Lessons Learned from Heart Failure Trials with Respect to Renal Outcomes

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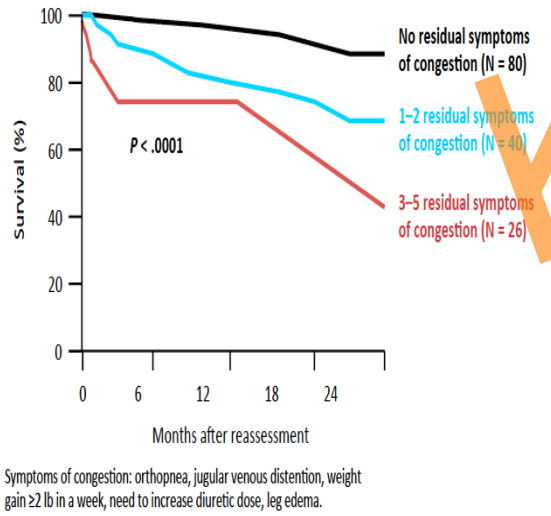
KDIGO

Persistent Congestion and Outcomes in Acute Heart Failure

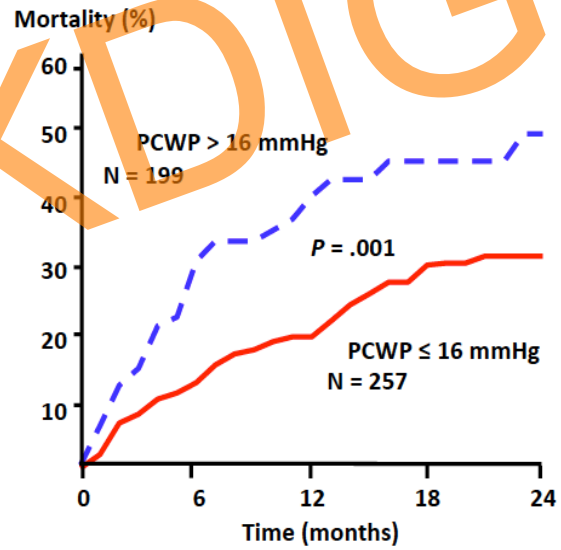
- Persistent clinical and sub-clinical congestion at discharge after an AHF hospitalization is associated with worse outcomes.

Signs and symptoms



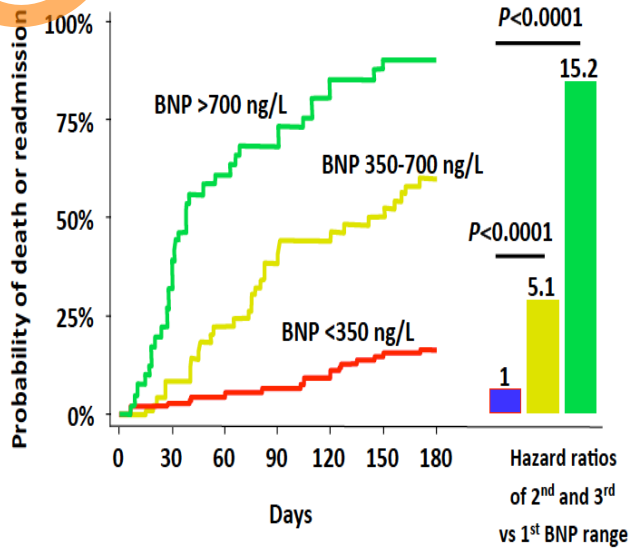
Lucas C, et al. *Am Heart J.* 2000;140:840-847.

Pulmonary Capillary Wedge Pressure



Fonarow GC, et al. *Circulation.* 1994;90(pt. 2):1-488.

Natriuretic Peptide Levels



Logeart D, et al. *J Am Coll Cardiol.* 2004;43:635-641

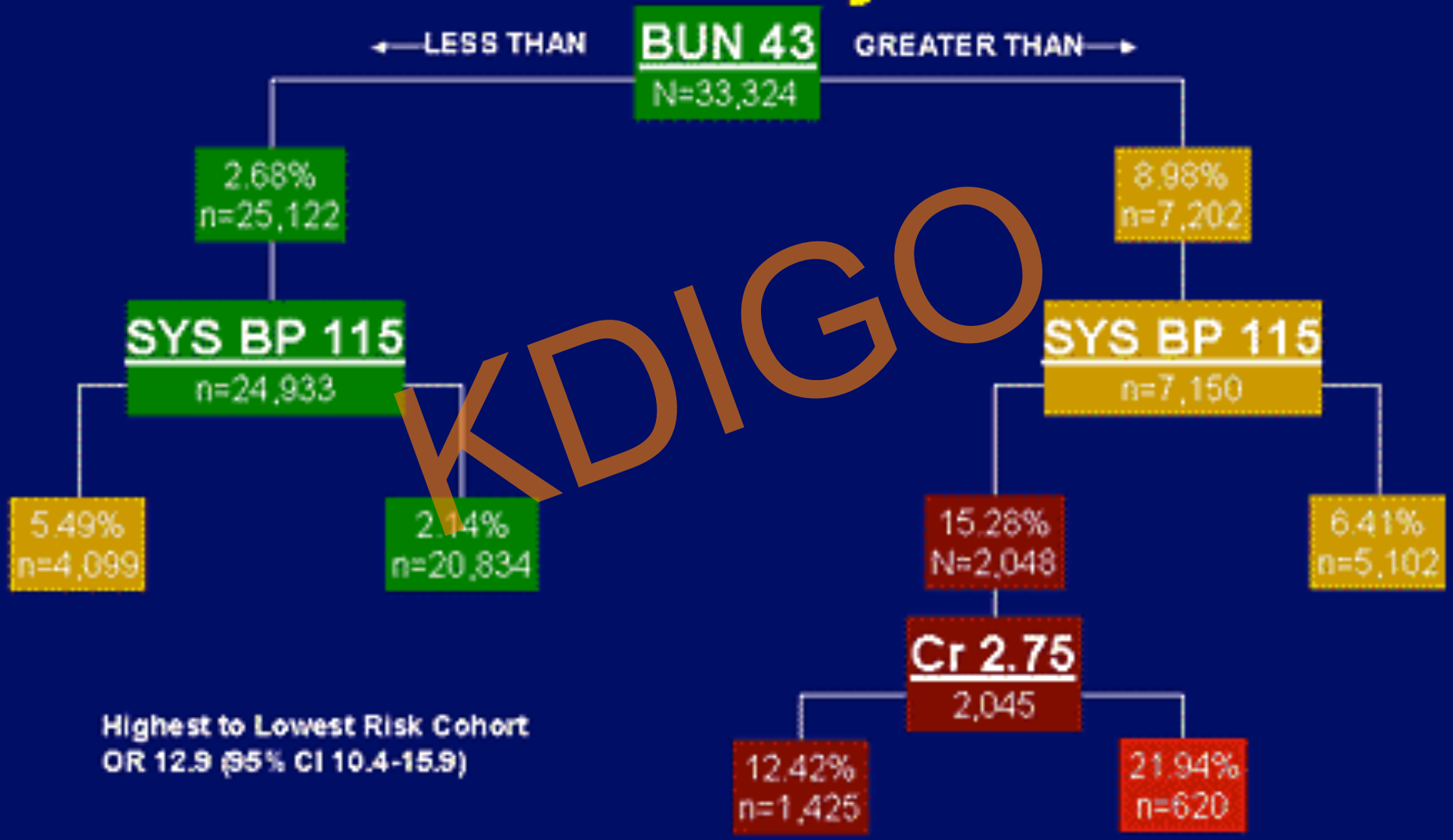
Predictive Value Of Renal Dysfunction In Heart Failure

- 6797 HF subjects (NYHA III-IV) from SOLVD Trials
- Multivariate analysis of survival in subjects with baseline serum Cr < 1.5 vs. Cr 1.5-2.0 (Cr > 2.0 excluded)

Outcome	RR	95% CI	p-value
All Cause Mortality	1.41	1.25-1.59	p<0.001
Pump Failure Death	1.5	1.25-1.8	p<0.001
Sudden Death	1.28	0.99-1.63	p=0.051

Dries et al., 1998

ADHERE CART: Predictors of Mortality



Highest to Lowest Risk Cohort
OR 12.9 (95% CI 10.4-15.9)

Fonarow *Circulation* 2003;108:IV-693

Effect of Worsening Renal Function in Hospitalized Heart Failure Patients

- Average length of stay was 7±4 days for cases and 5±3 days for controls (p=0.001)
- Proportion of patients who stayed in the hospital for > 10 days was 14% for cases and 3% for controls (p<0.05)
- Hospital mortality rate was 5.2% for cases and 1.6% for controls (p<0.05)

- Butler J et al Am Heart J 2004; 147:331-338

Heart Failure With Preserved Ejection Fraction

A Kidney Disorder?

James C. Fang, MD

Heart failure with preserved ejection fraction (HFpEF) is a frustrating problem. Although stiffening of the heart is common and can be frequently demonstrated, other mechanisms have been implicated to account for the common symptoms

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

Piero Ruggenenti[1,2] and Giuseppe Remuzzi[1,2]*

[1]Mario Negri Institute for Pharmacological Research, Bergamo, Italy; and [2]Unit of Nephrology, Azienda Ospedaliera Ospedali Riuniti, Bergamo, Italy

Online publish-ahead-of-print 23 July 2011

Question

- 68 year old patient
  - HTN, DM, CKD, and HF
  - Baseline EF 20% - comes in with AHF
  - BP 110/70, HR 82, Cr 2.0
  - On Lisinopril 20 qd, spironolactone 25 qd, carvedilol 12.5 bid, furosemide 40 bid, ASA
- Day 1 – started on lasix 80 IV bid
- MRA
- ACEI
- Lower ACEi dose
- Day 2 – BP 106/72, Cr 2.4, UO net negative 800cc

Very complex topic

- Will not discuss epidemiology, outcomes, or (speculated) pathophysiology of both diseases co-existing

- Renal function as target of therapy
- Renal function changes in heart failure trials

The story of worsening renal function
(i.e. change in serum creatinine ≥ 0.3mg/dl)

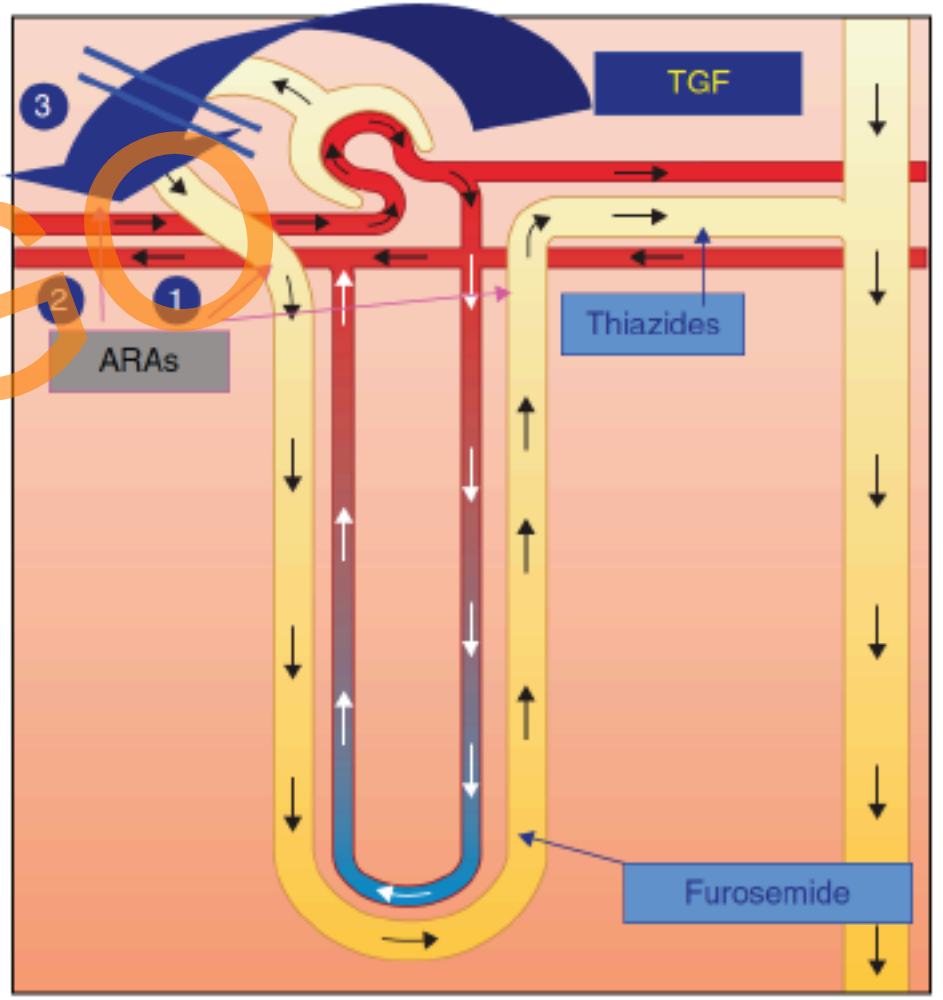
KDIGO

Biological Plausibility of Adenosine A1 Antagonism in Acute Heart Failure and Cardiorenal Syndrome

Slawsky MT, Givertz MM. *Expert Opin Pharmacother* 2009;10:311-322.

Mechanism of potential benefit:

1) Inhibit reabsorption of sodium and water in the proximal and distal tubules, leading to enhanced diuresis and natriuresis;
2) Inhibit afferent arteriolar vasoconstriction;
3) Block tubuloglomerular feedback (TGF), thereby maintaining glomerular filtration rate.

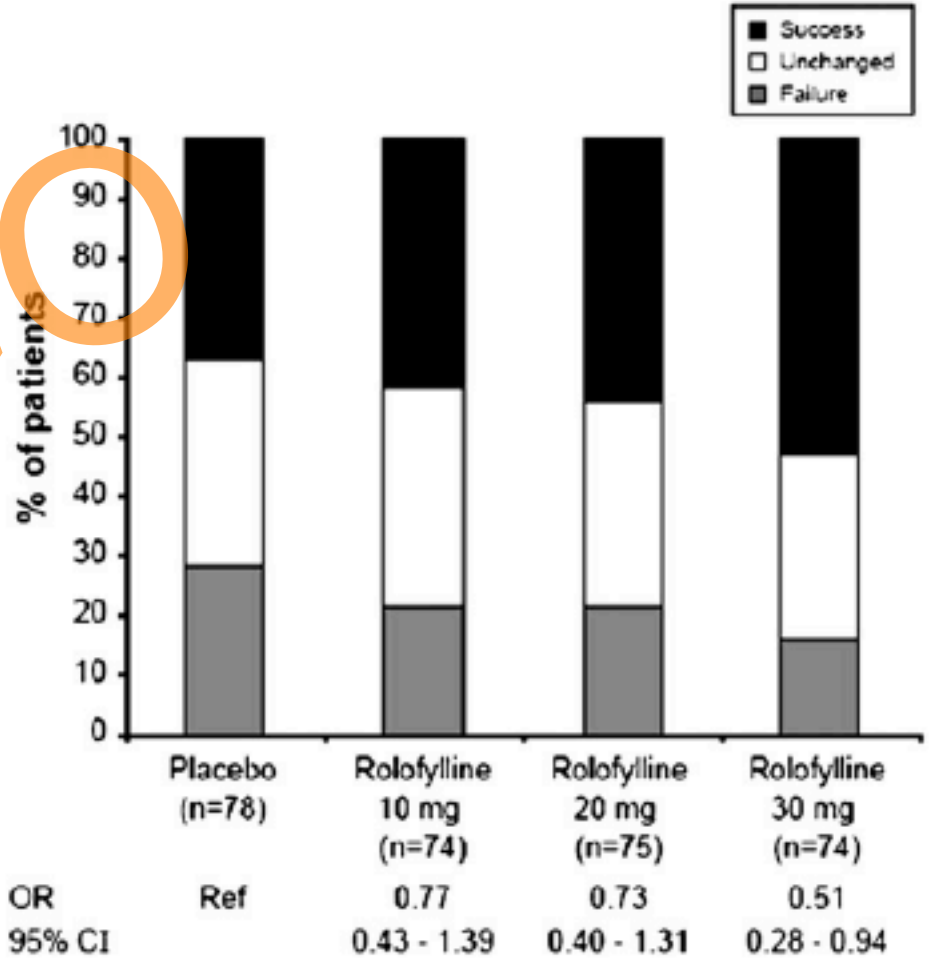


PROTECT-Pilot: Trichotomous Endpoint

Cotter G, *et al. J Cardiac Fail* 2008;14:631-640.

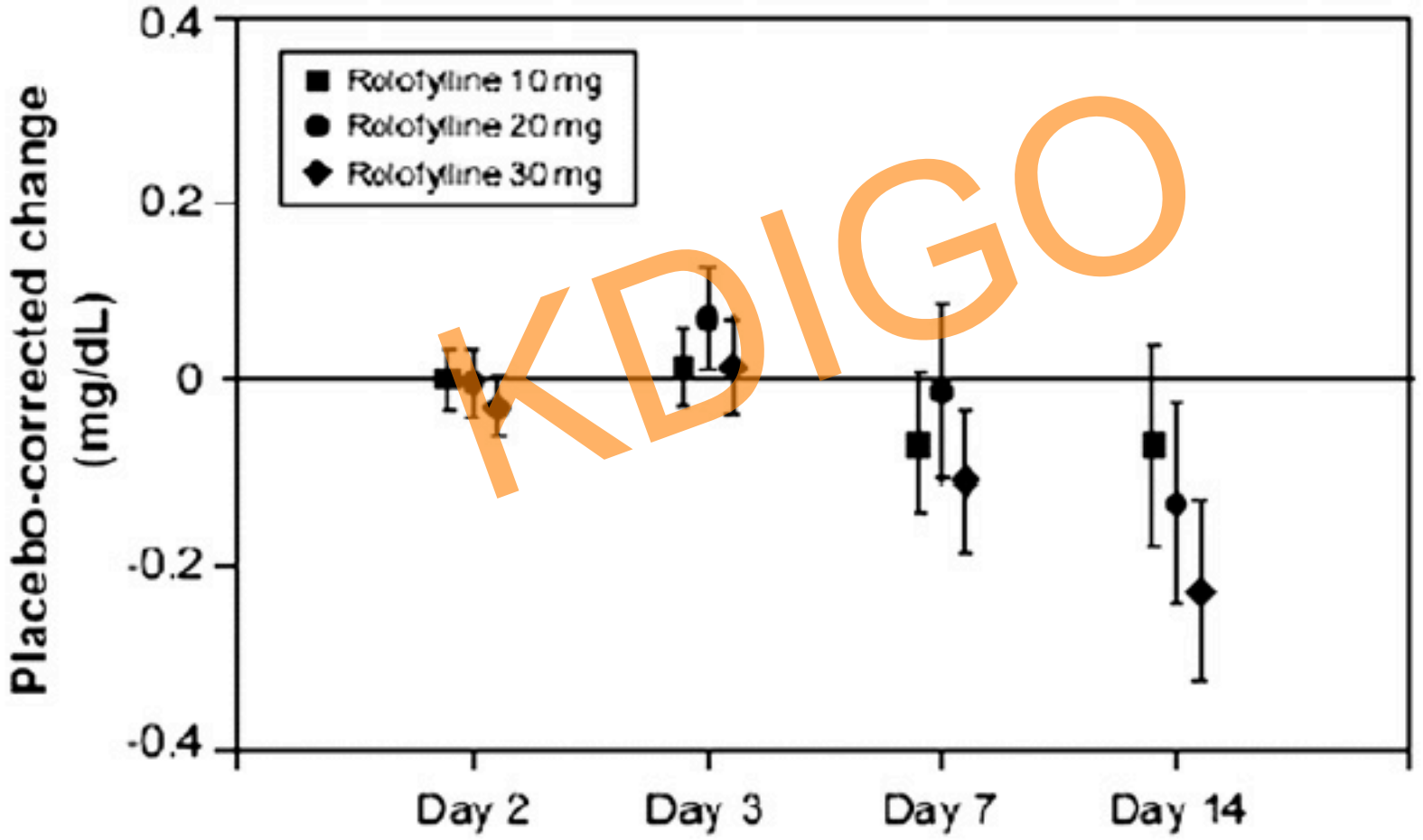
Trichotomous Endpoint:

1) **Success.** Improvement in dyspnea (moderately or markedly better than baseline on 7-level Likert) at 24 and 48h after study start or day of discharge if earlier, without any of the criteria for failure.
2) **Failure.** Death, early HF readmission (within 7 days of study drug initiation), worsening HF as defined daily by the physician assessment by day 7, or persistent renal impairment (Cr increase >0.3 mg/dL to day 7 confirmed at day 14 or the initiation of hemofiltration or dialysis through day 7).
3) **Unchanged.** Patients were classified as unchanged if neither criteria for success or failure were met.



PROTECT-Pilot: Change in Creatinine

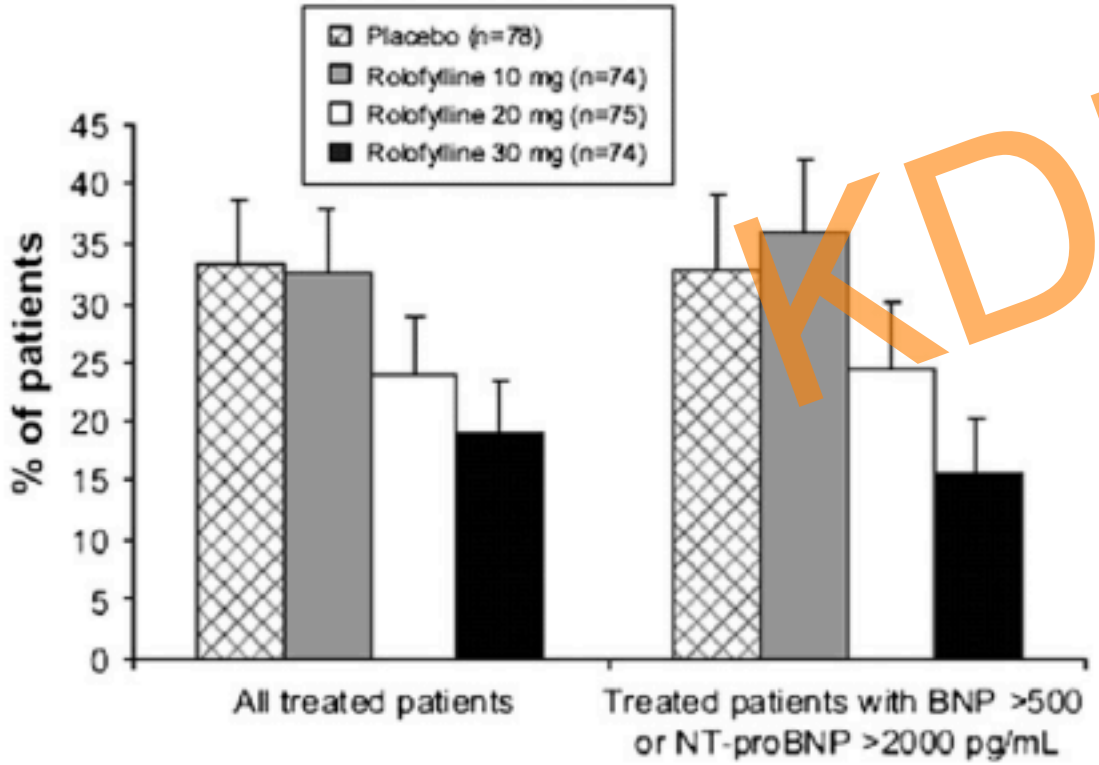
Cotter G, *et al. J Cardiac Fail* 2008;14:631-640.



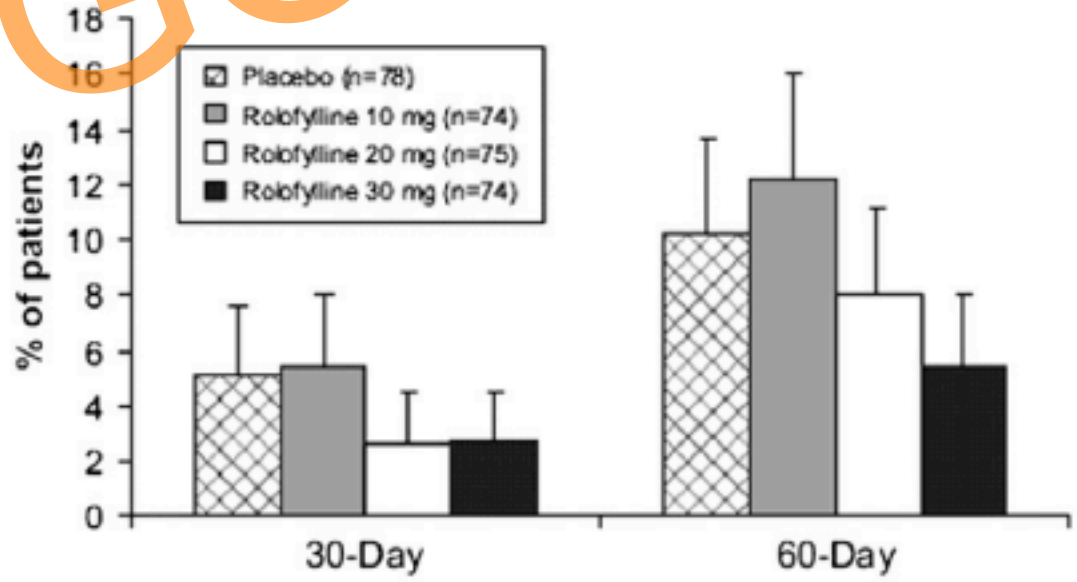
PROTECT-Pilot: Morbidity and Mortality

Cotter G, *et al. J Cardiac Fail* 2008;14:631-640.

60-day All-cause Mortality or CV/Renal Hospitalization



All-cause Mortality



PROTECT: Demographics

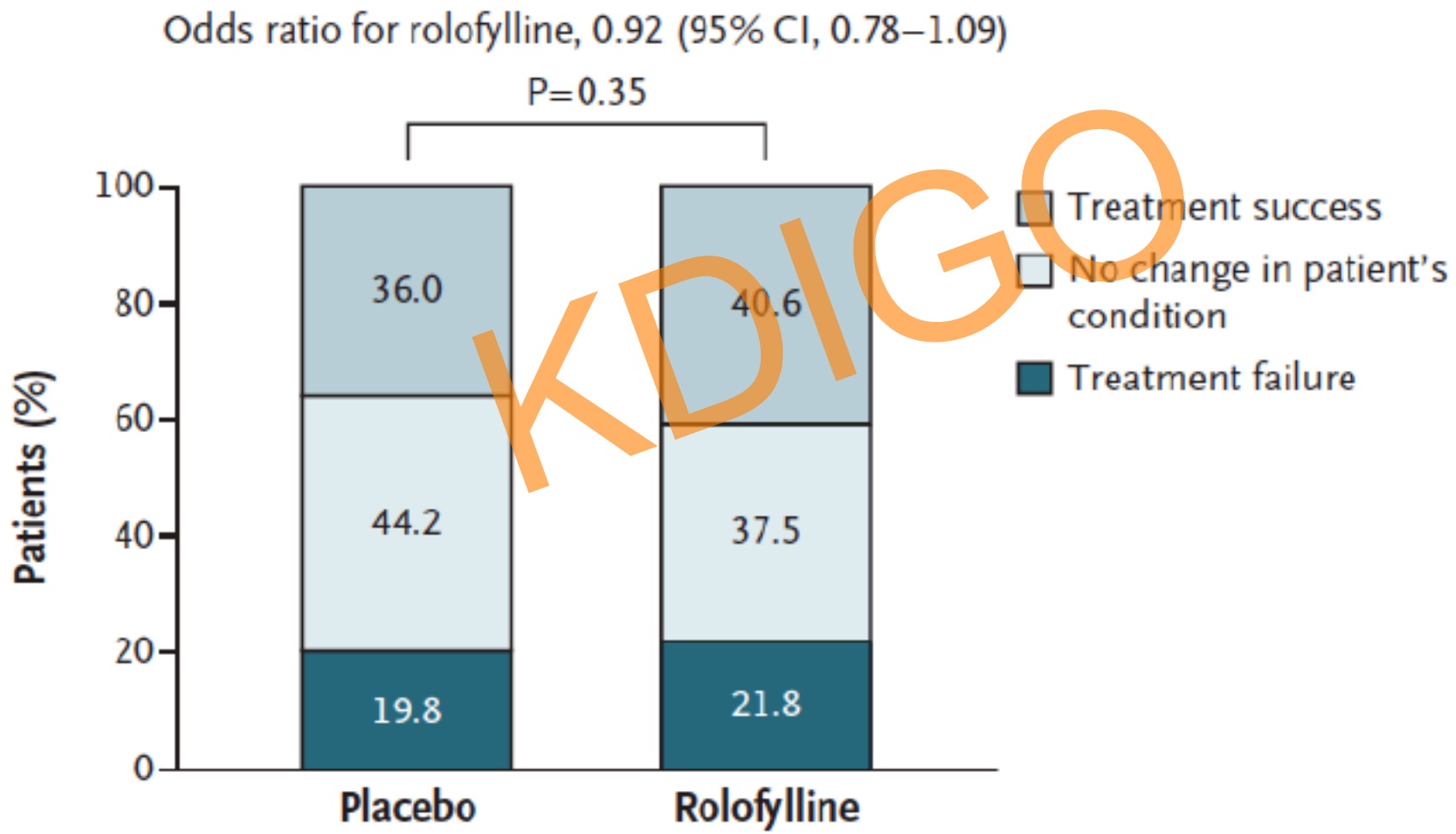
Massie BM, *et al. N Engl J Med* 2010;363:1419-28.

Variable	Rolofylline (N=1356)	Placebo (N=677)	P Value†
Demographic characteristics			
Age (yr)	70.2±11.7	70.2±11.5	0.94
Sex (%)			0.82
Male	67.3	66.8	
Female	32.7	33.2	
Race (%)‡			0.73
White	95.2	95.5	
Other	4.8	4.5	
Measurements			
Body-mass index§	28.9±6.1	28.8±6.2	0.65
Blood pressure (mm Hg)			
Systolic	124.3±17.6	124.2±17.7	0.85
Diastolic	73.6±11.8	74.0±11.9	0.47
Heart rate at rest in the supine position (beats/min)	79.8±15.3	80.7±15.7	0.22
Respiratory rate (breaths/min)	21.2±4.5	21.3±4.4	0.50
BNP (pg/ml)¶			0.62
Median	1290	1198	
Interquartile range	833–2222	773–2235	
NT-proBNP (pg/ml)¶			0.85
Median	3000	3000	
Interquartile range	3000–3832	3000–3800	
Creatinine clearance (ml/min)	50.4±20.0	51.0±20.5	0.55
Left ventricular ejection fraction within previous 6 mo‖	0.323±0.129	0.325±0.135	0.76

Variable	Rolofylline (N=1356)	Placebo (N=677)	P Value†
Medical history (%)			
Heart failure 1 mo before admission	94.6	95.1	0.63
Ischemic heart disease	70.5	68.5	0.36
Myocardial infarction	50.8	46.3	0.06
Hypertension	80.2	77.8	0.21
Atrial fibrillation	53.5	57.0	0.14
Implantable cardioverter–defibrillator	16.2	15.5	0.69
Biventricular pacemaker	10.5	9.8	0.63
Diabetes	45.2	45.8	0.79
COPD or asthma	20.0	19.4	0.75
Treatment before admission (%)			
ACE inhibitor or ARB	76.3	74.4	0.36
Beta-blocker	76.5	75.7	0.71
Aldosterone blocker	44.5	42.4	0.36
Nitrates (oral or topical)	27.0	23.9	0.13
Digoxin	27.3	29.6	0.27

PROTECT: Primary Endpoint

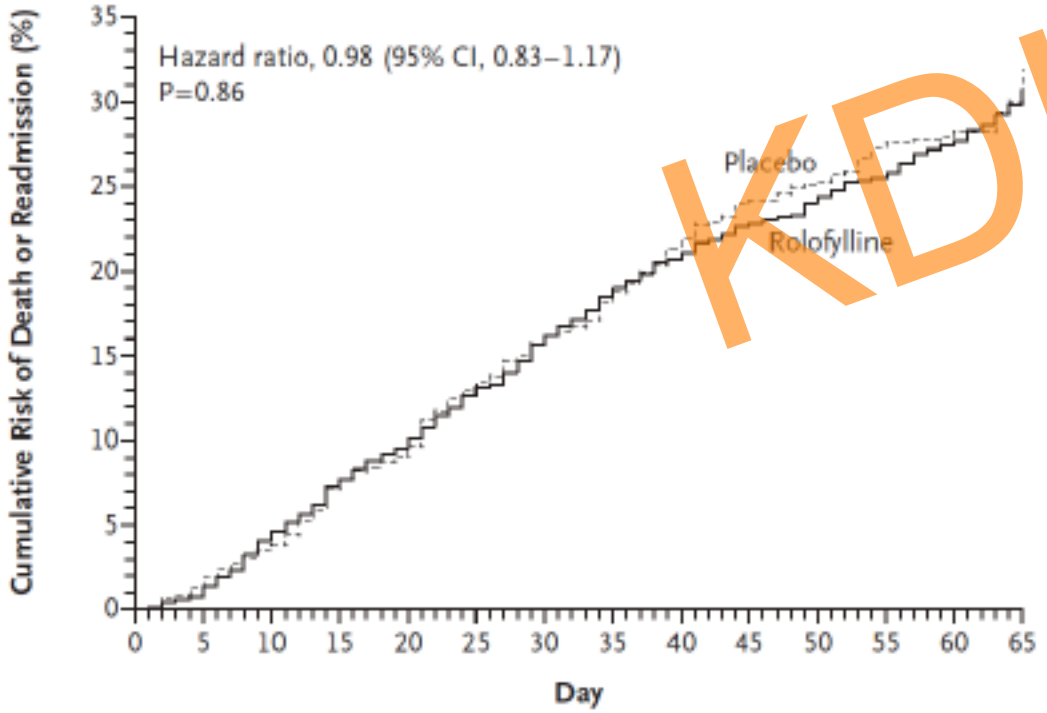
Massie BM, *et al. N Engl J Med* 2010;363:1419-28.



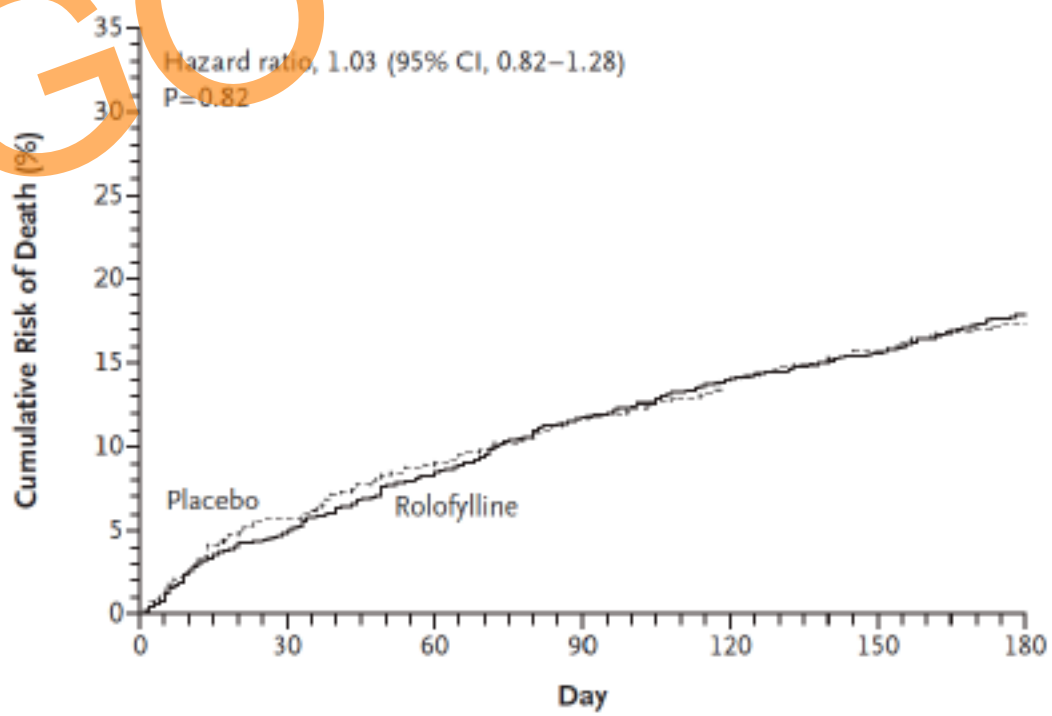
PROTECT: Morbidity & Mortality

Massie BM, *et al. N Engl J Med* 2010;363:1419-28.

60-day All-cause Mortality or CV/Renal Hospitalization



180-day All-cause Mortality



"Your Honor, we feel the trial failed to deliver on its pretrial publicity."

But the question is – who decided that a change in serum creatinine ≥ 0.3 mg/dl – aka WRF is a problem and a target of therapy?

Journal of Cardiac Failure Vol. 8 No. 3 2002

Clinical Investigators

The Prognostic Importance of Different Definitions of Worsening Renal Function in Congestive Heart Failure

STEPHEN S. GOTTLIEB, MD,[1] WILLIAM ABRAHAM, MD,[2]
JAVED BUTLER, MD,[3] DANIEL E. FORMAN, MD,[4]
EVAN LOH, MD,[5] BARRY M. MASSIE, MD,[6]
CHRISTOPHER M. O'CONNOR, MD,[7] MICHAEL W. RICH, MD,[8]
LYNNE WARNER STEVENSON, MD,[9] JAMES YOUNG, MD,[10]
AND HARLAN M. KRUMHOLZ, MD[11]

Baltimore, Maryland; Lexington, Kentucky; Nashville, Tennessee; Boston, Massachusetts; Radnor, Pennsylvania; San Francisco, California; Durham, North Carolina; St. Louis, Missouri; Cleveland, Ohio; New Haven, Connecticut

Table 2. Frequency (in the Entire Population) of Worsening Renal Function (Using Different Definitions)

Definition	Frequency
Increase in creatinine (mg/dl) of	
0.1	72%
0.2	53%
0.3	39%
0.4	27%
0.5	20%
Increase in creatinine of	
10%	55%
20%	30%
30%	15%
40%	6%
50%	3%
Final creatinine of ≥ 1.5 mg/dl and increase in creatinine of	
0.1	40%
0.2	35%
0.3	29%
0.4	24%
0.5	18%
Final creatinine of ≥ 2.0 mg/dl and increase in creatinine of	
0.1	22%
0.2	20%
0.3	18%
0.4	16%
0.5	13%
Final creatinine of ≥ of 2.0 mg/dl and increase in creatinine of	
10%	18%
20%	11%
30%	7%
40%	4%
50%	2%

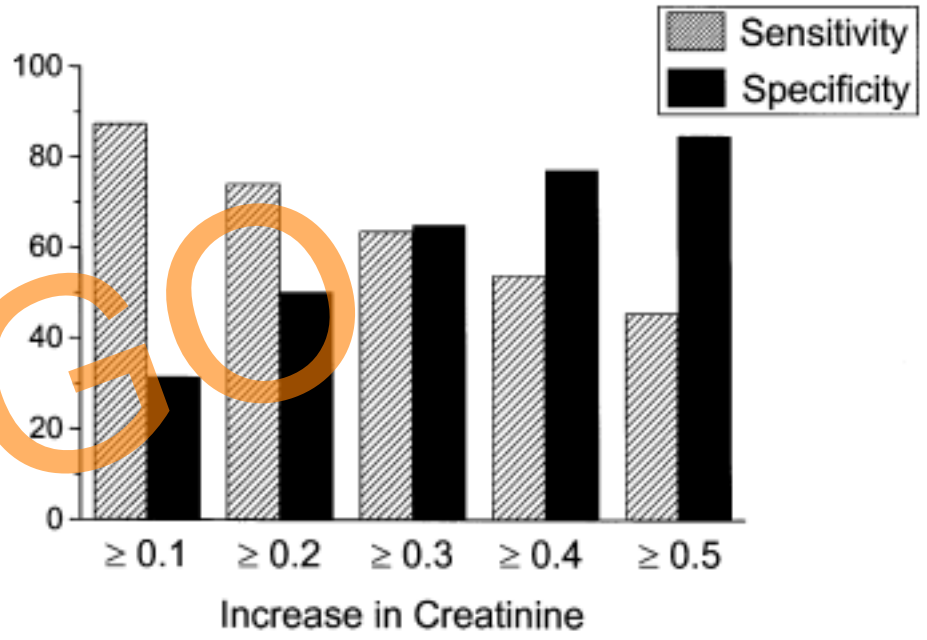


Fig. 2. The sensitivity and specificity of increased serum creatinine for predicting a length of stay of at least 10 days. Using increasing values of serum creatinine, sensitivity decreased while specificity increased.

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Incidence, Predictors at Admission, and Impact of Worsening Renal Function Among Patients Hospitalized With Heart Failure

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Boston, Massachusetts; Nashville, Tennessee; New Haven and Middletown, Connecticut; Columbus and Cleveland, Ohio; Durham, North Carolina; Baltimore, Maryland; Philadelphia, Pennsylvania; San Francisco, California; and St. Louis, Missouri

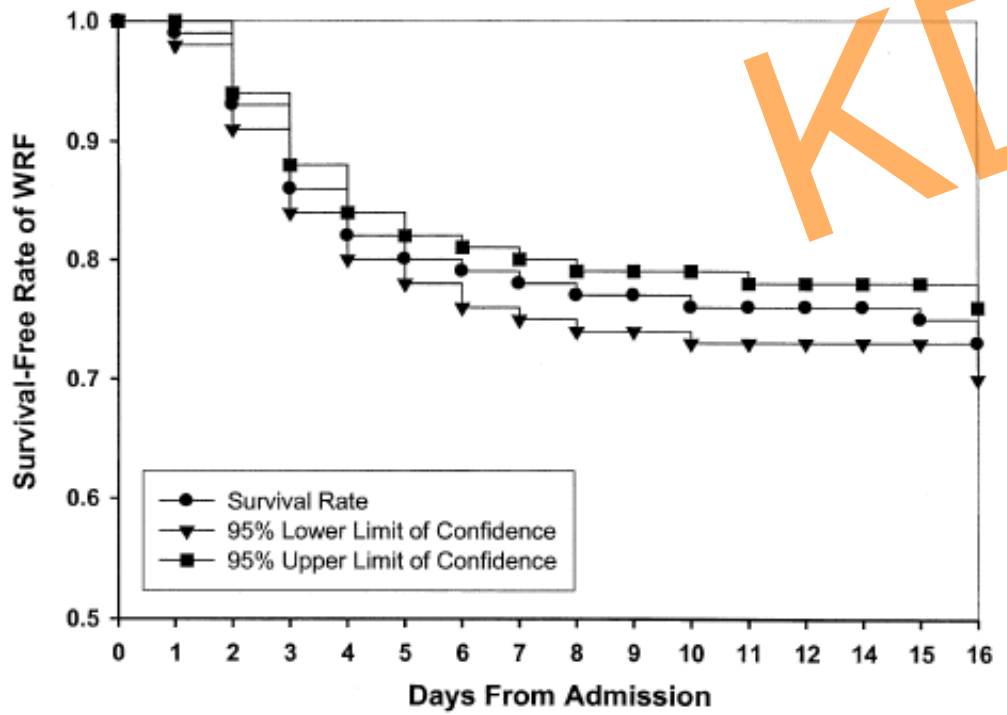


Table 4. Risk Score and WRF

Score	#	%	WRF #	WRF %	Relative Risk
0	123	12.25	12	9.76	1 (Reference)
1	257	25.60	48	18.68	1.91
2	251	25.00	51	20.32	2.08
3	155	15.44	47	30.32	3.11
4+	218	21.71	115	52.75	5.40
Cochran-Armiage trend test (p value)				<0.001	
Total	1,004	100	273	27.19	

Score for "1.5 ≤ creatinine <2.5" is 2 and for "creatinine ≥2.5" is 3.
WRF = worsening renal function.

KDIGO

Over 700 papers published related to WRF

European Heart Journal (2011) **32**, 2563–2572
doi:10.1093/eurheartj/ehr238

Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial

John E.A. Blair[1], Peter S. Pang[2], Robert W. Schrier[3], Marco Metra[4], Brian Traver[5], Thomas Cook[5], Umberto Campia[2], Andrew Ambrosy[2], John C. Burnett Jr[6], Liliana Grinfeld[7], Aldo P. Maggioni[8], Karl Swedberg[9], James E. Udelson[10], Faiez Zannad[11], Marvin A. Konstam[10], and Mihai Gheorghiade[2]*, on behalf of the EVEREST Investigators

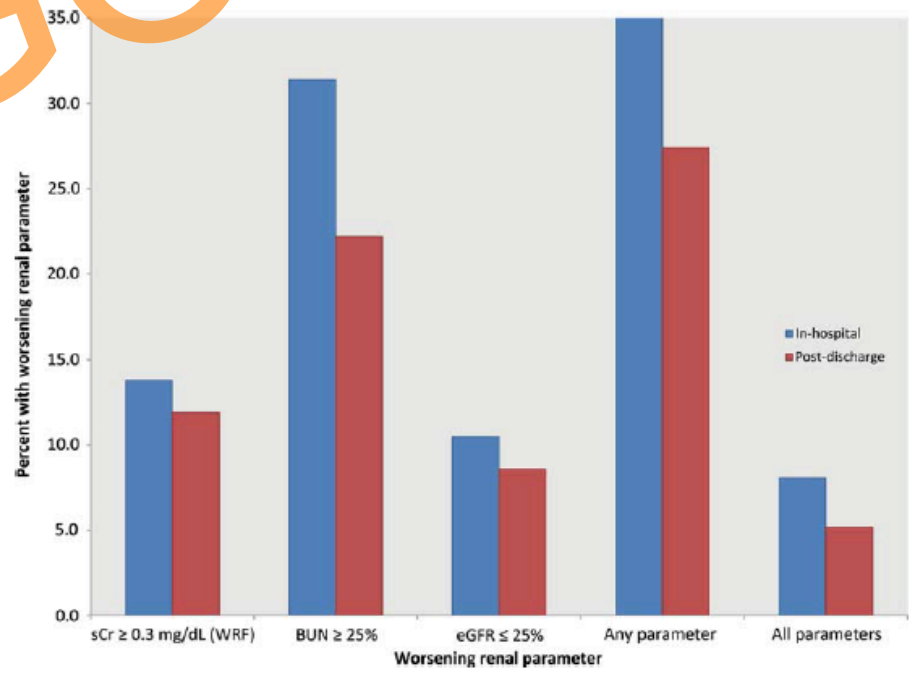


Figure 1 In-hospital and post-discharge changes in renal parameters.

Table 2 Baseline characteristics by composite congestion score at discharge/day 7

	0	1	2	3–9	*P*-value
Total, *n* (%)	890 (45.90)	505 (26.04)	247 (12.74)	297 (15.32)	
Serum BNP median[a] (IQR)	599.2 (1246.6)	683.1 (1406.7)	826.0 (1762.0)	1193.9 (2370.7)	<0.001
Serum NT-proBNP median[a] (IQR)	4145.2 (7589.1)	4244.4 (8107.5)	5456.1 (11250.0)	6385.4 (12007.5)	0.002

	Discharge CCS				Overall[a]
	0	1	2	3–9	
Total (*n*)	890	505	247	297	2061
HHF	233, 26.2%	176, 34.9%	86, 34.8%	103, 34.7%	629, 30.5%
ACM	170, 19.1%	125, 24.8%	62, 25.1%	127, 42.8%	543, 26.4%
ACM + HHF	317, 35.6%	231, 45.7%	113, 45.8%	177, 60.0%	912, 44.3%

Table 4 Changes of physical and laboratory parameters during the in-hospital and post-discharge periods for patients with and without worsening renal function

Characteristic	Renal function status						*P*-value*
	WRF			No WRF			
	n	Starting value (SD)	Change (SD)	*n*	Starting value (SD)	Change (SD)	
In-hospital period							
SBP, mmHg	270	123.7 (20.3)	−9.8 (17.2)	1672	119.8 (19.2)	−4.6 (16.0)	0.0001
DBP, mmHg	270	73.4 (11.8)	−5.8 (11.7)	1671	72.5 (12.7)	−3.0 (11.6)	<0.0001
Body weight, kg	265	83.5 (17.8)	−3.1 (3.5)	1633	83.2 (18.7)	−2.8 (3.4)	0.03
Congestion score	253	4.19 (1.88)	−3.11 (1.88)	1600	4.04 (1.83)	−2.94 (1.78)	0.2
Log_{10}BNP	169	2.82 (0.47)	−0.22 (0.36)	1075	2.80 (0.52)	−0.15 (0.33)	0.003
Log_{10}NT-pBNP	92	3.66 (0.47)	−0.22 (0.31)	547	3.60 (0.52)	−0.18 (0.27)	0.3

The Relationship Between Transient and Persistent Worsening Renal Function and Mortality in Patients With Acute Decompensated Heart Failure

DORON ARONSON, MD,[1] AND ANDREW J. BURGER, MD[2]

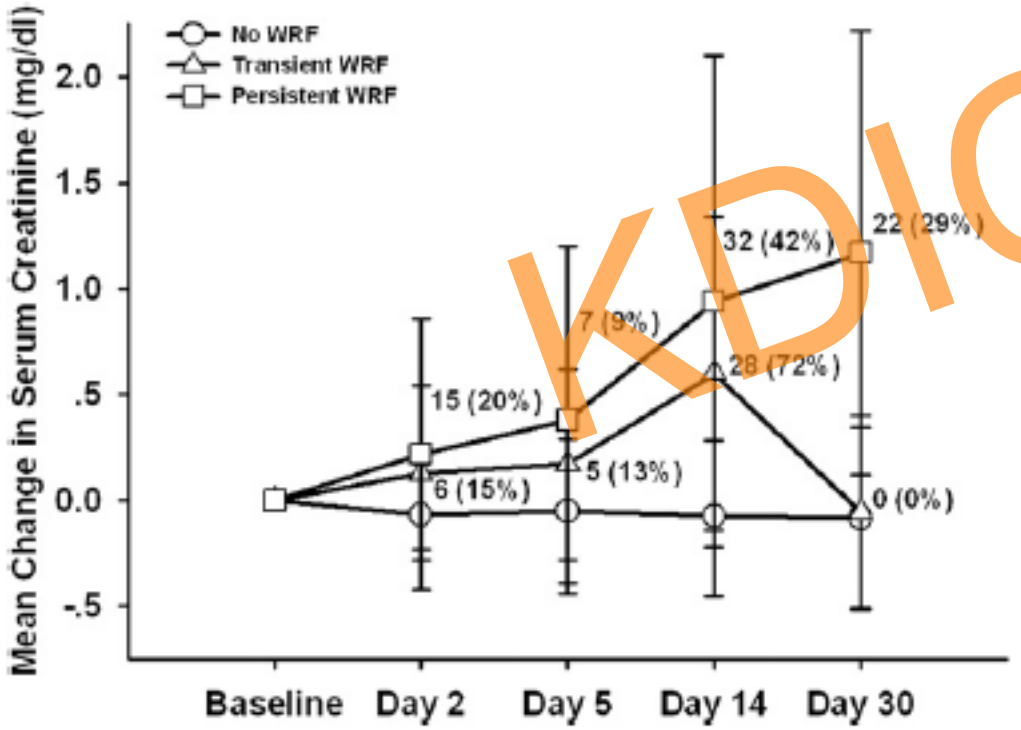
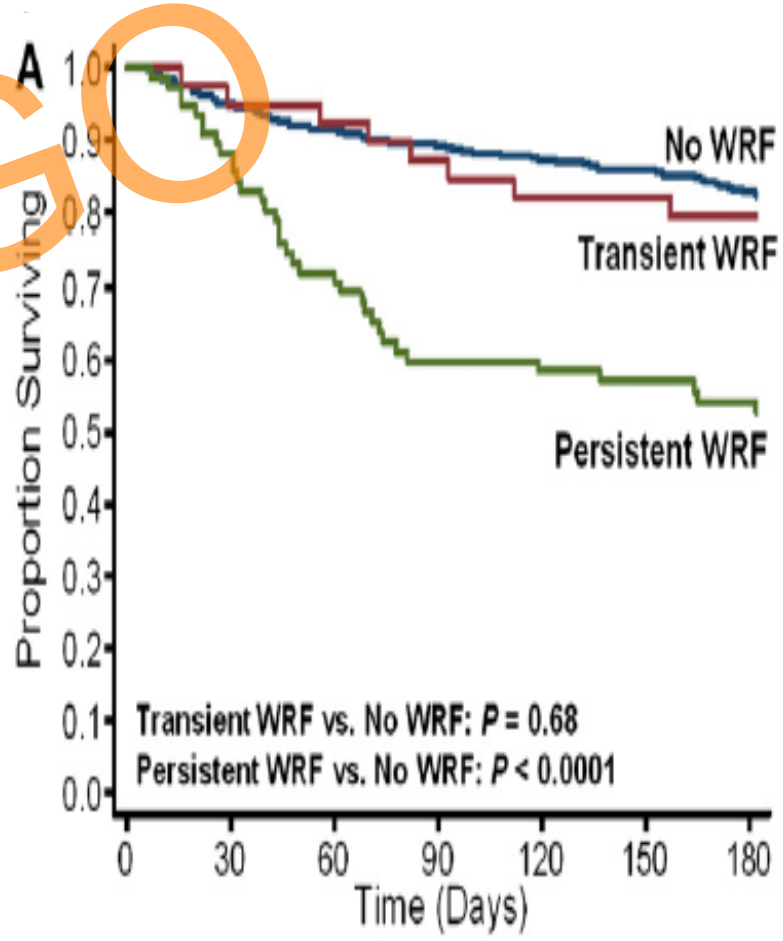


Fig. 1. Mean change in serum creatinine (SD) over time in the 3 study groups. The number and percent of patients who first experienced worsening renal function is presented at each time point.



Lesson

- Observational studies
  - Great for hypothesis generation
  - Great for safety assessment
  - Not great for causality ascertainment
- Understand pathophysiology
- Target of therapy should actually be present, or
- At risk population
  - WRF
    WHF

If you have time only to read 2 pages !

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

Piero Ruggenenti[1,2] and Giuseppe Remuzzi[1,2]*

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Online publish-ahead-of-print 23 July 2011

CONTROVERSIES IN HEART FAILURE

Jordan T. Shin, MD, PhD; G. William Dec, MD

(Circ Heart Fail. 2009;2:499-504.)

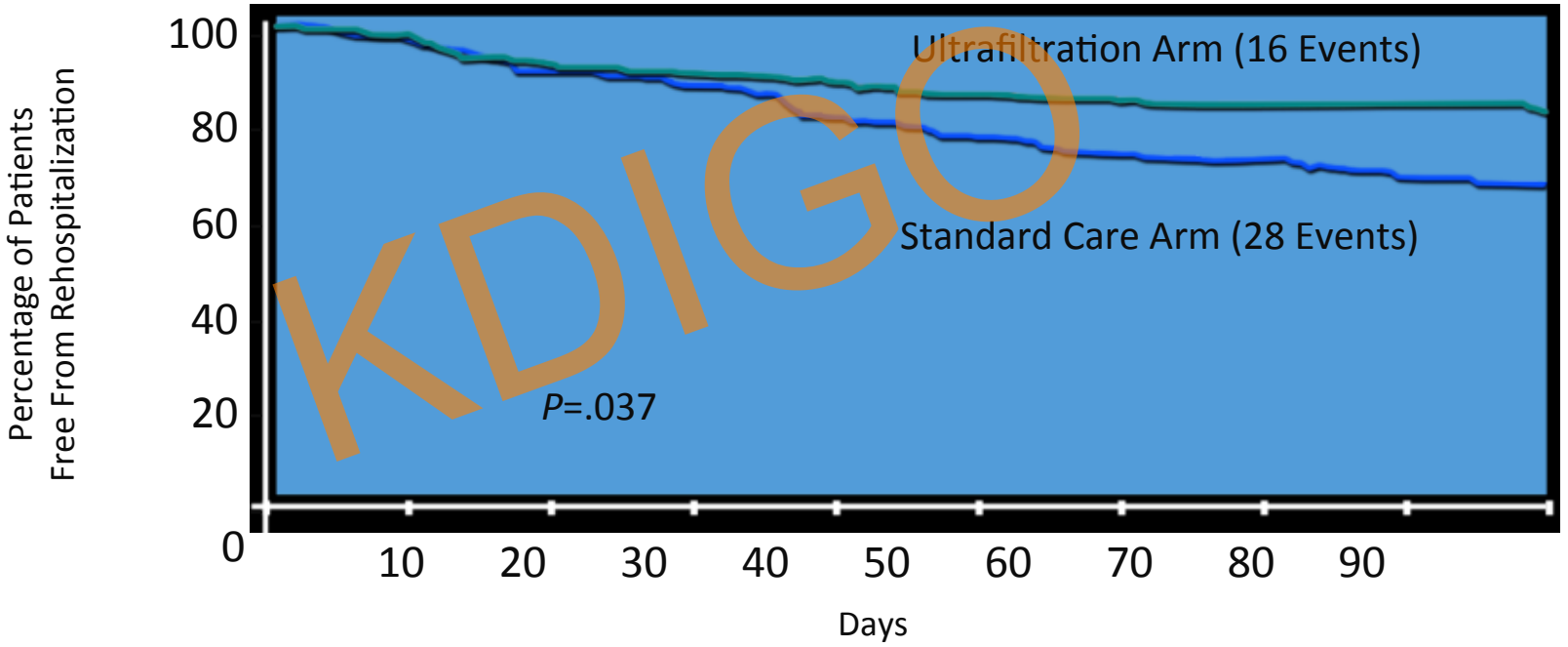
Should Ultrafiltration Be Used Perferentially Instead of Diuretics for the Initial Treatment of ADHF Patients?

- More rapid removal of fluid excess and improvement in symptoms
- Higher clearance of sodium load
- Isotonic fluid removal
- Decreased risk of electrolyte abnormalities (ie, hypokalemia)
- Decreased risk of worsening renal function
- Lack of activation of the RASS and the SNS
- Removal of proinflammatory cytokines
- Shortened LOS
- Decreased rate of readmissions for heart failure

- Significant cost per procedure
- Nursing training and staffing required
- Excessive volume removal resulting in hypotension, WRF, and ARF
- Allergic reaction to extracorporeal circuit
- Catheter-related complications (infection and thrombosis)
- Hemorrhage-complicating systemic anticoagulation
- Hemorrhage from venous return disconnection
- Air embolism
- Hemolysis and hyperkalemia

Ultrafiltration versus IV Diuretics for Patients Hospitalized for ADHF: UNLOAD Trial

Freedom From Readmission for HF



No. Patients at Risk										
Ultrafiltration Arm	88	85	80	77	75	72	70	66	64	45
Standard Care Arm	86	83	77	74	66	63	59	58	52	41

Costanzo MR et al. *J Am Coll Cardiol.* 2007;49:675-683.

Ultrafiltration versus IV Diuretics for Patients Hospitalized for ADHF: UNLOAD Trial

Resources Utilization for HF in 90 Days

Resource	UF	SC	*P* Value
Rehospitalizations/Patient	0.22	0.46	.037
Number of rehospitalization days per patient	1.4	3.8	.022
Days rehospitalized	123	330	.022
Unscheduled office + ED visits (%)	21	44	.009

Heart failure focused outcomes – need all cause related hospitalizations

Costanzo MR et al. *J Am Coll Cardiol.* 2007;49:675-683.

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

Eligibility Criteria

Inclusion

- Age 18 or older
- Admitted to hospital with ADHF
- Worsened renal function with increase in creatinine ≥ 0.3 mg/dL
- Persistent congestion

Exclusion

- Creatinine > 3.5 mg/dL
- Alternate explanation for worsening renal function
- Systolic blood pressure < 90 mm Hg
- Hematocrit > 45%
- Need for IV vasoactive drugs

Stepped Pharmacologic Care

First 2 days

- Adjust diuretics to maintain 3–5 liters urine/day

After 48 hours if urine output still inadequate

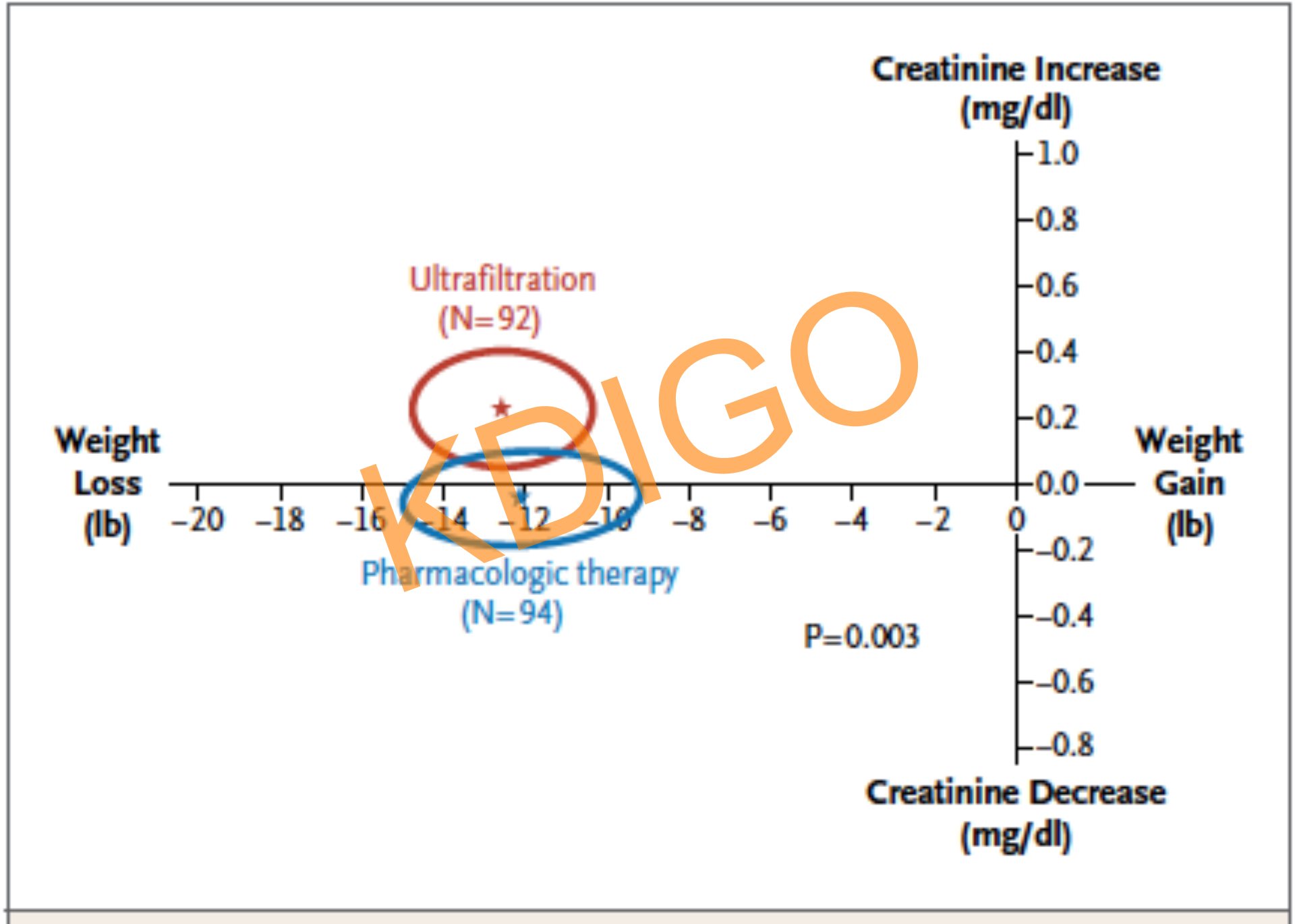
- Consider dopamine or dobutamine if SBP < 110 mm Hg and EF < 40%
- Nitroglycerin or nesiritide if SBP > 120 and severe symptoms

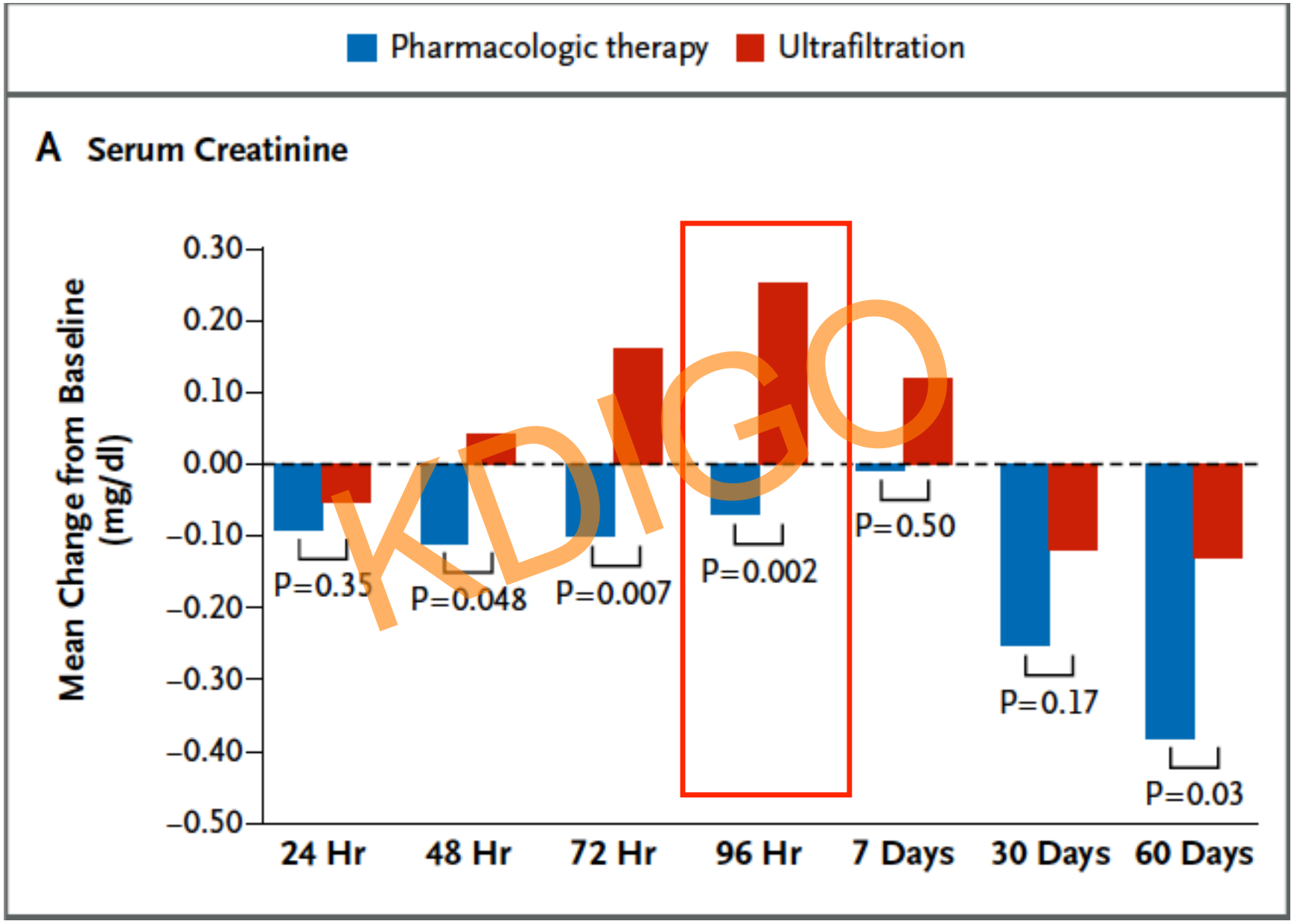
After 72 hours if urine output still inadequate

- Consider hemodynamic guided IV therapy, crossover to UF, or dialysis

Limitations

- Patient Population
  - CRS vs. diuretic resistant
  - Robust diuresis – not in CRS?
- Small N
- Treatment differences
  - 92 (56-138) hr. for stepped care
  - 40 (28-67) hr. for UF
  - UF – 9% cross over and 30% IV diuretics

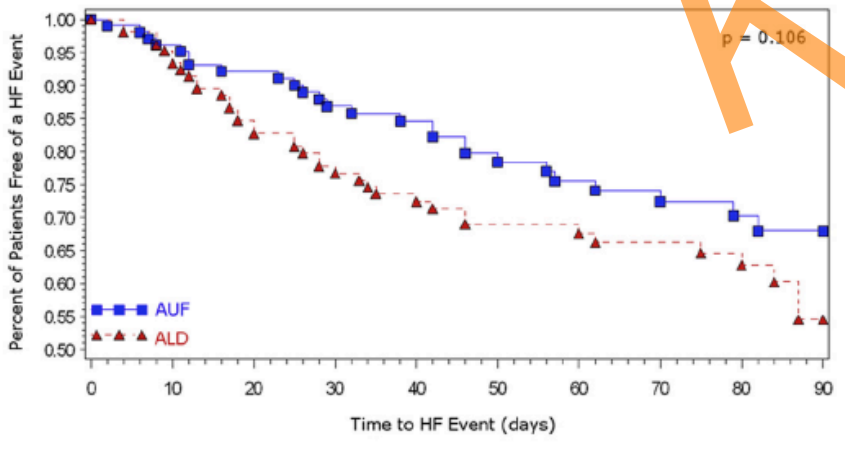

Creatinine Increase
(mg/dl)
1.0
0.8
0.6
0.4
0.2
0.0
–0.2
–0.4
–0.6
–0.8
Creatinine Decrease
(mg/dl)
Weight
Loss
(lb)
–20
–18
–16
–14
–12
–10
–8
–6
–4
–2
0
Weight
Gain
(lb)
Ultrafiltration
(N=92)
Pharmacologic therapy
(N=94)
P=0.003


Pharmacologic therapy
Ultrafiltration
A Serum Creatinine
Mean Change from Baseline (mg/dl)
0.30
0.20
0.10
0.00
−0.10
−0.20
−0.30
−0.40
−0.50
P=0.35
P=0.048
P=0.007
P=0.002
P=0.50
P=0.17
P=0.03
24 Hr
48 Hr
72 Hr
96 Hr
7 Days
30 Days
60 Days
KDIGO

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

Maria Rosa Costanzo, MD,[a] Daniel Negoianu, MD,[b] Brian E. Jaski, MD,[c] Bradley A. Bart, MD,[d] James T. Heywood, MD,[e] Inder S. Anand, MD, DPHIL (OXON),[f] James M. Smelser, MD,[g] Alan M. Kaneshige, MD,[h] Don B. Chomsky, MD,[i] Eric D. Adler, MD,[j] Garrie J. Haas, MD,[k] James A. Watts, MD,[l] Jose L. Nabut, MS,[m] Michael P. Schollmeyer, DVM,[m] Gregg C. Fonarow, MD[n]

FIGURE 2 Primary Endpoint: Time to Heart Failure Event after Discharge



	Baseline	30 Days	60 Days	90 Days
AUF	105	80	52	19
ALD	108	74	49	15

EDITORIAL COMMENT

When Business and Science Clash, How Can We Avoid Harming Patients?

The Case of AVOID-HF*

Daniel B. Mark, MD, MPH, Christopher M. O'Connor, MD

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure

Current Status and Prospects for Further Research

Maria Rosa Costanzo, MD,[a] Claudio Ronco, MD,[b,c] William T. Abraham, MD,[d] Piergiuseppe Agostoni, MD,[e,f] Jonathan Barasch, MD, PHD,[g] Gregg C. Fonarow, MD,[h] Stephen S. Gottlieb, MD,[i,j] Brian E. Jaski, MD,[k,l] Amir Kazory, MD,[m] Allison P. Levin, BA,[n] Howard R. Levin, MD,[o] Giancarlo Marenzi, MD,[e] Wilfried Mullens, MD,[p] Dan Negoianu, MD,[q] Margaret M. Redfield, MD,[r] W.H. Wilson Tang, MD,[s] Jeffrey M. Testani, MD, MTR,[t] Adriaan A. Voors, MD, PHD[u]

Lessons

- While we are trying to understand science and pathophysiology – need to give a lot of attention to how will we answer all the questions when
  - A. Interest in physiology is down
  - B. Conduct of clinical trials is very expensive
  - C. Regulatory requirements and academic support (including non-monetory) makes it even more difficult

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*

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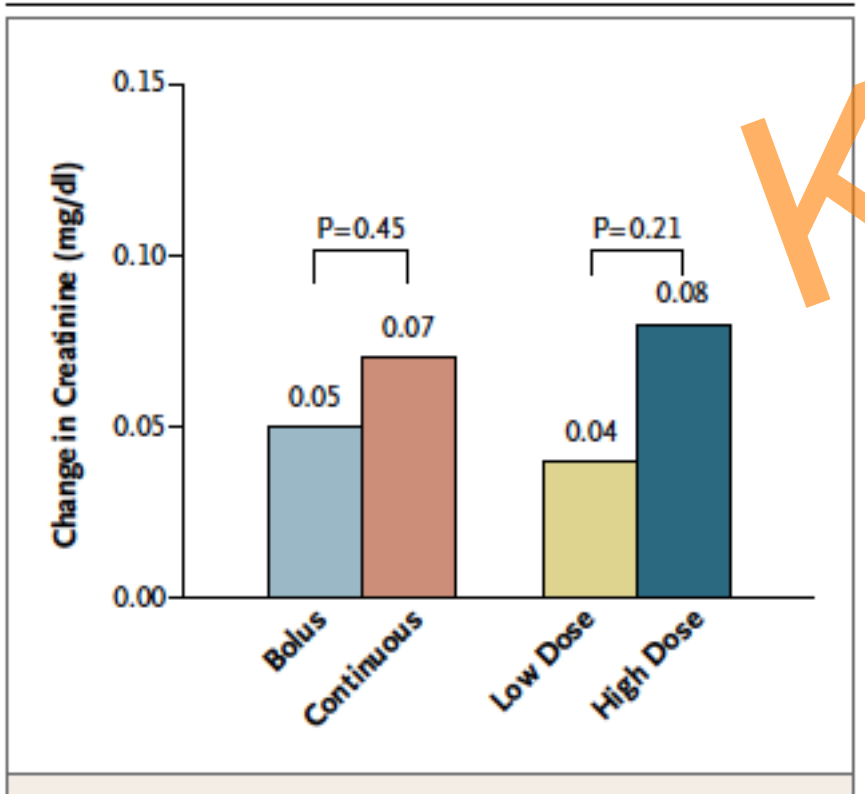


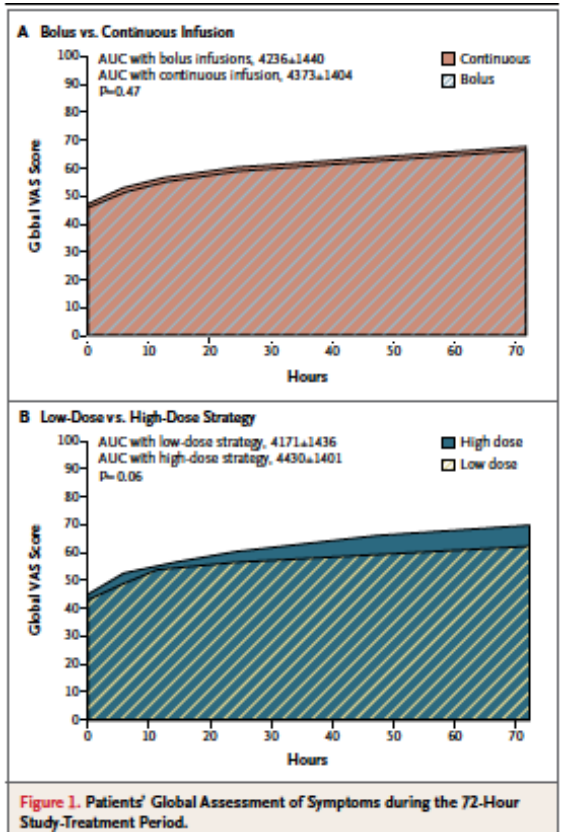
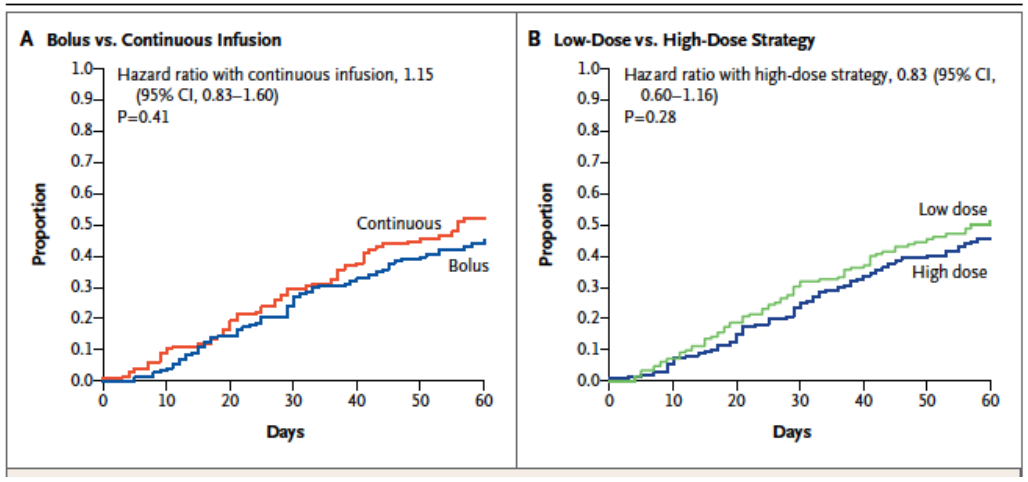


Figure 1. Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.



Lessons

- “Overt” diuresis
  - Met need
  - Current diuretics works
  - Aggressive stepped care approaches need to be implemented
- Curb the enthusiasm for pragmatic trials to appropriate circumstances
- Understand
  - Sub-clinical congestion
  - Redistribution

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

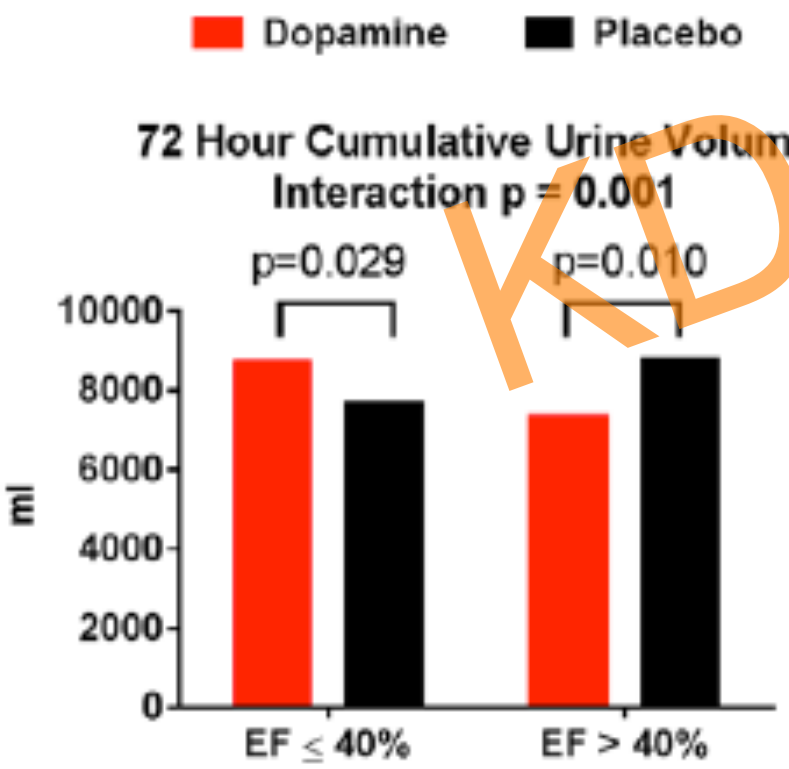
Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

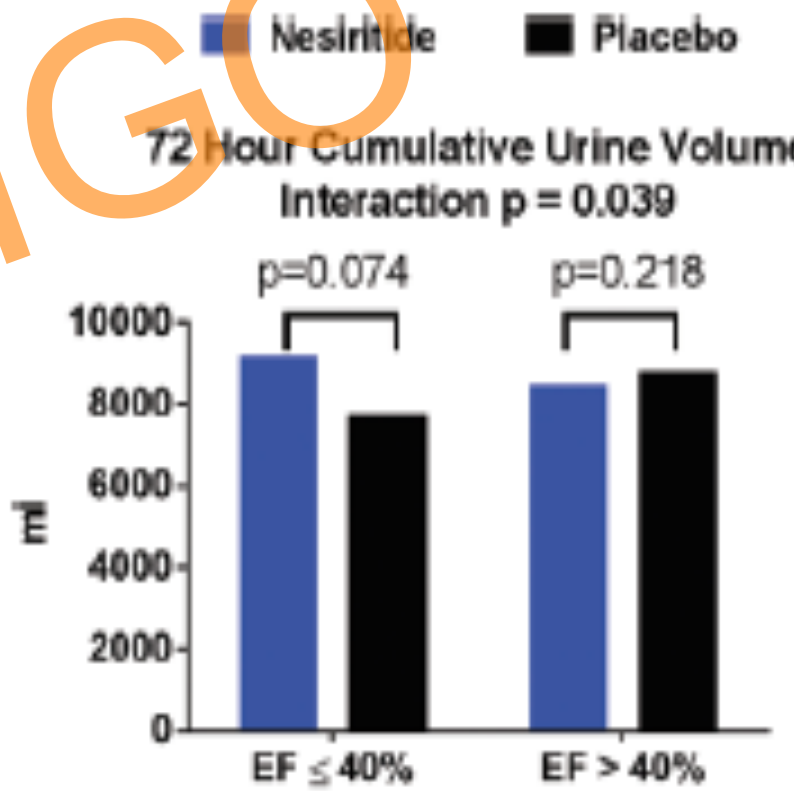
	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	Placebo (n = 119)	Dopamine (n = 122)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (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

Differential Response to Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Reduced or Preserved Ejection Fraction

Results From the ROSE AHF Trial (Renal Optimization Strategies Evaluation in Acute Heart Failure)

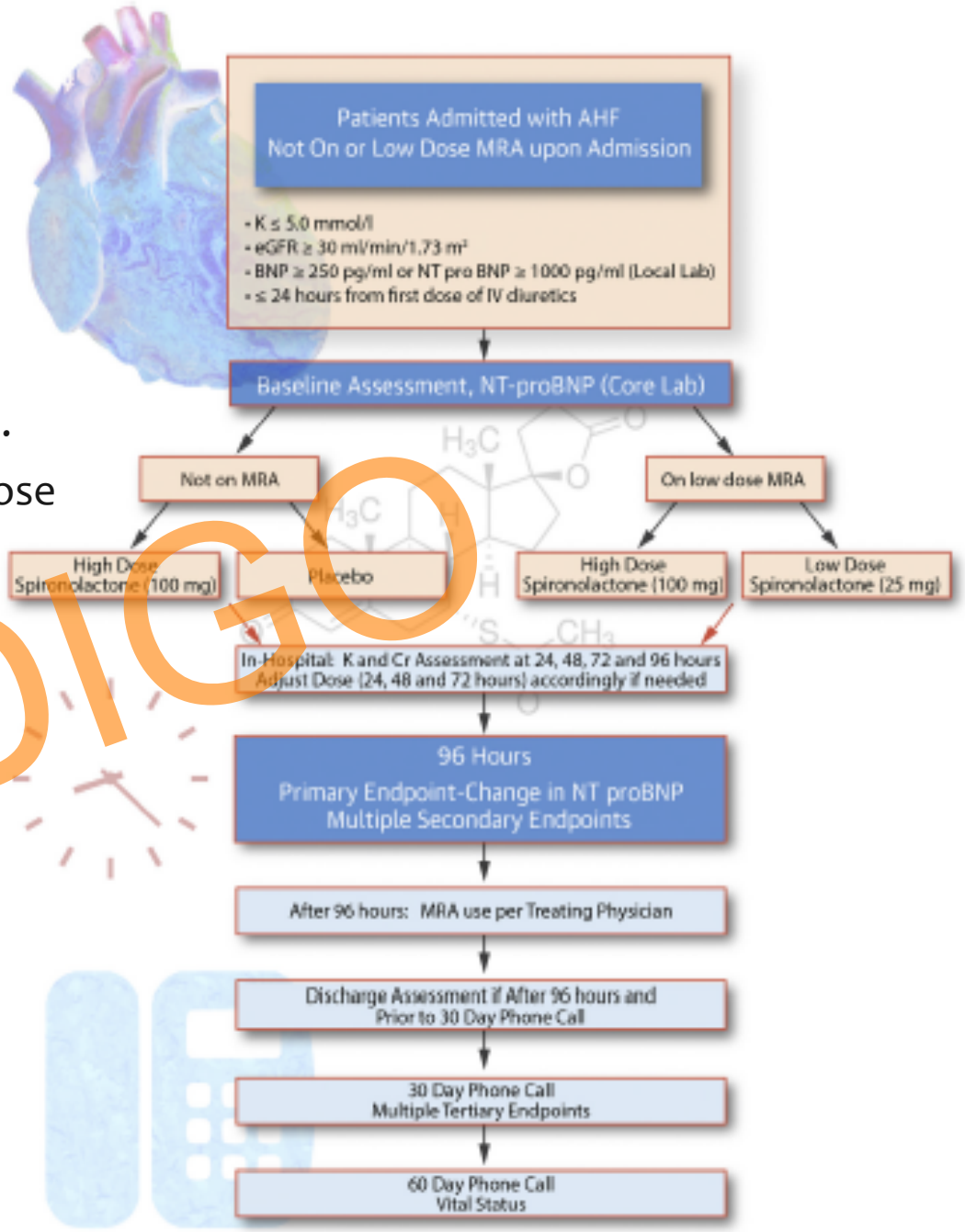
Siu-Hin Wan, MD; Susanna R. Stevens, MS; Barry A. Borlaug, MD; Kevin J. Anstrom, PhD; Anita Deswal, MD; G. Michael Felker, MD; Michael M. Givertz, MD; Bradley A. Bart, MD; W.H. Wilson Tang, MD; Margaret M. Redfield, MD; Horng H. Chen, MBBCh





Study Flow and Enrollment – ATHENA HF

- 12/2014 to 4/2016
- 360 patients enrolled from 22 sites.
- 182 patients randomized to high-dose spironolactone
- 178 to usual care
  - 132 placebo
  - 46 continued low dose spironolactone

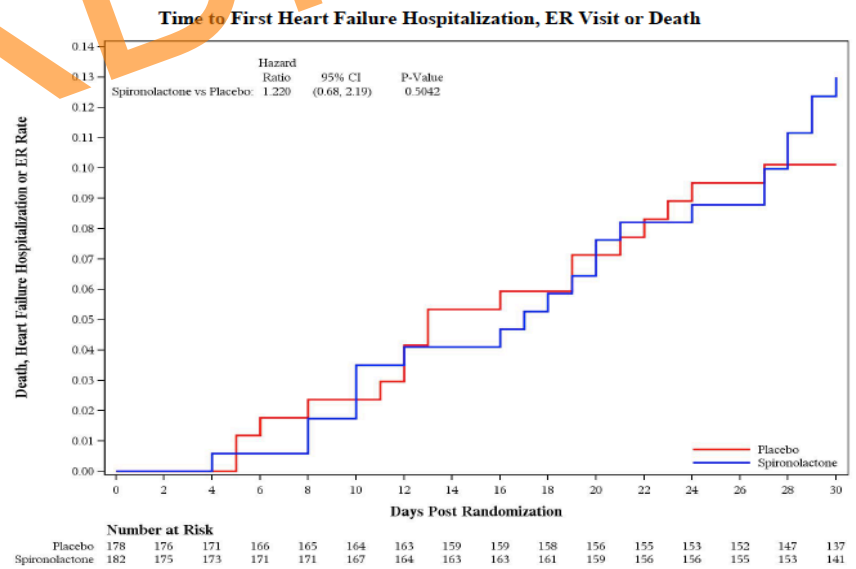


Butler, J. et al. J Am Coll Cardiol HF. 2016;4(9):726-35.

Results - *Primary Endpoint*

	Usual Care	Spironolactone	P
Log NTproBNP			
Baseline	8.23 (7.58, 8.94)	8.43 (7.90, 9.17)	
96 h (or discharge)	7.64 (6.93, 8.45)	7.89 (7.19, 8.68)	
Change	-0.49 (-0.98, -0.14)	-0.55 (-0.92, -0.18)	0.57

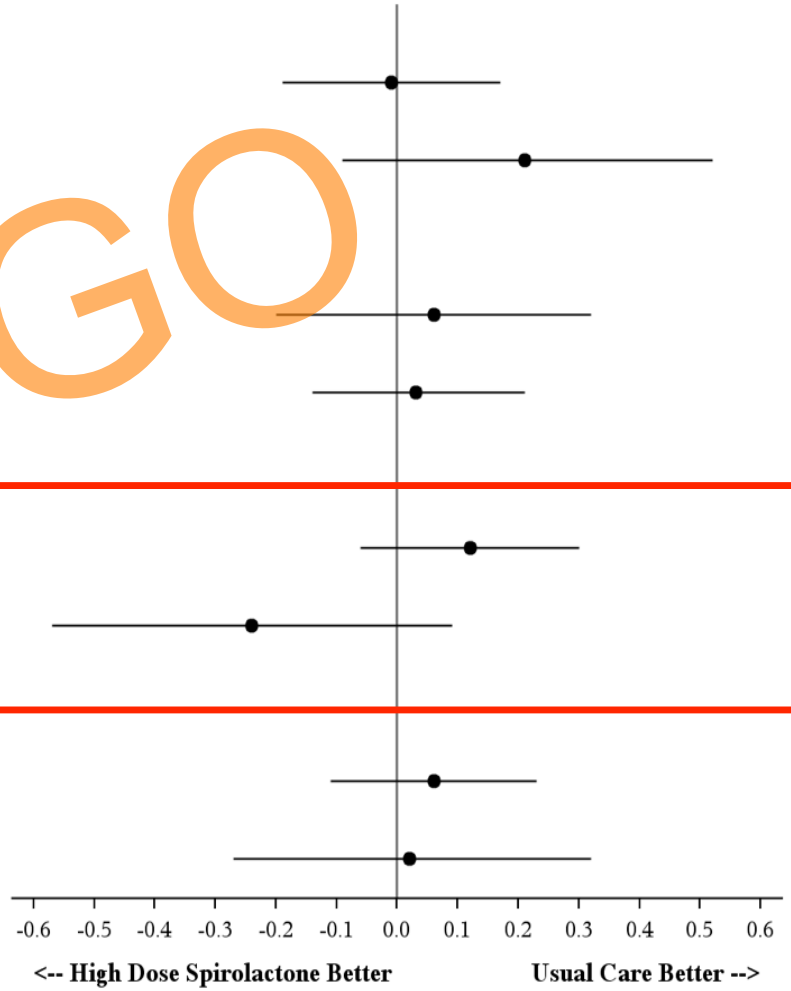
Dyspnea scale
Congestion score
Urine output
Weight
Loop diuretic use
In-hospital WHF



High Dose Spironolactone in Acute Heart Failure

ATHENA-HF

Description	Treatment Difference	95% CI	Interaction P-Value
Spironolactone Naïve	-0.01	-0.19, 0.17	0.22
Low Dose Spironolactone	0.21	-0.09, 0.52	
Age < 65	0.06	-0.20, 0.32	0.97
Age ≥ 65	0.03	-0.14, 0.21	
LVEF ≤ 45	0.12	-0.06, 0.30	0.08
LVEF > 45	-0.24	-0.57, 0.09	
Male	0.06	-0.11, 0.23	0.75
Female	0.02	-0.27, 0.32	



Lesson

- While we don't know how best to sub-segment patients (clinical, imaging, biomarker, others) – progress will require understanding pathophysiologic subgroups.

Response to Sexton: Inhibiting the Renin–Angiotensin–Aldosterone System in Patients With Heart Failure and Renal Dysfunction

Common Sense or Nonsense?

Javed Butler, MD, MPH; Michael M. Givertz, MD

Table. Interactive Effects of Neurohormonal Antagonists on Heart Failure and Renal Dysfunction

Study	Drug	Effect on Heart Failure	Effect on Renal Function
CIBIS[3]	Bisoprolol	Positive CKD≈non-CKD	Unknown
MERIT-HF[4]	Metoprolol succinate	Positive CKD>non-CKD	Unknown
SAVE[5]	Captopril	Positive CKD>non-CKD	Unknown
SOLVD[6]	Enalapril	Positive CKD≈non-CKD	Negative RR of WRF 1.33*
Val-HeFT[7]	Valsartan	Positive CKD>non-CKD	Negative mean eGFR ↓ 3.8
RALES[8]	Spironolactone	Positive CKD≈non-CKD	Unknown
EPHESUS[9]	Eplerenone	Positive Non-CKD>CKD	Unknown

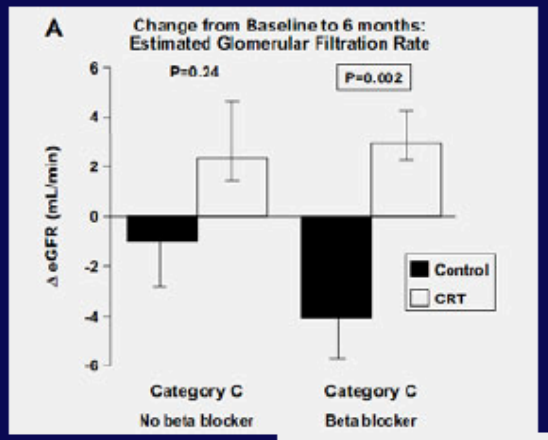
Journal of Cardiac Failure Vol. 14 No. 7 2008

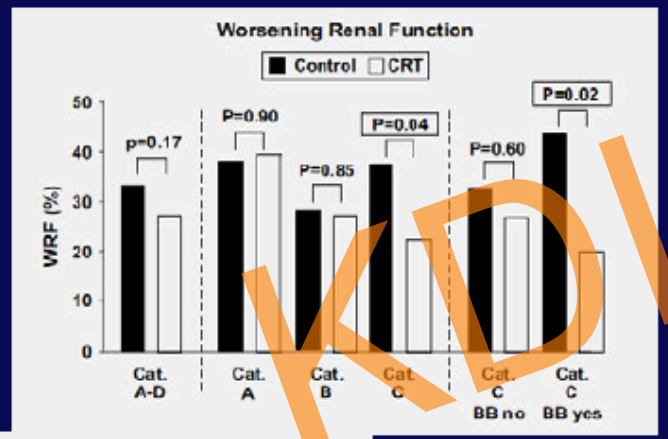
Clinical Trial

Cardiac Resynchronization Therapy Improves Renal Function in Human Heart Failure With Reduced Glomerular Filtration Rate

GUIDO BOERRIGTER, MD,[1] LISA C. COSTELLO-BOERRIGTER, MD, PhD,[1] WILLIAM T. ABRAHAM, MD,[2] MARTIN G. ST. JOHN SUTTON, MD,[3] DENISE M. HEUBLEIN,[1] KRISTIN M. KRUGER, BSN,[4] MICHAEL R.S. HILL, PhD,[4] PETER A. MCCULLOUGH, MD, MPH,[5] AND JOHN C. BURNETT JR, MD[1]

Rochester, Minnesota; Columbus, Ohio; Philadelphia, Pennsylvania; Minneapolis, Minnesota; Royal Oak, Michigan



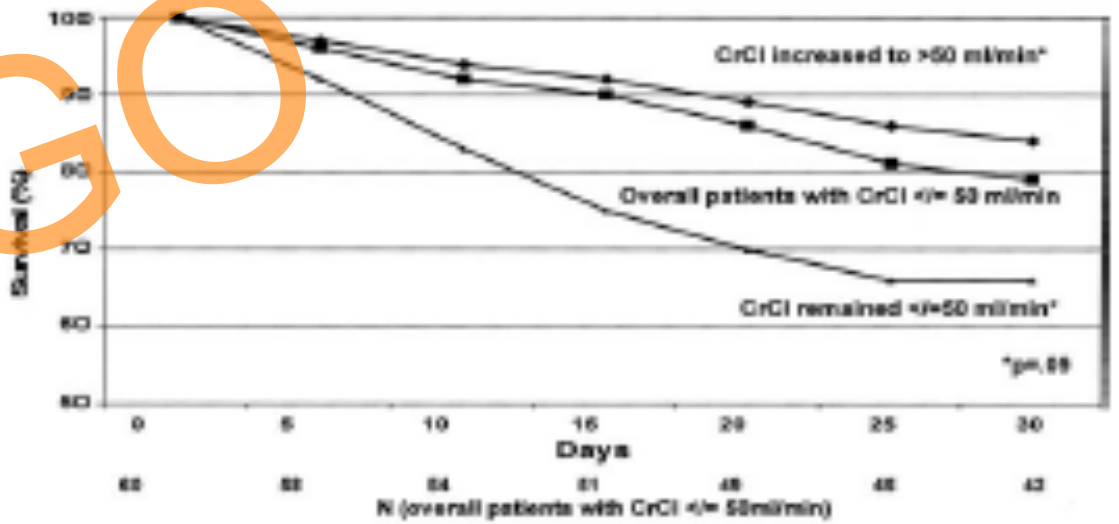


Journal of Cardiac Failure Vol. 14 No. 7 September 2008

Relationship Between Renal Function and Left Ventricular Assist Device Use

Javed Butler, MD, Carrie Geisberg, MD, Renee Howser, MSN, Peer M. Portner, PhD, Joseph G. Rogers, MD, Mario C. Deng, MD, and Richard N. Pierson III, MD

Cardiology Division, Vanderbilt University, Nashville, Tennessee, Radiology Department, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, WorldHeart, Inc, Oakland, California, Department of Cardiothoracic Surgery, Stanford University, Stanford, California, Division of Cardiology, Duke University, Durham, North Carolina, Division of Cardiology, Columbia University, New York, New York, Department of Cardiothoracic Surgery, University of Maryland, Baltimore, Maryland, and Baltimore Veterans Administration Medical Center, Baltimore, Maryland



However

- Data limited to GFR > 30
- Hyperkalemia and CKD intersection

- A whole world of heart failure patients with GFR <30 ml and those with hyperkalemia needs to be explored

Another issue

- Renal function is important to understand disease and treatment
- Be careful in making renal function as endpoint

So to end on a very depressing note

- Did know what cardio-renal syndrome is?
- HFrEF
  - Almost no data in those with GFR <30
  - Hyperkalemia
- HFpEF and AHF
  - No positive trial so far - so limited renal lessons from HF clinical trials
  - Renal function may be a primary learning, not necessarily secondary!

On the bright side

- KDIGO will continue to have opportunities to invite me to cool places to talk about this issues for the foreseeable future

- THANK YOU