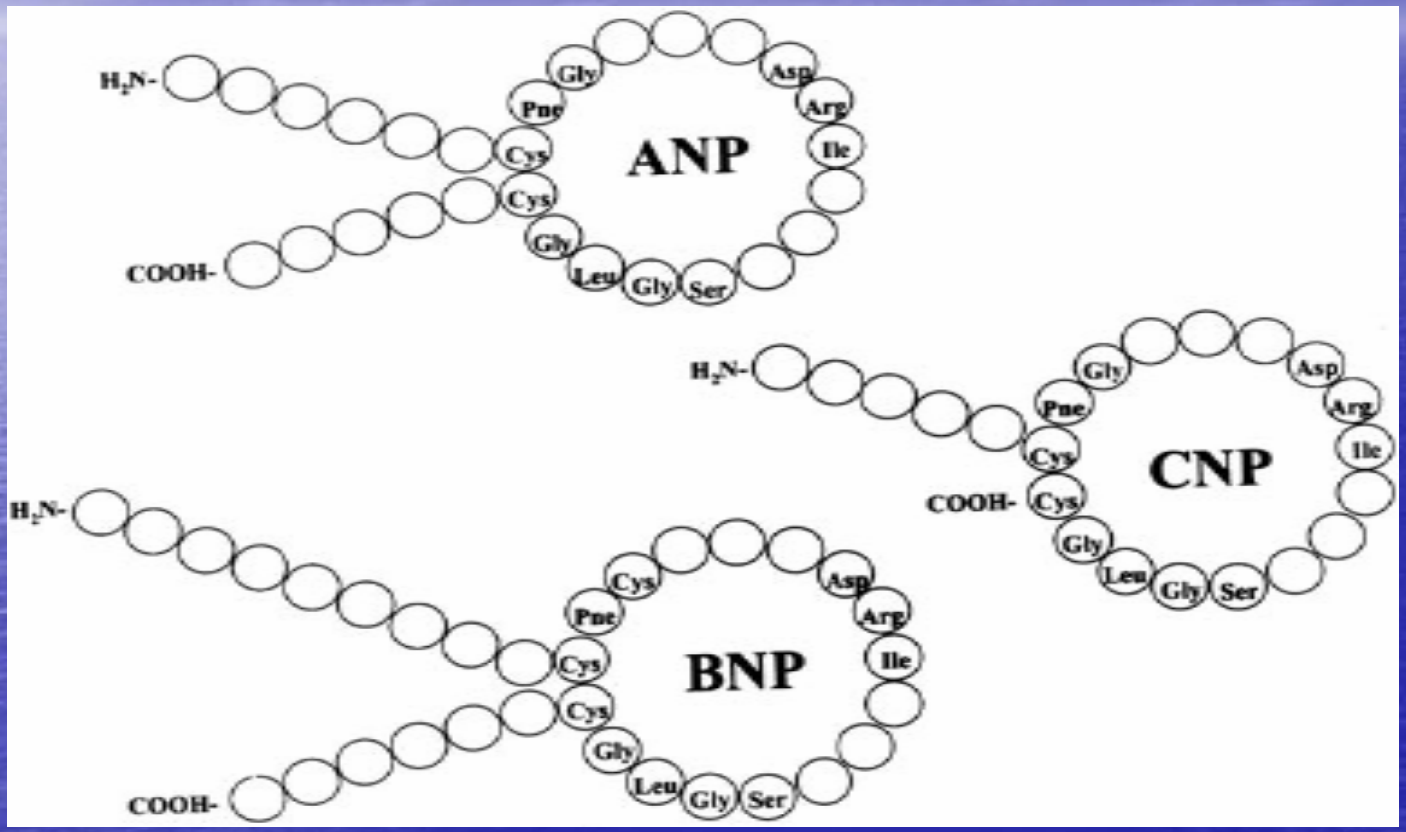
Brain Natriuretic Peptide

Structures of natriuretic peptide family

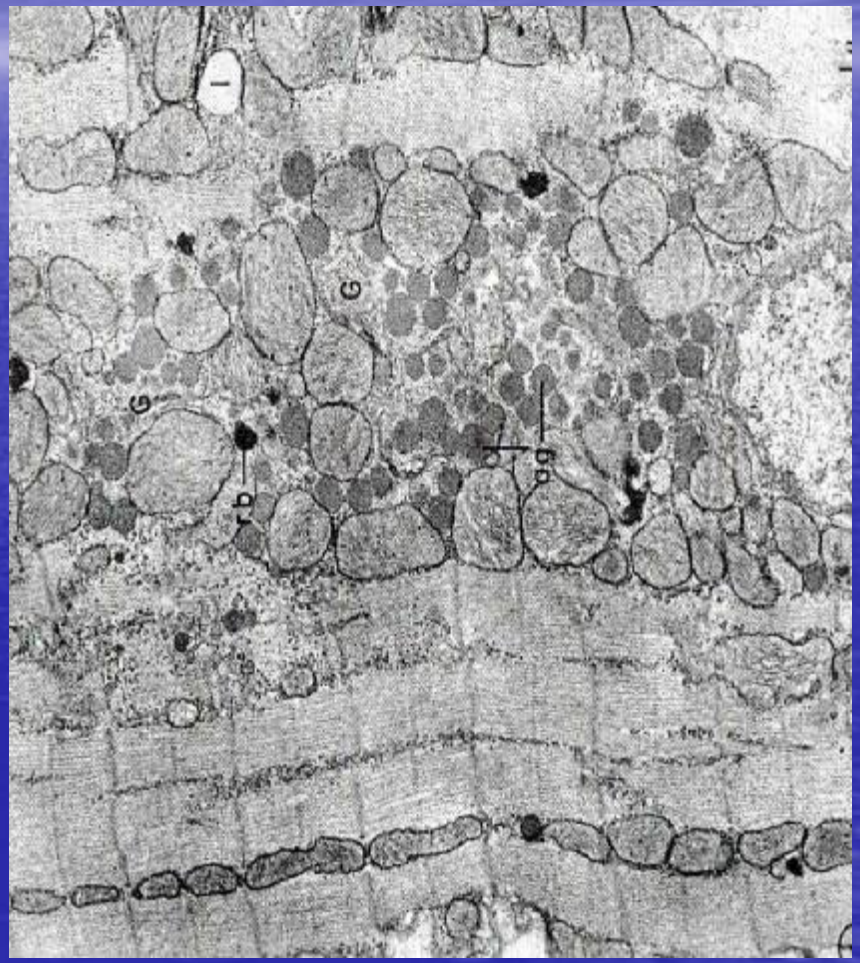


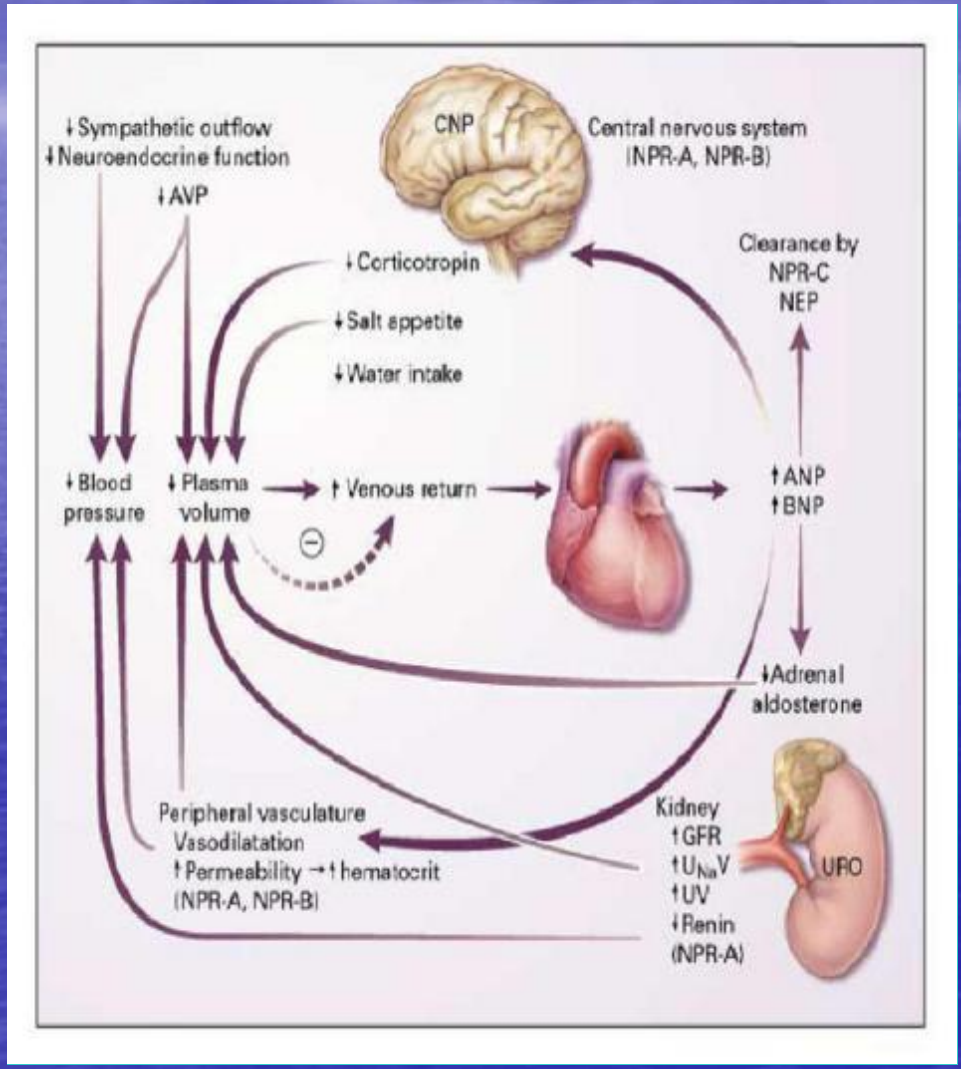
Stein Am Heart J 1998;135

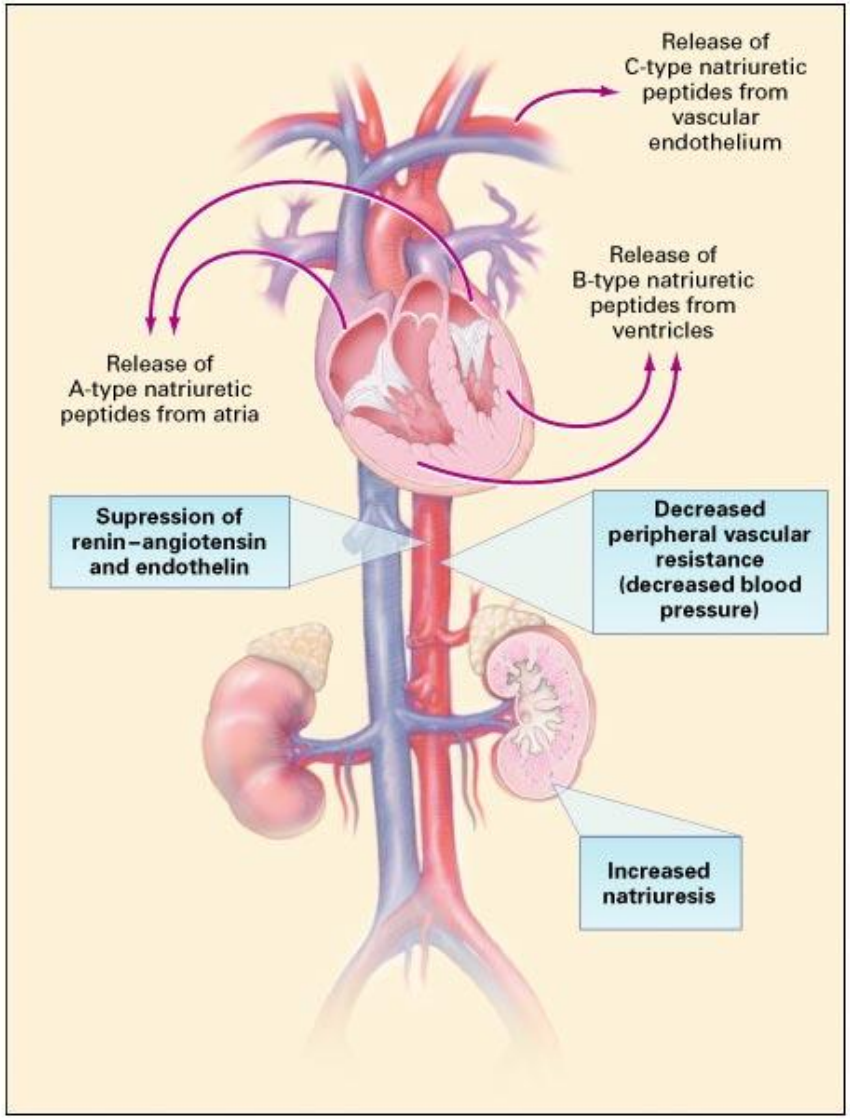
Secretory granules discovered in the atria-Kisch (1956)-Jamieson and Palade(1964)

Infusion of extracts of atrial tissue increased natriuresis and diuresis-deBold, et al (1981)

BNP was characterized by amino acid sequence and DNA clones(Sudoh, et al. 1988 and Seilhamer, et al. 1989).




↓Sympathetic outflow
↓Neuroendocrine function
↓AVP
CNP
Central nervous system
(NPR-A, NPR-B)
↓Corticotropin
↓Salt appetite
↓Water intake
Clearance by
NPR-C
NEP
↓Blood pressure
↓Plasma volume
↑Venous return
↑ANP
↑BNP
↓Adrenal aldosterone
Peripheral vasculature
Vasodilatation
↑Permeability → ↑hematocrit
(NPR-A, NPR-B)
Kidney
↑GFR
↑$U_{Na}V$
↑UV
↓Renin
(NPR-A)
UPO


Release of C-type natriuretic peptides from vascular endothelium
Release of B-type natriuretic peptides from ventricles
Release of A-type natriuretic peptides from atria
Supression of renin–angiotensin and endothelin
Decreased peripheral vascular resistance (decreased blood pressure)
Increased natriuresis

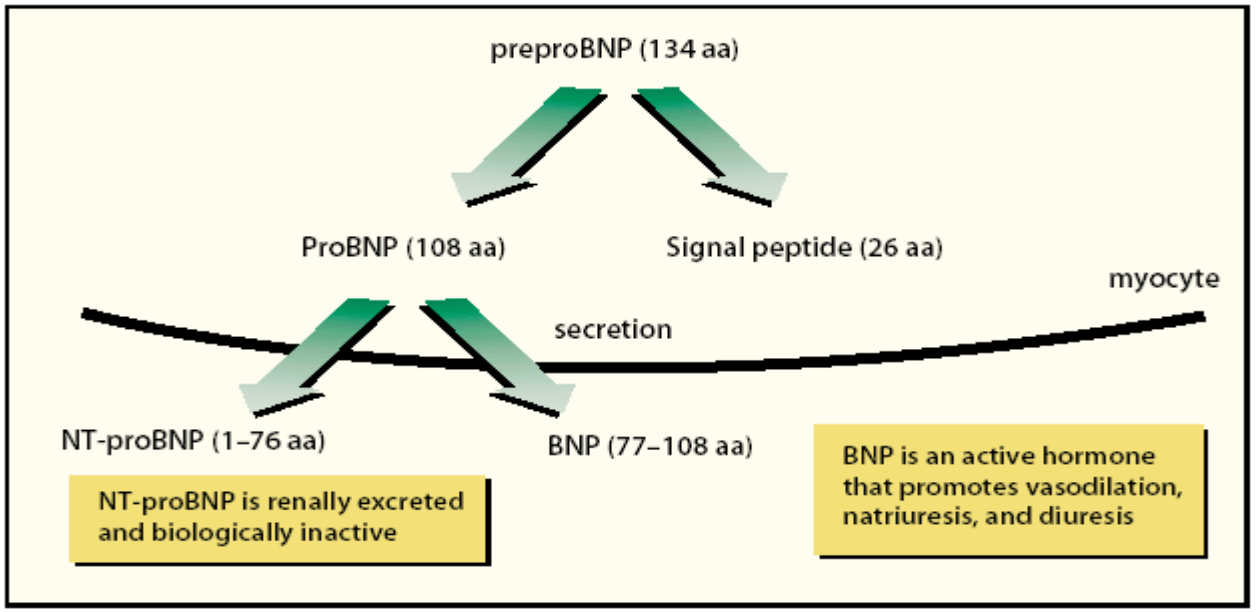


Figure 1. *The cardiac natriuretic peptide family. BNP, B-type natriuretic peptide; NT, N-terminal; aa, amino acid.*

Table 1
Key Distinguishing Features of the Ventricular Natriuretic Peptides

Characteristic	BNP	NT-proBNP
Components	BNP molecule	NT fragment (1–76) NT-proBNP (1–108)
Molecular weight	3.5 kd	8.5 kd
Hormonally active	Yes	No, inactive peptide
Genesis	Cleavage from NT-proBNP	Release from ventricular myocytes
Half-life	20 minutes	120 minutes
Clearance mechanism	Neutral endopeptidase clearance receptors	Renal clearance
Increases with normal aging	+	++++
Correlation with estimated glomerular filtration rate	−0.20	−0.60
Approved cutoff(s) for CHF diagnosis	100 pg/mL	Age < 75 years: 125 pg/mL Age ≥ 75 years: 450 pg/mL
Approved for assessment of CHF severity	Yes	No
Approved for prognosis in ACS	Yes	No
Prospective ED studies completed	Yes	No
Community screening studies completed	Yes	Yes
Available at the point of care	Yes	No
No. studies completed	1370	39
Date of entry on U.S. market	November 2000	December 2002

BNP, B-type natriuretic peptide; NT, N-terminal; CHF, congestive heart failure; ACS, acute coronary syndromes; ED, emergency department.

- Age
- Sex
- Exercise
- Drugs

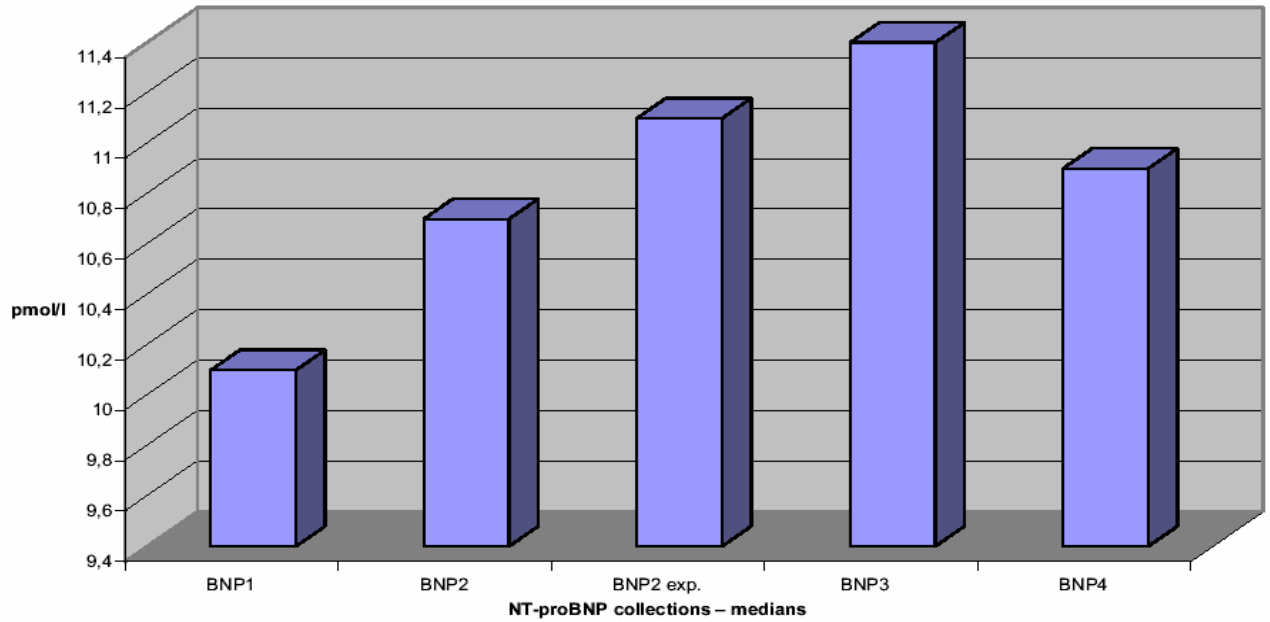
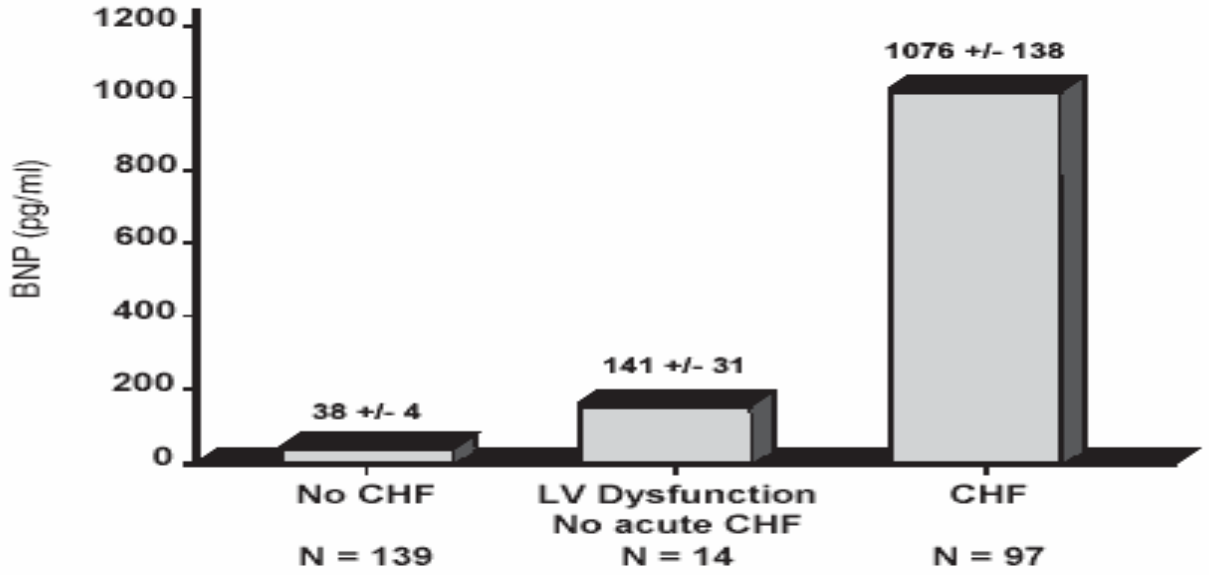


Fig. 1. NT-pro BNP concentrations before and after exercise.

BNP1	immediately before the test
BNP2	at peak exercise
BNP3	0 min after exercise
BNP4	60 min after exercise
BNP2 exp.	expected value according to changed plasma volume (0 min after exercise)

Figure 2. BNP Levels in Patients with CHF and Symptomatic LV Dysfunction



Reprinted with permission from: Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting.*J Am Coll Cardiol* 2001;37:379-385

BNP levels increase with severity of heart failure

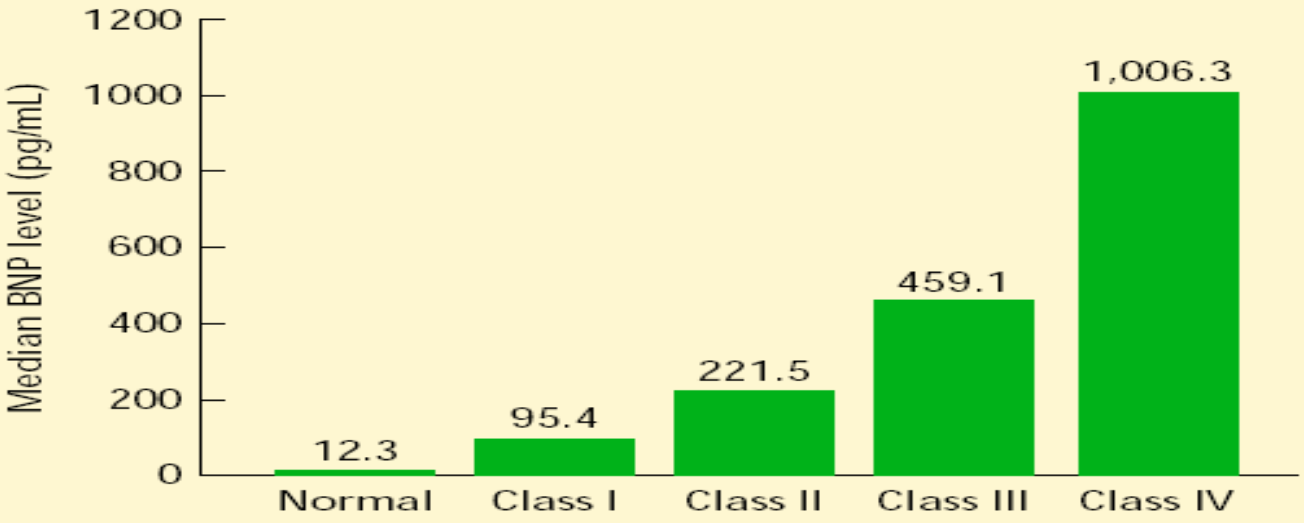


FIGURE 1. Brain natriuretic peptide (BNP) levels in normal subjects and in patients with heart failure.

DATA FROM BIOSITE PACKAGE INSERT

BNP levels correlate with Left Ventricular Ejection Fraction

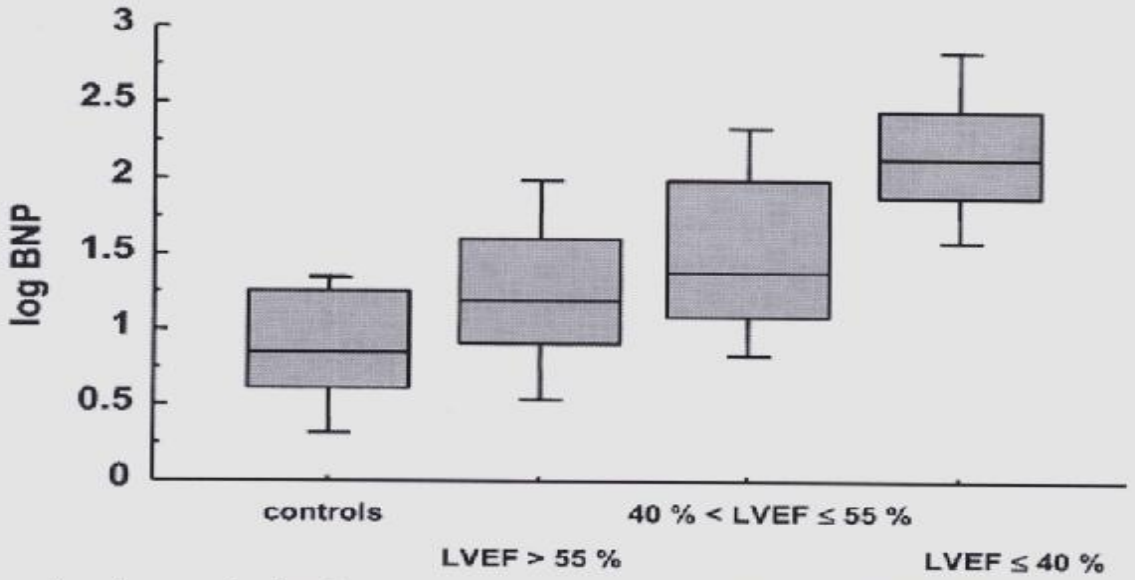
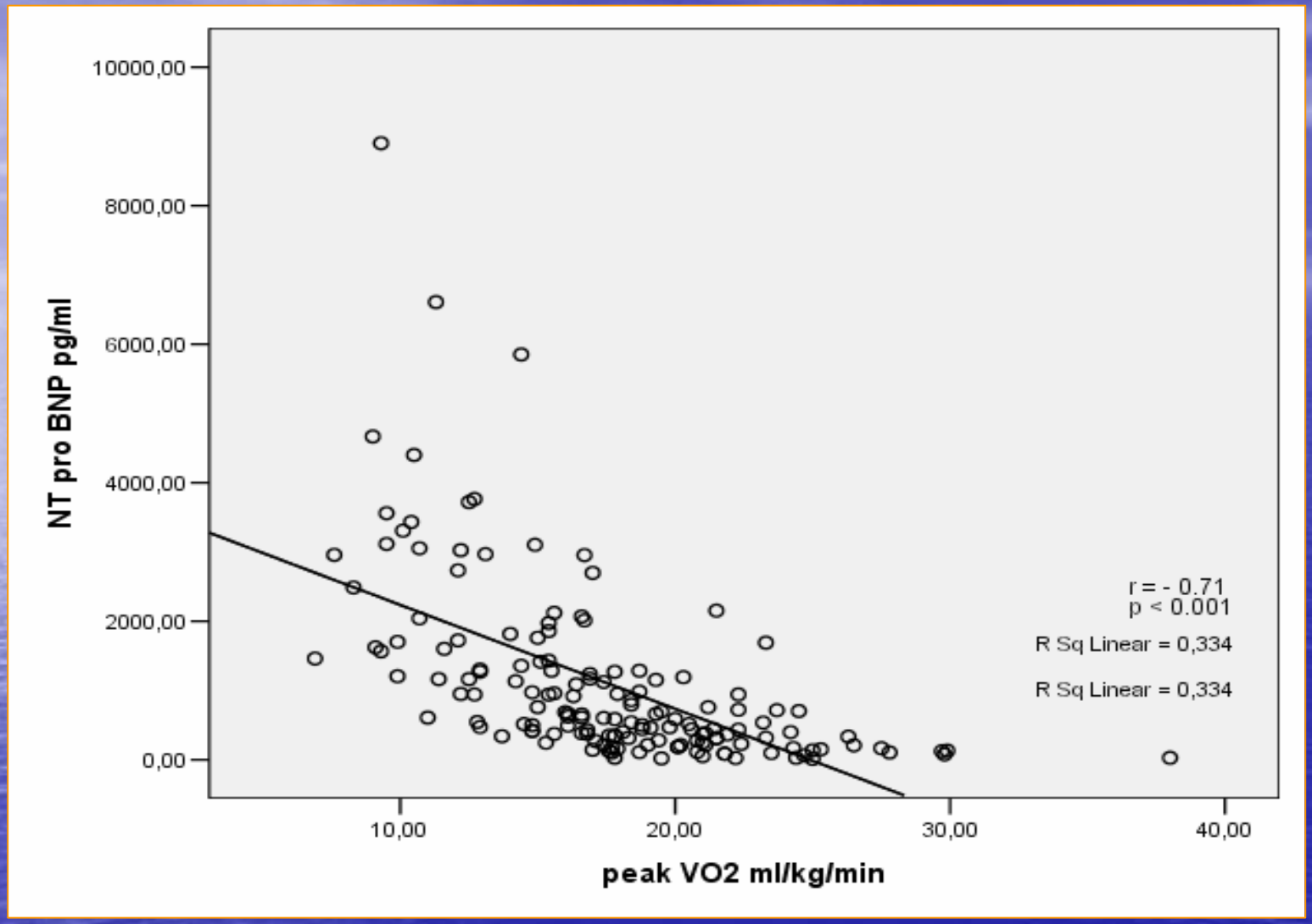


Fig. 1. BNP concentrations in control and patient groups. Boxes are median and IQRs, vertical lines are ranges of concentrations.

Patients with LVEF greater than 55%had lower BNP levels than those with LVEF less than 40%

Valliet al. ClinChimActa2001;306:19-26



Συσχετισμός του NT proBNP με τη μέγιστη κατανάλωση οξυγόνου

DIAGNOSTIC TOOL

Difficulty in the ER diagnosis of CHF

- Signs and symptoms of CHF –non-specific
- ECG, CXR often not helpful
- ECHO-gold standard but:
- Costly
- Pt is unable to hold still due to dyspnea
- “Poor window”

Maisel AS et al. NEJM 2002;347:161-167

-Prospective study on 1586 pts in ER with acute dyspnea

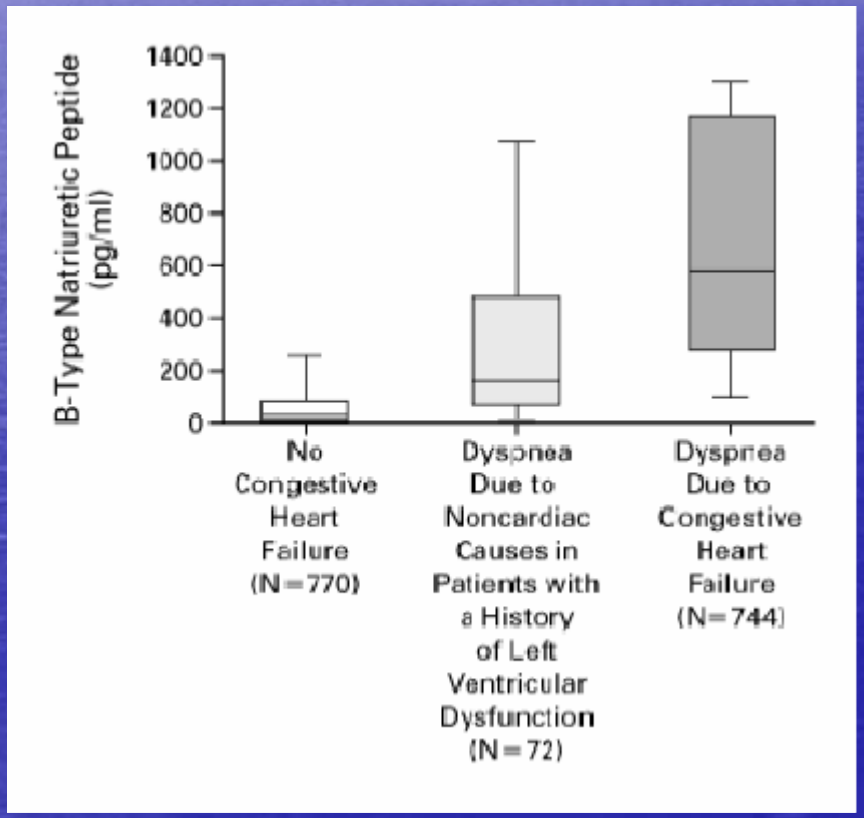
-ER Physicians blinded to BNP results assessed the probability of CHF as the cause of dyspnea on a scale of 0-100

-Patients divided in 3 groups:

- No CHF
- Dyspnea due to noncardiac cause with hx of CHF
- Dyspnea due to CHF

-Subsequently 2 cardiologists reviewed medical records during the hospitalization (CXR, ECHO, MUGA etc.)

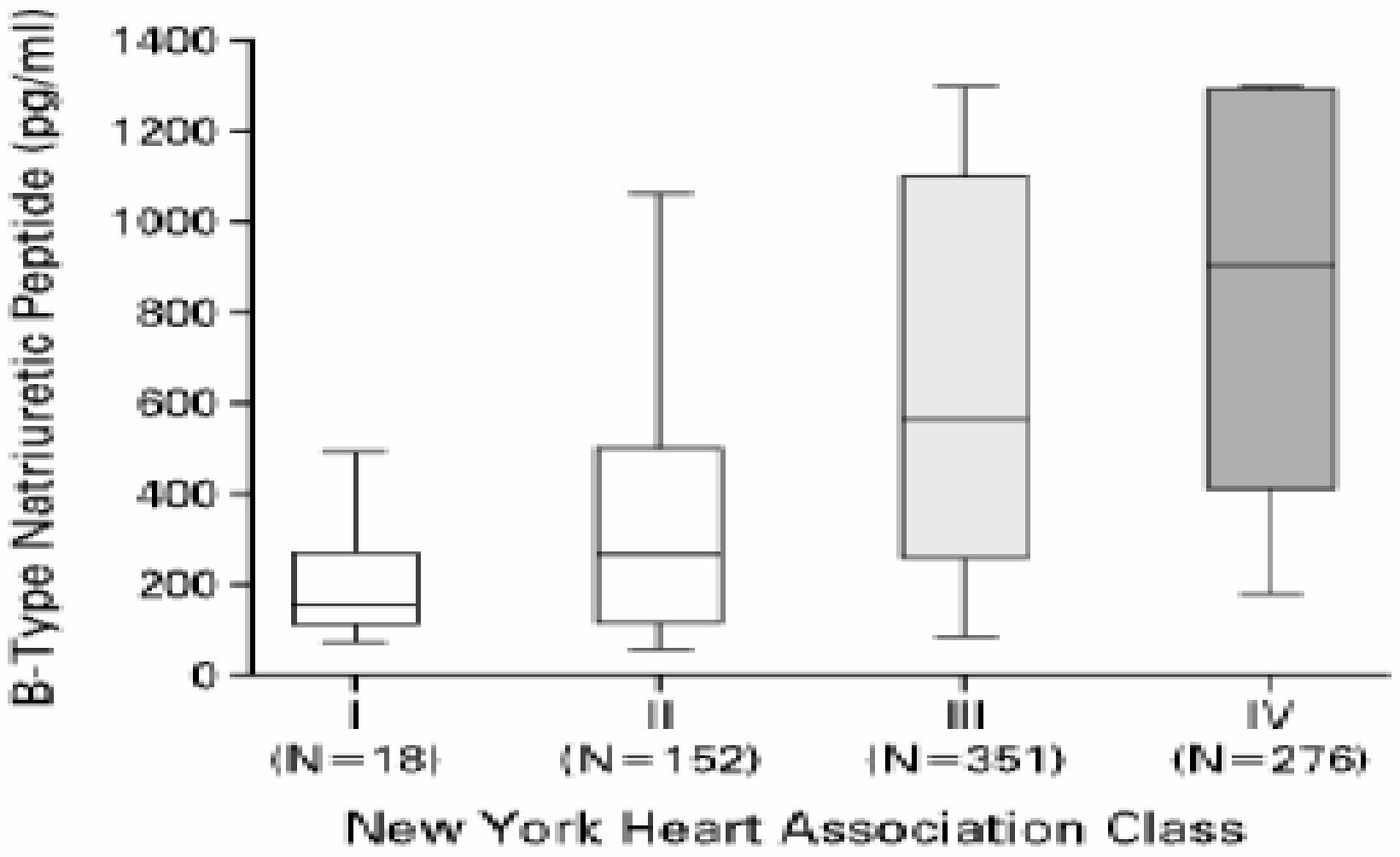
Median level of BNP measured in the ER



Results

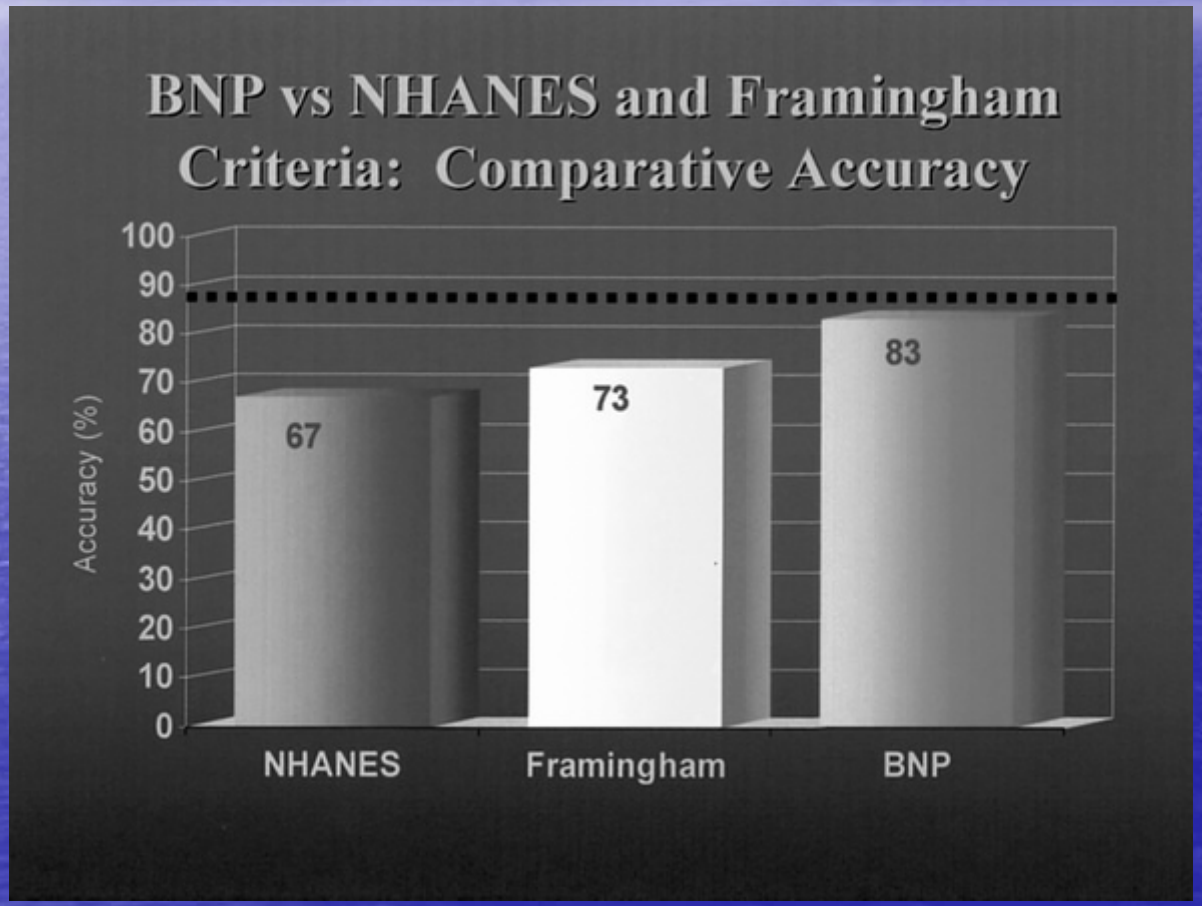
- CHF→BNP 675 ±450 pg/ml
- No CHF but hx of CHF →346 ±390 pg/ml
- No CHF→BNP 110 ±225 pg/ml

BNP values in relation to NYHA class



- BNP level was the single most accurate predictor of the presence or absence of CHF
- BNP cut-off of 100 pg/ml was more accurate (83%) than the Framingham criteria (73%)

Accuracy of a single BNP level (>100 pg/mL) in diagnosing CHF compared with established criteria of NHANES and Framingham.



BNP levels beat physical examination in diagnosing heart failure

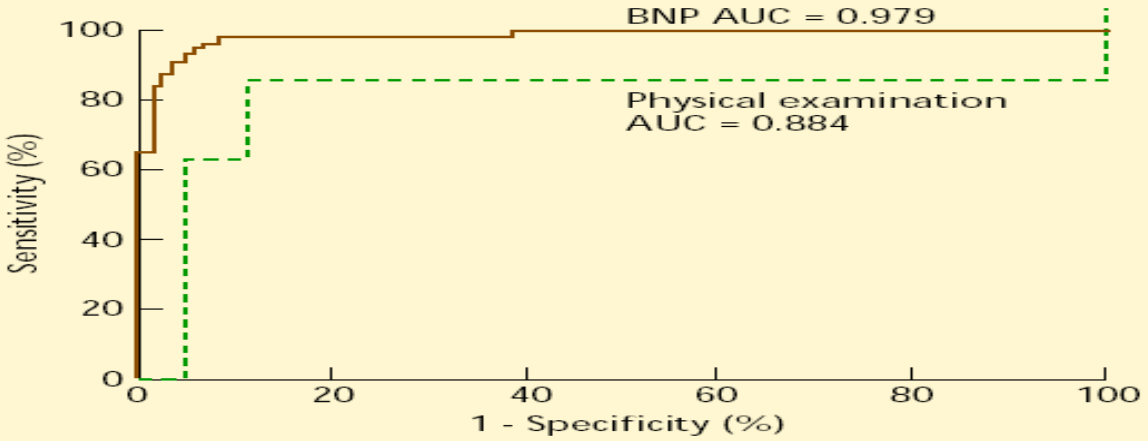


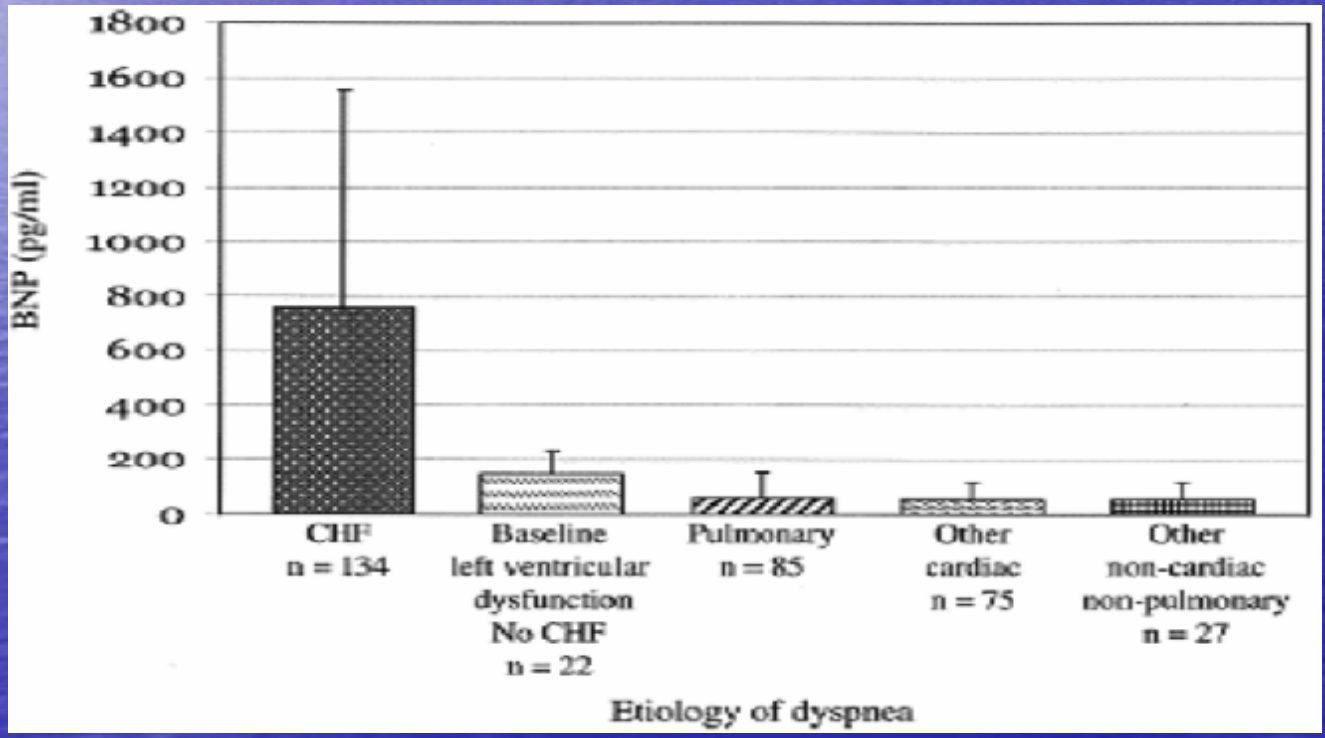
FIGURE 2. Receiver operating characteristic curves for the accuracy of elevated brain natriuretic peptide (BNP) levels and physical examination in the emergency department in 250 patients with suspected heart failure. AUC, area under the curve; the larger the AUC, the better the test.

FROM DAO Q, KRISHNASWAMY P, KAZANEGRA R, ET AL. UTILITY OF B-TYPE NATRIURETIC PEPTIDE IN THE DIAGNOSIS OF CONGESTIVE HEART FAILURE IN AN URGENT-CARE SETTING. J AM COLL CARDIOL 2001; 37:379–385.

Cardiac vs Pulmonary Causes of Dyspnea

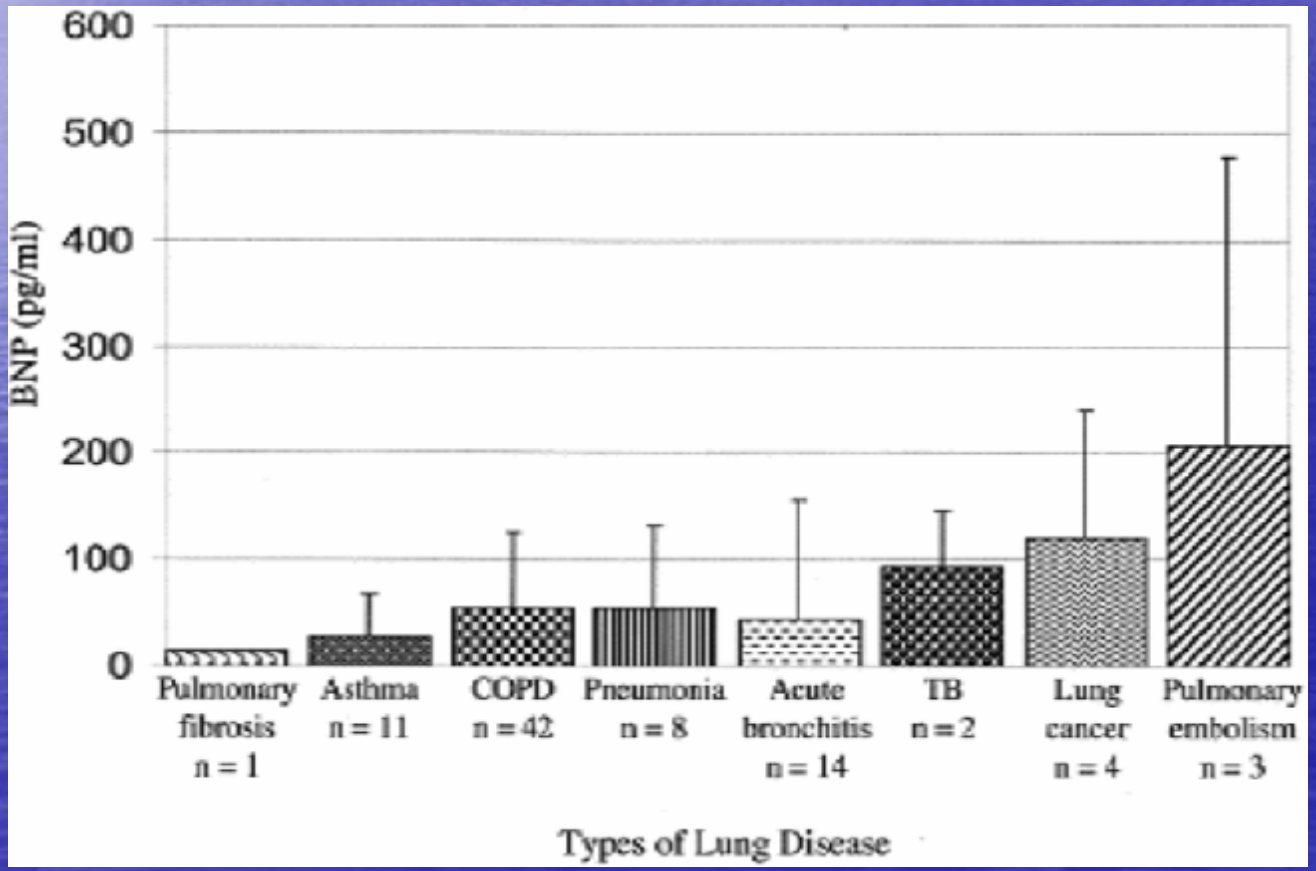
How accurate is BNP in differentiating between these two important clinical entities?

CHF vs. COPD



Morrison JACC 2002;39:202-209

Types of Lung Disease and BNP



Morrison JACC 2002;39:202-209

CHF vs. COPD

Confounding factors:

–Cor pulmonale

–Pneumonia leading to CHF exacerbation

–Acute RV failure due to PE

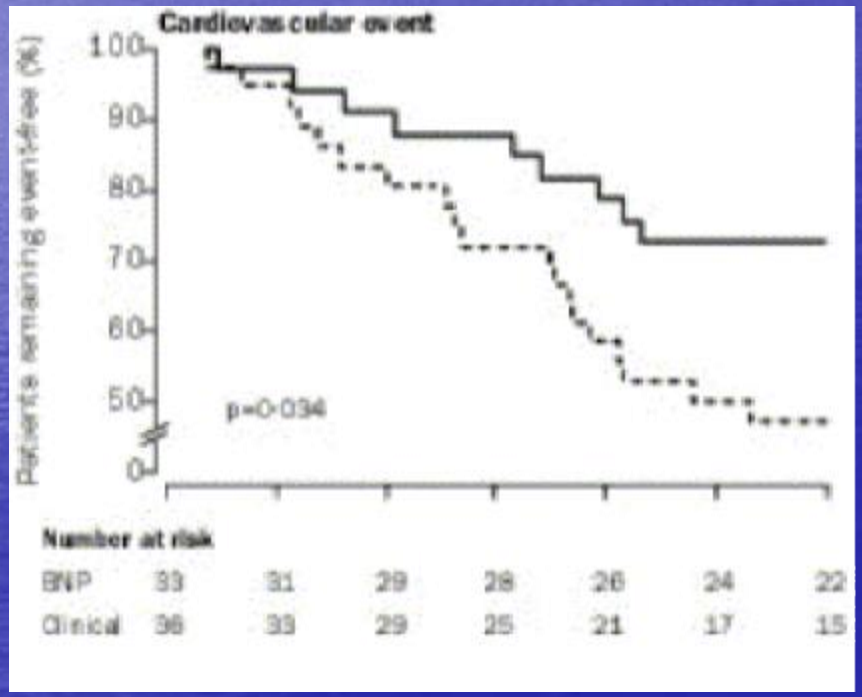
⇓

PPV of BNP decreases

BNP for therapeutic monitoring of CHF patients

Troughton et al. Lancet 2000;355:1126-1130

- 69 pts with EF < 40% and NYHA II-IV CHF
- Randomized to Rx guided by BNP or clinical assessment
- 6-month f/u
- End-point: total CV event (CV death or first readmission for CHF)


Cardiovascular event
Patients remaining event-free (%)
100
90
80
70
60
50
0
p=0·034
Number at risk
BNP 33 31 29 28 26 24 22
Clinical 36 33 29 25 21 17 15

- Fewer total CV events (death, admission, HF decompensation) in BNP group (19 vs. 54, p=0.02)
- At 6 mo, 27 % of BNP pts and 53% of the clinical group had experienced a first CV event (p=0.034)

Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure

The STARS-BNP Multicenter Study

Objectives: The aim of this multicenter study was to evaluate the prognostic impact of a therapeutic strategy using BNP levels.

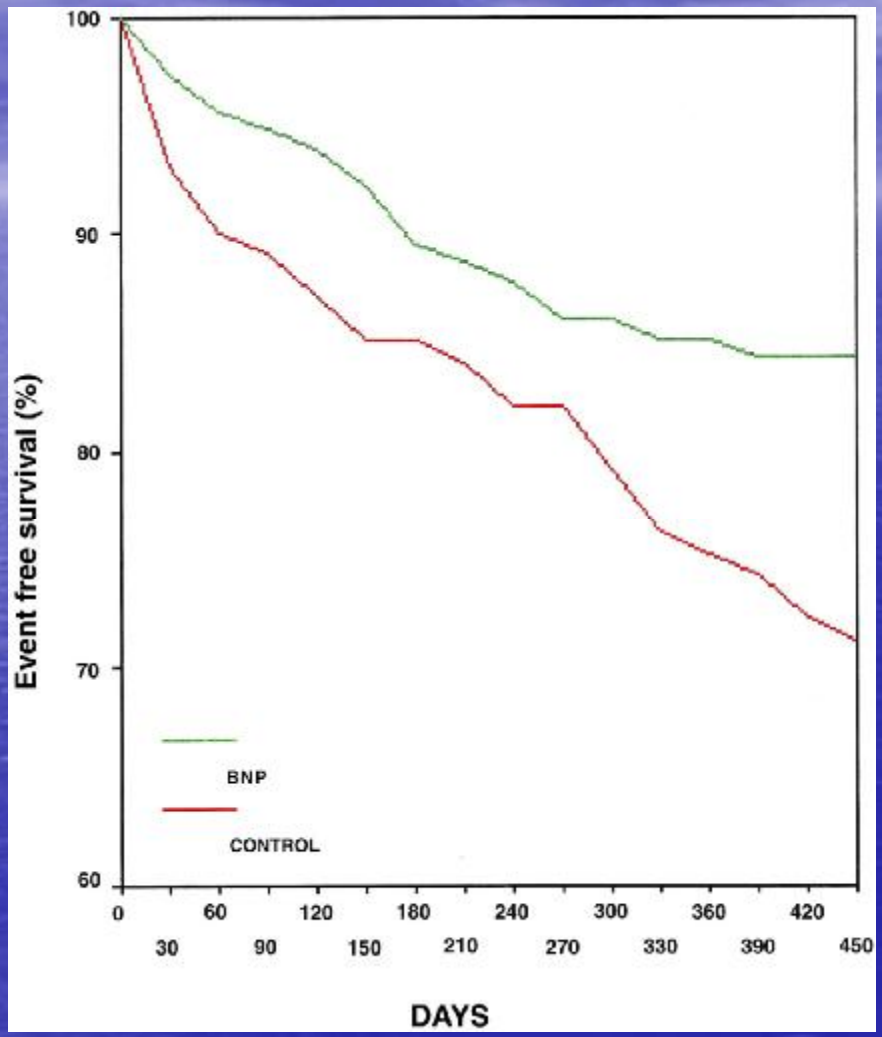
Methods: 220 NYHA II to III patients considered optimally treated with ACEIs, BBs, and diuretics were randomized to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels <100 pg/ml (BNP group). Outpatient visits were scheduled every month for 3 months, then every 3 months. The primary combined end point was CHF-related death or hospital stay for CHF.

Results: Both groups were similar for baseline clinical and biological characteristics. LV EF was slightly lower in the BNP group than in the clinical group (29.9 ± 7.7% vs. 31.8 ± 8.4%, $p = 0.05$). At the end of the first 3 months, all types of drugs were changed more frequently in the BNP group. Mean dosages of ACEIs and beta-blockers were significantly higher in the BNP group ($p < 0.05$), whereas the mean increase in furosemide dosage was similar in both groups. During follow-up (median 15 months), significantly fewer patients reached the combined end point in the BNP group (24% vs. 52%, $p < 0.001$).

Conclusions: In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages.

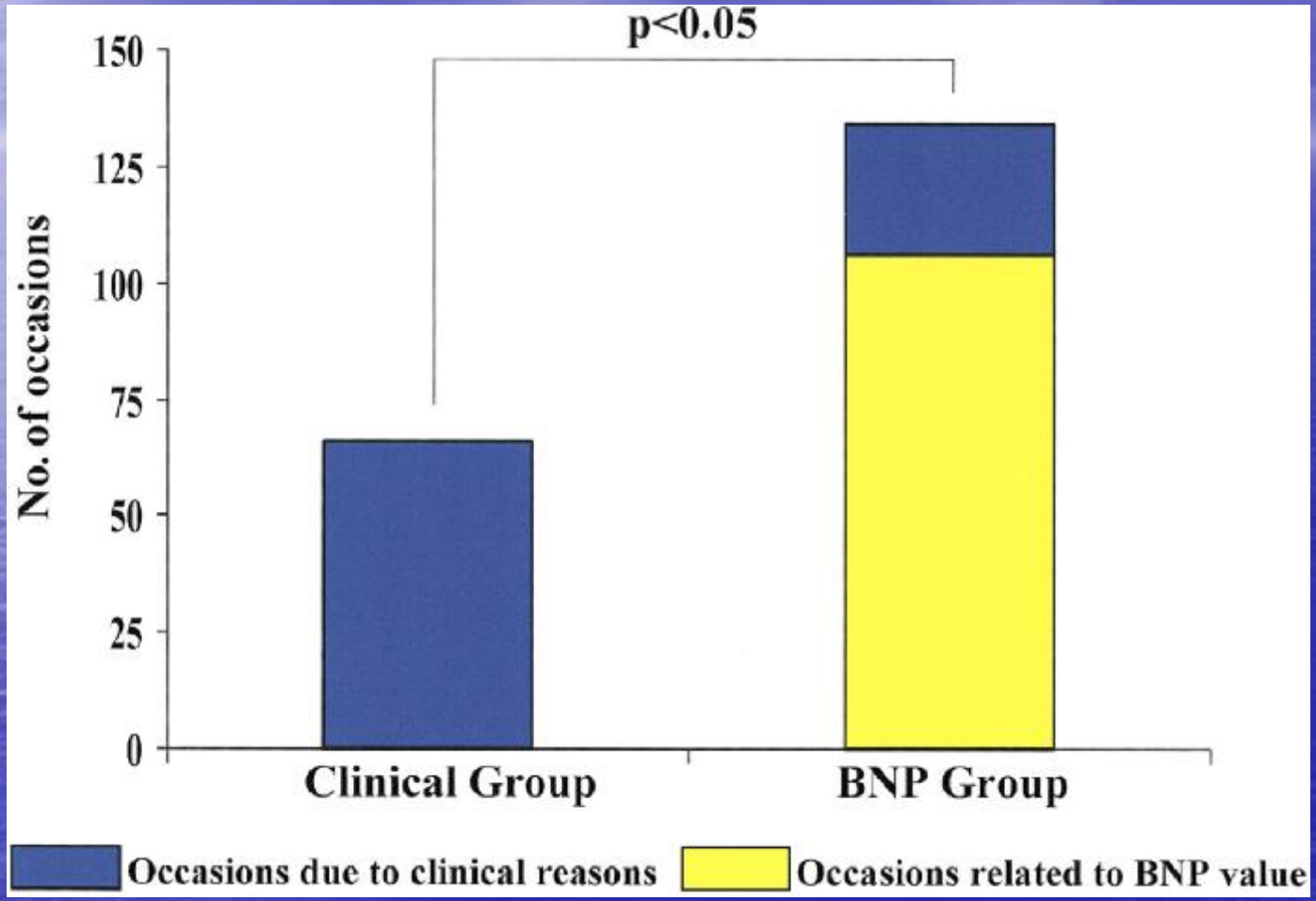
J Am Coll Cardiol, 2007; 49:1733-1739

Event-Free (Hospital Stay for Heart Failure or Death Related to Heart Failure) Survival in the 2 Groups



Jourdain, P. et al. J Am Coll Cardiol 2007;49:1733-1739

Number of Changes in Medical Therapy During the First 3 Months



Jourdain, P. et al. J Am Coll Cardiol 2007;49:1733-1739

BNP in Diastolic Heart Failure

Lubien et al. Circ.2002;105:595-601

- 294 pts referred for ECHO to evaluate. LVEF
- EF < 50% excluded
- Pt classification:

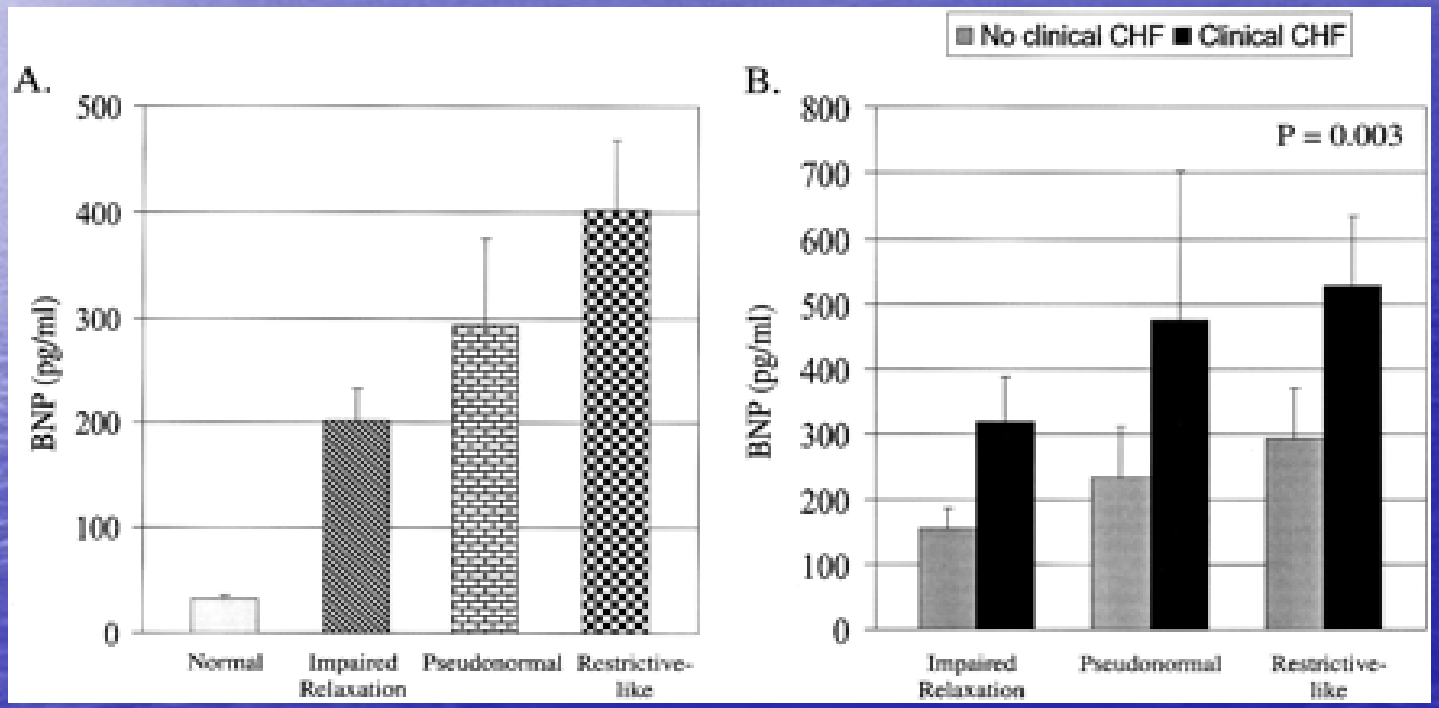
Normal

Impaired relaxation

Pseudonormal

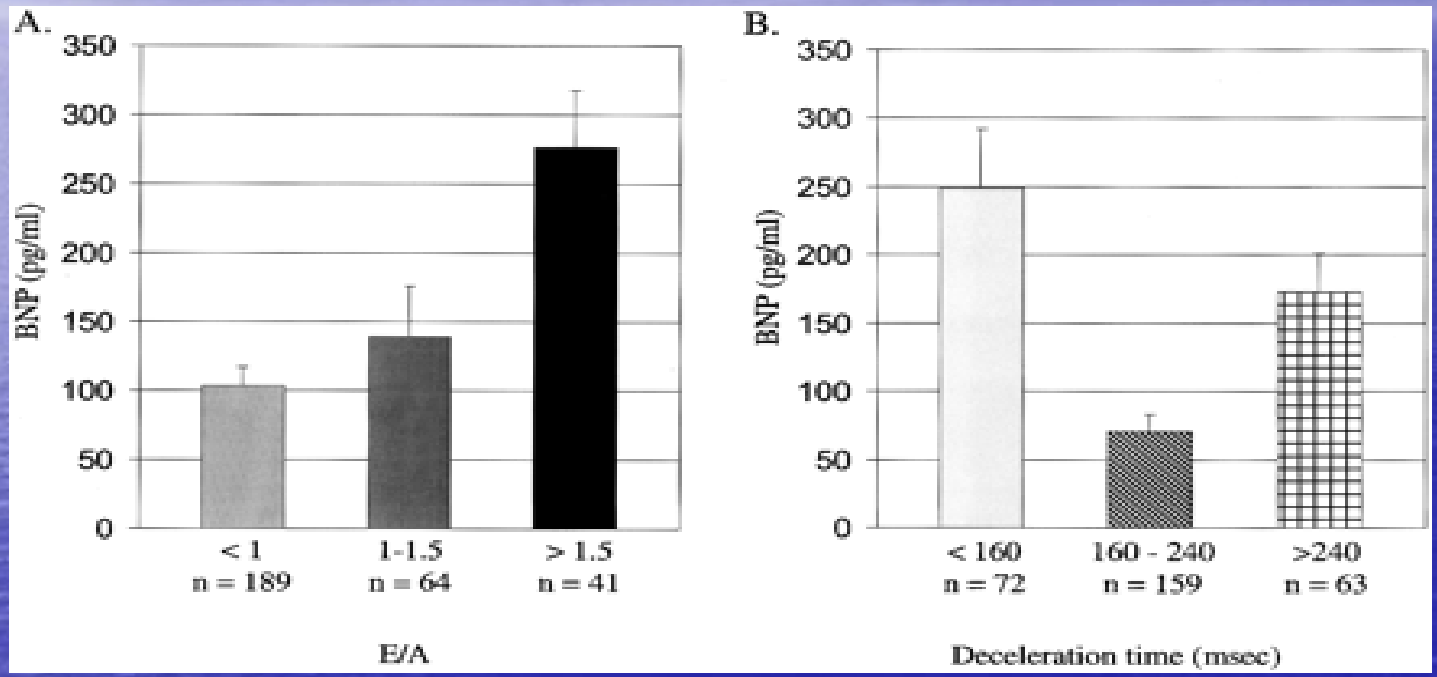
Restrictive like filling

BNP and diastolic HF



A, Mean±SEMfor normal BNP values vsimpaired relaxation, pseudonormal, and restrictivelikefilling patterns. Each abnormal group was different from normal group by post hoc Tukeytests (*P*<0.001). B, Comparison of 3 diastolic filling patterns subdivided by whether patients had symptoms. Values are mean±SEM. Subgroups of diastolic dysfunction patients with clinical CHF overall had higher BNP levels than those without symptoms. *P*<0.05 by post hoc Tukeytest .

Doppler measurements and BNP



BNP levels expressed as reflection of E/A ratios and DTs. Valuesare mean±SEM. BNP levels were highest in patients with E/A ratios >1.5 (227±61 pg/mL) and in those patients with DTs of <160 ms (249±43 pg/mL). In patients with normal E/A ratio (1 to 1.5), BNP levels were 139±65 pg/mL. However, when this group was separated by DTs, those with normal DTs (160 to 240 ms) had mean BNP levels of only 77±34 pg/mL.

Detecting Diastolic Heart Failure by BNP

BNP of 62 pg/ml:

-sensitivity 85%
-specificity 83%
-accuracy 84%

BNP and DRUGS

- Diuretics
- B-blockers
- Ace Inhibitors
- ARBS
- Digitalis
- Calcium Chanel Blockers

BNP a helpful tool for hospital discharge

When should we discharge a pt after CHF exacerbation?

End-point of our hospital treatment:?

–Symptomatic improvement

–Cardiac function tests do not correlate well with symptomatic changes

In-hospital mortality and readmission rates are extremely high

Most patients are discharged when they feel better

BNP correlates with falling wedge pressure

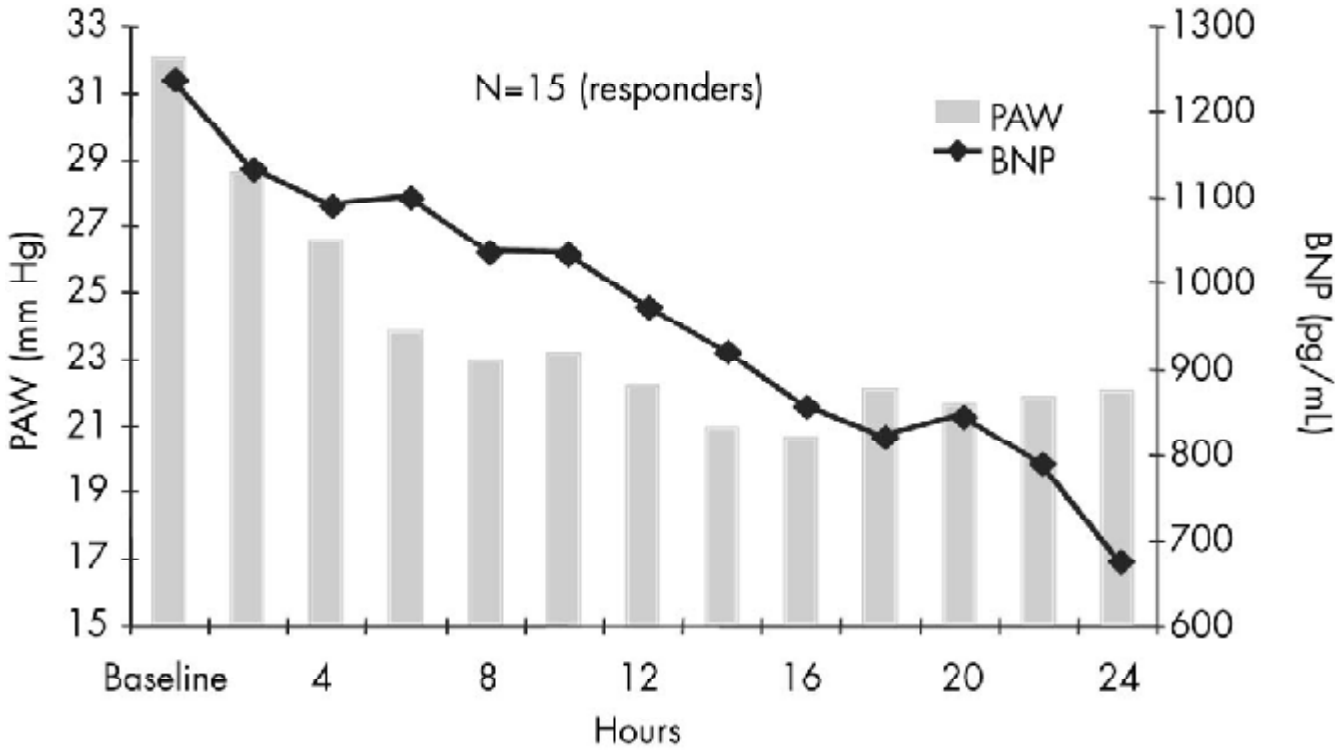
Kazanegra et al. J Cardiac Fail 2001;7:21-29

- Pilot study:

  - 22 pts with decompensated CHF
  - Hemodynamic monitoring with Swan-Ganz catheter
  - All pts in NYHA IV
  - Starting wedge pressure > 20 mmHg
  - Attempt made to decrease wedge pressure (<20) in 24 hours
  - BNP levels recorded at baseline an q2-4 h x 24-48h

BNP Consensus Panel 2004

B-Type Natriuretic Peptide Consensus Panel



Relationship of B-type natriuretic peptide (BNP) levels and pulmonary artery wedge(PAW) pressure in patientswith volume-overloaded congestive heart failure. Reprinted from *Journal of Cardiac Failure*, 7, KazanegraR, Cheng V, Garcia A, et al., A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensatedheart failure: a pilot study, 21-29, C.

15 responders in 24h:

- –wedge pressure ↓by 51%
- –BNP dropped by 55%
- –average fall of BNP/hour: 33 ±5pg/ml
- –When wedge pressure was kept low, the BNP fell an additional 37% in the next 24h

- Significant correlation between percent change in wedge pressure from baseline in hour and the percent change of BNP per hour
- $R = 0.73$ $P < 0.05$

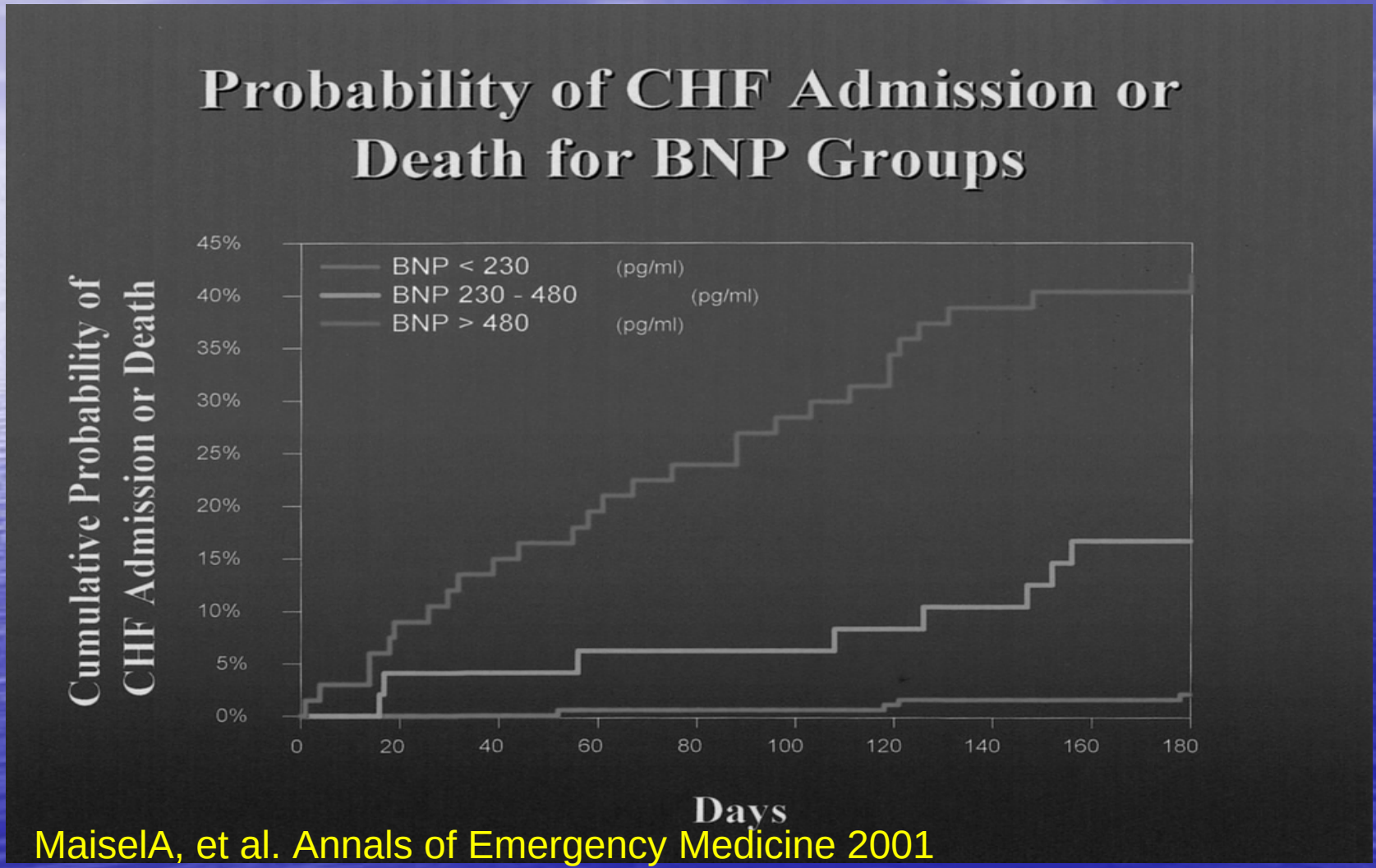
Can BNP predict outcome ?

- 13 end-points (4 death, 9 readmission)
- BNP increased (mean ↑233 pg/ml;P< .001)
- In pts without end-points BNP decreased (mean ↓215 pg/ml)

Can BNP predict outcome ?

- 13 end-points (4 death, 9 readmission)
- BNP increased (mean ↑233 pg/ml;P< .001)
- In pts without end-points BNP decreased (mean ↓215 pg/ml)

BNP Concentration for the Prediction of Clinical Events



MaiselA, et al. Annals of Emergency Medicine 2001

Reverse Kaplan-Meir plot showing cumulative risk of any hospitalization or death from CHF, stratified by BNP levels at the time of initial visit to the emergency department. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels >480 pg/mLhad a 6-month cumulative probability of CHF admission or death of 42%. Patients with BNP levels <230 pg/mLonly had a 2% chance of such an event