Hyponatremia:
Focus on Mortality in the Elderly and Pre-Menopausal Women

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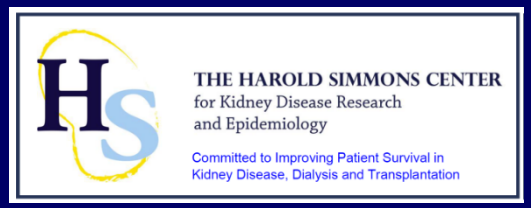


Disclosure of Financial Relationships

Kamyar Kalantar-Zadeh, MD, MPH, PhD

Alphabetical order:

Abbott: Grant, Speaker bureau
Alexion: consultation
Amgen: Advisory Board, Speaker bureau
DaVita: grant, medical directorship
Fresenius: Speaker, Consultant
Genzyme/Sanofi: Consultant, proctorship
NKF: Grants, advisory boards
NIH: Study sections, grants
Otsuka: Speaker bureau, consultation
Shire: Speaker bureau, consultation
Vifor: consultation

Hyponatremia
Urgencies and Emergencies

Sodium Intake and IV Fluid

Sodium Intake

Daily Sodium Intake: 100-200 mEq/day

- 1 meq **Na** = 23 mg
  Each g Na = 44 mEq
  2 gm Na = 87 mEq
  4 gm Na = 174 mEq

- 1 mmol **NaCl** = 23+35.5=58.5 mg
  Each gram salt contains 17 mmol NaCl
  5 gm salt = 85 mmol NaCl
  10 gm salt =171 mmol NaCl

IV Solutions

Saline Solutions:

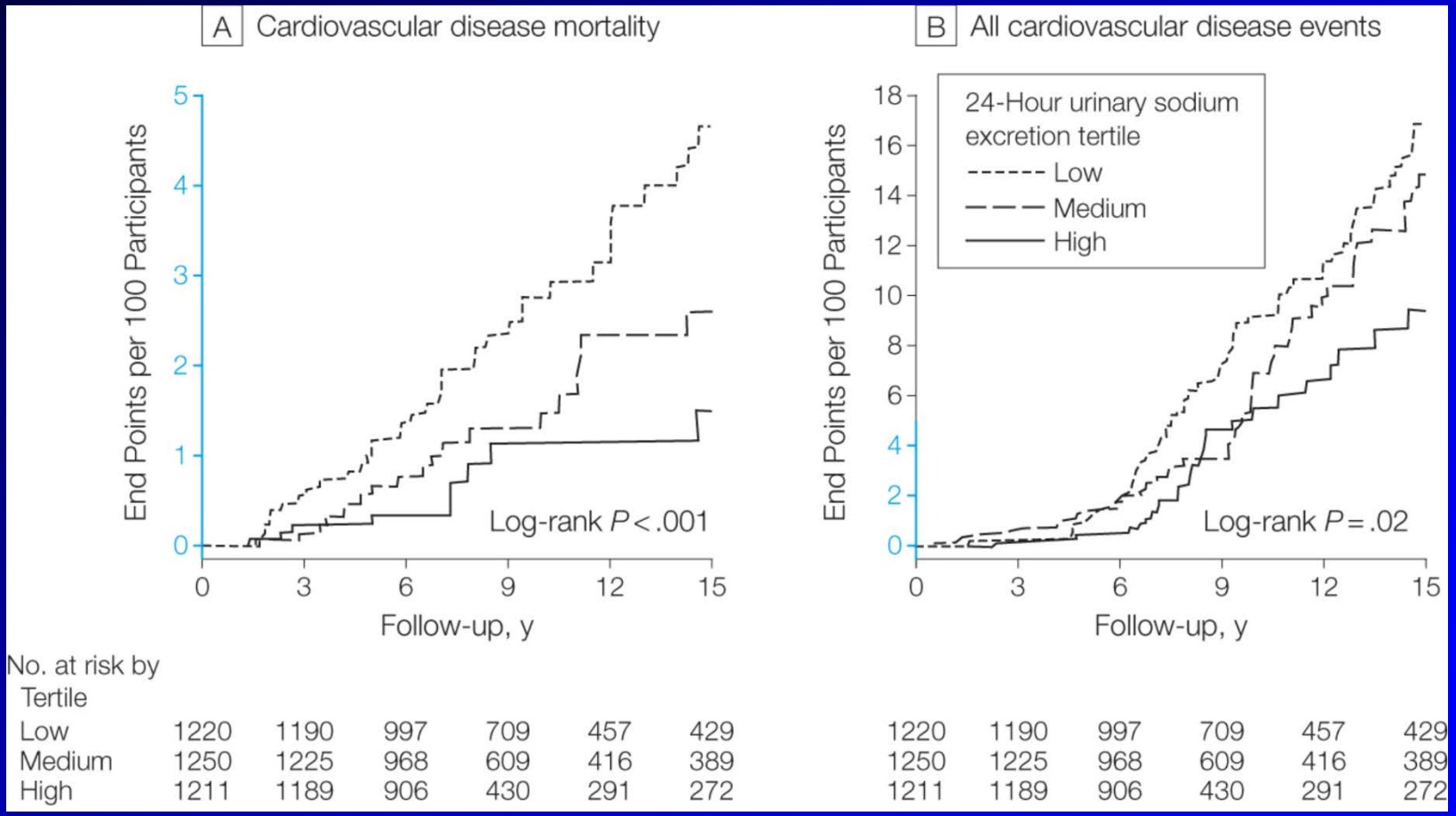
- **NS** = 0.9% = 154 mmol/L = 308 mosm/L
- **½ NS** = 0.45% = 77 mmol/L
- **HTS** = 3% = 512 mmol/L = 1,024 mosm/L
- Super-HTN = 23% = 4000 meq/L (4 meq/cc)

Combination Solutions:

- **½ NS + 40 KCl** = 117 mmol/L Na^+/K^+ *(~ ¾ NS)*
- **D5W + 1.5 amps NaBicarb** = 72 mmol/L Na
- **½ NS + 1.5 amps NaBicarb** = 149 mmol/L Na

Low Dietary Sodium Intake: Good or Bad

Lower sodium excretion is associated with higher CVD mortality.



Tertiles of 24-hour urinary sodium excretion are sex-specific based on baseline measures (see Table 2). This analysis includes the outcome cohort (see Figure 1 and Table 1). Regions of y-axis scales drawn in blue indicate range from 0 to 5.

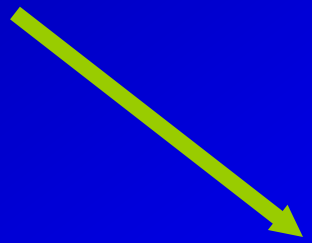
Stolarz-Skrzypek K et al. **Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion.** JAMA. 2011;305(17):1777-1785. doi:10.1001/jama.2011.574

Hyponatremia
Urgencies and Emergencies

Sodium Intake and IV Fluid
Osmoregulation vs. Volume Regulation

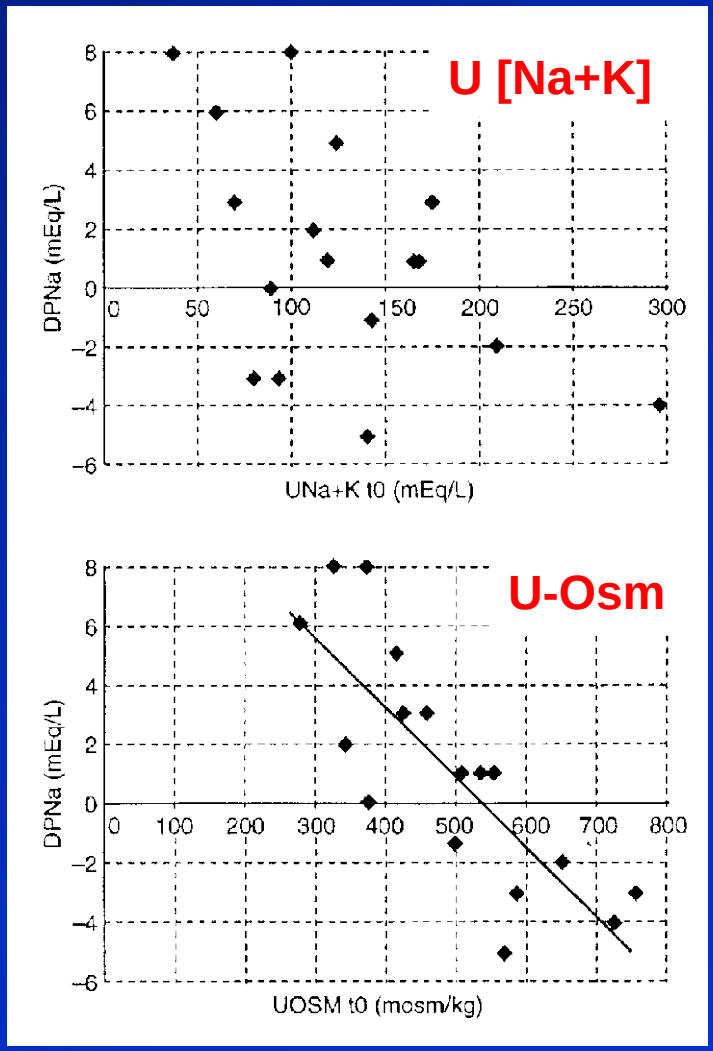
Comparing Osmo-regulation vs Volume regulation

	Osmo-regulation	Volume regulation
• What is sensed	osmolality	effective circulating volume
• Sensors	Osmoreceptors (hypothalamus)	> Carotid sinus > Afferent arteriols > Atria
• Effectors	1. ADH (2. Thirst)	1. Sympathetics 2. Renin-angio-aldo 3. ANP 4. Intra-renal hemod. 5. **ADH**
• What is affected	a. Urine Osm (b. Water intake)	Urinary Sodium



Which one is better?
Uosm vs. **Urine[Na+K]** vs. **U-Na**

- Musch & Decaux, QJM 1998:
- 17 pts with chronic SIADH:
  2 lit of NS → examined changes in serum Na
- U-osm was more reliable than U [Na+K] in predicting the magnitude and direction of change in S-Na.



Musch & Decaux, QJM 1998:

Back to Hyponatremia

Sx & Sx of Hyponatremia

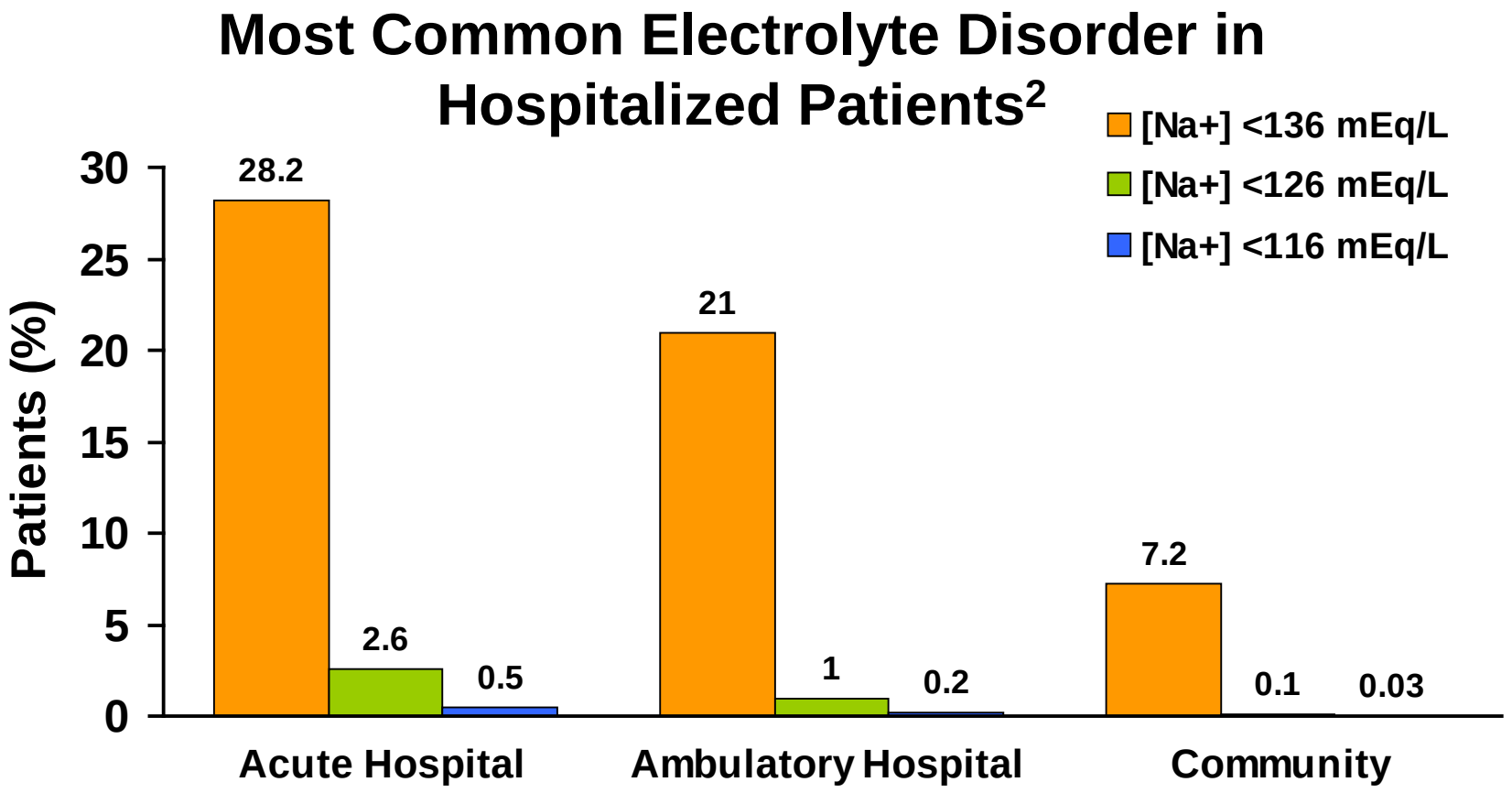
- **Rapidity**: Osmolyte adaptation theory (organic solutes)
- **Severity:** Na<120

- Abdominal pain, headache (*alarming in young women!*)
- Lethargy, confusion, nausea, vomiting
- Non-cardiogenic pulmonary edema
- Cerebral edema, seizure, coma, death

Poor outcome in pre-menopausal women!

- *But in old patients without acute hypo-Na, there is minimal Sx & Sx*

Prevalence of Hyponatremia in the Hospital and Community[1]

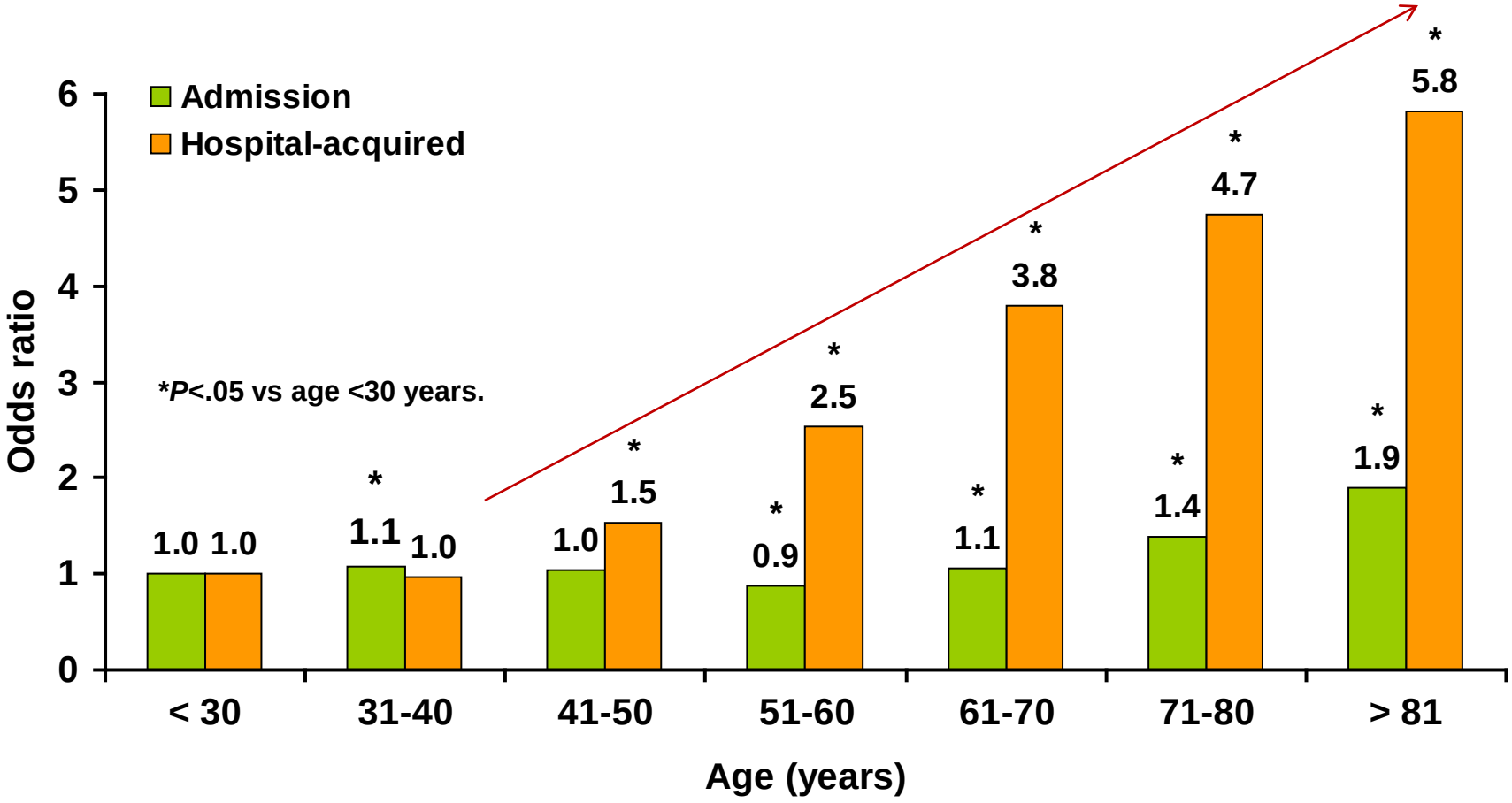


Data are from the Tan Tock Seng Hospital in Singapore, and are based on 303,577 samples from 120,137 patients available for analysis.

1. Hawkins RC. *Clin Chim Acta*. 2003;337(1-2):169-172.
2. Verbalis JG et al. *Am J Med*. 2007;120(11 suppl 1):S1-S21.

Hospital Acquired Hyponatremia (<135 mEq/L)

The Role of Age



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

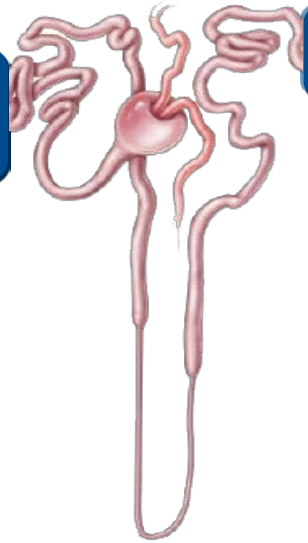
Mechanisms of Drug-Induced Hyponatremia

↑ Hypothalamic Production of Vasopressin

- Antidepressants (TCAs, SSRIs, MAOIs)
- Antipsychotics (phenothiazines, haloperidol)
- Antiepileptics (carbamazepine, valproic acid)
- Antineoplastic agents
- Opiates

↑ Vasopressin Effect at Renal Tubule Level

- Antidiabetic drugs (chlorpropamide, tolbutamide)
- Antiepileptics (carbamazepine, lamotrigine)
- IV cyclophosphamide
- NSAIDs



Alter Na/H_2O Homeostasis

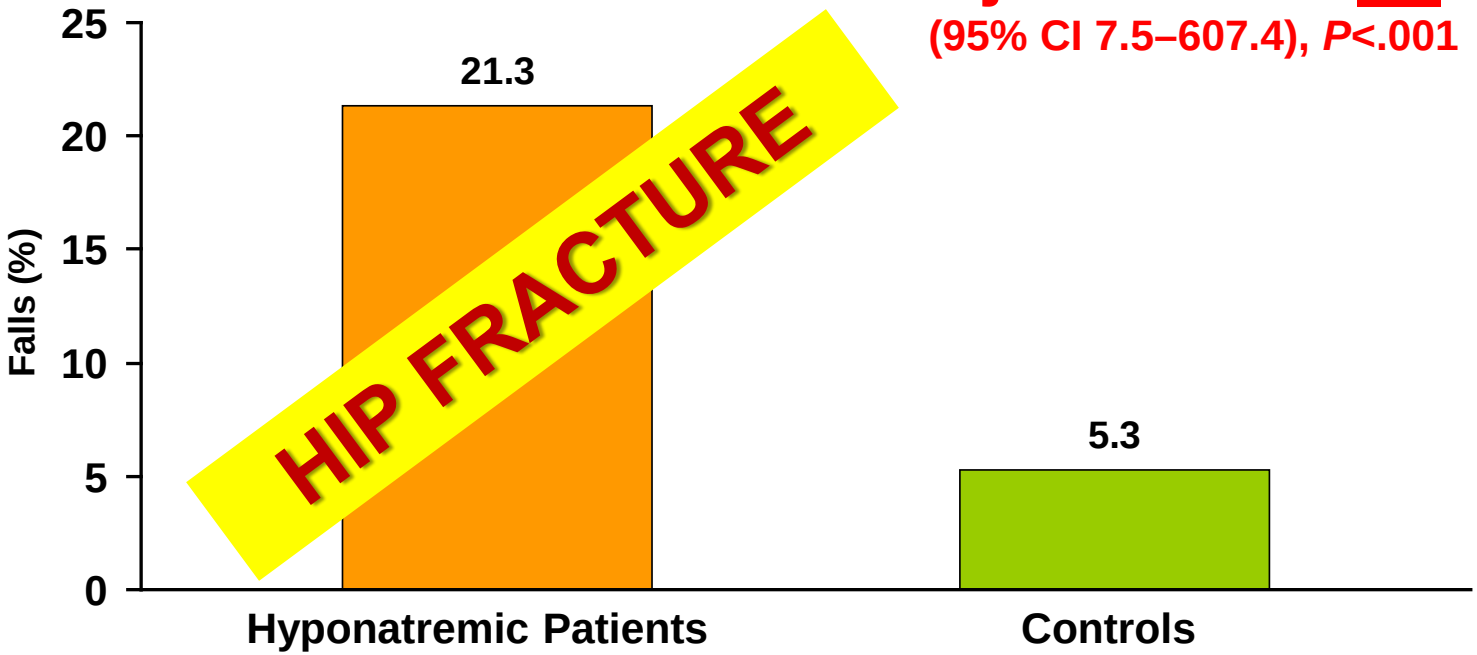
- Thiazide diuretics/indapamide
- Amiloride
- (Loop diuretics)

MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal antiinflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Adapted from Liamis G et al. Am J Kidney Dis. 2008;52(1):144-153.

Falls are Common Symptoms of Chronic "Asymptomatic" Hyponatremia

Adjusted OR 67.4
(95% CI 7.5–607.4), *P*<.001



	Hyponatremic Patients	Controls
Mean Serum [Na^+]:	126±5 mEq/L	139±2 mEq/L
No. of Patients:	(n=122)	(n=244)

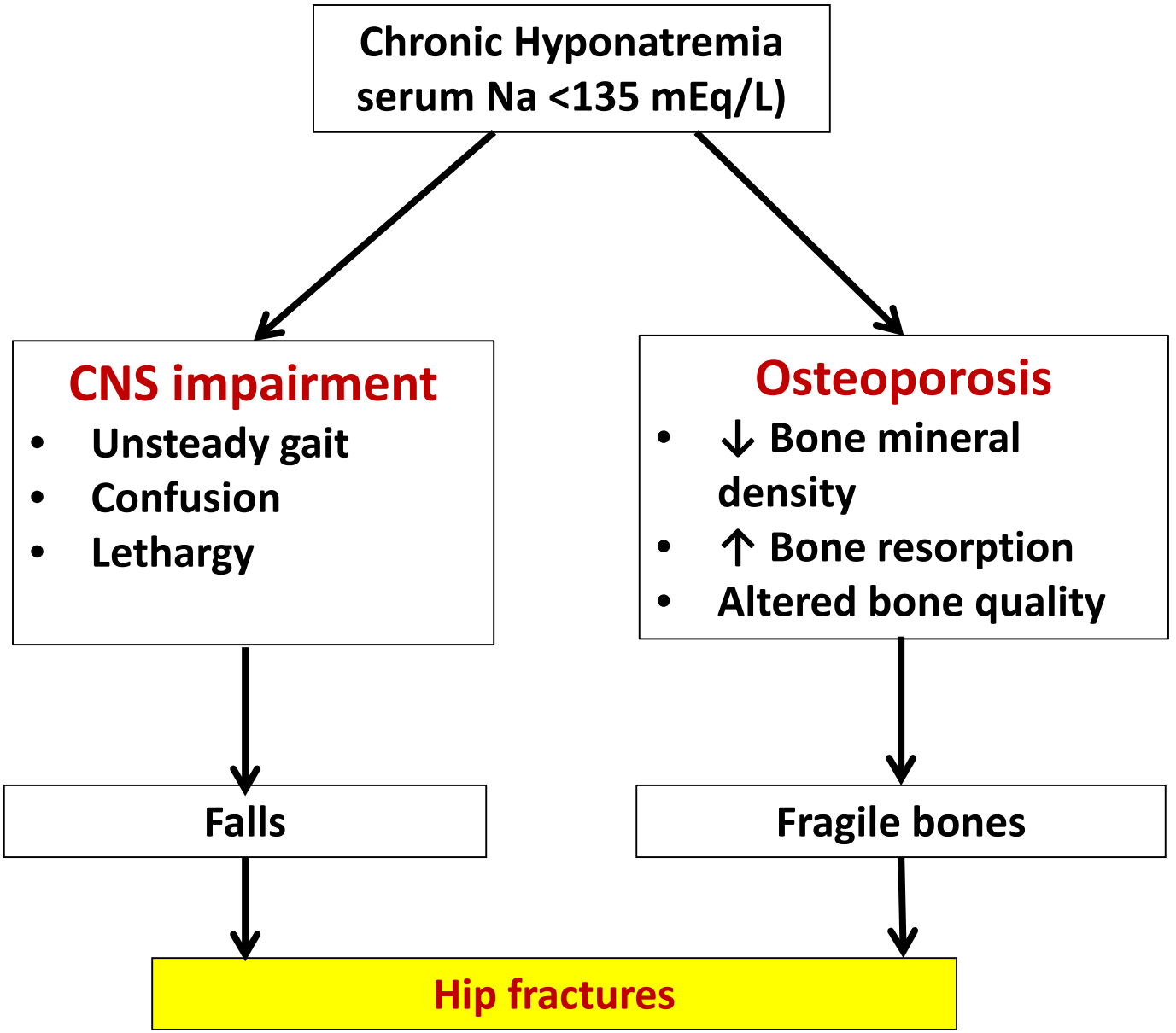
- Patients with chronic "asymptomatic" hyponatremia were admitted for falls significantly more frequently than patients with normal [Na^+] levels

Data based on a case-control study in a general Belgium hospital.
Renneboog B et al. Am J Med. 2006;119:71.e1-71.e8.

Table 3: Association between hyponatremia, **falls** and **fractures** in the elderly patients

Author	Study design	Mean Serum Na in HyNa group	N	Outcome
Ayus and Arieff 1999[22]	Prospective study of postmenopausal women with chronic symptomatic HyNa (Na <130 mmol/l).	111± 12	53	**19% presented with orthopedic injury.**
McPherson and Dunsmuir 2002[26]	Retrospective study; incidence of moderate HyNa (Na < 130 mmol/l) in patients with hip fractures.	N/A	107	**2.8% incidence HyNa at presentation.**
Renneboog et al 2006[30]	Case-control study; prevalence of falls in patients with chronic asymptomatic HyNa (Na < 133 mmol/l) vs. normonatremic controls.	126± 5	244	**21.3% incidence of falls in HyNa group vs. 5.3% controls.**
Renneboog et al 2006[30]	Prospective study evaluating gait disorders in patients with chronic asymptomatic HyNa (Na < 132 mmol/l).	128± 3	16	**Significant disorders in gait and attention.**
Gankam Kengne et al 2008[23]	Case-control study; Prevelance of HyNa in elderly patients (> 65 years) presenting with and without bone fracture.	131± 3	1,026	**13% incidence of HyNa in fracture patients vs. 3.9% in controls.**
Sandhu et al 2009[24]	Case Control study comparing the incidence of mild HyNa (Na < 135 mmol/l) in elderly patients (>65 years) with and without large bone fracture.	131± 2	728	**9.1% incidence of HyNa in patients with fractures vs. 4.1% in controls.**
Verbalis et al 2010[33]	Cross sectional cohort study; Evaluation of BMD in patients > 50 yrs with HyNa (Na < 135mmol/l) vs. normonatremic controls in the NHANES III	133 ± 2	N/A	**Adjusted OR of osteoporosis in HyNa adults was 2.87 times that among controls.**
Kinsella et al 2010[27]	Cross-sectional cohort study; incidence of HyNa (Na < 135 mmol/l) in women with and without a fracture who underwent previous bone densitometry measurement.	132.2 ± 1.8	1408	**8.7% incidence of HyNa in women with fracture vs. 3.2% in those without.**
Hoorn et al 2011[28]	Cross–sectional cohort study; Incidence of falls and fractures in an elderly population with and without HyNa (Na < 136 mmol/l)	133.4 ± 2	5,208	**23.8% incidence of falls in HyNa vs. 16.4% is those without. OR of V/ non-V fracture in HyNa 1.39 and 1.78, resp.**
Tolouian R et al. 2011[25]	Case-control study; Patients admitted for hip fracture secondary to fall compared to patients admitted for elective hip or knee replacement	131 ± 2	249	Prevalence of HyNa 16.9% in cases vs. 4.65 in controls (p=0.03). OR=4.80;p=0.04

Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML.
Is Chronic Hyponatremia a Novel Risk Factor for Falls and Fractures in the Elderly? ***Nephrol Dial Transplant*** 2012 [in press]



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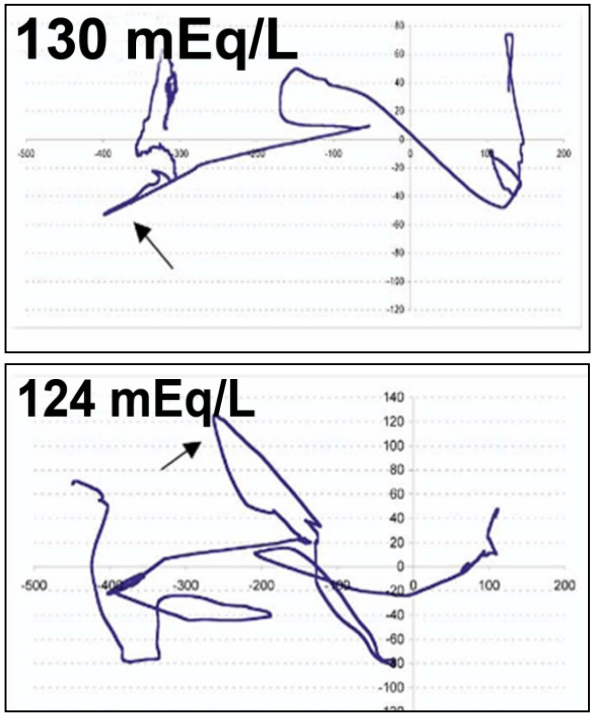
Is Chronic Hyponatremia a Novel Risk Factor for Falls and Fractures in the Elderly? ***Nephrol Dial Transplant*** 2012 [in press]

Correction of Hyponatremia Stabilizes Gait

Gait stability assessed in 16 hyponatremic patients ([Na^+] 124-130 mEq/L)

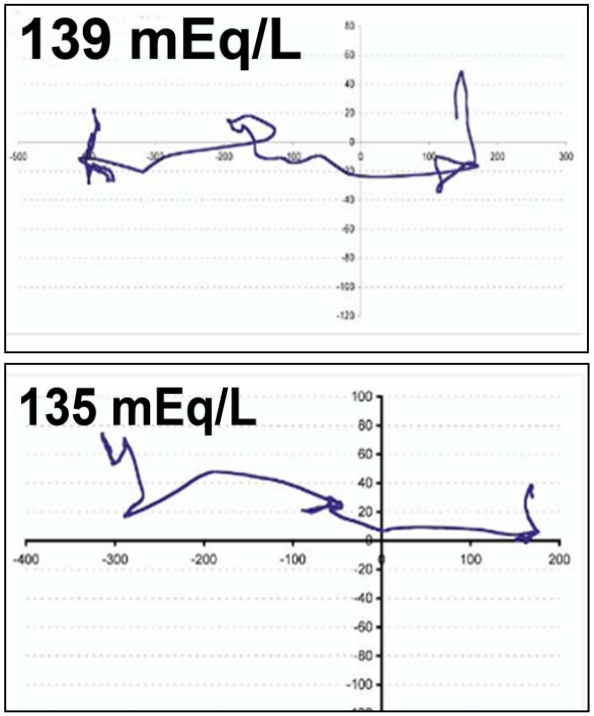
Patients asked to walk on ***pressure mat.*** Skew from midline of path measured as length of walk

Gait instability significantly increased in hyponatremia



Correction of hyponatremia

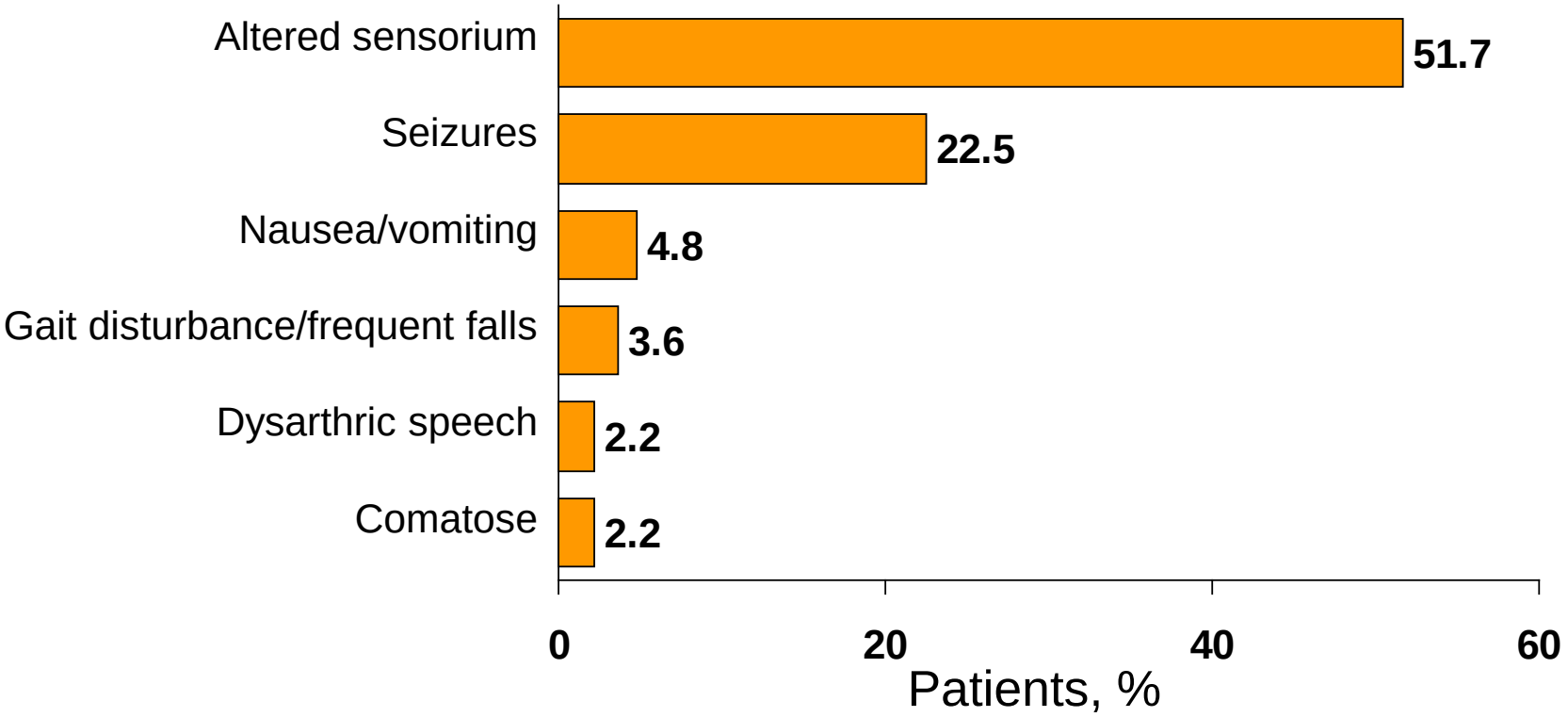
Gait stability normalized



Renneboog B et al. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.* 2006;199:71.e1-71.e8.

Clinical Symptoms in Severe Hyponatremia

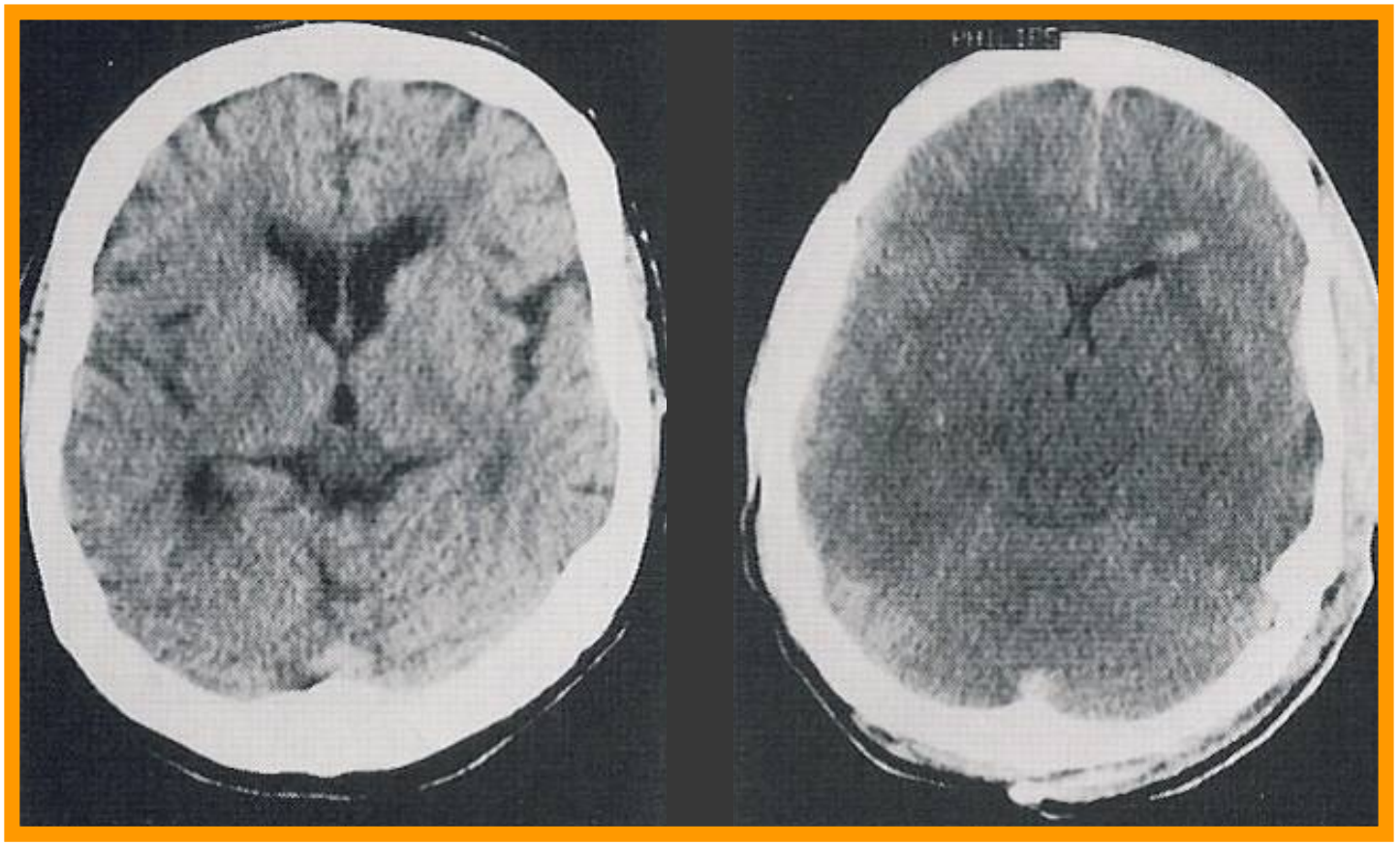
Incidence of Symptoms Observed in Hospitalized Patients With Severe Hyponatremia (serum [Na^+] <115 mEq/L)



Data from retrospective study of 168 hospitalized patients (89 of whom were symptomatic) with severe hyponatremia (serum [Na^+] <115 mEq/L) in a US medical center.

Nzerue CM et al. *J Natl Med Assoc*. 2003;95(5):335-343.

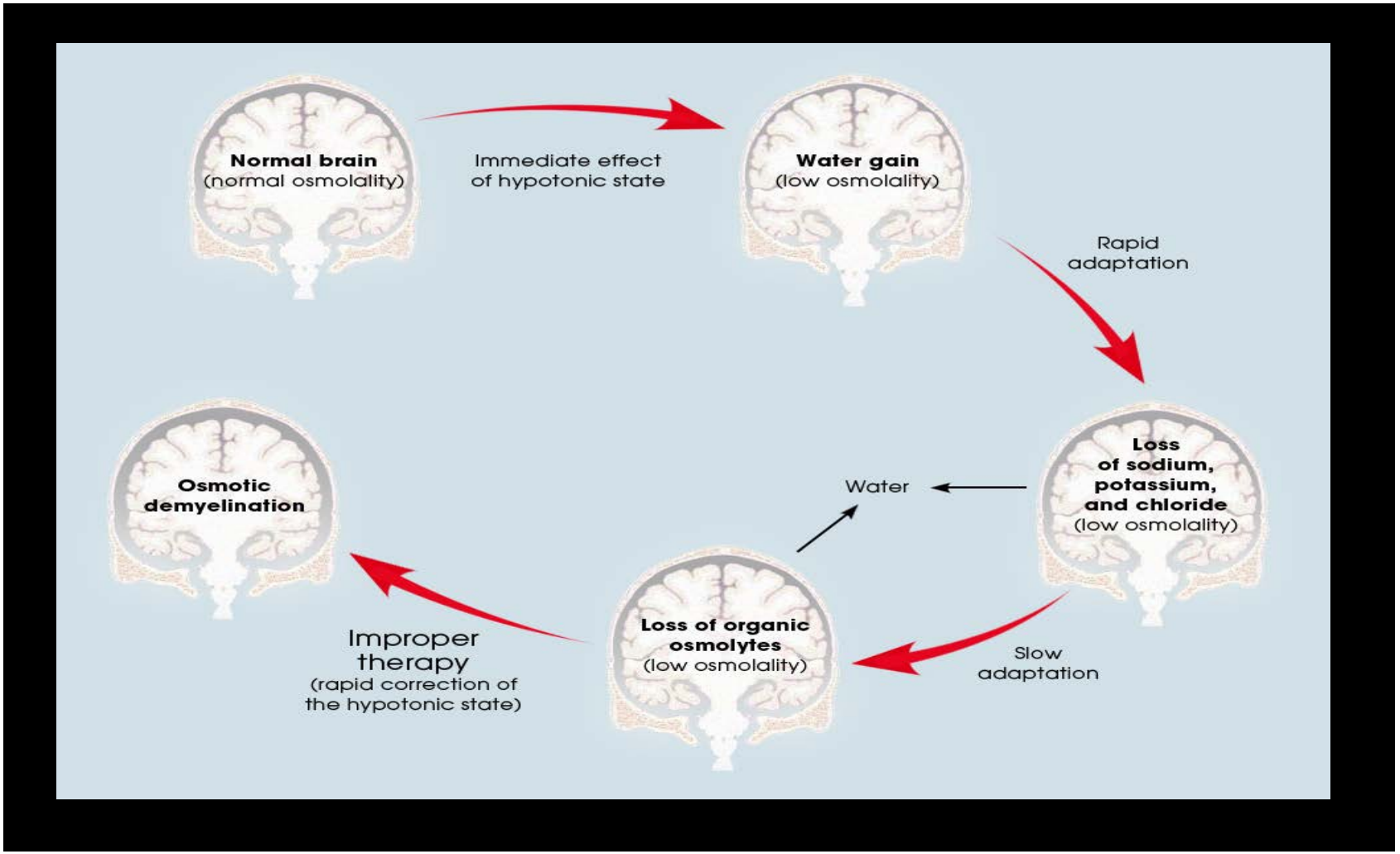
Acute Hyponatremia (<36–48 hrs): Severe Cerebral Edema



Normal Brain

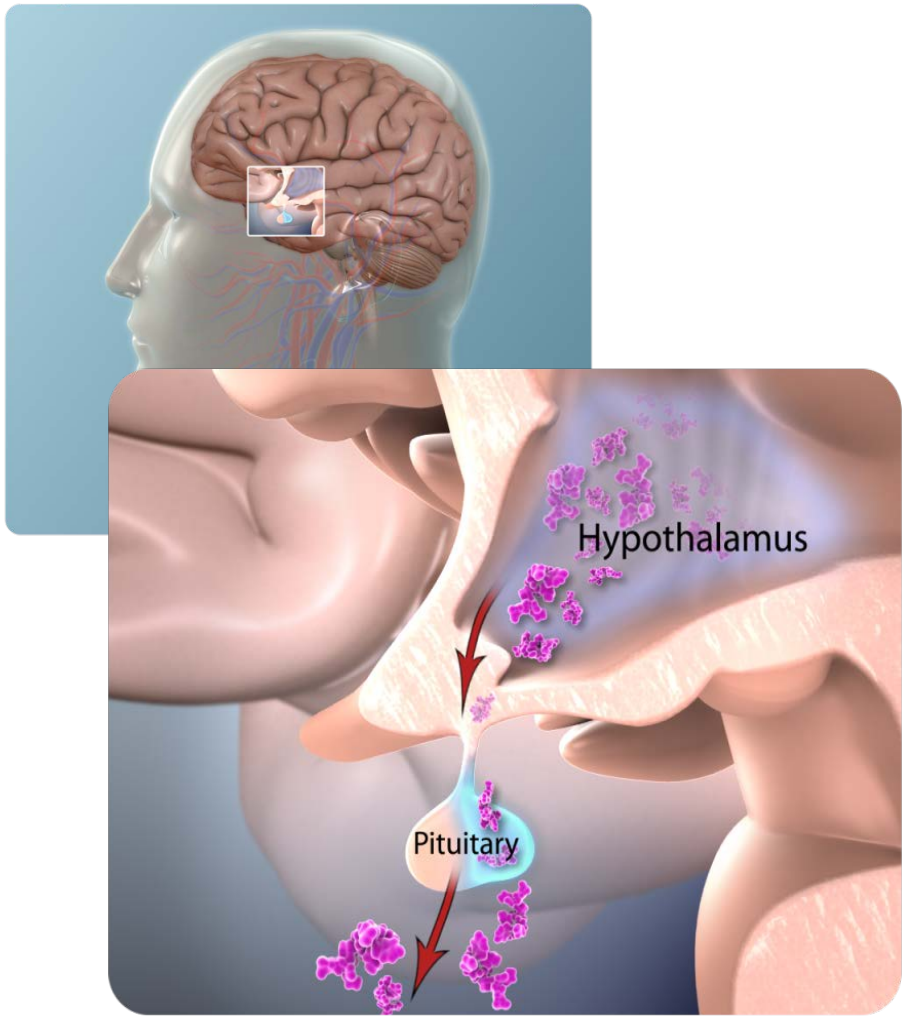
Acute/Severe Hyponatremic Brain

Brain Volume Adaptation With Hyponatremia



Reprinted from Adrogué HJ, Madias NE. *N Engl J Med*. 2000;342:1581-1589.

Role of Vasopressin (ADH) in the Pathophysiology of Hyponatremia



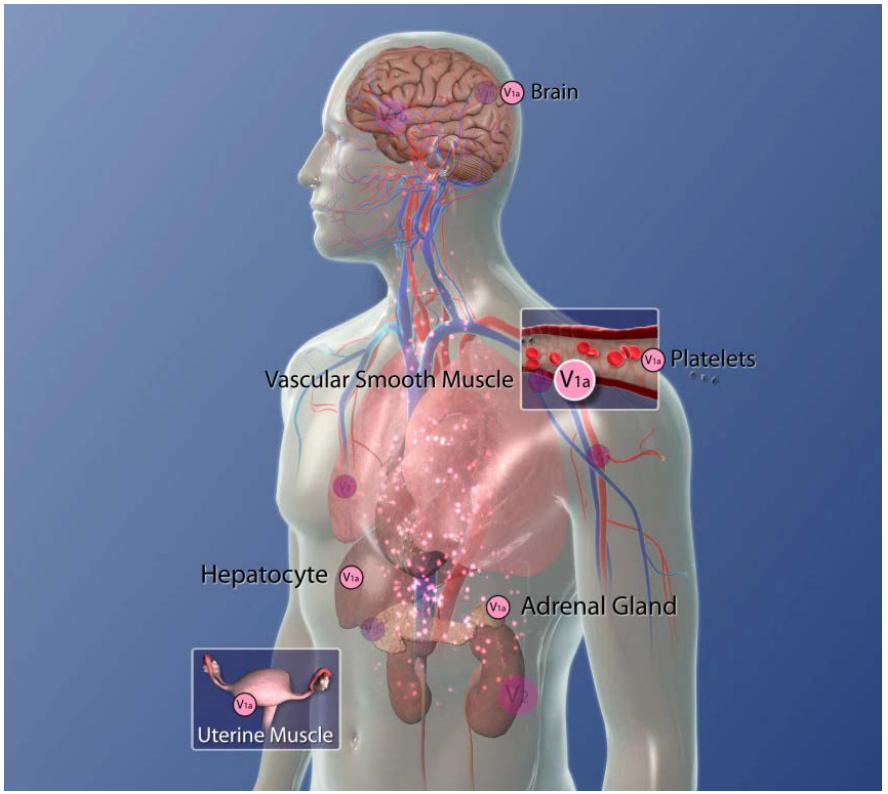
- Peptide hormone composed of 9 amino acids
- Synthesized within the supraoptic and paraventricular nuclei of the hypothalamus
  - Transported from the hypothalamus via nerve tracts to the neural lobe of the pituitary, where it is released into circulation
- Regulates urinary water excretion

Verbalis JG, Berl T. Disorders of water balance. In: Brenner BM. Brenner and Rector's The Kidney. 8th ed. Philadelphia, PA: Saunders; 2007:chap 13.

Vasopressin V_{1a} Receptor Subtype

V_{1a} Sites of Action
- Vascular smooth muscle
- Platelets
- Brain
- Hepatocyte
- Uterine muscle
- Adrenal gland

Physiologic Effects
- Vasoconstriction
- Myocardial hypertrophy
- Platelet aggregation
- Memory, BP and HR regulation, other*
- Glycogenolysis
- Uterine constriction
- Aldosterone and cortisol secretion



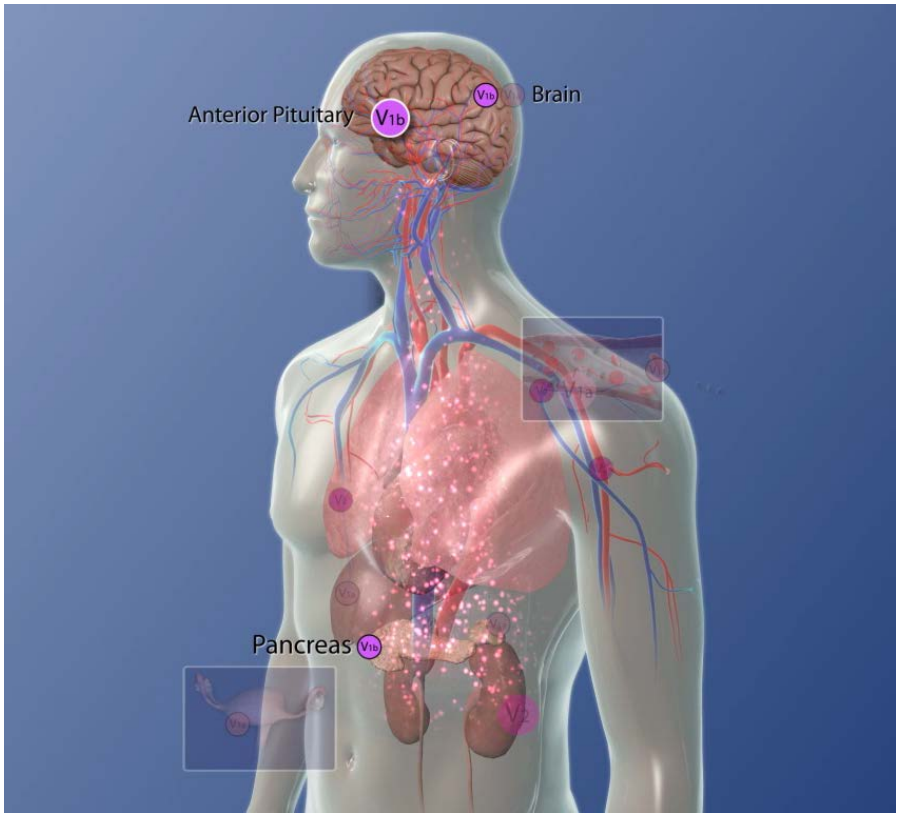
*Stress adaptation, social recognition, circadian rhythmicity, temperature regulation.

Decaux G et al. *Lancet.* 2008;371:1624-1632.

Vasopressin V_{1b} Receptor Subtype

V_{1b} Sites of Action
- Anterior pituitary
- Brain
- Pancreas

Physiologic Effects
- Release of ACTH/ β-endorphins
- Stress adaptation
- Insulin release

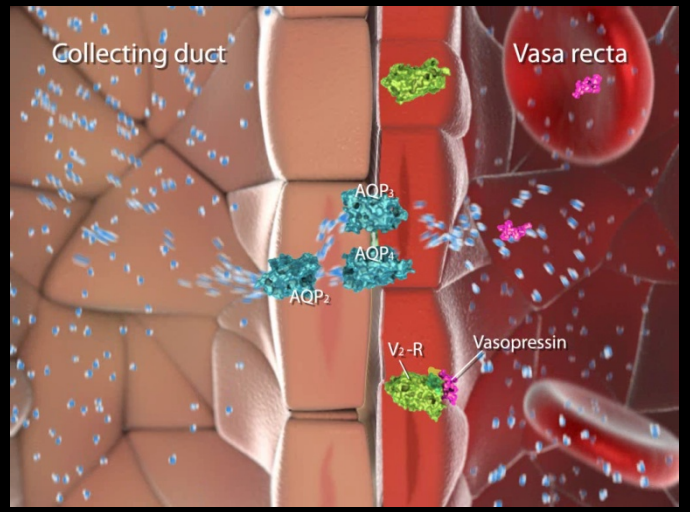


ACTH = adrenocorticotropic hormone.

Decaux G et al. *Lancet.* 2008;371:1624-1632.

Vasopressin V_2 Receptor

Effect of Vasopressin on Renal Water Handling



Which one is NOT an emergent case?

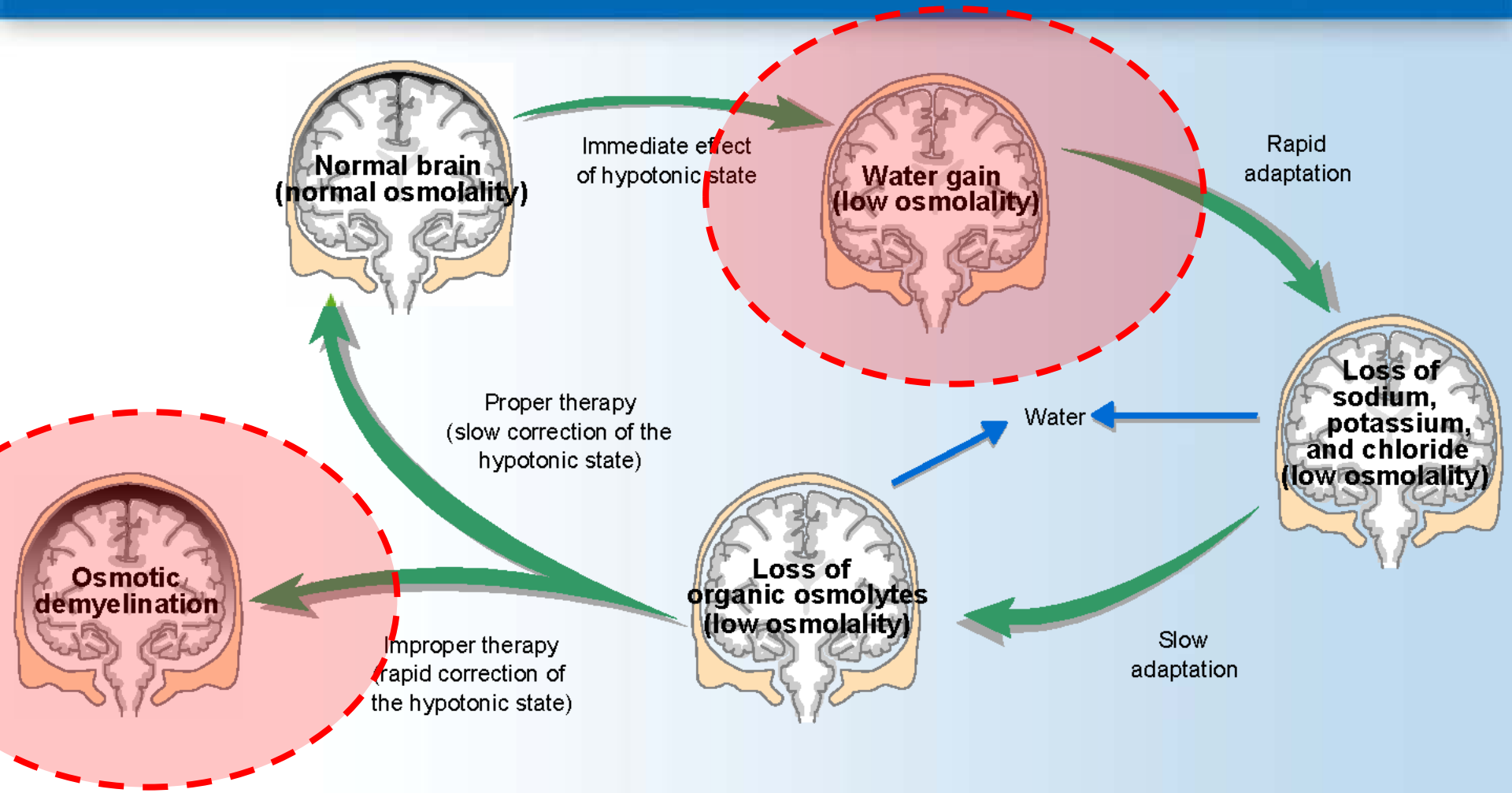
A. A 73 y/o Korean woman presenting with 10 days of weakness. She explains her PMD started her 2 wks ago on HCTZ 25 mg qd and told her to drink more fluid to prevent UTI. S-Na is **107** meq/L.

C. A 32 y/o Hispanic woman with s/p appendectomy earlier today has some SoB and mild abd. pain. S-Na is **122** meq/L post-OP (was 137 meq/L pre-OP this AM).

D. A 26 y/o AA female college student is brought to the urgent care Sunday evening following the LA Marathon. She is mildly confused and breathes slightly heavily. Her S-Na is **121** meq/L.

B. A 20 y/o otherwise healthy Asian College student brought in to ER Saturday AM with confusion, after attending a party Friday evening. S-Na of **123** meq/L. Pt is obtunded. PE reveals basal crackles. Friends admit that *ecstasy* was available in the party.

Effects of Hyponatremia on the Brain



Adapted with permission from Adrogué HJ et al. *N Engl J Med*. 2000;342:1581-1589.

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Normal Saline vs. Hypertonic Saline
Central Potine Myelinolysis
Conclusions

Annals of Internal Medicine

1992 Dec 1; 117(11): 891-7

Postoperative Hyponatremic Encephalopathy in Menstruant Women.

Ayus JC, Wheeler JM, Arieff AI.

Menstruant women are about 25 times more likely to die or have permanent brain damage compared with either men or postmenopausal women.

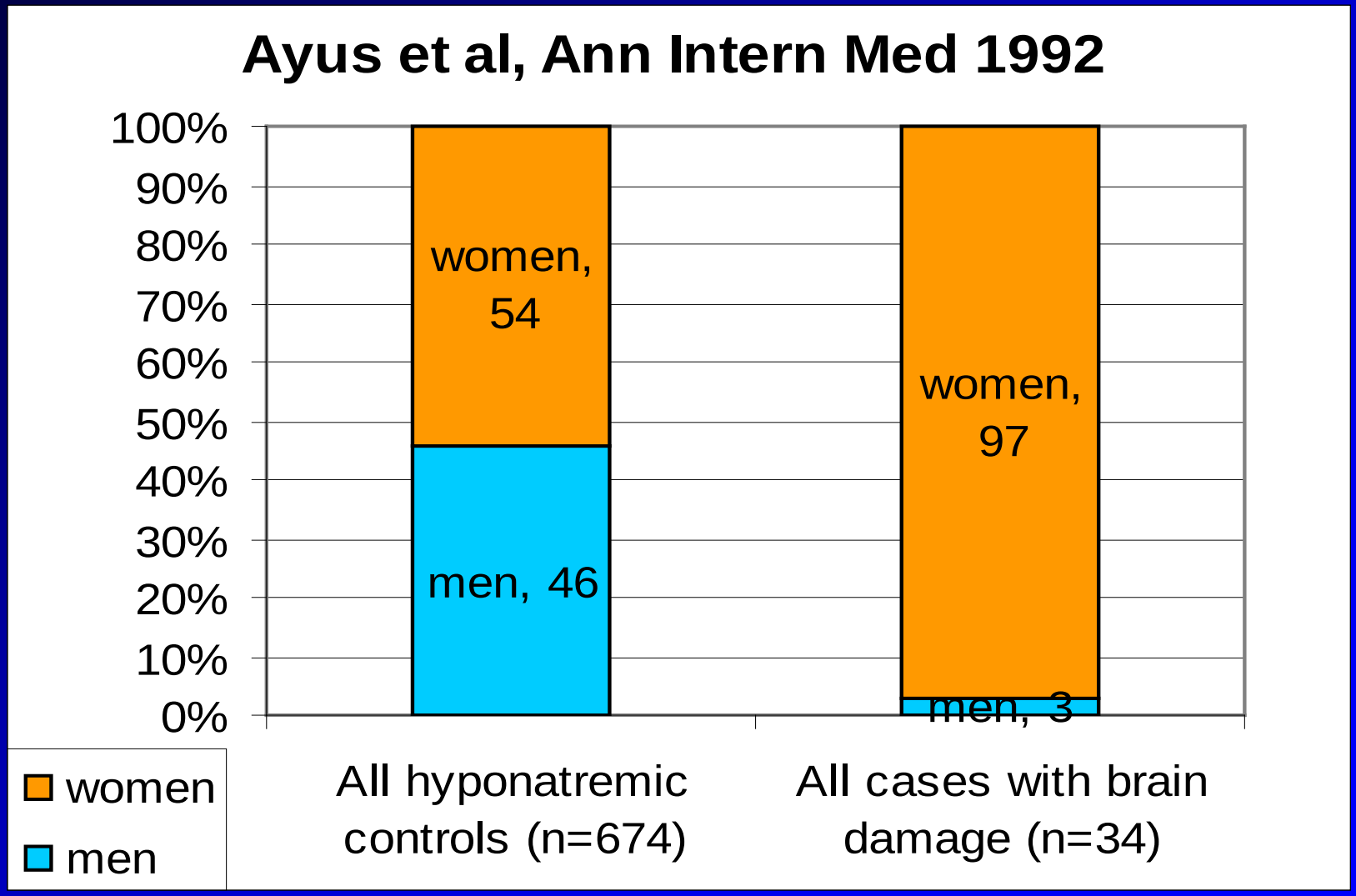
2000 May, 132(9):711-714

Hyponatremia, Cerebral Edema, and Noncardiogenic Pulmonary Edema in Marathon Runners

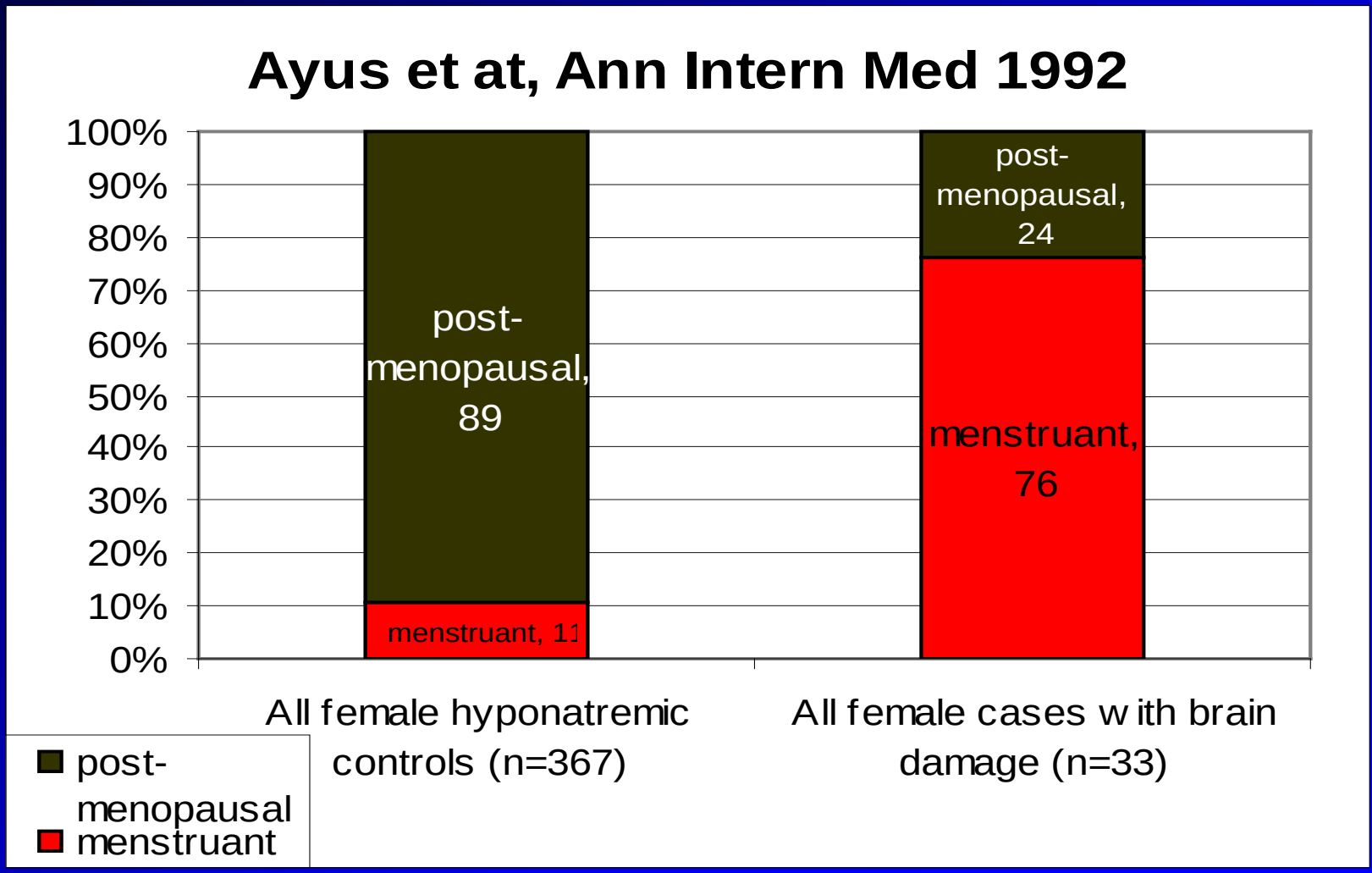
Ayus JC, Varon J, Arieff AI

Female marathon runners tend to develop conditions that lead to hyponatremia.

Effect of **Gender** on Brain Damage from Hyponatremic Encephalopathy



Effect of **Menstrual Status** on Brain Damage from Hyponatremic Encephalopathy



Conclusions

- Women and men are equally likely to develop hyponatremia and hyponatremic encephalopathy after surgery.

- However, when hyponatremic encephalopathy develops, menstruant women are about 25 times more likely to **die** or have permanent brain damage compared with either men or postmenopausal women.

Ayus et al, Annals, 1992

Annals of Internal Medicine

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Female marathon runners tend to develop conditions that lead to hyponatremia.

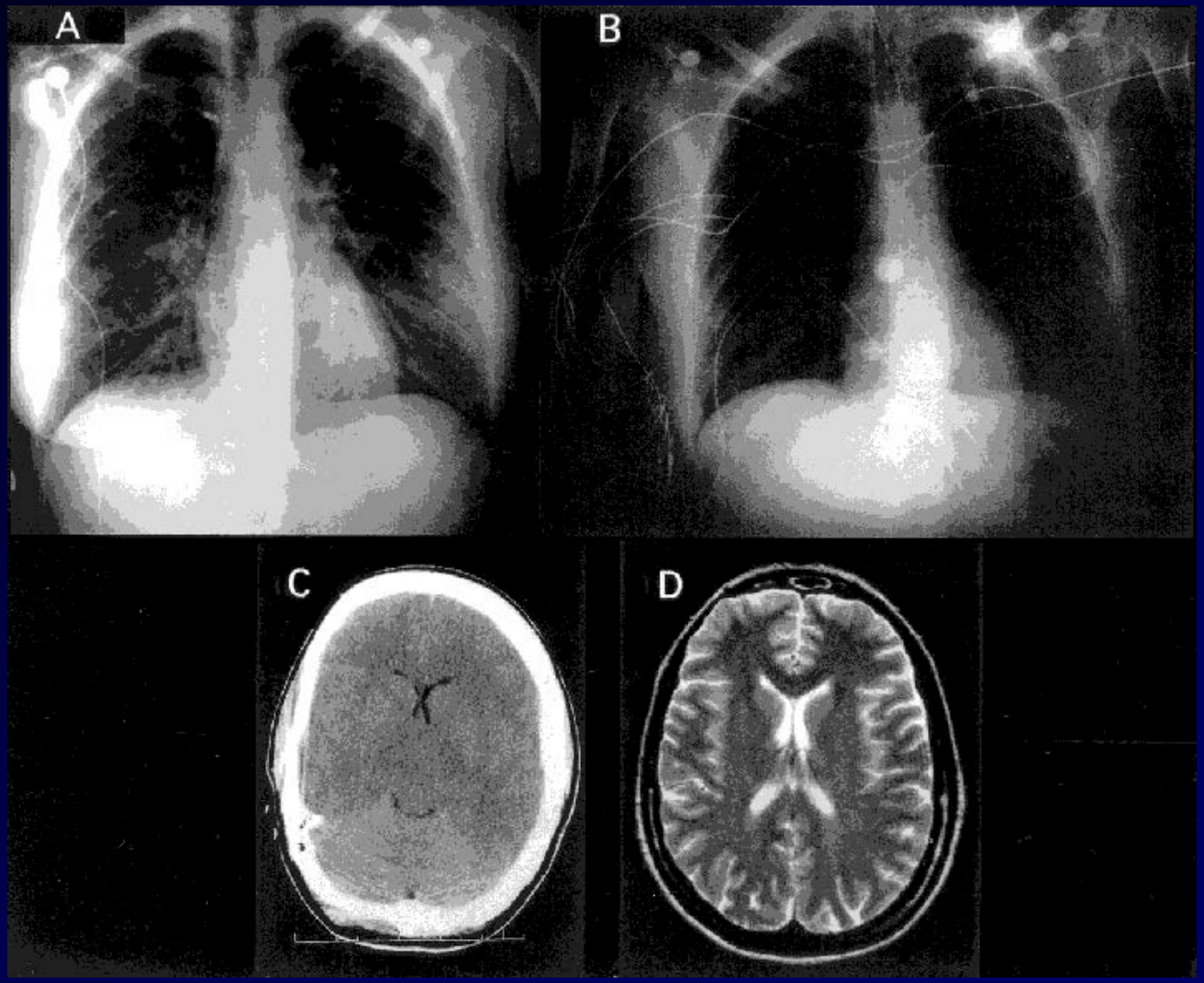
Noncardiogenic pulmonary edema with increased intracranial pressure

- 7 healthy marathon runners:
  The runners collapsed after competing in a marathon and were hospitalized with pulmonary edema.

- INITIAL Sx&Sx: nausea, emesis, abd pain, obtundation
- Serum Na: **121**±13 mmol/L
- O_2 sat: <70%.
- EKG and echo: normal
- CXR: Pulmonary edema w/ a normal heart
- CK-MB, troponin, & wedge pressure: not elevated.
- CT of the brain: cerebral edema

Ayus et al, Annals, 2000

Radiographs and scans obtained from a 44-year-old woman who was admitted to the ER with a plasma sodium level of 121 mmol/L and oxygen saturation of 66%. Bibasilar rales and copious pink frothy sputum were noted, and the respiratory rate was 38 breaths/min.



Ayus et al, Ann Intern Med. 2000;132:711-714

Noncardiogenic pulmonary edema with increased intracranial pressure

- All patients were intubated and mechanically ventilated.
- Rx: HTS (NaCl 514 mmol/L)
  increase S-Na levels by 10 mmol/L in 12 hrs
- Pulmonary and cerebral edema resolved as S-Na ↑
- Poor outcome if not treated:
  hyponatremic encephalopathy →death
  (of cardiopulmonary arrest b/o brainstem herniation).
- ***Conclusions:*** *In healthy marathon runners, noncardiogenic pulmonary edema can be associated with hyponatremic encephalopathy. The condition may be fatal in menstruant females and can be successfully treated with HTS.*

Ayus et al. Ann Intern Med. 2000;132:711-714

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Case #1 at Harbor-UCLA

- 20 yo female college student, with no significant PMH, was brought to ER after being found down, unresponsive and in respiratory distress. According to friends, she had taken multiple tablets of an unknown drug the night prior and attended a “wild party”. She was found by her friends early in the morning on the floor, unresponsive and foaming at the mouth. Paramedics reported shallow breathing, weak pulse, fixed and dilated pupils and no response to painful stimuli → intubated in ER

- PMH: none
- PSH: none
- NKDA
- Meds: unknown
- SH: college student at UCX, no known h/o tobacco, alcohol or drug use

- VS: T 94.5(rectal) HR 123 BP 88/49 RR 6 Pulse Ox 80%
- Gen: unresponsive, intubated
- HEENT: pupils fixed and dilated, no corneal or gag reflex, negative doll’s eyes
- Lungs: diffuse crackles bilaterally
- CV: tachycardic, no murmurs/rubs/gallops
- Abd: normoactive bowel sounds, soft, nondistended, no masses
- Rectal: guiaic (+), brown stool in vault
- Ext: no edema, flaccid tone
- Neuro: GCS 1-1-1, no reflexes

Case (cont.)

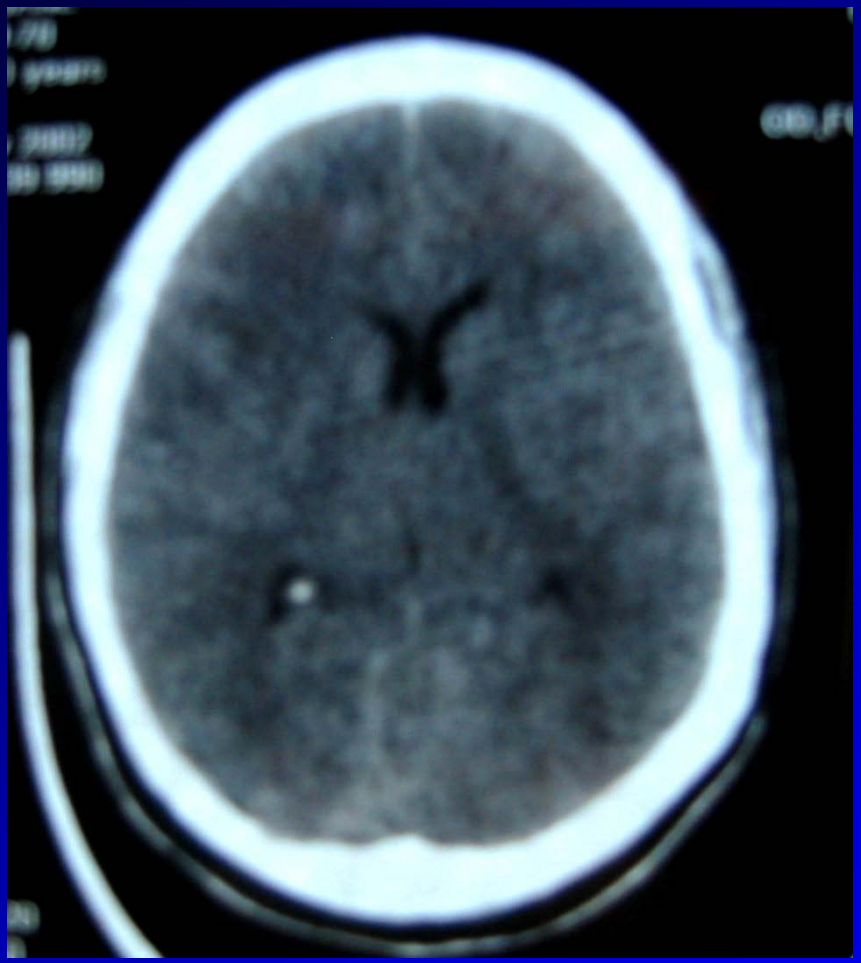
- In the ER she was emergently intubated upon arrival. She was hypotensive to SBP of 80's, received 3 liters of NS and was started on dopamine and norepinephrine drips. Labs were drawn at 08:30 AM

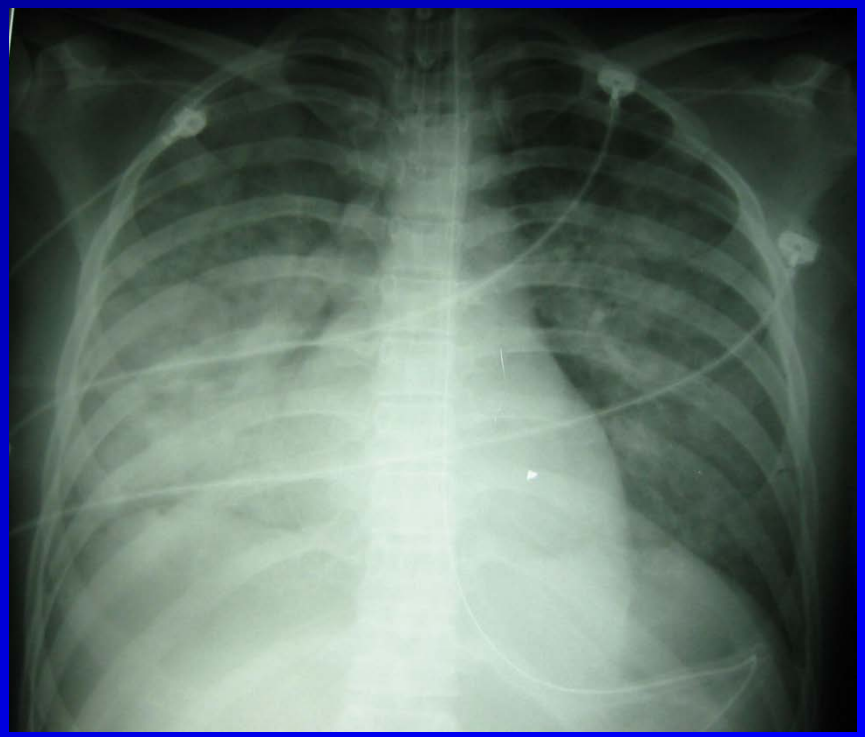
- (08:35 AM)
- Na 117 K 3.4 Cl 87 HCO3 15 BUN 9 Cr 1.0 Gluc 287 Ca 7.8
- WBC 18.3 (82N 15L) Hb 13.3 Hct 38.7 Plt 310
- Urinalysis: 1.015 pH 7.0 ketones 2+ glucose 2+

- EKG: Sinus tachycardia, rate 144
- CXR (07:50): severe pulmonary edema
- Head CT (09:00): severe cerebral edema

MDMA-abuser: CT and CXR

Cerebral edema and noncardiogenic pulm. edema





Kalantar-Zadeh et al, Nature Clin Nephrol, 2006

Course of Hospitalization (8 AM-8 PM)

Time	Na	Cl	HCO3	Cr	pH	CO2	O2	IVF	Urine
8:30	117	87	15	1	7.14	37	99	3L NS	2000 ml
10:00								3% saline (20 ml total)	
10:30	121	94	15	0.7	7.29	40	51	1L NS	
11:00								1L NS	180 ml/hr
12:00								3% saline (225 ml total)	200 ml/hr
13:15	120	91	19	0.9	7.24	29	119		200 ml/hr
15:30					7.29	27	75	500 ml NS (drips)	125 ml/hr
18:00	129	104	17	1.3				300 ml NS (drips)	150 ml/hr

20:15: Code Blue: Pt. with wide-complex tachycardia → PEA → converted to sinus with 500 ml NS and epinephrine → Ten min later: code blue again →brady to 30's

→ PEA→ asystole → expired at 21:43

Kalantar-Zadeh et al, Nature Clin Nephrol, 2006

CASE STUDY

www.nature.com/clinicalpractice/neph

Fatal hyponatremia in a young woman after ecstasy ingestion

Kamyar Kalantar-Zadeh*, Minhtri K Nguyen, Roger Chang and Ira Kurtz

SUMMARY

Background A 20-year old, otherwise healthy, female college student presented in an unresponsive state with respiratory distress after ingesting ecstasy (3,4-methylenedioxymethamphetamine). She had initial plasma sodium concentration of 117 mmol/l.

Investigations Physical examination, blood chemistry panel, urinary osmolality and electrolytes, arterial blood gas, chest X-ray, and CT scan of the brain.

Diagnosis Hyponatremia associated with noncardiogenic pulmonary edema and cerebral edema.

Management Administration of a total of 6.8 l of isotonic saline and 0.245 l of 3% hypertonic saline with sporadic administration of intravenous furosemide. The patient died approximately 12 h after admission.

KEYWORDS ecstasy, estrogen, hyponatremic encephalopathy, MDMA, noncardiogenic pulmonary edema

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

In 2002, a 20-year-old, Asian American woman was brought to the emergency room at Harbor-UCLA Medical Center after having taken multiple tablets of ecstasy (3,4-methylene-dioxymethamphetamine [MDMA]) and large quantities of water while dancing and drinking excessively during a party the night before. She did not report any symptoms upon returning home after the party. In the morning, however, she was found unresponsive and foaming at the mouth although no seizures were reported. She had rapid and shallow breathing, a weak pulse

Nature Clinical Medicine Nephrology, Apr 2006

Ecstasy Associated Hyponatremia in Premenopausal Women has a High Risk of Morbidity & Mortality

Hyponatremia Associated with 3,4-Methylenedioxymethylamphetamine ("Ecstasy") Abuse

MILOS N. BUDISAVLJEVIC, MD; LISA STEWART, MD; STEVEN A. SAHN, MD; DAVID W. PLOTH, MD

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Submitted January 9, 2003; accepted February 26, 2003.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Two fatal cases of MDMA toxicity

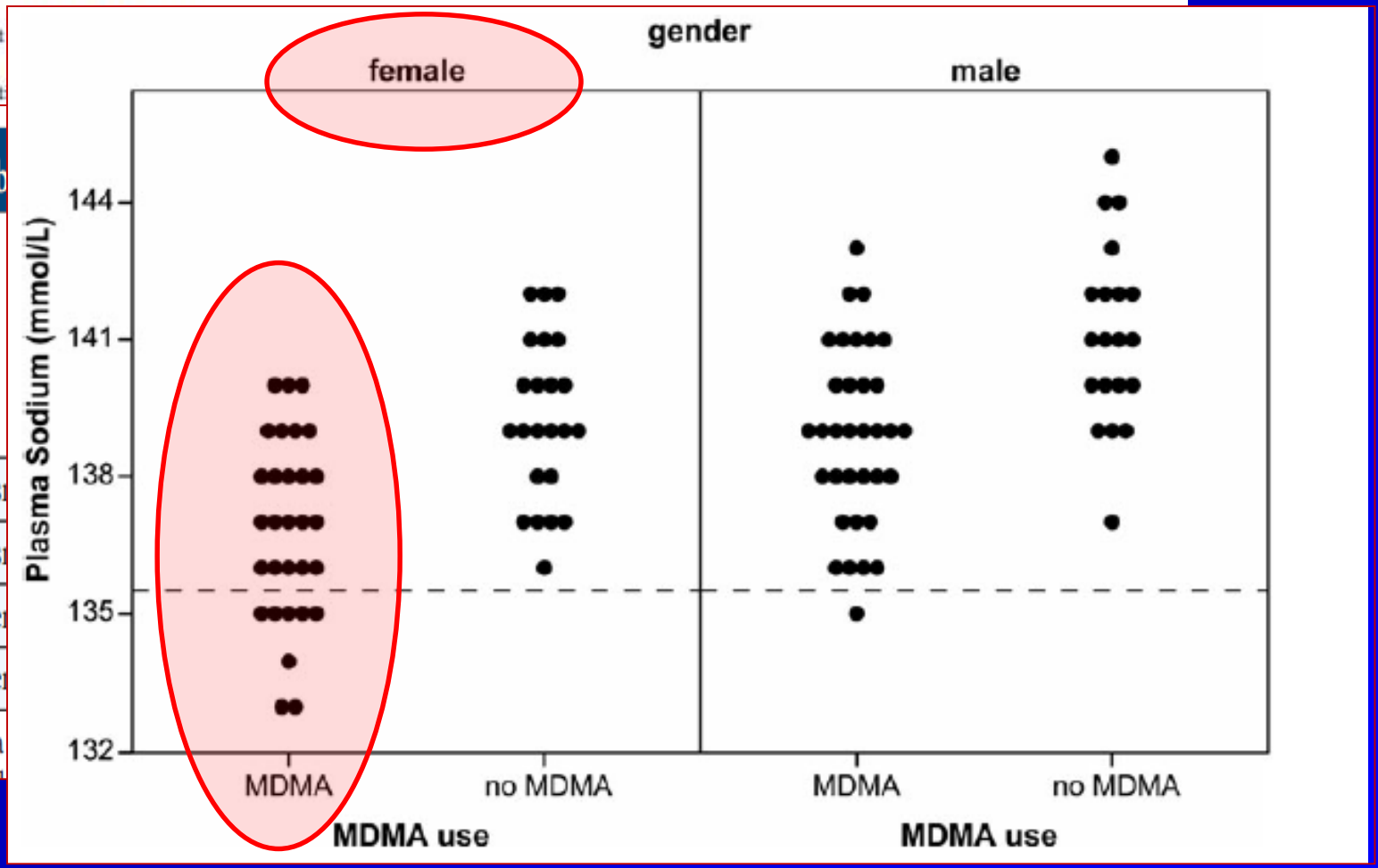
History	Patient 1	Patient 2
Age and sex	15 y/o female	18 y/o female
H/o MDMA abuse	Yes	Yes
Amount of MDMA	1 'ecstasy'*	1 'ecstasy'*
Time of ingestion	Midnight	7:45 PM
Behavioral pattern	Dancing, talking and drinking water (at least 3 lit)	Smoking cannabis, drinking EtOH + water
Onset of toxicity	05.00 AM: felt ill, vomited; given more water → convulsed; 08.00 AM: semi-conscious, urinary incontinent; 10.00: confused; SoB	00.15: felt ill; numb legs; drank 6–7 cups of water → vomiting, headache, vision loss, rigidity →respiratory arrest
Hospital transport	10.30: GCS 3/15; pulse 120; SBP 80; intubated /ventilated, 1.5 Lit IV fluid	00.55: unconscious; intubated/ventilation, IV fluid?
Hospital presentation	11.30: GCS 3/15; pupils fixed/dilated; absent brain stem reflexes; BP 80/50; T 32.6; 1 L of IV NS	01.30: GCS 3/15; pupils fixed and dilated; papilledema; T 33 °C; BP 108/60
Investigations	12.00 noon: **S-Na 125** mmol/L; calculated serum osmolality 269 mmol/kg; **CXR: pulmonary edema**; CT head: diffuse cerebral edema and cerebellar herniation→ IV mannitol, diuretic; 18.00: S-Na 135 mmol/l → declared brain dead on day 2	02.00 AM: **S-Na 126** mmol/L; **CXR: pulmonary edema**; CT head: marked cerebral edema, diuretic + IV NS; 09.00 AM: S-Na 145 mmol/L; 2 L negative fluid balance → declared brain dead on day 3
Post-mortem findings	**Brain swollen with evidence of herniation; haemorrhage in the vicinity of the pituitary**	**Brain diffusely softened and swollen, vessels distended, severe hypoxic brain damage**
Ante-mortem blood toxicology	MDMA 0.05 mg/l	MDMA 0.209 mg/l ; MDA 0.029 mg/l Ethanol 0.8 g/l

From: *Hartung et al. Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion.* ***QJM*** *2002; 95(7):431-437*

Ecstasy → Hyponatremia

- One single Mechanism?
- Most likely combination of several mechanisms:
  - Inducing ↑ADH
  - Increasing urine osm (similar to thiazide)?
  - Exercise → sweating → ↑ water intake
  - Nausea & vomiting → ↑ water intake
  - Water accumulation in GI → ↑ water absorption
  - In the hospital → ↑ IV fluid (NS)

High incidence of mild hyponatraemia in females using Ecstasy at a rave party



- FIGURE 1 : Plasma sodium of all participants. The plasma sodium of female MDMA users (136.9 ± 2.0 mmol/L, range 133–140 mmol/L) is significantly lower than in females not using MDMA (139.3 ± 1.8 mmol/L, range 136–142 mmol/L, P < 0.001). The mean plasma concentration in males using MDMA (138.9 ± 2.0 mmol/L, range 135–143 mmol/L) is significantly lower than in male nonusers (141 ± 2.0 mmol/L, range 137–145 mmol/L, P < 0.001)

Hyponatremia
Urgencies and Emergencies

Sodium Intake and IV Fluid
Osmoregulation vs. Volume Regulation
Serum Osmolality and Hyponatremia
Clinical Aspects of Hyponatremia
Hyponatremia in Menstruant Women: Recent Literature
Hyponatremia and Ecstasy: Case Report
Other Cases of Hyponatremia in Menstruant Women
Normal Saline vs. Hypertonic Saline
Central Potine Myelinolysis
Conclusions

Case #2: Marathon Runner

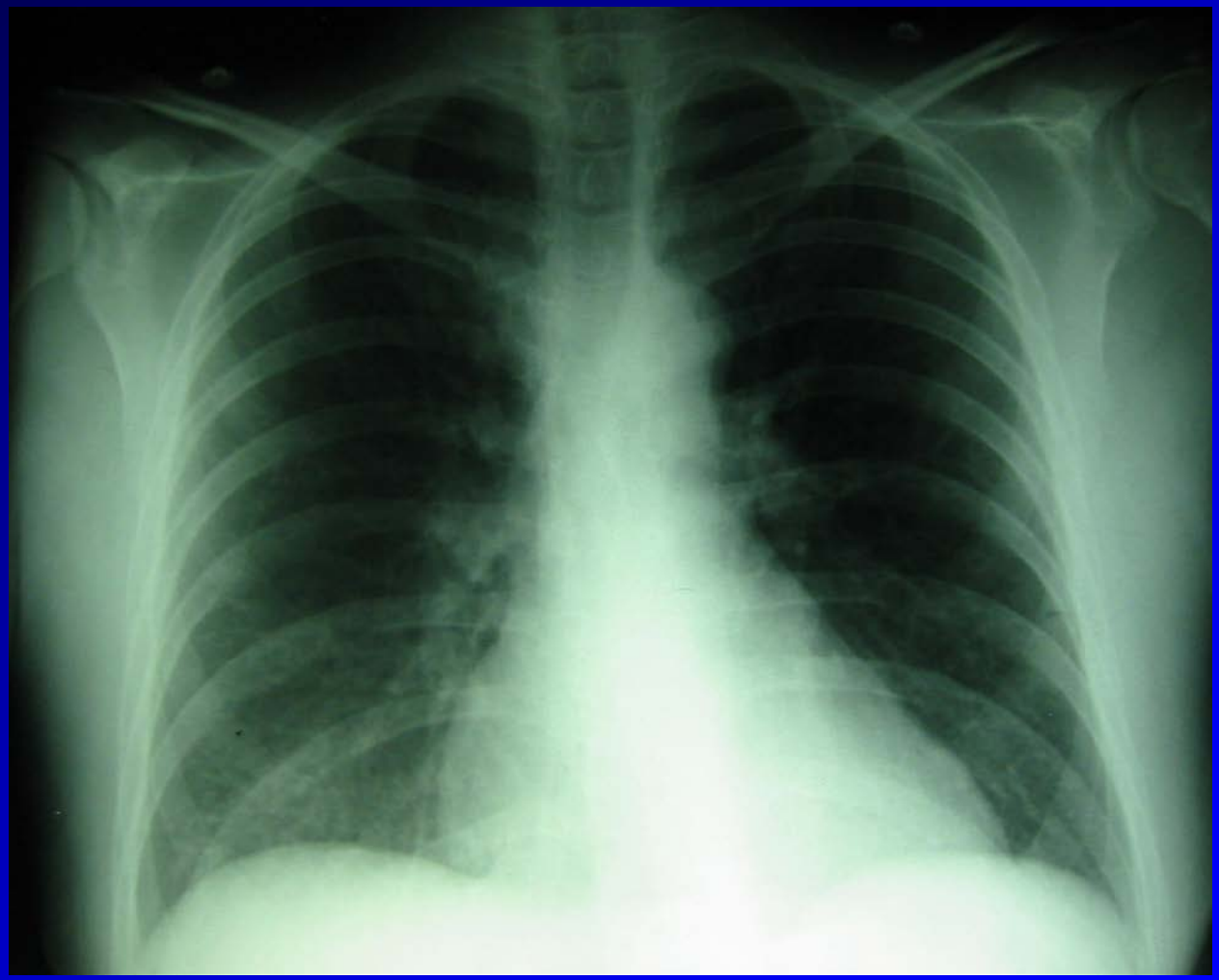
- 38-year-old, otherwise healthy Caucasian female presented to the ER at 7:00 PM on Sat with acute respiratory distress, nausea, vomiting, lose stools and headache after a 10-hour run of the annual San Francisco Marathon (~ 40 miles)
- She had drunk ~ 25 bottles of water (8.5 onz each).
- Upon returning home, she experienced headache and mild abdominal pain and became somewhat confused.

- In the ER: RR 35; HR 120, BP 150/90, O2 sat 85% on 4-6 L O2
  +Bilateral basal crackles
  + nonspecific abdominal tenderness periumbilically
  non-focal neurological examination.

- Lab: serum sodium 121 mEq/L, Urine specific gravity 1.020.
  ABG: PH 7.73, pCO2 9 mmHg, pO2 57 mmHg.
- A spot urine sample one hr after the above tests showed a urine osmolality of 245 mosm/kg and urine sodium 31 mEq/L.

- Nephrology consult recommended IV HTS, which was questioned by ER physician and intensivist on call.

Marathon Runner: CXR
non-cardiogenic pulmonary edema



Kalantar-Zadeh et al, Nature Nephrol 2006

Case #3: Post-OP Young Female

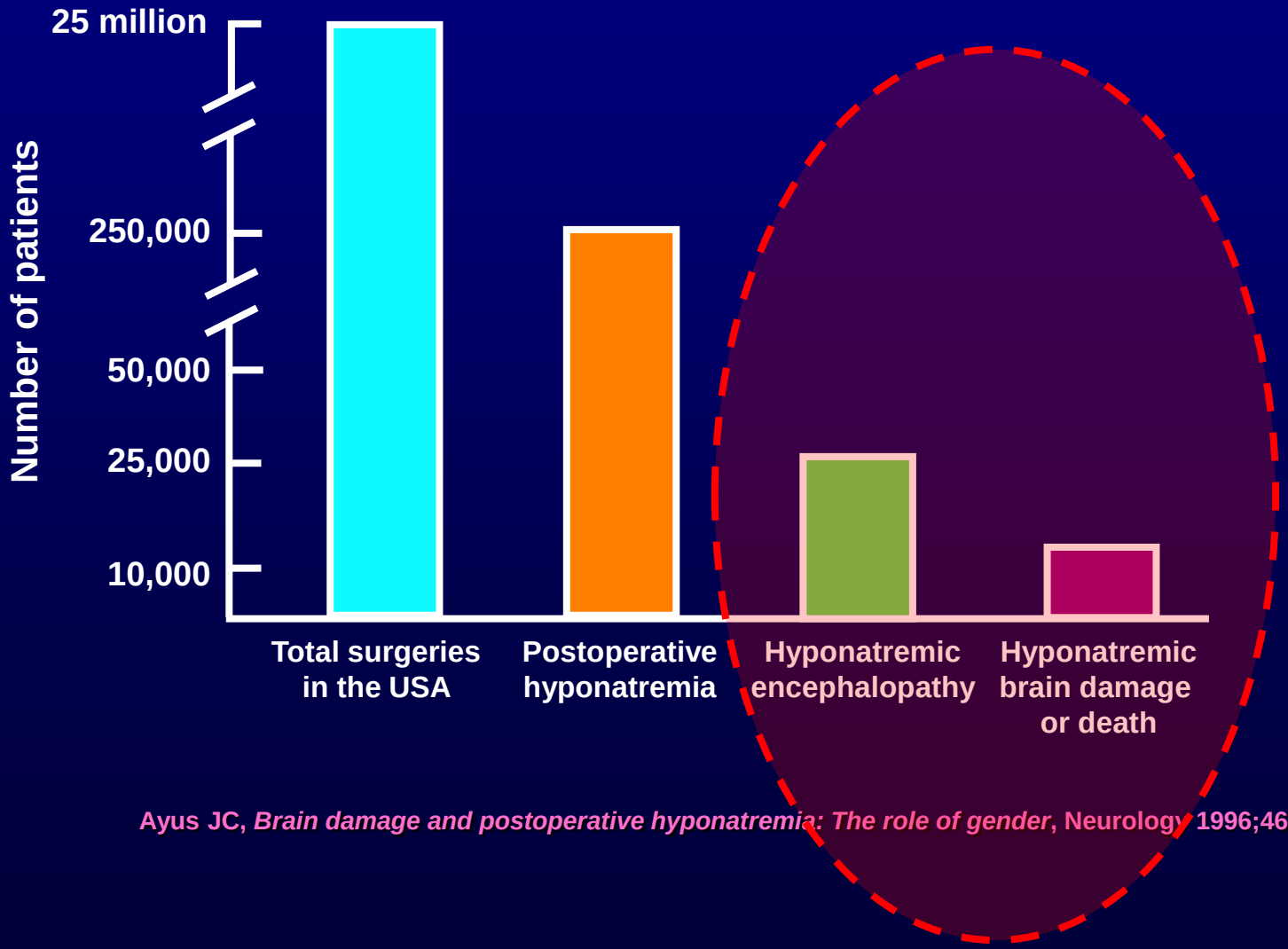
- 24-year-old Caucasian female, admitted with the working diagnosis of acute appendicitis and underwent appendectomy in the evening.
- Pre-OP S-Na 141 mEq/L. Blood sugar 55 mg/dL on admission → started on IV **D5W**, which was also administered overnight post-OP to avoid hypoglycemia.
- POD#1 AM: c/o headache and SoB.
  BP 106/55, HR 94, RR 30,O2 sat 88% on RA. PE: mild to moderate respiratory distress, + rales on both lungs. +mildly to moderately obtunded.
- Post-OP AM S-Na 119 mEq/L, S-osm 249 mosm/kg, U-osm 210 mosm/kg.
  CXR: **Pulmonary vascular congestion and edema**.

- Surgery: d/c'ed IVF + gave IV Lasix 40 mg → 2.5 liters of U/O over 4 hrs

- Nephrology consult in the afternoon: S-Na 130 mEq/L→ expressed major concerns re "*excessively rapid rate" of correction* → recommended D5W or ½ NS to be reinstituted.
- Meanwhile, pt's respiratory and neurological Sx improved.
  Surgery disregarded concerns/recommendations of nephrology.

- Pt was discharged home the following day with a final S-Na 136 mEq/L and without any respiratory or neurological issues.

PROJECTED MORBIDITY FROM POSTOPERATIVE HYPONATREMIA IN THE USA



Ayus JC, *Brain damage and postoperative hyponatremia: The role of gender*, Neurology 1996;46:323-328.

	Ecstasy user	Marathon runner	Post-surgical pt
Age and gender	20 years old female	38 years old female	24 years old female
Preceding events	Ecstasy, dancing, excessive water	40 mile marathon + 25 bottles of water	D5W pre- & post-OP to avoid hypoglycemia
Initial serum sodium	117 mEq/L	121 mEq/L	119 mEq/L
Serum osmolality	245 mosm/kg	253 mosm/kg	249 mosm/kg
Urine osmolality (Uosm) and/or specific gravity (SG)	SG: 1.015	Uosm: 245 mosm/kg SG: 1.020	Uosm: 210 mosm/kg
Initial symptoms	Found unresponsive the morning after	Confusion, headache, abdominal pain, SoB	Headache and shortness of breath
Symptoms upon presentation	Coma	Tachycardia, tachypnea respiratory distress	Respiratory distress and obtundation
Respiratory distress	Severe respiratory distress; intubated	Mod. respiratory distress hypoxemia	Mild to mod. resp distress & rales on both lung
Oxygen saturation	80% on NR mask	82% to 88% on 4-6 N/C	88% to 92% on room air
Chest X ray finding	Pulmonary edema	Pulmonary edema	Pulmonary edema
CT-scan of the head	Cerebral edema	Next day CT was normal.	Not done
Initial IV fluid/medications administered	Essentially NS (4 lit NS)	HTS + NS + furosemide	IV fluids d/c'ed, and IV Lasix administered
HTS recommendation questioned by other physicians	ER, med. and neph teams expressed concerns re HTS	Nephrologist presented recent annals paper to ER doc re HTS	Neither nephrology team nor other physicians recommended HTS
Repeat/final serum sodium	129 mEq/L after 10 hrs	125 mEq/L after 2.5 hrs 141 mEq/L after 48 hrs	136 mEq/L after 24 hrs
Outcome	Death	Improved with no sequalae	Improved with no sequalae

Kalantar-Zadeh et al, 2006 [

Pre-menopausal Women & Hyponatremia

Ayus-Arieff Syndrome

- Even borderline ACUTE hypo-Na is a serious condition.
- Most often encountered scenarios:
  - Post surgery in the hospital
  - Marathon runners, jogging, hiking
  - Ecstasy abuse with dancing and drinking
- Abdominal pain and mild headache along with mild change in MS are alarming signs and symptoms!
- Nausea/vomiting with subsequent water intake or IV fluid administration deteriorates the condition.
- Non-cardiogenic pulmonary edema and brain edema can develop rapidly leading to death.
- Rx: **Hypertonic saline** despite pulm/cereb. edema!

Why are women at Risk?

Nephrol Dial Transplant (2013) 0: 1–5
doi: 10.1093/ndt/gft192

ndt
Nephrology Dialysis Transplantation

In Focus

Ecstacy-assocatied hyponatremia: why are women at risk?

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Kamyar Kalantar-Zadeh[2,3]
and Juan Carlos Ayus[4,5]

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[4]Renal Consultants of Houston, Houston, TX, USA and
[5]Hospital Italiano, Buenos Aires, Argentina

- Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? NDT 2013

Ayus-Arieff Syndrome: ***Why Young Women?***

- ESTROGENIC hormones: 2 possible mechanisms:
  - (1) inhibition cerebral Na-K-ATPase activity
    → impairs the ability of brain cells to extrude Na+ in initial defense of cell volume
  - (2) increased vasoconstriction of cerebral blood vessels by vasopressin,
    → decrease of brain perfusion

- LESS MUSCLE MASS in young women:
  - half of total body water is in skeletal muscle cells!
  - low muscle mass → high risk for severe hyponatremia when a given volume of electrolyte-free water is retained.
  - Individuals with muscle atrophy (anorexia nervosa) are also at risk.

- BRAIN ADAPTATION differences:
  - women may be less able to adapt to cerebral edema than men

- AGING → BRAIN CELL ATROPHY
  - Young patients are affected more often, possibly due to the absence of age-related brain cell atrophy
    → higher proportion of intracellular brain volume.
    → greater increase in cell volume within the confined space of the skull if acute hyponatremia develops

Kalantar-Zadeh et al, Nature Clin Nephrol, 2006 [in press]

Ayus-Arieff Syndrome: ***Women at Risk?***

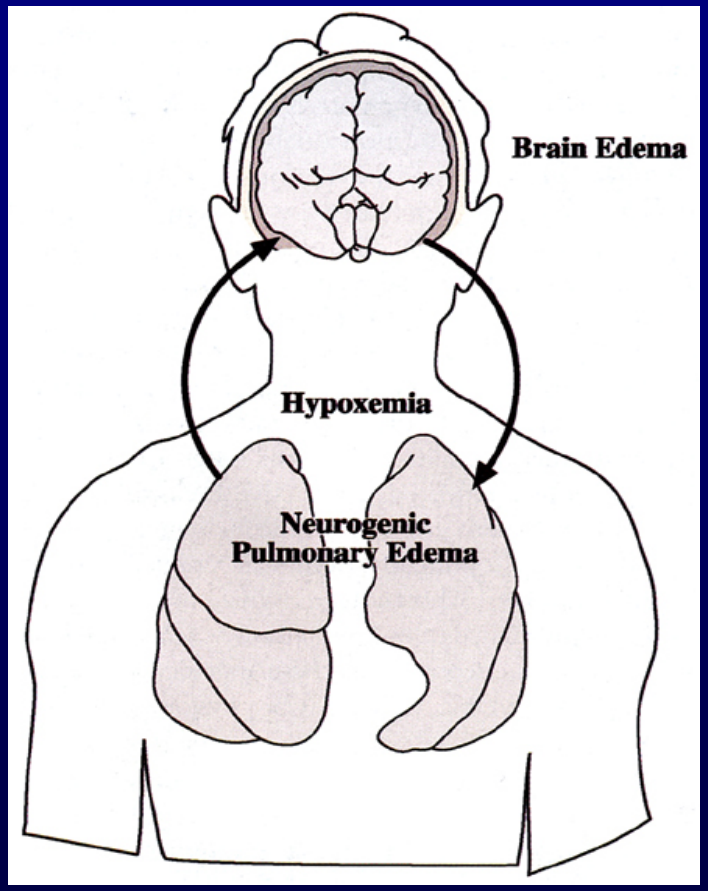
Table 1. Relationship between female gender and risk of developing hyponatremia or hyponatremic encephalopathy

Setting	Hyponatremia	Hyponatremic encephalopathy in females
Post-operative	–	++
Ecstasy	++	++
Exercise	+/–	++
Desmopressin	+	++
SSRI	+	++
Thiazide	–	++

Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? NDT 2013

Effects of Hypoxemia on Hyponatremic Encephalopathy

Non-Cardiogenic Pulmonary Edema



Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? ***Nephrol Dial Transplant*** 2013

Effects of Hypoxemia on Hyponatremic Encephalopathy

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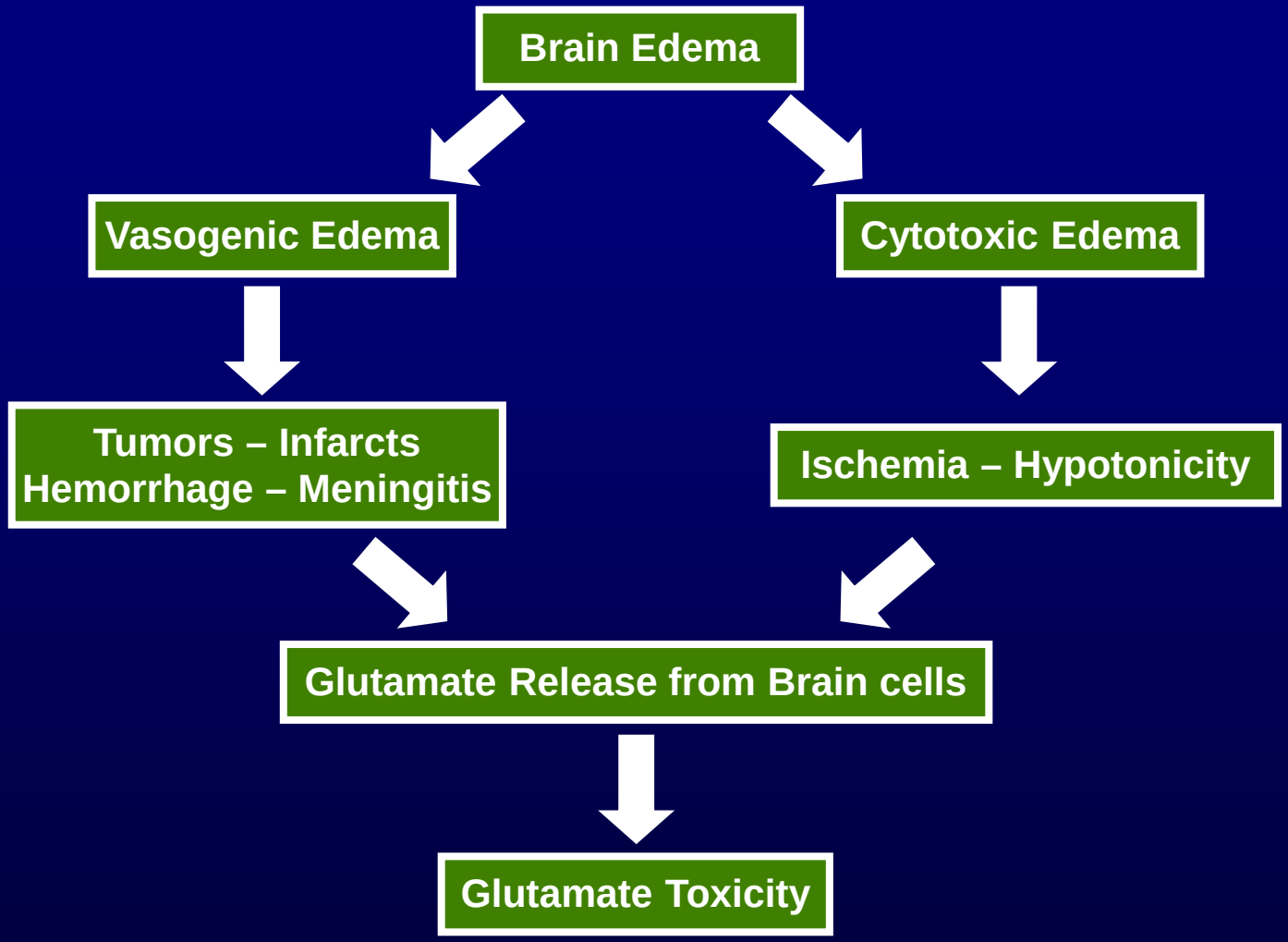


Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? *Nephrol Dial Transplant* 2013. Moritz ML, Ayus JC; *The Pathophysiology and Treatment of Hyponatremic Encephalopathy*, *Nephrol Dial Transplant* 18:2846-2491, 2003

NS as Hypontremia Rx?

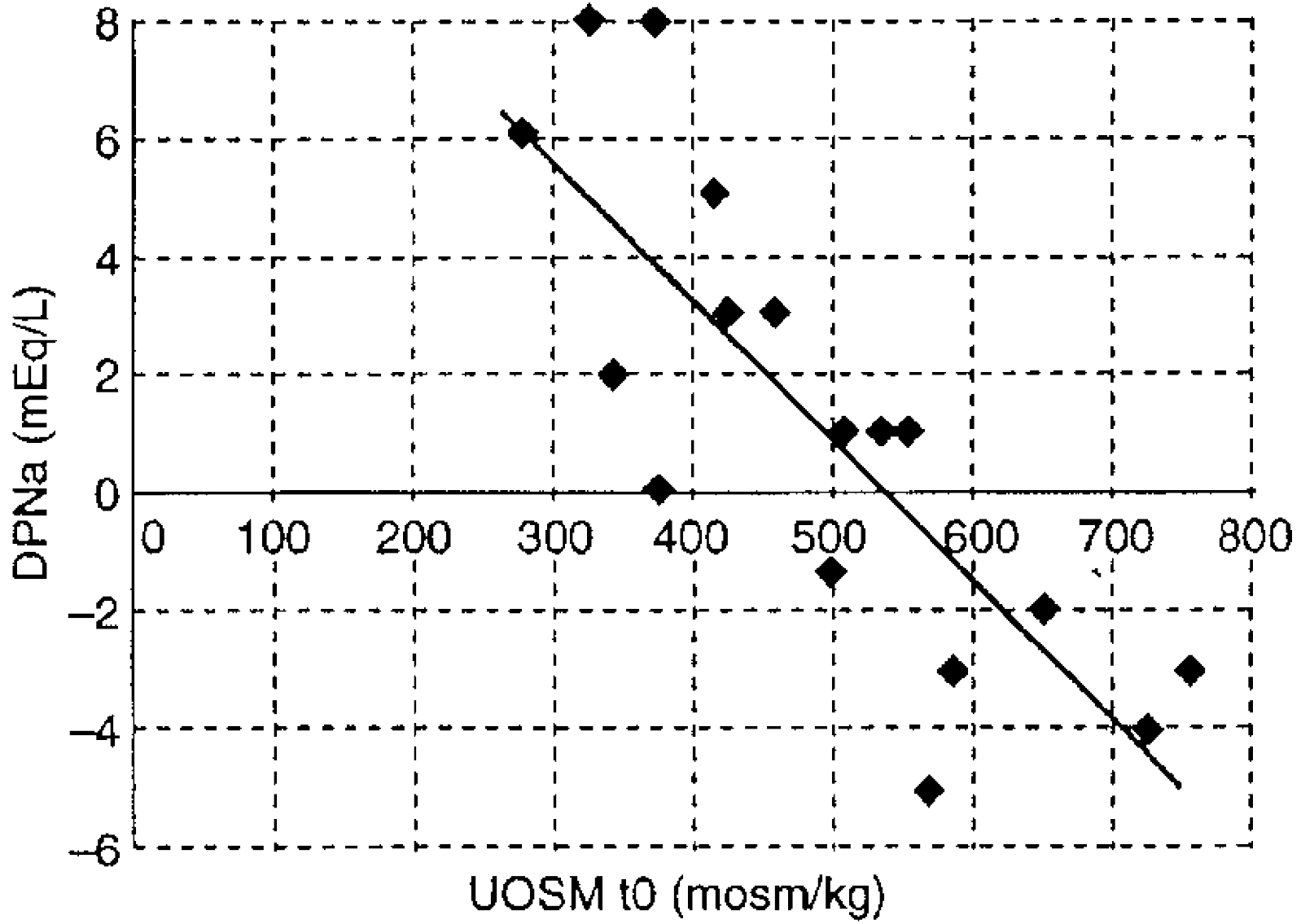
- **Can NS worsen hypo-Na? Yes! Esp if U-osm>>300**

- **A 60 y/o woman has a serum Na 112 meq/L and U-osm of 600 mosm/kg.**
  2 lit of NS is administered.
  Serum Na decreases to 109 meq/L. What happened?

- 1 Lit NS = 150 meq Na = 300 mosm
- 2 Lit Ns = 300 meq Na = 600 mosm
- One lit of urine excretes the whole administered solute
- One lit of pure water is retained

➔ *Give FUROSEMIDE along with NS, in order to diminish the concentrating ability of renal tubules.*

2 lit of NS to 17 pts with SIADH → changes in S-Na



Musch & Decaux, QJM 1998

TREATMENT of Hyponatremia

If not developed acutely, is NOT an emergency!

1. Water Intake Restriction

   Edematous sates, SIADH, primary polydipsia, advanced CKD

2. Salt Administration

   (saline only if U-osm<300, salt tablets)

   Volume depletion, s/p diuretics, adrenal insufficiency

Target Correction (if not developed acutely):

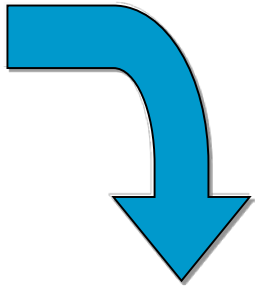
≤10 meq/L/day

≤ 0.5 meq/L/hr

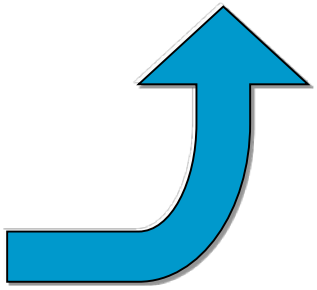
Oral vaptans can only be initiated & re-initiated in the hospital→ Advise drinking water if thirsty

Hyponatremia: Strategies for Correction

1. Add to the numerator



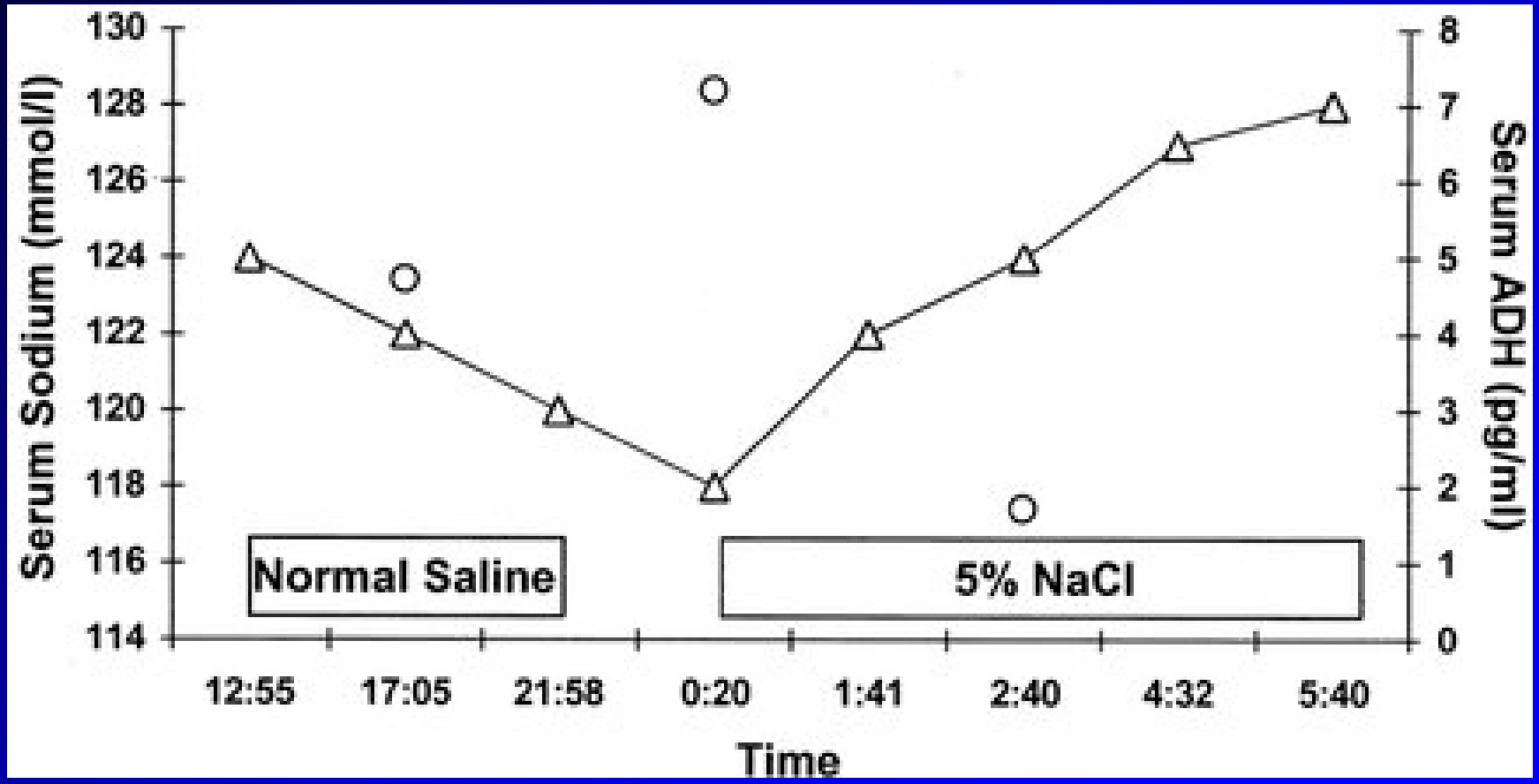
$$\text{Serum } [Na^+] \sim \frac{Na^+_E + K^+_E}{\text{Body water}}$$



2. Subtract from the denominator

Acknowledge Communication by R. H. Sterns.
Verbalis JG et al. Am J Med. 2007;120(11 suppl 1):S1-S21.

NS may worsen Hyponatremia



BUDISAVLJEVIC et al, Am J Med Sci, 2003; 326:89–93

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

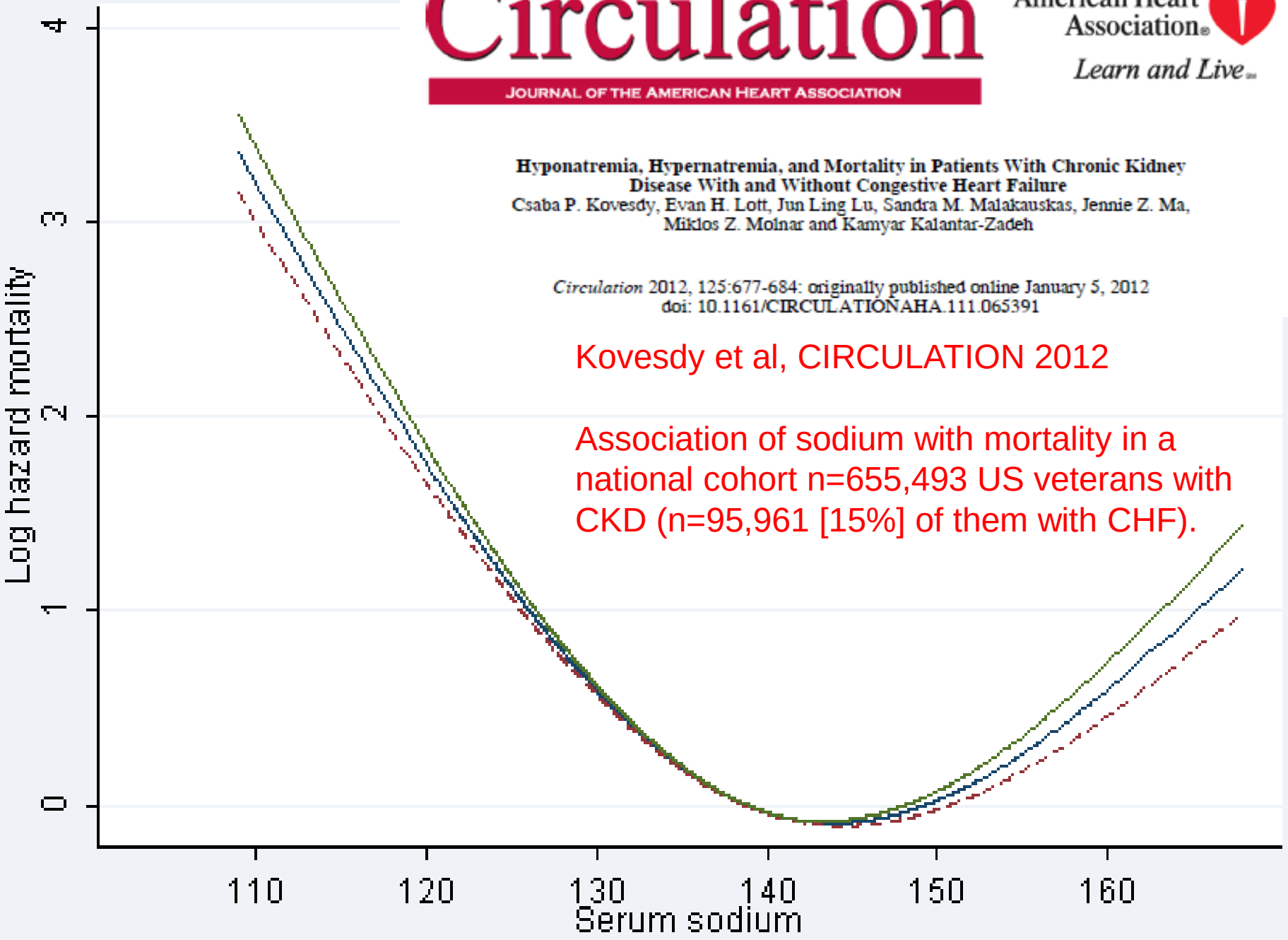
Hyponatremia, Hypernatremia, and Mortality in Patients With Chronic Kidney Disease With and Without Congestive Heart Failure

Csaba P. Kovesdy, Evan H. Lott, Jun Ling Lu, Sandra M. Malakauskas, Jennie Z. Ma, Miklos Z. Molnar and Kamyar Kalantar-Zadeh

Circulation 2012, 125:677-684: originally published online January 5, 2012
doi: 10.1161/CIRCULATIONAHA.111.065391

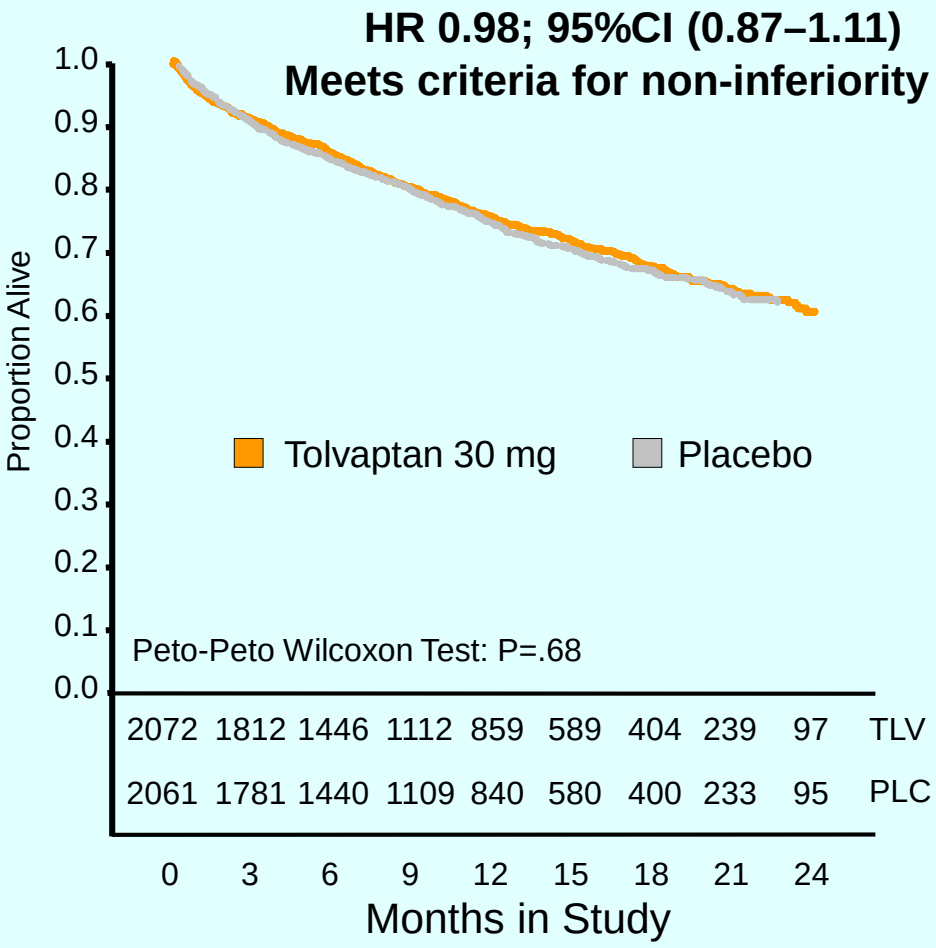
Kovesdy et al, CIRCULATION 2012

Association of sodium with mortality in a national cohort n=655,493 US veterans with CKD (n=95,961 [15%] of them with CHF).

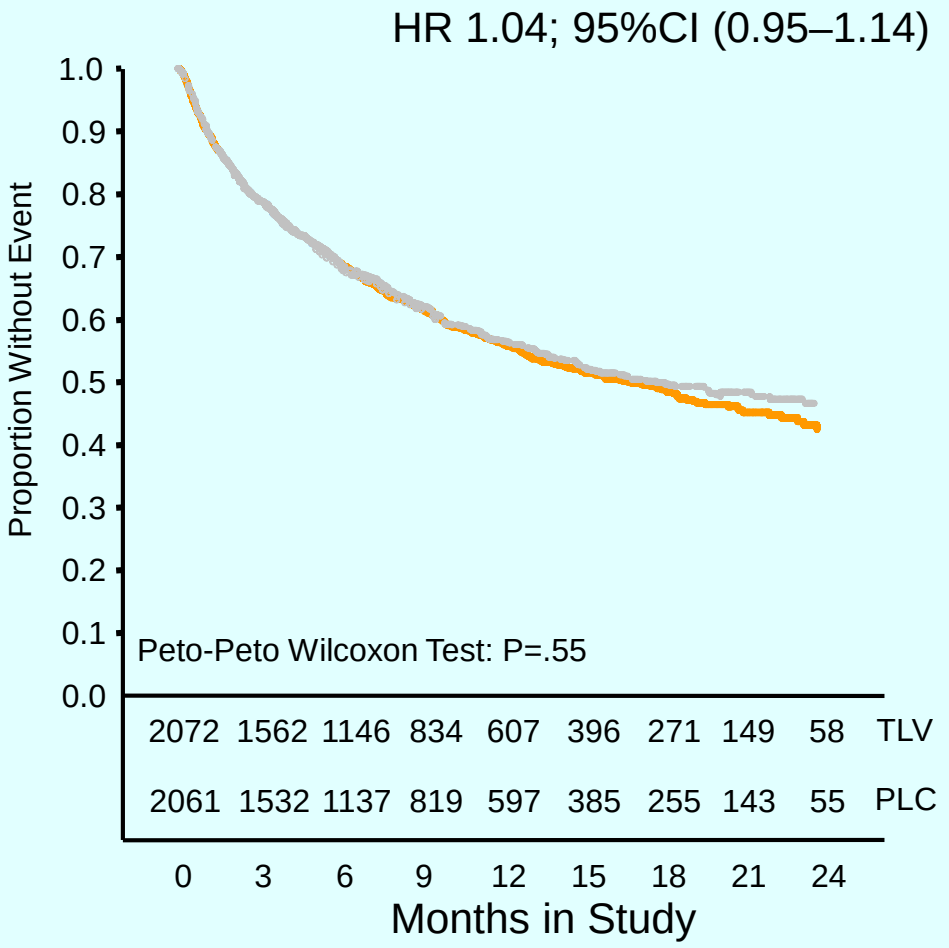


No Worsening or Improvement in Outcomes EVEREST Trial, All Patients

All-Cause Mortality



CV Mortality or HF Hospitalization



Konstam MA et al. *JAMA*. 2007;297(12):1319-1331.

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Urgencies and Emergencies

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Conclusions

Risk of Osmotic Demyelination: Central Pontine Myelinolysis

Due to osmotic shrinkage of brain cells.

In Rx of chronic or slowly progressive hypo-Na
if Na rise >20 meq/24hrs

MS changes, dysphagia, Babinski, paraparesis, coma

Dx: MRI (may not be + for up to 4 wks!)

In uremic/CKD/ESRD pts with hypo-Na: CPM is rare!
> b/o concurrent removal of urea during dialysis?
> azotemia expedites intracellular osmolyte shift?

A 30-y/o alcoholic woman presented with confusion and disorientation after a grand mal seizure. The pt's serum Na on admission was 99 mmol/L. Treatment was initiated with a slow infusion of NS, resulting in serum Na values of:

102 mmol/L 4 hours after admission,
104 mmol/L at 8 hours,
115 mmol/L at 12 hours,
118 mmol/L at 18 hours,
125 mmol/L at 24 hours.

The pt initially had dysarthria, with slurred speech, and a slow finger-to-nose test on cerebellar examination, although there was no Babinski reflex.

During days 2 to 6 with a normal serum Na concentration, her condition gradually improved, although she interacted slowly with staff members and family, and had difficulty following commands.

MRI of the brain (3rd day) was negative for CPM.

On the 7th day she became unresponsive to commands and painful stimuli and had a Babinski reflex.

Second MRI (7th day) demonstrates central pontine **myelinolysis** as a region of prominent low signal intensity on a sagittal T1-weighted image and high signal intensity on an axial T2-weighted image. The signal intensity on the periphery of the pons is normal on both images, and there is relative preservation of the corticospinal tracts (Panel B, arrowheads).

The patient remained in an unresponsive state for 7 weeks, but her sensorium gradually improved until she was fully responsive, alert, and oriented.

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CONCLUSIONS: Hypontremia

- Hyponatremia is the most common electrolyte disarray.
- The treatment urgency depends on the rate of development and patient's age and gender.
- Pre-menopausal women are at high risk of morbidity and mortality even with mild hypo-Na.
- Non-cardiogenic pulmonary edema and cerebral edema are fatal conditions in these patients.
- Elderly individuals are at high risk of "over-treatment" for otherwise clinically stable hyponatremia.

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