The use of amino-terminal fraction brain natriuretic peptide (NT-proBNP) assays in general practices in Waikato, New Zealand

Veronique Gibbons, Gerard Devlin, John Speed, Ross Lawrenson

Abstract

Aims To assess the use of the amino-terminal fraction brain natriuretic peptide (NT-proBNP) assay in the management of patients with suspected heart failure in general practice in Waikato District Health Board (DHB).

Methods We undertook an audit of all BNP requests to Waikato Health Laboratory from 1 March 2005 to 28 February 2006 inclusive. Data were analysed for age, gender, test result, and requesting general practitioner (GP). Crude incidence rate of BNP test by age group, sex, and by district was obtained. Second tests were analysed to ascertain numbers of patients re-tested in primary care.

Results 1553 tests were ordered on 1327 patients; 1182 (89%) of patients had only one test in primary care; 680 (51.2%) of first tests were <40 pmol/L, 409 (30.8%) were between 40 - 220 pmol/L; and 238 (17.9%) were >220 pmol/L. Of the estimated 250 GPs in Waikato DHB, 75% (189) of GPs had requested one or more BNP tests. 27% (51/189) of GPs requested a repeat test on one or more patient. 27% of patients with result >220 pmol/L had a further BNP test in general practice.

Conclusions The majority of Waikato GPs have experience with BNP testing in primary care. It appears to be used appropriately as a tool to rule out the diagnosis of heart failure by most GPs. A small number of doctors appear to use BNP more frequently, possibly to monitor treatment or change in condition (an indication for which it is not currently recommended). The use of BNP varies by district.

Heart failure is a common cause of morbidity and mortality in New Zealand. Symptoms are often non-specific and hence difficult to interpret, meaning diagnosis of heart failure by clinical means alone is inadequate.1 Studies have shown that over half of people suspected as having heart failure by their general practitioner (GP) do not have the condition confirmed on further evaluation by a specialist.2 Whilst the sensitivity and specificity of brain natriuretic peptide (BNP) is comparable to an electrocardiogram (ECG), the fact that specificity is poor in both tests has the potential to lead to over-investigation of abnormal results.3

B-type natriuretic peptide test alone cannot confirm if someone has heart failure, but the high negative predictive value helps GPs to rule out heart failure in symptomatic patients.2,4 In particular, plasma BNP is raised in dyspnoeic patients with heart failure and not in acutely breathless patients with primary lung disease—thus suggesting that BNP may assist in the diagnosis of patients with acute dyspnoea.5

The usefulness of BNP in unselected patients in the community is uncertain.6 A large body of observational data and a few evidence-based controlled trials are looking at...
the further implementation of plasma BNP and NT-proBNP in the diagnosis and treatment of acute and chronic heart failure. It has been recommended that those with a positive test (>40 pmol/L) should be referred to a specialist for diagnosis. Repeat tests as a means of monitoring heart failure management are not currently recommended in general practice.

Assays of B-type natriuretic peptides have recently emerged as an extremely helpful investigation (particularly in the exclusion of heart failure), and have been incorporated into international guidelines in the initial assessment of individuals with suspected heart failure. Laboratory and point-of-care assays that measure BNP and the inactive peptide NT-proBNP concentrations in the blood are now commercially available. BNP and NT-proBNP are known collectively as B-type natriuretic peptides.

Waikato Health Laboratory is the only publicly funded laboratory measuring either form of BNP in the Waikato region and the test used is for NT-proBNP. Serum or heparinised plasma samples for NT-proBNP are analysed on the Roche Modular E170 analyser (Roche Diagnostics, Indianapolis, IN, USA).

We wished to examine the use of BNP testing within general practice in Waikato District Health Board (Waikato DHB). Waikato DHB is one of the largest of New Zealand’s 21 district health boards covering 7.9% of New Zealand’s land mass (21,220 km²) and comprising 8.3% of the New Zealand’s population (337,390 people), of which 32% (107,661) people are over the age of 45 years (Census 2001). There are approximately 250 GPs in Waikato DHB.

Method

We obtained from Health Waikato Laboratory all requests for plasma BNP between 1 March 2005 and 28 February 2006. Assay samples for research purposes and validation were excluded. The data were categorised according to whether samples came from primary care or from a secondary provider, including specialists in private practice. Our report is based on samples from primary care. Samples were categorised <40 pmol/L, 40–220 pmol/L, or >220 pmol/L in line with the recommendation of Health Waikato Laboratory (Table 1).

<table>
<thead>
<tr>
<th>Reference interval</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 pmol/L</td>
<td>Reference interval in healthy persons</td>
</tr>
<tr>
<td>40–220 pmol/L</td>
<td>Does not rule out heart failure.</td>
</tr>
<tr>
<td>&gt;220 pmol/L</td>
<td>Suggests a high likelihood of heart failure in newly symptomatic (breathless) patients, but all clinical data must be taken into account.</td>
</tr>
</tbody>
</table>

Notes: BNP may be elevated by renal failure, atrial fibrillation, LVH, COPD, after myocardial infarction, in the elderly, and by treatment with beta-blockers or digoxin. BNP may be decreased by hypothyroidism treatment with diuretics, vasodilators, and ACE inhibitors.

Patients aged 45 years and over with a first plasma BNP request ordered by a general practitioner (GP) were included in the study. We did not include patients less than 45 years of age as the numbers were inadequate for meaningful analysis.

To identify incident BNP tests ordered by a GP, we included only the first tests ordered between 1 June 2005–28 February 2006, with no evidence of a BNP test in the prior 3 months. The 3-month cut-off was based on the median time for repeat tests. We also excluded patients who had been admitted in the
previous year to Waikato Hospital with heart failure. We analysed the use of the first test by age, gender, and district.

Data were checked and edited before analysis. For the analysis we used Microsoft Excel 2003 (Microsoft Corporation, Washington) and STATA v8 (Stata Corporation, Texas) software. Data were analysed by age, sex, test result, and requesting GP. Crude incidence rate of BNP test by age group and sex for Waikato DHB and by district was obtained using GP location as a proxy for domicile area.

This study received ethics approval by the Northern Y Regional Ethics Committee on 15 June 2006 (Ref: NTY/06/06/044).

Results

June 2005–February 2006 data—1327 primary care patients with no prior evidence of heart failure had their first test between 1 June 2005 and 28 February 2006. A total of 1553 BNP tests were performed on 1327 patients in primary care. Forty-nine percent of patients (651/1327) were male (mean age 72 years) compared with 51% (676/1327) female participants (mean age 74 years).

First tests—Results ranged from 1–7136 pmol/L (average 177.2, median 37). Individual results were categorised as described above. There was no difference in the proportion of <40 pmol/L, 40–220 pmol/L, or >220 pmol/L results by sex ($\chi^2=1.0143, p=0.602$).

680 (51.2%) of first tests were <40 pmol/L, 409 (30.8%) were 40–220 pmol/L, and 238 (17.9%) were >220 pmol/L. This differed by age, with 85% of 45–54 year olds having a <40 pmol/L result compared to 18.1% in patients aged 85+ years of age (Table 2). The results in men and women were similar.

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>&lt;40 pmol/L</th>
<th>40–220 pmol/L</th>
<th>&gt;220 pmol/L</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>85%</td>
<td>10%</td>
<td>5%</td>
<td>100.0%</td>
</tr>
<tr>
<td>55–64</td>
<td>75.1%</td>
<td>18.3%</td>
<td>6.6%</td>
<td>100.0%</td>
</tr>
<tr>
<td>65–74</td>
<td>65.0%</td>
<td>25.6%</td>
<td>9.5%</td>
<td>100.0%</td>
</tr>
<tr>
<td>75–84</td>
<td>36.7%</td>
<td>39.3%</td>
<td>24.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>85+</td>
<td>18.1%</td>
<td>42.7%</td>
<td>39.2%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>51.2%</td>
<td>30.8%</td>
<td>17.9%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Repeat tests—89% of patients (1182/1327) had only one test in primary care in the 9 months, 8% (107/1327) had 2 tests, with the remaining 2.8% (38/1327) having 3 or more BNP tests. Results showed that 94.2% (641/680) of <40 pmol/L results; 90.4% (370/409 of 40–220 pmol/L results; and 71.8% (171/238) of >220 pmol/L results were not repeated in primary care.

Second tests—We looked at differences between first and second tests to assess the timeframe between tests and to determine whether there was a change in category. All patients who had a first test requested by the general practitioner and a second test requested in either primary or secondary care were further investigated. In total, 186 patients were included. Time between tests ranged from 1–251 days, with a median time of 43 days. Results remained unchanged in 82.1% categorised as <40 pmol/L;
50.9% categorised as 40–220 pmol/L; and 86.9% categorised as >220 pmol/L respectively (Figure 1).

**Figure 1. Result of second test based on first test result**

Variations in results from first to second test were analysed by comparing the means for each result group. Upper and lower confidence intervals were calculated using t-test distribution for samples with less than 60 pairs (<40 pmol/L and 40–220 pmol/L groups). There was no statistically significant difference between means in the <40 pmol/L (15.44; 95%CI: -0.4–31.34) and >220 pmol/L (72.04; 95%CI: -98.89–242.96) result groups. In the 40–220 pmol/L group, the differences in means were statistically significant (177.73; 95%CI: 28.54–326.92).

**Requests by age and gender of population**—The rate of testing was highest overall in the 85+ years age group (45.5/1000) and lowest in the 45–54 years age group (2.04/1000). For each age group the rate of testing was higher in males than in females (Table 3).
Table 3. Crude rate per 1000 population of BNP tests by gender

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Female/1000</th>
<th>Male/1000</th>
<th>Total/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>2.06</td>
<td>2.02</td>
<td>2.04</td>
</tr>
<tr>
<td>55–64</td>
<td>6.31</td>
<td>7.77</td>
<td>7.02</td>
</tr>
<tr>
<td>65–74</td>
<td>17.68</td>
<td>19.94</td>
<td>18.79</td>
</tr>
<tr>
<td>75–84</td>
<td>33.97</td>
<td>47.93</td>
<td>39.82</td>
</tr>
<tr>
<td>85+</td>
<td>44.65</td>
<td>47.50</td>
<td>45.56</td>
</tr>
<tr>
<td>Total</td>
<td>12.41</td>
<td>13.14</td>
<td>12.75</td>
</tr>
</tbody>
</table>

Requests by geographical location—Waikato DHB consists of 10 districts. Due to the small numbers and lack of population data for Ruapehu District (District 3), it was excluded from analysis. The districts were randomly coded. BNP tests were extrapolated from 9 months data to give a 12-month figure.

Crude rates with confidence intervals were calculated, showing Districts 1, 6, and 7 were similar to the WDHB baseline rate. Districts 2, 4, 5, and 9 were below the baseline, and Districts 8 and 11 were above the baseline rate (Figure 2).

Tests by DHB—Of the 250 GPs in Waikato DHB, 75.6% (189) of GPs had requested one or more BNP tests that were eligible for inclusion. The number of tests requested by GPs in the 9 months ranged from 1–87 (average number of tests = 7, median = 3). 27% (51/189) of GPs had requested a repeat test on one or more of their patients (range = 1–15, average = 2.7, median = 1).
Discussion

Brain natriuretic peptide was first isolated in porcine brain tissue in 1988. It is synthesised and stored in ventricular myocytes, and is secreted in response to ventricular distension. The physiological role of natriuretic peptides involves the regulation of salt and water excretion and the maintenance of blood pressure.

Plasma levels reflect volume status and myocardial pressures and are elevated in heart failure due to increased synthesis and secretion from stretched cardiac myocytes. These features make B-type natriuretic peptides assays (BNP and NT-proBNP) attractive candidates as biomarkers of heart failure.

Numerous clinical trials have identified natriuretic peptides assays as important aids in the diagnosis of—and perhaps more importantly exclusion of—heart failure in patients with suspicious symptoms. This benefit has recently been acknowledged with the incorporation of B-type natriuretic peptides assays into European Society of Cardiology guidelines.

Although BNP is not widely used internationally in primary care, GPs in New Zealand are leading the way in using it to effectively identify people with heart failure. Indeed, there has been an exponential increase in use of BNP reported in New Zealand since its introduction.11

In the past, many patients were incorrectly labelled and treated for heart failure. Hence the use of BNP to rule out heart failure in people with non-specific symptoms is a valuable aide to general practitioners.2

Currently, limited evidence suggests that the optimal strategy in primary care could be to refer all patients to secondary cardiology services with abnormal ECGs or those with normal ECGs and abnormal B-type natriuretic peptides. This assumes all patients with suspected heart failure will receive an ECG.

Even at low specificity, using B-type natriuretic peptides is likely to be cost-efficient due to the relatively high cost of echocardiography and resultant waiting time. The high negative predictive value of B-type natriuretic peptides assays enables general practitioners to use the test as a first line to effectively rule out heart failure, and those patients with elevated natriuretic peptides should be referred to a specialist for further assessment particularly to ascertain the aetiology of heart failure.4,13

In our study, the results effectively ruled out heart failure in 50% of patients, but 30% of patients obtained a 40–220 pmol/L result. Whilst it is recommended that all of these patients be referred for specialist input if heart failure is strongly suspected, there are considerable resource implications with this strategy. Anecdotally, some GPs will manage these patients based on their clinical presentation. Further studies on the cost-effectiveness of referral are therefore needed.

It is also unknown whether the cut-off in Māori and Pacific peoples differs to the cut-off in New Zealand Europeans. A recent cohort study has highlighted the need for a satisfactory cut-off to be identified, which needs validating in general practice to allow “real-life” evaluation due to limitations within their study.14 Elevated BNP and NT-proBNP are frequently due to heart failure but it is important that all physicians requesting these tests are familiar with other possible causes of elevated natriuretic peptides (Table 1).
Our analysis of the use of BNP in the Waikato region shows that GPs use the test appropriately—ordering one new test every 3 months. However, approximately 25% of GPs did not use the test in a 12-month period, and there is still a great variation in its use—with the test being ordered for nearly 5/1000 patients per year in one district to over 32/1000 per year in another.

Without looking specifically at the demographics of each area, it would be difficult to suggest why this variation occurs, which may be due to GP training or education, variations in population structure, a higher Māori population (who have greater prevalence of heart disease), or lack of access to other services or equipment.

The study has shown that in those patients with an >220 pmol/L result, 26% of them have a repeat test. The test has a cost of approximately NZ$40, and re-testing patients is an inefficient use of resources for no clinical benefit. While the usefulness of repeat testing in primary care to guide treatment is predominantly experimental and currently not recommended, there is an optimistic outlook for its future utility in diagnosis and treatment of acute and chronic heart failure.\(^4,7,15\)

The reliability of the test is also in question in the 40–220 pmol/L range, with only 50% of patients returning the same result on re-test. Whilst re-testing has only been performed in a selected sub-group, and is unlikely to be a true measure of the reliability of the test, it does suggest that definitive work-up of these patients is required. It is known that BNP varies with age and gender, as does the incidence of heart failure. It is likely better algorithms are needed, particularly adjusting reference intervals for gender and increasing age.\(^16–21\)

The strengths of this study are that it is a population-based survey of the use of BNP in general practice. Data were available on age, gender, and requesting doctor, which enabled us to differentiate requests from primary and secondary care. All the tests have been performed in a single laboratory using the same method throughout.

A weakness of the study is the lack of ethnicity data, and so we cannot see whether the test is being used equally in Māori and non Māori. Indeed, there appears to be no published data on BNP use in Māori.

It is possible that some patients may have been diagnosed with heart failure in previous years and that the ‘first’ test in an individual patient was not in fact true. However, the median time between a first and second test in patients who were re-tested was 43 days, so we believe removing all those with a test in the prior 3 months, and all those with a hospital record of heart failure in the previous 12 months will remove the majority of these patients with established heart failure from the study. Thus we believe that we have correctly identified patients with a first BNP test in almost all cases.

Our study does not provide information on how the BNP test was used in clinical practice. The assumption is that BNP is used to ‘rule out’ heart failure, although studies report its use in differentiating cardiac from pulmonary disease.\(^22\)

Furthermore, despite a lack of guidance, BNP is possibly being used to guide pharmacotherapy in established heart failure.
Overall, the key findings from this study in the Waikato region are:

- Of those ordering BNP tests, the majority of GPs are ordering an average of one BNP test every 3 months on new patients.
- There is a big variation in use between districts from nearly 5 tests per 1000 population per year to over 32 tests per 1000 population per year.
- In patients under 55 years of age, 85% of tests are <40 pmol/L.
- In patients with a result of >220 pmol/L, 27% have the test repeated unnecessarily.

Competing interests: None.

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References:


