

Hyponatremia;

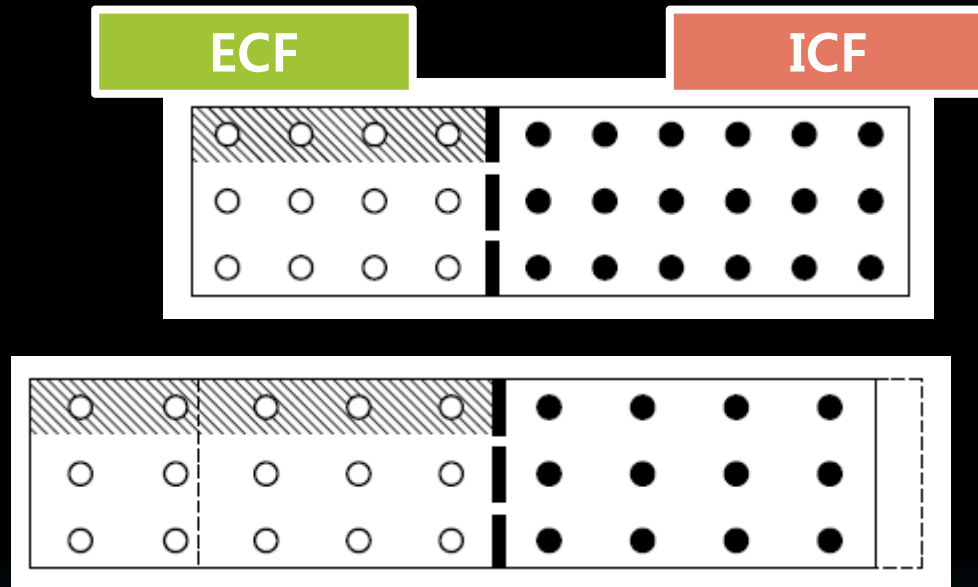
Pathophysiology and Management

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Definition of Hyponatremia

- Plasma Na⁺ conc. < 135mmol/L
- **Relative excess of water in relation to sodium**
 - 1) Free water intake
 - 2) Impaired free water excretion

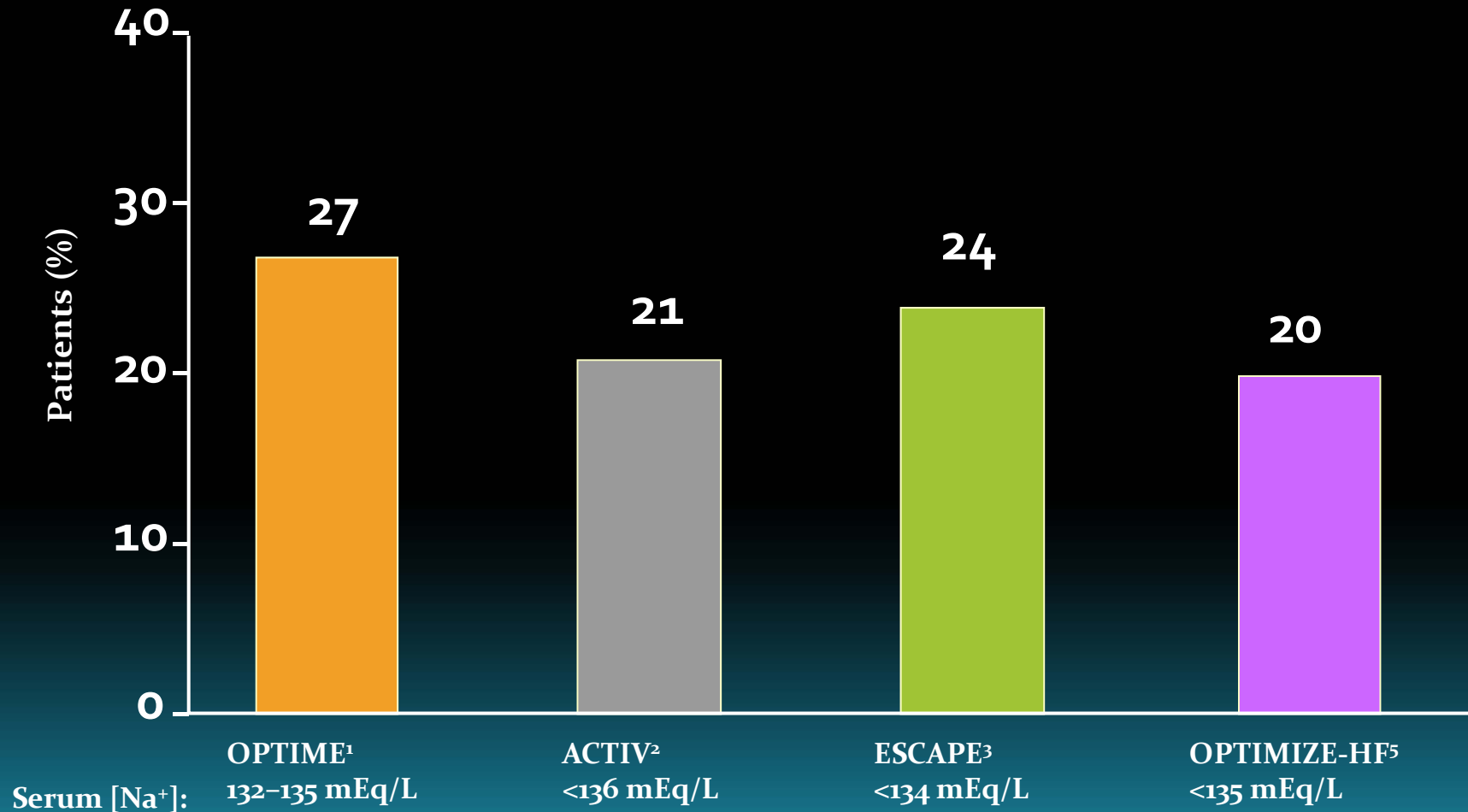
ECF & ICF Under Normal & HypoNa



Normal

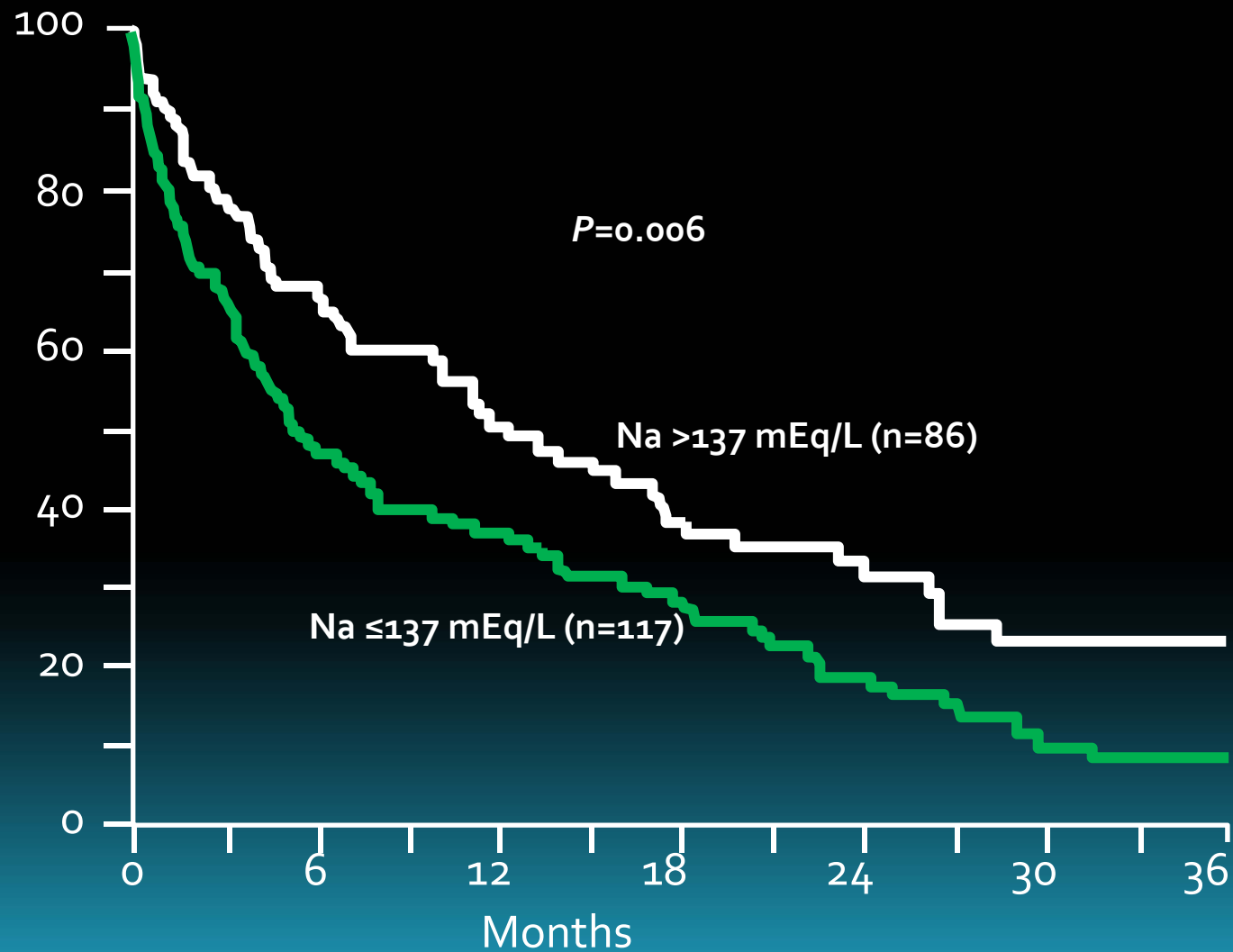
Hypovolemic hypoNa
TBW ↑↑, TB Na ↑

Prevalence of Hyponatremia (Patients Hospitalized with HF)

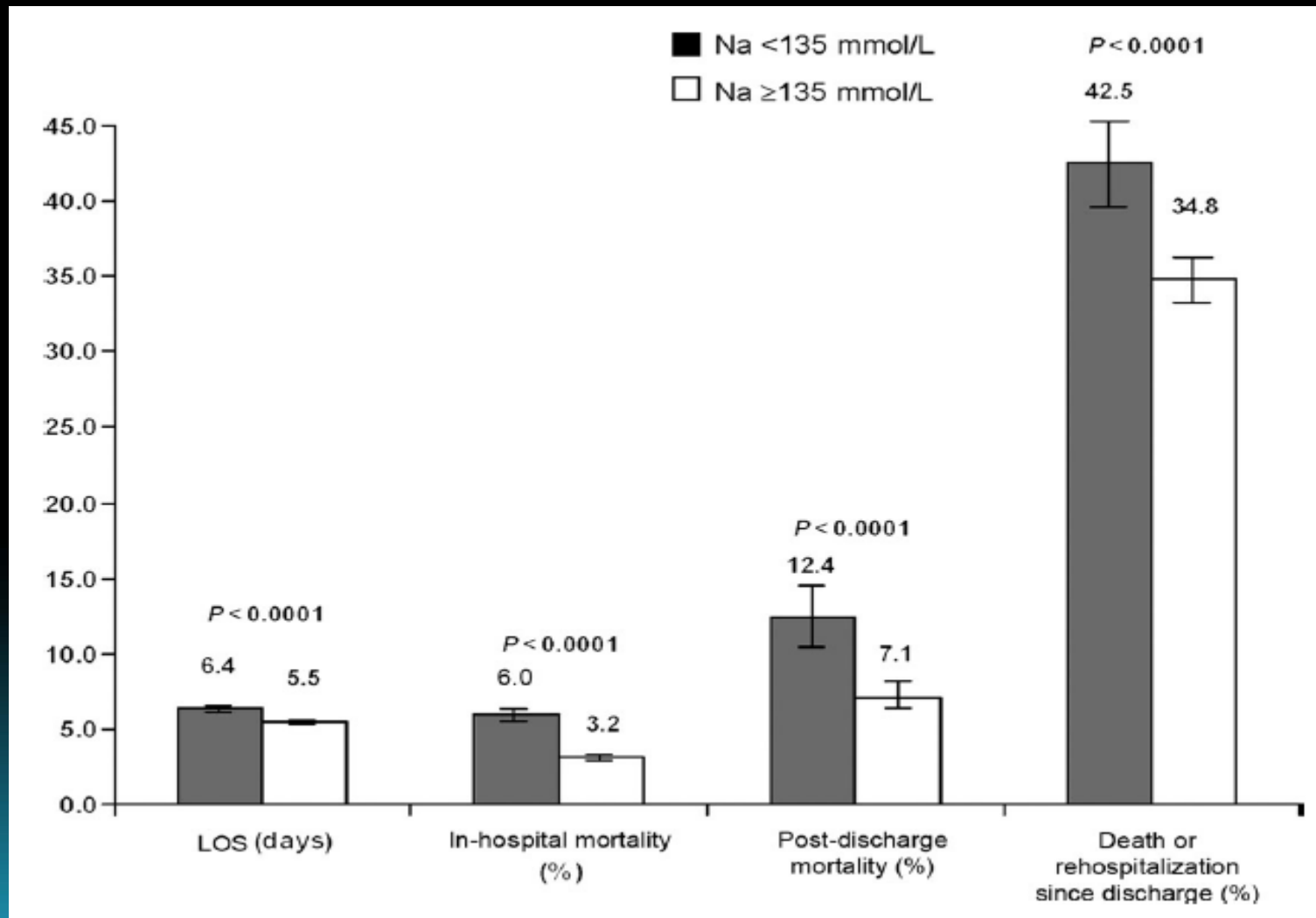


1. *Circulation*. 2005;111(19):2454-2460; 2. *JAMA*. 2004;291(16):1963-1971;
3. *Arch Intern Med*. 2007;167(18):1998-2005; 4. *Eur Heart J*. 2007;28(8):980-988.

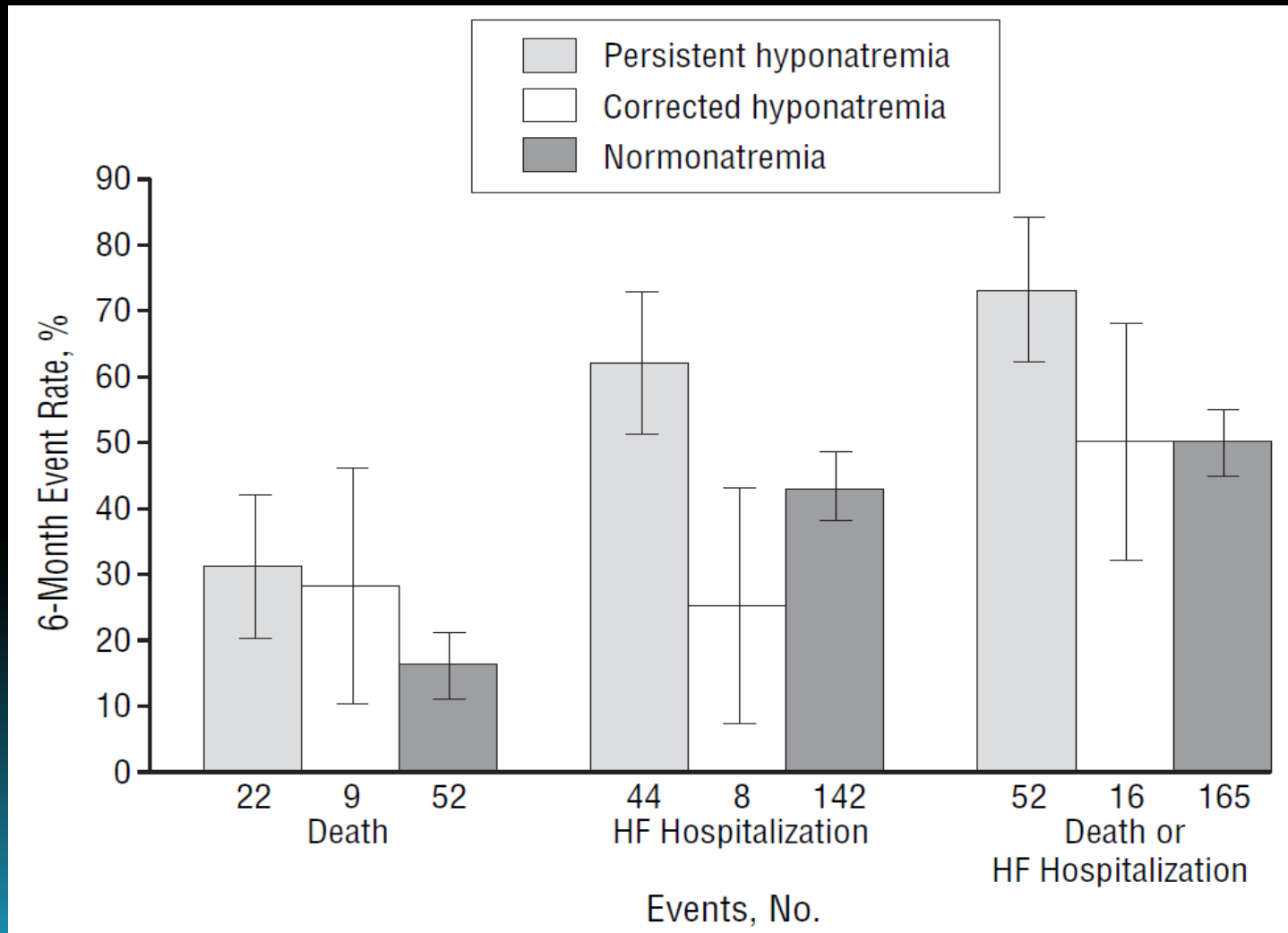
Cumulative Rates of Survival (Patients with Severe HF)



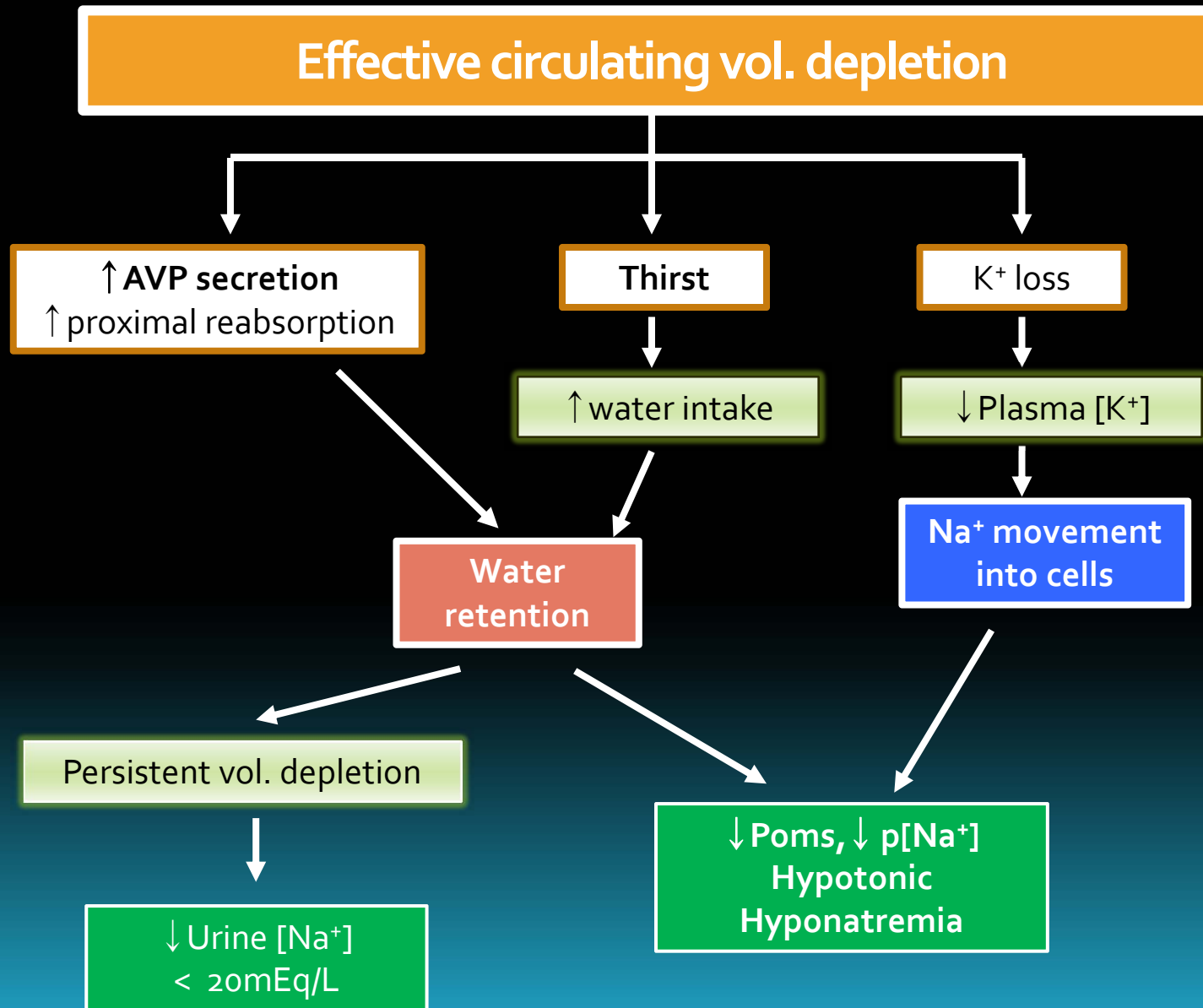
Adm s-Na conc. & Clinical outcomes (OPTIMIZE-HF registry)



Prognostic Value of Persistent Hyponatremia (ESCAPE trial in Severe HF)



Pathophysiology of HypoNa in HF

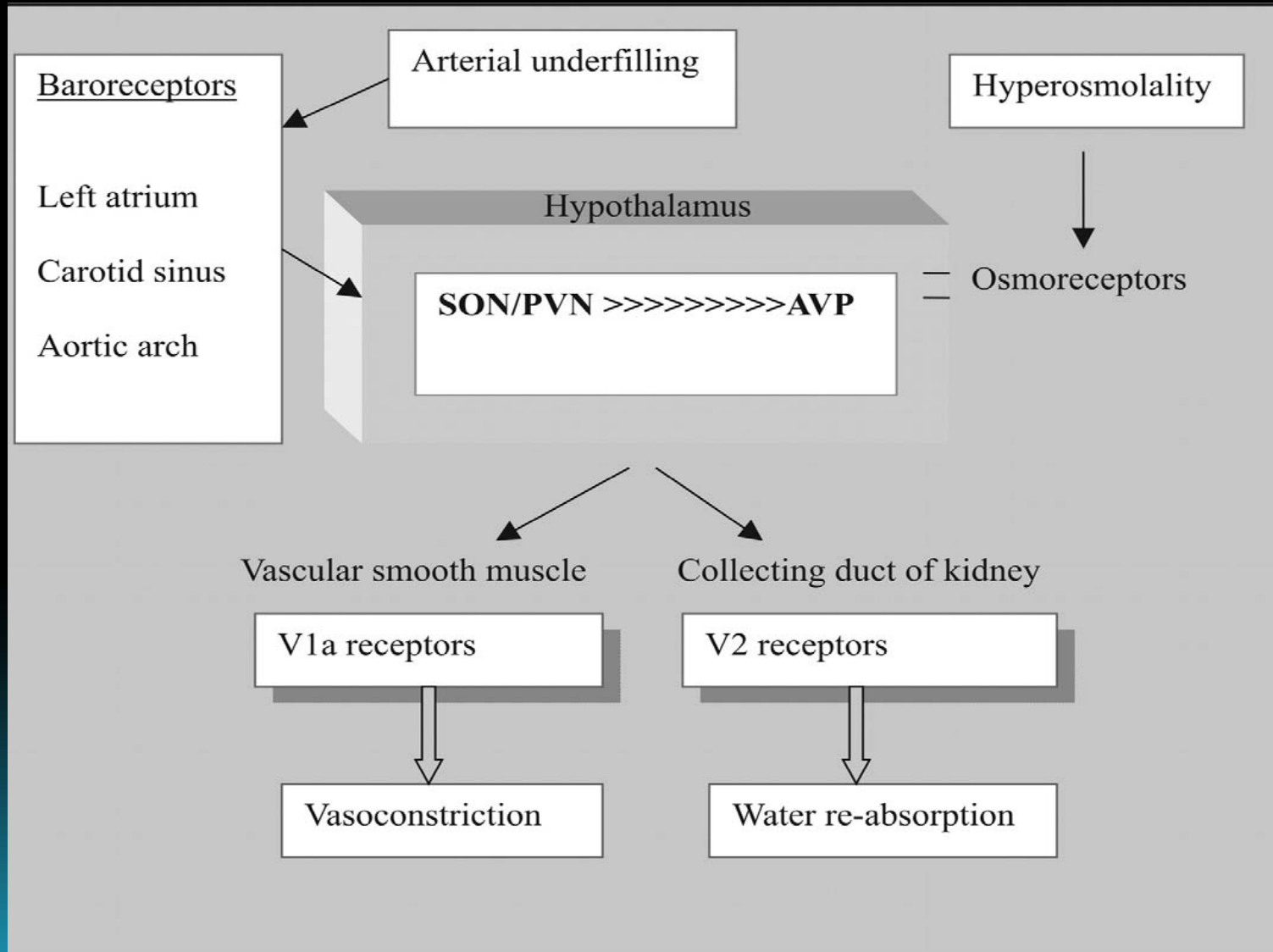


Plasma Vasopressin by HF Severity

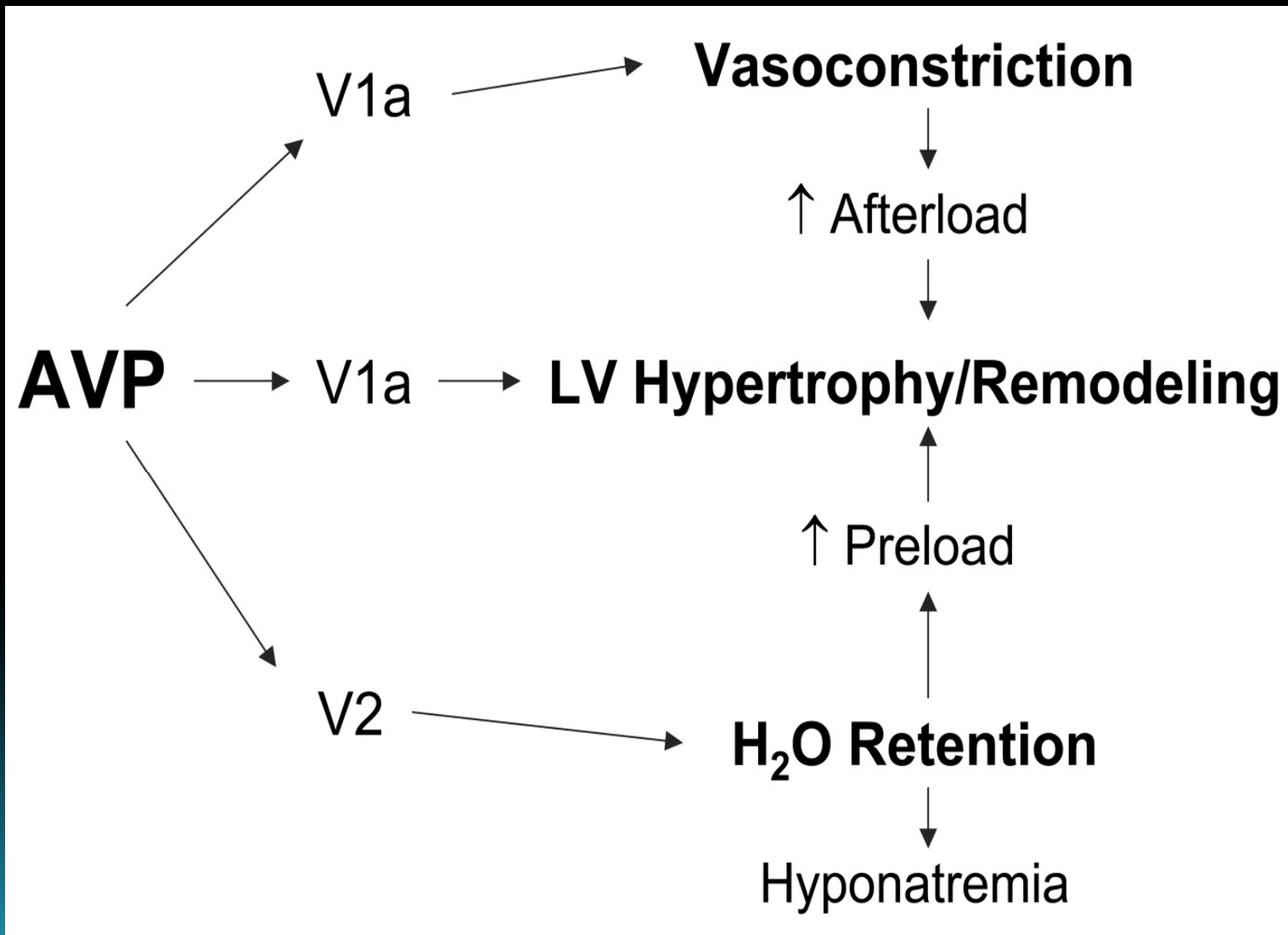


* $P < 0.05$ vs control; ** $P < 0.001$ vs control.
Int J Card. 2006;106(2):191-195.

Physiology; Vasopressin(AVP)



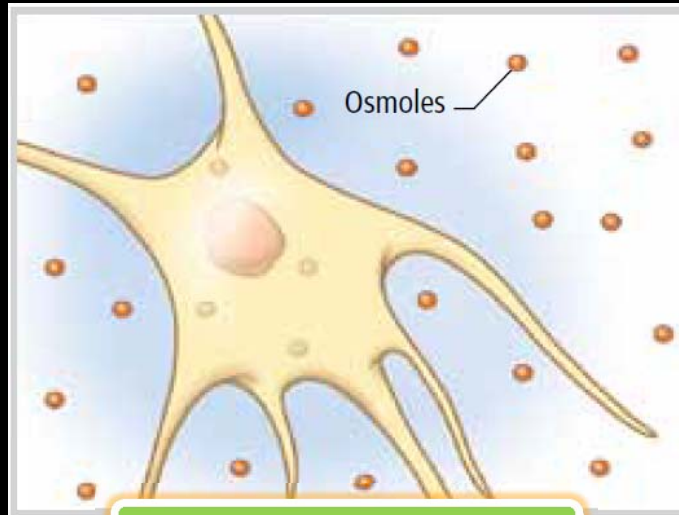
AVP in Progression of HF



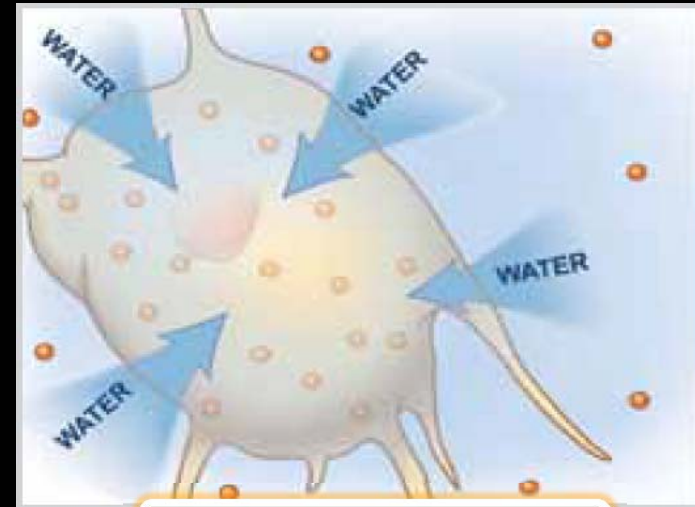
Clinical Feature of Hyponatremia

- **Acute (< 48 hr) - brain edema**
 - Nausea, headache, vomiting
 - Seizure, brainstem herniation, coma, death
- **Chronic (> 48 hr)**
 - Nausea, vomiting, confusion, seizure (<125mM)
 - Subtle gait, cognitive defects
 - Falls, bony fractures

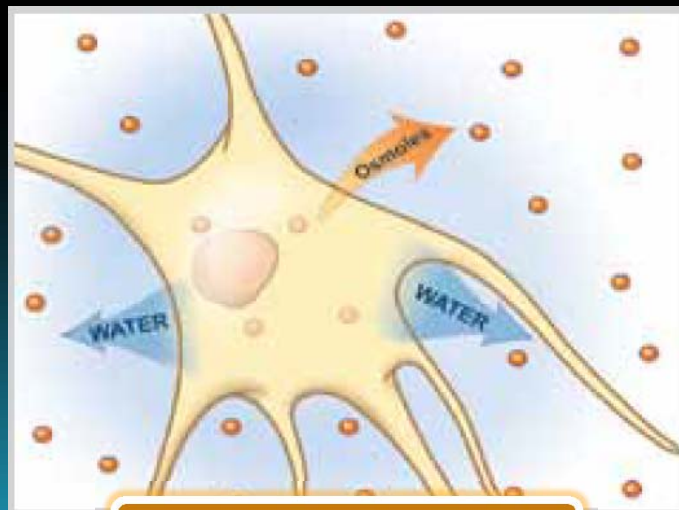
Effects of Hyponatremia on Brain



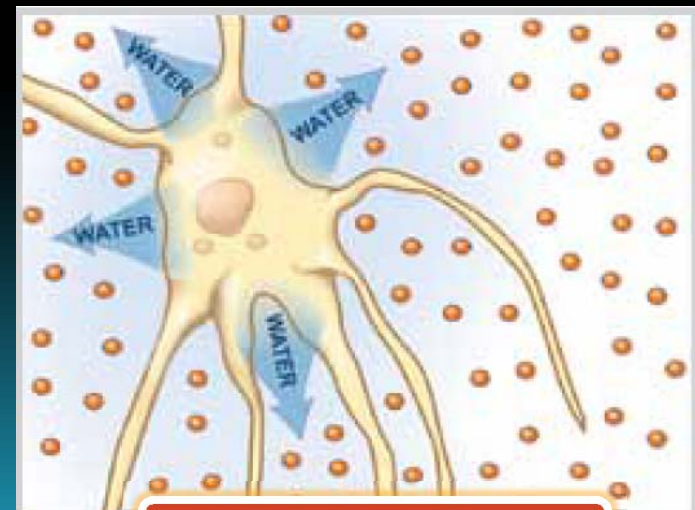
Normal



Acute Hyponatremia



Adaptation



Overly Aggressive Tx

Cause of Acute Hyponatremia

- **Iatrogenic**
 - Postop: Premenopausal women
 - Hypotonic fluids with postop patients(↑ AVP)
 - Glycine irrigation: TURP, uterine surgery
 - Colonoscopic preparation
 - Thiazide
- **Polydipsia**
- **Ecstasy**
- **Exercise-induced(marathon)**
- **Multifactorial - thiazide & polydipsia**

Hyponatremia – Cx of Diuretics

- **Thiazide:** inhibit NaCl reabsorption in distal tubule
not interfere with urinary concentration
→ AVP-induced water retention :hyponatremia
- **Furosemide:** inhibit NaCl reabsorption in MTAL
interfere with urinary concentration
→ limit AVP-induced water retention

Dx w/u of Hyponatremia

- **Clinical assessment**
 - Volume status
 - Drugs: Desmopressin, SSRI, TCA, NASID, ecstasy
 - Nausea, pain, stress
- **Radiologic imaging**
 - Chest X-ray, CT(lung , head)

Dx w/u of Hyponatremia

- **Laboratory investigation**

- 1) **Serum osmolality- exclude pseudohyponatremia**

Effective osmolality < 275mmol/kg : Hyponatremia

- 2) **Urine osmolality**

<100mmol/kg : polydipsia

>400mmol/kg: AVP excess

- 3) **Spot urine Na⁺ conc.**

< 20mmol/L : HF, LC, extrarenal loss

> 20mmol/L : renal loss(diuretics), SIAD

Tx of Severe Sx Hyponatremia

1) 3% hypertonic saline(513mM)

Na⁺ conc. : 1-2mM/hr, total 4-6mM ↑

- sufficient to alleviate acute symptoms

3% saline 1mL/kg/hr : Na⁺ conc. 1mM/hr ↑

2) Monitoring of plasma Na⁺ conc. : every 1-2hr

Tx of Chr. Sx Hyponatremia

1) Overcorrection of p[Na⁺] : risk for ODS

↑ Na⁺ conc. < 8-10mM/24hr

< 18mM/48hr

2) Hyponatremia reinduced

by DDAVP, free water(5%DW)

: prevent the development of ODS

Tx for Hyponatremia in HF

1) Fluid restriction

(urinary $[\text{Na}^+] + [\text{K}^+]$ /plasma $[\text{Na}^+]$)

; indicator of electrolyte free water excretion

> 1 : fluid restriction < 500cc/d

~ 1: < 500-700cc/d

< 1: < 1L/d

2) Loop diuretic

: interfere with urinary concentration

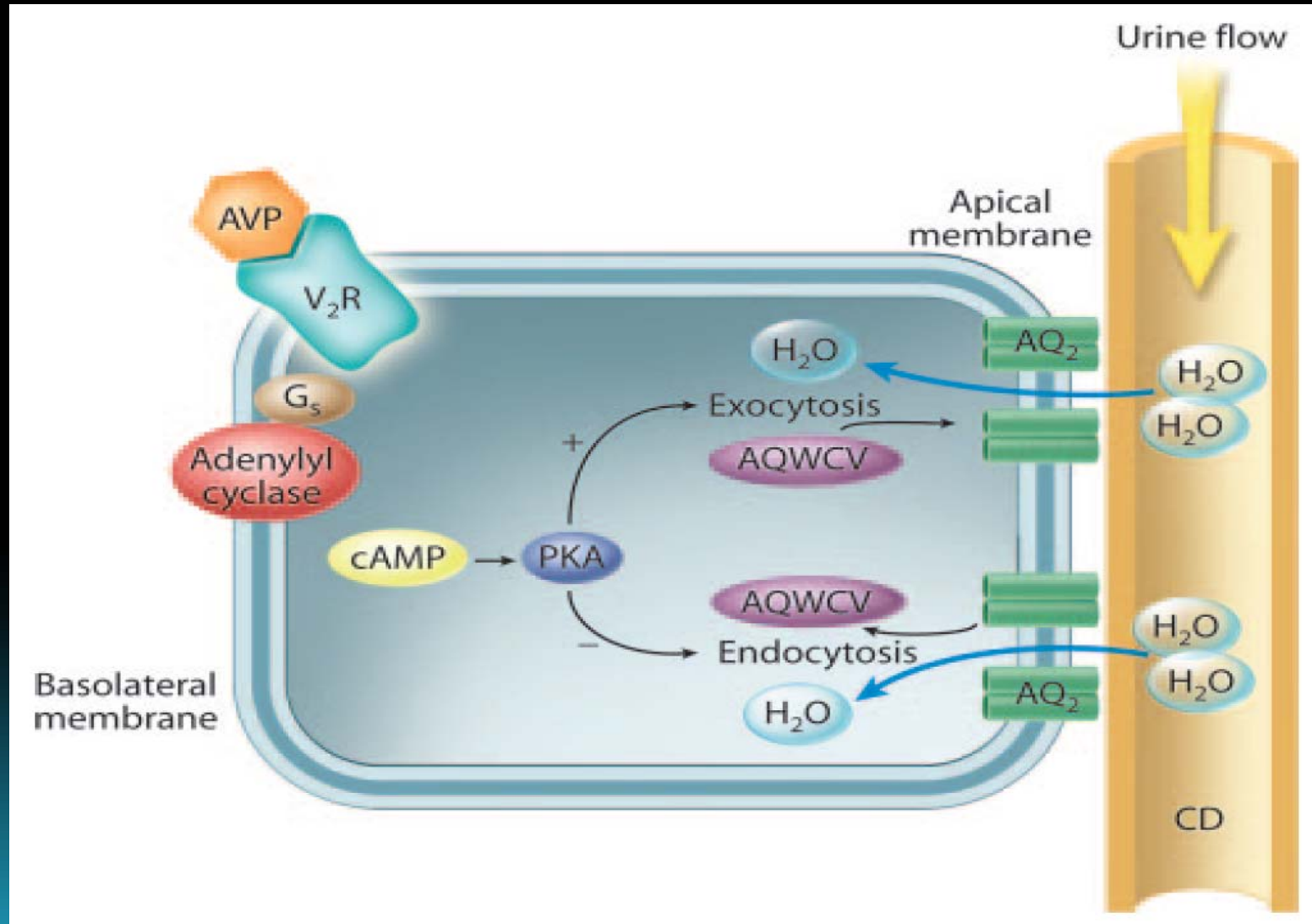
3) CHF Tx - ACEI

Tx for Hyponatremia in HF

4) Vasopressin antagonist(vaptan)

- Indication: CHF, cirrhosis, SIAD
- Initiated in hospital
- Liberal fluid intake (>2L/d)
- Close monitoring of plasma Na⁺ conc.

Vasopressin Antagonist(Vaptan)



Vasopressin Antagonist(Vaptan)

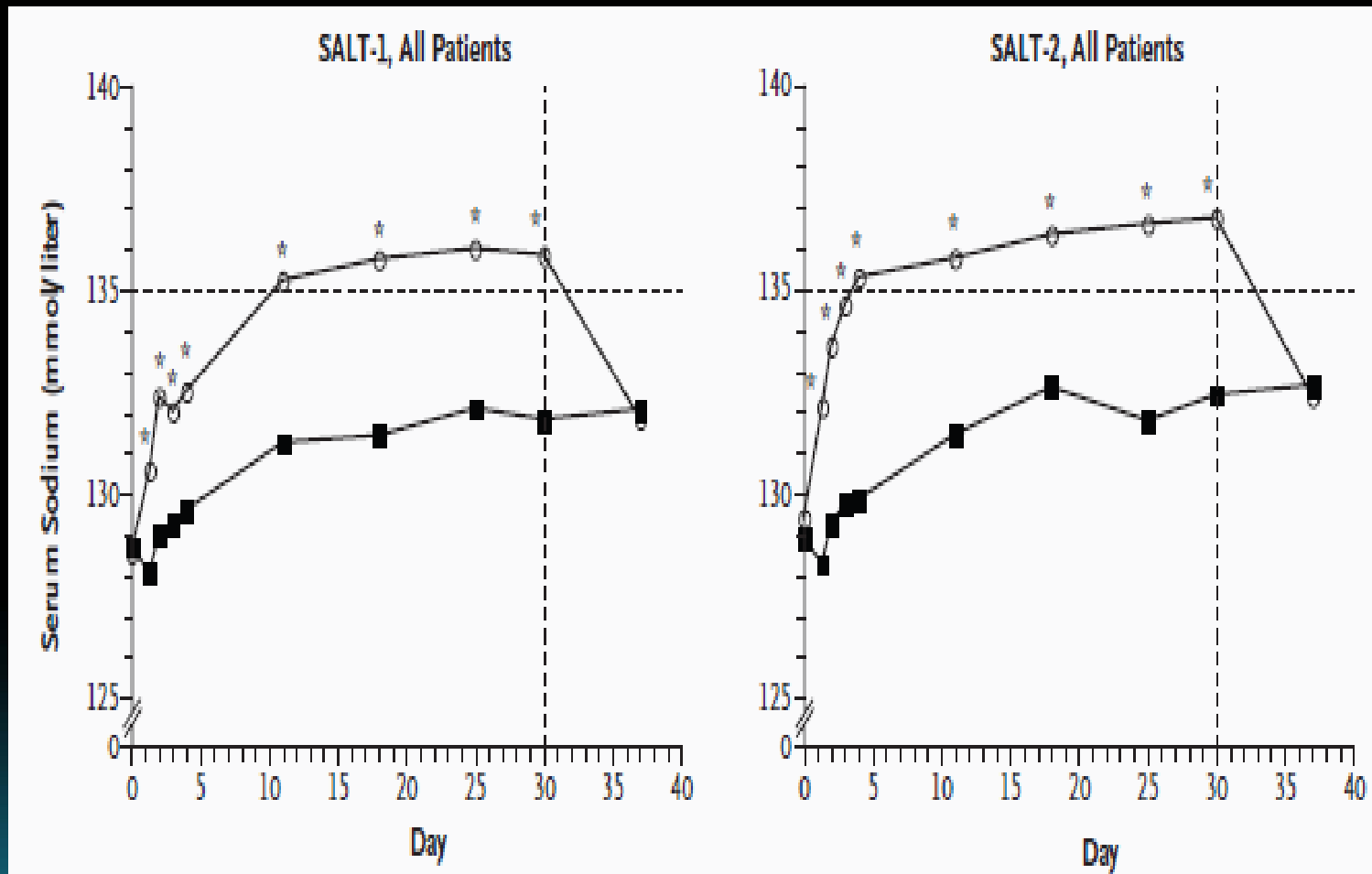
Drugs	Dose of Drug(mg/d)	AVP Receptor	Route	Urinary Volume	Urinary Osmolality	Sodium Excretion Over 24 hr
Conivaptan	20-40	V _{1A} , V ₂	IV	↑	↓	↔
Tolvaptan	15-60	V ₂	Oral	↑	↓	↔
Lixivaptan	100-200	V ₂	Oral	↑	↓	↔(low) ↑ (high)
Satavaptan	12.5-50	V ₂	Oral	↑	↓	↔

SALT I & II Trials

(Study of Ascending Levels of Tolvaptan in Hyponatremia I & II Trials)

- **Euvolemic or hypervolemic hyponatremia**
; HF, LC, SIAD
- **No fluid restriction**
- **Outpatient basis**
- **Flexible dosing (15 - 30 - 60 mg/day)**
- **Primary end points: change in the average daily area under the curve(AUC) for the s-Na⁺ conc. from baseline to day 4 & change from baseline to day 30**

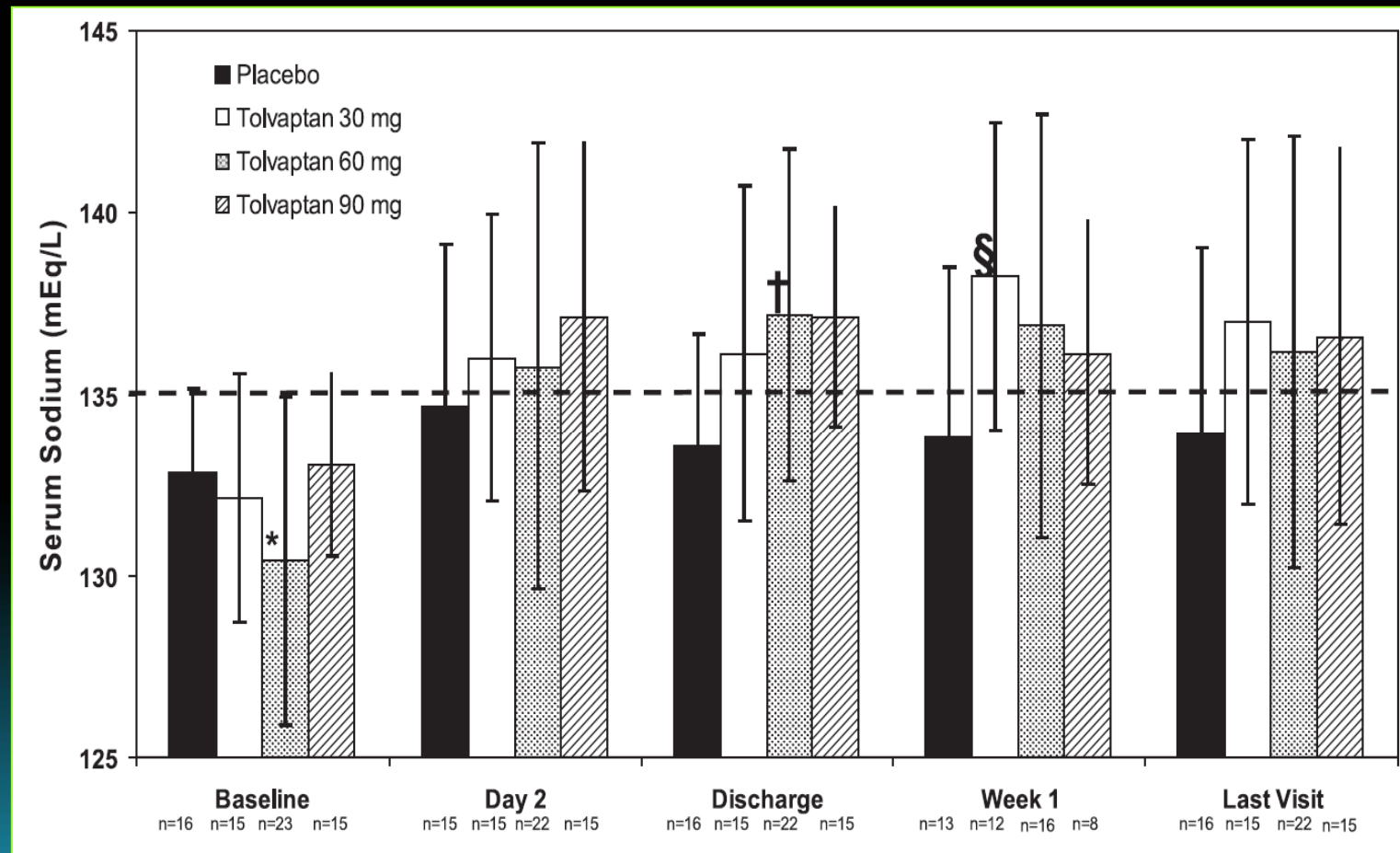
SALT I and II trials



Serum Na conc. increased more in the tolvaptan group than in the placebo group ($P < 0.001$)

ACTIV in CHF

Acute & Chronic Therapeutic Impact of Vasopressin Antagonist in CHF



Dashed horizontal line indicates cut point between hyponatremia (<135 mmol/l) and normonatremia.

* $P=0.03$ versus placebo; † $P=0.02$ versus placebo; § $P=0.01$ versus placebo

JAMA 291;1963, 2004

Conclusion 1

- ④ Hyponatremia is a prevalent comorbidity in patients hospitalized with HF
- ④ Patients with HF, vasopressin inappropriately elevated, with higher levels as HF Sx progress
- ④ Diuretics limited by neurohormonal activation, renal insufficiency & worsening hyponatremia

Conclusion 2

- ④ Vaptans specifically target hyponatremia in patients with HF, cirrhosis, SIAD
- ④ Severe symptomatic hyponatremia
 - urgent infusion of hypertonic saline to correct cerebral edema.
- ④ Overly rapid correction of chronic hyponatremia cause osmotic demyelination syndrome.

경청해주셔서 감사합니다