



Improving Awareness & Patient Outcomes

# Considerations in the Diagnosis of Hyponatremia

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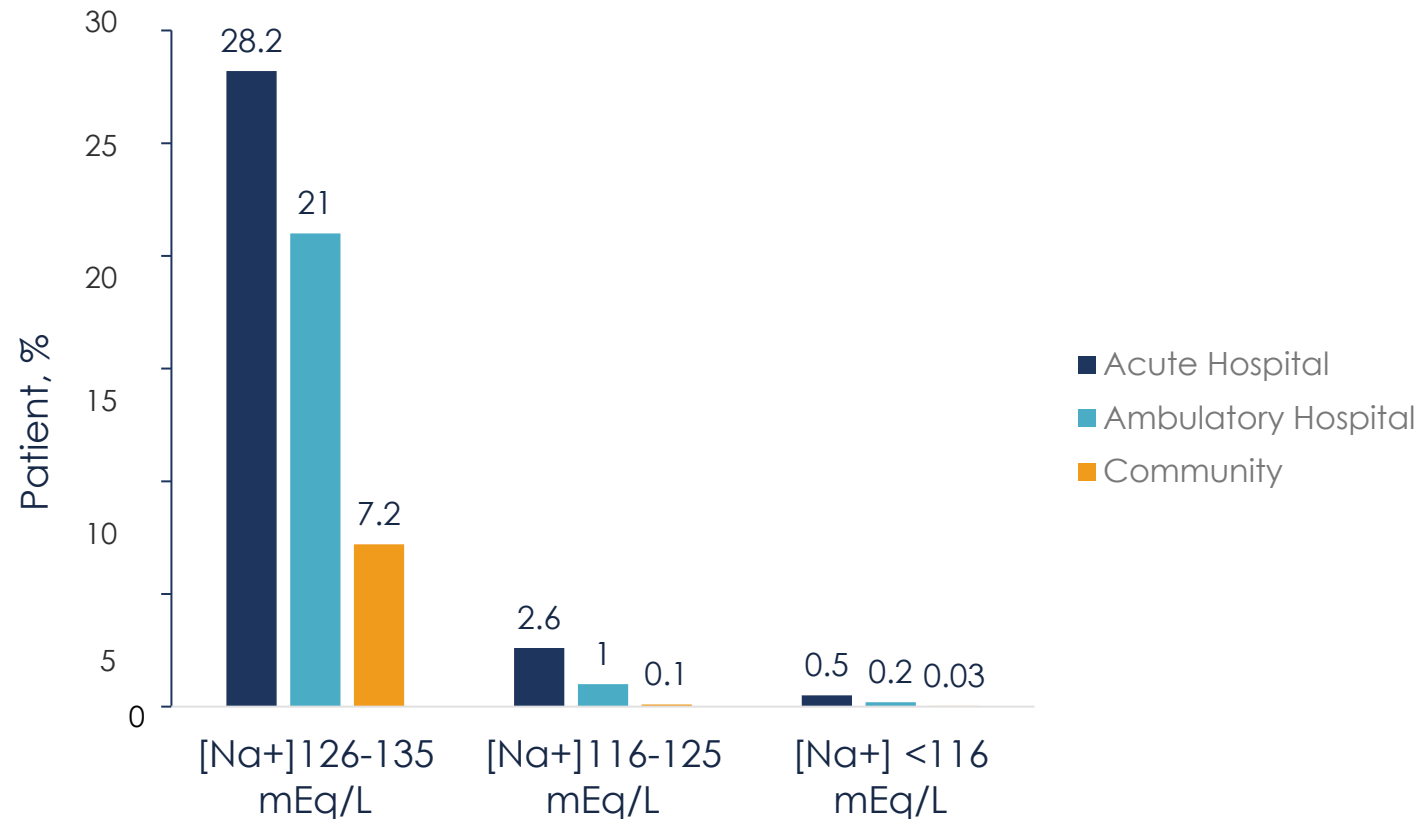
# Speakers

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Dr. Arthur Greenberg  
Professor of Medicine, Emeritus  
Division of Nephrology  
Duke University School of Medicine  
Durham, NC

# Prevalence of Hyponatremia in the Hospital and in the Community

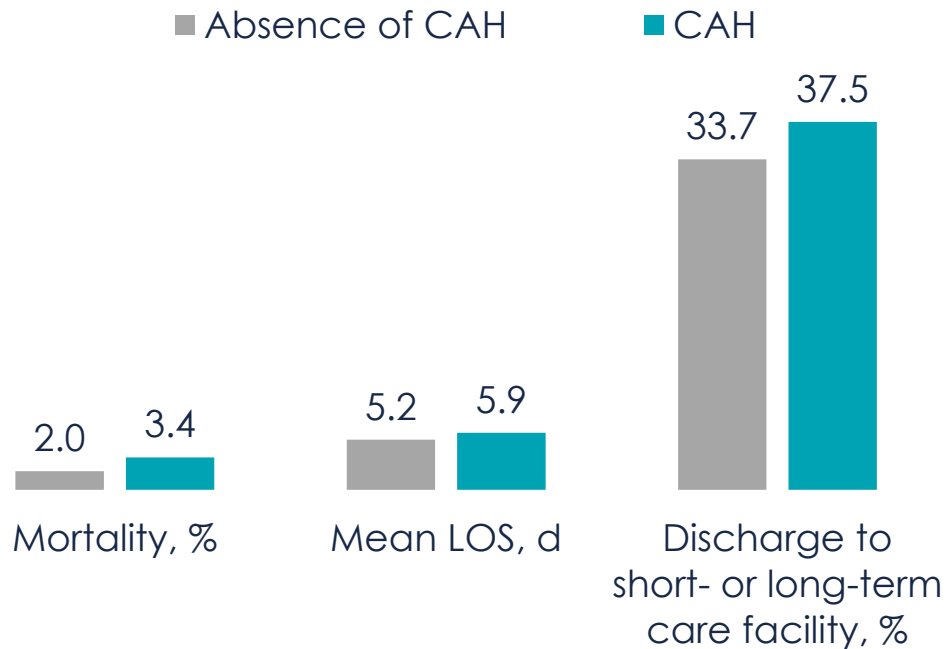


Data, obtained from the Tan Tock Seng Hospital in Singapore, are based on 303,557 samples from 120,137 patients available for analysis.

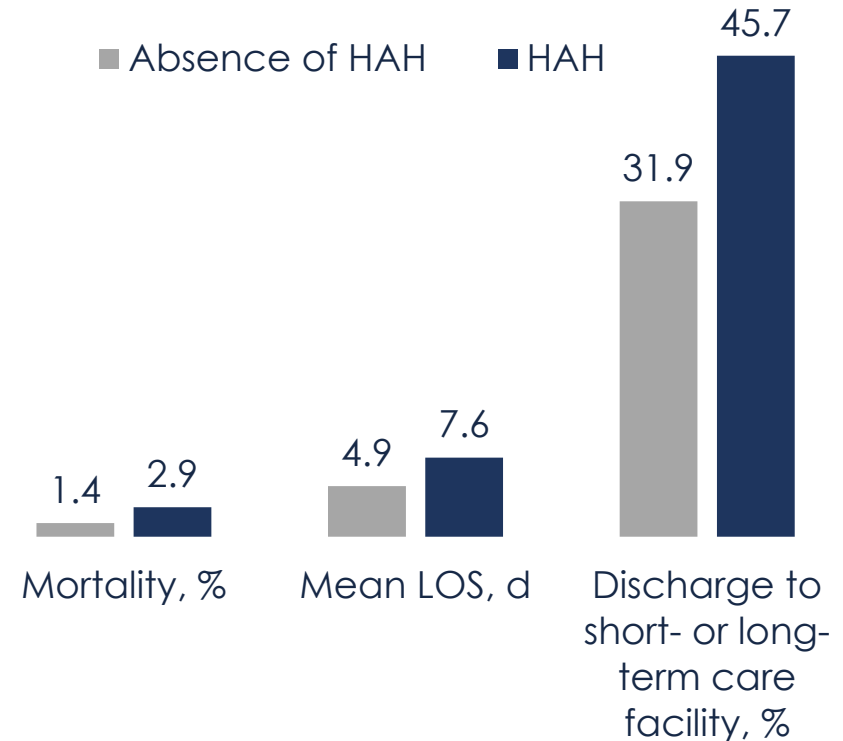
1. Hawkins R.C. (2003). *Clin Chim Acta*. 337(1-2):169-172.

# Hospital Outcomes in Community-Acquired and Hospital-Acquired Hyponatremia

## Community-Acquired Hyponatremia (CAH)



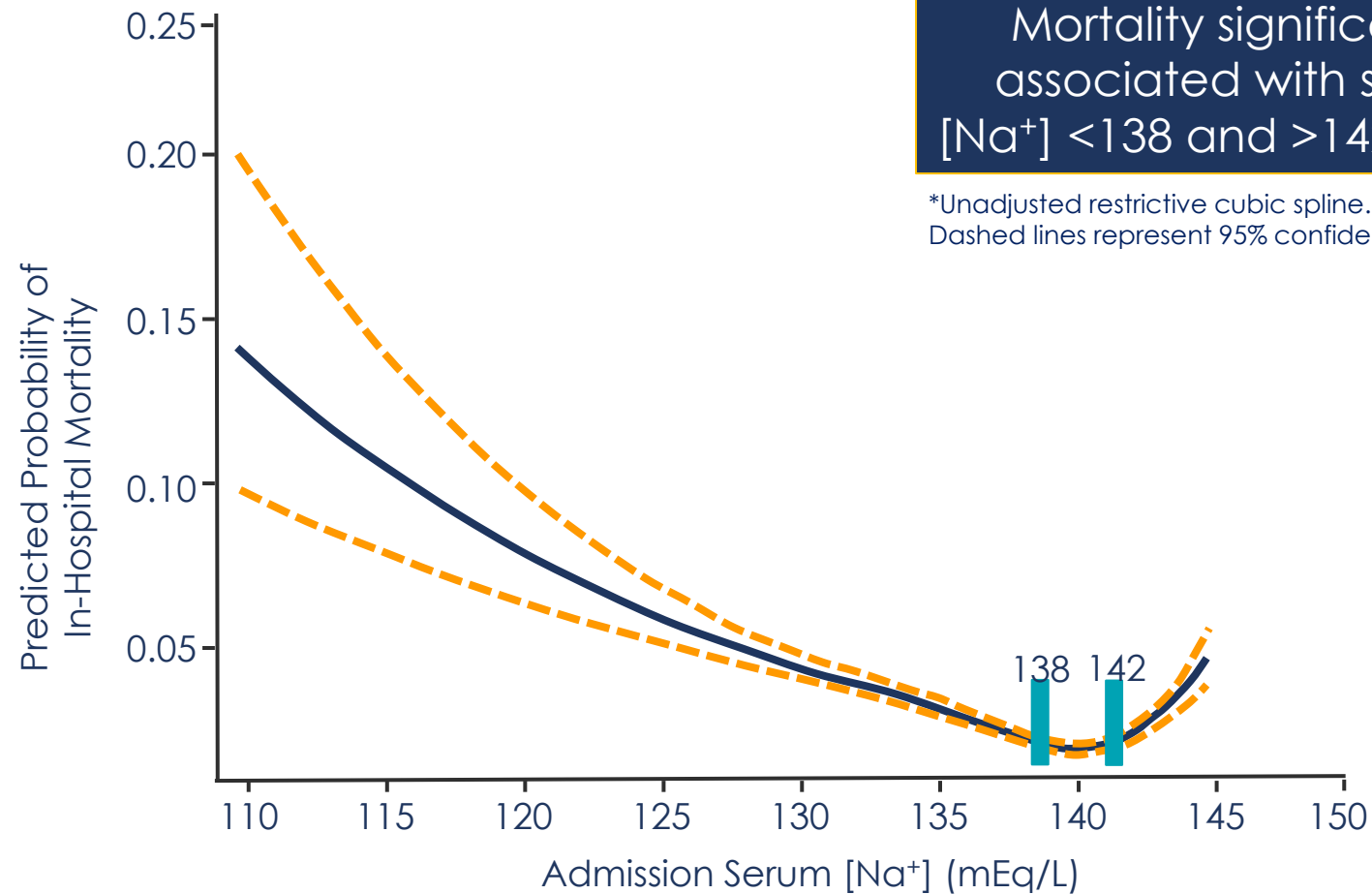
## Hospital-Acquired Hyponatremia (HAH)



LOS, length of stay

1. Wald R, et al. (2010). *Arch Intern Med*.170:294-302.

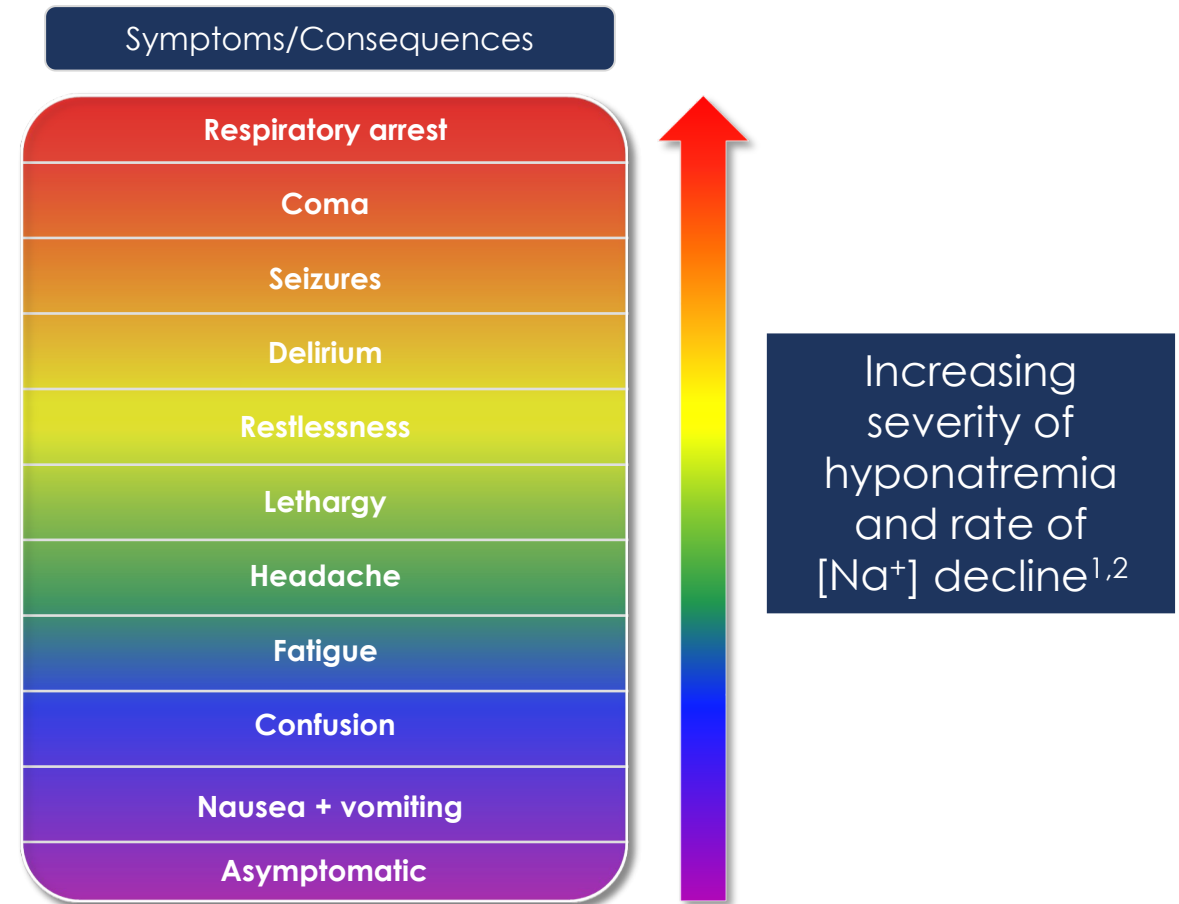
# Association Between Hospital Admission Serum [Na<sup>+</sup>] and In-Hospital Mortality\*



1. Wald R. et al. (2010). *Arch Intern Med* 170:294-302.

# Symptoms Correlate With Severity and Rate of Decline in Serum [Na<sup>+</sup>]

- Asymptomatic presentation common
- May present with mild, nonspecific symptoms
- Degree of symptomatology is surrogate for duration of hyponatremia
- Symptoms from underlying disease process also common



1. Bagshaw S.M, et al.(2009). *Anesth.*;56:151-67.  
2. Ghali J. (2008). *Cardiology.* 111:147-57.



# Arginine Vasopressin (AVP) in the Pathophysiology of Hyponatremia

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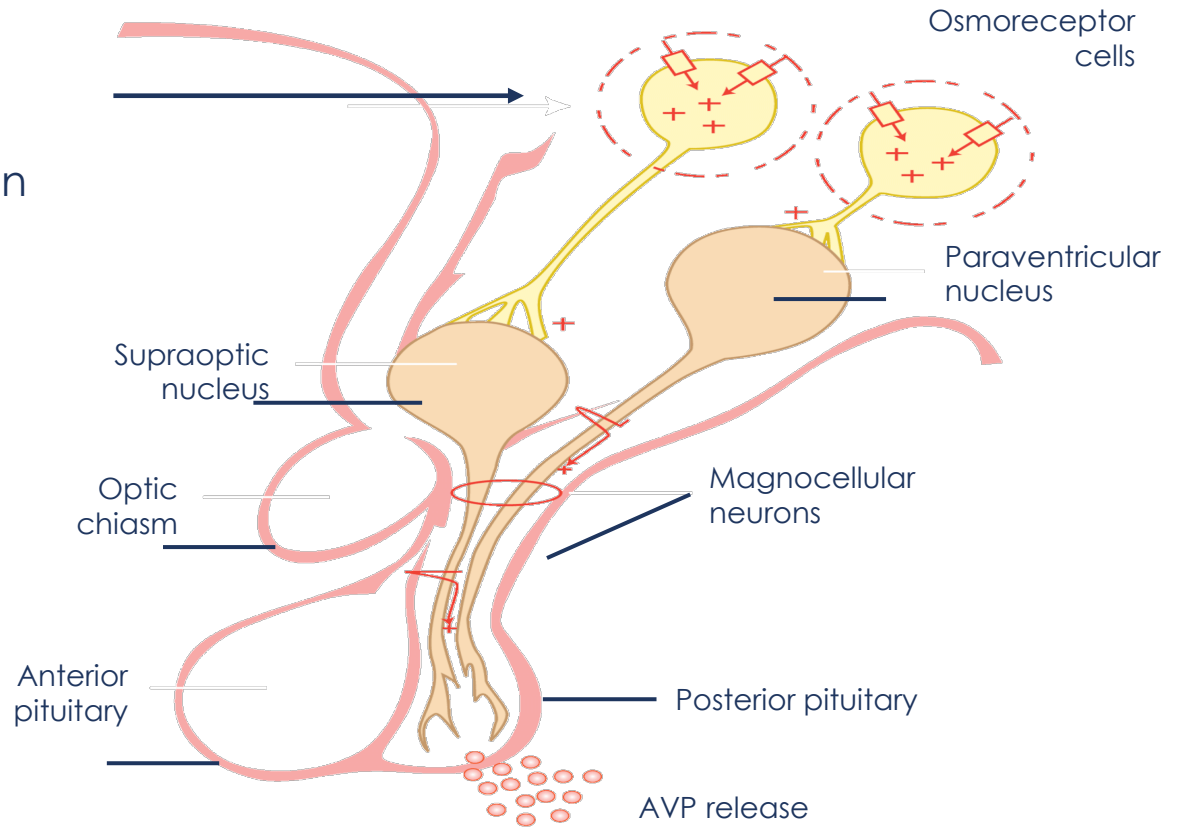
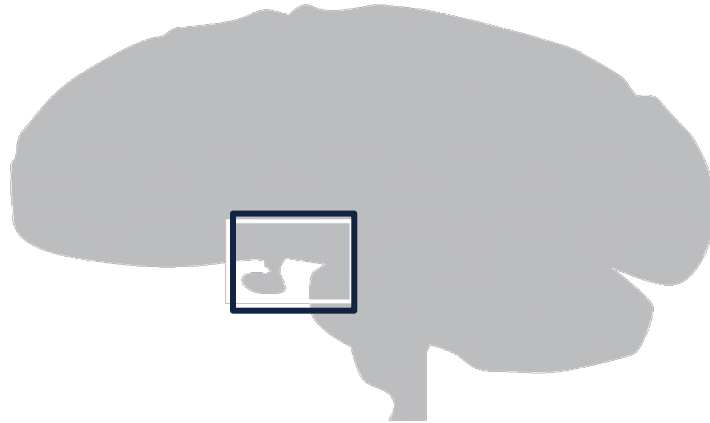
- AVP, also termed Vasopressin or Anti-Diuretic Hormone (ADH), is a peptide hormone composed of 9 amino acids
- Synthesized within supra-optic and paraventricular nuclei of hypothalamus
  - Transported from hypothalamus via nerve tracts to neural lobe of pituitary, where it is released into circulation
- Regulates urinary water excretion

1. Verbalis J.G, Berl T. (2007). Disorders of water balance. In: Brenner BM. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia, PA: Saunders.

# Osmoregulation of AVP Release

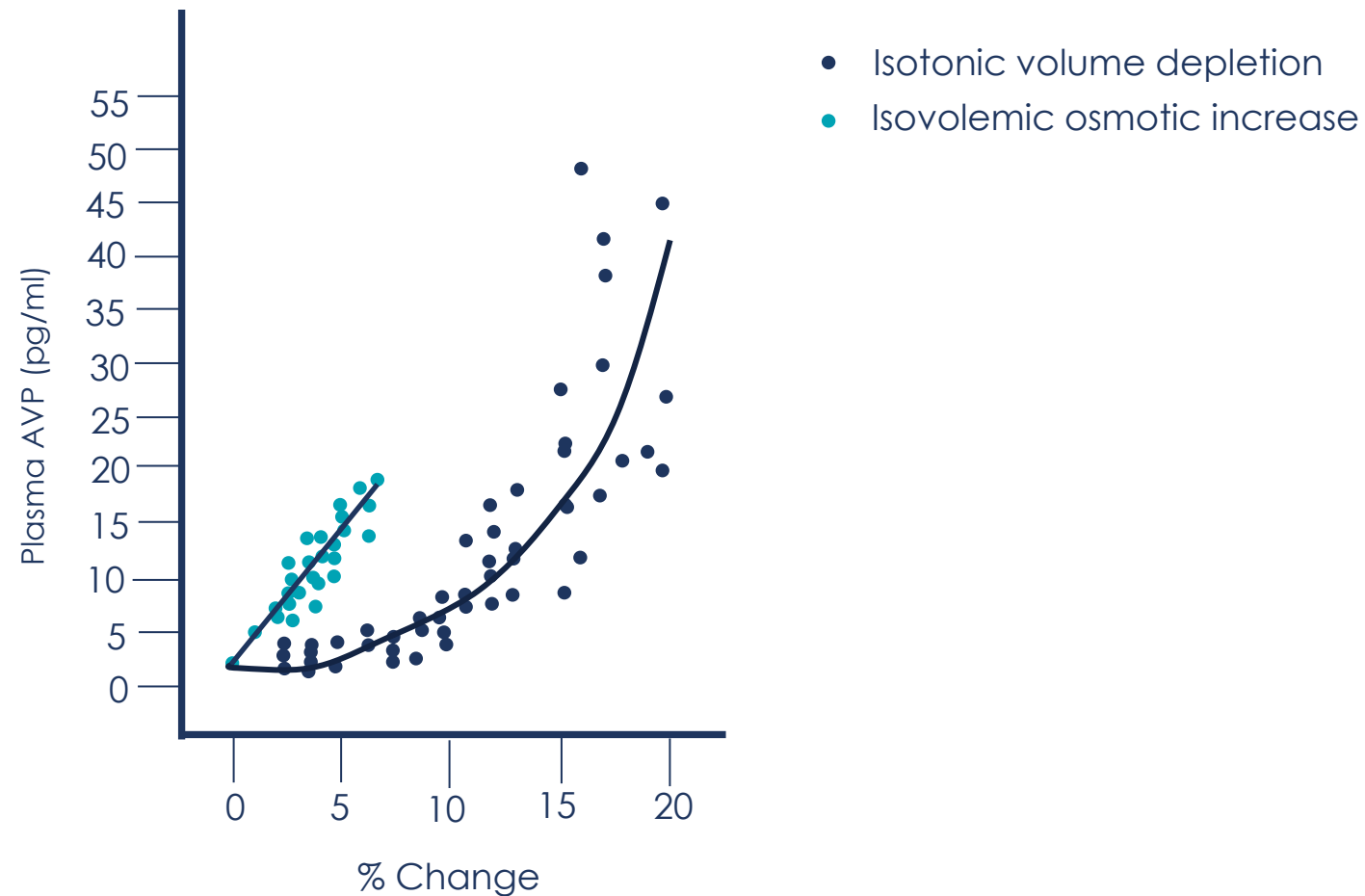
Increased extracellular tonicity causing shrinkage of osmoreceptor cell

↳ Activation of “stretch inhibitable” cationic channels and subsequent depolarization of the cell



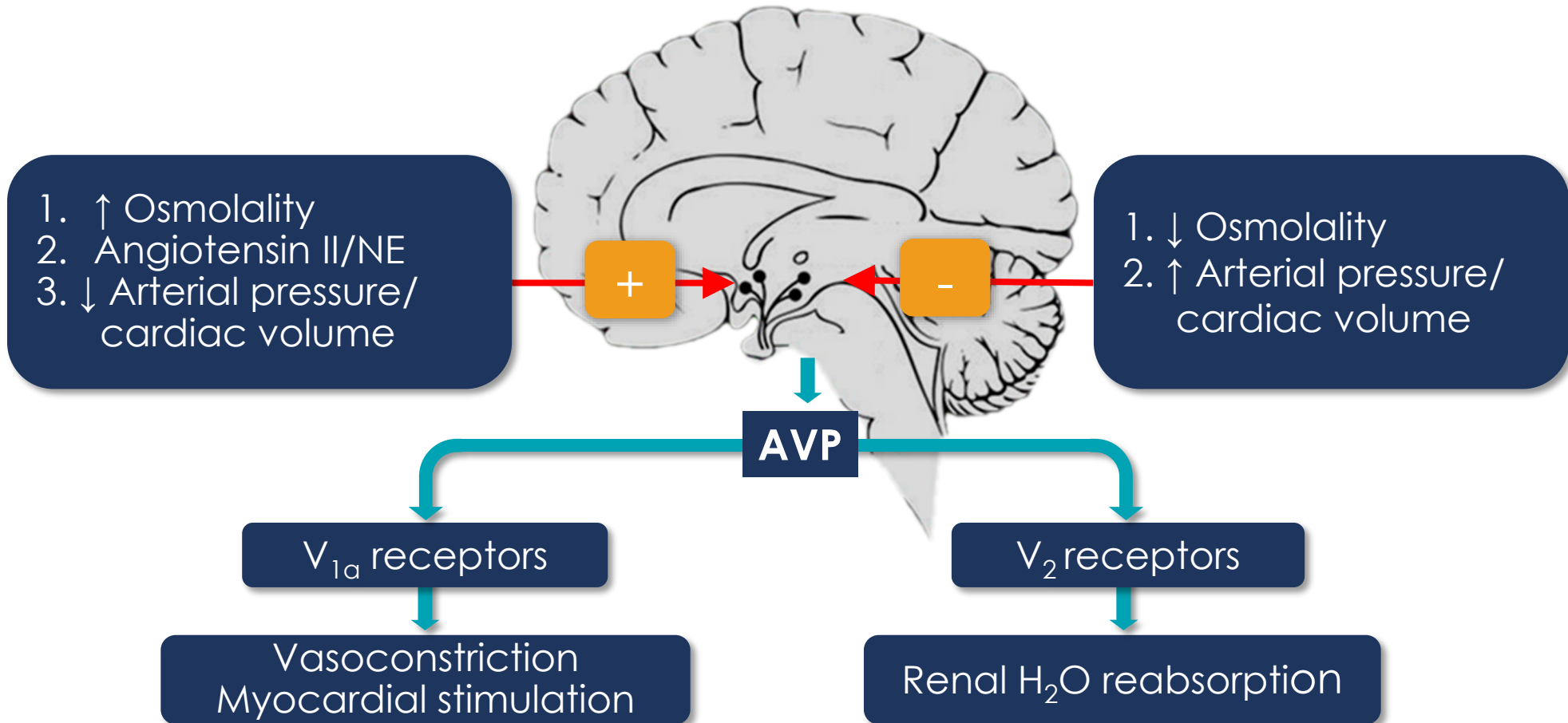
1. Zenenberg R.D. (2010). *Hosp Pract*;38:89-96.

# Stimulation of AVP Levels in Response to Changes in Intravascular Volume or Tonicity



1. Dunn J. (1973). *Clin Invest.* 52:3213.

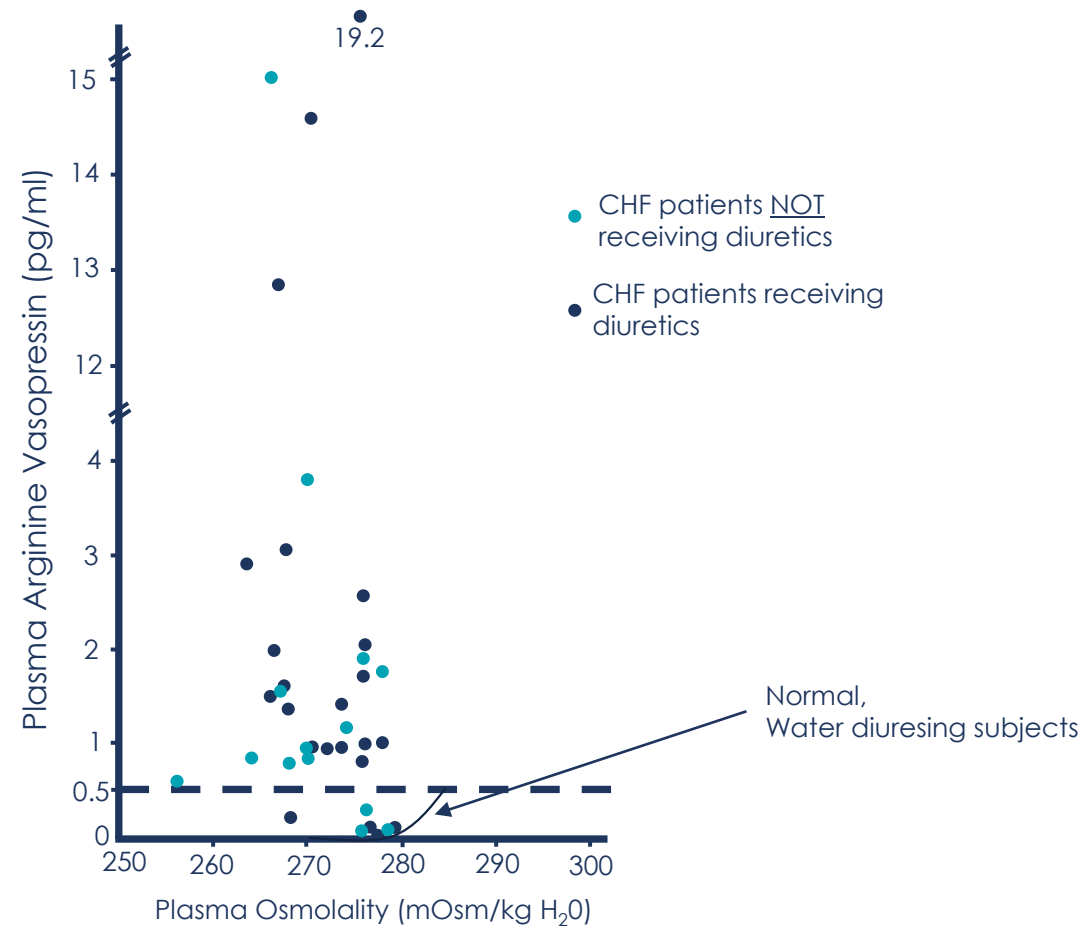
# AVP Stimulation and Effects



NE, norepinephrine.

1. Lee C.R. et al. (2003). *Am Heart J*, 146:9-18.

# AVP Levels and Plasma Osmolality in Patients with CHF



1. Szatalowicz V.L. et al. (1981). *New Engl J Med.* 305:263.

# Renal Diluting Mechanism (Vasopressin Absent)

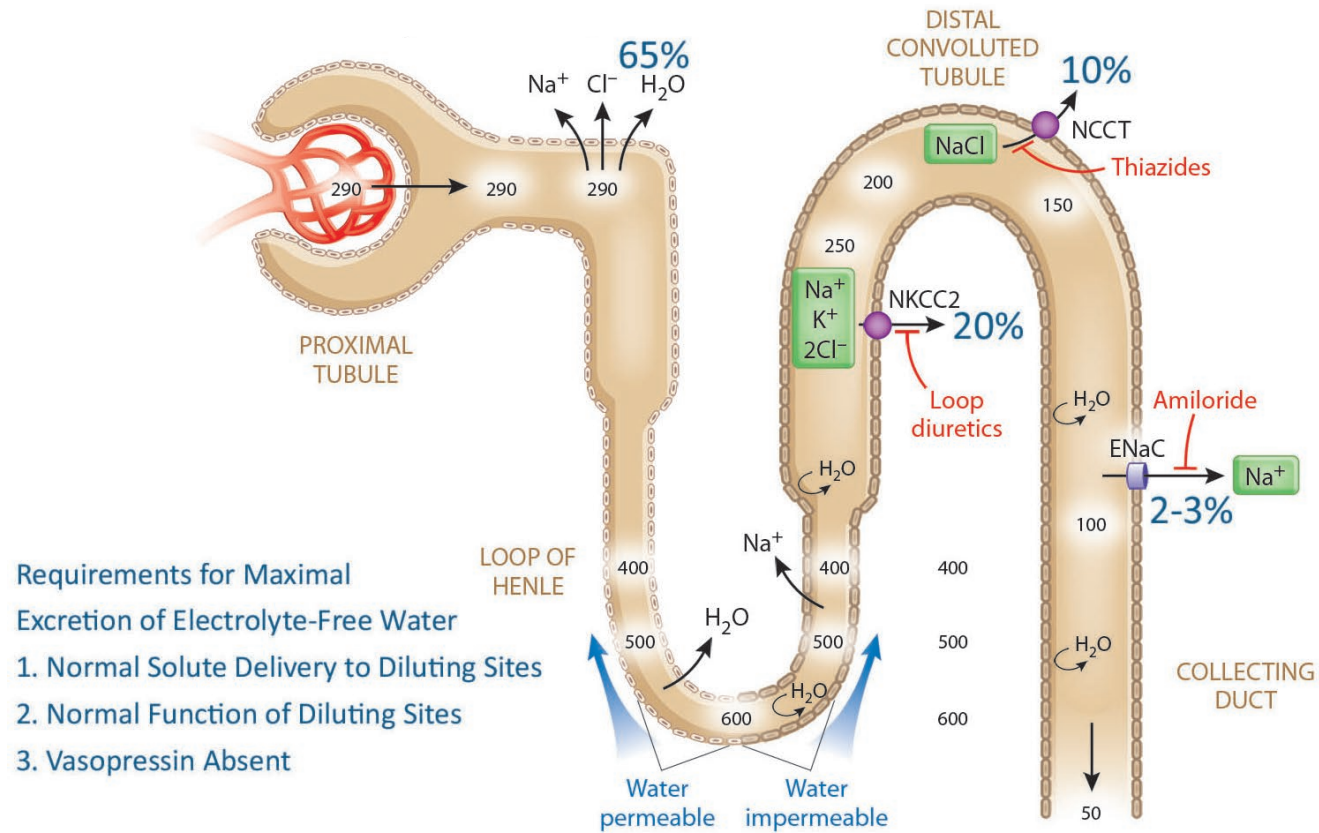
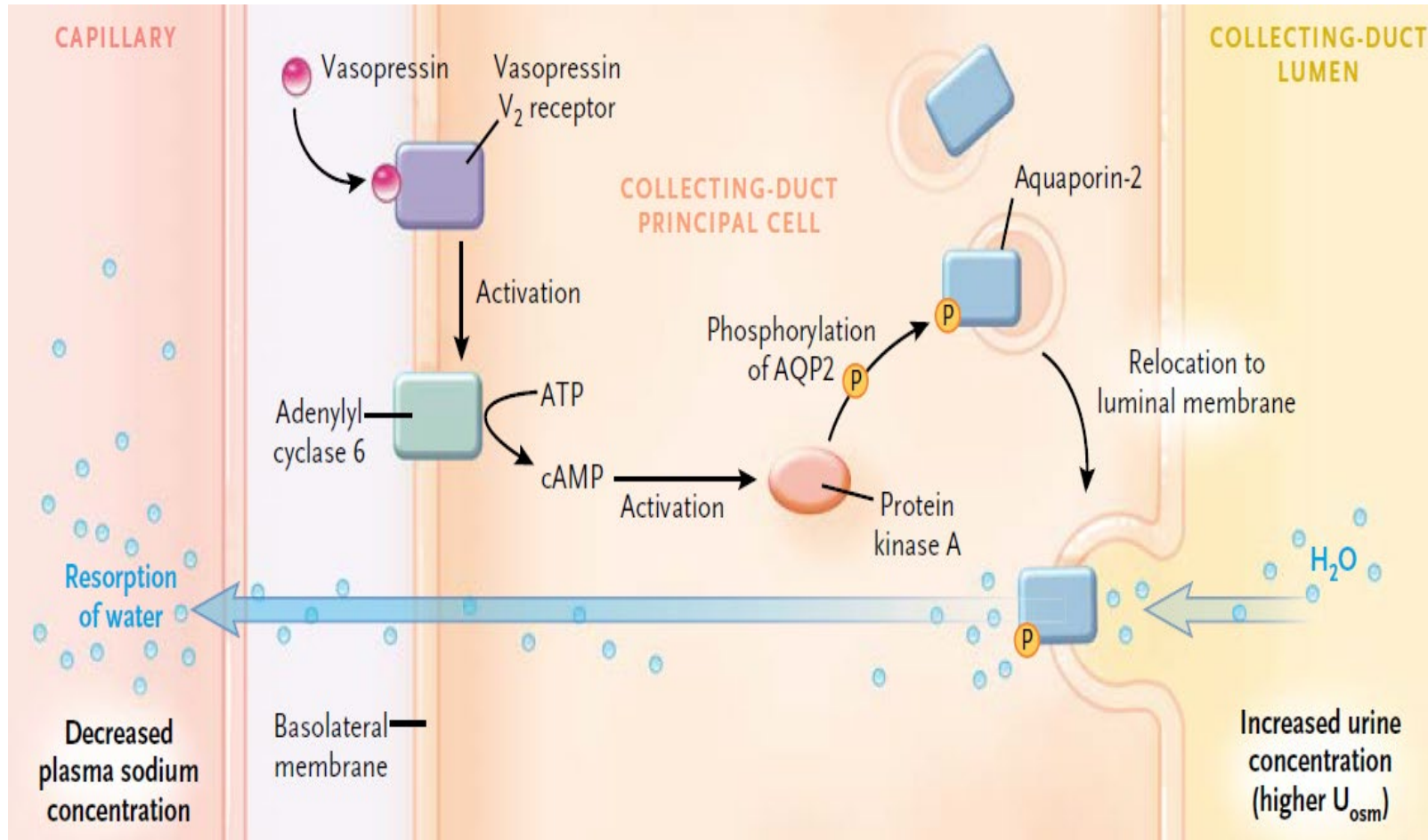


Figure from Greenberg; used with permission

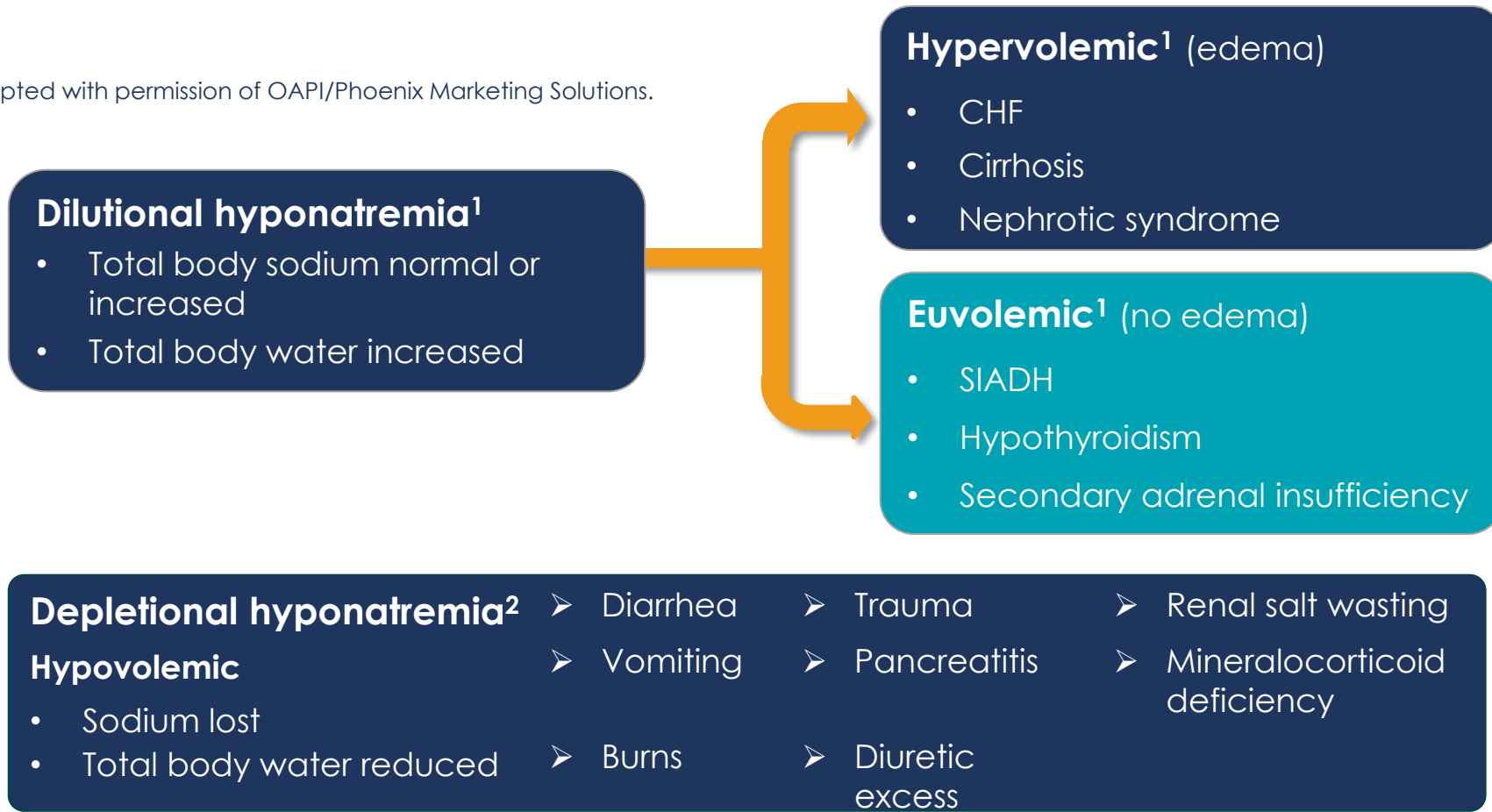
# Cellular Pathway of the Hydro-osmotic Effect of Vasopressin



1. Berl T. (2015). *NEJM*. 372:2207-2216.

# Dilutional vs Depletional Hyponatremia

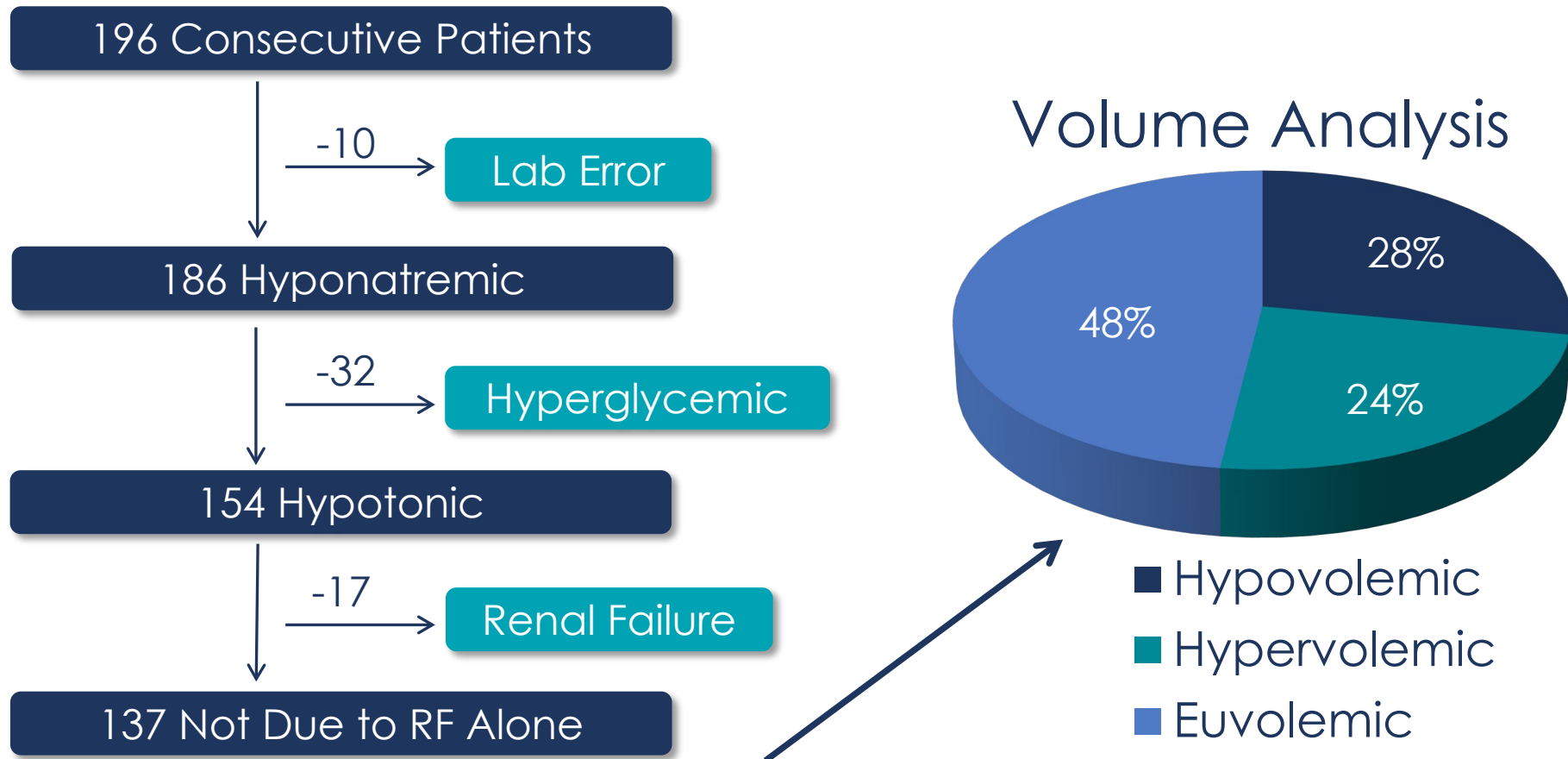
Adapted with permission of OAPI/Phoenix Marketing Solutions.



1. Douglas D. (2006). *Cleve Clin Med*. 73:S4-12.  
2. Kumar S, Berl T. *Lancet*. (1998). 352:2208.



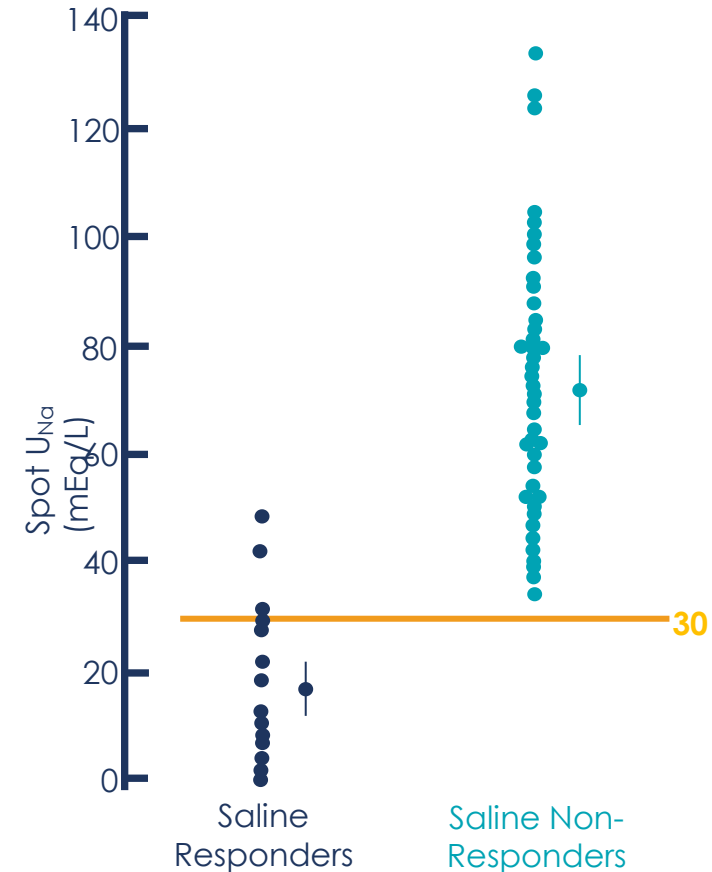
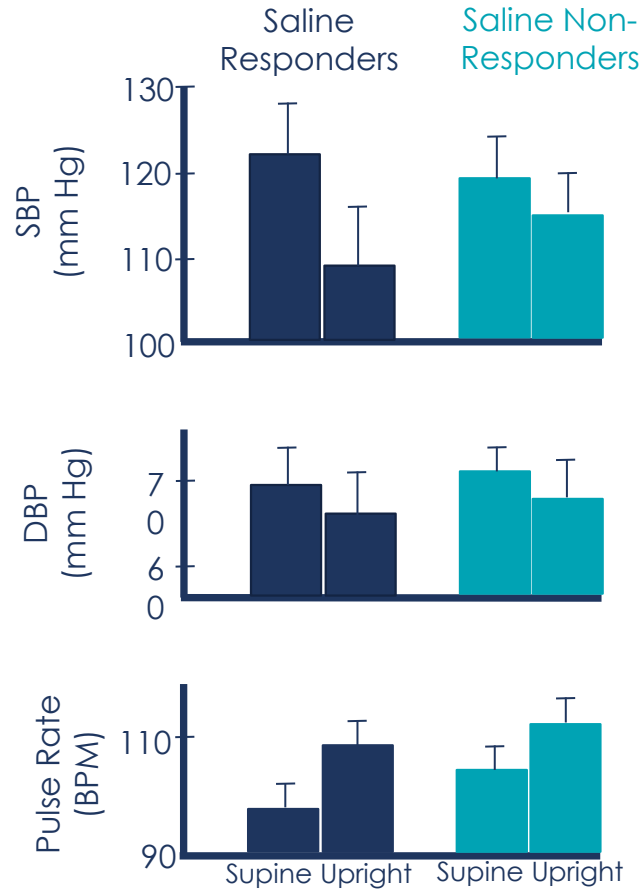
# Distribution of Hyponatremia in Hospitalized Patients



RF=Renal Failure

1. Anderson R. (1985). *Ann Intern Med* 102:164.

# Assessment of Extracellular Fluid Volume in Hyponatremia



SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; BPM=Beats Per Minute

1. Chung H.M. (1987). *Am J Med.* 83:905.

# Essential Criteria for Diagnosis of SIADH

## 1. ↓ Effective osmolality of ECF

$$P_{\text{osm}} < 275 \text{ mOsm/kg H}_2\text{O}$$

## 2. Inappropriate urinary concentration

$U_{\text{osm}} > 100 \text{ mOsm/kg H}_2\text{O}$  with normal renal function at some level of hypo-osmolality

## 3. Clinical euvolemia

No signs of hypovolemia (orthostasis, tachycardia, ↓'d skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)

## 4. Elevated urinary sodium excretion despite normal salt and water intake

## 5. No other potential causes of euvolemic hypo-osmolality (e.g., hypothyroidism, hypocortisolism, diuretic use)

$P_{\text{osm}}$  = plasma osmolality;  $U_{\text{osm}}$  = urinary osmolality

1. Janicic N, Verbalis J.G. (2003). *Endocrinol Metab Clin North Am*.32:459-81.

# Causes of SIADH

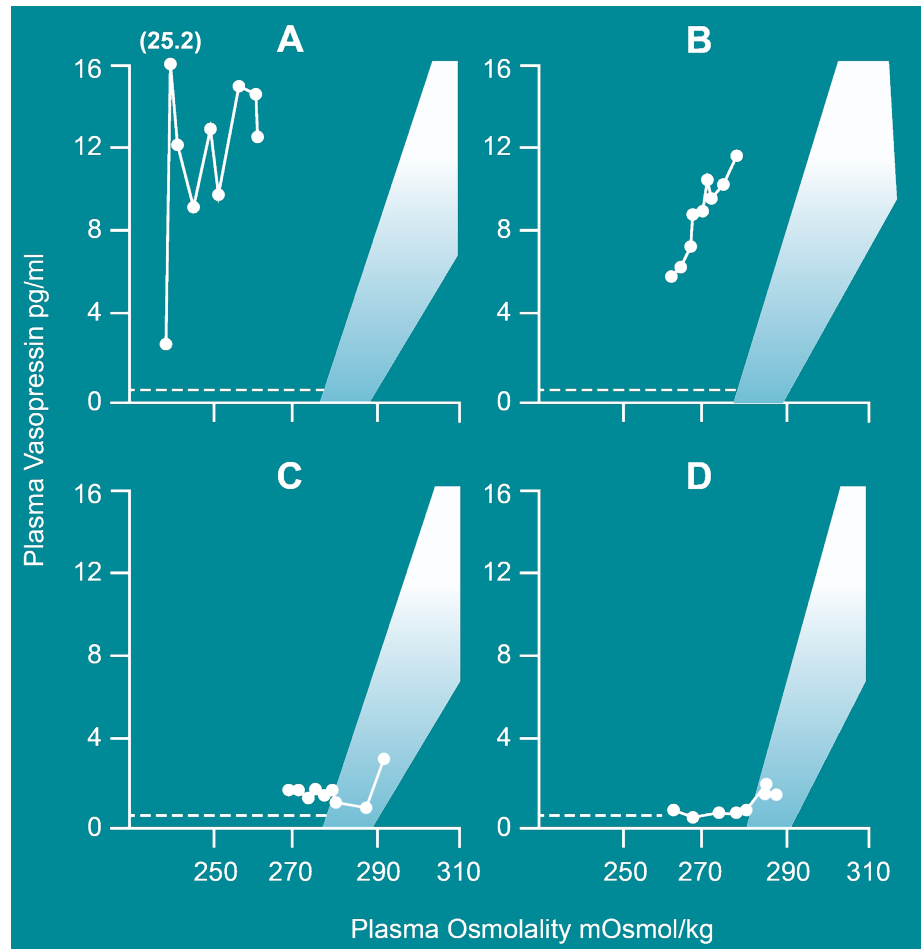
- CNS Disorders<sup>1</sup>
  - Vascular disease, mass lesions (tumor, abscess, SDH, SAH), trauma, hydrocephalus, infection, AIP, schizophrenia, encephalitis including lupus
- Neoplasms with ectopic ADH secretion<sup>1</sup>
  - Lung (especially small cell), nasopharynx, thymoma, lymphoma, leukemia, uterus, ureter & bladder, prostate
- Pulmonary Disease<sup>1,2</sup>
  - Pneumonia, lung abscess, empyema, bronchiectasis, tuberculosis, positive pressure ventilation, COPD
- Drugs<sup>2</sup>
  - Psychiatric: tricyclic antidepressants, SSRIs, atypical antipsychotics
  - Anti-seizure medications
  - Other: ACEI, anti-neoplastics
  - Opiates
- Miscellaneous<sup>1,2</sup>
  - AIDS
  - Idiopathic, especially elderly

SDH=subdural hemorrhage; SAH=subarachnoid hemorrhage; AIP=acute intermittent porphyria; COPD=chronic obstructive lung disease

1. Modified from Adrogué H.J. (2005). *Am J Nephrol*. 25:240-9.

2. Schrier R.W. (2007). (ed): *Disease of the Kidney*. Philadelphia, Lippincott Williams & Wilkins. 2214-2248.

# Patterns of Inappropriate AVP Release in SIADH

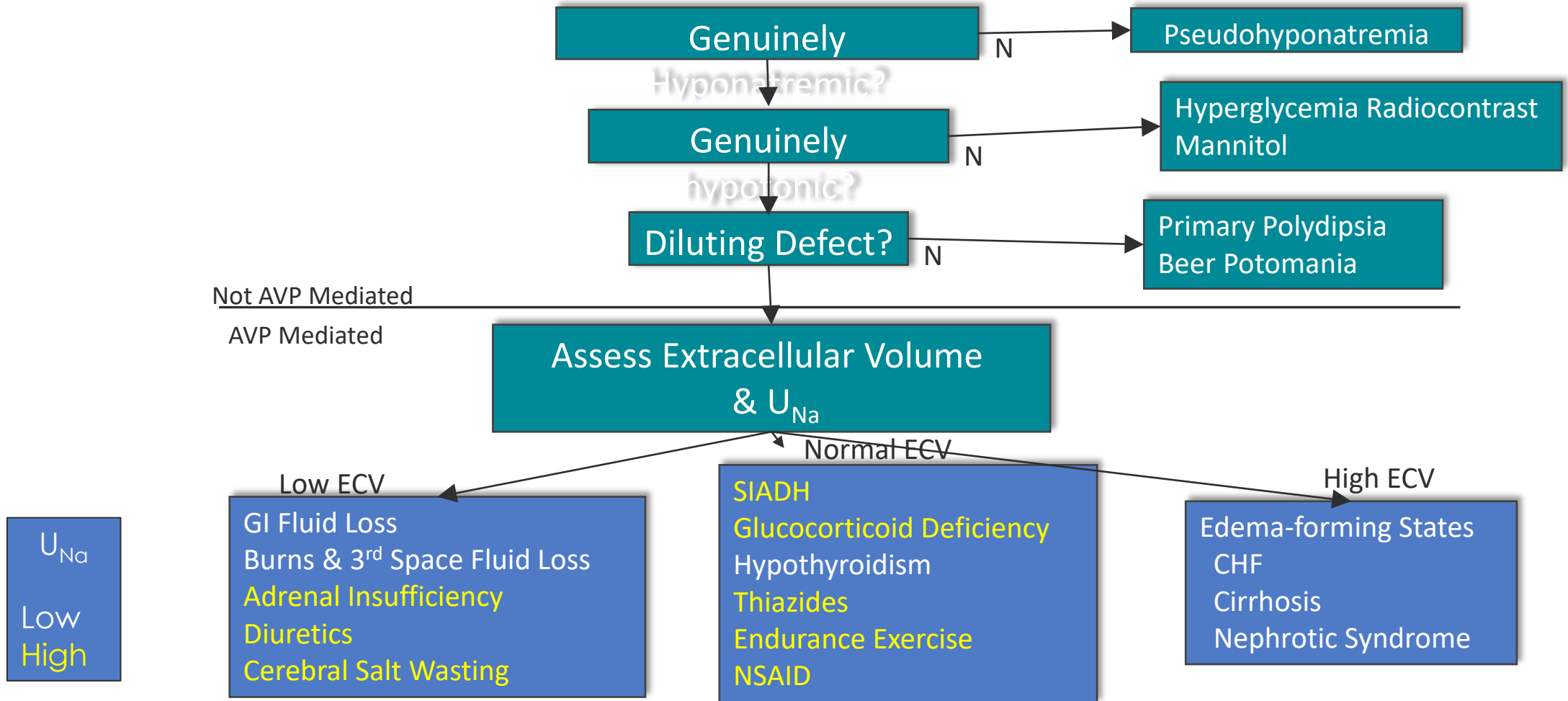


- A** = erratic release
- B** = reset osmostat
- C** = vasopressin leak
- D** = hypovasopressinemic antidiuresis

*Shaded areas represent range of normal values*

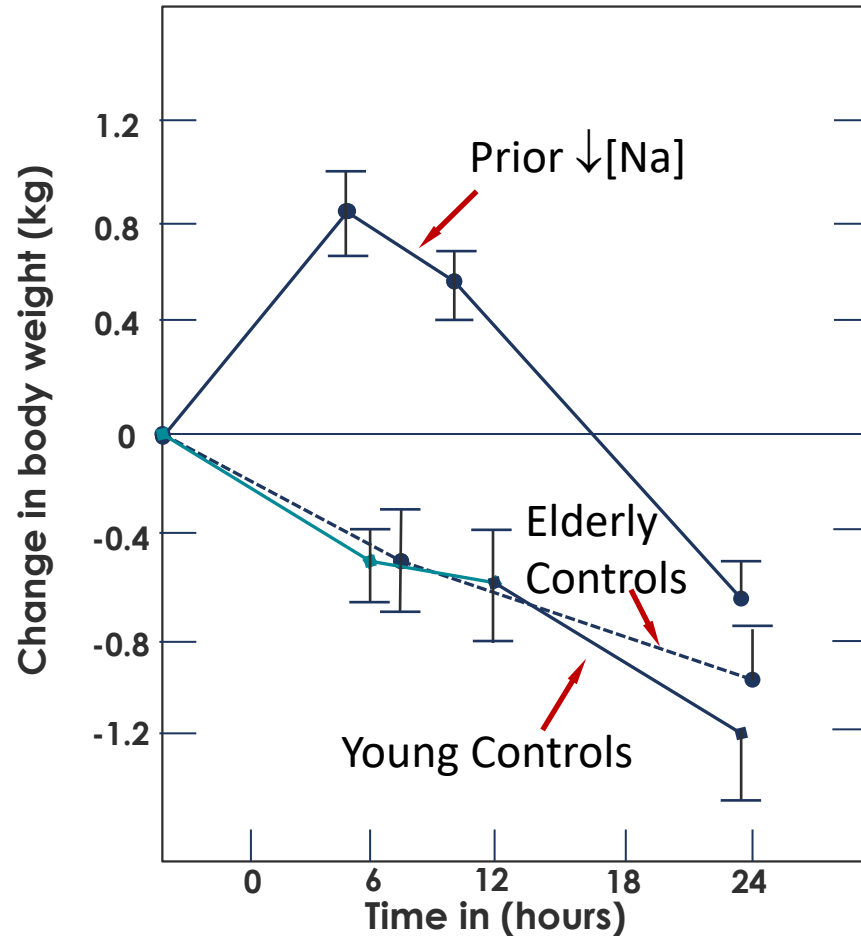
1. Zerbe R, et al. (1980). *Annu Rev Med.* 31:315-27.

# Diagnostic Approach to Hyponatremia



1. Winn N.S. et al. (2020). *Am J Kid Dis.* 75: 272-286.

# Results of Thiazide Rechallenge in Patients with a Prior Episode of Diuretic-induced $\downarrow$ [Na]

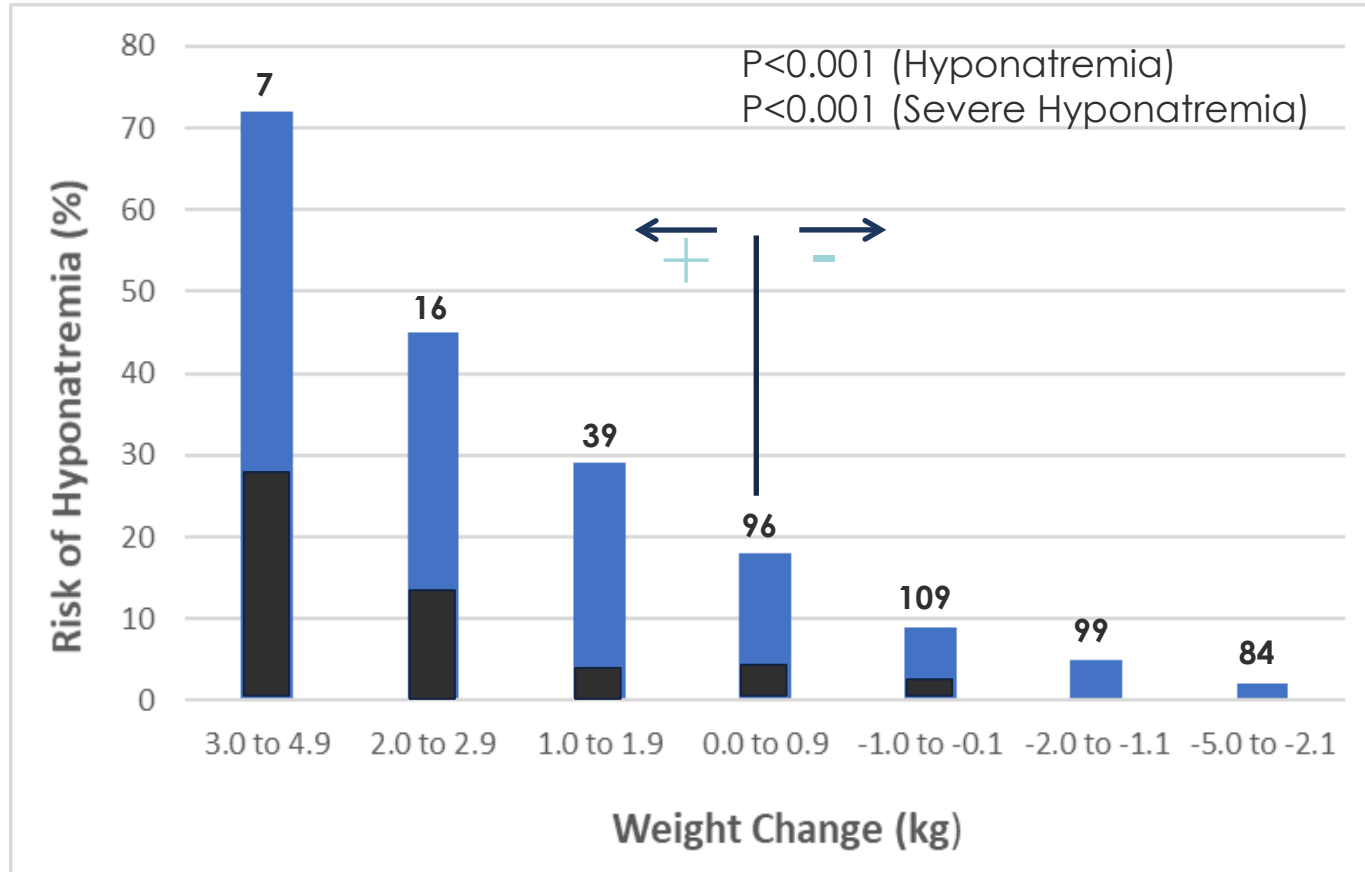


50 mg hydrochlorothiazide  
+ 5 mg amiloride =  $\Delta$  [Na]

Prior  $\downarrow$ [Na]: 5.5 mmol/L  
Elderly Controls: 1.8 mmol/L  
Young Controls: 1.2 mmol/L

1. Friedman, A. (et al. 1989). *Intern Med.*110:24.

# Risk of Hyponatremia and Severe Hyponatremia According to Weight Change among 488 Runners in the 2002 Boston Marathon who Volunteered for Study



## Risk Factors:

- Time > 4 h
- Female
- Low BMI
- Fluid Intake > 3 L
- Weight Gain

0.6% [Na] < 120 ■  
 13% [Na] < 135 ■

1. Almond C. et al. (2005). N Engl J Med. 352:1550.



# Nephrogenic Syndrome of Inappropriate Anti-Diuresis (NSIAD)

- Constitutively activated V2 receptor (stuck in “on” position)<sup>1</sup>
- Mirror image of nephrogenic diabetes insipidus<sup>2</sup>
- cAMP levels always high; AQP-2 always inserted in luminal membrane<sup>4</sup>
- Presents in infancy<sup>2</sup>
- Clinically indistinguishable from SIADH<sup>1</sup>
- Undetectable AVP or copeptin levels<sup>1</sup>
- X-linked dominant X-linked dominant heritability; carrier females affected.<sup>3</sup>

1. Feldman B.J, et al. (2005). *N Engl J Med.* 352:1884.
2. Bockenhauer D, et al. (2013). *Am J Kid Dis.* 59:566.
3. Bichet D.G, et al. (2020). *Euro J Endocrin.*183:R29-R40.
4. Levchenko et al. (2010). *Nephrol Dial Transplant.* 25: 2839-2843.

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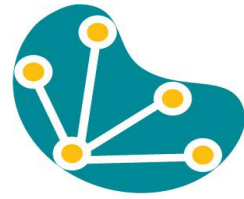
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*Reza Moqhadam, PharmD, MBA*

Executive Director

Head of Field Medical Affairs, OPDC

1 Contact Hour



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