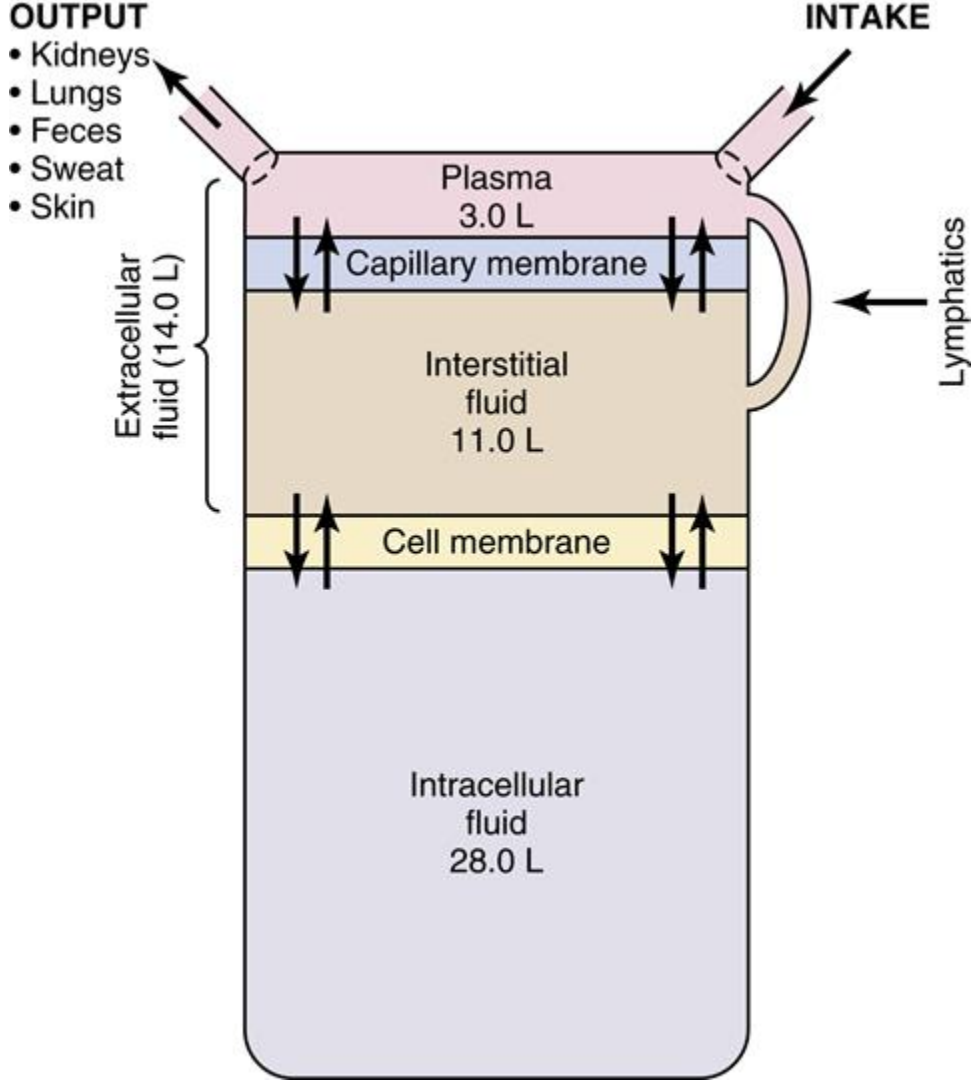
Hyponatremia

Abbal Koirala, MD
Clinical Assistant Professor of Medicine
Division of Nephrology
University of Washington, Seattle

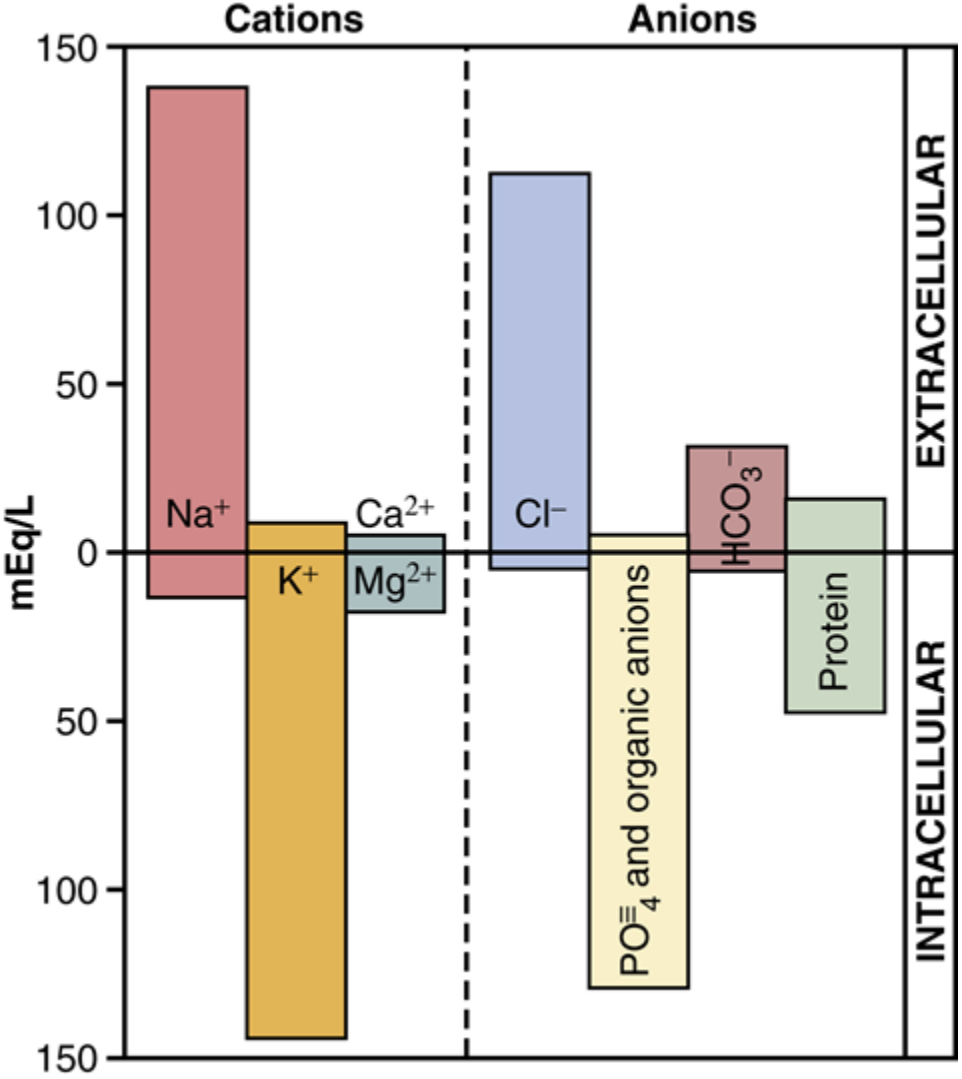
I have no disclosures

Learning Objectives

- Understand water balance and sodium regulation.
- Understand hyponatremia and their various etiologies.
- Understand the pathophysiology of SIADH and various treatment modalities.



Guyton and Hall 2021



Guyton and Hall 2021

What is hyponatremia?

Most common electrolyte abnormality in hospitalized patients.

Serum [Na] < 135 mEq/L

Hypo-osmolar state

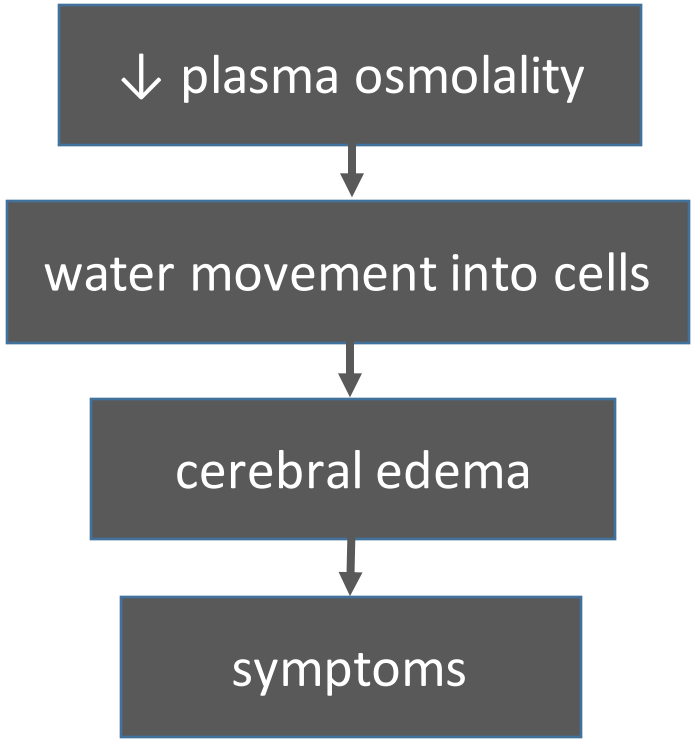
Imbalance of salt and water.

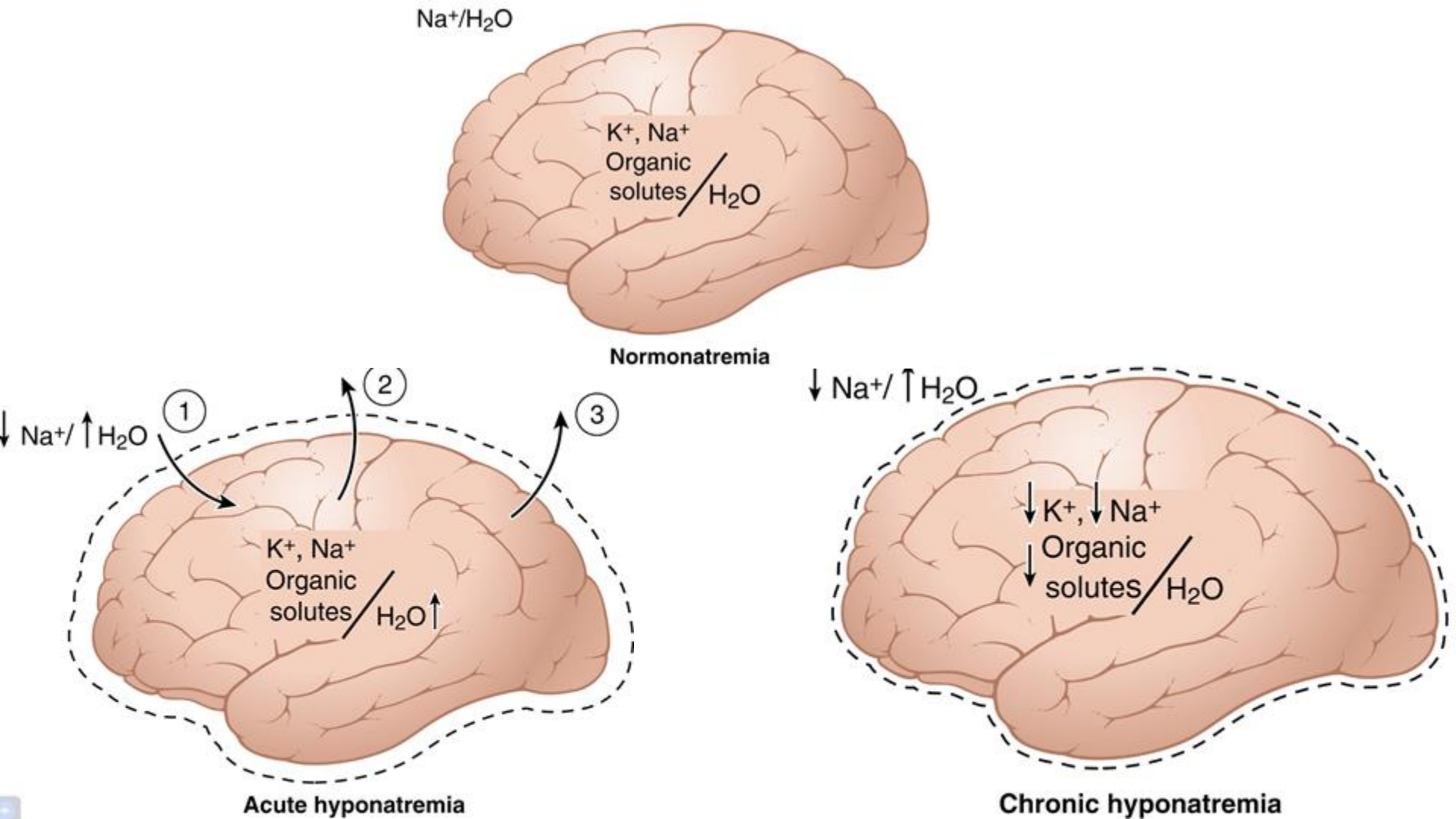
plasma [Na] ~ Na / TBW

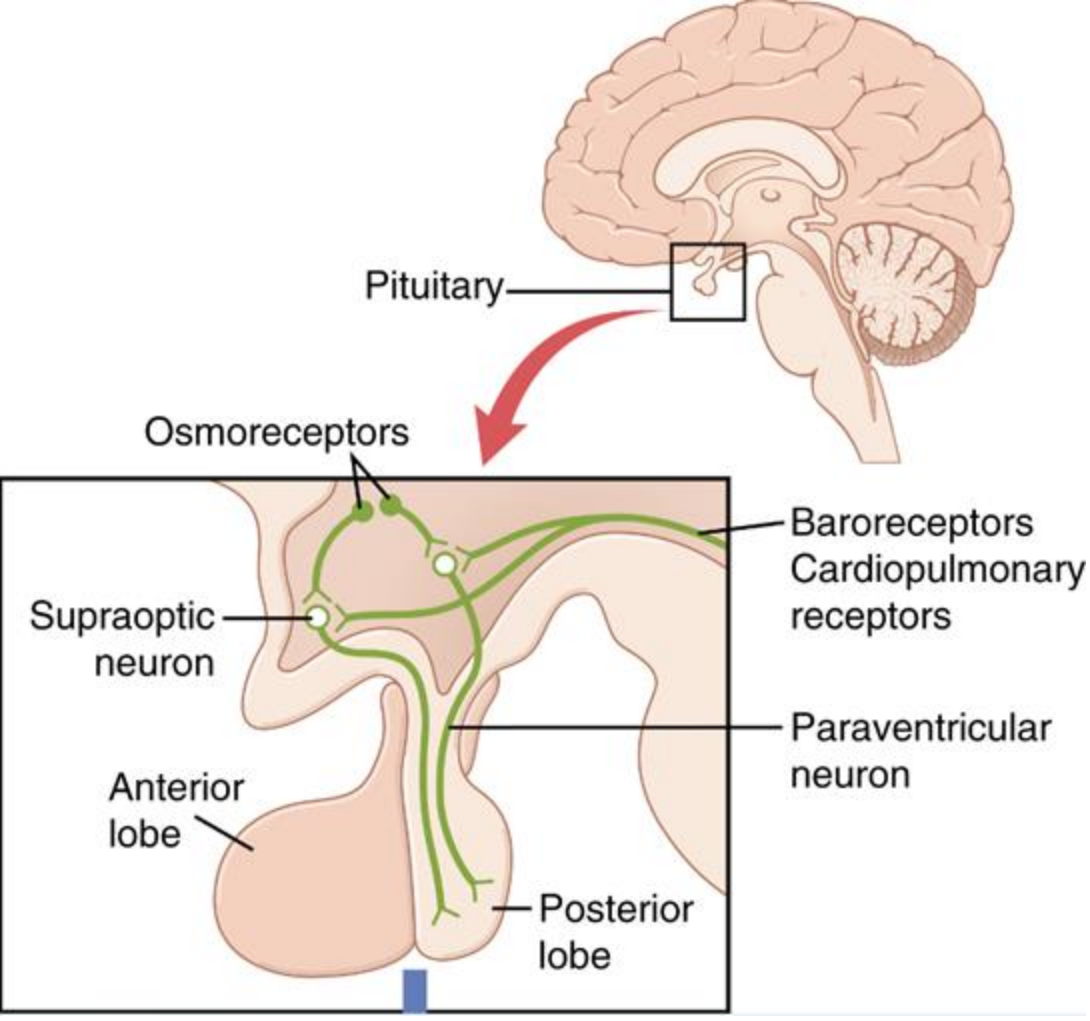
Symptomatic hyponatremia

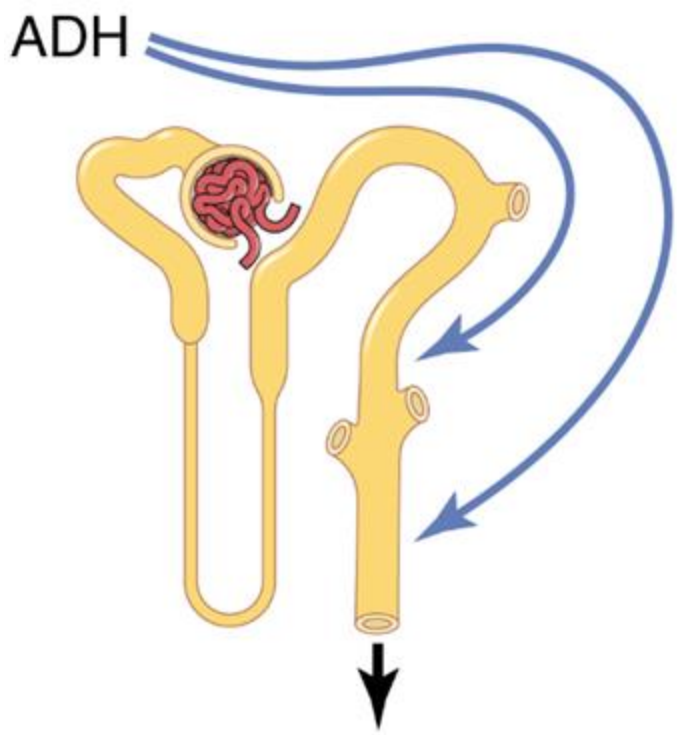
- Mild hyponatremia (129 - 135)
  - Falls, gait instability, mild cognitive impairment, muscle cramps
- Moderate hyponatremia (120 – 129)
  - Confusion, increasing gait instability, nausea, malaise
- Severe hyponatremia (<120)
  - Headache, lethargy, obtundation, seizure, coma, death

Why do we care about hyponatremia?

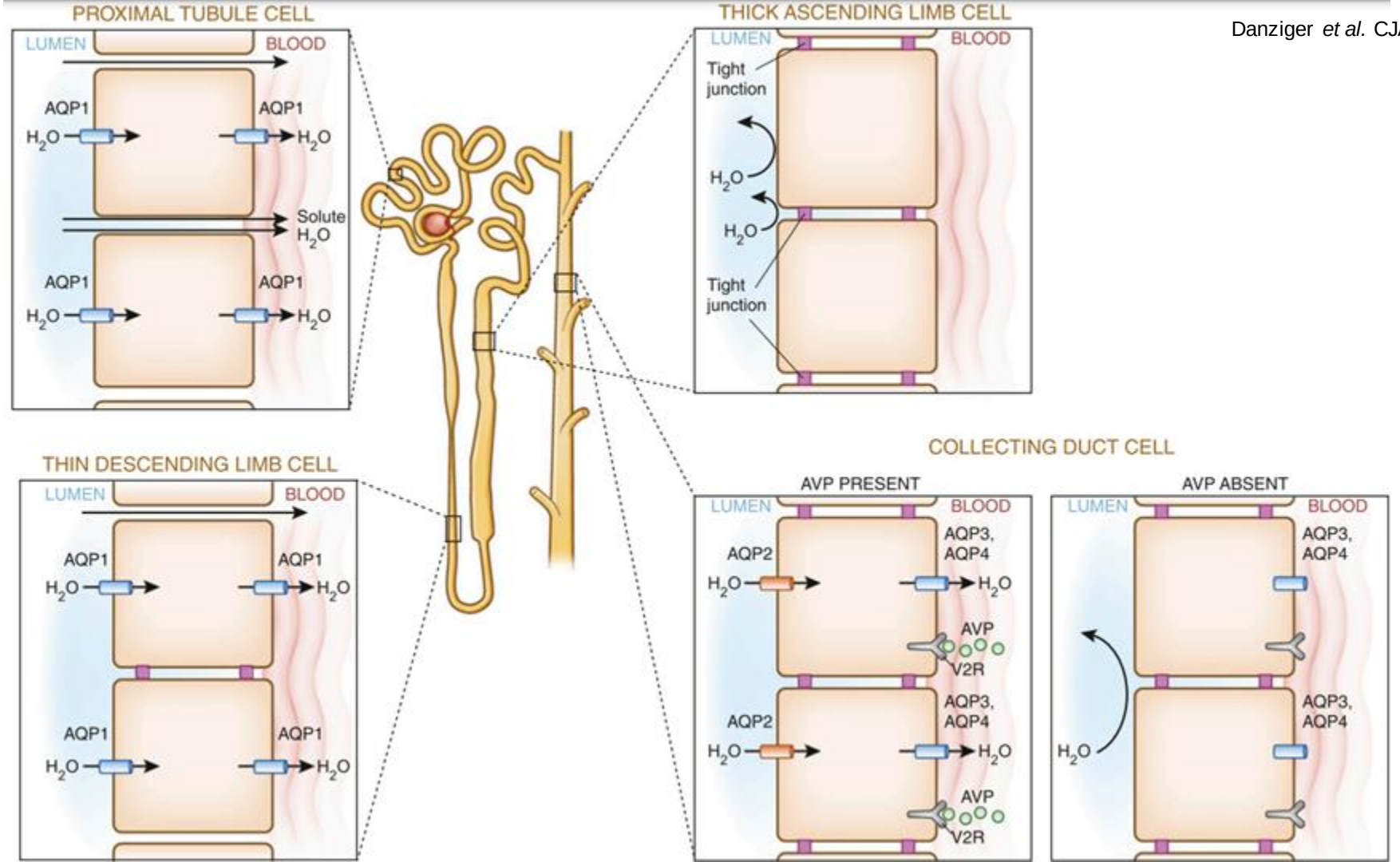



Na+/H2O
K+, Na+
Organic
solutes
H2O
Normonatremia
↓ Na+/ ↑ H2O
1
2
3
K+, Na+
Organic
solutes
H2O ↑
Acute hyponatremia
↓ Na+/ ↑ H2O
↓ K+, ↓ Na+
↓ Organic
solutes
H2O
Chronic hyponatremia





Urine:
decreased flow
and concentrated

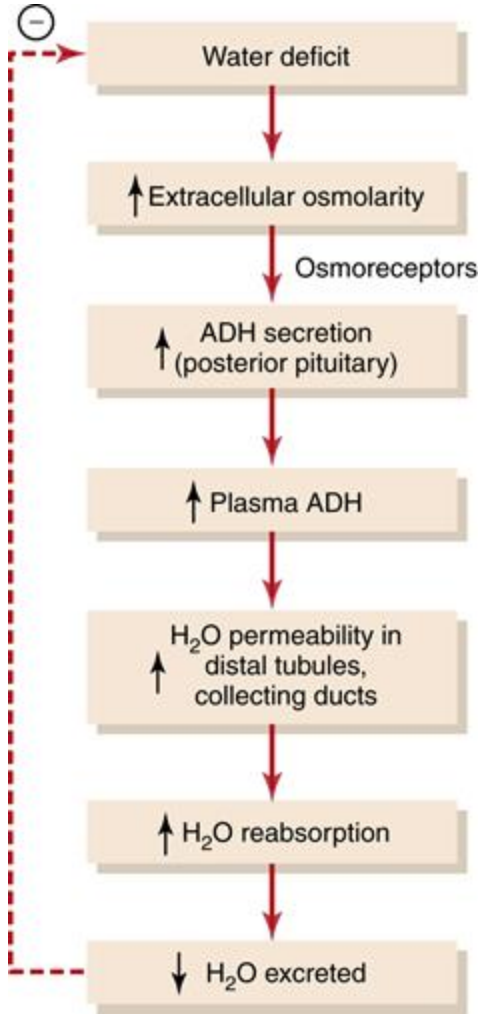


Danziger *et al.* CJASN 2015

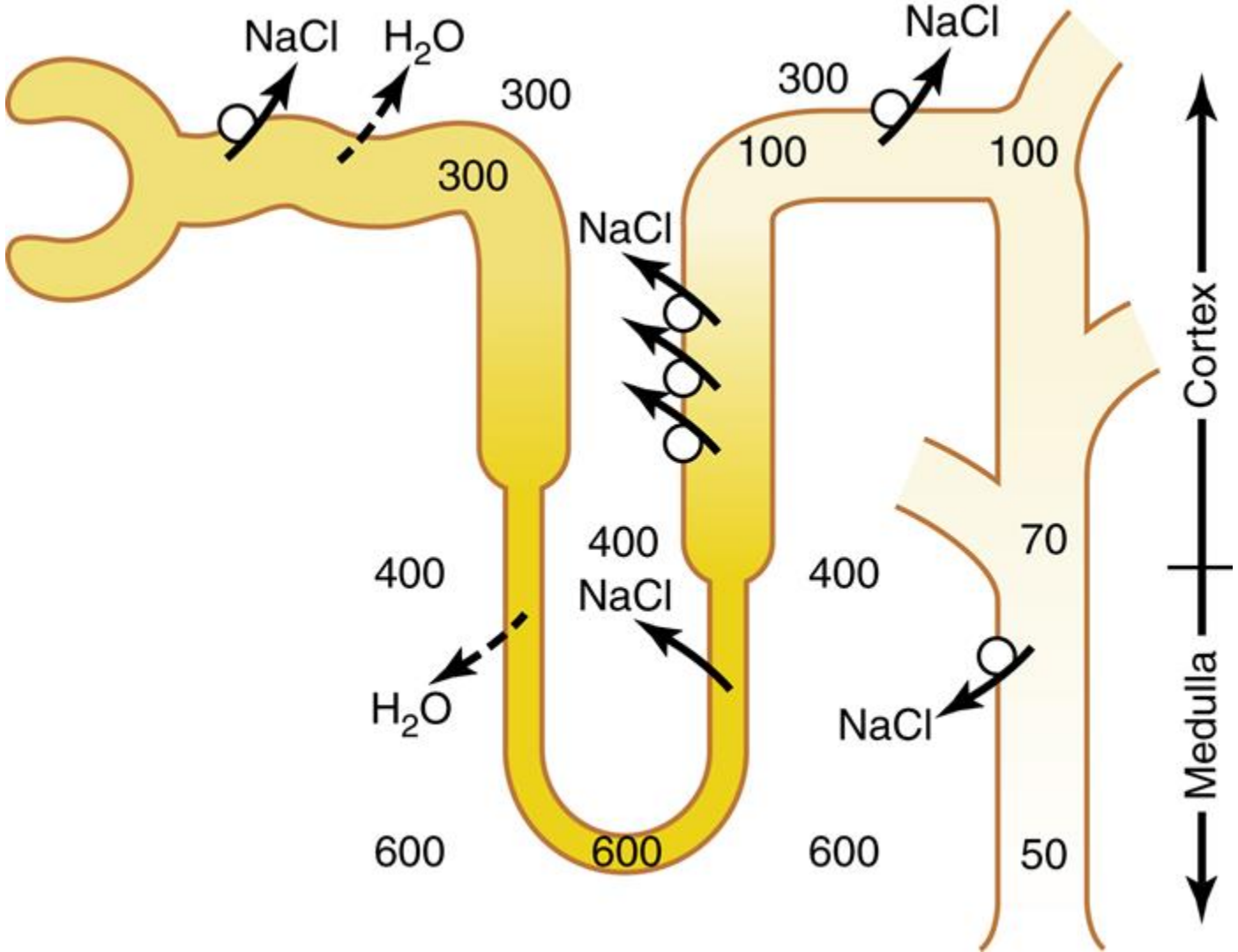
Stimuli for ADH release

Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Many Drugs	Drugs
Morphine	Alcohol
Nicotine	Clonidine
Cyclophosphamide	Haloperidol

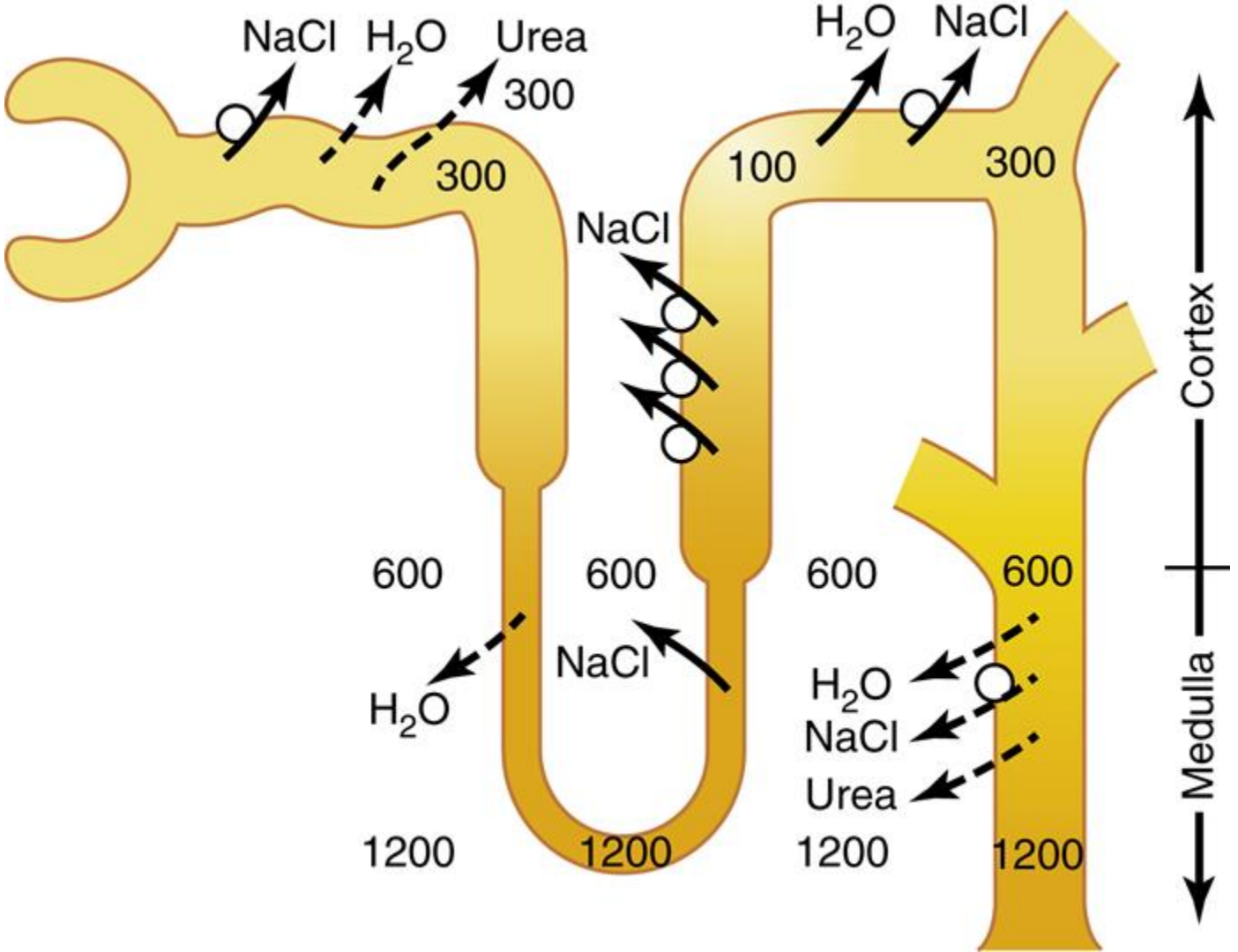
Increase Thirst	Decrease Thirst
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
↑ Angiotensin II	↓ Angiotensin II
Dry mouth	Gastric distention

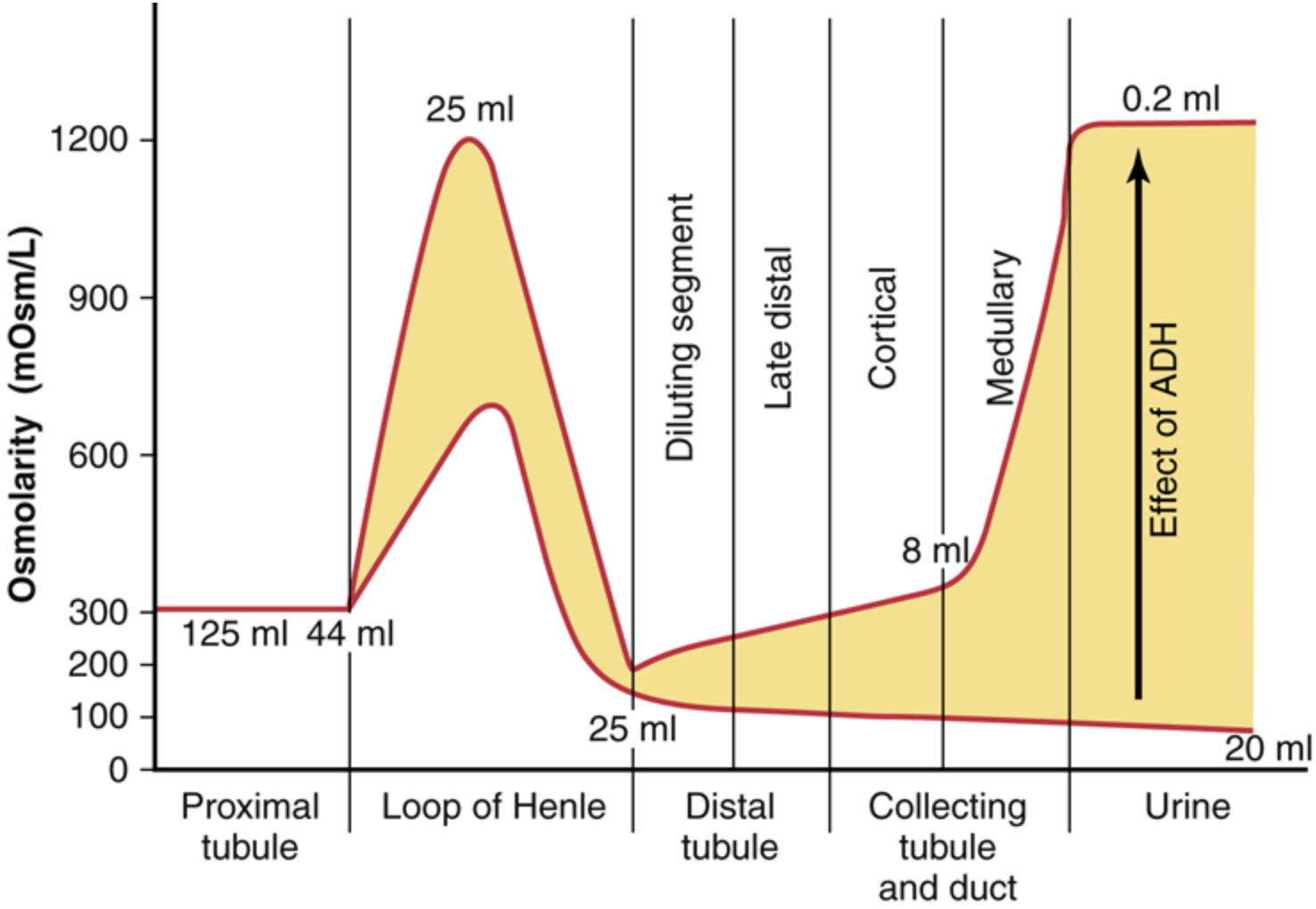

Water deficit
↑ Extracellular osmolarity
Osmoreceptors
↑ ADH secretion (posterior pituitary)
↑ Plasma ADH
↑ H_2O permeability in distal tubules, collecting ducts
↑ H_2O reabsorption
↓ H_2O excreted

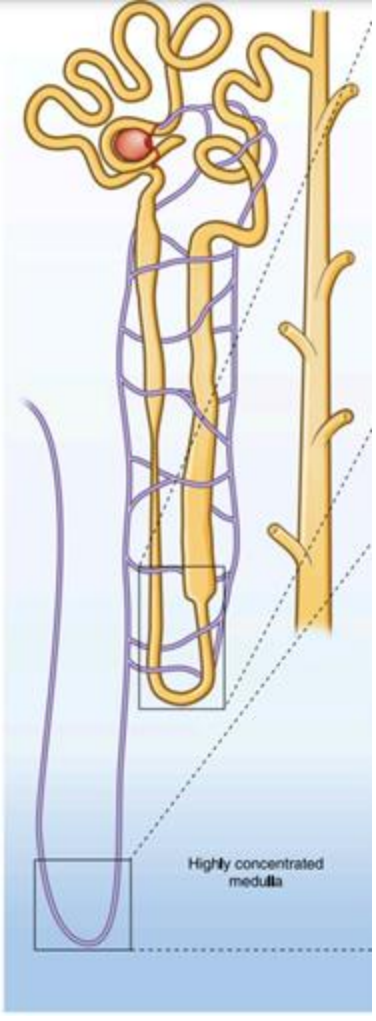
Formation of dilute urine

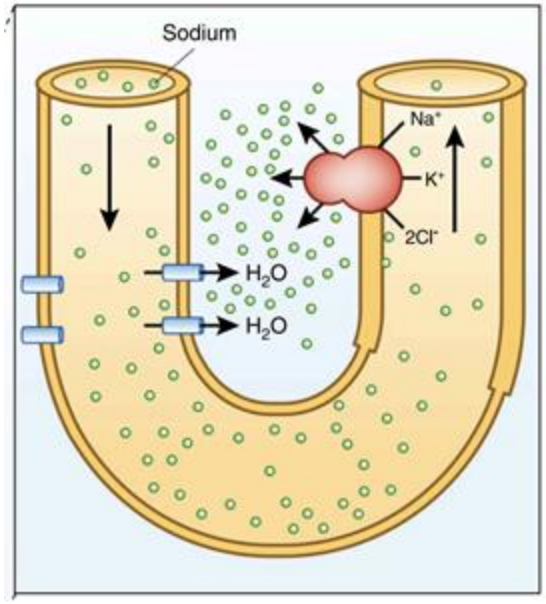

NaCl
H_2O
300
300
NaCl
300
NaCl
100
100
400
400
NaCl
400
70
H_2O
NaCl
600
600
600
50
Cortex
Medulla

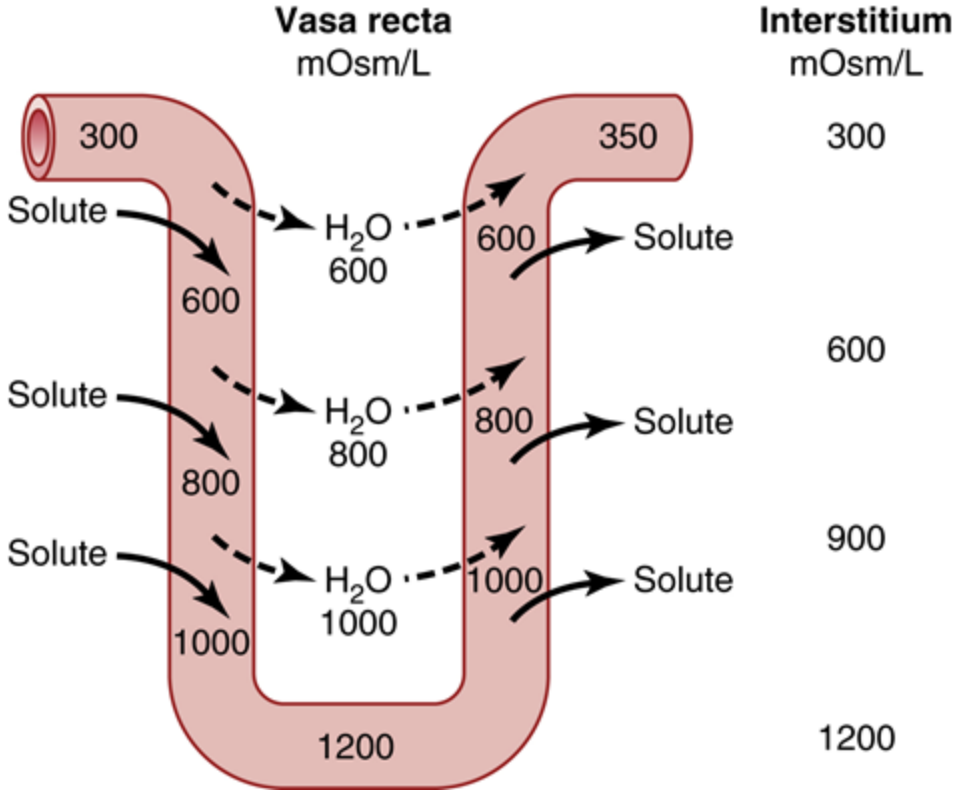
Formation of concentrated urine


NaCl
H_2O
Urea
300
300
100
300
H_2O
NaCl
NaCl
600
600
600
600
H_2O
NaCl
H_2O
NaCl
Urea
1200
1200
1200
1200
Cortex
Medulla


Osmolarity (mOsm/L)
1200
900
600
300
200
100
0
25 ml
0.2 ml
125 ml
44 ml
8 ml
25 ml
20 ml
Diluting segment
Late distal
Cortical
Medullary
Effect of ADH
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule and duct
Urine


Highly concentrated medulla


Sodium
Na+
K+
2Cl-
H2O
H2O


Vasa recta
mOsm/L
Interstitium
mOsm/L
300
350
300
Solute
H2O
600
600
Solute
600
600
Solute
H2O
800
800
Solute
800
900
Solute
H2O
1000
1000
Solute
1000
1200
1200

Obligate urine volume and oliguria

NORMAL SOLUTE INTAKE 600 mOsm/day

U.OUTPUT 600 mOsm/day

Low Solute Intake

Tea and toast diet
Beer Potomania
Eating disorders

Concentrated urine and obligate urine output

INTAKE
600
mOsm/day

U.OUTPUT
600
mOsm/day

Concentrated urine

UOsm 1200 mosm

$$\frac{600}{1200} = 0.5 \text{ L/d}$$

Dilute urine

INTAKE
600
mOsm/day

U.OUTPUT
600
mOsm/day

Dilute urine

UOsm 50 mosm

$$\frac{600}{50} = 12\ \text{L/d}$$

Teaching point #1:

In patients with normal kidney function and normal solute intake, in the presence of maximum ADH, the urine output can be as low as 0.5 L/d and still serum sodium would be 135 meq/L

In patients with normal kidney function and normal solute intake, in the presence of no ADH, the urine output can be as high as 12 L/d and still serum sodium would be 145 meq/L

Case#1

Mr. A is a 45 yo man who comes to the UWMC ED with nausea and vomiting for 2 days.

He is lightheaded. He denies any falls or syncope.

PMH

- Bipolar disorder previously treated with lithium, now on lamotrigine and carbamazepine
- HTN
- No known history of kidney disease
- 20 pack year smoking history

Physical exam:

- BP 110/70, HR 95, O2sat 100% on RA
- BP drops to 95/65 and HR increases to 110 with standing
- Rest of exam normal

Initial laboratory tests:

- Sodium 122, potassium 3.3, BUN 30, creatinine 1.4
- CBC normal

Patient is admitted to Medicine for management of hyponatremia.

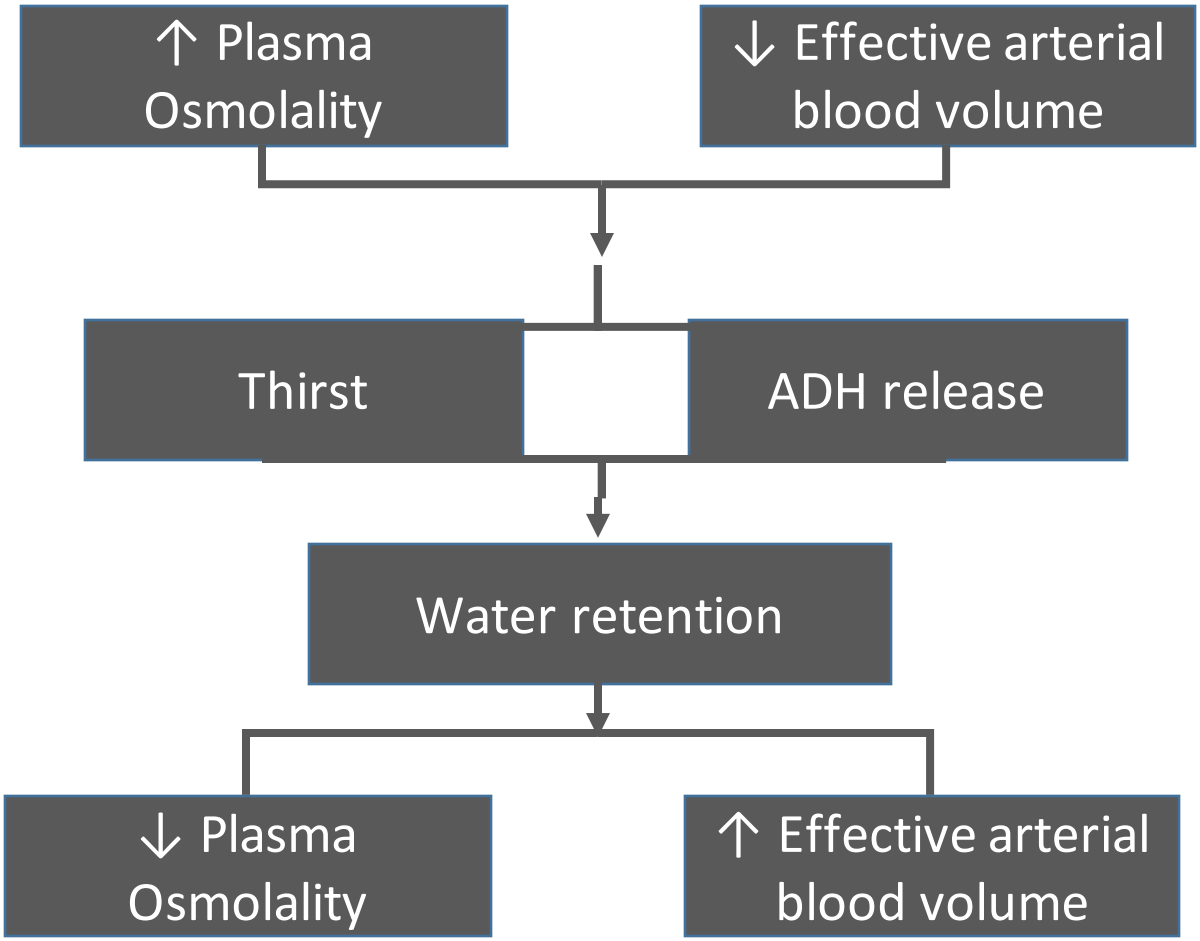
What impacts our ability to excrete water?

Kidney function

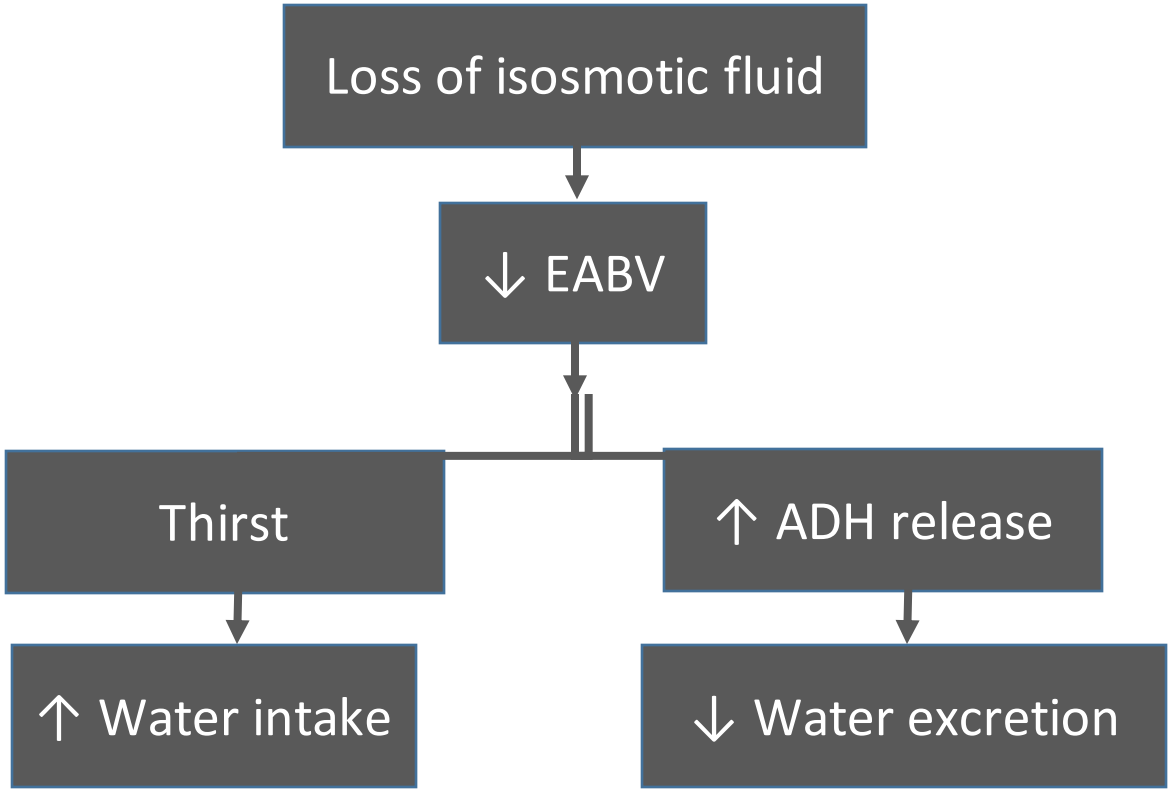
Solute load

ADH

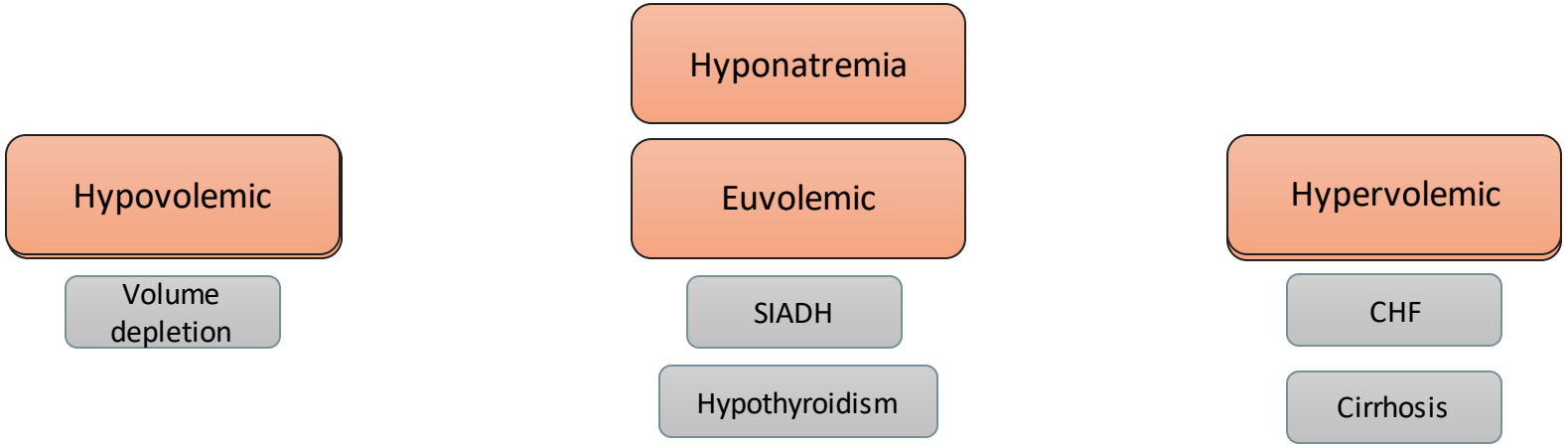
ADH


↑ Plasma Osmolality
↓ Effective arterial blood volume
Thirst
ADH release
Water retention
↓ Plasma Osmolality
↑ Effective arterial blood volume

Example: vomiting or diarrhea



What is our differential diagnosis for hyponatremia?



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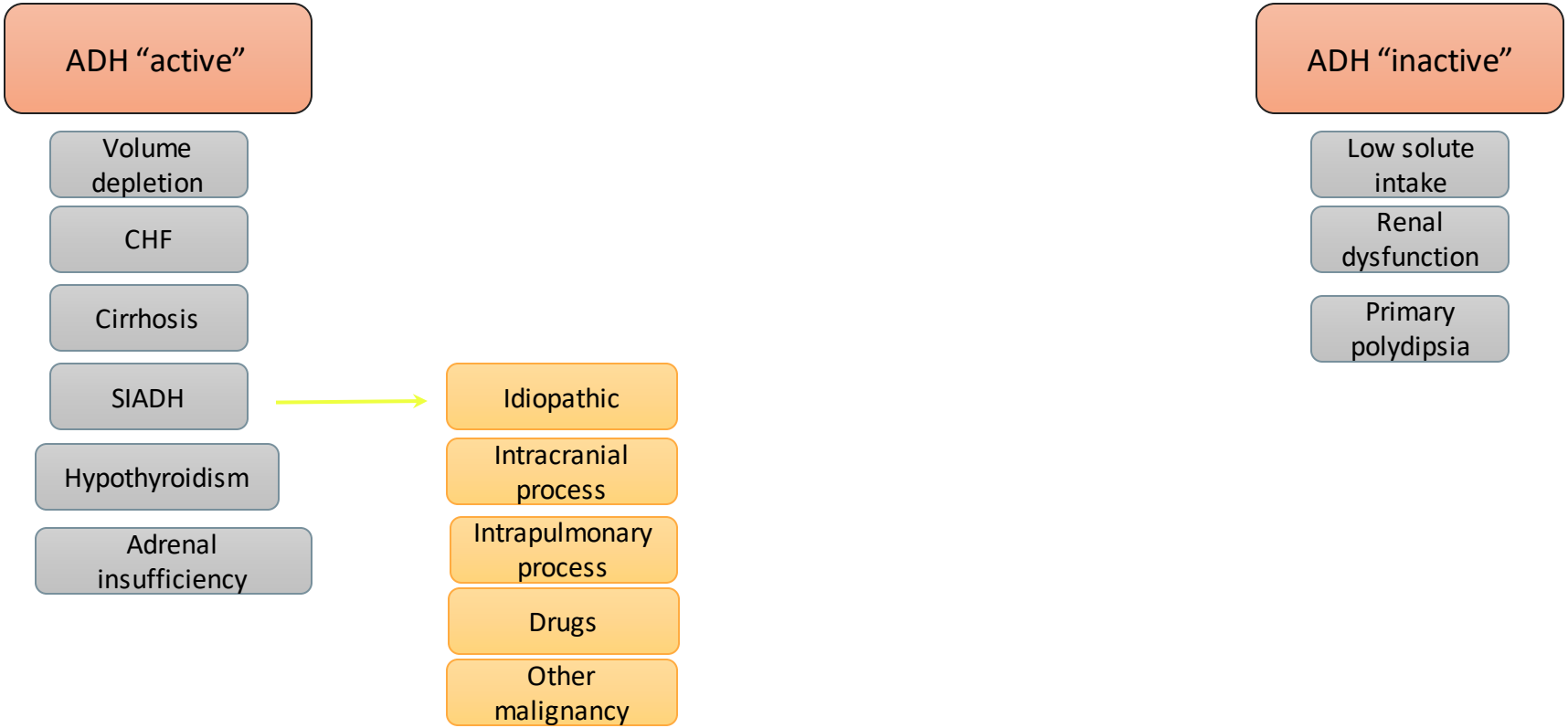
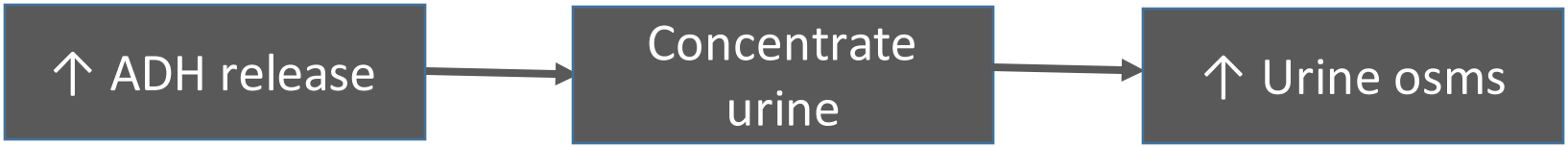
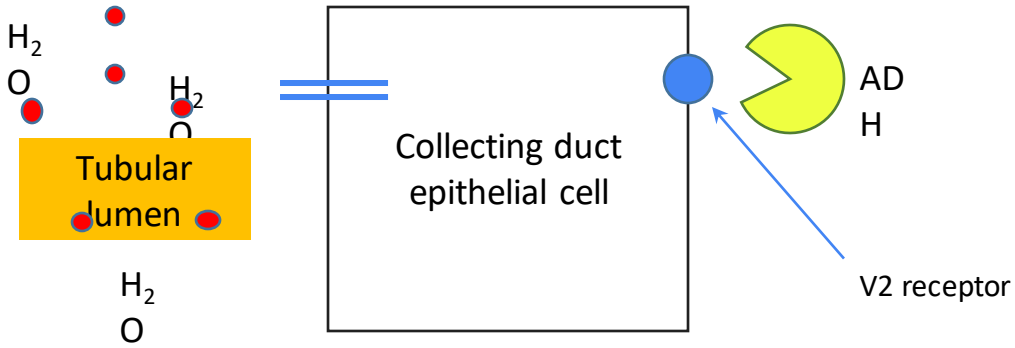
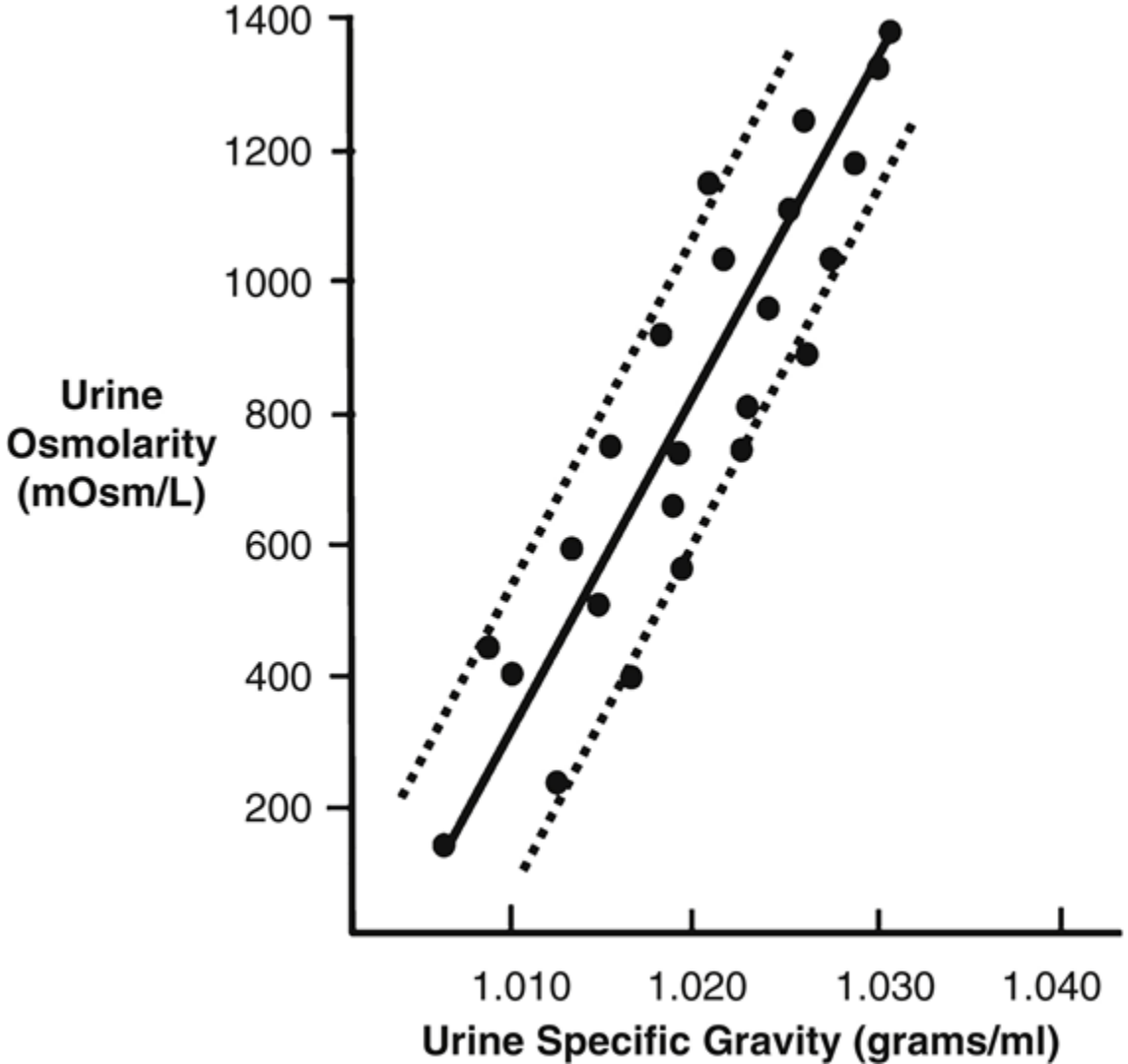


How can we assess ADH activity?

Urine osmolality






1400
1200
1000
800
600
400
200
Urine
Osmolarity
(mOsm/L)
1.010
1.020
1.030
1.040
Urine Specific Gravity (grams/ml)

Teaching point #2:

Urine osmolality is a surrogate marker for ADH activity.

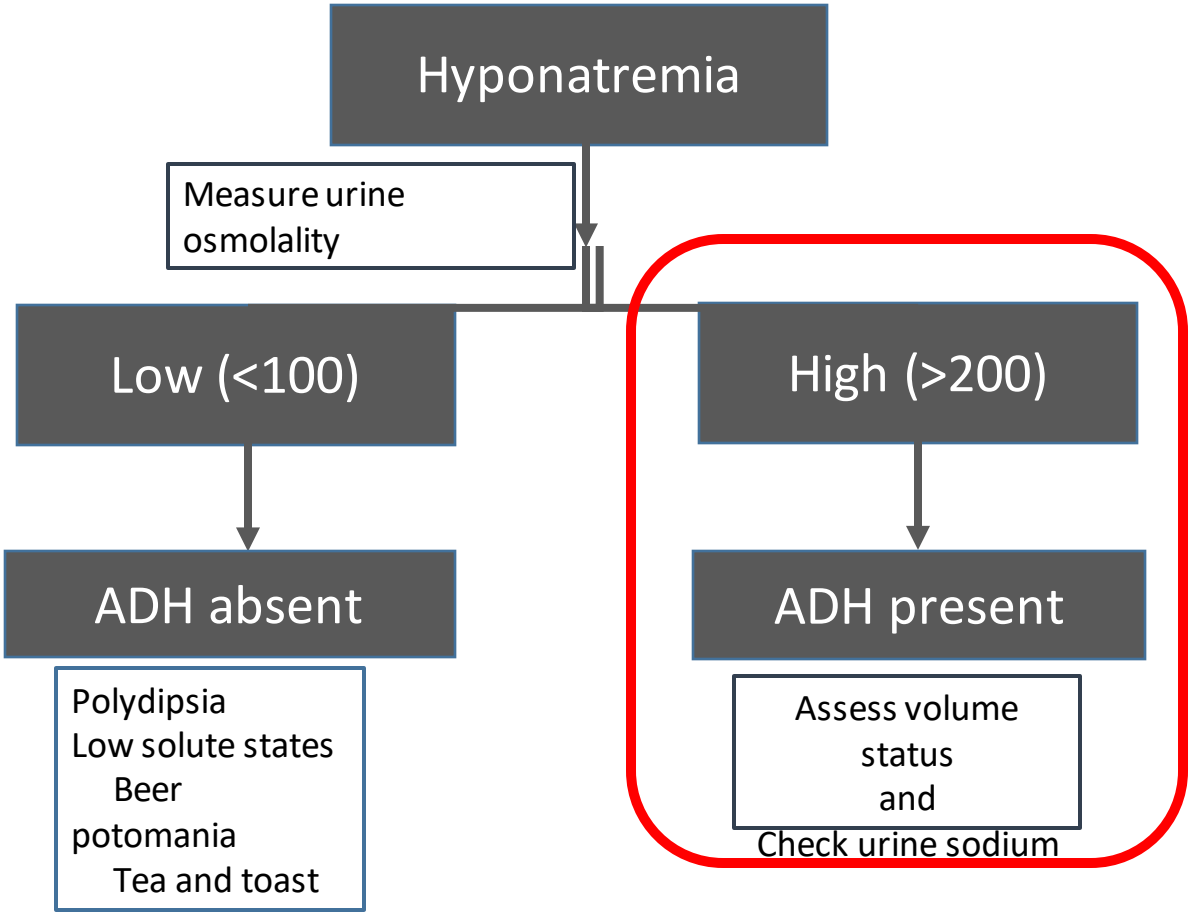
(If I could have only one test for assessing hyponatremia it would be urine osmolality.)

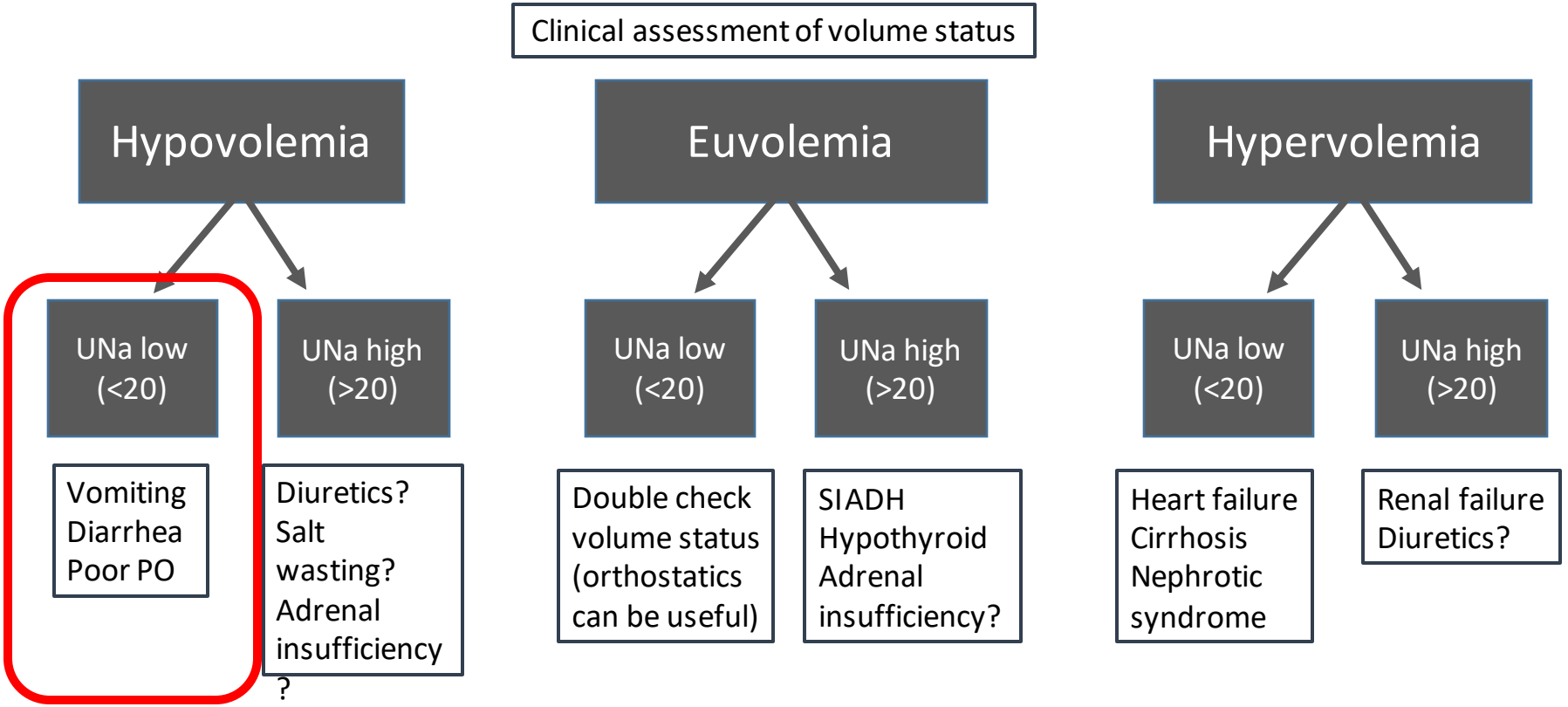
Case #1 continued

Initial urine osmolality was 600 mosm/L

Urine sodium was <10mEq/L

- What do you suspect?
- What is your initial treatment?


Hyponatremia
Measure urine osmolality
Low (<100)
High (>200)
ADH absent
ADH present
Polydipsia
Low solute states
Beer potomania
Tea and toast
Assess volume status and
Check urine sodium


Clinical assessment of volume status
Hypovolemia
Euvolemia
Hypervolemia
UNa low (<20)
UNa high (>20)
UNa low (<20)
UNa high (>20)
UNa low (<20)
UNa high (>20)
Vomiting
Diarrhea
Poor PO
Diuretics?
Salt wasting?
Adrenal insufficiency ?
Double check volume status (orthostatics can be useful)
SIADH
Hypothyroid
Adrenal insufficiency?
Heart failure
Cirrhosis
Nephrotic syndrome
Renal failure
Diuretics?

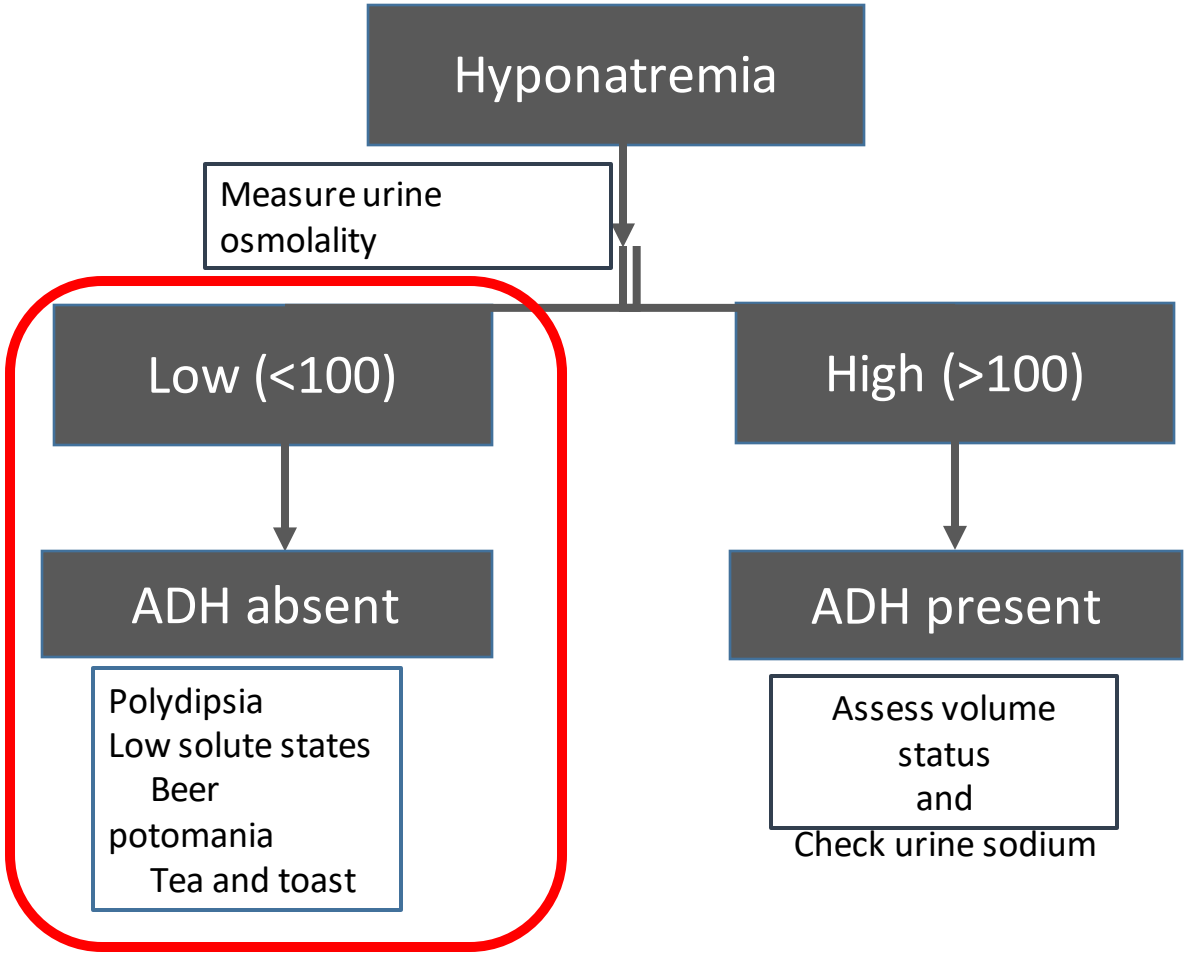
Case #1 continued

- The patient received 2L of normal saline in the ED prior to medicine admission.
- Next day BP 140/80, no longer orthostatic
- Nausea and vomiting improved
- Serum creatinine now 0.7 mg/dL
- Serum sodium now 129 meq/L

- HD#2 – ready for discharge!
- But wait, serum sodium still 129mEq/L

Case #1: Now what?

- Recheck urine osmolarity as a marker for ADH.
- This time 100 mosm/L
- Now what is your diagnosis?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Polydipsia
Low solute states
Beer potomania
Tea and toast
Assess volume status and
Check urine sodium

Primary polydipsia vs. Low solute intake

- Remember, hyponatremia ensues when water intake exceeds maximum urinary free water excretion

- Normal American diet (per day):

600 mosms ÷ 50 mOsms per liter = 12 liters urine /day

- Low solute intake (“tea-and-toast” or “beer potomania”)

200 mosms ÷ 50 mOsms per liter =4 liters urine /day

Case #1 concluded

Further history elicited:

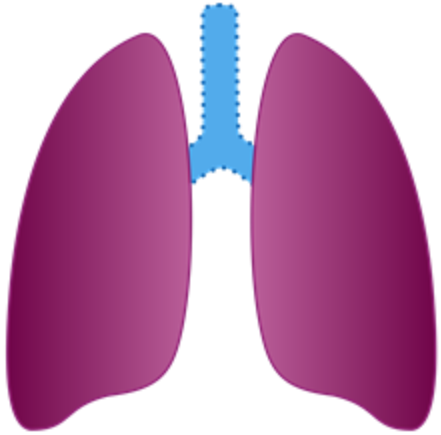
- Extremely depressed x 2 months, little food intake, often eating just crackers and toast at home with black coffee

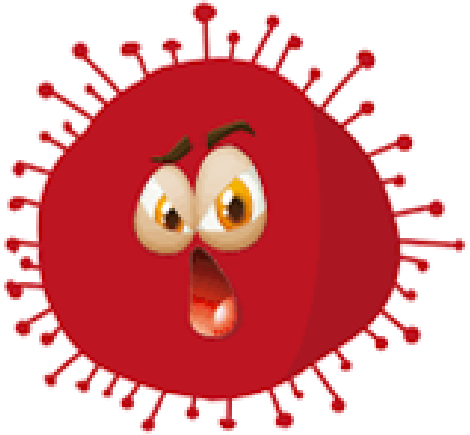
Treatment?

Teaching point #3

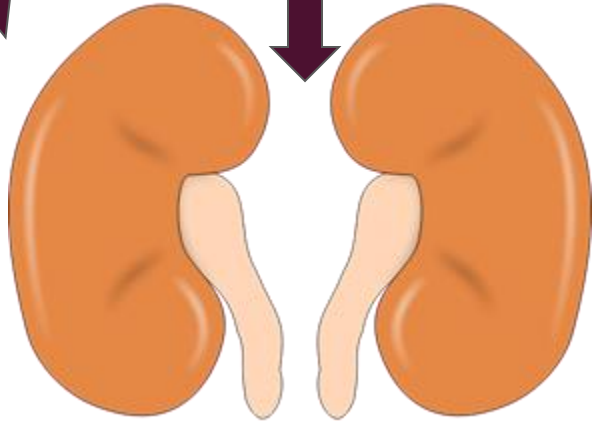
You can always recheck urine studies!

SIADH





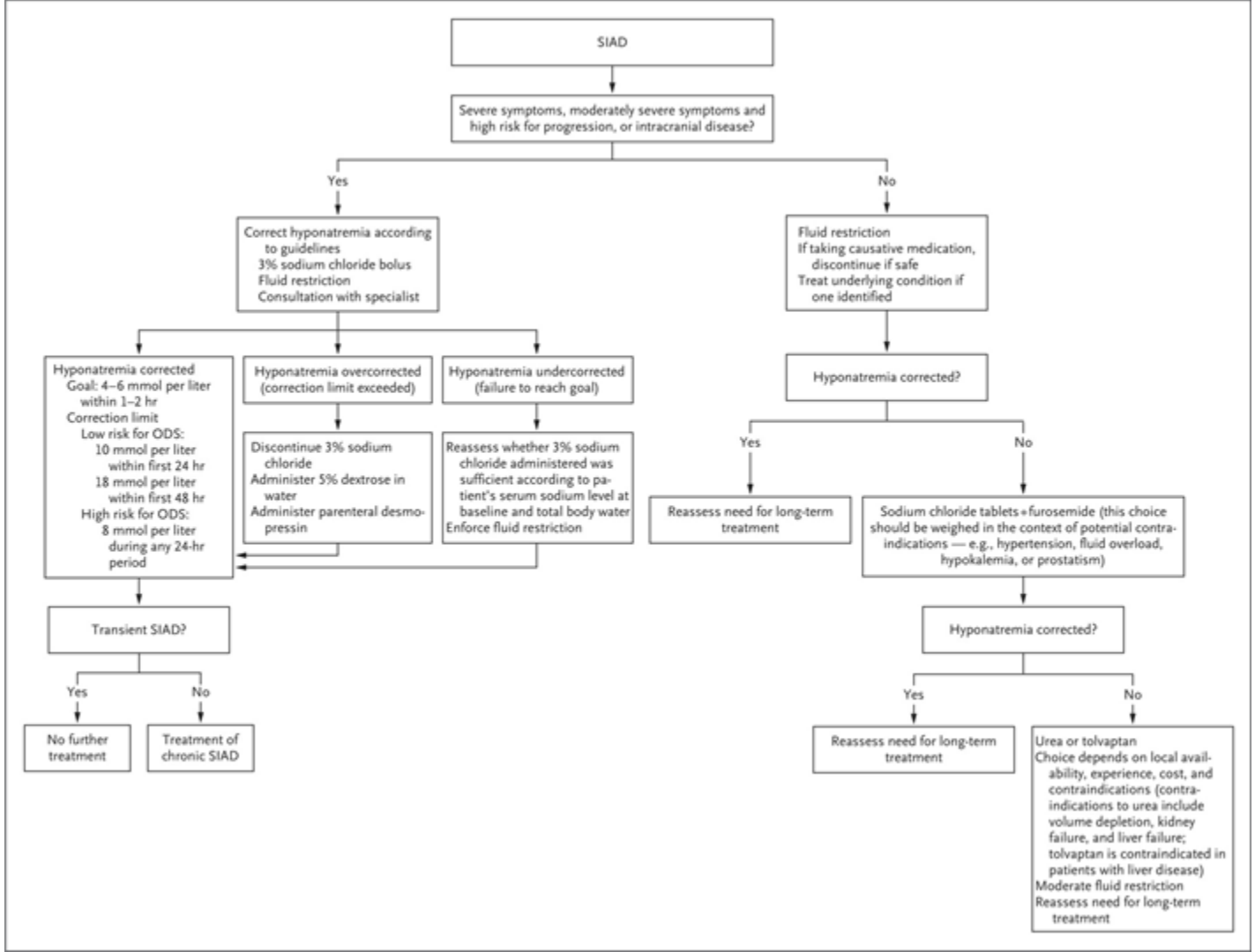
ADH



Treatment of SIADH

SIADH

- Treat the underlying cause.
- Stop the medications (often the last one or the NEW one).
- Rule out hypothyroidism
- Check for adrenal insufficiency
- Obtain urine cations (UNa+UK), serum uric acid and UOsm
- Often UOsm>SOsm and >100 mOsm/kg and UNa>40



Adrogué *et al.* NEJM 2023

Would fluid restriction work?

Electrolyte-Free Water Clearance (C_eH_20)

$$C_eH_20 = V \times \left\{ 1 - \left(\frac{UNa + UK}{PNa} \right) \right\}$$

V=Urine flow rate (ml/min)

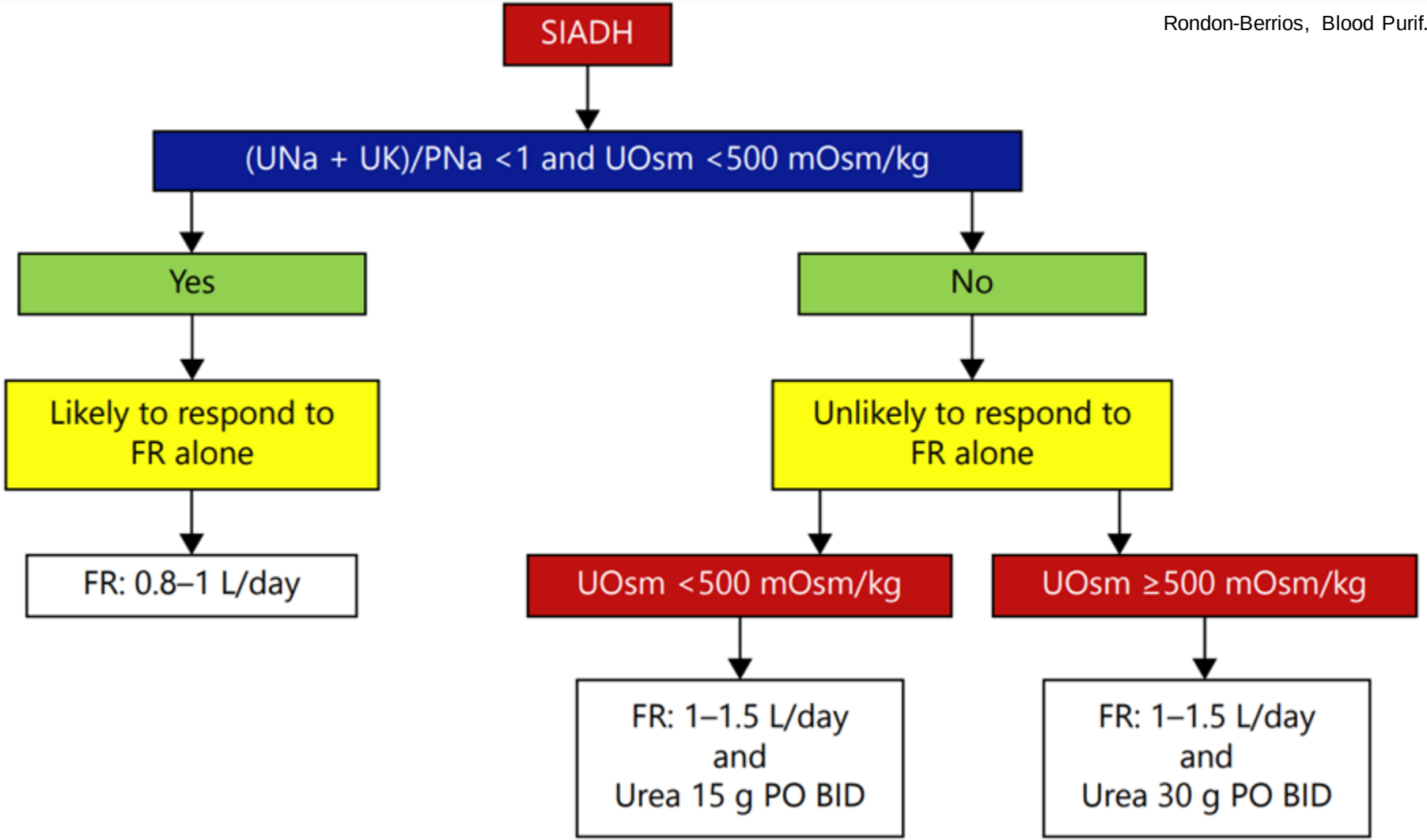
Urine Na+Urine K=Urine cations

$PNa+_{PK}$=Serum cations

When would fluid restriction not work?

- High urine osmolality (>500 mOsm/kg H_20)
- (U_{Na} + U_K) > plasma Na
- 24-hour urine volume < 1500 mL
- Initial rise in serum Na < 2 mmol/L/d after fluid restriction

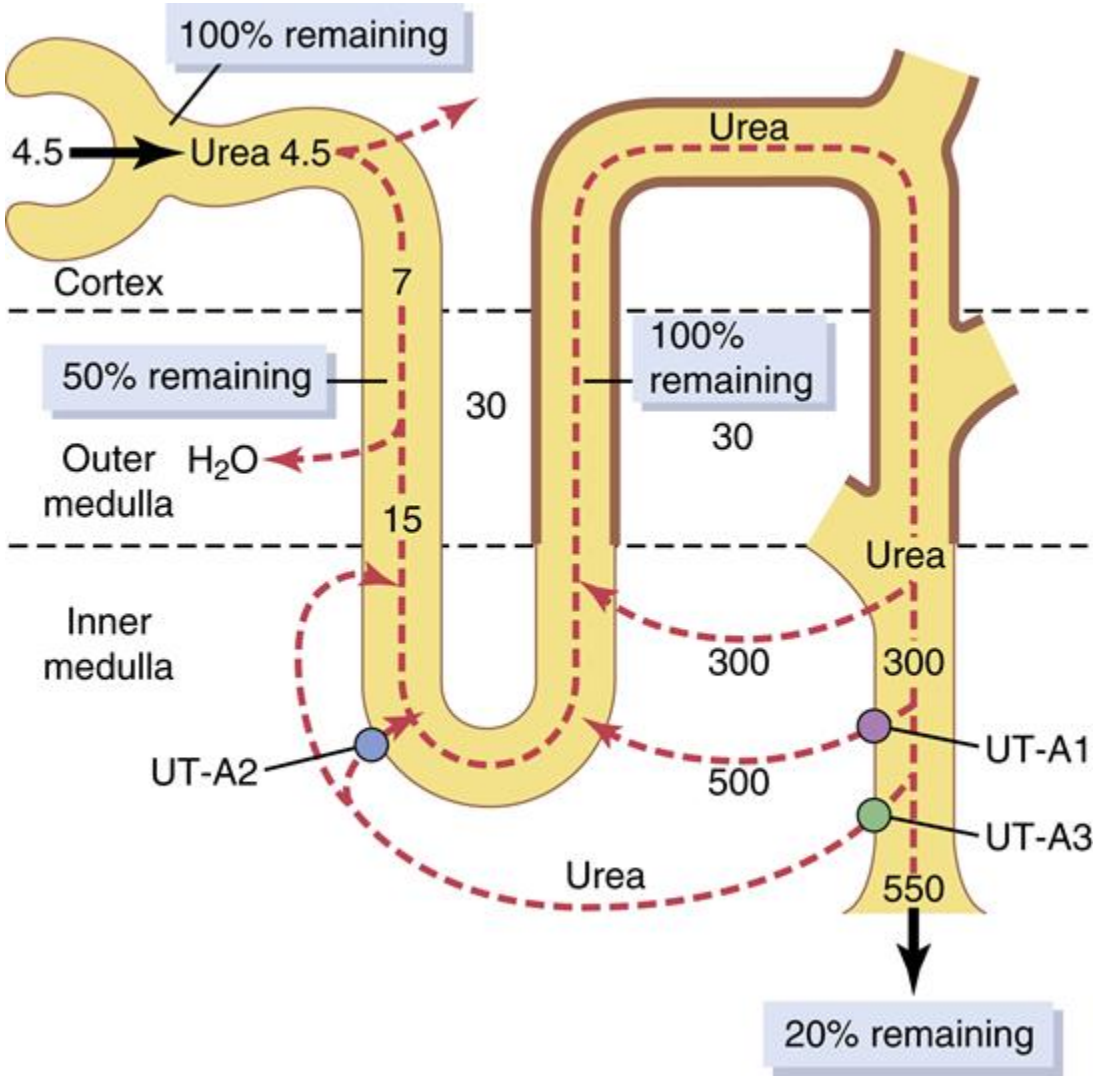
Rondon-Berrios, Blood Purif. 2019



~~Salt tablets+Furosemide~~

Setting	Solute intake mOsm/d	Water intake L/d	Urine osmolarity mOsm/L	Urine volume L/d	Water balance L/d
Normal	600	2	600/2=300	2	0
SIADH	600	2	500	600/500=1.2	+0.8
SIADH+ NaCL 6g/d	600+205=805	2	500	805/500=1.61	+0.39
SIADH+ Urea 30 g/d	600+500= 1100	2	500	1100/500=2.2	-0.2

Urea


100% remaining
4.5
Urea 4.5
Cortex
7
50% remaining
Outer medulla
H_2O
15
Inner medulla
30
Urea
100% remaining
30
Urea
300
300
UT-A2
UT-A1
500
UT-A3
Urea
550
20% remaining

How safe and effective is oral urea for the treatment of hyponatremia in hospitalized patients?

CJASN
Clinical Journal of American Society of Nephrology

Methods

- Retrospective EHR review
- 4 hospitals within UPMC system, Jul 2016 – Aug 2017
- Plasma Na < 135 mEq/L
- ≥ 1 Urea dose

Cohort

- 58 patients
  68 years
  81% SIADH
- 7.5-90 g/day for 4.5 days
- 24% treated with urea only

Results

- Na^+ change 124 → 131 mEq/L
- 1 patient did not tolerate urea
- Na^+ No overcorrection

Sub-group matched control

Treated only with urea
N=12

Na change at 24h	Final Na ≥ 135 mEq/L
+ 2.5 mEq/L	33%

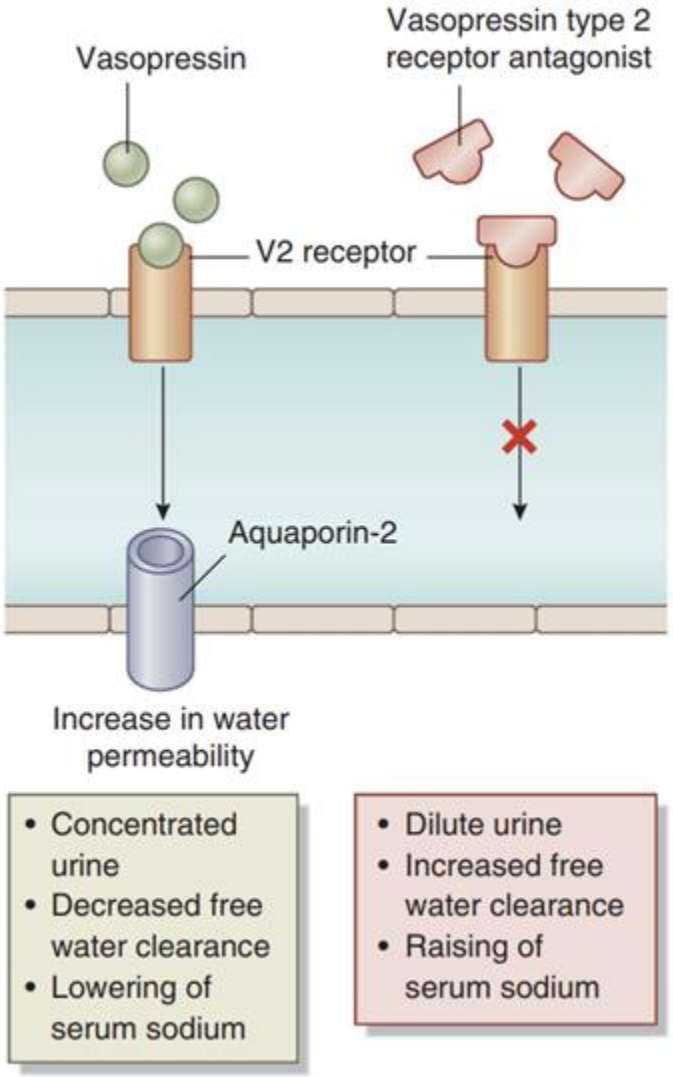
Treated without urea
N=12

Na change at 24h	Final Na ≥ 135 mEq/L
- 0.5 mEq/L	8%
p=0.04	p=0.08

Conclusions In this retrospective review of urea use in the hospital, urea was safe, well-tolerated, and effective for the correction of hyponatremia.

Helbert Rondon-Berrios, Srijan Tandukar, Maria K. Mor, Evan C. Ray, Filitsa H. Bender, Thomas R. Kleyman, and Steven D. Weisbord. ***Urea for the Treatment of Hyponatremia.*** CJASN doi: 10.2215/CJN.04020318

Vaptans



- Targets excessive AVP
- Safe and effective
- Predictable rise in sodium values
- No risk for concomitant electrolyte disorders

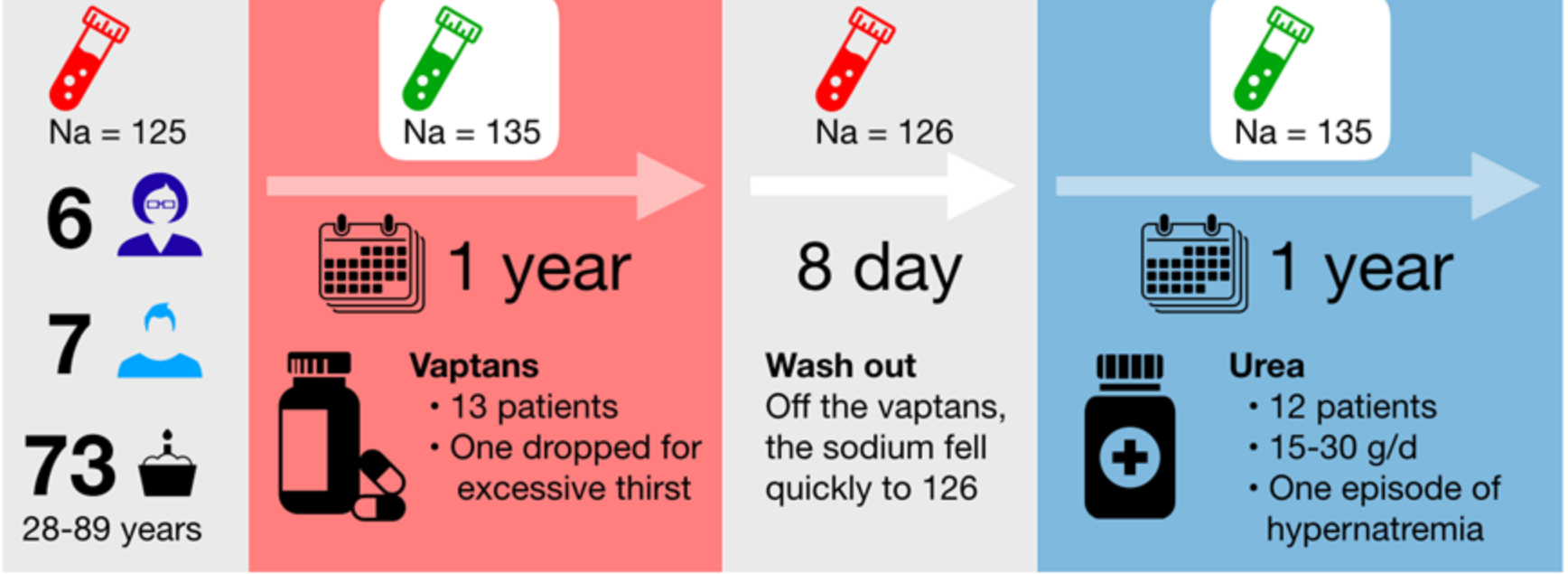
- Expensive

  15-mg tolvaptan ($438.29)

  15-g urea ($3.74)
- Induces polyuria
- Requires close monitoring of Na+

How do vaptans compare to urea for the long term management of SIADH and hyponatremia?

2018 NEPH MADNESS
presented by AJKD

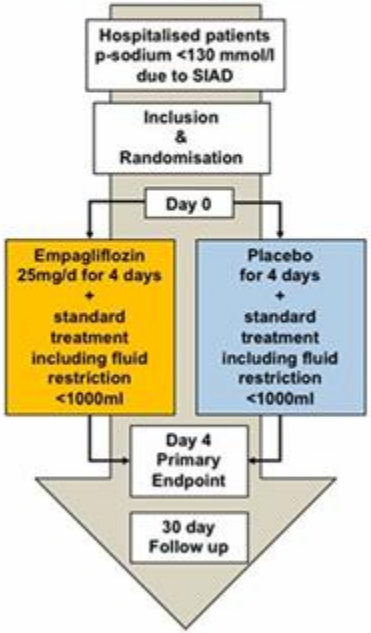


Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Clin J Am Soc Nephrol 7: 742–747, 2012. doi: 10.2215/CJN.06990711

Empagliflozin

Empagliflozin increases plasma sodium levels in patients with the syndrome of inappropriate antidiuresis (SIAD)

METHODS

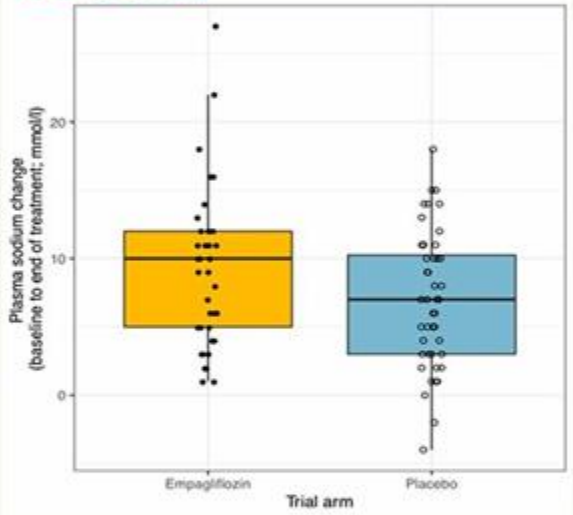


Median (IQR) increase p-sodium in mmol/l:

Empagliflozin 10 (5,10)

Placebo 7 (3,11)

OUTCOME



CONCLUSION Empagliflozin in addition to fluid restriction leads to a higher increase in plasma sodium levels compared to placebo in hospitalized patients with SIAD.

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Take home points

- Hyponatremia is the most common electrolyte abnormality encountered in hospitalized patients.
- The kidneys have the remarkable ability to dilute the urine to as low as 50 mOsm (no ADH) and concentrate urine to 1200 mOsm (max ADH).
- Urine osmolarity is a surrogate marker of ADH release.
- A typical american diet is 600 mOsm daily and low solute intake can contribute to hyponatremia (tea and toast diet and beer potomania).
- Fluid restriction, urea, empagliflozin and vaptans are used in the treatment of SIADH