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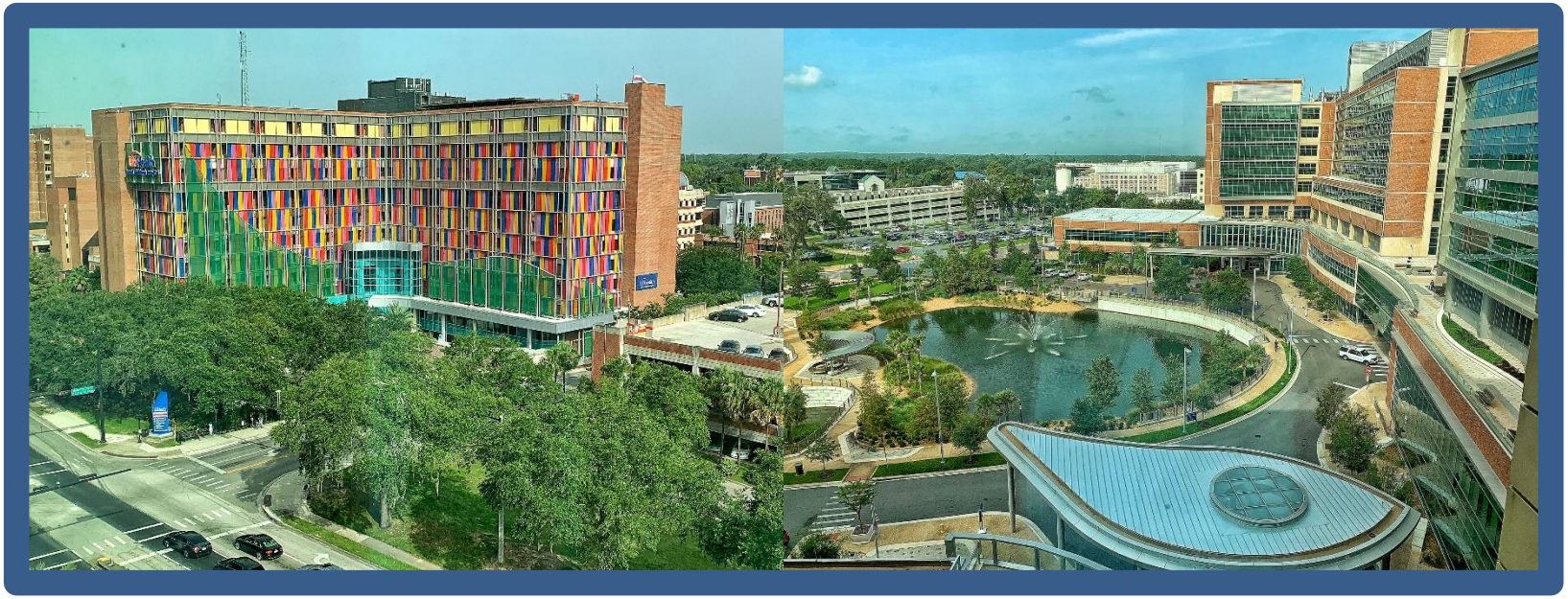
Rise in Serum Creatinine and Congestion in Acute Decompensated Heart Failure; What Do We Really Know?



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Professor and Vice-Chief of Clinical Affairs
Division of Nephrology, Hypertension, and Renal Transplantation
University of Florida

Disclosures

Baxter, Inc. – Cardiology Advisory Board

CHF Solutions, Inc. - Scientific Advisory Board

Otsuka America, Inc. - Consultant

Relypsa, Inc. - Consultant

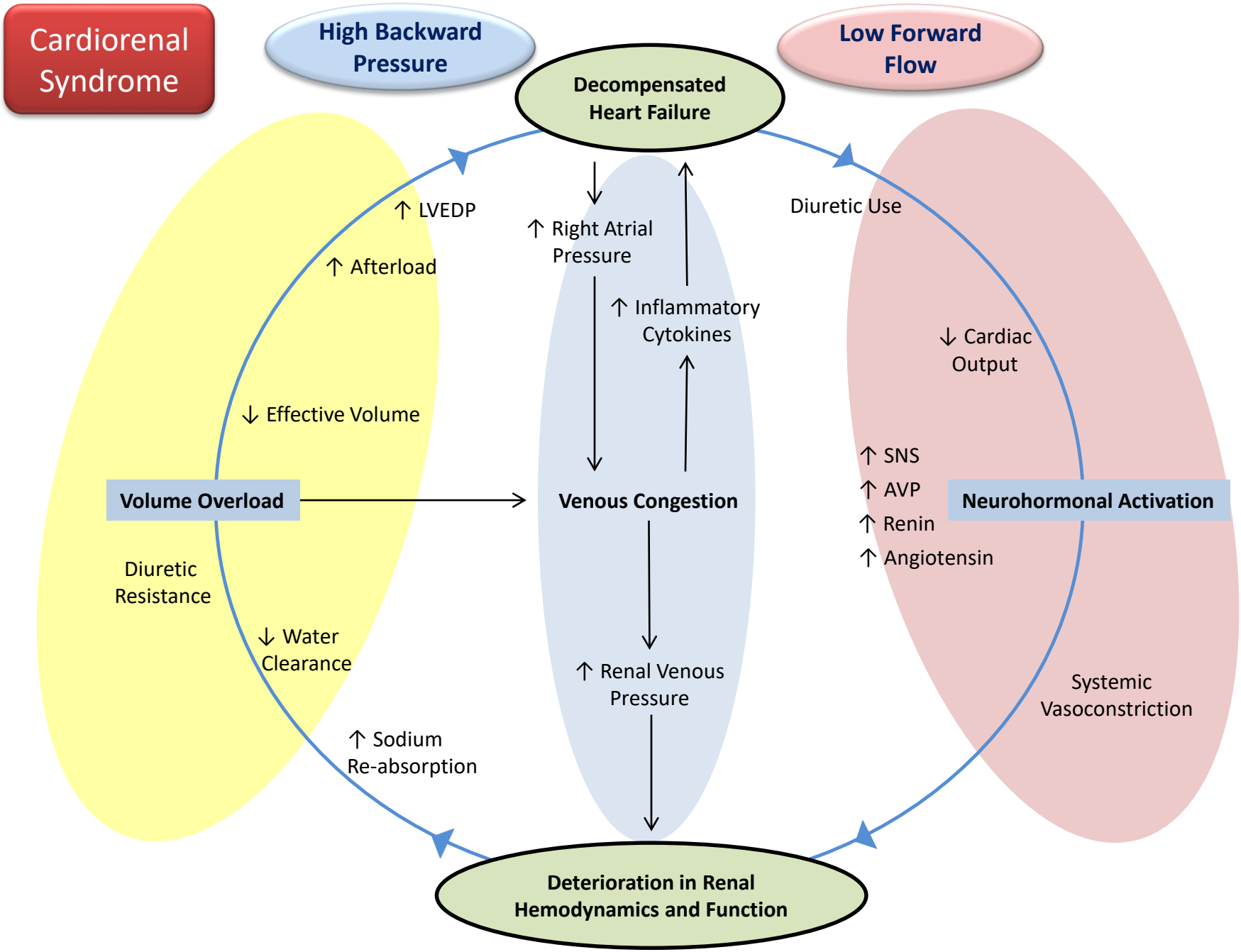
W.L. Gore Inc. - Consultant

Acute Decompensated Heart Failure (ADHF)

- Lifetime prevalence: 20–33 %
- Currently, over 5 million Americans with HF (more than 8 million by 2030)
- ADHF : the leading cause of hospitalization in patients over 65
- ADHF: the highest rate of 30-day re-hospitalization among all medical conditions
- ADHF: the 3-month re-hospitalization rate of 40%
- ADHF: the 1-year mortality rate of over 30%

- Total costs for HF: $31 billion in 2012, estimated at $70 billion in 2030

(80% due to hospitalization) – *Major Financial Burden on Healthcare*



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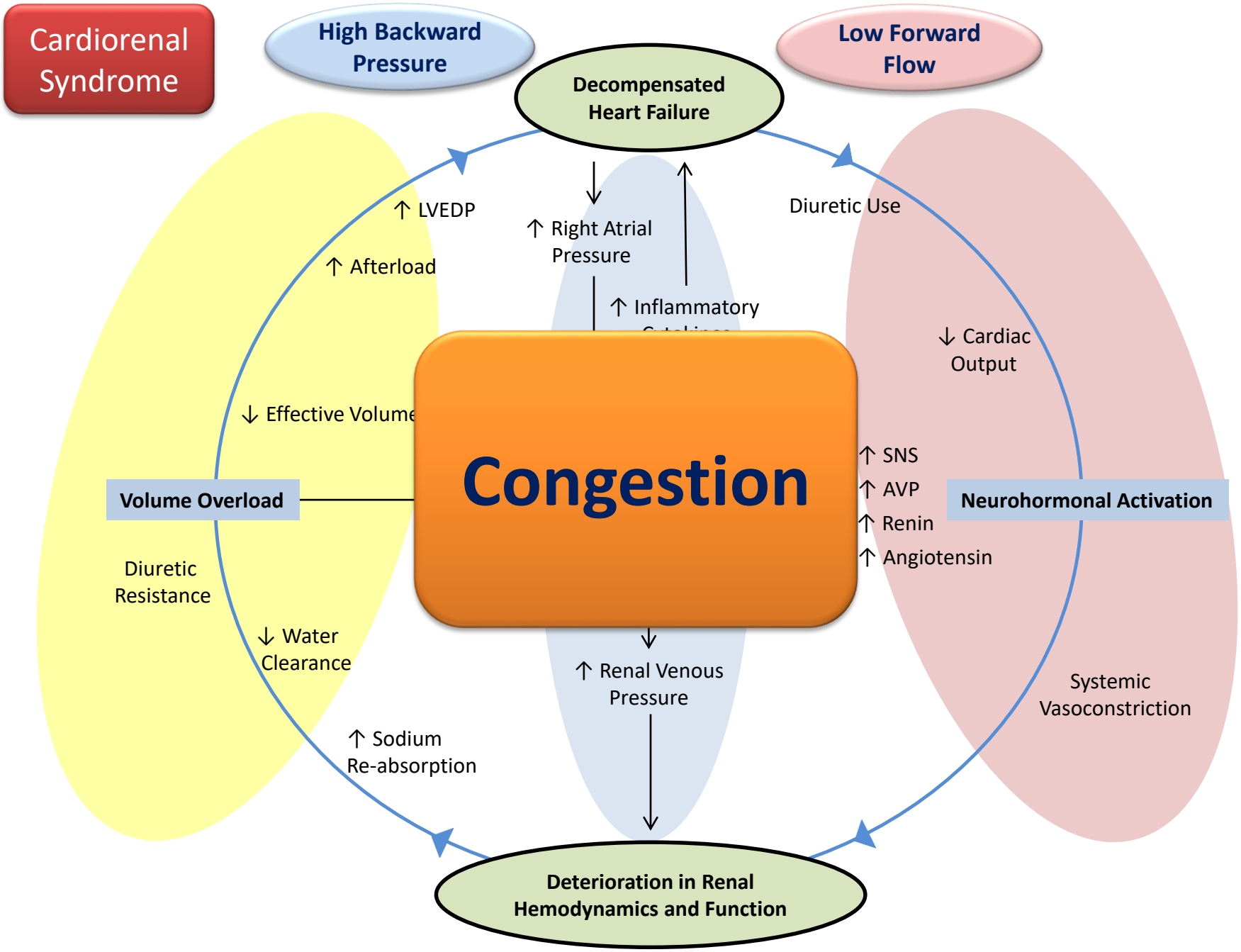
[Kazory A. Clin J Am Soc Nephrol 2013; 8: 1816-28]



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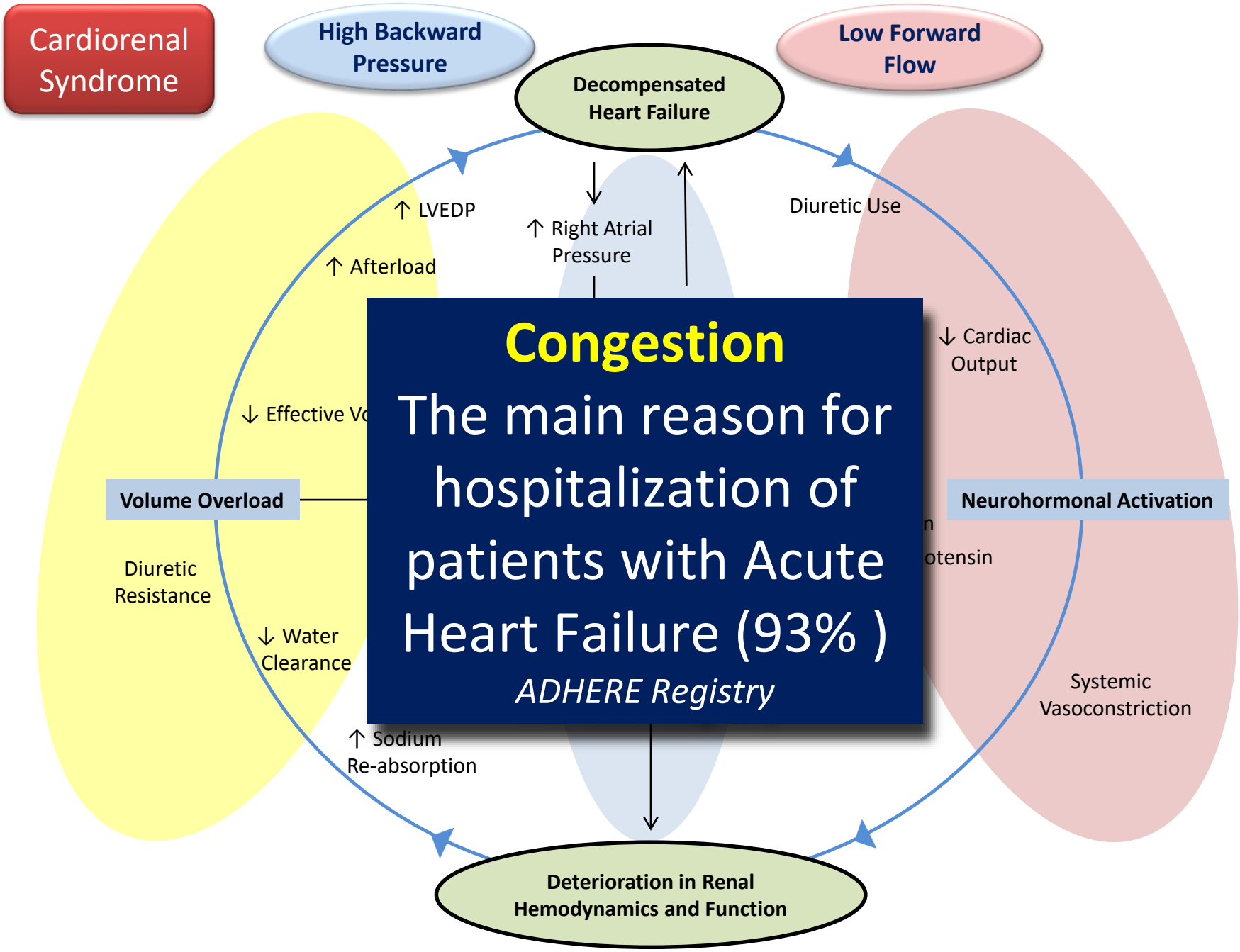

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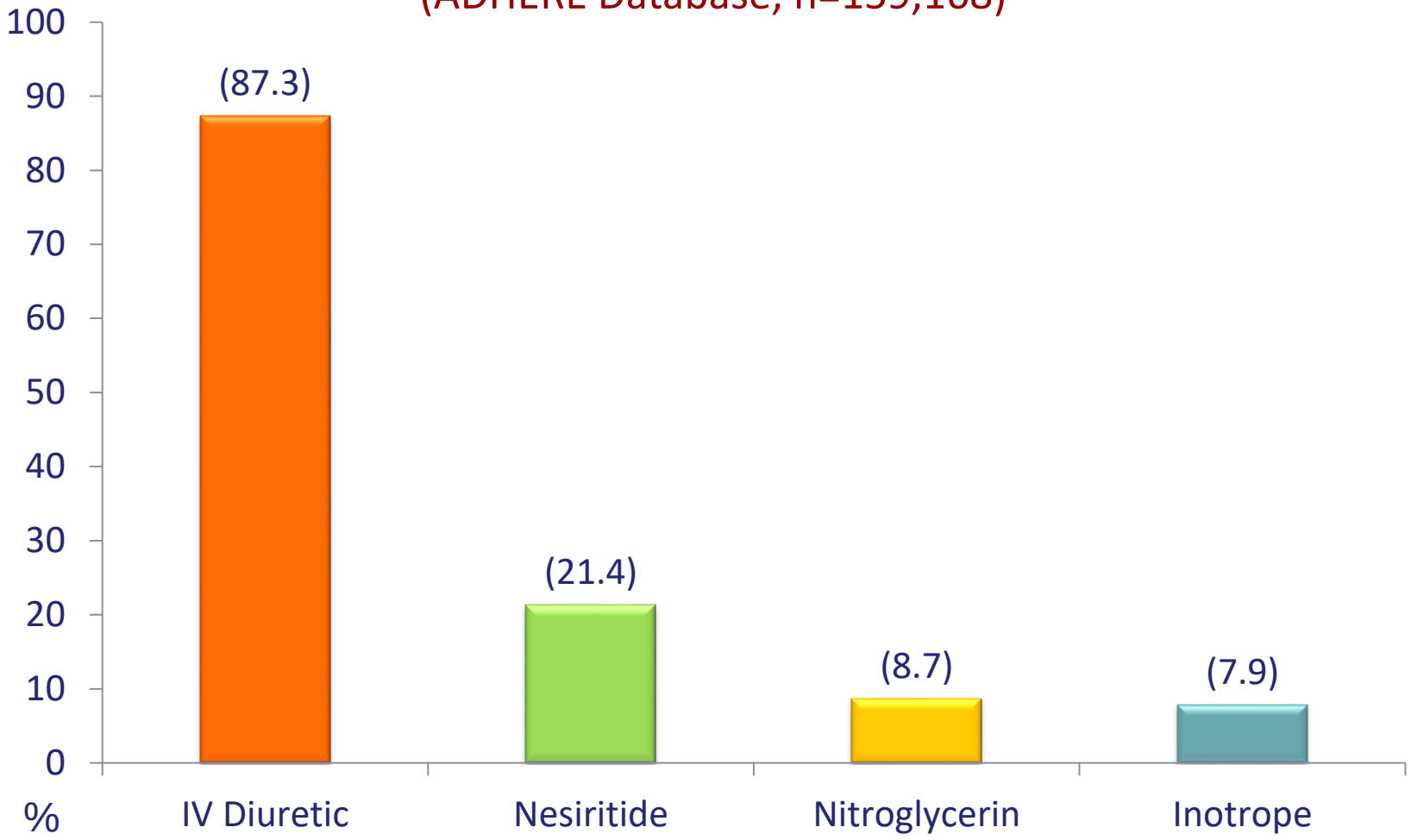
[Kazory A. Clin J Am Soc Nephrol 2013; 8: 1816-28]

How do we manage congestion in ADHF?

Contemporary Treatment of ADHF

(ADHERE Database, n=159,168)



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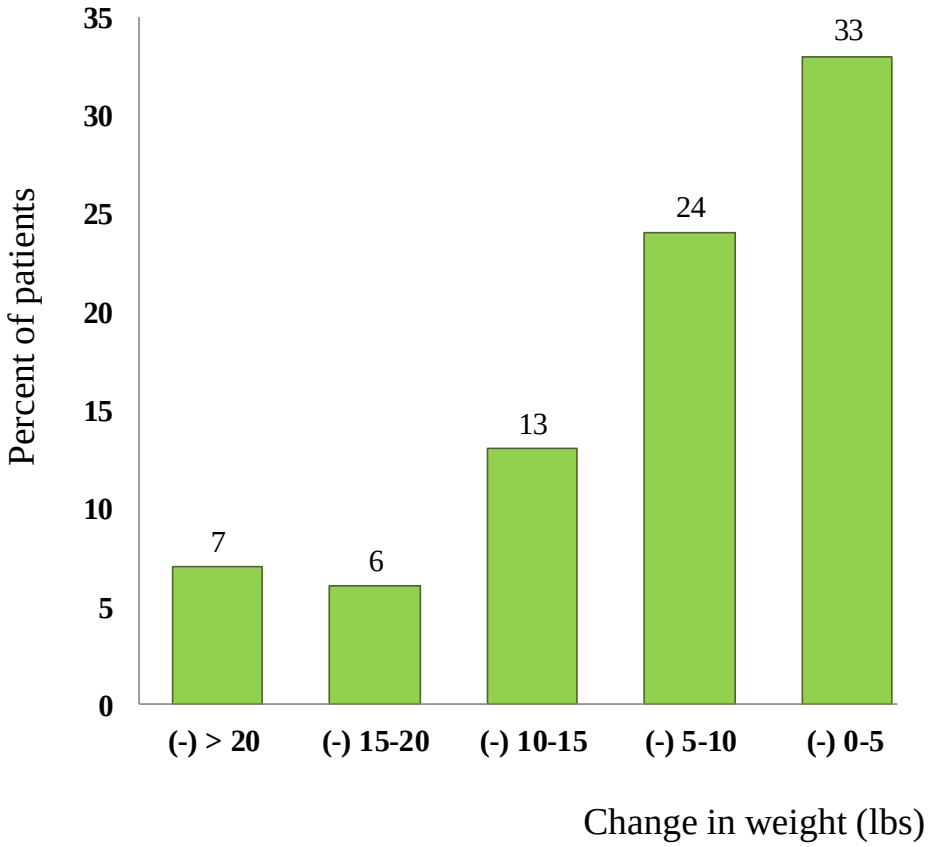
[Fonarow GC, et al. Am Heart J 2007; 153: 1021]-Adapted

How well are we managing congestion in ADHF now?

Change in Body Weight at Discharge

ADHERE Database (n= 51,013)



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[Gheorghiade M and Filippatos G. Eur Heart J 2005; 7: B13-B19]-Adapted

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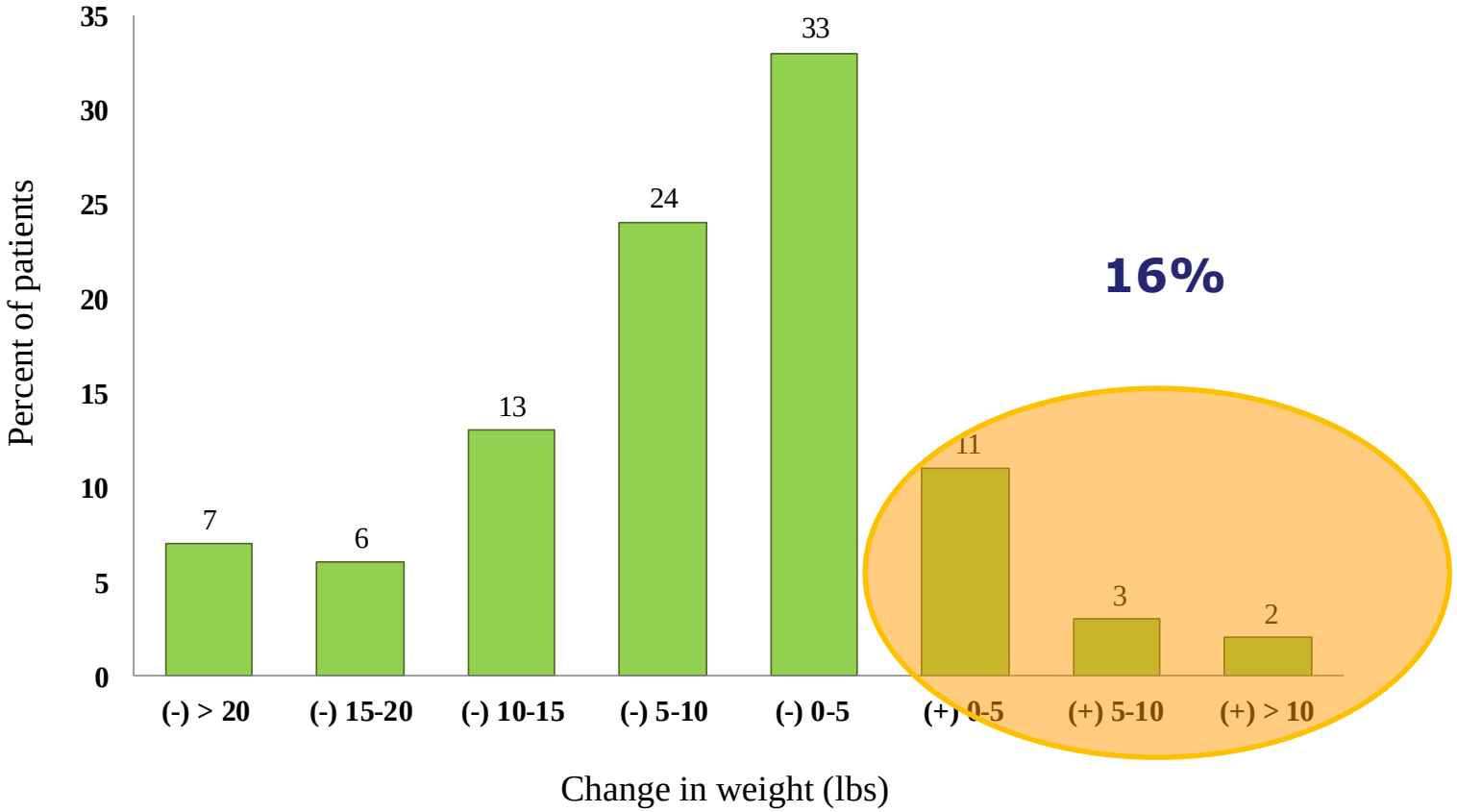

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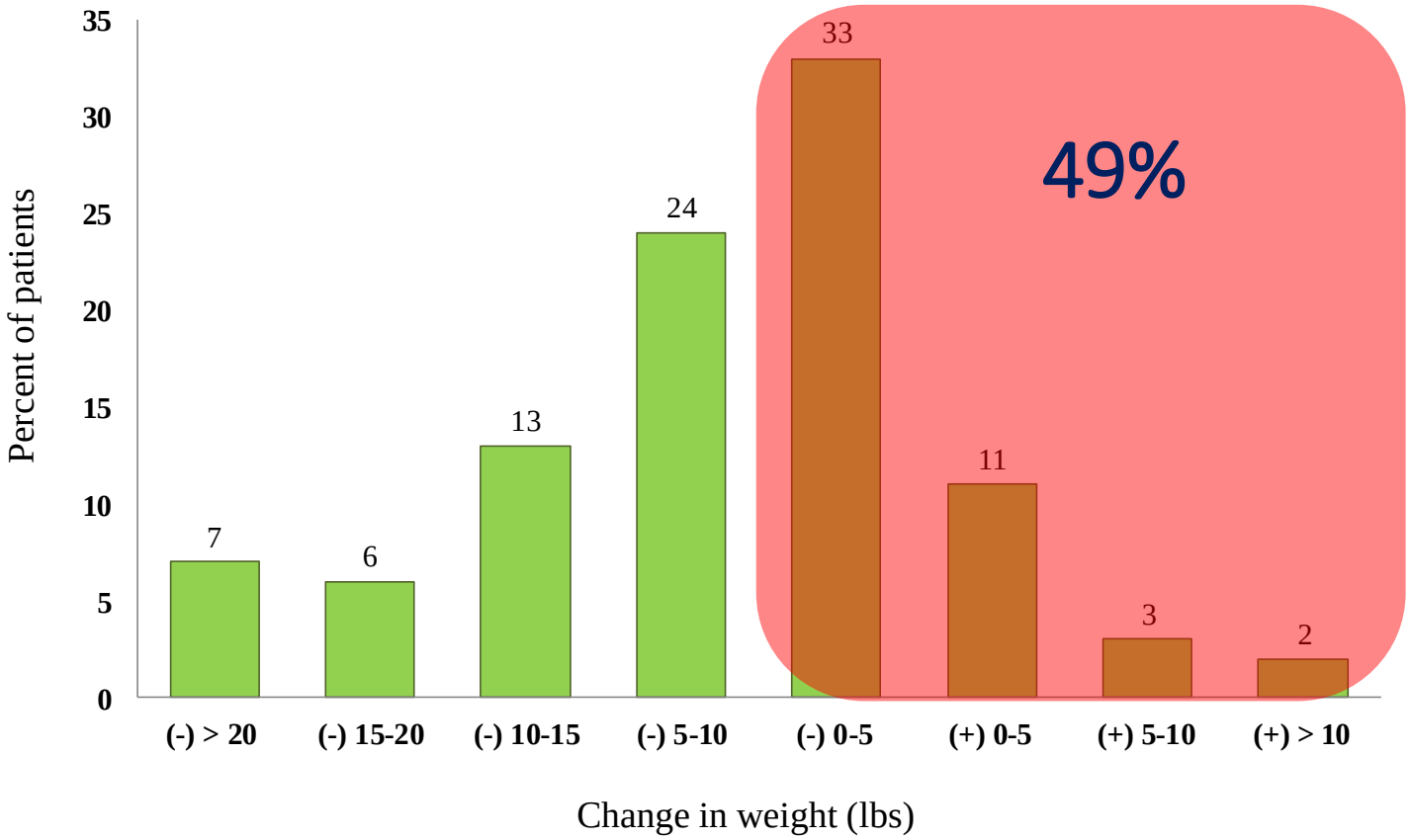

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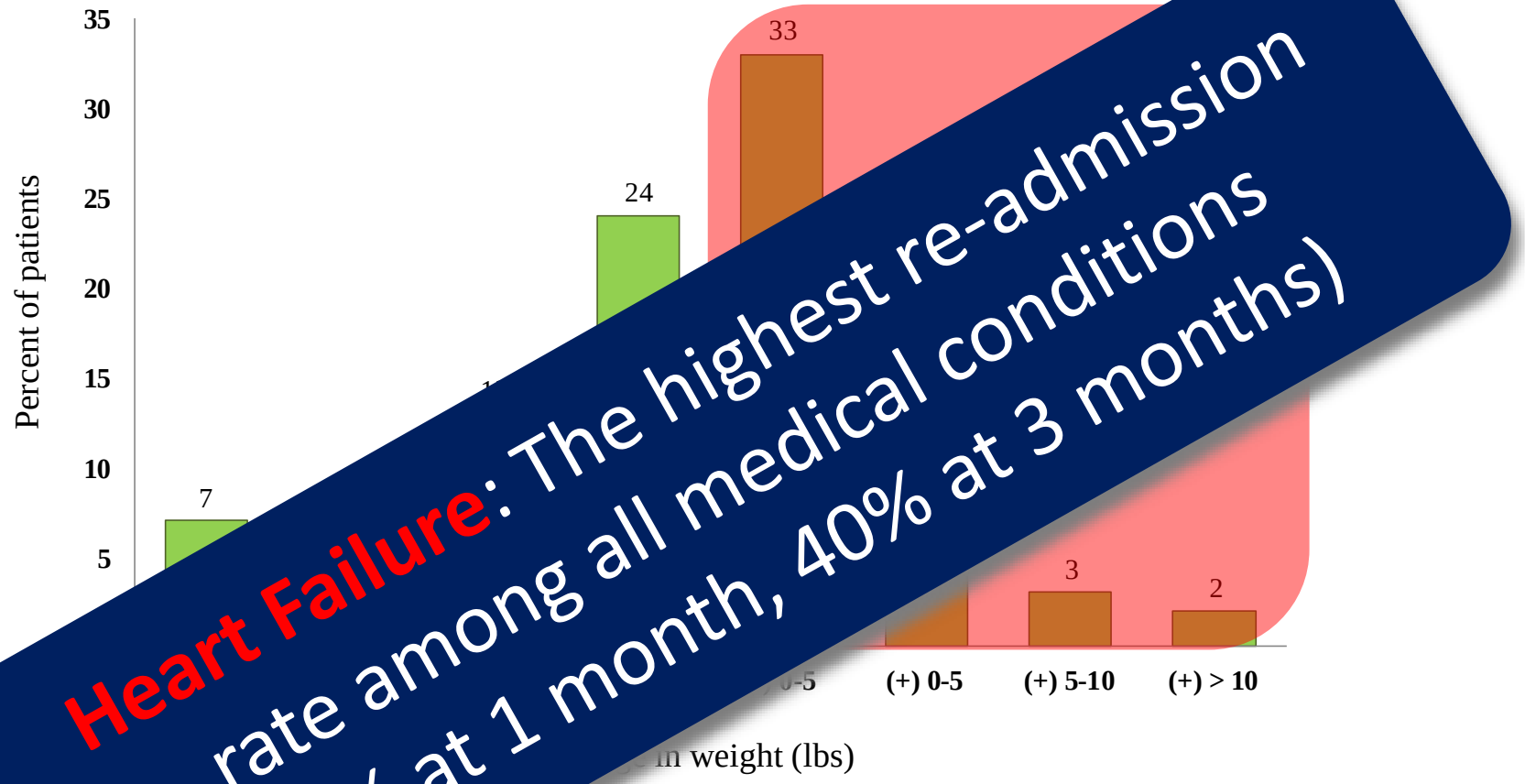

Heart Failure: The highest re-admission rate among all medical conditions (23% at 1 month, 40% at 3 months)

[Gheorghiade M and Filippatos G. Eur Heart J 2005; 7: B13-B19]-Adapted

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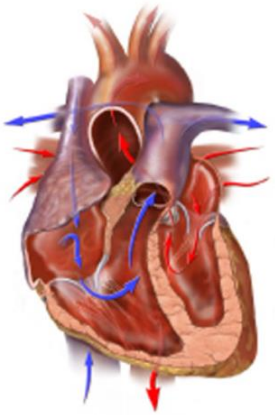
Identifying the Right CardioRenal Endpoints

Heart Failure



Identifying the Right CardioRenal Endpoints

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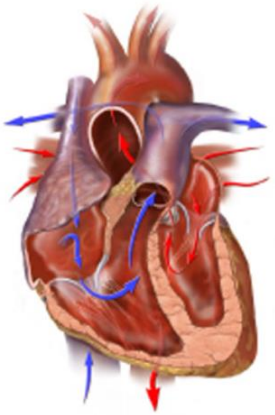

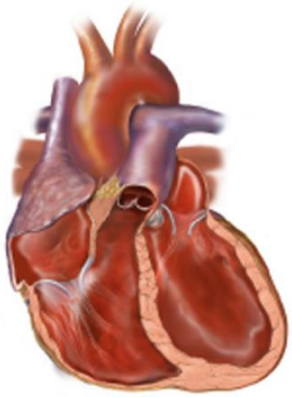

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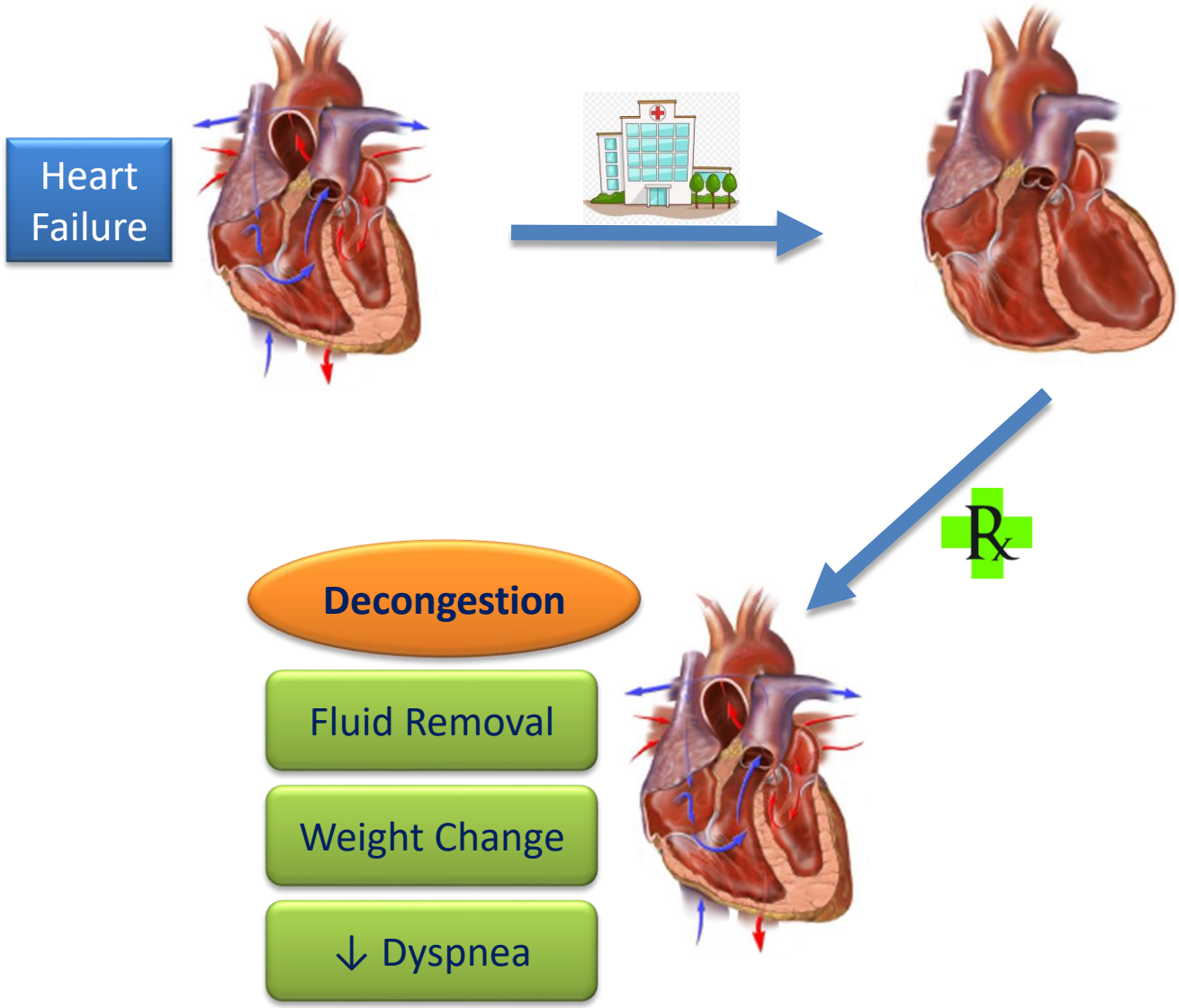

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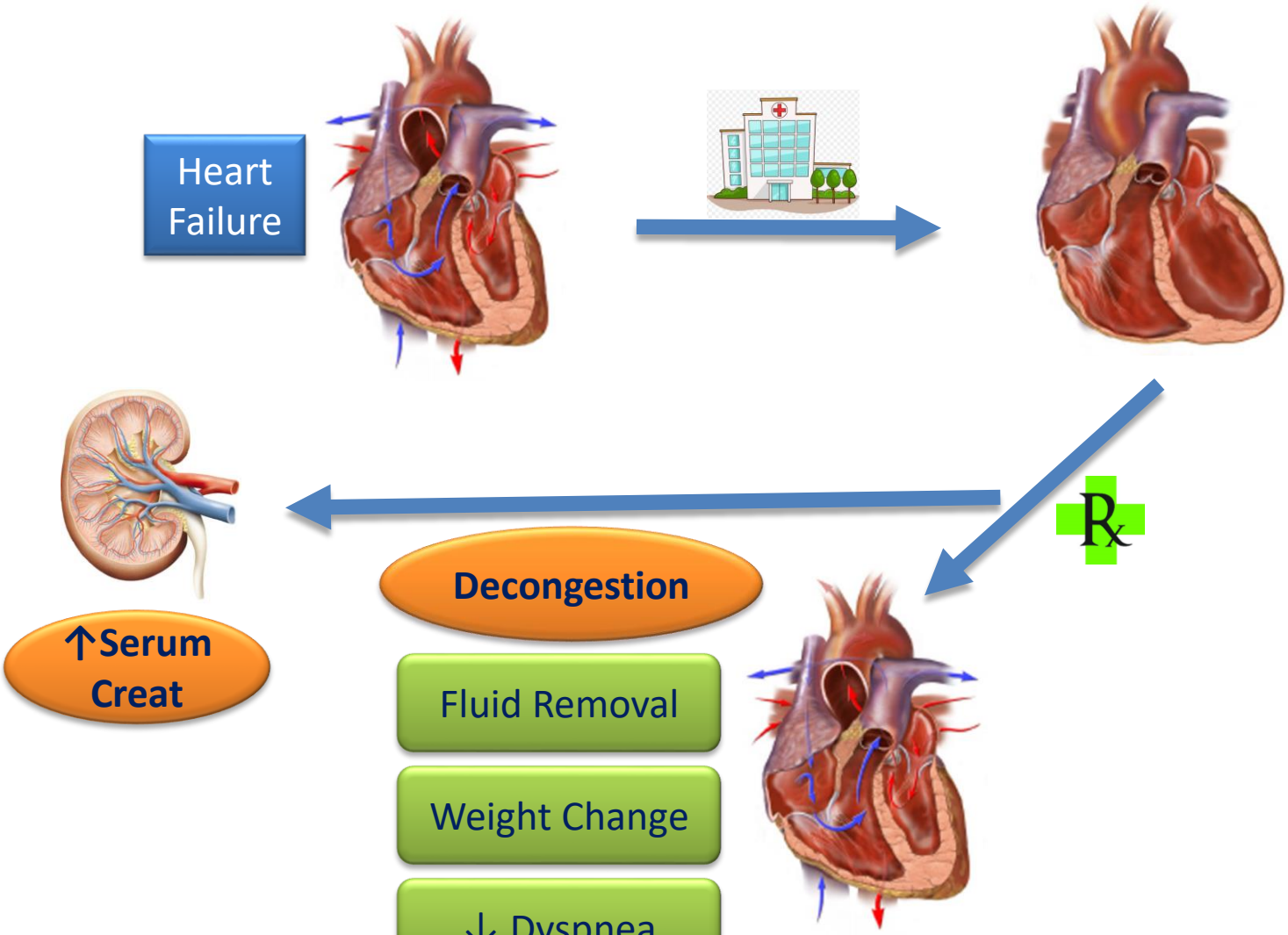

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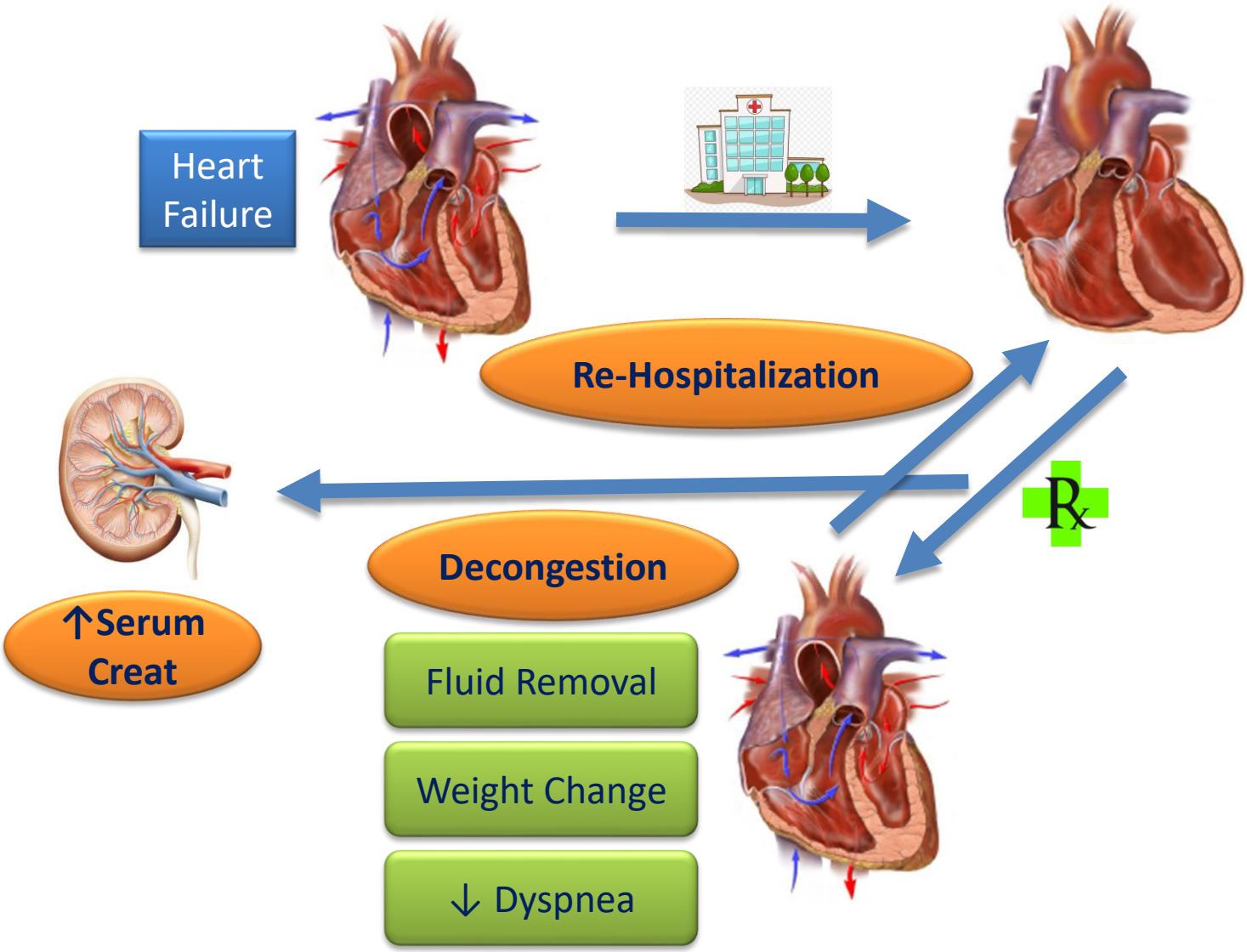

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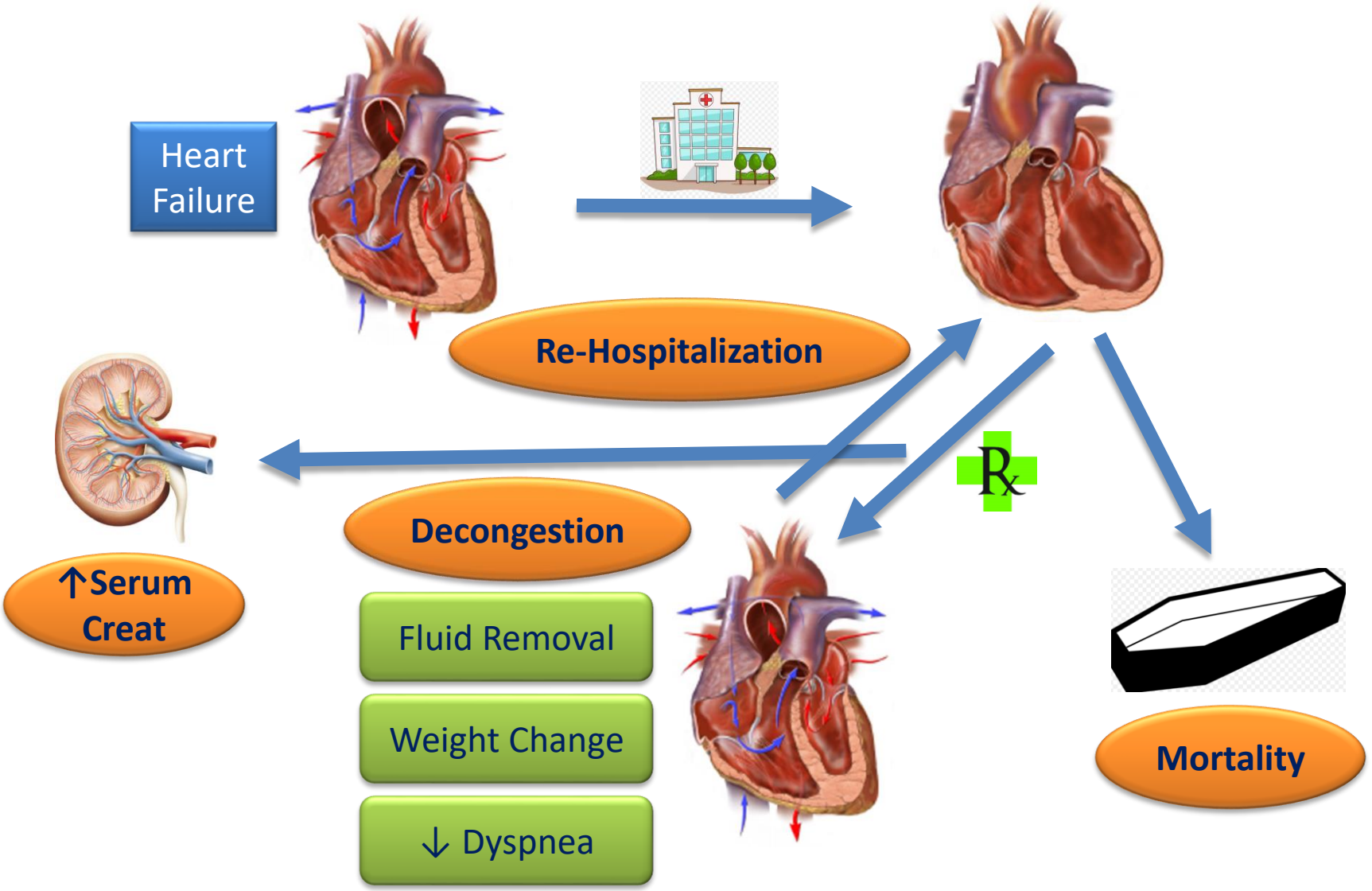

Identifying the Right CardioRenal Endpoints

- Efficacy
  - Fluid Removal
  - Change in Weight
  - Improvement of Dyspnea
- Safety
  - Renal Function
- Re-Hospitalization
  - Unscheduled clinic visit
  - ED visit
- Mortality
  - Heart Failure
  - All Cause-

- Jugular venous distention of < 8 cm
- Orthopnea
- Peripheral edema at hospital discharge

Changes in B-type natriuretic peptide

- Lung ultrasound, Bioimpedance Cardiography

- Serum creatinine (sCr)
- Blood urea nitrogen (BUN)
- BUN/sCr
- Glomerular filtration rate (eGFR)
- Renal biomarkers

- Length of stay during the index hospitalization
- Total number of days re-hospitalized for HF at 30 and 90 days
- IV therapy for HF , including diuretics and/or positive inotropic agents and/or vasodilators at 30 and 90 days after discharge
- Total number of HF re-hospitalizations at 30 and 90 days after discharge

-Total number of cardiovascular re-hospitalizations at 30 and 90 days after discharge

- Total number of days for CV re-hospitalizations at 30 and 90 days after discharge

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Why Use *"Increase in Serum Creatinine"* as a Surrogate Endpoint in HF Trials?

A surrogate endpoint (SE) is a laboratory measure or a physical sign that is intended to be used as a ***substitute for a clinically meaningful endpoint***.

1) Changes induced by a therapy on a SE are expected to reflect changes in a clinically meaningful endpoint.

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3) Ideally, the surrogate should exist within the therapeutic pathway between the treatment and meaningful benefit

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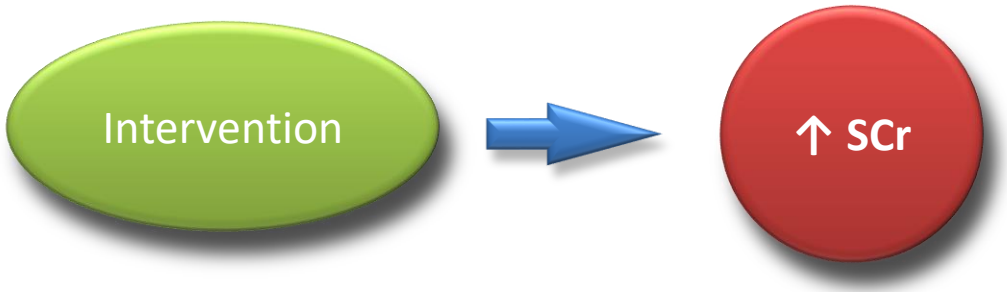

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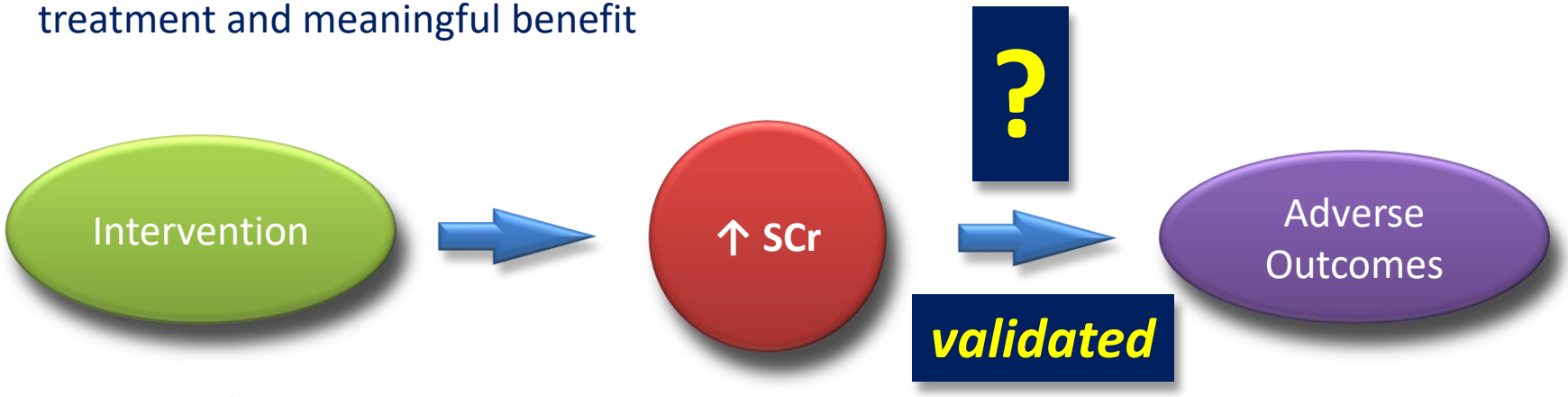

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WRF is associated with increased mortality in ADHF

1681 patients

Outcomes	Total	WRF Absent	WRF Present	Adjusted Estimate*
In-hospital mortality	68 (4%)	36 (3%)	32 (7%)	2.72 (1.62–4.58)
30-d mortality	123 (7%)	76 (6%)	47 (10%)	1.87 (1.25–2.80)
30-d readmission, all-cause	296 (18%)	201 (17%)	95 (20%)	1.29 (0.98–1.71)
30-d readmission, heart failure related	118 (7%)	80 (7%)	38 (8%)	1.17 (0.77–1.77)
6-month mortality	354 (21%)	235 (19%)	119 (25%)	1.56 (1.19–2.05)
6-month readmission, all-cause	790 (47%)	555 (46%)	235 (50%)	1.16 (0.93–1.44)
6-month readmission, heart failure related	380 (23%)	264 (22%)	116 (25%)	1.07 (0.82–1.39)
Length of hospital stay, mean (SD) (d)	7.55 (4.70)	6.93 (3.92)	9.14 (6.01)	2.28 (0.25)†
Hospital cost, mean (SD)	$6,823 ($5,175)	$6,327 ($4,874)	$8,085 ($5,665)	$1,758 ($287.2)†

Estimates were odds ratios and 95% confidence intervals for mortality and readmission outcomes, and regression coefficients and their standard errors for length of hospital stay and hospital cost outcomes; estimates adjusted for sex, age, diabetes, hypertension, rales, pulse, baseline creatinine, systolic blood pressure, and left ventricular ejection fraction.

† $p < 0.0001$.

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[Krumholz HM. Am J Cardiol 2000; 85: 1110-1113]

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[Krumholz HM. Am J Cardiol 2000; 85: 1110-1113]

Increase in S creat *("WRF")*: Impact on Survival

412 patients

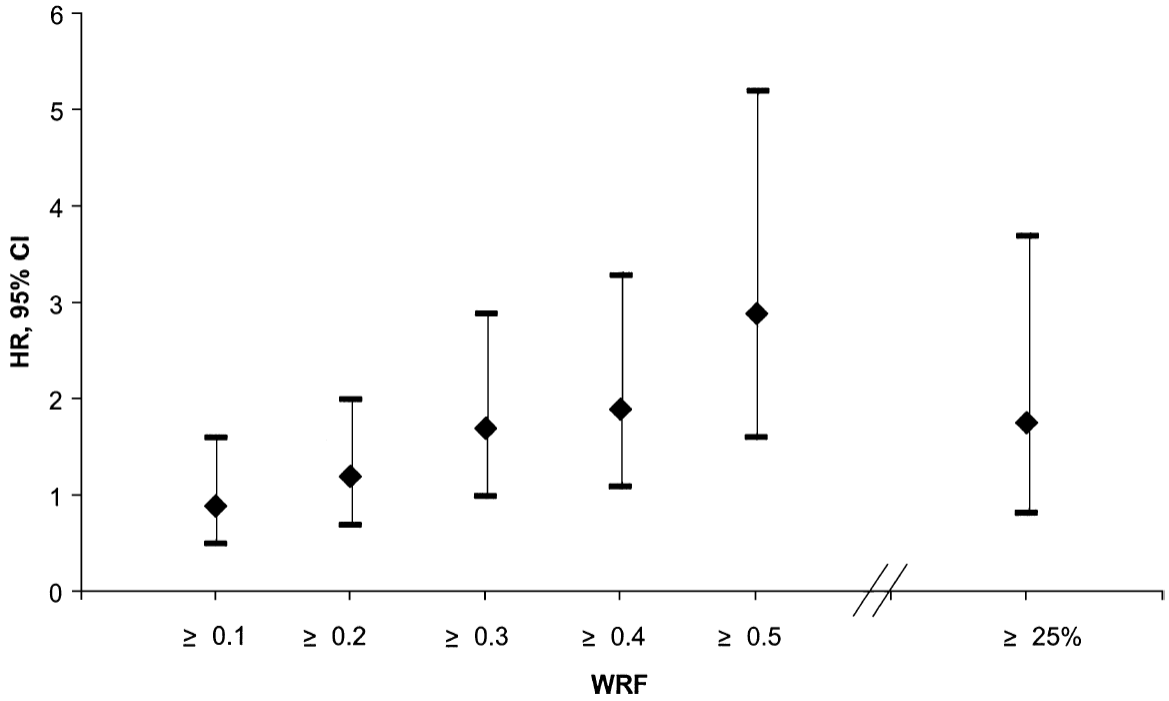

Fig. 3. Adjusted hazard ratio (HR) for mortality.

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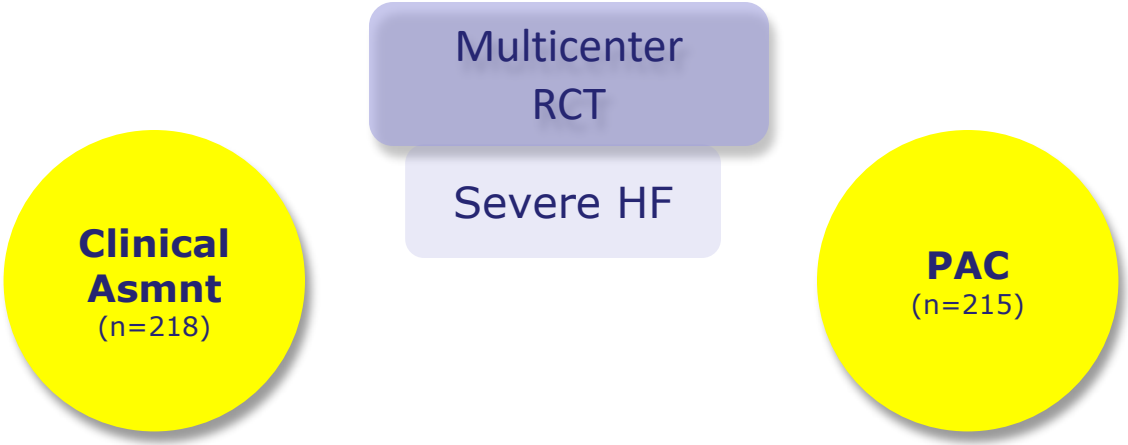
[Smith GL. J Card Fail 2003; 9: 13]

The ESCAPE Trial



The primary end point: days alive out of the hospital during 6 months following randomization, component end points included time to events.

Secondary End Points: physiologic secondary end points, focusing on mitral regurgitation, natriuretic peptides, and peak oxygen consumption, were selected as measurable without knowledge of group assignment. Other functional end points were 6-minute walk distance, the Minnesota Living with Heart Failure questionnaire, and the time trade-off tool.

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[Binanay C. JAMA 2005; 294: 1625]

The ESCAPE Trial

433 patients

Table 2 Relationship Between Renal Parameters and 6-Month Outcomes

	Time to Death			Time to Death or Rehospitalization		
	HR*	95% CI	p Value	HR*	95% CI	p Value
Baseline SCr	1.20	1.11–1.29	<0.0001	1.14	1.08–1.21	<0.0001
Baseline eGFR	1.25	1.13–1.38	<0.0001	1.10	1.05–1.15	<0.0001
Discharge SCr	1.30	1.20–1.41	<0.0001	1.14	1.08–1.21	<0.0001
Discharge eGFR	1.28	1.14–1.43	<0.0001	1.09	1.03–1.15	0.002
≥0.3 mg/dl ↑ SCr†	1.31	0.81–2.10	0.27	1.26	0.96–1.64	0.09
≥25% ↓ eGFR‡	1.49	0.91–2.44	0.12	1.06	0.79–1.43	0.69

*Hazard ratio (HR) calculated per 0.3-mg/dl increments in serum creatinine (SCr) and per 10-ml/min decrements in estimated glomerular filtration rate (eGFR). Worsening renal function, defined as: 1) †an increase in SCr ≥0.3 mg/dl; and 2) ‡a decrease in eGFR ≥25% from baseline to discharge, is treated as a dichotomous variable.
CI = confidence interval.

Baseline RF (and also discharge RF) can impact outcomes, but not WRF

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[Nohria A. J Am Coll Cardiol 2008; 51: 1268]

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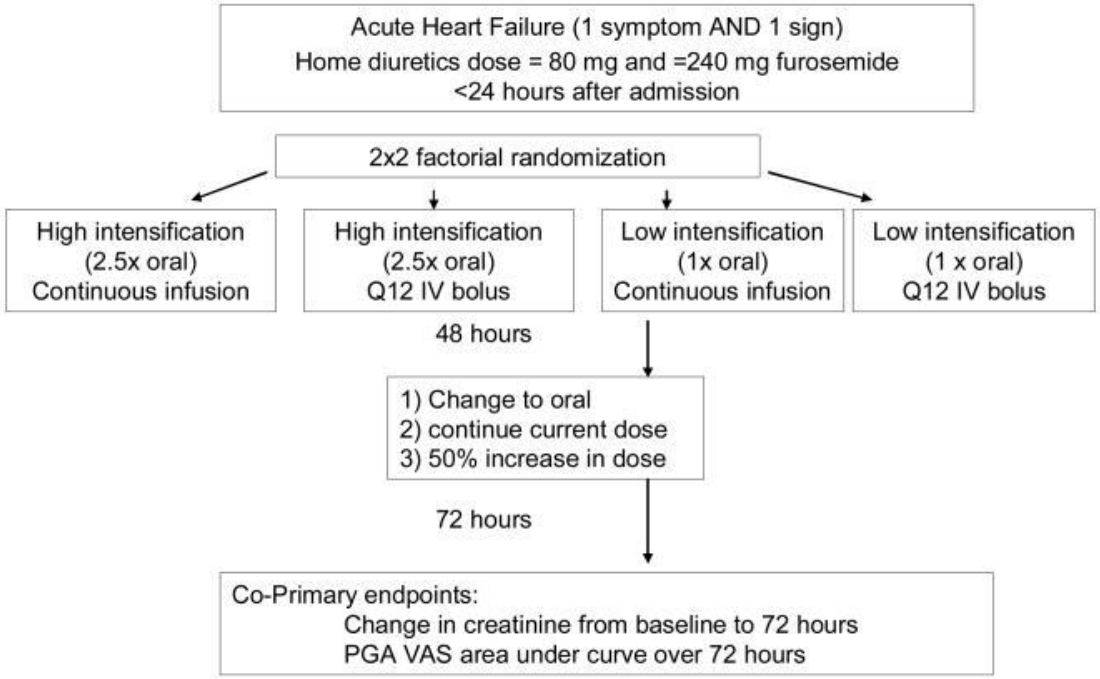
The Dose Trial



Diuretic Optimization Strategies Evaluation

* PGA = patient global assessment, VAS visual analog scale

[Felker GM. New Engl J Med 2011; 364: 797]

The Dose Trial

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

308 patients

HD group: better decongested, WRF more often, but no impact on outcome

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[Felker GM. New Engl J Med 2011; 364: 797]

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Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

308 patients

HD group: better decongested, WRF more often, but no impact on outcome

[Felker GM. New Engl J Med 2011; 364: 797]

The Dose Trial

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
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Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
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Interquartile range	42–55	38–55		39–54	42–56	

308 patients

HD group: better decongested, WRF more often, but no impact on outcome

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[Felker GM. New Engl J Med 2011; 364: 797]

The Dose Trial

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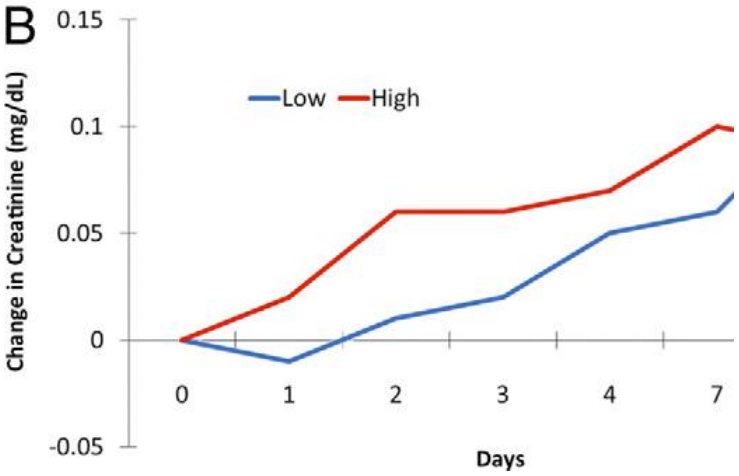
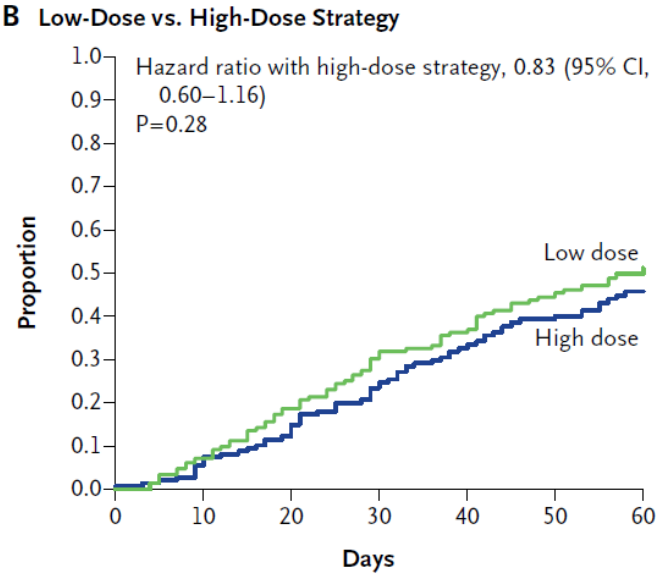
308 patients

HD group: better decongested, WRF more often, but no impact on outcome

[Felker GM. New Engl J Med 2011; 364: 797]

The Dose Trial





HD group: more WRF, but no impact on outcomes (death, re-hospit, ED visit)

[Felker GM. J Am Coll Cardiol 2012; 59: 2145]
[Felker GM. New Engl J Med 2011; 364: 797]

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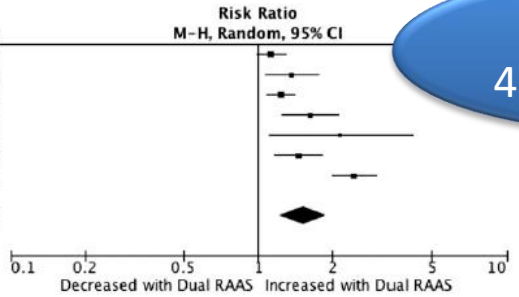
Short-term SCr as an EP in Clinical Trials

A **Event: AKI (Acute Increase in Serum Creatinine)**

Study or Subgroup	Dual RAAS Events	Dual RAAS Total	Single RAAS Events	Single RAAS Total	Weight	Risk Ratio M-H, Random, 95% CI
ALTITUDE	418	4250	371	4250	16.8%	1.13 [0.99, 1.29]
ASTRONAUT	134	808	98	810	14.7%	1.37 [1.08, 1.75]
EMPHASIS-HF	411	1364	335	1373	17.0%	1.23 [1.09, 1.40]
NEPHRON-D	130	724	80	724	14.3%	1.63 [1.25, 2.10]
ONTARGET	28	12500	13	12500	6.7%	2.15 [1.12, 4.16]
TOPCAT	175	1722	120	1723	15.1%	1.46 [1.17, 1.82]
Val-Heft	302	2511	123	2499	15.5%	2.44 [2.00, 2.99]
Total (95% CI)		**23879**		**23879**	**100.0%**	**1.52 [1.22, 1.89]**
Total events	1598		1140			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 46.50$, df = 6 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: Z = 3.80 (P = 0.0001)

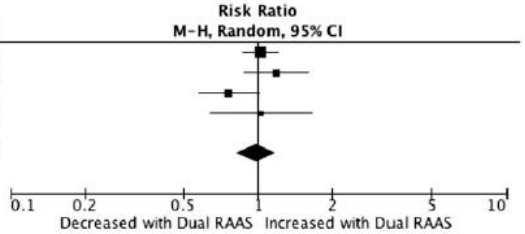


7 RCT's
48,436 patients

B **Event: CKD**

Study or Subgroup	Dual RAAS Events	Dual RAAS Total	Single RAAS Events	Single RAAS Total	Weight	Risk Ratio M-H, Random, 95% CI
ALTITUDE	257	4250	251	4250	40.7%	1.02 [0.86, 1.21]
ASTRONAUT	84	808	71	810	22.8%	1.19 [0.88, 1.60]
NEPHRON-D	77	724	101	724	25.1%	0.76 [0.58, 1.01]
ONTARGET	34	12500	33	12500	11.5%	1.03 [0.64, 1.66]
Total (95% CI)		**18282**		**18284**	**100.0%**	**0.98 [0.82, 1.18]**
Total events	452		456			

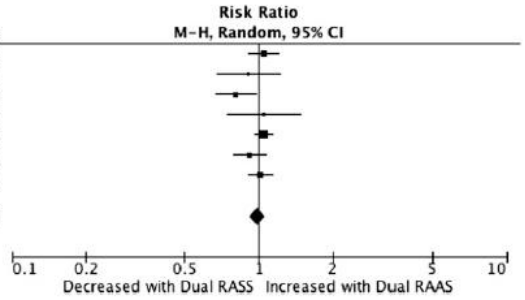
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.96$, df = 3 ($P = 0.17$); $I^2 = 40\%$
Test for overall effect: Z = 0.18 (P = 0.86)



C **Event: Mortality**

Study or Subgroup	Dual RAAS Events	Dual RAAS Total	Single RAAS Events	Single RAAS Total	Weight	Risk Ratio M-H, Random, 95% CI
ALTITUDE	376	4250	358	4250	16.4%	1.05 [0.91, 1.21]
ASTRONAUT	77	808	85	810	4.9%	0.91 [0.68, 1.22]
EMPHASIS-HF	171	1364	213	1373	10.5%	0.81 [0.67, 0.97]
NEPHRON-D	63	724	60	724	3.7%	1.05 [0.75, 1.47]
ONTARGET	1065	12550	1014	12550	29.3%	1.05 [0.97, 1.14]
TOPCAT	252	1722	274	1723	13.7%	0.92 [0.79, 1.08]
Val-Heft	495	2511	484	2499	21.4%	1.02 [0.91, 1.14]
Total (95% CI)		**23929**		**23929**	**100.0%**	**0.99 [0.92, 1.06]**
Total events	2499		2488			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.50$, df = 6 ($P = 0.20$); $I^2 = 29\%$
Test for overall effect: Z = 0.30 (P = 0.76)



Interventions that **increased** the risk of AKI (dual or add-on RAAS blockade)

[Coca SG, et al. J Am Soc Nephrol 2016; 27: 2529]

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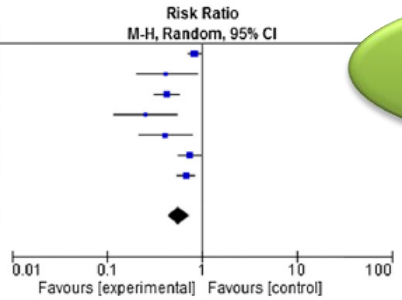
Short-term SCr as an EP in Clinical Trials

A **Event: AKI (Acute Increase in Serum Creatinine)**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
CORONARY	257	1472	304	1460	20.9%	0.84 [0.72, 0.97]
Miner	9	95	19	85	7.9%	0.42 [0.20, 0.89]
NU-HIT CKD	36	141	85	144	16.9%	0.43 [0.32, 0.59]
NU-HIT LVD	7	68	26	65	7.6%	0.26 [0.12, 0.55]
POSEIDON	12	178	28	172	9.4%	0.41 [0.22, 0.79]
SEPSISPAM	53	167	73	173	17.7%	0.75 [0.57, 1.00]
Yunos	122	773	176	760	19.6%	0.68 [0.55, 0.84]
Total (95% CI)		**2894**		**2859**	**100.0%**	**0.57 [0.44, 0.74]**
Total events	496		711			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 25.97$, $df = 6$ ($P = 0.0002$); $I^2 = 77\%$
Test for overall effect: $Z = 4.24$ ($P < 0.0001$)

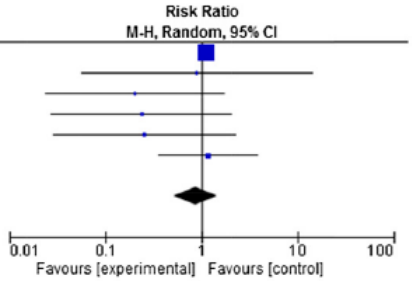


7 RCT's
5,817 patients

B **Event: CKD**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
CORONARY	252	1472	224	1460	65.6%	1.12 [0.95, 1.32]
Miner	1	95	1	85	3.4%	0.89 [0.06, 14.08]
NU-HIT CKD	1	141	5	144	5.4%	0.20 [0.02, 1.73]
NU-HIT LVD	1	68	4	65	5.3%	0.24 [0.03, 2.08]
POSEIDON	1	196	4	200	5.2%	0.26 [0.03, 2.26]
Yunos	6	773	5	760	15.1%	1.18 [0.36, 3.85]
Total (95% CI)		**2745**		**2714**	**100.0%**	**0.87 [0.52, 1.46]**
Total events	262		243			

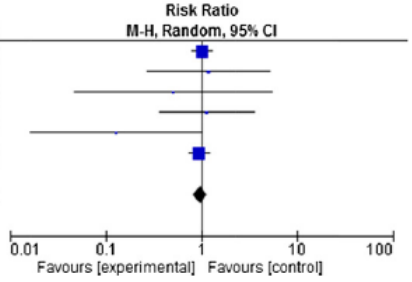
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 6.11$, $df = 5$ ($P = 0.30$); $I^2 = 18\%$
Test for overall effect: $Z = 0.53$ ($P = 0.60$)



C **Event: Mortality**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
CORONARY	122	2375	119	2377	48.4%	1.03 [0.80, 1.31]
Miner	4	95	3	85	1.4%	1.19 [0.27, 5.18]
NU-HIT CKD	1	141	2	144	0.5%	0.51 [0.05, 5.57]
NU-HIT LVD	6	68	5	65	2.3%	1.15 [0.37, 3.58]
POSEIDON	1	196	8	200	0.7%	0.13 [0.02, 1.01]
SEPSISPAM	67	161	74	168	46.8%	0.94 [0.74, 1.21]
Total (95% CI)		**3036**		**3039**	**100.0%**	**0.97 [0.82, 1.16]**
Total events	201		211			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.38$, $df = 5$ ($P = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 0.30$ ($P = 0.76$)



Interventions that **decreased** the risk of AKI

[Coca SG, et al. J Am Soc Nephrol 2016; 27: 2529]

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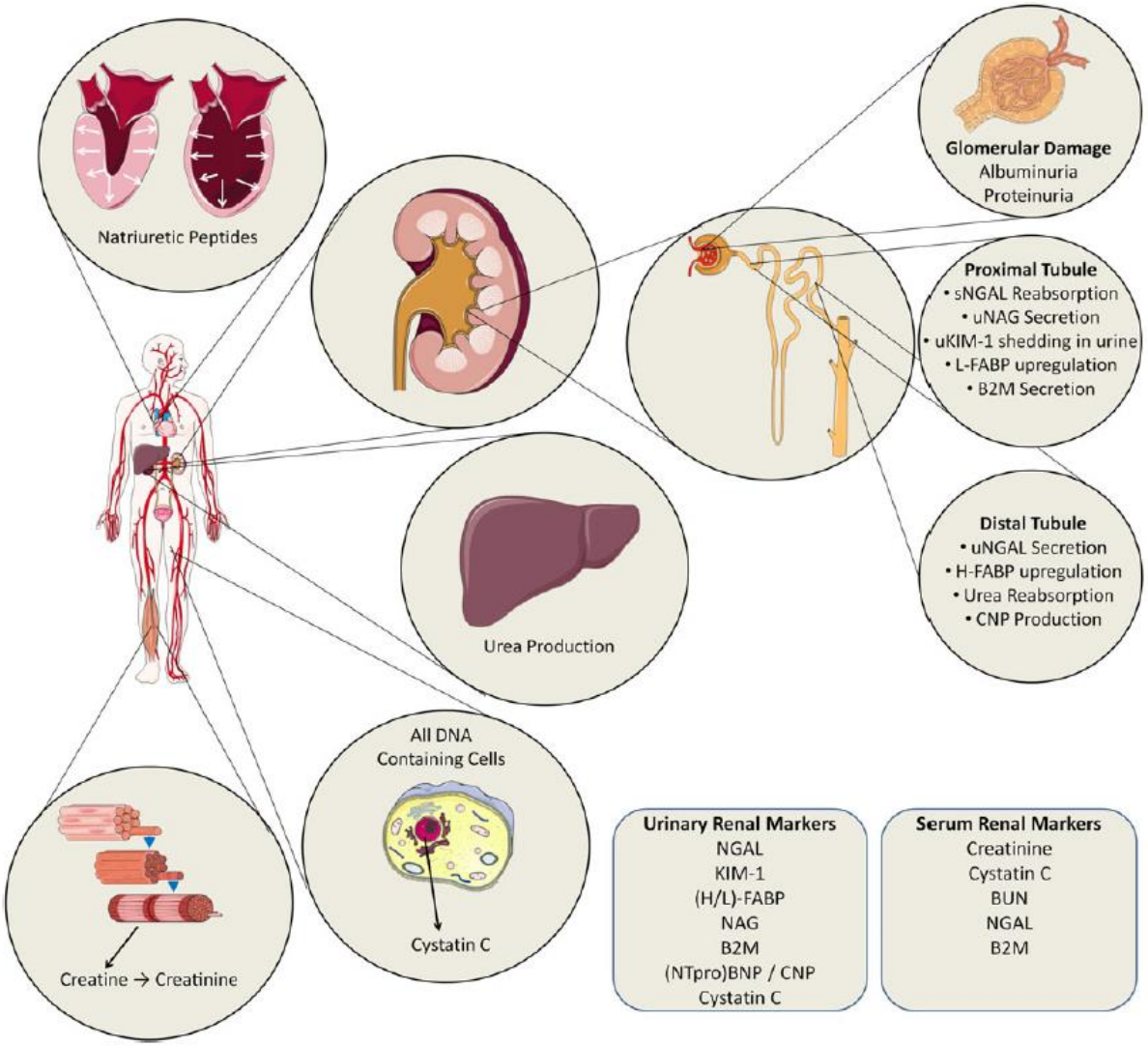
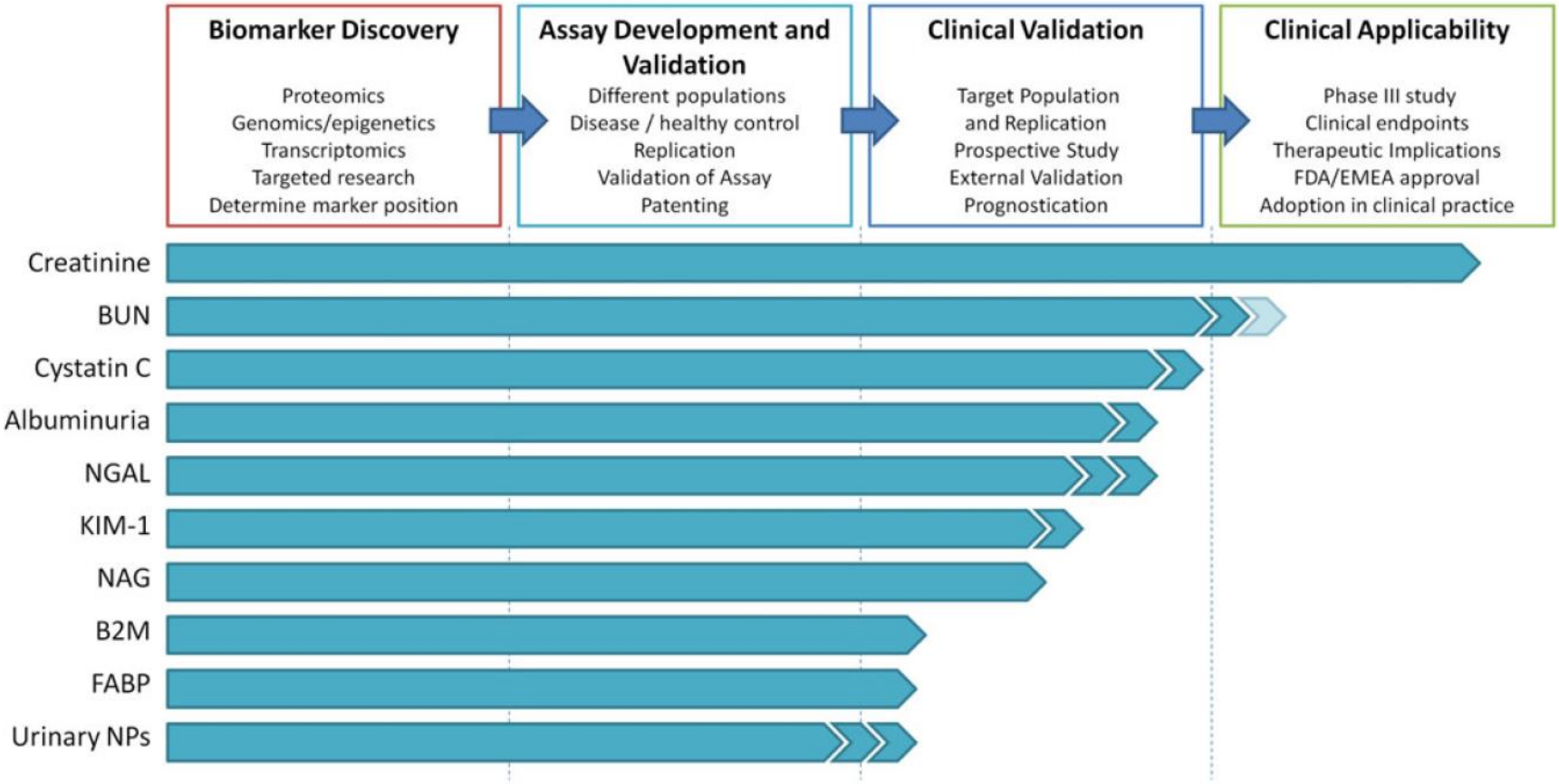
Biomarkers of Renal Injury and Function in HF



[van Veldhuisen DJ, et al. Eur Heart J 2016; 37:2577]

Biomarkers of Renal Injury and Function in HF



B2M, b-2-microglobulin; BUN, blood urea nitrogen; FABP, fatty acid-binding protein (types L and H); KIM-1, kidney injury molecule 1; NAG, N-acetyl-b-d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NP, natriuretic peptide

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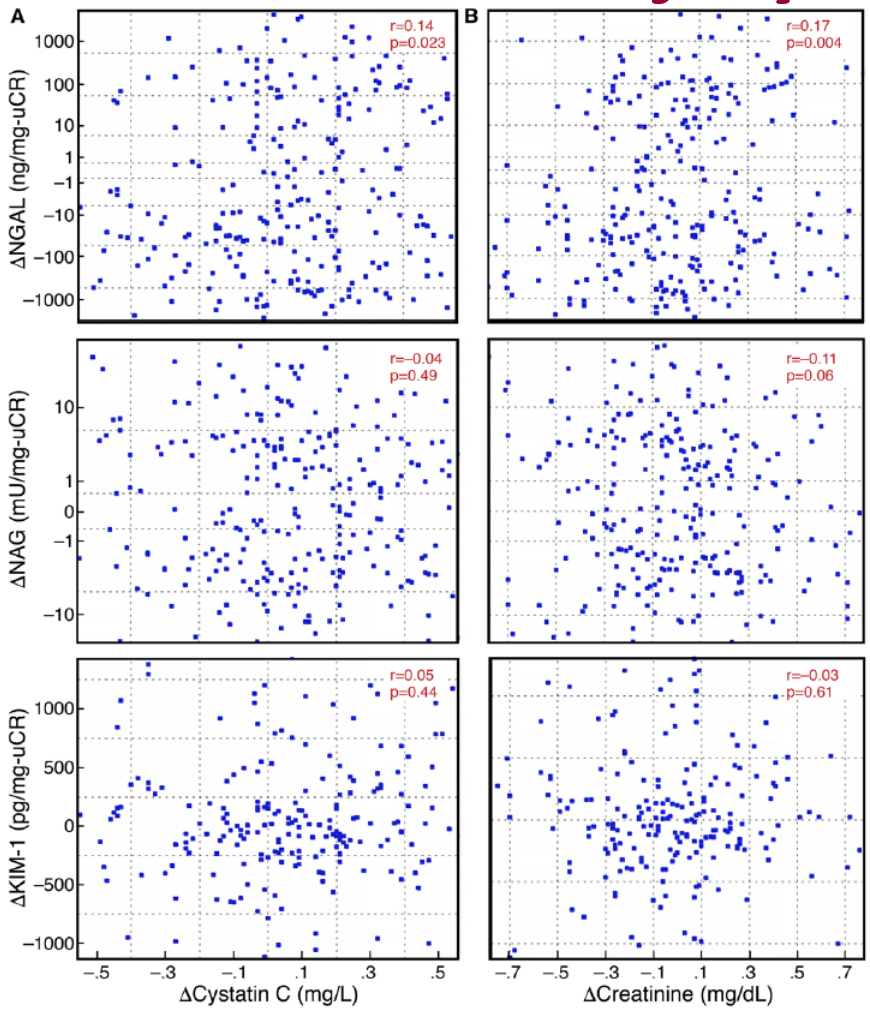
[van Veldhuisen DJ, et al. Eur Heart J 2016; 37:2577]

WRF in ADHF Undergoing Aggressive Diuresis; Not Tubular Injury



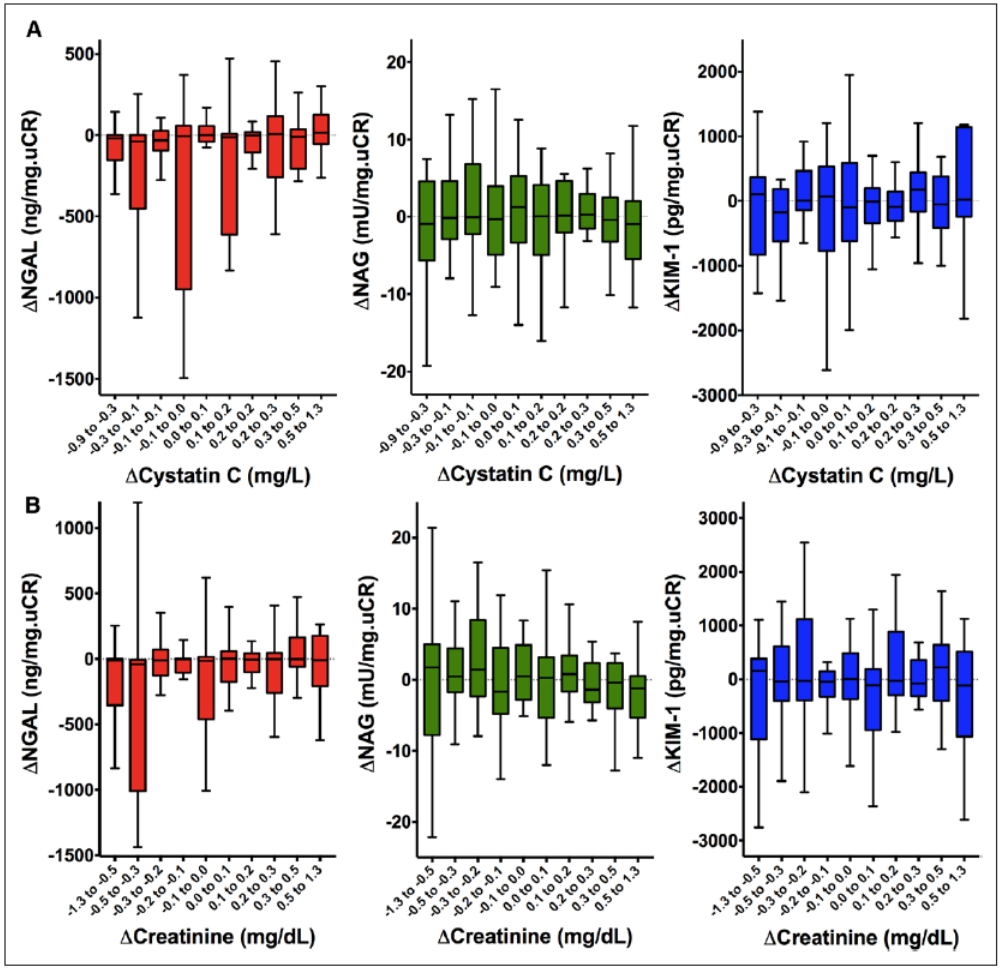
283 patients in ROSE-AHF

NAG and Kim-1 were not correlated with changes in cystatin C or SCr

idney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-d-glucosaminidase (NAG).

[Ahmad T, et al. Circulation 2018;137:2016]

WRF in ADHF Undergoing Aggressive Diuresis; Not Tubular Injury



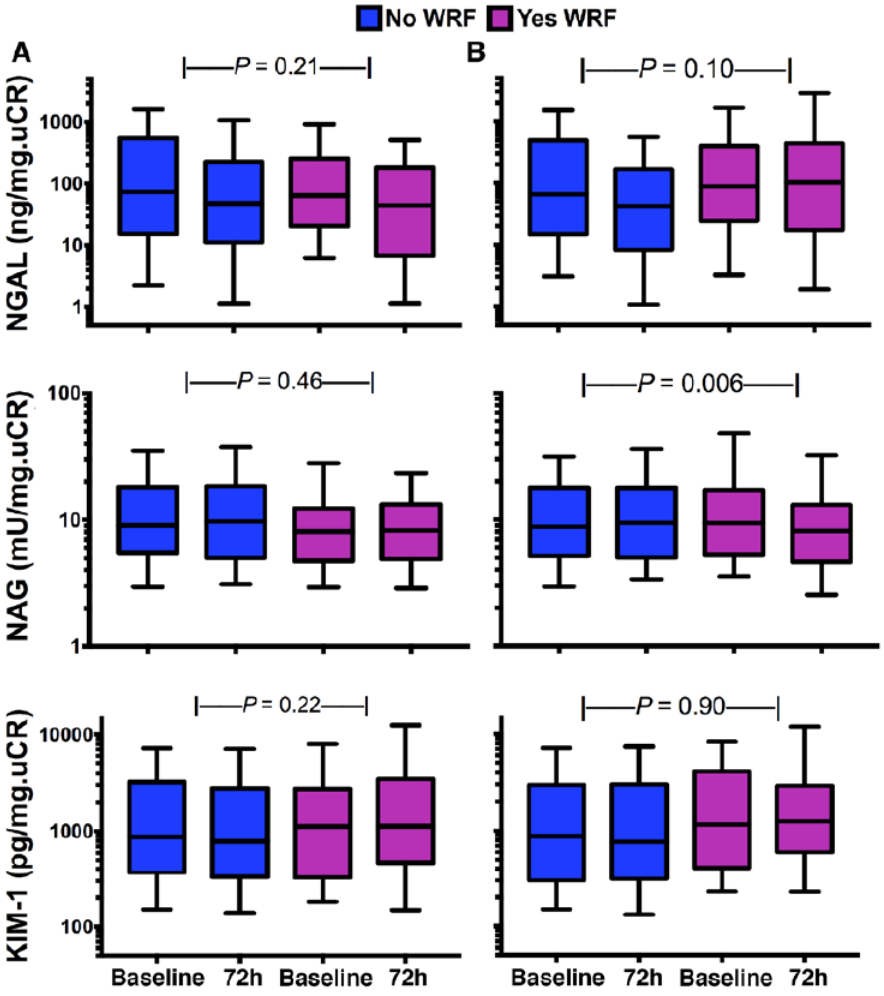
283 patients in ROSE-AHF

No clear threshold or non-linear relationship between changes in Cystatin C and SCr with biomarkers of tubular injury

[Ahmad T, et al. Circulation 2018;137:2016]

KIM-1 = Kidney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-d-glucosaminidase, NAG

WRF in ADHF Undergoing Aggressive Diuresis; Not Tubular Injury



283 patients in ROSE-AHF

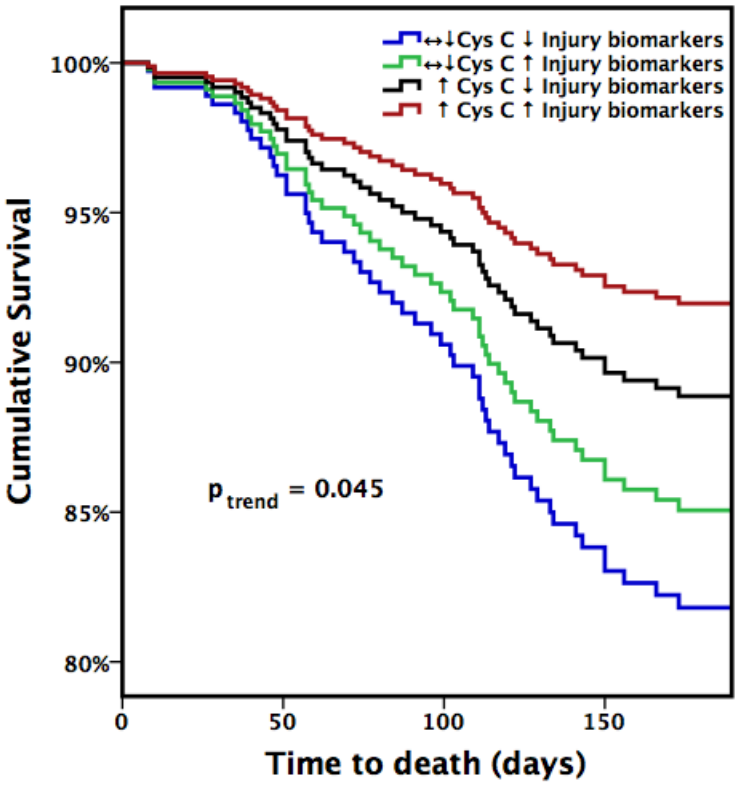
No difference in level of biomarkers between those with or without WRF

("reduction" in NAG among those with creatinine-based WRF)

[Ahmad T, et al. Circulation 2018;137:2016]

idney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-d-glucosaminidase (NAG).

WRF in ADHF Undergoing Aggressive Diuresis; Impact on Survival



283 patients in ROSE-AHF

Decline in kidney function and increase in tubular injury markers; the best outcomes
No change or improvement in kidney function/tubular injury biomarkers; the worst outcomes.

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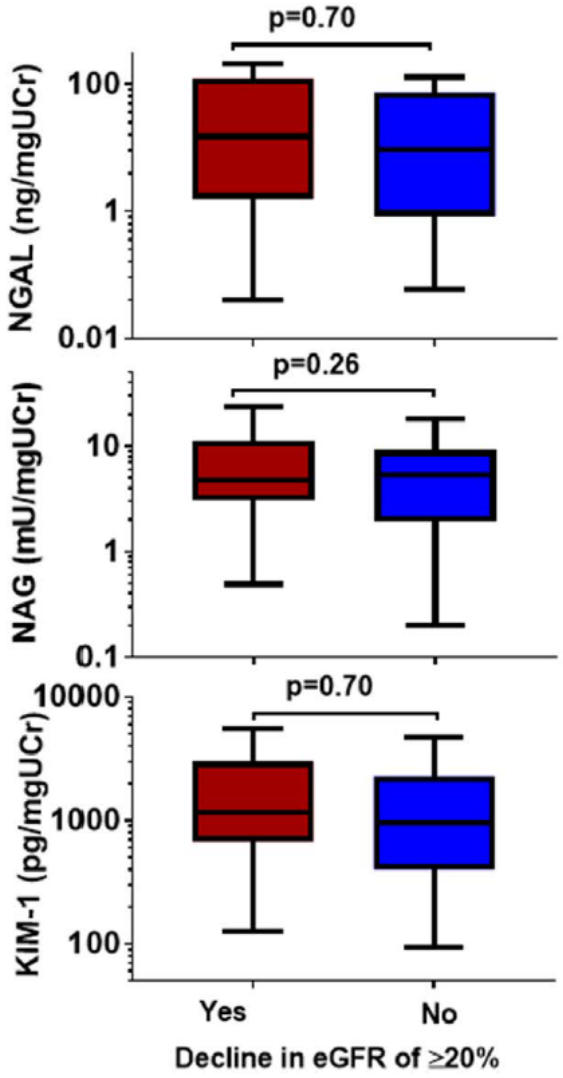
Kidney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-d-glucosaminidase (NAG).

[Ahmad T, et al. Circulation 2018;137:2016]

WRF in ADHF Undergoing Aggressive Diuresis; Creatinine vs. Biomarkers

105 patients in CARRESS-HF

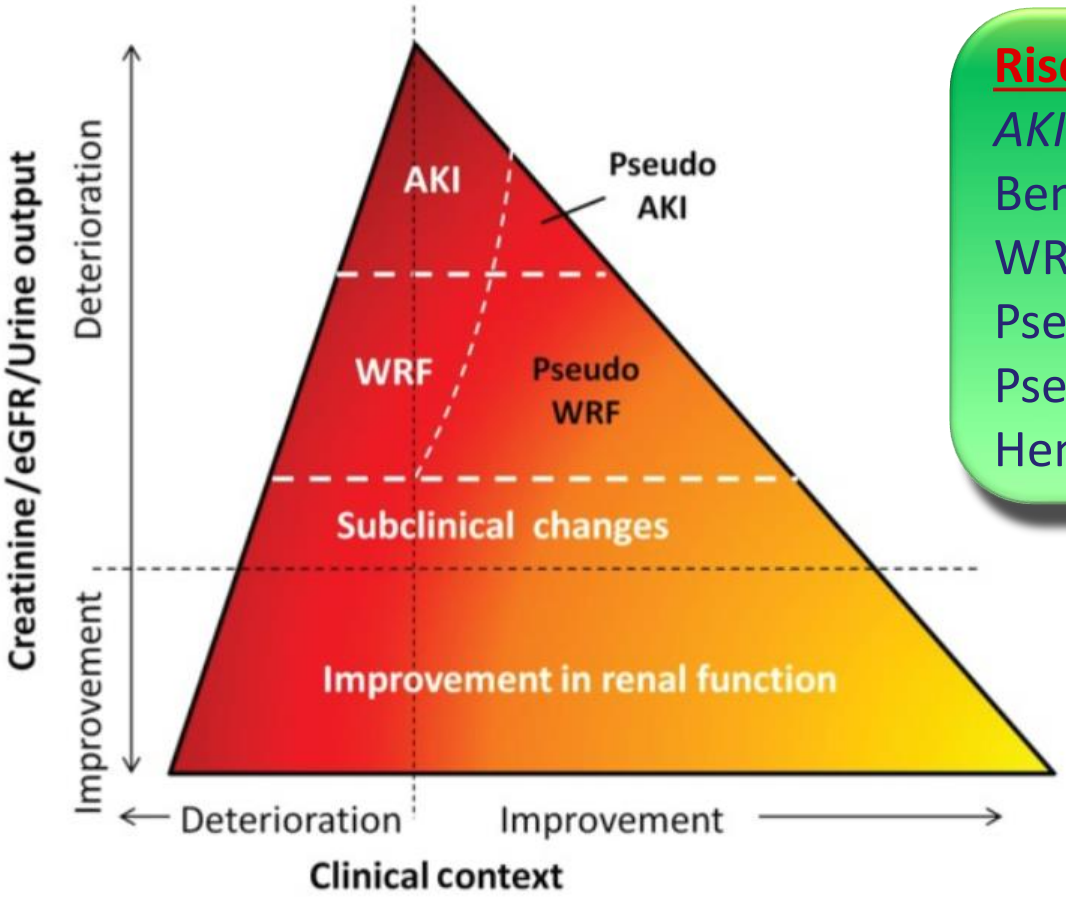


Lack of association between levels of the biomarkers between those with and without WRF (≥20% reduction in eGFR).

Kidney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-d-glucosaminidase (NAG).

[Rao VS, et al. Circulation Heart Fail 2019;12:In Press]

Good Endpoint for Renal Function in AHF: SCr-WRF-AKI?



Rise in SCr

AKI (tubular Injury)

Benign AKI

WRF

PseudoAKI

PseudoWRF

Hemodynamic AKI

Darker colors indicate higher mortality risk. Suggested cut-off values for WRF (chronic HF): ≥26.5 mmol/L and ≥25% increase in creatinine OR ≥ 20% decrease in eGFR over 1–26 weeks, and AKI (acute HF): increase of 1.5–1.9 times baseline creatinine within 1–7 days before or during hospitalization OR ≥ 26.5 mmol/L increase in creatinine within 48 h OR urine output , 0.5 mL/kg/h for 6–12 h

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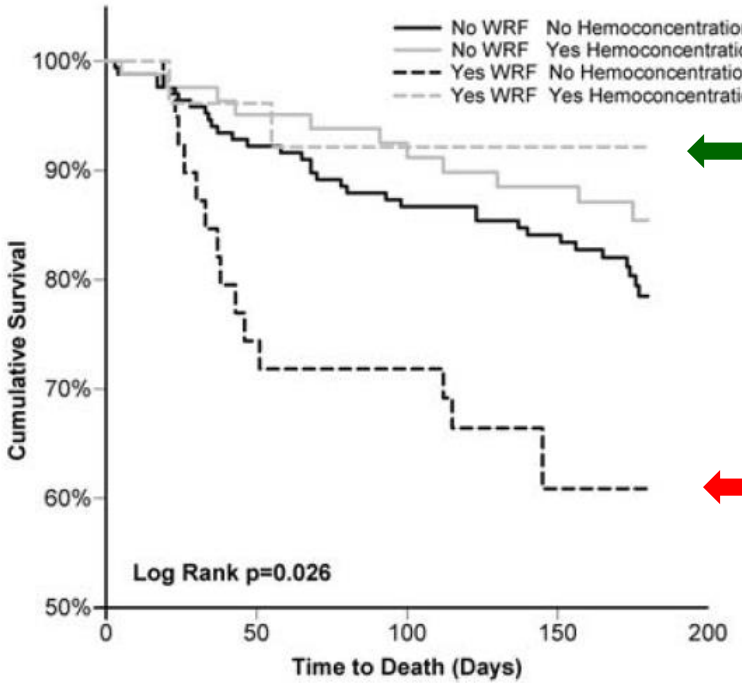
[Damman K, et al. Eur Heart J 2015;36:1437]

Maybe there is “something else” more important than Rise in Serum Creatinine that is driving the outcomes in AHF.

A Confounding Factor?

Congestion Modulates the Impact of ↑Scr in ADHF

386 patients



WRF +/ CONG –

WRF +/CONG +

In ADHF , WRF is associated with adverse outcome only when congestion persists.

- 386 patients with ADHF (from the ESCAPE trial)
- Hemoconcentration (HC) defined as a change in hematocrit in the top tertile (low number of events if defined as ≥ 2 out of 3 (protein, albumin, and Hct)
- WRF: ≥ 20% reduction in eGFR
- Primary objective: to determine whether WRF was associated with in-hospital BP reduction
- In patients who experienced HC, WRF was not associated with mortality (p= 0.429)
- WRF increased mortality if no HC (p=0.019)

[Testani JM. Eur J Heart Fail 2011; 13: 877]

Congestion Modulates the Impact of ↑Scr in ADHF

599 patients

Table 2. Predictors of Death

Variable	25th, 75th Percentiles	Death or Transplant: Univariable HR (95% CI)*	Univariable *P* Value	Multivariable HR (95% CI)*	Multivariable *P* Value
Clinical history					
CKD		1.83 (1.2, 2.78)	0.005	1.79 (1.15, 2.79)	0.0104
COPD		2.04 (1.29, 3.21)	0.0021	1.87 (1.17, 3)	0.0088
Clinical characteristics					
NYHA class, discharge, 4 versus other		7.58 (3.31, 17.39)	<0.0001	5.48 (2.02, 14.89)	0.0009
Systolic blood pressure, admission	110, 140	0.53 (0.41, 0.7)	<0.0001	0.68 (0.52, 0.88)	0.0031
Systolic blood pressure, discharge	100, 125	0.4 (0.29, 0.56)	<0.0001		
Heart rate, discharge	60, 75	1.99 (1.53, 2.59)	<0.0001	1.48 (1.14, 1.92)	0.0032
Weight, discharge	65.6, 82	0.69 (0.53, 0.89)	0.0051	0.72 (0.55, 0.93)	0.0108
Echocardiographic characteristics					
EF, admission	23, 41	0.73 (0.54, 0.98)	0.038		
Laboratory characteristics					
Plasma hemoglobin, discharge	11.2, 14	0.6 (0.42, 0.84)	0.0035		
Serum sodium admission	137, 141	0.6 (0.5, 0.73)	<0.0001		
Serum sodium, discharge†	137, 142	0.48 (0.27, 0.86)	<0.0001	0.69 (0.37, 1.3)	<0.0001
Congestion and WRF					
1: Yes WRF and yes congestion		5.35 (3, 9.55)	<0.0001	2.44 (1.24, 4.81)	0.0097
2: No WRF and yes congestion		1.95 (0.81, 4.7)	0.1364	1.35 (0.52, 3.5)	0.5324
3: Yes WRF and no congestion		1.24 (0.75, 2.03)	0.4037	1.04 (0.62, 1.73)	0.8811
Reference: No WRF and no congestion			Ref		Ref

In ADHF , WRF is associated with adverse outcome only when congestion persists.

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[Metra M. Circ Heart Fail 2012; 5: 54]

Congestion Modulates the Impact of ↑Scr in ADHF

599 patients

Table 2. Predictors of Death

Variable	25th, 75th Percentiles	Death or Transplant: Univariable HR (95% CI)*	Univariable *P* Value	Multivariable HR (95% CI)*	Multivariable *P* Value
Clinical history					
CKD		1.83 (1.2, 2.78)	0.005	1.79 (1.15, 2.79)	0.0104
COPD		2.04 (1.29, 3.21)	0.0021	1.87 (1.17, 3)	0.0088
Clinical characteristics					
NYHA class, discharge, 4 versus other		7.58 (3.31, 17.39)	<0.0001	5.48 (2.02, 14.89)	0.0009
Systolic blood pressure, admission	110, 140	0.53 (0.41, 0.7)	<0.0001	0.68 (0.52, 0.88)	0.0031
Systolic blood pressure, discharge	100, 125	0.4 (0.29, 0.56)	<0.0001		
Heart rate, discharge	60, 75	1.99 (1.53, 2.59)	<0.0001	1.48 (1.14, 1.92)	0.0032
Weight, discharge	65.6, 82	0.69 (0.53, 0.89)	0.0051	0.72 (0.55, 0.93)	0.0108
Echocardiographic characteristics					
EF, admission	23, 41	0.73 (0.54, 0.98)	0.038		
Laboratory characteristics					
Plasma hemoglobin, discharge	11.2, 14	0.6 (0.42, 0.84)	0.0035		
Serum sodium admission	137, 141	0.6 (0.5, 0.73)	<0.0001		
Serum sodium, discharge†	137, 142	0.48 (0.27, 0.86)	<0.0001	0.69 (0.37, 1.3)	<0.0001
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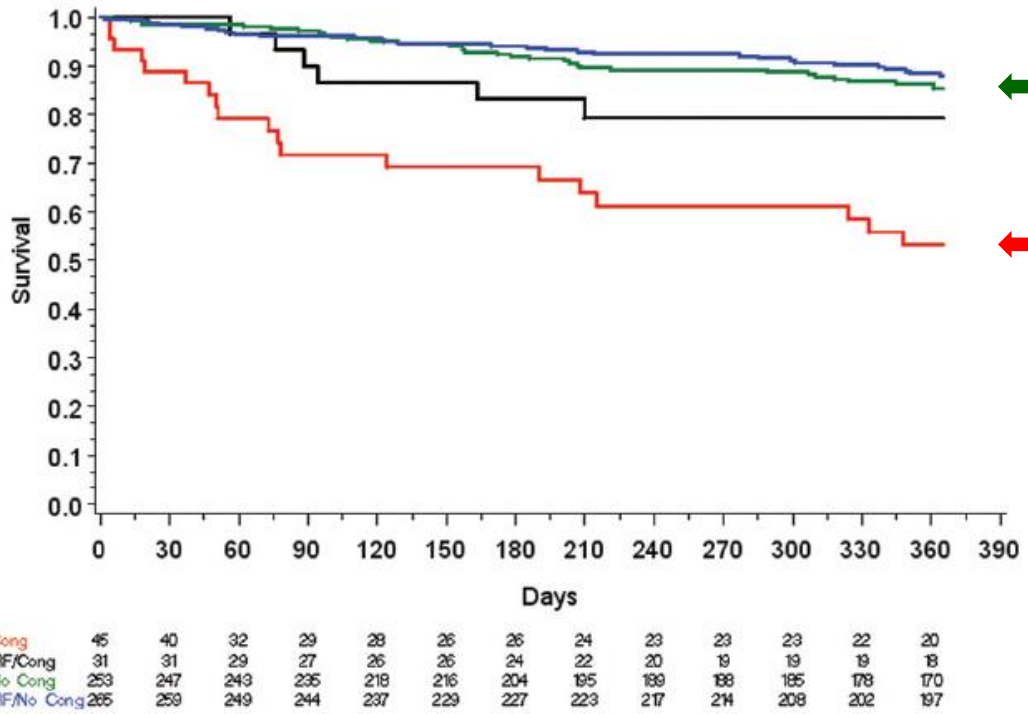
Congestion Modulates the Impact of ↑Scr in ADHF

599 patients



WRF +/ CONG –

WRF +/CONG +

Endpoints: 1 year death or urgent transplantation

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[Metra M. Circ Heart Fail 2012; 5: 54]

Congestion Modulates the Impact of ↑Scr in ADHF

1232 patients

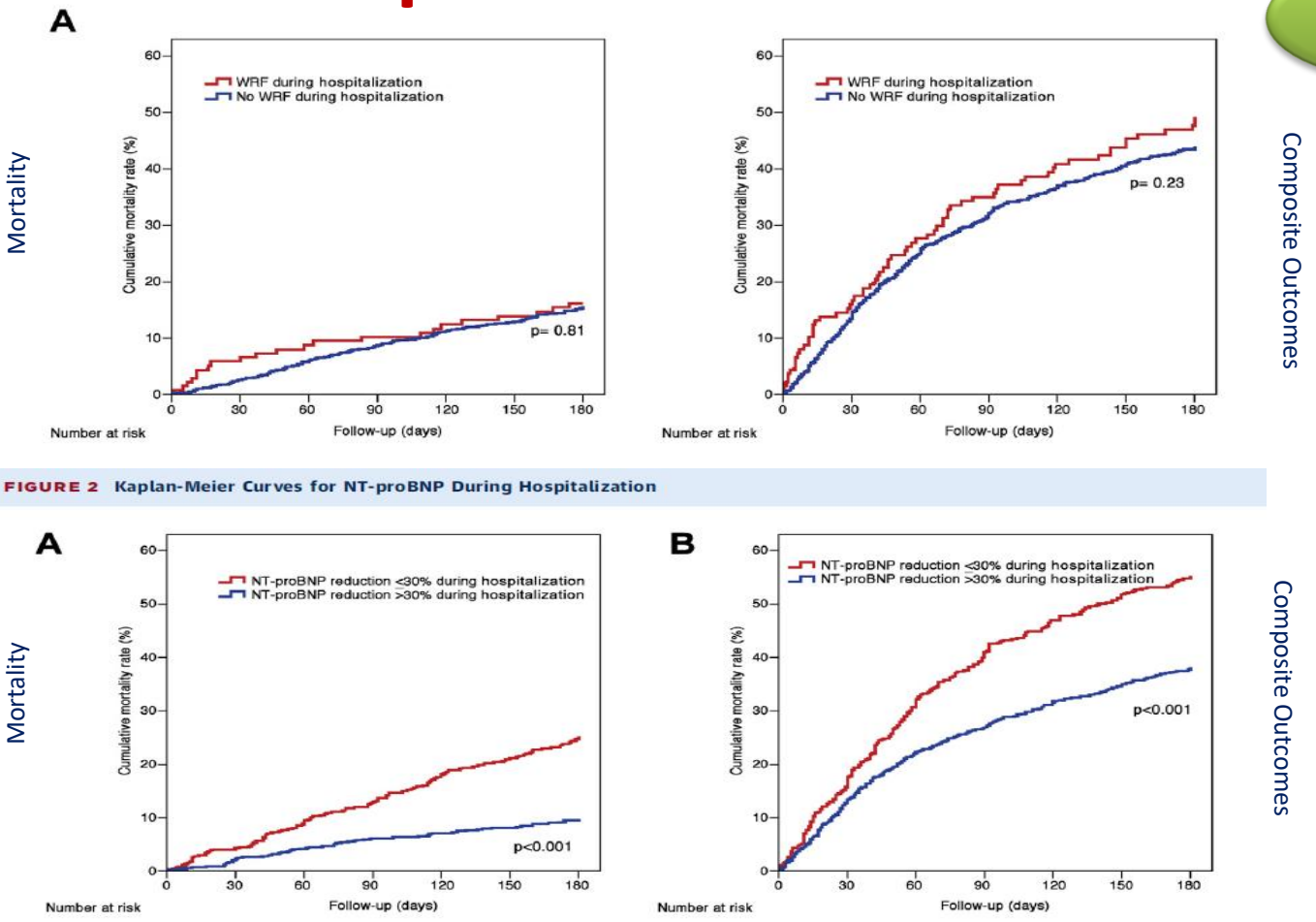

FIGURE 2 Kaplan-Meier Curves for NT-proBNP During Hospitalization

Persistent congestion, but not WRF, was associated with adverse outcomes

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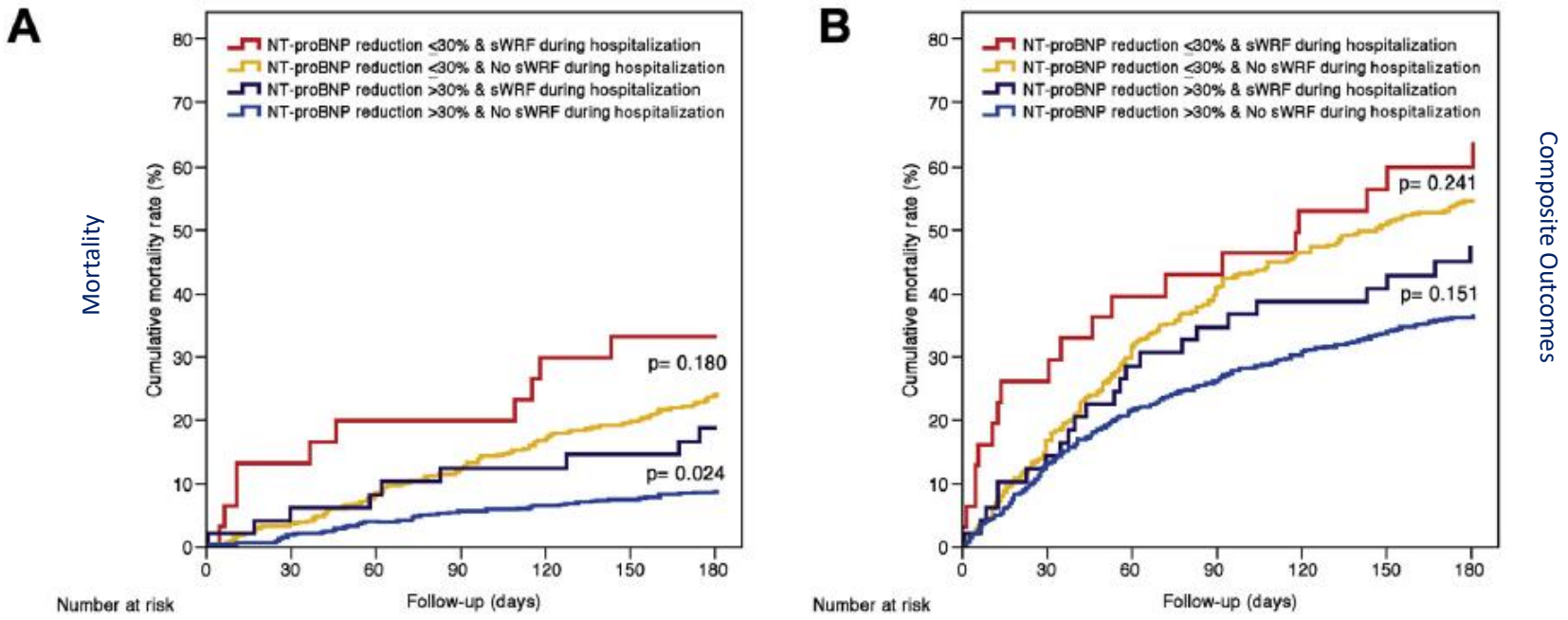
[Salah K. JACC HF 2015; 3: 751]

Congestion Modulates the Impact of ↑Scr in ADHF

1232 patients



Adverse outcomes are mainly driven by persistent congestion

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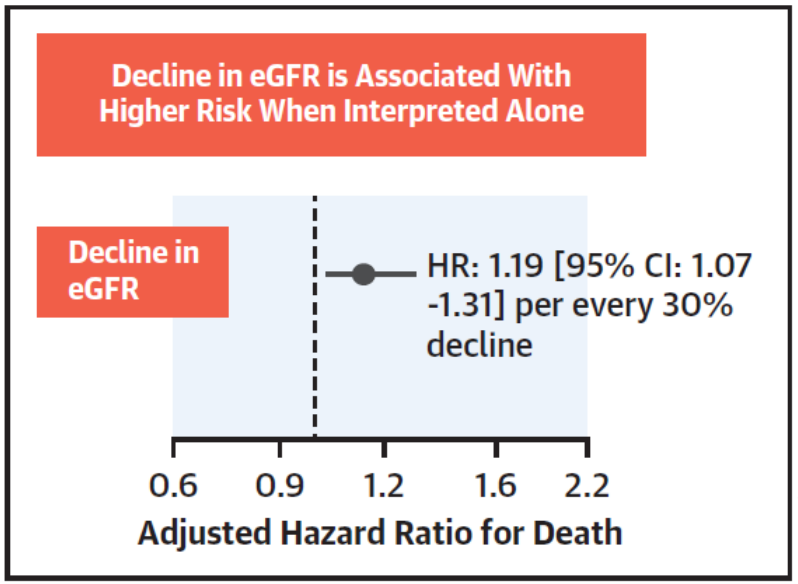
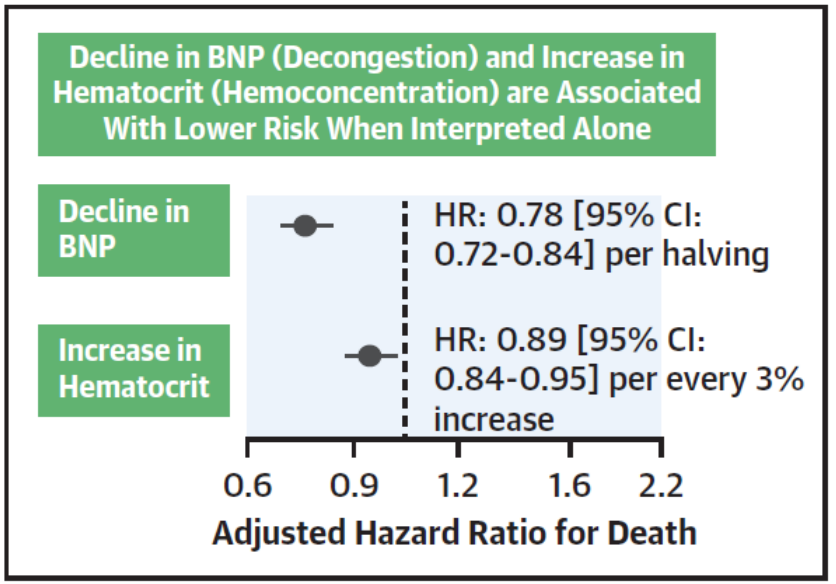
[Salah K. JACC HF 2015; 3: 751]

Congestion Modulates the Impact of ↑Scr in ADHF

3715 patients

EVEREST ad hoc





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[MaCallum W et al. JACC Heart Fail 2020;8:537]

Congestion Modulates the Impact of ↑Scr in ADHF

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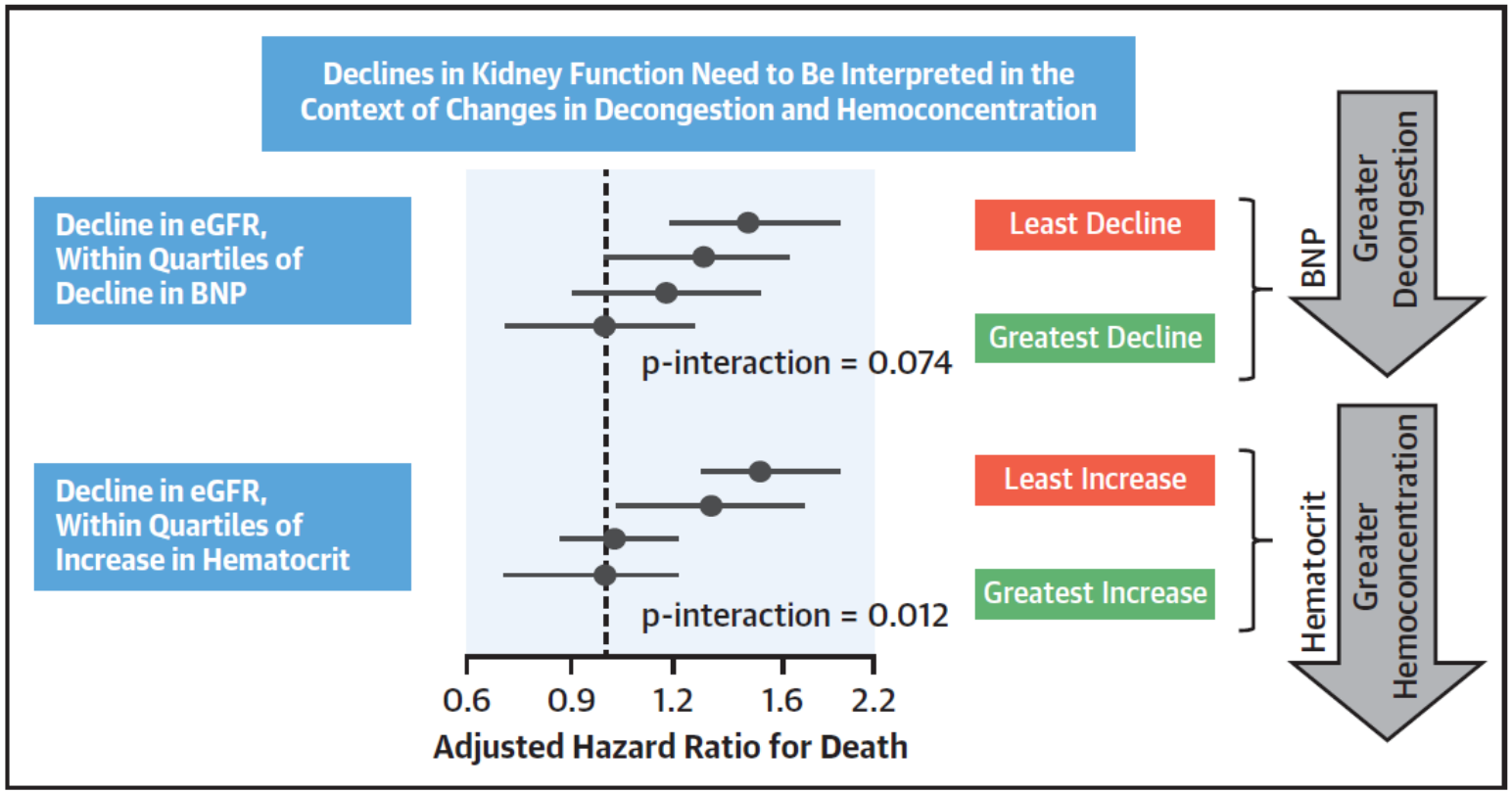

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[MaCallum W et al. JACC Heart Fail 2020;8:537]

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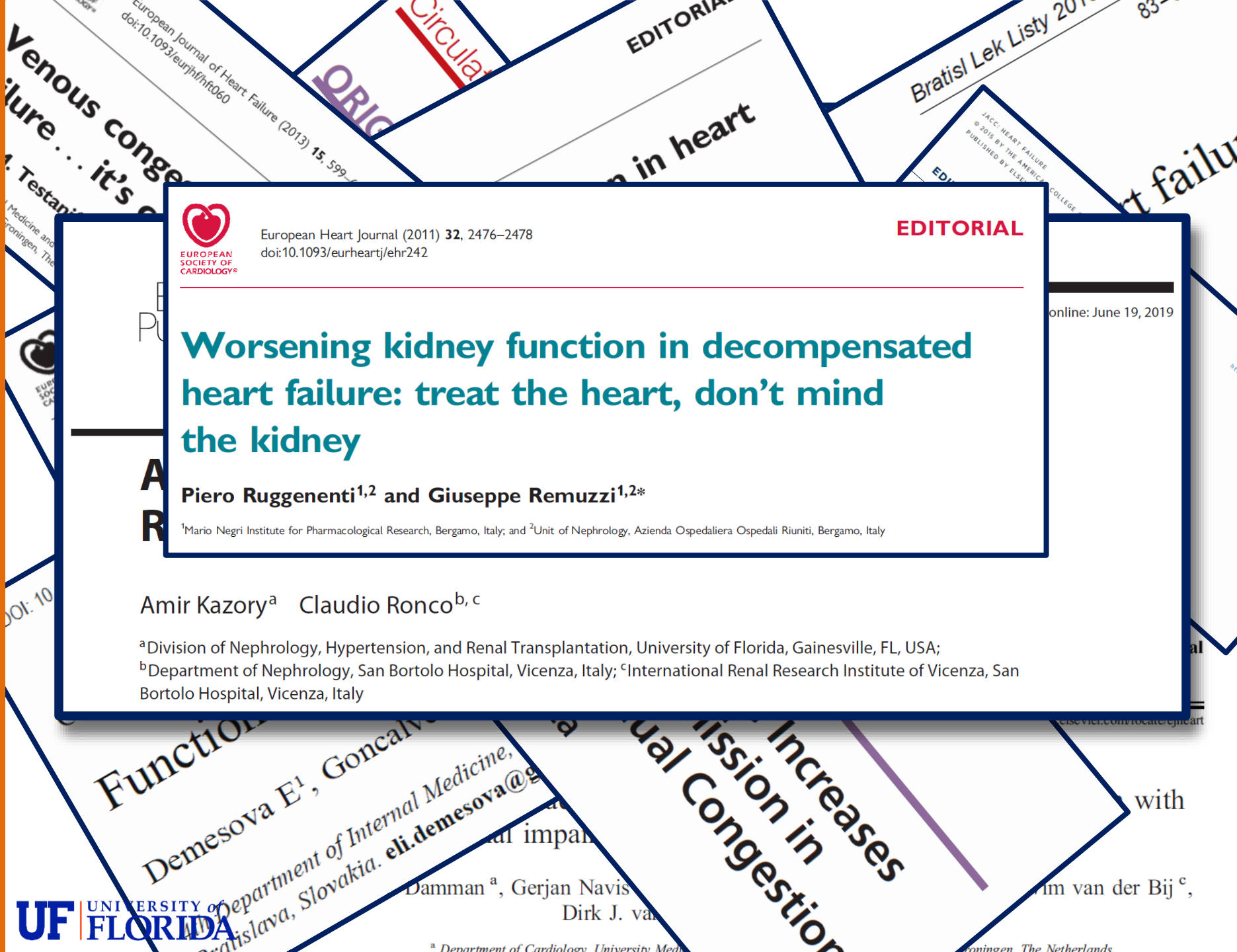

European Heart Journal (2011) **32**, 2476–2478
doi:10.1093/eurheartj/ehr242

EDITORIAL

Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney

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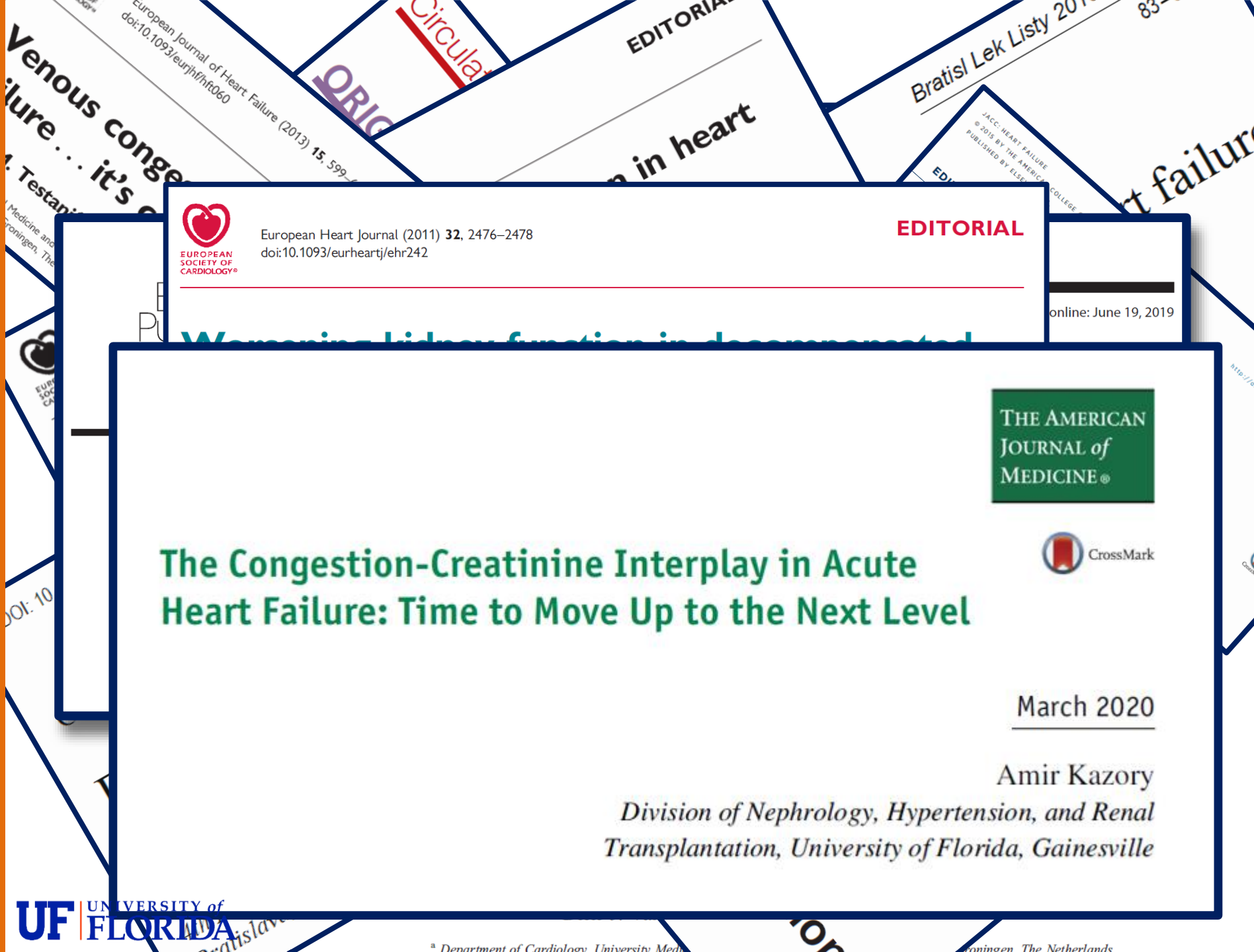

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Take-Home Message

- ✓ - Changes in SCr do not necessarily reflect tubular injury (AKI) in HF.
- ✓ - While renal biomarkers are promising, their therapeutic implications in HF are yet to be clarified.
- ✓ - Congestion is the main reason for hospital admission and the driver of outcomes in ADHF.
- ✓ - If renal function is used as an endpoint, it needs to be considered along with measures of decongestion (CARRESS-HF)


از توجهتون سپاسگزار هستم ...
Thank You...