Heart Failure and Renal Disease

Cardiorenal Syndrome

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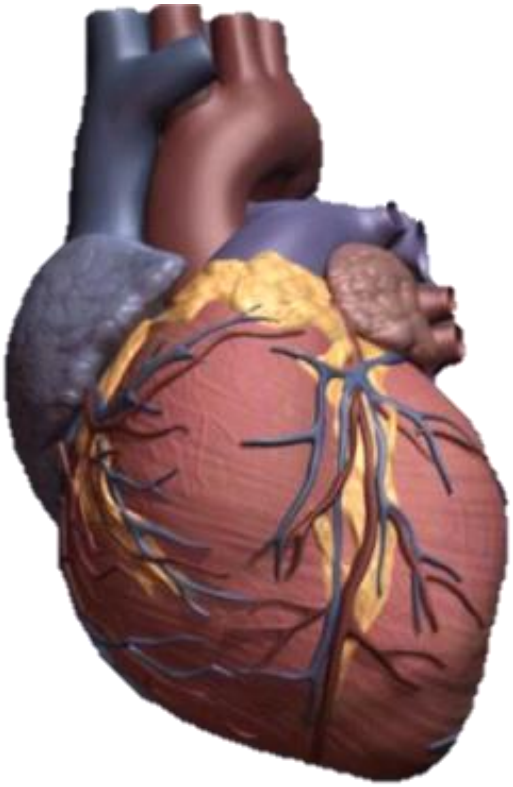
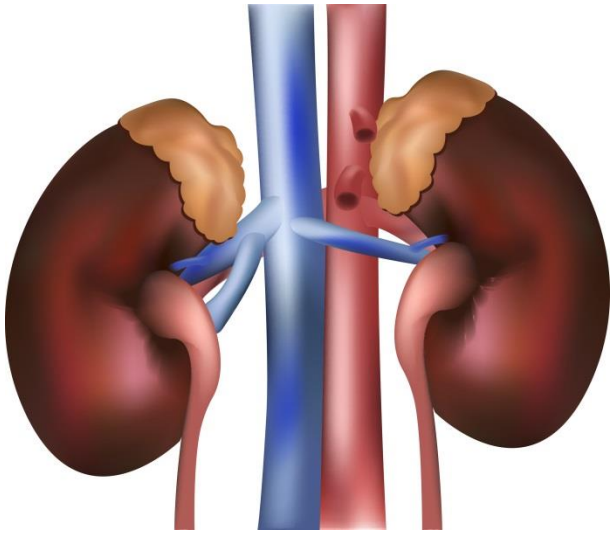
What is the “Cardiorenal syndromes” ?

Definition and Classification

Heart and Kidney





Mortality is increased in patients with HF who have a reduced GFR

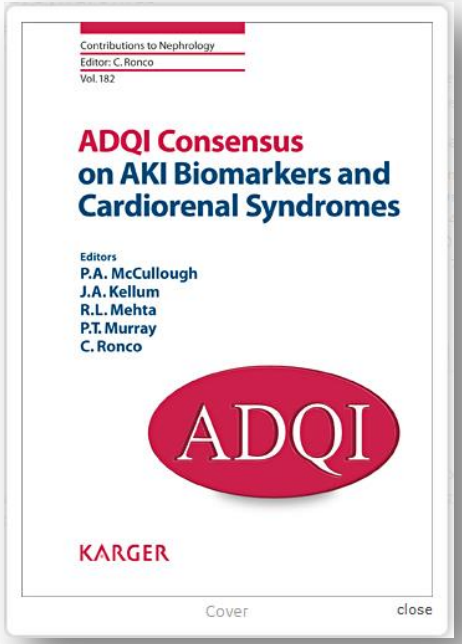
Patients with CKD have an increased risk of both atherosclerotic CV disease and HF

Acute or chronic systemic disorders can cause both cardiac and renal dysfunction

Definition : Cardiorenal syndromes

2004 NHLBI Report

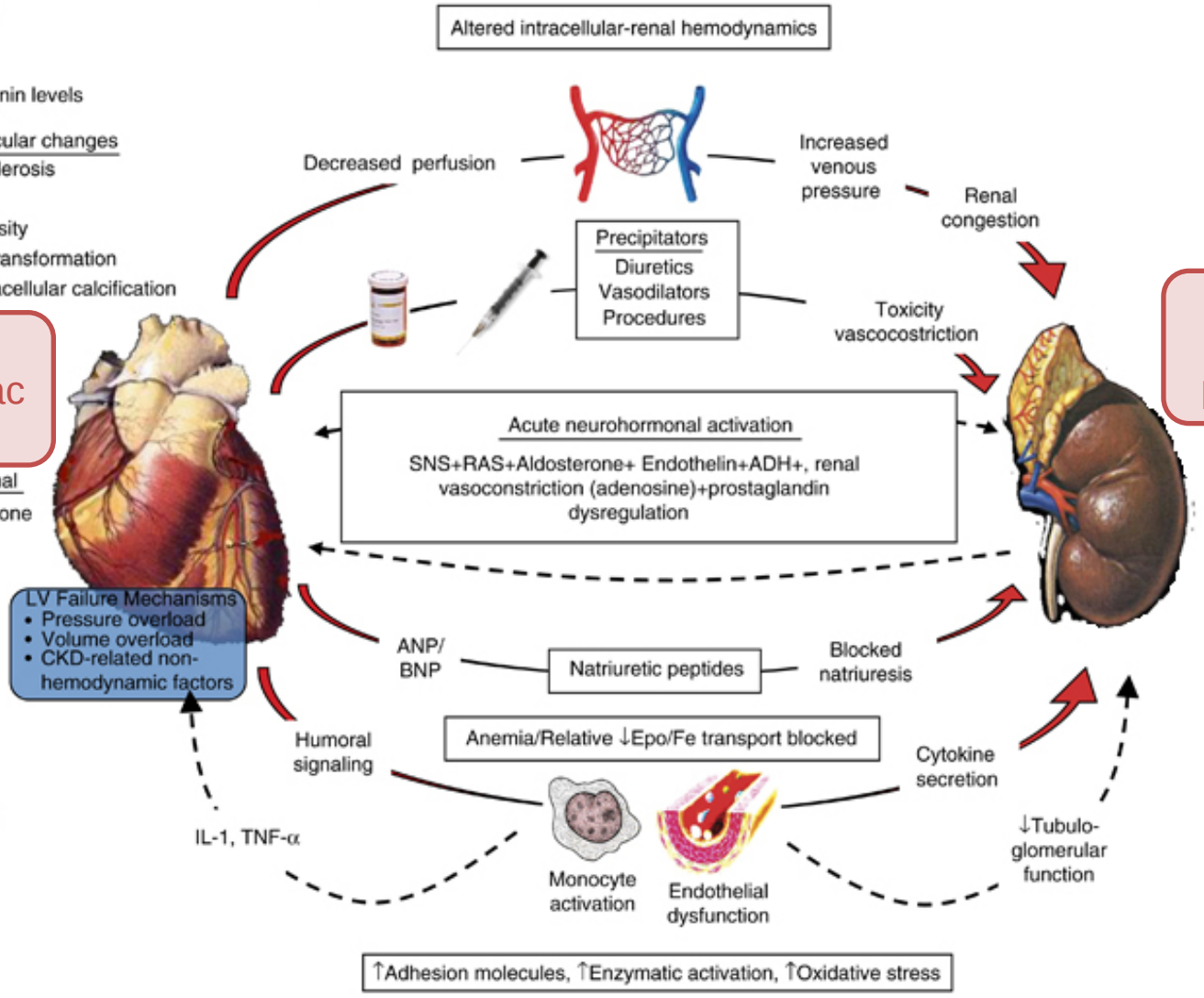
A condition in which therapy to relieve congestive symptoms of HF is limited by a decline in renal function



2013 11th ADQI Consensus Conference

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

Systolic or diastolic dysfunction or both



Acute on chronic cardiac disease

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
- Intracellular-and extracellular calcification

Chronic neurohormonal
- ↑SNS, RAS, Aldosterone
- ↓Vitamin D
- ↑PTH
- ↑PO4
- Hypotestesteronism
- ↓EPO
- ↓Fe utilization
- ↓Na-K ATPase

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

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McCullough PA, Diez J, KDIGO 2010 Workshop

Classification of the Cardiorenal syndromes

CRS Type 1 **[Acute Cardiorenal Syndrome]**

Abrupt worsening of cardiac function (e.g. Acutely decompensated congestive heart failure) leading to acute kidney injury

CRS Type 2 **[Chronic Cardiorenal Syndrome]**

Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type 3 **[Acute Renocardiac Syndrome]**

Abrupt worsening of renal function (e.g. acute kidney injury) causing acute cardiac disorder (acute heart failure)

CRS Type 4 **[Chronic Renocardiac Syndrome]**

Chronic kidney disease (diabetic nephropathy) contributing to decreased cardiac function, cardiac hypertrophy, fibrosis, and/or increased risk of adverse cardiovascular events

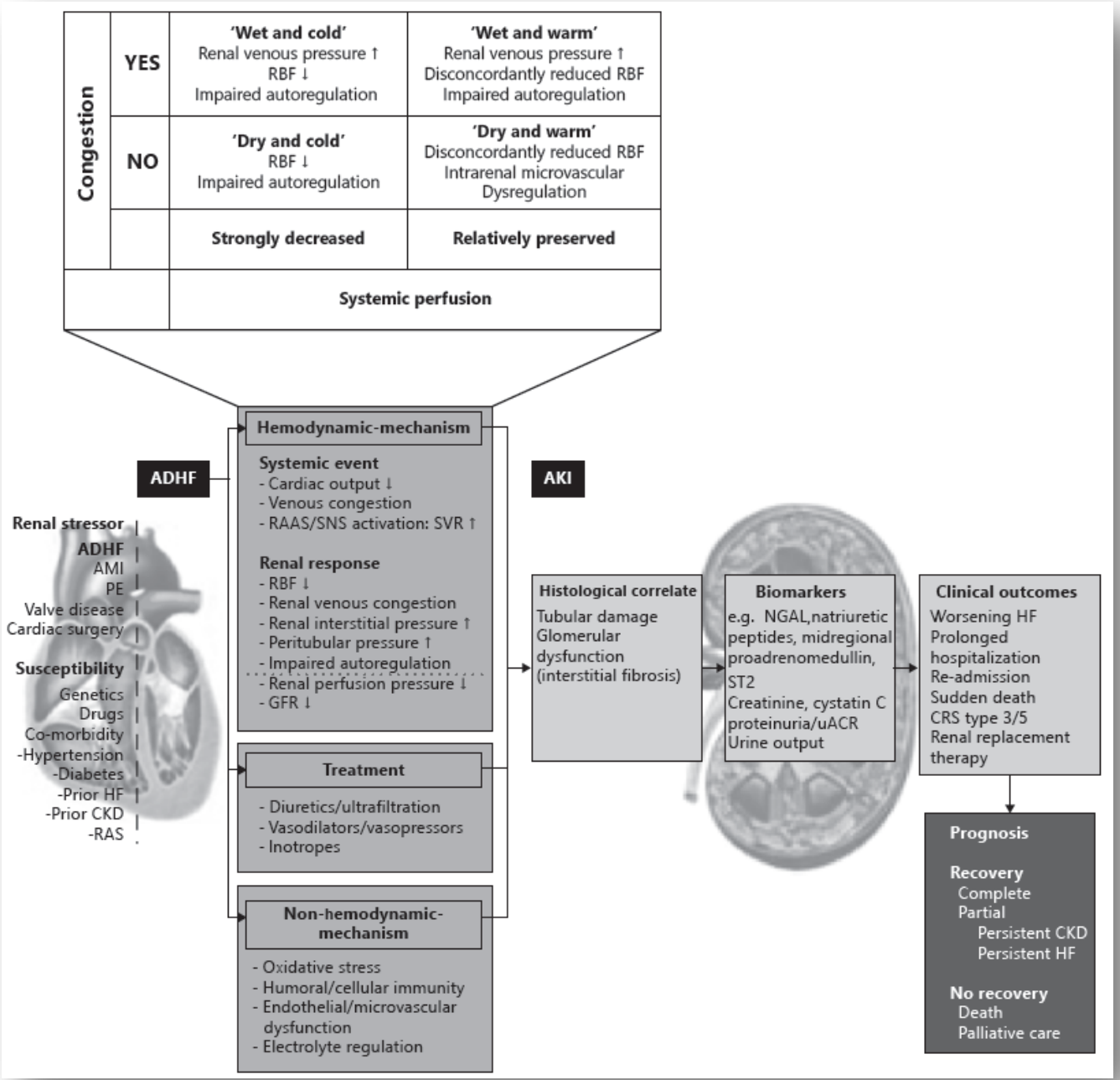
CRS Type 5 **[Secondary Cardiorenal Syndrome]**

Systemic condition (e.g. sepsis) causing both acute cardiac and renal injury and dysfunction

2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

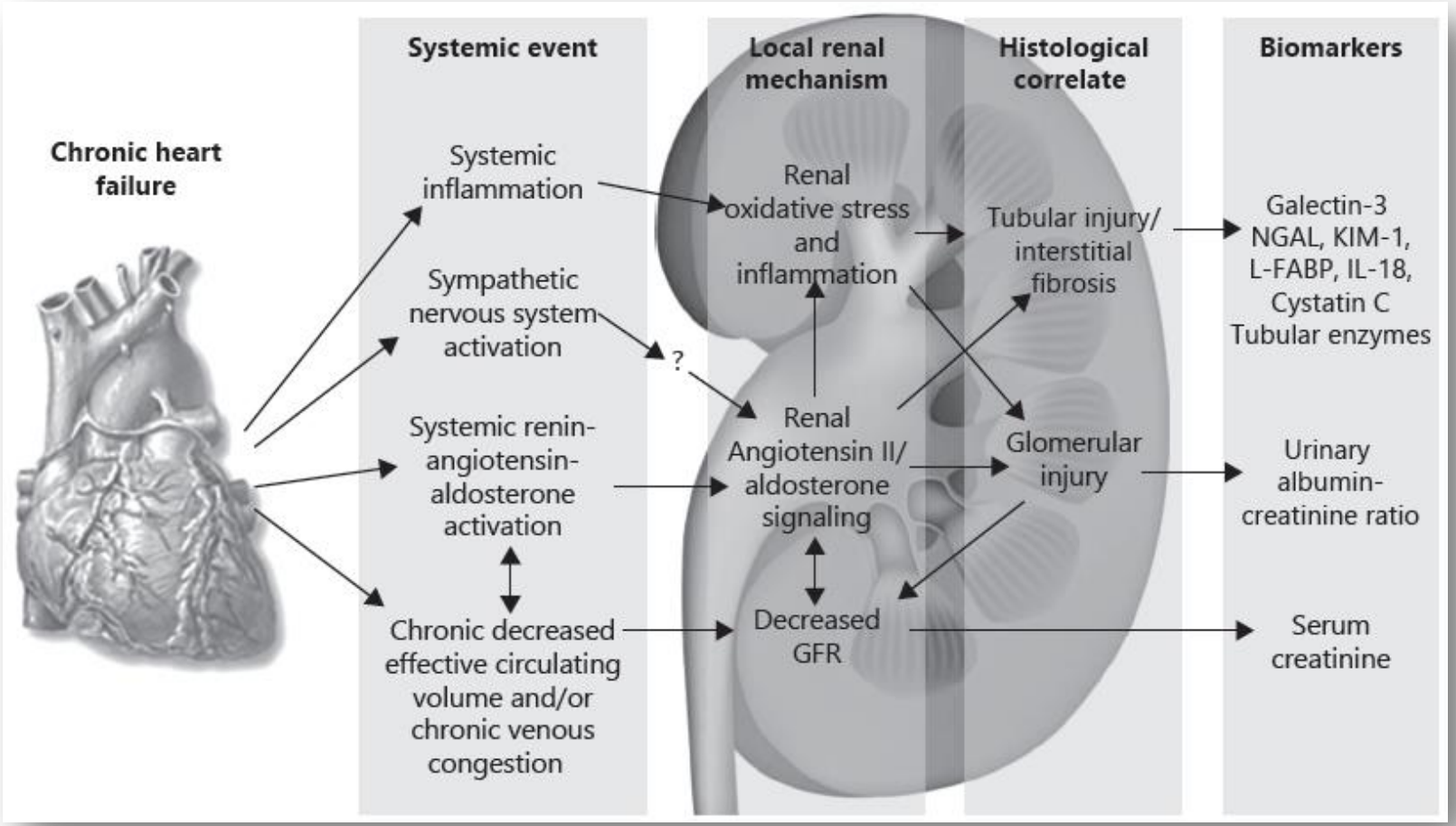
CRS Type 1

- Abrupt worsening of cardiac function leading to acute kidney injury
- A syndrome of worsening renal function that frequently complicates ADHF
- 27-40% of hospitalized ADHF patients develop AKI (sCr ≥ 0.3 mg/dL ↑)
- Higher mortality and morbidity, increased length of hospitalization



2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

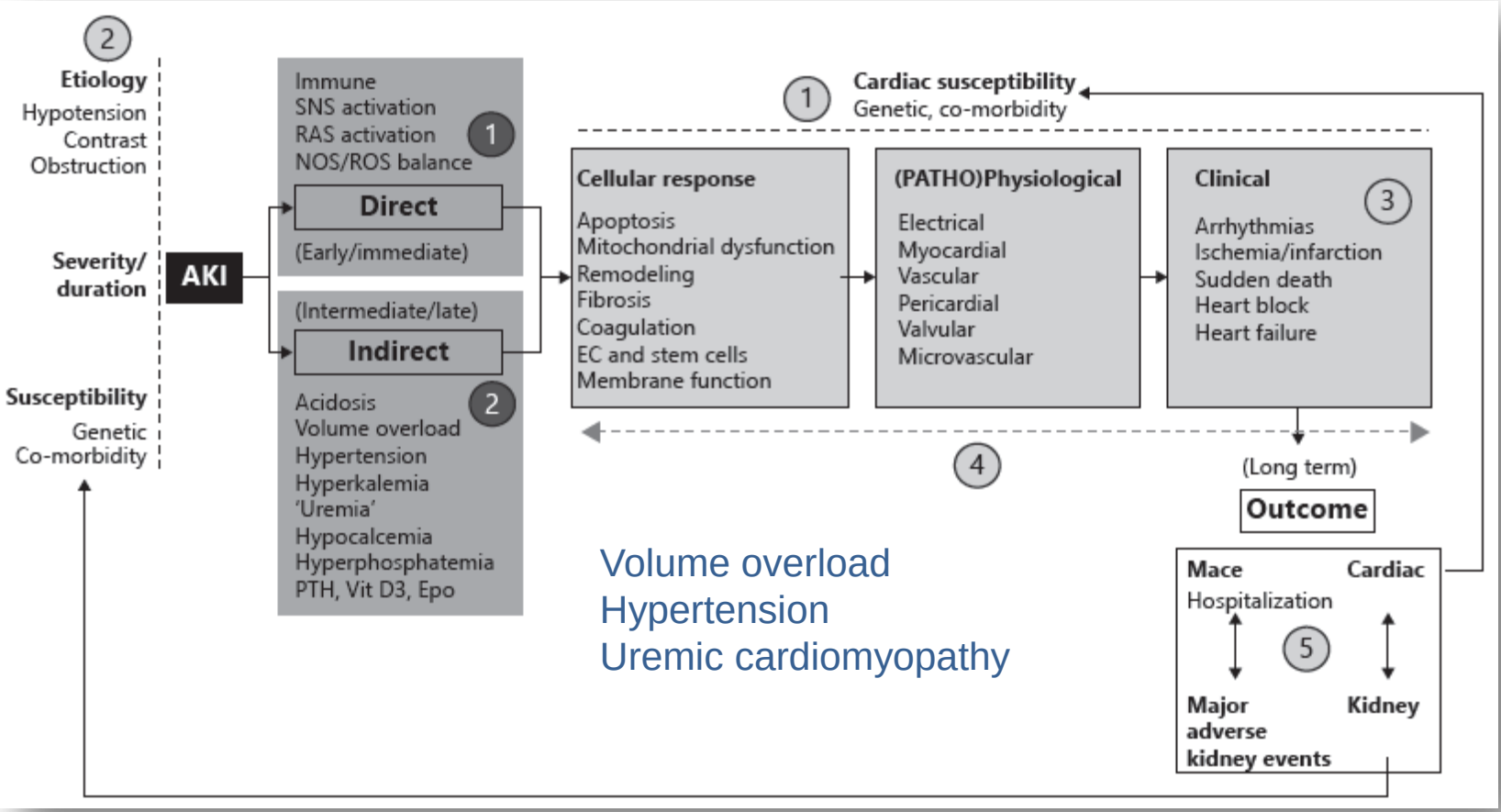
CRS Type 2



- More chronic HF hastening the progression of CKD
- Approximately 63% of patients with HF meet the definition of stage 3–5 CKD with an estimated GFR <60 ml/min/1.73 m^2

2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

CRS Type 3

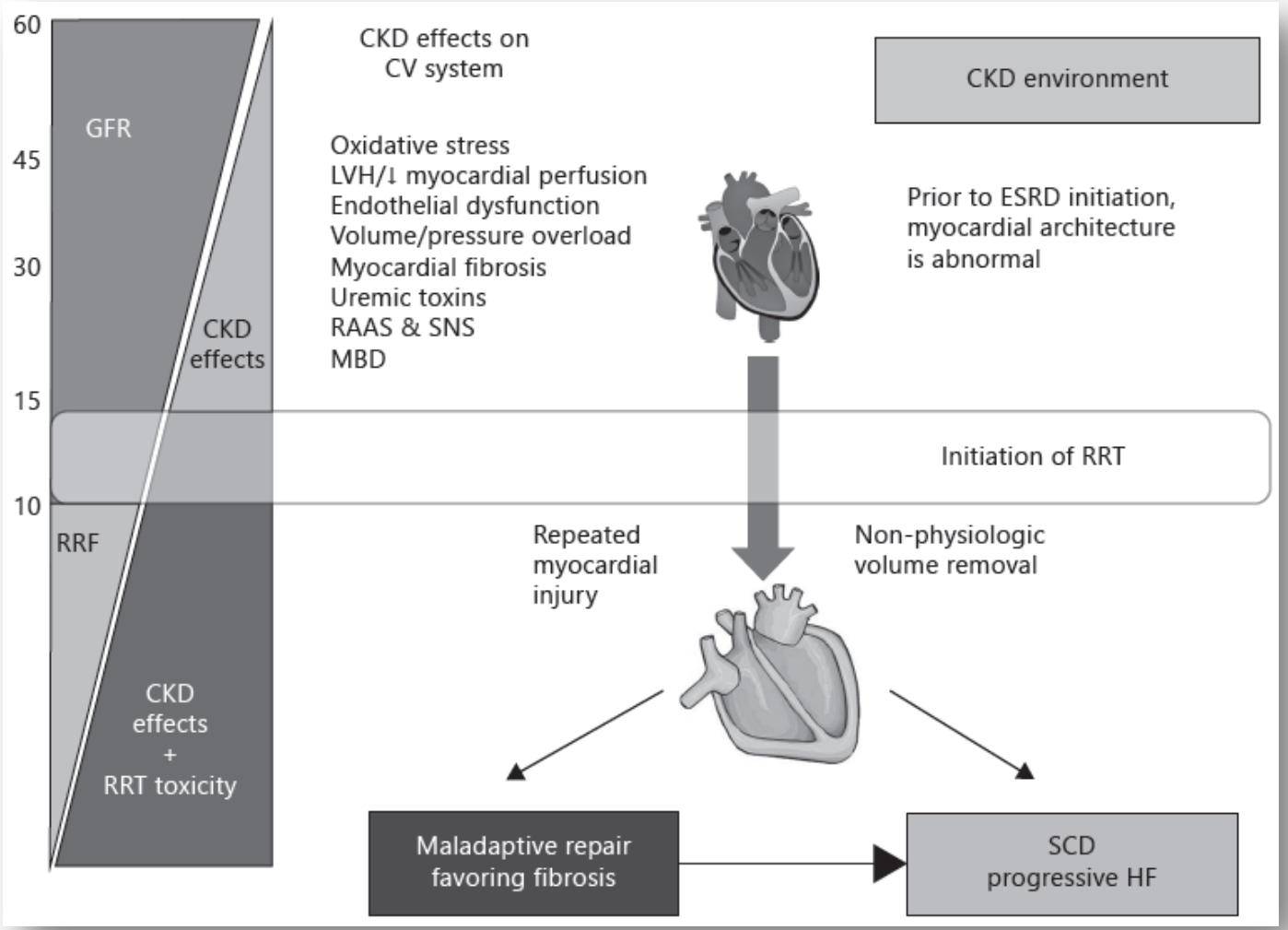


- Abrupt worsening of renal function causing acute cardiac disorder
- Little is known about the frequency of acute HF following AKI

2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

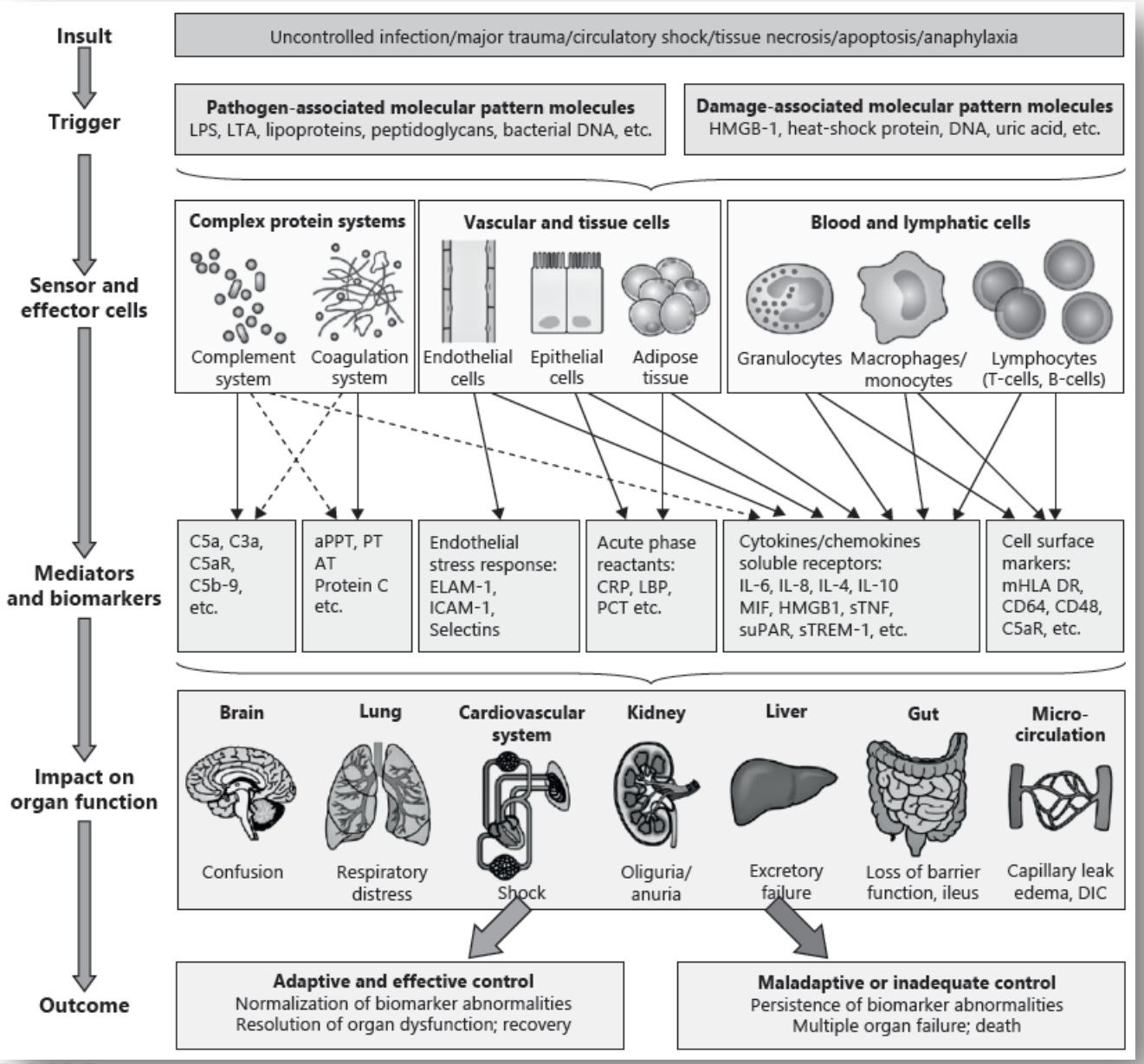
CRS Type 4

- CKD is an accepted independent determinant for the progression of HF to hospitalization, pump failure death, and sudden death.
- Exponential relation between the severity of renal dysfunction and the risk for all-cause mortality



2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

CRS Type 5



2013 ADQI Consensus on 'Pathophysiology of Cardiorenal Syndromes'

“Cardiorenal” Syndrome

Renal dysfunction in advanced HF : CRS 1 and 2

Renal disease in HF

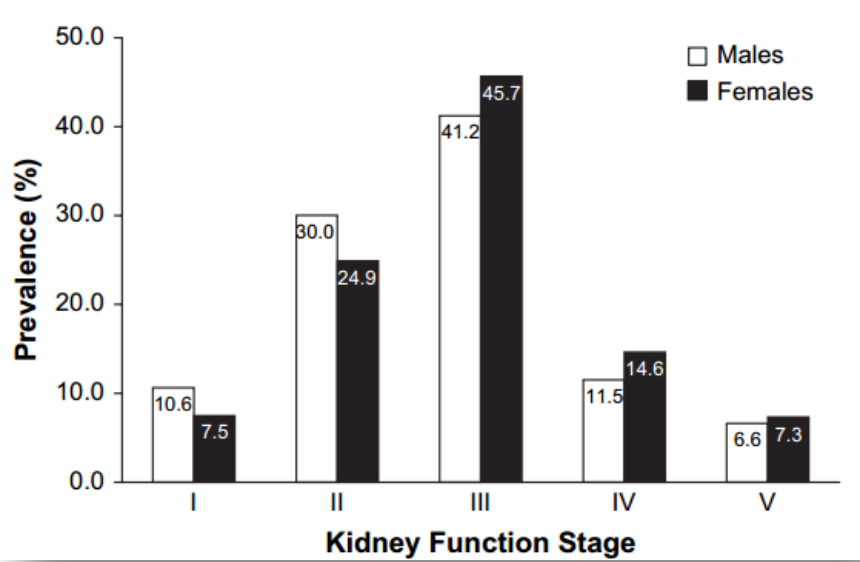
	VMAC* (N = 489)	OPTIME† (N = 949)	ADHERE‡ (N = 105388)
Demographics			
Age	60-62 (13-15)*	66 (14)/65(15)†	72.4 (14.0)
White (%)	58	65	72
Black (%)	24	33	20
Female (%)	31	29	52
Heart failure history			
NYHA II (%)	8	7	20§
NYHA III (%)	42	46	44§
NYHA IV (%)	42	47	32§
Prior hospitalizations	NA	1.9(2.0)/2.1 (2.2)† (last year)	1.0 (1.1) (last 6 mo)
LVEF			
Ejection fraction (prehospital)	27 (14)	24 (8)	34.4 (16.1) ‖
Ejection fraction >40% (prehospital) (%)	13.3 (>40)	NA	37 ‖
Ejection fraction >40%, or normal or mild impairment of systolic function (either before or during index hospitalization) (%)	NA	NA	46#
Medical history			
Coronary artery disease (%)	65	NA	57
Hypertension (%)	70	68	73
Myocardial infarction (%)	46	48	31
Diabetes mellitus (%)	47	44	44
Renal insufficiency (%)	NA	NA	30
Ventricular tachycardia (%)	13 (sustained)	NA	8
Ventricular fibrillation (%)	6	NA	1
Atrial fibrillation (%)	35	32	31
Baseline medications			
ACE inhibitors (%)	60	70	41
Diuretics (%)	86	90	70
β-Blockers (%)	33	22	48
Angiotensin receptor blockers (%)	10	13	12
Nitrates (%)	35	NA	26
Antiarrhythmics (%)	21	NA	11
Digoxin (%)	61	73	28
Physical and laboratory findings			
Systolic blood pressure (mm Hg)	121 (22)	120 (18)/120(19)†	144 (32.6)
Serum creatinine (mg/dL)	NA	1.5 (0.5)/1.4(0.5)†	1.8 (1.6)
Serum creatinine >2 mg/dL	21	NA	20

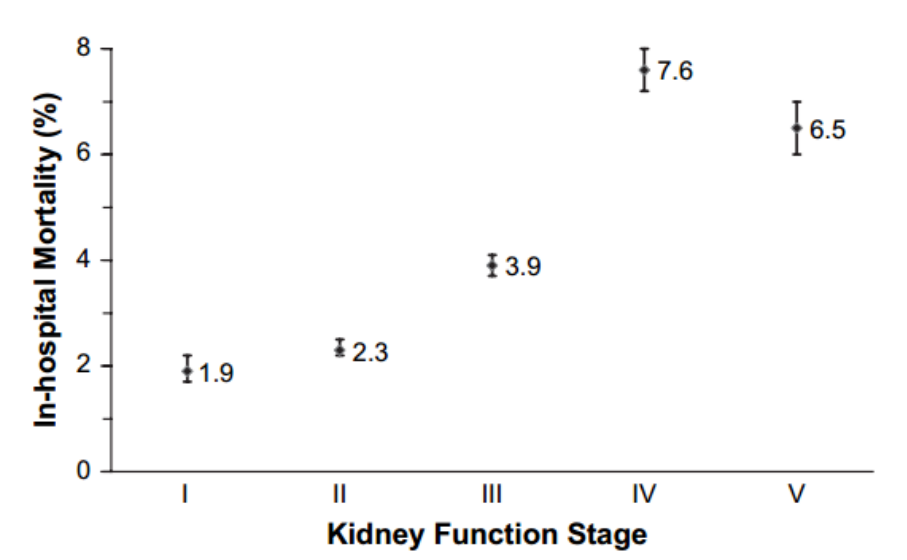
Adams KF Jr. Am Heart J 2005;149:209-16

Renal disease in HF

ADHERE database

118,456 hospitalized patients





- 59.3% of men and 67.6% of women had at least moderate renal dysfunction (stage III) at the time of admission
- only 33.4% of men and 27.3% of women were reported as having ‘‘renal insufficiency’’ in the database

- In-hospital mortality increased with severity of baseline renal dysfunction

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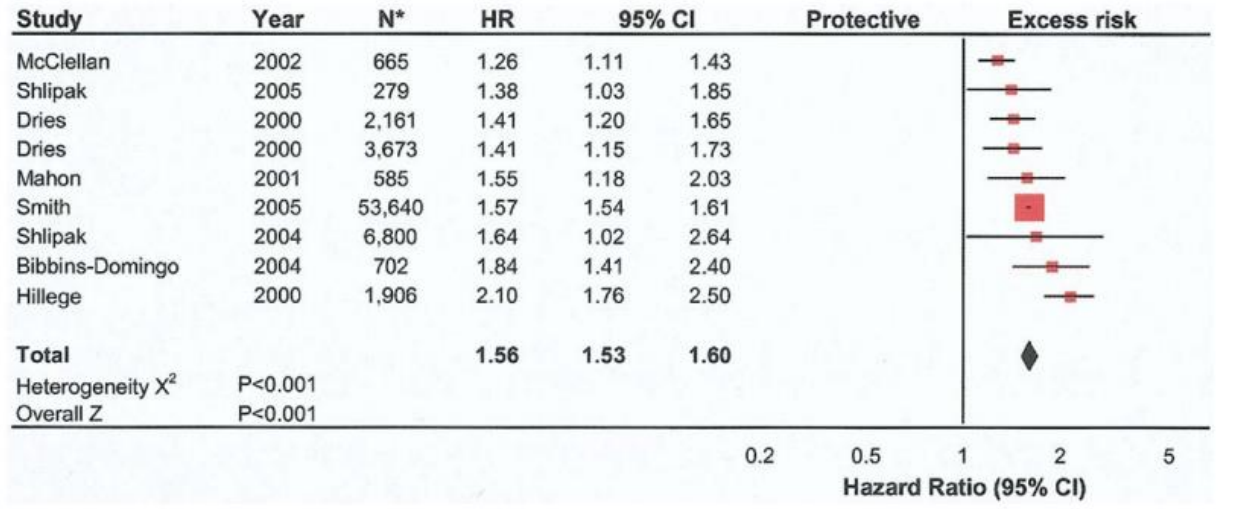
Heywood JT. J Cardiac Fail 2007;13:422-30

Renal disease in HF

Meta-analysis of 16 studies

More than 80,000 hospitalized and nonhospitalized patients with HF



Study	Year	N*	HR	95% CI		Protective	Excess risk
McClellan	2002	665	1.26	1.11	1.43		
Shlipak	2005	279	1.38	1.03	1.85		
Dries	2000	2,161	1.41	1.20	1.65		
Dries	2000	3,673	1.41	1.15	1.73		
Mahon	2001	585	1.55	1.18	2.03		
Smith	2005	53,640	1.57	1.54	1.61		
Shlipak	2004	6,800	1.64	1.02	2.64		
Bibbins-Domingo	2004	702	1.84	1.41	2.40		
Hillege	2000	1,906	2.10	1.76	2.50		
Total			**1.56**	**1.53**	**1.60**		
Heterogeneity X^2	P<0.001						
Overall Z	P<0.001						

- A total of 63% of patients had any renal impairment, and 29% had moderate to severe impairment.
- Adjusted all-cause mortality was increased for patients with any impairment (hazard ratio [HR] = 1.56; 95% confidence interval [CI] 1.53 to 1.60, p < 0.001) and moderate to severe impairment (HR = 2.31; 95% CI 2.18 to 2.44, p < 0.001).

	Renal Impairment			
	Any*		Moderate to Severe†	
Population	%	n/N	%	n/N
All patients	63	49,163/77,793	29	18,724/65,324
Non-randomized	69	38,218/55,475	32	17,703/55,475
Outpatients	51	11,621/23,007	10	1,049/10,538
Hospitalized	69	37,542/54,786	32	17,675/54,786

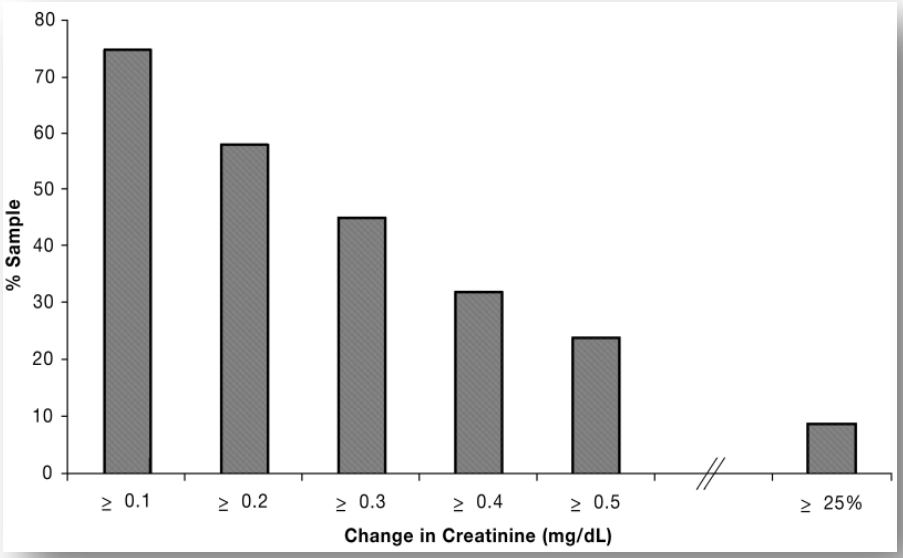
*Creatinine >1.0 mg/dl, creatinine clearance or estimated glomerular filtration rate <90 ml/min, or cystatin-C >1.03 mg/dl. †Creatinine ≥1.5 mg/dl, creatinine clearance or estimated glomerular filtration rate <53 ml/min, or cystatin-C ≥1.56 mg/dl.

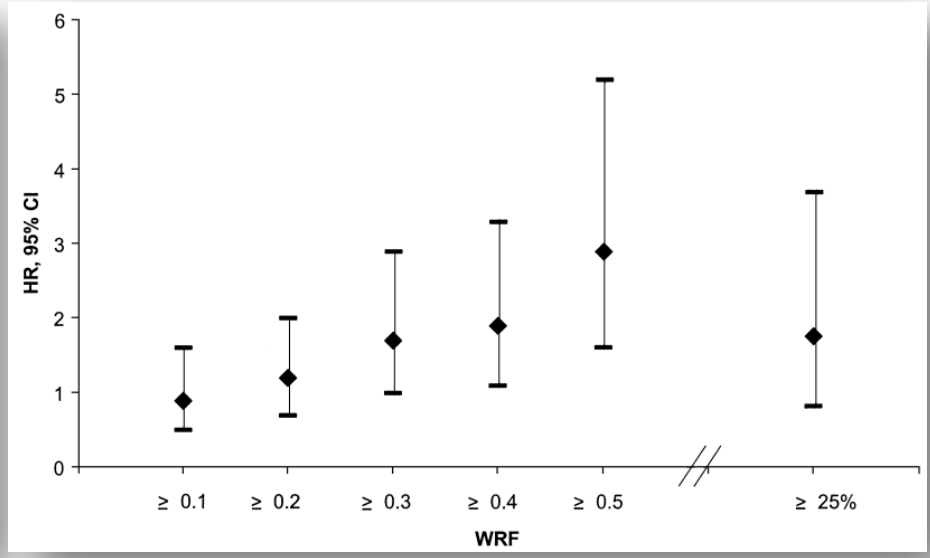
Smith GL. JACC 2006;47:1987-96

Worsening renal function

Worsening renal function (WRF)

A prospective cohort of 412 patients hospitalized for HF





- > 70% HF patients experience some increase in sCr during admission
- About 20-30% HF patients experience an increase of sCr >0.3 mg/dL

- Risk of death rose with higher creatinine elevations (adjusted hazard ratio [HR] = 0.89, 1.19, 1.67, 1.91, and 2.90 for elevations >/=0.1 to >/=0.5 mg/dL)

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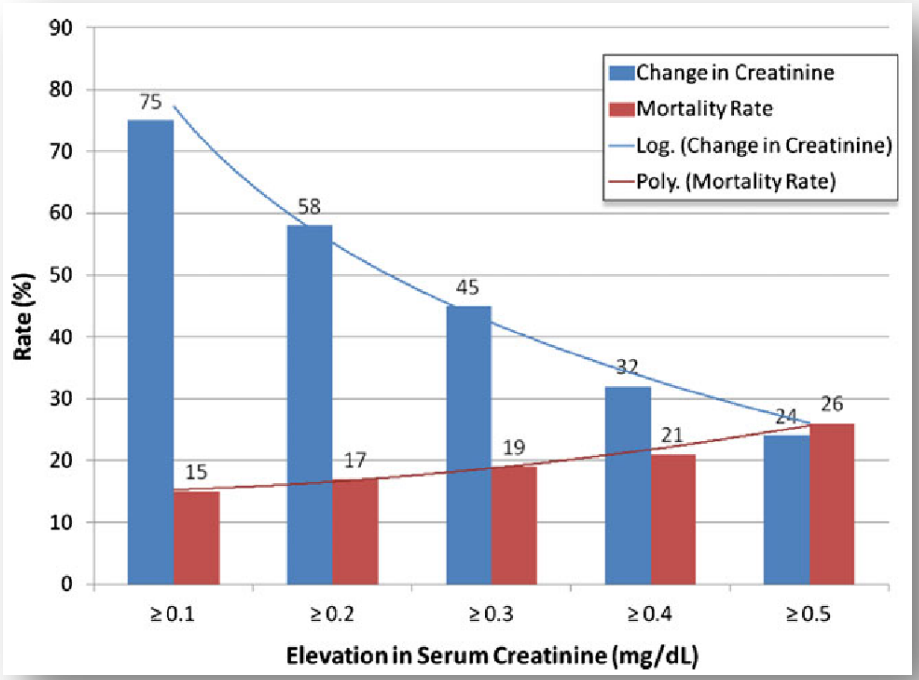
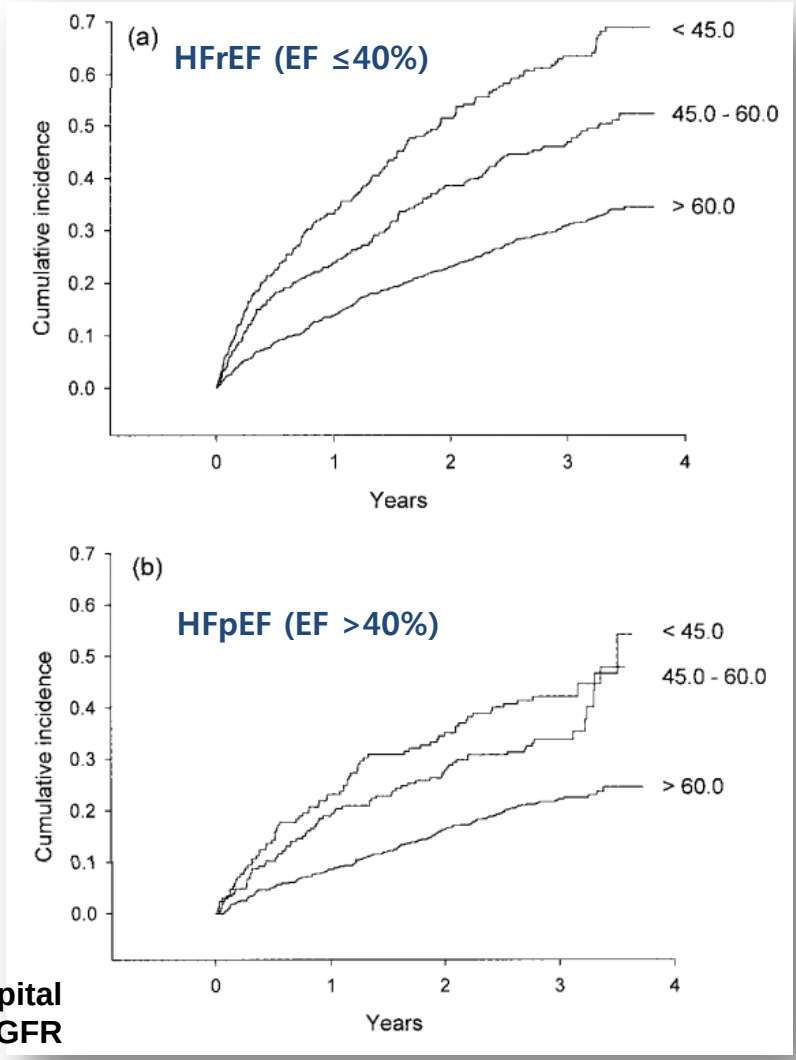
Smith G. J Card Fail 2003;9:13-25

WRF and prognosis



Incidence of WRF and 6 Mo mortality rates



Incidence of cardiovascular death or unplanned admission to hospital for the management of worsening CHF stratified by eGFR

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Hillege HL. Circulation 2006;113:671-8

Renal dysfunction in Korean HF Registry

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Characteristics, Outcomes and Predictors of Long-Term Mortality for Patients Hospitalized for Acute Heart Failure: A Report From the Korean Heart Failure Registry

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Renal dysfunction in Korean HF Registry

Table 1. Demographic and clinical features

Characteristics	Total, n=3,200	Female, n=1,600 (50%)	Male, n=1,600 (50%)	p*
Age (year, mean±SD)	67.6±14.3	70.7±13.5	64.5±14.5	<0.001
BMI (kg/m^2)	23.2±4.0	23.0±4.2	23.4±3.8	0.009
Previous medical history (%)				
Heart failure	871 (29.6)	453 (30.4)	418 (28.7)	0.313
Hypertension	1,486 (46.5)	787 (49.2)	699 (43.7)	0.002
Diabetes	975 (30.5)	489 (30.6)	486 (30.4)	0.927
Stroke	299 (18.9)	137 (18.0)	162 (19.8)	0.361
Chronic renal disease	295 (9.2)	134 (8.4)	161 (10.1)	0.970
Chronic pulmonary disease	104 (3.5)	43 (2.9)	61 (4.2)	0.055
Underlying disease (%)				
Ischemic heart disease	1,544 (52.3)	828 (53.6)	716 (46.4)	<0.001
Hypertension	1,143 (36.7)	596 (38.1)	547 (35.3)	0.103
Cardiomyopathy	760 (26.5)	351 (24.3)	409 (28.8)	0.007
Valvular heart disease	407 (12.7)	255 (16.4)	152 (9.7)	<0.001
Myocarditis	22 (0.7)	8 (0.6)	14 (1.0)	0.187
Infiltrative disease	12 (0.4)	5 (0.3)	7 (0.5)	0.545

*Comparison between the female and male groups. BMI: body mass index

Choi DJ. Korean Circ J 2011;41:363-71

Renal dysfunction in Korean HF Registry

Table 3. Clinical factors and predictors for the long-term clinical outcomes on univariate analysis

Characteristics	Total	Expired, n=652 (19.6%)	Alive, n=2,571 (80.4%)	HR	95% CI	p*
Age (mean)	67.6±14.3	71.6±13.1	66.6±14.5	1.027	1.021-1.034	<0.001
Women (%)				.026	0.874-1.205	0.752
BMI (<23 kg/m^2) (%)				.781	1.490-2.129	<0.001
Previous heart failure (%)				.690	1.428-2.001	<0.001
Non-ischemic heart failure (%				.352	1.146-1.596	<0.001
Clinical findings						
SBP (mmHg)				.991	0.988-0.994	<0.001
HR (bpm)				.000	0.997-1.004	0.780
Dyspnea at rest (%)				.499	1.238-1.815	<0.001
Echo results						
LVEF (%)				.995	0.990-1.001	0.113
LVEF ≥50% (%)				.948	0.774-1.160	0.601
Lab. Findings						
Hyponatremia (Na <135 m				.226	1.860-2.665	<0.001
Anemia (Hb <12 g/dL)	1,316 (41.4)	346 (55.5)	970 (38.0)	2.021	1.719-2.377	<0.001
Azotemia (Cr ≥2.0 mg/dL)	478 (14.9)	150 (24.3)	328 (13.0)	2.291	1.901-2.761	<0.001
Total-cholesterol (<160 mg/dL)	1,431 (51.1)	318 (58.3)	1,112 (49.3)	1.393	1.169-1.659	<0.001
NT-proBNP ≥1,000 ng/L	1,844 (85.1)	374 (92.6)	1,470 (83.4)	2.425	1.661-3.541	<0.001
Medication at discharge (%)						
Beta-blocker	1,109 (58.6)	137 (40.7)	927 (62.5)	0.441	0.352-0.551	<0.001
ACEi/ARB	648 (53.7)	103 (39.3)	545 (57.7)	0.504	0.391-0.650	<0.001
Aldosterone antagonist	913 (53.1)	159 (46.2)	754 (54.8)	0.700	0.563-0.869	0.001

*Comparison between the expired and alive groups. HR: hazard ratio, CI: confidence interval, BMI: body mass index, SBP: systolic blood pressure, LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, ACEi: angiotensin converting enzyme-inhibitors, ARB: angiotensin receptor blocker

Table 4. Clinical predictors of the clinical outcome on multivariate analysis

Characteristics of the patients	HR	95% CI	p*
Age (mean)	1.023	1.004-1.042	0.020
Previous heart failure	1.735	1.150-2.618	0.009
Anemia (Hb <12 mg/dL)	1.973	1.271-3.063	0.002
Hyponatremia (Na <135 mM)	1.861	1.184-2.926	0.007
NT-proBNP ≥1,000 ng/L	3.152	1.450-6.849	0.004
Beta-blocker at discharge	0.599	0.360-0.997	0.049

*Comparison between the expired and alive groups. HR: hazard ratio, CI: confidence interval, NT-proBNP: N-terminal pro-B-type natriuretic peptide

Choi DJ. Korean Circ J 2011;41:363-71

Renal dysfunction in Korean HF Registry

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STUDY DESIGN PAPER

A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry

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Renal dysfunction in Korean HF Registry

Table 1 Clinical characteristics of patients hospitalized with acute heart failure syndromes in Korea compared with other registries

	KorAHF	ATTEND[8]	ADHERE[9]	OPTIMIZE-HF[10]	EHFSII[11]	THESUS-HF[21]	ADHERE International[20]
Region	Korea	Japan	USA	USA	Europe	Nigeria (Africa)	8 Asia-Pacific countries
Time period	March 2011–	May 2007–September 2012	September 2001–January 2004	March 2003–December 2004	October 2004–August 2005	July 2007–June 2010	January 2006–December 2008
Sample size	2066 (May 2012)	1110 (June 2009)	159 168	48 612	3580	1006	10 171
Follow-up	>3 years	180 days	N/D	60, 90 days	3, 12 months	N/D	N/A
Demographics							
Age (SD), years	69 (14)	73 (14)	72 (14)	73 (14)	70 (13)	52 (18)	66 (53–77)[a]
Male (%)	55	59	48	48	61	49	57
Co-morbidities (%)							
Hypertension	59	71	74	71	63	56	64
Diabetes	36	34	44	42	33	11	45
Atrial fibrillation	27	40	31	31	39	18	24
Chronic lung disease	11	9	31	28	19	N/A	N/A
Aetiology (%)							
Ischaemic	38	33	58[b]	46	54[b]	8	50[b]
Hypertensive	6	18	N/A	23	11[c]	45	N/A
Clinical status on admission							
De novo HF (%)	50	63	24	12	37	N/A	36
Lung congestion (%)	78	96	67[d] or 75[e]	64[d]	N/A	N/A	80d
Pulse rate (/min)	91 (26)	99 (30)	N/A	87 (22)	Median 95	104 (22)	N/A
SBP (mmHg)	136 (31)	147 (38)	144 (33)	143 (33)	Median 135	130 (34)	N/A
LVEF <40% (%)	56	57	51	49	66 (EF <45%)	N/A	53
Creatinine (mg/dL)	1.5 (1.6)	1.4 (1.5)	1.8 (1.6)	1.8 (1.6)	N/A	1.4 (1.2)	N/A
Management (%)							
I.v. diuretics	72	80	87	N/A	84	93	85
I.v. inotropes	32	21	8	7	<29.8	~10.1	15
I.v. vasodilators	40	< 46	9	14	31	7.0 (nitrates)	14
ACEIs/ARBs	65	N/A	83	N/A	80	80–90	63
AAs	40	N/A	33	N/A	48	60–70	31
Beta-blockers	44	N/A	80	N/A	61	40–50	41
Outcomes							
Length of stay (median), days	8	21	4.3	4	9	7	6
In-hospital mortality (%)	6.1[f]	7.7	3.8	3.8	6.7	4.2	4.8

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Lee SE. Eur J Heart Fail 2014;16:700-8

Renal dysfunction in Korean HF Registry

Table 5 Multivariable logistic regression analysis for predictors of in-hospital mortality (n = 1831)

Variables	Adjusted OR (95% CI)	P-value
Lung congestion	2.38 (1.17–4.82)	0.016
SBP <100 mmHg	4.45 (2.69–7.37)	<0.001
Q waves at ECG	1.98 (1.07–3.65)	0.029
RBBB at ECG	2.68 (1.47–4.89)	0.001
White blood cell count ≥10 000/mm^3	1.82 (1.12–2.96)	0.016
Serum sodium <135 mmol/L	2.06 (1.27–3.34)	0.003
Serum creatinine ≥2.0 mg/dL	2.83 (1.66–4.81)	<0.001
LVEF <40%	1.88 (1.14–3.1)	0.014
Other miscellaneous aggravating factors	3.17 (1.71–5.86)	<0.001
Valvular heart disease as an aetiology of HF	2.12 (1.16–3.89)	0.015
C-statistic	0.807	

Azotemia (sCr ≥2.0 mg/dL) was independent predictors of in-hospital mortality

Lee SE. Eur J Heart Fail 2014;16:700-8

Management

Clinical Challenges

Management of CRS

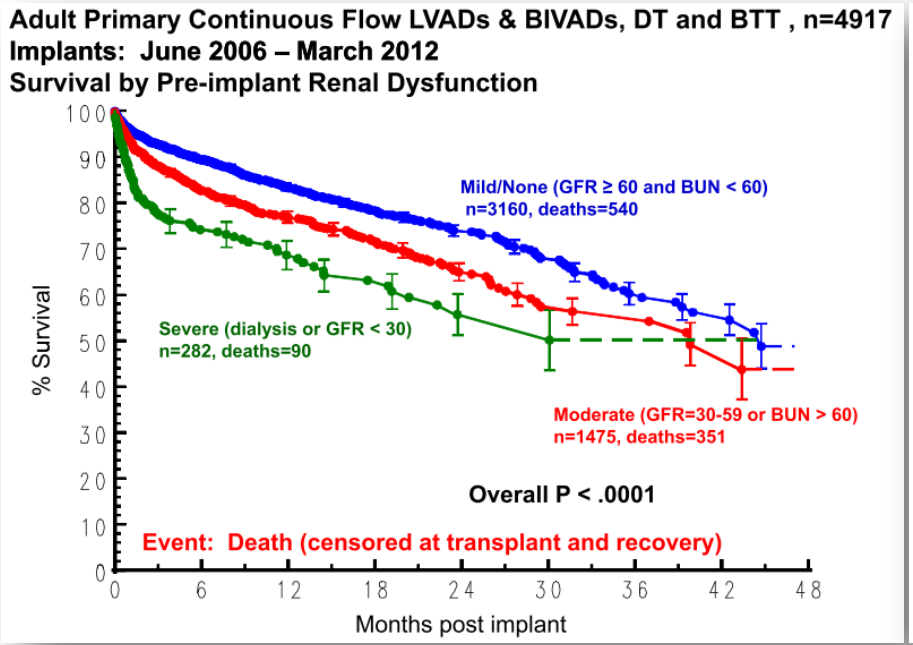
- Improvement in cardiac function
- Diuretics
- Renin-angiotensin-aldosterone-system antagonist
- Vasodilators
- Inotropic drugs
- Ultrafiltration
- Investigational therapies

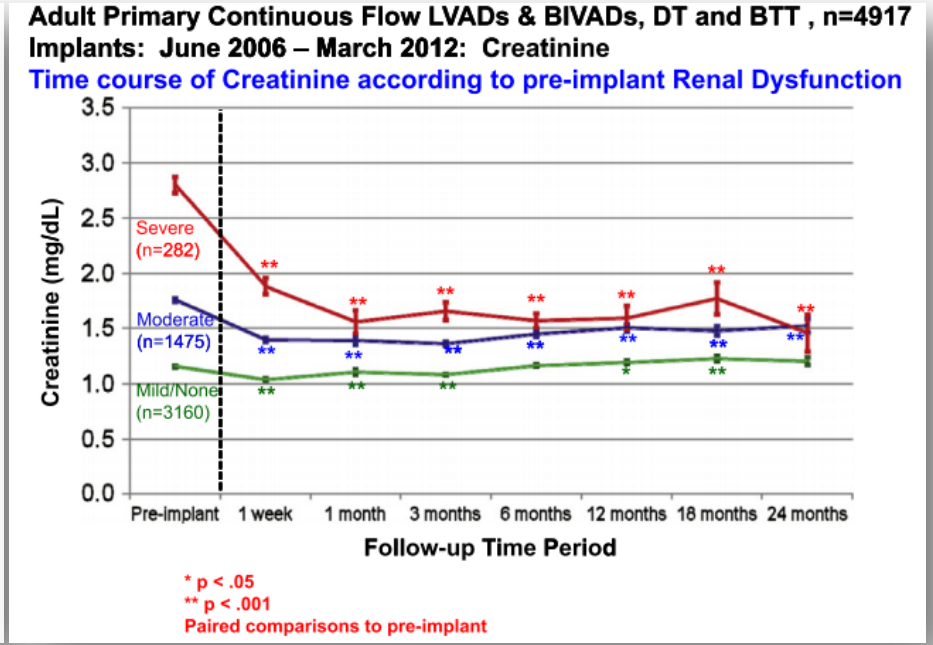
No definite medical therapy to directly increase the GFR

Improvement in cardiac function

INTERMACS registry

4,917 patients with continuous-flow LVADs





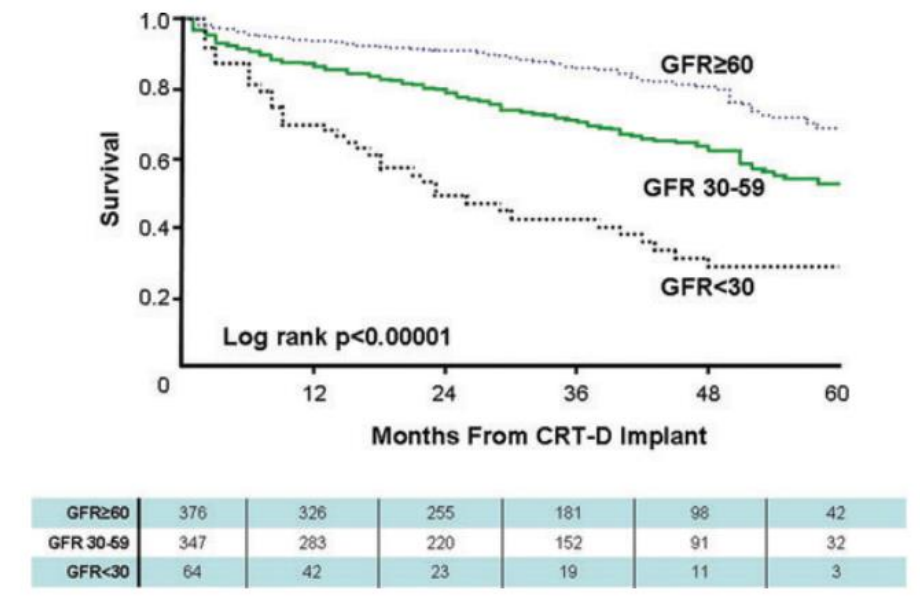
- Actuarial survival stratified by degree of renal function reveals that the major effect of severe pre-implant renal dysfunction is on mortality during the first 3 months
- Among all levels of pre-implant renal dysfunction, surviving patients showed significant improvement in eGFR, BUN, and creatinine within 1 month, which remained stable on average over the next 24 months

Kirklin JK. J Heart Lung Transplant 2013;32:1205-13

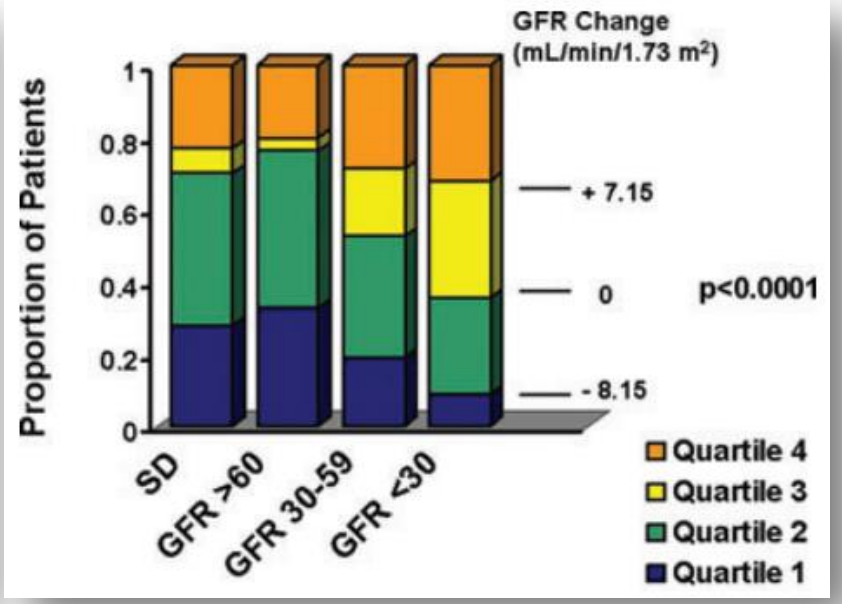
Improvement in cardiac function

MIRACLE trial

787 CRT-D recipients



GFR≥60	376	326	255	181	98	42
GFR 30-59	347	283	220	152	91	32
GFR<30	64	42	23	19	11	3



- Baseline renal function was highly predictive of survival among CRT-D patients; survival was shorter as GFR declined
- Renal function improved in CRT-D patients with a baseline GFR < 60 mL/min/1.73 m^2, whereas GFR was worsened in those with normal baseline renal function.

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Adelstein EC. PACE 2010;33:850-9

Improvement in cardiac function

- Reversible ?
  - Impaired renal function → limitation to correct volume overload
  - Impaired or worsening renal function → mortality ↑

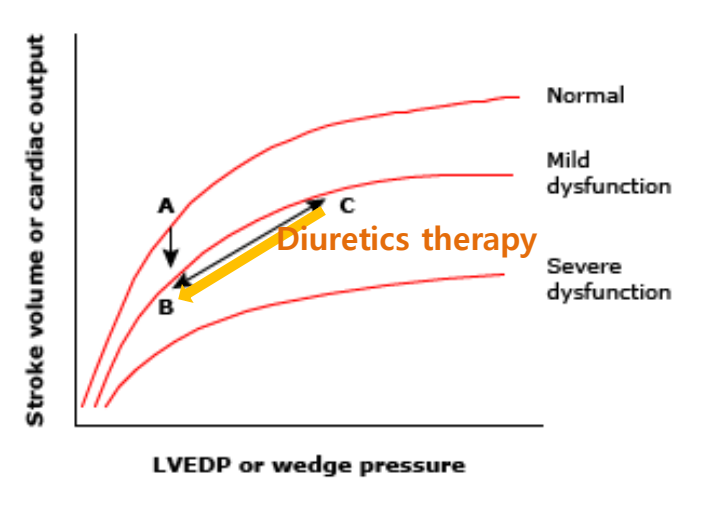
  - It is possible that effective treatment of the CRS could improve patient outcomes
  - Improving cardiac function can produce increases in GFR, indicating that types 1 and 2 CRS have substantial reversible components

- Irreversible ?
  - worse prognosis in patients with HF and impaired renal function could primarily reflect a reduced GFR being a marker of more severe cardiac disease
  - In this setting, improving renal function alone would not necessarily improve patient outcomes

Diuretics

- Diuretics
  - First line therapy for managing volume overload in patients with HF
  - An elevated BUN/Cr ratio should not deter diuretic therapy if clinical evidence of congestion is present

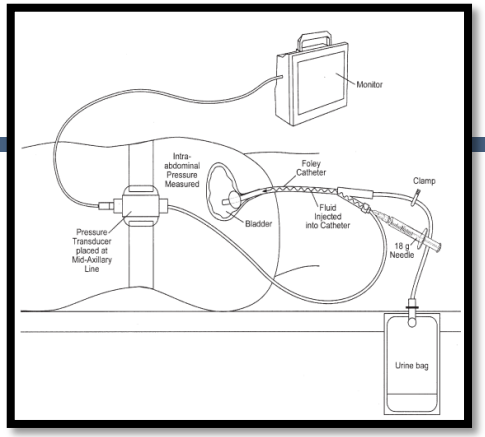
- Diuretics cause renal hypoperfusion ?
  - Vasodilators and diuretics normalize filling pressure without reducing CO
    → redistribution of extravascular volume against intravascular volume depletion
  - Renal blood flow is preserved until the CI below 1.5 L/m^2

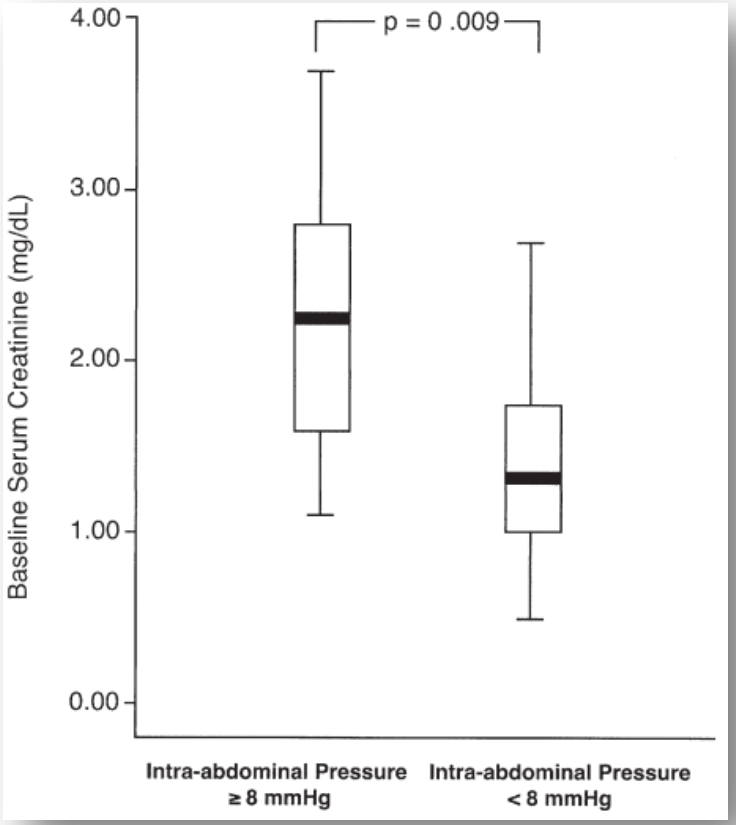


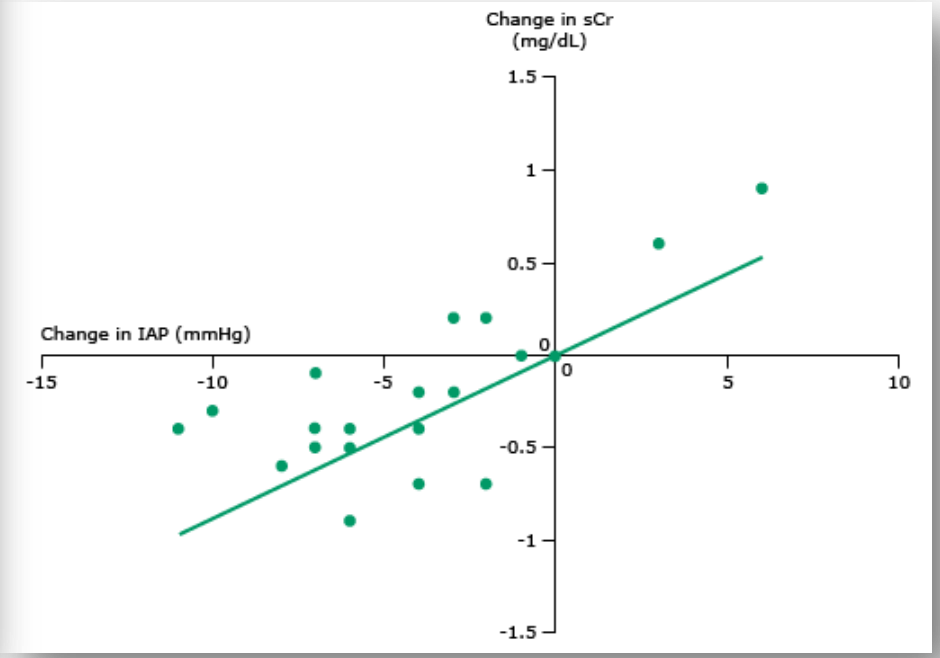
Frank-Starling curves in HF

Weinfeld MS. Am Heart J 1999;138:285-90
Ljungman S. Drugs 1990;39:10-21

Venous congestion in CRS







Changes in serum creatinine vs change in intra-abdominal pressure

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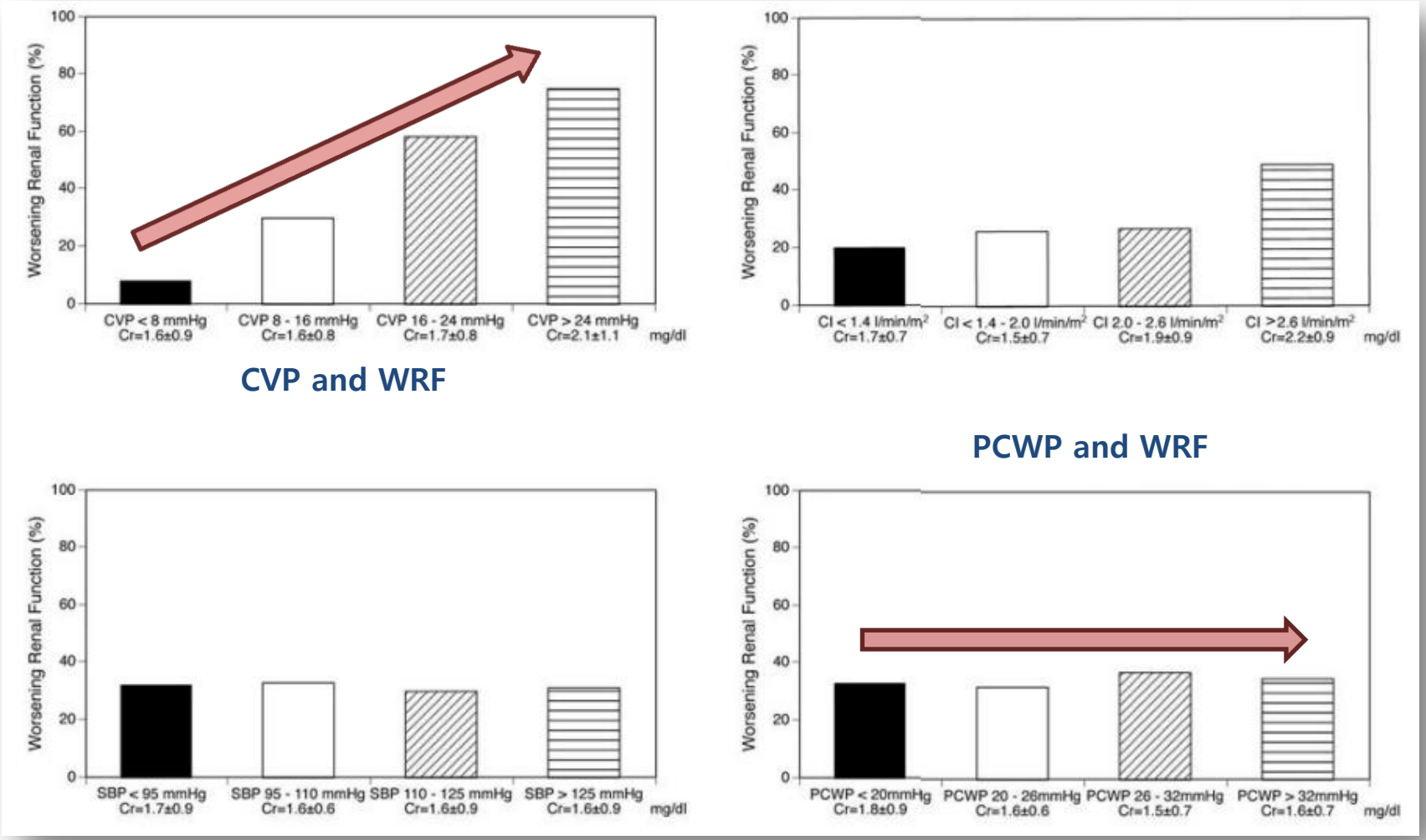
Mullens W. JACC 2008;51:300-6

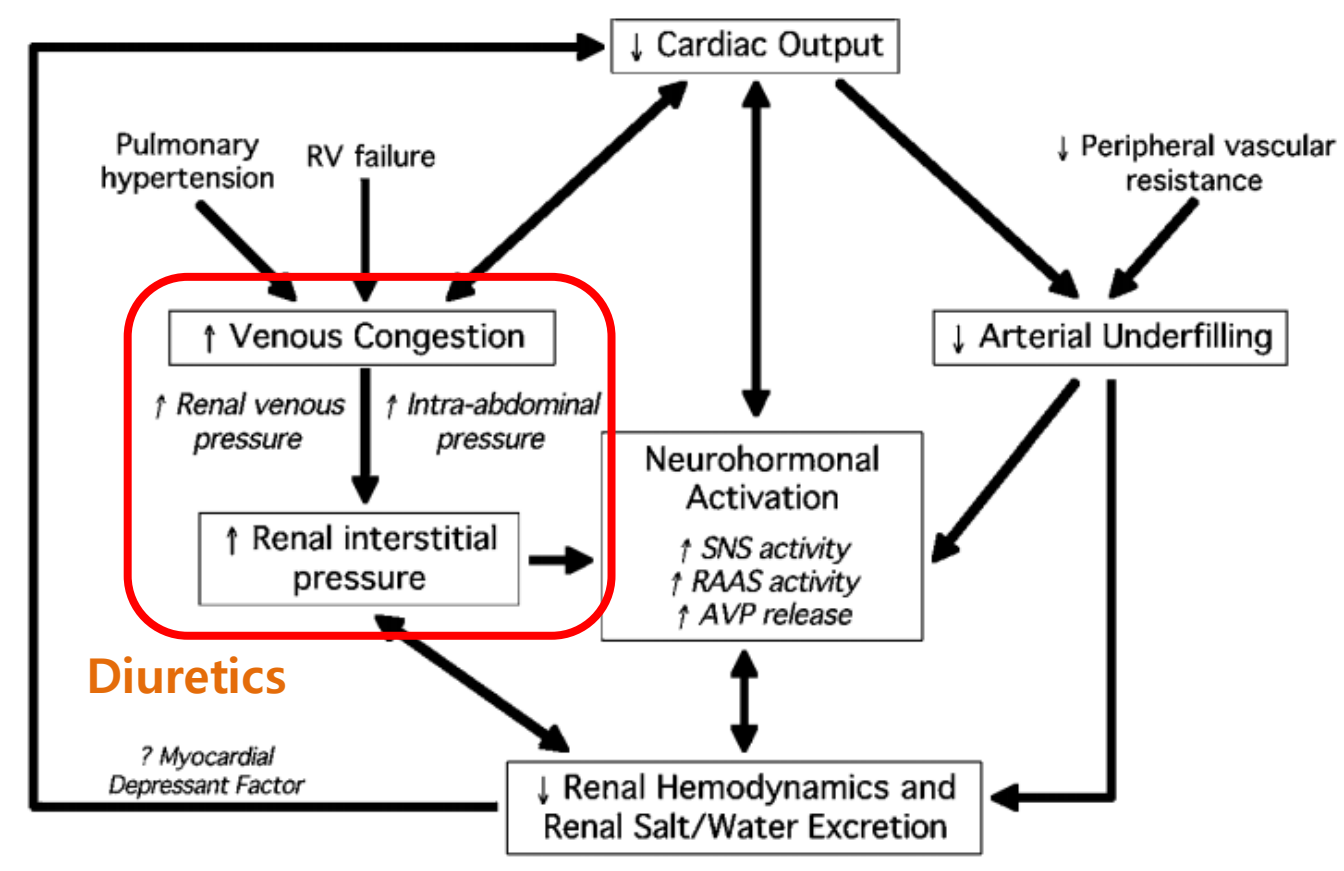
Venous congestion in CRS



Mullens W. JACC 2009;53:589-96

Diuretics

Reduced renal perfusion vs. Venous congestion

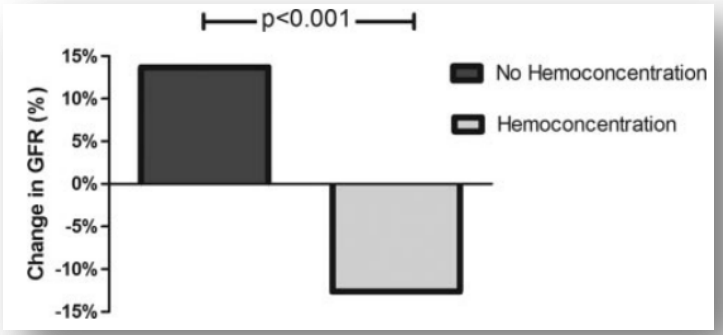


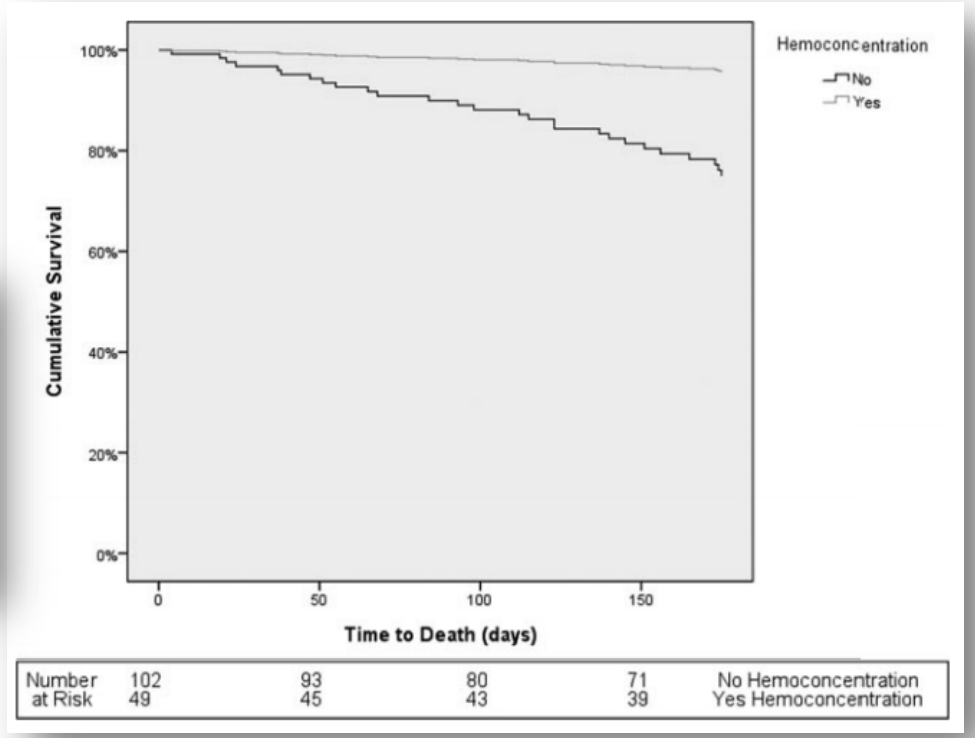
Tang WHW. Heart 2010;96:255-60

Diuretics

ESCAPE trial

336 patients with ADHF





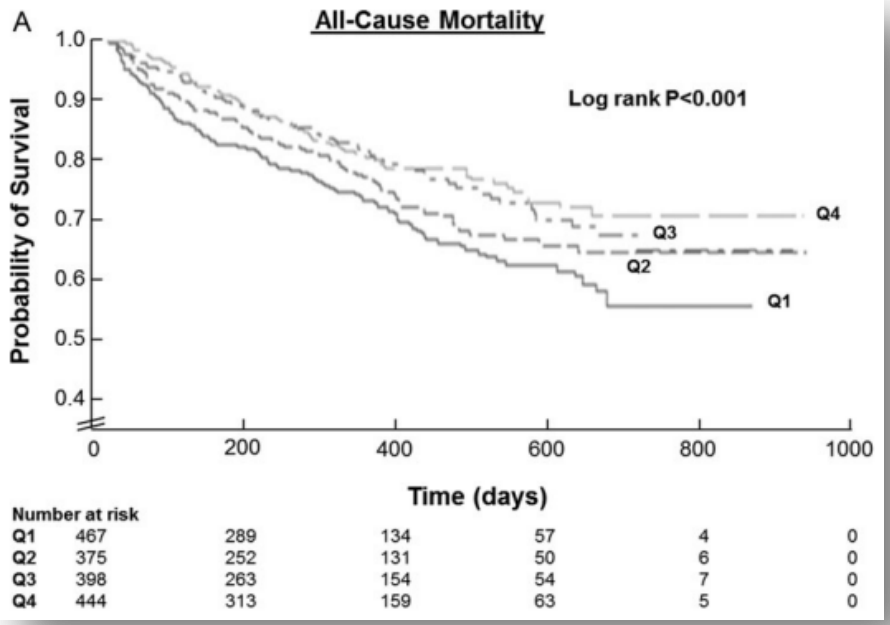
- Patients with hemoconcentration
  - treated with higher doses of loop diuretics, more fluid loss, greater reduction in filling pr
- Hemoconcentration was associated with WRF as well as lower mortality rate

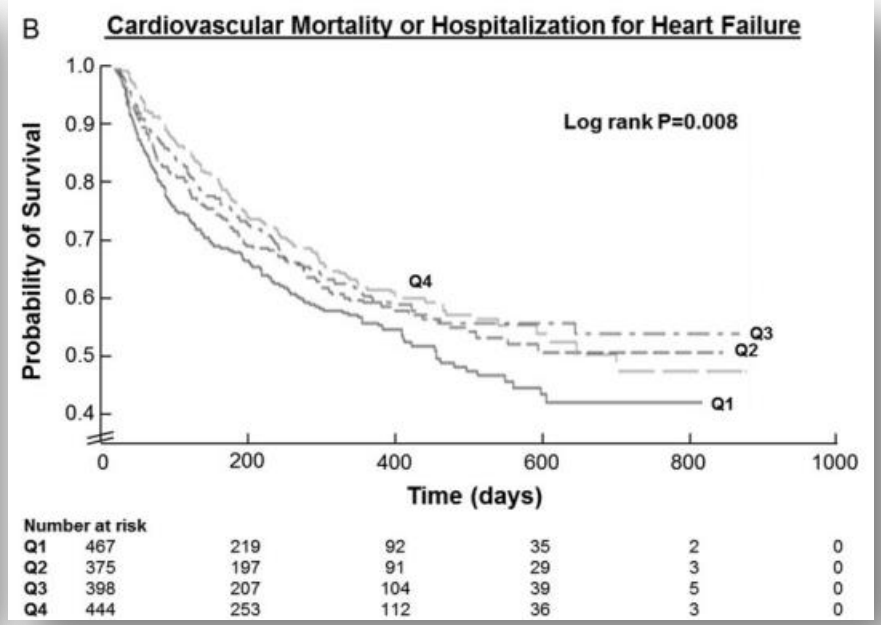
Testani JM. Circulation 2010;122:265-72

Diuretics

EVEREST trial

1,684 patients with hospitalized HF patients (tolvaptan vs placebo)





Stratified by absolute in-hospital haematocrit change quartile

- Hemoconcentration was associated with greater risk of in hospital WRF, though renal parameters generally returned to baseline within 4 weeks of discharge.
- Every 5% increase in-hospital Hct change was associated with a decreased risk of all-cause mortality

Greene SJ Eur J Heart Fail 2013;15:1401-11

Diuretics

ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American

Class I

1. **Diuretics are recommended in patients with HF*r*EF who have evidence of fluid retention, unless contraindicated, to improve symptoms. *(Level of Evidence: C)***

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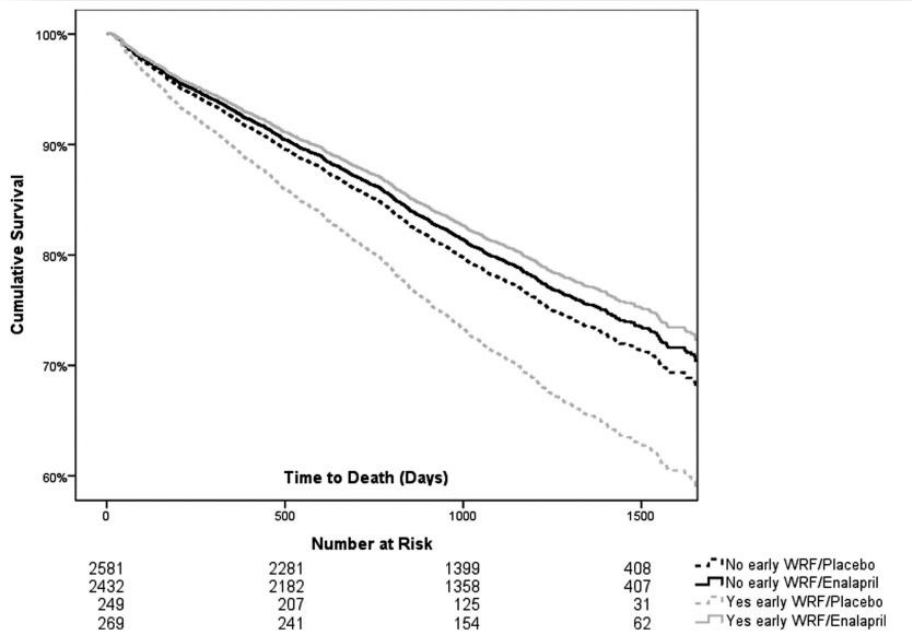
Bruce L. Wilkoff, MD, FACC, FHRS*††

Renin-angiotensin-aldosterone-system antagonist

- Variable effect on the GFR in patients with HF
  - Increases in sCr and BUN are often observed after initiation of an ACE inhibitor
  - CONSENSUS trial
    - The mean baseline serum creatinine concentration was 1.5 mg/dL
    - The serum creatinine increased by an average of 10 to 15 percent within the first three weeks
  - SOLVD trial
    - Early worsening renal function (decrease in estimated GFR ≥20 percent at 14 days) was not associated with increased mortality in the enalapril group, but was associated with increased mortality in the placebo group



Renin-angiotensin-aldosterone-system antagonist

- RAAS antagonists in CRS
  - Clinical trials not specifically focused on patients with the CRS
  - Subgroup analysis and cohort study
    - The beneficial effect of RAAS antagonism on clinical outcomes is not mitigated by concomitant CKD
  - Initiation of RAAS antagonists
    - 10 ~ 20% increase in sCr can be anticipated as ACEI is initiated
    - Increase of serum creatinine: frequently transient and reversible
    - Stabilization or even a decline of sCr levels d/t renoprotective effects of long-term ACEI administration
  - The risk of adverse events
    - The risk of adverse events including hyperkalemia and worsening renal function is higher than in patients without CKD
    - Patients with CKD should be monitored closely during periods of drug initiation and titration and should receive periodic monitoring of electrolytes and creatinine throughout the duration of therapy

Schoolwerth AC. Circulation 2001;104:1985-91

Vasodilators

ADHERE database

Table IV. Worsening Renal Function by propensity-matched comparison group

Comparison (treatment vs control group	WRF definition (increase in SCr of new dialysis)	WRF Treatment, % (n)	WRF Control, % (n)	RR (95% CI)	P
NES + DIUR vs NTG + DIUR	0.5 mg/dL	12.3 (937)	10.5 (937)	1.17 (0.91-1.51)	.216
	0.3 mg/dL with final >1.5 mg/dL	17.1 (937)	16.2 (937)	1.05 (0.86-1.29)	.620
NES + DIUR vs INO + DIUR	0.5 mg/dL	11.8 (654)	11.3 (654)	1.04 (0.77-1.41)	.795
	0.3 mg/dL with final >1.5 mg/dL	17.0 (654)	15.4 (654)	1.10 (0.86-1.41)	.453
SEQ NES vs SEQ NTG	0.5 mg/dL	15.1 (543)	14.2 (543)	1.1 (0.57-1.51)	.731
	0.3 mg/dL with final >1.5 mg/dL	20.3 (543)	19.2 (543)	1.07 (0.80-1.45)	.703
SEQ NES vs SEQ INO	0.5 mg/dL	13.1 (1692)	16.0 (1692)	0.82 (0.69-0.96)	.015
	0.3 mg/dL with final >1.5 mg/dL	17.9 (1692)	20.3 (1692)	0.88 (0.77-1.02)	.080
NTG + DIUR vs DIUR	0.5 mg/dL	10.1 (2288)	8.4 (9152)	1.20 (1.04-1.38)	.012
	0.3 mg/dL with final >1.5 mg/dL	14.4 (2288)	13.3 (9152)	1.08 (0.97-1.21)	.176
NES + DIUR vs DIUR	0.5 mg/dL	12.3 (1899)	8.5 (9495)	1.44 (1.26-1.65)	<.0001
	0.3 mg/dL with final >1.5 mg/dL	17.9 (1899)	13.2 (9495)	1.35 (1.21-1.51)	<.0001

Costanzo MR. Am Heart J 2007;154:267-77

Vasodilators

ASCEND-HF

Table 2. Primary and Secondary Clinical End Points and Safety End Points through Day 30.*

End Point	Nesiritide (N=3496)	Placebo (N=3511)	Percentage-Point Difference or Odds Ratio (95% CI)†	P Value
Primary clinical end points				
Death from any cause or rehospitalization for heart failure — no./total no. (%)	321/3423 (9.4)	345/3413 (10.1)	−0.7 (−2.1 to 0.7)	0.31
Death from any cause	126/3490 (3.6)	141/3499 (4.0)	−0.4 (−1.3 to 0.5)	
Rehospitalization for heart failure	204/3422 (6.0)	208/3411 (6.1)	−0.1 (−1.2 to 1.0)	
Secondary clinical end points				
Persistent or worsening heart failure or death from any cause through hospital discharge — no./total no. (%)	147/3459 (4.2)	165/3462 (4.8)	−0.6 (−1.5 to 0.5)	0.30
Days alive and out of hospital through day 30	20.9±6.9	20.7±7.1	0.2 (−0.13 to 0.53)	0.16
Rehospitalization or death from cardiovascular causes — no./total no. (%)	372/3423 (10.9)	402/3415 (11.8)	−0.9 (−2.4 to 0.6)	0.24
Safety end points				
Death from cardiovascular causes — no./total no. (%)	112/3498 (3.2)	124/3509 (3.5)	−0.3 (−1.2 to 0.5)	0.44
Sudden death from cardiac causes — no./total no. (%)	19/3324 (0.6)	16/3327 (0.5)	0.1 (−0.3 to 0.4)	0.61
Hypotension — no./total no. (%)	930/3498 (26.6)	538/3509 (15.3)	11.3 (9.4 to 13.1)	<0.001
Asymptomatic	748/3498 (21.4)	436/3509 (12.4)	9.0 (7.2 to 10.7)	<0.001
Symptomatic	250/3496 (7.2)	141/3509 (4.0)	3.2 (2.1 to 4.2)	<0.001
>25% decrease in estimated GFR from study-drug initiation — no./total no. (%)	1032/3289 (31.4)	968/3278 (29.5)	1.09 (0.98 to 1.21)	0.11
Baseline estimated GFR <60 ml/min/1.73 m²	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 m²	548/1575 (34.8)	519/1561 (33.2)	1.07 (0.92 to 1.24)	0.38

O'Connor CM. NEJM 2011;365:32-43

Vasodilators

ROSE trial

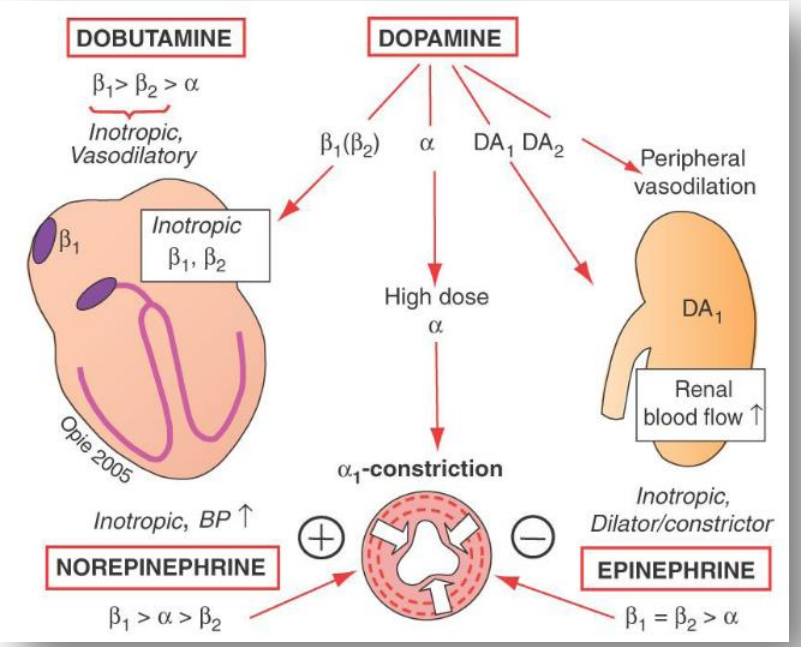
Nesiritide strategy	Placebo (n = 119)	Nesiritide (n = 119)	
Decongestion end points			
Cumulative urinary sodium excretion from randomization to 72 h, mmol	540 (485 to 595)	515 (468 to 563)	.52
Change in weight from randomization to 72 h, lb	−7.73 (−9.01 to −6.44)	−7.15 (−8.57 to −5.73)	.67
Change in NT-proBNP from randomization to 72 h, pg/mL	−2020 (−2724 to −1316)	−2273 (−3010 to −1536)	.10
Renal function end points			
Change in creatinine level from randomization to 72 h, mg/dL	0.02 (−0.4 to 0.08)	0.02 (−0.06 to 0.09)	.90
Development of type 1 cardiorenal syndrome[b] during 72 h, No. (%)	24 (22)	28 (25)	.55
Symptom relief end points			
Global well-being visual analog scale[c]; AUC from randomization to 72 h	4704 (4442 to 4965)	4498 (4257 to 4740)	.62
Dyspnea visual analog scale; AUC from randomization to 72 h	4998 (4723 to 5272)	4831 (4592 to 5070)	.89
Persistent or worsening HF[d] within 72 h, No. (%)	5 (4)	6 (5)	.77
Clinical outcomes			
Death from any cause within 72 h, No. (%)	0	0	NA
Treatment failure[e] within 72 h, No. (%)	32 (28)	48 (40)	.04
Study drug stopped or dose decreased because of hypotension, No./total No. (%)	12/115 (10.4)	22/117 (18.8)	.07
Study drug stopped or dose decreased because of tachycardia, No./total No. (%)	1/115 (0.9)	0/117	.50
Study drug stopped before 72 h for any reason, No./total No. (%)	29/115 (25)	29/117 (25)	.94
Death through day 60, No. (%)	12 (10)	8 (7)	.35
Serious adverse event through day 60, No. (%)	24 (20)	21 (18)	.62
Days alive and free from HF hospitalization at 60 d	46.6 (44.0 to 49.2)	47.3 (44.9 to 49.7)	.67
Mortality rate at 180 d, %	21.1 (14.7 to 29.9)	19.1 (13.0 to 27.6)	.74

Chen HH. JAMA 2013;310:2533-43

Inotropic drugs

- Intravenous inotropics
  - Dobutamine, dopamine, milinone
  - Has a role in the Tx of cardiogenic shock and in selected patients with ADHF
  - Routine use of short-term IV inotropics in ADHF : increase in mortality

- Inotropics in CRS
  - The role of inotropes in patients with CRS : **uncertain**
  - Lack of proven efficacy
  - Associated with adverse events



Inotropic drugs

DAD-HF

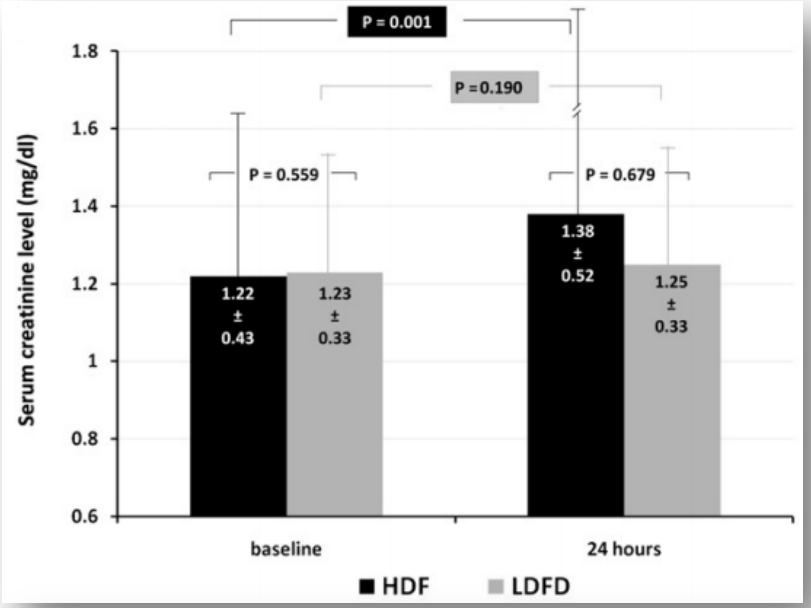
60 patients with ADHF

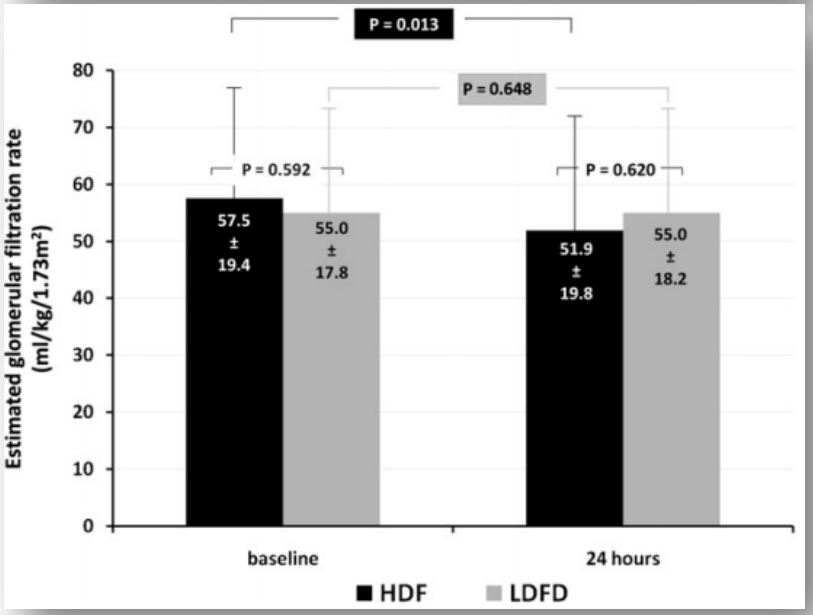
High dose furosemide vs.

low dose furosemide + low dose dobutamine

Table 3. Short-Term (60-Day) Outcomes in the Two Study Groups, n (%)

End Point	HDF Group (n = 30)	LDFD Group (n = 30)	*P* Value
Mortality			
All cause	3 (10%)	3 (10%)	1.000
Cardiovascular	3 (10%)	2 (6.7%)	1.000
Non–HF-related	0 (0%)	0 (0%)	1.000
Due to worsening HF	3 (10%)	2 (6.7%)	1.000
Rehospitalization			
All cause	2 (6.7%)	6 (20%)	.254
Cardiovascular	2 (6.7%)	4 (13.3%)	.671
Non–HF-related	0 (0%)	1 (3.3%)	1.000
Due to worsening HF	2 (6.7%)	3 (10%)	1.000





Giamouzis G. J Card Fail 2010;16:922-30

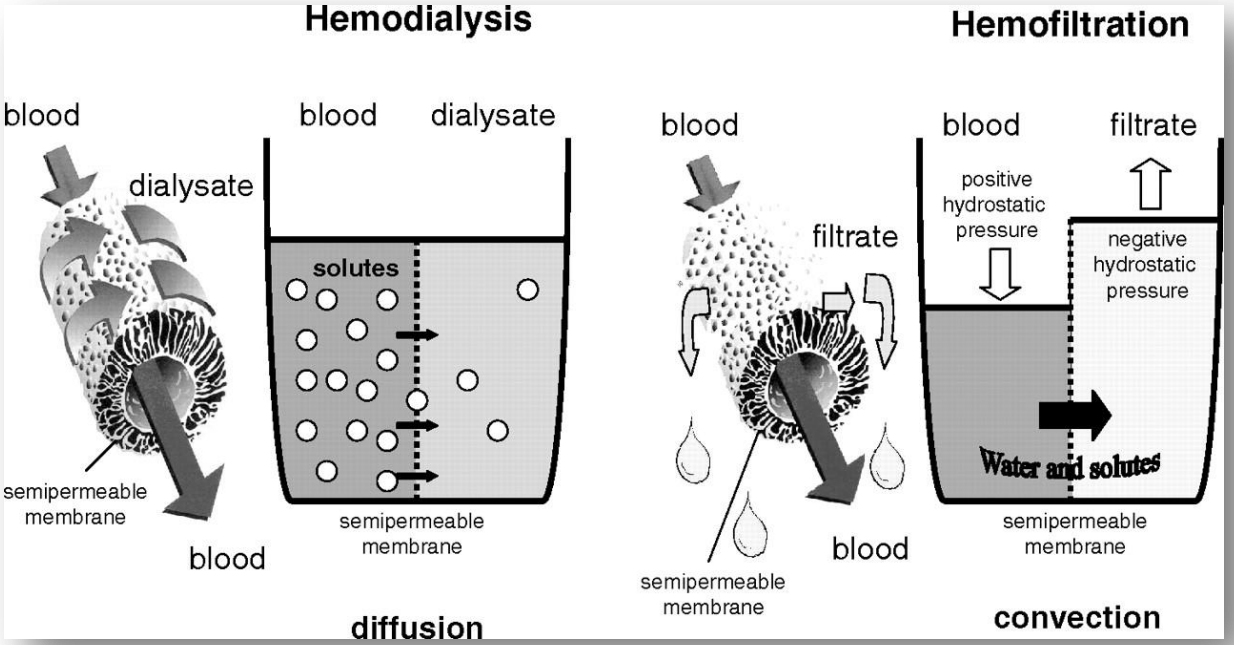
Inotropic drugs

ROSE trial

Dopamine strategy	Placebo (n = 119)	Dopamine (n = 122)	
Decongestion end points			
Cumulative urinary sodium excretion from randomization to 72 h, mmol	540 (485,595)	527 (473,581)	.75
Change in weight from randomization to 72 h, lb	−7.73 (−9.01 to −6.44)	−7.40 (−8.83 to −5.98)	.82
Change in NT-proBNP level from randomization to 72 h, pg/mL	−2020 (−2724 to −1316)	−2629 (−3470 to −1789)	.43
Renal function end points			
Change in creatinine level from randomization to 72 h, mg/dL	0.02 (−0.4 to 0.08)	0 (−0.7 to 0.08)	.78
Development of type 1 cardiorenal syndrome[b] during 72 h, No. (%)	24 (22)	23 (22)	.88
Symptom relief end points			
Global well-being visual analog scale; AUC from randomization to 72 h	4704 (4442 to 4965)	4553 (4305 to 4801)	.43
Dyspnea visual analog scale; AUC from randomization to 72 h	4998 (4723 to 5272)	4936 (4660 to 5211)	.92
Persistent or worsening HF[c] within 72 h, No. (%)	5 (4)	11 (9)	.14
Clinical outcomes			
Death from any cause within 72 h, No. (%)	0	0	NA
Treatment failure[d] within 72 h, No. (%)	32 (28)	35 (30)	.73
Study drug stopped or dose decreased because of hypotension, No./total No. (%)	12/115 (10.4)	1/111 (0.9)	<.001
Study drug stopped or dose decreased because of tachycardia, No./total No. (%)	1/115 (0.9)	8/111 (7.2)	<.001
Study drug stopped before 72 h for any reason, No./total No. (%)	29/115 (25)	25/111 (23)	.72
Death through day 60, No. (%)	12 (10)	11 (9)	.78
Serious adverse event through day 60, No. (%)	24 (20)	30 (25)	.41
Days alive and free from HF hospitalization at 60 d	46.6 (44.0 to 49.2)	47.3 (45.0 to 49.6)	.68
Mortality at 180 d, %	21.1 (14.7 to 29.9)	19.7 (13.5 to 28.1)	.87

Chen HH. JAMA 2013;310:2533-43

Ultrafiltration

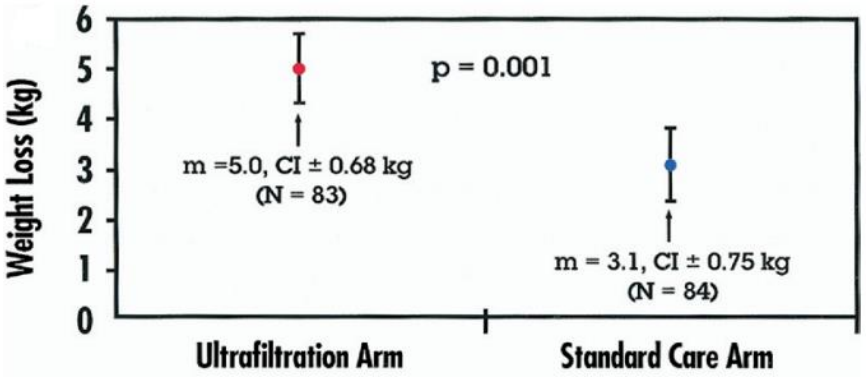


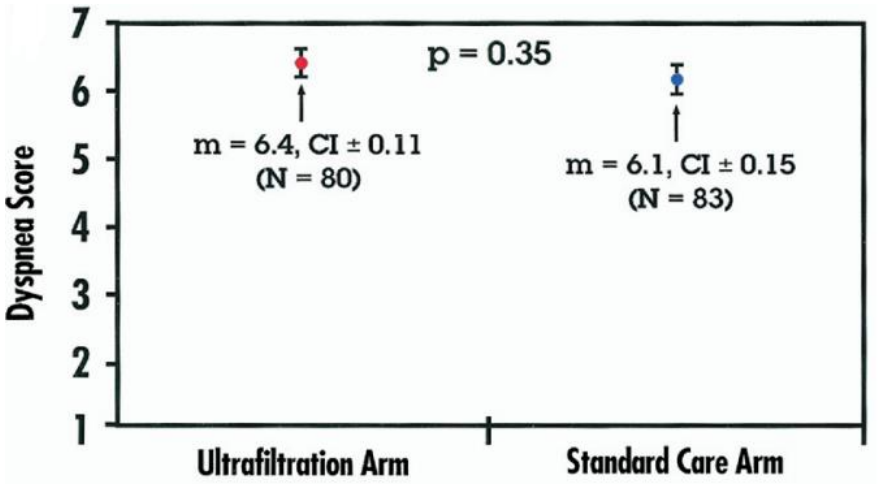
- Removal of isotonic fluid from the venous compartment via filtration of plasma across a semipermeable membrane.
- By removing isotonic fluid, ultrafiltration tends to maintain physiologic electrolyte balance, in contrast to diuretic therapy
- May be helpful for fluid removal in acute decompensated HF in patients unresponsive to diuretics
- Not recommended as first line therapy for AHDF or as an effective therapy for CRS

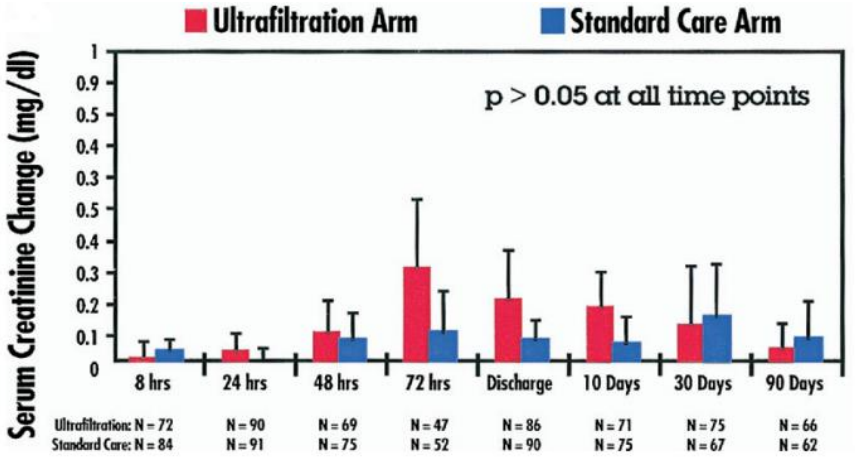
Ultrafiltration

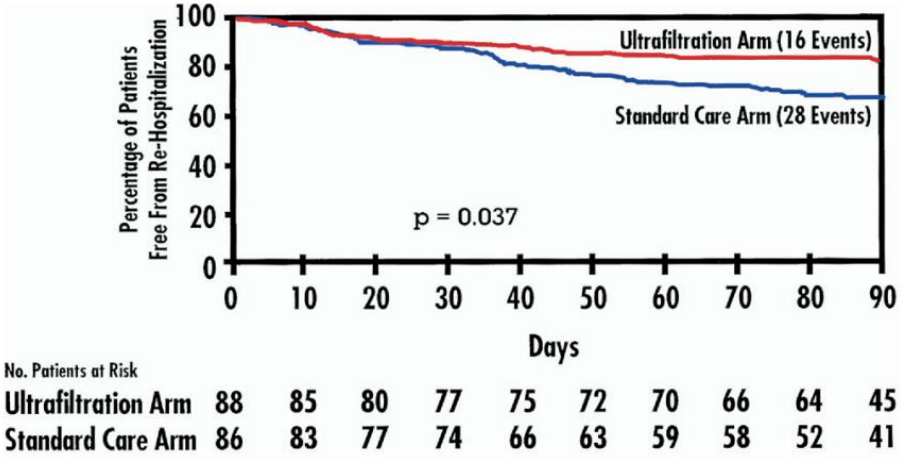
UNLOAD trial

200 hospitalized HF patients with hypervolemia : ultrafiltration vs. IV diuretics









CBNUH Cardiovascular Center

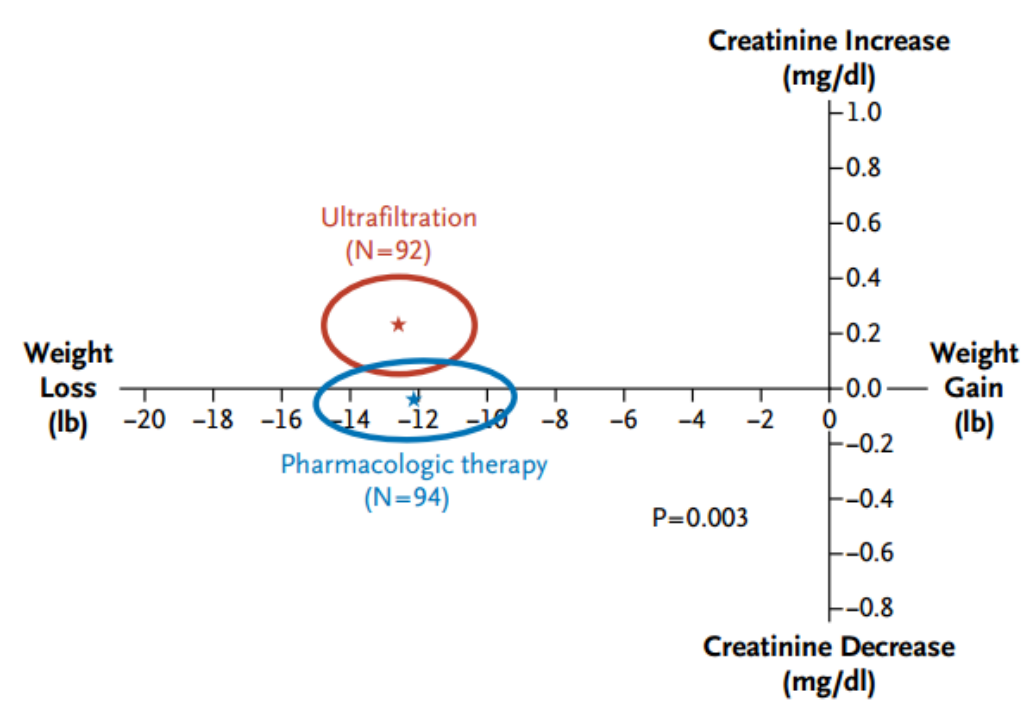
Costanzo MR. JACC 2007;49:675-83

Ultrafiltration

CARRESS-HF trial

188 ADHF patients with WRF and persistent congestion

Stepped pharmacologic therapy vs. ultrafiltration



- Although weight loss was similar in ultrafiltration and stepped pharmacologic therapy groups, ultrafiltration therapy caused an increase in serum creatinine and a higher rate of adverse events.

Bart BA. NEJM 2012;367:2296-304

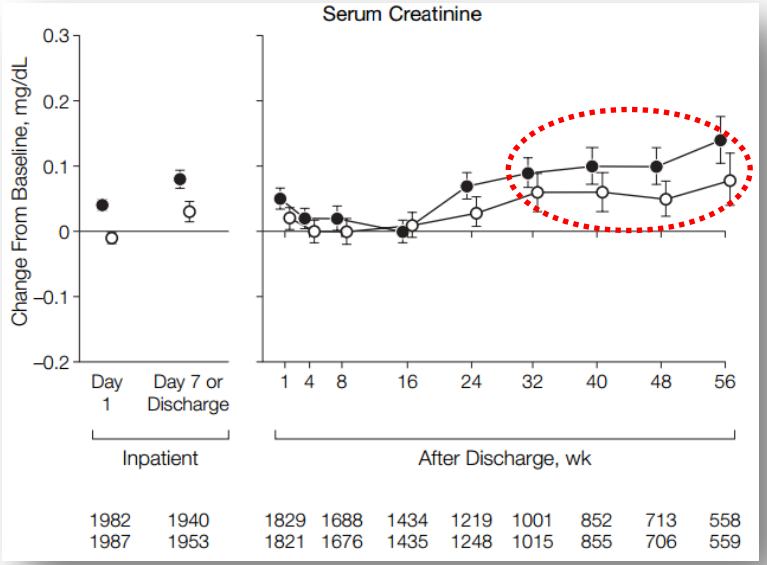
Investigational therapies

Tolvaptan

A selective vasopressin 2 receptor antagonist that produces a water diuresis

	No. (%) of Patients		Hazard Ratio (95% Confidence Interval)	*P* Value	
	Tolvaptan (n = 2072)	Placebo (n = 2061)		Superiority	Noninferiority
Primary end points					
All-cause mortality	537 (25.9)	543 (26.3)	0.98 (0.87-1.11)	.68*	<.001
Cardiovascular death or hospitalization for heart failure	871 (42.0)	829 (40.2)	1.04 (0.95-1.14)	.55*	
Secondary end points					
Cardiovascular death or cardiovascular hospitalization	1006 (48.5)	958 (46.4)	1.04 (0.95-1.14)	.52*	
Incidence of cardiovascular mortality	421 (20.3)	408 (19.8)		.67†	
Incidence of clinical worsening of heart failure (death, hospitalization, or unscheduled visits)	757 (36.5)	739 (35.8)		.62†	

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



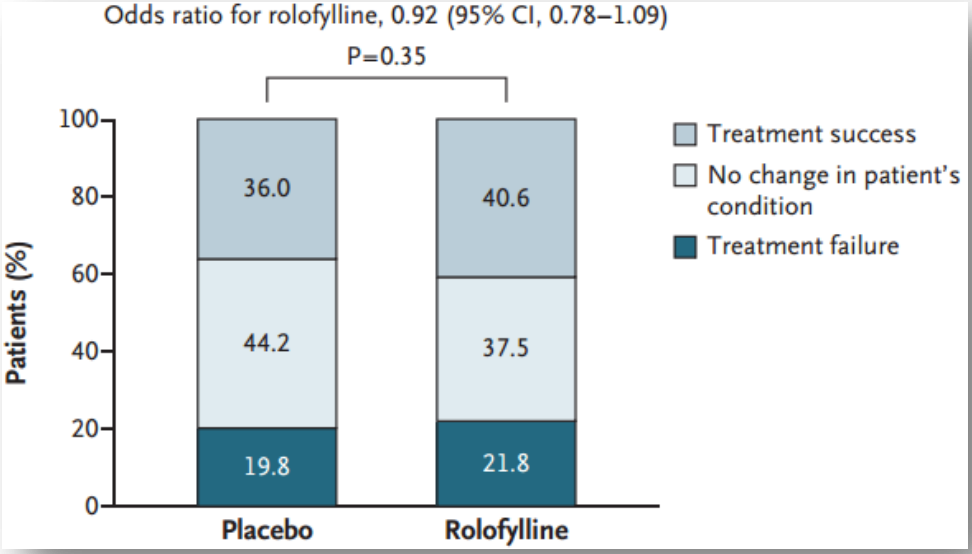
Constam MA. JAMA 2007;297:1319-31

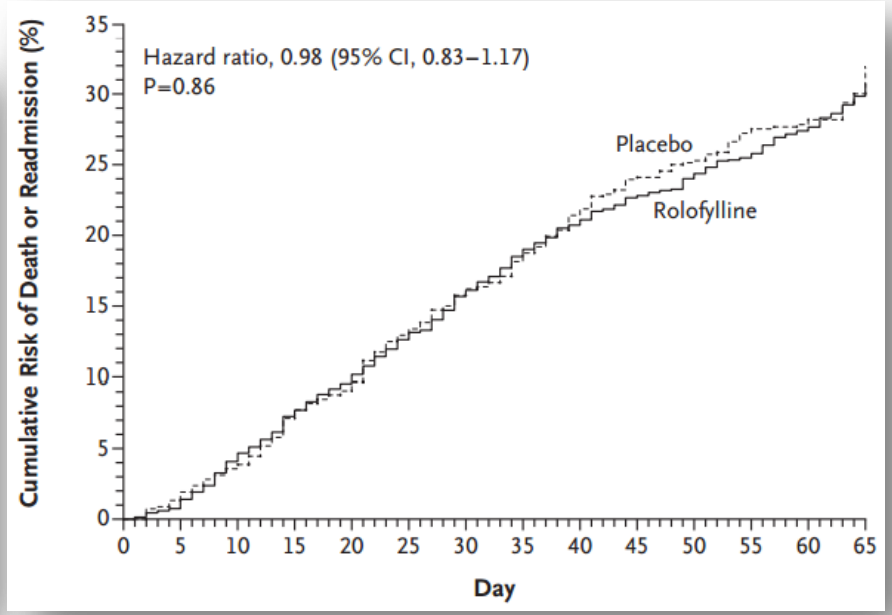
Investigational therapies

Adenosine A1 receptor antagonist

Adenosine : acting on the adenosine-1 receptor
constricts the afferent glomerular arteriole, reducing GFR

PROTECT trial
2,033 hospitalized HF patients with impaired renal function
Rolofylline vs. placebo





- Rolofylline therapy was associated with a higher rate of neurologic events (seizure and stroke)

Massie BM. NEJM 2010;363:1419-28

Summary

- Renal disease in heart failure
  - Bidirectional interaction of heart and kidney
  - CRS 1 and CRS 2 : relatively common, independent predictor of poor prognosis
- Pathophysiology of CRS
  - Neurohormonal adaptations
  - Reduced renal perfusion
  - Increased renal venous pressure
- Management of CRS
  - Reversible ?
    - May have reversible components
  - No definite medical therapy
    - The outcomes may be improved with aggressive fluid removal even if accompanied by sCr ↑
    - Ultrafiltration may be helpful for fluid removal in acute decompensated HF in patients unresponsive to diuretic therapy

Thank you for Your Attention !

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