



THE 29TH INTERNATIONAL CONFERENCE ON

ADVANCES IN CRITICAL CARE NEPHROLOGY

AKI & CRRT 2024

MARCH 12-15, 2024

MANCHESTER GRAND HYATT

SAN DIEGO, CALIFORNIA

Jointly Provided by

UC San Diego

SCHOOL OF MEDICINE

and

CRRT, INC.

SESSION I (Plenary-1): Organ Dysfunction in the Critically Ill Patient: Emerging Concepts

Hidden in Plain Sight; Chloride in Acute Heart Failure



Amir Kazory, MD, FASN, FAHA

**Division of Nephrology, Hypertension, and Renal Transplantation
University of Florida**



Disclosures

Baxter, Inc. – Cardiology Advisory Board

Daxor, Inc. - Consultant

DCI, Inc. – Directorship Fee

Elsevier, Inc. – Editorial Fee

Horizon Therapeutics USA, Inc. – Advisory Board

NuWellis, Inc. - Scientific Advisory Board

Relypsa, Inc. - Consultant

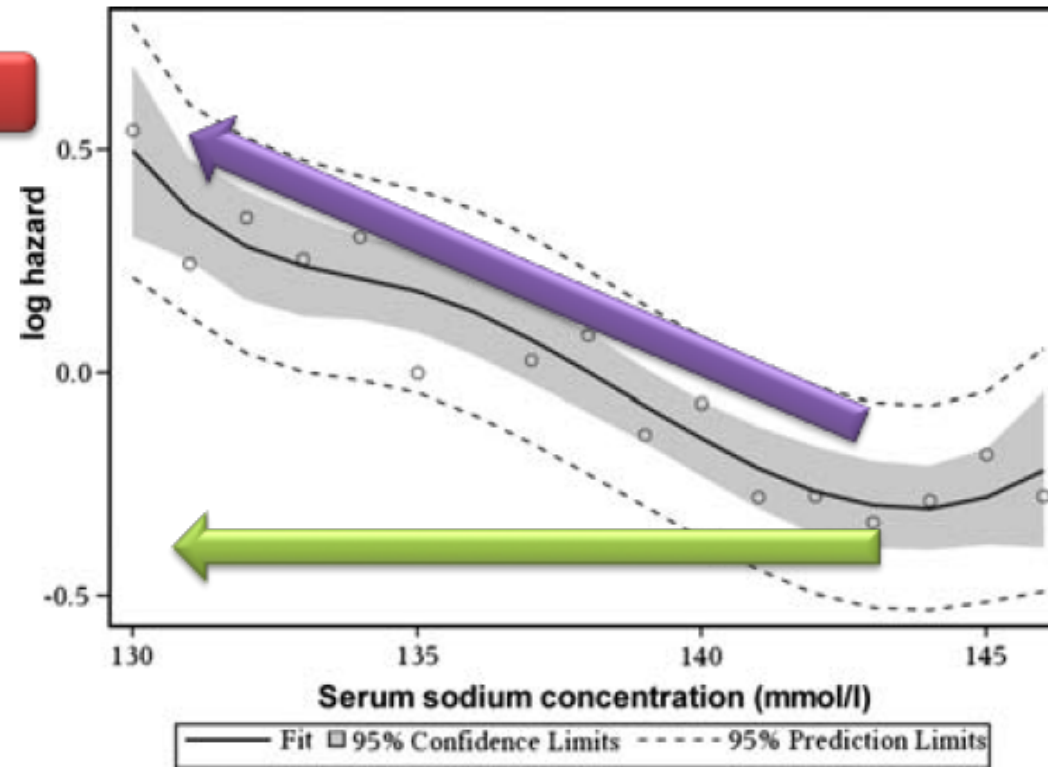
W.L. Gore Inc. - Consultant

Observation 1

Hyponatremia and Mortality in HF (MAGGIC)

14,766
patients

3-year Mortality

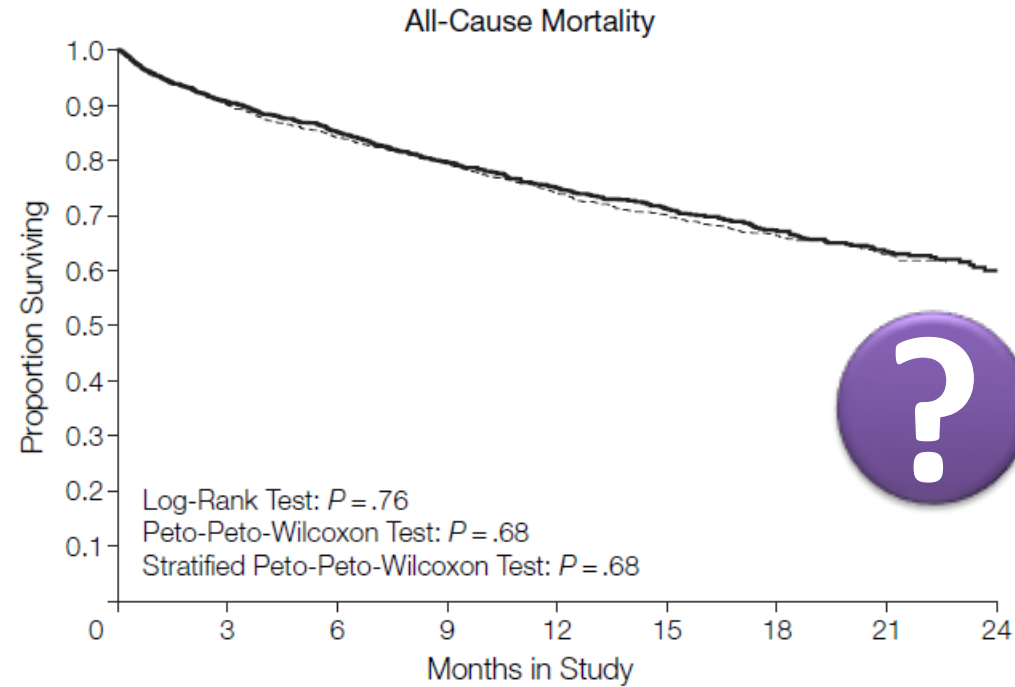


Hyponatremia: a powerful determinant of mortality in HF regardless of ejection fraction.

Correction of Hyponatremia (EVEREST)

Survival

4133
patients



No. at Risk									
Tolvaptan	2072	1812	1446	1112	859	589	404	239	97
Placebo	2061	1781	1440	1109	840	580	400	233	95

V2RA does not improve outcomes in HF
(tolvaptan vs. placebo in ADHF)

Observation 2

Dietary Sodium Restriction

Table 1 Guideline Recommendations for Sodium Intake in Heart Failure

Guideline and Reference	Year	Sodium Intake Recommendation	Level of Evidence
Cardiac Society of Australia and New Zealand ⁹	2018	< 2 g/d	Not stated
Canadian Cardiovascular Society ⁸	2017	2-3 g/d	Limited
Heart Failure Society, India ⁶	2017	< 3 g/d	Not stated
Royal College of Physicians ⁵	2016	Reduce intake for patients with high salt intake	Limited
Scottish Intercollegiate Guidelines Network ¹¹	2016	Salt intake of < 6 g/d	Not stated
American College of Cardiology/American Heart Association ⁴	2013	Restriction as reasonable	C
European Society of Cardiology ⁷	2012	Moderate restriction	Not stated
American Dietetic Association ¹²	2011	< 2 g/d	Fair
Heart Failure Society of America ¹⁰	2010	2-3 g/d; < 2 g/d in severe heart failure	C

Level of Evidence: C = consensus opinion of experts. Limited population evaluated; Fair = benefits more than harms, but quality of evidence is weak; Limited = more research is required

“Dietary Sodium Restriction”:
the most frequent self-care behavior recommended to patients with HF



Sodium Restriction in HF; Persistence of Uncertainty

JAMA Internal Medicine | Review

Reduced Salt Intake for Heart Failure A Systematic Review

Out of >2600 studies

Kamal R. Mahtani, PhD; Carl Heneghan, DPhil; Igbo Onakpoya, DPhil; Stephanie Tierney, MA, PhD;
Jeffrey K. Aronson, DPhil; Nia Roberts, MSc; F. D. Richard Hobbs, FMedSci; David Nunan, MSc, PhD

Table 2. Summary of Changes in the Clinical Signs and Symptoms of Heart Failure

Source	Country	No. of Participants	Difference, Intervention vs Control
Inpatient Studies			
Aliti et al, ¹⁵ 2013 ^a	Brazil	75	No difference
Velloso et al, ²¹ 1991 ^b	Brazil	32	No difference
Outpatient Studies			
Alvelos et al, ¹⁶ 2004 ^c	Portugal	24	No difference
Colín-Ramírez et al, ¹⁷ 2004 ^c	Mexico	65	Favors intervention
Colín-Ramírez et al, ¹⁸ 2015 ^c	Canada	38	No difference
Philipson et al, ¹⁹ 2013 ^c	Sweden	97	Favors intervention
Colín-Ramírez et al, ¹⁸ 2015 ^d	Canada	38	No difference
Hummel et al, ²² 2017 ^d	United States	66	No difference

All studies: less than
100 patients

The great majority
did not find
improvement with
sodium restriction
(2-3 g/day)

Sodium Restriction May Be Harmful in HF (HART)

260
patients



AMERICAN
COLLEGE of
CARDIOLOGY®



Clinical Topics

Latest In Cardiology

Education and Meetings

Too Little Sodium Can be Harmful to Heart Failure Patients

Cutting sodium below current recommendations could be counterproductive, study finds

Feb 23, 2023

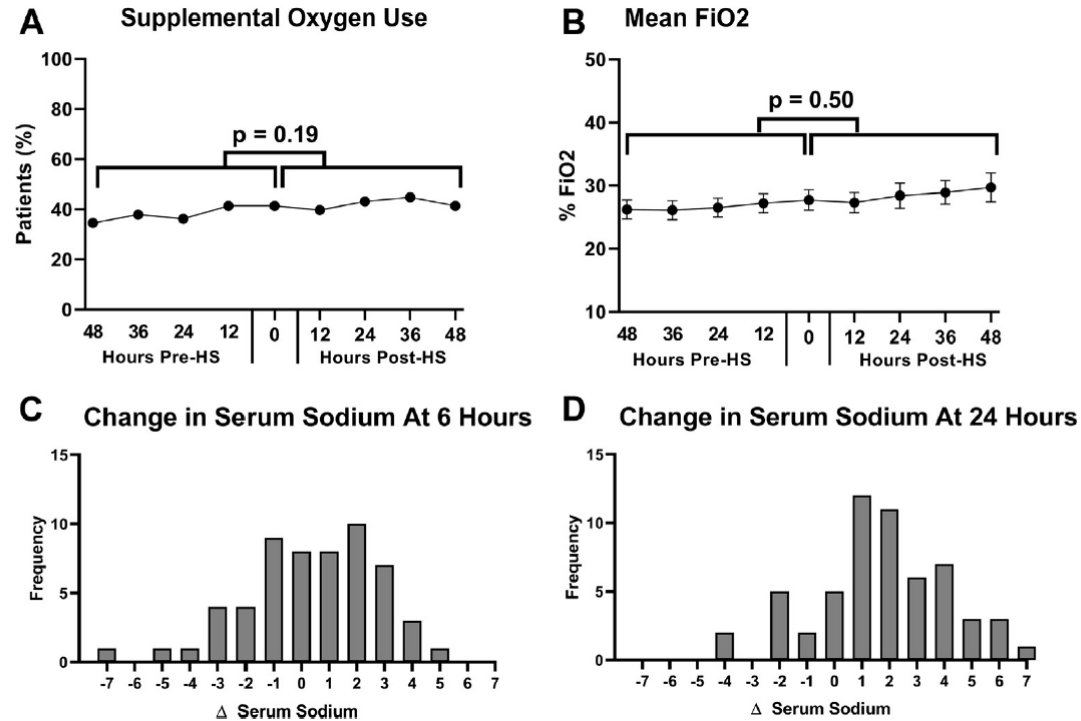
Observation 3

Treating ADHF with Hypertonic Saline

58 administrations
40 patients

150 ml of
3% NaCl over 30 min
(300 ml/h),
simultaneously with
high doses of loop
diuretics

FIGURE 1 Safety Profile of Hypertonic Saline

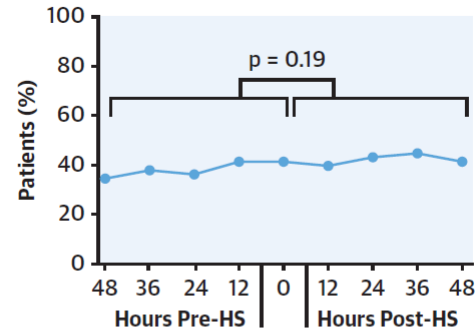


No increase in O2 requirement or over-correction of serum sodium

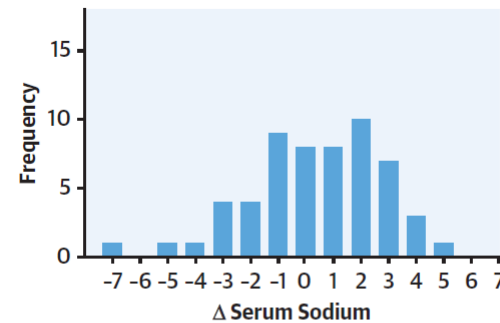
Treating ADHF with Hypertonic Saline

58 administrations
40 patients

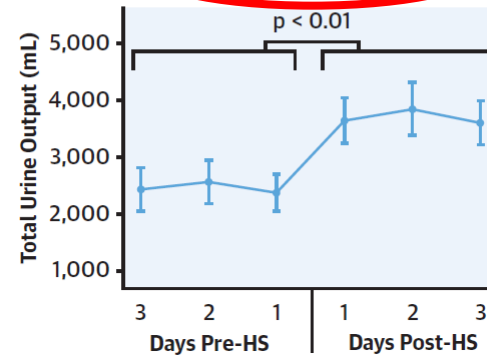
Supplemental Oxygen Use



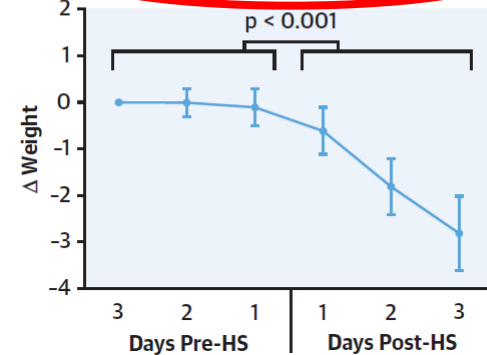
Change in Serum Sodium at 6 Hours



Total Urine Output



Weight Change from Baseline



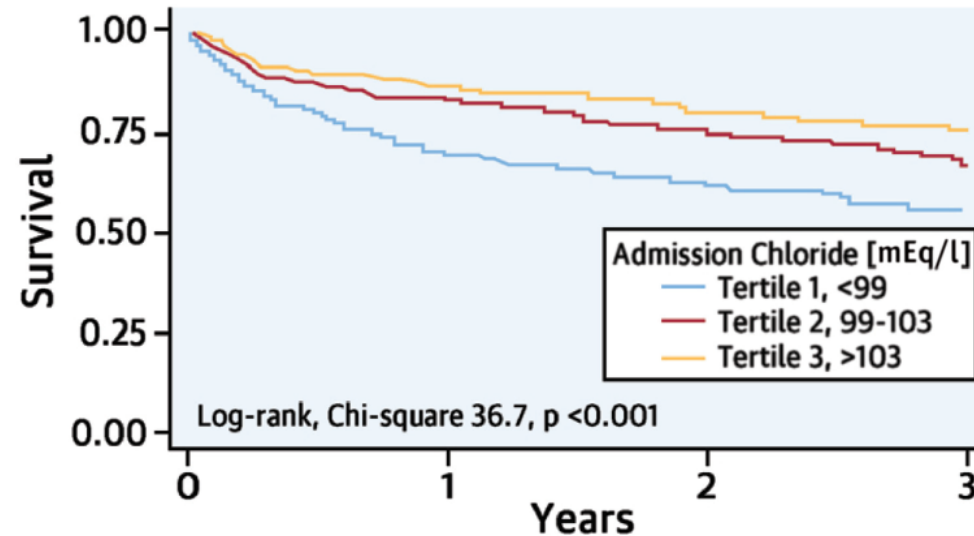
↑ in Urine output and ↓ in weight

Salt ≠ Sodium

2015

First Studies on Chloride-HF (ADHF-2015)

CENTRAL ILLUSTRATION Chloride in Acute Decompensated Heart Failure: Survival Estimates by Admission Chloride Levels



At-risk by Chloride Tertile

Tertile 1	456	235	148	82
Tertile 2	497	319	203	95
Tertile 3	365	243	147	78

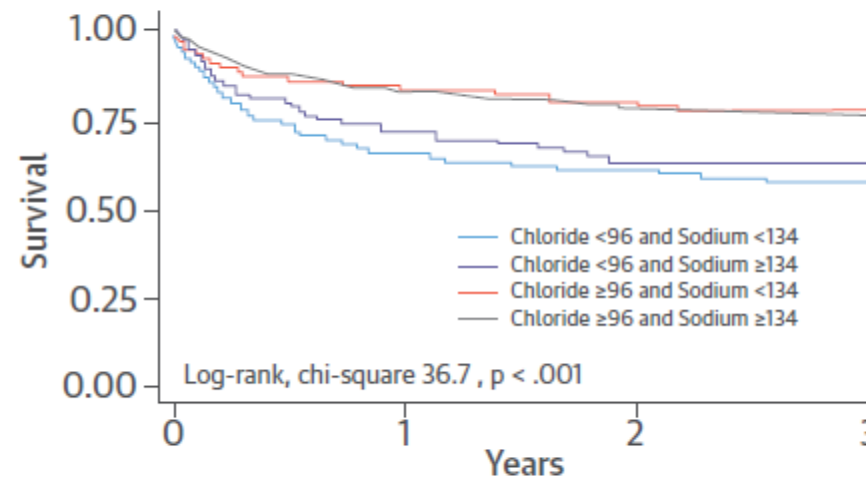
1318
patients

2261 person-years
of follow up

Tertiles of Admission Chloride – Cleveland Clinic Cohort

First Studies on Chloride-HF (ADHF-2015)

FIGURE 1 Survival Estimates Stratified by Admission Hypochloremia and Hyponatremia



At-risk by Chloride and Sodium Level [mEq/l]

Chloride <96 and Sodium <134	148	97	91	85
Chloride <96 and Sodium ≥134	86	61	55	54
Chloride ≥96 and Sodium <134	84	71	67	66
Chloride ≥96 and Sodium ≥134	1000	838	791	766

1318 patients

2261 person-years of follow up

Low Chloride

Admission chloride levels; possibly a stronger prognostic role than serum sodium levels

Follow Up Studies on Chloride-HF (CHF-2016)

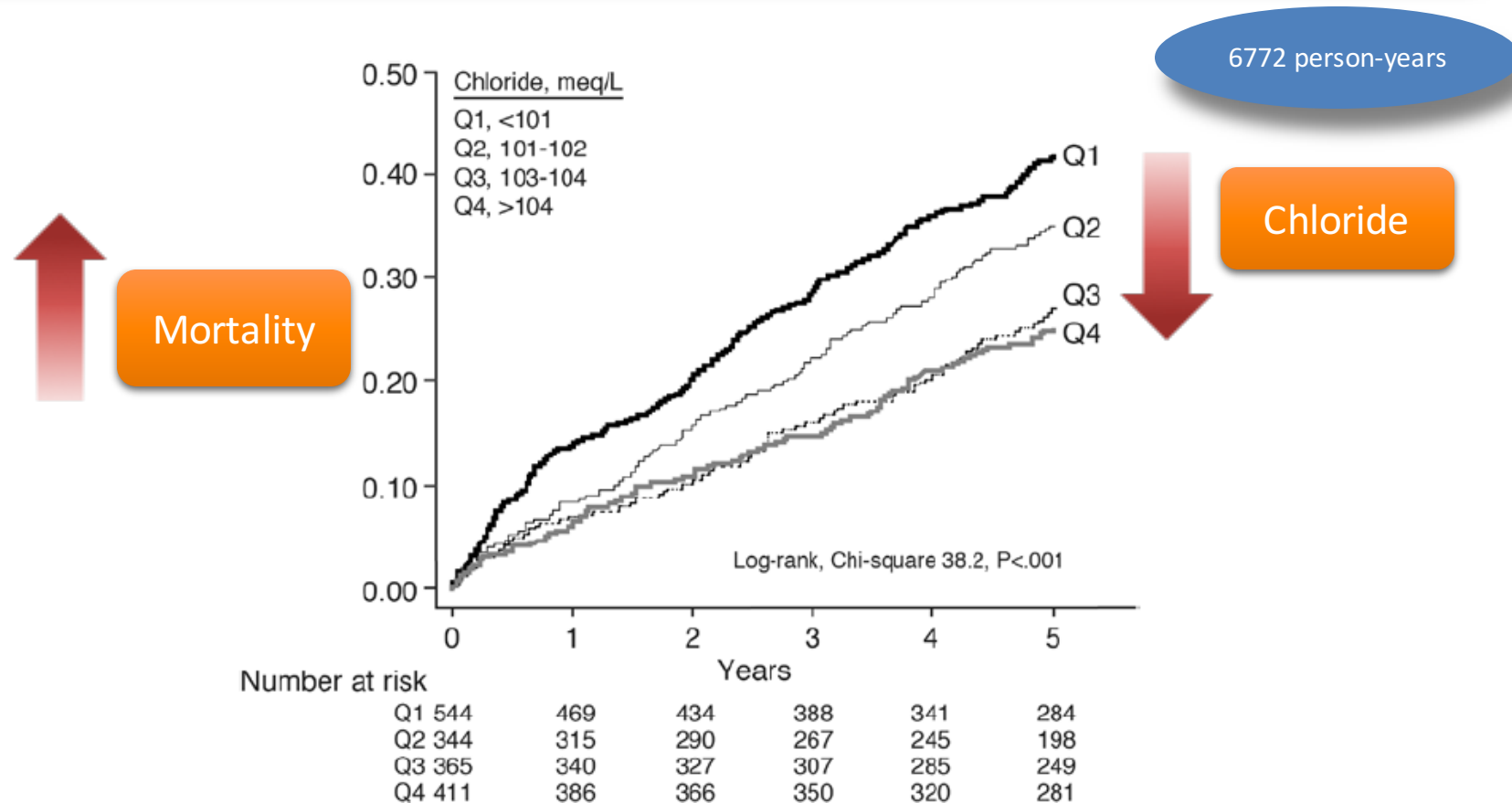


Figure 1. Kaplan–Meier estimated of 5-year mortality across chloride quartiles.

Follow Up Studies on Chloride-HF (CHF-2016)

6772 person-years

5-year Mortality

Table 2. Cox-Proportional Hazards Models for the Association of Chloride and 5-Year Mortality

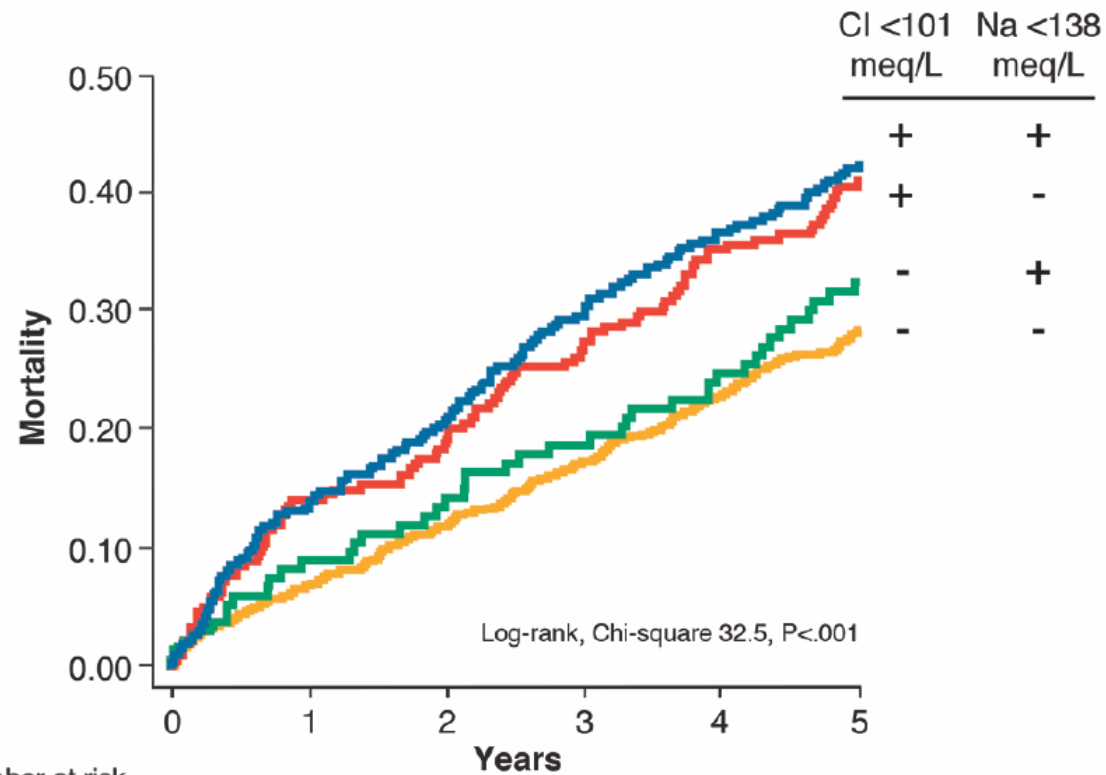
Model	HR* (95% CI)	P Value
Unadjusted	1.32 (1.22–1.43)	<0.001
Adjusted Model 1†	1.29 (1.12–1.49)	<0.001
Adjusted Model 2‡	1.26 (1.03–1.55)	0.027

For every standard deviation (4.1 mEq/L) decrement in Chloride level; 26-29% increase in 5-year mortality risk

Follow Up Studies on Chloride-HF (CHF-2016)

5-year Mortality

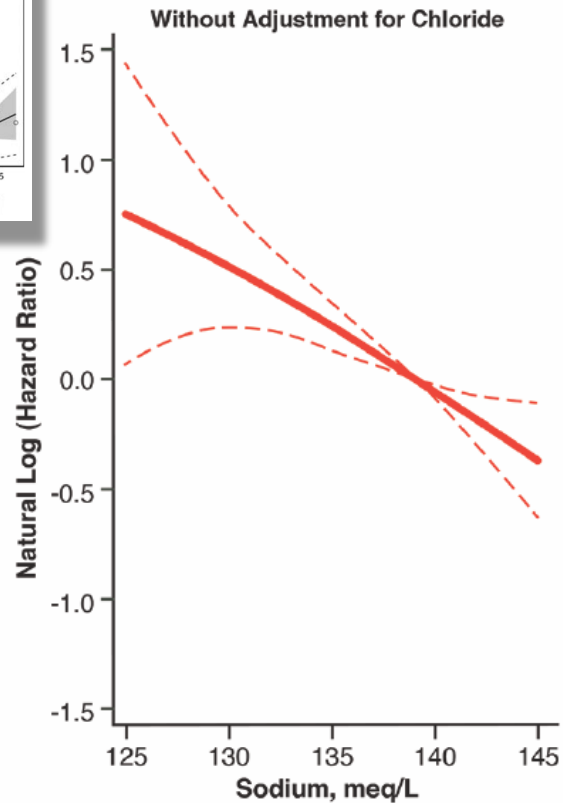
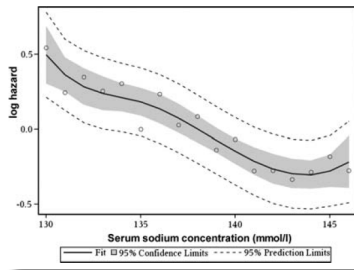
1673 patients



	Number at risk					
	0	1	2	3	4	5
Cl <101 meq/L & Na <138 meq/L	311	269	246	219	193	161
Cl <101 meq/L & Na ≥138 meq/L	233	200	188	169	148	123
Cl ≥101 meq/L & Na <138 meq/L	133	121	114	108	100	80
Cl ≥101 meq/L & Na ≥138 meq/L	987	920	869	816	750	648

Follow Up Studies on Chloride-HF (CHF-2016)

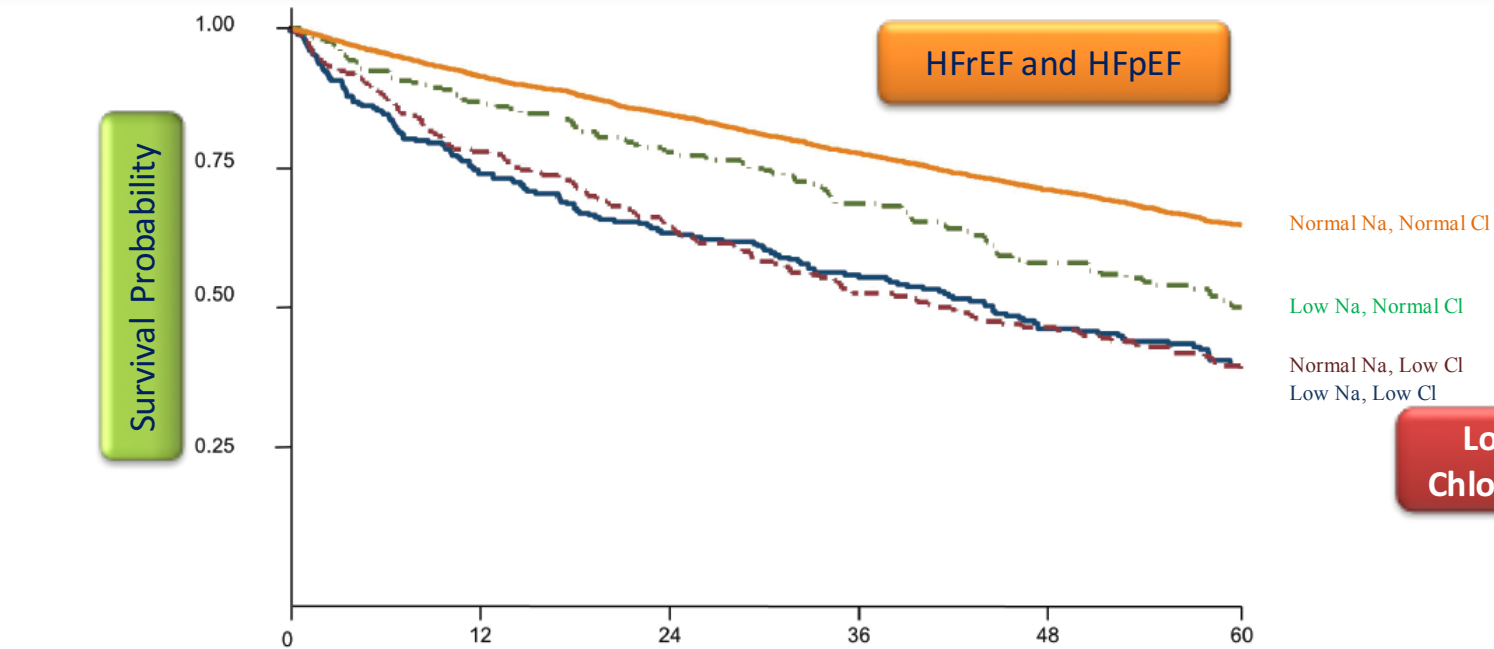
1673
patients



Predicted 5-Year Mortality of Sodium Level
with and without Adjustment for Chloride

Follow Up Studies on Chloride-HF (CHF-2018) Europe

5613 patients



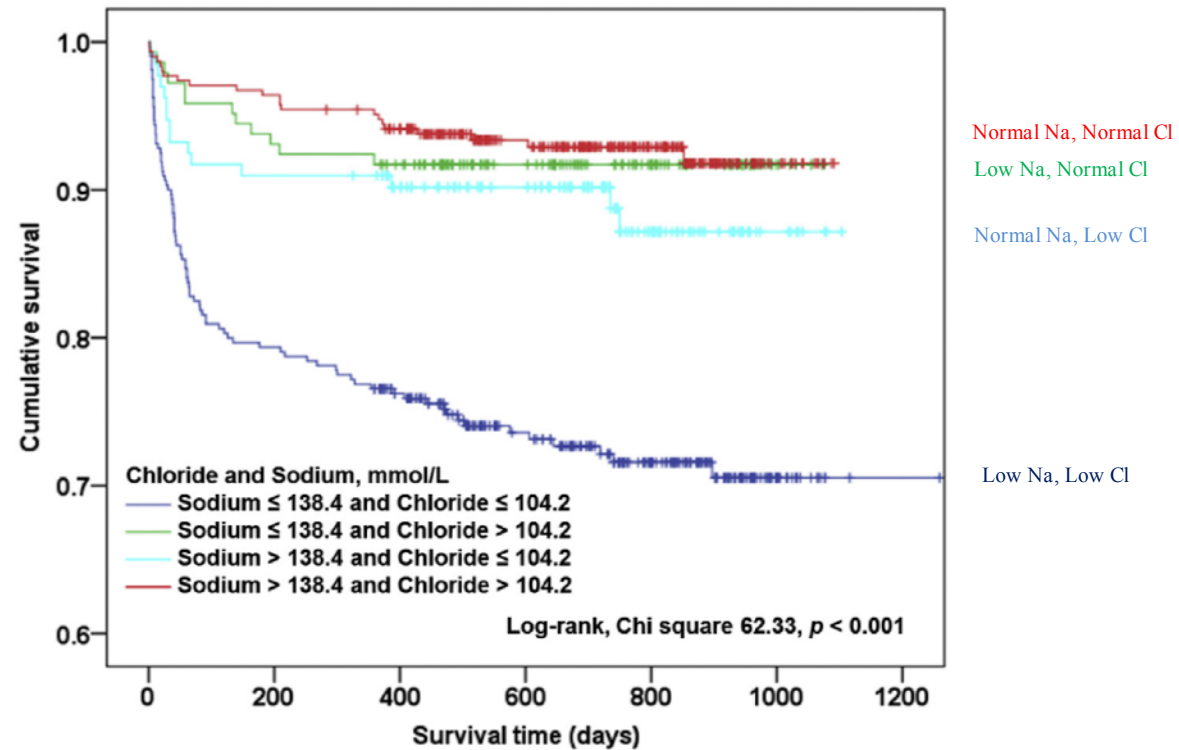
Number at risk	Follow up (months)					
	0	12	24	36	48	60
Group 1	285	198	160	137	102	82
Group 2	224	169	138	111	91	67
Group 3	254	203	167	132	89	74
Group 4	3942	3455	3090	2756	2346	1939

— 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

Follow Up Studies on Chloride-HF (CHF-2018) China

905 patients



Number at risk

Sodium \leq 138.4 and Chloride \leq 104.2	320	254	231	163	104	19
Sodium \leq 138.4 and Chloride $>$ 104.2	145	135	129	91	55	7
Sodium $>$ 138.4 and Chloride \leq 104.2	133	121	111	93	43	8
Sodium $>$ 138.4 and Chloride $>$ 104.2	307	296	283	201	109	16

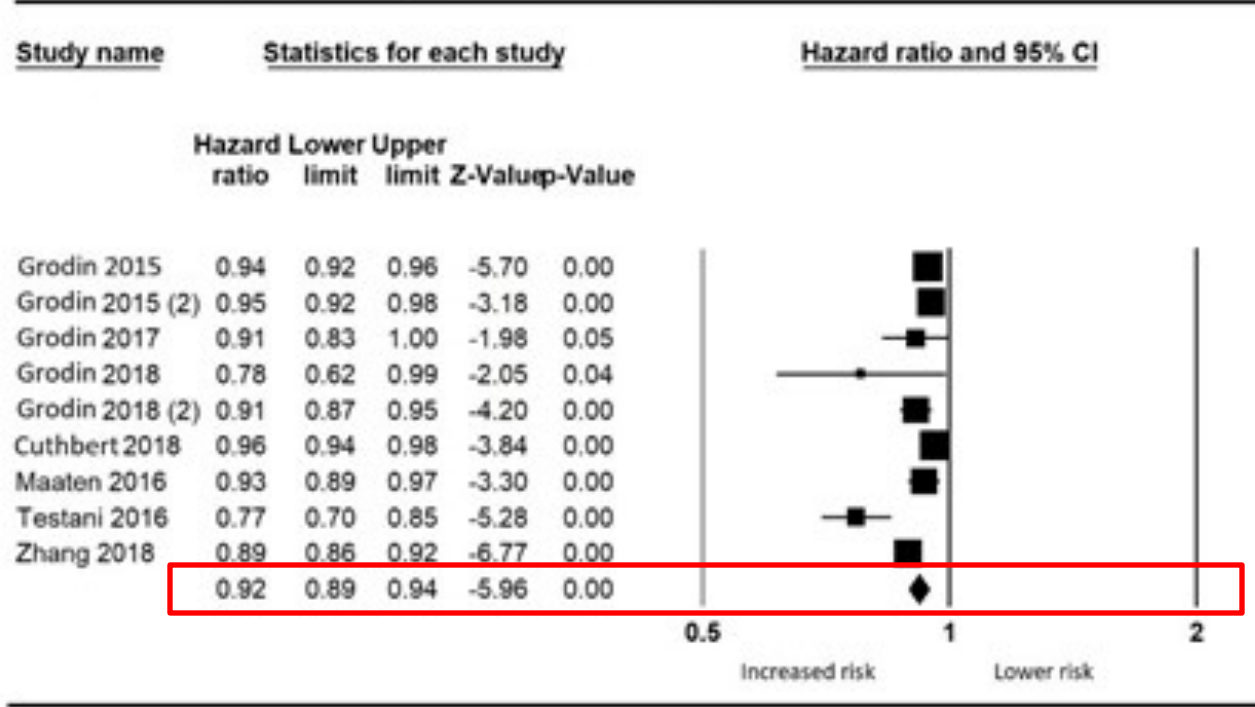
Serum Chloride Level and Mortality in HF

Systematic Review and Meta-Analysis

Meta-analysis evaluating the risk of mortality with serum chloride levels

9 studies

15,979 patients



Low serum chloride level is a strong independent predictor of mortality in various phenotypes of HF

Cardio-Renal Connections of Chloride in HF

Chloride and the Kidney

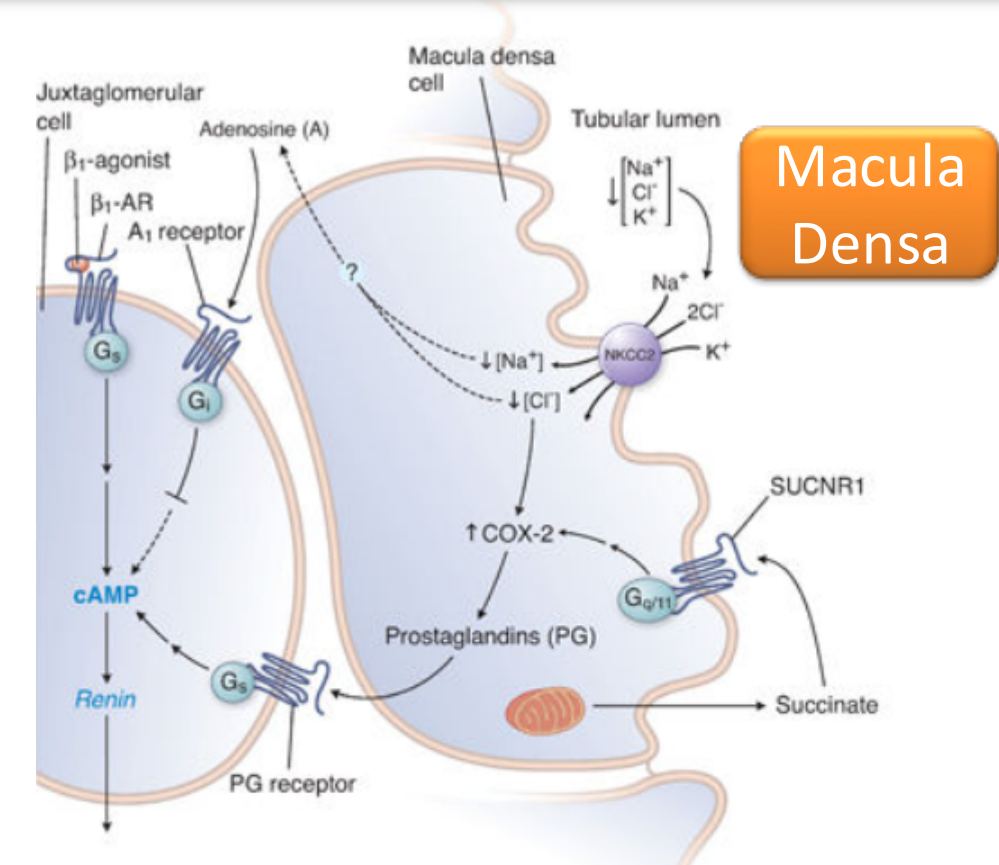
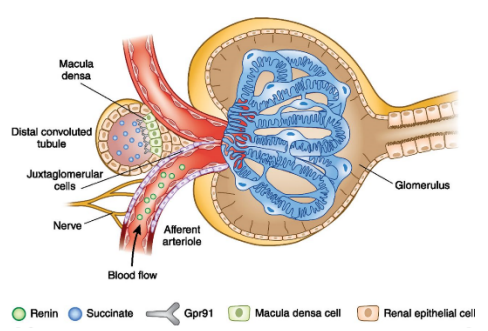
1

Neurohormonal Activation
(renin secretion)

2

Impact on Targets of Diuretic Therapy
(NKCC and NCC)

Low Chloride and Neurohormonal Activation



Macula Densa

↓ Chloride



↑ Renin Secretion

[Doukky R. JACC Heart Fail. 2016;4:24]

Intracellular Chloride and Cation-Chloride Cotransporters

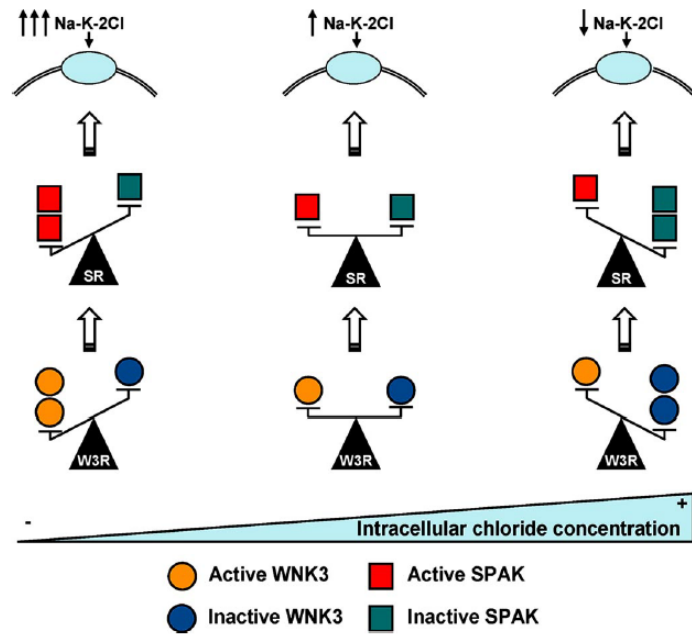
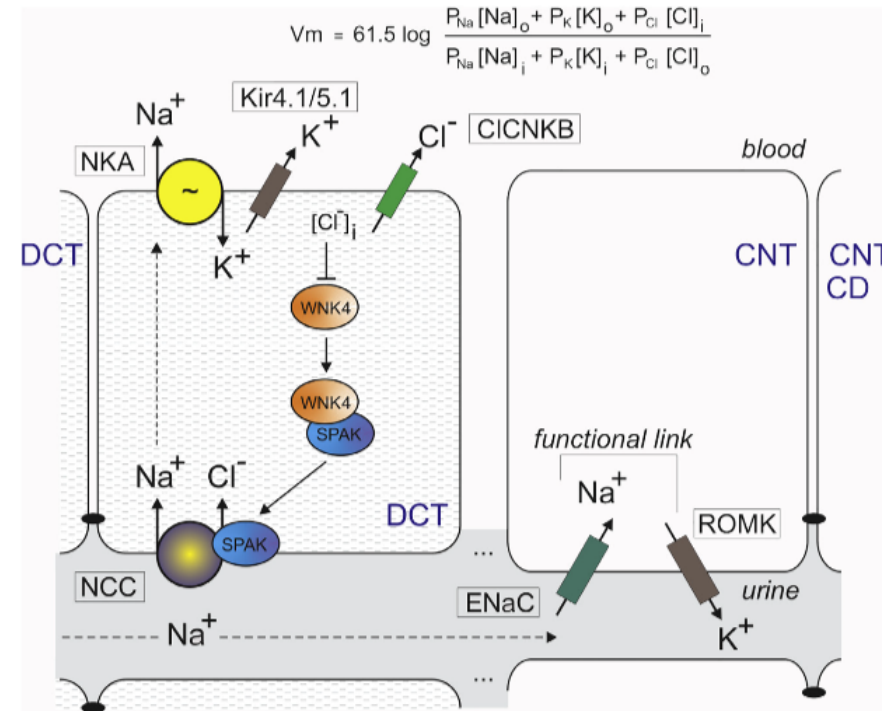


Fig. 5. Proposed model for intracellular chloride, WNK3, and SPAK interaction in the control of NKCC2 activity.

Low Intracellular chloride
increases NKCC activity in TAL



Low Intracellular chloride
increases NCC activity in DCT

Hypochloremia and Adverse Outcomes: Association or Causality?

Studying the Effects of
Increasing Serum Chloride Levels

Sodium-Free Chloride
Supplementation

Pharmacologic Increase in
Serum Chloride

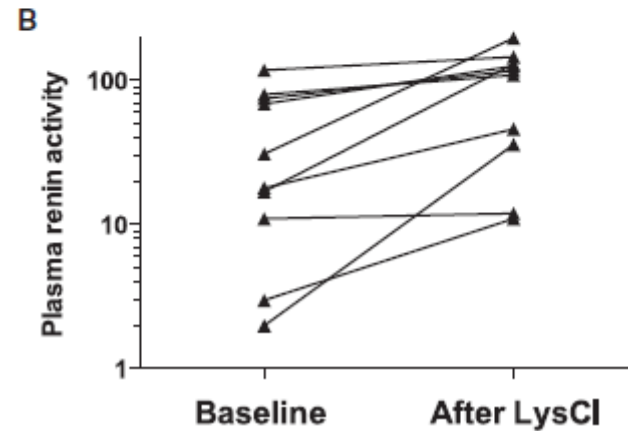
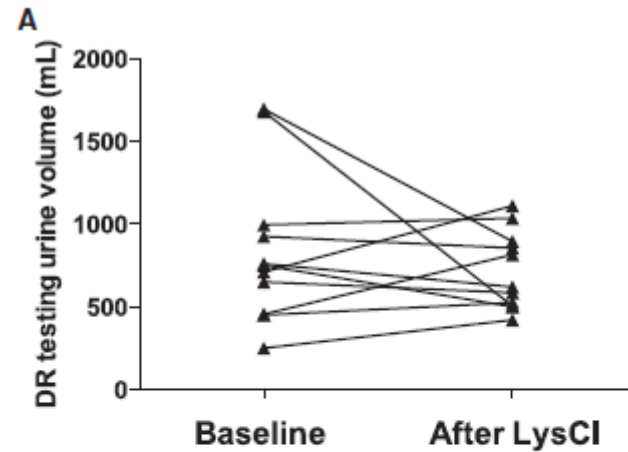
Sodium-Free Chloride Supplementation

Primary Endpoints

10 patients

Lysine Chloride

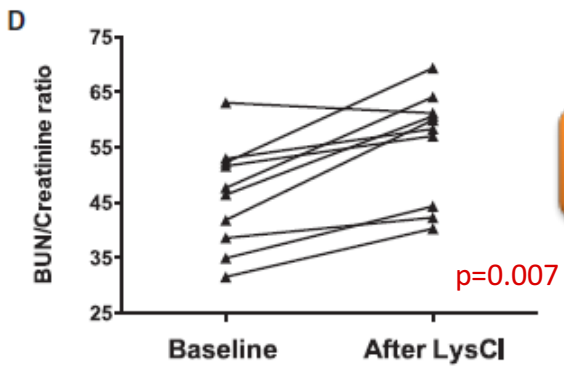
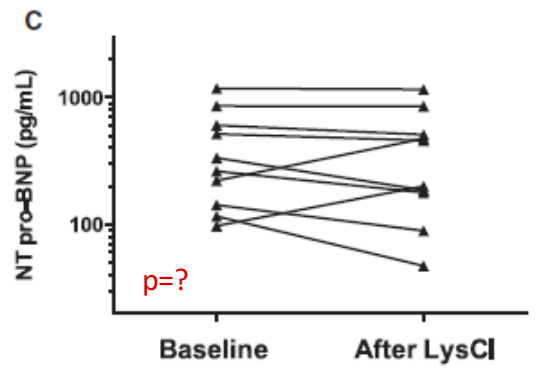
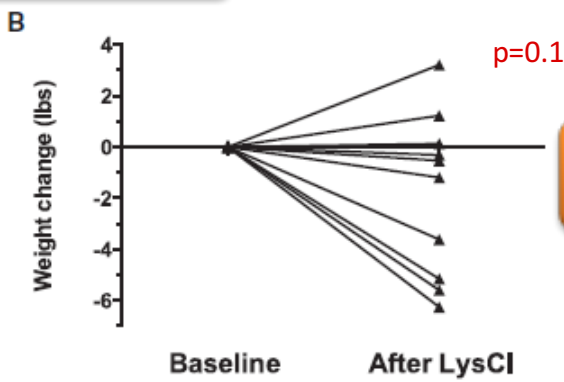
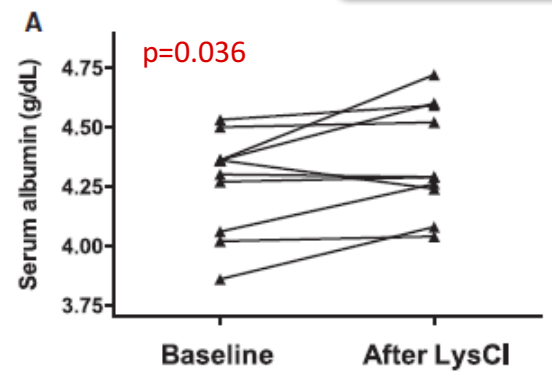
500 mg capsule or 7 g powder, TID for 3 days while on a low salt (<2 g/day) diet.



Sodium-Free Chloride Supplementation

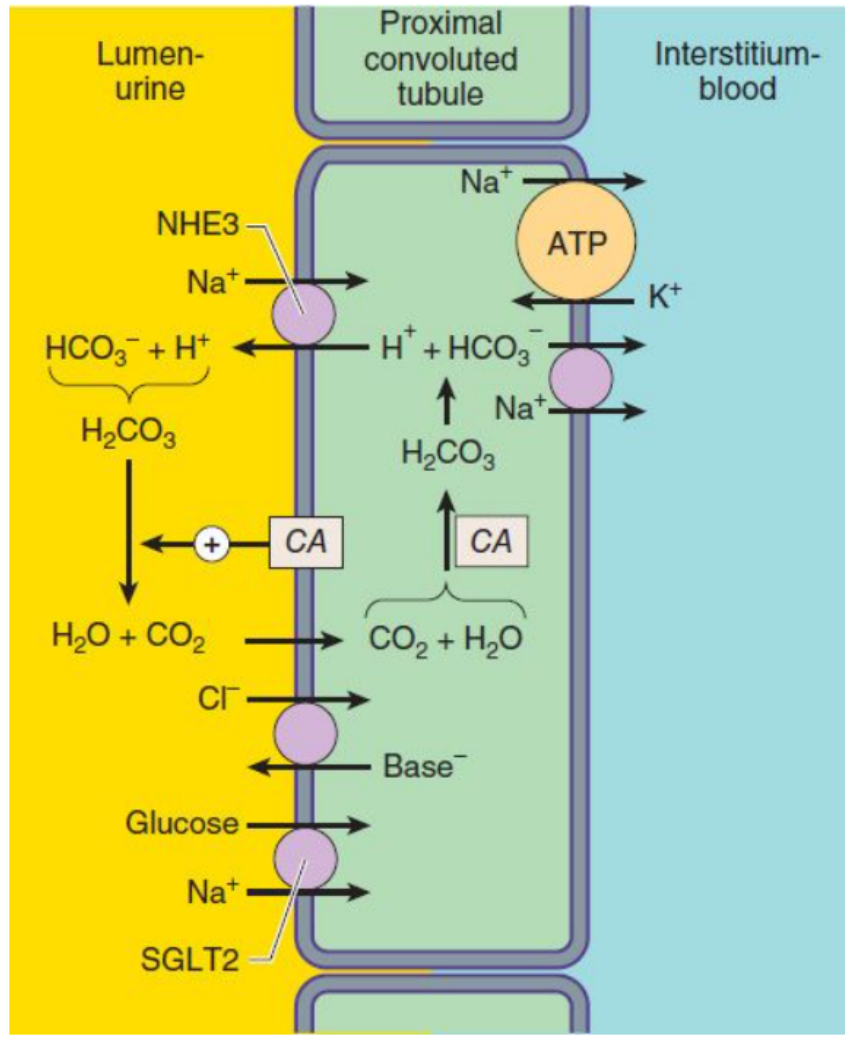
Markers of Volume Status

10 patients

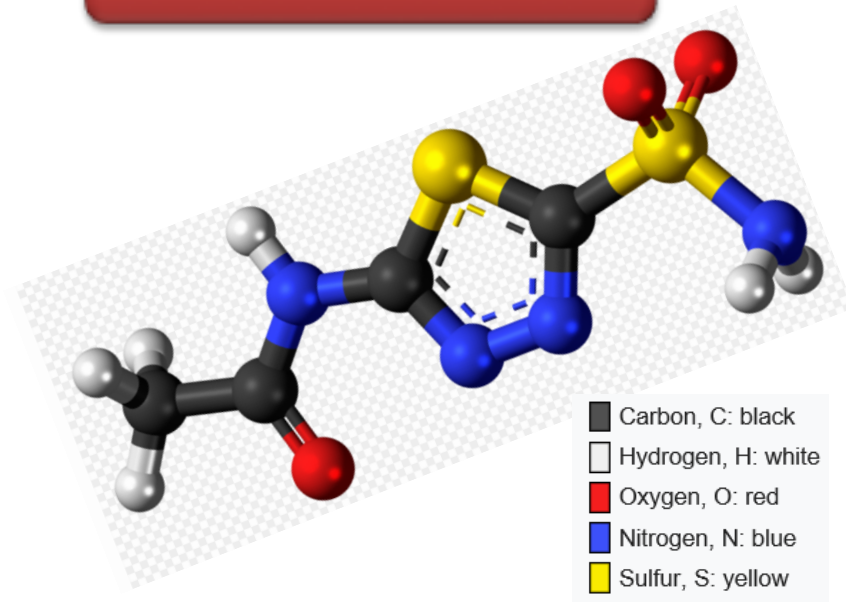


The available metrics suggested intravascular depletion after Chloride supplementation

Pharmacological Increase in Serum Chloride Level - Acetazolamide



Acetazolamide

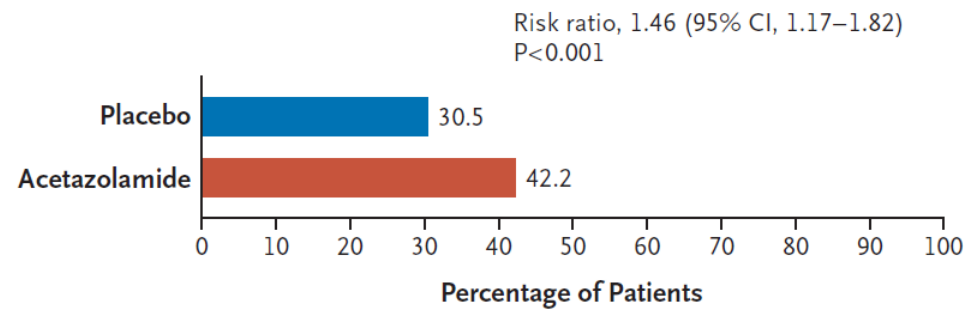


Metabolic Acidosis
Hyperchloremia
Hypokalemia

ADVOR

Acetazolamide in Decompensated Heart Failure with Volume Overload

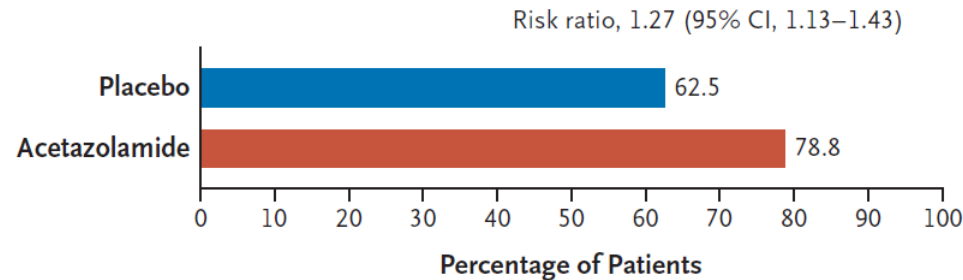
A Successful Decongestion within 3 Days after Randomization



519
patients

The primary end point
(successful
decongestion):
no edema, and
no ascites, and
no pleural effusion

C Successful Decongestion at Discharge

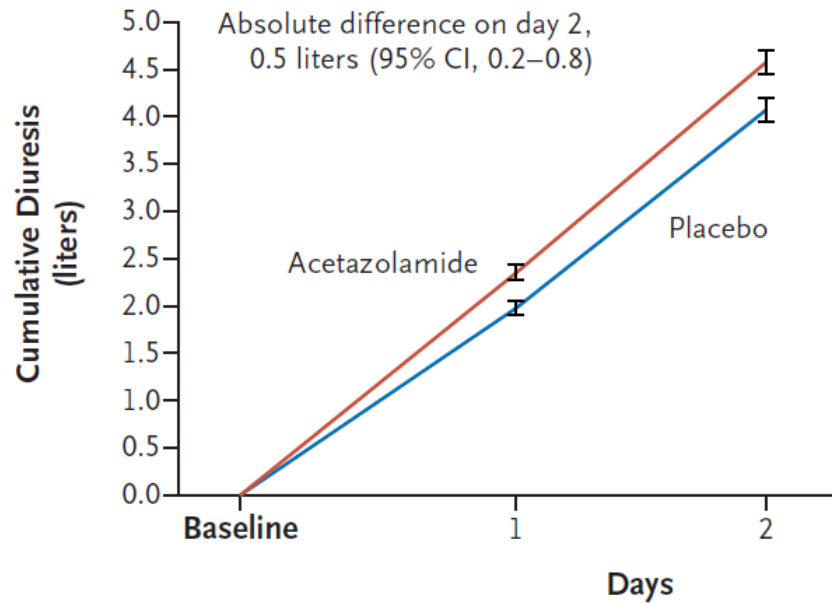


More patients in the acetazolamide arm achieved successful decongestion and it persisted until discharge

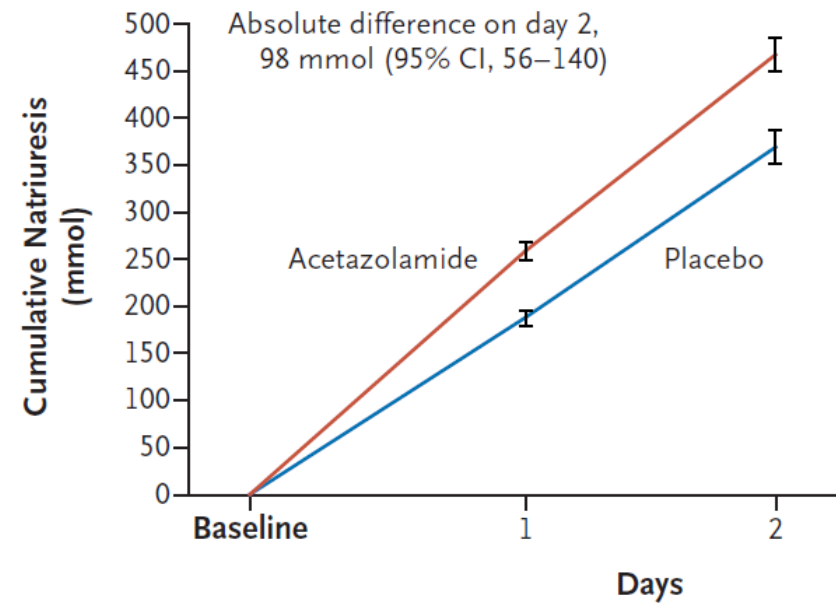
ADVOR

519 patients

Cumulative Urine Volume



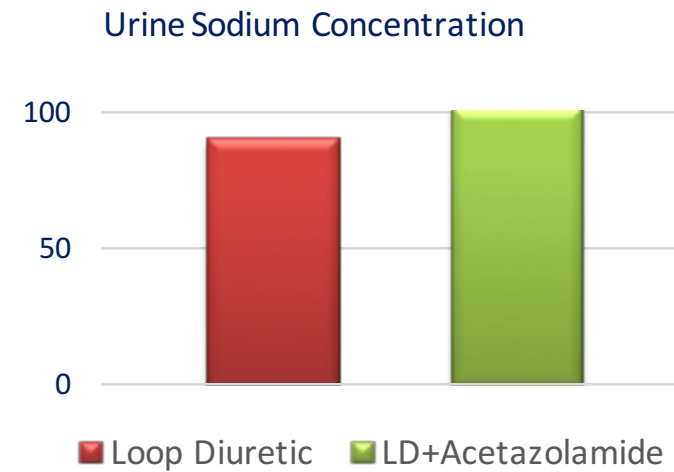
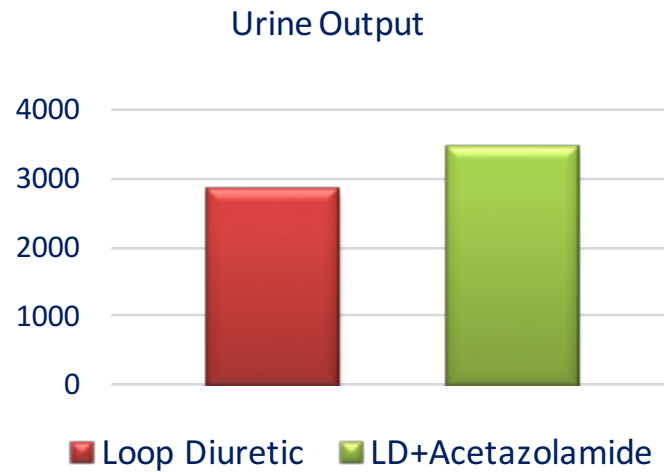
Cumulative Urine Sodium



Increased diuresis and natriuresis with acetazolamide
(0.5 liters and 98 mmol on day-2)

CAI and Urine Volume-Sodium

ADVOR



Day-1

Acetazolamide; higher urine volume and urine sodium concentration

What is in the Pipeline?

Mechanism and Effects of Manipulating Chloride Homeostasis in Acute Heart Failure (NCT03446651)

- Acute and Chronic Heart Failure
- Single-Center (Yale), randomized, double-blind, placebo-controlled trial
- patients are randomized to 7 days of therapy with either 115 mmol/day of lysine chloride or placebo.
- Primary Endpoint: Change in Blood Volume (Volumex)

CONCLUSION

- The current discrepancies/confusion regarding the sodium-centric approach to HF could be in part due to ignoring chloride.
- Chloride may be a stronger prognostic marker in all HF syndromes compared with sodium (CHF, ADHF, HFrEF, HFpEF)
[utility in risk prediction models of HF]
- Lingering congestion, low urine sodium, diuretic resistance, and low serum chloride levels; why not a touch of acetazolamide?



THE 29TH INTERNATIONAL CONFERENCE ON
ADVANCES IN CRITICAL CARE NEPHROLOGY

AKI & CRRT 2024

Jointly Provided by

UC San Diego
SCHOOL OF MEDICINE
and
CRRT, INC.

MARCH 12-15, 2024

MANCHESTER GRAND HYATT

SAN DIEGO, CALIFORNIA

Thank You...

E-mail: Amir.Kazory@medicine.ufl.edu

X (Twitter): @AmirKazory

