Diagnostic biochemical markers for heart failure

Here, Dr Wycliffe Mbagaya, Dr Alhai Luvai and Dr Ahmed Waise examine the utility of the recommended diagnostic tools for heart failure – B-type natriuretic peptide (BNP) and its inactive form NT-proBNP – referring in particular to testing in patients with diabetes.

Introduction
Heart failure is a major cause of morbidity and mortality. Early diagnosis of heart failure results in a better prognosis. There are a number of biochemical markers that can play a role in the pathophysiology of heart failure, such as catecholamines, the renin-angiotensin-aldosterone system, cytokines, endothelin-1 and natriuretic peptide. However, in clinical practice natriuretic peptides, B-type natriuretic peptide (BNP) and its inactive form NT-proBNP, are reliable diagnostic markers in routine use and have been reviewed by the National Institute for Health and Care Excellence (NICE).

What is BNP?
BNP is a diuretic peptide that is stored in the myocytes of mammalian hearts. It has important actions inducing down-regulation of the sympathetic nervous system, natriuresis and diuresis, inhibition of the renin-angiotensin system and decreasing the peripheral vascular resistance.

BNP is predominantly secreted by the cardiac ventricles in response to volume expansion or increasing pressure load. Increased serum BNP concentration correlates with severity in left ventricular dysfunction. BNP is released as a prohormone proBNP which is enzymatically cleaved to active mature BNP and inactive NT-proBNP, with both peptides released in equimolar concentrations in circulation.

BNP is made up of 32 peptides and is inactivated in 20 minutes. NT-proBNP is made up of 76 peptides, has a half-life of 120 minutes and is excreted by the kidneys.

The difference in half-life, stability and mode of excretion means that NT-proBNP concentration is four to six times that of mature BNP. Irrespective of these, both peptides have similar performance in diagnosis, screening and prognosis of heart failure. BNP and NT-proBNP are recommended diagnostic tools for heart failure by NICE and the European Society for Cardiology.

Reference intervals and decision limits
BNP and NT-proBNP are present in the circulation in normal physiological states with values dependent on age, sex and the assay used for measurement. Cut-off values should ideally be depending on the population and the assay used for measurement. NICE has published recommended decision limits for natriuretic peptides in suspected acute and chronic heart failure.

When to measure BNP?
BNP and NT-proBNP can be used in the diagnosis of heart failure in ambulatory patients with dyspnoea as well as establishing the severity or prognosis of patients with chronic heart failure. BNP and NT-proBNP can be used in acutely decompensated patients in whom diagnosis is uncertain. Similarly, they may be used for prognosis and severity classification in acute settings. There is increasing use of BNP measurement in medicine optimisation in patients with chronic heart failure. BNP is not a stand-alone test and must be used and applied in a wider clinical context. It should not replace full cardiac assessment and echocardiography.

How is BNP/NT-proBNP measured?
BNP and NT-proBNP are measured by immunoassay which is usually provided on laboratory analysers but is also available on point-of-care devices. BNP and NT-proBNP have equivalent performance as biomarkers of heart failure. NT-proBNP is, however, more stable in vivo than BNP.

Limitations of BNP/NT-proBNP testing
Comparability of results
There is no international reference measurement for BNP/NT-proBNP and no listed certified standard reference material. Comparative studies demonstrate marked differences between assays. The lack of equivalence between methods complicates result interpretation in relation to relevant clinical decision limits. Although NICE has published national cut-offs, clinical decisions are influenced by method dependent cut-offs.

Interfering substances
In general, BNP/NT-proBNP measurement is largely unaffected by icterus, haemolysis and lipaemia. All current BNP and NT-proBNP immunoassays cross-react with the precursor peptide proBNP though the effect on analytical specificity is more prominent with BNP. For patients on high-dose biotin therapy – e.g. certain inherited metabolic disease, some dermatologic conditions and multiple sclerosis – sampling should be undertaken at least 8 hours after the last dose.

Other factors that may influence BNP concentration
BNP and NT-proBNP concentrations are influenced by a variety of cardiac and non-cardiac factors unrelated to heart failure.

Diagnostic performance
BNP and NT-proBNP have high clinical sensitivity and negative predictive value. They are therefore of

| Decision limits in suspected heart failure (Adapted from NICE CG108 and CG187) |
|------------------------------------------|--------------------------|
| Rule out acute heart failure            | <100ng/L                 |
| Rule out chronic heart failure          | <100ng/L                 |
| Refer for echocardiography in 6 weeks   | 100–400ng/L              |
| Refer for echocardiography urgently     | >400ng/L                 |

Table 1. Decision limits in suspected heart failure. (Adapted from NICE CG108 and CG187)
most benefit when used with clinical assessment to rule out heart failure in patients with compatible symptoms.\textsuperscript{5} Table 3 shows the performance characteristics of NT-proBNP in heart failure.

BNP and NT-proBNP are increasingly used for monitoring the treatment of patients with chronic heart failure. NICE Clinical Guideline 108 recommends specialist monitoring of natriuretic peptides in selected patients, e.g. those admitted to hospital or in whom up-titration of treatment is difficult.\textsuperscript{3} The biological variation data of NT-proBNP demonstrate that it is a useful test for monitoring clinical progress through serial measurements.\textsuperscript{5}

**Sample type, sample requirements and precautions**

NT-proBNP can be measured in serum and either EDTA or heparinised plasma. BNP is prone to degradation. BNP samples must therefore be collected into plastic EDTA tubes and it is, therefore, advisable to confirm which assay is provided by your local laboratory. Most point-of-care testing (PoCT) devices require whole blood.

BNP samples must be processed within 4 hours of collection if stored at room temperature or within 24 hours of collection if stored at 2–8°C. There are no special requirements for NT-proBNP.

**BNP and NT-proBNP testing in diabetic patients**

The clinical utility of BNP and NT-proBNP in diabetic patients is similar to that for the general population: in diagnosis of heart failure, assessing severity and prognosis, and monitoring of heart failure treatment. However, clinical consideration should be given to the interpretation of results in this group of patients. Diabetic patients as a group have a higher incidence of silent myocardial infarction, left ventricular dysfunction and heart failure which increase BNP and NT-proBNP. BNP and NT-proBNP concentrations may similarly be increased in patients with poor diabetes control and diabetic nephropathy because of reduced renal clearance. Patients taking pioglitazone have been reported to have higher circulating BNP concentrations, while ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists, which are often prescribed to diabetic patients, lower BNP. While there are no dedicated cut-offs for diabetic patients, interpretation of BNP results in this group should consider diabetes control, end-organ damage and concomitant medications taken.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on BNP/NT-proBNP</th>
</tr>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>↑ May be related to underlying heart/renal disease</td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>↑ in myocardial infarction, pulmonary embolism, valvular heart disease, hypertension, tachyarrhythmias</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>↑ in hyperaldosteronism and hyperthyroidism</td>
</tr>
<tr>
<td>Dietary sodium intake</td>
<td>↑</td>
</tr>
<tr>
<td>Advancing age</td>
<td>↑</td>
</tr>
<tr>
<td>Gender</td>
<td>Higher in women. Reason unknown</td>
</tr>
<tr>
<td>Renal failure</td>
<td>↑ Due to impaired renal excretion and concomitant heart disease</td>
</tr>
<tr>
<td>Exercise</td>
<td>↑ Mechanism unknown</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↓ Inverse relationship. Increment of 10bpm resulting in 15% reduction in NT-proBNP</td>
</tr>
<tr>
<td>Drugs</td>
<td>↓ by ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, nitrates</td>
</tr>
<tr>
<td>Obesity</td>
<td>↓</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Table 2. Factors influencing BNP and NT-proBNP concentration**

<table>
<thead>
<tr>
<th>Decision limit (ng/L)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Accuracy (%)</th>
</tr>
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<tbody>
<tr>
<td>300</td>
<td>99</td>
<td>68</td>
<td>62</td>
<td>99</td>
<td>79</td>
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<tr>
<td>450</td>
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<tr>
<td>1000</td>
<td>87</td>
<td>86</td>
<td>78</td>
<td>91</td>
<td>87</td>
</tr>
</tbody>
</table>

**Table 3. Performance of NT-proBNP in diagnosis of heart failure.** (Reproduced from: Sodi R. © Copyright Association for Clinical Biochemistry and Laboratory Medicine 2014)\textsuperscript{6}

Clinical vignette

A 62-year-old man was seen in the community diabetes clinic for his annual review where he complained of some shortness of breath on exertion. He did not have any history of leg swelling, orthopnoea or cough. He had a 12-year history of type 2 diabetes complicated by chronic kidney disease stage 3 with microalbuminuria. He was an ex-smoker. His medications included metformin 1g twice daily, gliclazide 160mg twice daily, atorvastatin 40mg, ramipril 2.5mg daily and pioglitazone 30mg daily.

Chest examination revealed bibasal crackles but no features of fluid overload. There was no pitting oedema or ascites. His initial investigations revealed a creatinine of 124μmol/L, eGFR 46, C-reactive protein 6, haemoglobin 135g/L and HbA1c 79mmol/mol. His doctor was unsure if this patient had a chest infection or had developed cardiac failure in view of pioglitazone use. He requested an NT-proBNP
which was marginally raised at 401ng/L. This was a borderline result, for which the doctor sought cardiology advice.

Discussion
This patient has risk factors for heart failure – such as poorly-controlled type 2 diabetes, chronic kidney disease stage 3 and use of pioglitazone. These three factors are also known to increase NT-proBNP concentrations in the absence of heart failure and cannot be discounted as exerting an influence on his results. The magnitude of their relevance would be impossible to predict. His marginally raised NT-proBNP should be interpreted in its clinical context of a high-risk patient as well as factors that may contribute to a raised NT-proBNP. If he had previous NT-proBNP results, the trend should be evaluated. His bilateral basal crackles with no features of fluid overload may still indicate early heart failure. Heart failure cannot be excluded in this situation and this patient would benefit from echocardiography and referral to cardiology for further assessment. A normal NT-proBNP in this patient would make heart failure highly unlikely. Some clinicians advise checking baseline NT-proBNP concentrations in patients prior to starting pioglitazone, with review to detect early heart failure. Irrespective of this patient’s outcome, he would need optimisation of his medication, as a follow up of the Framingham Heart Study found that high levels of BNP were associated with increased risk of first cardiovascular event, congestive heart failure and all-cause mortality.10

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Declaration of interests
There are no conflicts of interest declared.

References

Key points
- B-type natriuretic peptide (BNP) is the most reliable biochemical marker for heart failure
- BNP can be used as a prognostic marker and risk stratification
- Interpretation of BNP should consider other conditions which can influence the results