Management of Acute Heart Failure: Review of New Guidelines

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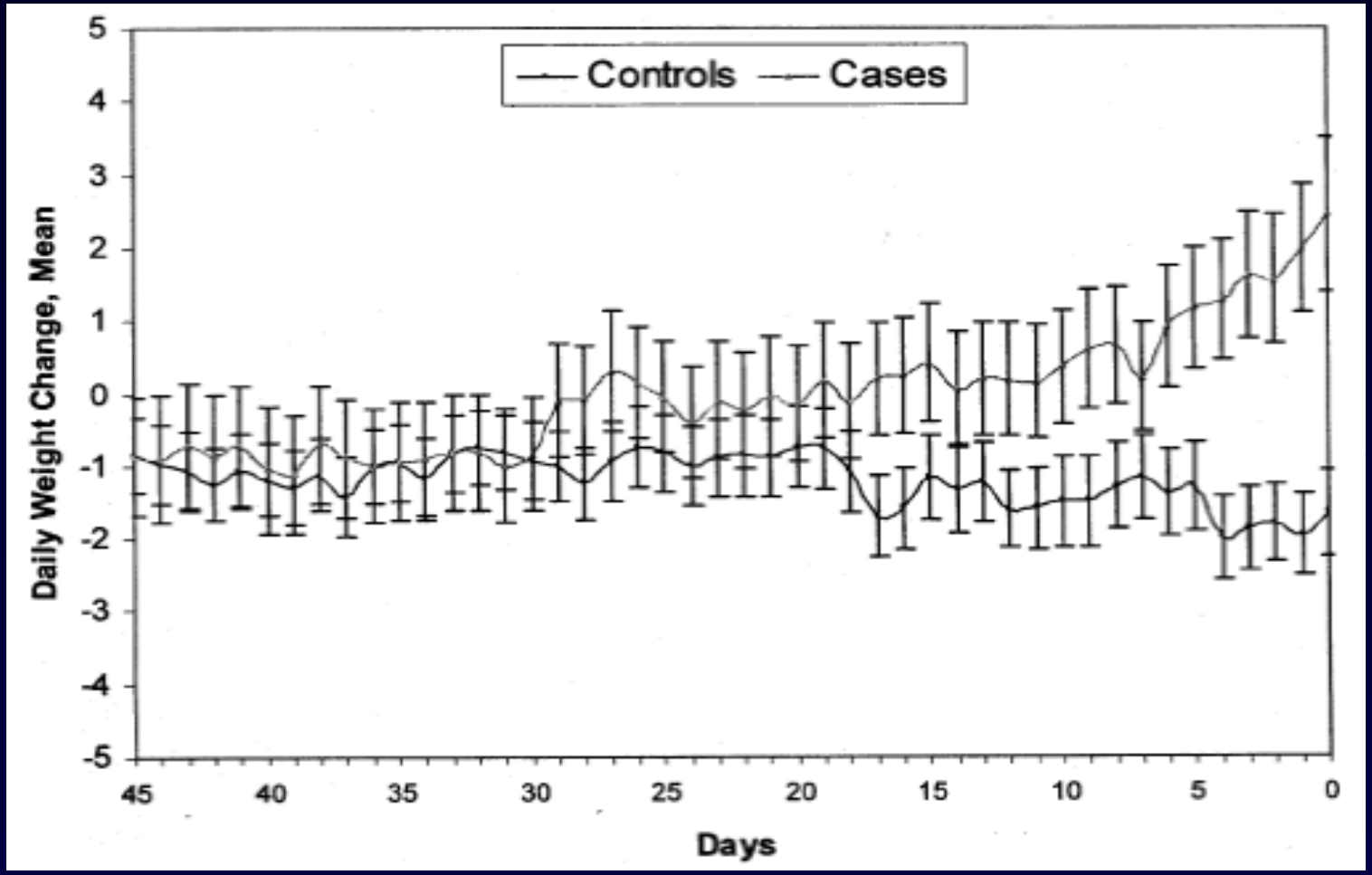
Acute Heart Failure Syndromes: Public Health Issues

- Over 1,000,000 admissions in the United States in 2004 and a similar number in Europe
- These hospitalizations account for over 75% of the 46 billion dollars spent on HF per year
- And have a significant effect on the quality of life of the patients and their families

Acute Heart Failure Syndromes: Clinical Classification

- **Group 1:** Worsening chronic HF with either reduced or preserved LV systolic function (80%)
- **Group 2:** Advanced HF with severe LV systolic dysfunction (Low CO - 10%)
- **Group 3:** Acute HF: sudden increase in BP, MI, arrhythmias (10%)

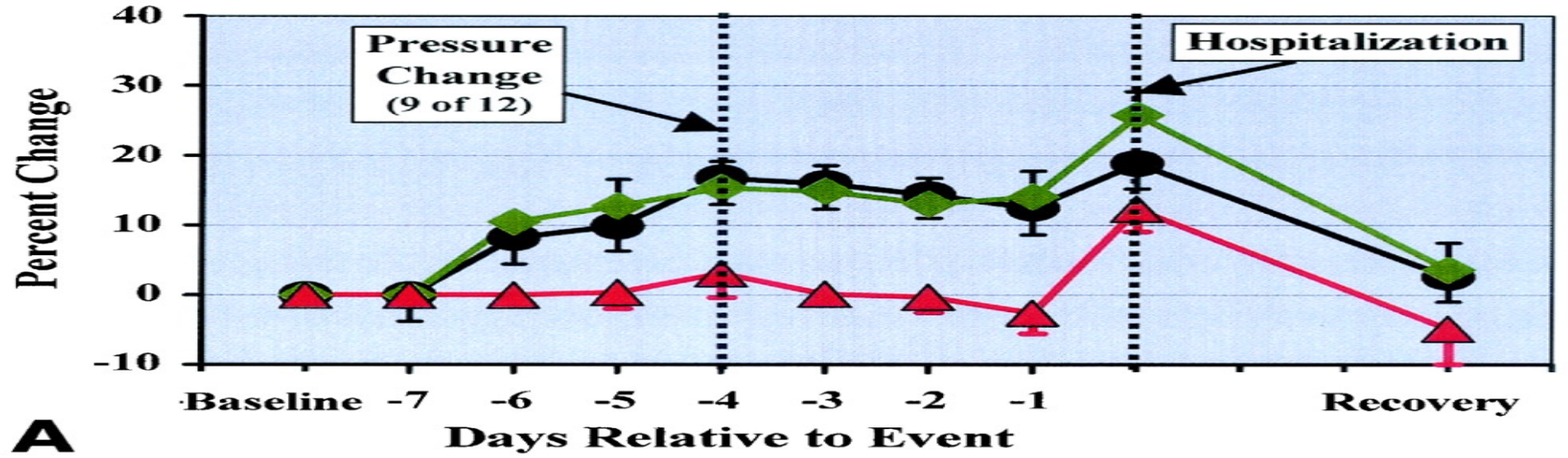
Weight Change Preceding HF Hospitalization

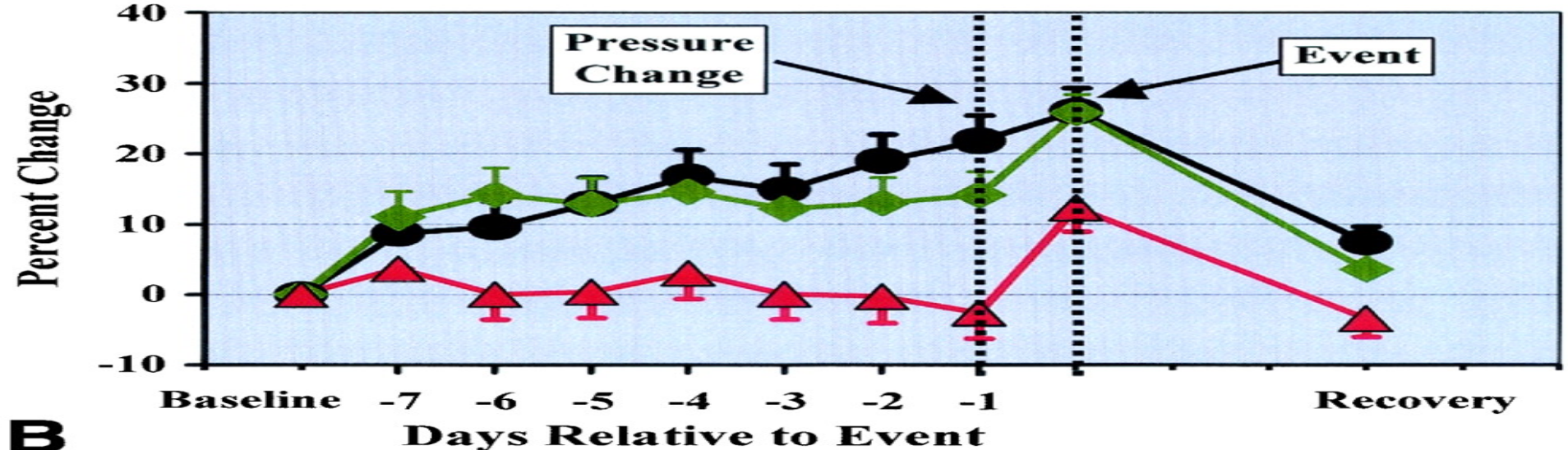


Chaudhary et al Yale University 2006

Change in PAD pressure prior to hospitalization

(Adamson et al JACC 2003:41:565)





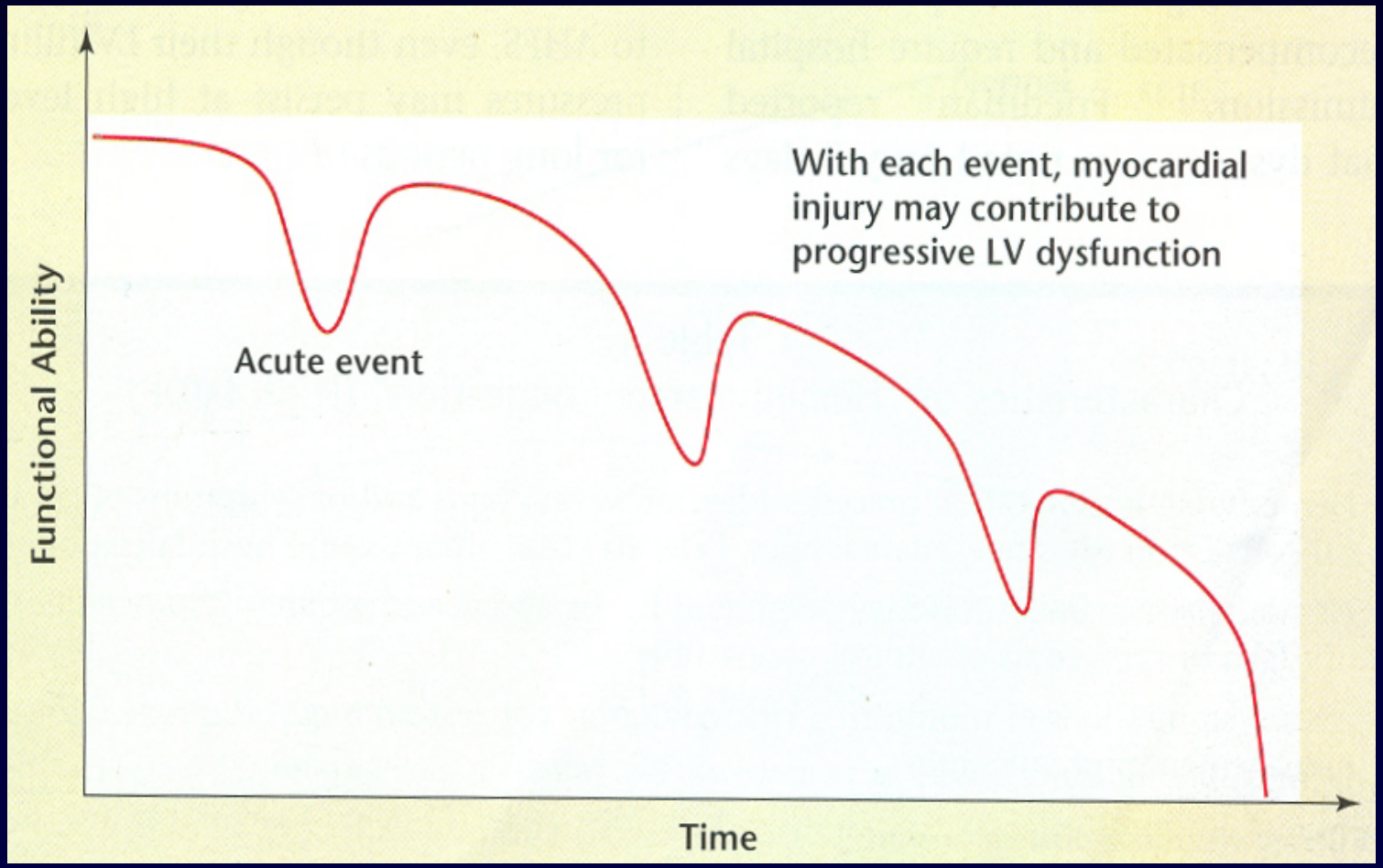
Deleterious Effects of High LV Filling Pressure

- Subendocardial ischemia/ necrosis (↓ cor perfusion, ↑ HR) especially in hibernating myocardium (↑ troponin)
- Worsening LV systolic and diastolic function
- Lower threshold for arrhythmias
- Change in LV shape (spherical) → ↑ MR and TR
- Decreased RBF and GFR*

*Firth JD et al. *Lancet.* 1988;1033-1034.

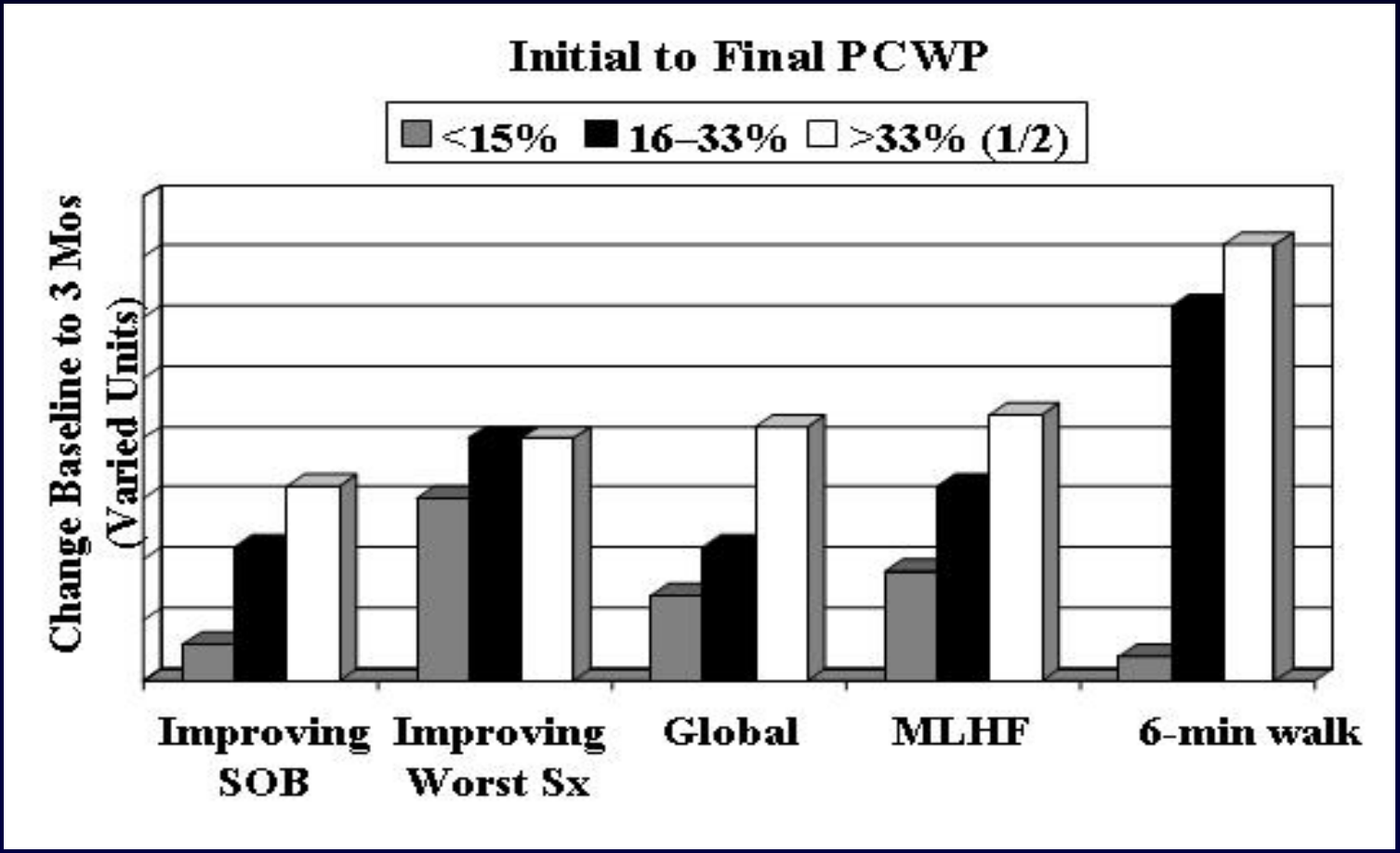
Filippatos G et al . *Am J Physiol.* 1999;277:H445-H451.

Episodes of Acute Exacerbation of Heart Failure



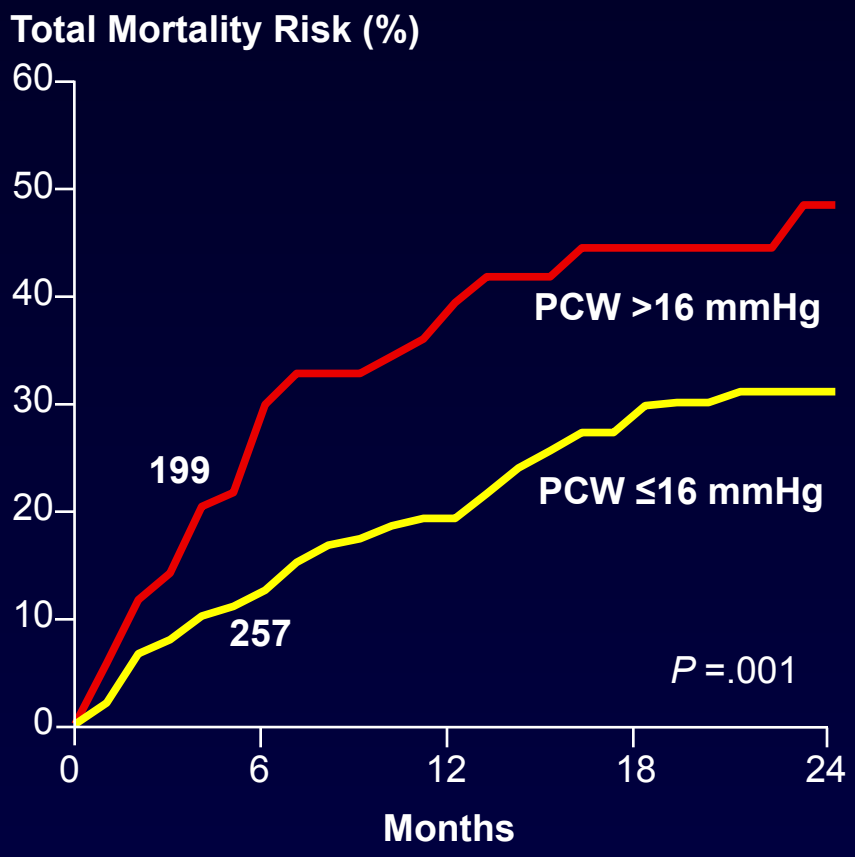
Episodes of an acute exacerbation of heart failure contribute to the progression of heart failure. LV, left ventricular. Adopted with permission from Gheorghiade M et al. *Rev Cardiovasc Med*. 2006;7(suppl 1):S12-S24.

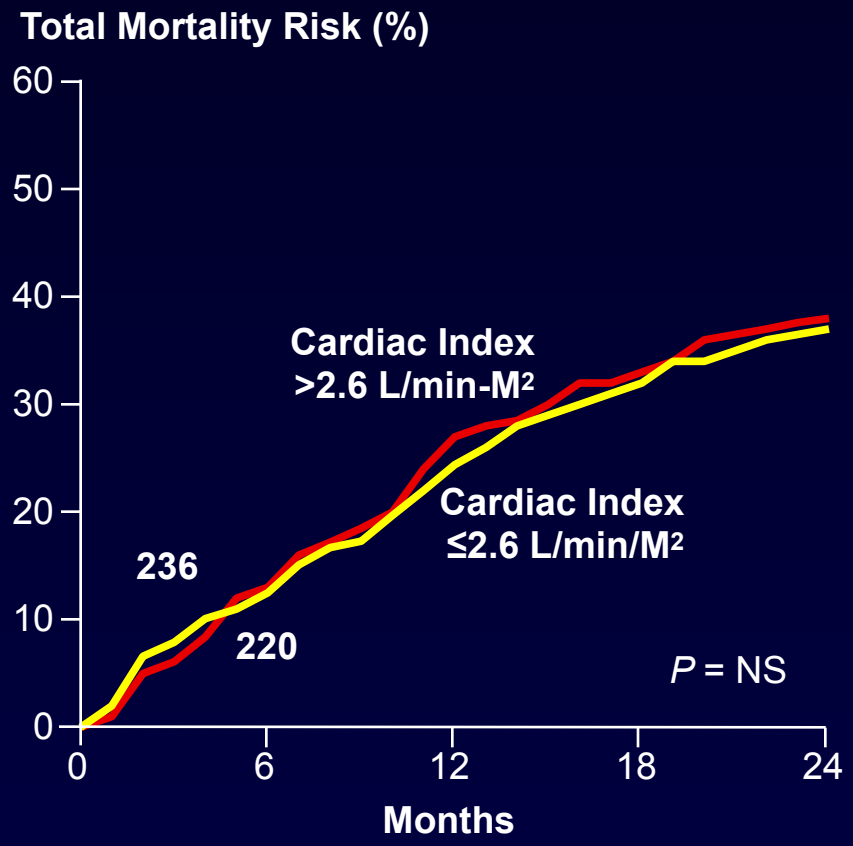
Reduction of Filling Pressures During Hospitalization Predicts Sustained Reduction in HF Symptoms



Roger et al submitted AHA 2006 Meeting

Early Response of PCW but Not CI Predicts Subsequent Mortality in Advanced Heart Failure





Final hemodynamic measurement in 456 advanced HF patients after tailored vasodilator therapy
Fonarow GC et al. *Circulation.* 1994;90:I-488.

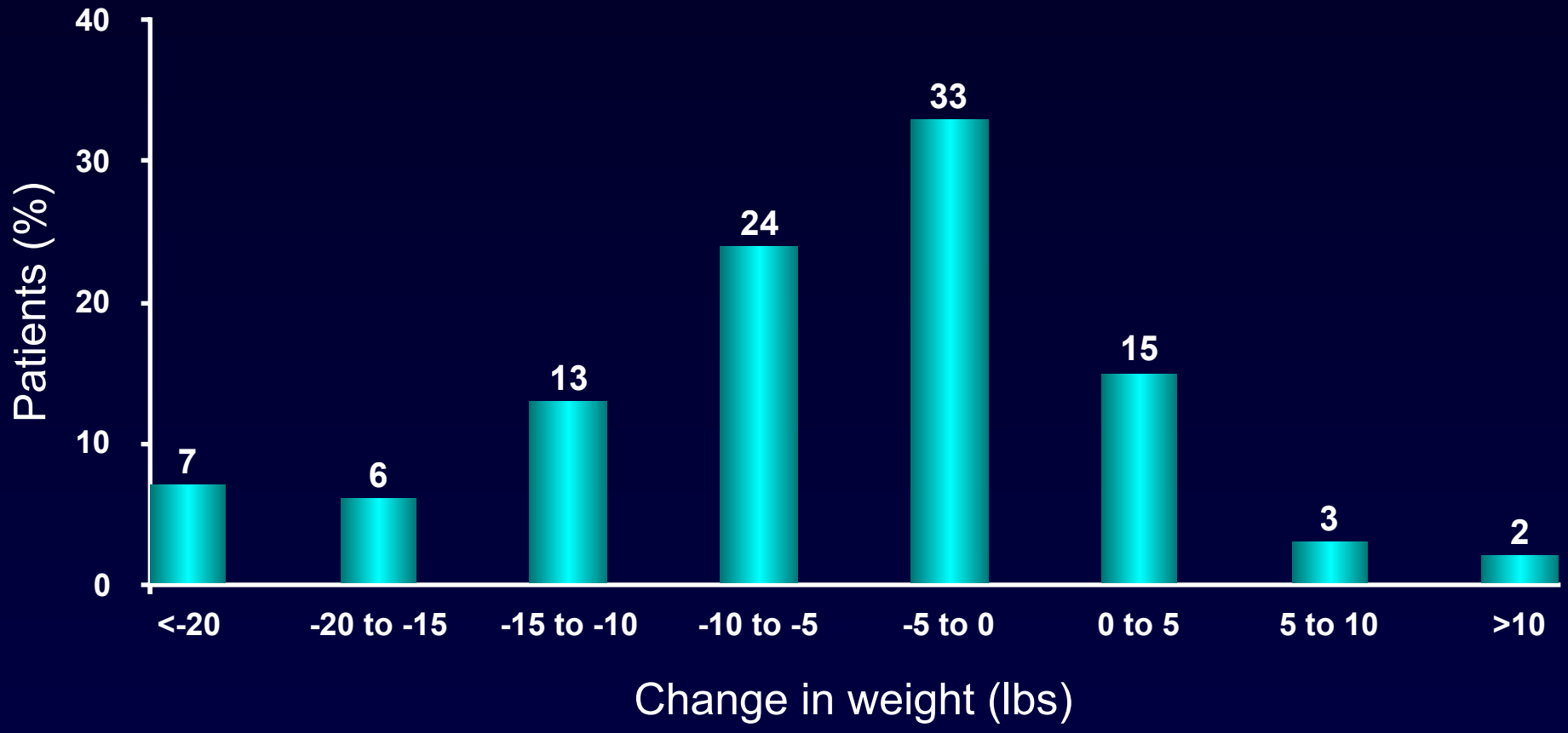
ADHF - Treatment

- Diuretics.
- Vasodilators.
- Inodilators.
- Ultrafiltration.

HFSA Practice Guidelines 2006: Diuretics

- Recommended at doses needed to produce diuresis at a rate sufficient to achieve optimal volume status and relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in IV volume, which may result in symptomatic hypotension and/or worsening renal function.(C)

Many Patients Have Little or No Weight Loss During Hospitalization



Fonarow GC. *Rev Cardiovasc Med*. 2003;4(suppl 7):S21-S30.

HFSA Practice Guidelines 2006: Diuresis – How much and how fast?

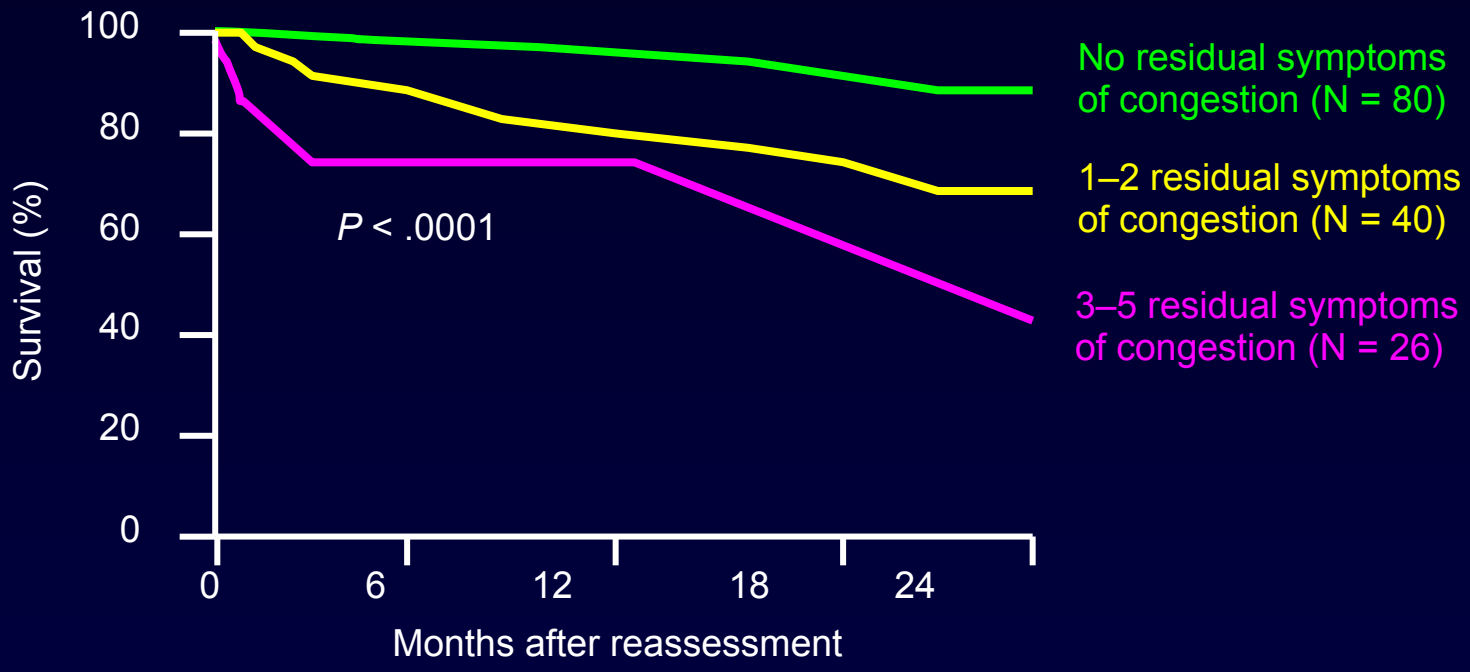
Edema of Cardiac Origin

	Extra Cellular Volume (mL/kg)	Plasma Volume (mL/kg)	Glomerular Filtration (mL/min/1.73/m^2)	Renal Plasma Flow (mL/min/1.73 m^2)
Patients	**301±24**	**58 ±3**	**65 ± 8**	**140 ± 25**
Controls	**227 ± 13**	**43 ±3.0**	**99 ± 2**	**479 ± 19**
***P* Value**	**.035**	**.012**	**.01**	**.009**

Extra volume ~ 85 ml/kg or ~ 6.0 L for 70 kg

Anand IS et al. *Circulation.* 1989;80:299-305.

Post-discharge Freedom of Congestion Is Associated with Better Prognosis



Symptoms of congestion: orthopnea, jugular venous distention, weight gain ≥ 2 lb in a week, need to increase diuretic dose, leg edema

Lucas C, et al. *Am Heart J.* 2000;140:840-7.

Primary and Secondary End Points, Ultrafiltration vs Standard Diuresis in UNLOAD

End points 48 hours	Ultrafiltration	Diuresis	*P*
▪ Weight loss, primary end point (mean kg)	5.0, n=83	3.1, n=84	.001
▪ Dyspnea score, primary end point (mean)	6.4, n=80	6.1, n=83	.35
▪ Net fluid loss (mean L)	4.6	3.3	.001
▪ K<3.5 mEq/L (%)	1	12	.018
▪ Need for Vasoactive drugs (%)	3	13	.015

Costanzo et al. *J Am Coll Cardiol.* 2007

Primary and Secondary End Points, Ultrafiltration vs Standard Diuresis in UNLOAD

End points 90 days	Ultrafiltration	Diuresis	*P*
▪ Rehospitalization (%)	18	32	.022
▪ Rehospitalization days (mean)	1.4	3.8	.022
▪ Unscheduled office/ED visits (%)	21	44	.009

ED- Emergency Department.

Costanzo et al. *J Am Coll Cardiol.* 2007

HEART FAILURE
LV SYSTOLIC AND DIASTOLC DYSFUNCTION

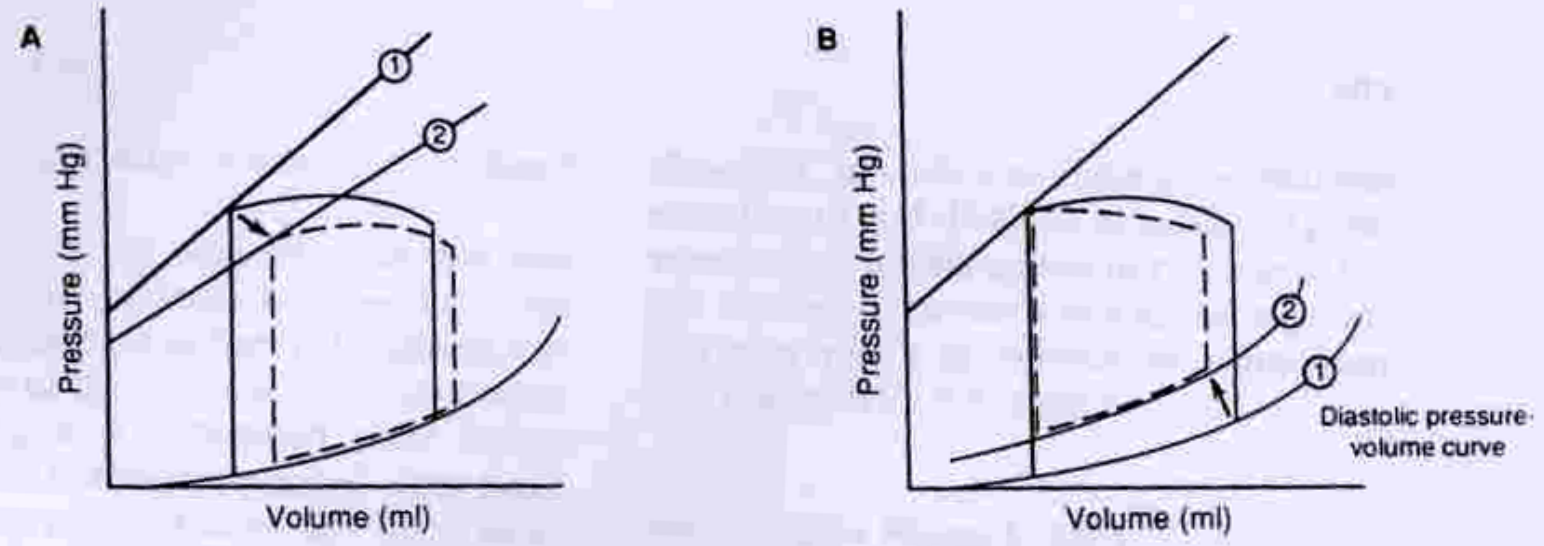
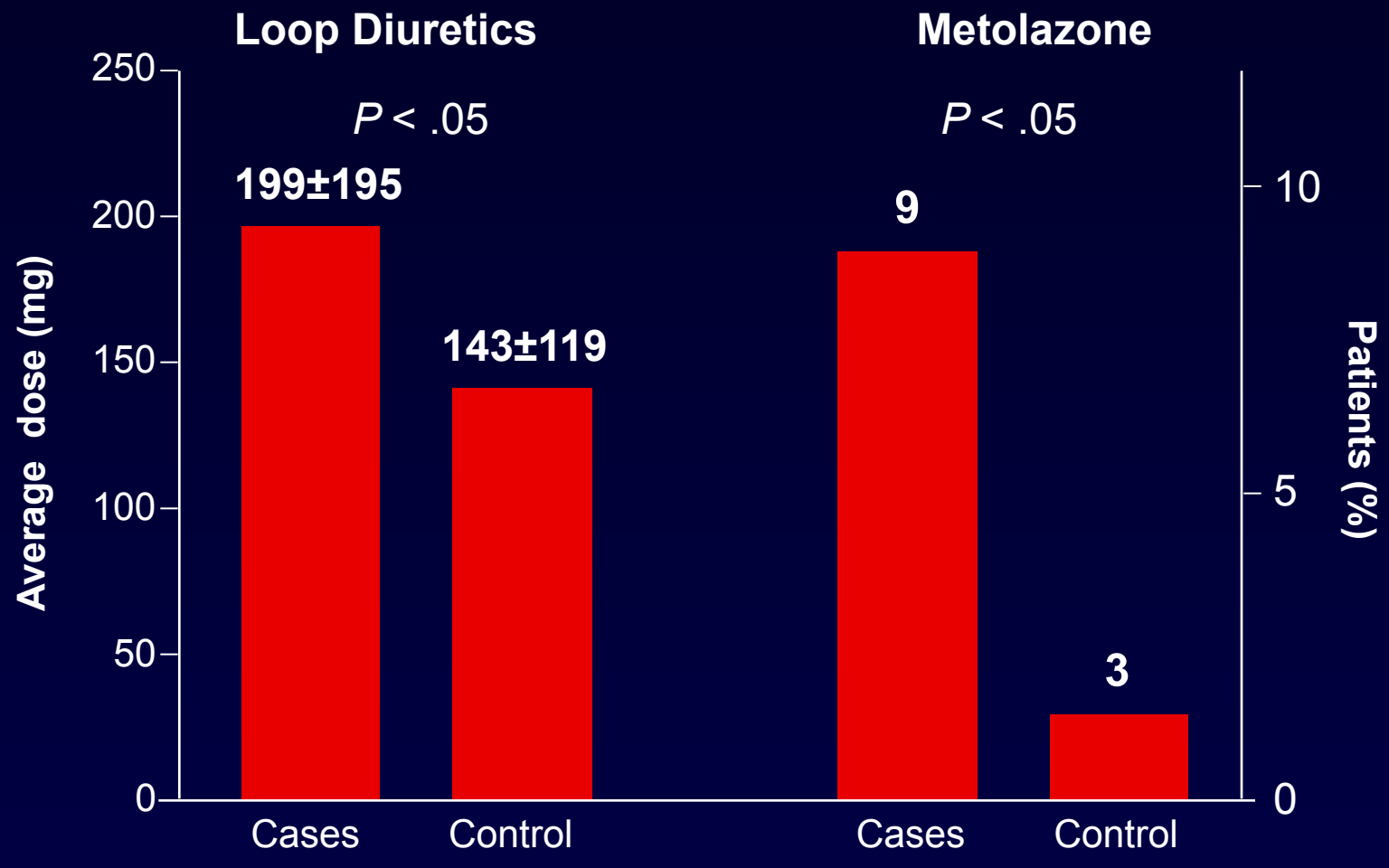


Figure 9.7. **A.** The normal pressure-volume loop (solid line) is compared with one demonstrating systolic dysfunction (dashed line). In systolic dysfunction due to decreased cardiac contractility, the end-systolic pressure-volume relation is shifted downward and rightward (from line 1 to line 2). As a result, the end-systolic volume (ESV) is increased (arrow). As normal venous return is added to the greater than normal ESV remaining in the ventricle, there is an obligatory increase in the end-diastolic volume (EDV) and pressure (preload), which serves a compensatory function by partially elevating stroke volume towards normal via the Frank-Starling mechanism. **B.** The pressure-volume loop of diastolic dysfunction due to increased stiffness (decreased compliance) of the ventricle (dashed line). The passive diastolic pressure-volume curve is shifted upward (from line 1 to line 2) such that at any diastolic volume, the ventricular pressure is greater than normal. The result is a decreased EDV (arrow) because of reduced filling of the stiffened ventricle, at a higher than normal end-diastolic pressure.

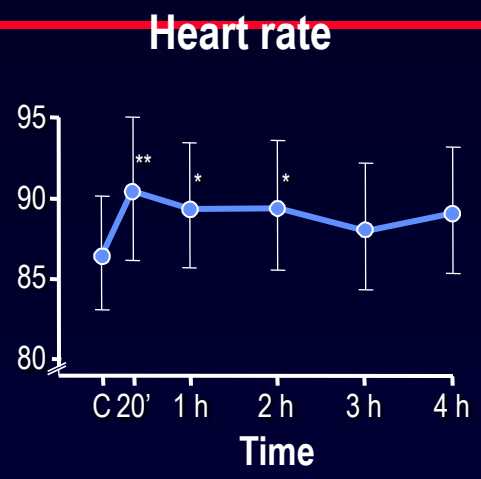
Diuretics in ADHF: How to Use Them

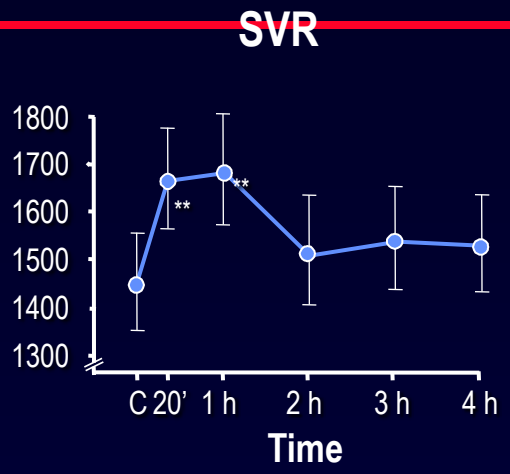
Relationship Between Diuretics and Worsening Renal Function in Decompensated HF

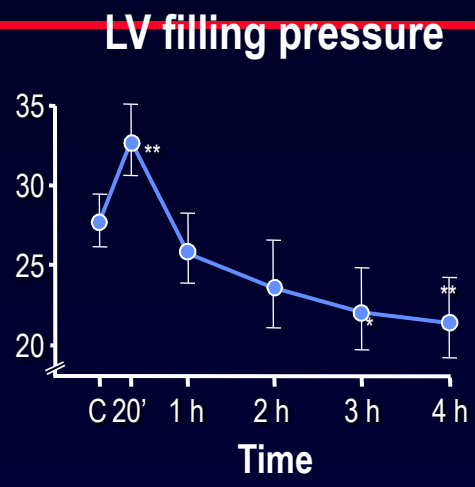


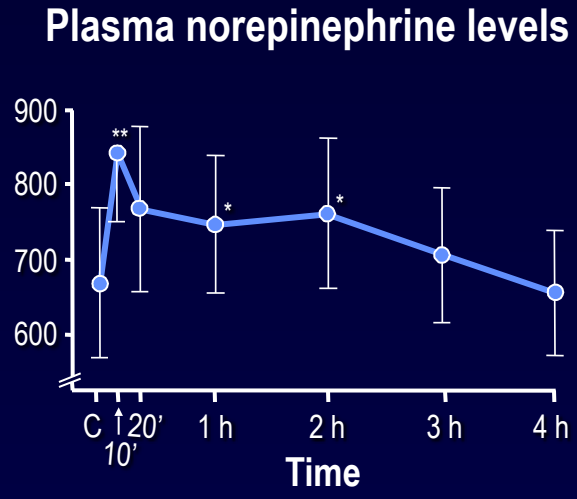
Butler J et al. *Am Heart J.* 2004;147:331-338.

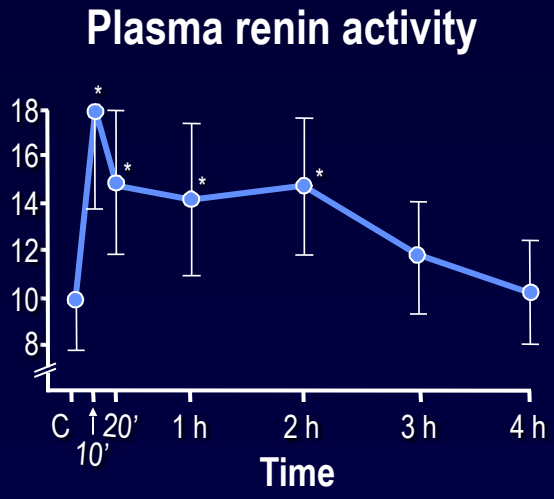
Intravenous Furosemide: Acute Effects

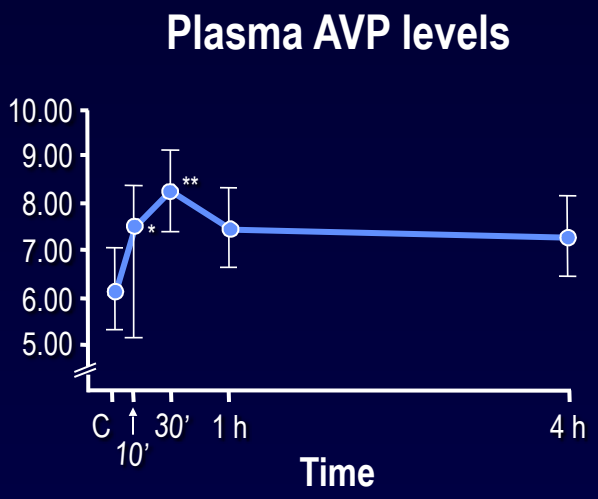










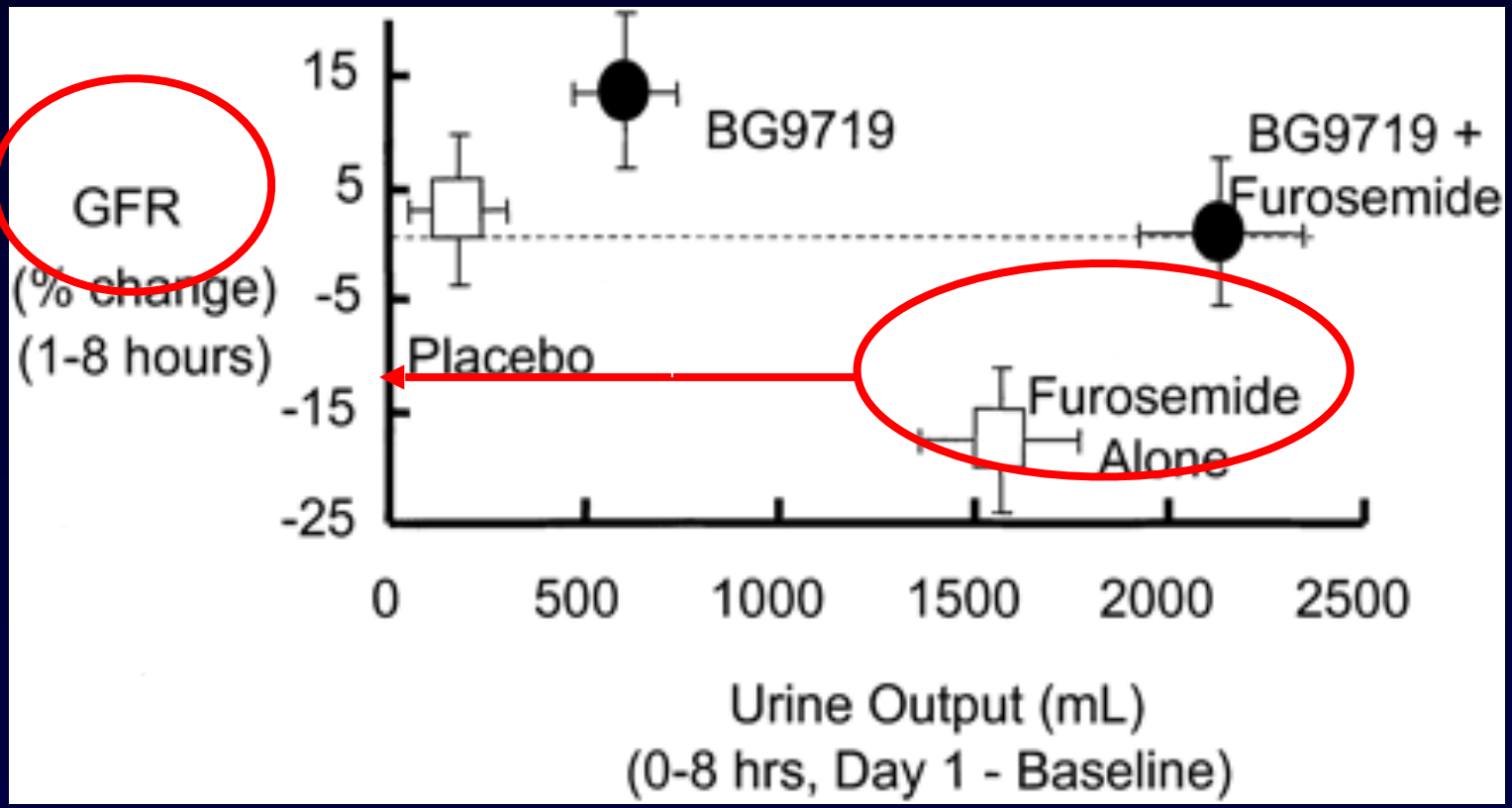


* $P < .05$
** $P < .01$

Francis GS, et al. *Ann Intern Med.* 1985;103:1-6.

A1 Adenosine Antagonists in CHF

Renal Function and Renal Output in Edematous Heart Failure Patients Treated with Furosemide (80 mg IV) and/or BG9719 (Biogen Study C97-1205)

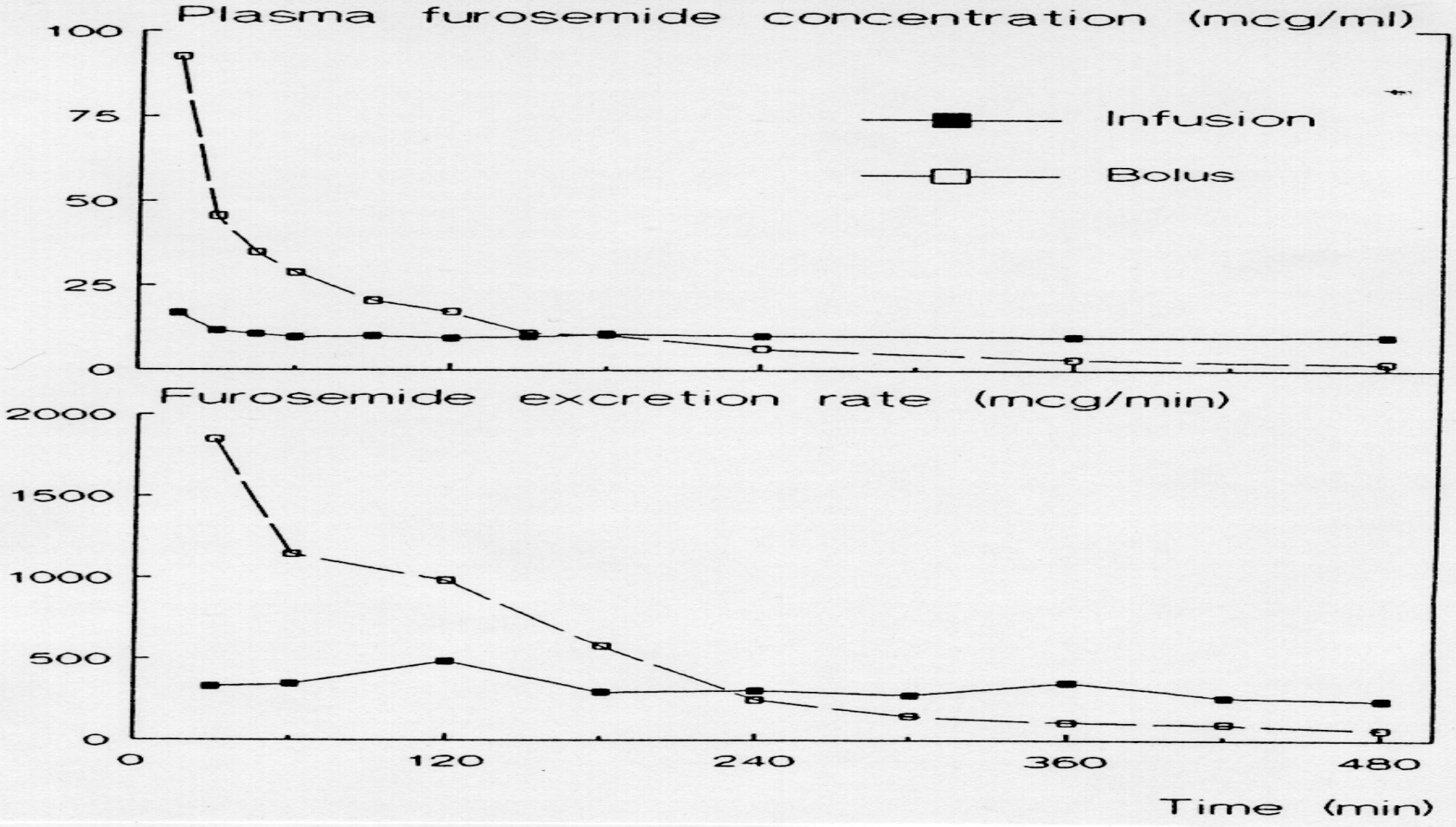


Gottlieb SS et al. *Circulation*. 2002;105:1348-1353.

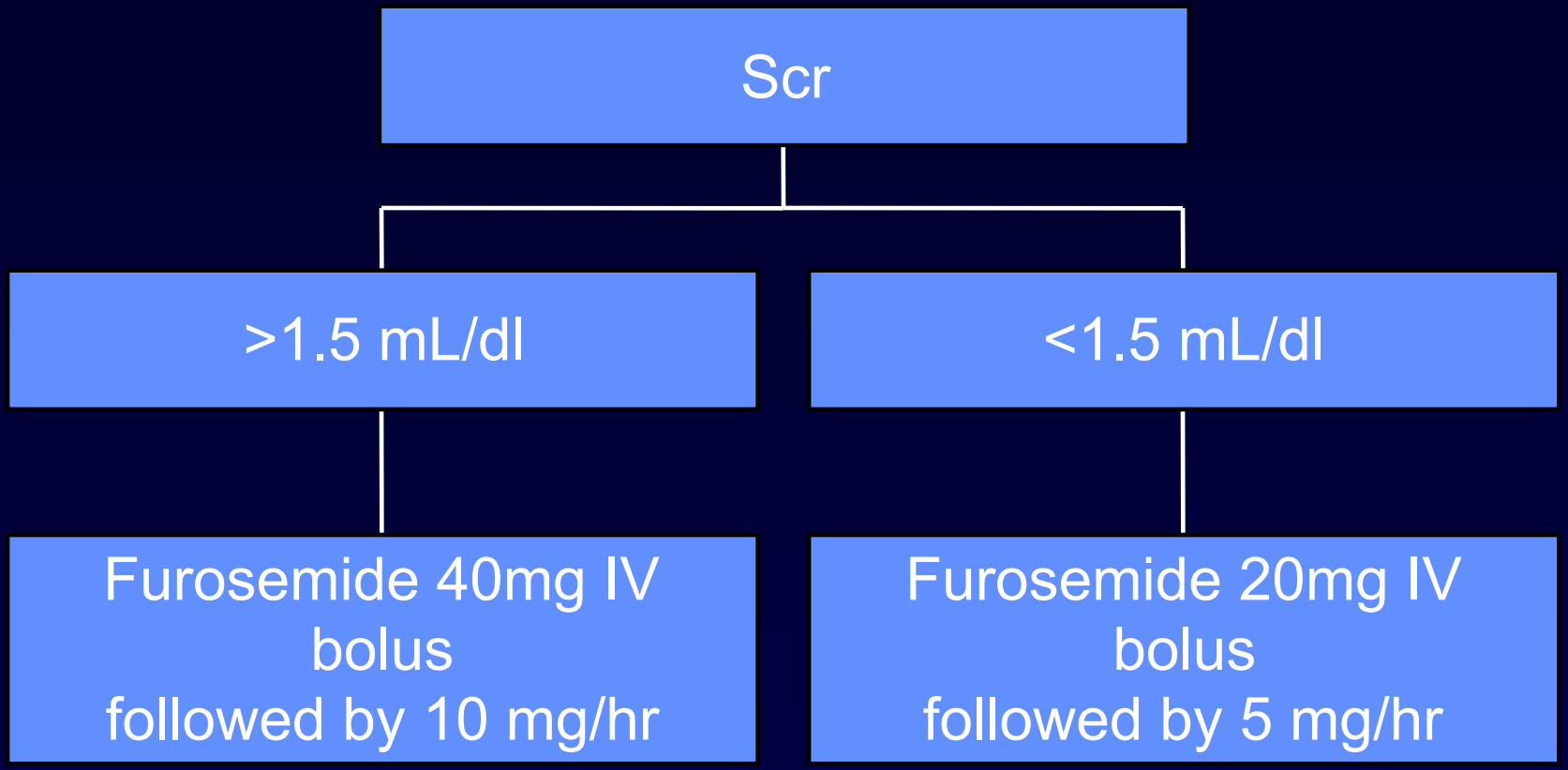
Furosemide in severe CHF: Bolus Injection vs Continuous Infusion

(Dormans et al JACC 1996;28:376-382)

Figure 1. Furosemide plasma concentration **(top)** and urinary furosemide excretion rate **(bottom)** for a representative study patient (Patient 1) after 500 mg of furosemide as a bolus injection or continuous infusion (50 mg/h during 8 h preceded by a loading dose of 100 mg).



Use of Furosemide in Patients With ADHF



Furosemide in HF: Bolus Injection vs Continuous Infusion

Parameters	Bolus	Infusion	*P* Value
Urinary volume (mL)	2260±150	2860±240	.0005
Urinary sodium (mmol)	150±20	210±40	.0045
Urinary potassium (mmol)	70±5	80±5	< .0001

Dormans TP et al. *J Am Coll Cardiol.* 1996;28:376-382.

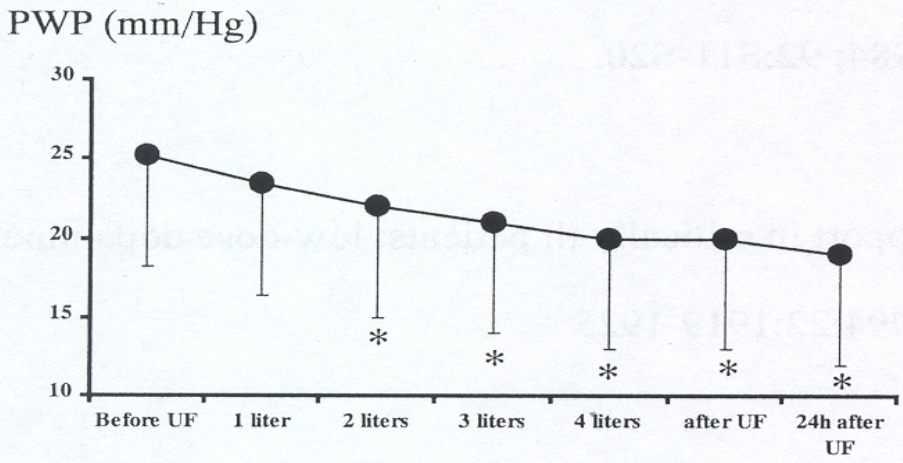
Relationship between volume removal and Δ in LVFP in systolic dysfunction

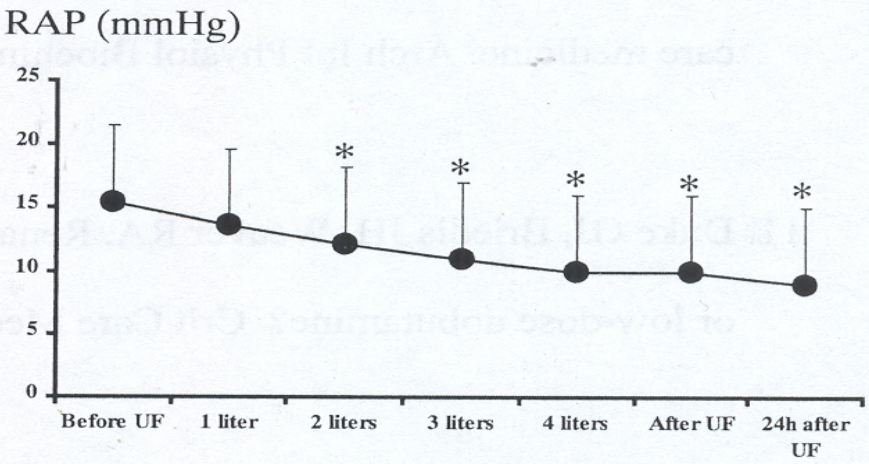
Time	HR bpm	MBP mmHg	Co L/min	RA mmHg	PA mmHg	PAW mmHg	SVR dynes/ s/cm^{-5}	FLUID BALANCE ml
4/30/07 5:30 pm	109	85	6.3	12	45/30	25	927	
5/2/07 6:00 am Lasix 3 mg/h	116	81	6.0	15	50/30	25	880	-3567
5/2/07 6:45am IV NTG 120mcg	119	78	7.2	6	29/18	12	800	

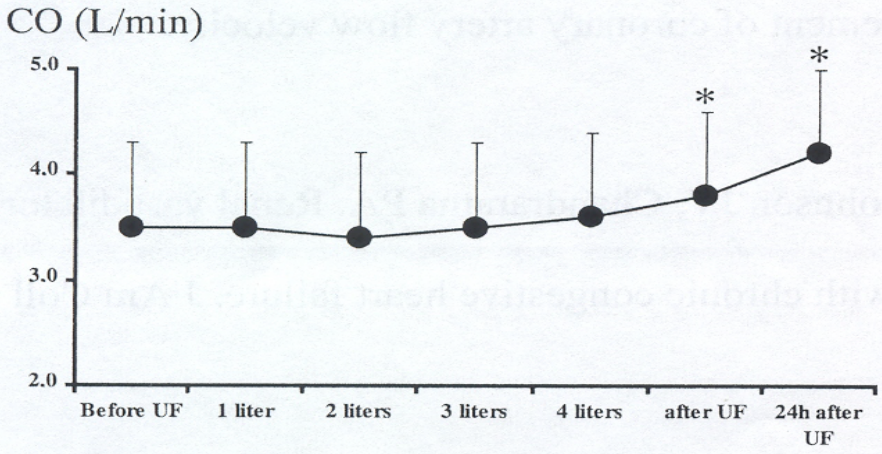
36 yo, IUP 38 weeks, Hx of alcohol and amphetamine abuse. Dilated cardiomyopathy , LVEF- 25-30%. D/C all medications, NYHA class II. Hemodynamic evaluation pre delivery.

Ultrafiltration in refractory HF

Marenzi et al, JACC 2001;38:963-8







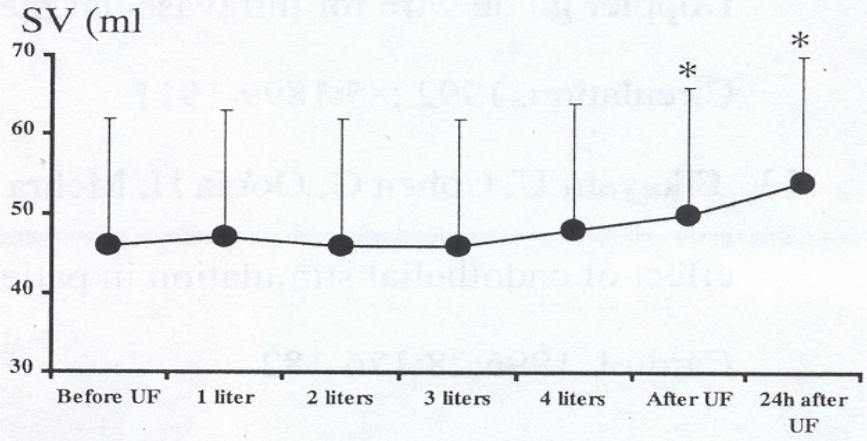


Figure 1. Mean pulmonary wedge pressure (PWP), mean right atrial pressure (RAP), cardiac output (CO) and stroke volume (SV) before, during and after extracorporeal ultrafiltration (UF). *p < 0.01 vs. before ultrafiltration.

Relationship between volume removal and Δ in LVFP in diastolic dysfunction

Time	HR bpm	MBP mmHg	Co L/min	RA mmHg	PA mmHg	PAW mmHg	SVR dynes/ s/cm^{-5}	PVR dynes/ s/cm^{-5}
6/4/07 6pm	86	110	6.5	13	61/30	28	1194	152
6/5/07 2pm	92	117	7.2	6	31/13	13	1233	67

19 yo, IUP 19 weeks, Hx of chronic HTN and DM for 10 years. GFR ~20 ml/ min.

ECHO – LVH, LAE, LVEF- 60%, ↑ LA pressure, Diastolic dysfunction.

Dialysis initiated. Fluid balance for the 18 hours of combined dialysis and diuresis -1400 ml.

Inotropes in the Treatment of ADHF

NTG* vs Milrinone in Decompensated Heart Failure

Drug	HR bpm	MBP mmHg	CIL/ min/kg	RA mmHg	MPA mmHg	PAW mmHg	SVR dynes/ s/cm^{-5}	PVR dynes/ s/cm^{-5}
Nitroglycerin	3±2%	-19±3%	34±6%	-46±12	-30±4	-36±4	-36±4	-41±10
Milrinone	11±4%	-8±1%	68±11%	-37±9	-36±5	-36±5	-40±4	-32±11
P value	< .01	< .01	< .05	NS	NS	NS	NS	NS

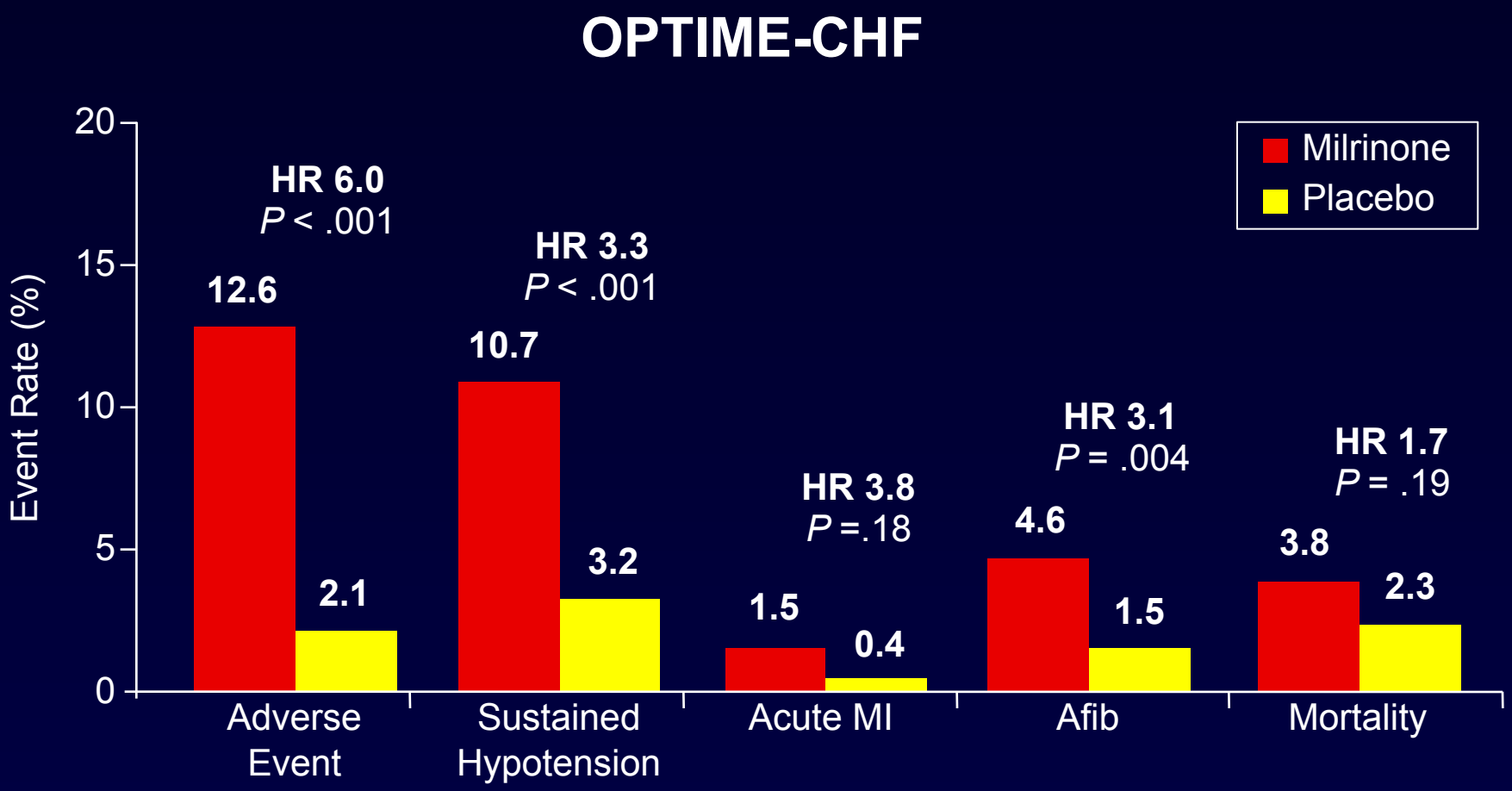
*Dose titrated to ↓ PAW ≥30%

Elkayam U et al. *Am J Cardiol*. 1996;77:41C-51C.

HFSA Practice Guidelines 2006: Inotropes

- Inotropes (milrinone or dobutamine) may be considered in patients with diminished peripheral perfusion or end organ dysfunction (low output), particularly those with symptomatic hypotension despite adequate filling pressure, who do not tolerate or fail to improve with IV vasodilator therapy or in whom severe symptomatic hypotension precludes use of vasodilators (C).

Intravenous Milrinone for Decompensated Heart Failure



HR, heart rate; MI, myocardial infarction; Afib, atrial fibrillation.

Cuffe MS et al. *JAMA*. 2002;287:1541-1547.

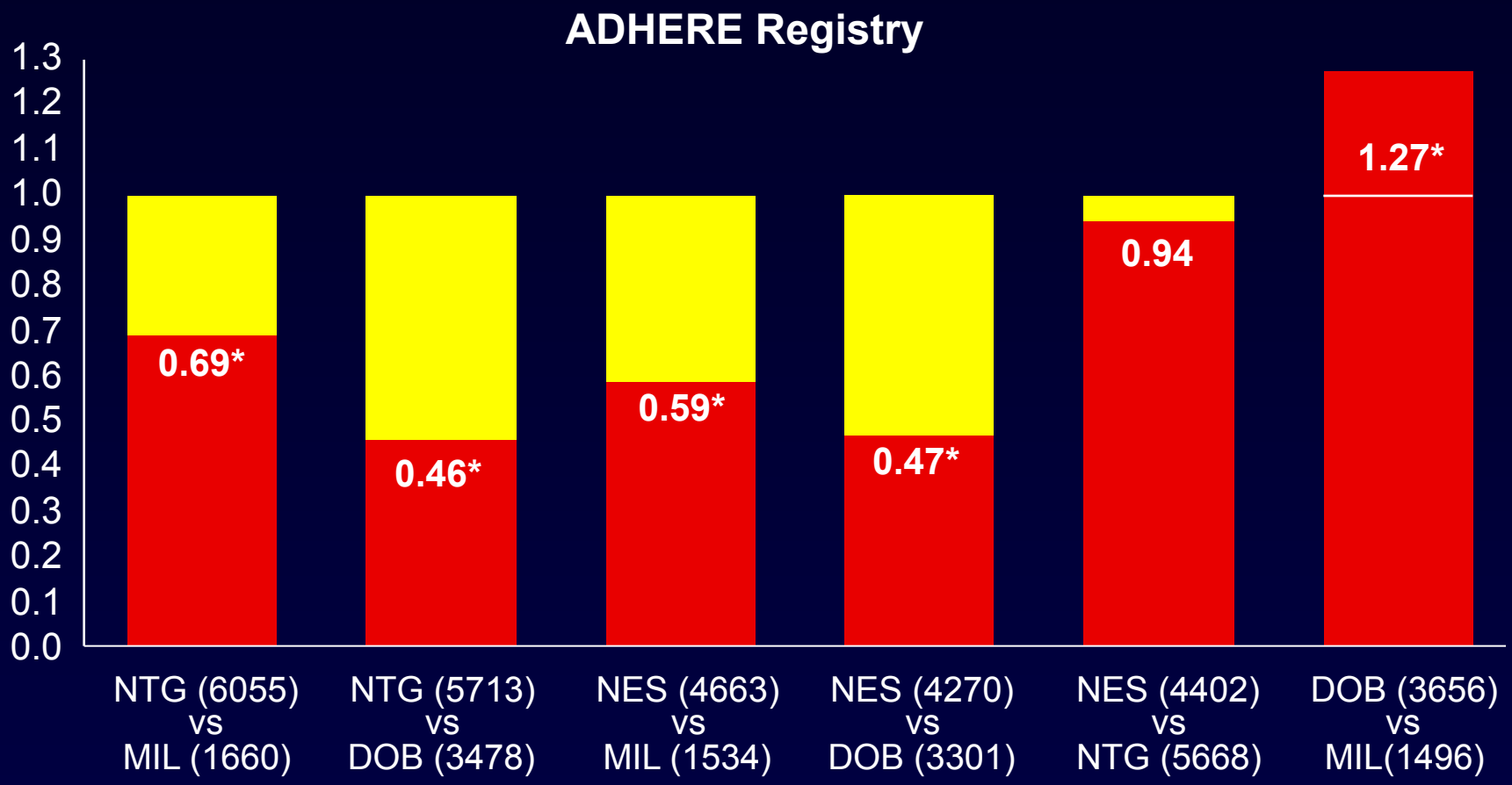
HF Etiology and Response to Milrinone in Decompensated HF (OPTIME Study)

	Ischemic		Non-Ischemic		
	Milrinone	Placebo	Milrinone	Placebo	*P* value*
Days hospitalized at 60 days	13.6±15.5	12.4±12.7	10.9±12.4	12.6±15.3	.055
In-hospital mortality	5.0%	1.6%	2.6%	3.1%	.04
60-day mortality	13.3%	10.0%	7.3%	7.7%	.21
Death + rehospitalization	42%	36%	28%	35%	.02

**P* value for the etiology*treatment interaction term in the multivariable model.

Felker et al. *J Am Coll Cardiol.* 2003;41:997-1003.

In-Hospital Mortality in Pts With ADHF Receiving Vasoactive Meds



*Risk factor and propensity score-adjusted odds ratios.

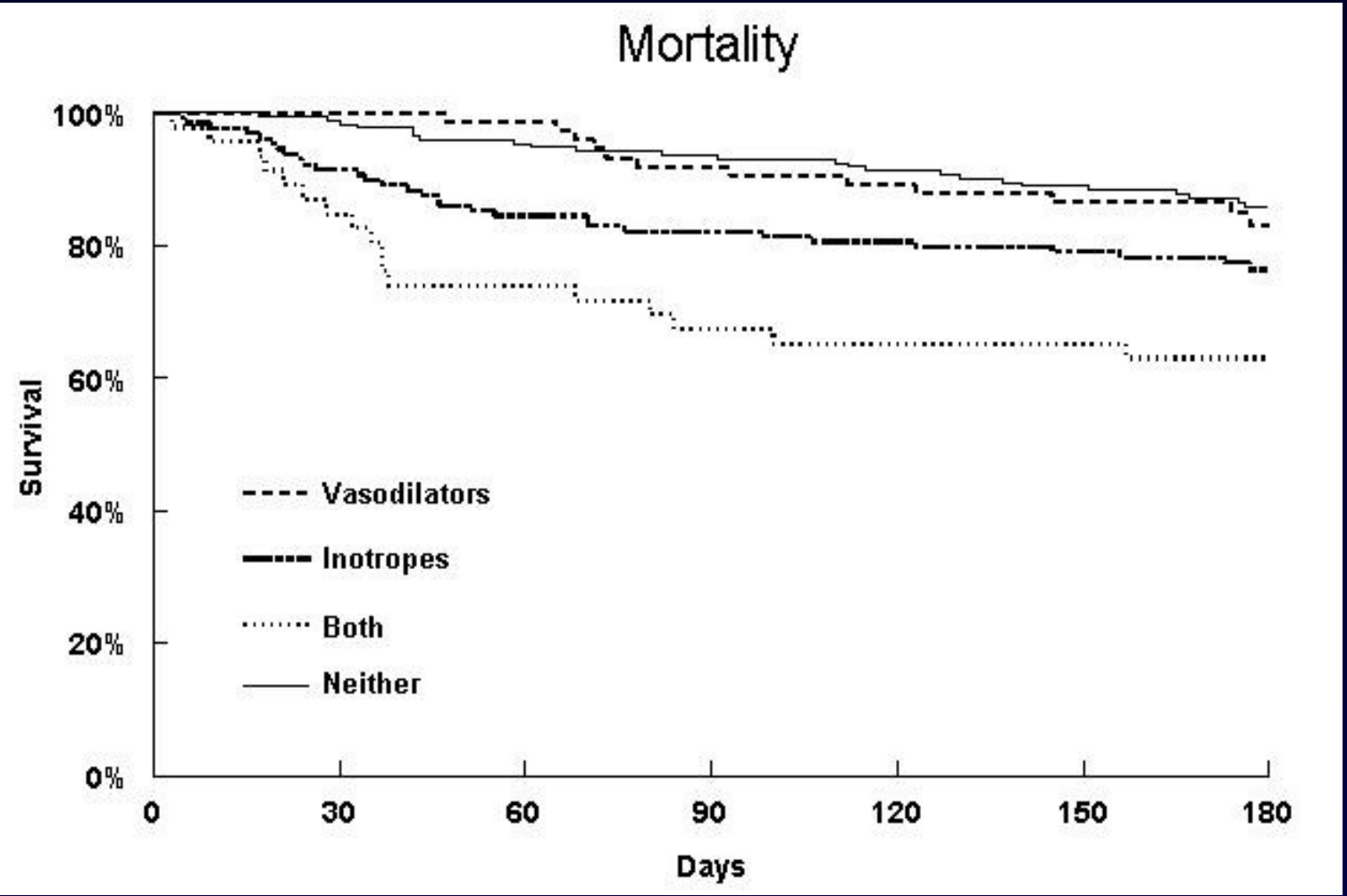
Abraham WT et al. *J Am Coll Cardiol.* 2005;46:57-64.

The ESCAPE Trial: Use of Inotropes and Vasodilators

Number of patients on inotropes	180	(42%)
Dobutamine	115	
Dopamine	42	
Milrinone	72	
Number of patients on vasodilators	122	(28%)
Nesiritide	66	
Nitroglycerin	12	
Nitroprusside	50	

Elkayam et al Am heart J, 2007;153:98-104

The ESCAPE Trial: Use of Inotropes and Vasodilators



Elkayam U et al. *Am Heart J.* 2007;153:98-104.

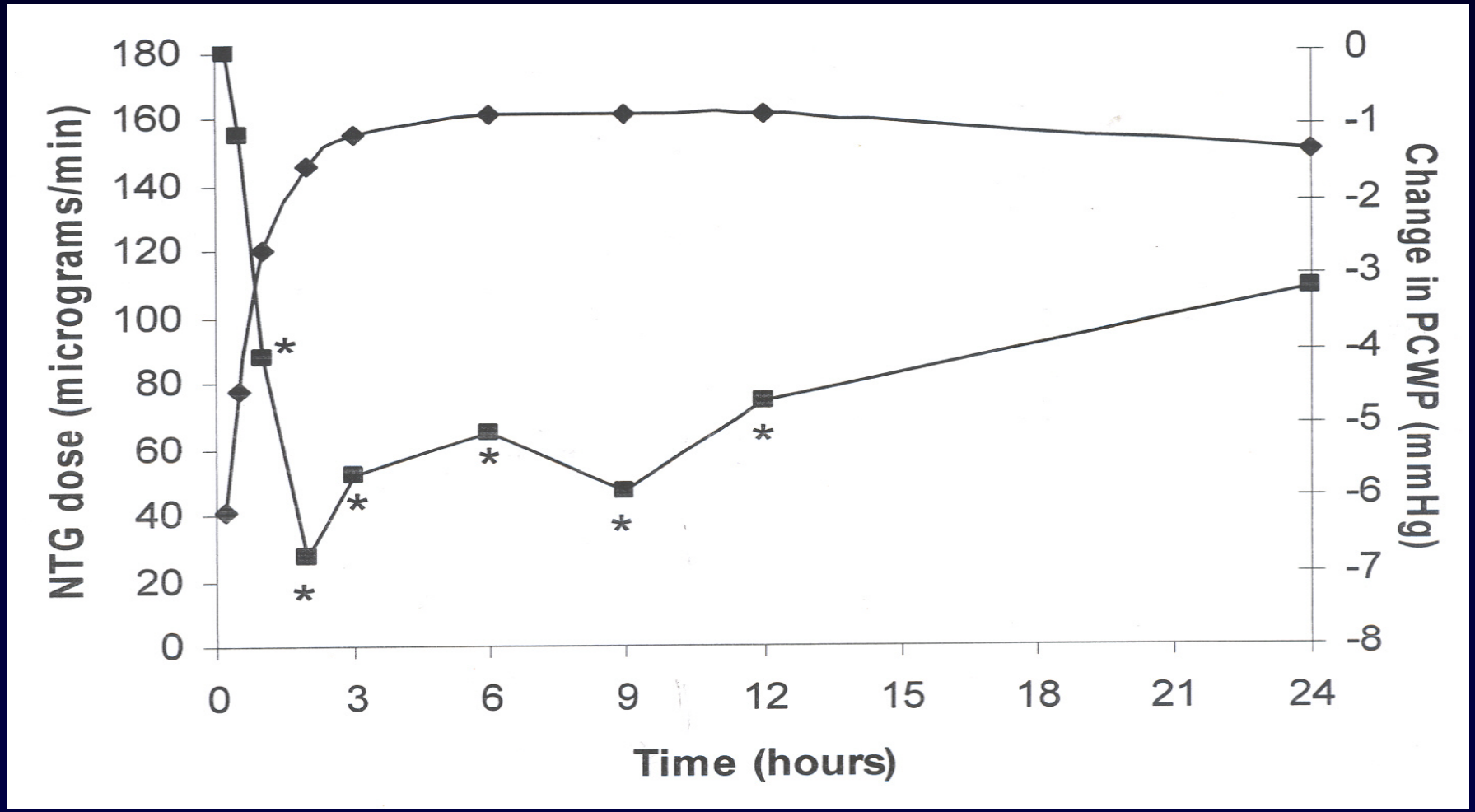
HFSA Practice Guidelines 2006: Vasodilators

- In the absence of symptomatic hypotension, IV nitroglycerine, nitroprusside or nesiritide may be considered as an addition to diuretics for rapid improvement of hemodynamic parameters and congestive symptoms in pts admitted with ADHF. *Strength of evidence=B*

IV Vasodilators in the Treatment of ADHF

Parameters	Nitroprusside	Nitroglycerin	Nesiritide
Clinical studies in HF	–	+	+++
Hemodynamic effect	+++	+++	+++
Tolerance	–	++	–
Need for dose titration	+++	+++	–
Effect on coronary blood flow	↓	↑ ↑	↑
Effect on ischemia	↑	↓	NA
Effect on urine output	NA	NA	↑↓
Effect on neurohormones	↑	↑	↓
Vascular resistance	+	+	+
Evidence of symptomatic improvement	–	–	+

IV NTG in the Treatment of ADHF:
Relationship Between Dose and Effect on PCWP

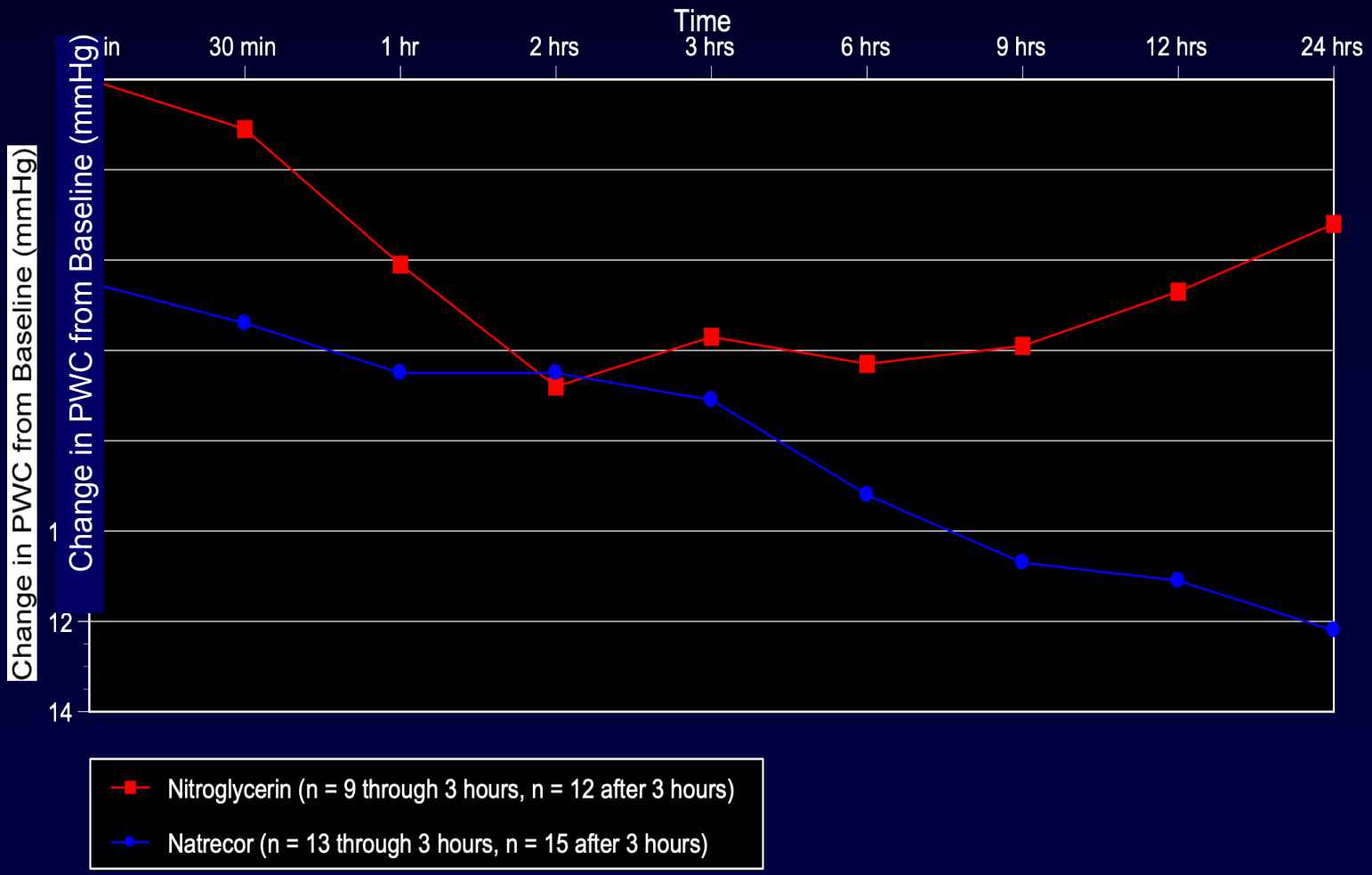


Elkayam U et al. *Am J Cardiol.* 2004;93:237-240.

Nesiritide VS High Dose Nitroglycerin

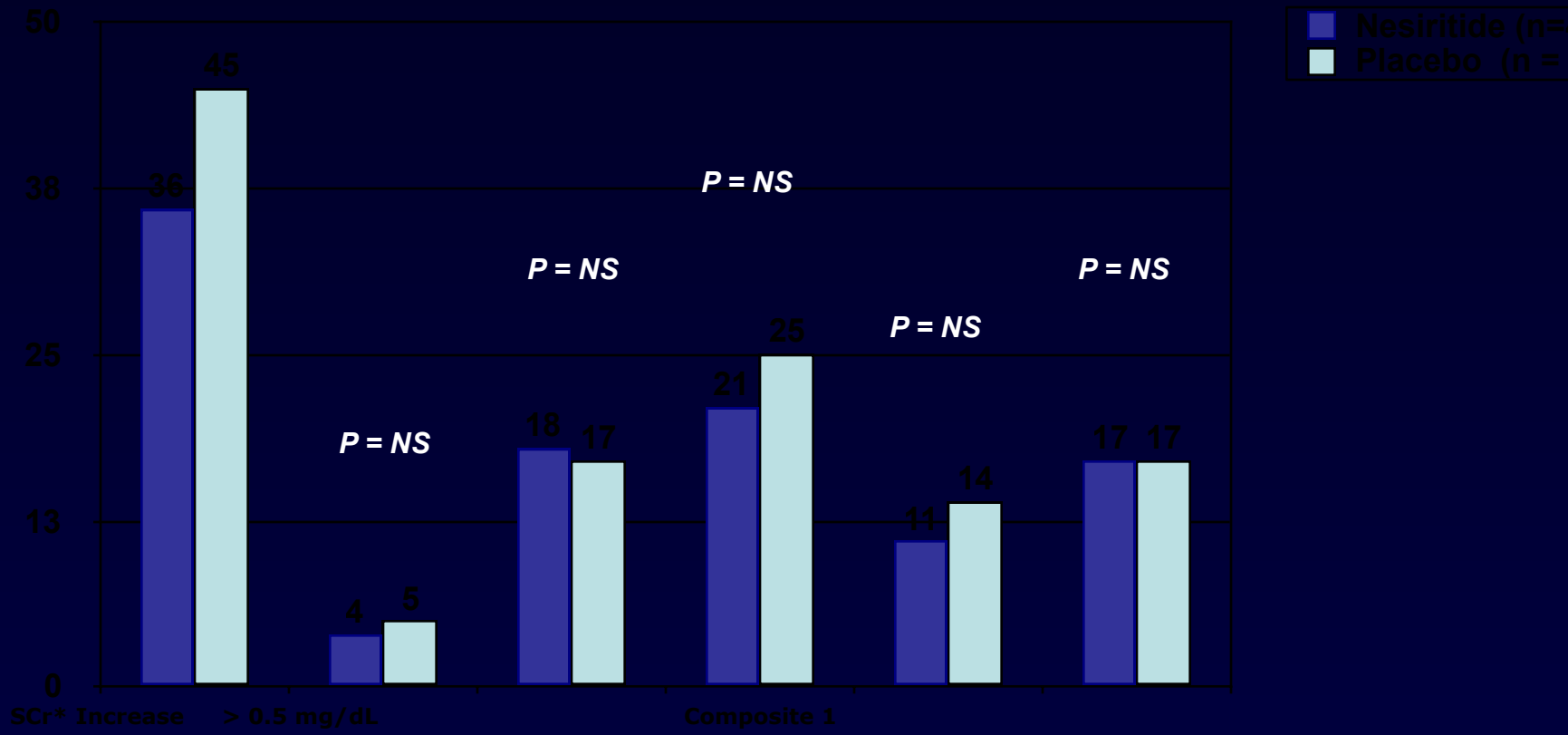
Elkayam et al Am J Cardiol 2004;93:237-240

Change in PCWP



FUSION-II
Percentage of Patients Meeting Renal Endpoint

Yancy C et al. JCF 2007;13:S136



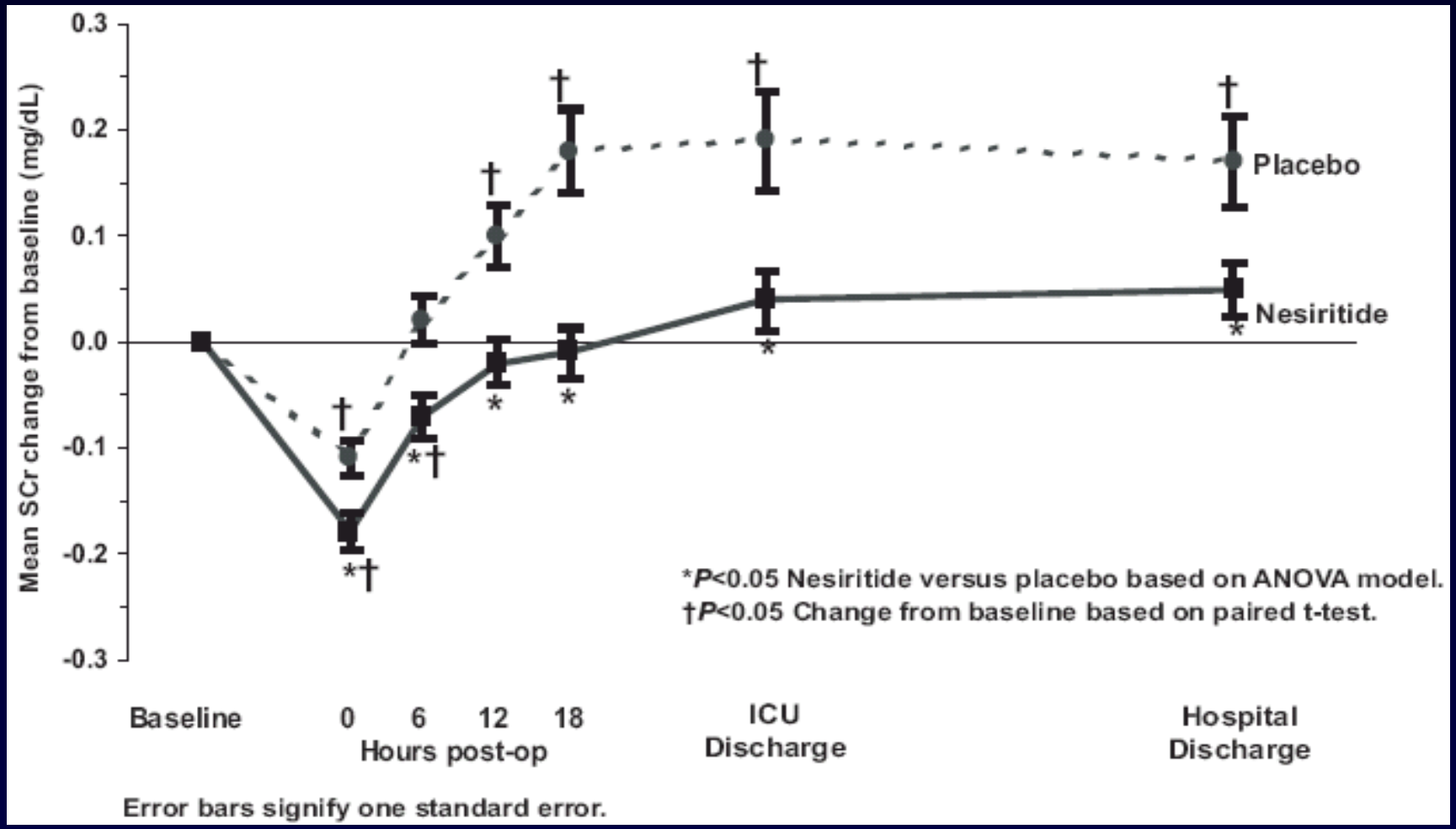
Protocol pre-specified changes in SCr were > 0.5 mg/dL increase; > 100% increase; and ≥ 50% to ≥ 2.0 mg/dL. An increase in SCr > 0.5 mg/dL is consistent with the threshold for FDA review.

Composite 1: Renal death, hospitalization, serious adverse event, or non-serious adverse event plus SCr* increase > 0.5 mg/dL

Composite 2: Renal death, hospitalization, serious adverse event, or non-serious adverse event plus SCr* increase > 100%

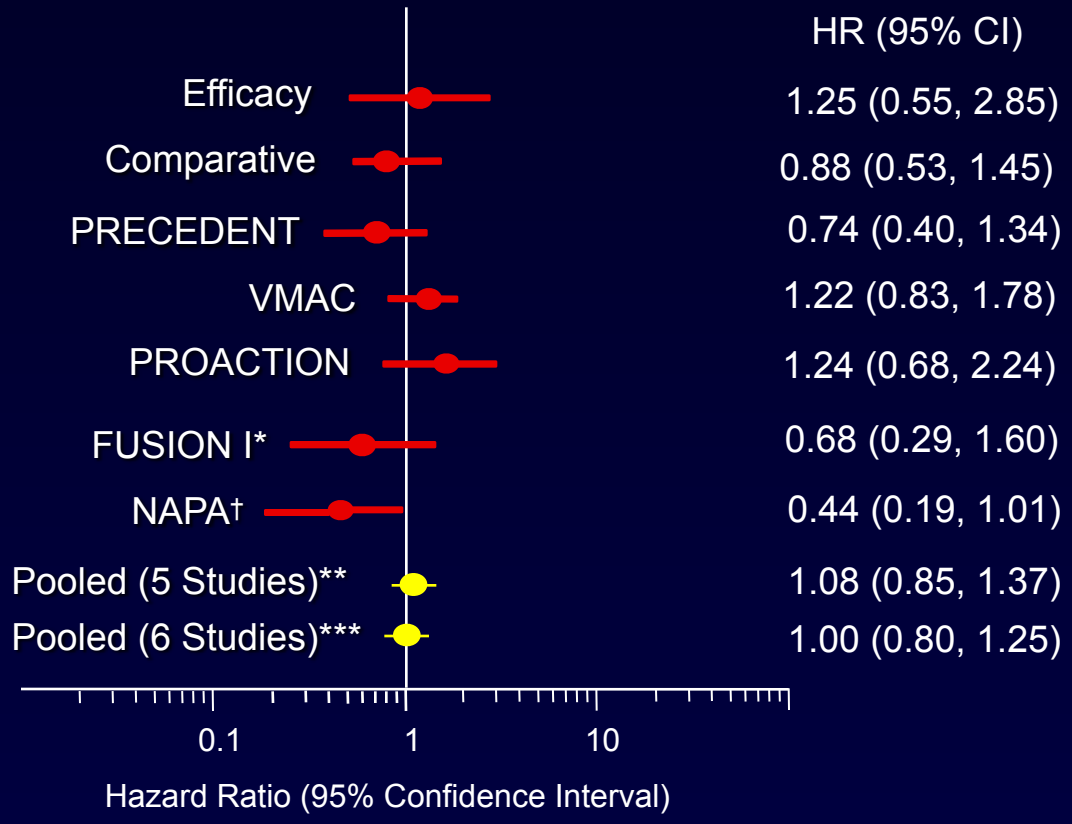
Composite 3: Renal death, hospitalization, serious adverse event, or non-serious adverse event plus SCr* increase ≥ 50% to ≥ 2 mg/dL

NAPA Trial:
Mean Change from Baseline in Post-Op SCr



Luber JM Jr; The NAPA Investigators. *JACC Feb 2007*

180-Day Unadjusted Mortality Hazard Ratios



* Data collected through week 16

† Luber JM Jr; The NAPA Investigators. *J Card Fail.* 2006;12(6 suppl):S73-S74. Abstract 235.

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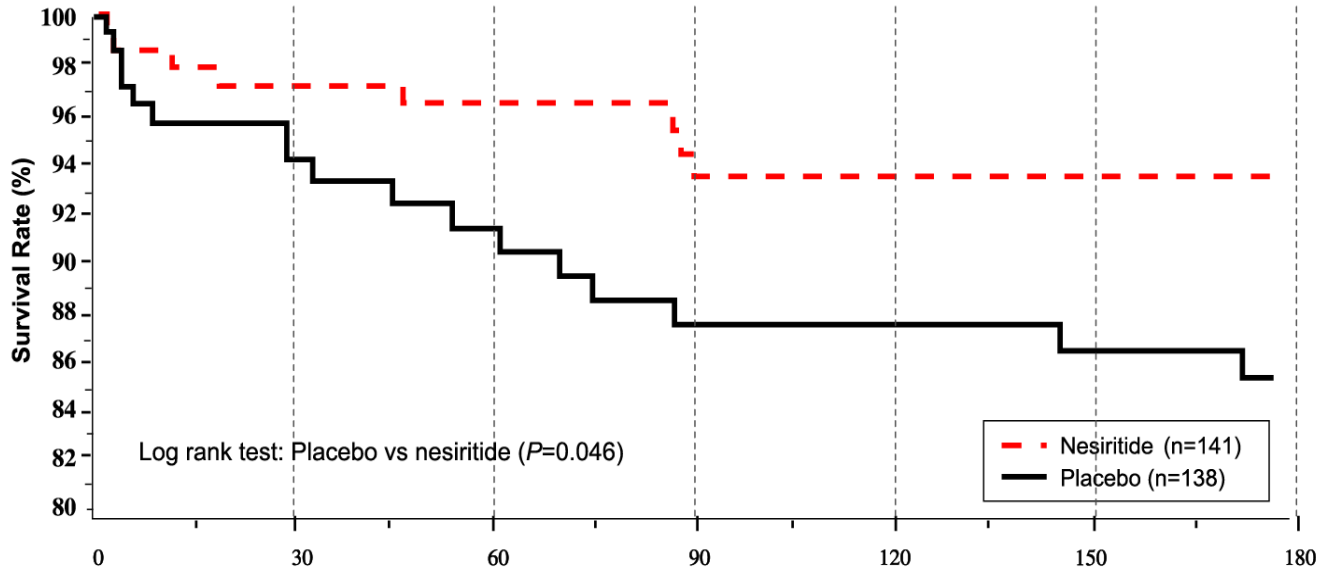
** Excludes FUSION I and NAPA

*** Excludes FUSION I

NAPA Trial: Kaplan-Meier Survival Curve by Treatment Group



Nesiritide:						
Death/Cumulative Death	4/4	1/5	3/8	0/8	0/8	0/8
Censored/Cumulative Censored	9/9	26/35	0/35	0/35	0/35	12/47
Remained at Risk	128	101	98	98	98	86
Placebo:						
Death/Cumulative Death	8/8	3/11	4/15	0/15	1/16	1/17
Censored/Cumulative Censored	11/11	24/35	0/35	0/35	0/35	8/43
Remained at Risk	119	92	88	88	87	78

Luber JM Jr; The NAPA Investigators. *JACC Feb 2007*

Acute Decompensated Heart Failure

Goals		Modalities
Early diagnosis **Improvement of hemodynamics and Sx** **Initiation of fluid removal**	Phase I	**Vasodilators** **Diuretics** **Ultrafiltration**
Correction of volume overload	Phase II	**Diuretics (IV to Oral)** **D/C Vasodilators** **Ultrafiltration**
Initial adjustment of oral meds		**ACE-1, spironolactone, digoxin**
Further adjustment of oral meds	Phase III	**Oral diuretics, ACE-I/ARB's** **Spironolactone, digoxin,** **BB's, Nitrates/Hydralazine.**
Evaluation for potential interventions including myocardial revascularization		**Myocardial revascularization, LV reconstruction, Valve surgery, AICD, CRT ,LVAD, transplantation.**

ADHERE®: Early Initiation of IV Vasoactive Therapy
Clinical Outcomes

	IV Vasoactive Started		P-value
	ED (n=4,096)	Inpatient Unit (n=3,499)	
Mortality (%)	4.3	10.9	<0.0001
Hospital LOS (days, median)	4.5	7.0	<0.0001
Transfer to ICU/CCU (%)	4	20	<0.0001
ICU/CCU time (days, median)	2.1	3.0	<0.0001
Invasive procedure (%)	19	27	<0.0001
Prolonged hospitalization (>7.1 days, 3rd quartile)	26	49	<0.0001

Reference: Peacock F, Emerman CL, Costanzo MR, Berkowitz RL, Cheng M. Early initiation of intravenous vasoactive therapy improves heart failure outcomes: an analysis from The Adhere Registry database. *Ann Emerg Med*. 2003;42(4):S26.

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