L’iposodiemia nell’insufficienza cardiaca: diagnosi e terapia

Enrico Fiaccadori
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Hyponatremia

- Epidemiology and outcome
- Pathophysiology as the basis for diagnosis and treatment
- The role of pharmacologic and non pharmacologic treatment

Table 1 | Prevalence of hyponatraemia in different patient populations

Patient group	Prevalence (%)	References
ICU patients	11.0–29.6	Stelfox *et al.* (2010)[16] DeVita *et al.* (1990)[17] Funk *et al.* (2010)[18]
Elderly outpatients	7.2–11.0	Caird *et al.* (1973)[19] Miller *et al.* (1996)[20]
Elderly inpatients	18.0–53.0	Anpalahan *et al.* (2008)[21] Miller (1998)[22] Kleinfeld *et al.* (1979)[23] Sunderam *et al.* (1983)[24] Miller *et al.* (1995)[25]
Patients with heart failure	10.2–27.0	Bettari *et al.* (2012)[26] Konstam *et al.* (2007)[27] Shorr *et al.* (2011)[28] DeWolfe *et al.* (2010)[29] Mohammed *et al.* (2010)[30] Klein *et al.* (2005)[31] Gheorghiade *et al.* (2007)[32]
Patients with cirrhosis	20.8–49.4	Solà *et al.* (2012)[33] Shaikh *et al.* (2010)[34] Kim *et al.* (2009)[35] Yun *et al.* (2009)[36] Angeli *et al.* (2006)[37]
Patients with cancer	3.7–47.0	Berghmans *et al.* (2000)[38] Doshi *et al.* (2012)[39]
Patients with pneumonia	8.1–27.9	Zilberberg *et al.* (2008)[12] Nair *et al.* (2007)[40]
Predialysis patients with CKD	13.6	Kovesdy *et al.* (2012)[41]
Patients on dialysis	29.3	Waikar *et al.* (2011)[42]
Marathon runners	3.0–13.0	Almond *et al.* (2005)[43] Knechtle *et al.* (2011)[44] Kipps *et al.* (2011)[45] Mettler *et al.* (2008)[46]
Elderly patients with falls	9.1–13.0	Gankam Kengne *et al.* (2008)[47] Sandhu *et al.* (2009)[48]

Hyponatremia: the most frequent electrolyte disorder

- HyponaNa: < 135 mEq/L
- Moderate hypona: 125-135 mEq/L
- Profound (severe) hypona:

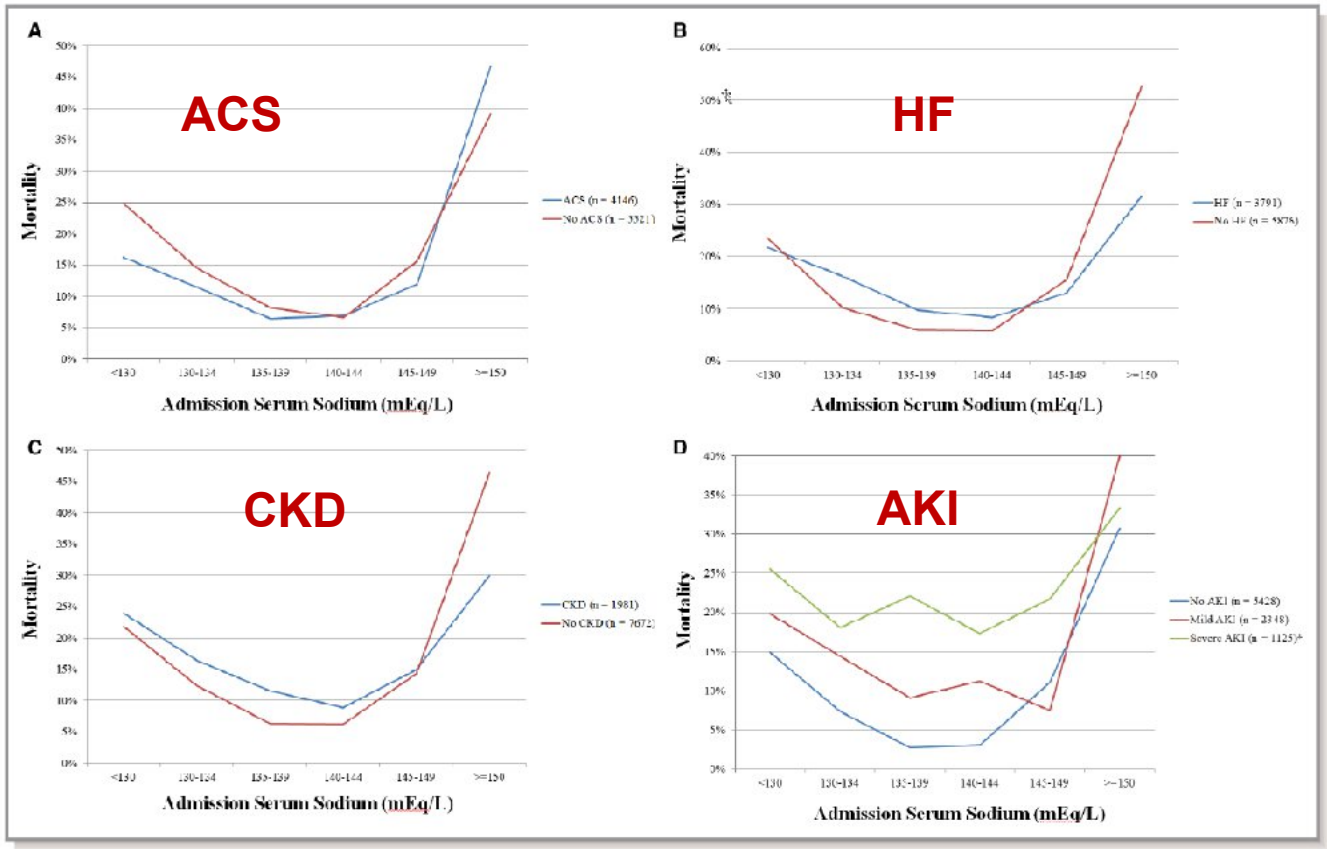
  < 125 mEq ERBP 2014

  < 120 mEq US panel 2013

Schrier, R. W. *et al. Nat. Rev. Nephrol.* 9, 37–50 (2013)

Abnormal Serum Sodium is Associated With Increased Mortality Among Unselected Cardiac Intensive Care Unit Patients

Thomas Breen, MD; Benjamin Brueske, RN; Mandeep S. Sidhu, MD; Dennis H. Murphree, PhD; Kianoush B. Kashani, MD, MS; Gregory W. Barsness, MD; Jacob C. Jentzer, MD



In-hospital mortality as a function of admission sodium in patients with (A) acute coronary syndrome (ACS); (B) heart failure (HF); (C) chronic kidney disease (CKD), and (D) acute kidney injury (AKI). P<0.001 for all mortality comparisons between sodium groups by chi-squared test, except in patients with severe AKI (*P=0.30).

9676 patients, 1706 (17.6%) with hyponatremia

J Am Heart Assoc 2020;9:e014140

Improvement of hyponatremia is associated with lower mortality risk in patients with acute decompensated heart failure: a meta-analysis of cohort studies

Jinhui Wang[1] · Weijian Zhou[1] · Xiaoning Yin[2]

Study or Subgroup	Improved HN Events	Total	Persistent HN Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Klein 2005	10	93	26	151	7.1%	0.62 [0.32, 1.24]
Rossi 2007	5	45	5	23	3.0%	0.51 [0.16, 1.59]
Gheorghiade 2007	9	32	22	71	7.6%	0.91 [0.47, 1.75]
Rusinaru 2009	10	45	26	46	8.6%	0.39 [0.22, 0.72]
Madan 2011	142	222	82	100	28.1%	0.78 [0.68, 0.89]
Lee 2012	59	274	50	190	17.7%	0.82 [0.59, 1.14]
Donzé 2016	126	2469	170	1799	23.3%	0.54 [0.43, 0.67]
Yoshioka 2016	6	62	15	64	4.7%	0.41 [0.17, 1.00]
Total (95% CI)		**3242**		**2444**	**100.0%**	**0.65 [0.53, 0.80]**
Total events	367		396			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.49$, $df = 7$ ($P = 0.04$); $I^2 = 52\%$

Test for overall effect: $Z = 4.09$ ($P < 0.0001$)

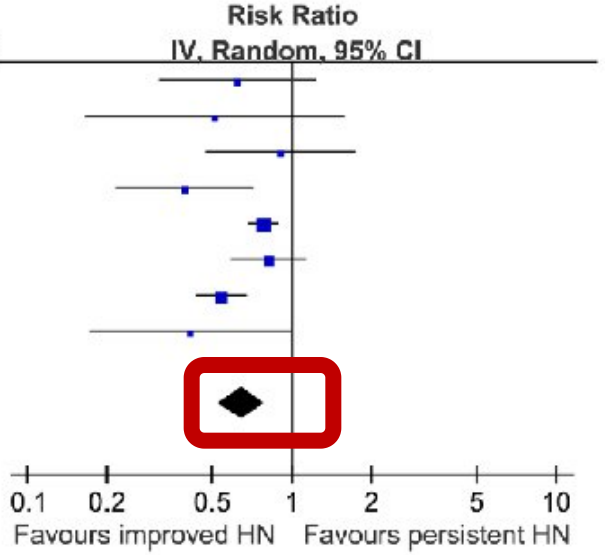


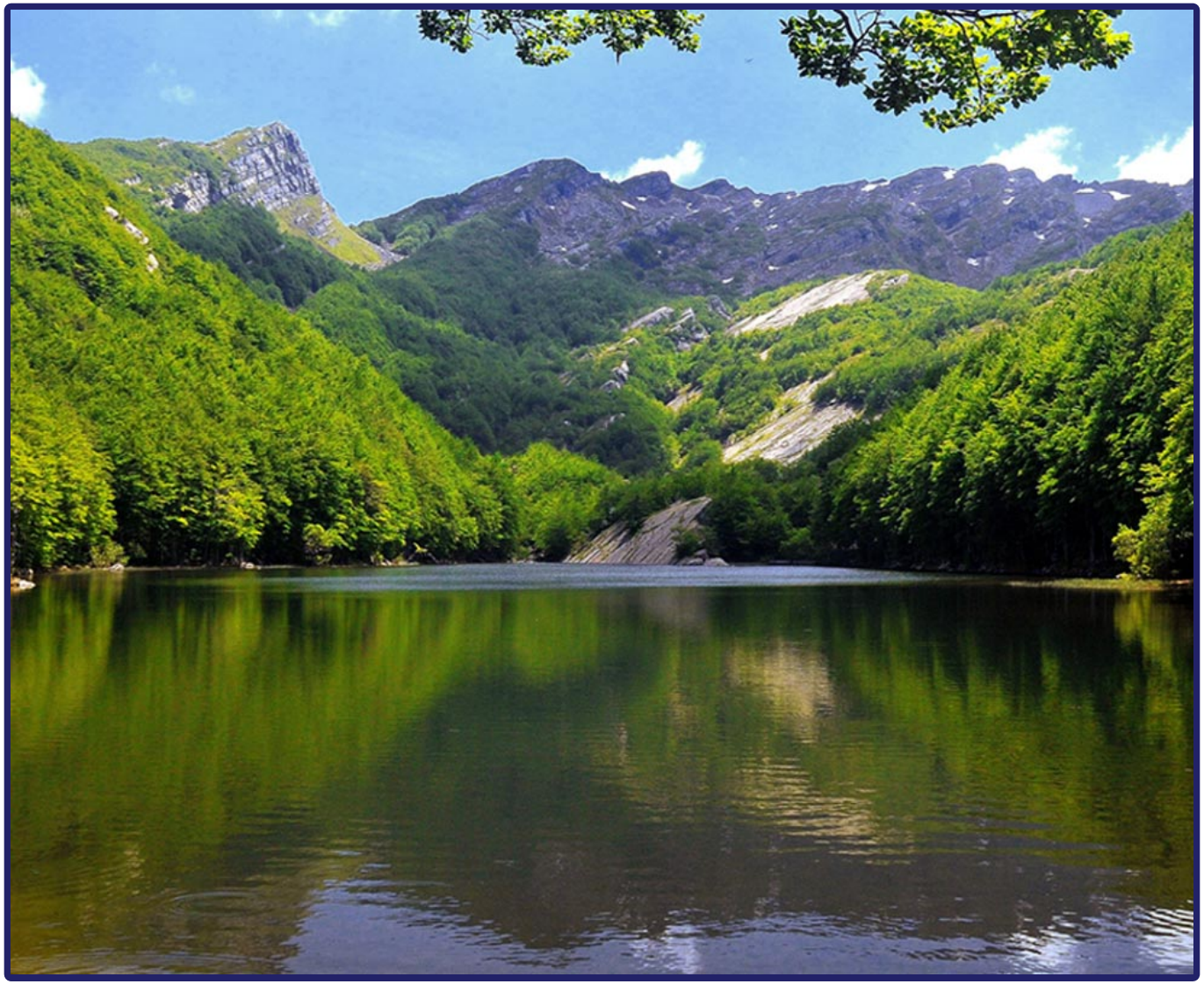
Fig. 2 Forest plot for the meta-analysis regarding the effect of hyponatremia improvement on mortality risk in patients with ADHF and hyponatremia: unadjusted result

Heart Failure Reviews (2019) 24:209–217

Hyponatremia

- Epidemiology and outcome
- Pathophysiology as the basis for diagnosis and treatment
- The role of pharmacologic and non pharmacologic treatment

Hyponatremia is mainly a problem of water (relative or absolute excess of water on sodium)



Mechanism of hyponatremia: relative or absolute excess of water on Na*

a) <u>Loss of sodium</u> (and K) more than H_2O

b) <u>Gain of water (more than Na)</u>

- Excess drinking hypotonic fluids, or excess parenteral hypotonic fluids

and/or

- Reduced/inappropriate water excretion

(ADH activated or not fully suppressed)

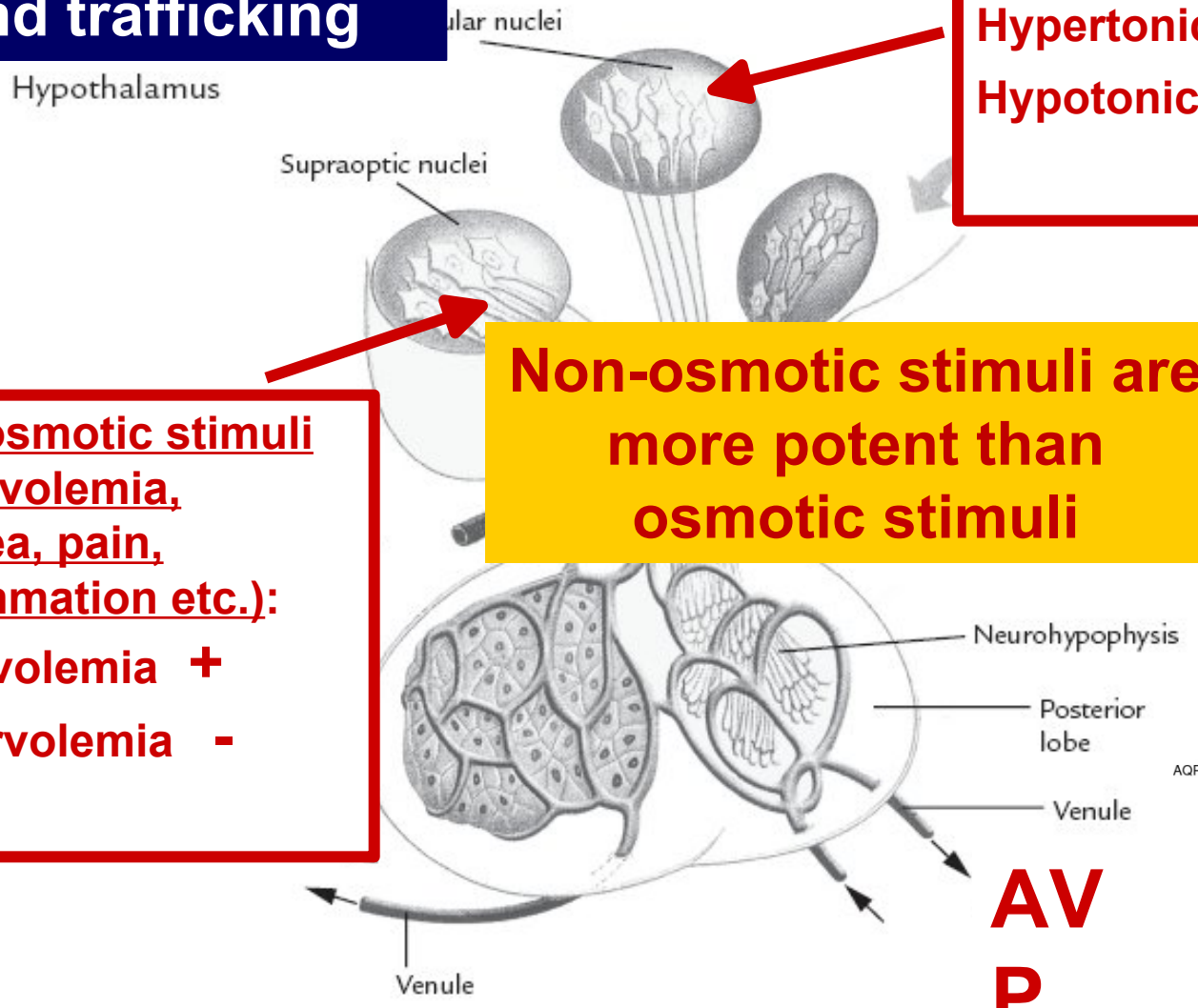
*Na excess can coexist but water is always in excess of sodium

1) AVP secretion and trafficking

Osmotic stimuli:

Hypertonicity +

Hypotonicity -



Non-osmotic stimuli are more potent than osmotic stimuli

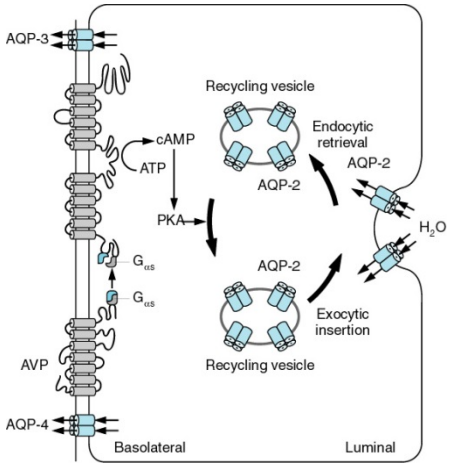
Non-osmotic stimuli (hypovolemia, nausea, pain, inflammation etc.):

Hypovolemia +

Hypervolemia -

AVP

2) Renal tubular cells



The brain-kidney axis is aimed at maintaining water balance homeostasis

Syndrome of inappropriate secretion of ADH (SIADH): inappropriate for the presence of hypotonicity

Table 3. Causes of SIADH

Malignancy	Lung disease	CNS disease	Drugs
Lung cancer (small cell, mesothelioma) Oropharynx GI-tract (stomach, duodenum, pancreas) Genitourinary tract Endocrine thymoma Lymphomas Sarcomas (Ewing)	Infections (bacterial, viral, tuberculosis, abscess) Cystic fibrosis Status asthmaticus	Infections (meningitis, encephalitis, AIDS, abscess) Stroke (CVA, subarachnoid, subdural) Hydrocephalus Brain tumour Head trauma Multiple sclerosis Guillain–Barré syndrome Shy–Drager syndrome Lewy body dementia	Antiepileptics Antidepressants (mainly SSRI's) Antipsychotics Anaesthetics Chemotherapy (ifosfamide, cylcofosfamide, vincristine) AVP analogues MDMA ('Ecstasy')

NDT Plus (2009) 2 [Suppl 3]: iii5–iii11

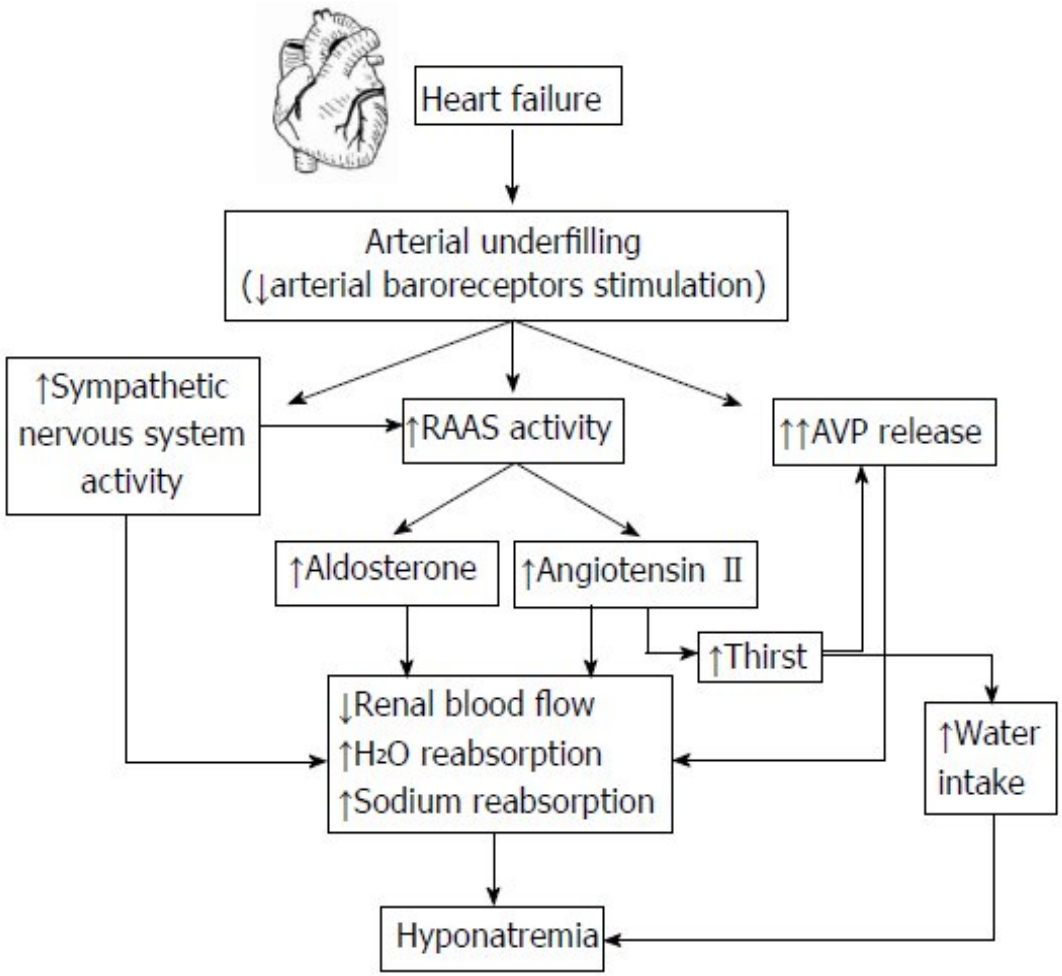
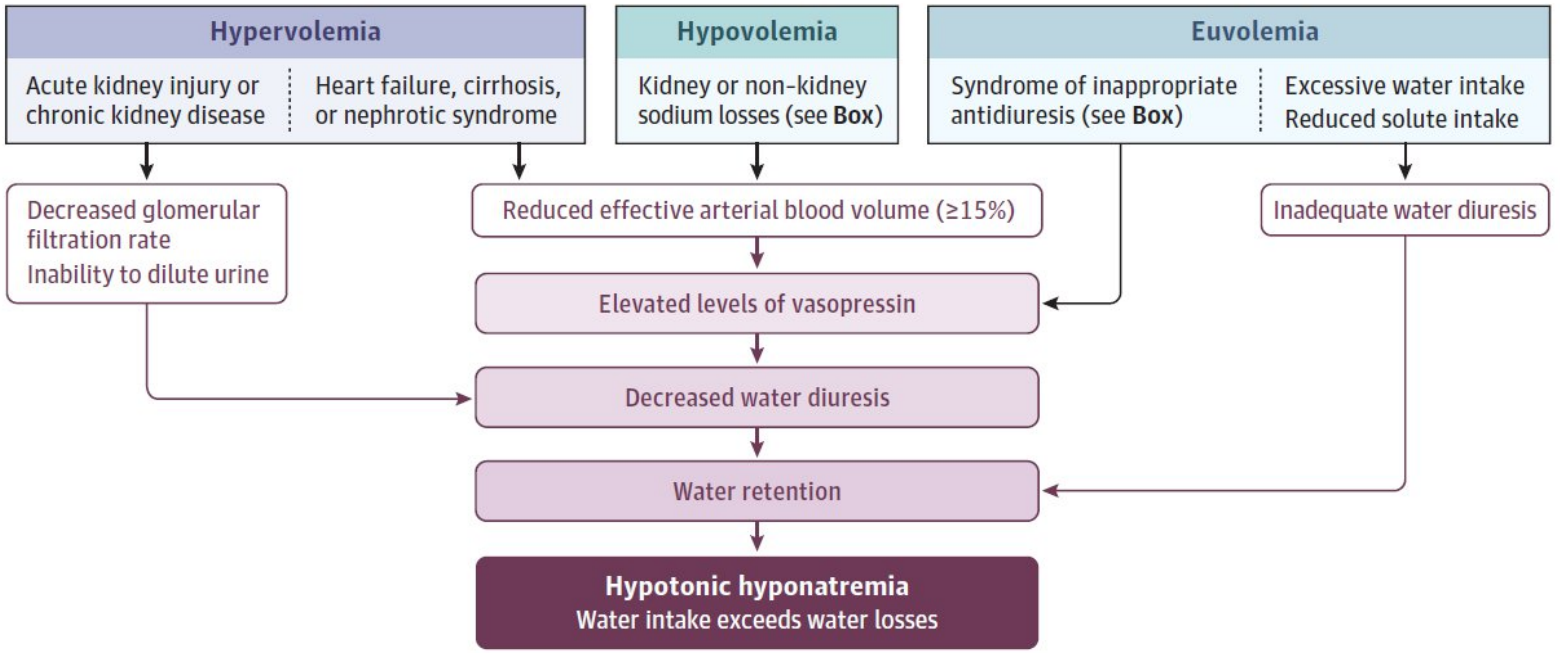


Figure 1 Mechanisms of hyponatremia in patients with heart failure.
RAAS: Renin-angiotensin-aldosterone system; AVP: Arginine-vasopressin.

Figure 1. Pathogenesis of Hypotonic Hyponatremia



Adroguè HJ et al., JAMA 2022;328:280-291

Differential diagnosis of hyponatremia

The conventional approach to DD is based on the evaluation of volume status of the patient

-Euvolemic hyponatremia: excess water, normal Na pool
-Hypovolemic hyponatremia: excess water in respect to a highly reduced Na pool
-Hypervolemic hyponatremia: excess water + excess Na pool (however more water than Na)

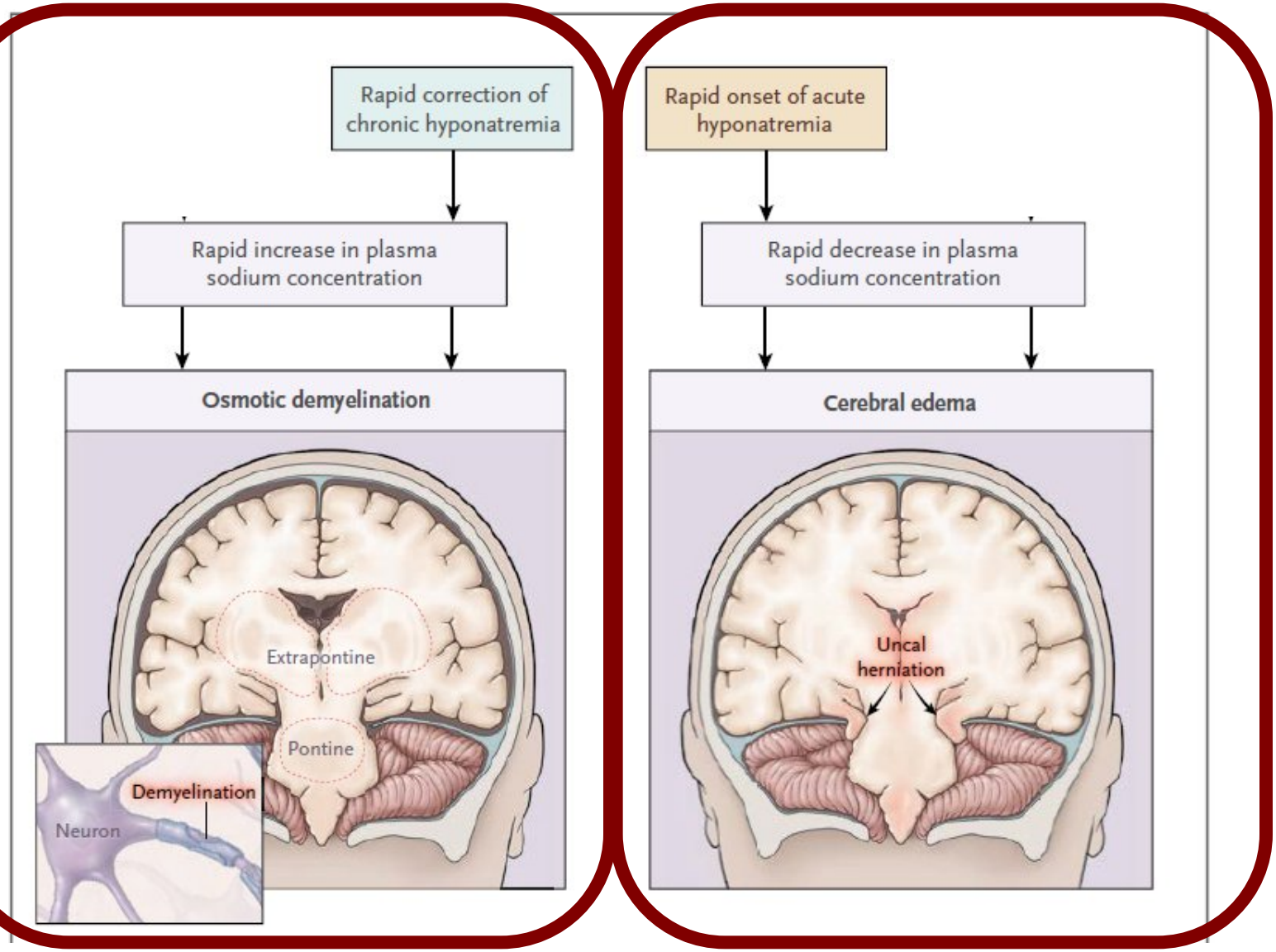
Pathophysiologic criteria for classification of hyponatremia aiming at treatment:

-Volume status

-Symptoms

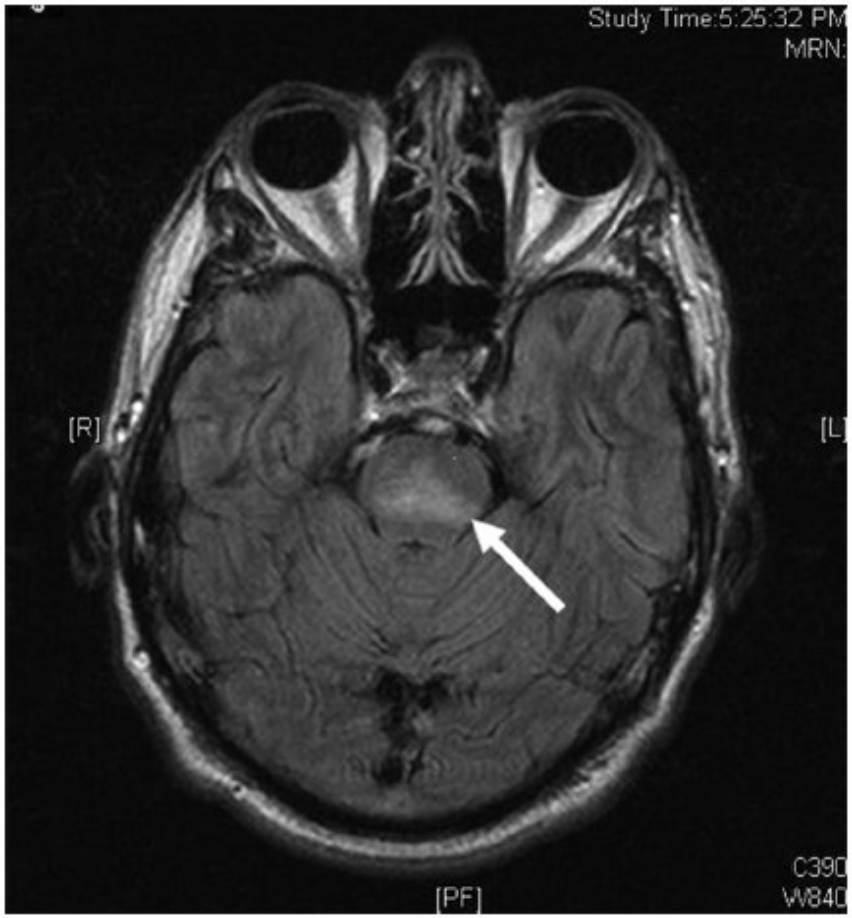
Patients with symptomatic hyponatremia have severe neurologic problems

Consequences of hyponatremia on CNS



N Engl J Med 2015;372:55-65

Osmotic Demielynation Syndrome



- Delayed, gradual neurologic deterioration (up to vegetative state, coma and death) appearing one to several days after a rapid correction of chronic hyponatremia
- Clinically defined, since imaging not always positive in the early phases
- Definite diagnosis by MR

Severerly symptomatic hypoNa vs «chronic hypoNa»: what is the best rate of correction?

No «best» rate can be defined a priori: it depends from the severity of symptoms, the type of hyponatremia (acute vs chronic), the underlying comorbidities, the accompanying electrolyte disorders

Hyponatremia

- Epidemiology and outcome
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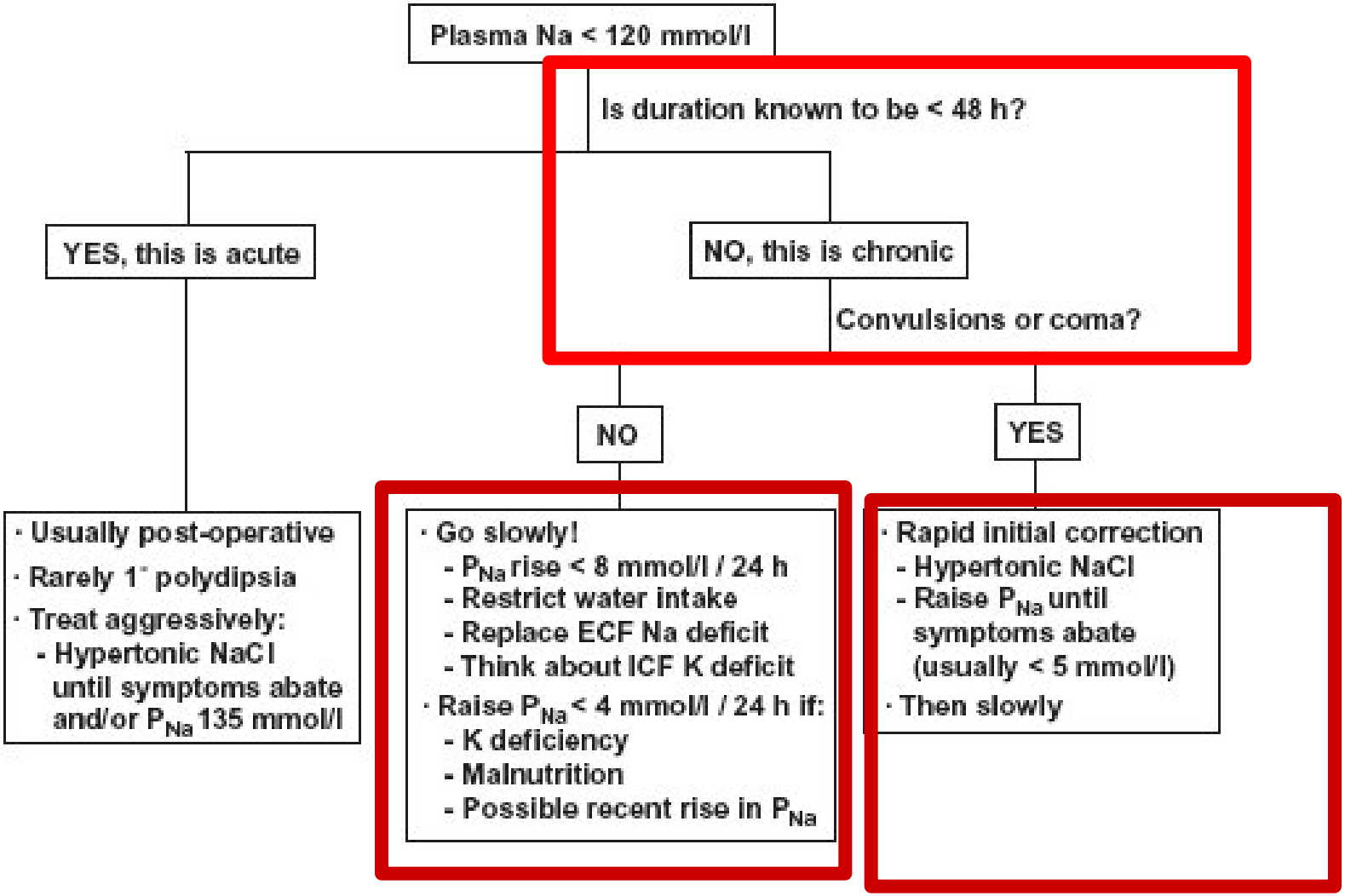
- The role of pharmacologic and non pharmacologic treatment

Determine if hyponatraemia is acute or chronic and design therapy accordingly



Hoorn EJ et al., Q J Med 2005; 98:529-540

Treatment of acute/symptomatic hyponatremia: practical aspects

- **First of all define the target and the rate of correction in mEq/hour for how many hours, then calculate how much of the saline solution available should be infused**

- **With 3% NaCl (513 mEq/L NaCl)**: to induce a correction rate of 1 meq/L/h using 3% saline, one should infuse the body weight as millilitres/hour ☾ a man with a BW of 70 Kg will increase serum Na by approximately 1 meq/hour when infused with 3% NaCl at a rate of 70 ml/hour (70 ml contain 35 mEq of NaCl)

- **With NaCl vials (20 mEq/10 ml):** to induce a correction rate of 1 meq/L/h using NaCl vials, one should infuse 20 ml/hour (i.e. 40 mEq) ☾ in a subject with a BW of 70 Kg and a total body water of 42 L, serum Na will increase by approximately 1 meq/hour

- **Potassium:** if K is needed (hypokalemia and K depletion), take it into account : if K is co-administered ☾ calculate it as sodium

- **Avoid fixed algorythms, be careful with formulas**

Therapy of chronic paucisymptomatic hyponatremia with normal or expanded ECF volume

- Water restriction
- Loop diuretics
- Urea (?)
- Vaptans

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

8.2. Nonpharmacological Management: Advanced HF

Recommendation for Nonpharmacological Management: Advanced HF

COR	LOE	RECOMMENDATION
2b	C-LD	1. For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain (1-4).

J Am Coll Cardiol 2022;79:e263-e421

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Fluid restrictions to less than 800-1000 mL/day may be indicated to achieve a negative water balance and treat hyponatraemia

European Heart Journal 2021; 42:3599-3726

Daily weight is the main parameter to check fluid balance

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

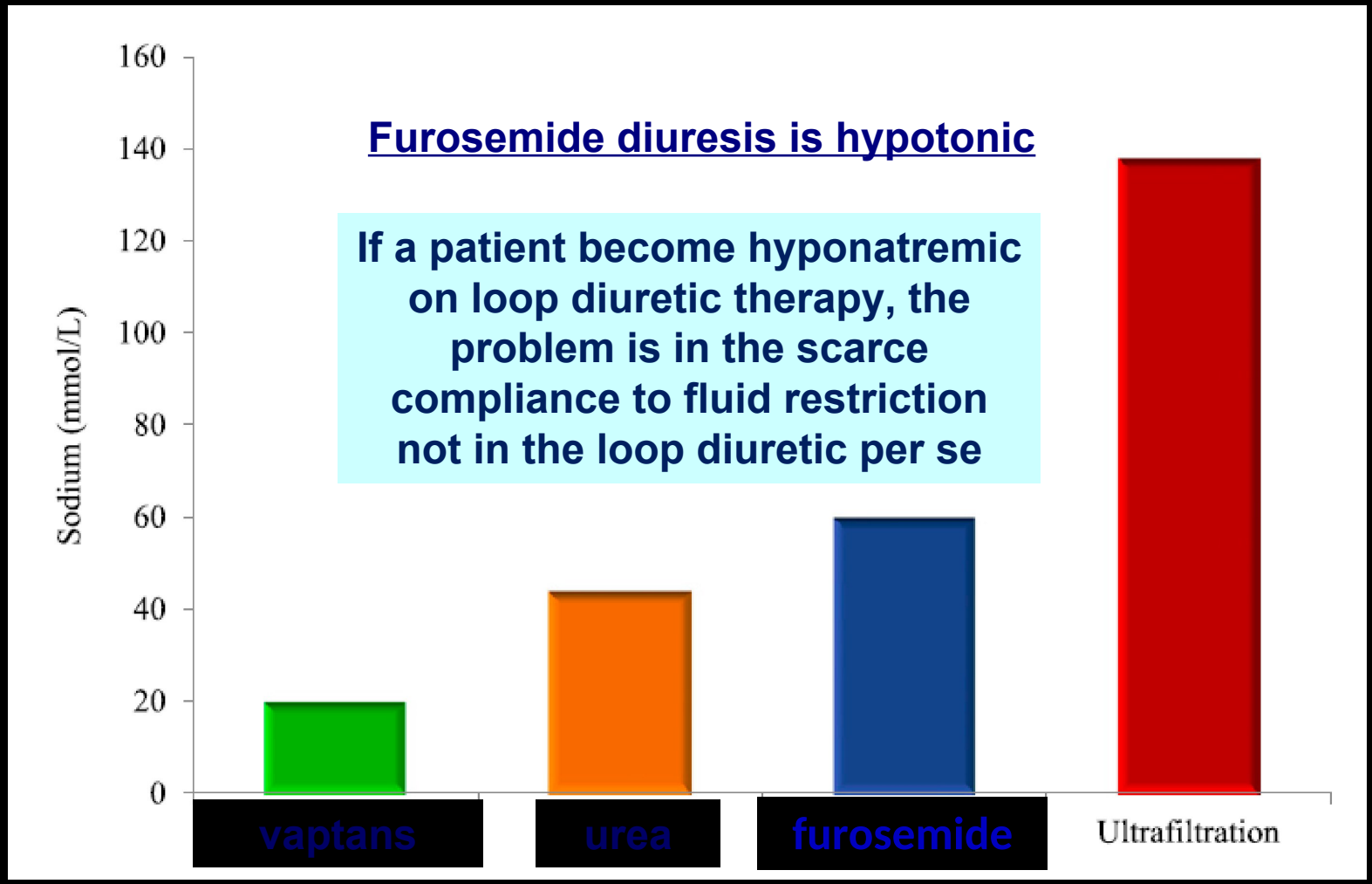
Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Table 12 Patient education and self-care

Education topic	Goal for the patient and caregiver	Professional behaviour and educational tools
		Consider and carefully discuss the benefits and deleterious effects of sleep medication.
Fluids	To avoid large volumes of fluid intake. A fluid restriction of 1.5–2 L/day may be considered in patients with severe HF/hyponatraemia to relieve symptoms and congestion. To avoid dehydration: where fluids are restricted, increase intake during periods of high heat/humidity and/or nau-sea/vomiting.	Provide information and discuss the advantages and disadvantages of fluid restriction. Advise to adapt fluid intake to weight, and in times of high heat and humidity, nausea/vomiting. Adjust advice during periods of acute decompensation and con-sider altering this advice towards end-of-life.
Healthy diet	To be able to prevent malnutrition and know how to eat healthily, avoiding excessive salt intake (>5 g/day) and maintaining a healthy body weight.	Discuss current food intake, role of salt, role of micronutrients. Discuss the need for supplementing in case of nutrient deficien-cies but there is no clear role for routine micronutrient supplementation.[321] Discuss maintaining a healthy body weight.
Alcohol	To be able to abstain from or avoid excessive alcohol intake, especially for alcohol-induced CMP.	Tailor alcohol advice to aetiology of HF; e.g. abstinence in alco-holic CMP.

280 mm

European Heart Journal 2021; 42:3599-3726



Comparison of sodium removal with various treatment options. Whereas ultrafiltration extracts isotonic fluid from plasma, pharmacologic agents produce hypotonic urine containing lower concentrations of sodium. Vaptans, vasopressin receptor antagonists

Clin J Am Soc Nephrol 8: 1816–1828, 2013

Box 2. Mechanisms of Impaired Maximal Free-Water Excretion Induced by Thiazides

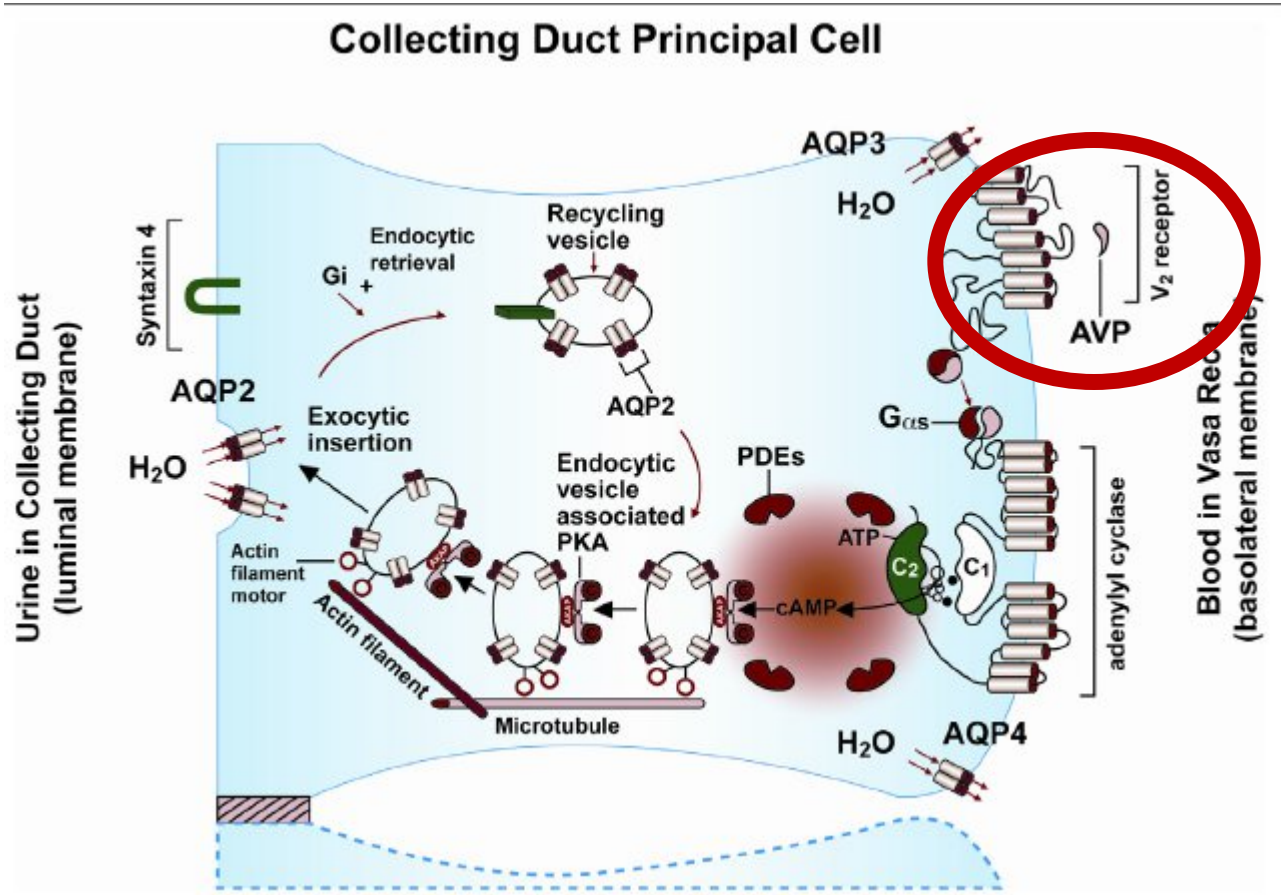
1) Reduced distal delivery of filtrate
   - Reduced GFR
   - Enhanced proximal tubule reabsorption
2) Reduced solute load (urea)
3) Inhibition of NCC impairing maximal dilution
4) Increased collecting duct water permeability
   - ADH dependent: hemodynamic ADH release mediated by diuretic-induced volume depletion
   - ADH independent:
     - ◇ Increased luminal PGE_2 from enhanced production and reduced prostaglandin transporter activity
     - ◇ Direct effect of thiazides on collecting duct permeability independent of ADH
     - ◇ Increased medullary tonicity fostering water reabsorption in the absence of ADH

Note: One or more of these mechanisms can exist in any given patient.
Abbreviations: ADH, antidiuretic hormone; GFR, glomerular filtration rate; NCC, sodium chloride cotransporter; PGE_2, prostaglandin E_2.

Thiazide diuretics directly induce hyponatremia (diuresis is hypertonic in Na and K)

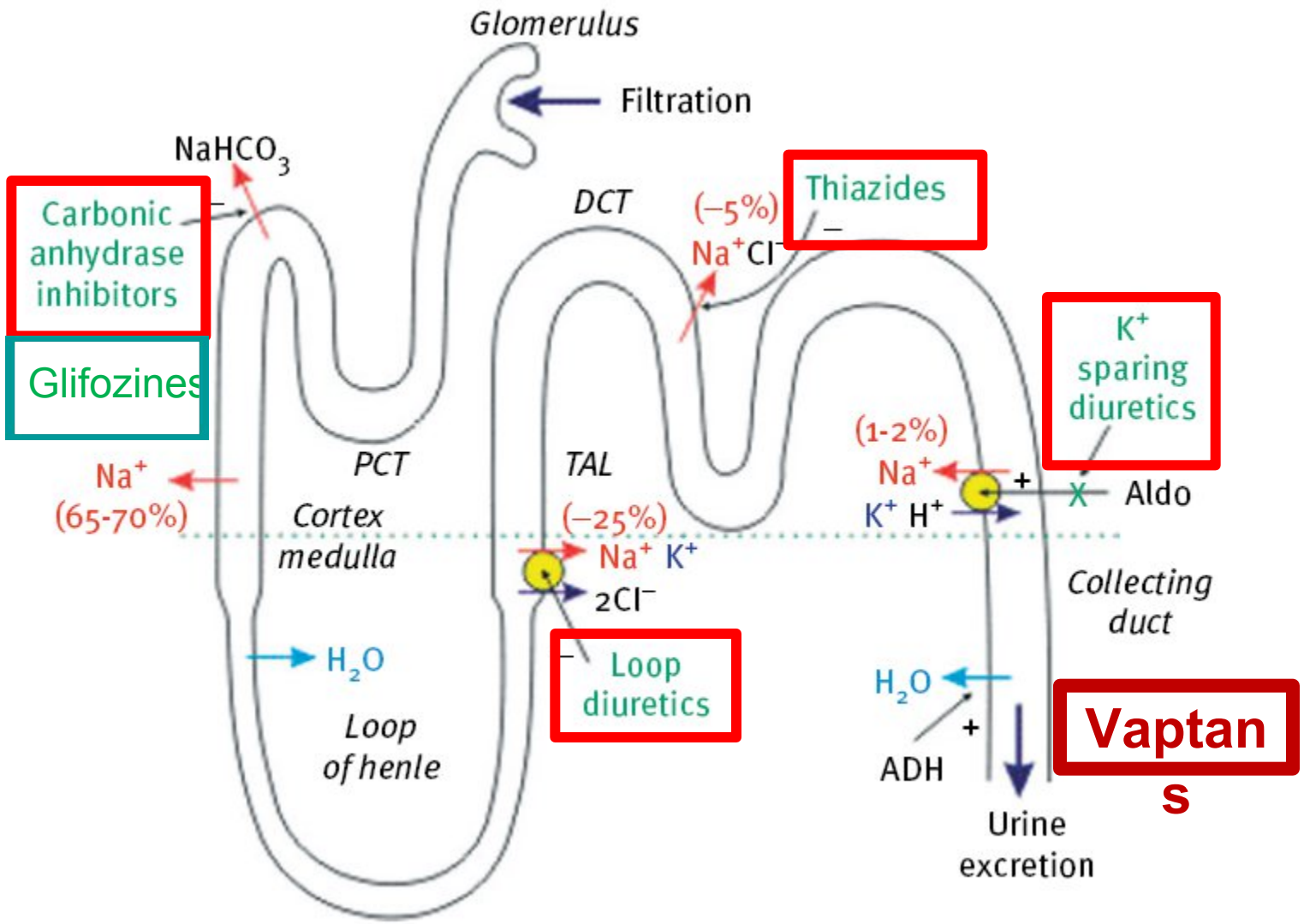
Filippone EJ et al., Am J Kidney Dis 2020; 7:256-264

Vaptans are the antagonists of vasopressin receptors



The American Journal of Medicine (2013) 126, S1-S42

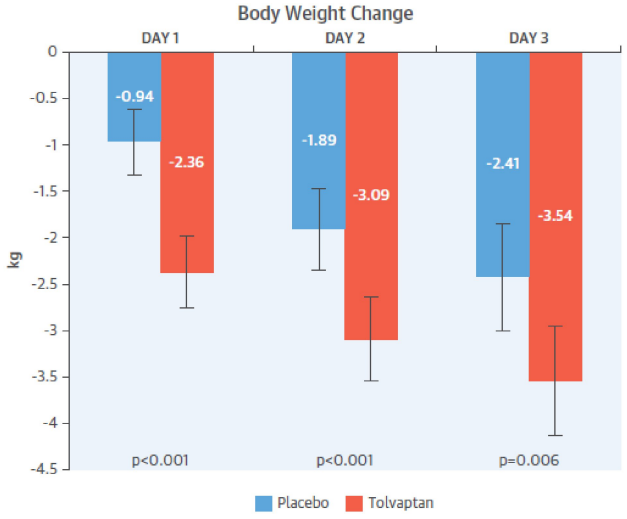
The rational pharmacodynamic/pharmacokinetic approach to diuretic use in heart failure: sequential nephron block

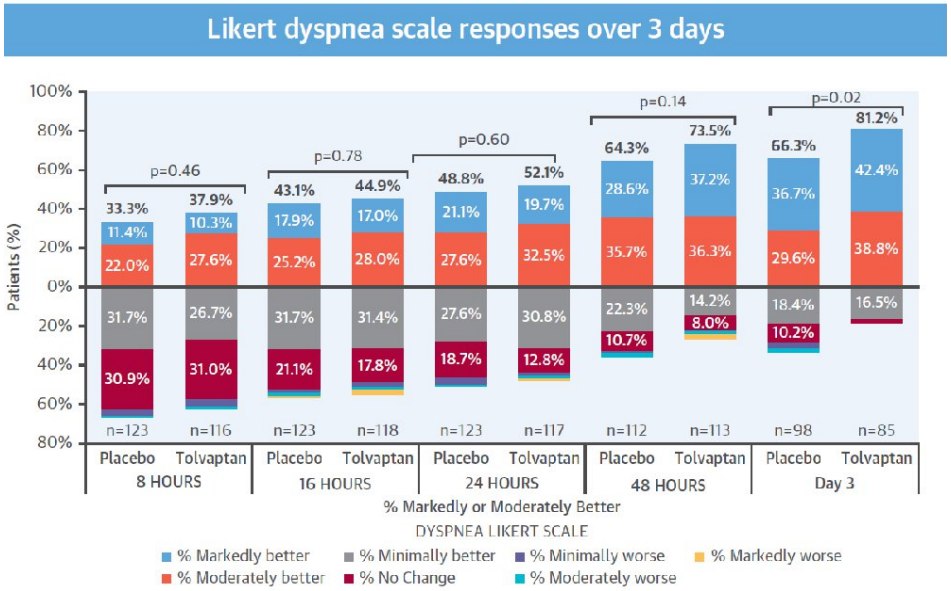


Take home messages

- Hyponatremia is a frequent finding among HF patients
- Hyponatremia is classified both by patient' volume status and the presence of severe CNS symptomatology/timing
- In **symptomatic hyponatremia** rapid, partial increase in serum Na levels to limit cerebral edema; iIn **chronic symptomatic hyponatremia** slow correction to avoid iatrogenic neurologic injury (ODS), based on the pathogenesis
- Fluid restriction is important in the prevention and treatment of hyponatremiain normovolemic and hypervolemic forms of hyponatremia; however it should be integrated with other therapies
- In-depth knowledge of pathophysiology the basis for a safe approach

Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload





Konstam, M.A. et al. J Am Coll Cardiol. 2017;69(11):1409-19.

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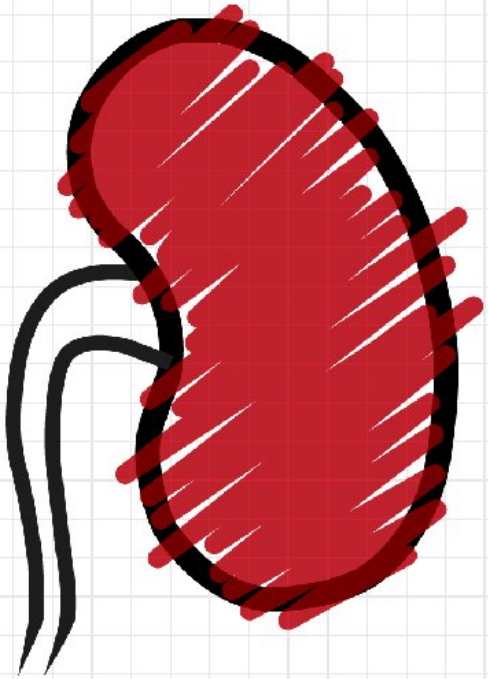

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Parma, 21-23 Giugno 2020

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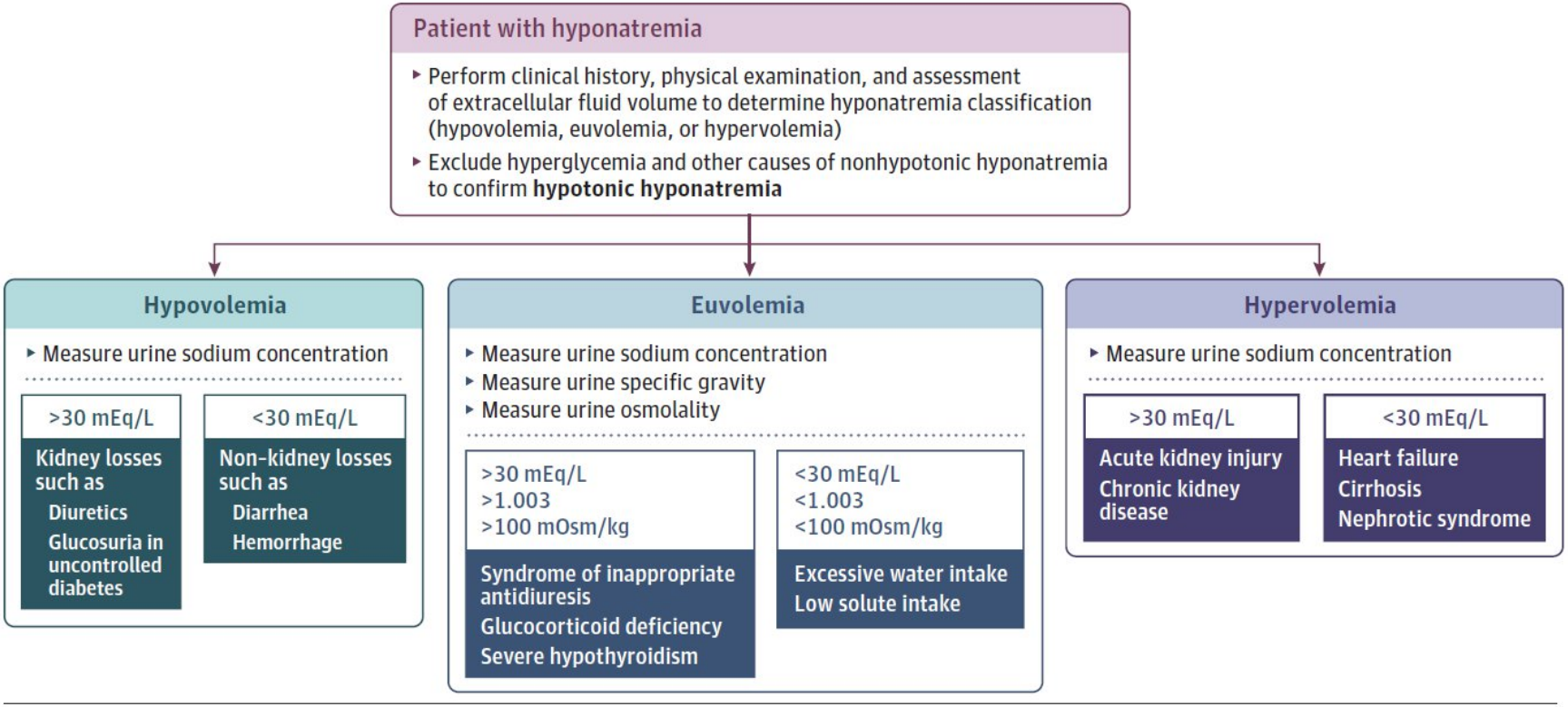
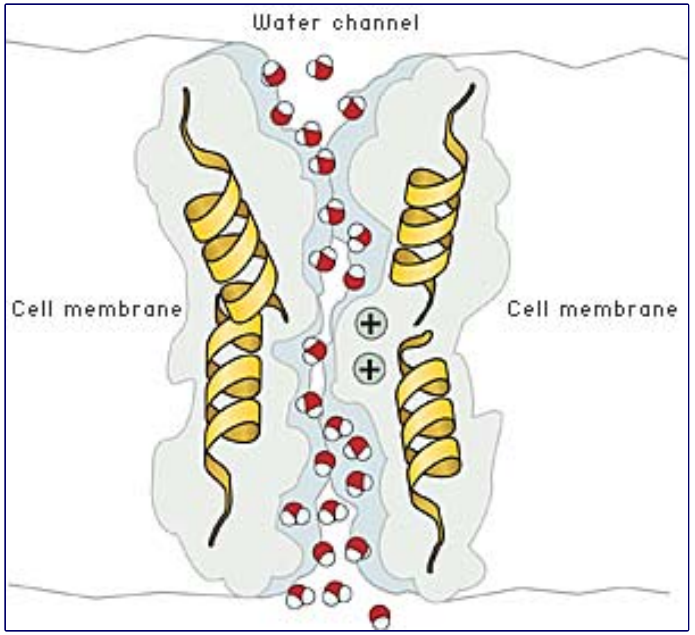
Figure 2. Clinical Approach to Hypotonic Hyponatremia



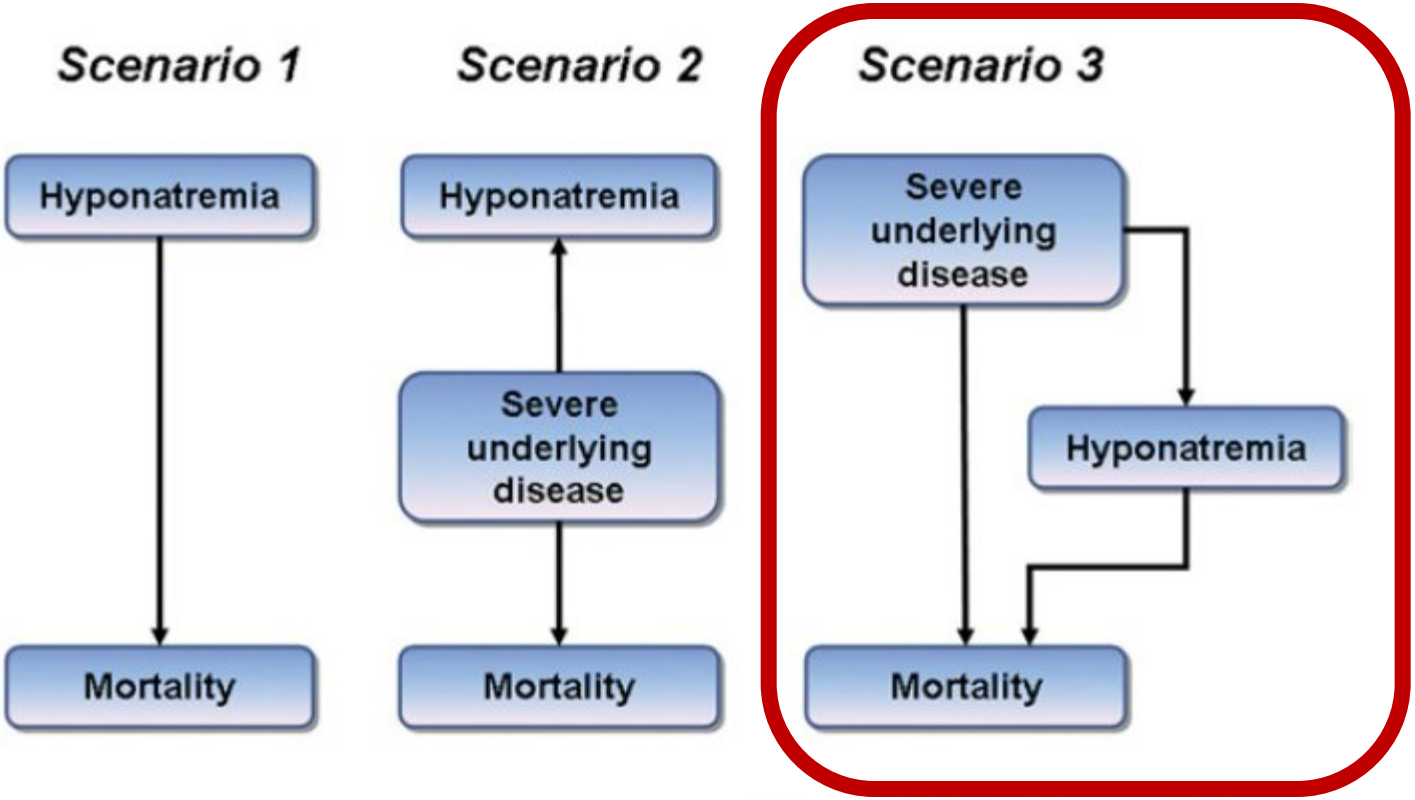
Adroguè HJ et al., JAMA 2022;328:280-291

AVP acts in the kidney through water channels (aquaporins) in the membranes of tubular cells



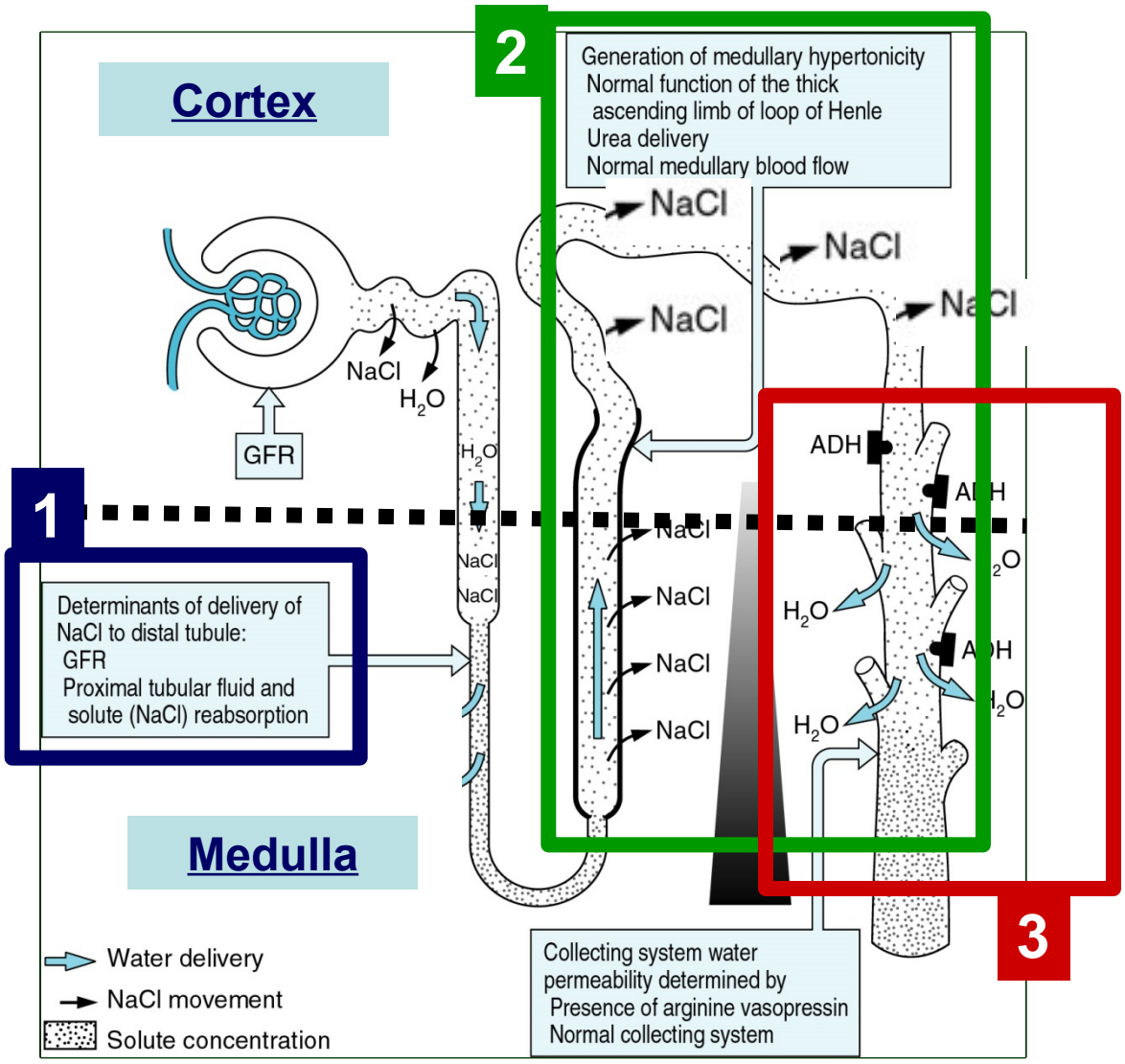
Hyponatremia and Mortality: Moving Beyond Associations

Ewout J. Hoorn, MD, PhD, and Robert Zietse, MD, PhD



Am J Kidney Dis. 2013;62(1):139-149

Excretion of large volume of diluted urine: what is needed in the kidney



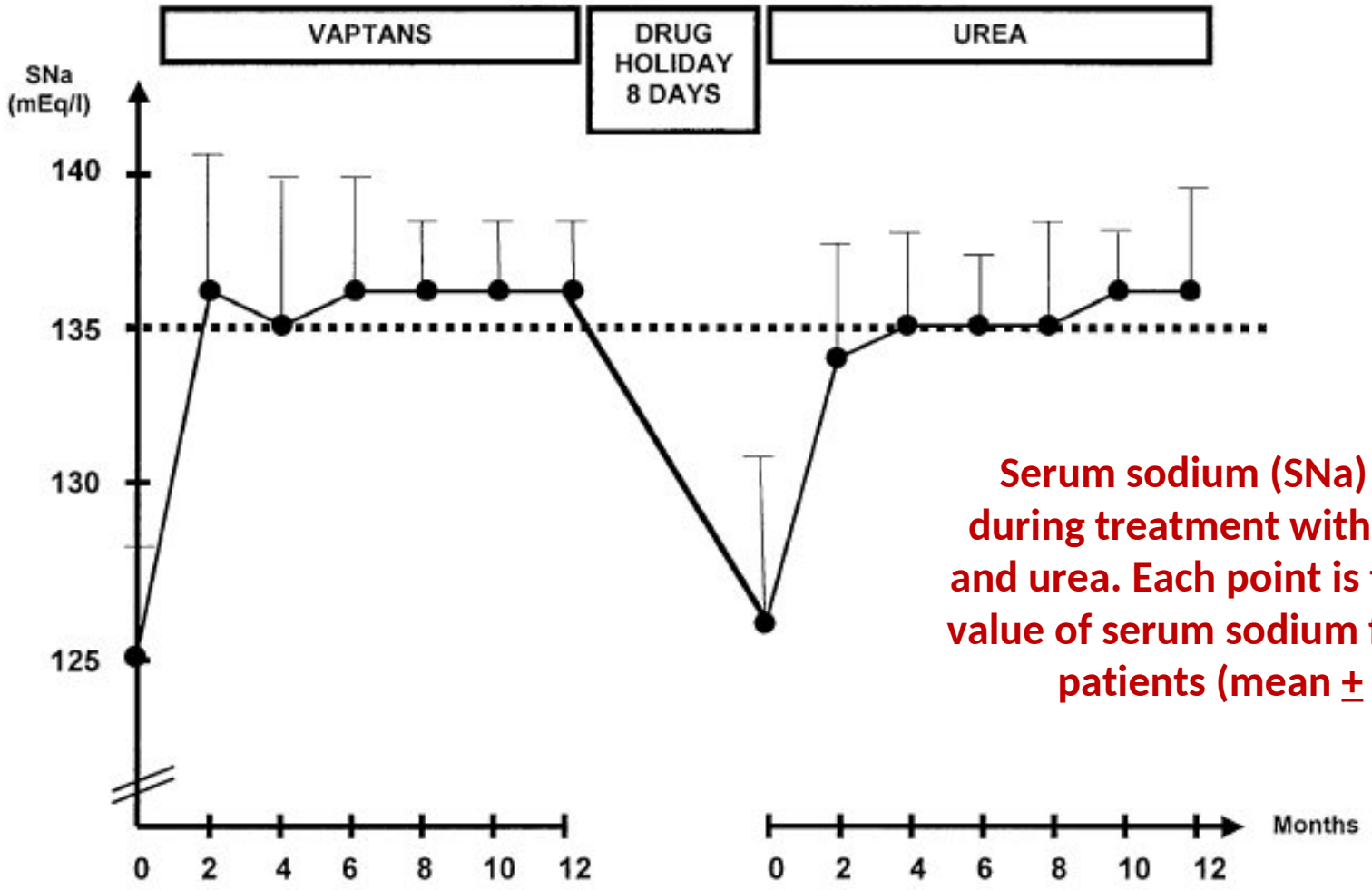
1) Distal delivery of filtrate (fluid as preurine) = GFR – volume of water reabsorbed in the proximal tubule (all subsequent nephron segments are impermeable to water when vasopressin fails to act): **normally about 14-21 L/day**

2) Reabsorption of Na and Cl in nephron segments that are impermeable to water ☾ preurine is made hypotonic, and medulla is made hypertonic

3) AVP suppressed by low serum Na and absence of nonosmotic stimuli ☾ collecting tubules are impermeable to water

Efficacy and Tolerance of Urea Compared with Vaptans for Long-Term Treatment of Patients with SIADH

Alain Soupart,† Michel Coffernils,* Bruno Couturier,† Fabrice Gankam-Kengne,† and Guy Decaux†*



Serum sodium (SNa) values during treatment with vaptans and urea. Each point is the mean value of serum sodium for the 12 patients (mean ± SD)

Clin J Am Soc Nephrol 7: 742–747, 2012.

Urea for the Treatment of Hyponatremia

Helbert Rondon-Berrios,[1] Srijan Tandukar,[1] Maria K. Mor,[2,3] Evan C. Ray,[1] Filitsa H. Bender,[1] Thomas R. Kleyman,[1,4,5] and Steven D. Weisbord[1,3,6]

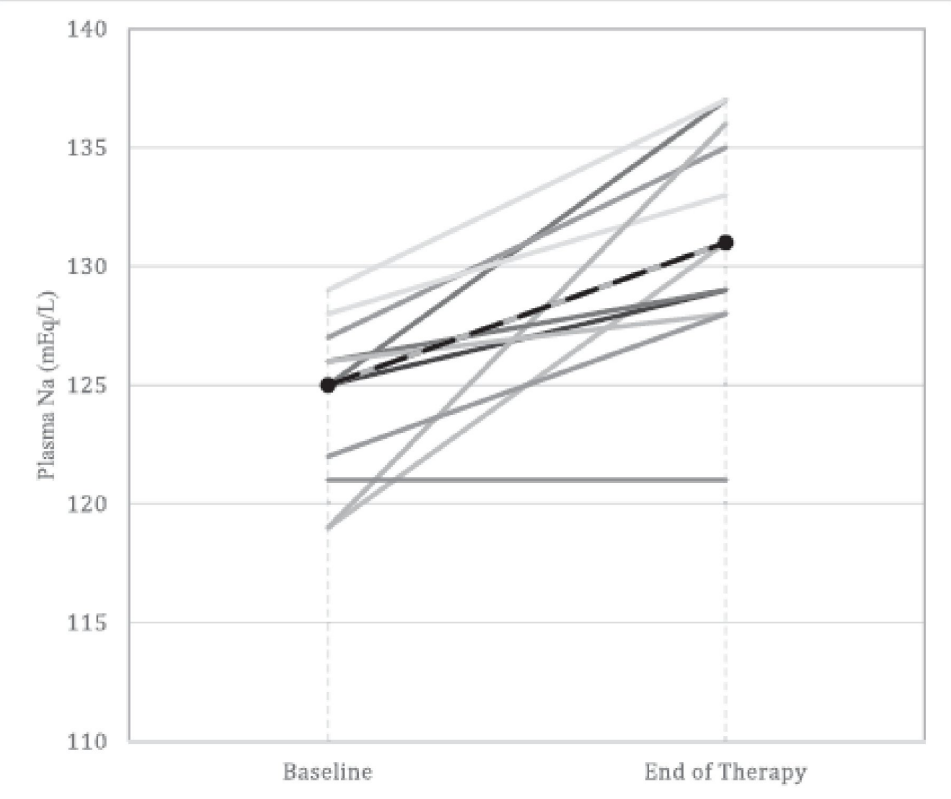


Figure 1. | Increase in plasma sodium (Na) from baseline to the completion of therapy among urea only–treated patients.

Clin J Am Soc Nephrol 13: 1627–1632, 2018.

Decaux et al. Critical Care 2010, 14:R184
http://ccforum.com/content/14/5/R184

CRITICAL CARE

RESEARCH Open Access

Treatment of euvolemic hyponatremia in the intensive care unit by urea

Guy Decaux[1*], Caroline Andres[1], Fabrice Gankam Kengne[1], Alain Soupart[1,2]

-SNa increased more than 12 mmol/L the first day in 12/35 patients (37%) and in 13 patients the increase in SNa was higher than 18 mol/L/48 hr

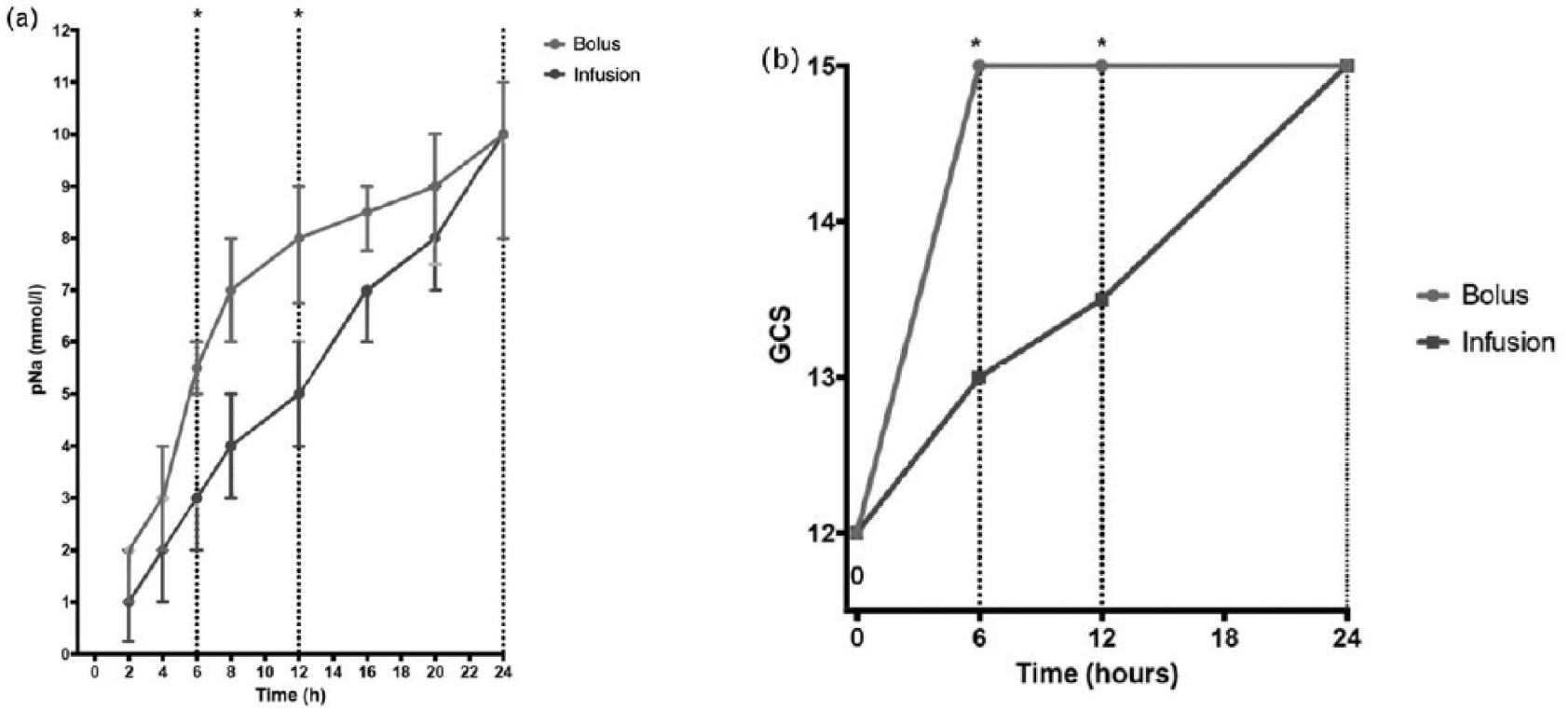
-In two of these patients the intensivist lowered the SNa again by giving desmopressin (DDAVP) and water

-No cases of clinical osmotic demyelination syndrome (ODS) developed

The best path to patient' safety when approaching hyponatremia

Know the pathophysiology

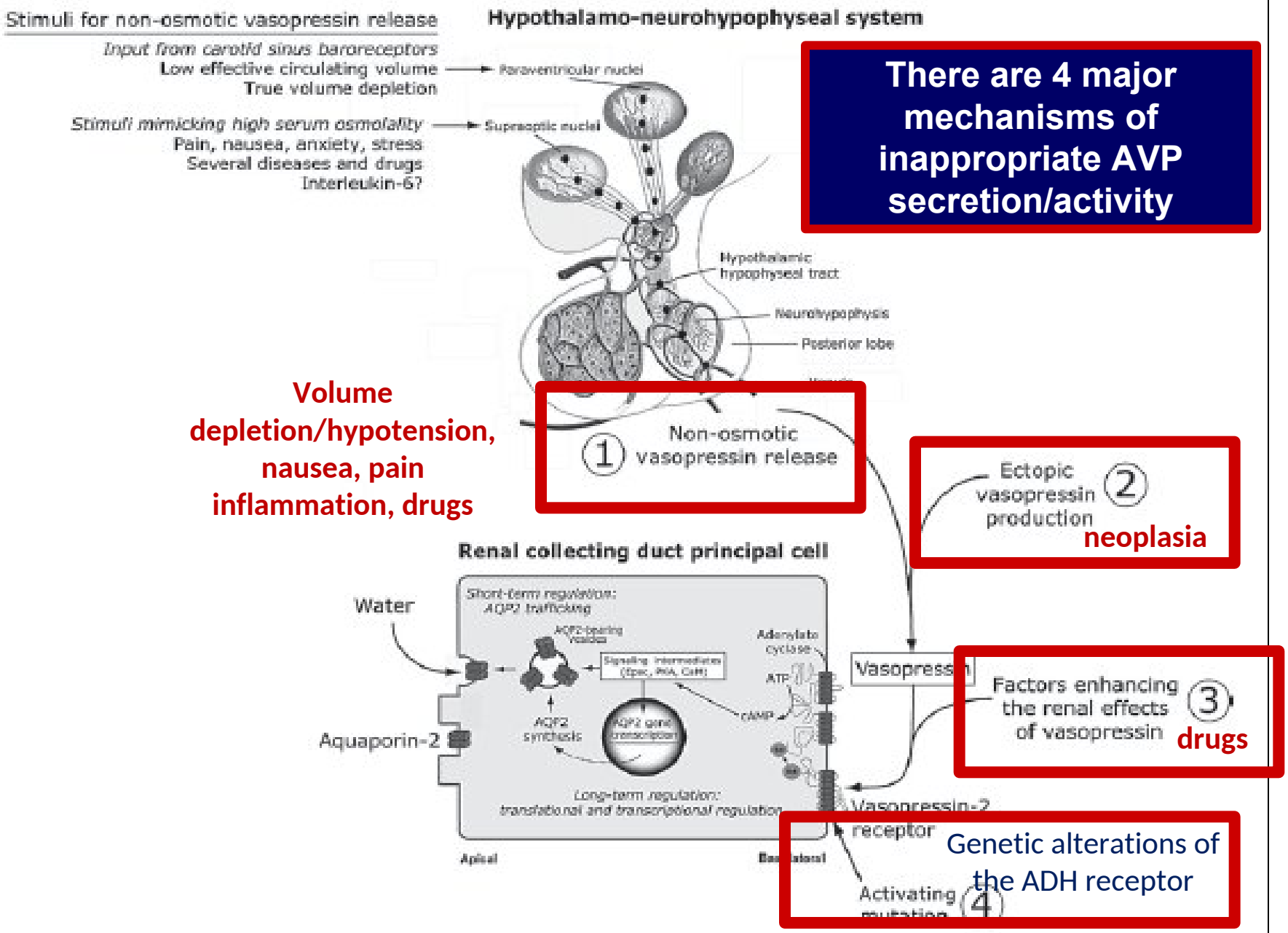
Hypertonic saline in hyponatremia: bolus vs continuous infusion

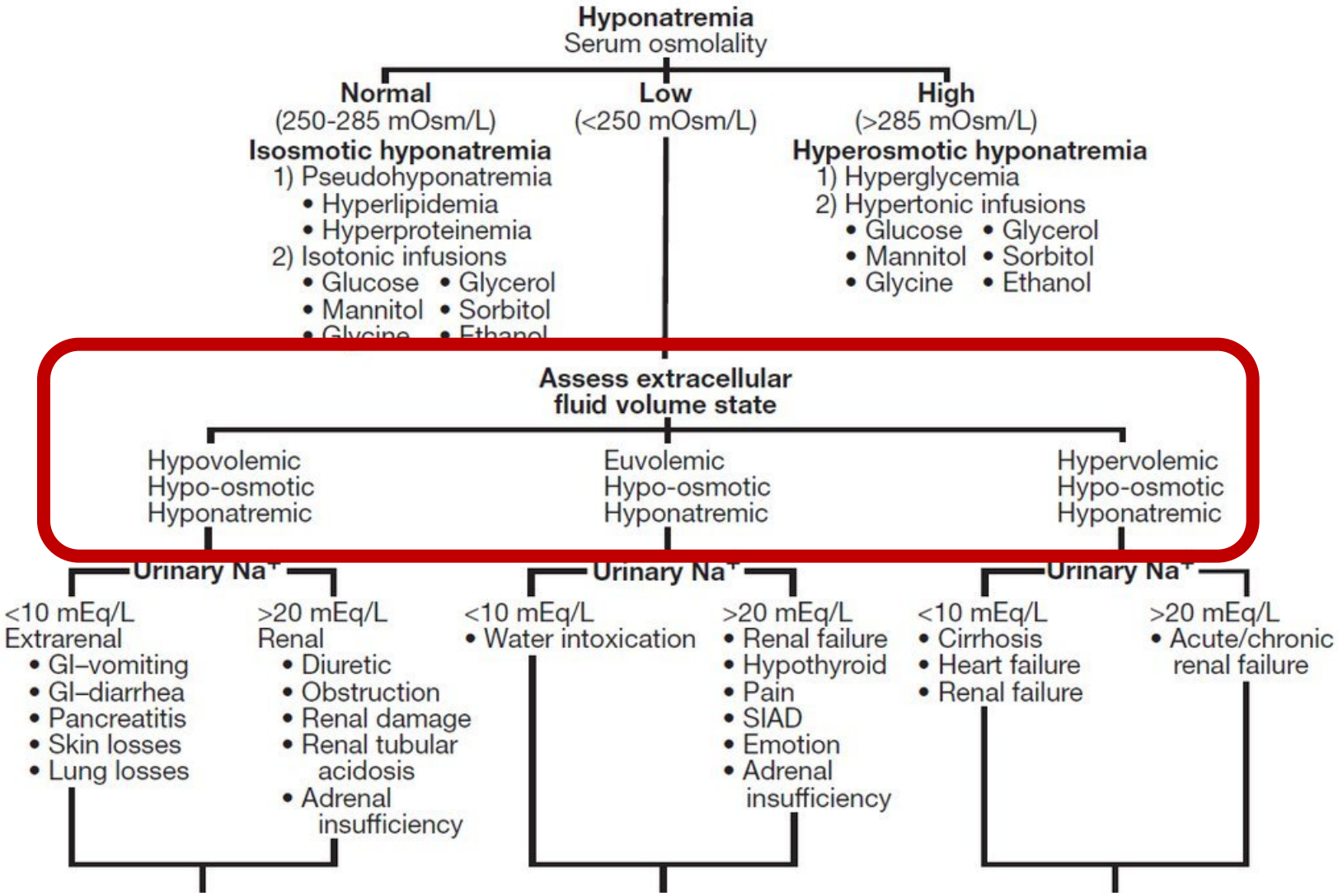


Serial measurements of plasma sodium (a) and serial assessments of Glasgow Coma Scale (b) in patients with symptomatic hyponatremia treated with hypertonic saline as a bolus (light grey line) or as a continuous infusion (dark grey line)

Garray A et al., J Clin Endocr Metab 2020, in press

There are 4 major mechanisms of inappropriate AVP secretion/activity





Diagnosis and Management of Hyponatremia. GI indicates gastrointestinal tract; Na, sodium; SIAD, syndrome of inappropriate antidiuresis.

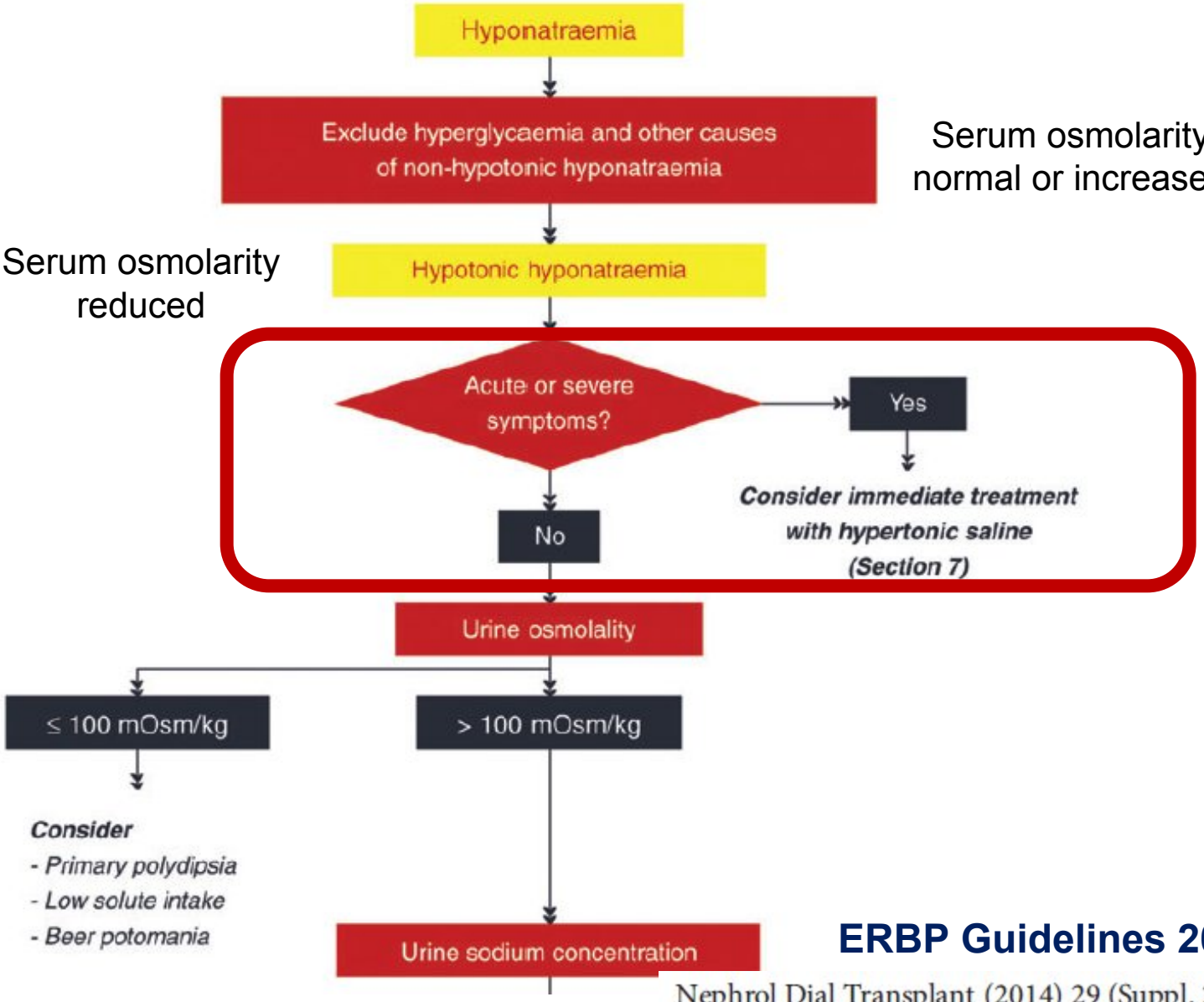
Source : Mayo Clinic Internal Medicine 8th

Studies on AVP antagonists in patients with acute decompensated heart failure and hyponatraemia

Study	Drug; [Total no. of patients; subjects on placebo or vaptans]	Outcome
Udelson et al (2001) [34]	Conivaptan [142; 38 placebo vs 37(10mg), 32(20mg), 35(40mg)]	Dose-dependent diuresis, no change in BP or serum electrolytes. Reduction in PCWP and right atrial pressure.
Palmer et al (2016) [41]	Conivaptan [251; 37(20mg) vs 314(40mg)]	Both dose regimens equally efficacious and well tolerated.
Gheorghiade et al (2003) [36]	Tolvaptan [254; 63 placebo vs 64(30mg), 64(45mg), 63(60mg)]	No change in BP, HR, serum potassium or renal function. Increased urine output and restoration of serum Na^+ levels.
Schrier et al (2006) [42]	Tolvaptan [448; 225(15mg then 30mg then 60mg depending on serum Na^+ level)]	Effective dose-dependent restoration of serum Na^+ levels.
Konstam et al (2007) [31]	Tolvaptan [4133; 2061 placebo vs 2072(30mg)	Short-term benefits of weight loss, restoration of Na^+ levels, improvement in symptoms with no change in renal function. No mortality or morbidity benefits.
Udelson et al (2007) [33]	Tolvaptan [240; 120 placebo vs 120(30mg)	No change in renal function or serum electrolytes. No change in left ventricular remodelling. Long-term use is safe and well-tolerated with better mortality and morbidity outcomes.
Nakada et al (2015) [43]	Tolvaptan [206; 180mg usual diuretics vs 26 tolvaptan]	Patients who benefited from Tolvaptan were more likely those who had severe tricuspid regurgitation, increased left atrial size and dilated inferior vena cava on echocardiography.
Tanaka et al (2015) [44]	Tolvaptan [20; all on Tolvaptan]	No change in renal function. Effective dose-dependent diuresis.
Shanmugam et al (2016) [45]	Tolvaptan [51; 26 placebo vs 25(15mg)	Effective diuresis and restoration of Na^+ levels without change in renal function.

Tee SL et al, Int Med 2020; 50:659-666

Algorhytm for the differential diagnosis of hyponatremia (1)



ERBP Guidelines 2014

Nephrol Dial Transplant (2014) 29 (Suppl. 2): ii1–ii39

Potential use of tolvaptan in selected clinical cases of hyponatremia

- Cancer patients with mild to moderate hyponatremia and life expectancy > 6 months, in whom water restriction may be not effective/tolerated/feasible
- Epileptic patients with mild to moderate hyponatremia, in whom anti-epilectic drugs cannot be withdrawn or changed
- Patients with heart failure, as an adjunct to loop diuretics and thiazides?

Table 1. Guideline-Recommended Treatment of Severely Symptomatic Hyponatremia With Hypertonic Saline

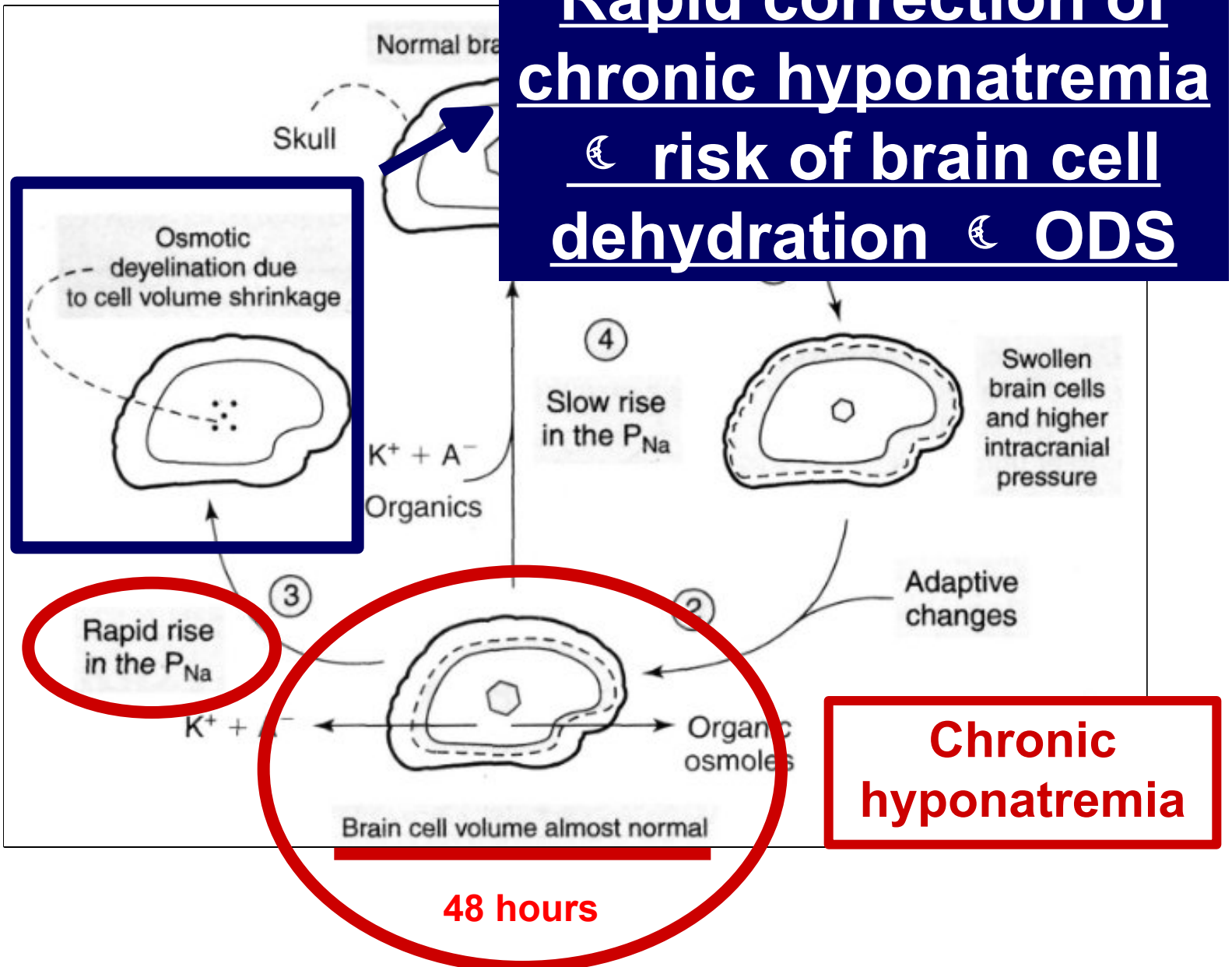
	US guideline	European guideline
Patients requiring treatment with hypertonic saline	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications
Rate of increase in serum sodium level desired (goal for change in serum sodium level)	4-6 mEq/L within 1-2 h	5 mEq/L within 1-2 h
Recommended treatment with hypertonic saline (3% sodium chloride)	100-mL bolus via central or peripheral vein over 10 min up to 3 times as needed to attain desired serum sodium level	150-mL bolus via central or peripheral vein over 20 min, repeating this step twice until the desired serum sodium level is achieved
Recommended frequency of measuring serum sodium level	After each bolus and every 4-6 h over the first 24 h	After each bolus and every 6 h over the first 24 h
Recommended increase in serum sodium level that should not be exceeded (correction limit)	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]

[a] Other experts recommend a more strict correction limit of 8 mEq/L during any 24-hour period.

[b] Other experts recommend a more strict correction limit of 6 mEq/L during any 24-hour period.

Adroguè HJ et al., JAMA 2022;328:280-291

Rapid correction of chronic hyponatremia ☾ risk of brain cell dehydration ☾ ODS



Simple goals for the treatment of severe chronic hyponatremia

Rule of Sixes:

- Six-a-day makes sense for safety — **Acute and chronic**
- Six in six hours for severe sxs and *stop* — **Acute/symptomatic**

Explanation:

For all patients with chronic hyponatremia, the goal is 6 mEq/L during the initial 24 hours. For those with severe symptoms (seizure, severe delirium, and unresponsiveness), the goal is preloaded in the first six hours, postponing subsequent efforts to increase serum sodium level until the next day.

Abbreviation: sx, symptom.

Sterns RH et al., Am J Kidney Dis 2010; 56:774-779