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Ultrafiltration for Heart Failure

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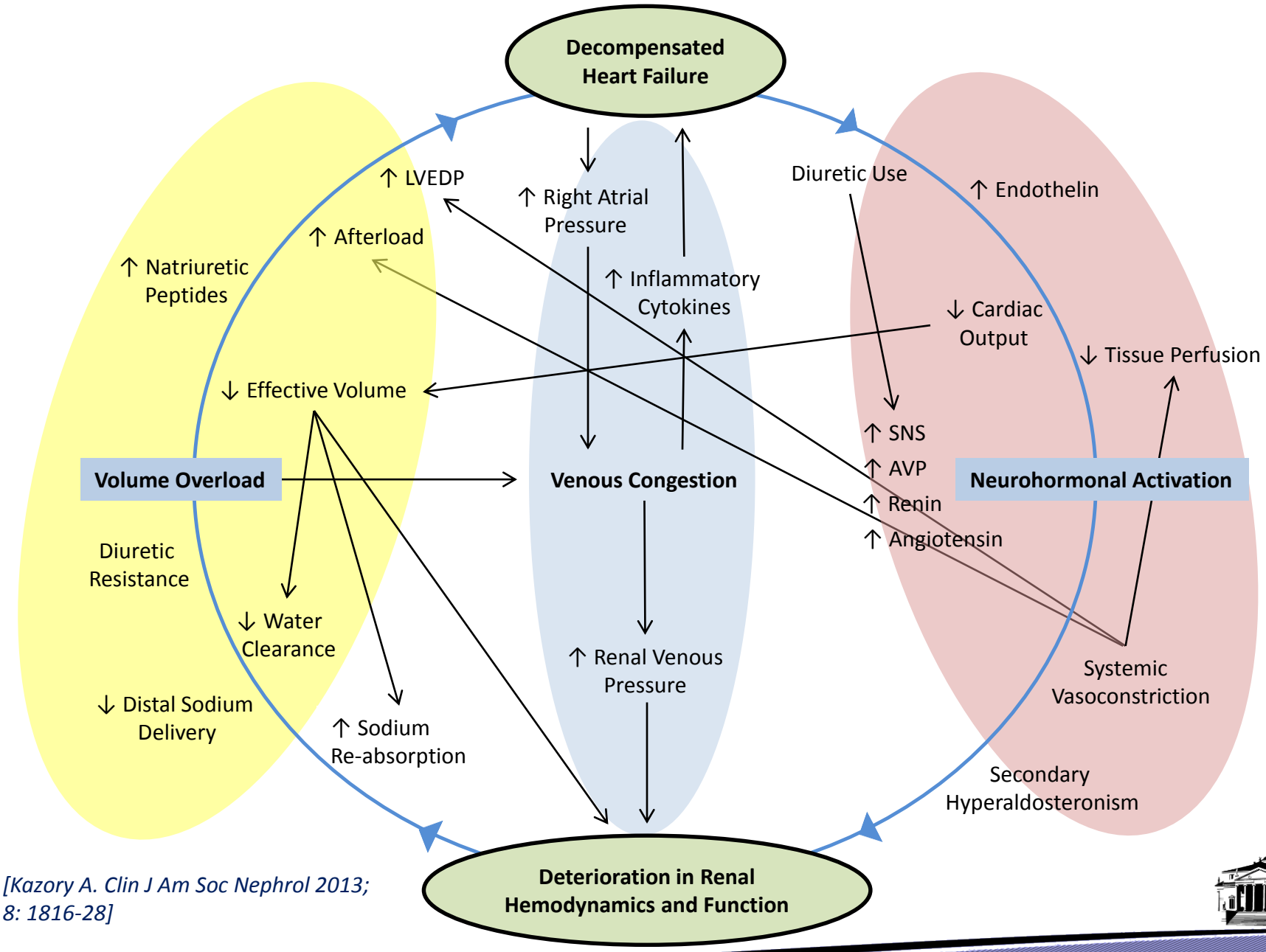
University of Florida

Disclosures

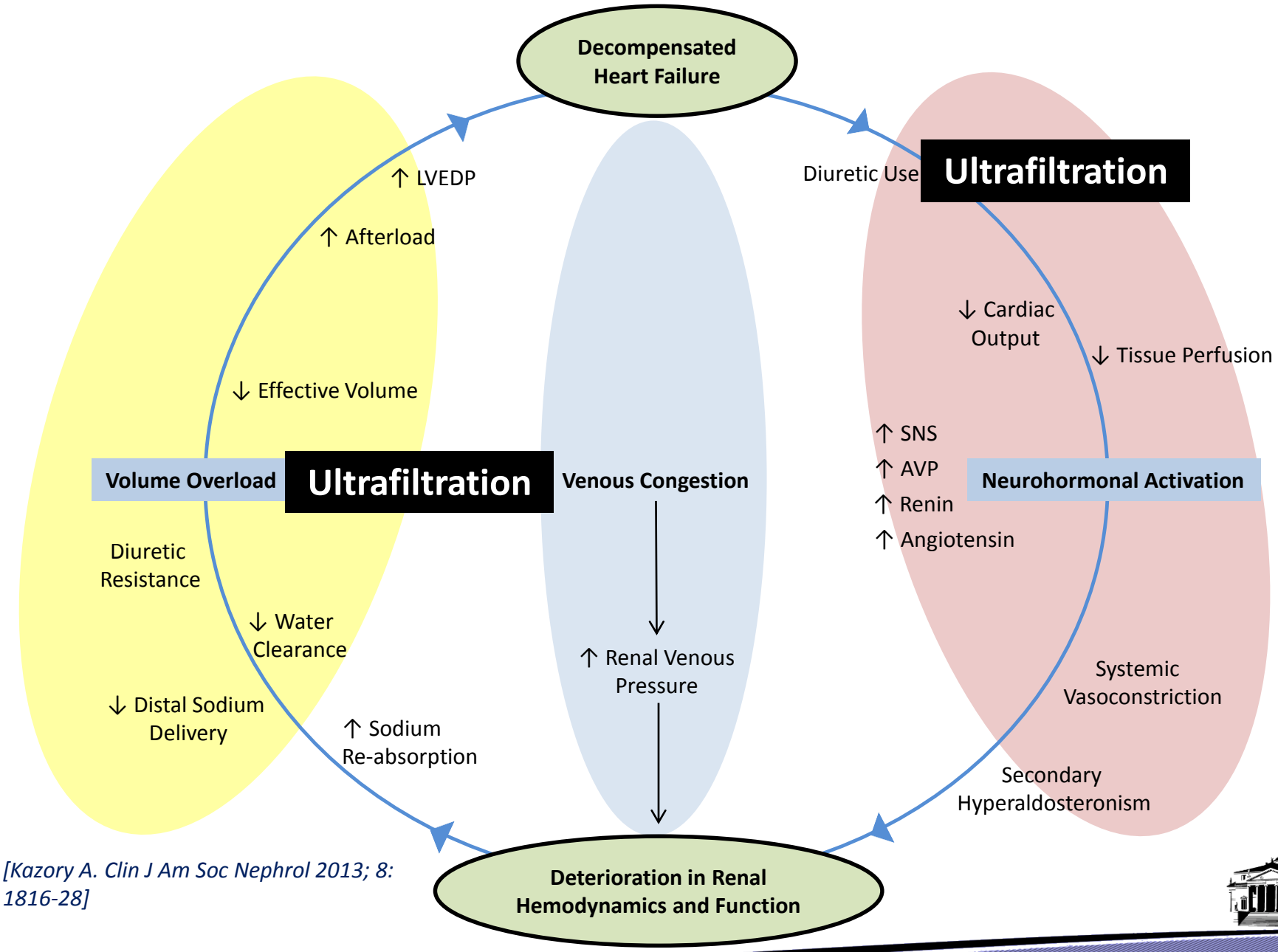
CHF Solutions, Inc. - Scientific Advisory Board

Otsuka America Pharmaceutical, Inc. - ADPKD Expert Advisory Board

W.L. Gore Inc. - Consultant



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



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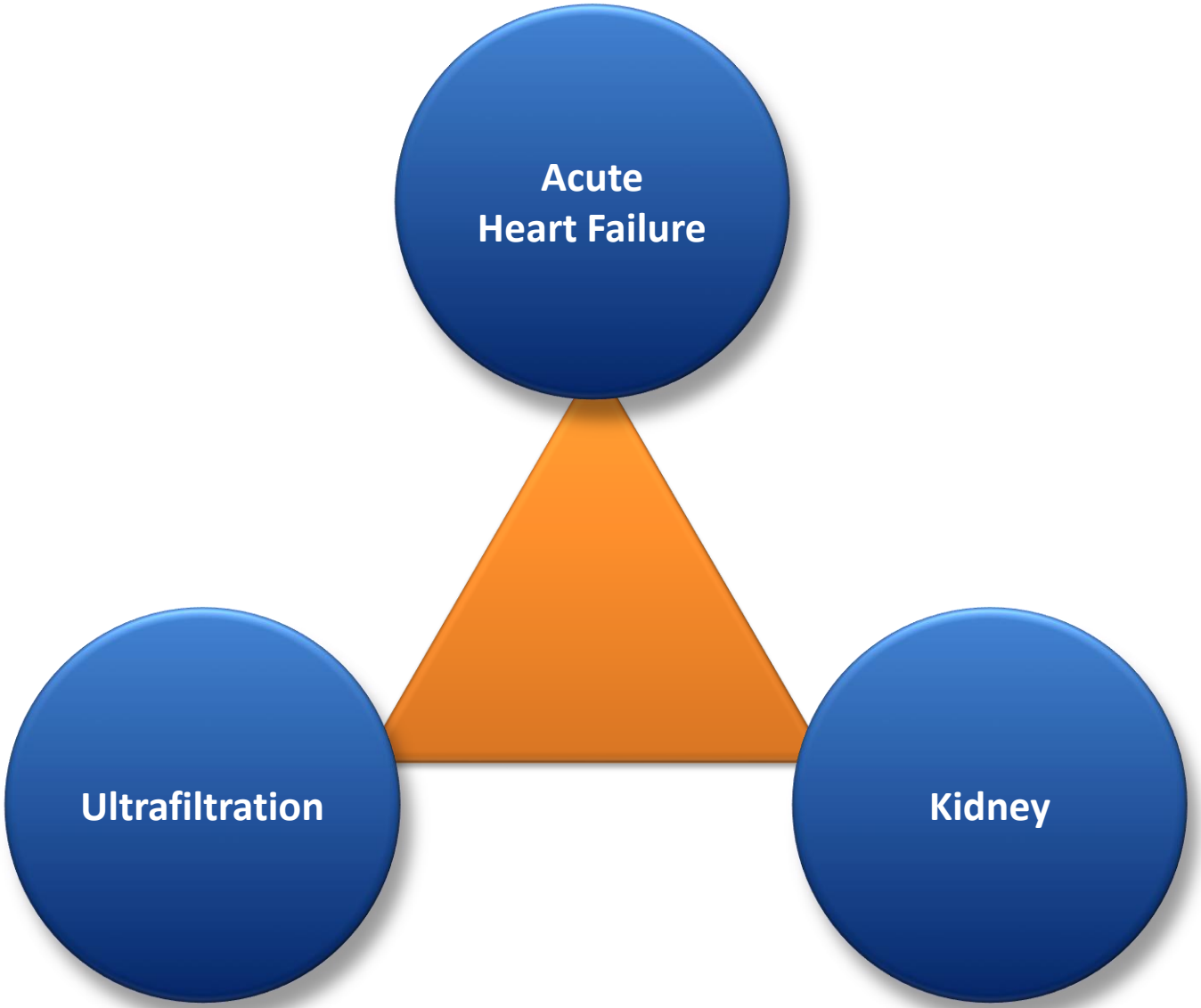

Acute
Heart Failure
Ultrafiltration
Kidney

United States Food and Drug Administration (

"Feels, Functions, or Survives"

All drugs have safety risks. Therefo
patient would want to take a

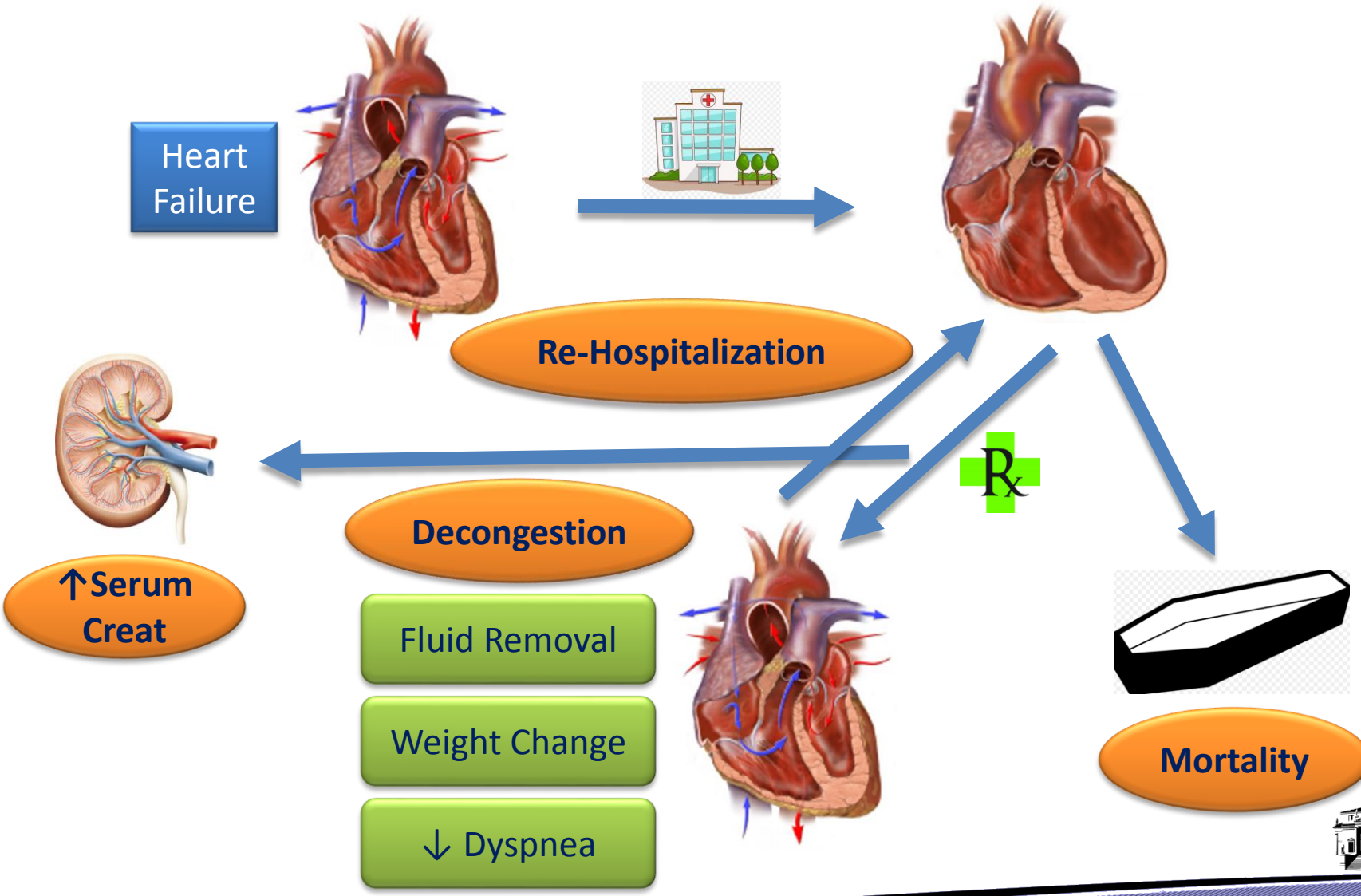
Primary endpoint should be a direct measure of one of these.

vement
in survival

g in a benefit that
s detectable by the
patient (e.g. improvement
in dyspnea or functional
capacity)

at
to the
undesirable
(e.g. H rehospitalization)

Identifying the Right CardioRenal Endpoints



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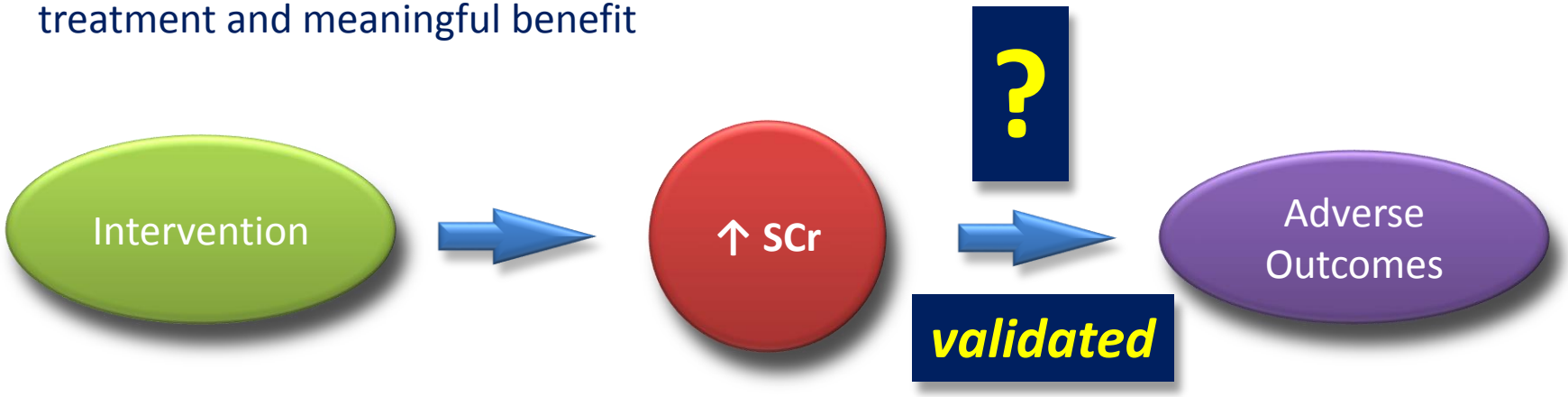
Why Use *"Increase in Serum Creatinine"* as a Surrogate Endpoint in HF Trials?

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.

2) This expectation must be supported by strong data ("**validation**").

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



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

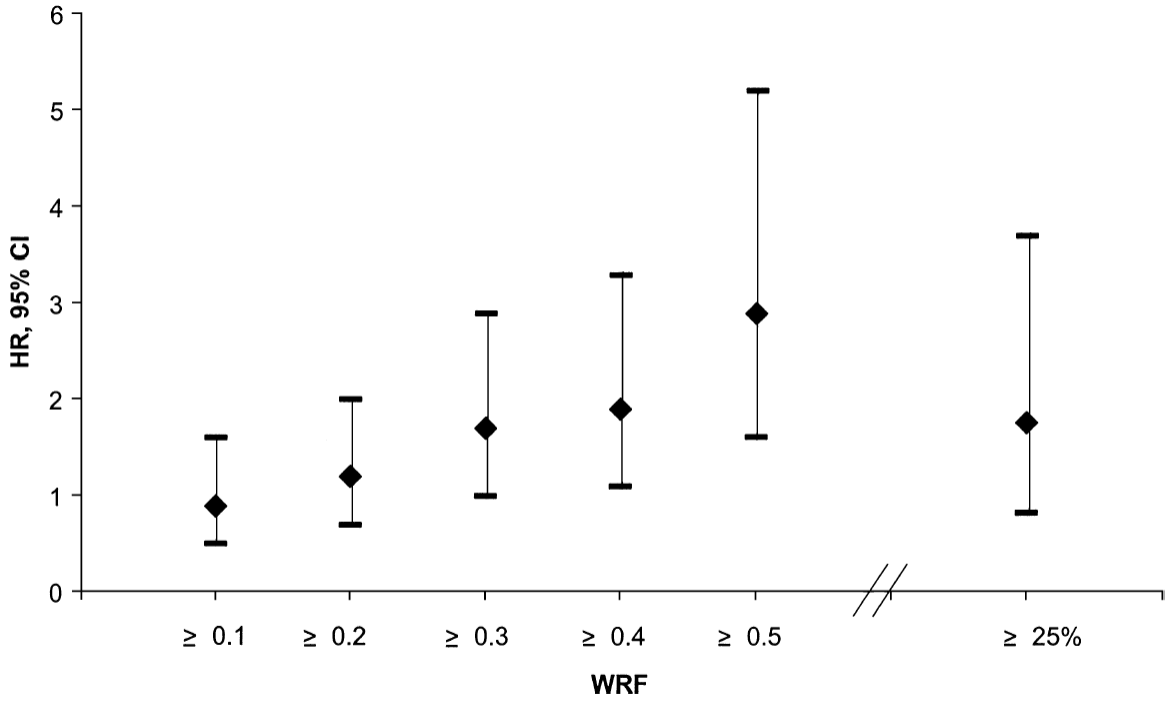


Fig. 3. Adjusted hazard ratio (HR) for mortality.

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

The Dose Trial

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

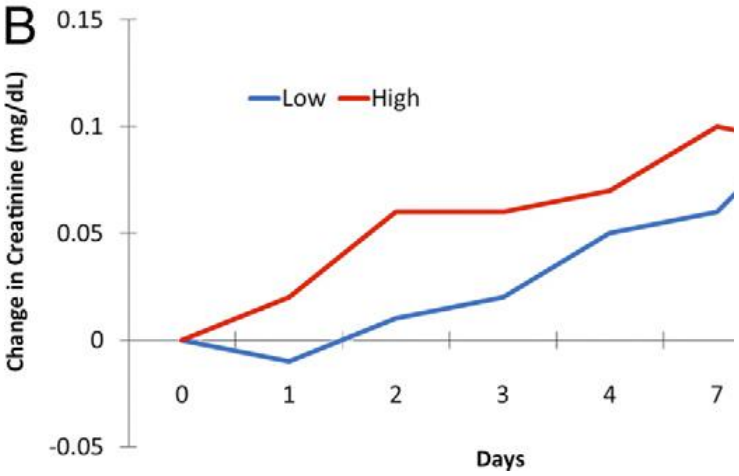
End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
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	

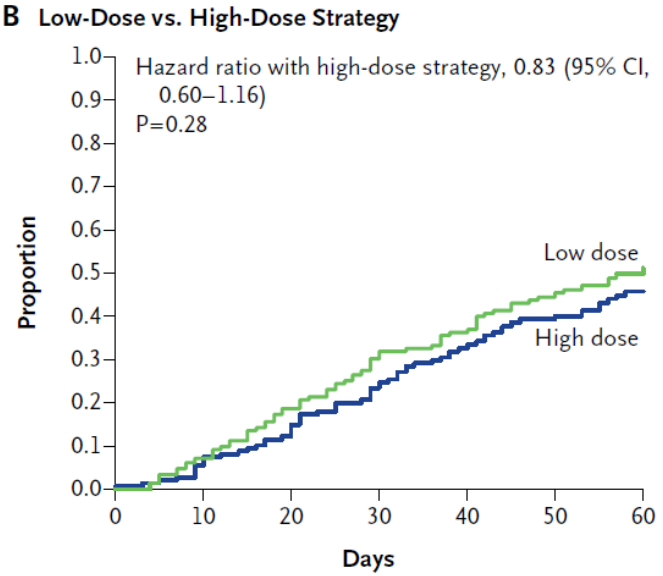
308 patients

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

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

The Dose Trial

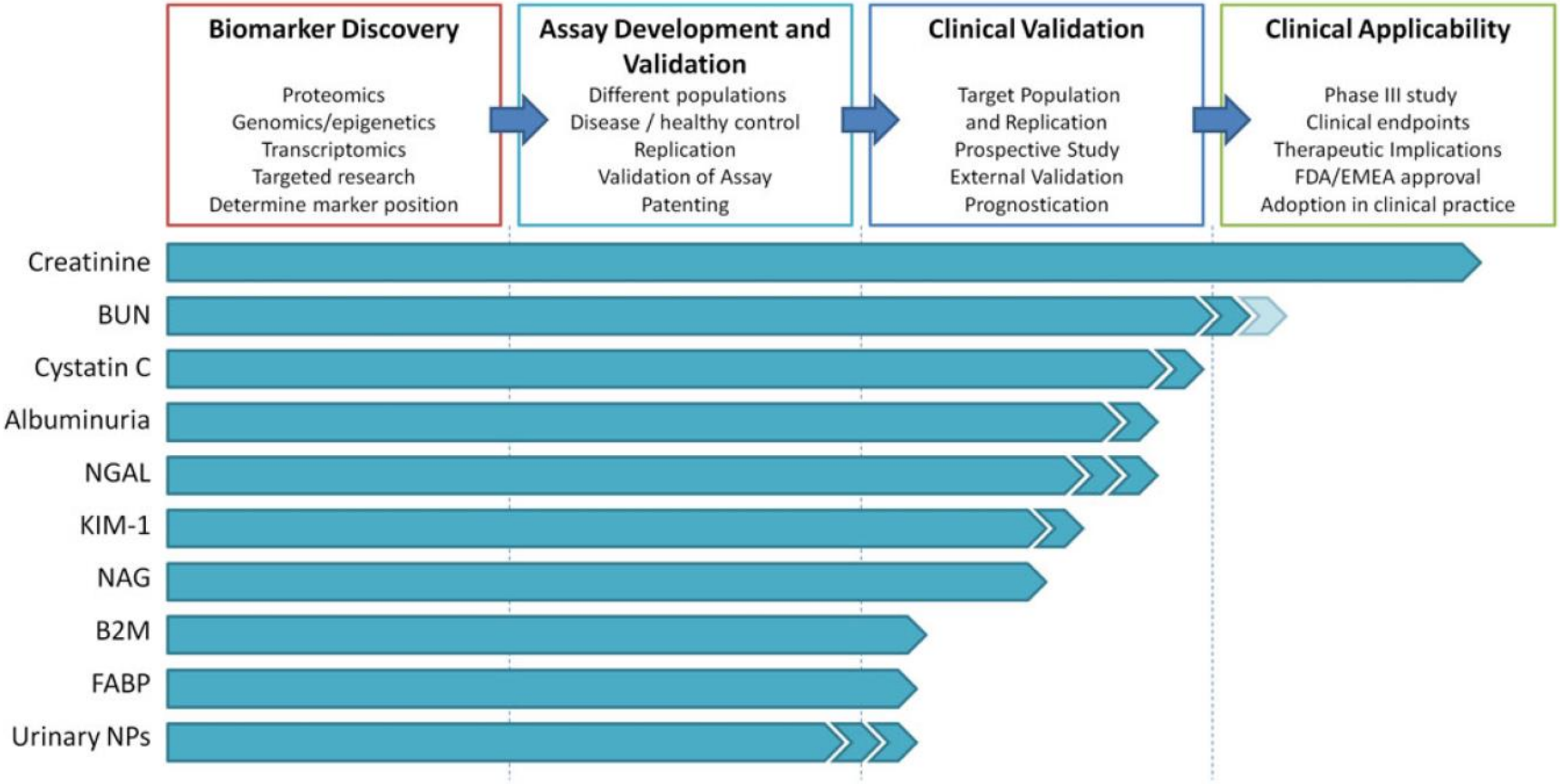




HD group: more WRF, but no impact on outcomes (death, re-hospit, ED visit)

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

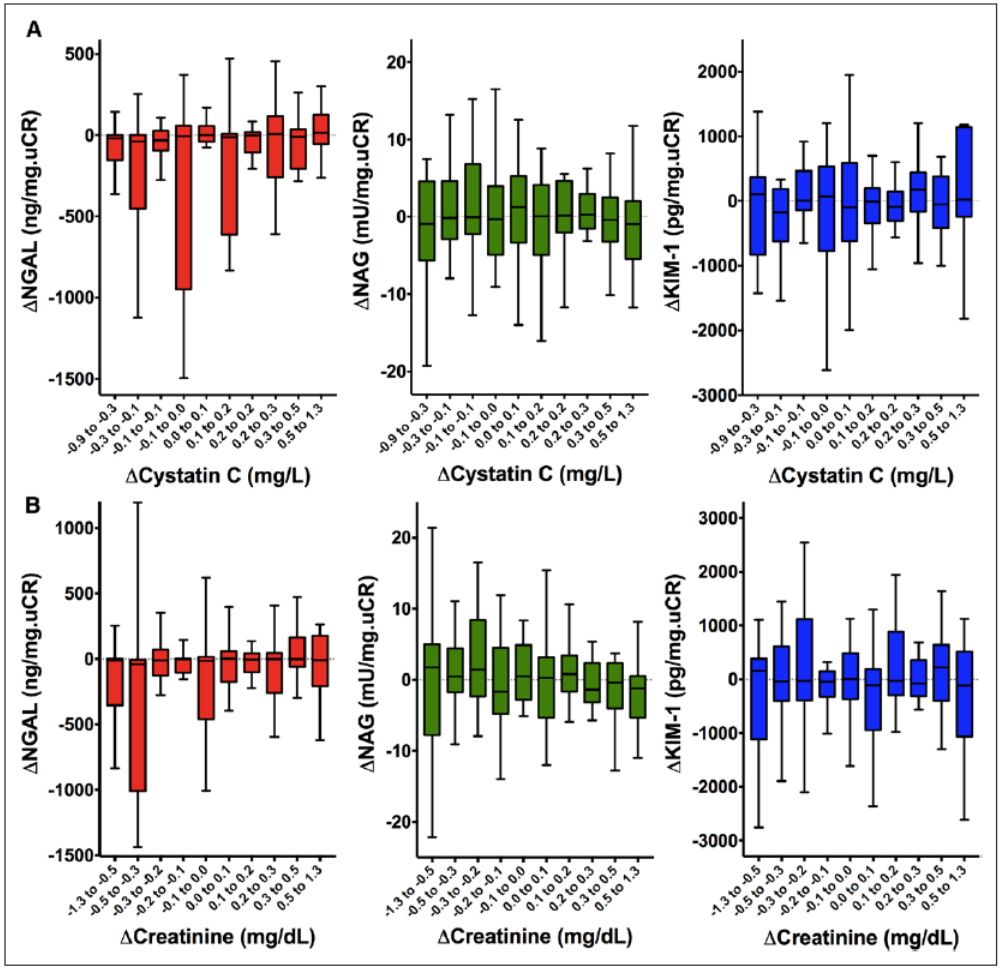
Biomarkers of Renal Injury and Function in HF



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

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

WRF in ADHF Undergoing Aggressive Diuresis; Not Tubular Injury



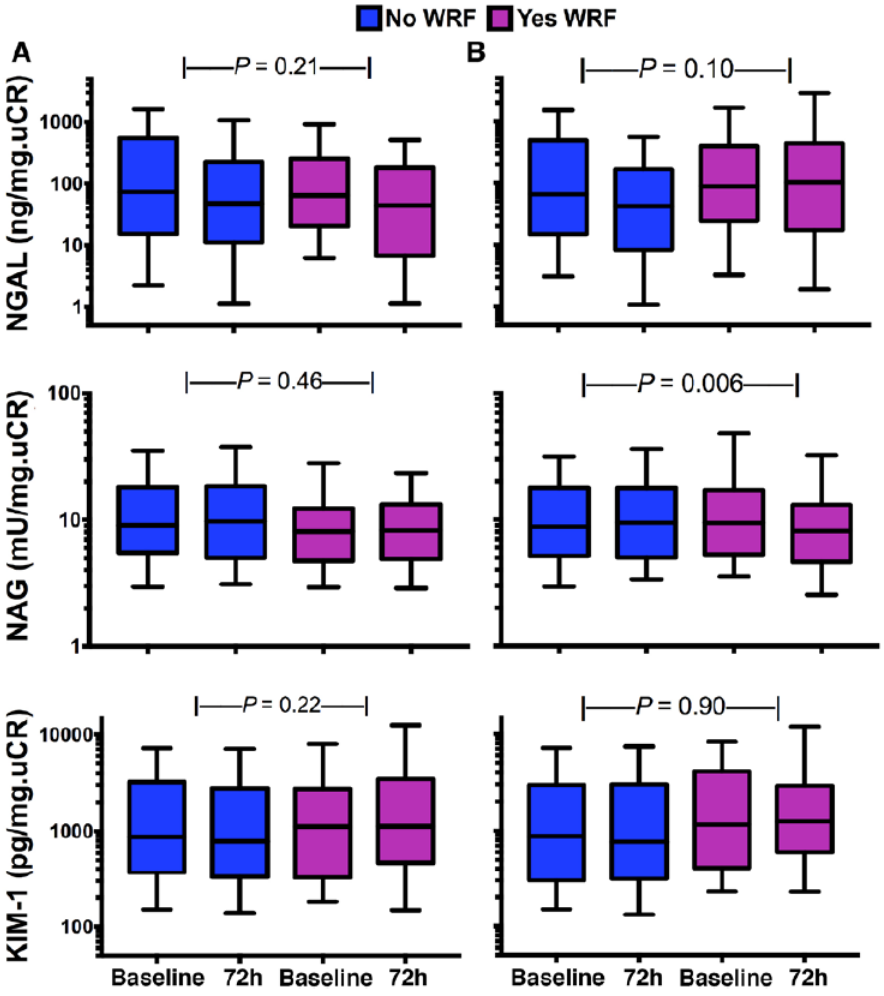
283 patients in ROSE-AHF

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

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; Not Tubular Injury



283 patients in ROSE-AHF

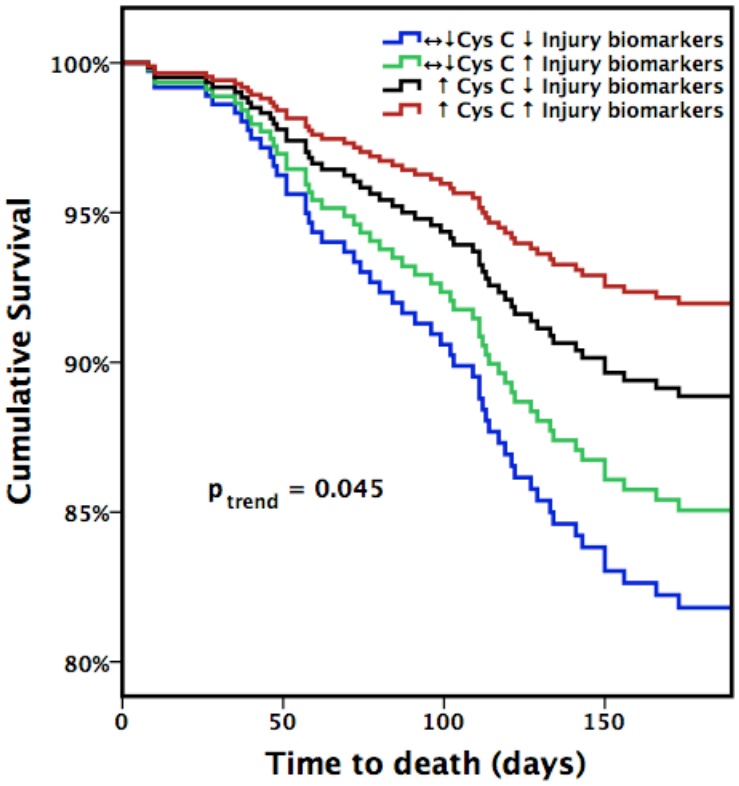
No difference in level of biomarkers between those with or without WRF

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

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; Impact on Survival



283 patients in ROSE-AHF

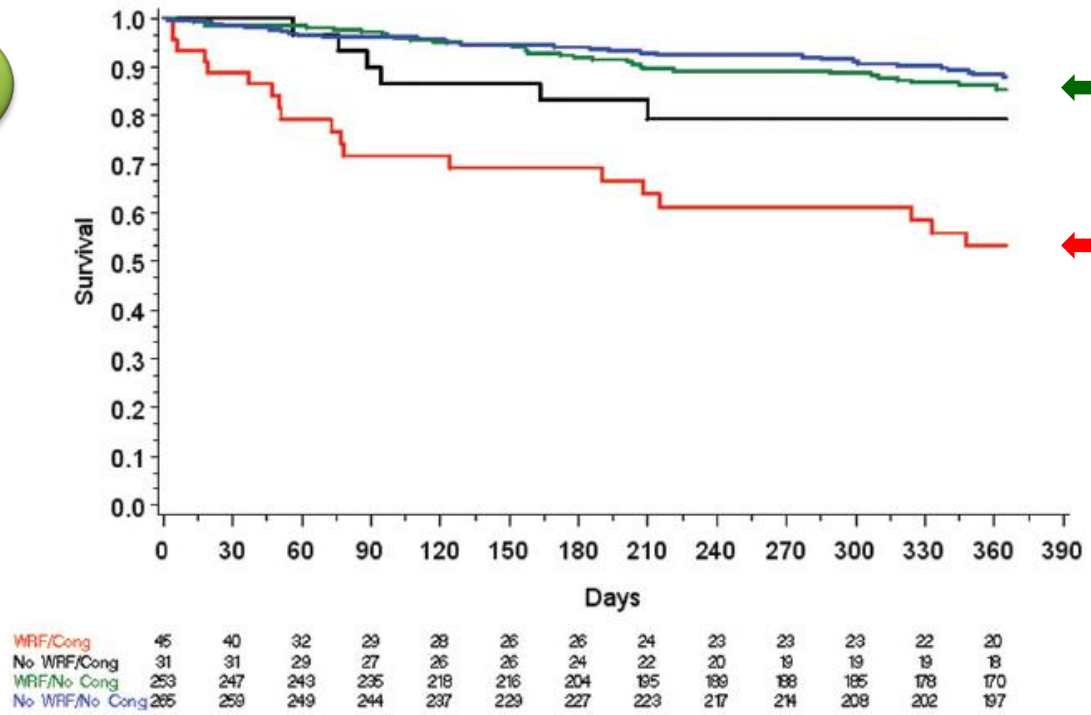
Decline in kidney function and increase in tubular injury markers; the best outcomes
No change or improvement in kidney function/tubular injury biomarkers had the worst outcomes.

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

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

Congestion Modulates the Impact of ↑Scr in ADHF

599 patients



WRF +/ CONG –

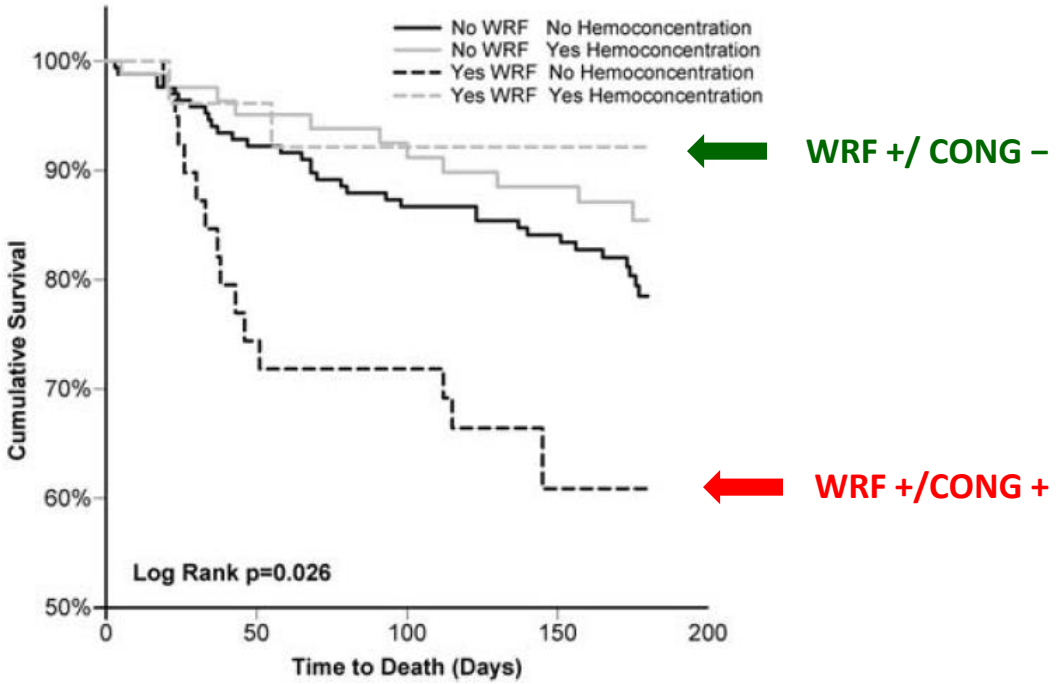
WRF +/CONG +

Endpoints: 1 year death or urgent transplantation

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

Congestion Modulates the Impact of ↑Scr in ADHF

386 patients



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

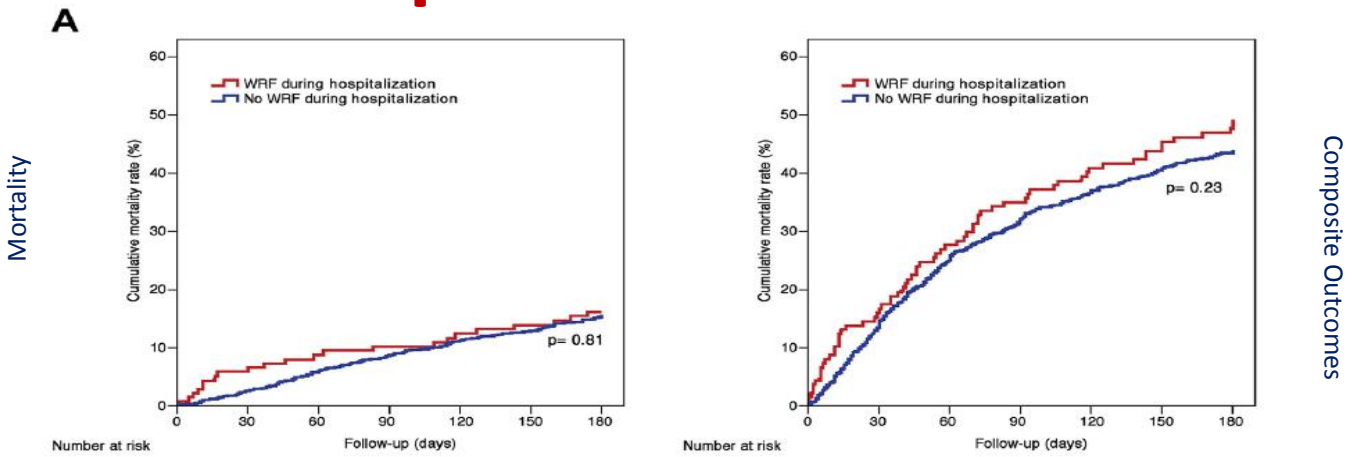
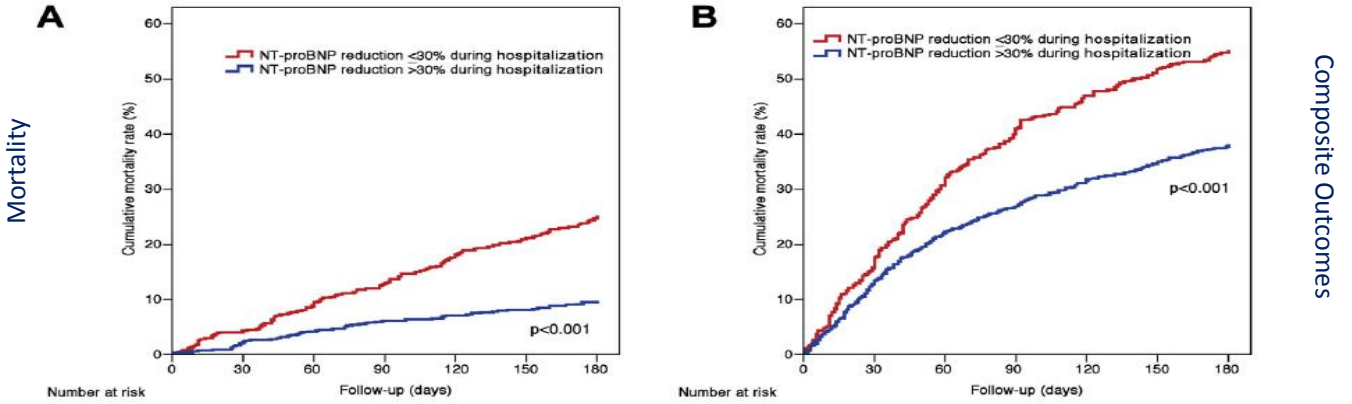


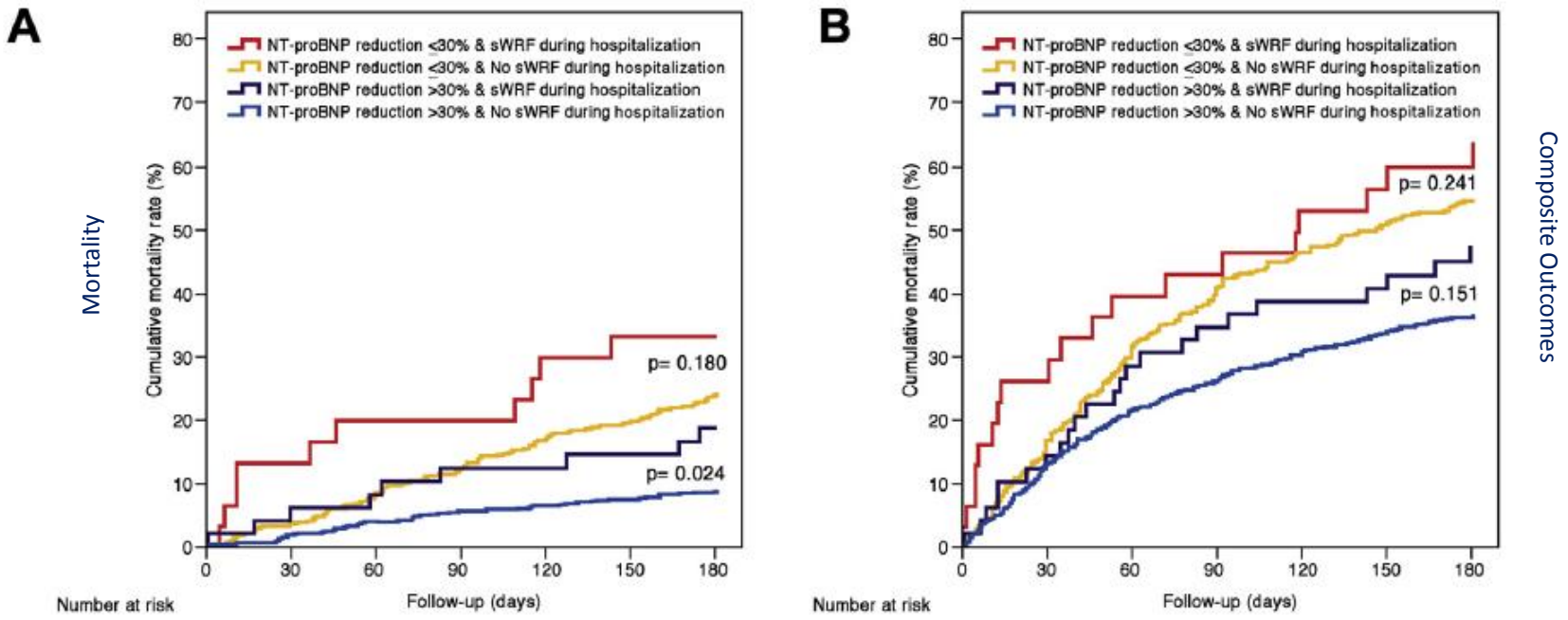
FIGURE 2 Kaplan-Meier Curves for NT-proBNP During Hospitalization



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

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

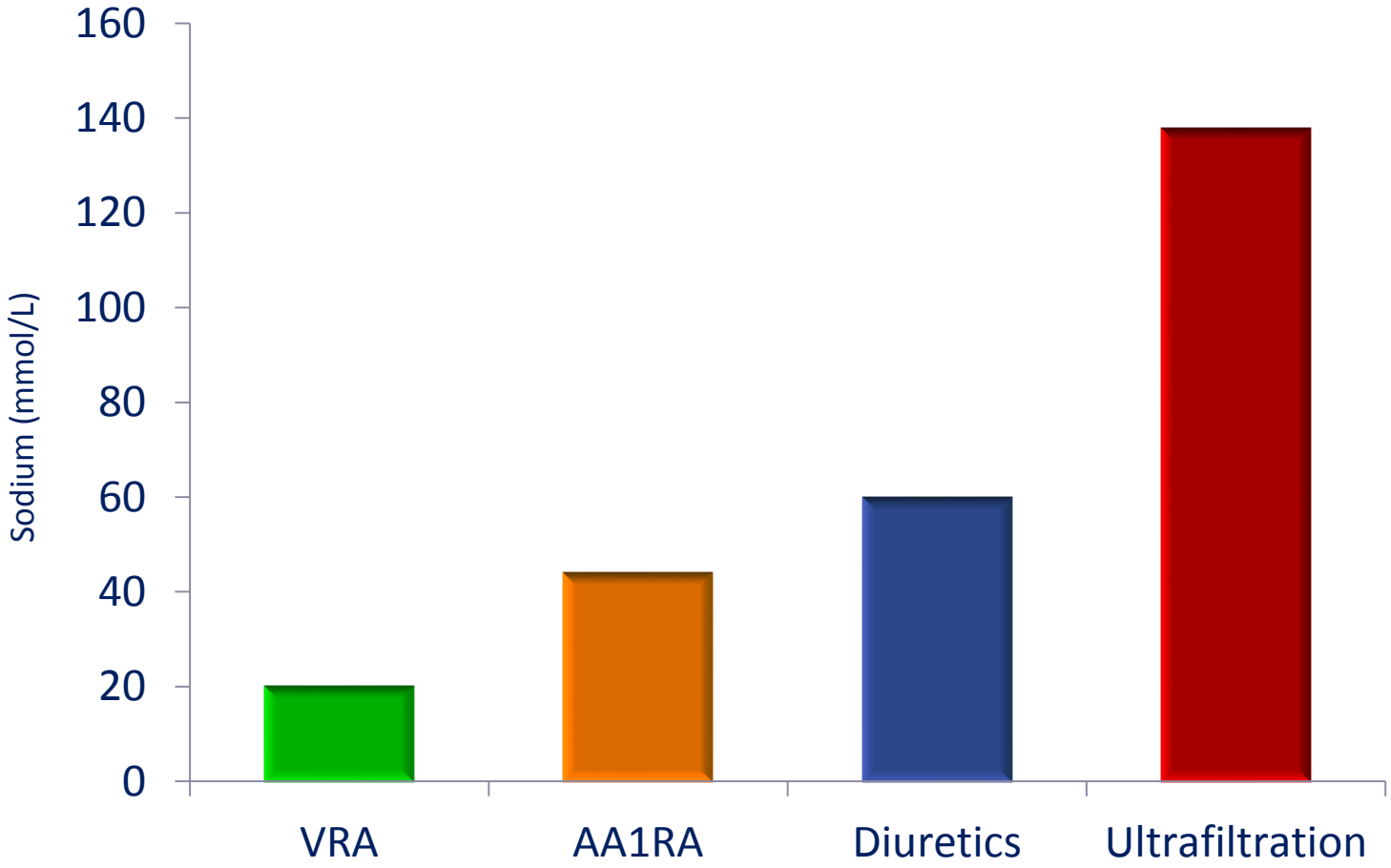
Congestion Modulates the Impact of ↑Scr in ADHF



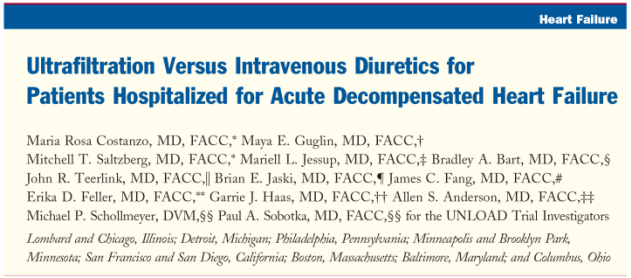
Adverse outcomes are mainly driven by persistent congestion

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

Higher Mass Clearance of Sodium



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



Heart Failure

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

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Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

The UNLOAD Trial

Multicenter RCT

ADHF

Diuretic (n=100)

UF (n=100)

The primary efficacy end points: weight loss and patients' dyspnea assessment 48 h after randomization

The primary safety end points:

1- changes in serum blood urea nitrogen, creatinine, and electrolytes at 8, 24, 48, and 72 h after randomization, discharge, 10, 30, and 90 days

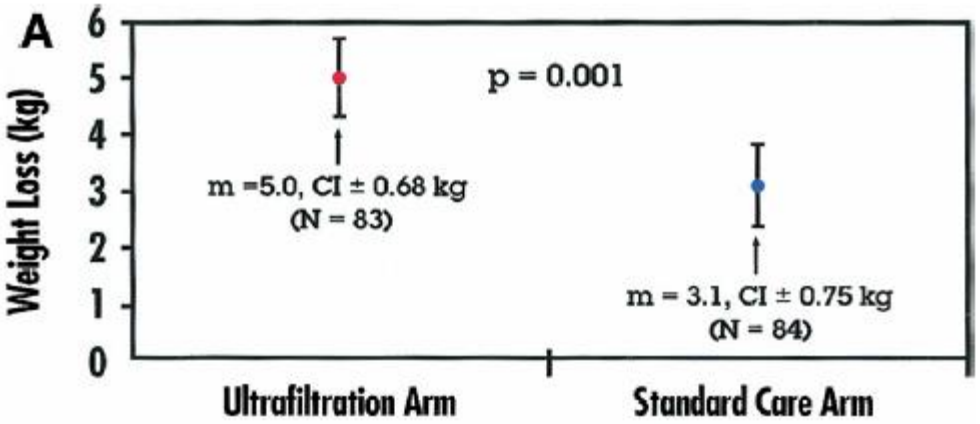
2- episodes of hypotension (a decrease in systolic blood pressure requiring therapeutic intervention) at 48 h after randomization.

The secondary efficacy end points: 1) net fluid loss 48 h after randomization; 2) length of index hospitalization; 3) change in B-type natriuretic peptide levels at 48 h after randomization, 30, and 90 days; 4) changes in New York Heart Association functional class, Minnesota Living with Heart Failure Questionnaire scores, Global Assessment scores, 6-min walk distance and loop diuretic doses at discharge, 30, and 90 days; and 5) rehospitalizations for HF, percentage of patients rehospitalized for HF, days of rehospitalization, and unscheduled office and emergency department visits within 90 days. Cause of death was adjudicated by 2 independent observers.

[Costanzo MR. J Am Coll Cardiol 2007; 49: 675]

The UNLOAD Trial

Primary Efficacy Endpoint: Weight Loss

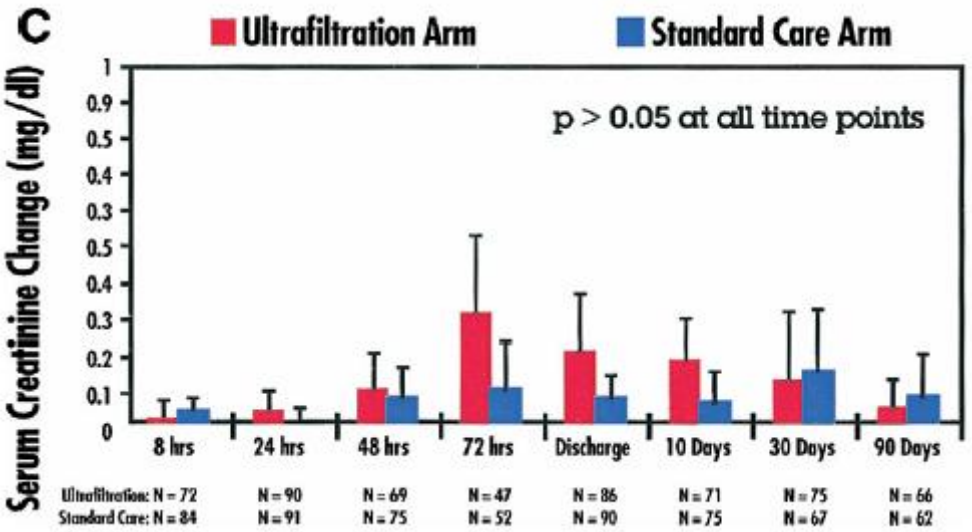


At 48 hours, significantly greater amount of weight loss seen with ultrafiltration as compared to diuretics (5 kg vs. 3.1 kg)

[Costanzo MR. J Am Coll Cardiol 2007; 49: 675]

The UNLOAD Trial

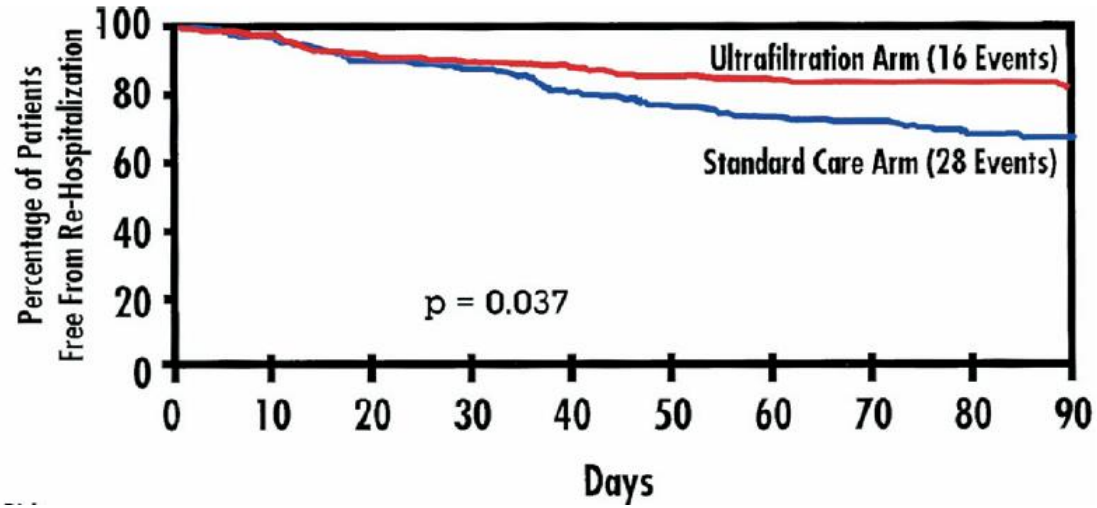
Primary Safety Endpoint: Change in Serum Creatinine



Ultrafiltration: trend for WRF

[Costanzo MR. J Am Coll Cardiol 2007; 49: 675]

The UNLOAD Trial



	Ultrafiltration	Standard Care	P Value
Patients rehospitalized for HF, %	18	32	.037
HF re-hospitalizations, #	0.22	0.46	.022
Rehospitalization days per patient	1.4	3.8	.022
Unscheduled office + ED visits, %	21	44	.009

Ultrafiltration: better outcomes

[Costanzo MR. J Am Coll Cardiol 2007; 49: 675]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O'Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

The CARRESS-HF Trial

Multicenter RCT

CRS

SPT (n=94)

UF (n=92)

The primary end point: the change in the serum creatinine level and the change in weight, considered as a bivariate response, between the time of randomization and 96 hours after randomization

Secondary End Points: a) Primary endpoint (change in serum creatinine AND weight together as a "bivariate" endpoint) assessed after randomization on hospital days 1 - 3 and at one week. b) Significant weight loss and renal improvement assessed at 96 hours and one week. c) Treatment failure during the first seven days after randomization. d) Changes in renal function from randomization to days 7, 30 and 60. Peak creatinine during hospitalization. e) Changes in electrolytes from randomization to 96 hours and one week. f) Changes in weight measured daily from randomization to one week, 30 and 60 days. g) Percent of patients achieving clinical decongestion at 96 hours, one week, 30 and 60 days. h) Total net fluid loss from randomization to 96 hours and 1 week. i) Changes in biomarkers from randomization to 96 hours, at one week and at 60 days. j) Changes in global assessment and visual analogue scores from enrollment to 96 hours and one week.

[Bart BA. New Engl J Med 2012; 367: 2296]

The CARRESS-HF Trial

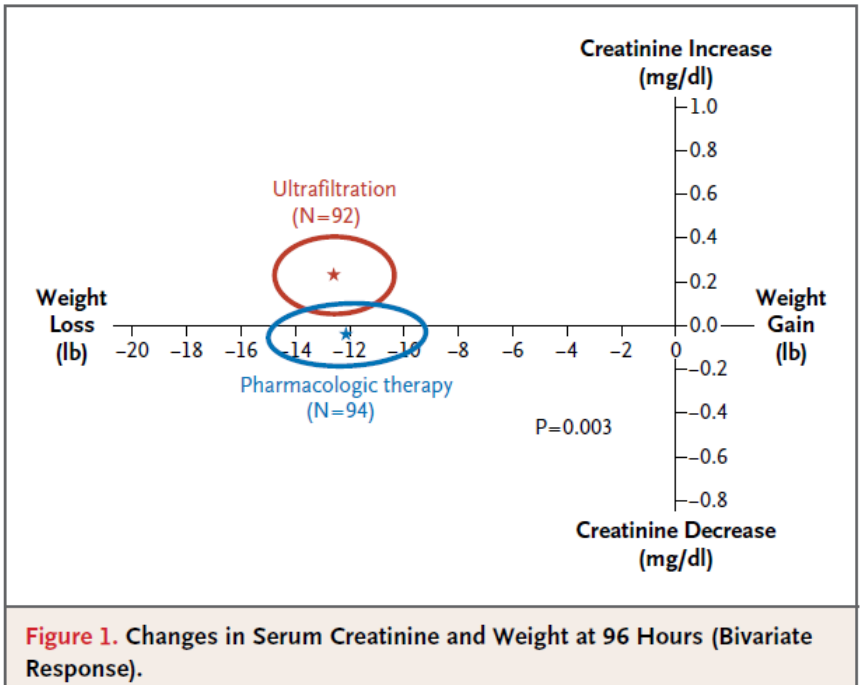
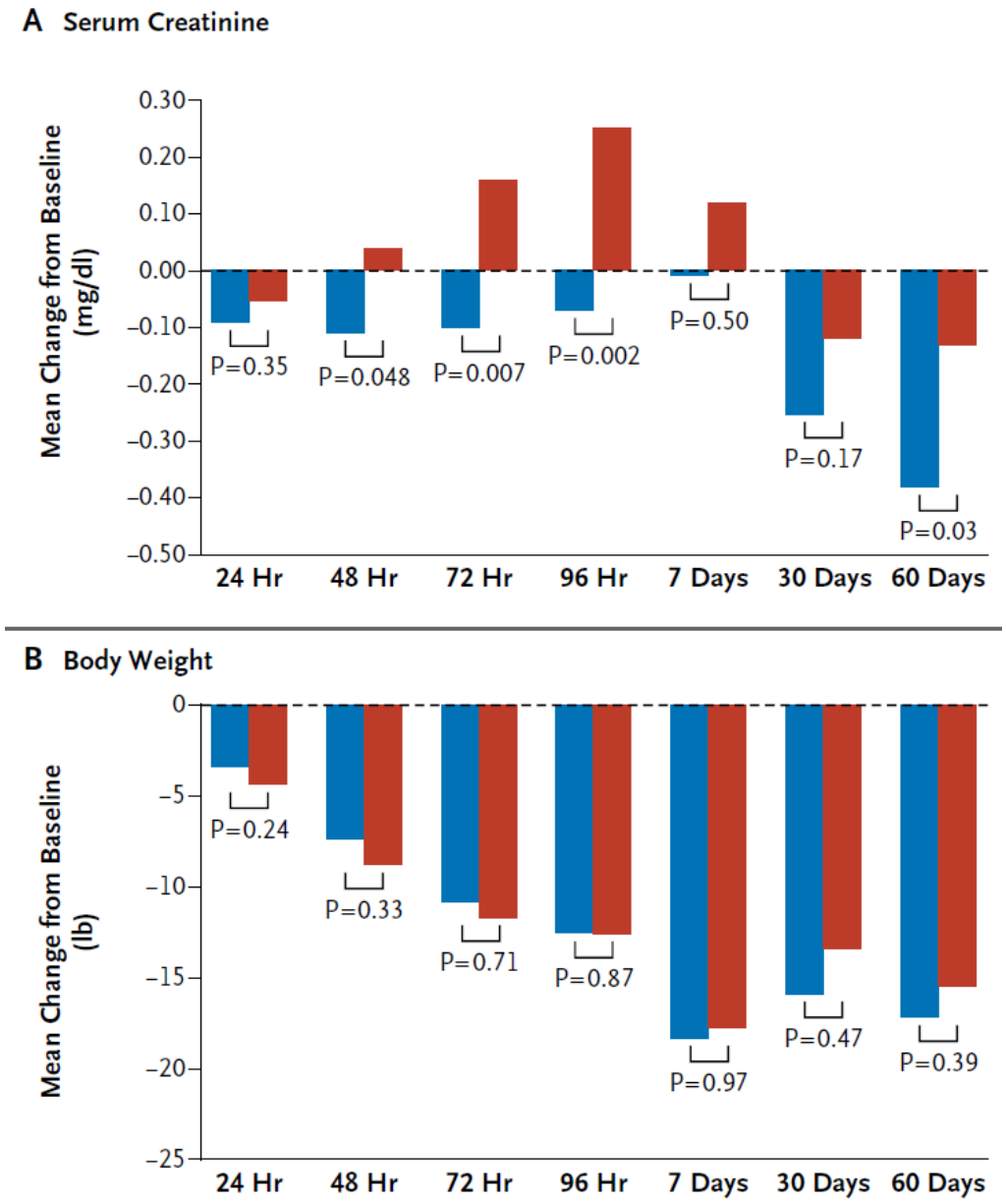


Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).

Primary Endpoint: changes in weight and serum creatinine
UF and SPT: comparable decongestion, WRF only with UF

[Bart BA. New Engl J Med 2012; 367: 2296]



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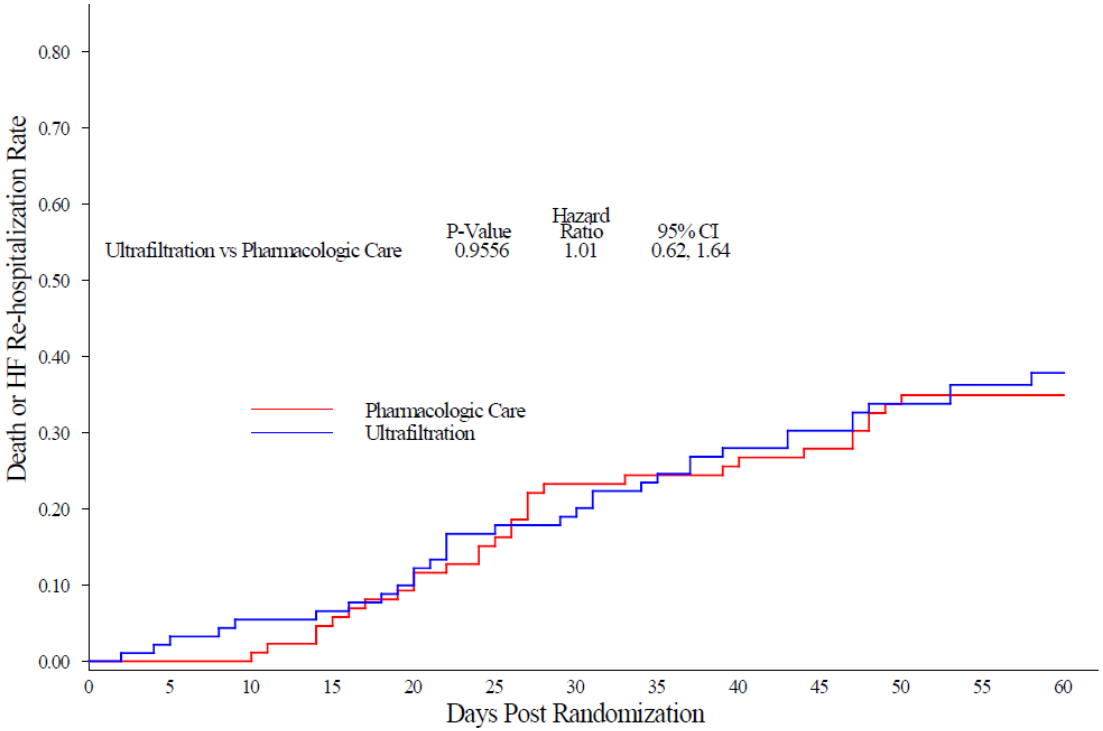
The CARRESS-HF Trial



UF and SPT: comparable outcomes

[Bart BA. New Engl J Med 2012; 367: 2296]

Comparing UNLOAD with CARRESS-HF

Table I. Baseline characteristics of the patients in the UNLOAD and CARRESS-HF trials

Characteristics	UNLOAD		CARRESS-HF	
	Ultrafiltration	Pharmacologic therapy	Ultrafiltration	Pharmacologic therapy
Age (y)*	62	63	69	66
Weight (lb)*	222	211	207	234
Ejection fraction (%)	NR	NR	30	35
Ejection fraction ≤40% (%)	71	70	NR	NR
Hospitalization for heart failure in previous year (no./total no.)	89/100	90/100	70/93	73/92
Ischemia as cause of heart failure (%)†	56	48	66	48
History of diabetes (%)	50	49	61	63
ACE inhibitor or ARB received before hospitalization (%)	63	68	52	49
Aldosterone antagonist received before hospitalization (%)	21	22	21	17
Dose of furosemide-equivalent diuretic received before hospitalization (mg/d)*	129	119	120	125
Blood urea nitrogen (mg/dl) *	32	33	48.7	50.5
Serum creatinine level (mg/dL)*	1.5	1.5	1.9	2.09
NT-proBNP (pg/mL)	NR	NR	5013	4007
B-type natriuretic peptide level (pg/mL)	1256	1309	NR	NR

[Kazory A. Am Heart J 2013; 166: 799-803]

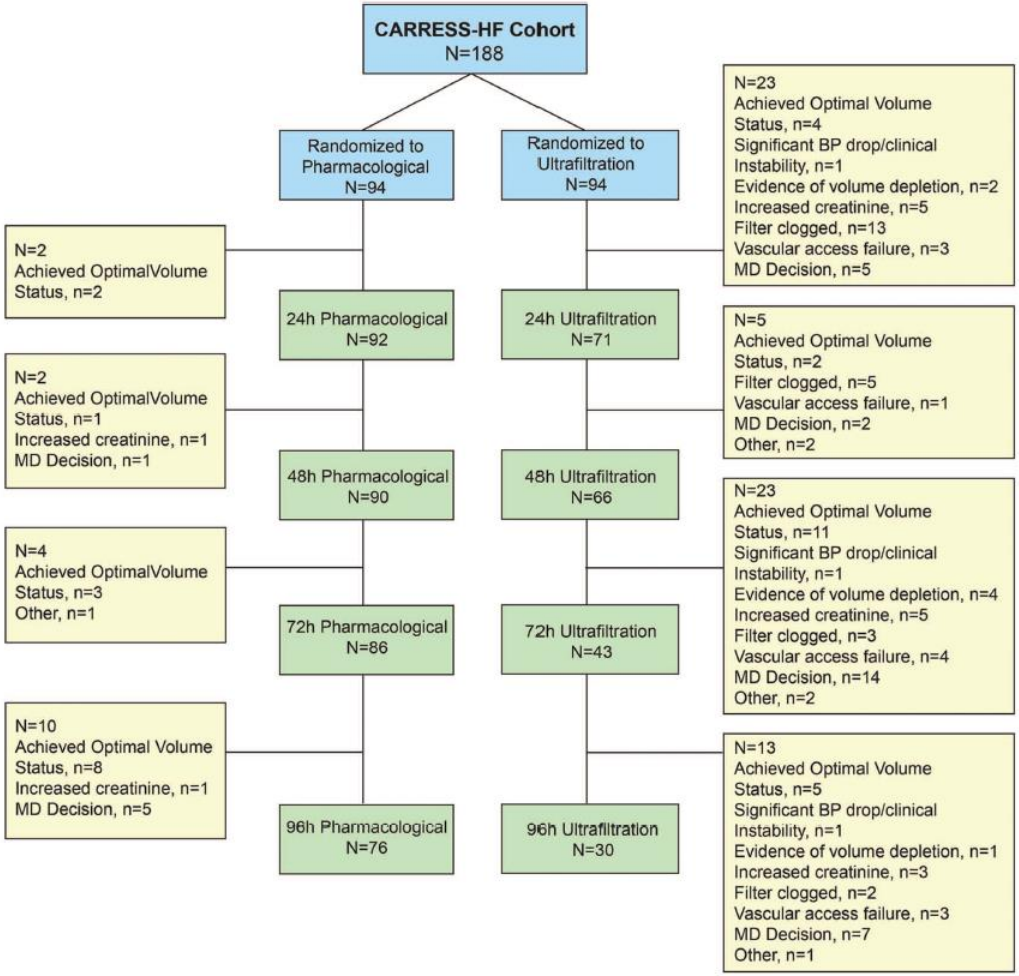
Comparing UNLOAD with CARRESS-HF

Table II. The design and findings of the two major studies on ultrafiltration for acute decompensated heart failure

	Recruitment period	Target population	No. of patients	Control group	Primary efficacy end point(s)	Primary safety end point(s)	Weight loss in the UF group	Weight loss in control group	Change in serum creatinine in UF group	Change in serum creatinine in control group	Comment
UNLOAD	June 2004-July 2005	ADHF and volume overload	200	Intravenous diuretics	Weight loss and change in dyspnea	Change in serum creatinine, BUN, and serum electrolytes, and episodes of hypotension	5 kg at 48 h	3.1 kg at 48 h	Increased by >0.3 mg/dL in 26.5% at 48 h	Increased by >0.3 mg/dL in 20.3% at 48 h	Significant reduction in 90-d rehospitalization rate in UF group, no difference in adverse events between the 2 groups, funded by CHF Solutions
CARRESS-HF	June 2008-January 2012	ADHF and worsening renal function	184	Stepped pharmacologic therapy	Changes in serum creatinine level and weight as a bivariate end point		5.7 kg at 96 h	5.5 kg at 96 h	Increased by 0.23 mg/dL at 96 h	Decreased by 0.04 mg/dL at 96 h	Higher rate of adverse events in the UF group, funded by NIH

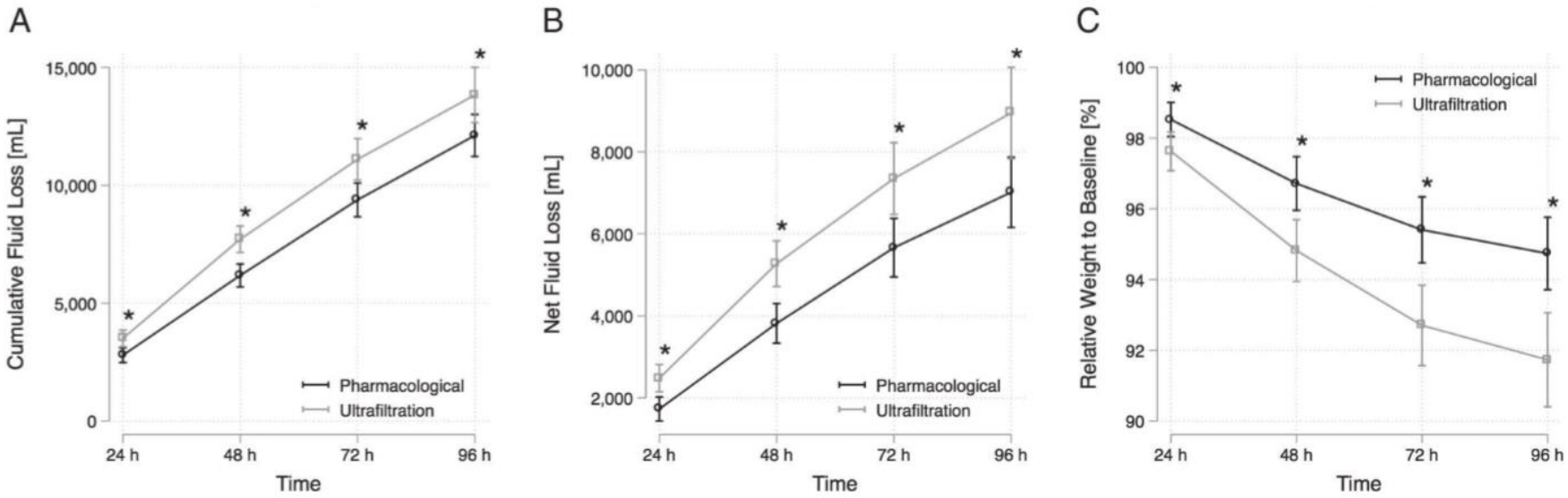
[Kazory A. Am Heart J 2013; 166: 799-803]

The CARRESS-HF Trial (per-protocol analysis)



[Grodin JL, Europ J Heart Fail 2018doi:10.1002/ejhf.1158]

The CARRESS-HF Trial (per-protocol analysis)



In contrast to the original trial (intention-to-treat), UF was associated with significantly more fluid loss and weight reduction

[Grodin JL, Europ J Heart Fail 2018doi:10.1002/ejhf.1158]

Pooling the Data

(Meta-Analysis)

PRISMA Protocol

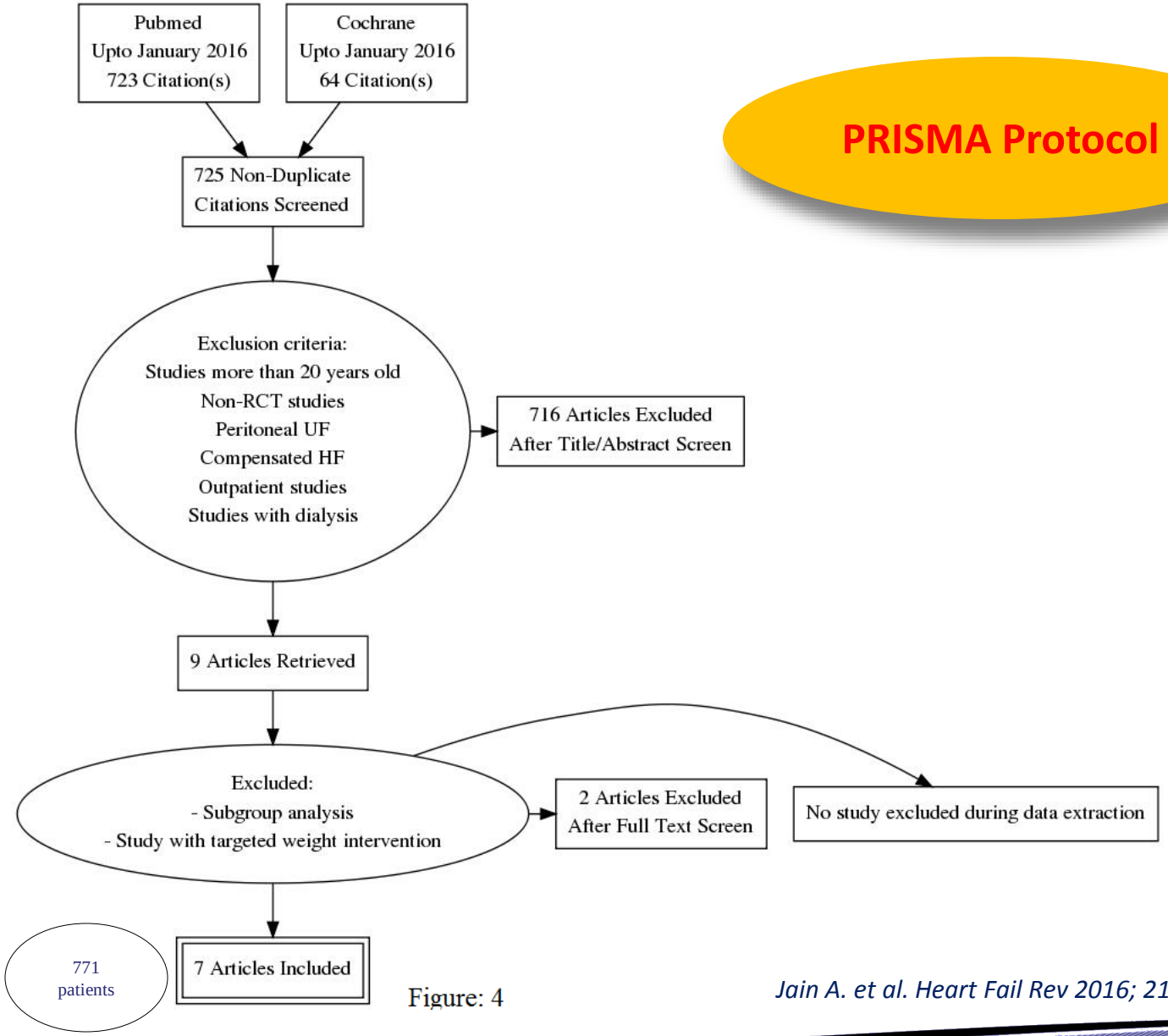


Figure: 4

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Table-1: General characteristics of the included studies

	RAPID-CHF	UNLOAD	ULTRADISCO	Hanna et al.	CARRESS-HF	CUORE	AVOID-HF
Year of Publication	2005	2007	2011	2012	2012	2014	2016
Country	US	US	Italy	US	US - Canada	Italy	US
Number of Centers	6	28	1	1	22	2	30
Number of Patients	40 (20 UF, 20 PT)	200 (100 UF, 100 PT)	30 (15 UF, 15 PT)	36 (17 UF, 19 PT)	188 (94 UF, 94 PT)	56 (27 UF, 29 PT)	224 (110 UF, 114 PT)
Age (years)	67.5 UF, 69.5 PT	62 UF, 63 PT	72 UF, 66 PT	60 UF, 59 PT	69 UF, 66 PT	75 UF, 73 PT	67 UF, 67 PT
Male Gender (%)	70 UF, 70 PT	70 UF, 68 PT	87 UF, 87 PT	84 UF, 76 PT	78 UF, 72 PT	81 UF, 83 PT	69 UF, 73 PT
Weight (kg)	NR	101 UF, 96 PT	74 UF, 83 PT	93 UF, 98 PT	94 UF, 106 PT	83 UF, 89 PT	110 UF, 111 PT
LVEF (%)	69 UF, 78 PT†	71 UF, 70 PT †	34 UF, 30 PT	19 UF, 18 PT	30 UF, 35 PT	32 UF, 32 PT	36 UF, 37 PT

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Table-1: General characteristics of the included studies

	RAPID-CHF	UNLOAD	ULTRADISCO	Hanna et al.	CARRESS-HF	CUORE	AVOID-HF
Baseline SCr (mg/dL)	1.6 UF, 1.8 PT	1.5 UF, 1.5 PT (Scr > 3 mg/dL excluded)	2.2 UF, 1.9 PT (Scr > 3.0 mg/dL excluded)	55 UF, 51 PT ϕ (eGFR < 15 excluded)	1.9 UF, 2.09 PT (Scr > 3.5 mg/dL excluded)	1.7 UF, 1.9 PT (Scr > 3 mg/dL excluded)	1.5 UF, 1.6 PT (Scr ≥ 3 mg/dL excluded)
Diabetes (%)	35 UF, 53 PT	50 UF, 49 PT	40 UF, 60 PT	37 UF, 30 PT	61 UF, 63 PT	59 UF, 45 PT	62 UF, 64 PT
CAD (%)	45 UF, 40 PT ¶	56 UF, 48 PT	60 UF, 60 PT	21 UF, 30 PT *	70 UF, 51 PT *	59 UF, 55 PT *	64 UF, 61 PT
HTN (%)	60 UF, 65 PT	74 UF, 74 PT	20 UF, 60 PT	42 UF, 53 PT	NR	48 UF, 66 PT	88 UF, 83 PT
Primary Endpoint	Weight loss	Weight loss and dyspnea §	Change in clinical, biohumoral, and hemodynamic parameters	Time for PCWP to be kept at ≤ 18 mmHg	Change in Scr and weight	Incidence of HF rehospitalization	Time to first HF event
Follow Up (months)	1	3	[36 hours]	3	2	12	3

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Endpoints of Interest

Efficacy – Decongestion

- Weight Change
- Fluid Removal

Safety – Renal Function

- Change in Serum Creatinine

Clinical Outcomes

- HF Re-hospitalization
- Mortality

Adverse Events

- Infection
- Bleeding

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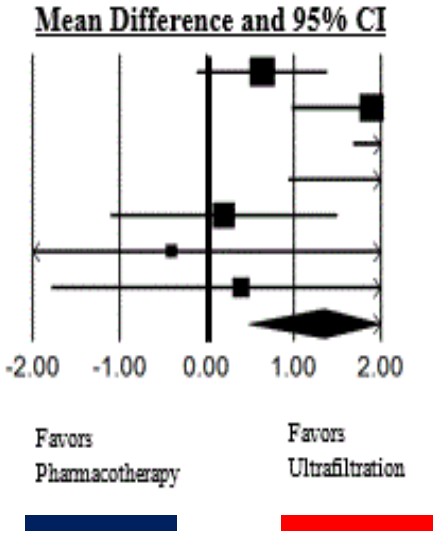
A: WEIGHT CHANGE

Study	Ultrafiltration Mean	SD	Total	Pharmacotherapy Mean	SD	Total	WMD [95% CI]	p-Value	Weight
RAPID-CHF	2.5	1.2	20	1.86	1.2	20	0.64 [-0.10, 1.38]	0.09	21.89
UNLOAD	5.0	3.1	100	3.1	3.5	100	1.9 [0.98, 2.82]	0.00	20.19
Hanna et al.	4.7	3.5	19	1.0	2.5	17	3.7 [1.69, 5.71]	0.00	10.82
ULTRADISCO	9.1	1.7	15	6.9	1.8	15	2.2 [0.95, 3.45]	0.00	16.85
CARRESS-HF	5.7	3.9	94	5.5	5.1	94	0.2 [-1.10, 1.50]	0.76	16.43
CUORE	7.5	5.6	27	7.9	9.0	29	-0.4 [-4.36, 3.56]	0.84	4.02
AVOID-HF	10.7	7.2	110	10.3	9.2	111	0.4 [-1.78, 2.58]	0.72	9.8
Random							1.35 [0.49, 2.21]	0.00	

Heterogeneity: Q = 16.20; df = 6 (p = 0.013); $Tau^2 = 0.74$; $I^2 = 62.97\%$
Egger's Test: p (2-tailed) = 0.80
Overall Z = 3.07



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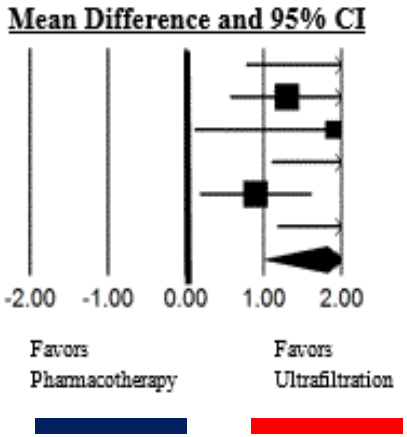
B: FLUID REMOVAL

	Ultrafiltration			Pharmacotherapy					
Study	Mean	SD	Total	Mean	SD	Total	WMD [95% CI]	p-Value	Weight
RAPID-CHF	8.42	3.65	20	5.38	3.65	20	3.04 [0.78, 5.30]	0.01	9.49
UNLOAD	4.60	2.61	100	3.30	2.61	100	1.3 [0.58,2.02]	0.00	29.27
ULTRADISCO	9.70	2.90	15	7.80	2.00	15	1.9 [0.12,3.68]	0.04	13.28
Hanna et al.	5.22	3.41	19	2.17	2.38	17	3.05 [1.11,4.99]	0.00	11.83
CARRESS-HF	4.70	2.60	94	3.80	2.40	94	0.9 [0.18,1.62]	0.01	29.43
AVOID-HF	12.91	10.70	110	8.91	10.70	111	4.0 [1.18,6.82]	0.01	6.69
Random							1.81 [1.01,2.62]	0.00	



Heterogeneity: Q = 10.30; df = 5 (p = 0.07); $Tau^2 = 0.44$; $I^2 = 51.44\%$
Egger's Test: p (2-tailed) = 0.01
Overall Z = 4.43

Figure: 2

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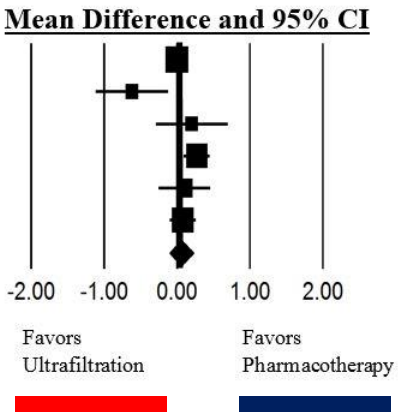
CHANGE IN CREATININE

	Ultrafiltration			Pharmacotherapy					
Study	Mean	SD	Total	Mean	SD	Total	WMD[95% CI]	p-Value	Weight
UNLOAD	0.1	0.4	69	0.1	0.4	75	0.00 [-0.13, 0.13]	1.00	25.63
ULTRADISCO	-0.55	0.75	15	0.07	0.63	15	-0.62 [-1.12, -0.12]	0.01	8.05
Hanna et al.	0.2	0.7	19	0	0.8	17	0.20 [-0.29, 0.69]	0.42	8.19
CARRESS-HF	0.23	0.7	94	-0.04	0.53	94	0.27 [0.09, 0.45]	0.00	22.53
CUORE	0.1	0.63	27	0	0.7	29	0.10 [-0.25, 0.45]	0.58	12.78
AVOID-HF	0.13	0.88	110	0.05	0.3	111	0.08 [-0.09, 0.25]	0.36	22.83
Random							0.06 [-0.11, 0.22]	0.48	



Heterogeneity: Q = 13.73; df = 5 (p = 0.017); Tau^2 = 0.023; I2 = 63.57%
Egger's Test: p (2-tailed) = 0.65
Overall Z = 0.70

Figure: 3

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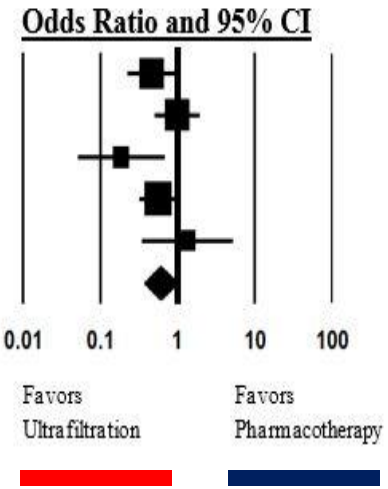
A: HEART FAILURE REHOSPITALIZATION

Study	Ultrafiltration		Pharmacotherapy				
	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					0.60[0.37,0.98]	0.04	



Heterogeneity: Q = 7.26; df = 4 (p = 0.12); Tau^2 = 0.13; I^2 = 44.90%

Egger's Test: p (2-tailed) = 0.82

Overall Z = -2.05

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B: MORTALITY

Study	Ultrafiltration		Pharmacotherapy				
	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					1.03 [0.68, 1.57]	0.89	

Heterogeneity: Q = 2.34; df = 5 (p = 0.80); $Tau^2 = 0.00$; $I^2 = 0.00\%$
Egger's Test: p (2-tailed) = 0.99
Overall Z = 0.14

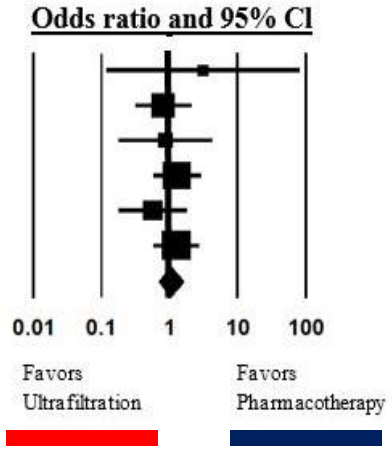

Figure: 4

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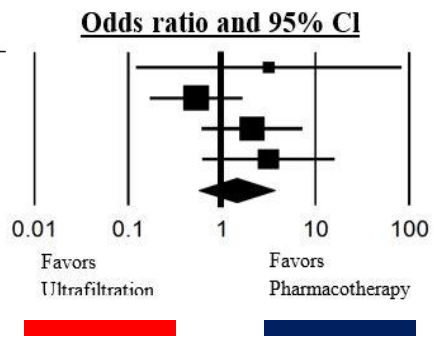
ADVERSE EVENTS (INFECTION)

Study	Ultrafiltration		Pharmacotherapy		M-H Odds Ratio	p-Value	Weight
	Events	Total	Events	Total			
BART RAPID-CHF	1	20	0	20	3.15 [0.12, 82.16]	0.49	7.35
COSTANZO UNLOAD	5	100	9	100	0.53 [0.17, 1.65]	0.27	36.49
BART CARESS-HF	8	94	4	94	2.09 [0.61, 7.20]	0.24	32.99
COSTANZO AVOID-H	6	110	2	111	3.14 [0.62, 15.93]	0.17	23.17
Random					1.44 [0.57, 3.64]	0.44	

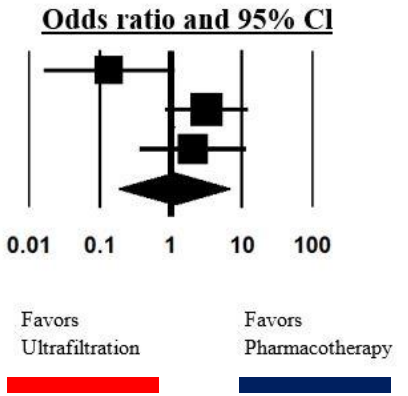
Heterogeneity: Q = 4.39; d.f. = 3 (p = 0.22); Tau^2 = 0.28; I2 = 31.68%
Egger's Test: p (2-tailed) = 0.47; d.f. = 2
Overall Z = 0.77



ADVERSE EVENTS (BLEEDING)

Study	Ultrafiltration		Pharmacotherapy		M-H Odds Ratio	p-Value	Weight
	Events	Total	Events	Total			
COSTANZO UNLOAD	1	100	7	100	0.13 [0.02, 1.11]	0.06	28.77
BART CARESS-HF	9	94	3	94	3.21 [0.84, 12.26]	0.09	37.90
COSTANZO AVOID-HF	4	110	2	111	2.06 [0.37, 11.47]	0.41	33.33
Random					1.11 [0.19, 6.64]	0.91	

Heterogeneity: Q = 6.62, d.f. = 2 (p = 0.04); Tau^2 = 1.73; I^2 = 69.77%
Egger's Test: p (2-tailed) = 0.27; d.f. = 1
Overall Z= 0.11



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Ultrafiltration vs. Medical Therapy

Greater Weight Loss

Greater Fluid Removal

?Lower HF-Related Cost

?Lower HF Re-Hospitalization Rate

More Efficient Decongestion

(with no negative impact on renal function, mortality, or adverse events)

Peripheral Ultrafiltration for the Relief From Congestion in Heart Failure (PURE-HF)

Multicenter, prospective, randomized, parallel-group, controlled

Fresenius Medical Care Deutschland GmbH – 11 centers in Germany and Sweden

Actual Study Start Date: November 3, 2017
Actual Study Completion : April 30, 2019
Estimated Study Completion Date: October 31, 2019 (as of May 2019)

Estimated Enrollment: 864 participants (48 participants)

Primary Outcome Measures:

1)Heart Failure Event [within 90 days after discharge]
Heart failure hospitalization or unscheduled outpatient or emergency department treatment with IV loop diuretics or ultrafiltration.
2.Cardiovascular death up to 90 days after randomization

Take Home Message

1) Changes in SCr do not necessarily reflect tubular injury in HF; not an ideal endpoint when used alone.

2) Decongestion should be considered as an Endpoint along with measures of renal function.

3) UF is an efficient option for decongestion in ADHF; changes in SCr should be considered in this context

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