Brigham and Women's Hospital
Founding Member, Mass General Brigham

Brigham Renal Board Review

"Cardiorenal syndrome"

Finnian R. Mc Causland, MBBCh, MMSc, FRCPI
Associate physician
Renal Division, Department of Medicine
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Finnian Mc Causland, MBBCh, MMSc

- University College Dublin, Ireland
- Medicine Residency @ Mater Misericordiae University Hospital, Dublin, Ireland
- Nephrology Specialist Registrar @ Mater Misericordiae University Hospital, Dublin
- Nephrology Fellowship @BWH/MGH
- Assistant Professor of Medicine@ HMS
- Co-Director, Master of Medical Sciences in Clinical Investigation @ HMS
  - Clinical focus: ESRD
  - Research focus: Cardiovascular disease in CKD

Disclosures

- Research Grants from NIDDK, Lexicon, Novartis, AstraZeneca, Satellite Healthcare, and Fifth Eye, paid directly to BWH
- Consulting: GSK, Zydus therapeutics
- Expert Witness: Rubin-Anders Scientific

Outline

- Classification and Epidemiology
- Pathophysiology of CRS 1
- Diagnostic approaches
- Therapeutic approaches
- Summary

Classification (ADQI)

Table 1. Classification of CRS Based on the Consensus Conference of the Acute Dialysis Quality Initiative

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
Type 3 CRS	Acute renocardiac syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia
Type 4 CRS	Chronic renocardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	Secondary CRS	Systemic process resulting in HF and kidney failure	Amyloidosis, sepsis, cirrhosis

Rangaswami et al, Circ (2019)

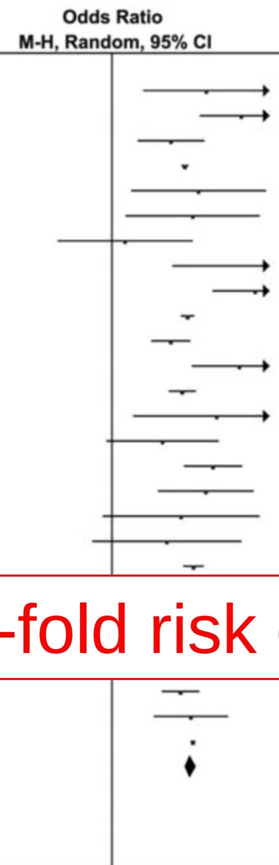
Epidemiology

Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis

Kevin Damman[1*], Mattia A.E. Valente[1], Adriaan A. Voors[1], Christopher M. O'Connor[2], Dirk J. van Veldhuisen[1], and Hans L. Hillege[1,3]

	CKD		no CKD			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Acute Heart Failure							
Madsen	22	44	38	146	0.7%	2.84 [1.42, 5.71]	1994
Akhter (VMAC)	80	215	33	266	1.2%	4.18 [2.65, 6.61]	2004
Aronson	112	284	65	257	1.6%	1.92 [1.33, 2.78]	2004
Smith (NHCP)	8948	17207	11869	36433	3.4%	2.24 [2.16, 2.33]	2005
Anwaruddin (PRIDE)	17	207	13	392	0.6%	2.61 [1.24, 5.48]	2006
Pimenta	13	44	35	239	0.6%	2.44 [1.17, 5.12]	2007
Petretta	15	51	27	102	0.6%	1.16 [0.55, 2.44]	2007
Filippatos	17	145	3	157	0.2%	6.82 [1.95, 23.79]	2007
Lassus (FINN-AKVA)	94	240	28	240	1.2%	4.87 [3.04, 7.81]	2007
Heywood (ADHERE)	3731	75382	949	43083	3.3%	2.31 [2.15, 2.49]	2007
Patel (GWTG-HF)	384	10074	111	5486	2.5%	1.92 [1.55, 2.38]	2008
Klein (OPTIME-CHF)	69	468	19	469	1.0%	4.10 [2.42, 6.93]	2008
Amsalem	759	2145	331	1648	2.9%	2.18 [1.88, 2.53]	2008
Takagi	14	75	8	119	0.4%	3.18 [1.27, 8.02]	2009
Campbell	32	119	21	121	0.8%	1.75 [0.94, 3.26]	2009
Hamaguchi (JCARE-CARD)	300	1139	50	478	1.8%	3.06 [2.22, 4.22]	2009
Kimura	61	388	20	323	1.0%	2.83 [1.67, 4.79]	2009
Manzano-Fernandez	17	66	10	72	0.5%	2.15 [0.90, 5.12]	2009
Martin-Pfitzenmeyer	28	41	34	63	0.5%	1.84 [0.81, 4.19]	2009
Velavan (Euro HF Survey)	704	3398	700	7303	3.1%	2.47 [2.20, 2.76]	2010
Harjola	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Vaz Perez	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Carrasco	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Manzano - Fernandez	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Blair (EVEREST)	353	1055	184	966	2.5%	2.14 [1.74, 2.62]	2011
Tarantini (IS-AHF)	104	592	34	416	1.4%	2.39 [1.59, 3.61]	2011
Kao	11847	163402	13383	433054	3.4%	2.45 [2.39, 2.51]	2011
Subtotal (95% CI)		**277499**		**534640**	**39.5%**	**2.39 [2.25, 2.54]**	
Total events	27998		28483				

Heterogeneity: Tau² = 0.01; Chi² = 60.36, df = 26 (P = 0.0001); I^2 = 57%
Test for overall effect: Z = 28.65 (P < 0.00001)



- Over 1 million individuals
- 32% had CKD

CKD associated with 2.4-fold risk of death in aHF

Eur Heart J (2014) 35, 455–469

WRF (↑SCr 0.3 mg/dL) occurred in 23% of the ~50K patients

Subtotal (95% CI)	**8705**	**29898**	**76.4%**	**1.75 [1.47, 2.08]**
Total events	3376	10762		

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 99.75$, df = 22 ($P < 0.00001$); $I^2 = 78\%$

Test for overall effect: $Z = 6.26$ ($P < 0.00001$)

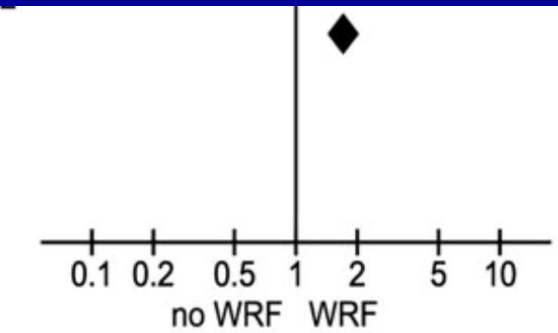
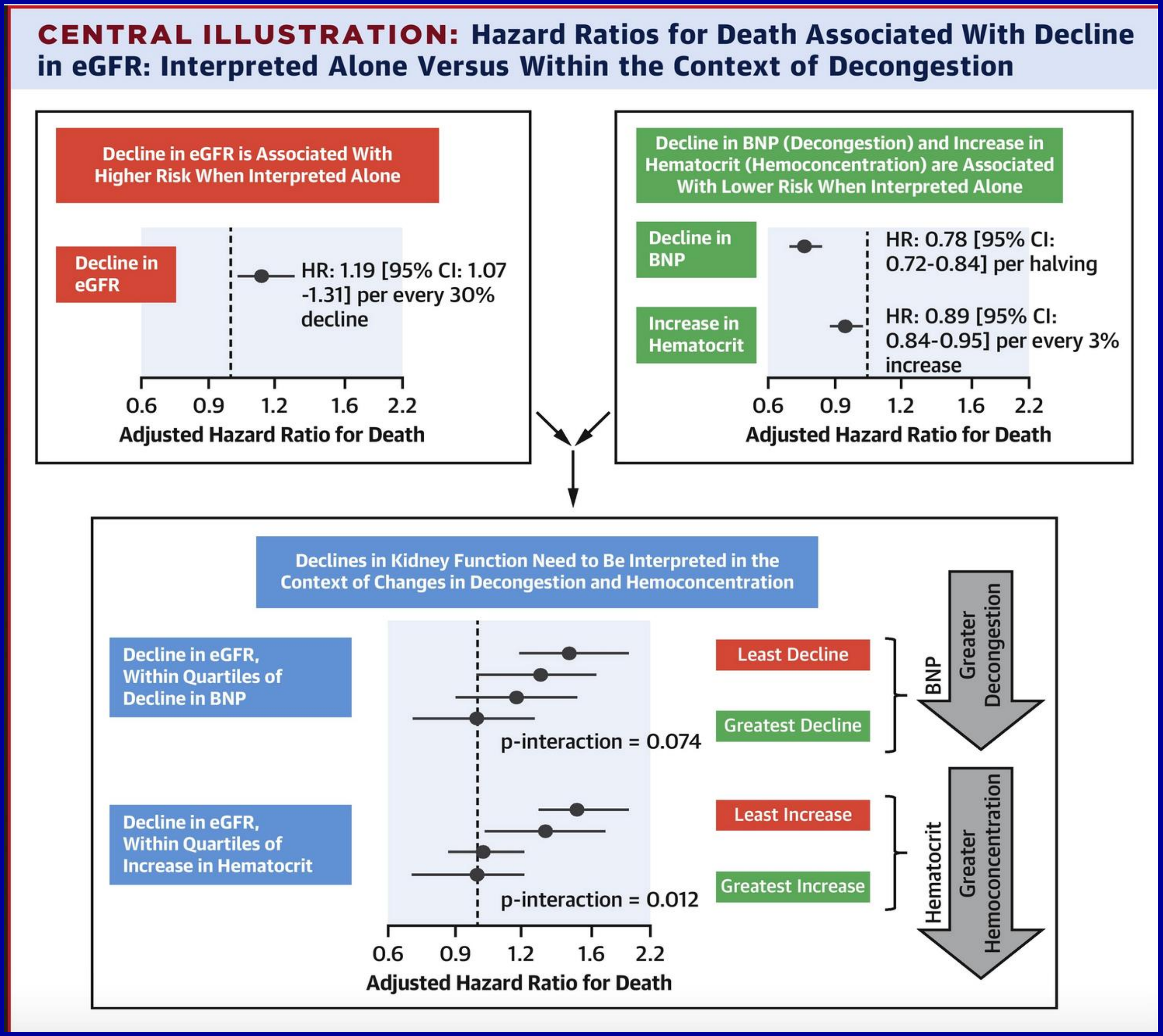


Table 4 Predictors of the occurrence of worsening renal function in meta-analysis across studies

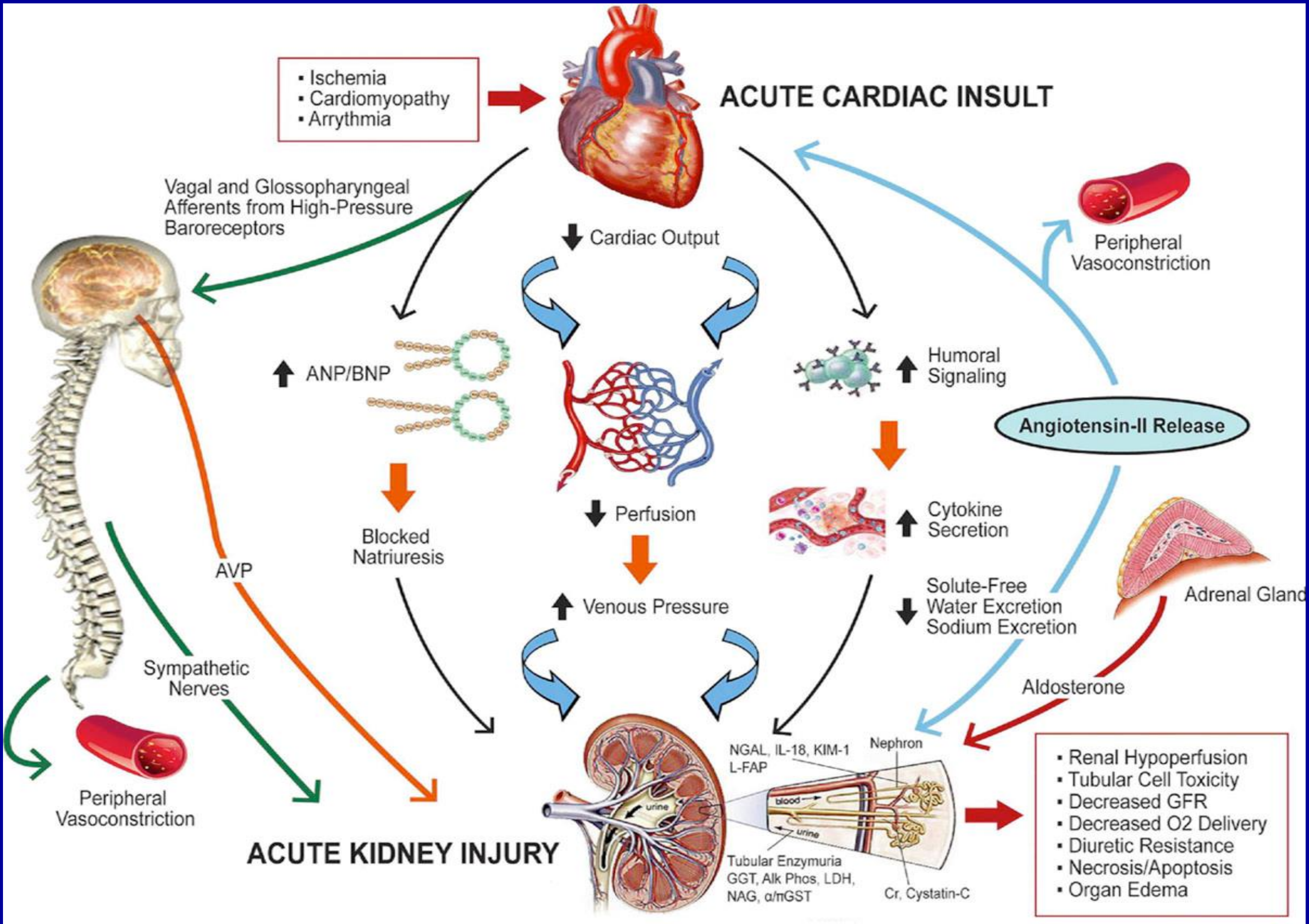
Predictor	Number of studies	Number of patients	Adjusted HR (95% CI)	*P*-value
Baseline CKD[a]	9	5477	2.17 (1.79–2.63)	<0.001
Hypertension	5	11 611	1.36 (1.08–1.71)	0.009
Diabetes	5	11 081	1.23 (1.12–1.36)	<0.001
Age (per 10 years)	5	9993	1.38 (1.14–1.68)	0.001
Diuretic use[b]	5	13 502	1.52 (1.07–2.15)	0.02

Not all WRF is the same



Wendy McCallum et al. *J Am Coll Cardiol HF* 2020; 8:537-547.

Pathophysiology – CRS 1



Importance of Venous Congestion for Worsening of Renal Function in Advanced Decompensated Heart Failure

2009

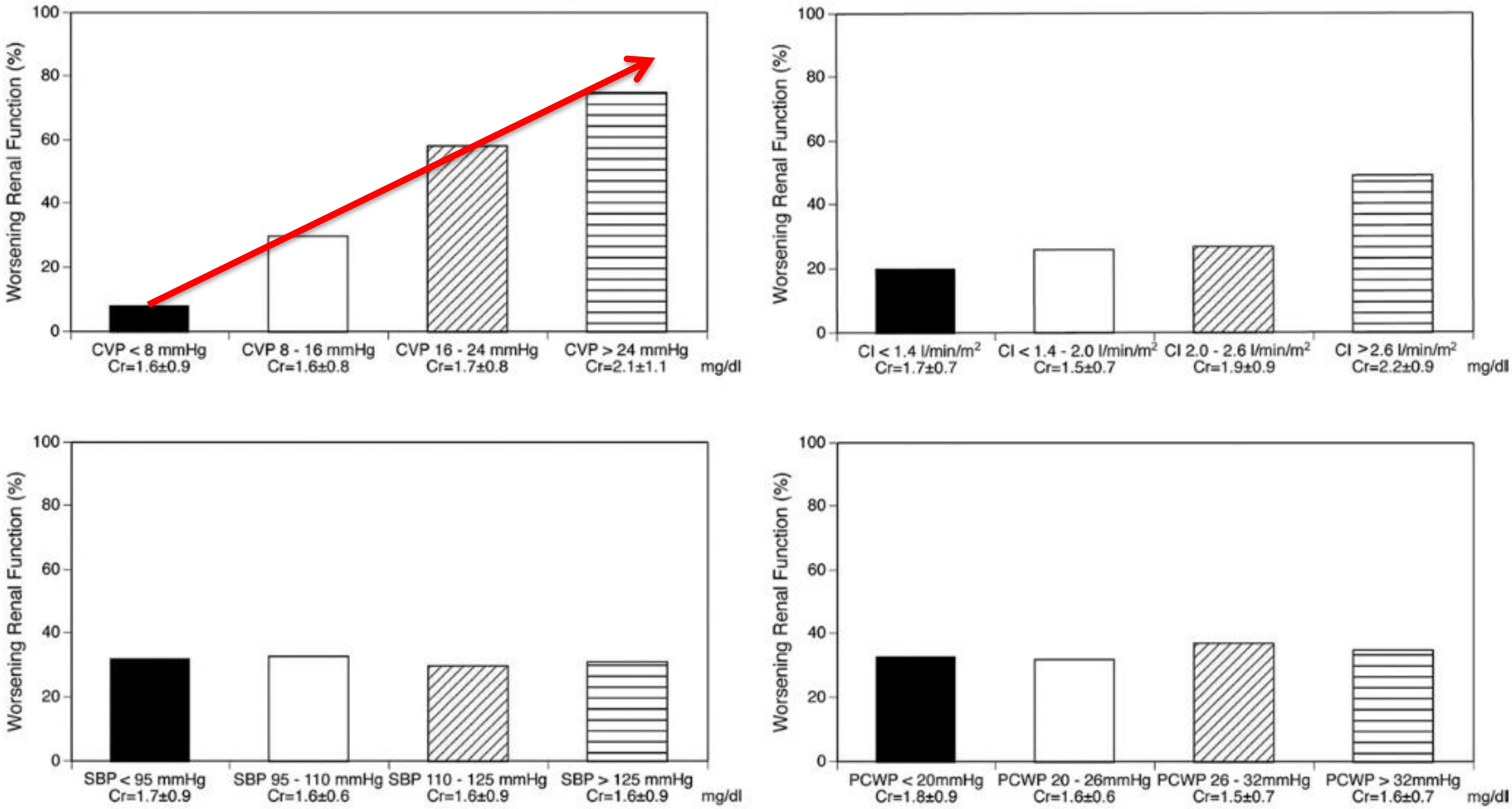


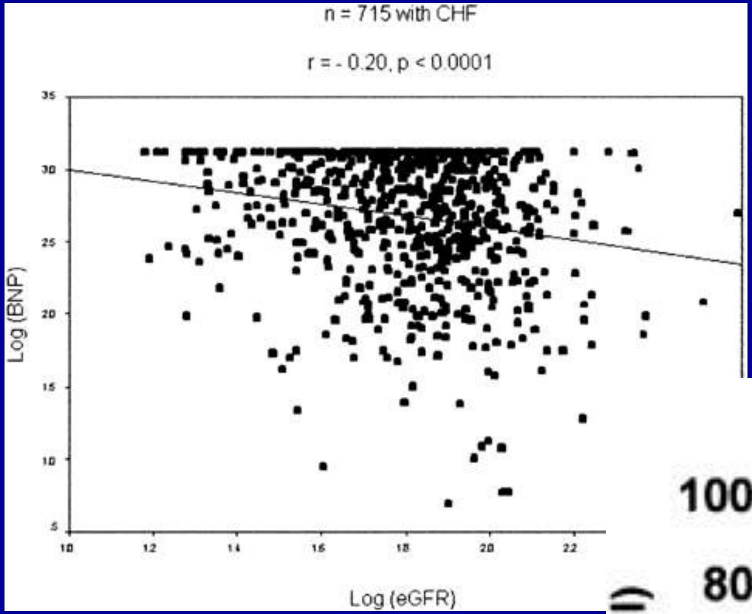
Figure 1 **Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP**

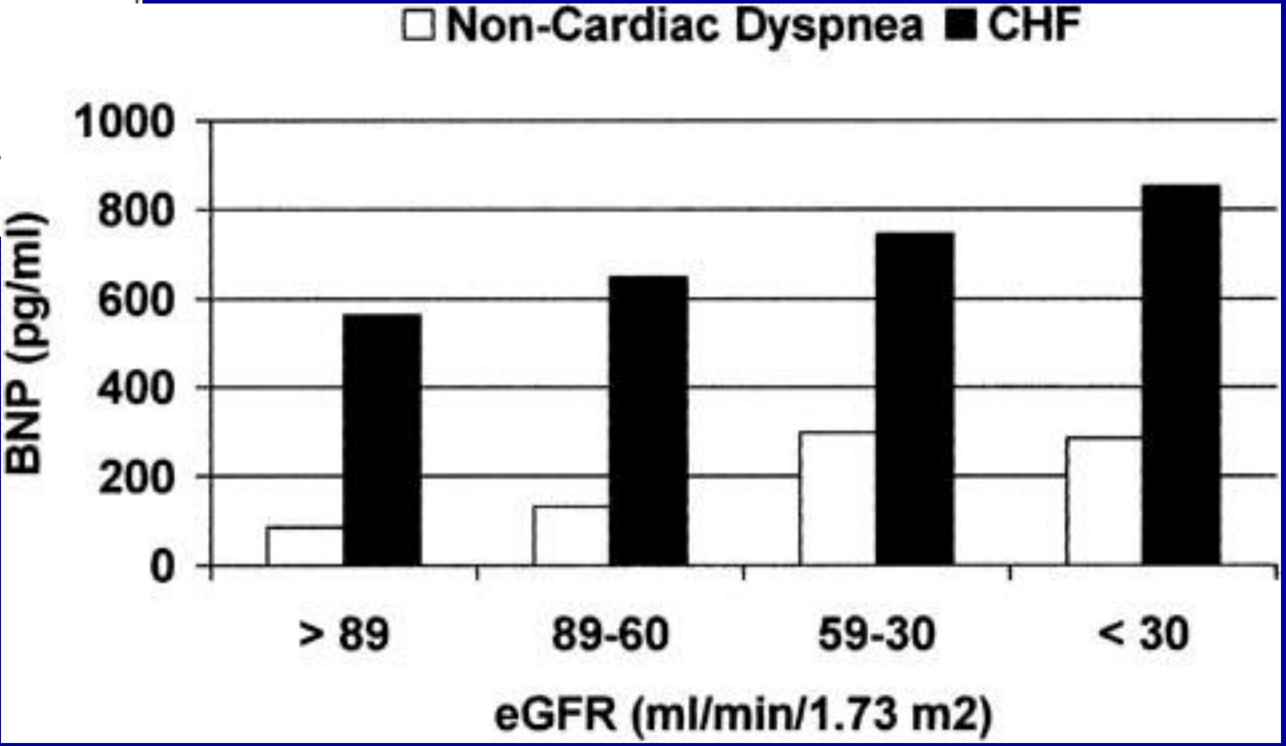
Mullens et al, JACC 2009

Diagnosis

- Biomarkers
  - Cardiac
    - Injury (cTn)
    - Stretch (BNP and NTproBNP)
  - Kidney
    - Glomerular Integrity (CyC, SCr; Albuminuria)
    - Tubular Injury (KIM-1, L-FABP, NGAL, NAG, IL-18…)
- Imaging
  - Cardiac (echo, cardiac MRI)
  - Kidney (U/sound, intra-renal venous flow patterns)
- Volume Status
  - Lung US, IVC diameter, Bioimpedance, intra-abdominal pressure
  - Implantable monitoring devices
  - Invasive haemodynamic monitoring

Interpretation of Cardiac Biomarkers



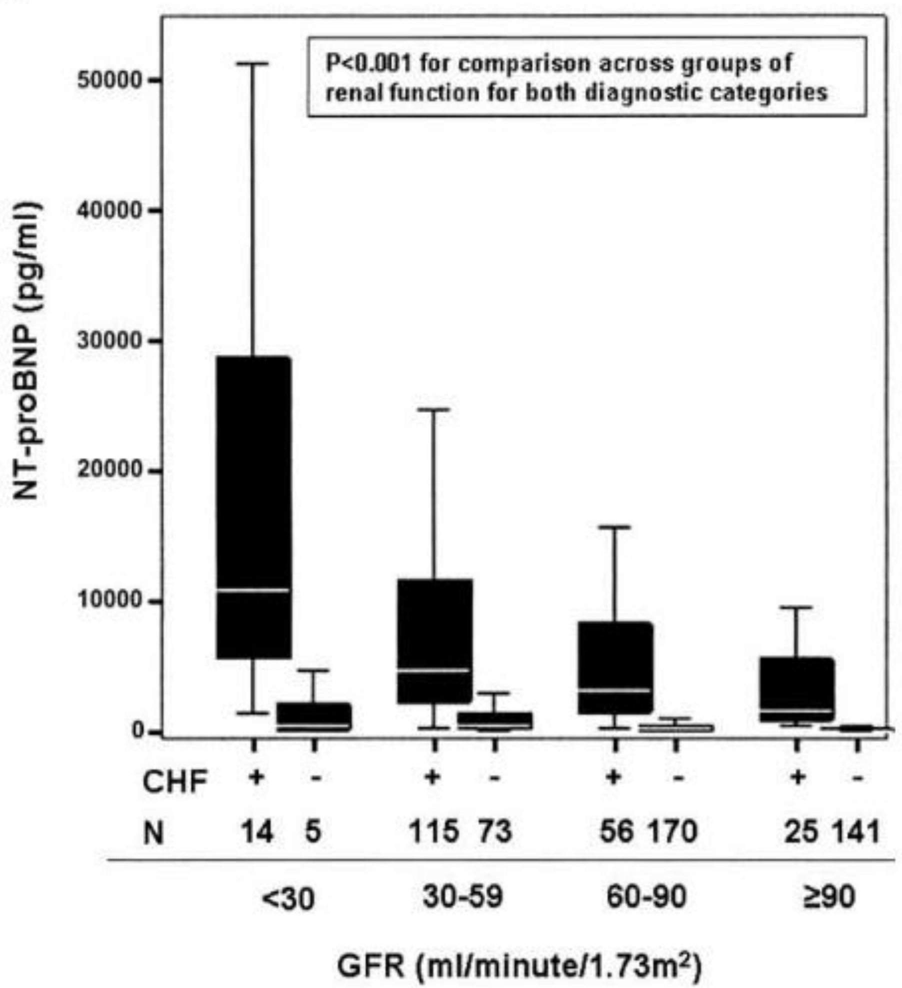


McCullough AJKD 2003

Renal Function, Congestive Heart Failure, and Amino-Terminal Pro-Brain Natriuretic Peptide Measurement

Results From the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study

Anwaruddin, JACC 2005



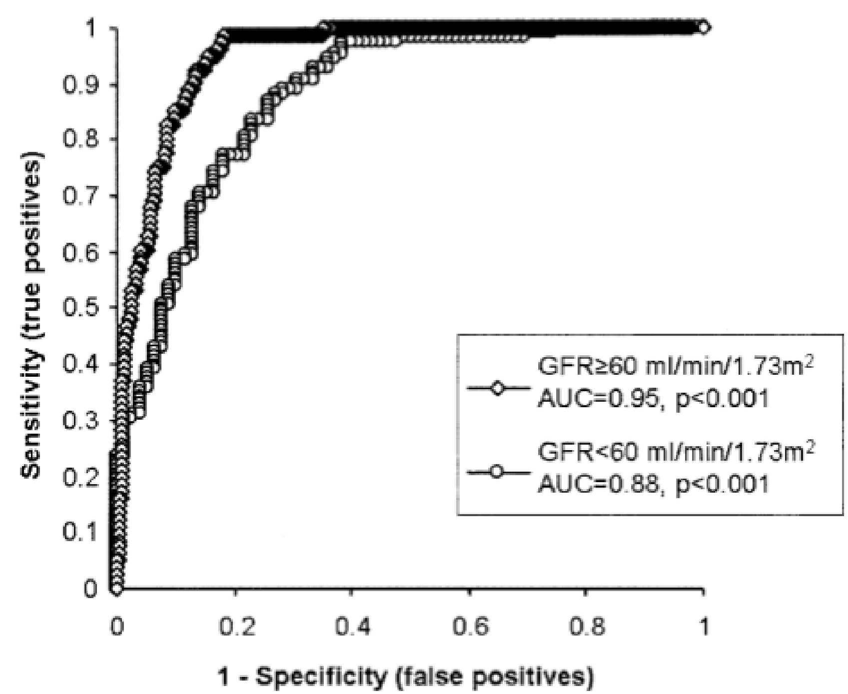
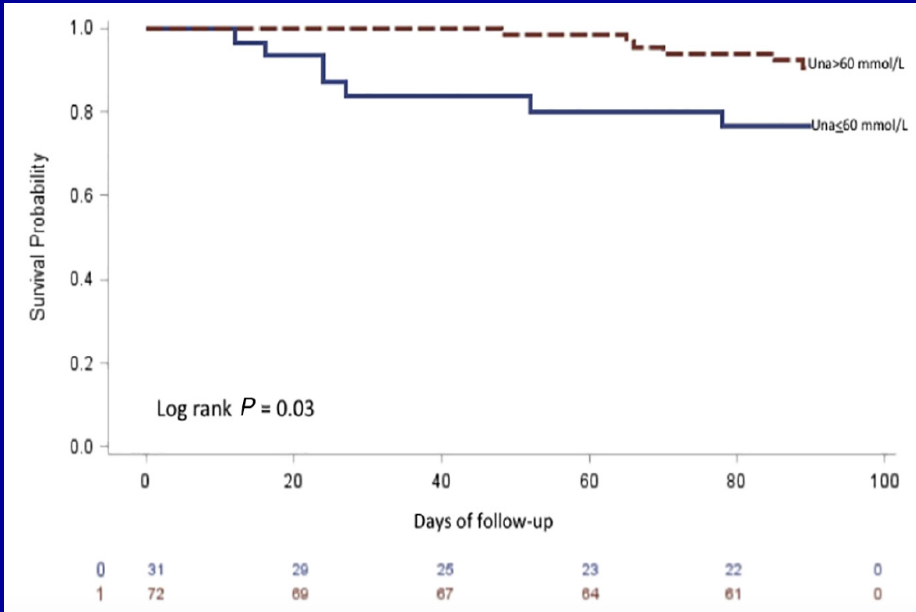


Figure 3. Receiver-operating characteristic curves comparing the performance of amino-terminal pro-brain natriuretic peptide for the diagnosis of acute congestive heart failure in breathless subjects with normal-to-mild renal insufficiency (glomerular filtration rate [GFR] ≥60 ml/min/1.73 m^2, n = 393) versus moderate-to-severely impaired renal function (GFR <60 ml/min/1.73 m^2, n = 206). The difference between the two curves was not statistically significant (p = 0.34). AUC = area under the curve.

Caveats of Kidney Function Assessment

- Creatinine
  - Cardiac cachexia may lead to reduced muscle mass
- eGFR
  - Estimating equations require stable SCr concentration
- Bun/Cr ratio
  - Typically associated with 'pre-renal' states
  - Should not deter initiation of decongestive therapy if needed
- Urine Na
  - Lower UNa strongly associated with adverse outcomes



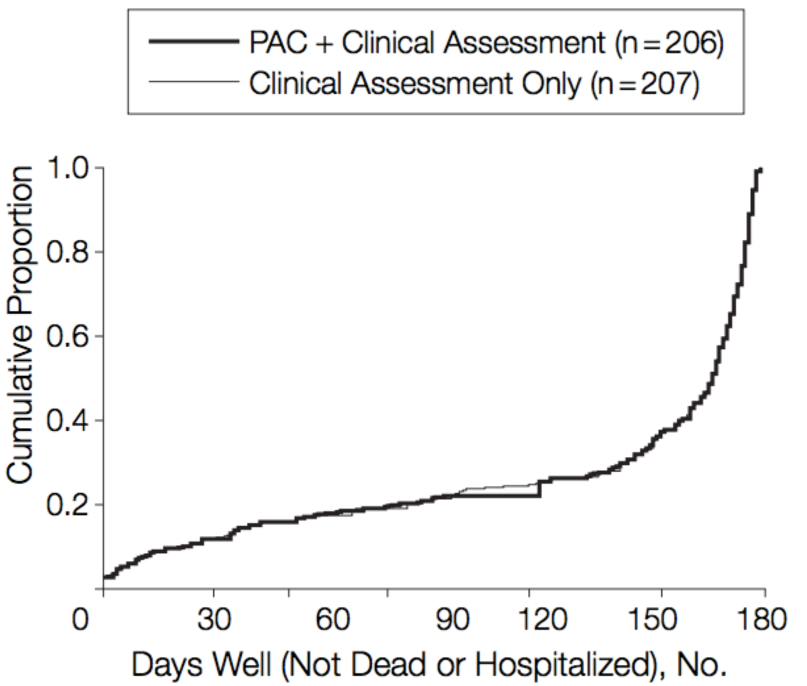
Luk et al, Am Heart J. 203 (2018) 95–100

Haemodynamic Assessment

Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness

The ESCAPE Trial

Figure 2. Cumulative Primary End Point (Days Alive and Out of Hospital)



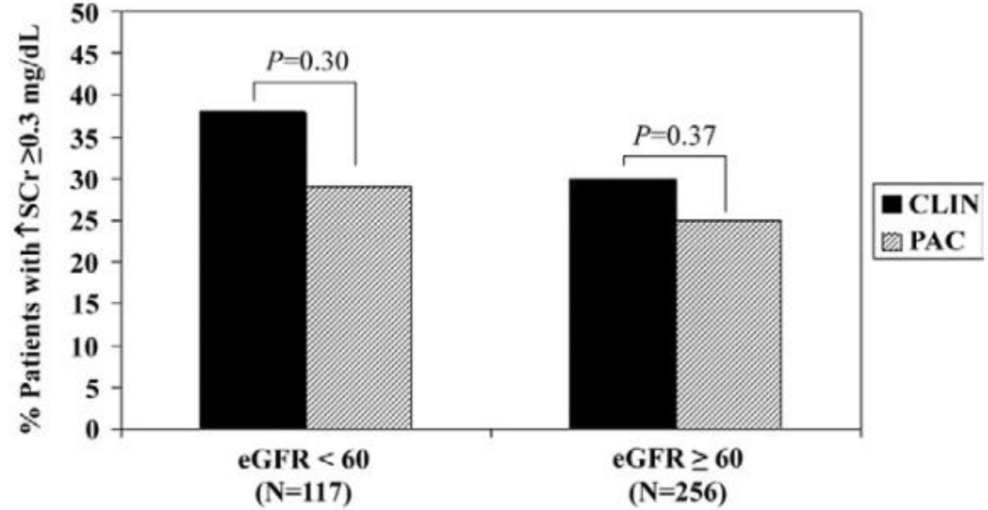


Figure 1 Impact of PAC on Worsening Renal Function in Patients Stratified by Baseline Renal Function

JAMA The Journal of the American Medical Association

N=433; 2005

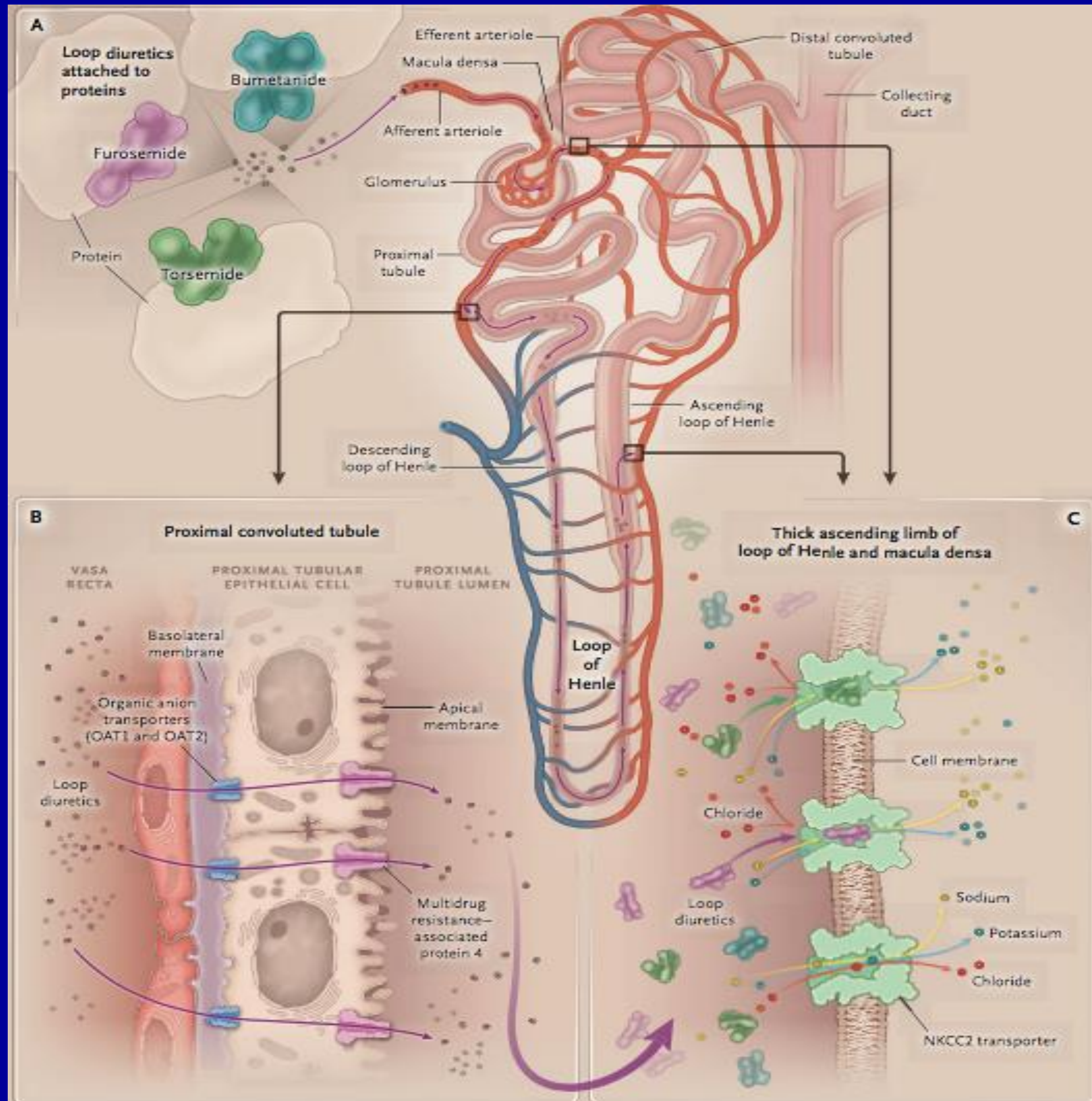
Nohria et al, 2008

Treatment Strategies

- Decongestion
  - Diuretics
    - Given to around 90% of those with acute HF
    - Class 1 recommendation based on expert opinion alone
  - Ultrafiltration
    - Conflicting results
    - Limited data in CRS 1 suggest no benefit
  - Reduce Intra-abdominal pressure
- Neurohormonal modulation
- Inotropes

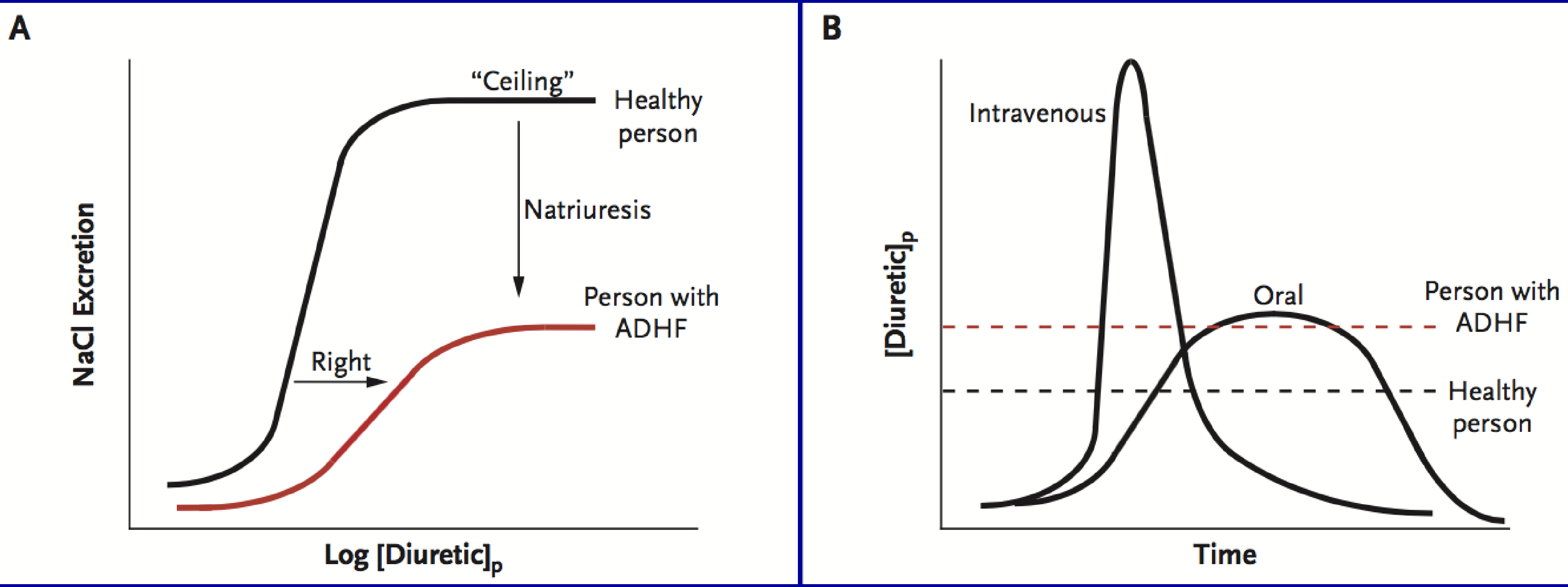
Fonarow et al, Am Heart J. 2007; 153:1021–1028
Yancy et al, Circulation. 2017; 136:e137–e161

Diuretics

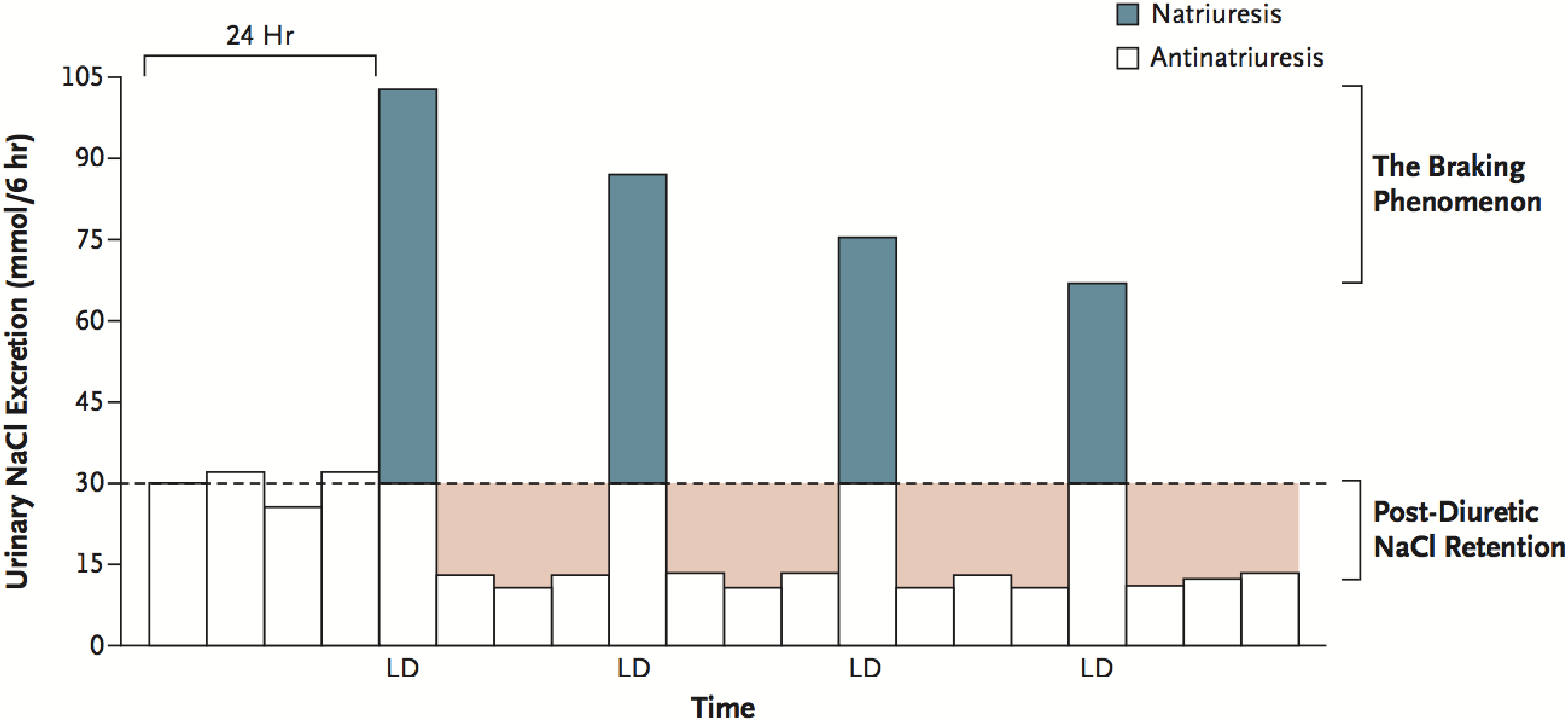


Ellison et al, NEJM, 2017

Diuretic PK in Heart Failure



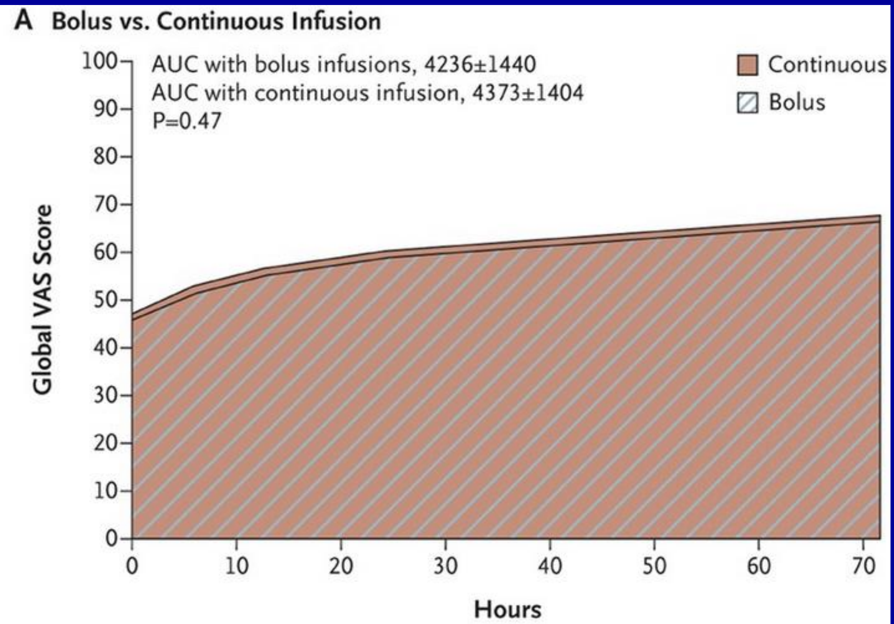
Diuretic PK in Heart Failure

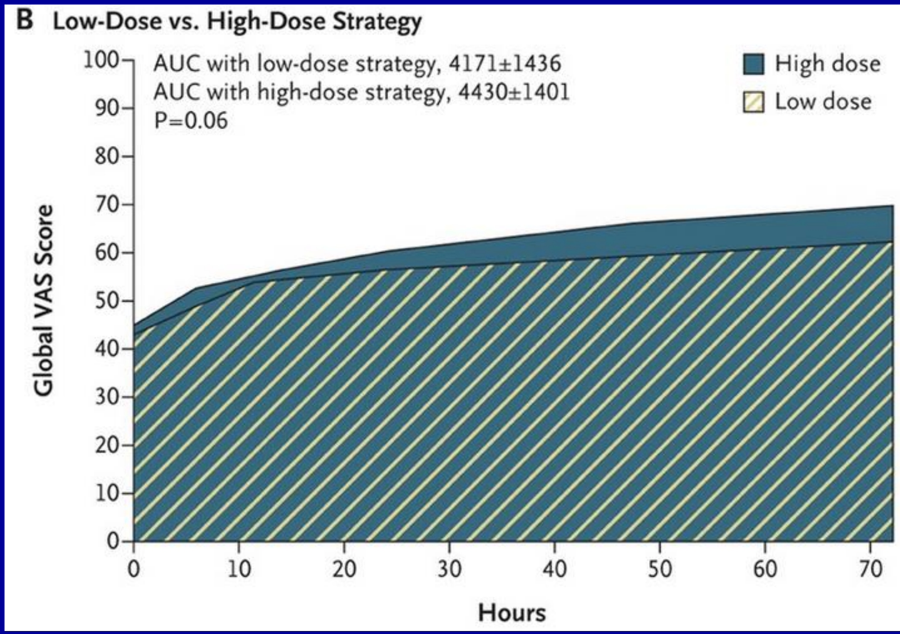


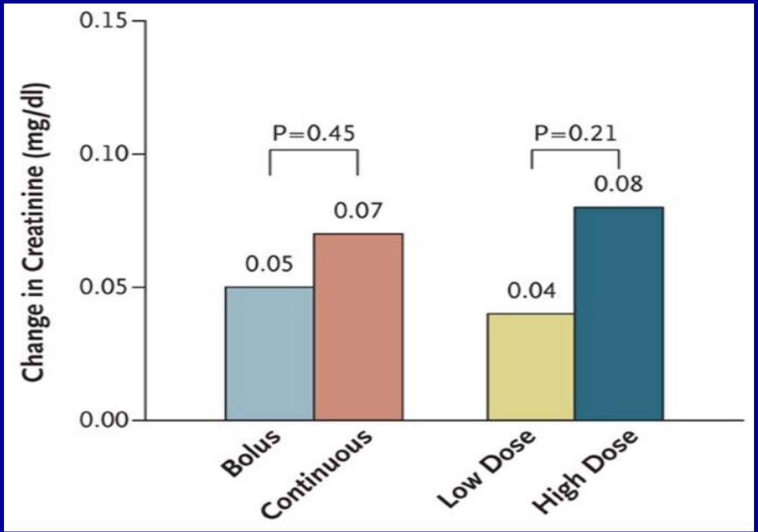
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., et al., for the NHLBI Heart Failure Clinical Research Network*

2011







DOSE-AHF; N=308

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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2011

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	

Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial

Alberto Palazzuoli[1*], Marco Pellegrini[1], Gaetano Ruocco[1], Giuseppe Martini[1], Beatrice Franci[1], Maria Stella Campagna[1], Marilyn Gilleman[1], Ranuccio Nuti[1], Peter A McCullough[2] and Claudio Ronco[3]

CRITICAL CARE
2014

DIUR-AHF; N=82

Table 3 Co-primary endpoints expressed as change from baseline to discharge in values

	Confinuous infusion	Bolus	*P*-value
Δ Serum creatinine (mg/dl)	+0.8 ± 0,4	-0.8 ± 0.3	<0.01
Δ eGFR (mL/min/173 m^2)	-9 ± 7	+5 ± 6	<0.05
Δ BNP (pg/mL)	-576 ± 655	-181 ± 527	0.02

Results are presented as mean ± SD. Δ: mean change from admission to discharge, Difference; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial

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CRITICAL CARE
2014

DIUR-AHF; N=82

Table 4 Secondary endpoints in the continuous infusion versus bolus arm

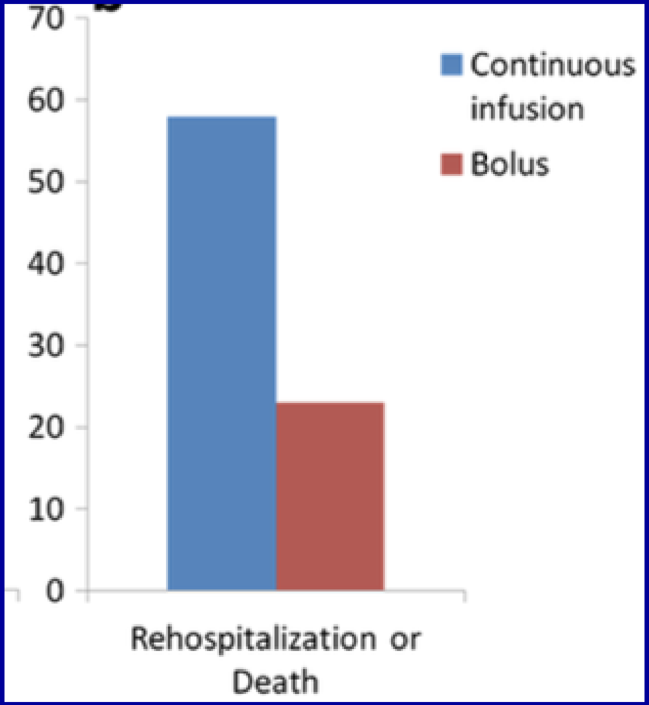
	Continuous infusion	Bolus	*P*-value
Acute kidney injury	22%	15%	0.30
Hypertonic saline solution	33%	18%	0.01
Inotropes infusion	35%	23%	0.02
Length of hospital stay (days), mean ± SD	14 ± 5	11 ± 5	<0.03
Death or rehospitalization	58%	23%	0.001
Weight loss (kg), mean ± SD	-4.1 ± 1,9	-3.5 ± 2.4	0.23

Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial

CRITICAL CARE
2014

Alberto Palazzuoli[1*], Marco Pellegrini[1], Gaetano Ruocco[1], Giuseppe Martini[1], Beatrice Franci[1], Maria Stella Campagna[1], Marilyn Gilleman[1], Ranuccio Nuti[1], Peter A McCullough[2] and Claudio Ronco[3]

DIUR-AHF; N=82

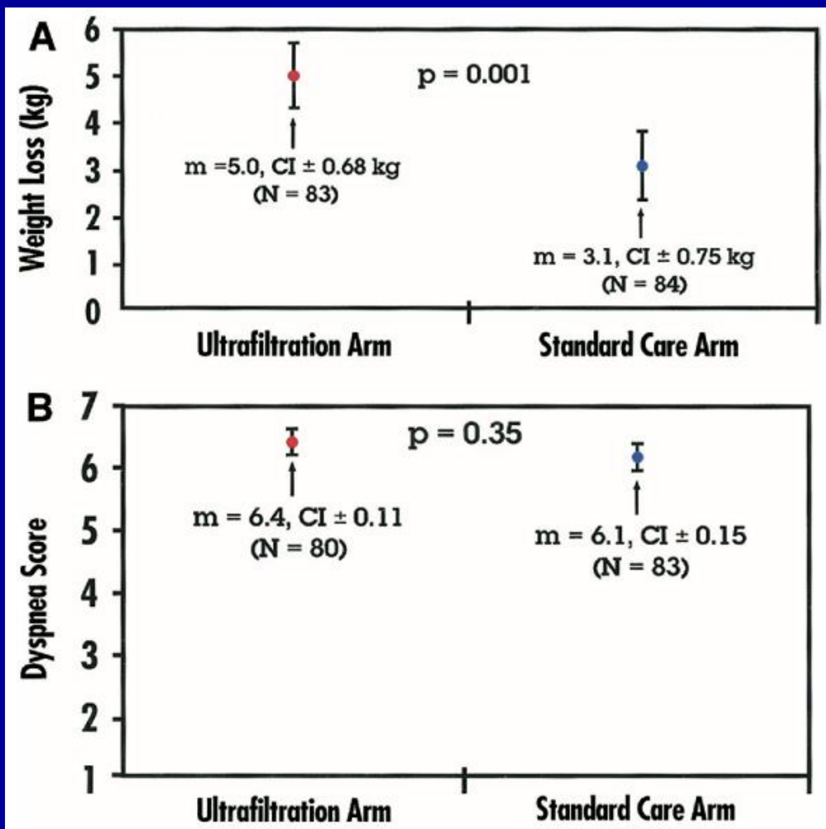


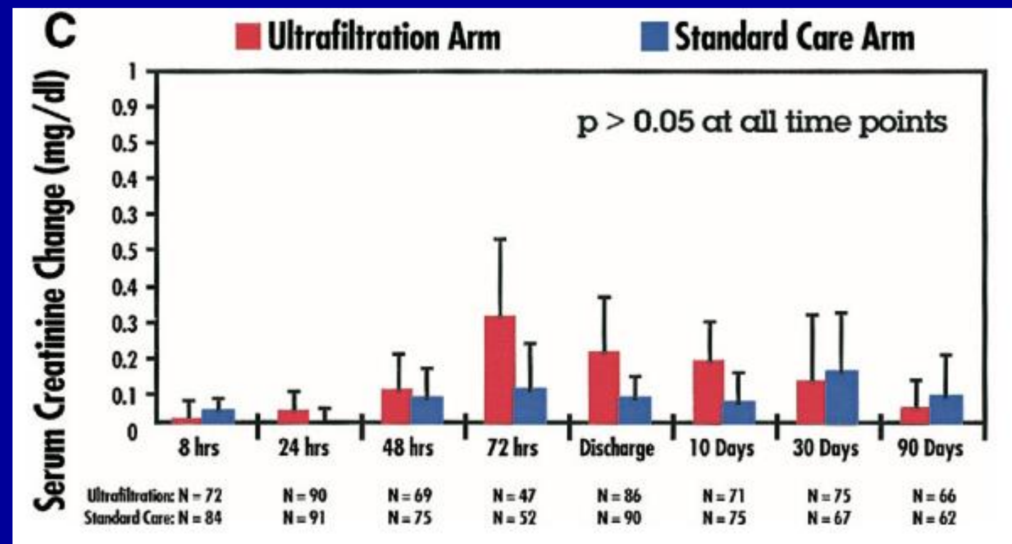
aHR 2.57 (1.01-6.58)

Ultrafiltration

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

Maria Rosa Costanzo, MD, FACC,* Maya E. Guglin, MD, FACC,†
Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§
John R. Teerlink, MD, FACC,|| Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,#
Erika D. Feller, MD, FACC,** Garrie J. Haas, MD, FACC,†† Allen S. Anderson, MD, FACC,‡‡
Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators





UNLOAD; N=200; JACC 2007

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

CARRESS-HF; N=188; 2012

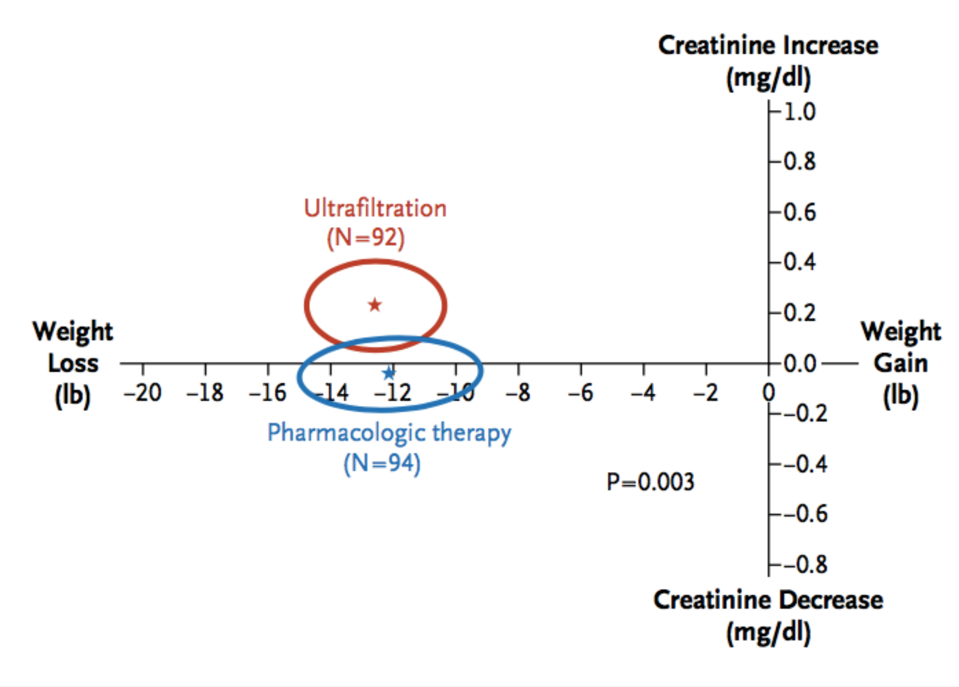
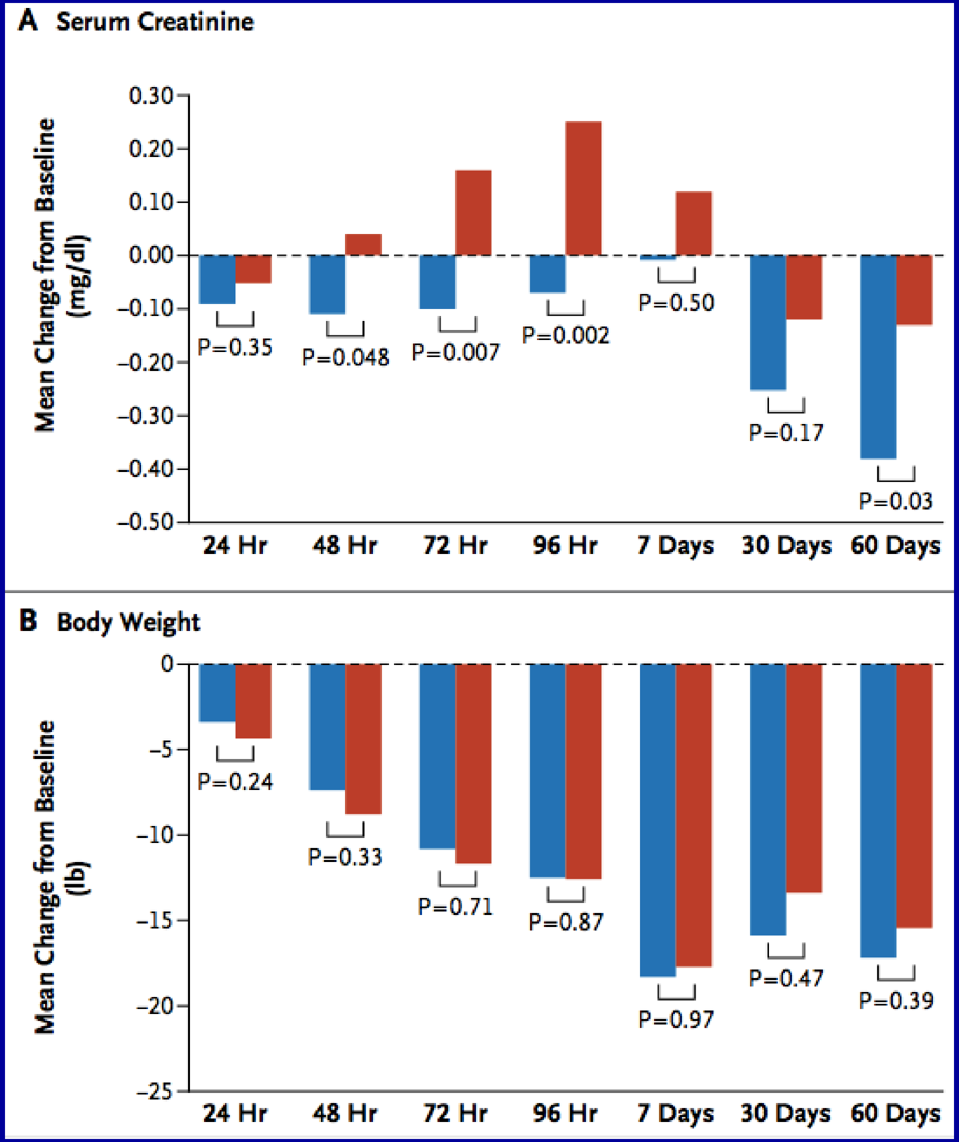


Figure 1. **Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).**

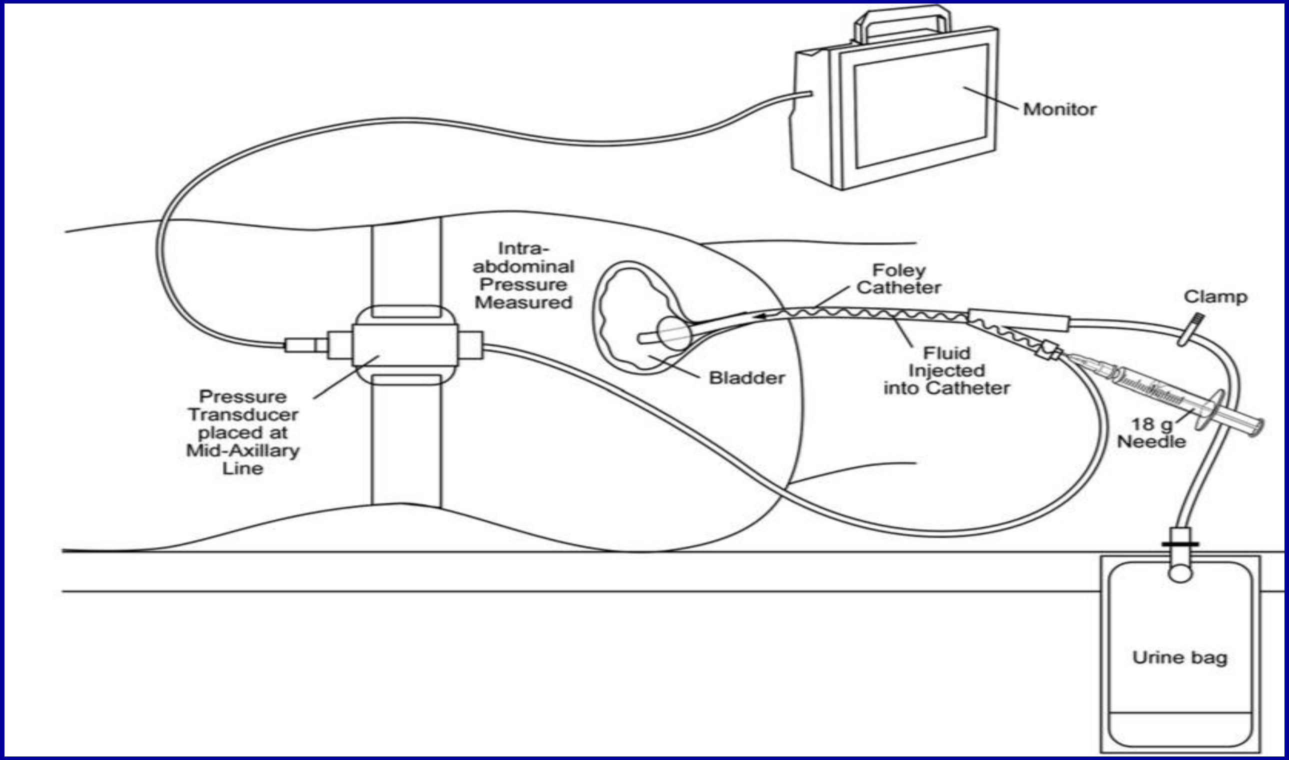
'Sicker' popn than UNLOAD – Only trial with CRS 1 patients!
Fixed UF protocols
UF group
- Higher SCr at 96 hrs
- More adverse events (72 vs. 53%)

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome



Ultrafiltration
Pharmacological

Intra-abdominal Hypertension



Mullens et al J Card Fail. 2008

Intra-abdominal Hypertension

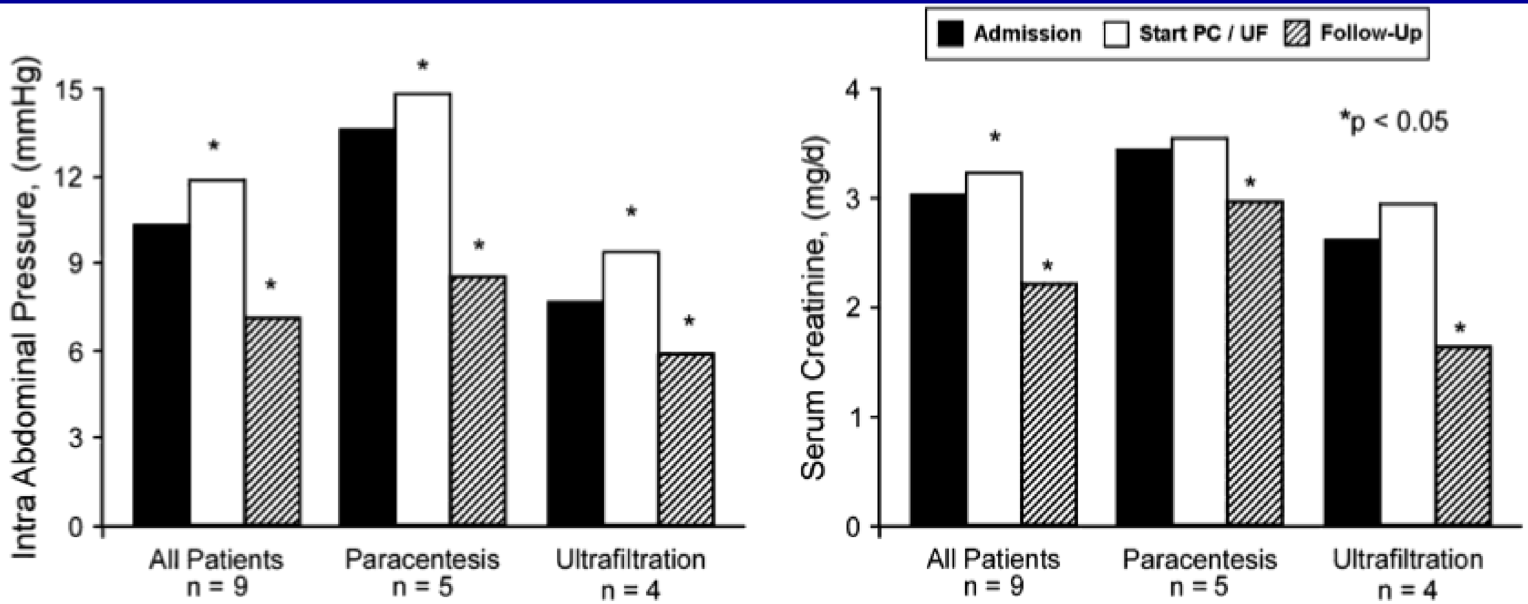


Fig. 3. Change in IAP and serum creatinine in patients who underwent paracentesis or ultrafiltration. Note the initial increase in IAP and creatinine during intensive medical therapy. A significant reduction in IAP was only seen 12 hours (follow-up) after starting ultrafiltration or paracentesis, which coincided with a significant improvement in renal function. *PC*, Paracentesis; *UF*, ultrafiltration.

Mullens et al J Card Fail. 2008

AVP antagonists

Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure
The EVEREST Outcome Trial

Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

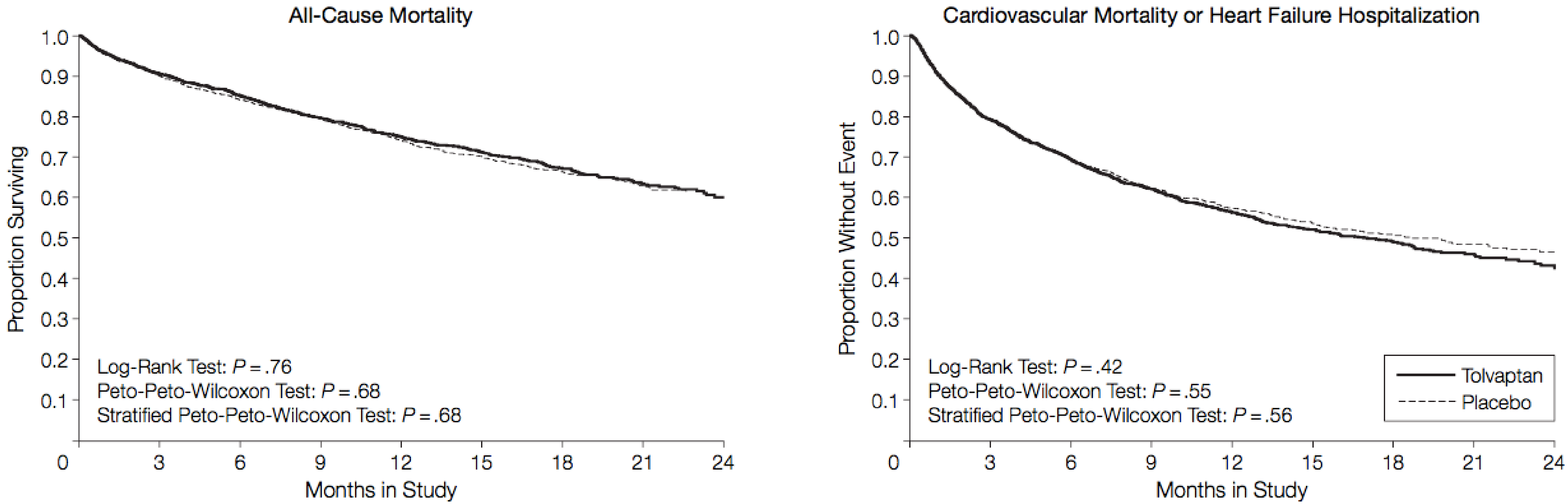
	Tolvaptan	Placebo	*P* Value
Change in body weight at 1 day, mean (SD), kg	−1.76 (1.91) [n = 1999]	−0.97 (1.84) [n = 1999]	<.001*
Change in dyspnea at 1 day, % showing improvement in dyspnea score†	74.3 [n = 1835]	68.0 [n = 1829]	<.001‡
Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L§	5.49 (5.77) [n = 162]	1.85 (5.10) [n = 161]	<.001*
Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement†	73.8 [n = 1600]	70.5 [n = 1595]	.003‡
Change in KCCQ overall summary score at postdischarge week 1, mean (SD)	19.90 (18.71) [n = 872]	18.52 (18.83) [n = 856]	.39*

JAMA
The Journal of the American Medical Association

N=4133; 2007

Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial



No. at Risk

Tolvaptan	2072	1812	1446	1112	859	589	404	239	97	2072	1562	1446	834	607	396	271	149	58
Placebo	2061	1781	1440	1109	840	580	400	233	95	2061	1532	1137	819	597	385	255	143	55

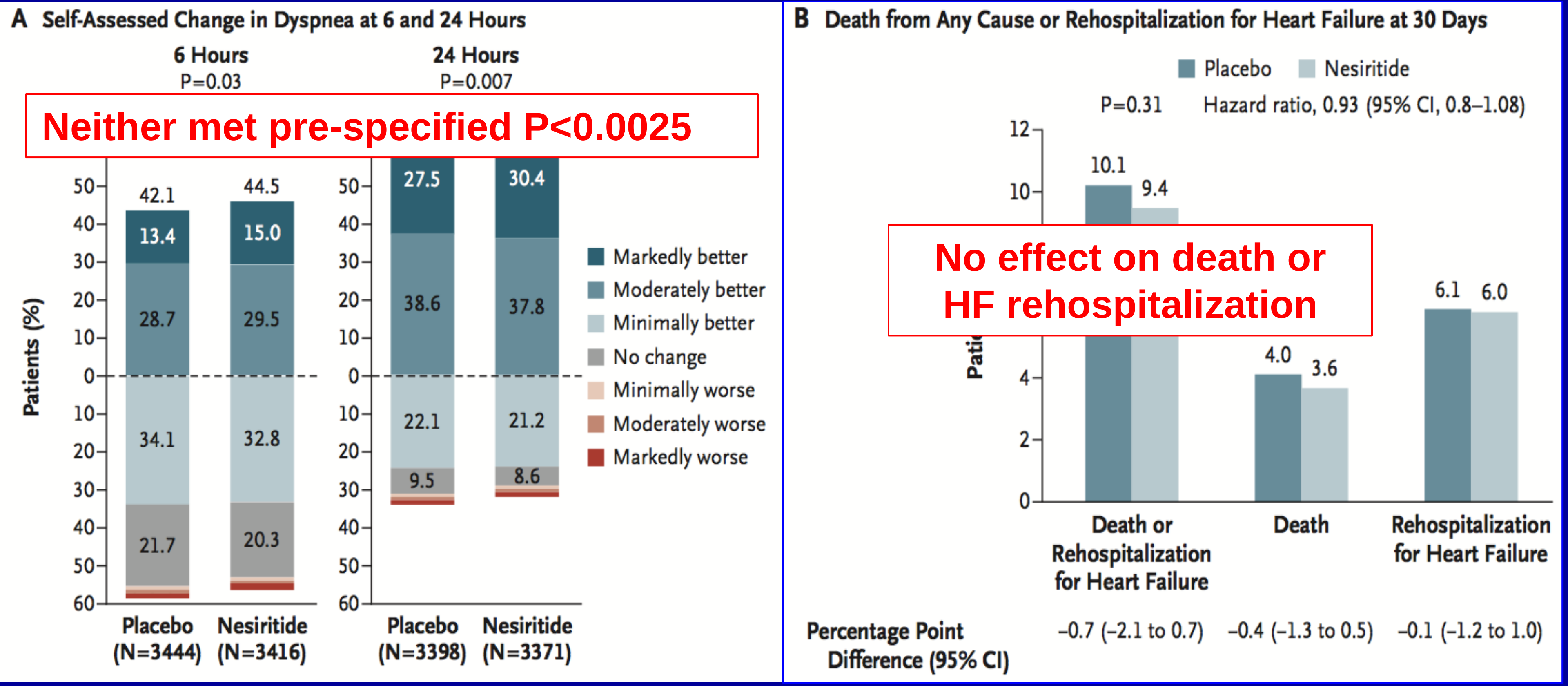
JAMA® The Journal of the American Medical Association

N=4133; 2007

Recombinant BNP

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

ASCEND-HF; N=7141; 2011



Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

N=7141; 2011

Safety end points				
Death from cardiovascular causes — no./total no. (%)	112/3498 (3.2)	124/3509 (3.5)	−0.3 (−1.2 to 0.5)	0.44
Sudden death from cardiac causes — no./total no. (%)	19/3324 (0.6)	16/3327 (0.5)	0.1 (−0.3 to 0.4)	0.61
Hypotension — no./total no. (%)	930/3498 (26.6)	538/3509 (15.3)	11.3 (9.4 to 13.1)	<0.001
Asymptomatic	748/3498 (21.4)	436/3509 (12.4)	9.0 (7.2 to 10.7)	<0.001
Symptomatic	250/3496 (7.2)	141/3509 (4.0)	3.2 (2.1 to 4.2)	<0.001
>25% decrease in estimated GFR from study-drug initiation — no./total no. (%)	1032/3289 (31.4)	968/3278 (29.5)	1.09 (0.98 to 1.21)	0.11
Baseline estimated GFR <60 ml/min/1.73 m^2	484/1714 (28.2)	449/1717 (26.2)	1.11 (0.96 to 1.3)	0.16
Baseline estimated GFR ≥60 ml/min/1.73 m^2	548/1575 (34.8)	519/1561 (33.2)	1.07 (0.92 to 1.24)	0.38

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

Enrolled patients with ADHF and renal dysfunction
1º outcome – success/failure/no change in survival, HF status or WRF

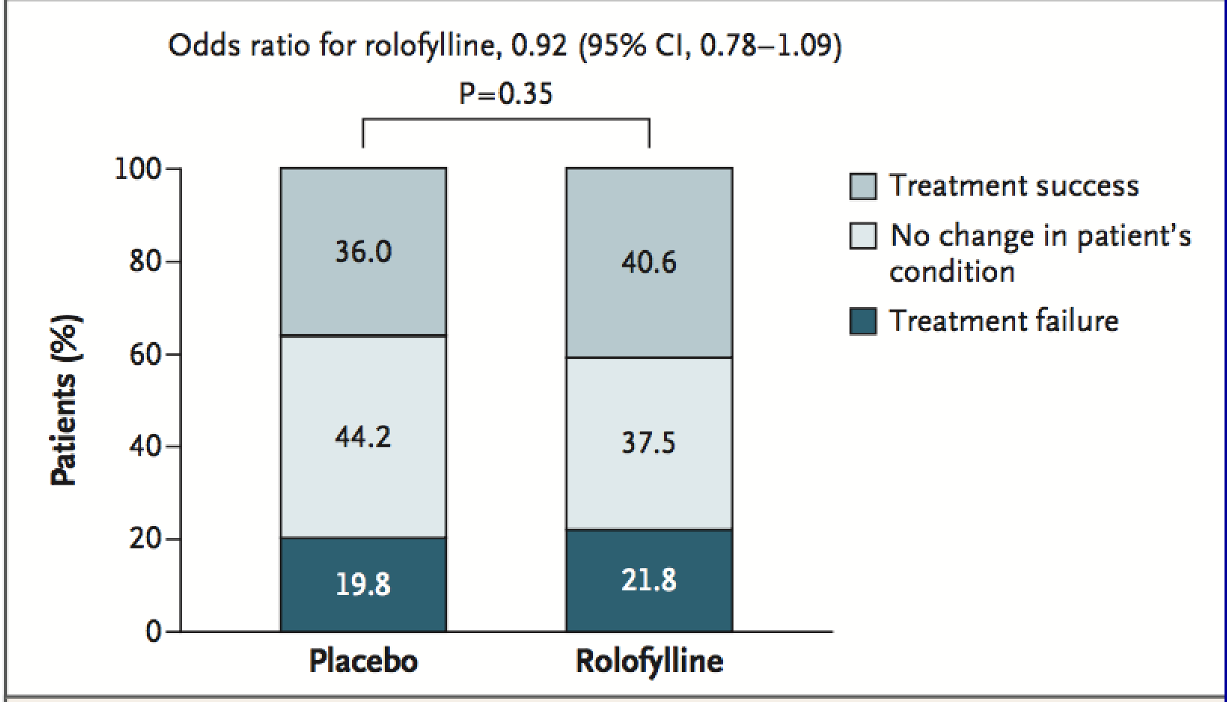


Figure 1. Distribution of the Primary Composite End Point in the Rolofylline and Placebo Groups.

Persistent renal impairment (0.3 SCr from day 0 to 7) developed in 15.0% vs 13.7% (P=0.44)

N=2033; Massie et al, 2010

Effects of Serelaxin in Patients with Acute Heart Failure

M. Metra, J.R. Teerlink, G. Cotter, B.A. Davison, G.M. Felker, G. Filippatos, B.H. Greenberg, P.S. Pang, P. Ponikowski, A.A. Voors, K.F. Adams, S.D. Anker, A. Arias-Mendoza, P. Avendaño, F. Bacal, M. Böhm, G. Bortman, J.G.F. Cleland, A. Cohen-Solal, M.G. Crespo-Leiro, M. Dorobantu, L.E. Echeverría, R. Ferrari, S. Goland, E. Goncalvesová, A. Goudev, L. Køber, J. Lema-Osores, P.D. Levy, K. McDonald, P. Manga, B. Merkely, C. Mueller, B. Pieske, J. Silva-Cardoso, J. Špinar, I. Squire, J. Stępińska, W. Van Mieghem, D. von Lewinski, G. Wikström, M.B. Yilmaz, N. Hagner, T. Holbro, T.A. Hua,* S.V. Sabarwal, T. Severin, P. Szecsödy, and C. Gimpelewicz, for the RELAX-AHF-2 Committees Investigators†

Effects of Serelaxin in Patients with Acute Heart Failure

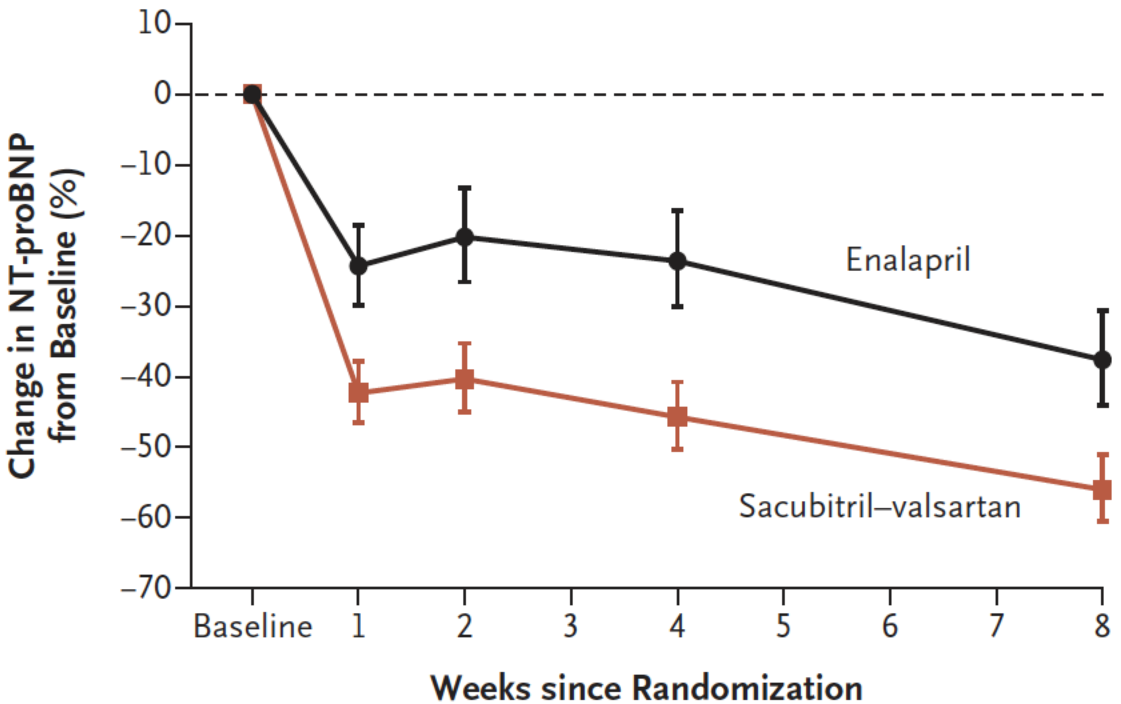
Table 2. Protocol-Specified Efficacy End Points.

End Point	Serelaxin Group (N=3274)	Placebo Group (N=3271)	Hazard Ratio or Mean Difference (95% CI)*	P Value
Primary efficacy end points — no. (%)				
Death from cardiovascular causes at 180 days	285 (8.7)	290 (8.9)	0.98 (0.83 to 1.15)	0.77†
Worsening heart failure at 5 days	227 (6.9)	252 (7.7)	0.89 (0.75 to 1.07)	0.19‡
Key secondary efficacy end points				
Death from any cause at 180 days — no. (%)	367 (11.2)	388 (11.9)	0.94 (0.81 to 1.08)	
Median length of index hospital stay (IQR) — days§	6.8 (5.0 to 10.0)	6.9 (5.0 to 10.0)	−0.183 (−0.645 to 0.280)¶	
Composite of death from cardiovascular causes or rehospitalization for heart failure or renal failure at 180 days — no. (%)	794 (24.3)	813 (24.9)	0.97 (0.88 to 1.07)	
Death from cardiovascular causes	285 (8.7)	290 (8.9)	0.98 (0.83 to 1.15)	
Rehospitalization for heart failure or renal failure	604 (18.4)	632 (19.3)	0.95 (0.85 to 1.06)	

Angiotensin/Neprilysin Inhibition

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H.,
Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D.,
Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D.,
for the PIONEER-HF Investigators*



No. at Risk

	Baseline	1	2	4	8
Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

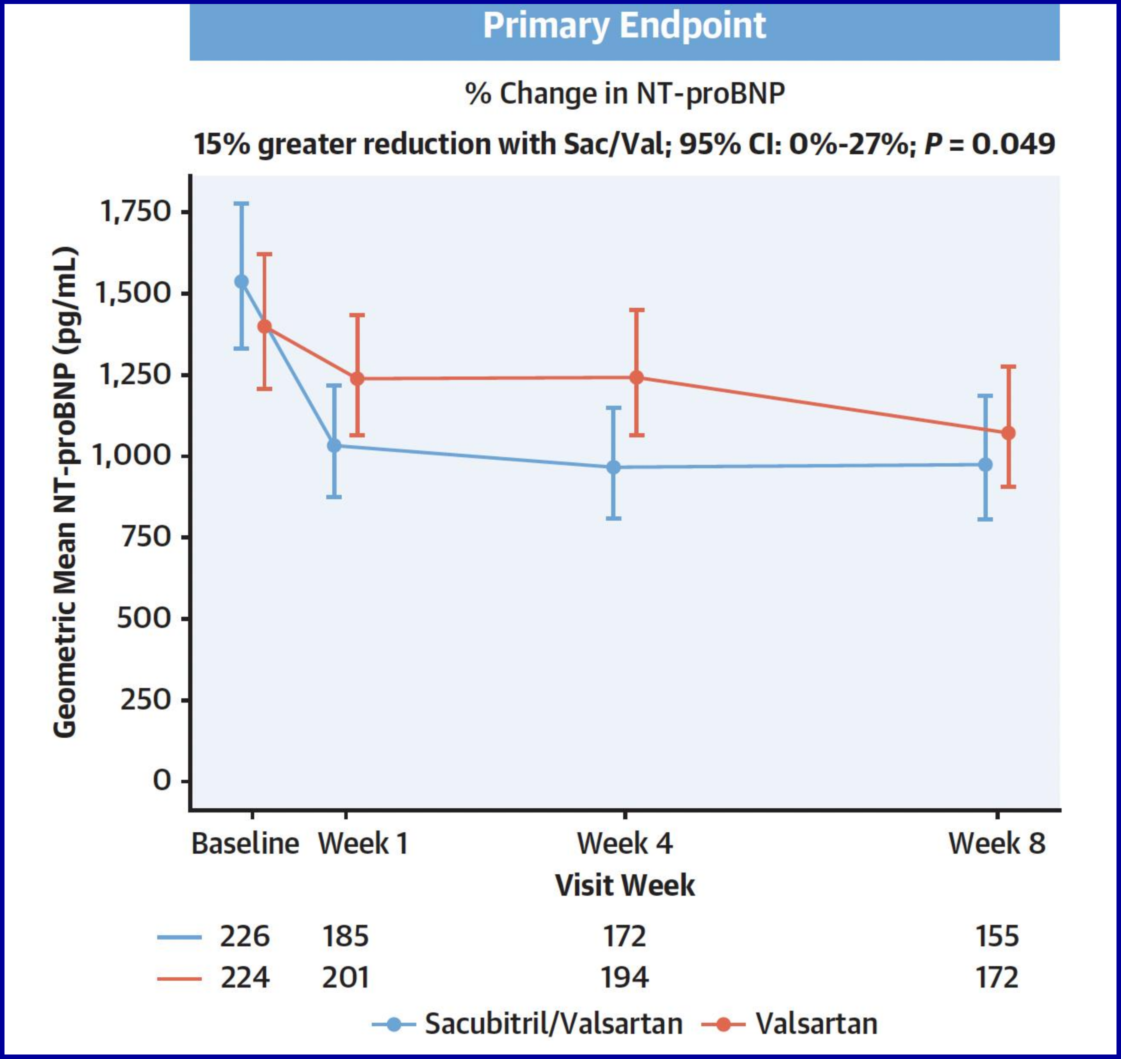
N=881

-47% vs -25%

Ratio of change:
0.71 (0.63 to 0.81)

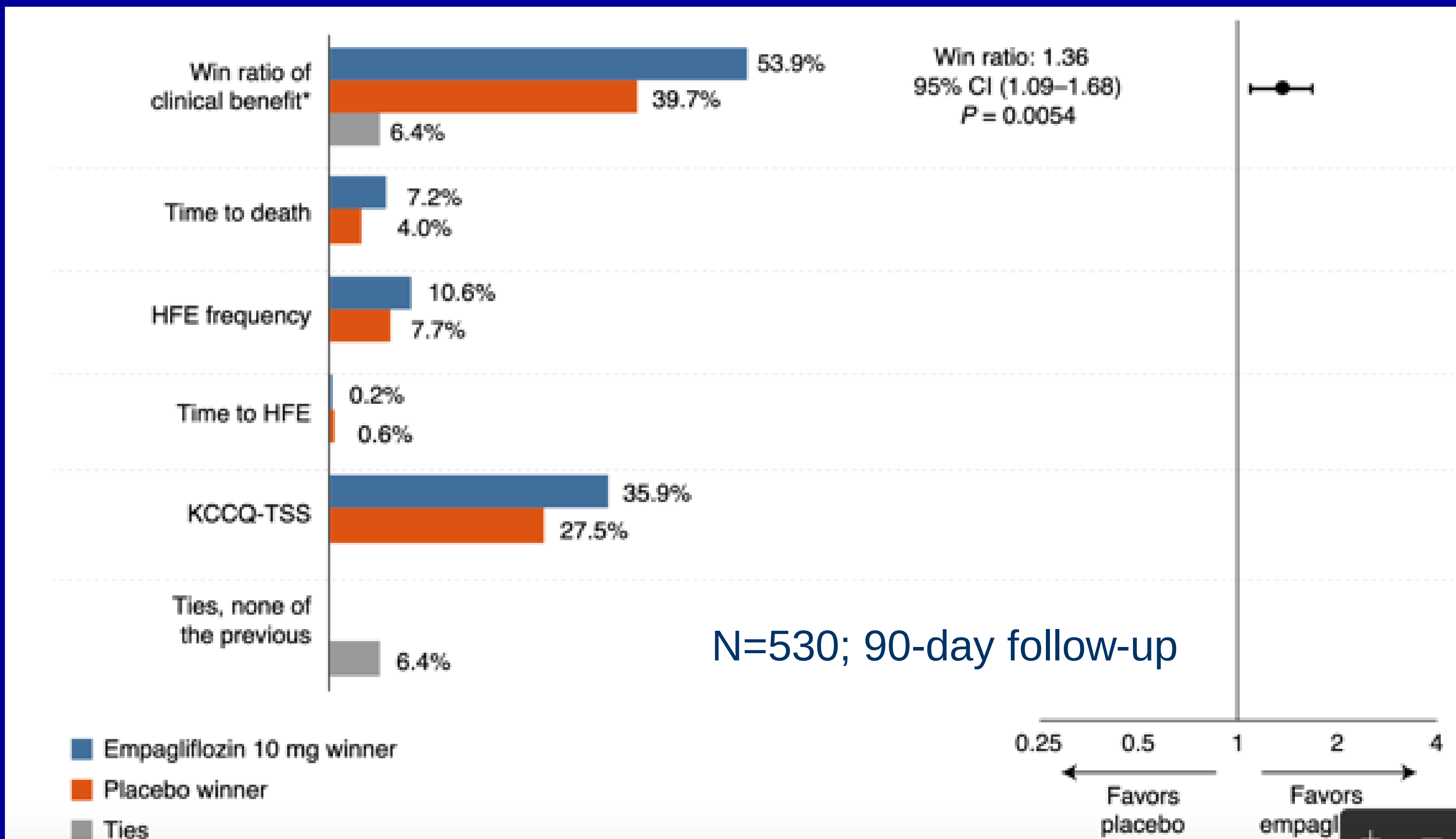
Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
July 2023



The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

nature medicine



Voors et al. 2022

Inotropes

Meta-Analysis: Low-Dose Dopamine Increases Urine Output but Does Not Prevent Renal Dysfunction or Death

Jan O. Friedrich, MD, DPhil; Neill Adhikari, MD, CM; Margaret S. Herridge, MD, MPH; and Joseph Beyene, PhD

Table 2. Effect of Low-Dose Dopamine on Clinical and Renal Outcomes

Outcome	Trials (Patients) with Outcomes Data, *n (n)**	Treatment Effect (95% CI)†	*P* Value	Homogeneity‡	
				I^2 Statistic, %	*P* Value
Mortality	15 (1387)	Relative risk, 0.96 (0.78–1.19)	>0.2	0	>0.2
Need for renal replacement therapy	12 (1216)	Relative risk, 0.93 (0.76–1.15)	>0.2	0	>0.2
Adverse effects	18 (1660)	Relative risk, 1.13 (0.90–1.41)	>0.2	6	>0.2
Urine output (day 1)	33 (1654)	Ratio of means, 1.24 (1.14–1.35)	<0.001	77	<0.001
Urine output (day 2)	17 (723)	Ratio of means, 1.09 (0.99–1.20)	0.07	75	<0.001
Urine output (day 3)	8 (326)	Ratio of means, 1.02 (0.87–1.20)	>0.2	85	<0.001
Creatinine level (day 1)	32 (1807)	Ratio of means, 0.96 (0.93–0.99)	0.01	73	<0.001
Creatinine level (day 2)	26 (1301)	Ratio of means, 0.99 (0.92–1.08)	>0.2	92	<0.001
Creatinine level (day 3)	15 (741)	Ratio of means, 0.97 (0.88–1.07)	>0.2	94	<0.001
Creatinine clearance (day 1)	22 (1077)	Ratio of means, 1.06 (1.01–1.11)	0.02	0	>0.2
Creatinine clearance (day 2)	12 (580)	Ratio of means, 1.02 (0.90–1.15)	>0.2	54	<0.01
Creatinine clearance (day 3)	8 (339)	Ratio of means, 1.09 (0.96–1.24)	0.18	36	0.14

None of these studies included participants with CRS 1

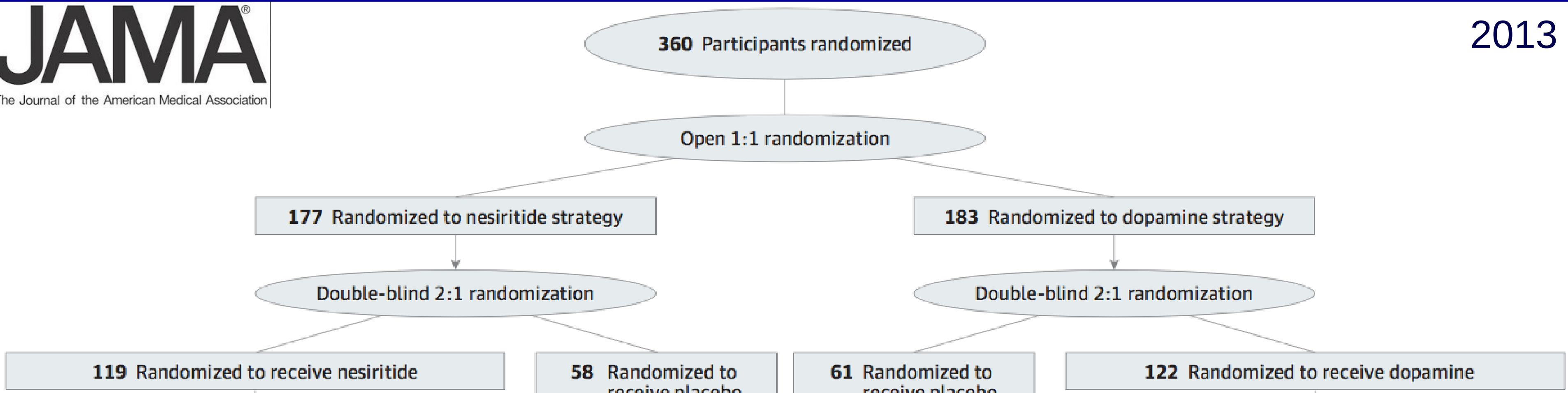
Annals of Internal Medicine

2005

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

JAMA
The Journal of the American Medical Association

2013



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

No significant difference in either decongestion or renal endpoint

Summary

- Diagnosis of Cardiorenal Syndrome is challenging
- Classifications are a start, but should not detract from the need to identify the underlying pathophysiology
- Decongestion is a key strategy for patients with CRS 1
- Distinguishing true AKI from functional changes in SCr in setting of diuresis is critical for delivery of goal-directed therapies
- Overcoming diuretic resistance requires focused research effort
- Still a paucity of proven beneficial therapies

Suggested Reading

- Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Rangaswami et al. Circulation 2019 Apr 16;139(16):e840-e878

- Diuretic Treatment in Heart Failure. Ellison DH, Felker GM. N Engl J Med. 2017 Nov 16;377(20):1964-1975

- Cardiorenal Syndrome: An Overview. Ronco C, Bellasi A, Di Lullo L. Adv Chronic Kidney Dis. 2018 Sep;25(5):382-390.

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