Original Article

Serum Chloride and Sodium Interplay in Patients With Acute Myocardial Infarction and Heart Failure With Reduced Ejection Fraction

An Analysis From the High-Risk Myocardial Infarction Database Initiative

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Background—Serum chloride levels were recently found to be independently associated with mortality in heart failure (HF).

Methods and Results—We investigated the relationship between serum chloride and clinical outcomes in 7195 subjects with acute myocardial infarction complicated by reduced left ventricular function and HF. The studied outcomes were all-cause mortality, cardiovascular mortality, and hospitalization for HF. Both chloride and sodium had a nonlinear association with the studied outcomes ($P<0.05$ for linearity). Patients in the lowest chloride tertile (chloride ≤100) were older, had more comorbidities, and had lower sodium levels ($P<0.05$ for all). Serum chloride showed a significant interaction with sodium with regard to all studied outcomes (P for interaction <0.05 for all). The lowest chloride tertile (≤100 mmol/L) was associated with increased mortality rates in the context of lower sodium (≤138 mmol/L; adjusted hazard ratio [95% confidence interval] for all-cause mortality=1.42 (1.14–1.77); $P=0.002$), whereas in the context of higher sodium levels (>141 mmol/L), the association with mortality was lost. Spline-transformed chloride and its interaction with sodium did not add significant prognostic information on top of other well-established prognostic variables ($P>0.05$ for all outcomes).

Conclusions—In post–myocardial infarction with systolic dysfunction and HF, low serum chloride was associated with mortality (but not hospitalization for HF) in the setting of lower sodium. Overall, chloride and its interaction with sodium did not add clinically relevant prognostic information on top of other well-established prognostic variables. Taken together, these data support an integrated and critical consideration of chloride and sodium interplay.

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Key Words: alkalosis ■ anion ■ attention ■ heart failure ■ myocardial infarction

Hydro-electrolyte disturbances are frequent in post–myocardial infarction (MI) with or without associated heart failure (HF). Water and electrolyte disorders are often associated with dismal prognosis despite prompt correction.[1,2]

See Clinical Perspective

In particular, the occurrence of hyponatremia in MI and HF settings is a well-established, strong, and independent predictor of short- and long-term morbidity and mortality.[3–7] On the contrary, despite being broadly available in routine blood chemistry panels and its involvement in contraction alkalosis during excessive decongestion therapy, the anion chloride has not received the same attention as its sodium counterpart.[8]

Recently published studies have analyzed independent cohorts of acute and chronic HF.[9–12] In these samples, serum chloride levels were found to be independently and inversely associated with mortality after multivariable adjustment for several well-established prognostic factors including serum sodium concentration. Whether this may also apply to high-risk MI (*ie,* MI complicated by left ventricular systolic dysfunction and HF)

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populations is yet to be determined. Moreover, these variables may be likely to have a nonlinear association with outcomes; hence, linearity should be tested to perform informative analysis.

In light of the above, our aims were (1) to study the shape of the association between chloride, sodium, and the studied outcomes; (2) to evaluate the prognostic value and independency of chloride levels in high-risk MI populations; (3) to study the correlation and interplay between serum chloride and sodium; and (4) to assess the prognostic information gain provided by serum chloride levels on top of sodium.

Methods

Study Sample: The High-Risk MI Database Initiative

For this study, we used a previously published cohort of pooled patient data.[13] In the present analysis, data from the EPHESUS[14,15] trial (Eplerenone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction) and the CAPRICORN[16,17] randomized trial (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left-Ventricular Dysfunction) were used in which serum chloride levels were available (measured at randomization from 12 hours to 21 days after MI). Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the end points, and the results have been published previously.[13] Each trial enrolled patients with left ventricular systolic dysfunction and HF between 12 hours and 21 days after acute MI. HF was defined by the presence of pulmonary rales, chest radiography showing pulmonary congestion, or the presence of a third heart sound.

A total of 7195 patients with available chloride values were included: 5959 patients included from the EPHESUS trial and 1236 from the CAPRICORN trial. The pooled data were used to increase the power and precision of the associations. There were no significant differences (ie, interactions) in the prognostic value of chloride (and sodium) between these studies (P value for interaction >0.1 for all outcomes), thereby avoiding the introduction of heterogeneity to the results. The characteristics of the patients included and excluded from the analysis are shown in Table I in the Data Supplement, and the interaction tests between the analyzed studies are provided in Table II in the Data Supplement.

The respective chairpersons of the Steering Committees of the 4 trials initiated the pooling project.

The study was conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the trials.

Chloride Determination

Data from routine laboratory testing at a central core laboratory for each trial were collected in all patients enrolled in these trials. Laboratory measurements were obtained at the time of randomization.

Outcomes

The present study analyzed all-cause mortality (ACM), cardiovascular mortality (CVM), and hospitalization for HF (HHF) as outcomes. These outcomes were independently adjudicated and recorded within each trial.

Statistical Methods

In descriptive analyses, continuous variables are expressed as mean±SD if normally distributed or as median (percentile$_{25-75}$) if skewed. Ordinal variables are expressed as frequencies and proportions (%). Missing values were excluded from the analysis.

The linearity assumption of the relationship between chloride and the log-hazard of outcome was assessed using restricted cubic splines with 3 knots located to the 10th, 50th, and 90th percentiles according to the Harrell rule (respectively 96, 102, and 108 mmol/L). This generates 2 components: one linear and the other nonlinear. If the Wald test associated with the nonlinear component was statistically significant, a nonlinear relationship was assumed (P value for linearity <0.01 for ACM and CVM and P=0.092 for HHF; Table III in the Data Supplement).

Univariable time-to-event comparisons were performed using the log-rank test, and survival was estimated with the Kaplan–Meier method for ordinal dependent variables. Cox proportional hazard regression models were used to model long-term survival as a function of the formulas both in univariable and multivariable analysis. Proportional hazards assumptions for dependent variables were visually assessed by plotting the log(−log(S(t))) function as a function of survival time (t), where S(t) represents the survival function. An interaction term between the variable of interest and time was tested within the Cox model. In the multivariable models, the covariates were chosen from demographic (age and sex), clinical (systolic blood pressure, history of diabetes mellitus, body mass index, atrial fibrillation, Killip class, left ventricular ejection fraction, diuretic use, and HF history), and laboratory variables (hemoglobin, plasma blood urea nitrogen levels, and estimated glomerular filtration rate calculated by the chronic kidney disease- epidemiology collaboration equation[18]) that were previously found to be clinically relevant.[19] The interaction between chloride*sodium with each outcome was systematically tested using cubic spline variable transformation and categories. Subsequent subgroup analyses were performed to clearly interpret the effect modification.

The relative importance and the discriminative capacity of chloride on top of a prognostic model including the aforementioned covariates and sodium*chloride interaction with regard to the studied outcomes was evaluated by the Harrell c-index[20] and compared with the correlated c-indices using the approach proposed by Kang et al.[21] The value of serum chloride for prediction improvement on top of the same adjustment model and sodium*chloride interaction was performed with the net reclassification improvement (NRI) method and assessed at the median follow-up time for each outcome.[22,23] This method assesses the ability of a new model to reclassify subjects with and without a clinical event during follow-up. The ability of the new model to reclassify is summarized by the NRI statistic. The continuous NRI method developed by Uno et al[23] and implemented in the survIDINRI package of the R software (The R Foundation for Statistical Computing) was used. The continuous NRI method does not require a previous definition of strata risk, thus considering the change in the estimation prediction as a continuous variable. The integrated discrimination improvement (IDI) was also calculated. It evaluates the difference between the integrated sensitivity gain and the integrated specificity loss because of the addition of the chloride estimator to the prognostic model.

Statistical analyses were performed using SPSS 23 software (Released 2013; IBM SPSS Statistics for Windows, version 23.0; IBM Corporation, Armonk, NY) and the R software (The R Foundation for Statistical Computing).

A P value <0.05 was considered statistically significant, except for interaction and linearity tests where a P value <0.1 was considered significant.[24]

Results

Baseline (ie, Randomization) Characteristics of the Study Sample

A total of 7195 patients were included in the study. Patients in the lowest chloride tertile (chloride ≤100) were older, were more often diabetic, and had a higher prevalence of atrial fibrillation, previous MI, HF history, and peripheral artery disease. They also were more frequently in Killip class III/IV and had a lower systolic blood pressure, higher heart rate, worse renal function, lower sodium level, and lower mean left ventricular ejection fraction. They were more frequently receiving diuretics and digoxin (P<0.05 for all; Table 1). Patients in the lowest sodium tertile (sodium ≤138) also had higher heart rate and lower systolic blood pressure, left ventricular

Table 1. Baseline Characteristics of the Study Sample

		Baseline Chloride, mmol/L				
Variable	Total	≤100	>100 to ≤104	>104	*P* Value for Trend	% MV
Demographic						
Patients, n (%)	7195	2525 (35.1)	2555 (35.5)	2115 (29.4)	…	0
Age, y	63.6±11.6	64.0±11.6	63.1±11.6	63.8±11.4	0.008	0
Male sex, n (%)	5183 (72)	1780 (71)	1877 (74)	1526 (72)	0.069	0
Clinical						
Hypertension, n (%)	4180 (58)	1498 (59)	1469 (58)	1213 (57)	0.27	0
Diabetes mellitus, n (%)	2254 (31)	932 (37)	788 (31)	534 (25)	<0.001	0
Atrial fibrillation, n (%)	891 (12)	371 (15)	294 (12)	226 (11)	<0.001	0
Previous MI, n (%)	1978 (28)	747 (30)	662 (26)	569 (27)	0.010	0
HF history, n (%)	1392 (19)	531 (21)	458 (18)	403 (19)	0.017	0
PAD, n (%)	834 (12)	307 (12)	284 (11)	244 (12)	0.50	0
SBP, mm Hg	119.1±16.6	118.5±16.8	119.0±16.6	120.0±16.2	0.011	0.2
Heart rate, beats per min	75.3±11.9	76.6±12.1	75.0±11.7	74.0±11.7	<0.001	0.3
BMI, kg/m^2	27.4±4.5	27.2±5.0	27.6±4.5	27.4±4.4	0.035	0.9
Killip III/IV, n (%)	1221 (17)	503 (20)	373 (15)	345 (16)	<0.001	0.6
Laboratory						
Serum Cr, mg/dL	1.14±0.32	1.16±0.34	1.14±0.31	1.12±0.32	0.010	0.1
eGFR, mL/min/1.73 m^2	67.8±20.6	66.6±20.8	68.5±20.3	68.3±20.7	0.001	0.1
Serum BUN, mg/dL	26.8±16.0	27.9±17.0	25.7±15.3	26.7±15.5	<0.001	1.7
Serum sodium, mmol/L	139.3±4.1	137.4±4.3	139.4±3.4	141.5±3.6	0.001	0.1
≤138	2928 (41)	1545 (61)	994 (39)	388 (18)	<0.001	
>138 to ≤141	2277 (32)	615 (24)	949 (37)	714 (34)	<0.001	
>141	1985 (28)	361 (14)	610 (24)	1014 (48)	<0.001	
Serum potassium, mmol/L	4.3±0.5	4.3±0.5	4.3±0.4	4.4±0.4	<0.001	0.4
Hemoglobin, g/dL	13.3±1.7	13.4±1.7	13.4±1.7	13.2±1.7	0.003	1.0
Echocardiographic						
LVEF, %	33.0±6.2	32.6±6.3	33.1±6.2	33.5±5.9	<0.001	0.3
LVEF ≤35%, n (%)	4319 (60)	1564 (62)	1555 (61)	1200 (57)	0.001	…
Medications						
ACEi/ARB, n (%)	5991 (83)	2111 (84)	2148 (84)	1732 (82)	0.12	0.1
β-blocker, n (%)	4132 (69)	1434 (67)	1456 (72)	1242 (69)	<0.001	17.2
Digoxin, n (%)	919 (13)	393 (16)	302 (12)	224 (11)	<0.001	0.1
Diuretics, n (%)	3703 (52)	1509 (60)	1237 (48)	957 (45)	<0.001	0.1

Results expressed as mean±SD if the distribution is normal; median (percentile$_{25–75}$) if the distribution is skewed; and number (n) and proportions (%) if ordinal. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate by chronic kidney disease–epidemiology collaboration formula and expressed in mL/min/1.73 m^2; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MV, missing values; PAD, peripheral artery disease; and SBP, systolic blood pressure.

ejection fraction, and chloride levels but did not present the other characteristics associated with lower chloride (ie, age, diabetes mellitus, atrial fibrillation, HF history, previous MI, and peripheral artery disease), and Killip class were not significantly different between sodium subgroups (Table IV in the Data Supplement).

The median (percentile$_{25–75}$) follow-up time was 485 days (352–631 days) for ACM and CMV and 456 days (302–612 days) for HHF. The end point ACM occurred in 1084 patients (15%), CVM in 937 patients (13%), and HHF in 948 patients (13%) during the follow-up.

Chloride and Sodium Correlation

Pearson correlation between serum chloride and sodium was 0.413 (P<0.001) meaning that these variables potentially incorporate distinct information.

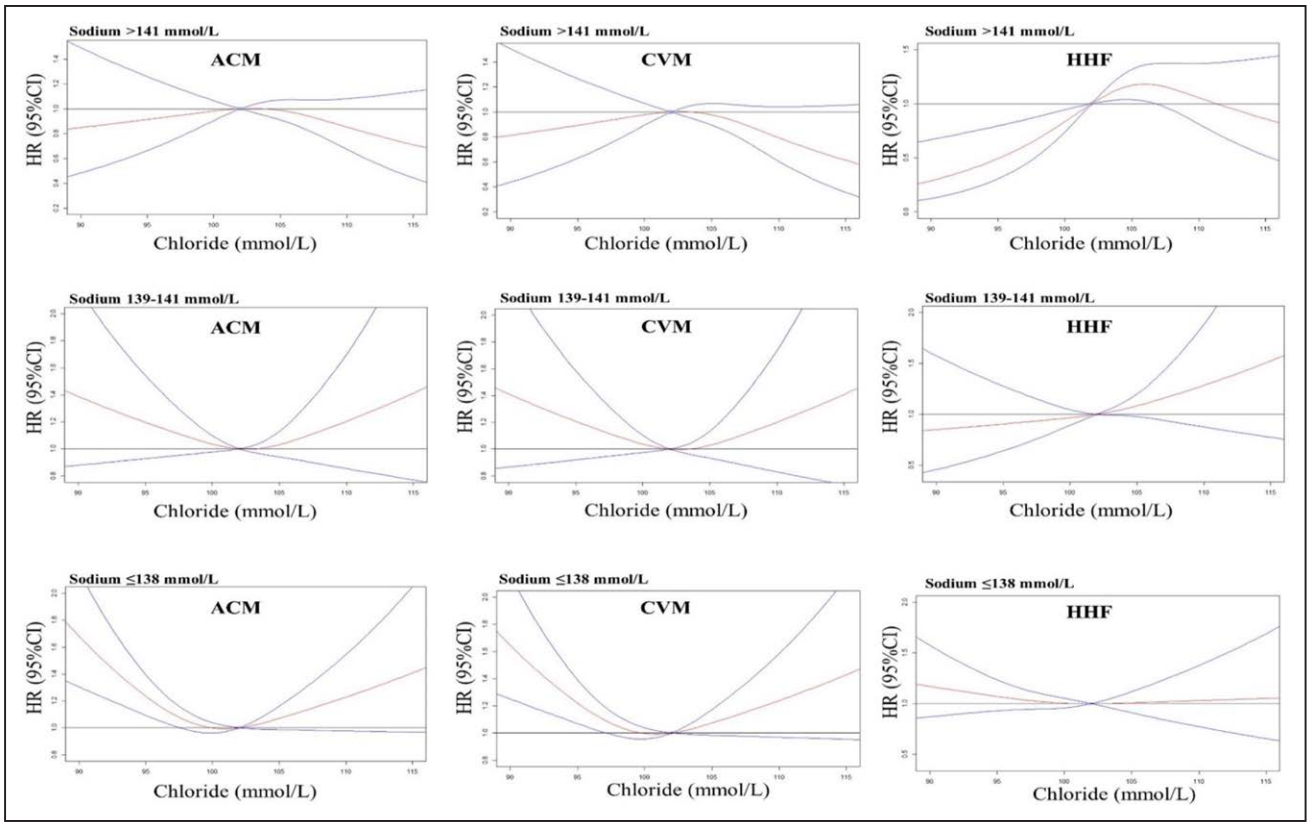

Figure 1. Relationship between serum chloride and all-cause mortality (ACM), cardiovascular mortality (CVM), and hospitalization for heart failure (HHF) within sodium tertiles. Red line, fitted curve; blue lines, 95% confidence interval (CI). Models adjusted for sex, age, systolic blood pressure, diabetes mellitus, atrial fibrillation, heart failure history, peripheral artery disease, hemoglobin, estimated glomerular filtration rate, blood urea nitrogen, left ventricular ejection fraction, Killip class, diuretic use, and body mass index. HR indicates hazard ratio.

Survival Analysis

Serum chloride had a nonlinear association with all studied outcomes (Figure 1). A significant interaction was found between chloride and sodium regarding the 3 studied outcomes, both as continuous splines (ACM *P* for interaction=0.023; CVM *P* for interaction=0.019; and HHF *P* for interaction=0.002) and ordinal variables (ACM *P* for interaction=0.027; CVM *P* for interaction=0.028; and HHF *P* for interaction <0.001; Table 2).

Serum chloride as a continuous cubic spline variable was only independently associated with ACM and CVM in the lower serum sodium tertile (ie, sodium <138 mmol/L). The chloride cutoff point below which these associations became significant was ≈97 mmol/L. For the other sodium categories (ie, 139–141 and >141 mmol/L), the associations were not significant. Although low chloride concentrations were associated with increased mortality in the context of lower sodium, high serum chloride was also likely to be associated with an increase in ACM and CVM in this setting because the association was U shaped; however, the associations for higher chloride were less precise and statistically nonsignificant (Figure 1). Low serum chloride was not significantly associated with increased HHF in the lower serum sodium tertile. However, in the higher serum sodium tertile (ie, sodium >141 mmol/L), low serum chloride (ie, <102 mmol/L) was associated with reduced HHF events, although only 19 events were observed in this subgroup along with (broad, wide) confidence intervals (CIs; Figure 1).

A lower serum chloride tertile (ie, <100 mmol/L) was associated with increased ACM, CVM, and HHF in the context of the lower sodium category (ie, <138 mmol/L; adjusted hazard ratio [HR] [95% CI]=1.42 [1.14–1.77]; *P*=0.002 for ACM, adjusted HR [95% CI]=1.40 [1.11–1.77]; *P*=0.005 for CVM, and adjusted HR [95% CI]=1.34 [1.07–1.67]; *P*=0.009 for HHF). Statistically significant associations regarding ACM and CVM for the lower chloride tertile were also observed in the context of midrange sodium levels (ie, >138 to ≤141 mmol/L; adjusted HR [95% CI]=1.35 [1.03–1.78]; *P*=0.03 for ACM and adjusted HR [95% CI]=1.40 [1.11–1.77]; *P*=0.005 for CVM), whereas the associations for lower chloride in the context of midrange sodium regarding HHF were not significant (adjusted HR [95% CI]=1.07 [0.79–1.46]; *P*=0.65; Table 2). Of note, and as also evidenced by the continuous spline analysis, lower serum chloride tertile (ie, <100 mmol/L) was associated with reduced HHF events in the context of higher serum sodium (ie, >141 mmol/L; HR [95% CI]=0.42 [0.25–0.69]; *P*=0.001; Table 2).

As observed in the univariable Kaplan–Meier curves in Figure 2, the cumulative survival (for ACM and CVM) was poorer in the lower chloride tertile only within the lower sodium tertiles, with the notable exception of HHF (ie, lower chloride tertile was also significantly associated with lower HHF rates within the higher sodium tertile).

On the contrary, after adjustment for potential confounders, lower serum sodium was not associated with outcomes (except for HHF; Table V in the Data Supplement).

Table 2. Analysis of Sodium×Chloride Interaction for ACM, CVM, and HHF

		Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
ACM	Overall				
	Chloride ≤100 mmol/L	1.48 (1.28–1.71)	<0.0001	1.29 (1.11–1.51)	0.0008
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.17 (0.99–1.37)	0.062	1.16 (0.98–1.37)	0.091
	Sodium ≤138 mmol/L				
	Chloride ≤100 mmol/L	1.69 (1.37–2.08)	<0.0001	1.42 (1.14–1.77)	0.002
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.33 (0.98–1.80)	0.066	1.32 (0.96–1.81)	0.085
	Sodium >138 to ≤141 mmol/L				
	Chloride ≤100 mmol/L	1.62 (1.24–2.12)	0.0004	1.35 (1.03–1.78)	0.030
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.31 (1.00–1.72)	0.051	1.30 (0.99–1.72)	0.061
	Sodium >141 mmol/L				
	Chloride ≤100 mmol/L	0.91 (0.64–1.29)	0.60	0.97 (0.68–1.39)	0.88
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	0.86 (0.66–1.13)	0.27	0.89 (0.68–1.17)	0.41
	Interaction sodium tertiles×chloride tertiles		0.027		0.22
	Interaction sodium tertiles×chloride splines		0.023		0.055
CVM	Overall				
	Chloride ≤100 mmol/L	1.48 (1.27–1.73)	<0.0001	1.29 (1.09–1.51)	0.002
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.14 (0.95–1.36)	0.15	1.12 (0.94–1.35)	0.20
	Sodium ≤138 mmol/L				
	Chloride ≤100 mmol/L	1.66 (1.33–2.08)	<0.0001	1.40 (1.11–1.77)	0.005
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.23 (0.88–1.72)	0.22	1.21 (0.86–1.72)	0.28
	Sodium >138 to ≤141 mmol/L				
	Chloride ≤100 mmol/L	1.68 (1.26–2.24)	0.0004	1.40 (1.05–1.88)	0.023
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.35 (1.01–1.80)	0.044	1.35 (1.00–1.82)	0.047
	Sodium >141 mmol/L				
	Chloride ≤100 mmol/L	0.88 (0.61–1.29)	0.52	0.92 (0.62–1.35)	0.66
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	0.82 (0.61–1.10)	0.18	0.85 (0.63–1.14)	0.26
	Interaction sodium tertiles×chloride tertiles		0.028		0.16
	Interaction sodium tertiles×chloride splines		0.019		0.039
HHF	Overall				
	Chloride ≤100 mmol/L	1.28 (1.10–1.49)	0.002	1.07 (0.91–1.26)	0.39
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.18 (0.99–1.40)	0.063	1.17 (0.98–1.40)	0.076
	Sodium ≤138 mmol/L				
	Chloride ≤100 mmol/L	1.66 (1.34–2.05)	<0.0001	1.34 (1.07–1.67)	0.009
	Chloride >100 to ≤104 mmol/L	Reference		Reference	

(*Continued*)

Table 2. Continued

		Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
	Chloride >104 mmol/L	1.31 (0.96–1.79)	0.093	1.37 (1.00–1.88)	0.052
	Sodium >138 to ≤141 mmol/L				
	Chloride ≤100 mmol/L	1.31 (0.98–1.76)	0.072	1.07 (0.79–1.46)	0.65
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	1.13 (0.85–1.52)	0.40	1.15 (0.85–1.55)	0.38
	Sodium >141 mmol/L				
	Chloride ≤100 mmol/L	0.38 (0.23–0.63)	0.0002	0.42 (0.25–0.69)	0.0006
	Chloride >100 to ≤104 mmol/L	Reference		Reference	
	Chloride >104 mmol/L	0.91 (0.68–1.21)	0.51	0.91 (0.68–1.21)	0.51
	Interaction sodium tertiles×chloride tertiles		<0.0001		0.001
	Interaction sodium tertiles×chloride splines		0.002		0.041

Two *P* values for interaction are provided: one for the crude model and another for the adjusted model. ACM indicates all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; HHF, hospitalization for heart failure; and HR, hazard ratio.

*Adjusted for sex, age, systolic blood pressure, diabetes mellitus, atrial fibrillation, heart failure history, peripheral artery disease, hemoglobin, estimated glomerular filtration rate, blood urea nitrogen, left ventricular ejection fraction, Killip class, diuretic use, and body mass index.

The interplay between chloride and sodium is furthermore illustrated in a 3-dimensional contour surface graph in Figure I in the Data Supplement.

Prognostic Impact Assessment

The addition of chloride (as continuous cubic spline) and its interaction with sodium (in tertiles and continuous cubic spline)

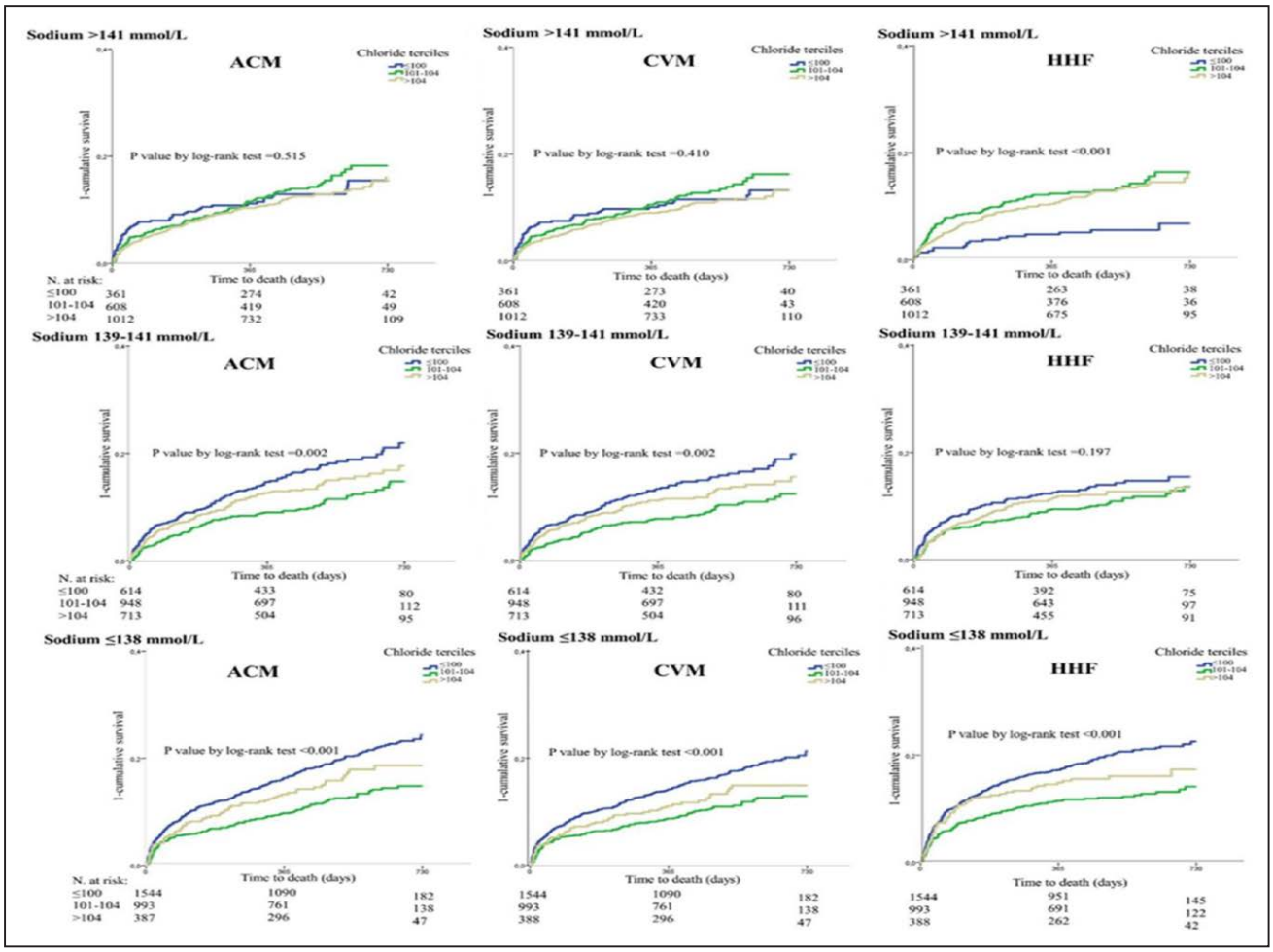

Figure 2. Kaplan–Meier curves for the studied outcomes of all-cause mortality (ACM), cardiovascular mortality (CVM), and hospitalization for heart failure (HHF) according to serum chloride tertiles within serum sodium subgroups. Chloride is expressed in mmol/L. The above panels represent illustrative univariable models. N indicates number.

Table 3. Net Reclassification Index, Integrated Discrimination Index, and C-Index Using Chloride as Continuous Cubic Spline and Its Interaction With Sodium in Tertiles and in Continuous Cubic Spline

		+Chloride in Spline+Interaction With Sodium in Tertiles		+Chloride in Spline+Interaction With Sodium in Spline	
		Overall		Overall	
		Index (95% CI)	*P* Value	Index (95% CI)	*P* Value
ACM	NRI, %	5.2 (−0.7 to 9.3)	0.080	1.9 (−1.4 to 8.5)	0.10
	IDI, %	0.4 (0.2 to 0.9)	<0.0001	0.2 (0.0 to 0.7)	0.014
	C-index	0.003 (0.000 to 0.006)	0.043	0.002 (−0.000 to 0.004)	0.11
CVM	NRI, %	5.7 (−0.3 to 9.8)	0.060	3.0 (−2.6 to 8.3)	0.17
	IDI, %	0.4 (0.2 to 1.0)	<0.0001	0.2 (0.1 to 0.8)	0.004
	C-index	0.003 (−0.000 to 0.006)	0.087	0.002 (−0.001 to 0.004)	0.18
HHF	NRI, %	3.2 (−1.7 to 9.1)	0.18	6.3 (−1.2 to 10.1)	0.12
	IDI, %	0.3 (0.1 to 0.7)	<0.0001	0.2 (−0.0 to 0.8)	0.078
	C-index	0.001 (−0.002 to 0.004)	0.43	0.001 (−0.002 to 0.004)	0.56

All models were adjusted for sex, age, systolic blood pressure, diabetes mellitus, atrial fibrillation, heart failure history, peripheral artery disease, hemoglobin, estimated glomerular filtration rate, blood urea nitrogen, left ventricular ejection fraction, Killip class, diuretic use, and body mass index. For NRI and IDI, the time point of event definition was the median follow-up for each end point.

ACM indicates all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; HHF, heart failure hospitalization; IDI, integrated discrimination index; and NRI, net reclassification index.

to a prognostic model (including sex, age, systolic blood pressure, diabetes mellitus, atrial fibrillation, HF history, peripheral artery disease, hemoglobin, estimated glomerular filtration rate, blood urea nitrogen, left ventricular ejection fraction, Killip class, diuretic use, and body mass index) did not add prognostic information to the model for any outcome using the NRI method (Table 3). Using IDI, the additional prognostic information was modest and clinically irrelevant (IDI for ACM plus interaction with spline sodium=0.2% [0.0%–0.7%]; *P*=0.014; IDI for CVM plus interaction with spline sodium=0.2% [0.1%–0.8%]; *P*=0.004; IDI for HHF plus interaction with spline sodium=0.2% (−0.0 to 0.8); *P*=0.078; Table 3). The discrimination of risk estimation as assessed by C statistics was also not improved by serum chloride (Table 3).

The prognostic improvement assessment was also performed within sodium tertiles (Table VI in the Data Supplement).

Discussion

In a large population of post-MI complicated by reduced left ventricular function and HF, a significant interaction between sodium and chloride was observed: low serum chloride (<97 mmol/L as continuous variable) was associated with mortality, but not hospitalization for HF, in the setting of lower sodium. Overall, chloride and its interaction with sodium did not add clinically relevant prognostic information on top of other well-established prognostic variables nor increased the discriminative capacity of the model. Taken together, these data suggest that sodium and chloride should be considered together for outcome prediction.

Chloride Pathophysiology and Interplay With Sodium

Chloride is the most important anion in plasma and interstitial fluid, the 2 compartments that make up extracellular fluid. It accounts for approximately one third of plasma tonicity and for two thirds of all negative charges in plasma.[25] Despite its major importance, chloride has received little attention in cardiovascular diseases.[9]

Dietary sodium chloride is the main source of chloride in the body, and its excretion is mainly performed by the kidney, although >80% of filtered chloride is reabsorbed in the proximal tubule.[26] In addition, gastrointestinal secretions are also rich in chloride, with gastric secretions being the predominant source.[27]

Hyper- and hypochloremia are frequent in hospitalized patients with acute and unstable conditions.[25] The most frequent and reversible cause of hyperchloremia is the administration of intravenous chloride-rich fluids, such as 0.9% NaCl (saline) with supraphysiological chloride content.[28] On the contrary, hypochloremia is much more frequent in association with congestive states/neurohormonal activation, either by chloride loss via diuretic administration or by water gain (eg, congestive HF and inappropriate secretion of arginine vasopressin).[25,29,30] Neurohormonal activation with impaired arginine vasopressin secretion is also important in patients with left ventricular dysfunction even without overt HF and increases when diuretics are added to the therapy because of volume depletion induction.[31] Hence, lower chloride levels may be associated either with dilutional states or with electrolyte depletion states, especially when chloride is lower relative to sodium, which can occur in the setting of diuretic-induced salt wasting (with predominant excretion of chloride in the urine in exchange of bicarbonate that is retained to maintain electroneutrality).[32]

Hyponatremia is the most common electrolyte disorder in hospitalized patients.[33] The presence of hyponatremia at admission or during index hospitalization is associated

with increased rates of adverse outcomes,[34] and in which, patients with acute MI are no exception.[35] In HF and acute MI, hyponatremia may be dilutional or depletional[29] because loop diuretics are frequently used in the acute HF and MI settings.[36,37] These agents block the sodium/potassium/chloride cotransporter in the thick ascending limb of Henle loop, which is relatively impermeable to water. This interference of loop diuretics with renal capacity to concentrate urine may result in the production of relatively hypotonic urine (≈120 mmol/L of urinary sodium)[38] and, therefore, offer a relative protection against hyponatremia because sodium will thereafter be reabsorbed in the distal tubule. However, loop diuretics do not protect against hypochloremia because, contrary to sodium, chloride will not be distally reabsorbed.[39,40] On the contrary, thiazides generate less hypotonic urine by inhibiting reabsorption of sodium and chloride from the distal convoluted tubules and, therefore, may aggravate both hyponatremia and hypochloremia.[41,42] Hypothetically, patients with more severe congestion would more often display dilutional hyponatremia, which, as stated above, is associated with worse prognosis. These patients are also more likely to be submitted to higher diuretic doses (in attempts to relieve congestion), which, in turn, may induce (or aggravate) hypochloremia. This putative mechanism could provide an explanation as to why prognosis is worse when a patient has both lower sodium and low chloride. These distinctions may have clinical implications in diuretic strategies for acute HF and MI.[40] In our study, diuretics were systematically considered as adjustment parameters in all multivariable analyses; however, no interaction was observed between diuretic use at randomization and chloride regarding the studied outcomes, particularly HHF in which a lower serum chloride was associated with lower event rates only in the context of higher sodium. This finding could potentially translate into effective decongestion via loop diuretic use, which is also supported by the association of the lower sodium tertile (but not the higher tertile) with increased HHF rates (Table V and Figure I in the Data Supplement). In other words, patients undergoing effective decongestion may present lower chloride levels with normal/high sodium, which may provide a putative explanation for the lower HHF in this subgroup.

Serum Chloride as Prognostic Marker

Our findings derived from a large sample of complicated post-MI patients suggest that lower chloride levels at randomization were associated with higher ACM and CVM rates in the presence of low serum sodium levels (*P* for interaction <0.05). This finding is represented in Figure 1 for continuous chloride (represented as restricted cubic splines adjusted models). When analyzing chloride and sodium categories/subgroups (ie, tertiles), lower serum chloride was also associated with ACM and CVM within the lower sodium tertile and in the midrange sodium tertile. This information captured in categories is not as refined as the information represented for continuous observations because categories capture all events within that subgroup, that is, very low and normal–low electrolyte levels are treated the same way incorporating less accurate information. Of more significant interest, serum chloride (and serum sodium) and its interaction with sodium did not add relevant prognostic information on top of age, sex, systolic blood pressure, diabetes mellitus, atrial fibrillation, HF history, peripheral artery disease, hemoglobin, estimated glomerular filtration rate, urea, left ventricular ejection fraction, Killip class, diuretic use, and body mass index, nor did it increase the discriminative capacity of this model. Intriguingly, for the outcome of first HHF, low serum chloride was associated with lower event rates only in the context of higher sodium (>141 mmol/L), although only 19 HHF events were observed in this subgroup, and these data may, therefore, be imprecise; however, this lower rate may be because of a more effective decongestion via loop diuretic use, as discussed above.

These results are complementary to those described by Grodin et al[9] derived from 2 independent acute HF cohorts. In these cohorts, the prognostic value of serum chloride was stronger than and independent from sodium levels with regard to ACM (although neither CVM nor HHF were tested in these studies). Nonetheless, in these acute HF cohorts, there was also no increase in the overall C statistic of the multivariable model with the addition of chloride (0.68 versus 0.69; *P*=0.50), whereas adding chloride to the multivariable model offered modest risk reclassification improvement (NRI=17.2%; *P*=0.006 and IDI=10%; *P*<0.001).[9,43] Of note, these acute HF cohorts had a much smaller sample size than the present series, limiting the power for the assessment of interaction analysis, which is a statistically weak test depending on sample size and event rate.[24] In this regard, our data supplement those assessed by Grodin et al, thus providing further insight into sodium/chloride interplay. Chloride is likely a stronger prognosticator than sodium (as also demonstrated herein), although the interpretation of these electrolytes should be considered together. Such chloride/sodium interplay is also supported by mechanistic data in which both serum chloride and sodium were associated with poor diuretic efficiency and negatively correlated with plasma renin levels, with chloride being the main independent driver of these associations. Moreover, chloride supplementation has been associated with an improvement in diuretic response.[44] In the chronic HF setting, low serum chloride has also been associated with dismal outcome.[10,11] An additional explanation for the differences found between these different populations is that HF and post-MI are distinct settings with different presentations, treatments, and prognosis, despite the fact that ≈60% of our population had left ventricular ejection fraction <35% and ≈20% had HF history, without significant interaction in these subgroups (Table VII in the Data Supplement). In particular, fluid management plays a central role in HF therapy. In this regard, serum chloride is essential for osmotic pressure maintenance and movement of water between fluid compartments.[45] Moreover, despite repeated associations of serum sodium with morbidity and mortality in patients with HF, pharmacological therapies that target serum sodium levels, such as vasopressin antagonists, have not improved patient outcomes,[46] suggesting a potential role of serum chloride in disease progression.[8] In the MI context (even if complicated by HF), serum chloride is likely to have a less important role because effective reperfusion and myocardial protection are the cornerstone therapies in this setting.[47]

Clinical and Research Implications

Despite obvious challenges, these results provide further insight on electrolyte management: in the setting of post-MI with heart failure with reduced ejection fraction, our findings suggest that sodium and chloride should be interpreted together. Analyzing their interplay and potential causes for their dysregulation may help clinicians in refining their outcome prediction and in tailoring therapeutic strategies. For example, patients with low chloride and low sodium are likely to have higher mortality rates than those with normal levels of these electrolytes, and therefore, prompt correction should be attempted. However, low serum chloride in the context of high sodium may translate in the use of loop diuretics and effective decongestion, which may be protective in the case of congestive HF. Moreover, high and very-high chloride levels are also likely to be associated with increased mortality rates (as the curves are U shaped, despite the wide CIs crossing the HR=1 level) even in the context of low/normal sodium.

Study Limitations

Several limitations should be acknowledged in this study. First, given the post hoc nature of this study, the limitations inherent to retrospective analyses are, thus, applicable. Second, because of their absence in the database, we did not account for the change in chloride/sodium levels over time, which can potentially add predictive information to the randomization-only measurement. In a recent analysis of acute HF patients, low serum chloride at hospital admission was strongly associated with impaired decongestion. Moreover, new or persistent hypochloremia 14 days later was also independently associated with reduced survival, whereas hypochloremia that was resolved by day 14 was not.[12] Third, the patients herein were from high-risk MI trials with strict inclusion/exclusion criteria that can produce a sample that may not be representative of general clinical practice, therefore also affecting the generalizability of our findings. Fourth, although bicarbonate/chloride interplay has been explored in other cohorts,[9] serum bicarbonate levels were not available in the present data set. Fifth, there were no available data regarding diuretic doses and type of diuretics used nor regarding the congestive status of the patients, which could provide further insight on sodium/chloride interplay. Sixth, chloride and sodium levels were measured at randomization, which varied between 12 hours and 21 days after admission; hence, the electrolyte levels may not reflect actual baseline admission values. Moreover, these randomization values are subject to the impact of treatments or post-MI complications. However, these varying timings do not represent a systematic error but rather represent a random error (ie, imprecision), reinforcing the strength of the associations.[48] Nonetheless, further studies are required to understand the underlying conditions associated with this dysregulation and its ensuing correction or aggravation. Seventh, the High-Risk MI Database Initiative data set does not contain the randomized study treatment, so no comparisons could be made between the agents investigated.[13] Finally, also lacking were data regarding patient decisions and medication changes that could possibly have an impact on chloride levels and prognosis (such as loop diuretics dose).

Conclusions

In a large post-MI database with systolic dysfunction and HF in which only half of the patients were on diuretics, we observed a significant interaction between serum chloride and sodium: low serum chloride was associated with mortality (but not HHF) in the setting of lower sodium. Overall, chloride and its interaction with sodium did not add clinically relevant prognostic information on top of other well-established prognostic variables. Taken together, these data support an integrated and critical consideration of chloride and sodium interplay.

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CLINICAL PERSPECTIVE

In the setting of postmyocardial infarction with heart failure and reduced ejection fraction, our findings suggest that sodium and chloride should not be interpreted is isolation but rather should be interpreted together. Analyzing their interplay and potential causes for their dysregulation may help clinicians in refining their outcome prediction and in tailoring therapeutic strategies. For example, patients with low chloride and low sodium are likely to have higher mortality rates than those with normal levels of these electrolytes, and therefore prompt correction should be attempted. However, low serum chloride in the context of high sodium may translate in the use of loop diuretics and effective decongestion, which may be protective in the case of congestive heart failure. Moreover, high and very-high chloride levels are also likely to be associated with increased mortality rates (as the association of chloride levels and outcomes is U shaped) even in the context of low/normal sodium.