HYPONATREMIA IN HEART FAILURE: TO LOAD OR UNLOAD?

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HYPONATREMIA

Plasma sodium level < 135 mEq/L

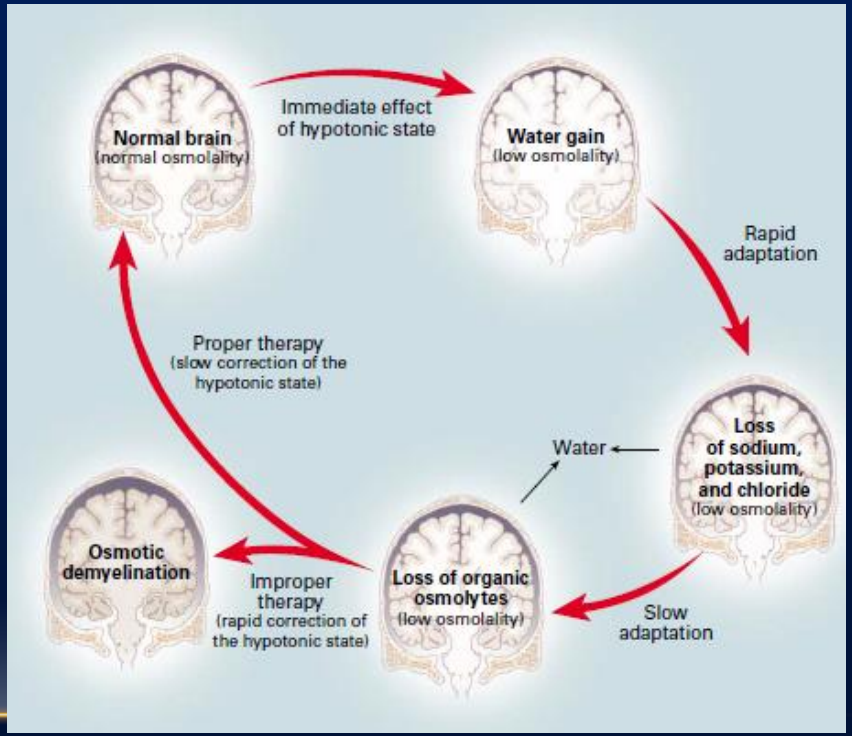
- Mild : 130-134 mEq/L
- Moderate : 125-129 mEq/L
- Severe : < 125 mEq/L

- The most common electrolyte disorder in hospitalized patients

Mohan et al. Am J Med 2013; 126: 1127-37

WHY IT IS IMPORTANT

- Headache
- Irritability
- Nausea/vomiting
- Mental slowing
- Unstable gait/falls
- Confusion/delerium
- Disorientation
- Stupor/coma
- Conculsions
- Respiratory arrest



SODIUM HOMEOSTASIS

Antiduretic hormone (ADH/AVP)

- osmoreceptor and baroreceptor
- regulate water excretion

RAA system (Aldosterone)

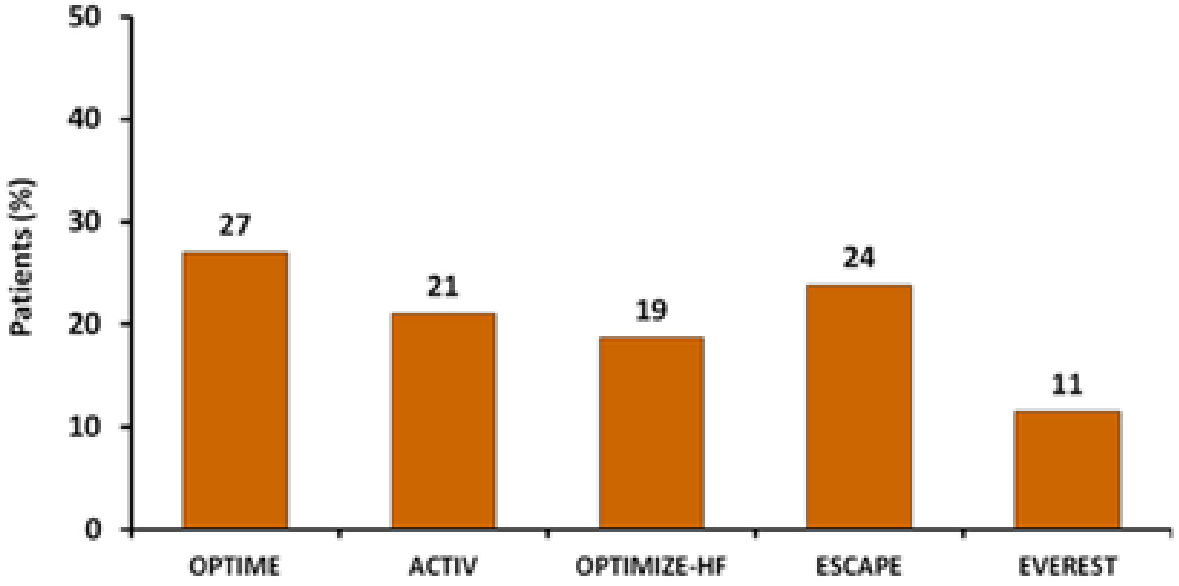
- baroreceptor
- regulate sodium excretion

Atrial natriuretic peptide

- baroreceptor
- regulate sodium and water excretion

Prevalence of Hyponatremia in HF

- Hyponatremia (serum sodium < 135 mEq/L) is common in patients hospitalized with HF.



HF = heart failure

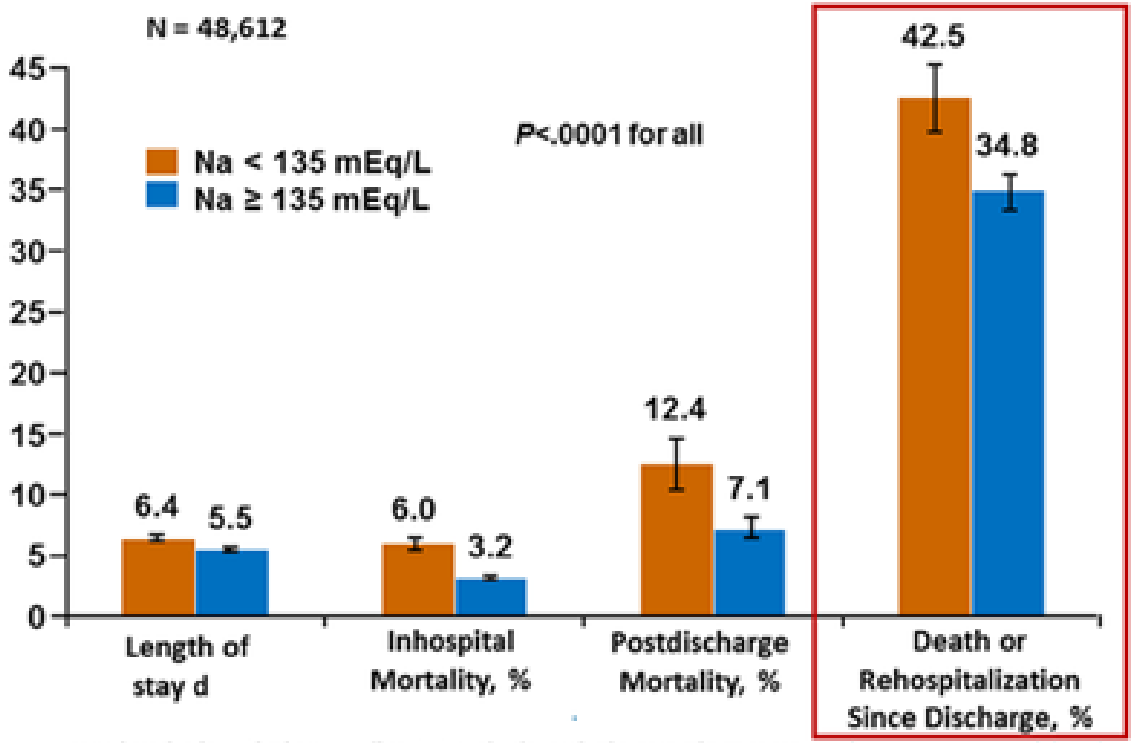
Klein L, et al. *Circulation*. 2005;111:2454-2460; Gheorghiade M, et al. *JAMA*. 2004;291:1963-1971; Gheorghiade M, et al. *Eur Heart J*. 2007;28:980-988; Gheorghiade M, et al. *Arch Intern Med*. 2007 ;167:1998-2005; MA Konstam, personal communication, October 2011

HYPONATREMIA IN HEART FAILURE PATIENTS

- High mortality
- High recurrent hospitalization
- High morbidity
- Advance disease

→ bad prognosis

OPTIMIZE-HF: Hyponatremia Associated With Rehospitalization in HF Patients



From Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*.2007;28:980-8. Republished with permission.

Heart Failure and Hyponatremia

Decreased cardiac output

Neurohormonal activation

- SNS
- RAS
- Vasopressin

Increased venous pressure

Diminished blood flow

Decreased renal perfusion

Impaired renal function

Increased water and sodium retention (congestion)

Decreased cardiac performance

PATHOPHYSIOLOGY OF HYPONATREMIA IN ADHF

TABLE 1 Pathophysiology of Hyponatremia in Acute Decompensated Heart Failure

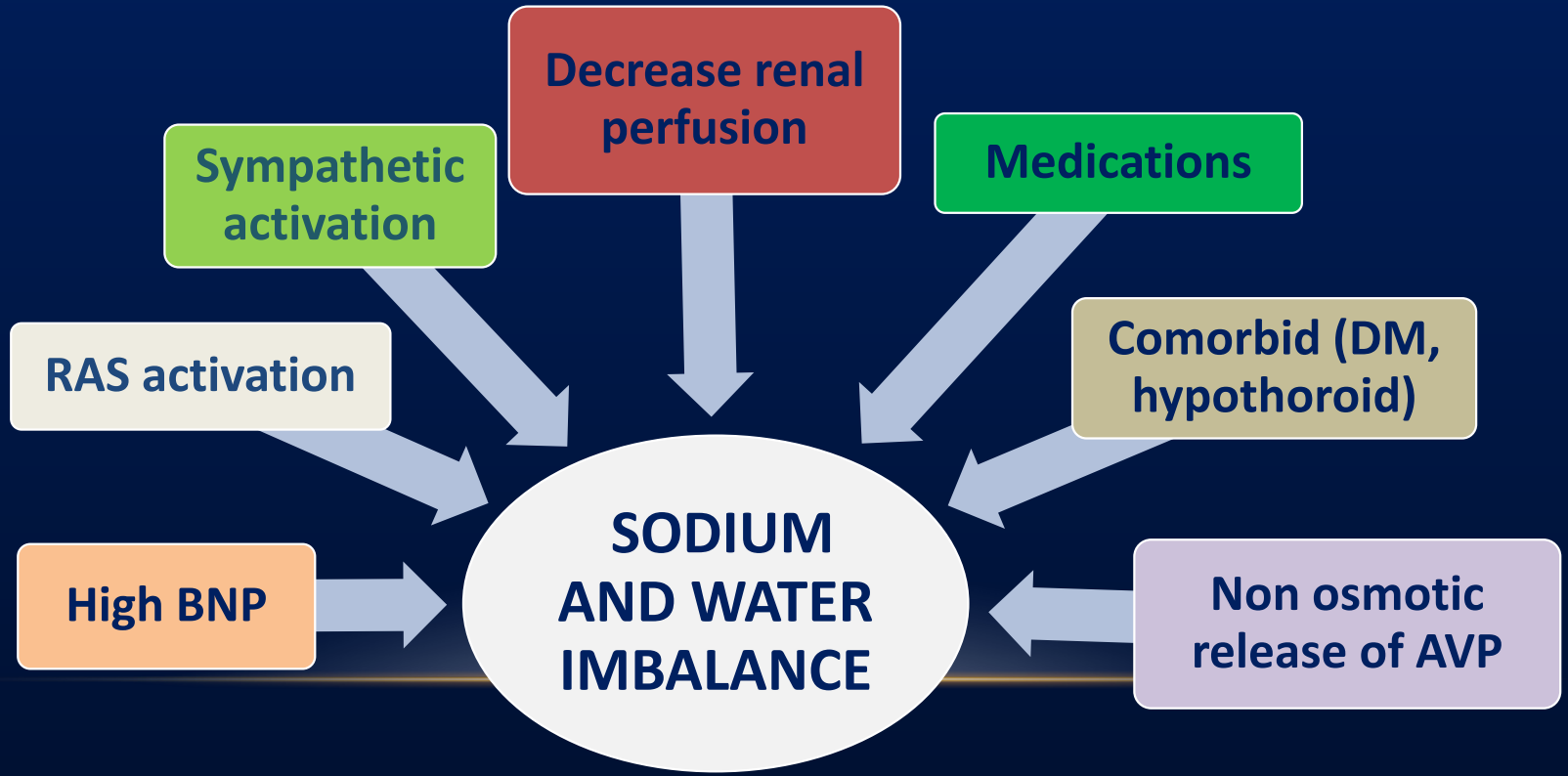
	Mechanism of Action
Dilutional hyponatremia	
Increased sensitivity of osmotic AVP release → Lower osmo-checkpoint*	Baroreceptor activation/angiotensin II
Increased nonosmotic AVP release	Baroreceptor activation/angiotensin II
Impaired AVP degradation	Liver and/or kidney dysfunction
Increased thirst	Baroreceptor activation/angiotensin II
Decreased distal nephron flow	Impaired glomerular filtration/Increased proximal tubular reabsorption
Depletional hyponatremia	
Low sodium intake	Salt-restricted diet
Exaggerated nonurinary sodium losses	Diarrhea, ascites
Exaggerated natriuresis	Diuretics, osmotic diuresis
Sodium shift toward the intracellular compartment	Potassium and/or magnesium deficiency

*This is the level of plasma osmolality that is pursued by the homeostatic mechanisms of the body.

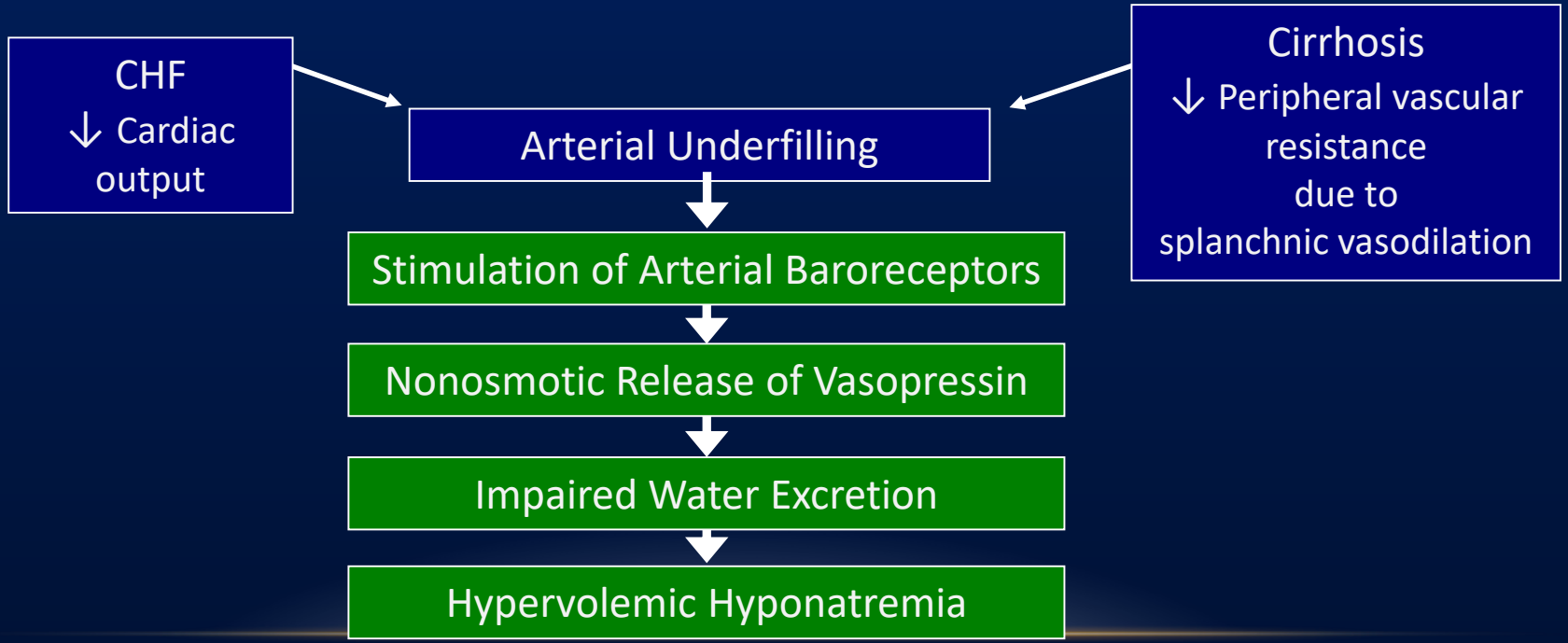
AVP = arginine vasopressin.

Verbrugge et al. JACC 2015;65:480-92

HYPONATREMIA IN HF

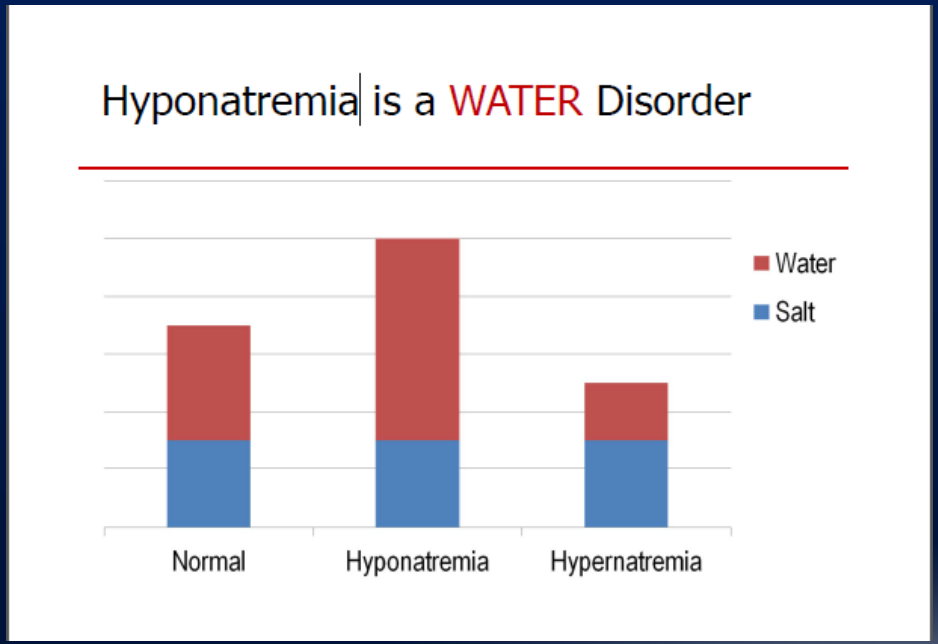


ROLE OF VASOPRESSIN IN EDEMATOUS DISORDERS

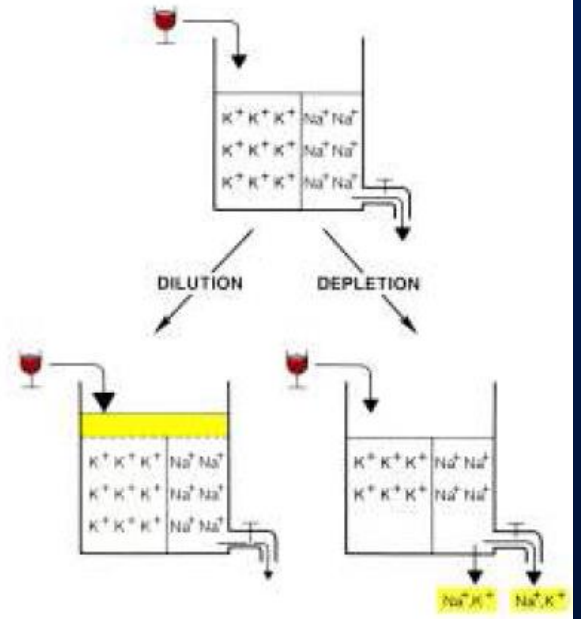


Janicic N, Verbalis JG. Endocrinol Metab Clin North Am. 2003;32:459-481.

HYPONATREMIA PRINCIPLE



hyponatremia can be caused by dilution from retained water, or by depletion from electrolyte losses in excess of water



CLASSIFICATION OF HYPONATREMIA

Dilutional hyponatremia[1]

- Total body sodium normal or increased
- Total body water increased

Hypervolemic[1] (edema)

- Heart failure
- Cirrhosis
- Nephrotic syndrome

Euvolemic[1] (no edema)

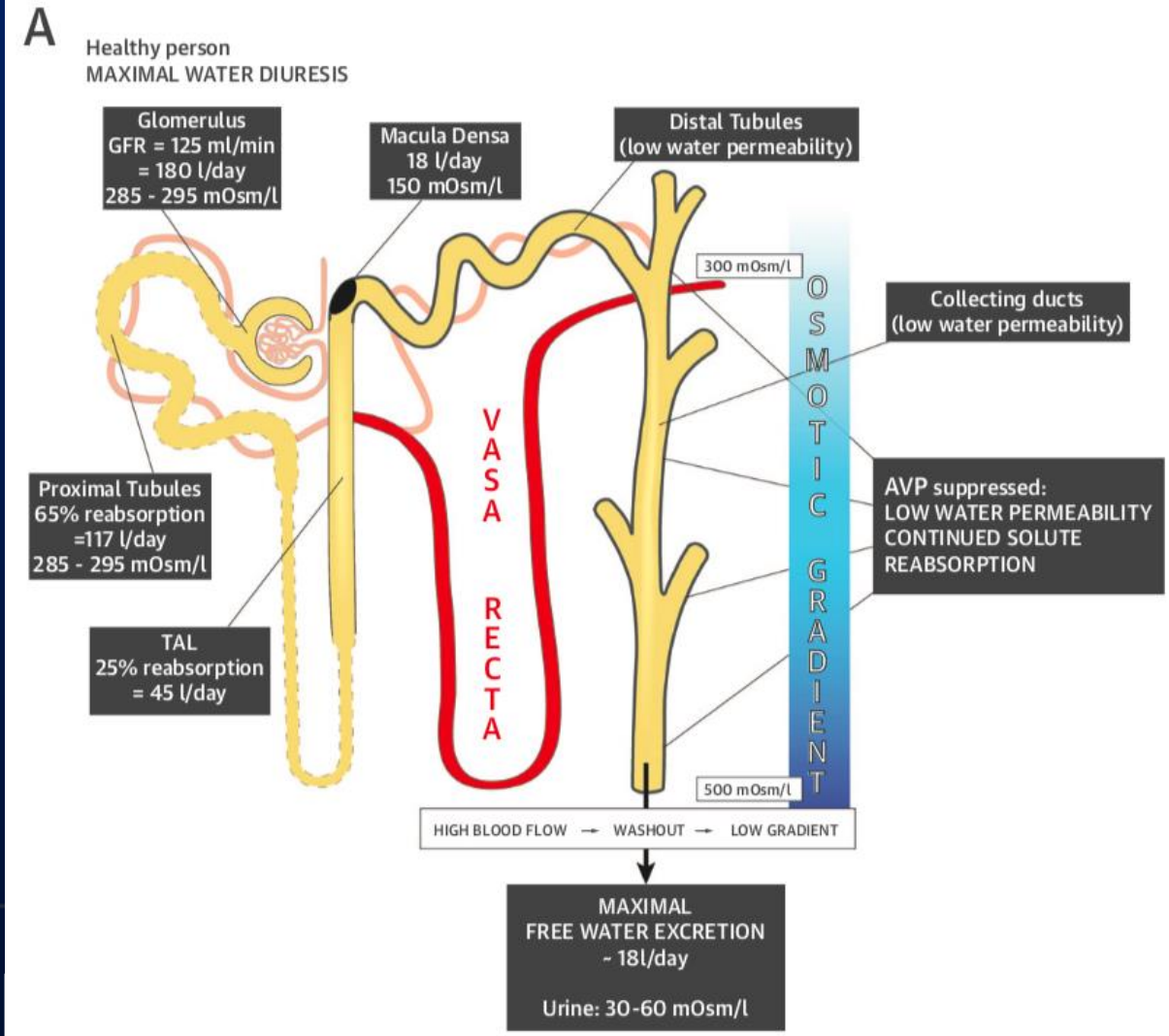
- SIADH
- Hypothyroidism
- Secondary adrenal insufficiency

Depletional hyponatremia[2]

Hypovolemic

- Sodium lost
- Total body water reduced
  - Diarrhea
  - Vomiting
  - Burns
  - Trauma
  - Pancreatitis
  - Diuretic excess
  - Renal salt wasting
  - Mineralocorticoid deficiency

1. Douglas I. Cleve Clin J Med. 2006;73(suppl 3):S4-S12.
2. Kumar S, Berl T. Lancet. 1998;352(9123):220-228.



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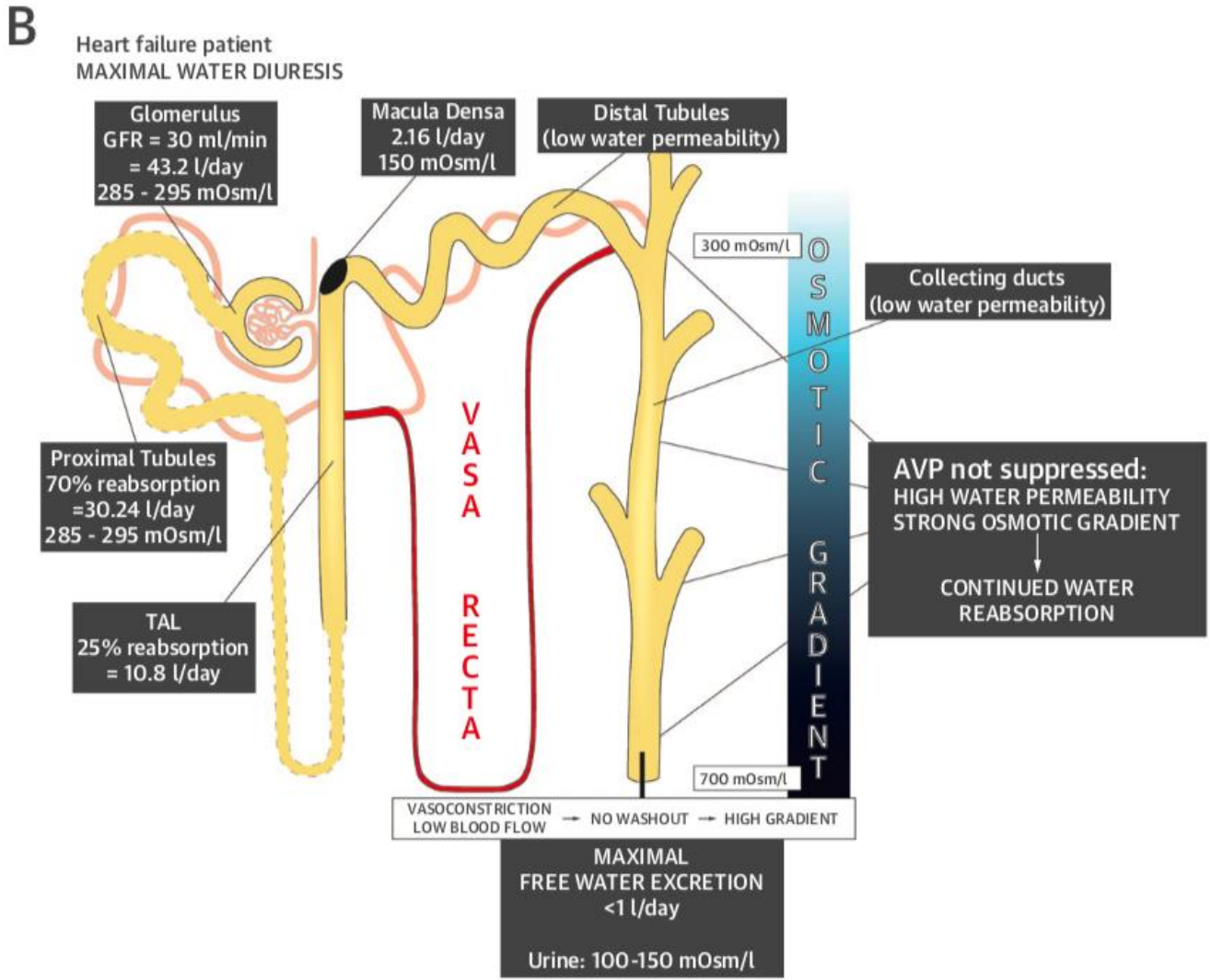

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HOW TO ASSESS

1. Careful history and physical examination (VOLUME STATUS)
2. Measure PLASMA OSMOLALITY

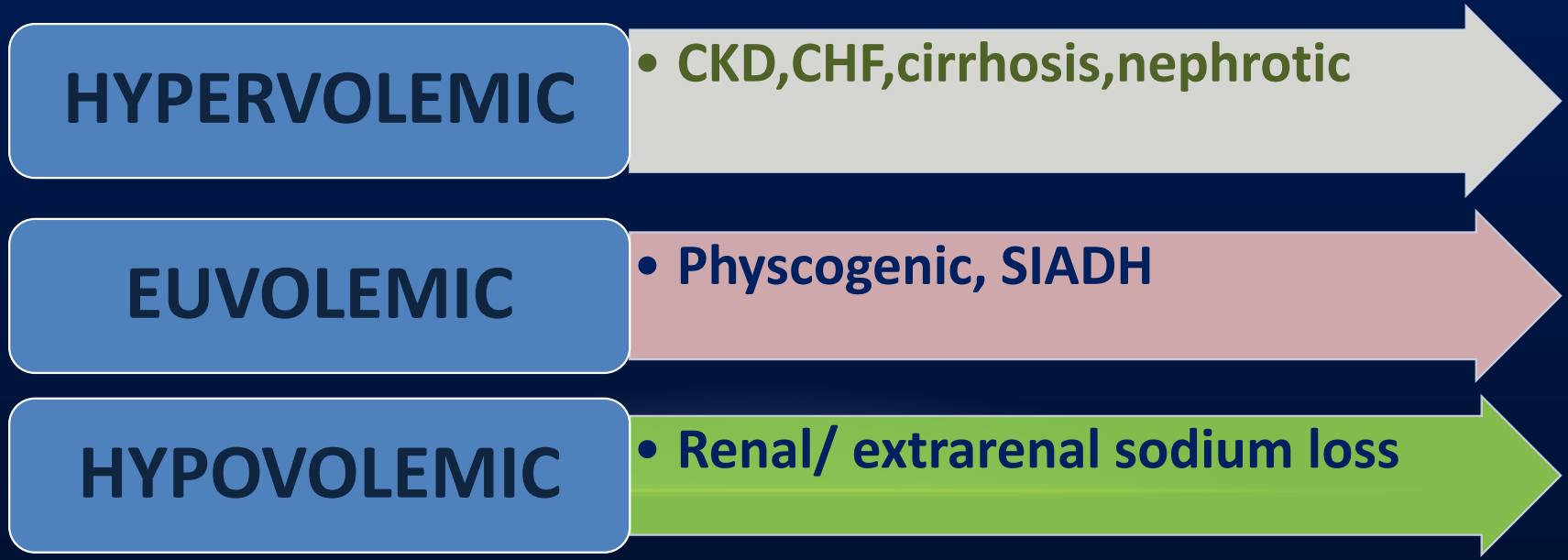
Calculated Plasma Osmolality[2]

(2 x serum [Na^+]) + (Plasma glucose/18) + BUN/2.8)

NORMAL : 285-295 mOsm/kg

HOW TO ASSESS

3. Assess volume status



CONFIRM PLASMA HYPOTONICITY

- Reference value of plasma osmolality : 285-295 mOsm/l
- This may not be necessary when hyponatremia is mild (serum Na concentration 130 to 134 mEq), asymptomatic, and easily corrected by empiric treatment
- The presence of effective osmoles raising serum osmolality—most notably glucose in uncontrolled diabetes and/or hyperosmolar radiocontrast media— may result in hyponatremia with normal, or even high, plasma tonicity
- Manage underlying causes appropriately

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DIFFERENTIATE BETWEEN DEPLETIONAL AND DILUTIONAL HYPONATREMIA

- Depletional hyponatremia → requiring administration of saline
- Urine osmolality : < 100 mOsm/L, low urinary Na and/or Cl (<50mEq/L)
- Acute GI or third-space losses, clinical signs of hypovolemia, and recent use of diuretic agents—especially at high doses or in combination therapy—increase the likelihood of depletional hyponatremia
- In this case, production of hypotonic urine is promoted by the administration of isotonic saline → normalization of serum sodium levels

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DIFFERENTIATE BETWEEN DEPLETIONAL AND DILUTIONAL HYPONATREMIA

- Dilutional hyponatremia → free water excretion should be promoted
- Urine osmolality : ≥ 100 mOsm/L
- Signs of volume overload indicate a component of dilutional hyponatremia → isotonic solutions should certainly be avoided, as administration would result in further worsening of hyponatremia and further deteriorating signs of congestion

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FOR BOTH DEPLETIONAL AND DILUTIONAL HYPONATREMIA

- In pts with hypotonic hyponatremia, it is best to avoid thiazide-type diuretic agents, MRAs, and ENaC blockers (e.g., amiloride) → interfere directly with kidney's capacity to produce hypotonic urine

- K and Mg stored should be replenished if serum levels are low (target : K $\geq$ 4 mEq/L; Mg $\geq$ 1.7 mEq/L)

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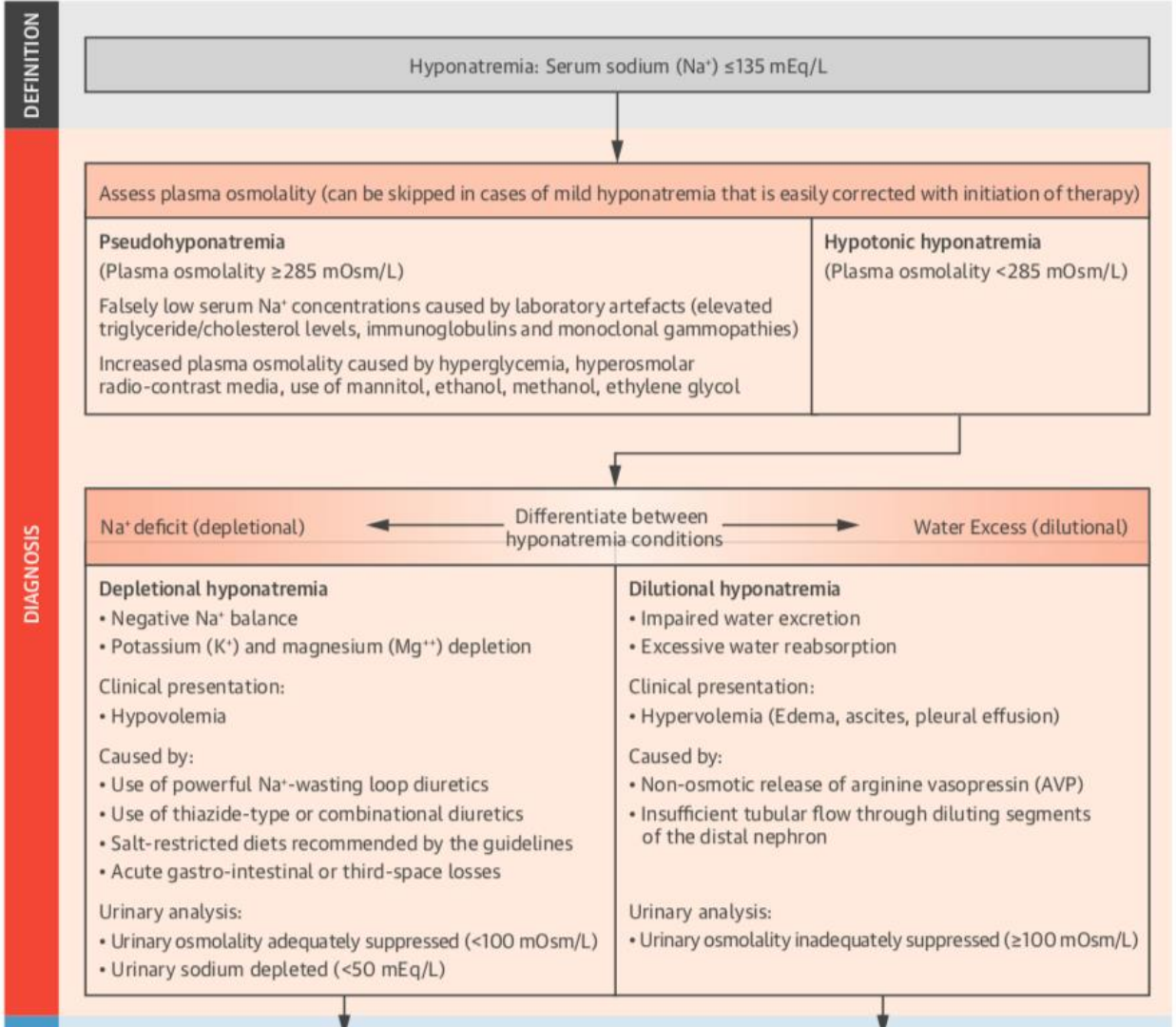
APPROACH TO HYPONATREMIA IN HF



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GENERAL RECOMMENDATIONS

For both depletional and dilutional hyponatremia

- Stop distally working diuretics (thiazide-type, amiloride, mineralocorticoid receptor antagonists)
- Correction of K^+ and Mg^{++} deficiencies (aiming for serum K^+ levels ≥4 mEq/L and Mg^{++} levels ≥1.7 mEq/L)

Depletional hyponatremia

- Administer saline. One liter of infusate is expected to change the serum sodium concentration with:

$$\frac{(Na^+)\text{infusate} + (K^+)\text{infusate} - (Na^+)\text{serum}}{(TBW + 1)}$$

TBW = α x body weight (kg); α = 0.6 in children and non-elderly men, 0.5 in non-elderly women and elderly men, 0.45 in elderly women

Dilutional hyponatremia

- Limit water intake
- Promote free water excretion
  - AVP
  - Improve distal nephron flow (loop diuretics with or without hypertonic saline, acetazolamide, renin-angiotensin system blockers, inotropes and vasodilator therapy)

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TREATMENT OF DEPLETIONAL HYPONATREMIA

- Hypertonic saline will correct hyponatremia faster and with a lower water load than isotonic saline, which might be preferred in patients who are already normovolemic on clinical examination
- If no severe hyponatremia symptoms are present, it is recommended to correct the serum Na concentration slowly, at a maximal rate of 5 mEq/l per day
- If hyponatremia is profound (<125 mEq/l), correction up to 10 mEq/l per day is acceptable
- Increasing the serum Na concentration >10 mEq/l in 24 h should be avoided → the risk of central pontine myelinolysis

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TREATMENT OF HYPOTONIC DILUTIONAL HYPONATREMIA

- Focused on promoting free water excretion to restore normal serum sodium levels
- Distal nephron should be increased
- AVP levels should be lowered, or
- AVP effects should be antagonized

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LOOP DIURETIC AGENTS WITH OR WITHOUT HYPERTONIC SALINE

- Loop diuretic agents remain the first-line th/ in ADHF with dilutional hyponatremia and volume overload

- The addition of hypertonic saline to improve loop diuretic efficacy in ADHF → controversial issue

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- Counterintuitive from pathophysiological point of view
- Small studies : more efficient decongestion and better renal preservation when loop diuretic agents are combined w/ hypertonic saline
- Difficult to draw any firm conclusions, because the use of high doses of loop diuretic agents that might have induced these alterations might have confounded these improvements with sodium loading → Still controversial

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TABLE 2 Studies on Hypertonic Saline in Patients With Acute Decompensated Heart Failure

First Author (Ref. #)	n	Treatment	Outcome
Paterna et al. (65)	60	IV furosemide 500–1,000 mg with vs. without 150 ml 1.4%–4.6% hypertonic saline BID	Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; and shorter hospitalization time with hypertonic saline
Licata et al. (66)	107	IV furosemide 500–1,000 mg with vs. without 150 ml 1.4%–4.6% hypertonic saline BID	Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; and improved survival with hypertonic saline
Paterna et al. (71)	94	IV furosemide 500–1,000 mg with vs. without 150 ml 1.4%–4.6% hypertonic saline BID	Increase in diuresis and natriuresis; decrease in BNP levels; shorter hospitalization time; and lower 30-day readmission rate with hypertonic saline
Parrinello et al. (67)	133	IV furosemide 250 mg plus 150 ml 3% hypertonic saline BID vs. IV furosemide 250 mg BID plus low sodium diet (<80 mmol)	Increase in diuresis, natriuresis, and serum sodium levels; improved renal function; and faster reduction of echo-PCWP with hypertonic saline
Paterna et al. (68)	1,771	IV furosemide 250 mg plus 150 ml 3% hypertonic saline BID vs. IV furosemide 250 mg BID plus low sodium diet (<80 mmol)	Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; shorter hospitalization time; lower readmission rate; and improved survival with hypertonic saline
Issa et al. (69)	34	100 ml 7.5% hypertonic saline BID vs. placebo for 3 days	Improved in glomerular and tubular biomarkers with hypertonic saline
Okuhara et al. (70)	44	500 ml 1.7% hypertonic saline vs. glucose 5% with 40 mg furosemide	Improved GFR and better diuresis with hypertonic saline

ACETAZOLAMIDE

- Combinational diuretic treatment with loop diuretic agents and acetazolamide ensures minimal tubular Na reabsorption proximal from the macula densa and maximal flow through the distal nephron

- Acetazolamide should be preferred over thiazide-type diuretic agents, MRAs, or ENaC blockers
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AVP ANTAGONISTS

- The only medication class to directly promote free water excretion by prevention of aquaporin-2 channel availability in the collecting ducts of the nephron
- Three oral V2 receptor antagonists (tolvaptan, satavaptan, and lixivaptan) have been tested for ADHF, with the former 2 shown to be efficacious in restoring serum Na levels in patients with volume overload and hyponatremia

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TABLE 3 Studies on AVP Antagonists in Patients With Acute Decompensated Heart Failure and Hyponatremia

First Author (Ref. #)	n/N	Treatment	Outcome
Gheorghiade et al. (77)	71/254 (subgroup analysis)	Tolvaptan 30, 45, or 60 mg vs. placebo	Normalization of serum sodium after 24 h, greater decrease in body weight and edema, increased urine output with tolvaptan
Gheorghiade et al. (78)	51/319 (subgroup analysis)	Tolvaptan 30, 60, or 90 mg vs. placebo	Normalization of serum sodium with tolvaptan
Ghali et al. (79)	19/74 (subgroup analysis)	Conivaptan 40 or 80 mg vs. placebo	Normalization of serum sodium with conivaptan
Zeltser et al. (80)	28/84 (subgroup analysis)	Conivaptan 40 or 80 mg vs. placebo	Increase in serum sodium concentration with conivaptan
Konstam et al. (81)	1,157/4,133 (subgroup analysis)	Tolvaptan 30 mg vs. placebo	No effect on mortality or rehospitalization, significant increase in serum sodium with tolvaptan
Aronson et al. (75)	90/118 (subgroup analysis)	Satavaptan 25 or 50 mg vs. placebo	Increase in serum sodium concentration with satavaptan

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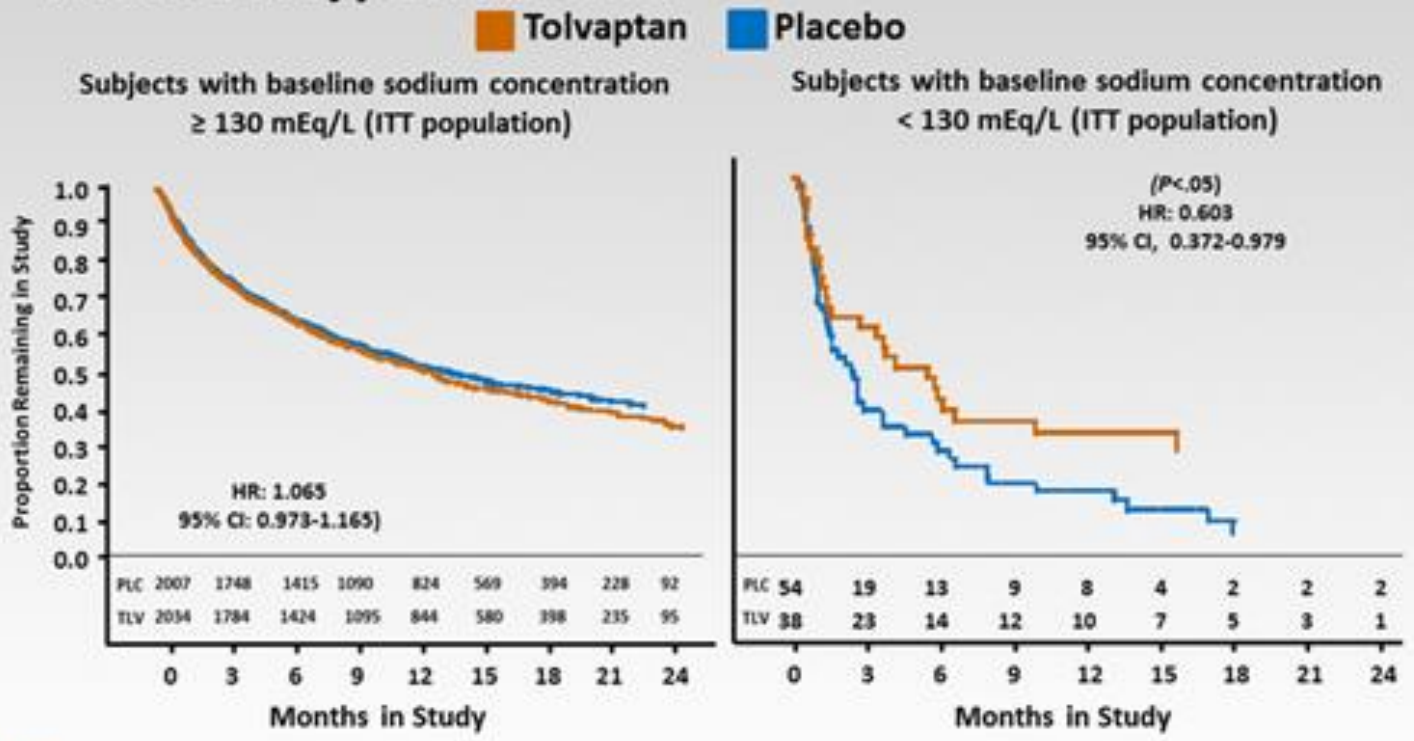
EVEREST: CV Mortality/Morbidity in Patients With Heart Failure With and Without Hyponatremia



Heart failure

Konstam MA. ACC 2007.

WATER RESTRICTION

- Whilst limiting free water intake certainly aids to prevent a positive free water balance, few data support its long-term efficacy, and adherence might be a problem
- Thirst is a frequent, underrecognized, and distressing problem in heart failure, and many patients may find it difficult to comply with strict water restriction (<1 Lt/day)
- A recent study found that ADHF patients with mild hyponatremia had improvements in quality of life with such a strategy

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RAS BLOCKERS

- RAS blockers are known to increase renal blood flow and decrease proximal tubular sodium reabsorption

- Up-titration of RAS blockers should always be promoted if there are no contraindications

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INOTROPES AND VASODILATOR THERAPY

- Increasing the effective circulatory volume in heart failure is expected to result in less non-osmotic AVP release and better renal blood flow, which, from a pathophysiological perspective, might help to correct dilutional hyponatremia
- Because cardiac output in ADHF is rather insensitive to changes in cardiac pre-load—as the Frank-Starling mechanism is depleted—improvements can only be obtained through direct stimulation of contractility with inotropes or reducing afterload with vasodilator therapy

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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure – Web Addenda

PROBLEM SOLVING

Asymptomatic low blood pressure:

- Dose may be reduced if no symptoms or signs of congestion.

Symptomatic hypotension:

- Causing dizziness/light headedness – reduce dose if no symptoms or signs of congestion.
- Reconsider need for nitrates, CCBs[d] and other vasodilators.
- If these measures do not solve problem, seek specialist advice.

Hypokalaemia/hypomagnaesaemia:

- Increase ACE-I/ARB dose.
- Add MRA, potassium supplements; magnesium supplements.

Hyponatraemia:

- Volume depleted:
  - o Stop thiazide or switch to loop diuretic, if possible.
  - o Reduce dose/stop loop diuretics if possible.
- Volume overloaded:
  - o Fluid restriction.
  - o Increase dose of loop diuretic.
  - o Consider AVP antagonist (e.g. tolvaptan if available).
  - o i.v. inotropic support.
  - o Consider ultrafiltration.

SUMMARY

- The pathophysiology of hyponatremia in ADHF is complex, and a 1-size-fits-all approach is therefore likely to fail
- Appropriate differentiation between dilutional and depletional hyponatremia is crucial and depends on good history taking, clinical examination, and correct interpretation of laboratory results
- A targeted, pathophysiology-based approach should help to treat this challenging condition efficiently, thereby minimizing adverse events