The reign of the natriuretic peptides in patients with heart failure continues

**Roy S Gardner^{1†} &
Theresa A McDonagh²**

[†]Author for correspondence

¹Scottish Advanced Heart
Failure Service, Golden
Jubilee National Hospital,
Clydebank, UK

Tel.: +44 141 951 5000;

Fax: +44 141 211 4950;

E-mail: rsgardner@
doctors.org.uk

²Department of Cardiology,
Royal Brompton Hospital,
UK

Tel.: +44 207 351 8703;

E-mail: t.mcdonagh@
imperial.ac.uk

'...B-type natriuretic peptides are consistently shown to be more powerful prognostic markers than their traditional counterparts...'

It was encouraging to see that there were several sessions dedicated to biomarkers at the annual meeting of the European Society of Cardiology (ESC) in September 2008, particularly in relation to patients with heart failure. However, the large number of novel markers currently being investigated in this field only highlights our rudimentary understanding of the complex interaction of the neurohormonal systems involved. Still, the diagnostic and prognostic power of some of these biomarkers is without question, and despite this (like many successes in clinical studies) they are slow to be adopted into standard clinical practice.

This is particularly true of the B-type natriuretic peptides (BNPs) [1]. Discovered 20 years ago [2], the BNPs are now well known to be increased in both asymptomatic and symptomatic left ventricular systolic dysfunction (LVSD), rising in proportion to the severity of chronic heart failure [3–5]. BNP can accurately detect LVSD in the general population [6], but it is particularly useful as a 'rule-out' test owing to its high negative predictive value. As such, the BNPs are now recommended by the ESC [7] and American College of Cardiology/American Heart Association [8] for the diagnosis of both acute and chronic heart failure.

The return of atrial natriuretic peptide? Although atrial natriuretic peptide (ANP) was discovered prior to BNPs, its diagnostic potential in chronic heart failure (for both its C- and N-terminal fragment) was inferior to BNPs, and assays were not developed further. However, recent evidence suggests that an assay targeting the more stable region of mid-regional pro-ANP (MR-proANP) is just as accurate as BNPs in diagnosing heart failure. In a retrospective study by Gegenhuber *et al.* involving over 250 patients presenting to the emergency room with dyspnea,

MR-proANP concentrations were found to be significantly higher in patients with dyspnea secondary to acute heart failure than for other causes (338 pmol/l vs 98 pmol/l; $p < 0.001$) [9]. In another study by von Haehling *et al.*, MR-proANP was found to be an independent predictor of mortality in patients with chronic heart failure [10].

The Biomarkers in the Assessment of Congestive Heart Failure (BACH) study was, therefore, a timely study [11]. Presented at the ESC annual meeting by Dr Alan Maisel, it is a large prospective trial involving 1600 patients across three continents and is currently the largest natriuretic peptide diagnostic study in acute heart failure. MR-proANP was compared with BNP and N-terminal pro-BNP (NT-proBNP) in patients presenting to the emergency room with dyspnea. MR-proANP was found to be as useful as (i.e., not inferior to) BNP and NT-proBNP in the diagnosis of acute heart failure upon receiver operating characteristic (ROC) analysis (area under the curve = 0.904, 0.904 and 0.890, respectively). The secondary end point was also reached in that MR-proANP added diagnostic power to that of BNPs in the logistic regression analysis, particularly in the gray zone where BNPs can have some problems, namely in those with renal dysfunction, obesity, the elderly and those with edema.

The findings of the BACH trial are important and they continue the theme of a multimarker approach to the diagnosis of heart failure being superior to just using one. However, some questions remain to be answered as a result of this study. Of particular clinical relevance, what would be the additional cost of adding MR-proANP to BNP/NT-proBNP evaluation in the emergency room? Would the cost justify these modest gains in diagnostic accuracy? This will be challenging to prove in a study conducted in many different healthcare settings. This is particularly true, as we now have convincing evidence from three randomized studies of BNP/NT-proBNP in the diagnosis of heart failure in the emergency room, demonstrating that such an approach reduces costs, improves length of stay and may lower readmission rates. The

challenge is now to show this for MR-proANP, although the results of the aforementioned three studies suggest that there may be a role for MR-proANP analysis in the future.

Prognosis

Presently, the role of the natriuretic peptides in prognostication outwith clinical studies is less clear. BNP's have been shown to be powerful prognostic markers in patients with acute [12] and chronic [13] heart failure, acute coronary syndromes [14], pulmonary emboli [15], as well as in the general population [4]. However, it is in the risk stratification of patients with heart failure syndromes that the BNP's have had the most interest.

'B-type natriuretic peptides should now be used routinely in clinical practice, particularly... in heart failure.'

There are, at our last count, over 100 clinical, hemodynamic and neurohormonal markers of prognosis in patients with heart failure. Unfortunately, these variables vary in their success at predicting outcome owing to the heterogeneous nature of heart failure together with the availability and reproducibility of investigatory tools. However, BNP's, are consistently shown to be more powerful prognostic markers than their traditional counterparts [13,16,17] and, although they have become the benchmark against which novel markers are now compared, further studies need to be performed to see how they fit in clinically.

Treatment monitoring

Following on from the original work of Troughton *et al.* [18], where titration of therapy guided by NT-proBNP concentration appeared to be superior to current best practice and, more recently, Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) [19], where a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF, the Trial of Intensified Versus Standard Medical Therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) study was presented at a hotline session of the ESC annual meeting [20]. Involving nearly 500 patients over the age of 60 years (average age 77 years), TIME-CHF revealed

that intensified, BNP-guided therapy was no more effective than a standard, symptom-guided approach in elderly heart-failure patients aged 75 years or over in reducing the number of deaths and all-cause hospitalizations. This was not true for the younger cohort in the study (60–74 years), and this may partly be explained by the greater number of co-morbidities and reduced applicability of treatment recommendations in the very elderly.

The next treatment-monitoring trial to be formally reported is BNP-Assisted Treatment To Lessen Serial Cardiovascular Readmissions and Death (BATTLE-SCARRED) [21]. Provisional results were presented by Mark Richards at the Heart Failure Meeting of the ESC earlier this year [22], and they appear to corroborate the results of TIME-CHF. Patients were randomized to have therapy guided by NT-proBNP or to standard care. It appeared that those patients aged less than 70 years randomized to the NT-proBNP-guided group had a reduction in morbidity and mortality, but this was not seen in those over the age of 70 years. We believe that the formal results are due to be published imminently, and we await them with great interest.

Where to now?

With the current body of evidence, BNP's should now be used routinely in clinical practice, particularly in areas where that evidence is greatest – in heart failure. Further research needs to be undertaken to clarify whether they can be used to identify patients in greatest need of advanced heart-failure therapies, such as implantable cardioverter defibrillators, cardiac resynchronization therapy or cardiac transplantation. For certain, the BNP's are here to stay and with greater experience will come greater utility.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

- Gardner RS, Chong KS, McDonagh TA: B-type natriuretic peptides in heart failure. *Biomark. Med.* 1(2), 243–250 (2007).
- Sudoh T, Kangawa K, Minamino N, Matsuo H: A new natriuretic peptide in porcine brain. *Nature* 332(6159), 78–81 (1988).
- Lerman A, Gibbons RJ, Rodeheffer RJ *et al.*: Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. *Lancet* 341, 1105–1109 (1993).

4. McDonagh TA, Cunningham AD, Morrison CE *et al.*: Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart* 86(1), 21–26 (2001).
5. Tsutamoto T, Wada A, Maeda K *et al.*: Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. *Eur. Heart J.* 20(24), 1799–1807 (1999).
6. McDonagh TA, Robb SD, Murdoch DR *et al.*: Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351(9095), 9–13 (1998).
7. Dickstein K, Cohen-Solal A, Filippatos G *et al.*: ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Eur. Heart J.* 29, 2388–2442 (2008).
8. Hunt SA, Abraham WT, Chin MH *et al.*: ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 112(12), e154–e235 (2005).
9. Gegenhuber A, Struck J, Poelz W *et al.*: Midregional pro-A-type natriuretic peptide measurements for diagnosis of acute destabilized heart failure in short-of-breath patients: comparison with B-type natriuretic peptide (BNP) and amino-terminal proBNP. *Clin. Chem.* 52(5), 827–831 (2006).
10. von Haehling S, Jankowska EA, Morgenthaler NG *et al.*: Comparison of midregional pro-atrial natriuretic peptide with N-terminal pro-B-type natriuretic peptide in predicting survival in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 50(20), 1973–1980 (2007).
11. Maisel A: The BACH (Biomarkers in the Assessment of Congestive Heart Failure) study. *European Society of Cardiology Annual Congress*. Munich, Germany, 30 August–3 September 2008.
12. Cheng V, Kazanagra R, Garcia A *et al.*: A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J. Am. Coll. Cardiol.* 37(2), 386–391 (2001).
13. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA: N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur. Heart J.* 24(19), 1735–1743 (2003).
14. de Lemos JA, Morrow DA, Bentley JH *et al.*: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N. Engl. J. Med.* 345(14), 1014–1021 (2001).
15. ten Wolde M, Tulevski II, Mulder JW *et al.*: Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation* 107(16), 2082–2084 (2003).
16. Gardner RS, Chong V, Morton I, McDonagh TA: N-terminal brain natriuretic peptide is a more powerful predictor of mortality than endothelin-1, adrenomedullin and tumour necrosis factor- α in patients referred for consideration of cardiac transplantation. *Eur. J. Heart Fail.* 7(2), 253–260 (2005).
17. Gardner RS, Henderson G, McDonagh TA: The prognostic use of right heart catheterization data in patients with advanced heart failure: how relevant are invasive procedures in the risk stratification of advanced heart failure in the era of neurohormones? *J. Heart Lung Transplant.* 24(3), 303–309 (2005).
18. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM: Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 355(9210), 1126–1130 (2000).
19. Jourdain P, Jondeau G, Funck F *et al.*: Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J. Am. Coll. Cardiol.* 49(16), 1733–1739 (2007).
20. TIME-CHF (Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure) study. *European Society of Cardiology Annual Congress*. Munich, Germany, 30 August–3 September 2008.
21. Lainchbury JG, Troughton RW, Frampton CM *et al.*: NTproBNP-guided drug treatment for chronic heart failure: design and methods in the 'BATTLESCARRED' trial. *Eur. J. Heart Fail.* 8(5), 532–538 (2006).
22. Richards AM: BATTLESCARRED. Presented at: *European Society of Cardiology: Heart Failure Congress*. Munich, Germany, 30 August–3 September 2008.