Cardiac natriuretic peptides for cardiac health

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Abstract

The cardiac natriuretic peptides, ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide), are secreted by the heart in proportion to cardiac transmural pressures. They possess a wide range of effects in multiple tissues facilitating overall pressure/volume homoeostasis. The close relationship between plasma concentrations of these peptides and ‘cardiac load’ has led to their use as biomarkers of cardiac health with diagnostic and prognostic applications in a variety of disorders affecting the cardiovascular system. BNP and its N-terminal fragment (NT-BNP) are especially sensitive indicators of cardiac dysfunction and remodelling, and correlate strongly with severity. Given that cardiac ischaemia is also an important trigger for the release of these ventricular peptides, they may likewise play a role in the detection of coronary artery disease. Measurement of BNP/NT-BNP shows particular promise as a ‘rule out’ test for suspected cases of HF (heart failure) in both emergency care and outpatient settings, and may assist in identifying individuals with asymptomatic ventricular impairment who will benefit from therapy preventing progression to overt HF. The BNP peptides also predict subsequent haemodynamic deterioration and adverse events in cardiovascular disease, and can therefore be used to monitor those at high risk and act as a guide to optimization of treatment. The favourable biological properties of the natriuretic peptides have also led to their use as therapeutic agents.

Introduction

The cardiac natriuretic peptides, ANP and BNP (atrial and brain natriuretic peptides respectively), are hormones secreted predominantly by the heart. ANP is synthesized most abundantly in the atria where it is stored in specific intramyocyte granules as the prohormone [ANP(1–126)]. Final processing during release into the circulation yields the biologically active C-terminal peptide, ANP(99–126) (ANP-28), and the N-terminal fragment ANP(1–98). Lesser quantities of ANP are also secreted directly from the ventricle. BNP, on the other hand, is primarily a ventricular hormone which is secreted constitutively from myocytes as the mature peptide, although small amounts are co-stored with ANP in atrial granules [1]. In man, both the bioactive BNP(77–108) (BNP-32) and NT-BNP [N-terminal BNP(1–76)] forms circulate in plasma, together with a higher-molecular-mass component, probably the prohormone [BNP(1–108)] [2].

The most important stimulus to the secretion of ANP is an increase in atrial wall tension (due to any cause of increased central blood volume and pressure), although many other factors may also affect secretion, including a range of mechanical (e.g. heart rate), physiological (e.g. hypoxia, age, gender and renal function) and neurohumoral [e.g. ET-1 (endothelin-1), Ang II (angiotensin II) and catecholamines] stimuli. Although BNP secretion appears to be regulated in a similar fashion to that of ANP, with the major determinant of secretion being the degree of ventricular stretch and work,
The close relationship of plasma cardiac natriuretic peptide levels with ‘cardiac load’ has led to their use as biomarkers of cardiac health, with diagnostic and prognostic applications in clinical practice. BNP and NT-BNP especially, by virtue of their predominantly ventricular origin, more rapid gene induction and slower clearance rate from plasma, appear to be more accurate and sensitive indicators of cardiac dysfunction and remodelling, and to correlate better with severity. The favourable bioactivity profile of the natriuretic peptides (Table 1) has also led to their use as therapeutic agents in cardiovascular disease.

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**Diagnostic applications**

**HF**

HF, already a leading cause of morbidity and mortality worldwide, is increasing in both incidence and prevalence. Although the survival rate of patients diagnosed with HF has improved over the past decade due to advances in anti-HF therapy, the prognosis remains poor [8]. On this background and in light of evidence from clinical trials demonstrating marked benefits in treating asymptomatic patients [9], it is clear that early detection of LV (left ventricular) dysfunction and intervention to prevent, or at least delay, the clinical manifestations of HF is essential to contain this pandemic. Unfortunately, the accurate diagnosis of HF can be difficult as the signs of the condition have limited sensitivity and specificity, particularly in cases where symptoms are mild or absent. Although echocardiography is considered the ‘gold standard’ for the detection of LV dysfunction, it is a costly procedure and not readily available in all institutions and settings. In addition, the information derived from this procedure is sometimes subjective, resulting in misdiagnosis or under-diagnosis of the disease.

The discovery of especially close correlations between cardiac impairment and plasma levels of BNP [10] and NT-BNP [11] in the 1990s laid the basis for a series of studies which effectively raised both the awareness and clinical significance of the peptides as markers of LV function, leading to the development of commercial point-of-care BNP and NT-BNP assays in 2000 and 2004 respectively, that have been approved by the FDA (Federal Drug Administration) to aid in the diagnosis of HF. The performance of the Triage BNP assay (Biosite Diagnostics, San Diego, CA, U.S.A.) to both diagnose and evaluate the severity of HF was recently assessed in a multicentre trial [12] where plasma BNP levels were measured in 1050 subjects grouped according to NYHA (New York Heart Association) classification, and a diagnostic reference range was established. Circulating BNP levels determined from this bedside assay increased significantly with HF severity (Figure 1). At a threshold of 100 pg/ml, the assay demonstrated 82% sensitivity and 99% specificity for distinguishing normal controls and patients with HF. A BNP level below 100 pg/ml was shown to have a strong negative predictive value.

The ability of the natriuretic peptides to detect not only overt HF, but also pre-clinical ventricular impairment,
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was evaluated in a recent head-to-head comparison of the diagnostic utility of BNP and NT-BNP in symptomatic and asymptomatic structural heart disease [13]. In this investigation, the two peptides were measured in 180 consecutive subjects classified according to ACC (American College of Cardiology)/AHA (American Heart Association) guidelines to yield 43 patients with symptomatic HF and 137 asymptomatic subjects. The authors found that BNP and NT-BNP were highly specific in diagnosing overt HF (92% and 84% respectively) and, although the diagnostic accuracy of both peptides was reduced, they were still capable of detecting cardiac impairment in asymptomatic patients, with a specificity of 78% for NT-BNP and 69% for BNP. These findings suggest that NT-BNP, in particular, which exhibits proportionately greater increases than BNP, due to its comparatively extended half-life, and is less likely to be perturbed by acute stimuli, may be useful for identifying persons with pre-clinical dysfunction for further cardiac evaluation.

The use of NT-BNP in primary care has also recently been assessed. The Natriuretic Peptides in the Community Study recruited 305 patients presenting to their general practitioner with symptoms of dyspnoea and/or peripheral oedema [14]. The general practitioners formulated an initial diagnosis based on clinical assessment, and then NT-BNP levels were measured and randomly provided or not to the doctor prior to review. Knowledge of NT-BNP concentrations improved diagnostic accuracy by 21%, with the main impact of NT-BNP measurement being improved ability to correctly rule out HF.

Thus a rapid (within 20 min) and readily available blood test measuring BNP or NT-BNP should facilitate efficient and accurate diagnosis of HF, as well as playing an important role in improving early detection of LV dysfunction and enabling more timely treatment of this progressive and deadly disease. This test also has the potential to generate long-term cost savings by reducing demand for echocardiography, inappropriate therapy and hospital admissions. The normal plasma ranges and BNP (Biosite assay) and NT-BNP (Roche assay) cut-off values for diagnosing HF (as indicated in assay package inserts [15]), along with other features distinguishing these two peptides, are shown in Table 2. However, as BNP/NT-BNP levels rise with age and are affected by gender, comorbidity and some drug therapies, measurements should not be used in isolation from the clinical context.

#### Acute dyspnoea of cardiac origin

Dyspnoea is one of the most common symptoms for presentation to an emergency department, and a rapid and accurate diagnosis is essential in providing prompt and appropriate treatment. However, establishing the cause in the acute setting can be complex, since the shortness of breath may be due to HF, primary pulmonary disease or other causes.

In a pioneering study, Davis et al. [16] evaluated the usefulness of plasma BNP in confirming or disproving HF in 52 elderly patients coming to the emergency department with acute dyspnoea. They found admission BNP more accurately reflected the final diagnosis of HF than either ANP or LVEF (LV ejection fraction) by radionuclide scan. This study launched a number of further investigations culminating in the Breathing Not Properly (BNP) multinational study [17] that enrolled 1586 patients presenting with breathlessness. This study demonstrated that BNP levels by themselves were more accurate than any historical or physical findings in identifying HF as the cause of dyspnoea. A plasma
BNP cut-off of 100 pg/ml was 83.4% accurate in diagnosing HF, whereas a level of 50 pg/ml had a negative predictive value of 96%, indicating that BNP is highly sensitive in ruling out HF in such a setting. Indeed, the rapid point-of-care test for BNP has been shown to increase the accuracy of emergency department physician’s diagnosis (from 74% to 81.5%) [17], in association with reducing in-hospital mortality (3%), intensive care admissions (9%), hospitalization (10%), time to discharge (27.7%), hospital re-admissions (10%) and overall cost of treatment (25.5%) [18]. Clearly, a rapid triage test for plasma BNP in the emergency department, in conjunction with other clinical information, saves time and resources, as well as improving evaluation and treatment of this critical group of patients.

A recent study by Lainchbury et al. [19] directly comparing the effectiveness of plasma BNP with that of NT-BNP in the diagnosis of HF in 205 patients with dyspnoea found that, although both peptides were useful in discriminating dyspnoea due to ‘cardiac’ reasons from non-cardiac in the emergency room when using the optimum cut-offs, NT-BNP measurement was 17% more specific for the diagnosis of HF than BNP (Figure 2).

**Diastolic HF**

Diastolic HF, characterized by impaired cardiac filling with the presence of preserved LVEF, is especially challenging to diagnose. It constitutes a third or more of all clinical cardiac failure and leads to a poor prognosis. In a study by Redfield et al. [20], BNP concentrations measured in 2042 randomly selected subjects (≥ 45 years) were found to increase with increasing severity of diastolic impairment (Figure 3). For preclinical diastolic dysfunction, the areas under the receiver operating characteristics curve were higher for those with moderate-to-severe (0.74–0.79) than any (0.52–0.68) diastolic dysfunction, with optimal discriminatory values of BNP varying with age and sex. In another study [21], BNP levels were found to be significantly elevated in patients with diastolic HF and preserved systolic function independent of L V hypertrophy. It should be noted that even in systolic HF, BNP concentrations are reported to reflect severity of diastolic abnormality (impaired relaxation and restrictive filling pattern) [22].

**RV (right ventricular) dysfunction**

Plasma BNP levels are proportionately raised in disorders associated with RV overload and structural abnormalities. In patients with acute pulmonary embolism, primary RV dysfunction is frequent and is associated with increased in-hospital complications (cardiogenic shock, inotropic therapy and mechanical ventilation). BNP concentrations are significantly raised in pulmonary embolism patients with RV dysfunction (340 ± 362 pg/ml) compared with those without RV impairment (55 ± 69 pg/ml), with a BNP cut-off of > 90 pg/ml being highly predictive of RV HF [23]. Circulating BNP is also reported to be predictive of RV functional impairment in primary pulmonary hypertension [24] and to detect cor pulmonale in patients with respiratory failure [25]. Although the degree of BNP elevation with RV dysfunction appears to be somewhat attenuated compared with disorders associated with LV overload, the test may be particularly useful in identifying...
patients with a poor prognosis in whom more aggressive treatment might be warranted.

ACS (acute coronary syndrome)

ACS is a serious condition, difficult to diagnose in the emergency room due to the insensitivity of clinical, electrocardiographic and biological signs (increased troponin). Cardiac ischaemia is an important trigger for the release of the ventricular natriuretic peptides, and the diagnostic utility of BNP for ACS was assessed in a study of 65 patients admitted to the emergency room for chest pain without ST elevation and without clinical, radiological or echocardiographic signs of LV dysfunction [26]. The results of BNP measurements were masked until the final diagnosis was established on the usual investigations (ECG changes, troponin I values, myocardial scintigraphy and coronary angiography). BNP levels were significantly raised in patients with non-Q wave infarction and unstable angina compared with those with non-coronary chest pain (Figure 4), and were determined to be not only a better criterion of ACS than increased troponin (with a diagnostic accuracy > 90%), but also a reliable diagnostic marker of unstable angina in the presence of normal ECG and undetectable troponin. Measurement of BNP may be particularly useful in the initial risk assessment of ACS in women [27]. These findings suggest that measurement of BNP may allow detection of coronary disease at a pre-clinical phase.

LV hypertrophy in hypertension

A major complication of hypertension is LV hypertrophy, a known risk factor for all the cardiovascular complications of this disease that is independent of the severity of blood pressure elevation. Concentric hypertrophy, in particular, is associated with increased morbidity and mortality [28], as well as more advanced extra-cardiac target-organ damage. Thus early detection of LV hypertrophy in hypertensive patients is important. A number of studies have reported that natriuretic peptide levels are raised in patients with essential hypertension and show a correlation with LVMI (LV mass index). In a study by Nishikimi et al. [29], 90 hypertensive patients were classified into one of four groups based on LV geometric patterns according to echocardiographic findings. Although circulating ANP doubled in a gradual stepwise fashion from normotensives to hypertensives with normal heart geometry, concentric remodelling, eccentric hypertrophy and concentric hypertrophy, BNP levels increased approx. 6-fold in patients with concentric hypertrophy (Figure 5), with a concentration of ≥18 pg/ml predicting concentric hypertrophy with a sensitivity of 75% and a specificity of 74%. Similar significant rises in circulating levels and relationships with LV dimensions in hypertension have been reported for NT-BNP [30]. Measurement of the natriuretic peptides may be useful in screening for cardiac hypertrophy in hypertensive patients, identifying a group warranting more aggressive investigation and treatment.

Symptom onset in valve disease

The onset of symptoms in cardiac valve disease is associated with increased morbidity and mortality, and is the best accepted indication for valve replacement. Early and accurate recognition and interpretation of symptoms not only identifies an at-risk group of patients that would benefit from timely valve replacement, but may also allow for surgery with lower operative morbidity/mortality compared with the higher surgical risk when dysfunction and decompensation is advanced. However, symptoms
can be non-specific (most commonly including exertional dyspnoea and fatigue), subtle at onset, sometimes difficult to assess because of inactivity or under-reporting and, therefore, often difficult to evaluate clinically.

In a recent ground-breaking study by Gerber et al. [31], the potential of the natriuretic peptides as markers of both disease severity and the presence of relevant symptoms was evaluated in 74 patients with isolated aortic stenosis. The subjects underwent independent assessment of symptoms, transthoracic echocardiography and measurement of plasma ANP, BNP and NT-BNP. Although all indices were strongly associated with the presence of symptoms in these patients, plasma natriuretic peptide levels demonstrated much less overlap between asymptomatic and symptomatic cases than peak aortic velocity and aortic valve area measurements. Using the optimum cut-off values for discriminating for symptoms, the sensitivity of NT-BNP (60 pmol/l; 78 %), BNP (14 pmol/l; 76 %) and ANP (25 pmol/l; 70 %) were markedly greater than that of aortic valve area (0.75 cm²; 56 %). Furthermore, the natriuretic peptides (NT-BNP in particular) provided additional predictive value to the aortic valve area and LVEF for the presence of symptoms.

In mitral regurgitation, plasma levels of the cardiac natriuretic peptides also rise with increasing disease severity (greatest for NT-BNP) and are highest in symptomatic patients, even when the LVEF is normal [32]. Similarly, in chronic aortic regurgitation, natriuretic peptides levels are higher in symptomatic than asymptomatic patients, and may provide information on LV function in addition to echocardiography [33]. In a retrospective study looking at 51 patients with valve disease undergoing single valve surgery (mitral stenosis, n = 13; mitral regurgitation, n = 6; aortic stenosis, n = 14; aortic regurgitation, n = 8), pre-operative plasma BNP levels demonstrated no relationships with pre-operative cardiac function, but correlated significantly with post-operative NYHA functional class [34].

Syncope of cardiac origin
Identifying the cause of syncope remains difficult in many cases, and patients in whom heart disease is suspected or those with exertional syncope who are at higher risk for adverse outcomes, undergo extensive cardiac testing. In a study by Tanimoto et al. [35], the feasibility of using BNP measurements in a screening test for cardiac causes of syncope was investigated retrospectively in 118 patients. BNP concentrations in the group identified as having syncope of cardiac origin (118 ± 42 pg/ml, n = 61) were significantly higher than in the reflex-mediated (18 ± 7 pg/ml, n = 20), neurological (26 ± 13 pg/ml, n = 8) and unknown (28 ± 12 pg/ml, n = 29) groups. At a cut-off value of 40 pg/ml, the sensitivity and specificity of BNP for identification of cardiac syncope were 82 % and 92 % respectively. Thus measurement of BNP merits consideration for incorporation into the algorithm used to investigate syncope and may well assist in identifying a cardiac cause.

Prognostic applications
HF
Because of their significant relationship with LVEF, the natriuretic peptides were put forward as a non-invasive means of identifying patients at high risk of death who require more intensive monitoring and treatment. Numerous studies have shown that BNP levels are higher in patients with more severe symptoms and are able to differentiate between moderate and more extreme impairment of LV function. In a study by Koglin et al. [36], 78 patients were classified into three different prognostic groups according to the HFSS (HF survival score). Mean BNP concentrations were found to increase from 98 ± 11 to 244 ± 33 pg/ml and to 420 ± 56 pg/ml over the low, medium and high risk groups respectively. The authors also demonstrated that BNP levels were associated with changes in cardiovascular functional class over time, with concentrations falling in patients who improved over the ensuing 12 months (42 ± 9 pg/ml) and rising in those who deteriorated.

In multivariate analyses, BNP has been shown to be a prognostic marker of cardiovascular and all-cause mortality in HF, both independent of, and more accurate than, NYHA class and LVEF [37]. BNP levels are also strong independent predictors of sudden death, suggesting the peptide might be a useful tool in selecting individuals who may benefit from implantable cardioverter-defibrillators [38]. In addition to its association with death, BNP levels in HF are predictive of exercise capacity [39], future hospitalization and worsening HF [40,41]. A recent study has suggested that pre-discharge BNP levels (rather than admission measurements) may exhibit the best discriminative power [42]. The prognostic utility of BNP for morbidity and mortality in HF appears to hold true regardless of the differing underlying aetiologies of the disease [43] and treatment regimes [44], and levels of the peptide may also act as a guide to the introduction of β-blockade therapy [40]. Similar to BNP, NT-BNP has been shown to be a strong prognostic marker of all-cause mortality (Figure 6), HF mortality, worsening HF and hospital admission with HF [41]. NT-BNP is also reported to be an independent predictor of need for urgent cardiac transplantation, whereas LVEF, maximum oxygen uptake and HFSS were not [45].

ACS
Raised plasma concentrations of the natriuretic peptides following acute MI (myocardial infarction) also identify patients at risk for adverse LV remodelling, LV dysfunction, HF and death, independent of LVEF, age and previous history of hypertension, MI or HF [37,46]. Of
the peptides, NT-BNP demonstrates the greatest absolute and proportional increases post-MI [47] and appears to be the best prognostic marker of mortality (Figure 7). A recent report indicates that plasma NT-BNP and LVEF may be complementary independent predictors of major adverse events post-MI [48]. In this study, a combination of elevated (supramedian) NT-BNP with reduced LVEF (<40%) was found to confer a greater than additive 3-year risk of death of 37% (NT-BNP alone, 14%; LVEF alone, 6%) and of HF of 18% (NT-BNP alone, 8%; LVEF alone, 11%). In addition, supramedian NT-BNP was associated with a 26% risk of future MI only when LVEF was reduced. These findings suggest combined measurement of these indices may provide risk stratification following MI substantially better than that provided by either alone.

Similarly, raised BNP/NT-BNP levels in ACS are associated with increased risk of death, new or recurrent MI, or clinical HF [49–51]. The relationship between NT-BNP and mortality appears to be independent of, and stronger than, other well-known predictors of outcome in this syndrome, such as age, previous MI, HF, troponin T, C-reactive protein, interleukin-6, ECG changes and LVEF. A highly significant graded relationship exists between BNP peptide concentrations and subsequent survival. This is illustrated in a study of 6809 ACS patients by James et al. [52] where increasing quartiles of NT-BNP related to a predicted 1-year mortality of 1.8%, 3.9%, 7.7% and 19.2% respectively. A combination of NT-BNP and creatinine clearance provided the best prediction, with a mortality of 25.7% at 1 year [52]. Even in patients with stable angina, BNP peptide concentrations may be useful for the prediction of recurrence of anginal attacks [53].

Circulating BNP peptide levels change dramatically over time following an ischaemic episode, rising rapidly to peak at approx. 24 h post-MI (with the peak concentration proportional to infarct size), suggesting the optimal timing for peptide measurement is around this period. However, studies performed over the past 5 years looking at the association of plasma BNP peptide levels and outcomes in patients presenting with ACS/MI demonstrate that, regardless of whether BNP/NT-BNP are measured at admission, 24 h after symptom onset or 2–7 days after the index event, both peptides appear to maintain their prognostic performance. Many of these studies are shown in Table 3 [48,49,52,54–64] and are arranged according to approximate length of time between onset of symptoms and sampling. These data, together with a report by Galvani et al. [65], indicate that the prognostic value of the BNP peptides is similar both at short- and long-term, whether measured at first patient contact or during hospital stay, and in patients with ST elevation MI or no ST elevation ACS.

**Hypertension**

NT-BNP predicts LV mass in arterial hypertension and, even in patients with preserved LV function, the peptide has been demonstrated to be a very strong prognostic marker of future cardiovascular events [30]. This is particularly true when combined with a history of cardiovascular disease, indicating a use for NT-BNP in risk stratification of patients with arterial hypertension.
Table 3  Relationship between BNP peptide levels and clinical outcome in ACS/MI

Studies looking at the prognostic value of the BNP peptides in patients presenting with ACS or MI. CF, coronary flow; SCD sudden cardiac death; STE, ST elevation.

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Patients</th>
<th>Symptoms/sampling</th>
<th>Plasma cut-off (peptide; assay)</th>
<th>Predicted outcomes (follow-up period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mega et al. [54]</td>
<td>438</td>
<td>&lt; 6h</td>
<td>80 pg/ml (BNP; Bayer)</td>
<td>Death (30 days), impaired CF and continued STE</td>
</tr>
<tr>
<td>Jernberg et al. [55]</td>
<td>775</td>
<td>6h</td>
<td>400 pg/ml (NT-BNP; Roche)</td>
<td>Death (3.3 years)</td>
</tr>
<tr>
<td>Galvani et al. [56]</td>
<td>1756</td>
<td>&lt; 12h</td>
<td>353 pg/ml (NT-BNP; Roche)</td>
<td>Death (30 days)</td>
</tr>
<tr>
<td>James et al. [52]</td>
<td>6809</td>
<td>9.5h</td>
<td>669 pg/ml (NT-BNP; Roche)</td>
<td>Death (30 days and 1 year)</td>
</tr>
<tr>
<td>Bazzino et al. [57]</td>
<td>1483</td>
<td>&lt; 24h</td>
<td>586 pg/ml (NT-BNP; Roche)</td>
<td>Death (in-hospital and 180 days)</td>
</tr>
<tr>
<td>Jernberg et al. [58]</td>
<td>2019</td>
<td>&lt; 24h</td>
<td>906 (men)/1345 (women) pg/ml (NT-BNP; Roche)</td>
<td>Death (2 years)</td>
</tr>
<tr>
<td>Morrow et al. [59]</td>
<td>1676</td>
<td>&lt; 24h</td>
<td>80 pg/ml (BNP; Biosite)</td>
<td>Death (7 days and 6 months), and HF (by 30 days)</td>
</tr>
<tr>
<td>Katayama et al. [60]</td>
<td>130</td>
<td>24h</td>
<td>290 pg/ml (BNP; Roche)</td>
<td>Death (20 days), and LV remodelling</td>
</tr>
<tr>
<td>de Lemos et al. [49]</td>
<td>2525</td>
<td>40 h</td>
<td>81.2 pg/ml (BNP; Biosite)</td>
<td>Death (30 days and 10 months), new MI and HF</td>
</tr>
<tr>
<td>Omland et al. [61]</td>
<td>609</td>
<td>&lt; 3 days</td>
<td>4611 pg/ml (NT-BNP; Local)</td>
<td>Death (4.25 years)</td>
</tr>
<tr>
<td>Richards et al. [62]</td>
<td>220</td>
<td>1−4 days</td>
<td>94 pg/ml (BNP; Local)</td>
<td>Death (1.2 years), HF and LVEF &lt; 40 % (3−5 months)</td>
</tr>
<tr>
<td>Richards et al. [48]</td>
<td>666</td>
<td>1−4 days</td>
<td>103 and 1371 pg/ml (BNP and NT-BNP)</td>
<td>Death (3 years), new MI and HF</td>
</tr>
<tr>
<td>Tapanainen et al. [63]</td>
<td>521</td>
<td>7 days</td>
<td>80 pg/ml (BNP; Local)</td>
<td>Death (3.6 years), SCD and non-SCD</td>
</tr>
<tr>
<td>Crilley et al. [64]</td>
<td>133</td>
<td>3−7 days and 2 months</td>
<td>629 pg/ml (BNP; Local)</td>
<td>Death (1 year), and LV remodelling</td>
</tr>
</tbody>
</table>

Cardiac transplantation/surgery

The prognostic value of BNP as a non-invasive screening tool for cardiac allograft pathology in heart transplant recipients has been assessed in a number of studies. Plasma BNP is elevated in heart transplant patients and correlates with cardiopulmonary haemodynamic impairment (despite preserved systolic function) and severity of rejection [66,67]. Other investigators report that BNP levels serve as prognostic markers for hospitalization, acute rejection episodes and overt rejection [66–68]. In paediatric heart transplant recipients, BNP levels (> 100 pg/ml) demonstrated 100 % sensitivity and negative predictive value for identifying cardiac graft pathology [69].

Pre-operative BNP levels may also be useful in predicting post-operative complications, hospital stays (> 10 days) and 1-year mortality in patients undergoing open-heart surgery [70]. Post-operatively, elevated BNP levels were associated with prolonged hospital stay and mortality within 1 year.

Valve disease

In valvular heart disease, pre-operative BNP levels have been shown to correlate with 1-year post-operative NYHA functional class [32]. NT-BNP measurement in patients with aortic stenosis predicts symptom-free survival as well as the development of symptoms in asymptomatic patients [71]. In those patients undergoing surgery because of symptoms, pre-operative NT-BNP independently predicts 1-year post-operative outcome with regard to survival, symptomatic status, and LV function.

AF (atrial fibrillation)

Measurement of the natriuretic peptides may provide not only a means of monitoring the success of cardioversion in patients with AF, but may also predict post-cardioversion reversion to AF. In a study of 151 patients with chronic AF, ANP, BNP and NT-BNP were measured before, immediately after and 6 weeks following cardioversion [72]. Plasma levels of all three peptides fell immediately following successful cardioversion (but not in patients in which cardioversion failed), and were significantly higher at all three sampling times in those destined to be in AF at 6 months. Pre- and post-cardioversion BNP and NT-BNP concentrations were shown to be predictive of reversion to AF, independent of age, LV function or the prophylactic prescription of β-blockers. These findings suggest that the BNP peptides may identify AF patients who may be more rationally treated with rate control and anticoagulation rather than undergoing single or serial electrical cardioversion.

General population/elderly

A number of studies have investigated the diagnostic and prognostic utility of the BNP peptides in the general population. In one study, NT-BNP was measured in 672 participants (50–85 years) recruited from randomly selected general practitioners and followed up for a median period of 805 days [73]. NT-BNP identified individuals with symptoms of HF and LVEF ≤ 40 % with a sensitivity of 0.92 % and a specificity of 0.86 %. Levels above the study median (32.5 pmol/l) were strong independent predictors of mortality, hospital admissions for HF and other cardiac admissions. In a report by
McDonagh et al. [74] looking at a random sample of 1640 subjects aged 25–74 years, BNP concentrations > 17.9 pg/ml predicted 4-year all cause mortality. In a retrospective study, the cost-effectiveness of screening high-risk subjects (those with symptomatic ischaemic heart disease, blood pressure > 160/95 mmHg and abnormal ECGs) in 1257 community subjects by BNP before echocardiography was calculated to have reduced the cost per detected case of LV systolic dysfunction by 26 % for the cost ratio of 1/20 (BNP/ECG) [75].

The elderly population, in particular, have been the focus of potential screening by the BNP peptides. In 1997, Wallen et al. [76] assessed BNP levels and current disease states in 545 85-year-old subjects. Although BNP concentrations were found to be significantly increased in relation to aging, multivariate analysis revealed the peptide was predictive for ischaemic heart disease, AF, renal dysfunction, congestive HF and treatment with β-adrenergic blockers. BNP also predicted 5-year mortality in individuals both with and without a defined cardiovascular disorder. In another study [77], raised plasma BNP concentrations in 111 persons aged ≥ 80 years who had no history of hospitalization for cardiac disease were a marker of increased risk of 2-year cardiac morbidity and total mortality, with each 50 pg/ml increase in BNP associated with a 1.6-fold increase in the risk of cardiac events and a 1.4-fold increase in total mortality.

These findings suggest measurement of the BNP peptides may be useful as both a screening tool for cardiovascular disease in the general population and as a marker of an increased risk of cardiac morbidity and total mortality, especially in the elderly.

**HF management/treatment optimization**

Uncertainties exist as to how proven HF therapies should be implemented and what doses are optimum. In addition, the complexity of treatment has escalated, with an increasing spectrum of therapeutic agents now available. Effective anti-HF therapy is associated with haemodynamic and clinical improvement and reductions in morbidity and mortality, with corresponding falls in plasma levels of the natriuretic peptides [36–78]. Likewise, deterioration in cardiovascular function increases circulating peptide concentrations [36], with persistently high BNP levels despite aggressive HF treatment identifying individuals at especially high risk for adverse outcomes [79]. These findings suggest measurement of the natriuretic peptides may be helpful for monitoring the efficacy of therapy.

In 2000, Troughton and colleagues [80] compared the treatment of HF dictated by clinical acumen to treatment titrated to reduce plasma NT-BNP concentrations. Sixty-nine patients with impaired systolic function (LVEF < 40 %) and symptomatic HF (NYHA class II–IV) were randomized into two groups (33 in the NT-BNP group and 36 in the Clinical group) and were followed up for a mean of 9.5 months. The treatment target in the Clinical group was clinically compensated HF according to an objective score (HF score < 2) and, in the NT-BNP group, NT-BNP values below 200 pmol/l. Treatment targets were assessed at 2-week intervals, and treatment intensified according to a strict and predetermined stepwise protocol until targets were met. The authors found that, although changes in LV function, quality of life, renal function and adverse events were similar in both groups, the NT-BNP group exhibited fewer total cardiovascular events (death, hospital admission or HF decompensation) than the Clinical group (19 compared with 54 respectively; Figure 8), as well as a doubling of time to occurrence of the first cardiovascular event.

In the current setting of variable clinical expertise available to diagnose and manage an increasing number of HF patients (often for an extended duration), the BNP peptides may act as objective indicators to assist optimal pharmacotherapy. Measurement of NT-BNP, rather than BNP, is clearly necessary in situations where synthetic BNP is administered as a therapeutic. A more thorough investigation of BNP-guided HF treatment is currently underway in the BATTLESCARRED trial (BNP Assisted Treatment To Lessen Serial CARDiac REadmissions and Death), which involves a larger patient group with a broader spectrum of LV function, age, comorbidity and with a modernized drug algorithm.

**Treatment**

The cardiac natriuretic peptides possess protean physiological properties (vasodilation, natriuresis/diuresis, inhibition of renin–angiotensin–aldosterone and sympathetic nervous systems; Table 1) that are beneficial in conditions associated with volume overload and vasoconstriction [81]. As a result, interest has focused on development of agents that reproduce the actions of these
peptides. Two approaches have been employed: direct administration of synthetic ANP/BNP and the use of NEP inhibitors.

**Nesiritide**

Nesiritide (Natrecor or Scios), the recombinant form of human BNP, was approved by the FDA in 2001 for the treatment of acute decompensated HF. The clinical efficacy of this drug was evaluated by the Nesiritide Study Group in 127 patients hospitalized because of symptomatic congestive HF. Nesiritide infusion decreased pulmonary-capillary wedge pressure, systemic vascular resistance, right atrial pressure, cardiac index and plasma aldosterone levels, improved global clinical status, and reduced dyspnoea and fatigue. The most common side-effect was dose-related hypotension, which was usually asymptomatic [82].

Subsequent studies compared nesiritide with other standard intravenous therapies for decompensated HF. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with DobutaminE or Natrecor Therapy) study, 255 hospitalized HF patients were randomized to receive intravenous nesiritide or dobutamine. Both drugs were equally effective in improving the signs and symptoms of HF; however, whereas dobutamine was associated with substantial pro-arrhythmic and chronotropic effects, nesiritide had a neutral effect or actually reduced ventricular ectopy [83]. Nesiritide therapy also reduces duration of treatment, 6-month mortality, length of stay in both coronary care and hospital, re-admission rate and use of additional treatments compared with dobutamine [84,85]. In the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, nesiritide was found to be more effective and better tolerated than the vasodilator nitroglycerine, with a trend towards reduced re-admissions [86]. Other studies have shown nesiritide exhibits a more rapid and sustained haemodynamic profile [87,88], as well as greater improvements in dyspnoea and global clinical scores than nitroglycerine [88]. In a comparative study with milrinone, nesiritide improved patient haemodynamics and decreased infusion duration and time in intensive care relative to milrinone therapy, with trends towards decreases in overall length of stay in hospital and re-hospitalization. The total cost of treatment (cost of bed, supplies and drug) was also lower with nesiritide [89].

In view of these findings, nesiritide represents an attractive choice for first-line therapy for patients with acutely decompensated HF. Nesiritide also appears to be effective and well tolerated in patients receiving concomitant β-blocker therapy and in HF patients with ACS and renal insufficiency [88,90]. ANP/BNP might also prove useful as an adjunctive therapy to percutaneous coronary intervention for acute MI [91] and in the treatment of post-operative cardiac patients [92], non-cardiogenic acute pulmonary oedema [93], cor pulmonale [94] and acute renal failure [95]. A preliminary report of BNP use in paediatric care suggests the agent is also safe and effective in this population [96].

A novel therapeutic strategy currently under investigation is the SC (subcutaneous) administration of BNP. Chen et al. [97] injected eight HF patients (NYHA class II–III) with nesiritide every 12 h for 3 days. SC nesiritide elevated plasma BNP concentrations in association with increases in cardiac output, urinary volume and sodium excretion, and reductions in systolic blood pressure, plasma renin and aldosterone levels (duration of effects approx. 2 h). The treatment was generally well tolerated. These findings suggest SC administration of BNP may be an efficacious route for delivery of this peptide.

In another study, ANP gene therapy in hypertensive rats is reported to reduce blood pressure for up to 12 weeks [98]. Longer-term actions of the natriuretic peptides to restrain vascular and cardiac cell growth should also be taken into account.

**NEP inhibition**

Although NEP inhibition enhances endogenous levels of the natriuretic peptides by blocking their enzymic breakdown, the enzyme also acts on a number of other substrates, including the vasodilator bradykinin and the vasoconstrictors Ang II and ET-1. Hence NEP inhibition has the potential to both promote and attenuate vascular tone. This problem has largely been overcome by the development of agents that simultaneously inhibit ACE (angiotensin-converting enzyme) and NEP. These new classes of drugs have been termed vasopeptidase inhibitors, of which omapatrilat was the prototype. Early clinical studies with this combined inhibitor looked promising, with administration of the agent in HF patients increasing plasma levels of the natriuretic peptides in association with reductions in capillary wedge pressure and systolic blood pressure and improvements in LVEF and renal function [99]. In subsequent phase 2 and 3 trials comparing the effects of omapatrilat with the ACE inhibitors lisinopril [IMPRESS (Inhibition of Metallo Protease by BMS-186716 in a Randomized Exercise and Symptoms Study in Subjects With Heart Failure) trial] [100] and enalapril [OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial] [101] in patients with HF (NYHA class II–IV), it was found that randomization to omapatrilat was associated with a reduced risk of death, worsening HF, hospitalization and deterioration of renal function. In a comparative study with enalapril in hypertension [OCTAVE (Omapatrilat Cardiovascular Treatment vs. Enalapril) study] [102], omapatrilat induced greater decreases in blood pressure. However, the occurrence of angioedema (thought to be due to increased levels of bradykinin which is degraded by both ACE and NEP) in
hypertensive patients on omapatrilat (2.17 %) was greater than in those given enalapril (0.68 %). Rates were even higher in African-Americans (5.54 % versus 1.62 %) and smokers (3.93 % versus 0.81 %) in this study. A similar trend of increased angioedema with omapatrilat was observed in the OVERTURE trial (0.83 % versus 0.49 %). Although it appears that vasopeptidase inhibitors offer some slight advantage over pure ACE inhibitors to date, the future of this new class of drug may depend on developing agents with an improved risk/benefit ratio (that cause less angioedema) or identifying high-risk populations likely to benefit from dual ACE/NEP inhibition, such as patients with concomitant renal dysfunction.

Other therapeutic strategies involving NEP inhibition currently under investigation include the combination of NEP inhibition with ECE (endothelin-converting enzyme) inhibition [103]. A mixed NEP/ECE inhibitor (SLV-306) is presently undergoing phase 2 clinical trials in Belgium [104].

THE FUTURE

As biomarkers of LV dysfunction, BNP/NT-BNP appear to be promising tools to facilitate the diagnosis of a variety of cardiovascular diseases. Measurement of these peptides is now possible by rapid automated assays that are relatively cheap, non-invasive and readily available. They already have proven utility in the emergency department diagnosis of HF in patients presenting with dyspnoea, and it is likely that measurement of these peptides will become a routine part of care for evaluating patients with known or suspected HF in the primary care environment in the future. Although the BNP peptides appear to be less accurate as a general screening test in diagnosing mild or asymptomatic LV dysfunction, or in detecting other cardiac pathologies such as coronary artery disease or hypertrophy, they might be helpful in identifying individuals that require further investigation (thereby improving early disease detection and enabling more timely treatment) and in monitoring high-risk populations.

However, a number of issues need to be taken into account when considering the use of the BNP peptides as diagnostic tools. One of these is the choice of which peptide to measure. Current evidence would tend to suggest that NTI-BNP, with its greater absolute and proportional changes following cardiac impairment/injury, together with its longer plasma half-life and lower biological variability relative to BNP, may be a better marker for detecting changes in BNP secretion. Another point to be considered is the optimal cut-off concentration to be used in clinical decision-making. An effective comparison of published studies is difficult given the different assay systems used to detect different clinical and study end-points in different types of patient cohorts. In addition, these studies have accentuated different threshold peptide concentrations (with varying sensitivities and specificities) for positive/negative test interpretations. Although a higher discriminatory cut-off for a positive test will improve specificity, the sensitivity will be reduced and the diagnosis may be missed. In some situations, such as where the disease is rapidly fatal and a correct diagnosis is critical, a lower threshold with a higher sensitivity may be required (even if it results in a greater number of false positives). Thus further work is required to establish the appropriate reference ranges for each assay, as well as the optimum cut-offs for different cardiac conditions. Furthermore, since BNP peptide concentrations are higher in women than men and increase with advancing age, cut-offs used should be adjusted upwards in women [58] and in the very elderly population [105] for optimal test interpretation. Other conditions that could affect concentrations, such as obesity or renal failure, also need to be evaluated.

BNP/NT-BNP levels also constitute promising markers of prognosis in a number of cardiovascular disease states, including HF and in cardiac ischaemic syndromes. Treatment of these and other conditions using the BNP peptides as guides for the titration of pharmacological therapy shows potential to reduce adverse clinical outcomes.

Nesiritide, the synthetic form of BNP, has been approved for use in the treatment of acute decompensated HF and may have advantages over current drug therapy. Vasopeptidase inhibition awaits an improved safety/efficacy profile or perhaps identification of an appropriate recipient population that will benefit considerably from dual ACE/NEP inhibition.

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