Tolvaptan

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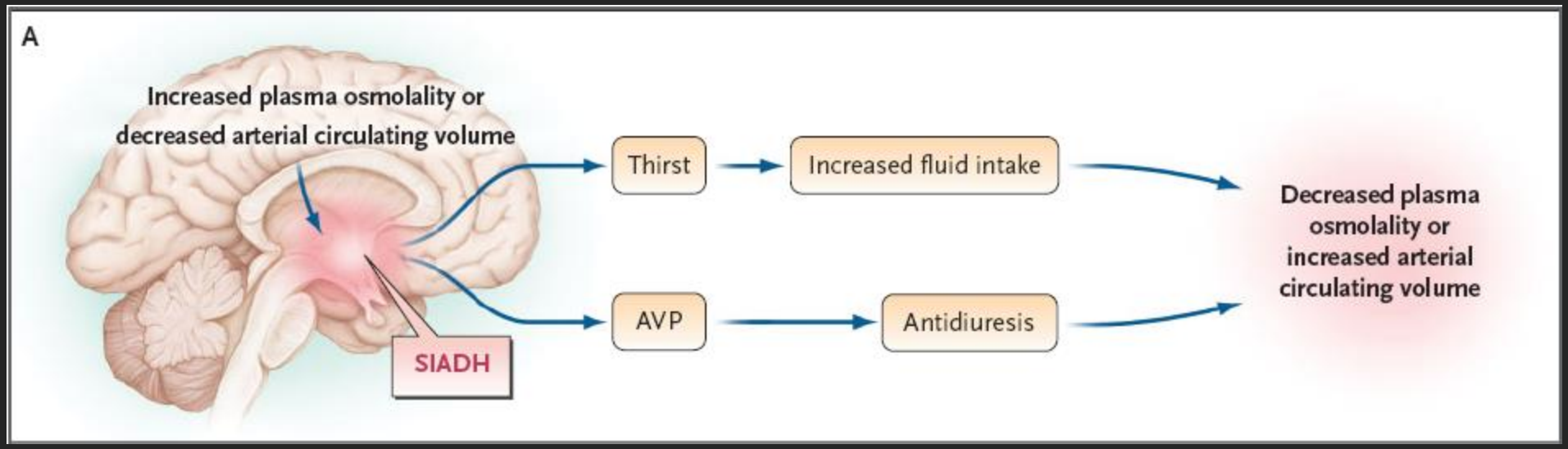


N Engl J Med 2005

Vasopressin can activate three different types of receptor

- Once released into the circulation, vasopressin can activate three types of G-protein-coupled receptors: V_{1a}, V_{1b} and V_2[12]

Receptor	Localisation	Function
V_{1a}	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy
	Platelets	Platelet aggregation
	Hepatocytes	Glycogenolysis
	Myometrium	Uterine contraction
V_{1b} (V_3)	Anterior pituitary	ACTH release
V_2	Basolateral membrane collecting tubule	Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis
	Vascular endothelium	vWF and factor 8 release
	Vascular smooth muscle	Vasodilatation

ACTH = adrenocorticotropin; AQP-2 = aquaporin 2; vWF = von Willebrand Factor

12. Greenberg A, Verbalis JG. *Kidney Int* 2006; 69: 2124 –2130.

Hypotonic hyponatraemia is classified according to volume status

	Hypervolaemic hyponatraemia	Euvolaemic hyponatraemia	Hypovolaemic hyponatraemia
Total body water (TBW)[15]	↑↑	↑	↓
Total body sodium[15]	↑	↔	↓↓
Extracellular fluid (ECF) volume[16]	↑↑	↔	↓
Oedema[16]	Present	Absent	Absent
Cause[2-15]	Congestive heart failure, cirrhosis, nephrotic syndrome, renal failure (acute or chronic)	SIADH, glucocorticoid deficiency, hypothyroidism	*Renal solute loss:* Diuretic therapy, cerebral salt wasting, mineralocorticoid deficiency, salt wasting nephropathy *Extrarenal solute loss:* Vomiting, diarrhoea, pancreatitis, third space burns

2. Verbalis J, et al. *Am J Med*. 2007; 120(11 Suppl 1): S1-21.
15. Schrier RW, Bansal S. *Curr Opin Crit Care*. 2008;14:627-634.
16. Douglas I. *Cleve Clin J Med*. 2006;73(3):S4-S12.

Patients with SIAD(H) are clinically euvolemic, but…

Criteria for the diagnosis of SIADH

Essential

- Decreased measured plasma osmolality (<275 mOsm/kg H_2O)
- Urinary osmolality > 100 mOsm/kg H_2O during hypo-osmolality
- Clinical euvolaemia
  - No clinical signs of volume depletion of extracellular fluid (e.g., no orthostasis*, tachycardia, decreased skin turgor, or dry mucous membranes)
  - No clinical signs of excessive volume of extracellular fluid (e.g., no oedema or ascites)
- Urinary sodium > 30 mmol/l with normal dietary sodium intake**
- Normal thyroid and adrenal function determined by both clinical and laboratory assessment
- No use of diuretic agents within the week prior to evaluation

Supporting

- Plasma uric acid < 4 mg/dl (< 0.24 mmol/l)
- Blood urea nitrogen < 10 mg/dl (< 3.57 mmol/l)
- Fractional sodium excretion > 1%; fractional urea excretion >55%***
- Failure to improve hyponatraemia after 0.9% saline infusion, or improvement of hyponatraemia with fluid restriction

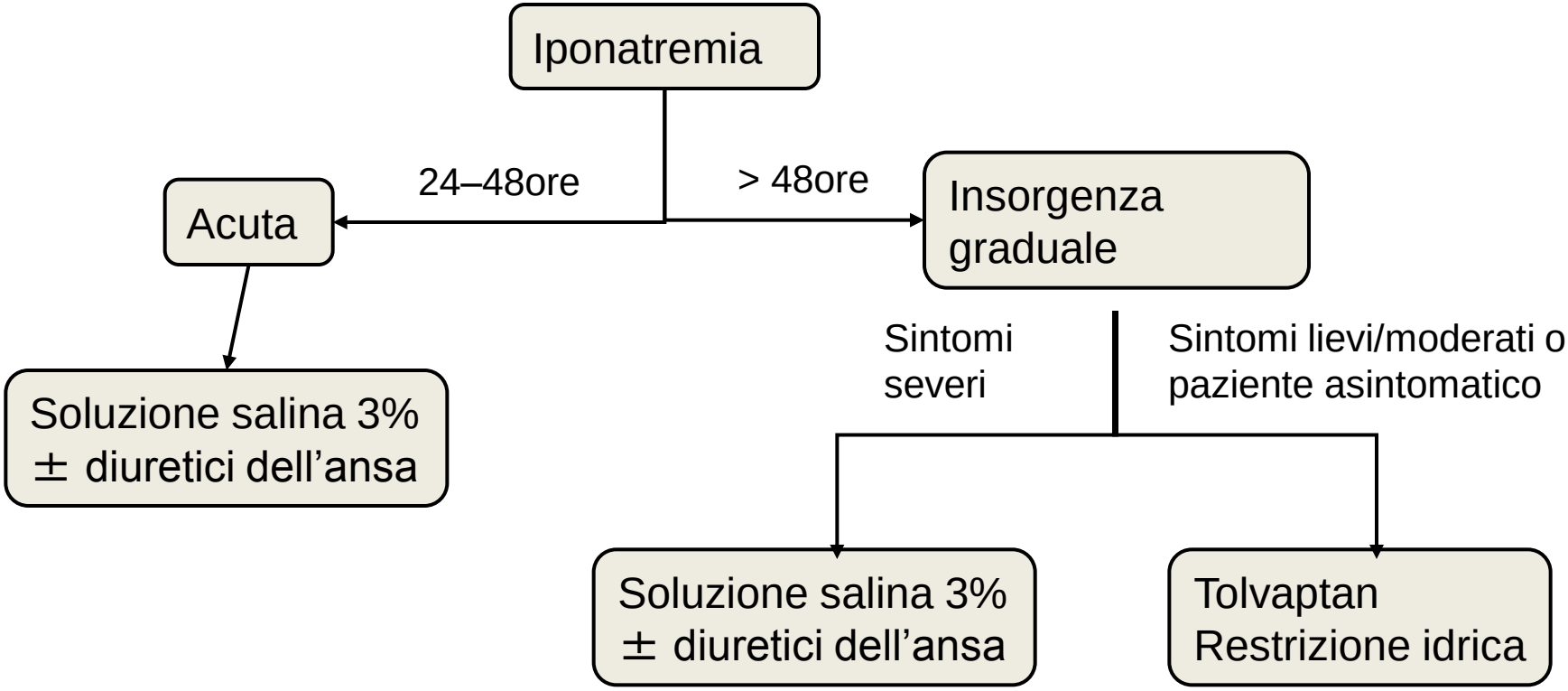
* Orthostatic changes in blood pressure and pulse rate are defined as a ≥ 20 mm decrease in systolic BP and/or a ≥20 bpm increase in pulse rate upon going from a supine to a standing position.

** Although high urine sodium excretion generally occurs in patients with SIADH, its presence does not confirm the diagnosis, nor does its absence rule out the diagnosis; urine sodium can also be high in renal causes of solute depletion such as diuretic use or Addison's disease, and conversely some patients with SIADH can have low urinary sodium if they become hypovolaemic or solute depleted, which are conditions sometimes produced by imposed sodium and water restriction.

*** Fractional sodium excretion = (urinary sodium / plasma sodium) / (urinary creatinine / plasma creatinine) X 100;
Fractional urea excretion = (urinary urea / plasma urea) / (urinary creatinine / plasma creatinine) X 100.

Developed with input from KOLs within the field of hyponatraemia and SIADH.

Utilizzare la modalità di insorgenza dell'iponatremia secondaria a SIAD(H) come guida per la scelta del trattamento



Se non si conosce la rapidità con cui è insorta, l'iponatremia dovrebbe essere trattata come se fosse ad esordio graduale

Verbalis J, et al. *Am J Med*. 2007;120(11 Suppl 1):S1-21 (modified).

V_2 receptor antagonists

- Several V_2 receptor antagonists are in clinical trials for the treatment of *euvolaemic* and *hypervolaemic hyponatraemia*
- V_2 receptor antagonists may also be called 'aquaretics' *as they induce a diuresis without affecting electrolyte excretion*[1,2]
  - Different from diuretics, which cause water and electrolyte elimination[1,2]
- Phase III clinical trials indicate that V_2 receptor antagonists:[3]
  - *increase electrolyte-free water excretion*
  - *raise serum sodium concentrations*
  - *reduce urine osmolality*

1. Decaux G, et al. *Lancet* 2008;371:1624-32.
2. Verbalis JG, et al. *Am J Med*. 2007;120(11A):S1-S21.
3. Greenberg A, et al. *Kidney Int*. 2006;69:2124-2130.

Vasopressin Receptor Antagonists for the Treatment of Hyponatremia: Systematic Review and Meta-analysis

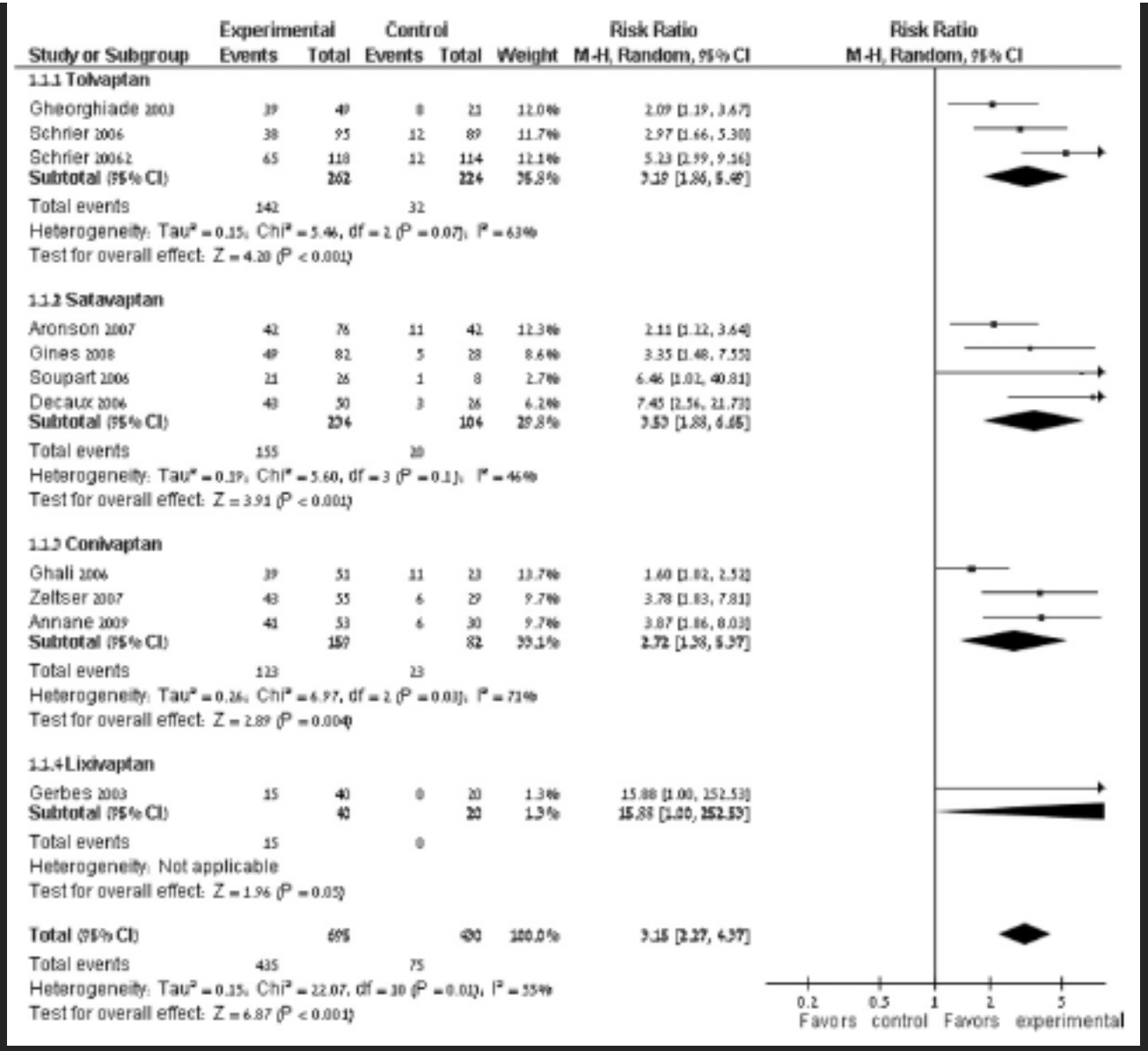
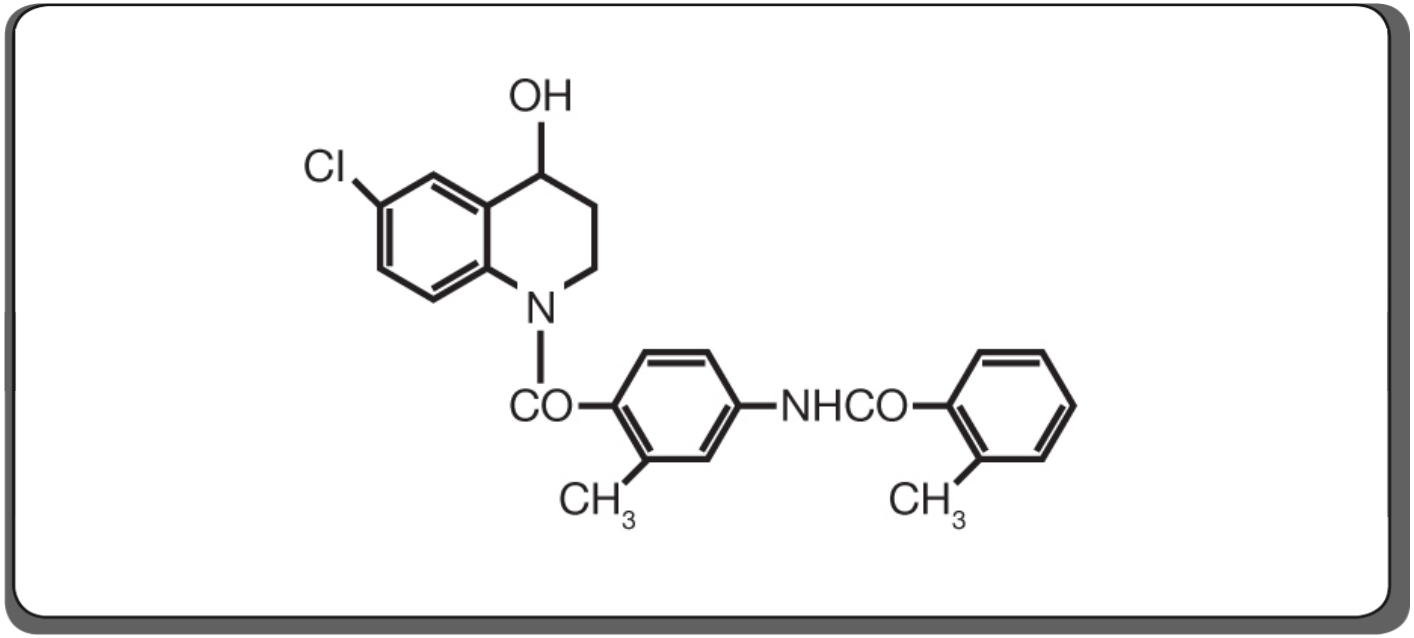


Figure 2. Early response rate

Am J Kidney Dis 56:325-337.

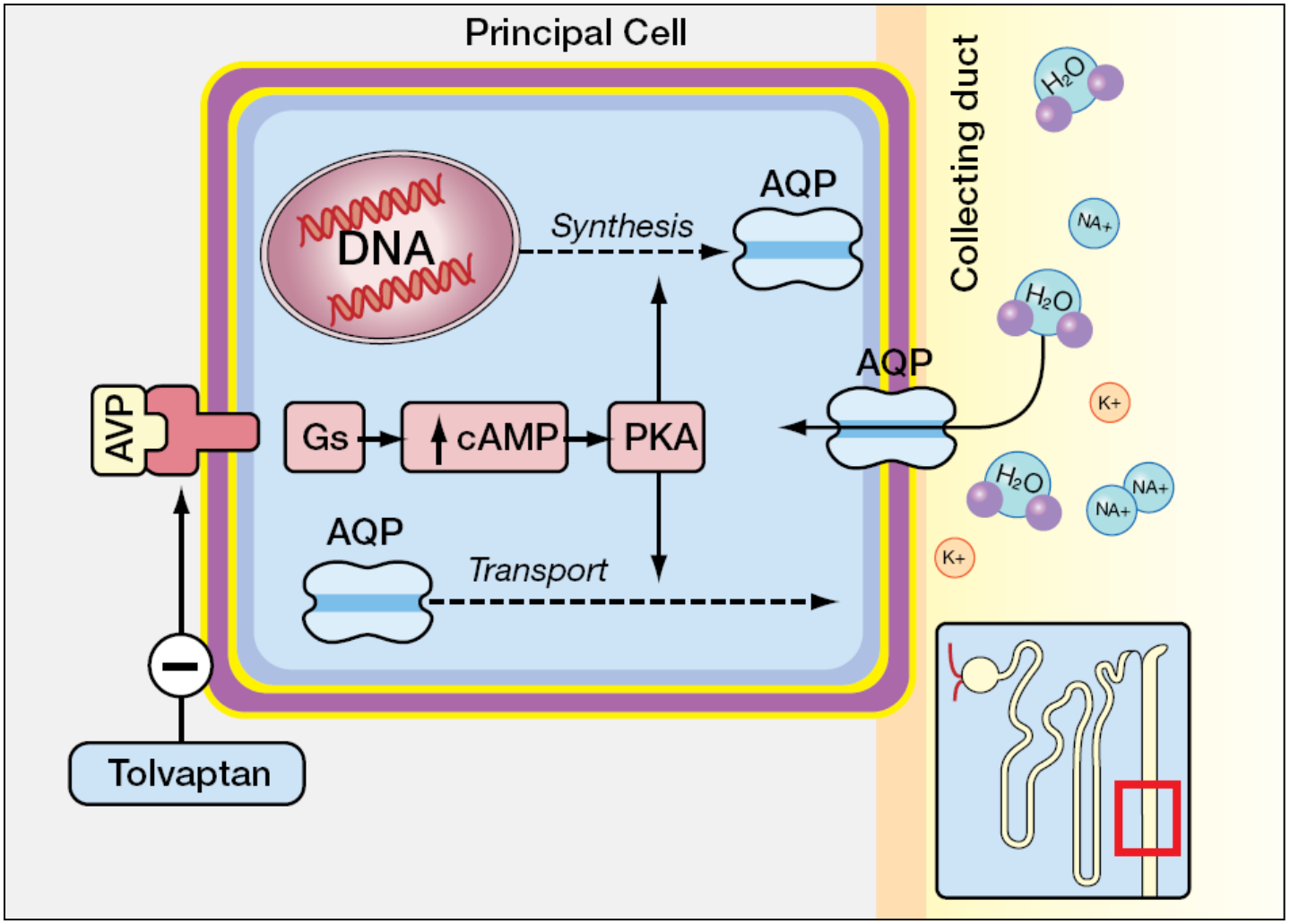
Tolvaptan (Samsca)



- Samsca (tolvaptan, study name OPC-41061)
- Benzazepine derivative[1]
- Oral Selective V2-Receptor Antagonist

1. Yamamura Y, et al. *J Pharmacol Exp Ther*. 1998;287(3):860-867.

Vasopressin activation of V_2 receptor[1]



AVP = vasopressin; AQP = aquaporin; cAMP = cyclic 3'-5'-adenosine monophosphate; Gs = guanine nucleotide binding proteins; PKA = protein kinase A

1. deGoma EM, et al. *J Am Coll Cardiol*. 2006;48:2397-2409.

SALT-1 and SALT-2: Study design (1)

- Objective
  - To examine the effect of Samsca on non-acute hypervolaemic and euvolaemic hyponatraemia of diverse causes[35,36]
- Study design
  - Two identical, randomised, double-blind, placebo-controlled phase III studies[36]
  - 448 adult patients with euvolaemic* or hypervolaemic hyponatraemia were randomised to receive once daily Samsca or placebo[36]
  - Samsca was titrated from 15 mg to 30 or 60 mg if necessary on the basis of serum sodium concentrations[36]
  - Hyponatraemia was defined as serum sodium of < 135 mmol/l[36]
  - SIADH was the most common cause of hyponatraemia in both studies (42%)[36]

* Samsca is licensed for hyponatraemia secondary to SIADH, which is a form of euvolaemic hyponatraemia

35. Samsca Summary of Product Characteristics. 2009.
36. Schrier RW, et al. *N Engl J Med*. 2006;355(20):2099-2112.

SALT-1 and SALT-2: Inclusion and exclusion criteria [36]

- Eligible patients:
  - Over 18 years of age
  - Non-acute hypervolaemic or euvolaemic hyponatraemia due to heart failure, liver cirrhosis or SIADH and others
  - Hyponatraemia defined as a serum sodium < 135 mmol/l
    - Marked hyponatraemia defined as < 130 mmol/l, mild hyponatraemia as 130-134 mmol/l
    - Mean serum sodium concentration at study entry 129 mmol/l
  - SIADH was the most common cause of hyponatraemia
- Excluded patients:
  - Symptomatic
  - Likely to require saline therapy
  - Acute and transient hyponatraemia associated with head trauma or postoperative state
  - Hyponatraemia due to primary polydipsia, uncontrolled adrenal insufficiency or uncontrolled hypothyroidism were excluded

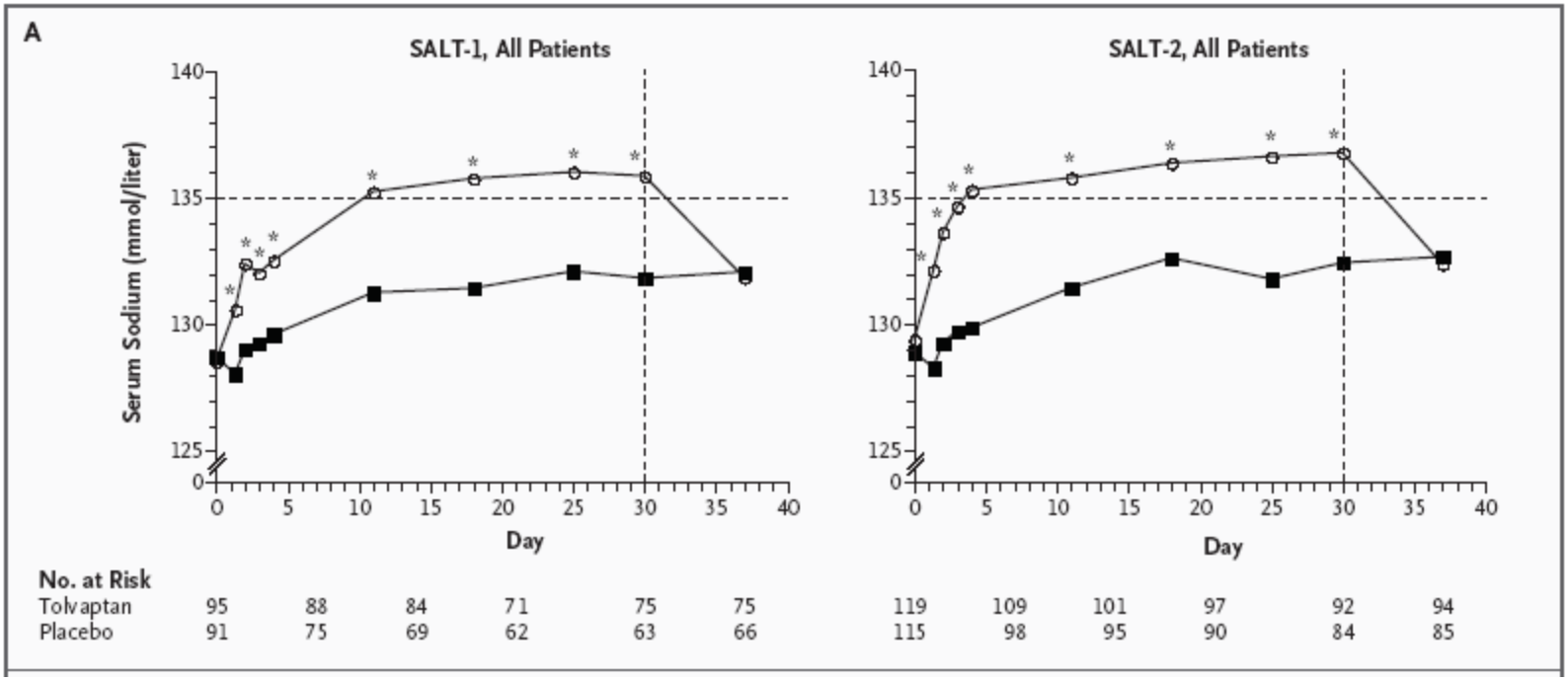
36. Schrier RW, et al. *N Engl J Med*. 2006;355(20):2099-2112.

The NEW ENGLAND JOURNAL of MEDICINE

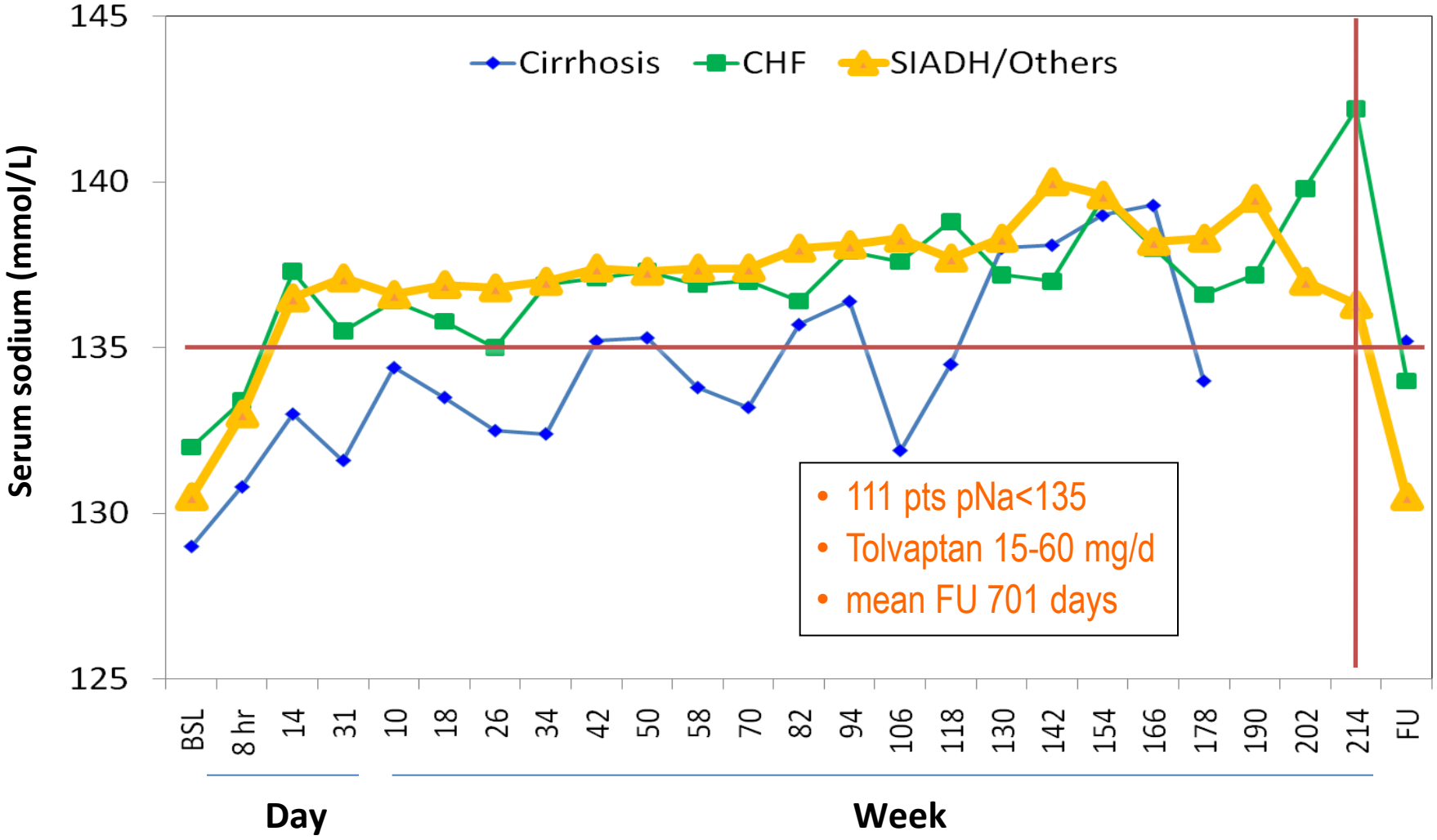
ORIGINAL ARTICLE

Tolvaptan, a Selective Oral Vasopressin V_2-Receptor Antagonist, for Hyponatremia

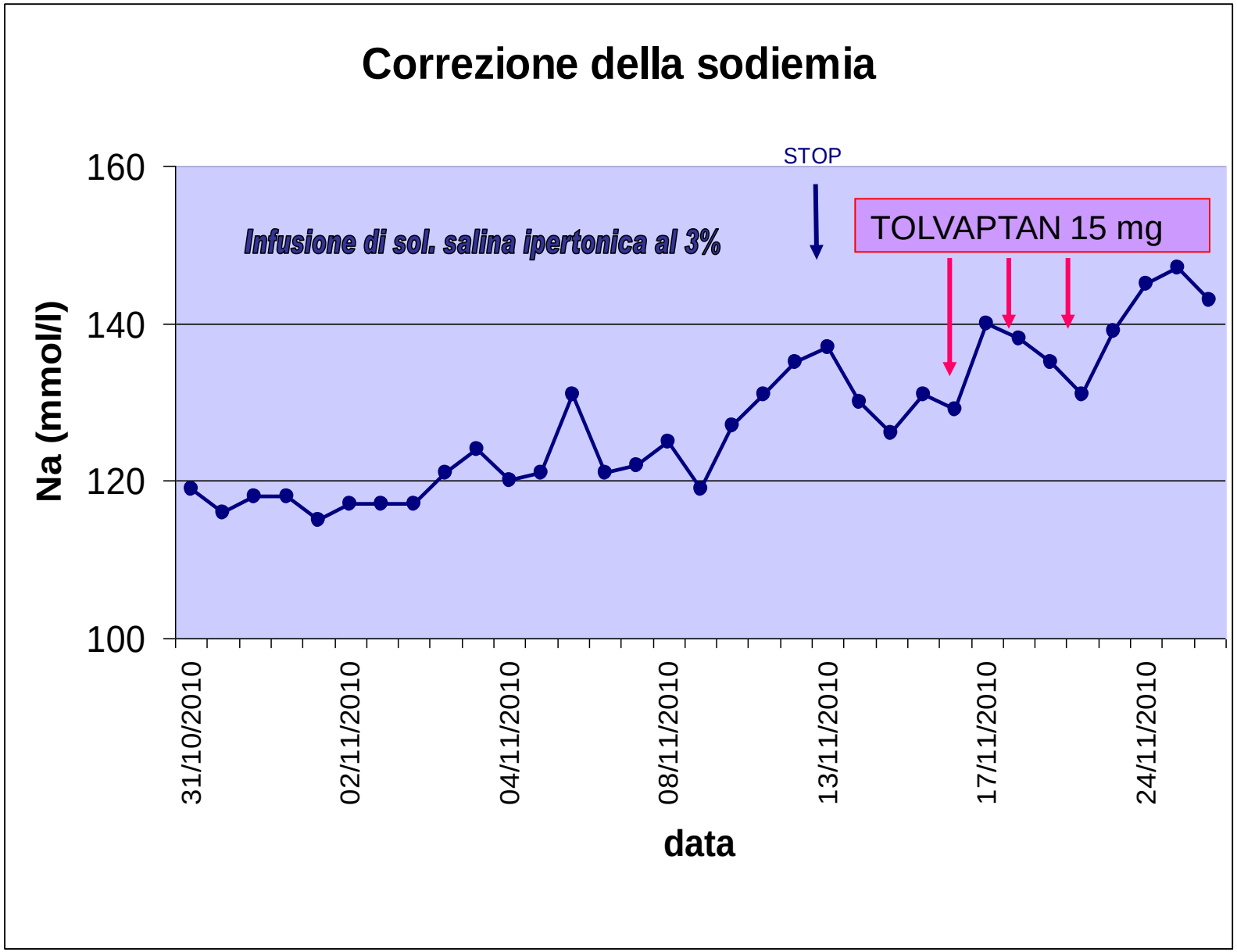
Robert W. Schrier, M.D., Peter Gross, M.D., Mihai Gheorghiade, M.D., Tomas Berl, M.D., Joseph G. Verbalis, M.D., Frank S. Czerwiec, M.D., Ph.D., and Cesare Orlandi, M.D., for the SALT Investigators*



SALTWATER



Berl (SALTWATER), JASN 2010


Correzione della sodiemia
STOP
TOLVAPTAN 15 mg
Infusione di sol. salina ipertonica al 3%
160
140
120
100
Na (mmol/l)
31/10/2010
02/11/2010
04/11/2010
08/11/2010
13/11/2010
17/11/2010
24/11/2010
data

Key points: Samsca (tolvaptan) (1)

- Samsca is an orally active, potent, non-peptide, selective V2 receptor antagonist, which prevents renal reabsorption of water[38]
- Samsca has an aquaretic effect and increases the excretion of electrolyte-free water[2,38]
  - Characterised by an increase in urine volume and a decrease in urine osmolality followed by an increase in serum sodium concentration
- Samsca is indicated for the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[35]

2. Verbalis JG. et al. Am J Med. 2007; 356(20):2064-72
35. Samsca Summary of Product Characteristics. 2009.
38. Yamamura Y, et al. *J Pharmacol Exp Ther.* 1998;287(3):860-867.

Key points: Samsca (tolvaptan) (2)

- Samsca is available in 15 mg and 30 mg tablets
  - Initiated in hospital at a dose of 15 mg once daily[35]
  - Dose may be increased at intervals of ≥ 24 hours to a maximum of 60 mg once daily as tolerated to achieve the desired serum sodium concentration
- Unlike fluid restriction, patients receiving Samsca can and should continue ingestion of fluids in response to thirst[35]
- Prescribers should consult the Summary of Product Characteristics for full prescribing details

35. Samsca. Summary of Product Characteristics. 2009.

Contraindications[35]

- Hypersensitivity to the active substance or to any of the excipients
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy
- Breastfeeding

35. Samsca Summary of Product Characteristics. 2009.

Interaction with other medicinal products and other forms of interaction[35]

- CYP3A4 inhibitors
  - Samsca plasma concentrations have been increased by up to 5.4-fold after the administration of strong CYP3A4 inhibitors
  - May enhance the effect of Samsca or other drugs
  - Patients taking Samsca should avoid ingesting grapefruit juice
- CYP3A4 inducers
  - Samsca plasma concentrations have been decreased by up to 87% after administration of CYP3A4 inducers
  - Anticipated clinical effect of Samsca may not be seen at the recommended dose
- CYP3A4 substrates
  - Samsca, a CYP3A4 substrate, can potentially increase exposure to other CYP3A4 substrates e.g. Samsca produced a 1.3- to 1.5-fold increase in lovastatin

35. Samsca Summary of Product Characteristics. 2009.

CYP3A4 è responsabile del metabolismo di molti farmaci

- Chetoconazolo (inibizione)
- Itraconazolo (inibizione)
- Macrolidi (inibizione)
- Ritonavir (inibizione)
- Indinavir (inibizione)

- Statine (simvastat, lovastat, atorvastat) (substrato)

- Barbiturici (attivazione)
- Fenitoina (attivazione)
- Carbamazepina (attivazione)

Special warnings and precaution for use[35]

- Urgent need to raise serum sodium acutely
  - Samsca has not been studied in a setting of urgent need to raise serum sodium acutely
  - For such patients, alternative treatment should be considered.
- Urinary outflow obstruction
  - These patients (e.g. those with prostatic hypertrophy or impairment of micturition) have an increased risk of developing acute retention
- Diabetes mellitus
  - Pseudohyponatraemia should be excluded prior to treatment
  - Patients with diabetes mellitus should be managed cautiously as Samsca may cause hyperglycaemia

35. Samsca Summary of Product Characteristics. 2009.

Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure

The EVEREST Clinical Status Trials

Mihai Gheorghiade, MD
Marvin A. Konstam, MD
John C. Burnett, Jr, MD
Liliana Grinfeld, MD
Aldo P. Maggioni, MD
Karl Swedberg, MD
James E. Udelson, MD
Faiez Zannad, MD
Thomas Cook, PhD
John Ouyang, PhD
Christopher Zimmer, MD
Cesare Orlandi, MD
for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators

Context Heart failure causes more than 1 million US hospitalizations yearly, mostly related to congestion. Tolvaptan, an oral, nonpeptide, selective vasopressin V_2-receptor antagonist, shows promise in this condition.

Objective To evaluate short-term effects of tolvaptan when added to standard therapy in patients hospitalized with heart failure.

Design, Setting, and Patients Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) between October 7, 2003, and February 3, 2006. A total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion were studied.

Intervention Patients were randomized to receive either tolvaptan (30 mg/d) or matching placebo, within 48 hours of admission.

Main Outcome Measures Primary end point was a composite of changes in global clinical status based on a visual analog scale and body weight at day 7 or discharge if earlier. Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge).

Results Rank sum analysis of the composite primary end point showed greater improvement with tolvaptan vs placebo (trial A, mean [SD], 1.06 [0.43] vs 0.99 [0.44]; and trial B, 1.07 [0.42] vs 0.97 [0.43]; both trials $P<.001$). Mean (SD) body weight reduction was greater with tolvaptan on day 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; $P<.001$; and trial B, 1.82 [2.01] vs 0.96 [1.85] kg; $P<.001$) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; $P<.001$; and trial B, 3.77 [3.59] vs 2.79 [3.46] kg; $P<.001$), whereas improvements in global clinical status were not different between groups. More patients receiving tolvaptan (684 [76.7%] and 678 [72.1%] for trial A and trial B, respectively) vs patients receiving placebo (646 [70.6%] and 597 [65.3%], respectively) reported improvement in dyspnea at day 1 (both trials $P<.001$). Edema at day 7 or discharge improved significantly with tolvaptan in trial B ($P=.02$) but did not reach significance in trial A ($P=.07$). Serious adverse event frequencies were similar between groups, without excess renal failure or hypotension.

Conclusion In patients hospitalized with heart failure, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.

Trial Registration clinicaltrials.gov Identifier: NCT00071331

JAMA. 2007;297:1332-1343 www.jama.com

HEART FAILURE (HF) IS A MAJOR international public health problem presenting significant medical and economic challenges. In the United States, HF has high prevalence (>5 million individuals), high incidence (550 000 new cases yearly), increasing hospitalization rates (400 000 in 1979 to >1 million in 2004), and exorbitant cost (estimated to exceed $33 billion in 2007).[1] A considerable share of the burden of HF is accounted for by the acute HF syndromes (AHFS), defined as conditions with gradual or rapid changes in the signs and symptoms of HF that require urgent therapy.[2] Patients hospitalized with AHFS have poor overall prognosis.[3-6]

Congestion characterized by dyspnea, edema, rales, jugular venous dis-

See also pp 1319 and 1374.

Author Affiliations and a **Complete List of the EVEREST Investigators** appear at the end of this article.
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Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

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Liliana Grinfeld, MD
Aldo P. Maggioni, MD
Karl Swedberg, MD
James E. Udelson, MD
Faiez Zannad, MD
Thomas Cook, PhD
John Ouyang, PhD
Christopher Zimmer, MD
Cesare Orlandi, MD
for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators

Context Vasopressin mediates fluid retention in heart failure. Tolvaptan, a vasopressin V_2 receptor blocker, shows promise for management of heart failure.

Objective To investigate the effects of tolvaptan initiated in patients hospitalized with heart failure.

Design, Setting, and Participants The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study. The outcome trial comprised 4133 patients within 2 short-term clinical status studies, who were hospitalized with heart failure, randomized at 359 North American, South American, and European sites between October 7, 2003, and February 3, 2006, and followed up during long-term treatment.

Intervention Within 48 hours of admission, patients were randomly assigned to receive oral tolvaptan, 30 mg once per day (n=2072), or placebo (n=2061) for a minimum of 60 days, in addition to standard therapy.

Main Outcome Measures Dual primary end points were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Secondary end points included changes in dyspnea, body weight, and edema.

Results During a median follow-up of 9.9 months, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (hazard ratio, 0.98; 95% confidence interval [CI], 0.87-1.11; $P=.68$). The upper confidence limit for the mortality difference was within the prespecified noninferiority margin of 1.25 ($P<.001$). The composite of cardiovascular death or hospitalization for heart failure occurred in 871 tolvaptan group patients (42.0%) and 829 placebo group patients (40.2%; hazard ratio, 1.04; 95% CI, 0.95-1.14; $P=.55$). Secondary end points of cardiovascular mortality, cardiovascular death or hospitalization, and worsening heart failure were also not different. Tolvaptan significantly improved secondary end points of day 1 patient-assessed dyspnea, day 1 body weight, and day 7 edema. In patients with hyponatremia, serum sodium levels significantly increased. The Kansas City Cardiomyopathy Questionnaire overall summary score was not improved at outpatient week 1, but body weight and serum sodium effects persisted long after discharge. Tolvaptan caused increased thirst and dry mouth, but frequencies of major adverse events were similar in the 2 groups.

Conclusion Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure–related morbidity.

Trial Registration clinicaltrials.gov Identifier: NCT00071331

JAMA. 2007;297:1319-1331 www.jama.com

DURING THE PAST 2 DECADES, there have been substantial advances in drug therapy for chronic heart failure (HF), with much of the improvement in clinical outcomes achieved through pharmacologic inhibition of neurohormonal systems. Nevertheless, the number of annual hospitalizations for HF continues to rise, and mortality rates among patients hospitalized with HF remain high.[1-7]

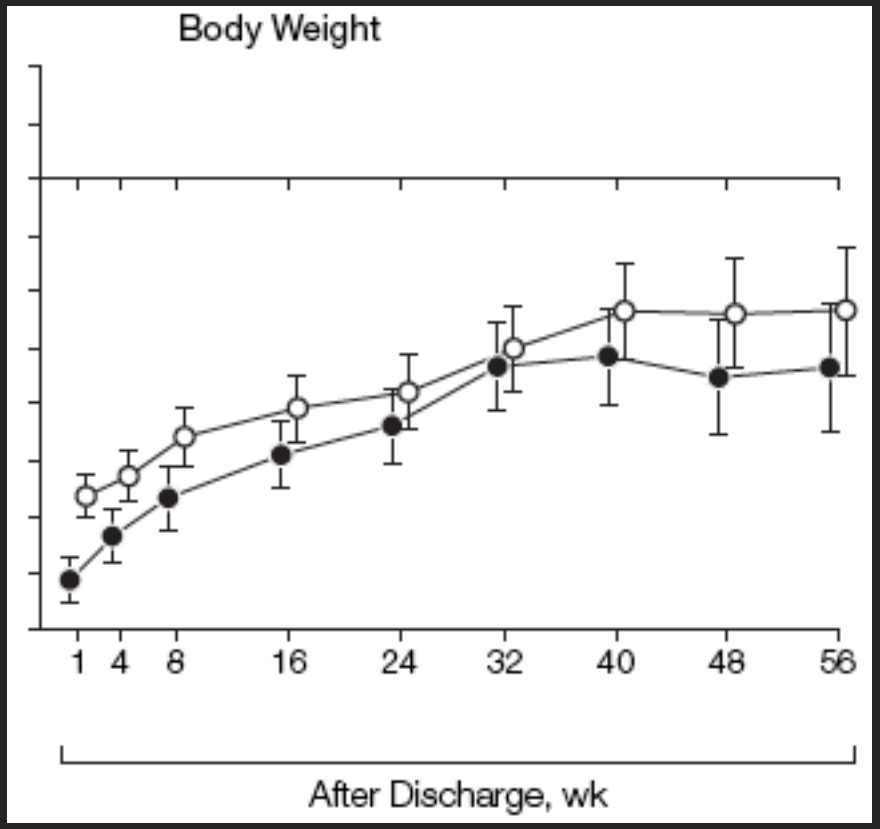
To date, no treatment initiated at the time of hospitalization for acute decompensated HF has been found to improve clinical outcomes. In fact, in randomized controlled trials of such treatments, the observed clinical benefits have been marginal at best,[8,9] and

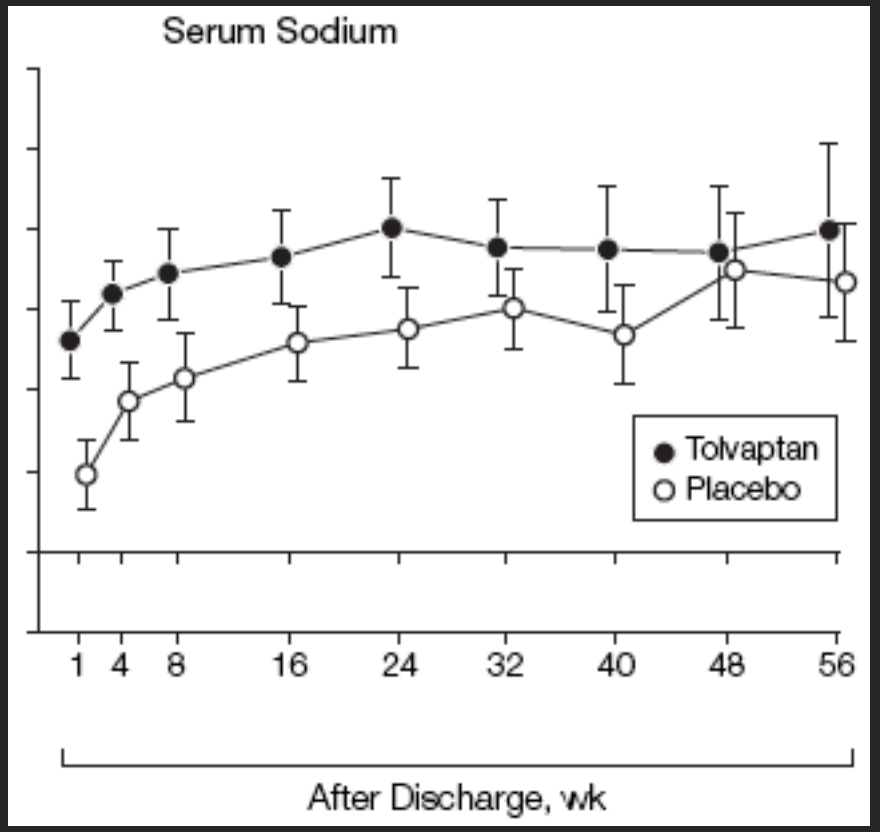
See also pp 1332 and 1374.

Author Affiliations: Tufts–New England Medical Center, Boston, Mass (Drs Konstam and Udelson); Northwestern University Feinberg School of Medicine, Chicago, Ill (Dr Gheorghiade); Mayo Clinic, Rochester, Minn (Dr Burnett); Hospital Italiano, Buenos Aires, Argentina (Dr Grinfeld); Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy (Dr Maggioni); Sahlgrenska University Hospital/Östra, Gothenburg, Sweden (Dr Swedberg); Institut National de la Santé et de la Recherche Médicale (INSERM), Centre d'Investigations Cliniques, Nancy, France (Dr Zannad); University of Wisconsin, Madison (Dr Cook); and Otsuka Maryland Research Institute, Rockville (Drs Ouyang, Zimmer, and Orlandi).
A complete list of the EVEREST Investigators appears at the end of this article.
Corresponding Author: Marvin A. Konstam, M.D, Division of Cardiology, Box 108, Tufts–New England Medical Center, 750 Washington St, Boston, MA 02111 (mkonstam@tufts-nemc.org).

JAMA. 2007;297:1332-1343

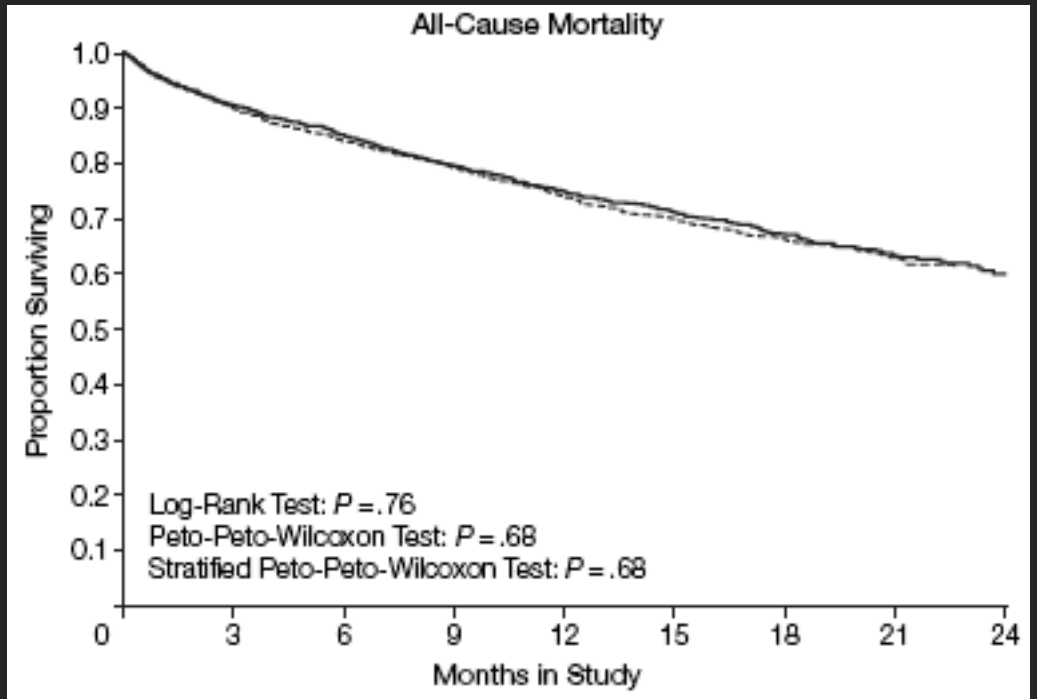
JAMA. 2007;297:1319-1331

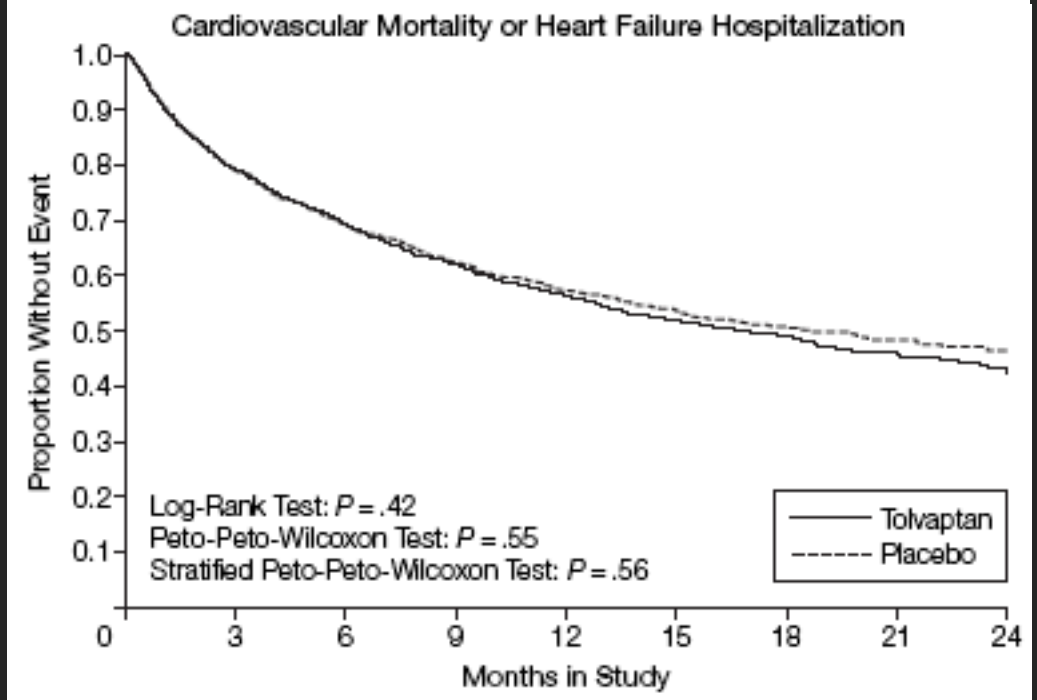




The EVEREST Outcome Trial

The EVEREST Outcome Trial





JAMA, March 28, 2007

The Bellaria Hospital's jazz band

Giorgio Frank (trumpet and conductor)

Diego Mazzatenta

Matteo Zoli

Ernesto Pasquini

Vittorio Sciarretta

Marco Faustini Fustini

Antonella Bacci