# The kidney in heart failure-the cardio-renal syndrome

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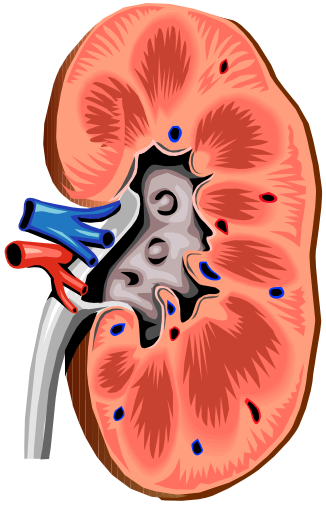
## Patients with ESRD often have left ventricular hypertrophy at autopsy

Richard Bright.

RICHARD BRIGHT, M.D.F.R.S.
Physician Extraordinary to the Queen

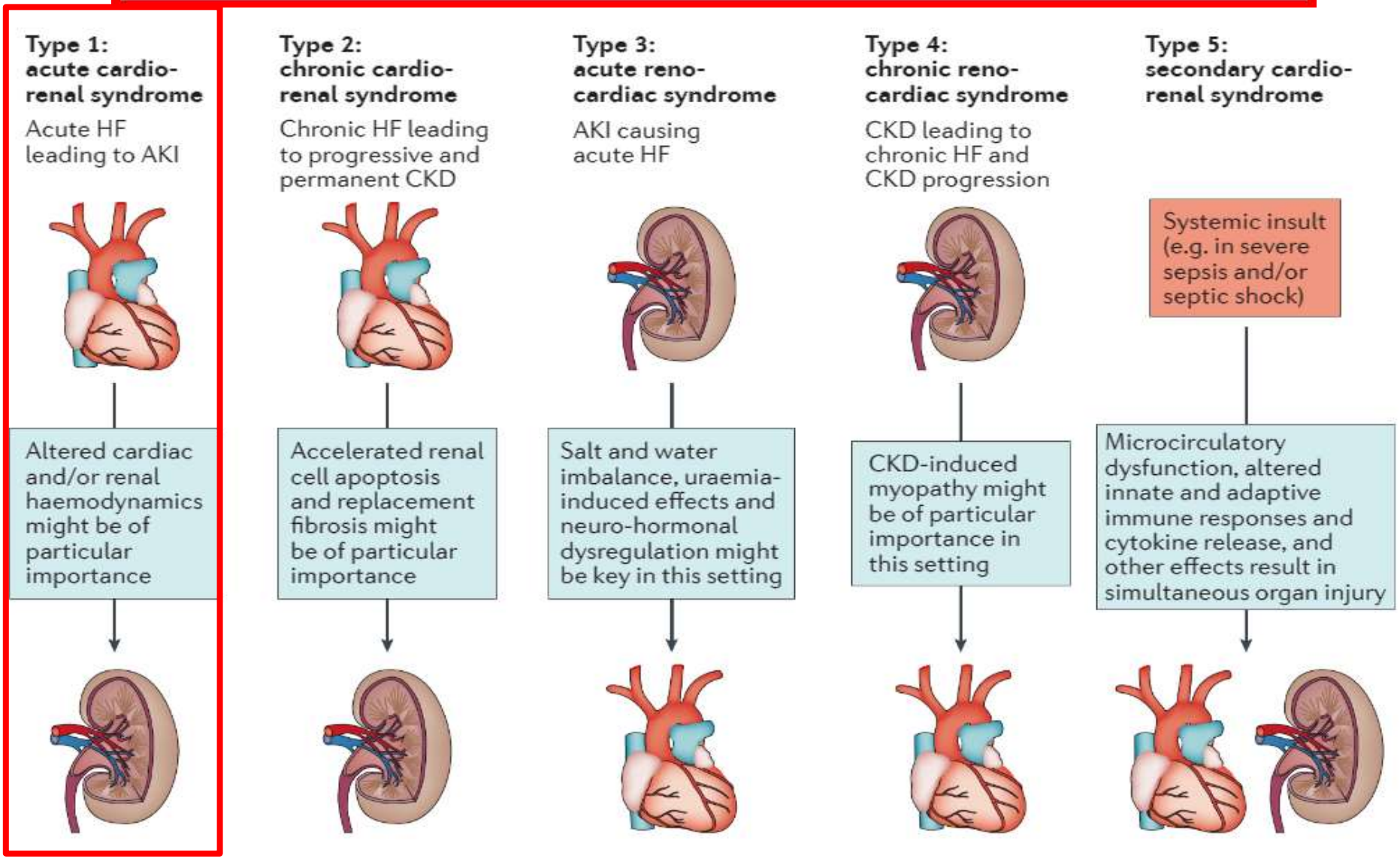


Guy Hospital Report
1:338,1836

J Am Coll Cardiol. 2008 Nov 4;52(19):1527-39. doi: 10.1016/j.jacc.2008.07.051.

# Cardiorenal syndrome.

Ronco C[1], Haapio M, House AA, Anavekar N, Bellomo R.




Schefold et al Nature Rev Nephrol, 16: 610-623, 2016

# Common SCr- based definitions of CRS

| | | |
|---|---|---|
| *AKIN* | | |
| Stage 1 | Increase in serum creatinine of ≥26.2 μmol/l or increase to ≥150–199% (1.5- to 1.9-fold) from baseline | Acute serum creatinine changes occur within a 48-hour period during hospitalization |
| Stage 2 | Increase in serum creatinine to 200–299% (>2- to 2.9-fold) from baseline | |
| Stage 3 | Increase in serum creatinine to 300% (≥3-fold) from baseline or serum creatinine ≥354 μmol/l with an acute rise of at least 44 μmol/l or initiation of RRT | |
| *KDIGO* | | |
| Stage 1 | ≥1.5 times baseline* or 0.3-mg/dl increase** | * Defintion of AKI requires serum creatinine changes ≥1.5 times baseline to have occurred within 7 days, or ** a 0.3-mg/dl increase in serum creatinine must occur within a 48-hour time period |
| Stage 2 | ≥2 times baseline | |
| Stage 3 | ≥3 times baseline or increase in creatinine to ≥4.0 mg/dl | |
| *WRF* | | |
| | Increase in serum creatinine from baseline of ≥0.3 mg/dl (26.5 μmol/l) | Serum creatinine change can occur at any time during admission |

# Definition of CRS-1

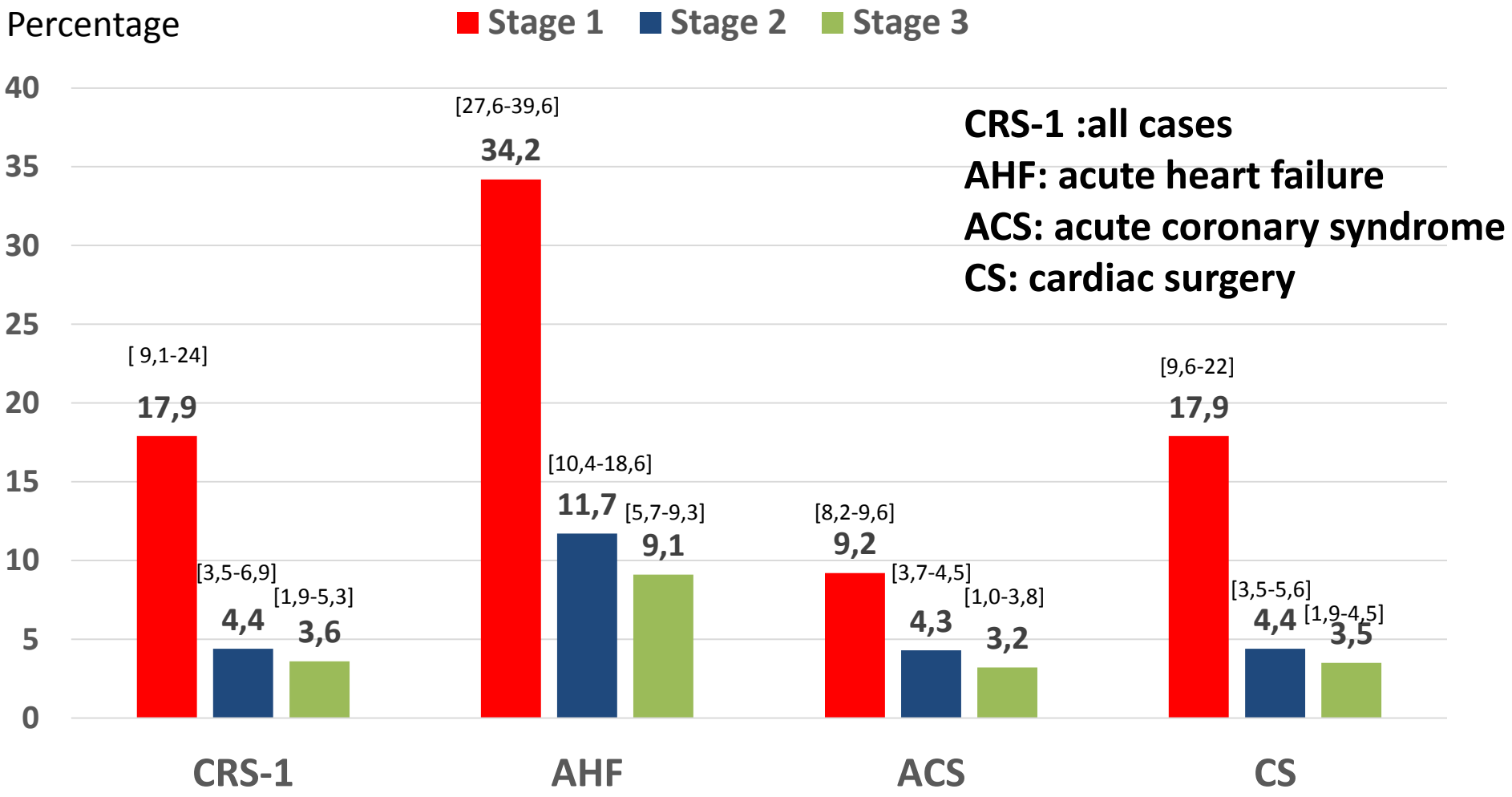
- **CRS type 1 or acute cardiorenal syndrome (CRS-1) is characterized by an acute cardiac disease leading to AKI.**
- **The most common etiologies for an acute cardiac disease include**
  - ✓ **acute decompensated heart failure (AHF), or acute worsening of pre-existing heart failure**
  - ✓ **acute coronary syndrome (ACS),**
  - ✓ **cardiac surgery (CS),**
  - ✓ **(coronary angiography)**

# Characteristics of definitions of AKI and worsening renal function

| KDIGO | | | HF literature | | Suggested definition[a] | |
|---|---|---|---|---|---|---|
| Acute kidney injury (AKI) | | | Worsening renal function (WRF) | | WRF in chronic HF/AKI in acute HF | |
| Stage | Serum creatinine | Urine output | Definitions used | | Serum creatinine/eGFR | Additional criteria |
| 1 | Increase 1.5–1.9 times baseline within 1–7 days OR ≥ 26.5 µmol/L increase within 48 h | <0.5 mL/kg/h for 6–12 h | Definitions based on creatinine | >/≥26.5 µmol/L increase<br>≥26.5 µmol/L and ≥25% increase<br>>/≥44 µmol/L increase<br>≥ 1.5 times baseline<br>≥ 25% increase and above 176 µmol/L | **Chronic HF (WRF)[a]**<br>≥26.5 µmol/L and ≥ 25% increase in sCr[b] OR ≥ 20% decrease in eGFR over 1–26 weeks | Deterioration in HF status but not leading to hospitalization |
| 2 | Increase 2.0–2.9 times baseline | <0.5 mL/kg/h for ≥12 h | Definitions based on cystatin C | > 0.3 mg/L increase in cystatin C | **Acute HF (AKI)[a]**<br>Increase 1.5–1.9 times baseline sCr within 1–7 days before or during hospitalization OR ≥26.5 µmol/L increase in sCr[b] within 48 h OR Urine output <0.5 mL/kg/h for 6–12 h | Deterioration in HF status or failure to improve OR Need for inotropes, ultrafiltration or renal replacement therapy |
| 3 | Increase ≥3.0 times baseline OR Increase >354 µmol/L OR Initiation of renal replacement therapy | < 0.3 mL/kg/h for ≥24 h OR Anuria ≥12 h | Definitions based on eGFR | ≥ 20% decrease<br>≥ 25% decrease<br>> 5 mL/min/year decrease | | |

Damman et al, European Heart Journal (2014) 35, 3413–3416

# AKI according to the 3 stages of AKI and subclasses of CRS-1




Vandenberghe et al, Cardiorenal Med 2016;6:116–128

# Updated meta-analysis on CKD, WRF and mortality in heart failure

– **CKD, eGFR < 60 ml/min** (57 studies; 1076101 subjects)

Prevalence: 32%

– Increased all cause mortality: OR 2.34

– More so for HFpEF than for HFrEF

**- WRF (28 studies; 48890 subjects)**

Occurred in 23%

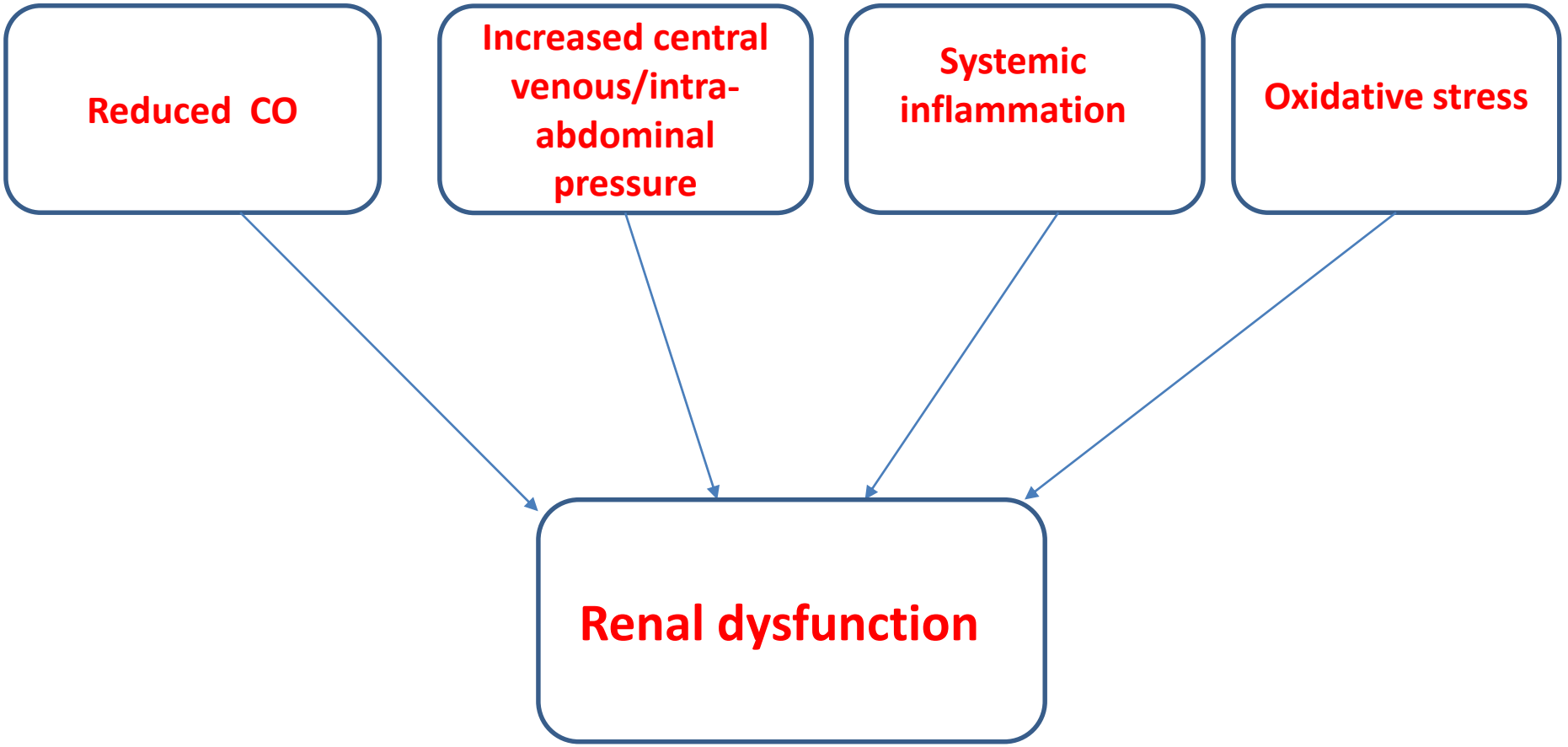
- 23% in ADHF; 25% in chronic HF

- Increased overall all cause mortality: OR:1.81

1.75 in ADHF; 1.96 in chronic HF

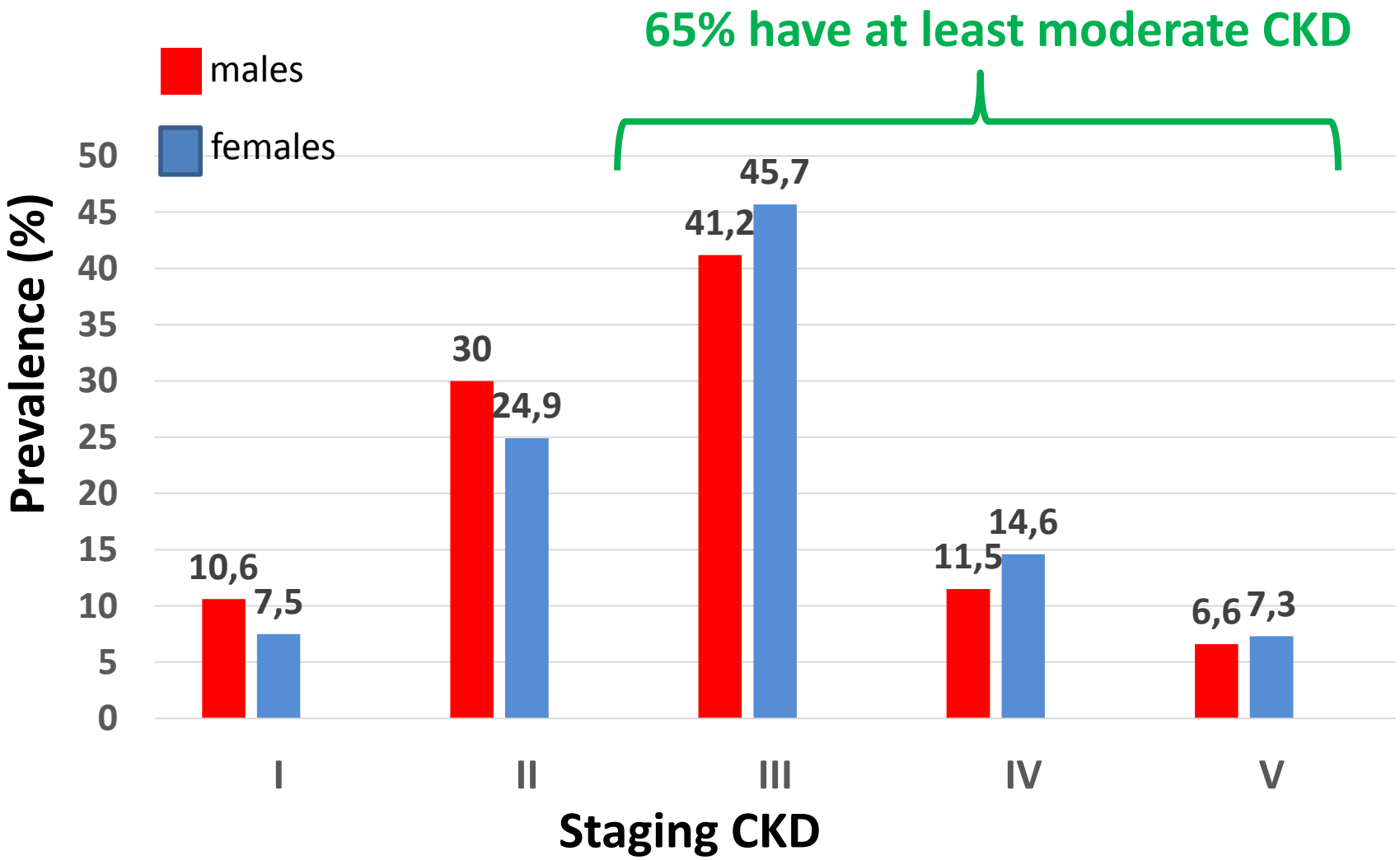
Damman et al European Heart Journal (2014) 35, 455–469

# Simplified pathogenesis of CRS type 1- a combination of factors

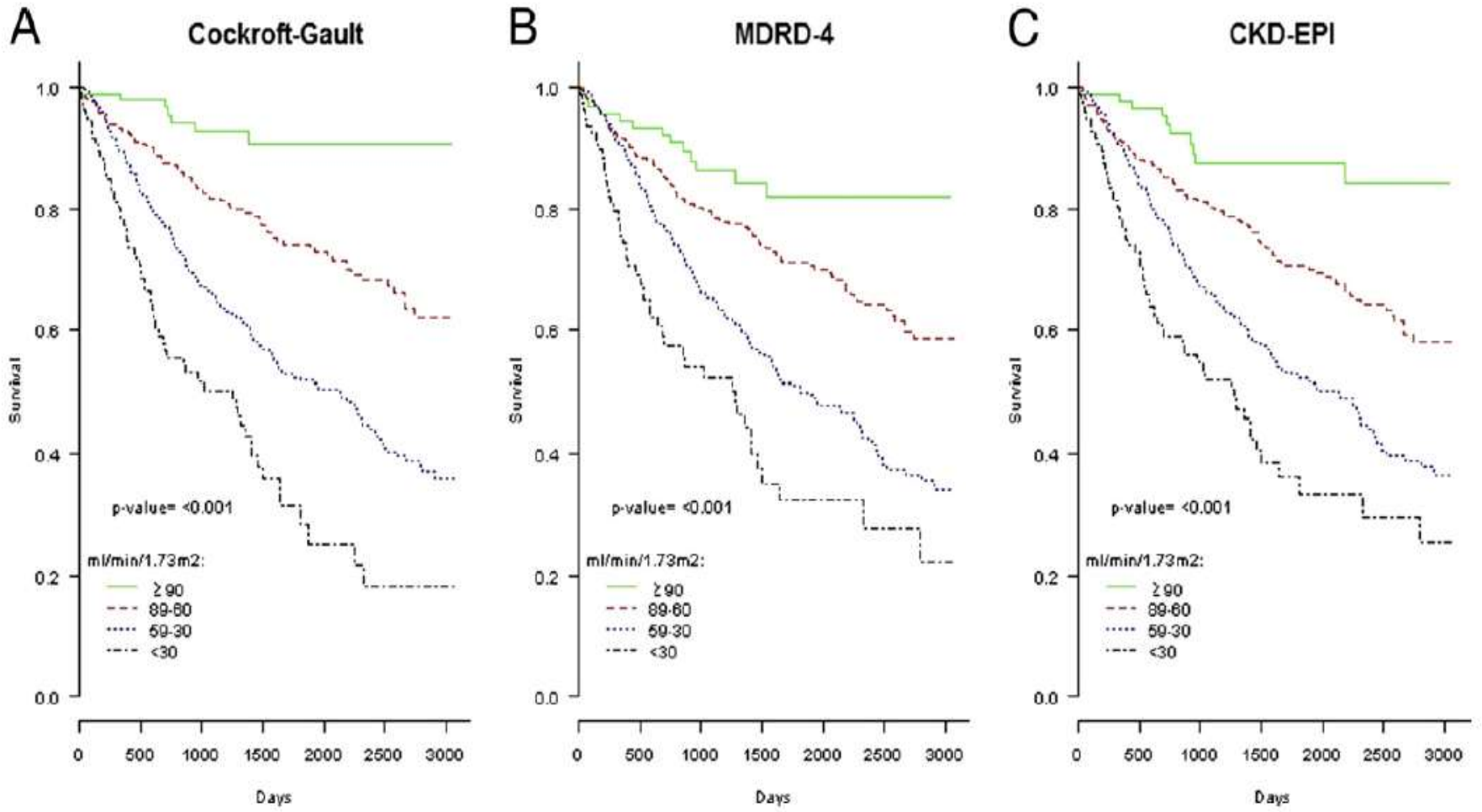


# Majority of patients with acute heart failure have kidney dysfunction

## ADHERE database ( n= 118465)

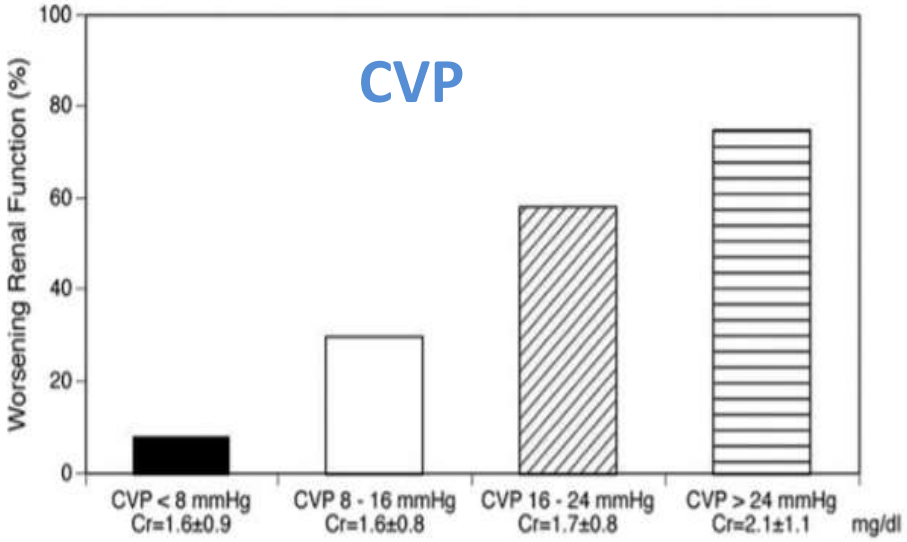


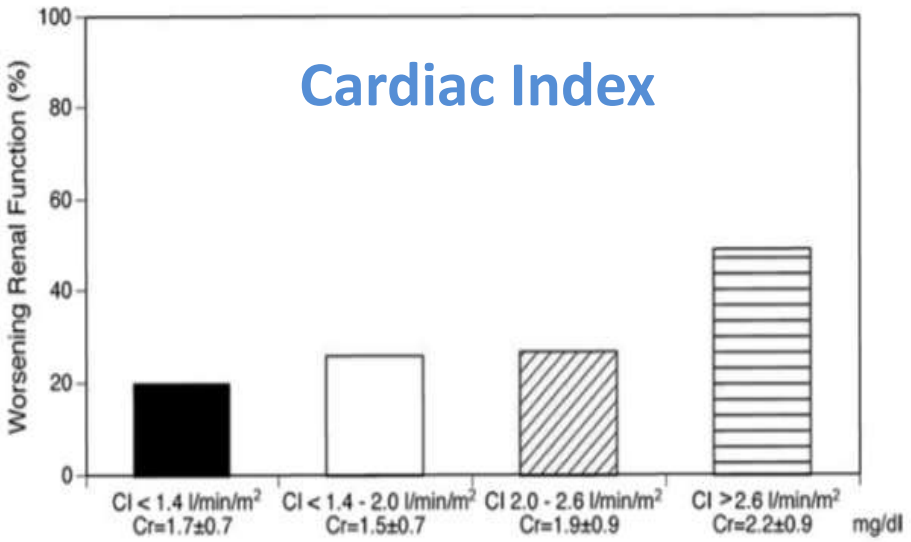
# Impact on survival:eGFR calculations in heart failure patients

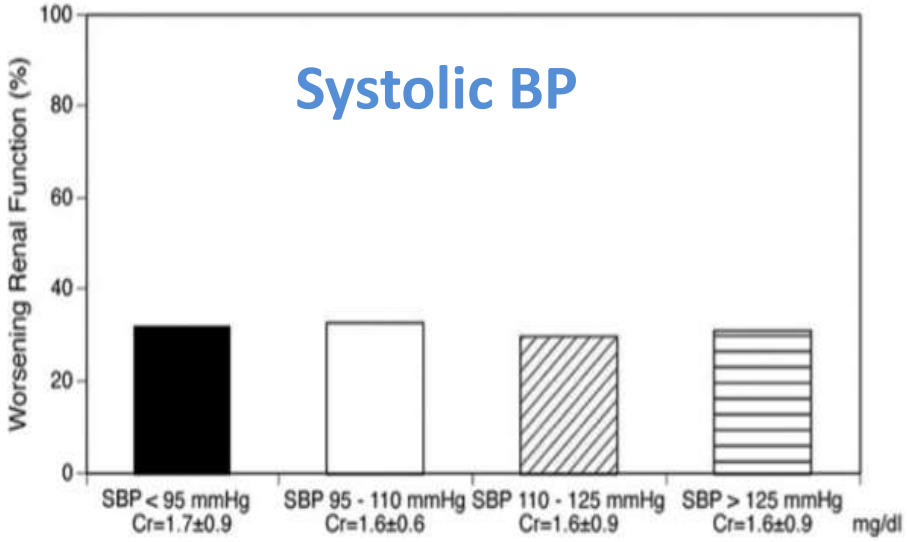


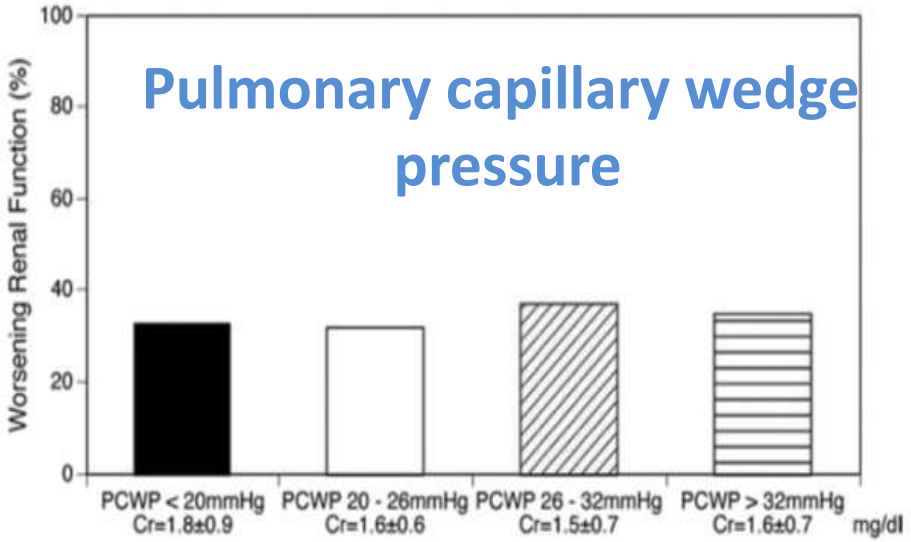

Zamora et al, J Am Coll Cardiol 2012;59:1709–1715

# Prevalence of WRF During Hospitalization –no major role for general hemodynamicsAccording to Categories of Admission CVP, CI, SBP, and PCWP



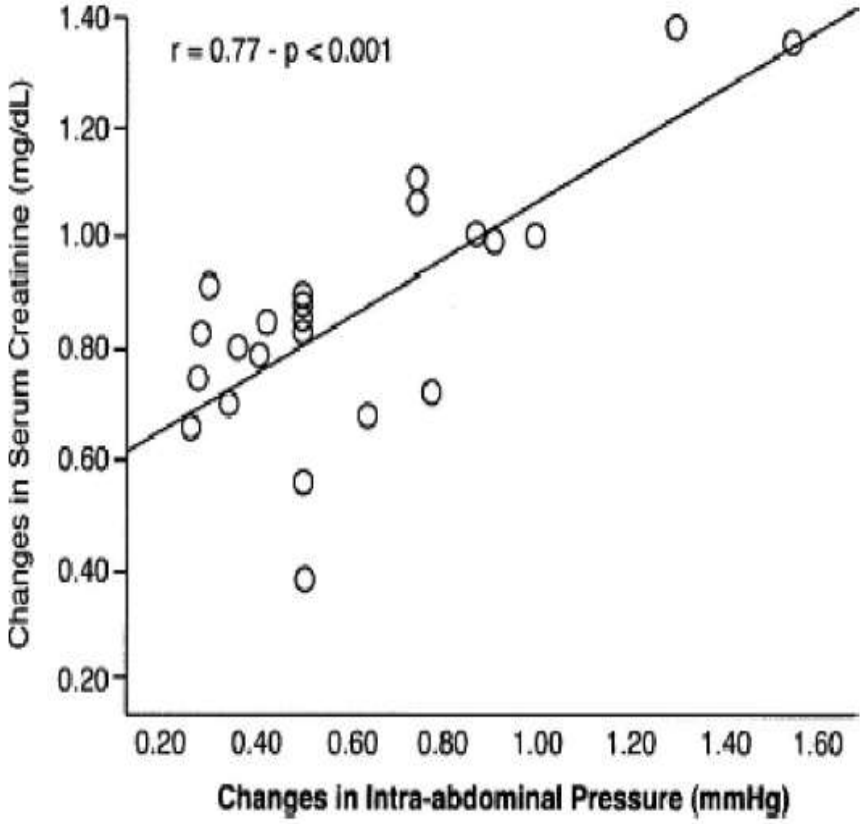




Mullens et al, J Am Coll Cardiol 2009;53:589–596

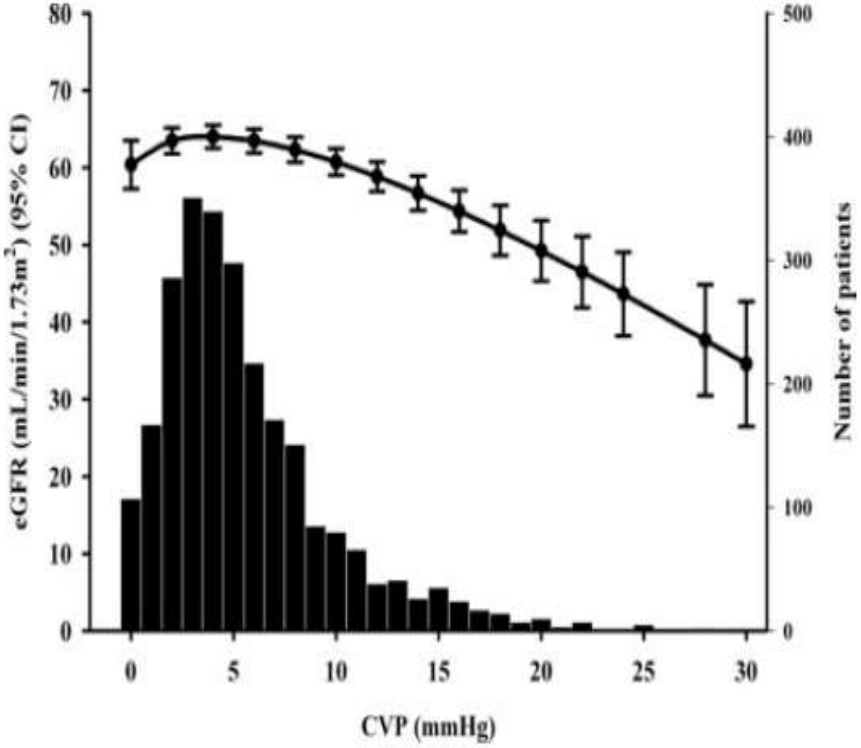
# Two important pathophysiological mechanisms in the cardio-renal syndrome

**Intra-abdominal pressure**




*Mullens et al, J Am Coll Cardiol*. 2009;53:589 –596.

**Central venous pressure**




Damman et al, *J Am Coll Cardiol*. 2009;53:582–588.

# Fluid removal and kidney function in ADHF

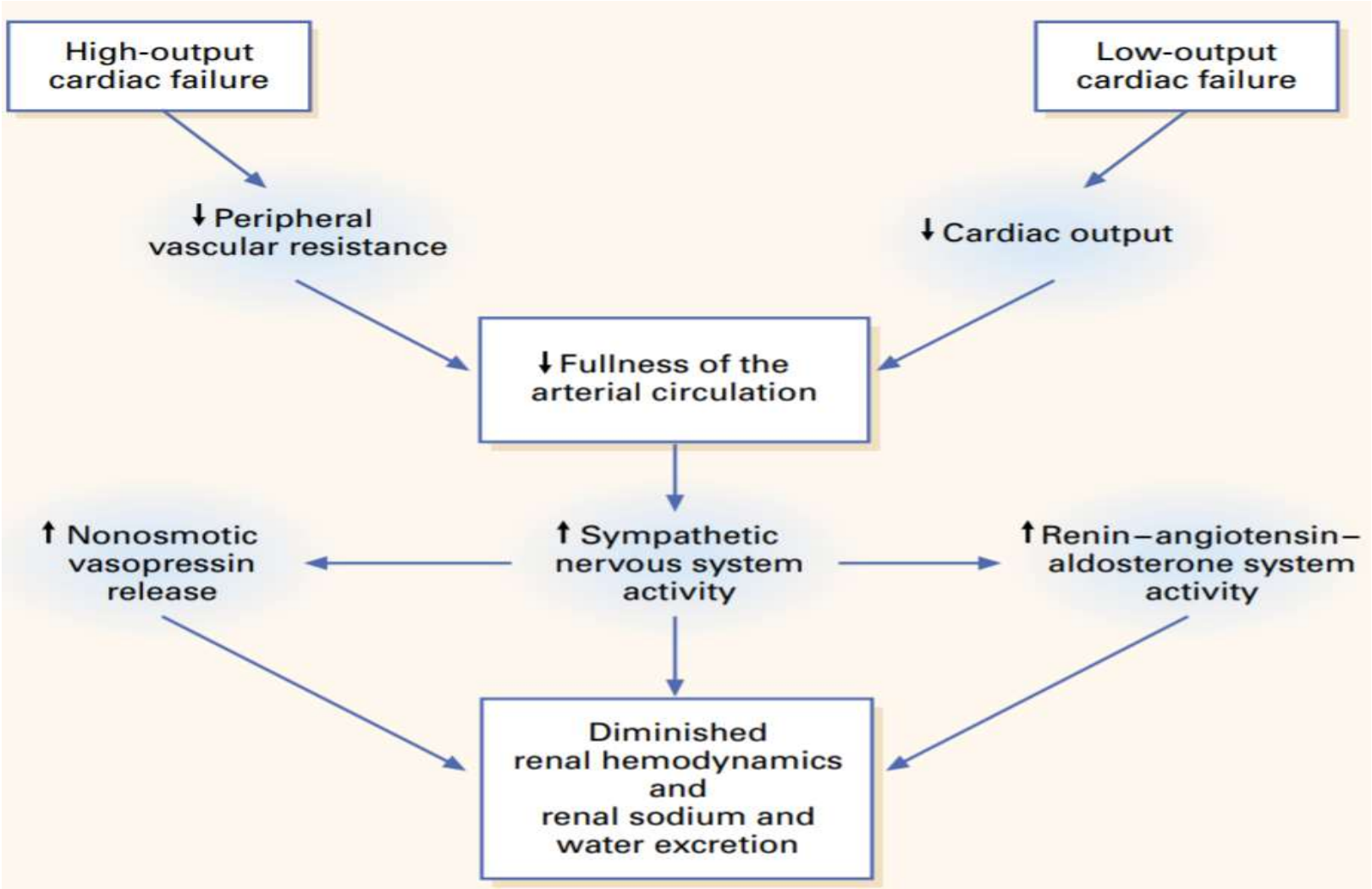
- High vs low dose diuretic → ↑ fluid and weight loss, but more WRF in DOSE
- Ultrafiltration
  - No improvement in renal function vs loop diuretics in ADHF in UNLOAD and RAPID-CHF
  - Further worsening of renal function during hospitalization and 30 days after discharge in patients with ADHF and WRF in CARRESS-HF

# Findings indicating a higher risk of superimposed (acute) renal dysfunction in patients with severe heart disease

- Persistently low urinary sodium, in spite of the use of maximal doses of combined diuretics
- Increased plasma urea/creatinine ratio and uric acid
- Mean arterial pressure < 80 mmHg
- Hyponatremia: indicates maximal neurohumoral compensatory systems
- Changes –even minor- in effective circulating volume,e.g. salt restriction, diarrhea, vomiting, insensitive fluid loss, blood loss, high t°, tachypnea
- Other : angiographic contrast, diabetes,older age, major surgery

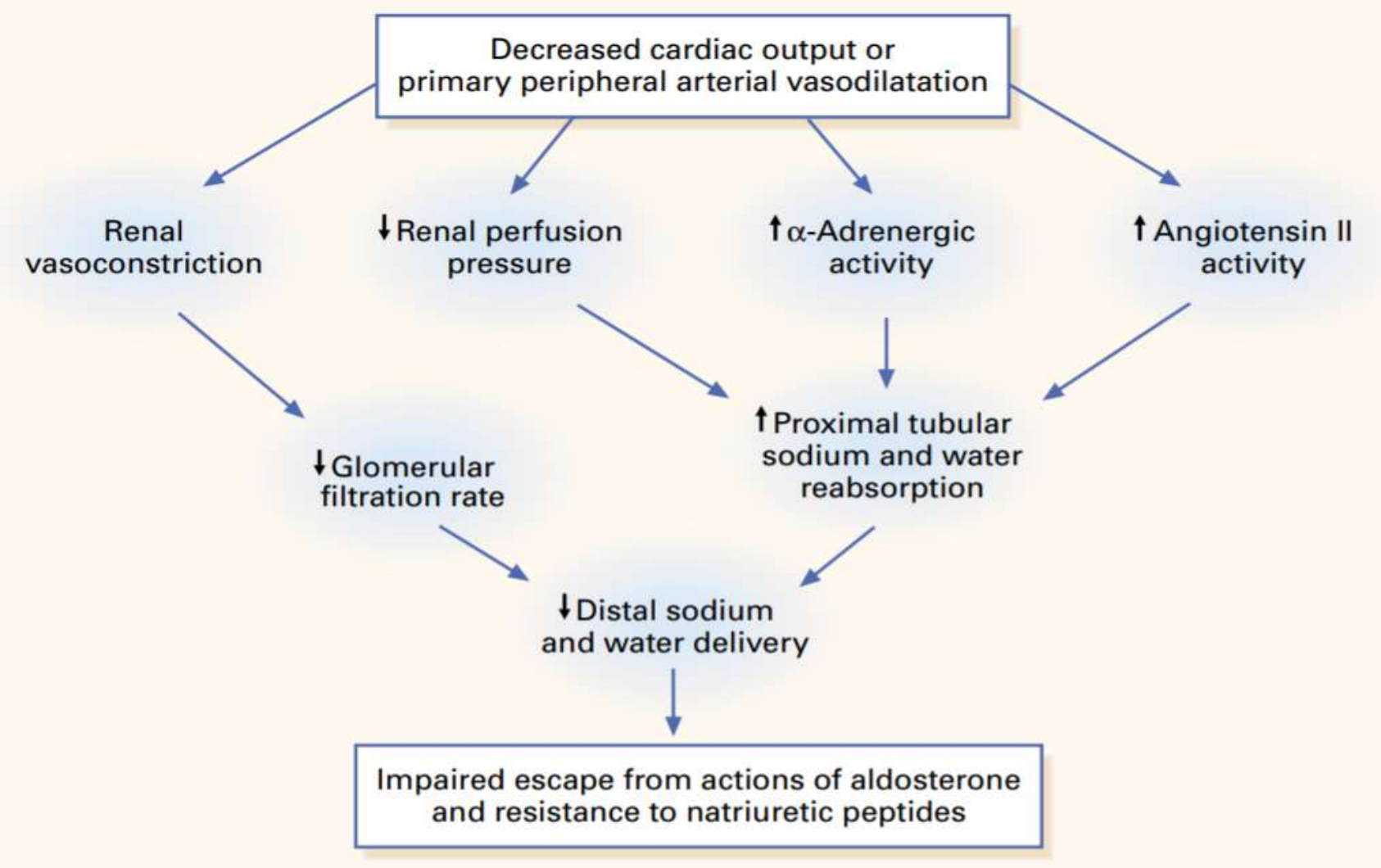
*Many of these circumstances make use of ACEi or ARB's difficult

# The mechanism explaining the defect in renal sodium and water excretion in both high- and low-output heart failure.




Schrier, Abaraham, N Engl J Med 1999, 341, 577- 585

# Arterial Underfilling Leads to Diminished Distal Tubular Sodium and Water Delivery, Impaired Aldosterone Escape, and Resistance to Natriuretic Peptide Hormone.




Schrier, Abaraham, N Engl J Med 1999, 341, 577- 585.

# Outcome of CRS according the definition of AKI in heart failure, coronary syndrome and cardiac surgery

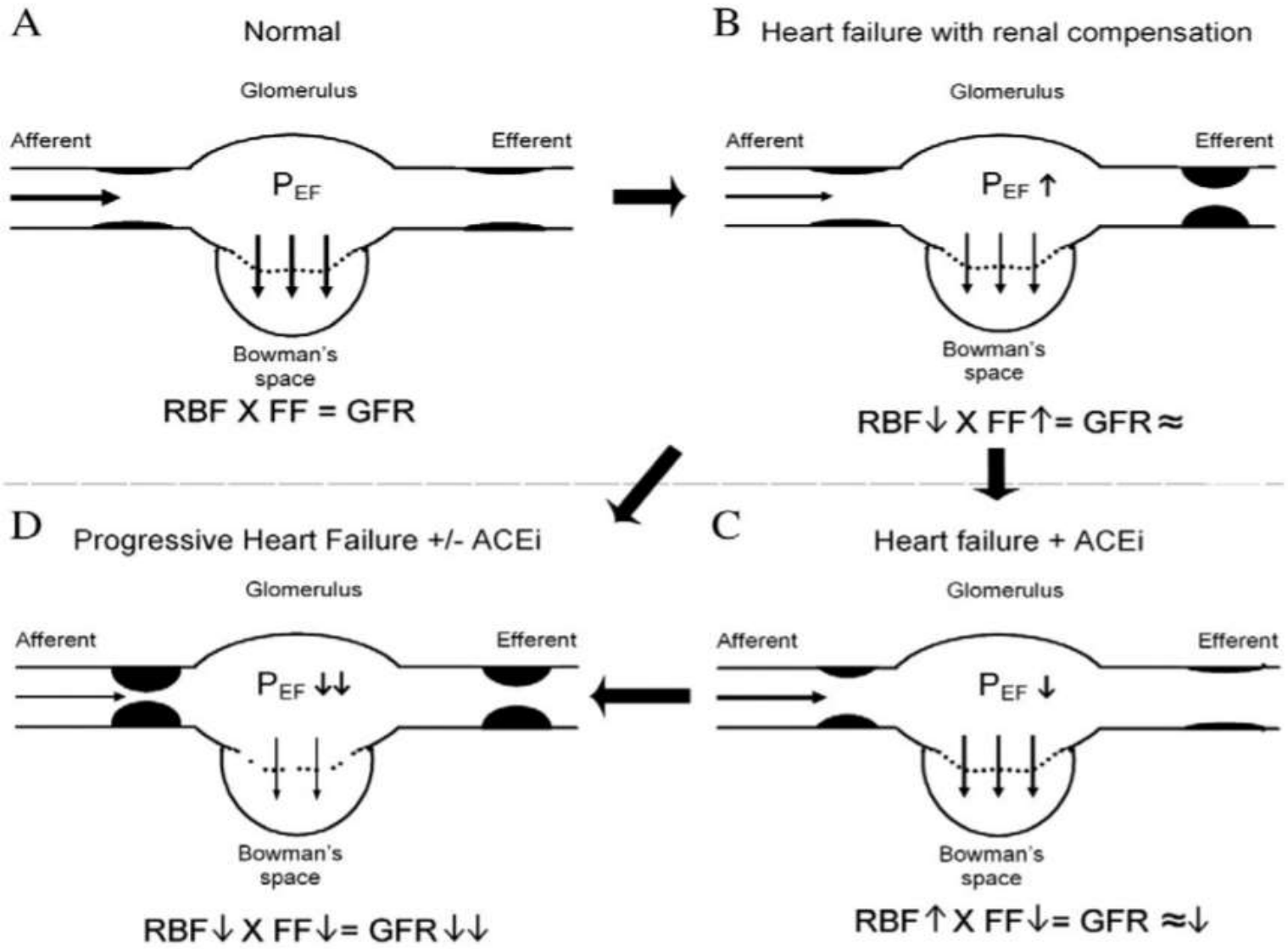
| Outcome | Sub-group | AKI | Studies/ Patients | WRF | Studies/ Patients | RRT | Studies/ Patients |
|---|---|---|---|---|---|---|---|
| Mortality | AHF | 2.89 (2.14–3.89) | 5/4,018 | 2.37 (1.65–3.38) | 8/5,050 | | |
| | ACS | 3.53 (2.04–6.10) | 3/5,088 | 16.95 (12.00–23.93) | 2/4,621 | 2.72 (1.52–4.88) | 1/97 |
| | CS | 7.51 (5.58–10.11) | 16/26,121 | 17.11 (9.53–30.73) | 2/42,134 | 7.55 (1.28–44.39) | 4/5,605 |
| $LOS_{ICU}$ | AHF | 0.35 (−0.80–1.51) | 3/2,119 | 3.00 (0.04–5.96) | 1/97 | | |
| | ACS | 2.00 (1.88–2.12) | 1/3,210 | | | | |
| | CS | 1.68 (0.38–2.97) | 5/5,429 | | | 10.63 (3.51–17.74) | 3/5,799 |
| $LOS_{hosp}$ | AHF | 5.79 (1.21–10.37) | 4/2,172 | 2.65 (0.75–4.54) | 5/2,084 | | |
| | ACS | 2.08 (1.01–3.15) | 1/236 | | | | |
| | CS | 3.56 (−1.05–8.16) | 4/4,241 | | | 20.20 (12.17–28.23) | 3/6,045 |

**Vandenberghe et al , Cardiorenal Med 2016;6:116–128**

# Frequent causes of in- hospital AKI in CRS type 1 in heart faiure

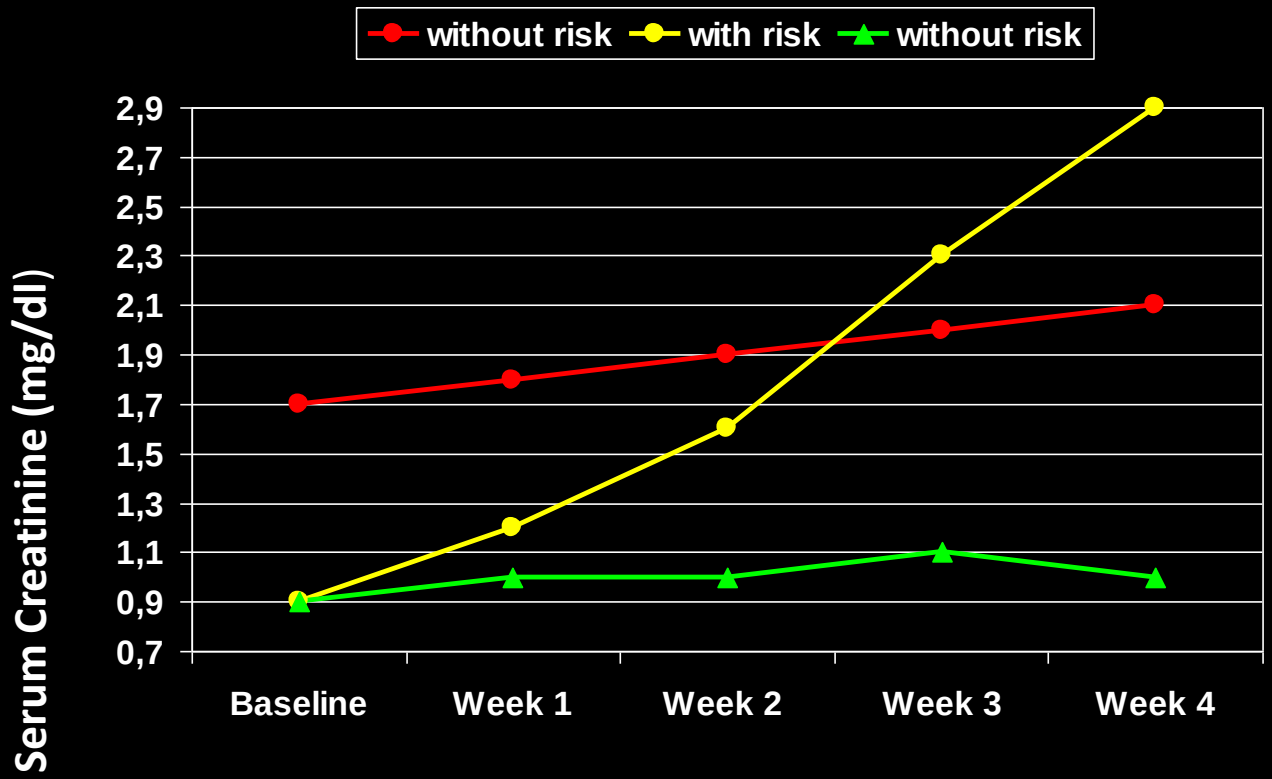
- **Treatment with ACEi and /or angiotensin receptor blockers**
- **Over dehydration by diuretics**
- **Treatment with NSAID**

# Decreased renal perfusion and progression of renal failure in Heart Failure



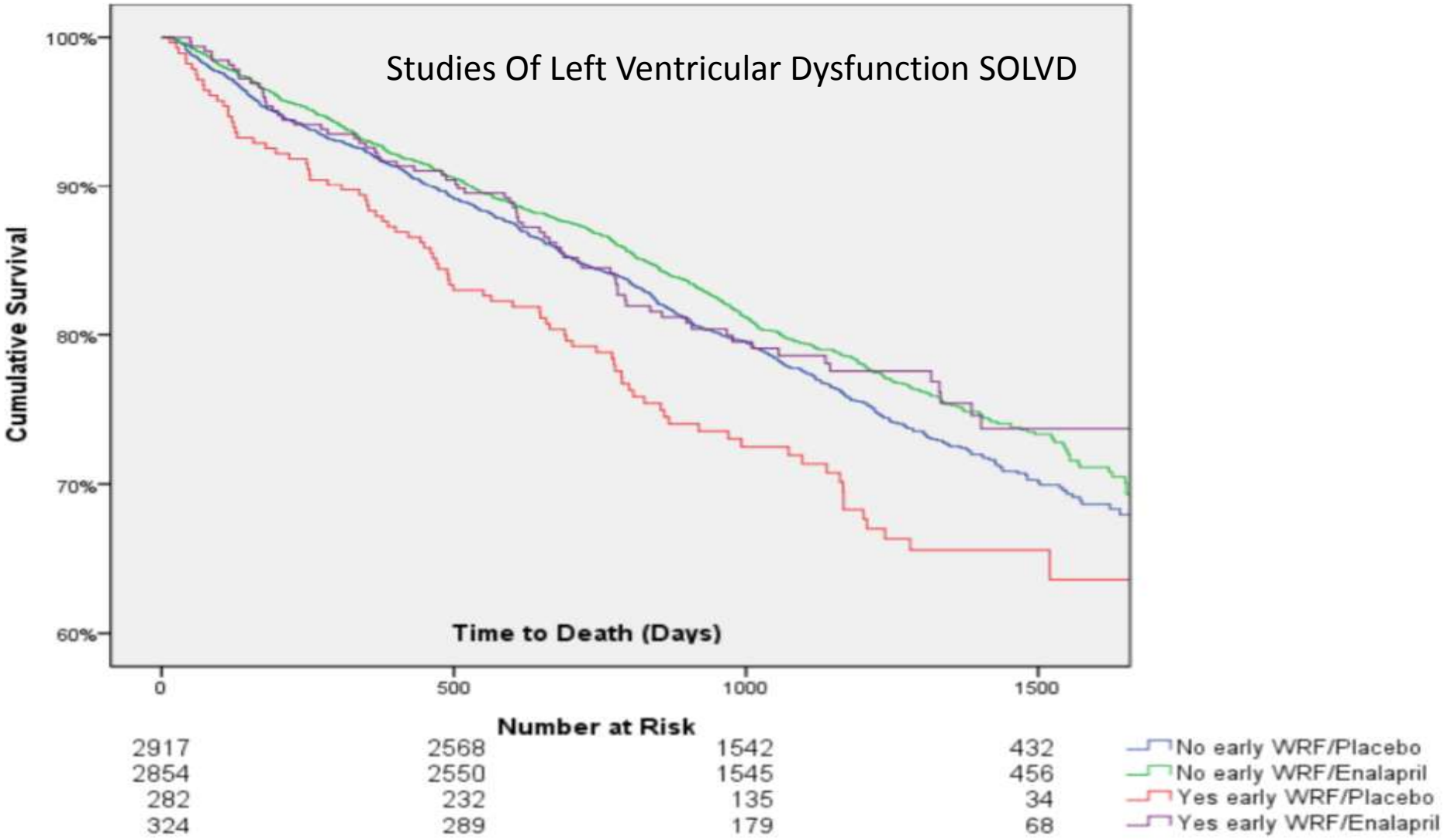

Damman et al, Progress in Cardiovascular Diseases 54 (2011) 144–153

# Possible changes in Screat levels after starting ACE inhibitors




Bakris, Weir Arch Int Med 2000,160: 685-693

# Prognostic Importance of Early WRF Following Initiation of ACE inhibitor in Patients with Cardiac Dysfunction



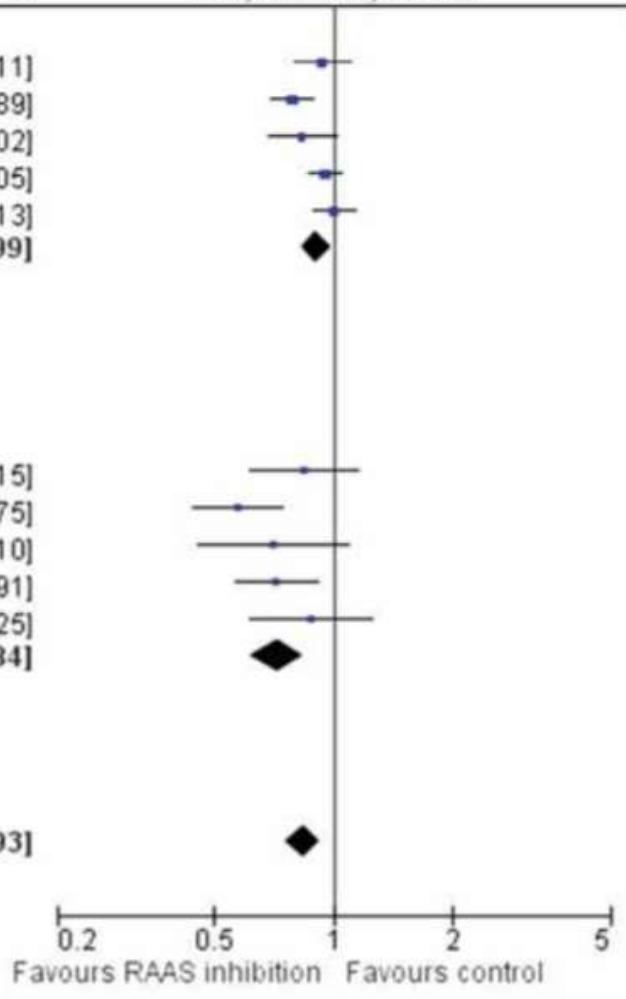

Testani et al, Circ Heart Fail. 2011, 4: 685–691.

**Early WRF:20% fall in GFR from baseline to 14 days post randomization**

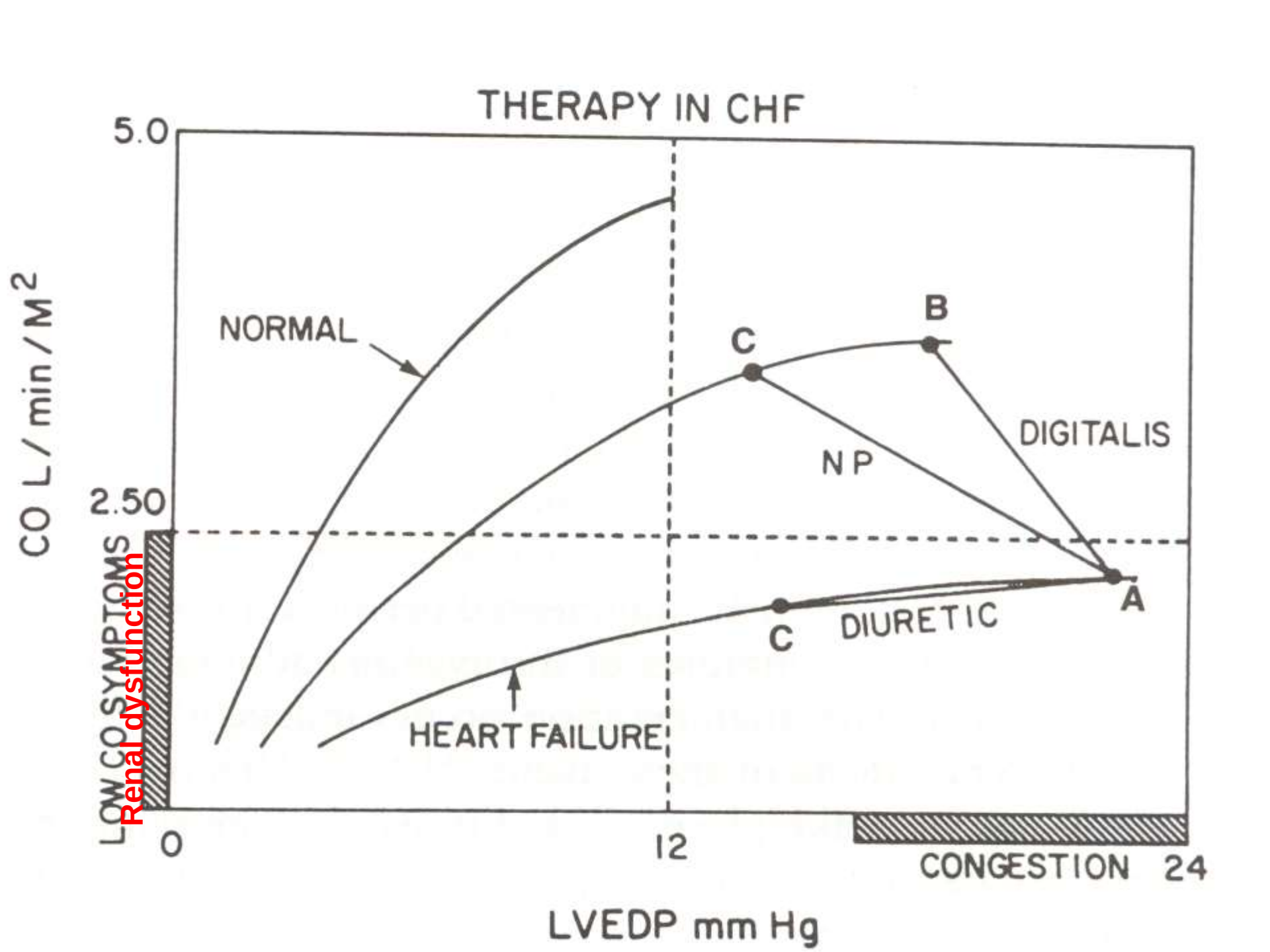
# WRF during RAAS inhibitior initiation and long-term outcomes in patients with LV systolic dysfunction

## A meta-analysis

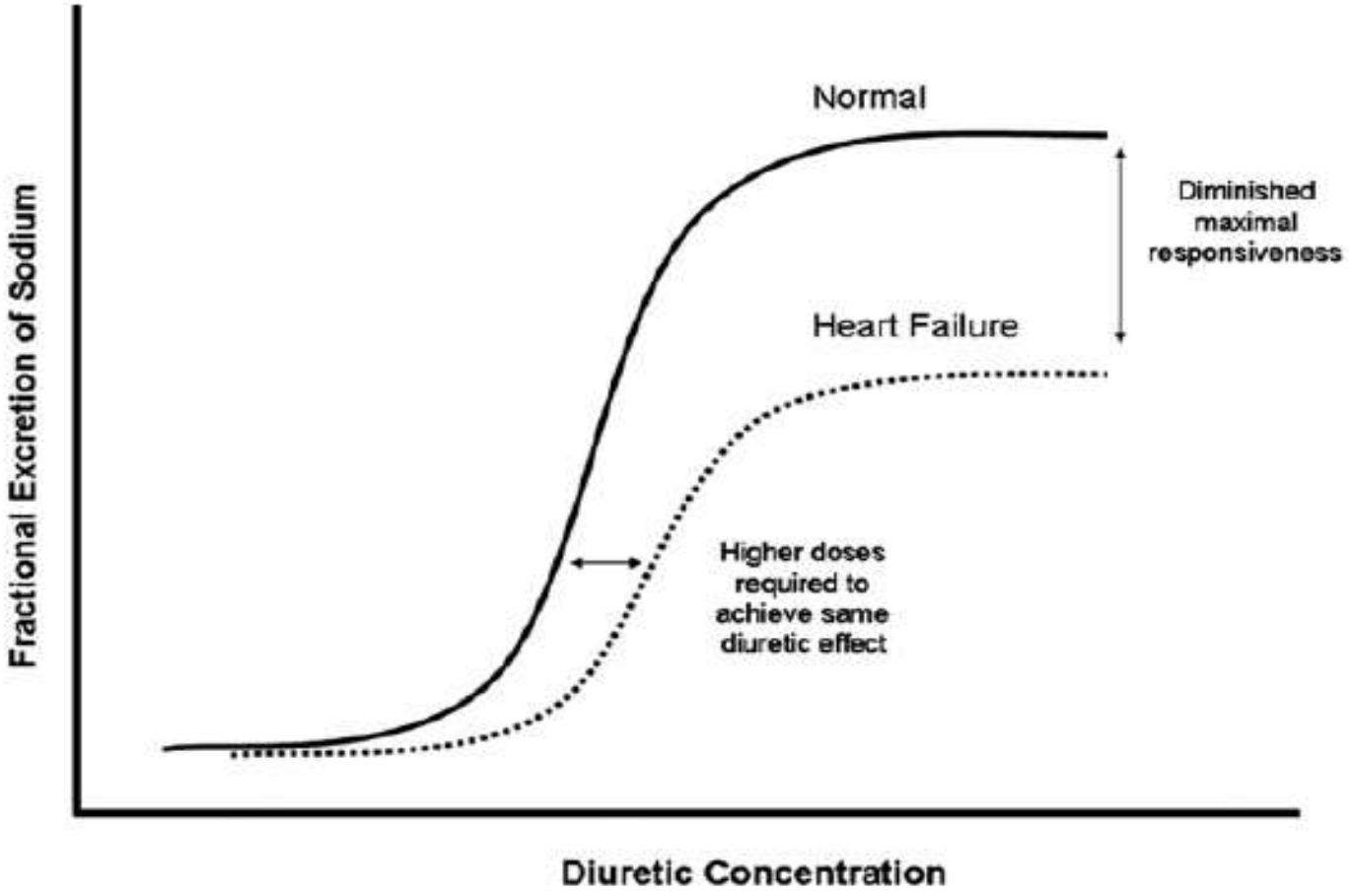
| Study or Subgroup | RAAS inhibition Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 no WRF intervention vs control** | | | | | | |
| EPHESUS (Rossignol 2011) | 255 | 2425 | 274 | 2453 | 12.4% | 0.94 [0.80, 1.11] |
| RALES (Vardeny 2012) | 256 | 683 | 371 | 781 | 14.3% | 0.79 [0.70, 0.89] |
| SAVE (Jose 2006) | 137 | 781 | 171 | 812 | 10.5% | 0.83 [0.68, 1.02] |
| SOLVD (Testani 2011) | 599 | 2854 | 642 | 2917 | 15.4% | 0.95 [0.86, 1.05] |
| VaL-HeFT (Lesogor 2013) | 404 | 2162 | 436 | 2341 | 14.3% | 1.00 [0.89, 1.13] |
| **Subtotal (95% CI)** | | **8905** | | **9304** | **66.8%** | **0.91 [0.83, 0.99]** |
| Total events | 1651 | | 1894 | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.59$, df = 4 (P = 0.05); $I^2 = 58\%$ | | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.04) | | | | | | |
| **2.1.2 WRF intervention vs control** | | | | | | |
| EPHESUS (Rossignol 2011) | 66 | 493 | 67 | 421 | 6.6% | 0.84 [0.61, 1.15] |
| RALES (Vardeny 2012) | 56 | 139 | 42 | 60 | 8.1% | 0.58 [0.44, 0.75] |
| SAVE (Jose 2006) | 26 | 116 | 33 | 104 | 4.1% | 0.71 [0.45, 1.10] |
| SOLVD (Testani 2011) | 84 | 324 | 102 | 282 | 8.9% | 0.72 [0.56, 0.91] |
| VaL-HeFT (Lesogor 2013) | 71 | 302 | 33 | 123 | 5.5% | 0.88 [0.61, 1.25] |
| **Subtotal (95% CI)** | | **1374** | | **990** | **33.2%** | **0.72 [0.62, 0.84]** |
| Total events | 303 | | 277 | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.19$, df = 4 (P = 0.27); $I^2 = 23\%$ | | | | | | |
| Test for overall effect: Z = 4.10 (P < 0.0001) | | | | | | |
| **Total (95% CI)** | | **10279** | | **10294** | **100.0%** | **0.84 [0.76, 0.93]** |
| Total events | 1954 | | 2171 | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.39$, df = 9 (P = 0.003); $I^2 = 65\%$ | | | | | | |
| Test for overall effect: Z = 3.40 (P = 0.0007) | | | | | | |
| Test for subgroup differences: $Chi^2 = 6.09$, df = 1 (P = 0.01), $I^2 = 83.6\%$ | | | | | | |




Clark et al, European Journal of Heart Failure (2014) 16, 41–48

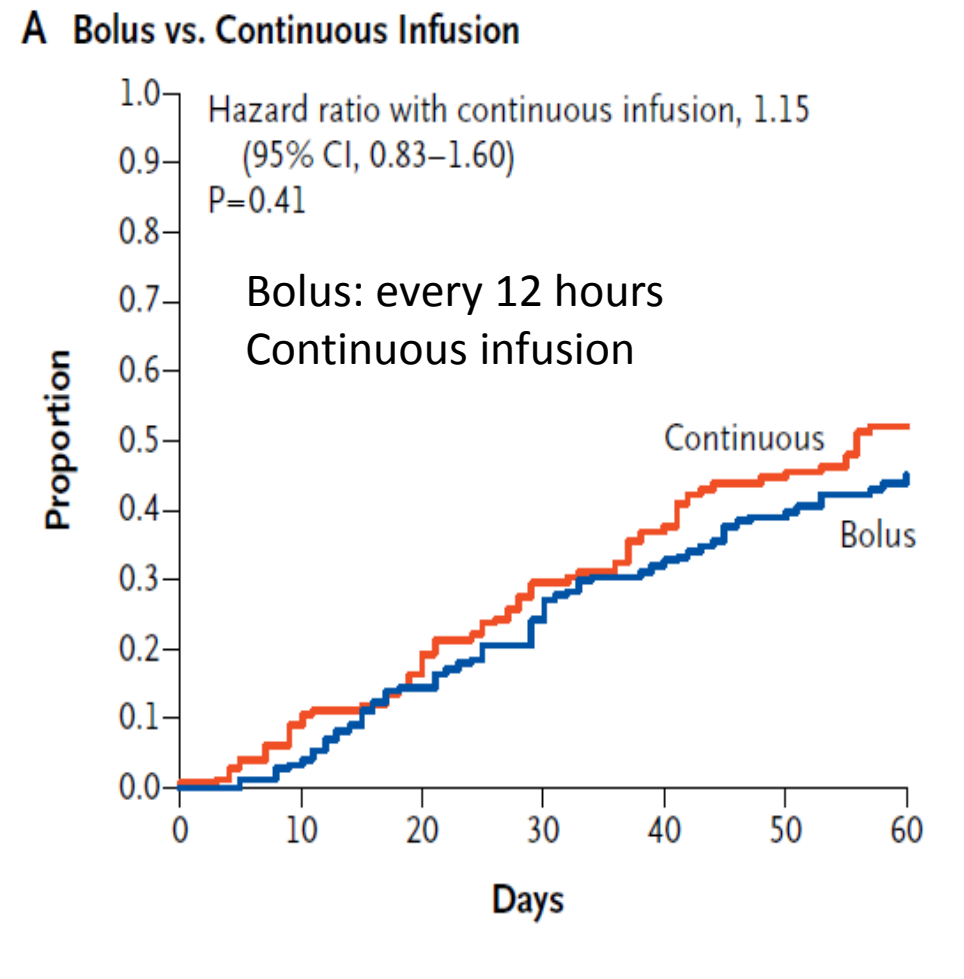

THERAPY IN CHF
5.0
2.50
CO L / min / M2
NORMAL
B
C
DIGITALIS
NP
A
C
DIURETIC
HEART FAILURE
LOW CO SYMPTOMS
Renal dysfunction
0
12
CONGESTION
24
LVEDP mm Hg

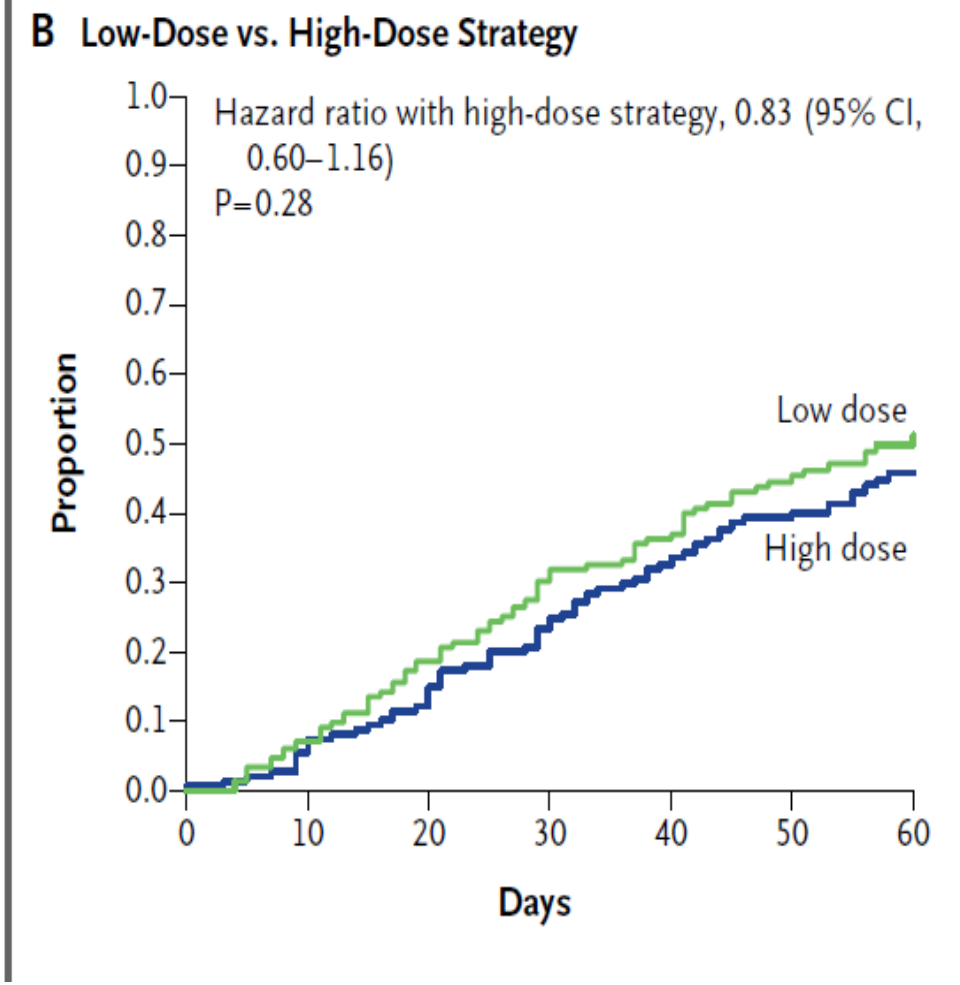
# Schematic of Dose–Response Curve of Loop Diuretics in Heart Failure Patients Compared With Normal Controls




Ellison DH. Cardiology 2001;96:132– 143.

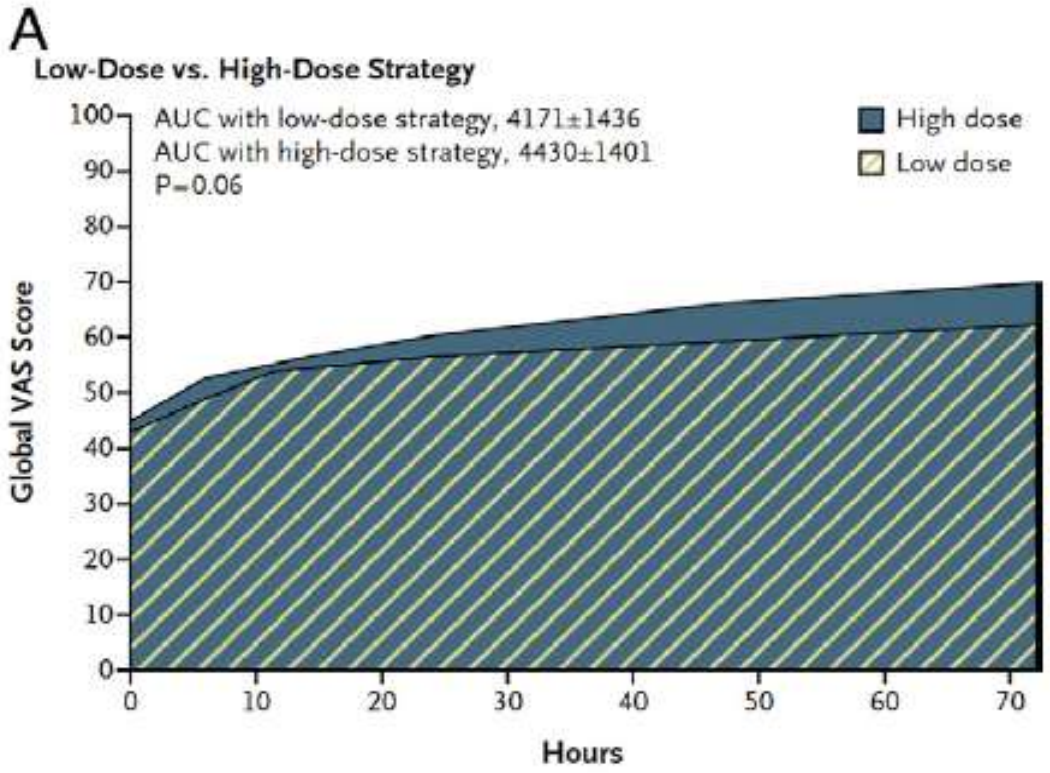
# Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit (diuretic trial).



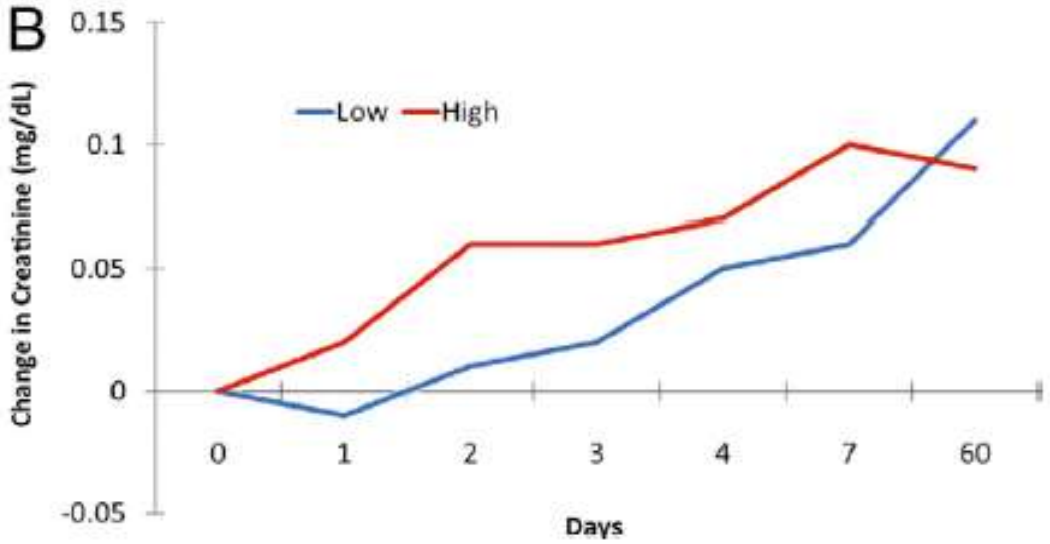

Felker et al, N Engl J Med 2011;364:797-805.

IV High dose: 2.5 times the home oral dose
IV Low dose: dose equivalent home oral dose




# Diuretic DOSE study

## Global Assessment of Symptoms (by Visual Analog Scale) During the 72-h Study Treatment




## Changes in sCr Over Time

Felker et al, N Engl J Med 2011;364:797-805

**Despite the use of diuretics,**

**a significant percentage of patients admitted for acute decompensated CHF**

**are discharged with a little or no weight loss and persistent symptomatology[1]**

**and**

**in 90% of patients, 20% gain weight on discharge[2],**

**44% are readmitted within 6 months[3]**

*1 ADHERE® Registry. 3rd Quarter. 2003 National Benchmark Report. http://www.adhereregistry.com/national_BMR/index.html*

*2 Adams et al. Am Heart J. 2005;149:209-216*

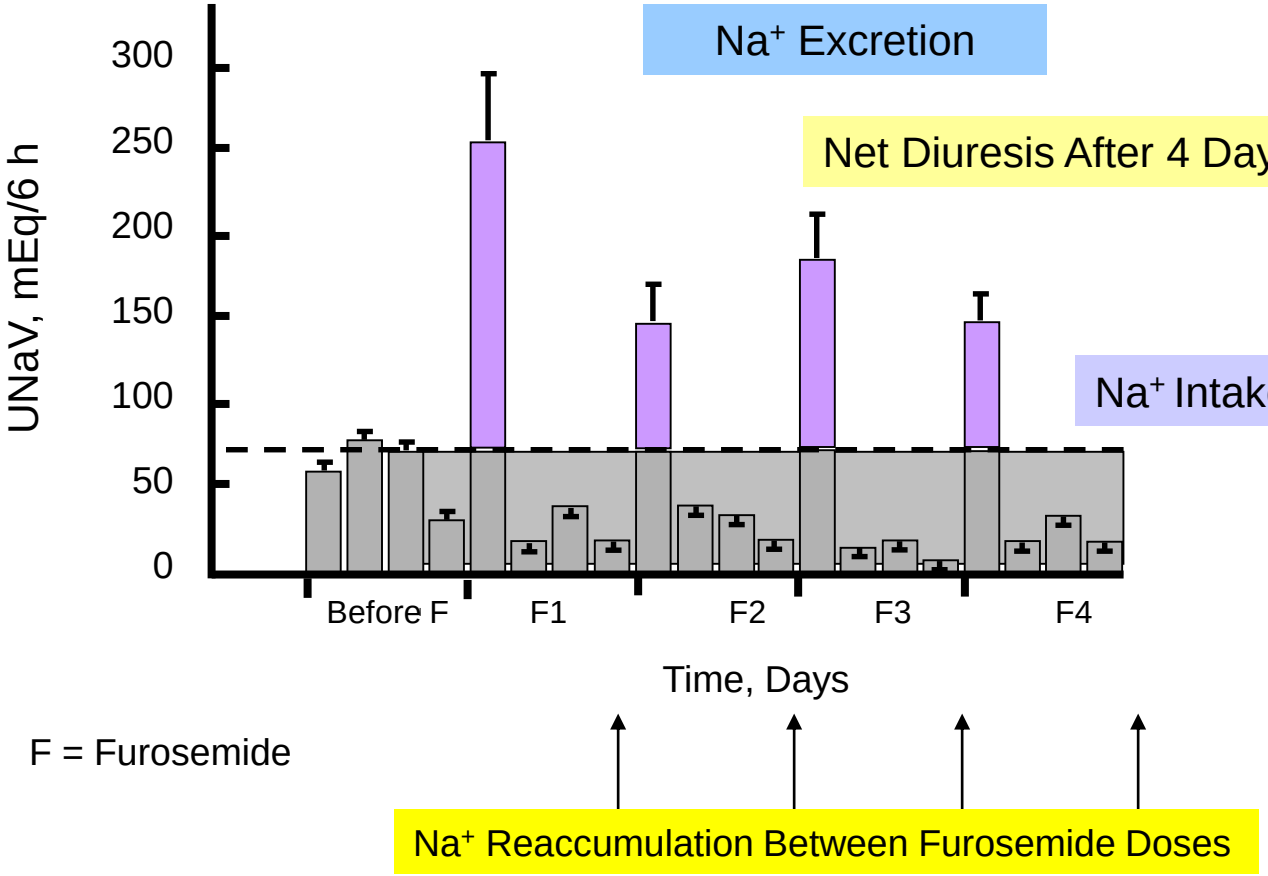
*3 Costanzo MR, J ACC 2007*

# Definition of Diuretic Responsiveness (DR) by Study and Associated Patient Outcomes

| Definition of Diuretic Responsiveness | Outcomes |
|---|---|
| Urine output/40 mg of furosemide [1] | Increased mortality in low DR |
| Weight change/diuretic dose over 5 days [2] | Increased mortality and rehospitalization rates in low DR |
| Weight change/40 mg of furosemide [3] | Increased mortality and rehospitalization rates in low DR |


1.Testani et al. Circ Heart Fail 2014;7:261–270.
2. Voors et al. Eur J Heart Fail 2014;16:1230–1240.
3. Valente et al. Eur Heart J 2014;35:1284–1293.

# Reaccumulation of $Na^+$ despite continuation of furosemide treatment

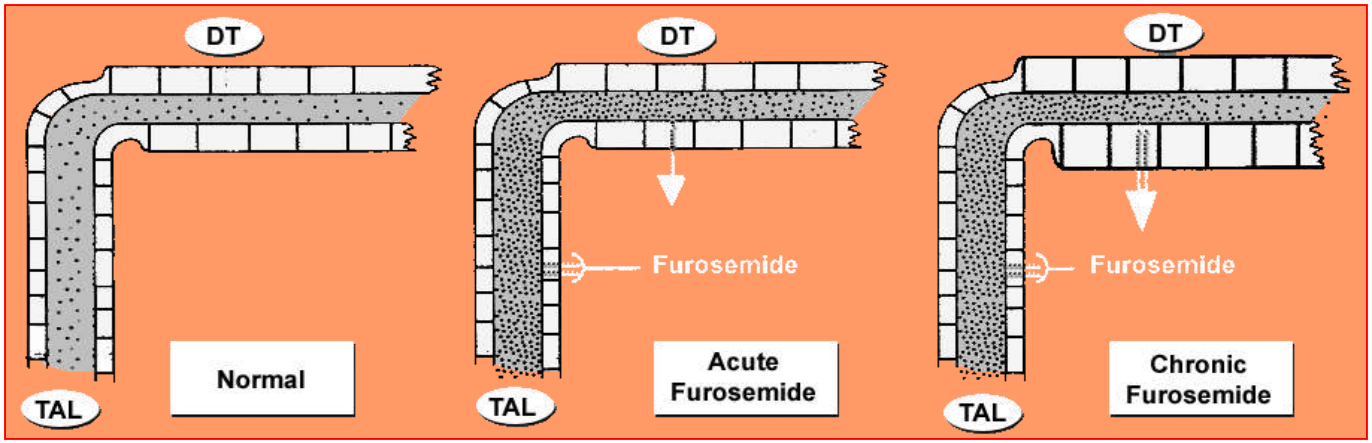



**Wilcox et al. *Kidney Int.* 1987;31:135.**

# Two mechanisms of diuretic resistance

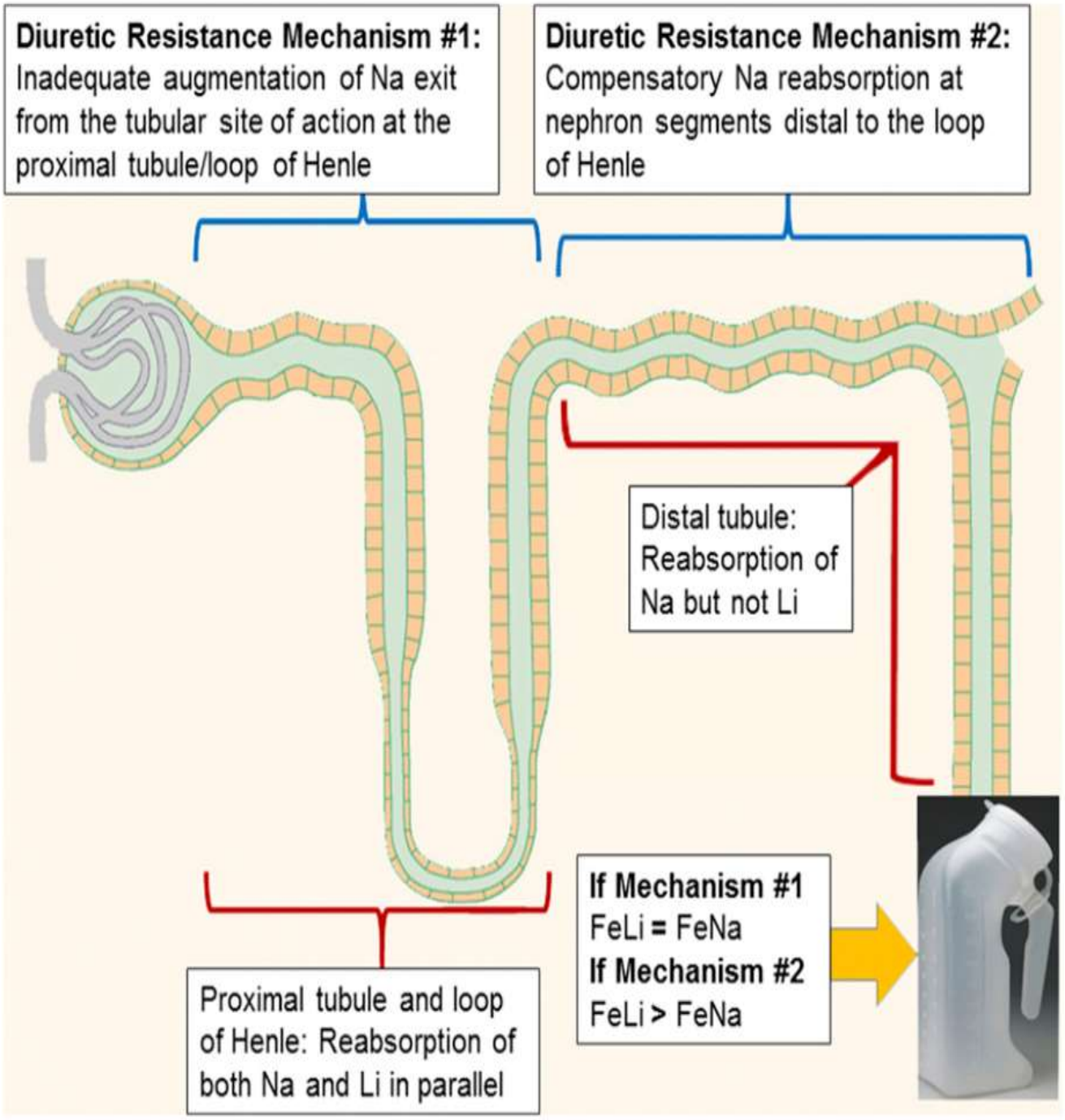
- **“Braking” phenomenon**
  - –A decrease in response to a diuretic after the first dose has been administered

- **Long-term tolerance**
  - –Tubular hypertrophy to compensate for salt loss



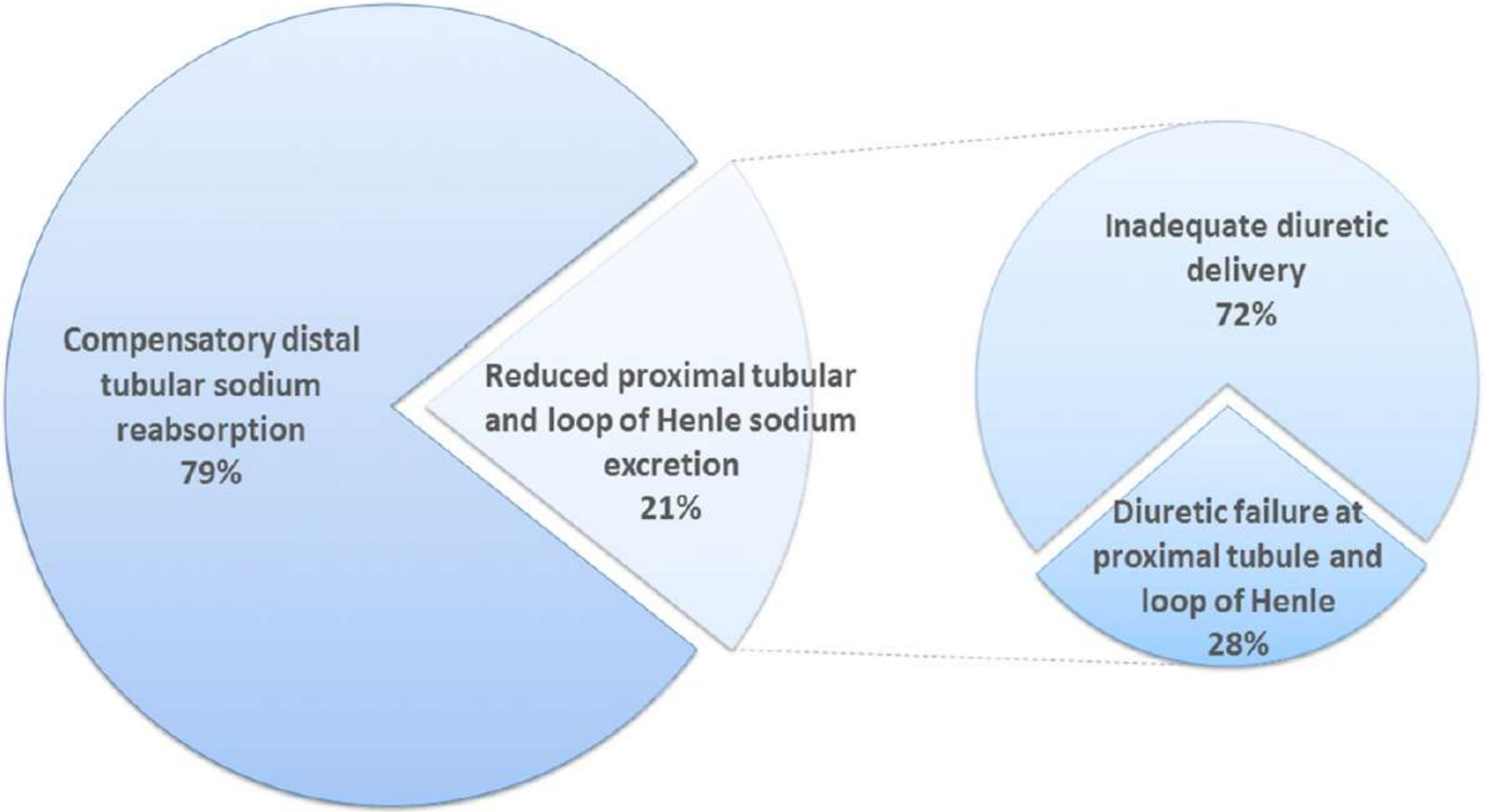

Brater. *N Engl J Med*. 1998;339:387.

# Localization of the diuretic resistance, using the FE Lithium




Rao et al J Am Soc Nephrol 28: ccc–ccc, 2017.

# Relative contribution of different intrarenal mechanisms to diuretic-induced increase in FENa.




Rao et al J Am Soc Nephrol 28: ccc–ccc, 2017.

# Management of Diuretic Resistance in CRS

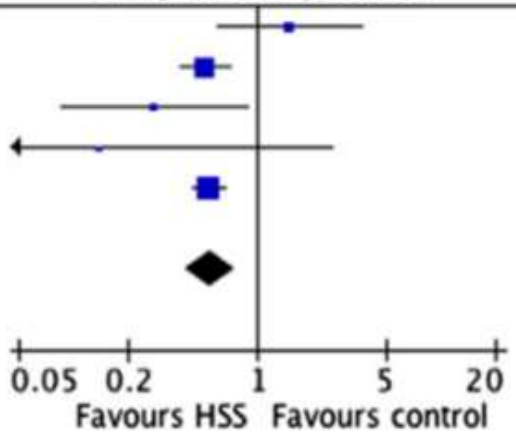
- Restrict daily fluid intake (1.0 L)
- Moderate restriction of daily salt intake (≤2 g)
- Avoid NSAIDs
- Institute and uptitrate ACE inhibitors and/or angiotensin receptor blocker
- Give short-acting loop diuretic orally in several divided (and increasing) doses, bolus, or continuous intravenous administration
- Use sequential nephron blockade via combination loop diuretic and thiazide diuretic
- Add small doses of spironolactone (12.5–25 mg)
- Consider short-term acetazolamide in selected patients

# Hypertonic saline with furosemide for the treatment of acute congestive heart failure: A systematic review

| Study or Subgroup | HSS Events | HSS Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Issa 2011 | 10 | 20 | 4 | 12 | 9.9% | 1.50 [0.60, 3.74] |
| Licata 2002 | 24 | 53 | 47 | 54 | 36.6% | 0.52 [0.38, 0.71] |
| Paterna 2000 | 3 | 30 | 11 | 30 | 6.5% | 0.27 [0.08, 0.88] |
| Paterna 2005 | 0 | 48 | 3 | 46 | 1.1% | 0.14 [0.01, 2.58] |
| Paterna 2011 | 114 | 881 | 212 | 890 | 45.9% | 0.54 [0.44, 0.67] |
| **Total (95% CI)** | | **1032** | | **1032** | **100.0%** | **0.56 [0.41, 0.76]** |
| Total events | 151 | | 277 | | | |

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 7.01$, df = 4 (P = 0.14); $I^2 = 43\%$

Test for overall effect: Z = 3.63 (P = 0.0003)

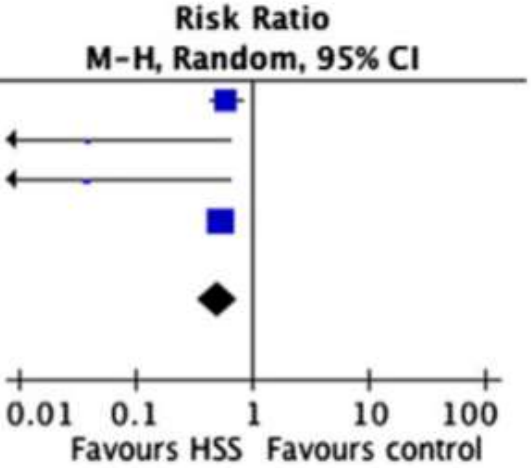



## Effect on mortality

| Study or Subgroup | HSS Events | HSS Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Licata 2002 | 25 | 53 | 43 | 54 | 43.1% | 0.59 [0.43, 0.81] |
| Paterna 2000 | 0 | 30 | 12 | 30 | 2.1% | 0.04 [0.00, 0.65] |
| Paterna 2005 | 0 | 48 | 12 | 46 | 2.1% | 0.04 [0.00, 0.63] |
| Paterna 2011 | 163 | 881 | 305 | 890 | 52.7% | 0.54 [0.46, 0.64] |
| **Total (95% CI)** | | **1012** | | **1020** | **100.0%** | **0.50 [0.33, 0.76]** |
| Total events | 188 | | 372 | | | |

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 7.74$, df = 3 (P = 0.05); $I^2 = 61\%$

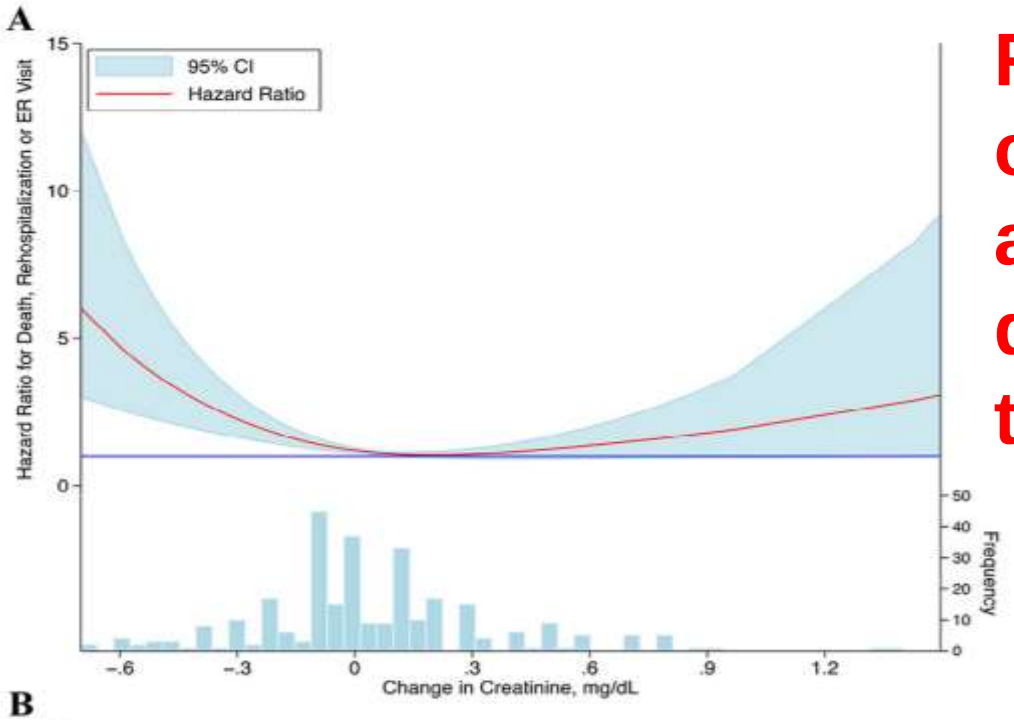
Test for overall effect: Z = 3.27 (P = 0.001)



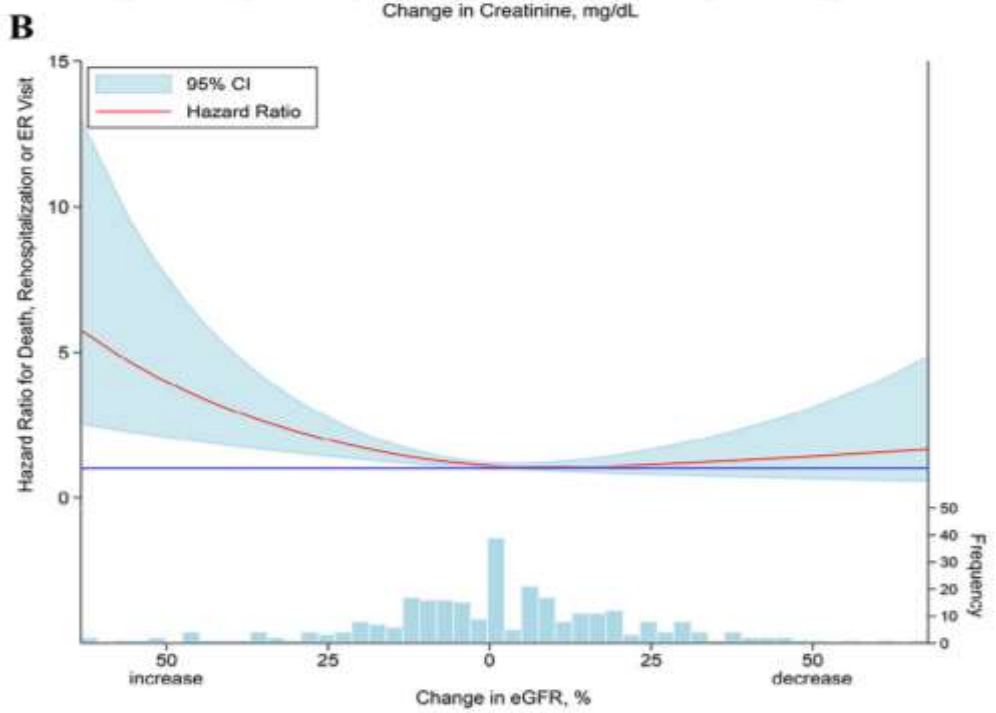

## Effect on rehospitalization

Gandhi et al , International Journal of Cardiology 173 (2014) 139–145

# Relationship between changes in renal function and clinical outcomes during decongestion therapies



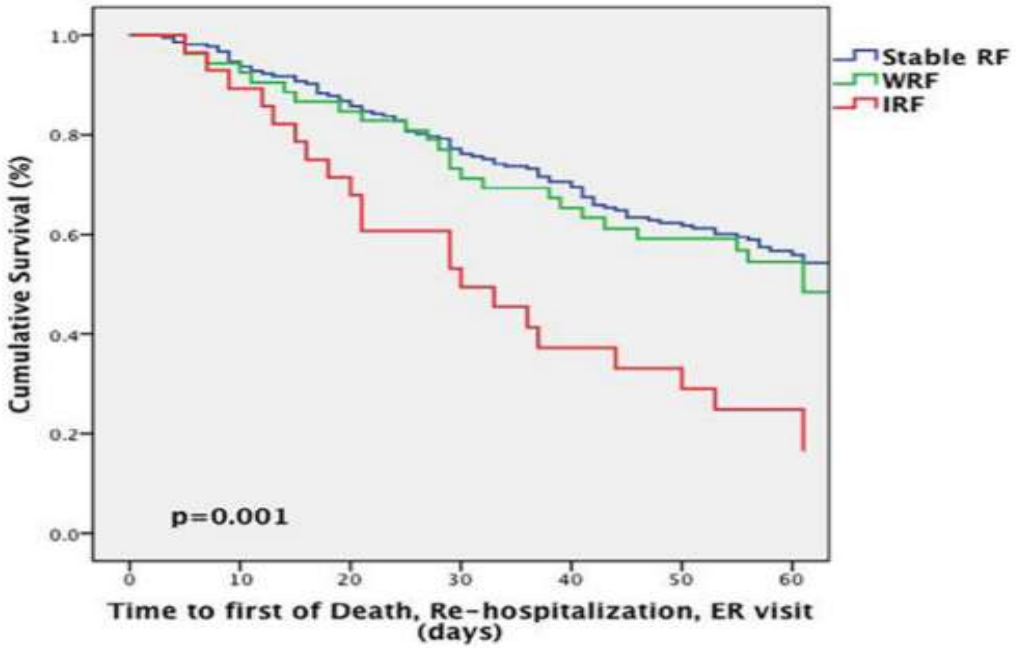

Change in SCr



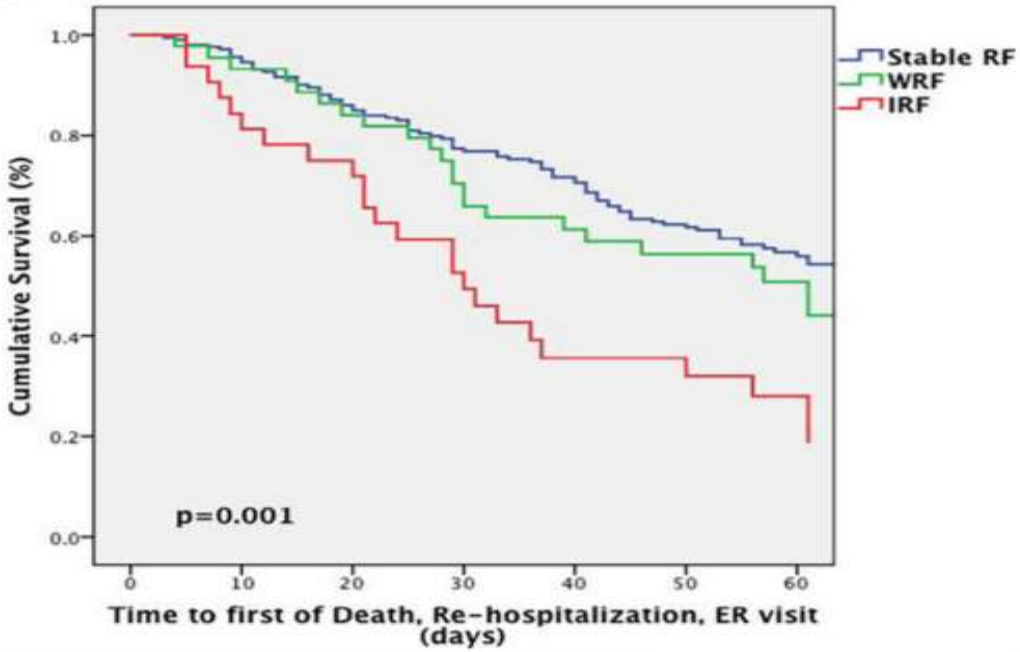

Change in eGFR

Brisco et al , J Cardiac Fail 2016;22:753–760

**A**




**B**



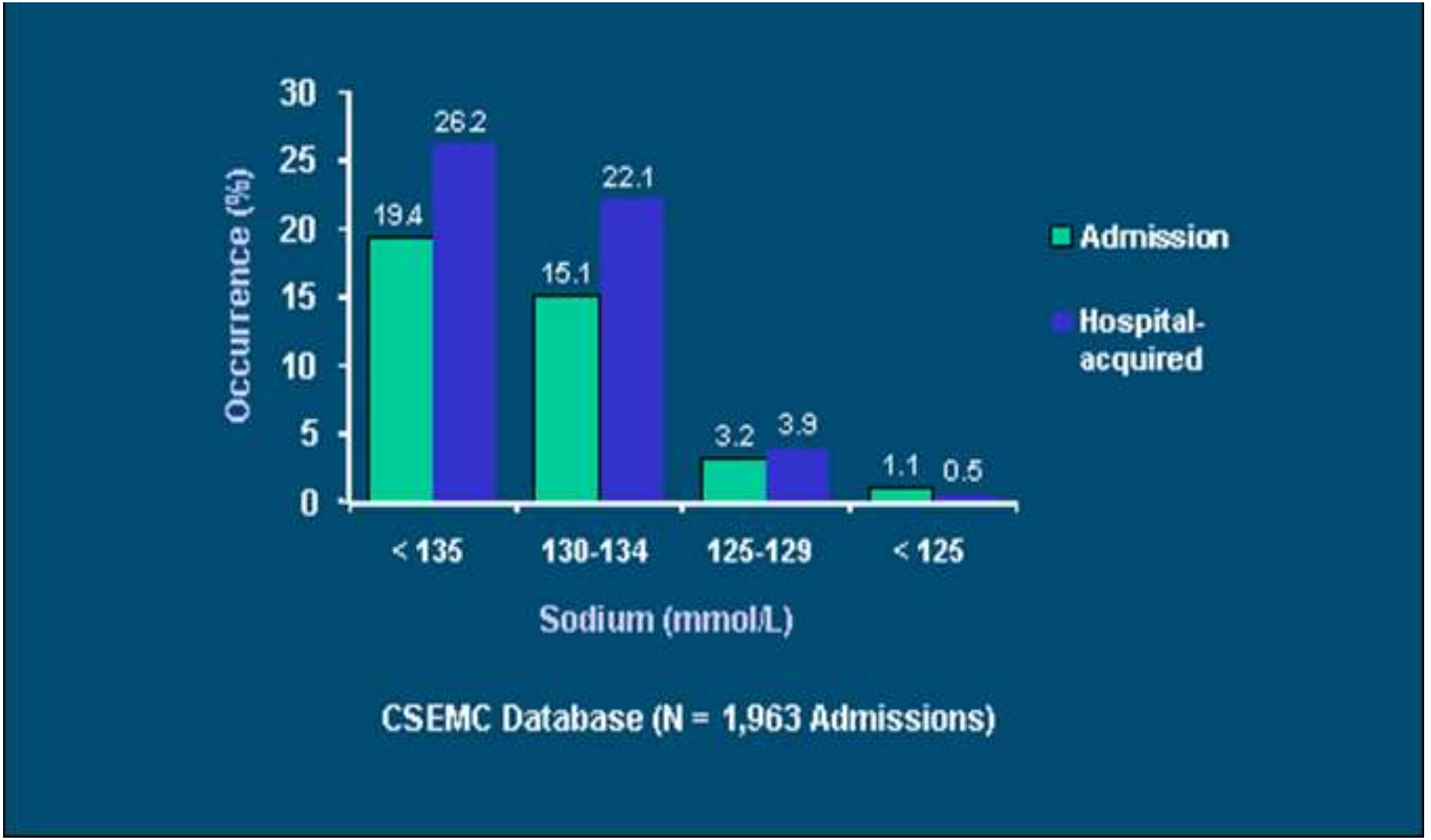

**Survival of the risk of death, rehospitalization, or emergency department visit by stable, worsening, or improvement in renal function during decongestive therapy**

Brisco et al , J Cardiac Fail 2016;22:753–760

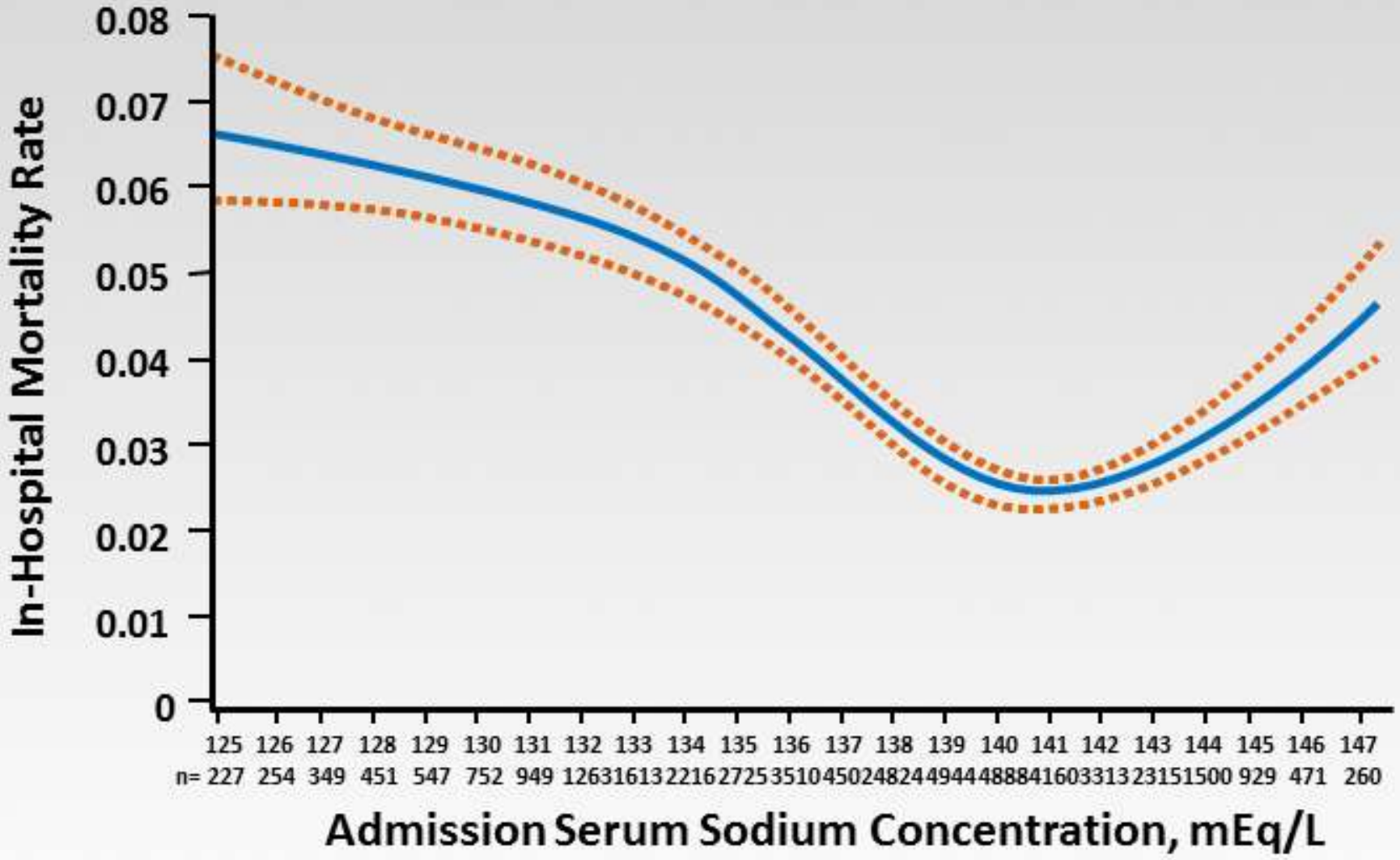
# Hyponatremia is associated with activation of neurohormones

- Renin angiotensin system
- Sympathetic nervous system
- Vasopressin

# Occurrence of Hyponatremia in Patients with Heart Failure Admitted to an Acute Care Hospital

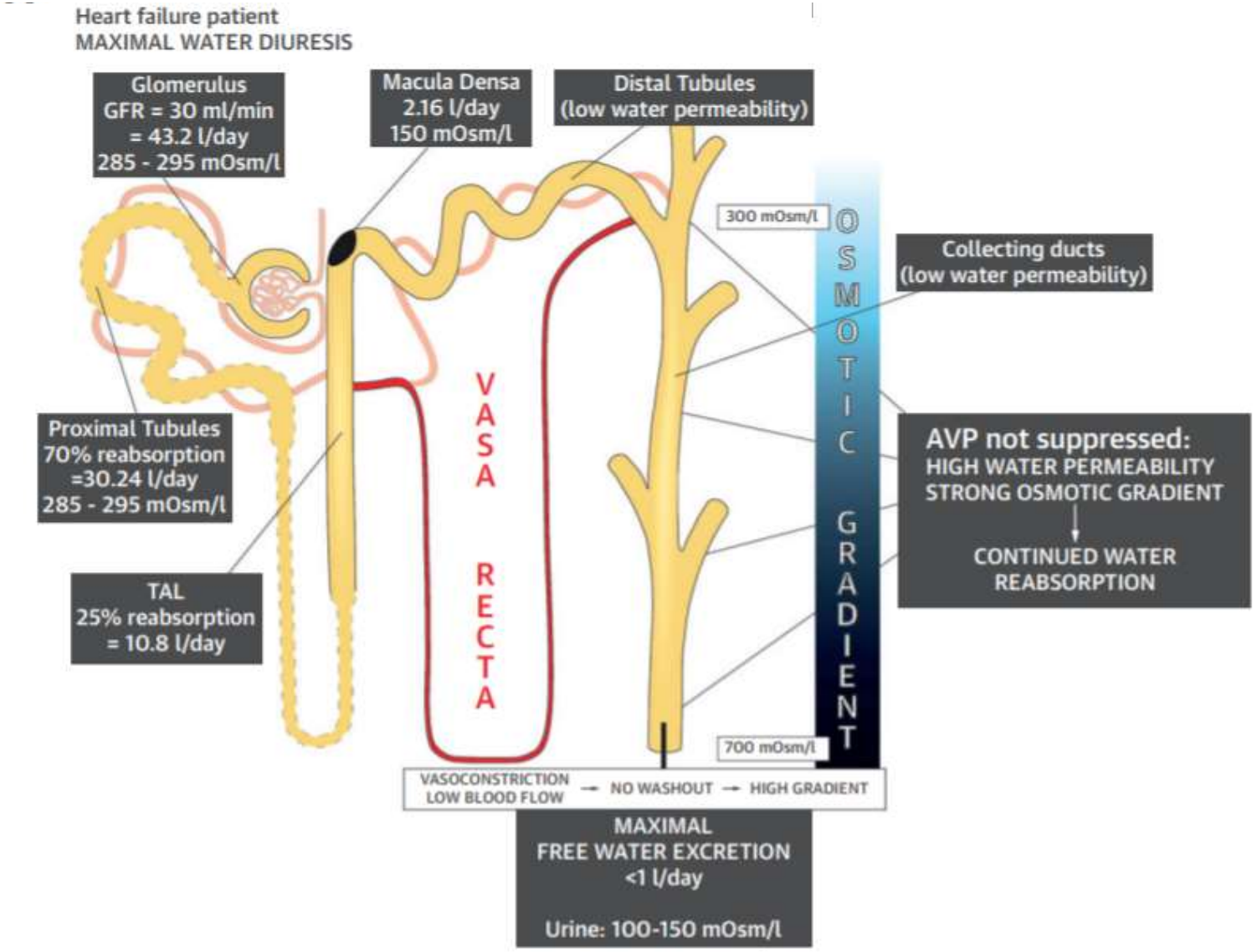


# Relationship between admission serum sodium level and in-hospital mortality (OPTIMIZE-HF Registry)




Gheorghiade et al, Eur Heart J, 2007, 28: 980- 988.

# Maximal free water excretion in heart failure and reduced GFR




Verbrugge et al, J Am Coll Cardiol 2015;65:480–492

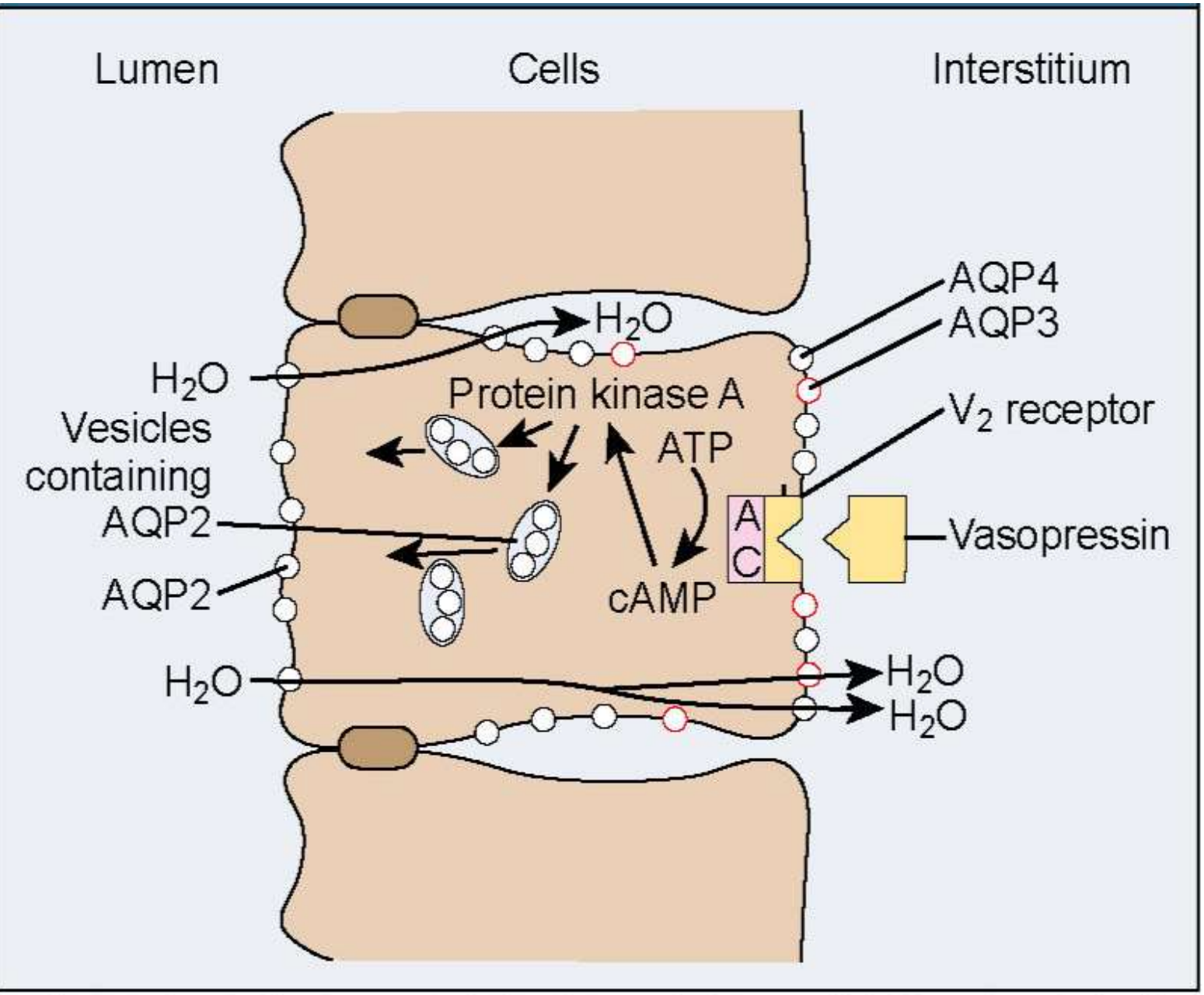
# Pathophysiology of hyponatremia in acute decompensated heart failure

| | Mechanism of Action |
|---|---|
| **Dilutional hyponatremia** | |
| Increased sensitivity of osmotic AVP release → Lower osmo-checkpoint* | Baroreceptor activation/angiotensin II |
| Increased nonosmotic AVP release | Baroreceptor activation/angiotensin II |
| Impaired AVP degradation | Liver and/or kidney dysfunction |
| Increased thirst | Baroreceptor activation/angiotensin II |
| Decreased distal nephron flow | Impaired glomerular filtration/Increased proximal tubular reabsorption |
| **Depletional hyponatremia** | |
| Low sodium intake | Salt-restricted diet |
| Exaggerated nonurinary sodium losses | Diarrhea, ascites |
| Exaggerated natriuresis | Diuretics, osmotic diuresis |
| Sodium shift toward the intracellular compartment | Potassium and/or magnesium deficiency |

*This is the level of plasma osmolality that is pursued by the homeostatic mechanisms of the body.

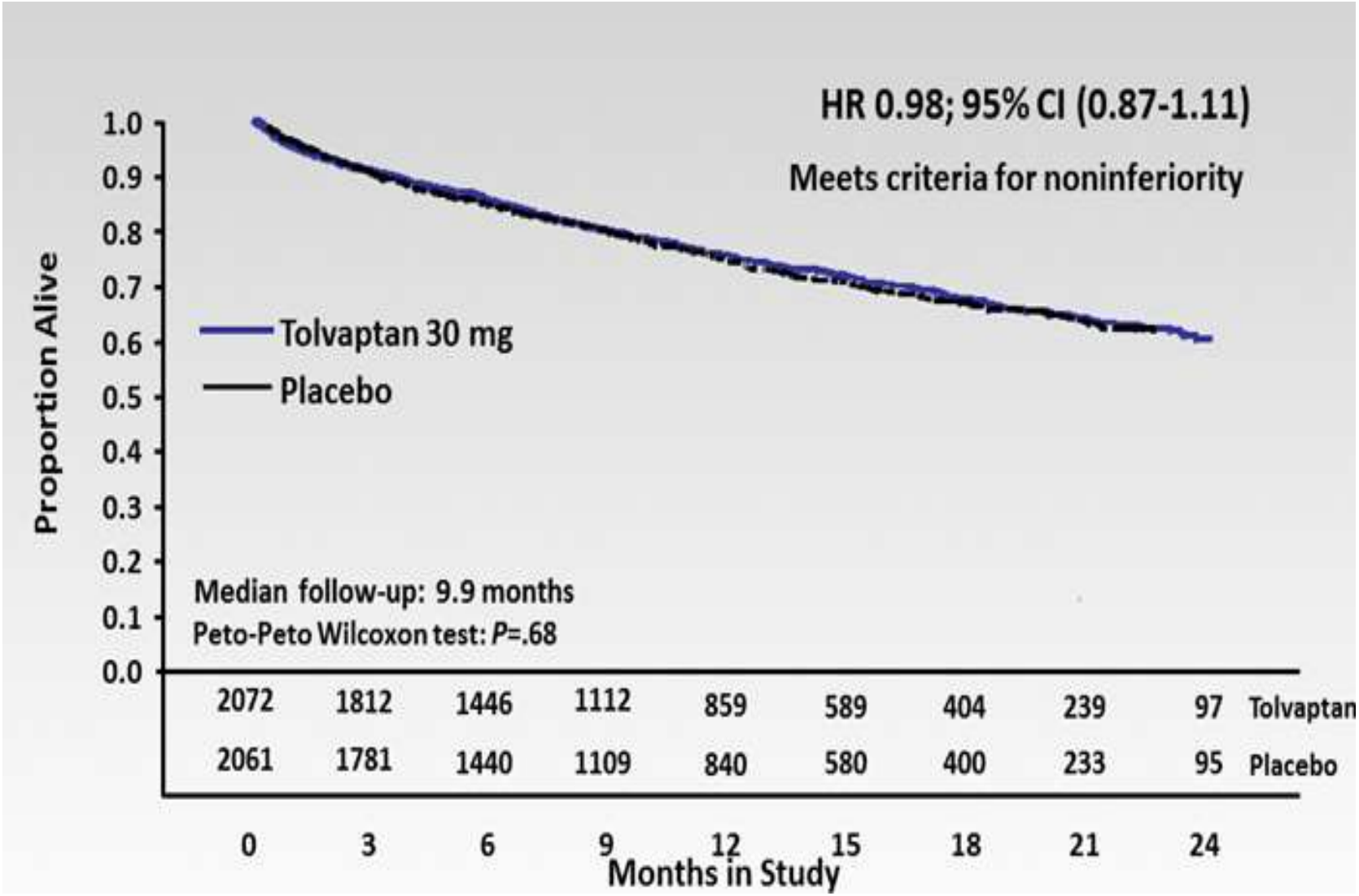
Verbrugge et al, J Am Coll Cardiol 2015;65:480–492

# Action of vasopressin

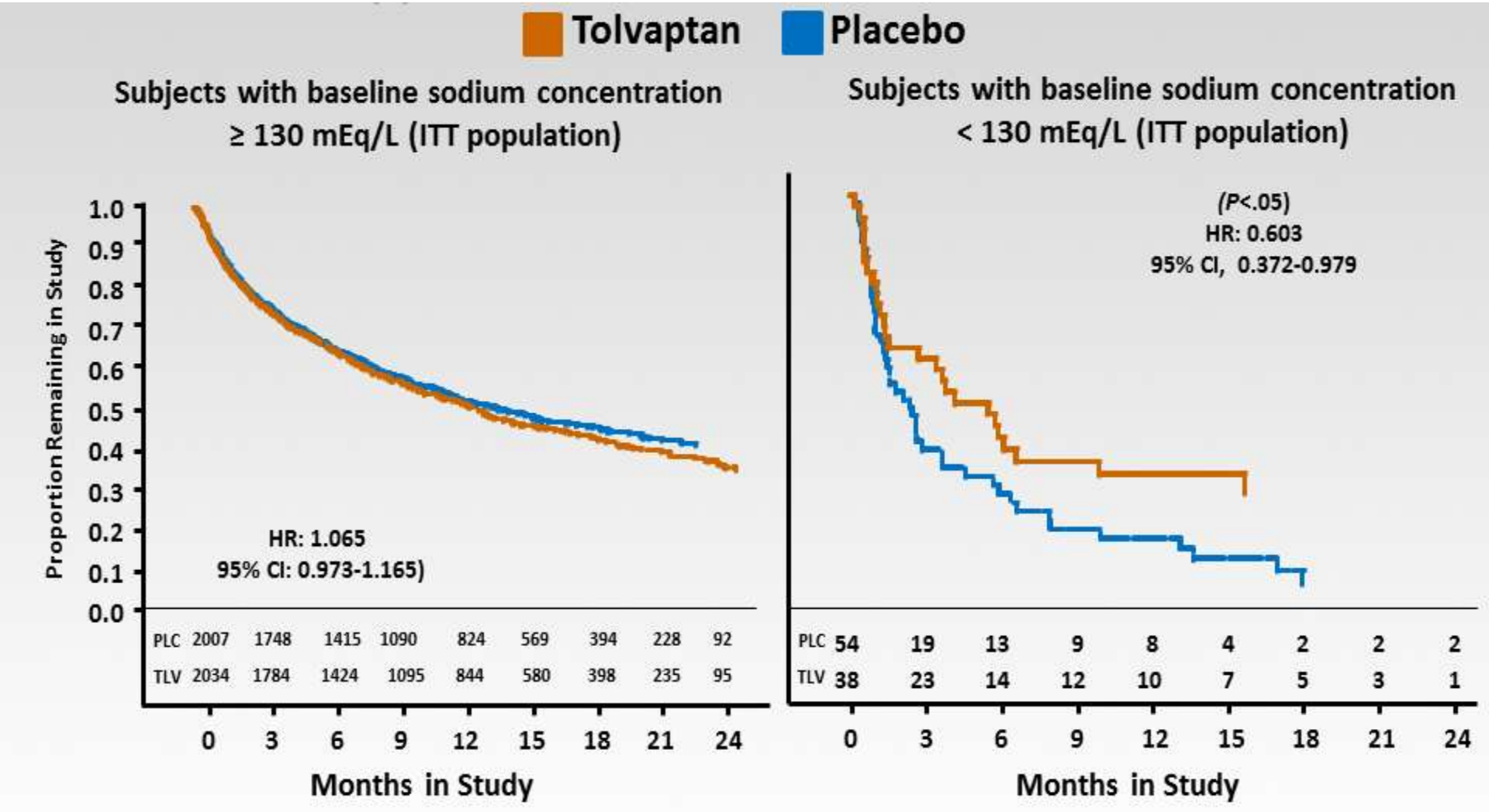



Comprehensive Clin Nephrology Eds Floege et al 2010

# Overall survival EVEREST trial

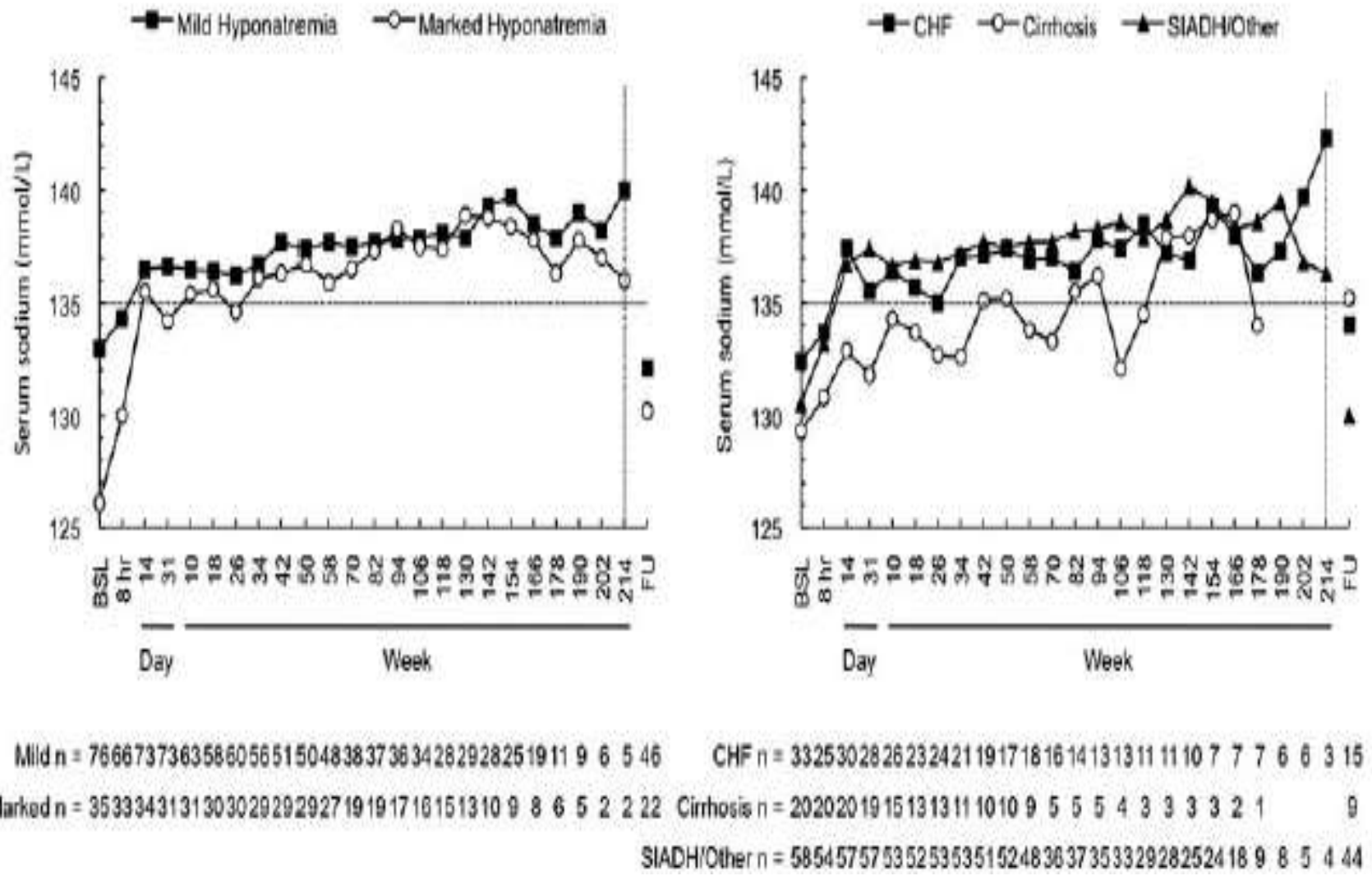


# EVEREST: CV Mortality/Morbidity in patients with heart failure with and without hyponatremia – effect of oral tolvaptan



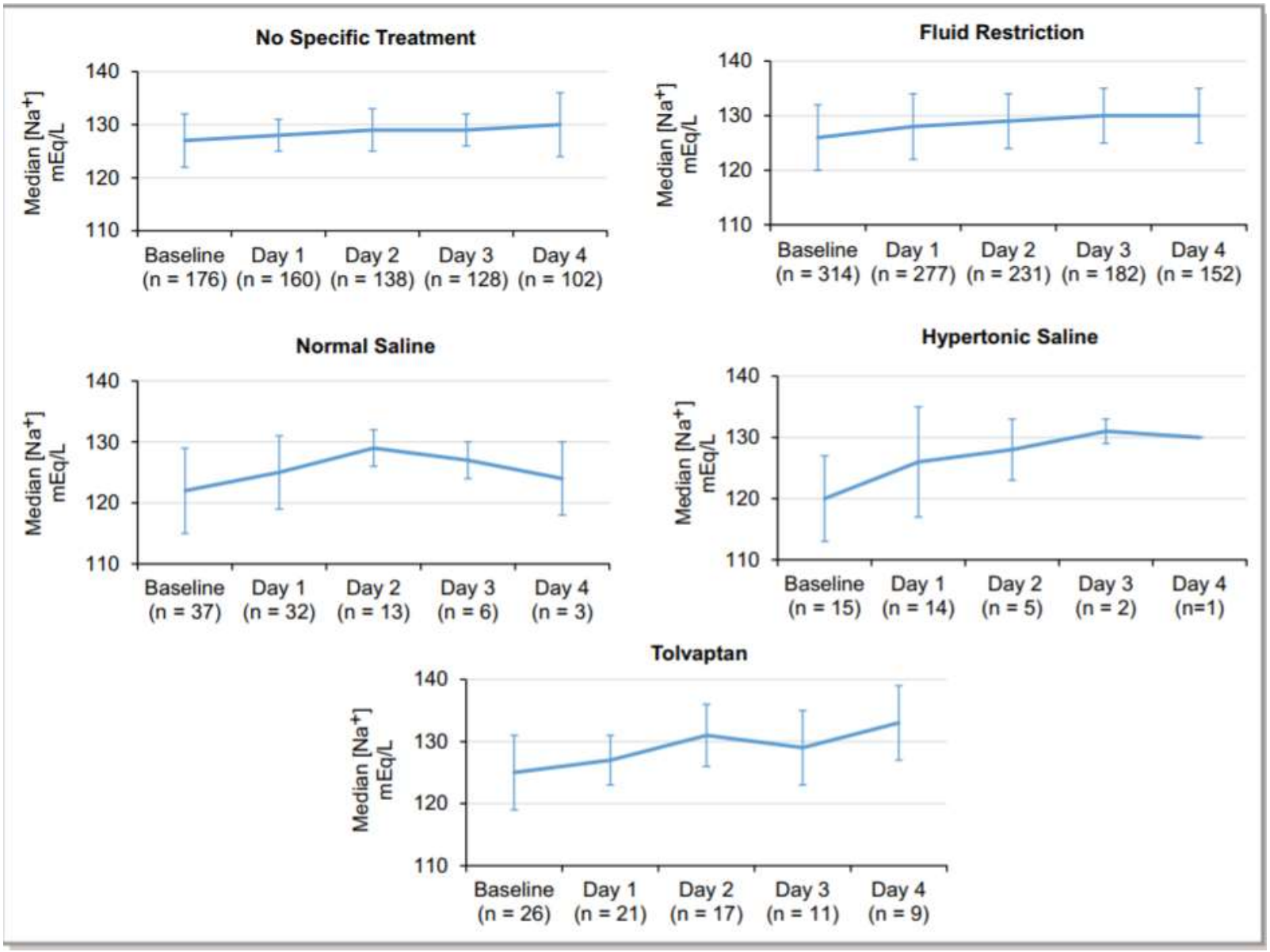

Konstam, et al. JAMA, 2007, 297: 1319-1331

# Long term safety of oral tolvaptan treatment in hyponatremia




Berl et al, *J Am Soc Nephrol 21: 705–712, 2010*

# Current management of hyponatremia in heart failure-changes in serum sodium concentration over time by treatment received

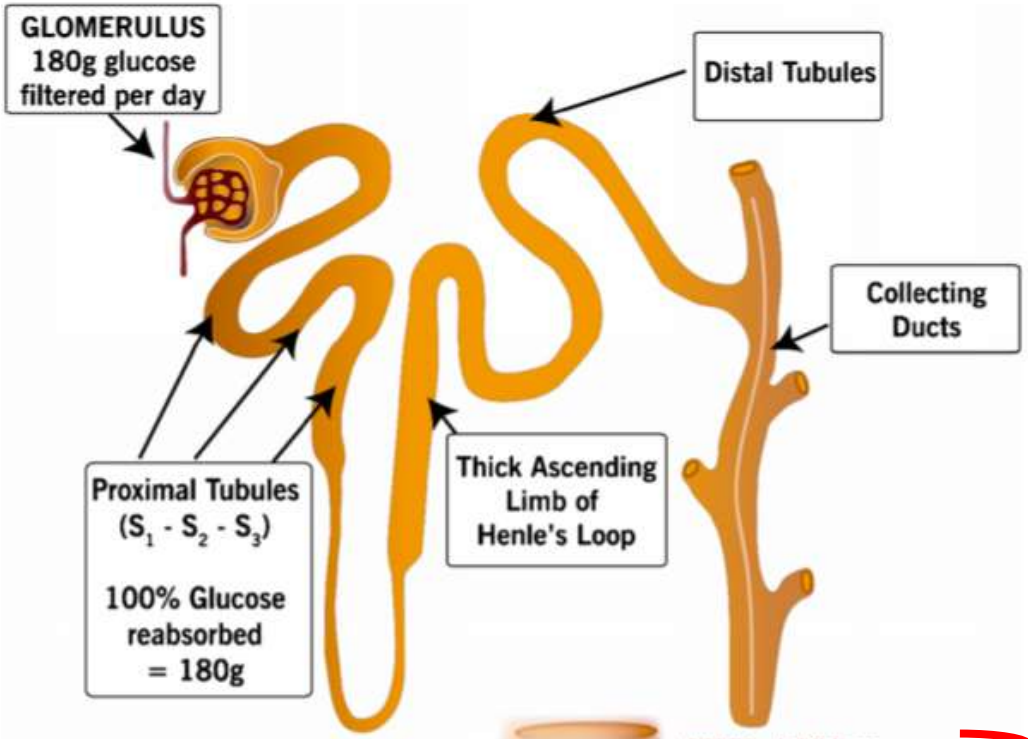


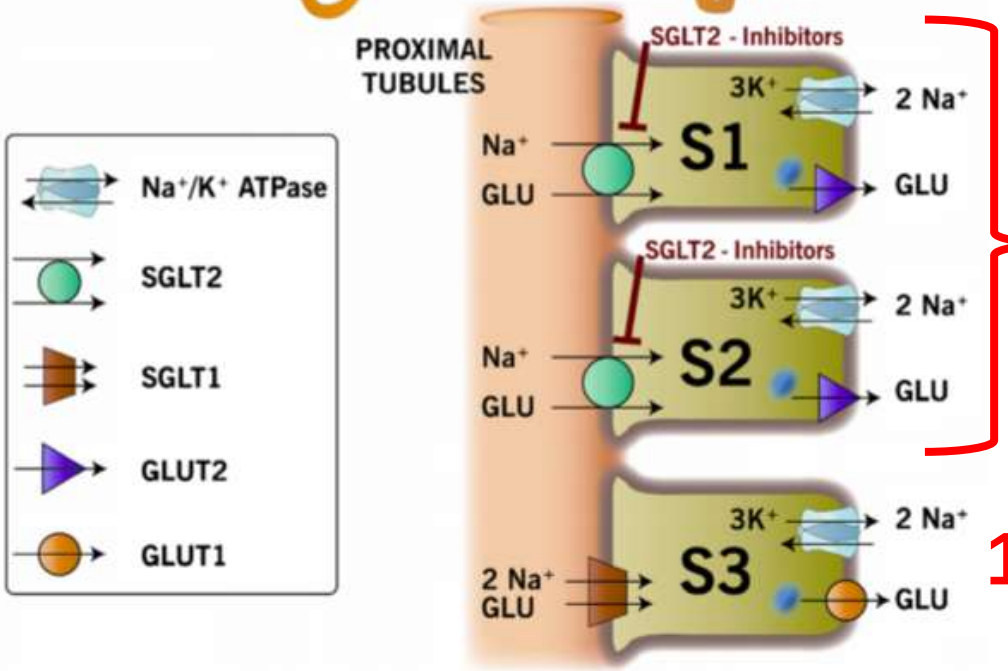

**Dunlap et al , (J Am Heart Assoc. 2017;6:e005261.**

# Side effects of tolvaptan

| Classification by systems and organs | Frequency |
|---|---|
| Metabolism and nutrition disorders | Common: polydipsia, dehydration, hyperkalemia, hyperglycemia, decreased appetite |
| Disorders of the nervous system | Uncommon: dysgeusia |
| Vascular disorders | Common: orthostatic hypotension |
| Gastrointestinal disorders | Very common: nausea; common: constipation, dry mouth |
| Disorders of skin and subcutaneous tissue | Common: bruises, itch |
| Renal and urinary disorders | Common: frequent urination, polyuria |
| Systemic disorders and administration site-related conditions | Very common: thirst; common: fatigue, low-grade fever |
| Diagnostic investigations | Common: increased serum creatinine |
| Other side effects | ommon: hypernatremia, hyperglycemia, hyperuricemia, syncope, dizziness; uncommon: pruritic rash |

# Glucose transport in the proximal tubule



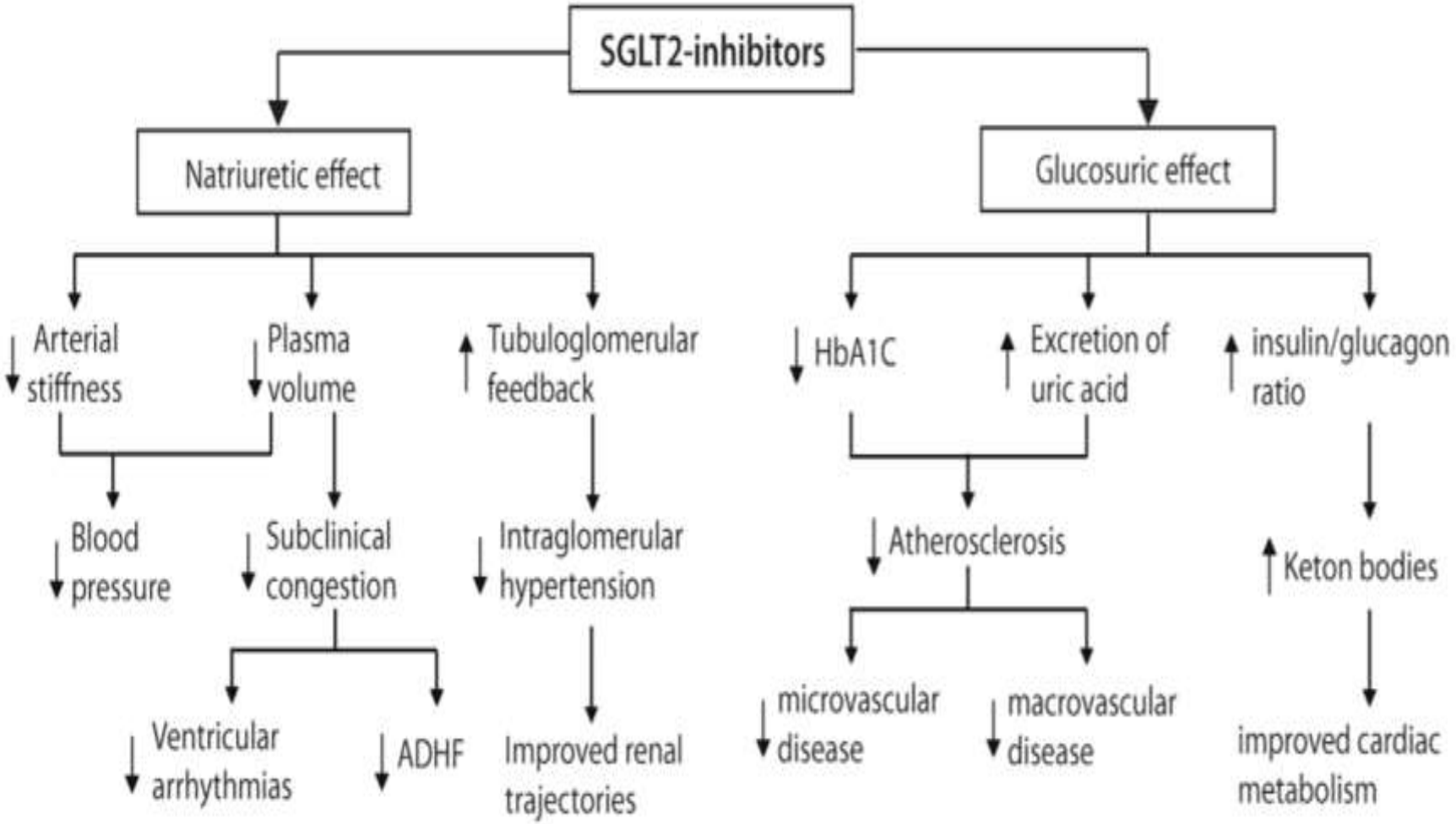




90 %

10%

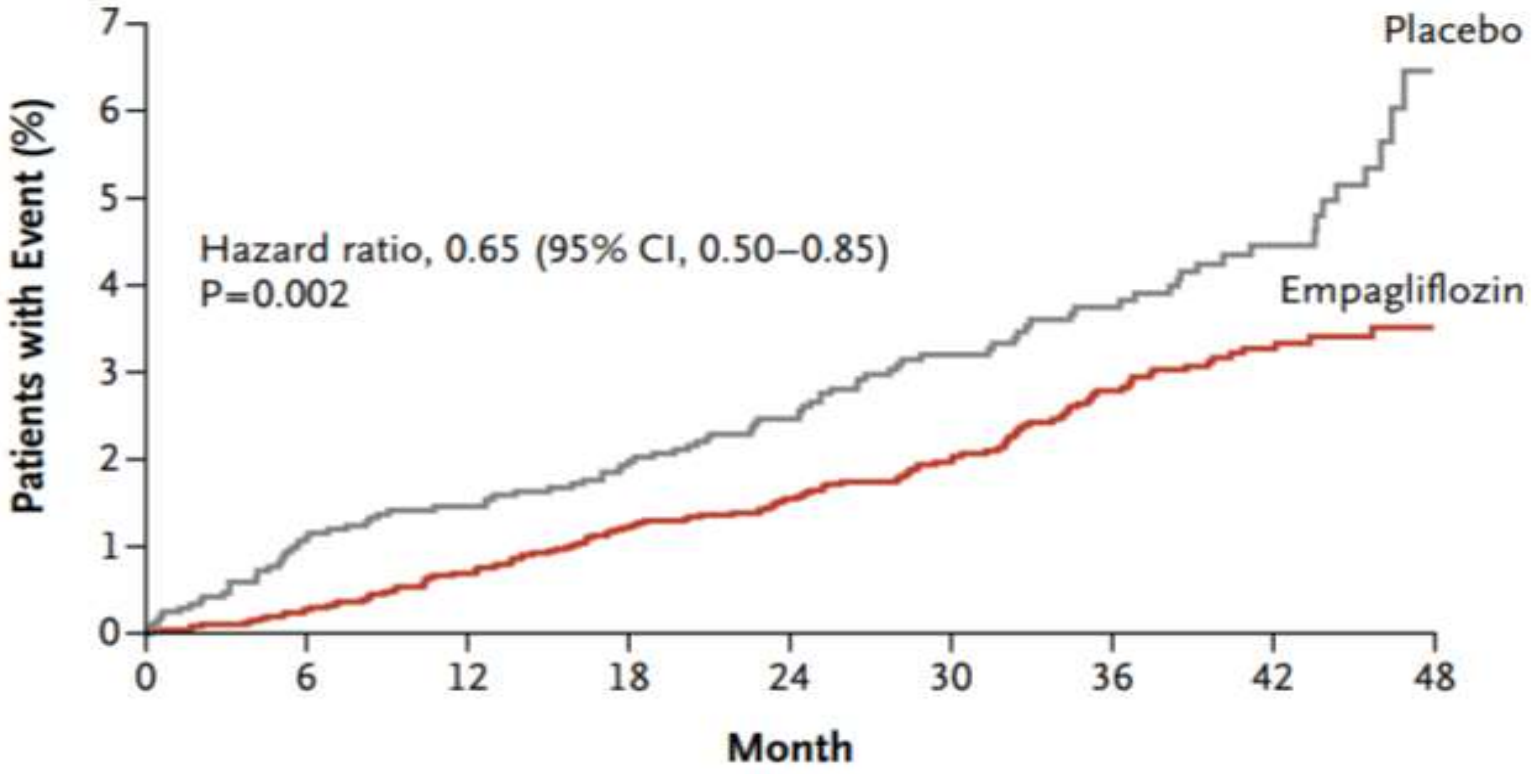
Verbrugge et al , Curr Cardiovasc Risk Rep. 2015;9:38.

# Pleiotropic effects of SGLT2 inhibitors in acute heart failure




Martens et al, Curr Treat Options Cardio Med (2017) 19: 23-37

# Empagliflozin and Hospitalization Rates for Heart Failure in Type 2 Diabetes- the EMPA-REG OUTCOME trial



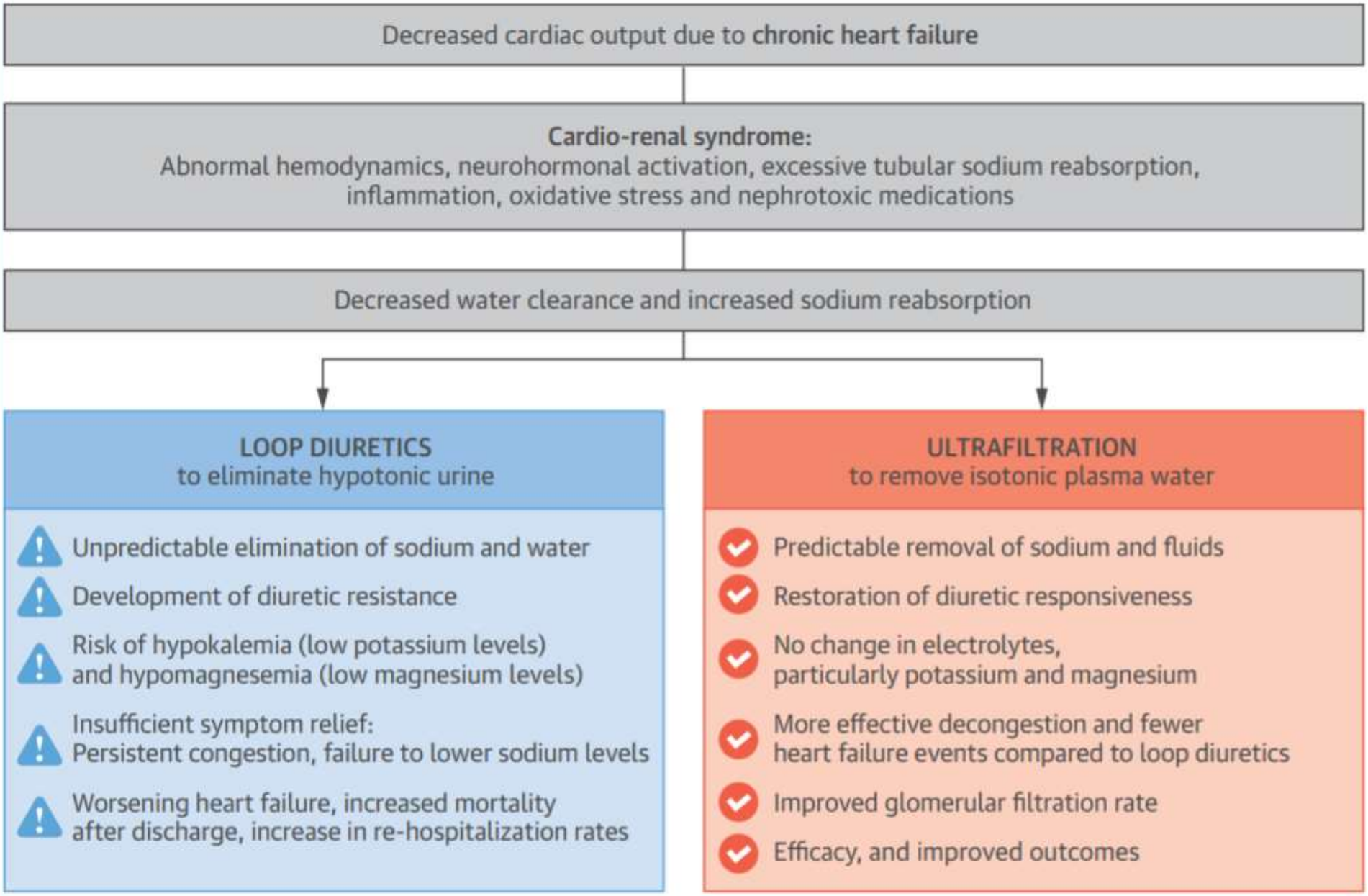

| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4687 | 4614 | 4523 | 4427 | 3988 | 2950 | 2487 | 1634 | 395 |
| Placebo | 2333 | 2271 | 2226 | 2173 | 1932 | 1424 | 1202 | 775 | 168 |

**Zinman et al, N Engl J Med 2015;373:2117-2128.**

# Ultrafiltration for severe heart failure

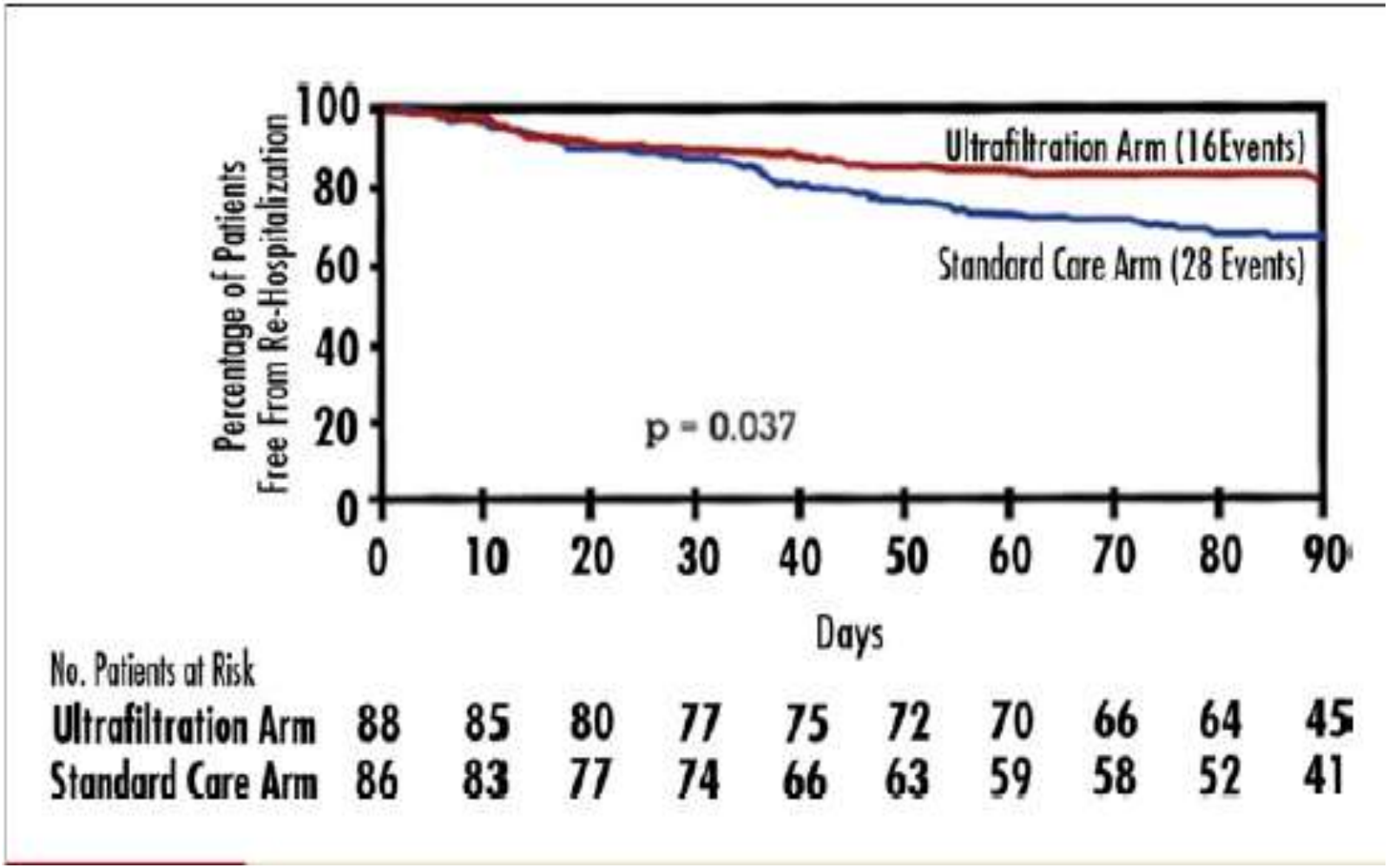
- Isolated ultrafiltration (IUF) or SCUF effectively remove fluid in diuretic- refractory congestive heart failure
- Numerous reports document improved cardiac performance and subsequent diuresis following UF
- Associated with decrease in counter-regulatory norepinephrine, plasma renin, aldosterone levels
- Hemofiltration may offer additional benefit by removal of myocardial depressing substances (??)

# Ultrafiltration for Fluid Overload in Heart Failure



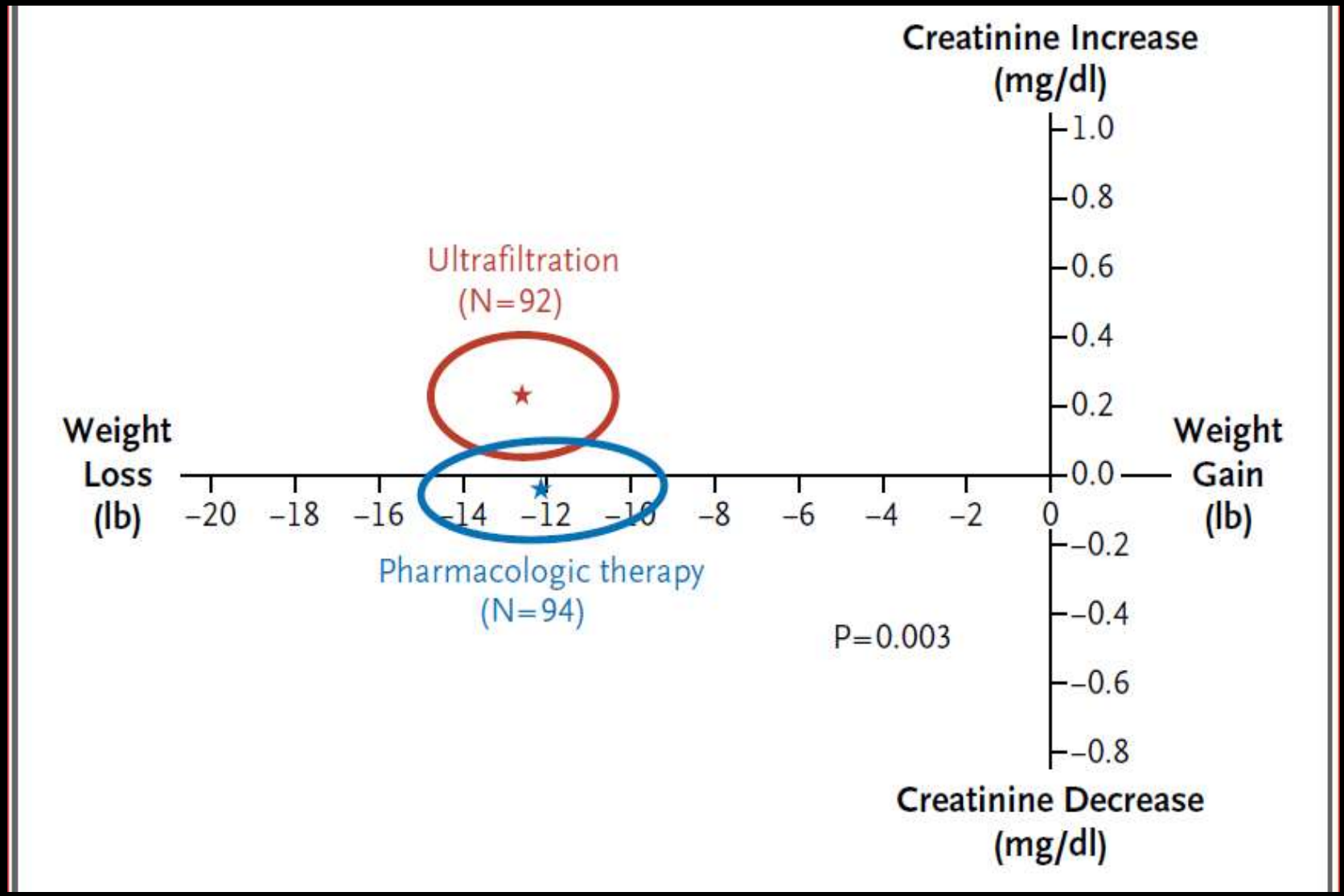

Costanzo, M.R. et al. J Am Coll Cardiol. 2017;69(19):2428-45.

# The UNLOAD (ultrafiltration) trial in congestive heart failure-results on free of hospitalization

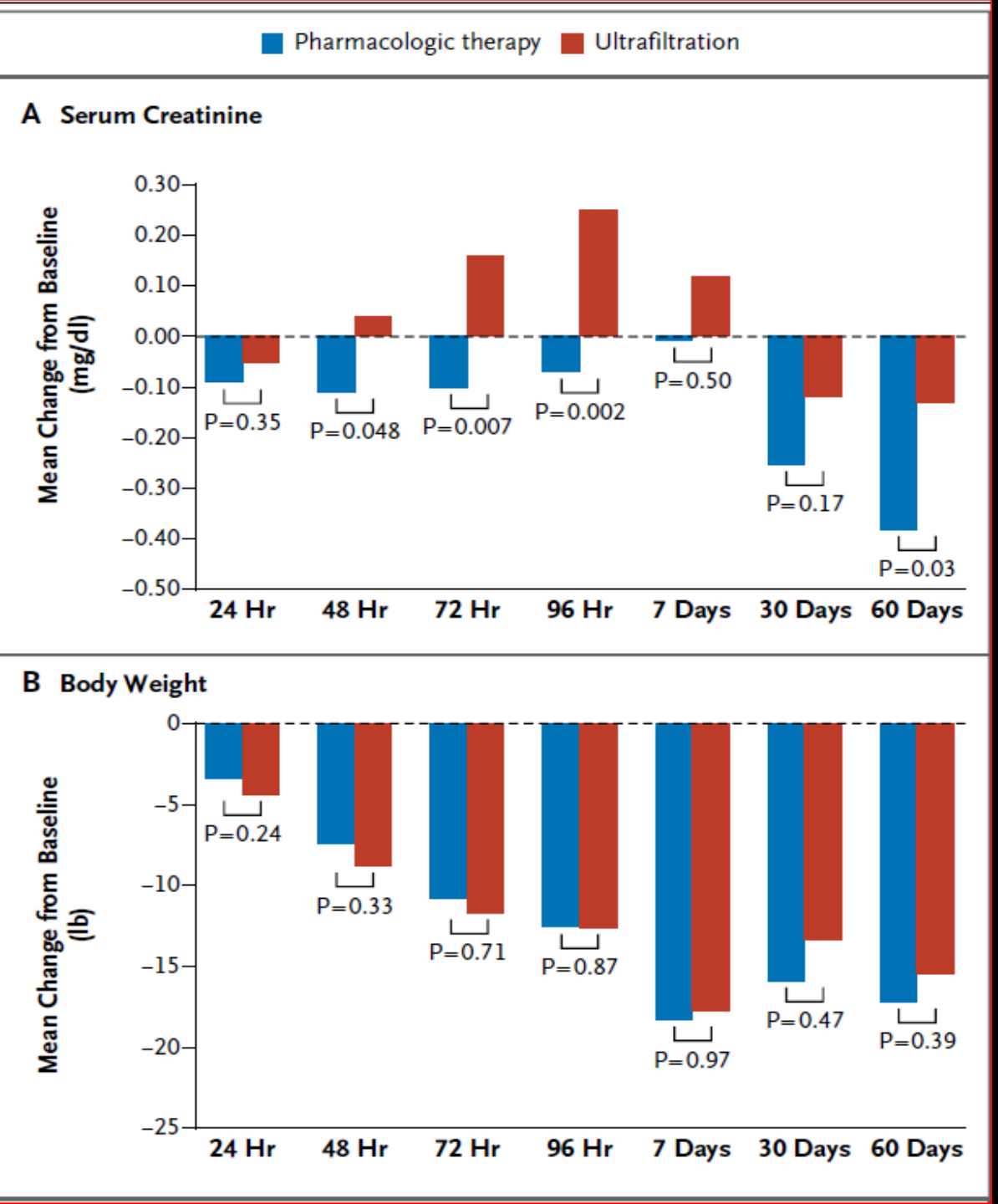



Costanzo et al, J Am Coll Cardiol 2007;49:675–683

# Changes in sCr and Body Weight at 96 Hours in the CARRESS-HF trial




Bart et al, N Engl J Med 2012;367:2296-304



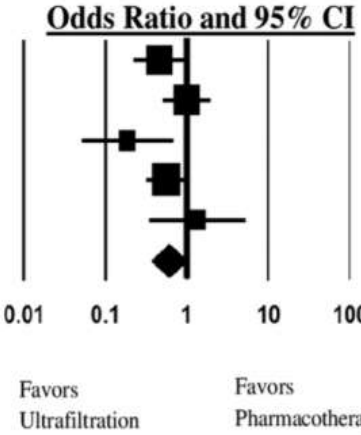

# Changes from Baseline in sCr and Body Weight at Various Time Points, According to Treatment Group- The CARRESS –HF trial

Bart et al, N Engl J Med 2012;367:2296-304

# Defining the role of ultrafiltration therapy in acute heart failure: a systematic review and meta-analysis

**A**: Heart failure rehospitalization

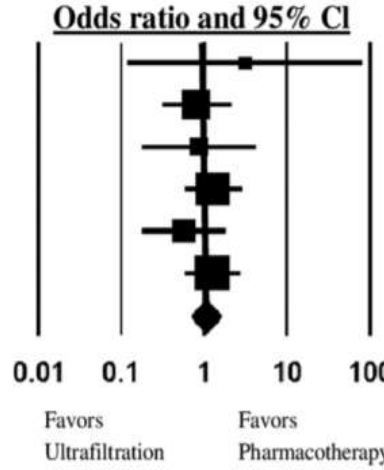
| | Ultrafiltration | | Pharmacotherapy | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Rehospitalization** | **Total** | **Rehospitalization** | **Total** | **M-H OR [95% CI]** | **p-Value** | **Weight** |
| UNLOAD | 16 | 89 | 28 | 87 | 0.46 [0.23,0.93] | 0.03 | 23.88 |
| CARRESS-HF | 23 | 90 | 24 | 93 | 0.99[ 0.51,1.92] | 0.97 | 25.26 |
| CUORE | 4 | 27 | 14 | 29 | 0.19[0.05,0.68] | 0.01 | 11.09 |
| AVOID-HF | 36 | 105 | 52 | 108 | 0.56[0.32,0.98] | 0.04 | 29.44 |
| Hanna et al. | 8 | 19 | 6 | 17 | 1.33[0.35,5.14] | 0.68 | 10.32 |
| Random | 87 | 330 | 124 | 334 | 0.60[0.37,0.98] | 0.04 | |




Heterogeneity: Q = 7.26; d.f. = 4 (p = 0.12); Tau² = 0.13; I² = 44.90%
Egger's Test: p (2-tailed) = 0.82
Overall Z = -2.05

**B** : Mortality

| | Ultrafiltration | | Pharmacotherapy | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Events** | **Total** | **Events** | **Total** | **M-H OR [95% CI]** | **p-Value** | **Weight** |
| RAPID-CHF | 1 | 20 | 0 | 20 | 3.15 [ 0.12, 82.16] | 0.49 | 1.64 |
| UNLOAD | 9 | 94 | 11 | 95 | 0.81 [ 0.32, 2.05] | 0.65 | 20.16 |
| Hanna et al. | 4 | 19 | 4 | 17 | 0.87 [ 0.18, 4.18] | 0.86 | 7.07 |
| CARRESS-HF | 16 | 94 | 13 | 94 | 1.28 [ 0.58, 2.83] | 0.55 | 27.65 |
| CUORE | 7 | 27 | 11 | 29 | 0.57 [ 0.18, 1.79] | 0.34 | 13.41 |
| AVOID-HF | 17 | 110 | 14 | 111 | 1.27 [ 0.59, 2.71] | 0.54 | 30.07 |
| Random | 54 | 364 | 53 | 366 | 1.03 [ 0.68, 1.57] | 0.89 | |




Heterogeneity: Q = 2.34; d.f. = 5 (p = 0.80); Tau² = 0.00; I² = 0.00%
Egger's Test: p (2-tailed) = 0.99
Overall Z = 0.14

Jain et al Heart Fail Rev (2016) 21:611–619

# Current recommendations for UF in heart failure

**American College of Cardiology/American Heart Association (2013) (49)**

- Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight (level of evidence: B)
- Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy (level of evidence: C)
- Consultation with a nephrologist is appropriate before initiating ultrafiltration, especially in circumstances where the non-nephrology provider does not have sufficient experience with ultrafiltration

**Canadian Cardiovascular Society (2012) (50)**

- Venovenous ultrafiltration may be of benefit in relieving congestion, particularly in patients who are diuretic resistant
- Patients with persistent congestion despite diuretic therapy with or without impaired renal function may, under experienced supervision, receive continuous venovenous ultrafiltration

**European Society of Cardiology (2012) (51)**

- Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with heart failure, although it is usually reserved for those unresponsive or resistant to diuretics
- If doubling the dose of loop diuretics and infusion of dopamine do not result in an adequate diuresis and the patient remains in pulmonary edema, venovenous isolated ultrafiltration should be considered

**Heart Failure Society of America (2010) (52)**

- It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics; ultrafiltration may be considered *in lieu* of diuretics (strength of evidence: B)
- When congestion fails to improve response to diuretic therapy, ultrafiltration may be considered (strength of evidence: C)

Kazory A, Clin J Am Soc Nephrol 11: 1463–1471, 2016.