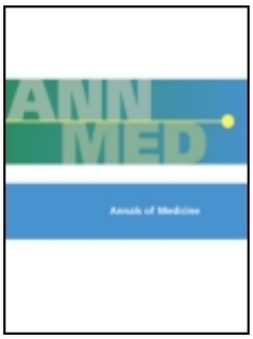

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Brain natriuretic peptide-guided therapy for heart failure

M Gary Nicholls, John G Lainchbury, A Mark Richards, Richard W Troughton and Timothy G Yandle

The drug treatment of heart failure, once simple, has become complex. Apart from a loop diuretic and digoxin, most patients should now be receiving an angiotensin-converting enzyme inhibitor (or angiotensin II receptor blocker), a beta-blocker and spironolactone. Newer drugs, such as endothelin-receptor antagonists and combined blockers of converting-enzyme and neutral endopeptidase, might soon become available. When to introduce these drugs and what dose is optimal for any individual, are questions that currently vex clinicians. We proposed that plasma levels of the cardiac hormone brain natriuretic peptide (BNP, or better, its 1–76 amino-acid N-terminal fragment, N-BNP), would provide an objective index for guiding drug treatment in patients with established, stable cardiac failure. In a pilot study, 69 patients were randomized to drug treatment based on clinical criteria, or based on plasma levels of N-BNP. After a median follow-up of 9.6 months, those in the N-BNP group had fewer clinical end-points than those in the group managed by clinical criteria alone (19 vs 54; $P = 0.02$). These preliminary data encourage the concept that the increasingly complex pharmacotherapy for heart failure, both chronic (as in this trial) and acute, might best be guided by an objective measure such as plasma levels of BNP or N-BNP.

Keywords: brain natriuretic peptides; cardiac natriuretic peptides; heart failure.

Ann Med 2001; 33: 422–427.

Introduction

Until the mid-1980s pharmacotherapy for heart failure was quite simple. It was based on inadequate evidence for benefit, particularly relating to any effects on longevity. In fact, studies reporting benefit from drug therapy had surrogate end-points, such as change in haemodynamic, renal or electrolyte indices. Sample size and duration of therapy was, in general, far short of adequate to demonstrate any impact on longevity. Chronic pharmacotherapy consisted of diuretic treatment, usually a loop diuretic (sometimes supplemented with a potassium-retaining diuretic such as spironolactone or amiloride), digoxin for those with atrial fibrillation and a rapid ventricular rate (and arguably for patients in sinus rhythm), complemented by prolonged bed rest and dietary sodium restriction.

In the 1970s, considerable enthusiasm had developed for the concept of unloading the struggling heart with arterial and/or venodilator agents (1, 2). Subsequent studies were disappointing in demonstrating that prazosin or hydralazine did not have sustained haemodynamic benefit when added to diuretic treatment, perhaps in part because they ultimately activated (or at least did not inhibit) neurohormonal systems (3–7). Although the combination of vasodilators hydralazine and isosorbide dinitrate proved superior to placebo and to prazosin regarding longevity (6), the angiotensin-converting enzyme (ACE) inhibitor, enalapril, was superior again (8). Now, for the first time, there was objective evidence that drug therapy, particularly with agents that interfered with activity of the renin–angiotensin system, increased longevity (9–11) while also improving exercise tolerance, electrolyte status and wellbeing.

Subsequent studies have demonstrated additional benefit, beyond that achieved by ACE inhibition, with beta blockade (12–20) and spironolactone (21) in regard to reduced mortality, and with digoxin in regard to reducing the hospitalization rate (22).

Suddenly, at the turn of the century, pharmacotherapy of heart failure has become complex. Most of the drug trials noted above have been quite selective in their entry criteria, and doses of drugs varied

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considerably within any one trial. Furthermore, most studies were carried out in special research clinics or hospital-based clinics where patients are unlikely to be representative of those seen in general medical services or primary care.

The dilemma for those who manage patients with heart failure is, first, when to introduce individual agents that have been shown in objective studies to be beneficial and, second, what dose of each agent to use. It would be extreme naivety to consider that all patients will best be treated by the average dose used in controlled drug trials. In the case of diuretics, which have not undergone controlled studies to determine their effects on longevity, determining the optimal dose in an individual patient is dependent largely on clinical acumen.

In deciding these issues, standard practice has been to take cognisance of drug doses used in controlled trials but making adjustments according to the patient's symptoms, signs (particularly the presence or absence of oedema, the level of the jugular venous pulse (JVP) as well as supine and standing arterial pressure), objective measures of renal function and perhaps appearances on chest radiology. Lack of objectivity is obvious for many of these indices.

The concept of using an objective marker for tailoring medical treatment in heart failure (23) is not new. Stevenson and co-workers showed that patients achieving a pulmonary artery wedge pressure equal to or less than 16 mmHg with drug treatment had a 1-year survival of 83% compared with 38% in patients who had higher wedge pressures (24). In that the cardiac natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated according to the severity of cardiac dysfunction (25–28), their plasma levels might, in theory, be used as an objective guide to pharmacotherapy.

Plasma levels of cardiac natriuretic peptides in heart failure

As already noted, plasma levels of ANP and BNP are elevated according to the severity of cardiac dysfunction. In mild heart failure, plasma ANP levels tend to be elevated more obviously than BNP. With increasing severity of dysfunction, however, BNP levels rise to similar or higher levels (28) and might, therefore, provide the superior index.

We have found (29) that the 1–76 N-terminal peptide of BNP (N-BNP), while circulating at similar levels to the bioactive 32-amino acid peptide BNP in healthy volunteers, increases more strikingly as heart failure worsens than does the bioactive BNP-32 itself (Fig 1). While both BNP and N-BNP are secreted primarily from the left ventricle in response to changes in left ventricular stretch, it is possible that N-BNP will prove to be superior to BNP-32, ANP or its propeptide as an index of cardiac dysfunction.

Key messages

- **The drug treatment for heart failure patients needs to be tailored to the individual.**
- **Objective guidance for drug type and dose by plasma levels of N-BNP (1–76 N-terminal peptide of brain natriuretic peptide) appears to be a promising approach.**

Effects of drug treatment on cardiac natriuretic peptides

If the cardiac natriuretic peptides are to prove useful in determining when to introduce drug therapy and what dose should be sought, such drug treatments should induce a decline in plasma levels of the peptide in question as cardiac function improves. Indeed, treatment with diuretics, ACE inhibitors and nitrates has been shown to reduce plasma natriuretic peptide levels in parallel with haemodynamic or clinical

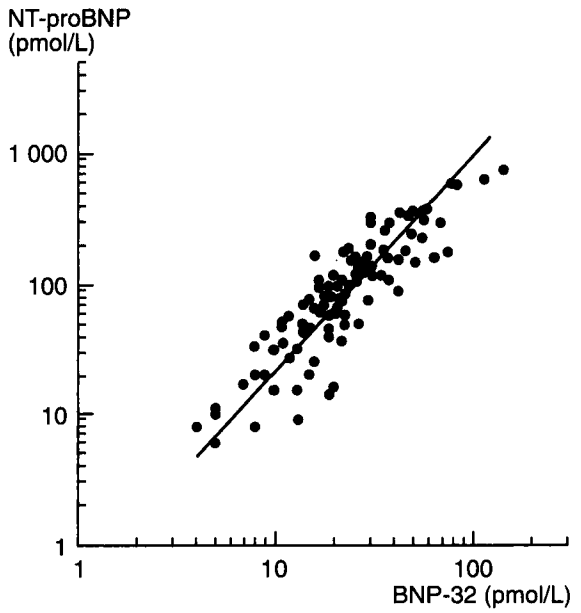

Figure 1. Plasma immunoreactive brain natriuretic peptide (BNP)-32 plotted against concomitant plasma immunoreactive NT-proBNP (the 1–76 N-terminal peptide of BNP, or N-BNP) concentrations in 111 patients with cardiac impairment ($r = 0.88$, $P < 0.001$). Note the difference in scales for the two axes. Patients with mild heart failure had similar levels for the two peptides but N-BNP became progressively higher than concomitant BNP-32 levels with increasingly severe heart failure. (Reproduced from (29) with permission.)

improvement (30–34). The situation in regard to beta blockers needs further research as variable effects on plasma ANP and BNP were described with acute beta blockade by Sanderson and co-workers (35), whereas levels of both peptides were reduced by metoprolol treatment over a 6-month period according to Hara and co-workers (36). In that ventricular volumes decline with chronic beta blockade therapy (37), one would anticipate a concomitant fall in plasma levels of the cardiac peptides, BNP and N-BNP in particular, with prolonged therapy. The same might apply in the case of digoxin where acute intravenous administration reportedly elevates plasma levels of ANP and BNP (38), but the opposite is more likely with chronic therapy.

Preliminary study of heart failure guided by plasma N-BNP

To test the hypothesis that titration of drug treatment to reduce plasma N-BNP in patients with systolic heart failure would prove superior to treatment with empirical, trial-based therapy according to usual clinical criteria, we carried out a study in 69 patients (39). All patients had impaired left ventricular systolic function (ejection fraction < 40% on echocardiography), symptomatic heart failure (NYHA class II–IV) and were receiving regular treatment with an ACE inhibitor, a loop diuretic with or without digoxin. The patients were followed every 3 months in a specialist heart failure clinic. They were randomized in a double blind manner to receive their drug treatment guided either by plasma N-BNP levels or by standardized clinical assessment alone. The treatment target in the former group was an N-BNP below 200 pmol/L (which discriminated between decompensated and compensated heart failure in an earlier study), while in the latter group the target was to achieve a clinical heart failure score according to Framingham criteria of less than 2. If these targets were not achieved, drug treatment was intensified according to a strict, predetermined, stepwise protocol consisting of the following: 1) increase ACE inhibitor dose to an enalapril equivalent of 20 mg twice daily; 2) increase loop diuretic to frusemide 500 mg twice daily; 3) addition of digoxin or increase the dose up to 0.25 mg per day; 4) additional diuretic (spironolactone 20–50 mg once daily) then metolazone 2.5–5 mg daily; 5) addition of a vasodilator (isosorbide mononitrate 60–120 mg daily then felodipine 2.5–5 mg once daily). For those patients not meeting treatment targets, clinical reassessments were carried out at 2 weekly intervals and treatment was intensified until targets were met at which stage 3 monthly reviews were resumed. The primary, prespecified end-point was total cardiovascular events (cardiovascular death plus hospital admission for any cardiovascular event plus any new outpatient episode of decompensated heart failure requiring increased medication).

There were no withdrawals from the trial that ended after a median follow-up of approximately 9.6 months, and data were available on all subjects to 6 months. Baseline matching for demographic and clinical features, left ventricular function and functional status was good. Medication doses were matched in the two groups at baseline, but increased significantly more for ACE inhibitors and frusemide in the N-BNP-guided group. Furthermore, more patients in the N-BNP group were receiving spironolactone at 6 months. There were only five subjects in the trial receiving beta blockers as the study was initiated before objective evidence of benefit from these agents was available.

The primary combined clinical end-point was significantly lower in the N-BNP group than in the clinical group (19 vs 54 events respectively, $P = 0.02$). The difference was even more significant when analysed as events per patient year, and remained significant after reanalysis to include hospitalization for decompensated heart failure only (17 vs 46 events, $P = 0.02$). Kaplan–Meier curves examining time to first event showed a clear divergence in favour of the hormone-guided group, already evident by 6 months and remained significant when reanalysed to include only heart failure events or death (Fig 2).

Plasma N-BNP concentrations fell by a mean of 79 pmol/L below baseline at 6 months in the N-BNP-guided group compared with 3 pmol/L in the clinical group. It is perhaps noteworthy that baseline N-BNP concentrations were higher in those who suffered clinical events than those who did not (289 vs 182 pmol/L), and 75% of clinical events occurred among those with a baseline N-BNP over 200 pmol/L.

This study confirms earlier findings that currently available drug treatments for heart failure reduce plasma levels of the cardiac natriuretic peptides (30–34, 36), in this case N-BNP. In that the study was performed before widespread use of beta blockers, additional information is needed where introduction and/or titration of beta blocker therapy is guided by cardiac natriuretic peptide levels. Nevertheless, the data suggest that drug treatment guided by N-BNP levels in plasma is associated with reduced cardiovascular events compared with usual clinical care. It should be noted that the ACE inhibitor dosage and the mortality rate in the clinically guided group were rather similar to observations in the CONSENSUS study (for ACE inhibitor dose) (9) and the SOLVD study (for mortality) (10). The data also fit with the concept that elevated levels of cardiac peptides define a population at heightened cardiovascular risk (40, 41). In these susceptible subjects higher doses and/or extra treatments that unload the left ventricle and

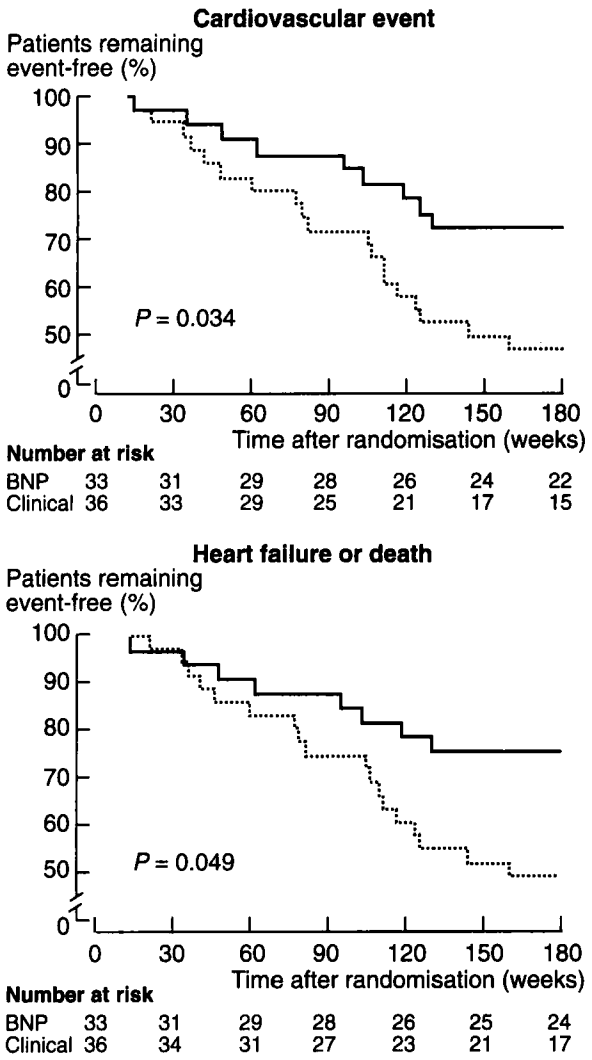

Figure 2. Kaplan–Meier event curves for time to first cardiovascular event (upper panel) and to heart failure event or death (lower panel) in 69 patients with chronic systolic heart failure. Drug treatment was guided either by clinical (Framingham) criteria (interrupted lines) or by plasma levels of N-BNP (the 1–76 N-terminal peptide of BNP, or N-BNP) (continuous line). (Reproduced from (39) with permission.)

reduce both left ventricular wall stress and myocardial oxygen requirements will probably lead to a slowing in the decline of myocardial function.

The above data are preliminary and require complementary information from much larger studies that make greater use of newer treatments shown to prolong life, particularly spironolactone and beta blockade. Furthermore, it remains unclear whether simply increasing medication doses as a routine beyond currently accepted regimens is just as protective and safe as selectively altering therapy in patients with elevated N-BNP levels.

Rapid BNP measurements and point-of-care testing for tailored treatment

The study of Troughton and co-workers described above relates to guiding drug therapy in patients with chronic, stable cardiac failure (39). Cheng and co-workers followed 72 patients admitted to hospital for decompensated heart failure (42). Plasma BNP levels were measured within 24 hours of admission and again within 24 hours of discharge or death. Patients were treated in standard fashion with diuretics and vasodilators. Those who died or were subsequently readmitted tended to have an increase in plasma BNP during their hospitalization, whereas those with successful treatment tended to have a decrease in BNP ($P < 0.05$). Indeed, there was a significant association between clinical end-points and rising vs falling BNP levels ($P < 0.001$). The authors considered that their results suggest that BNP-guided treatment might make 'tailored therapy' effective and might reduce the need for invasive haemodynamic monitoring in selected patients (42). In that Biosite Diagnostics Incorporated (San Diego, CA) has introduced a triage BNP test, capable of giving a plasma BNP result within 20 min, there is now the ability to measure BNP rapidly, not only as a diagnostic test (43) but also potentially as a guide to the intensity of pharmacotherapy for heart failure both in the acute and chronic situation.

The future

Although additional information is needed, it seems likely that BNP, or more likely N-BNP, will provide a useful, objective and ultimately cheap guide to drug treatment for patients with heart failure, both in the acute and the chronic setting. The pharmacological management of heart failure is already complex and will become more so in the near future with the likely introduction of agents that modify the action or clearance of, for example, endothelin-1, ANP and BNP and cytokines. The variable therapeutic requirements for individual patients are currently difficult to define based on 'soft' clinical criteria. The future augurs well for a more objective, scientific approach to the management of this increasingly common disorder.

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