Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations

Richard W Troughton, Christopher M Frampton, Timothy G Yandle, Eric A Espiner, M Gary Nicholls, A Mark Richards

Summary

Background There is currently no objective practical guide to intensity of drug treatment for individuals with heart failure. We hypothesised that pharmacotherapy guided by plasma concentrations of the cardiac peptide aminoterminal brain natriuretic peptide (N-BNP) would produce a superior outcome to empirical trial-based therapy dictated by clinical acumen.

Methods 69 patients with impaired systolic function (left-ventricular ejection fraction <40%) and symptomatic heart failure (New York Heart Association class II–IV) were randomised to receive treatment guided by either plasma N-BNP concentration (BNP group) or standardised clinical assessment (clinical group).

Findings During follow-up (minimum 6-months, median 9·5 months), there were fewer total cardiovascular events (death, hospital admission, or heart failure decompensation) in the BNP group than in the clinical group (19 *vs* 54, p=0·02). At 6 months, 27% of patients in the BNP group and 53% in the clinical group had experienced a first cardiovascular event (p=0·034). Changes in left-ventricular function, quality of life, renal function, and adverse events were similar in both groups.

Interpretation N-BNP-guided treatment of heart failure reduced total cardiovascular events, and delayed time to first event compared with intensive clinically guided treatment.

Lancet 2000; **355:** 1126–30
See Commentary page ???

Christchurch Cardioendocrine Research Group, Christchurch Hospital and Christchurch School of Medicine, Christchurch, New Zealand (R W Troughton MB, C M Frampton PhD, T G Yandle PhD, E A Espiner MD, M G Nicholls MD, A M Richards MD)

Correspondence to: Dr Richard Troughton, Department of Medicine, Christchurch Hospital, Riccarton Avenue, PO Box 4345, Christchurch, New Zealand
(e-mail: richard.troughton@chmeds.ac.nz)

Introduction

Treatment of systolic heart failure has advanced considerably in the past 20 years, due largely to a growing understanding of the pathophysiological role of neurohormonal factors.[1,2] Landmark trials established angiotensin-converting-enzyme (ACE) inhibitors as cornerstone therapy[3,4] and showed reductions in mortality and morbidity with spironolactone[5] and β-blockers.[6,7] In addition, an intensive multidisciplinary approach to follow-up reduces hospital readmission.[8,9]

Even with intensive treatment, mortality and morbidity are high.[3–6] Questions remain as to how proven therapies, such as ACE inhibitors, should be implemented and what doses are best.[10–13] Furthermore, it is not clear whether diuretic doses should be as low as possible to limit hypotension and renal impairment or as high as tolerable to reduce cardiac loading.

Current treatment strategies ignore plasma neurohormone concentrations, yet they are independent markers of cardiac status and prognosis in cardiac disease including heart failure.[14–16] To date, brain natriuretic peptide (BNP), and particularly its aminoterminal portion (N-BNP), appears to be the most powerful neurohormonal predictor of left-ventricular function and prognosis.[17–20] BNP and N-BNP are secreted primarily from the left ventricle in response to changes in left-ventricular wall stretch.[21] Concentrations of BNP and N-BNP are related to left-ventricular filling pressures[22] and wall stress.[23] BNP concentrations accurately discriminate between decompensated heart failure and other causes of breathlessness that lead to hospital admission.[24] BNP concentrations fall after treatment with loop diuretic and ACE inhibitors, reflecting a reduction in left-ventricular filling pressure.[22] Pilot data have shown that vasodilator treatment can be titrated to reduce BNP concentrations towards the normal range.[25]

We hypothesised that titration of treatment to reduce plasma N-BNP concentrations in patients with systolic heart failure would prove superior to treatment with empirical trial-based therapy dictated by clinical acumen.

Methods

Patients

Patients aged 35–85 were recruited after hospital admission with decompensated heart failure or from a specialist cardiology outpatient clinic. All had impaired left-ventricular systolic function (left-ventricular ejection fraction <40% on 2-dimensional echocardiography), established symptomatic heart failure (New York Heart Association [NYHA] class II–IV), and were treated with ACE inhibitors, loop diuretic with or without digoxin.

Patients were excluded by recent acute coronary syndrome (within 3 months), pending cardiac transplant or revascularisation, severe stenotic valvular heart disease, or by severe pulmonary (forced expiratory volume in 1 s <1 L) hepatic or renal (plasma creatinine >0·2 mmol/L) disease. The study was approved by the Canterbury ethics committee.

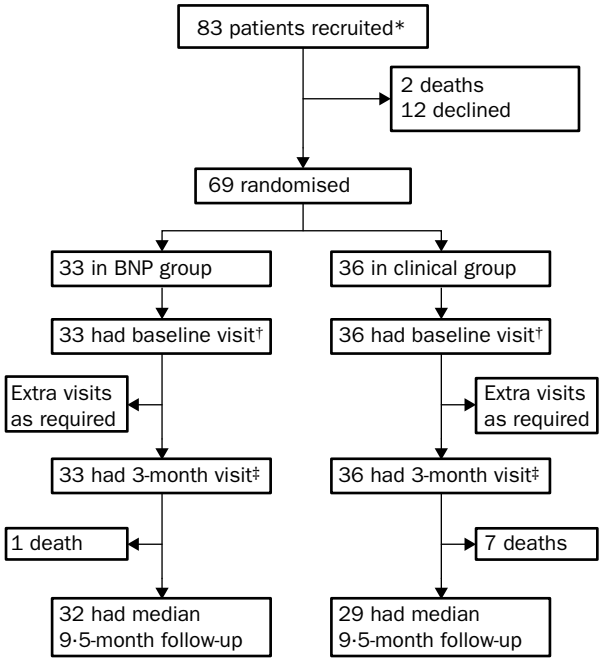

Figure 1: **Trial profile**

*Recruited after heart-failure admission or from cardiology clinic. †2-dimensional echocardiogram, Quality-of-life (QOL) questionnaire, 6-min walk, cycle ergometry, clinical assessment, blood for neurohormones. ‡Clinical assessment, neurohormones, QOL questionnaire, 6-min walk.

Study design

All patients received intensive follow-up every 3-months in a specialist heart-failure clinic (figure 1). Visits were between 0830–1200 h. After initial assessment and stabilisation, patients were randomised in a double-blind manner to treatment guided by either plasma N-BNP level (BNP group) or standardised clinical assessment alone (clinical group).

At every visit patients were assessed clinically by an investigator unaware of treatment allocation with an objective scoring system (heart-failure score) based on Framingham criteria for diagnosing decompensated heart failure.[26] Major and minor criteria were assigned values of 1 and 0·5 respectively to produce an objective score, with a total score of 2 or more taken to indicate decompensated heart failure (table 1). A venous blood sample was taken for plasma biochemistry and N-BNP. Patients completed the Minnesota Living With Heart Failure quality-of-life questionnaire, did a 6 min walk test, and cycle ergometry (baseline only) to assess myocardial oxygen consumption. Echocardiography was done at baseline and 3 months.

The treatment target in the clinical group was clinically compensated heart failure according to an objective score (heart-failure score <2), and in the BNP group, N-BNP below 200 pmol/L (which corresponds to the concentration of BNP-32 that discriminated decompensated from compensated heart failure in an earlier study[24]). If these targets were not achieved, drug treatment was intensified according to a strict and predetermined stepwise protocol comprising: maximisation of ACE inhibitors (up to enalapril equivalent of 20 mg twice a day); increase in loop diuretic to furosemide 500 mg twice a day; addition of digoxin up to 0·25 mg/day; additional diuretic (spironolactone 25–50 mg once a day, then metolazone 2·5–5 mg once a day); then additional vasodilator (isosorbide mononitrate 60–120 mg once a day then felodipine 2·5–5 mg once a day). Patients in either group not meeting treatment targets were reassessed at 2-week intervals (by an investigator unaware of allocation) and treatment intensified (by the investigator who did know the allocation) until targets were met, at which point 3-month reviews were resumed.

Endpoints

The primary prespecified clinical endpoint was total cardiovascular events (cardiovascular death plus hospital admission for any cardiovascular event—heart failure, acute coronary syndrome, cerebrovascular accident/transient ischaemic attack, peripheral vascular event, arrhythmia, syncope—plus any new outpatient episode of decompensated heart failure requiring an increase in medication). Secondary endpoints were plasma N-BNP concentration, left-ventricular function, functional capacity, and quality of life.

Statistical analysis

A power analysis done before recruitment showed we needed 37 patients per group to show a 50% reduction in the predicted total cardiovascular event rate within a year (α=0·05, β=0·2). We predicted a total cardiovascular event rate of up to 70% a year based on annual mortality rates of up to 50% in the treatment arm of landmark heart-failure studies,[3–6] annual readmission rates of 40% in the local population,[27] and additional events due to outpatient decompensated heart failure. Patient demographics, baseline variables, and follow-up duration were compared between the two groups by independent *t* tests, χ^2 and Mann-Whitney *U* tests as appropriate (SPSS for Windows, release 8.0.0, SPSS Inc, Chicago, USA). The primary clinical endpoint of total cardiovascular events was compared by the Mann-Whitney *U* test, as were cardiovascular hospital admission and new outpatient heart-failure events. Cardiovascular death was compared by Fisher's exact test. Kaplan-Meier curves were constructed to examine time to first event and compared using the log-rank test. A Poisson regression analysis (Statistix for Windows version 1.0, Analytic Software, Tallahassee, Florida, USA, 1996) was used to compare total cardiovascular event rates between groups with adjustment for differences in baseline variables. The significance of the difference between groups was assessed by the change in deviance associated with the addition of the group variable into a model already containing all relevant baseline covariates. Changes in N-BNP concentrations, clinical variables, left-ventricular function, ACE inhibitor, and furosemide doses, renal function, and functional status were analysed by ANOVA for repeated measures (SPSS). p less than 0·05 was taken to be significant.

Results

Baseline variables

Between Feb 1, 1998, and Jan 31, 1999, 69 patients were recruited of whom 33 were randomised to the BNP group and 36 to the clinical group. There were no withdrawals from the trial, which ended on July 31, 1999, with median follow-up of 9·7 months in the BNP group and 9·5 months in the clinical group (p=0·78) and complete 6 month follow-up on all patients. The groups were matched for demographic and clinical features, left-ventricular function, and functional status (table 2).

N-BNP concentrations

In the BNP group, mean N-BNP concentrations fell 79 pmol/L below baseline by 6 months, compared with 3 pmol/L in the clinical group (p=0·16). Baseline N-BNP concentrations were higher among patients who suffered clinical events than those who did not (289 [SD 39] *vs*

Symptom	Value
Orthopnoea	0·5
Paroxysmal nocturnal dyspnoea	1·0
Reduction in exercise tolerance	0·5
Resting sinus tachycardia (>100/min)	0·5
Jugular venous pressure >4 cm	0·5
Hepatojugular reflex positive	1·0
Third heart sound present	1·0
Basal crackles	1·0
Hepatomegaly	0·5
Peripheral oedema	0·5

Decompensated heart failure indicated by total score ≥2.

Table 1: **Standardised heart-failure scoring system**

	BNP	Clinical
Age (years)	68	72
Male	78%	75%
Ischaemic heart disease	73%	75%
Past myocardial infarction	27%	33%
CABG	24%	19%
Hypertension	64%	67%
Heart-failure admission*	30%	28%
Diabetes	12%	14%
Left-ventricular ejection fraction	28%	26%
NYHA class, mean for group (% in Class II)	2·3 (72%)	2·3 (67%)
MVO_2 (mL/kg per min)	13·9	13·7
Heart-failure score†	1·2	1·1
N-BNP (pmol/L)	217	251

*Heart-failure admission before index admission at time of recruitment. †Standardised heart-failure score. CABG=coronary artery bypass grafting. MVO_2=myocardial oxygen consumption.

Table 2: **Baseline variables for patients in the BNP and clinical groups**

182 [17] pmol/L, p=0·02). 75% of clinical events occurred among patients with a baseline N-BNP of greater than 200 pmol/L.

Clinical events

The primary combined clinical endpoint (cardiovascular death, hospital admission, and outpatient heart failure) was significantly lower in the BNP group than the clinical group (19 *vs* 54 events respectively, p=0·02, table 3). This difference was more significant when analysed as events per patient-year (0·7 *vs* 2, p=0·01) and remained significant when data were reanalysed to include hospitalisation for decompensated heart failure only (17 *vs* 46 events, p=0·02). When the primary endpoint was analysed by Poisson regression with baseline left-ventricular ejection fraction, N-BNP concentration, age, NYHA class, furosemide dose, ACE inhibitor dose, heart rate, and systolic blood pressure as covariates the difference between groups was more significant (χ^2=14·2, p<0·001). One patient died suddenly in the BNP group and seven (six sudden, one progressive heart failure) in the clinical group (p=0·06). There were seven admissions among seven patients in the BNP group compared with 21 admissions in 11 patients in the clinical group (p=0·38). Eleven episodes of decompensated heart failure needing intensification of treatment and extra review occurred among seven patients in the BNP group compared with 26 events in 16 patients in the clinical group (p=0·03).

Kaplan-Meier curves examining time to first event of the primary clinical endpoint showed a clear divergence between the groups by 6 months (p=0·034, figure 2) and remained significant when reanalysed to include only heart-failure events or death (p=0·049).

Clinical status by standardised score improved in both groups. The mean score for heart failure fell from baseline (table 2) by 0·5 for the BNP group and 0·2 for the clinical group at 6-months (p=0·25).

Secondary endpoints, renal, and haemodynamic effects

Left-ventricular ejection fraction increased over 3 months by 8·3 [SD 2·2]% in the BNP group and 5·3 [1·8]% in the clinical group (p=0·23). In both groups, 6 min walk test improved by a similar amount while quality-of-life scores remained stable.

Whereas mean supine blood pressures at baseline were similar (129/76 mm Hg in the BNP group and 124/75 mm Hg in the clinical group), levels had fallen at 6

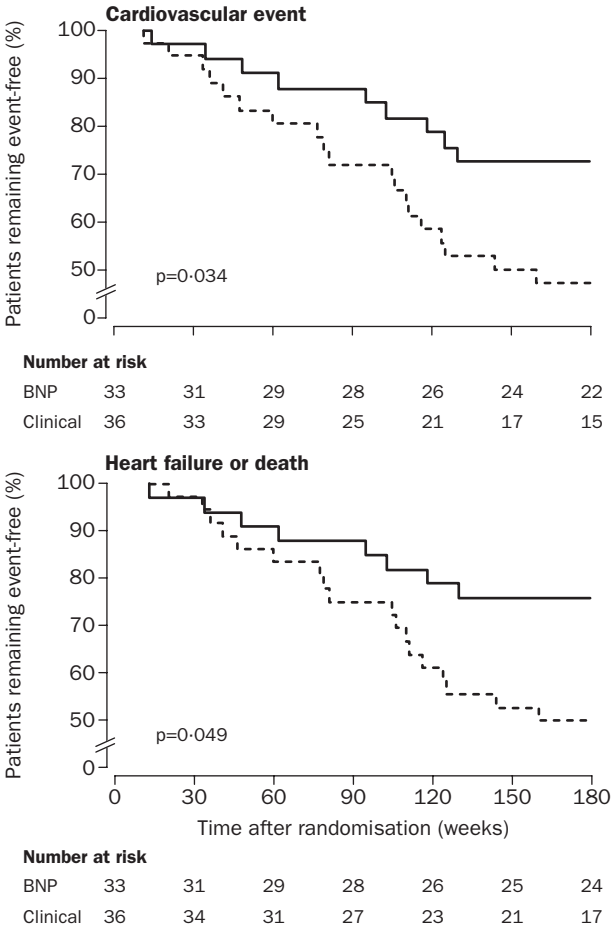

Figure 2: **Kaplan-Meier event curves for time to first cardiovascular event and to heart-failure event or death**

months in the BNP group (systolic −1·1 mm Hg, diastolic −1·5 mm Hg), but rose in the clinical group (systolic 8, diastolic 1·8 mm Hg, p=0·015).

Endogenous creatinine clearance at baseline was 0·9 [SD 0·07] mL/s in the clinical group and 1·0 [0·07] mL/s in the BNP group and fell by 0·05 and 0·13 mL/s, respectively, at 6 months (p=0·32).

Medications, extra visits, and adverse events

ACE-inhibitor doses were matched at baseline (15·3 [SD 7·9] mg enalapril-equivalent for BNP group *vs* 13·1 [6·7] mg for clinical group, p=0·32) but increased by 4·8 [5·9] mg in the BNP group versus 1·2 [6·9] mg in the clinical group at 6 months (p=0·027). Furosemide doses were not significantly different at baseline (p=0·27) and increased (baseline to 6 months) from a mean of 123[145] mg to 197 [237] mg in the BNP group versus 87 [119] mg to 141 [263] mg in the clinical group (p=0·34). Addition of baseline furosemide dose to the Poisson regression model leads to a significant reduction in deviance (χ^2=4·44, p=0·035) with those on higher baseline doses more likely to incur a cardiovascular event. More patients in the BNP group were receiving spironolactone at 6 months (6 *vs* 1, p=0·049). There was no difference in β-blocker use at baseline or 6 months (four and four patients in BNP group *vs* one and two patients in clinical-group, respectively). Felodipine (the final step in the treatment protocol) was not prescribed for any patient.

Additional visits to intensify treatment were needed in 18 patients in the BNP group and 14 patients in the

	BNP	Clinical	p
Deaths	1	7	0·06
Admission events			
Cardiovascular	7	21	0·38
Heart failure	5	13	0·52
All (including non-cardiovascular admissions)	17	25	0·83
Outpatient heart failure events	11	26	0·03
Total events			
Cardiovascular*	19	54	0·02
Heart failure†	17	46	0·02

*Death+cardiovascular admission+outpatient heart failure event. †Death+heart failure admissions+outpatient heart failure event.

Table 3: **Total cardiovascular events for patients in the BNP and clinical groups during median 9·5 months follow-up**

clinical group (p=0·34). The average number of extra visits per patient was 1·7 in the BNP group and 0·8 in the clinical group (p=0·19). Addition of total visits into the Poisson regression model showed a positive relationship with the rates of the primary endpoint (p<0·046) and the difference between groups remained significant (p<0·001).

13 patients in the BNP group experienced adverse events compared with nine in the clinical group (p=0·32). There was no difference in the rate of cough or symptomatic hypotension between groups (21% and 18% in the BNP group *vs* 11% and 8% in the clinical group, p=0·73 and 0·34 respectively). Spironolactone was withdrawn from one patient in the BNP group because of rash.

Discussion

Drug treatment of established heart failure is increasingly complex yet objective practical guidelines for management of individual patients are lacking. We surmised that pharmacotherapy guided by plasma N-BNP concentrations would prove more effective than usual clinical practice. First, our study shows that circulating N-BNP concentrations can be reduced by intensification of drug therapy in heart failure. Mean plasma N-BNP concentrations for patients for the BNP group declined to well within the target range but, by contrast, in the clinical group remained stable and above the target range of the BNP group.

Second, and more importantly, drug treatment guided by plasma N-BNP concentrations reduced the total number of cardiovascular events compared with clinically guided treatment by the same range of therapies. Cardiovascular death, admission, and new episodes of decompensated heart failure were all lower in the BNP group. These reductions were achieved with increased dosage of ACE-inhibitor and loop diuretic, and spironolactone use. Of note, ACE-inhibitor dosage and the mortality rate in the clinically guided group were similar to achieved ACE-inhibitor doses in the CONSENSUS and SOLVD studies and mortality rates in the latter.[3,4] Heart-failure readmission rates in the clinical group correspond to those seen in local demographical studies.[27] Felodipine was considered a safe vasodilator[28] and was included as the final step in the treatment protocol, but was not prescribed for any patient.

There are several possible reasons for an advantage of N-BNP-guided treatment over the standard clinical approach. Most likely, it represents a preventive strategy targeting more intensive pharmacotherapy and follow-up for patients with raised circulating N-BNP concentrations who are at high risk of cardiovascular events.[20] Although more frequent review of patients in the BNP group is a potential confounder, our regression analysis indicated that patients seen more often were more likely to suffer an event. This suggests that the benefit of BNP-guided treatment was due to more than just extra review and supports our hypothesis that treatment to lower N-BNP is beneficial.

N-BNP concentrations reflect severity of left-ventricular haemodynamic dysfunction.[21–23] Logically, treatment that reduces N-BNP concentrations should unload the left ventricle and reduce both left-ventricular wall stress and myocardial oxygen requirements, thereby possibly translating into a slowing in the decline of myocardial function. This effect may underlie the trend to reduced cardiac mortality seen in the BNP group in this study.[29] We cannot rule out other important neurohumoral interactions that may have contributed to the overall effect.

Potential weaknesses of this study include the small study size and minor variations between groups in baseline variables such as mean N-BNP concentration and furosemide doses. However, regression analysis showed that the difference in event rates between groups was independent of differences in these baseline variables. Another potential weakness is the low rate of β-blocker and spironolactone use, reflecting the uncertain status of these agents when the study commenced. The effects of β-blocker therapy on N-BNP are unknown, hence the usefulness of this objective index as a guide to β-blocker administration and dose titration is unclear.

These results set the scene for larger studies of hormone-guided treatment that could include more recently established therapies and possibly other agents such as vasopeptidase inhibitors and angiotensin-receptor blockers.

Contributors

M G Nicholls, A M Richards, E A Espiner, and R W Troughton were responsible for raising the concept for the study, its design and conduct, and for writing the paper. T G Yandle was responsible for the neurohormonal assays. C M Frampton was responsible for statistical analyses.

Acknowledgments

We thank Liz Campbell, the endocrine special test and Endolab staff, cardiology outpatient staff, and Barbara Griffin.

This trial was supported by grants from Health Research Council of New Zealand and Lottery Health. Prof A M Richards holds the National Health Foundation (NHF) of New Zealand chair of cardiovascular studies. R W Troughton is an NHF research fellow.

References

1 Remme WJ. Therapeutic strategies and neurohormonal control in heart failure. *Eur Heart J* 1994; **15** (suppl D): 129–38.

2 Cleland JG, Swedberg K, Poole-Wilson PA. Successes and failures of current treatment of heart failure. *Lancet* 1998; **352:** SI19–28.

3 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316:** 1429–35.

4 SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325:** 293–302.

5 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341:** 709–17.

6 CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999; **353:** 9–13.

7 MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–07.

8 Kornowski R, Zeeli D, Averbuch M, et al. Intensive home-care surveillance prevents hospitalization and improves morbidity rates

among elderly patients with severe congestive heart failure. *Am Heart J* 1995; **129:** 762–66.

9 Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995; **333:** 1190–95.

10 Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. *Am J Cardiol* 1989; **63:** 461–64.

11 Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. *Circulation* 1997; **96:** 1165–72.

12 Reis SE, Holubkov R, Edmundowicz D, et al. Treatment of patients admitted to the hospital with congestive heart failure: specialty-related disparities in practice patterns and outcomes. *J Am Coll Cardiol* 1997; **30:** 733–38.

13 van Veldhuisen DJ, Charlesworth A, Crijns HJ, Lie KI, Hampton JR. Differences in drug treatment of chronic heart failure between European countries. *Eur Heart J* 1999; **20:** 666–72.

14 Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; **311:** 819–23.

15 Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; **87:** VI 40–48.

16 Schrier RW, Abraham WT. Mechanisms of disease: hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341:** 577–85.

17 Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994; **90:** 195–203.

18 Hunt PJ, Espiner EA, Nicholls MG, Richards AM, Yandle TG. The role of the circulation in processing pro-brain natriuretic peptide (proBNP) to amino-terminal BNP and BNP-32. *Peptides* 1997; **18:** 1475–81.

19 Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation* 1998; **97:** 1921–29.

20 Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. *Heart* 1999; **81:** 114–20.

21 Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. *Endocrinology* 1993; **132:** 1961–70.

22 Richards AM, Crozier IG, Yandle TG, Espiner EA, Ikram H, Nicholls MG. Brain natriuretic factor: regional plasma concentrations and correlations with haemodynamic state in cardiac disease. *Br Heart J* 1993; **69:** 414–17.

23 Magga J, Vuolteenaho O, Tokola H, Marttila M, Ruskoaho H. B-type natriuretic peptide: a myocyte-specific marker for characterizing load-induced alterations in cardiac gene expression. *Ann Med* 1998; **30** (suppl 1): 39–45.

24 Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994; **343:** 440–44.

25 Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. *Am Heart J* 1999; **138:** 1126–32.

26 Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; **22:** 6A–13A.

27 Doughty R, Yee T, Sharpe N, MacMahon S. Hospital admissions and deaths due to congestive heart failure in New Zealand, 1988–91. *N Z Med J* 1995; **108:** 473–75.

28 Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III—Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation* 1997; **96:** 856–63.

29 Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1999; **33:** 598–604.