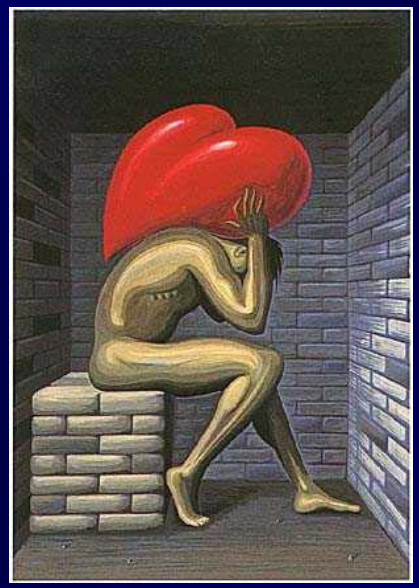
Acute Heart Failure Syndrome: Epidemiology and Emerging Predictors of Prognosis



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AHFS
Epidemiology

- 1 million admissions per year with the primary diagnosis of HF
- 3,000,000 admissions per year with primary or secondary diagnosis of HF
- Post discharge event rate (readmissions/ death): 35%* at 60 days

Much higher in pts. with BP<120;hyponatremia or high BUN*

AHFS: Hospitalizations

- Worsening chronic heart failure (HF)*
- Acute *de novo* heart failure (diagnosed for the first time)
- Advanced/end-stage/refractory HF

Gheorghiade et al Circulation 2005

Demographic and Clinical Characteristics of AHFS Patients

Data on approximately 200,000 patients

Median age (years)	75
Women	>50%
Hx of CAD	60%
Hx of Hypertension	70%
Hx of Diabetes	40%

Hx of Atrial Fibrillation	30%
Renal abnormalities	30%
SBP >140 mm Hg	50%
SBP 90-140 mm Hg	45%
SBP <90 mm Hg	5%

Adams KF, et al. *Am Heart J.* 2005;149: 209.
Cleland JGF et al. *Eur Heart J.* 2003; 24: 442;
Fonarow GC, et al. *J Am Coll Cardiol.* 2004; 844 – 4A.

AHFS: Clinical Presentation in US

- HF with SBP > 150 mm Hg (≅ 35%)
- HF with SBP 90 - 150 mm Hg (≅ 55%)
- HF with SBP < 90 mm Hg (≅ 8%)
- Cardiogenic shock (< 1%)
- Pulmonary edema (< 3%) *

*CXR in 91%; Radiographic pulmonary congestion in 74%.

- Isolated right-sided HF (?)
- ACS with HF
  - 25% of ACS have HF; 10% of AHFS have ACS

Gheorghiade M et al. *Circulation*. 2005; 112: 3958-3968.

Clinical Presentation of Patients Hospitalized with Heart Failure

(200,000 pts.)

Any Dyspnea (%)	**89**
Dyspnea at Rest (%)	**34**
Fatigue (%)	**32**
Rales (%)	**68**
Peripheral Edema (%)	**66**
Initial CXR Assessed (%)	**91**
Chest X Ray Congestion (%)	**75**

Fonarow GC. Rev Cardiovasc Med. 2003; 4 (Suppl. 7): 21
Cleland JG et al. Eur Heart J. 2003; 24: 442

AHFS

	ADHERE (>150,000 .)	EURO HF (11,327 pts.)	OPTIMIZE-HF (46,812 pts.) ¶
Prior heart failure (%)	75	65	87
New onset heart failure (%)	25	27	13
Cardiogenic shock (%)	2	< 1	< 1
LVEF < 40%	59	46	52

Adams KF, et al. *Am Heart J.* 2005;149: 209.
Cleland JGF et al. *Eur Heart J.* 2003; 24: 442;
Fonarow GC, et al. *J Am Coll Cardiol.* 2004; 844 – 4A.

AHFS: Outcomes

	ADHERE (>150,000 pts.)	EURO HF (11,327 pts.)	OPTIMIZE-HF (46,812 pts.) ¶
> 2.5 kg weight loss (%)	50	N/A	50
HF Symptoms			
Unchanged/worse	< 1		< 3
Better (symptomatic)	40		40
Better (asymptomatic)	50		51
Length of stay (days)	4.3 (3, 7)	11	4 (3, 7)
In-hospital mortality (%)	4	7	4
Mortality at 2-3 mos. (%)	N/A	6.5	9
Readmissions at 2-3 mos. (%)	N/A	24	31

Adams KF, et al. *Am Heart J.* 2005;149: 209.
Cleland JGF et al. *Eur Heart J.* 2003; 24: 442;
Fonarow GC, et al. *J Am Coll Cardiol.* 2004; 844 – 4A.

AHFS

Emerging Predictors of Prognosis:

a) Blood Pressure

b) Serum Sodium

c) BUN

d)Troponin

e)Congestion

The Relation Between Admission Systolic Blood Pressure and Outcomes in Hospitalized Patients with Heart Failure: An OPTIMIZE-HF Analysis

Characteristic % (SD)	Admission SBP mmHg			
	≤119 (n=12,252)	120-139 (n=12,096)	140-161 (n=12,099)	≥161 (n=12,120)
Mean Age, y	72.9 (14.0)	74.0 (13.5)	73.8 (13.6)	72.1 (14.6)
Women	43.4	49.1	45.2	48.7
African American	12.4	14.0	18.8	25.7
Mean EF (%)	33.3 (17.4)	37.8 (17.6)	40.9 (17.1)	44.4 (16.5)
ICD	9.3	5.2	3.6	2.3
Ischemic Etiology	50.7	48.8	44.1	39.2
HTN Etiology	13.4	18.1	25.4	34.8
Serum Cr>2 (mg/dl)	20.7	18.0	18.1	21.5
Mean Wt change (kg)	-2.45 (5.00)	-2.68 (4.82)	-2.60 (4.64)	-2.42 (4.62)
Mean SBP Admission	104.8 (10.9)	129.3 (5.8)	149.6 (6.5)	187.4 (21.7)
Mean SBP DC	111.6 (18.7)	120.6 (19.1)	128.3 (20.2)	138.2 (22.5)
Edema Admission	63.9	65.1	65.6	63.9
Edema DC	30.1	27.1	27.0	23.8
Total mortality in-hospital	**7.2**	**3.6**	**2.5**	**1.7**
Total mortality 60-90 days D/C	**14.0**	**8.4**	**6.0**	**5.4**
Readmission	**30.6**	**29.9**	**30.3**	**27.6**
Mean LOS, days	6.5 (6.6)	5.7 (5.3)	5.4 (5.0)	5.1 (4.8)

Gheorghiade M et al. J Card Fail. 2005; 11 (6A)

OPTIMIZE - HF

SBP Deciles	SBP Range	Total # of Patients	# of Inhospital Deaths	Inhospital Death Rate (%)
1	50 - 104 (mmHg)	5140	498	9.69
2	104 - 114 (mmHg)	4673	262	5.61
3	114 - 123 (mmHg)	5042	233	4.62
4	123 - 131 (mmHg)	4750	176	3.71
5	131 - 139 (mmHg)	4743	153	3.23
6	139 - 147 (mmHg)	4918	133	2.70
7	147 - 156 (mmHg)	4865	110	2.26
8	156 - 168 (mmHg)	4760	95	2.00
9	168 - 188 (mmHg)	4955	98	1.98
10	188 - 300 (mmHg)	4721	70	1.48
Total	50 - 300 (mmHg)	48567	1828	3.76

Gheorghiade M et al. J Card Fail. 2005; 11 (6A)

Clinical Presentation: Normal vs. High BP

High (VASCULAR FAILURE)

- Rapid worsening
- Fluid redistribution
- PCWP acute +++
- CXR pulm. congestion +++
- Weight gain/ Edema +
- LVEF relatively preserved

Normal (CARDIAC FAILURE)

- Gradual worsening (days)
- Fluid accumulation
- PCWP chronic +++
- CXR pulm. congestion +
- Weight gain/ Edema +++
- LVEF usually low

Gheorghiade, Metra et al Am J Cardiol 2005

AHFS: Therapeutic Groups

- High Blood Pressure
- Normal Blood Pressure
- Low Blood Pressure

AHFS

Emerging Predictors of Prognosis:

a) Blood Pressure

b) Serum Sodium

c) BUN

d)Troponin

e)Congestion

Lower Serum Sodium Is Associated With Increased Short-Term Mortality in Hospitalized Patients With Worsening Heart Failure

Results From the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study

Liviu Klein, MD; Christopher M. O'Connor, MD; Jeffrey D. Leimberger, PhD; Wendy Gattis-Stough, PharmD; Ileana L. Piña, MD; G. Michael Felker, MD; Kirkwood F. Adams, Jr, MD; Robert M. Califf, MD; Mihai Gheorghiade, MD; for the OPTIME-CHF Investigators

Background—The prognostic value of serum sodium in patients hospitalized for worsening heart failure has not been well defined.

Methods and Results—The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study randomized 949 patients with systolic dysfunction hospitalized for worsening heart failure to receive 48 to 72 hours of intravenous milrinone or placebo in addition to standard therapy. In a retrospective analysis, we investigated the relationship between admission serum sodium and the primary end point of days hospitalized for cardiovascular causes within 60 days of randomization, as well as the secondary end points of in-hospital mortality, 60-day mortality, and 60-day mortality/rehospitalization. The number of days hospitalized for cardiovascular causes was higher in the lowest sodium quartile: 8.0 (4.5, 18.5) versus 6 (4, 13) versus 6 (4, 11.5) versus 6 (4, 12) days ($P<0.015$ for comparison with the lowest quartile). Lower serum sodium was associated with higher in-hospital and 60-day mortality: 5.9% versus 1% versus 2.3% versus 2.3% ($P<0.015$) and 15.9% versus 6.4% versus 7.8% versus 7% ($P=0.002$), respectively. There was a trend toward higher mortality/rehospitalization for patients who were in the lowest sodium quartile. Multivariable-adjusted Cox proportional hazards analysis showed that serum sodium on admission, when modeled linearly, predicted increased 60-day mortality: sodium (per 3-mEq/L decrease) had a hazard ratio of 1.18 with a 95% CI of 1.03 to 1.36 ($P=0.018$).

Conclusions—In patients hospitalized for worsening heart failure, admission serum sodium is an independent predictor of increased number of days hospitalized for cardiovascular causes and increased mortality within 60 days of discharge. (*Circulation*. 2005;111:2454-2460.)

Key Words: heart failure ■ prognosis ■ sodium ■ risk factors

OPTIME-CHF: Hyponatremia as Predictor

	Na ≤ 136 mEq/l (N=256; 27%)	Na > 136 mEq/l (N=687; 73%)	p-value
60-day mortality (%)	16	7	0.0001*
Readmission or death within 60 days	42	33	0.017

* Log - rank statistic

Klein L et al. Circulation 2005

1075-149

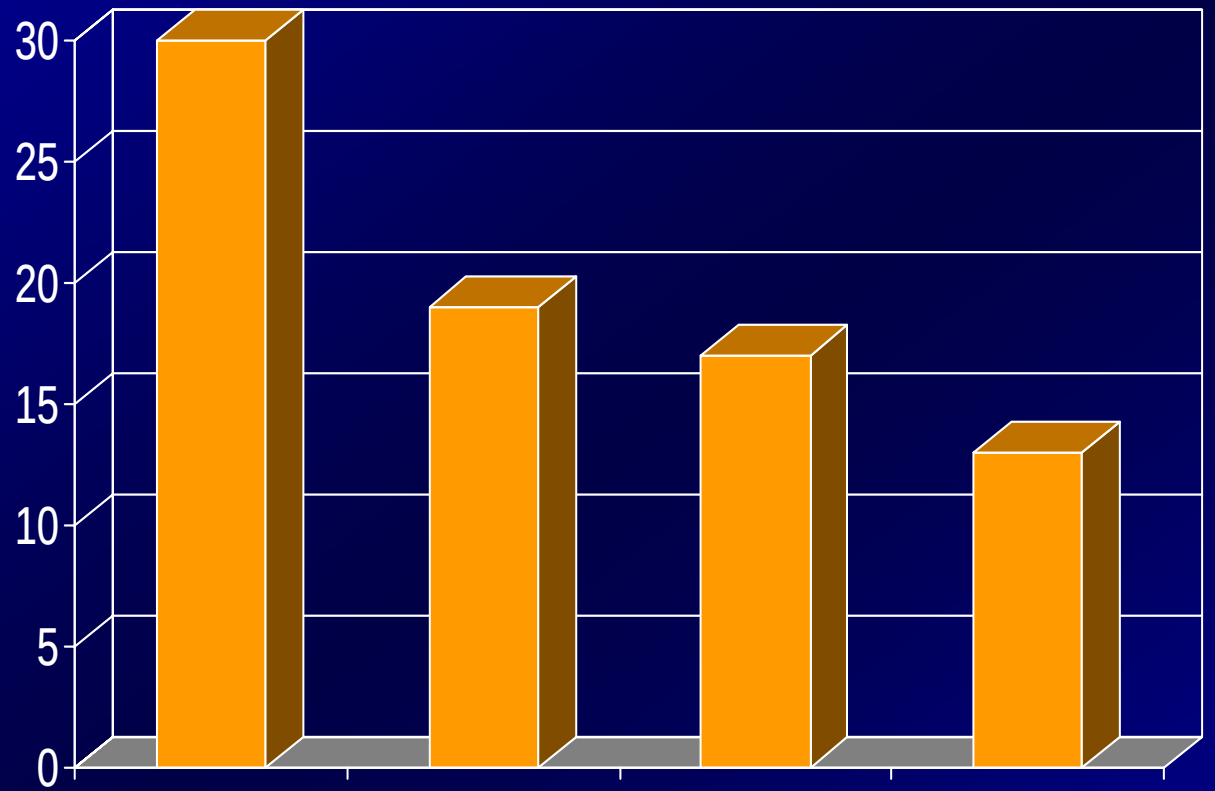
Hemodynamic Characterization and Prognostic Value of Persistent Hyponatremia in Patients With Severe Heart Failure in the ESCAPE Trial

Mihai Gheorghiade, Anne S. Hellkamp, Ileana L. Pina, Gregg C. Fonarow, Teresa De Marco, Daniel F. Pauly, Joseph Rogers, Thomas DiSalvo, Javed Butler, Joshua M. Hare, Gary S. Francis, Christopher M. O'Connor, Northwestern Feinberg School of Medicine, Chicago, IL

Background: The significance of hyponatremia (HN) and its correlation with hemodynamics have not been studied in heart failure (HF) patients (pts).
Methods: The ESCAPE trial randomly assigned 433 pts with severe HF to receive therapy guided by pulmonary artery catheter or by clinical assessment alone. Of these, 400 pts had serial serum Na measurements during hospitalization. Persistent HN was defined as Na ≤ 134 mEq/L throughout hospitalization. Cox proportional hazards models, with discharge Na as a continuous variable and adjusted for other predictors, were used to examine the association of Na and postdischarge outcomes. **Results:** At baseline, 82 pts (21%) had HN; 71 of them had HN at discharge. Also at baseline 318 pts (79%) had normal Na; of these, 266 had normal Na throughout hospitalization, while 52 had a decline by discharge. Discharge Na was a significant predictor of subsequent mortality (p=0.003; HR=1.25; 95% CI=1.08, 1.46 for each 3-mEq/L decrease) (Table) and of rehospitalization for HF (p=0.034; HR=1.11; 95% CI=1.01, 1.23 for each 3-mEq/L decrease). **Conclusions:** In pts with severe HF, HN is relatively common and usually not corrected during hospitalization. Compared with pts with normal Na, pts with HN have a higher pulmonary capillary wedge pressure and right atrial pressure after treatment, despite receiving higher diuretic doses and undergoing similar reductions in body weight. HN at discharge is associated with very high risk of early mortality and rehospitalization for HF.

Characteristic	Normal Na (n=266) median(25th,75th)	Persistent Hyponatremia (n=71) median (25th,75th)	p
Baseline ejection fraction (%)	20 (15, 25)	16 (14, 20)	0.006
Baseline BUN (mg/dL)	18 (13, 26)	33 (24, 56)	0.001
Baseline systolic blood pressure (mm Hg)	111 (97, 126)	102 (89, 116)	0.037
Baseline cardiac index (L/min/m^2)	1.94 (1.60, 2.40)	1.80 (1.57, 2.10)	0.073
Baseline PCWP (mm Hg)	24 (18, 32)	27.5 (19, 32)	0.62
Last measured PCWP (mm Hg)	16 (12, 20)	21 (16.5, 25)	0.015
Change in weight (kg)	-2.5 (-5.5, -0.6)	-3.7 (-8.1, -0.1)	0.21
Furosemide dose (mg/day)	133 (60, 218)	186 (108, 292)	0.003
Death within 6 months	15% (41)	31% (22)	0.003

Mortality at 6 months in pts. admitted with HF in the ESCAPE TRIAL



NA:	121-134	135-136	137-139	140-147
CI	1.8 → 2.3	1.9 → 1.2	2.1 → 2.1	1.9 → 2.1
PCWP	27 → 19	22 → 18	25 → 15	22 → 17
RAP	15 → 9	12 → 8	12 → 8	9 → 8

Gheorghiade 2005

JACC February 1, 2005

1075-148

Improvement in Hyponatremia During Hospitalization for Worsening Heart Failure Is Associated With Improved Outcomes: Insights From the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF)

Mihai Gheorghiade, Kirkwood Adams, Christopher O'Connor, Christopher Zimmer, Frank Czerwiec, Ouyang John, Orlandi Cesare, Feinberg School of Medicine-Northwestern University, Chicago, IL

Background: Hyponatremia (HYPO) is a known predictor of mortality in pts hospitalized for worsening heart failure. However, it is not known whether improving sodium levels in hyponatremic patients would lead to improved outcomes. We studied the relationship between changes in serum sodium during hospitalization and mortality in hyponatremic patients admitted for decompensated heart failure (HF) in a post-hoc analysis of the ACTIV in CHF trial.

Methods: The ACTIV in CHF trial randomized 319 pts with systolic dysfunction hospitalized for worsening HF to receive placebo or 30, 60, or 90 mg tolvaptan, a novel vasopressin V_2 receptor antagonist. Cox proportional hazards regression-analysis was used to explore the relationship between HYPO (Na^+<136 mEq/L) at baseline and improvements ≥2 mEq/L in serum sodium by hospital discharge, and mortality within sixty days.

Results: Mild to moderate HYPO was observed in 69 patients (21.6%), with median (IR) levels of 133 (131, 134) mEq/L at baseline. After adjustment for other covariates, HYPO was a highly statistically significant predictor of mortality at 60 days post hospital discharge ($p<0.005$). At hospital discharge, 45 out of 69 pts (65.2%) had improvements in serum sodium levels ≥2 mEq/L. These pts had a median (IR) baseline sodium of 133 (131, 134) mEq/L, as compared with 133 (132, 135) mEq/L in those who did not improve by hospital discharge. Pts with a serum sodium improvement at discharge had a mortality rate of 15.6% at 60 days post discharge, as compared with a 30.4% mortality rate in those showing no improvement ($p=0.0842$, log-rank). After adjustment for other covariates, change in serum sodium at hospital discharge was a statistically significant predictor of mortality at 60 days post hospital discharge ($p<0.0269$).

Conclusions: Hyponatremia appears to be a modifiable therapeutic target and not purely a marker of disease severity. Improvements in serum sodium levels during hospitalization were associated with improved mortality at 60 days. Prospective studies are necessary in this population to assess if therapies aimed at increasing serum sodium will result in improved outcome.

Serum Sodium Concentration and Mortality in Patients Admitted with Heart Failure: An OPTIMIZE-HF Analysis

Mihai Gheorghiade, MD*, Wendy Gattis Stough, PharmD†, Christopher M. O'Connor, MD†, William T. Abraham, MD‡, Barry H. Greenberg, MD§, James B. Young, MD‖, Nancy M. Albert, PhD, RN¶, Clyde W. Yancy, MD#, Lilin She, PhD†, and Gregg C. Fonarow, MD**, on behalf of the OPTIMIZE-HF Investigators and Coordinators

ABSTRACT

BACKGROUND

GOALS AND OBJECTIVES

METHODS

Table 1. OPTIMIZE-HF Registry and Process of Care Improvement Program

RESULTS

Table 2. Patient Characteristics at Hospital Admission and Discharge

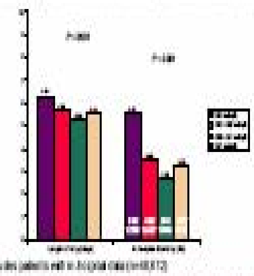


Figure 1. In-hospital Outcomes in Patients by Admission Serum Sodium

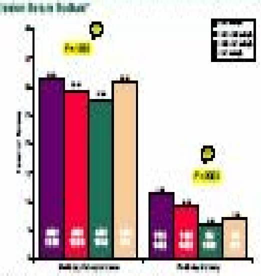


Figure 2. Outcomes in the Cohort of Patients with 60-90 day Follow-up by Admission Serum Sodium

Table 3. Clinical Outcomes in Patients With and Without LVSD by Admission Serum Sodium

Table 4. Effect of Serum Sodium (per 3 mEq/L decrease) on Clinical Outcomes by Multivariable Analysis

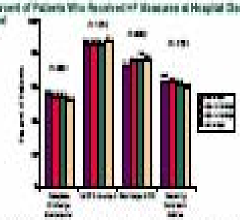


Figure 3. Percent of Patients Who Received HF Measures at Hospital Discharge by Serum Sodium Level

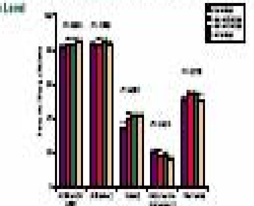


Figure 4. Eligible Patients Receiving Other Medications at Hospital Discharge by Serum Sodium Level

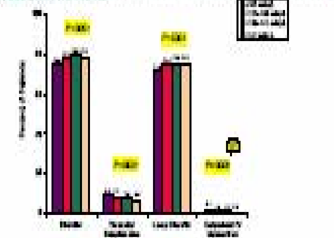


Figure 5. Use of Discharge Diuretics and Outpatient IV Vasoactive Therapies by Serum Sodium Level in All Patients

LIMITATIONS

CONCLUSIONS

REFERENCES

OPTIMIZE-HF

AHFS

Emerging Predictors of Prognosis:

a) Blood Pressure

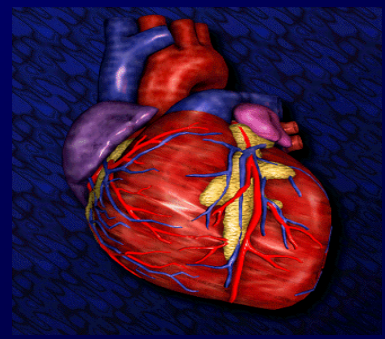
b) Serum Sodium

c) BUN

d)Troponin

e)Congeston

The Cardio-Renal Syndrome in Heart Failure



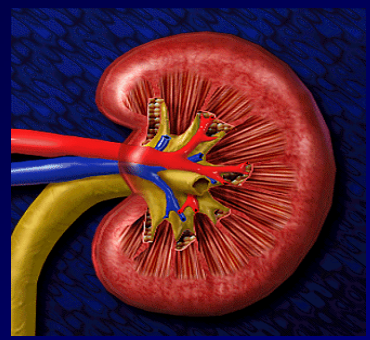
Decreased cardiac output

Neurohormonal Activation

Increased venous pressure

Diminished blood flow

Decreased renal perfusion



Impaired renal function

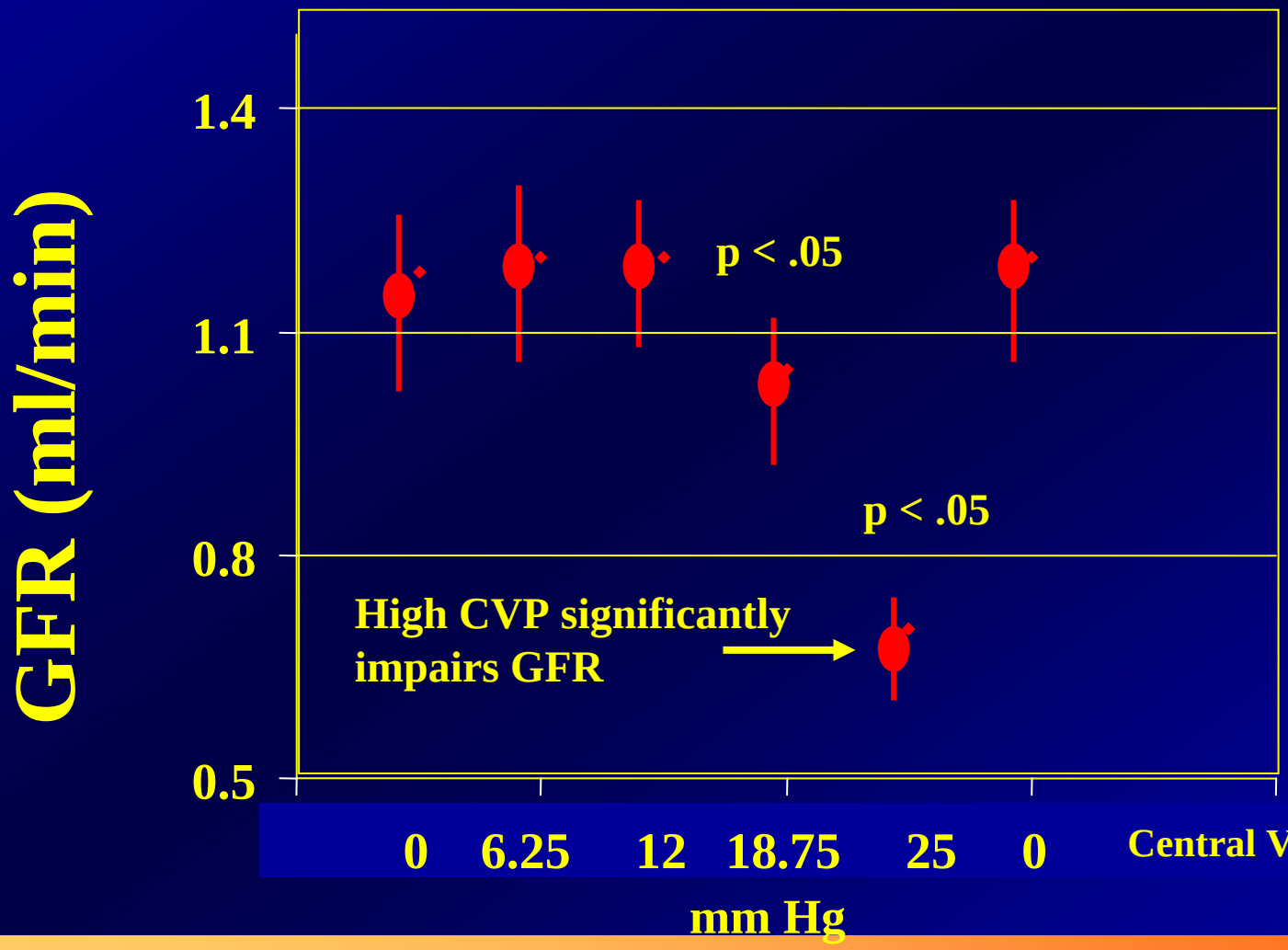
Increased water & Na^+ retention (Congestion)

Decreased cardiac performance

Modified from Abraham WT

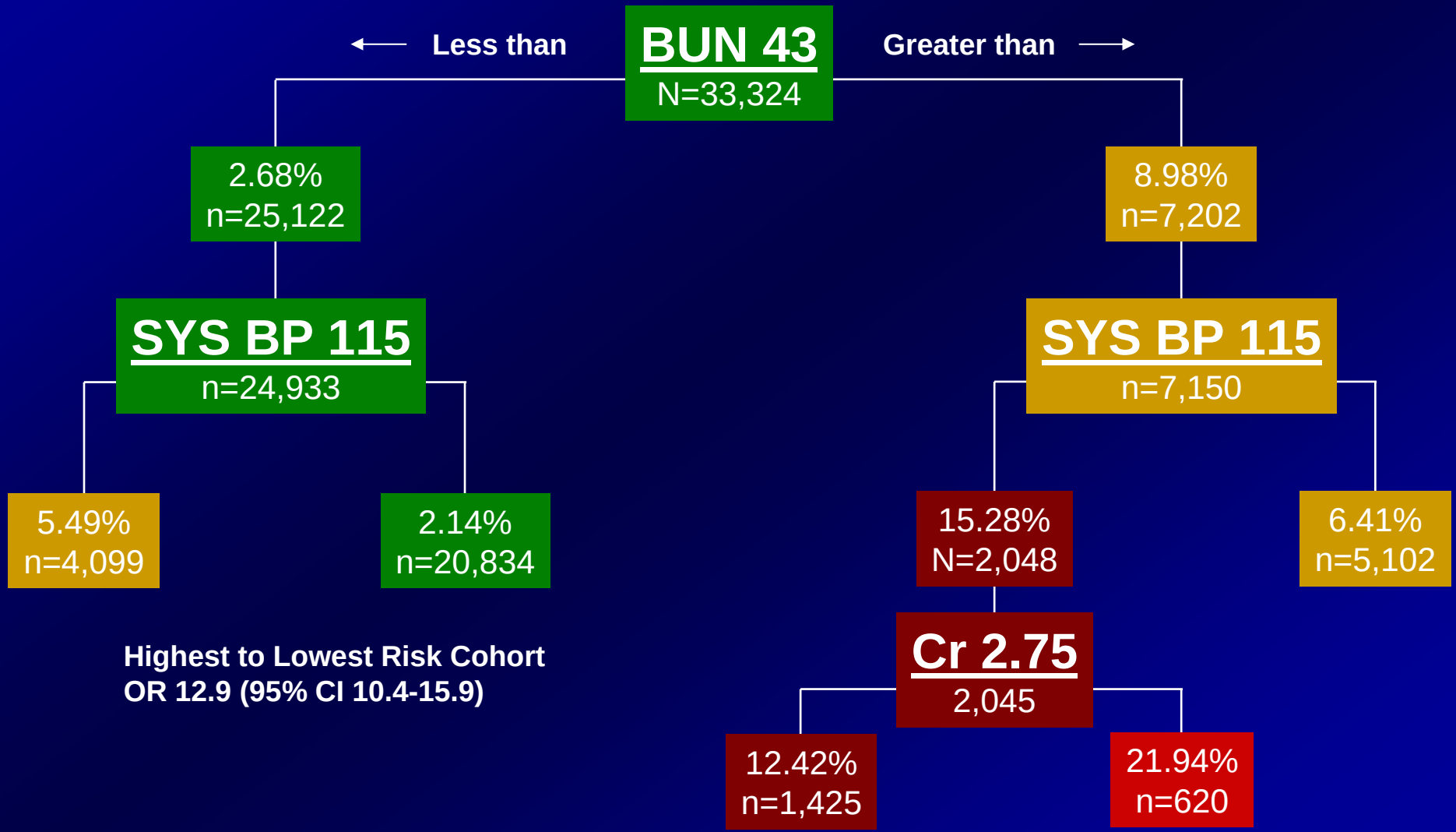
Effect of increasing central venous pressure on GFR in intact dogs with constant BP

Firth et al Lancet 5/7/88



Raised Venous Pressure: A direct cause of renal sodium retention

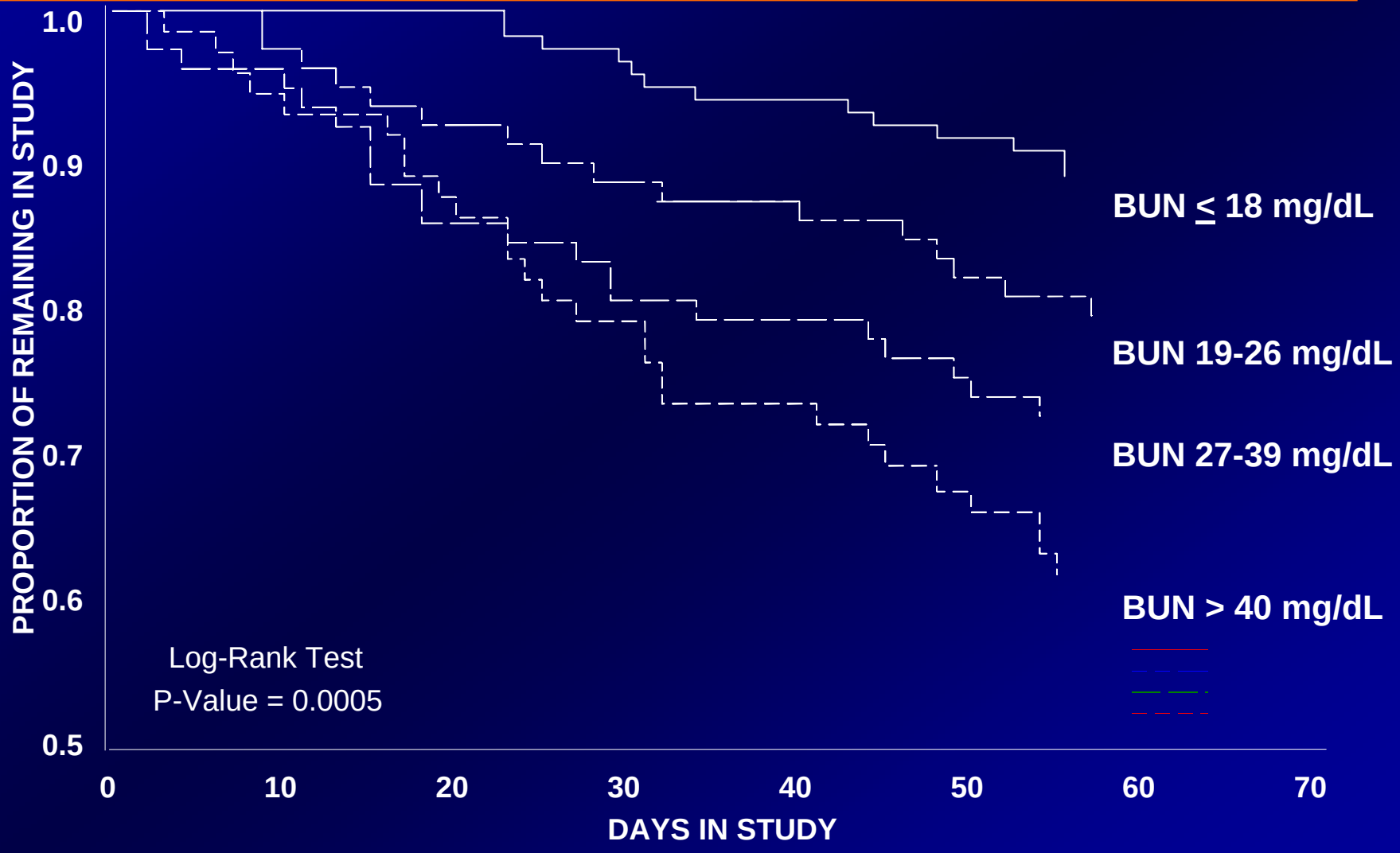
Predictors for In-hospital Mortality



Highest to Lowest Risk Cohort
OR 12.9 (95% CI 10.4-15.9)

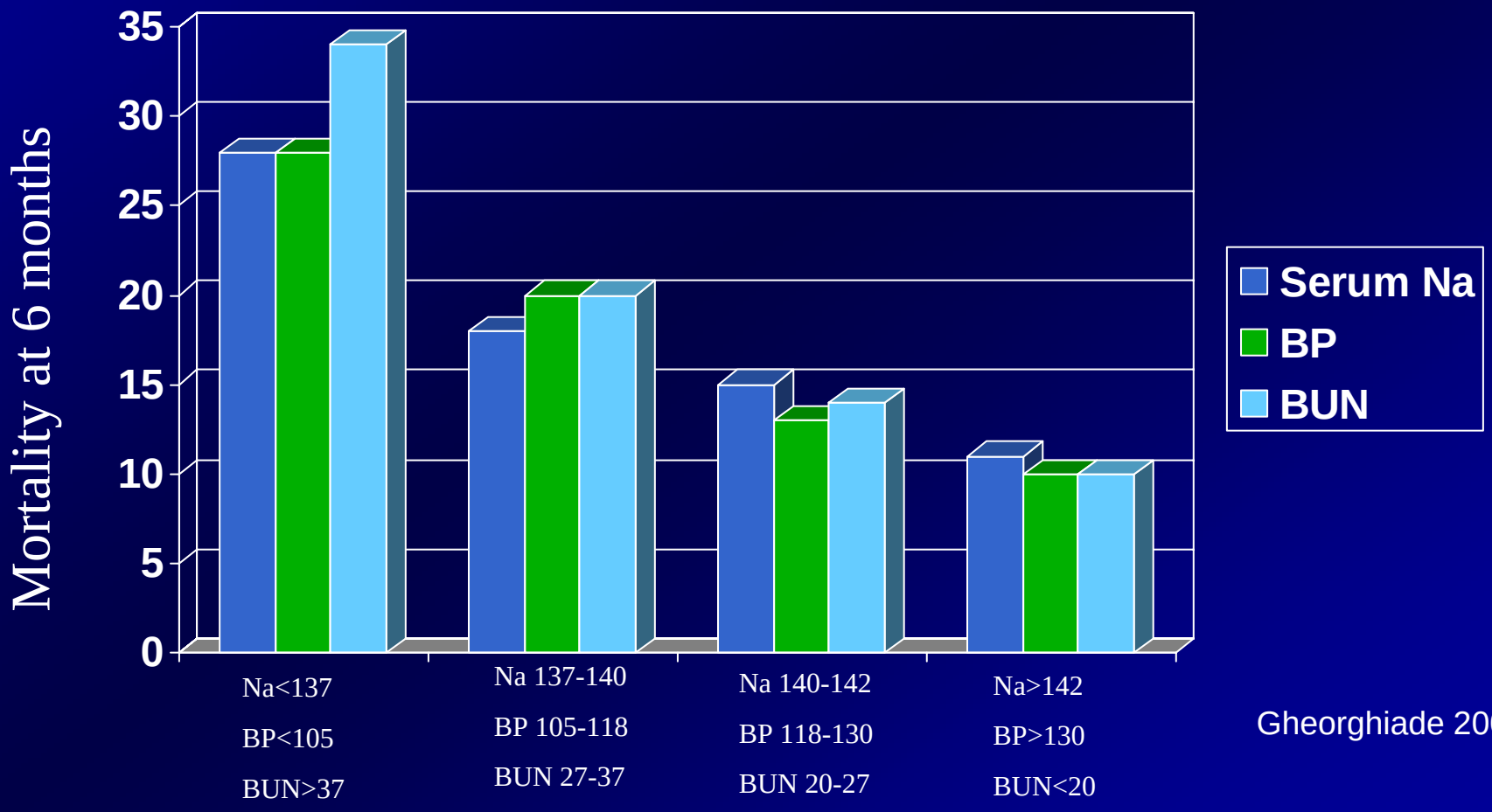
Fonorow GC et al. JAMA. 2005; 293: 572

Death or HF Rehospitalization: ACTIV in CHF Trial



Gheorghiade M et al. Circulation. 2004; 110: III-749

Prognostic value of baseline serum Na, BP and BUN in 4442 pts admitted with HF in The Everest Trial



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Emerging Predictors of Prognosis:

a) Blood Pressure

b) Serum Sodium

c) BUN

d)Troponin

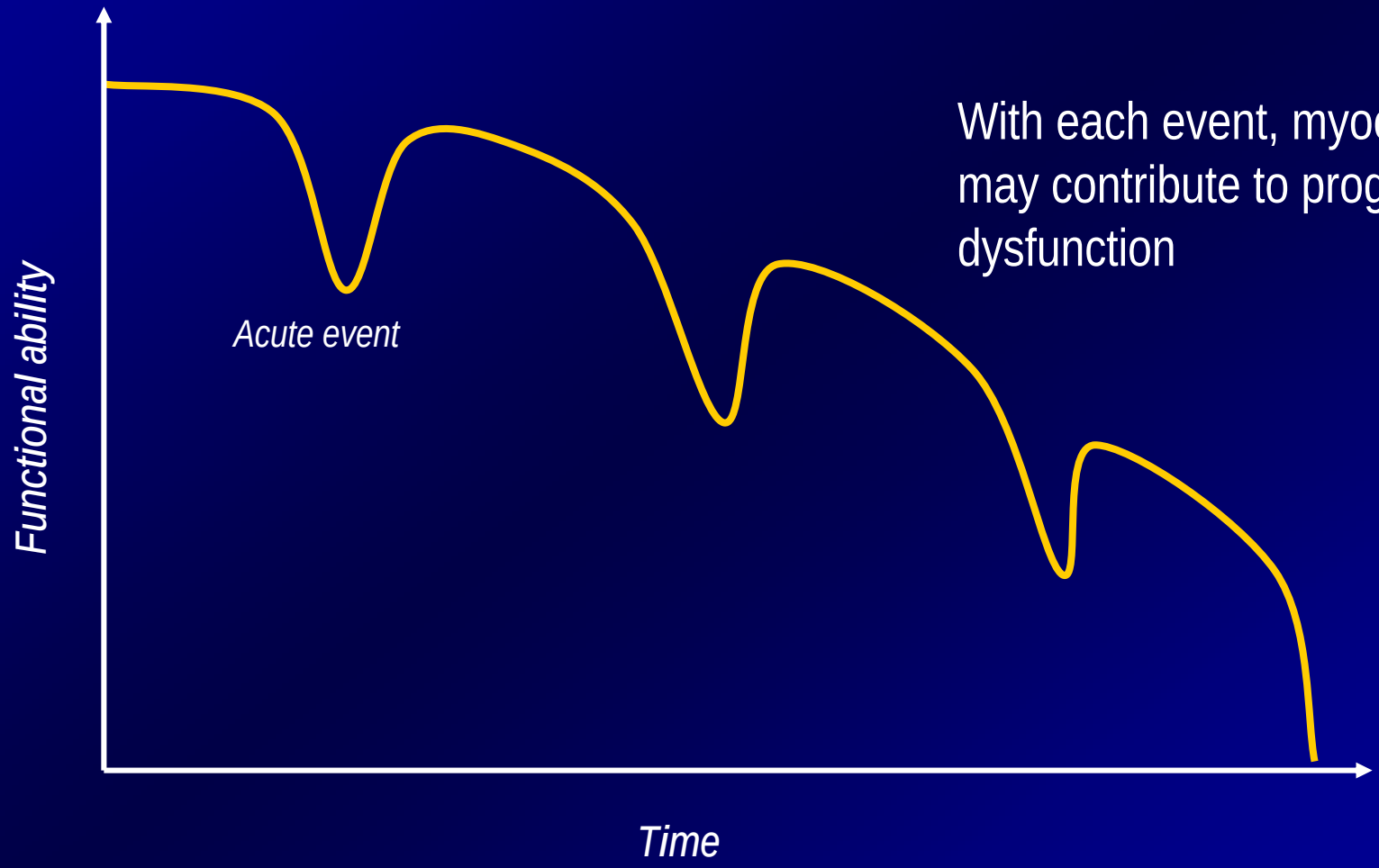
e)Congestion

Myocardial Injury in AHFS: “The Perfect Storm”

- Decreases coronary perfusion due to:
  - High LV and RV diastolic pressure +/- decreased systemic blood pressure
- Further activation of neurohormones/endothelial dysfunction
- CAD/ischemia/hibernating myocardium

Gheorghiade M et al. *Am J Cardiol*. 2005; 96 (6A)

Acute Exacerbations Contribute to the Progression of the Disease



With each event, myocardial injury may contribute to progressive LV dysfunction

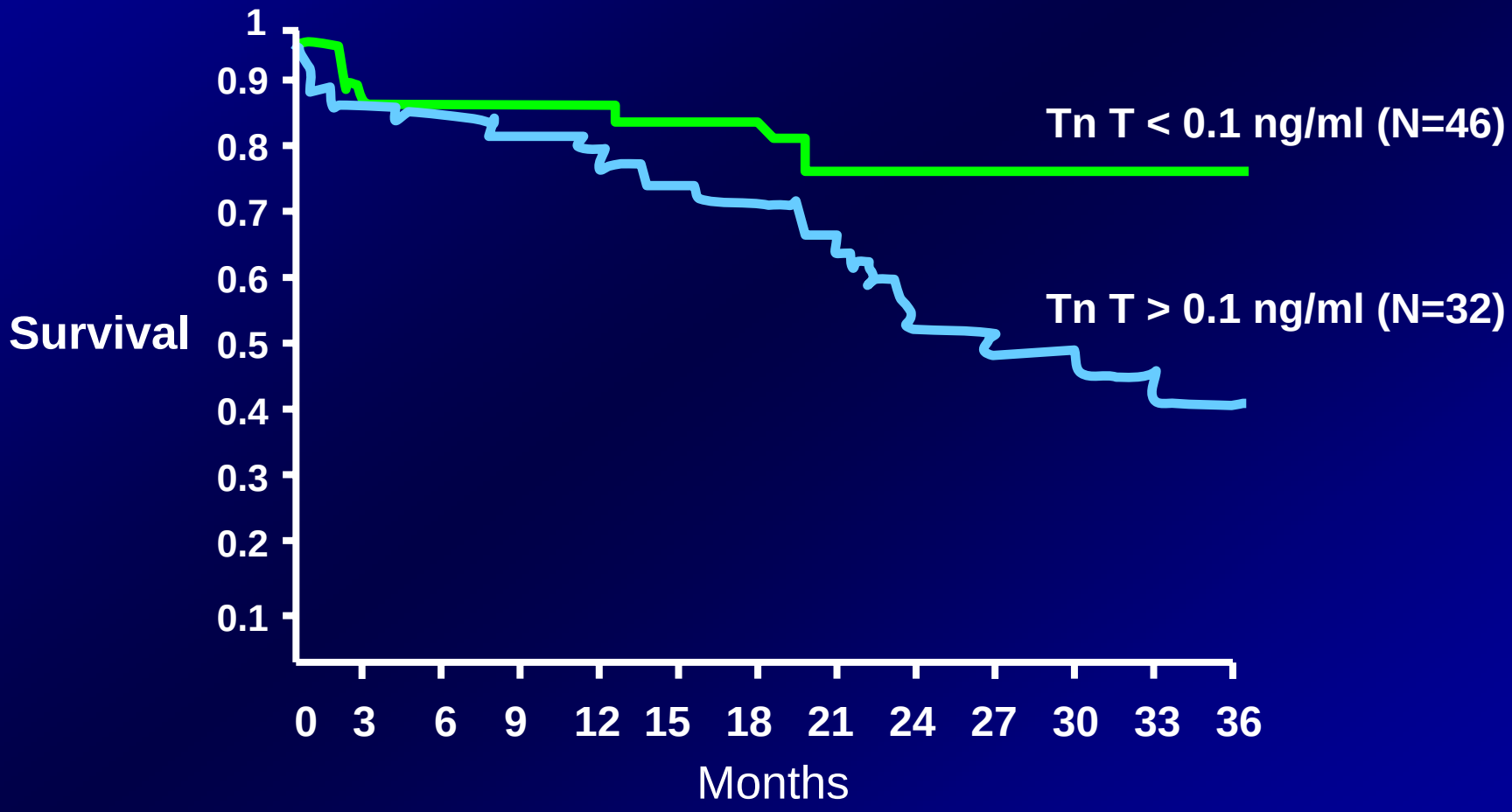
Gheorghiade M et al. *Am J Cardiol*. 2005; 96 (6A)

Pilot Randomized Study of Nesiritide vs. Dobutamine in Heart Failure (PRESERVD-HF) Patients with CAD

- At the time of admission for HF, elevations of TnT and TnI are present in 43% and 74% of pts.
- During hospitalizations, among those without elevated Tn at baseline, 42% of pts. will release TnI and 8% of pts. will release TnT.
- TnT/I correlated with short term outcomes.

Gheorghiade M et al. *Am J Cardiol*. 2005; 96 (6A)

AHFS: Prognostic Value of Tn T



Perna ER et al. *Am Heart J.* 2002; 143: 814.

AHFS

Emerging Predictors of Prognosis:

a) Blood Pressure

b) Serum Sodium

c) BUN

d)Troponin

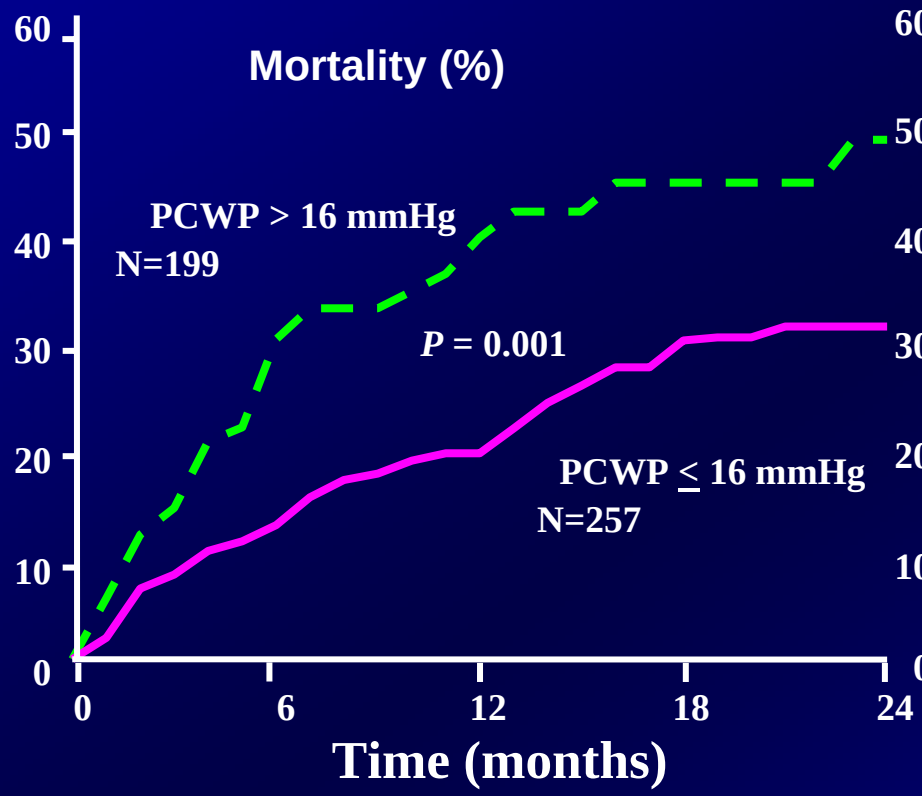
e) Congestion

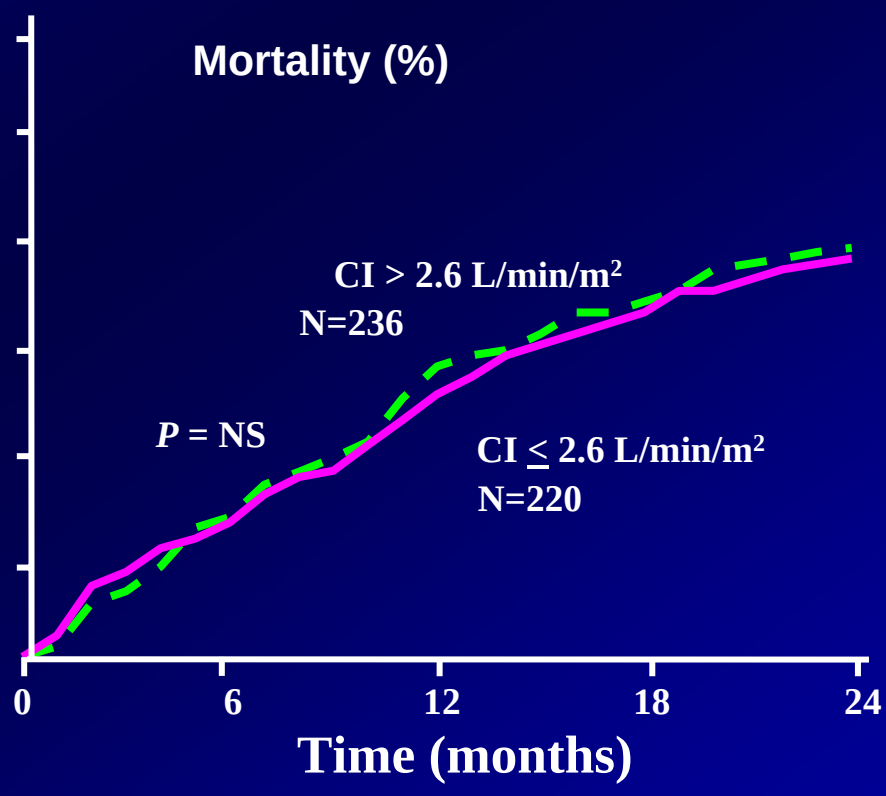
Congestion (PCWP/LVDP) in Heart Failure*

- Subendocardial ischemia/cell death by necrosis/apoptosis[1]
- Changes in extra cellular matrix structure and function[1]
- Changes in LV shape:
  - increased afterload
  - leads to mitral regurgitation
- Impaired cardiac venous drainage from coronary veins (diastolic dysfunction)
- Lower threshold for arrhythmias
- Progression of LV dysfunction/ remodeling

Gheorghiade et al Circulation 2006

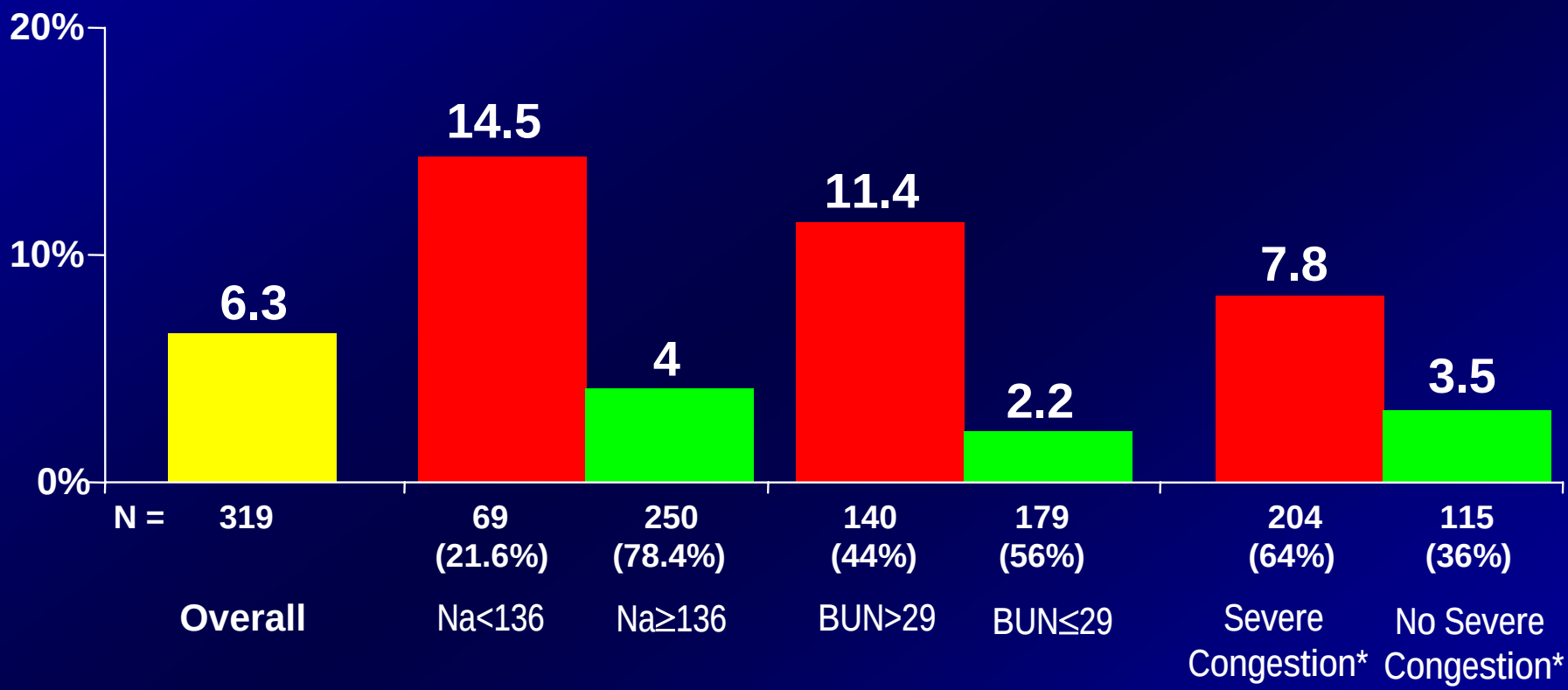
High PCWP at Hospital Discharge is Associated with Higher Long-Term Mortality





Fonarow GC et al. Circulation 1994; 90: I-488

Predictors for 60-day Mortality



*** Edema, Dyspnea, and JVD at baseline**

Adapted from Gheorghiade M et al. JAMA. 2004; 291: 1963

AHFS

Pathophysiologic Targets:

a) Blood Pressure

b) Serum Sodium

c) BUN

d)Troponin

e) Congestion