

SIADH

Nephrology Grand Rounds

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Hyponatremia

- History
- Physiology of Aquaporin channels / ADH
- Pathophysiology of SIADH
- Therapeutic options
- V2 receptor antagonists

History

- First reported in 1960's in 2 patients with lung cancer
- Criteria was developed by Schwartz and Bartter in 1967 and has remained unchanged since then.

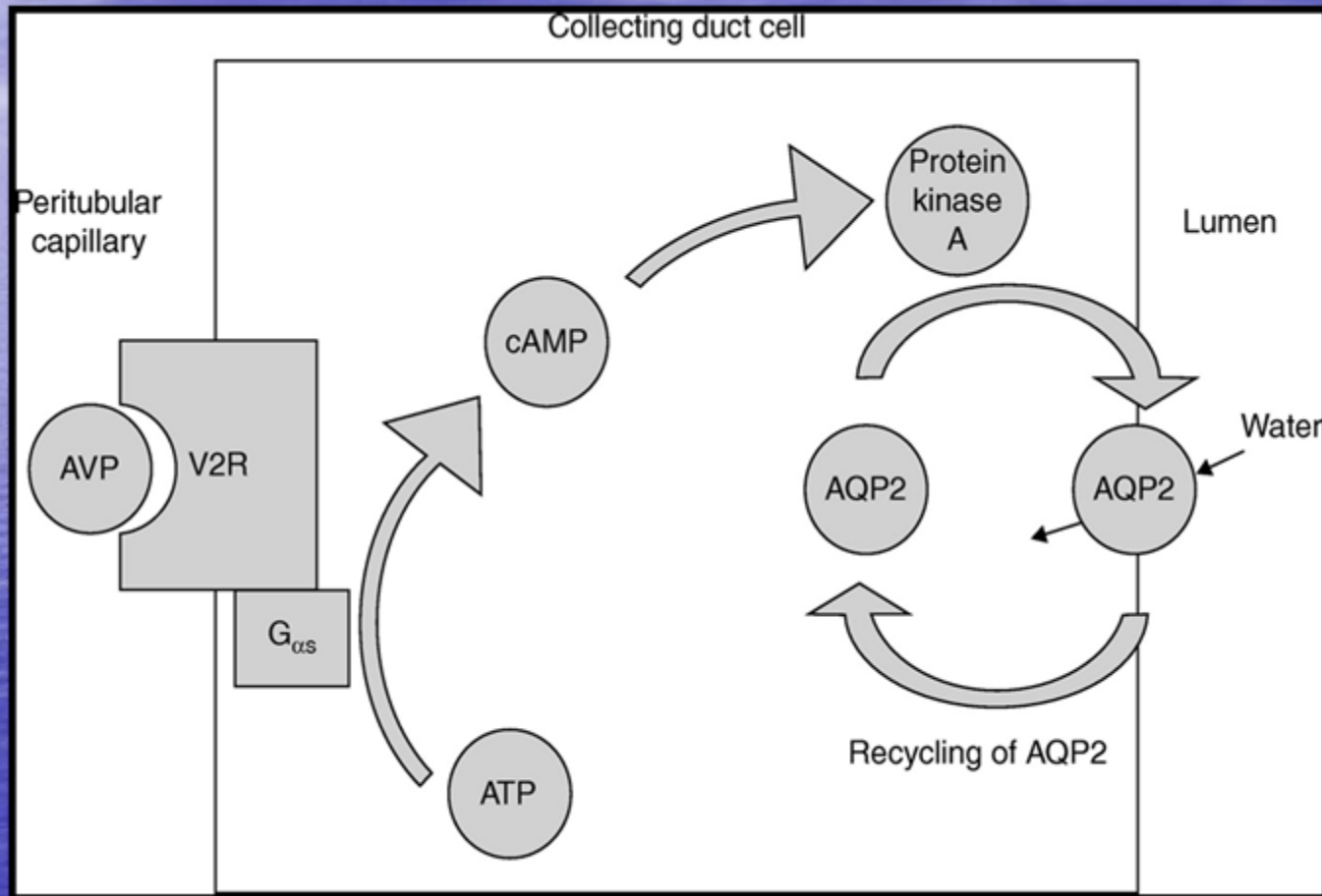
Discovery of Aquaporin channels

- Chance discovery by Peter Agre- John Hopkins University while isolating Rh antigen in 1992.
- Won Nobel prize for chemistry in 2003
- 9 Aquaporin isoforms- 6 present in kidney
- Though present at birth, initially resistant to ADH action- hypotonic urine in infants.

Aquaporins

- 9 aquaporin isopforms- 6 present in the kidney
- Aquaporin 1 main channel in Proximal and distal tubules
- Aquaporin 2 present in the CD is mediated by ADH
- Aquaporin 3 and 4 present in basolateral surface of collecting duct

Aquaporin channels



Pathophysiology of SIADH

Hyponatremia sec to ADH
induced water retention

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graph TD; A[Hyponatremia sec to ADH induced water retention] --> B[Volume expansion activates natriuretic mechanisms]; B --> C[Loss of sodium and water];
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Volume expansion activates
natriuretic mechanisms

Loss of sodium and water

Treatment of SIADH

- Fluid restriction
- Salt / urea tabs
- Furosemide / salt tablets or saline
- Demeclocycline / lithium
- Hypertonic saline
- Use of ADH receptor antagonist

Furosemide use in SIADH

- No good clinical studies
- Treatment of the SIADH with Furosemide
N Engl J Med 1981; 304:329-330 [February 5, 1981](#)

Case report of using long term lasix therapy
in the treatment of SIADH for 12weeks.

Effect of Lasix on serum Na

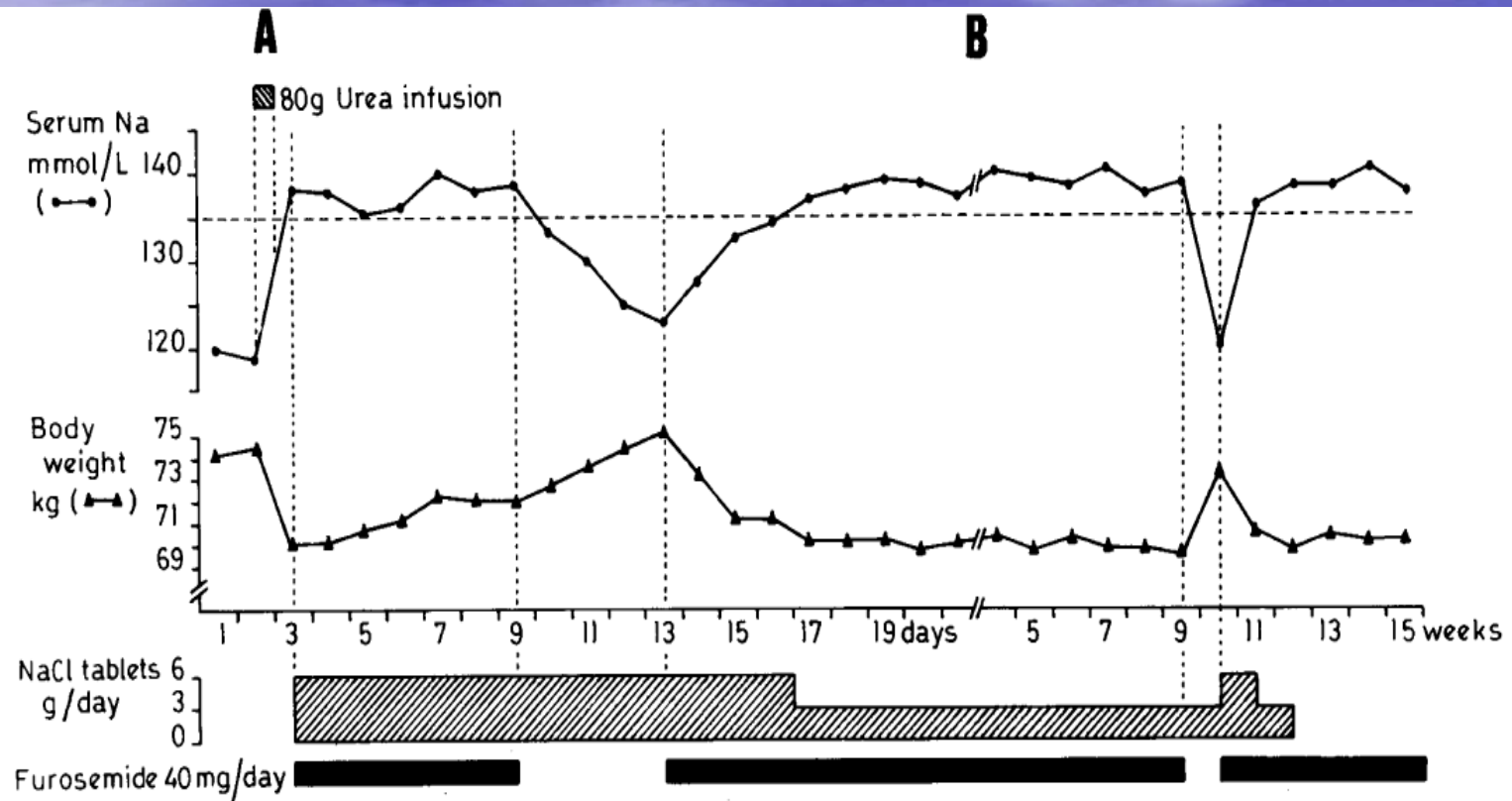


Figure 1. Serum Sodium and Weight during Long-Term Furosemide Treatment in a Patient with Inappropriate Secretion of Antidiuretic Hormone.

Part A describes the findings during 21 days of hospitalization; part B, the observations during the next 12 weeks. The horizontal dotted line denotes the lower limit of normal for the serum sodium concentration. Vertical dotted lines show the intermittent discontinuation of furosemide.

Use of lithium in SIADH

- Lithium-induced Downregulation of Aquaporin-2 Water Channel Expression in Rat Kidney medulla.
- Lithium treatment reduced AQP2 expression dramatically, to $31 \pm 8\%$ after 10 d coincident with development of severe polyuria.
- Administration of DDAVP / water deprivation and stopping lithium only partially reversed the effects.

(J.Clin. Invest. 1995. 95:1838-1845)

Use of Demeclocycline

- Small study comparing use of demeclocycline and lithium- 10 patients with Na -120-122
- 7 received Demeclocycline 600-1200mg for 4-14days and 3 received lithium. All patients in the demeclocycline group had improved Na to normal vs none in the lithium group

(N Engl J Med 298:173–177;1978)

V2 receptor antagonist

- Selectively blocks binding of arginine vasopressin from binding to V2 receptors causing excretion of electrolyte free water.
- Approved for use in patients with euvolemic and hypervolemic hyponatremia

SALT 1 and SALT 2 trials

- 2 multicenter, randomized, double-blind, placebo-controlled trials to study efficacy of tolvaptan in patients with euvolemic or hypervolemic hyponatremia.

(NEJM 2006; 355:2099-2112)

Study methods

- 2 identical studies for comparing results
- Conducted at 42 centers in US and 50 international centers
- Participants received oral tolvaptan 15mg or placebo for 30days.
- Primary end points- change in Serum Na from baseline to day 4 and day 30.

Study Demographics

Table 1. Demographic and Baseline Characteristics of Patients in the SALT-1 and SALT-2 Trials.*

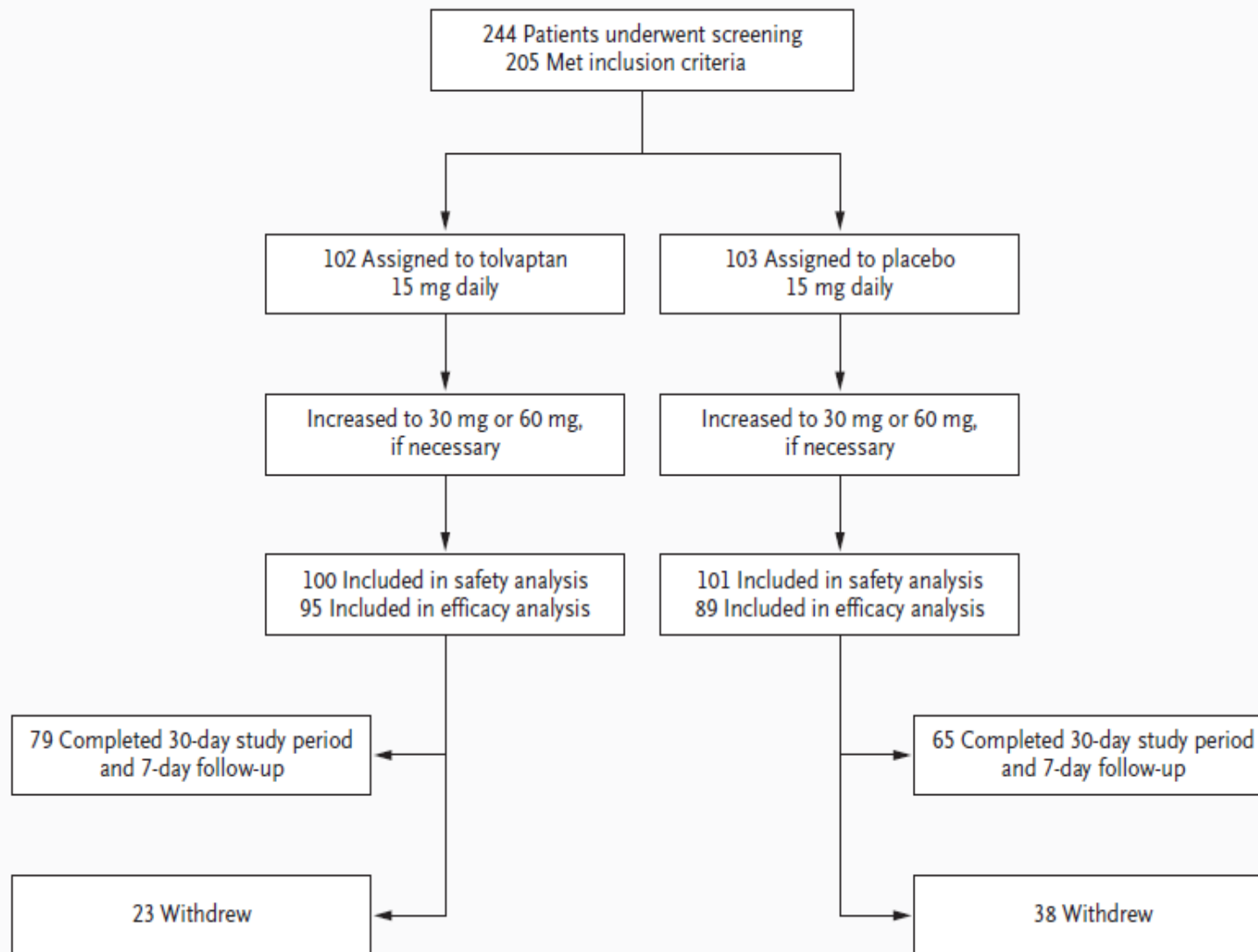
Characteristic	SALT-1		SALT-2		P Value		
	Tolvaptan (N= 102)	Placebo (N= 103)	Tolvaptan (N= 123)	Placebo (N= 120)	SALT-1	SALT-2	SALT-1 and SALT-2
Age — yr							
Mean	60±14	60±13	62±15	63±14	0.94	0.66	0.72
Range	18–86	35–90	27–92	28–100			
Female sex — no. (%)	50 (49)	41 (40)	48 (39)	47 (39)	0.21	1.00	0.39
Race — no. (%)					0.26	0.47	0.56
White	71 (70)	76 (74)	118 (96)	109 (91)			
Black	13 (13)	17 (17)	1 (1)	3 (2)			
Hispanic	13 (13)	9 (9)	3 (2)	6 (5)			
Other	5 (5)	1 (1)	1 (1)	2 (2)			
Mean body weight — kg	78±23	75±22	73±19	75±21	0.44	0.39	0.96
Mean height — cm	167±10	170±11	168±11	167±9	0.02	0.42	0.14
Fluid status — no. (%)					0.38	0.80	0.70
Euvolemic	61 (60)	67 (65)	63 (51)	60 (50)			
Hypovolemic	41 (40)	34 (33)	58 (47)	60 (50)			
Cause of hyponatremia — no. (%)					0.63	0.96	0.70
Chronic heart failure	35 (34)	33 (32)	36 (29)	34 (28)			
Cirrhosis	25 (25)	21 (20)	38 (31)	36 (30)			
SIADH and other	42 (41)	49 (48)	49 (40)	50 (42)			
Mean serum sodium — mmol/liter	128.7±4.5	128.8±4.1	129.5±3.5	129.1±4.5	0.85	0.37	0.60
Degree of hyponatremia — no. (%)					0.89	1.00	0.93
Mild	49 (48)	51 (50)	64 (52)	62 (52)			
Mean serum sodium — mmol/liter	132.4±1.5	132.1±1.3	132.3±1.6	132.4±1.3	0.37	0.56	0.88
Marked	53 (52)	52 (50)	59 (48)	58 (48)			
Mean serum sodium — mmol/liter	125.4±3.5	125.5±3.2	126.6±2.5	125.5±3.8	0.84	0.07	0.26
Mean score on SF-12 Health Survey†							
Physical Component Summary	33.4±10.7	33.9±10.5	33.0±10.6	33.1±10.8	0.78	0.95	0.81
Mental Component Summary	42.4±11.6	44.7±11.9	44.3±11.9	44.9±11.6	0.15	0.89	0.30

* Mild hyponatremia was defined as a baseline serum sodium concentration of 130 to 134 mmol per liter. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. SIADH denotes syndrome of inappropriate antidiuretic hormone secretion. Race was self-reported. Plus-minus values are means ±SD.

† Scores on the Physical Component Summary of the SF-12 range from 5 to 69, and those on the Mental Component Summary range from 8 to 73, with higher scores indicating better functioning.

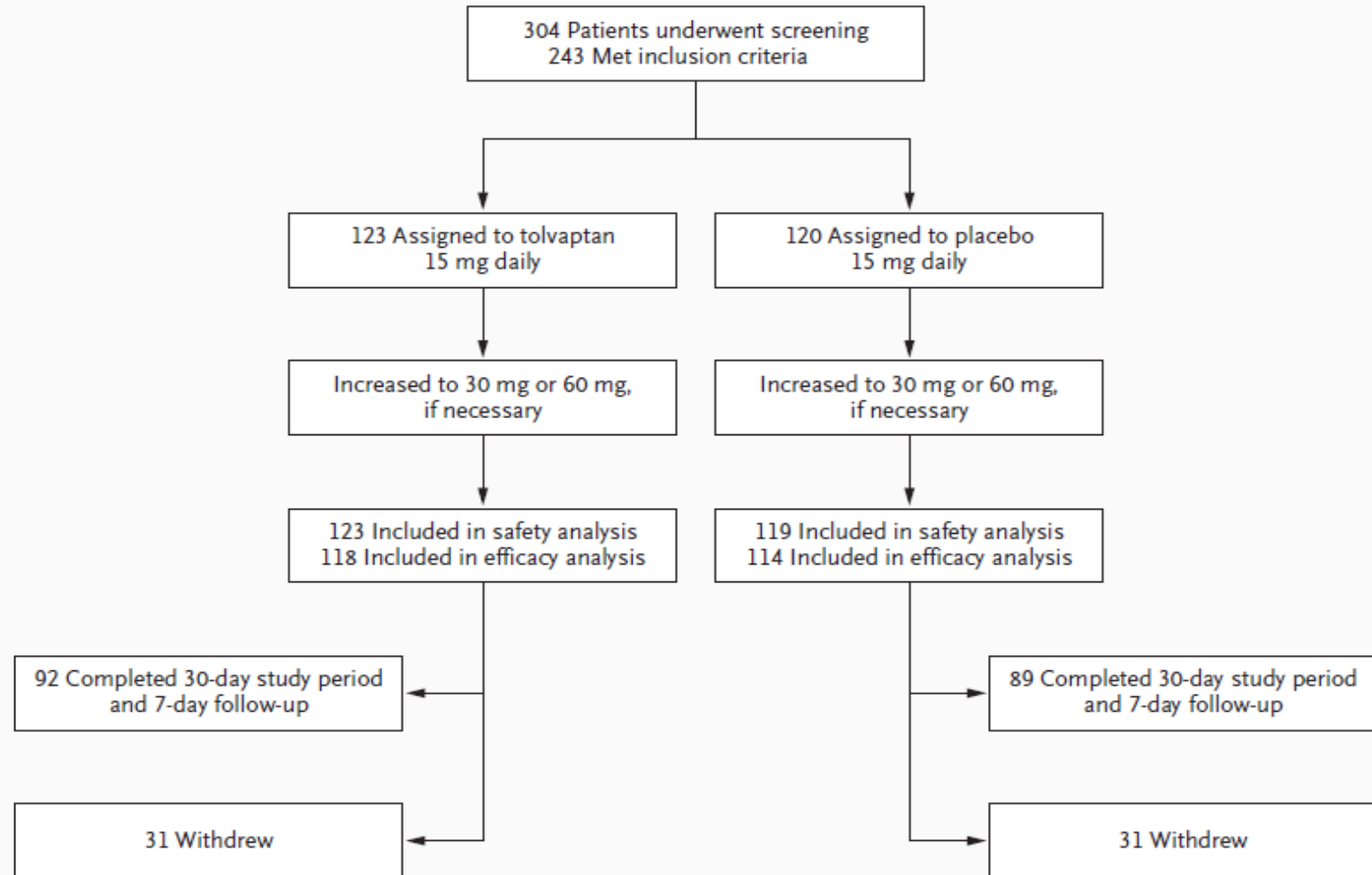
SALT- 1

A SALT-1

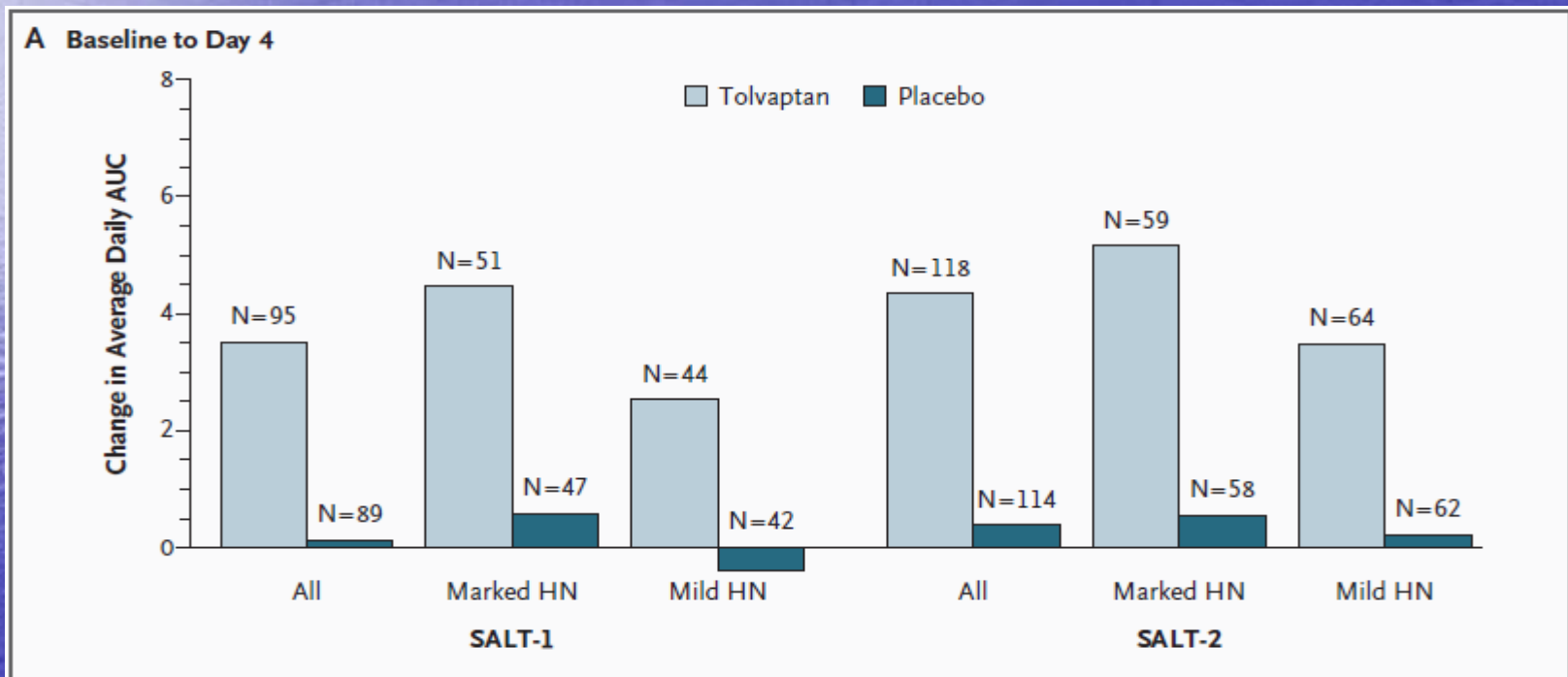


SALT - 2

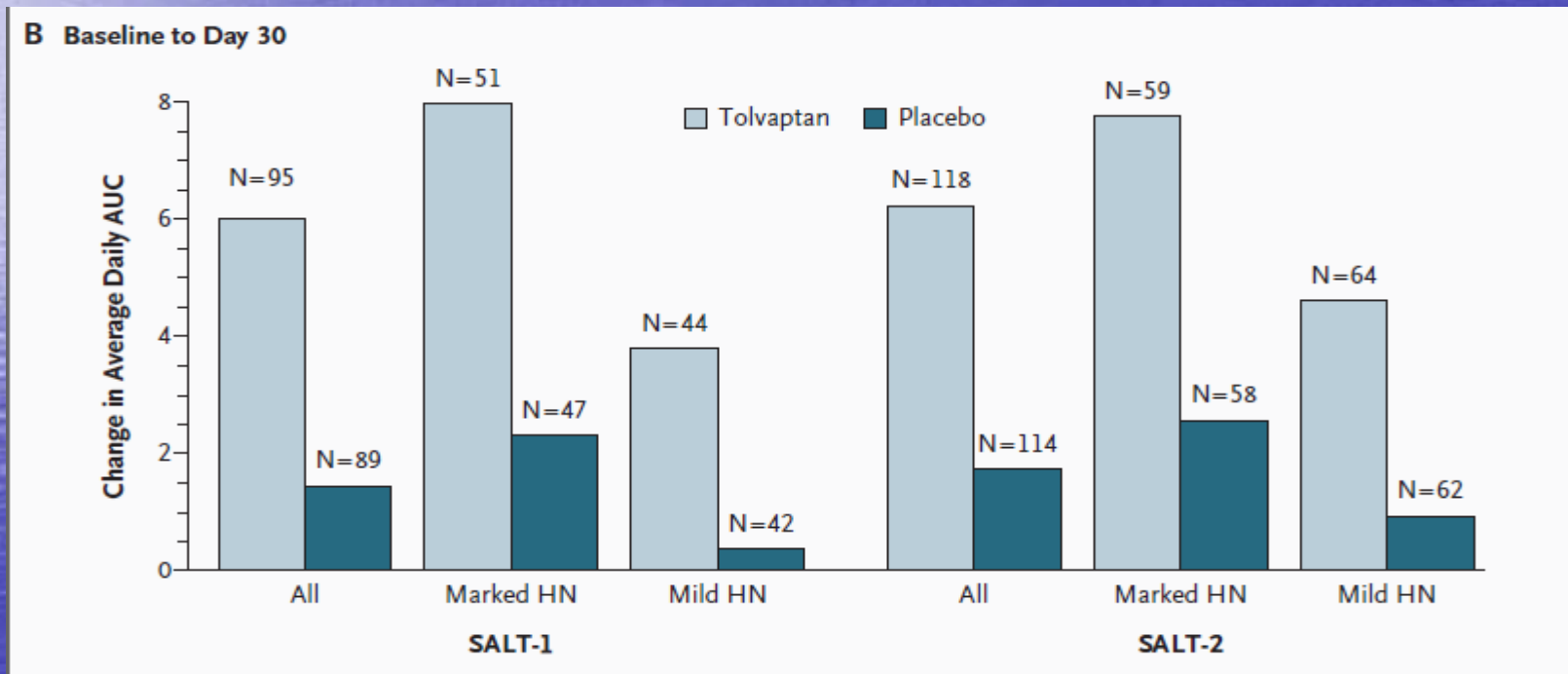
B SALT-2



Results- change in area under the curve for serum sodium- Day 4



Change in serum sodium - day 30

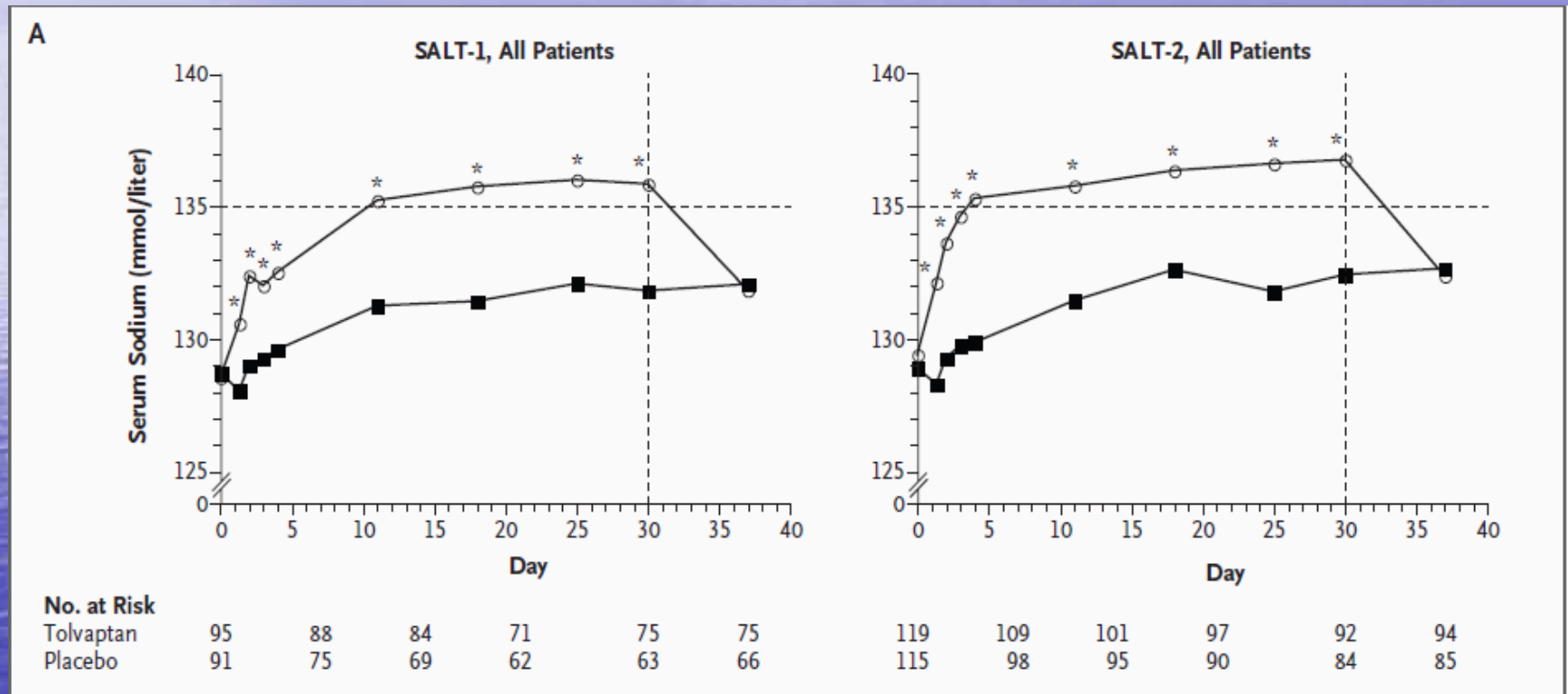


Efficacy analysis

Table 2. Results of Efficacy Analysis.*

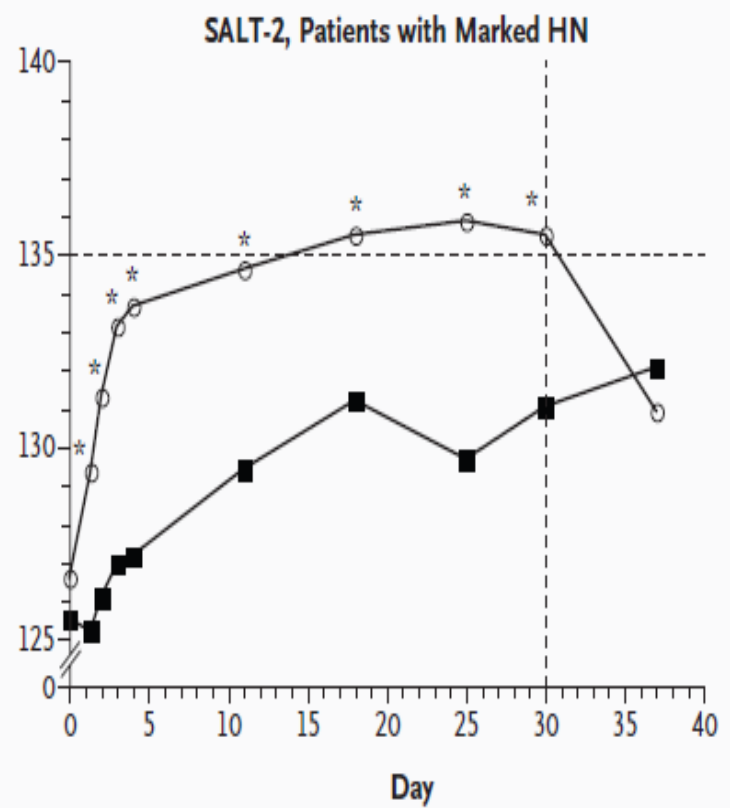
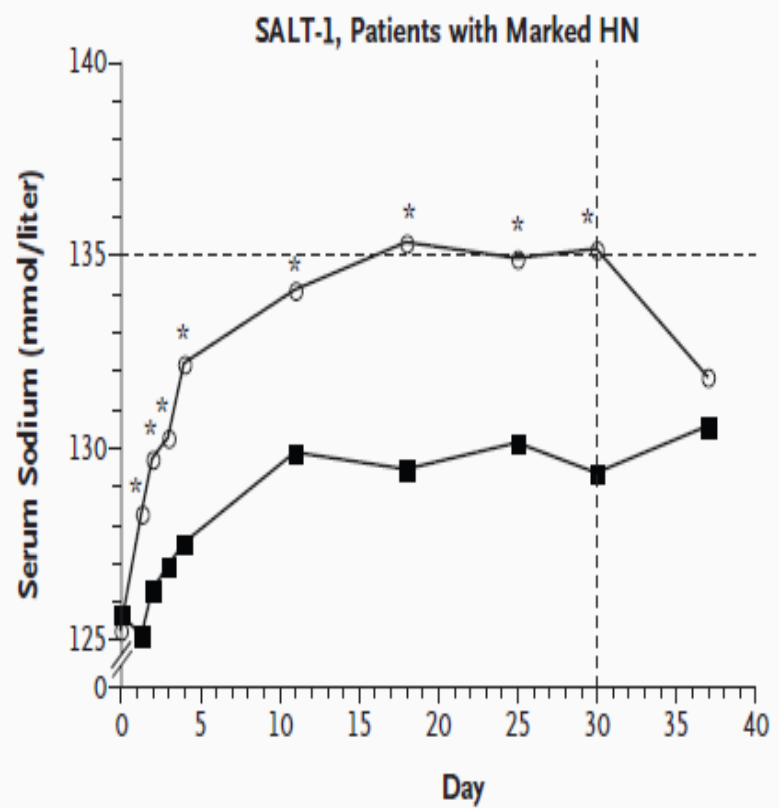
Variable	Tolvaptan (N=102)	SALT-1 Placebo (N=103)	P Value	Tolvaptan (N=123)	SALT-2 Placebo (N=120)	P Value
Primary end point: change in average AUC for serum sodium — mmol/liter						
All patients						
Day 4	3.62±2.68	0.25±2.08	<0.001	4.33±2.87	0.42±2.56	<0.001
Day 30	6.22±4.10	1.66±3.59	<0.001	6.20±3.92	1.84±3.83	<0.001
Mild hyponatremia						
Day 4	2.52±1.95	-0.32±2.27	<0.001	3.59±2.34	0.18±2.01	<0.001
Day 30	3.87±3.01	0.68±2.78	<0.001	4.68±2.91	0.94±2.89	<0.001
Marked hyponatremia						
Day 4	4.56±2.88	0.76±1.77	<0.001	5.06±3.16	0.7±2.99	<0.001
Day 30	8.24±3.84	2.54±4.01	<0.001	7.60±4.31	2.72±4.41	<0.001
Absolute change in serum sodium — mmol/liter						
Baseline	128.5±4.5	128.7±4.1		129.±3.5	128.9±4.5	
Day 4						
Mean	133.9±4.8	129.7±4.9	<0.001	135.3±3.6	129.6±5.2	<0.001
No. of patients	95	88		115	112	
Day 30						
Mean	135.7±5.0	131.0±6.2	<0.001	135.9±5.9	131.5±5.7	<0.001
No. of patients	95	89		114	98	
Categorical change in hyponatremia — no./total no. (%)						
Baseline						
Mild hyponatremia	49/102 (48)	51/103 (50)		64/123 (52)	62/120 (52)	
Marked hyponatremia	53/102 (52)	52/103 (50)		59/123 (48)	58/120 (48)	
Day 4						
Normal	38/95 (40)	12/89 (13)	<0.001	65/118 (55)	12/114 (11)	<0.001
Marked hyponatremia	12/95 (13)	44/89 (49)	<0.001	12/118 (10)	46/114 (40)	<0.001
Day 30						
Normal	50/95 (53)	22/89 (25)	<0.001	69/118 (58)	28/114 (25)	<0.001
Marked hyponatremia	7/95 (7)	31/89 (35)	<0.001	18/118 (15)	37/114 (32)	0.002
Fluid status						
Urine output on day 1 — ml	3218±1646	2076±1534	<0.001	3185±2543	1914±1366	<0.001
Fluid intake on day 1 — ml	1825±1057	1492±945	0.04	2129±2110	1705±1396	0.09
Difference on day 1 — ml	-1533±1429	-636±1275	<0.001	-1059±1877	-185±870	<0.001
Patients requiring fluid restriction — %	9.3	17.5	0.08	9.2	16.8	0.08

Serum sodium levels during study



Serum sodium levels in marked HN

B



No. at Risk

Tolvaptan	51	46	43	38	38	39
Placebo	48	39	34	31	31	34

Tolvaptan	59	52	51	48	45	46
Placebo	58	49	47	43	40	42

Adverse events

Table 3. Adverse Events.*

Variable	SALT-1		SALT-2	
	Tolvaptan (N=100)	Placebo (N=101)	Tolvaptan (N=123)	Placebo (N=119)
Total patient-days of drug exposure	2669	2292	3228	3055
	<i>no. of patients (%)</i>			
Adverse events occurring during study (all causes)	88 (88)	83 (82)	91 (74)	85 (71)
Serious adverse events	31 (31)	35 (34)	33 (27)	30 (25)
Withdrawal because of adverse events	9 (9)	17 (17)	14 (11)	9 (8)
Adverse events (potentially study-related)	50 (50)	34 (34)	42 (34)	29 (24)
Serious adverse events	2 (2) [†]	6 (6) [‡]	6 (5) [§]	4 (3) [¶]
Withdrawal because of adverse events	4 (4)	7 (7) ^{**}	4 (3) ^{††}	1 (1) ^{‡‡}
	Tolvaptan Group (N=223)		Placebo Group (N=220)	

Conclusions

- Tolvaptan was superior to placebo in the treatment of hyponatremia compared to placebo without fluid restriction or change in medications.
- Efficacy evaluation there was effect on menatl component summary
- Adverse effects comparable in the 2 grps with increase thirst and urination in tolvaptan group.

Limitations

- Study length only for 30 days and sodium levels decreased on discontinuation
- Did not compare with standard therapy of fluid restriction
- Cost effectiveness compared to standard therapy.

The background is a smooth blue gradient. On the left side, there is a bright, glowing area that resembles a sun or a light source, with a vertical streak of light extending downwards, creating a shimmering effect. The rest of the background is a deep, uniform blue.

Thank you