Cardiorenal syndrome

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Disclosures

Consultancy

- Astra Zeneca
- Boegringer
- MSD
- Novartis

68 y old man, ADHF

- *ICMP, ejection fraction 35 %: progressive dyspnea, NYHA IV*

  Lisinopril 10mg, Spironolacone 25mg, Cardvedilol 12.5mg BID, Bumetanide 2.5mg
- *115/85 mmHg, 90 bpm ,JVP >10, HJR+, peripheral edema*
- *Serum creatinin 1.7mg/dL, Na^+ 128*
- *Echocardiography :*
  - *Restrictive filling pattern*
  - *Ascites and pleural effusions.*
- *Treatment: IV nitrates & IV diuretics*
  - *Day 1: Fluid balance = -3.5L/24h*
  - *Day 2: UO: 0.4 mL/kg/h for 8 hours*

    Scr: 1.8 ➔ 2.5 mg/dL but still volume overloaded

Acute Kidney Injury

KDIGO definition of AKI	
Increase in Scr level of ≥ 0.3 mg/dL (26.5 µmol/L)	<48h
Increase in Scr level of ≥ 1.5 times baseline	<7 d
Urine output <0.5mL/Kg/h	>6h

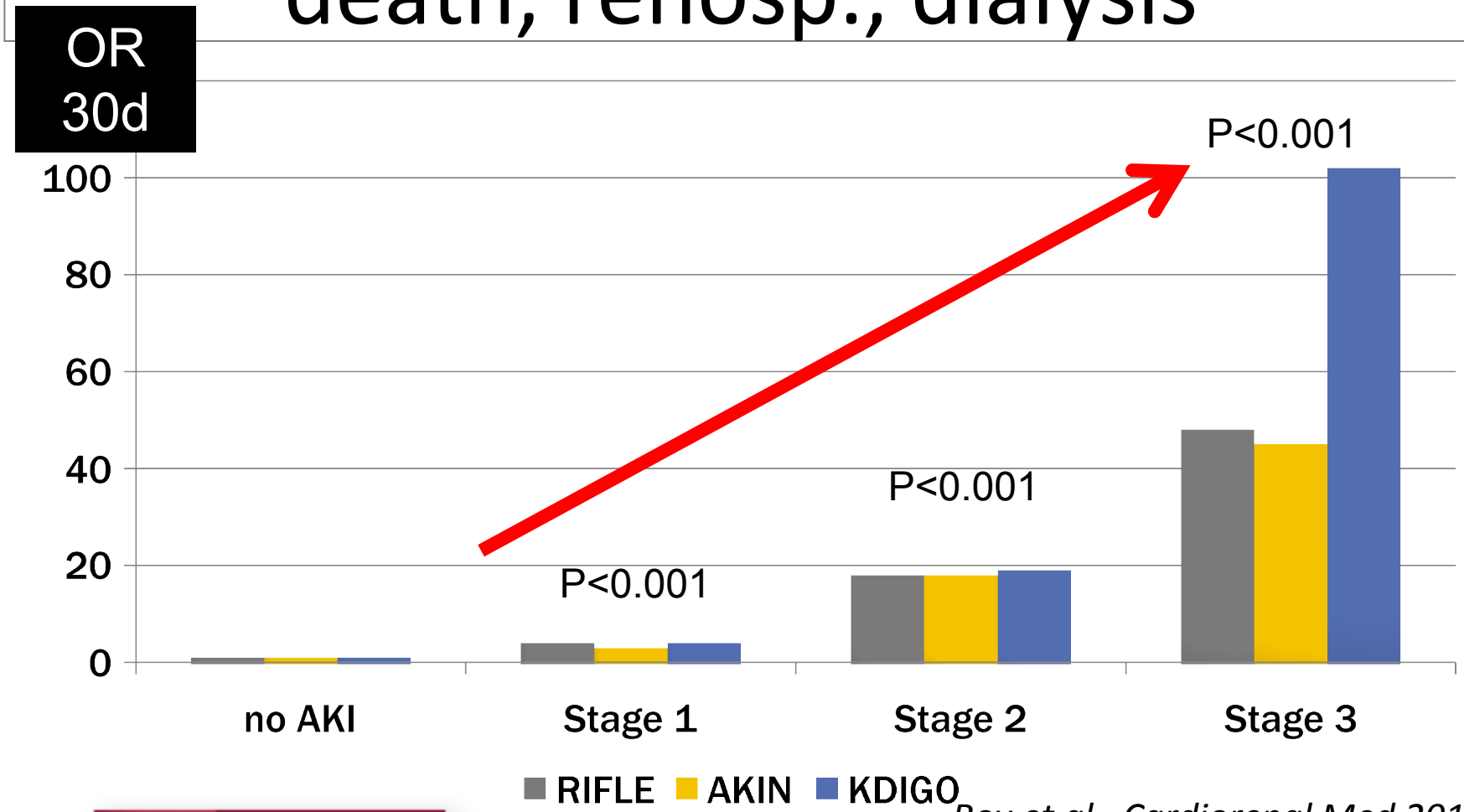
KDIGO is modification of RIFLE and AKIN

KDIGO, Kidney Int 2012

Staging of AKI

KDIGO staging of AKI		
Stage	Scr increase	Urine output
1	≥1.5-1.9 times baseline or ≥ 0.3mg/dL	<0.5mL/kg/h for 6-12h
2	≥2.0-2.9 times baseline	<0.5mL/kg/h for ≥ 12h
3	≥3times baseline or ≥ 4mg/dL or RRT	<0.3mL/kg/h for ≥ 24h or Anuria for ≥ 12h

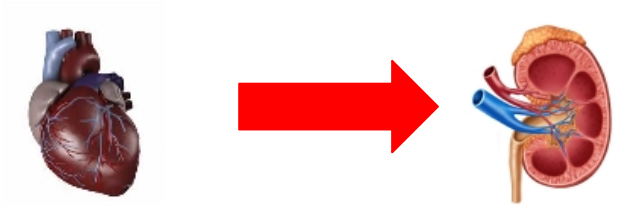
AKI predicts outcome death, rehosp., dialysis



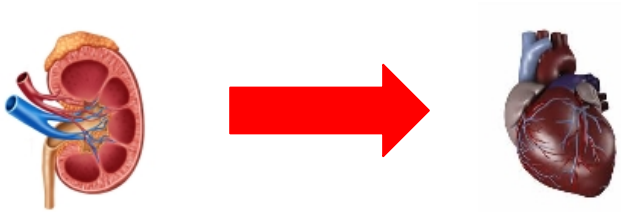
Roy et al., Cardiorenal Med 2013

*"Disorder of the heart and kidneys whereby **acute** or chronic dysfunction in one organ may induce **acute** or chronic dysfynction of the other"*

- **CRS type 1**: **acute** cardiorenal
- CRS type 2: chronic cardiorenal



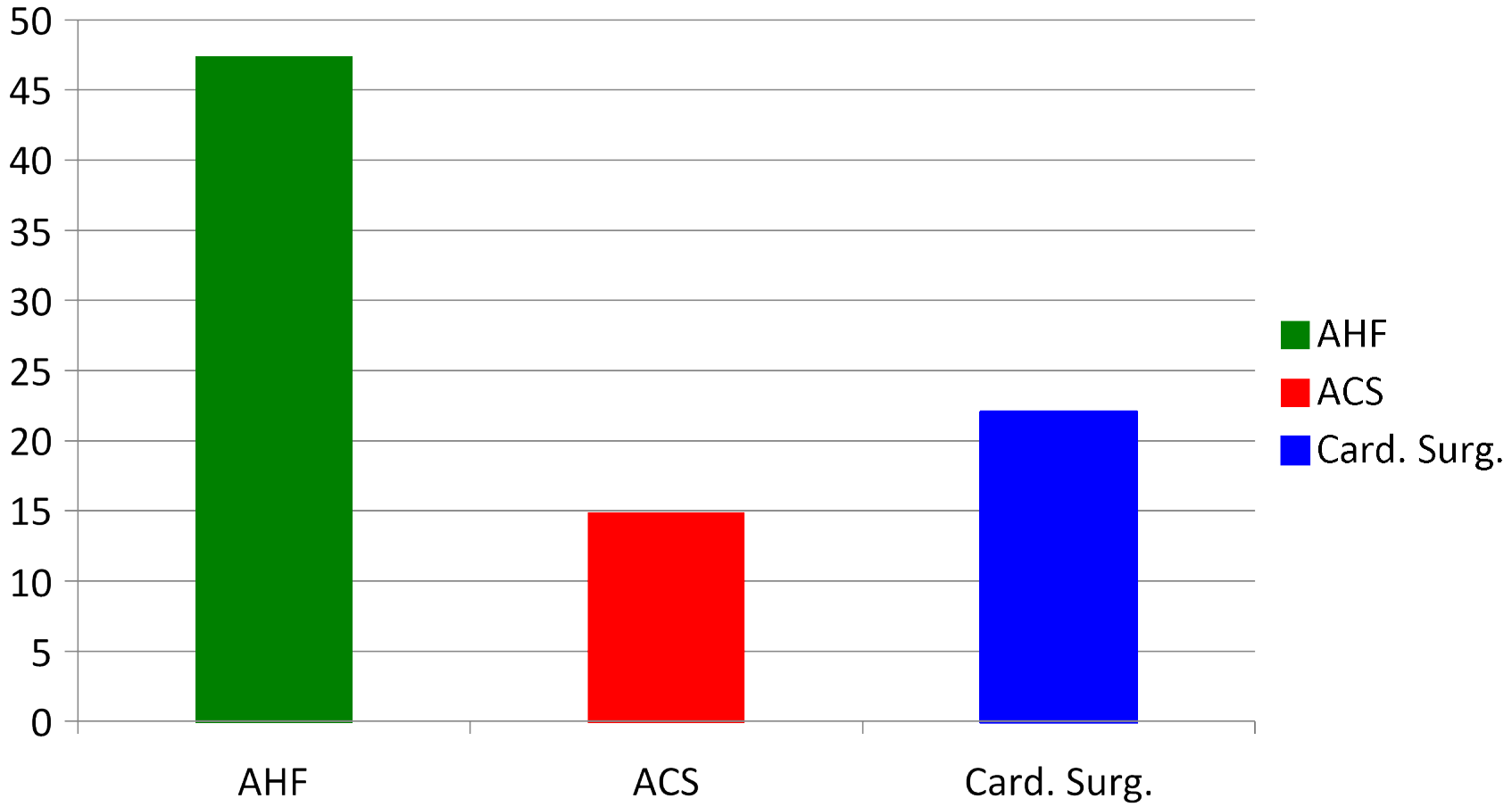
- **CRS type 3**: **acute** renocardiac
- CRS type 4: chronic renocardiac



- **CRS type 5**: **secondary** cardiorenal syndrome

Ronco et al., JACC 2008

Incidence of CRS type 1

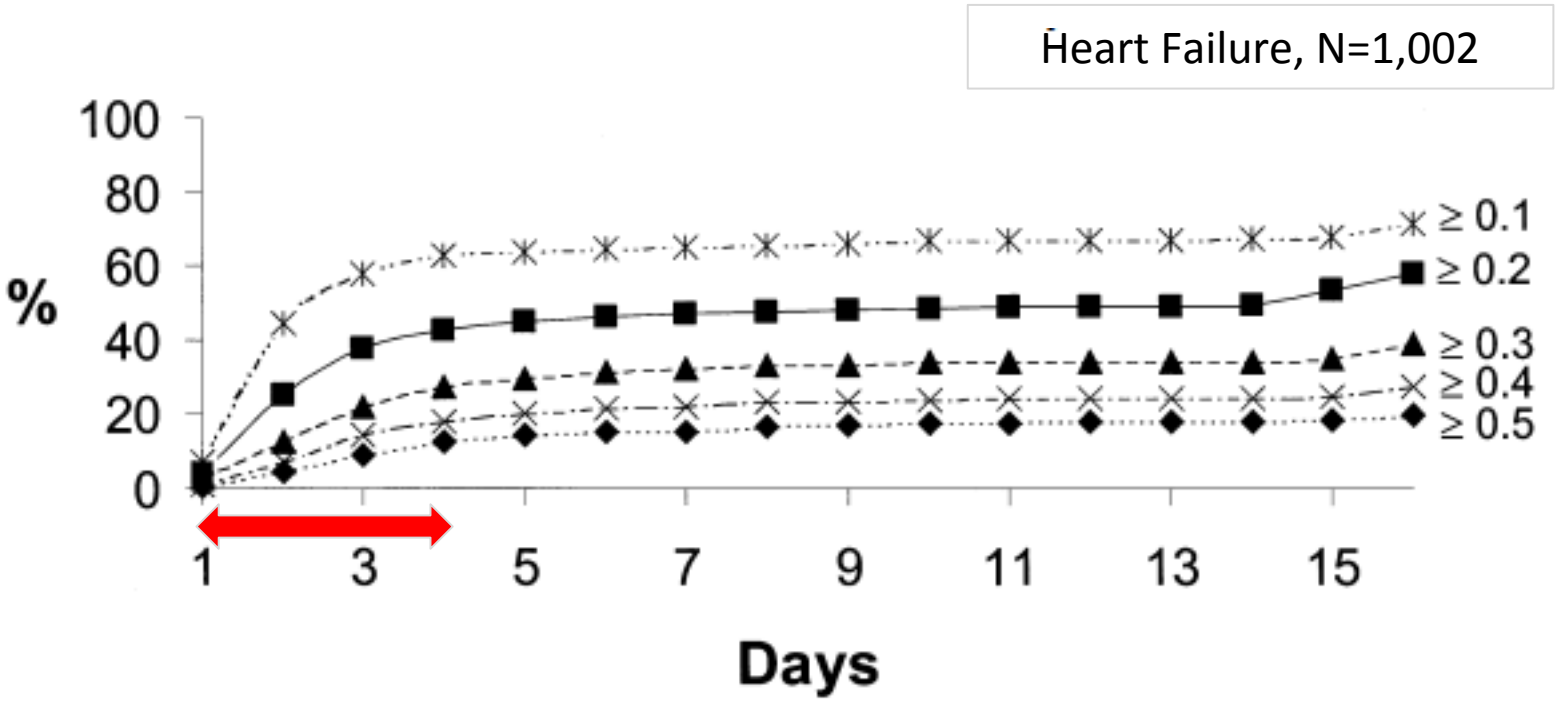


Meta-analysis, Vandenberghe et al., submitted 2015

Patients at risk

- Pre-existing CKD (30-40%)
- Diabetes
- Hypertension
- High dose diuretics
- Iodinated contrast
- Age
- Anaemia

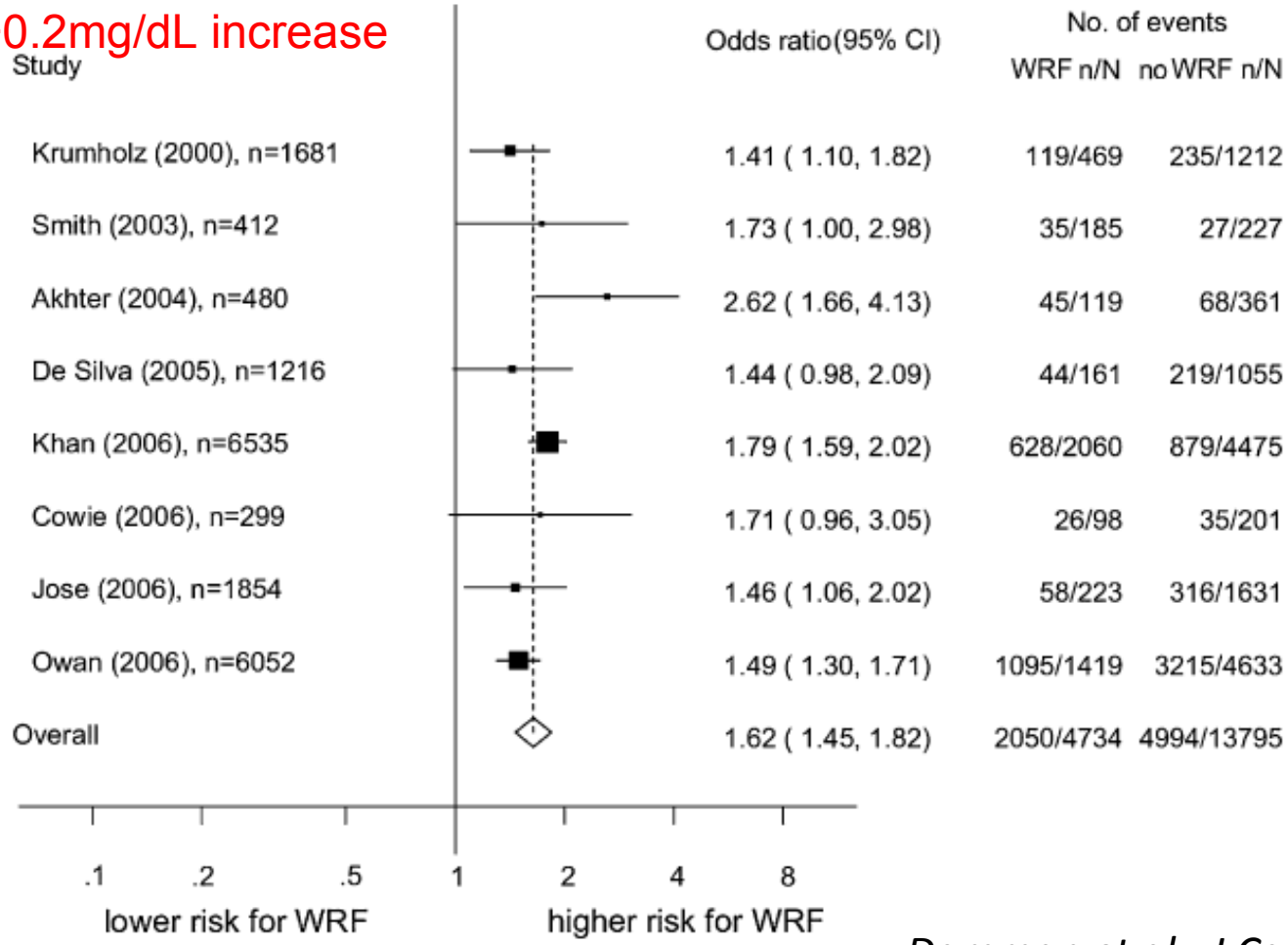
CRS in ADHF



Gottlieb et al., J cardiac Failure 2002

WRF and all cause mortality in AHF

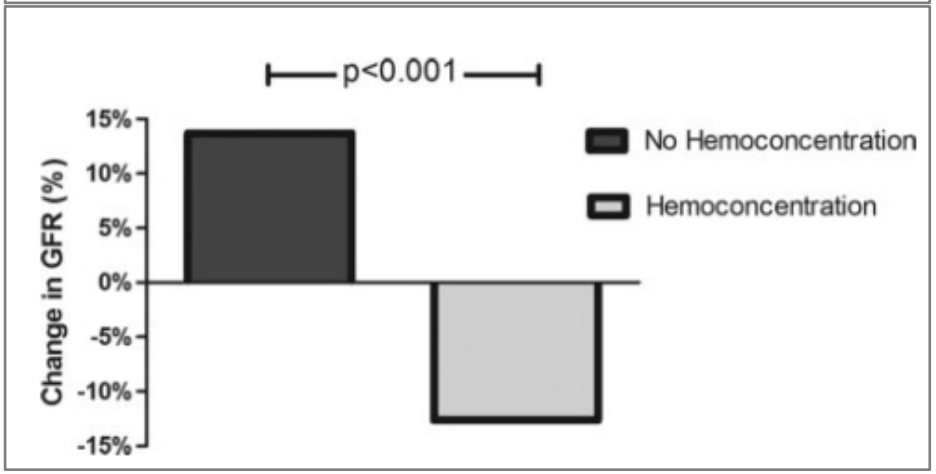
WRF= >0.2mg/dL increase

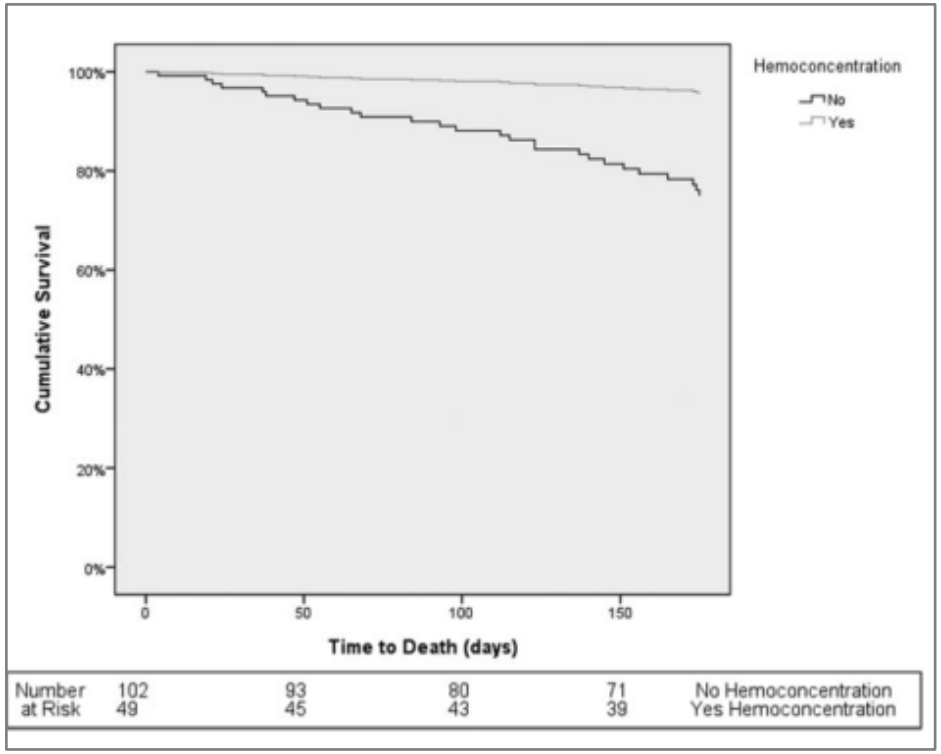


Damman et al., J Card Fail 2007

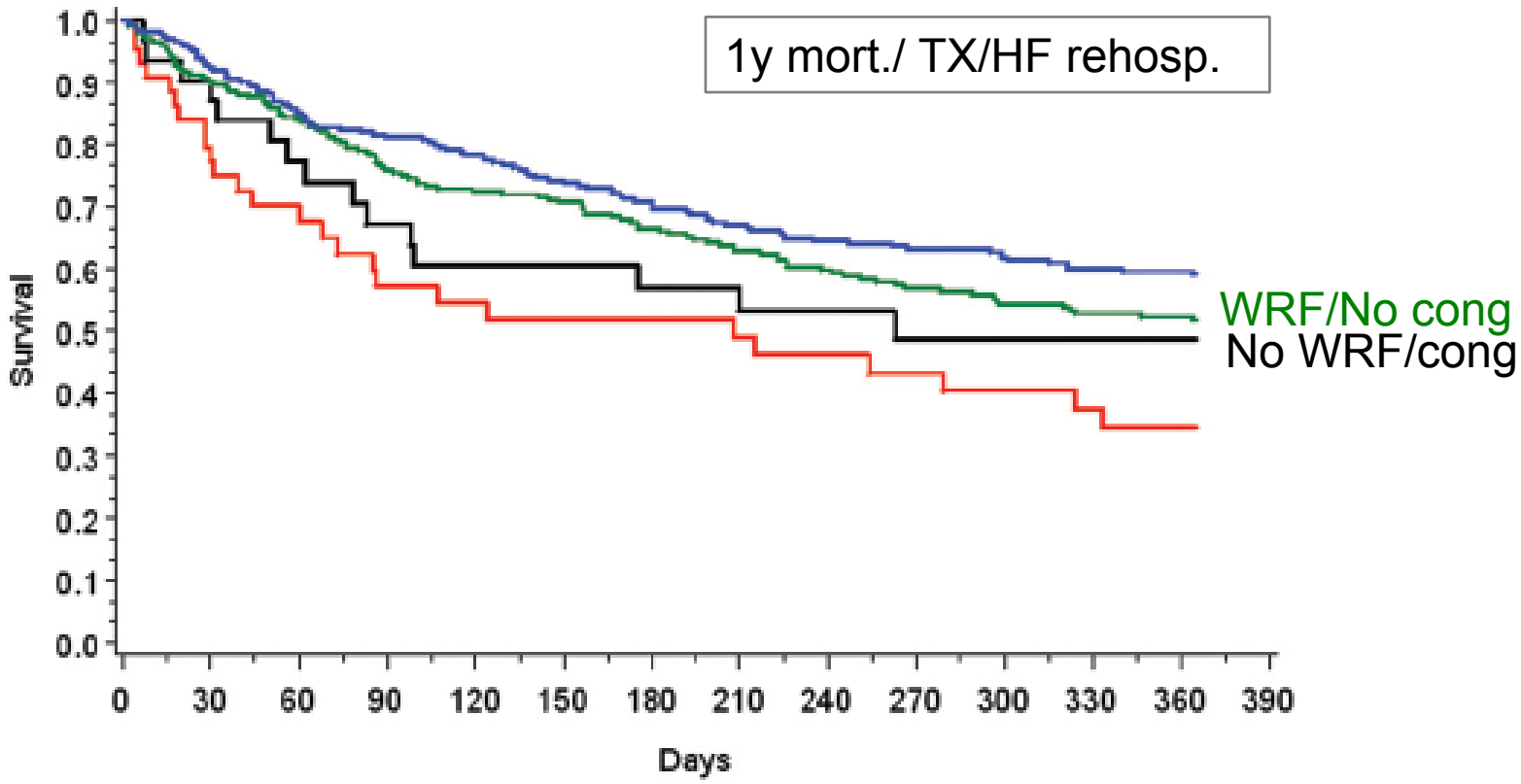
But...Agressive decongestion, even with WRF can improve post-discharge survival

Admission to discharge change in GFR





Testani et al., Circulation 2010



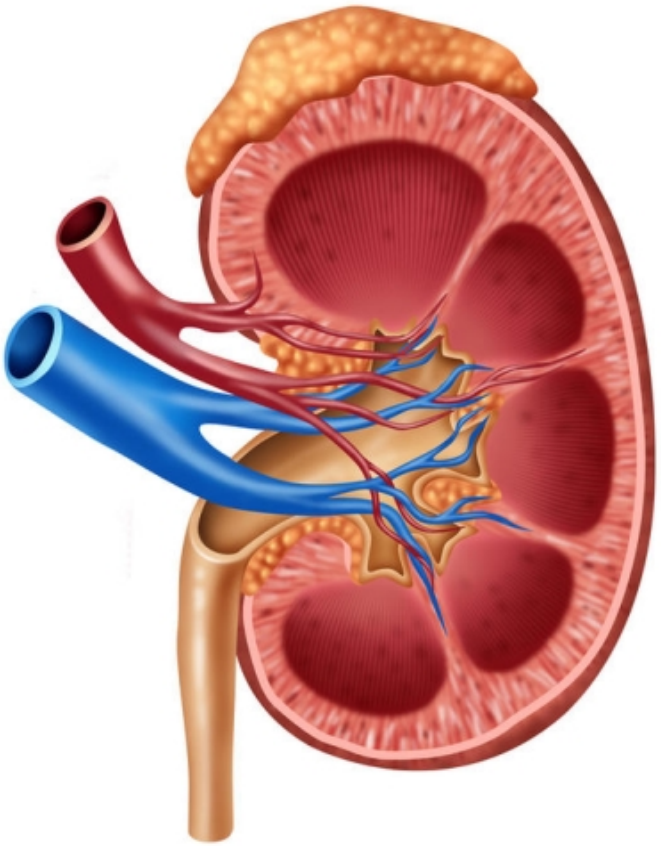
WRF/Cong	44	35	27	22	20	18	18	17	16	15	14	13	12
No WRF/Cong	31	28	23	20	18	18	16	15	13	11	11	11	11
WRF/No Cong	253	227	208	183	163	158	143	131	120	113	107	103	98
No WRF/No Cong	265	244	219	205	192	177	168	158	149	144	140	134	133

Metra et al., Circulation heart Fail 2012

Detoxification: glomeruli: GFR

Volume homeostatis: tubules

Neuro-endocrine function



Cockroft and Gould
MDRD
CKD-EPI

$$GFR = N \times L_P \times S \times (P_{GC} - P_B - \pi_{GC})$$

N = Number of functional nephrons
- ⊖ Chronic kidney diseases

L_P = Hydraulic conductivity glomerular capillary
- ⊖ Chronic kidney diseases
- ⊖ Aldosterone

S = Filtration area
- ⊖ Sympathic activation → Mesangial contraction
- ⊖ Poor renal perfusion → Filtration equilibrium

P_{GC} = Hydrostatic pressure glomerular capilla
- ⊖ Hypovolemia
- ⊖ Hypotension
- ⊖ Renin-angiotensin system antagonists

P_B = Hydrostatic pressure Bowman's space
- ⊕ Elevated central venous pressure
- ⊕ Elevated abdominal pressure

π_{GC} = Colloid osmotic pressure glomerular capillary
- ⊕ Hemoconcentration

an's space

Volume status
Renal perfusion
BP
CVP
IAP
Neurohormonal activation

Verbrugge et al., CardioRenal Med 2014

↘ Forward flow

Diuretics

RAAS

Na^+ retention

Intrarenal
Adenosine release

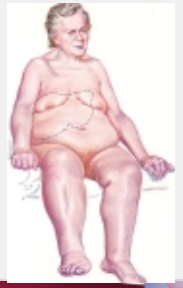
Sympathetic nervous system

Renal
vasoconstriction

Renal hypoperfusion

GFR↘

Interst. fibrosis
Tubular damage
Nephron loss



Venous congestion

Increased venous
pressure

Immunological factors
Hormonal factors
Anaemia
Inflammation
Oxidative stress
Endotelial dysfunction

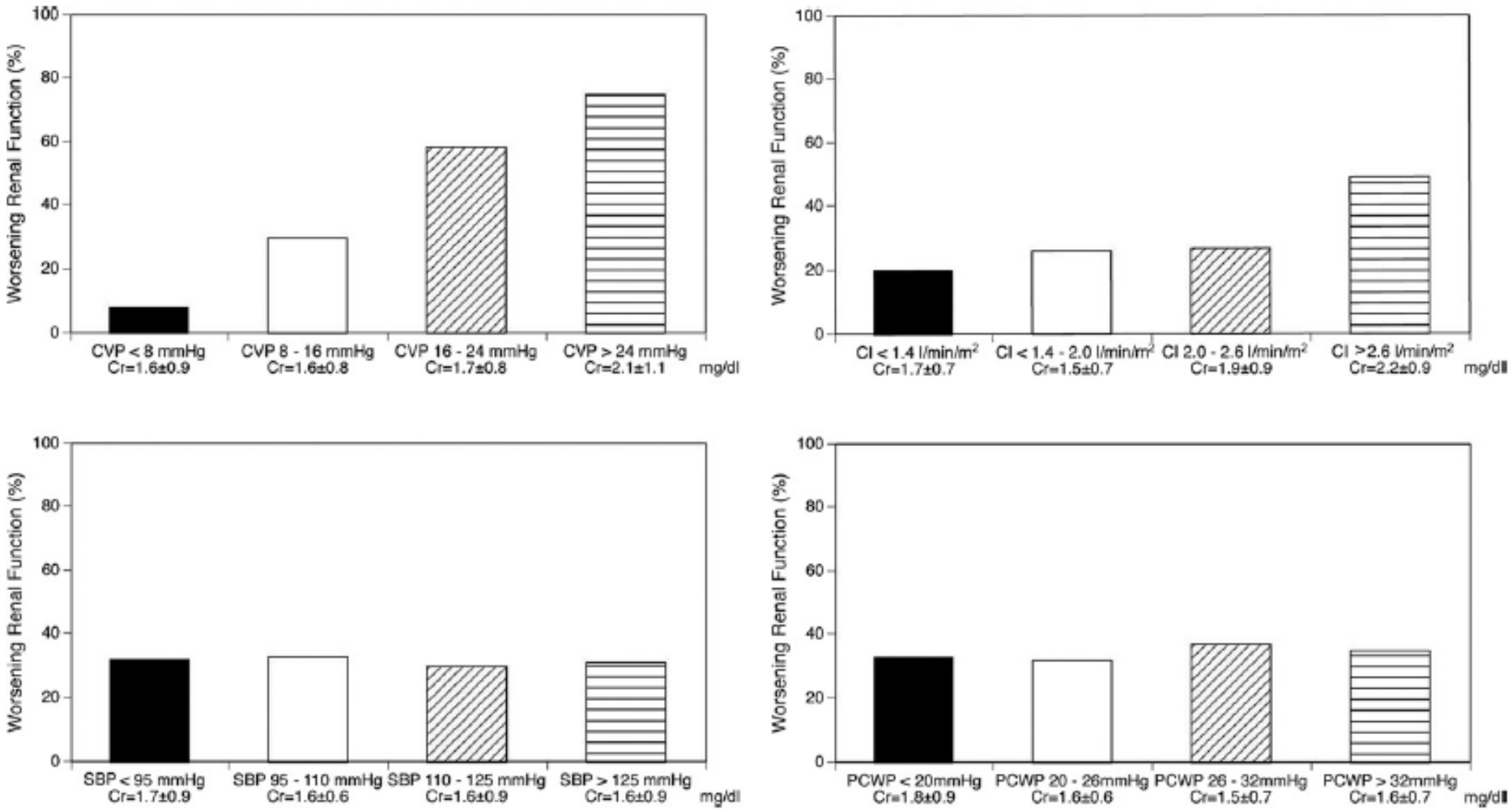


Figure 1 **Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP**

Mullens et al., JACC 2009

Managment CRS 1: Volume assessment

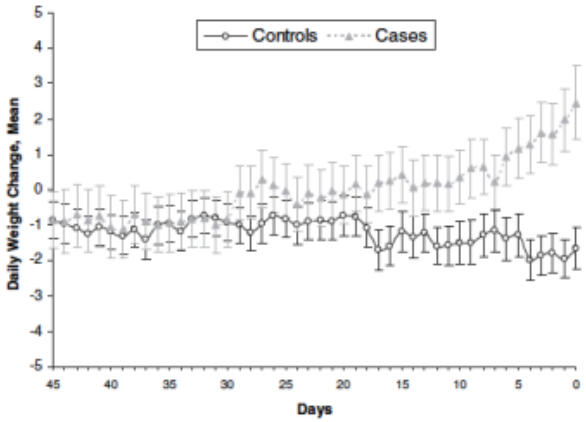


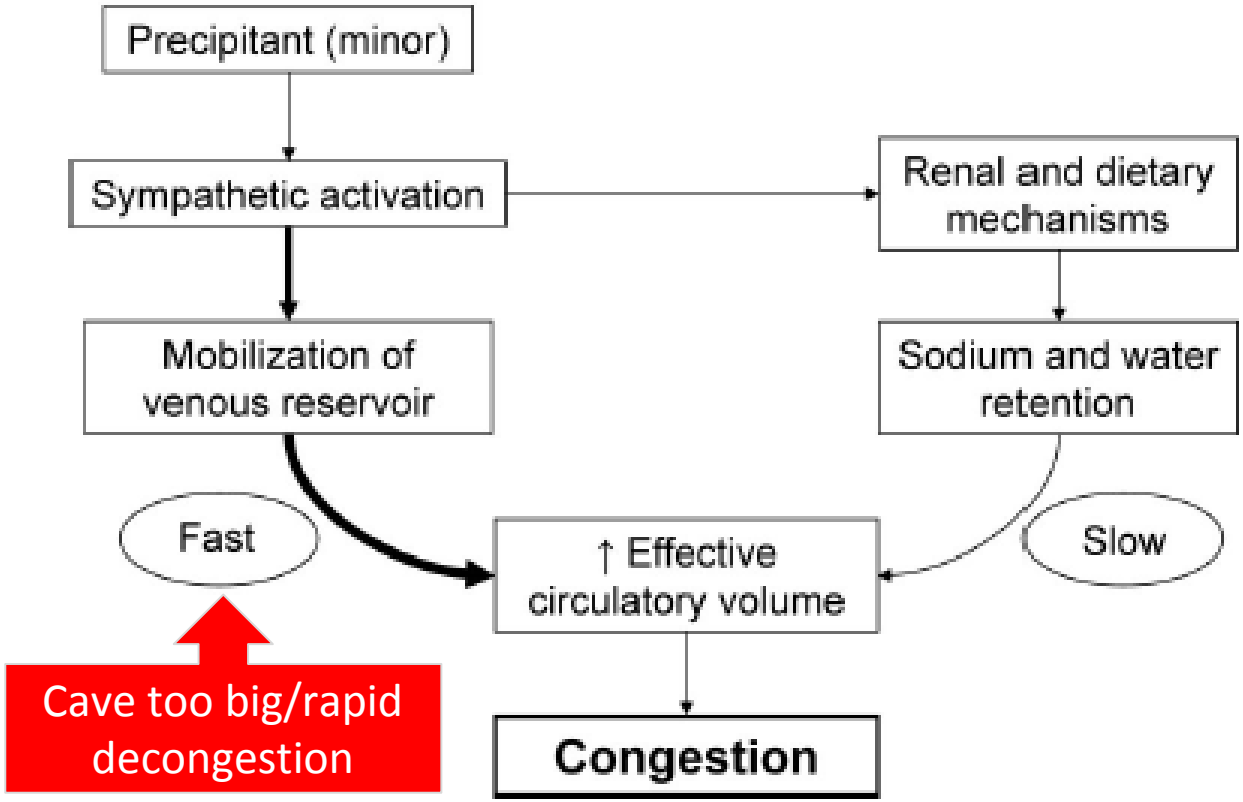
TABLE 2. Conditional Logistic Regression Models of Heart Failure Hospitalization (n=240)

Weight Gain, lbs	Case Patients, n (%)	Control Patients, n (%)	Matched Unadjusted OR (95% CI)	Matched Adjusted OR (95% CI)	Adjusted *P*
≤2	65 (54)	92 (77)	Reference group	...	...
>2 up to 5	21 (18)	16 (13)	2.40 (1.05–5.45)	2.77 (1.13–6.80)	0.026
>5 up to 10	17 (14)	8 (7)	3.81 (1.35–10.77)	4.46 (1.45–13.75)	0.009
>10	17 (14)	4 (3)	5.65 (1.81–17.65)	7.65 (2.22–26.39)	0.001

Weight gain is during 1 week preceding hospitalization of case patients. Results were adjusted for comorbid conditions and the medications shown in Table 1.

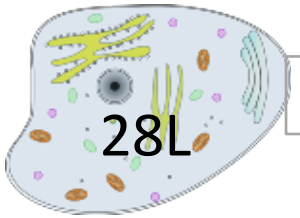
Chaudhry et al, Circulation 2007

Fast and slow mechanisms of circulatory congestion



Fallick et al, Circ Heart Fail 2011

Managment CRS 1: Congestion



Transcellular water flux

How much, how fast?

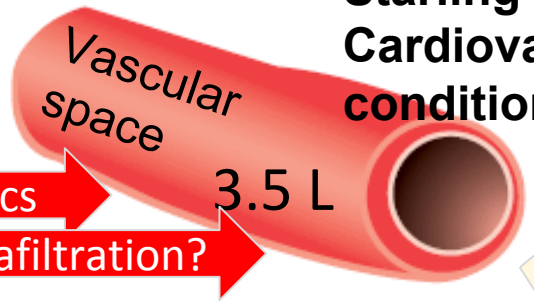
Osmolality

Paracentesis
Compression

Interstitium
10.5L

Intravascular refill

Starling forces
Cardiovascular condition



Diuretics

Ultrafiltration?

Diuretics

- Goal: normovolaemia
- Loop diuretics: tailored, assessment volume status
- Agressive treatment of volume overload

  but

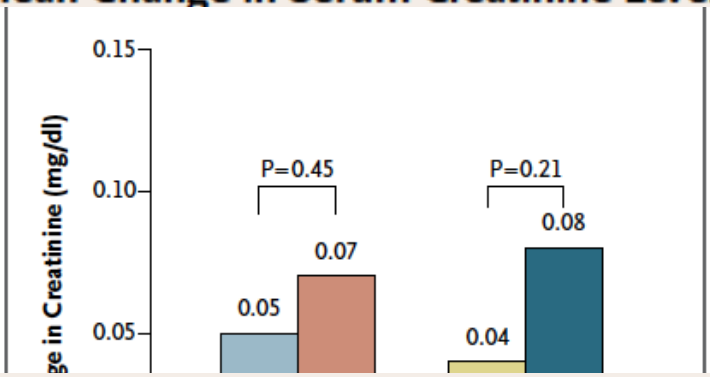
- Avoid hypotension and underfilling

  MAP≥65mmHG, or higher in chronic hypertensives

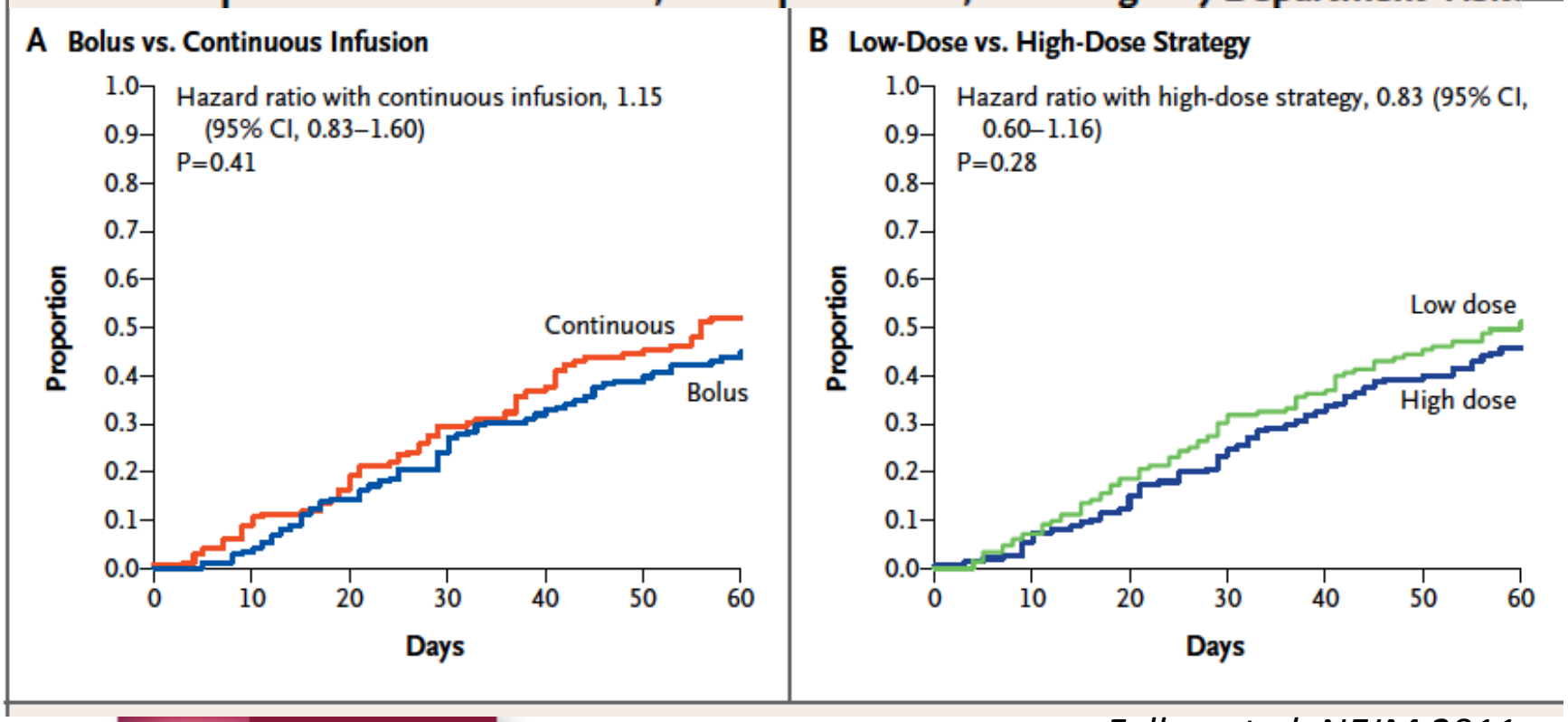
- Intermittent vs. Continuous?
- Monitor weight, Urine output

N=308

Mean Change in Serum Creatinine Level.



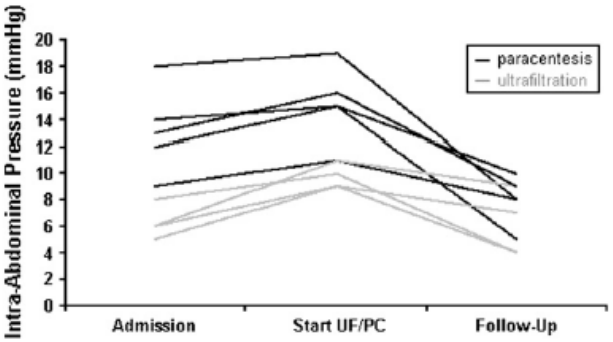
Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.



Felker et al, NEJM 2011

Removal Fluid 3rd space

- Paracentesis of ascites
  - ↘ Intra-abdominal pressure
  - ↗ GFR



- Compression therapy of lower extremities

  Lymphatic drainage

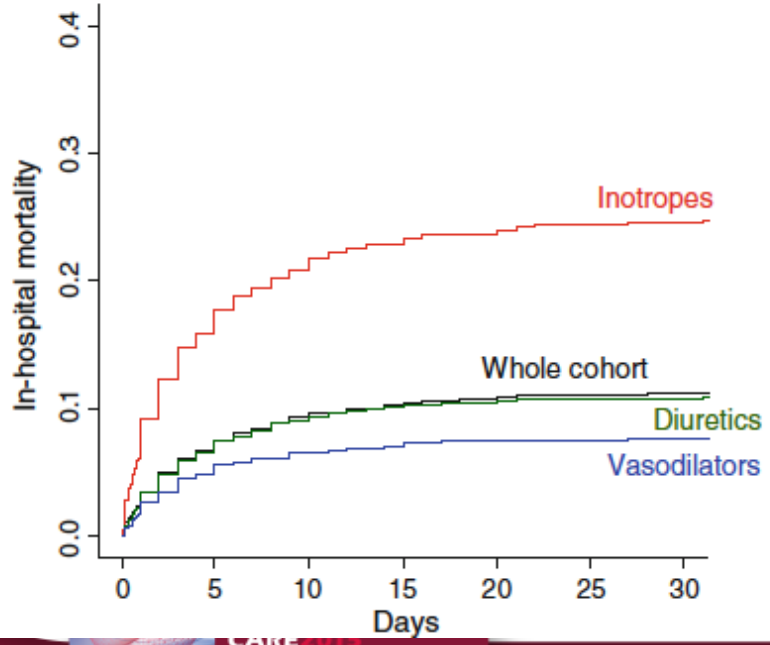
  Interstitial Fluid→ Systemic circulation

Mullens et al, J Card Fail 2008

Managment of CRS 1:

↗ Effective circulatory volume

- ↘Afterload: Vasodilators, if MAP >65mmHG
- ↗Contractility: Inotropes
- Mechanical support

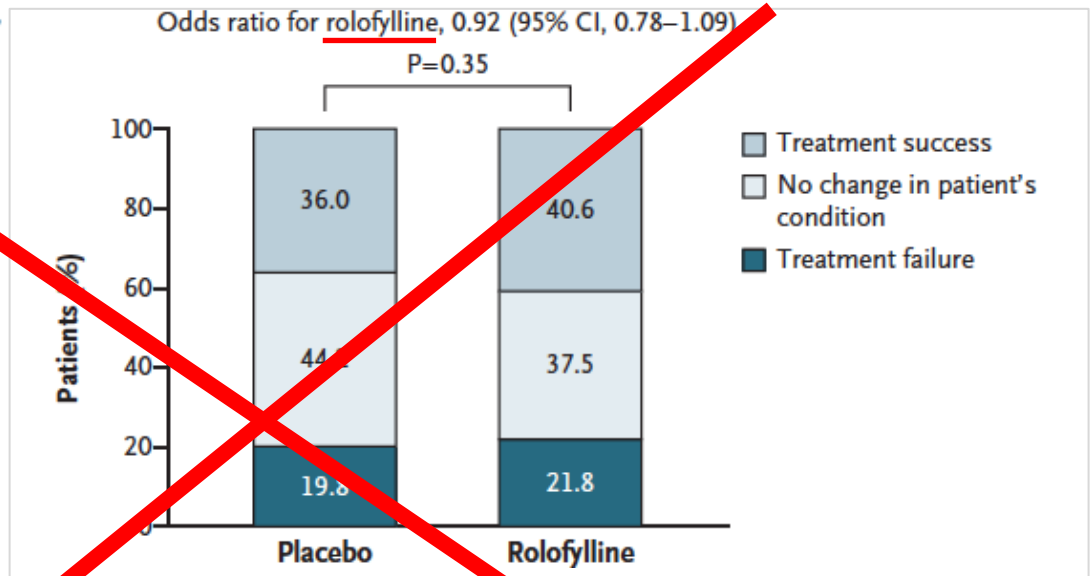


Mebazaa et al, Intensive Care Med 2011

Managment of CRS 1:

Improvement renal perfusion

Rolofylline, an Adenosine A_1–Receptor Antagonist, in Acute Heart Failure



Criterion for treatment failure§	Rolofylline (N=1356)	Placebo (N=677)
Death during the first 7 days	23 (1.7)	14 (2.1)
Readmission for heart failure during the first 7 days	5 (0.4)	4 (0.6)
Worsening heart failure, days 3–7	123 (9.1)	66 (9.7)
Persistent worsening of renal function during the first 7 days	172 (12.7)	75 (11.1)

Massie et al., NEJM 2010

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction

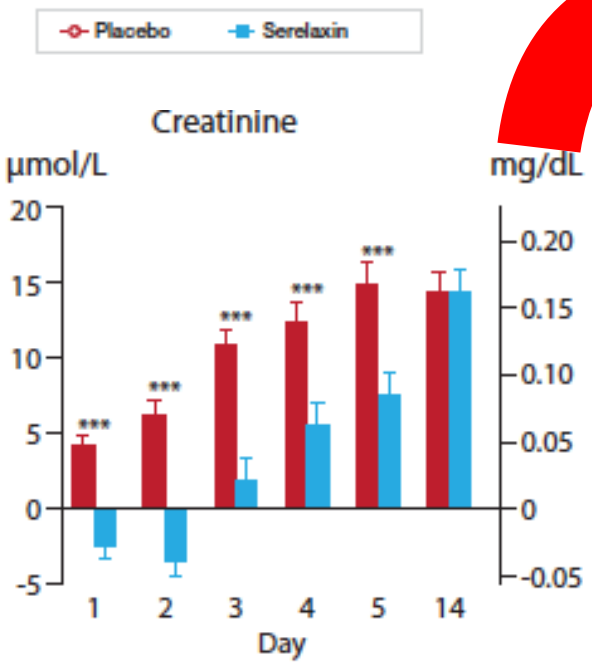
The ROSE Acute Heart Failure Randomized Trial

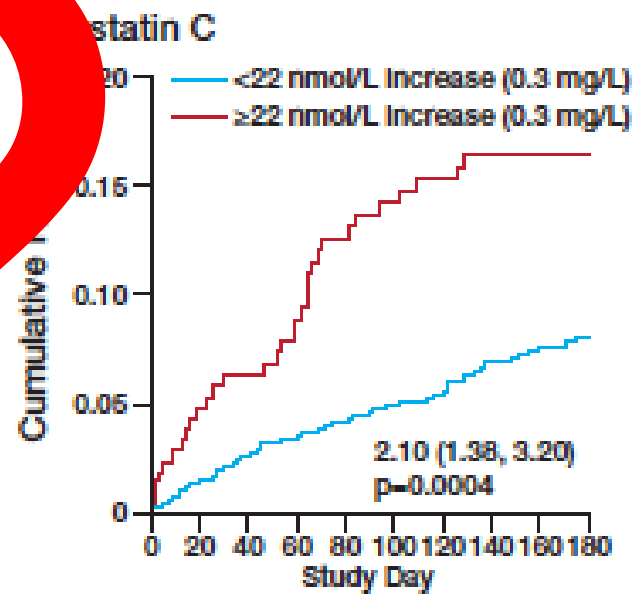
Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	Placebo (n = 119)	Dopamine (n = 122)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.12 (0.06 to 0.18)	0.01 (−0.08 to 0.10)	.72
Nesiritide strategy	Placebo (n = 119)	Nesiritide (n = 119)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8574 (8014 to 9134)	279 (−618 to 1176)	.49
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.07 (0.01 to 0.13)	−0.04 (−0.13 to 0.05)	.36

Chen et al, JAMA 2013

Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program



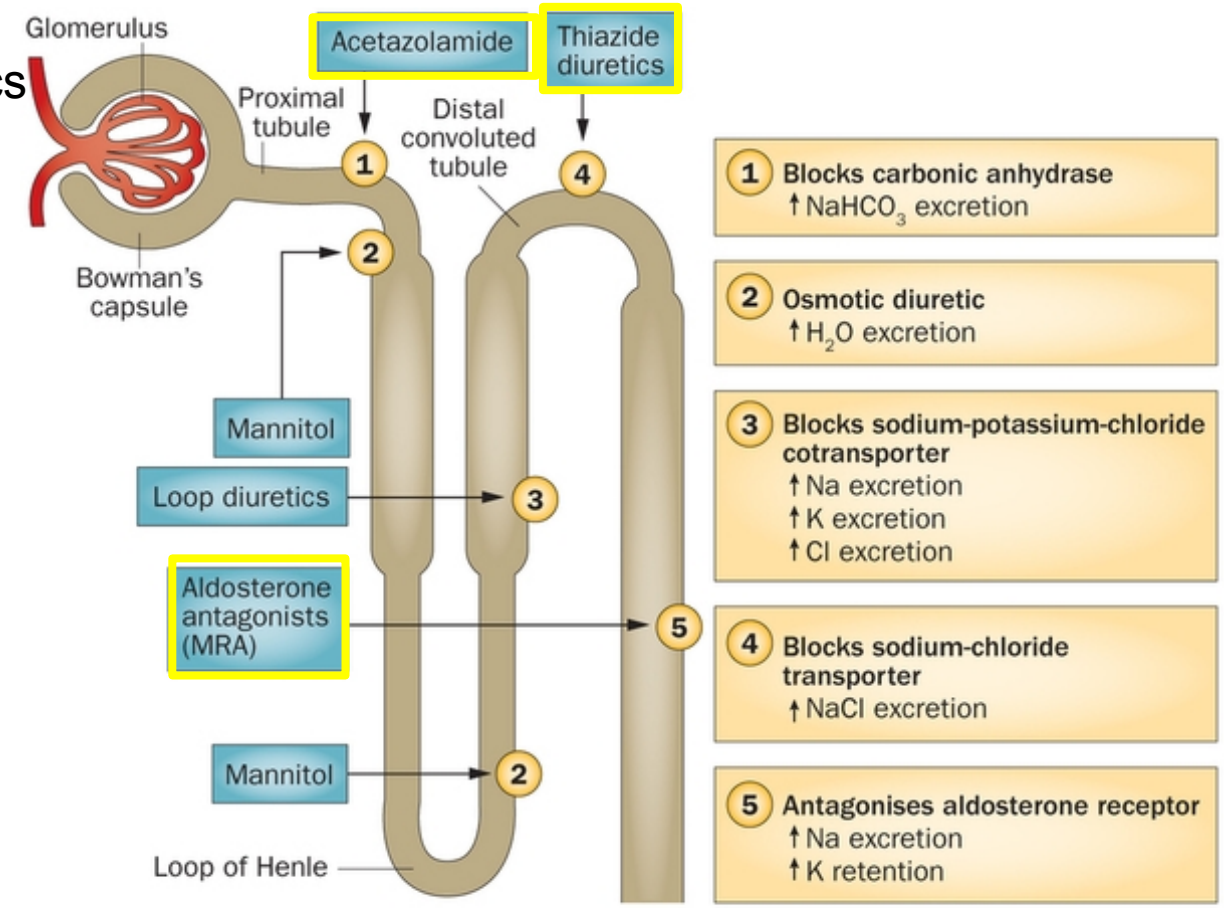


Metra et al., JACC 2013

Managment of CRS 1:

Diuretic Resistance:

-Increase Loop diuretics
-Combine



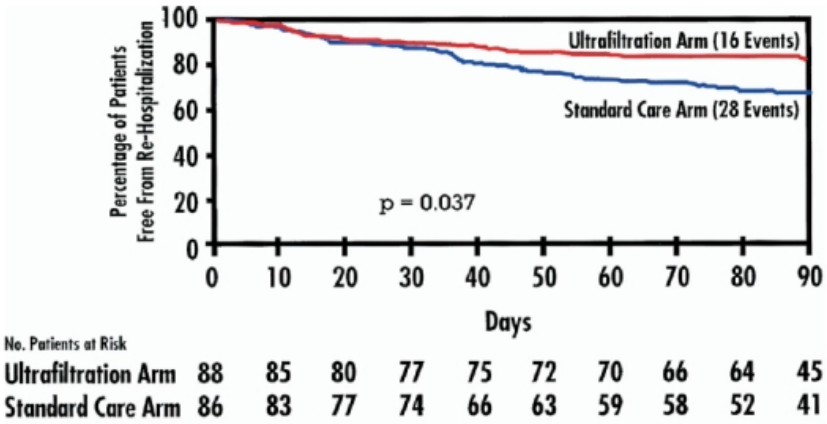
Nature Reviews | Cardiology

Ultrafiltration

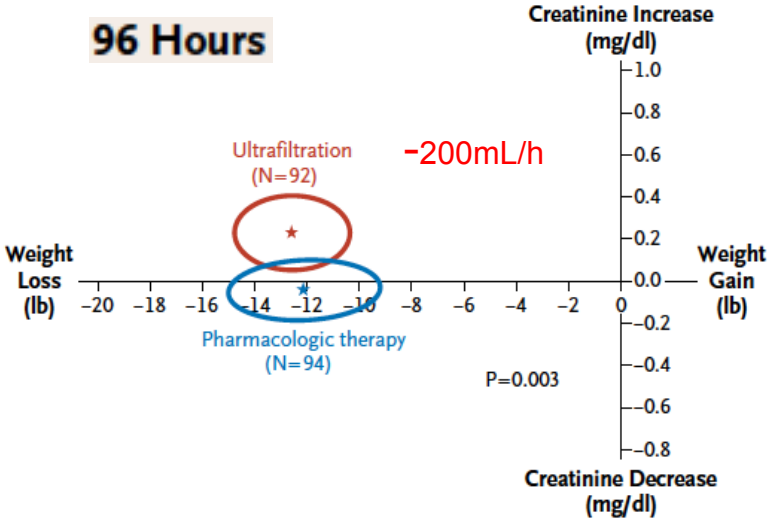
UNLOAD: ADHF and volume overload
N=200

CARESS: ADHF –WRF-persist. Cong.
N=188

Greater Fluid loss



Costanzo et al., JACC 2007



Bart et al., NEJM 2012

Hypertonic saline?

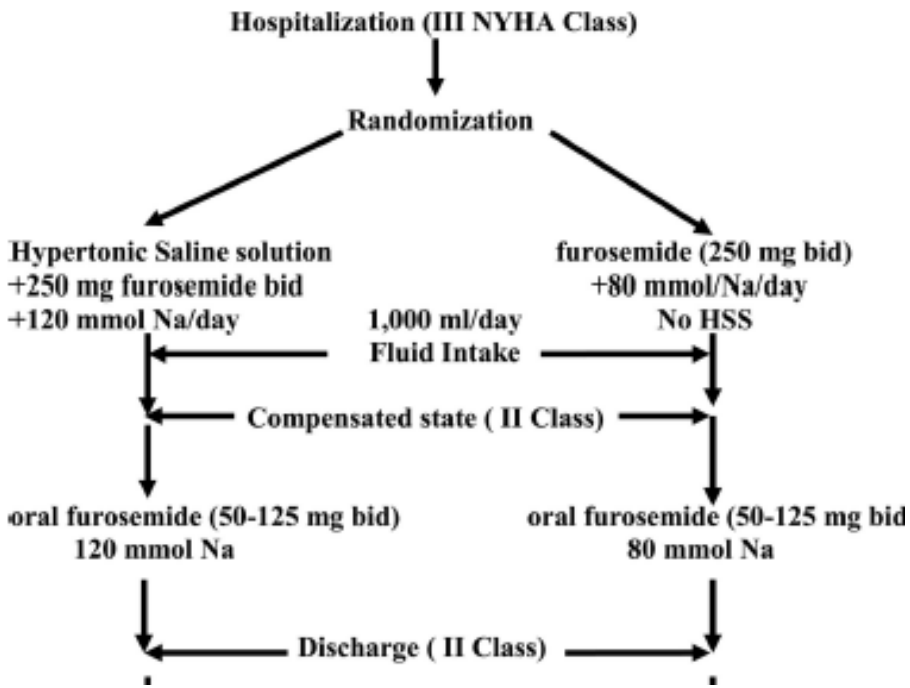


TABLE 3. Clinical results at discharge in both groups

	Furosemide with HSS	Furosemide without HSS	*P*
Side effects (tinnitus)	0	71 (7.2%)	<0.0001
NYHA class II	736 (77.2%)	813 (83.4%)	<0.29
NYHA class I	217 (22.8%)	161 (16.5%)	<0.006
Hospitalization time (days)	3.5 ± 1	5.5 ± 1	<0.0001
Ejection fraction (%)	37.3 ± 5	36.4 ± 6	<0.0001
BNP (pg/mL)	355 ± 105	385 ± 115	<0.0001
Creatinine clearance	55.4 ± 3.3	48.7 ± 2.1	<0.0001

NYHA, New York Heart Association; BNP, brain natriuretic peptide; HSS, hypertonic saline solution.

Paterna et al., Am J Med Sci 2011

68 y old man, ADHF

- *Dobutamine 4 µg/kg/min, interrupt β-blocker*
- *Diuresis ↗, Fluid balance -5L/3days*
- *Serum creatinin 2.5mg/dL → 1.5 mg/dL*
- *Na+ 128 → 138*
- *Salt and fluid restriction*

Conclusions

- CRS 1 : up to 50 % of your ADHF patients
- Complex pathofysiology:
  - Venous congestion
  - Low output
  - Neurohormonal activation
- DECONGESTION
  - Agressive Diuretics-Transient ↘ GFR-Avoid hypotension-3rd space
    - Combination
    - Ultrafiltration
- Increase effective circulatory volume
    - Vasodilator
    - Inotropes-mechanical support
- Improvement of renal perfusion?