Age and Ageing 2002; **31:** 295–301

B-type natriuretic peptide in the diagnosis of cardiac disease in elderly day hospital patients

STUART D. HUTCHEON, NEIL D. GILLESPIE, ALLAN D. STRUTHERS[1], MARION E. T. MCMURDO

Section of Ageing & Health, Departments of Medicine and [1]Clinical Pharmacology, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK

Address correspondence to: N. D. Gillespie. Fax: (+44) 1382 660675. Email: n.d.gillespie@dundee.ac.uk

Abstract

Objectives: heart failure is primarily a disease of elderly people. Current guidelines suggest all patients with suspected heart failure should undergo objective assessment, usually by echocardiography. In the UK resources are limited and not all patients have access to echocardiography. The electrocardiogram is widely used as a pre-screening investigation. Recently the natriuretic peptides have been shown to correlate well with left ventricular function, and evidence is accumulating which suggests that B-type natriuretic peptide may have a role in detecting cardiovascular disease. Elderly patients attending day hospital often have non-specific cardiovascular symptoms. B-type natriuretic peptide measurement in parallel with conventional electrocardiogram, may offer a novel method of identifying those with significant cardiac disease, which may warrant treatment. This study assessed the role of B-type natriuretic peptide and electrocardiogram in the detection of cardiac disease in patients attending Day Hospital.
Design: prospective cohort study of patients referred to Day Hospital with suspected cardiovascular disease.
Methods: this study prospectively evaluated 299 consecutive patients attending day hospital over a period of 13 months. Patients underwent clinical assessment, electrocardiography, echocardiography and natriuretic peptide measurement. Objective evidence of cardiac disease was based on electrocardiogram and echocardiographic findings.
Setting: Medicine for the Elderly Day Hospital, Royal Victoria Hospital, Dundee.
Main outcome measures: sensitivity, specificity, positive and negative predictive values of screening tests for left ventricular systolic dysfunction. Receiver-Operating-Characteristic curves for ability of B-type natriuretic peptide to detect cardiac disease (including left ventricular systolic dysfunction, valvular disease, atrial fibrillation and left ventricular hypertrophy). Mean B-type natriuretic peptide levels with 'incremental' levels of cardiovascular disease.
Results: 299 patients (mean age 79; 65% female) completed the assessment. Ten percent of patients had left ventricular systolic dysfunction but 50% had objective evidence of cardiac disease. B-type natriuretic peptide was significantly elevated in patients with left ventricular systolic dysfunction, atrial fibrillation, left ventricular hypertrophy and valvular disease. Both B-type natriuretic peptide and the electrocardiogram were sensitive in detecting left ventricular systolic dysfunction but lacked specificity. Combining B-type natriuretic peptide with the electrocardiogram improved detection of left ventricular systolic dysfunction. B-type natriuretic peptide levels increased progressively as the number of different cardiac abnormalities increased.
Conclusions: B-type natriuretic peptide may be a useful marker for cardiac disease in patients attending Day Hospital. Half of the patients assessed had cardiac disease detected. Both the electrocardiogram and B-type natriuretic peptide were sensitive in the detection of left ventricular systolic dysfunction but lacked specificity. B-type natriuretic peptide was superior to the electrocardiogram in the detection of valvular disease. If used to pre-screen cardiovascular disease in Day Hospital patients, B-type natriuretic peptide and the electrocardiogram could reduce the need for echocardiography in some patients before implementing evidence-based treatments. B-type natriuretic peptide increases progressively as the number of different cardiac abnormalities increases and this may explain why B-type natriuretic peptide is of such prognostic value in older patients.

Keywords: *cardiovascular disease, natriuretic peptides, electrocardiography, day hospital*

Introduction

Heart failure is an important and increasing problem [1–3]. Proven treatments have been well described for heart failure due to left ventricular systolic dysfunction (LVSD) in both symptomatic and asymptomatic patients [4–9]. Most new cases of heart failure present in elderly people [10] and the rising incidence and prevalence with advancing age is acknowledged [11].

Accurate clinical diagnosis of heart failure is notoriously difficult [12–14]. Many people attending Day Hospital are likely to have structural cardiac disease, the diagnosis of which is hindered by multiple pathology and atypical presentation of disease. Echocardiography remains the standard investigation for the diagnosis of left ventricular systolic dysfunction although availability is resource-limited [15]. Identifying patients with significant cardiovascular disease is often possible from a history of previous myocardial infarction or an abnormal electrocardiogram. Recent evidence also suggests that the natriuretic peptides may be useful in detecting cardiac disease including left ventricular systolic dysfunction [16–20]. Levels of natriuretic peptides rise in response to ventricular wall stress and have been shown to be elevated in patients with left ventricular systolic dysfunction. Elevated levels of natriuretic peptides have also been found to be elevated in apparently healthy elderly people [21] as well as in patients with hypertension [22]. There are a number of natriuretic peptides and it appears that B-type natriuretic peptide (BNP) is more accurate than other natriuretic peptides in the detection of LVSD [23]. It is stable in whole blood and simple affordable radioimmunoassays are available for testing [24] making it possible for use in the Day Hospital setting.

As a result, we tested the possibility that BNP might be a good composite test reflecting a whole range of cardiac diseases (including valvular heart disease, atrial fibrillation and left ventricular hypertrophy rather than just LVSD) at the Day Hospital, as it provides strong prognostic information [25].

Methods

The study prospectively evaluated all patients attending Day Hospital at the Royal Victoria Hospital in Dundee, over a period of 13 months from October 1998 to November 1999. A total of 440 patients were referred. Of these 55 failed to attend, 26 attended for repeated visits and 31 attended for one visit only or were admitted to hospital on their first attendance. Of the remaining 328, significant cognitive impairment was present in 24 who were unable to give informed consent, and thus excluded from study. All patients provided written informed consent and the study was approved by the Tayside Committee on Medical Research Ethics.

Clinical assessment was performed by a single experienced staff grade clinician. Symptoms, past medical history, medication and clinical signs including pulse, blood pressure, jugular venous pressure, basal crepitations, ankle oedema and murmurs were recorded. Each patient was categorised as either having definite evidence of heart failure or not. All patients had routine haematology and biochemistry including thyroid function and a standard 12-lead electrocardiogram (ECG). ECGs were analysed by two observers and coded according to Minnesota criteria [26, 27]. ECGs were coded abnormal if they showed: pathological Q-waves; bundle branch block pattern; interventricular conduction defect; ST/T segment abnormality; voltage criteria for LVH; atrial fibrillation/flutter. A detailed echocardiographic examination was performed in the Day Hospital by a single experienced sonographer using either a Toshiba Corevision system (SSA, UK) or Sim 7000 Challenge system (Esaote, Europe). Standard apical and parasternal views were obtained with patients supine in the left lateral position. M-mode recordings were made at the tips of the mitral leaflets from which end-diastolic and end-systolic diameters were derived to calculate fractional shortening if possible. Where M-mode measurements were suboptimal a regional wall motion score was calculated. Along with this a quantitative assessment was performed and overall left ventricular systolic function was graded as normal, mild, moderate or severely impaired. Full two dimensional and spectral Doppler studies were performed on each patient to define any coincidental valve disease. All images were stored on videotape. In cases where views were suboptimal or there was diagnostic doubt patients were referred for a second assessment performed by another experienced echocardiographer or for radionuclide ventriculography.

Following echocardiography patients were rested supine for a further 10 minutes. A 10 ml sample of venous blood was drawn into a tube containing edetic acid and aprotonin to prevent natriuretic hormone breakdown. Each sample was centrifuged for 15 minutes and plasma stored at –20°C initially then transferred to a –70°C freezer for long-term storage. Samples were measured in a single batch by an experienced technician who was unaware of clinical and echocardiographic findings. BNP was measured by a standard commercially available radioimmunoassay kit (Peninsula, UK) which has been used locally for several years [17, 20].

Results

Patient characteristics are shown in Table 1. Enquiring about a history of myocardial infarction (MI) was unrewarding as most patients were unsure whether a MI had been diagnosed. Two hundred and ninety-nine participants had an analysable echocardiogram, electrocardiogram and BNP measured. Thirty-one

Table 1. Characteristics of the 299 patients attending Day Hospital

Age years median (range)	79 (61–98)
Sex M : F	105 : 194
Reason for referral	
Reduced mobility	137 (46%)
Dizzy spells/collapse	36 (12%)
Breathlessness	30 (10%)
Stroke rehabilitation	21 (7%)
Pain control assessment	22 (7%)
Ward follow-up	19 (6%)
Others	34 (11%)
NYHA class	
Class I	134 (45%)
Class II	93 (31%)
Class III	65 (22%)
Class IV	7 (2%)
Smoking history	
Never smoked	141 (47%)
Ex-smoker	112 (38%)
Current smoker	46 (15%)
Past medical history	
History of CHF	48 (16%)
Atrial fibrillation	46 (15%)
Ischaemic heart disease	96 (32%)
Hypertension	123 (41%)
Diabetes	51 (17%)
Peripheral vascular disease	21 (7%)
Cerebro-vascular accident	87 (29%)
Obstructive airways disease	55 (18)
Signs of CHF	18 (6%)
Abnormal ECG	165 (55%)
Prescribed ACE inhibitor	32 (11%)
Prescribed diuretic	123 (41%)
Frusemide	33 (11%)
Bendrofluazide	154 (52%)

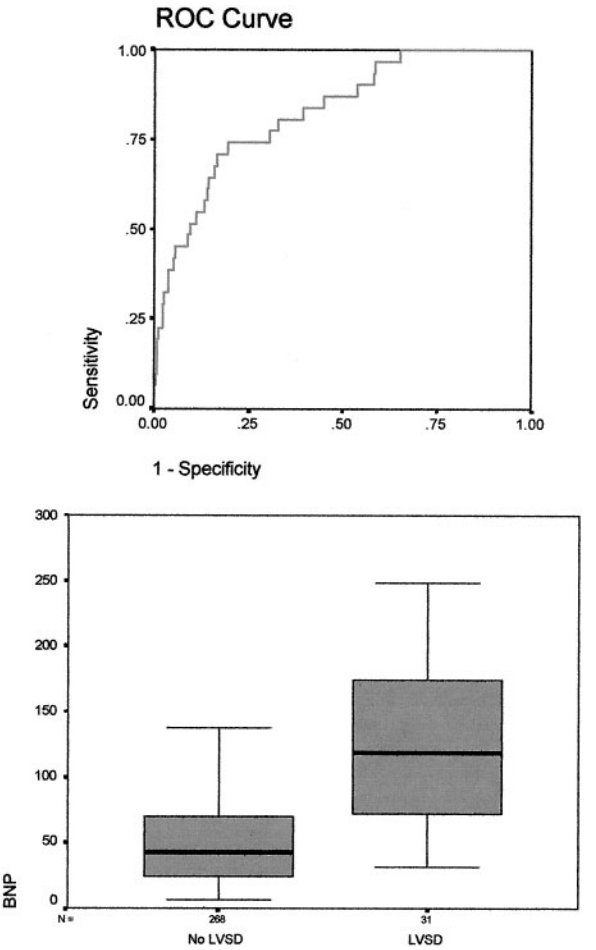

Figure 1. Receiver-operating-characteristic curve for ability of BNP to detect LVSD in study population (left). BNP concentration in-patients with and without LVSD, boxes are mean and IRQ's, vertical lines are ranges of concentrations (right).

patients (10.4%) had objective evidence of LVSD on echocardiography.

Ninety-two patients, (31%) had undergone echocardiography in the 4 years prior to assessment. Of the 48 patients with a previous diagnosis of Congestive Heart Failure (CHF) due to LVSD, 29 (60%) had undergone echocardiography. Of the 31 patients with confirmed LVSD 17 (55%) had previously undergone echocardiography.

One hundred and sixty-five (55%) of patients had an abnormal ECG. Twelve percent were in atrial fibrillation/flutter; 18% had voltage criteria for LVH; 16% had either pathological Q-waves or bundle branch block; 14% had poor r wave progression or inter-ventricular conduction defect; 16% had ST/T segment changes or ischaemic changes.

The mean concentration of BNP was significantly higher in patients with LVSD than in those with normal left-ventricular function ($P < 0.001$). Boxplots comparing BNP measurement in patients with LVSD and normal LV systolic function and receiver-operator-characteristic curves for BNP are shown in Figure 1.

One hundred and fifty-five patients (52%) had objective evidence of cardiac disease defined as: LVSD or valvular disease on echocardiography; atrial flutter or fibrillation; evidence of previous myocardial infarction (pathological Q-waves or bundle branch block) on electrocardiography; evidence of left ventricular hypertrophy on echocardiography or by ECG voltage criteria. BNP was significantly elevated in this group of patients compared to those with no objective evidence of cardiac disease ($P < 0.001$). Boxplots and receiver operator curves are shown in Figure 2.

Patients with atrial fibrillation, valvular disease and left ventricular hypertrophy had significantly elevated BNP compared to those with no cardiovascular disease. The median BNPs with inter-quartile ranges in specific groups of patients with cardiac diseases are shown in Table 2. Patients with cardiovascular disease showed a progressive rise in median BNP and IRQs with increasing number of cardiac diseases irrespective

of the combination of diseases. Figure 3 shows boxplots of BNP in patients with no objective evidence of cardiac disease; one, two, three and four cardiac diseases.

A normal electrocardiogram virtually excluded LVSD (sensitivity 97%) with 50% specificity. Definite evidence of previous MI on ECG was specific (88%) but not sensitive (48%). Table 3 gives the sensitivity, specificity and positive and negative predictive values for the detection of LVSD using ECG, BNP >35 and 49 pmol/l, history of ischaemic heart disease and combination of BNP and ECG.

Combining ECG and BNP improved specificity. Using a normal ECG as an initial pre screening tool, 134 of the 299 patients could be excluded and in those with an abnormal ECG and BNP <35 a further 37 were excluded with 2 missed cases of LVSD. Using BNP as the initial screening tool, 104 patients were excluded with one missed case of LVSD. In those with a BNP >35 pmol/l, a normal ECG excluded a further

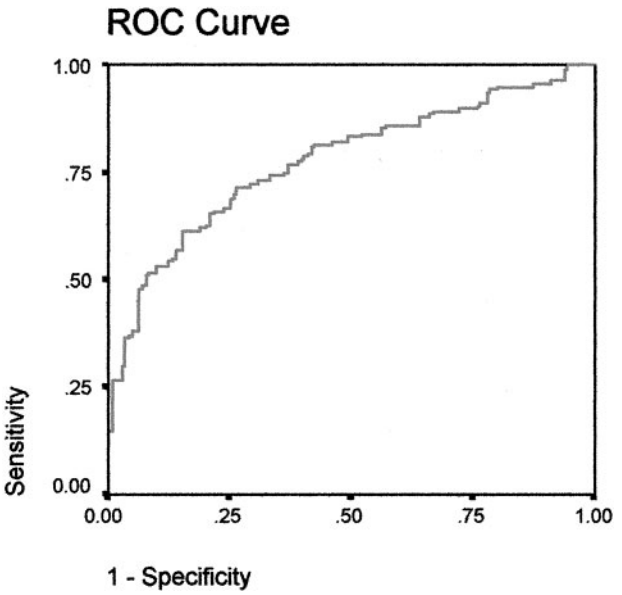

Figure 2. Receiver-operating-characteristic curve for ability of BNP to detect cardiac disease in study population (left). BNP concentration in patients with and without cardiac disease, boxes are mean and IRQ's, vertical lines are ranges of concentrations (Figure 3).

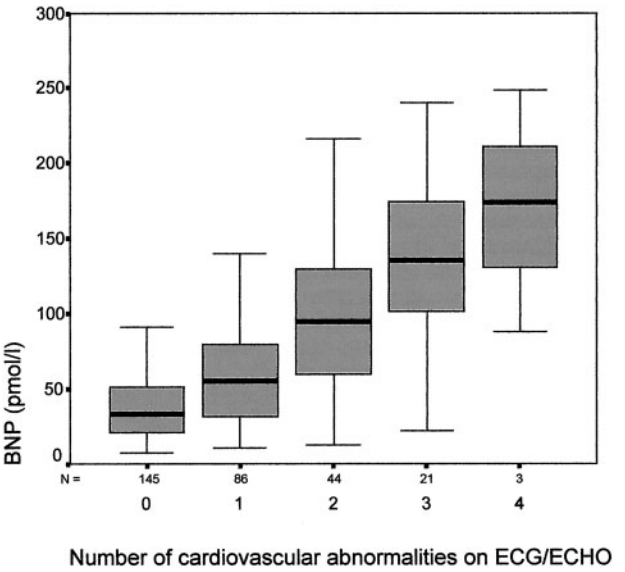

Figure 3. BNP boxplots for patients with no cardiovascular disease up to 4 cardiovascular diseases. Number of cardiovascular disease made up of any combination of the following: LVSD; atrial fibrillation on ECG; previous myocardial infarction on ECG; LVH on echo or ECG and significant valvular disease on echocardiogram.

Table 2. Mean, median and IRQ's BNP measurements in selected groups of patients

		BNP (pmol/l)	
	n	Mean	Median (IRQ)
All patients	299	87	49 (27–80)
No cardiovascular disease[a]	144	38	33 (21–52)
Cardiovascular disease[a]	155	132	71 (40–123)[b]
Left ventricular systolic dysfunction	31	294	118 (64–174)[b]
Atrial fibrillation alone	8	89	72 (56–121)[b]
Valve disease alone	19	60	65 (34–80)[c]
Atrial fibrillation and valve disease alone	6	85	68 (53–122)[b]
LVH on ECG or Echo alone	40	125	57 (38–82)[b]
Atrial fibrillation	37	102	94 (62–137)[c]
Valve disease	60	105	90 (63–134)[b]
Atrial fibrillation and valve disease	20	119	111 (74–163)[b]

[a]Cardiovascular disease = Objective evidence i.e. LVSD on echocardiography, atrial fibrillation on ECG, LVH on echo or ECG, ischaemia/MI on ECG and valve disease on echocardiography.
[b]$P<0.001$ (compared to those with non cardiac disease).
[c]$P=0.002$ (compared to those with non cardiac disease).

Table 3. Sensitivity, specificity, positive and negative predictive values of screening tests for left ventricular systolic dysfunction

Screening criteria	Sensitivity	Specificity	Positive predictive value	Negative predictive value
History of IHD	48	70	.16	.92
BBB or q-waves on ECG[a]	48	88	.32	.94
Abnormal ECG	97	50	.18	.99
History of IHD and abnormal ECG	48	83	.25	.93
BNP 35 (pmol/l)	97	38	.15	.99
49 (pmol/l)	87	54	.18	.97
BNP >35 and abnormal ECG	94	63	.23	.99
BNP >49 and abnormal ECG	84	69	.24	.97

[a]Bundle branch block or pathological q waves.
IHD = Ischaemic heart disease; ECG = Electrocardiogram.

67 patients. Thus using both BNP and ECG, it was possible to reduce the number of echocardiograms required to diagnose LVSD by 57% in this population.

For the purpose of detecting moderate or severe valve disease, abnormal ECG was 69% sensitive and 48% specific whereas BNP >35 was 87% sensitive and 40% specific for valvular disease. Using normal ECG 134 patients would be excluded from screening with 19 missed cases of moderate or severe valve disease. BNP improved detection, 104 patients would be excluded from screening with only 8 missed cases of valve disease.

Discussion

This study provides new information about the diagnostic role of BNP in a cohort of older people attending day hospital. Compared with younger patients with no evidence of cardiovascular disease, the mean BNP was higher in this population, which is compatible with suggestions that BNP rises in response to normal ageing. However, those older patients with cardiovascular disease in this cohort had significantly elevated BNP levels compared to those with 'healthy hearts'. Importantly, BNP levels rose progressively in patients with one, two, three and four cardiac diseases which may explain why BNP is such a good prognostic indicator in elderly patients in the community with no apparent cardiac disease [25]. These observations suggest that BNP may be a useful indicator of clinically significant cardiovascular disease in an older patient and may be useful in distinguishing 'normal' ageing from pathological cardiac abnormalities which could be treated.

Although raised BNP was extremely sensitive in detecting LVSD and cardiovascular disease it lacked specificity. Only one in 7 patients with a raised BNP over 35 would have LVSD. As in previous studies a normal ECG was extremely effective in ruling out LVSD and had similar sensitivity/specificity as BNP. Patients were often unable to tell if a previous episode of chest pain had been angina, a MI or non-cardiac chest pain. Review of casenotes and information from GP's was often unhelpful or inaccurate. Furthermore using definite evidence of MI on ECG was specific but lacked sensitivity, making it ineffective as a prescreening tool as many cases of LVSD would be missed. Clearly LVSD is not the only cause of breathlessness in the older patient. It may be that atrial fibrillation or valvular disease; diastolic dysfunction or chest disease could explain symptoms suggestive of heart failure. However the absolute levels of BNP are greater in patients with LVSD which is consistent with the relatively poor prognosis in these patients compared to those with normal systolic function heart failure. Currently the treatment options for LVSD are clear and this group should be a priority for identification because of its treatment implications. A moderately elevated BNP may suggest that a patient's symptoms could be a result of atrial fibrillation, valvular disease or left ventricular hypertrophy. These patients often have hypertension which should be treated and patients with atrial fibrillation should be considered for anticoagulation.

In this group of patients 40% were taking frusemide with only 16% of them having a prior diagnosis of heart failure. This highlights how common it is to suspect 'heart failure' in this population. There was little correlation between a patient being on frusemide and them having LVSD. This may be partially explained by normal systolic function heart failure. The current data suggests that half of the patients attending Day Hospital had some objective evidence of cardiovascular disease i.e. LVSD, valvular disease, atrial fibrillation or left ventricular hypertrophy.

Combining ECG and BNP improved detection of LVSD. Patients with an abnormal ECG and BNP >49 had a 1 in 4 chance of having LVSD with a 98% negative predictive value. This would obviate the need for echocardiography in about one-third of cases.

BNP was superior to ECG in the detection of valvular disease and again about one third of patients could be excluded from screening by echocardiography, but 8 cases of moderate to severe valvular disease would

still be missed in 299 patients (2.6%). However all of the missed 8 patients clinically had loud murmurs on auscultation and would probably have been referred for echocardiography on that basis. Therefore the absence of a murmur and a BNP <35 appeared to reliably exclude significant valvular disease.

The choice of prescreening tool used in practice depends on the setting and available resources. In this population attending Day Hospital, BNP and the ECG performed equally in identifying LVSD. Since most Day Hospitals already perform electrocardiography the ECG would remain the main way of identifying which patients should go forward for echocardiography for suspected LVSD.

However there are some potential theoretical advantages to BNP over the ECG in selecting patients for echocardiography, especially in general practice. Firstly, general practitioners are not as confident at analysing ECGs as hospital consultants. In one study where the ECGs were analysed by general practitioners, GP's missed 27% of cases of LVSD when they used an ECG to pre-screen [26]. In another study GP's missed 10% of LVSD cases [27]. Secondly, in our local area one third of GP practices have no ECG machine. Thirdly, the ECG is a categorical variable which has to be graded as normal or abnormal for this purpose. BNP has the advantage of being a continuous variable, which means one can choose any appropriate cut-off to suit the clinical purpose, i.e. BNP has more flexibility as a test than an ECG. The graded nature of BNP means that it not only identifies cardiac abnormalities but it also identifies the severity of the abnormality detected. Another advantage of BNP measurement is that it can be standardized better since it is measured more consistently by an approved laboratory with regular quality control rather than a multitude of different doctors interpreting the ECG, and it is now available for bedside testing like a glucometer, which gives instant results and makes it as simple if not quicker than an ECG.

In conclusion, BNP and ECG, performed equally well at excluding LVSD and other cardiac diseases in a cohort of older patients. However, BNP was superior to the ECG in excluding significant cardiac valvular disease. BNP levels increased progressively as the number of different cardiac abnormalities increased, which may explain why BNP is a good predictor of prognosis in patients with cardiovascular disease. More widespread use of BNP measurements in clinical practice may facilitate the optimum detection and treatment of cardiovascular disease while making the most efficient use of resources.

Key points

- Cardiac disease is common in the older patient.
- Symptoms are often non-specific and objective assessments of cardiac performance are essential before commencing treatment.
- B-Type natriuretic peptide can identify cardiac disease in a Day Hospital Population.
- BNP levels rise incrementally with the number of cardiac diagnoses.
- BNP measurement, in conjunction with ECG, may reduce the need for echocardiography in some patients before commencement of evidence-based treatments.

Acknowledgements

We thank Mrs Jess Robson (research sister) for the data collection. The assistance of Dr Hewitt and the patients and staff of Royal Victoria Day Hospital Dundee is gratefully acknowledged. We also thank the Dundee Levi-Strauss Community Action Group for providing the funds to purchase the portable echo machine. This study was supported by an educational grant form Servier Pharmaceuticals.

References

1. Hoes A, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. Eur Heart J 1998; 19 (suppl. L): L2–L9.

2. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997; 133: 703–12.

3. Sharpe N, Doughty R. Epidemiology of heart failure and ventricular dysfunction. Lancet 1998; 352 (suppl. 1): SI3–SI7.

4. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials [published erratum appears in JAMA 1995; 274: 462]. JAMA 1995; 273: 1450–6.

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

6. Packer M, Bristow MR, Cohn JN *et al.* The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334: 1349–55.

7. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. Lancet 1997; 349: 375–80.

8. 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: 2001–7.

9. Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. Eur Heart J 1997; 18: 560–5.

10. Cowie MR, Wood DA, Coats AJ *et al.* Incidence and aetiology of heart failure; a population-based study. Eur Heart J 1999; 20: 421–8.

11. Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J 1991; 121: 951–7.

12. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. Q J Med 1993; 86: 17–23.

13. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J 1991; 12: 315–21.

14. Marantz PR, Tobin JN, Wassertheil-Smoller S *et al.* The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. Circulation 1988; 77: 607–12.

15. Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. Br Med J 1994; 308: 321–8.

16. Cowie MR, Struthers AD, Wood DA *et al.* Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997; 350: 1349–53.

17. Motwani JG, McAlpine H, Kennedy N, Struthers AD. Plasma brain natriuretic peptide as an indicator for angiotensin converting-enzyme inhibition after myocardial infarction. Lancet 1993; 341: 1109–13.

18. Lerman A, Gibbons RJ, Rodeheffer RJ *et al.* Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. Lancet 1993; 341: 1105–9.

19. Yamamoto K, Burnett JC Jr, Jougasaki M *et al.* Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996; 28: 988–94.

20. Davidson NC, Naas AA, Hanson JK, Kennedy NS, Coutie WJ, Struthers AD. Comparison of atrial natriuretic peptide B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am J Cardiol 1996; 77: 828–31.

21. Wallen T, Landahl S, Hedner T, Saito Y, Masuda I, Nakao K. Brain natriuretic peptide in an elderly population. J Intern Med 1997; 242: 307–11.

22. Buckley MG, Markandu ND, Miller MA, Sagnella GA, MacGregor GA. Plasma concentrations and comparisons of brain and atrial natriuretic peptide in normal subjects and in patients with essential hypertension. J Hum Hypertens 1993; 7: 245–50.

23. McDonagh TA, Robb SD, Murdoch DR *et al.* Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998; 351: 9–13.

24. Struthers AD. Plasma concentrations of brain natriuretic peptide: will this new test reduce the need for cardiac investigations? Br Heart J 1993; 70: 397–8.

25. Wallen T, Landahl S, Hedner T, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. Heart 1997; 77: 264–7.

26. Sandler DA, Steds RP, Hadfield JW. Opening access to echocardiography for general practitioners in North Derbyshire. Br J Cardiol 2000; 7: 94–100.

27. Houghton AR, Sparrow NJ, Toms E, Cowley AJ. Should general practitioners use the electrocardiogram to select patients with suspected heart failure for echocardiography? Int J Cardiol 1997; 62: 31–6.

Received 3 December 2001; accepted in revised form 5 March 2002