Heart Failure

Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP

Consultant Cardiologist, Chief Academic and Scientific Officer

St. John Providence Health System

Providence Park Heart Institute

Novi, MI USA

e-mail: peteramccullough@gmail.com

Outline

- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together

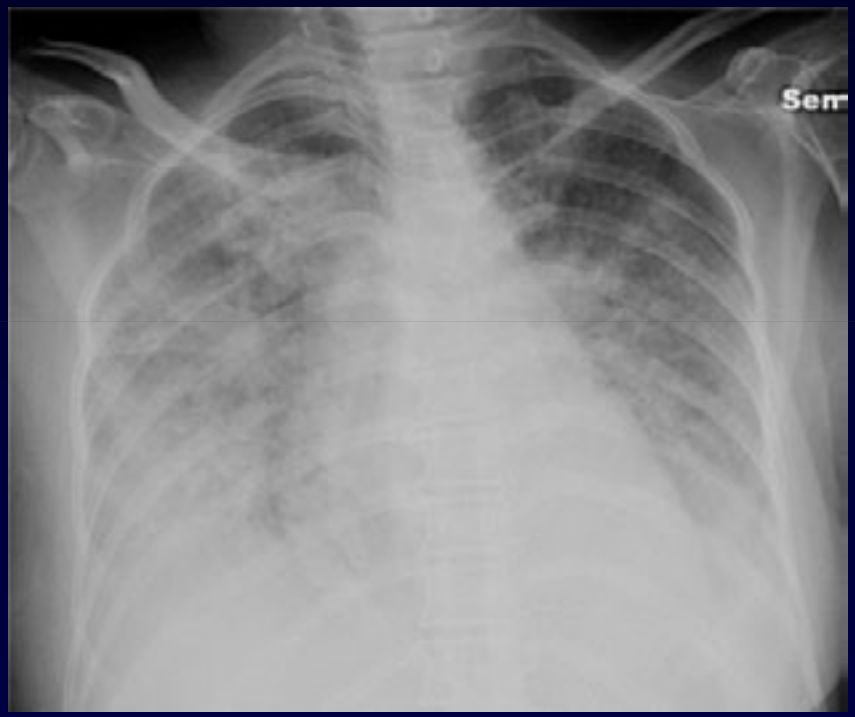
Outline

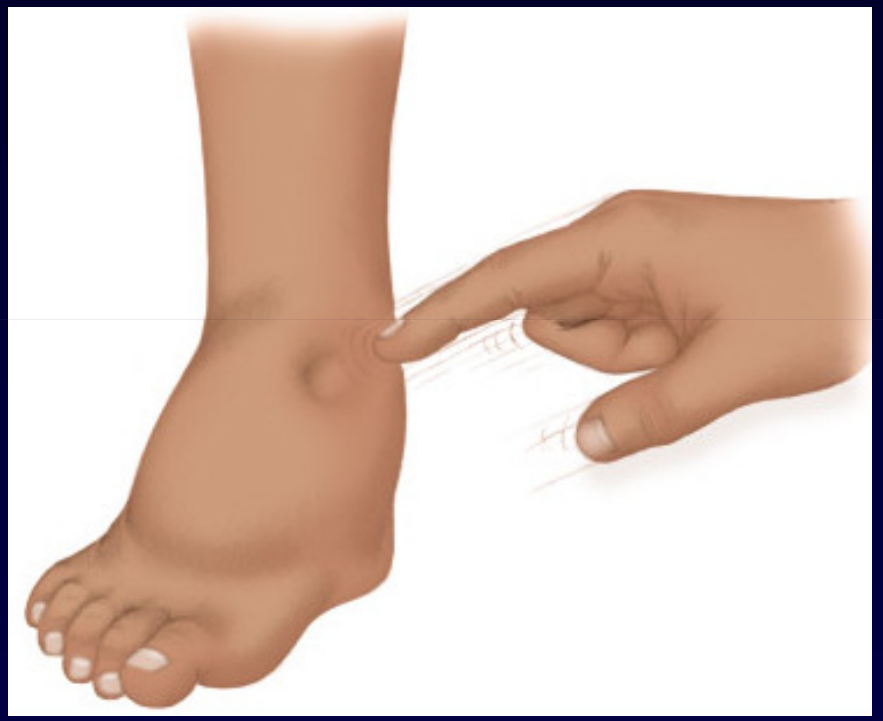
- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together

Definition of Heart Failure (HF)

- The failure of the heart as a pump resulting in inadequate cardiac output to peripheral tissues and stasis of blood in the lungs resulting most commonly in fatigue and pulmonary congestion.
- A complex mechanical and neurohumoral syndrome characterized by effort intolerance, fluid retention, and reduced longevity.
- At least 7 definitions in the literature based on tested scoring schemes and expert opinion.

Heart Failure as a Clinical Syndrome





Stasis of blood, tissue deposition of water and salt resulting in effort intolerance, progressive dyspnea, fatigue, edema

Definition and Classification of the Cardio-Renal Syndromes

Cardio-Renal Syndromes (CRS) General Definition:
Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other

Acute Cardio-Renal Syndrome (Type 1)
Acute worsening of cardiac function leading to renal dysfunction

Chronic Cardio-Renal Syndrome (Type 2)
Chronic abnormalities in cardiac function leading to renal dysfunction

Acute Reno-Cardiac Syndrome (Type 3)
Acute worsening of renal function causing cardiac dysfunction

Chronic Reno-Cardiac Syndrome (Type 4)
Chronic abnormalities in renal function leading to cardiac disease

Secondary Cardio-Renal Syndromes (Type 5)
Systemic conditions causing simultaneous dysfunction of the heart and kidney

Ronco, et al , JACC 2008

Long-term Risk of Mortality and Other Adverse Outcomes After Acute Kidney Injury: A Systematic Review and Meta-analysis

Steven G. Coca, DO,[1,2] Bushra Yusuf, MD,[1,2] Michael G. Shlipak, MD, MPH,[3,4] Amit X. Garg, MD, PhD,[5] and Chirag R. Parikh, MD, PhD[1,2]

Outcomes after an Episode of AKI (n=47,017)

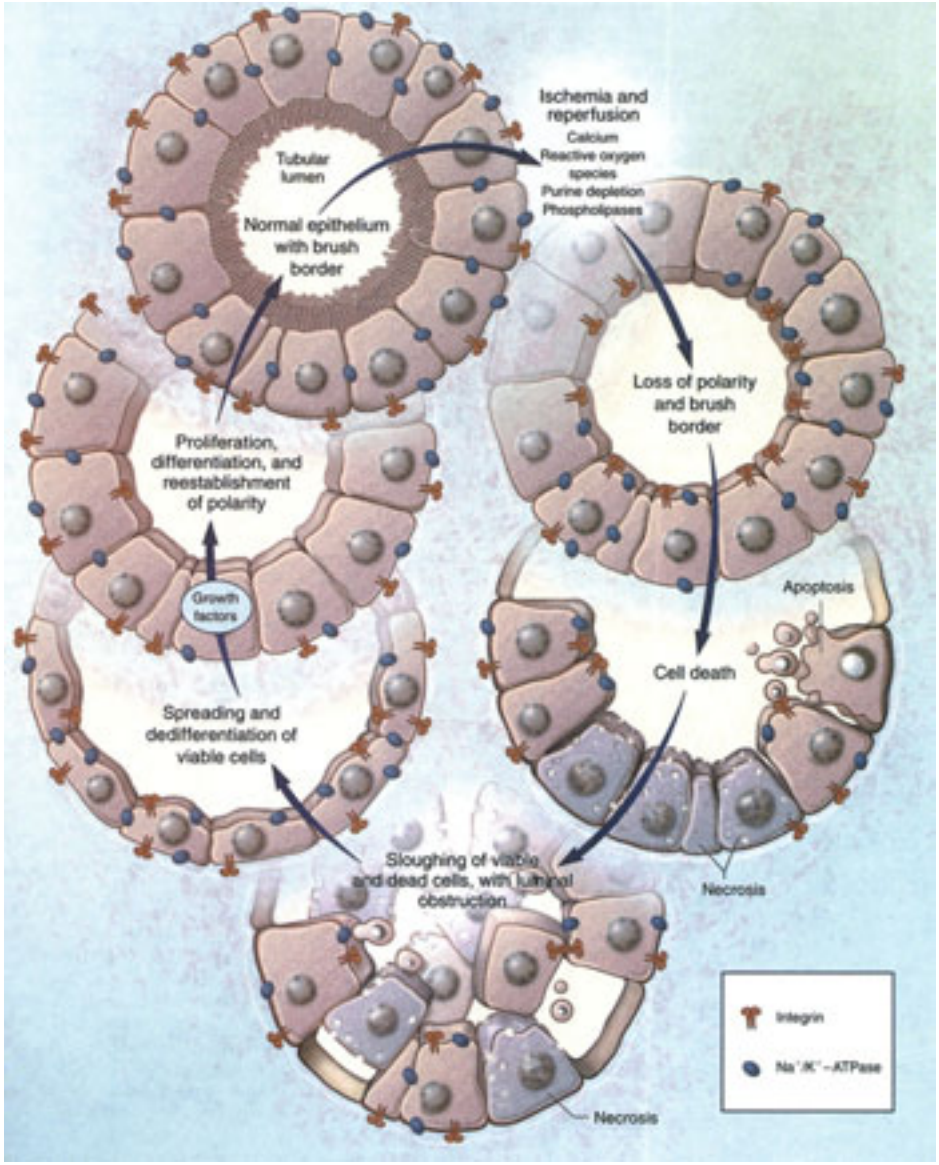
New CKD 7.8 events/100 patient-years
ESRD 4.9 events/100 patient-years
Mortality 8.9 deaths/100 patient-years

} **>6 mo F/U**

Subgroup	No. of Studies	Deaths/Person-Years (deaths/100 person-years) AKI	Deaths/Person-Years (deaths/100 person-years) No AKI	No. of Studies Showing Harm: Point Estimate > 1	No. of Studies Showing Harm: Lower Bound 95% CI > 1	Rate Ratio	Heterogeneity (I^2)
Overall	15	685/7,665 (8.9)	3,739/87,014 (4.3)	15	12	2.59 (1.97-3.42)	86%
Definition of AKI							
At least mild	3	250/3,972 (6.3)	340/9,908 (3.4)	3	3	1.67 (1.41-1.98)	0%
At least moderate	6	325/2,928 (11.1)	2,980/67,488 (4.4)	6	4	2.73 (1.81-4.14)	90%
Severe (RRT)	7	148/1,079 (13.7)	590/13,351 (4.4)	7	6	3.04 (2.13-4.33)	60%
Clinical setting							
Critical illness	2	48/347 (13.8)	173/3,743 (4.6)	2	1	2.41 (1.50-3.85)	0%
Cardiac surgery	3	97/1,335 (7.3)	327/11,956 (2.7)	3	3	3.72 (1.49-6.94)	85%
PCI	4	218/1,670 (13.1)	2,793/66,350 (4.2)	4	4	2.89 (2.32-3.61)	49%
Nonrenal transplant	3	92/1,632 (5.6)	204/2,884 (7.1)	3	1	1.89 (0.9-3.96)	82%
Left ventricular assist device	2	59/581 (10.2)	79/1,582 (5.0)	2	2	2.15 (1.53-3.03)	0%
Aortic surgery	1	171/3,840 (4.5)	163/5,290 (3.1)	1	1	1.45 (1.17-1.79)	NA
Duration							
Transient *v* none	2	201/2,298 (8.7)	301/9,645 (3.1)	2	2	2.54 (2.10-3.06)	0%
Persistent *v* none	2	124/1,370 (9.1)	301/9,645 (3.1)	2	2	2.46 (1.68-3.60)	49%
Persistent *v* transient	3	186/2,150 (8.7)	232/2,923 (7.9)	2	1	1.15 (0.84-1.57)	45%

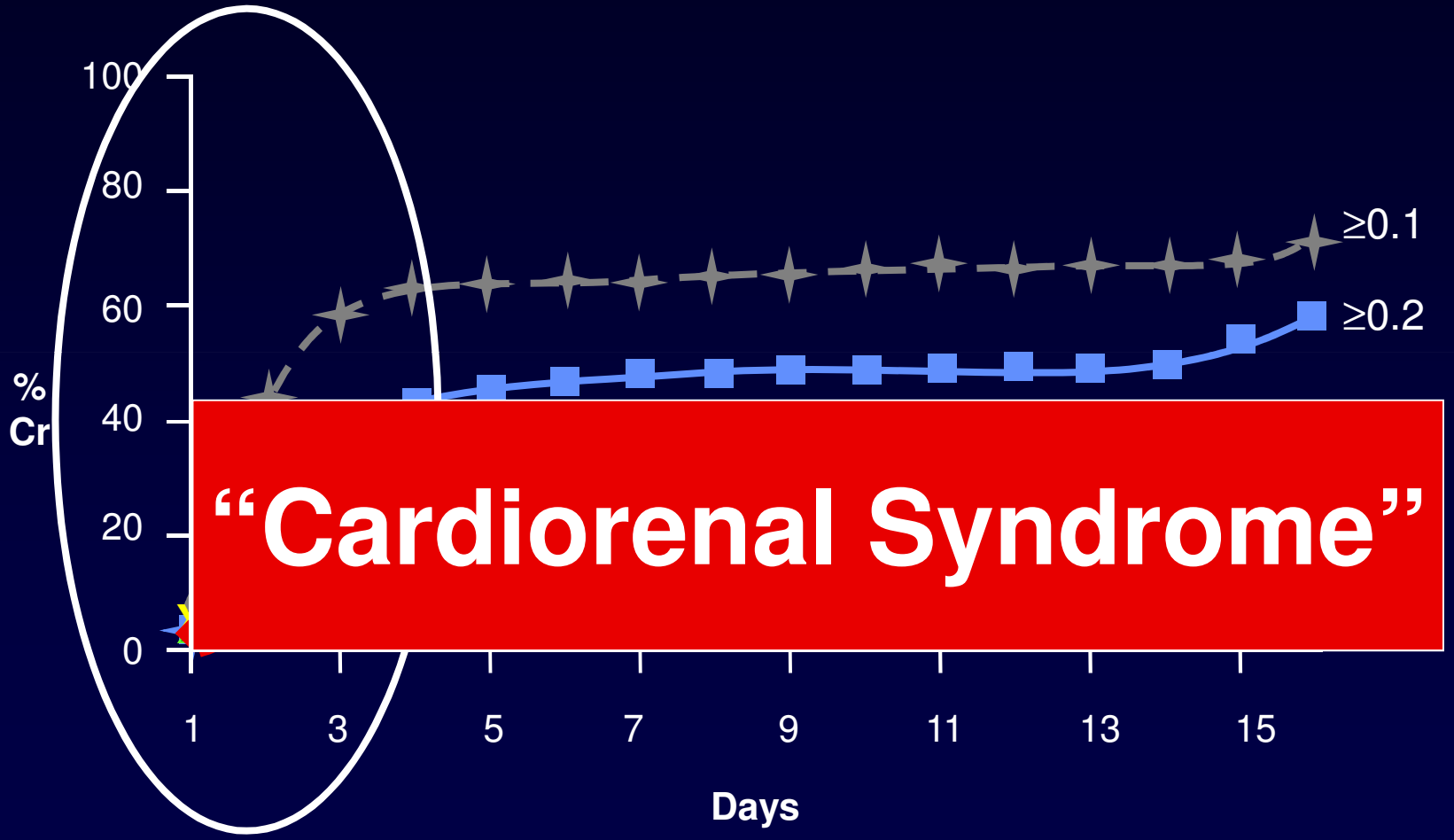
American Journal of Kidney Diseases, Vol 53, No 6 (June), 2009: pp 961-973

Tubular Injury in AKI



Thadhani et al., N Engl J Med 1996

Time Course of Development of Increasing Creatinine in Hospitalized HF Patients



Cr, serum creatinine.

Gottlieb SS et al. *J Card Fail.* 2002;8:136. Smith G, J Card Fail. 2003 Feb;9(1):13-25

CHF: Worsened Renal Function in Hospital

27% of 1,004 pts had worsened renal function (>0.3mg/dl)

	Hazard Ratio
History of CHF (1)	1.3 (1.01-1.7)
Diabetes (1)	1.4 (1.1-1.8)
SBP> 160 (1)	1.4 (1.1-1.7)
1.5<creat<2.5 (2)	2.1 (1.6-2.8)
Creat = 2.5 (3)	3.5 (2.5-4.8)

Score = 0 – 10% risk

Score = 4 – 53% risk

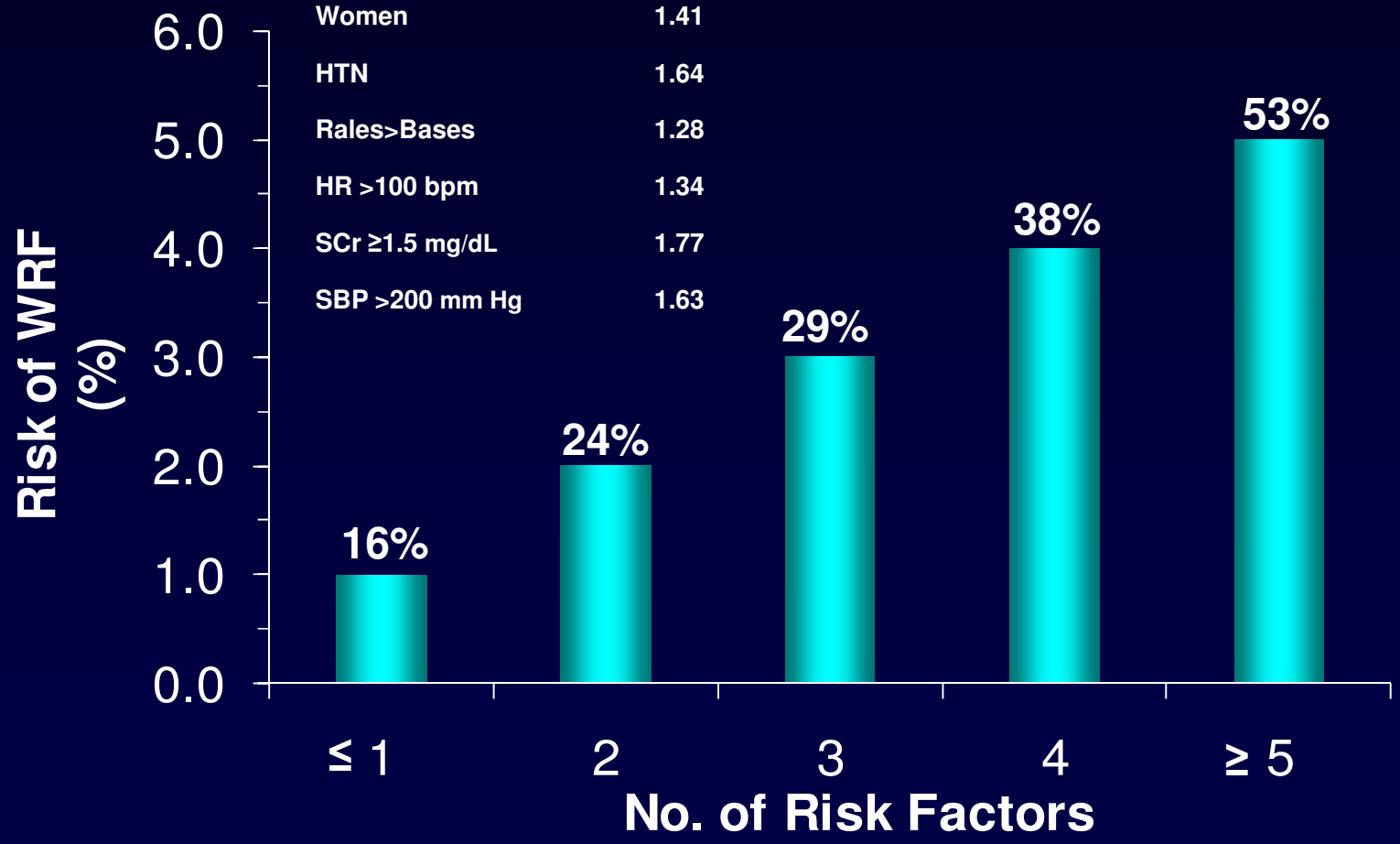
52% of WRF develops by day 3 and results in:

7X increase in risk of death
3X increase in length of stay
2X increase in complications
No relation to hypotension or hypovolemia

Krumholz. JACC 2004;43:61

Risk of Worsening Renal Function (WRF) by Number of Risk Factors

Characteristics	Adjusted OR
Women	1.41
HTN	1.64
Rales>Bases	1.28
HR >100 bpm	1.34
SCr ≥1.5 mg/dL	1.77
SBP >200 mm Hg	1.63



N=1,681, WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 µmol/l).

Krumholz HM et al. *Am J Cardiol*. 2000;85:1110.

Impact of Major In-hospital Complications: POSH Study

Table 4 Association of WRF with mortality up to 6 months after index hospitalization

Mortality, *n* (%)	WRF absent	WRF present	OR (95% CI)	*P*-value
For the 248 patients who did not develop a major in-hospital complication during the index admission[a]				
	n = 176	*n* = 72		
In-hospital	2 (1.1%)	3 (4.2%)	3.75 (0.62–23.1)	0.15
30 days	6 (3.4%)	3 (4.3%)	1.23 (0.30–5.1)	0.72
180 days	28 (16.5%)	12 (17.4%)	1.07 (0.51–2.24)	0.86
For the complete cohort of 299 patients hospitalized with worsening heart failure[b]				
	n = 201	*n* = 98		
In-hospital	3 (1.5%)	12 (12.3%)	9.2 (2.6–33.5)	0.002
30 days	9 (4.6%)	14 (14.6%)	3.5 (1.5–8.5)	0.003
180 days	35 (18.1%)	26 (28.0%)	1.8 (0.98–3.2)	0.08

[a]Follow-up by 30 days for mortality: 244/248 (98%) complete; follow-up by 180 days for mortality: 239/248 (96%) complete.
[b]Follow-up by 30 days for mortality: 291/299 (97%) complete; follow-up by 180 days for mortality: 285/299 (95%) complete.

- Worsening renal function (WRF) defined as an increase in serum creatinine of 0.26 mmol/L (0.3 mg/dL)
- Major complication included: circulatory shock, hypotension, cardiac arrest, sepsis, acute coronary syndrome

European Heart Journal (2006) 27, 1216–1222

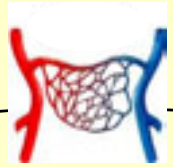
Outline

- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together

Cardio-Renal Syndrome Pathophysiology

Systolic or Diastolic Dysfunction or Both

Altered Intra-renal Hemodynamics



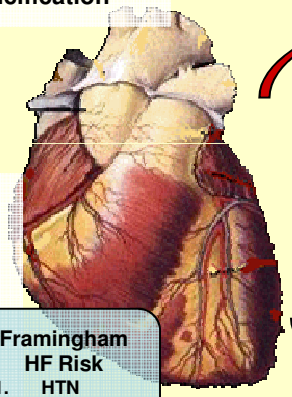
Decreased Perfusion

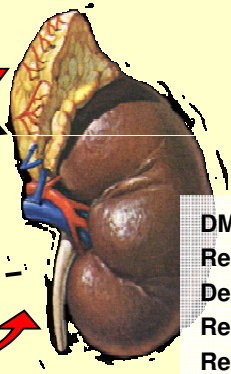
Increased venous pressure

Renal Congestion

Precipitators
Diuretics
Vasodilators
Procedures

Toxicity Vascocostriction





Acute Neurohoromonal Activation
SNS+RAS+Aldosterone+ Endothelin+ADH+, renal vasoconstriction (adenosine)+prostaglandin dysregulation

Framingham HF Risk
1. HTN
2. CAD/MI
3. Valve Dz

ANP/ BNP

Natruretic Peptides

Blocked Natriuresis

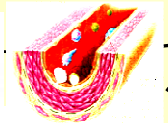
Humoral signalling

Anemia/Relative ↓Epo/Fe transport blocked

Cytokine secretion

IL-1, TNF-Alpha

Monocyte Activation



Endothelial Dysfunction

↓Tubulo-Glomerular Function

↑Adhesion Molecules, ↑Enzymatic Activation, ↑Oxidative Stress

Significantly and Severely Adapted, Courtesy Ronco, C 2009

CKD-Associated Myocardial Changes
Myocyte hypertrophy
Myocyte dysfunction
↑↑Interstitial Fibrosis
↓Capillary density
↑↑LV Mass
Elevated serum troponin levels

CKD-Associated Vascular Changes
Accelerated atherosclerosis
↑Vascular stiffness
↓Smooth muscle density
Osteoblastic VSMC transformation
Intra-and extracellular calcification

Acute on Chonic Cardiac Disease

Chronic Neurohormonal
↑SNS, RAS, Aldosterone
↓Vitamin D
↑PTH
↑PO4
Hypotestesteronism
↓EPO
↓Fe utilization
Marinobufagen

Inciting Events
↓Medical compliance
↑Sodium intake
Ischemia
Arrhythmias (AF)
OSAS

Added Insults
NSAIDS, TZDs

Acute on Chronic Kidney Injury

DM+HTN + other CKD
Renal hypoperfusion
Decreased GFR
Resistence to diuretics
Resistance to ANP/BNP
Na + H_2O retention
Necrosis / apoptosis
Fibrosis

Biomarkers
↑BNP/NT-proBNP
↑ N-GAL
↑ KIM-1
↑IL-18
Catalytic iron
↑Cystatin-C
↑Creatinine
Urine albumin
Many others

High Central Venous Pressure and CRS

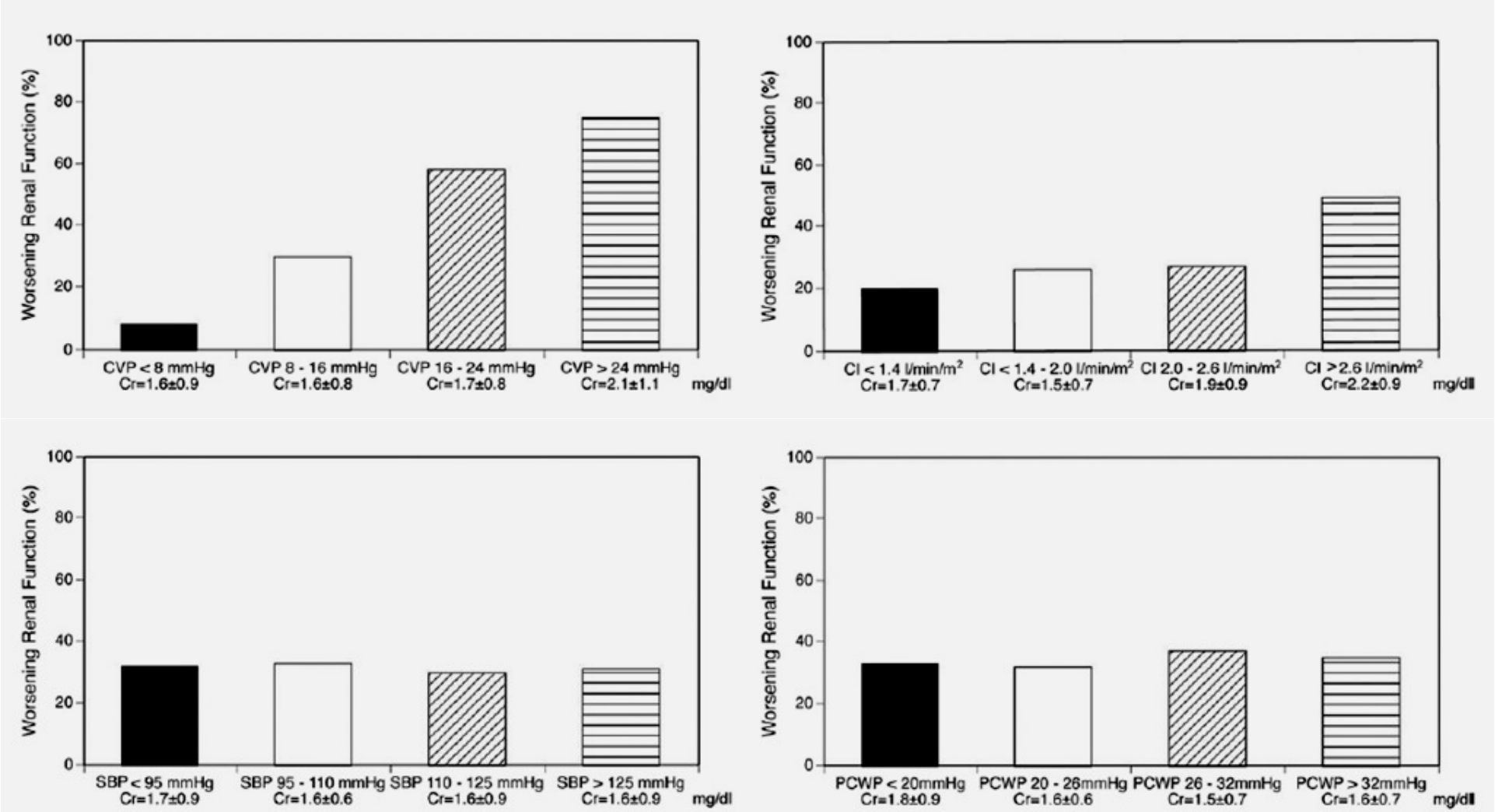
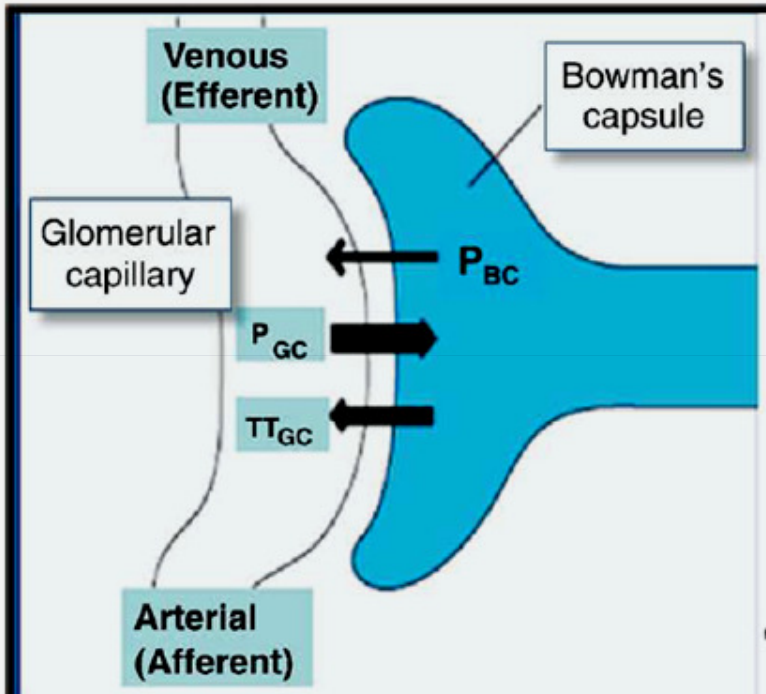


Figure 1 **Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP**

JACC Vol. 53, No. 7, 2009

CI = cardiac index; Cr = serum creatinine; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Venous Congestion and Glomerular Filtration



Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	60	58	55	63
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	15	15	15	15
b. Oncotic pressure in glomerular capillaries, π_{GC}	21	33	21	33
Net filtration pressure (1-2)	24	10	19	15
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Figure 1 **Impact of Venous Congestion on Glomerular Net Filtration Pressure**

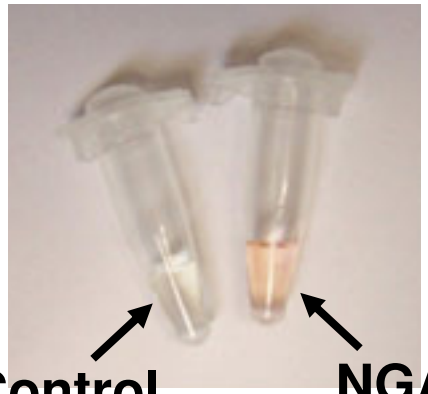
An illustration of the afferent and efferent pressures at a glomerular capillary in a patient with normal hemodynamics and a patient with increased right atrial (RA) pressure and venous congestion. P_{BC} = hydrostatic pressure in Bowman's capsule; P_{GC} = glomerular capillary hydrostatic pressure; π_{GC} = oncotic pressure in glomerular capillaries.

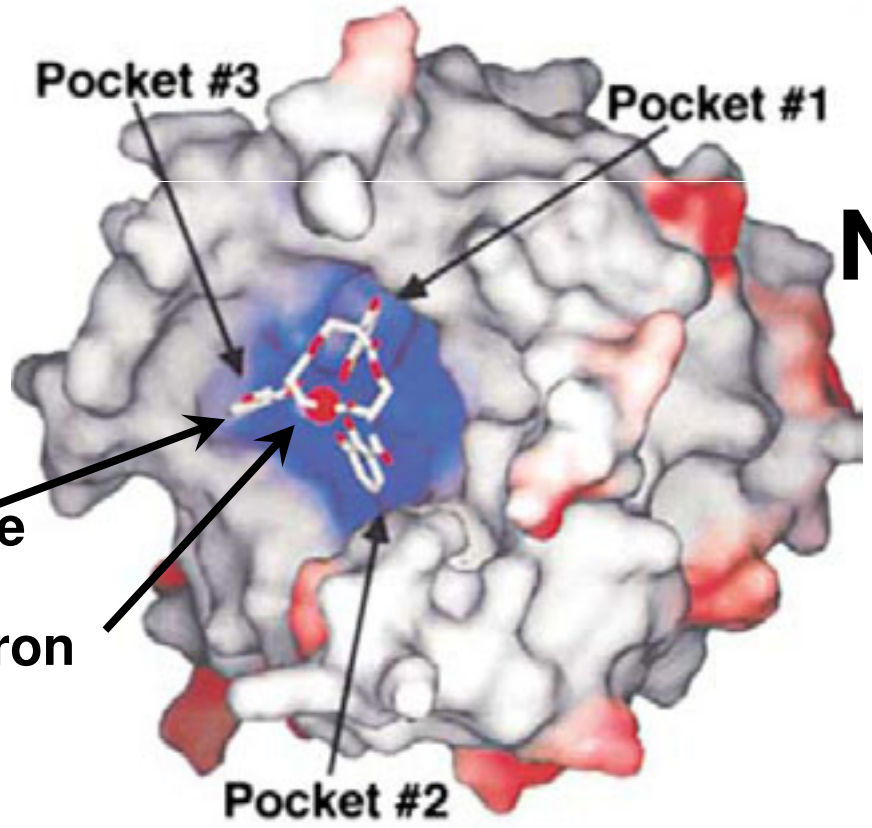
JACC Vol. 53, No. 7, 2009
February 17, 2009:597–9

Outline

- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together

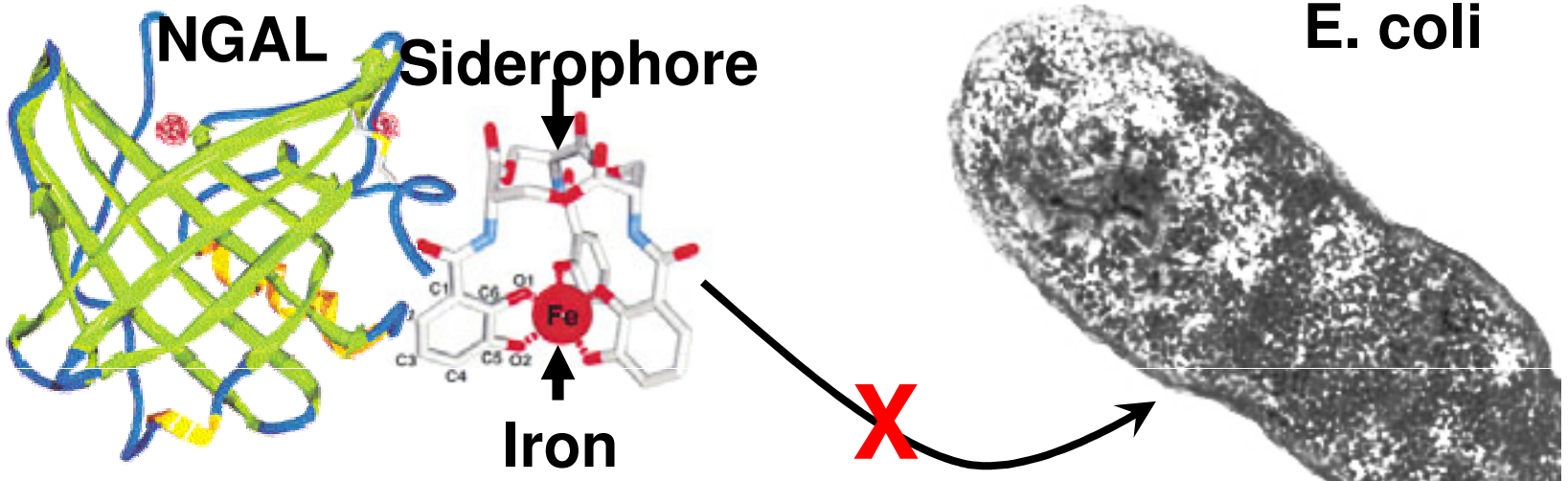
Neutrophil Gelatinase-Associated Lipocalin (NGAL) – a specific biomarker of acute kidney injury



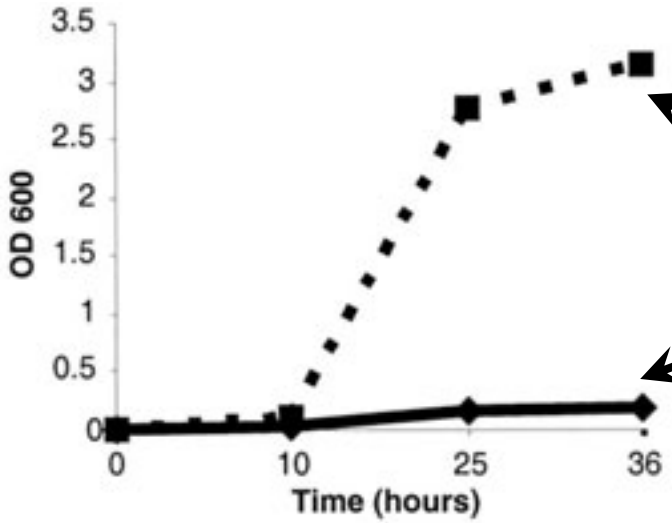


Goetz et al.
Mol Cell 2002

NGAL is an endogenous bacteriostatic protein by reducing available catalytic iron



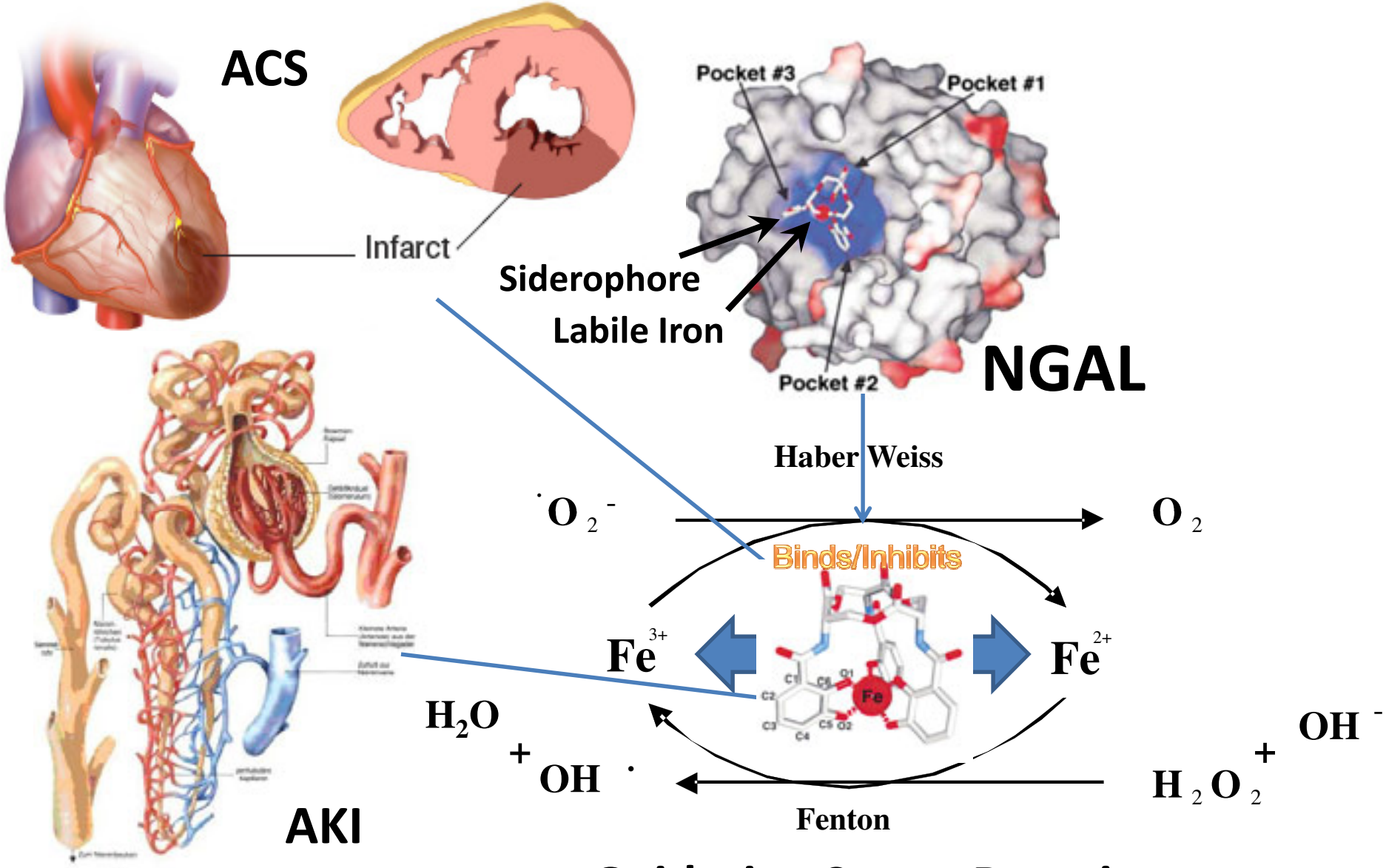
bacterial growth curves



without NGAL

with NGAL

Goetz et al.
Mol Cell 2002



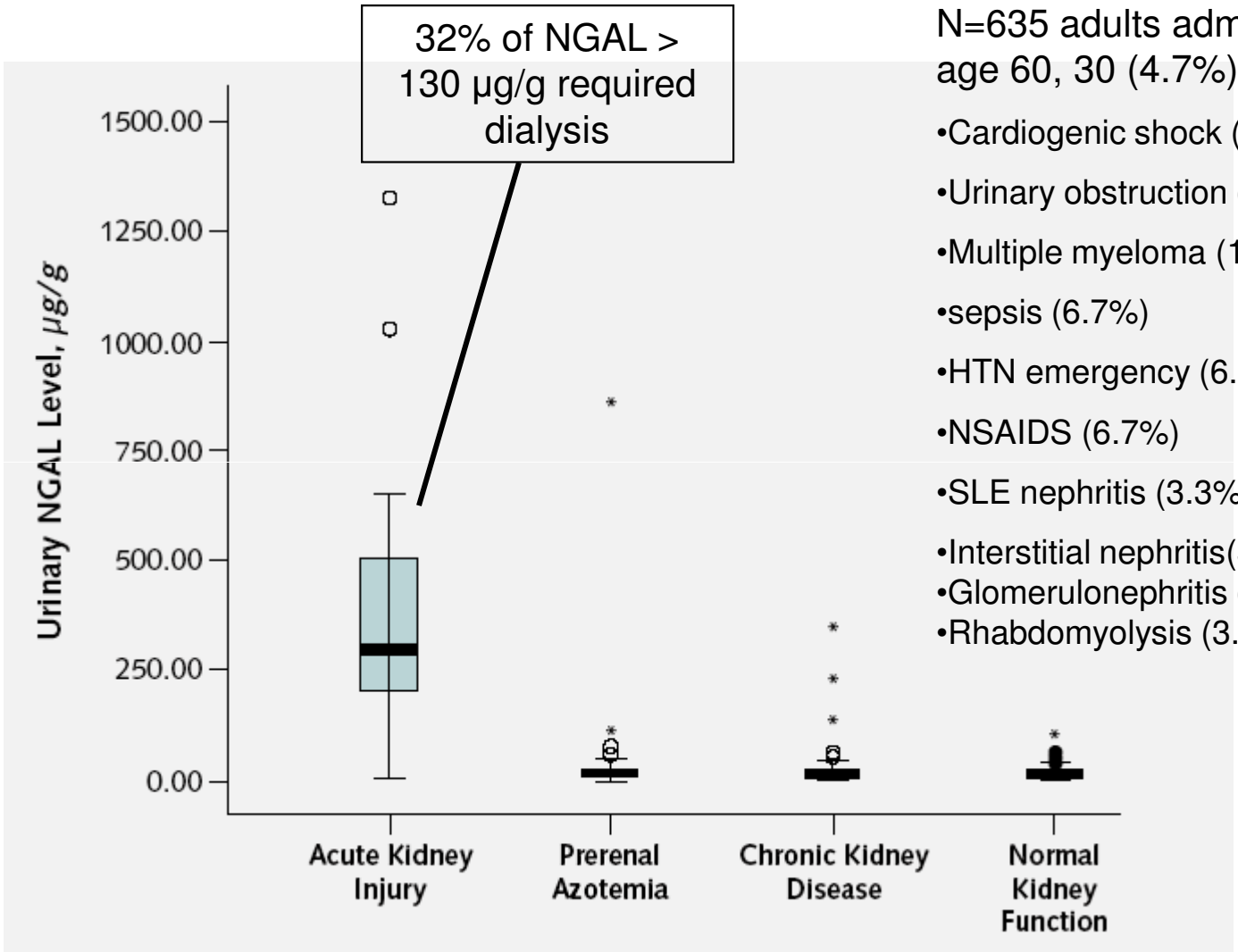
Oxidative Stress Reactions

Ferric Iron = Fe_3^+ ; Ferrous iron= Fe_2^+ ; hydrogen peroxide = H_2O_2 ;

Hydroxyl radical = $OH^{\cdot}$; Hydroxide anion = OH^- ; oxygen = O_2 ; superoxide anion = $^{\cdot}O_2^-$

Diagnosis of Early AKI in Emergency Department

Acute kidney injury was based on the RIFLE (risk, injury, failure, loss, and end-stage) criteria

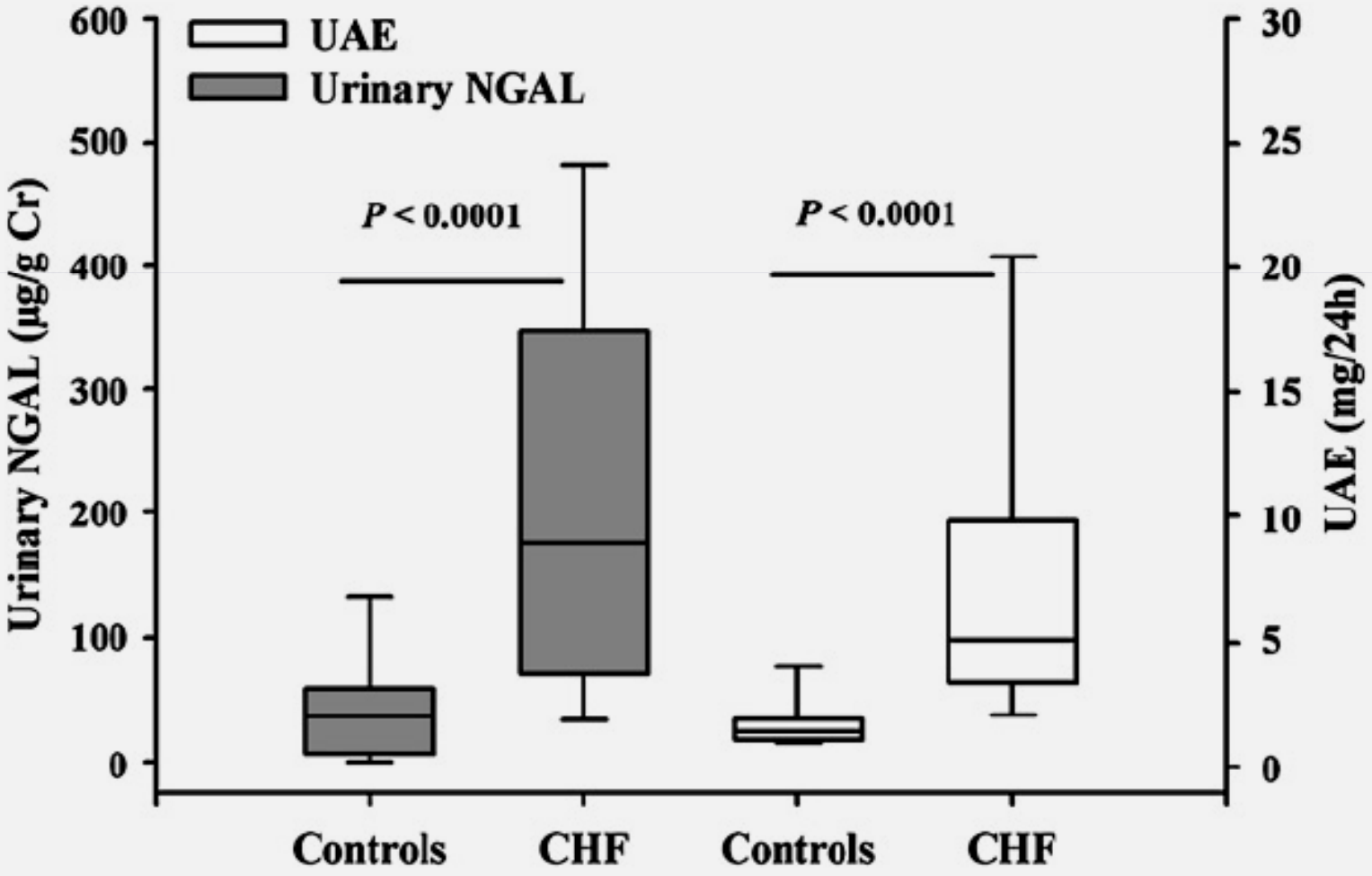


N=635 adults admitted to hospital, mean age 60, 30 (4.7%) developed AKI:

- Cardiogenic shock (40%)
- Urinary obstruction (16.7%)
- Multiple myeloma (10%)
- sepsis (6.7%)
- HTN emergency (6.7%)
- NSAIDS (6.7%)
- SLE nephritis (3.3%)
- Interstitial nephritis(3.3%)
- Glomerulonephritis (3.3%)
- Rhabdomyolysis (3.3%)

Ann Intern Med. 2008;148:810-819.

Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) Is Increased in Patients with Chronic Heart Failure



European Journal of Heart Failure 10 (2008) 997–1000

Serum Neutrophil Gelatinase Associated Lipocalin (NGAL) Is Increased in Patients with Diabetes and Microalbuminuria

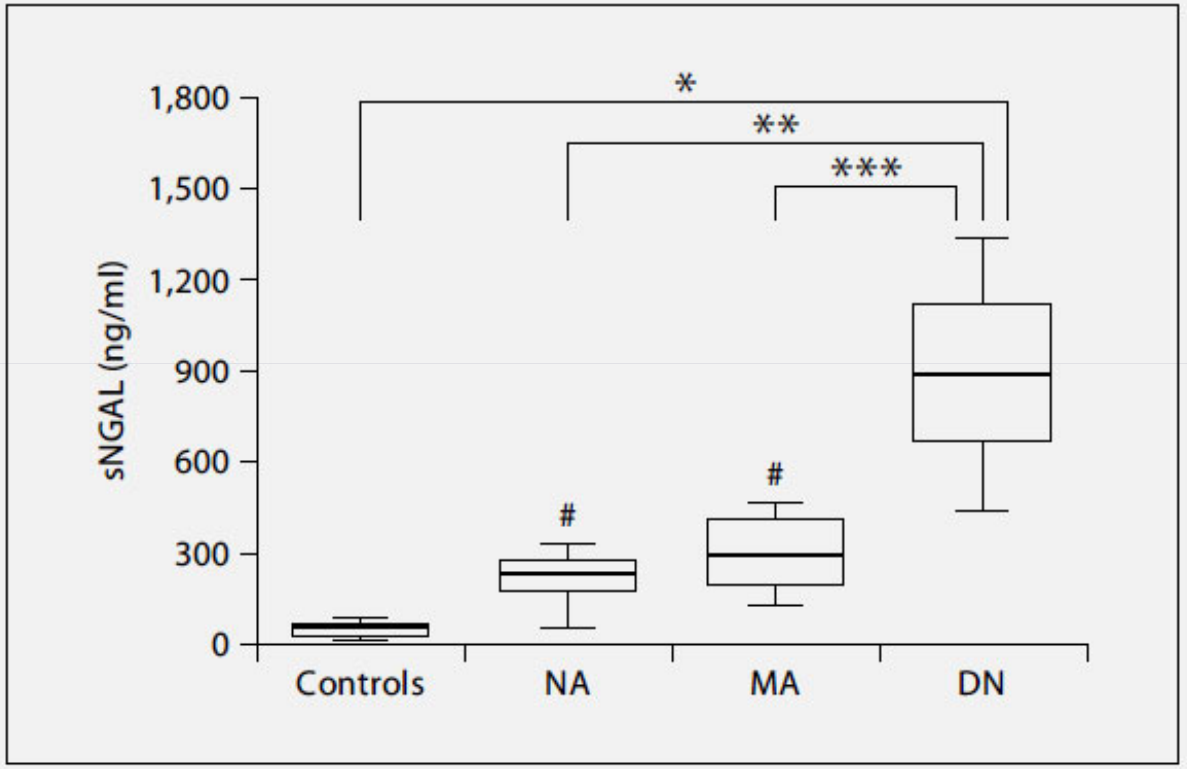


Fig. 1. sNGAL in control subjects and patient groups with normoalbuminuria (NA), microalbuminuria (MA) and diabetic nephropathy (DN). # $p < 0.01$ vs. controls; * $p < 0.001$ vs. controls; ** $p < 0.01$ vs. NA; *** $p < 0.01$ vs. MA.

Kidney Blood Press Res 2009;32:91–98

Overexpressed/Recombinant NGAL as a Preventive Strategy

- May play an extracellular role in cell defense against toxicants and/or facilitate the survival of the remaining cells (in vitro human adenocarcinoma A549 cells)

- Potent inducer of heme-oxygenase-1 and superoxide dismutase SOD(1) and SOD(2) and it appears that part of antioxidant property of NGAL could be attributed to the induction of HO-1 and SOD(1, 2)

- Protects against heat/cold stress

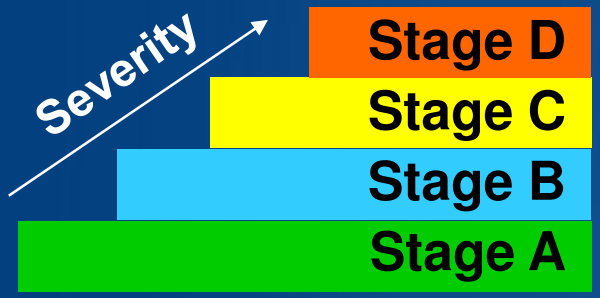
- Protects against H_2O_2 induced apoptosis

Biochem. J. (2005) 391 (441–448) , Cell Stress Chaperones. 2009 Nov 11. , Exp Cell Res. 2009 Nov 1;315(18):3140-51. Arch Med Res. 2008 Aug;39(6):560-6

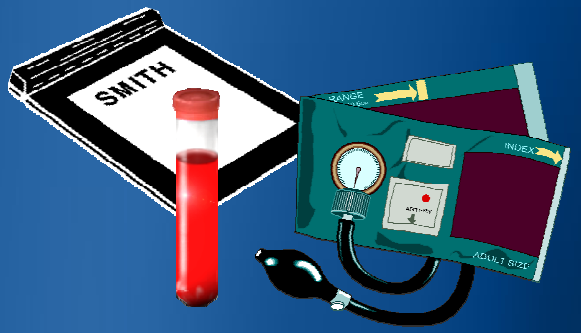
Outline

- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together

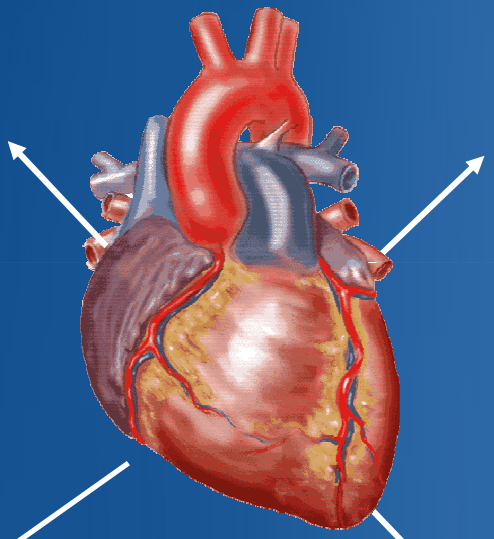
Heart Failure Management

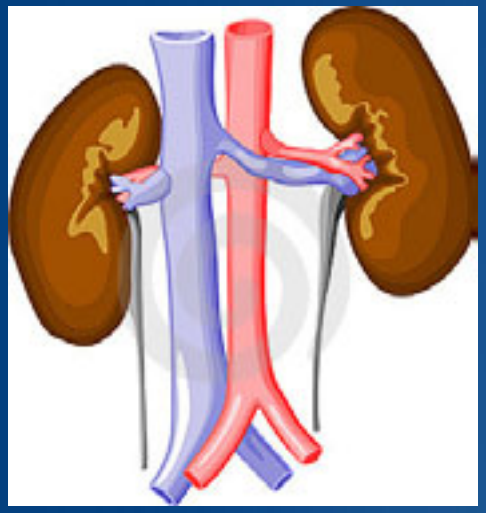


Revised Staging System

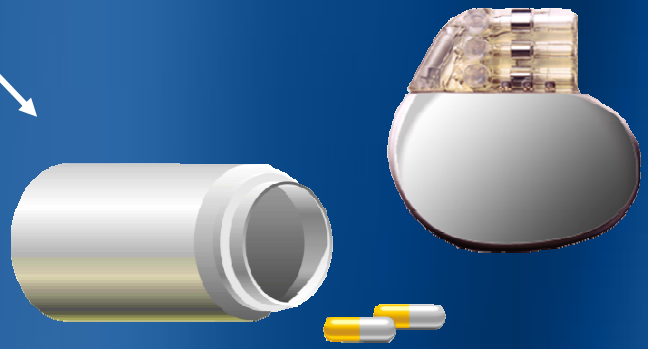


Early Recognition and Treatment





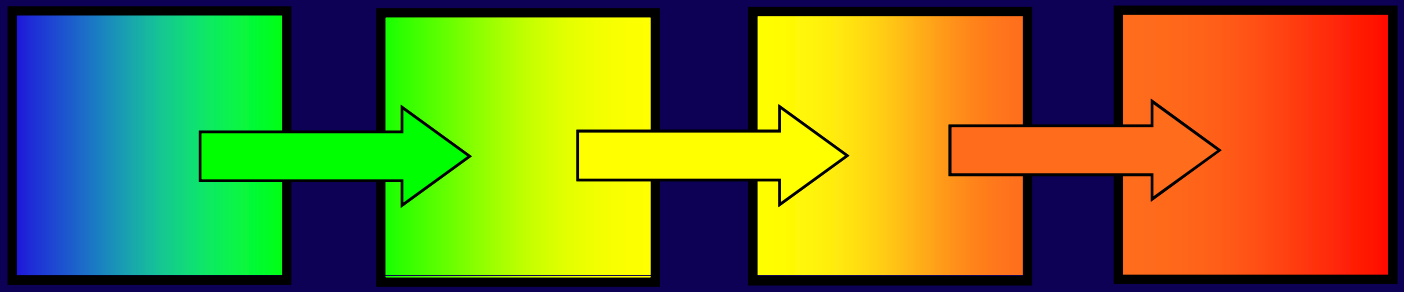
Preserve Renal Function



Pharmaceuticals and Devices

Adapted from: Hunt SA et al. ACC/AHA 2005 CHF Guideline Update. *Circulation* 2005;112:e154-235.

Pharmacologic Therapy and CRT



Post-MI LV Dysfunction	Mild HF	Moderate HF	Severe HF
AIRE/SAVE (ramipril/captopril)	SOLVD Treatment (enalapril)		CONSENSUS (enalapril)
VALIANT (valsartan)	CHARM (candesartan)	Val-HeFT (valsartan)	
CAPRICORN (carvedilol)	US Carvedilol/MERIT (carvedilol/metoprolol)		COPERNICUS (carvedilol)
EPHESUS (eplerenone)	CHARM/Val-HeFT (candesartan/valsartan)		RALES (spironolactone)
	A-HeFT		
	Long-acting nitrate/hydralazine		

CRT and/or ICD

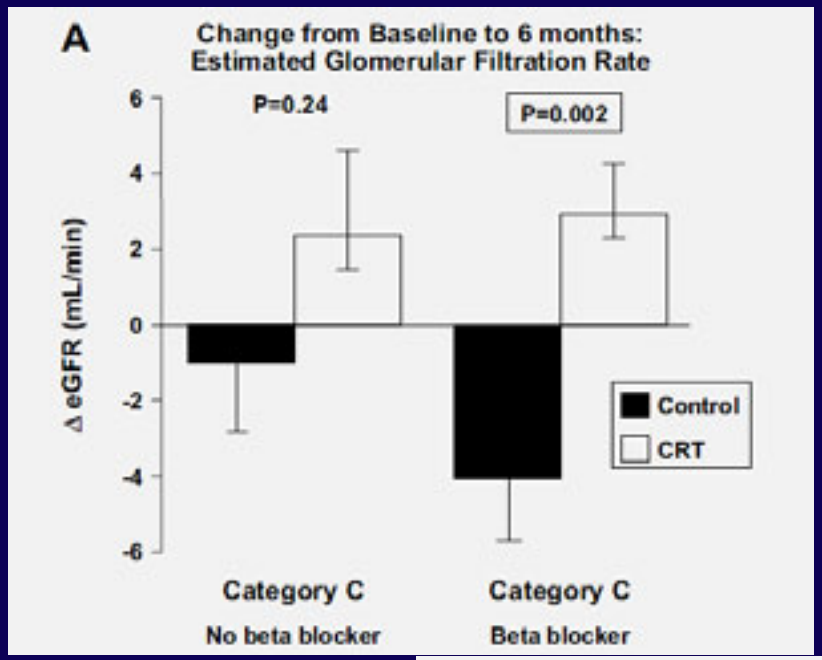
Journal of Cardiac Failure Vol. 14 No. 7 2008

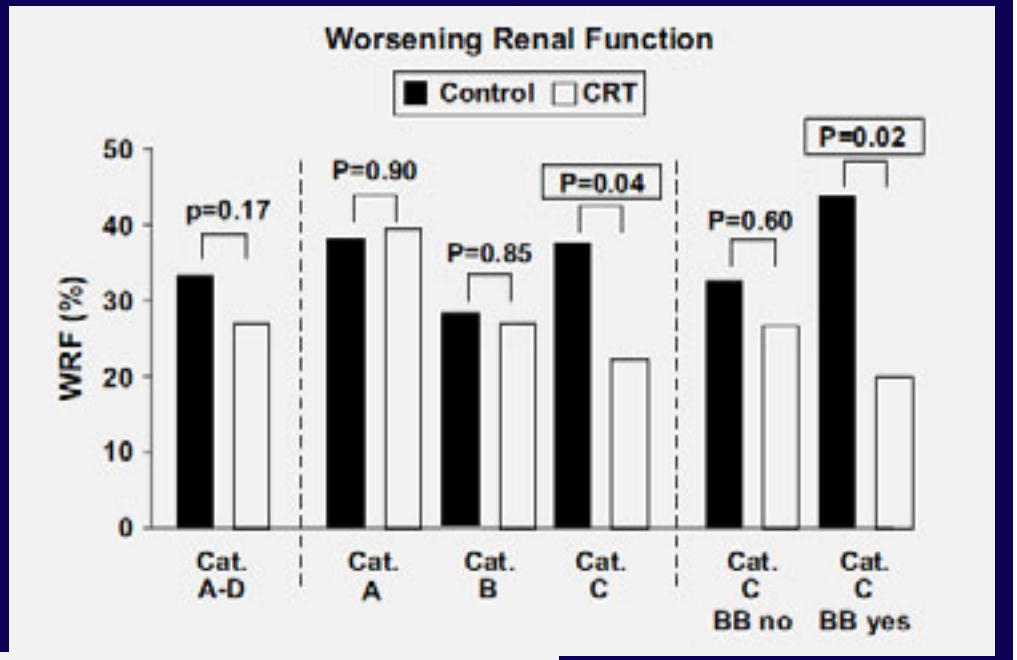
Clinical Trial

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



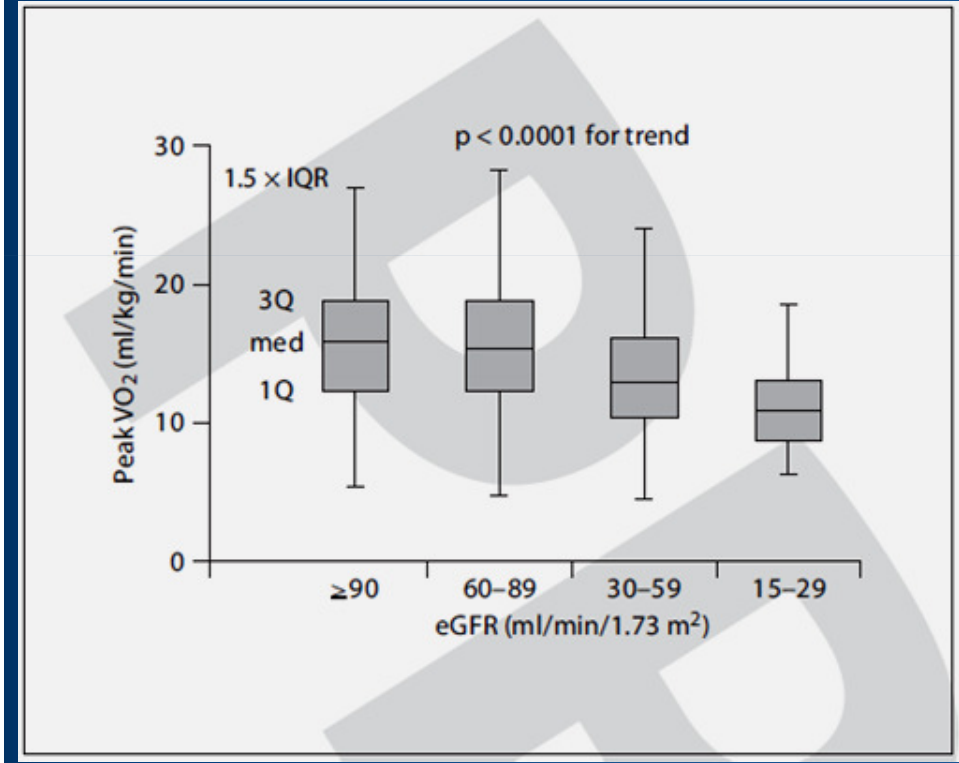


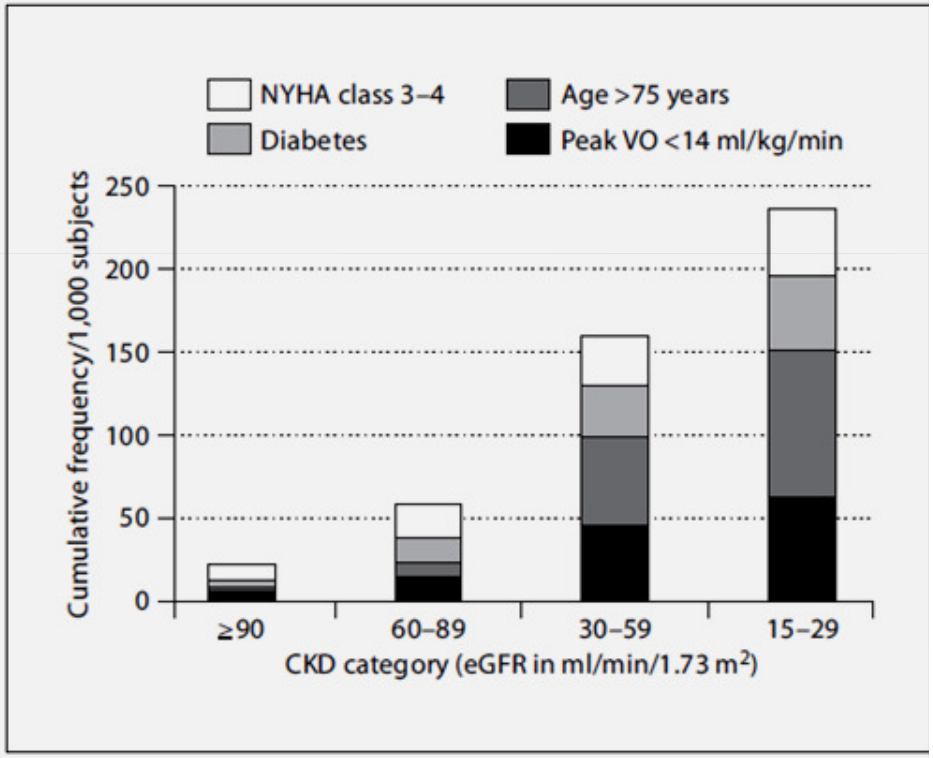
CKD in HF ACTION Trial (EF < 35%)

Characteristic	CKD level					p value for trend
	all	1 (>90)	2 (89–60)	3 (59–30)	4 (29–15)	
Number	2,091	338	947	728	78	
Demographics						
Age, years	59 ± 13	50 ± 13	57 ± 12	65 ± 11	67 ± 12	<0.0001
Age >75 years, %	11	3	6	19	31	<0.0001
Male, %	72	70	73	74	70	0.33
Caucasian, %	61	42	60	71	71	<0.0001
African American, %	33	53	34	24	26	<0.0001
Other race, %	5	5	5	5	4	0.58
Medical history, %						
Hypertension	61	57	59	63	68	0.02
Diabetes mellitus	33	33	26	40	45	<0.0001
Chronic obstructive pulmonary disease	11	7	11	13	13	0.008
Stable angina	26	25	26	28	22	0.53
Prior myocardial infarction	43	27	42	50	53	<0.0001
Prior coronary artery bypass surgery	26	15	22	35	36	<0.0001
Chronic prescribed medications, %						
Angiotensin-converting enzyme inhibitors	74	81	75	71	65	0.0001
ARB	24	20	23	27	22	0.04
Spironolactone/eplerenone	46	45	48	45	35	0.16
β-Blockers	95	96	95	94	95	0.19
Nitrates	25	18	23	30	32	<0.0001
Calcium channel blockers	7	7	7	7	3	0.77
Loop diuretics	79	70	76	87	88	<0.0001
Digoxin	46	46	45	48	35	0.92

Am J Nephrol. 2010;32(3):226-33. Epub 2010 Jul 22

CKD in HF ACTION Trial (EF < 35%): Peak VO2 and Clustered Risk Features





Am J Nephrol. 2010;32(3):226-33. Epub 2010 Jul 22

Pfizer Announces EMPHASIS-HF Trial to Halt Recruitment due to Significant Benefit Observed in Patients Treated With Inspra® (Eplerenone)

Like It

Announcement Follows Recommendation of Data Safety Monitoring Committee and Executive Steering Committee

NEW YORK, May 27 /PRNewswire-FirstCall/ -- Pfizer Inc. (NYSE: PFE) announced that it plans to halt recruitment to the EMPHASIS-HF trial early on the recommendations of the trial's independent Executive Steering Committee (ESC). The recommendations follow a second interim analysis by the independent Data Safety Monitoring Committee (DSMC) of the EMPHASIS-HF trial confirming the study has reached its primary efficacy endpoint early according to the protocol pre-defined stopping rules.

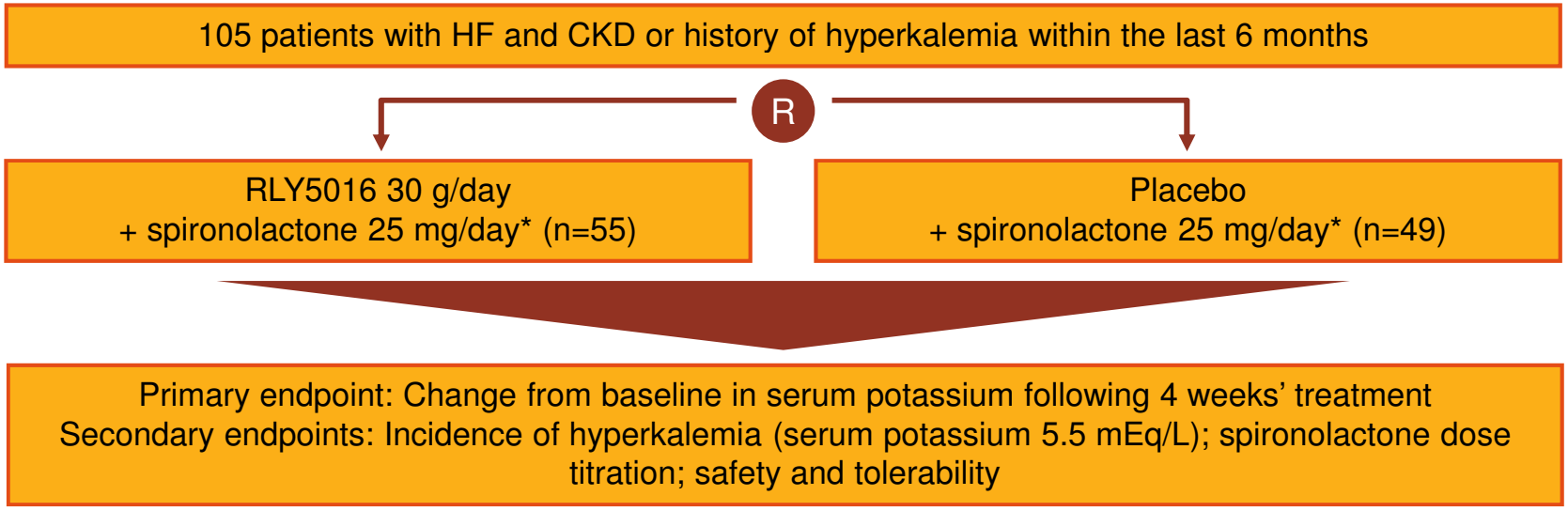
(Logo: http://photos.prnewswire.com/prnh/20100416/PFIZERLOGO)

The interim analysis showed that patients treated with INSPRA® (eplerenone), in addition to current standard of care, experienced a significant reduction in risk of cardiovascular (CV) death or heart failure (HF) hospitalization compared with those on the placebo arm of the trial where patients received standard of care in addition to a matching placebo.

Based upon the interim analyses by the independent data safety monitoring committee, eplerenone, generally, was well tolerated during the EMPHASIS-HF trial. Adverse events reported included hyperkalemia (elevated potassium) (8 per cent of the eplerenone group vs 3% in the placebo group; $p < 0.001$) and renal impairment (4 per cent in the eplerenone group vs 2% in the placebo group; $p < 0.05$). These adverse events are common with mineralcorticoid receptor antagonist agents.

PEARL HFStudy design and methods

- PEARL-HF was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study that compared RLY5016 30 g (non-absorbed, oral, potassium binding polymer) once daily with placebo
- Eligible patients were those with serum potassium 4.3–5.1 mEq/L, and CKD (eGFR <60 mL/min) on one or more HF therapies (ACEIs, ARBs, or β-blockers), or documented history of hyperkalemia (serum potassium >5.5 mEq/L) within the last 6 months leading to the discontinuation of an AA, ACEI, ARB, or β-blocker



*Spironolactone titrated to 50 mg/day if serum potassium ≤5.1 mEq/L at Day 15
AA = aldosterone antagonist; ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate; HF = heart failure

Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

Baseline patient characteristics

	RLY5016 30 g/day (n=55)	Placebo (n=49)	p
Age (years)	68.3±8.6	68.2±10.5	0.940
Male (%)	53	69	0.108
BMI (kg/m^2)	28.4±5.5	27.0±4.3	0.145
HF duration (years)	4.5±4.8	4.1±3.4	0.581
Ejection fraction (%)	39.6±11.7	41.2±11.8	0.561
NYHA class (%)			
I	4	2	0.936
II	53	57	
III	44	41	
IV	0	0	
eGFR (mL/min)	84.1	78.1	0.360
Diabetes (%)	27	37	0.399

BMI = body mass index; eGFR = estimated glomerular filtration rate
HF = heart failure; NYHA = New York Heart Association
Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

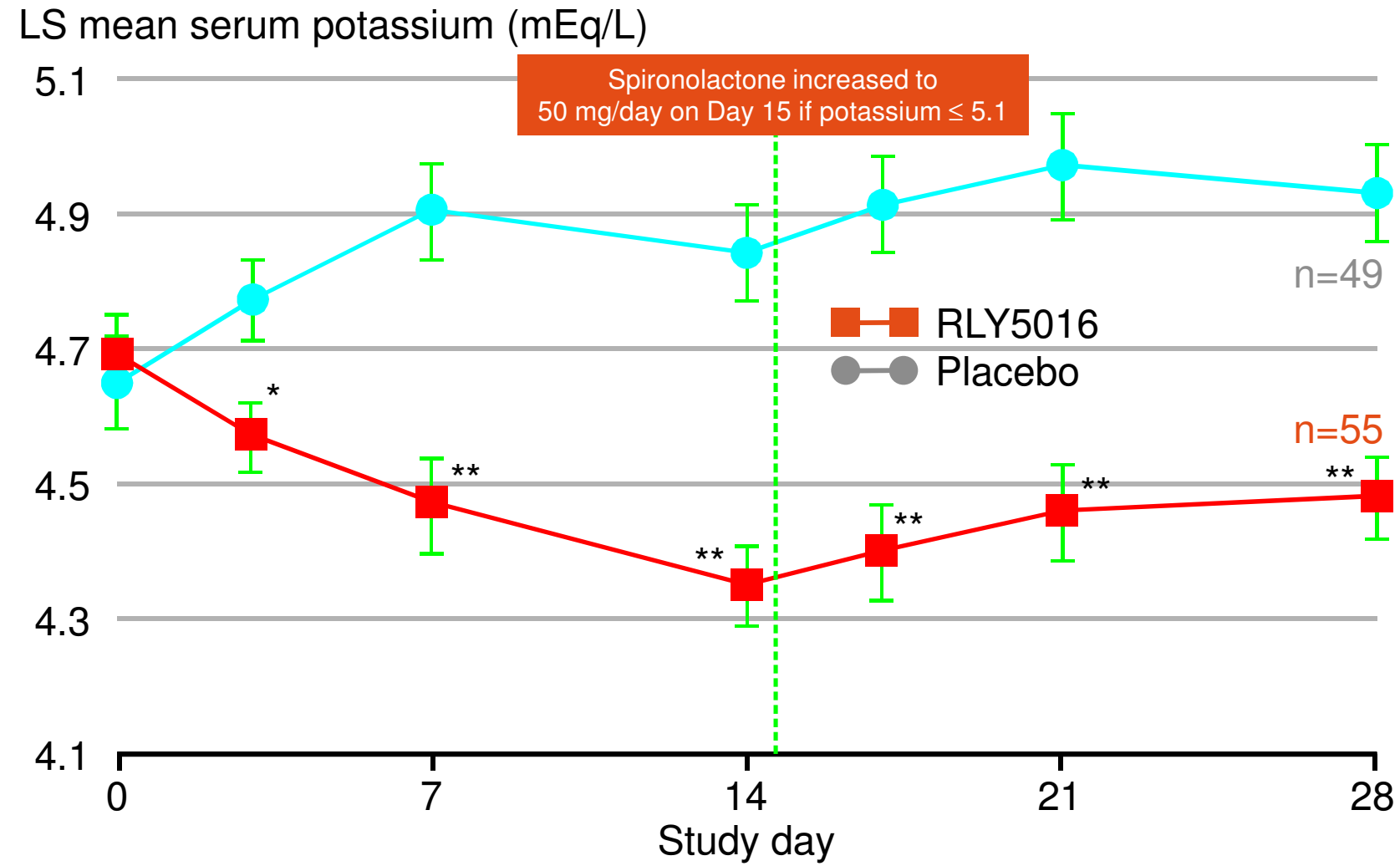
Baseline medications

	RLY5016 30 g/day (n=55)	Placebo (n=49)	p
No RAAS inhibitors or β-blockers*, n (%)	0	2 (4)	NS
ACEI, ARB or β-blocker only, n (%)	13 (24)	9 (18)	NS
ACEI or ARB + β-blocker, n (%)	40 (73)	37 (76)	NS
ACEI + ARB + β-blocker, n (%)	2 (4)	1 (2)	NS
Diuretics (Total), n (%)	41 (75)	36 (73)	NS
Thiazide, n (%)	10 (18)	6 (12)	NS
Loop, n (%)	32 (58)	27 (55)	NS
Indapamide, n (%)	4 (7)	5 (10)	NS

*Eligible under criteria of discontinuation of RAAS inhibitor due to hyperkalemia
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker
NS = not statistically significant; RAAS = renin-angiotensin-aldosterone system

Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

Change from baseline in serum potassium by visit



*p<0.01; **p<0.001

Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

Proportion of patients receiving up-titration to spironolactone 50 mg/day*

	RLY5016 30 g/day (n=55)	Placebo (n=49)	p
Patients receiving up-titration to spironolactone 50 mg/day, n (%)	50 (91)	36 (74)	0.019

*Spironolactone titrated to 50 mg/day if serum potassium ≤5.1 mEq/L at Day 15

Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

Summary of adverse events

	RLY5016 30 g/day (n=55)	Placebo (n=49)	p
At least one AE, n (%)	30 (54)	15 (31)	0.019
At least one GI AE, n (%)	12 (21)	3 (6)	0.028
SAEs, n (%)	2 (4)	2 (4)	NS
Deaths, n (%)	0	1 (2)	NS
Discontinuations due to AE, n (%)	4 (7)	3 (6)	NS

No SAEs were deemed to be drug-related by the investigators
AE = adverse event; GI = gastrointestinal; SAE = serious AE

Pitt B. ESC Scientific Session 2010. Stockholm, Sweden

Recognize Failures from Clinical Trials and Registries

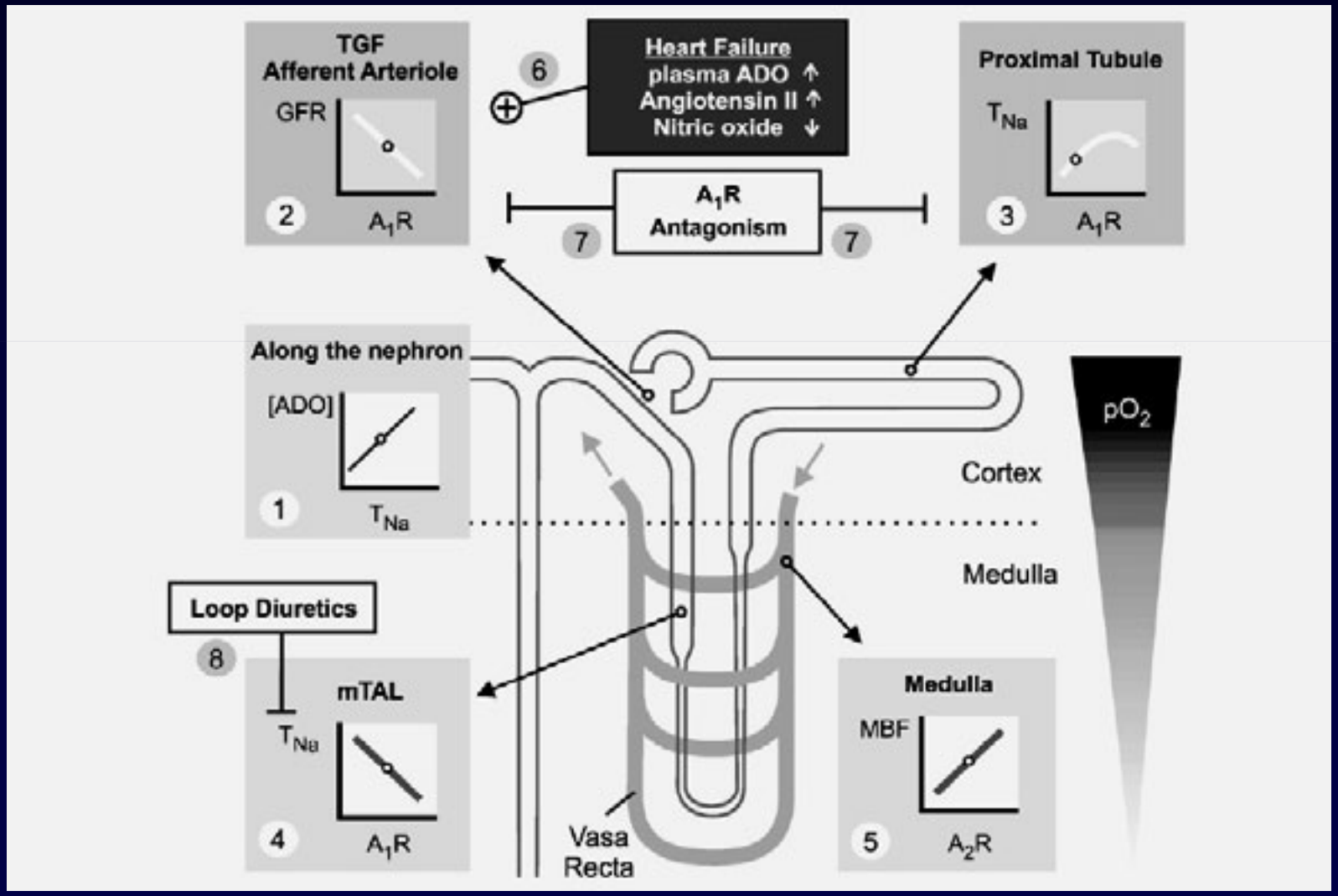
- Programmatic use of PA catheter (Nohria JACC 2008)
- Programmatic use of inotropes/indodilators (ACC/AHA Guidelines)
- High-dose loop diuretics (Heywood, ADHERE, HF Reviews, 2005)
- Beta-blocker withdrawal (Fonarow, JACC 2008)
- ACEI/ARB withdrawal (Shukla, CIRC, 2008)
- Digoxin withdrawal (Packer, NEJM, 1993)
- Rolophylline (PROTECT, ESC, 2009)
- Endothelin receptor antagonists (Forbes KI 2001)
- Argnine vasopressin receptor antagonists (Konstam JAMA 2007)
- ?Nesiritide (Sackner-Bernstein, CIRC, 2005)

Drug/Strategy Ineffective/Harmful

OR

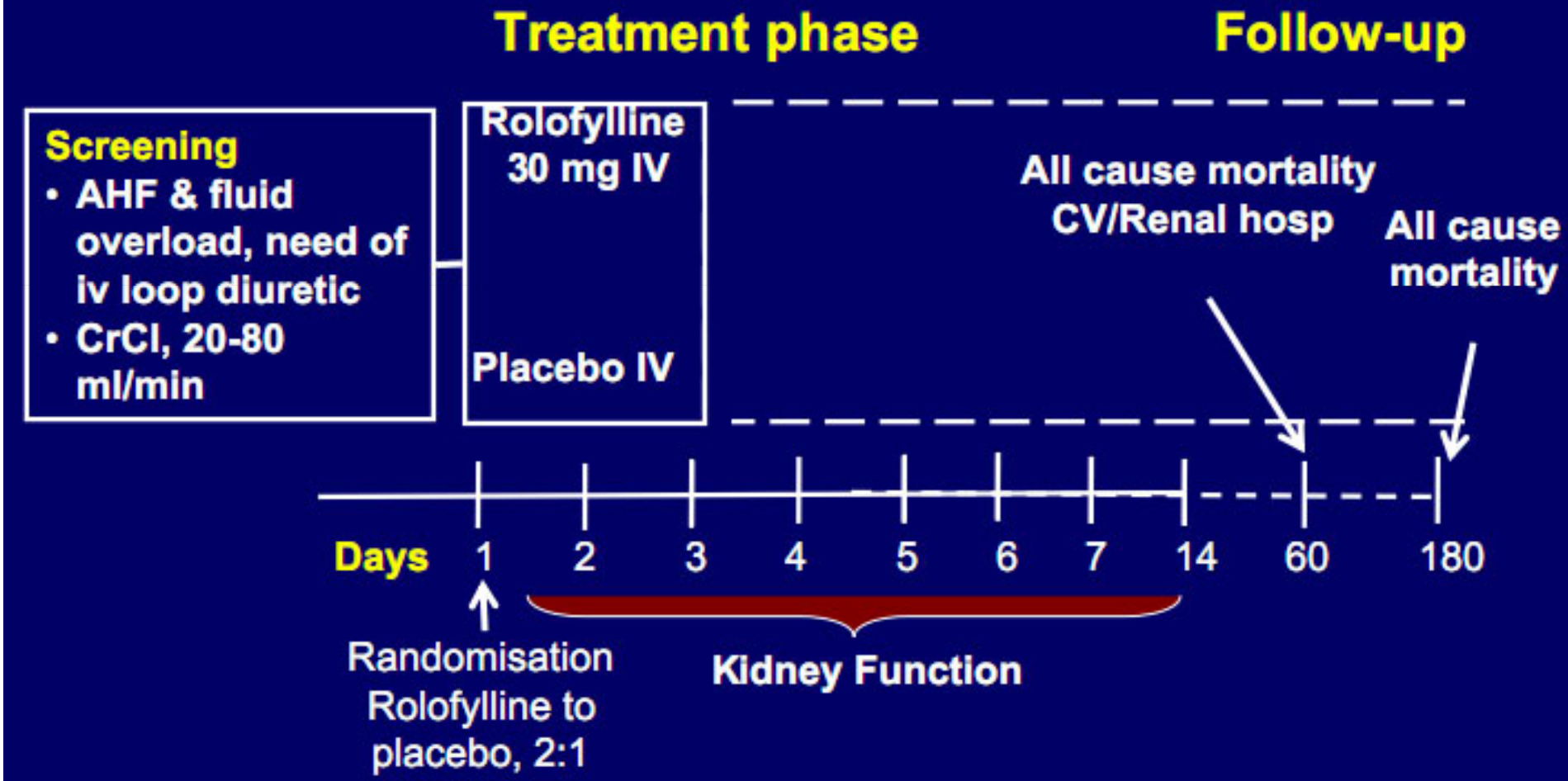
Have not identified the ideal patient subset for benefit

Role of Adenosine in the Kidney: Type 1 and Type 2 Adenosine Receptors



V. Vallon et al. Eur J Heart Fail 10 (2008) 176–187

PROTECT STUDY DESIGN



Metra M,, et al. Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT Study. ESC 2009

Inclusion/Exclusion Criteria

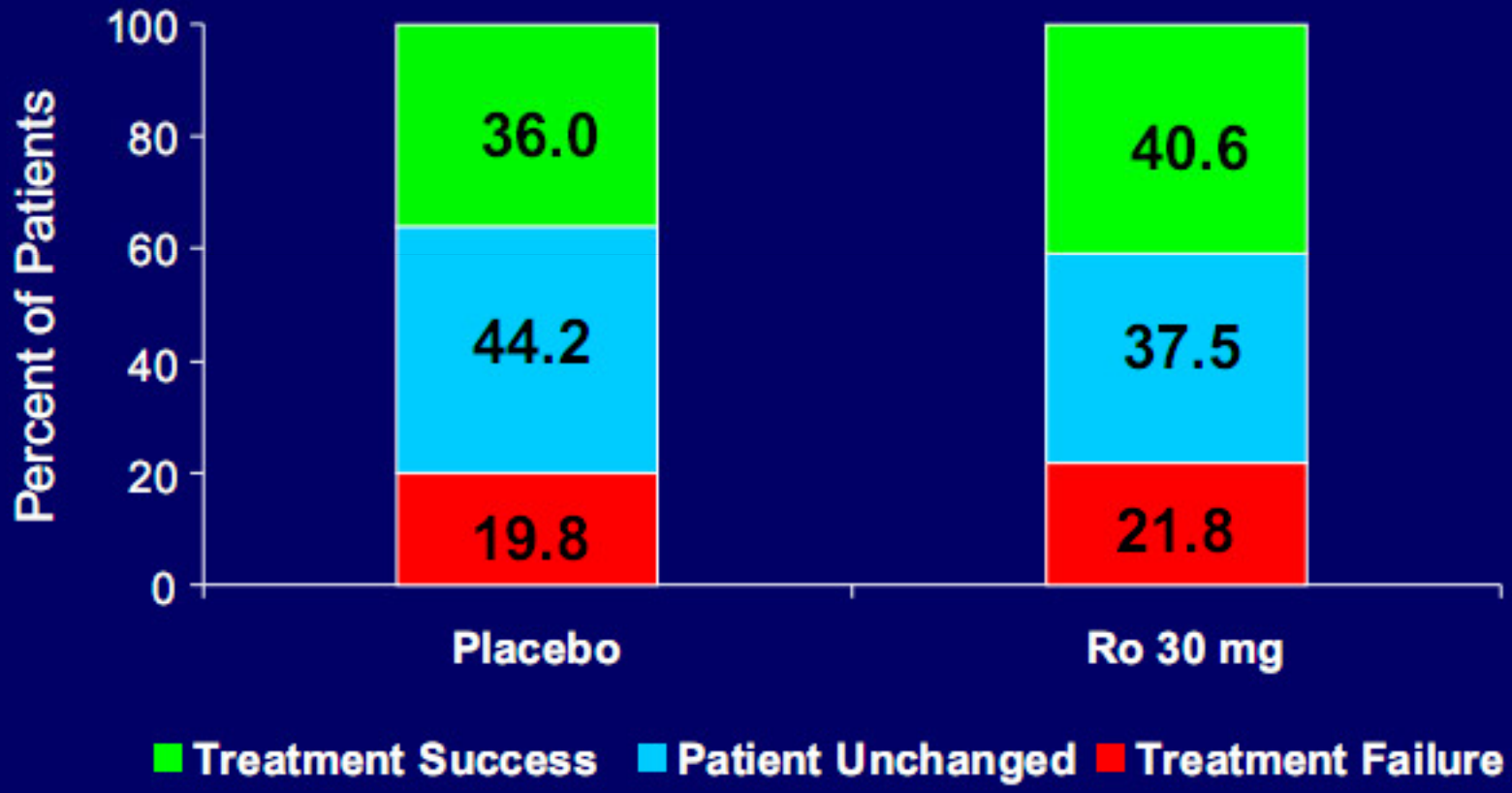
- **Inclusion Criteria**
  - Male or female; aged ≥18 years
  - History of heart failure of ≥14 days duration for which diuretic therapy has been prescribed
  - BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL
  - Hospitalized for AHFS requiring IV diuretics and anticipated need for IV diuretics for at least 24 hours
  - Impaired renal function (CrCl 20-80 mL/min, Cockcroft–Gault)
  - Systolic blood pressure ≥95 mm Hg (but < 160 mmHg) at randomization

- **Key Exclusion Criteria**
  - Severe pulmonary disease
  - Significant cardiac valve stenosis
  - Clinical evidence of ACS in the 2 weeks before screening
  - High risk for seizures (e.g., history of seizure, stroke within 2 years, brain tumor, brain surgery within 2 years)

Metra M,, et al. Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT Study. ESC 2009

Primary Endpoint

Odds ratio (95% CI) vs Pbo: 0.92 (0.78, 1.09)

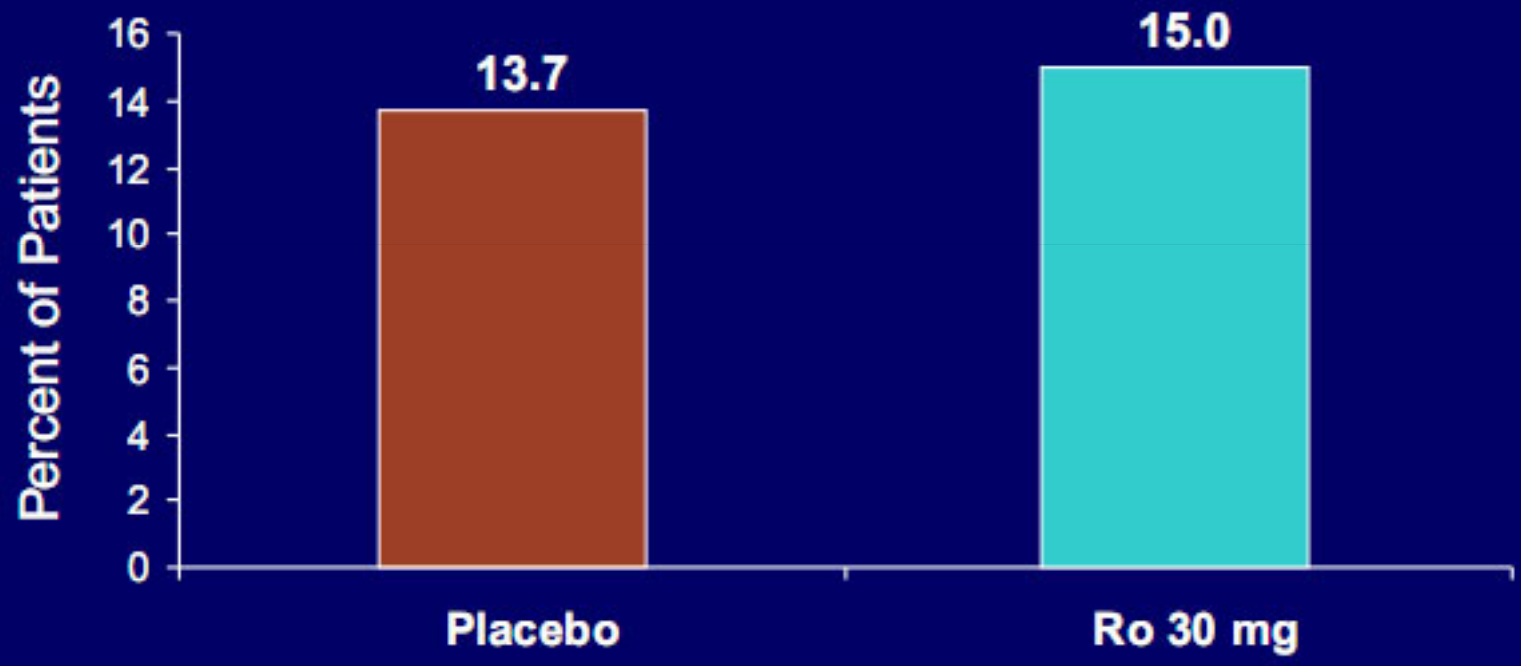


p=0.348 for comparison of distribution using the van Elteren extension of Wilcoxon test

Metra M,, et al. Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT Study. ESC 2009

Secondary Endpoint: Persistent Renal Impairment*

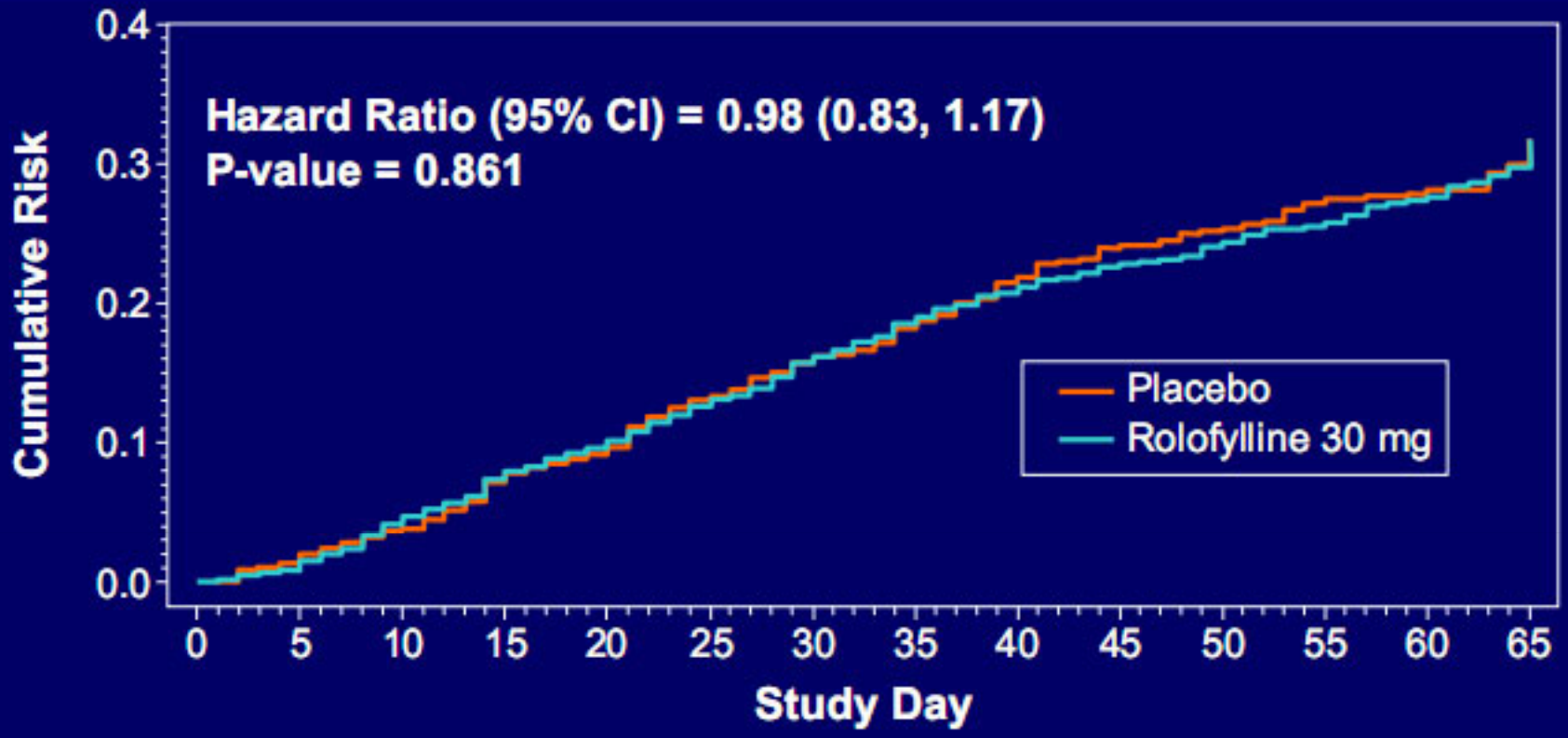
Odds ratio (95% CI) vs Pbo: 1.11 (0.85, 1.46); p = 0.441



*Persistent renal impairment SCr ↑ >0.3 mg/dL at both Day 7 and Day 14 or initiation of hemofiltration or dialysis through Day 7, or death by Day 7

Metra M,, et al. Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT Study. ESC 2009

Time to Death or CV or Renal Rehospitalization - Day 60



Study Day	7	14	30	55	65
No. of patients at risk					
Placebo (N=677)	657	633	566	489	74
Rolofylline (N=1356)	1322	1263	1134	1001	158

Death: Placebo 9.5% vs rolofylline 8.9%

Re-hospitalization: Placebo 25.6% vs rolofylline 25.7%

Metra M,, et al. Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT Study. ESC 2009

Dopamine in Acute Decompensated Heart FailureDopamine in Acute Decompensated Heart Failure (DAD-HF) trial

- ADHF, O_2 sat <90%, and BNP >400 pg/mL
- Excluded serum Cr >200 µmol/L (2.26 mg/dl), eGFR<30 mL/min per 1.73 m^2), SBP <90 mm Hg.
- Randomized to receive higher-dose IV furosemide (40-mg bolus followed by 20 mg/hr for 8 hrs) or lower-dose furosemide (40-mg bolus followed by 5 mg/hr for 8 hrs) plus dopamine (5 µg/kg per min for 8 hrs)
- N=300 planned for death or hospitalization endpoint, first 50 patients randomized at the centers in Greece reported

Triposkiadis F. Renoprotective and potassium-sparing effects of low-dose dopamine in acute decompensated heart failure. Heart Failure Society of America 2009 Scientific Meeting; September 16, 2009; Boston, MA. Late-Breaking Clinical Trials 2.

DAD-HF: Urine Output and Serum Creatinine

Cumulative urine output during eight-hour infusion of high-dose furosemide vs low-dose furosemide plus low-dose dopamine*

Infusion (h)	High-dose furosemide (mL), n=25	Low-dose furosemide/dopamine (mL), n=25
2	647	847
4	948	1272
6	1223	1510
8	2214	1888

*All differences between the groups nonsignificant

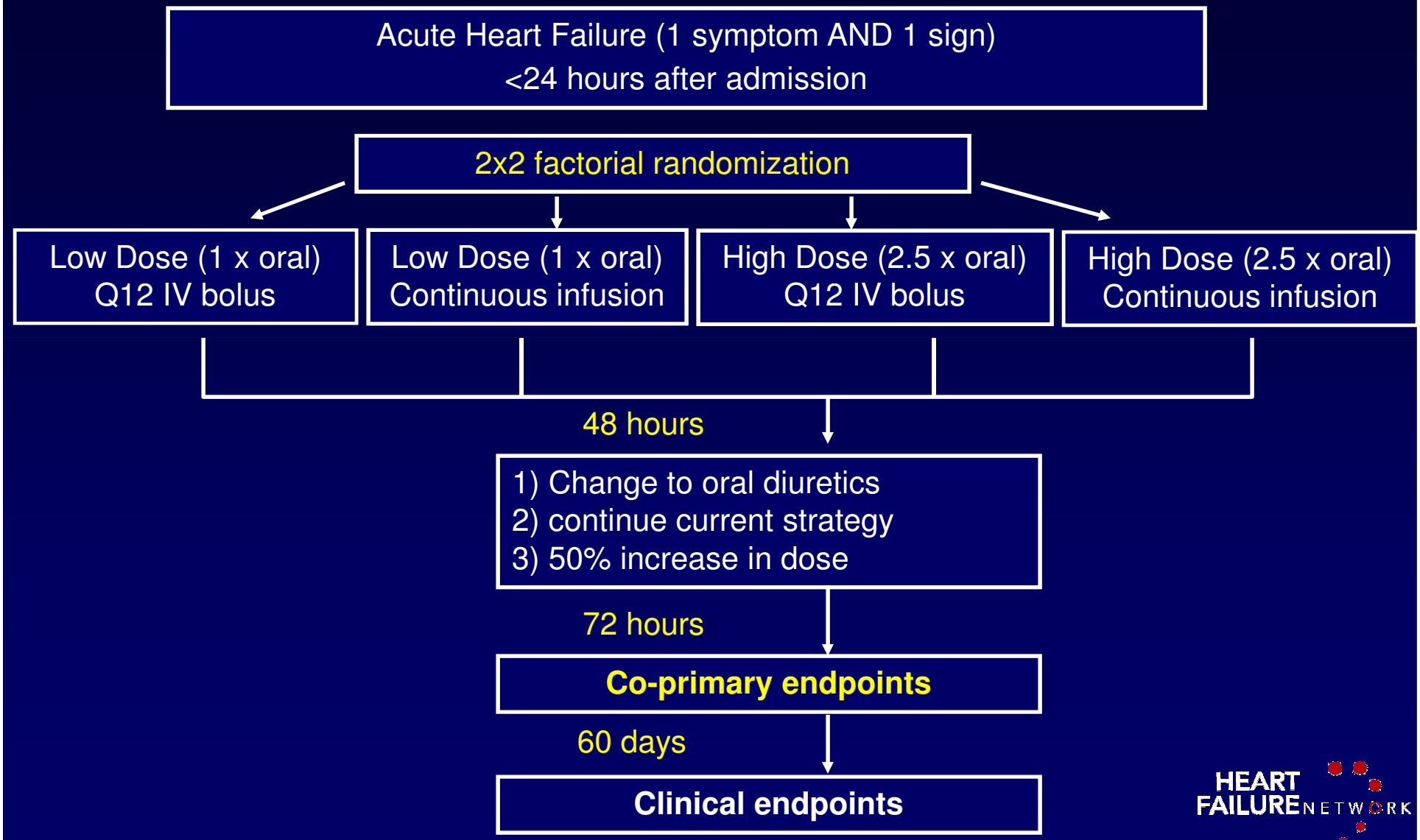
Measures of worsening renal function at 24 hours for high-dose furosemide vs low-dose furosemide plus low-dose dopamine

Measure	High-dose furosemide (%)	Low-dose furosemide/dopamine (%)	p
sCr, >0.3-mg/dL increase	36	4	0.005
sCr, >25% increase	36	4	0.004
eGFR, >10% decrease	64	28	0.011

sCr=serum creatinine; eGFR=estimated glomerular filtration rate

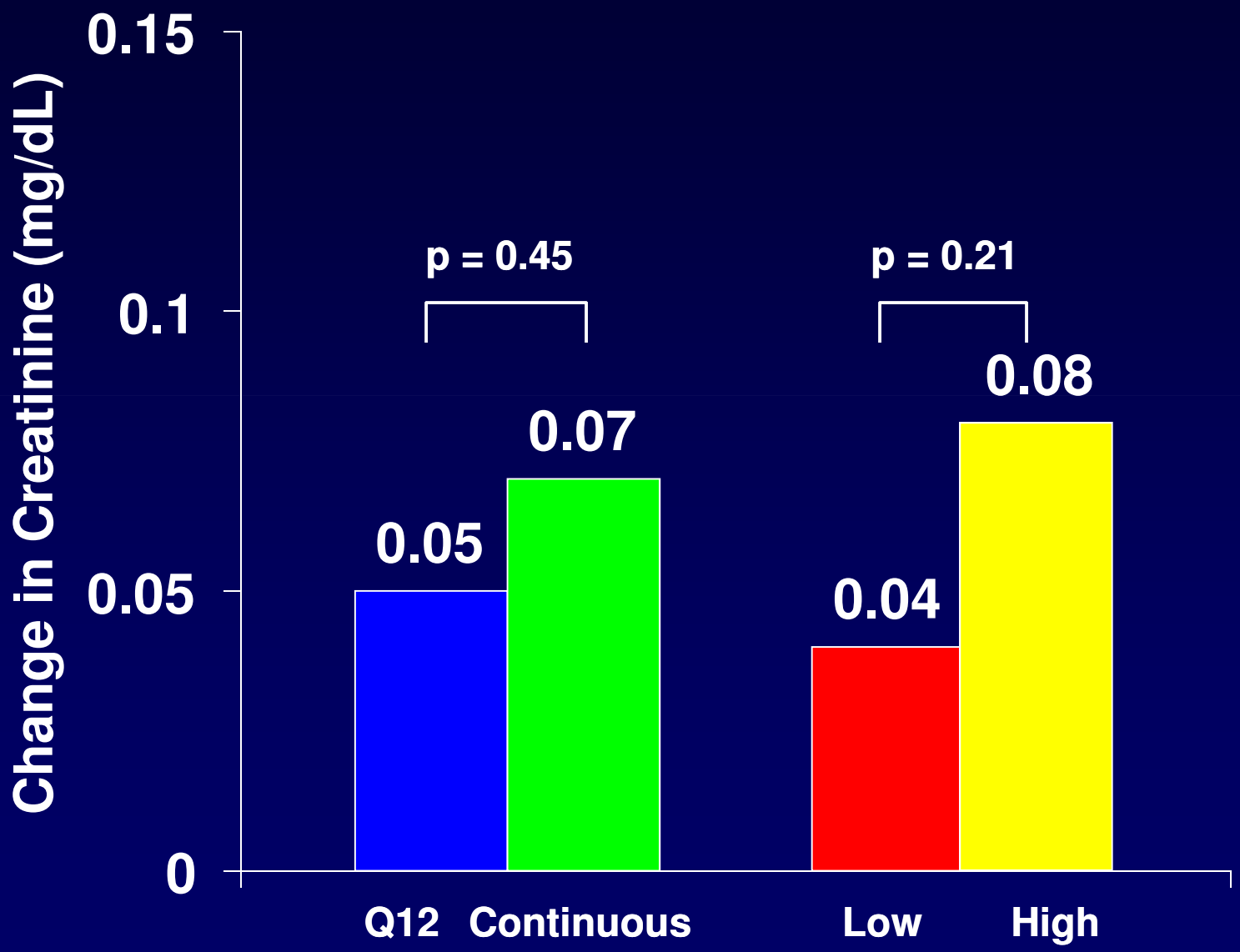
Triposkiadis F et al. Heart Failure Society of America 2009 Scientific Meeting; September 16, 2009: Boston, MA.

DOSE Trial: Study Design



HEART FAILURE NETWORK

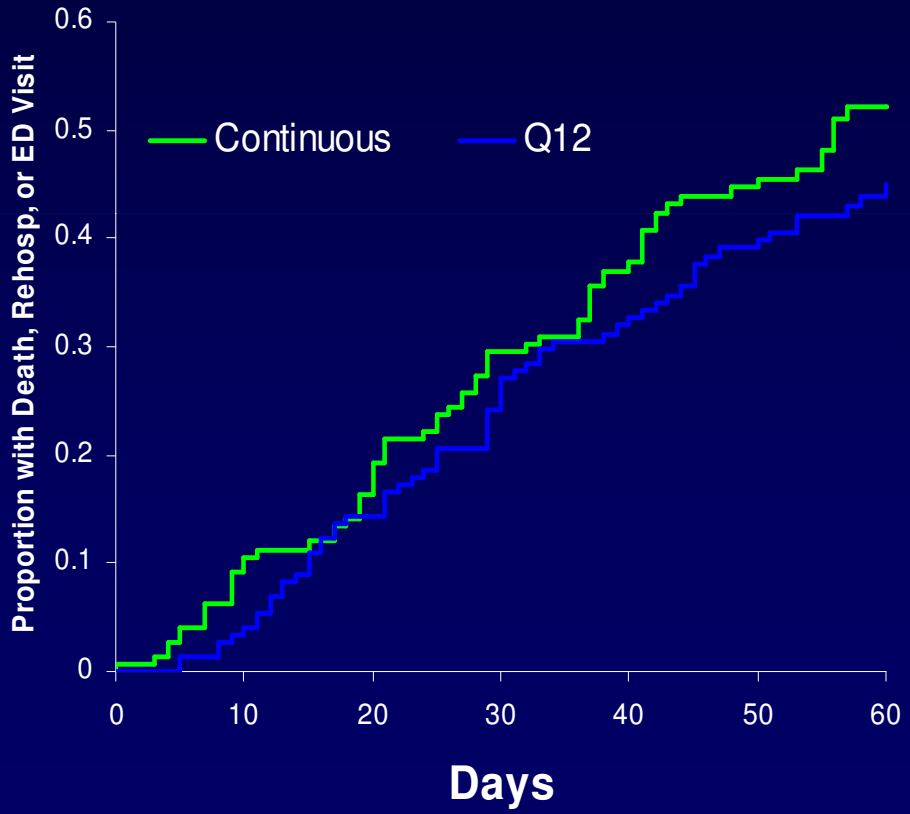
Change in Creatinine at 72 hours



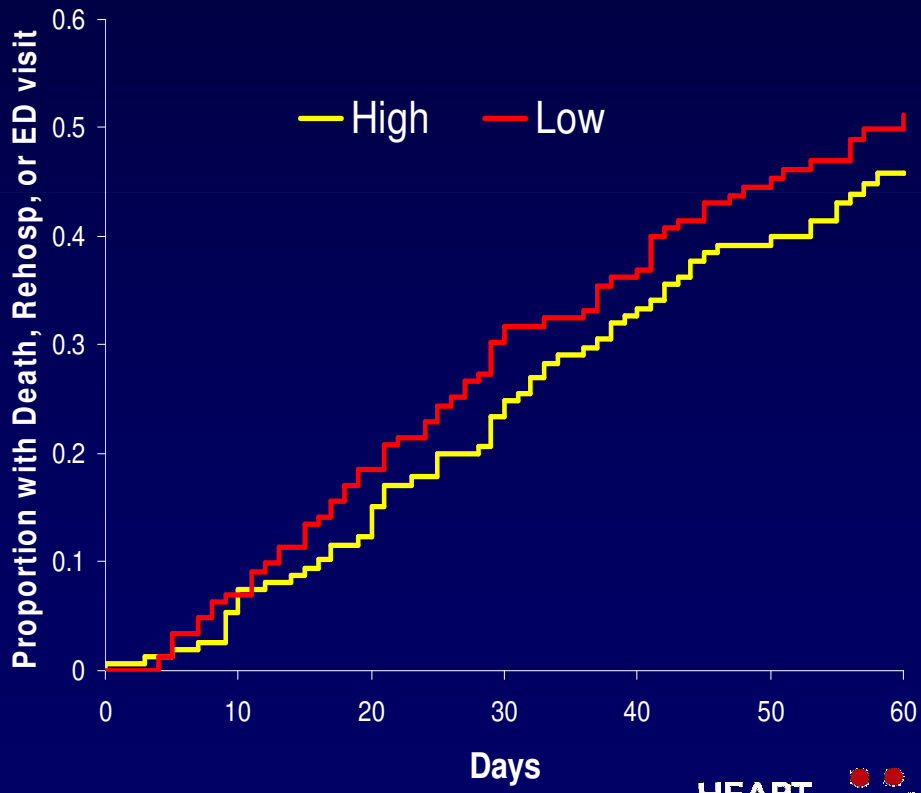
HEART FAILURE NETWORK

Death, Rehospitalization, or ED Visit

HR for Continuous vs. Q12 = 1.19
95% CI 0.86, 1.66, p = 0.30



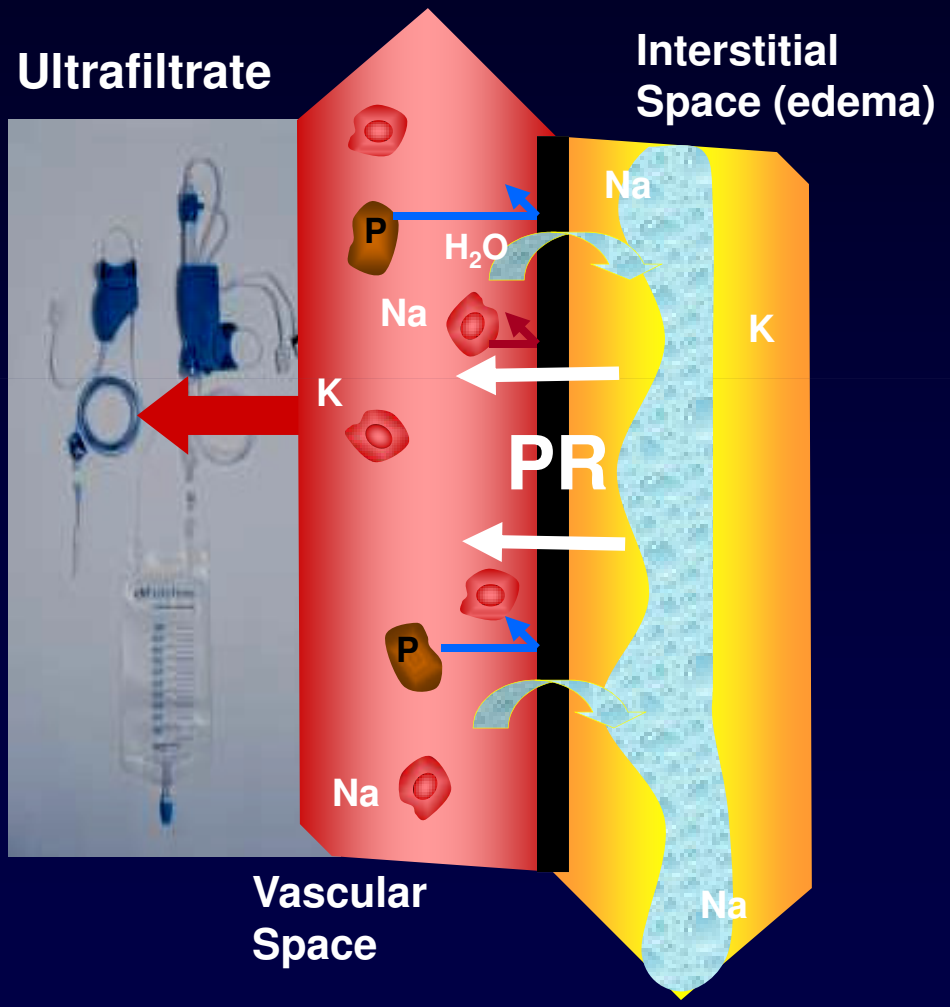
HR for High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28



HEART FAILURE NETWORK

Fluid Removal by Ultrafiltration

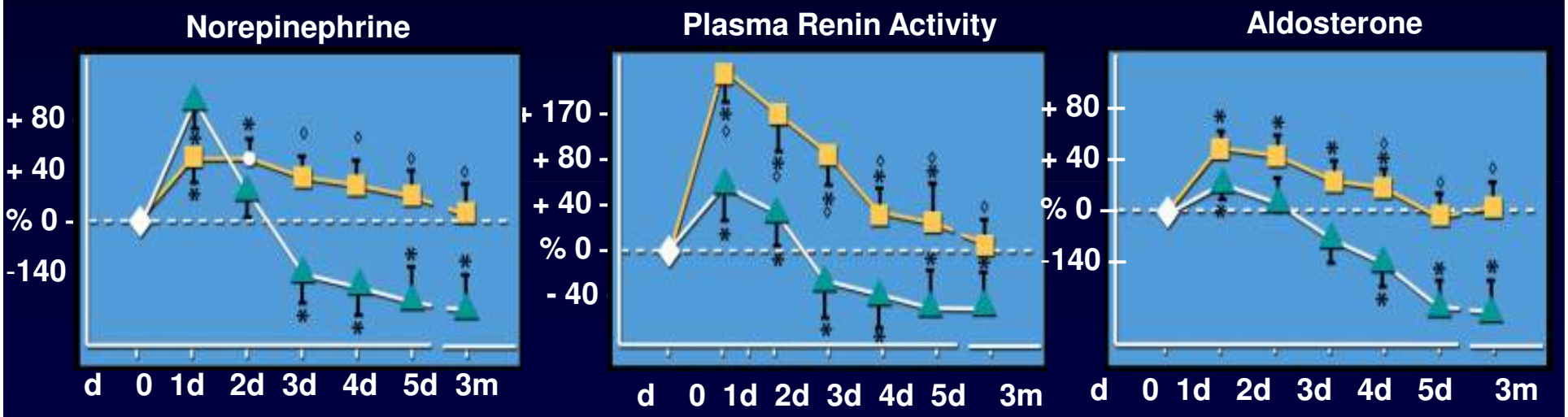
- Removes fluid from the blood at the same rate that fluid can be naturally recruited from the tissue
- Transient removal of blood illicits compensatory mechanisms, termed *plasma* or *intravascular refill* [1,2]
- Ultrafiltrate is isotonic with plasma,
- Removes more sodium than diuretic therapy
- Decreases ECF volume more than a comparable volume of diuretic-induced fluid loss without neurohormonal activation



1. Lauer et al. *Arch Intern Med.* 1983;99:455-460. 2. Marenzi et al. *J Am Coll Cardiol.* 2001;38:4.

Effects of Ultrafiltration vs IV Furosemide

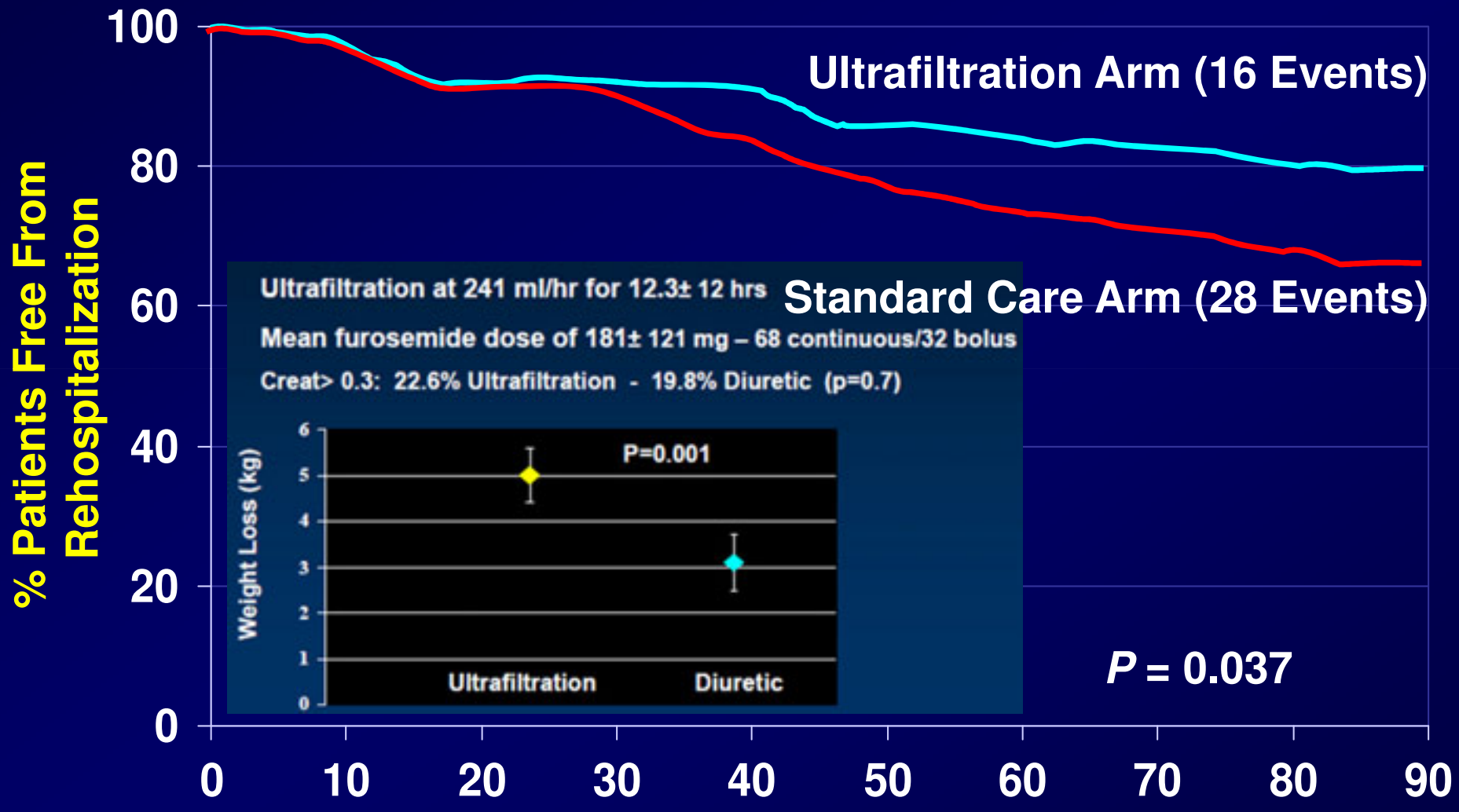
Neurohormones



Triangles = Ultrafiltration
Squares = Furosemide

Agostoni et al. *Am J Med.* 1994;96:191-199.

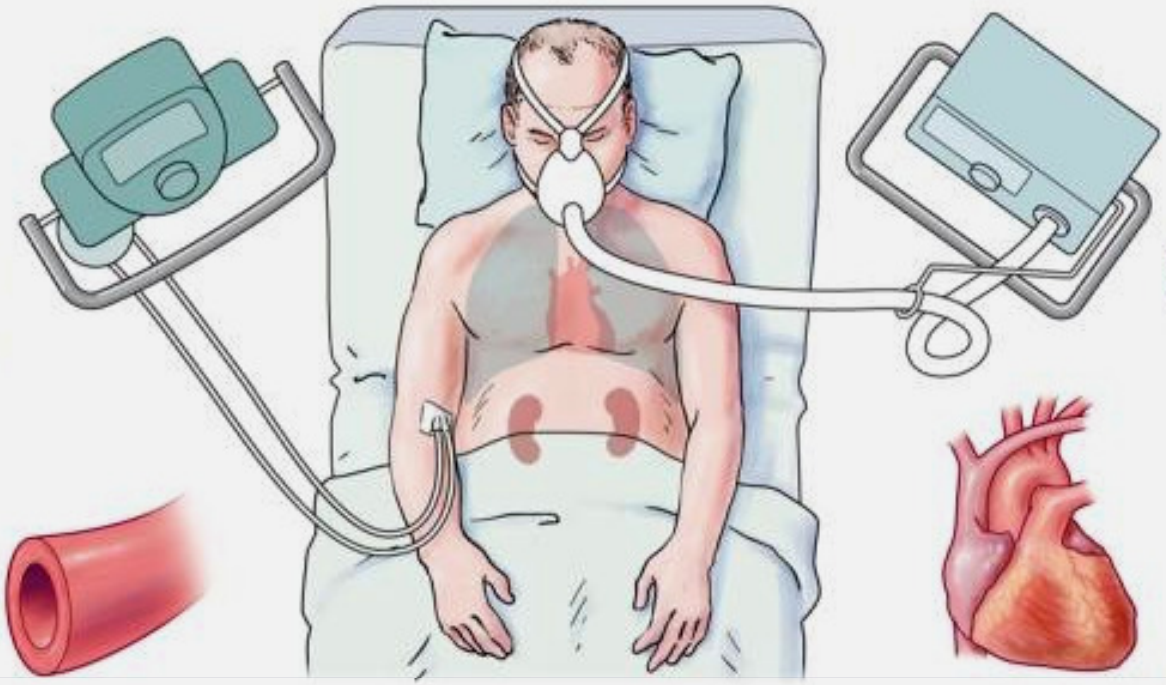
UNLOAD Trial: N=200, RCT, Freedom From Heart Failure Rehospitalization Within 90 Days After Discharge



Costanzo, M. et al., *J Am Coll Cardiol* 2007;49:675-83.

Outline

- Definitions
- Complex, bidirectional pathogenesis
- Example of novel target
- Therapy
- Putting it all together



Ultrafiltration:
Aqua/natriuresis

More effectively remove sodium, control blood volume, and avoid reflex neurohormonal activation see with loop diurectics

Bilevel or continuous positive airway pressure:
Preload reduction

Ideal for superimposed obstructive sleep apnea

Nitrates, nitroprusside, dobutamine:
Arterial vasodilation

Dobutamine, dopamine, milrinone:
Increased inotropy

Reserved for low cardiac output syndrome

Balanced to avoid arterial/venous flow mismatch

Nitrates, morphine:
Venodilation

Furosemide:
Natriuresis

"Go low, go slow"

Avoid or remove major precipitants: cardiac ischemia, sodium excess, NSAIDS, TZDs, iodinated intravascular contrast, medication non-compliance, abrupt diuresis with high-dose loop diurectics

Cardiorenal Syndromes

Ronco C, Bellomo R, McCullough PA (eds): Cardiorenal Syndromes in Critical Care. Contrib Nephrol. Basel, Karger, 2010, vol 165, pp 101–111