

## SCIENTIFIC LETTER

## N-terminal brain natriuretic peptide and subsequent hospital admission for worsening heart failure

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Recurrent and lengthy hospitalisation is common in patients with heart failure and accounts for much of the treatment cost. This has led to interventions aimed at reducing hospitalisation, but identifying patients at risk of hospitalisation is difficult using traditional risk factors.<sup>1</sup> Evidence accumulates for the value of brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide (NT-proBNP) in the diagnosis and management of heart failure.<sup>2</sup> In addition, one study has compared patients with plasma concentrations of NT-proBNP above and below a median of 825 pg/ml, observing a relative risk for hospitalisation with heart failure of 4.7 (95% confidence interval (CI) 2.2 to 10.3;  $p < 0.001$ ).<sup>3</sup> Patients in that study had chronic, stable heart failure caused by coronary artery disease (CAD) and were participating in a clinical trial. Trial exclusion criteria included a current New York Heart Association (NYHA) rating of IV. In the present study, we examined a UK population cohort of incident cases of heart failure to assess whether NT-proBNP could identify patients at risk of subsequent hospitalisation.

## METHODS

The Bromley heart failure study was designed to identify all new cases of heart failure in Bromley, UK, through general practitioner surveillance and daily screening of hospital admissions.<sup>1</sup> Heart failure was diagnosed if a patient had symptoms (shortness of breath or fatigue) with clinical signs of fluid retention in the presence of an underlying abnormality of cardiac structure or function.<sup>4</sup> If doubt remained, a positive response to treatment for heart failure confirmed the diagnosis.

At first contact with the study cardiologist, a venous blood sample was drawn into a glass tube containing edetic acid and aprotinin. This was approximately 30 minutes after arrival for 36 of 38 patients presenting in the study heart failure clinic, within two days of admission for 46 of 72 patients hospitalised at presentation, and more than one week after presentation for 10 patients. The blood sample was centrifuged and the plasma stored at  $-80^{\circ}\text{C}$  until sent, while frozen, to the Hoffman-La Roche laboratory for assay of NT-proBNP. Patients were followed up for death and hospital admission over a median of 20 months (90% range 14–24 months). Dates and certified causes of death were obtained from the UK National Health Service Central Registry.

The primary outcome measure was a subsequent hospitalisation for worsening heart failure. The association with NT-proBNP was evaluated using Cox's proportional hazards regression with patients' follow up being censored at death. Secondary outcomes were death before hospitalisation for worsening heart failure, and death or subsequent hospitalisation for worsening heart failure.

The local research ethics committee approved this study, and all participants gave informed consent.

## RESULTS

From the 332 patients enrolled, 110 samples were available for NT-proBNP measurement. Samples were not available from the other patients because of early death, refusal to have blood taken, and technical failures. Seventy one patients were male, median age was 75 years (range 49–91 years), CAD was the aetiology in 40 patients, 98 patients had impaired left ventricular systolic function, and 59 patients were NYHA rating IV at the time of first presentation. While males (65% v 54%) were over-represented, the subsample with NT-proBNP measurements was otherwise comparable to the whole study cohort. Median concentration of NT-proBNP was 637 pg/ml (90% range 110–3510 pg/ml).

Thirty patients had an unplanned admission for worsening heart failure during follow up and 17 died before such an admission. The results (table 1) show no evidence for an association between NT-proBNP concentration and subsequent hospitalisation. By contrast, despite the small number of deaths occurring without prior admission, there was strong evidence of an association between higher NT-proBNP and an increasing risk of death. The trend towards a greater hazard of the combined outcome of hospitalisation or death with higher NT-proBNP is because of the association with death.

## DISCUSSION

Our results suggest that the previous study may have overestimated the relation between NT-proBNP and the subsequent risk of hospitalisation for worsening heart failure.<sup>3</sup> This discrepancy may have arisen because our study is of a population based cohort of acutely ill patients with heart failure arising from a number of different aetiologies and a wide range of disease severity. Perhaps there is a stronger association in patients with specific aetiologies, such as CAD.<sup>3</sup> Alternatively, the timing of NT-proBNP measurement may be an important factor in maximising its predictive value for subsequent hospitalisation. While in our study NT-proBNP was measured shortly after first diagnosis, in the study by Richards and colleagues, patients were enrolled, and their NT-proBNP measured when they were in a stable state.<sup>3</sup> A recent study has addressed this issue directly, comparing measurements of NT-proBNP made on arrival at, and on discharge from, a coronary care unit.<sup>5</sup> Both measurements were available for 34 patients, who subsequently experienced 19 events (death, hospital admissions for heart failure, or worsening heart failure without hospitalisation). With both measurements included in the same regression analysis, only the pre-discharge concentration of NT-proBNP was independently associated with the composite outcome.<sup>5</sup> This limited evidence suggests that if the objective is to identify patients at

**Abbreviations:** BNP, brain natriuretic peptide; CAD, coronary artery disease; NYHA, New York Heart Association; NT-proBNP, N-terminal brain natriuretic peptide

**Table 1** Event rates for patients with NT-proBNP above and below the median value

End points	Event rate for patients with NT-proBNP		*Hazard ratio (95% CI)	*p Value
	≤ Median	>Median		
Hospital admission†	16/55	14/55	1.03 (0.79 to 1.35)	0.83
All cause mortality without prior hospital admission†	3/55	14/55	1.54 (1.08 to 2.19)	0.016
Hospital admission or all cause mortality†	19/55	28/55	1.19 (0.96 to 1.48)	0.11

\*Calculated using Cox's proportional hazards regression.  
 †Unplanned hospital admission for worsening heart failure only.  
 Hazard ratios indicate the increased hazard of an event with a doubling of plasma NT-proBNP concentration at time of first presentation.

risk of future hospitalisation, NT-proBNP should be measured after the patient is stabilised.

In our study we have found a strong association between NT-proBNP measured at diagnosis and subsequent survival. We suggest that the most likely reason for our failure to find a similar association with hospitalisation for worsening heart failure is the limited potential for any single patient characteristic to predict that outcome, as such admission arises through interplay of medical, social, and health service factors. We have previously found only age to be independently predictive of admission in patients with heart failure.<sup>1</sup> This association is conceivably because of age acting as a marker for several factors simultaneously, such as the resilience of the patient to heart failure, and the availability of social support.

While the increasing clinical use of NT-proBNP and BNP is supported by strong associations with diagnosis and mortality,<sup>2</sup> our study suggests that their value for identifying patients at risk of future hospitalisation is not yet established.

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**Conflicts of interest:** MRC advises several companies that manufacture assays for natriuretic peptides. MRC was the clinical adviser for the NICE guideline on the diagnosis and management of chronic heart failure, but the views expressed here are his own and should not be taken to necessarily reflect those published in the guideline

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**REFERENCES**

- 1 **Cowie MR, Fox KF, Wood DA, et al.** Hospitalisation of patients with heart failure. A population-based study. *Eur Heart J* 2002;**23**:877–85.
- 2 **Cowie MR, Mendez GF.** BNP and Congestive Heart Failure. *Prog Cardiovasc Dis* 2002;**44**:293–321.
- 3 **Richards AM, Doughty R, Nicholls MG, et al.** for the Australia-New Zealand Heart Failure Group. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2001;**37**:1781–7.
- 4 **Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology.** Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527–60.
- 5 **O'Brien RJ, Squire IB, Demme B, et al.** Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail* 2003;**5**:499–506.

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**Left subclavian artery stenosis with subclavian–subclavian bypass**



**A**n arch aortography demonstrates an occluded brachiocephalic trunk and subclavian–subclavian bypass graft (SSBG) in a 56 year old woman with left main and triple coronary artery disease requiring coronary artery bypass graft (CABG) surgery. A selective left subclavian arteriography revealed a moderate stenosis with a 40 mm Hg gradient proximal to the origin of the left vertebral artery and left internal mammary artery (LIMA). Stenting of the left subclavian stenosis was performed to improve distal flow and the utilisation of LIMA during CABG. To minimise cerebral embolisation of atherosclerotic material into the left vertebral artery and right carotid through the SSBG, left subclavian stenting was performed using induced hyperaemia of the left upper extremity and temporary manual compression of the SSBG. The procedure was uneventful and the patient was doing well one month later.

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