HOW DO YOU MEND A BROKEN HEART?

Management Strategies in Acutely Decompensated Heart Failure

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FINANCIAL DISCLOSURES

None

OBJECTIVES

- Identify the most common conditions leading to decompensated heart failure
- Identify patient profiles of the acutely decompensated heart failure patient and the specific treatments aimed at the respective profiles
- Identify strategies to reduce heart failure readmission

DEFINITION

"A family of syndromes characterized by new or worsening signs or symptoms of heart failure leading to hospitalization or unscheduled medical care."

Felker GM et al, AHJ 2001

DEFINITION

"A gradual or rapid change in heart failure signs and symptoms resulting in a need for urgent therapy."

Gheorghiade M et al. Circulation 2006

HEART FAILURE HOSPITALIZATIONS

Incidence & Cost

- 1 million admissions per year with primary diagnosis of Heart Failure
- 3 million admissions per year with primary or secondary diagnosis of Heart Failure
- Most frequent cause of hospitalization in the elderly
- ~ $37 billion spent annually on managing episodes of decompensation

HEART FAILURE HOSPITALIZATIONS

Short Term Morbidity & Mortality

- 20-30% readmission rate at 30 days
- 20% post hospitalization mortality at 6 months
- 30% post hospitalization mortality at 1 year

HEART FAILURE HOSPITALIZATIONS

Table 5. A Comparison of Characteristics, Pathophysiologic Targets of Therapy and Evidence in Management of Patients With ACS and AHFS

	ACS	AHFS
Incidence	1 million/y	1 million/y
Mortality		
Prehospital	High	?
In-hospital	3%–4%	3%–4%
60–90 d	2%	10%
Targets of therapy	Clearly defined-thrombosis	Unclear
Clinical trial results	Beneficial	Minimal, no benefit, harmful
ACC/AHA Guidelines	Level A	Minimal level A/B, mostly C

Weintraub et al., Circulation 2010; 122:1975-1999

CLINICAL CHARACTERISTICS OF THE ADHF PATIENT

- Elderly Females
- Mean LVEF 34.4%
- HFpEF: 46% of patients
- HTN & CAD highly prevalent
- Atrial fibrillation in 31%
- CKD in 30%
- Low utilization rates of GDMT
- Mean SBP 144 mmHg

Table II. Comparison of patients in acute heart failure trials and the ADHERE

	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 et al, Am Heart J 2005;149:209-16

KEY PRECIPITANTS

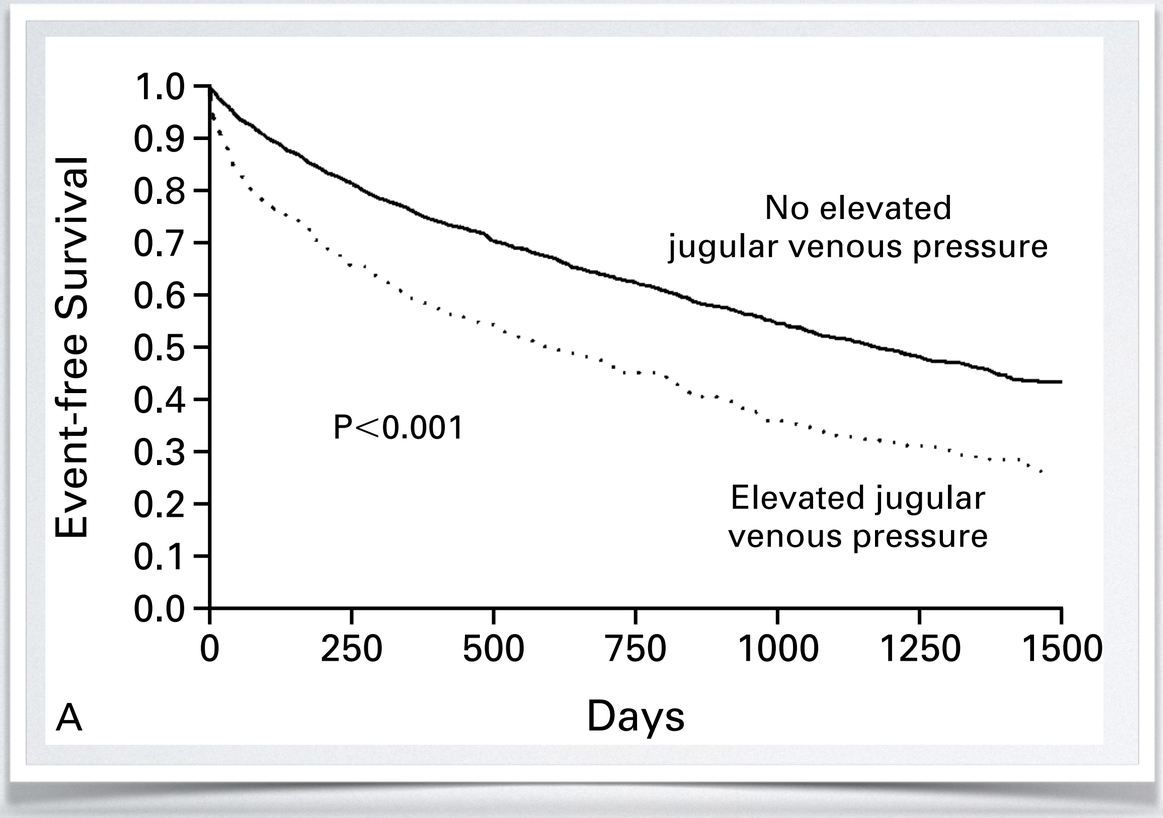
- Non-Adherence
- Poorly controlled HTN
- Myocardial ischemia
- Atrial fibrillation or other arrhythmias
- Loss of BiV pacing
- Worsening renal function
- Negative inotropic drugs
- Drugs that increase salt retention
- Excessive EtOH or drug usage
- Infections
- Pulmonary Embolism
- Hyper/Hypothyroidism

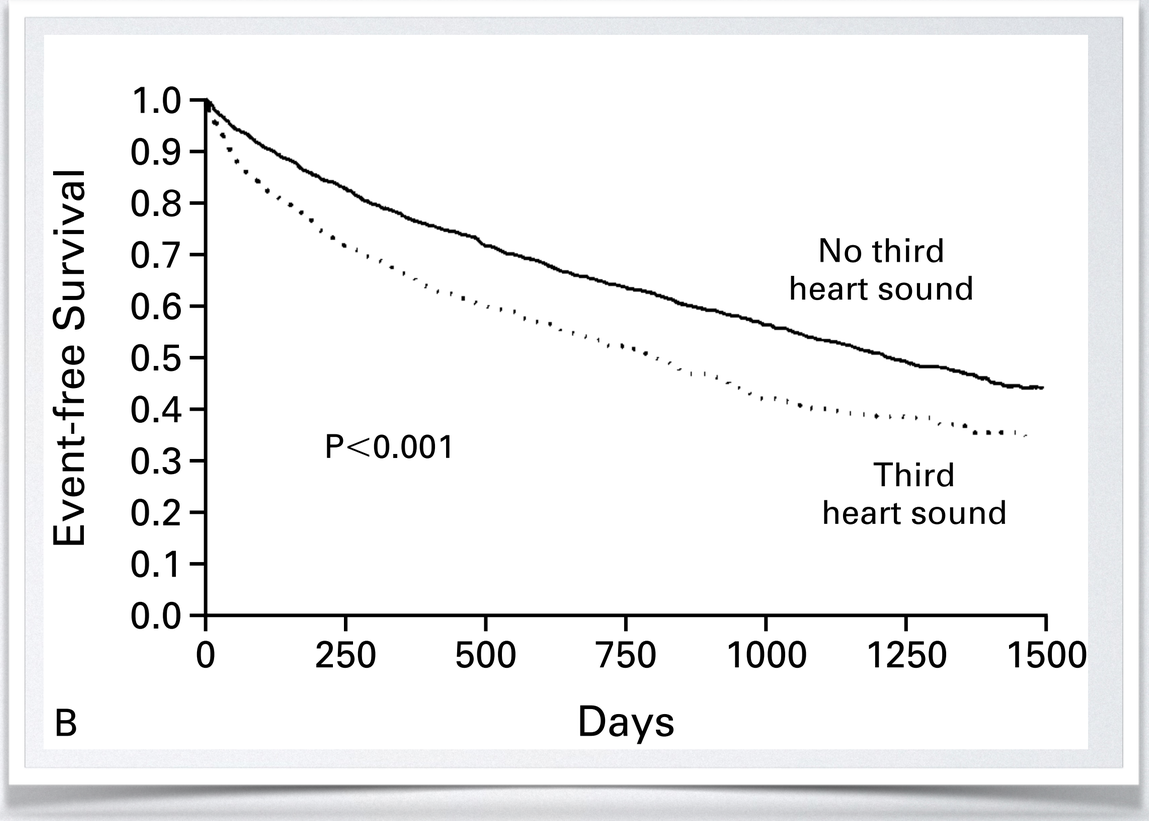
SIGNS & SYMPTOMS

- Jugular Venous Distension
- S3
- Rales or Pleural Effusion
- Edema
- Ascites
- Hepatojugular Reflux

- Dyspnea
- Orthopnea / PND / Bendopnea
- Fatigue & Lethargy
- Anorexia
- Early Satiety
- Confusion

PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE

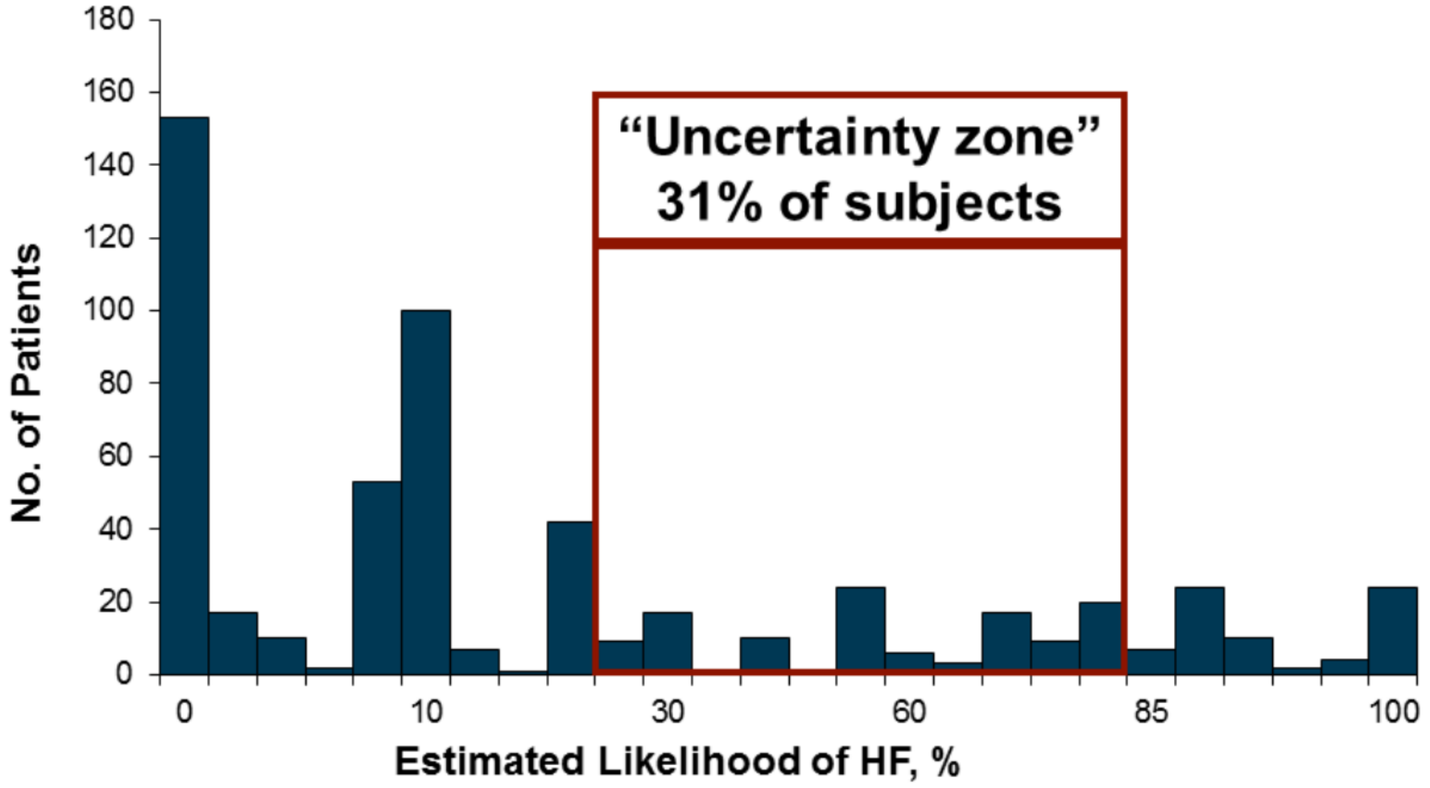




Drazner MH et al, N Engl J Med 2001; 345:574-81

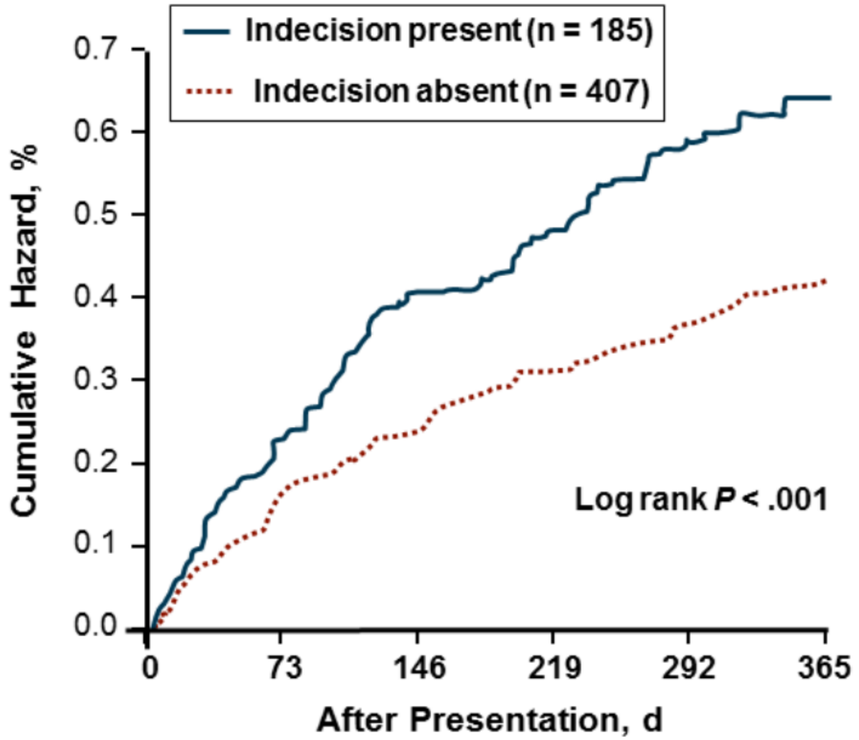
Diagnostic Uncertainty Is Common in Dyspnea Evaluation

- Following full evaluation, managing physician is asked to provide an estimate from 0% to 100% for the likelihood for HF as the cause of dyspnea.



Green SM, et al. *Arch Intern Med.* 2008;168:741.

Diagnostic Uncertainty Is Associated With Poor Prognosis in Acute Dyspnea



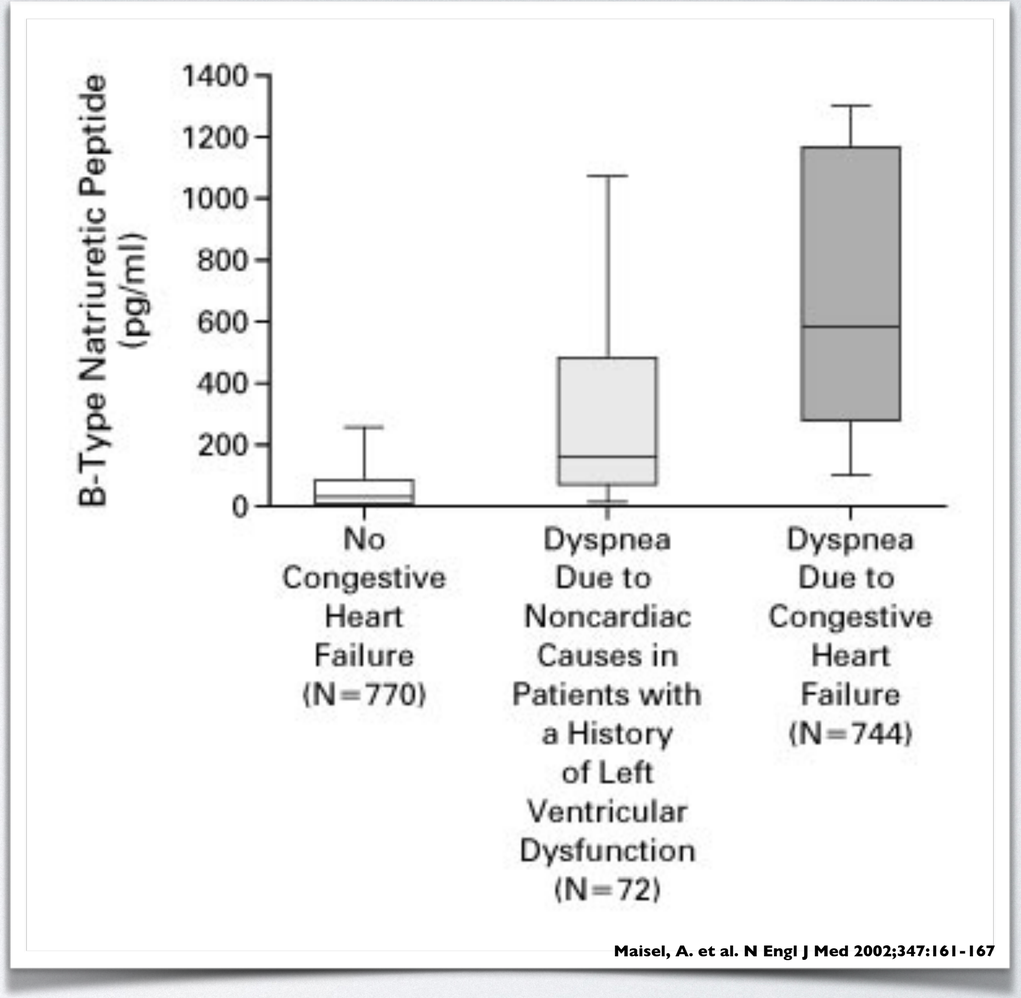
- 31% of subjects with dyspnea in PRIDE were judged uncertainly by the managing physician
- Their prognosis was significantly worse, with higher rates of death and rehospitalization and longer LOS

Green SM, et al. *Arch Intern Med.* 2008;168:741.

NATRIURETIC PEPTIDES

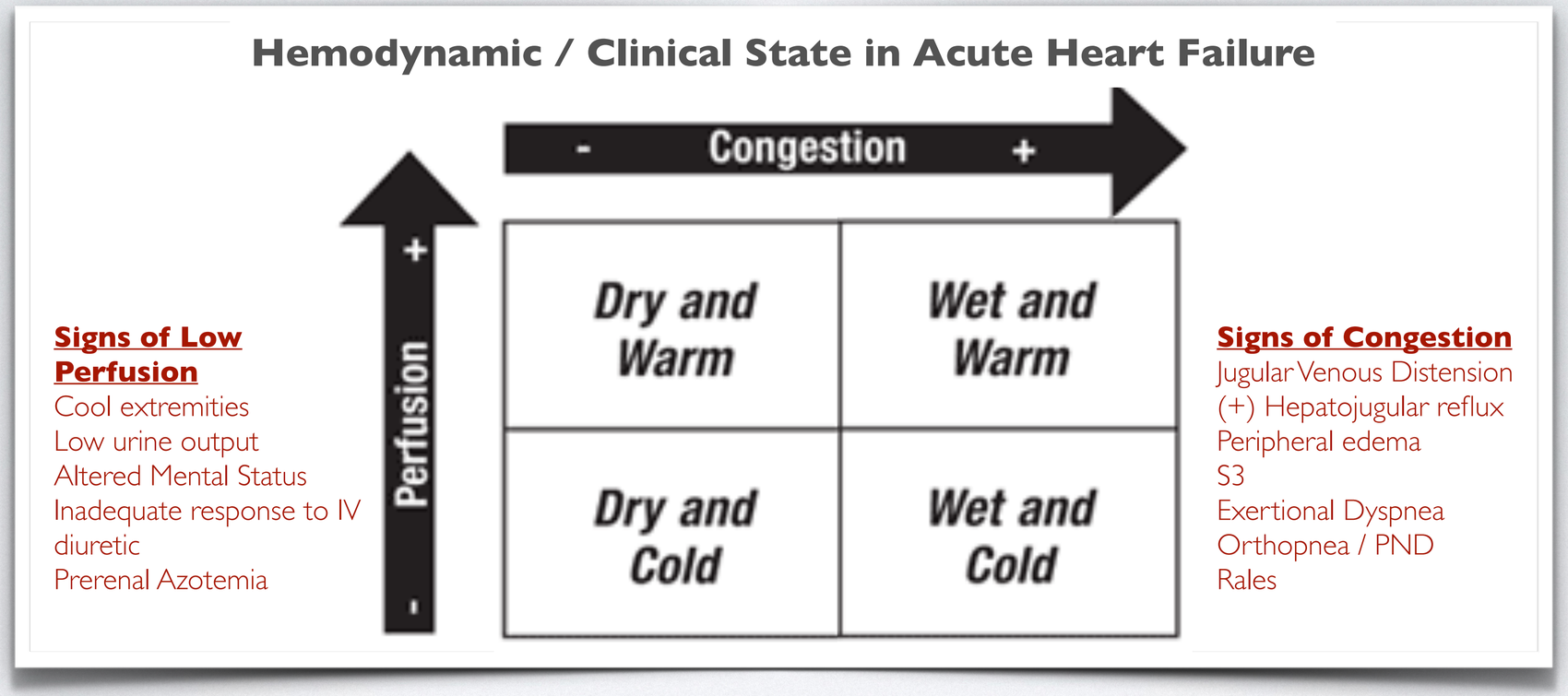
CHF Guideline Statement on Natriuretic Peptides

- Useful to support clinical judgement for the diagnosis of ADHF, especially in the setting of uncertainty. Class I. Level of Evidence A



Maisel, A. et al. N Engl J Med 2002;347:161-167

CLINICAL PRESENTATIONS



Nordeen JD, et al. US Pharm. 2010;35(2):HS8-HS19

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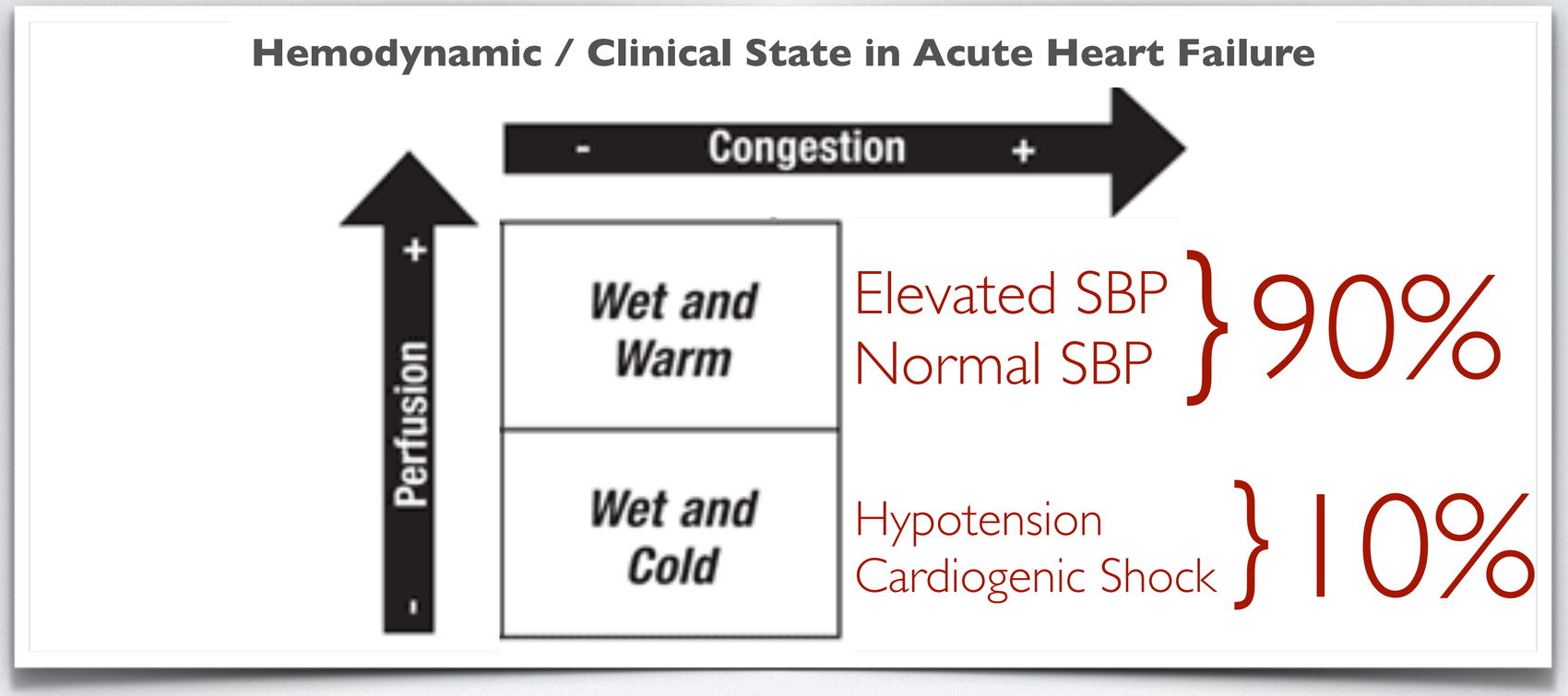


GOALS OF THERAPY

- Relieve Symptoms
- Optimize fluid Status
- Identify precipitating factors
- Optimize Chronic Oral Therapy
- Minimize Side Effects
- Educate Patient & Family

ARMAMENTARIUM

- Diuretics
- Ultrafiltration
- Vasodilators
- Inotropes
- Arginine Vasopressor Antagonists
- Mechanical Circulatory Support*

Diuretics

Diuretics

- **70% intravenous utilization rate during hospitalization**
- **90% of patients report feeling better at discharge**
- **40% feel better, but are still congested**

Gheorghiade M, et al. Circ 2005;112:3958-68

DIURETIC PHARMACOKINETICS

- Highly variable bioavailability of Furosemide
- Bumetanide & Torsemide more reliably absorbed
- Longer elimination half-life in CHF patients compared with normal

TABLE 1. PHARMACOKINETICS OF DIURETIC DRUGS.*

DIURETIC	ORAL BIOAVAILABILITY	ELIMINATION HALF-LIFE			
		NORMAL SUBJECTS	PATIENTS WITH RENAL INSUFFICIENCY	PATIENTS WITH CIRRHOSIS	PATIENTS WITH CONGESTIVE HEART FAILURE
	%	hr			
Loop					
Furosemide	10–100	1.5–2	2.8	2.5	2.7
Bumetanide	80–100	1	1.6	2.3	1.3
Torsemide	80–100	3–4	4–5	8	6
Thiazide					
Bendroflumethiazide	ND	2–5	ND	ND	ND
Chlorthalidone	64	24–55	ND	ND	ND
Chlorothiazide	30–50	1.5	ND	ND	ND
Hydrochlorothiazide	65–75	2.5	Increased	ND	ND
Hydroflumethiazide	73	6–25	ND	ND	6–28
Indapamide	93	15–25	ND	ND	ND
Polythiazide	ND	26	ND	ND	ND
Trichlormethiazide	ND	1–4	5–10	ND	ND
Distal					
Amiloride	Conflicting data	17–26	100	Negligible change	ND
Triamterene†	>80	2–5	Prolonged	No change	ND
Spironolactone	Conflicting data	1.5	No change	No change	ND
Active metabolites of spironolactone		>15	ND	ND	ND

*ND denotes not determined.

†Values are for the active metabolite.

Brater DC et al. N Engl J Med 1998; 339:387-395

DIURETIC PHARMACOKINETICS

- Bumex is the most potent of the loop diuretics followed by Torsemide and Furosemide
- 1:1 oral to IV conversion with Torsemide & Bumex
- 1:2 oral to IV conversion with Furosemide

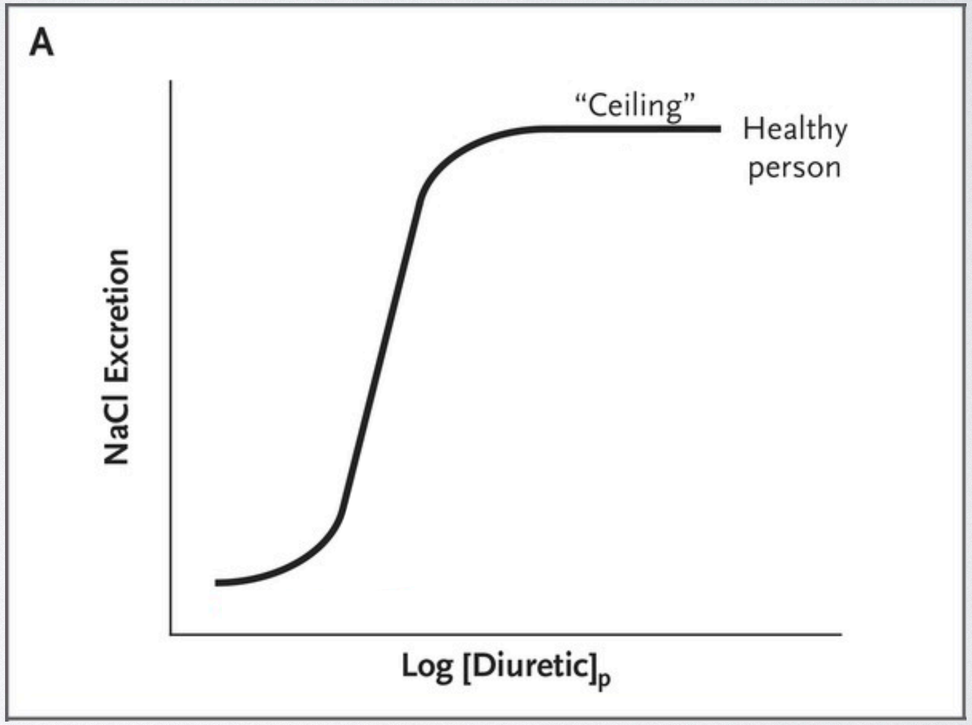
Table 1: Properties of Loop Diuretics

	Furosemide	Torsemide	Bumetanide
Relative intravenous potency (mg)	40	20	1
Oral : intravenous dosing	1 : 2	1 : 1	1 : 1
Bioavailability (%)	10–100	80–100	80–100
Drug half-life (h)	1.5–2.0	3–4	1.0–1.5
Duration of effect (h)	6–8	6–16	4–6

Reproduced from Felker & Mentz,[6] with permission from Elsevier.

DIURETIC PHARMACOKINETICS

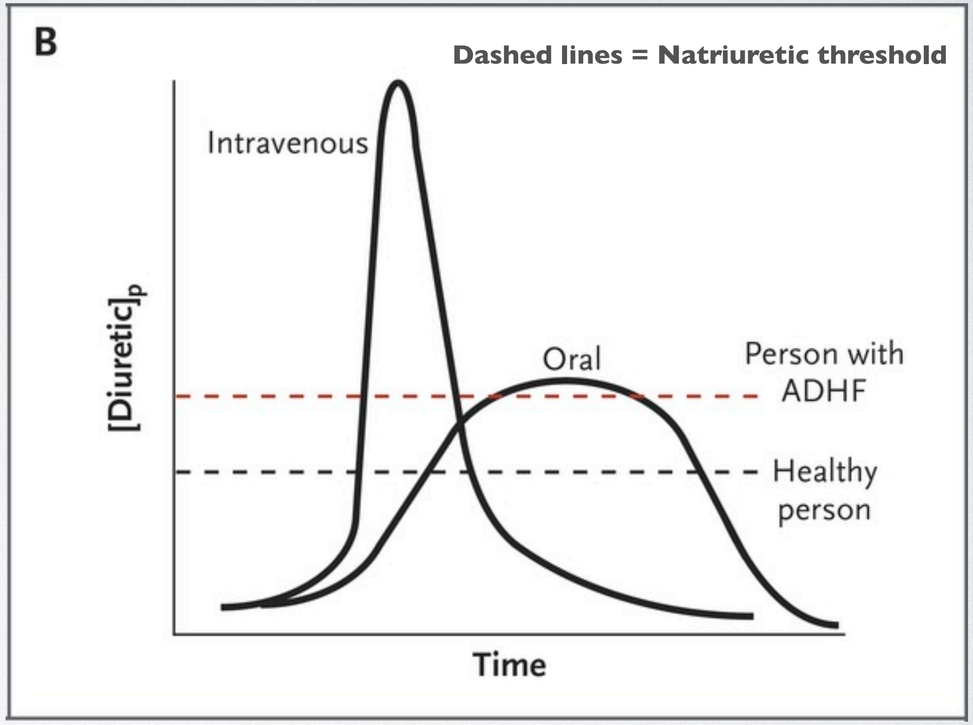
- Loop diuretics are threshold drugs with steep dose-response curves
- In ADHF the curve is shifted downward & rightward with less natriuresis despite higher doses of diuretic
- Increasing the dose above the threshold does not result in an increase in natriuretic efficiency



ELLISON DH, FELKER GM. N ENGL J MED 2017;377:1964-1975.

DIURETIC PHARMACOKINETICS

Increasing the dose above the ceiling dose can cause additional natriuresis by **increasing the time the plasma diuretic concentration exceeds the natriuretic threshold**



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DIURETIC THERAPY IN ADHF

Target of 3 - 5 L urine output / day until **clinical euvolemia** is achieved

Clinical Euvolemia = JVP < 8 cm H2O, Trace edema or less

DIURETIC THERAPY IN ADHF

Patients admitted with HF and with evidence of significant fluid overload should be treated with **intravenous loop diuretics.** Class I. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

DIURETIC THERAPY IN ADHF

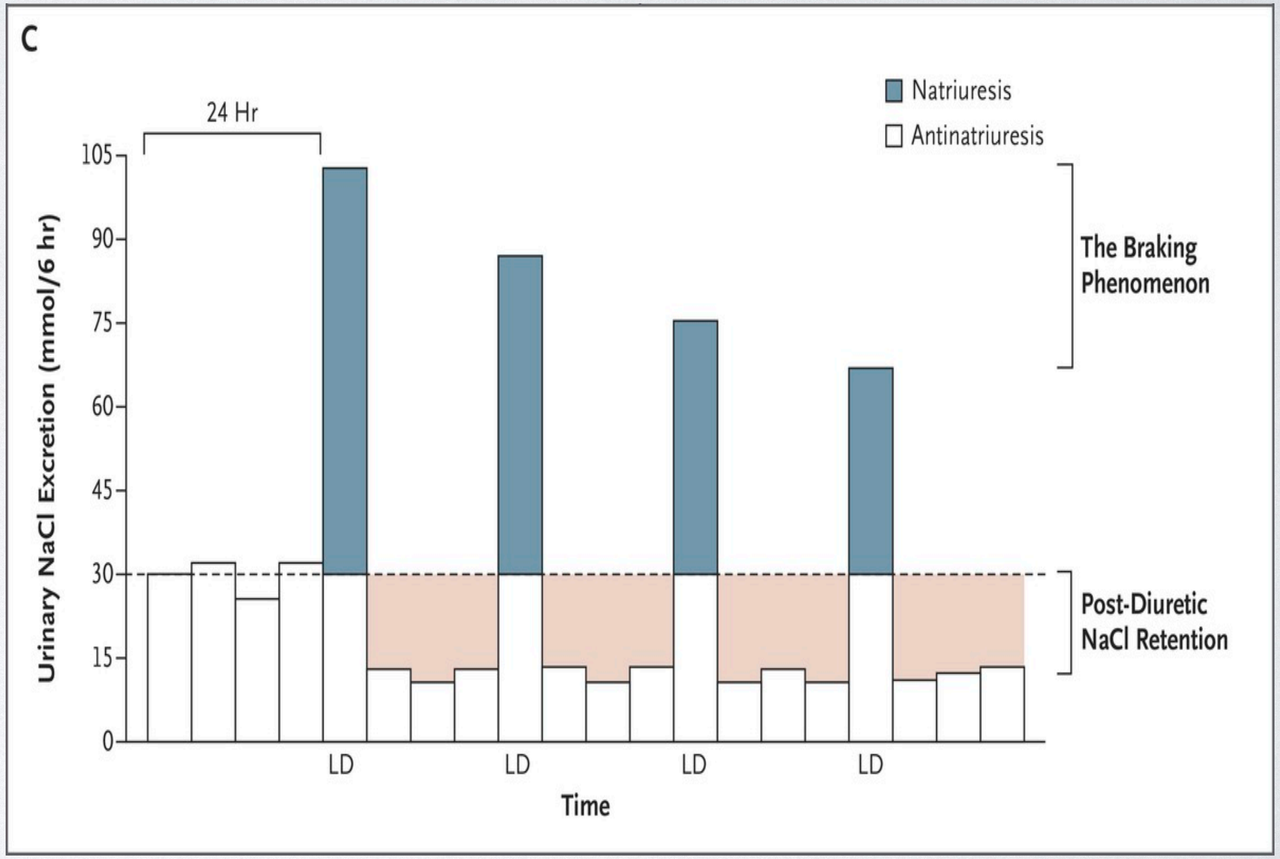
If patients are already receiving loop diuretic therapy, the initial IV dose should **equal or exceed** their chronic oral daily dose and should be given as either **intermittent boluses or continuous infusion.** Class I. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

DIURETIC PHARMACOKINETICS

- A reduction of natriuretic response to subsequent doses of diuretic.
- Causes include activation of the SNS & RAAS, depletion of extracellular fluid volume and **Distal Nephron Remodeling**

The Braking Phenomenon



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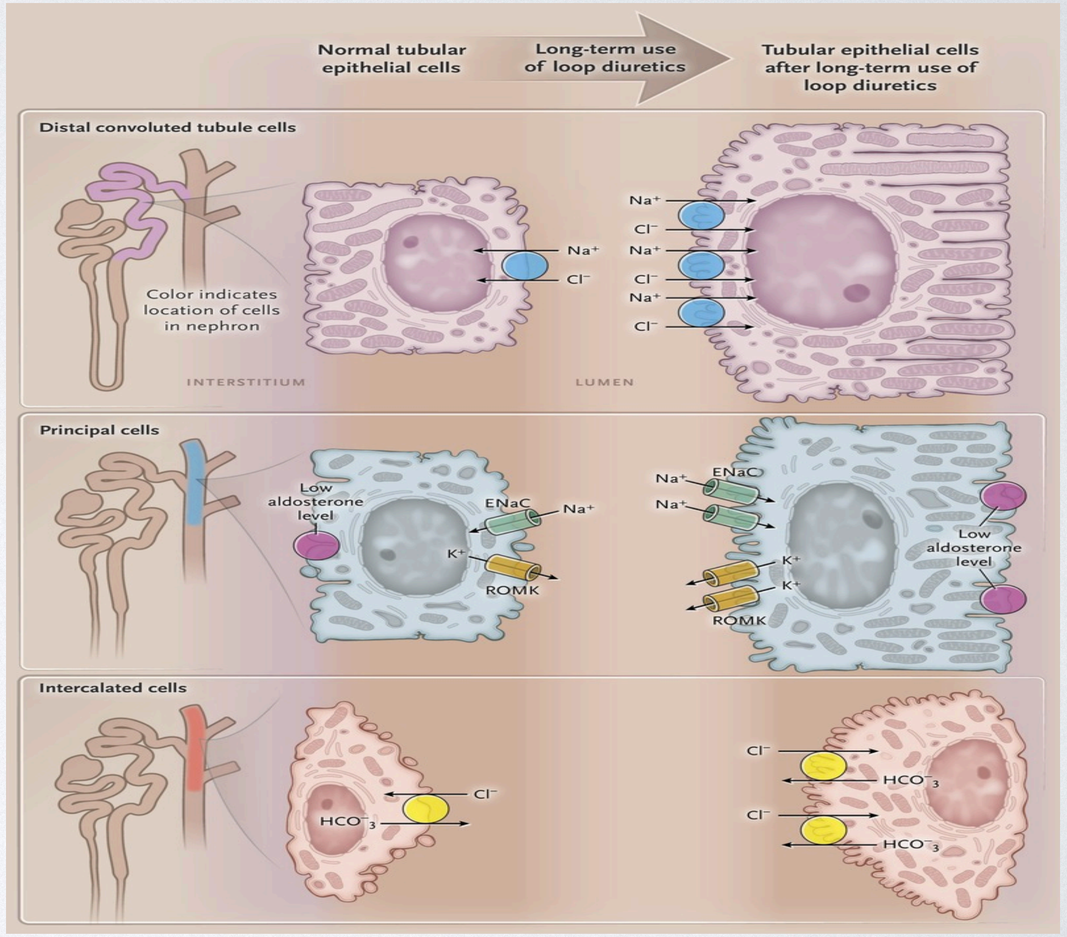
DIURETIC PHARMACOKINETICS

- More NaCl is delivered to the distal nephron
- The distal nephron hypertrophies
- Increased transcription of luminal NaCl transporters resulting in **more NaCl reabsorption in the distal nephron**
- This leads to **DIURETIC RESISTANCE**

Distal Nephron Remodeling



ELLISON DH, FELKER GM. N ENGL J MED 2017;377:1964-1975.

DIURETIC RESISTANCE

The failure of diuretics to achieve decongestion despite the use of **maximal recommended doses.**

Ellison DH et al. N Engl J Med 2017; 377:1964-1975

DIURETIC RESISTANCE

The failure of diuretics to achieve decongestion despite the use of **maximal recommended doses.**

TABLE 2. THERAPEUTIC REGIMENS FOR LOOP DIURETICS IN PATIENTS WITH DIMINISHED RESPONSES TO INITIAL THERAPY.

FACTOR	RENAL INSUFFICIENCY		PRESERVED RENAL FUNCTION*		
	MODERATE	SEVERE	NEPHROTIC SYNDROME	CIRRHOSIS	CONGESTIVE HEART FAILURE
Mechanism of diminished response	Impaired delivery to site of action		Diminished nephron response, binding of diuretic to urinary protein	Diminished nephron response	Diminished nephron response
Therapeutic approach	Administration of sufficiently high dose to attain effective amount of diuretic at site of action		Administration of sufficiently high dose to attain effective amount of unbound diuretic at site of action, more frequent administration of effective dose	More frequent administration of effective dose	More frequent administration of effective dose
Maximal intravenous dose (mg)†					
Furosemide	80–160	160–200	80–120	40	40–80
Bumetanide	4–8	8–10	2–3	1	1–2
Torsemide	20–50	50–100	20–50	10	10–20

*Preserved renal function is defined as a creatinine clearance of more than 75 ml per minute.

†If the maximal dose is reached without an adequate response, a thiazide diuretic should be administered as adjunctive therapy, with the dose determined according to renal function, and alternative treatment of the primary disease should be considered.

Brater DC. N Engl J Med 1998; 339:387-395

DIURETIC RESISTANCE

When **diuresis is inadequate** to relieve congestion the diuretic regimen should be intensified using either

a: **higher doses of loop diuretics**

b: **addition of a second diuretic** (Metolazone, Spironolactone or IV Chlorothiazide)

Class IIa. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

DIURETIC RESISTANCE

Low dose **Dopamine** infusion **may be considered** in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow. Class IIb. Level of Evidence B

Post hoc subgroup analysis of the ROSE-AHF trial suggests that in HFrEF patients Dopamine may have enhanced decongestion.

Yancey et al. JACC Vol. 62, No. 16, 2013

TREATMENT OF DIURETIC RESISTANCE

Table 2. Stepped-Care Pharmacologic Approach.*

Level	Furosemide			Metolazone†
	Previous Oral Dose‡	Bolus	Infusion Rate	Oral Dose
1	≤80 mg	40 mg	5 mg/hr	NA
2	81–160 mg	80 mg	10 mg/hr	5 mg daily
3	161–240 mg	80 mg	20 mg/hr	5 mg twice daily
4	>240 mg	80 mg	30 mg/hr	5 mg twice daily

Bart BA, Goldsmith SR, Lee KL, et al. N Engl J Med 2012;367:2296-304.
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4	>240 mg	80 mg	30 mg/hr	5 mg twice daily

AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

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4	>240 mg	80 mg	30 mg/hr	5 mg twice daily

AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms

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AT 72 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
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Advanced Cardiorenal Therapy Hemodynamic guided iv therapy, LVAD, Dialysis or UF
Cross over

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3	161–240 mg	80 mg	20 mg/hr	5 mg twice daily
4	>240 mg	80 mg	30 mg/hr	5 mg twice daily

AT 96 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
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Diuretics

Intermittent IV Bolus vs Continuous infusion?

Low intensity vs High Intensity?

Diuretics

The NEW ENGLAND JOURNAL of MEDICINE

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

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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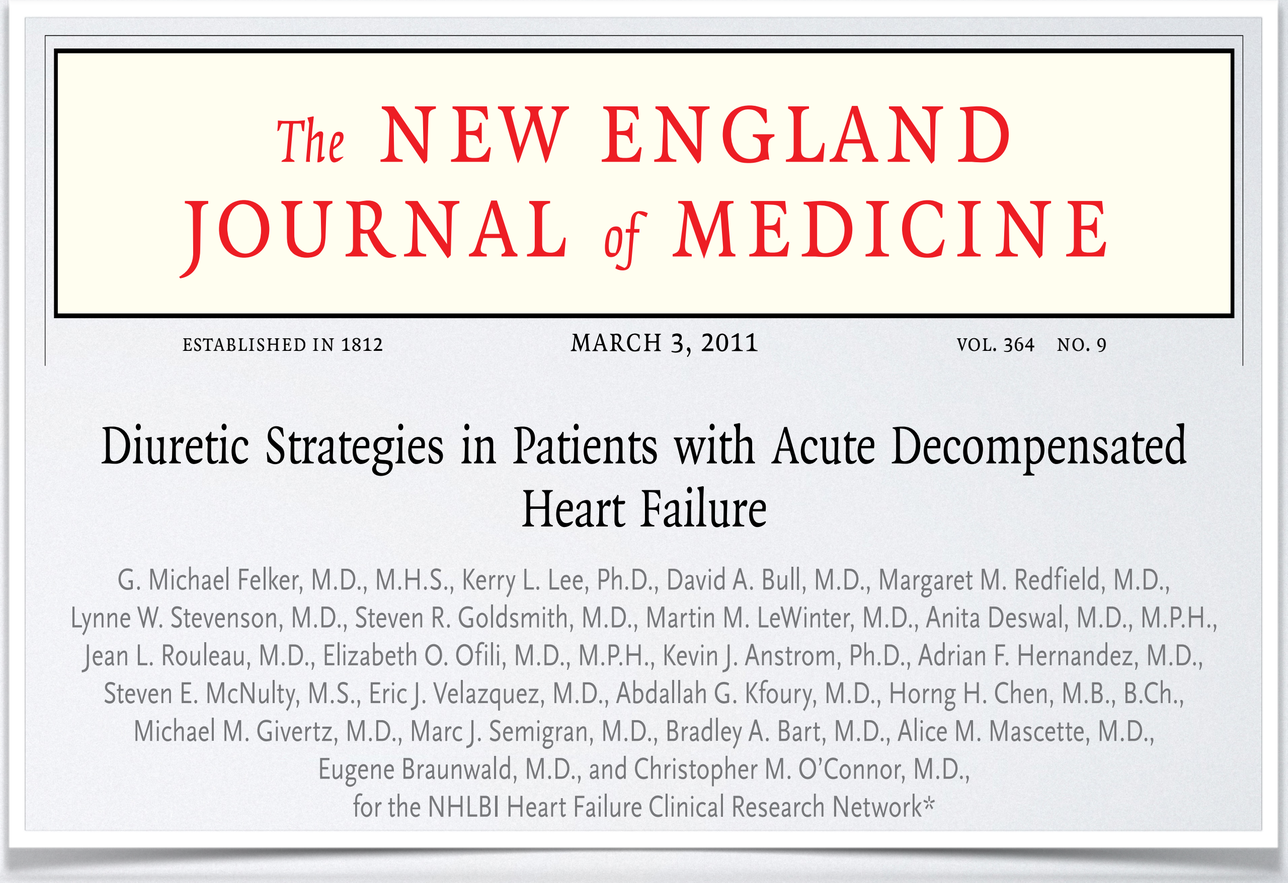
DIURETICS

- 308 pts with ADHF randomized to intermittent **IV bolus vs continuous infusion & low intensity vs high intensity**
- Co-primary endpoints being Pt's **Global Assessment of Symptoms at 72 hours & △ in Creatinine** (all assessed at 72 hours)



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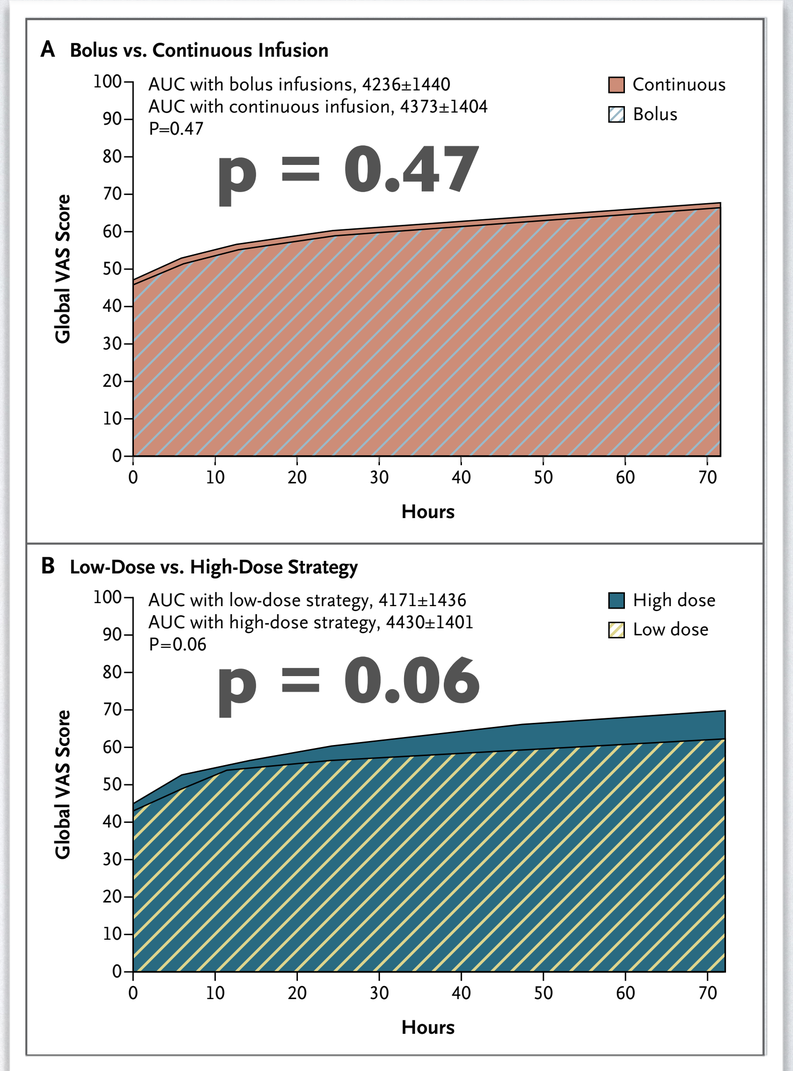
DIURETICS

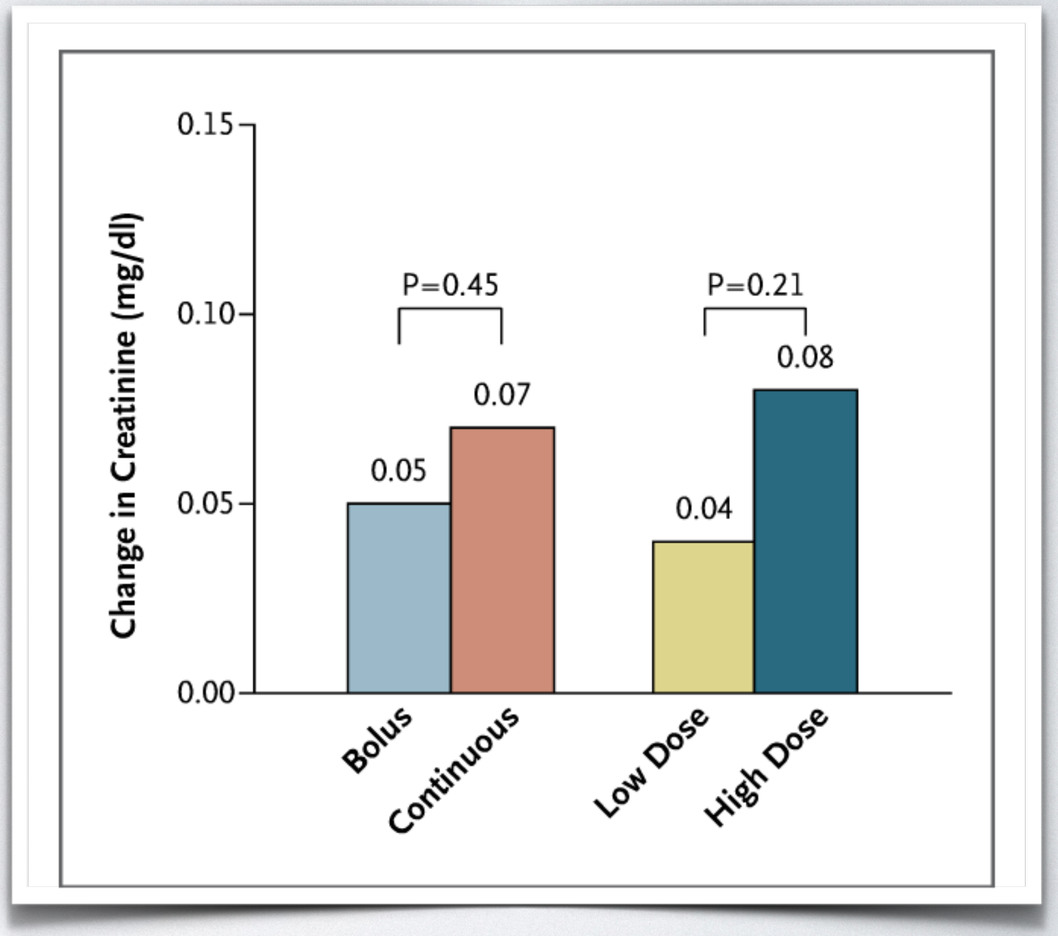
- **No difference** in △ in Global VAS at 72 hours in the Bolus vs Continuous infusion group
- **No difference** in △ in Global VAS at 72 hours in the Low dose vs High dose diuretic group

Global = Patient Well Being & Dyspnea



DIURETICS

- **No difference** in △ in Creatinine at 72 hours in the Bolus vs Continuous infusion group
- **No difference** in △ in Creatinine at 72 hours in the Low dose vs High dose diuretic group



DIURETICS

- Visual Analog Scale (AUC) for Dyspnea at 72◦
- Pts in **High Dose group** were **less dyspneic** at 72◦

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

DIURETICS

- A higher percentage of pts in the High Dose group experienced an increase in Creatinine > 0.3 mg/dl

Table 2. Secondary End Points for Each Treatment Comparison.*

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DIURETICS

- High Dose group also associated with greater weight loss & net fluid loss
- Trend towards greater reduction in NT-pro BNP

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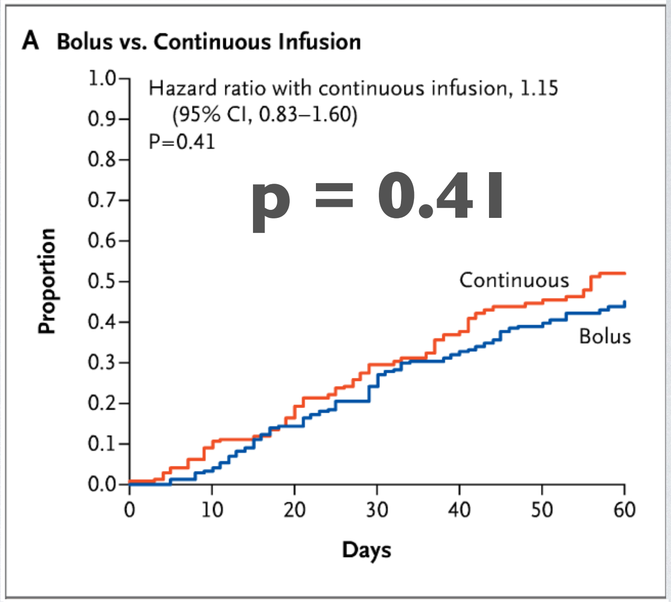
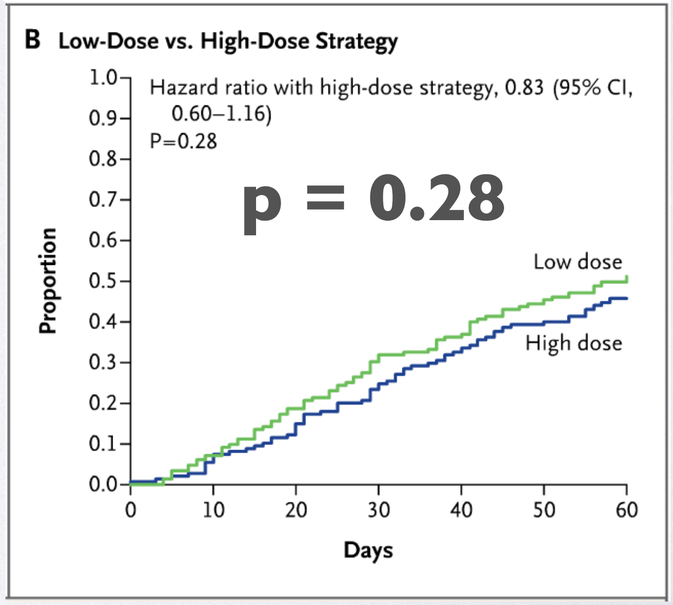
DIURETICS

- **No difference in composite endpoints of Death, Rehospitalization or ED visit** in the Bolus vs Continuous infusion group

- **No difference in composite endpoints of Death, Rehospitalization or ED visit** in the Low dose vs High dose diuretic group





ARMAMENTARIUM

- Diuretics
- Ultrafiltration
- Vasodilators
- Inotropes
- Arginine Vasopressor Antagonists
- Mechanical Circulatory Support*

Ultrafiltration

Ultrafiltration

Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight. Class IIb. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

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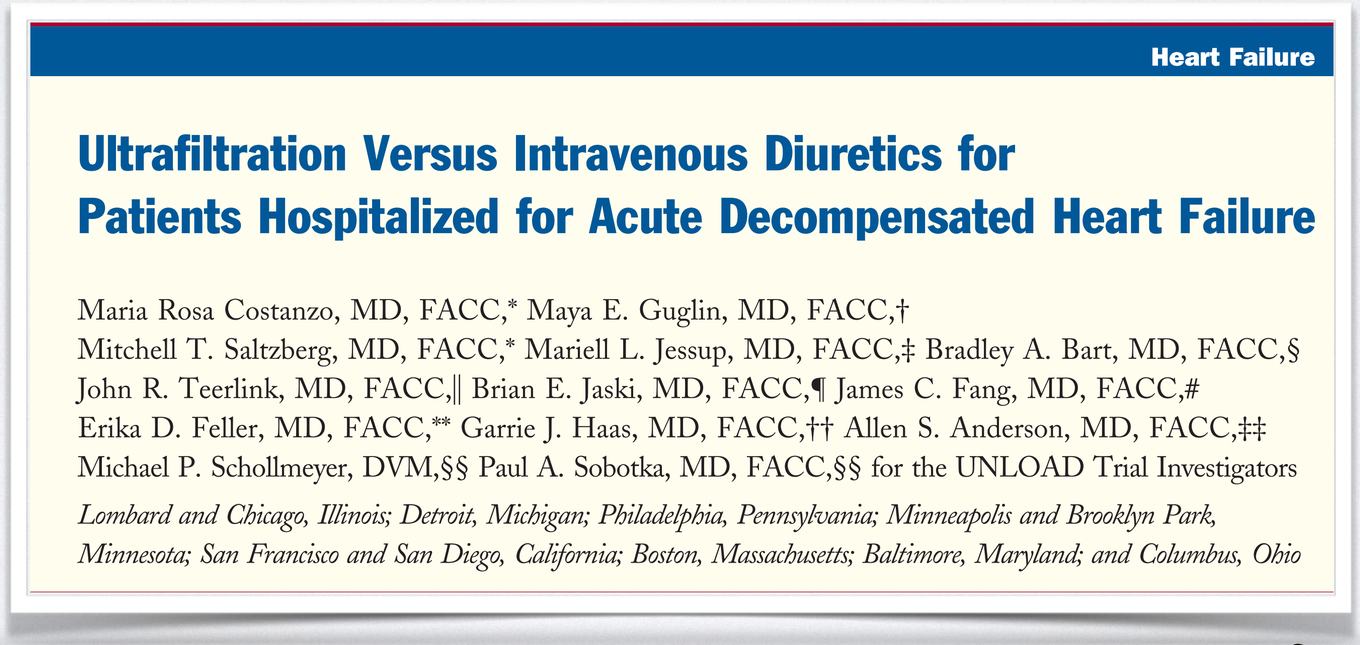


Heart Failure

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

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

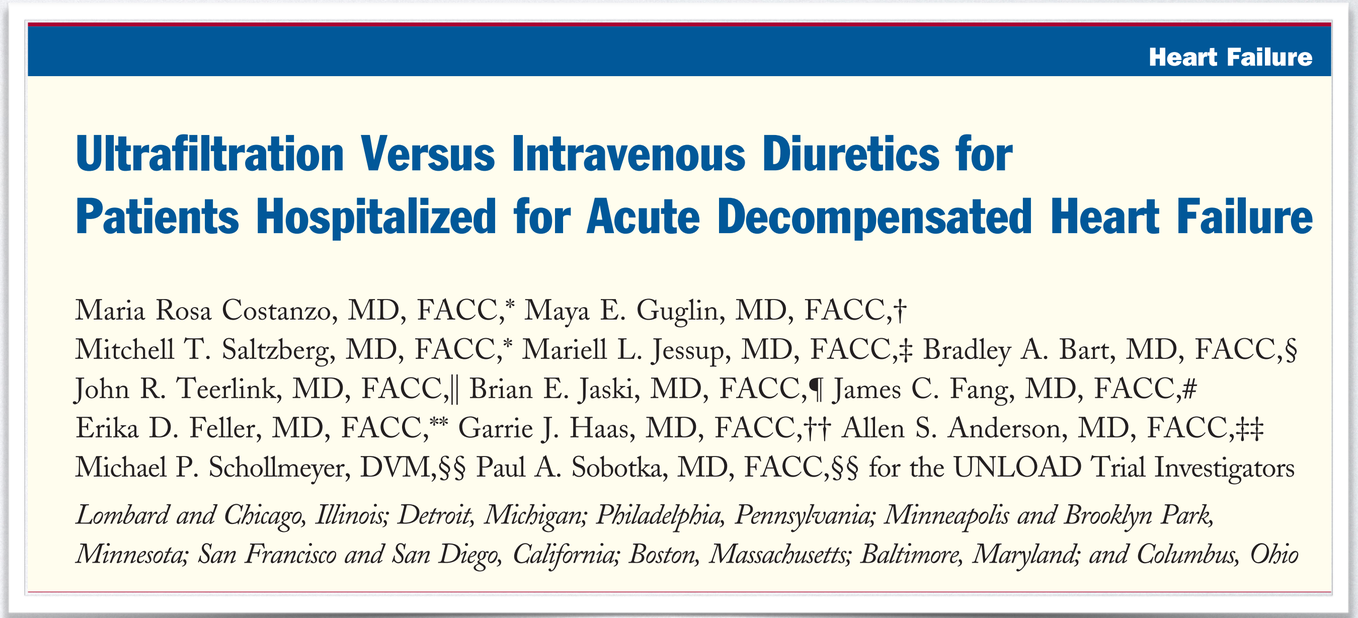
Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

Costanzo MR, et al. J Am Coll Cardiol 2007;49:675–83
Yancey et al. JACC Vol. 62, No. 16, 2013

Ultrafiltration

Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight. Class IIb. Level of Evidence B

- UF associated with greater weight and fluid loss
- No difference in change in creatinine
- UF associated with lower ADHF readmission rates
- BUT…the diuretic regimen in the standard of care arm was not very robust



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Bart BA, et al. N Engl J Med 2012; 367: 2296-304
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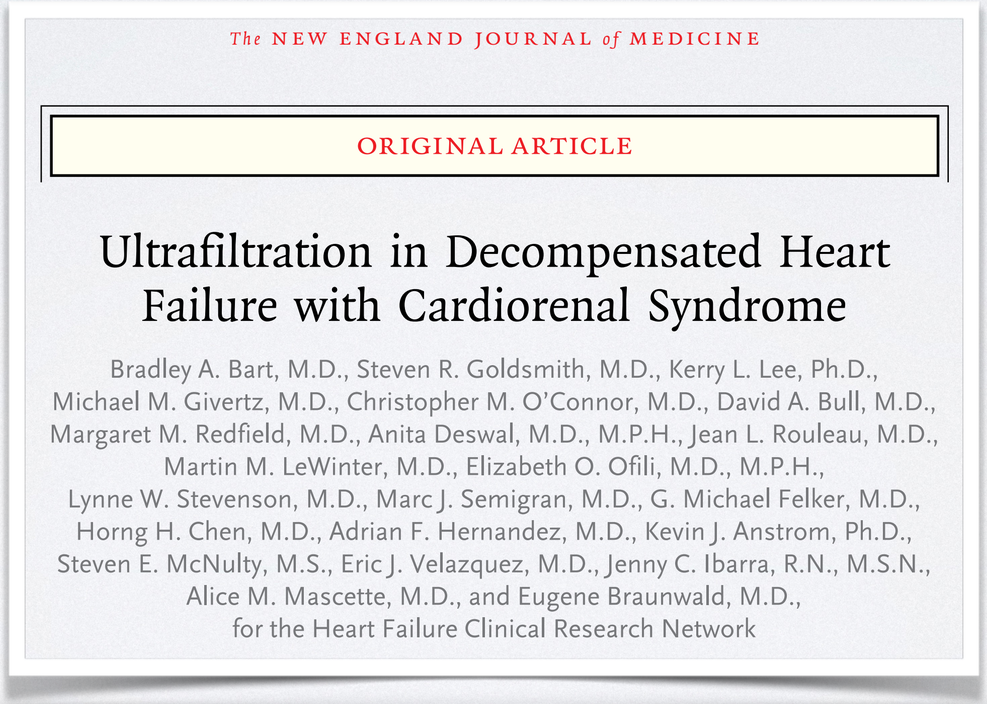

The NEW ENGLAND JOURNAL of MEDICINE

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

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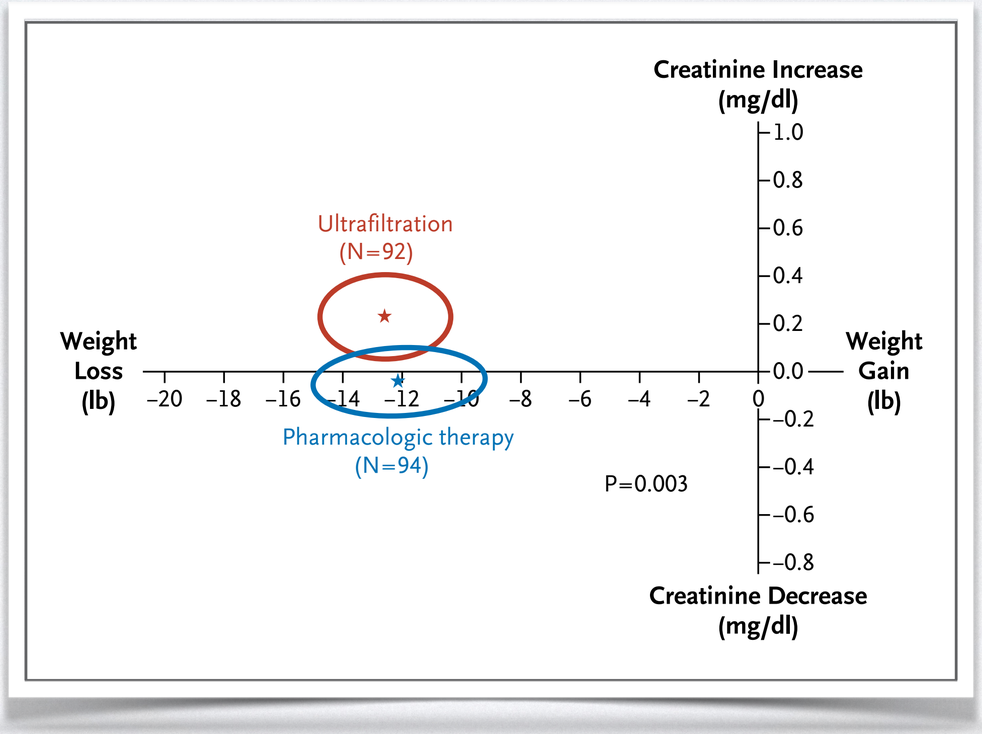

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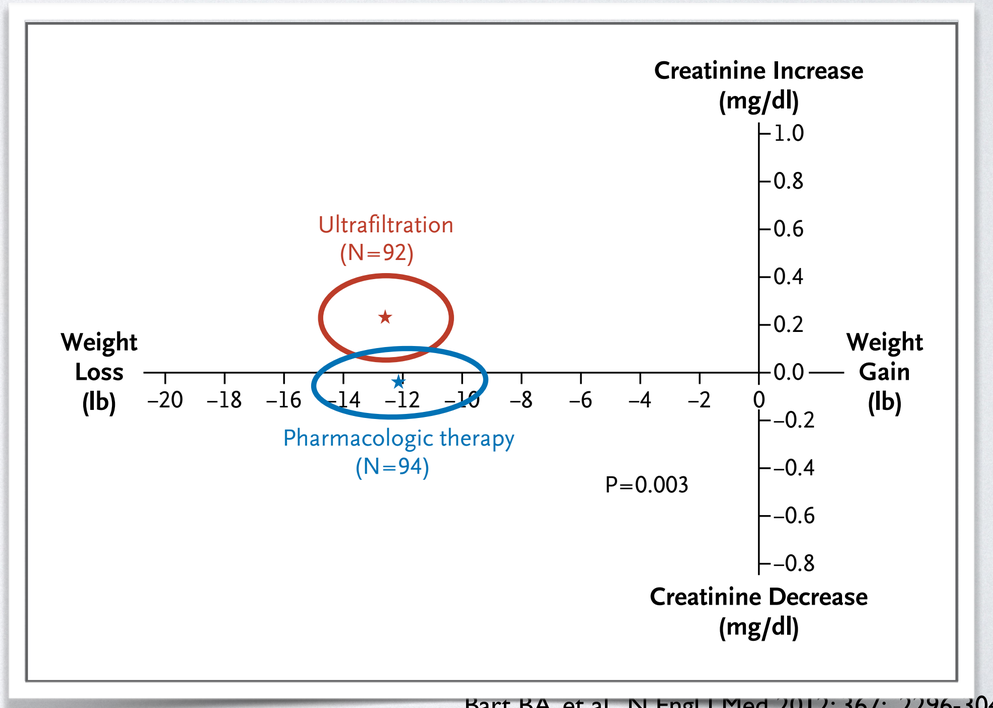
Table 2. Stepped-Care Pharmacologic Approach.*

Level	Furosemide			Metolazone†
	Previous Oral Dose‡	Bolus	Infusion Rate	Oral Dose
1	≤80 mg	40 mg	5 mg/hr	NA
2	81–160 mg	80 mg	10 mg/hr	5 mg daily
3	161–240 mg	80 mg	20 mg/hr	5 mg twice daily
4	>240 mg	80 mg	30 mg/hr	5 mg twice daily



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CARDIORENAL SYNDROME (TYPE I)

Acute worsening of heart function leading to kidney injury and/or dysfunction

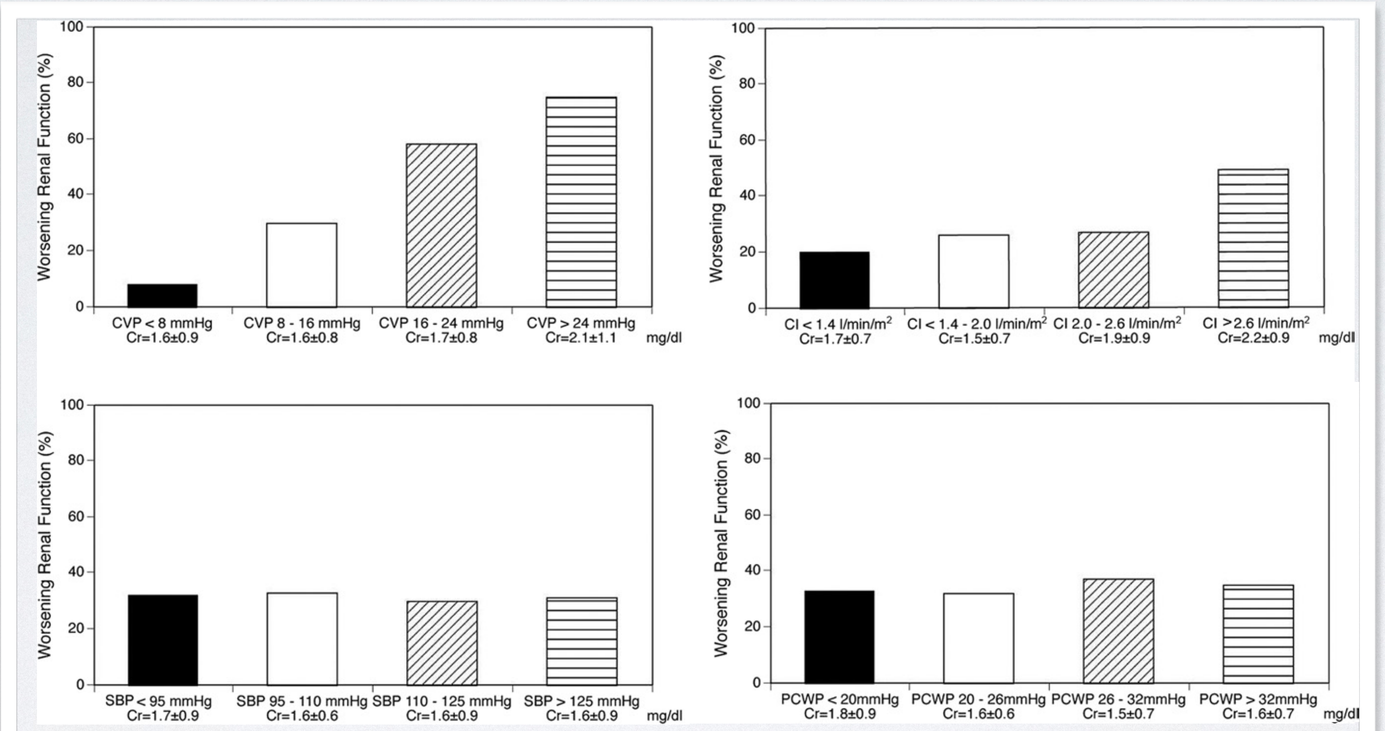

Figure 1 **Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP**

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

Mullens et al, JACC 2009 (53) 589-96

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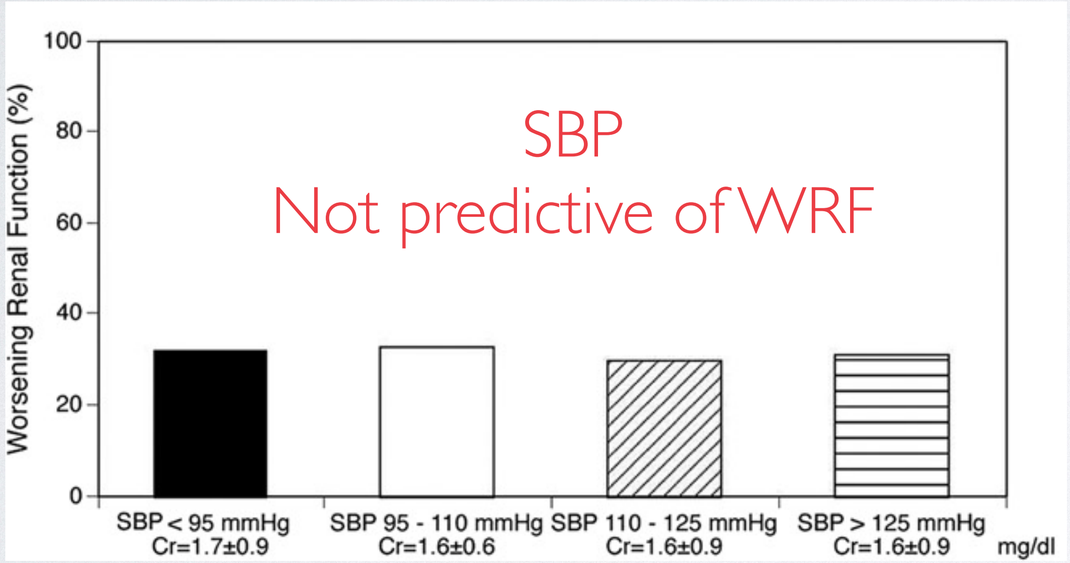

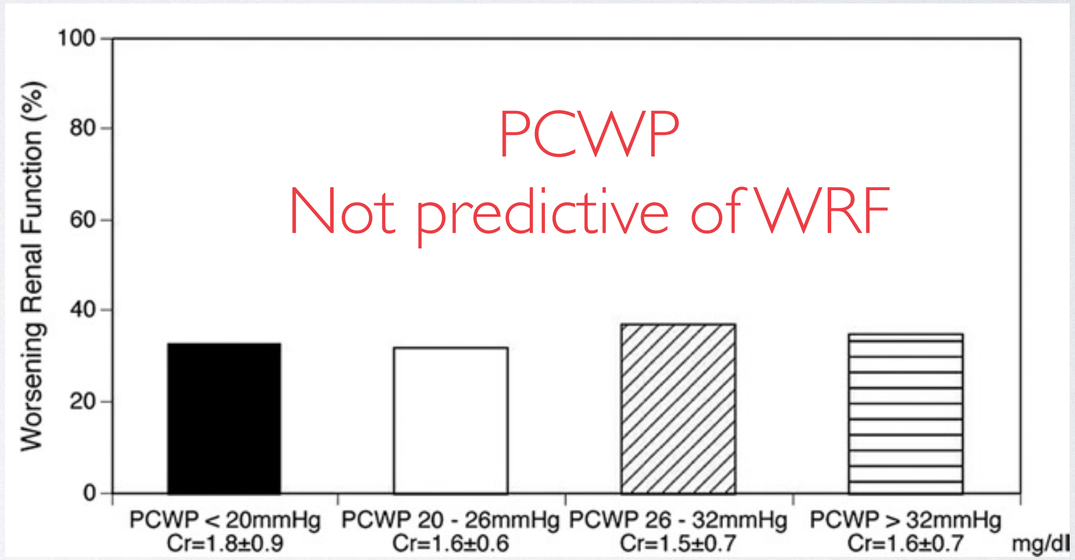

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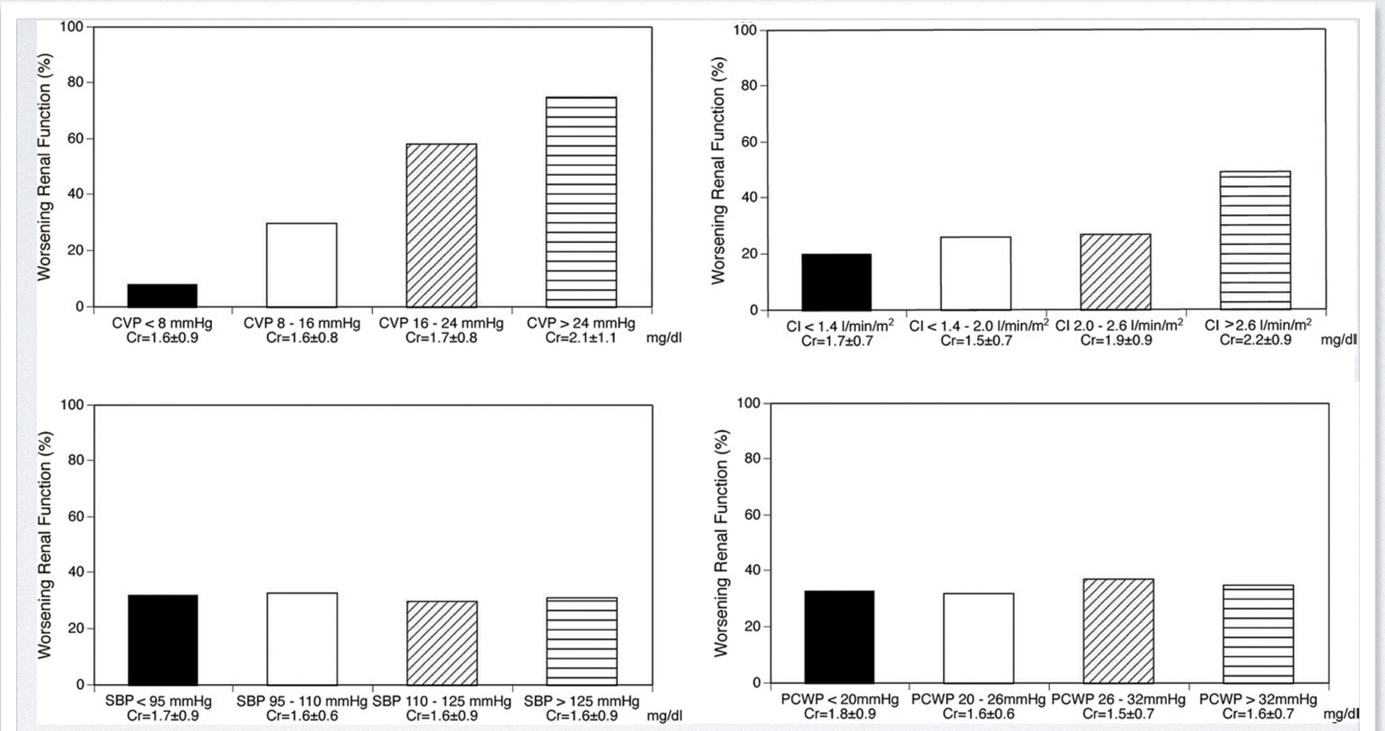

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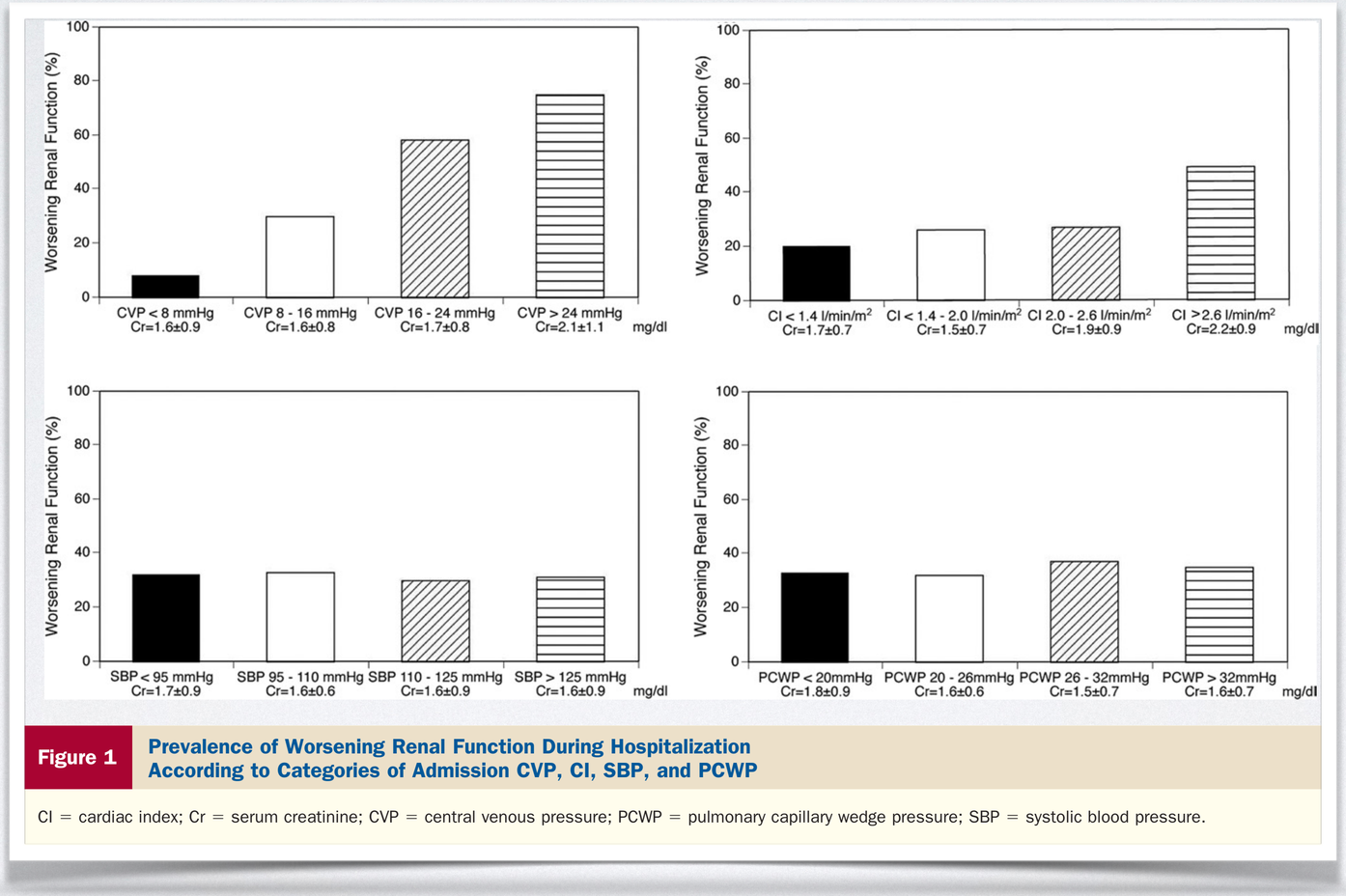

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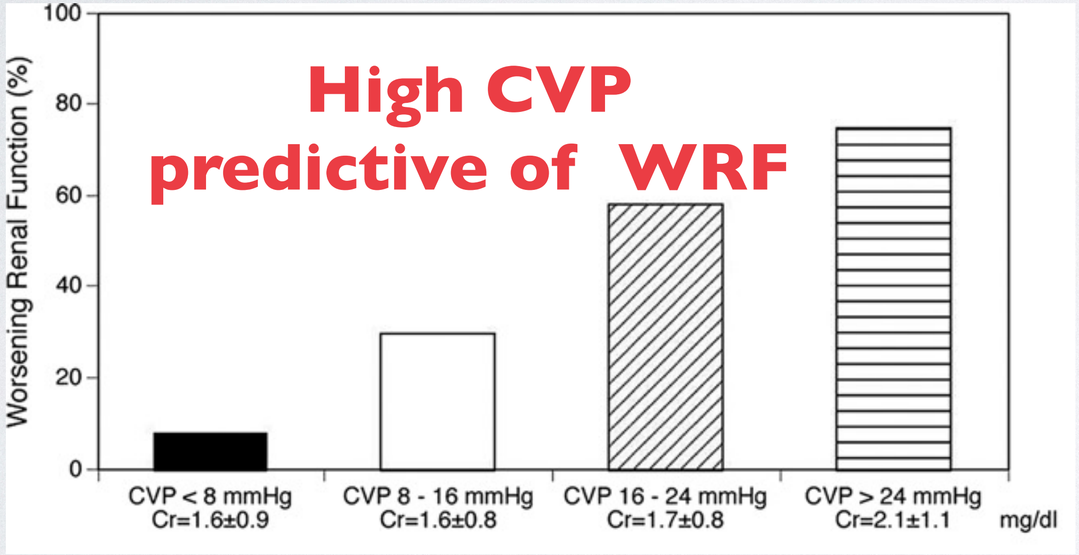

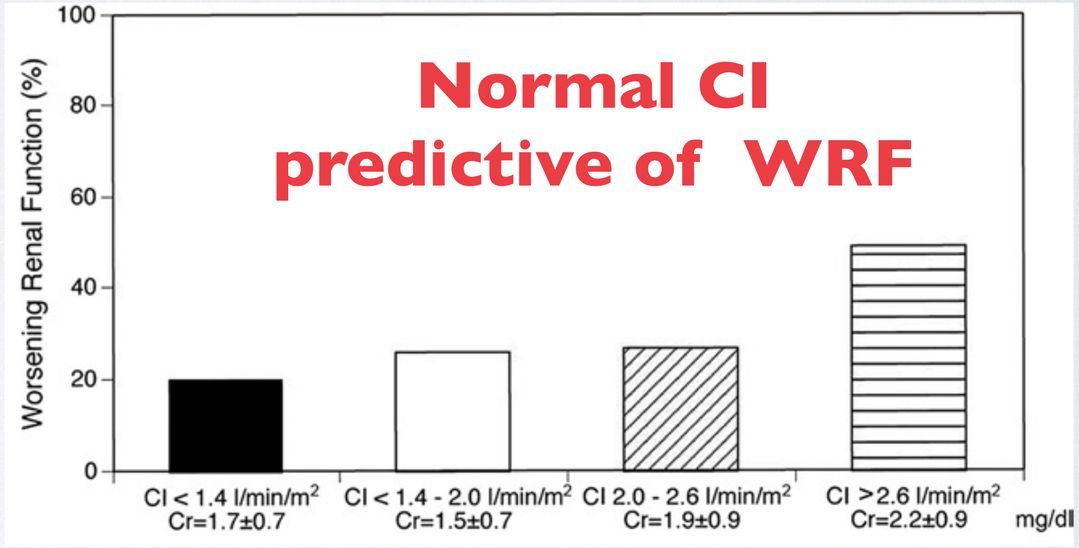

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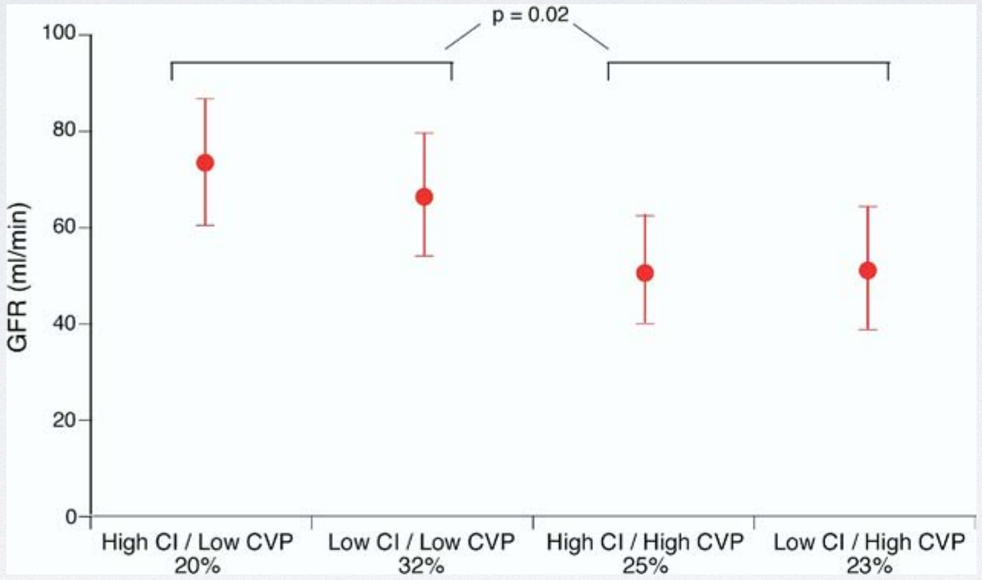

Figure 3 **Relative Contributions of CVP and CI to GFR at Time of PAC Removal**

Error bars represent 95% confidence intervals. Cutoff values for CI = 2.4 l/min/m^2 and CVP = 8 mm Hg. GFR = glomerular filtration rate; PAC = pulmonary artery catheter; other abbreviations as in Figure 1.

Mullens et al, JACC 2009 (53) 589-96

ARMAMENTARIUM

- Diuretics
- Ultrafiltration
- Vasodilators
- Inotropes
- Arginine Vasopressor Antagonists
- Mechanical Circulatory Support*

Vasodilators

Vasodilators

$$\textbf{Cardiac Output} = \frac{\textbf{MAP - CVP}}{\textbf{SVR}}$$

MAP = Mean Arterial Pressure
CVP = Central Venous Pressure
SVR = Systemic Vascular Resistance

Vasodilators

$$\textbf{Cardiac Output} = \frac{\textbf{MAP - CVP}}{\textbf{SVR}}$$

Cardiac Output and SVR are inversely proportional

MAP = Mean Arterial Pressure
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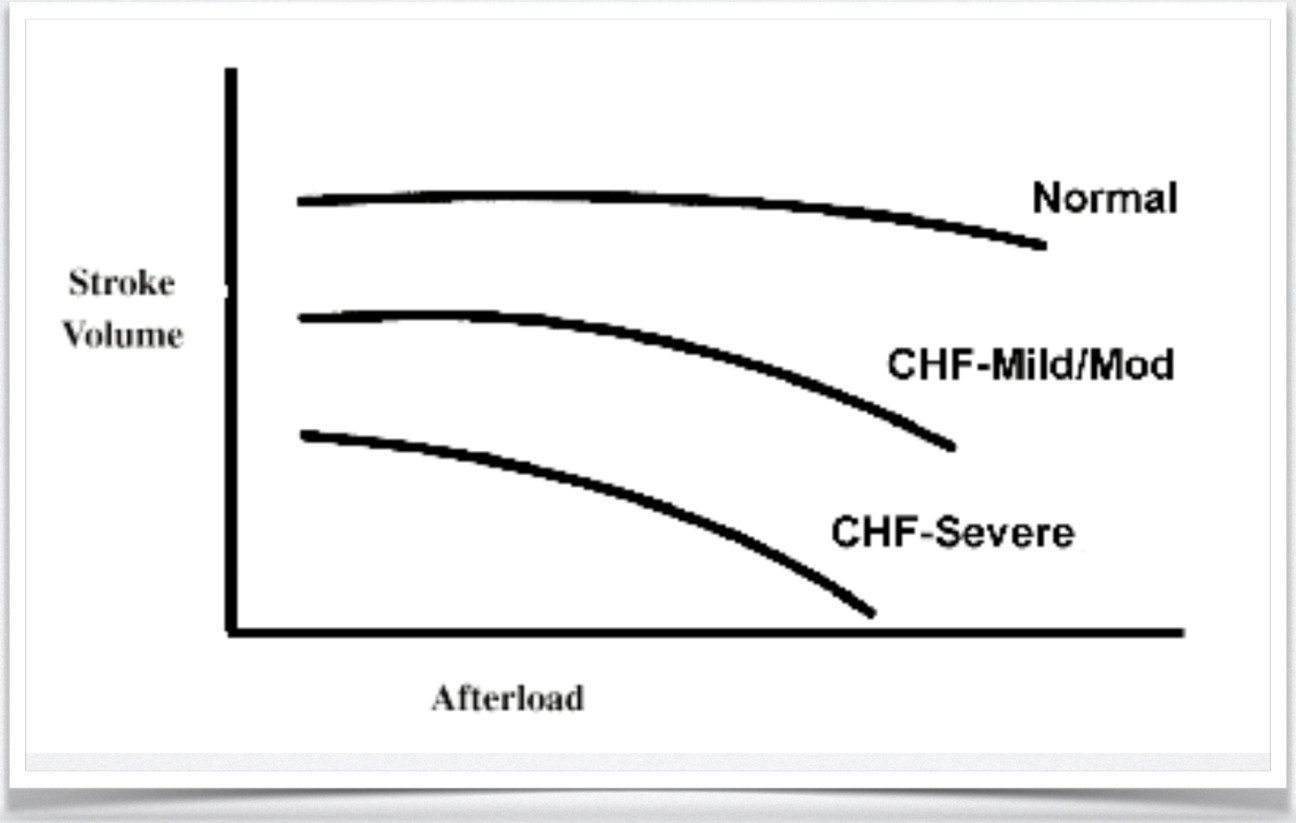
Vasodilators



Vasodilators

Hemodynamic Effects

- Lower mean PCWP
- Lower CVP
- Lower SVR
- Improved Cardiac output & Index

Vasodilators

If symptomatic hypotension is absent, IV Nitroglycerin, Nitroprusside, or ~~Nesiritide~~ may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with ADHF. Class IIb. Level of Evidence A

Yancey et al. JACC Vol. 62, No. 16, 2013

ARMAMENTARIUM

- Diuretics
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Inotropes

Inotropes

- Utilization rates vary from 0.9% to 44.6% across US Hospitals
- Frequent inappropriate usage (absence of hypoperfusion)
- Frequently associated with tachyarrhythmias
- Associated with increased mortality rates

Hemodynamic Effects of Inotropes

Table 26. Intravenous Inotropic Agents Used in Management of HF

Inotropic Agent	Dose (mcg/kg) Bolus	Dose (mcg/kg) Infusion (/min)	Drug Kinetics and Metabolism	Effects CO	Effects HR	Effects SVR	Effects PVR	Adverse Effects
Adrenergic agonists								
Dopamine	N/A	5 to 10	$t_{1/2}$: 2 to 20 min	↑	↑	↔	↔	T, HA, N, tissue necrosis
	N/A	10 to 15	R,H,P	↑	↑	↑	↔	
Dobutamine	N/A	2.5 to 5	$t_{1/2}$: 2 to 3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity
	N/A	5 to 20		↑	↑	↔	↔	
PDE inhibitor								
Milrinone	N/R	0.125 to 0.75	$t_{1/2}$: 2.5 h H	↑	↑	↓	↓	T, ↓BP

Yancey et al. JACC Vol. 62, No. 16, 2013

Inotropes

Short term continuous IV inotropic support may be reasonable in those hospitalized patients presenting with **documented severe systolic dysfunction** who present **with low BP and significantly depressed CO** to maintain systemic perfusion and preserve end organ performance. Class IIb. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

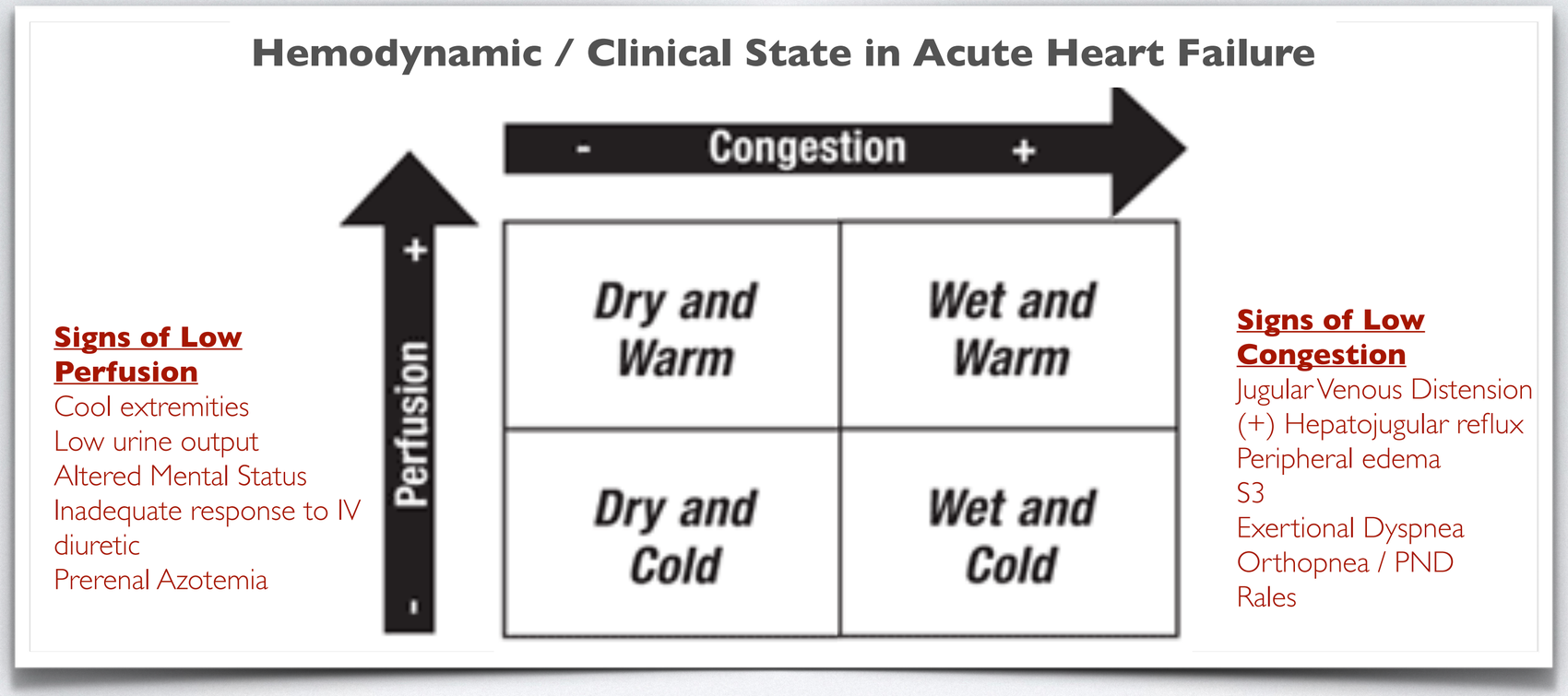
Inotropes

Use of parenteral inotropic agents in hospitalized patients **without documented severe systolic dysfunction**, **low blood pressure**, or **impaired perfusion** and evidence of significantly **depressed cardiac output**, with or without congestion, is **potentially harmful**.

Class III. Level of Evidence B

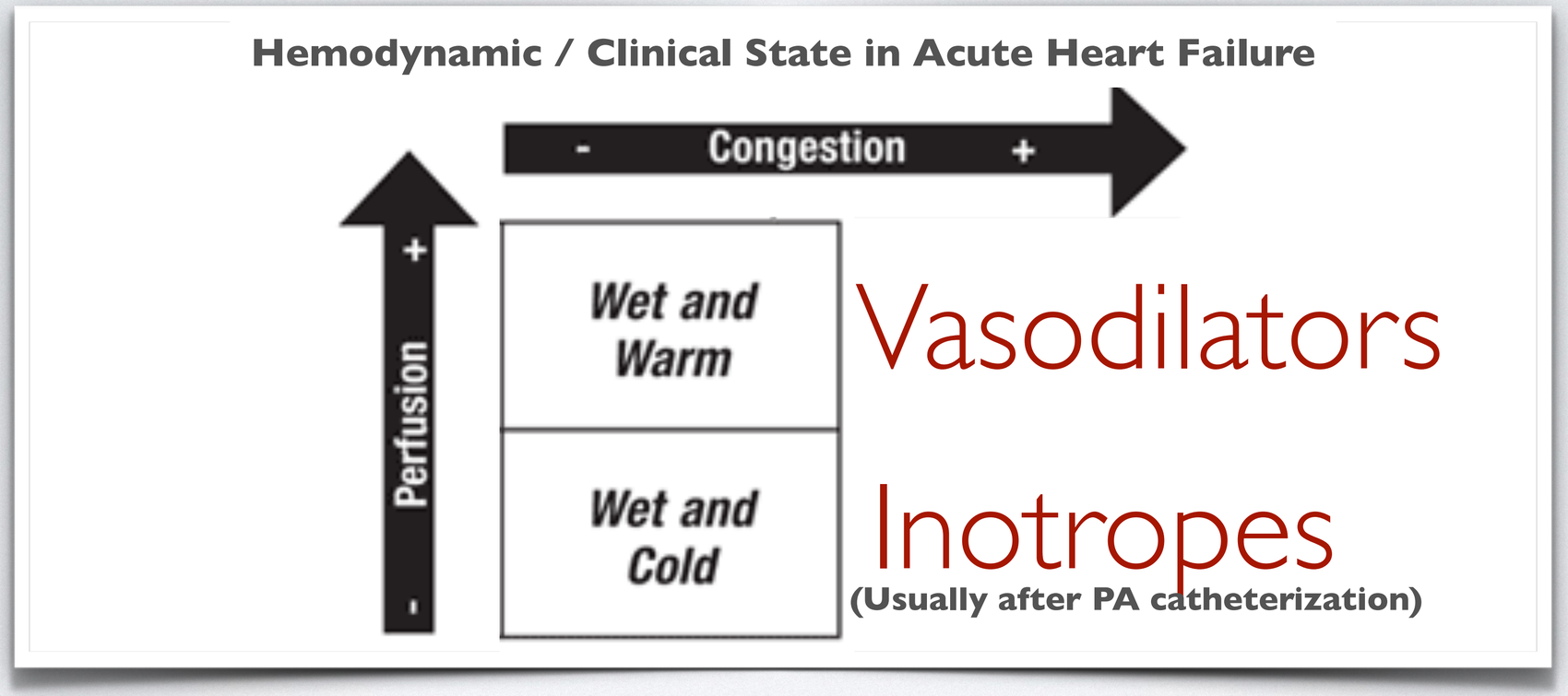
Yancey et al. JACC Vol. 62, No. 16, 2013

Vasodilators or Inotropes?



Nordeen JD, et al. US Pharm. 2010;35(2):HS8-HS19

Vasodilators or Inotropes?



Nordeen JD, et al. US Pharm. 2010;35(2):HS8-HS19

ARMAMENTARIUM

- Diuretics
- Ultrafiltration
- Vasodilators
- Inotropes
- Arginine Vasopressor Antagonists
- Mechanical Circulatory Support*

Arginine Vasopressor Antagonists

Arginine Vasopressor Antagonists

In patients hospitalized with volume overload, including HF, who have **persistent severe hyponatremia** and are at risk for or having active **cognitive symptoms despite water restriction and maximization of GDMT**, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V2 receptor selective or a non-selective vasopressin antagonist. Class IIb. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

Maintenance of Guideline Directed Medical Therapy

Maintenance of Guideline Directed Medical Therapy

In patients with HFrEF experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with GDMT, it is **recommended that GDMT be continued** in the absence of hemodynamic instability or contraindications. Class I. Level of Evidence B

Yancey et al. JACC Vol. 62, No. 16, 2013

Maintenance of Guideline Directed Medical Therapy

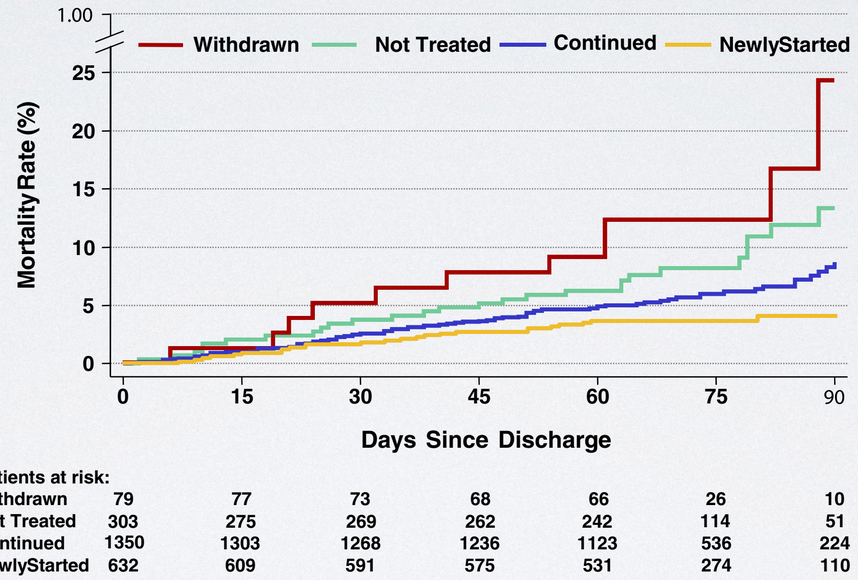


Figure 1 **Post-Discharge Survival by Beta-Blocker Treatment Groups**

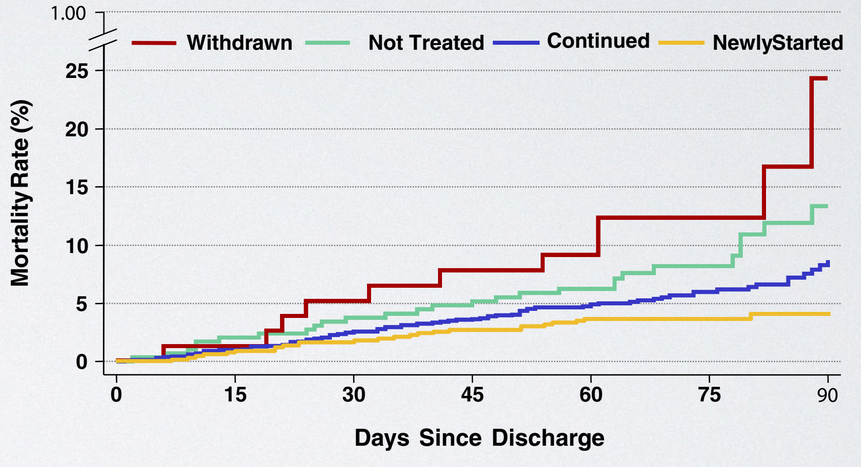
Kaplan-Meier survival curves by beta-blocker treatment groups. Log-rank test: $p < 0.001$.

Fonarow G, et al. JACC 2008; 52:190-9

Maintenance of Guideline Directed Medical Therapy

60-90 day post discharge mortality

B-blocker withdrawn: 24.4%
Not treated with B-blocker: 13.8%
B-blocker continued: 8.7%
Newly started B-blocker: 4.5%



Patients at risk:

Withdrawn	79	77	73	68	66	26	10
Not Treated	303	275	269	262	242	114	51
Continued	1350	1303	1268	1236	1123	536	224
NewlyStarted	632	609	591	575	531	274	110

Figure 1 **Post-Discharge Survival by Beta-Blocker Treatment Groups**

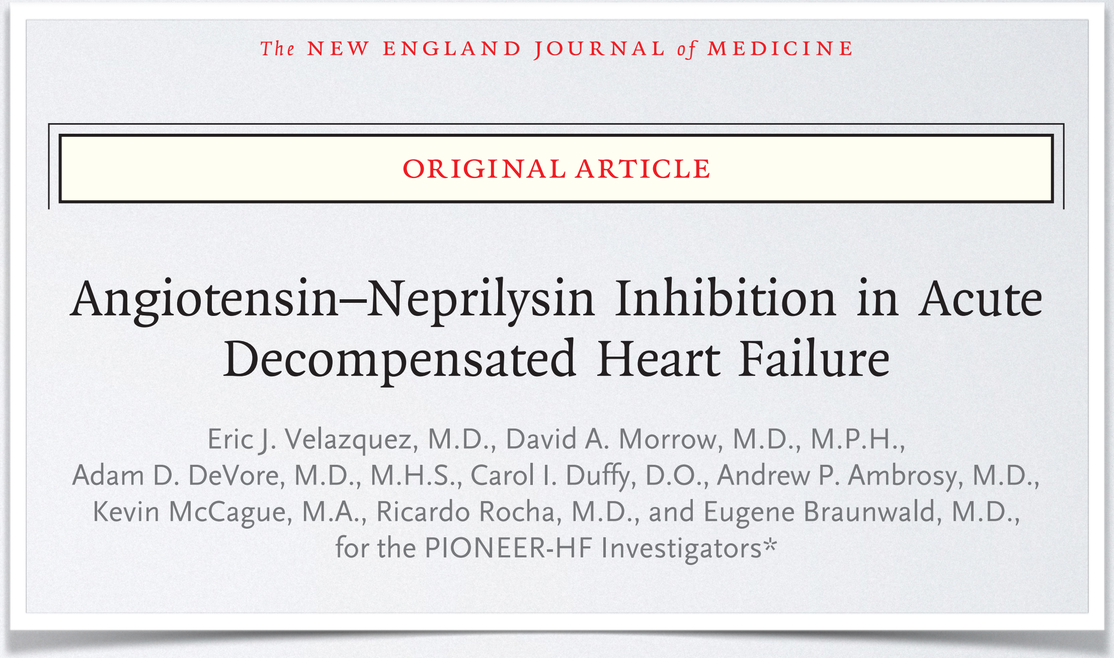
Kaplan-Meier survival curves by beta-blocker treatment groups. Log-rank test: $p < 0.001$.

Fonarow G, et al. JACC 2008; 52:190-9

Guideline Directed Medical Therapy During ADHF

PIONEER-HF Trial

- Multicenter, randomized, double blind trial
- 881 patients (HFrEF) admitted with ADHF
- Entresto (440) vs Enalapril (441)
- 1° efficacy outcome time averaged proportional change in the NT-pro BNP from baseline through weeks 4 and 8



Velazquez EJ, et al. N Engl J Med 2019;380:539-48

Guideline Directed Medical Therapy During ADHF

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- 881 patients (HFrEF) admitted with ADHF
- Entresto (440) vs Enalapril (441)
- 1° efficacy outcome time averaged proportional change in the NT-pro BNP from baseline through weeks 4 and 8
- Data supports initiation of Entresto prior to discharge

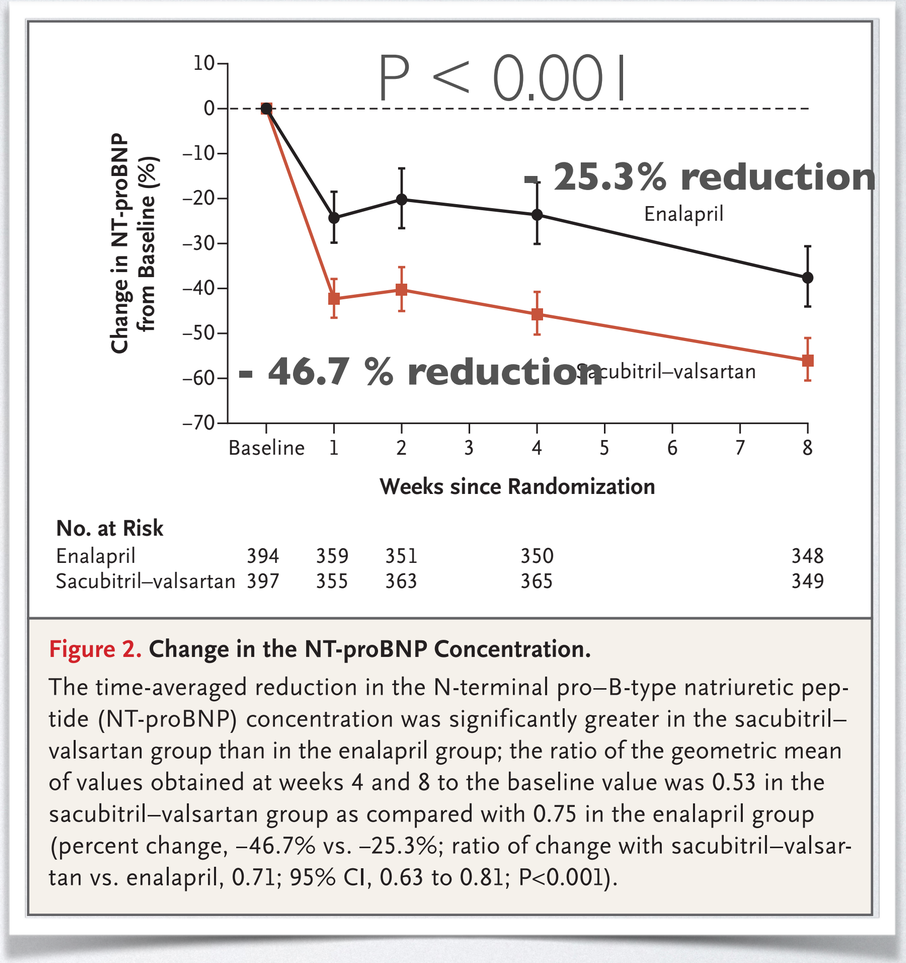


Figure 2. Change in the NT-proBNP Concentration.

The time-averaged reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs. −25.3%; ratio of change with sacubitril–valsartan vs. enalapril, 0.71; 95% CI, 0.63 to 0.81; P<0.001).

Velazquez EJ, et al. N Engl J Med 2019;380:539-48

Biomarkers During HF Hospitalization

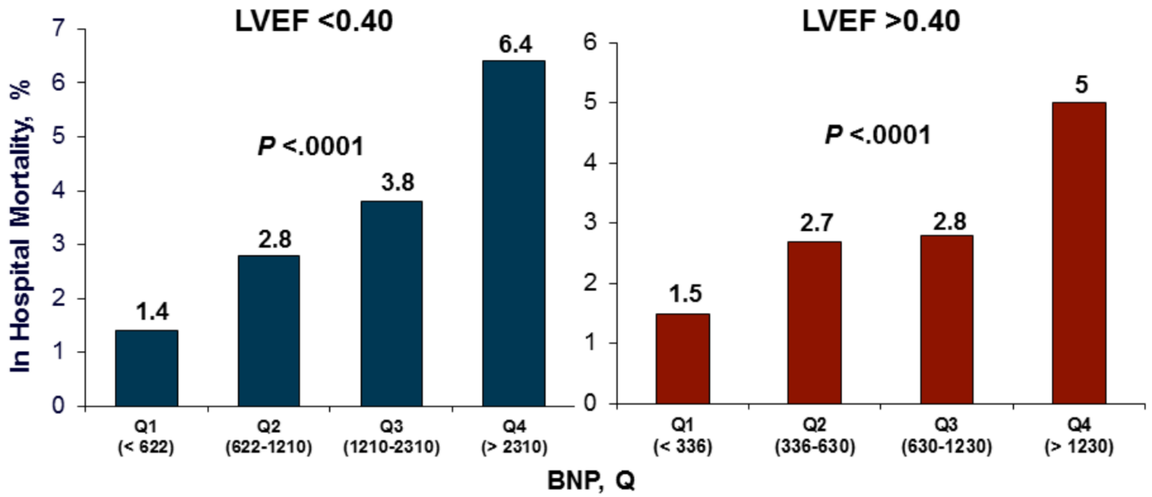
Biomarkers During HF Hospitalization

Measurement of **baseline levels** of natriuretic peptide biomarkers and/or cardiac troponin **on admission** to the hospital is useful to establish a prognosis in acutely decompensated HF. Class I. Level of Evidence I

Yancey et al. JACC Vol. 70, No. 6, 2017

Biomarkers During HF Hospitalization

In-Hospital Mortality Risk by Initial BNP Levels Reduced vs Preserved Systolic Function HF



- 48,629 (63%) of 77,467 patient episodes had BNP assessment at initial evaluation
- ADHERE Q2 2003 to Q4 2004

Fonarow GC, et al. *J Am Coll Cardiol.* 2007;49:1943-1950.

Biomarkers During HF Hospitalization

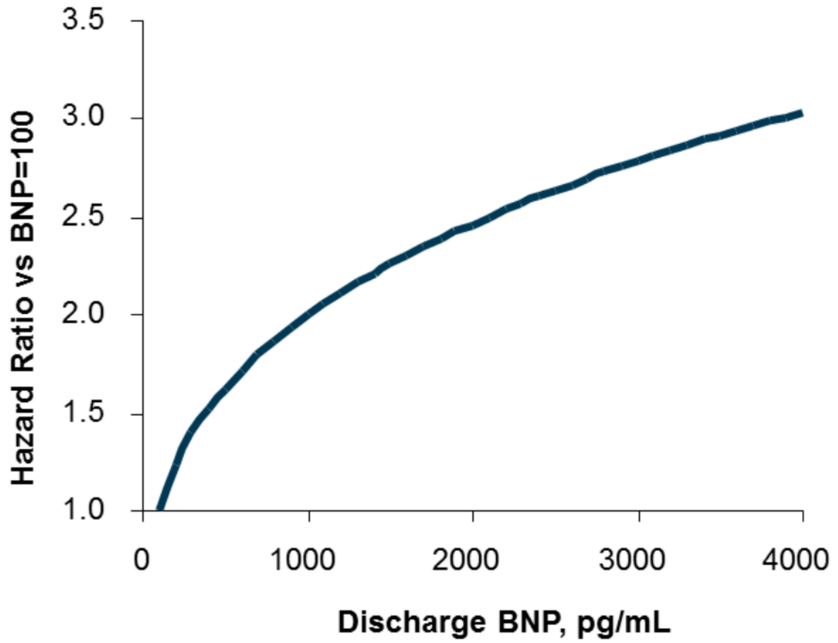
During a HF hospitalization, a **predischarge natriuretic peptide** level can be useful to establish a **postdischarge prognosis.**

Class IIa. Level of Evidence B-NR

Yancey et al. JACC Vol. 70, No. 6, 2017

Biomarkers During HF Hospitalization

Relationships Between Discharge BNP and Outcomes Are Curvilinear



Kociol RD. et al. *Circ Heart Fail*. 2011:4:628-636.

Preventing Heart Failure Readmissions

Preventing Heart Failure Readmissions

- Biomarkers
- Hospital to Home Initiatives
- Comprehensive Med Reconciliation
- Mandatory post-discharge HF clinic visit
- Telemonitoring & Home Based Care
- Scheduled Pre-Discharge appointment
- Process Mapping

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Percutaneously implanted PA sensor

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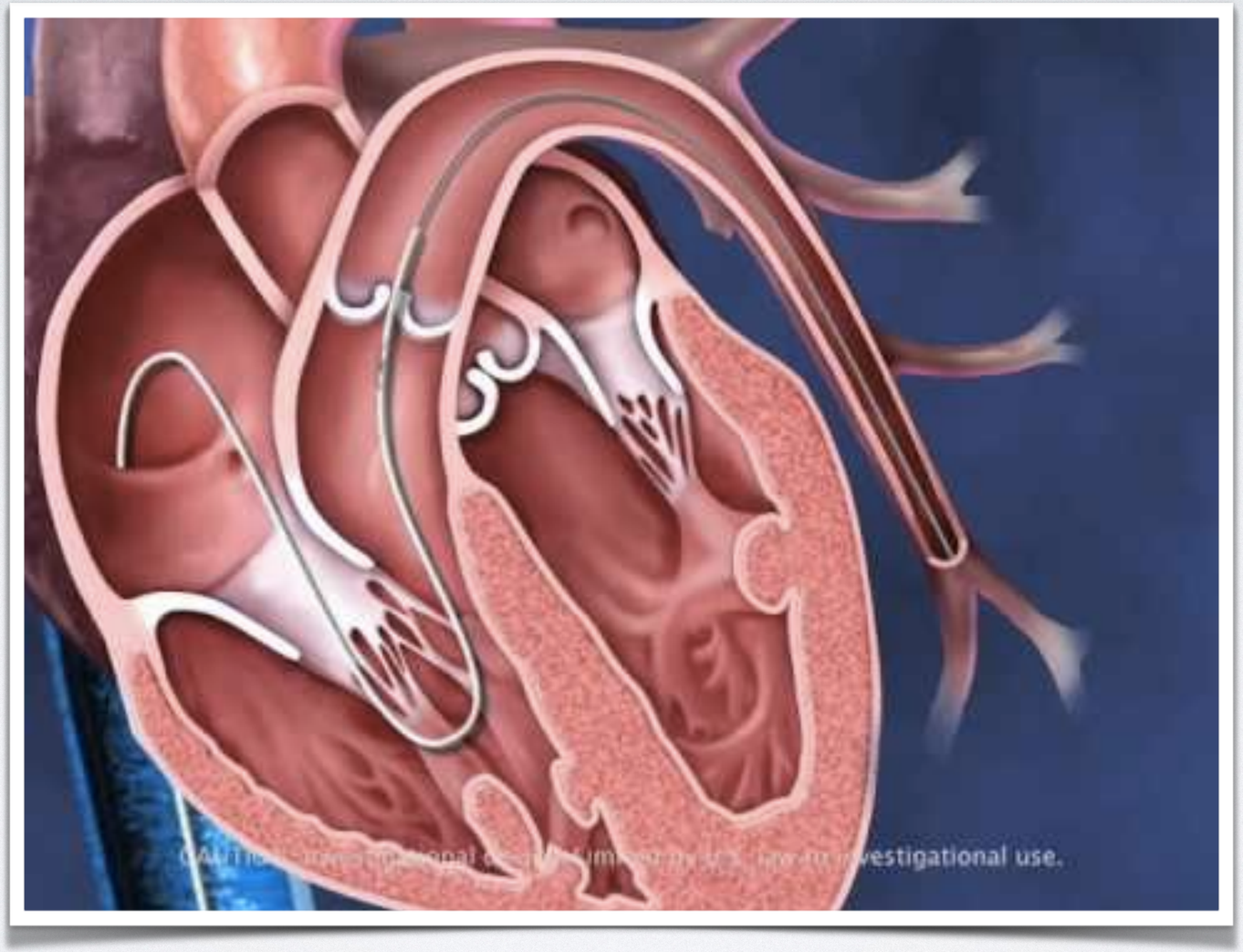

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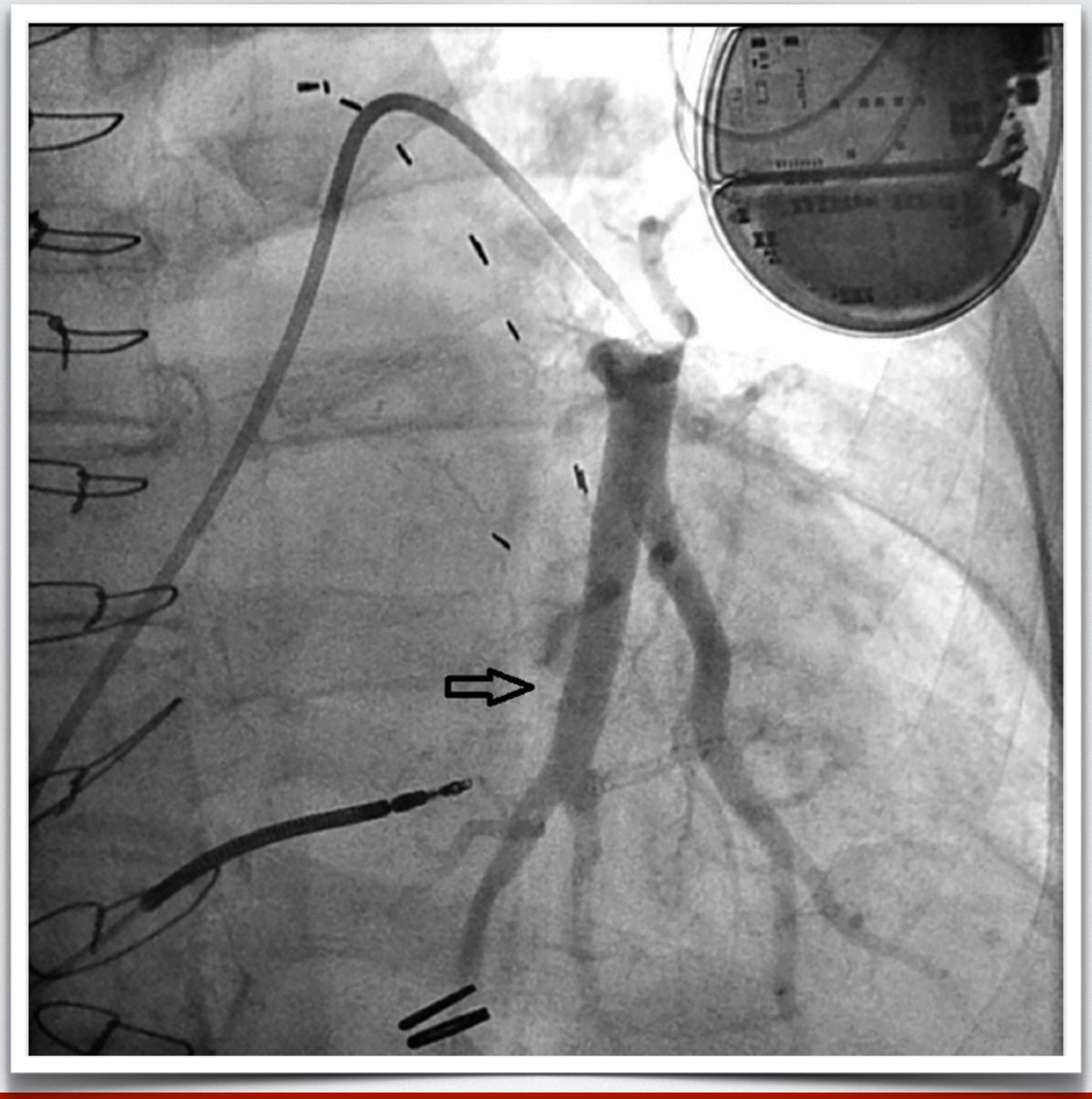

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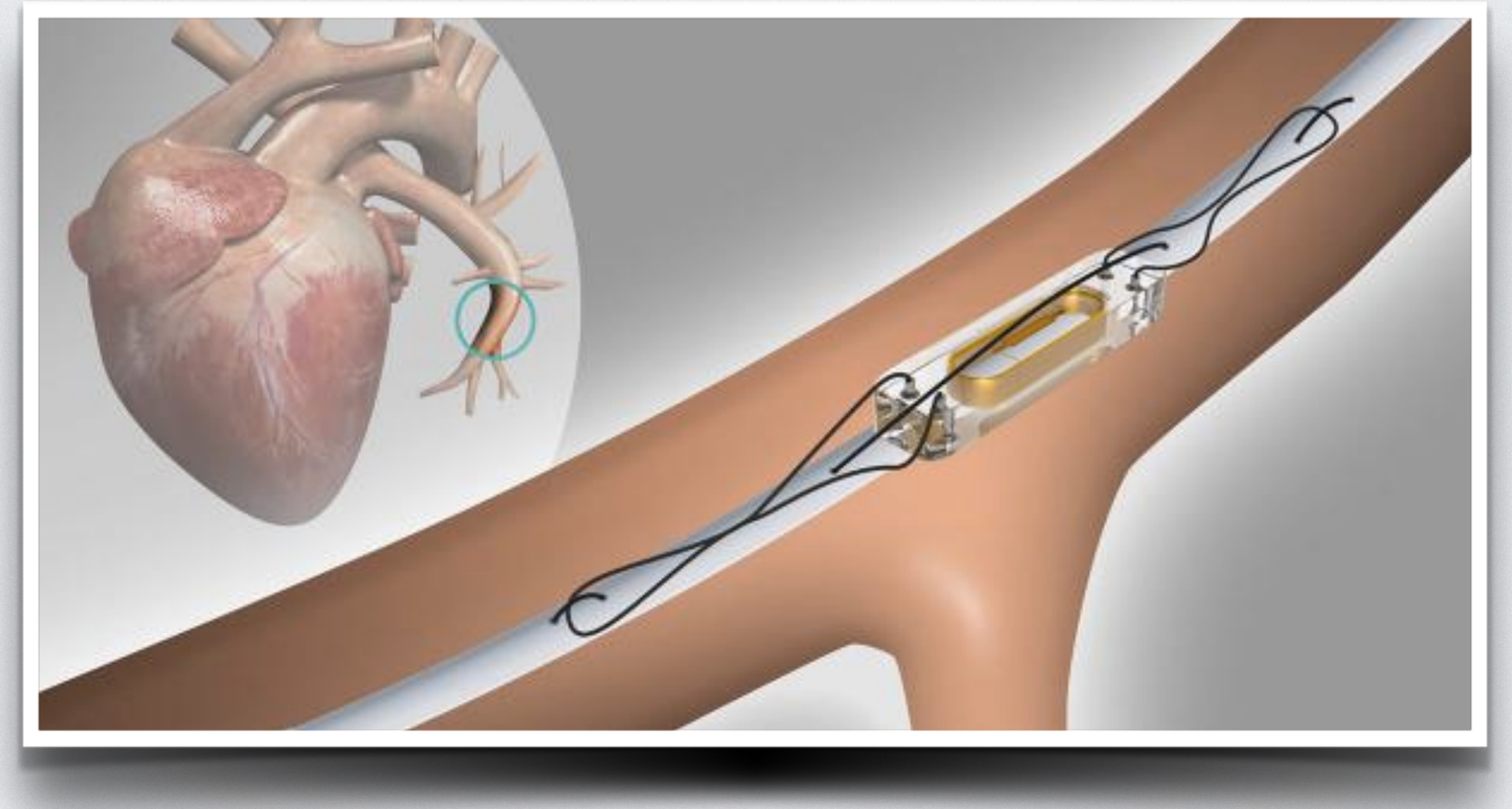

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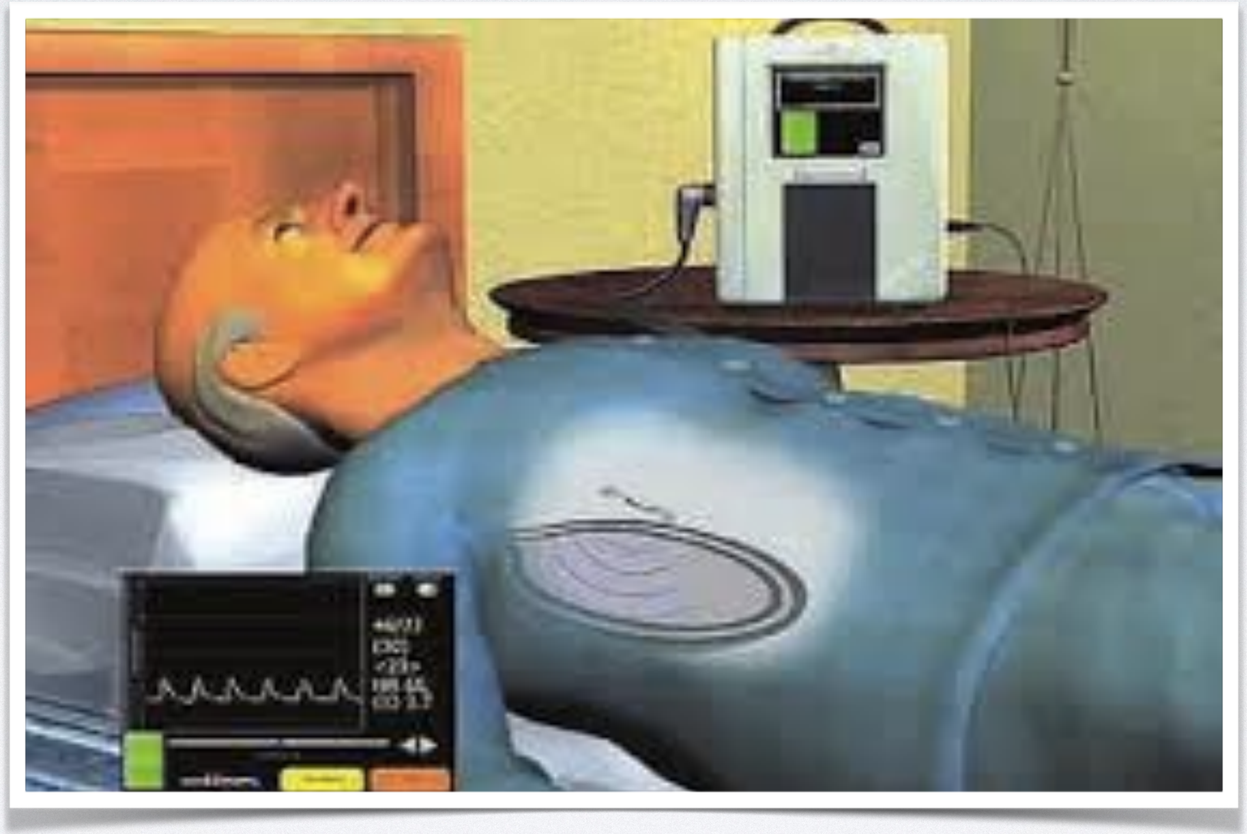

CardioMEMS

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CHAMPION Trial

- Randomized single blinded study
- 550 NYHA III HF pts (HFpEF&HFrEF)
- PA pressure guided vs Usual Care
- 1° efficacy endpt: HF admission at 6 months

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group*

Summary

Background Results of previous studies support the hypothesis that implantable haemodynamic monitoring systems might reduce rates of hospitalisation in patients with heart failure. We undertook a single-blind trial to assess this approach.

Methods Patients with New York Heart Association (NYHA) class III heart failure, irrespective of the left ventricular ejection fraction, and a previous hospital admission for heart failure were enrolled in 64 centres in the USA. They were randomly assigned by use of a centralised electronic system to management with a wireless implantable haemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. Only patients were masked to their assignment group. In the treatment group, clinicians used daily measurement of pulmonary artery pressures in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was the rate of heart-failure-related hospitalisations at 6 months. The safety endpoints assessed at 6 months were freedom from device-related or system-related complications (DSRC) and freedom from pressure-sensor failures. All analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00531661.

Findings In 6 months, 84 heart-failure-related hospitalisations were reported in the treatment group (n=270) compared with 120 in the control group (n=280; rate 0·32 *vs* 0·44, hazard ratio [HR] 0·72, 95% CI 0·60–0·85, p=0·0002). During the entire follow-up (mean 15 months [SD 7]), the treatment group had a 37% reduction in heart-failure-related hospitalisation compared with the control group (158 *vs* 254, HR 0·63, 95% CI 0·52–0·77; p<0·0001). Eight patients had DSRC and overall freedom from DSRC was 98·6% (97·3–99·4) compared with a prespecified performance criterion of 80% (p<0·0001); and overall freedom from pressure-sensor failures was 100% (99·3–100·0).

Interpretation Our results are consistent with, and extend, previous findings by definitively showing a significant and large reduction in hospitalisation for patients with NYHA class III heart failure who were managed with a wireless implantable haemodynamic monitoring system. The addition of information about pulmonary artery pressure to clinical signs and symptoms allows for improved heart failure management.

Abraham WT, et al. Lancet 2011; 377: 658–66

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CHAMPION Trial

- Randomized single blinded study
- 550 NYHA III HF pts (HFpEF&HFrEF)
- PA pressure guided vs Usual Care
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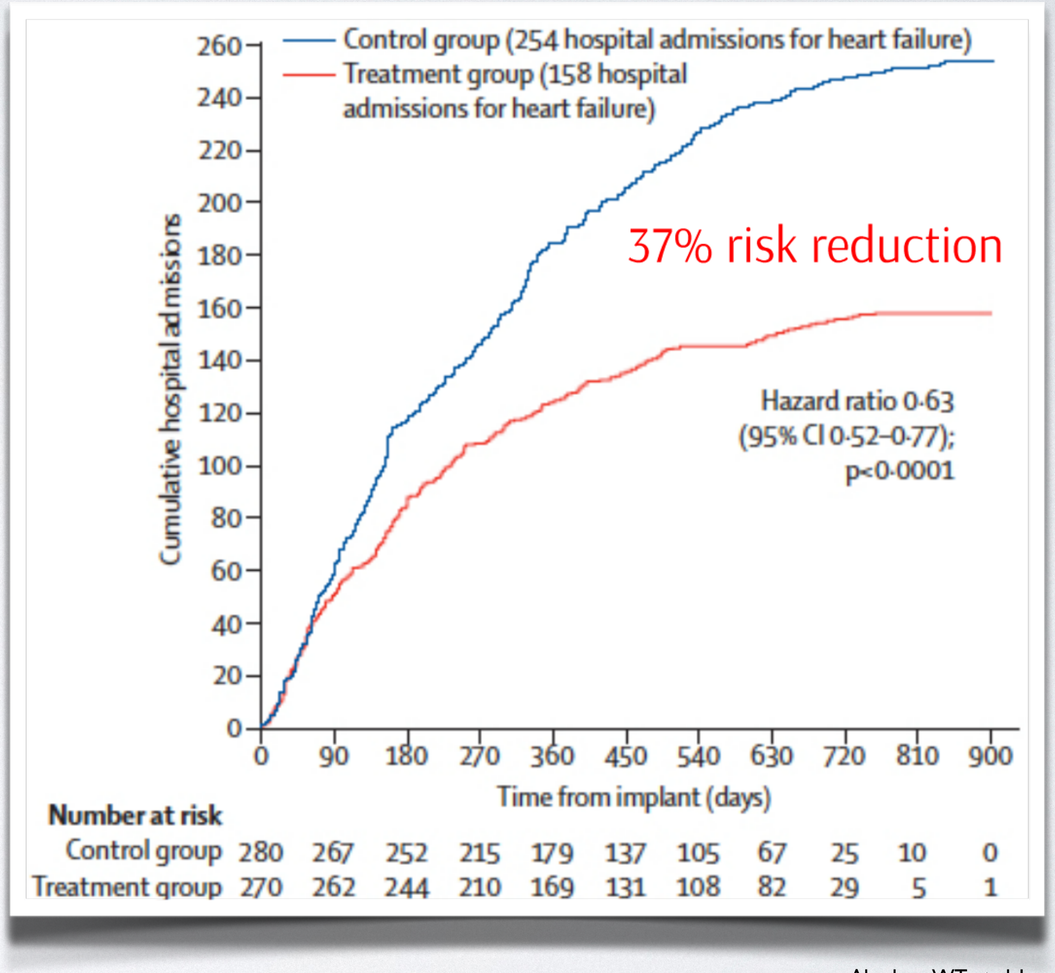

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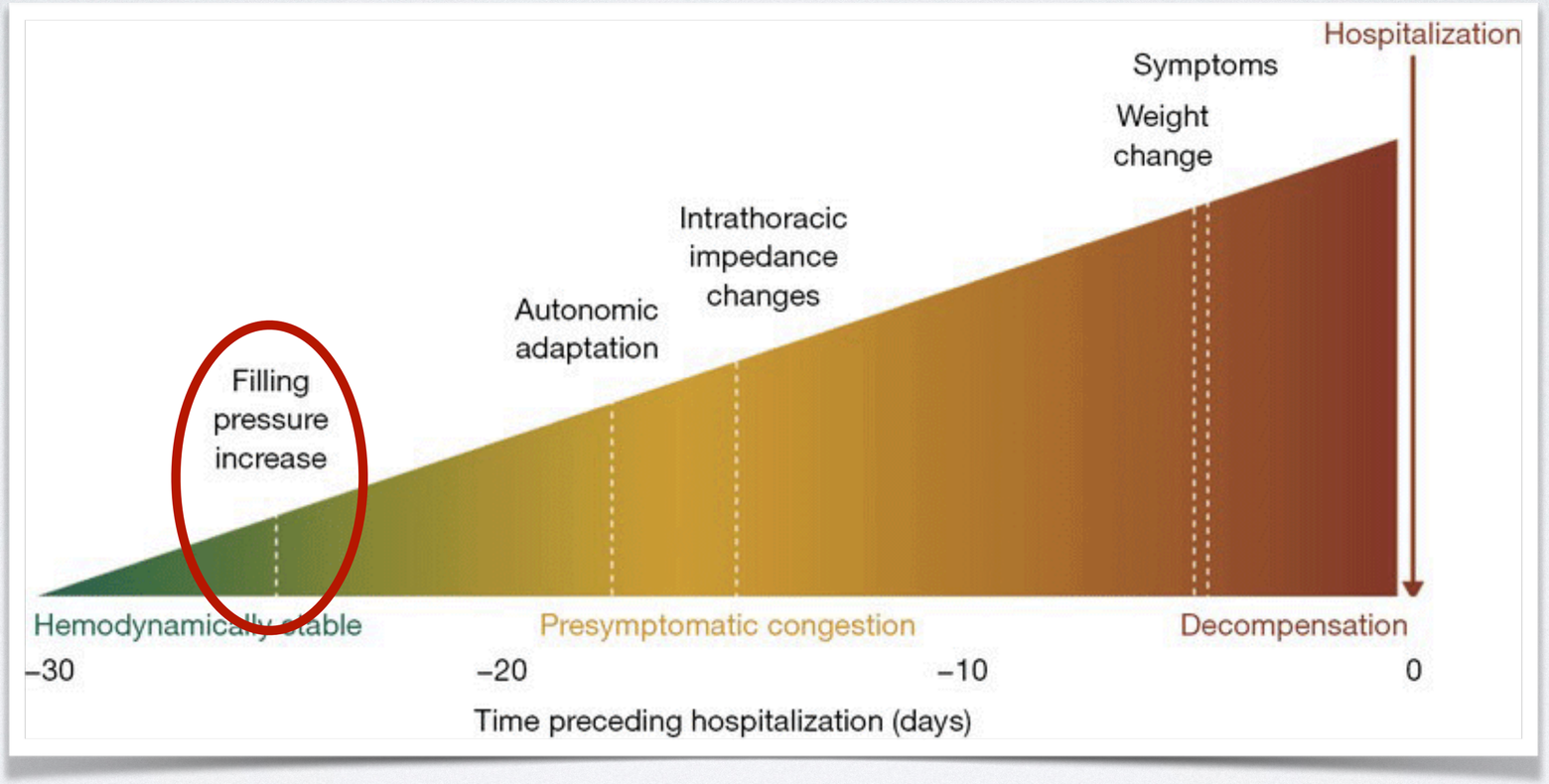
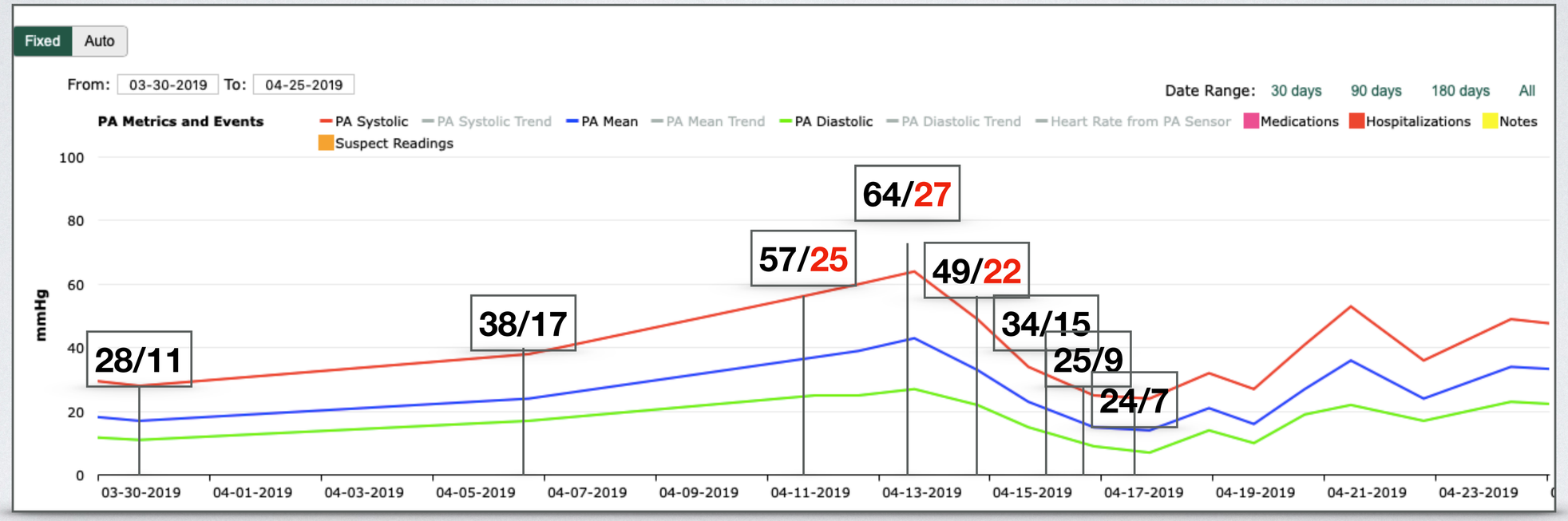

Hospitalization
Symptoms
Weight change
Intrathoracic impedance changes
Autonomic adaptation
Filling pressure increase
Hemodynamically stable
Presymptomatic congestion
Decompensation
–30
–20
–10
0
Time preceding hospitalization (days)

CardioMEMS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PA Systolic Trend
PA Mean
PA Mean Trend
PA Diastolic
PA Diastolic Trend
Heart Rate from PA Sensor
Medications
Hospitalizations
Notes
Suspect Readings
mmHg
100
80
60
40
20
0
28/11
38/17
57/25
64/27
49/22
34/15
25/9
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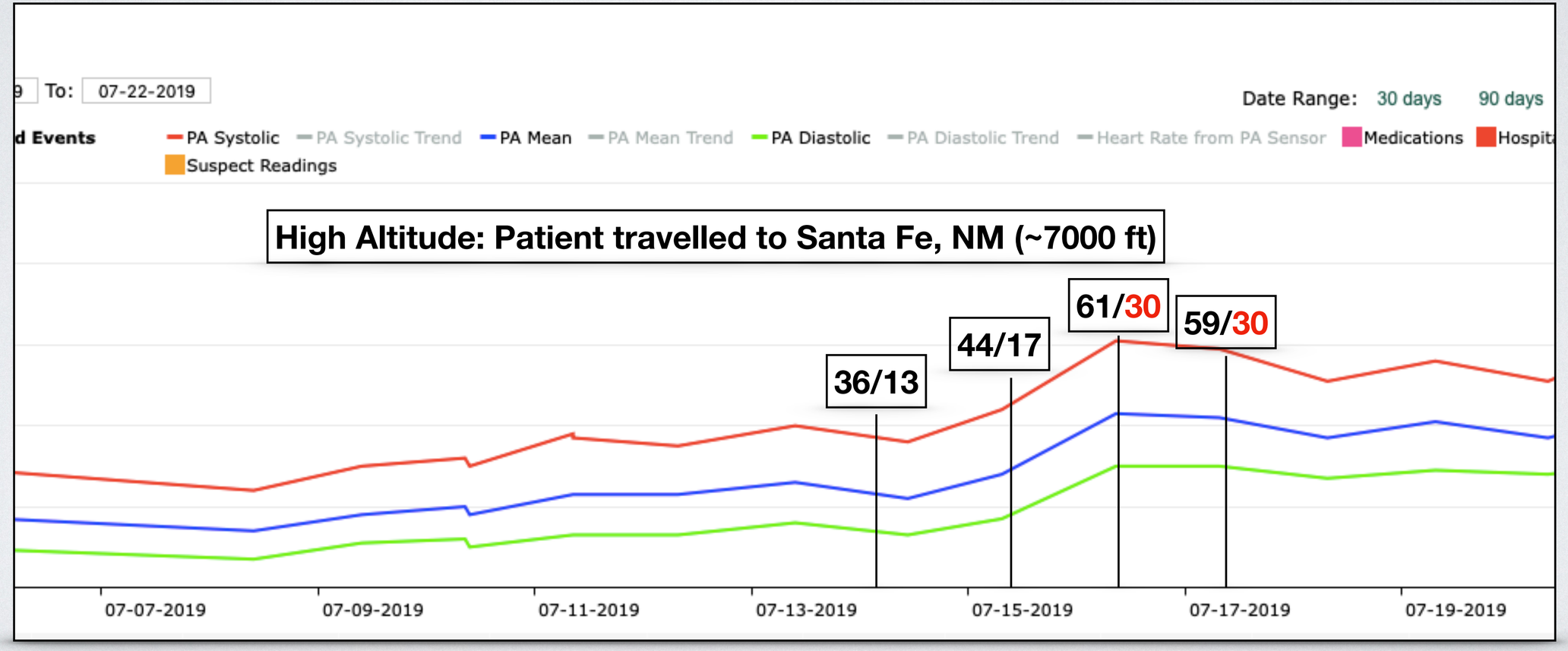
CardioMEMS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PA Systolic Trend
PA Mean
PA Mean Trend
PA Diastolic
PA Diastolic Trend
Heart Rate from PA Sensor
Medications
Suspect Readings
High Altitude: Patient travelled to Santa Fe, NM (~7000 ft)
36/13
44/17
61/30
59/30
07-07-2019
07-09-2019
07-11-2019
07-13-2019
07-15-2019
07-17-2019
07-19-2019

Thank You