Biomarkers for diagnosis and management of Heart Failure
BNP and NTproBNP in clinical practice

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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....

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

Heart Failure: A diagnostic challenge

- Dyspnea is a common but nonspecific presentation
- Physical signs are specific but not sensitive for HF
- co-morbidities are common in pts presenting with dyspnea / edema

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 centers.
- Echocardiography may not rule out HF just because valves work and ventricles contract; diagnosis of HF with preserved systolic function is often difficult!

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

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

CASE 2

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

Is it heart Failure?

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 of progression of HF.
- Ask yourself: Is it HF, Why HF, Why now?
Patients presenting to ER with SOB

<table>
<thead>
<tr>
<th></th>
<th>Hx HF</th>
<th>Hx COPD</th>
<th>HF &amp; COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>45%</td>
<td>40%</td>
<td>15%</td>
</tr>
</tbody>
</table>


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 of 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:
  - preproBNP (134 aa)
  - proBNP (108 aa)
  - secreted BNP (77-108)
- Released in response to stretch and increased volume in the ventricle.
- May be increased in any condition which increases load to the ventricles.
- Renal failure
- Cor pulmonale
- Increased age
- May be initially low in flash pulmonary edema
- BNP levels may be relatively increased in any condition which increases load to the ventricles.

BNP and NT-proBNP

- The terms BNP and NT-proBNP will be used interchangeably during most of this presentation for simplicity.

BNP Levels in Patients With Dyspnea Secondary to CHF or COPD

<table>
<thead>
<tr>
<th>Cause of Dyspnea</th>
<th>N</th>
<th>BNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>56</td>
<td>86 +/- 39</td>
</tr>
<tr>
<td>CHF</td>
<td>94</td>
<td>1076 +/- 138</td>
</tr>
</tbody>
</table>


BNP and NT-proBNP Levels in Patients With Dyspnea

<table>
<thead>
<tr>
<th>Cause of Dyspnea</th>
<th>N</th>
<th>BNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHF</td>
<td>139</td>
<td>38 +/- 4</td>
</tr>
<tr>
<td>LV Dysfunction</td>
<td>14</td>
<td>141 +/- 31</td>
</tr>
<tr>
<td>CHF</td>
<td>97</td>
<td>1076 +/- 138</td>
</tr>
</tbody>
</table>

BNP in LV Dysfunction

![Bar chart showing BNP levels in Normal, Systolic, Diastolic, and Systolic & Diastolic LV Dysfunction with numbers 567+/-113, 391+/-89, 1077+/-272, 30, 1000, 1200, and 800 g/mL.]


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

![Bar chart showing BNP levels in No CHF and CHF with numbers 63+/-16, 1038+/-163, 1000, 1200, 100, 200, 400, 600, and 300 pg/mL.]


BNP vs. NYHA Classification

![Bar chart showing BNP levels in Non-CHF, NYHA I, NYHA II, NYHA III, and NYHA IV with numbers 900, 1200, 1500, 1800, 900, 1200, 1500, 1800, 900, 1200, 1500, 1800, and 0 pg/mL.]

Roche Elecsys proBNP Product Insert 2003

Biosite Triage BNP Product Insert 2003

Frequency Histogram

Clinical Probability of CHF (Blinded to BNP)

![Bar chart showing Frequency Histogram of Pretest Probability of CHF with numbers 0, 100, 200, 300, 50, 100, 150, 200, 250, 300, and 43% for Significant Indecision Exists.]

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

<table>
<thead>
<tr>
<th>Age</th>
<th>HF unlikely</th>
<th>HF possible, other dx should be considered</th>
<th>HF very likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>&lt;100 pg/mL</td>
<td>100-400 pg/mL</td>
<td>&gt;400 pg/mL</td>
</tr>
<tr>
<td>NTproBNP</td>
<td>&lt;100 pg/mL</td>
<td>100-400 pg/mL</td>
<td>&gt;400 pg/mL</td>
</tr>
<tr>
<td>NTproBNP</td>
<td>100-250 pg/mL</td>
<td>400-600 pg/mL</td>
<td>&gt;600 pg/mL</td>
</tr>
<tr>
<td>NTproBNP</td>
<td>&gt;250 pg/mL</td>
<td>600-1400 pg/mL</td>
<td>&gt;1400 pg/mL</td>
</tr>
</tbody>
</table>


Clarification of Diagnosis and BNP

![Bar chart showing Clinical Evaluation and BNP with Clinical Evaluation and BNP increases by 43% and 11%, respectively.]

BNP reduces Clinical Uncertainty by 74%
**Is it heart Failure?**

**CASE 1**

42 yo male presents with cough and SOB

- 50 pk yr 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

BNP: 705 pg/ml

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

BNP: 200 pg/ml

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?

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

![ROC curve for detection of CHF by BNP (squares) or NT-proBNP (diamonds) in 285 patients using Diagnoses following hospital admission](image)
Caveats to BNP interpretation

- Obesity
  - Levels noted to be slightly decreased
  - Same is true for NT-proBNP
- Renal function
  - Levels slightly elevated but still useful as a diagnostic test
- Pulmonary embolism/Pulmonary HTN
  - Grey zone BNPs
- Diastolic Dysfunction
  - Usually less elevation than seen in systolic

BNP in HF management

- Clinical value
  - Diagnosis
    - Adjust assessment
    - Most - Educated use and interpretation is key!
    - Potential - diagnosis 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

Goals of Management of CHF

- Improve quality of life
- Increase life expectancy

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

<table>
<thead>
<tr>
<th>BNP</th>
<th>+ CV events</th>
<th>- CV events</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO DECREASE</td>
<td>15 (52%)</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>DECREASE</td>
<td>7 (16%)</td>
<td>36 (84%)</td>
</tr>
</tbody>
</table>

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

BNP and Prediction of Clinical Events


NT-proBNP Monitoring and Guidance of HF Therapy Improves Outcomes

<table>
<thead>
<tr>
<th>Cardiac events</th>
<th>Heart failure or death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free (%)</td>
<td>Event-free (%)</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
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<tr>
<td>80</td>
<td>80</td>
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<tr>
<td>70</td>
<td>70</td>
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<td>60</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

P = 0.034
P = 0.049

Time after randomisation (days)
Time after randomisation (days)

NT-proBNP Monitoring and Guidance of HF Therapy Improves Outcomes

Thorburn WR et al. Lancet 2004

BASEL: Resources utilization

Hospital adm. ICU adm. rate 30d readmission

p = 0.008 0.014 0.626
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

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 (i.e., not just yes or no for HF) particularly for prognosis and management.
- Use as screening for unselected population in not recommended.