SCOMPENSO CARDIACO ACUTO E REFRATTARIO:
MEET THE EXPERTS

Il paziente scompensato con iposodiemia

Luca Monzo M.D.

HF Outpatient Clinic
Policlinico Casilino - Rome

POLICLINICO CASILINO

"Il nostro Abbondio [...] s'era dunque accorto, prima quasi di toccar gli anni della discrezione, d'essere, in quella società, come un vaso di terra cotta, costretto a viaggiar in compagnia di molti vasi di ferro..."

A. Manzoni, I promessi Sposi (1840)

Review Article

HYPONATREMIA

HORACIO J. ADROGUÉ, M.D.,
AND NICOLAOS E. MADIAS, M.D.

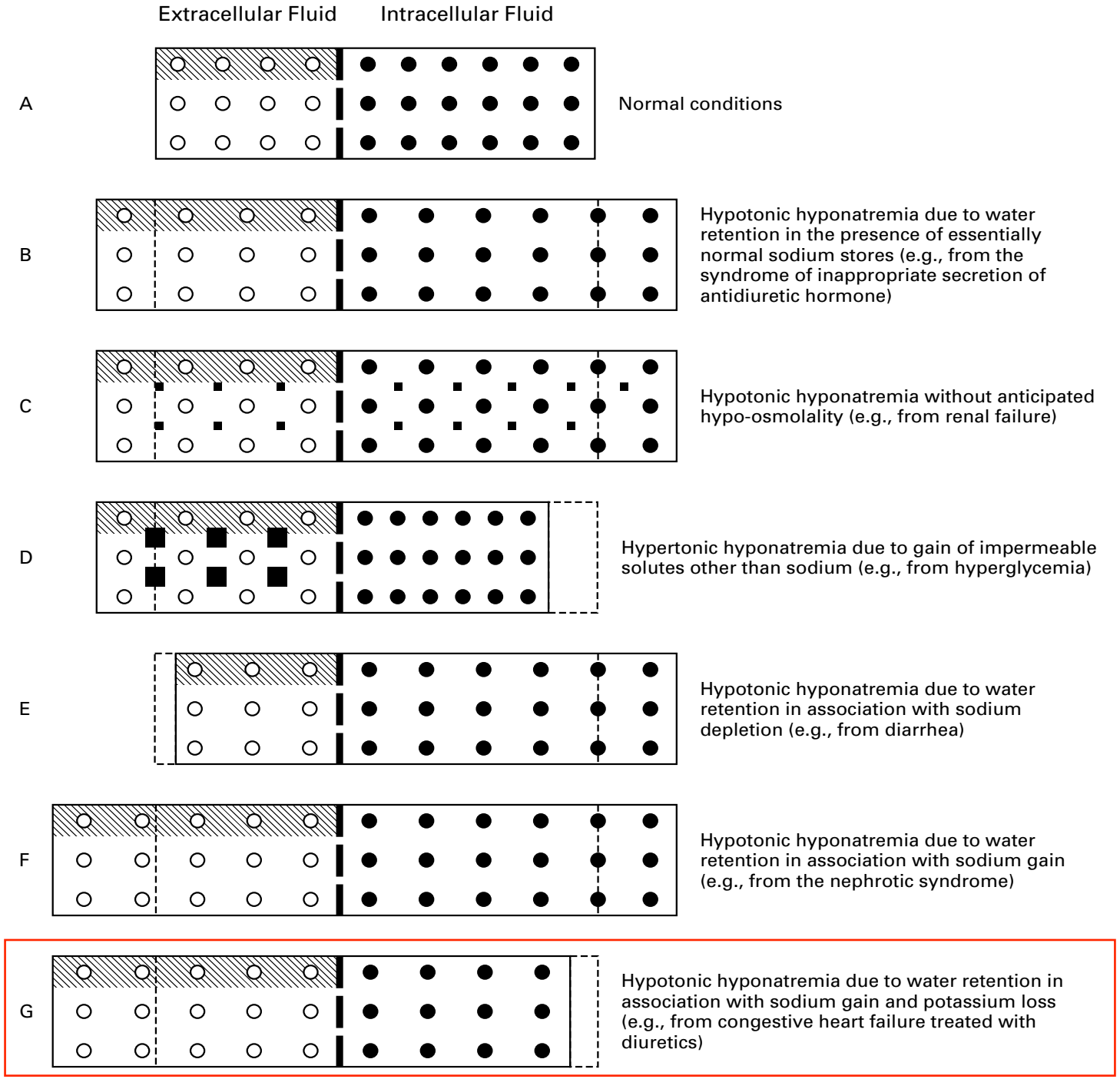
HYPONATREMIA is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter. Whereas hypernatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity.[1,2] Effective osmolality or tonicity refers to the

Severity	Neurologic Manifestations*	Sodium
Mild	Asymptomatic or associated with subtle changes in mental and physical function	130-135 mEq/L
Moderate	Nonspecific symptoms (nausea and malaise)	125-130 mEq/L
Severe	Progressive neurologic symptoms ranging from confusion to coma	< 125 mEq/L

*Neurologic manifestations are also influenced by the speed of onset of hyponatremia

Increased volume of extracellular fluid
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Renal failure (acute or chronic)
Pregnancy

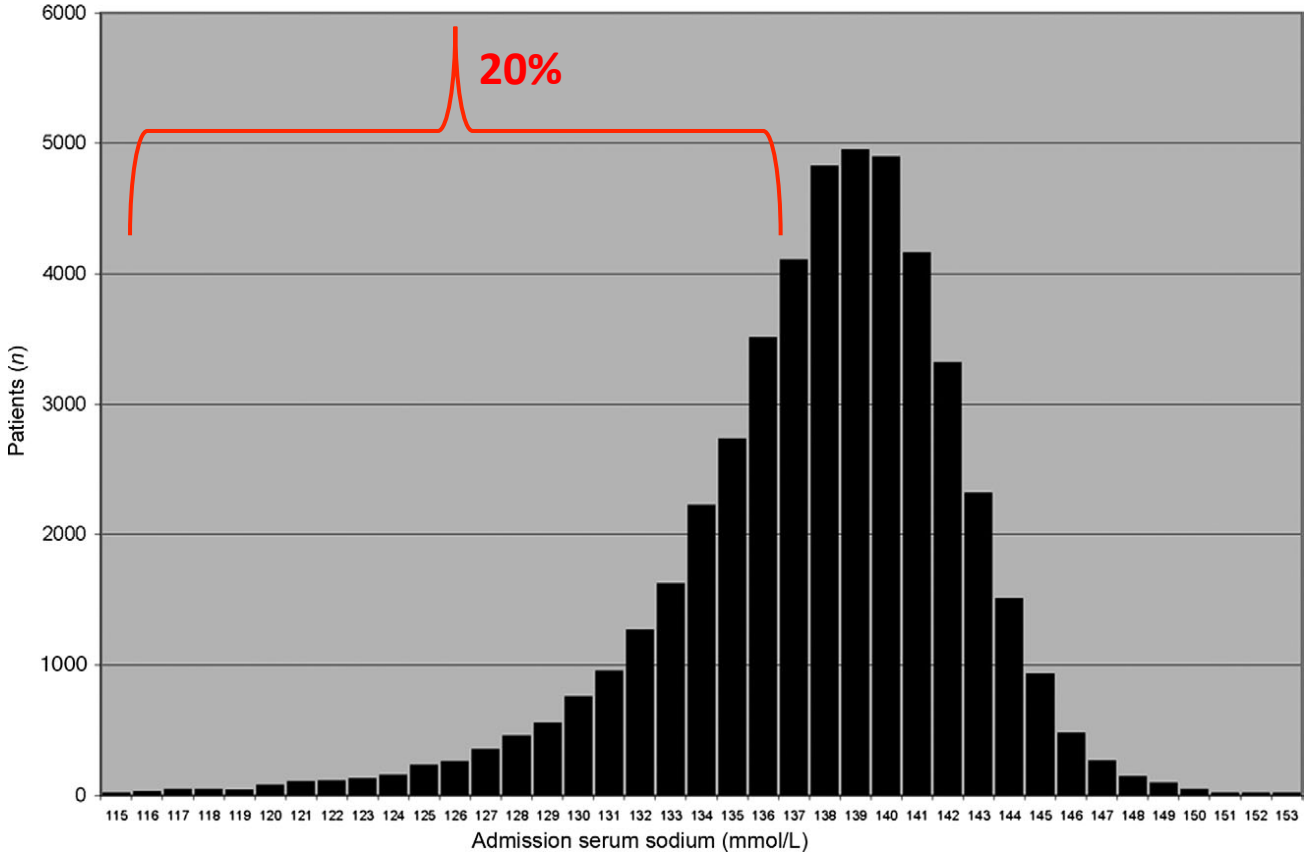
Adroguè HJ et al. N Engl J Med. 2000 May 25;342(21):1581-9



Hyponatremia is frequently encountered in patients with HF, both acute….

Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry

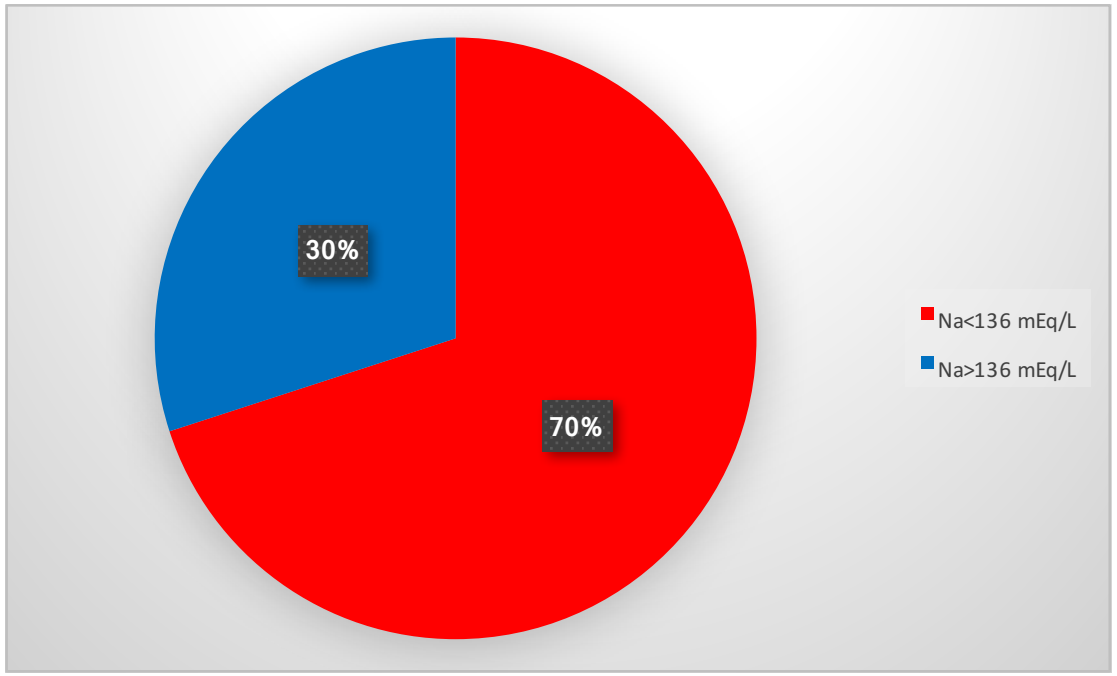
Mihai Gheorghiade[1]*, William T. Abraham[2], Nancy M. Albert[3], Wendy Gattis Stough[4,5], Barry H. Greenberg[6], Christopher M. O'Connor[7], Lilin She[8], Clyde W. Yancy[9], James Young[10], and Gregg C. Fonarow[11] on behalf of the OPTIMIZE-HF Investigators and Coordinators†



Georghiade M et al. Eur Heart J. 2007;28:980–988

And chronic….

Hyponatremia, Cognitive Function, and Mobility in an Outpatient Heart Failure Population

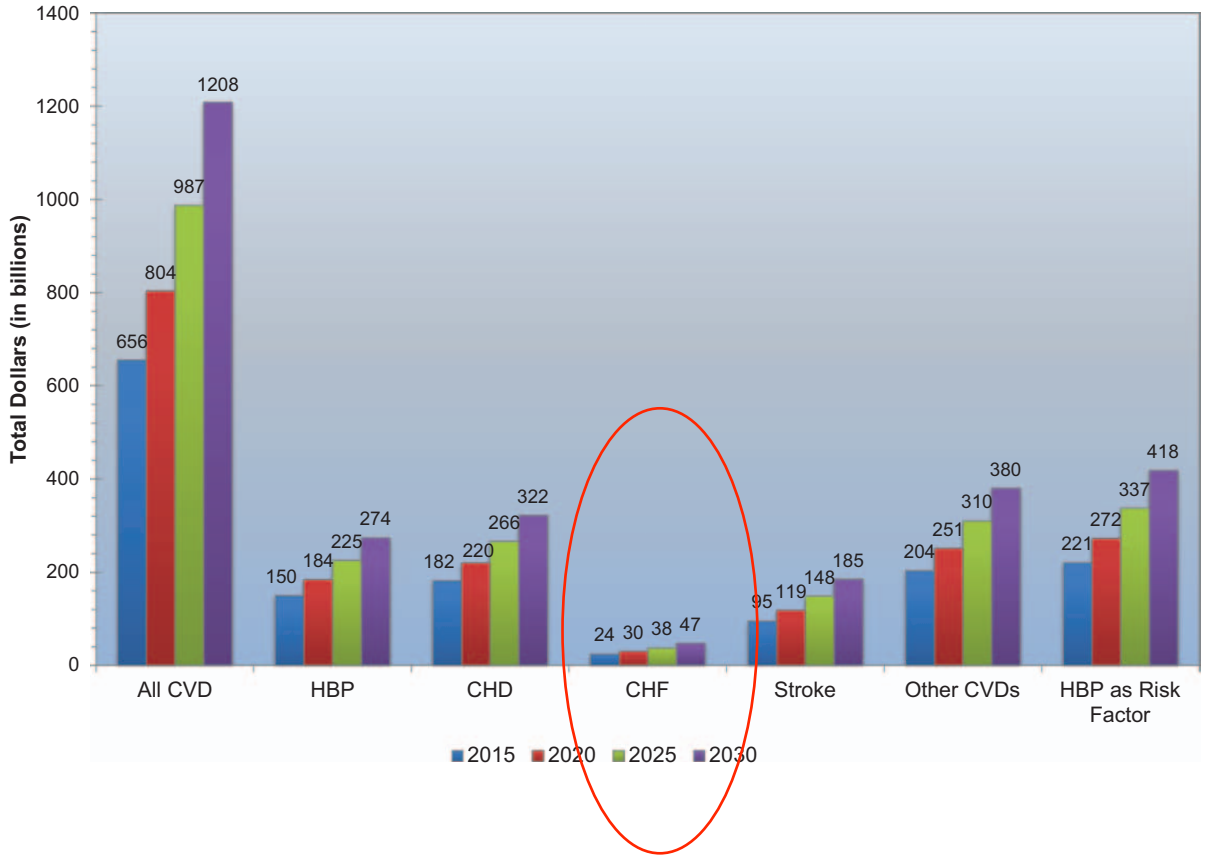


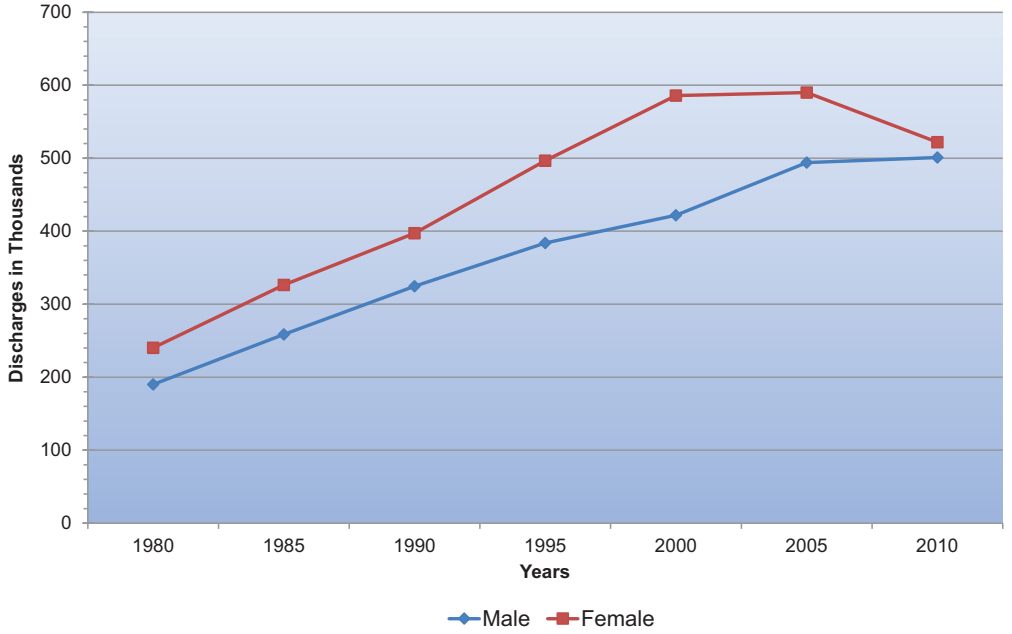
Characteristics [mean and standard deviation or N (%)]	No hyponatremia N=85 (70%)	Hyponatremia N=36 (30%)	P
Age	66.6±11.1	65.1±7.9	0.45
Sex			0.105
Male	75 (88)	35 (97)	
Female	10 (11.8)	1 (2.8)	
Serum Sodium (mEq/L)	139.5±1.8	134±1.9	<0.0001
HF characteristics			
Diagnosis	**N=85**	**N=36**	**0.14**
HFrEF	60 (70.6)	30 (83.3)	
HFpEF	25 (29.4)	6 (20)	
Etiology	**N=70**	**N=32**	**0.4**
Ischemic HF	40 (57.14)	20 (62.5)	
Non- Ischemic	30 (42.9)	12 (37.5)	

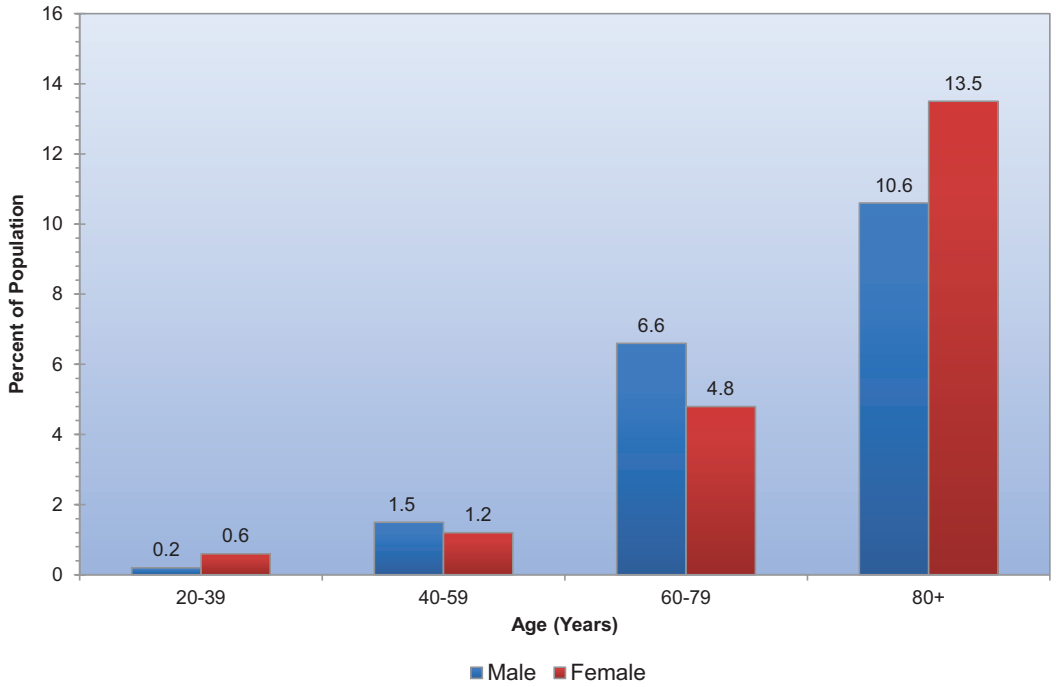
Albabtain M et al. Med Sci Monit, 2016; 22: 4978-4985

Heart Disease and Stroke Statistics––2016 Update: A Report From the American Heart Association

Dariush Mozaffarian, Emelia J. Benjamin, Alan S. Go, Donna K. Arnett, Michael J. Blaha, Mary Cushman, Sandeep R. Das, Sarah de Ferranti, Jean-Pierre Després, Heather J. Fullerton, Virginia J. Howard, Mark D. Huffman, Carmen R. Isasi, Monik C. Jiménez, Suzanne E. Judd, Brett M. Kissela, Judith H. Lichtman, Lynda D. Lisabeth, Simin Liu, Rachel H. Mackey, David J. Magid, Darren K. McGuire, Emile R. Mohler III, Claudia S. Moy, Paul Muntner, Michael E. Mussolino, Khurram Nasir, Robert W. Neumar, Graham Nichol, Latha Palaniappan, Dilip K. Pandey, Mathew J. Reeves, Carlos J. Rodriguez, Wayne Rosamond, Paul D. Sorlie, Joel Stein, Amytis Towfighi, Tanya N. Turan, Salim S. Virani, Daniel Woo, Robert W. Yeh and Melanie B. Turner







Mozzaffarian D et al. Circulation. 2016 Jan 26;133(4):e38-360

Pathophysiologic Mechanisms

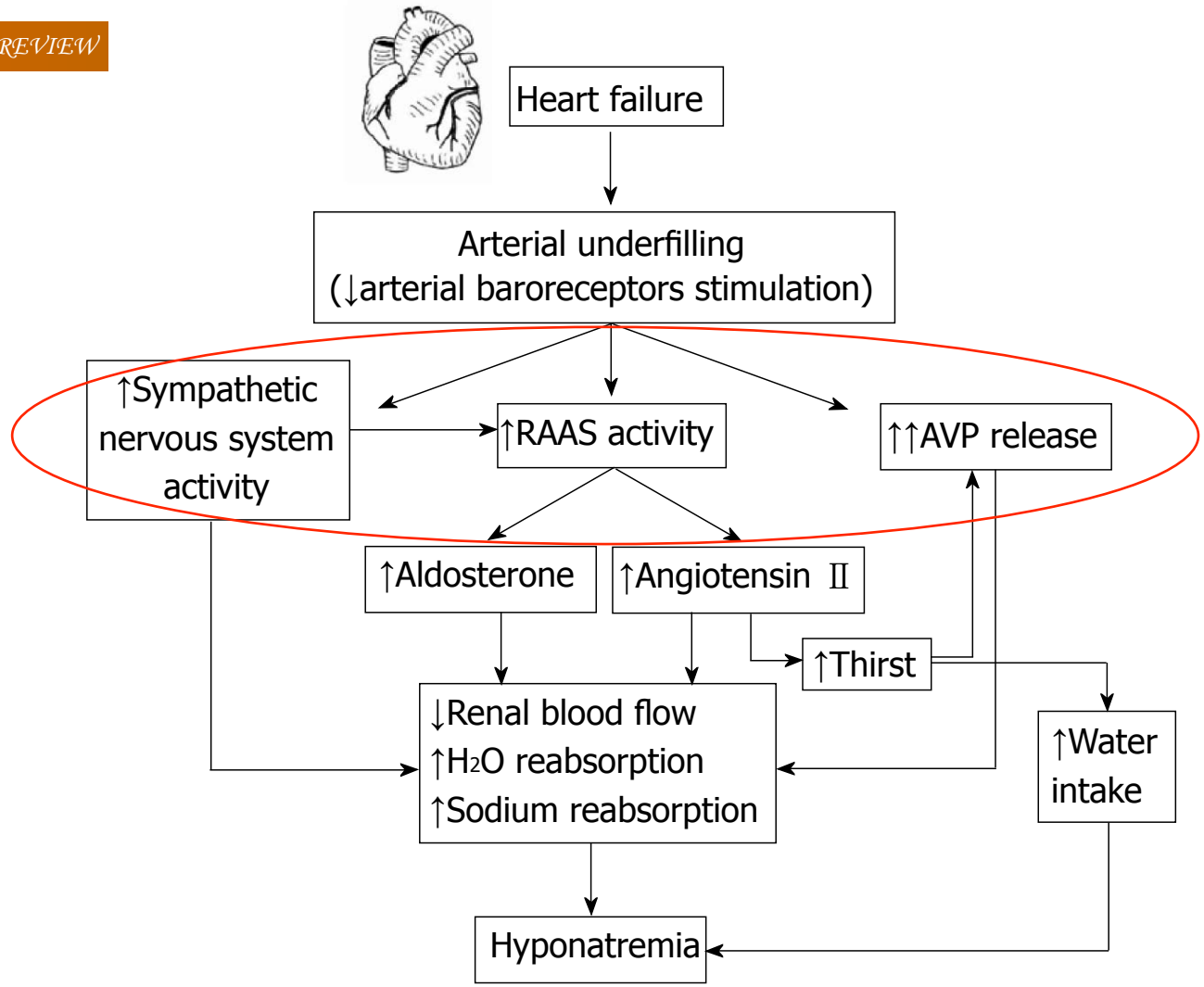
REVIEW

Hyponatremia in patients with heart failure

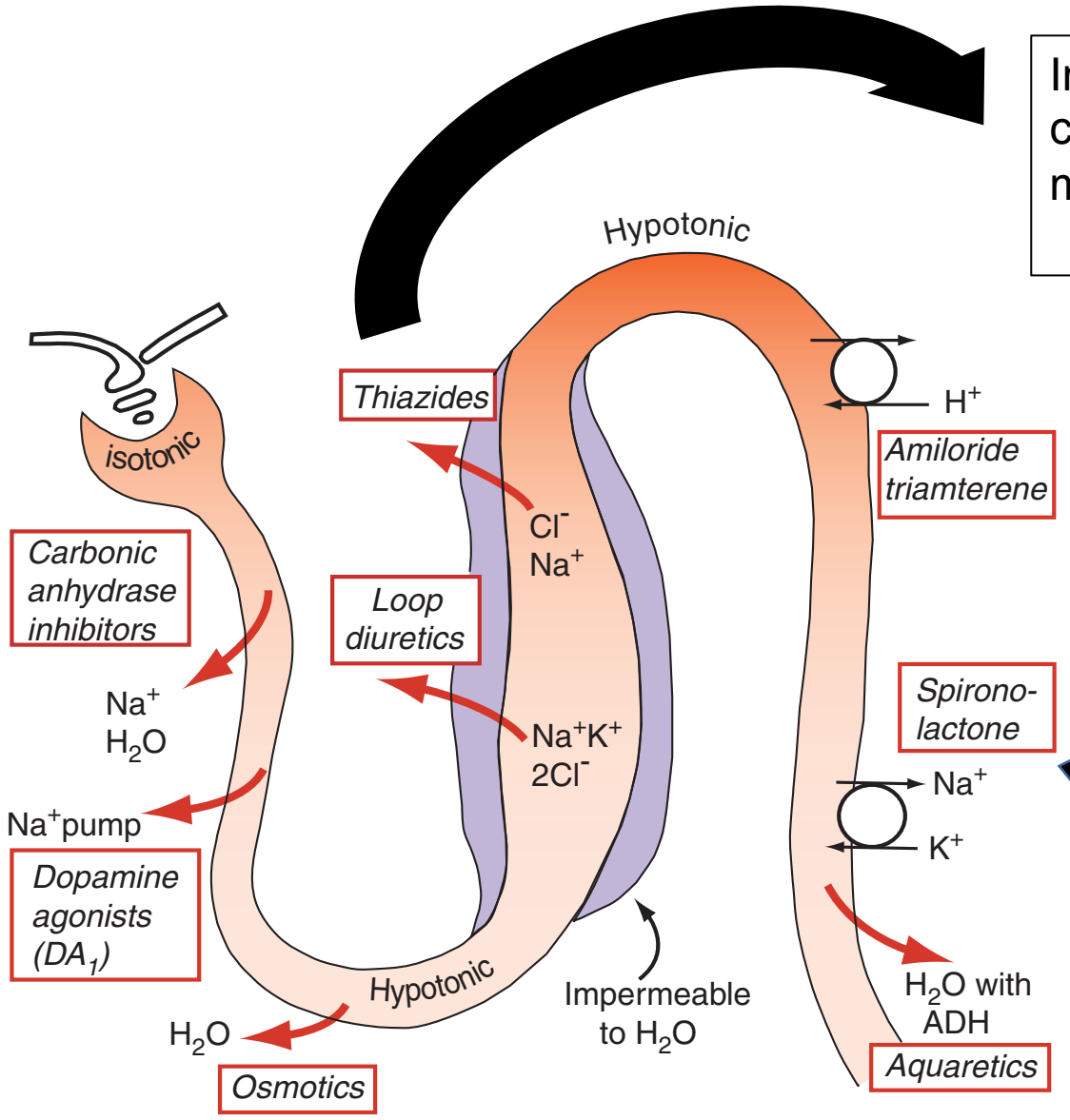
Theodosios D Filippatos, Moses S Elisaf

Table 2. Causes of Hyponatremia in HF

Activation of neurohormonal axis (ie, nonosmotic release of AVP, RAAS, SNS)
Increased thirst due to high levels of angiotensin II
Disturbance in renal diluting mechanisms and water excretion
Increased Na excretion (due to initially elevated levels of natriuretic peptides)
Medications (eg, thiazide diuretics and spironolactone)
Comorbidities (eg, uncontrolled hyperglycemia and hypothyroidism)



Filippatos TD et al. World J Cardiol 2013 September 26; 5(9): 317-328
Kazory A. Clin. Cardiol. 2010;33(6);322–329



Increased Na loss and disturbance in diluting capacity of the kidney remain the major mechanisms for thiazide-induced hyponatremia

Direct effect of amiloride on the collecting tubule increasing sodium loss. Moreover, amiloride spares potassium and, hence, aggravates thiazide-induced hyponatremia as a consequence of potassium retainment by exchanging it for sodium in the distal tubule

It has been suggested that excessive natriuretic response might result in volume loss, decrease in GFR, and enhanced reabsorption of water in proximal tubules

Opie L. Drugs for the Heart. 2013. 8th Edition. Elsevier


COSA FATE LI' VOI DUE CON QUELL'ARIA PREOCCUPATA?
ABBIAMO PAURA DEL FUTURO!

Hyponatremia in HF

- A problem of outcomes -

Predictors of short term mortality in heart failure — Insights from the Euro Heart Failure survey

Periaswamy Velavan [a,*], Nasrin K. Khan [a], Kevin Goode [a], Alan S. Rigby [a], Poay H. Loh [a], Michel Komajda [b], Ferenc Follath [c], Karl Swedberg [d], Hugo Madeira [e], John G.F. Cleland [a]

Multivariable analysis by binary stepwise logistic regression predicting mortality within 12 weeks of admission with heart failure.

Variable	*p*	Odds ratio	95% CI	Bootstrapp (97.5%)
Age [a] (SD=13 years)	<0.001	1.5	1.4–1.6	<0.001
Haemoglobin [a] (SD=2.2 g/dl)	<0.001	0.9	0.8–0.9	0.003
Creatinine [a] (SD=103 μmol/l)	<0.001	1.2	1.2–1.3	<0.001
Sodium [a] (SD=5 mmol/l)	<0.001	0.9	0.8–0.9	0.035
Severe LVSD (20% of all patients)	<0.001	1.8	1.5–2.1	<0.001
Atrial fibrillation (15%)	0.001	1.3	1.1–1.6	0.205
ACEI therapy (62%)	<0.001	0.5	0.5–0.6	<0.001
ARB therapy (5%)	0.001	0.5	0.4–0.8	0.073
Beta-blocker therapy (37%)	<0.001	0.7	0.6–0.8	0.006
Calcium channel blocker therapy (21%)	<0.001	0.7	0.6–0.8	0.018
Lipid lowering therapy (20%)	<0.001	0.6	0.5–0.7	0.001
Aspirin and anti-platelet drugs (53%)	<0.001	0.6	0.5–0.6	<0.001
Warfarin (23%)	<0.001	0.5	0.4–0.6	<0.001
Heparin (25%)	<0.001	1.7	1.4–1.9	<0.001
Need for IV inotropic agents (7%)	<0.001	5.5	4.6–6.6	<0.001

Velavan P et al. Int J Cardiol 2010;138:63-69

Predicting Mortality Among Patients Hospitalized for Heart Failure

Derivation and Validation of a Clinical Model

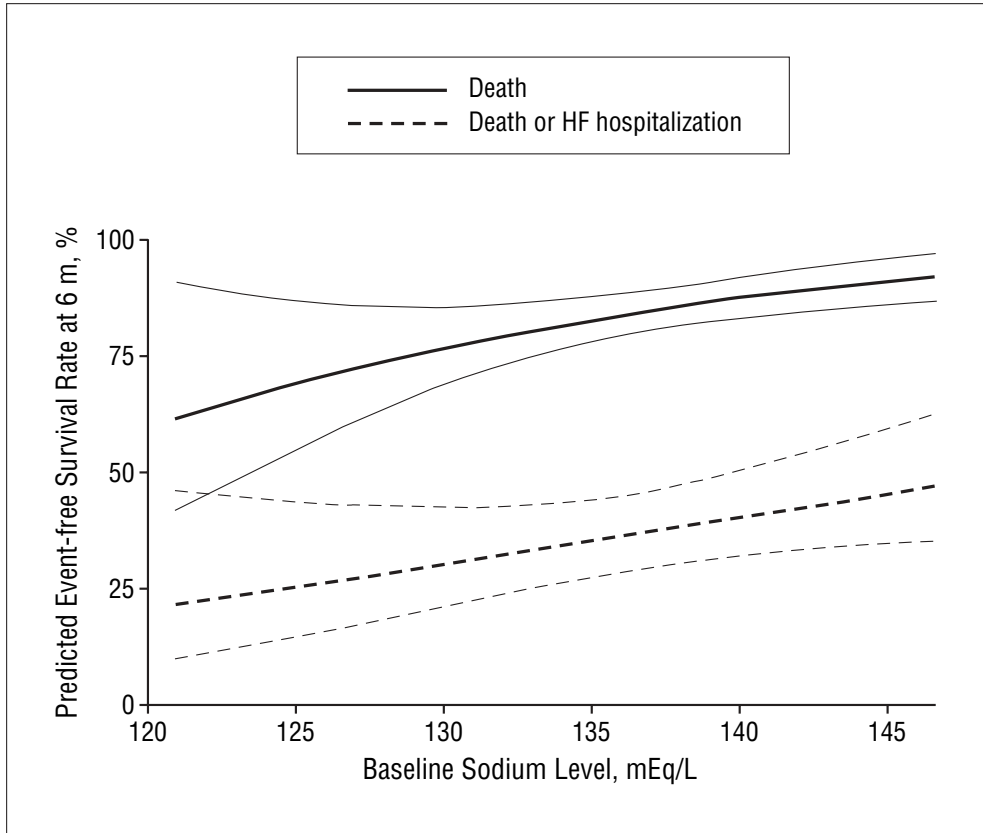
Table 3. Multivariable Predictors of Mortality

Variable	30-Day Model OR (95% CI)	30-Day Model *P* Value	1-Year Model OR (95% CI)	1-Year Model *P* Value
Age, y (per 10-unit increase)	1.70 (1.45-1.99)	<.001	1.61 (1.46-1.77)	<.001
Vital sign				
Systolic blood pressure, mm Hg (per 10-unit increase)	0.84 (0.80-0.88)	<.001	0.88 (0.85-0.90)	<.001
Respiratory rate, breaths/min (per 5-unit increase)	1.23 (1.12-1.36)	<.001	1.15 (1.08-1.24)	<.001
Serum concentration				
Sodium <136 mEq/L	1.53 (1.14-2.05)	.005	1.46 (1.19-1.80)	<.001
Hemoglobin <10.0 g/dL	NA	NA	1.37 (1.05-1.78)	.02
Urea nitrogen, mg/dL (per 10-unit increase)	1.55 (1.42-1.71)	<.001	1.49 (1.39-1.60)	<.001
Comorbid condition				
Cerebrovascular disease	1.43 (1.03-1.98)	.03	1.36 (1.08-1.71)	.01
Dementia	2.54 (1.77-3.65)	<.001	2.00 (1.47-2.72)	<.001
Chronic obstructive pulmonary disease	1.66 (1.22-2.27)	.002	1.41 (1.13-1.75)	.003
Hepatic cirrhosis	3.22 (1.08-9.65)	.04	5.80 (2.23-15.11)	<.001
Cancer	1.86 (1.28-2.70)	.001	1.85 (1.40-2.43)	<.001

Lee DE et al. JAMA 2003;290:2581-2587

Characterization and Prognostic Value of Persistent Hyponatremia in Patients With Severe Heart Failure in the ESCAPE Trial

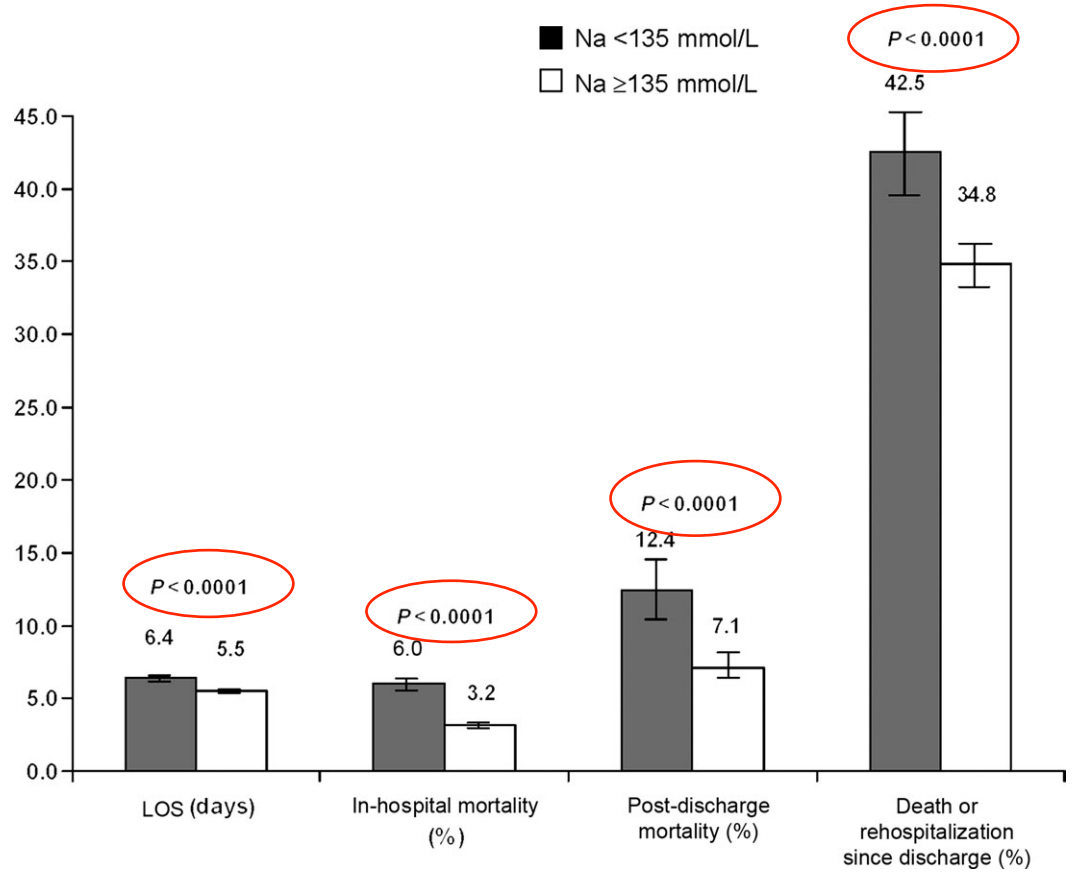
Mihai Gheorghiade, MD; Joseph S. Rossi, MD; William Cotts, MD; David D. Shin, MD; Anne S. Hellkamp, MS; Ileana L. Piña, MD; Gregg C. Fonarow, MD; Teresa DeMarco, MD; Daniel F. Pauly, MD, PhD; Joseph Rogers, MD; Thomas G. DiSalvo, MD, MPH; Javed Butler, MD; Joshua M. Hare, MD; Gary S. Francis, MD; Wendy Gattis Stough, PharmD; Christopher M. O'Connor, MD



Gheorghiade M et al. Arch Intern Med 2007;167:1998-2005

Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry

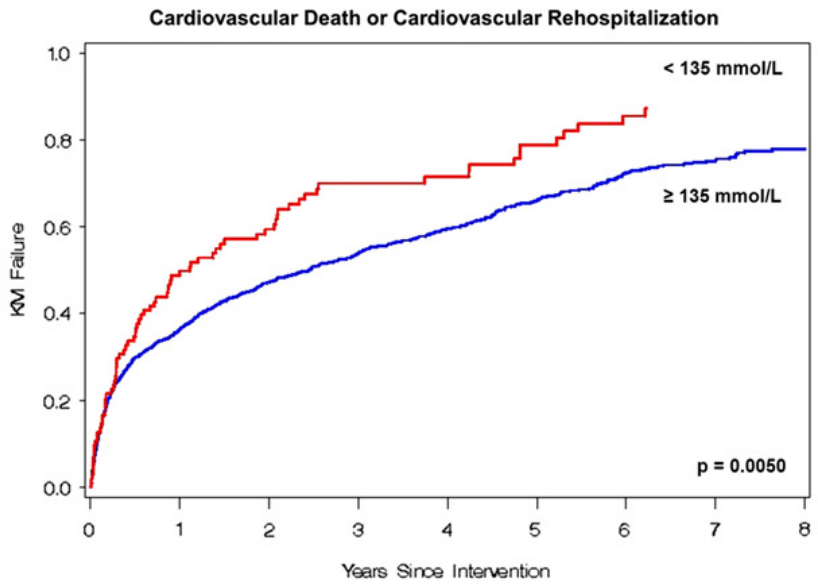
Mihai Gheorghiade[1]*, William T. Abraham[2], Nancy M. Albert[3], Wendy Gattis Stough[4,5], Barry H. Greenberg[6], Christopher M. O'Connor[7], Lilin She[8], Clyde W. Yancy[9], James Young[10], and Gregg C. Fonarow[11] on behalf of the OPTIMIZE-HF Investigators and Coordinators[†]



Georghiade M et al. Eur Heart J. 2007;28:980–988

Hyponatremia and Long-Term Outcomes in Chronic Heart Failure—An Observational Study From the Duke Databank for Cardiovascular Diseases

LUCA BETTARI, MD,[1,2] MONA FIUZAT, PharmD,[2] LINDA K. SHAW, MS,[2] DANIEL M. WOJDYLA, MS,[2]
MARCO METRA, MD,[1] G. MICHAEL FELKER, MD,[2] AND CHRISTOPHER M. O'CONNOR, MD[2]



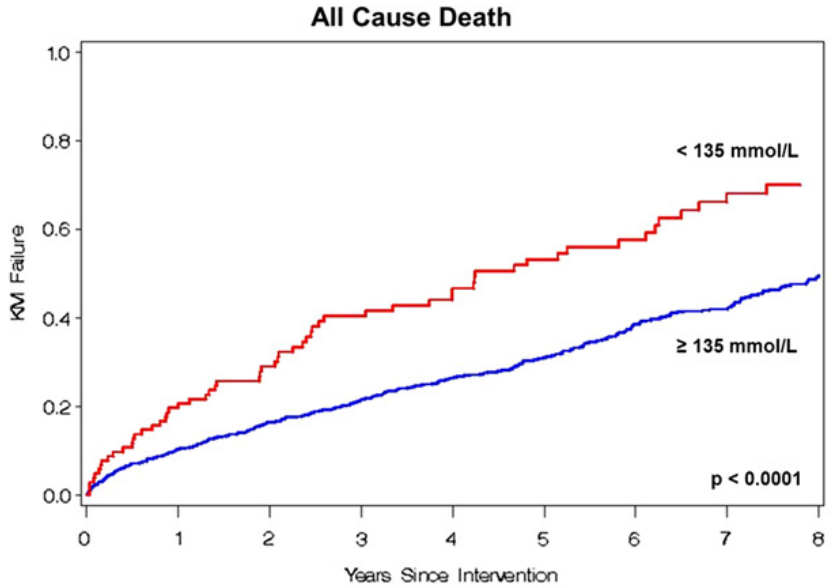


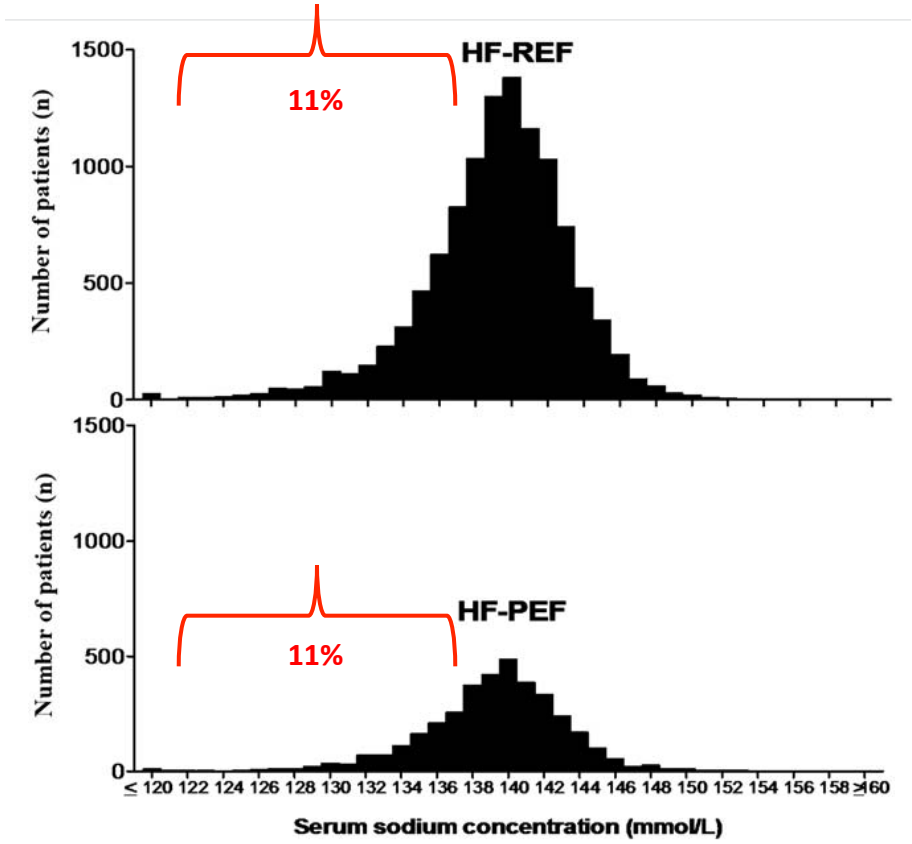
Table 4. Multivariable Cox Model for Cardiovascular Death or Rehospitalization Derived on Imputed Datasets (N = 1,045)

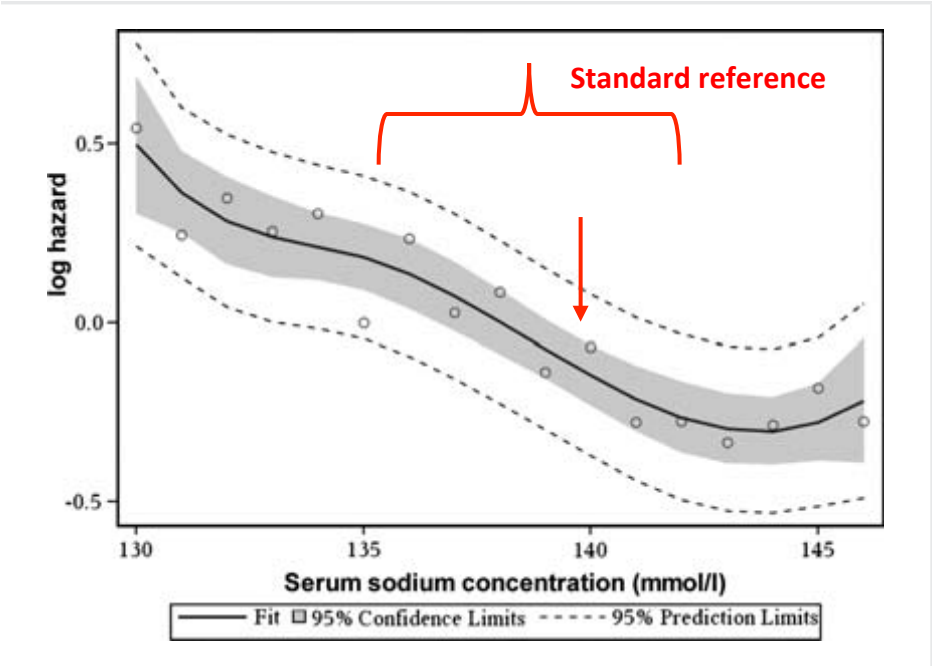
Parameter	Comparison	χ^2	*P* Value	HR (95% CI)
Hyponatremia (<135 mmol/L)	Yes vs no	8.81	.0030	1.45 (1.135−1.858)
Ejection fraction	5-unit increase	13.22	.0003	0.92 (0.88−0.96)
Heart rate	10-unit increase	7.62	.0058	0.94 (0.90−0.98)
Race (Black)	Black vs White	21.55 (3 *df*)	<.0001	0.73 (0.61−0.88)
Race (Indian)	Indian vs White			0.64 (0.46−0.90)
Race (Other)	Other vs White			0.21 (0.07−0.66)
Prior CABG	Yes vs no	4.51	.0338	1.25 (1.02−1.53)
Ischemic etiology	Yes vs no	17.58	<.0001	1.48 (1.23−1.78)
Hemoglobin	5-unit increase	5.05	.0246	0.78 (0.63−0.97)
Hyperlipidemia	Yes vs no	4.61	.0318	1.20 (1.02−1.41)

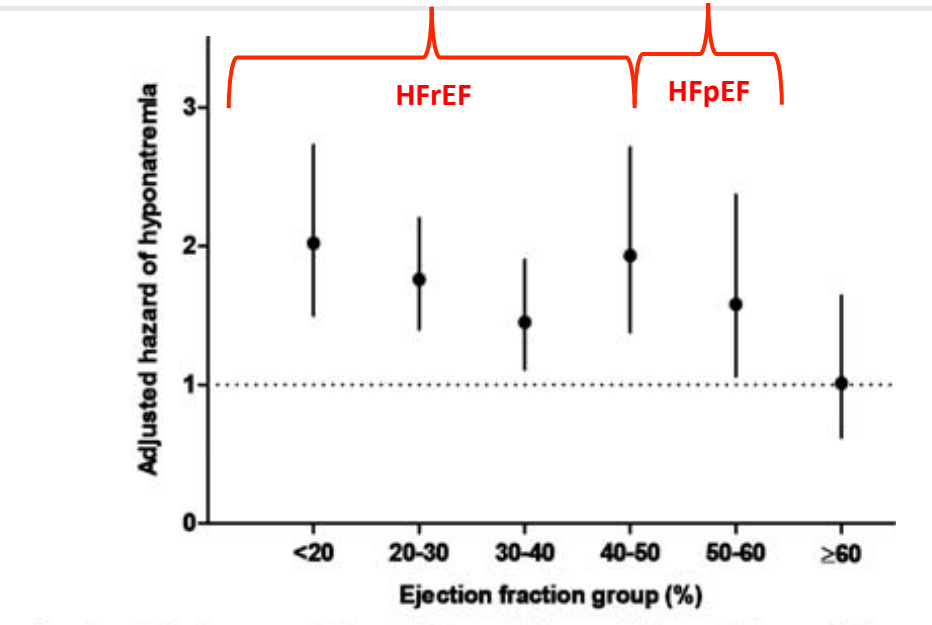
Bettari L et al. J Card Fail 2012;18:74-81

Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis†

Meta-Analysis Global Group in Chronic heart failure (MAGGIC)

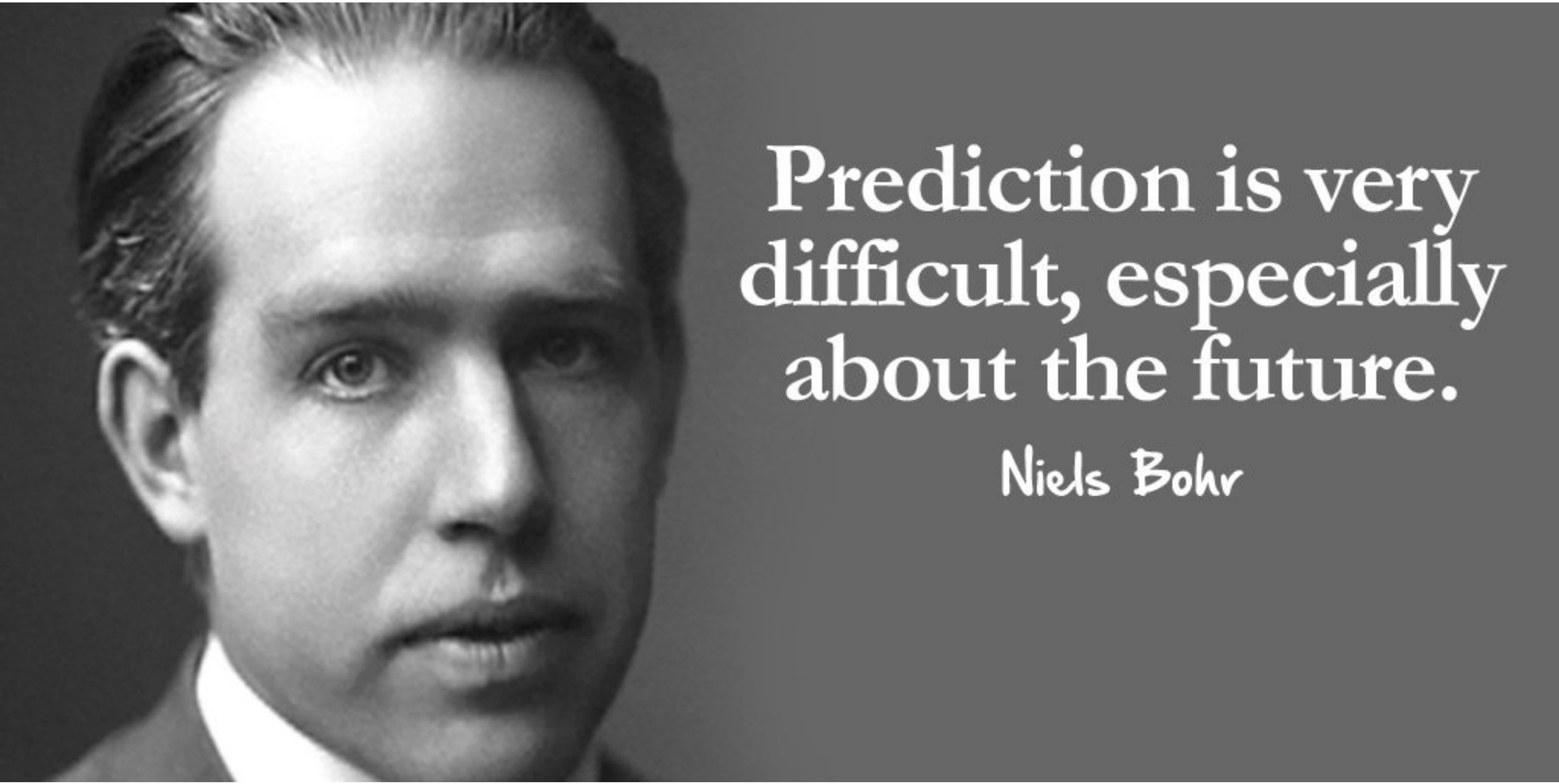






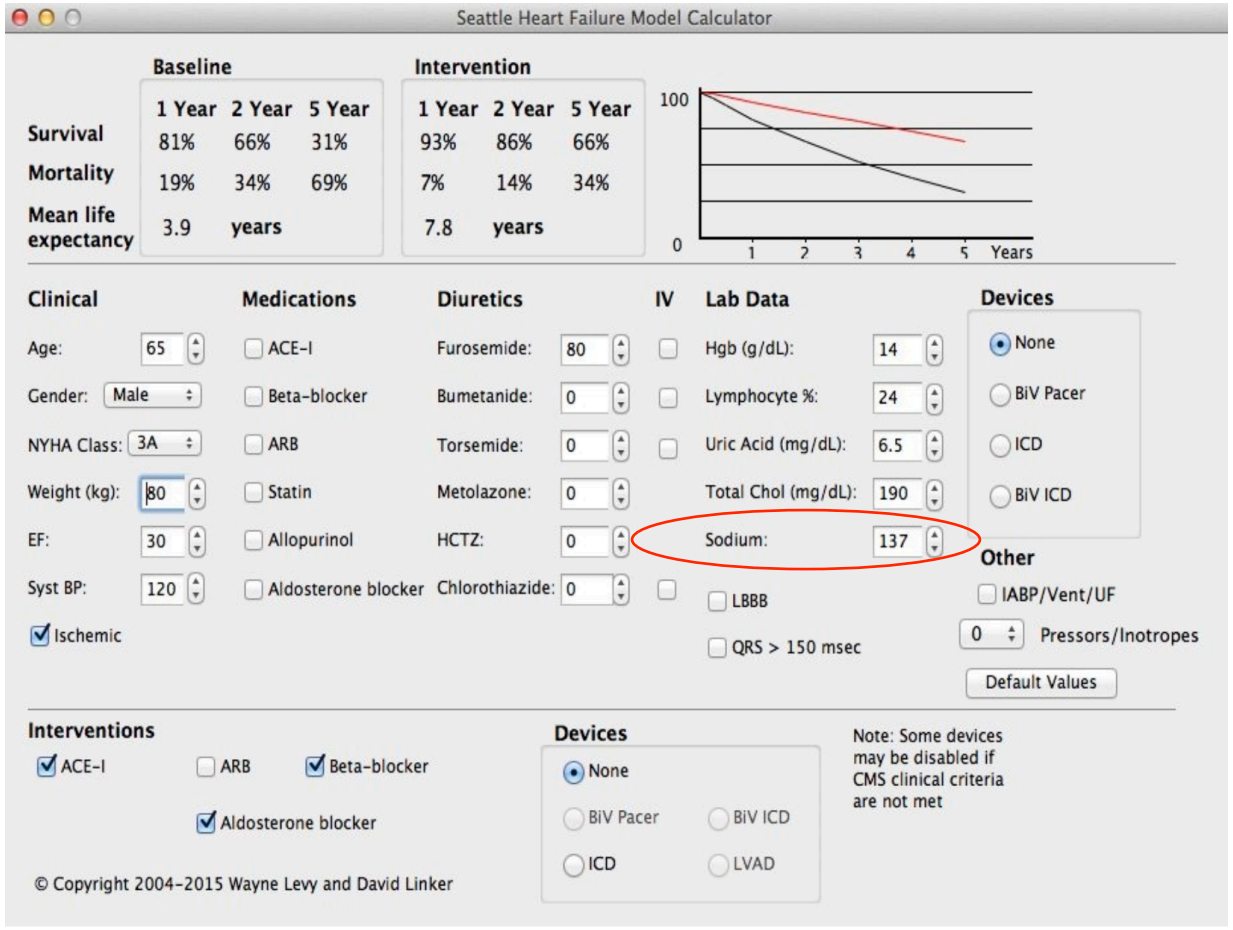
Conclusion Hyponatraemia is a powerful determinant of mortality in patients with HF regardless of ejection fraction. Further work is needed to determine if correction of hyponatraemia translates into clinical benefit.

Rusinaru D et al. Eur J Heart Fail 2012;14:1139-1146


Prediction is very difficult, especially about the future.
Niels Bohr

The Seattle Heart Failure Model: Prediction of Survival in Heart Failure

Wayne C. Levy, Dariush Mozaffarian, David T. Linker, Santosh C. Sutradhar, Stefan D. Anker, Anne B. Cropp, Inder Anand, Aldo Maggioni, Paul Burton, Mark D. Sullivan, Bertram Pitt, Philip A. Poole-Wilson, Douglas L. Mann and Milton Packer



The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure

Rafael Vazquez[1]*, Antoni Bayes-Genis[2], Iwona Cygankiewicz[2], Domingo Pascual-Figal[3], Lilian Grigorian-Shamagian[4], Ricardo Pavon[1], Jose R. Gonzalez-Juanatey[4], José M. Cubero[1], Luis Pastor[1], Jordi Ordonez-Llanos[5], Juan Cinca[2], and Antoni Bayes de Luna[2] on behalf of the MUSIC Investigators

	Total mortality	Cardiac mortality	Pump failure Death	Sudden death
Prior AVE	3	3		8
Indexed LA size >26 mm/m²	8	9	9	11
LV Ejection fraction ≤35%	5	5	5	
Atrial fibrillation	3			
LBBB or IVCD				7
NSVT and frequent VPBs	3	4		7
eGFR <60 ml/min/1.73 m²	4	4	5	
Hyponatremia ≤138 mEq/L	3	3	4	
NT-proBNP >1.000 ng/L	7	7	10	7
Troponin-Positive	4	5	7	
Maximum possible risk score	40	40	40	40
High risk patient if score >	20	20	20	20

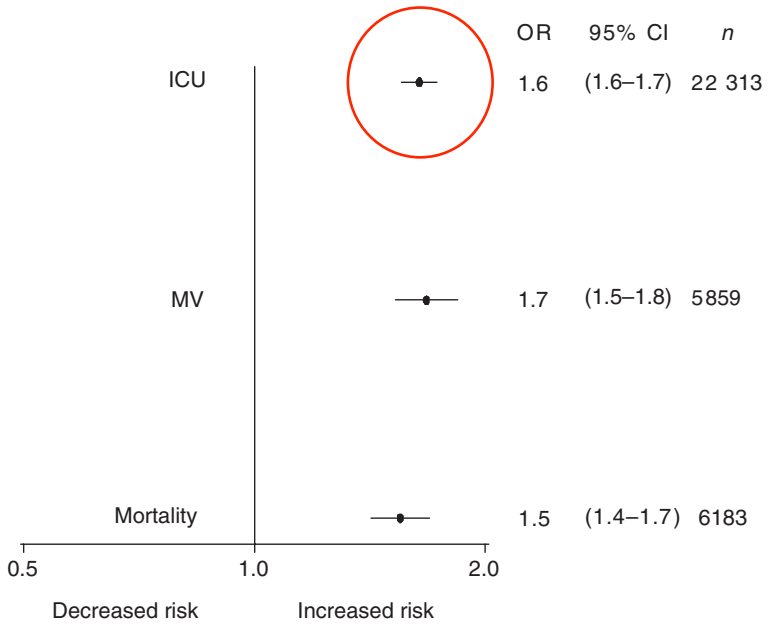
Vazquez R et al. Eur Heart J 2009;30:1088-1096

Levy WC et al. Circulation 2006;113:1424-1433

ORIGINAL ARTICLE

Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients*

Marya D. Zilberberg[a], Alex Exuzides[b], James Spalding[c], Aimee Foreman[b], Alison Graves Jones[b], Chris Colby[b] and Andrew F. Shorr[d]



	Hyponatremia present ($n = 10,899$)	Hyponatremia absent ($n = 187,382$)	p value*
Hospital mortality (%)	5.9	3.0	<0.001
Proportion on MV (%)	5.0	2.8	<0.001
Proportion in ICU (%)	17.3	10.9	<0.001
Mean (SD) HLOS (days)	8.6 (8.0)	7.2 (8.2)	<0.001
Median (25–75 IQR) HLOS (days)	6 (4–10)	5 (3–9)	<0.001
Mean (SD) hospital costs ($)	$16,502 ($28,984)	$13,558 ($24,640)	<0.001
Median (25–75 IQR) hospital costs ($)	$8,361 ($4,234 – $17,171)	$6,628 ($3,240 –$14,340)	<0.001

	Hyponatremia present ($n = 1,886$)
Mean (SD) ICU LOS (days)	6.1 (6.7)
Median (25–75 IQR) ICU LOS (days)	4 (3–7)
Mean (SD) HLOS (days)	10.9 (10.5)
Median (25–75 IQR) HLOS (days)	8 (5–13)
Mean (SD) hospital costs ($)	$23,738 ($36,868)
Median (25–75 IQR) hospital costs ($)	$13,134 ($6,966–$26,296)

Medical Costs of Abnormal Serum Sodium Levels

Alisa M. Shea,* Bradley G. Hammill,* Lesley H. Curtis,*‡ Lynda A. Szczech,†§ and Kevin A. Schulman*‡

Resource Use	Serum Sodium Category[a]		
	Hyponatremia	Normal	Hypernatremia
6 mo			
medical costs, $ [mean (SD)]	11,078 (390)	5571 (34)	6491 (246)
inpatient costs only, $ [mean (SD)]	5853 (276)	2125 (24)	2969 (174)
inpatient discharges per 1000 patients (95% CI)	39.8 (36.7–42.9)	16.6 (16.4–16.9)	21.4 (19.4–23.4)
1 yr			
medical costs, $ [mean (SD)]	19,215 (702)	9257 (62)	10,972 (443)
inpatient costs only, $ [mean (SD)]	10,636 (474)	3468 (42)	4734 (299)
inpatient discharges per 1000 patients (95% CI)	71.5 (66.4–76.7)	27.3 (26.8–27.7)	34.8 (31.5–38.0)

Zilberberg MD et al. Curr Med Res Opin 2008;24:1601-1608
Shea AM et al. J Am Soc Nephrol 2008;19:764-770

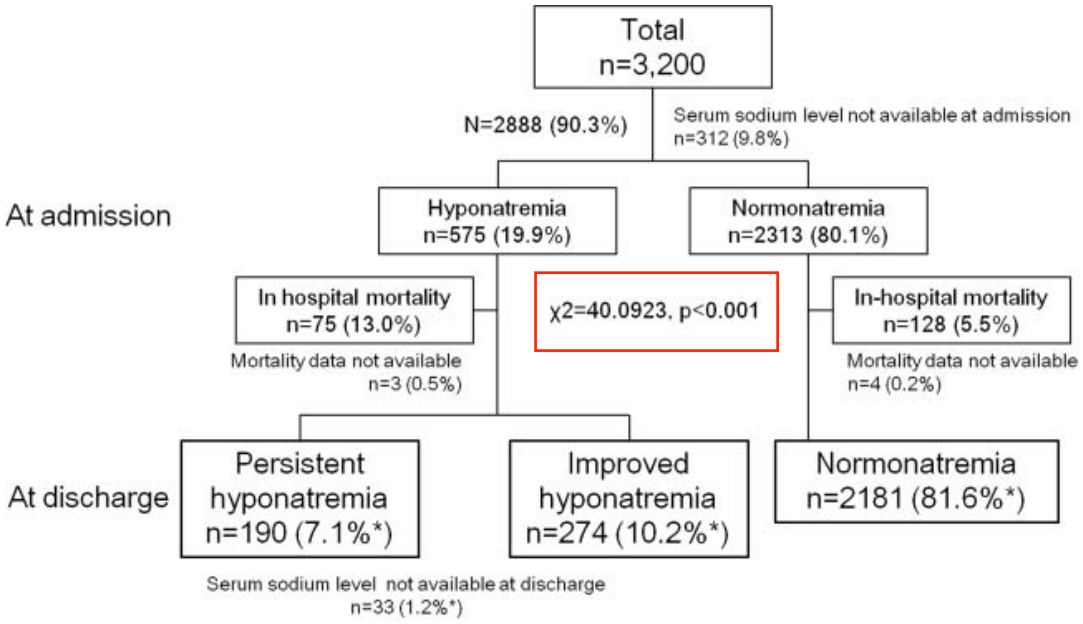
There is always an easy solution to every problem - neat, plausible, and wrong.

— H. L. Mencken —

Heart

Improvement of hyponatraemia during hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry

Sang Eun Lee, Dong-Ju Choi, Chang-Hwan Yoon, Il-Young Oh, Eun-Seok Jeon, Jae-Joong Kim, Myeong-Chan Cho, Shung Chull Chae, Kyu-Hyung Ryu and Byung-Hee Oh



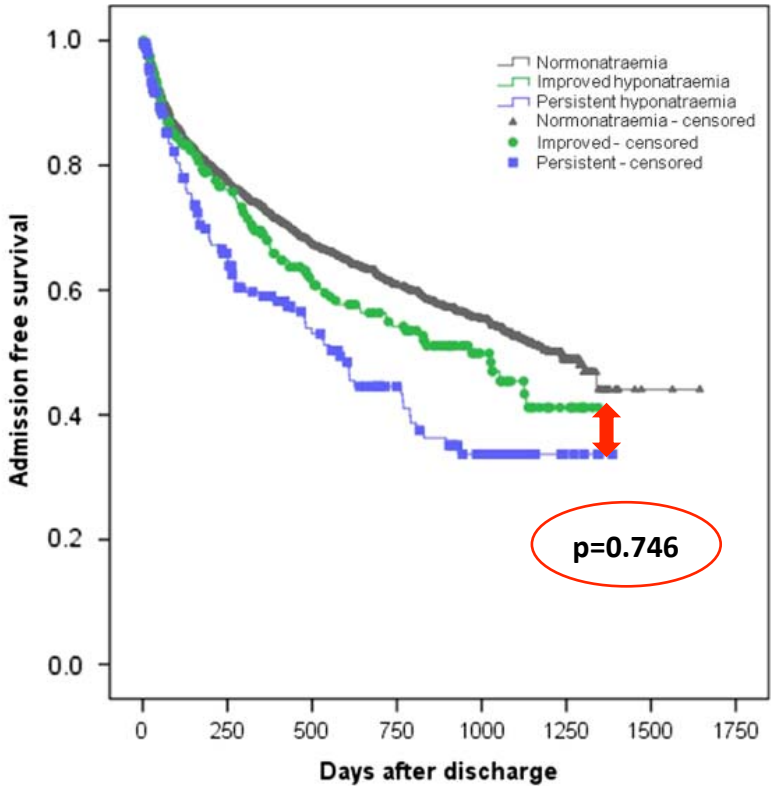


Table 3 Multivariate Cox proportional hazard model for composite endpoint in patients with hyponatraemia at admission

	HR	95% CI	p Value
Improved hyponatraemia	1.084	0.709 to 1.659	0.709
BUN at discharge, mg/dl	2.052	1.336 to 3.152	0.001
Previous heart failure history	1.705	1.280 to 2.271	<0.001
Age, years	1.477	1.100 to 1984	0.009
Parenteral use of diuretics	1.655	1.178 to 2.326	0.004
Improved hyponatraemia* BUN at discharge	0.554	0.311 to 0.988	0.045

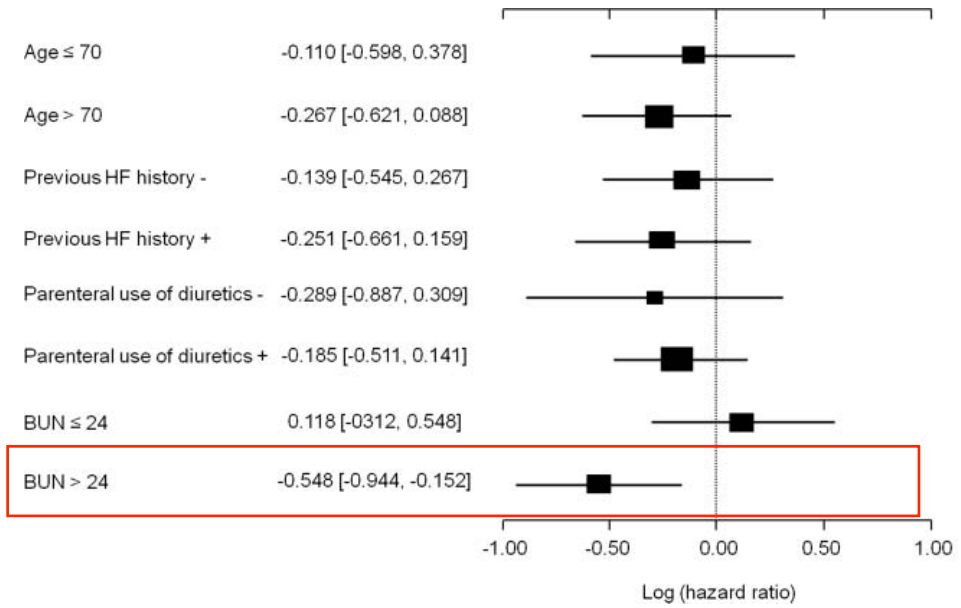
Lee SE et al. Heart 2012;98:1798-1804

Are we just making up?

Heart

Improvement of hyponatraemia during hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry

Sang Eun Lee, Dong-Ju Choi, Chang-Hwan Yoon, Il-Young Oh, Eun-Seok Jeon, Jae-Joong Kim, Myeong-Chan Cho, Shung Chull Chae, Kyu-Hyung Ryu and Byung-Hee Oh



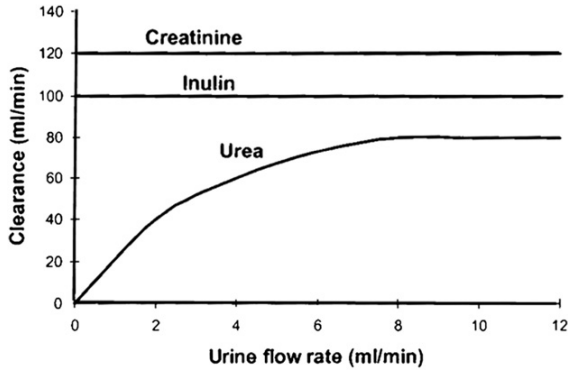
and results in poor outcome.[24 25] Recently, an elevated BUN level in HF is considered as a surrogate for the neurohormonal activation.[26 27] In this regard, our result may imply that hyponatraemia, an indicator of free water excess, might have a pathogenic role only in high neurohormonal activation condition and, thus, its improvement only in this condition may have clinical significance. This result suggests that in those patients with high BUN at discharge, improved or persistent hyponatraemia can be used as a predictor of postdischarge clinical outcome and a criterion for intensive postdischarge care.

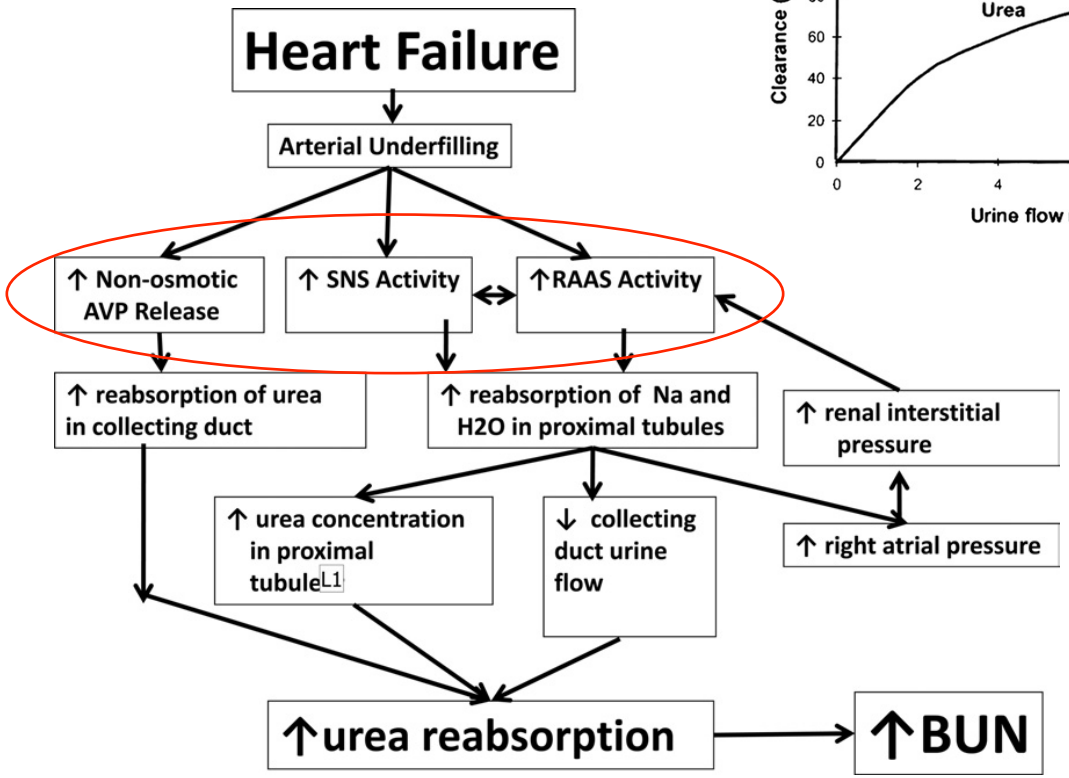
EDITORIAL COMMENT

Blood Urea Nitrogen

A Marker for Adverse Effects of Loop Diuretics?*

JoAnn Lindenfeld, MD,† Robert W. Schrier, MD‡





Lindenfeld JA et al. JACC 2011;58(4):383–5

How to treat

- conventional management strategies -

Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations

Joseph G. Verbalis, MD,[a] Stephen R. Goldsmith, MD,[b] Arthur Greenberg, MD,[c] Robert W. Schrier, MD,[d] and Richard H. Sterns, MD[e]

Establish the diagnosis of HF-related hypervolemic hyponatremia via history, physical exam, and laboratory studies; rule out noncardiac causes (eg, hyperglycemia, medications, and diarrhea).

Limit Na-free fluid intake (replace IV medication carriers to isotonic Na-containing solution in the inpatient setting).

Prescribe IV loop diuretics with close monitoring of serum Na (can be accompanied by simultaneous administration of hypertonic or isotonic saline solution in selected patients under supervision of an experienced physician).

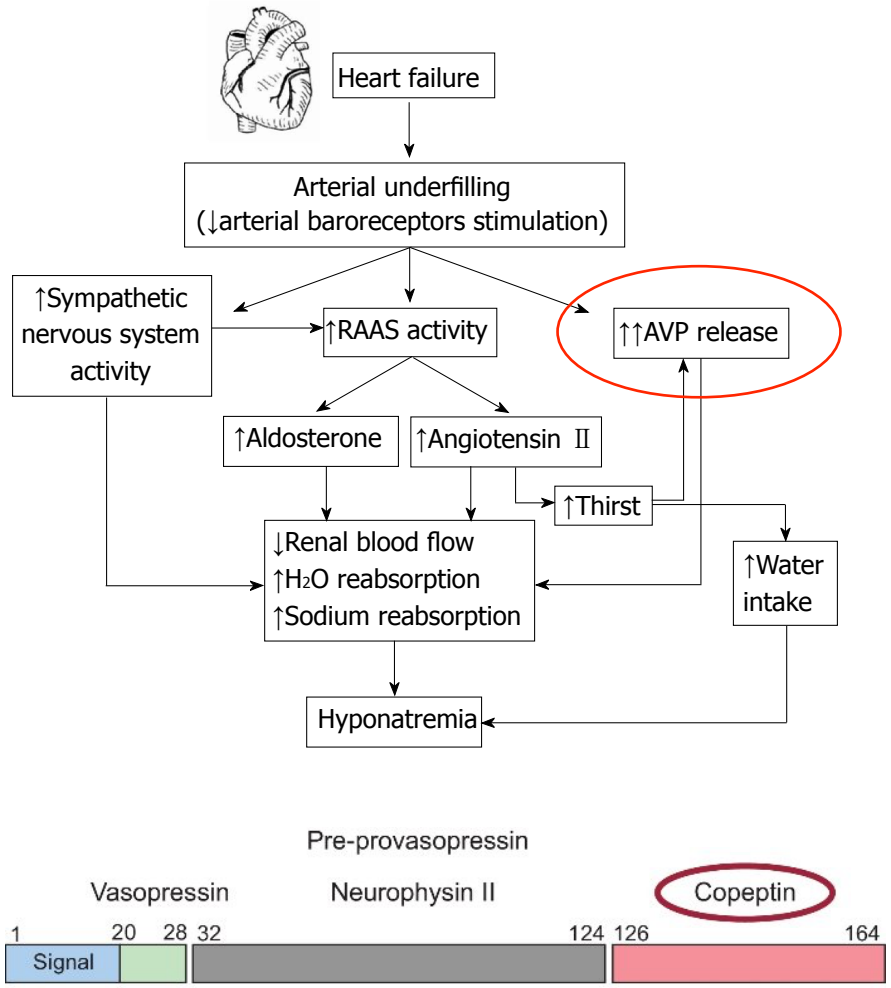
Many physicians have reservations about using loop diuretics in the setting of HF-associated hyponatremia, with the fear of further decreasing serum Na levels. Although Na excretion leads to a reduction in total body Na content, the urine produced by loop diuretics is hypotonic and contains only about 60mEq/L Na.

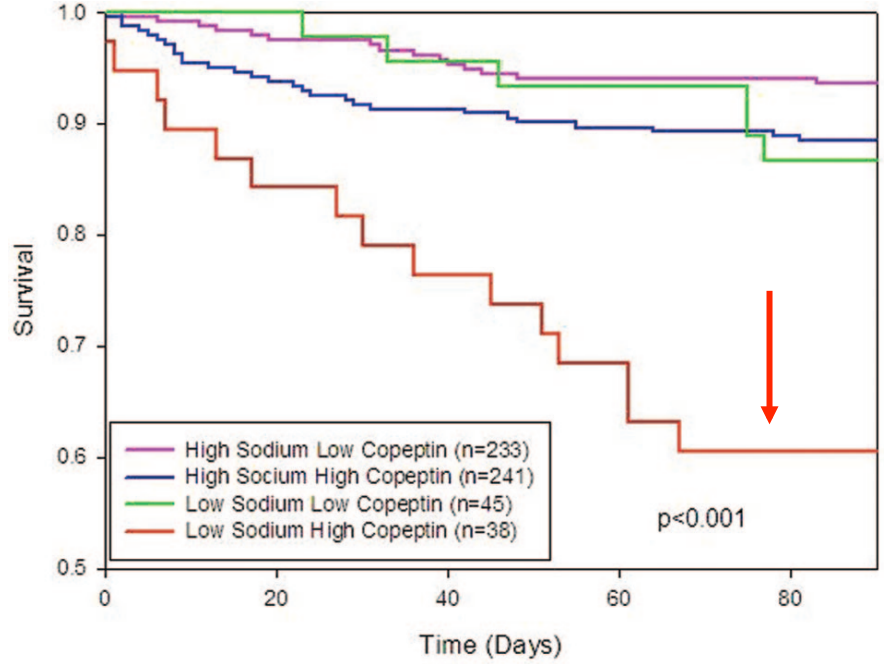
Therefore, while decreasing both total body water volume and Na content, the net effect of loop diuretics on fluid and electrolyte balance is expected to be a gradual increase in serum Na concentrations.

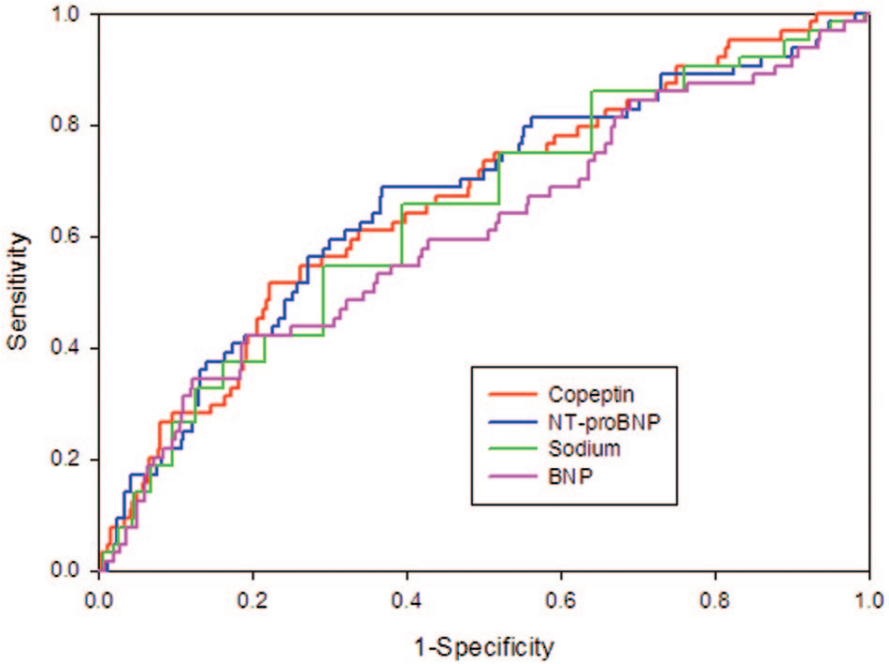
Verbalis JG et al. Am J Med. 2007;120(11 Suppl. 1):S1 – S21

Increased 90-Day Mortality in Patients With Acute Heart Failure With Elevated Copeptin

Secondary Results From the Biomarkers in Acute Heart Failure (BACH) Study







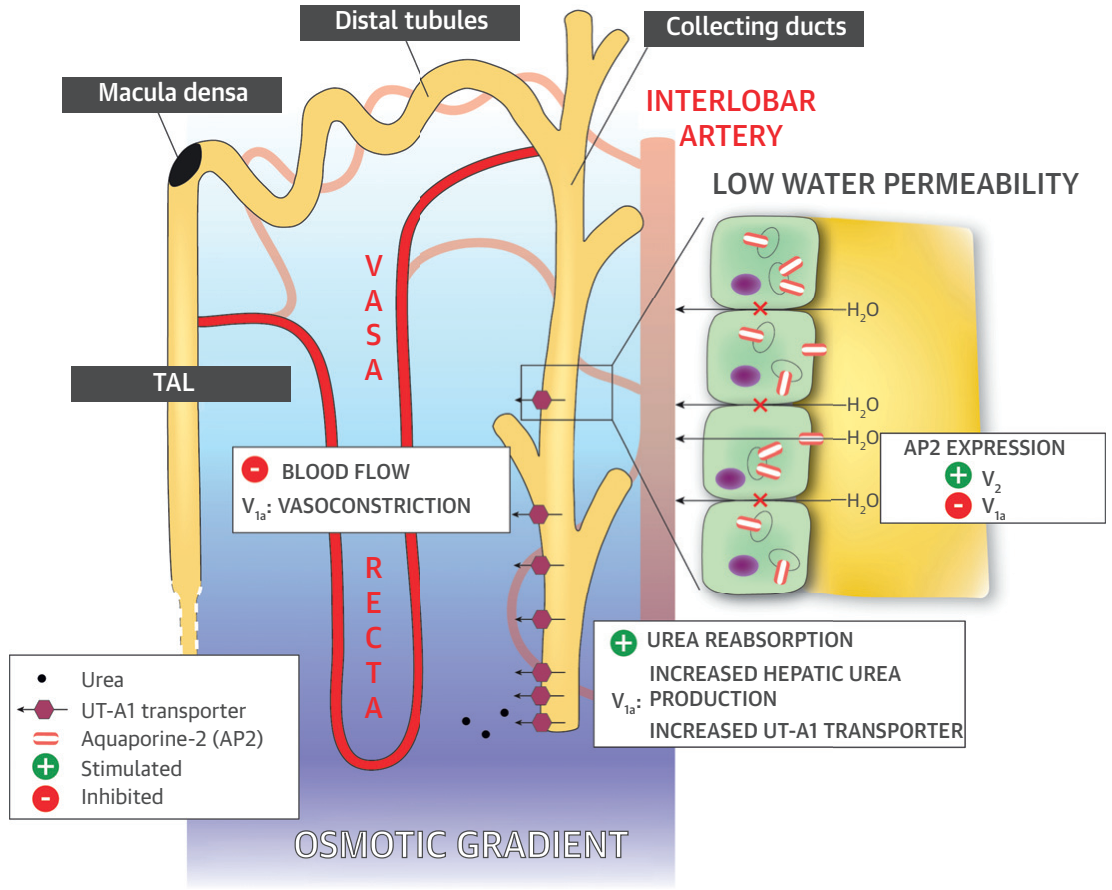
Maisel A et al. Circ Heart Fail 2011;4:613-620

How to treat

- newer management strategies -

- Vasopressin receptor antagonists (**VRA**), also called aquaretics or vaptans, represent the emerging strategy for treatment of HF-associated hyponatremia
- Three types of vasopressin receptors have been identified with distinct functions: **V1a**, **V1b (V3)**, and **V2**
- Vasopressin increases blood volume and decreases Na concentration by promoting free water retention through the V2 receptors on principal cells of the renal cortical collecting ducts
- VRA, originally used for the correction of hyponatremia in the context of SIADH secretion or cirrhosis, are potentially capable of ameliorating fluid overload and hyponatremia in HF patients through excretion of **electrolyte-free water**
- The VRA that have been most extensively studied are the selective V2 receptor antagonists **tolvaptan** and **lixivaptan**, in addition to the dual V1a/V2 receptor antagonist **conivaptan**

FIGURE 1 Effects of AVP in the Nephron

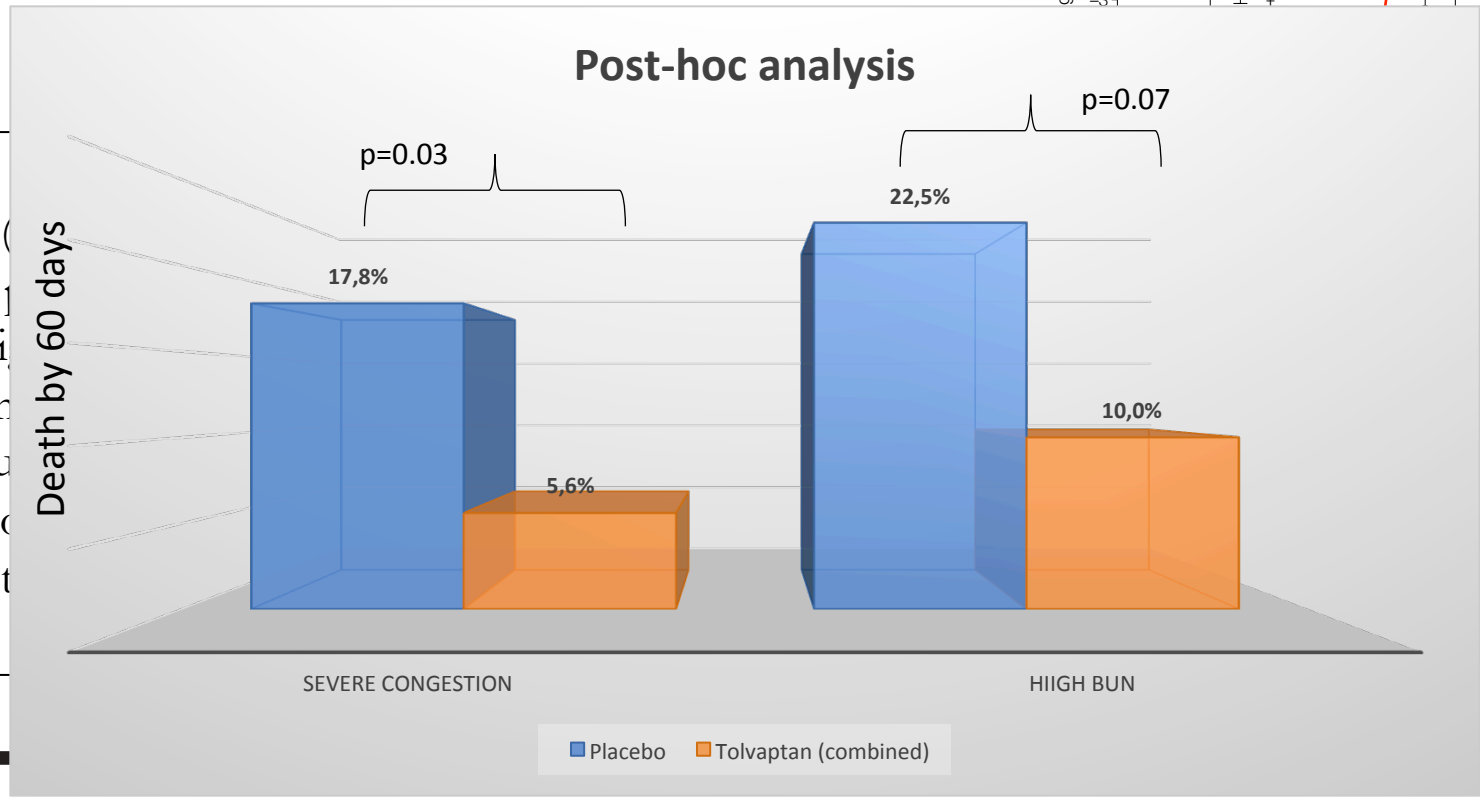


Verbrugge FH et al. J Am Coll Cardiol 2015;65:480–92

Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure

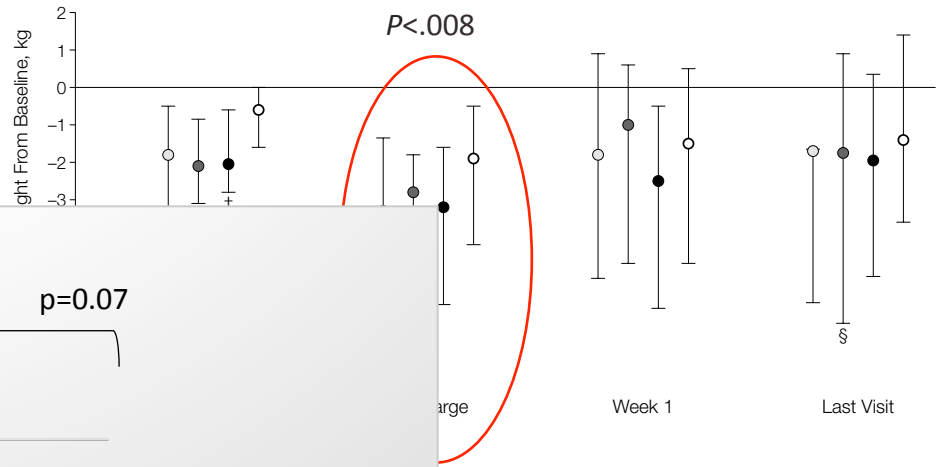
A Randomized Controlled Trial

In the ACTIV in CHF
tolvaptan administration (
90 mg/d) in hospitalized
(*n* = 319) resulted in a si
body weight at 24h with
heart rate or blood pressu
rates of hypokalemia
function (vs placebo, on t
therapy)



In-hospital outcome

Figure 2. Median Changes in Body Weight Over Time



rt Failure at Day 1 and at Hospital Discharge

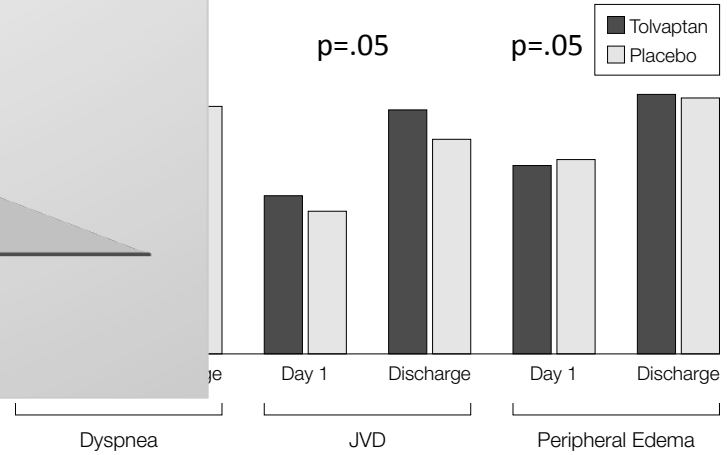


Table 2. Clinical Events*

Event	Tolvaptan 30 mg (n = 78)	Tolvaptan 60 mg (n = 84)	Tolvaptan 90 mg (n = 77)	Tolvaptan Combined (n = 239)	Placebo (n = 80)	*P* Value for Trend
Death by 60 days	3 (3.8)	8 (9.5)	2 (2.5)	13 (5.4)	7 (8.7)	.18
In-hospital death	0	1 (1.1)	0	1 (0.4)	2 (2.5)	.16
Rehospitalization	13 (16.7)	19 (22.6)	12 (15.6)	44 (18.4)	14 (17.5)	>.99
Worsening heart failure†	20 (25.6)	29 (34.5)	15 (19.4)	64 (26.7)	22 (27.5)	.88

outpatient outcome

Gheorghiade M et al. JAMA 2004;291:1963-1971

Multicenter, Randomized, Double-Blind, Placebo-Controlled Study on the Effect of Oral Tolvaptan on Left Ventricular Dilation and Function in Patients With Heart Failure and Systolic Dysfunction

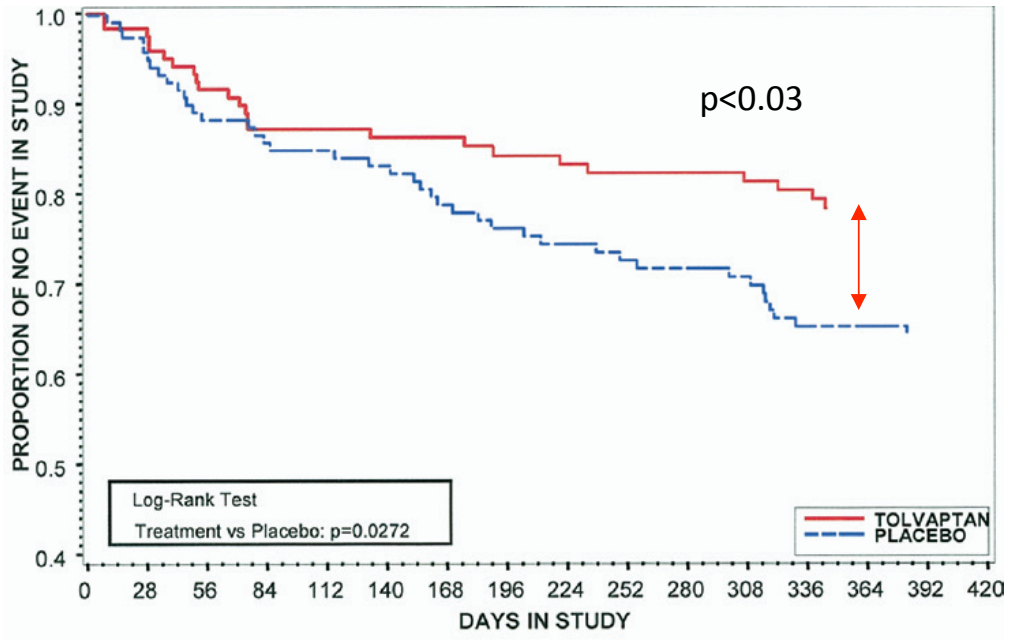
James E. Udelson, MD,* Frank A. McGrew, MD,† Enrique Flores, MD,‡ Hassan Ibrahim, MD,§ Stewart Katz, MD,¶ Gregory Koshkarian, MD,‖ Terrence O'Brien, MD,** Marvin W. Kronenberg, MD,†† Christopher Zimmer, MD,‡‡ Cesare Orlandi, MD,‡‡ Marvin A. Konstam, MD*

Methods This was a multicenter, randomized, double-blind, placebo-controlled trial conducted to evaluate the effect of long-term administration of the vasopressin V_2-receptor antagonist tolvaptan (30 mg/day) on reducing left ventricular end-diastolic volume (LVEDV) compared with placebo in patients with HF and reduced systolic function, using quantitative radionuclide ventriculography at baseline, repeated after 1 year of therapy, and repeated again approximately 1 week after withdrawal of study drug.

Results A total of 120 patients were randomized to tolvaptan and 120 were randomized to placebo. In the placebo group, there was no change in LVEDV over the course of follow-up (change of 0.0 ± 10.0 ml/m^2). After 1 year of tolvaptan, there was a small reduction in LV volume (decrease of 1.8 ± 10.7 ml/m^2); the between-group difference was not significant ($p = 0.21$). During the course of the trial, there were 6 deaths (5%) and 21 HF hospitalizations (18%) in the tolvaptan group, compared with 11 deaths (9%) and 34 HF hospitalizations (28%) in the placebo group. In a time-to-event analysis, there was a significant favorable effect of tolvaptan on the composite of mortality or heart failure hospitalization ($p < 0.03$ by log-rank test).

Conclusions In a well-treated population of stable HF patients, there was no significant effect of tolvaptan therapy on LV volumes observed during 1 year of therapy. Nonprespecified natural history data favored therapy with tolvaptan, with a reduction in the combined end point of mortality and heart failure hospitalization observed. (Multicenter, Randomized, Double-Blind, Placebo Controlled, Efficacy Study on the Effects of

Figure 1 Effect of TLV on Time to Death or Heart Failure Hospitalization



- not a prespecified end point
- events were not adjudicated by a blinded central events committee

Udelson JE et al. J Am Coll Cardiol 2007;49:2151-2159

Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure

The EVEREST Clinical Status Trials

Objective To evaluate short-term effects of tolvaptan when added to standard therapy in patients hospitalized with heart failure.

Design, Setting, and Patients Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) between October 7, 2003, and February 3, 2006. A total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion were studied.

Intervention Patients were randomized to receive either tolvaptan (30 mg/d) or matching placebo, within 48 hours of admission.

Main Outcome Measures Primary end point was a composite of changes in global clinical status based on a visual analog scale and body weight at day 7 or discharge if earlier. Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge).

Table 5. Adverse Events Occurring Between Randomization and Day 7 or Discharge if Earlier

	No. (%) of Patients					
	Trial A			Trial B		
Adverse Events	Tolvaptan (n = 1015)	Placebo (n = 1027)	*P* Value	Tolvaptan (n = 1048)	Placebo (n = 1028)	*P* Value
Treatment-emergent	498 (49.1)	411 (40.0)	<.001	586 (55.9)	492 (47.9)	<.001
Serious	60 (5.9)	49 (4.8)	.28	45 (4.3)	60 (5.8)	.11
Adverse events of incidence ≥1%*						
Dry mouth	43 (4.2)	7 (0.7)	<.001	63 (6.0)	7 (0.7)	<.001
Thirst	79 (7.8)	5 (0.5)	<.001	118 (11.3)	10 (1.0)	<.001
Pollakiuria	13 (1.3)	3 (0.3)	.01	10 (1.0)	4 (0.4)	.18
Polyuria	6 (0.6)	2 (0.2)	.18	35 (3.3)	5 (0.5)	<.001
Hypernatremia	14 (1.4)	0 (0.0)	<.001	5 (0.5)	0 (0.0)	.06
Ventricular extrasystoles	5 (0.5)	5 (0.5)	>.99	11 (1.0)	2 (0.2)	.02
Constipation	35 (3.4)	20 (1.9)	.04	38 (3.6)	49 (4.8)	.23
Adverse events of clinical interest						
Atrial fibrillation	3 (0.3)	5 (0.5)	.75	15 (1.4)	11 (1.1)	.56
Ventricular tachycardia	21 (2.1)	16 (1.6)	.41	18 (1.7)	19 (1.8)	.87
Cardiac failure	10 (1.0)	22 (2.1)	.04	17 (1.6)	16 (1.6)	.90
Hypotension	44 (4.3)	30 (2.9)	.10	30 (3.2)	34 (3.3)	.61
Hyponatremia	4 (0.4)	5 (0.5)	>.99	4 (0.4)	5 (0.5)	.75
Hypokalemia	23 (2.3)	28 (2.7)	.57	25 (2.4)	37 (3.6)	.12
Hypomagnesemia	3 (0.3)	2 (0.2)	.69	5 (0.5)	10 (1.0)	.20
Renal failure	21 (2.1)	20 (1.9)	.72	29 (2.8)	25 (2.4)	.63

*Significant ($P<.05$) differences between treatment groups.

Table 2. Changes From Baseline in Secondary Efficacy End Points

	Trial A			Trial B		
	Tolvaptan	Placebo	*P* Value	Tolvaptan	Placebo	*P* Value
Changes in patient-assessed global clinical status at day 7,* mean VAS score (SD) [No.]	18.25 (22.26) [903]	17.73 (22.47) [910]	.51†	18.72 (21.71) [931]	18.28 (21.59) [900]	.52†
Changes in body weight at day 1, mean (SD) [No.], kg	−1.71 (1.80) [978]	−0.99 (1.83) [997]	<.001†	−1.82 (2.01) [1021]	−0.95 (1.85) [1002]	<.001†
Changes in body weight at day 7,* mean (SD) [No.], kg	−3.35 (3.27) [997]	−2.73 (3.34) [1007]	<.001†	−3.77 (3.59) [1031]	−2.79 (3.46) [1008]	<.001†
Change in patient-assessed dyspnea at day 1, % showing improvement in dyspnea score (No.)§	76.74 (894)	70.61 (915)	<.001‡	72.06 (941)	65.32 (914)	<.001‡
Change in edema scores at day 7,* % showing at least a 2-grade improvement (No.)§	73.83 (772)	70.25 (790)	.07‡	73.67 (828)	70.81 (805)	.02‡

p<0.01

Conclusion In patients hospitalized with heart failure, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.

Gheorghiade M et al. JAMA. 2007;297:1332-1343

Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

Objective To investigate the effects of tolvaptan initiated in patients hospitalized with heart failure.

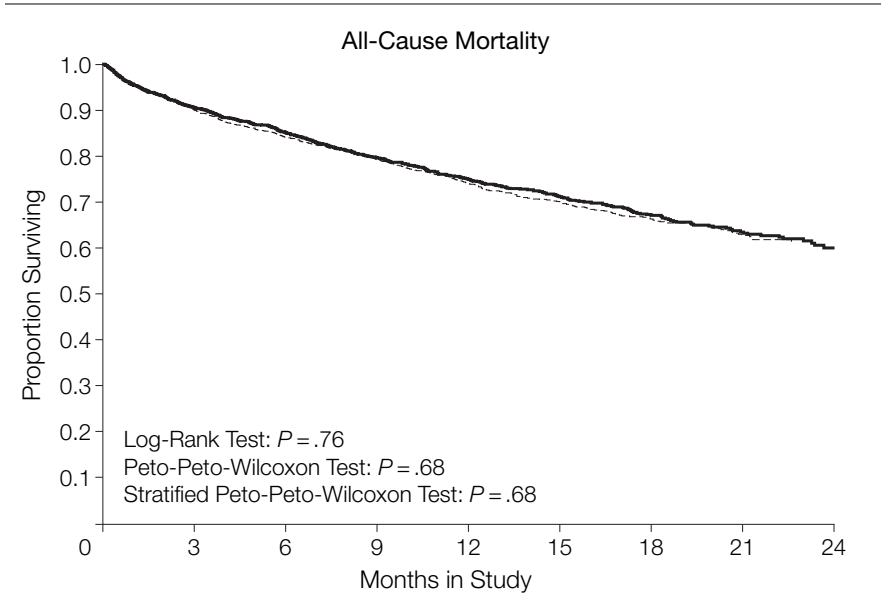
Design, Setting, and Participants The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study. The outcome trial comprised 4133 patients within 2 short-term clinical status studies, who were hospitalized with heart failure, randomized at 359 North American, South American, and European sites between October 7, 2003, and February 3, 2006, and followed up during long-term treatment.

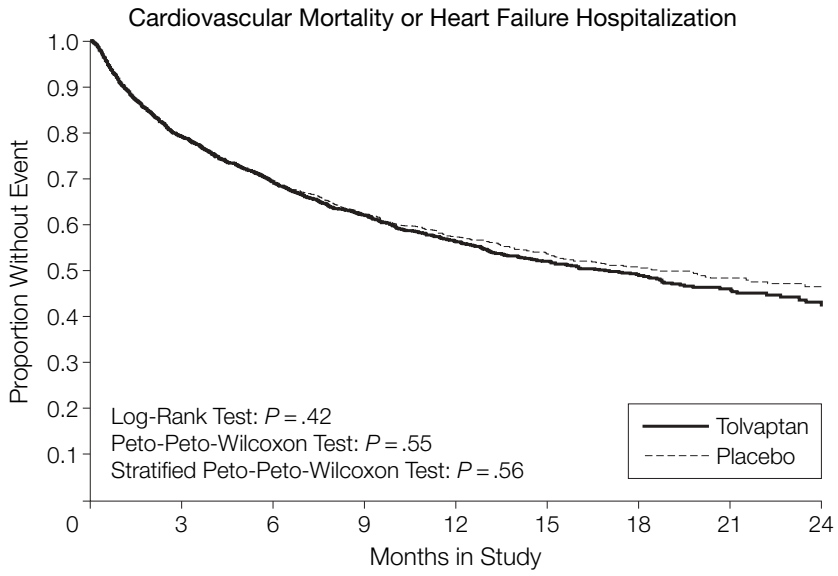
Intervention Within 48 hours of admission, patients were randomly assigned to receive oral tolvaptan, 30 mg once per day (n=2072), or placebo (n=2061) for a minimum of 60 days, in addition to standard therapy.

Main Outcome Measures Dual primary end points were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Secondary end points included changes in dyspnea, body weight, and edema.

Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

	Tolvaptan	Placebo	*P* Value
Change in body weight at 1 day, mean (SD), kg	−1.76 (1.91) [n = 1999]	−0.97 (1.84) [n = 1999]	<.001*
Change in dyspnea at 1 day, % showing improvement in dyspnea score†	74.3 [n = 1835]	68.0 [n = 1829]	<.001‡
Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L§	5.49 (5.77) [n = 162]	1.85 (5.10) [n = 161]	<.001*
Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement†	73.8 [n = 1600]	70.5 [n = 1595]	.003‡
Change in KCCQ overall summary score at postdischarge week 1, mean (SD)	19.90 (18.71) [n = 872]	18.52 (18.83) [n = 856]	.39*



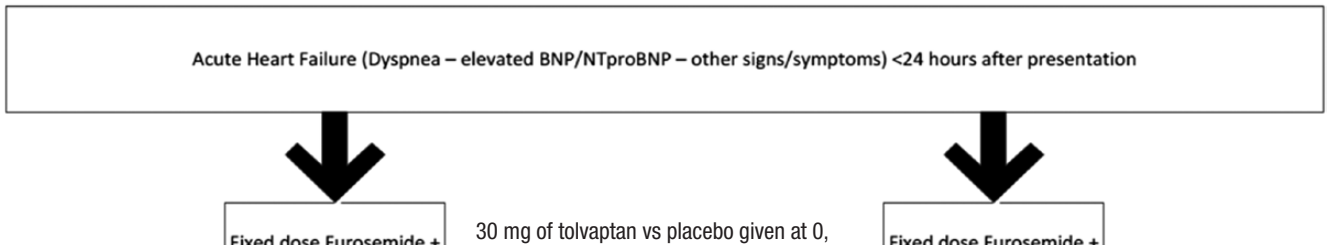


Konstam MA et al. JAMA 2007;297:1319-1331

Tolvaptan in Patients Hospitalized With Acute Heart Failure: Rationale and Design of the TACTICS and the SECRET of CHF Trials

G. Michael Felker, Robert J. Mentz, Kirkwood F. Adams, Robert T. Cole, Gregory F. Egnaczyk, Chetan B. Patel, Mona Fiuzat, Douglas Gregory, Patricia Wedge, Christopher M. O'Connor, James E. Udelson and Marvin A. Konstam

TACTICS Study Design



No Study Results Posted on ClinicalTrials.gov for this Study

About Study Results Reporting on ClinicalTrials.gov

Study Status:	This study has been completed.
Study Completion Date:	February 2016
Primary Completion Date:	February 2016 (Final data collection date for primary outcome measure)

SECRECT of CHF Study Design

No Study Results Posted on ClinicalTrials.gov for this Study

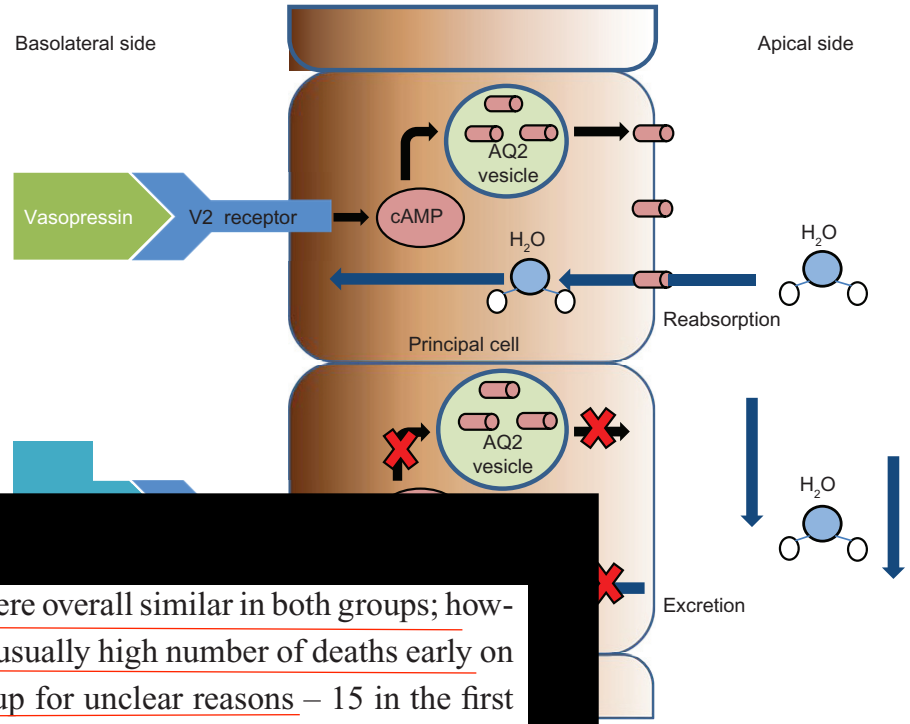
About Study Results Reporting on ClinicalTrials.gov

Study Status:	This study has been completed.
Study Completion Date:	August 2016
Primary Completion Date:	July 2016 (Final data collection date for primary outcome measure)

Felker GM et al. Circ Heart Fail. 2015;8:997-1005

Lixivaptan – an evidence-based review of its clinical potential in the treatment of hyponatremia

- Lixivaptan is a newer, nonpeptide, once-daily oral V2-receptor-specific antagonist
- In phase II trials the administration of lixivaptan was associated with significant increases in urine volume and solute-free water excretion (Abraham et al, JACC 2006) and reduction in body weight and improved dyspnea and orthopnea (Ghali JK et al, EJHF 2012)
- Lixivaptan v
  more frequ
  group



lixivaptan. Statistically significant differences in secondary endpoints were similarly modest, and there was no difference in the Trail Making Test Part B. Of note, the only hard clinical endpoint in any of the three trials – days alive and out of the hospital at 60 days, was not different between the two groups.

Adverse events were overall similar in both groups; however, there was an unusually high number of deaths early on in the lixivaptan group for unclear reasons – 15 in the first 10 days of treatment versus four in the placebo group. This prompted the data safety monitoring committee to deliver a letter urging termination of the trial as soon as possible.

Table I Summary of

Number of subjects		
Age (years)		
% Subjects on fluid restriction – baseline	62.6%	65.0%
Initial dose lixivaptan (mg)	N/A	50
Mean baseline Na (mmol/L)	132.6	132.9
Mean Na Δ day 7 (mmol/L)	1.3	2.5
Mean Na Δ by trial end (mmol/L)	1.9	2.6
% of subjects with normalized Na day 7	24.3%	30.1%
Net treatment effect day 7 (mmol/L)	1.2	

p=0.001

Placebo (n=325)

Primary Endpoint:
- Δ from baseline in Serum Na+ at day 7

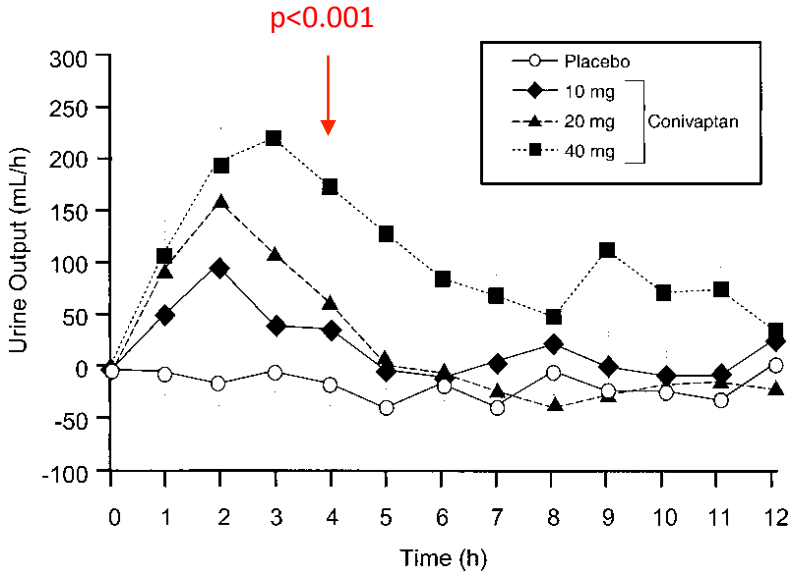
Secondary Endpoints
- Trail-making Test-B
- Days Hospital Free Survival

Abraham WT et al. JACC 2006;47:1615-1621
Ghali JK et al. EJHF 2012;14:642-651
Abraham WT et al. Clin Transl Sci 2010;3:249-253
Bowman BT et al. Core Evidence 2013:8 47–56

Acute Hemodynamic Effects of Conivaptan, a Dual V_{1A} and V_2 Vasopressin Receptor Antagonist, in Patients With Advanced Heart Failure

James E. Udelson, William B. Smith, Grady H. Hendrix, Christopher A. Painchaud, Maha Ghazzi, Ignatius Thomas, Jalal K. Ghali, Paulina Selaru, Francoise Chanoine, Milton L. Pressler and Marvin A. Konstam

- Conivaptan is administered iv and is a V1a/V2 receptor blocker; the aquaretic effect is due to antagonism of the V2 receptor
- 142 patients with symptomatic heart failure (NYHA III/IV) were randomized to double-blind, short-term treatment with conivaptan, at a single intravenous dose (10, 20, or 40 mg) or placebo
- No data on symptoms relief and outcomes



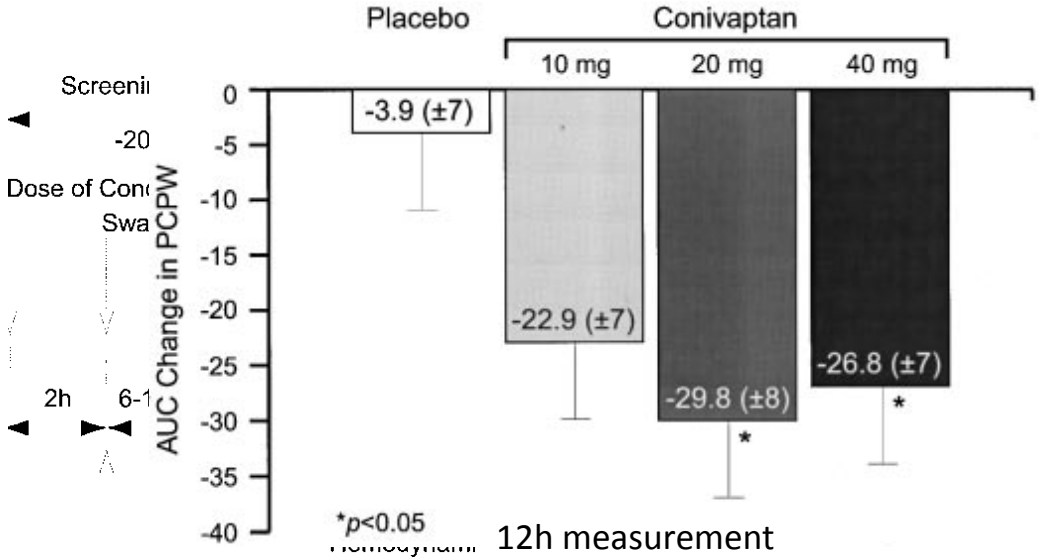


TABLE 2. Effect of Conivaptan on Hemodynamic Parameters (Peak Change at 3–6 hours)

		Conivaptan		
	Placebo	10 mg	20 mg	40 mg
PCWP, mm Hg	−2.6±0.7	−3.7±0.7	−5.4±0.7†	−4.6±0.7*
CI, L · min^{-1} · m^{-2}	0.3±0.1	0.2±0.1	0.4±0.1	0.2±0.1
MAP, mm Hg	−4.1±1.3	−5.4±1.3	−6.0±1.4	−4.2±1.3
PVR, dynes · s · cm^{-5}	−53.4±14.9	−38.0±15.1	−59.1±16	−36.1±15.3
SVR, dynes · s · cm^{-5}	−185.2±43.8	−182.3±44.5	−284.2±47.1	−128.9±45
PAP, mm Hg	−4.2±1.1	−6.0±1.1	−5.9±1.2	−6.3±1.1
RAP, mm Hg	−2.0±0.4	−2.0±0.4	−3.7±0.4†	−3.5±0.4*
HR, bpm	−2.4±1.0	−1.1±1.0	−1.9±1.1	−0.4±1.1

*P<0.05, †P<0.01.

Udelson JE et al. Circulation 2001;104:2417-2423

Efficacy and Safety of the Vasopressin V1A/V2-Receptor Antagonist Conivaptan in Acute Decompensated Heart Failure: A Dose-Ranging Pilot Study

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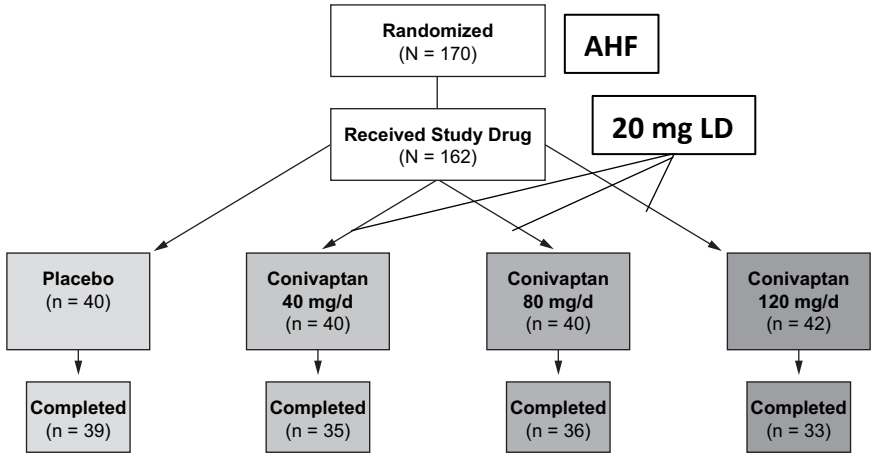
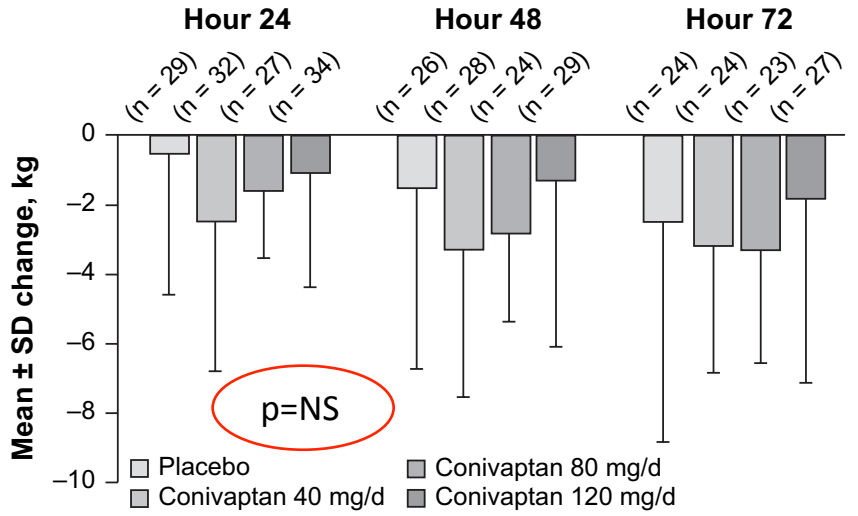
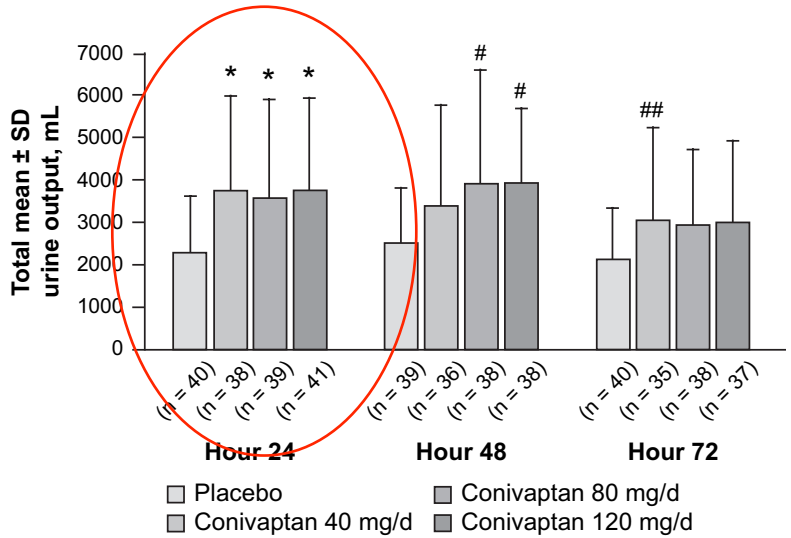


polypropylene glycol buffer

Table 3. Summary of Adverse Events

Event, no. (%)	Placebo (n = 40)	Conivaptan 40 mg/d (n = 40)	Conivaptan 80 mg/d (n = 40)	Conivaptan 120 mg/d (n = 42)
Deaths*	1 (2.5)	2 (5.0)	1 (2.5)	6 (14.3)
Patients with serious AEs	7 (17.5)	4 (10.0)	5 (12.5)	10 (23.8)
Discontinuations due to AEs	1 (2.5)	2 (5.0)	3 (7.5)	6 (14.3)
Patients with treatment-related AEs	10 (25.0)	16 (40.0)	20 (50.0)	25 (59.5)
Most common AEs†				
Infusion-site phlebitis	2 (5.0)	7 (17.5)	13 (32.5)	14 (33.3)
Exacerbated dyspnea	5 (12.5)	7 (17.5)	7 (17.5)	5 (11.9)
Hyperkalemia	2 (5.0)	5 (12.5)	2 (5.0)	1 (2.4)
Injection-site cellulitis	0	4 (10.0)	2 (5.0)	3 (7.1)
Headache	3 (7.5)	2 (5.0)	1 (2.5)	4 (9.5)
Limb pain	0	3 (7.5)	2 (5.0)	2 (4.8)
Hypernatremia	0	2 (5.0)	3 (7.5)	2 (4.8)
Cough	2 (5.0)	3 (7.5)	1 (2.5)	1 (2.4)
Dizziness	2 (5.0)	3 (7.5)	0	1 (2.4)
Hematuria	1 (2.5)	1 (2.5)	3 (7.5)	0
Infusion-site erythema	0	0	3 (7.5)	1 (2.4)
Decreased blood magnesium	0	1 (2.5)	3 (7.5)	0
Decreased urine sodium	0	1 (2.5)	3 (7.5)	0
Infusion-site tenderness	0	0	3 (7.5)	0





Global and respiratory status at 48h did not differ significantly between conivaptan and placebo groups

Vaptans

- other considerations -

- fluid should not be restricted in patients with hyponatremia who start AVP-receptor antagonists and serum sodium concentration should be monitored every 6-8 h in order to avoid rapid correction of sodium levels
- although osmotic demyelination has not been reported with the use of AVP-receptor antagonists in studies with HF patients, a warning letter was recently published concerning the occurrence of neurological sequelae in some patients treated with tolvaptan in whom the correction of serum sodium exceeded the suggested rate (FDA, 2013)
- AVP-receptor antagonists should not be used in patients with hypovolemic hyponatremia, who should instead be treated with isotonic saline
- adverse effects of AVP-receptor antagonists include dry mouth, thirst and increased urination in most patients
- FDA based on a recent large clinical trial of tolvaptan in patients with autosomal dominant polycystic kidney disease has determined that tolvaptan should not administrated for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death

Conclusions

- take home messages -

- Many patients with heart failure have decreased sodium levels due to neurohormonal mechanisms (non-osmotic AVP rise play a key role)
- In HF patients decreased sodium levels are usually (or mainly) due to an hypervolemic (diluitional) mechanism, although drugs may play a role
- Patients with HF and hyponatremia have increased morbidity and worse prognosis compared with subjects with normal sodium levels
- Treatment options for hyponatremia in HF such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues
- AVP-receptor antagonists increase effectively sodium levels and their use seems promising in patients with hyponatremia. However, it is not clear whether normalization of serum sodium also leads to an improved prognosis.
- In patients with HF and hyponatremia the effects of AVP-receptor antagonists on the mortality, quality of life and length of hospital stay, as well as their cost-effectiveness, have not been thoroughly examined in double-blind, placebo-controlled trials and should be field for future researches


I think your HF patient is drinking too much water!!!