Pathophysiology of Acute Heart Failure

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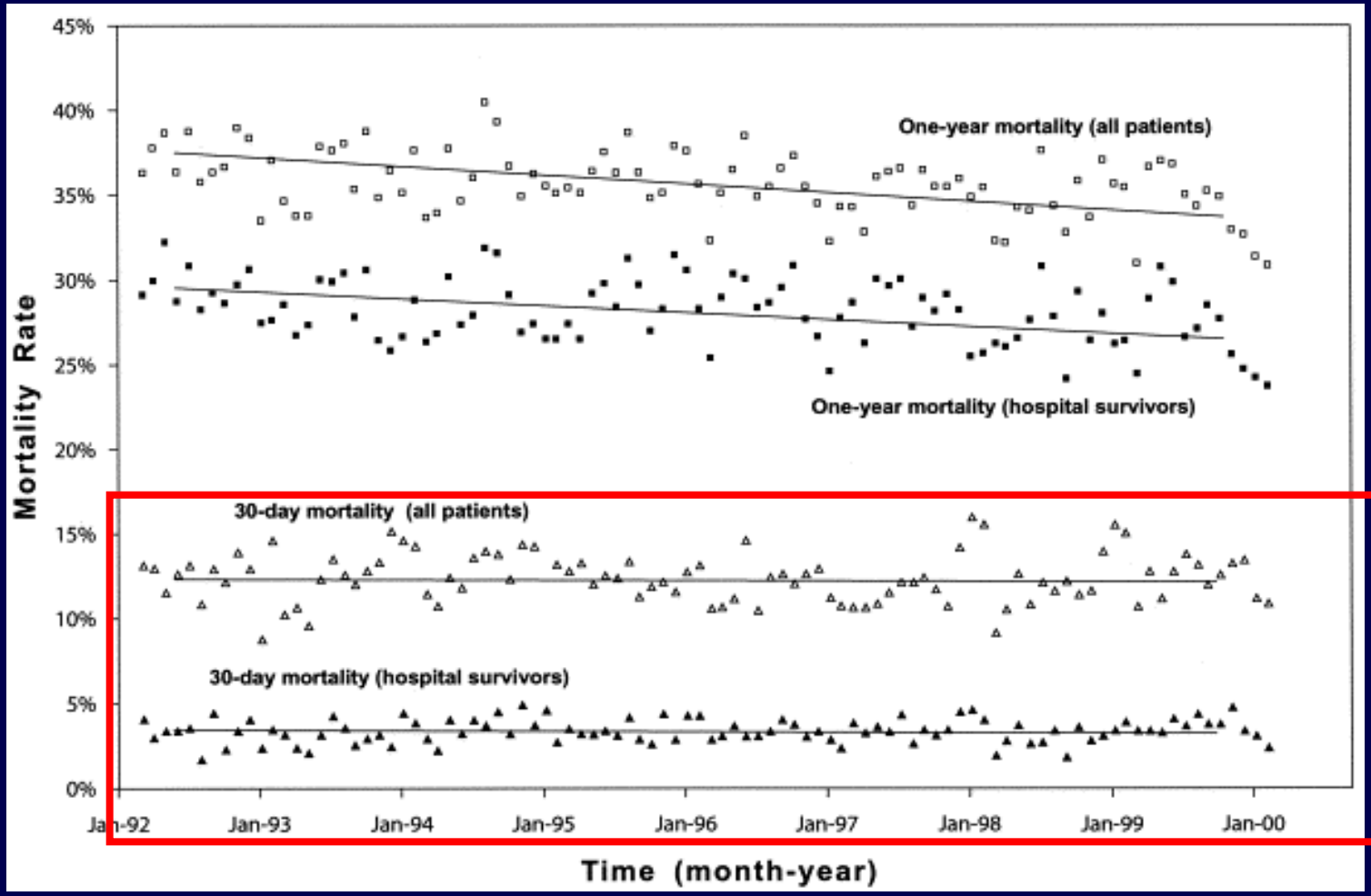
Disclosures

- Research Support and/or Consulting
  - NHLBI
  - Amgen
  - Cytokinetics
  - Roche Diagnostics
  - Otsuka
  - BG Medicine

Progress in AHF Outcomes



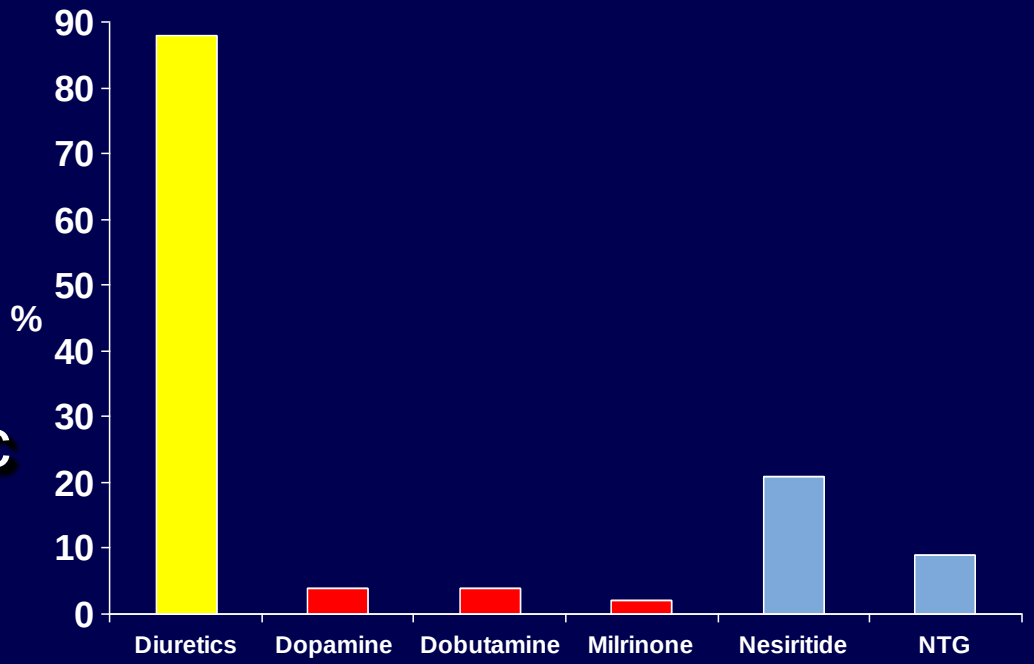
Lee DS, et al Am J Med 2004

Contemporary Pharmacotherapy for ADHF

1974

- Diuretics
- Vasodilators
- Oxygen
- Consider inotropic therapy

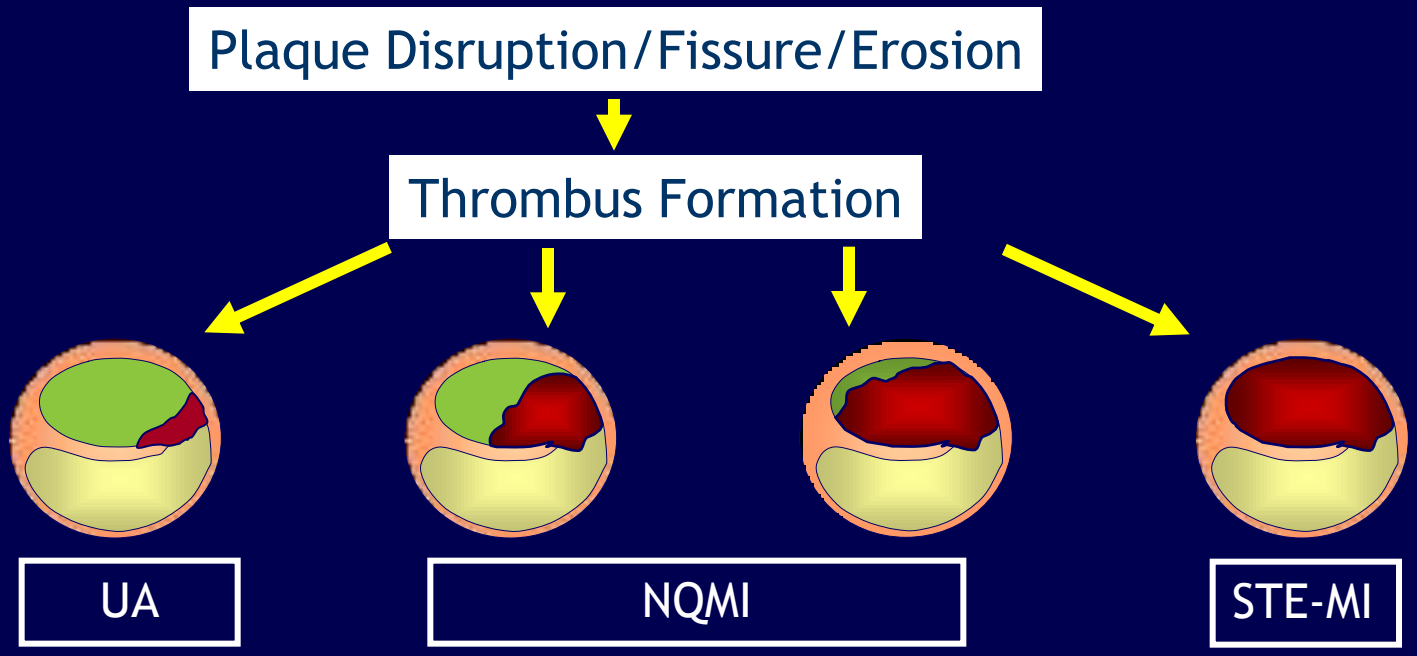
2004



Ramirez, New Engl J Med, 1974

Fonarow, GC et al. AHJ 2007

Underlying Pathophysiology Drives Classification in Acute Coronary Syndromes



What is the “thrombus” of AHF?

ACS	AHF
“The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a nonocclusive thrombus that developed on a disrupted atherosclerotic plaque and is usually nonocclusive.” AHA/ACC Guidelines	??????????????????

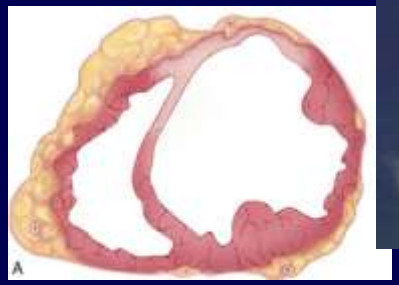
Will greater insight into pathophysiology lead to better therapies?

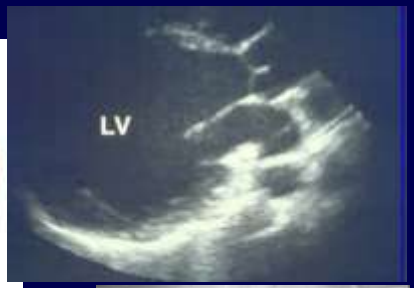
A Fundamental Issue: Are These Patients the Same or Different?

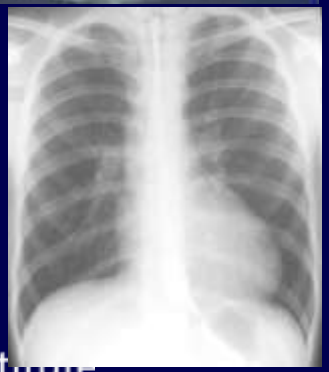
60 yo man with long history of HF

3 weeks of gradually worsening symptoms

BP 85/40



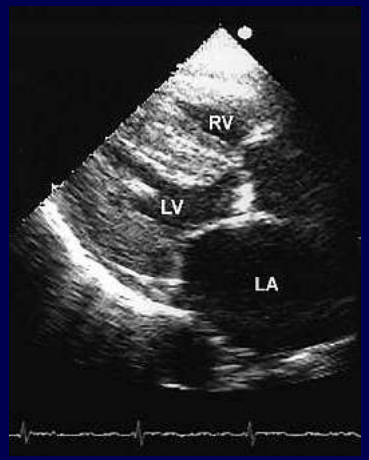


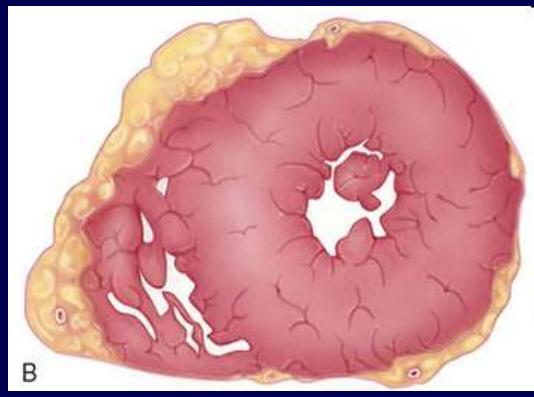


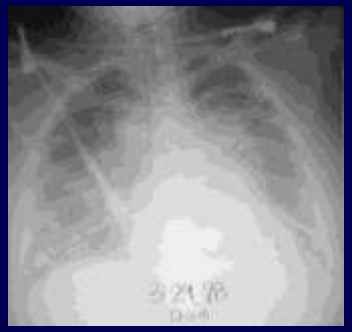
80 yo woman with long history of HTN

1 hour of sudden onset of symptoms

BP 185/120





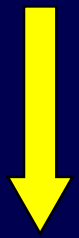


Old Paradigms:

- Acute MI is just a worsening of chronic angina that needs to be treated with bed rest and morphine until people feel better and can go home
- Acute HF is just a worsening of chronic HF that needs to be treated with bed rest and diuretics until people feel better and can go home

AHF is More Complex than We Think

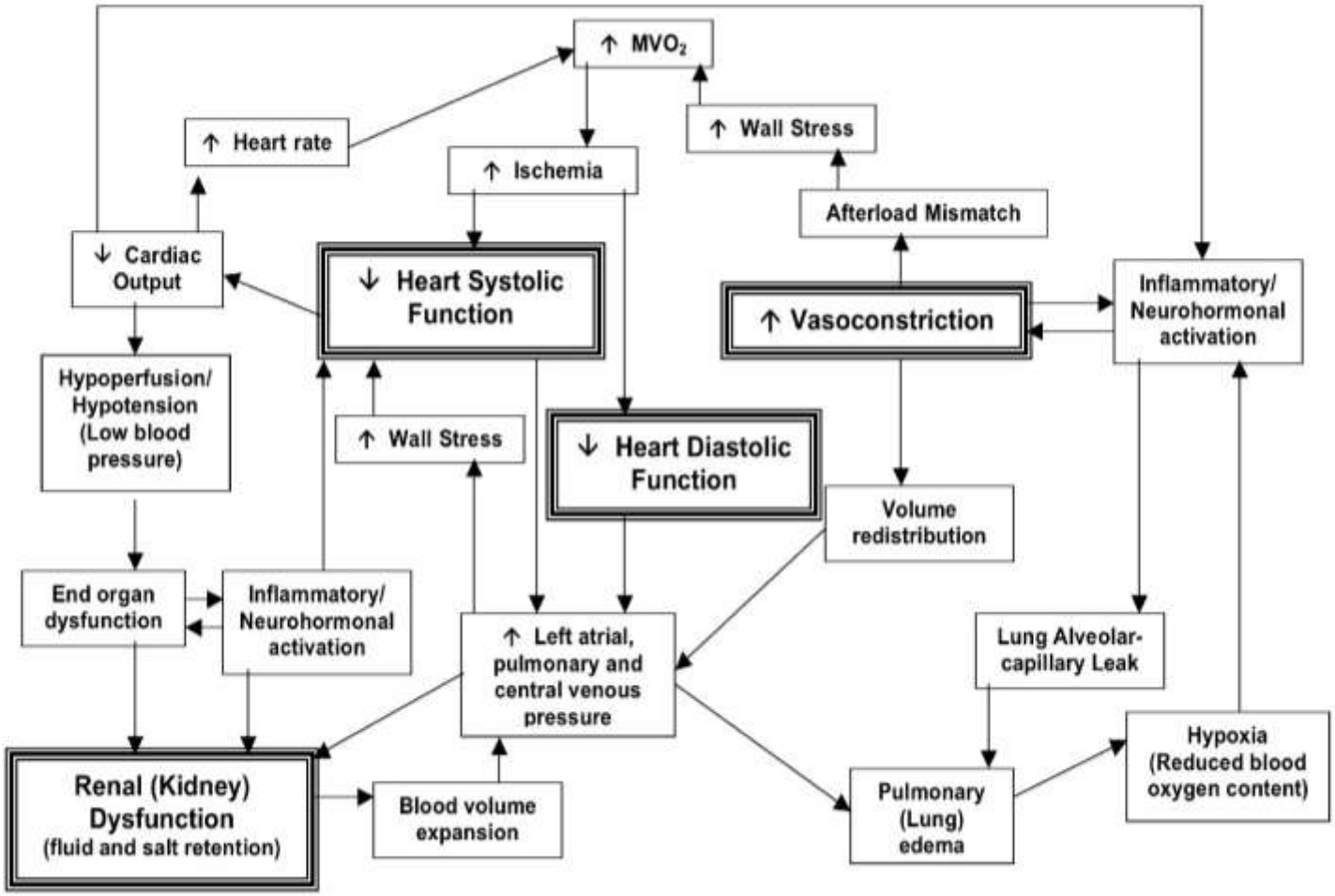
AHF as a volume overload disorder



AHF as a cardio-renal-vascular-inflammatory disorder

Cotter, G and Felker, GM. *Am Heart J 2008*

Schematic of Pathophysiology of AHF



Teerlink. Braunwald, A Textbook of Heart Disease. 8th edition

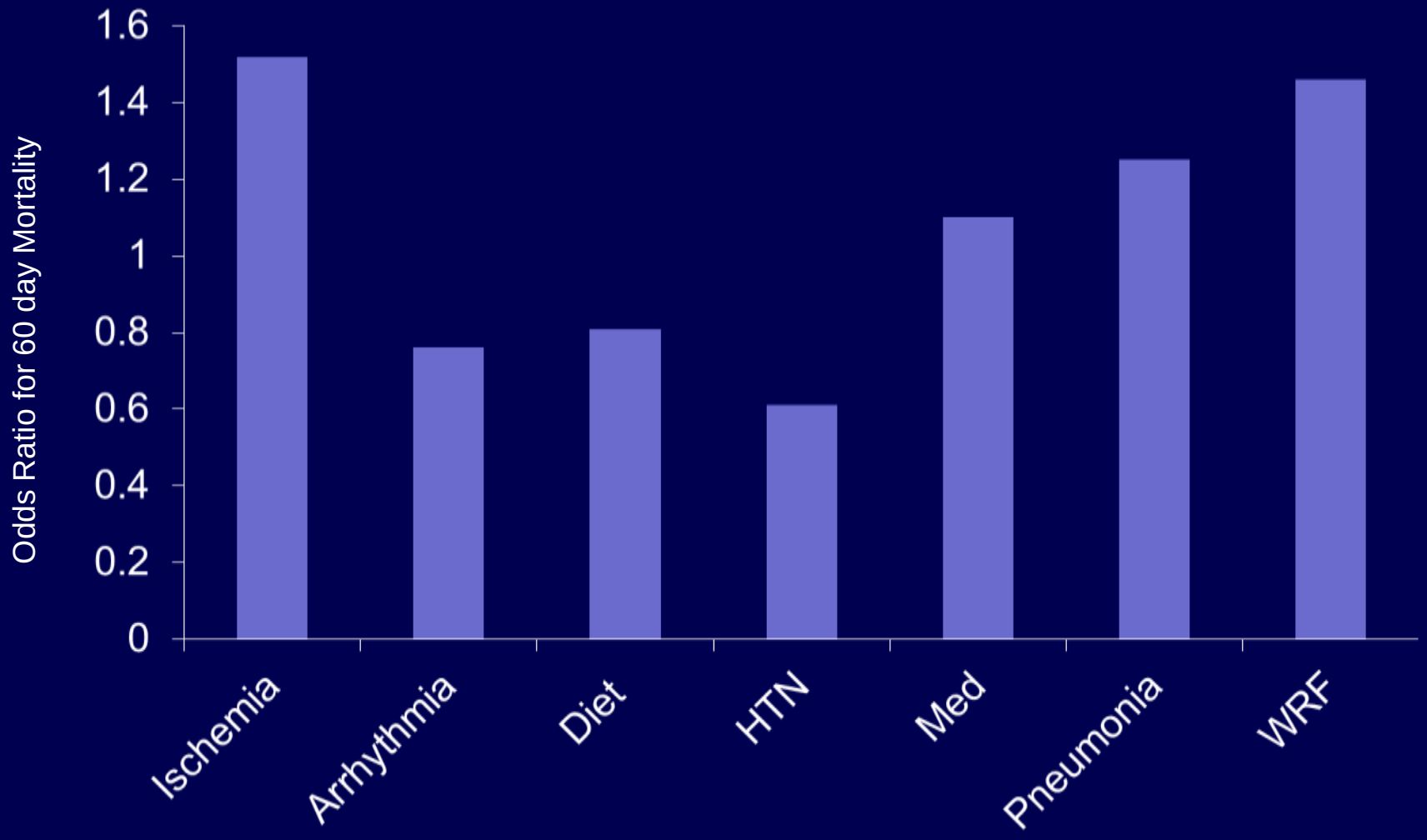
Pathophysiology of ADHF

- Initiating factors/triggers
- Congestion
- Myocardial injury
- Renal mechanisms
- Vascular mechanisms

Key Precipitants:

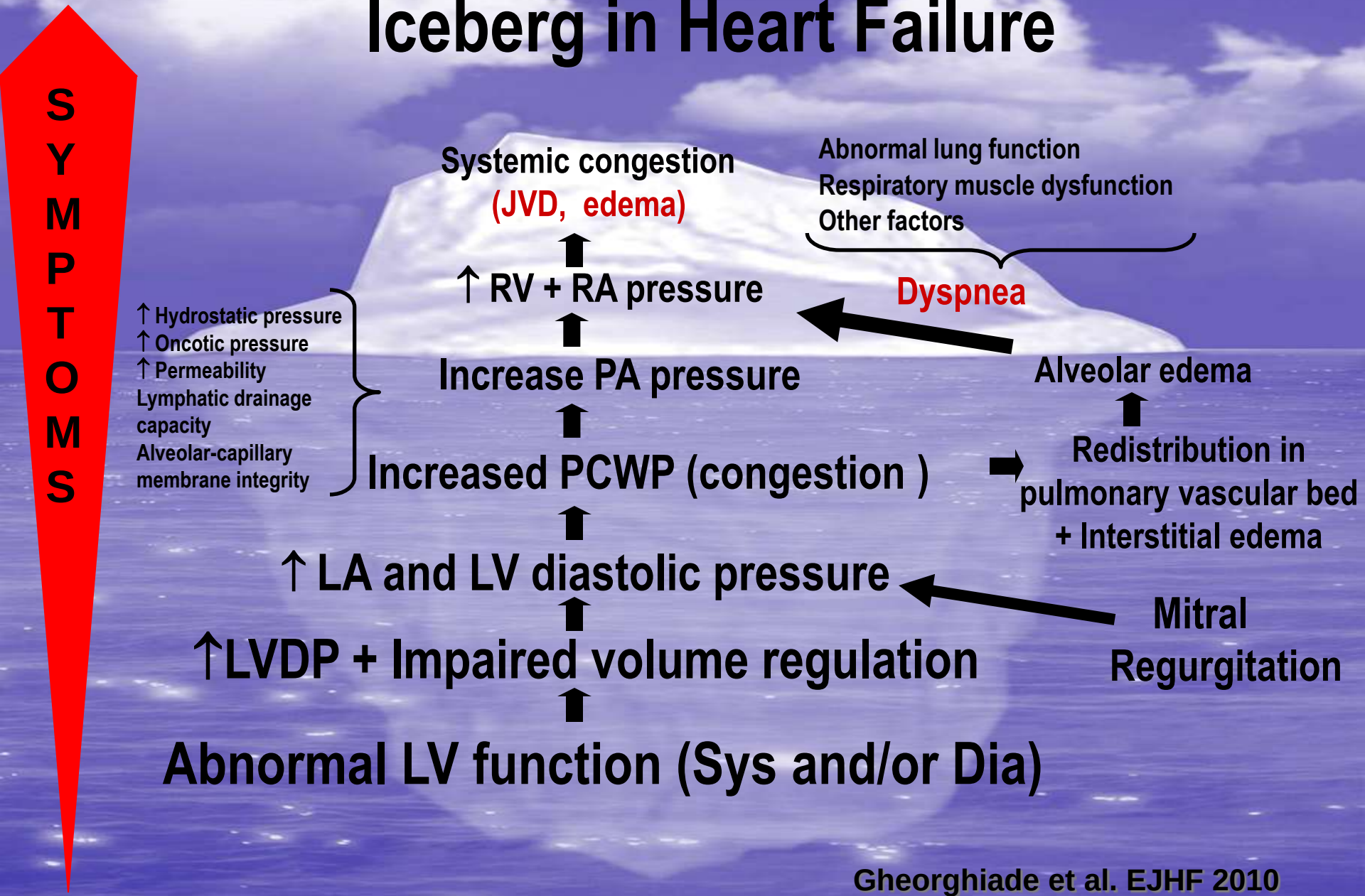
- Non-compliance
- Poorly controlled HTN
- Ischemia/ACS
- Afib or other arrhythmias
- Infections
- Pulmonary emboli
- Worsening renal function

Different Precipitants Lead to Different Risk



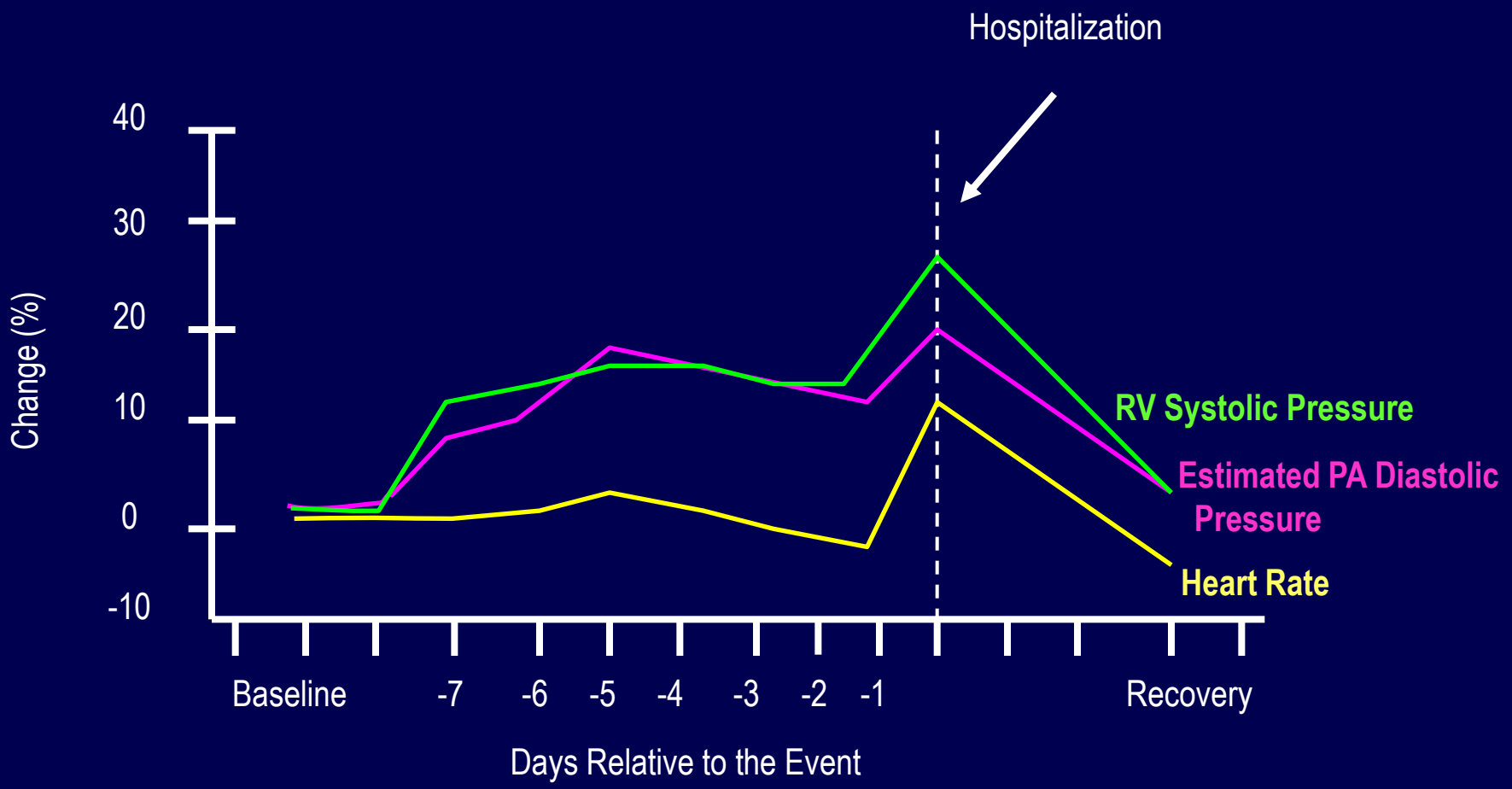
Fonarow, Arch Int Med 2008

Symptoms: The Tip of the Congestion Iceberg in Heart Failure



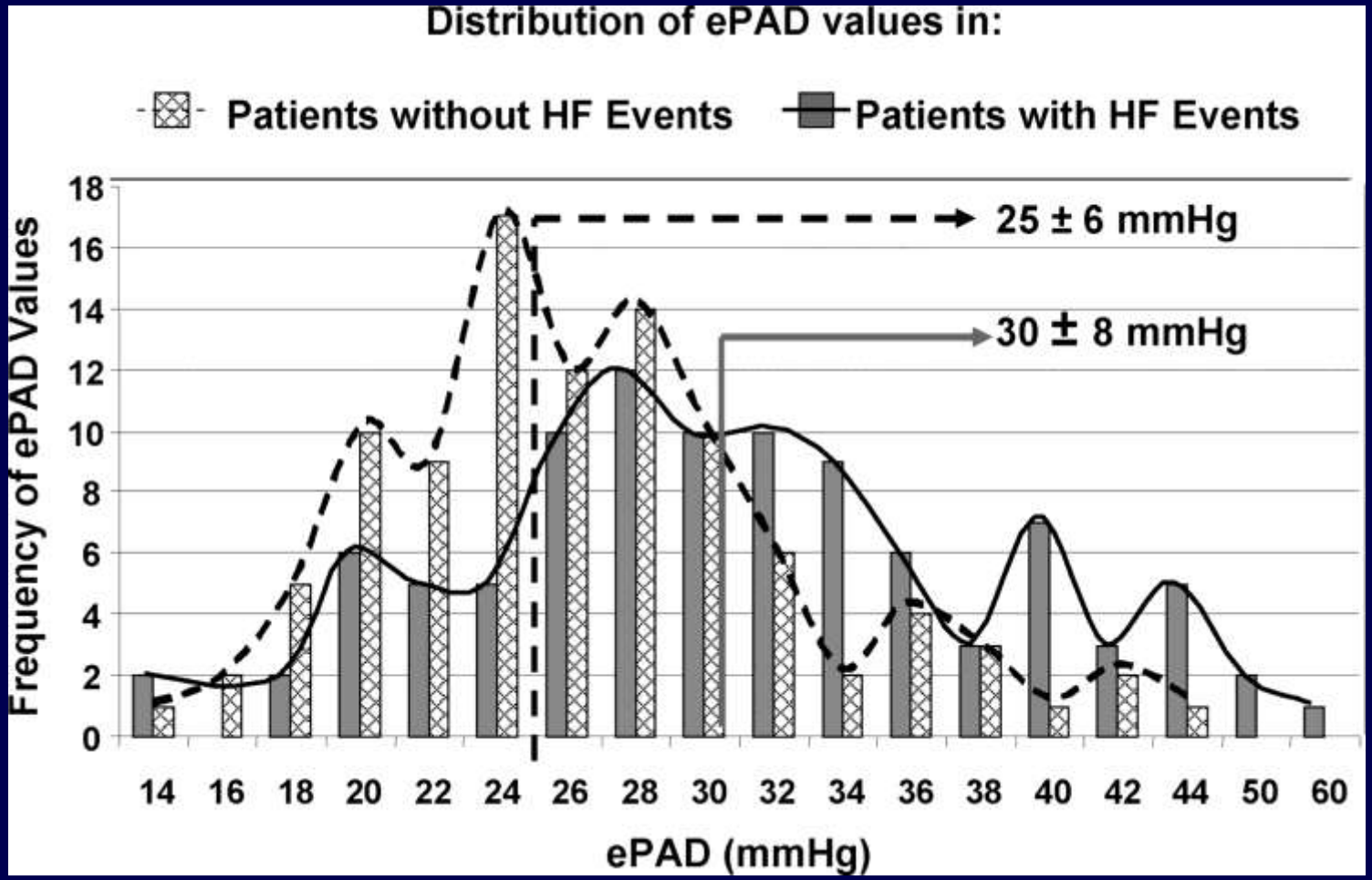
Gheorghiade et al. EJHF 2010

Elevated Filling Pressures Precede Hospitalization



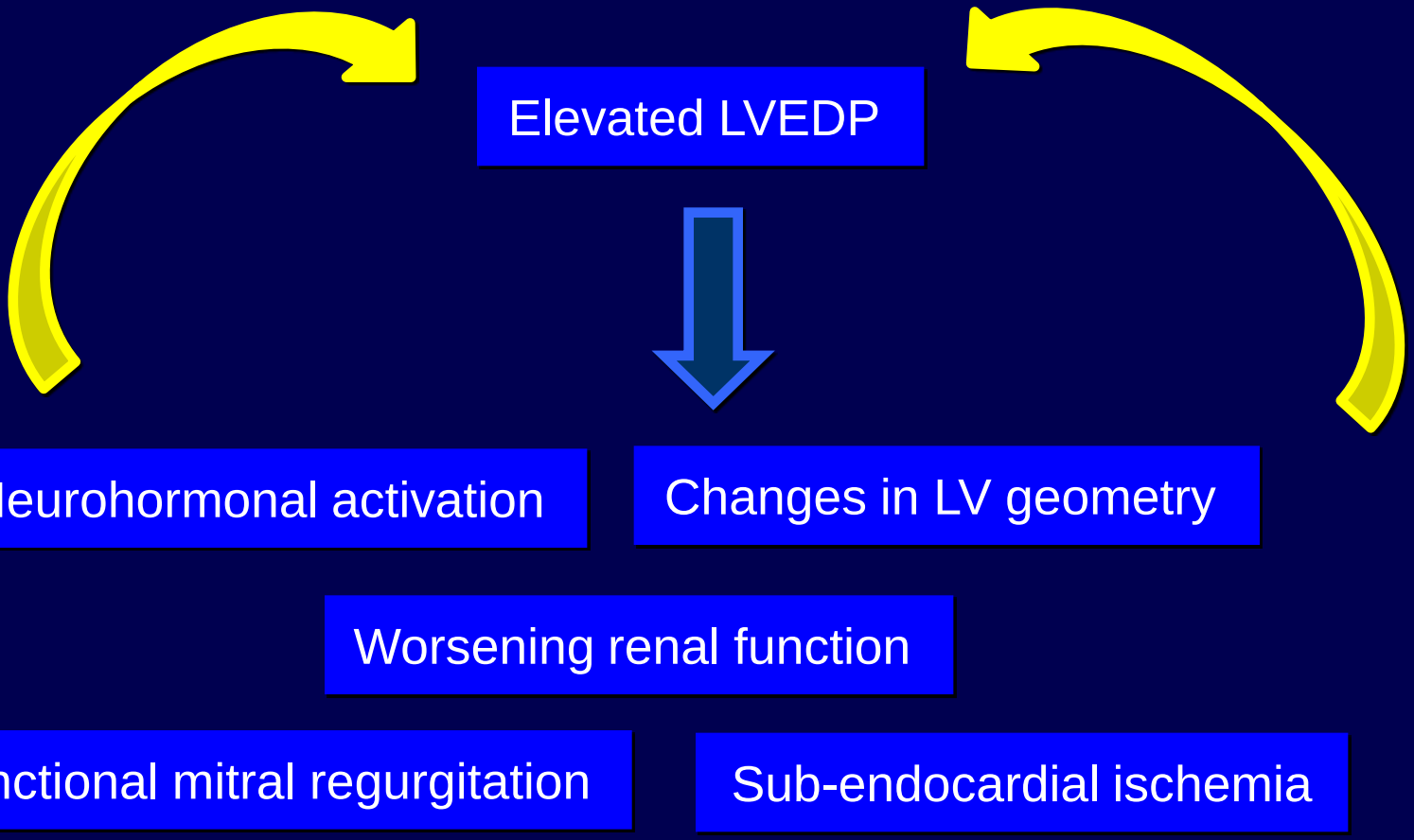
Adamson PB, JACC 2003

Chronic Congestion Predisposes to AHF

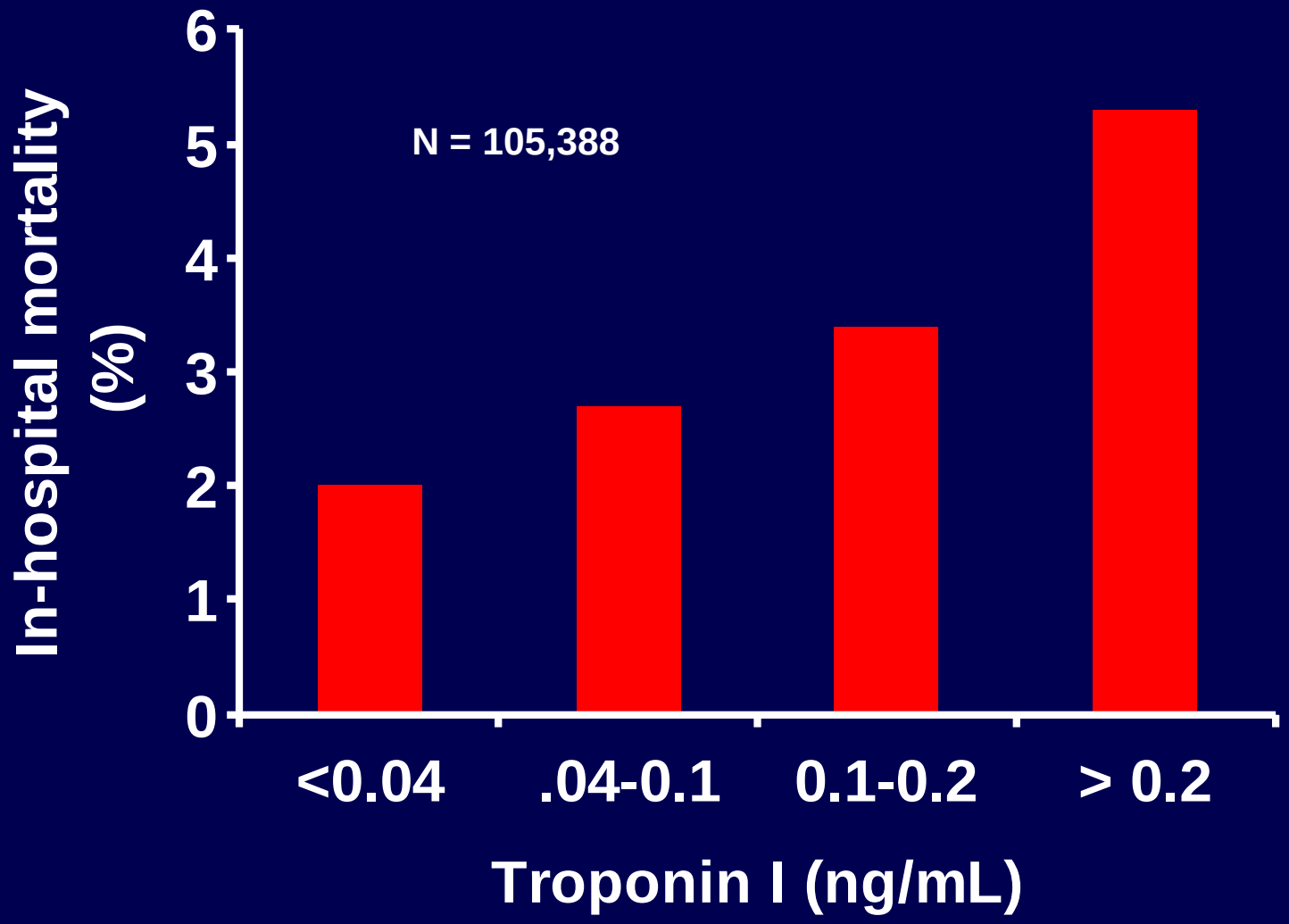


Stevenson, L. W. et al. Circ Heart Fail 2010

Congestion is both Cause and Effect

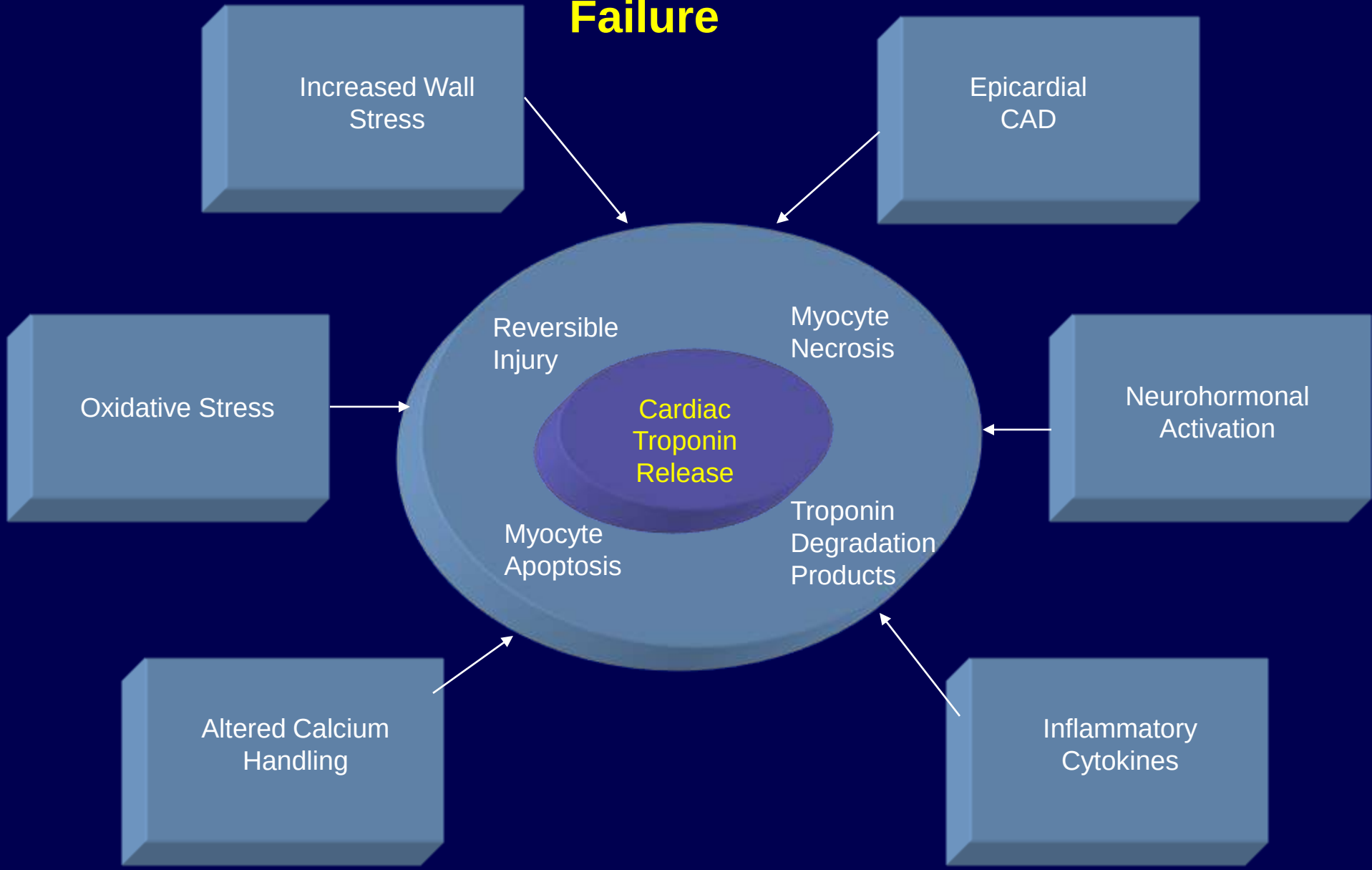


Troponin I and In-hospital Mortality in ADHF



Peacock, F. NEJM 2008

Mechanism of Cardiac Troponin Release in Heart Failure



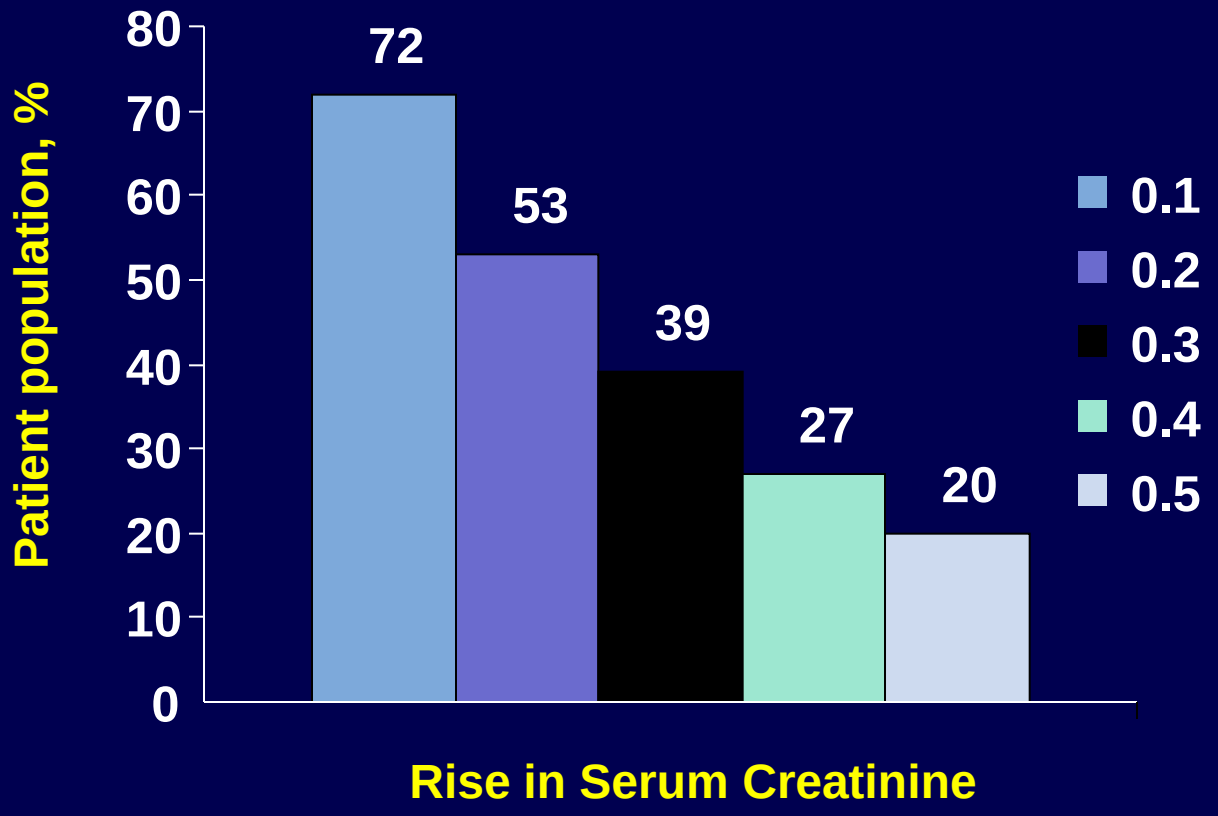
Kociol, et al. JACC 2010

Questions about Myocardial Injury in AHF

- Cause or effect?
- Time course?
  - Pre-hospital
  - In-hospital
- What can we do to prevent or ameliorate it?
- What should we do when it is present?

Renal Function as a Risk Marker in ADHF

Multicenter, retrospective chart review of 1002 patients

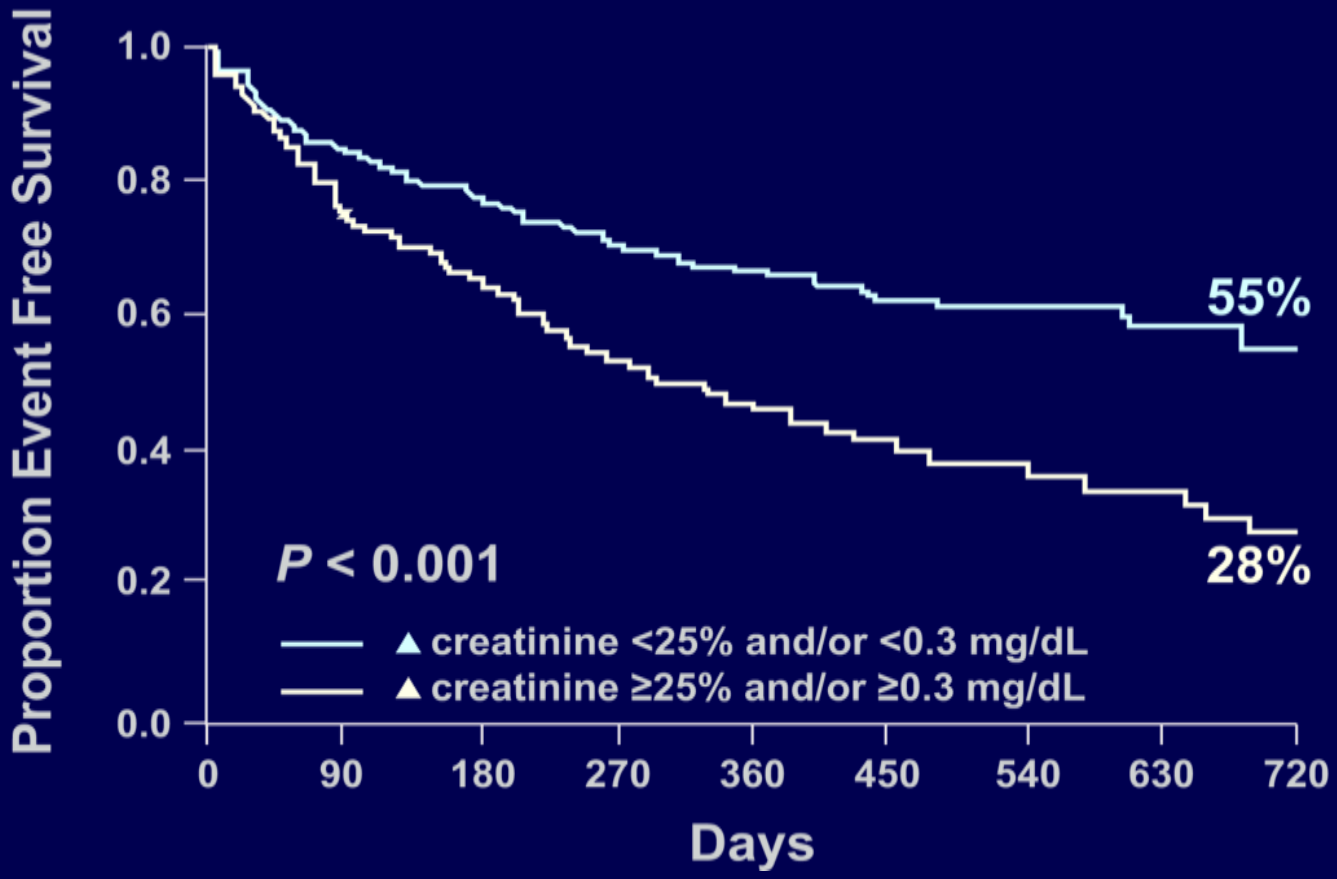


Increase of ≥0.3 associated with significantly higher hospital and post discharge mortality, length of stay, readmission rate, and cost

Gottlieb SS et al. *J Card Fail*. 2002.

Effect of Worsening Renal Function on Outcomes in Patients With Acute Heart Failure

HF Hospitalizations and Cardiovascular Mortality-Free Survival



Metra M et al. *Eur J Heart Fail*. 2008;10:188-195.

The Cardiorenal Syndrome of Heart Failure

Decreased cardiac output

Neurohormonal Activation

Diminished blood flow

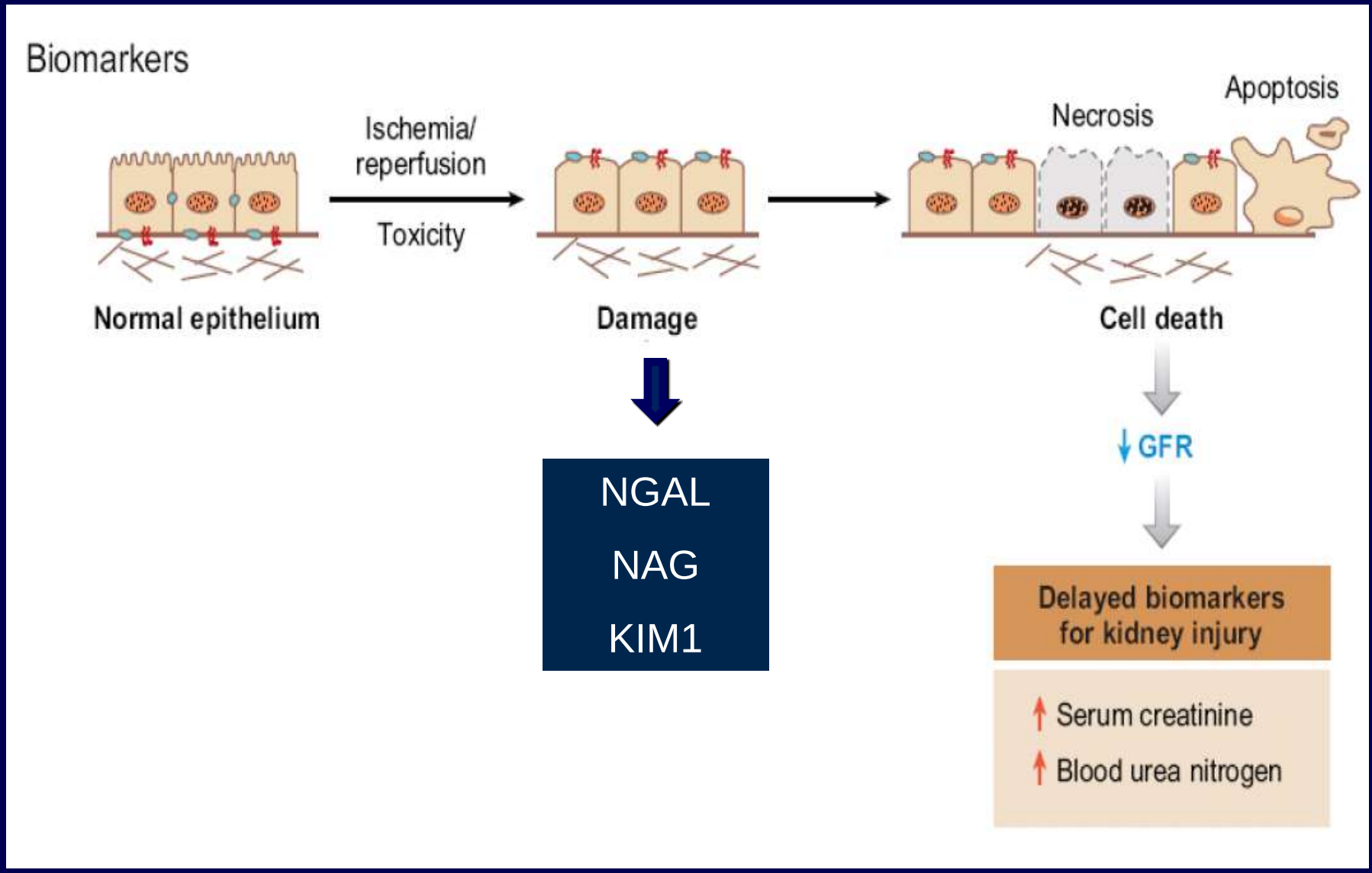
Decreased renal perfusion

Impaired renal function

Increased water & Na^+ retention

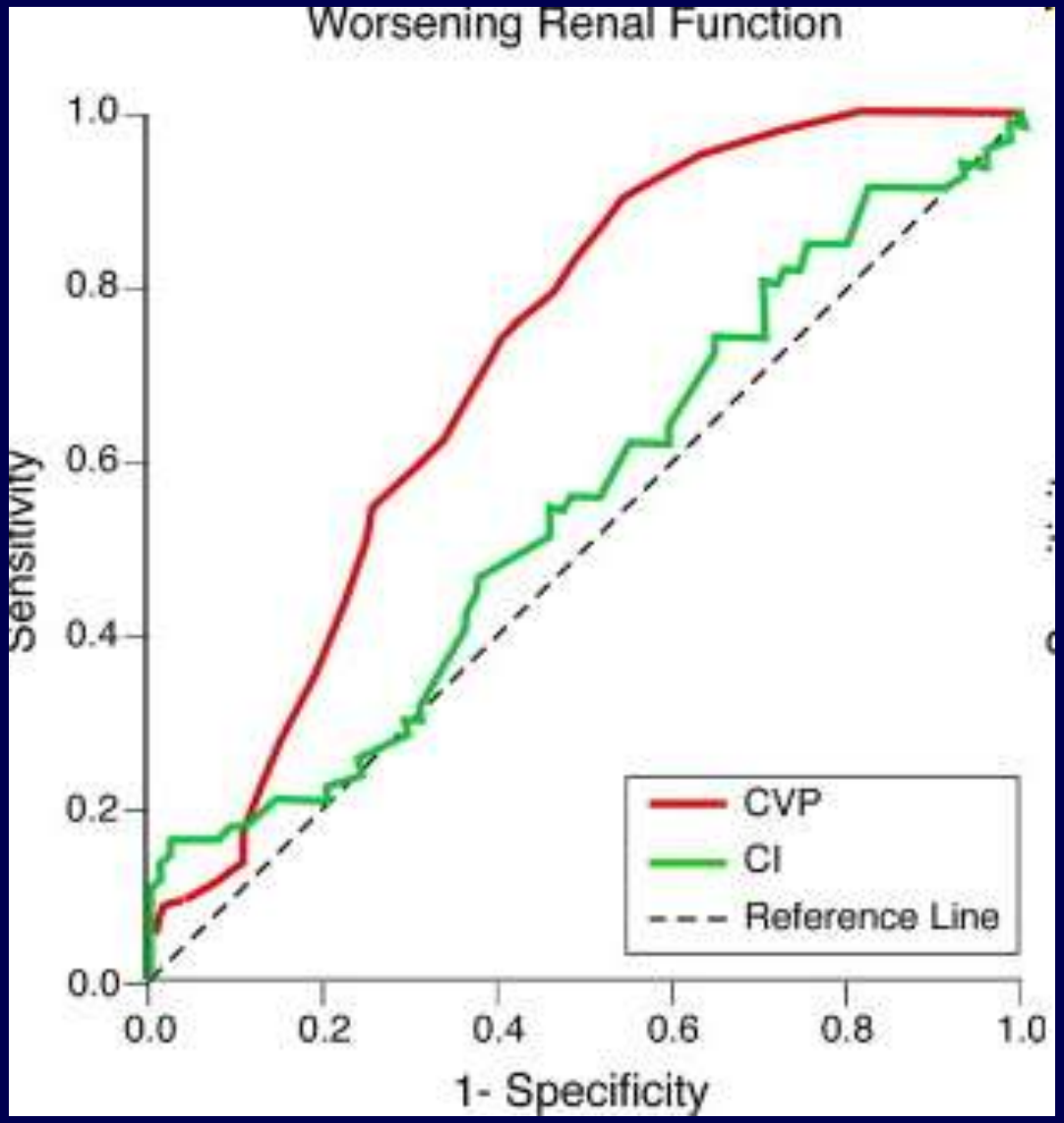
Decreased cardiac performance

BUN and Creatinine are Late Biomarkers of AKI



Vaidya, Ann Rev Pharmacol Toxicol 2008

Congestion Drives Worsening Renal Function



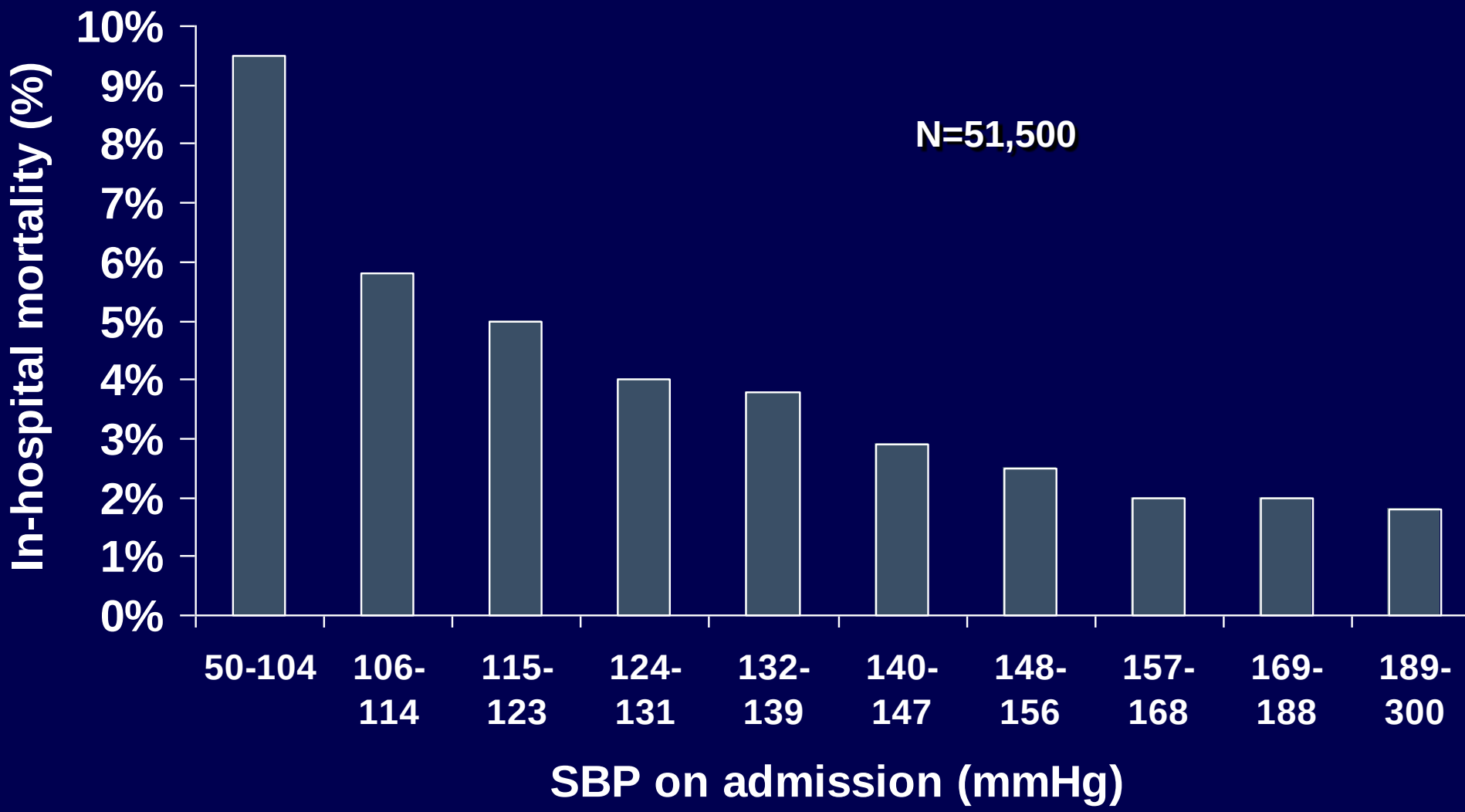
Mullens, W, et al. *JACC 2009*

"Vascular" Mechanisms in Acute Heart Failure

- Hypertension (not hypotension) is the norm in AHF
  - ADHERE =143 mmHg, OPTIMIZE=143 mmHg
  - Pre-hospital community registry w mean SBP=168 mmHg
- "Vascular HF" related to afterload-contractility mismatch?
  - Increase LVEDP despite modest or no volume overload
  - "Volume redistribution" rather than "volume overload"

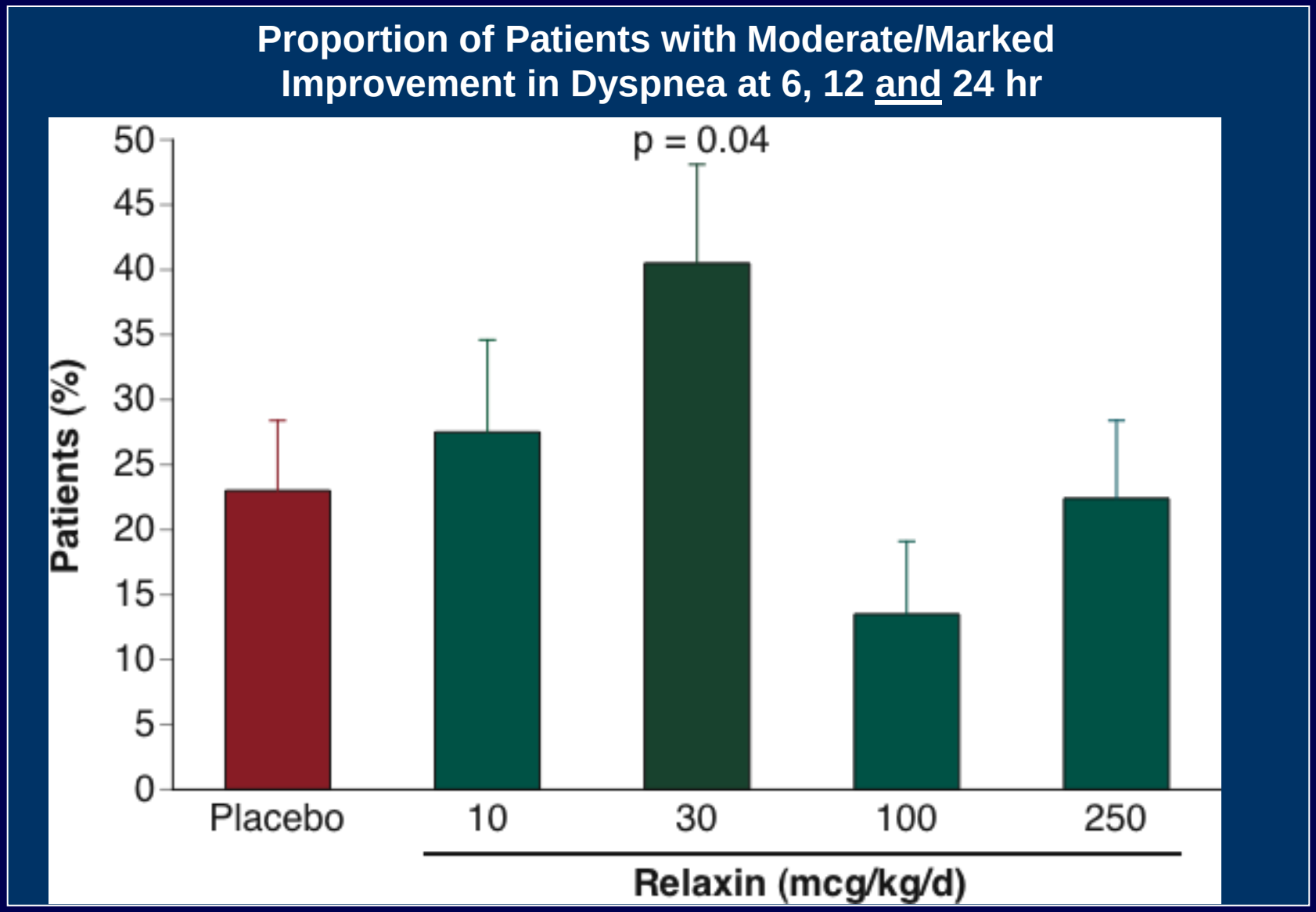
Fonarow, GC et al. JAMA 2005
Gheorghiade, M et al. JAMA 2006
Milo, O et al. Eur J Heart Failure 2007

SBP in AHF: Higher is Better?



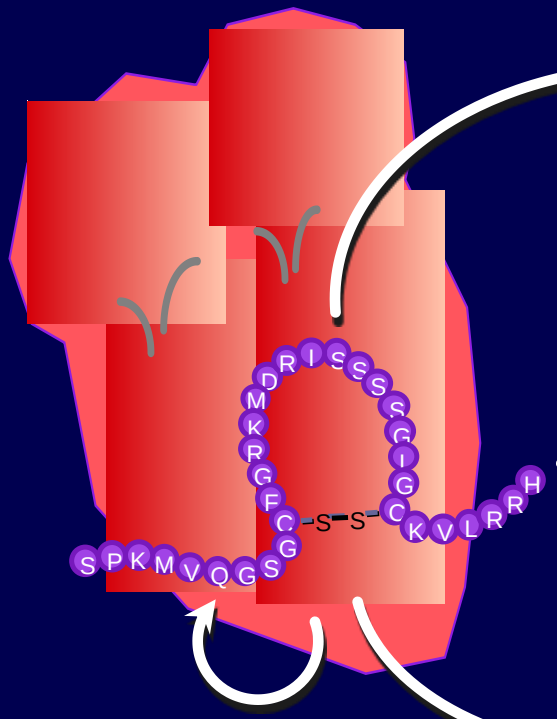
Gheorghiade M et al JAMA 2007

Rapid Dyspnea Improvement through 24 hours (Likert Scale)



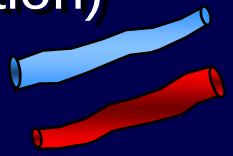
Teerlink, et al. Lancet 2009

Pharmacologic Actions of hBNP



Hemodynamic
(balanced vasodilation)

- veins
- arteries
- coronary arteries

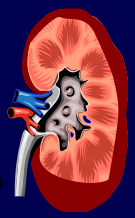


Neurohumoral

- ↓ aldosterone
- ↓ endothelin
- ↓ norepinephrine

Renal

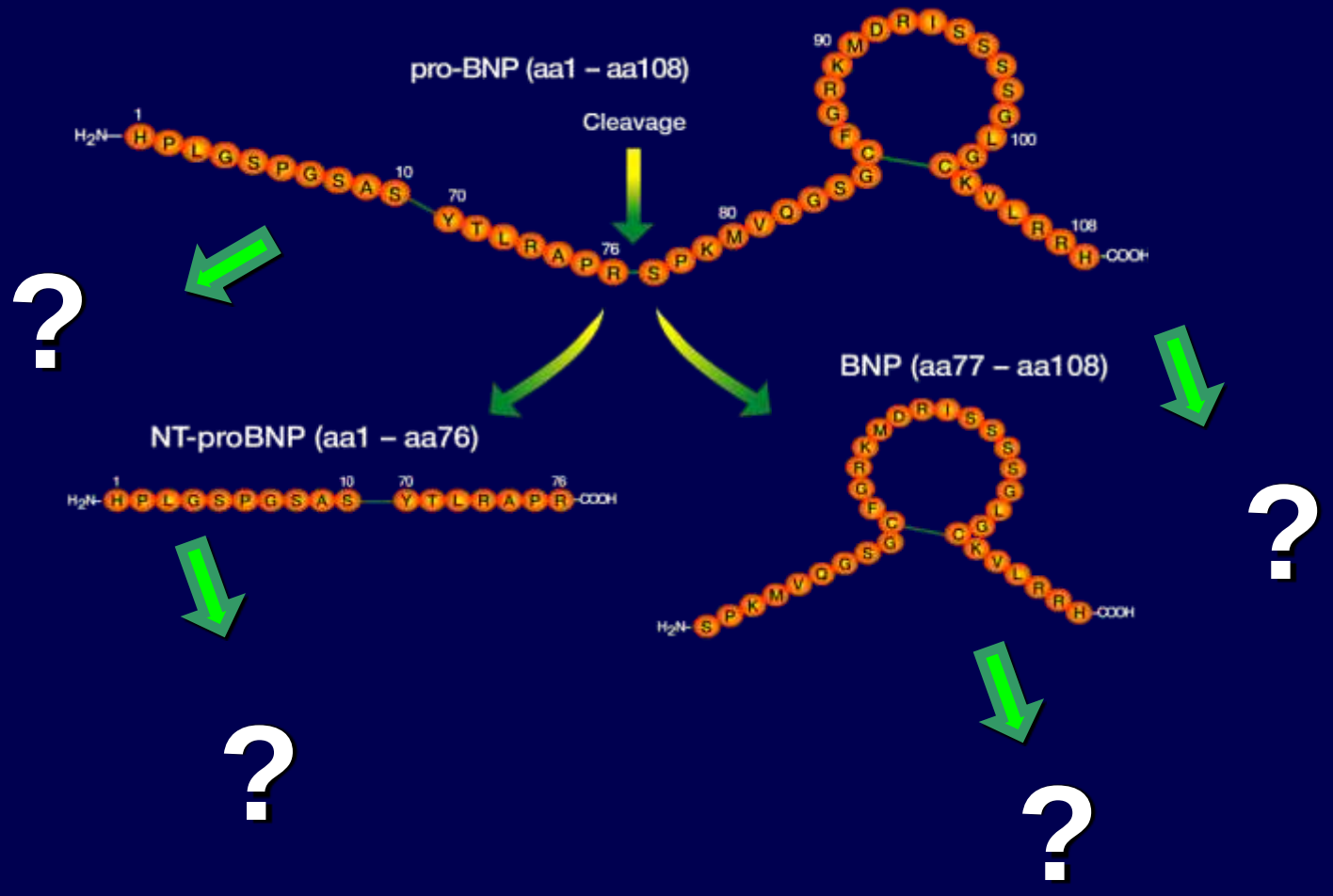
- ↑ diuresis
- ↑ natriuresis
- ↑ GFR



Cardiac

- lusitropic
- antifibrotic
- anti-remodeling

Which BNP are you Talking About? The Choices are Multiplying



The BNP Paradox: My Patient has a BNP >500—Why isn't all the BNP Doing Him Any Good?

- Available assays for NTproBNP and BNP are influenced by HMW forms
- Experimental assays for proBNP suggest proBNP may be primary circulating form in some patients with advanced heart failure
- ProBNP less biologically active (~ 8 fold difference) than BNP--? "defective" BNP in some patients with HF?

Liang, F JACC 2007

Waldo, SW. JACC 2008

Conclusions

- Pathophysiology of AHF is
  - Complex
  - Heterogeneous
  - Poorly understood
- Better understanding of the interaction between specific treatments and specific mechanisms will be key to success moving forward