Pivotal Role of Renal Function in Acute Heart failure

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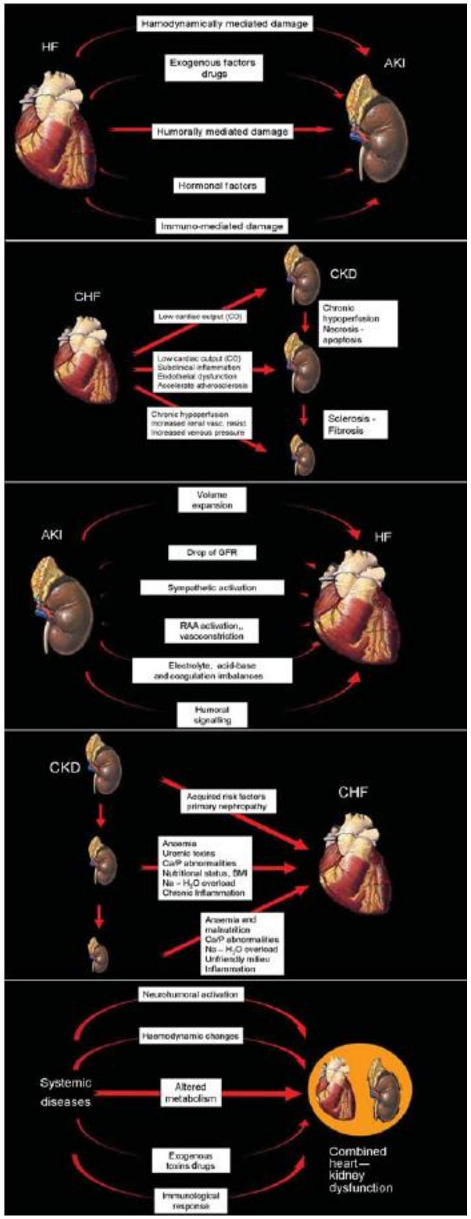
Classification and definitions of cardiorenal syndromes



CRS type I (acute CRS): abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to AKI

CRS type II (chronic CRS): chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS type III (acute renocardiac syndrome): abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)

CRS Type IV (chronic renocardiac syndrome): chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

CRS type V (secondary CRS): systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

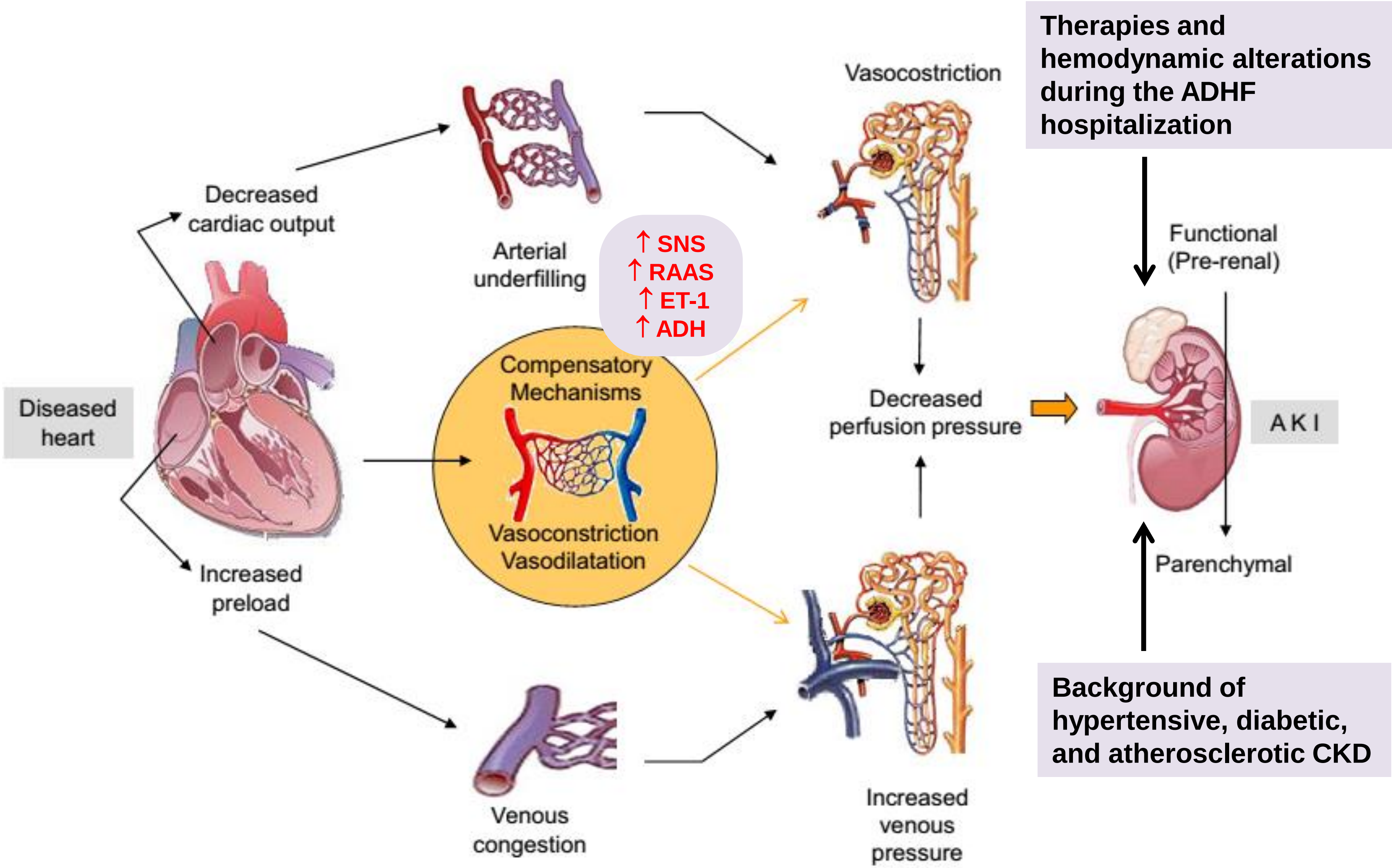
European Heart Journal (2010) 31, 703–711

Prevalence and Clinical Significance

- **Meta analysis including studies on HF patients and mortality risk with CKD and/or worsening renal function (WRF)**
- **57 studies (1 076 104 patients) that investigated CKD and 28 studies (49 890 patients) that investigated WRF**
- **The prevalence of CKD was 32% and associated with all-cause mortality: odds ratio (OR) 2.34, 95% CI 2.20–2.50, P < 0.001)**
- **Worsening renal function was present in 23%**
- **WRF was associated with increased mortality risk (OR 1.81,95%CI 1.55–2.12, P < 0.001)**

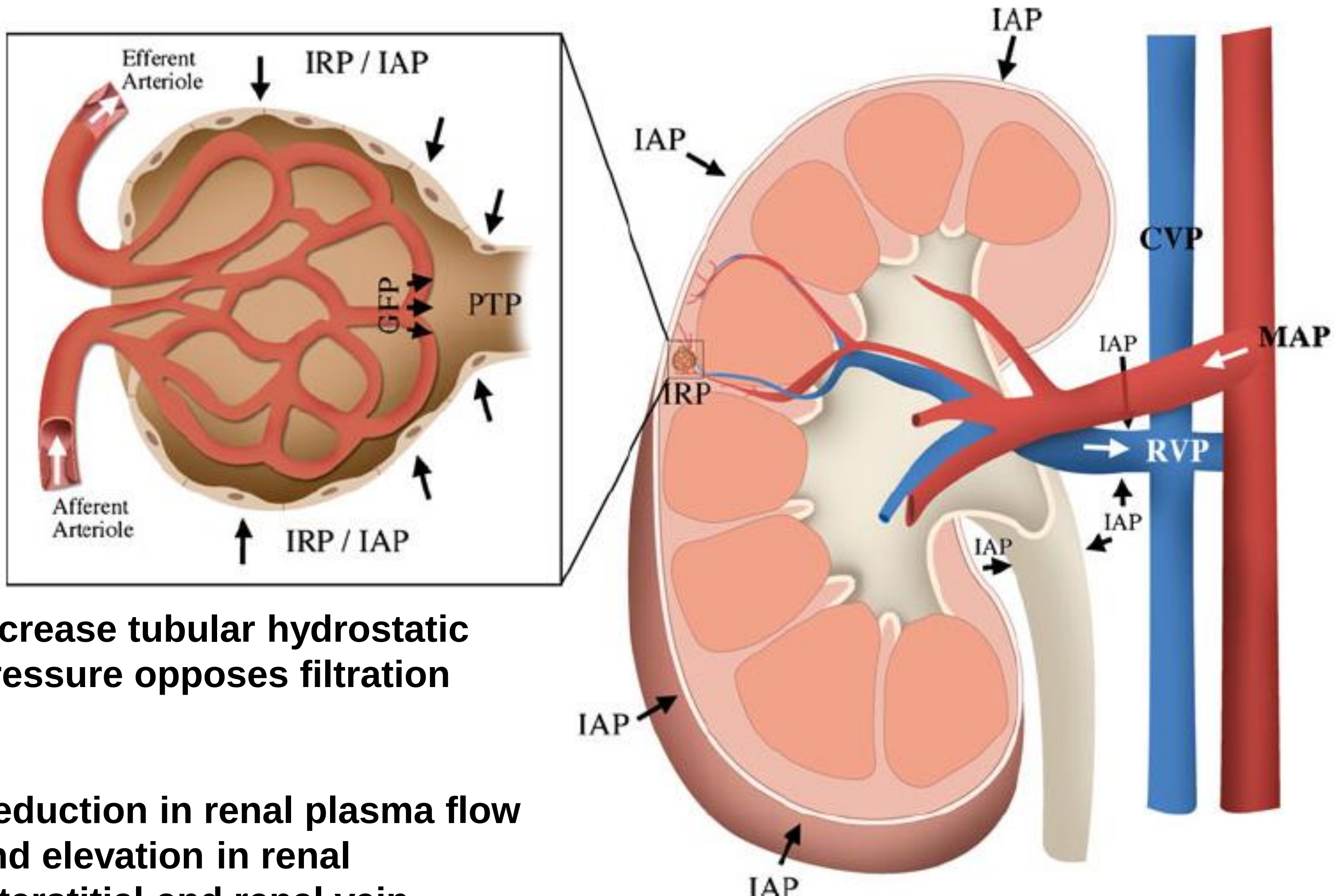
Damman et al. *Eur Heart J 2013*;35:455-469

Pathogenesis of Type 1 CRS



Ronco et al. *Semin Nephrol. 2012;32:129-141*

Effect of venous congestion and intra-abdominal pressure on renal function

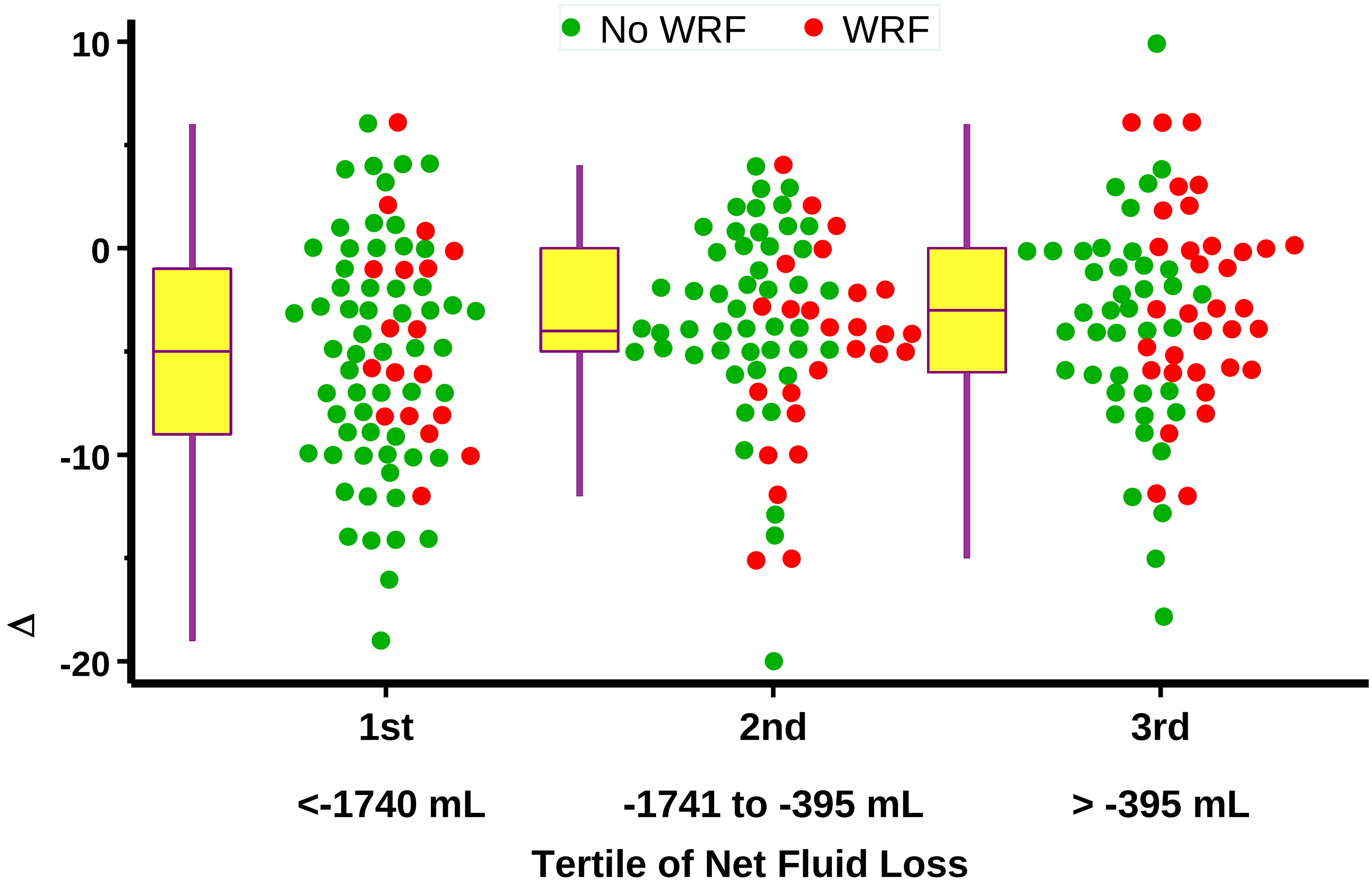


- Increase tubular hydrostatic pressure opposes filtration

- Reduction in renal plasma flow and elevation in renal interstitial and renal vein pressures

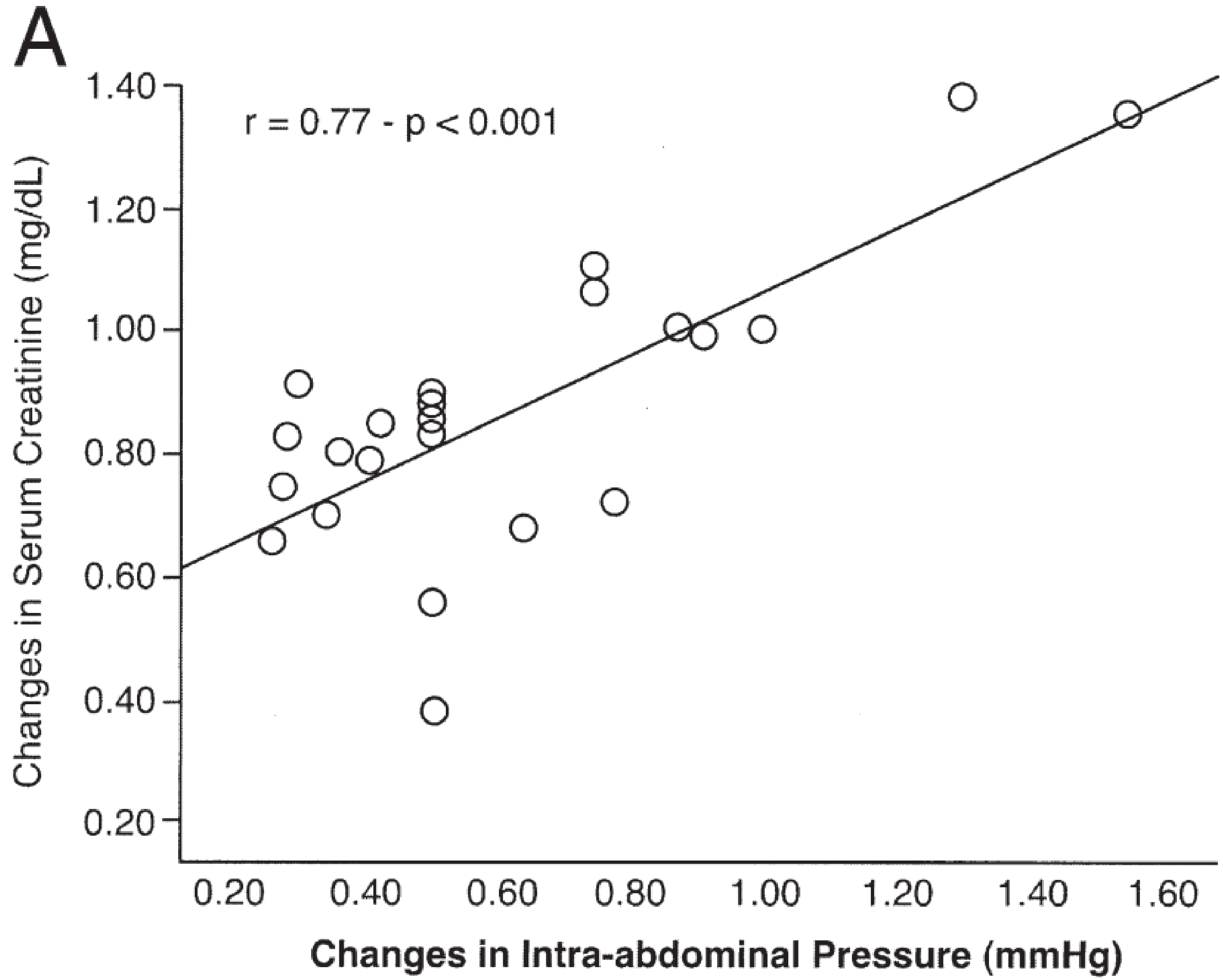
Dupont et al. *Curr Heart Fail Rep 2011;8:233-241*

Change in right atrial pressure in patients with (red) and without (green) worsening renal function



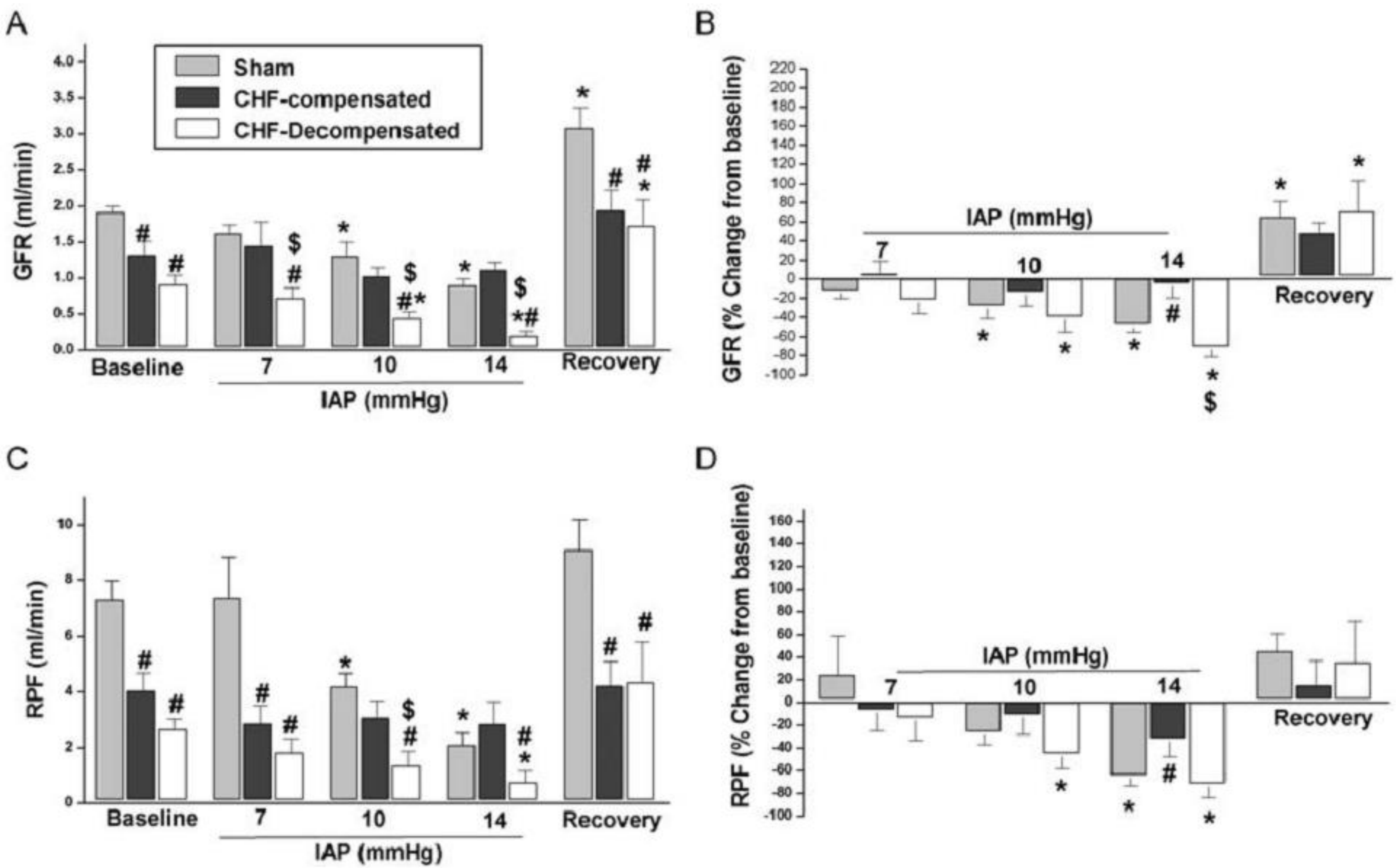
Aronson et al. *Eur J Heart Fail. 2013;15:637-643*

Relationship between changes in renal function and changes in intra-abdominal pressure



Mullens at al. Am Coll Cardiol. 2008;51:300-306

Renal Effects of Increasing Intra-Abdominal Pressure in Rats with CHF



Bishara et al. Eur J Heart Fail. 2012;14:1104-1111

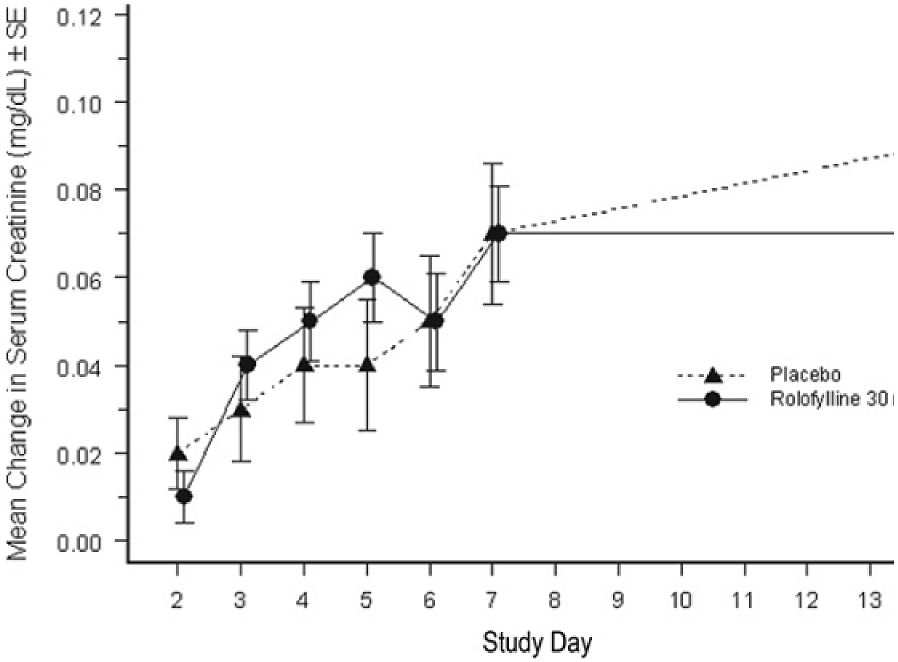
The Concept of Renal Adjuvant Therapy for ADHF

- **Inotropes or vasodilators are commonly used to increase cardiac output in ADHF and may enhance renal function via an effect on the heart and systemic vasculature**

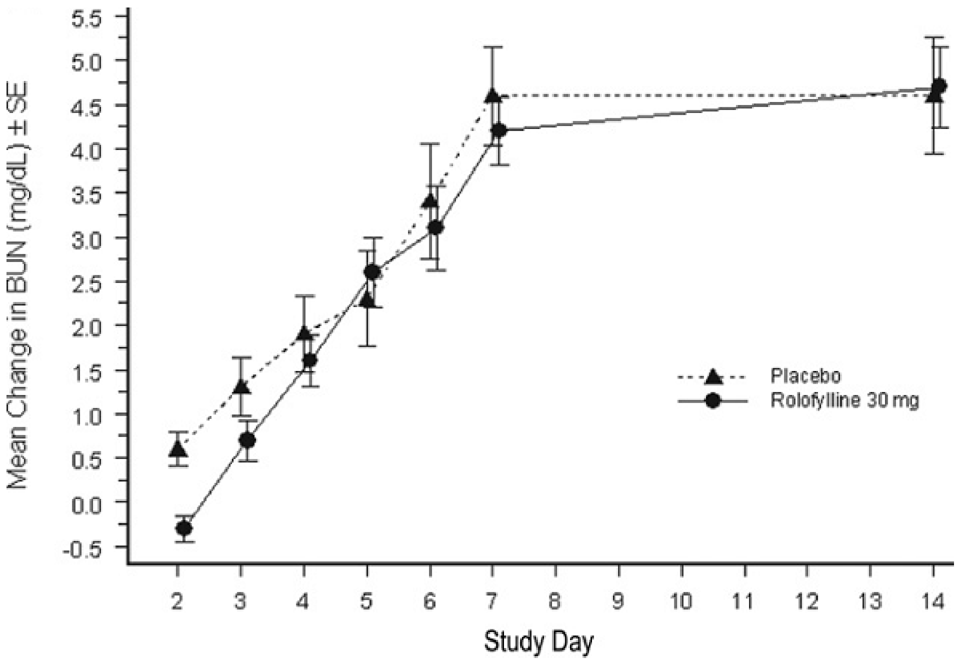
- **Therapies that specifically target the kidney to enhance decongestion and preserve renal function can be considered as renal adjuvant therapies for ADHF**

Chen et al. ***Circ Heart Fail. 2013;6:1087-1094***

PROTECT: Effect of Rolofylline (Adenosine A1 Receptor Antagonists) on Renal Function



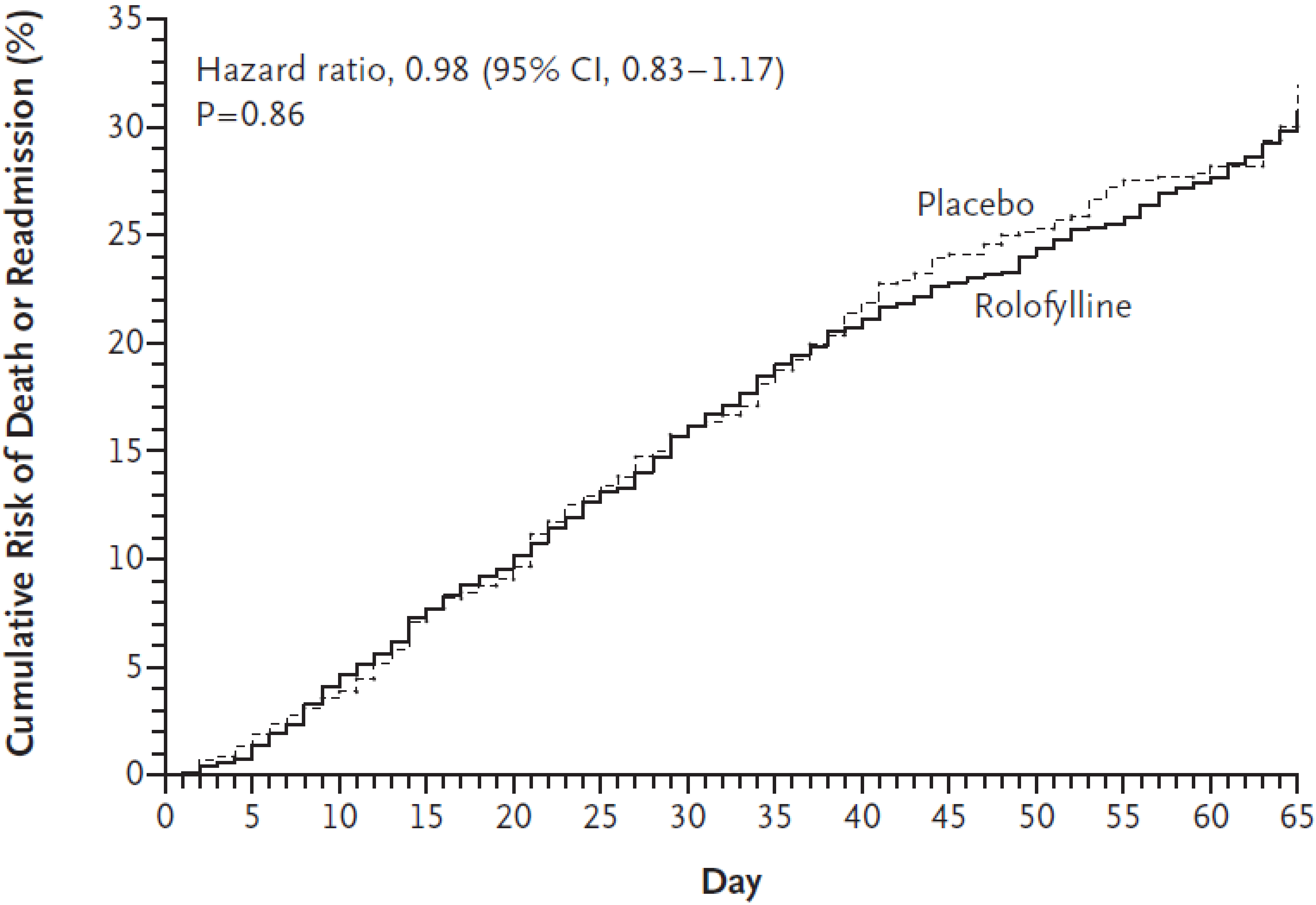
Change in Creatinine



Change in BUN

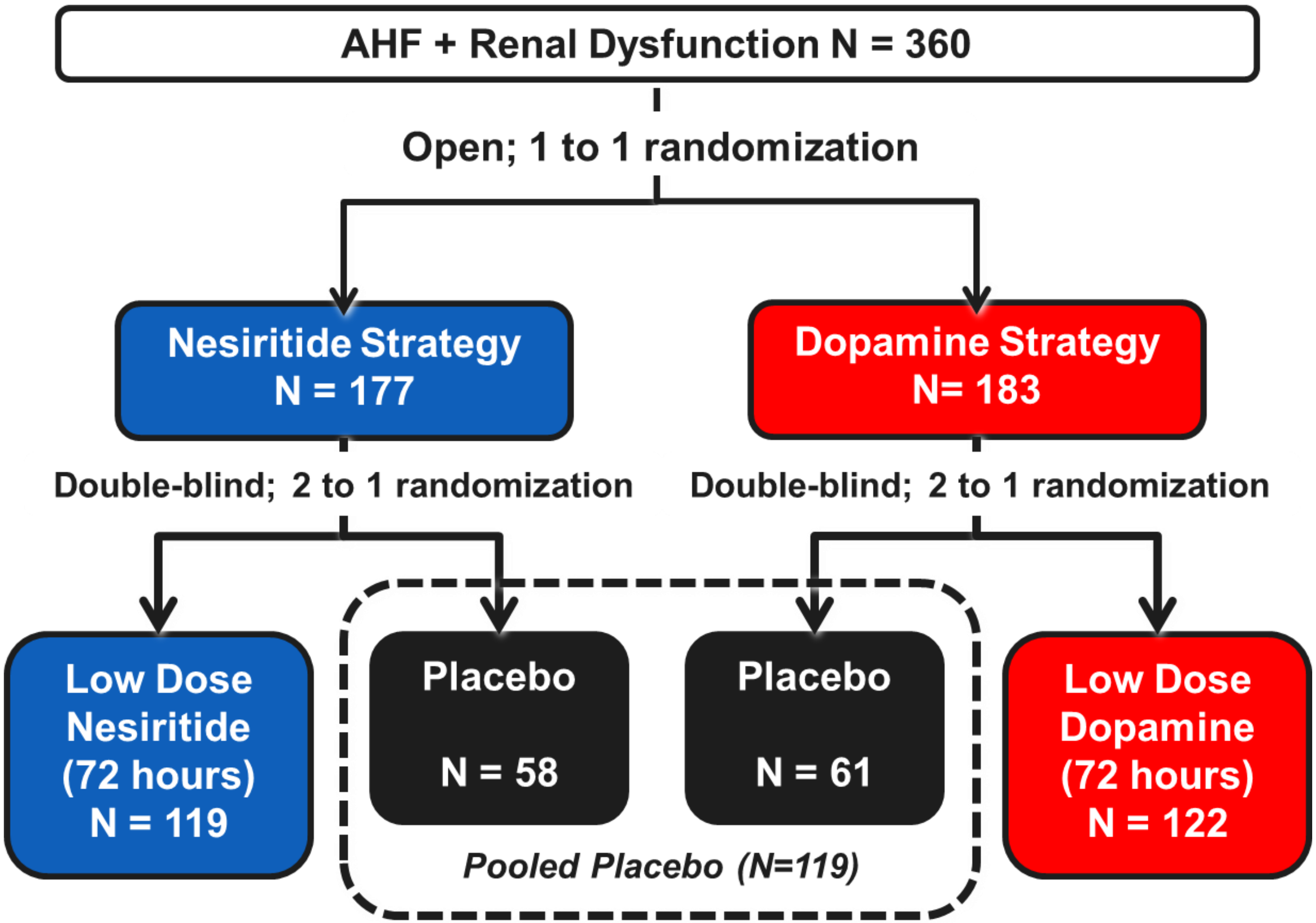
Voors et al. *J Am Coll Cardiol. 2011;57:1899-1907*

PROTECT: Cumulative Risk of Death or Readmission for Cardiovascular or Renal Causes



Massie et al. N Engl J Med 2010;363:1419-28

ROSE AHF Study Design



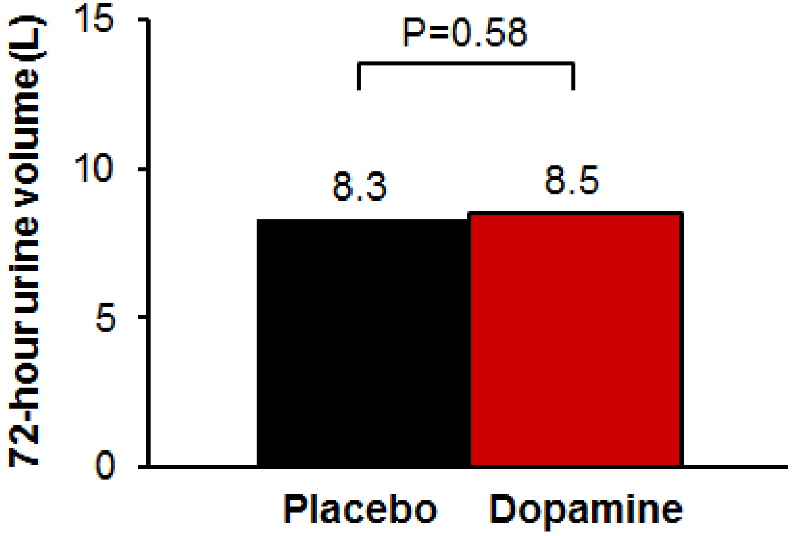
Standardized Diuretic Dosing For 1st 24 hours

2.5 x Outpt Furosemide Equivalent in Divided (BID) IV Doses

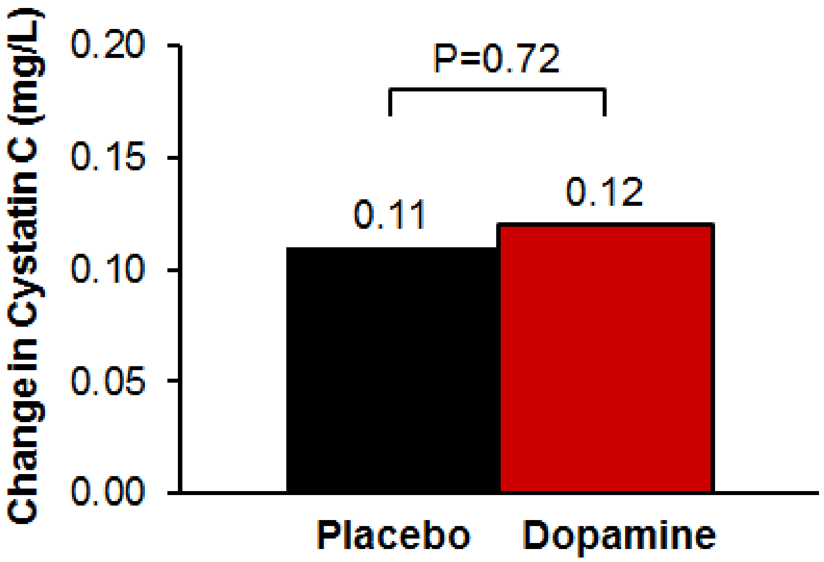
Chen et al. *JAMA. 2013;*310:2533-2543

Low Dose Dopamine: *Co-primary End-points*

72 Hour Urine Volume



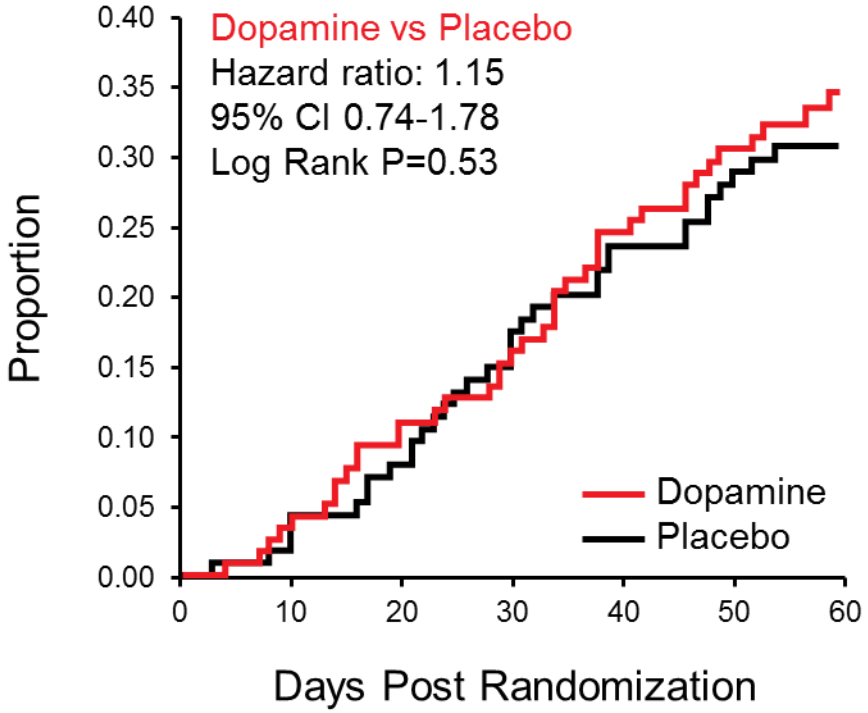
Change in Cystatin-C



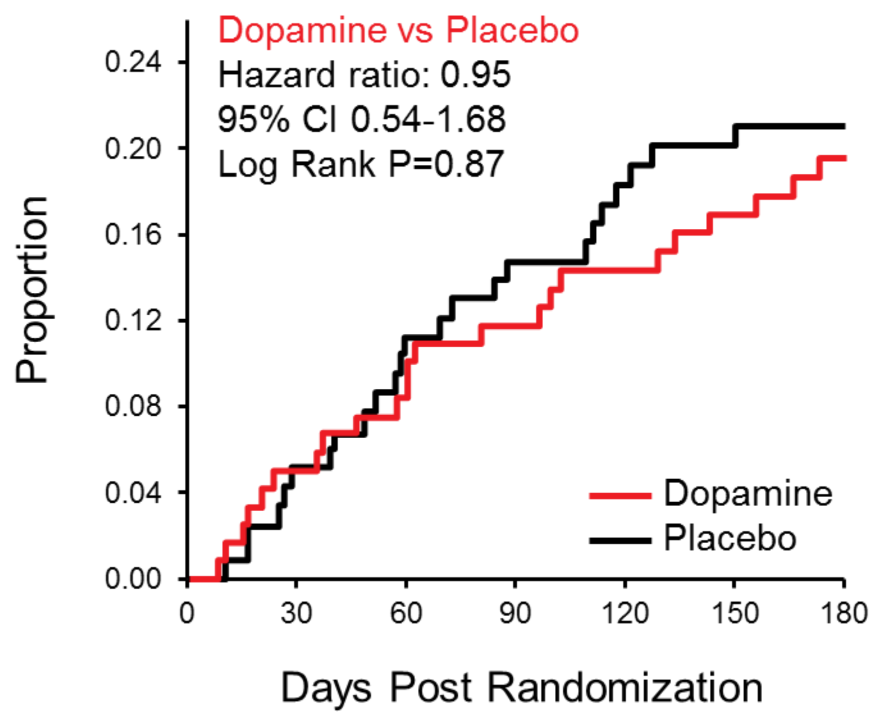
Chen et al. *JAMA. 2013;*310:2533-2543

Low Dose Dopamine: Clinical Outcomes

60 Day Death/ Unscheduled office visit/ HF Readmission

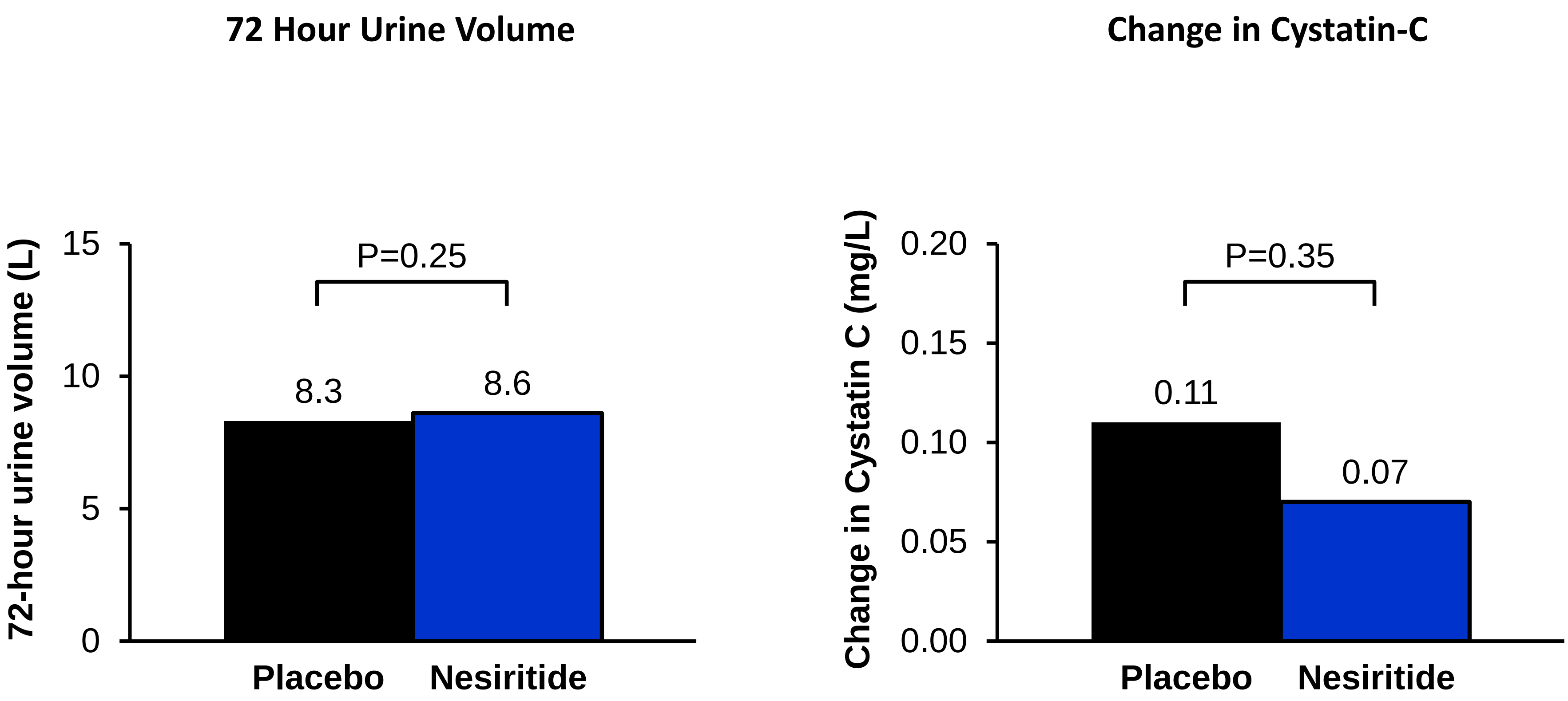


180 Day Mortality



Chen et al. *JAMA. 2013;*310:2533-2543

Low Dose Nesiritide: *Co-primary* End-points



Chen et al. *JAMA. 2013;*310:2533-2543

Low Dose Nesiritide: *Clinical Outcomes*

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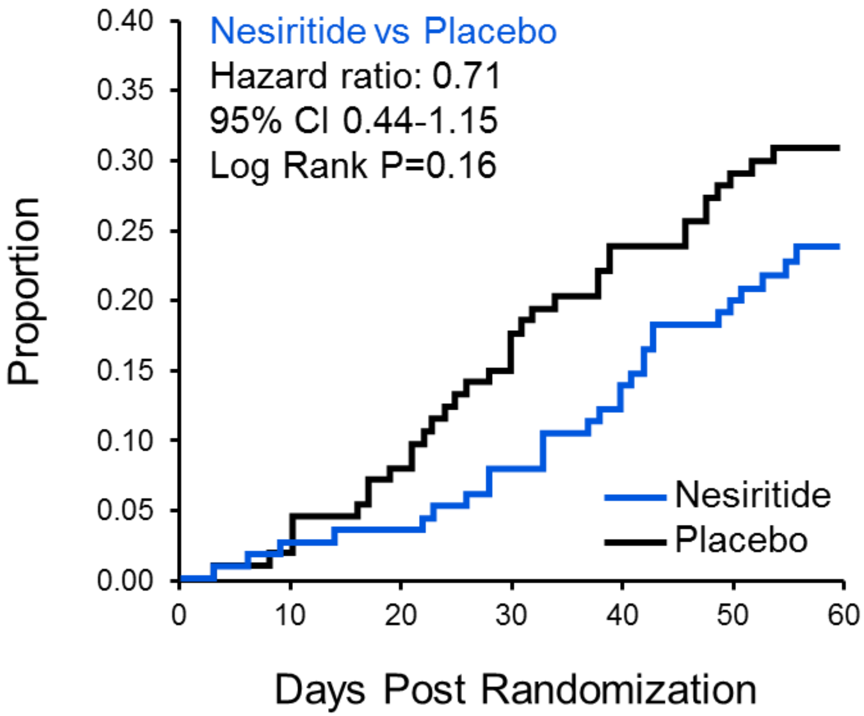

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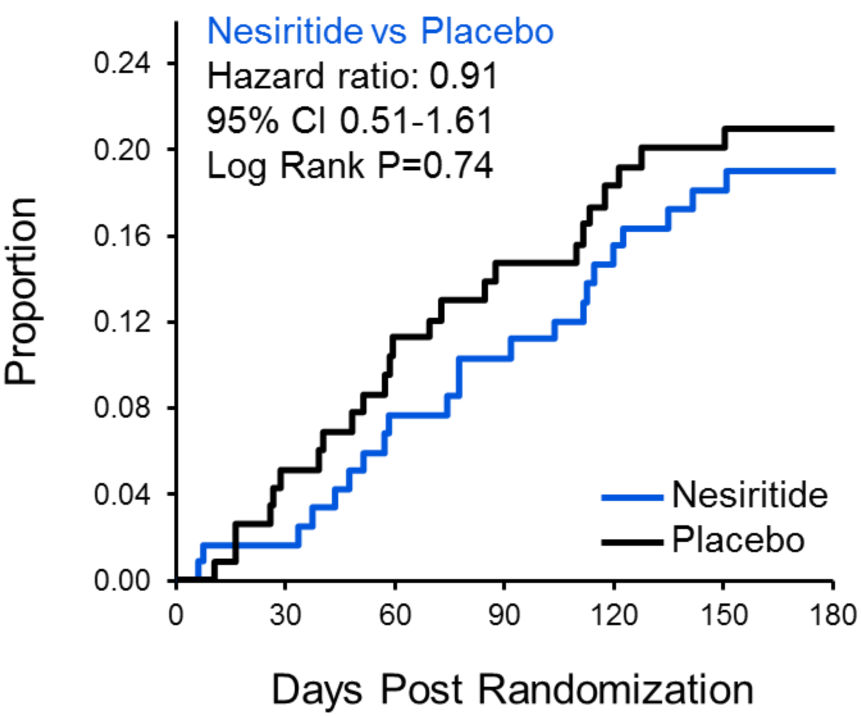


Chen et al. *JAMA. 2013;*310:2533-2543

CARRESS-HF – therapeutic intervention

- 2l fluid restriction and low salt diet
- Continuation of ACE-I, b-blockers, digoxin

Ultrafiltration of 200ml/hr +

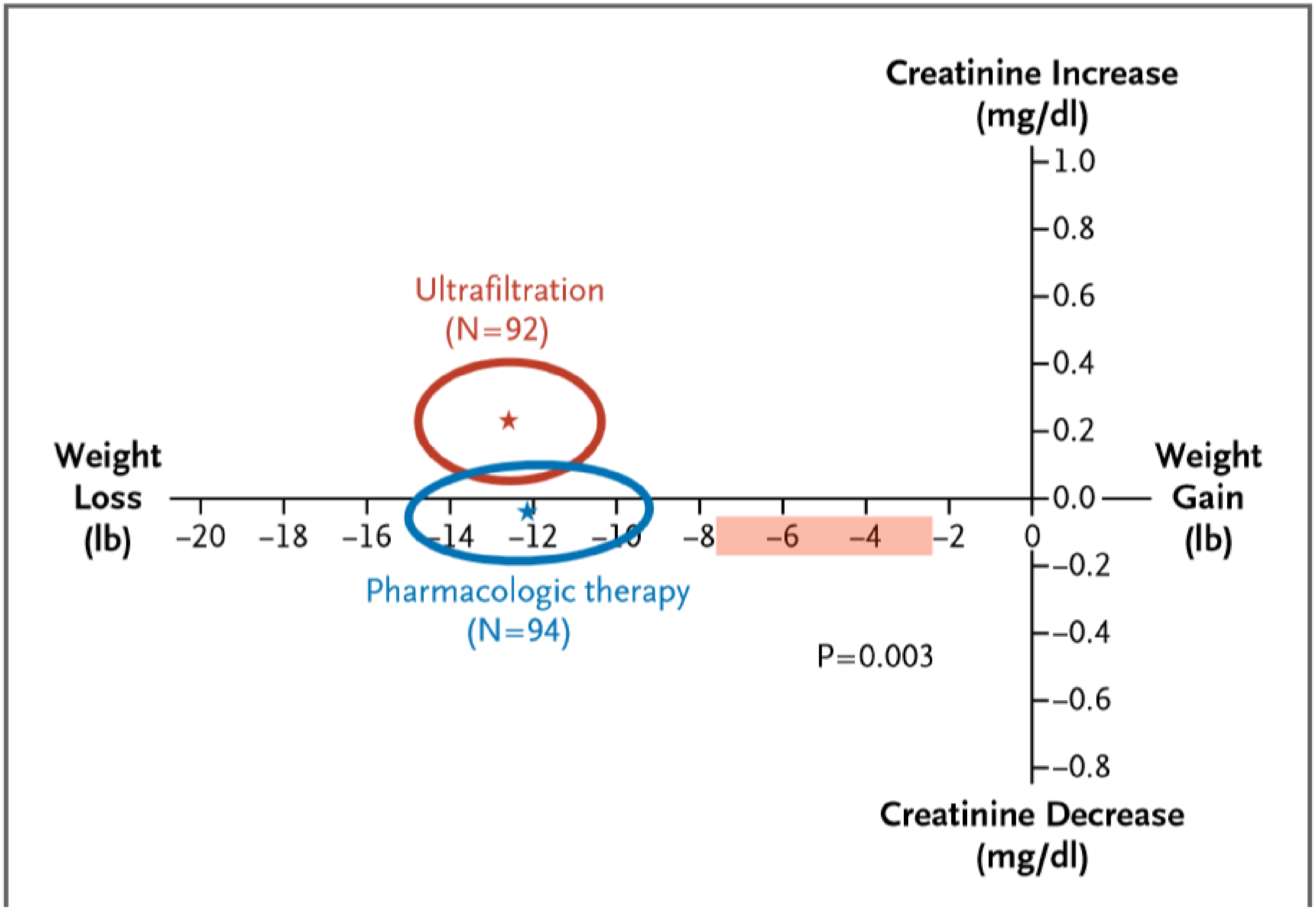
discontinuation of iv diuretics

Stepped pharmacological approach

Management was to be continued until clinical decongestion: JVP≤ 8cm
No more than trace of peripheral oedema and lack of orthopnoea

Bart et al. *N Engl J Med. 2012;367:2296-2304*

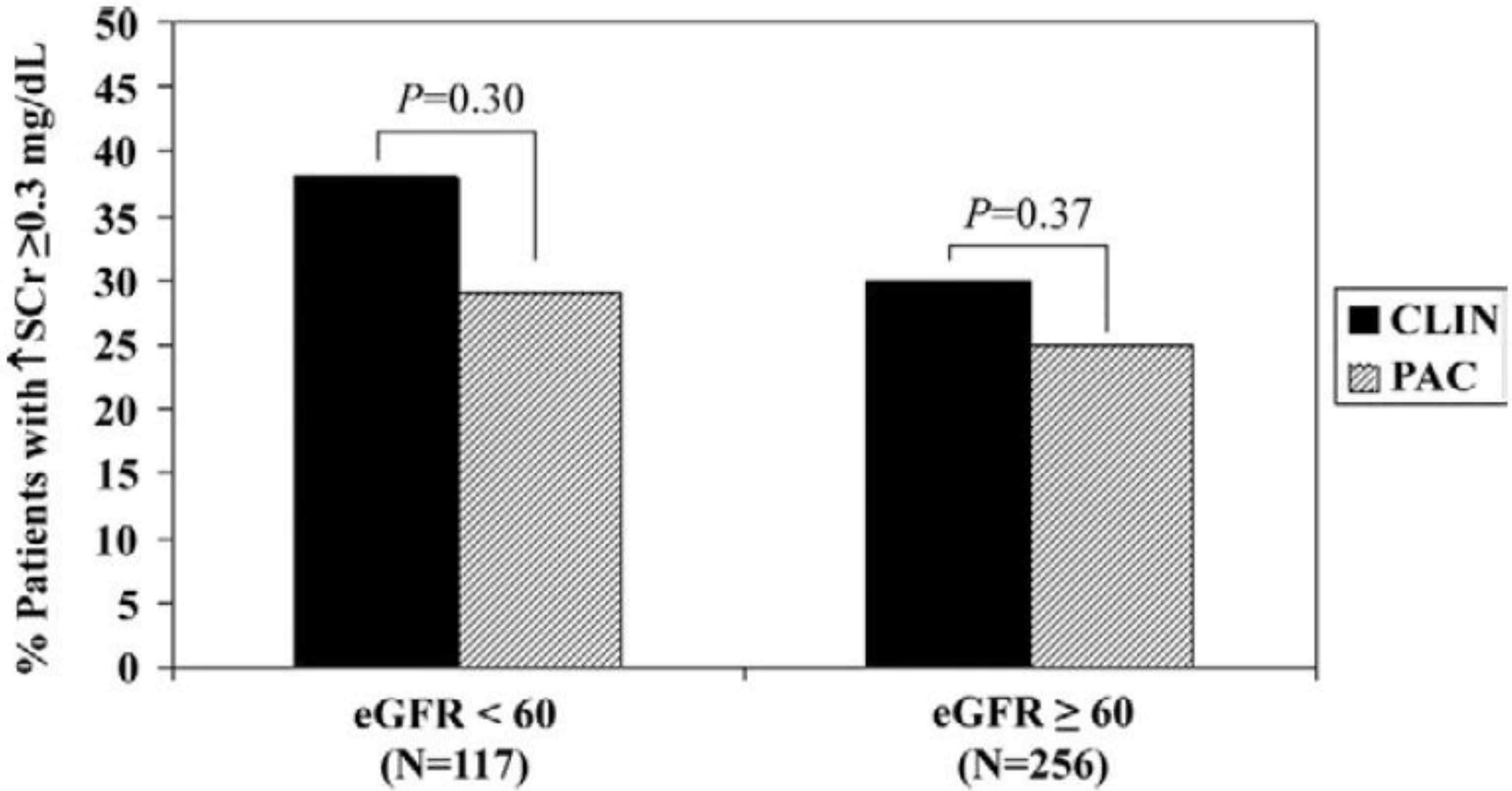
CARRESS-HF – Changes in Creatinine and Weight at 96h



- **Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrollment (P = 0.003), owing primarily to an increase in the creatinine level in the ultrafiltration group.**

Bart et al. *N Engl J Med. 2012;367:2296-2304*

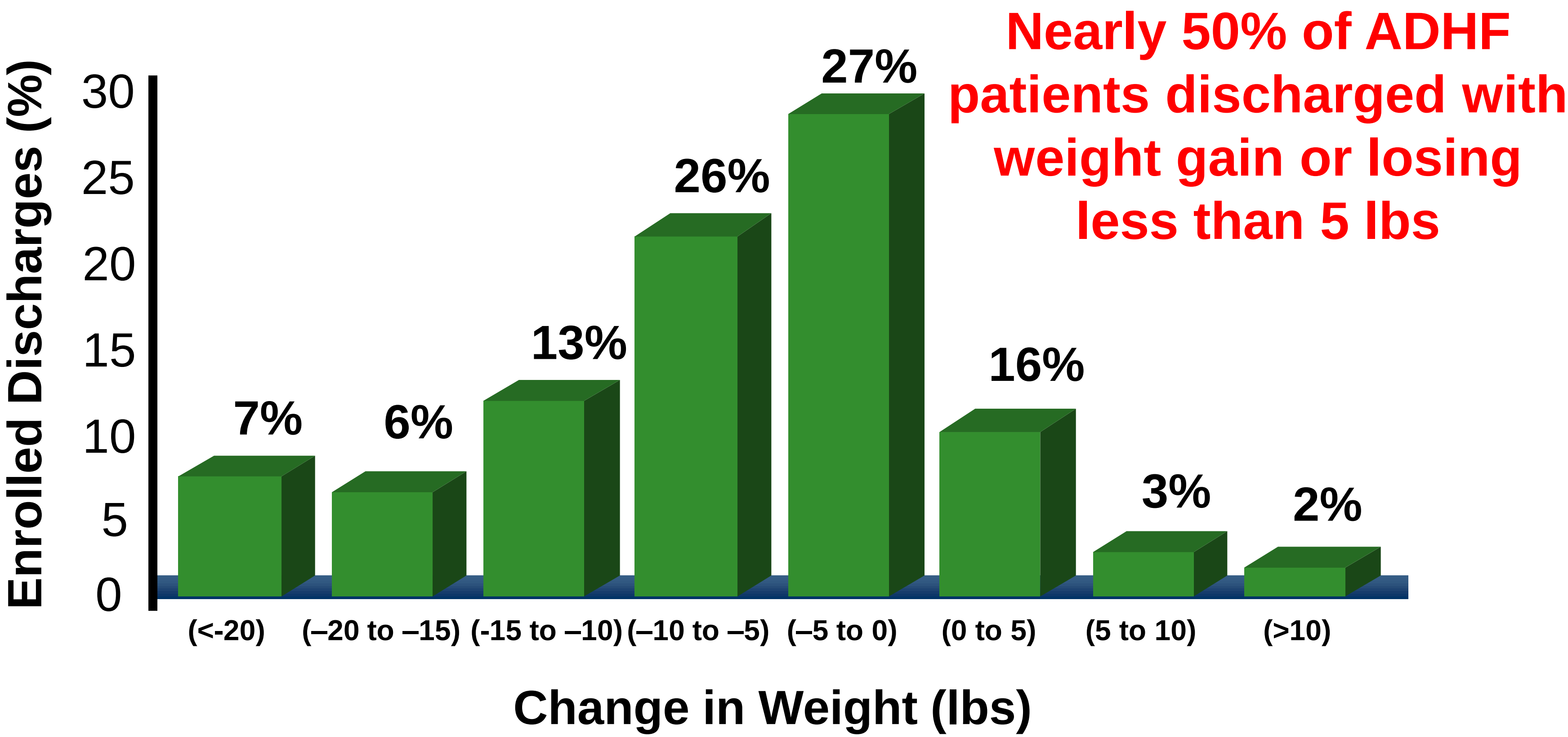
PA catheter guided therapy



- A PAC did not reduce the incidence of worsening renal function (defined as a 0.3 mg/dl increase in serum creatinine from baseline to discharge) relative to a strategy based on clinical assessment alone

Nohria et al. J Am Coll Cardiol 2008;51:1268–74

The Inextricable Link Between Congestion and Renal Function



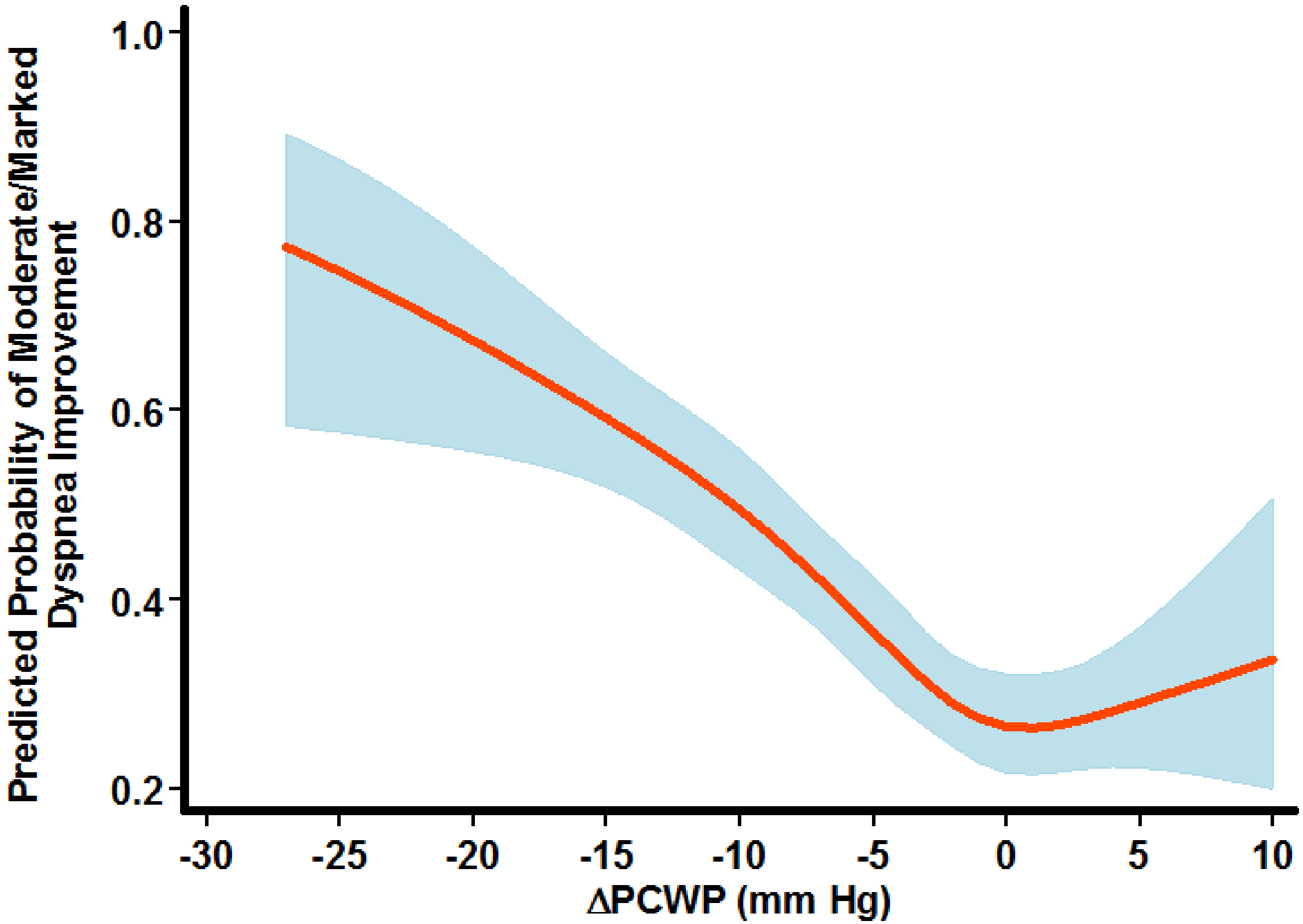
Adhere National Benchmark Report Data, January 2001 to April 2006

Persistent Congestion Predicts Readmission and Mortality

- **A post-hoc analysis of the DOSE-HF and CARRESS-HF trials of AHF patients with congestion found that baseline congestion was moderate in 22% of patients and severe in 62%**
- **Following aggressive inpatient therapy targeting decongestion, more than one-third of patients (35%) had persistent moderate to severe congestion at discharge**
- **Higher congestion scores at admission and discharge were both associated with increased risk for 60-day death or HF hospitalization**

Mentz et al. *Eur J Heart Fail 2014*

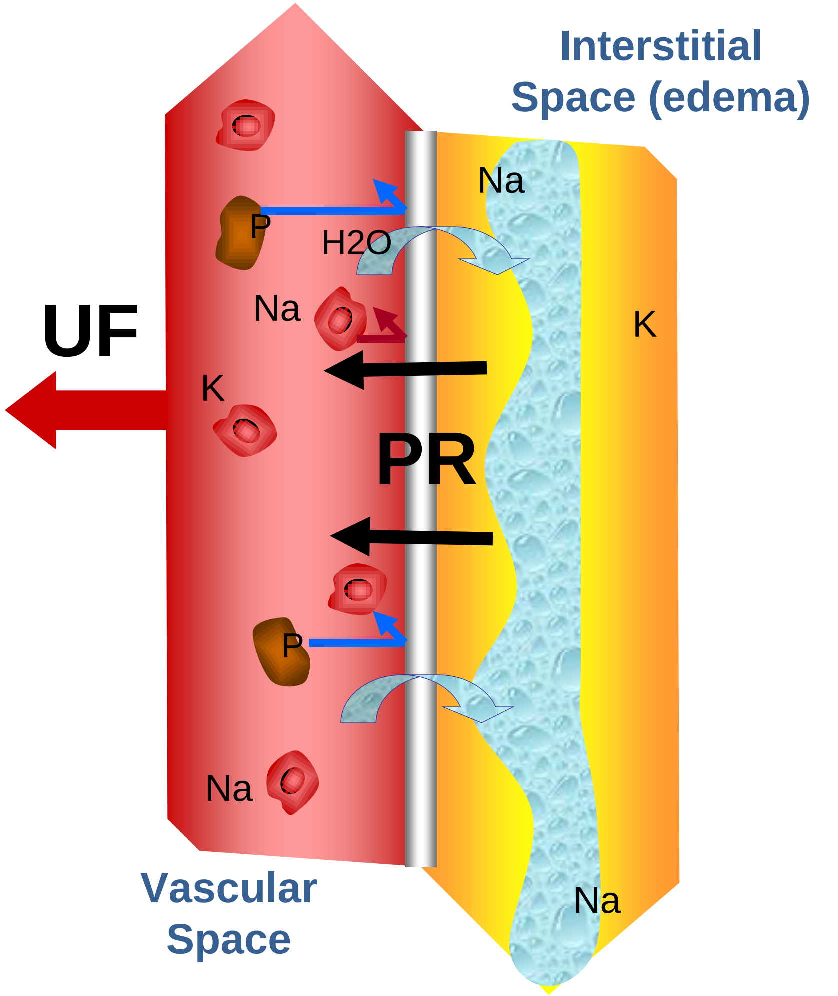
PCWP Change and Dyspnea Relief in ADHF



Solomonica, Burger & Aronson. *Circ Heart Fail. 2013;6:53-60*

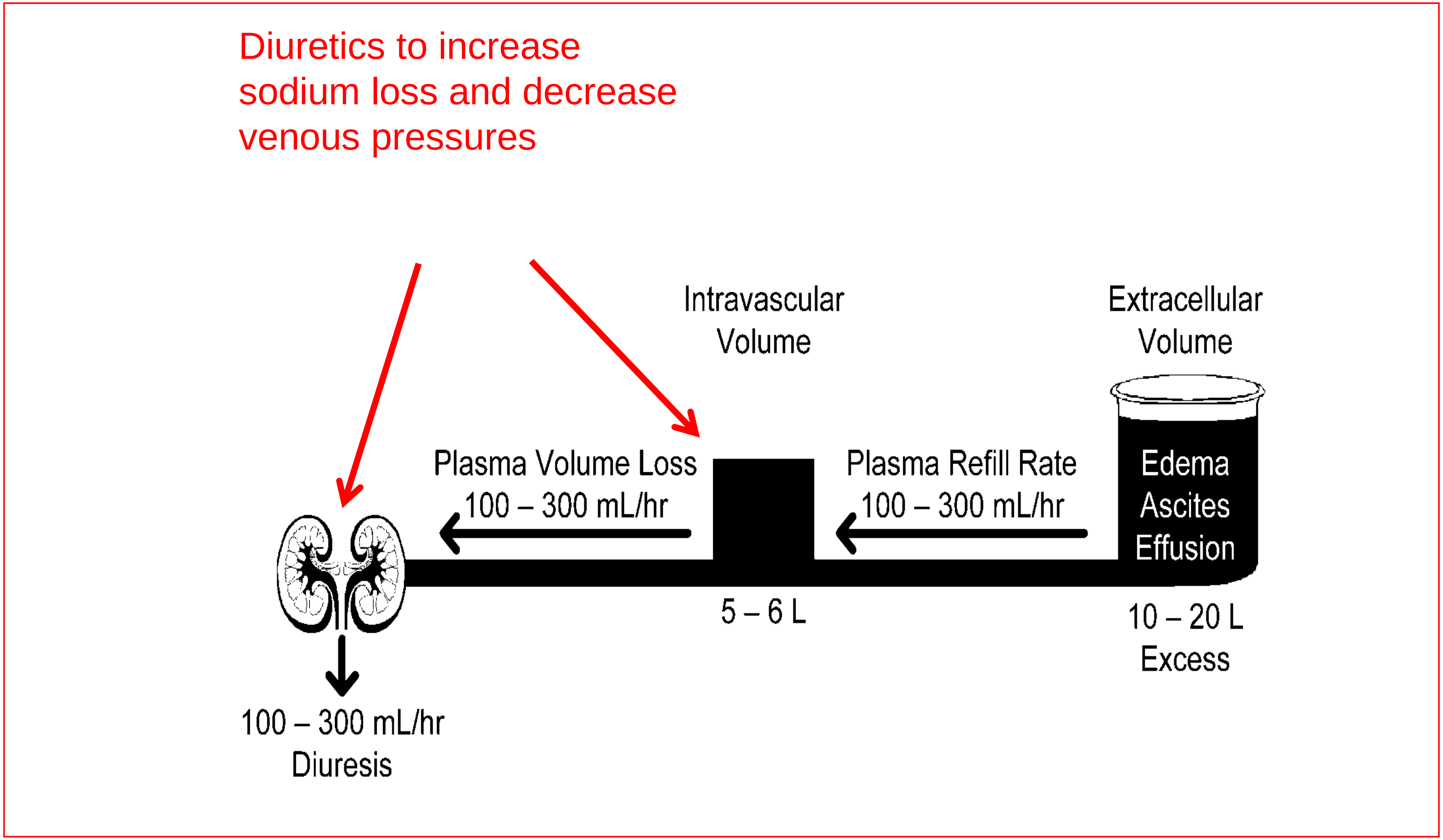
Concept of Plasma Refill Rate in ADHF

- The transient removal of fluids from the intravascular space by diuresis or ultrafiltration triggers compensatory mechanisms, termed *plasma* or *intravascular refill* (PR), aimed at recruiting fluid from the tissue into the intravascular space



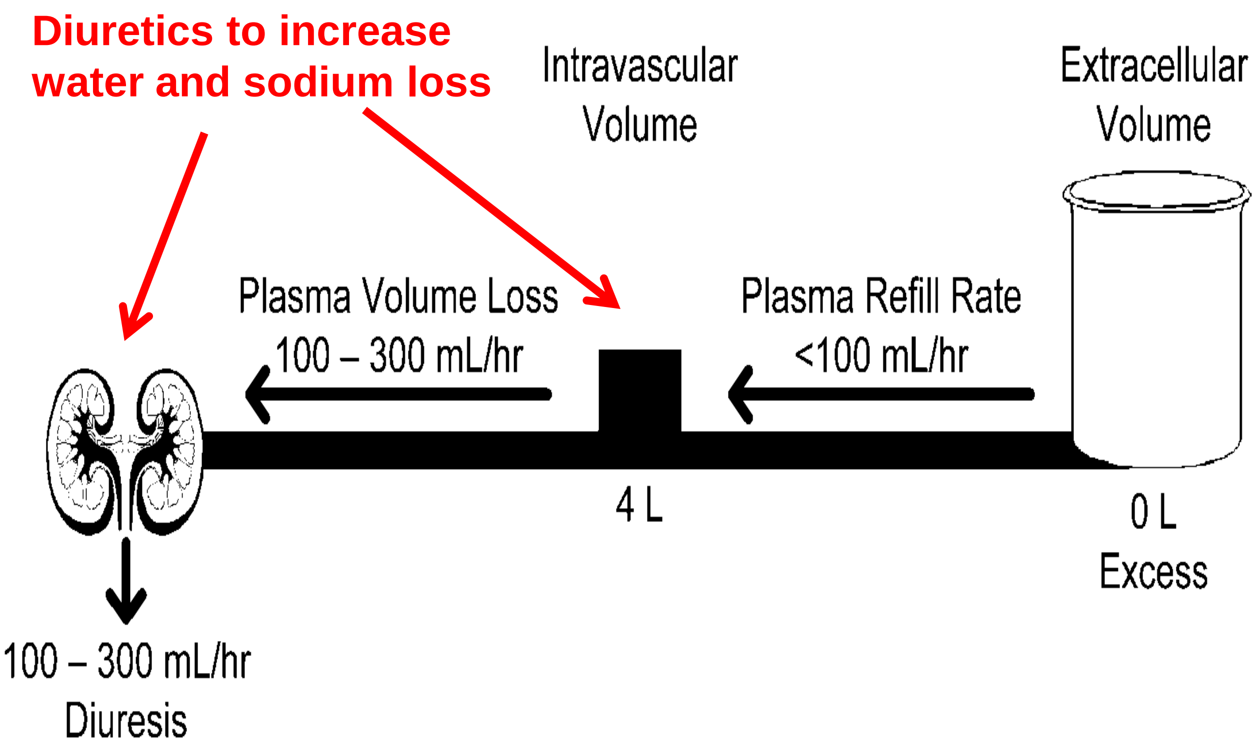
Lauer et al. *Arch Intern Med*. 1983;99:455-460
Marenzi et al. *J Am Coll Cardiol*. 2001;38:4

Concept of Plasma Refill Rate in ADHF



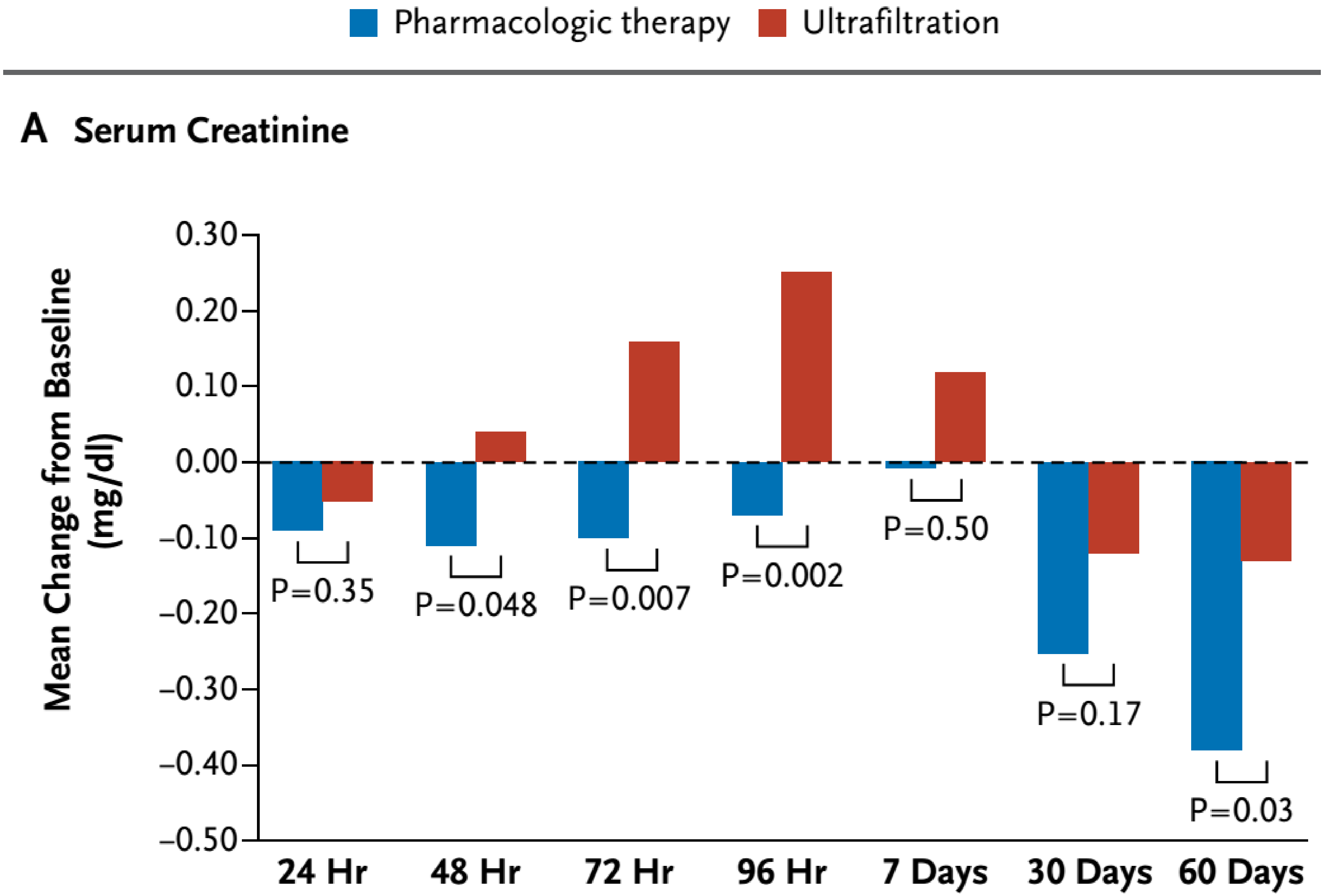
Boyle A, Sobotka PA. *J Card Fail. 2006;12:247-249*

Concept of Plasma Refill Rate in ADHF



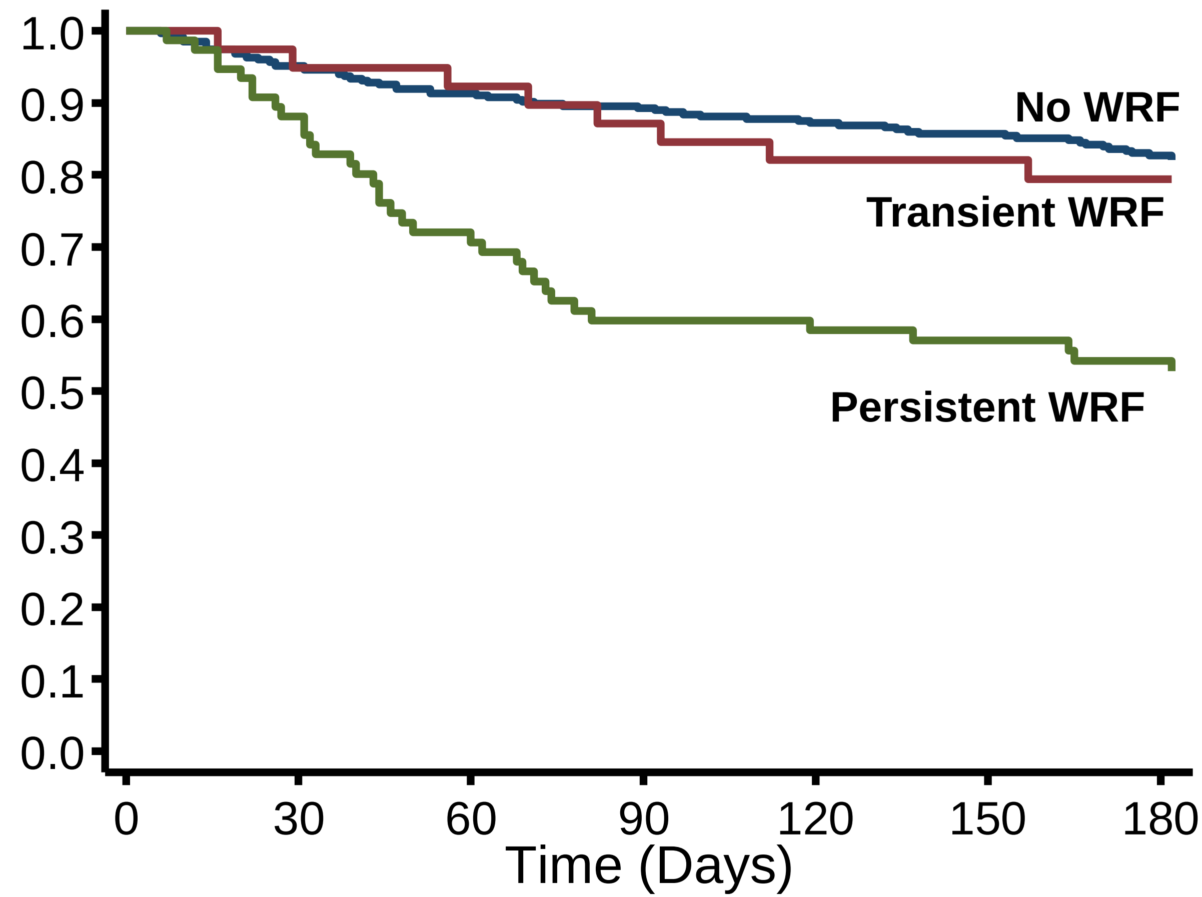
- In clinical practice, the diuresis rate is never titrated to match the PRR and, therefore, may randomly either exceed the PRR or remain below the potential maximal PRR
- If the intravascular volume declines during diuresis at a rate greater than the PRR, renal perfusion may decline, leading to WRF

CARRESS-HF: Changes from Baseline in Serum Creatinine



Bart et al. *N Engl J Med. 2012;367:2296-2304*

Survival with Transient or Persistent Worsening Renal Function in ADHF



Aronson et al. *J Card Fail 2010;16:541-547*

Transient WRF may be a reasonable trade-off for decongestion

- **In the UNLOAD trial, a trend toward worsening renal function and greater weight loss in the ultrafiltration group was associated with a reduction in the rate of hospitalization for heart failure**

- **In the DOSE trial, higher dose diuretics were superior to lower dose diuretics for dyspnea relief and fluid loss at the cost of transient WRF that did not appear to have long-term consequences**

Mentz et al. *Eur J Heart Fail 2014*
Costanzo et al. J Am Coll Cardiol 2007;49:675-683
Felker et al. N Engl J Med 2011;364:797–805

Approach to the patient with WRF and persistent congestion

1. **Optimize diuretic dosing** (initial i.v. furosemide dose of 2.5 times the patient's home oral diuretic dose generally results in substantial diuresis and dyspnoa relief; thiazide-type diuretics; MRA at natriuretic doses)

2. **Vasodilators – For patients with elevated BP (>120 mm Hg)**

3. **Inotrops – For patients with hypotension (BP < 80 mm Hg)**

4. **Ultrafiltration – Should be used with caution**

5. **Consider renal-specific therapies? – No proven value of renal-dose dopamine/Nesiritide/Adenosine antagonists/Vasopressin antagonists**

6. **Hemodynamics guided IV therapy – Not Effective in ESCAPE**

Conclusions

- Therapy of patients with the CRS is not evidence-based and remains a clinical challenge

- The concept of renal adjuvant therapy remains to be proven

- Given the complexity and heterogeneity of this clinical syndrome … Can a single agent that acts on single pathway exert a meaningful clinical benefit ?

Conclusions

- **In many patients, it is extremely difficult to identify a predominant mechanism that leads to CRS in a specific patient with ADHF**

- **The attempt to relieve congestion often involves therapeutic decisions that may seem contradictory, reflecting a compromise between potential benefits and harm**

Thank You for your Attention !