

Biomarkers of Heart Failure



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Disclosures

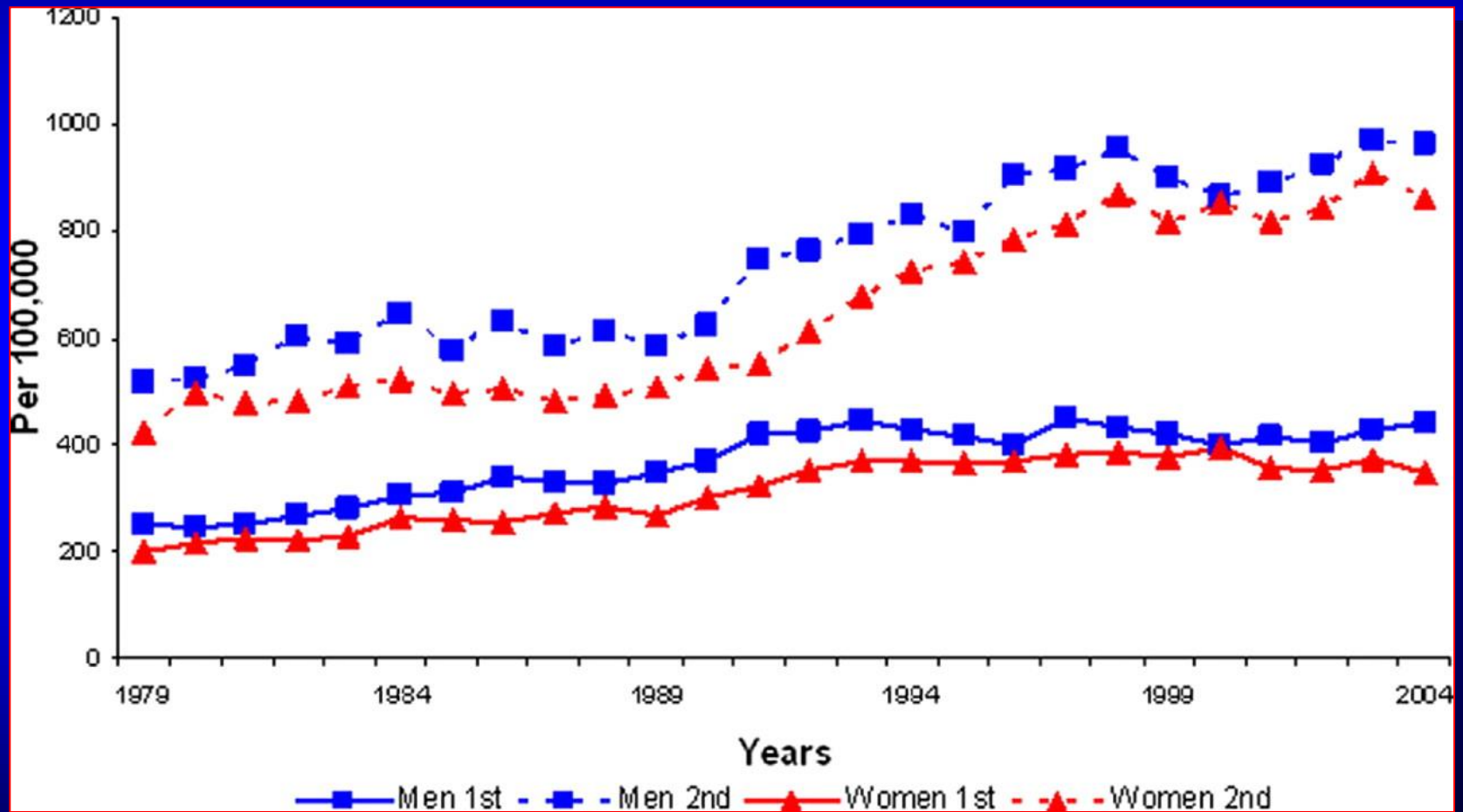
- Grants: Roche Diagnostics, Siemens, Critical Diagnostics, Thermo Fisher, Singulex, BG Medicine, NHLBI
- Consulting: Roche Diagnostics, Critical Diagnostics, BG Medicine, Zensun, Amgen, Novartis



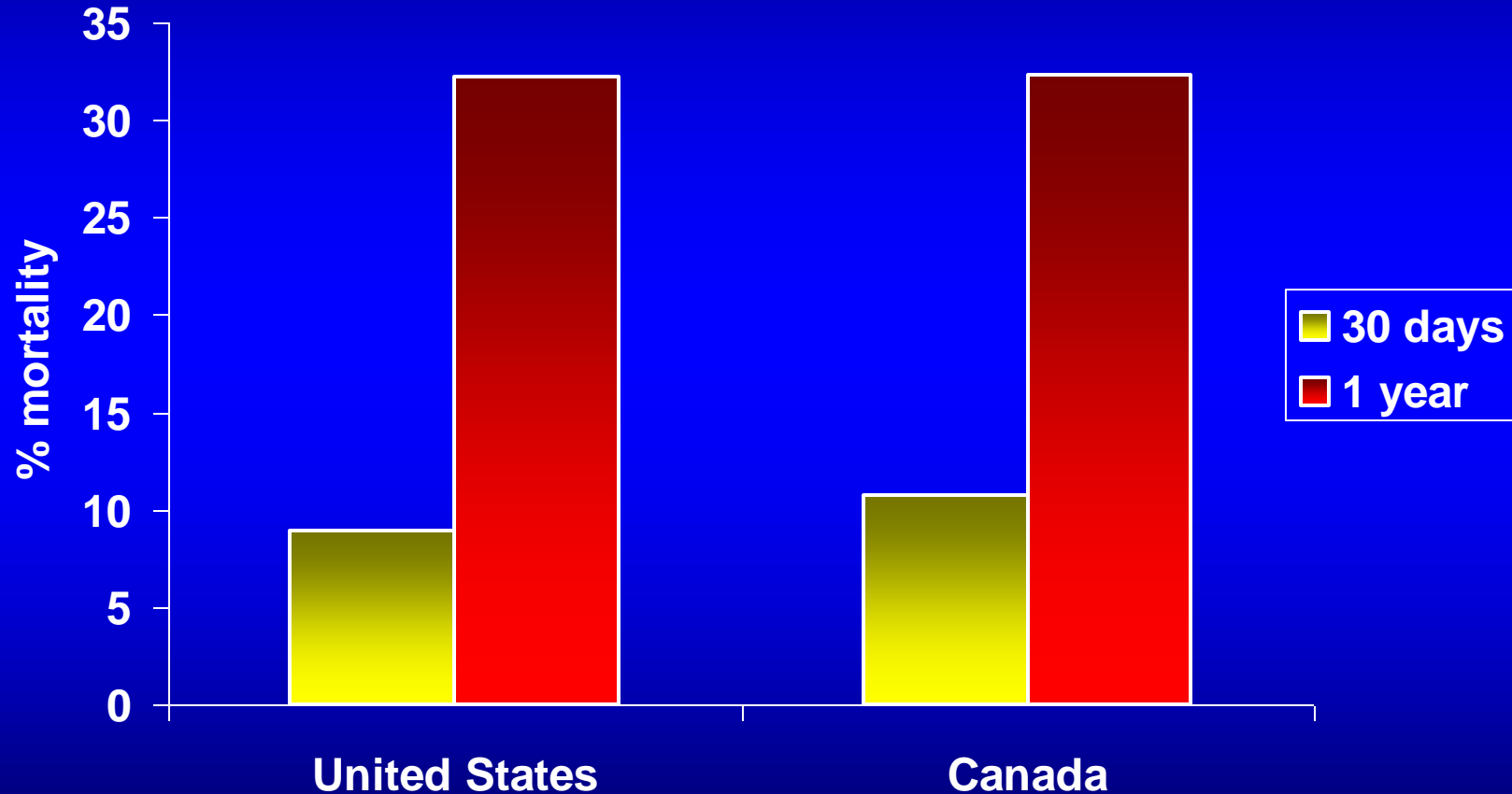
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Age-adjusted hospitalization rates for heart failure



Acute/sub-acute HF outcomes



Assessment of Heart Failure

No gold standard for the evaluation of HF exists!



What about diagnostic testing?

History and Physical

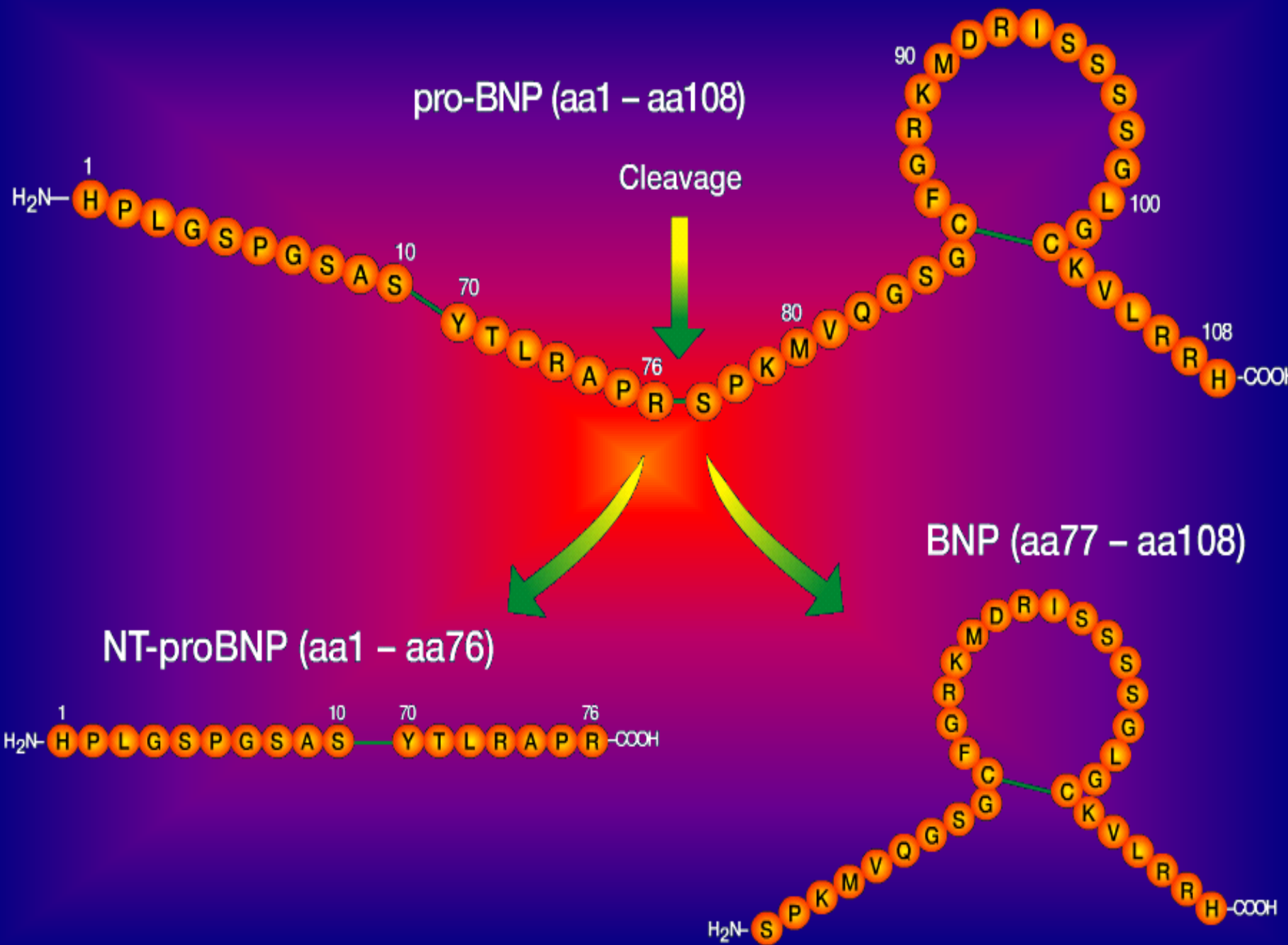
Table 1. Examples of candidate biomarkers in HF, divided into categories.

Inflammation	Neurohormones
CRP	Norepinephrine
TNF- α	Renin
TNF-like weak inducer of apoptosis	Angiotensin II
IL-1, -6, -10, and -18	Aldosterone
Lipoprotein-associated phospholipase A2	Arginine vasopressin, copeptin
soluble TNF receptors 1 and 2	Endothelin-1
YKL-40	Urocortin
IL-1 receptor antagonist	Chromogranin A and B
Midkine	MR-proADM
Leucine-rich 2-glycoprotein	Myocyte injury and apoptosis
PTX3	Troponins I and T
CA-125	Myosin light-chain kinase I
S100A8/A9 complex	Heart-type fatty-acid binding protein
Osteoprotegerin	Creatine kinase MB fraction
Serine protease PR3	Soluble apoptosis-stimulating fragment
Soluble endoglin	Heat shock protein 60
Adiponectin	Soluble TNF-related apoptosis-inducing ligand
Oxidative stress	Myocyte stress
Oxidized LDLs	BNP, NT-proBNP, MR-proANP
Myeloperoxidase	sST2
Urinary biopyrrins	GDF-15
Urinary and plasma isoprostanes	Extracardiac involvement
Urinary 8-hydroxy-2'-deoxyguanosine	RDW
Plasma malondialdehyde	Cystatin-C, β -trace protein
Extracellular-matrix remodeling	NGAL, N-acetyl- β -(D)-glucosaminidase, kidney injury molecule-1
MMPs (MMP2, MMP3, MMP9)	β 2-microglobulin
TIMP1	Urinary albumin-to-creatinine ratio
IL-6	Triiodothyronine
Collagen propeptides	
N-terminal collagen type III peptide	
Myostatin	
Syndecan-4	
Galectin-3	

New recommendations for biomarkers in HF

the 2013 ACC/AHA guideline update

Biomarker, Application	Setting	Rec	LOE
<i>Natriuretic peptides</i>			
Diagnosis or exclusion of HF*	Ambulatory, Acute	I	A
Prognosis of HF	Ambulatory, Acute	I	A
Guidance of Chronic HF	Ambulatory	IIa	B
Guidance of ADHF	Acute	IIb	C
<i>Troponin</i>			
Additive risk stratification	Acute, Ambulatory	I	A
<i>Galectin-3, ST2</i>			
Additive risk stratification	Ambulatory	IIb	B
	Acute	IIb	A



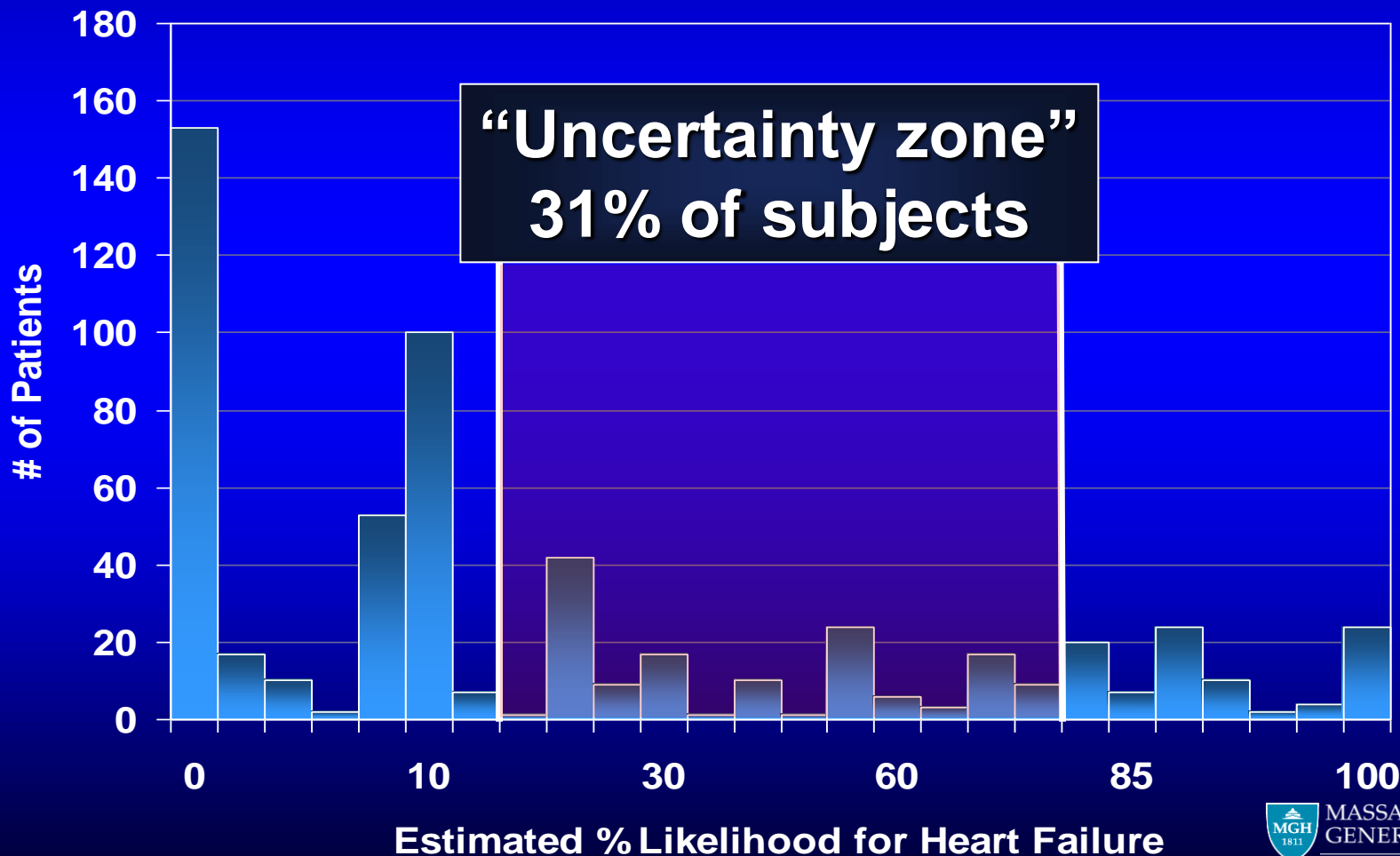
Accepted applications of BNP or NT-proBNP in HF

- ✓ Diagnosis
- ✓ Estimation of HF severity
- ✓ Prognostication
- ? Management



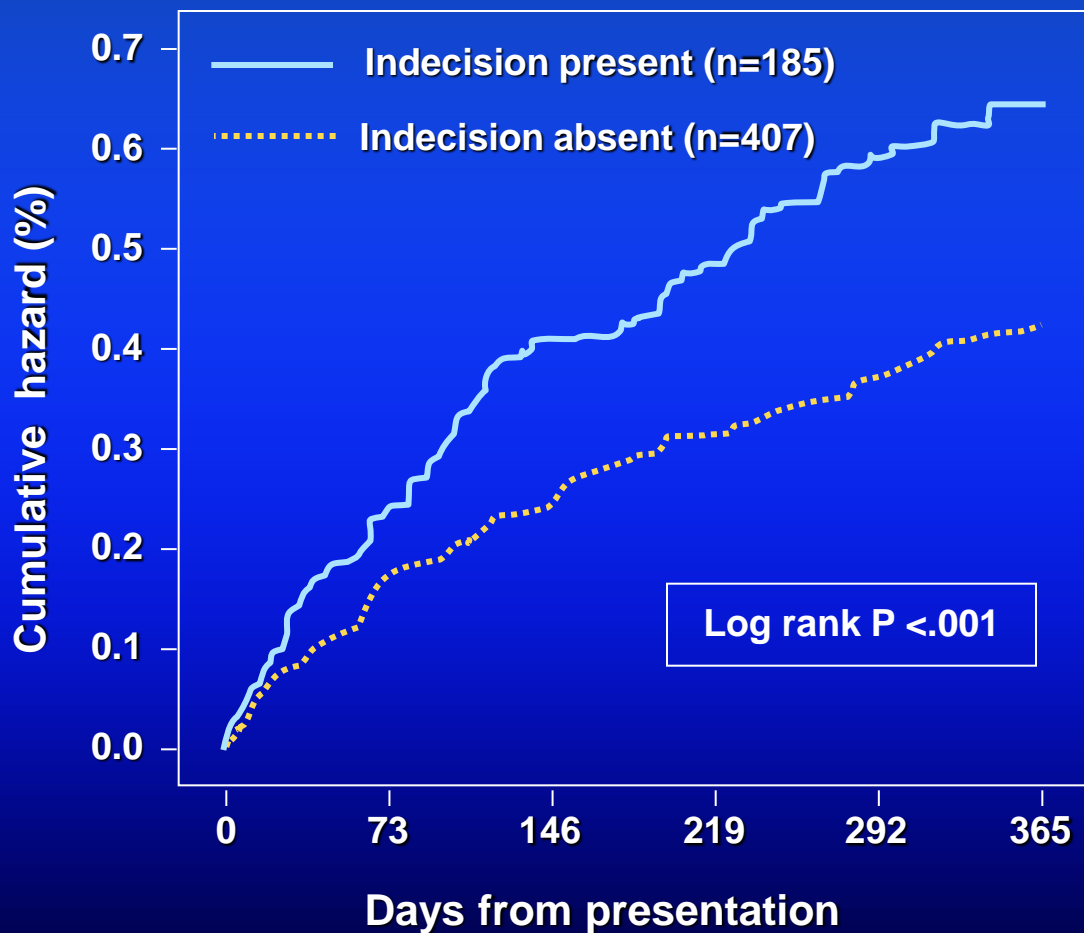
Diagnostic Uncertainty is Common in Dyspnea Evaluation

Following full evaluation, managing physician asked to provide an estimate from 0% to 100% for the likelihood for heart failure as the cause of dyspnea





Diagnostic Uncertainty is Associated with Poor Prognosis in Acute Dyspnea

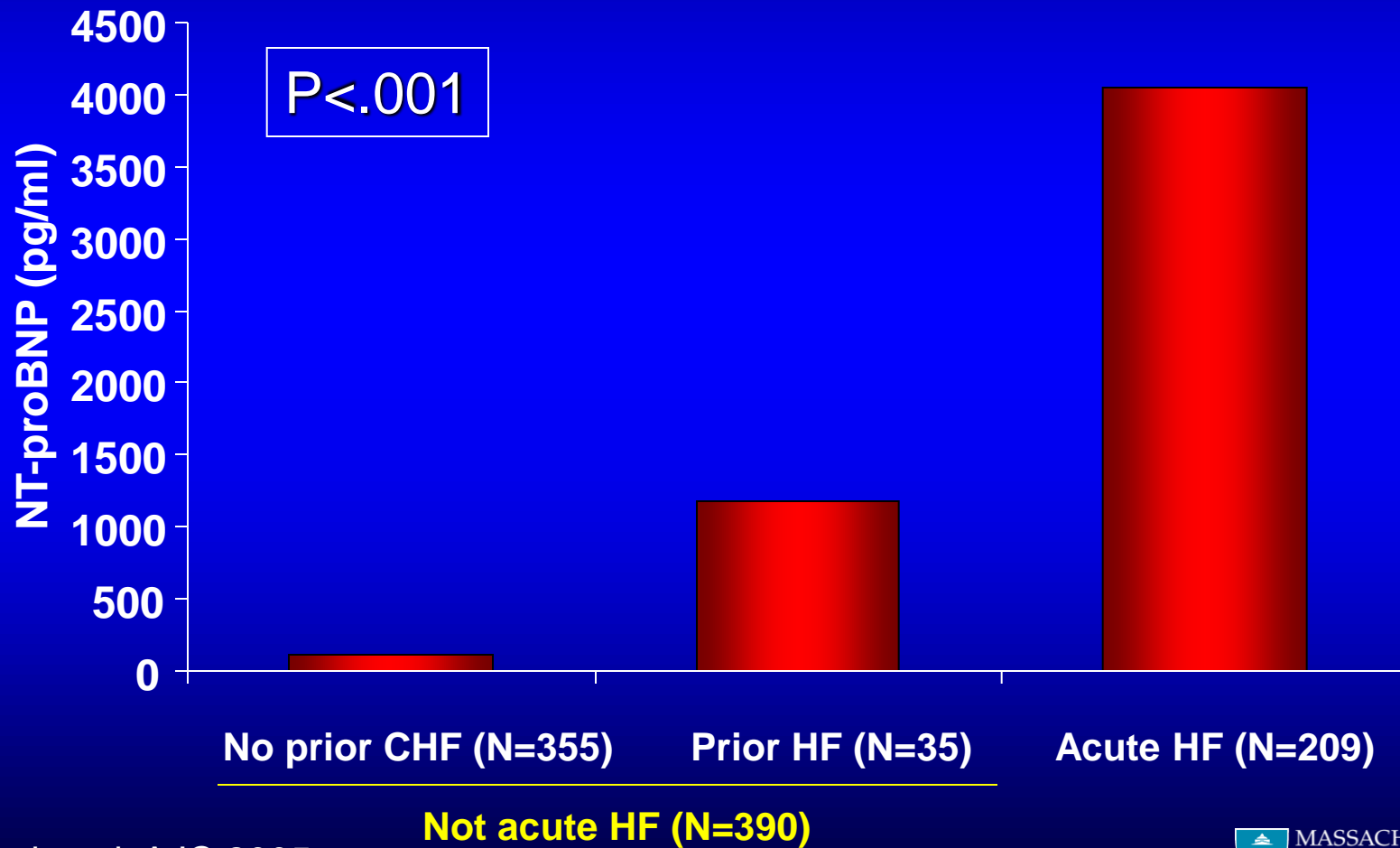


31% of subjects in PRIDE were judged uncertainly by the managing physician

Their prognosis was significantly worse, with higher rates of death and re-hospitalization and longer lengths of stay!



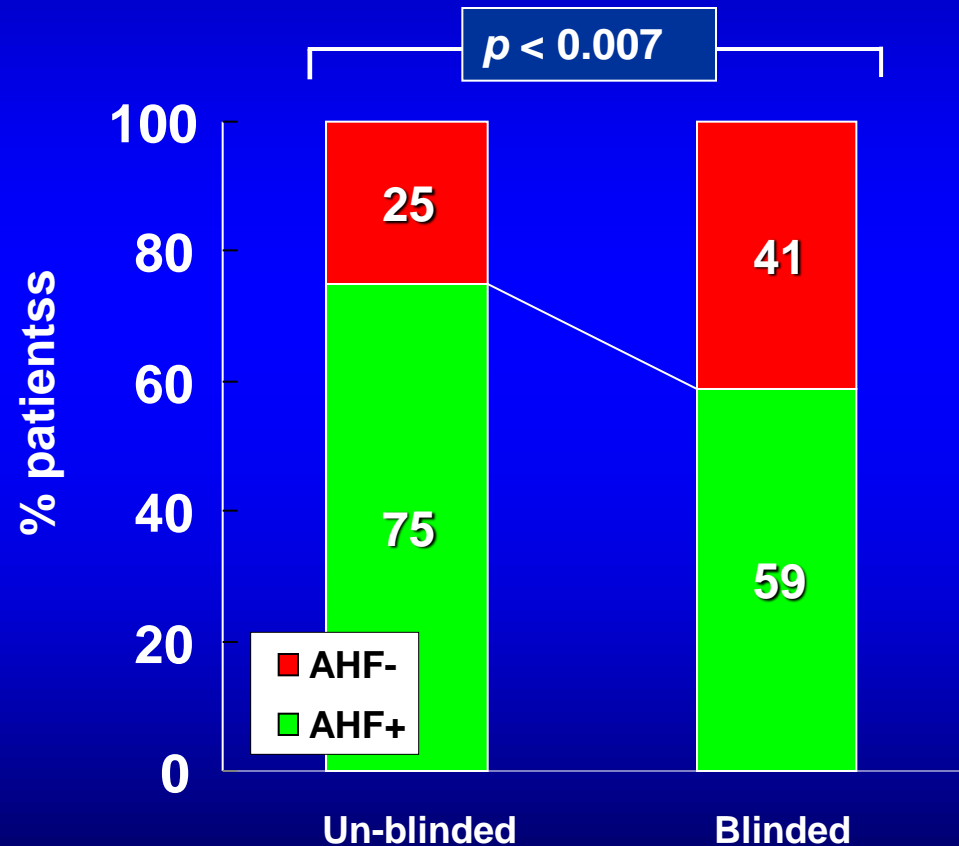
Results: NT-proBNP Levels



NT-proBNP improves accuracy of ADHF diagnosis

All subjects had an NT-proBNP > age-adjusted URL

Un-blinded NT-proBNP results led to considerable increase in the correct diagnosis of ADHF



Where does NT-proBNP help most?

Data from the Canadian IMPROVE-CHF Study

Although NT-proBNP added incremental information at both ends of the spectrum of heart failure likelihood...

Clinician impression	Model impression	Not HF	HF	% Appropriately Reclassified
Low prob (n=343) (Accuracy =89%)	LP (n=282)	276	6	(2.1)*
	IP (n=58)	30	28	48.3
	HP (n=3)	0	3	100
Int prob (n=139)	LP (n=38)	37	1	97.3
	IP (n=77)	25	52	-
	HP (n=24)	0	24	100
High prob (n=91) (Accuracy =95%)	LP (n=0)	0	0	0
	IP (n=18)	4	14	22.2
	HP (n=73)	1	72	(1.4)*

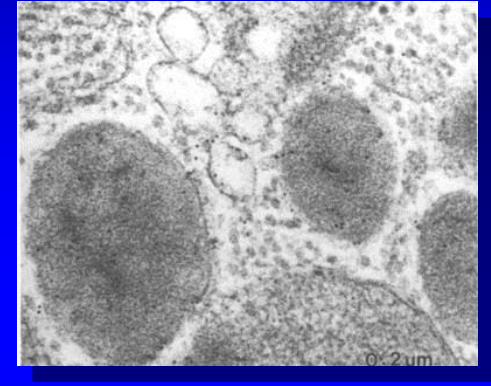
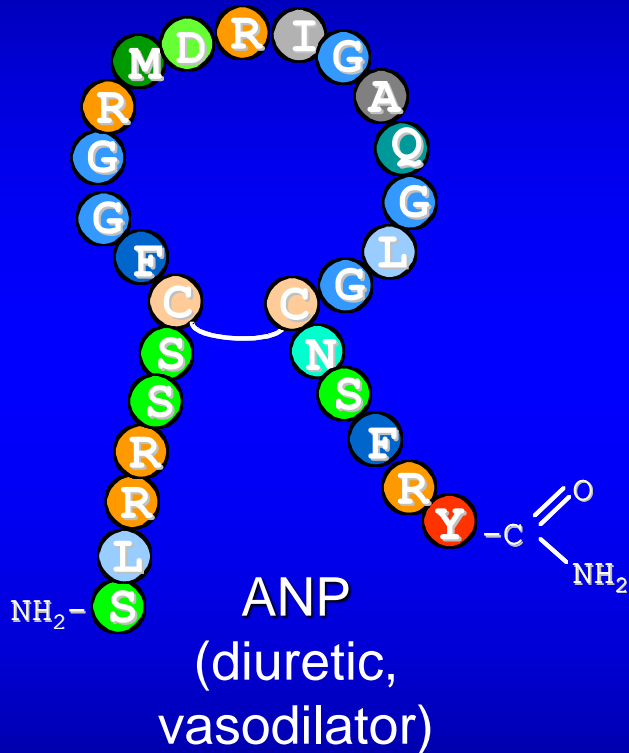
Where does NT-proBNP help most?

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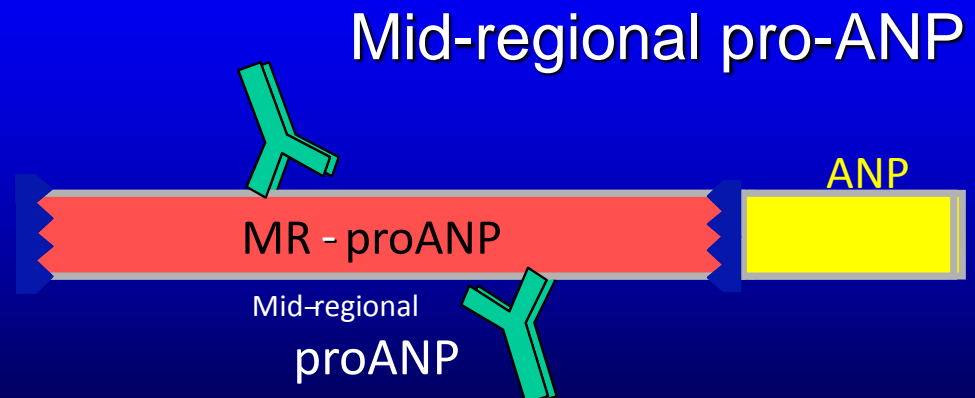
Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses suggested the biggest benefit was in the indecision zone...

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MR-proANP as a biomarker of heart failure



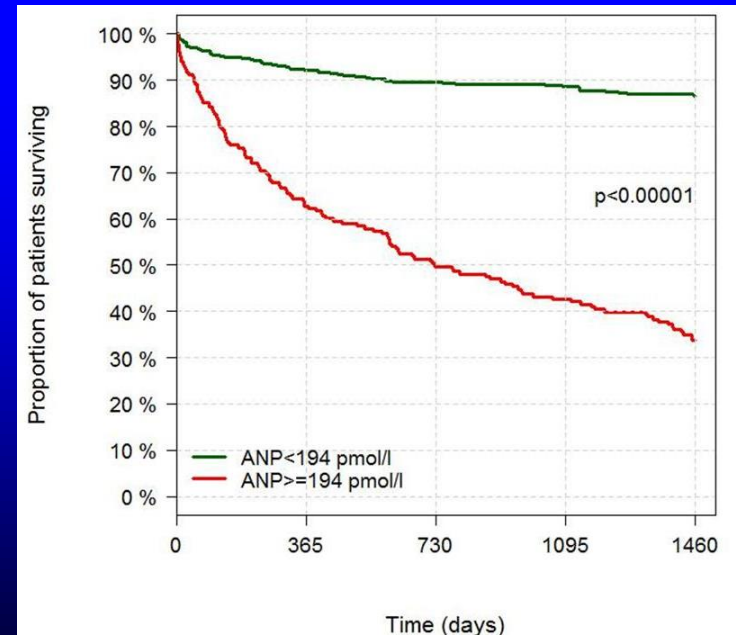
ANP is unstable *in vivo* and *in vitro*, therefore not suitable for clinical diagnosis.



Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea

Ravi V. Shah¹, Quynh A. Truong¹, Hanna K. Gaggin¹, Jens Pfannkuche², Oliver Hartmann², and James L. Januzzi Jr^{1*}

	OR	95% CI	P
Elevated age-adjusted MR-proANP ^a	4.34	2.11–8.92	<0.001
Elevated age-adjusted NT-proBNP ^b	9.73	4.63–20.43	<0.001
Radiographic pulmonary oedema	7.28	3.11–17.04	<0.001
Orthopnoea	6.60	2.87–15.17	<0.001
Use of loop diuretic on presentation	2.87	1.50–5.49	<0.001
Presence of rales on exam	2.26	1.11–4.60	0.03
Age (by decade)	1.74	1.37–2.21	<0.001
Cough	0.47	0.24–0.91	0.03
Fever	0.13	0.04–0.40	<0.001

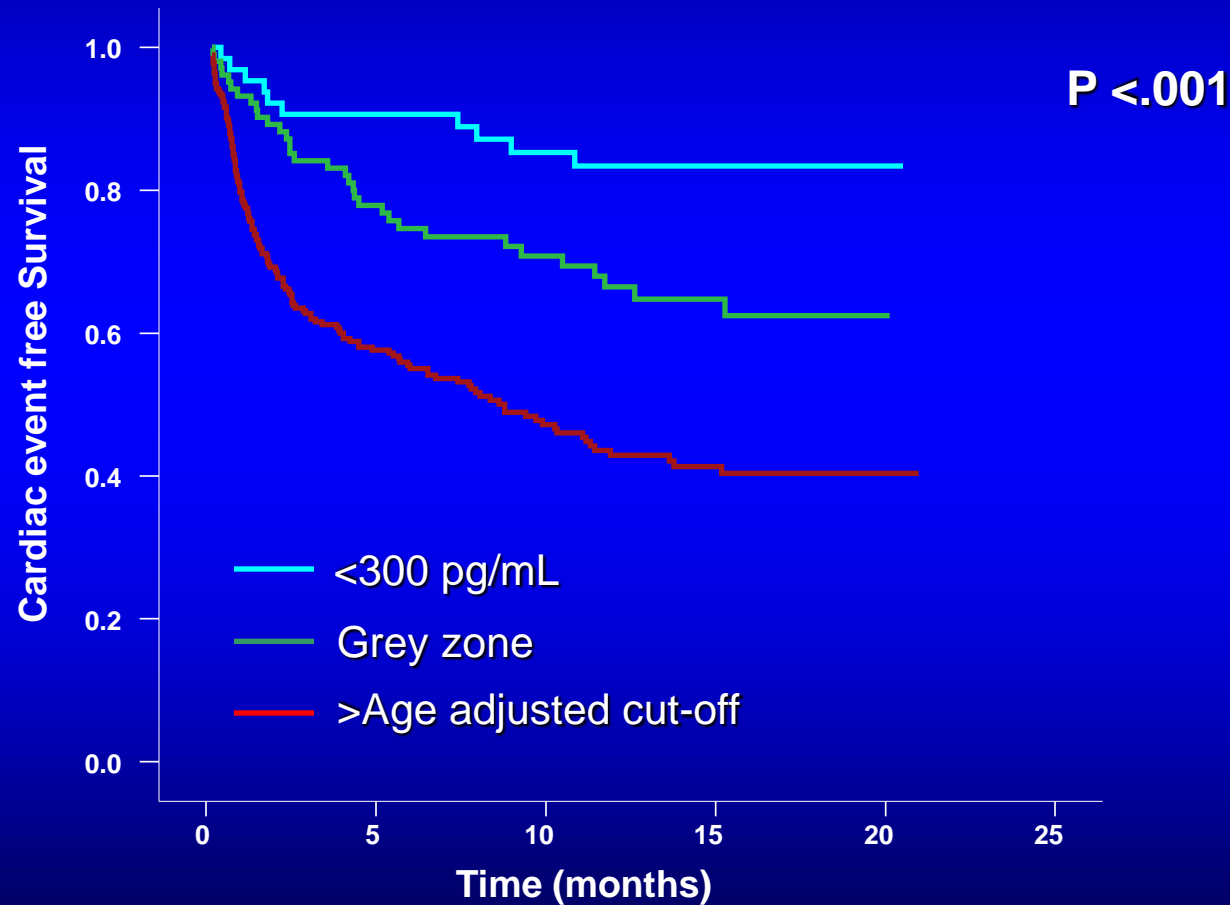


Shah, Eur Heart J, 2012

Accepted applications of BNP or NT-proBNP in HF

- ✓ Diagnosis
- ✓ Estimation of HF severity
- ✓ Prognostication
- ? Management

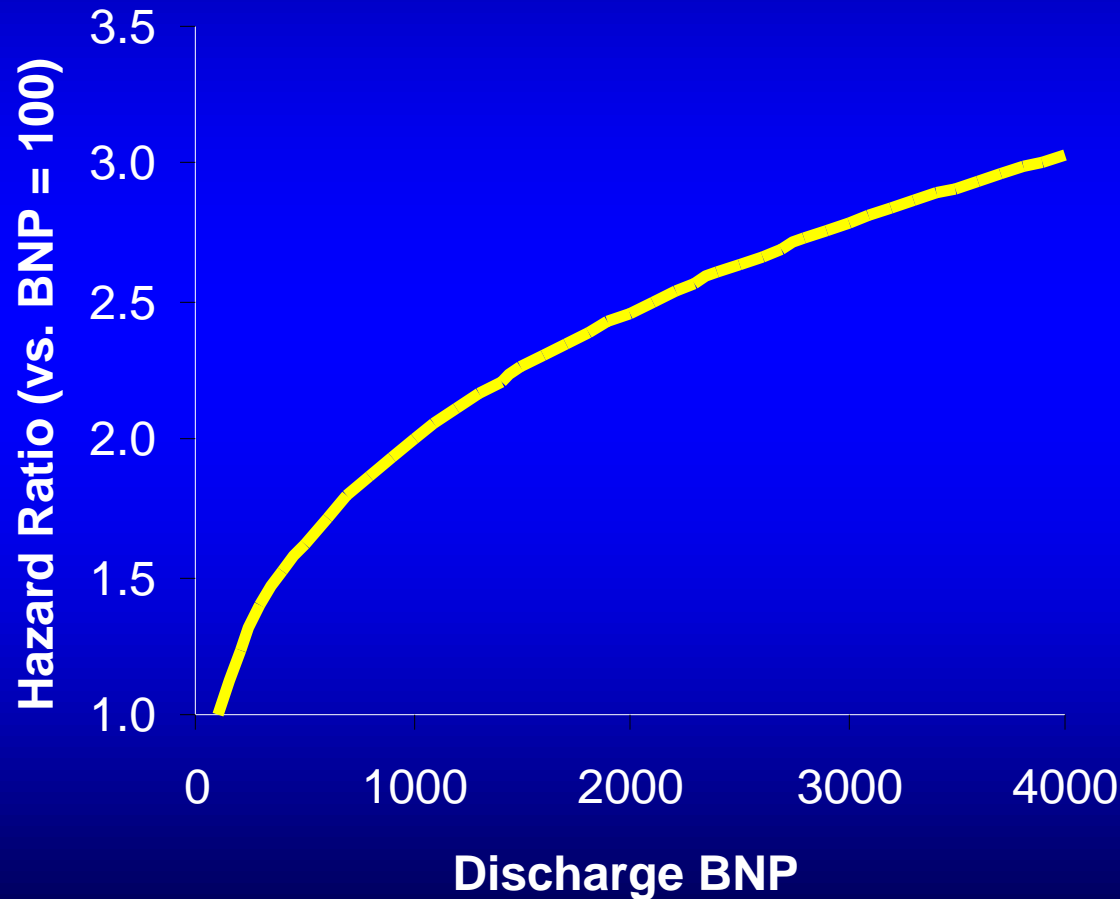
Prognostic importance of baseline NT-proBNP in ADHF



Interpreting Unexpectedly Elevated B-type Natriuretic Peptide Levels: *Know the Differential Diagnosis*

- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic insults

Relationships between discharge BNP and outcomes are curvilinear



Accepted applications of BNP or NT-proBNP in HF

- ✓ Diagnosis
- ✓ Estimation of HF severity
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- ? Management

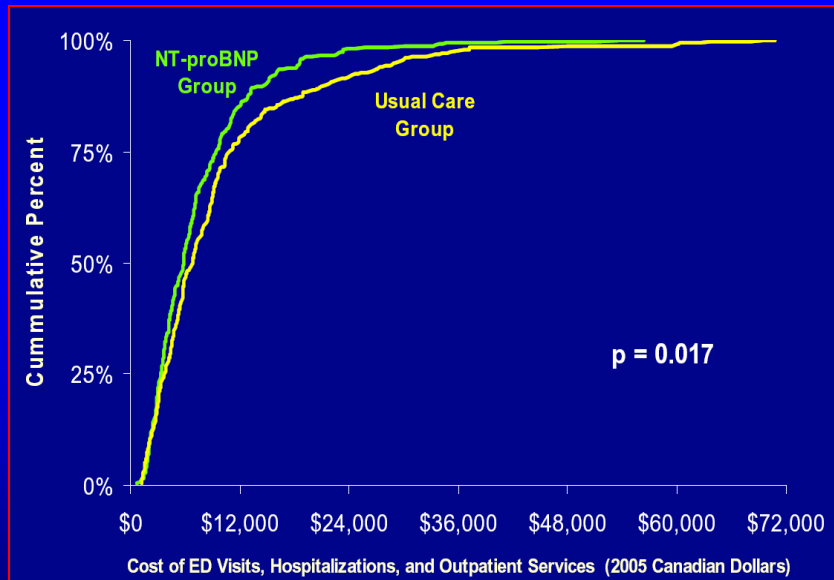
Why might natriuretic peptide testing assist with heart failure management?

- ✓ Earlier diagnosis
- ✓ Better triage
- As a target of therapy?

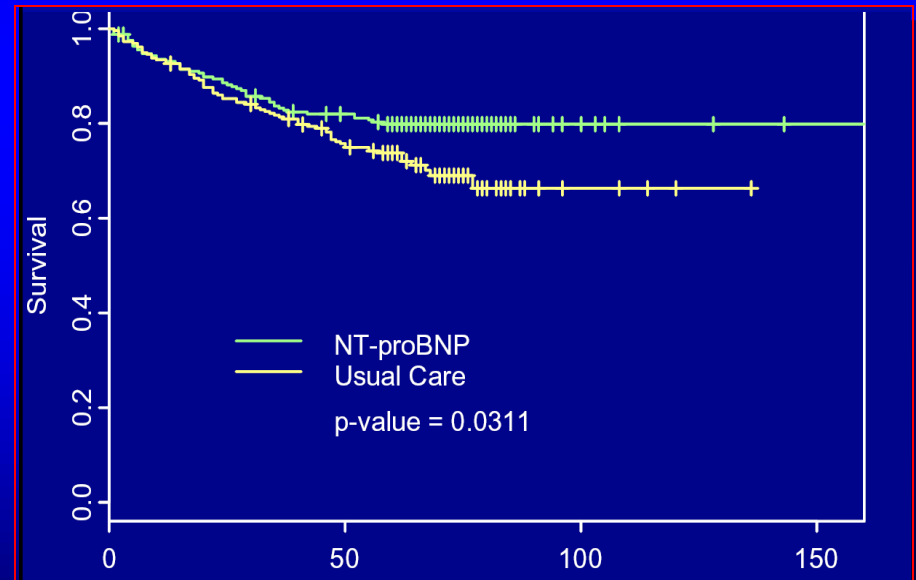
Effect of Selective NT-proBNP Testing On Costs/Outcomes:

Results of the Randomized IMPROVE-CHF Trial

Effect of Selective NT-proBNP Testing on Utilization/Costs



Effect of Selective NT-proBNP Testing on Outcomes



Moe, et al, 2007, Circulation

Why might natriuretic peptide testing assist with heart failure management?

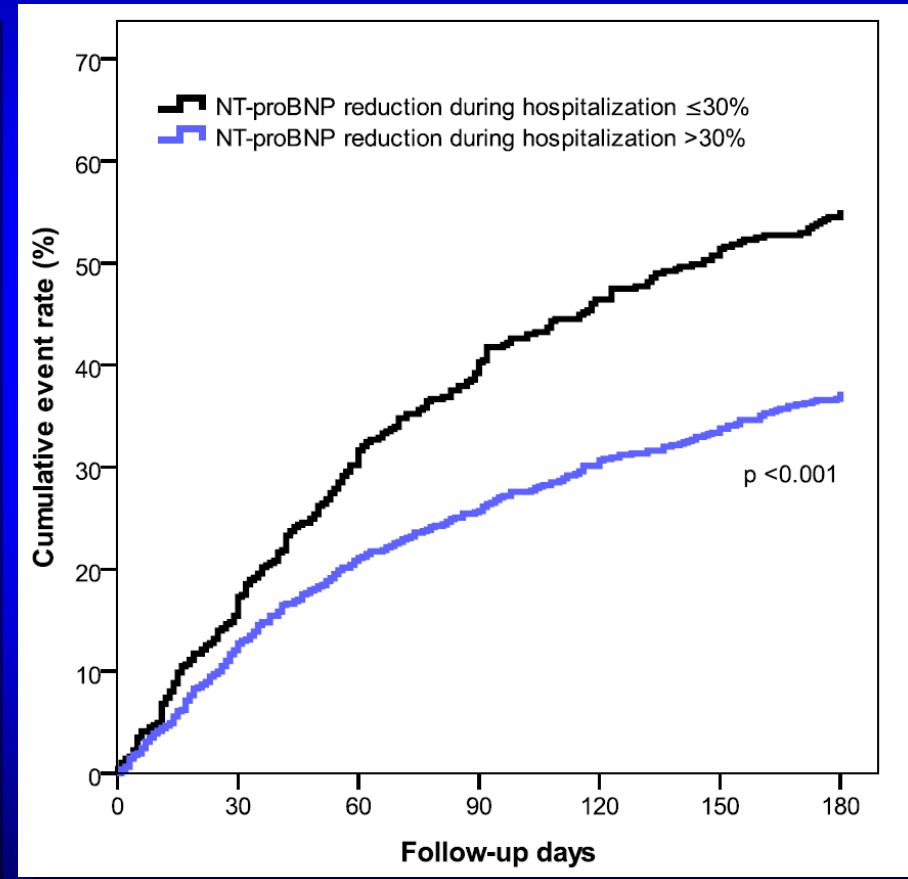
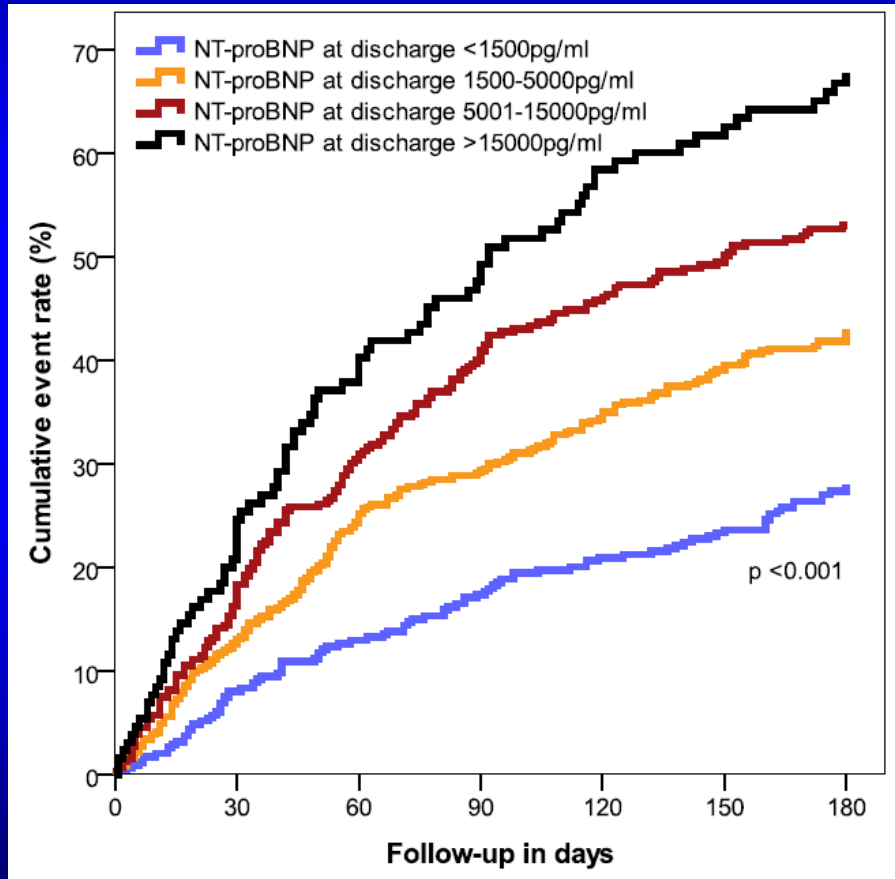
✓ Earlier diagnosis

- As a target of therapy?

Therapies with Effects on B-Type Natriuretic Peptide Levels

Therapy	Effect on BNP/NT-proBNP
Diuresis	↓
ACE-I	↓
ARB	↓
β-blockers	↓
Aldosterone antagonists	↓
BiV pacing	↓
Exercise	↓
Rate control of AF	↓
ANP/BNP infusions	↓

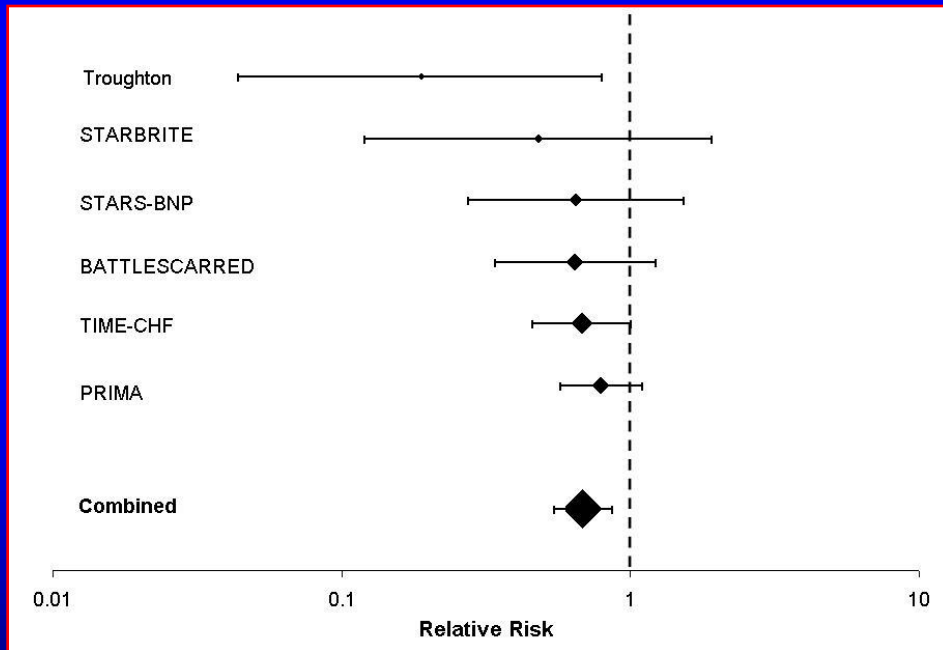
Natriuretic peptide treatment response: *Absolute target and % change*



Data courtesy of Yigal Pinto, MD

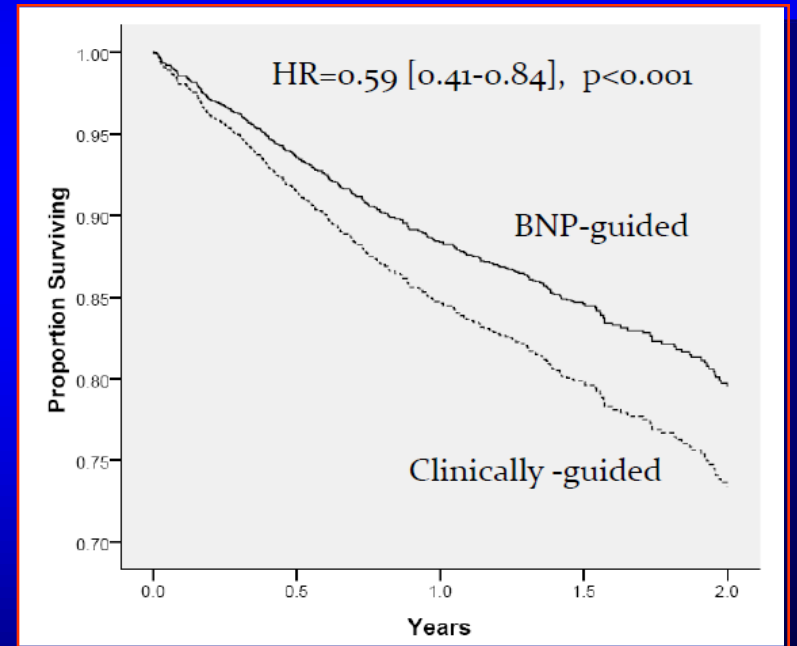
Guided therapy combined analyses

Meta analysis of publication data



Felker et al, Am Heart Journal, 2009

Pooled patient data from all available trials



Troughton et al, ESC 2011

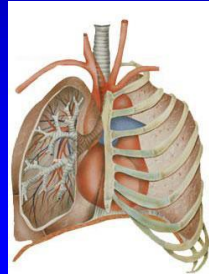
Beyond the natriuretic peptides

- “Fibrosis”/remodeling markers
 - ST2
 - Galectin 3
 - GDF-15
 - hs Troponin
- Inflammatory markers
 - Take your pick...
- Salt and water derangement
 - Copeptin
- Co-morbidity markers
 - Hemoglobin
 - RDW
 - Renal markers
 - ET-1
 - Adipokines
- Hemodynamic stress
 - MR-proADM
- Genetic markers
 - Pharmacogenomics

Biologic role of adrenomedullin

Adrenomedullin

Lung

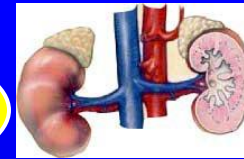


↓ pulmonary hypertension

↓ synthesis of ET-1 and NO

vasoprotective

Kidney



– Sodium excretion

– Urine volume

– Renal blood flow

↓ Aldosterone

Vascular System



↑ Vasodilation

↓ blood pressure

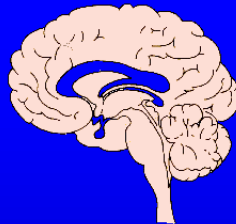
Heart



– Contractility

↓ ANP

CNS and endocrine glands



↓ Thirst

↓ Salt Appetite

↓ Vasopressin secretion

↓ ACTH secretion

↓ Insulin secretion

Reproductive System

– Stimulatory Effect
on FSH



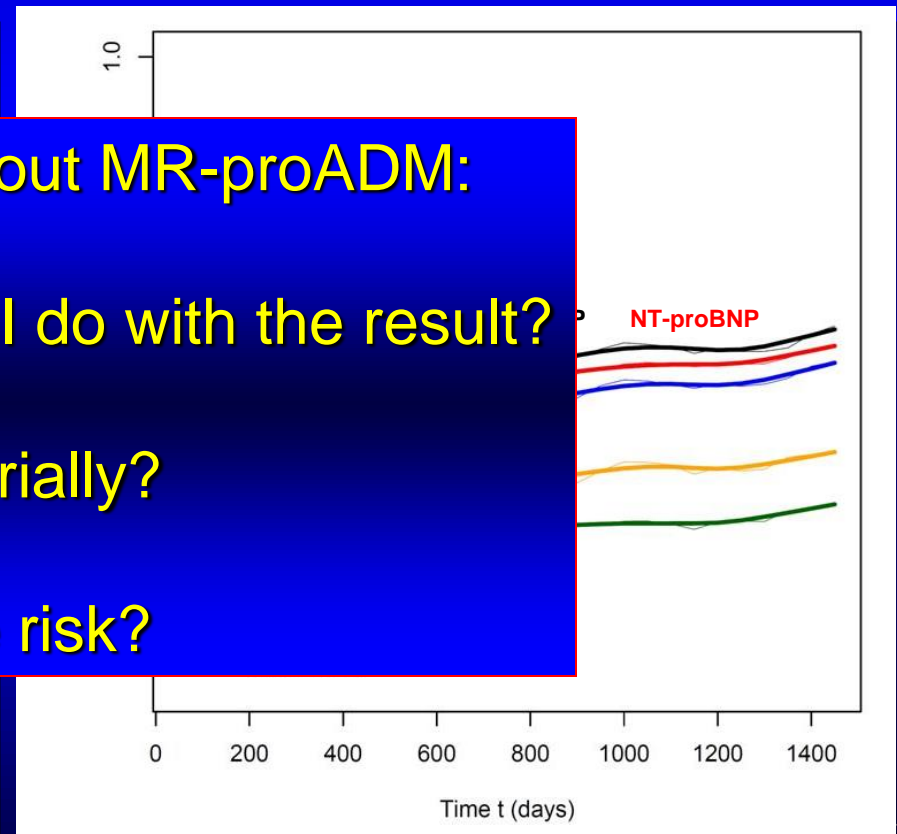
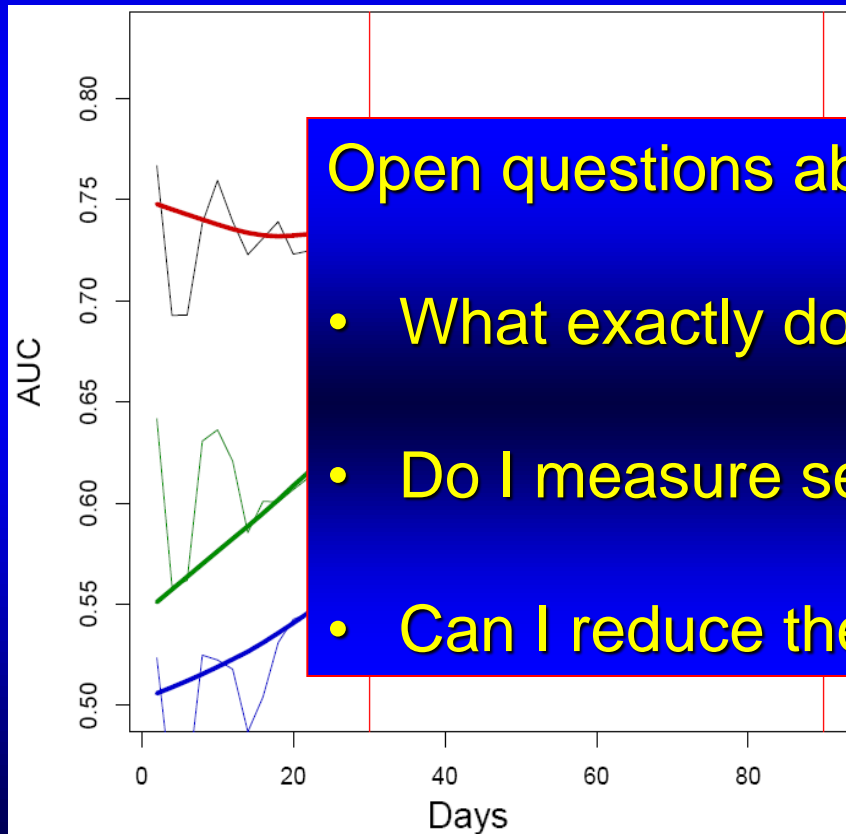
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MR-proADM is prognostic for death in HF (particularly early events)

BACH Study

PRIDE Study



Open questions about MR-proADM:

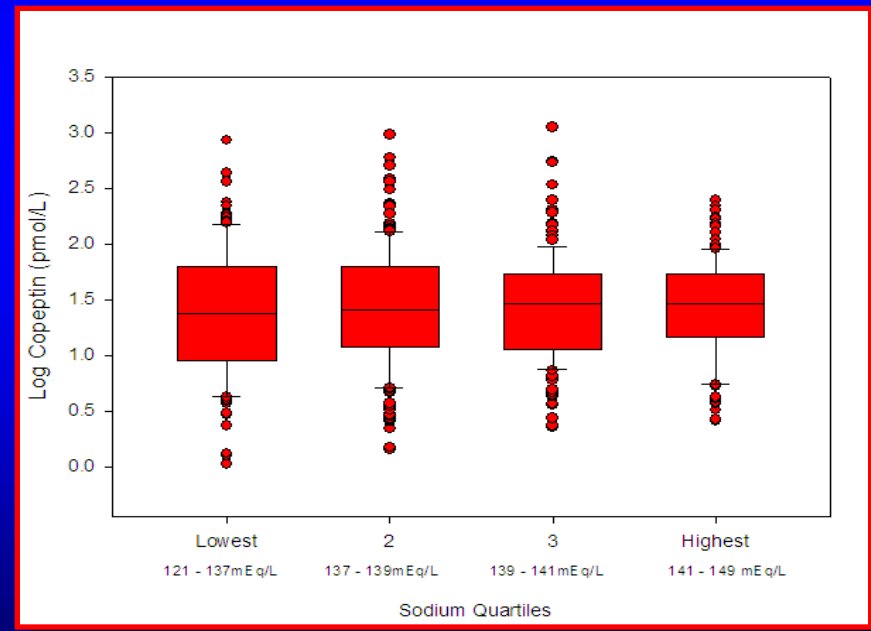
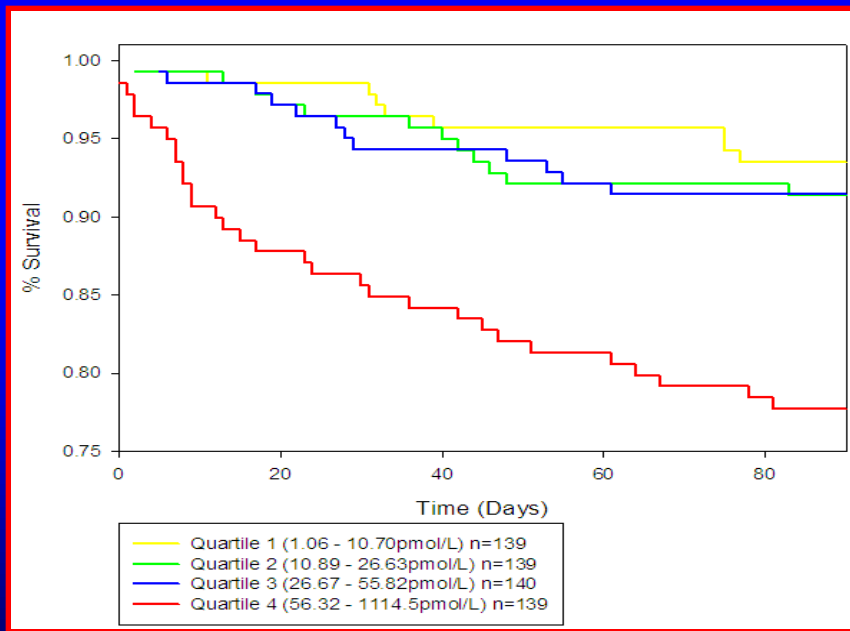
- What exactly do I do with the result?
- Do I measure serially?
- Can I reduce the risk?

Copeptin (CT-proAVP) and outcomes in ADHF

Results from the BACH Study

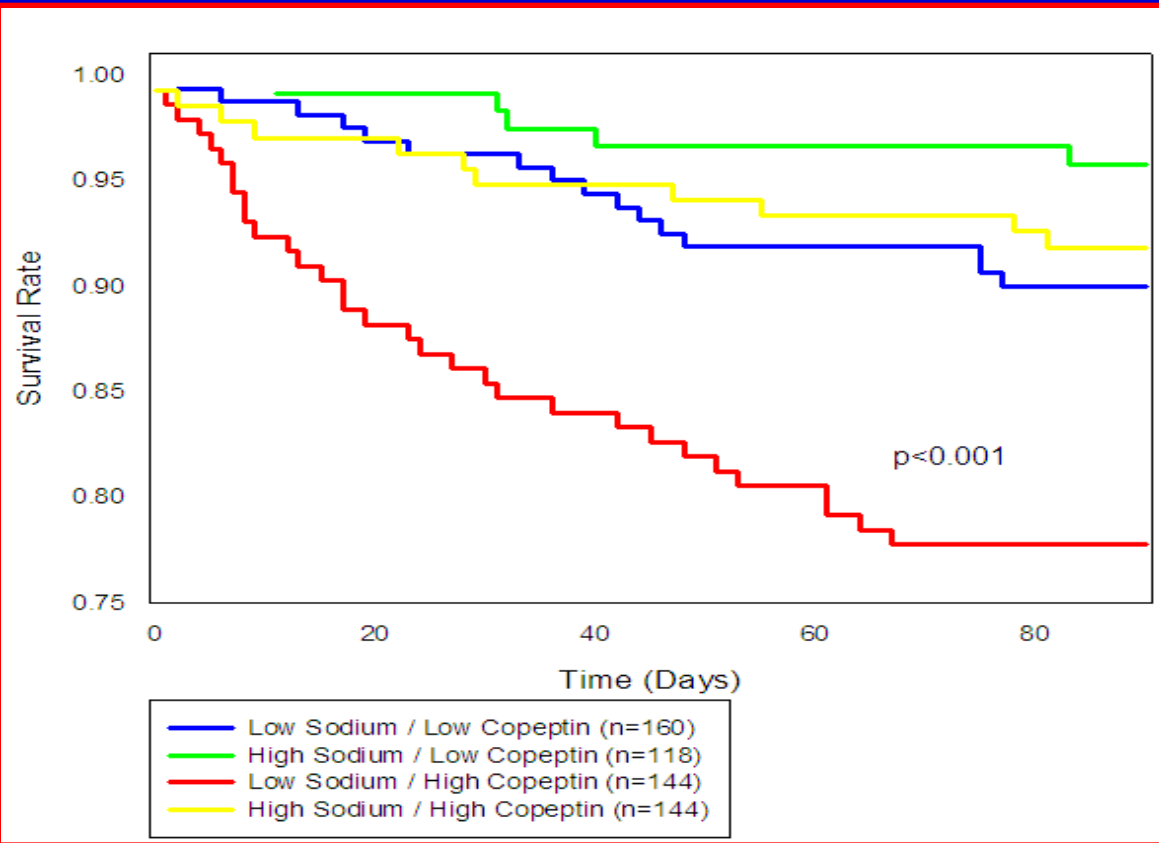
Concentrations of copeptin were prognostic in all HF subjects...

And seemingly unrelated to serum sodium concentrations...



Copeptin and outcomes in ADHF

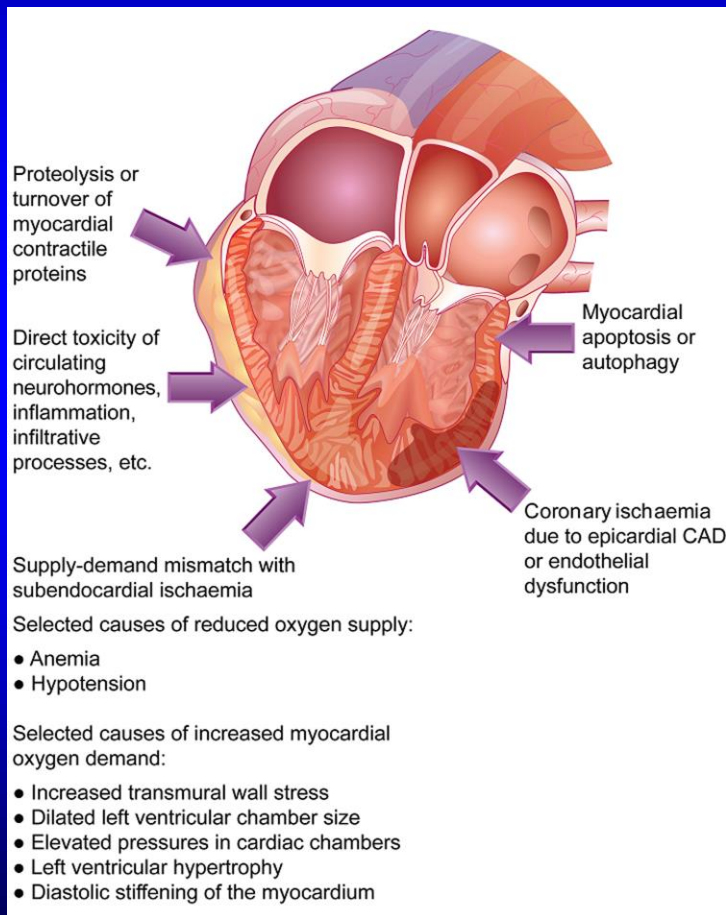
Results from the BACH Study



However, considered as a function of low sodium and high copeptin, more refined ability to risk stratify emerged...

The ACTIVATE study will examine the importance of copeptin to identify benefit from tolvaptan in hyponatremic subjects

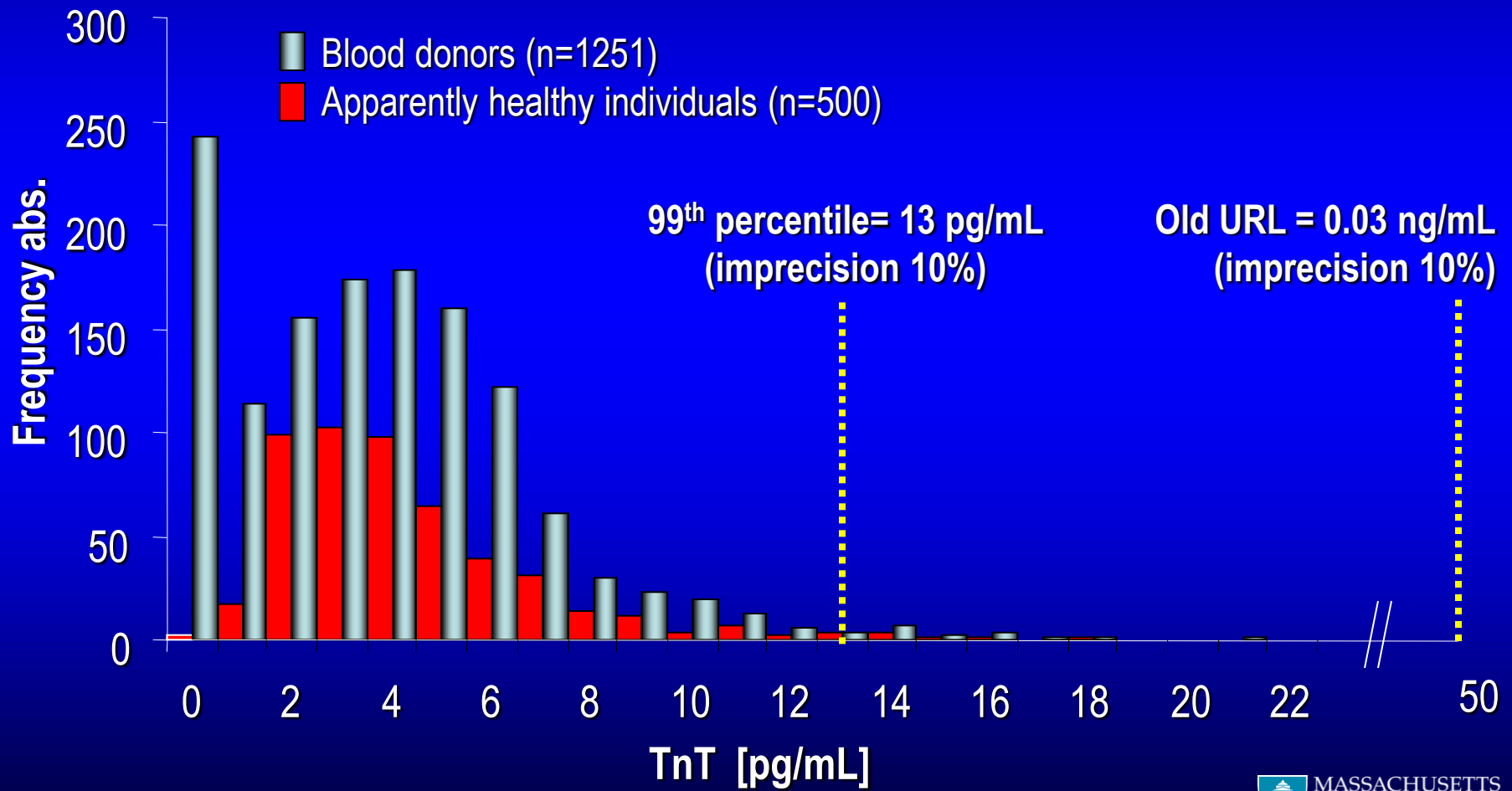
Hypothesized links between troponin and incident HF



Troponin elevation in HF is:

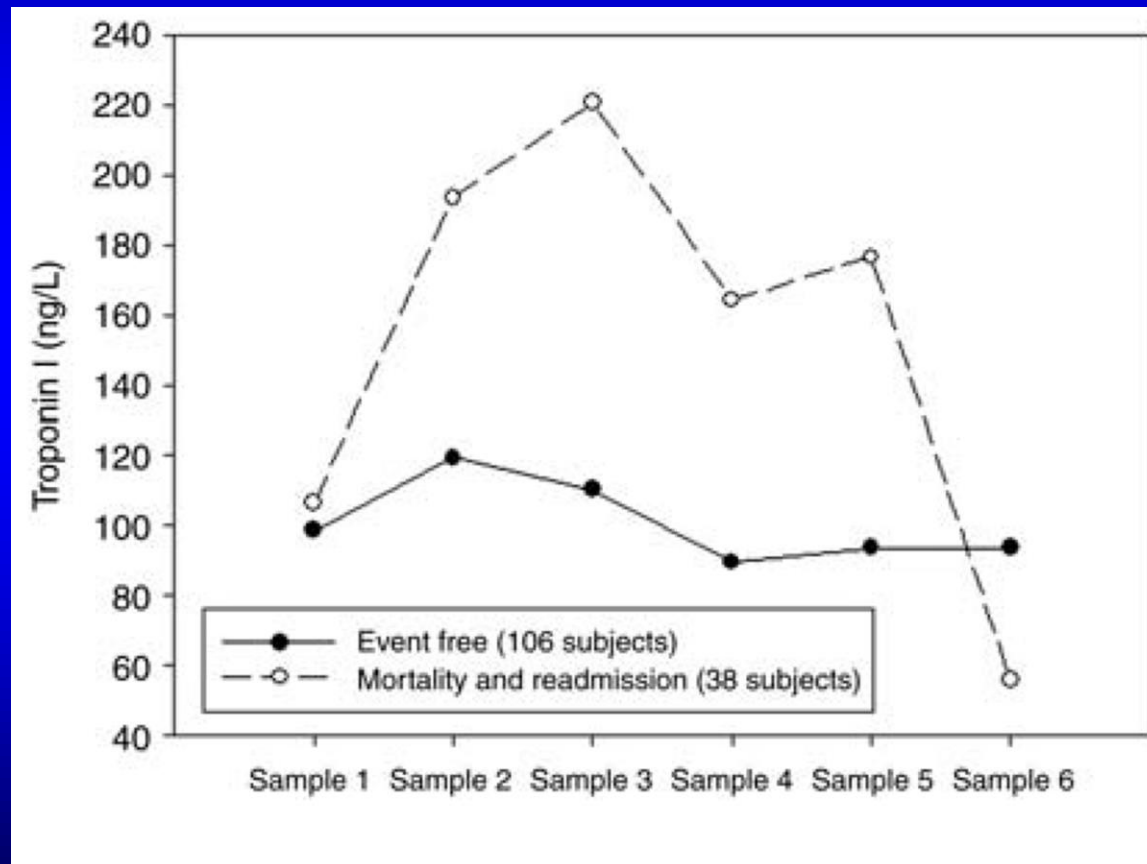
- Common
- Not always related to CAD
- Caused by many mechanisms
- Prognostic!

99th Percentile for Troponin T



High sensitivity troponin in acutely decompensated heart failure

Serial measures



Galectin-3 in HF

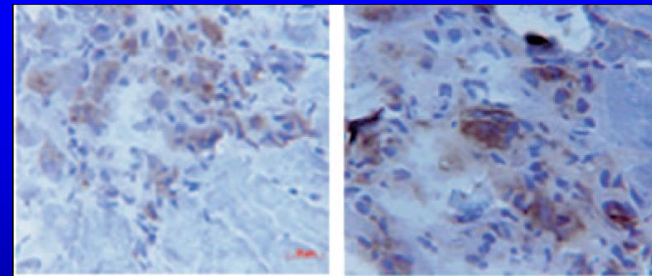
Scientific Discovery

- In animal models of heart failure, Galectin-3 highly expressed in failing versus functionally compensated hearts

Galectin-3



Control Compensated Heart Failure

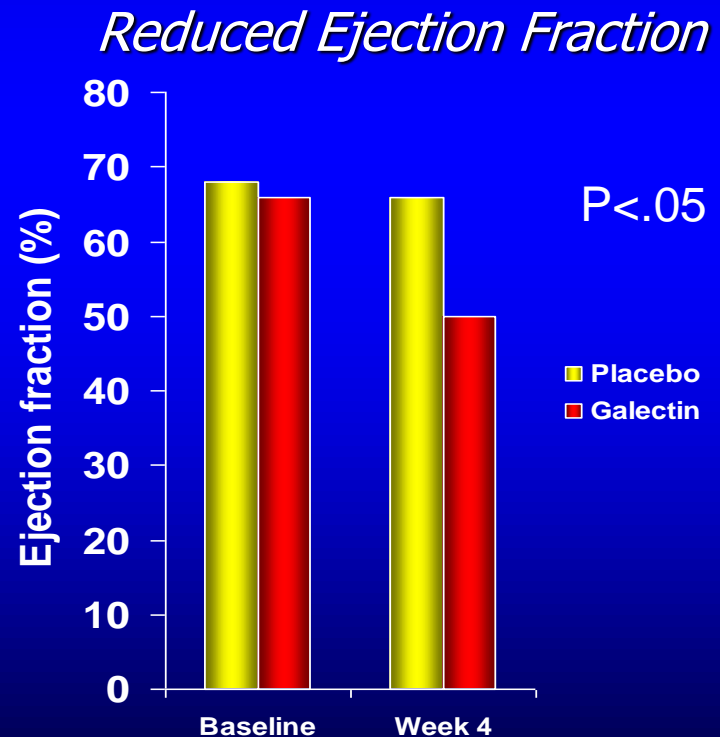
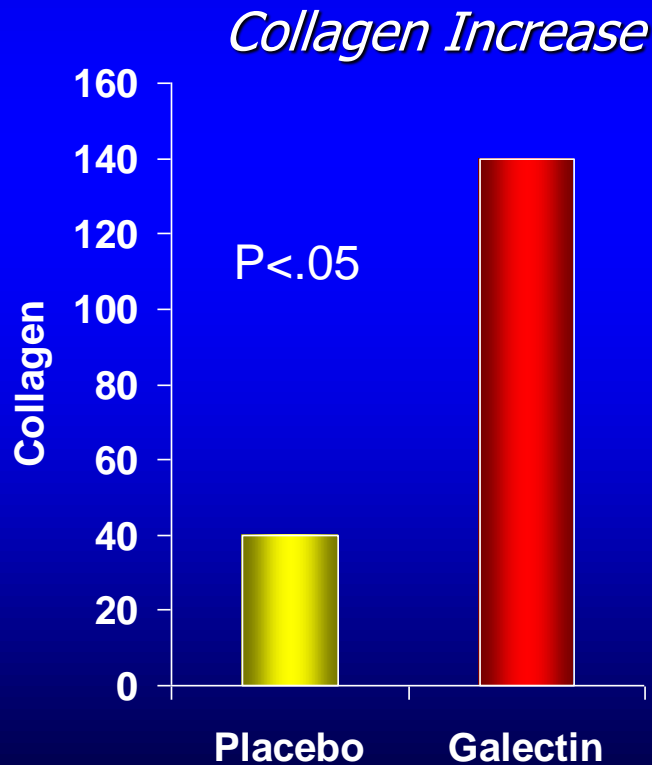


Normal

Heart failure

Galectin-3 Promotes Remodeling

Intrapericardial administration of galectin-3 significantly increases LV collagen content and reduces LV ejection fraction





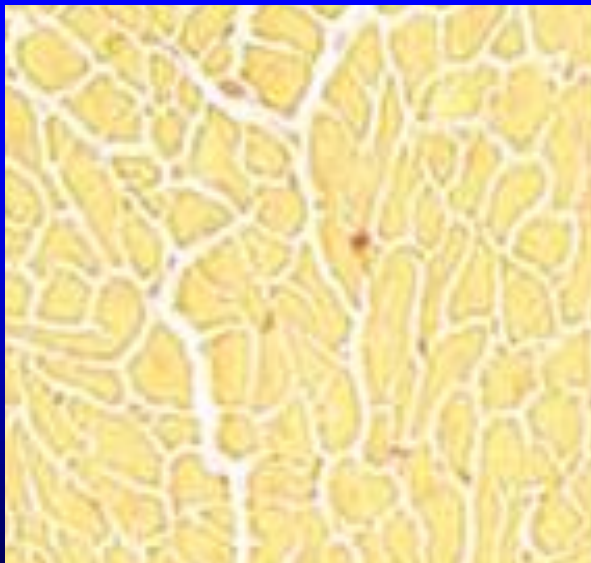
Galectin-3 and long term outcomes in ADHF



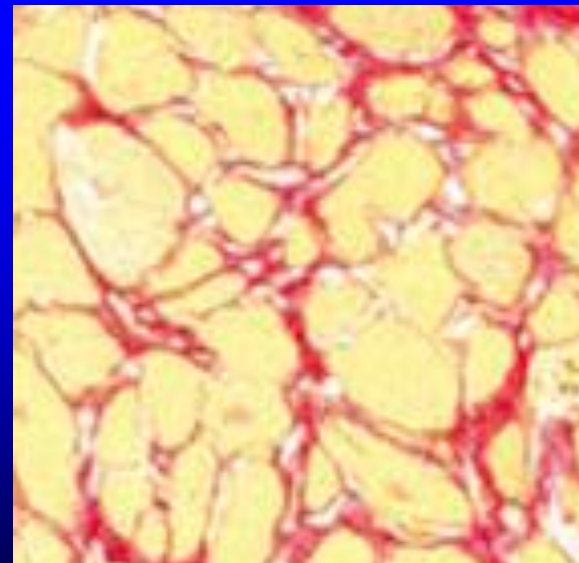
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure

Intact sST2

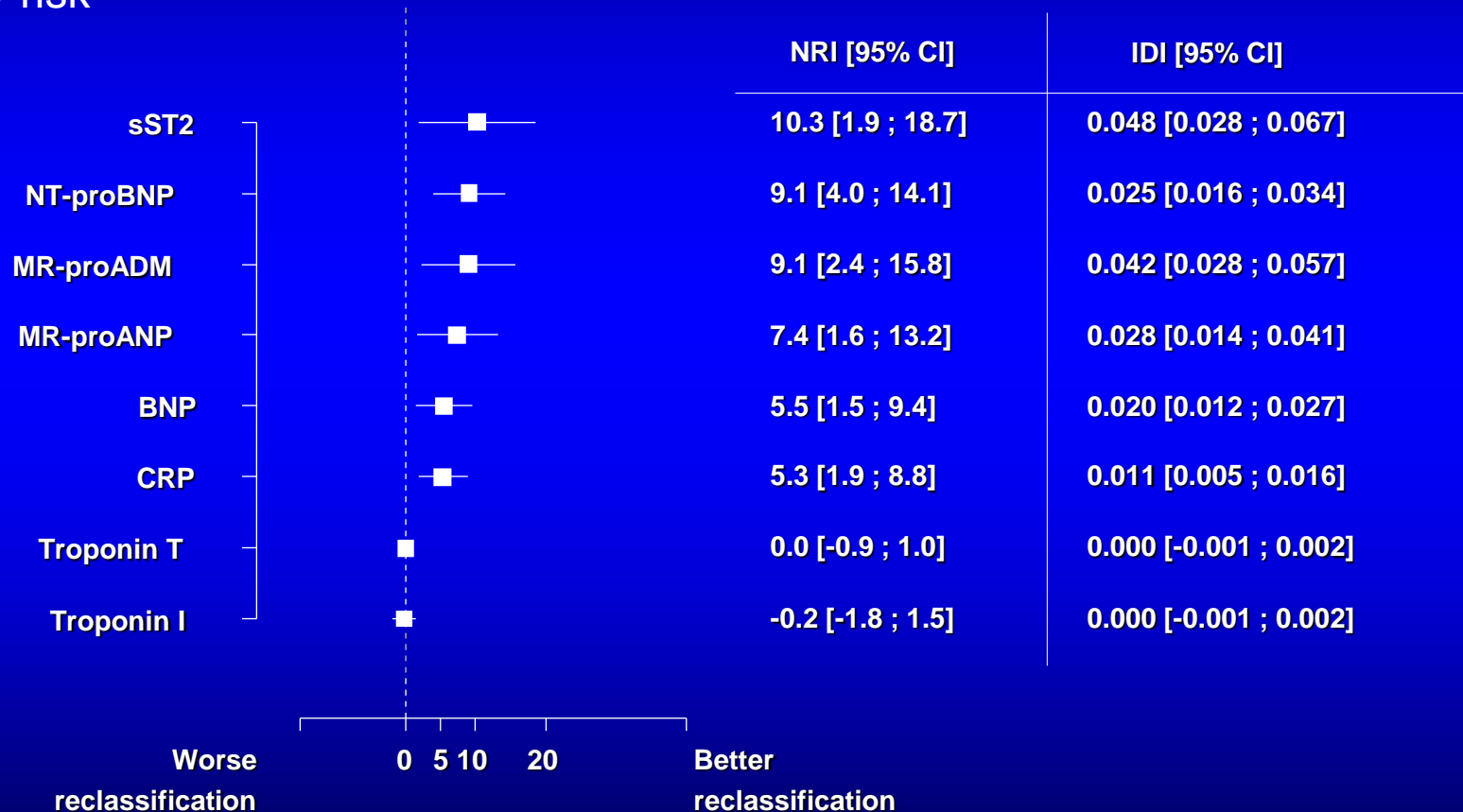


sST2 knock out



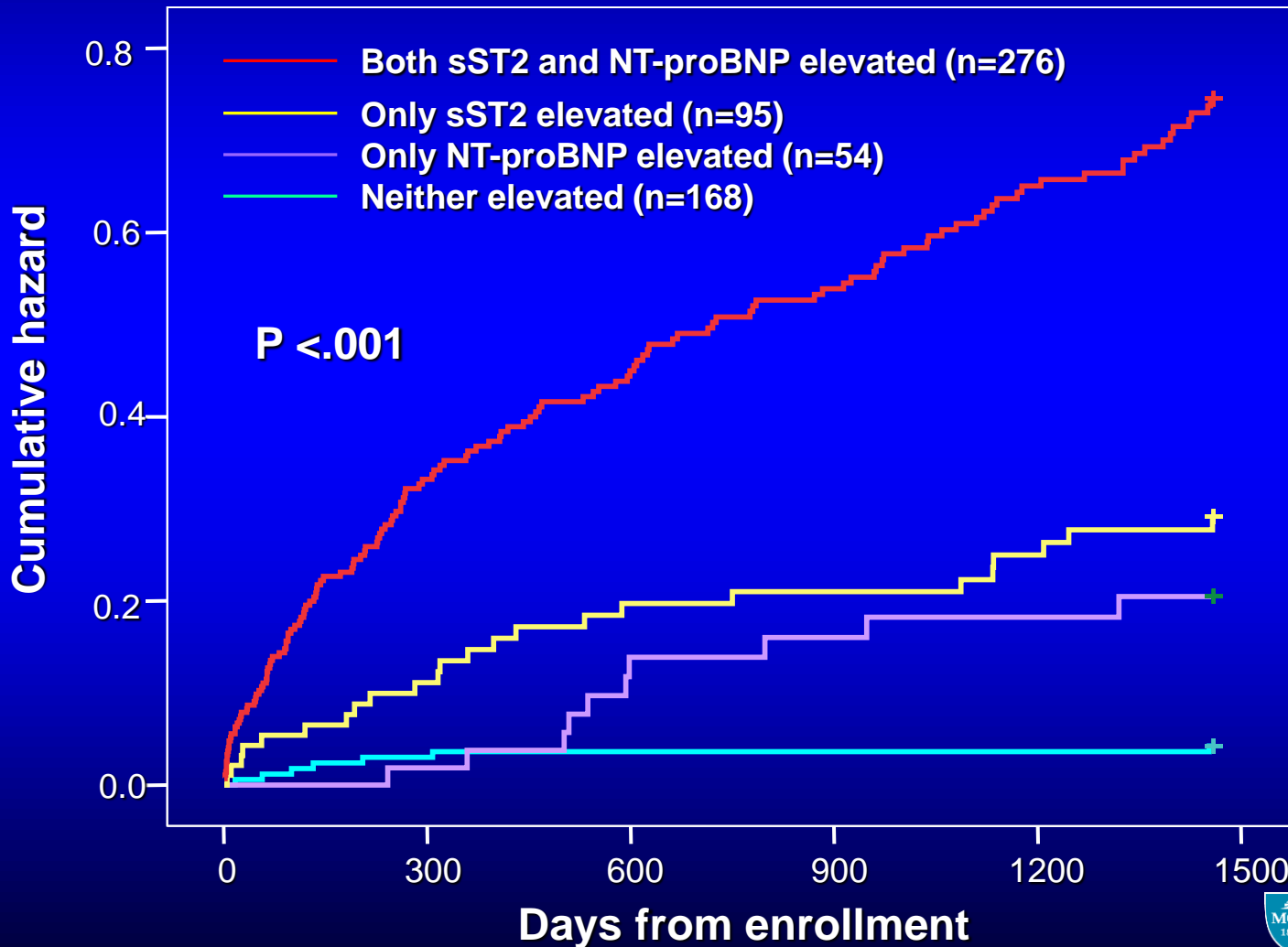
Multiple biomarkers in ADHF: *the GREAT Network Analysis*

365 day risk

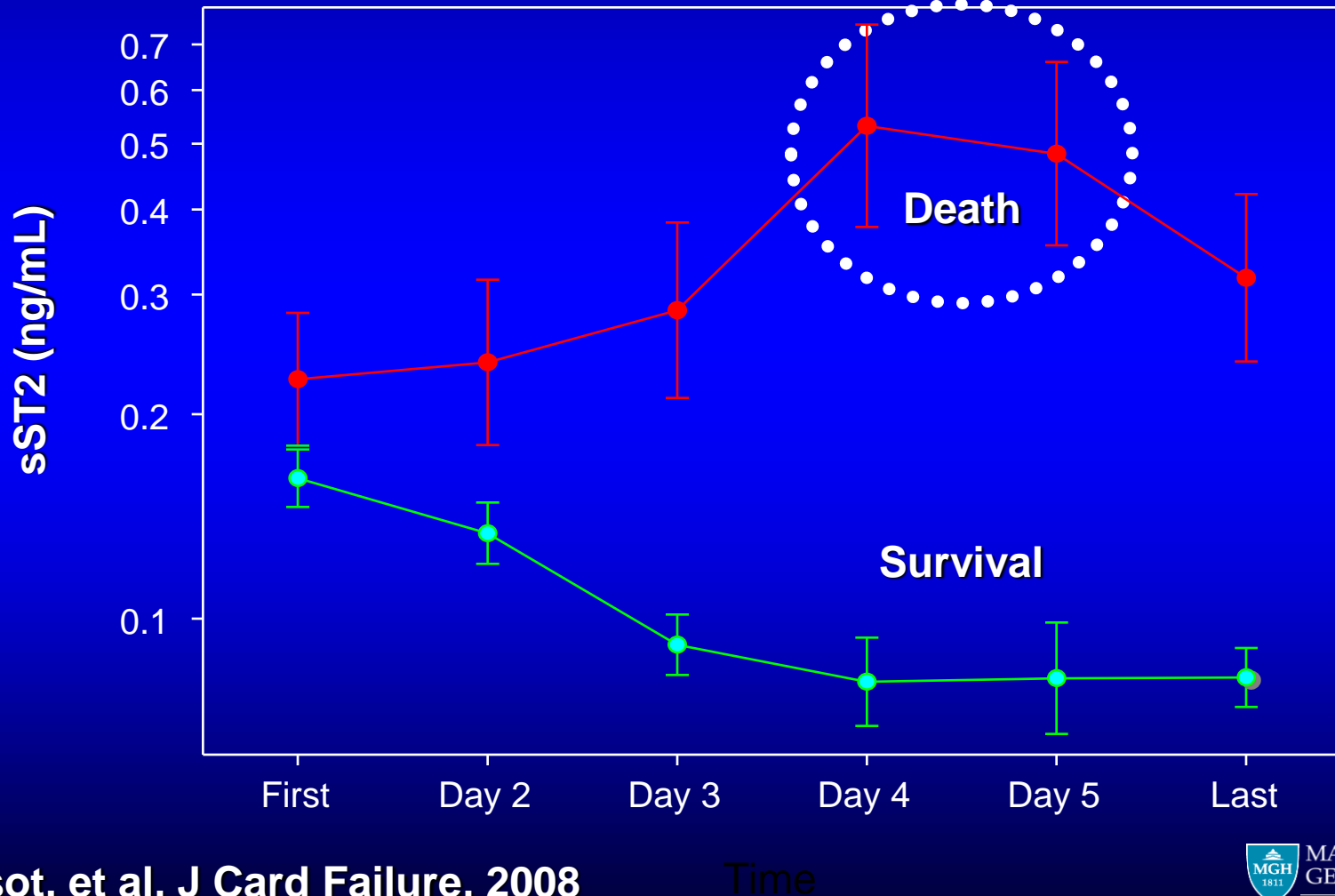




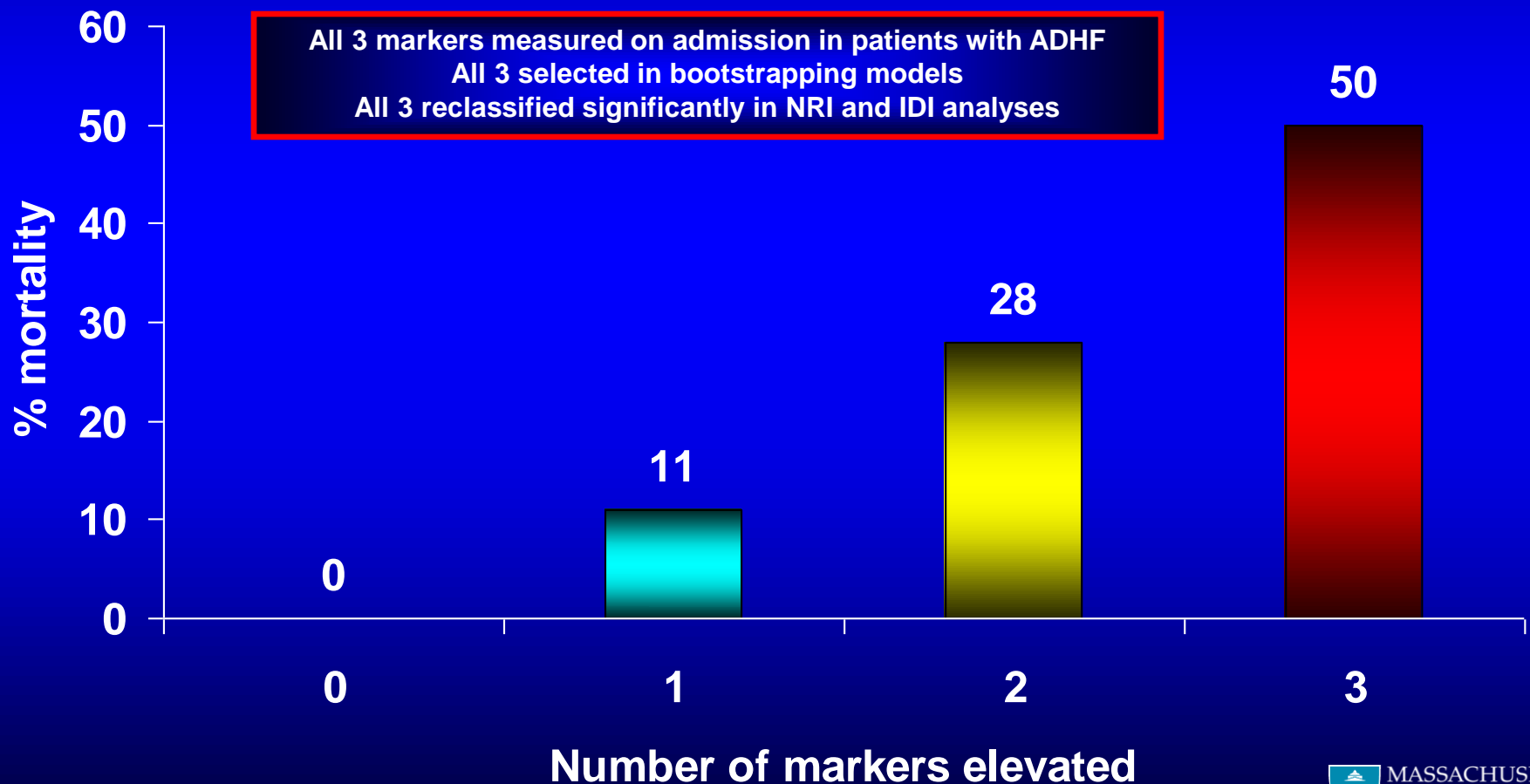
Additive value of ST2 to NT-proBNP in long term prognosis



ST2 Trends as a Function of Mortality



NT-proBNP, hsTnT, and sST2 in ADHF: *Multi-marker profiling*



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