

Biomarkers for diagnosis and management of Heart Failure

BNP and NTproBNP in clinical practice

Debra Isaac BN, MD, FRCP(C)
 Clinical Professor of Medicine
 University of Calgary
 Director – Cardiac Transplant
 Foothills Medical Centre
 Calgary, Alberta



Canadian Cardiovascular Society

Leadership. Knowledge. Community.

Biomarker: Definition and Expectation

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"
 - NIH working group 2001

A cardiac biomarker can enhance clinicians' abilities to optimally manage patients with a cardiac disorder.

We've been using biomarkers to diagnosis and risk stratify patients with cardiac ischemia for decades...

Arnold JMO, et al. Can J Cardiol 2007;23(1):21-45.

- ▼ Issues pertinent to use of BNP in Canadian Centres
- ✓ hospital / lab administrators fear additional costs of adding new tests
 - ✓ cardiologists fear the BNP equivalent of "troponitis" - and negation of cost savings
 - ✓ need for education and optimization of use of biomarkers in HF

Approach to optimal management of CHF:

▼ First task in the management of the dyspneic patient is correct diagnosis.... Is it heart Failure?

Sometimes obvious....sometimes not

Approach to optimal management of CHF:

▼ Is it heart failure?

- Symptoms of heart failure are common but nonspecific presentation

- Physical signs are specific but not sensitive for HF

- co-morbidities are common in pts presenting with dyspnea / edema

...in LV... always... in LV... ening...

Heart Failure: A diagnostic challenge

■ Difficult diagnosis - especially in the early stage > 60% belong to NHYA class I or II with mild or non-conclusive symptoms

Fraction falsely diagnosed CHF in primary health care:

- Framingham: 40% (McKee 1971)
- Boston: 42% (Carlson 1985)
- Kuopio: 50% (Remes 1991)

Why do we need better ways to diagnose HF?

- ❑ HF is prevalent, but may be missed or misdiagnosed, especially in its earlier stages or in the presence of multiple co-morbidities: Too many times patients are treated (sometimes multiple times) for pneumonia or asthma when the diagnosis was heart failure
- ❑ Added cost to health care system with misdiagnosis: Studies have shown that early diagnosis and appropriate rx of HF leads to improved mortality and morbidity... reduced costs if less progression and hospitalization
- ❑ echocardiography not always available in timely fashion outside of tertiary care centres
- ❑ echocardiography may not rule out HF just because valves work and ventricles contract: diagnosis of HF with preserved systolic function is often difficult!

Approach to optimal management of CHF:

♥ Is it heart Failure?

CASE 1

42 yo male presents with cough and SOB

- 50 pkyr smoker, no HTN/DM, no cardiac hx
- flu-like illness started 6 weeks ago
- rx with antibiotics X 2 courses in last 4 weeks for pneumonia - this is his 3rd clinic visit
- still SOB, fatigued, coughing (esp. at night)
- no edema, no palpitations, no chest pain
- no recent fever

♥ Is it heart Failure?

CASE 1

- BP 100/70, HR 95 bpm (regular), RR 26
- JVP difficult to see (obese and bearded!)
- Chest clear, no significant edema

Approach to optimal management of CHF:

♥ Is it heart Failure?

CASE 2

- 73 year old farmer presents with SOB
- “lifelong” smoker
- HTN, on diuretic rx, doesn't monitor closely
- “small” MI 10 years ago
- chronic cough, increased over last month or so
- no fever or significant sputum production
- vague re; orthopnea, PND
- no edema
- no chest pain

♥ Is it heart Failure?

CASE 2

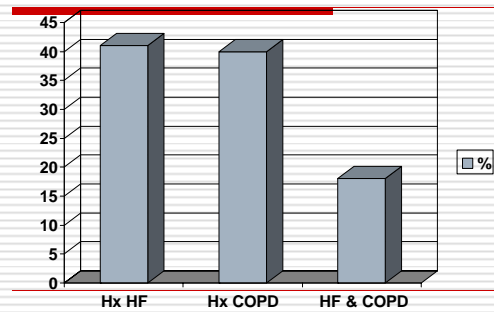
- O/E:
- clearly working to breathe (RR 32)
- BP 170/100, HR 98 bpm, afebrile
- JVP 4cm asa
- S4
- hyperinflated chest with reduced a/e, bibasilar crackles, expiratory wheeze
- no edema

Diagnosis of Heart Failure

CCS Recommendations:

- ✓ Clinical *hx, physical exam and laboratory testing* should be performed on all patients with suspected HF to **establish diagnosis and identify modifiable factors** that may affect the development or progression of HF
(ask yourself: is it HF, Why HF, Why now?)

Patients presenting to ER with SOB



Harrison et al, Ann Emerg Med 2002;39:131-138

Diagnosis of Heart Failure

CCS Recommendations:

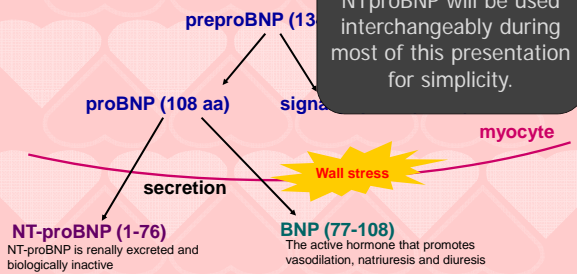
- ✓ Clinical hx, physical exam and laboratory testing should be performed on all patients with suspected HF to establish diagnosis and identify modifiable factors that may affect the development or progression of HF
(ask yourself: is it HF, Why HF, Why now?)
- ✓ **Measurement of plasma B-type natriuretic peptides should be considered, where available, in patients with suspected HF when clinical uncertainty exists**

B-Type Natriuretic Peptide (BNP)

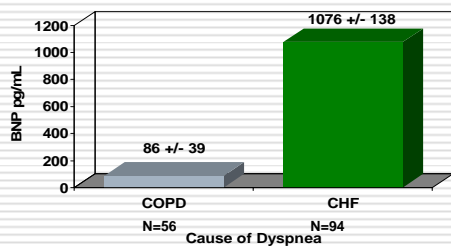
- Found in the heart
- Released in response to increased ventricular load to the ventricles:
 - Renal failure
 - Cor pulmonale
 - Increased age
- BNP levels lower in obesity
- May be initially low in flash pulmonary edema
- Left HF
- NYH

BNP and NT-proBNP

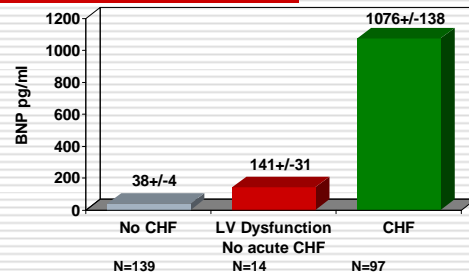
Synthesis and Secretion:



BNP Levels in Patients With Dyspnea Secondary to CHF or COPD

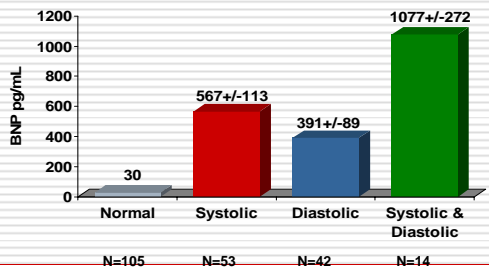


Dao, Q., Maisel, A. et al. J. American College of Cardiology, Vol 37, No. 2, 2001



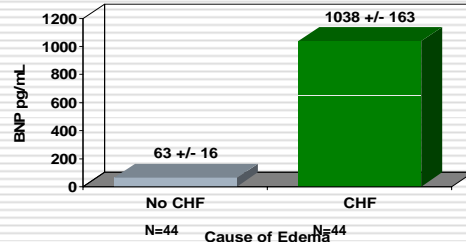
Dao, Q., Maisel, A. et al. J. American College of Cardiology, Vol 37, No. 2, 2001

BNP in LV Dysfunction



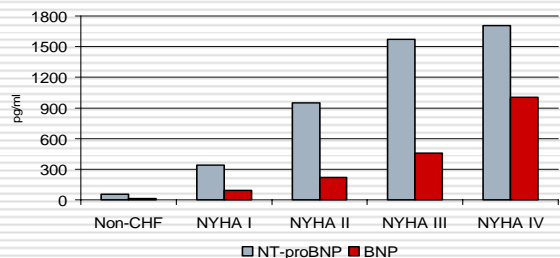
Maisel, A., De Maria, A. et al. American Heart Journal, Vol. 141, No. 3, 2001

BNP Levels in Patients With Edema Diagnosed With CHF or Without CHF



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

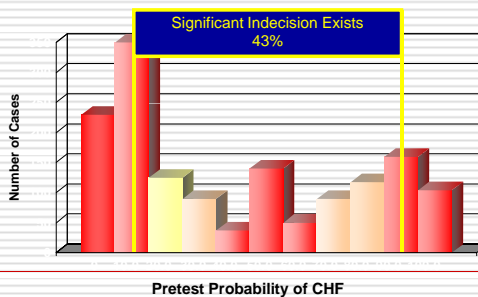
BNP vs. NYHA Classification



Roche Elecsys proBNP Product Insert 2003
Biosite Triage BNP Product Insert 2003

Frequency Histogram

Clinical Probability of CHF (Blinded to BNP)

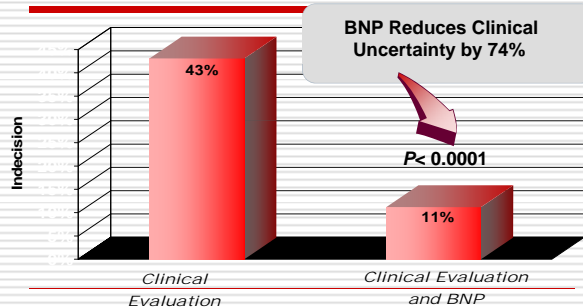


BNP and NTproBNP assay cut-off points for the diagnosis of HF

	Age	HF is unlikely	HF possible; other dx should be considered	HF is very likely
BNP	all	<100pg/ml	100-500pg/ml	>500pg/ml
NTproBNP	<50	<300pg/ml	300-450pg/ml	>450pg/ml
NTproBNP	50-75	<300pg/ml	300-900pg/ml	>900pg/ml
NTproBNP	>75	<300pg/ml	800-1800pg/ml	>1800pg/ml

ADAPTED FROM Arnold JMO et al. Can J Cardiol 2007; 23(1): 21-45

Clarification of Diagnosis and BNP



♥ Is it heart Failure?

CASE 1

42 yo male presents with cough and SOB

- 50 pkyr smoker, no HTN/DM, no cardiac hx
- flu-like illness started 6 weeks ago
- rx with antibiotics X 2 courses in last 4 weeks for pneumonia - this is his 3rd clinic visit
- still SOB, fatigued, coughing (esp. at night)
- no edema, no palpitations, no chest pain
- no recent fever



Is this HF?

- 1) Definitely yes
- 2) Possibly
- 3) Probably not
- 4) Definitely not

♥ Is it heart Failure?

CASE 2

73 year old farmer presents with SOB

- “lifelong” smoker
- HTN, on diuretic rx, doesn't monitor closely
- “small” MI 10 years ago
- chronic cough, increased over last month or so
- no fever or significant sputum production
- vague re: orthopnea, PND
- mild bilateral pre-tibial edema
- no chest pain

Is this HF?

- 1) Definitely yes
- 2) Possibly
- 3) Probably not
- 4) Definitely not

-Why is BNP >100?
-How did BNP help you in this case?

Diagnostic Accuracy of BNP and NT-proBNP in pts with multiple co-morbidities presenting to Calgary EDs with SOB

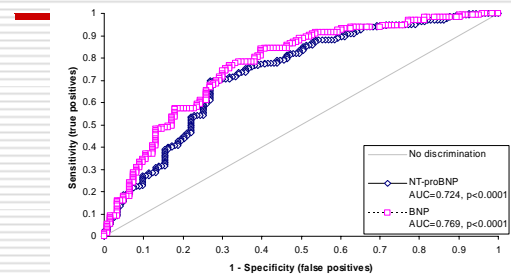
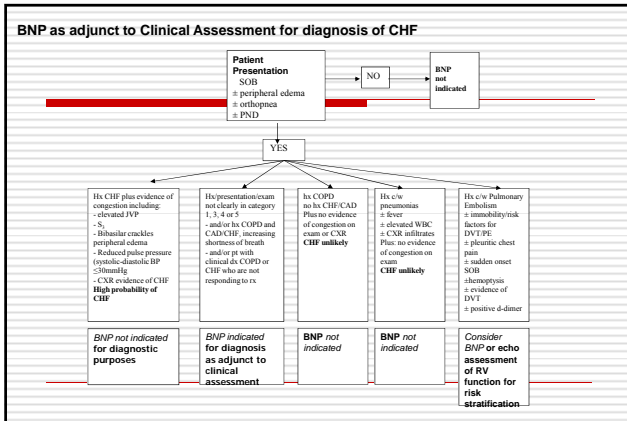


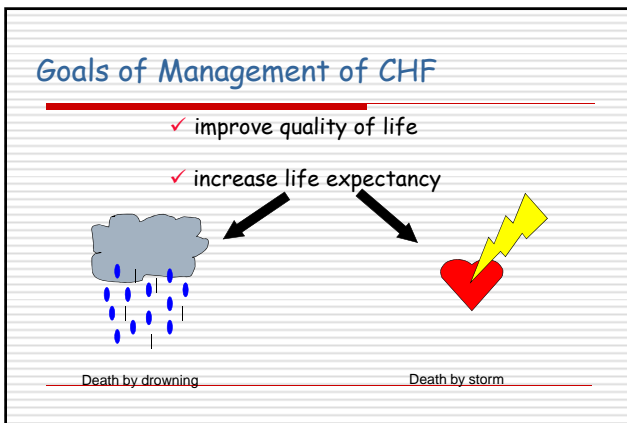
Fig: ROC curve for detection of CHF by BNP (squares) or NT-proBNP (diamonds) in 285 patients using Diagnoses following hospital admission



- ### Caveats to BNP interpretation
- ❑ **Obesity**
 - Levels noted to be slightly decreased¹
 - Same is true for NT-proBNP²
 - ❑ **Renal function**
 - Levels slightly elevated but still useful as a diagnostic test³
 - ❑ **Pulmonary embolism/Pulmonary HTN**
 - Grey zone BNP⁴
 - ❑ **Diastolic Dysfunction**
 - Usually less elevation than seen in systolic⁵
- 1 - Mahon et al. JACC 2004
2 - Kober et al. Eur Heart J 2005
3 - McCullough Am J Kidney Dis 2003
4 - Levine BNP in PEH JACC 2004, Kushner Clin 2003
5 - Marini JACC 2003

- ### BNP in HF management
- ♥ **clinical value**
 - ✓ **diagnosis**
 - ❖ **Adjunct to clinical assessment**
 - ❖ **Mosely: Educated use and interpretation is key!**
 - ❖ **Potential for misdiagnosis in indeterminate / unclear scenarios**

- ### Why Do We Need Better Ways to Manage HF?
- ❑ Despite evidence based Rx, HF related mortality and morbidity remain high, and HF related costs are high and increasing
 - ❑ HF hospitalizations: high cost, frequent readmissions – what can we do better?
 - ❑ Still clinical uncertainty about when to proceed with some of the more aggressive (and expensive) HF therapies



- ### BNP-in HF Management
- ✓ prognosis
 - ✓ therapies



- ❑ In patients presenting with shortness of breath to the ED, there is a large “disconnect” between perceived severity of CHF and the BNP level.
- ❑ Even in the setting where CHF severity is perceived as severe, a low BNP level portends a favorable short and long term prognosis
- ❑ Potential to guide admission from ER

Maisel, A et al. JACC 2004;44:1328-33

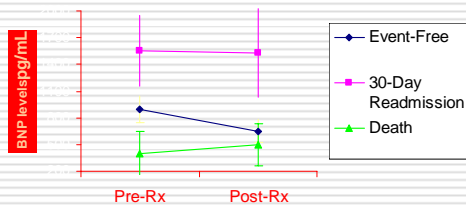
BNP and Prediction of Clinical Events

➤ 72 pts admitted with adHF followed for serial BNP and 30 day events

BNP	+ CV events	- CV events
NO DECREASE	15 (52%)	14 (48%)
DECREASE	7 (16%)	36 (84%)

Cheung V et al. JACC 2001;37:386-391

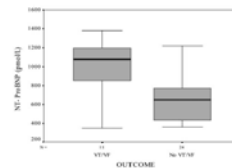
BNP and Prediction of Clinical Events



Cheng V, et al. J Am Coll Cardiol. 2001;37:386

Amino-Terminal Pro-Brain Natriuretic Peptide Predicts Ventricular Arrhythmogenesis in Patients With Ischemic Cardiomyopathy and Implantable Cardioverter-Defibrillators

Emmanuel G. Manios, Eleftherios M. Kallergis, Emmanuel M. Kanoupakis, Hercules E. Mavrikakis, Despina C. Kambouraki, Dimitris A. Arfanakis and Panos E. Vardas

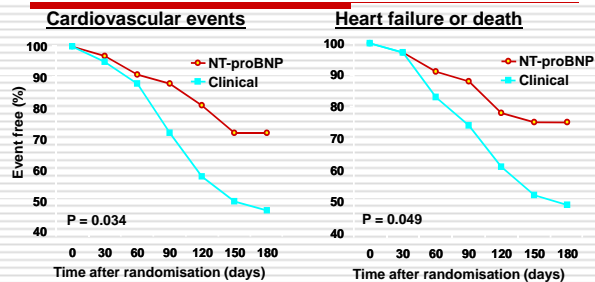


- 35 patients with previous MI,
- LVEF < 35%,
- ICDs for primary prevention (MADIT-II)

FIGURE 1. Box plots showing median levels of NT-proBNP measured at the beginning of the study in patients with and without sustained VT (VT+). Boxes show medians, and bars represent highest and lowest values.

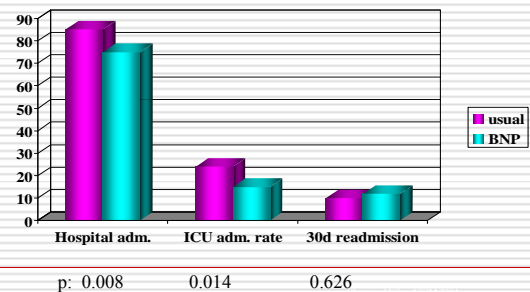
CHEST 2005; 128:2604-2610

NT-proBNP Monitoring and Guidance of HF Therapy Improves Outcomes

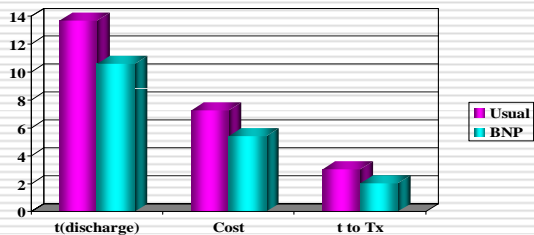


Troughton RW et al. Lancet 2000

BASEL: Resources utilization



BASEL results



All p < 0.01

Christian Müller, NEJM 2004

Conclusions:

BNP as a Heart Failure biomarker

BNP Testing has the potential to be a valuable adjunct to clinical assessment in:

- Determining presence and severity of HF
- Following / assessing efficacy of therapy
- Making clinical and economic decisions in HF patient treatment

Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers

(Moderator: D. Atwood MD FRCPC, Chair: Jonathan G. Piccini MD FRCPC, Co-Chair: Paul Connor MD FRCPC, Angelo Di Lorenzo MD FRCPC, Nadia Gattuso MD FRCPC, Hansman Haddad MD FRCPC, George A. Heikkinen MD FRCPC, Andrew Ignaszewski MD FRCPC, Debra Isaac MD FRCPC, Philip Tang MD FRCPC, Peter Tan MD FRCPC, Elizabeth Thomas MD FRCPC, Robert S. Yeh MD FRCPC, Gordon W. Ross MD FRCPC, John D. Parker MD FRCPC, Arava M. Tardif MD FRCPC, Ross T. Tsuyuki MD FRCPC, Kelly D. Halloran MD FRCPC, Heather J. Ross MD FRCPC, Vicki Ryan MD FRCPC, David J. Sengers MD FRCPC, Michael White MD FRCPC)

BIOMARKERS IN HEART FAILURE

Recommendations

- BNP/NT-proBNP levels should be measured to help confirm or rule out a diagnosis of heart failure in the acute or ambulatory care setting in patients in whom the clinical diagnosis is in doubt (class I, level A).
- Measurement of BNP/NT-proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification (class IIa, level A).
- Sequential measurements of BNP/NT-proBNP levels may be considered to guide the therapy of patients with heart failure (class IIb, level B).

FYI - BC guidelines for use of BNP:

MSP Guidelines on BNP

- BNP will be reimbursed by MSP at \$47.25 (break-even) for the following indications:
 - Assessment of symptomatic patients where the **diagnosis** of heart failure remains in doubt after standard assessment (once/year/patient)
 - Repeat testing is only reimbursed if ordered for a **new** clinical episode suspicious for CHF or in a tertiary care center for **prognostic stratification**
 - No reimbursement for repeat testing for **monitoring therapy**

How to use BNP as a Heart Failure biomarker: DIAGNOSIS

- "primary diagnosis" in difficult clinical scenarios
- Differentiate worsening HF from other causes of SOB in pt with known cardiac dysfunction and other co-morbidities

How we use BNP as a Heart Failure biomarker: MANAGEMENT/PROGNOSIS

- "dry BNP" assessment valuable in pts with severe / recurrent HF
- Assessment of adequacy of therapy prior to discharge
- Determination of management plan:
 - ✓ need for admission from ER
 - ✓ need for intensive follow up / reassessment
 - ✓ need for more aggressive therapies

♥ clinical and economic value depends on appropriate use of BNP measurement

-
- ✓ use as adjunct (not replacement for) clinical assessment
 - ✓ educated use and interpretation of values - knowledge of "confounders", optimally used as non-binary result (ie not just yes or no for HF) particularly for prognosis and management
 - ✓ use as screening for unselected population in *not* recommended

