# Management of Acute Heart Failure: Review of New Guidelines

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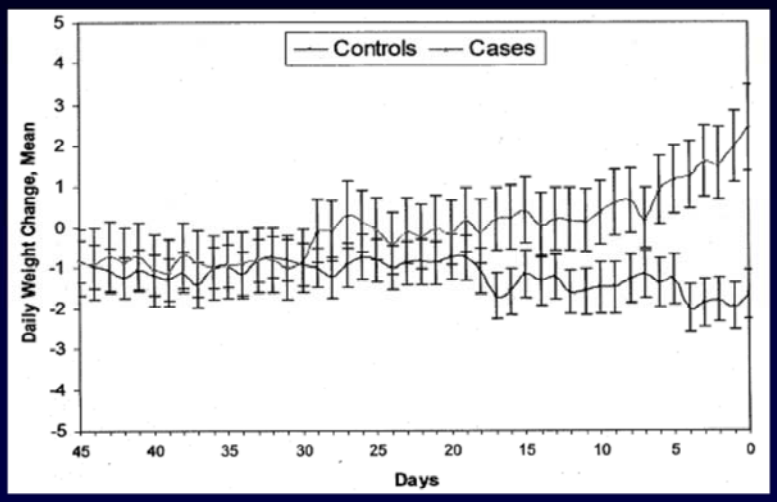
# Acute Heart Failure Syndromes: Public Health Issues

- 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%)

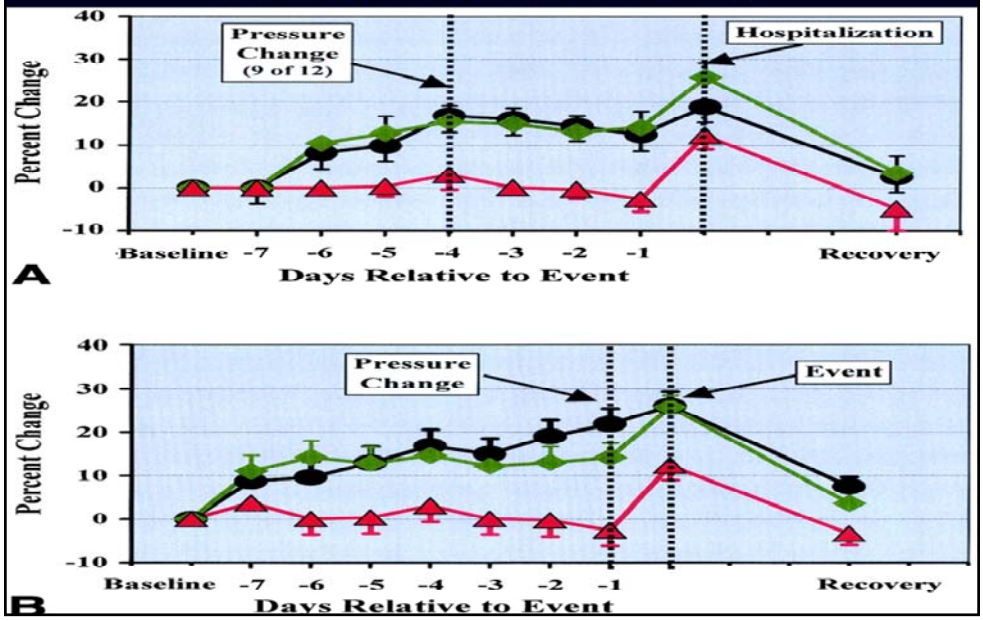
# Weight Change Preceding HF Hospitalization




Chaudhary et al Yale University 2006

## Change in PAD pressure prior to hospitalization

(Adamson et al JACC 2003:41:565)

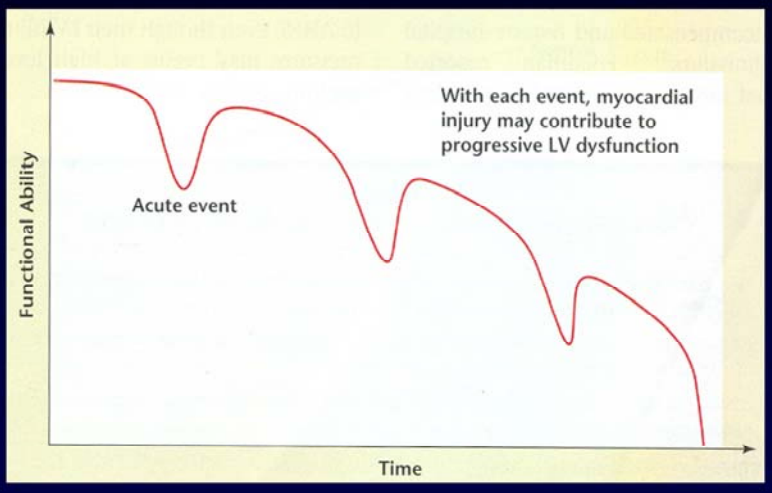


# Deleterious Effects of High LV Filling Pressure

- 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*

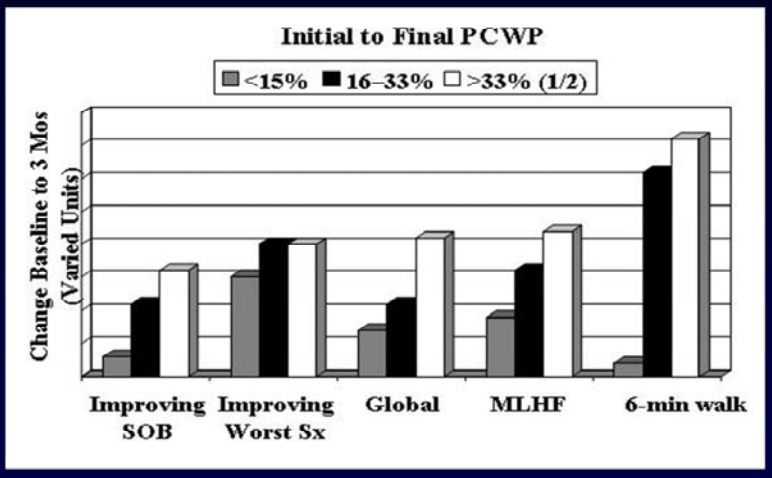
*Firth JD et al. *Lancet.* 1988;1033-1034.
Filippatos G et al . *Am J Physiol.* 1999;277:H445-H451.

# Episodes of Acute Exacerbation of Heart Failure

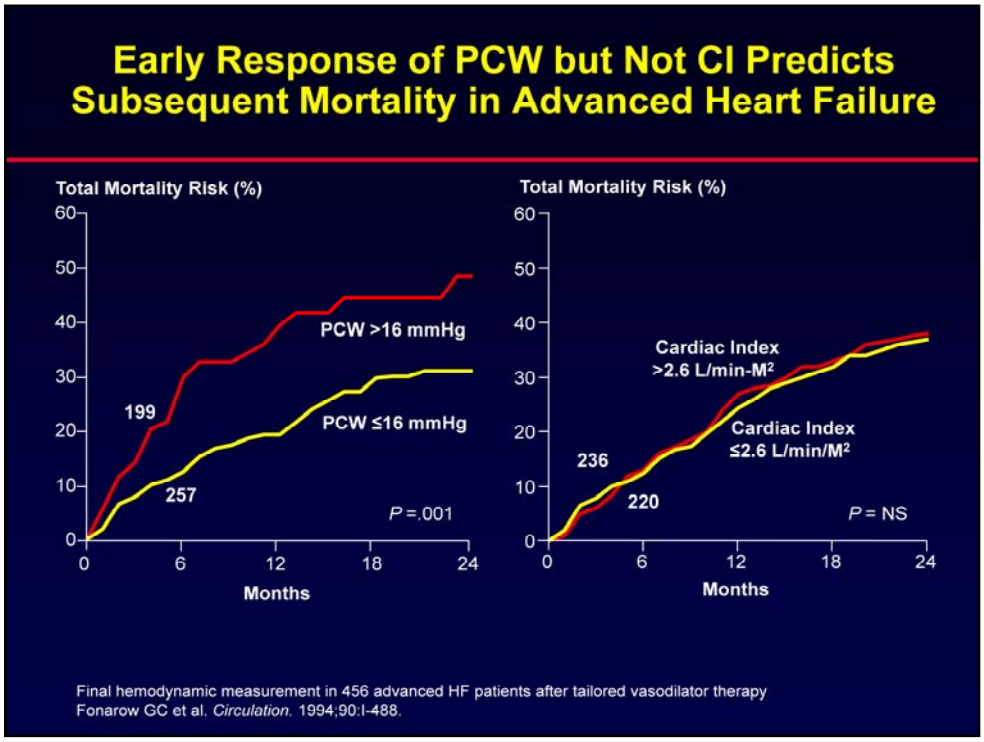



Episodes of an acute exacerbation of heart failure contribute to the progression of heart failure. LV, left ventricular.
Adopted with permission from Gheorghiade M et al. *Rev Cardiovasc Med.* 2006;7(suppl 1):S12-S24.

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




Roger et al submitted AHA 2006 Meeting




Advanced heart failure is characterized by hemodynamic abnormalities which may contribute to fatal decompensation and sudden death. To assess the importance of left ventricular (LV) filling pressures achieved early with intravenous vasodilator therapy in predicting clinical outcome, total mortality as a function of PCW was determined for 456 patients with advanced HF (EF .20+.07). IV vasodilators were titrated to approach PCW≤15 and SVR≤1200. High PCW on therapy predicted outcome by both life-table and Cox analysis. In patients with PCW >16 mm on Rx, 2-year mortality was 48% vs. 29% with PCW <16 (p<.001). High PCW was an independent predictor of overall mortality for HF patients. In contrast, both baseline and final resting cardiac index was not a predictor of mortality. Even when treated as a continuous variable cardiac index had no predictive role.

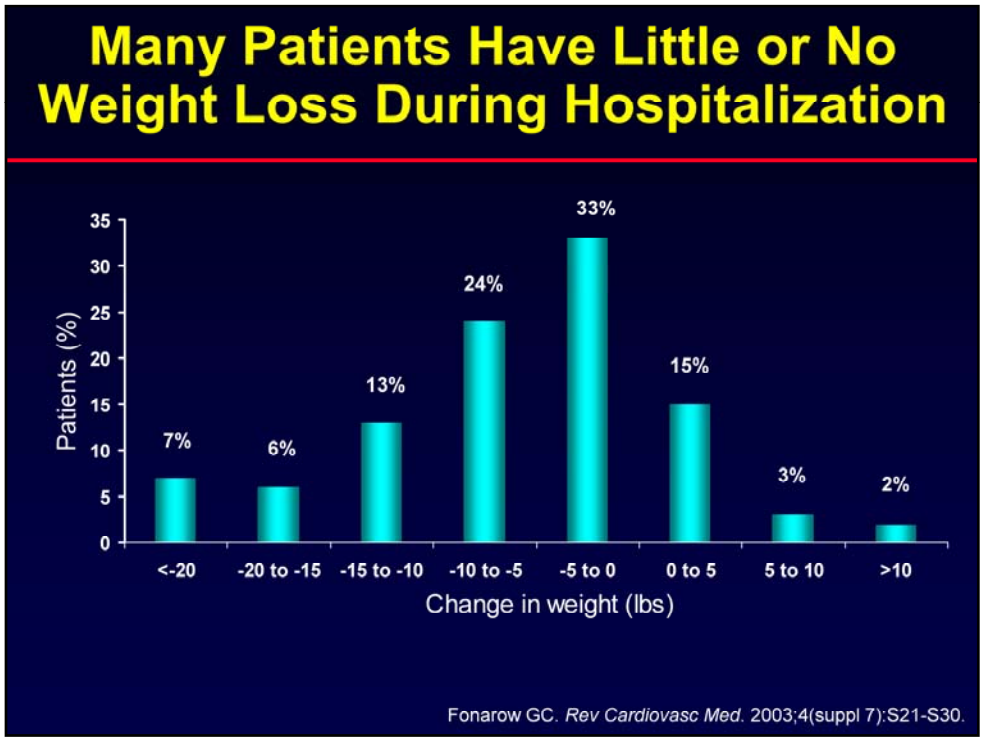
Both neurohumoral activation and high left ventricular filling pressures contribute to mortality in patients with advanced HF. Persistently high PCW identifies patients at high risk who should be considered for additional therapy or transplantation.

## 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)




Although congestion is the main reason for heart failure hospitalizations, the ADHERE Registry data showed that close to 50% of patients have minimal or no weight loss during their hospital stay. N=96,094

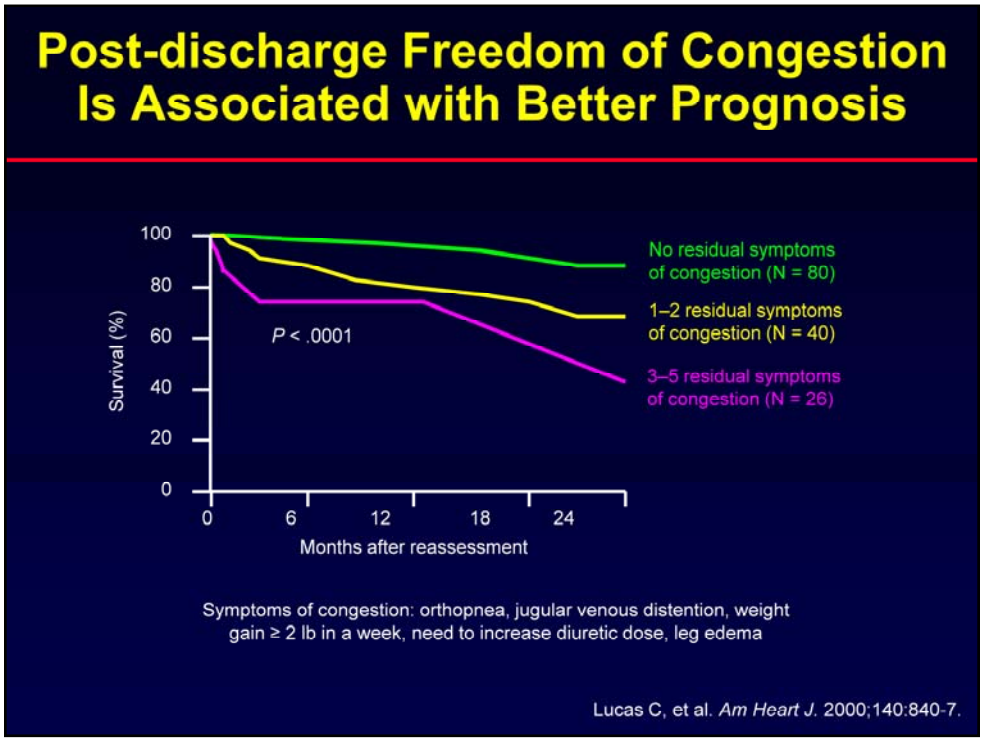
# HFSA Practice Guidelines 2006: Diuresis – How much and how fast?

# 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.




Patients with Class IV heart failure were assigned a congestion score 1 month post-discharge, then followed for 2 years. The differences between the 3 groups are significant (Mantel-Cox statistic). 2-year survival rates:

No residual symptoms: 87%

1-2 residual symptoms: 67%

3-5 residual symptoms: 41%

## 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

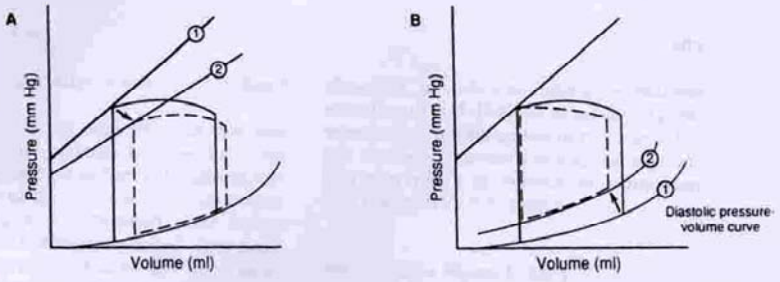
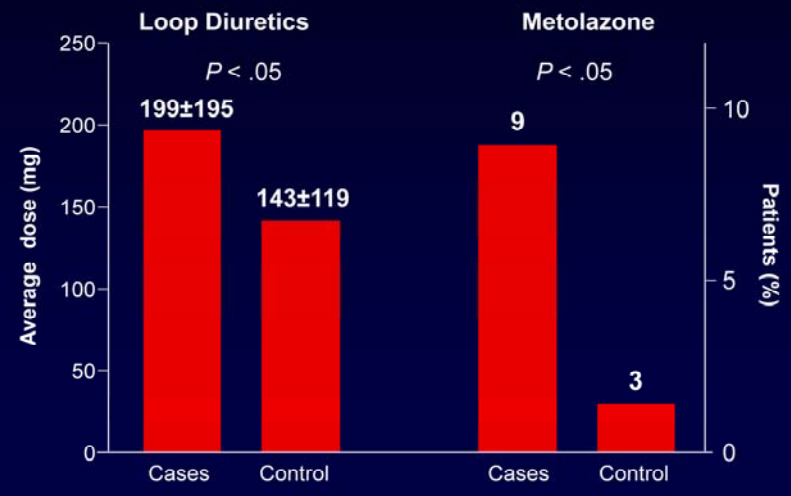


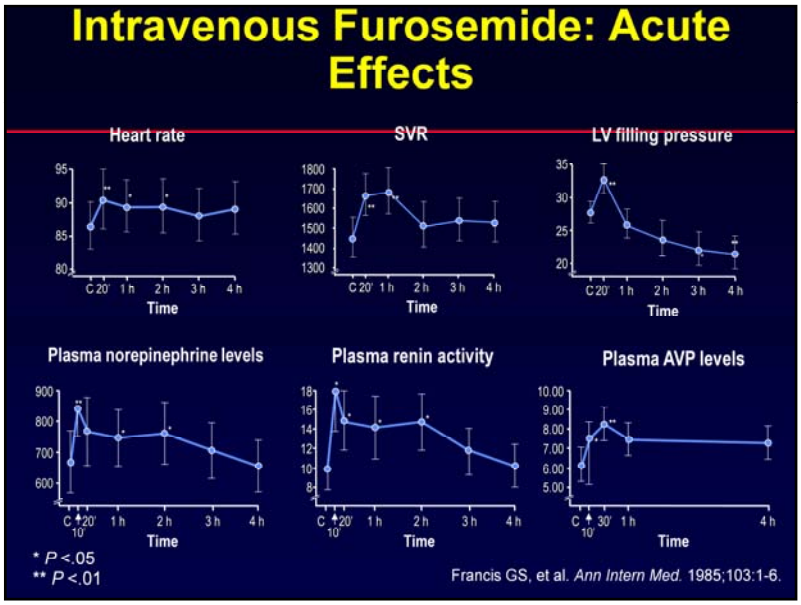

**Figure 9.7.** **A.** The normal pressure-volume loop (solid line) is compared with one demonstrating systolic dysfunction (dashed line). In systolic dysfunction due to decreased cardiac contractility, the end-systolic pressure-volume relation is shifted downward and rightward (from line 1 to line 2). 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.




Francis et al examined neurohormonal responses to diuretic therapy (IV furosemide 1.3 mg/kg) in 15 patients with severe chronic HF. Vasodilator therapy was withheld for 72 hours prior to neurohormonal assessments. After determining baseline values, hemodynamic measurements and blood samples were taken periodically up to 4 hours following furosemide injection.

As seen in this slide showing the response of hemodynamic variables at baseline (C) and following administration of the study drug, a significant impact was noted on the variables of HR, SVR, and LV filling pressure in association with furosemide administration. These indicators returned to control levels after 4 hours.

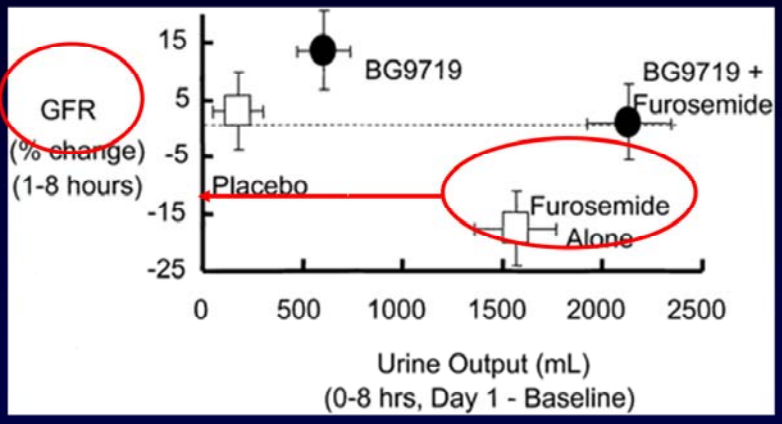
Also, plasma norepinephrine levels, plasma renin activity, and plasma AVP levels were above normal at baseline in all patients, demonstrating that neurohormonal activation was already present in those patients with severe HF. As seen in this slide, injection of furosemide caused further significant increases in the 3 variables measured: at 10 minutes, plasma renin increased from 9.9±8.5 to 17.8±16 ng/mL (*P*<.05); plasma norepinephrine increased from 667±390 to 839±368 pg/mL (*P*<.01); and AVP increased from 6.2±1.3 to 7.6±1.9 pg/mL (*P*<.05). All of these variables returned to baseline levels after 2 hours.

In addition, LV output was reduced within 20 minutes following furosemide administration (stroke volume index fell from 27±8 to 24±7 mL/min · $m^2$ body surface area [*P*<.01]).

Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure: activation of the neurohumoral axis. *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)**

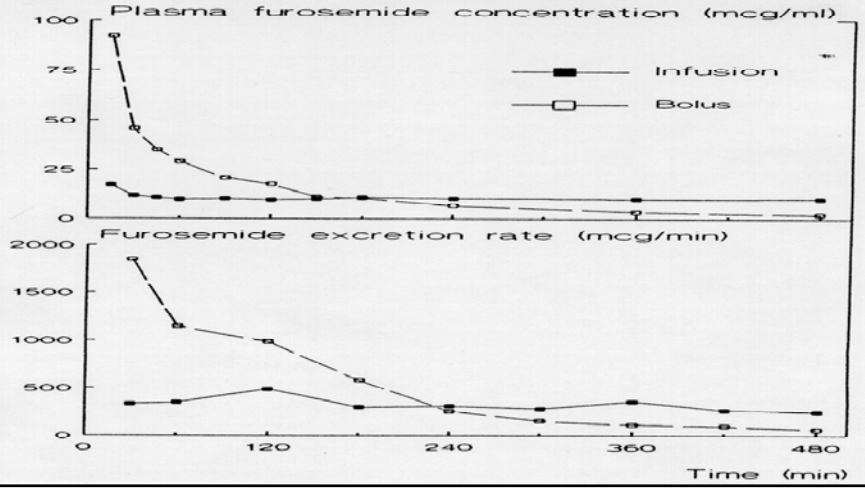



Gottlieb SS et al. *Circulation*. 2002;105:1348-1353.

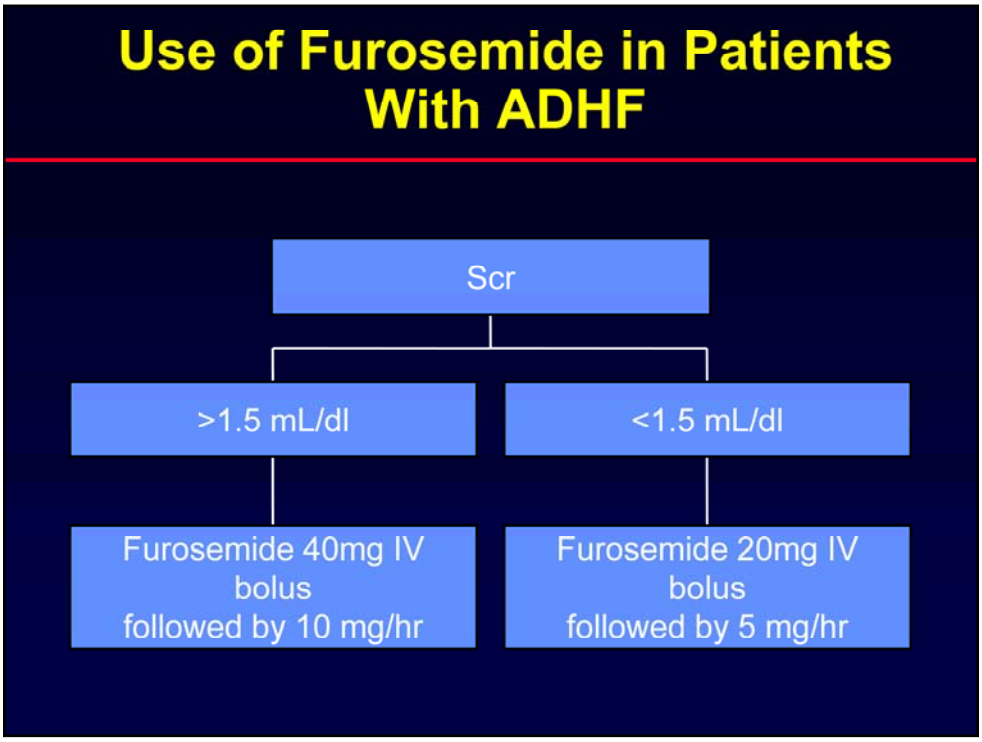
# Furosemide in severe CHF: Bolus Injection vs Continuous Infusion

## (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

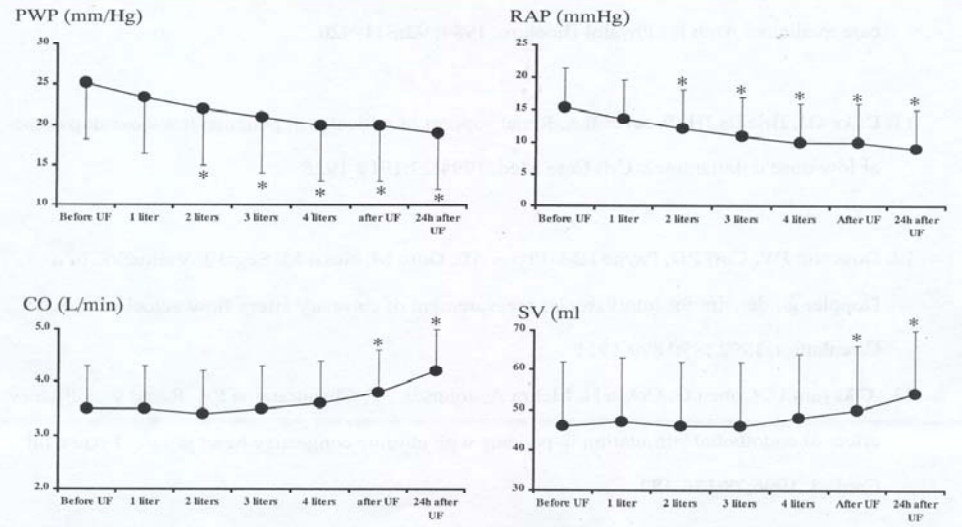



**Figure 1.** Mean pulmonary wedge pressure (PWP), mean right atrial pressure (RAP), cardiac output (CO) and stroke volume (SV) before, during and after extracorporeal ultrafiltration (UF). *$p < 0.01$ vs. before ultrafiltration.

# 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 |

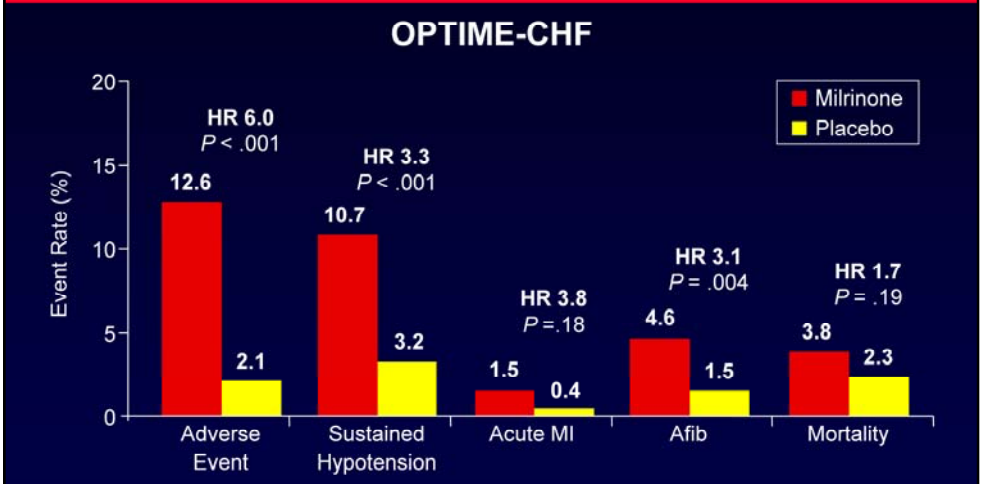
*Dose titrated to ↓ PAW ≥30%

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.

Despite this trial providing compelling evidence of a significant increase in adverse events, large numbers of patients hospitalized with acutely decompensated heart failure in the absence of cardiogenic shock or systemic hypoperfusion continue to be treated with inotropic agents.

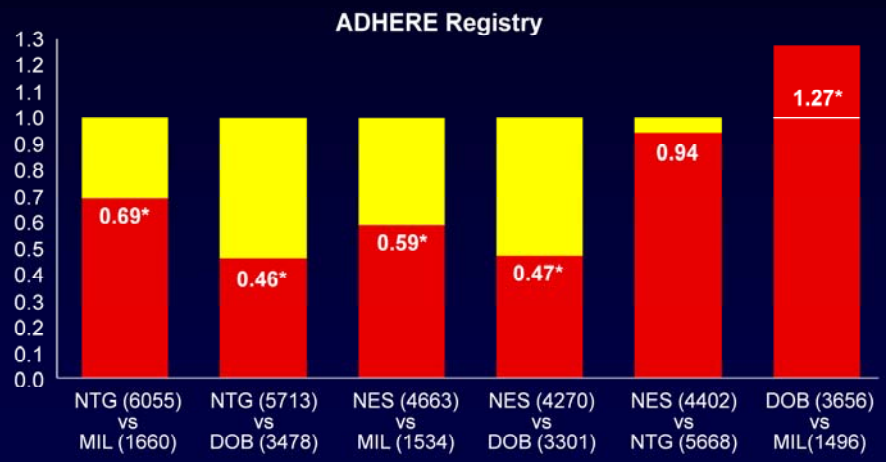
# HF Etiology and Response to Milrinone in Decompensated HF (OPTIME Study)

| | 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.

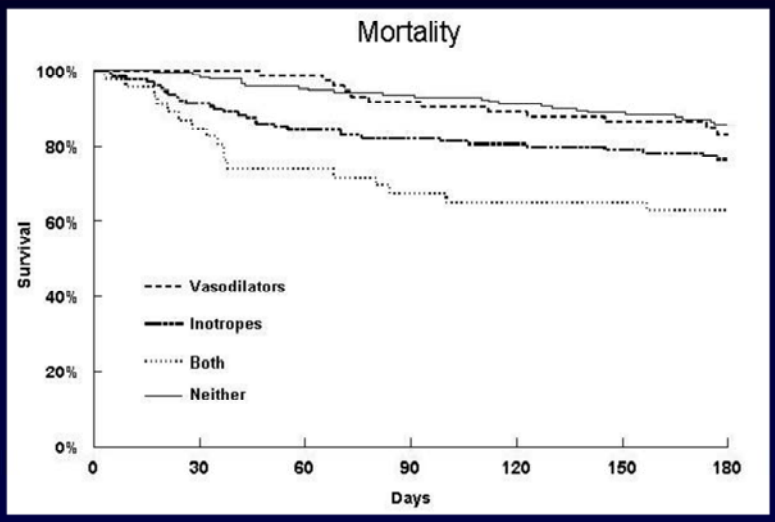
Abraham WT et al. *J Am Coll Cardiol.* 2005;46:57-64.

# 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.

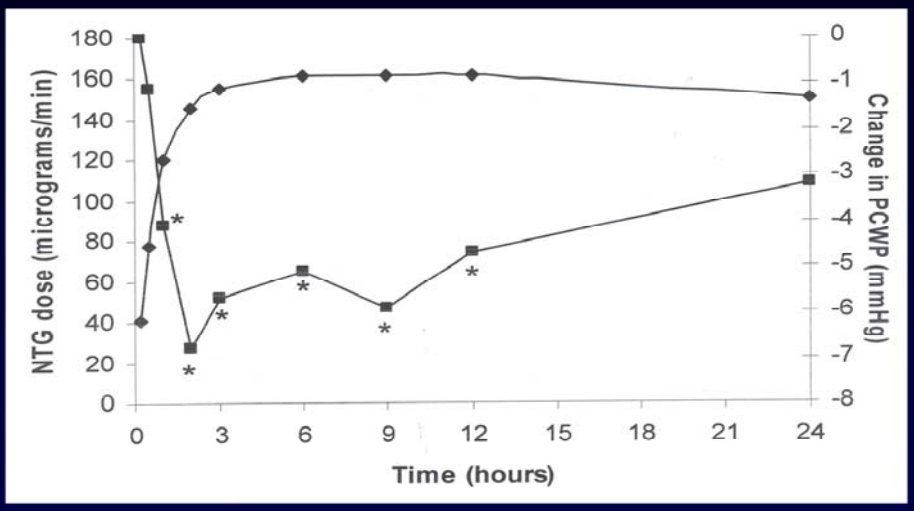
## HFSA Practice Guidelines 2006: Vasodilators

- 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

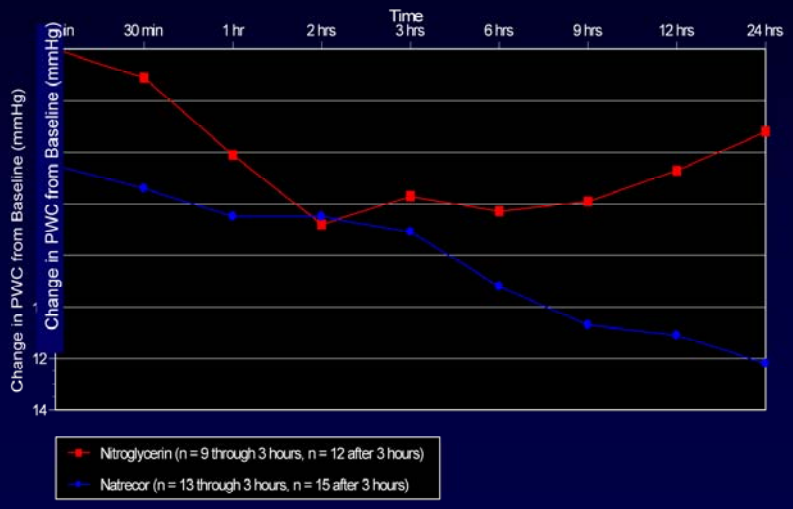



Elkayam U et al. *Am J Cardiol.* 2004;93:237-240.

# Nesiritide VS High Dose Nitroglycerin

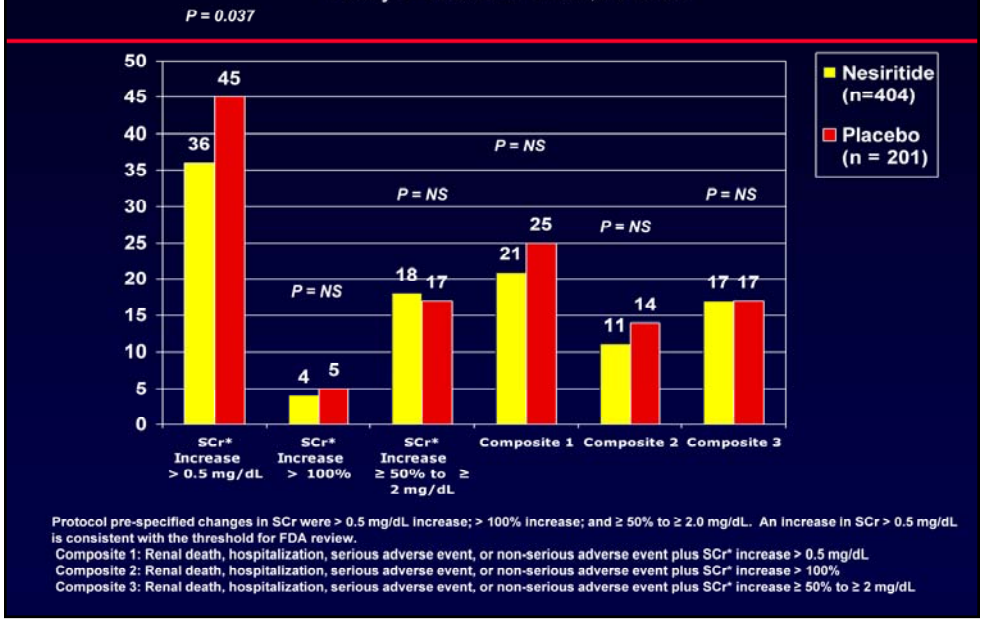
## Elkayam et al Am J Cardiol 2004;93:237-240

## Change in PCWP



# FUSION-II
## Percentage of Patients Meeting Renal Endpoint

Yancy C et al. JCF 2007;13:S136



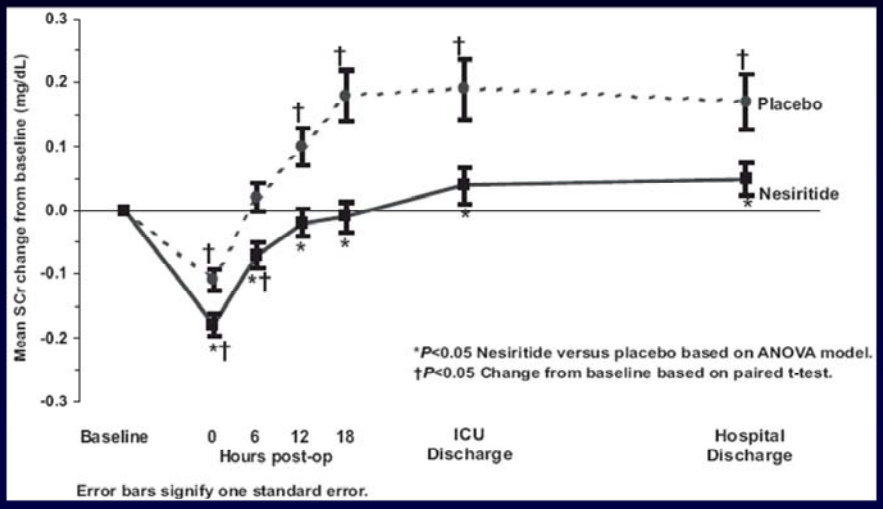

Protocol pre-specified changes in SCr were > 0.5 mg/dL increase; > 100% increase; and ≥ 50% to ≥ 2.0 mg/dL. An increase in SCr > 0.5 mg/dL is consistent with the threshold for FDA review.

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%

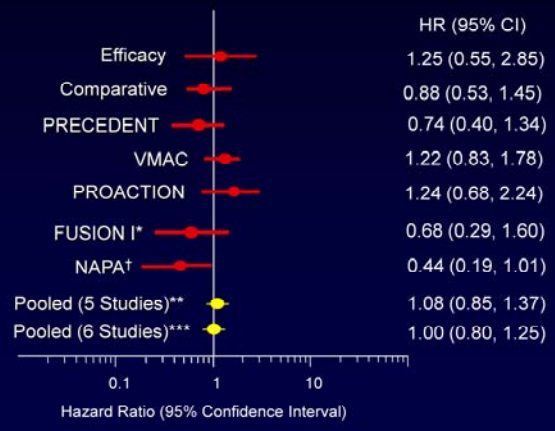
Composite 3: Renal death, hospitalization, serious adverse event, or non-serious adverse event plus SCr* increase ≥ 50% to ≥ 2 mg/dL

# 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



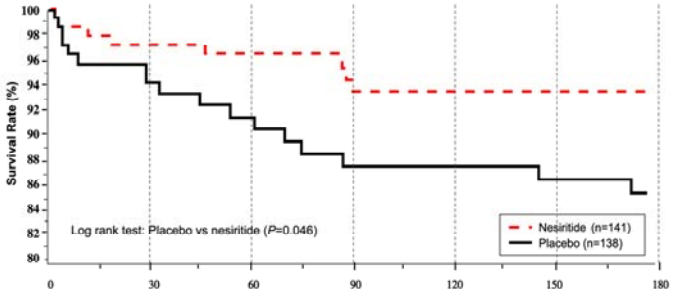

* Data collected through week 16

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

** 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<br>Improvement of hemodynamics and Sx<br>Initiation of fluid removal | Phase I | Vasodilators<br>Diuretics<br>Ultrafiltration |
| | Phase II | |
| Correction of volume overload | | Diuretics (IV to Oral)<br>D/C Vasodilators<br>Ultrafiltration |
| Initial adjustment of oral meds | | ACE-1, spironolactone, digoxin |
| | Phase III | |
| Further adjustment of oral meds | | Oral diuretics, ACE-I/ARB's<br>Spironolactone, digoxin,<br>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.

•The difference in the timing of treatment appeared to be reflected in clinical outcomes.

# Acute Decompensated Heart Failure

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