Optimal Use of B-type Natriuretic Peptide in Heart Failure : Diagnostic and Risk Stratification Value
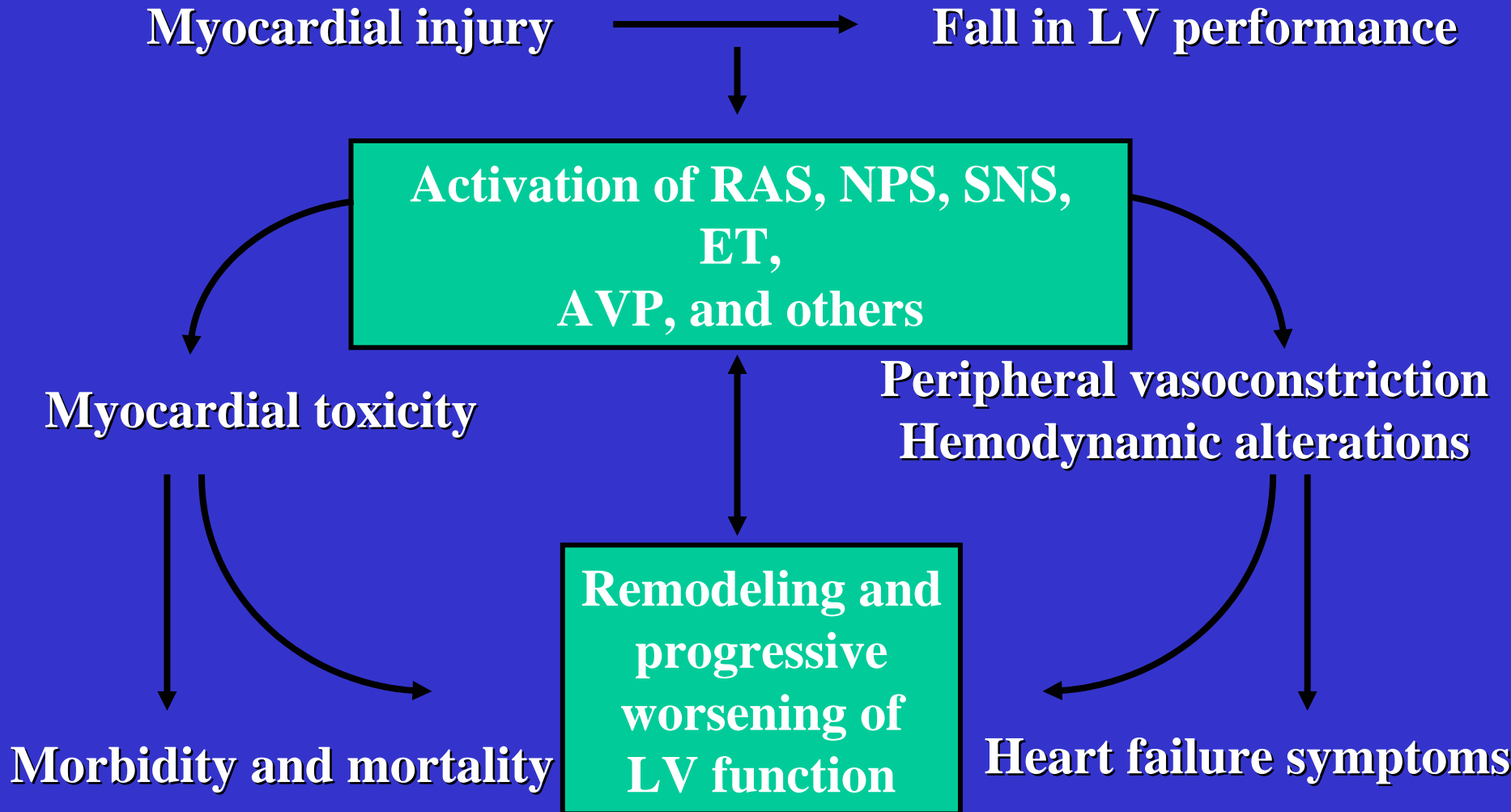
Diagnostic & prognostic value using a BNP or NT-proBNP

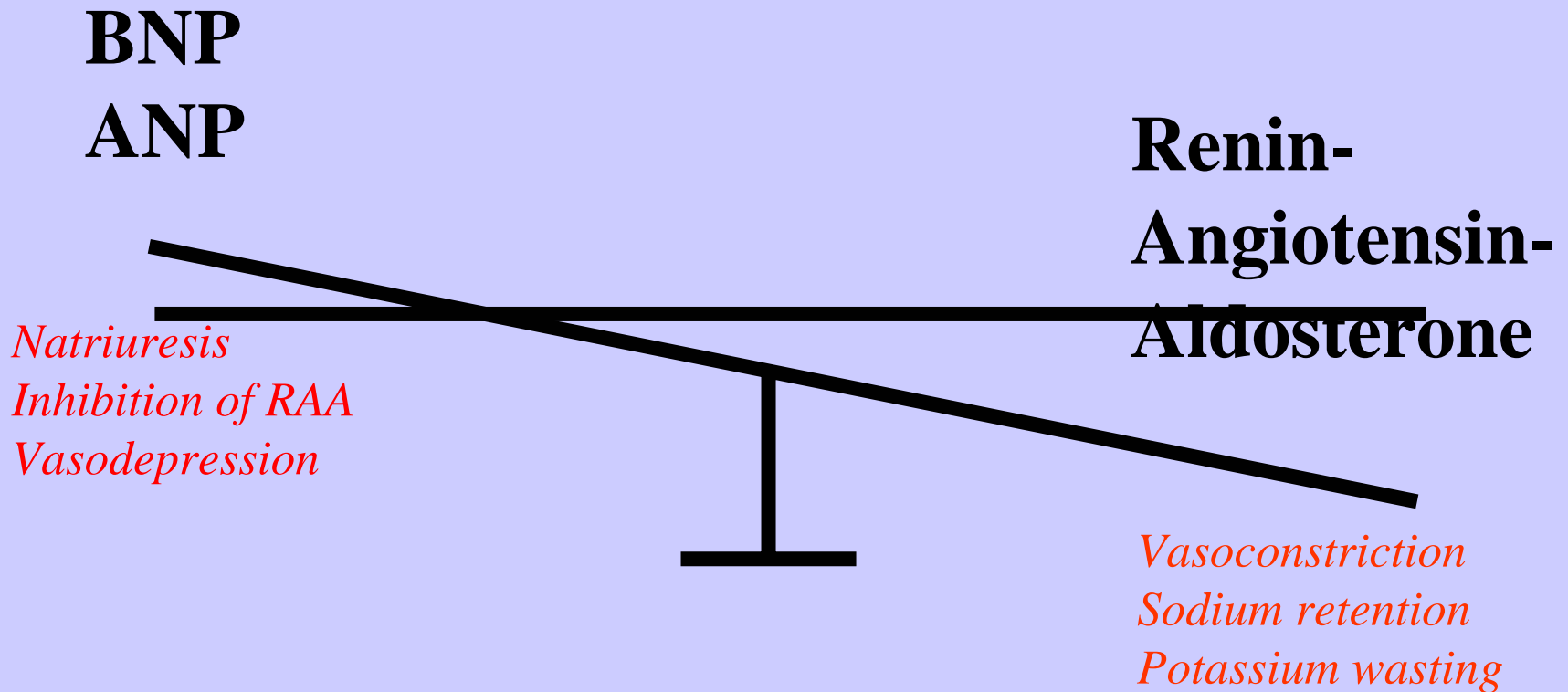- **Introduction & measurement issue**
- Emergency room or acute clinical setting
- Chronic stable HF or out-patient clinic
- Post myocardial infarction
- The general population
- Prognosis
- Treatment monitoring
- Conclusion

Heart Failure Pathophysiology:
Neurohormonal Theory

Myocardial injury → Fall in LV performance

Activation of RAS, NPS, SNS, ET, AVP, and others

Myocardial toxicity

Peripheral vasoconstriction
Hemodynamic alterations

Remodeling and progressive worsening of LV function

Morbidity and mortality

Heart failure symptoms

It's All About Balance

BNP
ANP

Renin-Angiotensin-Aldosterone

Natriuresis
Inhibition of RAA
Vasodepression

Vasoconstriction
Sodium retention
Potassium wasting

Many markers in CHF

- **Many "markers" are elevated in CHF (cytokines, catecholamines, etc.) but are not useful in :**
  - **Wide variability in values**
  - **Difficult to measure**
  - **Not often elevated until CHF is severe**
- **Until now there has been <u>no single blood test</u> that differentiates a patient with heart failure from a patient without heart failure.**
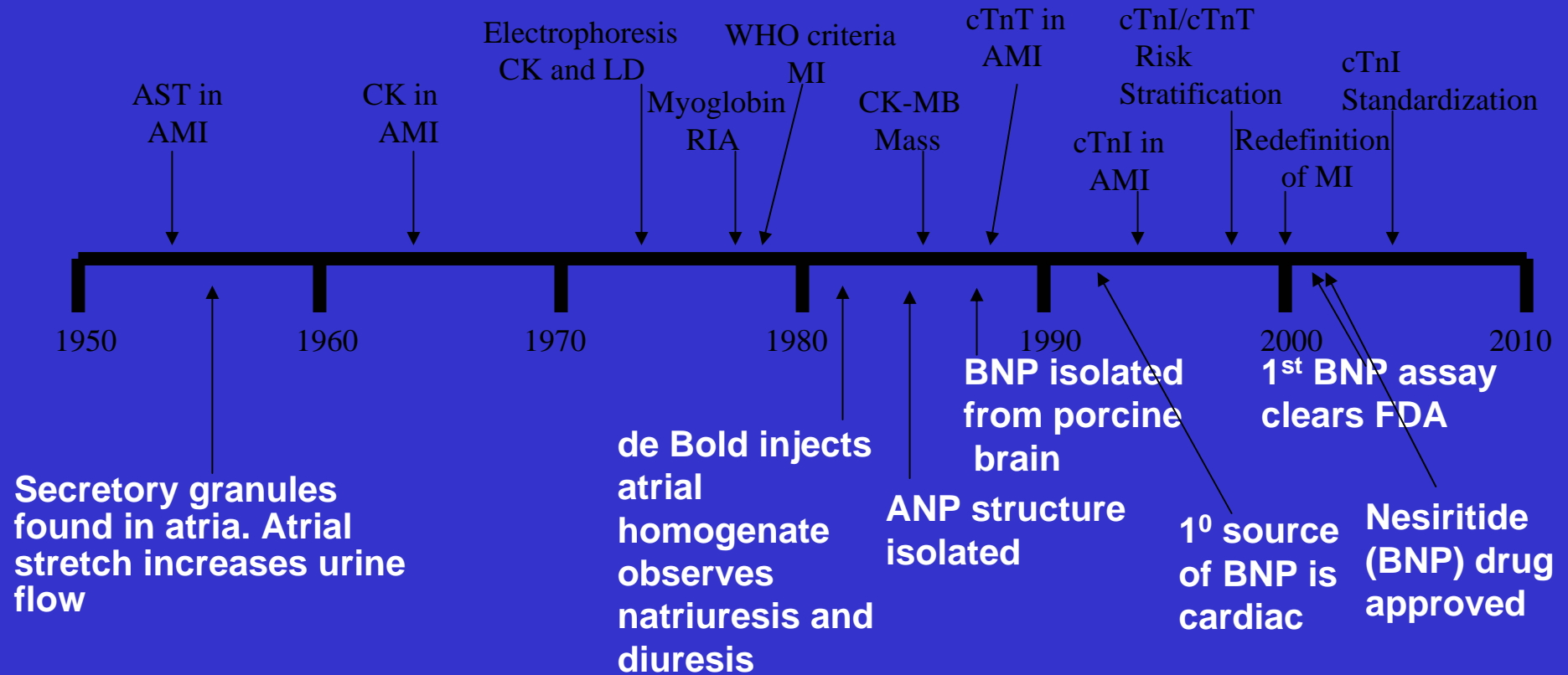
Definition of heart failure
Based on ESC guidelines

> **Objective : Evidence of important cardiac dysfunction**

New Diagnostic Method : BNP, NT-proBNP

Acute Setting - ED
Plasma BNP in assessment of acute dyspnea

- Admission plasma BNP concentration more accurately reflected the final diagnosis of HF (93% sensitivity and 90% specificity when BNP > or = 22 pmol/L) than LVEF or plasma ANP.

- Shionoria® BNP (Shionogi, RIA)

- As intriguing as those results were, it was not until a rapid assay became available that BNP testing could be applied in the urgent-care or clinic setting.

Davis M, Lancet. 1994 Feb 19;343(8895):440-4.

Methods of determination

POCT

Automatic System

VS.

Single use fluroscence immunoassay device

Chemiluminescent immunoenzymatic assay

POCT (point of care test)

- Completely automatic
- Uses 2 cc's of <u>whole blood</u> or plasma
- Gives reproducible results within ~ 15 minutes
- Small enough to use at <u>the bedside, emergency room, or in any point-of-care laboratory</u>
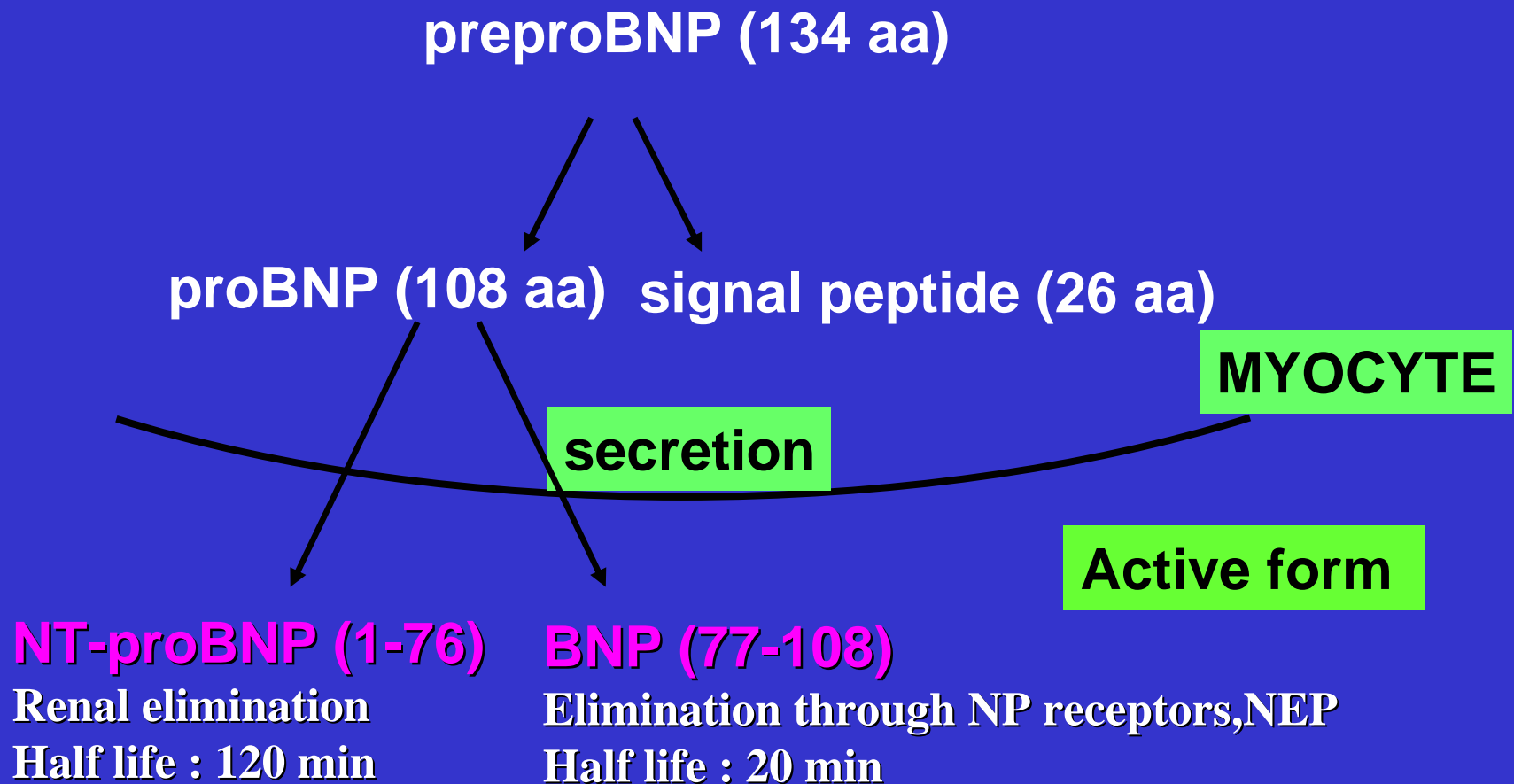
(BNP, Triage®, Biosite)

Automatic System

- No need person for Lab.
- Fits into routine laboratory work flow (both TnT and proBNP from one sample)
- Very high precision
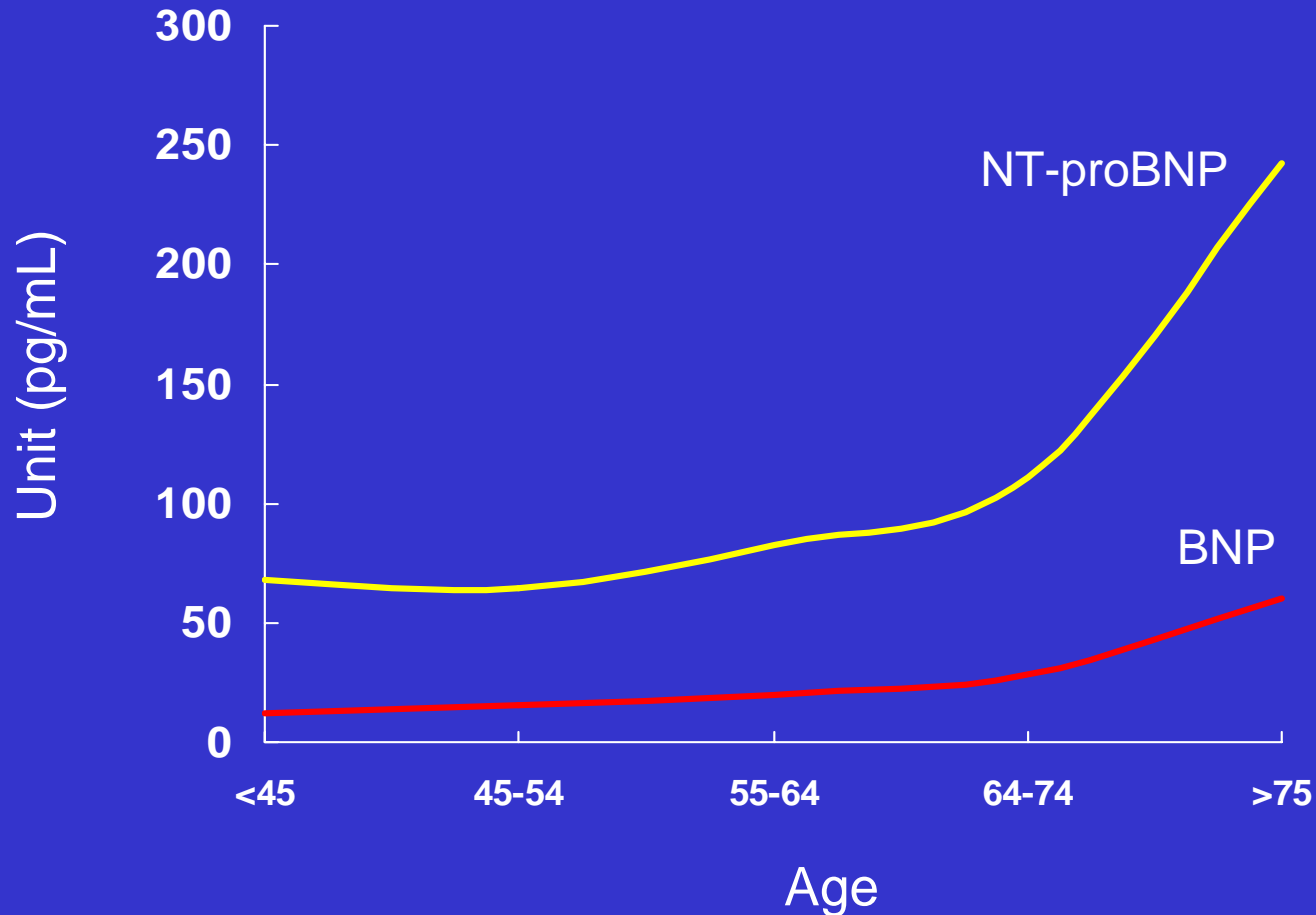- Out-patient, Screening

NT-proBNP, Elecsys®, Roche
BNP, ADVIA Centaur®, Bayer
BNP, AxSYM®, Abbort
BNP, Beckman®, Biosite

Comparing BNP & NT-proBNP

- **Influence of age**

Comparing BNP & NT-proBNP

■ **Influence of renal impairment**

- BNP would be more useful in the follow-up of cardiac complications in patients with end-stage renal disease (Clerico et al.)

- Correlation with estimated GFR (McCullogh et al.,)
  - BNP: r = -0.20
  - NT-proBNP: r = -0.60

Comparing BNP & NT-proBNP

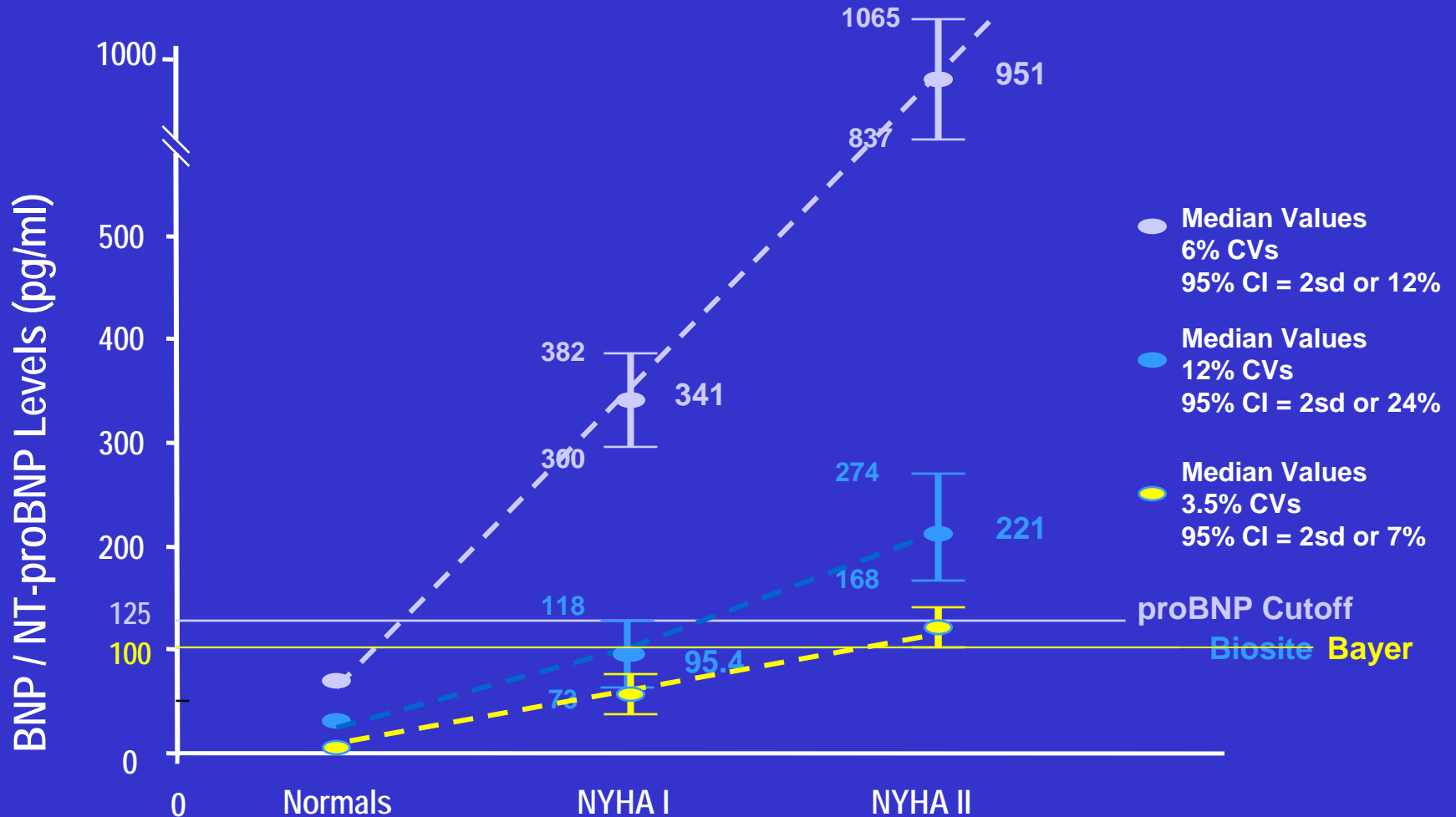- **_In-vitro_ stability & Specimen collection**
  - BNP
    - assay within 24 hours
    - recovery rate (24 hours): 91%
    - -20°C storage: 9 months
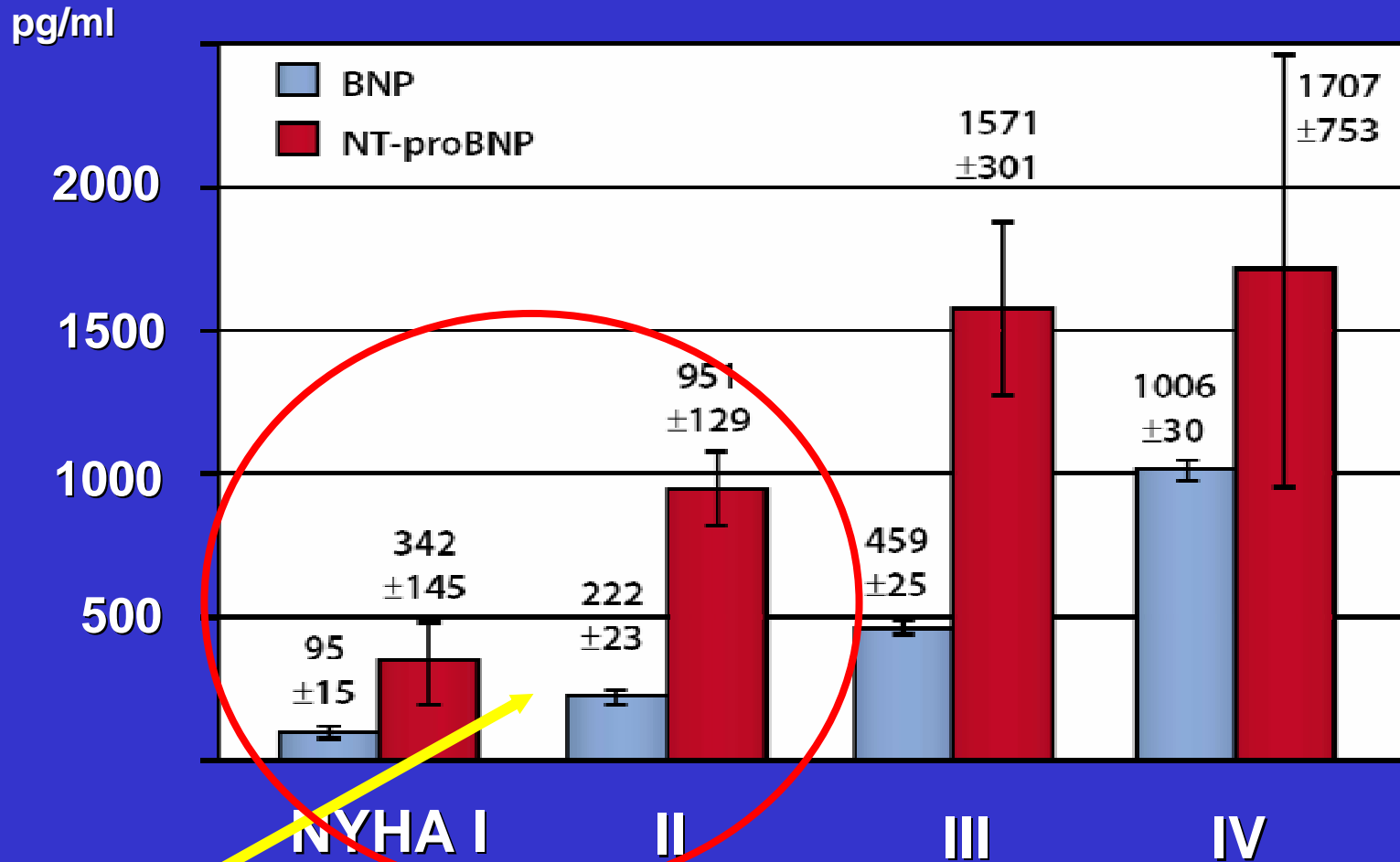   - plastic EDTA tube, Whole blood (POCT)
  - NT-proBNP
    - 2-8°C storage: 3 days
    - -20°C storage: 12 months
    - Plasma or serum (Plasma level is lower than serum level)
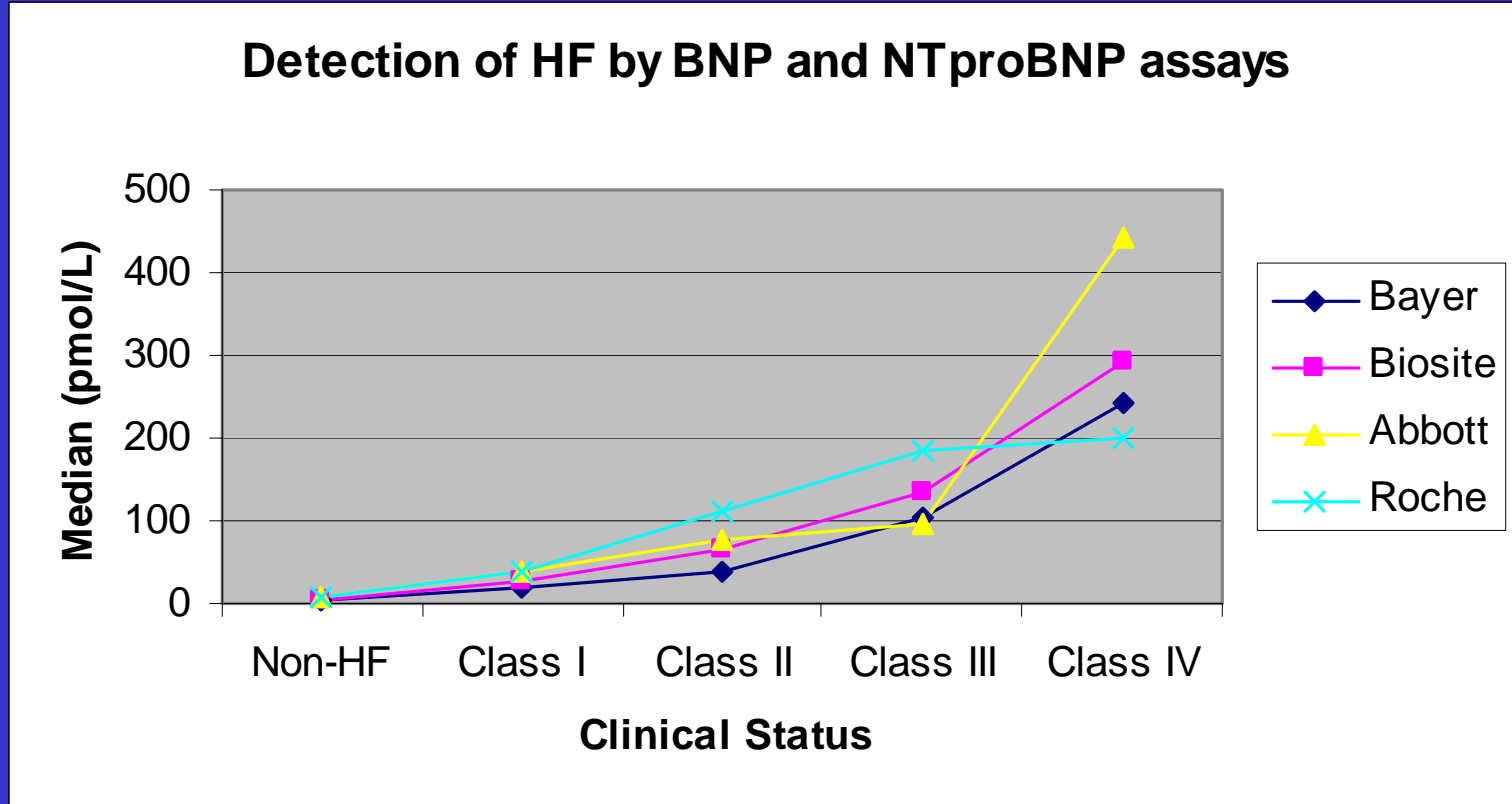
Comparing BNP & NT-proBNP
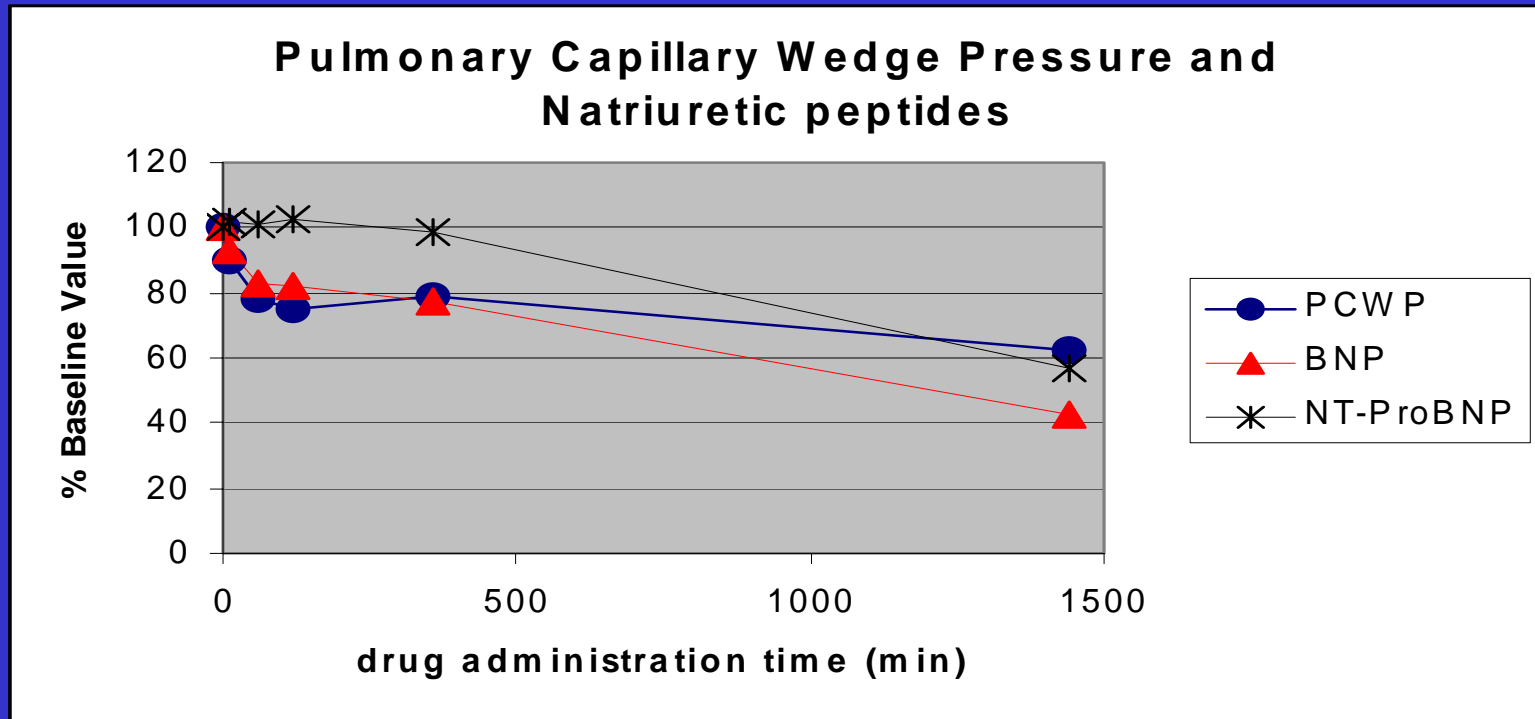
Comparing BNP & NT-proBNP

Comparing BNP & NT-proBNP

**Detection of HF by BNP and NTproBNP assays**

Median Values of non-HF and NYHA I-IV Heart Failure (pmol/L)
Bayer BNP, Abbott AxSYM BNP, Biosite Triage BNP and Roche proBNP package insert information

Comparing BNP & NT-proBNP

Pulmonary Capillary Wedge Pressure and Natriuretic peptides

% Baseline Value vs. drug administration time (min)

Legend:
- PCWP
- BNP
- NT-ProBNP

"When comparing relative changes with baseline measurements, BNP concentrations significantly decreased within 60 min, whereas NT-proBNP showed a significant decrease not earlier than 24 h after initiation of levosimendan infusion.
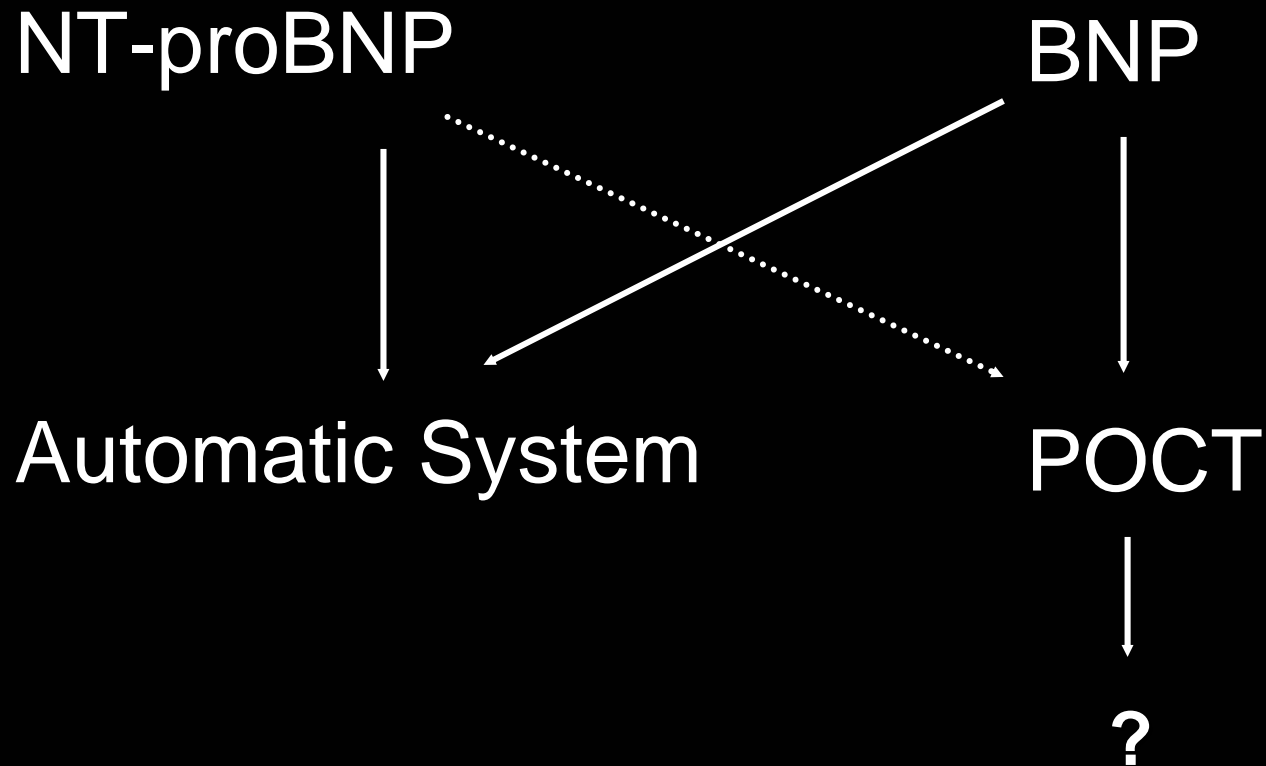
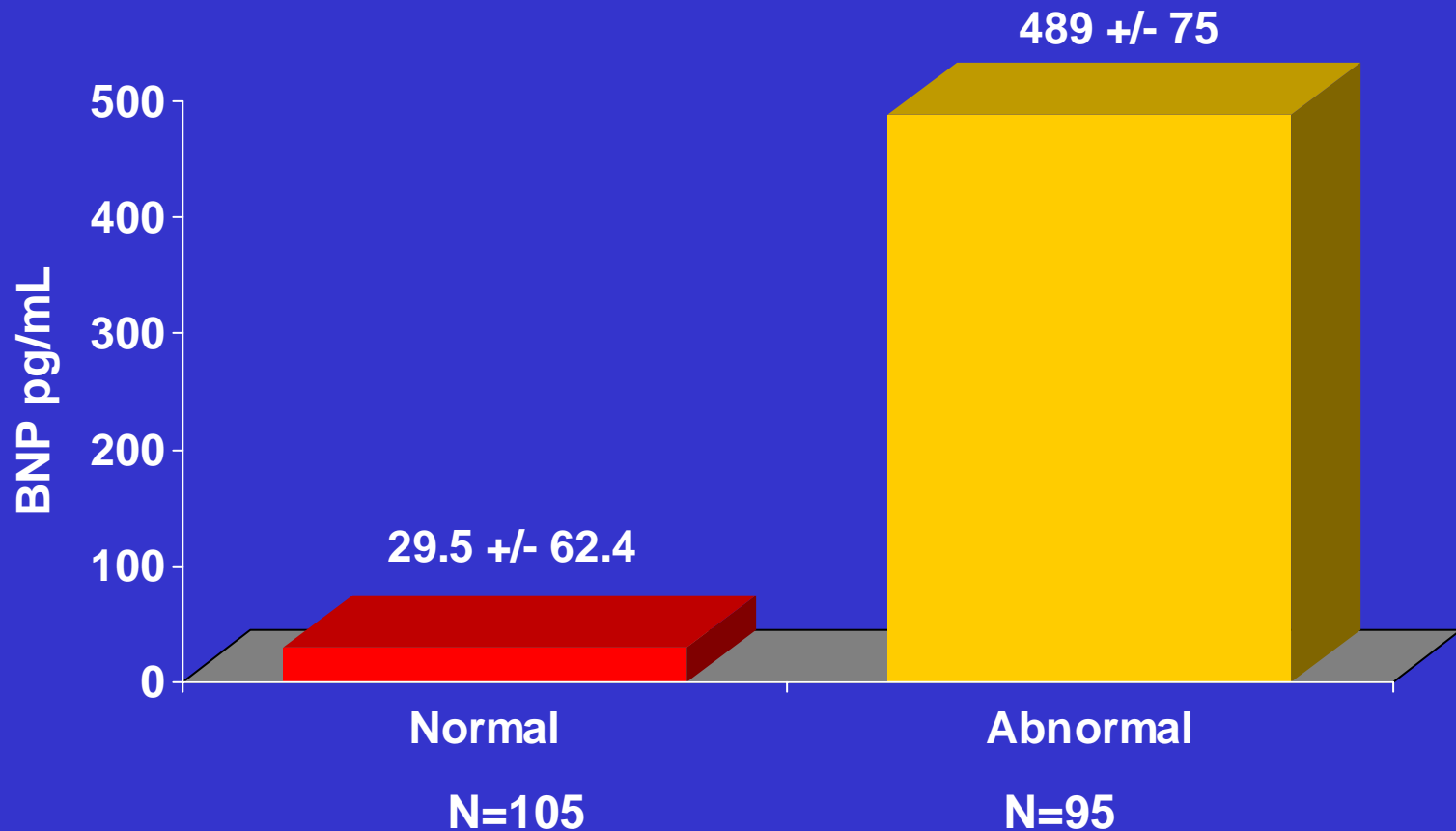Gegenhuber, *Clinical Chemistry* 50, No. 2, 2004, 454-456

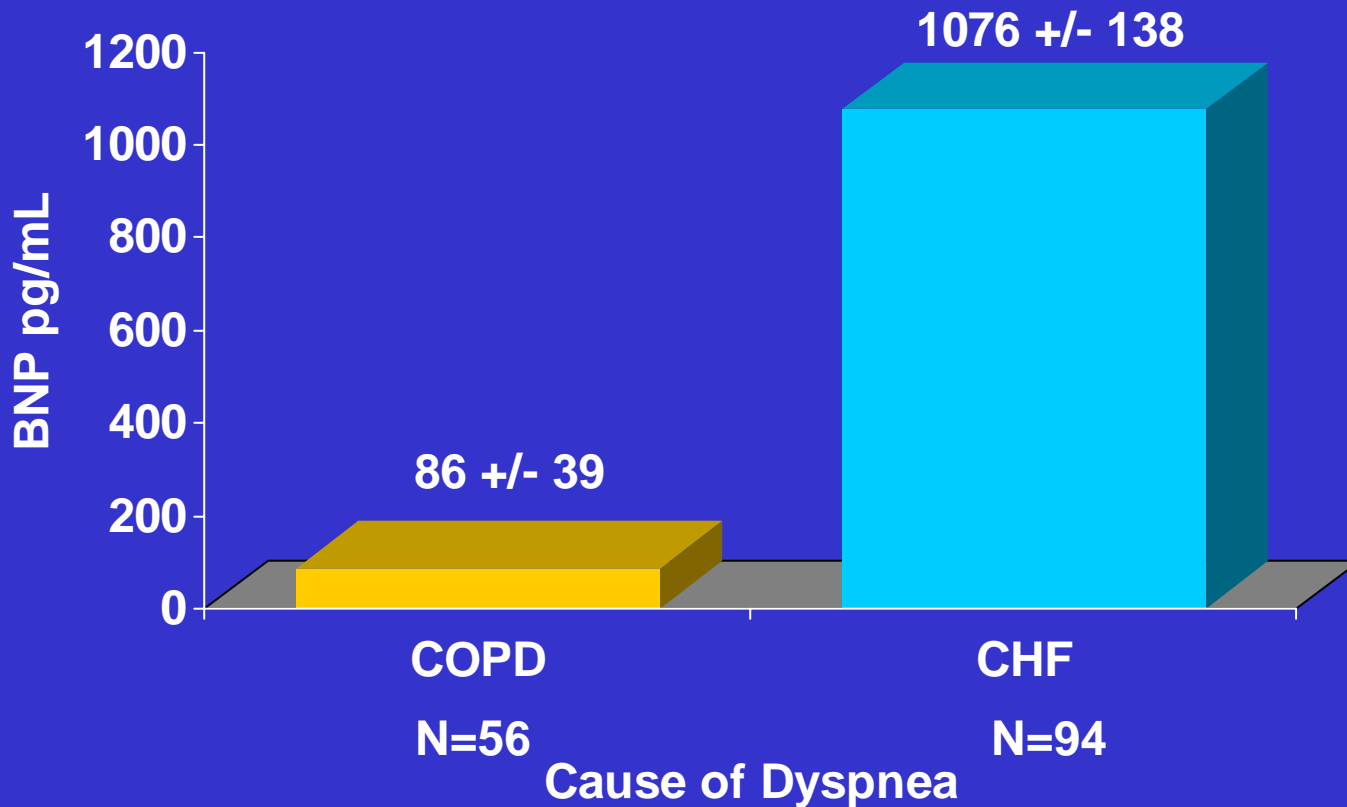# Diagnostic & prognostic value using a BNP or NT-proBNP

- **Introduction & measurement issue**
- **Emergency room or acute clinical setting**
- **Chronic stable HF or out-patient clinic**
- **Post myocardial infarction**
- **The general population**
- **Prognosis**
- **Treatment monitoring**
- **Conclusion**

BNP Levels with Dyspnea

BNP pg/mL (y-axis)

489 +/- 75 — Abnormal (N=95)

29.5 +/- 62.4 — Normal (N=105)

Maisel AS et al, JACC. 2003::2010

BNP Levels with Dyspnea
Secondary to CHF or COPD

COPD N=56 — 86 +/- 39

CHF N=94 — 1076 +/- 138

BNP pg/mL vs Cause of Dyspnea

Dao, Q., Maisel, A. et al. *J. American College of Cardiology*, Vol 37, No. 2, 2001

BNP Levels with Dyspnea
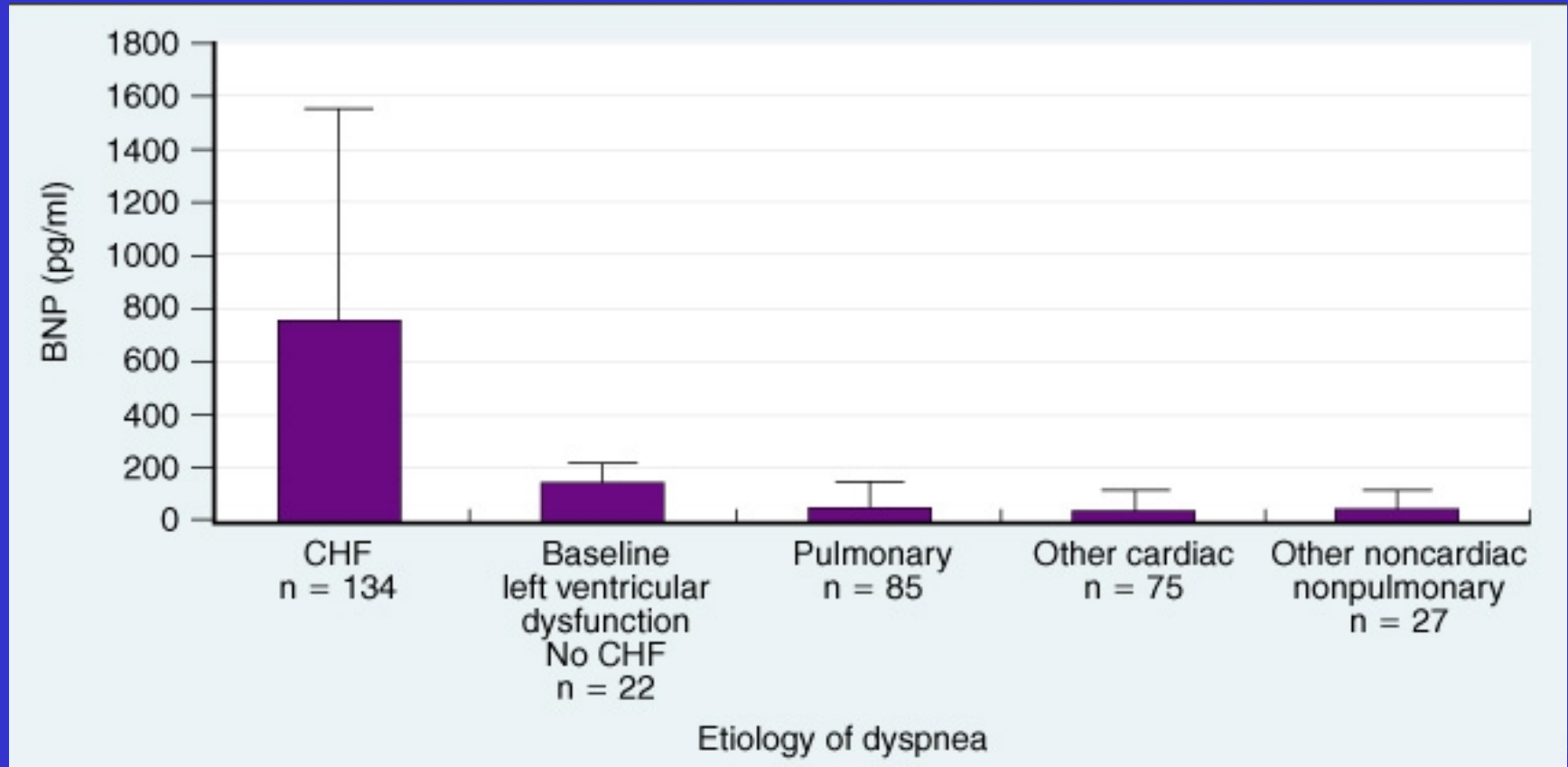
BNP Concentration and Degree of CHF Severity

BNP (pg/ml)

2500
2000
1500
1000
500
0

Mild
N = 27

186 ± 22

Moderate
N = 34

791 ± 165

Severe
N = 36

2013 ± 266

Maisel AS et al, JACC. 2003::2010.
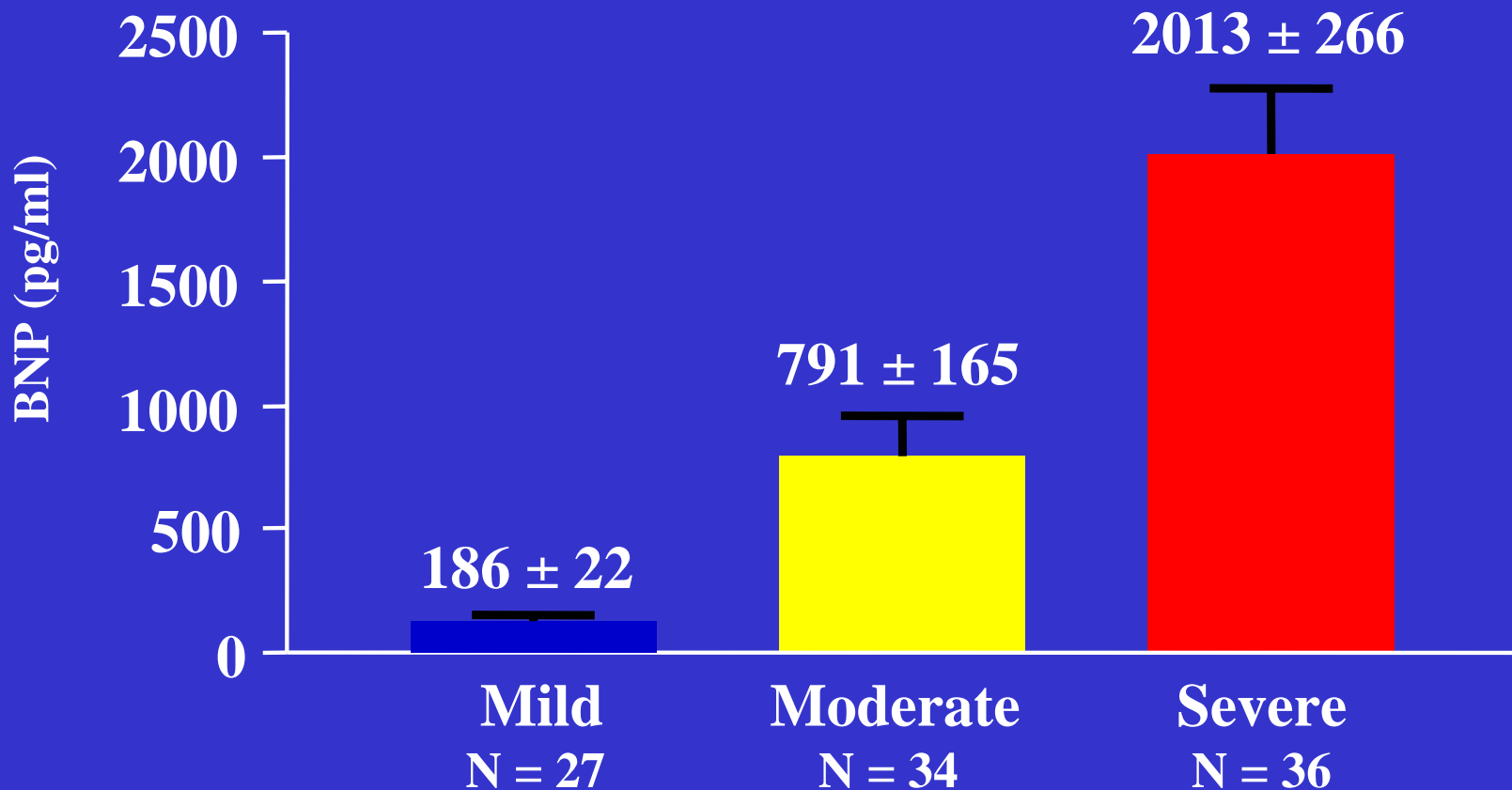
BNP as a CHF marker
Diastolic dysfunction (n=904)

Yoo et al . Kor Circ J . 2004
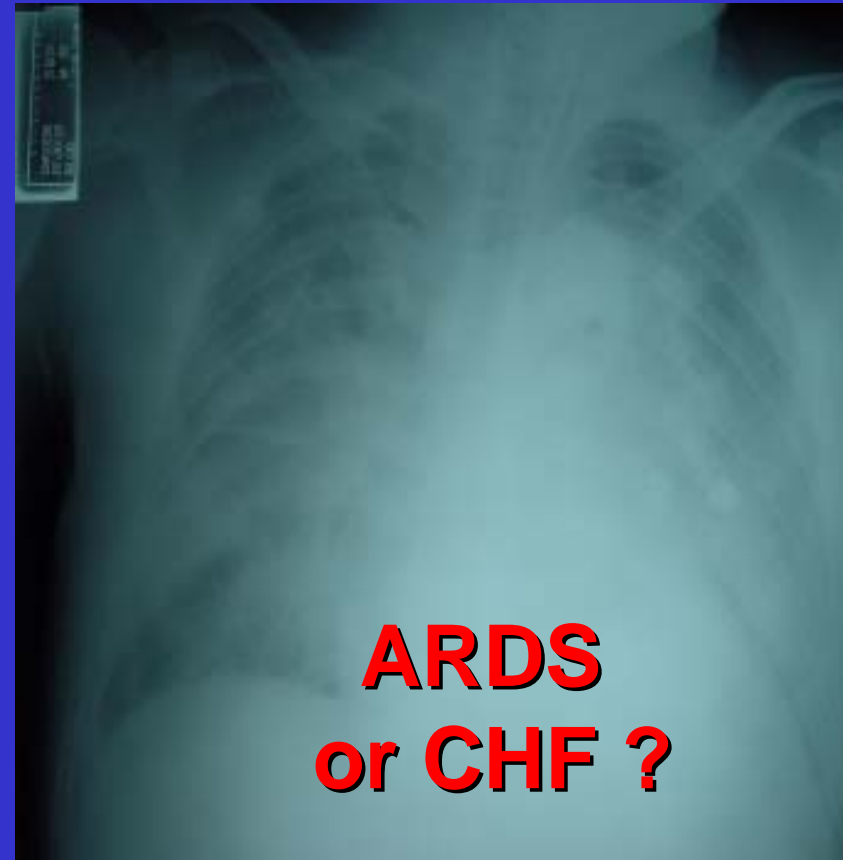
Diagnosis of Acute Clinical Setting

SOB or Dyspnea

↓

- Acute or Severe Sx.
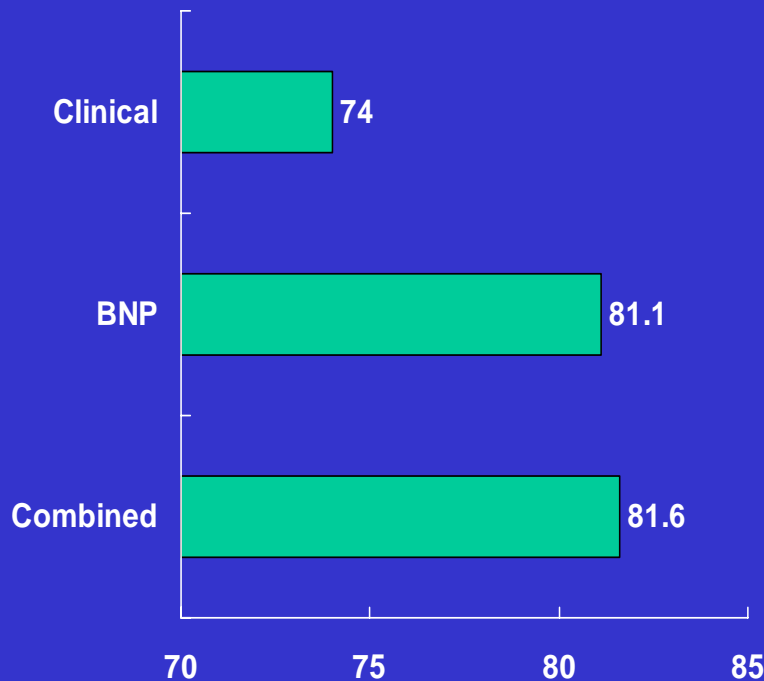- DDx lung vs. heart
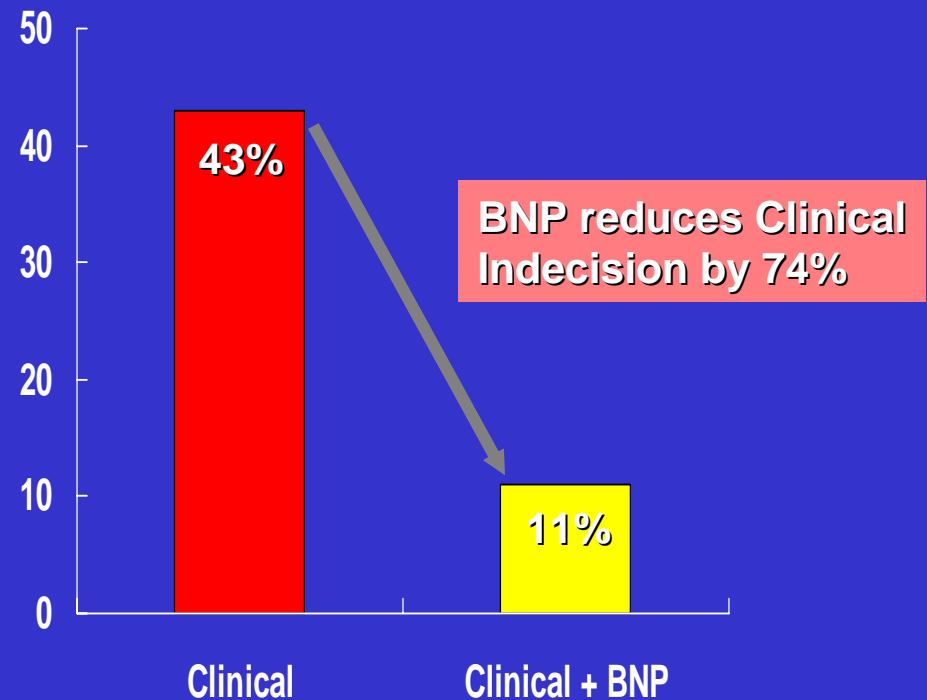- Inaccessible Echo.

↓

Urgent Decision

ARDS
or CHF ?

BNP : 2800 pg/mL

BNP vs Clinical Judgment :
Comparative Accuracy

BNP multinational investigator

Accuracy (%)

Clinical: 74
BNP: 81.1
Combined: 81.6

Clarification of Dx & BNP

Clinical: 43%
Clinical + BNP: 11%

BNP reduces Clinical Indecision by 74%

Diagnostic Value of BNP & x—ray in Patients with Acute Dyspnea

Variable	Odds Ratio	(95% Confidence Interval)	P Value
History of myocardial Infarction	2.5	(1.5-4.2)	<0.001
History of chronic heart failure	4.3	(2.7-6.9)	<0.001
Rales	1.6	(1.0-2.6)	0.04
Lonser extremity edema	2.3	(1.5-3.6)	<0.001
Cardiomegily	2.3	(1.4-3.7)	0.001
Cephalization	6.4	(3.3-12.5)	<0.001
Interstitial edema	7.0	(2.9-17.0)	<0.001
Abnormal electrocardiogram	1.9	(1.2-3.0)	0.007
BNP level ≥100 pg/mL	12.3	(7.4-20.4)	<0.001

Diagnostic flow of diagnosis for SHF

34 pg/ml 100 pg/ml 274 pg/ml

possible maximal range (mean + 2SD)

possible minimal range (mean + 2SD)

31.5±24.0

534.2±224.0

Yoo BS, et al. *European journal of Heart Failure.* 2004;57:241.

Diagnostic flow of diagnosis

BNP level

Low level
< 34 pg/ml

Intermediate

High Level
> 274 pg/ml

in cases withinadequate range of BNP
for the LV functon : Consider Gray Zone

Exclude SHF

Confirm SHF
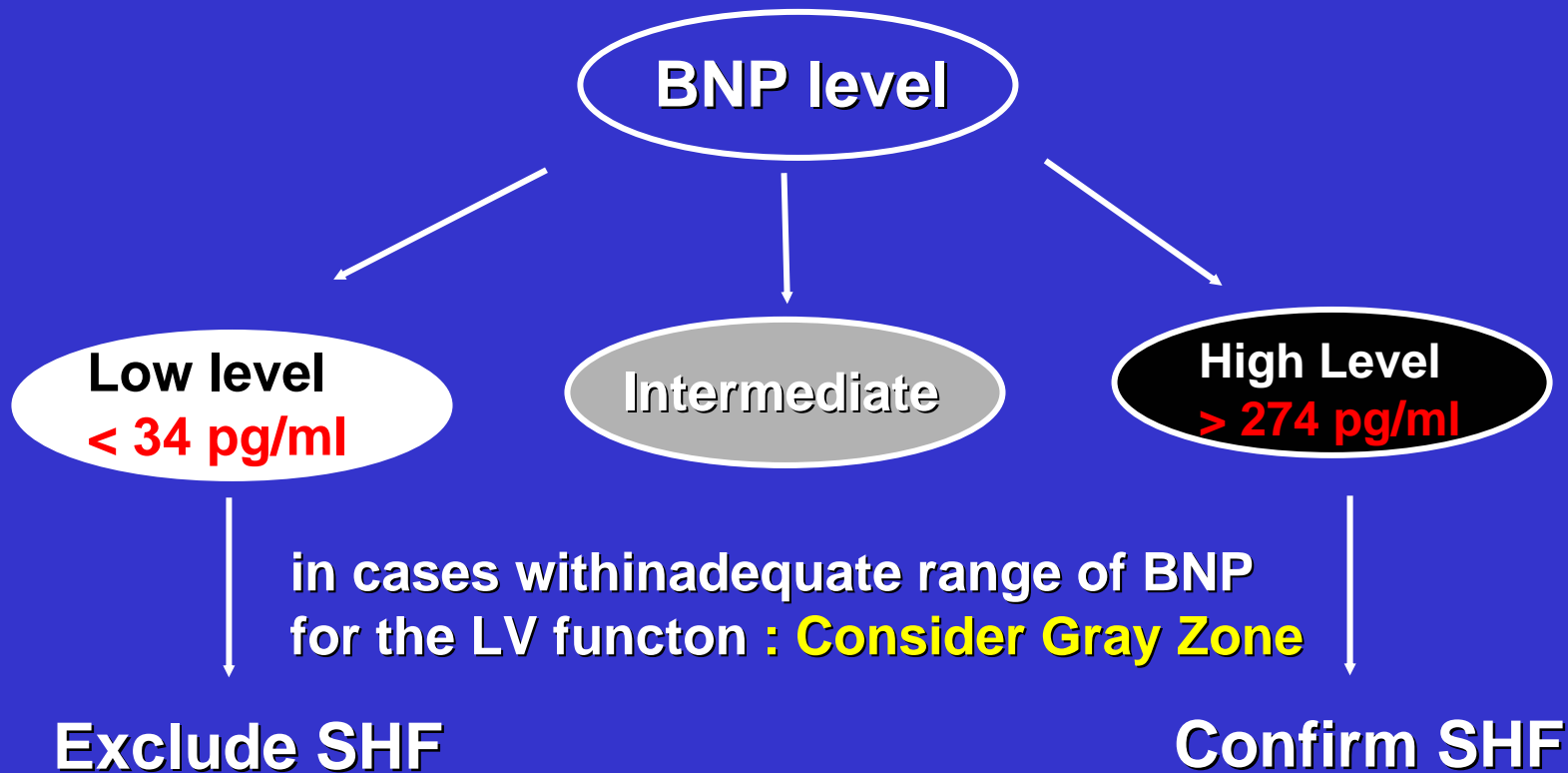
In gray zone, plasma BNP assay showed never be used
as "Stand – Alone Test" but always in the clinical assessment.

Yoo BS, et al. *European journal of Heart Failure.* 2004;57:241.

Discrepant Value of BNP
in diagnosis for CHF

Factors that can account for high BNP levels and no CHF

    Age

    Sex

    Renal failure

    Myocardial infarction

    Lung disease with right−sided failure

    Acute, large pulmonary embolism

Factors that can account for low BNP levels with CHF

    Obese

    Flash pulmonary edema

    CHF secondary to causes upstream from left ventricle

        Acute mitral regurgitation

        Mitral stenosis

        Atrial myxoma

   Stable NYHA class I patients with low ejection fractions.

Tabbibizar/Maisel Curr Opinion Card 2002;340

Factors that can account for high BNP levels and no CHF

- **Age**
- **Renal failure**
- **AMI**
- **Acute coronary syndrome**
- **Lung disease with right-sided failure**
- **Acute, large pulmonary embolism**

Right-sided CHF

- **Cor Pulmonale: 200-500 pg/ml**
- **Primary pulmonary hypertension: 300-500 pg/mL**
- **Acute pulmonary embolism: 150-500 pg/mL**

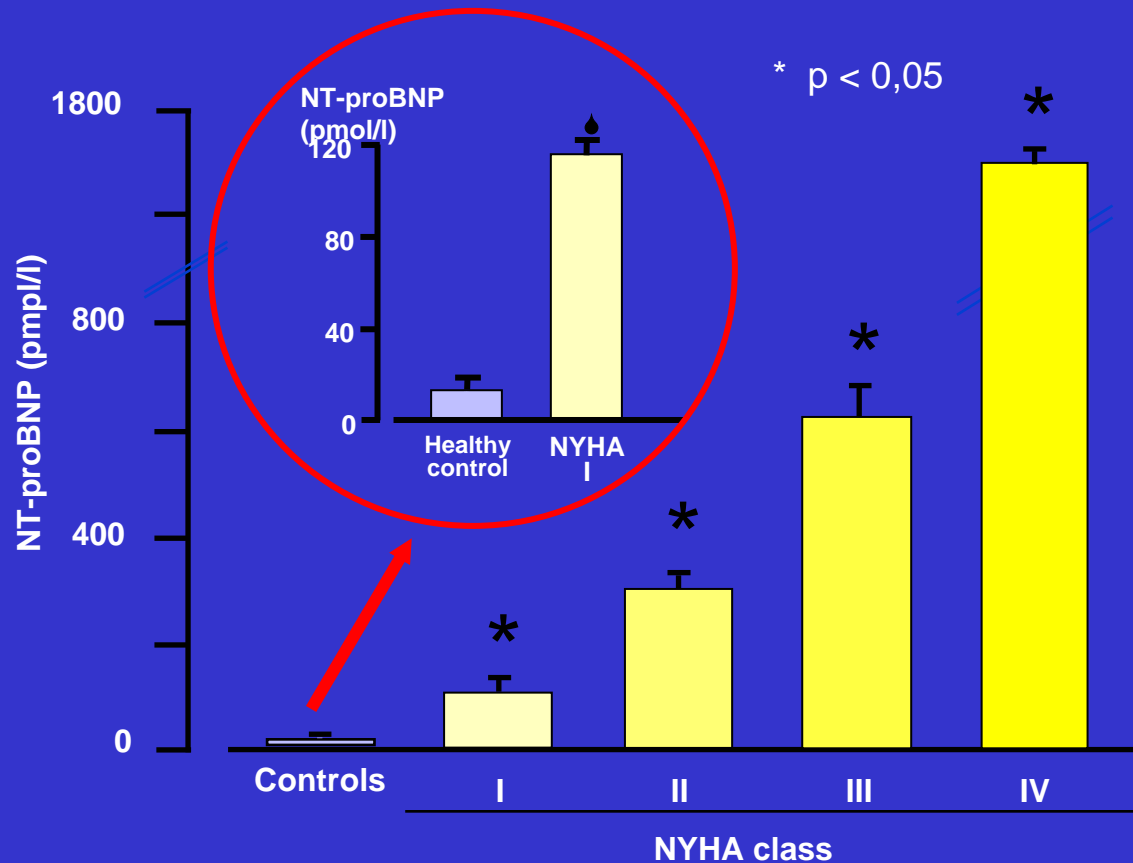# Diagnostic & prognostic value using a BNP or NT-proBNP

- **Introduction & measurement issue**
- **Emergency room or acute clinical setting**
- **Chronic stable HF or out-patient clinic**
- **Post myocardial infarction**
- **The general population**
- **Prognosis**
- **Treatment monitoring**
- **Conclusion**
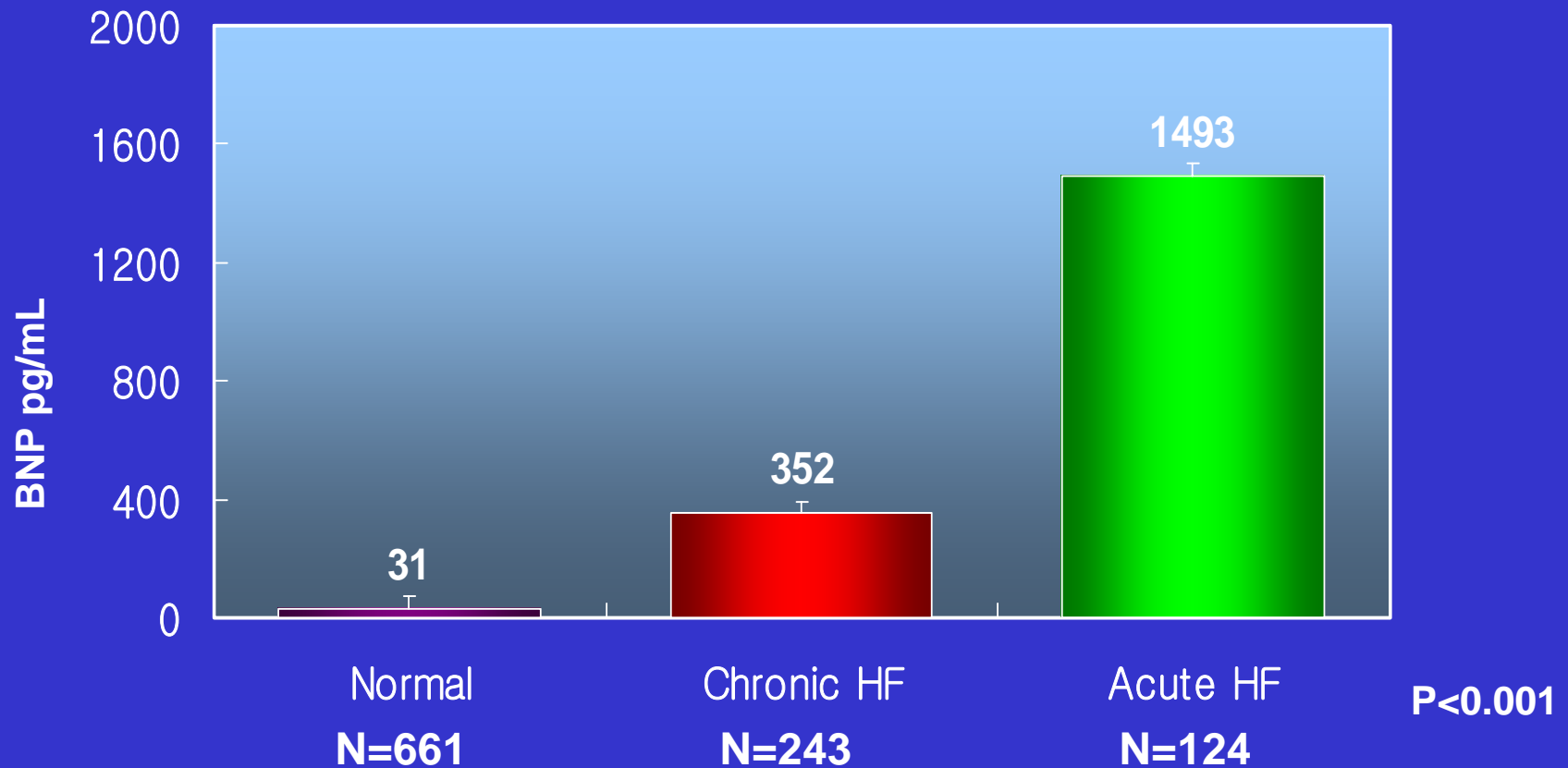
Out-patients Clinics:
NT-proBNP

NT-proBNP correlates with the severity of CHF and can identify asymptomatic patients

Haass et al., EJC, 2002

Out-patients Clinics:
BNP levels in ambulatory patients with established chronic symptomatic SHF

Younger, Female, Nonischemic, Better-preserved cardiac , renal function, and less atrial fibrillation

21%

■ Normal
■ 100 pg/ml 이상

579±452

P<0.01

267±378

Non-ischemic   Ischemic
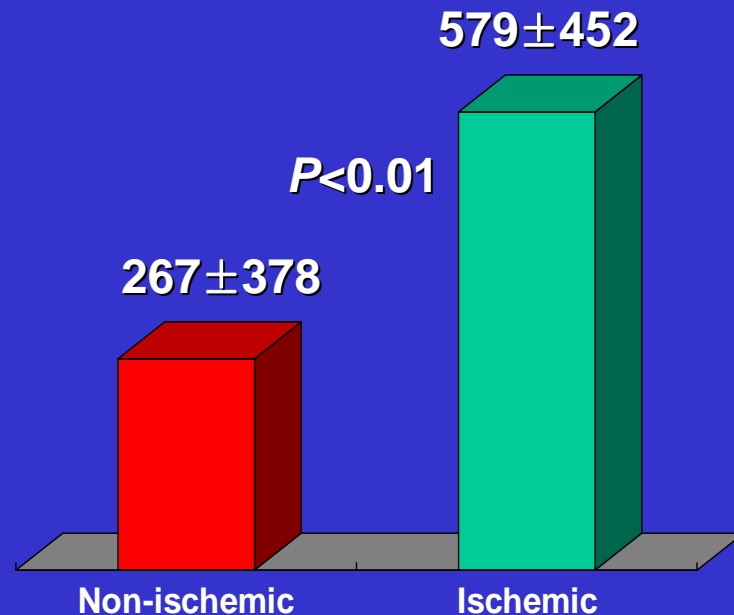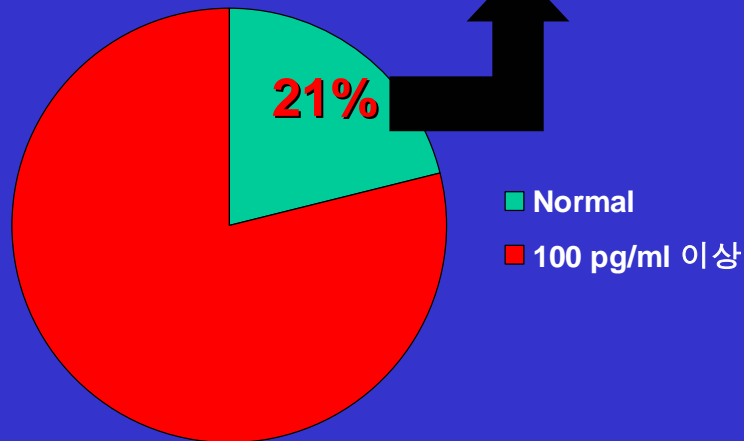
In a subset of symptomatic patients, plasma BNP levels are below what would be considered "diagnostic".

Tang WH Circulation. 2003,16:2964

Diagnostic & prognostic value using a BNP or NT-proBNP

- **Introduction & measurement issue**
- **Emergency room or acute clinical setting**
- **Chronic stable HF or out-patient clinic**
- **Post myocardial infarction**
- **The general population**
- **Prognosis**
- **Treatment monitoring**
- **Conclusion**

Stage of HF
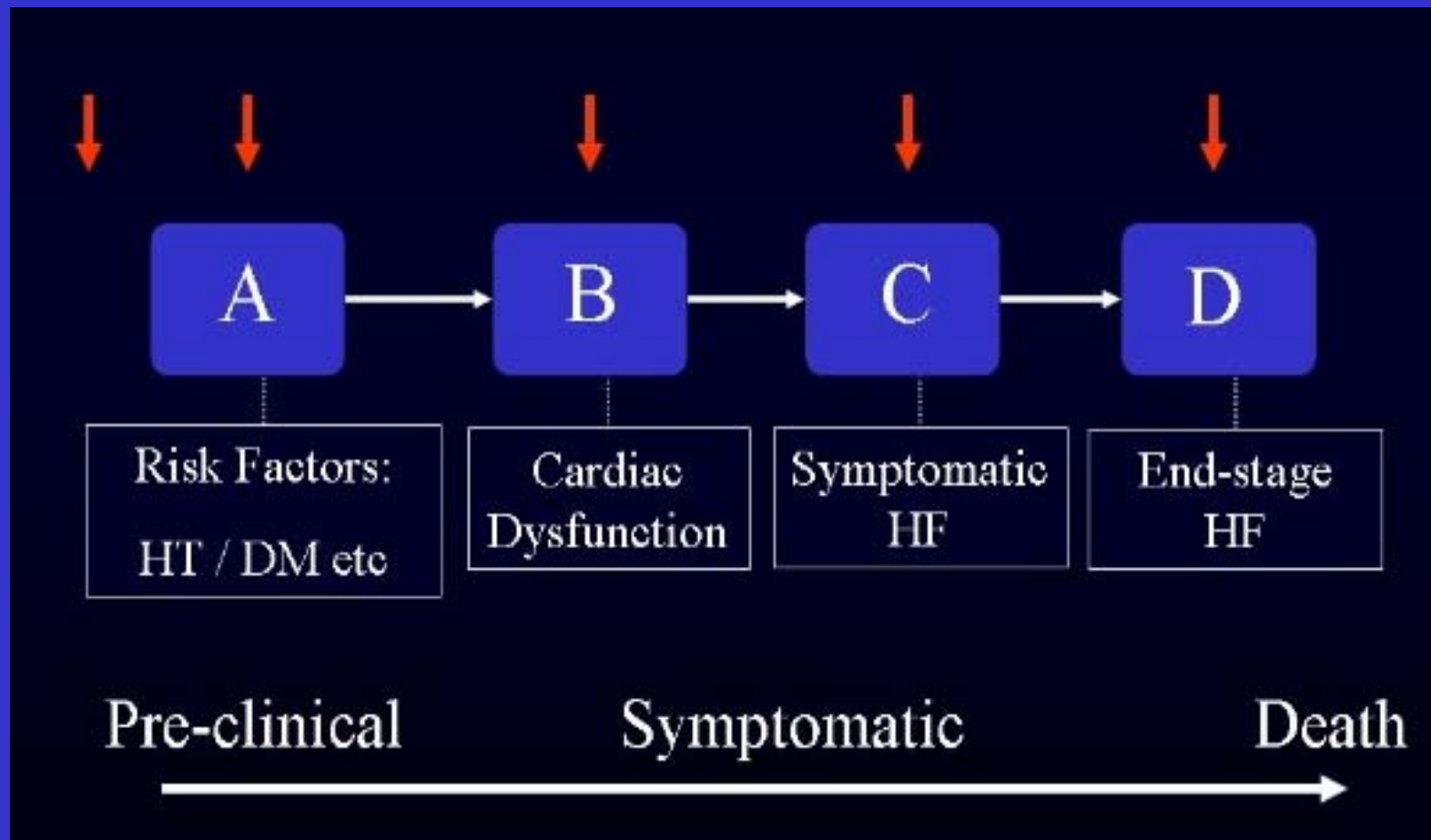
# Pre-Stage A : Screening for left ventricular systolic dysfunction

- **Community-wide screening for LVSD :** limiting the enthusiasm for a screening program targeting the general population due to low prevalence, especially true for women.
- **Useful screening test :** Men with high-risk individuals in whom other clinical indications for Echo.

Plasma BNP Levels and the Risk of Cardiovascular Events and Death
## in apparently asymptomatic persons

### Framingham offspring prospective study
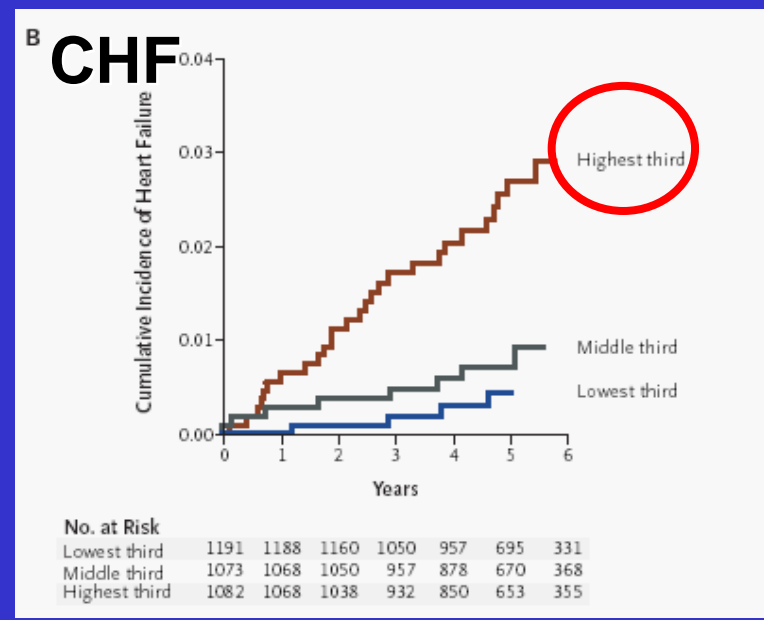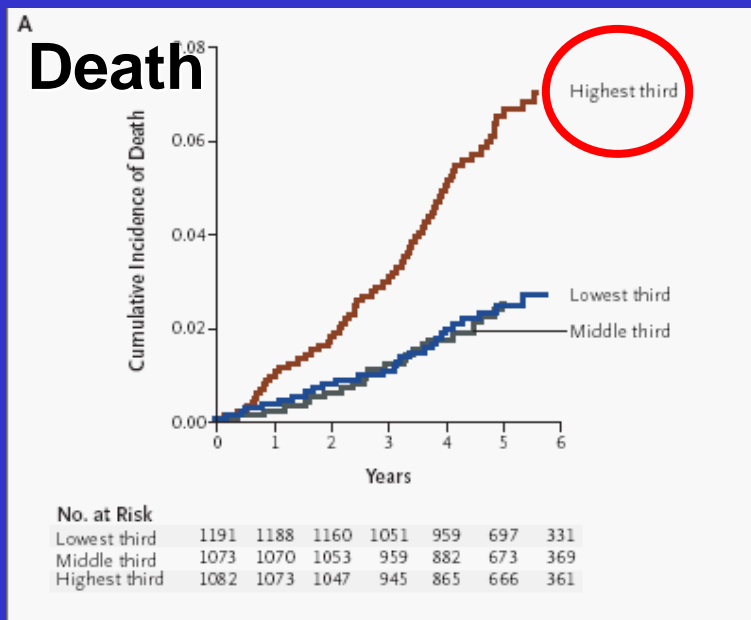
BNP level : most powerful predictor

Stage A : Risk Factor, LVH

- **To test a hypothesis that elevation of the plasma level of BNP is one of the characteristics of patients with diastolic HF independent LVH.**

- **An elevation of BNP may be a hallmark of patients with or at risk of DHF among subjects with preserved systolic function independent of LV H.**

J Am Coll Cardiol 2004;43:55– 60

Stage A : Risk Factor, DM

Epshteyn V, Diabetes Care. 2003:2081
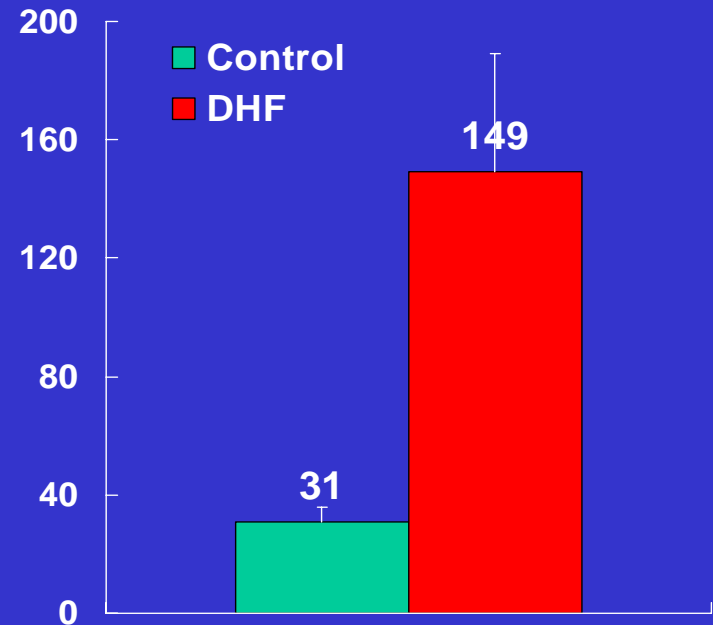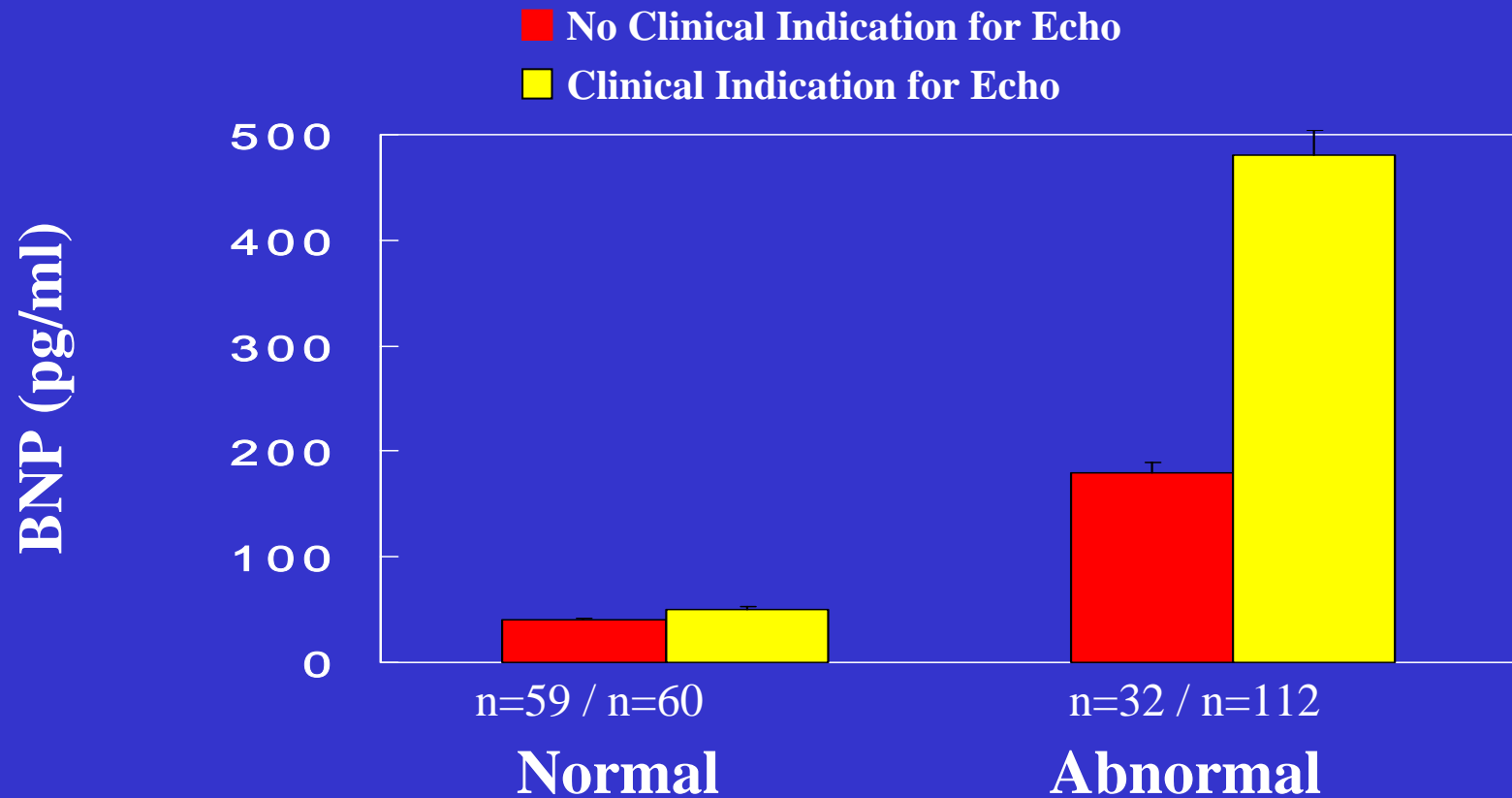
Stage B: Pre-clinical HF, AMI

Predictable value for CHF

	Sensitivity	Specificity	PPV	NPV
Clinical HF	63	70	45	82
Radiologic HF	63	48	48	76
Both	73	42	34	81
NT-proBNP >240	85	56	41	91

Stage B: Pre-clinical HF, AMI

Richards et al, Circulation 2003:107:2786

Stage B: Pre-clinical HF, AMI

P<0.001

Event Free Survival %

Heart Failure &/or Death

Group						Events	%
↓ n-bnp, ↑ LVEF	296	245	196	137	53	(16)	(5)
↑ n-bnp, ↑ LVEF	193	144	116	63	29	(38)	(20)
↓ n-bnp, ↓ LVEF	36	30	23	15	3	(6)	(17)
↑ n-bnp, ↓ LVEF	141	87	58	34	13	(66)	(47)

Days

Richards et al, Circulation 2003:107:2786

Stage C : BNP and Prognosis in Symptomatic HF

Tsutamoto T, Circulation, 1997:509

Stage C: BNP and Prognosis in Symptomatic HF

Stage C: BNP and Prognosis in Symptomatic HF
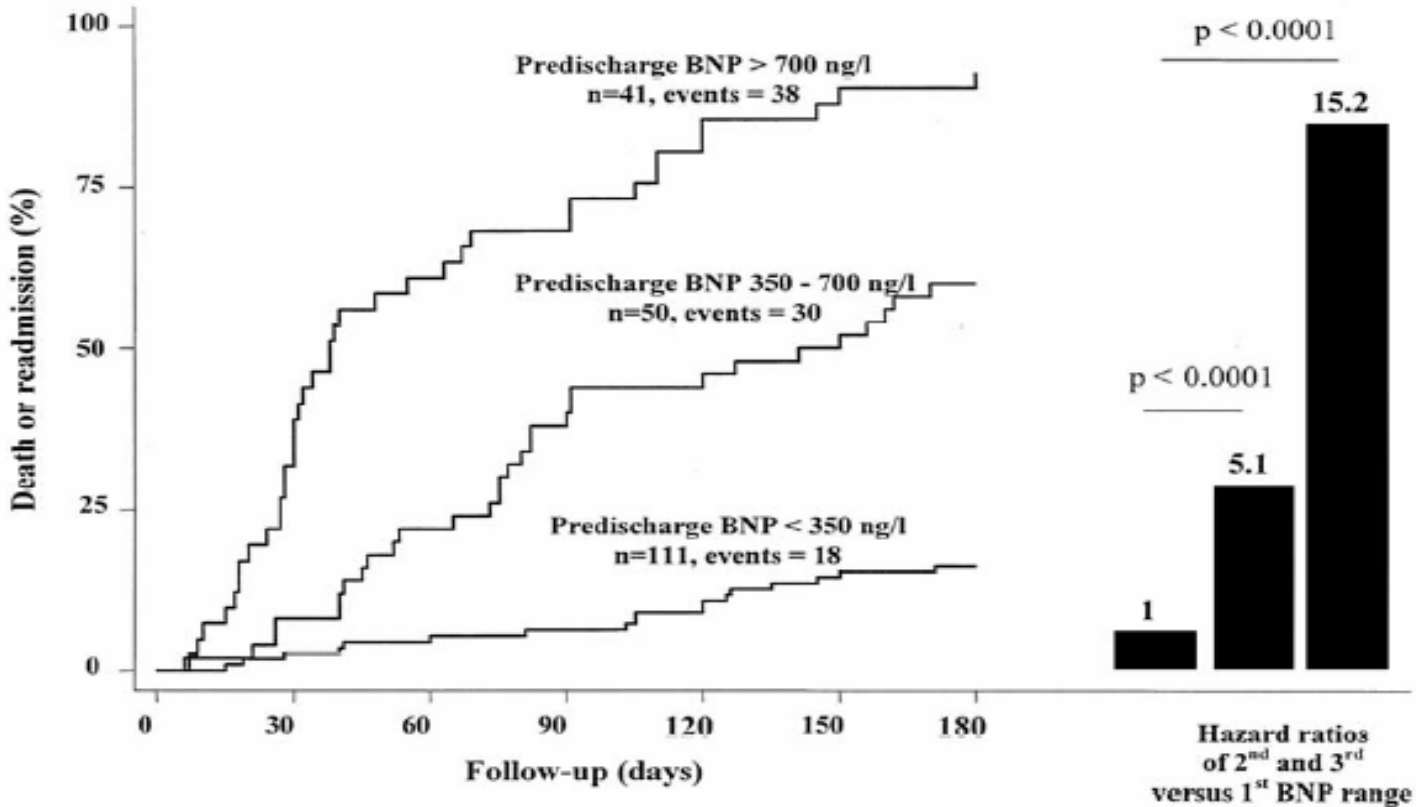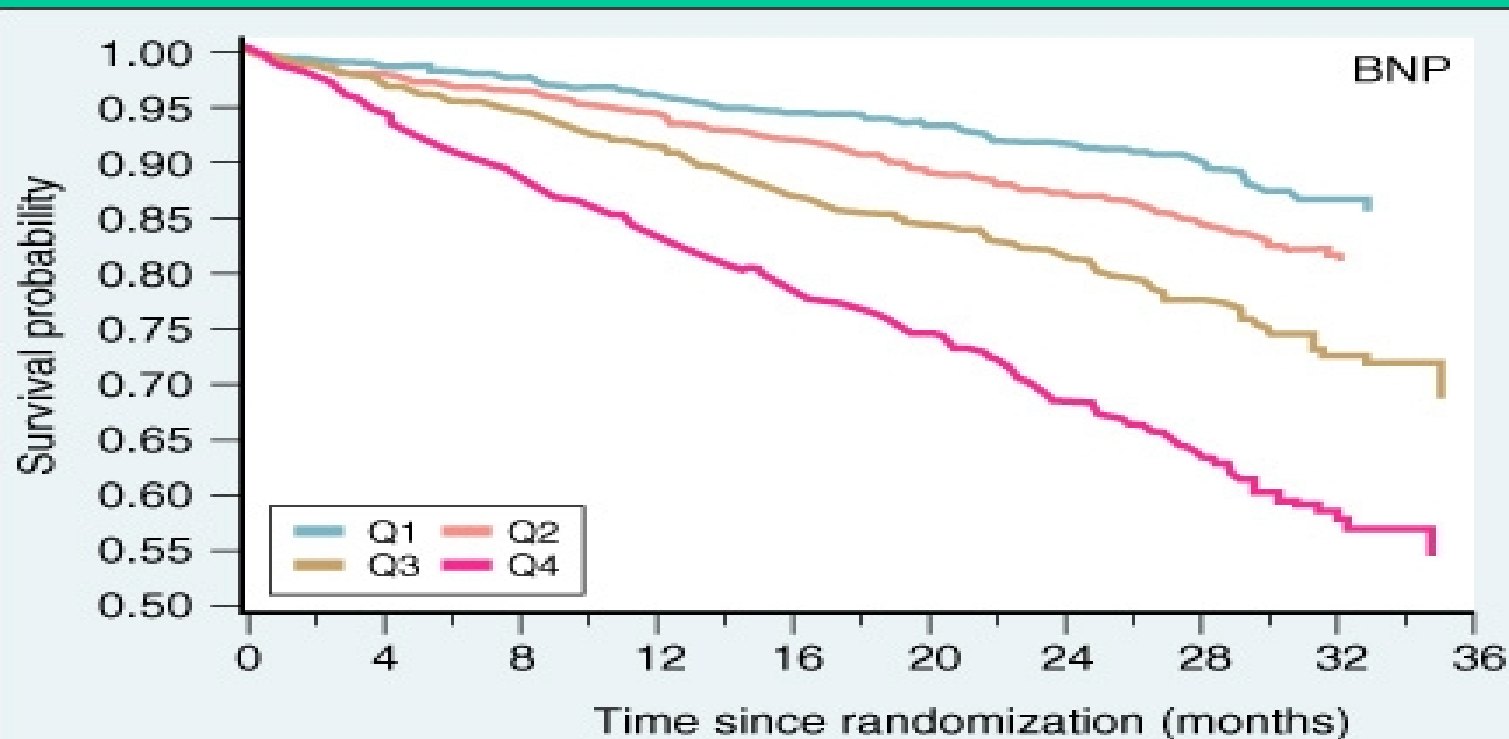
Stage D : BNP and Prognosis in Advanced HF
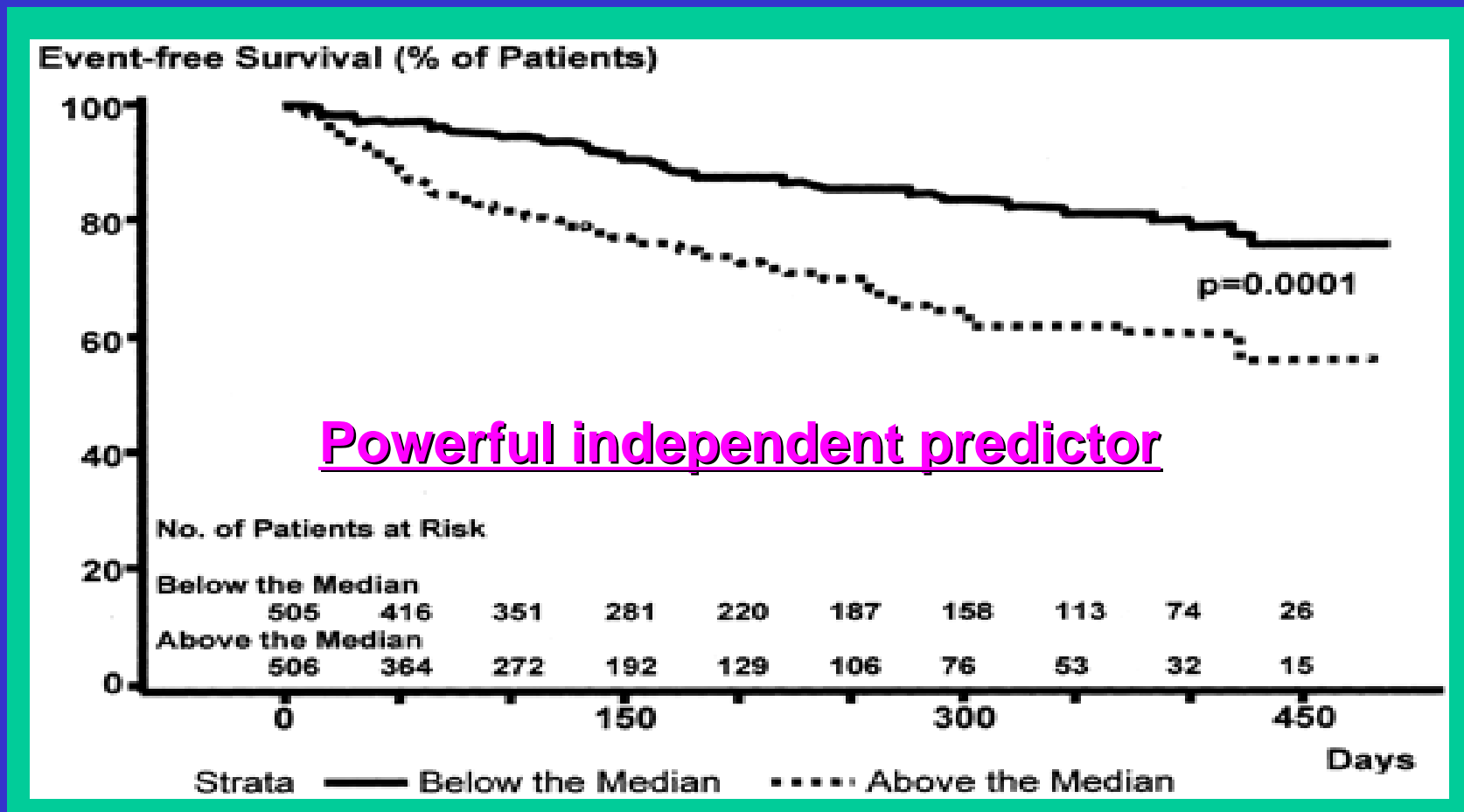
COPERNICUS trial , Circulation 2004:110:1789

Diagnostic & prognostic value using a BNP or NT-proBNP

- **Introduction & measurement issue**
- **Emergency room or acute clinical setting**
- **Chronic stable HF or out-patient clinic**
- **Post myocardial infarction**
- **The general population**
- **Prognosis**
- **Treatment monitoring**
- **Conclusion**

BNP as a biochemical PCWP

Changes in BNP and PAW* Levels

N = 15

Legend: PAW, BNP

X-axis: Hours (baseline, 4, 8, 12, 16, 20, 24)
Left Y-axis: PAW (mm Hg) (15–33)
Right Y-axis: BNP (pg/ml) (600–1300)

Maisel, A., *J Cardiac Failure,*, 2001 :124
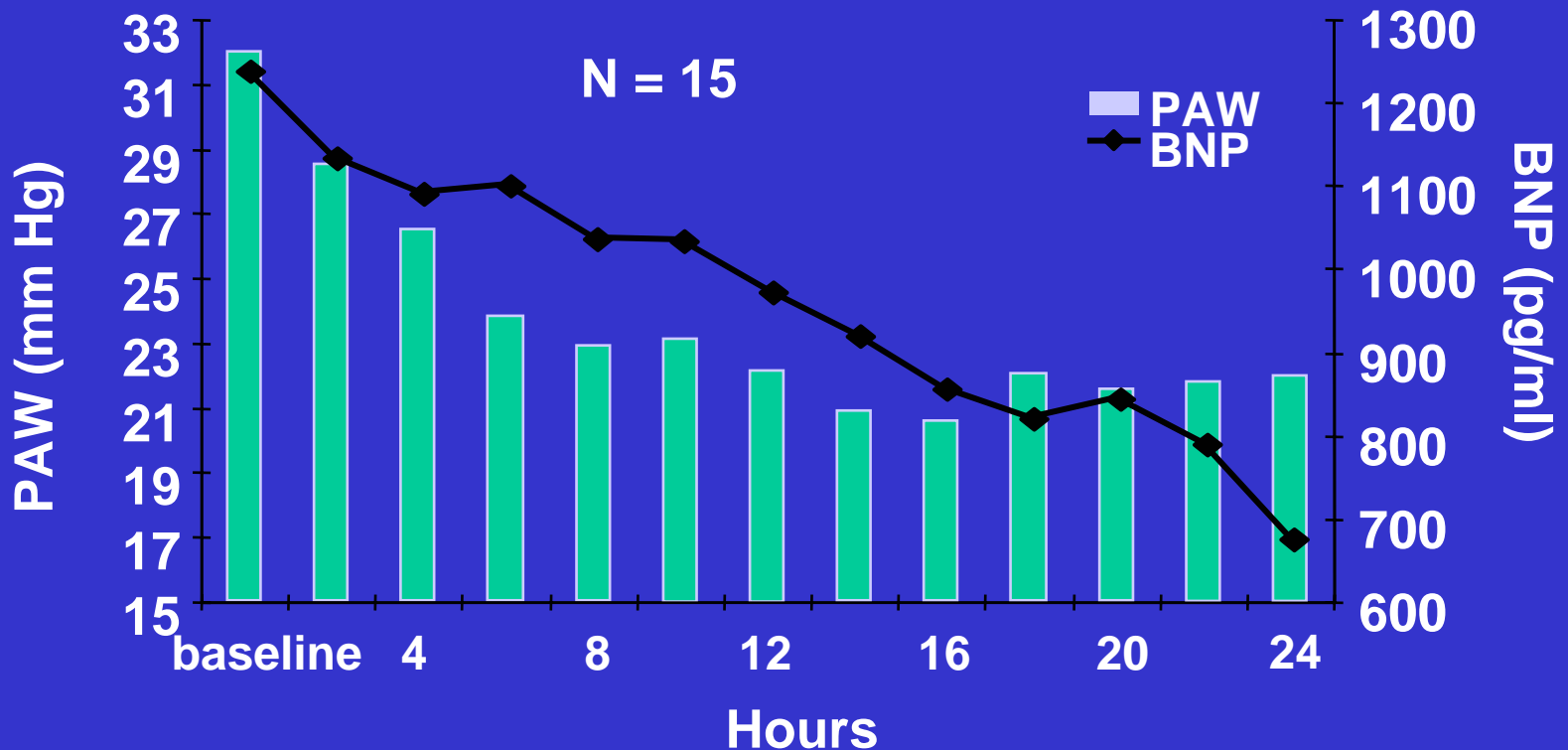
Percent reduction in NT-proBNP according to the clinical course

Lopez L. et al. EJHF 2004:301

Percent reduction in BNP levels according to the clinical course

Yoo BS et al. *Journal of Cardiac Failure.* 2004:10:51
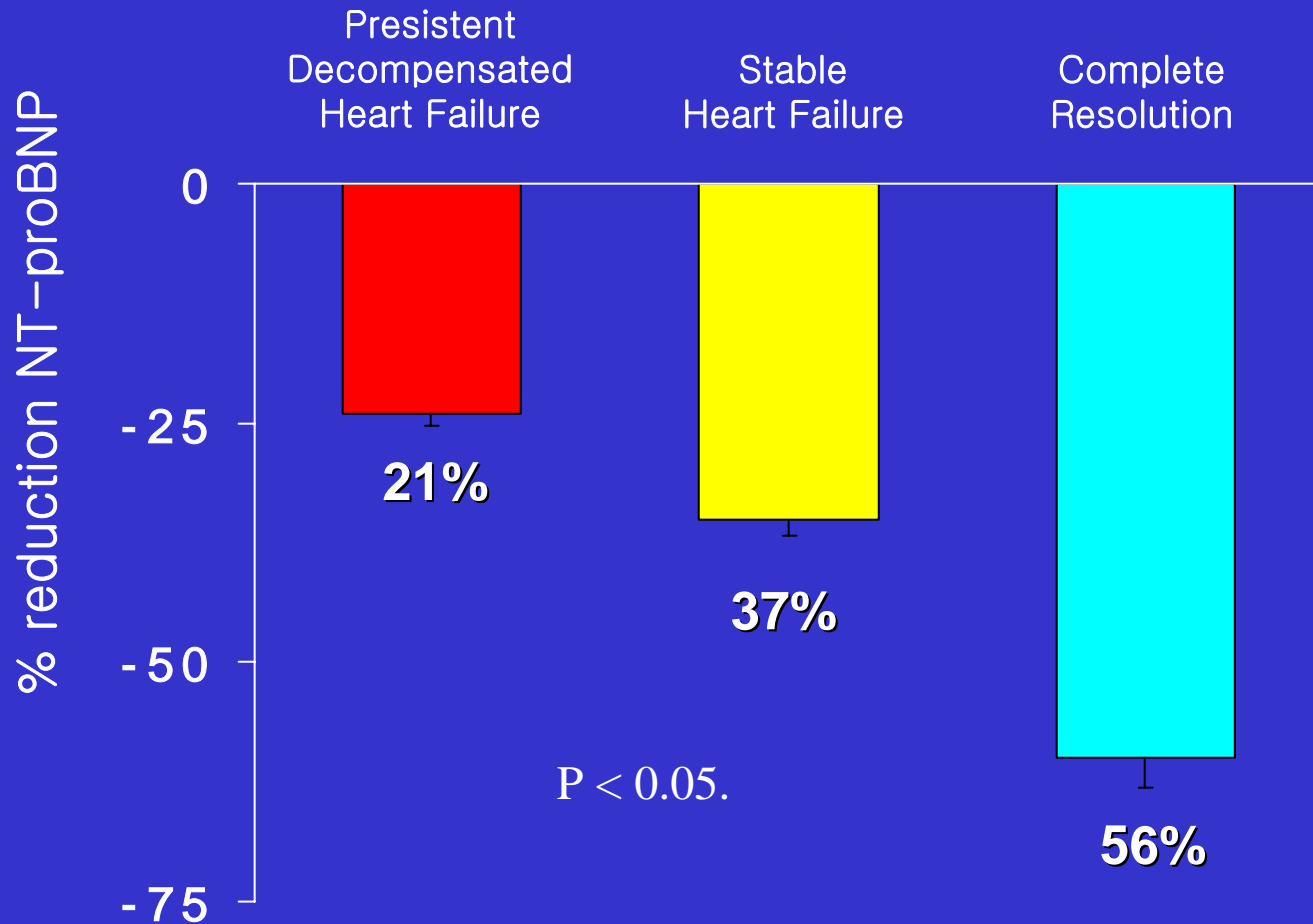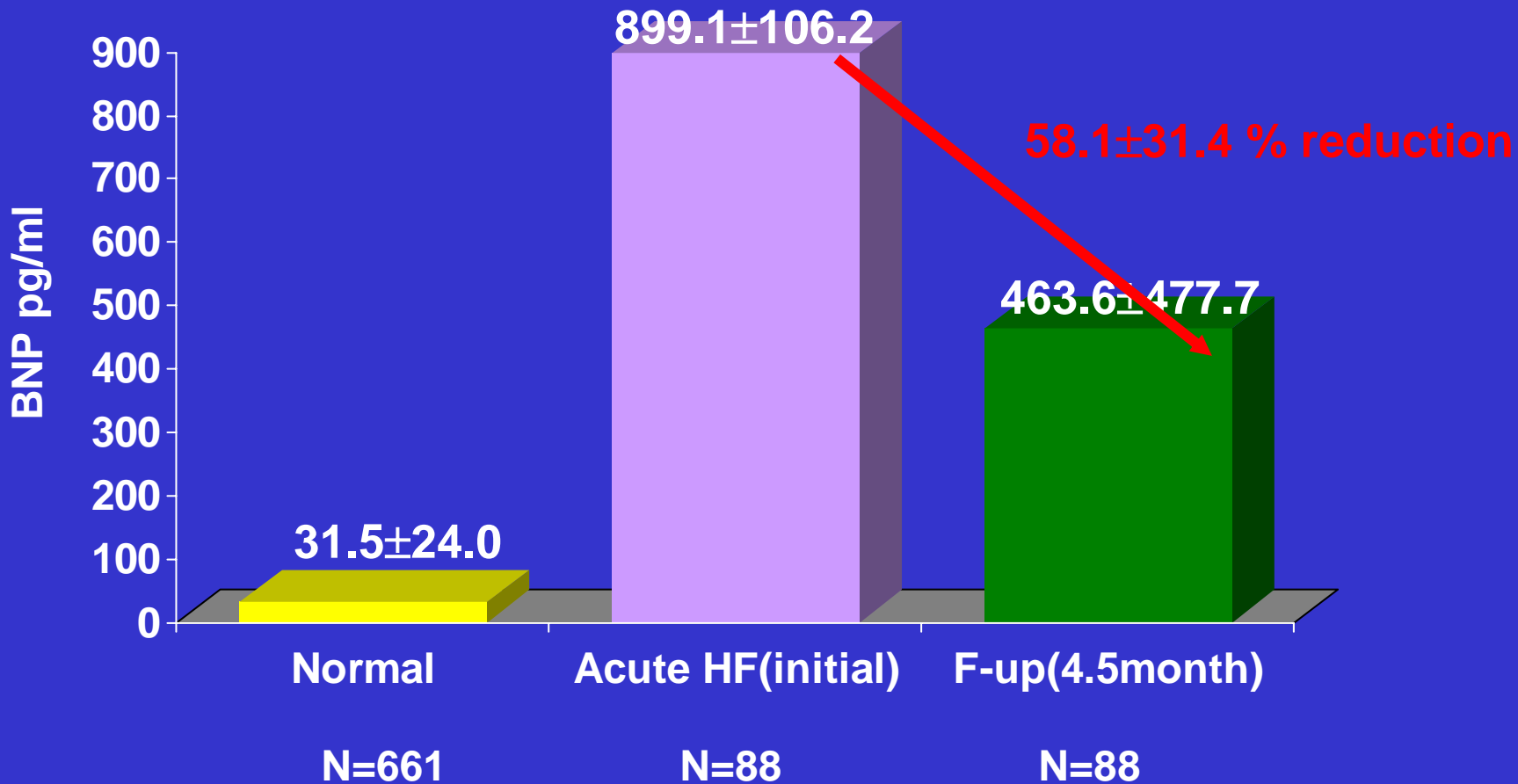
Percent reduction in BNP levels according to the clinical course
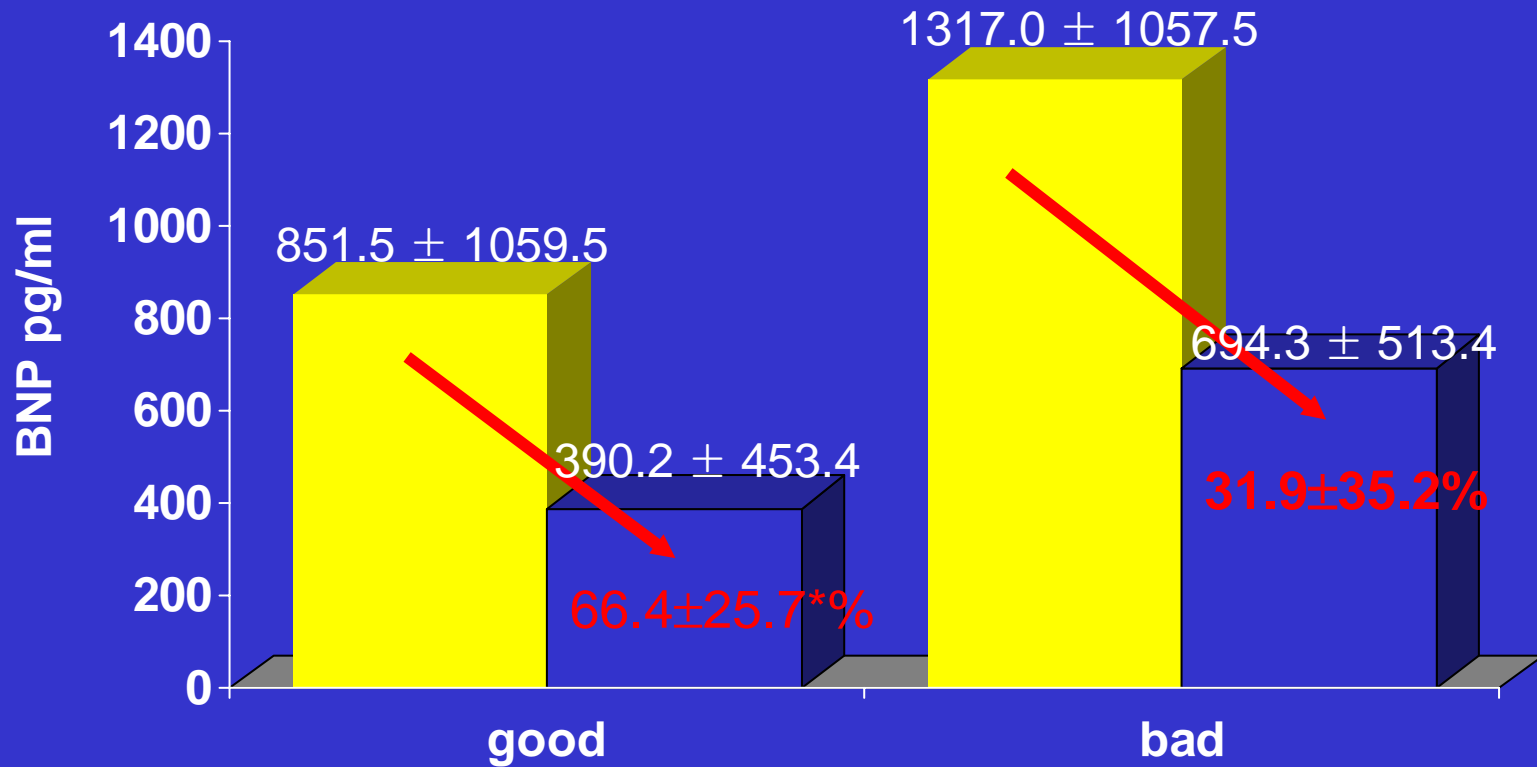
*:p<0.05, BNP reduction ratio

Yoo BS et al. *Journal of Cardiac Failure.* 2004:10:51

BNP : Target to Treatment or monitoring

BNP : 2800 pg/mL

BNP : 560 pg/mL
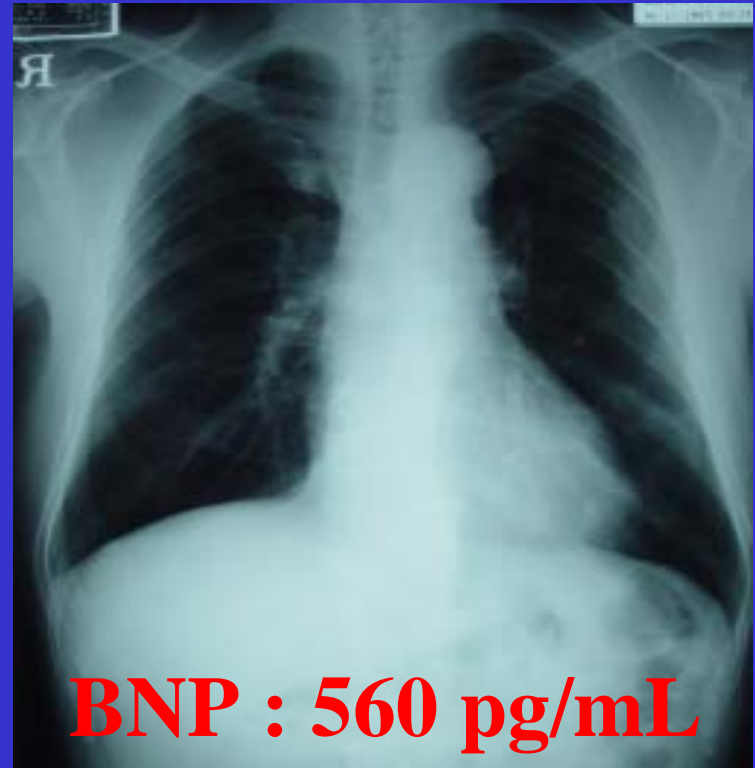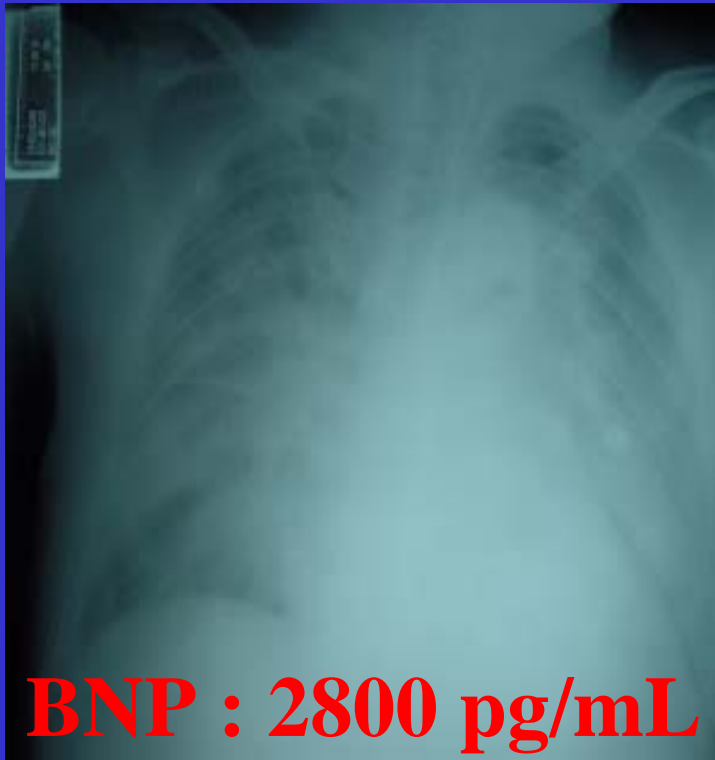
Hypertension ----------------- Blood Pressure
Hypercholesterolemia ------ LDL- chol
DM ------------------------------- Blood sugar, HbA1c

Conclusions :

Is BNP test an ideal chemical marker for diagnosis of CHF ?

Clinical Applications of Serum (Tumor) Markers

1. 암의 조기진단을 위한 선별검사**(screening test)**로 활용한다**.**

2. 암의 진단에 활용한다 **(**감별 진단**).**

3. 암의 예후인자로 활용한다**.**

4. 암 치료의 효과 판정**(monitoring therapy)**에 활용한다**.**

5. 암 치료 후 재발의 조기진단을 위한 추적검사로 활용한다**.**

CHF   = Medical malignant disease

Conclusions :

Ready for Prime time? (BNP)

"Cardiologists may now have a tool with which to determine whether a patient has CHF and to measure its severity, much as physicians routinely measure sCr in patients with renal disease and perform LFT in patients with liver disorders."

Baughman KL, NEJM 2002:347:158-159

Conclusions :

BNP or NT-proBNP ≈ Marker for Cardiac Health

Predisposition screening	Targeted screening	Diagnosis	Prognosis	Treatment stratification	Treatment/ recurrence monitoring

Providing actionable health information

Prevention	Early Diagnosis	Differential Dx	Management strategy	Differential treatment	Treatment optimization
Community based screening	HTN, DM, After AMI ChemoTX	Patients with dyspnea	Patients with LVD, Post MI patients	Carvedilol Diuretics ACEI,	Treatment Adjustment optimization

경청해 주셔서 감사 드립니다.

Comparing BNP and NT-proBNP

- **Measurement of Natrecor and other drugs used to treat CHF-** Natrecor is a drug made of recombinant BNP

- **NT-proBNP is the best molecule to measure Natrecor in order to properly assess the level of drug (won't interfere with naturally-occurring BNP)**

- **Current standard of practice is:**
  - **BNP level taken before infusion starts**
  - **BNP level taken ~2 hours after infusion ends**
  - **Possible because of the short half-life of BNP (20 minutes)**
    - **In less than 2 hours after cessation of infusion, all administered nesiritide is cleared from the system, making post-infusion measurement of BNP an accurate indicator of patient status with regard to ventricular dysfunction and response to nesiritide therapy.**

Clinical Guideline of diagnosis using a biomarker

1) 표지자 단독 검사가 무증상의 일반인(저위험군)에서 조기진단을 위한 선별검사로 추천되고 있지 않음.

2) 단독 표지자 검사 치에만 의존하여서는 안 됨.

3) 표지자 검사를 연속적으로 시행할 경우 동일한 검사실에서 동일한 검사시약을 이용.

4) 재발을 추적검사하기 위해 선택한 표지자는 치료 전 수치가 상승되어야 함.

5) 검사의 결과를 해석할 때는 표지자의 반감기를 고려.

6) 표지자가 어떻게 대사되고 배설되는지를 고려.

7) 민감도와 특이도를 높이기 위해서는 다른 검사를 실시.

8) 일부 위양성 및 위음성을 고려.

Algorithm to detect decompensation
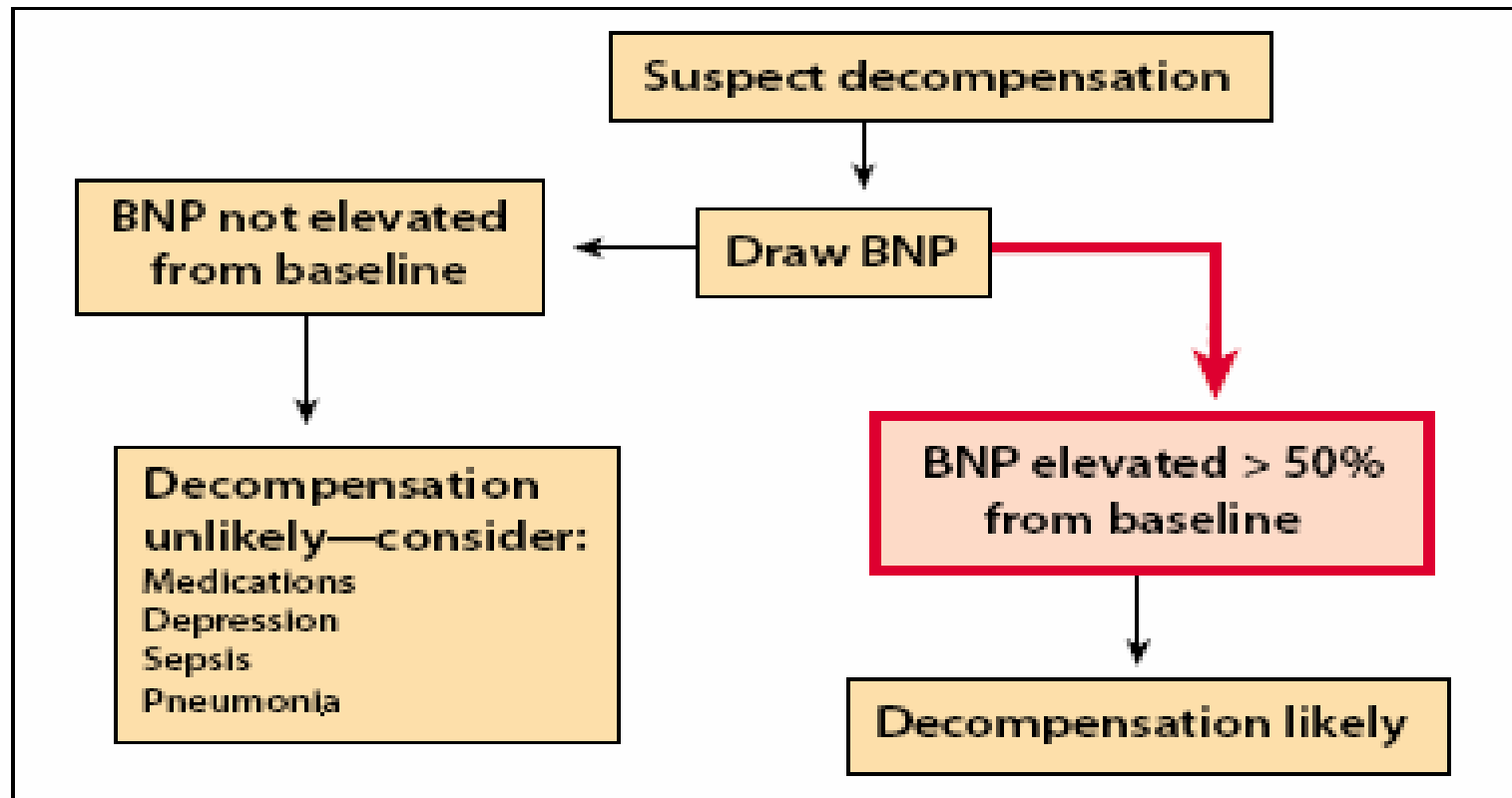
Figure 6. Algorithm to detect decompensation in patients with established heart failure and baseline B-type natriuretic peptide (BNP) values. BNP levels can confirm whether patient's congestive heart failure has truly decompensated.

Profile of plasma NT-proBNP following AMI
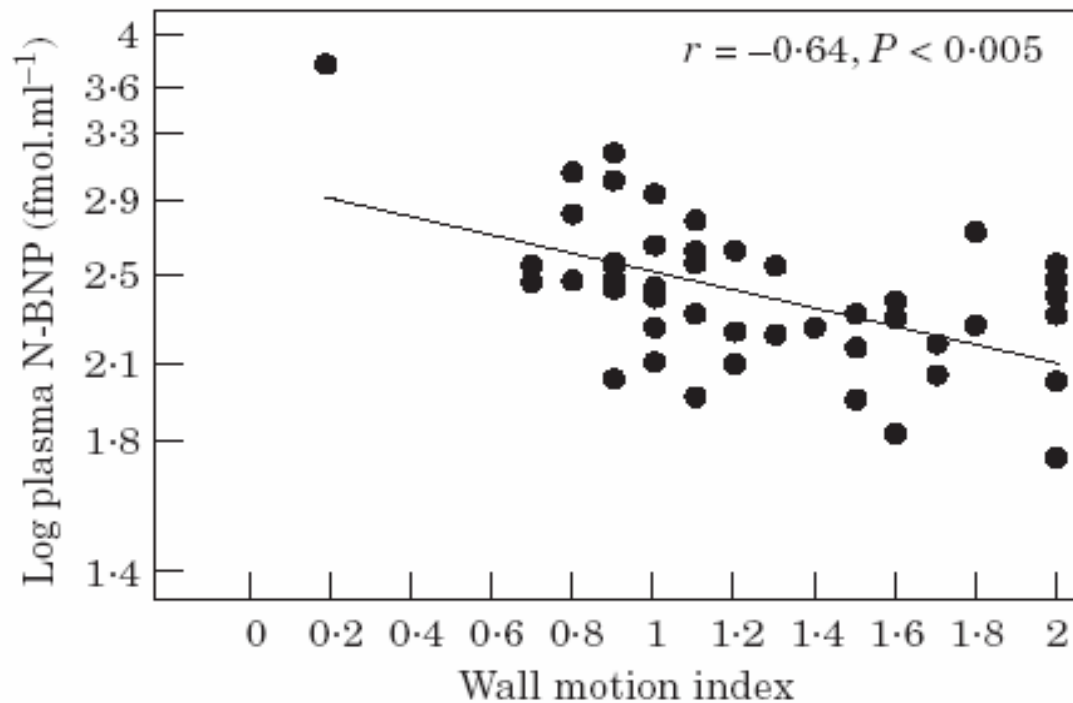
Blood sample: 73-120 hr

Screening for left ventricular systolic dysfunction: DM
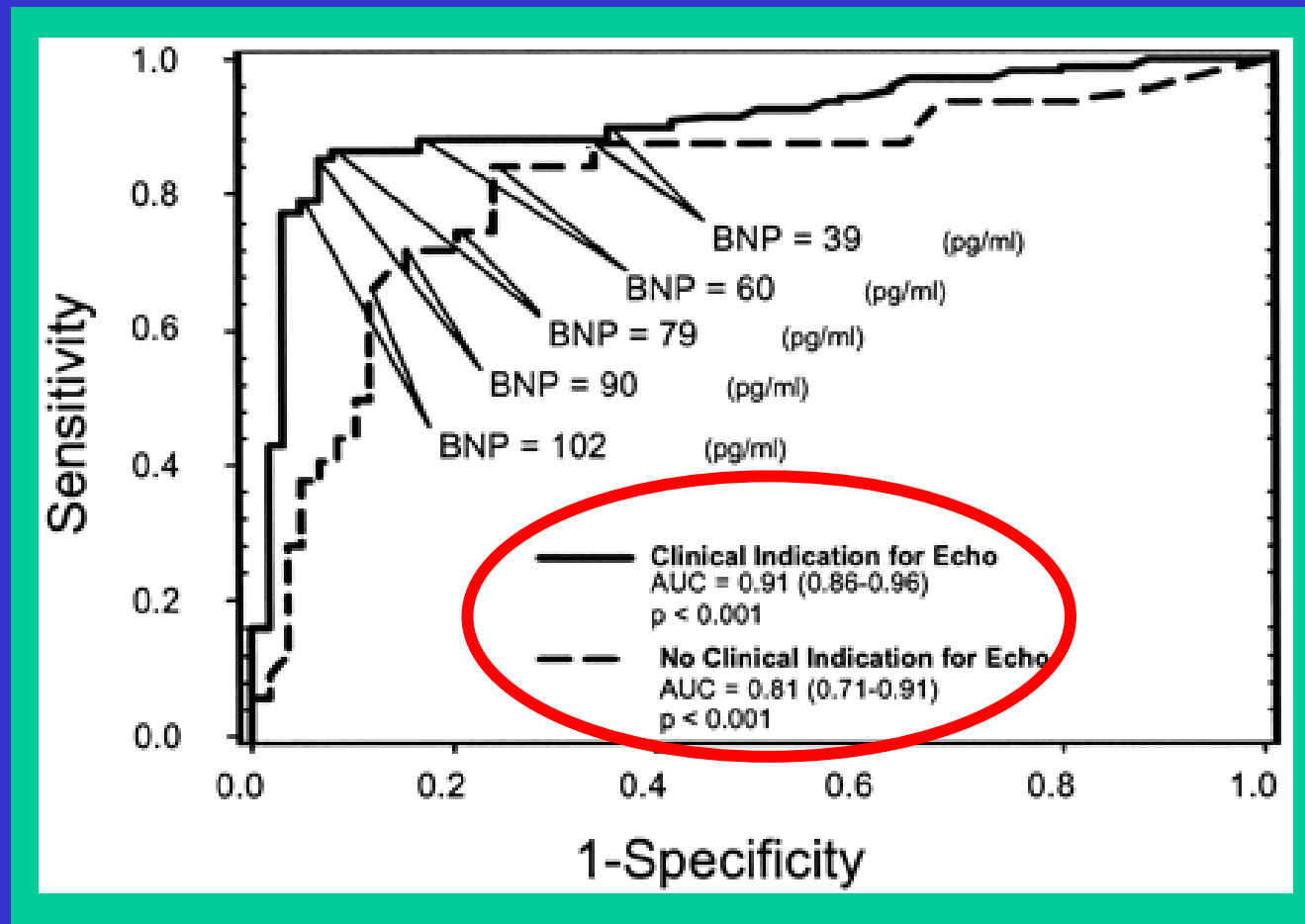
Out-patients Clinics:
ROC curves for NP and CT ratio
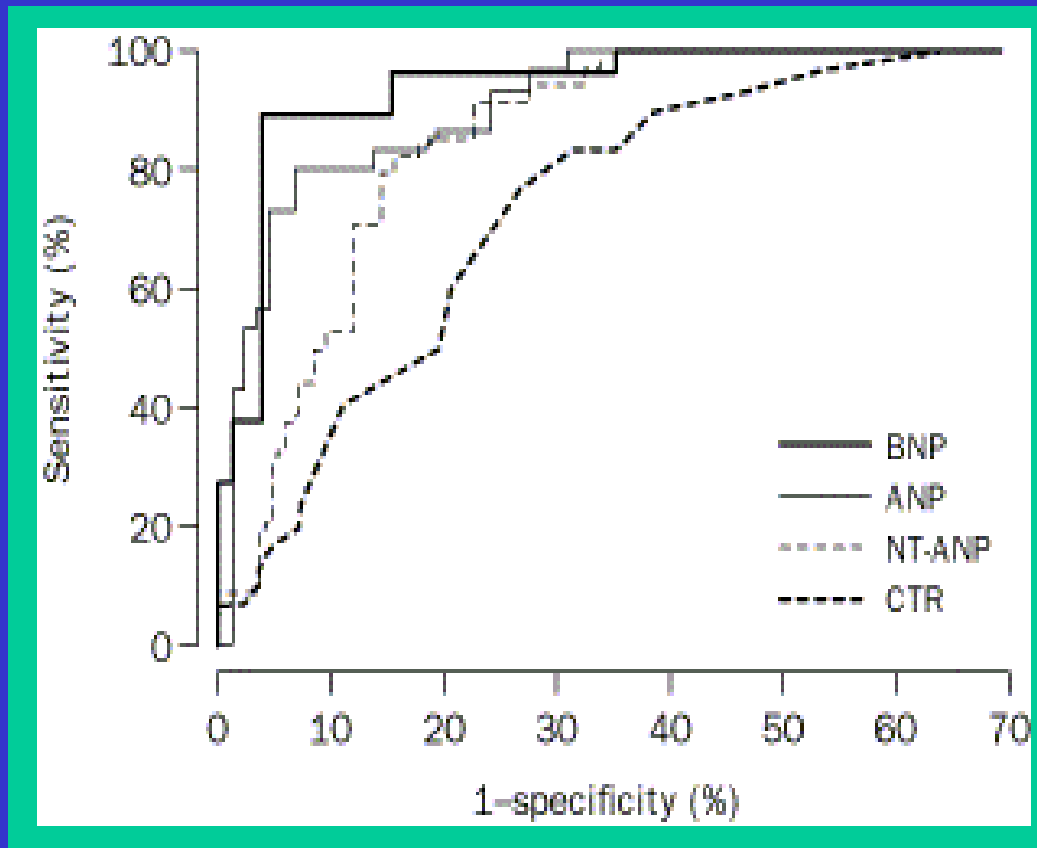
- **The diagnostic and prognostic values of plasma B-type natriuretic peptide (BNP) testing are established.**

- **However, the range of plasma BNP levels present in the setting of chronic, stable systolic heart failure (HF) is unclear.**

Evolution of Clinical Stages (AHA/ACC Guideline of CHF)

Stage A	Stage B	Stage C	Stage D
Ath high risk for heart failure but without structural heart disease or symptoms of HF	Structural heart disease but without symptoms of HF	Structural heart disease with prior or current symptoms of HF	Refractory HF requiring specialized interventions

Stage A: e.g Patients with:
−hypertension
−coronary artery disease
−diabetes mellitus or patients
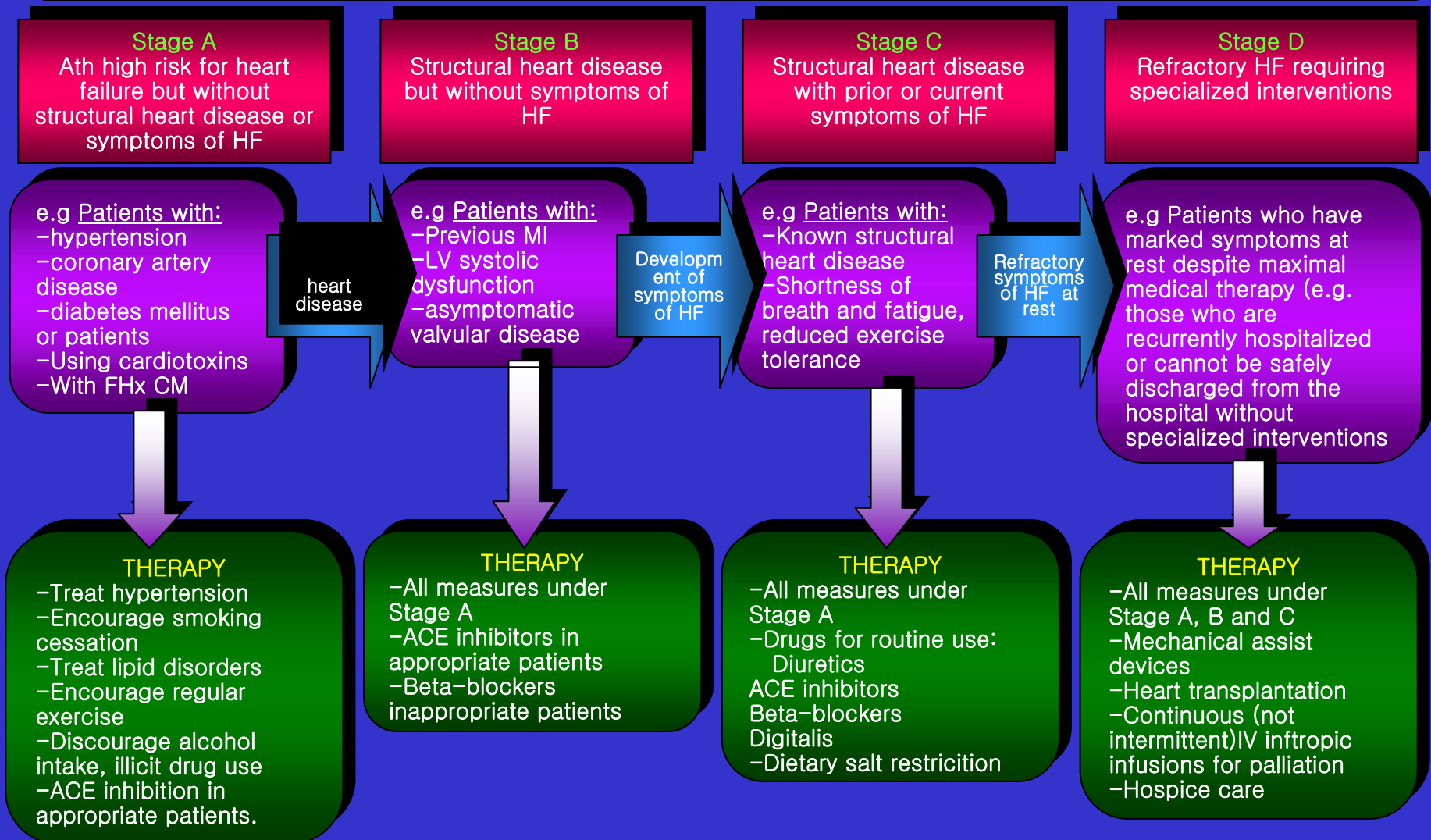−Using cardiotoxins
−With FHx CM

→ heart disease →

Stage B: e.g Patients with:
−Previous MI
−LV systolic dysfunction
−asymptomatic valvular disease

→ Development of symptoms of HF →

Stage C: e.g Patients with:
−Known structural heart disease
−Shortness of breath and fatigue, reduced exercise tolerance

→ Refractory symptoms of HF at rest →

Stage D: e.g Patients who have marked symptoms at rest despite maximal medical therapy (e.g. those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions

THERAPY (Stage A)
−Treat hypertension
−Encourage smoking cessation
−Treat lipid disorders
−Encourage regular exercise
−Discourage alcohol intake, illicit drug use
−ACE inhibition in appropriate patients.

THERAPY (Stage B)
−All measures under Stage A
−ACE inhibitors in appropriate patients
−Beta−blockers inappropriate patients

THERAPY (Stage C)
−All measures under Stage A
−Drugs for routine use:
  Diuretics
ACE inhibitors
Beta−blockers
Digitalis
−Dietary salt restriction

THERAPY (Stage D)
−All measures under Stage A, B and C
−Mechanical assist devices
−Heart transplantation
−Continuous (not intermittent)IV inftropic infusions for palliation
−Hospice care

Evolution of Clinical Stages (AHA/ACC Guideline of CHF)

Stage A
Ath high risk for heart failure but without structural heart disease or symptoms of HF

Stage B
Structural heart disease but without symptoms of HF

e.g Patients with:
−hypertension
−coronary artery disease
−diabetes mellitus or patients
−Using cardiotoxins
−With FHx CM

Structural heart disease →

e.g Patients with:
−Previous MI
−LV systolic dysfunction
−asymptomatic valvular disease

ECG
Chest X-ray
BNP
Echocardiography

THERAPY
−Treat hypertension
−Encourage smoking cessation
−Treat lipid disorders
−Encourage regular exercise
−Discourage alcohol intake, illicit drug use
−ACE inhibition in appropriate patients.

THERAPY
−All measures under Stage A
−ACE inhibitors in appropriate patients
−Beta−blockers inappropriate patients

Hazard ratios for all-cause mortality& morbidity
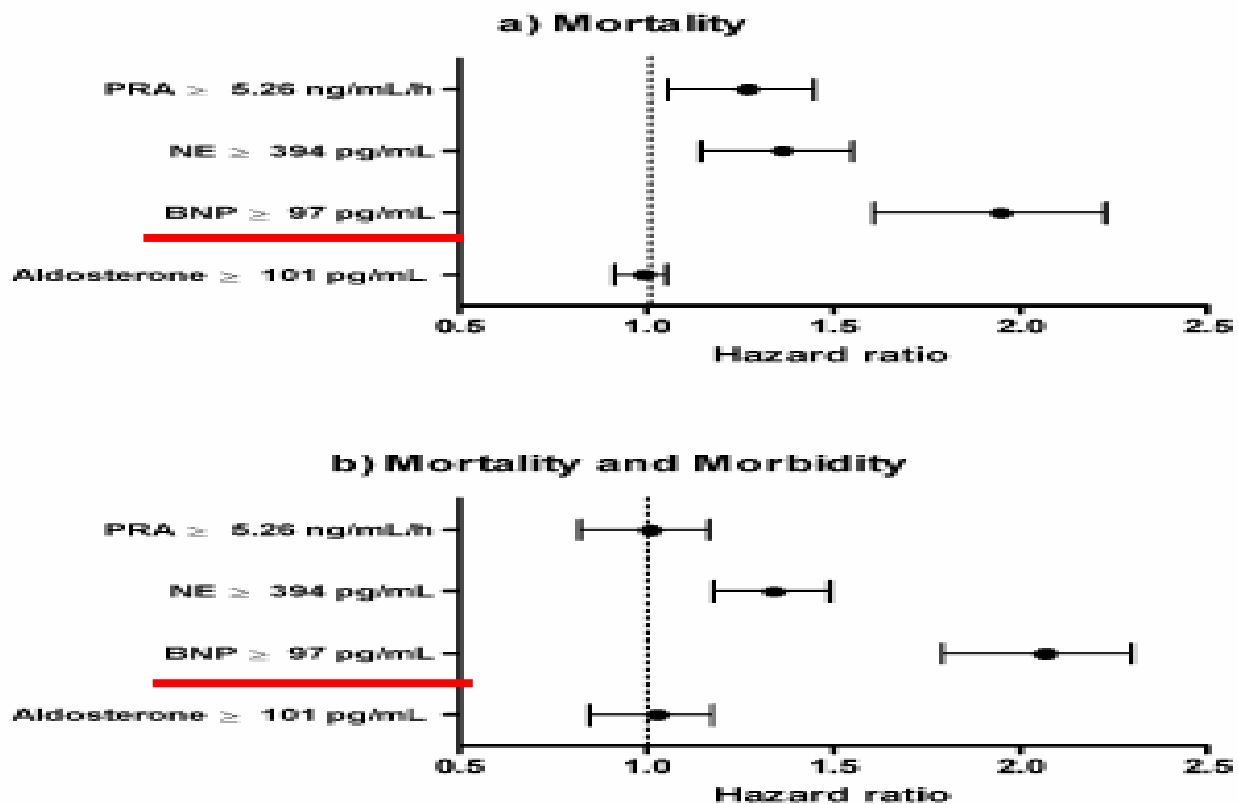
B-type Natriuretic Peptide (BNP) vs. NT-proBNP Assay

Charateristics	BNP	NT−ProBNP
Molecular Weight	3.5 KD	8.5KD
Origin	Left ventricle	Left ventricle
Activity	Hormonally Active.	Inactive peptide
Clearance	Clearance receptor & Endopeptidase	No clearance receptor 100% renal clearance
Half−life	20 Minutes	120 Minutes
Stability at room temperature	++	+++
Cut−off value	100pg/mL	Age < 75 :125 pg/mL Age ≥ 75 :450 pg/mL
Increase with normal aging	++	++++
POCT kit	Available	Not available
Accuracy in mild or early HF	+++	++++

Use of BNP levels to titrate treatment for HF

Troughton RW, Lancet 2000, 355
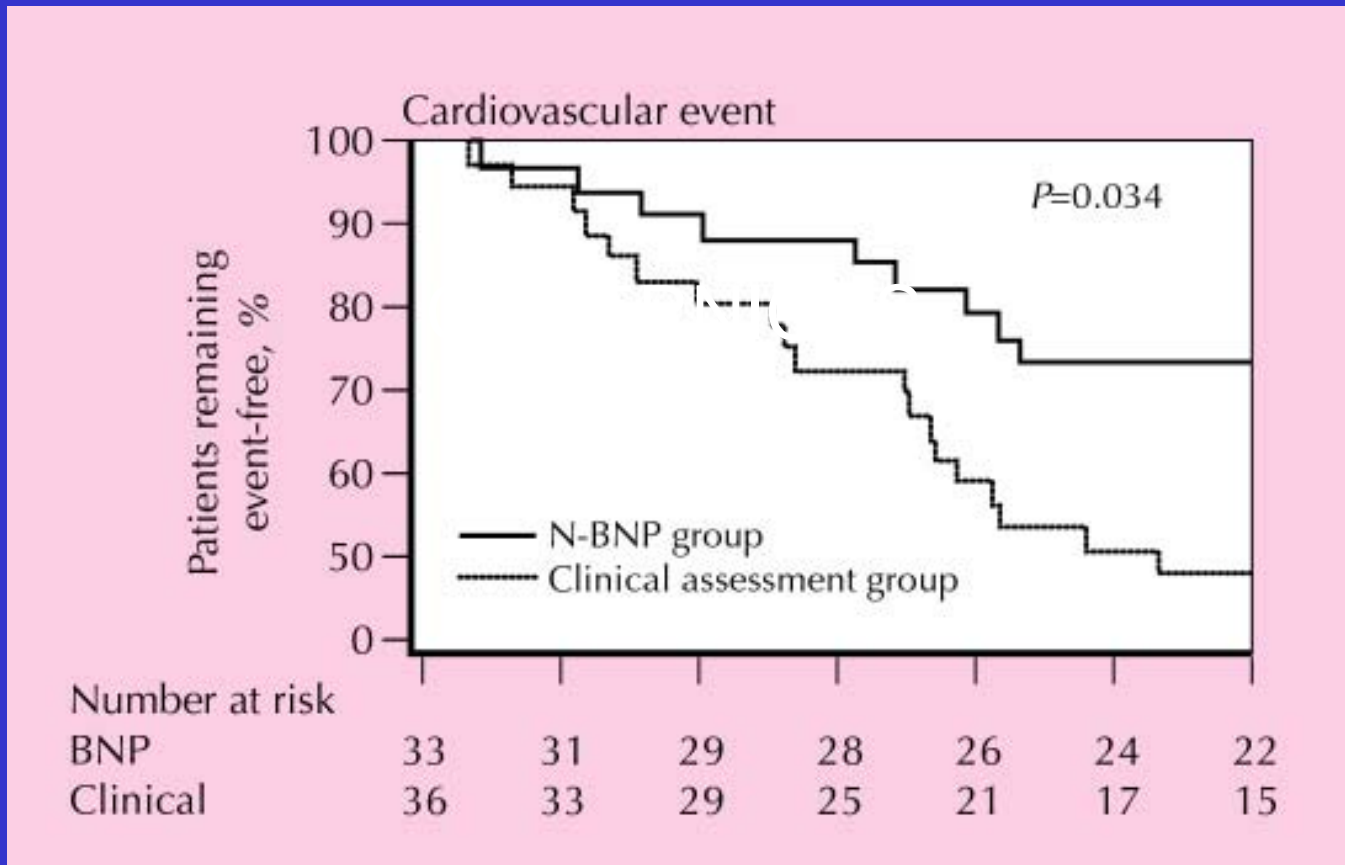
Comparing BNP & NT-proBNP

Normal/NYHA I+II (n= 116)

	AUC	Sens	Spec	
BNP	0.867	78%	87%	p < 0.0001
NT-proBNP	0.932	87%	94%	

Normal/NYHA III+IV

|	AUC	Sens	Spec	
BNP	0.993	97%	99%	p = 0.332
NT-proBNP	0.998	97%	99%	

- NT-proBNP is significantly better than BNP in discriminating patients from healthy subjects, especially when only patients with mild disease (NYHA class I and II) are considered

Prontera C. et al. Clin Chem Lab Med 2003;41

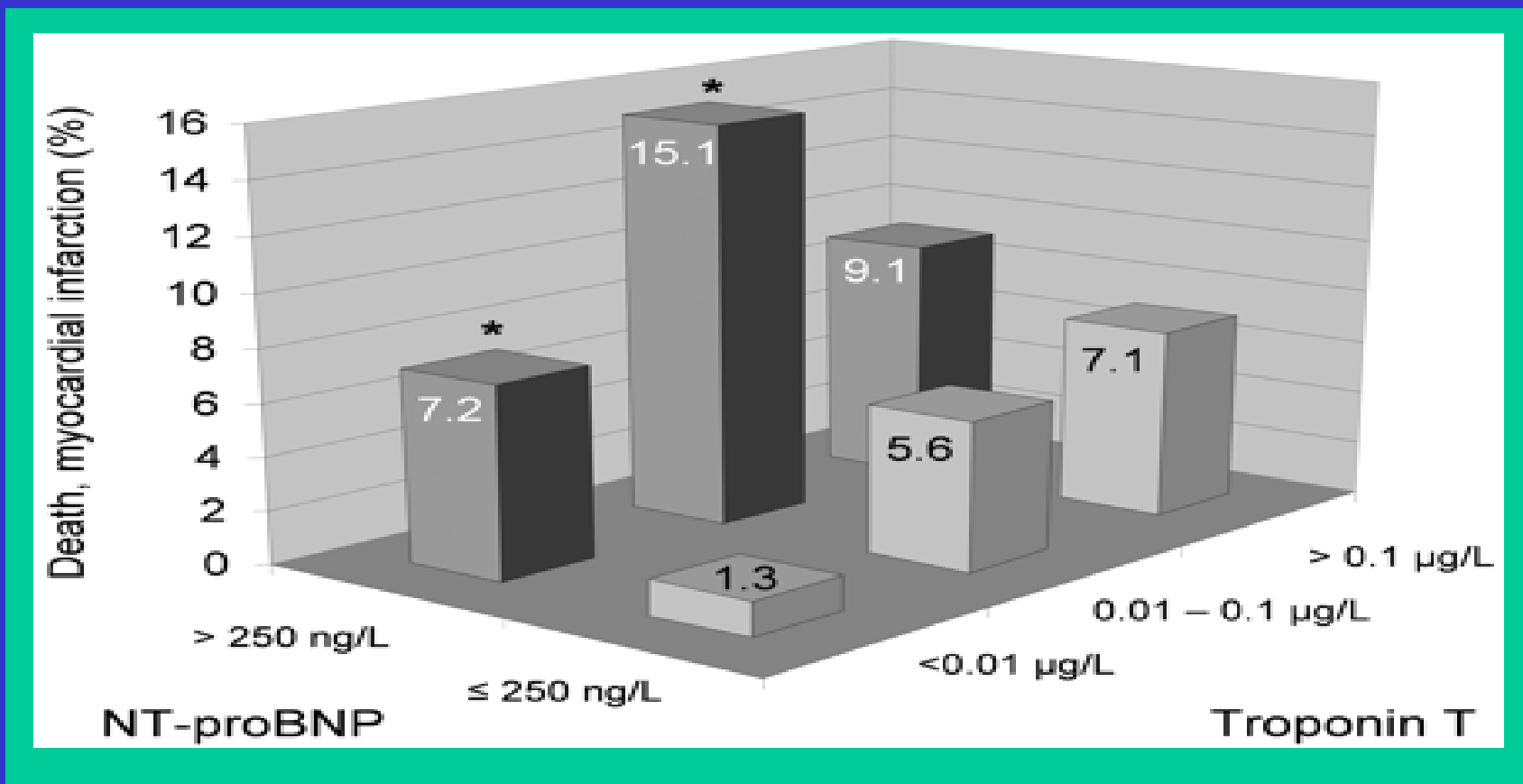# BNP as a Prognosis Marker of a CHF and ACS
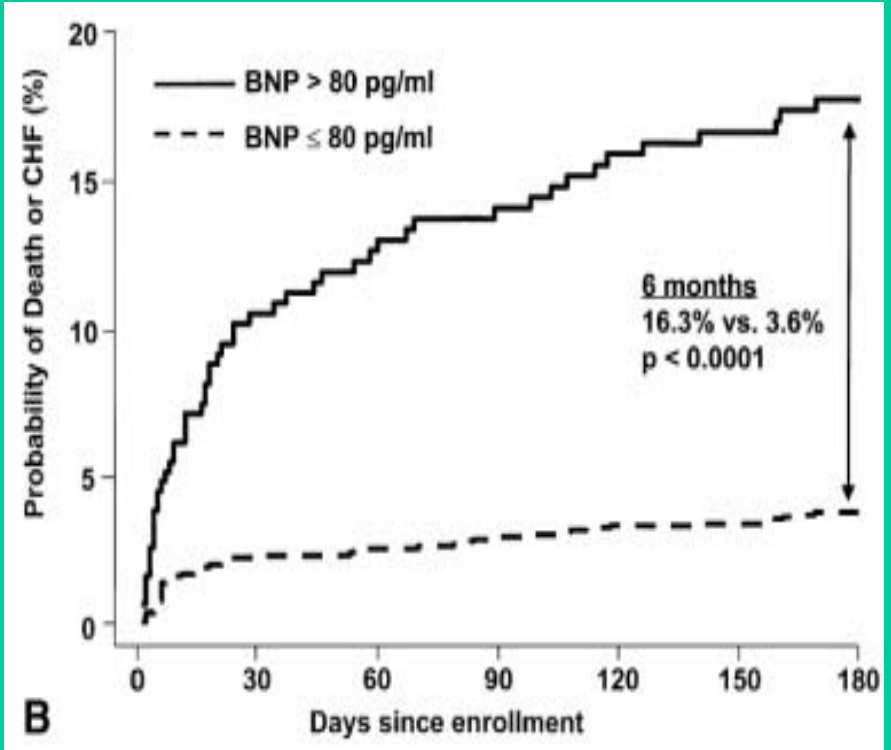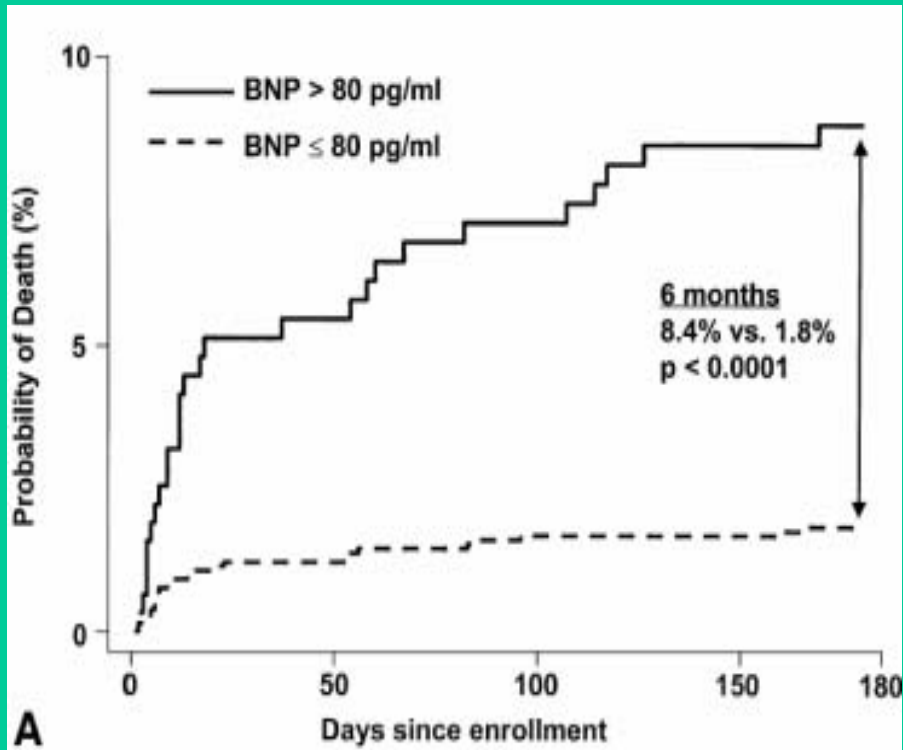
B-Type Natriuretic Peptide and Prognosis in
TACTICS-TIMI 18, J Am Coll Cardiol 2003;41:1264
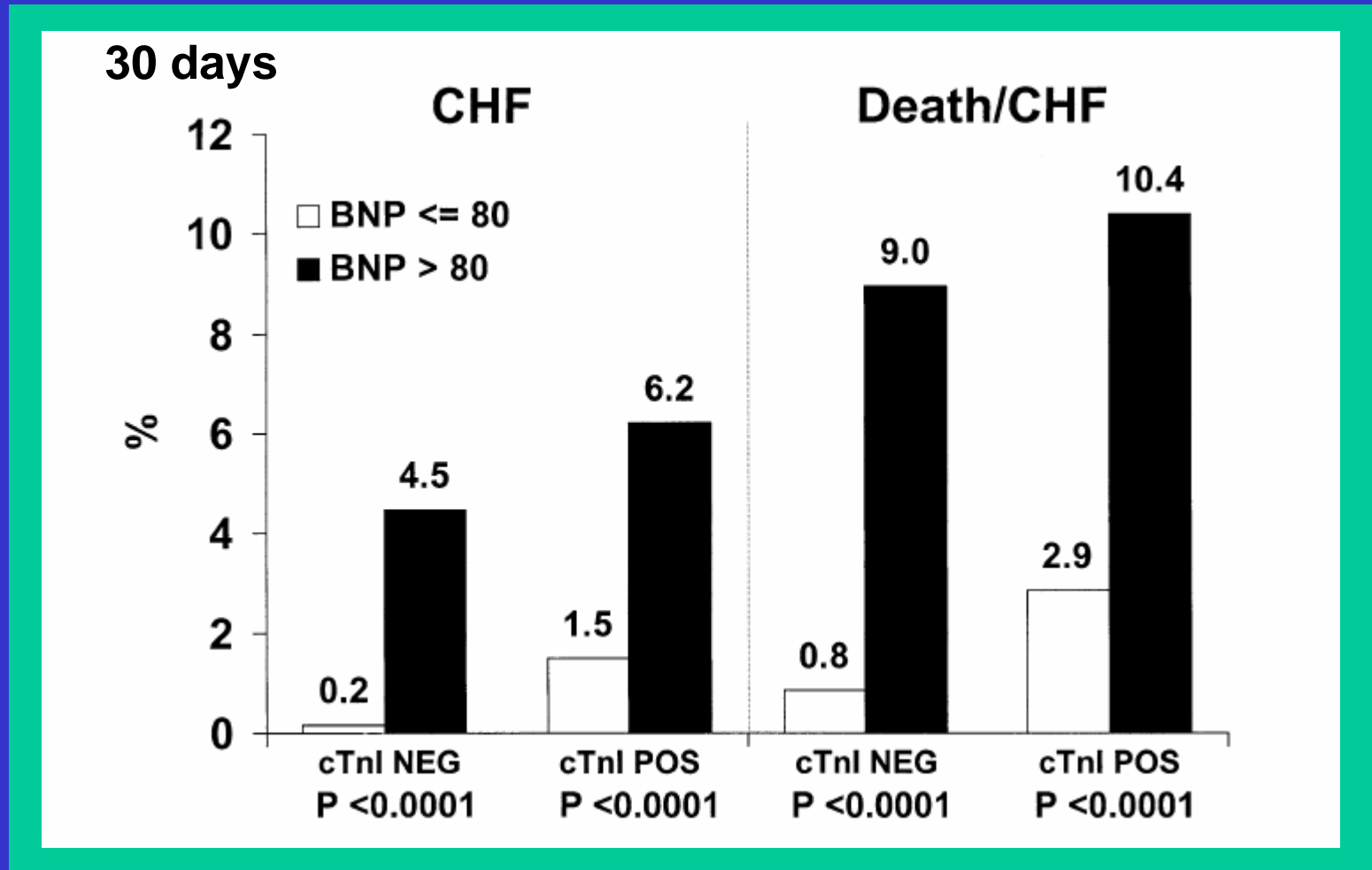
BNP as a Prognosis Marker of a CHF and ACS
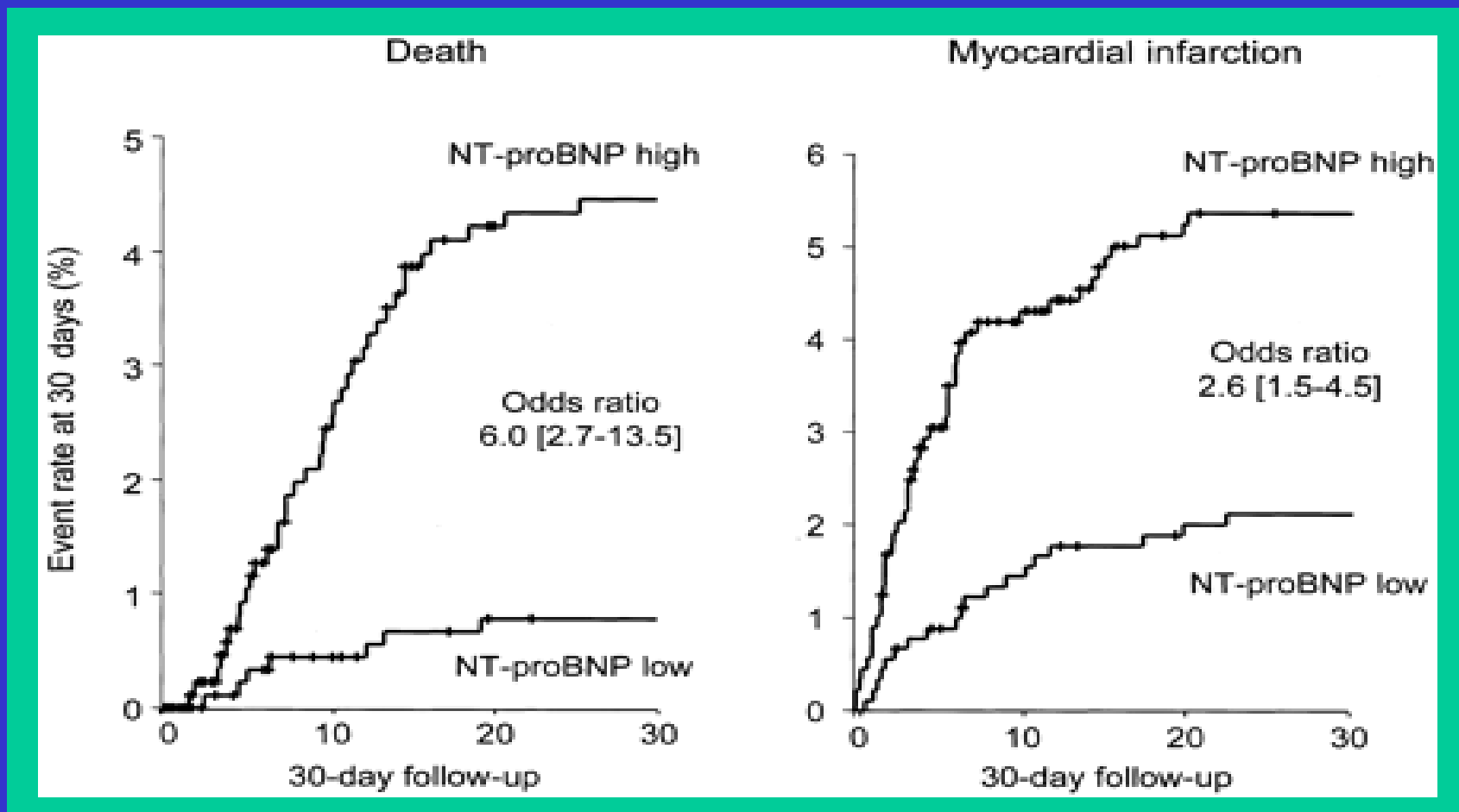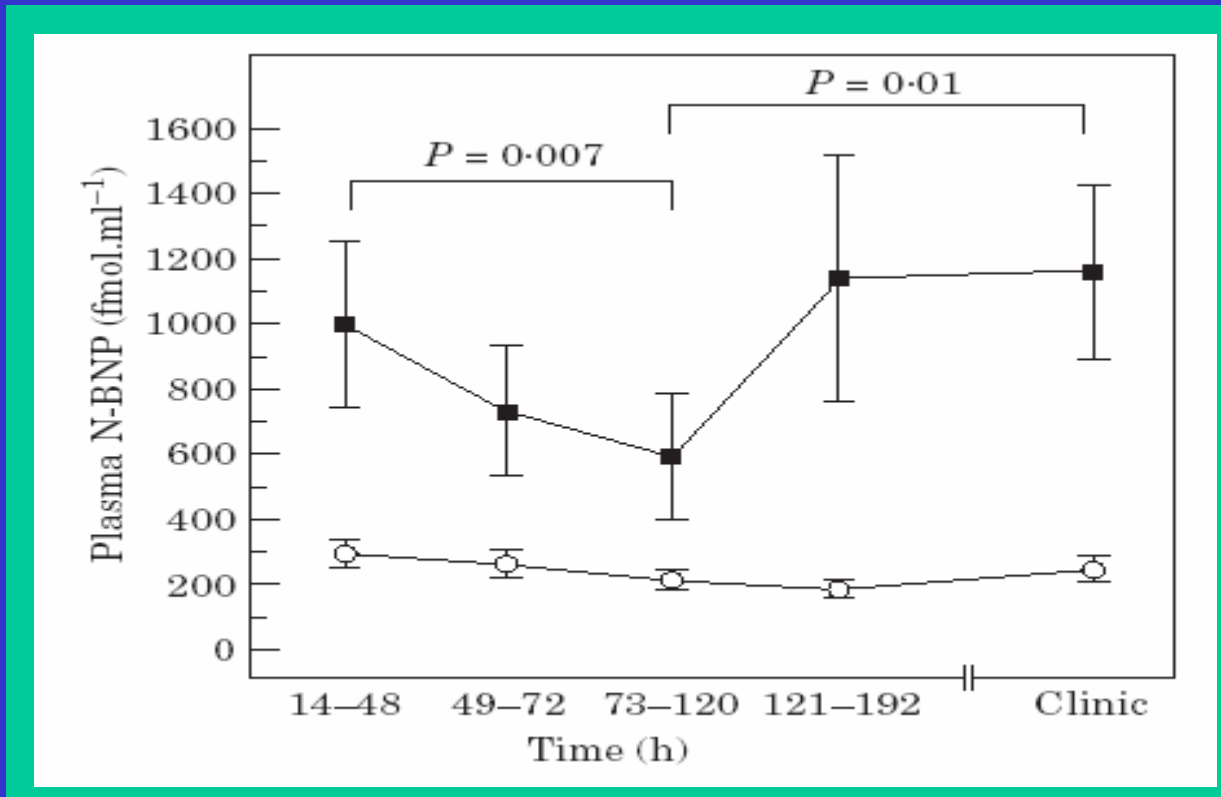
BNP as a Prognosis Marker of a CHF and ACS

Predictive value of baseline NT-proBNP
in relation to presence or absence of myocardial necrosis

Heeschen C et al (PRISM), Circulation. 2004 ;:3206

BNP as a Prognosis Marker of a CHF and ACS

Stage B: Pre-clinical HF, AMI

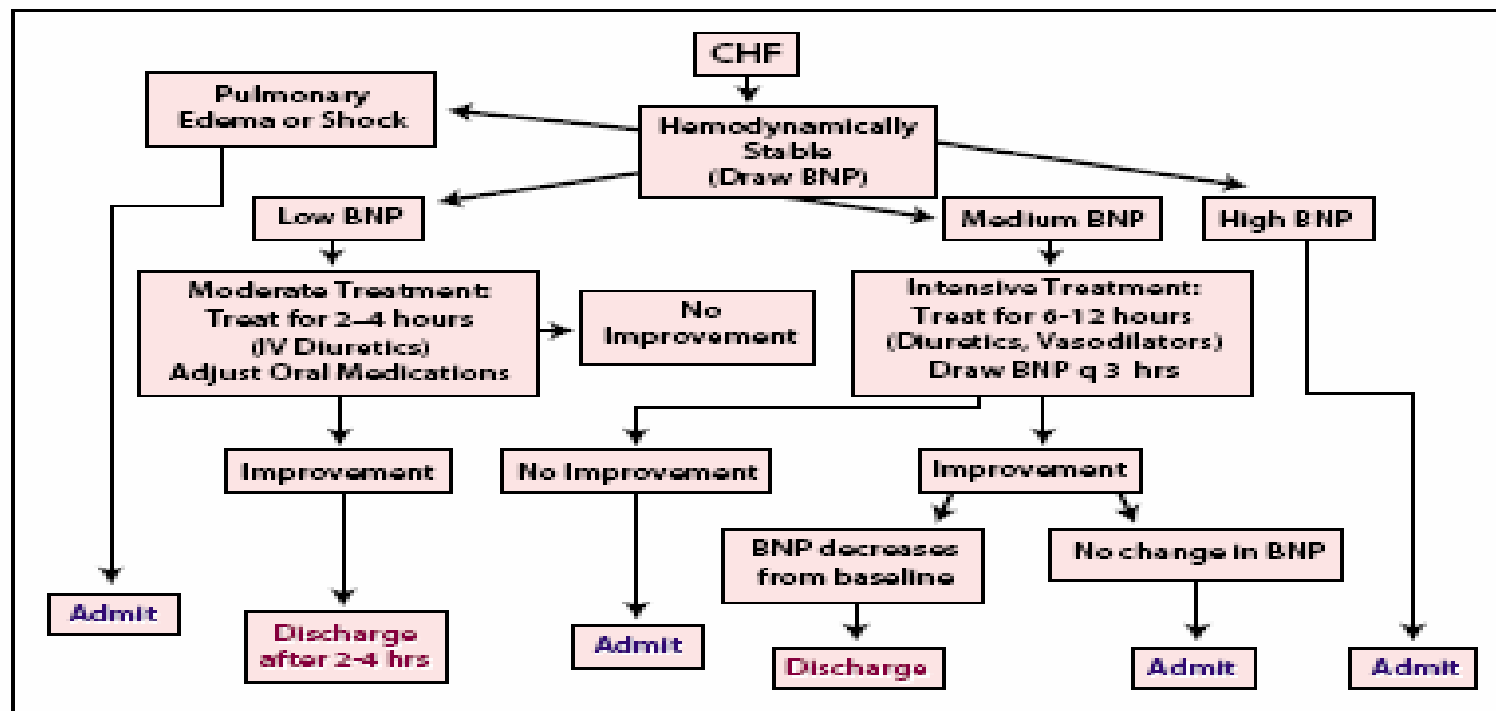

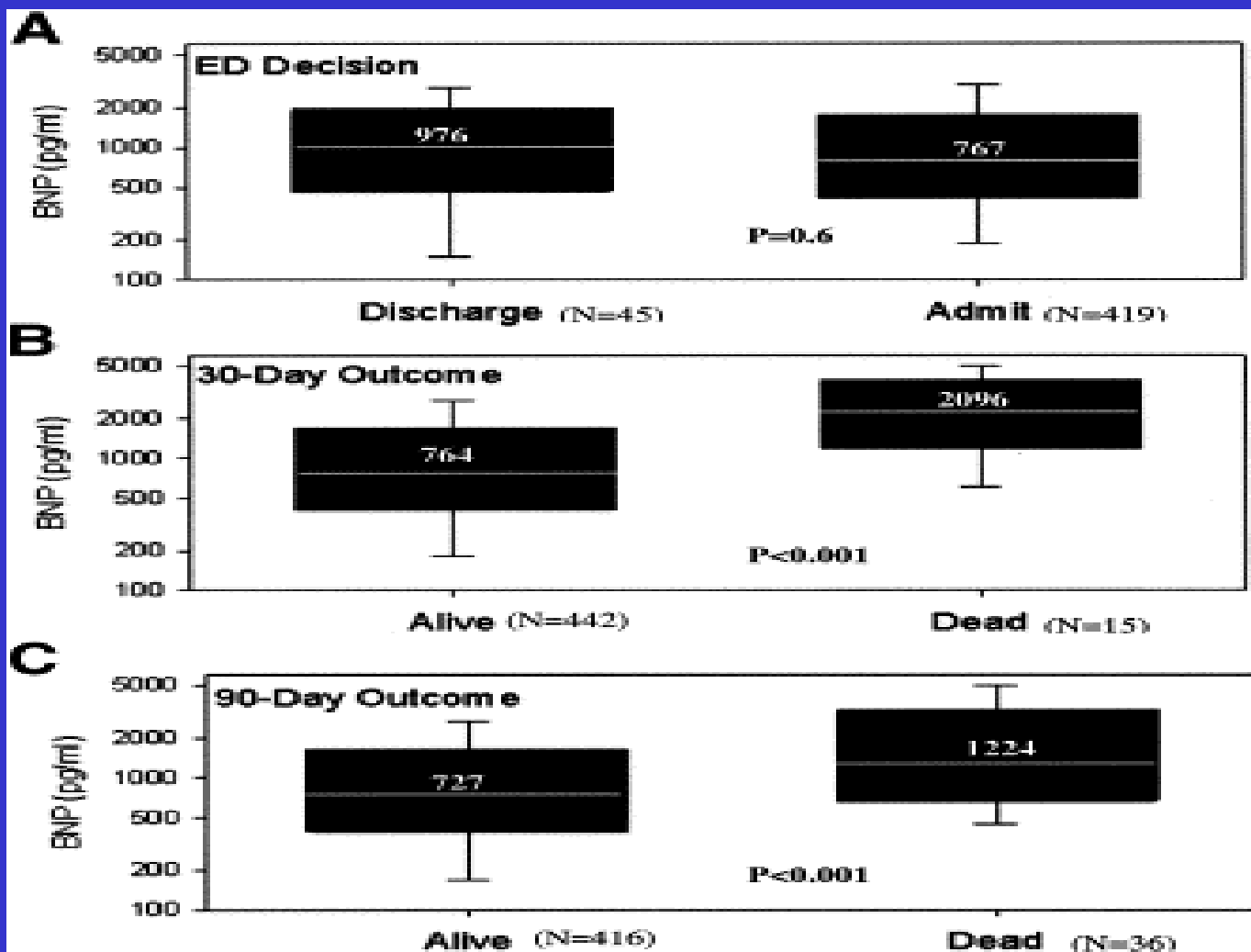■ : anterior wall
○ : inferior wall

REDHOT trial

Figure 8. Algorithm for using B-type natriuretic peptide (BNP) levels in the triage and treatment of emergency department patients presenting with heart failure, from the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). CHF, congestive heart failure; IV, intravenous.

High BMI and *Low* BNP?
Potential Mechanisms

- Increased BNP clearance in obesity
  - Natriuretic peptide clearance receptors are abundant on adipocytes
  - Vascularity of adipose tissue may allow for increased clearance of BNP by neutral endopeptidase
- Decreased BNP production in obesity
- Overweight and obese HF patients have less advanced HF

Future Investigation

- Mechanisms of low BNP in obesity
- BNP interpretation based on BMI

BNP as predictors of non-sudden & SCD after AMI in the β-blocking era
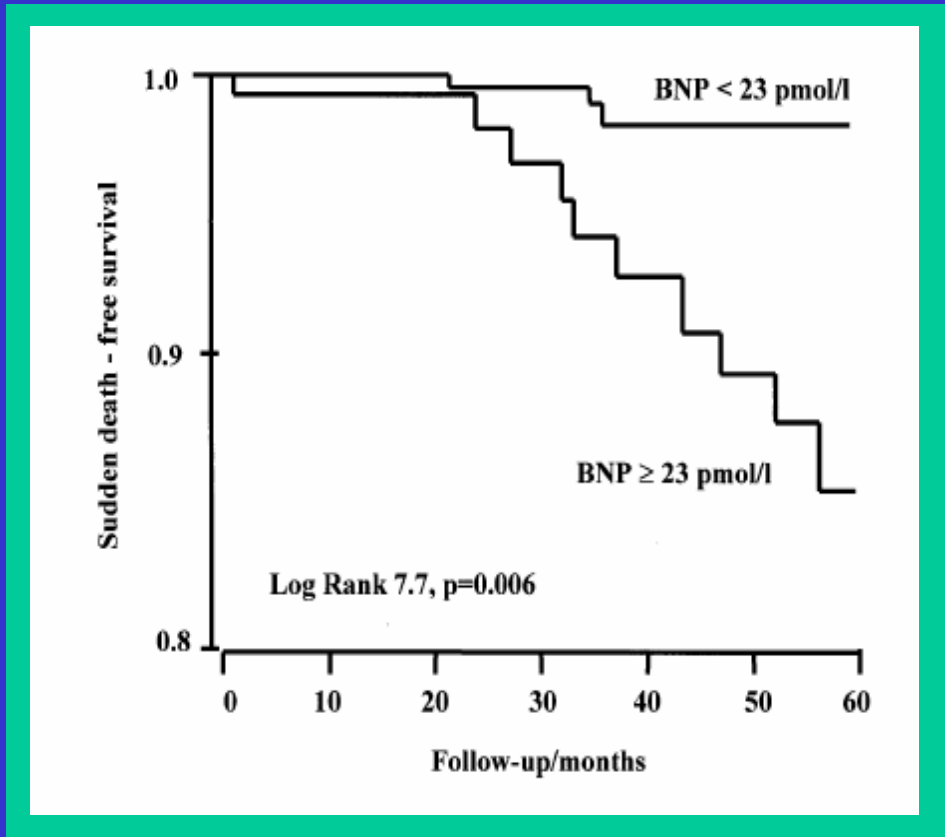
- **Natriuretic peptides retain their prognostic value in the beta-blocking era among survivors of AMI.**
- **Elevated BNP provides information on the risk of subsequent SCD, independent of clinical variables and EF.**

Stage B: Pre-clinical HF, AMI

Mortality at 1-year follow-up among strata of patients, according to deciles of NT-proBNP levels
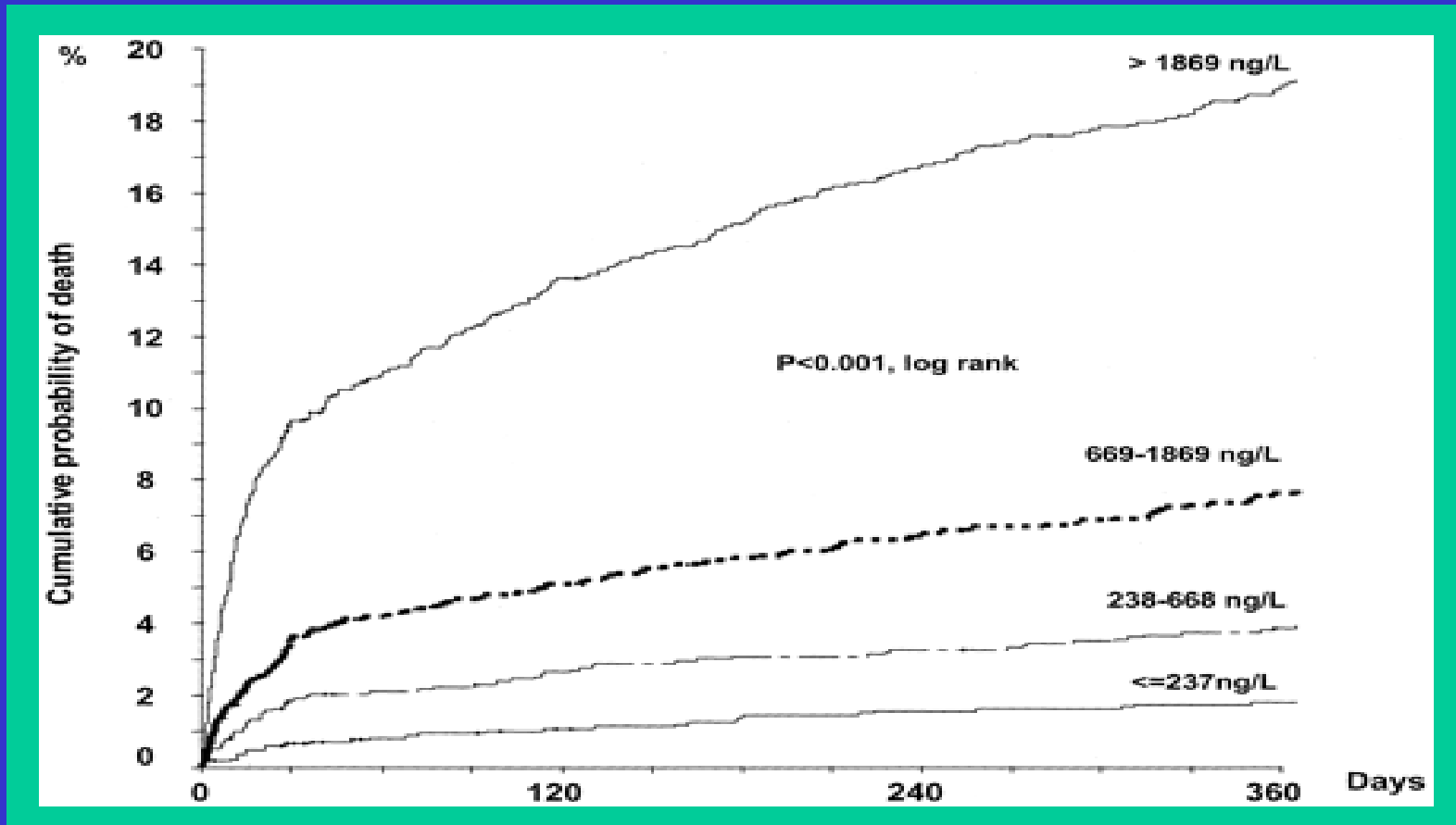
TABLE 3. N-BNP, BNP, and NE as Predictors of Death/Heart Failure (n=126 events)

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (0 to 1.0)
N-BNP (162 pmol/L)	80	72	25	97	0.81
BNP (30 pmol/L)	71	76	25	96	0.81
NE (2670 pmol/L)	57	57	13	92	0.55
LVEF (40%)	78	64	25	95	0.76

Values in parentheses are the optimum, ie, nearest Euclidean distance from perfect sensitivity and specificity. PPV indicates positive predictive value; NPV, negative predictive value; and AUC, area under the curve.

Evolution of Clinical stages in CHF

NORMAL

No symptoms
Normal exercise
Normal LV fxn

Asymptomatic LV Dysfunction

No symptoms
Normal exercise
Abnormal LV fxn

Compensated CHF

No symptoms
⬇ Exercise
Abnormal LV fxn

Decompensated CHF

Symptoms
⬇⬇ Exercise
Abnormal LV fxn

Refractory CHF

Symptoms not controlled
with treatment