

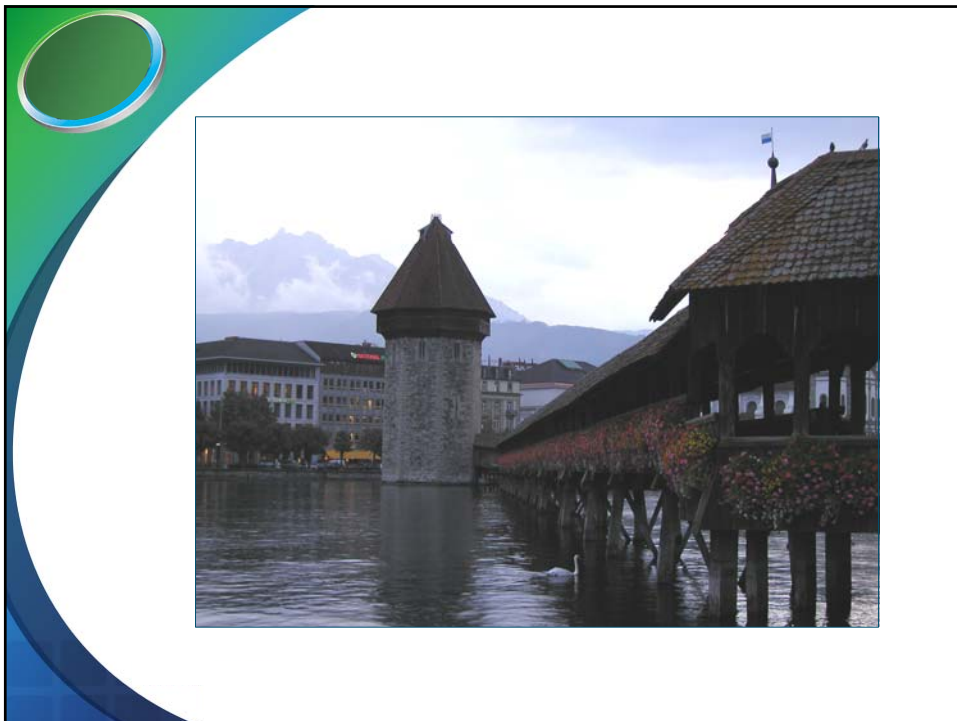


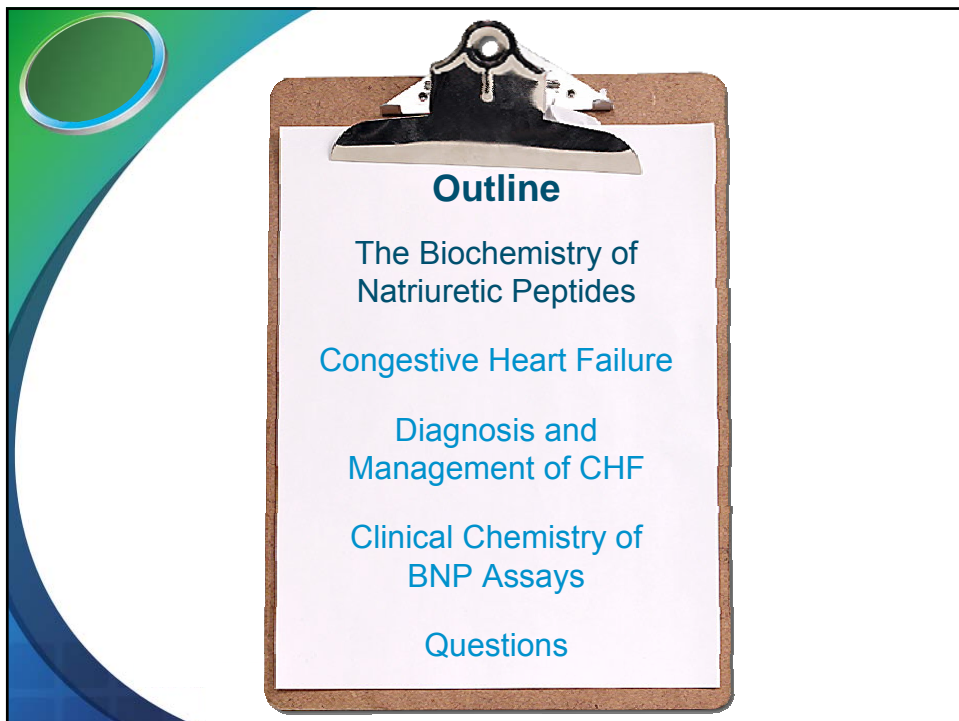
The slide features a central diagram illustrating the processing of BNP. At the top, a heart is shown with a red spot on the ventricle wall labeled 'proBNP'. An arrow points down to a blue area containing 'NT-proBNP' and 'BNP' molecules. To the right, another heart diagram is shown. The background is a dark blue circle with green and blue curved borders.

# BNP

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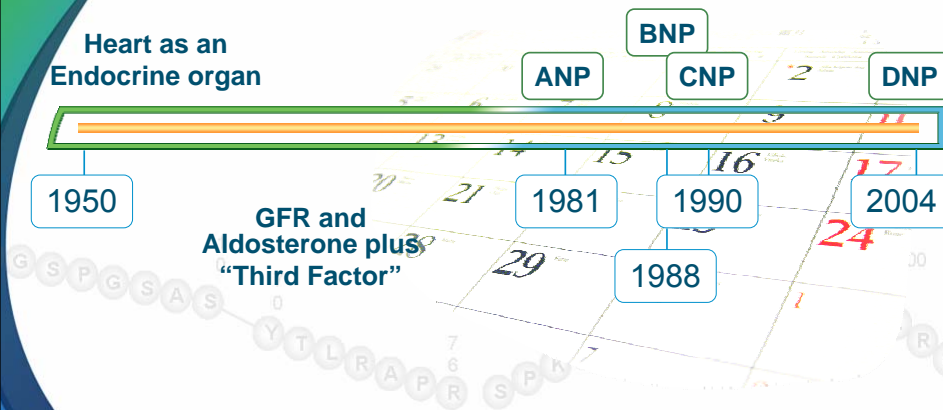
October 10, 2005





## Background

Heart as an Endocrine organ

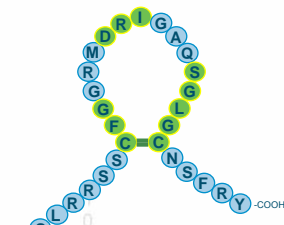


## Natriuretic Peptides

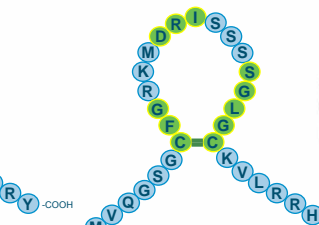
Half-life of 3-5 minutes

Half-life of 18 minutes

Half-life of 2.6 minutes



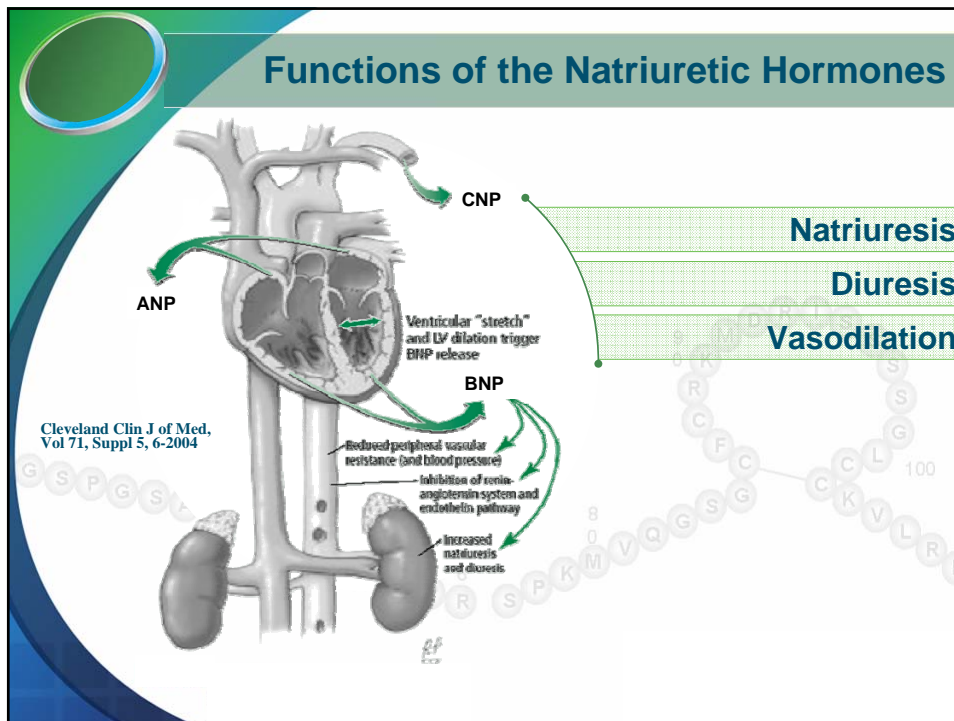
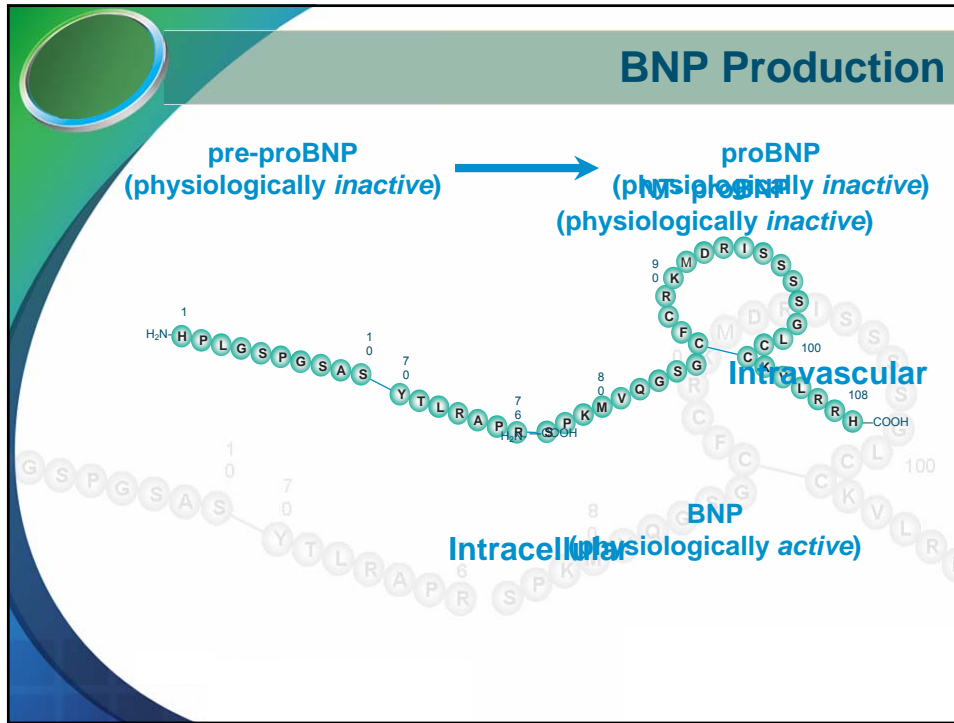
**ANP**  
28 aa peptide



**BNP**  
32 aa peptide



**CNP**  
22 aa peptide

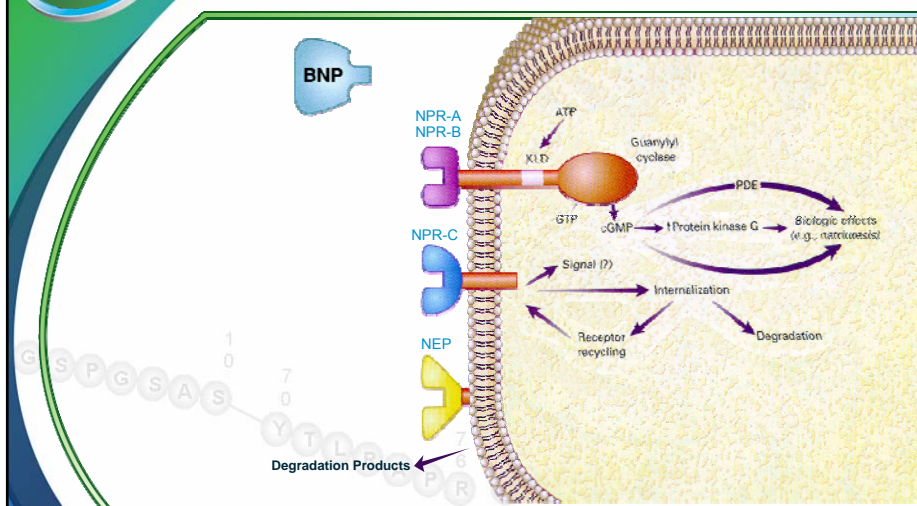


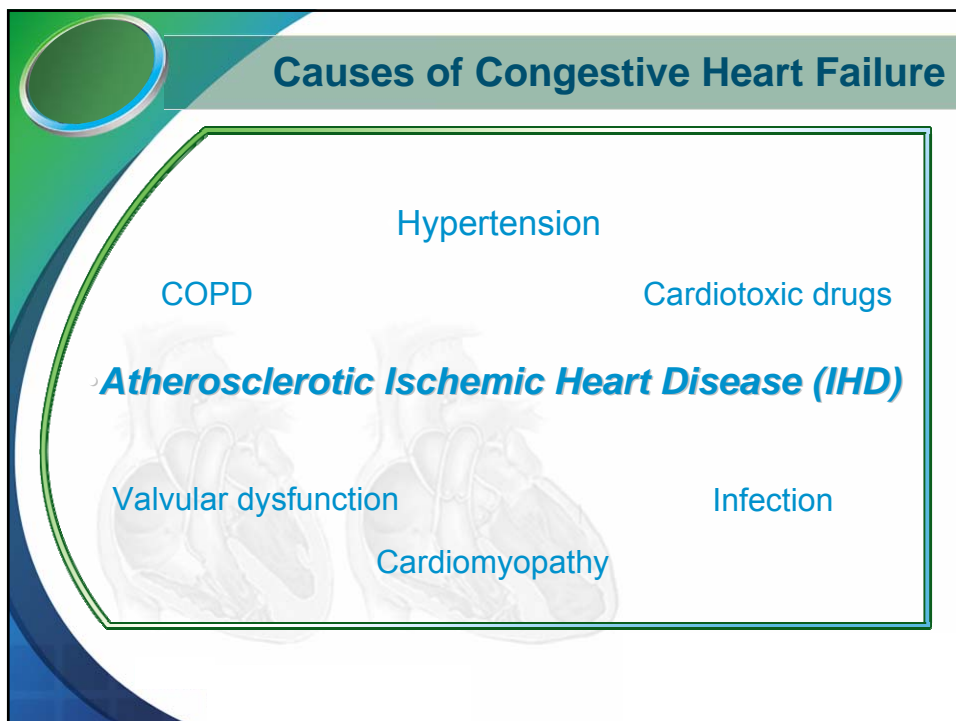
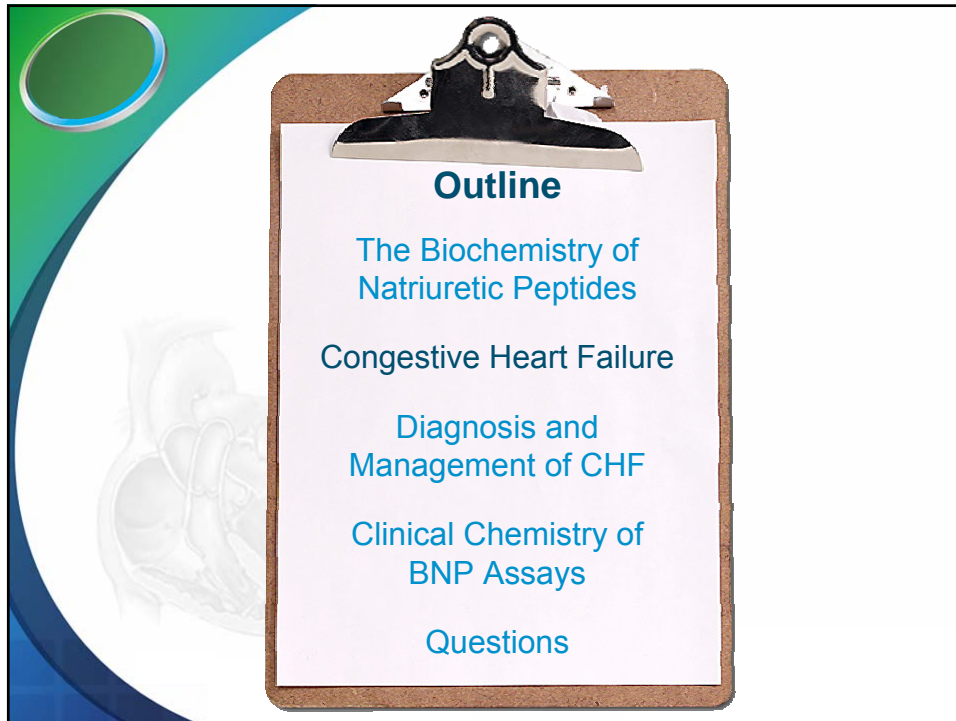
## Characteristics of Natriuretic Peptides

|                               | ANP   | BNP  | CNP                                  |
|-------------------------------|---|--|--------------------------------------|
| Structure                     | 28 amino acids  | 32 amino acids   | 22 amino acids                       |
| Major sites of synthesis      | Cardiac myocytes, production shifts from atria to ventricles in cardiac overload; induction of gene expression slow | Cardiac myocytes, central nervous system; induction of gene expression rapid   | Vasculature, central nervous system  |
| Major regulators of secretion | Myocyte stretch, vasoactive factors; stored in granules, plasma levels regulated at the level of hormone secretion  | Myocyte stretch; regulation of secretion occurs mainly at the level of synthesis, especially in ventricular myocytes | Cytokines, growth factors            |
| Major effects                 | Natriuresis, diuresis, vasodilatation, inhibition of renin secretion and angiotensin II actions                     | Natriuresis, diuresis, vasodilatation, inhibition of renin secretion and angiotensin II actions                      | Vasodilatation; inhibition of growth |

Ruskoaho H et al. J Mol Med 1997;75:876-885

## Mechanism of Action





## Epidemiology of CHF

Acute CHF affects over 1,000,000 annually in the US

Direct mortality - 42,000 deaths/year  
Indirect mortality - 220,000 deaths/year

Incidence - 500,000 new cases/year

Prevalence - 5 million (1.8%); 10% after age 75

CHF is the #1 cause of hospitalization for people over 65

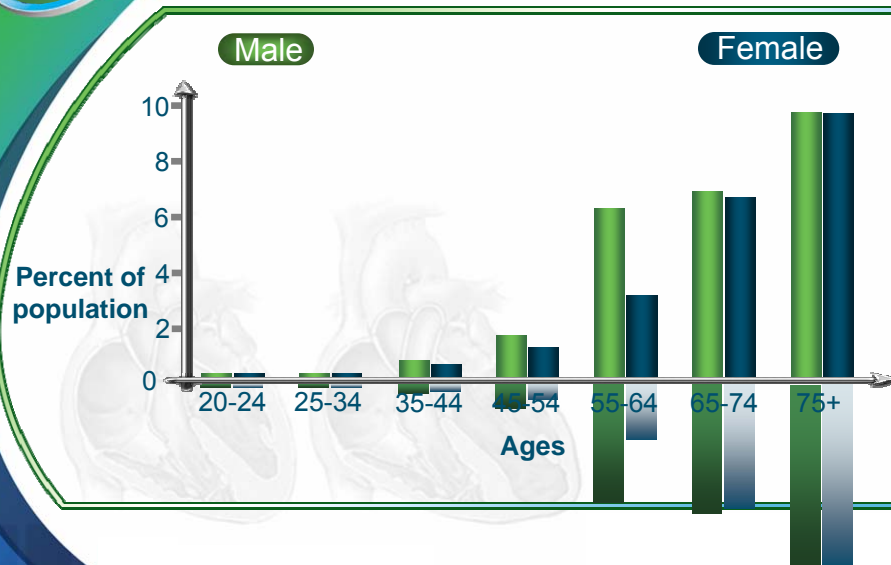
Associated with a readmission rate of 30 - 40% in 90 days

CHF causes significant morbidity and mortality; 60% of men and 49% of women die within 5 years of diagnosis

Sudden death occurs at 6 - 9x the rate for the general population

**Costs: \$21 Billion/year**

## Prevalence in U.S. 1988 - 1994



## Neurohumoral Changes

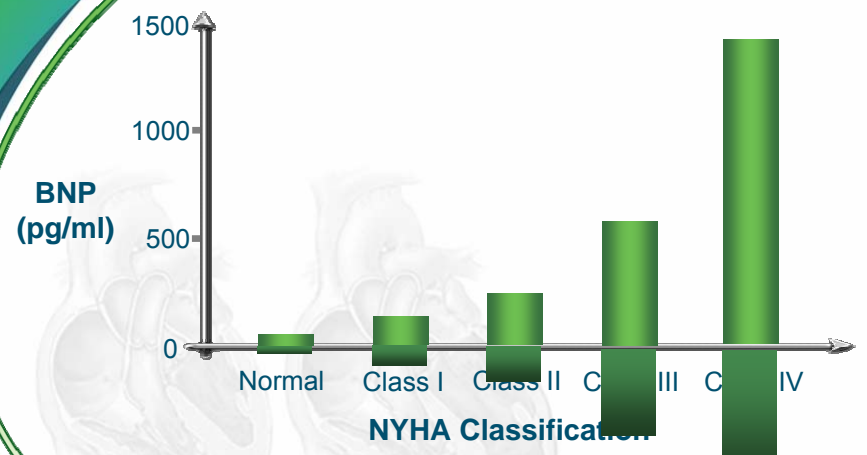
Heart Failure

Increases...


- Sympathetic nervous system activity (Epinephrine, NE)
- Endothelin
- Arginine vasopressin
- Renin and Angiotensin II
- Aldosterone
- Neuropeptide Y
- ANP and BNP
- Insulin, Cortisol, Growth hormone, Tumor necrosis factor- $\alpha$ , Interleukin 6, Vasoactive intestinal peptide, Adrenomedullin, Urodilatin
- Dopamine
- Prostaglandins (PGI<sub>2</sub>, PGE<sub>2</sub>)
- Vasodilator peptides, (e.g., Bradykinin)

NOTE: Measurements in individual patients vary significantly; changes may not always be present.

## BNP Levels Correlate to NYHA Class



Alan Maisel et al, Clinical Laboratory News. Volume 27(3), March, 2001.



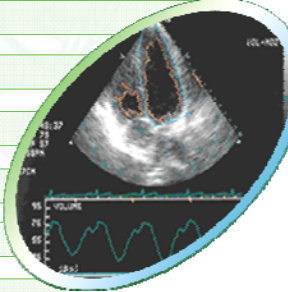
**Outline**

- The Biochemistry of Natriuretic Peptides
- Congestive Heart Failure
- Diagnosis and Management of CHF
- Clinical Chemistry of BNP Assays
- Questions

A clipboard with a silver clip at the top, holding a white sheet of paper with the text. The background features a green and blue circular graphic on the left and a faint circular seal of the American Medical Association on the right.

## CHF May Be Difficult to Diagnose

- Non-specific clinical signs and symptoms
- No simple near-patient diagnostic test
- Usual hospital diagnostic procedures:
  - Echocardiography
  - Cardiac catheterization
  - Radiography (radionuclide ventriculography)
- Problems: Not always available
  - Time-consuming
  - Expensive



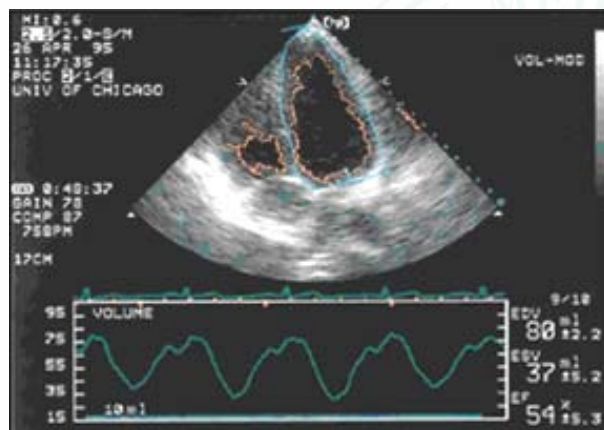
An echocardiogram image showing a cross-section of the heart with a red overlay indicating blood flow. Below the image is a waveform graph. The background features a green and blue circular graphic on the left and a faint circular seal of the American Medical Association on the right.

## Left Ventricular Ejection Fraction (LVEF)

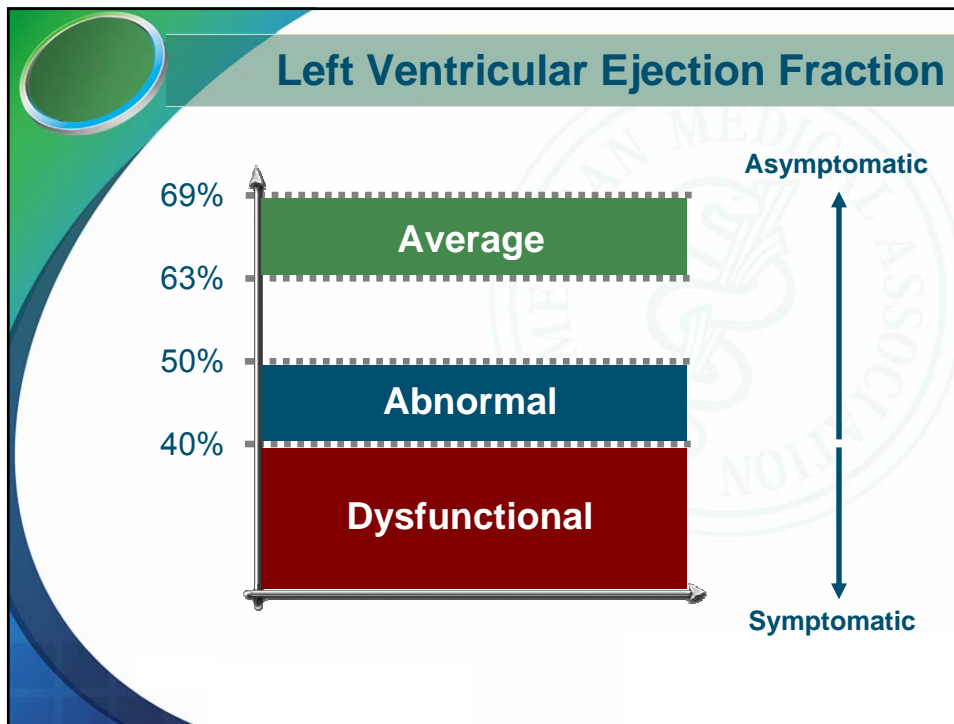
$$LVEF = \frac{\text{Stroke Volume}}{\text{End Diastolic Volume}}$$

Stroke Volume = (End Diastolic Volume – End Systolic Volume)

## Two-dimensional Doppler Echocardiogram



Blue Line – Left Ventricle  
Orange Line – Blood Endocardial Border



### Why Test for Natriuretic Peptides?

Simply, rapidly, inexpensively measured potential uses

- Diagnosis
- Prognosis
- Guiding Therapy

## Diagnosis

| Predictor                 | P-value | Odds Ratio |
|---------------------------|---------|------------|
| HTN                       | 0.03    | 2.3        |
| Male sex                  | 0.002   | 4.0        |
| IHD                       | 0.0003  | 6.0        |
| BNP<br>(> 12.9 pg/mL)     | 0.005   | 13.0       |
| NT-proBNP<br>(> 86 pg/mL) | <0.0001 | 14.5       |

HTN, Hypertension; IHD, Ischemic Heart Disease; BNP, B-type Natriuretic Peptide, NT-proBNP, N-terminal proBNP

## Diagnosis: BNP for CHF Screening

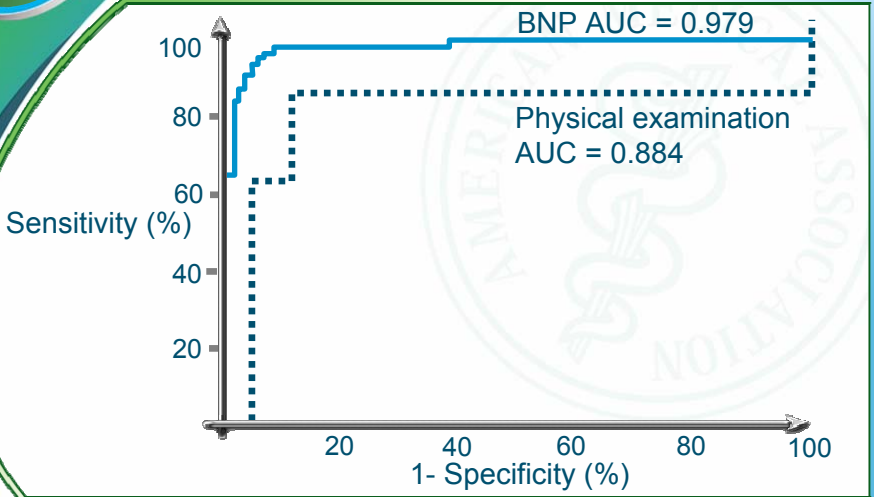
### Type of patient population

|             | General | Symptomatic PC |
|-------------|---------|----------------|
| Sensitivity | 76      | 97             |
| Specificity | 87      | 84             |
| PPV         | 16      | 70             |
| NPV         | 98      | 98             |

PC, Primary Care  
PPV, Positive Predictive Value  
NPV, Negative Predictive Value

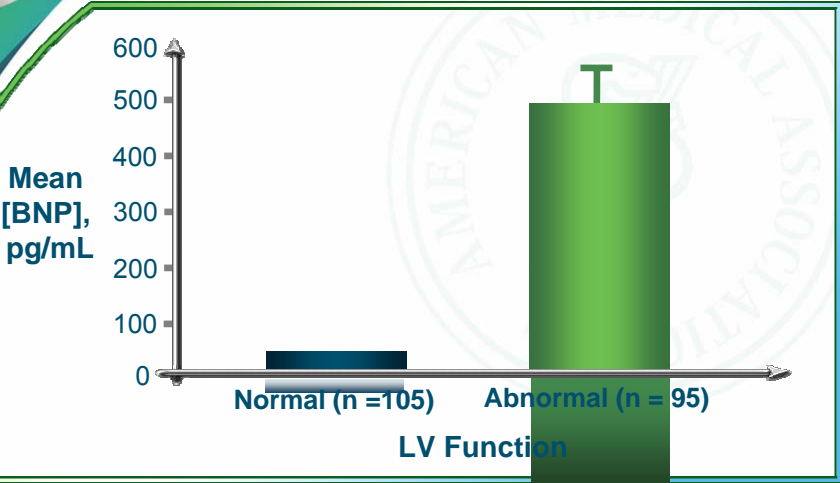
Source: Struthers A. Heart 2000;84:334-38.

# BNP versus Physical Exam



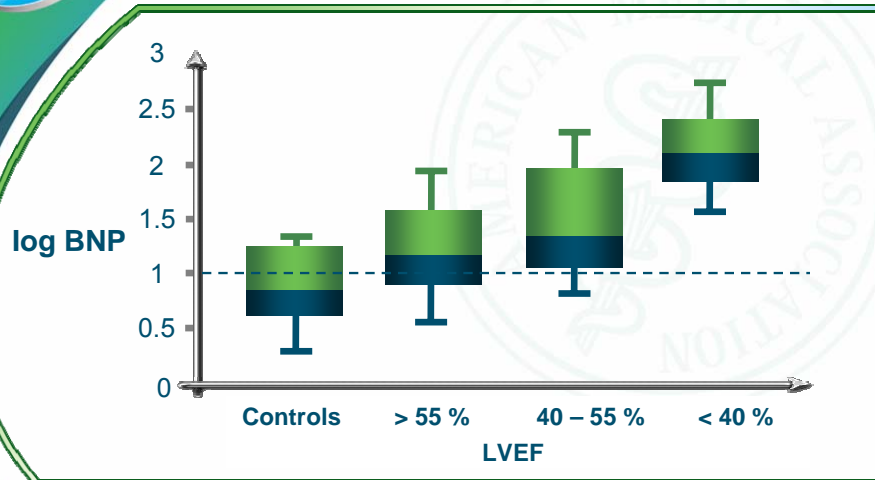
Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type Natriuretic Peptide in the Diagnosis of Congestive Heart Failure in an Urgent-care Setting. J Am Coll Cardiol 2001; 37:379-385.

# Diagnosis: BNP Predicts Abnormal LV Function



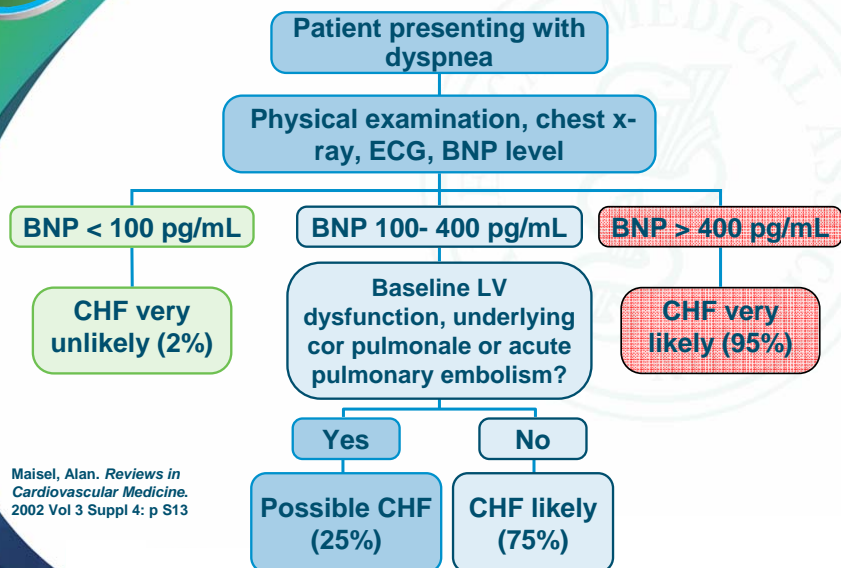
Source: Maisel AS et al. Am Heart J 2001; 141:367-74

## Diagnosis: BNP vs LVEF

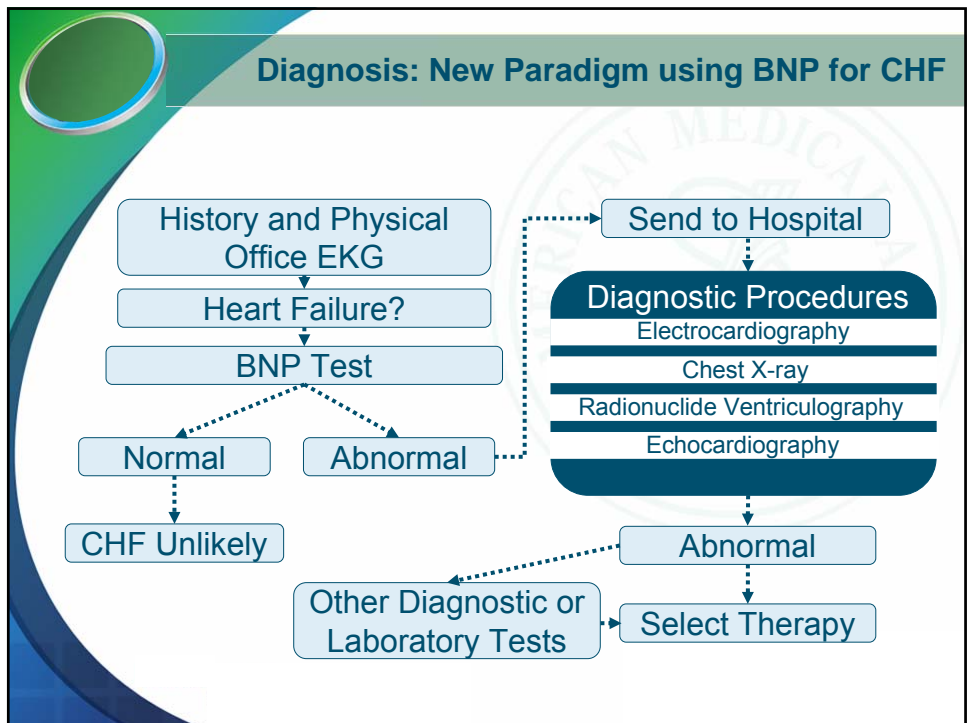
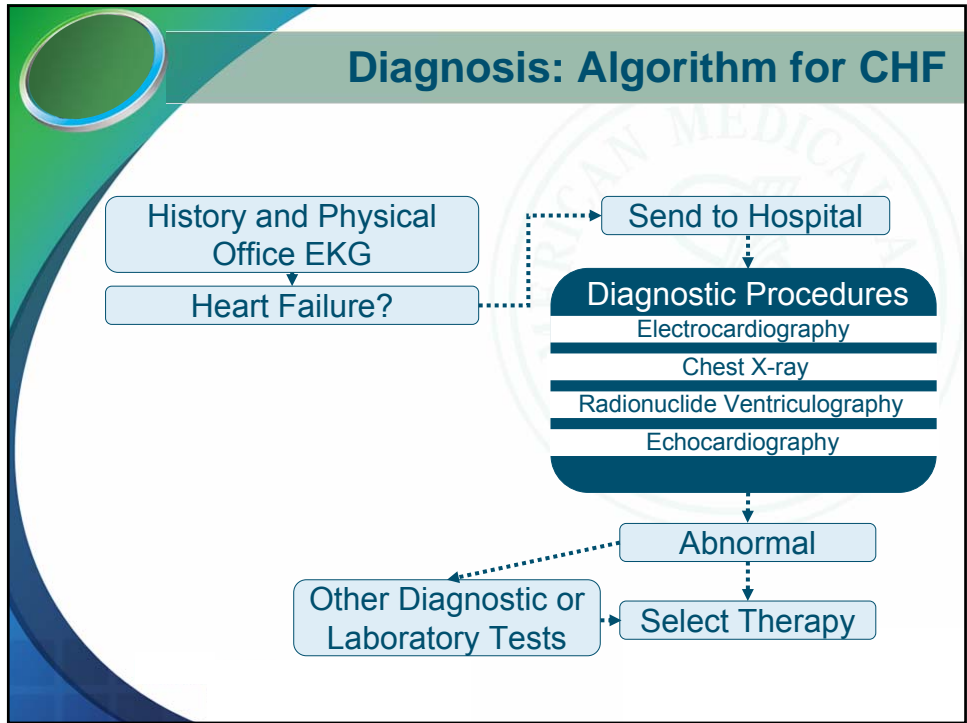


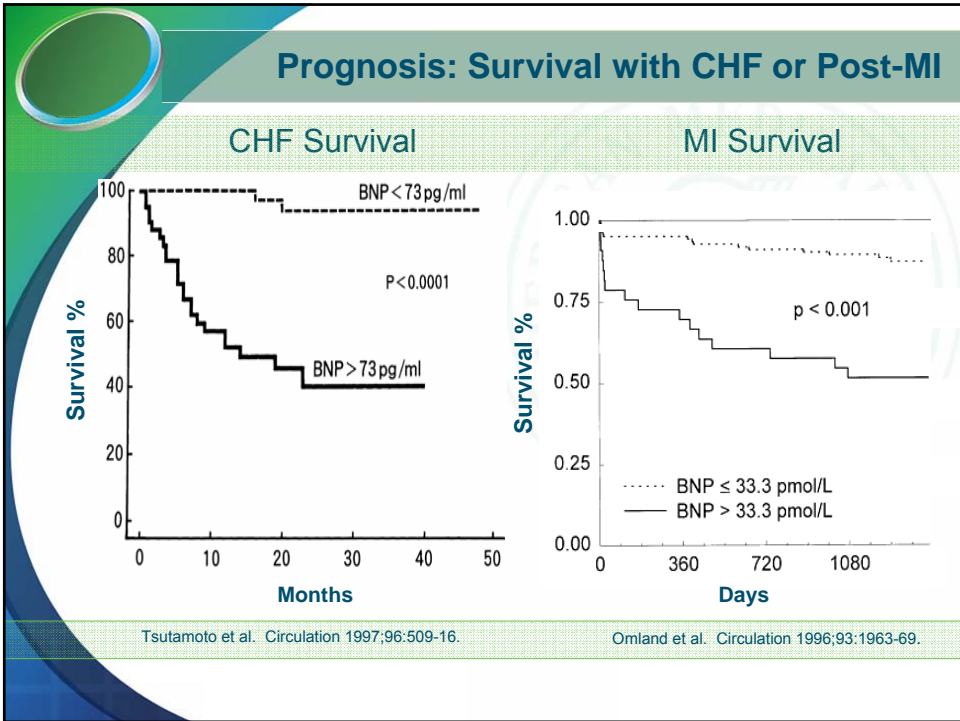
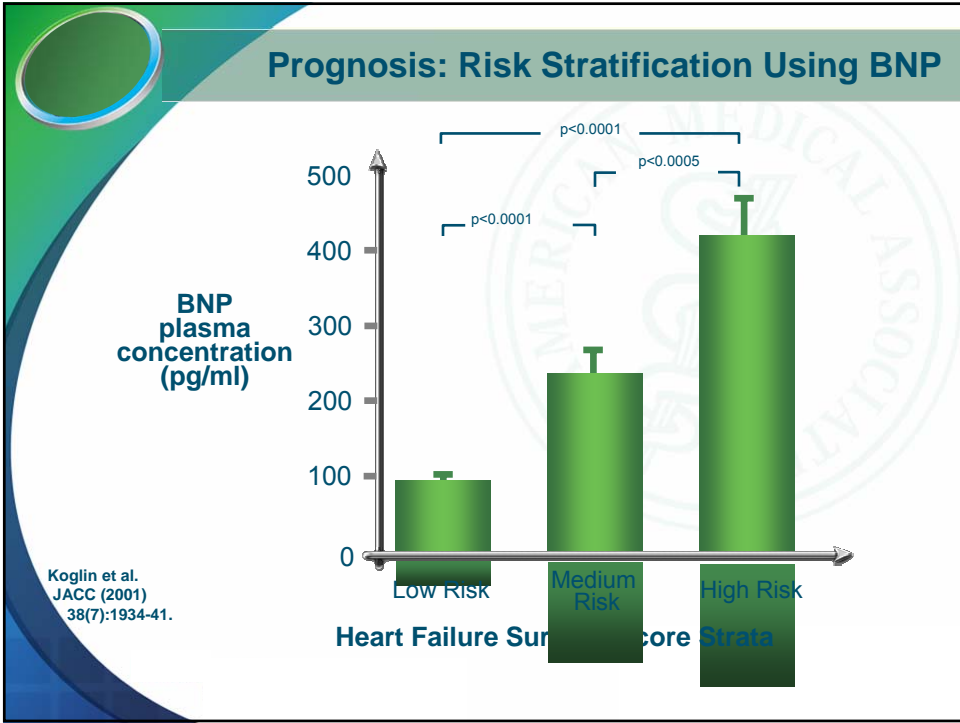
Valli et al. Clin Chim Acta 2001;306:19-26

## Clinical Algorithm for Interpreting BNP



Maisel, Alan. *Reviews in Cardiovascular Medicine*. 2002 Vol 3 Suppl 4: p S13





## BNP Guided Therapy for CHF

Trial

69 patients (LVEF <40% ) and symptomatic HF (NYHA class IV)

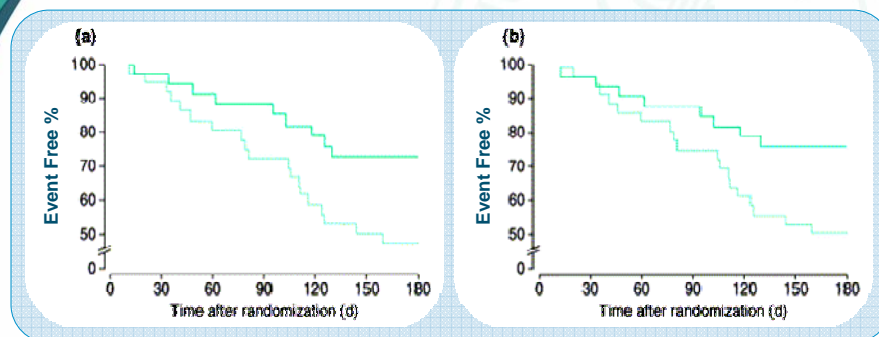
Plasma BNP (n = 33) or standardized clinical assessment alone (n = 36).

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

## Guided Therapy for CHF

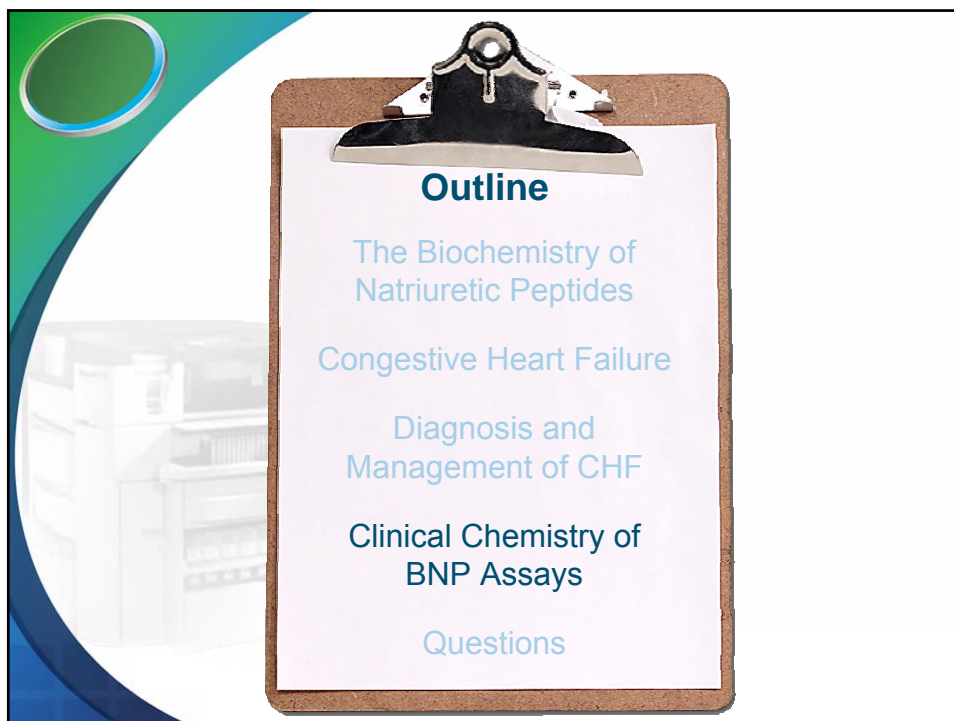
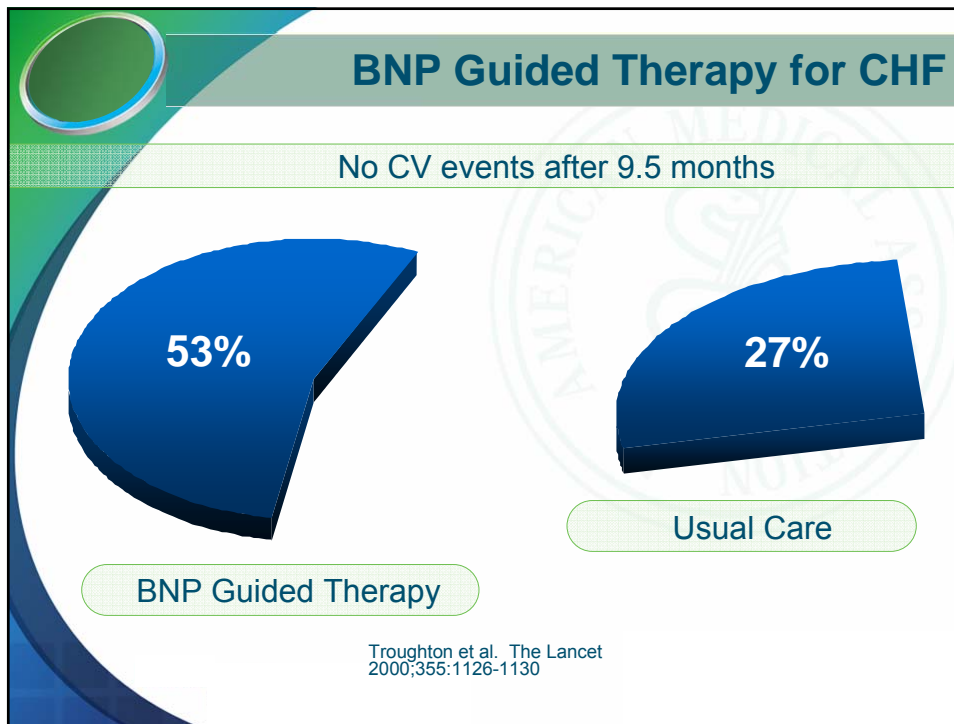
Total Cardiac Events

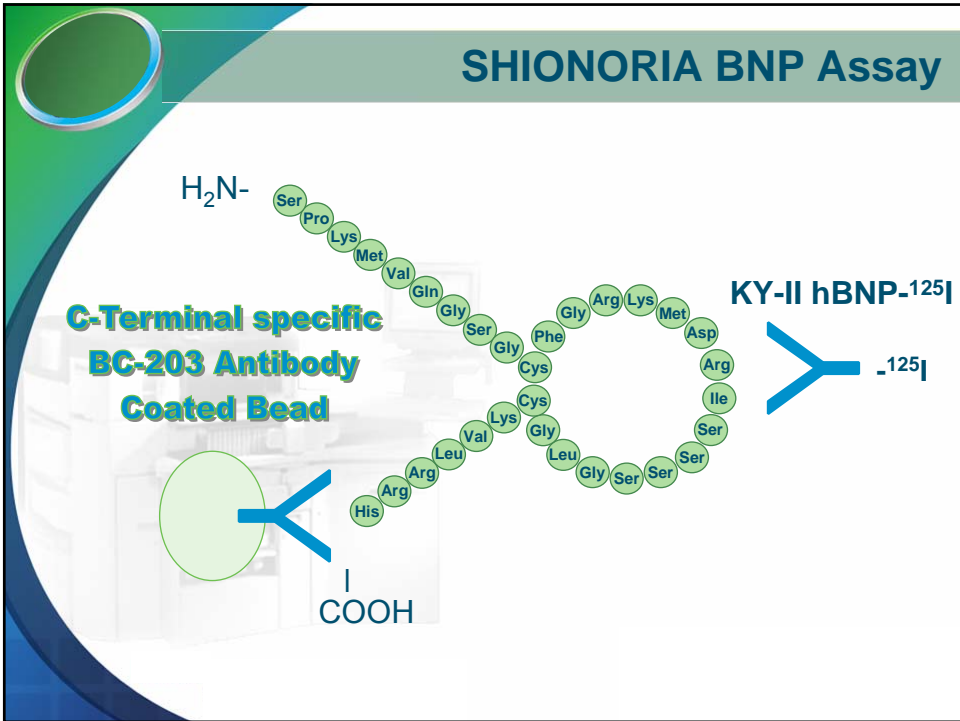
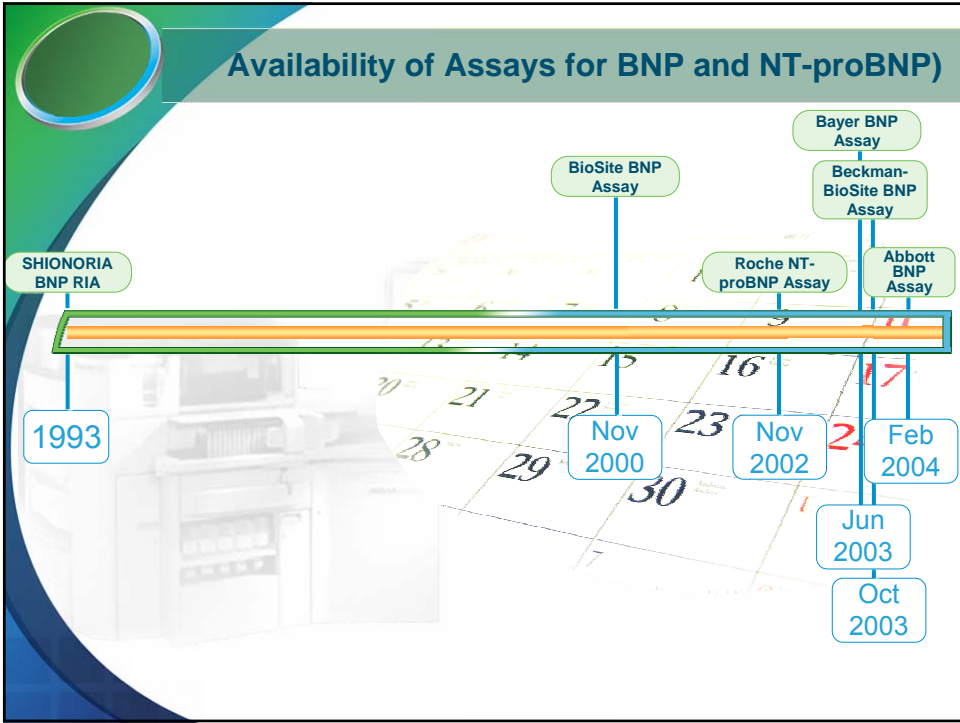
Episodes of CHF

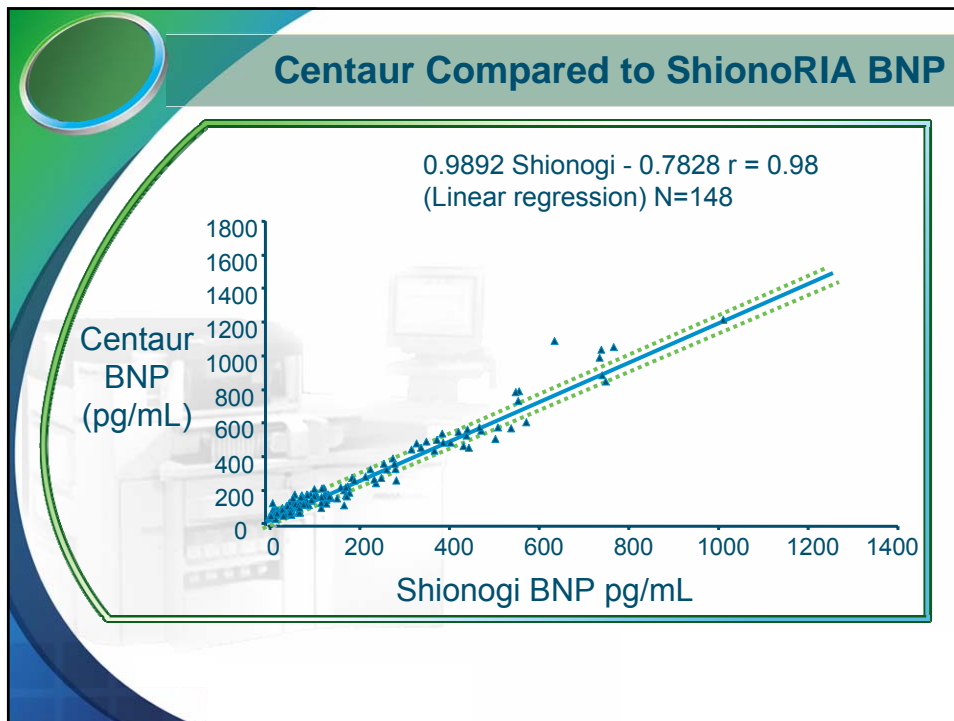
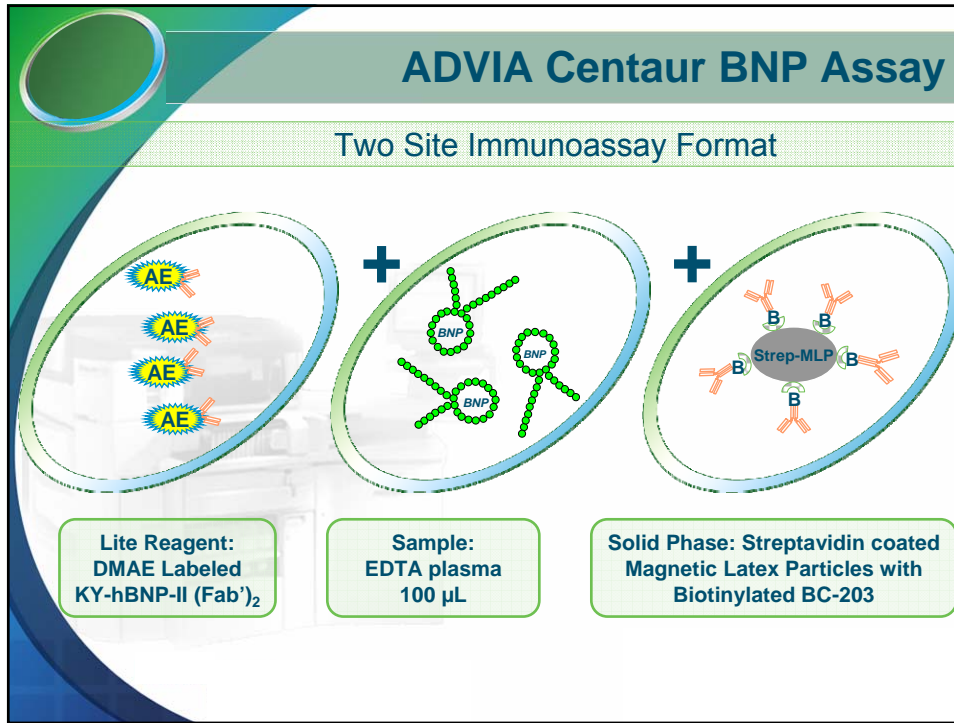


NT-proBNP (upper line)  
vs.  
Usual Clinical Care

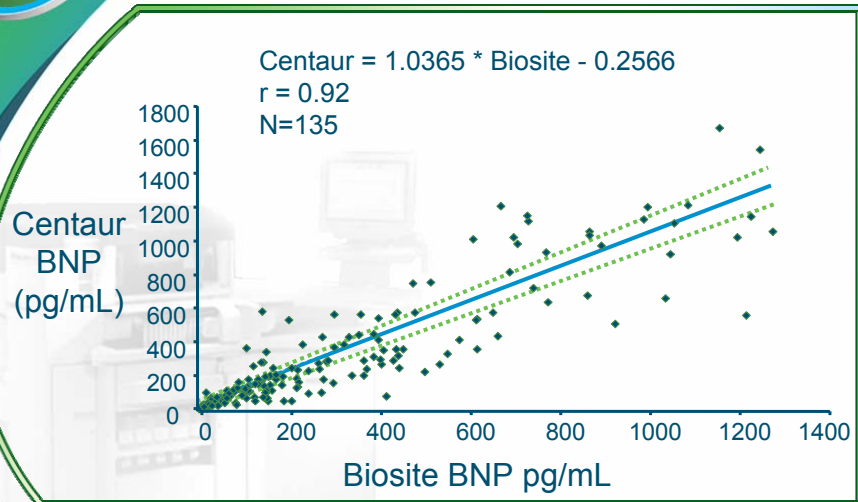
Richards et al. Trends in  
Endo & Metab 2002;13:151-5







## Centaur Compared To Triage BNP



## Use of NT-proBNP Versus BNP

BNP has been used in more studies & seems to correlate better with disease status.

NT-proBNP circulates at higher levels

NT-proBNP has a longer half-life (1-2 hours)

BNP has a short half-life (<20 minutes)

NT-proBNP will not cross-react with exogenous BNP

Clearance of NT-proBNP dependent upon renal function

## BNP and pro-BNP Degradation

### *In vivo:*

**BNP:** Natriuretic peptide receptors (A,B,C)  
Neutral Zn<sup>2+</sup>-dependent glycoprotein metalloproteinases  
Renal Excretion?

**proBNP:** Reticulo-endothelial system  
Renal Excretion

From: Allen Wu

## BNP and NT-proBNP Degradation

### *In vitro:*

**BNP:** Shimizu et al. suggested that BNP is degraded by contact activation of the kallikrein system (extrinsic clotting).

Glass collection tubes can activate this extrinsic system

Arginine and kallikrein-specific inhibitors superior to serine proteinase inhibitors

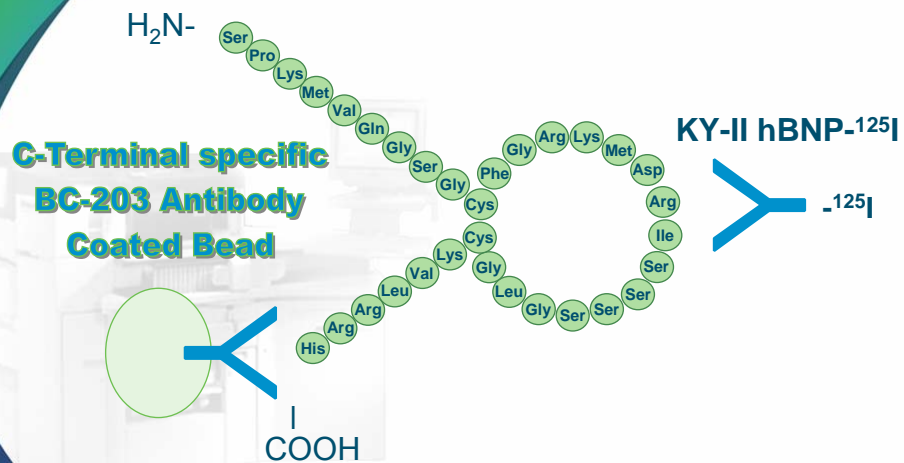
**NT-proBNP:** More stable in vitro because it is not degraded by proteinases.

## Stability of Natriuretic Peptides in EDTA Whole Blood

### Stability of Natriuretic Peptides

| Storage Temperature | BNP       | NT-proBNP |
|---------------------|-----------|-----------|
| Room temperature    | 24 h      | 5 - 72 h  |
| 4 °C (2 - 8 °C)     | 24 - 48 h | 48 - 72 h |
| -20 °C              | 9 mo      | 12 mo     |

## SHIONORIA BNP Assay



## BNP ASSAY EPITOPES

Clinical Chemistry / ORIGINAL ARTICLE

**Table 3**  
Summary of Molar Immunoreactivity of B-Type Natriuretic Peptides\*

| Peptide | Method   |               |       |
|---------|----------|---------------|-------|
|         | Access 2 | ADVIA Centaur | AxSYM |
| 1-32    | 82       | 126           | 106   |
| 3-32    | 69       | 126           | 118   |
| 4-32    | 159      | 175           | 164   |
| 10-32   | <1       | 163           | <1    |
| 1-31    | 87       | <1            | <1    |

\* Data are given as percentages. For proprietary information, see the text.

## BNP Results Interpretation

### Caveats

Age and Sex

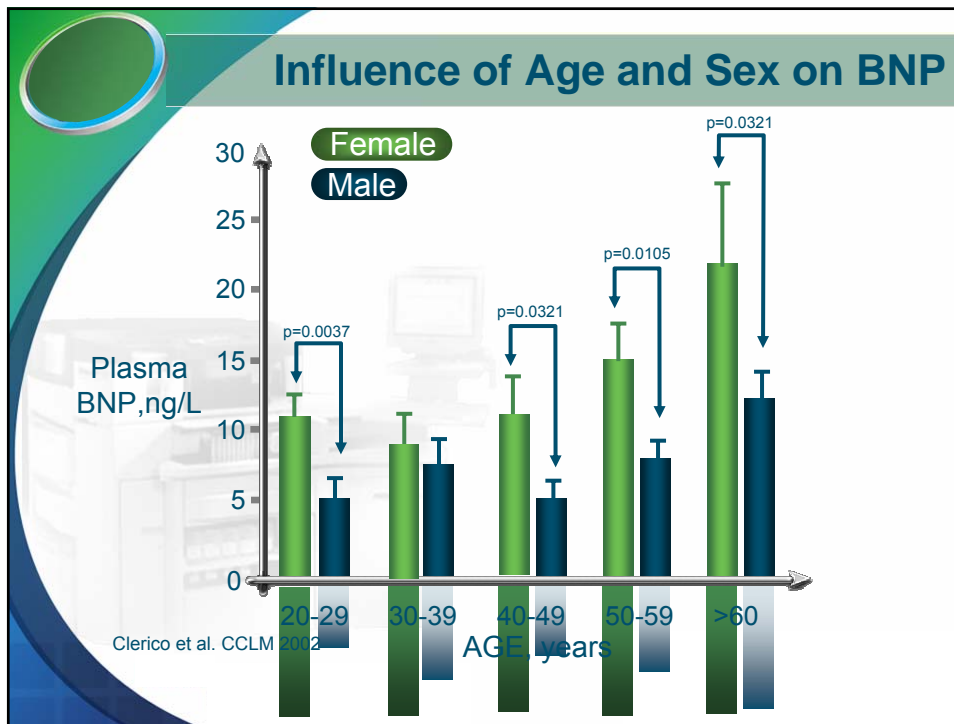
Renal failure

Cirrhosis

Obesity

Other Conditions

Assays may not compare



- ### Possible Reasons for Sex/Age Differences
1. Women have thicker walled hearts than men
  2. Estrogen effect (HRT) with postmenopausal women
  3. Declining GFR with age
  4. Obesity effect (BMI decrease with age)

## BNP Results Interpretation

### Caveats

|                        |
|------------------------|
| Age and Sex            |
| Renal failure          |
| Cirrhosis              |
| Obesity                |
| Other Conditions       |
| Assays may not compare |

## Other Diseases with Increases in BNP

Left Ventricular Hypertrophy  
Cardiac Inflammation (eg, Myocarditis, Cardiac Allograft Rejection)  
Arrhythmogenic Right Ventricle With Reduced Ejection Fraction  
Kawasaki Disease  
Primary Pulmonary Hypertension  
Pulmonary Embolism  
Renal Failure  
Ascitic Cirrhosis  
Endocrine (Primary Hyperaldosteronism, Cushing Syndrome)

Adapted, With Permission, From: Peacock WF IV. The B-type Natriuretic Peptide Assay: A Rapid Test For Heart Failure. Cleve Clin J Med 2002; 69:243-251.

## BNP Results Interpretation

### Caveats

|                        |
|------------------------|
| Age and Sex            |
| Renal failure          |
| Cirrhosis              |
| Obesity                |
| Other Conditions       |
| Assays may not compare |

## Summary

BNP is secreted by the ventricular myocardium in response to volume overload and increase stretch

BNP is more commonly used but NT-proBNP will probably be equally useful

The effectiveness of nesiritide validates the basic pharmacological properties of endogenously-produced BNP

## Summary

### Diagnosis

Strong NPV (~98%) for R/O of CHF  
Potential use as a screening test (~70% PPV) in “at risk” population

### Prognosis

BNP and NT-proBNP levels increase proportionately with CHF disease severity. Correlates to the NYHA classification system  
Correlates with Left Ventricular Ejection Fraction (LVEF).  
Assess risk of future episodes of CHF and Cardiac Events

### Guidance and monitoring of drug therapy

Guide the selection therapy and monitor its efficacy.  
Aids the physician in the choice and dosage of medication

Questions?