2016 Heart Failure Essentials for Cardiology Fellow
July 30, 2016

Diuretic Resistance
and
Cardiorenal syndrome

Srisakul Chirakarnjanakorn, MD
Siriraj Hospital
Mahidol University

Definition of Cardiorenal Syndrome (CRS)

NHLBI working group definition (2004)

The extreme cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function.

ADQI Classification (2009)

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

Ronco C, et al. EHJ 2009, ADQI guidelines.

Definition of Cardiorenal Syndrome (CRS)

Worsening renal failure (WRF) + **Persistent congestion (Diuretic resistance)**

Increase in creatinine of ≥ 0.3 mg/dl
or 25% increase from baseline

5

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Definition & Classification of Cardiorenal Syndrome

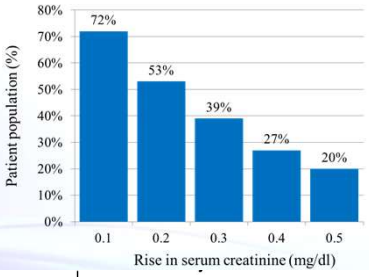
A complex pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

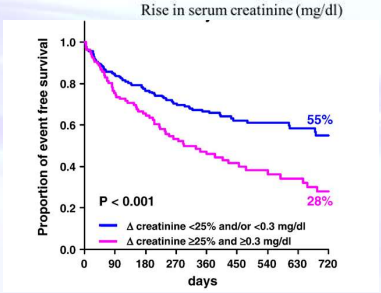
CRS Type 1 (acute cardiorenal syndrome)
Acute worsening of cardiac function (e.g. ADHF or ACS) leads to AKI
CRS Type 2 (chronic cardiorenal syndrome)
Chronic cardiac dysfunction leads to progressive and potentially permanent CKD
CRS Type 3 (acute renocardiac syndrome)
AKI leads to acute cardiac dysfunction (eg. acute HF, arrhythmia, or ischemia)
CRS Type 4 (chronic renocardiac syndrome)
CKD leads to progressive cardiac dysfunction
CRS Type 5 (secondary cardiorenal syndrome)
Systemic conditions (eg. sepsis or DM) cause simultaneous cardiac & renal dysfunction

Adapted from Ronco C, et al. Contrib Nephrol 2010, 164:33–8.

Prevalence and Prognostic Importance of WRF in ADHF

- Prevalence: 23%
- Serum creatinine $\geq$ 0.3 mg/dL
- In-hospital mortality:
  - Sensitivity of 65%
  - Specificity of 81%
- 2.3 days increase in LOS
- 67% ↑ risk of death within 6 months after discharge
- 33% ↑ risk for readmission

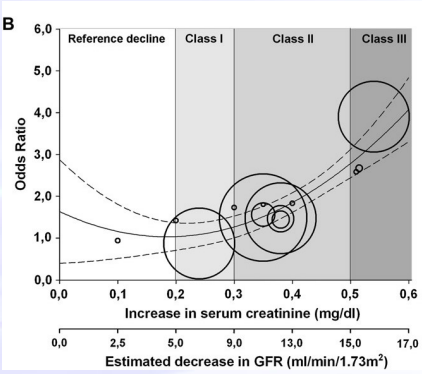


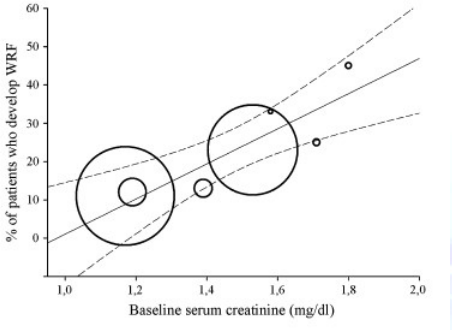


Gottlieb SS, J Card Fail 2002. Metra M, Euro J HF 2008.

12

Degree of Worsening Renal Function, Serum Creatinine and Mortality



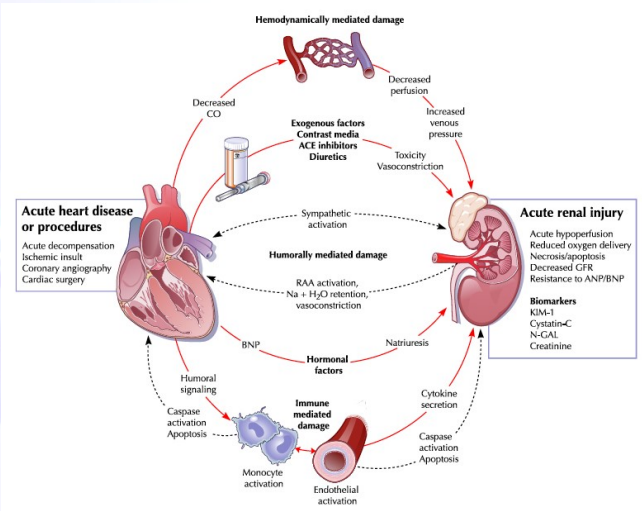


15

Damman K, et al. JCF 2007.

Cardiorenal syndrome Type 1

- Hemodynamic alterations
- Pharmacological intervention
- Neurohormonal activation
- Biochemical dysregulation



18

Ronco C, et al. J Am Coll Cardiol 2008;52:1527–39.

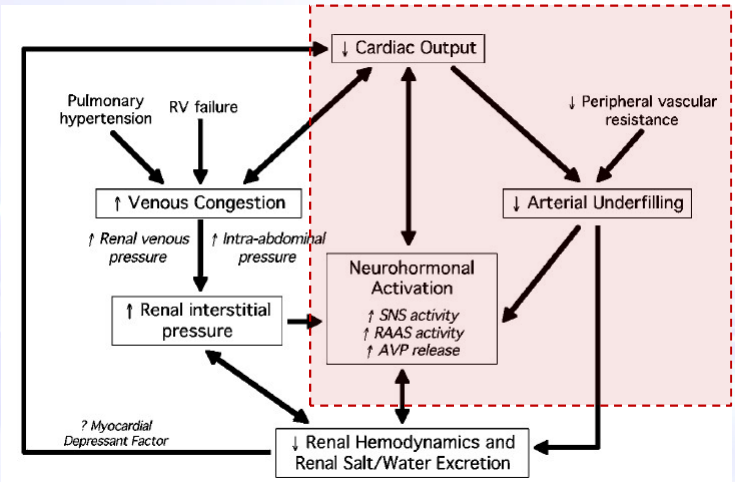
คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Cardiorenal syndrome: Pathophysiology
Hemodynamic Abnormalities

- Low cardiac output
- Venous congestion
- Increased intraabdominal pressure

19

Complex Interplay in Cardiorenal syndrome: Hemodynamic Abnormalities

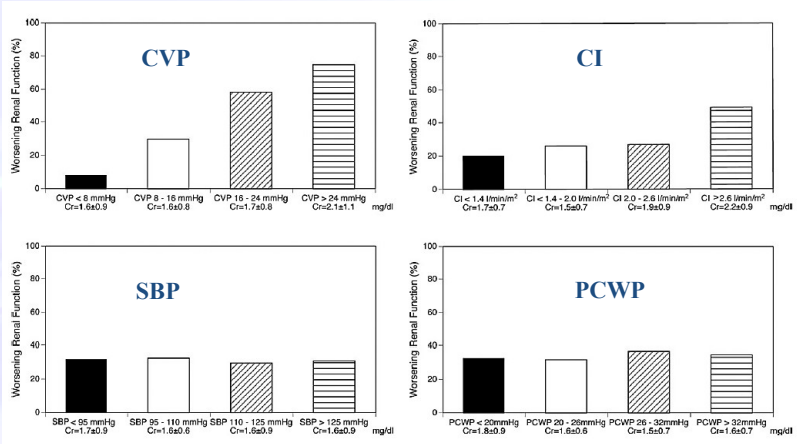


Tang WH and Mullens W. Heart 2010;96::255-60.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Venous Congestion and Worsening Renal Function in Advanced HF

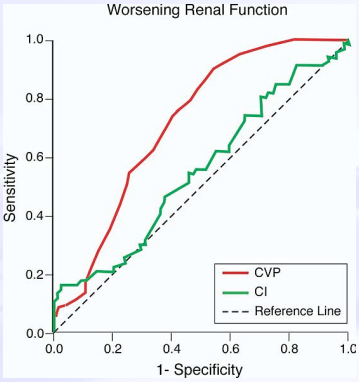
WRF defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization

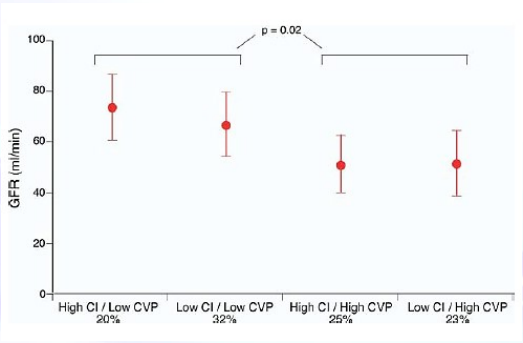


Mullens W, Tang WH, et al. J Am Coll Cardiol 2009;53:589–96.

Venous Congestion and Worsening Renal Function in AHF

WRF defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization

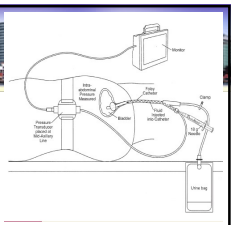




Cutoff values for CI = 2.4 l/min/m2 and CVP = 8 mm Hg.

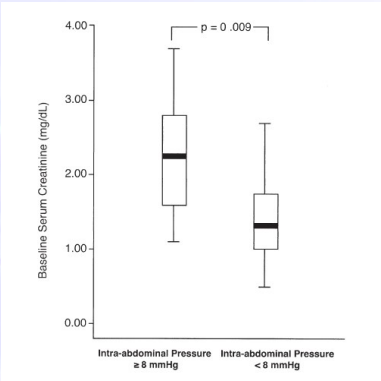
26 *Mullens W, Tang WH, et al. J Am Coll Cardiol 2009;53:589–96.*

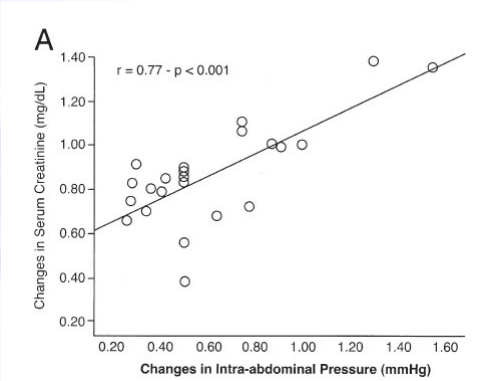
คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University



Elevated Intraabdominal Pressure and Worsening Renal Function in AHF

Elevated IAP : ≥ 8 mm Hg, Prevalence 60% (24/40)

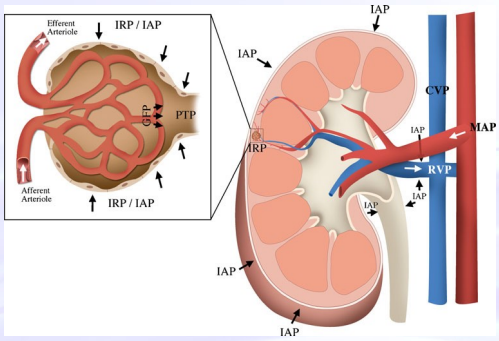




29 *Mullens W, et al. J Am Coll Cardiol 2008;51:300–6.*

Glomerular Hemodynamic Changes in Heart Failure

GFP = RPP – RVP



- ↓ CO/MAP
- ↑ Renal venous congestion
- ↓ GFP
- **↓ GFR**
- ↑ PTP
- ↑ IAP and RIP

GFP = glomerular filtration pressure
RPP = renal perfusion pressure
RVP = renal venous pressure
PTP = proximal tubule pressure
IAP = intraabdominal pressure
RIP = renal interstitial pressure

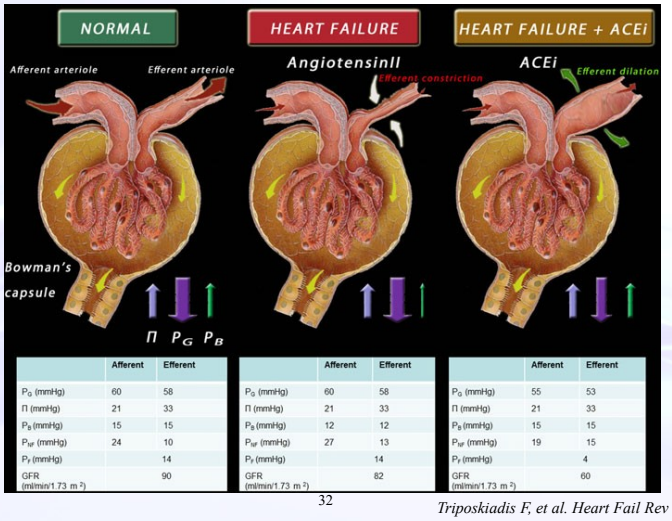
30

Dupont M, et al. Curr Heart Fail Rep 2011.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Glomerular hemodynamics:

Effects of ACEI on Renal Hemodynamics



	Afferent	Efferent
P_G (mmHg)	60	58
Π (mmHg)	21	33
P_B (mmHg)	15	15
P_{HF} (mmHg)	24	10
P_T (mmHg)		14
GFR (ml/min/1.73 m²)		90

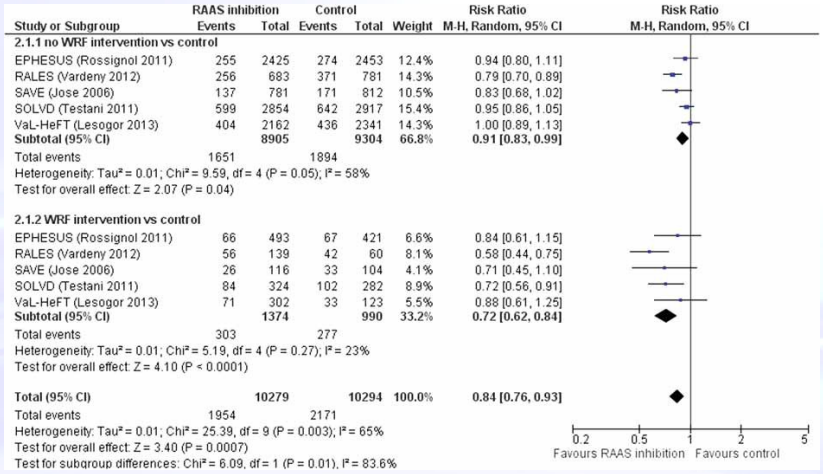
	Afferent	Efferent
P_G (mmHg)	60	58
Π (mmHg)	21	33
P_B (mmHg)	12	12
P_{HF} (mmHg)	27	13
P_T (mmHg)		14
GFR (ml/min/1.73 m²)		82

	Afferent	Efferent
P_G (mmHg)	55	53
Π (mmHg)	21	33
P_B (mmHg)	15	15
P_{HF} (mmHg)	19	15
P_T (mmHg)		4
GFR (ml/min/1.73 m²)		60

32

Triposkiadis F, et al. Heart Fail Rev 2012, 17:355–66.

WRF after RAAS inhibitor use in Heart Failure



Study or Subgroup	RAAS inhibition Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 no WRF intervention vs control						
EPHESUS (Rossignol 2011)	255	2425	274	2453	12.4%	0.94 [0.80, 1.11]
RALES (Vardeny 2012)	256	683	371	781	14.3%	0.79 [0.70, 0.89]
SAVE (Jose 2006)	137	781	171	812	10.5%	0.83 [0.68, 1.02]
SOLVD (Testani 2011)	599	2854	642	2917	15.4%	0.95 [0.86, 1.05]
VaL-HeFT (Lesogor 2013)	404	2162	436	2341	14.3%	1.00 [0.89, 1.13]
Subtotal (95% CI)		**8905**		**9304**	**66.8%**	**0.91 [0.83, 0.99]**
Total events	1651		1894			
Heterogeneity: Tau² = 0.01; Chi² = 9.59, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 2.07 (P = 0.04)						
2.1.2 WRF intervention vs control						
EPHESUS (Rossignol 2011)	66	493	67	421	6.6%	0.84 [0.61, 1.15]
RALES (Vardeny 2012)	56	139	42	60	8.1%	0.58 [0.44, 0.75]
SAVE (Jose 2006)	26	116	33	104	4.1%	0.71 [0.45, 1.10]
SOLVD (Testani 2011)	84	324	102	282	8.9%	0.72 [0.56, 0.91]
VaL-HeFT (Lesogor 2013)	71	302	33	123	5.5%	0.88 [0.61, 1.25]
Subtotal (95% CI)		**1374**		**990**	**33.2%**	**0.72 [0.62, 0.84]**
Total events	303		277			
Heterogeneity: Tau² = 0.01; Chi² = 5.19, df = 4 (P = 0.27); I² = 23%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Total (95% CI)		**10279**		**10294**	**100.0%**	**0.84 [0.76, 0.93]**
Total events	1954		2171			
Heterogeneity: Tau² = 0.01; Chi² = 25.39, df = 9 (P = 0.003); I² = 65%						
Test for overall effect: Z = 3.40 (P = 0.0007)						
Test for subgroup differences: Chi² = 6.09, df = 1 (P = 0.01), I² = 83.6%						

Risk Ratio M-H, Random, 95% CI

0.2 0.5 1 2 5

Favours RAAS inhibition Favours control

33

Clark H, et al. Eur J Heart Fail 2014.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Original Investigation

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

Horng H. Chen, MBBCh; Kevin J. Anstrom, PhD; Michael M. Givertz, MD; Lynne W. Stevenson, MD; Marc J. Semigran, MD; Steven R. Goldsmith, MD; Bradley A. Bart, MD; David A. Bull, MD; Josef Stehlik, MD; Martin M. LeWinter, MD; Marvin A. Konstam, MD; Gordon S. Huggins, MD; Jean L. Rouleau, MD; Eileen O'Meara, MD; W. H. Wilson Tang, MD; Randall C. Starling, MD, MPH; Javed Butler, MD, MPH; Anita Deswal, MD; G. Michael Felker, MD; Christopher M. O'Connor, MD; Raphael E. Bonita, MD, ScM; Kenneth B. Margulies, MD; Thomas P. Cappola, MD, ScM; Elizabeth O. Ofili, MD; Douglas L. Mann, MD; Víctor G. Dávila-Román, MD; Steven E. McNulty, MS; Barry A. Borlaug, MD; Eric J. Velazquez, MD; Kerry L. Lee, PhD; Monica R. Shah, MD, MHS, MSJ; Adrian F. Hernandez, MD, MHS; Eugene Braunwald, MD; Margaret M. Redfield, MD; for the NHLBI Heart Failure Clinical Research Network

- Hypothesis: low-dose dopamine or low-dose nesiritide may enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction
- Low-dose dopamine (2 µg/kg/min) vs. Low-dose nesiritide (0.005 µg/kg/min without bolus) vs placebo ontop standard diuretic
- Multicenter, double-blind, placebo-controlled clinical trial
- 360 hospitalized patients with acute HFand renal dysfunction (eGFR 15-60 mL/min/1.73m^2), randomized within 24 hours of admission.

37

ROSE-AHF study. Chen HH, et al. JAMA 2013.

ROSE-AHF Study

Renal Optimization Strategies Evaluation

Co-primary end points:
- 72-hour cumulative urine volume (decongestion end point) and
- Change in serum cystatin C from enrollment to 72 hours (renal function end point).

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

38

ORIGINAL ARTICLE

ASCEND-HF Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

C.M. O'Connor, R.C. Starling, A.F. Hernandez, P.W. Armstrong, K. Dickstein, V. Hasselblad, G.M. Heizer, M. Komajda, B.M. Massie, J.J.V. McMurray, M.S. Nieminen, C.J. Reist, J.L. Rouleau, K. Swedberg, K.F. Adams, Jr., S.D. Anker, D. Atar, A. Battler, R. Botero, N.R. Bohidar, J. Butler, N. Clausell, R. Corbalán, M.R. Costanzo, U. Dahlstrom, L.I. Deckelbaum, R. Diaz, M.E. Dunlap, J.A. Ezekowitz, D. Feldman, G.M. Felker, G.C. Fonarow, D. Gennevois, S.S. Gottlieb, J.A. Hill, J.E. Hollander, J.G. Howlett, M.P. Hudson, R.D. Kociol, H. Krum, A. Laucevicius, W.C. Levy, G.F. Méndez, M. Metra, S. Mittal, B.-H. Oh, N.L. Pereira, P. Ponikowski, W.H.W. Tang, S. Tanomsup, J.R. Teerlink, F. Triposkiadis, R.W. Troughton, A.A. Voors, D.J. Whellan, F. Zannad, and R.M. Califf

- Multicenter, double-blind, placebo-controlled clinical trial
- 7141 patients who were hospitalized with acute heart failure
- Nesiritide vs. Placebo for 24 to 168 hours in addition to standard care.
- Within 24 hours after admission/48 hours after diagnosis of acute HF

ASCEND-HF study. N Engl J Med 2011; 365: 32-43.

ASCEND-HF Study

Acute Study of Clinical Effectiveness of Nesiritide in ADHF

Renal Outcomes

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

ASCEND-HF study. N Engl J Med 2011; 365: 32-43.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2011 VOL. 364 NO. 9

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., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O'Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*

- Prospective, double-blind, randomized trial
- 308 pts with ADHF Dx within 24 hr, chronic HF, on oral loop diuretic (furosemide 80-240 mg/d, or equivalent) for ≥ 1 mo
- IV bolus vs. IV continuous
- Low-dose strategy (1x) vs. High-dose strategy (2.5x)

45

Felker GM. New Engl J Med 201; 364: 797-805.

DOSE trial: Secondary end points

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	

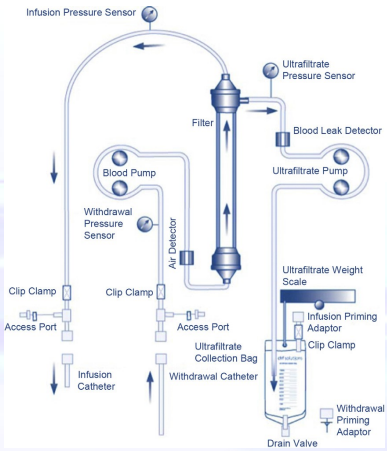
47

Felker GM. New Engl J Med 2011; 364: 797-805.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Ultrafiltration as a Therapy for Congestion?

- Removes both sodium and free water (isotonic solution)
- Allows for titration of rate of fluid removal to match plasma refill rate
- Allows for reduction in diuretic use
- Remove inflammatory cytokines



48

Felker GM and Mentz RJ, et al. JACC 2012.

UNLOAD study Heart Failure

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

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

Objectives This study was designed to compare the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for hypervolemic heart failure (HF) patients.

Background Early ultrafiltration may be an alternative to intravenous diuretics in patients with decompensated HF and volume overload.

Methods Patients hospitalized for HF with ≥2 signs of hypervolemia were randomized to ultrafiltration or intravenous diuretics. Primary end points were weight loss and dyspnea assessment at 48 h after randomization. Secondary end points included net fluid loss at 48 h, functional capacity, HF rehospitalizations, and unscheduled visits in 90 days. Safety end points included changes in renal function, electrolytes, and blood pressure.

Results Two hundred patients (63 ± 15 years, 69% men, 71% ejection fraction ≤40%) were randomized to ultrafiltration or intravenous diuretics. At 48 h, weight (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; p = 0.001) and net fluid loss (4.6 vs. 3.3 l; p = 0.001) were greater in the ultrafiltration group. Dyspnea scores were similar. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (16 of 89 [18%] vs. 28 of 87 [32%]; p = 0.037), HF rehospitalizations (0.22 ± 0.54 vs. 0.46 ± 0.76; p = 0.022), rehospitalization days (1.4 ± 4.2 vs. 3.8 ± 8.5; p = 0.022) per patient, and unscheduled visits (14 of 65 [21%] vs. 29 of 66 [44%]; p = 0.009). No serum creatinine differences occurred between groups. Nine deaths occurred in the ultrafiltration group and 11 in the diuretics group.

Conclusions In decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy. (The UNLOAD trial; http://clinicaltrials.gov/ct/show/NCT00124137?order=1; NCT00124137). (J Am Coll Cardiol 2007;49:675–83)

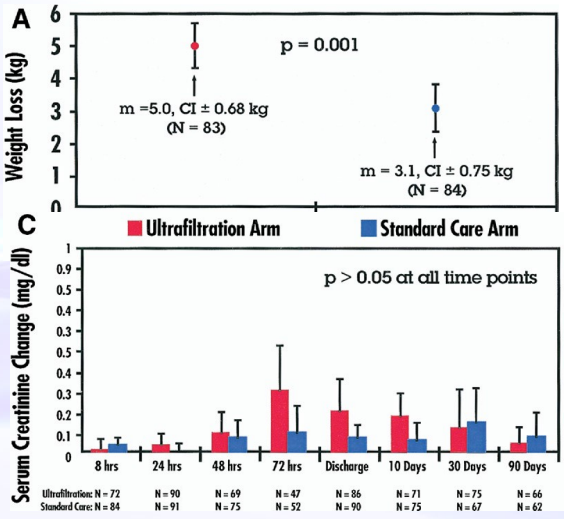
Costanzo MR, et al. JACC 2007.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

UNLOAD study: Primary endpoint

Primary efficacy endpoint:
Mean weight loss at 48 hr

Primary safety endpoint:
Serum creatinine change



51

Costanzo MR, et al. JACC 2007.

CARRESS study 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

- 188 patients with acute decompensated heart failure, worsened renal function (defined as increase in serum creatinine of ≥ 0.3 mg/dL within 12 weeks before or 10 days after the index admission for heart failure), and persistent congestion
- Stepped pharmacologic therapy vs. ultrafiltration (UF 200 ml/hr)
- Mean LVEF 30%, on ACEI 55%, MRA 22%, on oral furosemide 120 mg/day,
- Mean BUN 48.7 mg/dL, Cr 1.90 mg/dL

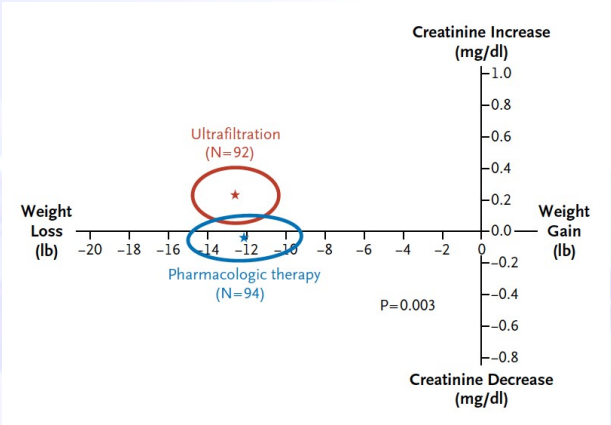
52

Bart BA. New Engl J Med 2012; 367: 2291-304.

CARRESS study: Primary endpoint

Mean changes in creatinine and weight at 96 hours

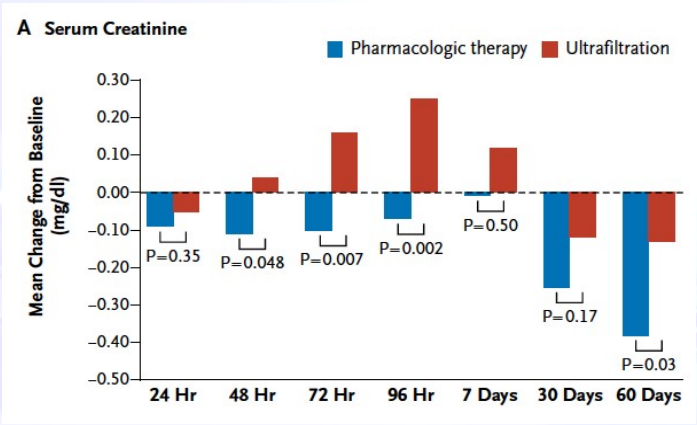
188 patients with ADHF, WRF (↑Cr ≥0.3 mg/dL in 12 wks), and persistent congestion



53

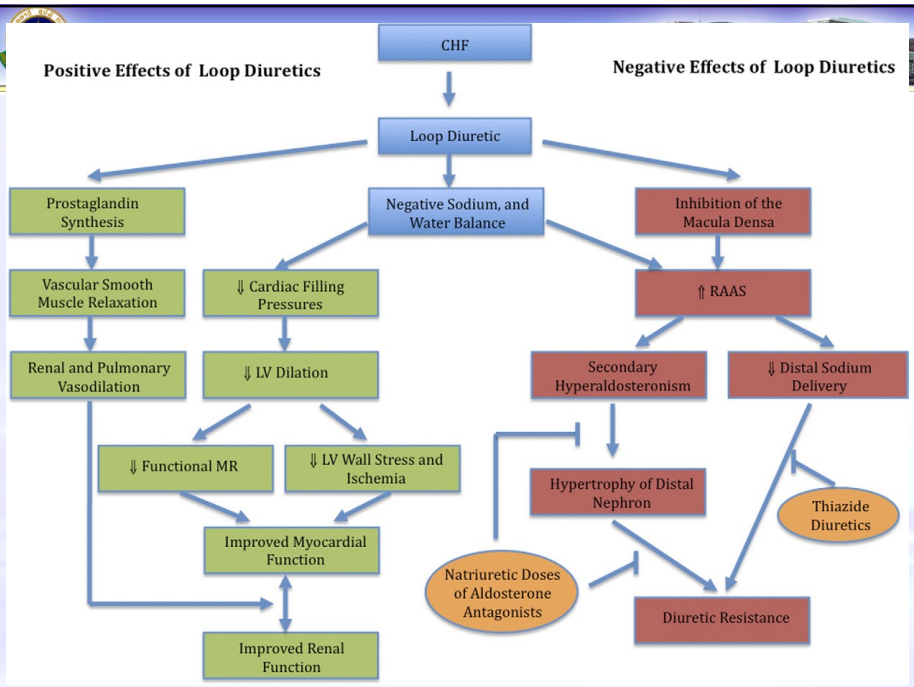
Bart BA. New Engl J Med 2012; 367: 2291-304.

CARRESS study: Changes in Serum Creatinine



54

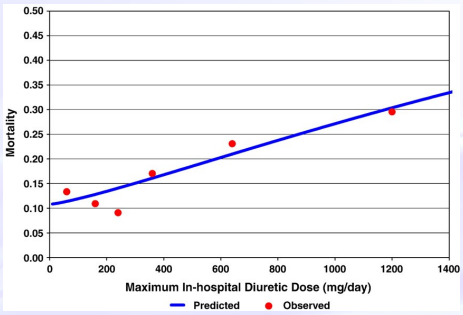
Bart BA. New Engl J Med 2012; 367: 2291-304.



56

Felker GM and Mentz RJ, et al. JACC 2012.

ESCAPE Study: Inpatient Mortality by Diuretic Dose



- Sicker patients gets higher doses of diuretics?
  - Older
  - Greater severity of heart failure
  - More chronic kidney disease
- Relationship between diuretic dose and outcomes are confounded by indication

57 *Hasselblad V, et al. Eur J Heart Fail 2007; 9: 1064-9.*

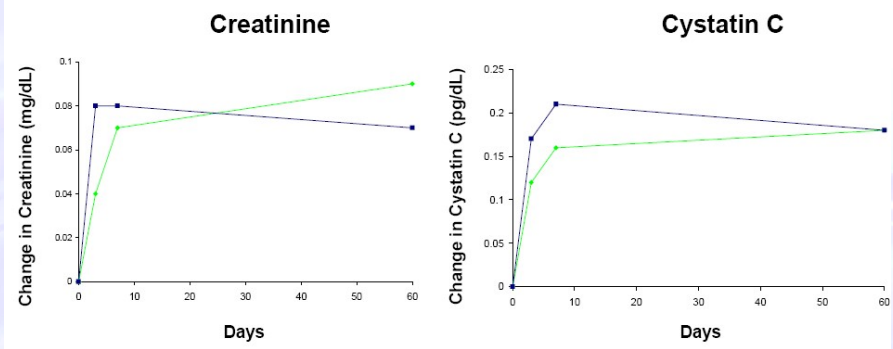
คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

DOSE trial:

Mean Change in Serum Creatinine

Low dose
High dose

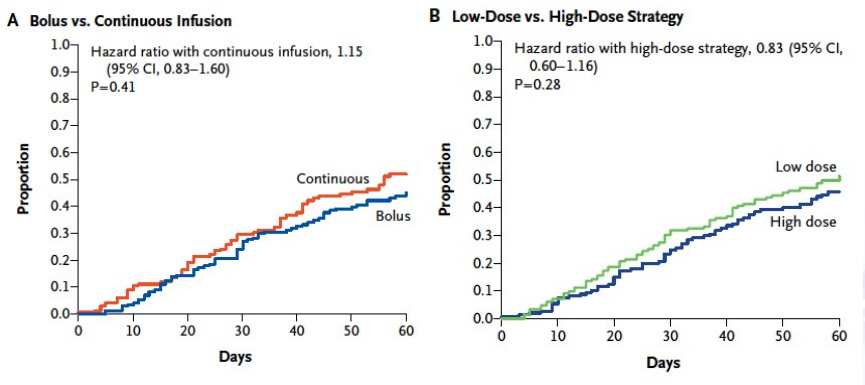
P > 0.05 for all timepoints



60 *Felker GM. New Engl J Med 2011; 364: 797-805.*

DOSE trial:

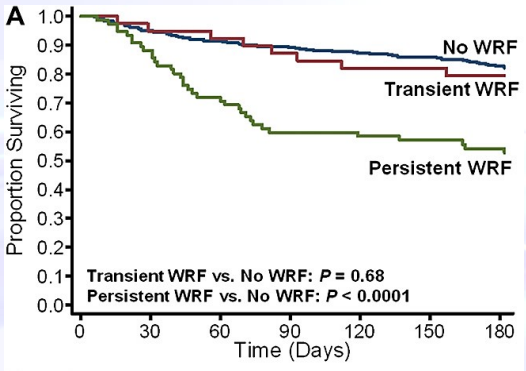
Death, HF Rehospitalization, ED Visit



61 *Felker GM. New Engl J Med 2011; 364: 797-805.*

Persistent vs. Transient Worsening Renal Function in AHF

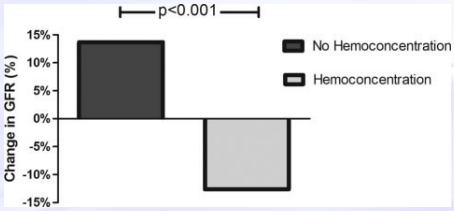
WRF: ≥0.5 mg/dL increase in serum creatinine above baseline at any time point
Persistent WRF: WRF throughout Day 30
Transient WRF: Creatinine levels subsequently decreased to <0.5 mg/dL above baseline.

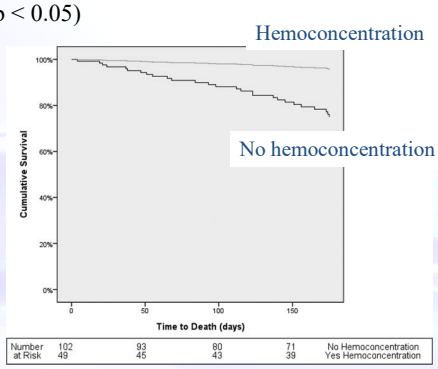


63 *Aronson D, and Burger AJ. J Cardiac Fail 2010;16:541-7.*

Hemoconcentration is Associated More WRF, but Better Survival – Data from ESCAPE study

Hemoconcentration defined as top tertile of ≥ 2 of the change in protein, albumin and Hct
Higher dose of loop diuretic, lost more weight/fluid and greater reduction in filling pressures ($p < 0.05$)





65

Testani AJ, et al. Circulation. 2010;122:265-272.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
Faculty of Medicine Siriraj Hospital, Mahidol University

Confounding issued in AKI definition in CRS

- Intravascular volume has direct and indirect impact on renal hemodynamics
- Serum creatinine may rise due to azotemia or hemoconcentration
- Decongestive therapy with loop diuretics may obscure AKI urine output criteria
- Change in renal biomarkers may not reflect clinical status in CRS

72

Dupont M, et al. Curr Heart Fail Rep 2011.

Other treatment causes of WRF with different prognostic implications

- NSAIDs
- Nephrotoxic ATB
- AKI secondary to contrast or other nephrotoxic agents
- Urinary tract obstruction
- ATN secondary to hypotension/hypovolemia as result of medications or blood loss

76