

# NT-proBNP Testing For Diagnosis of Acutely Destabilized Heart Failure

*Comments from the International  
NT-proBNP Consensus Panel*

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**An International Consensus Statement  
Regarding Amino-Terminal Pro-B-  
Type Natriuretic Peptide Testing: The  
International NT-proBNP Consensus Panel**

GUEST EDITORS:

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CardioEndocrine Research Group  
University of Otago, Christchurch  
Christchurch, New Zealand

# The International NT-proBNP Consensus



# Topics

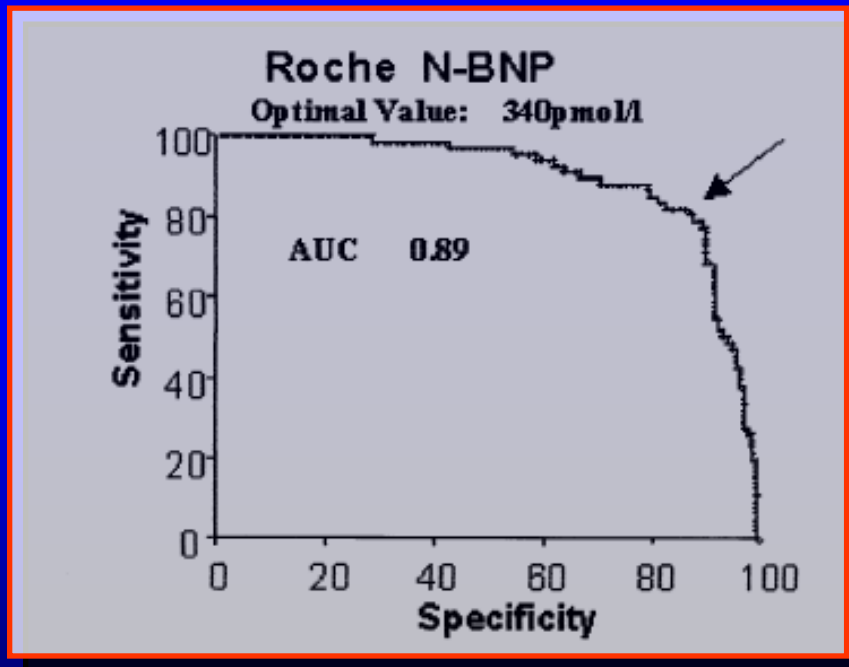
- **Natriuretic peptide biology**
- **NT-proBNP: Lab Aspects**
- **Population Testing**
  - **High Risk Populations**
- **NT-proBNP testing in Primary Care Diagnosis of HF**
- **NT-proBNP Testing for Diagnostic Evaluation of Acute Dyspnea**
- **The Differential Diagnosis of an Elevated NT-proBNP**
- **Grey Zone NT-proBNP Values**
- **NT-proBNP in Ischemic Heart Disease**
- **NT-proBNP for Prognosis in Acute Dyspnea**
- **NT-proBNP for Prognosis in Chronic Heart Failure**
- **NT-proBNP for Inpatient Monitoring of Acute Heart Failure**
- **NT-proBNP for Outpatient Monitoring of Chronic Heart Failure**
- **NT-proBNP and Renal Disease**
- **NT-proBNP and Obesity**
- **Pediatric Applications of NT-proBNP**

# Background studies

*NT-proBNP in acute dyspnea...*

# Brain Natriuretic Peptide and N-Terminal Brain Natriuretic Peptide in the Diagnosis of Heart Failure in Patients With Acute Shortness of Breath

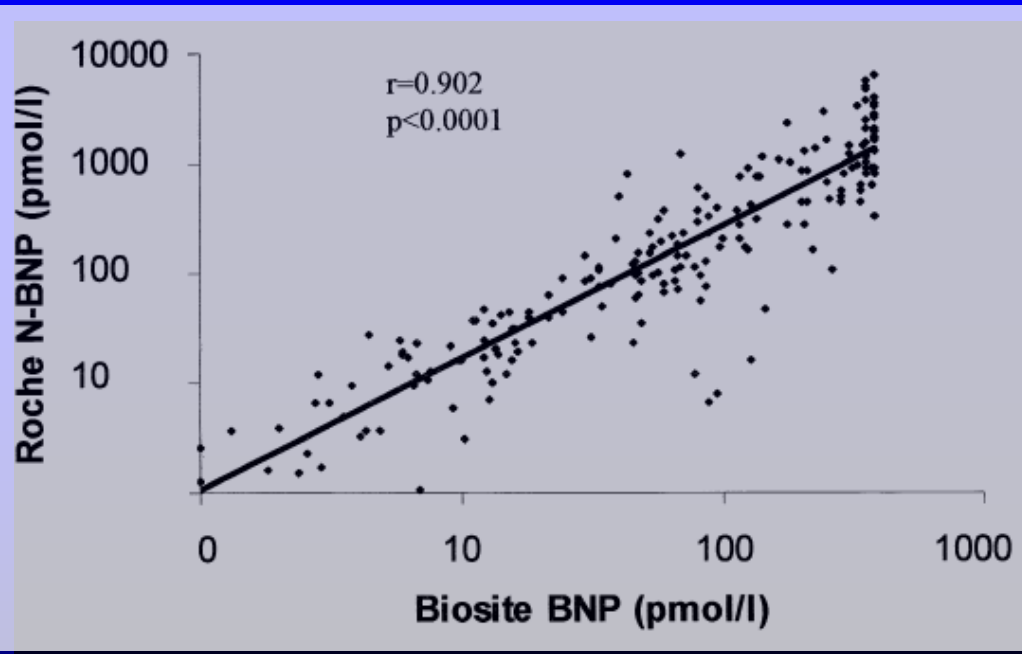
John G. Lainchbury, MD, Elizabeth Campbell, BSc (HONS), Christopher M. Frampton, PhD,  
Timothy G. Yandle, PhD, M. Gary Nicholls, MD, FACC, A. Mark Richards, MD, PhD  
*Christchurch, New Zealand*



- Mean age 71 years
- Optimal “rule in” cut point = 2875 ng/L

# Brain Natriuretic Peptide and N-Terminal Brain Natriuretic Peptide in the Diagnosis of Heart Failure in Patients With Acute Shortness of Breath

John G. Lainchbury, MD, Elizabeth Campbell, BSc (HONS), Christopher M. Frampton, PhD,  
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*Christchurch, New Zealand*

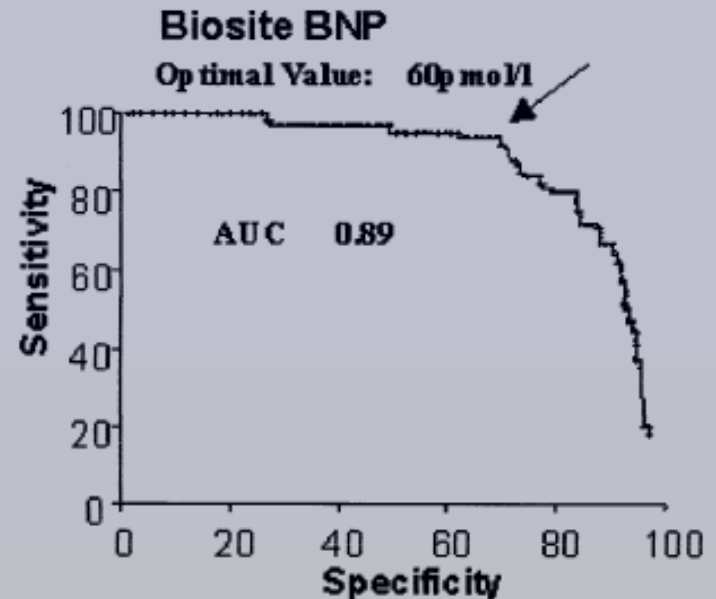
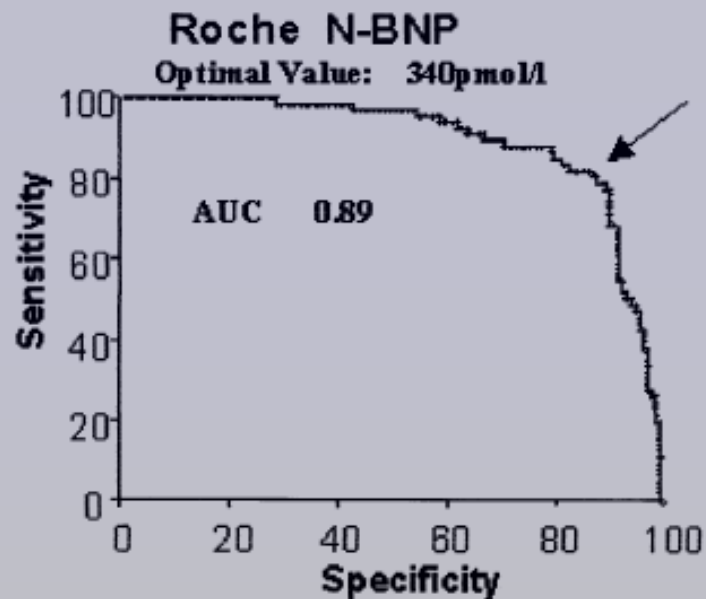


NT-proBNP is strongly  
correlated to BNP in  
acute dyspnea

# Brain Natriuretic Peptide and N-Terminal Brain Natriuretic Peptide in the Diagnosis of Heart Failure in Patients With Acute Shortness of Breath

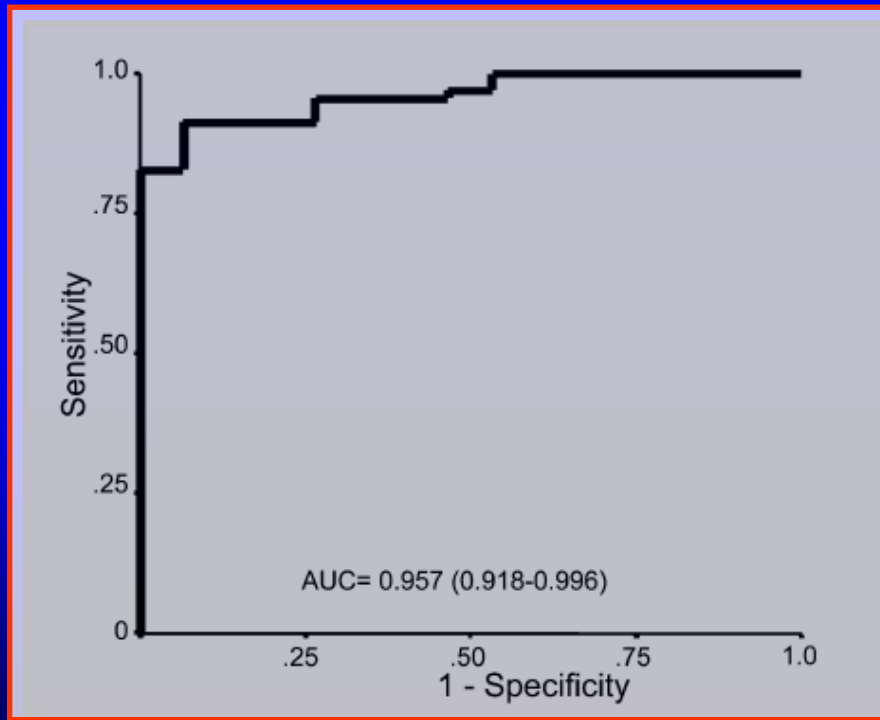
John G. Lainchbury, MD, Elizabeth Campbell, BSc (HONS), Christopher M. Frampton, PhD,  
Timothy G. Yandle, PhD, M. Gary Nicholls, MD, FACC, A. Mark Richards, MD, PhD

*Christchurch, New Zealand*



# N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction<sup>☆</sup>

Antoni Bayés-Genís<sup>a,e,\*</sup>, Miquel Santaló-Bel<sup>b</sup>, Edgar Zapico-Muñoz<sup>c</sup>, Laura López<sup>a</sup>, Carlos Cotes<sup>a</sup>, Jesús Bellido<sup>d</sup>, Rubén Leta<sup>a</sup>, Pere Casan<sup>d</sup>, Jordi Ordóñez-Llanos<sup>c,f</sup>



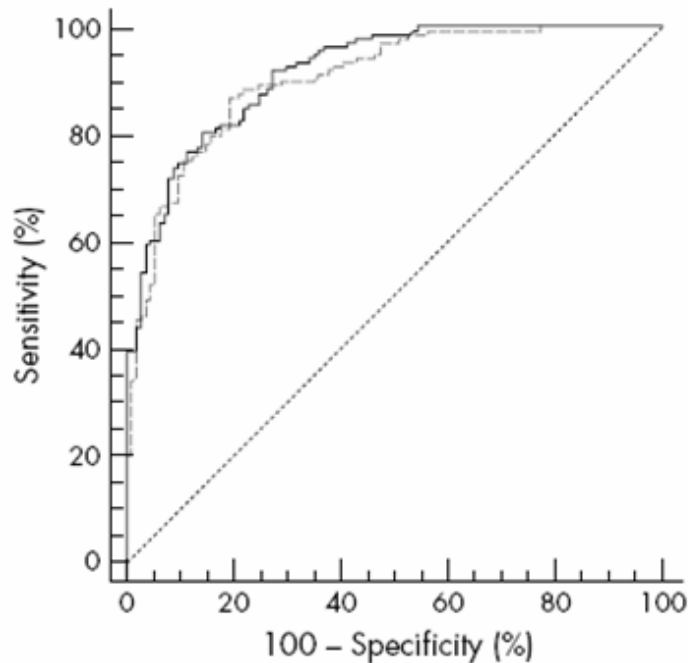
- **Mean age 71 years**
- **Optimal “rule out” cut point=253 ng/L**
- **Optimal “rule in” cut point=973 ng/L**

# Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure

T Mueller, A Gegenhuber, W Poelz and M Haltmayer

*Heart* 2005;91;606-612

doi:10.1136/hrt.2004.037762



- Mean age 72.5 years
- Optimal NT-proBNP cut point=825 ng/L.
- Equivalent diagnostic accuracy to optimal BNP cut point.



# The PRIDE Study

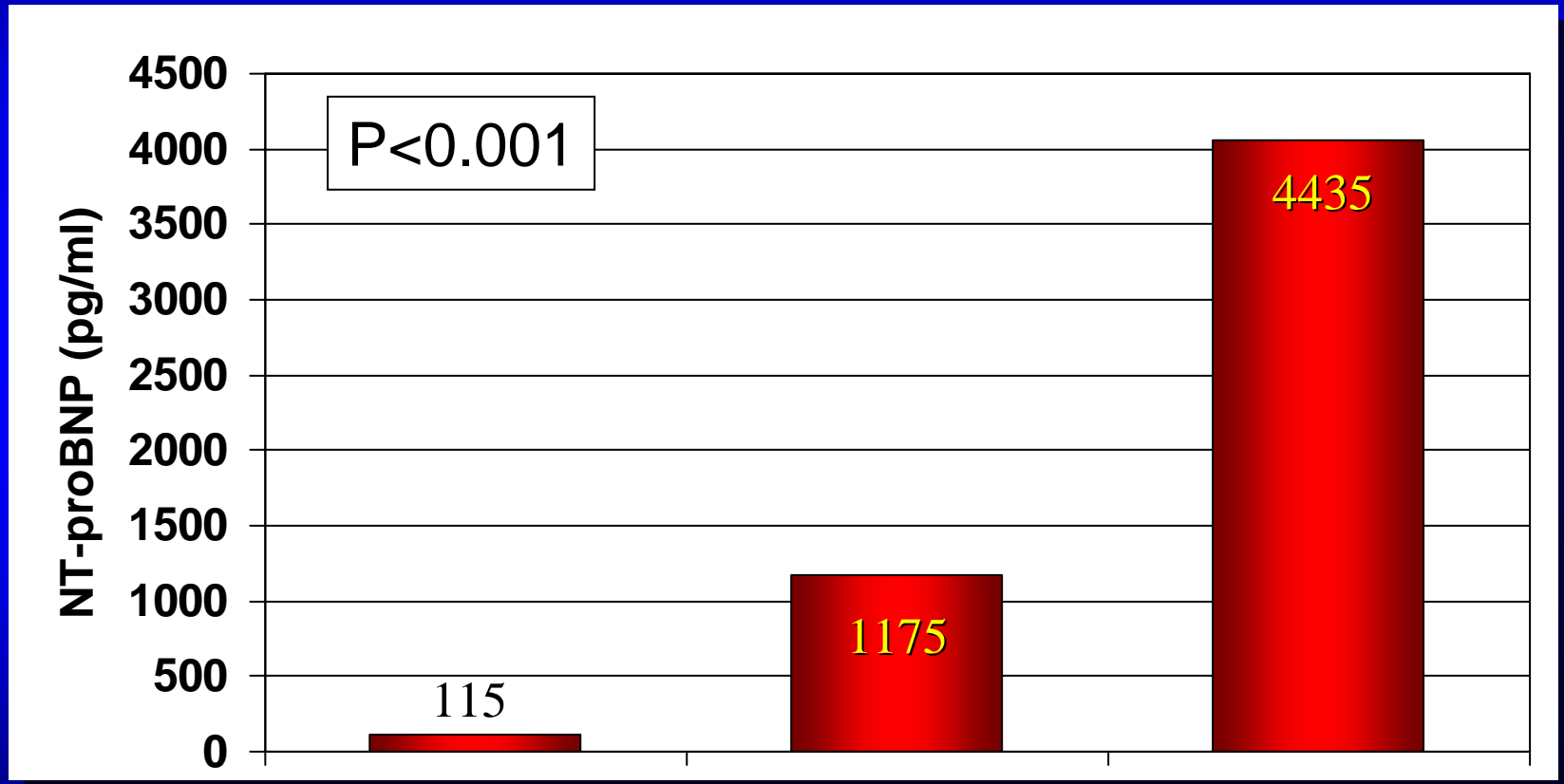
## **The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study**

James L. Januzzi, Jr., MD, Carlos A. Camargo, MD, PhD, Saif Anwaruddin, MD,  
Aaron L. Baggish, MD, Annabel A. Chen, MD, Daniel G. Krauser, MD,  
Roderick Tung, MD, Renee Cameron, MS, J. Tobias Nagurney, MD,  
Claudia U. Chae, MD, MPH, Donald M. Lloyd-Jones, MD, ScM, David F. Brown, MD,  
Stacy Foran-Melanson, MD, PhD, Patrick M. Sluss, MD, PhD,  
Elizabeth Lee-Lewandrowski, PhD, MPH, and Kent B. Lewandrowski, MD

- Prospective, blinded study of 599 patients presenting to the ED at Massachusetts General Hospital with complaints of dyspnea.



# Results: NT-proBNP Levels



No prior CHF (N=355)

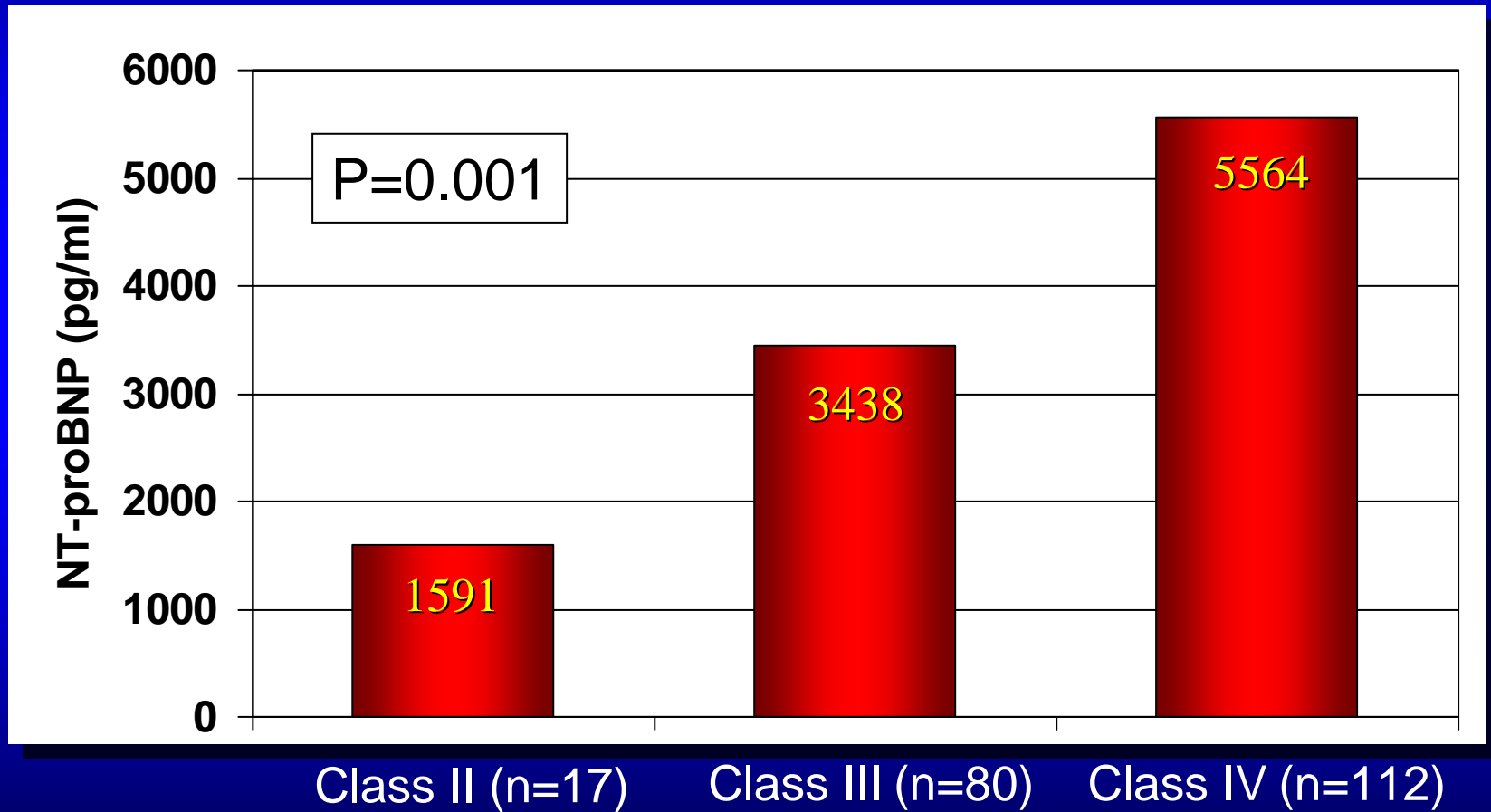
Prior CHF (N=35)

Acute CHF (N=209)

**Not acute CHF (N=390)**



# NT-proBNP Levels and Symptoms



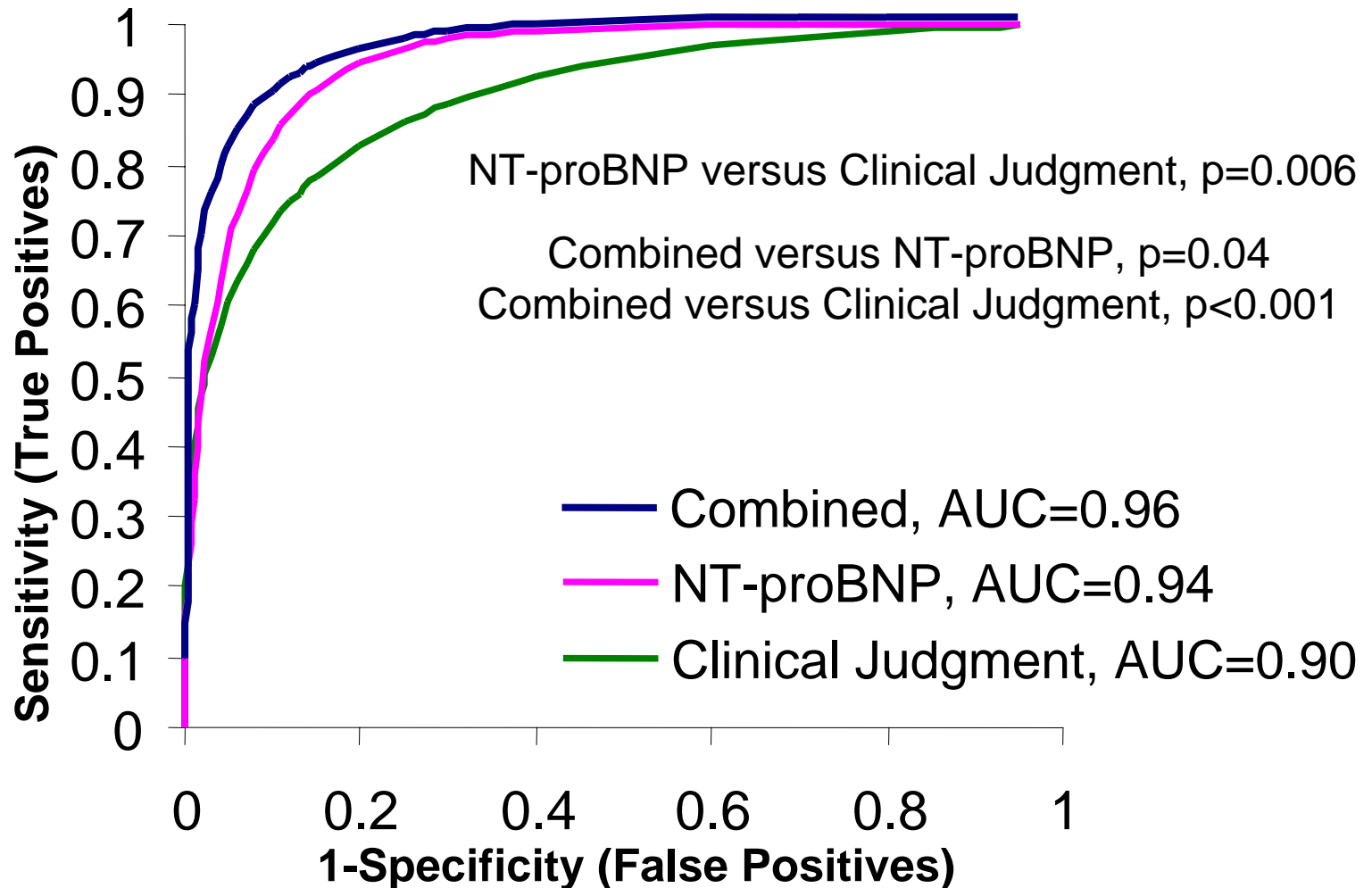


# Results: Predictors of CHF

Predictor	Odds Ratio	95% CI	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

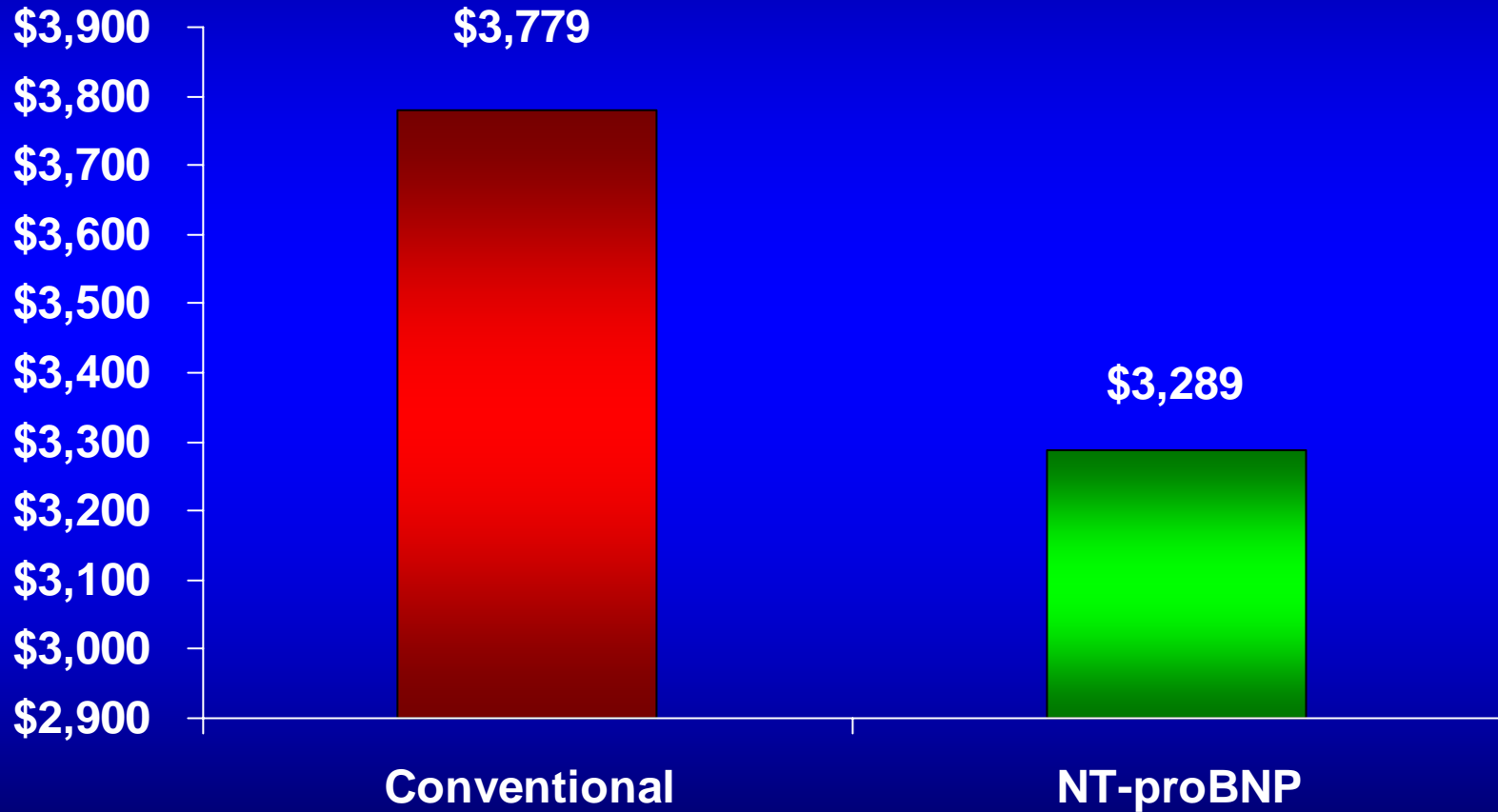


# Results: Primary Endpoint





# Projected Cost Savings: PRIDE



Siebert, et al, Am J Cardiol, 2006;98:800.



# The IMPROVE-CHF Study

## Prospective, Randomized Support of NT-proBNP Testing

**N-Terminal Pro-B-Type Natriuretic Peptide Testing  
Improves the Management of Patients With Suspected Acute  
Heart Failure**

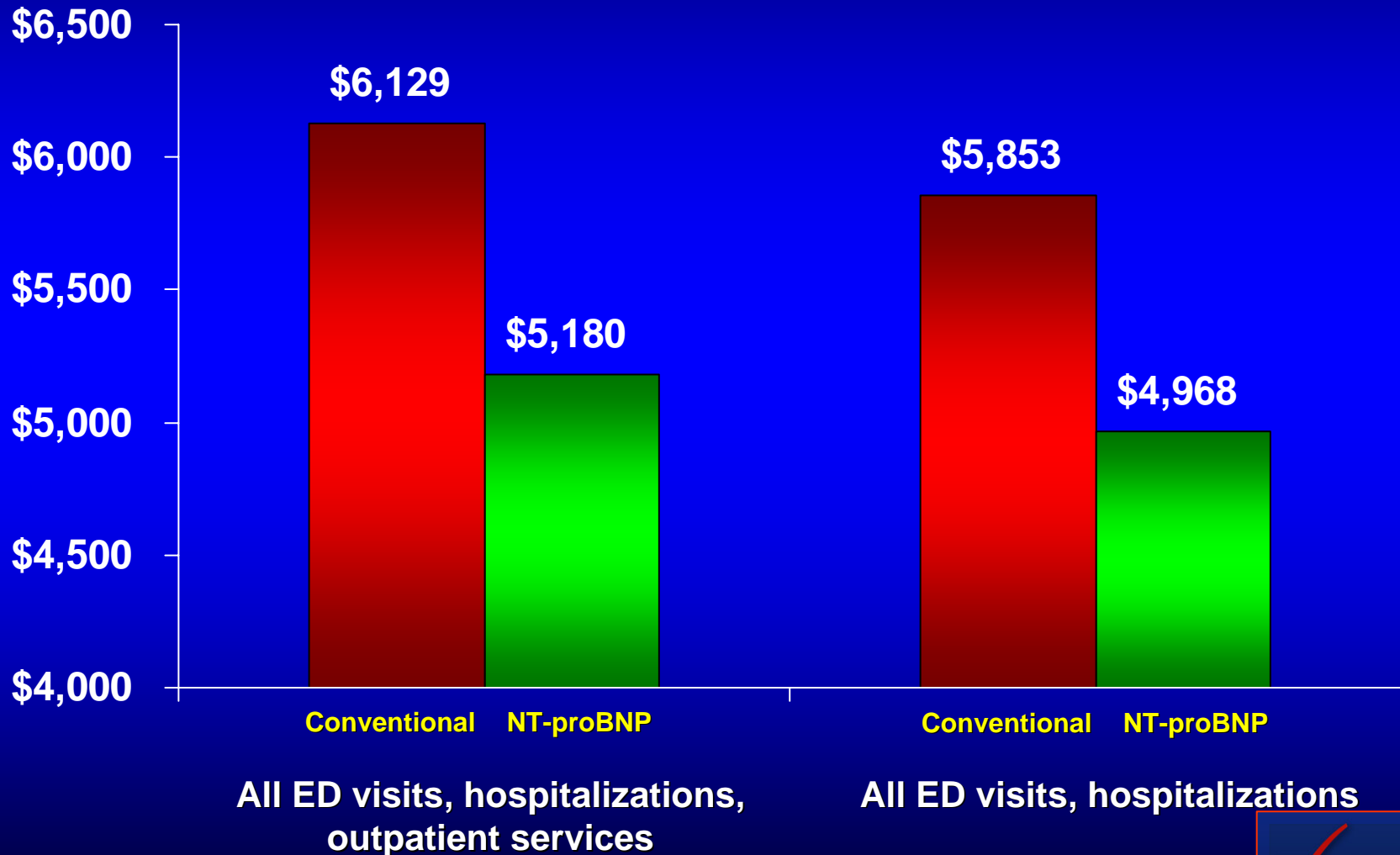
**Primary Results of the Canadian Prospective Randomized Multicenter  
IMPROVE-CHF Study**

Gordon W. Moe, MD; Jonathan Howlett, MD; James L. Januzzi, MD; Hanna Zowall, MA; for the  
Canadian Multicenter Improved Management of Patients With Congestive Heart Failure  
(IMPROVE-CHF) Study Investigators

**Circulation, 2007**



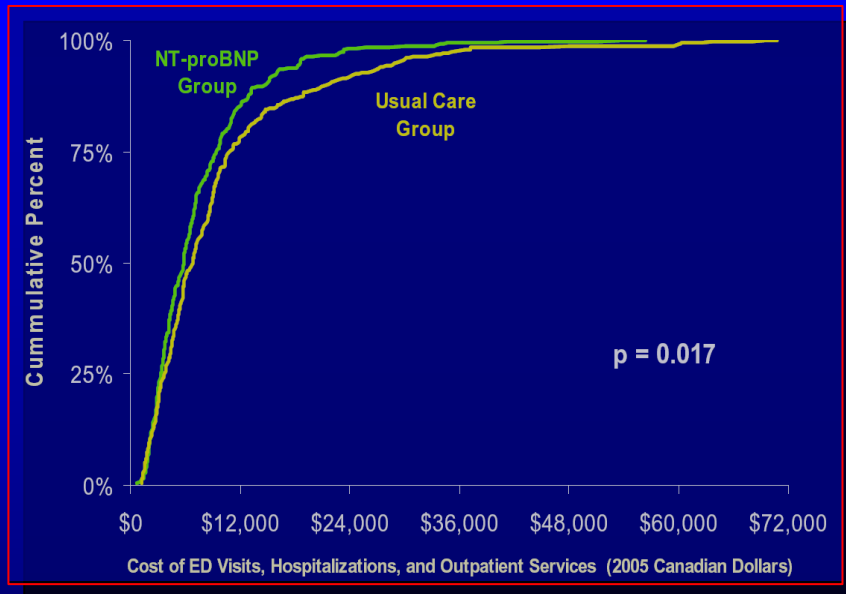
# Randomized, Prospective Data Illustrating Cost-Effectiveness of NT-proBNP



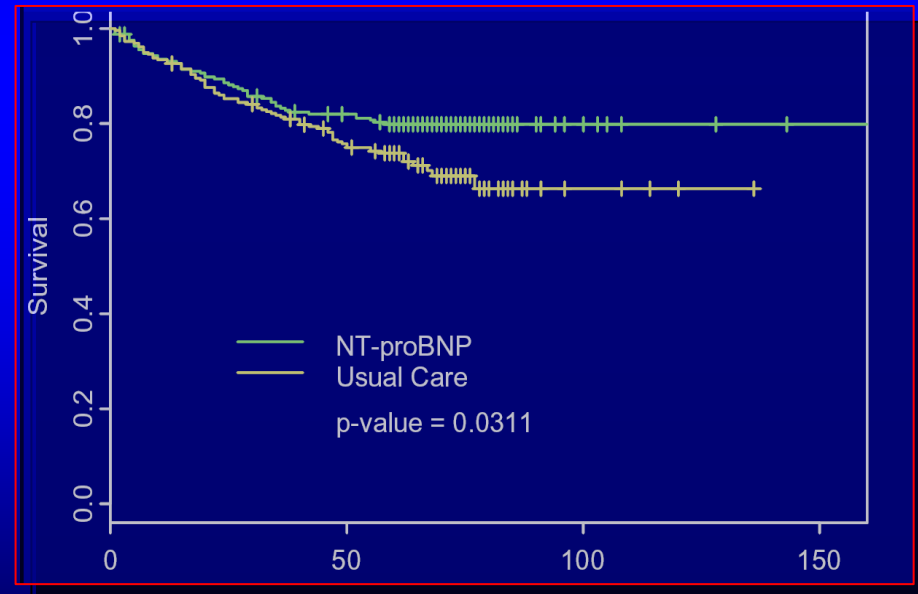
# Effect of Selective NT-proBNP Testing On Costs/Outcomes:

## *Results of the Randomized IMPROVE-CHF Trial*

### Effect of Selective NT-proBNP Testing on Utilization/Costs



### Effect of Selective NT-proBNP Testing on Outcomes

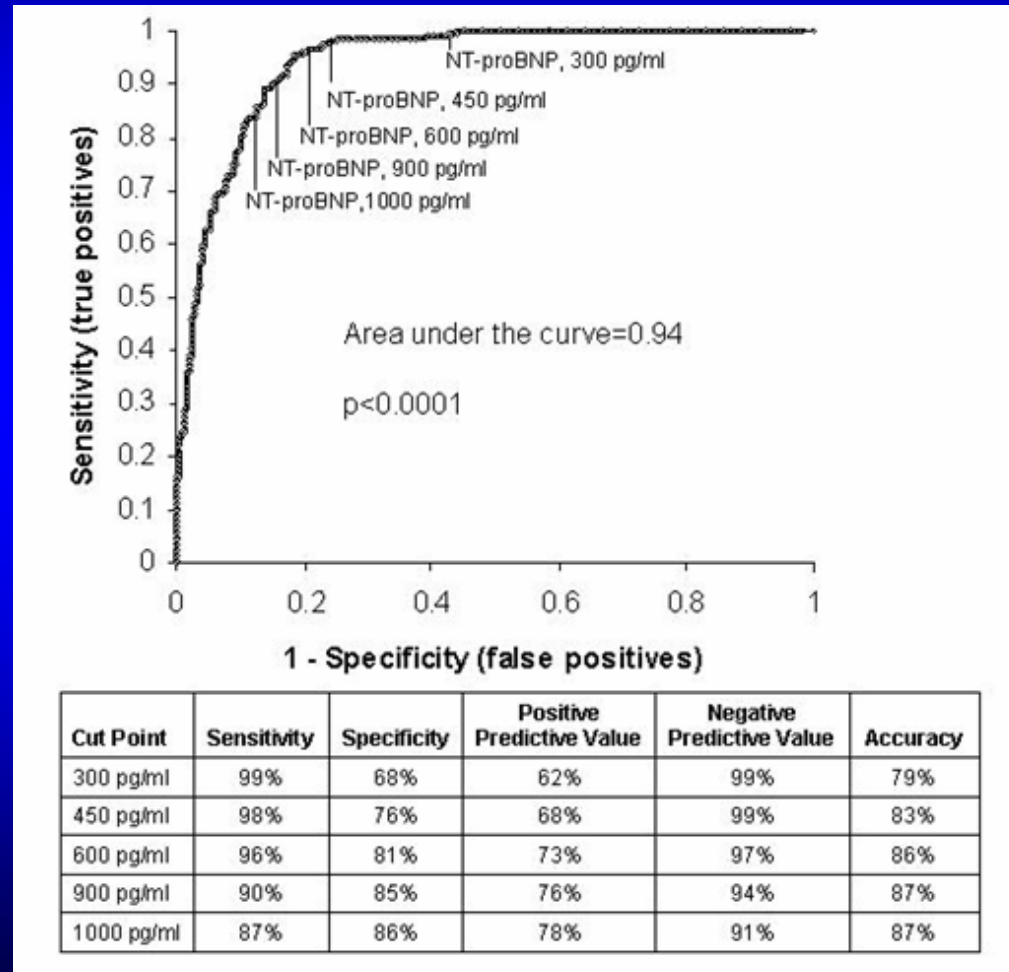


Moe, et al, Circulation, 2007;115:3103

**Which cut-points should we  
be using?**

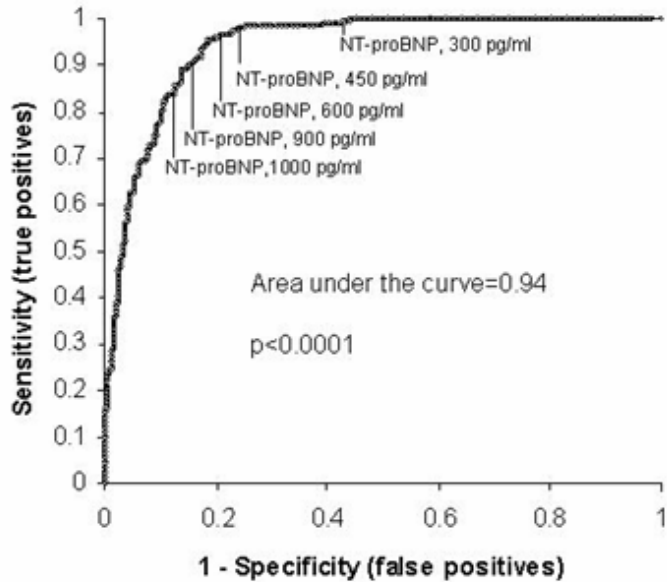


# ROC for NT-proBNP in PRIDE



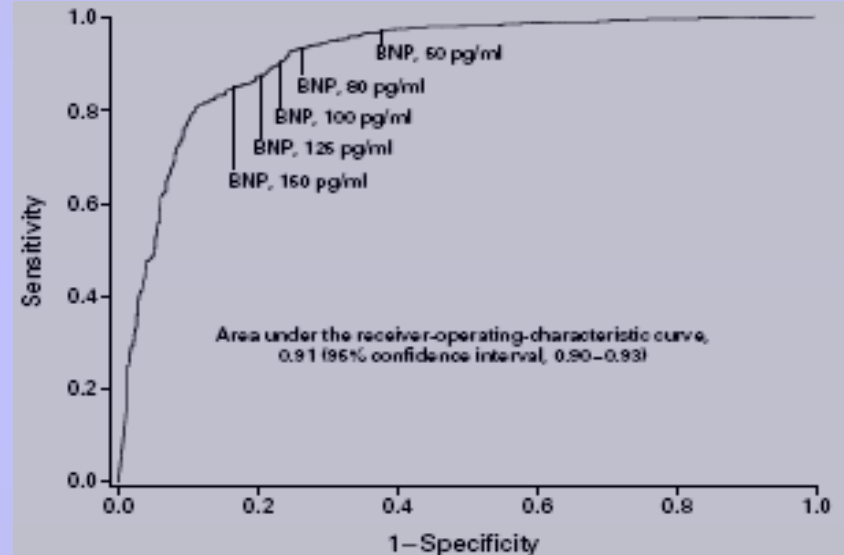
# Looks an awful lot like BNP...

## PRIDE



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%

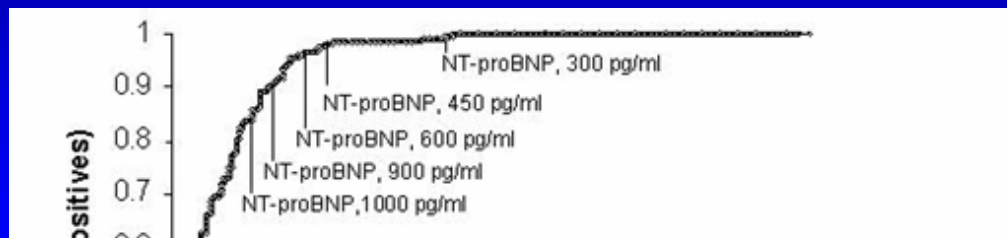
## Breathing Not Properly



BNP pg/ml	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	ACCURACY
	(95 percent confidence interval)				
50	97 (96-98)	62 (59-66)	71 (68-74)	96 (94-97)	79
80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)	83
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)	83
125	87 (86-90)	79 (76-82)	80 (78-83)	87 (84-89)	83
150	85 (82-88)	83 (80-85)	83 (80-85)	85 (83-88)	84



# What is the best single cut point?

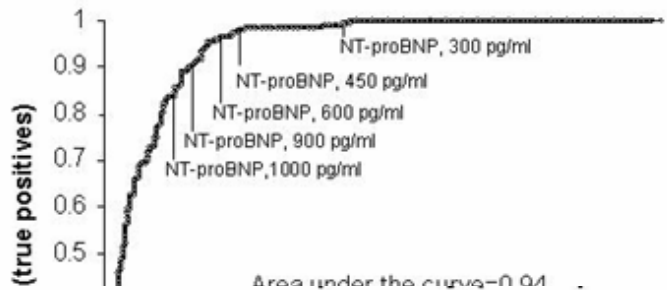


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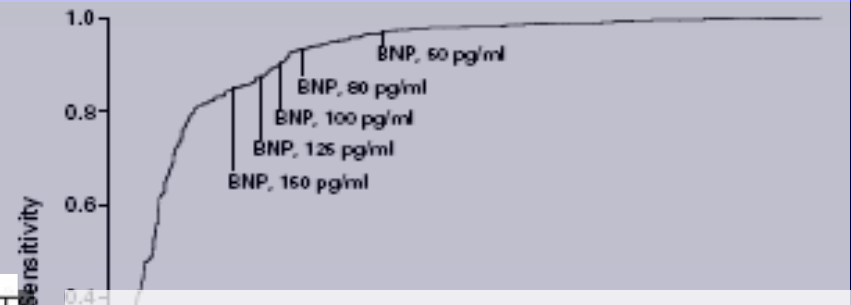
# Is there anything to do to improve the comparatively poor PPV of NP's?

## PRIDE



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
300 pg/ml	99%	68%	62%	99%
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## Breathing Not Properly



BNP pg/ml	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
	(95 percent confidence interval)			
60	97 (96-98)	62 (59-66)	71 (68-74)	98 (94-97)
80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)
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# Causes of lower positive predictive value of natriuretic peptides

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

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

Variable	Multivariate OR	Multivariate CI 95%
<b>Demographics</b>		
Age/10-y increase	1.3	1.0–1.6
<b>Physical findings</b>		
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 <sup>2</sup> decrease)	1.4	1.2–1.6
<b>Chest radiograph findings</b>		
Cardiomegaly	3.2	1.9–5.3
Pleural effusion	2.0	1.0–3.7
Interstitial edema	2.5	1.1–5.8
<b>Blood value</b>		
Creatinine (increase per mg/dL)	2.4	1.6–3.6
Hemoglobin (decrease per g/dL)	1.3	1.2–1.4
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<sup>1\*</sup>, Roland van Kimmenade<sup>2†</sup>, John Lainchbury<sup>3</sup>, Antoni Bayes-Genis<sup>4</sup>,  
Jordi Ordonez-Llanos<sup>5</sup>, Miguel Santalo-Bel<sup>6</sup>, Yigal M. Pinto<sup>2</sup>, and Mark Richards<sup>3</sup>

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

**ICON Study Group:**  
**Januzzi, Baggish (Boston)**  
**Bayes-Genis, Ordonez, Santalo (Barcelona)**  
**van Kimmenade, Pinto (Maastricht)**  
**Richards, Lainchbury (Christchurch)**

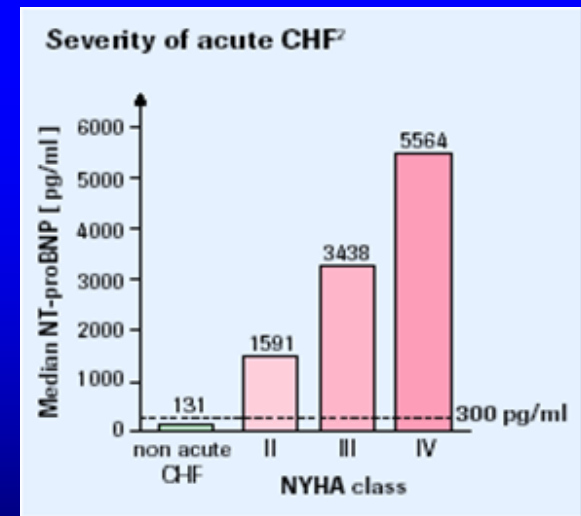


# Age-independent “rule out” cut point

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

– 300 pg/ml, age independent

- 99% sensitive
- 60% specific
- 98% NPV





# Age-stratified “rule in” cut point

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

*To diagnose acute HF: the “triple cut point”*

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

**Superior to single cut-point strategy in multivariable bootstrapping models**

Select pt

[Patient Name]

MGH 1674634

MGH E1010B

Admitted: 05/23/2005

Pt Details

63y M FREE CARE FULL

PCP: PEARL, DIANE

- Blood Bank
- Reports
- Report Mgmt
- LMR Summary
- Big Board
- Labs
- Clinical Summary
- Last Known Values
- Microbiology

Full System Panels

Set

Add Panel(s) to Grid

05/24/2005 --> 05/14/2005

Copy

- Chemistry
  - Lytes/Renal/Glucose
  - General Chemistries
  - Cardiac Tests
  - Lipid Tests
  - Anemia Related Studies
  - Thyroid Studies
  - Chemistry Miscellaneous
- Hematology

Clear Grid	MGH	MGH	MGH	
Print Grid	05/24/05	05/24/05	05/24/05	
	09:15	00:10	00:06	
NT-BNP			7038(HT)	
CK	207	253		
CK-MB	6.2	8.3(H)		
CKMBRI	3.0	3.3		
TROP-T	0.06	0.06		

(1674634) cimem Detail Display - Microsoft Internet Explorer provided by Partners HealthCare Syst...

Specimen Comment: (no comments)

Test name	Result	Ref Range	Units	Completed
NT-proBNP	7038 (H)	0-900	pg/ml	05/24/2005 00:57
<p>(NOTE)Reference Range:            Age &lt;50 years: 0-450 pg/ml            Age 50-75 years: 0-900 pg/ml            Age &gt; 75 years: 0-1800 pg/ml            Among patients with dyspnea, NT-proBNP is highly sensitive for the detection of acute congestive heart failure. In addition, a NT-proBNP &lt;300 pg/ml effectively rules out acute congestive heart failure, with 99% negative predictive value.            Knowledge of each individual patient's NT-proBNP range may be more useful than using similar cut-points for every patient.            Marked elevations in NT-proBNP levels may be observed in states other than left ventricular congestive failure, including: acute coronary syndromes, right heart strain/failure (including pulmonary embolism and cor pulmonale), critical illness, renal failure, as well as advanced age.            Falsely low NT-proBNP in congestive heart failure patients may be observed with increasing body-mass index.</p>				

ONY J

Navigation arrows

# Optimal Application of NT-proBNP testing

Troubleshooting:

Elevated NT-proBNP

Prior heart failure

Low NT-proBNP

Grey Zone NT-proBNP

# 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

# Interpreting NT-proBNP in those with Prior Heart Failure

- Those with prior heart failure who are not destabilized at the time of evaluation usually have considerably lower NT-proBNP values than those who are destabilized.
- It is useful to have a comparison to “dry” NT-proBNP values (i.e. a measurement taken in the office when the patient appears stable).
- A change  $>25\%$  from the “dry” NT-proBNP generally suggests a significant clinical change.
- Irrespective of clinical stability, the “dry” NT-proBNP value is profoundly prognostic!

# Know the Differential Diagnosis of an Unexpectedly Low Natriuretic Peptide

- Obesity
- Non-systolic heart failure
- Mild acute heart failure
- Isolated right heart failure
- Partially treated heart failure

# Managing Grey Zone Values

- Grey zone values are defined as those values between the 'rule out' (300 ng/L) and the age adjusted 'rule in' value for NT-proBNP.
- Although age stratification reduces grey zone results, they are still present in up to 20% of patients with acute dyspnea.
- Knowledge of the differential diagnosis for the causes of a grey zone NT-proBNP result is important.

# Non-Heart Failure Associations with Grey Zone Values

Diagnosis	Patients (n =99)
Chronic obstructive pulmonary disease/asthma	12 (12%)
Pneumonia/bronchitis	12 (12%)
Acute coronary syndrome/chest pain	12 (12%)
Arrhythmia/bradycardia	8 (8%)
Lung cancer (including metastases)	5 (5%)
Anxiety disorder	5 (5%)
Pulmonary emboli	3 (3%)
Pulmonary hypertension	1 (1%)
Pericarditis	1 (1%)
Other*	21 (21%)
Unknown	19 (19%)

van Kimmenade, et al, Am J Cardiol, 2006; 98:386

# Predictors of Acute Heart Failure in those with Grey Zone Values

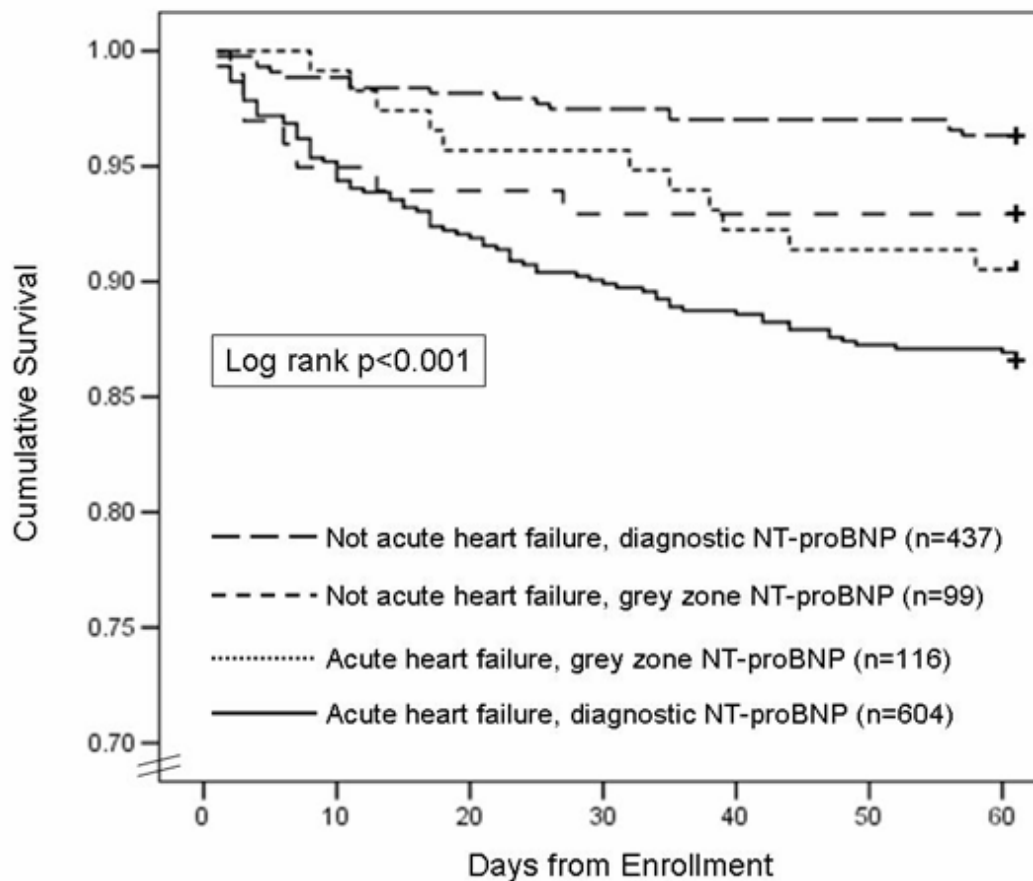
*Clinical variables matter in patients with grey zone NT-proBNP values*

Characteristic	Odds Ratio	95% CI	P value
Cough	0.18	0.06-0.52	.001
Use of loop diuretic on presentation	3.99	1.58-10.1	.003
Paroxysmal nocturnal dyspnea	4.50	1.32-15.4	.02
Jugular vein distention	3.05	1.06-8.79	.04
Prior heart failure	2.63	1.02-6.80	.05
Lower extremity edema	2.96	0.94-9.31	.06
S3 gallop	10.4	0.82-130.7	.07

van Kimmenade, et al, Am J Cardiol, 2006; 98:386

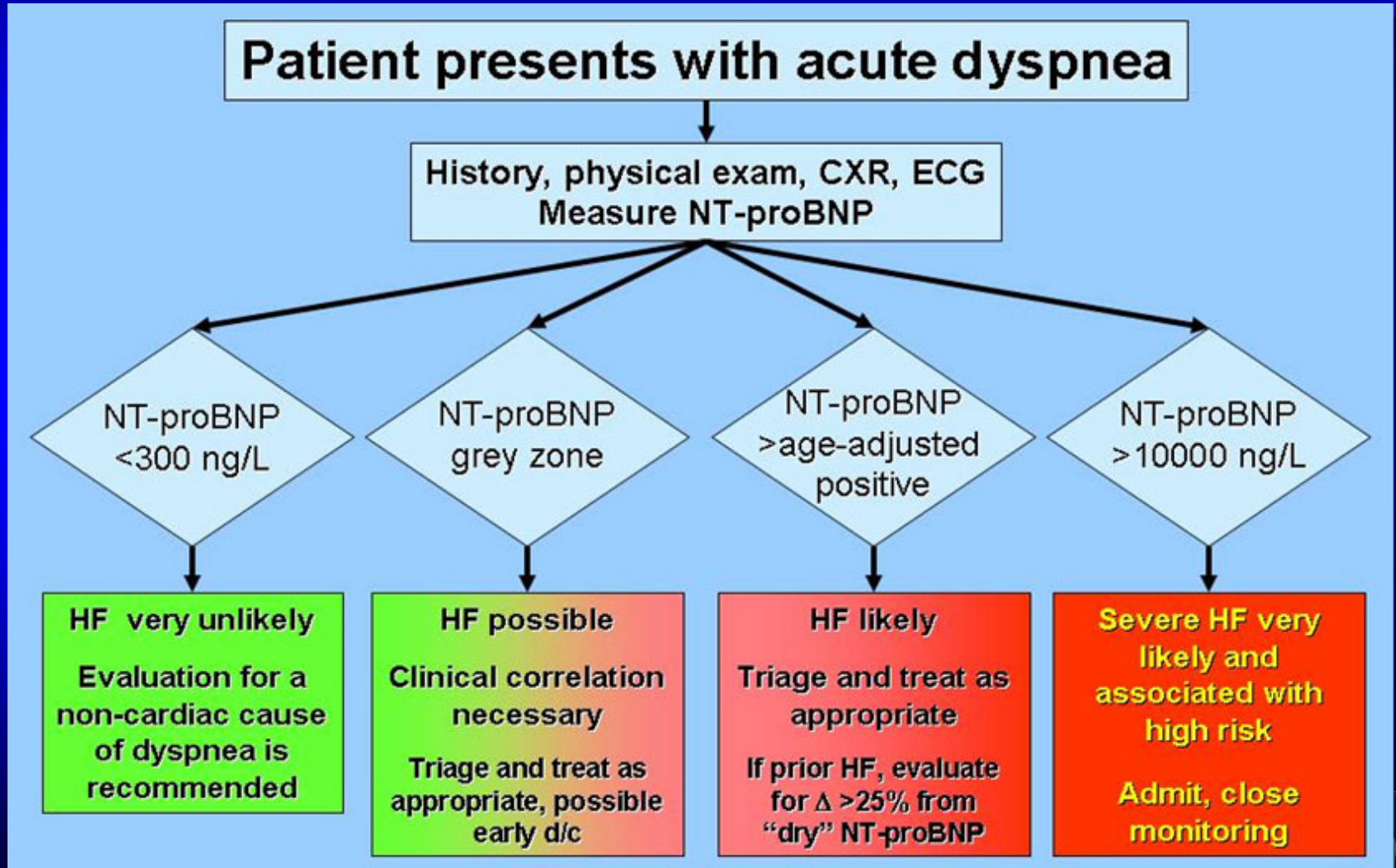


# Outcomes in the 'grey zone'



van Kimmenade, et al, AJC, 2006

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



# Conclusions

- **NT-proBNP testing is a useful adjunct to history and physical examination for the evaluation of the dyspneic patient in the ED.**
- **When evaluating a dyspneic patient, results of NT-proBNP testing should be used in context with history and physical examination.**
- **Logical use of NT-proBNP testing is cost-effective for the evaluation and triage of the patient with suspected acute HF.**

# Conclusions

- To exclude acute destabilized heart failure an NT-proBNP  $<300$  ng/L is recommended.
- To identify acute destabilized heart failure, an age-independent NT-proBNP cut-point of 900 ng/L has similar sensitivity/specificity/PPV as BNP = 100 ng/L.
- Age stratification of NT-proBNP reduces false negatives and false positives, and improves PPV without a change in overall sensitivity or specificity.
- The ICON 'triple-cut point' of 450/900/1800 ng/L is recommended for its superior performance.

# Conclusions

- **Optimal application of an elevated NT-proBNP is in the context of knowledge of the correct differential diagnosis.**
- **In a patient with prior HF a change of 25% or more from the “dry” NT-proBNP is a significant rise.**
- **Grey zone values should not be ignored.**

# NT-proBNP Testing For Diagnosis of Acutely Destabilized Heart Failure

*Comments from the International  
NT-proBNP Consensus Panel*

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