Do Natriuretic Peptides Have a role in Primary Care?

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Chronic Heart Failure Definition

• Complex clinical syndrome resulting from a cardiac disorder that impairs the ability of the heart to fill with or eject blood.

ACC/AHA Guidelines CHF, 2009
Epidemiology and Public Health Significance

• **Common**
  – Prevalence increased sharply with age
  – 30,000 new cases diagnosed each year in Australia
    AHIW 2004
  – Approx. 300,000 Australians have CHF
  – Incidence growing with aging of the population

• **Costly**
  – In 2001-02 there were 41,874 hospitalisations for CHF (1%), average stay 9.1 days (Aust)
    AIHW 04
  – Consistently makes up 1% of the total health care budget in Western countries (Aust)
    Krum et al. Med J Aust01
Symptoms of Heart Failure

• Dyspnea
• Ankle Oedema
• Fatigue
• Orthopnea - may be present, reasonable specificity for heart failure
• Paroxysmal Nocturnal Dyspnea - may be present, reasonable specificity for heart failure
• Abdominal discomfort due to liver congestion - non specific
• Palpitations/Syncope

Symptoms are non-specific
Clinical Examination

- Pulse – tachyarrhythmia, regular or irregular
- Blood pressure
- Raised jugular venous pressure
- Third heart sound
- Dyskinetic apex beat
- Murmur - may be significant cause of heart failure
- Pulmonary crepitations
- Peripheral oedema - evidence of varicose veins or chronic venous stasis might support a non-heart failure cause of swollen ankles.

Other pertinent information:
- Previous cardiac history, cardiovascular risk factors
- Previous pulmonary disease – COPD, sleep apnoea
Heart Failure

- Acute
  - Acute pulmonary oedema
  - Cardiogenic shock
  - Decompensated CHF

- Subacute
  - Decompensated CHF

- Chronic

- ProBNP as a marker in subacute presentation
Causes

• Loss of myocardium
  – Infarction
  – Myocarditis (inflammatory, viral)
  – Myopathy (genetic, peripartum, alcohol, toxic)
  – Idiopathic

• Pressure load
  – Hypertension
  – Aortic stenosis
  – Obstructive sleep apnea

• Volume load
  – Mitral/Aortic regurgitation

• Abnormal myocardium
  – Hemochromatosis
  – Sarcoid
  – Amyloid
  – HOCM

• Tachycardia
Heart failure clinical presentation pathway

- Management pathway for subacute presentation of CHF
- Uses of point of care biomarker technology
Patient Presentation

• Dyspnoea
• Ankle oedema
• Fatigue
• Orthopnea – *may be present and is specific for Heart Failure*
• Paroxysmal nocturnal dyspnoea – *may be present and is specific for Heart Failure*
• Abdominal discomfort due to liver congestion - *non specific*
• Palpitations/syncope
Clinical Assessment

- Previous cardiac history
- Pulse – *exclude tachyarrhythmia*
- Blood pressure
- Pulmonary crepitations
- Peripheral oedema – *evidence of varicose veins or chronic venous stasis might support a non-Heart Failure cause of swollen ankles*
- Raised jugular venous pressure – *difficult sign*
- Third heart sound – *difficult sign*
- Dyskinetic apex beat – *difficult sign*
- Murmur – *may be significant cause of Heart Failure*
Heart Failure suspected because of history and clinical findings
Other Recommended Tests to Exclude Other Conditions

- **CXR** – exclude primary lung pathology
  - see evidence of pulmonary oedema or cardiomegaly
- **FBE** – exclude infection or anaemia
- **ECU** – baseline K and creatinine for renal function
- **LFT** – often abnormal due to liver congestion
- **Troponin T** – exclude active component of acute ischaemia
- **Thyroid Function Test** – important if atrial fibrillation
- **Glucose**
- **Lipids**
Exclude Heart Failure

- ECG
- NT-proBNP
Natriuretic Peptides

- Family of peptides with natriuretic, diuretic and vasorelaxant effects
- Role in body’s defense against hypertension and plasma volume expansion

Atrial Natriuretic Peptide (ANP)
- from atria in response to increased atrial wall tension

Brain / B-type Natriuretic Peptide (BNP)
- predominately from ventricle in response to increased ventricular wall tension

C-type Natriuretic Peptide (CNP)
- predominately in brain, very low plasma concentrations

Natriuretic Peptides as Plasma Markers

• Synthesis
  – circulating ANP and BNP levels correlate with LVEDP in LV dysfunction
    Maeda et al Am Heart J 98
  – ANP and BNP are increased in CHF
    Wilkins et al Lancet 97

• Clearance
  – action via high-affinity NP receptors A, B & C (clearance)
  – circulating NP are inactivated by cleavage by neutral endopeptidases in renal tubular cells and by direct renal clearance
CHF diagnosis: Natriuretic peptides

BNP/NT-proBNP

• Diagnosis of dyspnea “rule out heart failure”
  – Presenting with dyspnea
  – BNP  BNP trial *N Engl J Med*02
  – NT-proBNP  PRIDE trial *Am J Cardiol*05
  – Both superior to clinical judgment alone in diagnosing acute heart failure
Normal ECG & NT-proBNP < 300 pg/ml

↓

Heart Failure unlikely

↓

Consider alternative diagnosis.

If diagnostic/clinical doubt persists consider referral for specialist assessment
Age <50 yrs: NT-proBNP 300-450 pg/ml
Age 50-75 yrs: NT-proBNP 300-900 pg/ml
Age > 75 yrs: NT-proBNP 300-1800 pg/ml

Consider confounding factors that may elevate NT-proBNP: renal insufficiency, ACS, PE

Heart Failure remains a possibility

– Cardiology consult/ECHO required in a timely fashion to confirm Heart Failure diagnosis
– Commence Heart Failure treatment while waiting for diagnosis
Age <50 yrs: NT-proBNP > 450 pg/ml
Age 50-75 yrs: NT-proBNP > 900 pg/ml
Age > 75 yrs: NT-proBNP > 1800 pg/ml

Consider confounding factors: renal insufficiency, ACS, PE

Heart Failure highly likely

- Echocardiogram recommended
- Organise referral to Cardiologist
- Commence immediate management
All newly diagnosed cases of Heart Failure should have at least one specialist review
Immediate Management

- Frusemide – 40 mg oral
- ACE inhibitor
  - check renal function
  - hold if systolic blood pressure less than 100 mmHg
  - start with low dose eg Perindopril 2.5 mg daily or Ramipril 2.5 mg daily
- Wait for echocardiogram result before considering commencement of other medications such as B-blockers or Spironolactone

If Atrial Fibrillation:
- Digoxin is safest medication to give prior to knowledge of cardiac structure and function from echocardiogram
  - check renal function, load with digoxin 500 mcg oral, repeat next day with further 500 mcg oral then maintenance dose 125-250 mcg daily until reviewed by Cardiologist
On-going Management

• Patient should be given education on Heart Failure
• Exercise should be recommended for all Heart Failure patients with stable heart and stable volume status
• Cardiac risk factor screening
• Daily monitoring of weight
• Excessive weight gains or worsening of symptoms should be reported to GP
• Sodium Intake – should be limited for all Heart Failure patients
• Fluid intake should be limited for all patients with hyponatraemia, on high dose diuretics or with severe Heart Failure
• Regular review of medications to optimise management
Chronic heart failure beyond city limits

- Australian Study by Clark, Stewart et al 2005 looking at prevalence of heart failure across Australia (Rural and Remote Health)
- 335,280 estimated cases in Australia.
- 60% in capital cities, 20% in urban areas and 20% in rural and remote regions.
- Sig. higher prevalence of CHF in rural and remote regions (19.84/1000) and urban areas (19.01/1000) compared with capital cities (16.94/1000), p<0.001
- CHF rates are higher in remote regions
- Specialist + echocardiography services are limited in rural and remote region

Need to consider alternative methods of identifying CHF across Australia
Echocardiography

• Gold standard test to diagnose heart failure
• Limited access to echo in primary care particularly in rural and remote areas – requires referral to specialist which could take some time
• Many referrals don’t end up being heart failure

Unnecessary burden may be placed on overstretched Cardiology Services potentially leading to unnecessary tests
B-Type Natriuretic Peptide Levels

• Both BNP and NT-proBNP have been reported to be useful in differentiating between cardiac and pulmonary causes of shortness of breath.
  Isakson SL, Maisel A, Point of Care 2006;6-12

• Need to be aware of both cardiac and non-cardiac causes of B-Type Natriuretic Peptide Levels
Potential Causes of Elevated B-Type Natriuretic Peptide Levels

**Cardiac**
- Heart failure
- Diastolic dysfunction
- Acute coronary syndromes
- Hypertension with left ventricular hypertrophy
- Valvular heart disease (aortic stenosis, mitral valve regurgitation)
- Atrial fibrillation

**Non-cardiac**
- Acute pulmonary embolism
- Pulmonary hypertension (primary or secondary)
- Sepsis (possibly due to tissue hypoxia or secondary myocardial depression)
- Chronic obstructive pulmonary disease
- Hyperthyroidism
Randomised Controlled Trial in GP

Initial GP Visit
319 patients referred to study

12 patients excluded: 5 declined, 1 death, 6 hospital admissions

307 patients consented to the study

Randomisation, n=307

2 exclusions. (1 withdrew consent, 1 unable to attend study visit due to severe comorbidity)

Study Visit, n=305

BNP group, n=153

Control group, n=152

GP Review Visit (with N-BNP result) n=153

GP Review Visit (without N-BNP result) n=152
# Diagnosis of CHF Control vs Intervention

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n= 153)</th>
<th>BNP group (n= 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP Diagnosis at Initial Visit</td>
<td>GP Diagnosis at Final Visit</td>
</tr>
<tr>
<td>Correct diagnosis of HF, n (%)</td>
<td>33 (21)</td>
<td>31 (20)</td>
</tr>
<tr>
<td>Correct diagnosis of not HF, n (%)</td>
<td>46 (30)</td>
<td>60 (39)</td>
</tr>
<tr>
<td>Total correct diagnoses, n (%)</td>
<td>79 (51.6)</td>
<td>91 (59.5)</td>
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</tbody>
</table>
Study Conclusions

- This study shows that NT-proBNP measurement significantly improves the diagnostic accuracy of HF by GPs.
- NT-proBNP is particularly important in decreasing the over-diagnosis of HF that occurs in primary care.
- Provides evidence that availability of NT-proBNP measurement to GPs will significantly improve the diagnostic accuracy of HF in primary care.
B-Type Natriuretic Peptides and GP


• HF cause of 25-35% dyspnea presenting to GP (50% in ED)

• Echocardiography is a gold standard test for determining cardiac dysfunction but not for determining whether HF is underlying cause of dyspnea

• Echocardiography and BNP should be considered complimentary methods

• Studies such as the Wright study strongly encourages use of BNP in patient’s presenting with dyspnea
Discriminating Between Cardiac and Pulmonary Dysfunction in the General Population With Dyspnea by ProBNP

- 2,929 participants randomly selected from 4th Copenhagen City Heart study
- All had echocardiography, spirometry and NT-proBNP
- 959 reported SOB

![Flow Diagram of the Study Population](Figure 2)

Study Results

- [proBNP] higher in patients with dyspnea
- [proBNP] increases with severity of dyspnea
- [proBNP] increased in groups with cardiac dysfunction
- Not affected by pulmonary status

Protect Study

Design and methods of the Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) Study

Anju Bhardwaj, MD, Shafiq U. Rehman, MD, Asim Mohammed, MD, Aaron L. Baggish, MD, Stephanie A. Moore, MD, and James L. Januzzi, Jr, MD Boston, MA

Singe-centre, investigator initiated randomised controlled trial

American Heart Journal, 2010;159:532-538
Study Hypothesis

Primary Hypothesis
• Standard aggressive HF care with the adjunctive addition of NT-proBNP (goal decrease NT-proBNP \( \leq 1000\text{pg/ml} \)) would be superior to standard care with respect to cardiovascular events for 1 year period – for patients with impaired systolic function

Secondary Hypothesis
• NT-proBNP guided therapy would be associated with improved cardiac structure and function compared to standard group
• Same or better effects on quality of life
• Reduced costs of care
Study Design

Patient with Class II-IV symptoms, EF ≤ 40%, recent HF event

Randomization echocardiogram

Standard of Care
Minnesota Living With HF Questionnaire quarterly

Therapy adjusted to achieve optimal drug targets
Visits q3 months
Extra visits as needed for treatment goals

Standard of Care + NT-proBNP
Minnesota Living With HF Questionnaire quarterly

Therapy adjusted to achieve optimal drug targets PLUS NT-proBNP ≤ 1000 pg/mL
Visits q3 months
Extra visits as needed for treatment goals

Close-out echocardiogram
Total cardiovascular events assessed
Study Flow

- 151 patients consented and randomised
- 75 patients were admitted to standard of care plus NT-proBNP arm.
- 76 patients received standard of care only.
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Std Care + NT-proBNP (N=75)</th>
<th>Std Care (N=76)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>63.0 ± 14.5</td>
<td>63.5 ± 13.5</td>
<td>.41</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>28.0 ± 8.7</td>
<td>25.9 ± 8.3</td>
<td>.52</td>
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<tr>
<td>NYHA Class II or III (%)</td>
<td>65 (85.5)</td>
<td>64 (84.2)</td>
<td>.46</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>67 (88.2)</td>
<td>61 (81.3)</td>
<td>.24</td>
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<tr>
<td>Caucasian (%)</td>
<td>65 (85.5)</td>
<td>66 (88.0)</td>
<td>.65</td>
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<tr>
<td>Cause of heart failure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic (%)</td>
<td>40 (53.3)</td>
<td>18 (24.0)</td>
<td>.17</td>
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<tr>
<td>Non-ischemic (%)</td>
<td>25 (33.3)</td>
<td>12 (16.0)</td>
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<tr>
<td>Other (%)</td>
<td>10 (13.3)</td>
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<tr>
<td>Past medical history</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension (%)</td>
<td>42 (55.3)</td>
<td>50 (66.7)</td>
<td>.09</td>
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<tr>
<td>Coronary artery disease (%)</td>
<td>28 (36.8)</td>
<td>30 (40.0)</td>
<td>.69</td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>31 (40.8)</td>
<td>30 (40.0)</td>
<td>.92</td>
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<tr>
<td>Atrial fibrillation (%)</td>
<td>23 (30.3)</td>
<td>21 (28.0)</td>
<td>.76</td>
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<tr>
<td>Ventricular tachycardia (%)</td>
<td>15 (19.7)</td>
<td>16 (21.3)</td>
<td>.81</td>
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<tr>
<td>Obstructive airways disease (%)</td>
<td>30 (39.5)</td>
<td>32 (42.7)</td>
<td>.19</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td></td>
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<tr>
<td>Implanted devices</td>
<td></td>
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<tr>
<td>Cardioverter-defibrillator (%)</td>
<td>52 (69.3%)</td>
<td>50 (65.8%)</td>
<td>.70</td>
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<tr>
<td>Biventricular pacemaker (%)</td>
<td>30 (40.0%)</td>
<td>30 (39.4%)</td>
<td>.68</td>
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Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>NT-proBNP (n = 75)</th>
<th>SOC (n = 76)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Total cardiovascular events</td>
<td>58</td>
<td>100</td>
<td>0.009</td>
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<tr>
<td>Discrete outcome measures</td>
<td></td>
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<tr>
<td>Worsening heart failure</td>
<td>27</td>
<td>54</td>
<td>0.001</td>
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<tr>
<td>HF hospitalization</td>
<td>11</td>
<td>27</td>
<td>0.002</td>
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<tr>
<td>Acute coronary syndromes</td>
<td>9</td>
<td>9</td>
<td>0.72</td>
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<tr>
<td>Significant ventricular arrhythmia</td>
<td>7</td>
<td>4</td>
<td>0.41</td>
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<tr>
<td>Cerebral ischemia</td>
<td>0</td>
<td>0</td>
<td>0.98</td>
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<tr>
<td>Cardiovascular death</td>
<td>4</td>
<td>6</td>
<td>0.52</td>
</tr>
<tr>
<td>Subjects with at least 1 event</td>
<td>28.3%</td>
<td>48.6%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

A significant reduction in the primary endpoint of total cardiovascular events was driven by improvements in rates of worsening HF and reduced HF hospitalizations.
Echo Results

Figure 3: Echocardiographic Results Among Patients as a Function of NT-proBNP Versus SOC Management

Those with heart failure management guided by NT-proBNP had greater improvement in ventricular function and more favorable reverse remodeling. LV = left ventricular; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 2.

J Am Coll Cardiol 2011;58:1881–9)
Kaplan-Meier Curves

Log rank P = .03

Event-free survival

Days from enrollment

NT-proBNP (N=75)

Standard-of-care (N=76)

Treatment arm

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>74</th>
<th>68</th>
<th>67</th>
<th>65</th>
<th>62</th>
<th>57</th>
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<th>46</th>
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<tbody>
<tr>
<td>NT-proBNP</td>
<td>75</td>
<td>69</td>
<td>62</td>
<td>56</td>
<td>53</td>
<td>48</td>
<td>37</td>
<td>35</td>
<td>34</td>
<td>32</td>
<td>30</td>
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<tr>
<td>Standard-of-care</td>
<td></td>
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J Am Coll Cardiol 2011;58:1881–9)
Clinical Use of B-Type Natriuretic Peptides in GP

• Increasing evidence for utility in general practice
• Education required on how to use marker efficiently – prevent inappropriate and overuse
• Clinical pathways to be developed incorporating B-Type Natriuretic Peptides
Conclusions

• Incidence of HF growing with aging population
• Significantly higher prevalence of HF in rural and remote areas where access to echocardiography and specialist services are limited
• B-Type Natriuretic Peptides as part of a Heart Failure Clinical Pathway would be useful in GP to exclude HF as a cause of dyspnea.
• Protect study showed a significant reduction in cardiovascular adverse events with NT-proBNP guided therapy
• B-Type Natriuretic Peptides may be useful to help prioritise echocardiography requests
• B-Type Natriuretic Peptides may prevent unnecessary echocardiography requests
• Point of Care platforms extremely useful in rural and remote areas