

DECONGESTION TREATMENT IN HEART FAILURE : WHAT IS THE TRICK?

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Primary Goals and Management of Heart Failure

Relieve Symptoms

- Salt restriction
- Diuretics
- Digoxin
- (Vasopressin antagonist ?)

Slow/Reverse Disease Progression

- ACEIs
- Beta blockers
- ARBs
- CRT
- ARNi

Decrease Mortality

- ACEIs
- ARBs
- Beta blockers
- Aldosterone antagonists
- Isosorbide dinitrate + hydralazine
- CRT
- ICD
- Ivabradine
- ARNi



Diuretics for Volume Overload NYHA II-IV HF Patients

Diuretics to relieve symptoms and signs of congestion

If LVEF $\leq 35\%$ despite OMT
or a history of symptomatic VT/VF, implant ICD

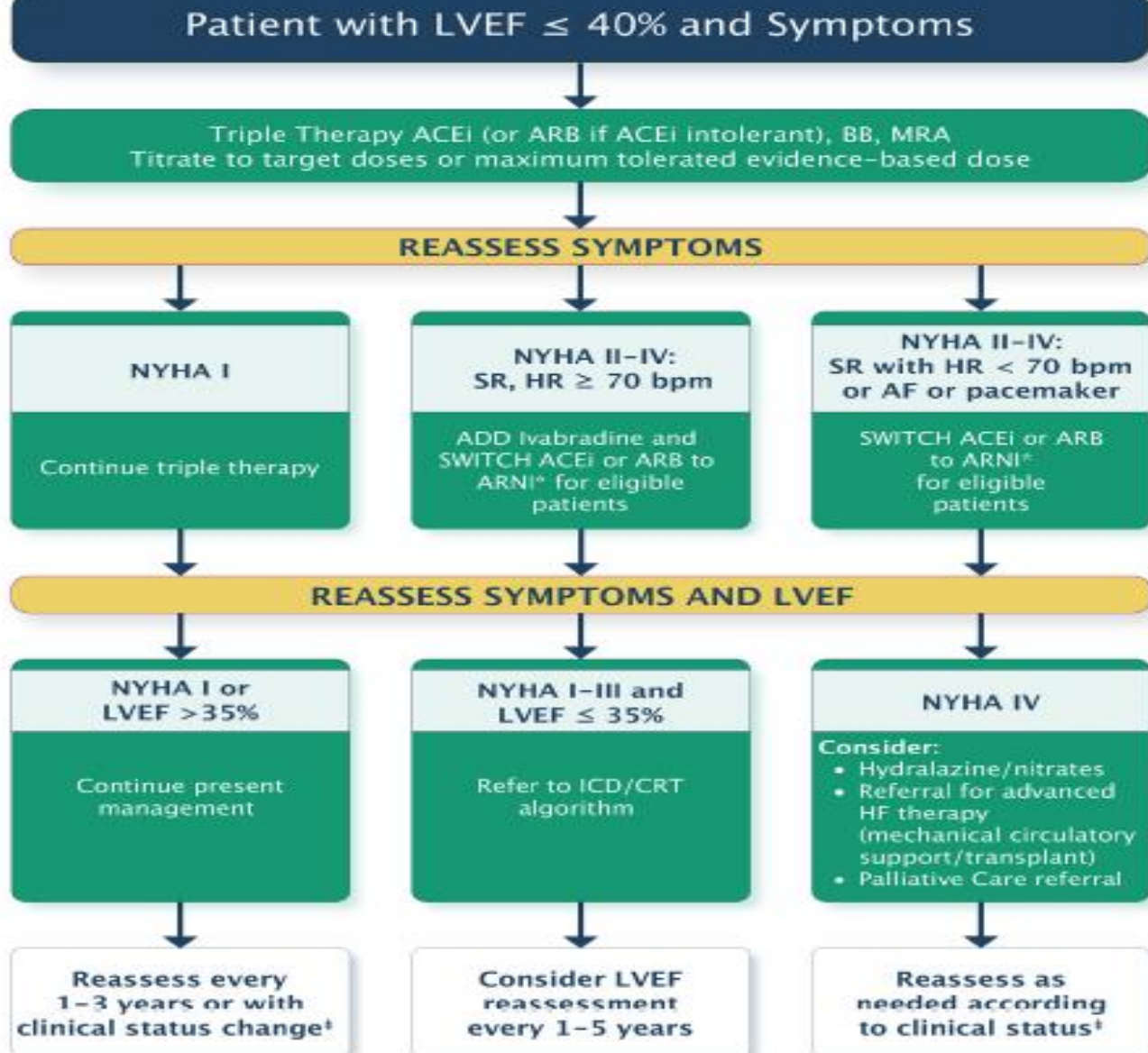
Patient

Therapy
(Up-titrate)

(up-titrate)

Diuretics to Relieve Congestion

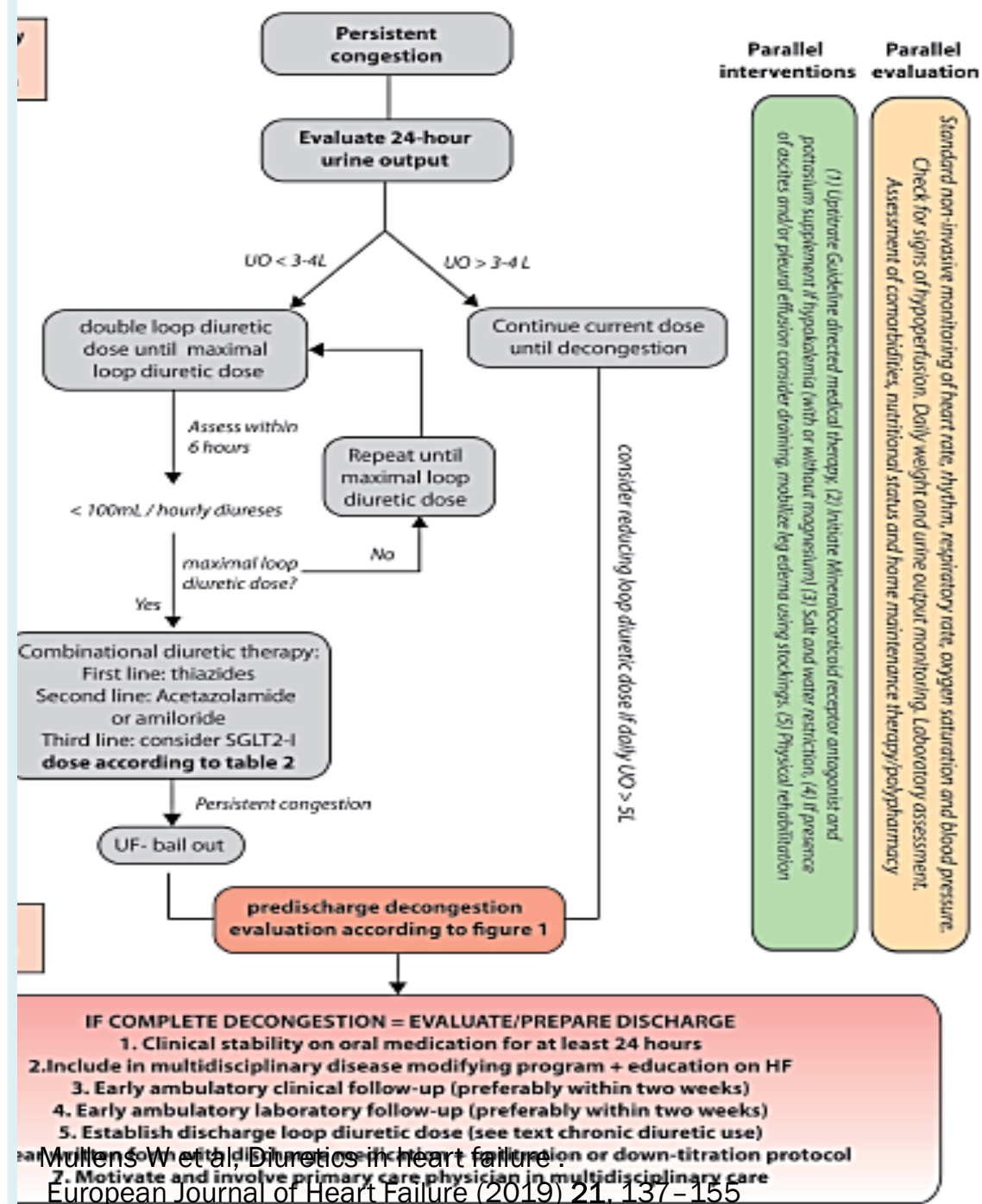
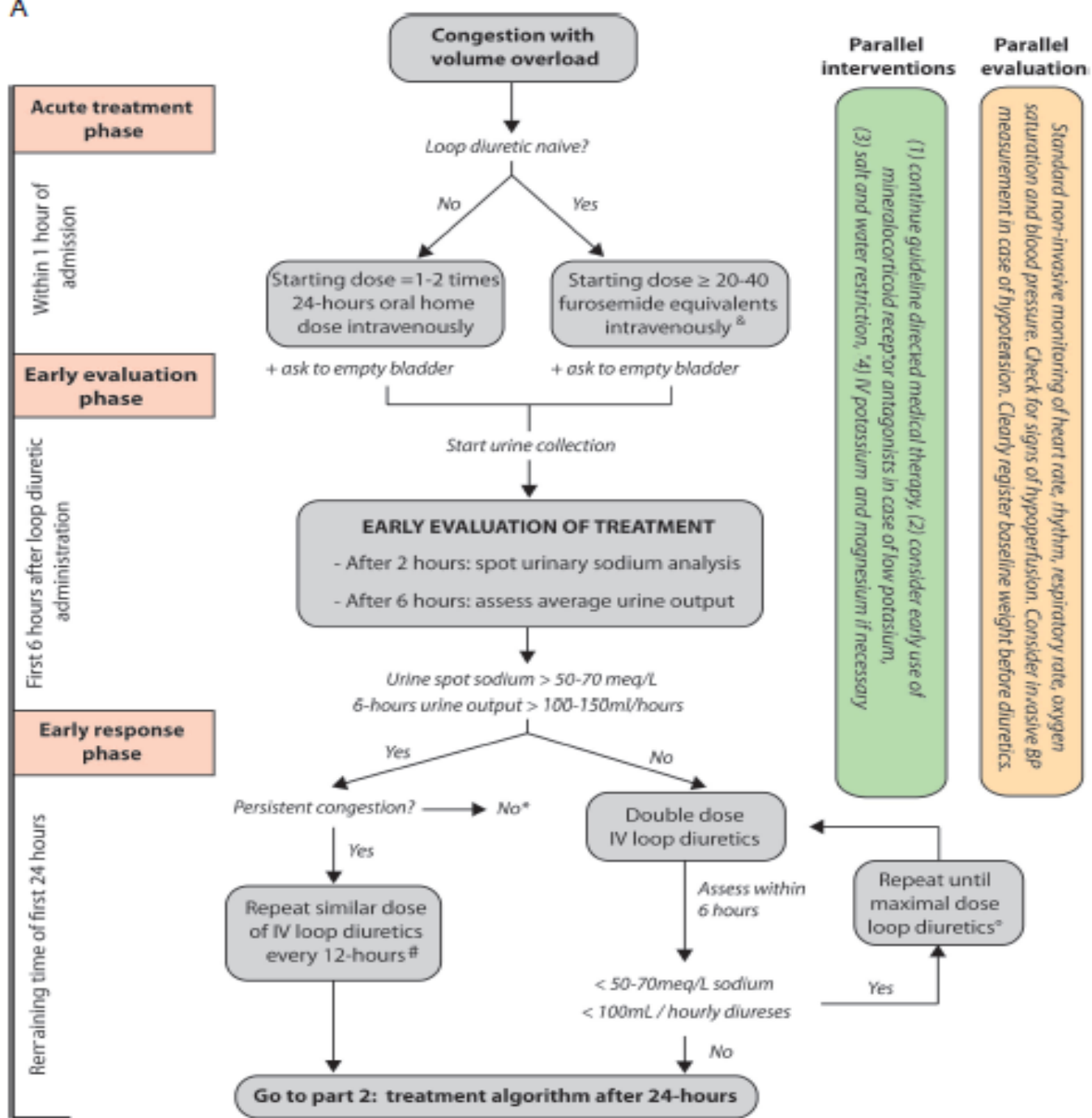
Titrate to minimum effective dose to maintain euvoolemia



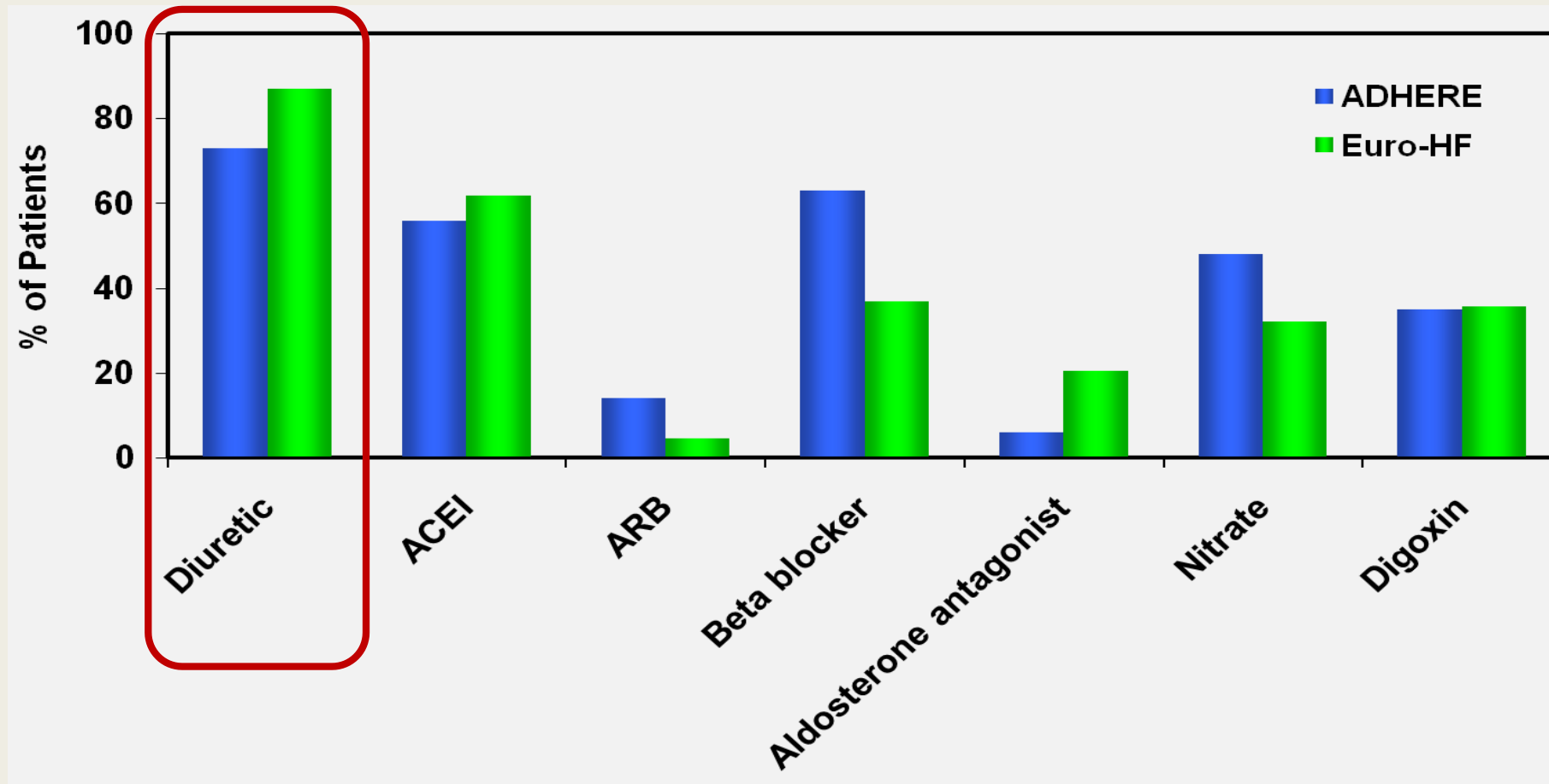
Non-pharmacologic therapies (teaching self care, exercise)

Advance Care Planning and Documentation of Goals of Care

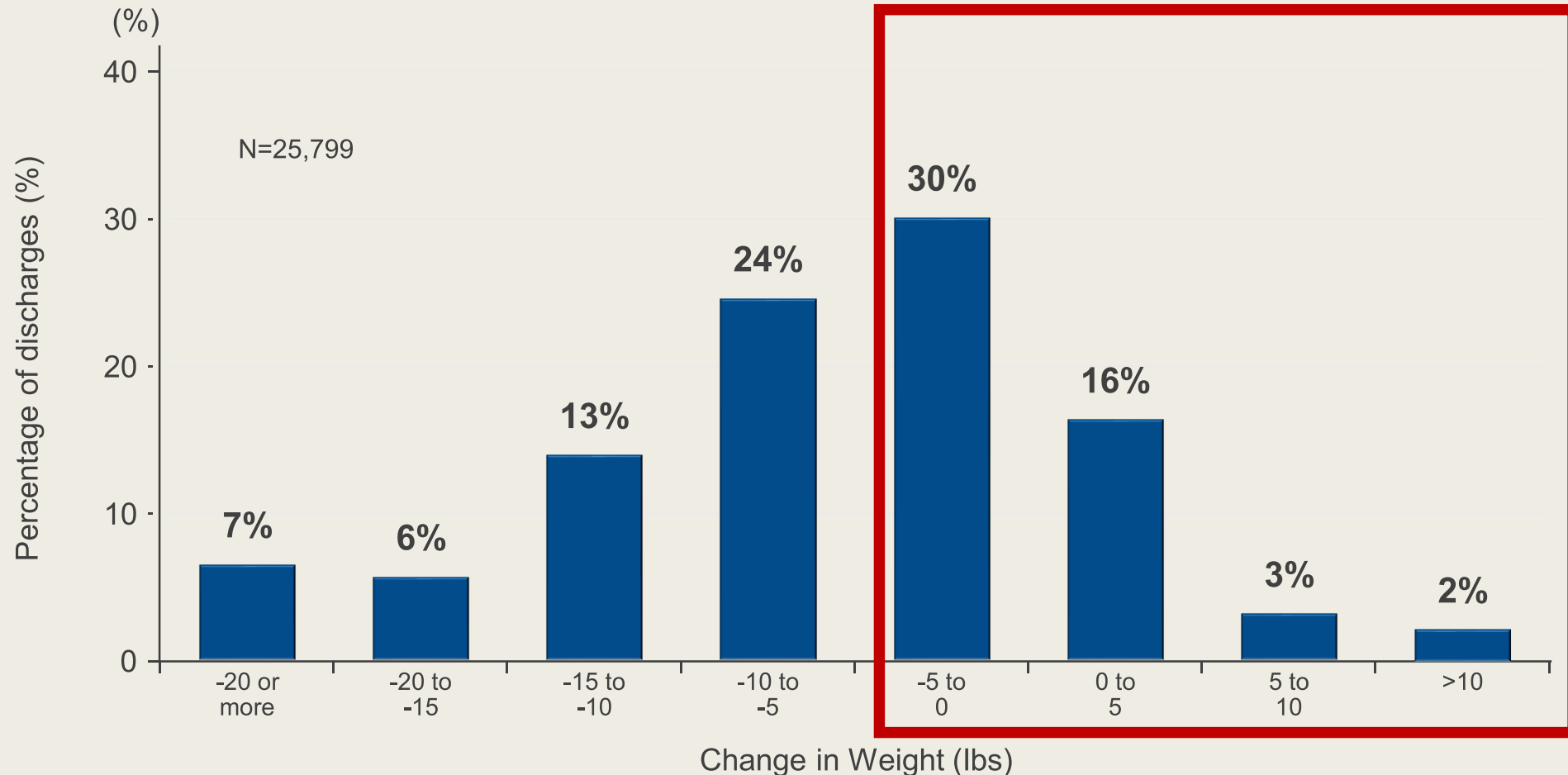
A



Diuretics : Most Common Medication Given to Hospitalized HF Patients



More than 50% of Patients have Little or No Weight Loss During Hospitalization



Loop Diuretics in Acute Decompensated Heart Failure: Necessary? Evil? A Necessary Evil?

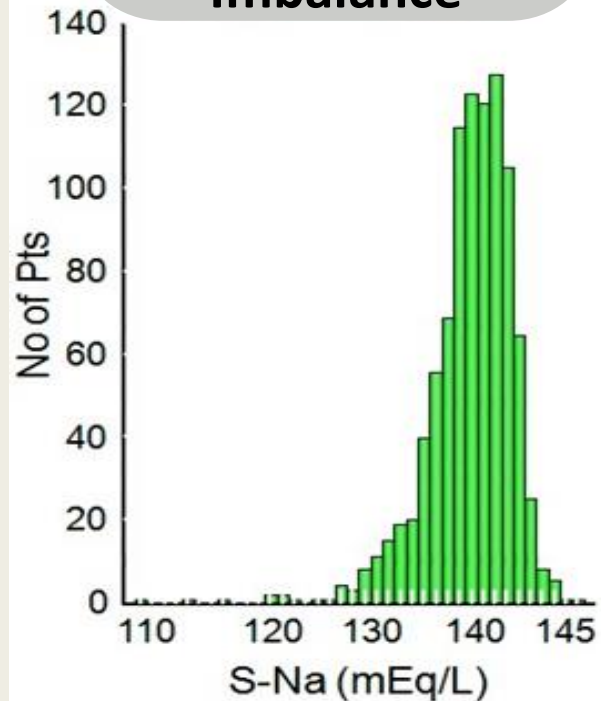
Observational Studies of Diuretics and Outcomes in Heart Failure

| Study | Population | n | Comparison | End Point | Risk | 95% CI |
|---|---|------|--|---|--|-----------------------|
| Studies of Left Ventricular Function ¹⁹ | Left ventricular dysfunction with or without HF | 6797 | Oral diuretics vs none | Mortality | 1.37 | 1.08-1.73 |
| Digitalis Investigation Group ²¹ | Chronic HF | 2782 | Oral diuretics vs none | Mortality | 1.31 | 1.11-1.55 |
| Butler et al ²² | ADHF | 382 | Dose of IV loop diuretics | Worsening renal function (change of 0.3mg/dL) | 1.04 per 20-mg increment of furosemide | 1.004-1.076 |
| Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness ²³ | Advanced HF in-patients | 395 | Dose of IV loop diuretics | Mortality | 1.15 per doubling of dose | 1.025-1.28 |
| Eshaghian et al ²⁴ | Advanced HF in-patients | 1354 | Dose of oral diuretics | Mortality | 3.4 per quartile of dose | 2.4-4.7 |
| Neuberg et al ²⁵ | Chronic HF | 1153 | Diuretic oral dose (<>80mg furosemide) | Mortality | 1.37 for dose above median | Not provided, P=0.004 |
| Philbin et al ²⁶ | ADHF | 1150 | No. of IV diuretic doses | In-hospital mortality | 1.11 per No. of doses | 1.16-1.17 |
| Mielniczuk et al ²⁷ | Chronic HF | 183 | Oral diuretic dose | HF events | 1.53 for dose >80mg | 0.58-4.03 |

Higher doses of diuretics are associated with adverse outcomes!

Limitations of Diuretics

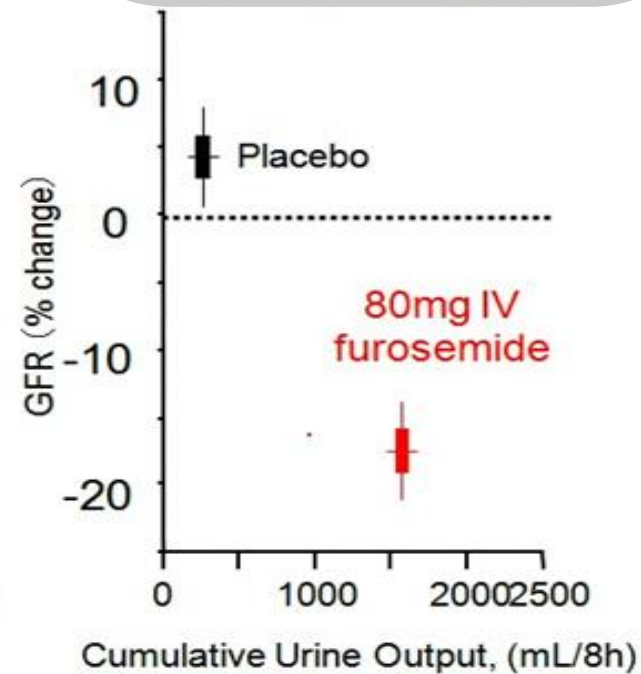
Electrolyte Imbalance



Thiazide diuretics causes HN in 13.7% of patients with HF

Clayton JA, Br J Clin Pharmacol 2006;61:87.

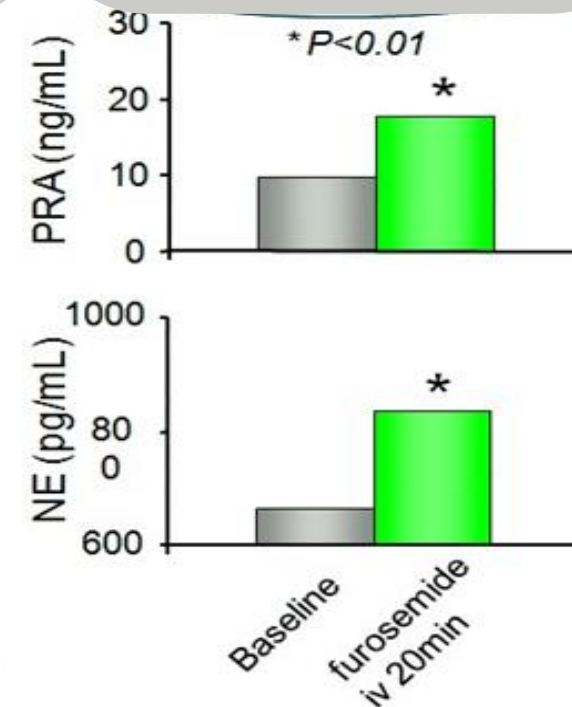
Renal Dysfunction



Loop diuretics increased urine volume, but decreased GFR

Gottlieb SS, Circulation 2002;105:1348.

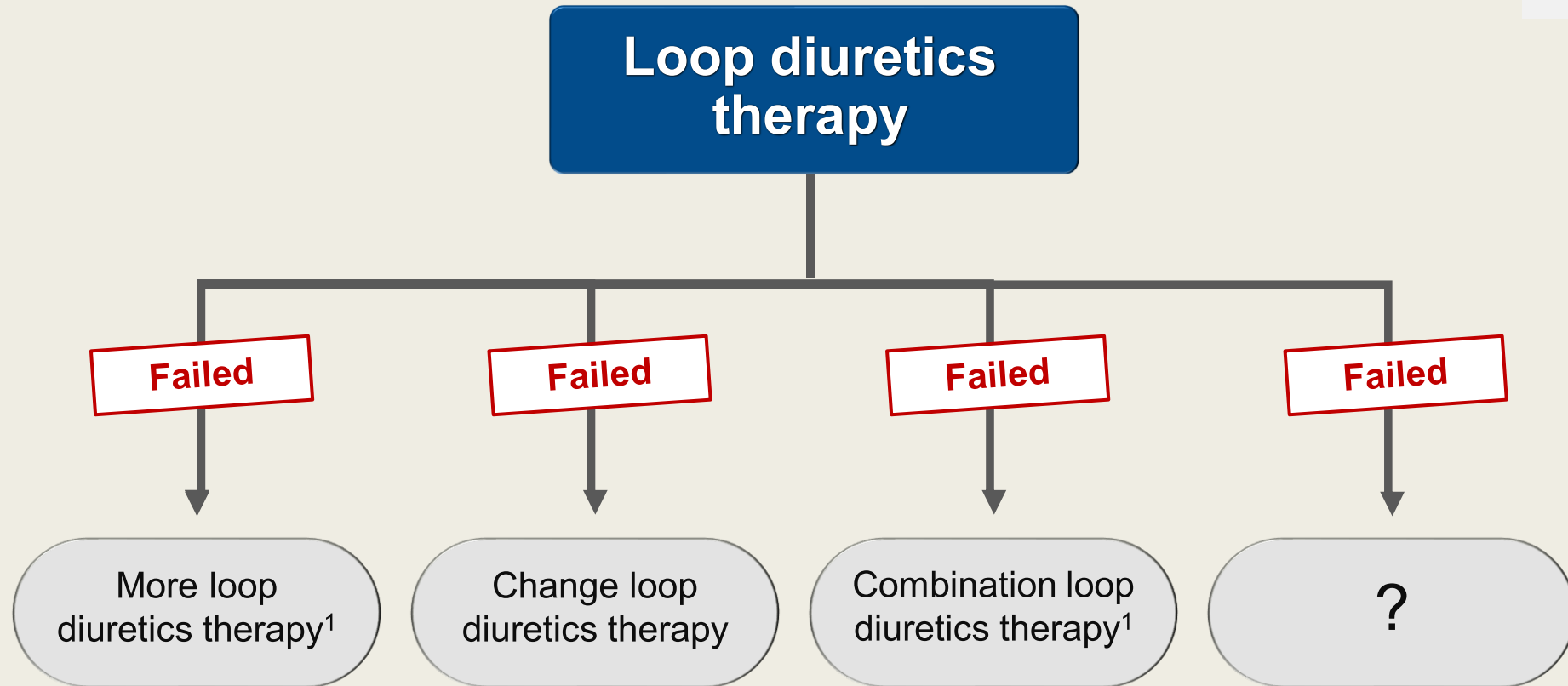
NH Activation

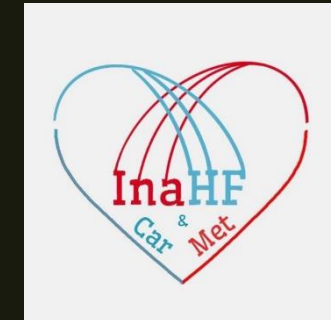


After administration of loop diuretics, PRA and NE increased

Francis GS, Ann Intern Med 1985;103:1.

Conventional Treatment Regimen for Congestion in AHF





IS THERE A ROLE FOR AQUARETICS IN HF BEYOND HYPONATREMIA?

New Japanese Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure 2017

急性・慢性心不全診療ガイドライン (2017年改訂版)

Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/JHFS 2017)

- I. Vasopressin antagonist is “the only diuretic” for acute HF whose evidence level is A.
- II. Vasopressin antagonist is to be used (chronic) when the treatment by other diuretics is ineffective, regardless of EF.
- III. Vasopressin antagonist can be safely used for patients with impaired renal function.

急性・慢性心不全診療ガイドライン (2017年改訂版) Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/JHFS 2017)

X. Acute Heart Failure

4. Drug for treatment

4.4. Cardiotonic・vasopressor drugs

4.4.2. ジギタリス

Table 58. Recommended diuretics and evidence levels for acute heart failure

| | Recommend ed class | Evidence level | Minds recommen ded grade | Minds evidence classification |
|--|--------------------|----------------|--------------------------|-------------------------------|
| Diuretic | | | | |
| Loop diuretic | | | | |
| IV and oral administration for excess water retention in acute heart failure | I | C | B | II |
| Long-acting IV when there is resistance to the one-time IV | IIa | B | B | IVb |
| Vasopressin v2 receptor antagonist (tolvaptan) | | | | |
| To be administered for excess water retention when the treatment by other diuretics including loop diuretics is ineffective (excluding hyponatremia) | IIa | A | B | II |
| Administration for Volume overload with Hyponatremia | IIa | C | C1 | II |
| MRA | | | | |
| Co-administration when loop diuretics is not effective | IIb | C | C1 | III |
| Administration for hypokalemia with preserved RF | IIa | B | B | II |
| Administration for hyperkalemia with WRF | III | C | D | VI |
| Thiazide diuretic | | | | |
| Co-administration when loop diuretics is not effective | IIb | C | C1 | III |

IX. 併存症の病態と治療

8. CKD - 心腎症候群

8.2 治療 (表41)

8.2.6 主に急性心不全、急性増悪時に使用される薬剤

トソプレシンは受容体拮抗薬である。トソプレシンが新薬市場として広く使用されるようになっている。EVERESTのサブ解析²⁰⁾では、腎機能低下患者で腎機能悪化・血圧低下をきたさずに安全に使用できるとされており、

IX. Pathology and Treatment of Comorbidities

8. CKD - Cardio renal syndrome

8.2. Treatment

8.2.6. Drug mainly used for heart failure with acute exacerbation.

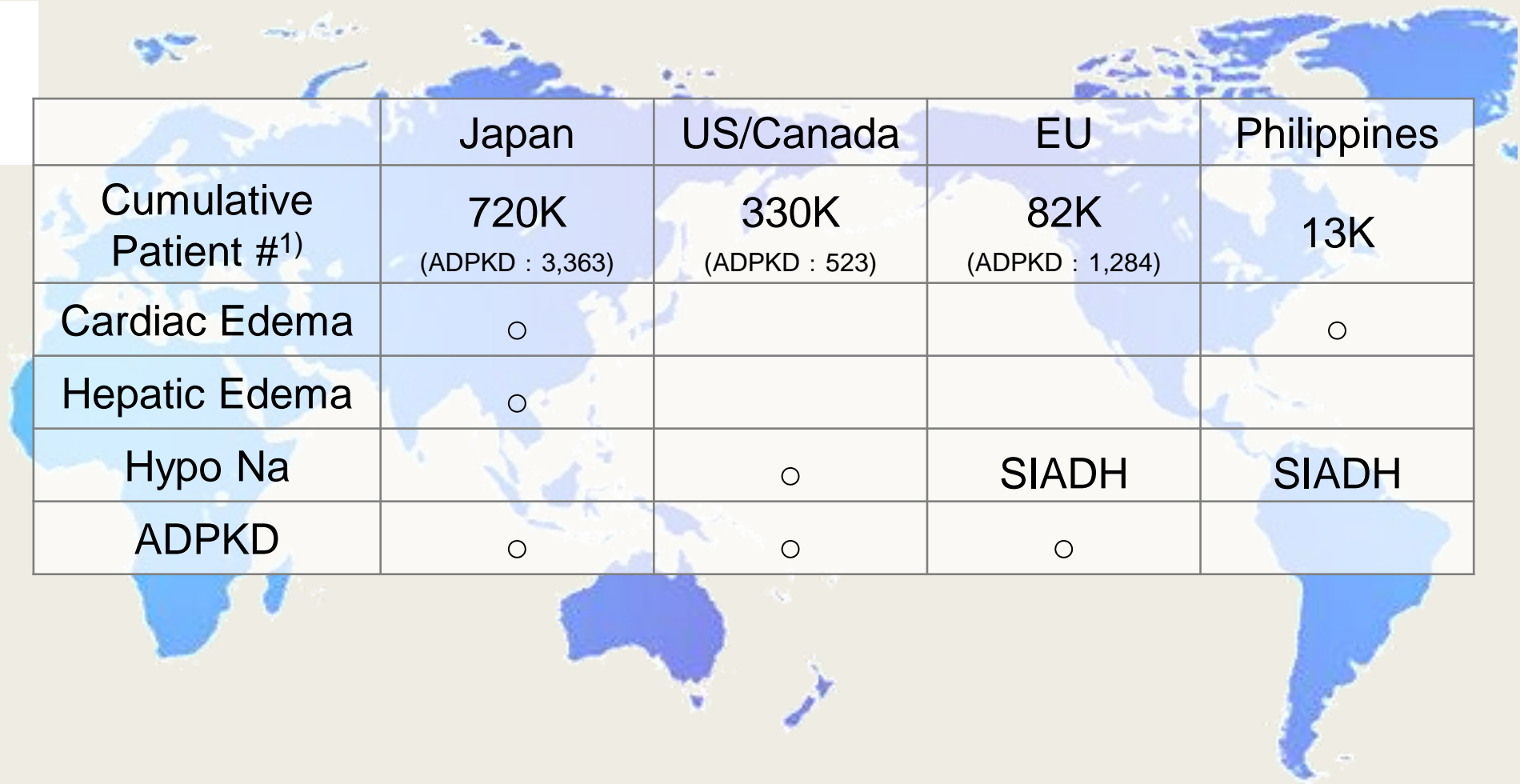
Tolvaptan, a vasopressin V₂ receptor antagonist, is becoming widely used as a diuretic. According to EVEREST sub analysis, tolvaptan can be safely used for patients with impaired renal function.

Table 4. Recommendations regarding diuretic use in patients with AHF

| Recommendations | COR | LOE |
|---|------------|----------|
| Intravenous loop diuretic is recommended in patients with signs and symptoms of fluid overload to reduce congestive symptoms. | I | C |
| In patients not receiving oral diuretics, an initial 20 to 40 mg intravenous dose of furosemide is recommended. In those receiving oral diuretics, an initial equivalent dose of intravenous furosemide is recommended. | I | B |
| Intravenous loop diuretics can be given either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patient symptoms and clinical status. | I | C |
| Regular daily monitoring of urine output, body weight, renal function, and electrolytes is recommended during the use of intravenous diuretics. | I | C |
| Intravenous loop diuretic dose should be adjusted according to patient renal function. | IIa | C |
| In patients with insufficient diuretic response... | | |
| Increase the dose of loop diuretics. | I | B |
| Re-evaluate patient clinical status for tissue perfusion and volume status. | I | C |
| Low sodium diet (sodium<2 grams/day) is recommended in patients with recurrent or refractory volume overload despite appropriate diuretic therapy. | I | C |
| Tolvaptan (V2-receptor antagonist) should be considered in patients with congestion and/or hyponatremia. It should be given for a short duration. | IIa | B |
| Switch from intermittent bolus to continuous infusion of loop diuretics. | IIa | C |
| Combination of loop diuretic with either thiazide-type diuretic or spironolactone should be considered in patients with insufficient diuretic response. | IIa | C |
| Ultrafiltration may be considered in patients with refractory congestion who fail to respond to a diuretic-based strategy. | IIb | B |

Tolvaptan Global Approval/Launch Status

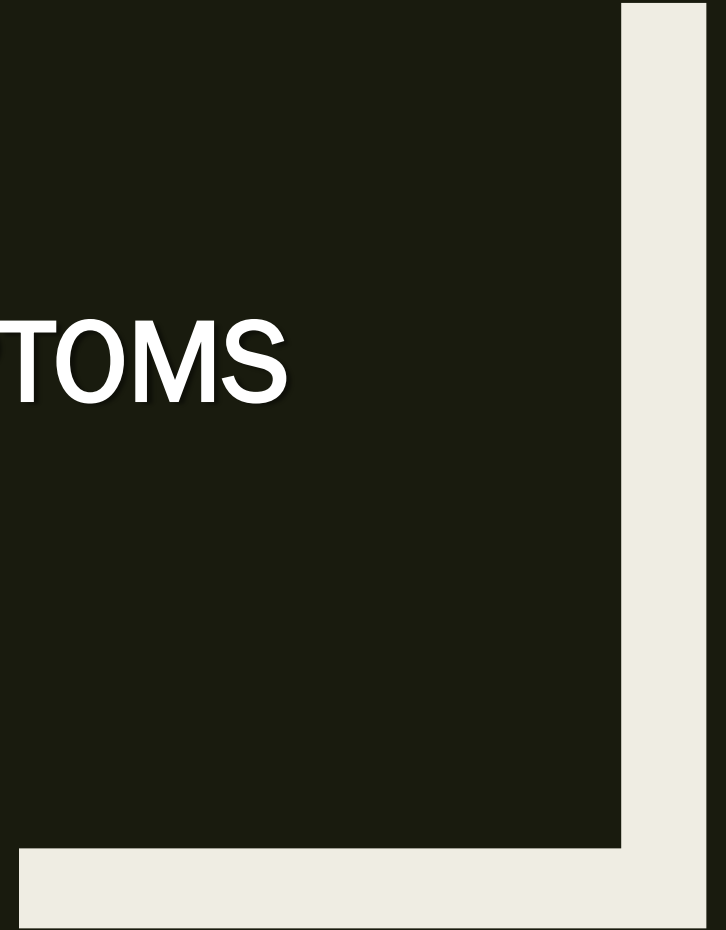
Launched in 25 and approved in more than 40 countries



| | Japan | US/Canada | EU | Philippines |
|------------------------------------|-------------------------|-----------------------|------------------------|-------------|
| Cumulative Patient # ¹⁾ | 720K (ADPKD : 3,363) | 330K (ADPKD : 523) | 82K (ADPKD : 1,284) | 13K |
| Cardiac Edema | ○ | | | ○ |
| Hepatic Edema | ○ | | | |
| Hypo Na | | ○ | SIADH | SIADH |
| ADPKD | ○ | ○ | ○ | |

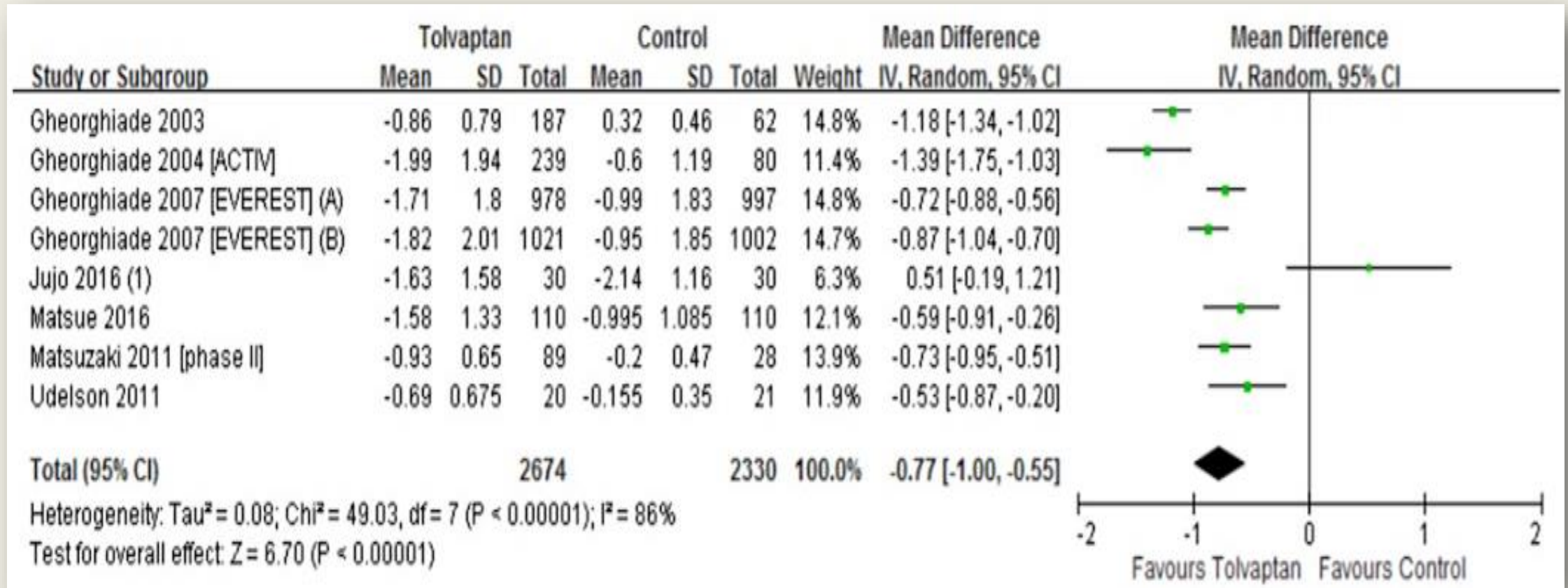
1) Cumulative Patient: estimate as of Mar 2017、ADPKD: as of Feb 2017

RELIEF OF SYMPTOMS



Effects of Tolvaptan in Patients with Acute Heart Failure: A Systematic Review and Network Meta-analysis

Efficacy Outcome: Body Weight Change at 24 Hours

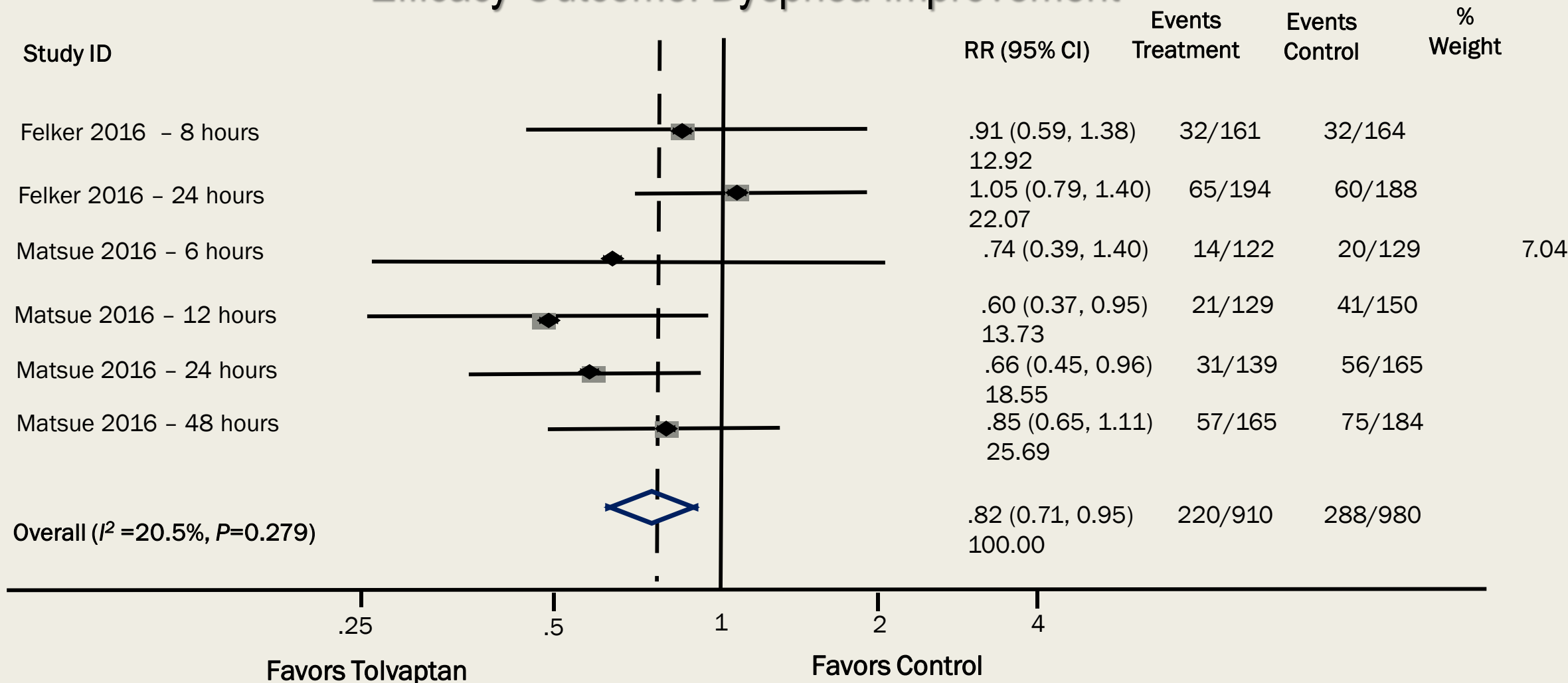


Footnotes:

(1)Tolvaptan group: hold furosemide; Control group: furosemide 40mg IV)

Effects of Tolvaptan in Patients with Acute Heart Failure: A Systematic Review and Meta-analysis

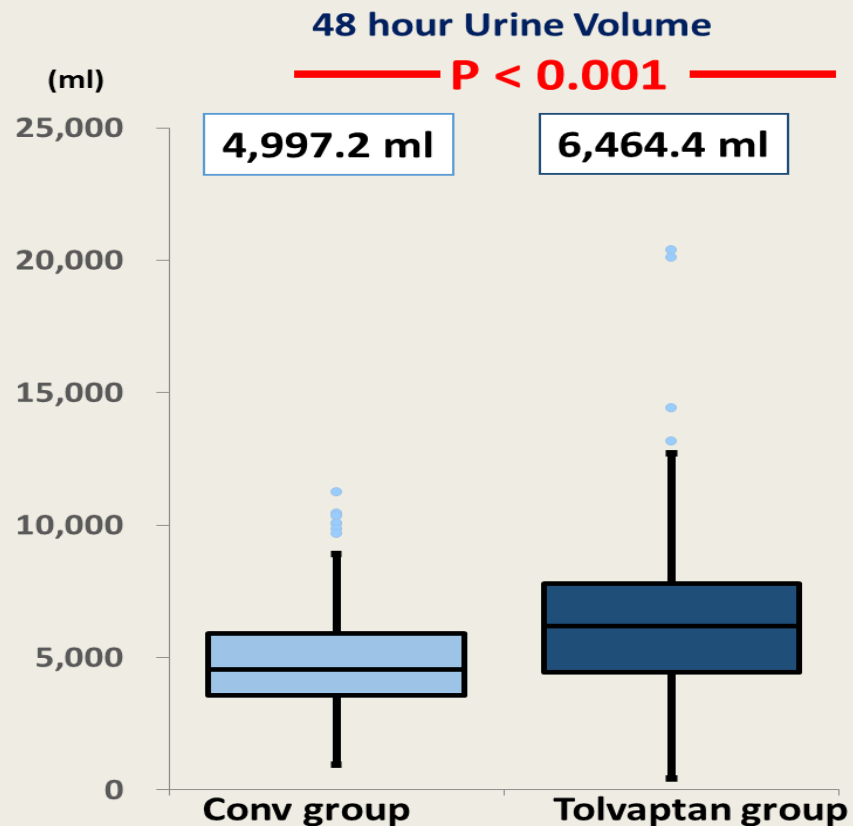
Efficacy Outcome: Dyspnea Improvement



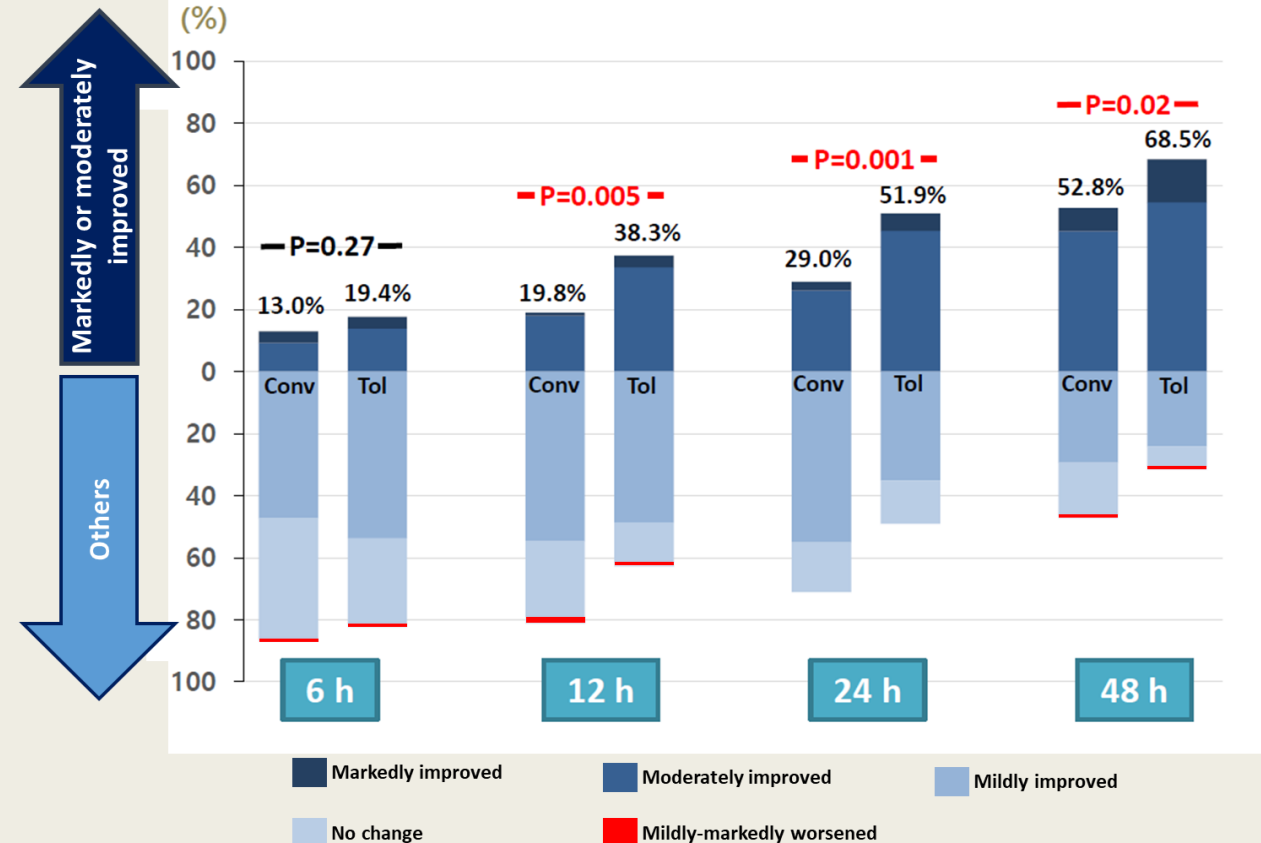
**EFFECT ON RENAL FUNCTION
/DECREASED DIURETIC USE**

AQUAMARINE: Tolvaptan Resulted to More Urine Volume and Dyspnea Relief vs. Conventional Therapy in AHF w/ Renal Dysfunction

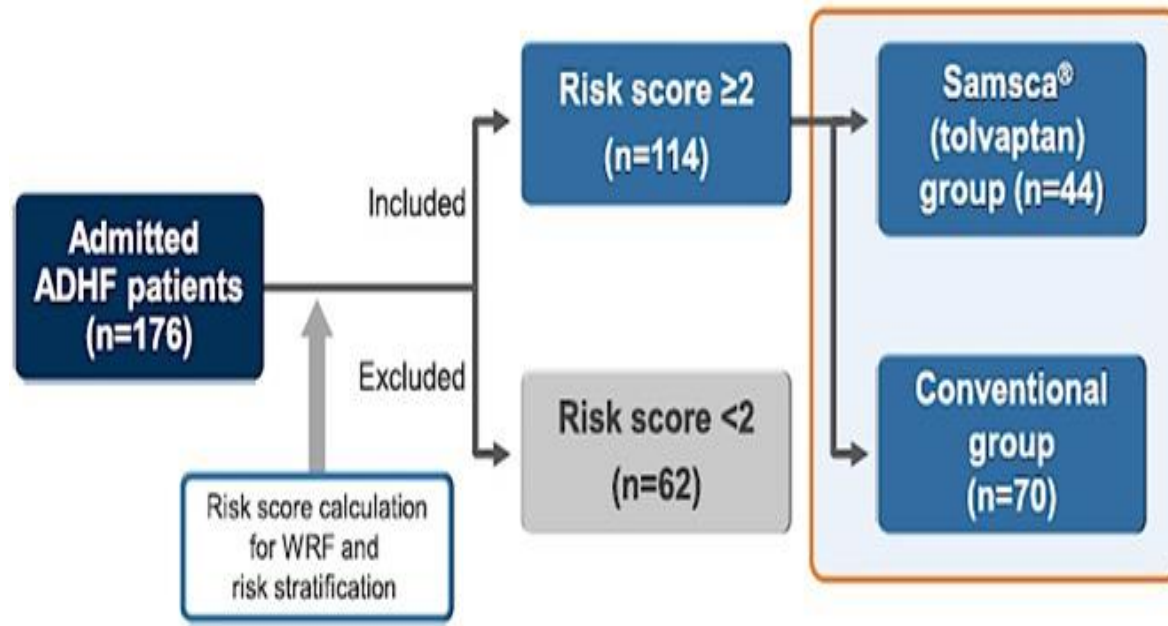
Tolvaptan significantly resulted to more urine volume



Tolvaptan significantly improved dyspnea as early as 12 hours of initiation



KAMEDA Trial: Tolvaptan Reduced the Risk of WRF in Patients with ADHF in High-Risk Population

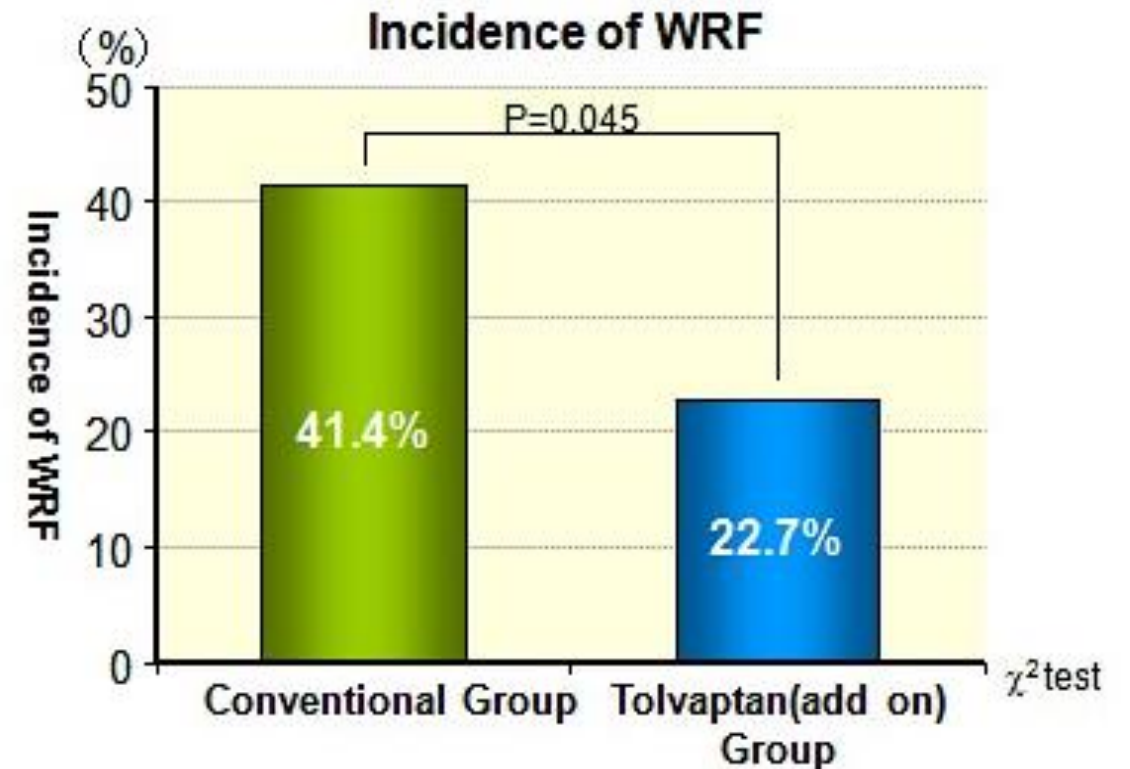


Risk Scoring:

| | |
|--------------------------------|--------------|
| Hx of HF, DM & SBP >160mmHg: | 1 point each |
| S Creatinine 1.5–2.4 mg/dL : | 2 points |
| S Creatinine ≥ 2.5 mg/dL: | 3 points |

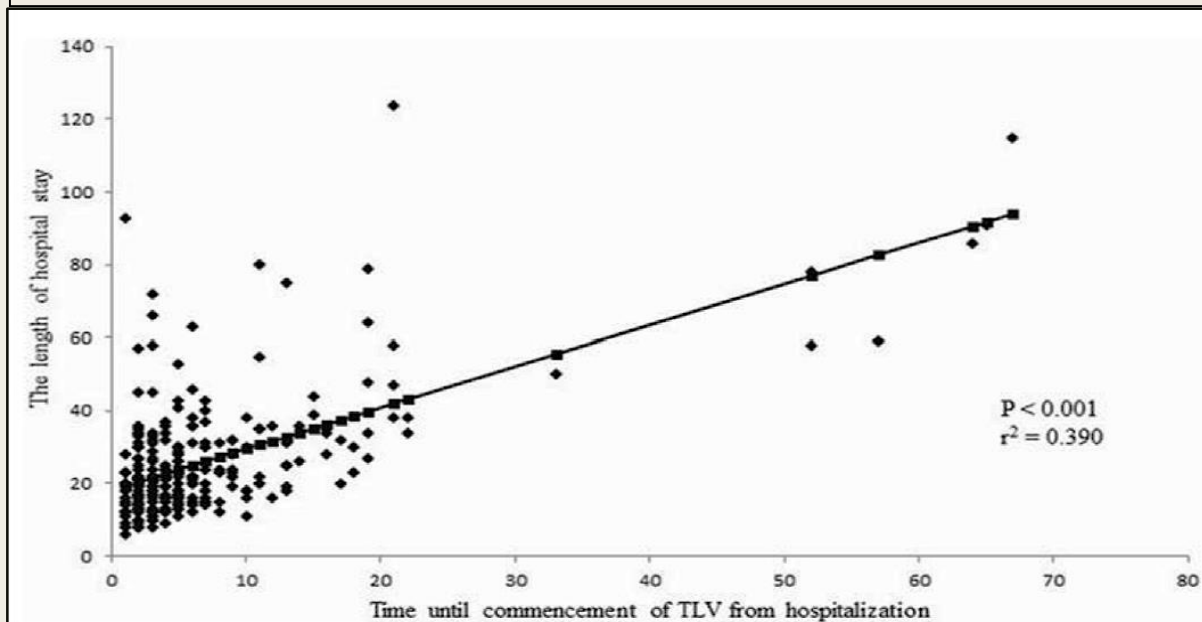
Primary Endpoint: Incidence of WRF (S Crea elevation of > 0.3 mg/dL or 50% above baseline in 48hrs)

Secondary Endpoint: Urine volume, Furosemide dose, BNP change from baseline



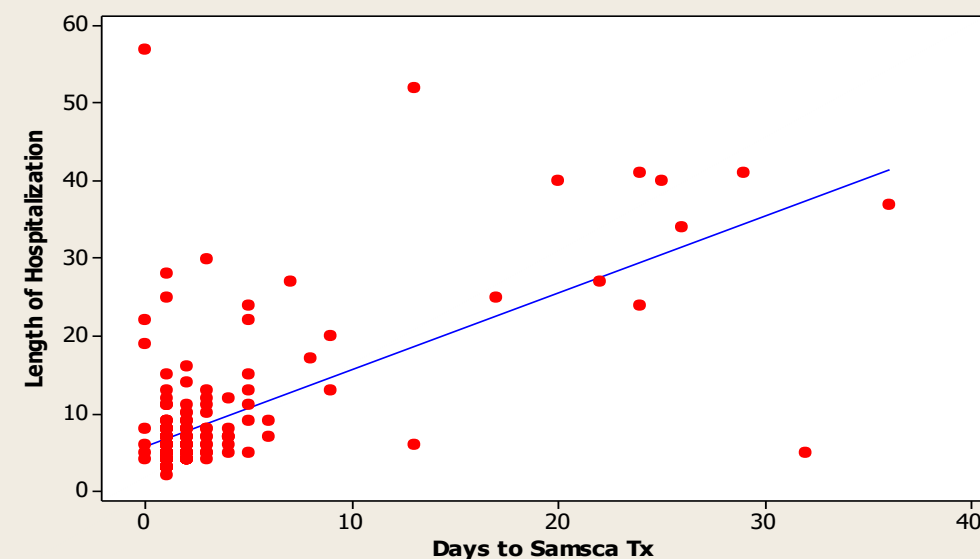
Early Initiation of Tolvaptan In-hospital Shortened Length of Hospital Stay

The relationship between the time until commencement of tolvaptan and the length of hospital stay in heart failure patients¹



Regression curve of the relationship between time and commencement of TVT from hospitalization and the length of hospital stay. Time until commencement of TVT from hospitalization were strongly correlated with the length of hospital stay : $P < 0.001$, $r^2 = 0.390$.

The Philippine Tolvaptan Experience²



Scatterplot Showing Relationship between Days to oral Tolvaptan tablets and Length of Hospitalization. Correlation Coefficient: 0.6350; p value: < 0.0001 .

The earlier, the better!

1. Kiuchi, S. et al. The relationship between the time until commencement of tolvaptan and the length of hospital stay in heart failure patients. *Heart Vessels*. 2018 Apr;33(4):367-373. 2. Data on file. Based on the result of the Tolvaptan Philippine Early Experience

Shortening LoS with Tolvaptan Resulted to Cost Minimization

Resource Reduction Due to Tolvaptan Usage (per admission)⁷ in the US

| Type of resource | EVEREST trial | | | | Cost offset model |
|--------------------------|---------------|-----------|-------------------------|----------------------------------|---------------------------------|
| | Placebo | Tolvaptan | Difference ^a | Relative Difference ^b | Resource reduction ^c |
| Length of stay (days) | 11.44 | 9.72 | 1.72 | 15.0% | 0.81 |
| Total hospital cost (\$) | \$17,926 | \$15,230 | \$2,695 | 15.0% | \$1,265 |

^aPlacebo - Tolvaptan

^bDifference/placebo

^cMean per admission LOS/Cost for HCUP HF patients x relative difference

TOLVAPTAN FOR CHRONIC USE?

Recommendation on Diuretics in the Management of Chronic HFrEF and HFpEF

| Chronic HFrEF | Class of Recommendation | Level of Evidence | *MINDS Recommendation Grade | *MINDS Evidence Classification |
|--|-------------------------|-------------------|-----------------------------|--------------------------------|
| Loop Diuretics, Thiazide diuretics | | | | |
| Administration for symptom related with volume overload | I | C | C1 | III |
| Vasopressin V2 Receptor Antagonist (Tolvaptan) | | | | |
| To be initiated during hospitalization to improve a symptom due to excess water retention in heart failure when the treatment by other diuretics including loop diuretics is ineffective | IIa | A | B | II |
| Carbonate Dehydrase Inhibitor, Osmotic Diuretics, etc. | | | | |
| Diuretics except for loop, thiazide and MRA | IIb | C | C2 | III |
| Chronic HFpEF | | | | |
| Diuretics to alleviate the subjective symptoms due to congestion | I | C | C1 | VI |
| The long-acting loop diuretics to choose among the loop diuretics | IIb | C | C1 | III |
| Tolvaptan, initiated during hospitalization for acute heart failure, to be used continuously after discharge to control congestion* | IIa | C | C1 | IVb |

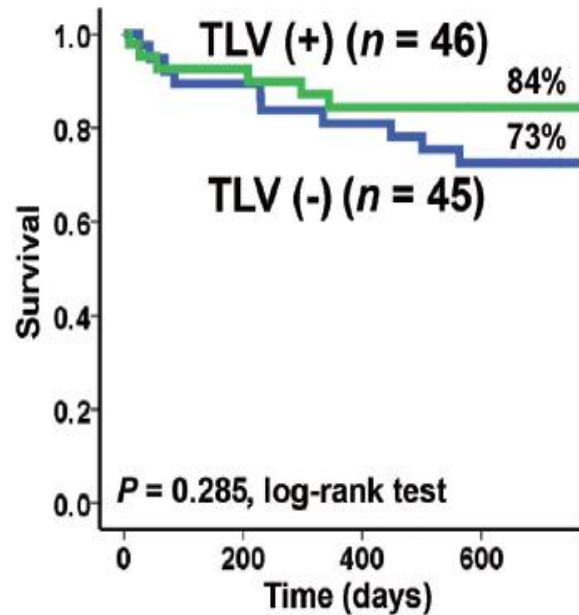
*Medical Information Network Distribution Service

*Tolvaptan is to be initiated during hospitalization.

Tolvaptan therapy significantly reduced the two-year readmission rates in both HFrEF and HFpEF populations

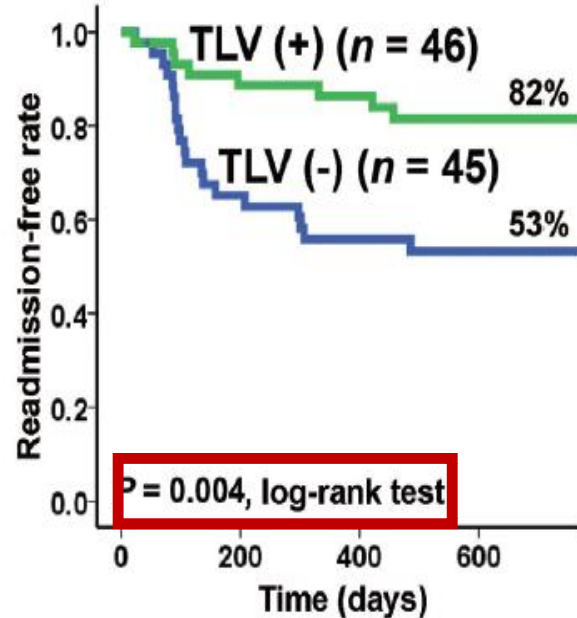
A. Survival

HFrEF



B. Readmission

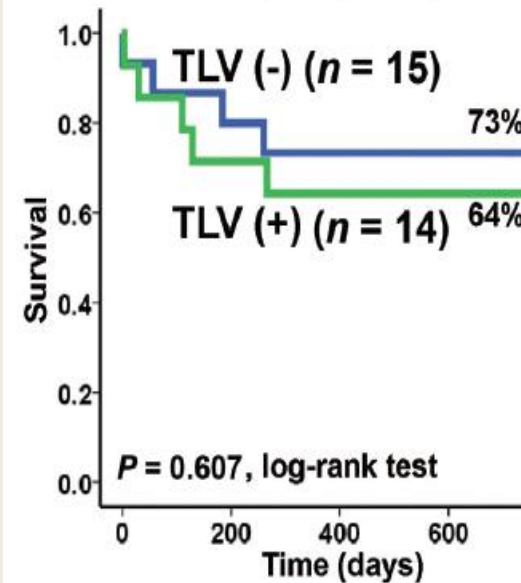
HFrEF



- TLV significantly reduced readmission rate among patients with HFrEF

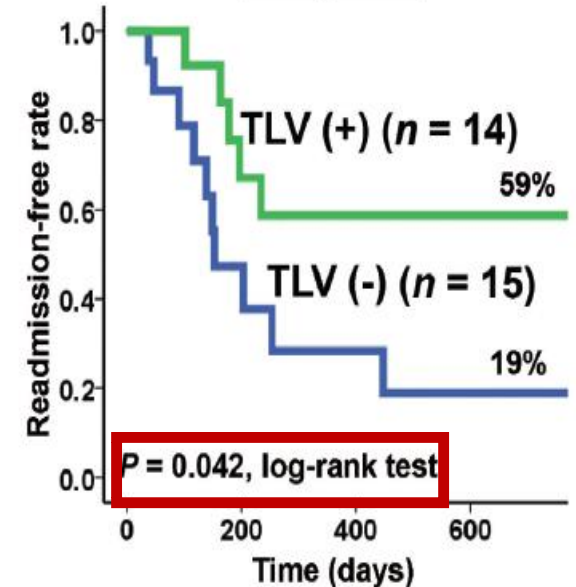
A. Survival

HFpEF



B. Readmission

HFpEF

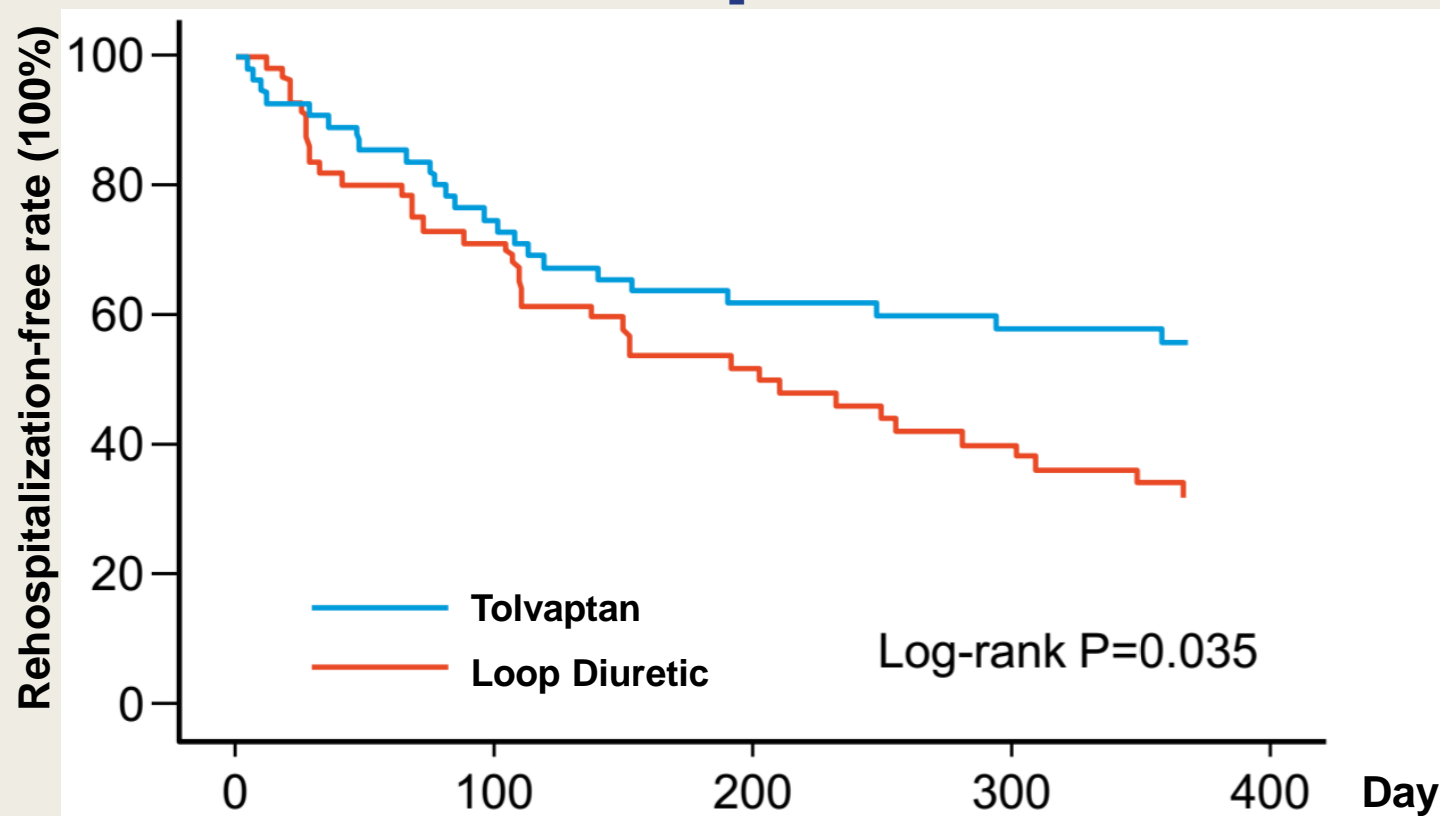


- TLV significantly reduced readmission rate among patients with HFpEF

Lower Rehospitalization Rates with Tolvaptan in Patients with Chronic Kidney Disease



Estimates of Rehospitalization-free Rates

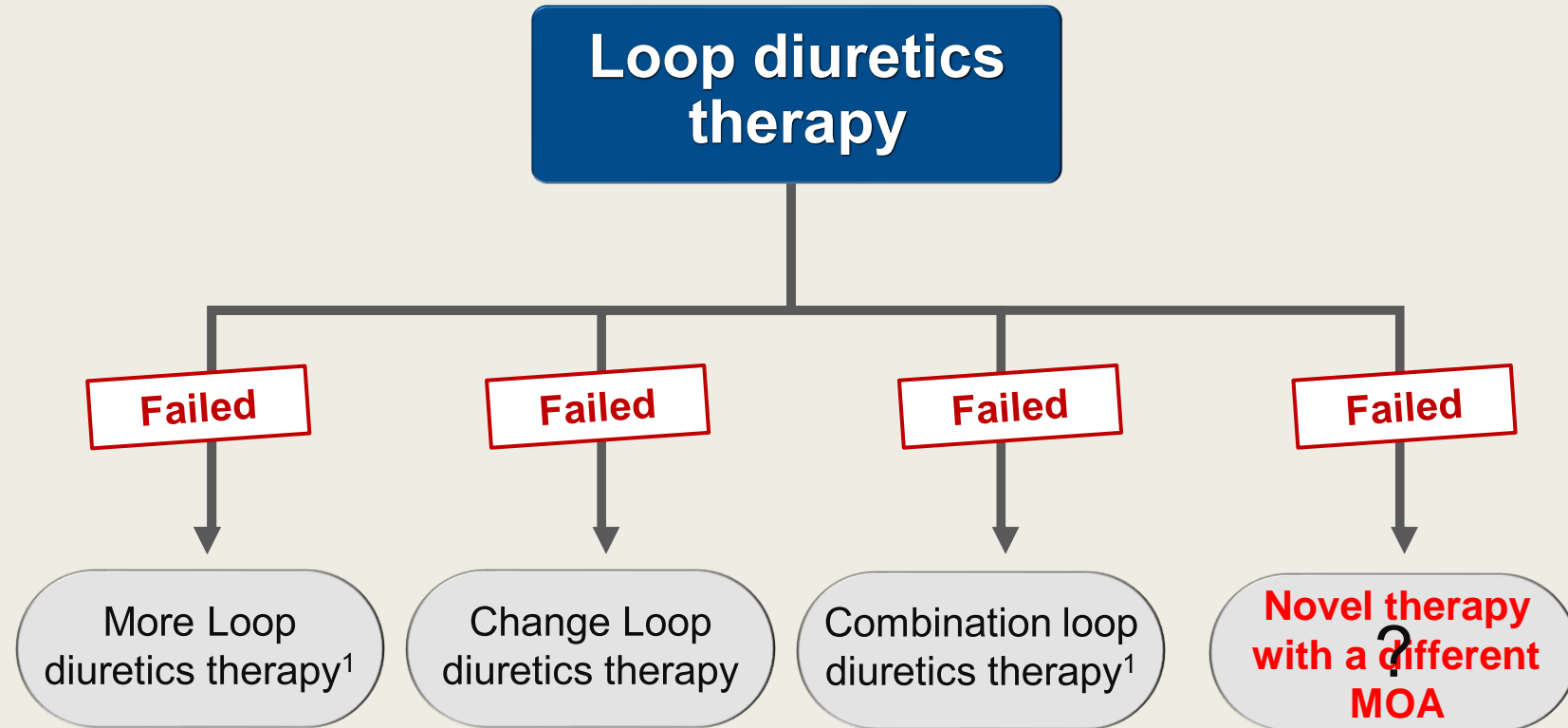


Patients who received Tolvaptan on top of standard therapy exhibited lower rate of rehospitalization for heart failure compared to those who received loop diuretics alone.

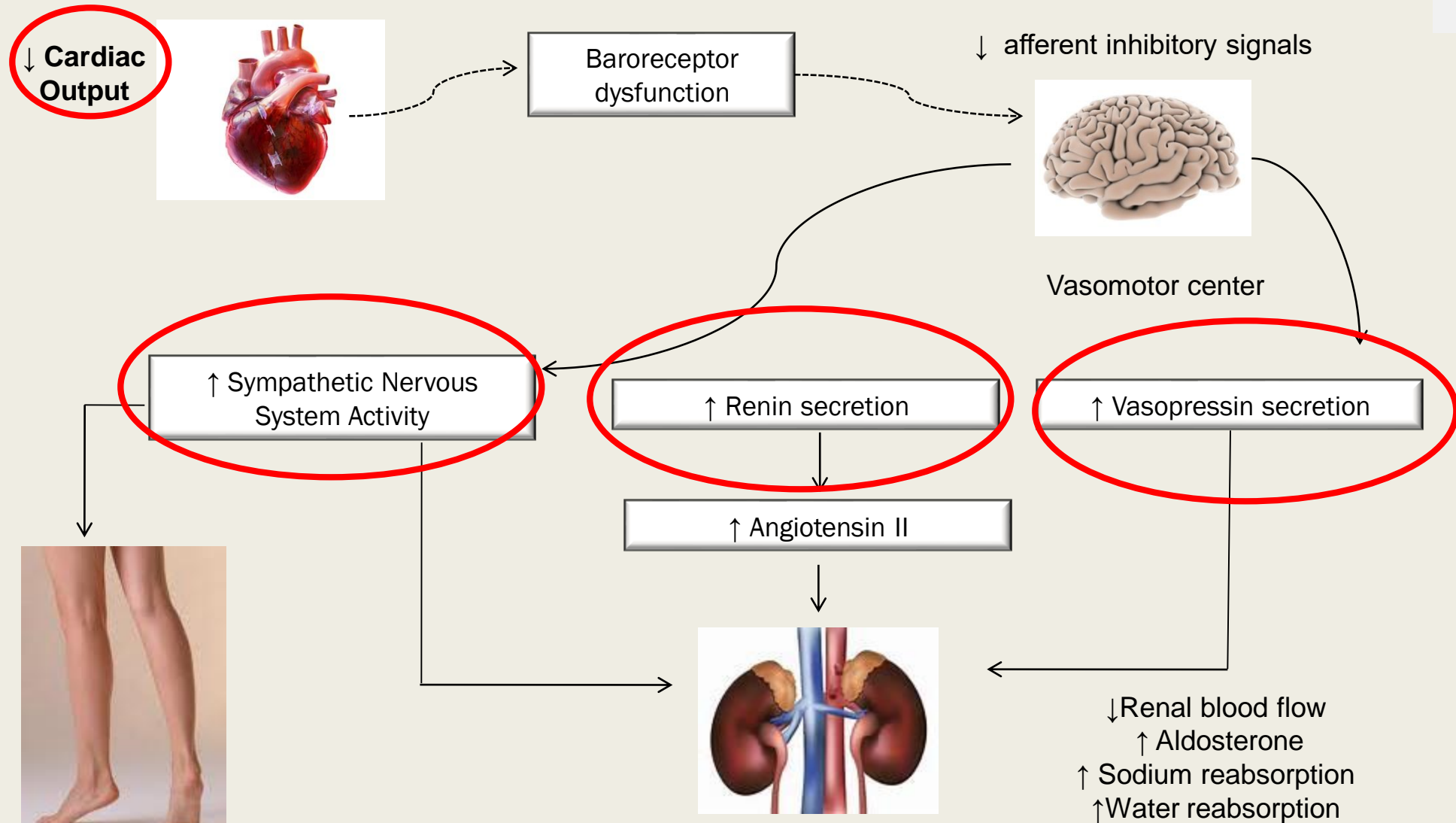
AQUARESIS VIA AVP RECEPTOR ANTAGONISM



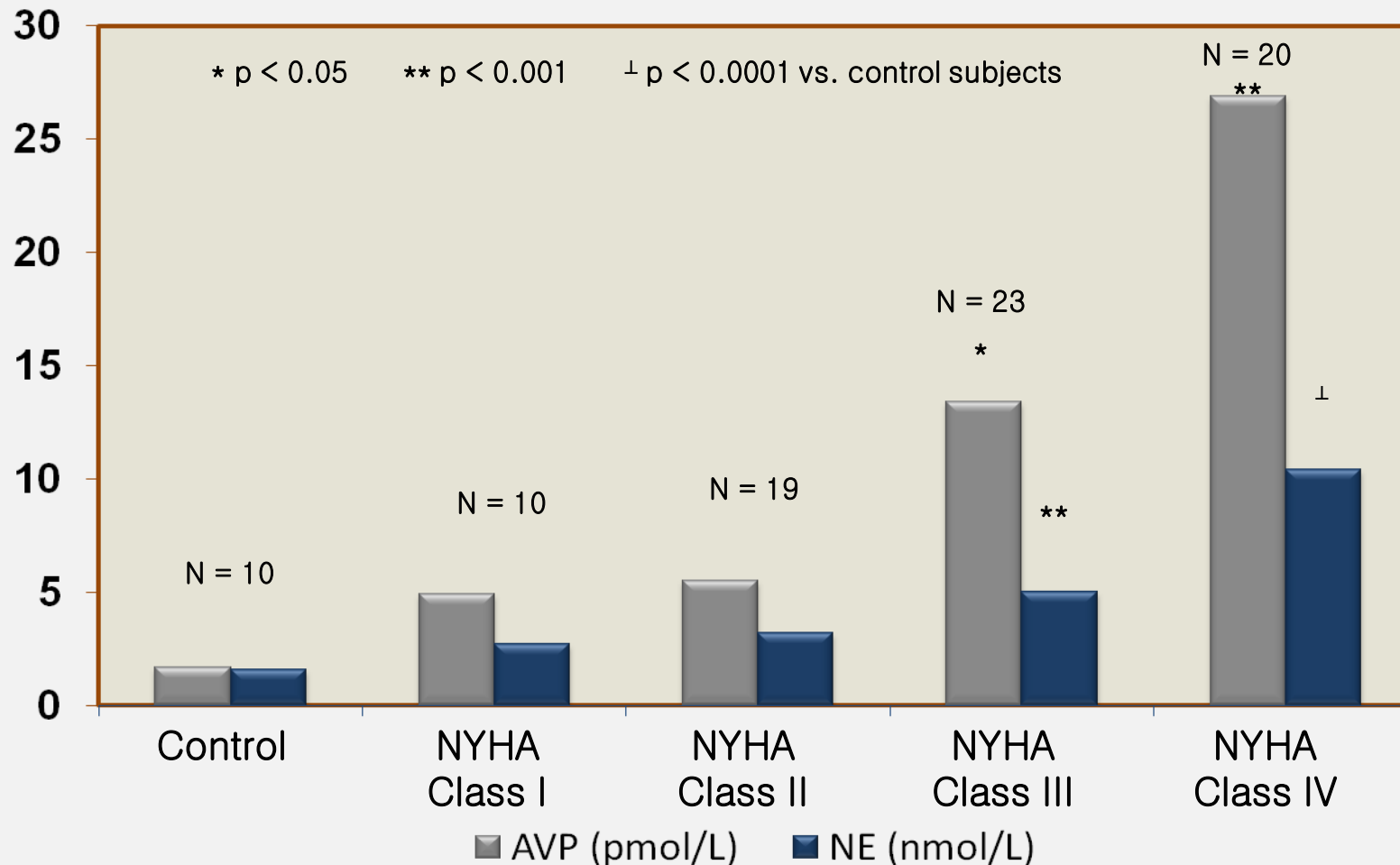
Conventional Treatment Regimen for Congestion in AHF



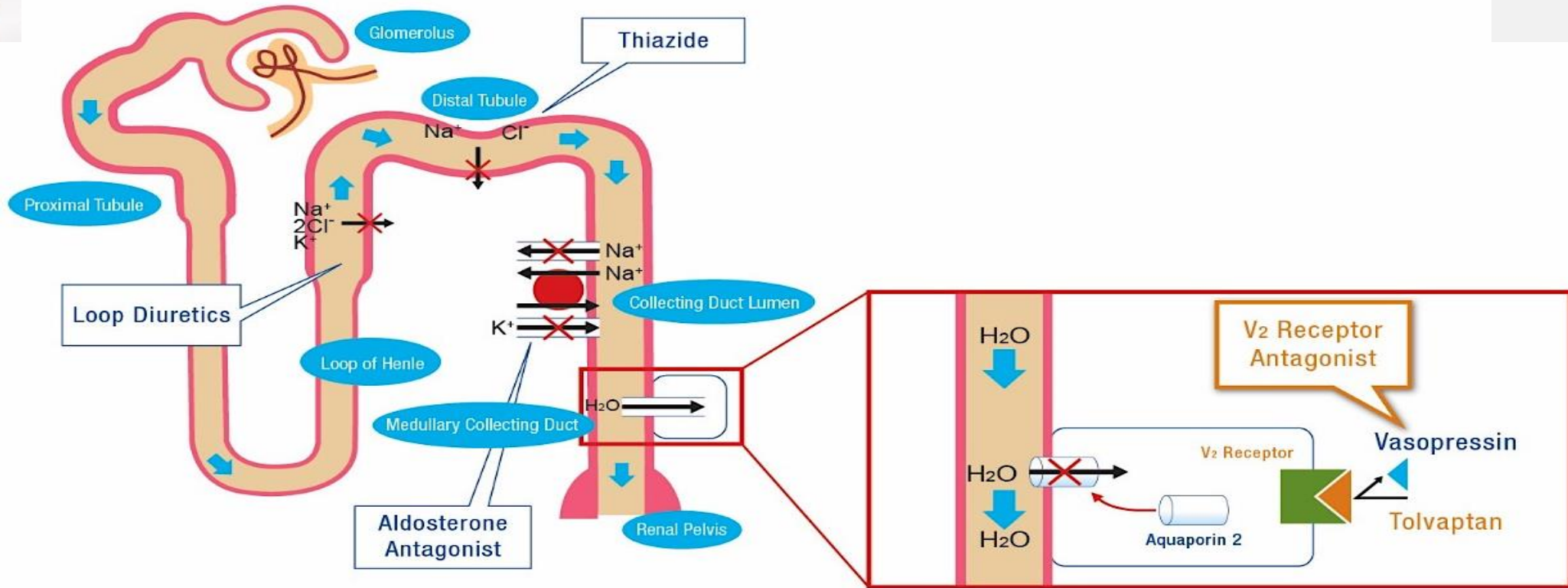
Neurohormonal Activation in HF



Arginine Vasopressin (AVP) Levels are Elevated According to Heart Failure Severity



Site of Action of Diuretics & Tolvaptan



Tolvaptan acts by blocking the binding of ADH (Antidiuretic Hormone) or AVP (Arginine Vasopressin) to **V₂ receptors** in the collecting duct of the kidney, preventing the insertion of **Aquaporin 2** water channels to the apical membrane of the collecting duct principal cells resulting to electrolyte-free water clearance or **aquaresis**.



Comparison of Tolvaptan and Diuretics



Treatment

Arrhythmia

Activation of plasma renin

Blood pressure

Creatinine / BUN

Free water excretion

GFR

Heart rate

Serum sodium

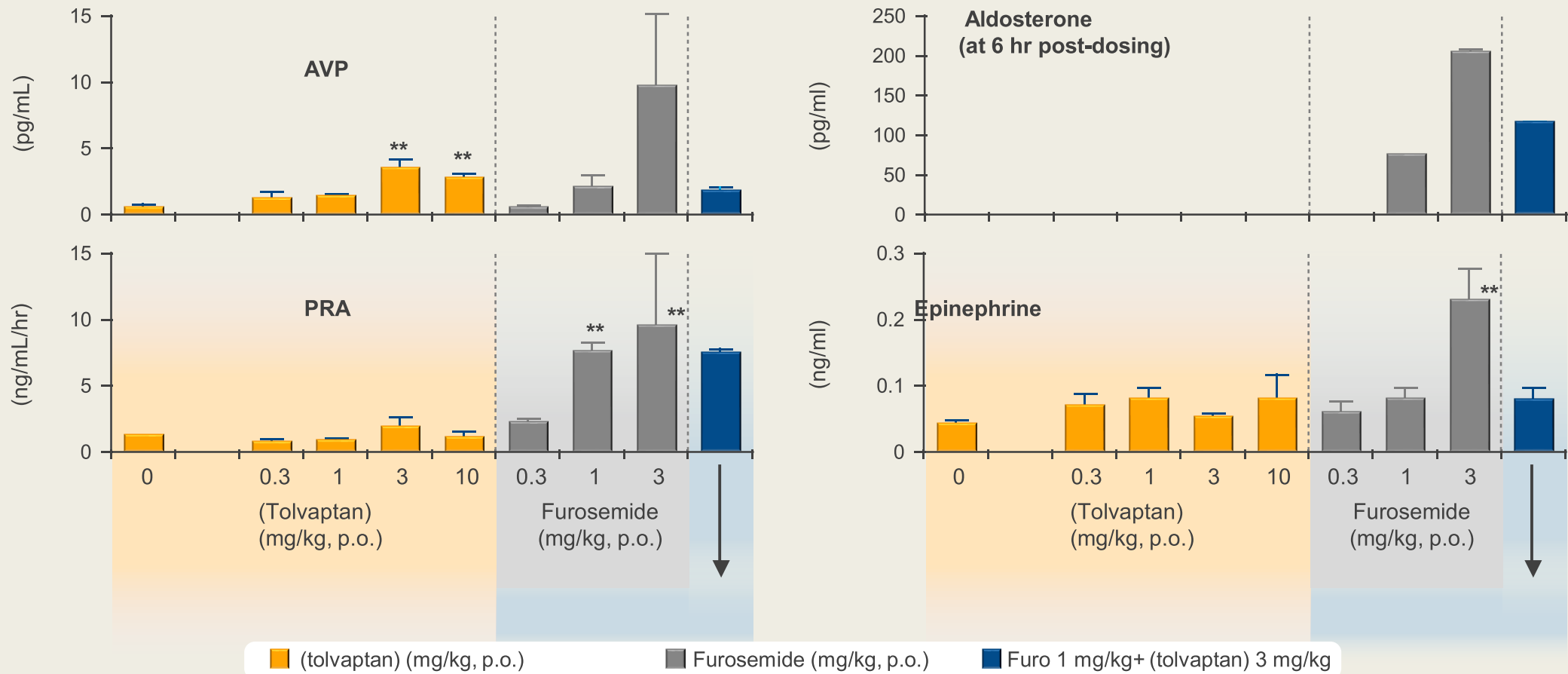
Serum potassium

Serum osmolality

Sympathetic nervous system

1. Narayen G, et al. Indian J Endocrinol Metab 2012;16(2):183-91.
2. Sarraf M, et al. Clin J Am Soc Nephrol 2009;4:2013-26.
3. Ambrosy A, et al. Expert Opin Pharmacother 2011;12:961-76.

Tolvaptan DOES NOT Activate Neurohormonal Mechanisms



n=6, Mean +SEM * $p < 0.05$, ** $p < 0.01$ vs. control, ## $p < 0.01$ vs. Furo 1 mg/kg
 AVP: arginine vasopressin, PRA: plasma renin activity

3 Practical Points to Remember When Using Tolvaptan

1

**Start in-hospital, *frequently monitor serum Na
(at least twice on the first day and daily while in hospital;)**

**Tolvaptan medication can be taken home as long as it is initiated in-hospital.*

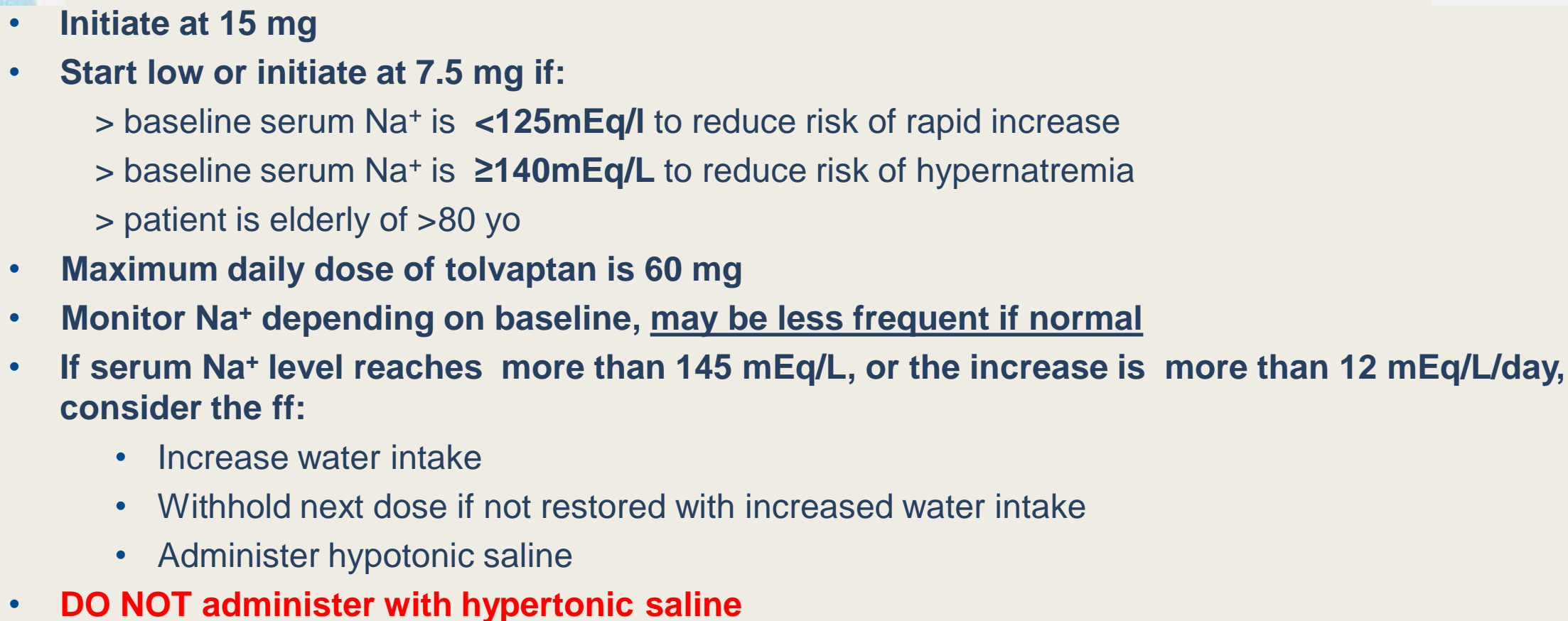
2

**Stop all fluid restriction
(especially during the first 24 hours of therapy)**

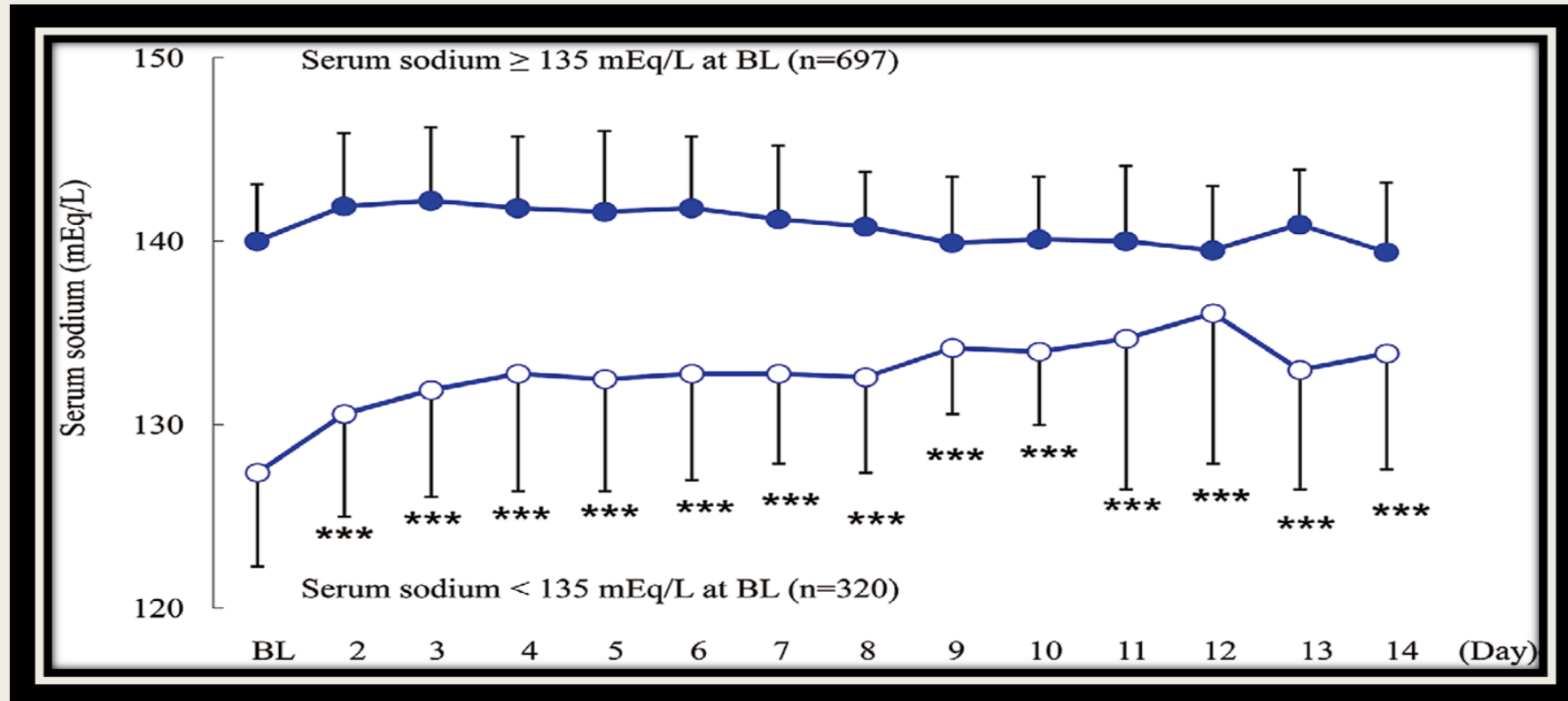
3

**Patients should be able to appropriately sense thirst and have
access to water**

**Na⁺ monitoring for chronic use may be done 1 week after discharge, every month for 2 months and every 2 months thereafter (EVEREST) or depending on patient status or the physician's discretion*



Treatment with Tolvaptan is safe for normonatremic & beneficial for hyponatremic heart failure patients



The time course of serum sodium between <135 and ≥ 135 mEq/L. Open circles show data from patients with serum sodium levels ≥ 135 mEq/L at baseline (BL). Closed circles show <135 mEq/L. Values are presented as mean —

- Expect 2-3 mEq/L increase in serum sodium when initiated to patients with normal baseline
- Patients' thirst mechanism should protect normonatremic patients from hypernatremia

Summary

- Congestion is a major reason for hospitalization in acute heart failure. Hence, feeling better (symptom relief) is equally important as living longer (decrease in mortality) ¹
- Conventional therapy for congestion management involves diuretics with addition of vasodilators for dyspnea relief if hemodynamics allow. Diuretics often cause worsening renal function and neuro-humoral activation.²
- Aquaretic via AVP receptor antagonism with tolvaptan reduce congestion, fluid retention and can potentially improve outcomes especially when initiated early in hospital and may reduce readmission rate when given continuously.
- Aquaretic reduces the risk of electrolyte abnormalities, worsening renal function, & neuro-humoral activation.²

1. Mentz R, et al. Eur J Heart 2014;16(5):471-82.

2. Sarraf M, et al. Clin J Am Soc Nephrol 2009;4:2013-26.

THANK YOU

