEF. Additionally, the proportion of patients with hypochloraemia who were taking a loop diuretic was higher in patients with HFREF compared to patients with HFPEF (91% vs. 69%; P<0.001).

Patient characteristics by serum chloride and sodium concentrations

Patients with hypochloraemia and either low (group 1) or normal (group 2) sodium had similar demographics and disease severity (table 2).

However, there were several biochemical differences between the two groups possibly identifying two distinct groups of patients with hypochloraemia. For example, patients with hypochloraemia and *normal* sodium had higher bicarbonate, haemoglobin, haematocrit and rate of hypokalaemia than patients with hypochloraemia and hyponatraemia (P<0.001) (table 2). Haemoglobin and haematocrit were similar in those with hyponatraemia regardless of chloride levels (group 1 and 3) (table 2).

Disease severity, NTproBNP and rate of high dose diuretic prescription were lower in patients with normal chloride levels regardless of sodium levels (group 3 and 4) compared to those with low chloride levels regardless of sodium levels (group 1 and 2) (table 2) (P<0.001).

Associations with serum chloride

In all patients with heart failure and in both the HFREF and HFPEF subgroups, there was a strong positive correlation between chloride and sodium and a strong negative correlation with bicarbonate in multivariable analysis (supplementary figure 1). In all patients with heart failure and in both the HFREF and HFPEF subgroups, chloride had a weak negative correlation with log[NTproBNP] in univariable analysis. However, log[NTproBNP] was only associated with chloride after adjustment for other variables amongst patients with HFREF (supplementary figure 1); the association was of borderline significance (correlation co-efficient $\beta = -0.326$; t-statistic = -2.81; p=0.05). The strength and direction of other associations with serum chloride were similar between heart failure phenotypes.

Predictors of outcome

During a median follow up of 1691 days (IQR 754-1825), 1643 patients died and there were 919 hospitalisations with heart failure. A total of 1946 patients either died or were hospitalised with heart failure.

Low serum chloride was strongly and independently associated with increasing mortality (figure 1) and all-cause mortality or heart failure hospitalisation in all patients with heart failure and in the HFREF and HFPEF subgroups.

Other independent predictors of all-cause mortality (ACM) or ACM or hospitalisation with heart failure in both HFREF and HFPEF were increasing age, increasing heart rate, severe symptoms (NYHA III or IV), loop diuretic use, increasing log[NTproBNP], increasing urea and decreasing albumin. No variable was an independent predictor of one endpoint but not the other.

Variables that were independent predictors of outcome in patients with HFPEF and not HFREF were male sex, decreasing haemoglobin and increasing potassium levels. Variables that were independent predictors of outcome in patients with HFREF and not HFPEF were increasing bilirubin and the presence of ischaemic heart disease (IHD) (data not shown). However, neither haemoglobin, potassium, bilirubin or the presence of IHD were associated with outcome in *all* patients with heart failure (supplementary tables 5 and 6)..

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Chloride as a predictor of adverse outcome

With each unitary decrease in chloride, there was a 4% increase in mortality (hazard ratio (HR) = 1.04 (95% confidence interval (CI) = 1.02 – 1.06, P<0.001) and a 3% increase mortality *or* hospitalisation with heart failure (HR = 1.03 (95% CI = 1.02 – 1.05, P<0.001) independent of age, sex, body mass index, systolic blood pressure, heart rate, diabetes, IHD, NYHA class, log[NTproBNP], sodium, bicarbonate, calcium, potassium, haemoglobin, creatinine, urea, eGFR, albumin, alkaline phosphatase, alanine transferase, bilirubin, prescription of loop diuretics and CHF phenotype (HFREF vs. HFPEF) (supplementary table 5 and 6). Patients in Q1 had around a 2 fold increased risk of mortality compared to patients in Q4 (figure 2).

There was a tendency for mortality to increase as chloride increased substantially above the normal range (>105 mmol/L). However, there were very few patients with very high chloride levels and thus, the event rate was low. Patients in Q4 were at a slightly higher risk of adverse outcome compared to Q3, but the association was not statistically significant.

Patients with hypochloraemia had a similar prognosis, regardless of whether sodium was low (group 1) or normal (group 2); and both groups had a markedly worse prognosis than patients with an isolated low sodium (group 3) or those with both a normal sodium and chloride (group 4) (figure 3). The unadjusted odds ratio for mortality for patients with hypochloraemia was 2.64 compared to 1.71 for patients with hyponatraemia.

In 25-fold cross validation using all variables listed in table 1, chloride featured in 22 models (88%) as a predictor of outcome. By comparison, sodium, potassium, bicarbonate and haemoglobin did not feature in any model. However, chloride did not add to the prognostic value of two models:

1) Harrell's C-statistic for a model including all variables that featured in >80% of cross validation models (age, sex, body mass index, atrial fibrillation, NYHA class, log[NTproBNP], chloride, urea, albumin, ALT, ALP and loop diuretic) was 0.742 without chloride and 0.748 with chloride.

2) C-statistic for an *a priori* model of age, sex, creatinine, albumin, IHD, NTproBNP, NYHA class, and use of loop diuretics was 0.734 without chloride and 0.738 with chloride.

Cause of death after 1 year follow up

Amongst the 4505 patients with follow up data to one year, 11% died, 60% from cardiovascular causes (table 3).

Death due to terminal heart failure was more common for patients in Q1 (including those with hypochloraemia) compared to Q2-4. Sudden death was more common in Q4 compared to Q1-3 but the event rate was much higher in Q1 (table 3).

Similar trends were seen across the quartiles in the HFREF and HFPEF subgroups although mortality rate was higher in patients with HFREF compared to HFPEF (12% vs. 9%) and cardiovascular death was a more common mode of death amongst patients with HFREF compared to patients with HFPEF (69% vs. 52%) (supplementary table 4).

Sudden death was more common among patients with hypochloraemia (groups 1 and 2) compared to those with normal chloride levels and hyponatraemia (group 3) (supplementary table 3). The proportion of sudden deaths was greatest in patients with normal chloride and sodium levels (group 4) but the event rate was low.

Discussion

Our results add to the validity of findings of other studies:[4-10] low serum chloride is associated with increased risk of morbidity and mortality in patients with heart failure regardless of phenotype and independent of more established prognostic variables such as NTproBNP or sodium.

There are novel findings from the current study: 1) There may be an association between abnormal chloride levels and sudden death. 2) Hypochloraemia in patients with CHF might exist in two distinct biochemical phenotypes with implications for management. 3) Mortality risk increases substantially with chloride concentrations less than 100 mmol/L

Chloride and NTproBNP

Previous studies have either not included NTproBNP,[7,10] found no difference,[5,6,8,9] or found only a weakly significant difference[4] in natriuretic peptides between patients with low and

normal serum chloride concentrations. In a very large cohort, we found a significant but weak inverse relation between chloride and NT-proBNP: however, the two were not related when corrections were made for other variables.

Hypochloraemia was an indicator of severe disease, regardless of heart failure phenotype, and both decreasing chloride and increasing NTproBNP were strong independent predictors of an adverse outcome, suggesting that they are assessing different aspects of the heart failure syndrome.

Chloride and sudden death

Low serum chloride concentrations may have a stimulatory effect on a family of enzymes, with-no-lysine (WNK) kinases,[13,14] which increase activity of Na^+-K^+-$2Cl^-$ (NKCC) and Na^+-Cl^- (NC) co-transporters.[15,16] NKCC and NC co-transporters have a role in maintaining myocyte volume and pH.[17,18] Dysregulation of myocyte intracellular pH is arrhythmogenic,[19] and impairs contractility.[20] Furthermore, cardiac chloride channels are implicated in sino-atrial pacing ,[21] and arrhythmogenesis.[22] Thus, there are plausible mechanisms by which abnormal chloride levels might affect cardiac rhythm. However, how serum chloride affects the function of chloride channels or chloride-dependent co-transporters in humans is unknown. Further work is required.

Chloride and sodium

Hypochloraemia, regardless of sodium levels, was associated with higher risk of mortality and mortality or heart failure hospitalisation than isolated hyponatraemia. Sodium was not

associated with adverse outcome after adjustment for other variables, including chloride. Monitoring serum sodium levels is recommended as an important prognostic marker in patients with heart failure, but it may be that chloride should have similar prominence in guidelines and clinical practice.

Our results support the assertions of Ferreira et al (2017) that chloride should be assessed in the context of serum sodium levels.[10] There seem to be two biochemical phenotypes:

1) In patients with hypochloraemia *and* hyponatraemia who have low haemoglobin, haematocrit and mean cell volume: in such patients, haemodilution may be an important contributor to the biochemical abnormalities.[23,24] (Group 1 – table 2).

2) In patients with hypochloraemia and normal sodium levels who have higher haemoglobin with higher bicarbonate and a higher rate of hypokalaemia: in such patients, the hypochloraemia may be due to depletion.[11,25] (Group 2 – table 2).

Metabolic alkalosis is the most common acid-base disturbance in patients with HF,[26] and chloride depletion in the context of alkalosis is a well-recognised complication of diuretic treatment.[26,27]

Both phenotypes have similar prevalence and risk of adverse outcome but the distinction may have implications for treatment, especially considering a similar proportion of patients have clinical signs of congestion in the two groups: while increasing the dose of loop diuretic might be appropriate to treat haemodilution, diuretic might also cause or worsen hypochloraemia. Patients with CHF who are prescribed loop diuretic have a poorer prognosis than those not needing diuretic treatment.[28] Electrolyte abnormalities, such as hypochloraemia, may contribute to such findings.

Acetazolamide, a carbonic anhydrase inhibitor that reduces bicarbonate and sodium re-absorption and increases chloride re-absorption in the proximal tubule, can increase chloride levels whilst also having a diuretic action (a 'chloride-sparing' diuretic), and warrants further attention.[29]

It is important to note that not all patients with hypochloraemia were taking a loop diuretic, suggesting that other aspects of the heart failure syndrome, such as haemodilution, can cause hypochloraemia. This was particularly the case in the HFPEF subgroup; perhaps a reflection of the difficultly of making a clinical diagnosis of heart failure in patients with a normal ejection fraction, leading to a lower rate of diuretic prescription.

Redefining the normal limits for serum chloride

The U-shaped relation between chloride and mortality shows a substantial increase in risk of death at chloride concentrations less than 100 mmol/L (figure 1). Redefining hypochloraemia as <100 mmol/L would undoubtedly increase the number of patients who might be declared suitable for 'chloride-sparing diuretics' such as acetazolamide in future trials and clinical practice.

We did find that very high levels of chloride were associated with an adverse outcome. However, the absolute number of patients at the high end of the chloride distribution was small and the absolute number of events smaller still, making it impossible to draw conclusions with certainty.

Limitations

The limitations of retrospective analyses apply to our study and confounding factors cannot be excluded. A substantial proportion of patients referred to our clinic was naïve to treatment; initiation or adjustments of current treatment might have led to improved electrolyte balance. Our data is a snapshot of a single time-point and no conclusions can be drawn on the importance of changing chloride levels over time. Data on urinary electrolyte concentrations is also missing which would be useful in further delineating the different phenotypes of hypochloraemia. Some might not accept an NTproBNP > 125 pg/ml as diagnostic for heart failure with preserved ejection fraction, although it is consistent with recent European Society of Cardiology guidelines,[30] diagnosis of HFPEF remains difficult in most cases.

Although we recorded cause of death in a carefully prescribed manner, we were not able to use autopsy data to confirm mode and cause of deaths.

Conclusion

Hypochloraemia is an important adverse prognostic marker in patients with chronic heart failure and sudden death is a common mode of death amongst patients with heart failure and low chloride levels. Whether chloride is a target for treatment is not clear and should be tested in future clinical trials.

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Conflicts of interest

None.

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Figure legends

Figure 1

Title: Association between mortality and serum chloride in patients with heart failure

Caption: Probability of all-cause mortality at 5-year follow up by serum chloride levels in patients with heart failure with a reduced ejection fraction or heart failure with a preserved ejection fraction. Frequency bars show the proportion of patients with a specific chloride concentration. The population was divided into quartiles based on serum chloride concentration, denoted by different coloured areas of the figure.

Figure 2

Title: Kaplan-Meier curve for quartiles of serum chloride

Caption: Kaplan-Meier curves for all-cause mortality in patients with heart failure and a reduced ejection fraction or heart failure and a preserved ejection fraction divided by quartiles of serum chloride. Unadjusted hazard ratios for different quartiles compared to quartile 4 also included.

Figure 3

Title: Kaplan-Meier curve for groups based on the presence of hypochloraemia and/or hyponatraemia

Caption: Kaplan-Meier curves for all-cause mortality in patients with heart failure and a reduced ejection fraction or heart failure and preserved ejection fraction divided by groups based on the presence of hypochloraemia and/or hyponatraemia. Group 1 – hypochloraemia and hyponatraemia; group 2 – hypochloraemia and normal sodium levels; group 3 – normal chloride levels and hyponatraemia; group 4 – normal chloride and sodium levels. Unadjusted hazard ratios for different groups compared to group 4 also included.

Supplementary figure 1

Title: Univariable correlation matrix for variables associated with serum chloride levels in all patients with heart failure and in the HFREF or HFPEF subgroups.

Caption: List of abbreviations used: ALP – alkaline phosphatase; ALT – alanine aminotransferase; BMI – body mass index; eGFR – estimate glomerular filtration rate; HF – heart failure; HFPEF – heart failure with preserved ejection fraction; HFREF – heart failure with reduced ejection fraction; HR – heart rate; LAD – left atrial diameter; LVEF – left ventricular ejection fraction; no. – number; NTproBNP – N-terminal B-type natriuretic

peptide; SBP – systolic blood pressure. * P≤0.05 on multivariable linear regression. ** P>0.05 on multivariable linear regression. Variables entered into the multivariable model for all patients included: age, BMI, sodium, potassium, bilirubin, haemoglobin, ALT, albumin, ALP, Urea, eGFR, bicarbonate, SBP, HR, log[NTproBNP]. Variables entered into the multivariable model for patients with HFREF included: age, BMI, sodium, potassium, bilirubin, haemoglobin, ALT, albumin, ALP, Urea, eGFR, bicarbonate, SBP, HR, log[NTproBNP]. Variables included in the multivariable model for patients with HFPEF included: age, BMI, sodium, potassium, bilirubin, haemoglobin, albumin, ALP, Urea, eGFR, bicarbonate, SBP, HR, log[NTproBNP].

Tables

Table 1

Patient characteristics by quartile of serum chloride in patients with heart failure.

Variable	Missing	All patients N=4705	Hypochloraemia <96 mmol/L N=503	Q1 N=1177	Q2 N=1176	Q3 N=1176	Q4 N=1176	Hyperchloraemia >105 mmol/L N=622	P for trend
Chloride – (mmol/L)	**0**	**102 (99 – 104)**	**93 (91-95)**	**96 (94-98)**	**100 (100-101)**	**103 (102-103)**	**106 (105-107)**	**107 (106-108)**	NA
Demographics									
Age – years	0	73 (11)	74 (11)	74 (10)	73 (10)	71 (11)	72 (10)	73 (10)	<0.001
Sex (male) - no. (%)	0	2885 (61)	262 (52)	628 (53)	737 (63)	742 (63)	778 (66)	414 (67)	<0.001
SR – no. (%)	239	3129 (70)	311 (62)	725 (62)	769 (65)	819 (70)	816 (69)	440 (71)	<0.001
Diabetes - no. (%)	0	1152 (25)	146 (29)	339 (29)	306 (26)	22 (25)	252 (21)	126 (20)	<0.001
Hypertension - no. (%)	0	2006 (43)	198 (39)	477 (41)	496 (42)	511 (44)	522 (44)	277 (44)	0.26

IHD -- no. (%)	0	2306 (49)	227 (45)	525 (45)	566 (48)	604 (51)	611 (52)	343 (55)	0.001
Signs and symptoms									
NYHA Class III/IV - no. (%)	230	1320 (29)	217 (44)	439 (38)	338 (30)	256 (22)	287 (25)	152 (25)	<0.001
Blood results									
NTproBNP – ng/L	0	2408 (397 – 2535)	1817 (722-4203)	1476 (604-3763)	1040 (422-2439)	871 (334-2000)	873 (333-2206)	917 (346- 2271)	<0.001
Haemoglobin – g/dL	315	13.3 (12.1 – 14.4)	12.8 (11.7-14.0)	13.0 (11.9-14.2)	13.3 (12.1-14.4)	13.5 (12.4-14.6)	13.4 (12.1-14.5)	13.3 (12.1-14.4)	<0.001
Haematocrit	280	0.406 (0.374 – 0.438)	0.390 (0.359-0.423)	0.398 (0.366-0.433)	0.406 (0.375-0.438)	0.412 (0.382-0.441)	0.409 (0.377-0.439)	0.408 (0.376-0.438)	<0.001
Sodium – mmol/L	7	139 (137 – 140)	134 (131-136)	136 (133-138)	138 (136-140)	139 (138-141)	140 (139-142)	140 (139-142)	<0.001
Hyponatraemia – no. (%)	7	533 (11)	279 (56)	407 (35)	100 (9)	20 (2)	6 (1)	3 (1)	
Potassium – mmol/L	38	4.4 (4.1-4.7)	4.3 (3.9-4.6)	4.3 (3.9-4.7)	4.3 (4.0-4.7)	4.4 (4.1-4.7)	4.4 (4.1-4.7)	4.4 (4.1-4.7)	<0.001
Hypokalaemia – no. (%)	38	143 (3)	49	84	27	22	10	4	<0.001

			(9.7)	(7.2)	(2.3)	(1.9)	(0.9)	(0.6)	
Bicarbonate – mmol/L	0	28 (26 – 30)	30 (28-32)	30 (28-32)	29 (27-30)	28 (26-30)	27 (25-28)	26 (25-28)	<0.001
eGFR – ml/min/1.73m²	152	60 (45 – 74)	55 (41-72)	56 (42-71)	59 (45-73)	64 (51-77)	60 (45-74)	60.0 (45.1-73.4)	0.001
Medications									
Loop diuretic- no. (%)	0	2965 (63)	403 (80)	935 (79)	805 (69)	580 (49)	645 (55)	279 (45)	<0.001
Furosemide Dose ≥80 mg/day – no. (%)	0	1212 (41)	246 (61)	549 (59)	322 (40)	175 (30)	166 (35)	75 (27)	<0.001
MRA- no. (%)	0	950 (20)	177 (35)	366 (31)	251 (21)	170 (15)	163 (14)	84 (14)	<0.001
ACE-I or ARB- no. (%)	0	3245 (69)	344 (68)	819 (70)	848 (72)	797 (68)	781 (66)	402 (65)	0.02
BB - no. (%)	0	2741 (58)	235 (47)	613 (52)	698 (59)	713 (61)	717 (61)	378 (61)	<0.001
Echocardiography									
LVSD = severe - no. (%)	0	372 (8)	65 (13)	130 (11)	103 (9)	71 (6)	68 (6)	37 (6)	<0.001

Legend

ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blocker; BMI – body mass index; eGFR – estimate glomerular filtration rate; no. – number; IHD – ischaemic heart disease; LVSD – left ventricular systolic dysfunction; MRA – mineralocorticoid receptor antagonist; NYHA – New York Heart Association; SR – sinus rhythm.

Table 2

Patient characteristics by groups based on the presence of hypochloraemia and/or hyponatraemia

Variable	Missing	Group 1 N=279	Group 2 N=224	Group 3 N=254	Group 4 N=3942	P
Chloride – (mmol/L)	**0**	**93 (90-94)**	**94 (93-95)**	**99 (97-100)**	**102 (100-104)**	<0.001
Sodium – mmol/L	**0**	**131 (129-133)**	**137 (135-139)**	**133 (132-134)**	**139 (138-141)**	<0.001
Demographics						
Age – years	0	74 (11)	74 (10)	75 (10)	73 (11)	0.001
Sex (male) - no. (%)	0	138 (50)	124 (55)	162 (64)	2456 (62)	<0.001
SR – no. (%)	204	186 (66)	128 (57)	175 (69)	2639 (67)	0.60
Diabetes - no. (%)	0	82 (29)	64 (29)	83 (33)	923 (23)	0.001
Hypertension - no. (%)	0	104 (37)	94 (42)	104 (41)	1701 (43)	0.26
IHD -- no. (%)	0	133 (48)	94 (42)	126 (50)	1950 (50)	0.17

Symptoms						
NYHA Class III/IV - no. (%)	108	124 (45)	93 (43)	82 (33)	1018 (26)	
Blood results						
NTproBNP – ng/L	0	1816 (777-4298)	1805 (678-4143)	1193 (520-2591)	956 (371-2325)	<0.001
Haemoglobin – g/dL	243	12.5 (11.5-13.7)	13.2 (12.0-14.5)	12.5 (11.4-13.8)	13.4 (12.2-14.5)	<0.001
Haematocrit	273	0.379 (0.343-0.410)	0.406 (0.372-0.452)	0.378 (0.347-0.408)	0.410 (0.379-0.440)	<0.001
Potassium – mmol/L	29	4.4 (4.1-4.7)	4.0 (3.6-4.5)	4.5 (4.2-4.8)	4.4 (4.1-4.7)	<0.001
Hypokalaemia – no. (%)	29	8 (3)	41 (18)	3 (1)	90 (2)	<0.001
Bicarbonate – mmol/L	0	28 (27-30)	32 (30-35)	26 (25-27)	28 (26-30)	<0.001
eGFR – ml/min/1.73m^2	128	58 (43-77)	52 (38-67)	59 (40-73)	61 (46-74)	<0.001
Medications						
Loop diuretic- no. (%)	0	207 (74)	196 (88)	167 (66)	2390 (61)	<0.001
Furosemide Dose ≥80 mg/day	0	119 (58)	127 (65)	66 (40)	897 (38)	
MRA- no. (%)	0	104 (37)	73 (33)	89 (35)	682 (17)	<0.001

ACE-I or ARB- no. (%)	0	204 (73)	140 (63)	196 (77)	2701 (69)	0.002
BB - no. (%)	0	135 (48)	100 (45)	160 (63)	2342 (59)	<0.001
Echocardiography						
Severe LVSD - no. (%)		41 (15)	24 (11)	16 (6)	291 (7)	<0.001

Legend

ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blocker; BMI – body mass index; eGFR – estimate glomerular filtration rate; no. – number; IHD – ischaemic heart disease; LVSD – left ventricular systolic dysfunction; MRA – mineralocorticoid receptor antagonist; NYHA – New York Heart Association; SR – sinus rhythm.

Group 1 = Na <135mmol/L & Cl <96mmol/L

Group 2 = Na ≥135mmol/L & Cl <96mmol/L

Group 3 = Na <135mmol/L & Cl ≥96mmol/L

Group 4 = Na ≥135mmol/L & Cl ≥96mmol/

Table 3

Mode of death in patients with heart failure and reduced ejection fraction or heart failure and a preserved ejection fraction by serum chloride quartile and hypo- and hyperchloraemia.

	All (N=4505)	Quartile 1 N=1128	Quartile 2 N=1118	Quartile 3 N=1121	Quartile 4 N=1138	Hypochloraemia (<96 mmol/L) N=483	Chloride levels 96-105 mmol/L N=3421	Hyperchloraemia (>105 mmol/L) N=601
Dead by 12m (All Cause)	**481**	**204**	**110**	**78**	**89**	**119**	**312**	**50**
Annual mortality rate	**11%**	**18%**	**10%**	**7%**	**8%**	**25%**	**9%**	**8%**
Cardiovascular (Primary)	291 (60)	126 (62)	58 (53)	43 (55)	64 (72)	68 (57)	184 (59)	39 (78)
Terminal HF (Primary)	*103 (21)*	*55 (27)*	*20 (18)*	*12 (15)*	*16 (18)*	*31 (26)*	*63 (20)*	*9 (18)*
Sudden Death (Primary)	*154 (32)*	*64 (31)*	*26 (24)*	*26 (33)*	*38 (43)*	*35 (29)*	*96 (31)*	*23 (46)*
Non CV (Primary Cause)	169 (35)	72 (35)	47 (43)	29 (37)	21 (24)	47 (39)	113 (36)	9 (18)
Unknown cause	21 (5)	6 (3)	5 (4)	6 (8)	4 (4)	4 (4)	15 (5)	2 (4)

Legend

Total of patients with minimum FU of 1 year=4505. Figures in brackets are percentages of all deaths. List of abbreviations used: CV – cardiovascular; HF – Heart failure.

Supplementary Table 1

Patient characteristics by quartile of serum chloride in patients with heart failure and a reduced ejection fraction.

Variable	Missing	All HFREF N=1988	Hypochloraemia N=251	Q1 N=497	Q2 N=497	Q3 N=497	Q4 N=497	Hyperchloraemia N=233	P for trend
Chloride – (mmol/L)	**0**	**101 (98-104)**	**93 (91-95)**	**95 (93-97)**	**100 (99-101)**	**102 (102-103)**	**105 (104-107**	**107 (106-108)**	**n/a**
Demographics									
Age – years	0	71(11)	71 (11)	72 (11)	71 (11)	70 (12)	70 (11)	70 (11)	0.004
Sex (male) - no. (%)	0	1485 (75)	165 (66)	337 (68)	364 (73)	390 (79)	394 (79)	185 (79)	<0.001
SR – no. (%)	118	1368 (69)	158 (63)	312 (63)	352 (71)	345 (69)	359 (72)	169 (73)	0.004
Diabetes - no. (%)	0	472 (24)	86 (34)	151 (30)	132 (27)	98 (20)	91 (18)	41 (18)	<0.001
Hypertension - no. (%)	0	651 (33)	78 (31)	151 (30)	168 (34)	163 (33)	169 (34)	80 (34)	0.60
IHD -- no. (%)	0	1278 (64)	150 (60)	297 (60)	32 (65)	327 (66)	332 (67)	154 (66)	0.01

Signs and symptoms									
NYHA Class III/IV - no. (%)	22	686 (35)	123 (50)	217 (44)	181 (37)	149 (30)	139 (29)	75 (33)	<0.001
Blood results									
NTproBNP – ng/L	0	1750 (750-3984)	2731 (1192-5848)	2296 (969-5250)	1716 (746-4014)	1536 (607-3077)	1463 (697-3601)	1593 (733-3844)	<0.001
Haemoglobin – g/dL	101	13.5 (12.2-14.6)	13.0 (11.9-14.1)	13.1 (12.0-14.2)	13.5 (12.2-14.5)	13.7 (12.4-14.9)	13.6 (12.5-14.6)	13.5 (12.5-14.7)	<0.001
Haematocrit	99	0.411 (0.379-0.443)	0.394 (0.362-0.429)	0.400 (0.370-0.437)	0.410 (0.379-0.441)	0.421 (0.390-0.449)	0.417 (0.384-0.445)	0.419 (0.386-0.444)	<0.001
Sodium – mmol/L	5	138 (136-140)	134 (131-136)	135 (133-138)	138 (136-140)	139 (138-141)	140 (139-142)	140 (139-142)	<0.001
Hyponatraemia – no. (%)	5	259 (13)	142 (57)	198 (36)	47 (9)	9 (2)	5 (1)	3 (1)	<0.001
Potassium – mmol/L	13	4.4 (4.1-4.7)	4.3 (3.9-4.6)	4.3 (4.0-4.7)	4.4 (4.1-4.7)	4.4 (4.2-4.7)	4.4 (4.1-4.7)	4.4 (4.1-4.8)	0.004

Hypokalaemia – no. (%)	13	58 (2.9)	28 (11.1)	38 (6.9)	10 (2.0)	5 (1.1)	5 (1.1)	7 (3.0)	<0.001
Bicarbonate – mmol/L	0	28 (26-30)	30 (28-32)	30 (28-32)	29 (27-31)	28 (27-30)	27 (25-28)	26 (25-28)	<0.001
eGFR – ml/min/1.73m^2	76	59 (44-73)	55 (41-70)	54 (40-70)	58 (43-73)	62 (47-76)	60 (45-73)	60 (45-75)	<0.001
Medications									
Loop diuretic- no. (%)	0	1490 (75)	229 (91)	449 (90)	399 (80)	338 (68)	302 (61)	133 (57)	<0.001
Furosemide Dose ≥80 mg/day	0	689 (46)	148 (65)	279 (62)	204 (51)	114 (33)	92 (30)	41 (30)	<0.001
MRA- no. (%)	0	661 (33)	124 (49)	231 (47)	180 (36)	130 926)	120 (24)	57 (25)	<0.001
ACE-I or ARB- no. (%)	0	1614 (81)	198 (79)	402 (81)	405 (82)	407 (82)	400 (81)	186 (80)	0.94
BB - no. (%)	0	1333 (67)	135 (54)	295 (59)	343 (69)	342 (69)	353 (71)	168 (72)	<0.001
Echocardiography									
Severe LVSD - no. (%)	0	372 (19)	65 (26)	100 (20)	130 (26)	67 (14)	75 (15)	37 (16)	<0.001
LAD – cm	281	4.4(0.8)	4.4 (0.8)	4.4 (0.8)	4.4 (0.8)	4.3 (0.8)	4.4 (0.7)	4.4 (0.7)	0.37

LVEF by Simpsons – %	796	32(8)	30 (8)	31 (9)	31 (7)	33 (7)	32 (8)	33 (8)	0.01

Legend

ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blocker; BMI – body mass index; eGFR – estimate glomerular filtration rate; no. – number; HFREF – heart failure with a reduced ejection fraction; IHD – ischaemic heart disease; LVSD – left ventricular systolic dysfunction; MRA – mineralocorticoid receptor antagonist; NYHA – New York Heart Association; SR – sinus rhythm.

Supplementary Table 2

Patient characteristics by quartile of serum chloride in patients with heart failure and a preserved ejection fraction.

Variable	Missing	All HFPEF	Hypochloraemia	Q1	Q2	Q3	Q4	Hyperchloraemia	P for

		N=2717	N=252	N=679	N=679	N=679	N=680	N=389	trend
Chloride – (mmol/L)	**0**	**102 (99-104)**	**94 (92-95)**	**96 (95-98)**	**101 (100-101)**	**103 (102-104)**	**106 (105-107)**	**107 (106-108)**	**N/A**
Demographics									
Age – years	0	75 (10)	77 (9)	77 (9)	75 (10)	74 (10)	73 (10)	74 (9)	<0.001
Sex (male) - no. (%)	0	1400 (52)	97 (39)	269 (40)	373 (55)	362 (53)	397 (58)	229 (59)	<0.001
SR – no. (%)	86	1761 (65)	153 (61)	414 (61)	426 (63)	438 (65)	483 (71)	271 (70)	0.001
Diabetes - no. (%)	0	680 (25)	60 (24)	182 (27)	186 (27)	165 (24)	147 (22)	85 (22)	0.06
Hypertension - no. (%)	0	1355 (50)	120 (48)	345 (51)	330 (49)	338 (50)	342 (50)	197 (51)	0.87
IHD -- no. (%)	0	1028 (38)	77 (31)	196 (29)	248 (37)	263 (39)	321 (47)	189 (49)	<0.001
Signs and symptoms									
NYHA Class III/IV - no. (%)	86	634 (24)	94 (39)	211 (32)	152 (23)	142 (21)	129 (19)	77 (20)	<0.001

Blood results									
NTproBNP – ng/L	0	734 (289-1672)	1175 (549-2898)	929 (356-2192)	672 (287-1498)	676 (277-1551)	634 (263-1566)	664 (273-1644)	<0.001
Haemoglobin – g/dL	142	13.2 (12.0-14.3)	12.6 (11.5-13.9)	13.0 (11.9-14.1)	13.2 (12.1-14.3)	13.2 (12.1-14.3)	13.3 (12.1-14.4)	13.1 (11.9-14.3)	0.18
Haematocrit	181	0.403 (0.370-0.435)	0.384 (0.349-0.42)	0.395 (0.363-0.431)	0.404 (0.370-0.435)	0.405 (0.377-0.436)	0.405 (0.372-0.436)	0.401 (0.368-0.433)	0.03
Sodium – mmol/L	1	139 (137-141)	134 (131-136)	136 (134-138)	139 (137-140)	139 (138-141)	140 (139-142)	140 (139-142)	<0.001
Hyponatraemia – no. (%)	1	274 (10)	137 (54)	209 (34)	53 (8)	11 (2)	1 (0)	0 (0)	<0.001
Potassium – mmol/L	16	4.3 (4.0-4.6)	4.3 (3.9-4.6)	4.3 (3.9-4.6)	4.3 (4.0-4.6)	4.3 (4.1-4.6)	4.4 (4.1-4.7)	4.4 (4.1-4.7)	<0.001
Hypokalaemia – no. (%)	16	85 (3.1)	21 (8.3)	46 (6.8)	17 (2.5)	17 (2.5)	5 (0.7)	1 (0.3)	<0.001
Bicarbonate – mmol/L	0	28 (26-30)	30 (28-33)	30 (28-32)	28 (27-30)	28 (26-30)	27 (25-28)	26 (24-28)	<0.001

eGFR – ml/min/1.73m^2	52	61 (49-75)	55 (41-74)	58 (43-75)	61 (48-75)	62 (49-76)	61 (47-75)	60 (45-73)	0.01
Medications									
Loop diuretic- no. (%)	0	1475 (54)	174 (69)	449 (66)	374 (55)	372 (55)	280 (41)	146 (38)	<0.001
Furosemide Dose ≥80 mg/day – no. (%)	0	523 (35)	98 (56)	236 (53)	125 (33)	98 (26)	64 (23)	34 (23)	<0.001
MRA- no. (%)	0	289 (11)	53 (21)	113 (17)	70 (10)	52 (8)	54 (8)	27 (7)	<0.001
ACE-I or ARB- no. (%)	0	1631 (60)	146 (58)	404 (60)	428 (63)	404 (60)	395 (58)	216 (56)	0.29
BB - no. (%)	0	1408 (52)	100 (40)	306 (45)	343 (51)	387 (57)	372 (55)	210 (54)	<0.001
Echocardiography									
No LVSD - no. (%)	0	1652 (61)	169 (67)	467 (69)	420 (62)	38 (56)	382 (56)	236 (60)	<0.001

Legend

ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blocker; BMI – body mass index; eGFR – estimate glomerular filtration rate; no. – number; HFPEF – heart failure with a preserved ejection fraction; IHD – ischaemic heart disease; LVSD – left ventricular systolic dysfunction; MRA – mineralocorticoid receptor antagonist; NYHA – New York Heart Association; SR – sinus rhythm.

Supplementary Table 3

Mode of death in patients with heart failure and reduced ejection fraction or heart failure and a preserved ejection fraction by groups based on the presence of hypochloraemia and/or hyponatraemia.

	All (N=4502)	**Group 1 N=265**	**Group 2 N=218**	**Group 3 N=235**	**Group 4 N=3784**
Dead by 12m (All Cause)	**481**	**70**	**49**	**32**	**330**
Annual mortality rate	**11%**	**26%**	**22%**	**14%**	**9%**
Cardiovascular (Primary)	291 (60)	40 (57)	28 (57)	21 (65)	202 (61)
Terminal HF (Primary)	*103 (21)*	*17 (24)*	*14 (29)*	*11 (34)*	*61 (18)*

Sudden Death (Primary)	*154 (32)*	*22 (31)*	*13 (27)*	*6 (19)*	*113 (34)*
Non CV (Primary Cause)	169	27	20	9	113
Unknown cause	21	3	1	2	15

Legend

Total of patients with minimum FU of 1 year=4502. 6 patients were excluded because they did not have sodium available Figures in brackets are percentage of all deaths. List of abbreviations used: CV – cardiovascular; HF – Heart failure.

Group 1 = Na <135mmol/L & Cl <96mmol/L

Group 2 = Na ≥135mmol/L & Cl <96mmol/L

Group 3 = Na <135mmol/L & Cl ≥96mmol/L

Group 4 = Na ≥135mmol/L & Cl ≥96mmol/L

Supplementary Table 4

Mode of death in patients with heart failure by heart failure phenotype.

Patients with HFREF with minimum follow up of 1 year (N = 1901)							
	All (N=1901)	**Hypochloraemia (<96 mmol/L) N=240**	**Quartile 1 N=533**	**Quartile 2 N=494**	**Quartile 3 N=445**	**Quartile 4 N=429**	**Hyperchloraemia (>105 mmol/L) N=224**
Dead by 12m (All Cause)	**237**	**65**	**110**	**49**	**34**	**44**	**26**
Annual mortality rate - %	**12**	**27**	**21**	**10**	**8**	**10**	**12**
Cardiovascular (Primary)	163 (69)	43 (66)	75 (68)	28 (57)	25 (73)	35 (80)	21 (81)
Terminal HF (Primary)	64 (27)	22 (34)	35 (32)	13 (27)	6 (18)	10 (23)	4 (15)
Sudden Death (Primary)	85 (36)	21 (32)	36 (33)	13 (27)	15 (44)	21 (48)	13 (50)
Non CV (Primary Cause)	65	20	32	18	7	8	5

Unknown cause	9	2	3	3	2	1	0
Patients with HFPEF with minimum follow up of 1 year (N = 2604)							
	All (N=2604)	**Hypochloraemia (<96 mmol/L) N=243**	**Quartile 1 N=595**	**Quartile 2 N=624**	**Quartile 3 N=676**	**Quartile 4 N=709**	**Hyperchloraemia (>105 mmol/L) N=377**
Dead by 12m (All Cause)	**244**	**54**	**94**	**61**	**44**	**45**	**24**
Annual mortality rate - %	**9**	**22**	**16**	**10**	**7**	**6**	**6**
Cardiovascular (Primary)	128 (52)	25 (46)	51 (54)	30 (49)	18 (41)	29 (64)	18 (75)
Terminal HF (Primary)	38 (16)	9 (17)	20 (21)	7 (11)	6 (14)	6 (13)	5 (21)
Sudden Death (Primary)	69 (28)	14 (26)	28 (30)	13 (21)	11 (25)	17 (38)	10 (42)
Non CV (Primary Cause)	104	27	40	29	22	13	4
Unknown cause	12	2	3	2	4	3	2

Legend

Figures in brackets are percentages of all deaths. List of abbreviations used: HFREF – heart failure with a reduced ejection fraction; HFPEF – heart failure with a preserved ejection fraction; CV – cardiovascular; HF – Heart failure.

Supplementary Table 5

Univariable and Multivariable analysis for all-cause mortality in all patients with heart failure

Variable	Univariable			Multivariable		
	HR	X2 - Wald	p	HR	X2 - Wald	p
Demographics						
Age – years	1.06 (1.05-1.06)	573	<0.001	1.05 (1.04-1.05)	251	<0.001
Sex (male vs female) - no. (%)	1.13 (1.05-1.23)	9	0.002	1.30 (1.18-1.45)	25	<0.001
BMI – kg/m^2	0.97 (0.96-0.98)	65	<0.001			
SBP – mmHg	1.00 (0.99-1.00)	34	<0.001			

HR – bpm	1.01 (1.00-1.01)	36	<0.001			
AF (vs SR)	1.38 (1.27-1.50)	54	<0.001			
Diabetes (vs non-diabetic)	1.26 (1.15-1.38)	25	<0.001	1.12 (1.01-1.25)	5	0.033
Hypertension (vs non-hypertensive)	0.95 (0.88-1.03)	1	0.243			
IHD (vs no IHD)	1.16 (1.07-1.25)	13	<0.001			
Signs & Symptoms						
NYHA Class (III/IV vs I/II)	1.99 (1.83-2.16)	261	<0.001	1.42 (1.29-1.57)	53	<0.001
Peripheral oedema (≥ankles vs none or trace)	1.84 (1.68-2.02)	176	<0.001			

Lung crackles (present vs absent)	1.93 (1.73-2.16)	141	<0.001			
JVP (raised vs not raised)	1.92 (1.72-2.16)	125	<0.001			
Bloods						
Log(NTproBNP) – ng/L	2.79 (2.60-3.00)	757	<0.001	1.47 (1.33-1.63)	53	<0.001
Haemoglobin – g/dL	0.81 (0.80-0.83)	288	<0.001			
Sodium – mmol/L	0.94 (0.93-0.95)	124	<0.001			
Chloride – mmol/L	0.94 (0.93-0.95)	207	<0.001	0.96 (0.94-0.98)	17	<0.001
Calcium – mmol/L	0.14 (0.10-0.18)	180	<0.001			

Potassium – mmol/L	1.10 (1.00-1.18)	4	0.045			
Bicarbonate – mmol/L	1.01 (1.00-1.03)	2	0.126			
Creatinine-umol/L	1.00 (1.00-1.00)	265	<0.001			
Urea - mmol/L	1.07 (1.06-1.07)	617	<0.001	1.03 (1.01-1.04)	15	<0.001
eGFR – ml/min/1.73m^2	0.98 (0.98-0.98)	461	<0.001			
Albumin – g/l	0.89 (0.89-0.90)	451	<0.001	0.95 (0.93-0.96)	58	<0.001
Bilirubin – umol/L	1.02 (1.01-1.02)	34	<0.001			
ALP – iu/L	1.01 (1.01-	300	<0.001	1.00 (1.00-	47	<0.001

	1.01)			1.00)		
ALT – iu/L	0.99 (0.99-0.99)	25	<0.001	0.99 (0.99-1.00)	18	<0.001
Medications						
Loop diuretic (vs no loop diuretic)	2.00 (1.84-2.18)	244	<0.001	1.26 (1.14-1.40)	19	<0.001
Furosemide Dose (>80mg day vs 1-79mg/day)	1.38 (1.26-1.52)	47	<0.001			
Echocardiography						
HFrEF vs HFpEF	1.29 (1.19-1.39)	40	<0.001			
LAD – cm	1.30 (1.24-1.38)	98	<0.001			
LVEF by Simpsons – %	0.99 (0.98-0.99)	57	<0.001			

Supplementary Table 5 – Univariable and Multivariable analysis for all-cause mortality in all patients with heart failure

Legend

Only variables associated with outcome in univariable analysis ($p<0.1$) were entered in multivariable models. Variables with >10% missing values were excluded. Variables that were non-significant in multivariable analysis were not recorded. Variables included in multivariable model: age, sex, BMI, SBP, HR, diabetes, IHD, NYHA class; log(NT-pro-BNP), sodium, calcium, potassium, haemoglobin, chloride, creatinine, urea, eGFR, albumin, ALP, ALT, bilirubin, loop diuretics, HFrEF, HFpEF.

HF – heart failure; HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; no. – number; BMI – body mass index; SBP – systolic blood pressure; HR – heart rate; SR – sinus rhythm; IHD – ischaemic heart disease; NYHA – New York Heart Association; JVP – jugular venous pulse; eGFR – estimate glomerular filtration rate; LAD – left atrial diameter; LVEF – left ventricular ejection fraction

Supplementary table 6

Univariable and Multivariable analysis for all-cause mortality or heart failure hospitalisation in all patients with heart failure

Variable	Univariable			Multivariable		
	HR	X2 - Wald	P	HR	X2 - Wald	p
Demographics						
Age – years	1.05 (1.04-1.05)	434	<0.001	1.04 (1.03-1.04)	159	<0.001
Sex (male vs female) - no. (%)	1.14 (1.05-1.23)	10	0.001	1.25 (1.13-1.38)	20	<0.001
BMI – kg/m^2	0.98 (0.97-0.99)	40	<0.001			

SBP – mmHg	1.00 (0.99-1.00)	51	<0.001			
HR – bpm	1.01 (1.01-1.01)	50	<0.001			
AF (vs SR)	1.39 (1.28-1.50)	60	<0.001			
Diabetes (vs non-diabetic)	1.28 (1.17-1.40)	31	<0.001	1.12 (1.01-1.24)	5	0.027
Hypertension (vs non-hypertensive)	1.01 (0.94-1.09)	0	0.833			
IHD (vs no IHD)	1.17 (1.09-1.26)	17	<0.001			
Signs & Symptoms						
NYHA Class (III/IV vs I/II)	2.02 (1.87-2.19)	300	<0.001	1.40 (1.28-1.53)	53	<0.001

Peripheral oedema (≥ankles vs none or trace)	1.98 (1.79-2.20)	164	<0.001			
Lung crackles (present vs absent)	1.99 (1.79-2.21)	161	<0.001			
JVP (raised vs not raised)	1.94 (1.74-2.17)	139	<0.001			
Bloods						
Log(NTproBNP) – ng/L	2.90 (2.71-3.11)	893	<0.001	1.63 (1.47-1.80)	92	<0.001
Haemoglobin – g/dL	0.82 (0.80-0.84)	294	<0.001			
Sodium – mmol/L	0.94 (0.93-0.95)	111	<0.001			
Chloride – mmol/L	0.94 (0.93-0.95)	208	<0.001	0.97 (0.95-0.98)	14	<0.001

Calcium – mmol/L	0.16 (0.12-0.21)	166	<0.001			
Potassium – mmol/L	1.07 (0.99-1.16)	3	0.081			
Bicarbonate – mmol/L	1.01 (1.00-1.03)	4	0.038			
Creatinine-umol/L	1.00 (1.00-1.00)	246	<0.001			
Urea - mmol/L	1.06 (1.06-1.07)	565	<0.001	1.02 (1.01-1.03)	9	0.003
eGFR – ml/min/1.73m^2	0.98 (0.98-0.98)	441	<0.001			
Albumin – g/l	0.90 (0.90-0.91)	394	<0.001	0.96 (0.95-0.97)	33	<0.001
Bilirubin – umol/L	1.02 (1.01-	48	<0.001			

	1.03)					
ALP – iu/L	1.01 (1.01-1.01)	290	<0.001	1.00 (1.00-1.00)	38	<0.001
ALT – iu/L	0.99 (0.99-1.00)	12	<0.001	1.00 (0.99-1.00)	9	0.003
Medications						
Loop diuretic (vs no loop diuretic)	2.15 (1.98-2.34)	324	<0.001	1.37 (1.24-1.51)	37	<0.001
Furosemide Dose (>80mg day vs 1-79mg/day)	1.38 (1.26-1.51)	51	<0.001			
Echocardiography						
HFrEF vs HFpEF	1.46 (1.35-1.57)	98	<0.001			
LAD – cm	1.35 (1.29-1.42)	140	<0.001			

LVEF by Simpsons – %	0.98 (0.98-0.99)	103	<0.001			

Legend

Only variables associated with outcome in univariable analysis ($p<0.1$) were entered in multivariable models. Variables with >10% missing values were excluded. Variables that were non-significant in multivariable analysis were not recorded. Variables included in multivariable model: age, sex, BMI, SBP, HR, diabetes, IHD, NYHA class; log(NT-pro-BNP), sodium, calcium, potassium, bicarbonate, haemoglobin, chloride, creatinine, urea, eGFR, albumin, ALP, ALT, bilirubin, loop diuretics, HFREF, HFPEF.

HF – heart failure; HFREF – heart failure with reduced ejection fraction; HFPEF – heart failure with preserved ejection fraction; no. – number; BMI – body mass index; SBP – systolic blood pressure; HR – heart rate; SR – sinus rhythm; IHD – ischaemic heart disease; NYHA – New York Heart Association; JVP – jugular venous pulse; eGFR – estimate glomerular filtration rate; LAD – left atrial diameter; LVEF – left ventricular ejection fraction

Figures

Figure 1 - Association between mortality and serum chloride in patients with heart failure

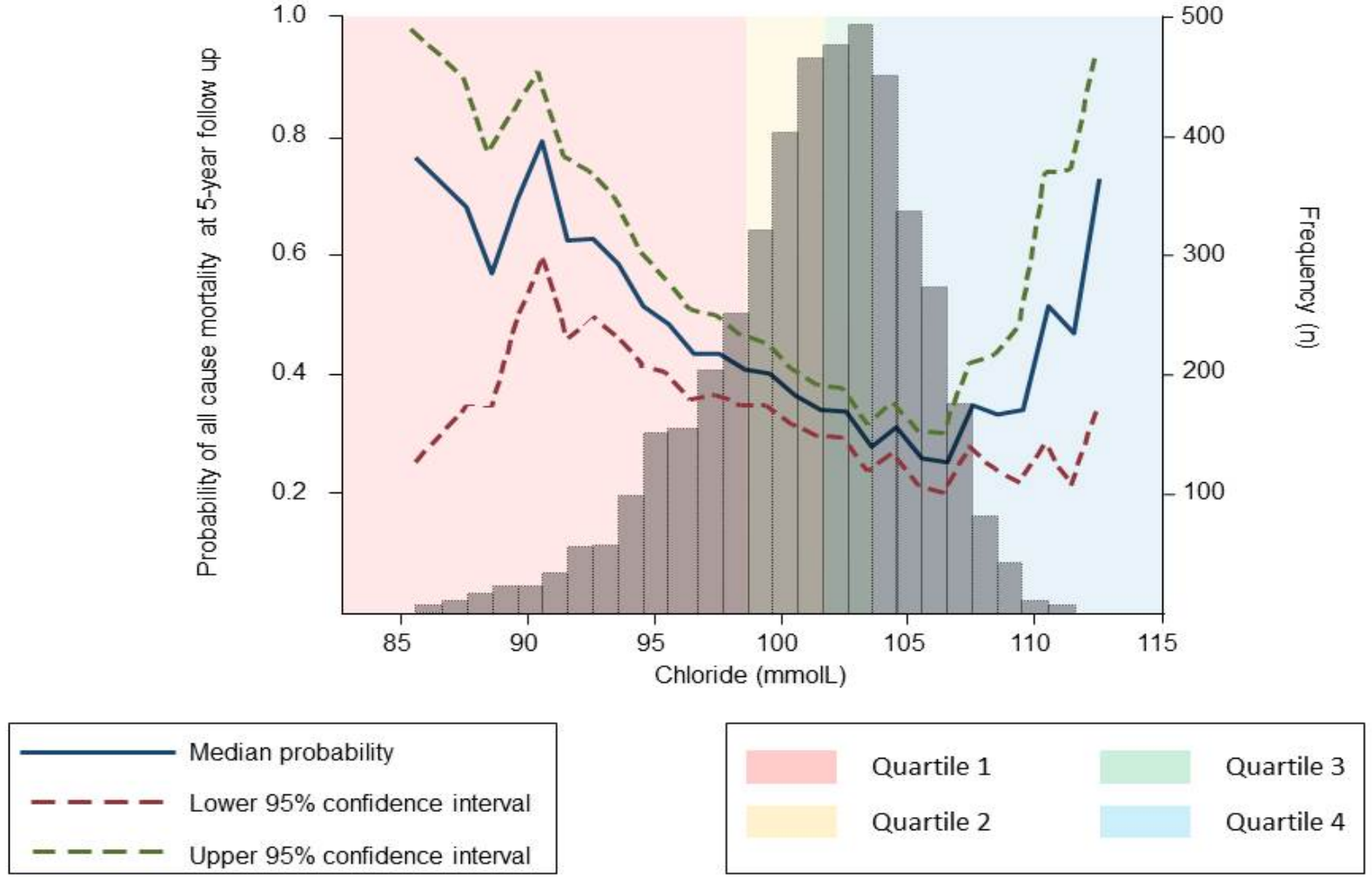
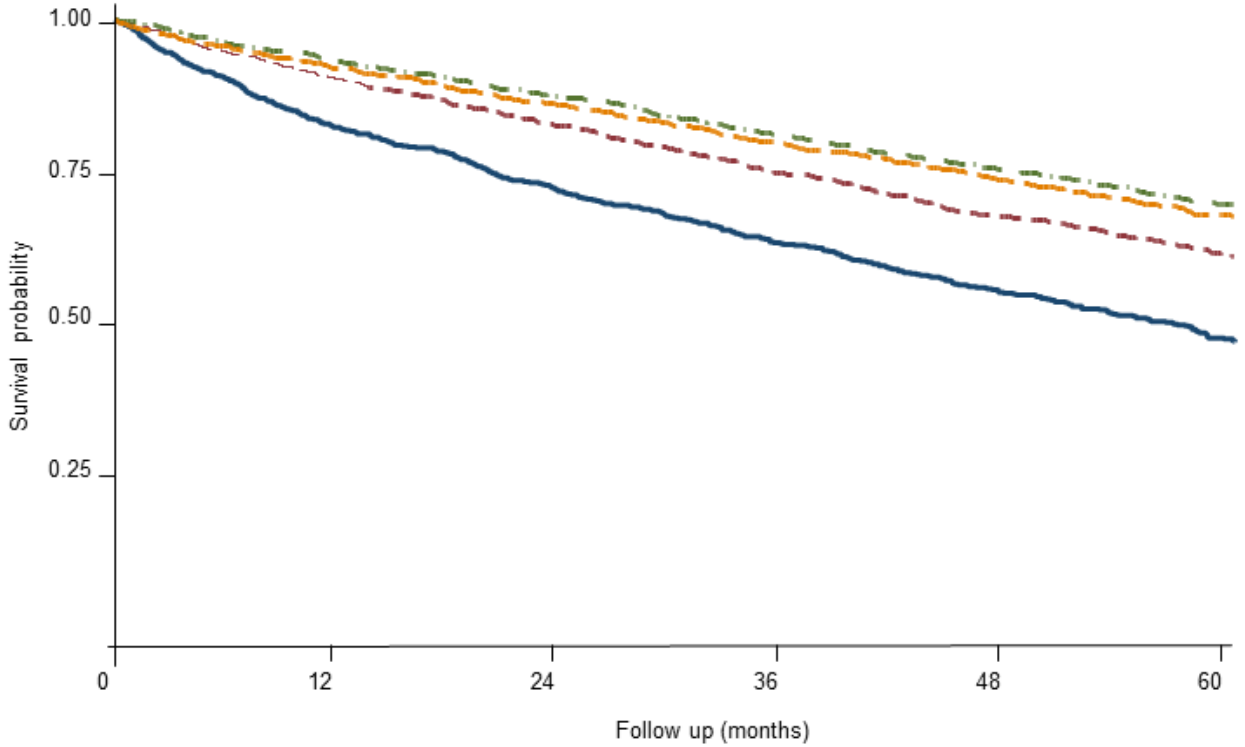


Figure 2 – Kaplan-Meier curve for quartiles of serum chloride



Number at risk

Quartile 1	1177	924	770	652	516	391
Quartile 2	1176	1008	876	768	642	522
Quartile 3	1176	1044	951	852	729	610
Quartile 4	1176	1049	958	864	741	639

Quartile 1 - median Cl^- 96 mmol/L (94-98 mmol/L)
Quartile 2 - median Cl^- 100 mmol/L (100-101 mmol/L)
Quartile 3 - median Cl^- 103 mmol/L (102-103 mmol/L)
Quartile 4 - median Cl^- 106 mmol/L (105-107 mmol/L)

Compared to Q4	Hazard ratio	p
Q1	1.99 (1.74-2.27)	<0.001
Q2	1.26 (1.09-1.45)	0.002
Q3	0.93 (0.80-1.08)	0.337

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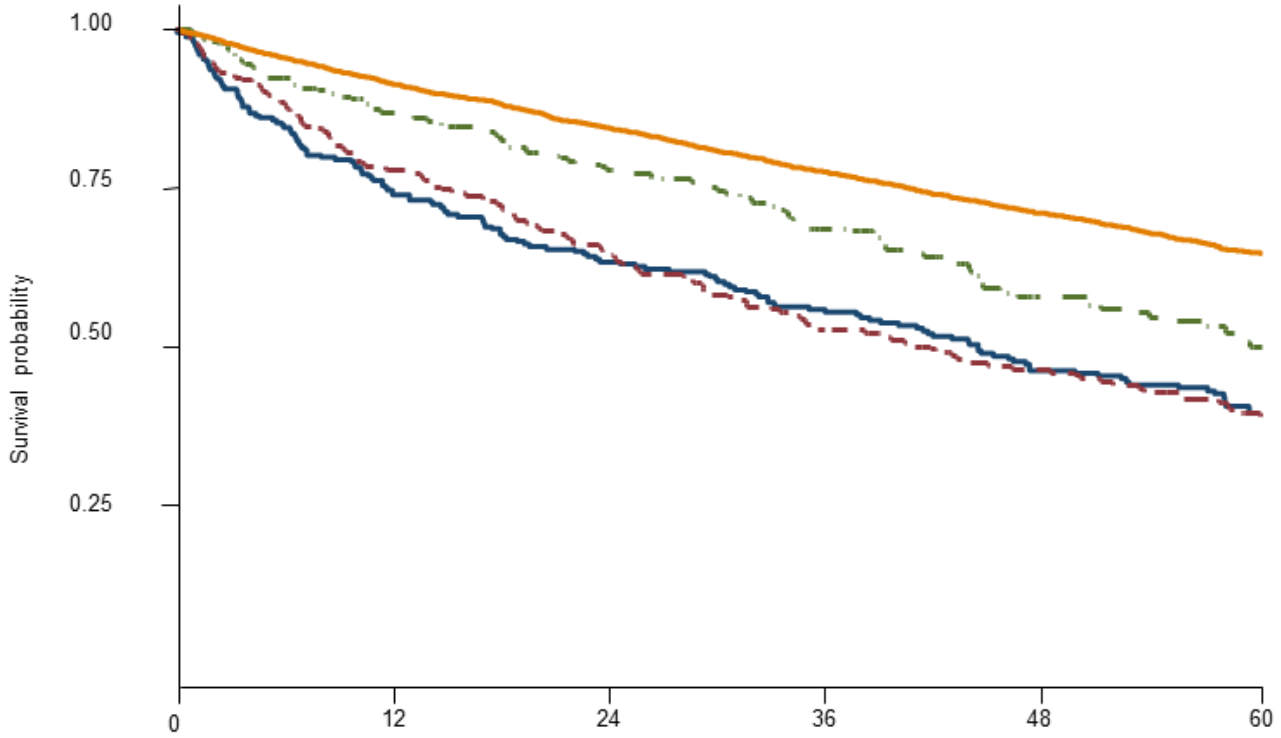
Figure 3 – Kaplan-Meier curve for groups based on the presence of hypochloraemia and/or hyponatraemia



Number at risk

Group 1	285	198	160	137	102	82
Group 2	224	169	138	111	91	67
Group 3	254	203	167	132	89	74
Group 4	3942	3455	3090	2756	2346	1939

Group 1: Na <135mmol/L & Cl <96mmol/L
Group 2: Na >135mmol/L & Cl <96mmol/L
Group 3: Na <135mmol/L & Cl >96mmol/L
Group 4: Na >135mmol/L & Cl >96mmol/L

Compared to Group 4	HR	p
Group 1	2.16 (1.86-2.50)	<0.001
Group 2	2.07 (1.77-2.42)	<0.001
Group 3	1.57 (1.32-1.87)	<0.001

Supplementary figure 1 – Univariable correlation matrix for selected variables associated with serum chloride levels in patients with HFREF or HFPEF

	Age (years)	Log[NTproBNP] (ng/L)	Sodium (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)	eGFR (ml/min/1.73m²)	
Chloride (mmol/L	-0.07**	-0.17**	0.61*	0.12*	-0.41*	0.05*	All HF
	-0.06*	-0.16*	0.62*	0.10*	-0.38*	0.01**	HFREF
	-0.11**	-0.14**	0.60*	0.14*	-0.43*	0.08*	HFPEF