Therapeutic Advances in Heart Failure: From diuretics to Aquaretic Agents

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ER consultation: Meet Mrs Wang

*75 y/o woman
*Progressive dyspnea for 3 days

*HFrEF, NYFA Fc II, diag for 3 yrs
LVEF=25%, global hypokinesia
OPD: Valsartan 160mg/d, bisoprolol 5 mg/d,
furosemide 20mg/d, spironolactone 5mg/d

*PE: Chest: bil rales
heart: RHB, S3 (+)
Ext: lower leg edema (3+)

* BUN/CRE: 63/2.5 (baseline 2.2) ,
eGFR: 23 mL/min/1.73m^2

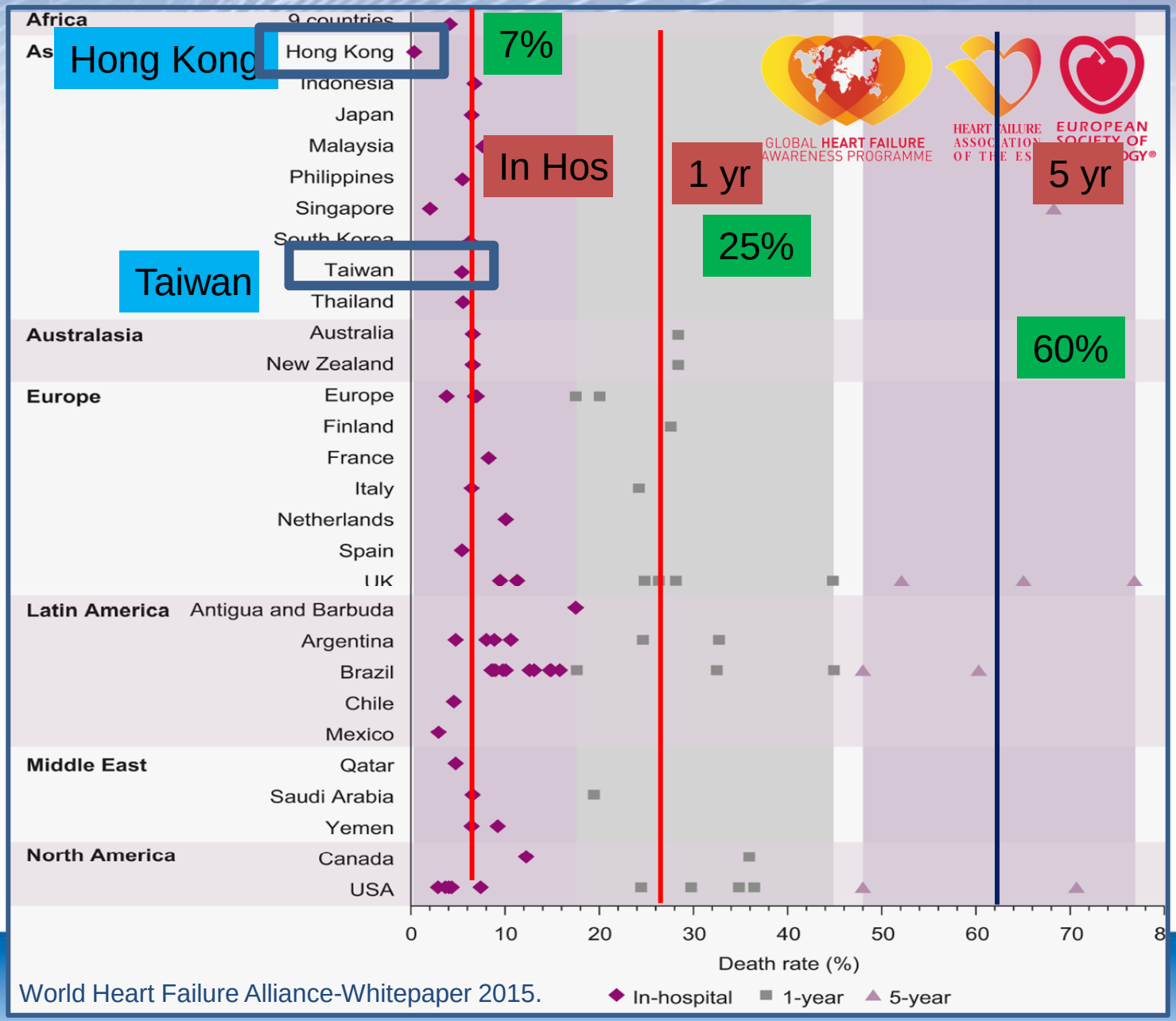
- NA: 125 mEq/L , K: 3.6
- NT-proBNP: 8754 pg/ml

75 y/o woman

@HFrEF with ADHF (acute decompensated HF)
(volume overload)
@Hyponatremia
@CKD

How to treat volume overload?

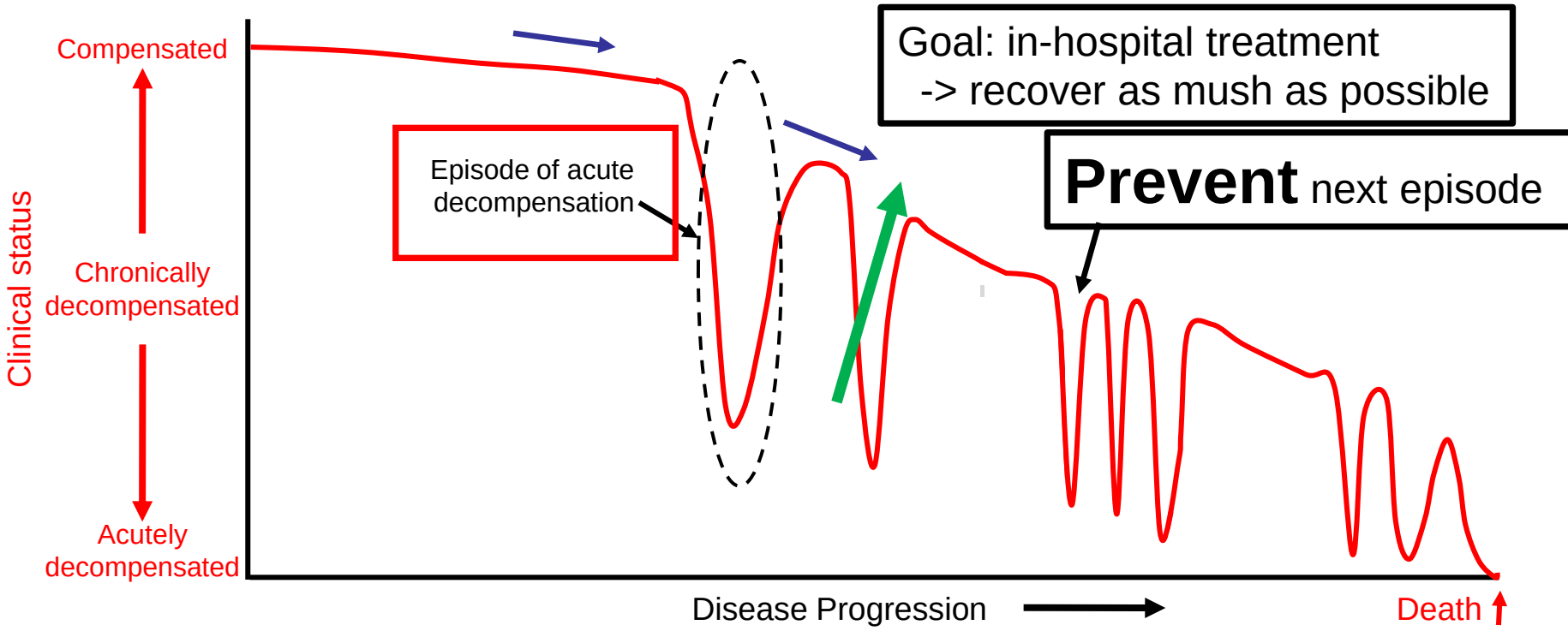
Death rates for patients hospitalized with HF across the globe



World Heart Failure Alliance-Whitepaper 2015.

Natural History of a HF patient

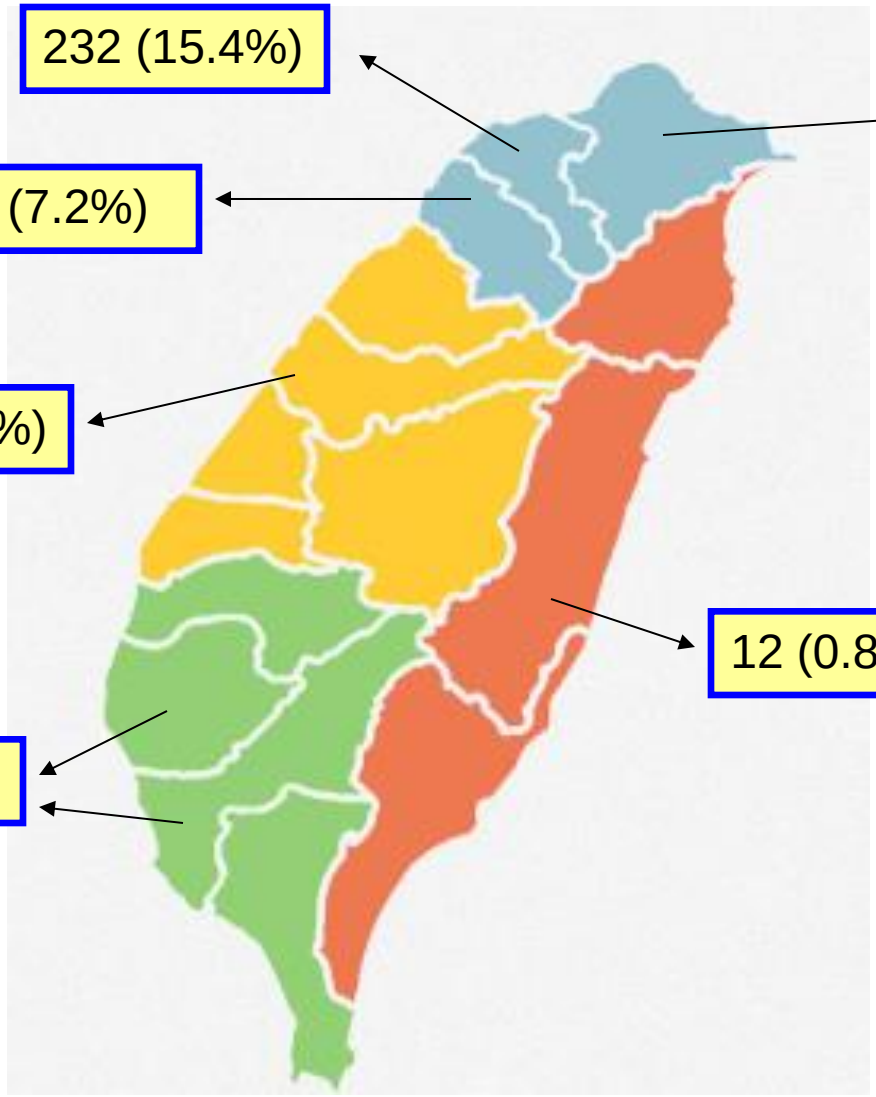
- Outcomes:
1. Death
2. Recovery: Not easy back to baseline
- Later: Speed the disease progression



Adapted from Gheorghiade et al. 2005[2]

1. Ahmed et al. Am Heart J 2006;151:444–50; 2. Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; 3. Gheorghiade, Pang. J Am Coll Cardiol 2009;53:557–73; 4. Holland et al. J Card Fail 2010;16:150–6; 5. Muntwyler et al. Eur Heart J 2002;23:1861–6; 6. McCullough et al. J Am Coll Cardiol 2002;39:60–9; 7. McMurray JJ. et al. Eur Heart J. 2012;33(14):1787–1847

Taiwan HFrEF registry (2013-4) n=1,507



Total 20 hospitals

Characteristics at Admission

	N=1,507
Age	**63.9** ±16.1 y/o
Male	1093 (**72.5** %)
Day of hospitalization	**13.0** ±15.1 days (median 8)
Stay in ICU	497 (**33.0 %**) (7.2 ± 12.9 days, median 4)
NYHA Fc I / II / III / IV	0.7 / 11.1 / 50.3 / 37.8 %

631 Patients completed 6-month F/U

	N=631
F/U period	5.7 ± 1.0 months
Mortality (Cardiac / Non-cardiac)	38 / 23 (6 / 3.6 %) **9.6%**
MACE	263 (41.7%)
Hospitalization due to HF	200 (31.7%) (1.5 ± 0.8 times, median 1)
CABG	7 (1.1%)
Valvular surgery	8 (1.3%)
SAVER surgery	0
Heart transplantation	7 (1.1%)
LVAD	4 (0.6%)
F/U NYHA Fc I / II / III / IV	24.6 / 44.8 / 19.7 / 10.9 %

Average admission day	8 days
ICU admission %	33%
ICU admission day,	4 d
Patients with Hyponatremia *	**19.9%**
Serum Na, Ave	138mEq

*(serum Na^+<135mEq)

N=1509

IV diuretics, %	62.6%
CKD, %	32%**
Stage 3 CKD	36.6%
Stage 4-5 CKD	27.4%

*EGFR<30ml/min

Table 1. Laboratory findings of TSOC-HFrEF registry patients

	Index Hospitalization		6-month		12-month	
	Mean/ percentage	Median (IQR)	Mean/ percentage	Median (IQR)	Mean/ percentage	Median (IQR)
BUN (mg/dL)	32.2 ± 23.3	24.7 (17.3-38.0)	37.7 ± 26.8	29.0 (19.0-47.0)	35.2 ± 25.3	25.6 (17.9-45.6
Creatinine (mg/dL)	1.9 ± 1.8	1.3 (1.0-1.9)	2.0 ± 2.1	1.3 (1.0-2.1)	2.0 ± 2.1	1.3 (1.0-1.9)
eGFR (mL/min/m^2)	55.5 ± 40.2	48.0 (27.9-73.7)	56.9 ± 38.4	48.6 (29.0-79.9)	57.1 ± 39.3	46.4 (30.9-75.5
Stage III CKD	36.6%		33.8%		39.4%	
Stage IV or V CKD	27.4%		27.1%		23.4%	
Sodium (mEq/L)	137.7 ± 4.6	138 (135-140)	138.1 ± 4.3	138 (136-141)	138.3 ± 4.8	139 (136-141)
Hyponatremia (< 135 mEq/L)	19.9%		17.1%		16.0%	
Potassium (mEq/L)	4.0 ± 0.6	4 (3.6-4.4)	4.2 ± 0.7	4.2 (3.8-4.6)	4.2 ± 0.6	4.2 (3.8-4.6)
Hyperkalemia (≥ 5.5 mEq/L)	2.6%		3.8%		3.2%	

16%

Predictor of 1 yr Mortality

Table 3. Predictors of one-year all-cause mortality in TSOC-HFrEF registry

	Univariate analysis			Multivariate analysis	
	Morality	Alive	p value	HR (95% CI)	p value
Baseline and hospitalization characteristics					
Age (y/o)	69.0 ± 14.1	62.8 ± 16.2	< 0.001		
Hospital length (day)	17.9 ± 18.1	11.5 ± 12.3	< 0.001	1.01 (1.00-1.02)	0.007
Systolic blood pressure	126.3 ± 27.2	131.8 ± 27.3	0.006		
Body mass index (kg/m^2)	23.9 ± 5.1	25.5 ± 5.0	< 0.001	0.95 (0.91-0.99)	0.02
ICU admission		31.1%	0.006		
Severe symptoms at discharge (NYHA Fc III/IV)		25.6%	< 0.001	1.88 (1.28-2.77)	0.001
Past and personal history					
Current smoker	12.9%	25.2%	< 0.001		
Diabetes mellitus	55.1%	41.7%	< 0.001		
Chronic kidney disease	45.8%	28%	< 0.001		
Atrial fibrillation	31.6%	25.2%	0.05		
Peripheral arterial disease	10.7%	5.9%	0.009		
COPD/asthma	16%	9.8%	0.006		
Hypothyroidism	6.2%	1.3%	< 0.001	3.97 (1.96-8.05)	< 0.001
Valvular surgery	8.4%	4.2%	0.006		
ICD/CRT implantation	9.8%	2.1%	< 0.001		
Coexisting problem during index hospitalization					
Infection	21.8%	16.1%	0.04		
Acute kidney injury	22.2%	12.6%	< 0.001		
COPD/asthma with acute exacerbation	6.7%	2.4%	0.001		
Electrocardiography					
QRS duration (mesc)	120.3 ± 31.9	111.6 ± 29.1	< 0.001		
Laboratory studies					
BUN (mg/dL)	41.9 ± 27.5	29.8 ± 21.5	< 0.001		
Hyponatremia (serum Na ≤ 135 meq/L)	35.7%	23.8%	< 0.001	1.86 (1.27-2.72)	0.001
Glucose (mg/dL)	± 73.8	146.3 ± 81.7	0.04		
Discharge medication					
RAS blockade	5%	63.5%	< 0.001		
Beta blocker	50.0%	61.9%	0.001		
MRA	40.8%	49.6%	0.02		
Guideline-directed medical therapy ≤ 1 type	56.9%	36.8%	< 0.001	1.59 (1.07-2.38)	0.02
Digoxin	32.6%	24.8%	0.02		
Anti-arrhythmic drugs	21.1%	14.9%	0.02		

Hospital length

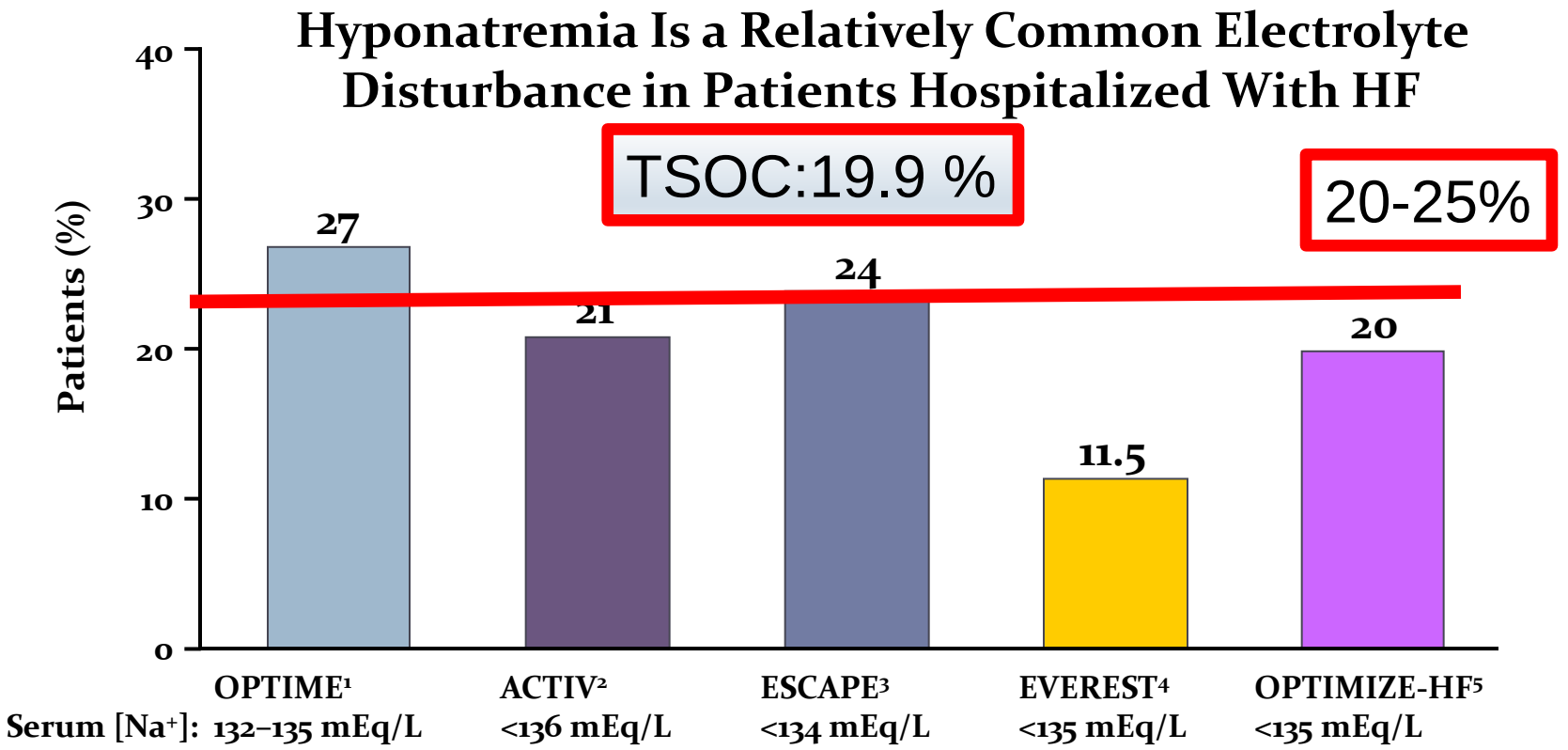
BMI

Fc at discharge

Hypothyrodism

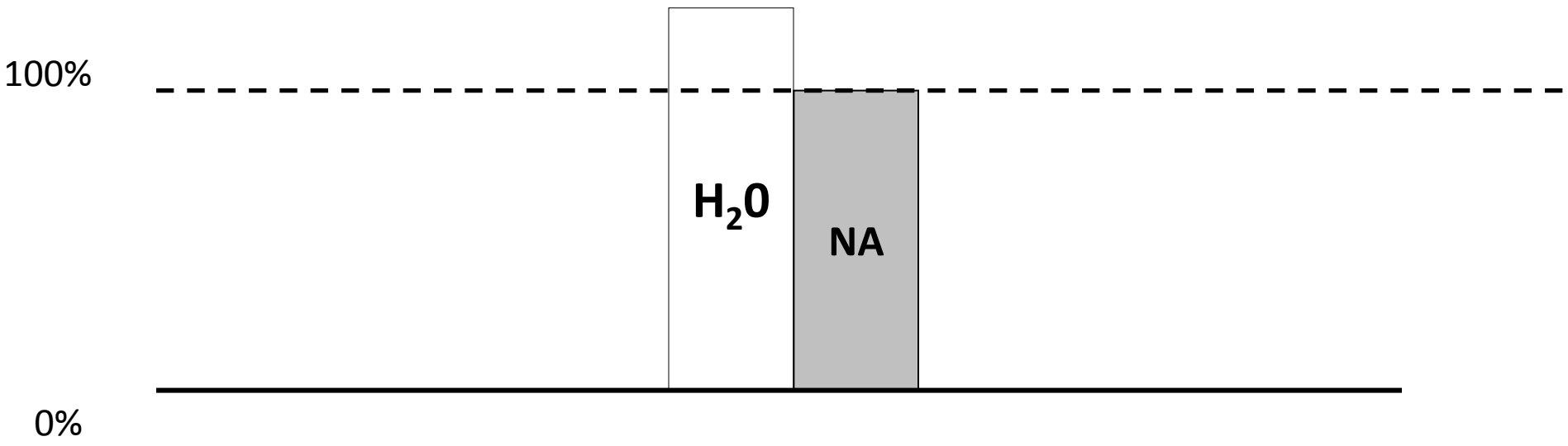
Hypo-Na

Prevalence of Hyponatremia in Patients Hospitalized With HF

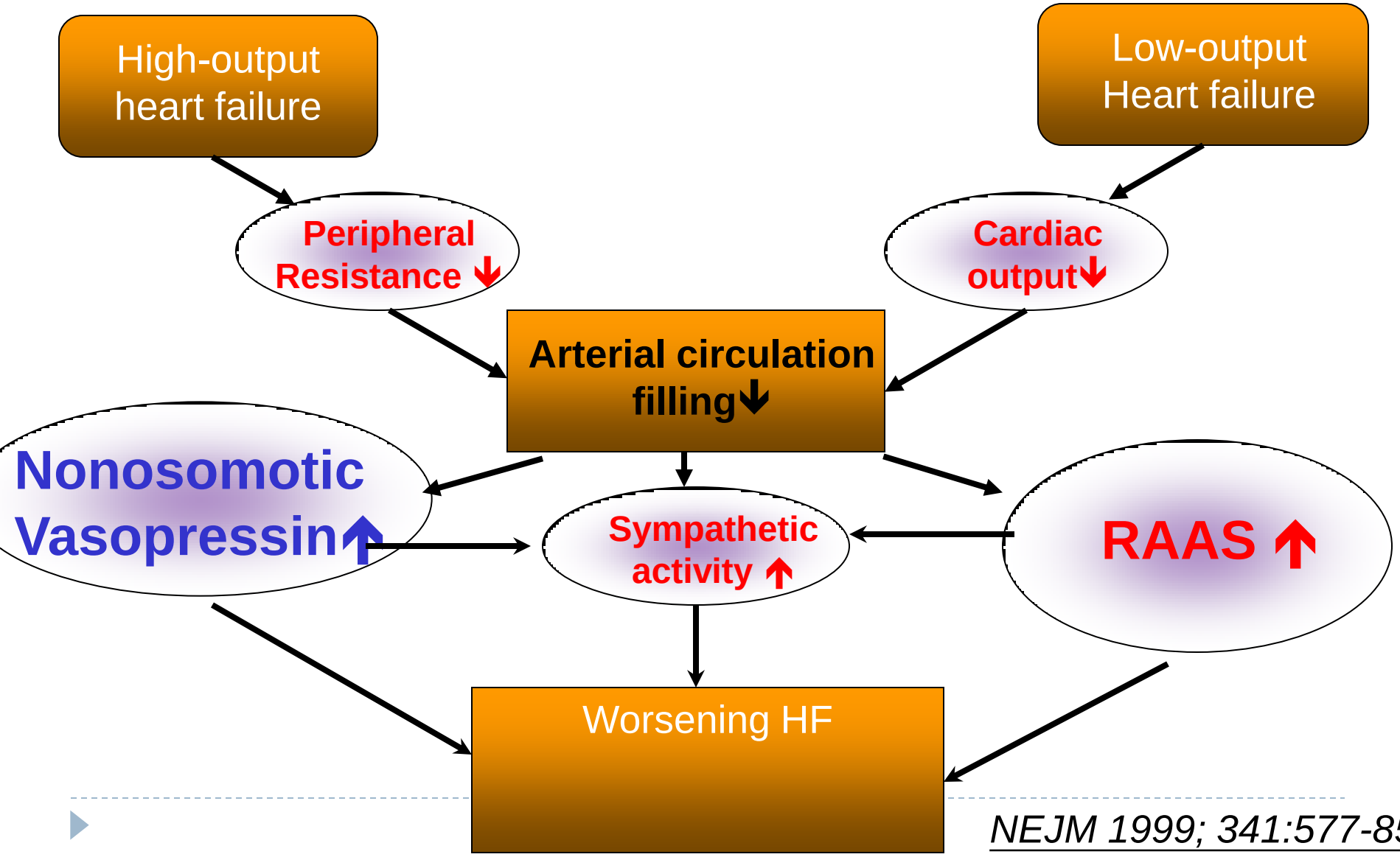


1. Klein L et al. *Circulation*. 2005;111(19):2454-2460; 2. Gheorghiade M et al. *JAMA*. 2004;291(16):1963-1971;
3. Gheorghiade M et al. *Arch Intern Med*. 2007;167(18):1998-2005; 4. Data on file: Protocol 156-02-236;
5. Gheorghiade M et al. *Eur Heart J*. 2007;28(8):980-988.

Hyponatremia in HF -> free water excess

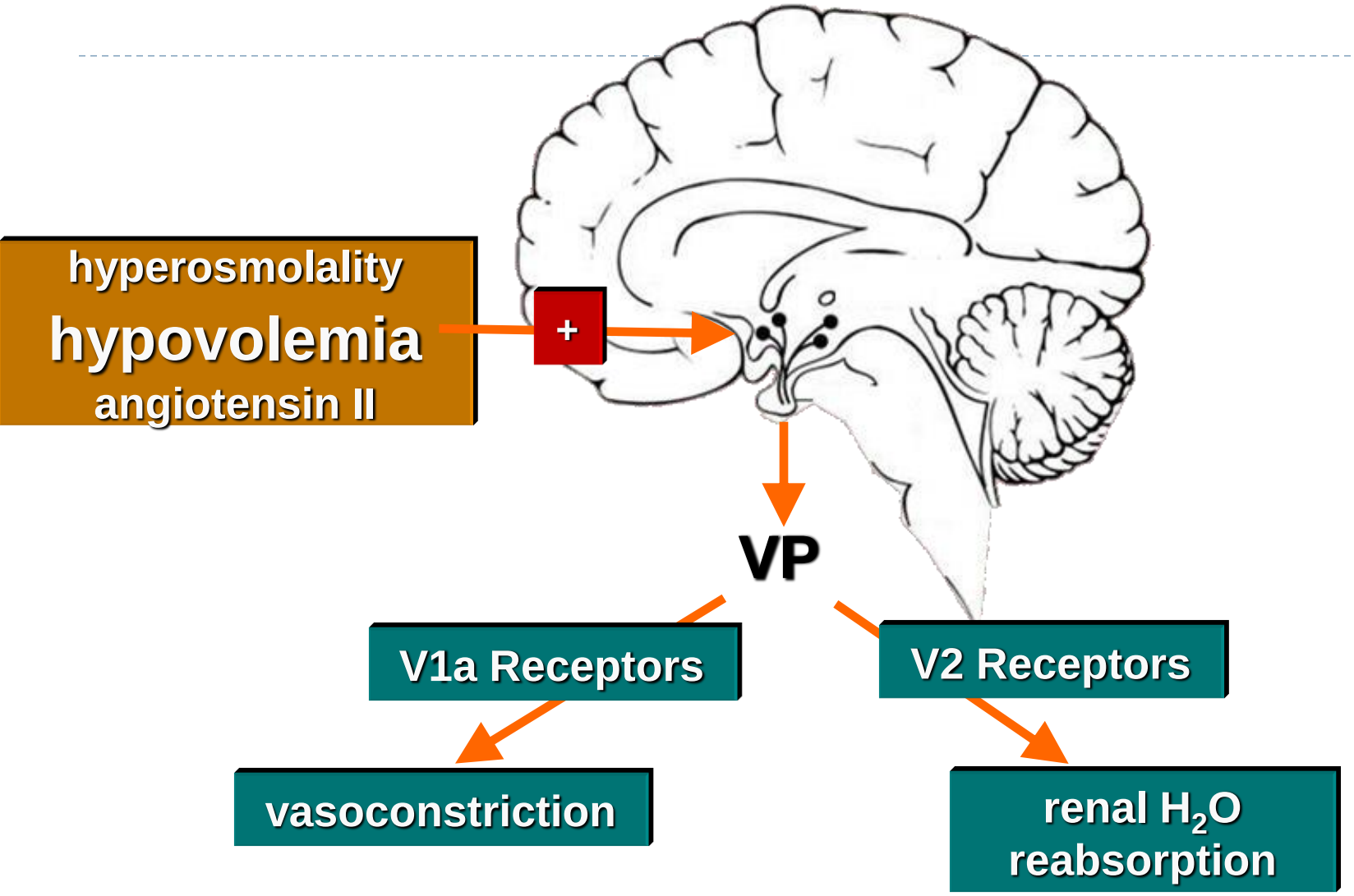


Neurohormonal aberrance of HF

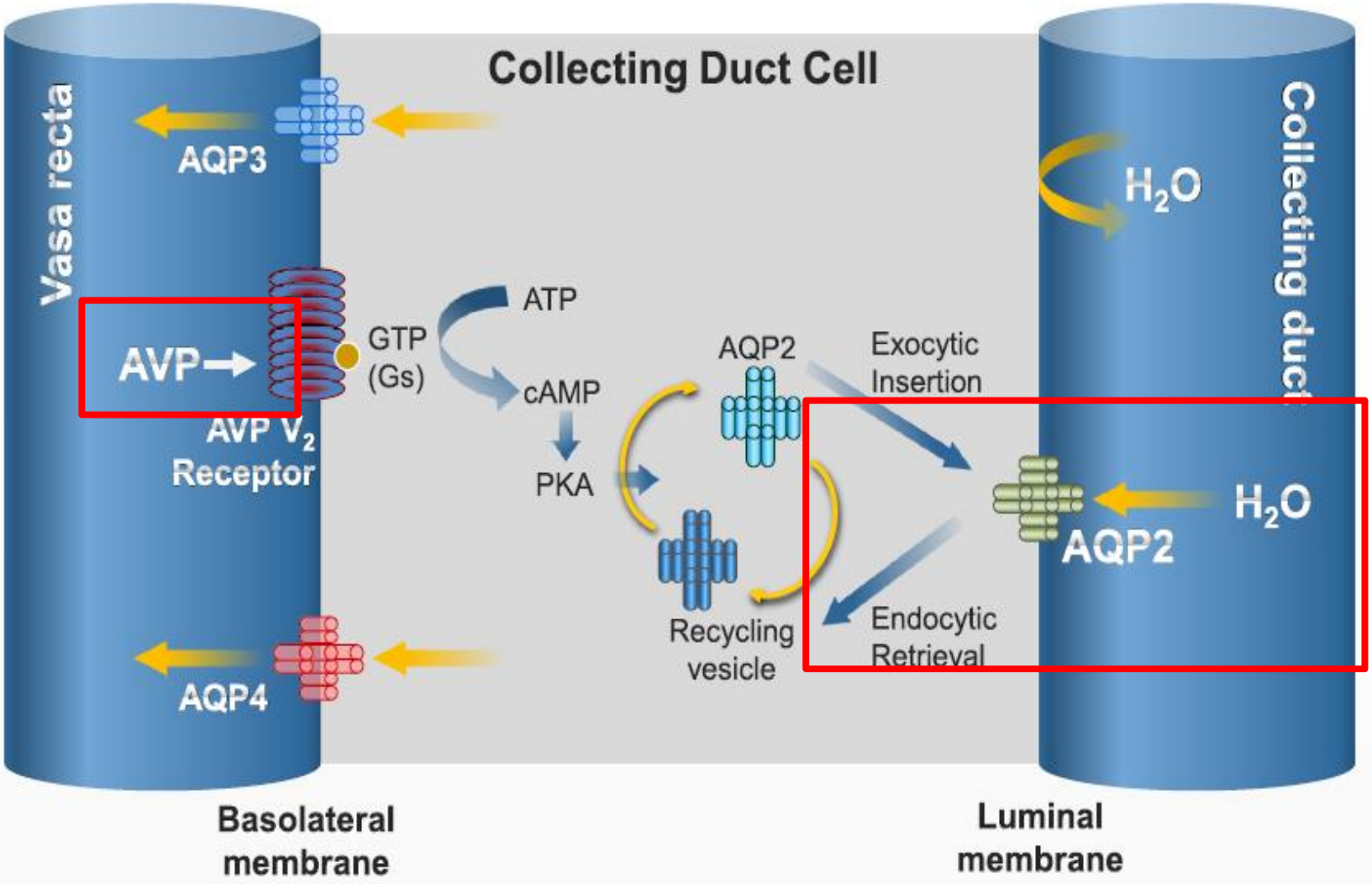


NEJM 1999; 341:577-85

Vasopressin Stimulation and Effects



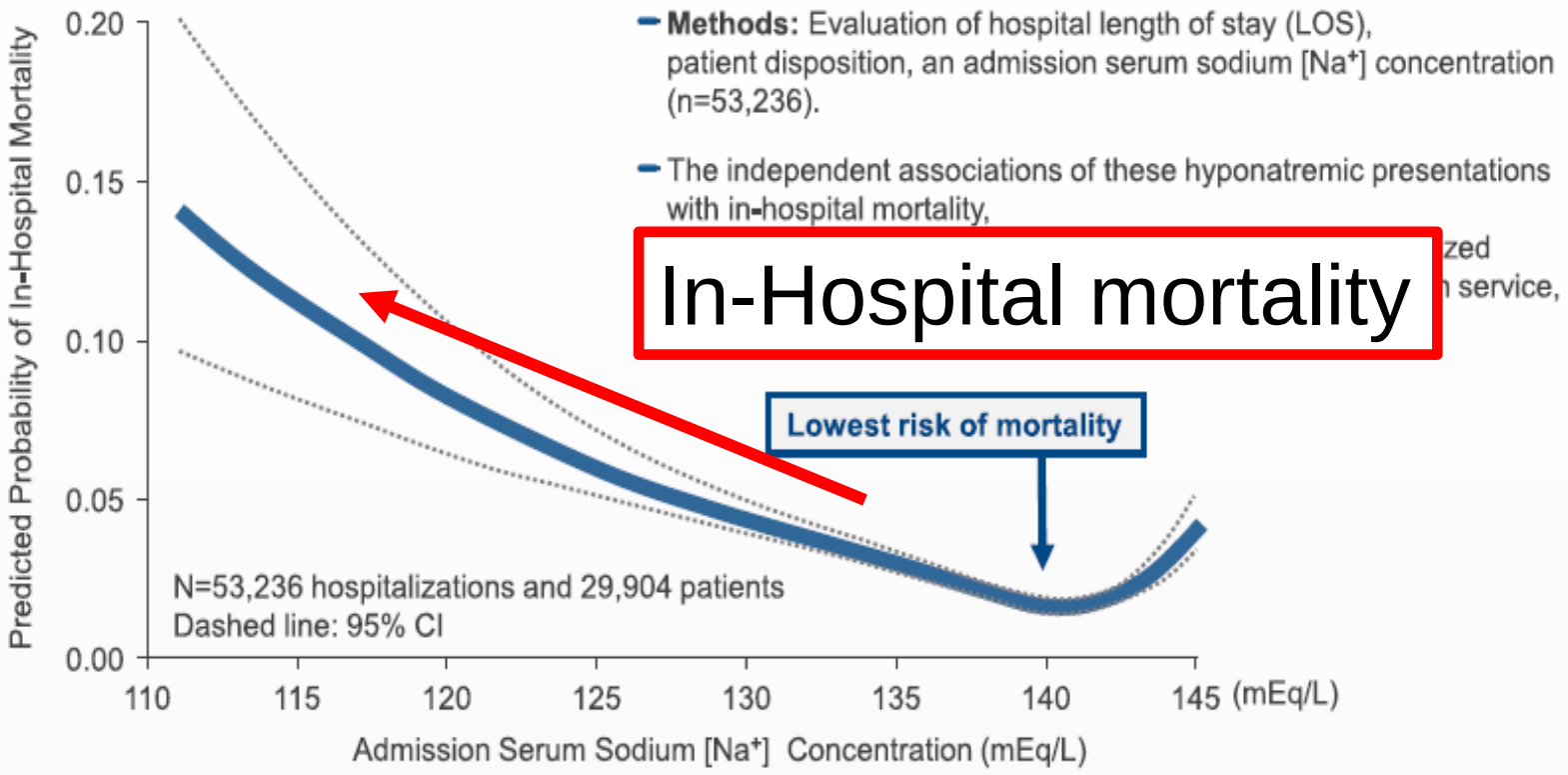
Vasopressin Regulation of Water Reabsorption from Renal Tubular Cells



Mayinger et al. Exp Clin Endocrinol Diab 1999;107:157-65.

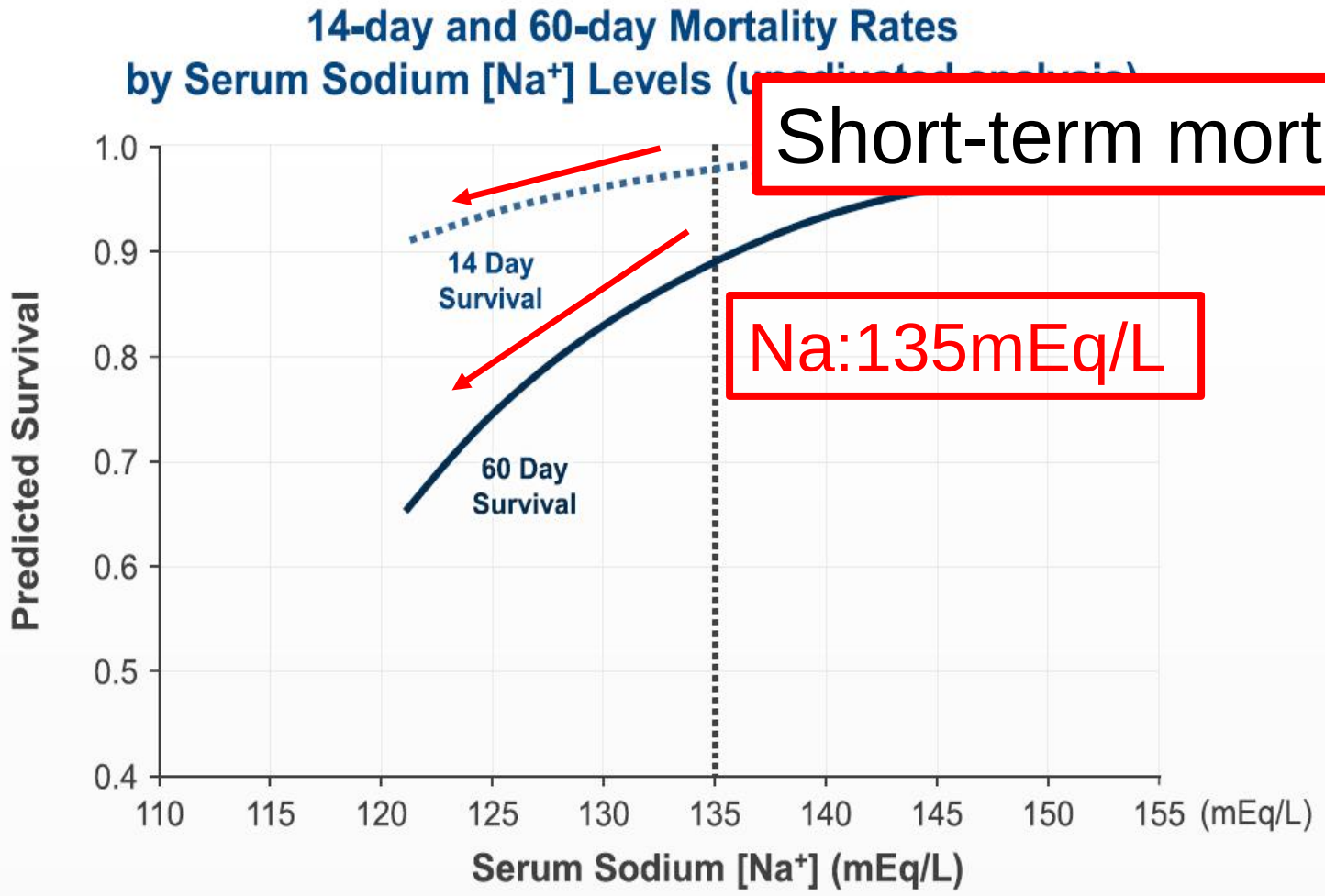
Prognostic of Hyponatremia on Heart Failure Patients (In-hospital Mortality)

Restrictive Cubic Spline Depicting the Unadjusted Relationship between Hospital Admission Serum Sodium [Na⁺] Concentrations and in-hospital Mortality



Upadhyay M, et al. Arch Intern Med 2010;170:294-302.

Prognostic of Hyponatremia on Heart Failure Patients (Mortality) : OPTIME-CHF



Klein L. et al. Circulation 2005;111:2454-560.

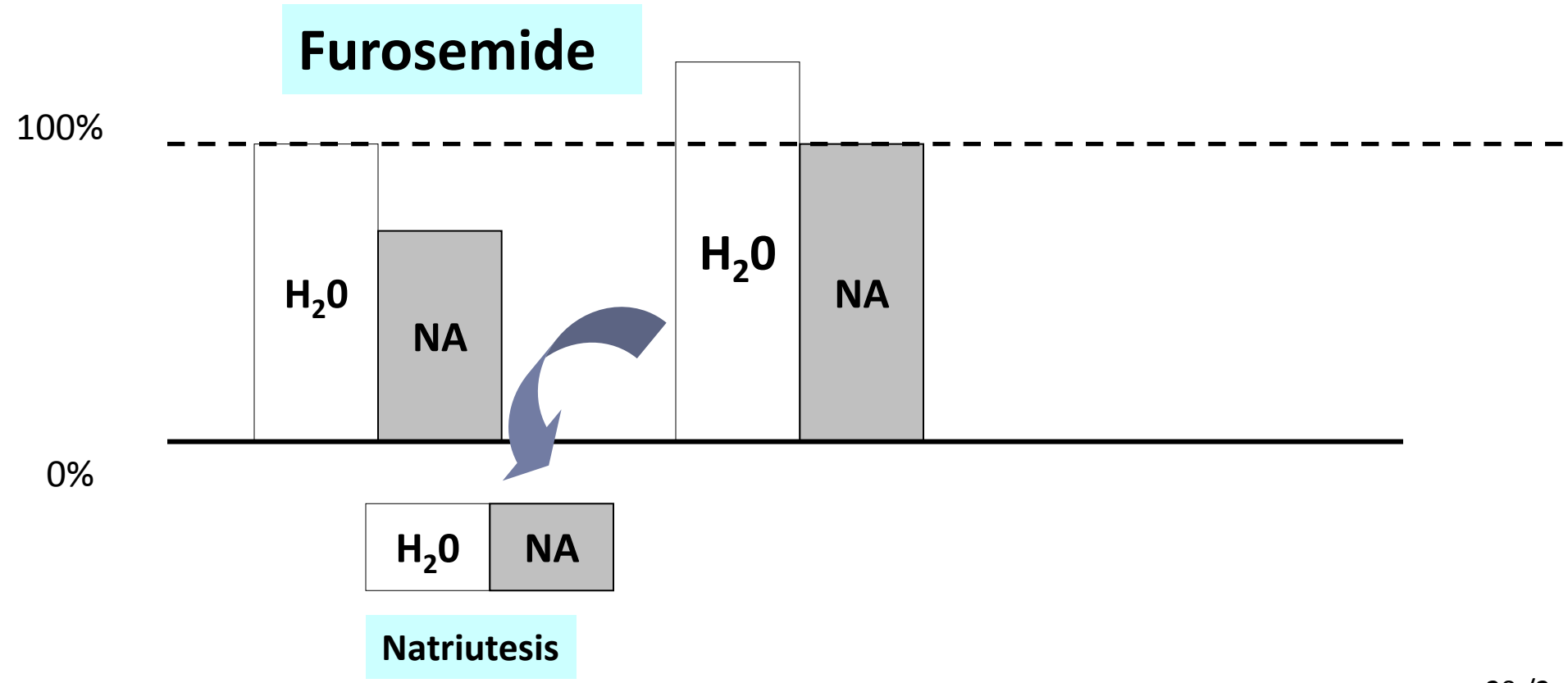
75 y/o woman

@HFrEF with ADHF (acute decompensated HF)
@Hyponatremia
@CKD

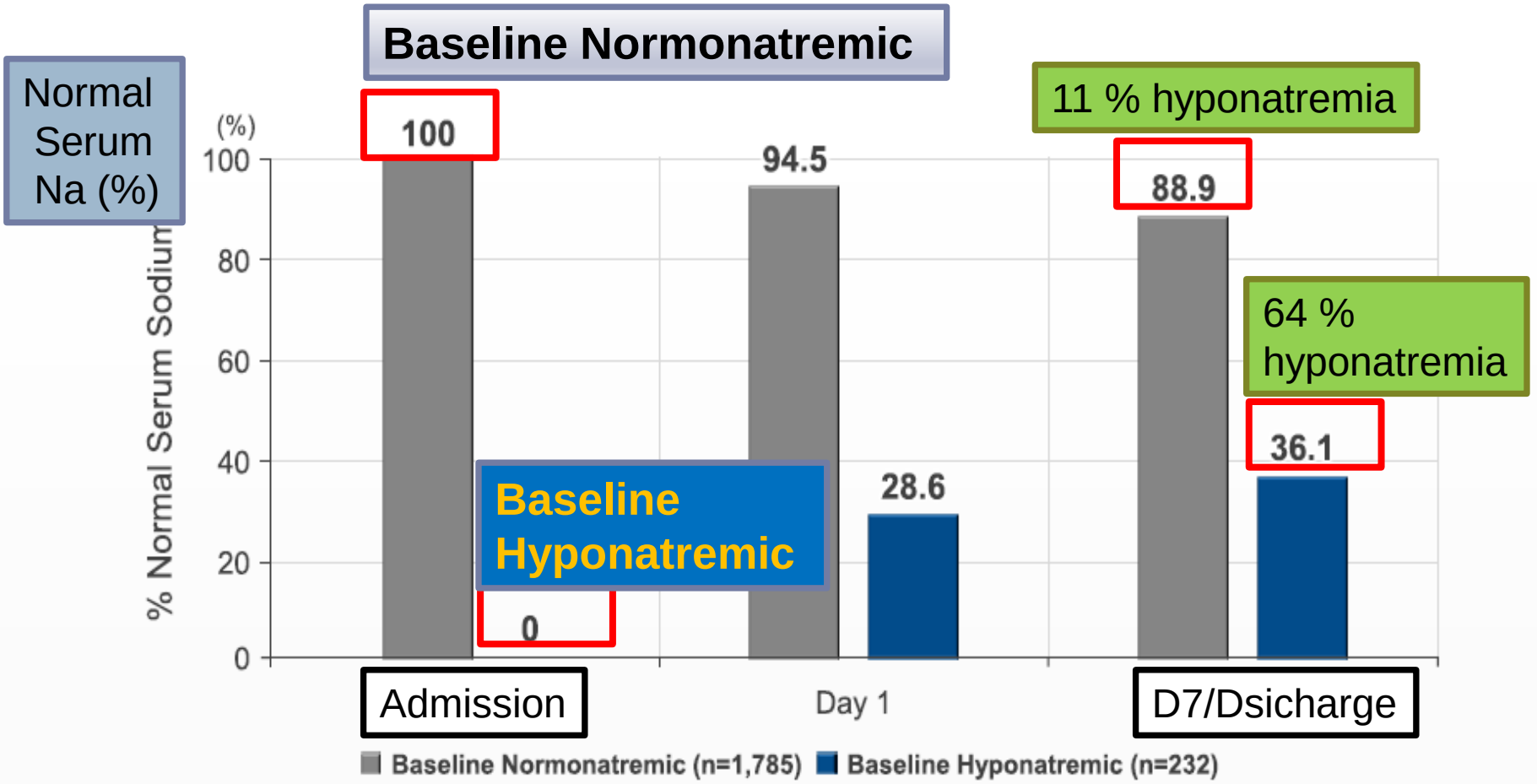
How to treat volume overload?

Diuretics

Loops diuretics -> isotonic urine-> Natriutesis



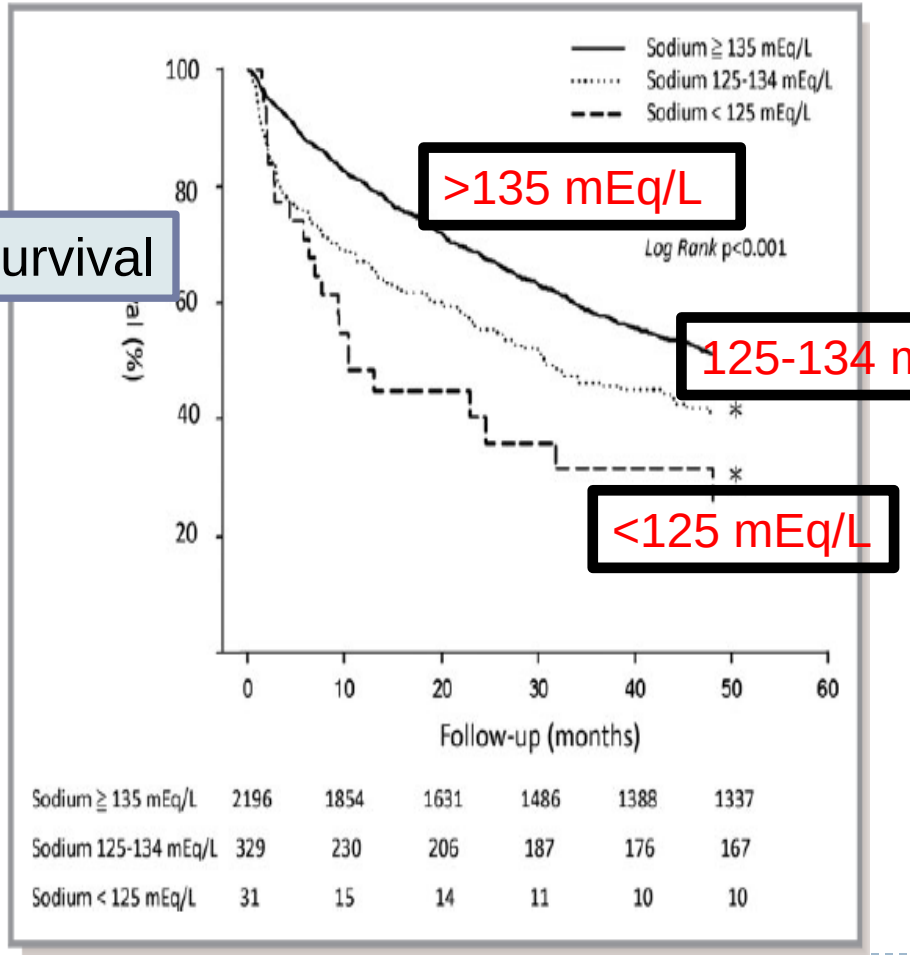
Standard Therapy and Development of Hyponatremia During HF Hospitalization



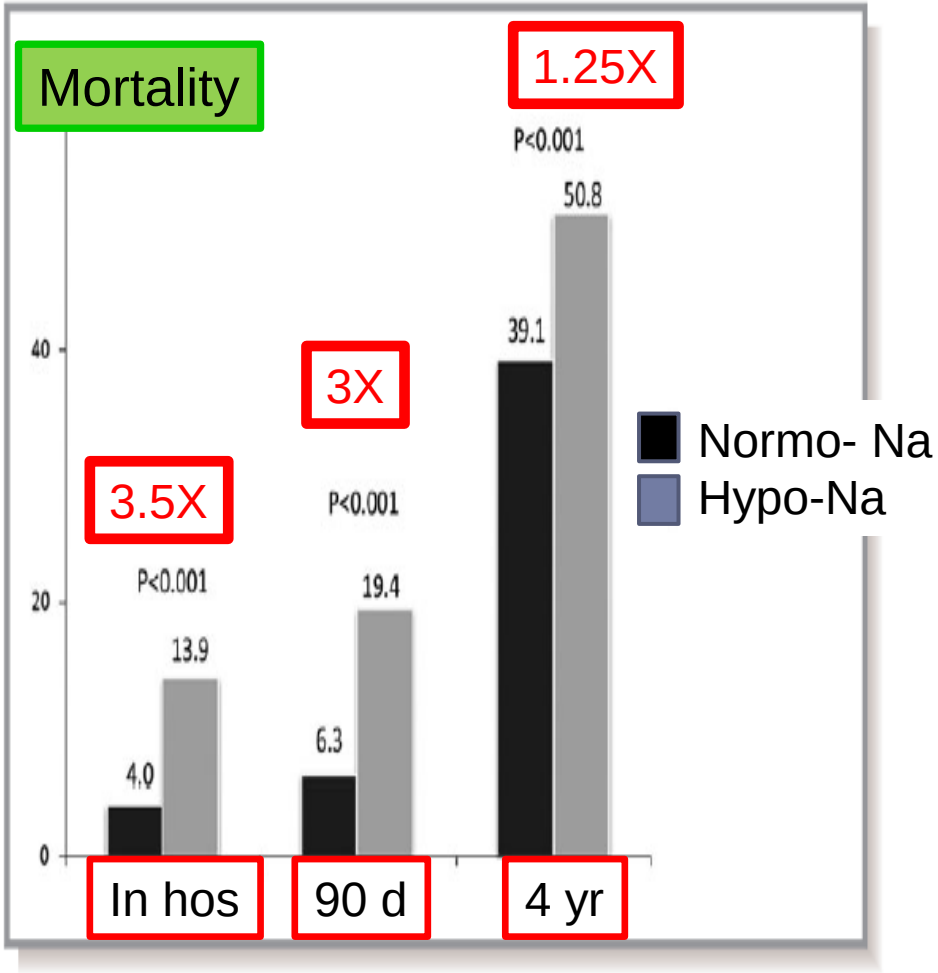
Hyponatremia and Worsening Sodium Levels Are Associated With Long-Term Outcome in Patients Hospitalized for Acute Heart Failure

Dai-Yin Lu, MD; Hao-Min Cheng, MD, PhD; Yu-Lun Cheng, MD; Pai-Feng Hsu, MD; Wei-Ming Huang, MD; Chao-Yu Guo, PhD; Wen-Chung Yu, MD;* Chen-Huan Chen, MD; Shih-Hsien Sung, MD, PhD

Survival



Mortality



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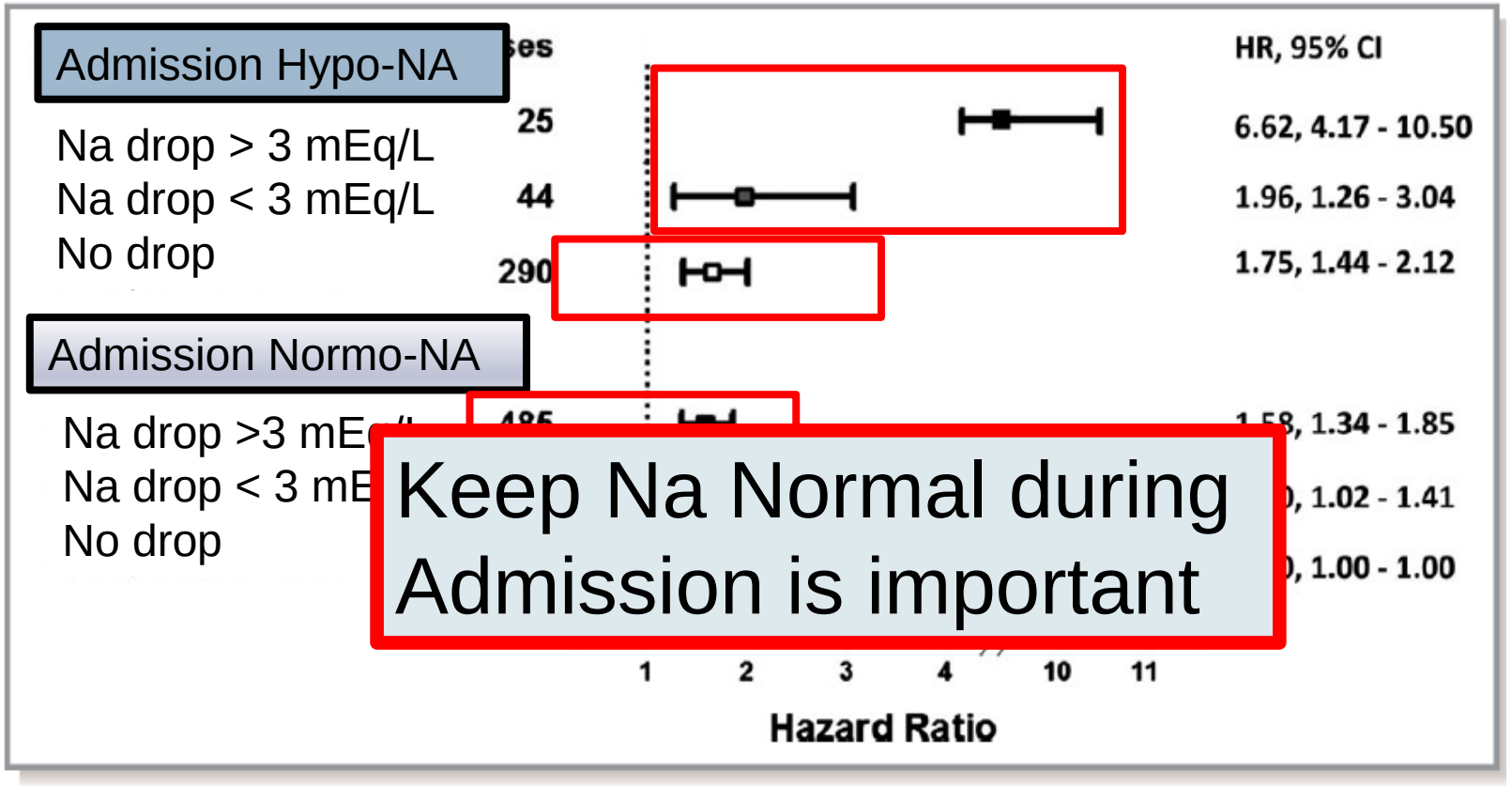
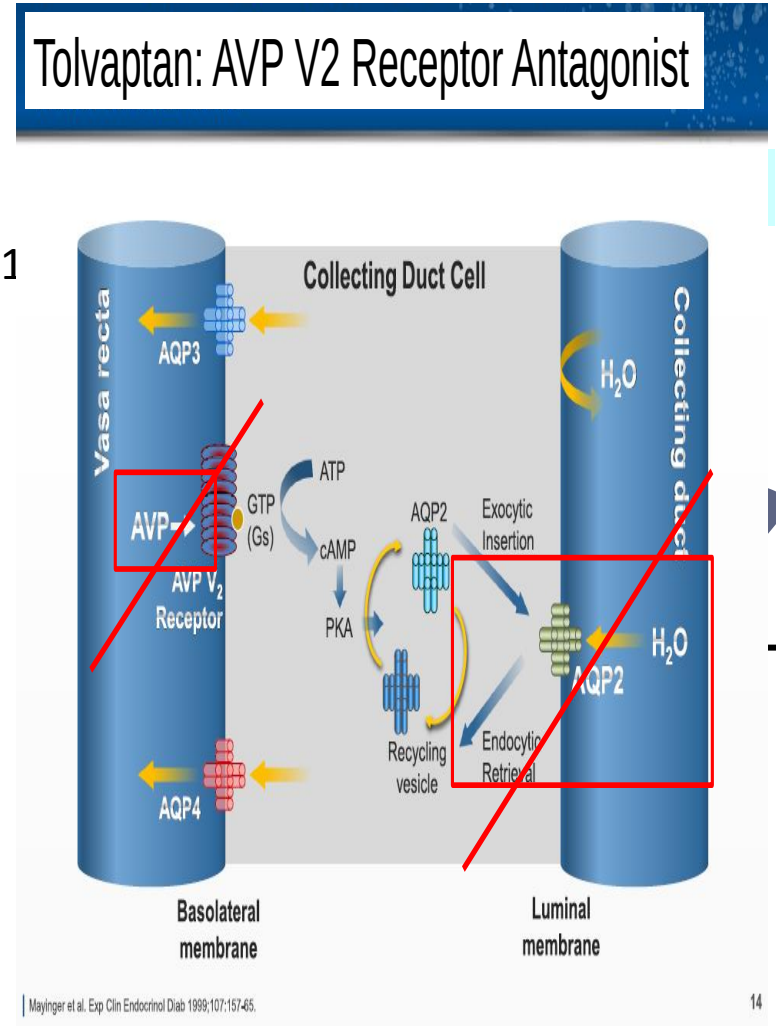
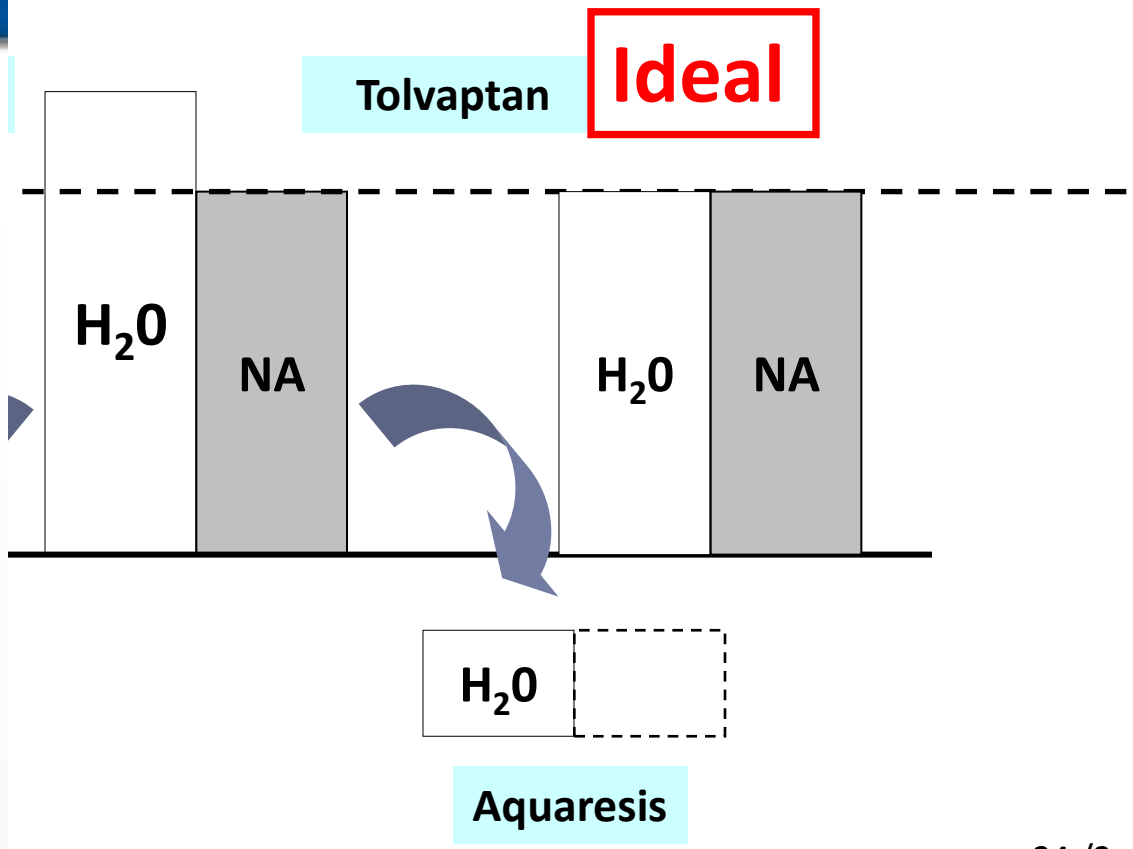
Harvest registry



Tolvaptan: AVP V2 Receptor Antagonist



1



Is tolvaptan effective in patients with hyponatremia?

Case 2

@97 y/o man

Chief complaint: mild **conscious disturbance** for several days

Past history
1. HFpEF
2. atrial fibrillation,
3. hyperthyroidism,
4. hyponatremia,
5. hypertension,
6. chronic obstructive pulmonary disease
7. benign prostate hyperplasia

Causes of hyponatremia was attributed to **multiple** factors, including diuretic therapy, HF and partial SIADH (diagnosed in USA one year ago)

Physical examination and Laboratory data

BP: 137/68 mmHg
Body temperature: 36 °C
Pulse rate: 67 bpm; respiratory rate: 18 breaths/min
Ext: mild leg pitting edema

Serum Na^+: 119 mmol/L

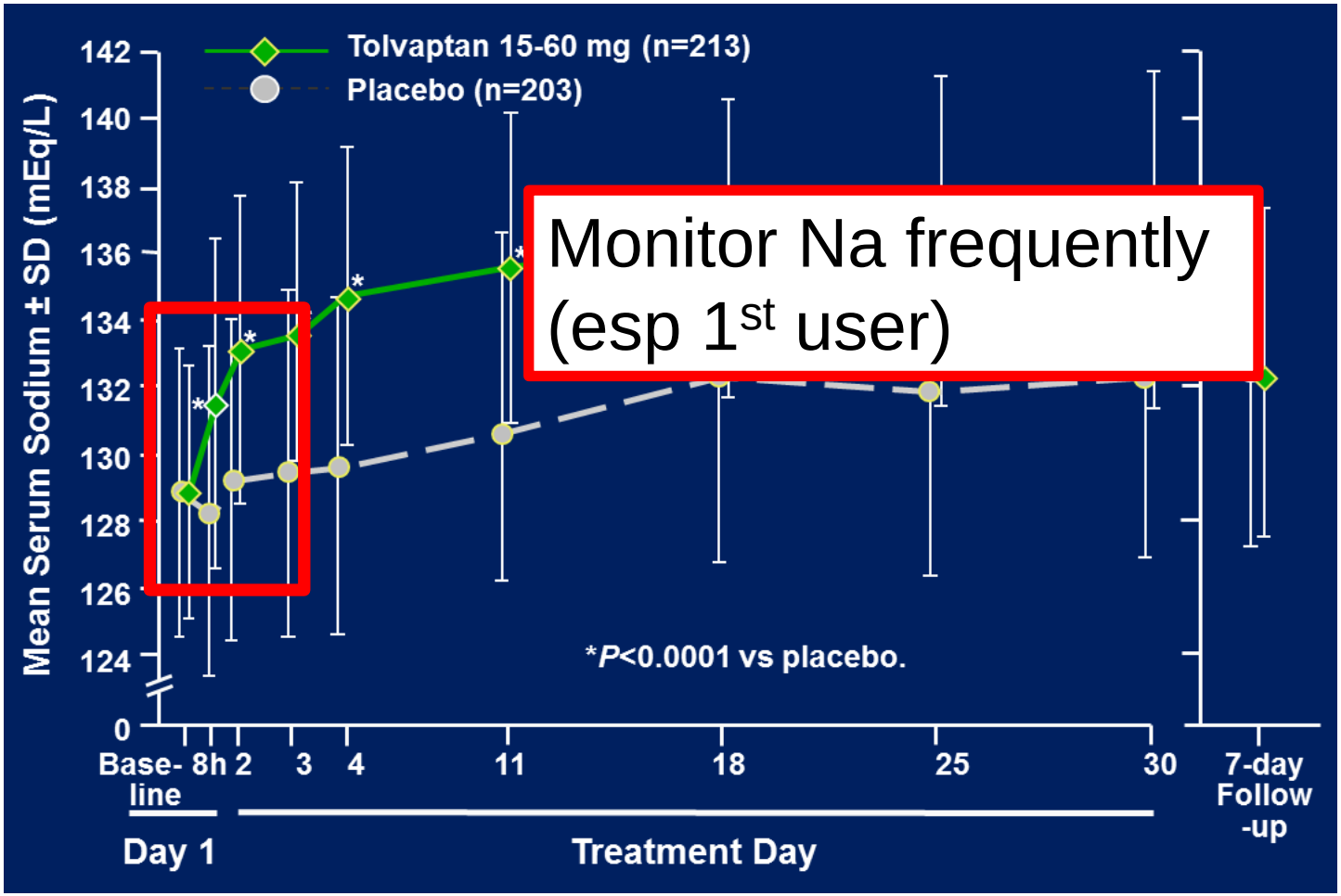
FE_{Na}: 1.57%; Na (U): 57 mmol/L -> not favor diuretics effect
FE_{UN}: 35.3%

NT-proBNP: 1,770 pg/mL
Free T4: 1.44 ng/dL; serum creatinine: 0.8 mg/dL

Tolvaptan increase Na rapidly (in first 3 days)

Hyponatremia - SALT

Enrolled patients Na< 135



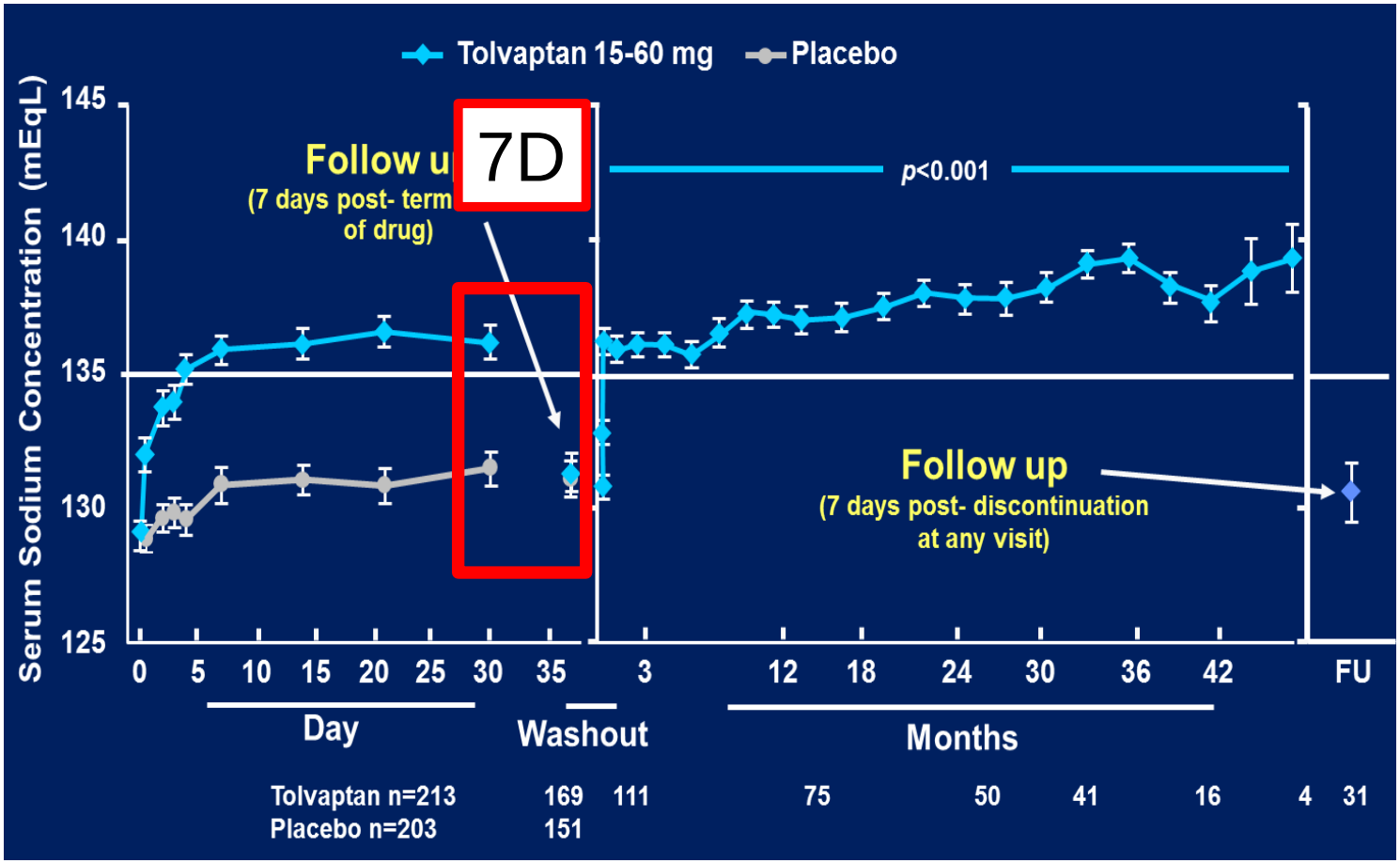
Schrier RW et al. *N Engl J Med.* 2006;355:2099-2112.

Some question of tolvaptan in this case

- How long is the effect ?
- Should I have to use regularly?
- Is it harmful or beneficial for long term usage ?

Serum Na drop rapidly after discontinue

Hyponatremia – SALTWater



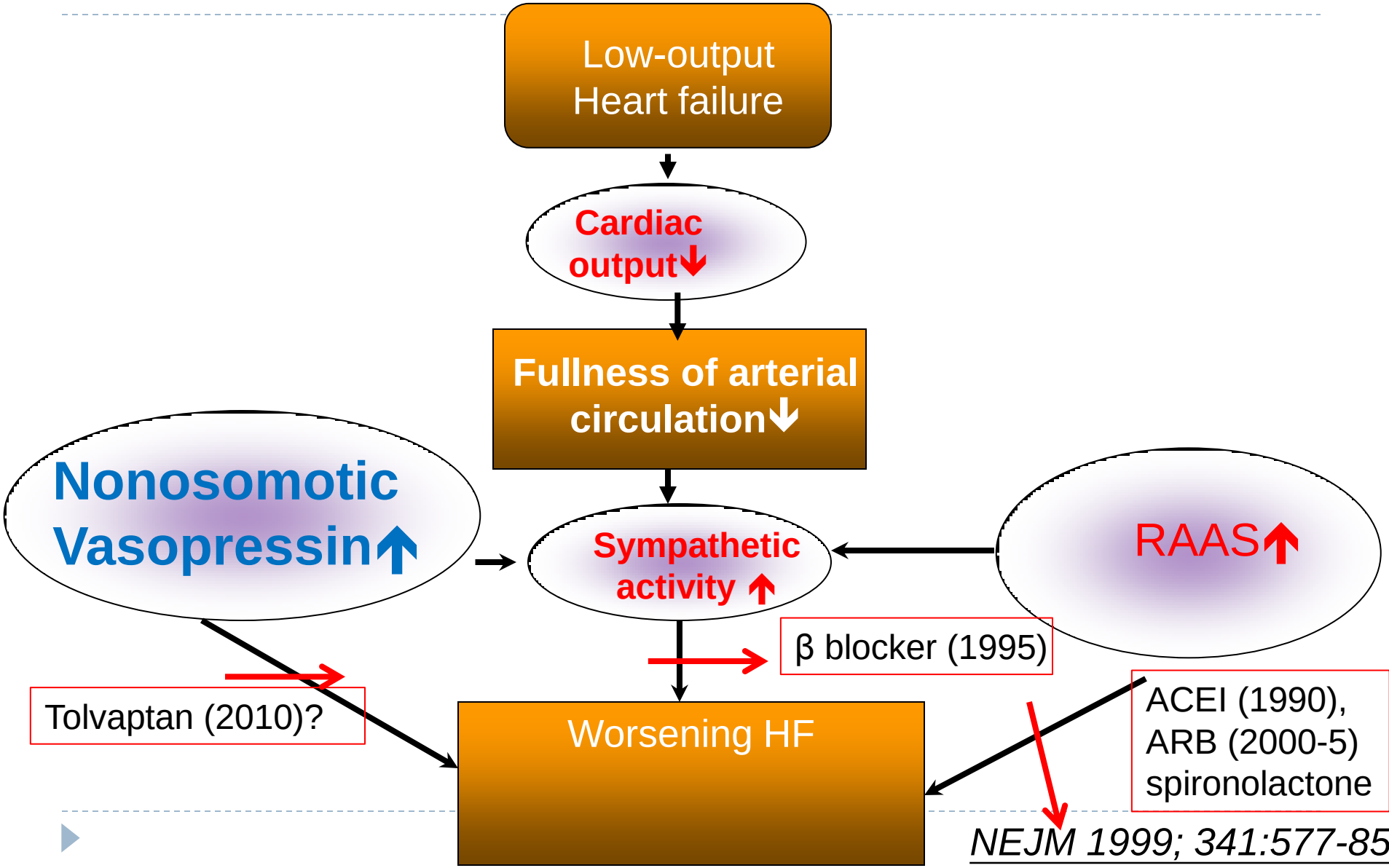
J Am Soc Nephrol 21: 705–712, 2010

- How long is the effect ? Not very long
-
- Should I continue ? Probably yes

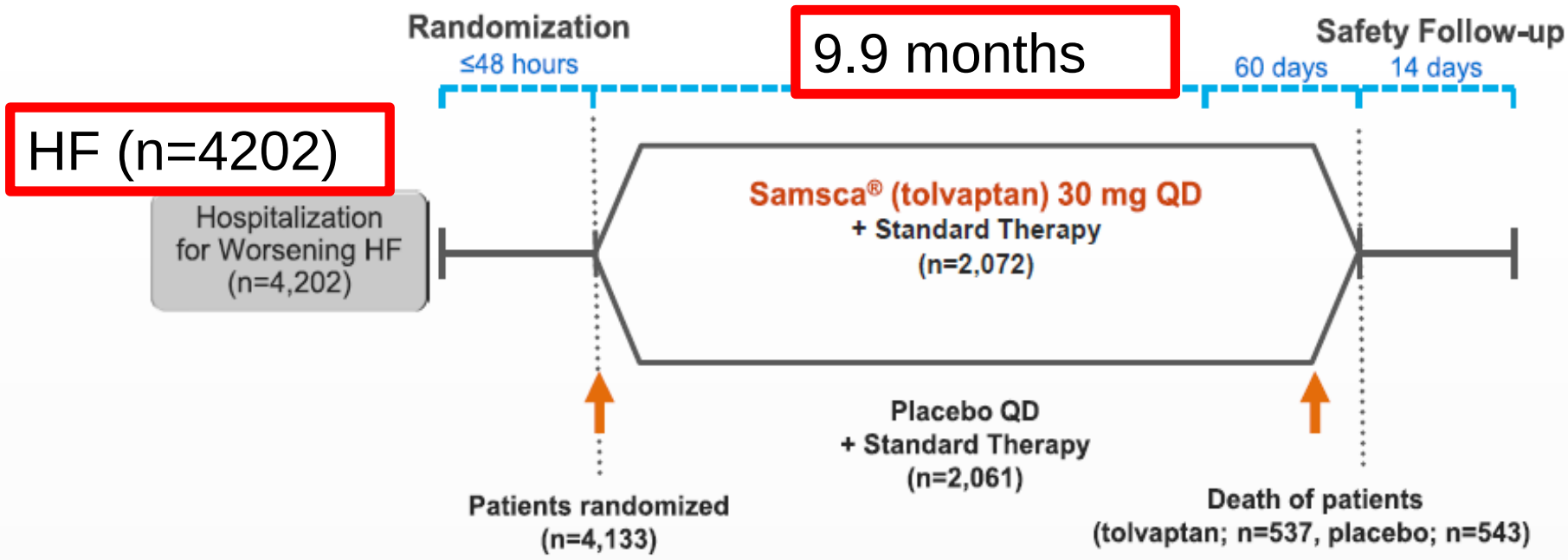
- How often? Depend on case
- Treatment duration? Depend on case

Is it harmful or beneficial for long term usage ?

Potential of VP block in HF



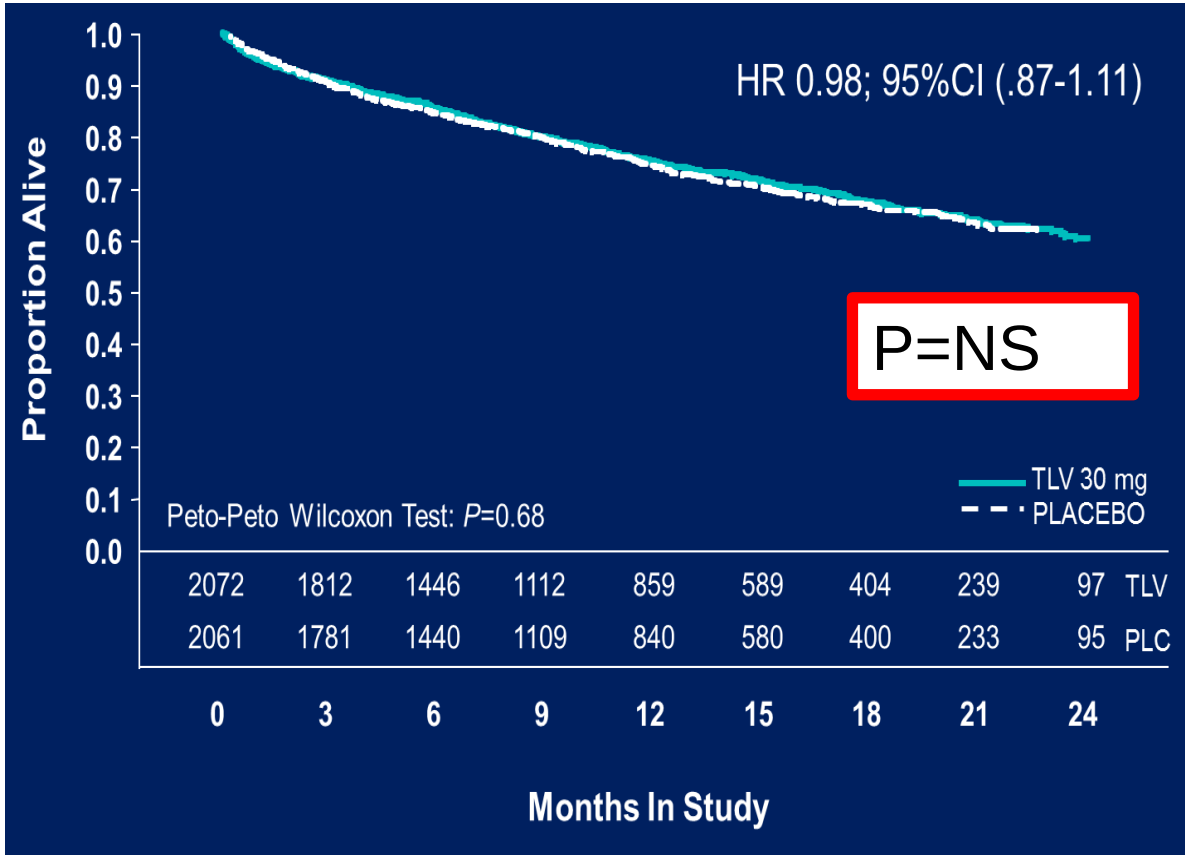
EVEREST Outcomes Trial Design



- **Dual Primary Endpoints**
  - All-cause mortality
  - CV death or HF hospitalization
- **Short-Term Endpoints**
  - Composite of change in weight and VAS between baseline and Day 7 or discharge

Konstam MA, et al. JAMA 2007;297(12):1319-31.

Result

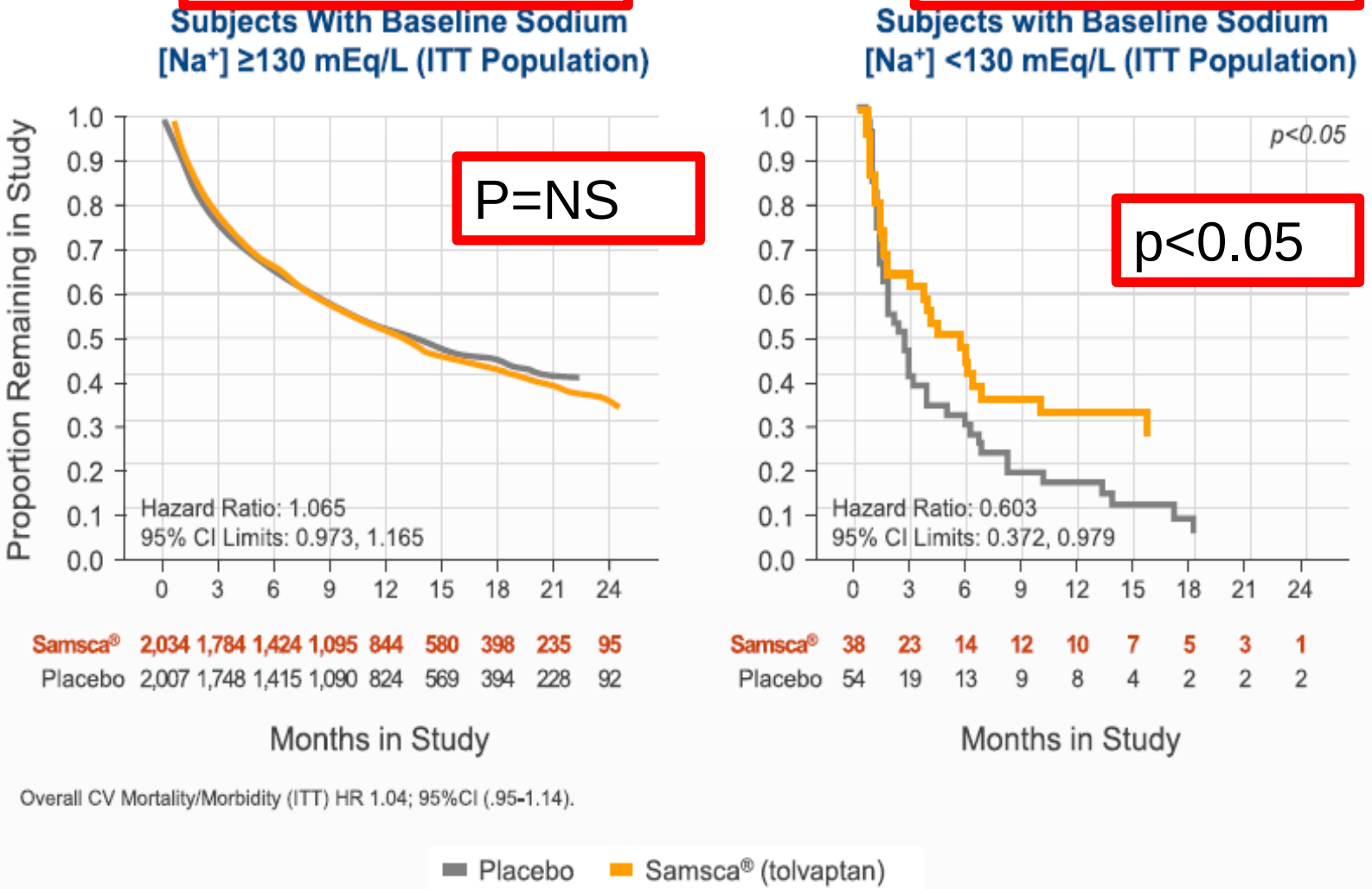


Mihai G, et al. JAMA. 2007;297:1332-43.

Patients with Heart Failure and Hyponatremia

Na>130 mEq/L

Na<130 mEq/L

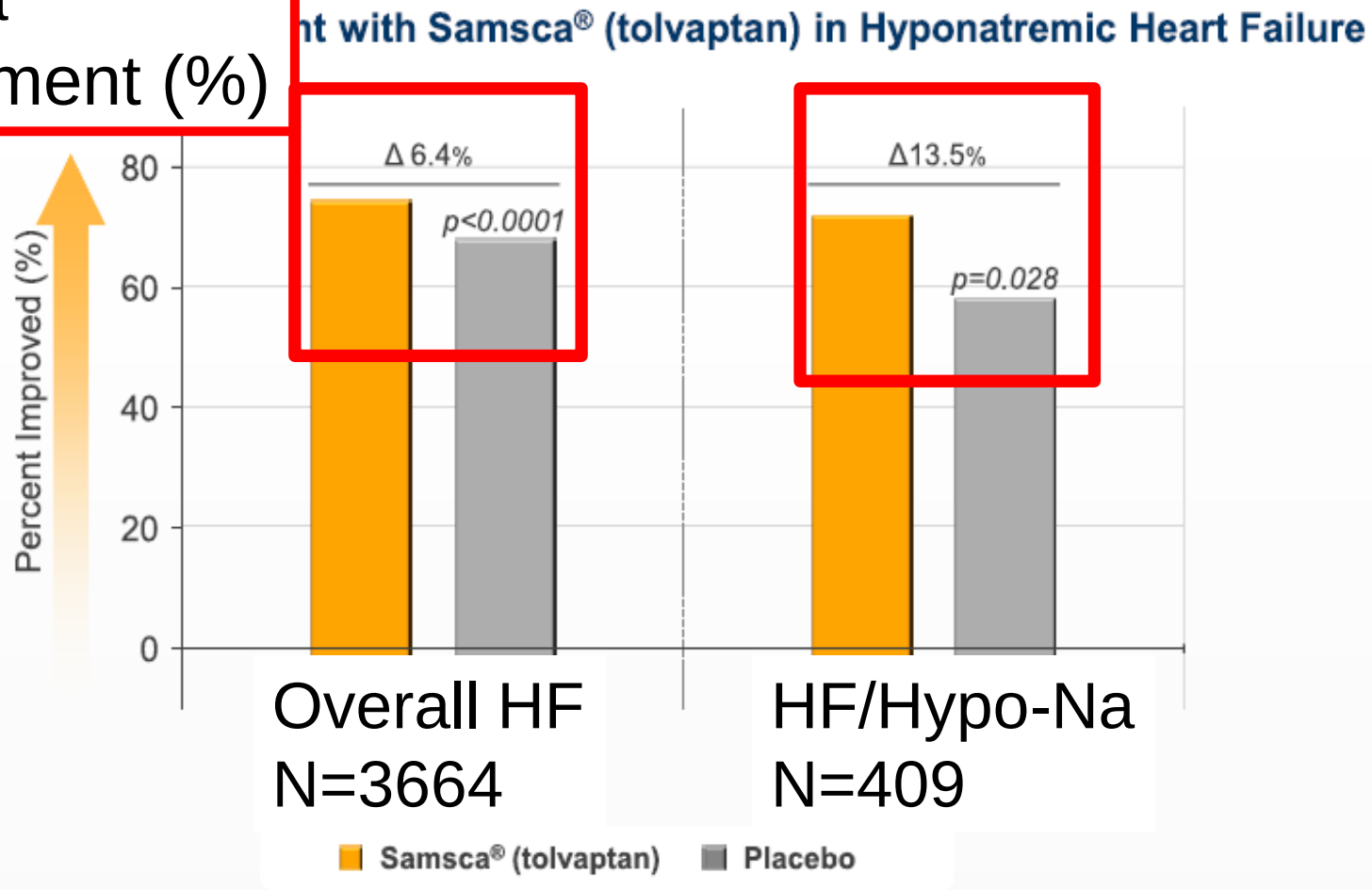


Overall CV Mortality/Morbidity (ITT) HR 1.04; 95%CI (.95-1.14).

Placebo Samsca® (tolvaptan)

Greater Dyspnea Improvement with Samsca® (tolvaptan) in Hyponatremic Heart Failure

Dyspnea Improvement (%)



Hauptman et al. J Card Fail 2013;19:390-7.

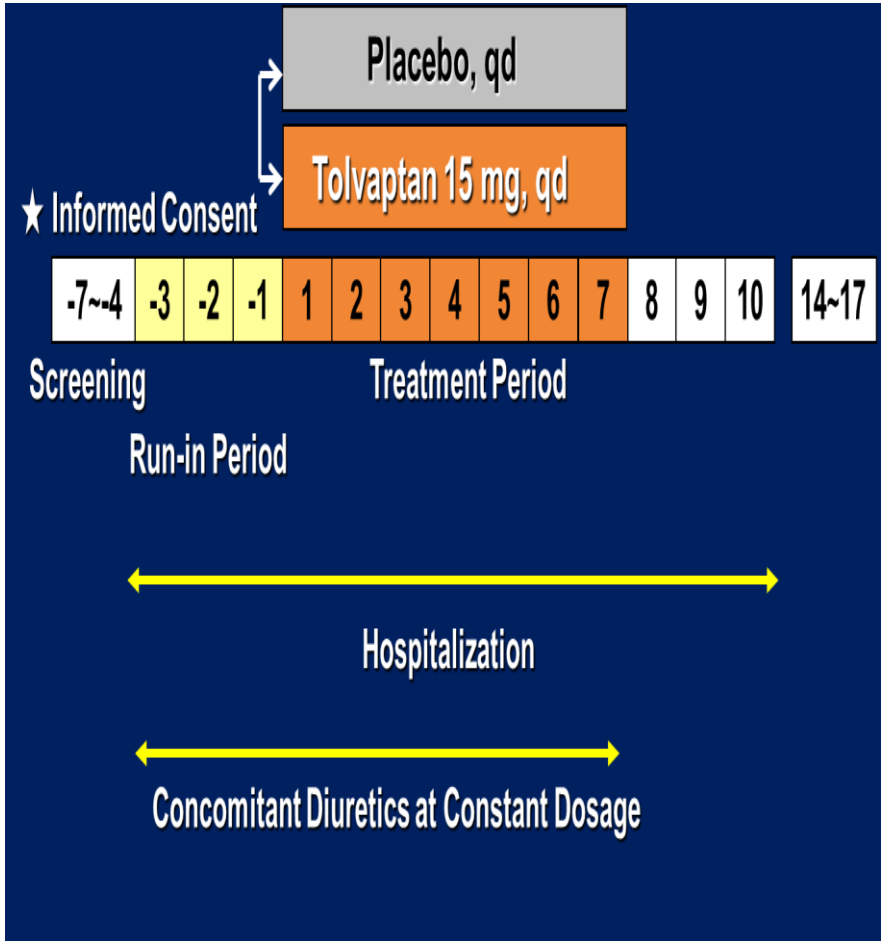
- Role of tolvaptan in acute decompensated HF patients with normonatremia ?
  - @ Effective? the aquaresis function
  - @ Safe ? Na too high?

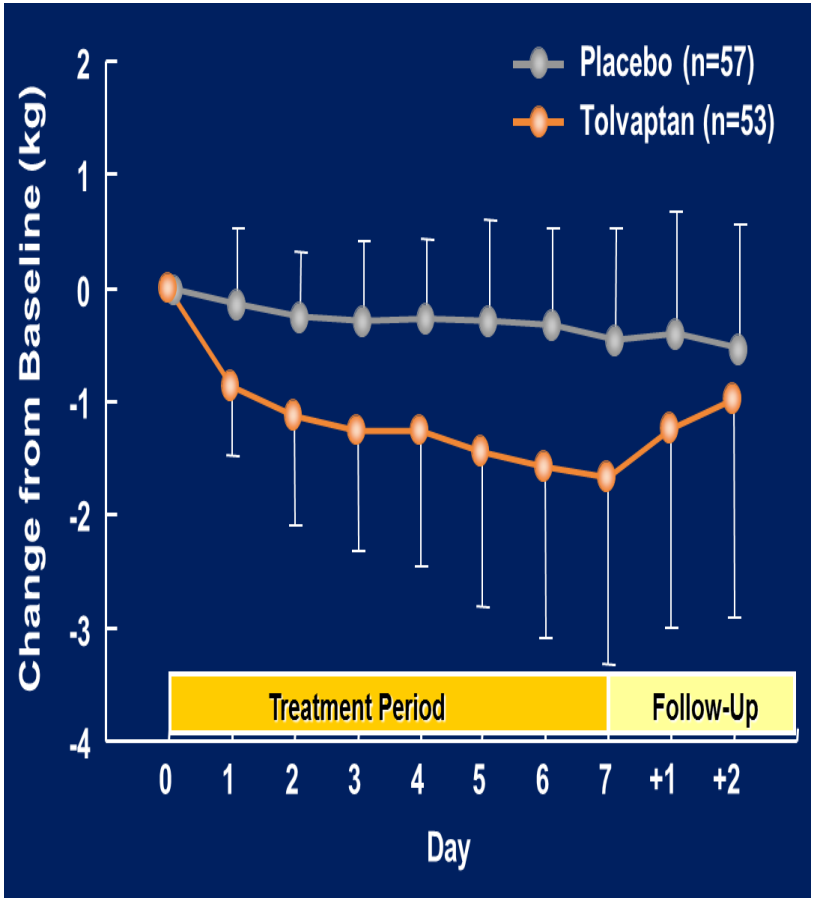
Tolvaptan decrease BW in ADHF

QUEST (Japan)

7 days tolvaptan

Further decrease BW





Masunori Matsuzaki et al. Cardiovasc Drugs Ther. 2011 Suppl 1:S33-45

Approved Indication

Indication(Japan)

Volume overload in heart failure when adequate response is not obtained with other diuretics (e.g., loop diuretics)

Benefit

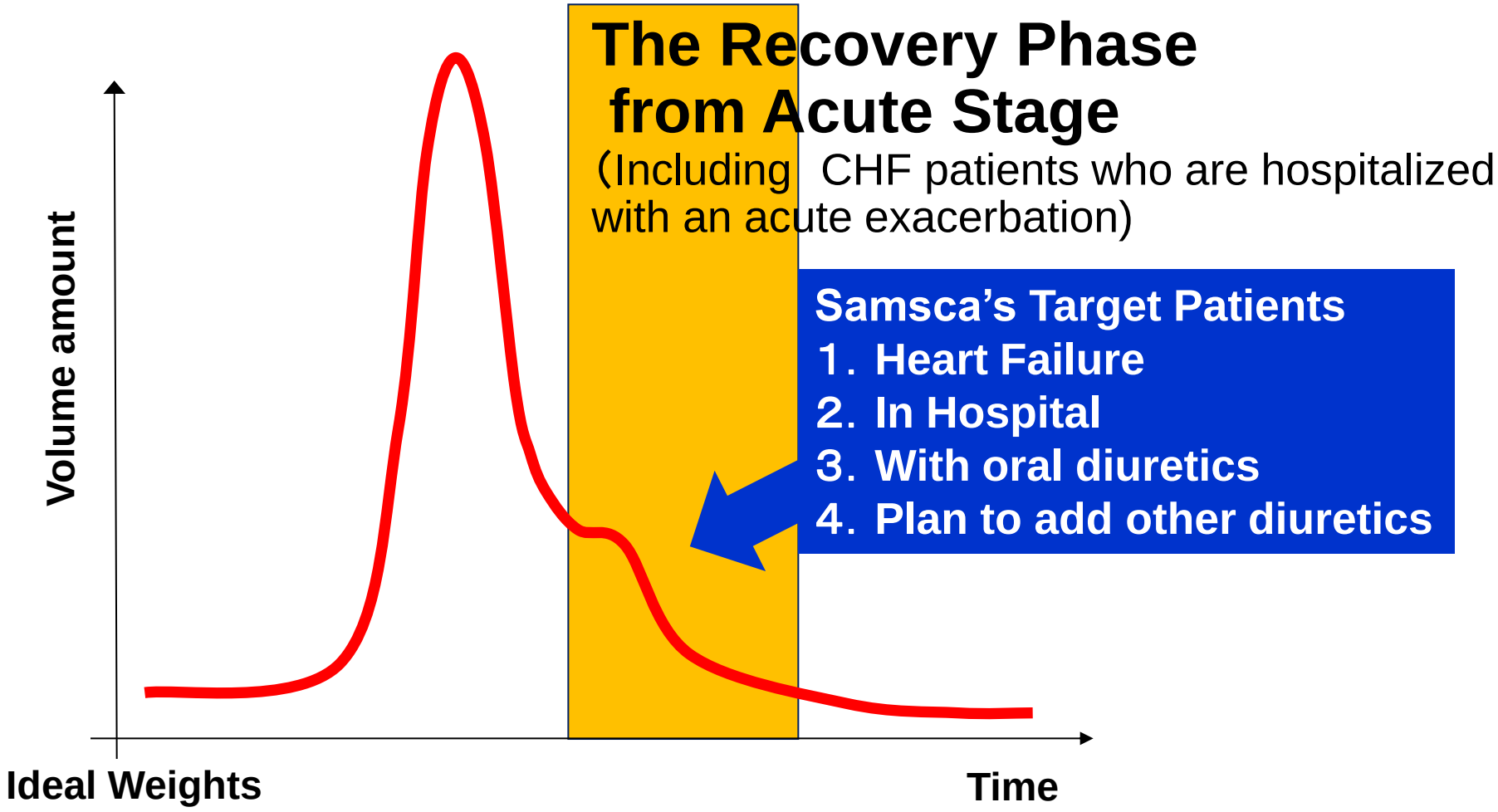
1. **Reliable effect of urine excretion**
2. **No influence on electrolytes**
3. **No influence on blood pressure**
4. **No influence on heart rate**
5. **Little effect on renal function**

@Do not lower Na

@More stable hemodynamic data

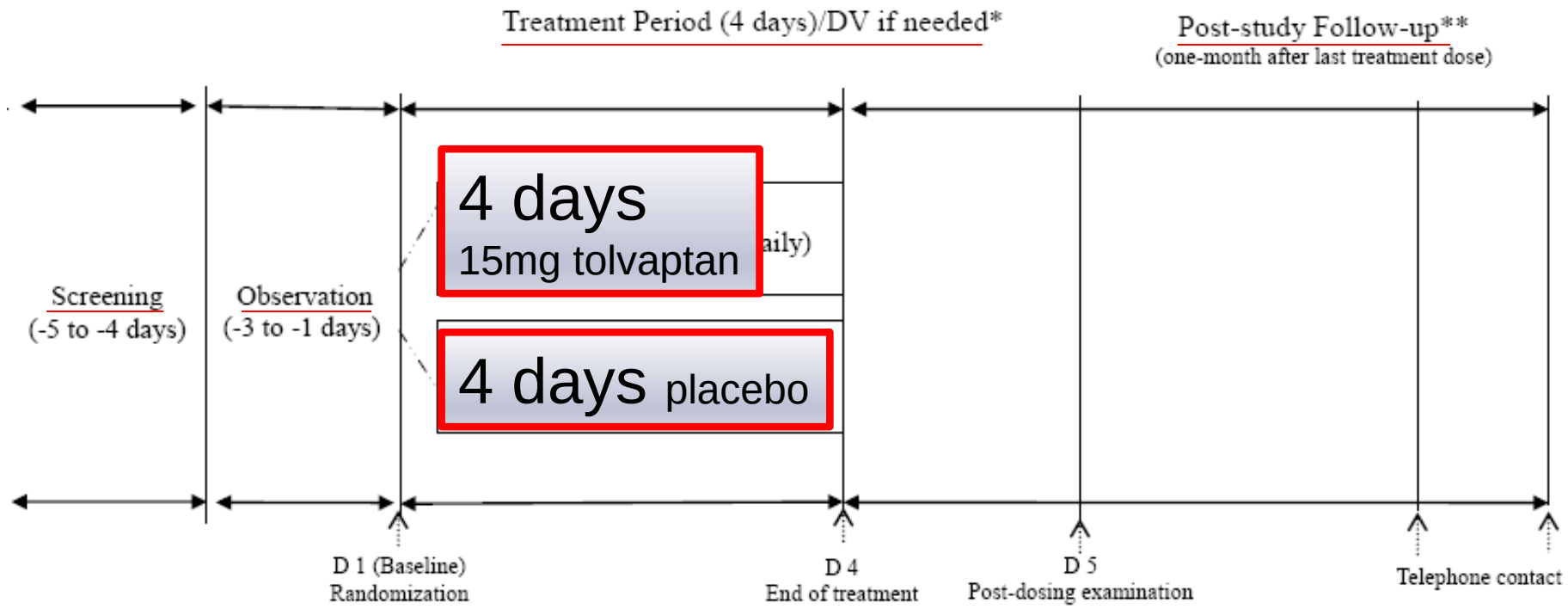
Circulation. 2003;107:2690-2696.

Tolvaptan Phase III Study in Taiwan



Lin YH et al. paper in preparation

Tolvaptan Phase III Study in Taiwan

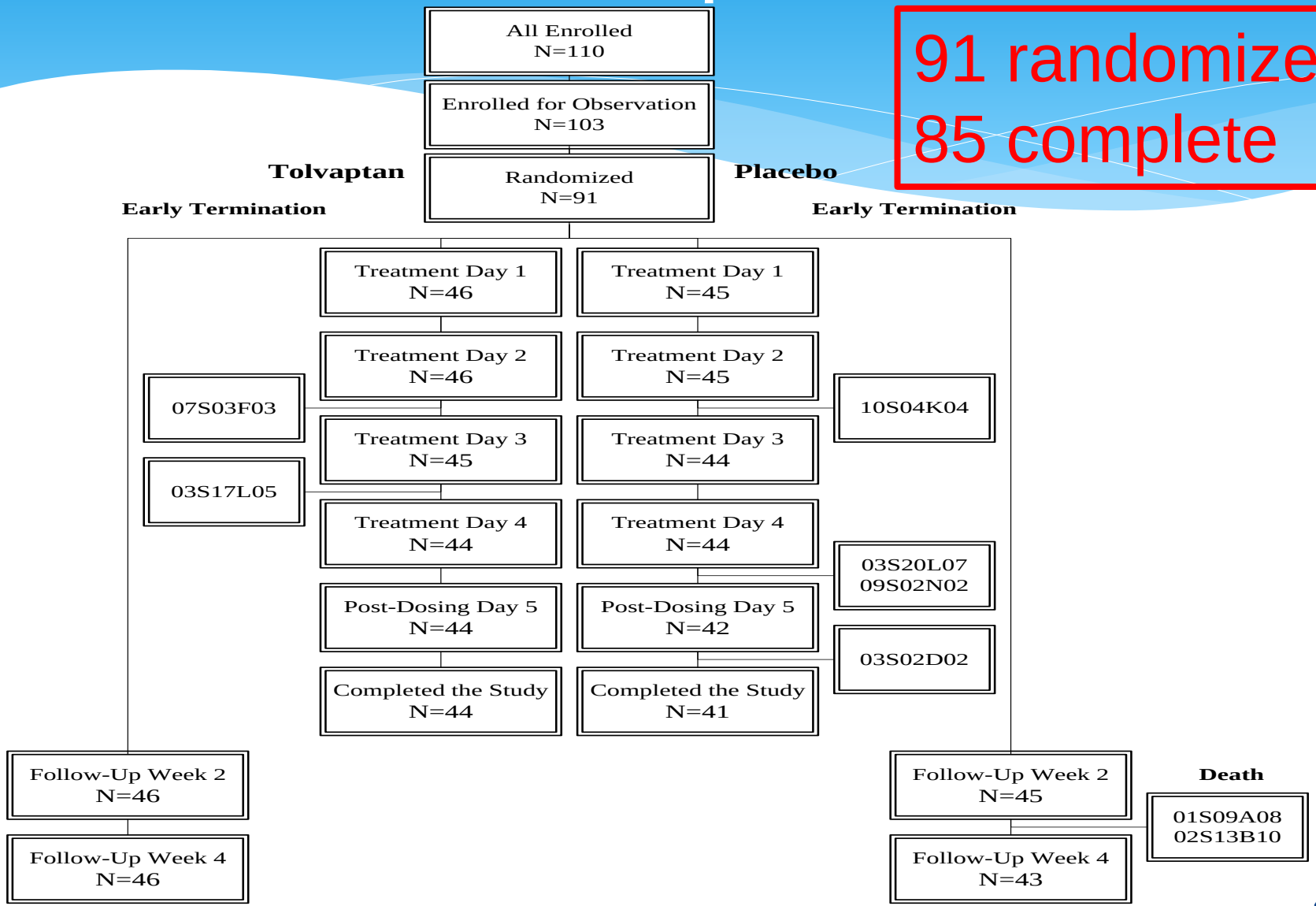


- Primary endpoint
- Mean BW change from baseline (D 1) to D5.

Lin YH et al. paper in preparation

Patient Disposition

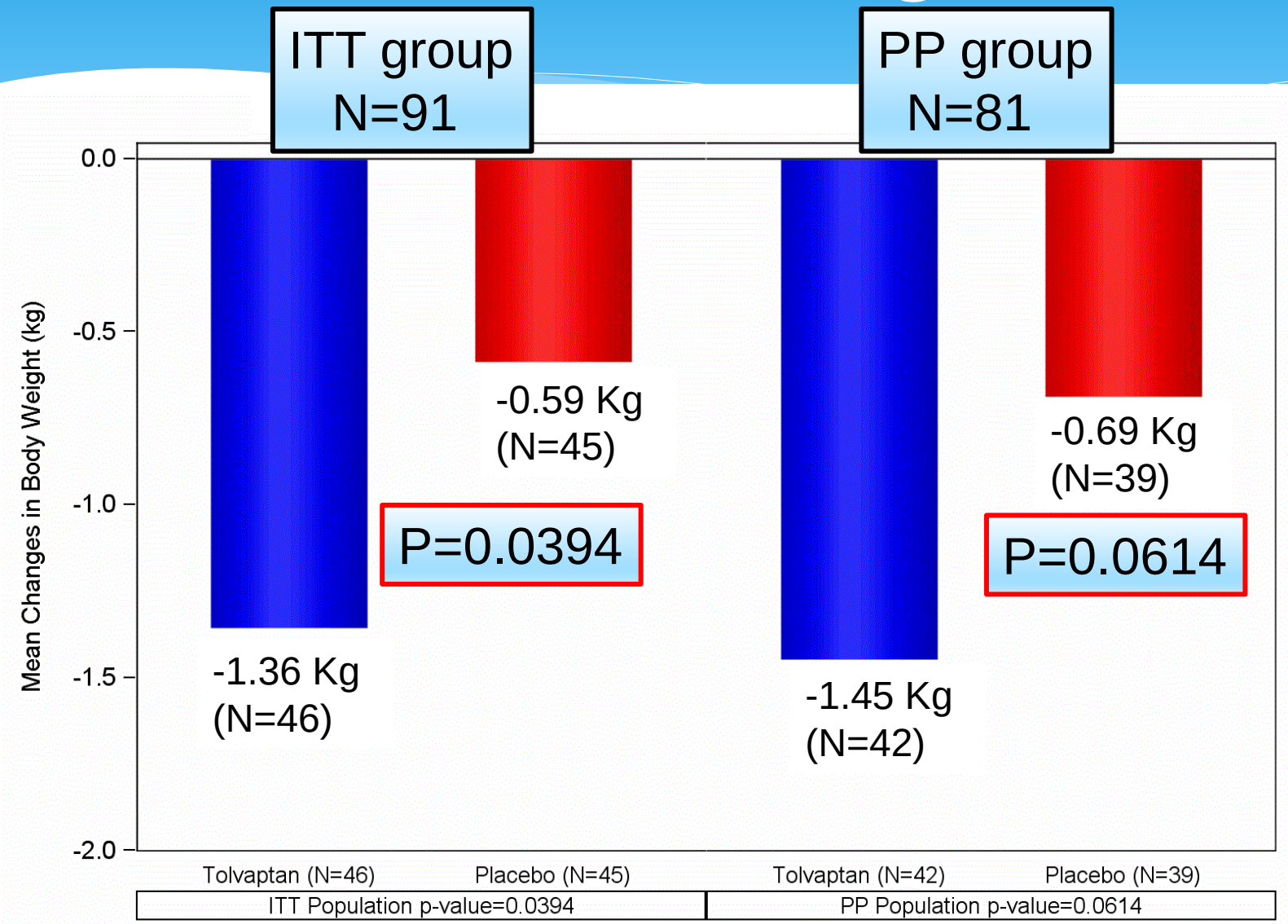
91 randomized
85 complete



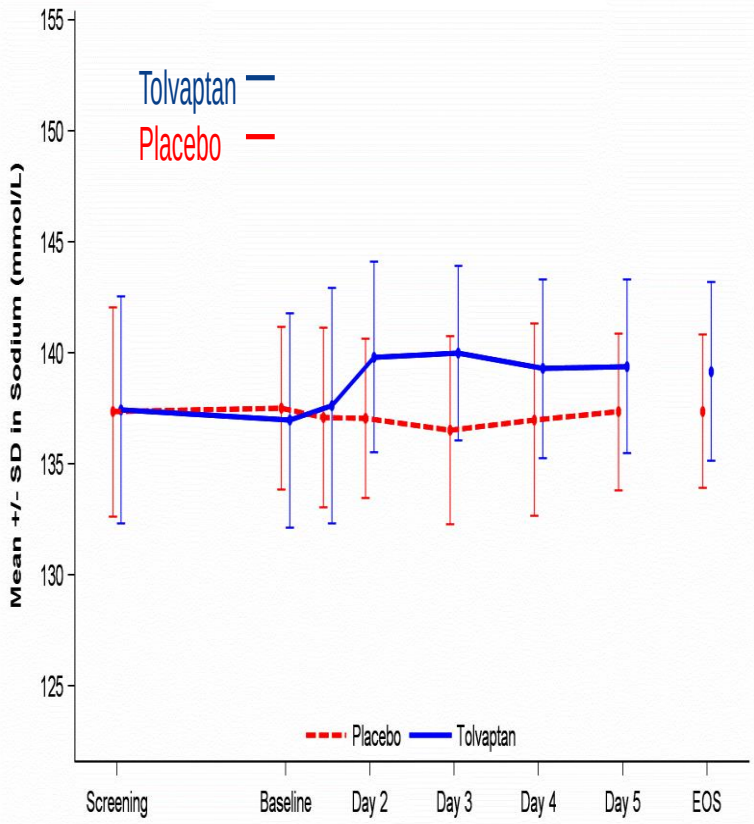
Heart Failure Condition at Baseline

	Tolvaptan N=46	Placebo N=45	P-value
New York Heart Association			
Class II	20 43.5%	22 48.9%	0.1811
Class III	22 47.8%	23 51.1%	
Class IV	4 8.7%	0 0.0%	
Creatinine (mg/dL) Mean (SD)	1.44 (0.55)	1.41 (0.61)	0.8425
Serum Sodium (mmol/L) Mean (SD)	137.0 (4.8)	137.5 (3.7)	0.5618
Serum Potassium (mmol/L) Mean (SD)	3.95 (0.81)	4.16 (0.57)	0.1720

Mean BW Changes

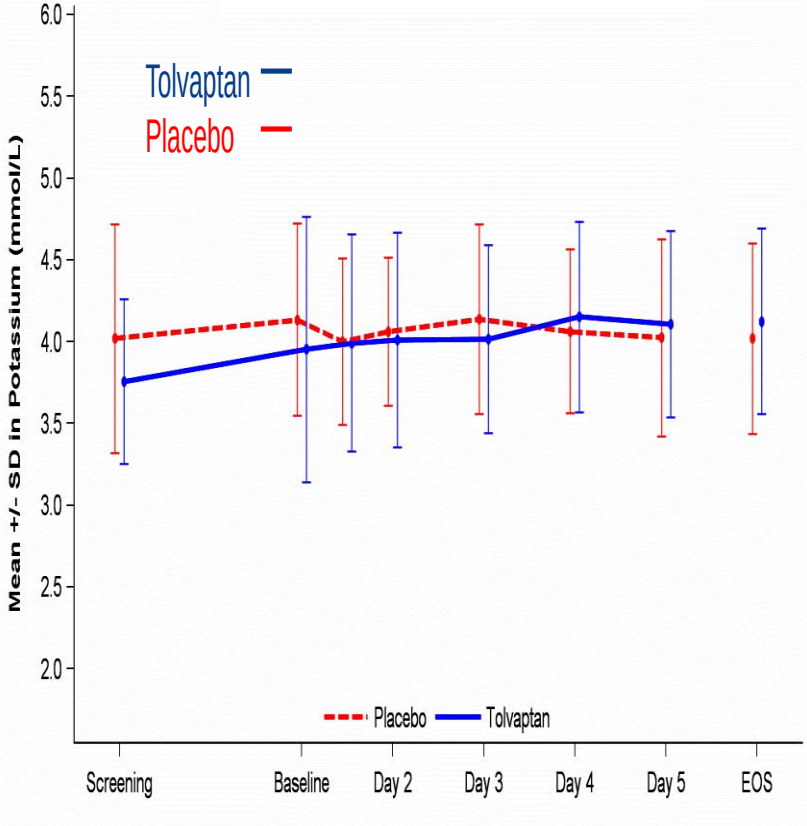


Lin YH et al. paper in preparation



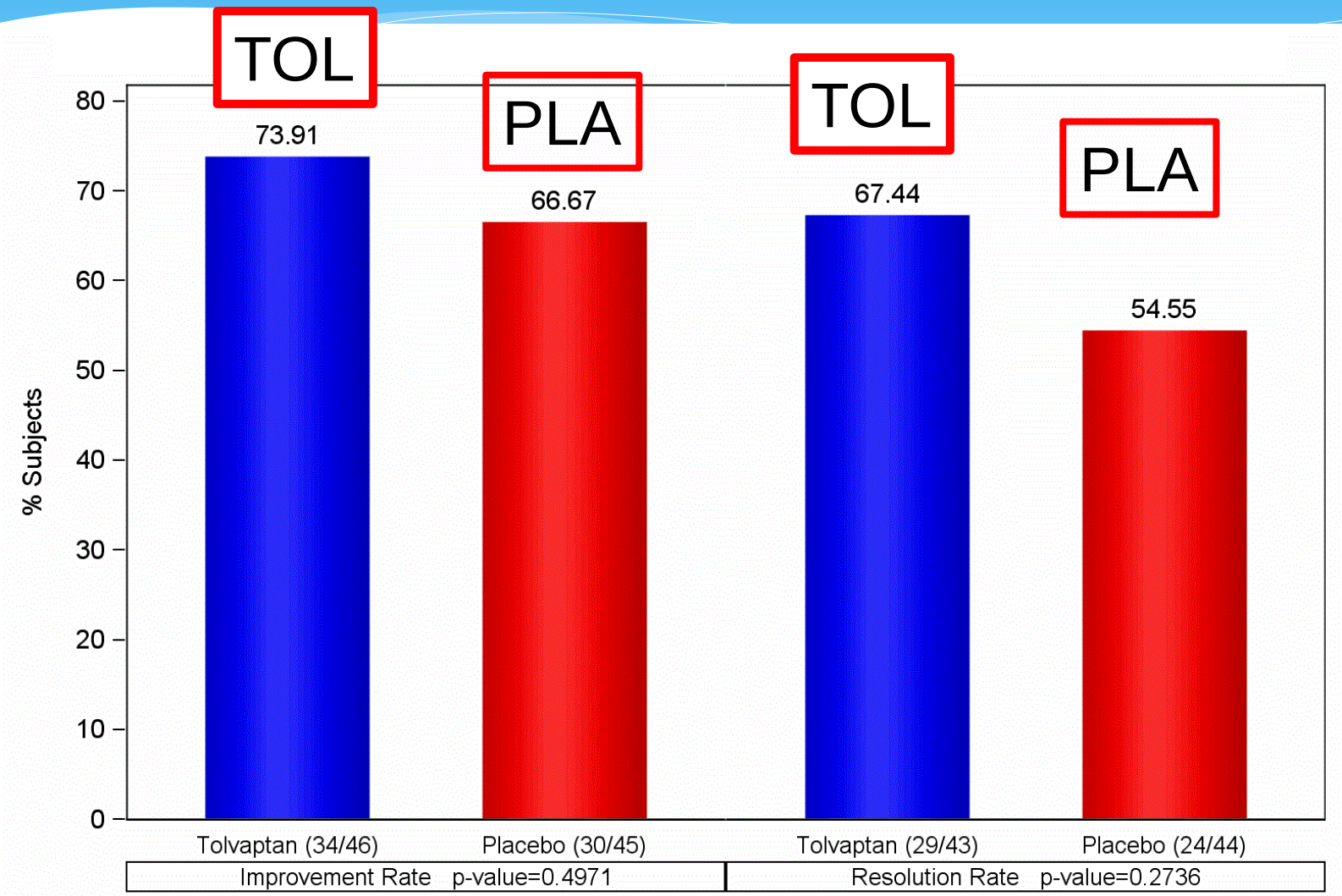
Placebo	137.4	137.5	137.1	137.1	136.5	137.0	137.4	137.4
Tolvaptan	137.5	137.0	137.6	139.8	140.0	139.3	139.4	139.2

None of the subjects showed values of serum sodium exceeding 150 mEq/L during the treatment period.



Placebo	4.02	4.14	4.00	4.06	4.14	4.06	4.02	4.02
Tolvaptan	3.76	3.95	3.99	4.01	4.02	4.15	4.11	4.12

Improvement/Resolution rate in dyspnea



p-value: Fisher's exact test for categorical data

Conclusion

* Tovalptan significantly further decreased body weight (−0.78 kg; p=0.0394)

Summary

- HF: serious dz with high mortality/morbidity -> Avoid HF re-admission / Mortality
- Hyponatremia (on / during admission) is esp harmful
- Aqauresis maybe a better strategy in treating fliud overloaded in HF patients (esp hyponatremia)

Summary : Role of tolvaptan in HF

- @ In hyponatremia patients
- 1. (acute) rapid elevation of Na level
- 2. (acute) Aquaresis
- 3. (Chronic) good effect for symptoms relief
- 4. (Chronic) ->probably good to CV outcome (sub-group)

@ In normonatremic patients

- 1. (acute)-> further aquaresis with good safety
- 2. (chronic) -> no effect in current study

Thanks for your attention