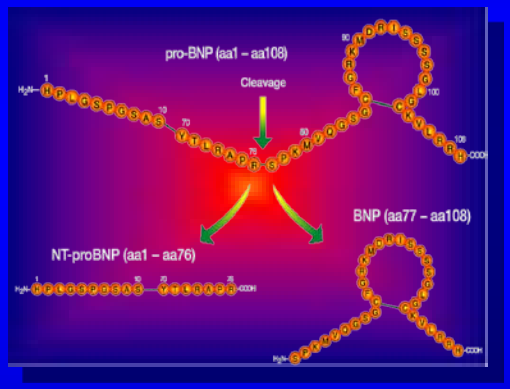
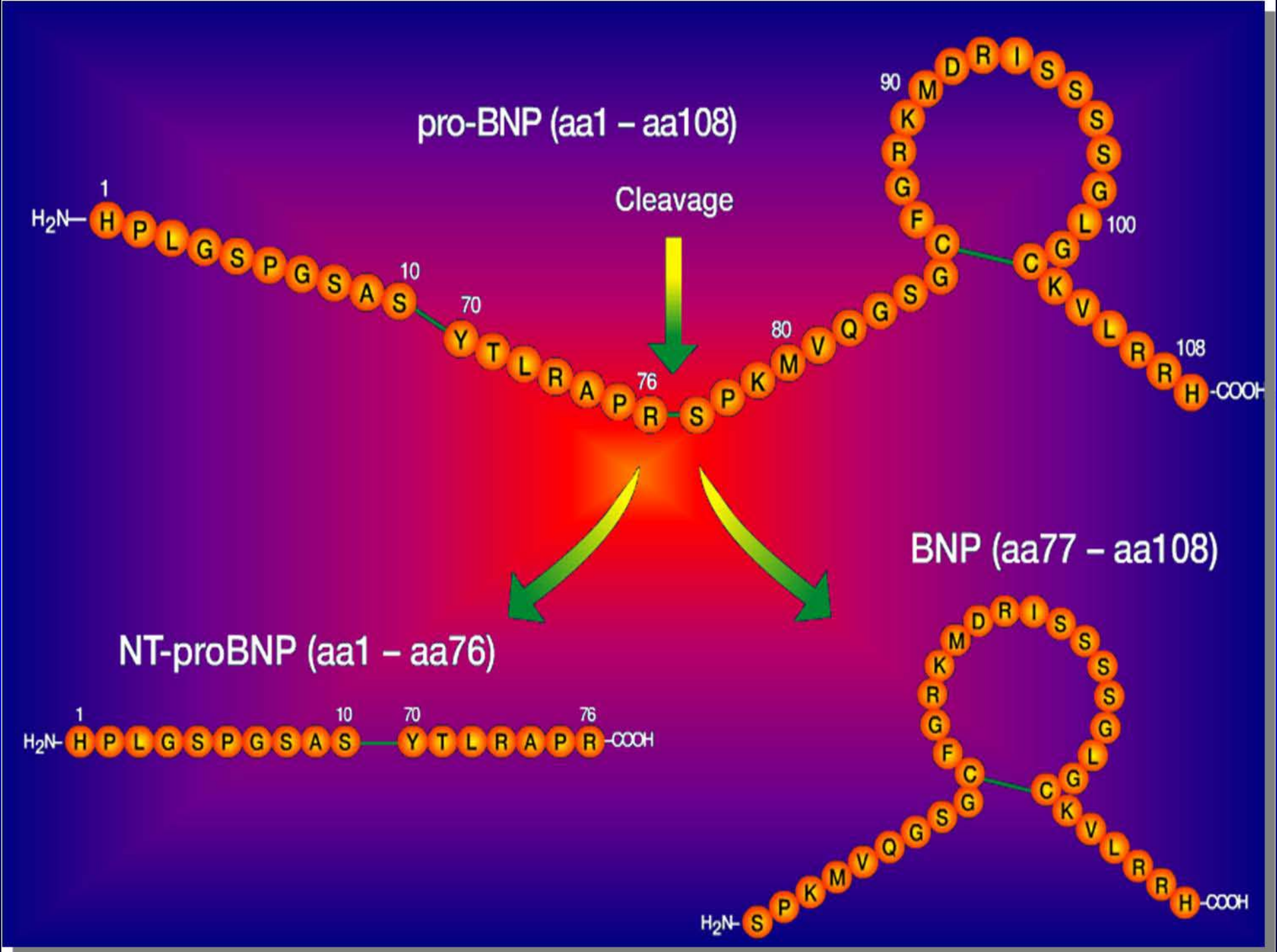
The clinical value of natriuretic peptide testing in heart failure



James L. Januzzi, Jr, MD, FACC, FESC
Associate Professor of Medicine
Harvard Medical School
Roman W. DeSanctis Endowed Clinical Scholar
Director, Cardiac ICU
Massachusetts General Hospital

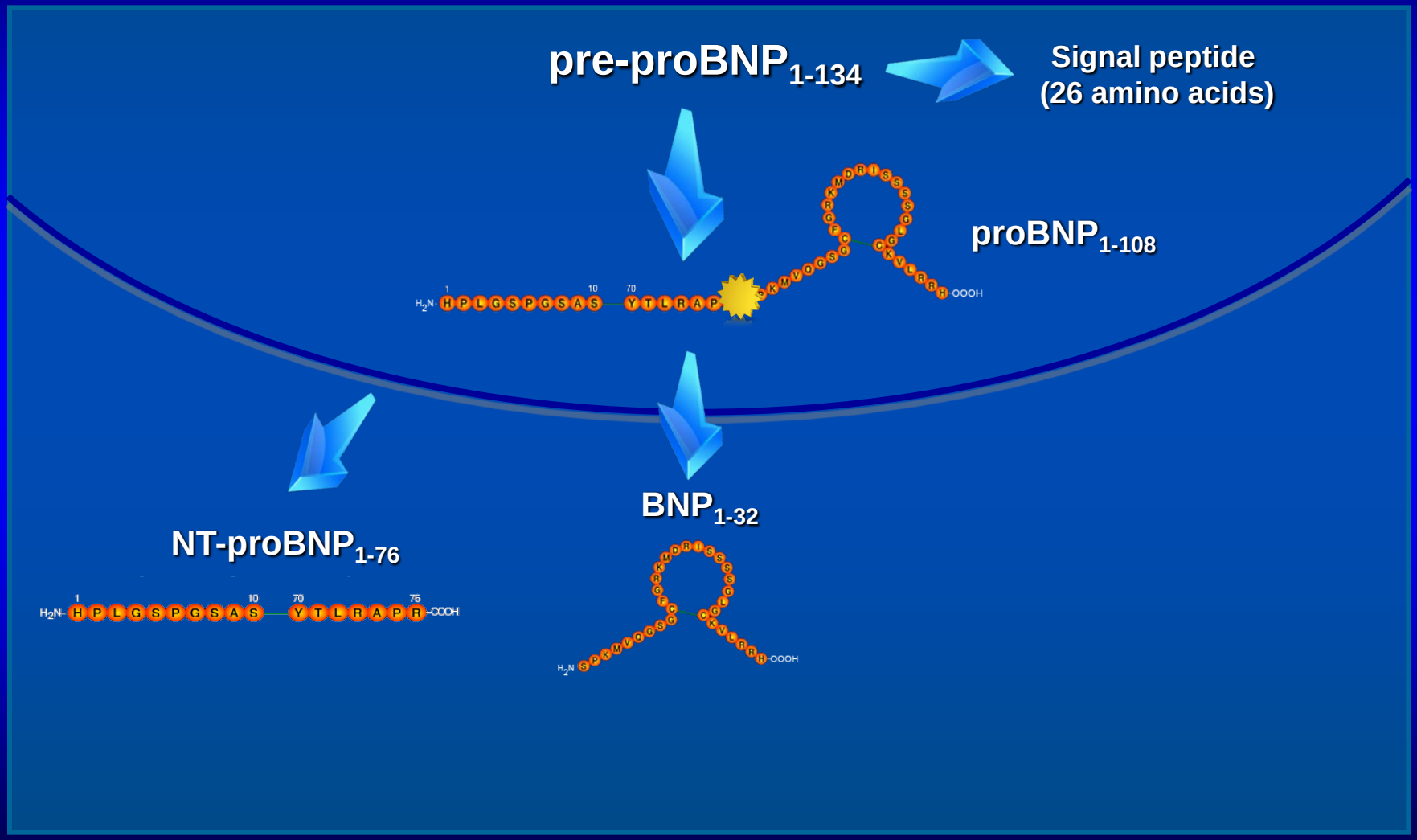
Disclaimer

- During this lecture will you not hear me suggest that we should stop thinking critically about our patients, put our stethoscopes away, or apply natriuretic peptide testing without thinking about every possibility.


pro-BNP (aa1 – aa108)
Cleavage
NT-proBNP (aa1 – aa76)
BNP (aa77 – aa108)
H2N-HPLGSPGSAS-YTLRAPR-COOH
H2N-SPKMVQGSG-CKVLRRH-COOH

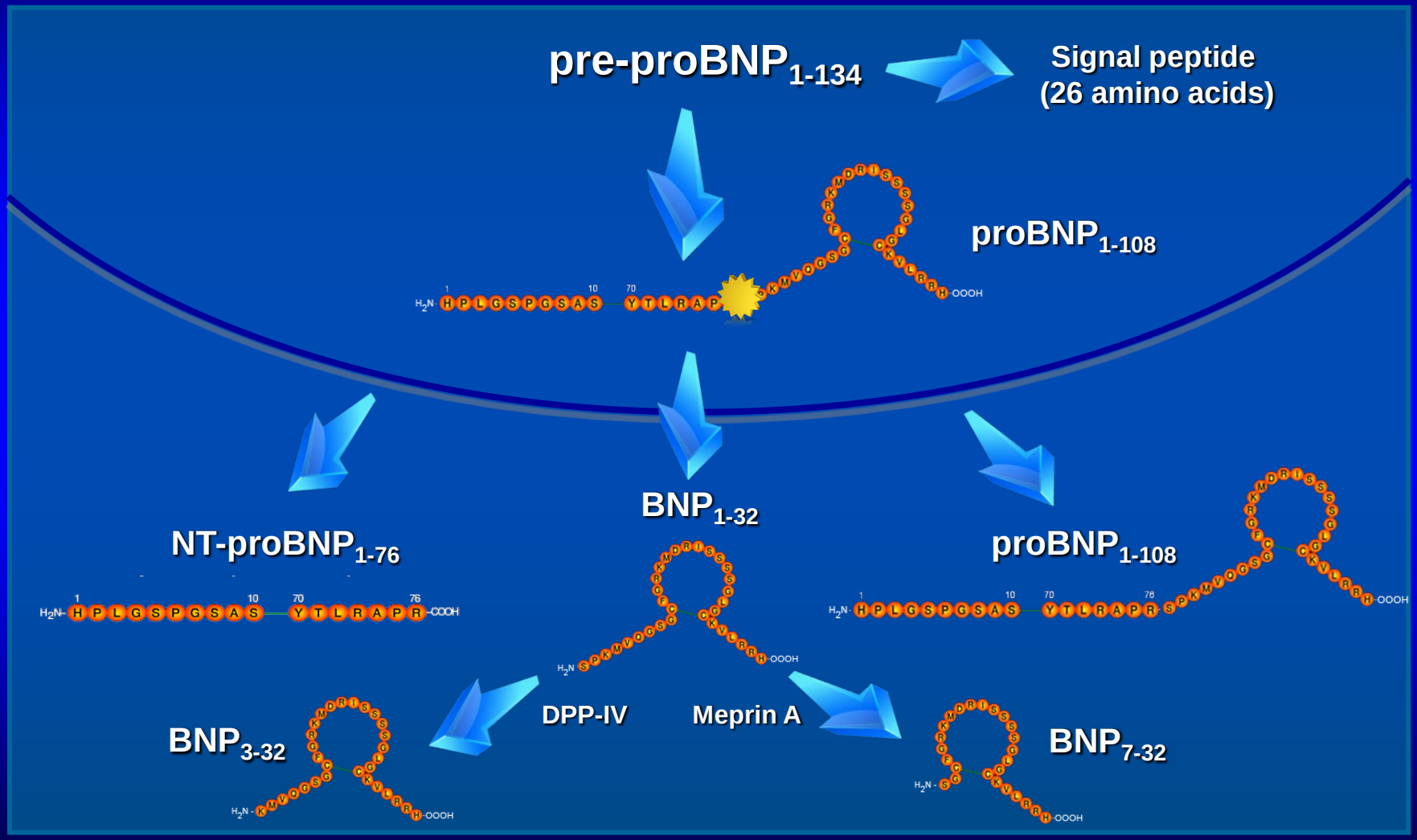
Biology of the NP System

Synthesis and Release



Biology of the NP System

Synthesis and Release



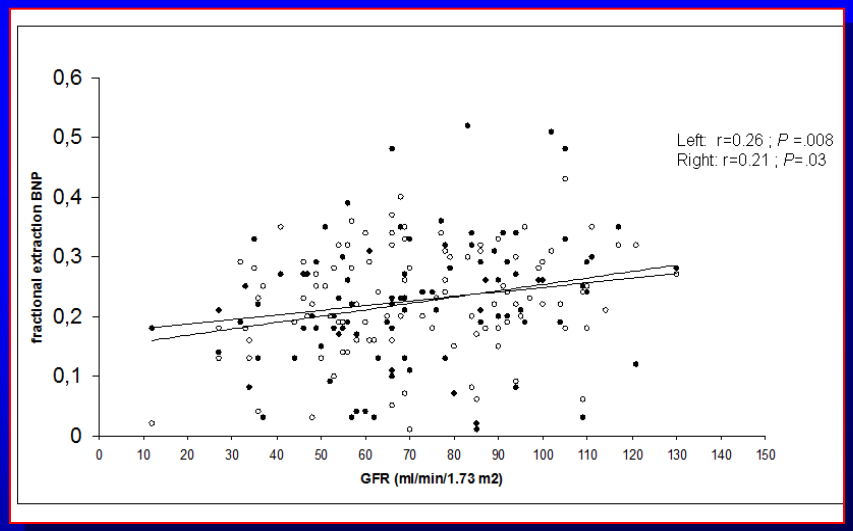
DPP-IV = dipeptidyl peptidase–IV

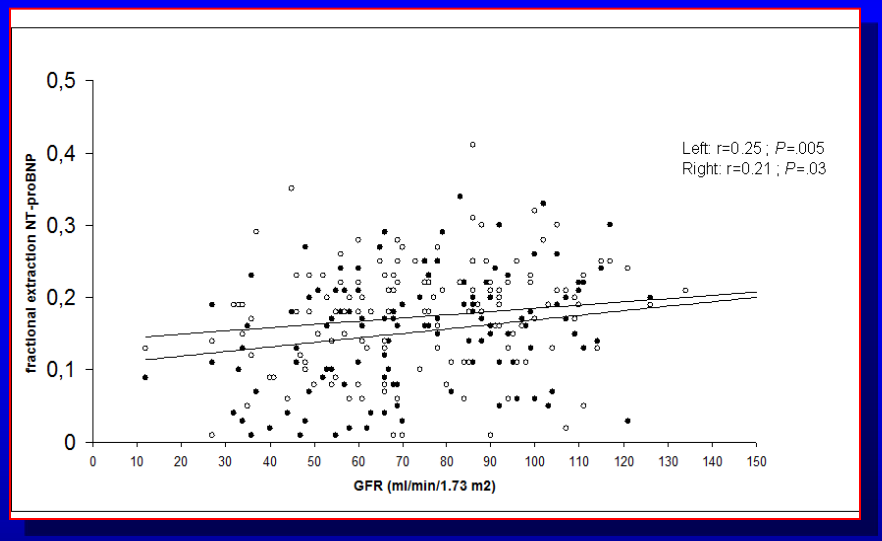
Natriuretic Peptide Clearance

- **BNP**
  - **NPR**
  - **Neutral endopeptidases**
  - **Renal excretion**
- **NT-proBNP**
  - **Less well understood**
  - **Renal excretion partially responsible**

Equal Renal Clearance of BNP and NT-proBNP

In simultaneously sampled renal artery and vein:
NO DIFFERENCE BETWEEN CLEARANCE OF BNP AND NT-proBNP





van Kimmenade et al, JACC, 2009

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Correlations of Natriuretic Peptides with Cardiac Structure and Function

- Left ventricle
  - Size
  - Systolic function
  - Diastolic function
- Right ventricle
  - Size
  - Systolic function
- Atrial size and pressure
- Valve disease
  - Aortic
  - Mitral
  - Tricuspid
- Heart rhythm
- Ischemic heart disease
- Pericardial disease

Correlations of Natriuretic Peptides with Cardiac Structure and Function

- Left ventricle
  - Size
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- Valve disease
  - Aortic
  - Mitral
  - Tricuspid
- Heart rhythm
- Ischemic heart disease
- Pericardial disease

How not to get burned by NP's:

Know the Differential Diagnosis of an ***Elevated*** Natriuretic Peptide

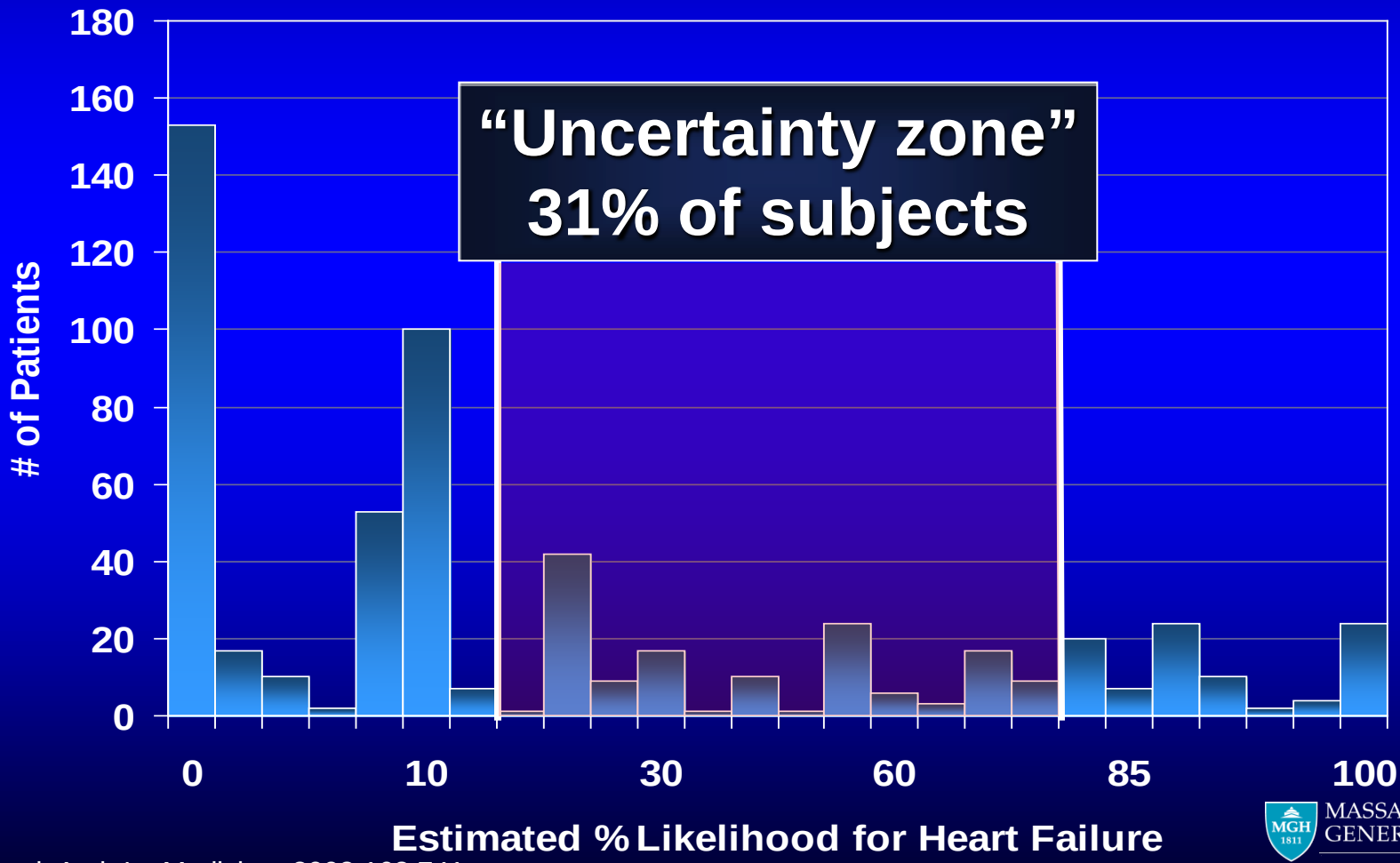
- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Congenital heart disease
- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic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

Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring HF therapy

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



Green et al, Arch Int Medicine, 2008;168:741

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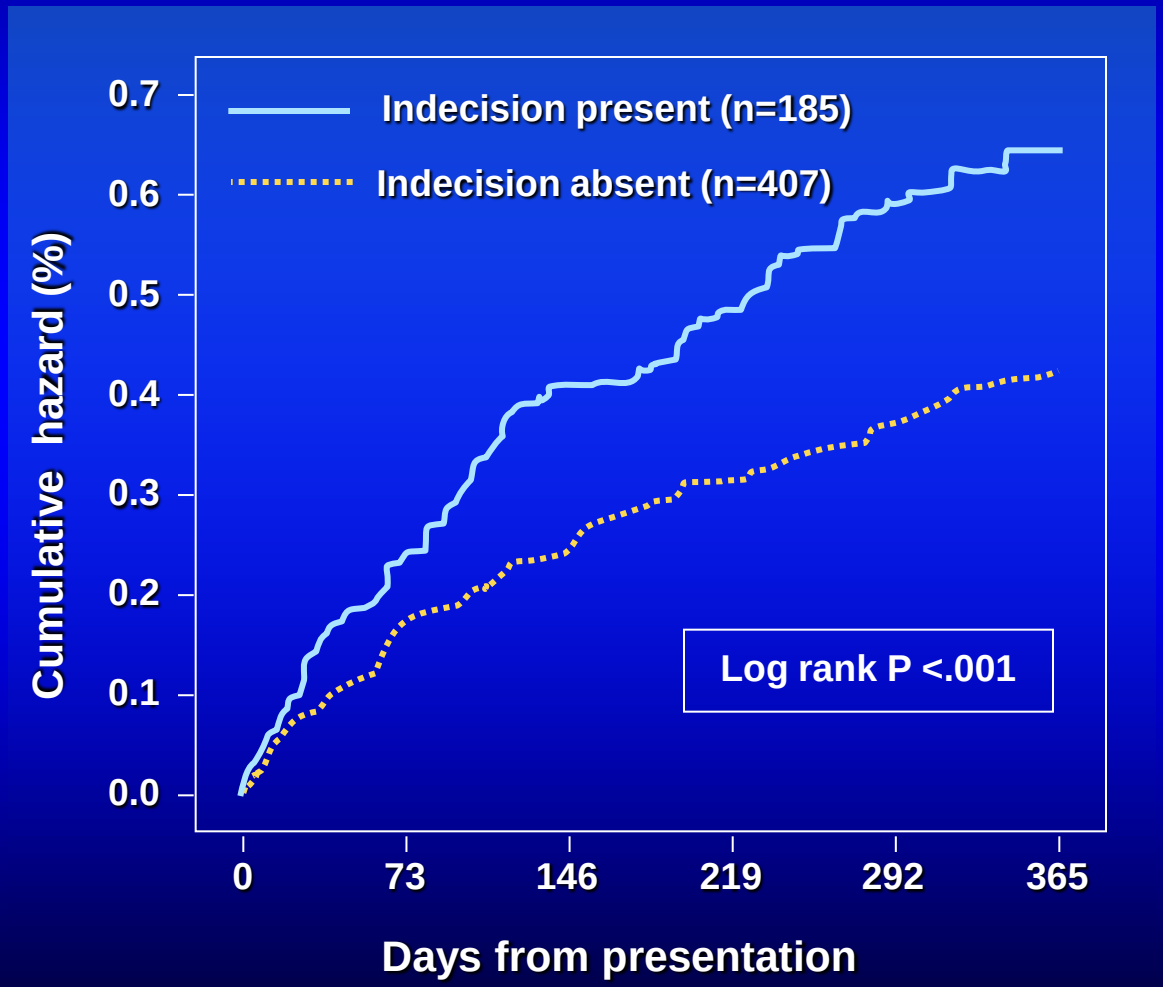
Diagnostic Uncertainty is Associated with Poor Prognosis in Acute Dyspnea



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!

Green et al, Arch Int Medicine, 2008;168:741

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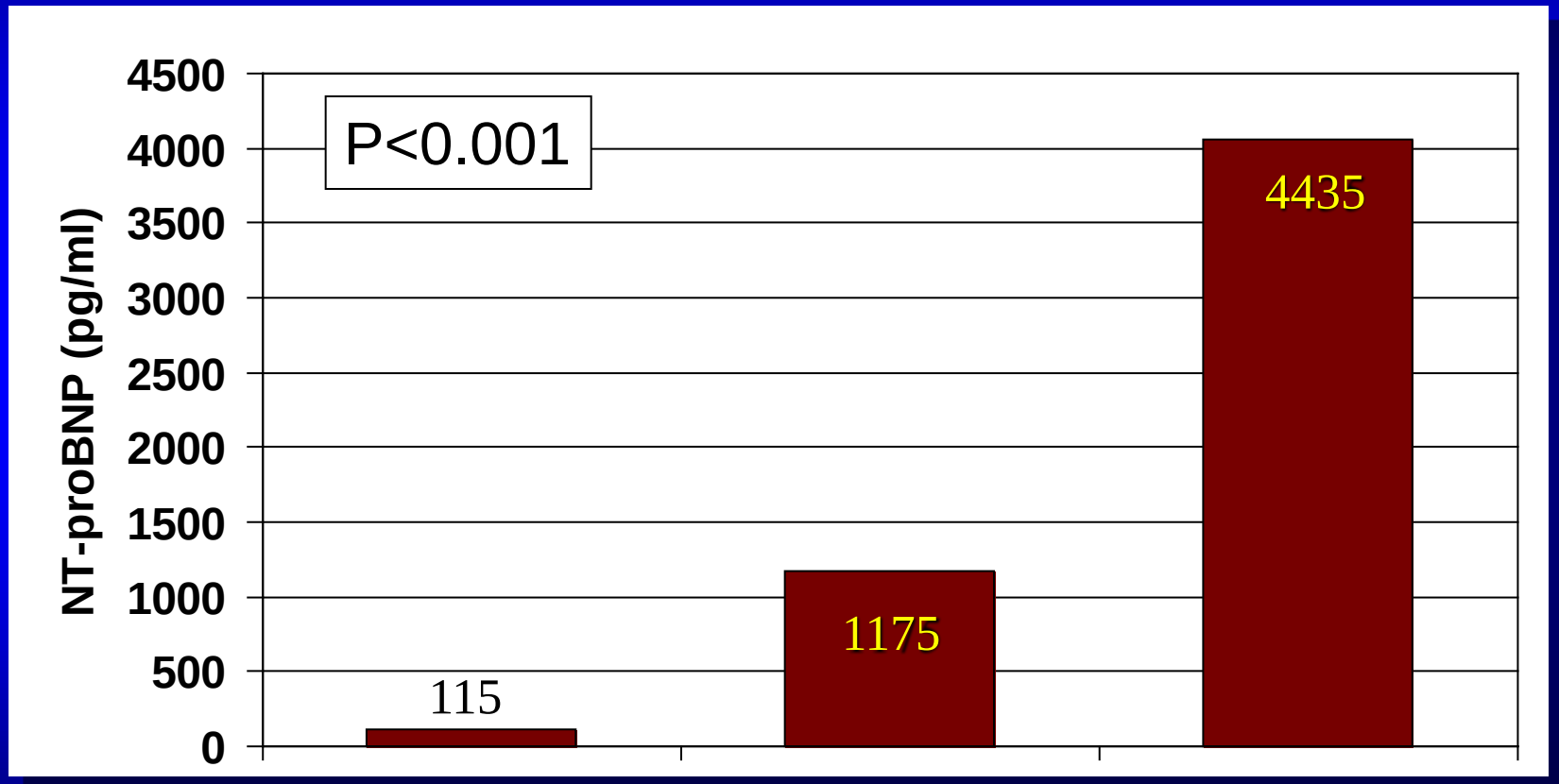
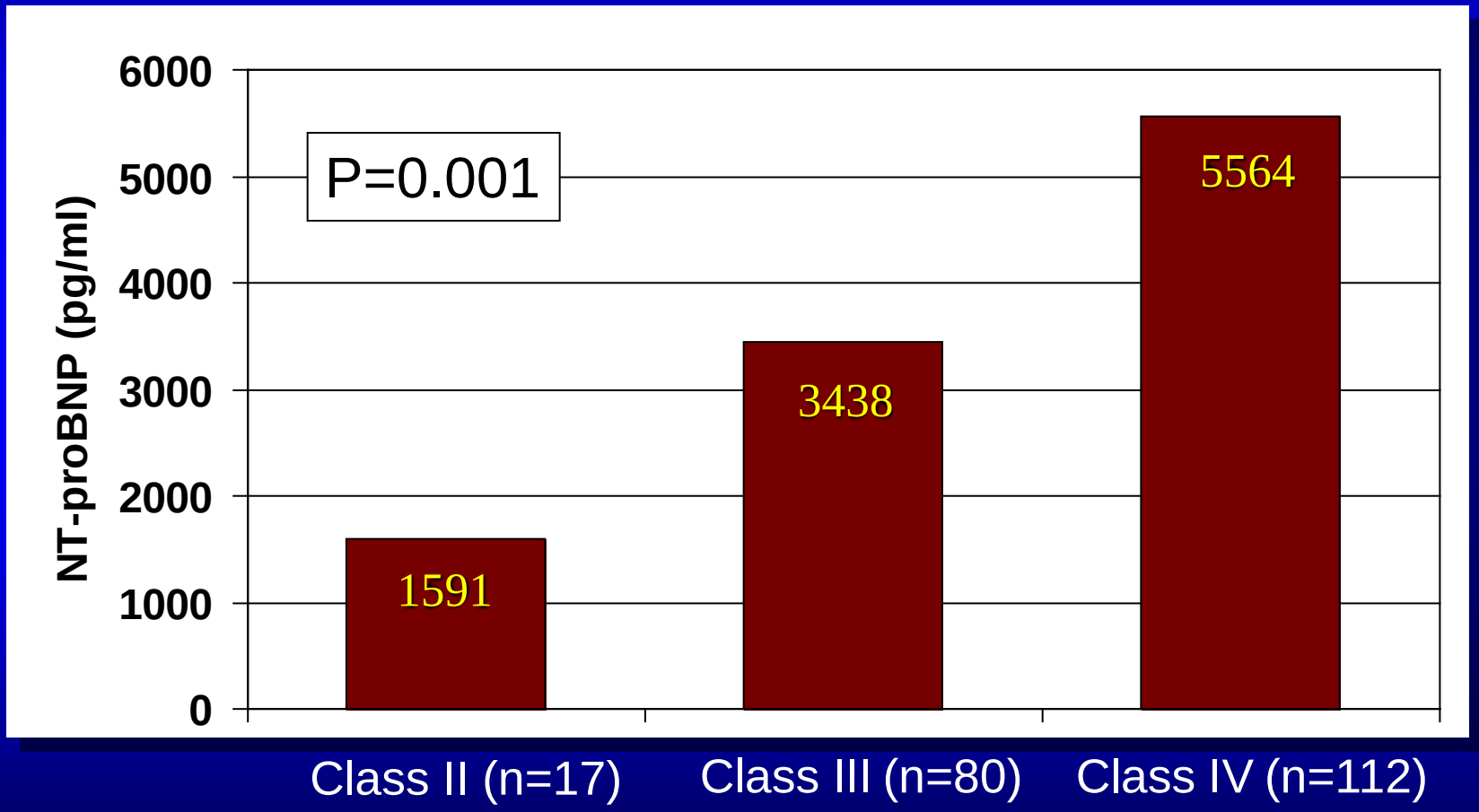
Results: NT-proBNP Levels



Januzzi et al, AJC 2005

NT-proBNP Levels and Symptoms



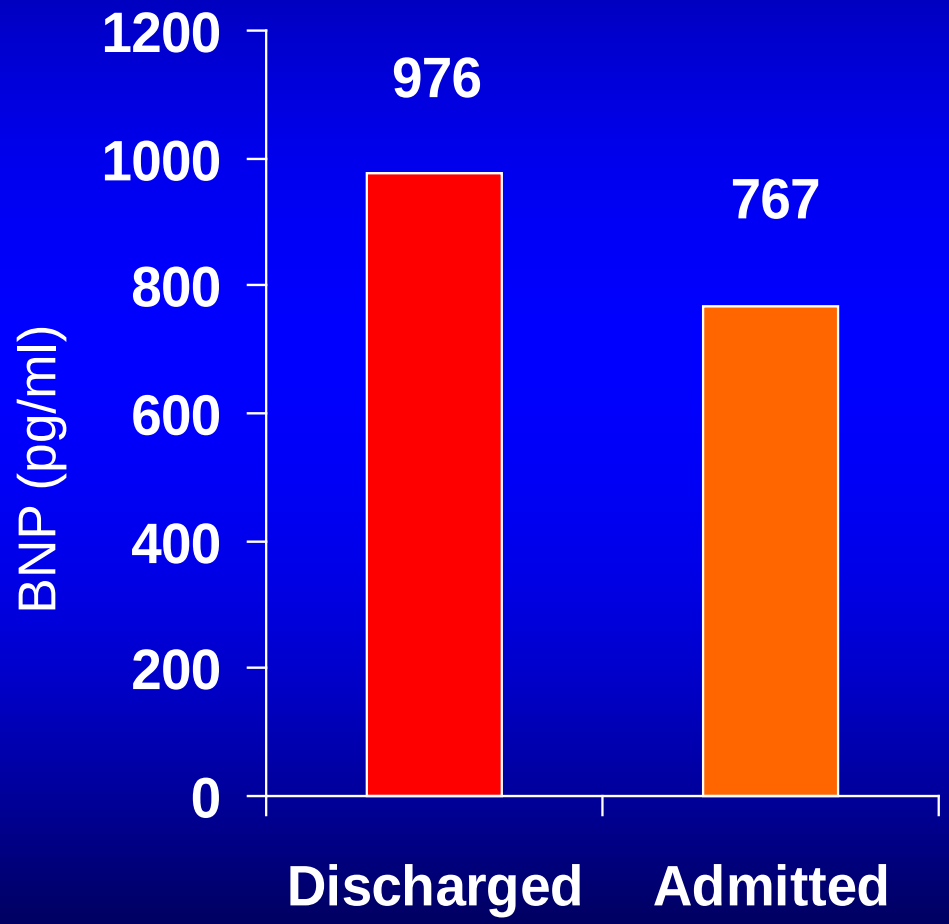
Januzzi et al, AJC 2005

Results: Predictors of HF

Predictor	Odds Ratio	95% Confidence Intervals	P value
Elevated NT-proBNP	44	21.0-91.0	<0.0001
Interstitial edema on chest X-ray	11	4.5-26.0	<0.0001
Orthopnea	9.6	4.0-23.0	<0.0001
Loop diuretic use at presentation	3.4	1.8-6.4	0.01
Rales on pulmonary examination	2.4	1.2-5.2	0.05
Age (per year)	1.03	1.01-1.05	0.01
Cough	0.43	0.23-0.83	0.05
Fever	0.17	0.05-0.50	0.03

Januzzi et al, AJC 2005

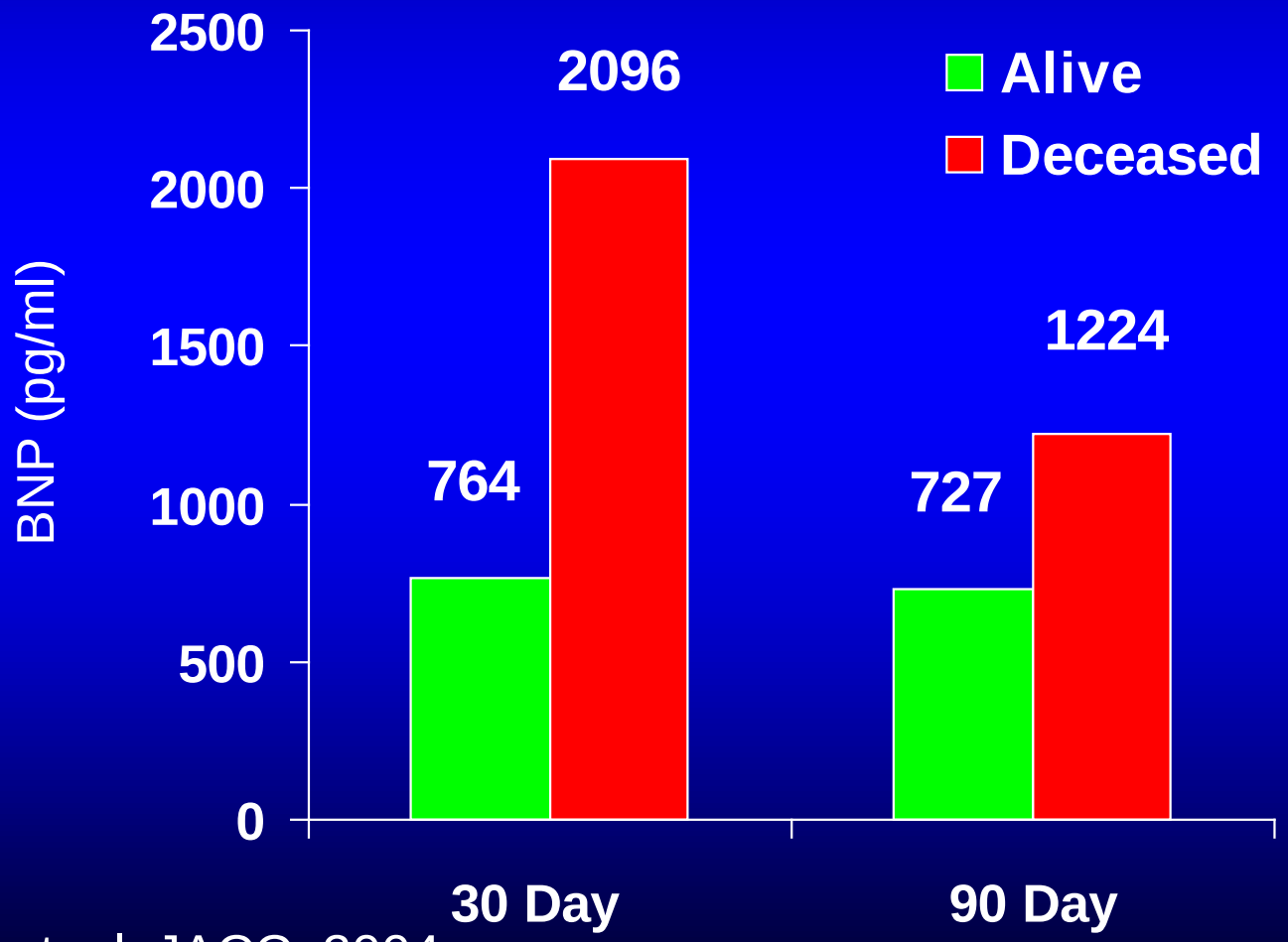
REDHOT Study: BNP Values & Patient Disposition



- **BNP values blinded to physicians judging severity of HF**
- **BNP median values ~22% higher in patients discharged home from E.D.**

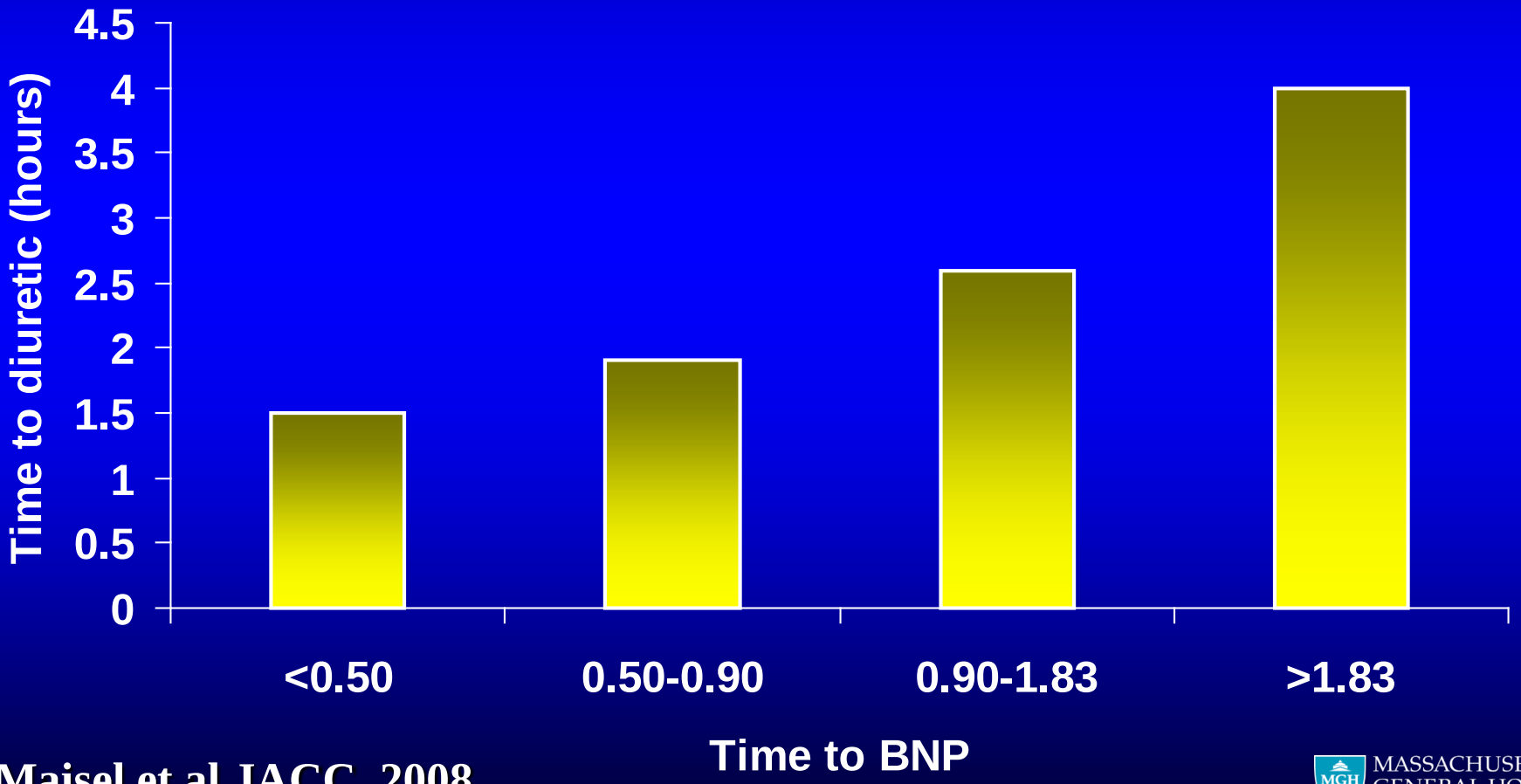
Maisel, et. al, JACC, 2004

REDHOT Study: Baseline BNP Values and Mortality



Maisel, et. al, JACC, 2004

Delayed BNP Equals Delayed Treatment



Maisel et al JACC, 2008

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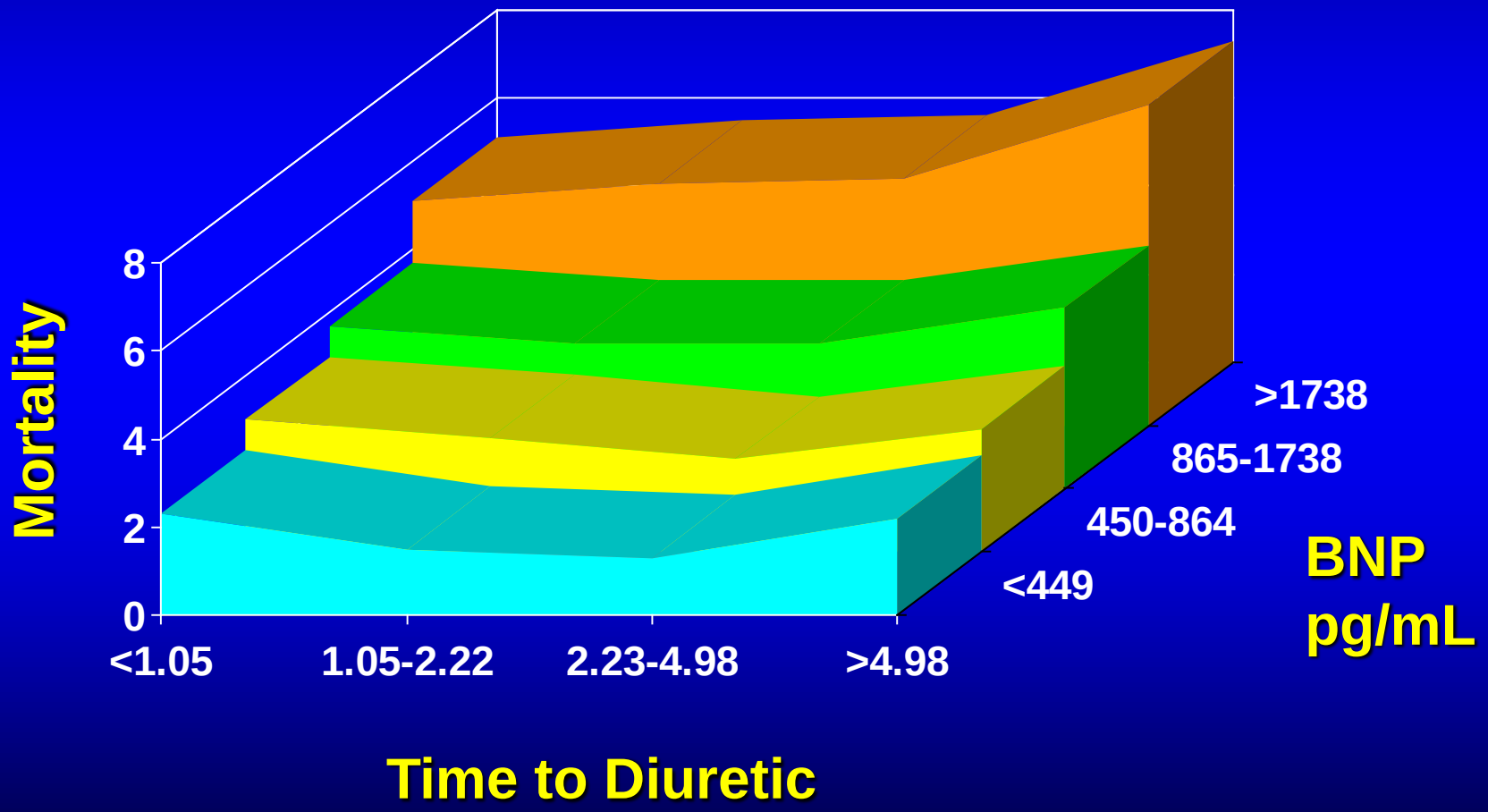
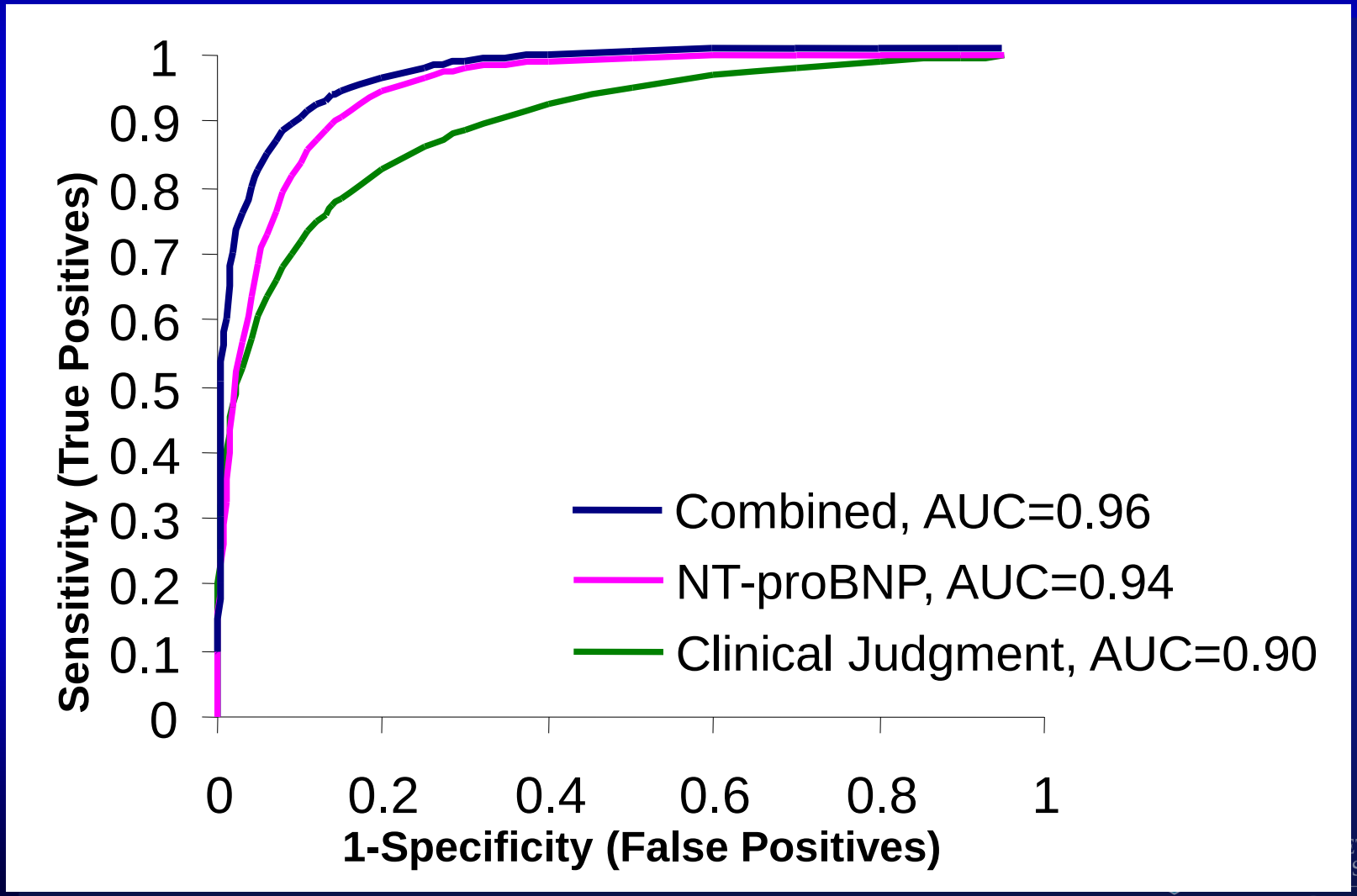
Mortality vs. Quartiles of Diuretic Time & BNP Level



Maisel et al JACC, 2008

Results: Primary Endpoint



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)	LP (n=282)	276	6	(2.1)*
(Accuracy =89%)	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)	LP (n=0)	0	0	0
(Accuracy =95%)	IP (n=18)	4	14	22.2
	HP (n=73)	1	72	(1.4)*

Steinhart, et al, JACC, 2009.

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Where does NT-proBNP help most?

Data from the Canadian IMPROVE-CHF Study

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses suggested the biggest "bang" was in the indecision zone…

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
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Steinhart, et al, JACC, 2009.

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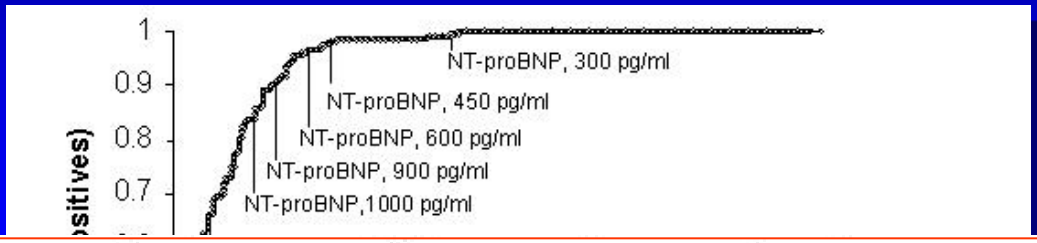
What is the best single cut point?



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300 pg/ml	99%	68%	62%	99%	79%
450 pg/ml	98%	76%	68%	99%	83%
600 pg/ml	96%	81%	73%	97%	86%
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	86%	78%	91%	87%

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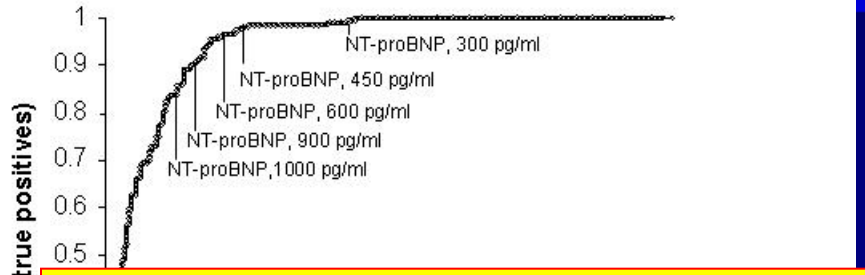
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	86%	78%	91%	87%

Looks an awful lot like BNP…

PRIDE



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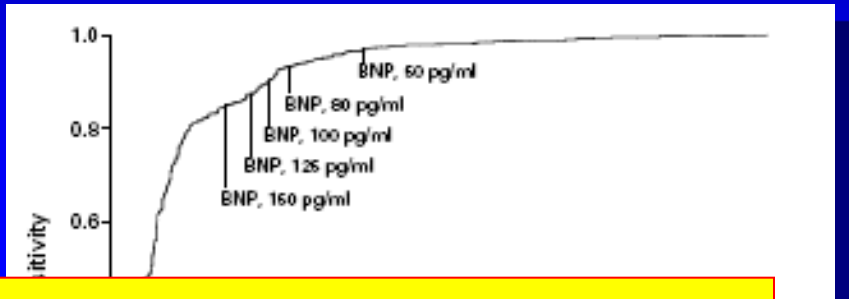
Breathing Not Properly



BNP pg/ml	Sensitivity	Specificity	Predictive Value	Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–96)	74 (70–77)	77 (76–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	86 (82–88)	83 (80–85)	83 (80–85)	86 (83–88)	84

An NT-proBNP of 900 pg/mL provides identical performance to a BNP of 100 pg/mL

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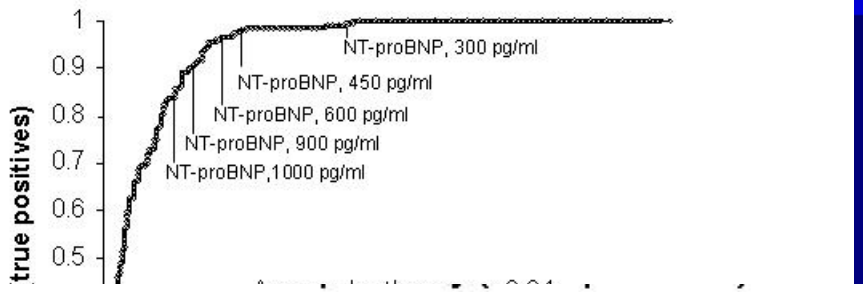
Is there anything to do to improve the comparatively low PPV of NP's?

PRIDE



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
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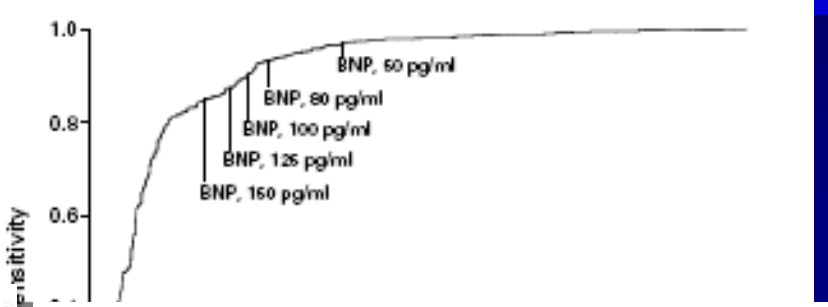
Breathing Not Properly



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150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)

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150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

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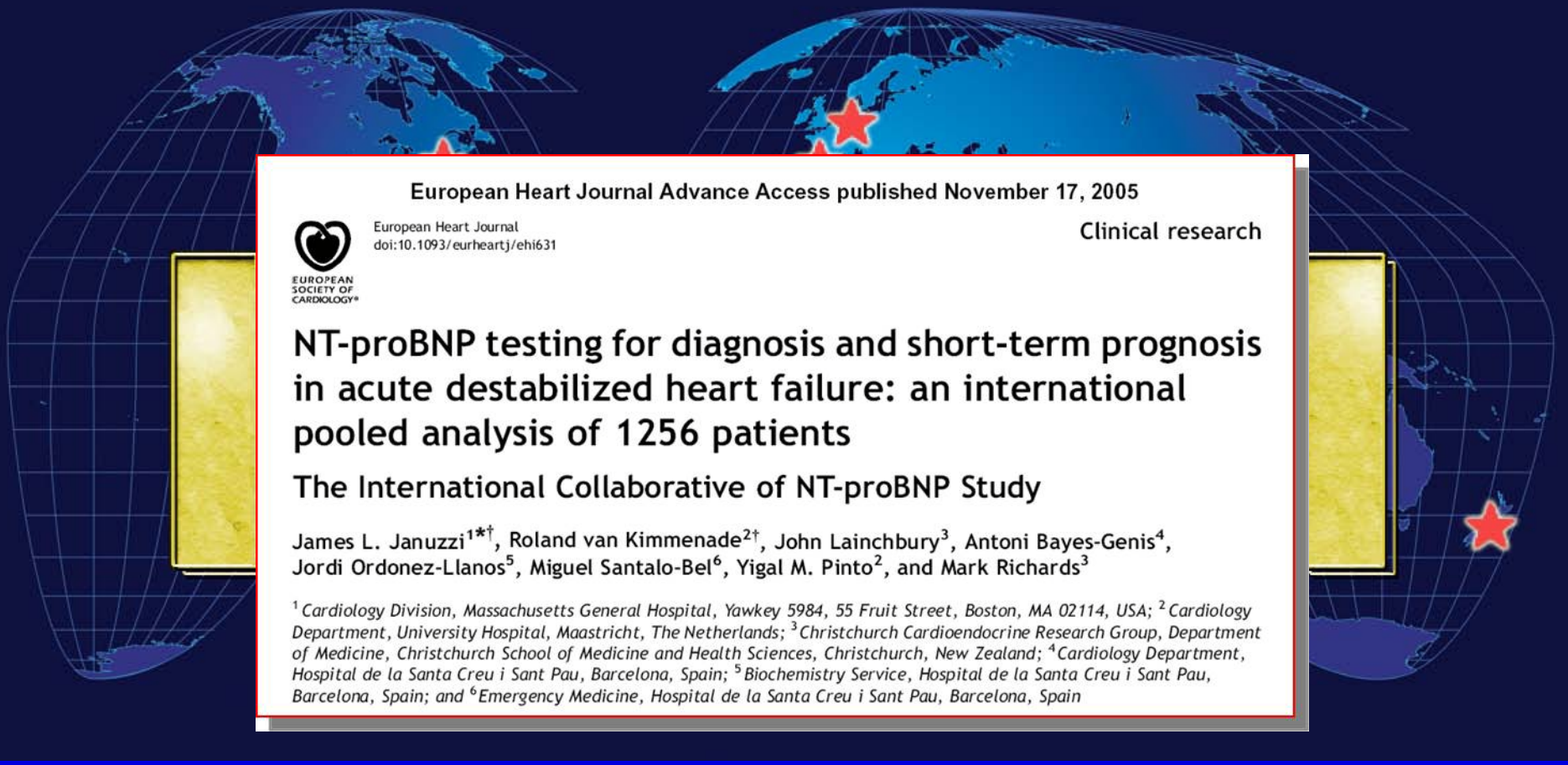
Causes of lower positive predictive value of natriuretic peptides

Table 3. Variables associated with elevated BNP in the absence of acute heart failure.

Predictors of Elevated B-Type Natriuretic Peptide Concentrations in Dyspneic Patients Without Heart Failure: An Analysis From the Breathing Not Properly Multinational Study

Variable				ltivariate CI 95%
Demographics				
Age/10-y increase				1.0–1.6
Medical history				
Chronic congestive heart f				
Atrial fibrillation				1.4–6.7
Hypertension	1.6	1.1–2.3		
Clinical findings				
O_2 saturation (per 5% decrease)	1.2	1.1–1.4		
JVD	1.8	1.1–3.1		
Absence of wheezing	1.9	1.2–2.8		
Murmurs	2.4	1.5–3.9		
Rales	1.8	1.3–2.7		
Body mass index (per 5 kg/m^2 decrease)	1.4	1.2–1.6	1.2	1.0–1.5
Chest radiograph findings				
Cardiomegaly	3.2	1.9–5.3	2.0	1.0–4.1
Pleural effusion	2.0	1.0–3.7		
Interstitial edema	2.5	1.1–5.8		
Blood value				
Creatinine (increase per mg/dL)	2.4	1.6–3.6		
Hemoglobin (decrease per g/dL)	1.3	1.2–1.4	1.2	1.1–1.4
ECG abnormal	3.0	2.0–4.4		



European Heart Journal Advance Access published November 17, 2005

European Heart Journal
doi:10.1093/eurheartj/ehi631

Clinical research

NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients

The International Collaborative of NT-proBNP Study

James L. Januzzi[1*†], Roland van Kimmenade[2†], John Lainchbury[3], Antoni Bayes-Genis[4], Jordi Ordonez-Llanos[5], Miguel Santalo-Bel[6], Yigal M. Pinto[2], and Mark Richards[3]

[1] *Cardiology Division, Massachusetts General Hospital, Yawkey 5984, 55 Fruit Street, Boston, MA 02114, USA;* [2] *Cardiology Department, University Hospital, Maastricht, The Netherlands;* [3] *Christchurch Cardioendocrine Research Group, Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand;* [4] *Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [5] *Biochemistry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; and* [6] *Emergency Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

ICON Study Group:
James Januzzi, Aaron Baggish (Boston)
Antoni Bayes-Genis (Barcelona)
Roland RJ van Kimmenade, Yigal Pinto (Maastricht)
A. Mark Richards, John Lainchbury (Christchurch)

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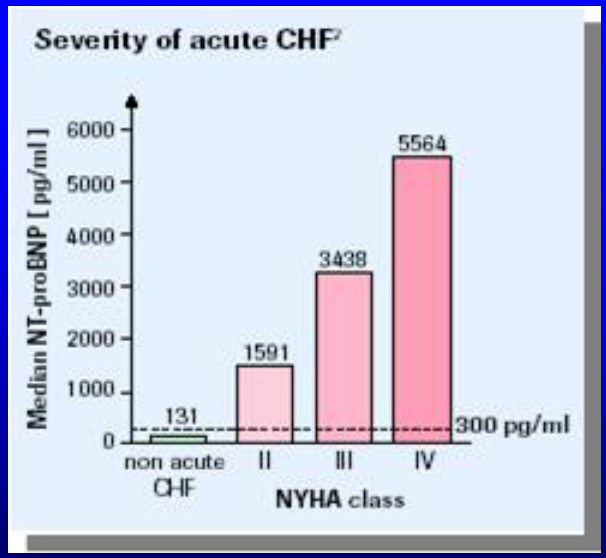
Age-independent rule out cut point

- International NT-proBNP Collaboration data (acute setting):
  - 300 pg/ml, age independent
    - 99% sensitive
    - 60% specific
    - *98% NPV*



Januzzi, et al, Eur H Journal 2005

Age-stratified “rule in” cut point

- International NT-proBNP Collaboration data (acute setting):

To diagnose acute HF

Age strata	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
All <50 years (n=183)	450 pg/ml	97%	93%	76%	99%	95%
All 50-75 years (n=554)	900 pg/ml	90%	82%	82%	88%	85%
All >75 years (n=519)	1800 pg/ml	85%	73%	92%	55%	83%
Overall		90%	84%	***88%***	66%	86%

***Very superior to single cut-point strategy in multivariable bootstrapping models**

Januzzi, et al, Eur H Journal 2005

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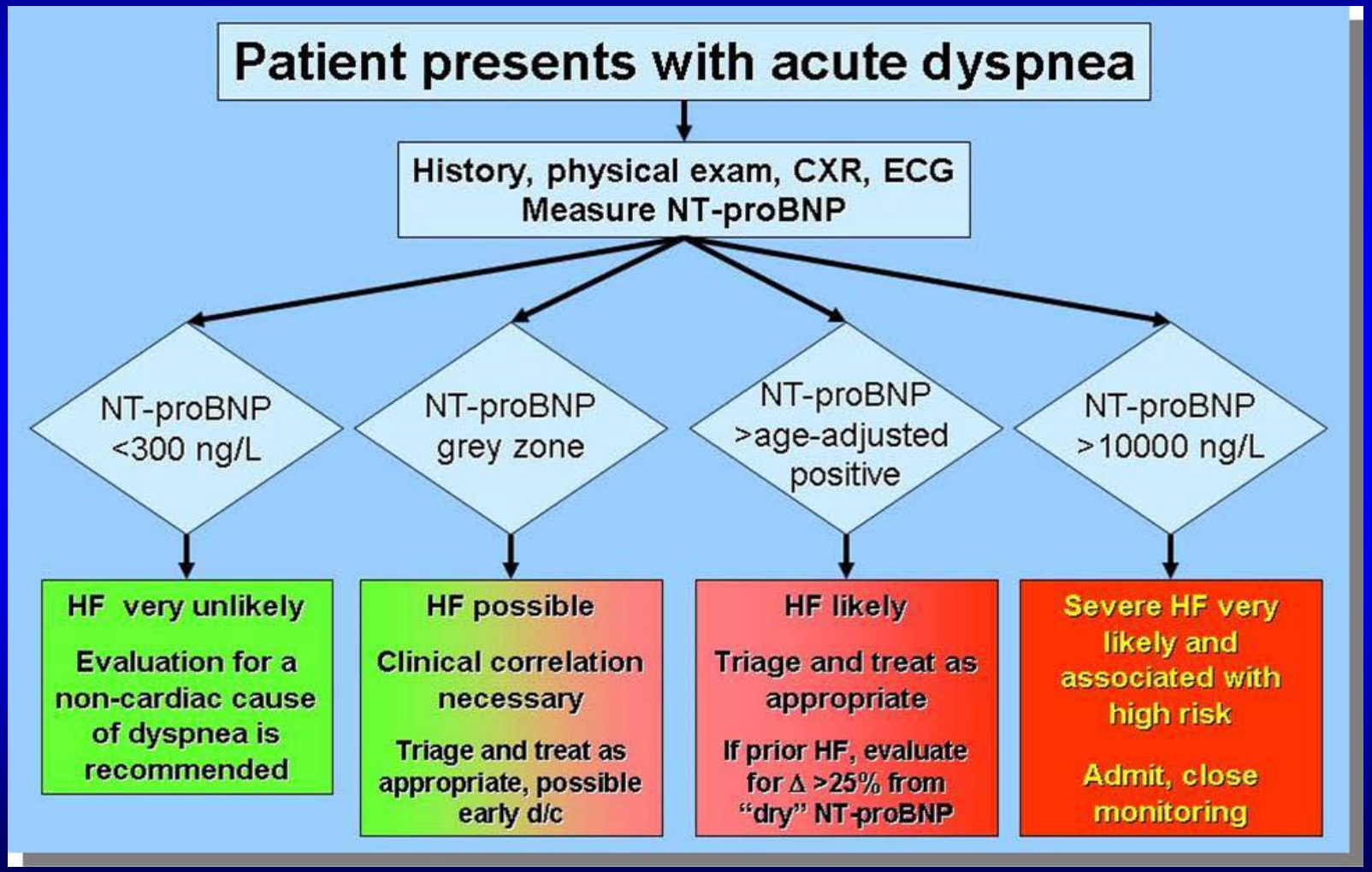
Logical use of natriuretic peptide values: it isn't black and white!!



Januzzi, et al, Am J Cardiol, 2008

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Optimizing Natriuretic Peptide Use in Acute Diagnosis:

Not everything with a high natriuretic peptide level is HF!

How Not to Get **Burned** by 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

Baggish, et al, Crit Path Cardiol, 2004

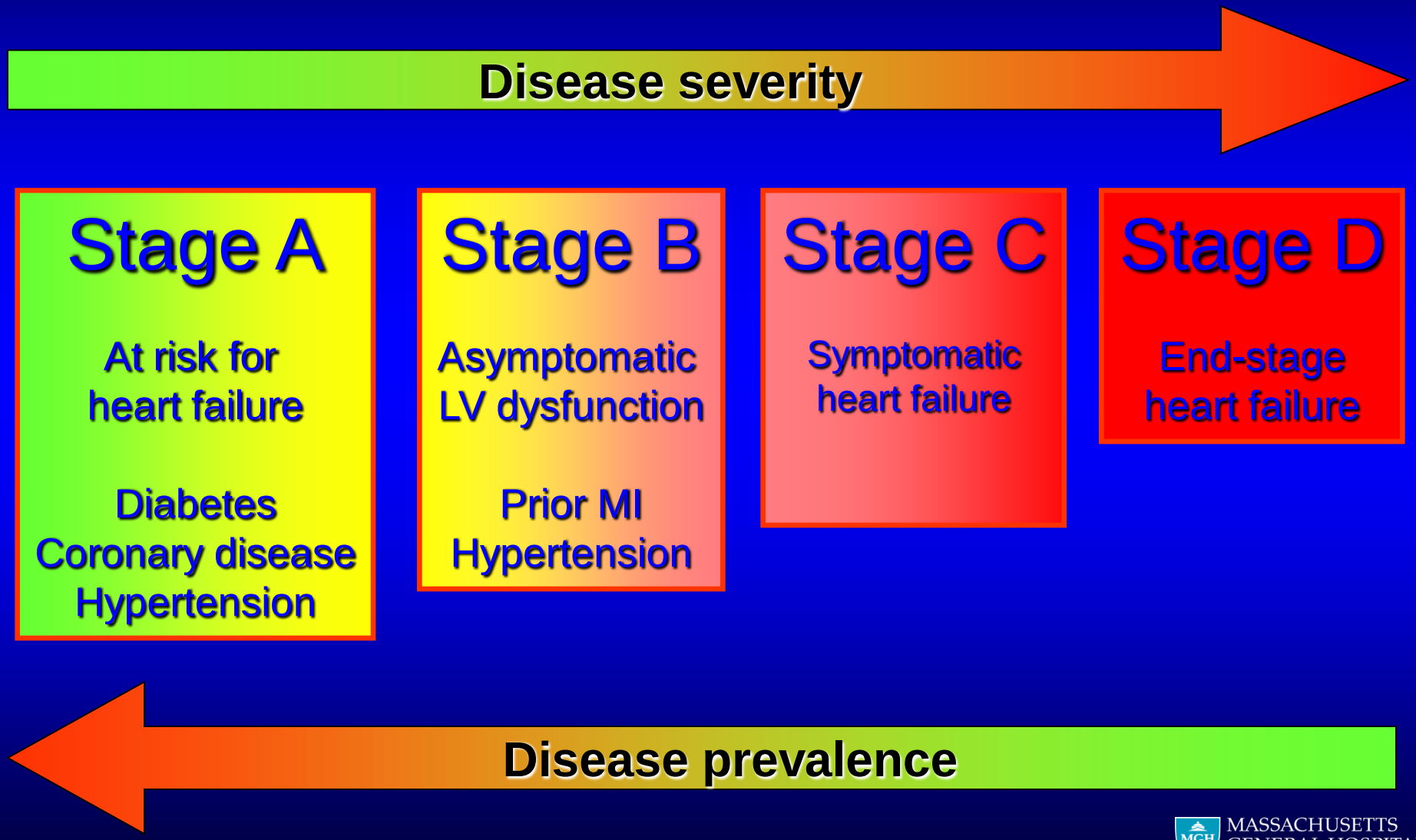
What Causes "False Negative" B-type Natriuretic Peptides?

- **It happens, sometimes without explanation!**
- **Right heart failure**
- **Mild HF**
- **Chronic, more compensated HF (consider cut-points!)**
- **Non-systolic HF**
- **Obesity**

Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring therapy

AHA Stages



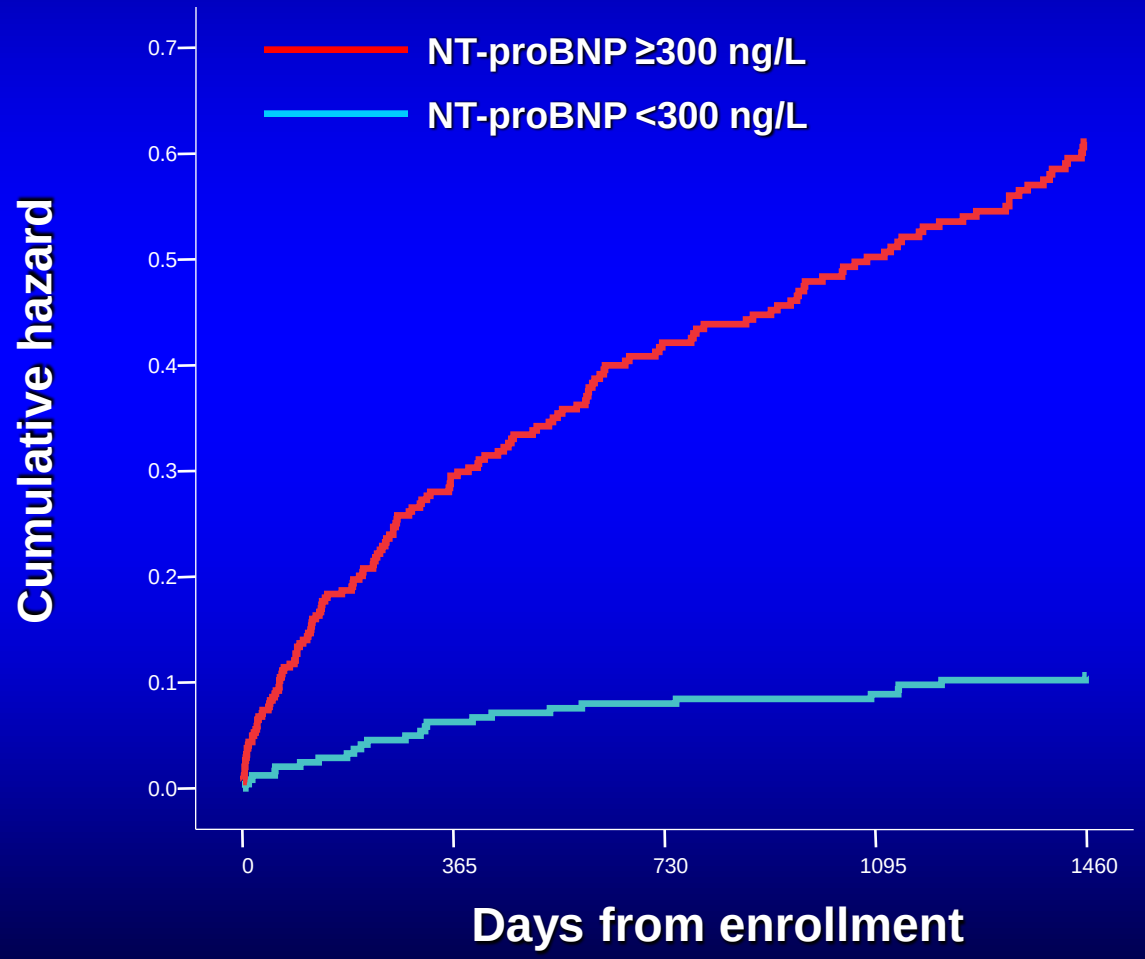
Results: Bayesian information criterion

Predictors of mortality at 4 years among those with acute HF

Variable	BIC
Age	974.66
NT-proBNP	961.90
Tobacco use	953.35
hsCRP	947.72
No loop diuretic at D/C	945.44
Blood urea nitrogen	944.99
Creatinine clearance	941.43

Januzzi, et al., Clin Chem 2010

Cumulative Hazard: NT-proBNP



***P* <.0001**

Januzzi, et al., Clin Chem 2010

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Natriuretic Peptides: Major Clinical Utilities

- Acute patient evaluation
- Estimation of prognosis
- Monitoring therapy

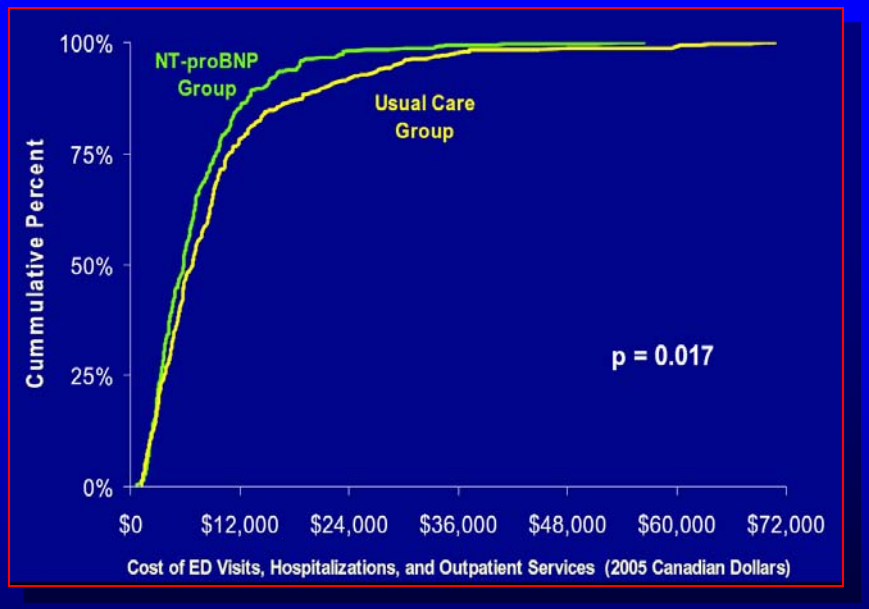
Why might natriuretic peptide testing assist with heart failure management?

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

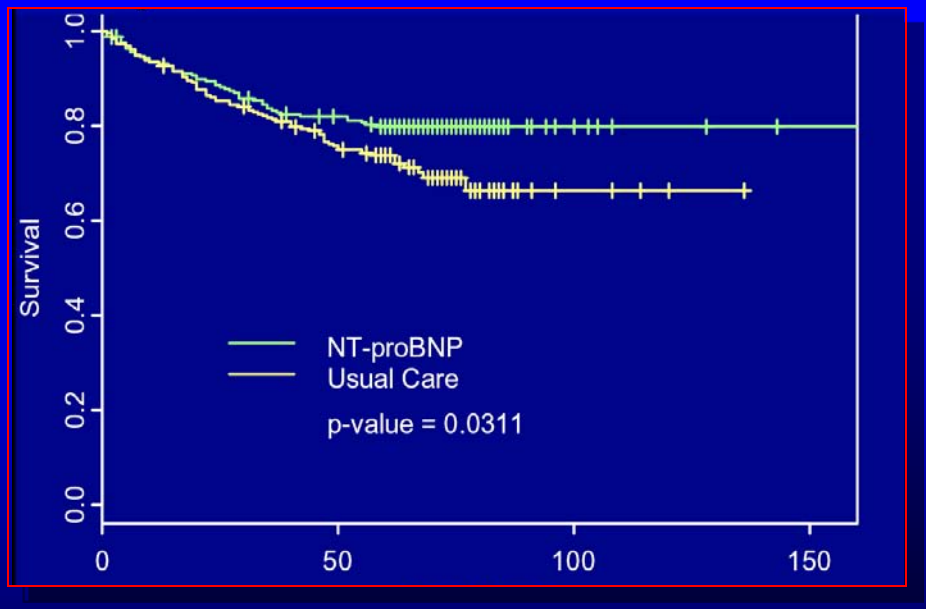
Effect of Selective NT-proBNP Testing On Costs/Outcomes:

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, Howlatt, Januzzi, Zowall on behalf of the IMPROVE-CHF Investigators, 2007, Circulation

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Why might natriuretic peptide testing assist with heart failure management?

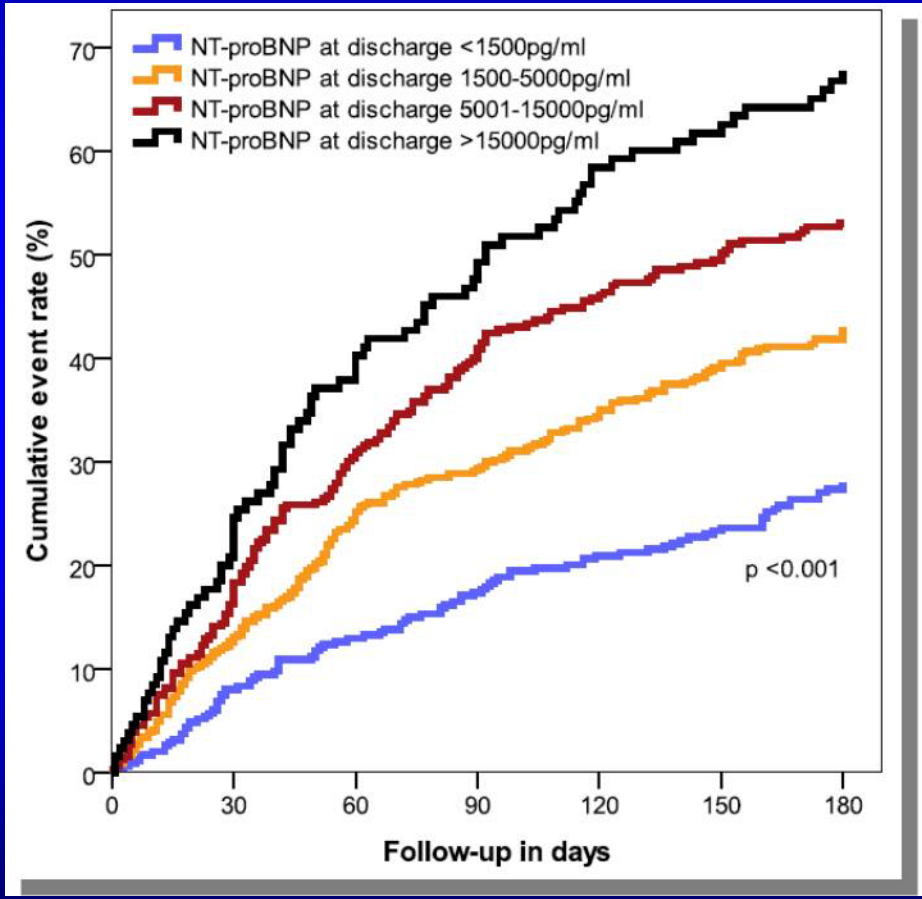
✓Earlier diagnosis

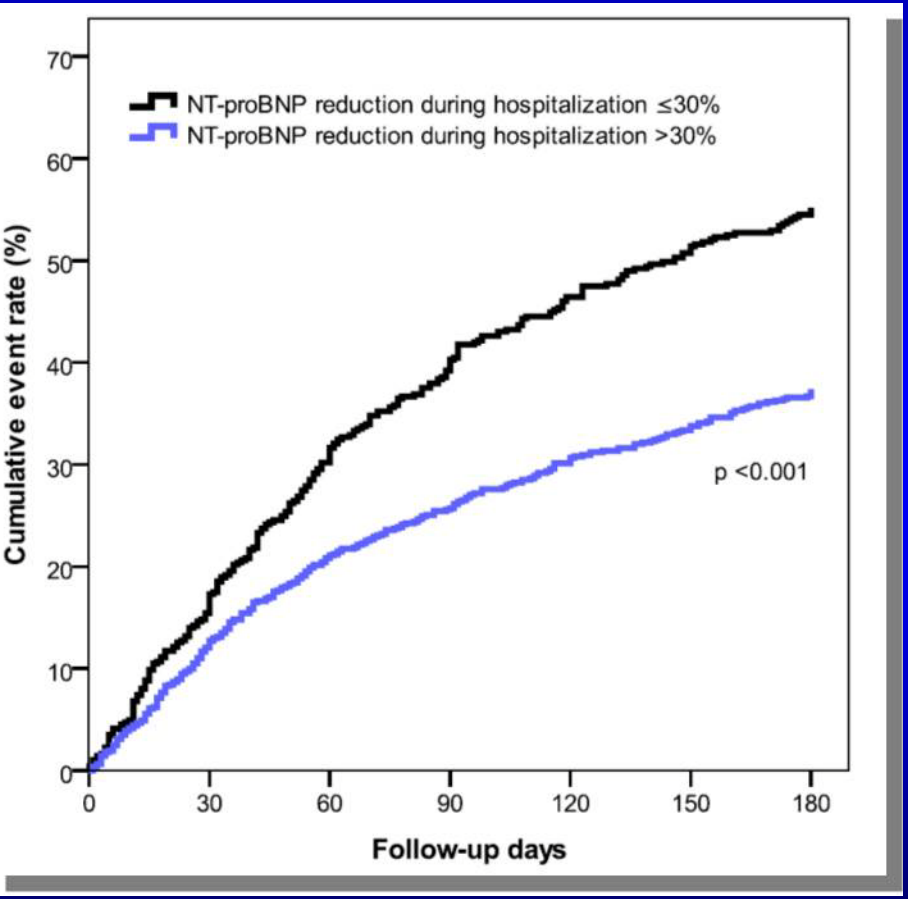
- As a target of therapy?

Therapies with Effects on B-Type Natriuretic Peptide Levels

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

Natriuretic peptide treatment response:
Absolute target or % change?



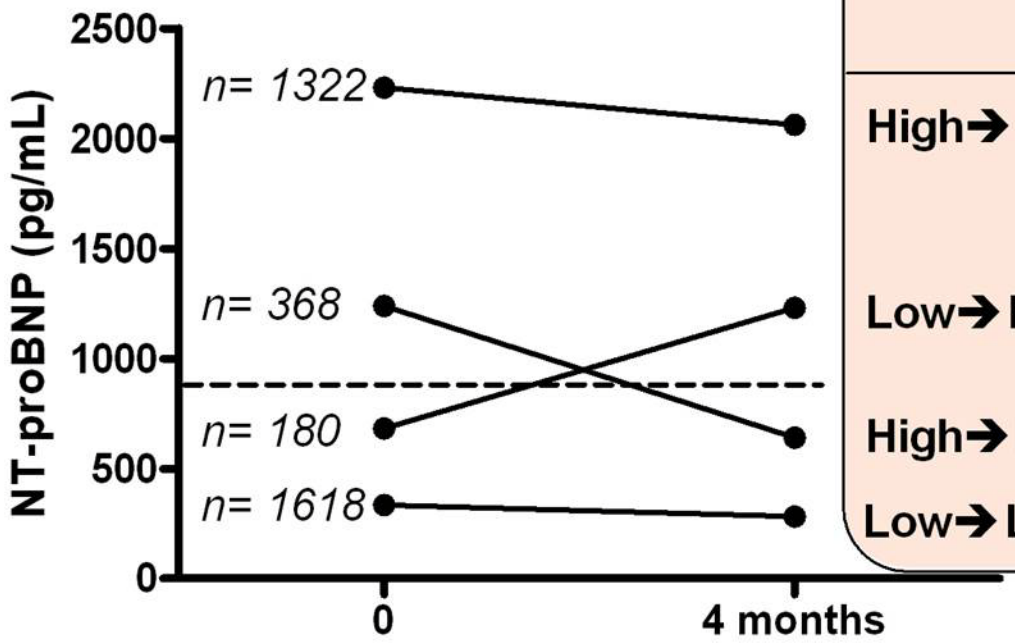


Data courtesy of Yigal Pinto, MD

Recommended Protocol for NT-proBNP Testing in Acute HF

- Baseline measurement for diagnosis
- Pre-discharge measurement for both 'dry' NT-proBNP estimation and to assess for treatment response:
  - If rise >30%: discharge delayed, ↑Rx
  - If change <30%: possible discharge delay
  - If fall >30%: discharge authorized

The Importance of Serial NT-proBNP Measurements for Prognostication in Chronic HF



	Mortality (%)	Hospitalization for HF (%)
High → High	25.6	26.8
Low → High	17.2	21.1
High → Low	13.6	10.1
Low → Low	8.6	6.7

Val-HeFT

Rationale for “guided” therapy

- *Proactively* identify those on an inadequate medical program
- *Reactively* identify those at high risk for impending complication
- Directly address the underlying biology of HF guided by tools that reflect it

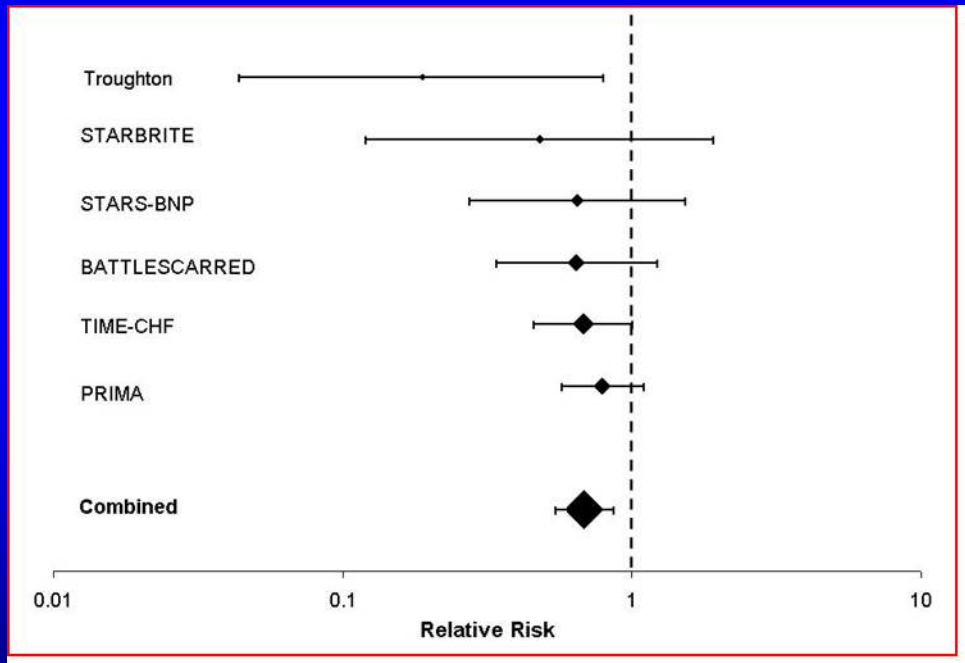
Characteristics of ‘guided therapy’ trials

- Well tolerated
- More often up-titration of therapies in biomarker guided arm
- When a low target was selected and natriuretic peptide lowering was achieved, better outcomes were observed

Januzzi, Journal of Cardiac Failure, 2011

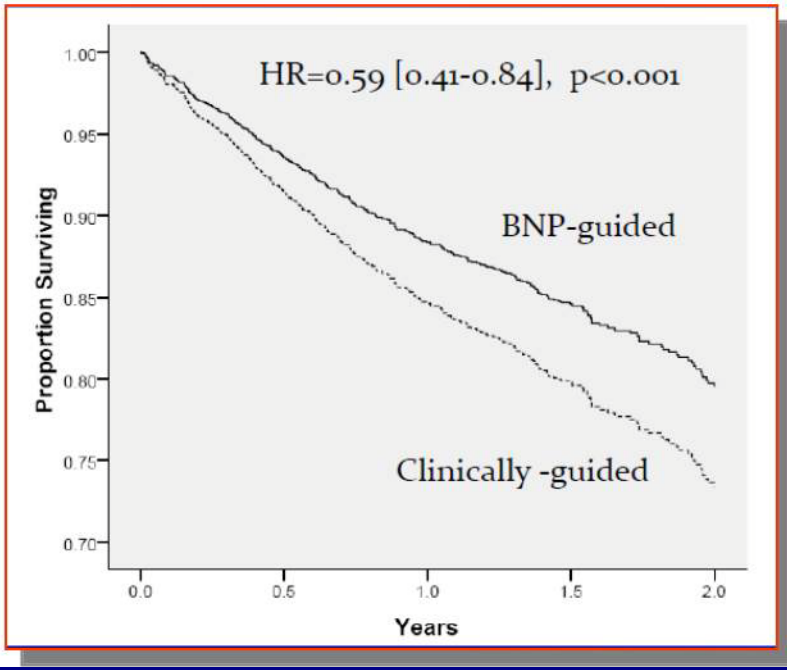
Guided therapy combined analyses

Meta analysis of publication data



Felker et al, Am Heart Journal, 2009

Pooled patient data from all available trials



Troughton et al, ESC 2011

NT-proBNP Concentrations

	Baseline	Follow-up	*P*
Overall	2118 [1122-3831]	1321 [554-3197]	.02
By treatment allocation			
Treatment	Baseline	Follow-up	*P*
SOC	1946 [951-3488]	1844 [583-3603]	.61
NT-proBNP	2344 [1193-4381]	1125 [369-2537]	.01

***P* = .40 for SOC baseline versus NT-proBNP baseline**

NT-proBNP Concentrations

	Baseline	Follow-up	*P*
Overall	2118 [1122-3831]	1321 [554-3197]	.02
By treatment allocation			
Treatment	**Baseline**	**Follow-up**	***P***
SOC	1946 [951-3488]	1844 [583-3603]	.61
NT-proBNP	2344 [1193-4381]	1125 [369-2537]	.01

P = .03 for SOC follow-up versus NT-proBNP follow-up

44.3% of NT-proBNP subjects ≤1000 pg/mL

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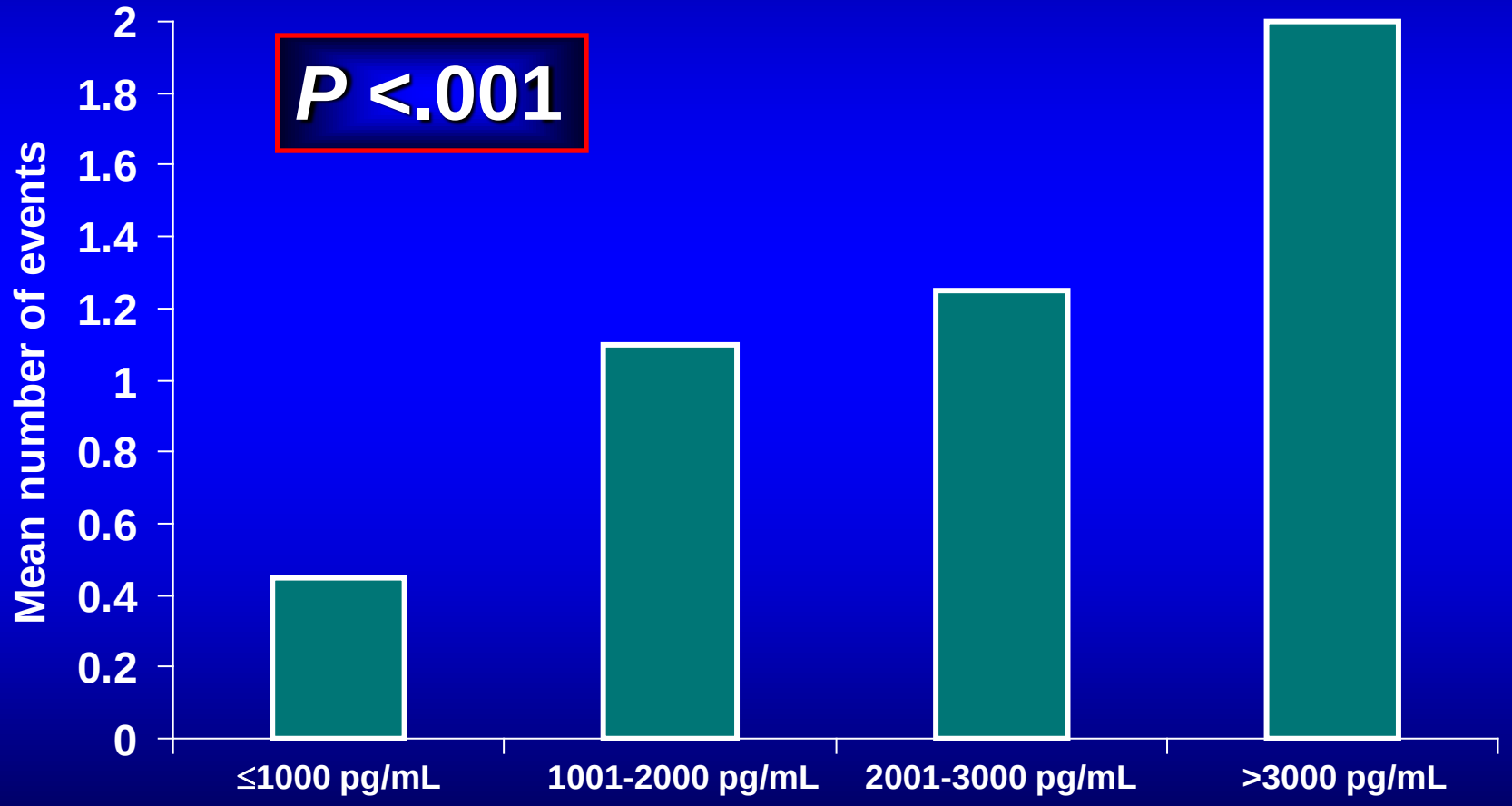
Events as a function of NT-proBNP



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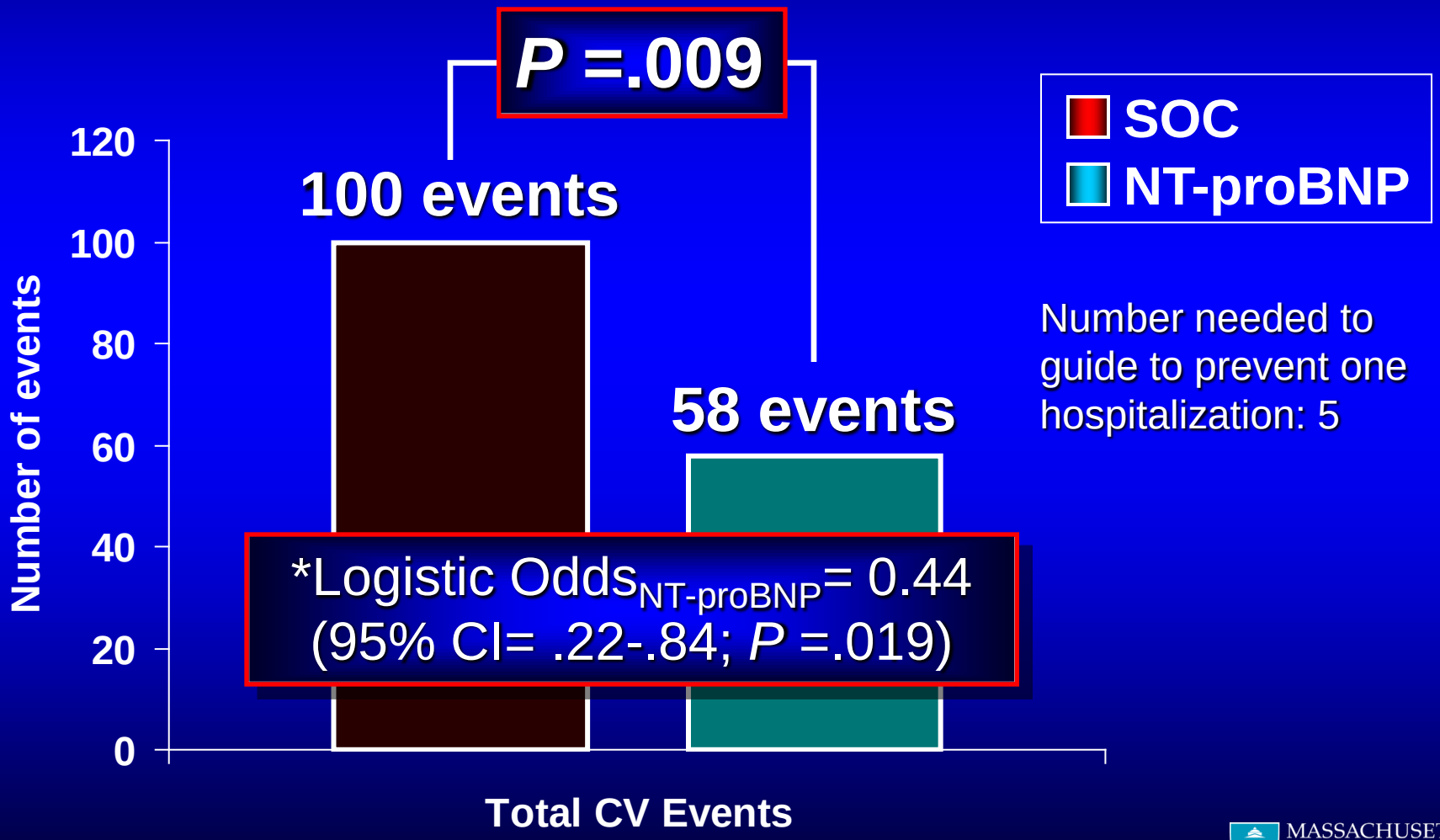
Primary Endpoint



Number needed to guide to prevent one hospitalization: 5

*Adjusted for age, LVEF, NYHA Class, and eGFR

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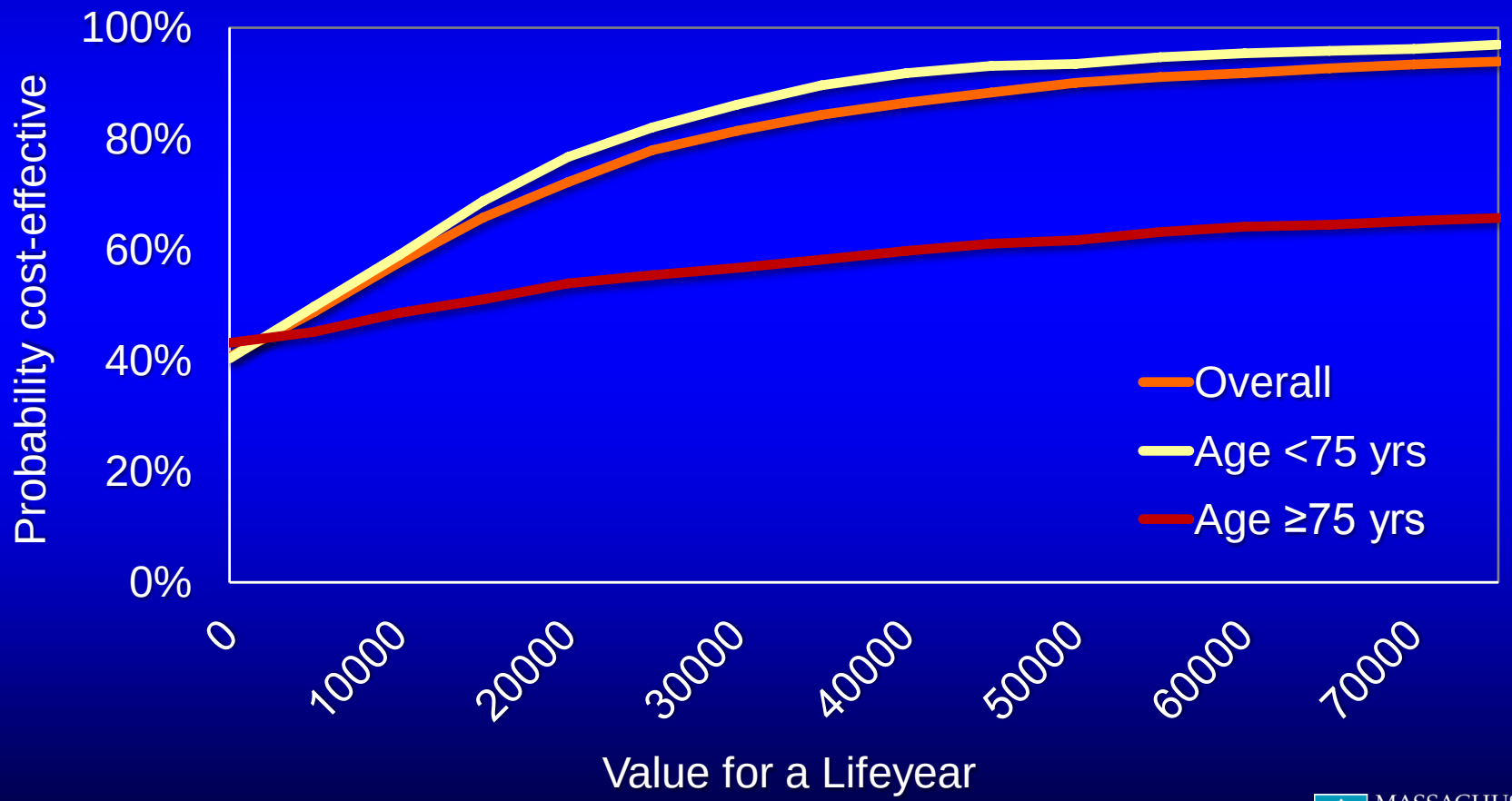
TIME-CHF Cost-Effectiveness

Acceptibility curves for LY's without residence costs



Sanders-van Wijk, JACC: HF, 2013

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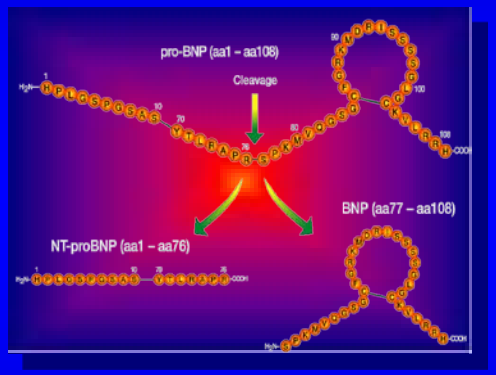
The clinical value of natriuretic peptide testing



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