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

M R Cowie, C Metcalfe, K F Fox, G C Sutton

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.

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. 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. 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 aprotonin. 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°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.

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. 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. 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.

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. 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. This limited evidence suggests that if the objective is to identify patients at high risk of subsequent hospitalisation, using only the pre-discharge concentration of NT-proBNP would be an important factor in maximising its predictive value.

Abbreviations: BNP, brain natriuretic peptide; CAD, coronary artery disease; NYHA, New York Heart Association; NT-proBNP, N-terminal brain natriuretic peptide.
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. 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, our study suggests that their value for identifying patients at risk of future hospitalisation is not yet established.

ACKNOWLEDGEMENTS
The Imperial College Clinical Epidemiology Group in Cardiac Medicine undertook the Bromley Heart Failure Study, with grant support from the British Heart Foundation (project grant 97010) and the Royal Brompton NHS Trust Joint Research Committee. We thank Sharon Bond and Patsy Devane (research nurses), Neil Mclellan (data manager) and Jane Ingham (research administrator) for collecting and collating the data. The assay of NT-proBNP was provided free of charge by Hoffman-La Roche, Basle, Switzerland. Chris Metcalfe worked on this study while funded by a UK Medical Research Council/National Health Service Training Fellowship.

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

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

*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.

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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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Accepted 2 June 2004

**REFERENCES**

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Left subclavian artery stenosis with subclavian–subclavian bypass

An 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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Heart 2005 91: 371-372
doi: 10.1136/hrt.2003.030650

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