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CONTEXT AND POLICY ISSUES:

Natriuretic peptide (NP) levels including the B-type natriuretic peptide (BNP) and the N-terminal proBNP (NT-proBNP) are widely used in clinical practice and cardiovascular research. The primary site of synthesis of BNP is localized to the cardiac ventricular myocytes. After synthesis, the proBNP peptide is cleaved from the C-terminus to release the biologically active BNP (32 amino acids) and the inactive amino terminal fragment, NT-proBNP (76 amino acids). BNP is a hormone that acts as a natriuretic, diuretic, and vasodilator. The release of BNP serves to improve myocardial relaxation in response to acute increases in ventricular volume.

It has been suggested that BNP testing be considered for patients at risk for heart failure, when presenting to the emergency department with acute dyspnea. The rule-out level of BNP to exclude heart failure is <100 pg/ml and the rule-in level of BNP to include heart failure is >400 pg/ml. The rule-out level of NT-proBNP for heart failure is <300 pg/ml. The rule-in level of NT-proBNP for heart failure depends on patient’s age (>450 pg/ml for <50 years; >900 pg/ml for 50 – 75 years; >1800 pg/ml for >75 years). A modest increase of BNP and NT-proBNP levels into the grey zone (between low and high values) may be an indication of non-cardiac pathology that causes myocardial stress, including pulmonary hypertension, pulmonary embolism, acute coronary syndrome, atrial fibrillation, or chronic obstructive pulmonary disease and requires additional testing.

There is increased interest in adding BNP testing the laboratory services for the diagnosis, screening and prognosis of congestive heart failure in the hospital and primary care settings. This report reviews the clinical effectiveness, the cost-effectiveness, and the guidelines for BNP testing.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of brain natriuretic peptide (BNP) testing in diagnosis of congestive heart failure and coronary heart disease?

2. What is the cost-effectiveness of BNP testing in diagnosis of congestive heart failure and coronary heart disease?

3. What are the guidelines for the use of BNP testing in diagnosis of congestive heart failure and coronary heart disease?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2006 and October 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, guideline studies, and economic studies. Internet links are provided, where available.

SUMMARY OF FINDINGS:

Nine systematic reviews and meta-analyses, three guidelines, and eight economic studies were identified.

Clinical effectiveness of BNP testing

Nine systematic reviews and meta-analyses were identified on the use of BNP and NT-proBNP testing in congestive heart failure and coronary artery disease.

Ewald et al. (2008) assessed the validity of tests for BNP and NT-proBNP in the diagnosis of heart failure in primary care and hospital settings. They also examined the effect of age on the accuracy of the test in population screening for left ventricular systolic dysfunction (LVSD). The rigorous systematic review included twenty-seven studies. For BNP testing of patients with an average age less than 80 years, the diagnostic odd ratio (DOR) was 27.7 (95% CI 21.6 – 35.6). For NT-proBNP, the DOR was 37 (95% CI 26.6 – 51.6). Meta-analysis of studies directly comparing the two peptides showed that DOR for BNP was 1.77 (95% CI 1.06 – 2.95) times greater than that for NT-proBNP. The performance of both tests decreased with increasing age of patients. In the screening setting, tests for BNP adequately detected LVSD (DOR: 19.9 (95% CI 12.5 – 31.9)) and were better than those for NT-proBNP (DOR: 9.3 (95% CI 4.7 – 19)). It was concluded that tests for BNP are helpful in the diagnosis of heart failure or in screening for LVSD, and are superior to NT-proBNP.

Hill et al. (2008) determined the screening and diagnostic properties of BNP and NT-proBNP for heart failure in primary care. Seventeen observational studies were included. There was substantial heterogeneity within the study populations, reference standard for diagnosis, and NP cutoff points. Sensitivity ranged from 26% to 98%; specificity ranged from 44% to 88%; DOR for screening ranged from 2.7 to 29; DOR for diagnosis ranged from 2.8 to 137. It was concluded that BNP testing is not suitable for screening asymptomatic patients. For diagnosis in primary care, low NP values may be used to rule out but, due to poor specificity, high values cannot be used to rule-in heart failure.
Oremus et al. (2008) examined whether BNP can predict mortality and other cardiac endpoints in patients with coronary artery disease (CAD). Eighteen studies were included. BNP concentrations were found to be positively associated with poor prognosis in CAD patients. The pooled prognostic effect odd ratio was 3.41 (95% CI 2.31 – 5.02). The point estimates for mortality ranged from 1.33 to 2.94, and for non-fatal outcomes ranged from 1.01 to 3.03. The funnel plot showed the presence of publication bias. There was a lack of control for comorbidity in all included studies. No data across included studies to assess whether an optimal cutoff point existed. It was concluded that although BNP concentrations are positively associated with poor CAD prognosis, further research is needed before the concentrations of BNP could be used for certain to predict the prognosis of patients with CAD.

Worster et al. (2008) compared the diagnostic performance of BNP and NT-proBNP measurements in patients presenting to the emergency department with dyspnea. Nine studies were included for meta-analysis. There was substantial heterogeneity between study populations of both BNP and NT-proBNP. The pooled estimates of sensitivity and specificity for BNP were 0.97 (95% CI 0.96 – 0.98) and 0.70 (95% CI 0.56 – 0.85), and for NT-proBNP were 0.95 (95% CI 0.90, 1.01) and 0.72 (95% CI 0.53 – 0.90). Both BNP and NT-proBNP also had similar results for the likelihood and diagnostic odd ratios. It was concluded that BNP and NT-proBNP have very similar diagnostic performance characteristics, and can be used to rule-out heart failure in patients presenting to the emergency department with dyspnea.

Clerico et al. (2007) compared the diagnostic accuracy of BNP and NT-proBNP assays for the diagnosis of heart failure. Fifteen clinical studies of chronic heart failure and nine clinical studies of acute heart failure were included. There was substantial heterogeneity between studies regarding patient population, diagnostic criteria, end-points, and assay methods. In chronic heart failure, the DOR for BNP (8.44, 95% CI 4.66 – 15.30) was not significantly different from that of NT-proBNP (23.36, 95% CI 9.38 – 58.19). In acute heart failure, DOR for BNP (16.46, 95% CI 10.65 – 25.43) was also not significantly different from that of NT-proBNP (18.61, 95% CI 12.99 – 26.65). The authors concluded that “both BNP and NT-proBNP assays have a high degree of diagnostic accuracy and clinical relevance for both acute and chronic heart failure”.

Davenport et al. (2006) investigated the relative test accuracy of electrocardiogram (ECG), BNP, NT-proBNP, and a combination of two or more tests in the diagnosis of LVSD in the primary care setting. Thirty-two studies were included. There was substantial heterogeneity among included studies. All three tests (BNP, NT-proBNP and ECG) had similar sensitivity (>80%), but had poor specificity. Due to high heterogeneity, pooling of DOR for three tests was not performed. Similar for the combination of ECG and BNP compared with BNP alone or ECG alone, the pooled DOR was heterogeneous, therefore a summary estimate for test accuracy was not possible. It was concluded that ECG, BNP, and NT-proBNP are useful to rule-out a diagnosis of LVSD (high sensitivity). There is no evidence to justify the use of one test over another or the use of tests in combination.

Balion et al. (2006) evaluated BNP and NT-proBNP to a) identify the determinants for clinical use, b) establish the diagnostic performance, c) determine the prognosis with respect to mortality and other cardiac endpoints, and d) determine their value in monitoring treatment of heart failure. There were 144 studies that met the inclusion criteria. Determinants – 103 determinants including age, gender, disease treatment, as well as biochemical and physiological measures have been found to be associated with the levels of BNP. The value of these associations for clinical use was not clear. Diagnosis – The pooled sensitivity and specificity values were 94% and 66% for BNP and 92% and 65% for NT-proBNP. Prognosis – Both BNP and NT-proBNP have been found to be independent predictors of mortality and other cardiac composite endpoints in patients with risk of coronary artery disease, diagnosed coronary artery disease, and diagnosed heart failure patients. BNP and NT-proBNP showed
poor screening test characteristics. Monitoring treatment – there was limited and inconsistent evidence to suggest that BNP or NT-BNP may be useful to monitor therapy in heart failure patients.

Latour-Pérez et al. (2006)\textsuperscript{10} evaluated the accuracy of BNP in the diagnosis of left ventricular dysfunction and heart failure. Fifty-five studies with a total population of 16,730 patients were included. There was substantial heterogeneity between studies. After exclusion of low-quality studies, 11 studies were included to assess the diagnostic accuracy of BNP against a clinical diagnosis of heart failure, and seven studies were included to assess the diagnostic accuracy of BNP in identifying patients with systolic and diastolic dysfunction. The BNP levels were found highly accurate for the diagnosis of clinical heart failure (DOR 44, 95% CI 23 – 74). The negative likelihood ratios were relatively homogeneous (pooled negative likelihood ratio 0.11, 95% CI 0.08 – 0.16), despite the wide range of cut-off points used in the studies. The studies for the identification of left ventricular dysfunction were heterogeneous, with signs of publication bias, and had less diagnostic accuracy than those studies of heart failure (DOR 25, 95% CI 6 – 118). The authors concluded that BNP levels are useful for ruling out heart failure.

Battaglia et al. (2006)\textsuperscript{11} compared the diagnostic accuracy of the enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) tests for BNP to exclude congestive heart failure. Nineteen studies (6 ELISA and 13 RIA) were included. Studied populations and settings were heterogeneous. The pooled negative likelihood ratio was lower for ELISA (0.12, 95% CI 0.09 – 0.16) than for RIA (0.23, 95% CI 0.16 – 0.32). Assuming a pre-test probability of 20% for patients with suspected heart failure in primary care, a negative result of the ELISA test would produce a post-test probability of 2.9%, and a negative RIA test would produce a post-test probability of 5.4%. The ELISA tests appeared to perform better than the RIA tests; however, ELISA had a higher unit cost compared with RIA.

Guidelines for BNP testing

Three guidelines were identified on the use of BNP testing for congestive heart failure and cardiac dysfunction.

The Canadian Cardiovascular Society Consensus Conference update 2007\textsuperscript{12} made recommendations on the use of BNP or NT-proBNP testing in the diagnosis and treatment of heart failure. A systematic review was conducted, and panel members reviewed the evidence and recommendations were agreed by consensus. The evidence was graded as class 1 – III and level of evidence A – C (see appendix 1 for description of grading). The following recommendations were made:

- BNP/NT-proBNP levels should be measured to help confirm or rule out a diagnosis of heart failure in the acute or ambulatory care setting in patients in whom the clinical diagnosis is in doubt (class I, level A).
- Measurement of BNP/NT-proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification (class Ila, level A).
- Sequential measurement of BNP/NT-proBNP levels may be considered to guide the therapy of patients with heart failure (class IIb, level B)\textsuperscript{(p35)}\textsuperscript{12}

The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines (2007)\textsuperscript{13} made recommendations on the use of biochemical markers. No information was provided about how the guidelines were developed or about the grading of the guidelines.
a) Use of biochemical markers in the initial evaluation of heart failure:

- BNP or NT-proBNP testing can be used in the acute setting to rule-out or to confirm the diagnosis of heart failure among patients presenting with ambiguous signs and symptoms (class I, level A)

- BNP or NT-proBNP testing can be helpful to exclude the diagnosis of heart failure among patients with signs and symptoms suspicious of heart failure in the non-acute setting (class IIa, level C)

- In the diagnosis of heart failure, routine blood BNP or NT-proBNP testing for patients with an obvious clinical diagnosis of heart failure is not recommended (class III, level C)

- In the diagnosis of heart failure, blood BNP or NT-proBNP testing should not be used to replace conventional clinical evaluation or assessment of the degree of left ventricular structural or functional abnormalities (e.g., echocardiography, invasive hemodynamic assessment) (class III, level C)

b) Use of biochemical markers in screening for cardiac dysfunction:

- Blood BNP or NT-proBNP testing can be helpful to identify selected patients with left ventricular systolic dysfunction in the post-infarction setting or to identify patients at high risk of developing heart failure (e.g., history of myocardial infarction, diabetes mellitus). However, the diagnosis ranges and cost-effectiveness in different populations remain controversial (class IIb, level B)

- Routine blood BNP or NT-proBNP testing is not recommended for screening large asymptomatic patient populations for left ventricular dysfunction (class III, level B)

- Routine BNP or NT-proBNP testing is not warranted for making specific therapeutic decisions for patients with acute or chronic heart failure because of the still emerging but incomplete data as well as intra- and inter-individual variations (class III, level B)

The National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines (2007) made recommendations addressing the analytical aspects of BNP and NT-proBNP for clinical use in heart failure. There are four recommendations of class I and three recommendations of class IIa (no information was provided about the grading of the recommendations). The guidelines stated that pre-analytical and analytical characterization of BNP and NT-proBNP assays must be carried out. Reference limits need to be established, comparisons and regression analysis of patient specimens to establish degree of harmonization, and the clinical effectiveness of assays needs to be established.

Cost-effectiveness of BNP testing

Eight studies with cost analysis of BNP testing were identified.

Rutten et al. (2008) assessed the beneficial effects of NT-proBNP testing in patients with acute dyspnea presenting to the emergency department. A total of 477 patients were randomly assigned to NT-proBNP measurement group (n=236) or control group (n=241). For ruling out heart failure, the cutoff values for male and female were 93 pg/ml and 144 pg/ml. For ruling in heart failure, a cutoff value of 1,017 pg/ml was used. The median time to discharge from the hospital was 1.9 days (interquartile range, 0.12-8.4 days) in the NT-proBNP group compared with 3.9 days (interquartile range, 0.16-11 days) in the control group. NT-proBNP testing resulted in cost-reduction compared to the control group (mean difference: $1,364 per patient (95% CI $-246 to $3,215). There was no difference in hospital mortality rate within 30-day...
follow-up between both groups (14 patients in the NT-proBNP group versus 15 patients in the control group). It was concluded that the use of NT-proBNP testing for heart failure in the emergency department reduces the time to discharge and the associated costs.

Goode et al. (2007)\textsuperscript{16} conducted a cost-benefit analysis of pre-screening using NT-proBNP and QRS width to rule out heart failure in the primary care setting. This was a prospective cohort study of 94 patients recruited from a community-based service. Measurement of NT-proBNP was obtained in primary care. All patients were referred for cardiologist assessment with echocardiograms irrespective to NT-proBNP result. The results showed that NT-proBNP <180 pg/ml ruled out major LVSD, avoiding 385 echocardiograms and 23% of costs compared with direct referral for echocardiography. NT-proBNP <93 pg/ml ruled out major structural heart disease, avoiding 20% of echocardiograms and 8% of costs. QRS-width was less effective as a diagnostic test and added little cost benefit when combined with NT-proBNP. It was concluded that NT-proBNP provides cost-avoidance compared to direct referral for specialist heart failure assessment.

Lim et al. (2007)\textsuperscript{17} performed a cost-analysis of NT-proBNP testing, electrocardiogram (ECG), and portable echocardiography (PE) for the assessment of patients from the community with suspected heart failure. This was a prospective cohort study where a total of 137 symptomatic patients from the community underwent NT-proBNP and ECG estimation prior to PE. There were five screening strategies: 1) PE alone, 2) abnormal NT-proBNP followed by PE, 3) abnormal ECG followed by PE, 4) ECG followed by NT-proBNP, followed by PE, and 5) NT-proBNP followed by ECG, followed by PE. The costs associated with PE alone (strategy 1), abnormal NT-proBNP followed by PE (strategy 2), and abnormal ECG followed by PE (strategy 3) were €296, €313, and €310 respectively for the detection per case of LVSD. The cost of ECG followed by NT-proBNP followed by PE was €263 (strategy 4) and the cost of NT-proBNP followed by ECG followed by PE was €270 (strategy 5). The costs of PE for the detection of cardiac abnormalities were the lowest compared with other strategies. It was concluded that PE is the most cost-effective strategy to assess patients from the community with suspected heart failure.

Moe et al. (2007)\textsuperscript{18} performed a cost-analysis of the use of NT-proBNP testing to assess patients presenting with dyspnea to the emergency department in Canada. The analysis was conducted from a perspective of third party payers with an analytic horizon of 60 days. A total of 500 patients were randomly assigned to the NT-proBNP-guided care group (n=246) or the usual care group (n=254). The median NT-proBNP level of patients diagnosed with heart failure was 3,697 pg/ml compared with 212 pg/ml in those without heart failure. The NT-proBNP-guided care resulted in reduction of duration of emergency department visit (5.6 h versus 6.3 h, p=0.03), the number of patients re-hospitalized over 60 days (13% versus 20%, p=0.046), and total direct medical costs to the health care system (US$5,180 versus US$6,129, p=0.023). It was concluded that adding NT-proBNP testing to clinical judgment improves the management of patients presenting to emergency department with dyspnea through improved diagnosis, improvement of selected outcomes, and cost savings.

Hawkins and Chung (2007)\textsuperscript{19} retrospectively examined the effect of BNP use on resource utilization (length of stay, payable amount) and clinical outcome (discharge status) in hospitalized patients with a primary and secondary diagnosis of heart failure over 12 months at a large Singapore general hospital. The use of BNP measurement in patients with a secondary diagnosis of heart failure was associated with an average decrease of $Singapore 1305 in payable amount, which was related with reduced use of echocardiography. No cost saving was seen in patients with a primary diagnosis of heart failure. The authors concluded that the use of BNP measurement was associated with reduced cost of hospitalization and the use of echocardiography in patients with secondary diagnosis of heart failure.
Goode et al. (2007) investigated the cost-benefit of screening of high-risk patients in primary care for LVSD using echocardiography, electrocardiography and NT-proBNP testing. Using a logistic regression model, a combination of NT-proBNP testing, QRS width, symptoms, and evidence of myocardial infarction would avoid 24% of cost and 50% of the numbers of echocardiograms compared to screening using echocardiography alone.

Mueller et al. (2006) conducted a cost-effectiveness study of BNP testing in 452 patients who presented to the emergency department with acute dyspnea. The study was a randomized controlled trial where patients were randomly assigned to a diagnostic strategy involving BNP measurement (n=225) or standard assessment (n=227). BNP testing resulted in a reduction of initial hospital admission rate (75% versus 85%), the use of intensive care unit (15% versus 24%), and total days in hospital at 180 days of follow-up (median, 10 days [interquartile range, 2-24 days] in the BNP group versus 14 days [interquartile range, 6-27 days] in the control group, p=0.005). BNP significantly reduced total treatment cost (US$7,930 versus US$10,503).

Analysis of incremental cost-effectiveness at 180-day follow-up showed that in 80.6% of replications, BNP guidance was less expensive and resulted in lower mortality than control, whereas higher mortality and lower cost was found in 19.3%, and the remaining 0.1% had higher cost, with higher or lower mortality. The results were sensitive to changes in re-hospitalization. The authors concluded that BNP testing is cost-effective in patients with acute dyspnea.

Seibert et al. (2006) assessed the cost-effectiveness of NT-proBNP testing for the evaluation and initial management of patients with dyspnea presenting to the emergency department. A decision model was developed based on clinical data obtained from a prospective study. The model included the diagnostic accuracy of the two strategies (standard assessment versus assessment guided by NT-proBNP) for congestive heart failure and 60-day follow-up. The use of NT-proBNP guidance was associated with a relative reduction of 58% in the use of echocardiography, 13% initial hospitalizations, 12% hospital days, 1.6% serious adverse events, 1.0% post-discharge mortality, and 9.4% direct medical costs (or US$ 474 per patient). The study suggested that the use of NT-proBNP in the diagnostic assessment and subsequent management of patients presenting the emergency department with dyspnea could lead to improved patient care and provide cost savings.

Limitations

Although the reference standards used in the included systematic reviews and meta-analyses were clearly stated, there was variation in which reference standard was used between studies. It is unclear whether differences in reference standard would affect the evaluation of BNP or NT-proBNP testing, and these may be subject to verification bias. Many of the studies included in the systematic reviews were observational studies, which do not control for potential selection bias. Although Clerico et al. stated it was a systematic review, it was unclear how the search was conducted and whether more than one author was involved in article selection and data extraction. The study populations were heterogeneous in many of the included studies.

Two of the guidelines that were identified did not report on the methods used to develop the guidelines. In addition, although the recommendations were graded, no information about the grades was reported.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Based on the reviewed literature, BNP and NT-proBNP testing can be helpful and can be used interchangeably in the diagnosis of heart failure in a variety of settings. Some of the studies suggested that BNP and NT-proBNP were effective at ruling-out heart failure. The cutoff levels of BNP and NT-proBNP are different. The plasma levels of BNP and NT-proBNP could be influenced by comorbidities as well as age and gender. BNP and NT-proBNP testing can be helpful in screening for LVSD in symptomatic populations, but not in asymptomatic ones. Economic studies showed that BNP and NT-proBNP testing provided cost benefit for diagnosis of heart failure in patients presenting with symptoms in the emergency department or in primary care settings. BNP and NT-proBNP measurement for the management of heart failure may be cost-effective. Serial measurement and timing of measurement of BNP levels to determine patient’s prognosis in response to treatment has yet to be defined.

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APPENDIX 1: Class of recommendations and grade of evidence for the Canadian Cardiovascular Society guidelines on heart failure

**Class I:** Evidence or general agreement that a given procedure or treatment is beneficial, useful and effective.

**Class II:** Conflicting evidence or a divergence of opinion about the usefulness or efficacy of the procedure or treatment.

**Class IIa:** Weight of evidence is in favour of usefulness or efficacy.

**Class IIb:** Usefulness or efficacy is less well established by evidence or opinion.

**Class III:** Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

**Level of evidence A:** Data derived from multiple randomized clinical trials or meta-analyses.

**Level of evidence B:** Data derived from a single randomized clinical trial or nonrandomized studies.

**Level of evidence C:** Consensus of opinion of experts and/or small studies (p22)