

<b>Title:</b>	<b>B-type natriuretic peptide assays in the diagnosis of heart failure.</b> <i>Part A: in the hospital emergency setting</i> <i>Part B: in the non-hospital setting</i>	
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## AIM

To assess the safety, effectiveness and cost-effectiveness of B-type natriuretic peptide (BNP) assays in the diagnosis and monitoring of heart failure.

## PART A CONCLUSIONS AND RESULTS

Part A of this report assessed the use of two BNP assay types in three key areas (diagnosis, monitoring and prognosis) for suspected and diagnosed heart failure (HF) patients, with the diagnostic use occurring in the hospital emergency setting. The safety, effectiveness and cost-effectiveness of BNP testing in addition to conventional diagnostic testing for HF, was assessed relative to conventional diagnostic testing alone. With respect to BNP testing as a monitoring tool, the comparator was monitoring using clinical criteria. The role of BNPs as prognostic indicators, although reviewed, did not impact on the reimbursement decision and so is not discussed below.

### Safety

The likelihood of adverse events occurring during BNP testing was small and similar to that of other venepuncture blood tests. There were no studies in the available evidence base that reported physical or psychological adverse events as a result of BNP testing.

### Effectiveness

The effectiveness of BNP testing was evaluated by a large volume of evidence, with the highest quality evidence being one good quality level II direct intervention study as well as two good quality level II diagnostic accuracy studies. Overall, the body of evidence was relatively consistent in its findings that BNP tests are sensitive with a high negative predictive value which effectively ‘rules out’ HF in a patient with a negative test. A strong pooled diagnostic odds ratio indicated that BNP tests effectively discriminate between the presence or absence of HF in patients. Time to discharge, time to treatment and hospital and intensive care unit admissions were reduced in patients receiving BNP-supplemented diagnostic assessment compared to conventional assessment. The impact on patient health outcomes was in the right direction (a reduction in mortality rate). However, the main trial was limited by a lack of statistical power and so the result was only statistically significant in a pre-specified subgroup of elderly patients. One good quality, but small, randomised controlled trial demonstrated that monitoring HF patients with BNP tests results in fewer cardiovascular deaths and total cardiovascular events than in patients monitored via clinical criteria.

### Cost-effectiveness

A trial-based economic analysis was conducted from a societal perspective. It was determined that the introduction of BNP testing into the emergency departments of Australian hospitals could lead to cost savings of \$338 per patient presenting with acute dyspnoea (point estimate). The point estimate of incremental costs and incremental lives saved at both 30 days and 180 days suggests that the addition of BNP testing to the diagnostic workup dominates conventional diagnostic strategies alone. The balance of probability, from the joint probability distribution of the incremental cost-effectiveness ratio, suggests that BNP testing in the hospital setting leads to a superior health outcome at a lower cost. The drivers for cost-effectiveness of BNP testing in this setting are: the time from presentation to the initiation of appropriate therapy is shorter; fewer patients are

admitted to hospital; and fewer patients are admitted to intensive care. Avoidance of echocardiography in test negative patients might be expected but was not reported in the key trial.

With respect to financial outlays, the Australian Government would likely incur an additional expenditure of approximately \$352,000 per annum under Medicare listing of BNP testing for private patients in private hospital emergency departments. Offsetting this further would be a reduction in hospitalisation and length of stay, which will reduce private sector outlays. Although the majority of BNP tests would be performed in public hospital emergency departments, this is unlikely to lead to Australian health system expenditure savings because of capacity constraints, but may make additional public resources available for other patients in need.

### **Recommendations**

‘MSAC finds that there is sufficient evidence of the safety, effectiveness and cost-effectiveness of the use of these assays in the diagnosis of heart failure but insufficient evidence of effectiveness and cost-effectiveness for their use in monitoring the progress of patients with heart failure.

MSAC recommends that public funding be provided for the use of assays of BNP in the diagnosis of heart failure in the hospital emergency setting.’

The Minister for Health and Ageing accepted this recommendation on 5 February 2007.

## **PART B CONCLUSIONS AND RESULTS**

Part B of this report assessed the diagnostic use of the two BNP assays to rule out HF in patients presenting in a non-hospital setting. The safety, effectiveness and cost-effectiveness of BNP testing in addition to conventional diagnostic testing for HF, was assessed relative to conventional diagnostic testing alone.

### **Safety**

The likelihood of adverse events as a consequence of the BNP testing procedure in the non-hospital setting was low and similar to that of any blood test. As the population of interest in the non-hospital setting is not acutely ill, delayed treatment associated with (the very low likelihood of) a false negative test result is unlikely to be harmful. None of the included studies in this report identified physical or psychological harms as a consequence of BNP testing of patients in the non-hospital setting.

### **Effectiveness**

There was no direct evidence available evaluating the effect of BNP testing on patient health outcomes in the non-hospital setting, thus a linked evidence approach was used. The effectiveness of supplementing conventional diagnostic assessment in the non-hospital setting with BNP testing was evaluated by a small volume of evidence, with the most reliable evidence obtained from one high quality level II diagnostic accuracy study and one level II intervention study. Overall, this body of evidence was relatively consistent in its findings that the BNP and NT-proBNP blood tests have high sensitivity but variable specificity. The main role of BNP testing, therefore, appears to be as a ‘first line’ test as a negative result on the test ‘rules out’ the diagnosis of heart failure (HF), so that differential diagnoses for symptomatic patients can be investigated. The impact of the introduction of BNP testing on the management of patients by GPs was assessed in one good quality randomised controlled trial that reported a clinically important improvement (13%) in the proportion of correct HF diagnoses from those GPs receiving NT-proBNP test results. The main impact occurred by enabling GPs to correctly ‘rule out’ HF. High level evidence suggests that early treatment for HF is beneficial for the patient. It is unlikely, however, that BNP testing would result in an earlier identification of HF than currently for these symptomatic patients because of its low positive predictive value in the non-hospital setting. Patients still require an echocardiogram and/or a cardiology consultation to receive a definitive diagnosis of HF. Use of the test is, however, likely to assist in earlier identification of alternative diagnoses for those patients ‘ruled out’ from HF—and most of these alternative diagnoses (pulmonary diseases, asthma, anaemia) have established treatments. Should this alternative pathology be severe enough, early identification and treatment of the condition is likely to be beneficial to the patient.

### **Cost-effectiveness**

The economic analysis was primarily limited to a population of symptomatic patients (in line with the evidence base), that is those presenting with dyspnoea and/or oedema of recent onset and suspected of HF. Appraisal of the economic implications of using BNP testing in the non-hospital setting was hampered by the absence of any

trial in that setting with a health outcome as an endpoint. There were also insufficient data to populate a decision analytic model to assess the cost-effectiveness of these assays in this setting (ie determining the increased cost per improved health outcome, such as life-years saved or QALYs). Therefore, this economic analysis aimed to identify those circumstances which might substantially reduce the cost-effectiveness of BNP testing.

It was determined that the costs and outcomes associated with B-type natriuretic peptide testing will usually depend on the GP's referral propensity. The extent of immediate cost offsets depends on whether or not the GP decides to order an echocardiogram and initially undertake self-management of the patient; or to refer the test positive patient to a cardiologist who may or may not order an echocardiogram. The extent of downstream costs (or savings) also depends on the same referral propensity, and on the proportions of patients correctly diagnosed. Three scenarios were presented illustrating different types of possible GP referral patterns that have increasing levels of resource use. In all three scenarios the use of BNP testing was cost saving (from \$50 to \$86 per patient tested), primarily through savings on echocardiogram and cardiologist referrals in test negative patients.

However, these scenarios reflect current clinical practice guideline recommendations and *assume* that in Australia all patients (over 45 years of age) presenting with dyspnoea and/or oedema of recent onset, and suspected of HF, would receive an echocardiogram. The *data available* suggests that actual echocardiogram referral may range from 3.8 per cent to 17.7 per cent for patients with new symptoms suggestive of HF. Results of a one-way sensitivity analysis suggest that BNP testing would not be cost saving if GPs currently refer this patient group to echocardiography at a rate of 60 per cent or lower.

The additional Australian Government expenditure due to the introduction of BNP testing into the non-hospital setting for patients presenting with dyspnoea and/or oedema of recent onset is estimated to range between \$4.0 million and \$11.3 million annually.

### **Recommendations**

'MSAC finds that there is sufficient evidence that B-type natriuretic peptide assays, when used in the diagnosis of heart failure in patients presenting with dyspnoea, are safe and effective (diagnostically accurate).

MSAC finds that there is major uncertainty around the cost effectiveness in the non-hospital setting.

MSAC recommends that public funding is not supported for the use of assays of B-type natriuretic peptides in the diagnosis of heart failure in patients presenting with dyspnoea in the non-hospital setting at this time.

MSAC further recommends research on the use of BNP in the general practice setting to identify appropriate usage and the patient group most likely to benefit in the non hospital setting.'

The Minister for Health and Ageing accepted this recommendation on 29 August 2007.

### **METHOD**

Systematic literature reviews were conducted to assess the role of B-type natriuretic peptides in (1) the diagnosis of heart failure in the (a) hospital and (b) non-hospital settings, (2) the monitoring of heart failure, and (3) patient prognosis. Medline, Embase, The Cochrane Library, and several other biomedical databases, HTA and other internet sites were searched from when BNP testing was first described in the literature (1988) until August 2005. Specific journals were handsearched and reference lists pearled. Studies were included in the review using pre-determined PICO selection criteria. Study quality was appraised and data extracted in a standardised manner. Meta-analyses were conducted where relevant. A direct evidence approach was used for Part A and complemented (in Parts A and B) with a linked evidence approach to address gaps in the evidence-base. Methods of economic analysis are provided in the discussions of cost-effectiveness above.