



University  
of Glasgow

Mirjafari, Hoda et al. (2014) N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: results from the Norfolk Arthritis Registry (NOAR). *Annals of the Rheumatic Diseases*, 73 (4). pp. 684-690. ISSN 0003-4967

Copyright © 2013 The Authors

<http://eprints.gla.ac.uk/92885>

Deposited on: 02 April 2014

Enlighten – Research publications by members of the University of Glasgow\_  
<http://eprints.gla.ac.uk>



OPEN ACCESS

## EXTENDED REPORT

# N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: results from the Norfolk Arthritis Registry (NOAR)

Hoda Mirjafari,<sup>1</sup> Paul Welsh,<sup>2</sup> Suzanne M M Verstappen,<sup>1</sup> Paddy Wilson,<sup>3</sup> Tarnya Marshall,<sup>3</sup> Helena Edlin,<sup>4</sup> Diane Bunn,<sup>1,3</sup> Jacqueline Chipping,<sup>1,3</sup> Mark Lunt,<sup>1</sup> Deborah P M Symmons,<sup>1,5</sup> Naveed Sattar,<sup>2</sup> Ian N Bruce<sup>1,5</sup>**Handling editor** Tore K Kvien<sup>1</sup>Arthritis Research UK Epidemiology Unit, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK<sup>2</sup>BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and medical Sciences, University of Glasgow, Glasgow, UK<sup>3</sup>Norfolk and Norwich University Hospital, Norwich, UK<sup>4</sup>Department of Vascular Studies, Manchester Royal Infirmary, Manchester, UK<sup>5</sup>NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK**Correspondence to**Professor Ian N Bruce, Arthritis Research UK Epidemiology Unit, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Oxford Road, Manchester, UK; [ian.bruce@manchester.ac.uk](mailto:ian.bruce@manchester.ac.uk)Accepted 16 February 2013  
Published Online First  
19 March 2013Open Access  
Scan to access more  
free content**To cite:** Mirjafari H, Welsh P, Verstappen SMM, et al. *Ann Rheum Dis* 2014;**73**:684–690.**ABSTRACT****Background** We measured N-terminal pro-brain natriuretic peptide (NT-pro-BNP), a marker of cardiac dysfunction, in an inception cohort with early inflammatory polyarthritis (IP) and assessed its association with disease phenotype, cardiovascular disease (CVD), all-cause and CVD related mortality.**Methods** Subjects with early IP were recruited to the Norfolk Arthritis Register from January 2000 to December 2008 and followed up to death or until March 2010 including any data from the national death register. The associations of baseline NT-pro-BNP with IP related factors and CVD were assessed by linear regression. Cox proportional hazards models examined the independent association of baseline NT-pro-BNP with all-cause and CVD mortality.**Results** We studied 960 early IP subjects; 163 (17%) had prior CVD. 373 (39%) patients had a baseline NT-pro-BNP levels  $\geq 100$  pg/ml. NT-pro-BNP was associated with age, female gender, HAQ score, CRP, current smoking, history of hypertension, prior CVD and the presence of carotid plaque. 92 (10%) IP subjects died including 31 (3%) from CVD. In an age and gender adjusted analysis, having a raised NT-pro-BNP level ( $\geq 100$  pg/ml) was associated with both all-cause and CVD mortality (adjusted HR (95% CI) 2.36 (1.42 to 3.94) and 3.40 (1.28 to 9.03), respectively). These findings were robust to adjustment for conventional CVD risk factors and prevalent CVD.**Conclusions** In early IP patients, elevated NT-pro-BNP is related to HAQ and CRP and predicts all-cause and CVD mortality independently of conventional CVD risk factors. Further study is required to identify whether NT-pro-BNP may be clinically useful in targeting intensive interventions to IP patients at greatest risk of CVD.**BACKGROUND**N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) is an inactive and stable amino acid fragment cosecreted, alongside the neuroendocrine peptide BNP, from the ventricular cardiac myocytes. It is released in response to left ventricular strain or ischaemia and has been found to be an important biomarker for left ventricular systolic dysfunction and left ventricular stress in the general population.<sup>1</sup> Levels are also elevated even in thosewithout clinical cardiovascular disease (CVD) and even minimally elevated NT-pro-BNP levels are predictive of future CVD and mortality in a range of cohort and general healthy population studies.<sup>2–5</sup> These observations have also been confirmed in a meta-analysis of 40 studies involving 87 474 subjects and 10 625 incident CVD outcomes.<sup>6</sup> In clinical practice, an NT-pro-BNP level of  $\geq 100$  pg/ml has high sensitivity and specificity for congestive heart failure (CHF) and can be used to stratify patients at high risk of cardiac failure in the acute setting.<sup>7–9</sup> Circulating NT-pro-BNP is also associated with pro-inflammatory cytokines such as tumour necrosis factor (TNF) and interleukin 6 (IL-6).<sup>10</sup> Acute inflammatory conditions including pneumonia and septic shock are also associated with raised NT-pro-BNP levels<sup>11–17</sup> and TNF blockade in rheumatoid arthritis (RA) lowers NT-pro-BNP, suggesting a link between inflammation and cardiac stress. This has raised interest in the role of NT-pro-BNP in chronic inflammatory conditions such as inflammatory polyarthritis (IP).IP and RA are associated with an excess CVD risk including coronary heart disease, stroke and CHF.<sup>18–21</sup> In two recent meta-analyses, the standardised mortality ratio (95% CI) for coronary heart disease and stroke in RA was 1.50 (1.39 to 1.61)<sup>22</sup> and 1.46 (1.31 to 1.63),<sup>23</sup> respectively. CHF has also been noted to be a common cause of death in RA and chronic inflammation may contribute to this outcome.<sup>24</sup>A small number of studies have examined the potential relevance of NT-pro-BNP levels in RA patients. Crowson *et al*<sup>25</sup> noted higher NT-pro-BNP levels in RA compared with population controls. In established RA, NT-pro-BNP was associated with disease activity, disease duration as well as with C reactive protein (CRP), TNF and IL-6 concentrations.<sup>26–29</sup> One study from our group found that a reduction in NT-pro-BNP correlated with the reduction in erythrocyte sedimentation rate observed after starting adalimumab therapy.<sup>30</sup> A further study also noted an association between NT-pro-BNP and carotid intima-medial thickness (cIMT).<sup>28</sup> To date, only one study has looked at the predictive value of NT-pro-BNP levels with future CVD mortality in established RA;<sup>29</sup> however, little is known about NT-pro-BNP in early IP patients.

The aim of this study was to measure serum NT-pro-BNP levels in a large, well characterised inception cohort of patients with early IP. First, we aimed to examine the baseline association of NT-pro-BNP levels with IP disease phenotype, clinical CVD risk markers and subclinical atherosclerosis surrogates. Second, we also examined the predictive value of raised NT-pro-BNP levels for future all-cause and CVD related mortality.

## METHODS

### Setting

Subjects aged 16 years and older with early IP ( $\geq 2$  joints swollen for  $\geq 4$  weeks) were recruited to the Norfolk Arthritis Register (NOAR) from January 2000 to December 2008. In this study, we restricted inclusion to subjects with  $\leq 24$  months' symptom duration.

### Data collection at recruitment

All subjects underwent a clinical assessment including swollen and tender joint count (51 joints), measurement of height and weight to calculate body mass index (BMI). Smoking status was recorded and patients were categorised into never smokers, previous smokers or current smokers. Subjects were specifically asked about past history of CVD events such as angina, heart attacks and heart failure, as well as current prescribed and over-the-counter medications and any history of disease modifying antirheumatic drugs use. All patients completed the Health Assessment Questionnaire (HAQ). Hypertension was defined as being present if patients reported a physician diagnosis of hypertension or if they were taking antihypertensive therapy at the baseline clinical assessment. Diabetes mellitus was also defined by patient self-report of a physician diagnosis or if they were taking oral hypoglycaemic agents or injected insulin.

### Blood sample analysis

At recruitment blood samples were collected, aliquoted and frozen at  $-80^{\circ}\text{C}$  in Norfolk before being transported to the Arthritis Research UK Epidemiology Unit in Manchester. A Nephrostar Galaxy automated analyser was used to determine CRP concentration (BMG Labtech, Aylesbury, UK); this was used to calculate the 28-joint disease activity score (DAS<sub>28</sub><sup>CRP</sup>). Rheumatoid factor (RF) was measured using a particle enhanced immunoturbidimetric assay where  $>40$  iU/ml was considered positive for RF (BMG Labtech). Antibodies to citrullinated protein antigens (ACPA) were measured using the Axis-Shield DIASAT kit (Axis-Shield, Dundee, UK) where  $>5$  U/ml was considered positive for ACPA. Patients were considered 'seropositive' if they had a positive RF and/or ACPA.

Serum NT-pro-BNP concentrations were determined using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK), calibrated using the manufacturer's reagents at the University of Glasgow (PW, NS). Manufacturer's controls were used with limits of acceptability defined by the manufacturer. The limit of detection was 5 pg/ml. Low control coefficient of variance (CV) was 6.7% and high control CV was 4.9%. Patients were classified as having a raised NT-pro-BNP level if their NT-pro-BNP measurement was  $\geq 100$  pg/ml as per local clinically used threshold and published data.<sup>7-9</sup>

### Cardiovascular substudy

In a subset of the main cohort, consecutive patients ( $n=327$ ) recruited between 2004 and 2008 and aged 18-65 years at cohort entry were invited to participate in a detailed cardiovascular assessment. A fasting blood sample was used to measure the lipid profile and plasma glucose. Blood pressure

was measured in each arm and the higher of the two measurements was used in analyses. For the purposes of this study, however, hypertension was defined in all cases as described above. They also underwent a B-mode Doppler carotid ultrasound examination at the Department of Vascular Radiology at the Norfolk and Norwich University Hospital. The images were stored on super video home system (VHS) video and analysed at The University of Manchester, Department of Vascular Surgery using a standardised research protocol. Preliminary validation has revealed good intraobserver correlation using this technique.<sup>31</sup> Briefly, the right and left common carotid artery, carotid bulb and the first 1.5 cm of the internal and external carotid arteries were examined in longitudinal and cross-sectional planes. Carotid IMT measurements were made in a longitudinal plane at a point of maximum thickness on the far wall of the common carotid artery along a 1 cm section of the artery proximal to the carotid bulb. Measurements were repeated three times on each side, unfreezing the image on each occasion and relocating the maximal cIMT. The average of these three measurements was then calculated and used as the mean cIMT.<sup>32</sup> The higher of the right or left mean cIMT was used as the cIMT for analyses. Carotid plaque was defined as present if any of the following parameters was met and then graded according to standard definitions:<sup>33</sup>

1. plaque present with  $<30\%$  vessel diameter loss
2.  $30\%$ - $50\%$  vessel diameter loss
3.  $>50\%$  vessel diameter loss.

Total cholesterol, high density lipoprotein (HDL) and triglycerides were assayed on fresh fasting serum using cholesterol oxidase phenol aminopienazone (CHOD-PAP), a homogenous direct method (Abbott Diagnostics, Berkshire, UK), and glycerol-3-phosphate oxidase (GPO-PAP) methods respectively at the Norfolk and Norwich University Hospital. Low density lipoprotein (LDL) levels were mathematically derived using the Friedwald's equation.

### Follow-up and mortality

In NOAR all patients are flagged with the National Health Service Information Service (NHS-IS). Patients were followed up until March 2010, death or embarkation, whichever came first. Death certificates were provided by the NHS-IS for all those who had died. For this study we took the underlying cause of death, coded using ICD10,<sup>34</sup> as the main cause of death. CV deaths were defined as those where the underlying cause of death fell within chapter I of ICD10. All patients provided written informed consent to take part and the study was approved by the Norfolk Research Ethics Committee (REC no. 2003/075).

### Statistical analyses

As the NT-pro-BNP levels were positively skewed, we log-transformed these values for our analysis. The associations among log-transformed NT-pro-BNP and baseline demographic, IP and CVD parameters including the presence or absence of carotid plaque at recruitment were assessed using linear regression. These analyses were subsequently adjusted for age at recruitment and gender. Forward stepwise multivariable regression analysis was carried out that included age and gender to assess key IP and CVD related factors associated with log NT-pro-BNP levels at baseline on univariate analyses ( $p<0.05$ ).

We examined the association of raised NT-pro-BNP ( $\geq 100$  pg/ml) with mortality (all-cause and CVD) using Cox proportional hazards regression. Analyses were adjusted for key CVD risk factors, namely, age, gender, BMI, prior CVD,

## Clinical and epidemiological research

**Table 1** Baseline characteristics of the IP cohort and the CVD substudy population

Variables	Number of subjects with data in total population	Total study population Median (IQR)/mean (SD)/n(%) n=960	Number of subjects with data in CVD substudy	CVD substudy population Median (IQR)/mean (SD)/n(%) n=327
<b>Demographics</b>				
Age (years)	960	58 (47–68)	327	51 (42–58)*
Female	960	617 (64%)	327	232 (71%)
<b>IP disease parameters</b>				
RF/ACPA positive	823	484 (59%)	322	162 (50%)
RA, 1987 ACR criteria	960	436 (45%)	327	152 (46%)
HAQ score	946	0.88 (0.38–1.50)	325	0.88 (0.38–1.38)
DAS28 <sub>CRP</sub>	842	3.7 (2.8–4.6)	305	3.8 (3.0–4.8)
Swollen joints (/28)	960	2 (0–6)	327	3 (1–6)
Tender joints (/28)	960	3 (0–8)	327	4 (1–10)
CRP (mg/l)	842	11 (5–22)	305	11 (8–20)
Symptom duration (months)	960	5.9 (3.2–10.5)	327	6.5 (4.2–11.2)
<b>Treatments</b>				
DMARDs	960	496 (52%)	327	182 (56%)
Steroids	960	245 (26%)	327	60 (18%)
NSAIDs	960	344 (36%)	327	212 (65%)
COX-2 inhibitor	960	83 (9%)	327	15 (5%)
Paracetamol	960	164 (17%)	327	129 (39%)
Antihypertensive therapy	960	193 (20%)	327	42 (13%)
Statin therapy	960	17 (2%)	327	24 (7%)
<b>CVD parameters</b>				
BMI (kg/m <sup>2</sup> )	940	26.4 (23.6–30.1)	320	26.7 (24.1–31.0)
Diabetes	960	88 (9%)	327	31 (9%)
Current smoker	845	211/845 (25%)	269	74 (28%)
Previous smoker	845	378/845 (45%)	269	127 (47%)
Never smoker	845	256/845 (30%)	269	68 (25%)
Prior CVD	960	163 (17%)	327	14 (4%)
Hypertensive	960	208 (22%)	327	44 (13%)
BP (mm Hg)	NA	–	327	134/83 (17/10)
Systolic BP (mm Hg)	NA	–	327	133 (17)
Diastolic BP (mm Hg)	NA	–	327	83 (10)
Total cholesterol (mmol/l)	NA	–	327	5.3 (4.7–6.0)
LDL (mmol/l)	NA	–	327	3.3 (2.7–3.9)
HDL (mmol/l)	NA	–	327	1.4 (1.1–1.7)
Fasting glucose (mg/dl)	NA	–	327	4.8 (4.5–5.1)
<b>CVD surrogates</b>				
cIMT (mm)	NA	–	327	0.06 (0.05–0.07)
Carotid plaque	NA	–	327	150 (46%)

\*Statistically significantly different at  $p < 0.05$ .

ACPA, anticitrullinated protein antibody; ACR, American College for Rheumatology; BMI, body mass index; BP, blood pressure; cIMT, carotid intima-medial thickness; COX-2, cyclo-oxygenase-2 inhibitor; CRP, C reactive protein; CVD, cardiovascular disease; DAS28, disease activity score based on 28 joint count; DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IP, inflammatory polyarthritis; mm Hg, millimetres of mercury; NA, data not available; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor.

diabetes, smoking status and hypertension. Subsequently analyses were adjusted for IP related factors associated with log NT-pro-BNP in our cross-sectional analysis. Incremental prognostic information was calculated using the Harrell's C-statistic (C-index) and these values were compared using the  $\chi^2$  test. Sensitivity analyses were also undertaken in the subsets who (i) were negative for ACPA and RF and (ii) had no reported history of prior CVD at baseline recruitment.

## RESULTS

### Cross-sectional association of baseline NT-pro-BNP concentration with IP disease phenotype and CVD risk markers

We studied 960 IP subjects with a median (IQR) age and symptom duration of 58 (47–68) years and 5.9 (3.2–10.5)

months, respectively. The cohort included 617 (64%) female subjects; there were 211 (25%) current smokers. In all, 484/823 (59%) were positive for RF and/or ACPA and 436 (45%) fulfilled the 1987 American College for Rheumatology Criteria for RA at first assessment (table 1). A history of prior CVD was reported by 163 (17%) patients (table 1). The demographic, IP phenotype and CVD parameters were comparable in the subset of 327 patients who had carotid Doppler scans relative to the entire cohort, with the exception of a younger median age at recruitment into this substudy as per protocol (table 1).

NT-pro-BNP levels were positively skewed with a median (IQR) of 74 (38–153) pg/ml; 373 (39%) patients had NT-pro-BNP levels  $\geq 100$  pg/ml, including 89 of 163 (55%) patients with a prior history of CVD. In univariate linear regression analyses, higher log NT-pro-BNP levels were associated

**Table 2** Cross-sectional association between log NT-pro-BNP and demographic and disease related factors measured at baseline n=960

Variable	Log NT-pro-BNP* β-Coefficient (95% CI) Adj A&G†	Log NT-pro-BNP* β-Coefficient (95% CI) Stepwise regression‡
Age (per year)	0.035 (0.031 to 0.039)	0.025 (0.020 to 0.030)
Female (Y/N)	0.211 (0.085 to 0.336)	–
ACR 1987 criteria (Y/N)	0.061 (–0.060 to 0.182)	
RF/ACPA (Y/N)	0.009 (–0.111 to 0.129)	
HAQ score (per unit)	0.119 (0.036 to 0.201)	0.250 (0.149 to 0.351)
DAS28 <sub>CRP</sub> (per unit)	–0.024 (–0.089 to 0.041)	
Swollen joints (/28) (per joint)	0.008 (–0.005 to 0.020)	
Tender joints (/28) (per joint)	–0.009 (–0.018 to –0.0004)	–0.021 (–0.032 to –0.010)
CRP (per mg/l)	0.003 (0.001 to 0.004)	0.002 (0.001 to 0.004)
Symptom duration (per month)	–0.009 (–0.020 to 0.002)	
DMARDs/steroids (Y/N)	0.045 (–0.079 to 0.169)	
Duration of DMARD/steroid therapy (per month)	0.002 (–0.004 to 0.008)	
Hypertension	0.282 (0.128 to 0.436)	0.196 (0.017 to 0.375)
BMI (per kg/m <sup>2</sup> )	–0.020 (–0.031 to –0.008)	–0.019 (–0.032 to –0.006)
Diabetes (Y/N)	0.011 (–0.020 to 0.222)	
Current smoker (vs never smokers)	0.087 (–0.068 to 0.241)	
Previous smoker (vs never smokers)	0.198 (0.021 to 0.376)	–
Prior CVD (Y/N)	0.175 (0.014 to 0.337)	0.245 (0.059 to 0.431)
Statin therapy (Y/N)	0.022 (–0.462 to 0.507)	

\*Log NT-pro-BNP, NT-pro-BNP levels that have been log transformed.

†Linear regression models adjusted for age and gender.

‡Stepwise regression includes age, gender, HAQ score, tender joint count, CRP, hypertension, BMI, smoking status and prior CVD in the entire cohort.

ACPA, antibodies to citrullinated protein antigens; ACR, American College for Rheumatology; BMI, body mass index; CRP, C reactive protein; CVD, cardiovascular disease; DAS28, disease activity score based on 28 joint count; DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; NA, not applicable; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; RF, rheumatoid factor.

with being older at recruitment ( $\beta$ -coefficient (95% CI) 0.035 (0.031 to 0.039) per year) and female ( $\beta$ -coefficient (95% CI) 0.211 (0.085 to 0.336)). In univariate age and gender adjusted analyses (table 1), a number of factors were associated with log NT-pro-BNP including prior CVD, classic risk factors such as previous smoking and hypertension and several IP related factors, including HAQ score, and CRP. Both BMI and tender joint counts were negatively associated with log NT-pro-BNP (table 2).

In a multivariable forward stepwise linear regression analysis containing all risk markers showing significance on univariate analyses, age, prior CVD and hypertension all remained positively associated and BMI remained negatively associated with log NT-pro-BNP (table 2). IP related factors that remained associated on multivariable analysis were HAQ score ( $\beta$ -coefficient (95% CI) 0.250 (0.149 to 0.351)), CRP ( $\beta$ -coefficient (95% CI) 0.002 (0.001 to 0.004)) and tender joint count ( $\beta$ -coefficient (95% CI) –0.021 (–0.032 to –0.010)).

### Cross-sectional association of baseline NT-pro-BNP concentration with subclinical atherosclerosis

The presence of plaque was significantly associated with log NT-pro-BNP levels ( $\beta$ -coefficient (95% CI) 0.253 (0.063 to 0.442)). This association did not however persist after age and gender adjustment ( $\beta$ -coefficient (95% CI) 0.109 (–0.100 to 0.319)). Carotid IMT was not significantly associated with NT-pro-BNP levels on univariate analysis.

### NT-pro-BNP levels and mortality

During 5526 patient years of follow-up over a median (IQR) follow-up period of 5.5 (3.7–7.7) years, 92 (10%) IP subjects died. Of the 92 deaths, 31 (34%) had the main underlying cause of death as CVD (Chapter I of ICD10), 31 (34%) died

due to neoplastic conditions (Chapter II of ICD10), 15 (16%) due to respiratory disease (Chapter X of ICD10) and the remaining 15 (16%) had other causes of death cited.

The overall and CVD related mortality rates were 16.8 (95% CI 16.7 to 16.9) and 5.8 per 1000 patient years (95% CI 5.6 to 5.9), respectively. Of the subjects with a baseline NT-pro-BNP level <100 pg/ml, 25 (4%) died during the follow-up period. This accounted for 27% of all deaths. In subjects with NT-pro-BNP  $\geq$ 100 pg/ml, 67 (18%) died which accounted for 73% of all deaths in the cohort.

In a Cox proportional hazards model adjusted for age and gender (table 3, model A), NT-pro-BNP  $\geq$ 100 pg/ml was associated with all-cause (HR (95% CI) 2.36 (1.42 to 3.94)) and CVD mortality (HR (95% CI) 3.40 (1.28 to 9.03)). These associations remained when we adjusted for additional CVD risk factors (model B) or additional IP related factors (model C) (table 3). Our final adjusted model (model D) also demonstrated an independent association between NT-pro-BNP and all-cause mortality (HR (95% CI) 2.15 (1.19 to 3.88)). The association between NT-pro-BNP and CVD mortality was no longer significant in the model (model D) that included both CVD and IP related factors (HR (95% CI) 2.18 (0.76 to 6.27)) (table 3).

We examined the additional prognostic value of NT-pro-BNP on mortality. The model predicting overall mortality using only age and gender had a C-index of 0.787 which increased to 0.796 with the addition of standard CVD risk parameters; this increase was not significant (model A vs B  $p=0.15$ ). The addition of NT-pro-BNP to standard CVD risk factors increased the C-index to 0.812 which was a statistically significant increase from the model including CVD risk factors (model B vs B plus NT-pro-BNP  $p=0.0014$ ). The model predicting CVD mortality using only age and gender had a C-index of 0.817 which increased to 0.831 with the addition of standard CVD risk

## Clinical and epidemiological research

**Table 3** Raised NT-pro-BNP ( $\geq 100$  pg/ml) level associations with increased all-cause and cardiovascular mortality in early inflammatory polyarthritis

Model	All-cause mortality HR (95% CI)	CVD mortality HR (95% CI)
Unadjusted	4.58 (2.89 to 7.25)	7.09 (2.91 to 17.30)
A		
Age and gender adjusted	2.36 (1.42 to 3.94)	3.40 (1.28 to 9.03)
B		
Age, gender, hypertension, BMI, diabetes, smoking status, prior CVD	2.32 (1.36 to 3.96)	2.71 (1.00 to 7.37)
C		
Age, gender, RF and/or ACPA positive, HAQ score, tender joint count, CRP	2.22 (1.28 to 3.86)	2.76 (1.00 to 7.63)
D		
Fully adjusted model*	2.15 (1.19 to 3.88)	2.18 (0.76 to 6.27)

\*Fully adjusted model included age at recruitment, gender, hypertension, BMI, diabetes, smoking status, prior CVD, RF and/or ACPA status, HAQ score, tender joint count and CRP. ACPA, antibodies to citrullinated protein antigens; BMI, body mass index; CRP, C reactive protein; CVD, cardiovascular disease; HAQ, Health Assessment Questionnaire; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; RF, rheumatoid factor.

parameters; this increase was not significant (model A vs B  $p=0.17$ ). The addition of NT-pro-BNP to model B of standard CVD risk factors increased the C-index to 0.848 which was a statistically significant increase from the model including CVD risk factors alone (model B vs B plus NT-pro-BNP  $p=0.04$ ).

#### Additional sensitivity analyses

The association of raised NT-pro-BNP with all-cause mortality remained in an analysis restricted to patients who were seronegative for RF and ACPA ( $n=339$ ) (HR (95% CI) 6.36 (3.01 to 13.44), fully adjusted HR (95% CI) 2.94 (1.04 to 8.23)) and in those patients with no prior CVD ( $n=721$ ) (HR (95% CI) 3.97 (2.38 to 6.62), fully adjusted HR (95% CI) 1.93 (1.00 to 3.72)), respectively. In these smaller subsets, the association with CVD mortality was not statistically significant (data on file).

#### DISCUSSION

In a large inception cohort of patients with early IP we found that NT-pro-BNP was associated with both a prior history of CVD and also with higher CRP and HAQ scores. More importantly, NT-pro-BNP was independently associated with all-cause and CVD mortality even after adjustment for conventional CVD risk factors. As far as we are aware this is the first study to address these questions in early IP and therefore our results are of importance in further examining the value of NT-pro-BNP measurement in stratifying IP patients for future mortality risk from the outset of their disease.

A number of previous studies have shown that NT-pro-BNP concentrations are elevated in RA compared with population controls.<sup>26 27</sup> Some of these have also noted an association between inflammation and NT-pro-BNP levels.<sup>25–27</sup> Inflammation has been proposed as an important contributor to the pathogenesis of cardiac dysfunction in RA patients. Maradit-Kremers *et al*<sup>24</sup> showed that in a study of 575 patients with RA, episodes of heart failure were often temporally associated with elevations in erythrocyte sedimentation rate. They hypothesised that inflammation directly compromised left ventricular function, akin to the model of myocardial depression and dysfunction seen in acute sepsis.<sup>35</sup> Our data support this paradigm as raised NT-pro-BNP has previously been associated with IL-6 levels in other studies<sup>26</sup> and in our population was independently associated with higher CRP. The association with HAQ scores was also significant in our multivariate analysis. In early IP, HAQ scores tend to be closely associated with inflammatory disease activity.<sup>36</sup> Disability and functional status may also be associated with a more sedentary lifestyle and may

also in part reflect unmeasured ‘frailty’ or other comorbidities which may add to the association between HAQ and NT-pro-BNP that we observed.

No prior studies have reported on the association of NT-pro-BNP and BMI in early arthritis. We found log NT-pro-BNP levels to be associated with lower BMI in early IP which accords with the results of Wang *et al* who found that in the Framingham cohort individuals with a high BMI had low NT-pro-BNP levels.<sup>37</sup> This association is broadly in agreement with recent data showing that genetic predisposition to slightly elevated circulating NT-pro-BNP is protective of diabetes.<sup>38</sup> In the patients who had a more detailed cardiovascular assessment, we found that log NT-pro-BNP was not significantly associated with atherosclerotic plaque or carotid IMT after age and gender adjustment. This is also in agreement with data in patients with diabetes.<sup>39</sup> This may be partially because carotid IMT is a relatively weak surrogate of CVD risk, although plaque presence may be a more credible marker of vascular risk.<sup>40 41</sup> Recent evidence indicates that NT-pro-BNP predicts risk of CVD even in middle-aged men without minor ECG abnormalities and thus the association of NT-pro-BNP with CVD appears to extend beyond abnormalities in cardiac function and atherosclerosis.<sup>42</sup>

From a prognostic viewpoint, our raw data demonstrated a much higher mortality rate among patients with elevated NT-pro-BNP at baseline; indeed, 73% of all deaths over a median follow-up of 5.5 (3.7–7.7) years were in this subset. Following adjustment for age, sex and IP related covariates or CVD related covariates this association was attenuated but remained statistically significant. The lack of association with CVD mortality after full adjustment may reflect the smaller numbers in this subgroup relative to the number of dependent variables we adjusted for. Overall our study had 69% power to detect a doubling of overall mortality and 19% power to detect a doubling of CVD mortality. Nevertheless, our observations have prognostic relevance as NT-pro-BNP assessment in early IP may identify patients with a particularly high risk of future mortality and in particular cardiovascular death. Our study extends and confirms the previous study by Provan *et al*<sup>29</sup> who studied 182 patients from the EURIDISS cohort with 5–9-year disease duration. In this cohort, NT-pro-BNP was independently associated with all-cause mortality over a 10-year follow-up period. Previous work has noted that the anti-TNF agent adalimumab is associated with a reduction in NT-pro-BNP concentrations and may also improve pulse pressure in RA.<sup>30</sup> It will be interesting to determine whether there will be added value in using either

anti-TNF drugs or IL-6 blockade in this particular subset of early RA patients not only to improve inflammation but improve cardiac dysfunction.

This study has a number of strengths. It is a prospective study of a large well described inception cohort with comprehensive data on mortality. The clinical and laboratory data collections were standardised and well established. There are some limitations that are also worth considering. A limitation of the study is that we do not have available to us a large control group of healthy individuals drawn from the same population who have prospective data in which to examine the influence of NT-pro-BNP on future mortality. Despite this, the findings in our early IP cohort can be compared with that in similar studies in the general population. In agreement with our study population studies have shown that NT-pro-BNP is associated with worse CVD outcomes. A previous study from a Dutch population found that 16.6% of individuals had raised NT-pro-BNP compared with 39% in our study. As expected the mortality in the general population was lower than in our study.<sup>4</sup> The NT-pro-BNP levels were measured on serum samples collected at baseline recruitment into NOAR. We have only included subjects with  $\leq 24$  months of symptom duration but nevertheless it is possible that subjects had subclinical inflammatory disease for a longer, albeit unspecified, period of time prior to being recruited. It is also possible that some patients will have received anti-inflammatory treatments which may have altered their NT-pro-BNP levels, although raised NT-pro-BNP levels were not associated with the duration of symptoms or disease modifying antirheumatic drug and/or steroid use. Another potential limitation of the study was that certain comorbid conditions which may influence NT-pro-BNP levels were not included and adjusted for in our analysis. The major variables that are known to affect NT-pro-BNP levels such as age, gender, diabetes, prior CVD, hypertension, smoking status and BMI were however included. Echocardiographic and electrocardiographic data were not available for this study; therefore, it is uncertain whether the increase in NT-pro-BNP is solely due to increased cardiac strain. Raised NT-pro-BNP levels are also associated with other variables contributing to mortality in patients with IP which we have not measured such as anaemia of chronic disease, renal impairment, impaired glucose tolerance and concomitant infection as found in patients affected with HIV.<sup>43</sup> Studies are also needed to investigate why these patients have apparently increased cardiac stress. Advanced atherosclerosis, both that which is clinically evident and subclinical cardiac disease, is arguably the principal contributor to the left ventricular strain. Crowson *et al*<sup>25</sup> noted that echocardiographic evidence of left ventricular diastolic dysfunction was not as strongly associated with raised NT-pro-BNP in RA than in population controls. Therefore, while the prognostic value of NT-pro-BNP in RA is clear from our study, further work is necessary to dissect the precise mechanisms by which this association is mediated. Certainly, our data suggest NT-pro-BNP may also capture some aspects of a chronic inflammatory state and in this way pick up vascular risk from both conventional and RA related risk pathways.

In conclusion, our results suggest NT-pro-BNP may have utility as part of a screening strategy to identify IP patients who may benefit from a more aggressive risk management programme for CVD. In particular, better understanding of the relationship between NT-pro-BNP and cardiac/vascular outcomes in patients with inflammatory disease may help achieve more targeted anti-inflammatory and cardioprotective approaches in this high risk population.

**Acknowledgements** NOAR is funded by Arthritis Research UK, Chesterfield, UK (Grant reference 17552). This report includes independent research supported by the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

**Contributors** HM, PW and SMMV contributed to the design, analysis, interpretation and drafting of the manuscript. DB contributed to the design and data collection and reviewed the draft of the manuscript. HE, TM and PW contributed to the design and data collection and drafting of the manuscript. ML, DPMS, NS and INB contributed to the concept, design, funding application, data collection, interpretation of data and drafting of the manuscript. All authors have reviewed and approved the final version of the manuscript.

**Funding** Arthritis Research UK, grant no. 17552.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Norfolk and Norwich REC.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

## REFERENCES

- Groening BA, Raymond I, Hildebrandt PR, *et al*. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population. *Heart* 2004;90:297–303.
- De Sutter J, De Bacquer D, Cuyppers S, *et al*. Plasma N-terminal pro-brain natriuretic peptide concentration predicts coronary events in men at work: a report from the BELSTRESS study. *Eur Heart J* 2005;26:2644–9.
- Embersson JR, Ng LL, Armitage J, *et al*. N-terminal Pro-B-type natriuretic peptide, vascular disease risk, and cholesterol reduction among 20,536 patients in the MRC/BHF heart protection study. *J Am Coll Cardiol* 2007;49:311–19.
- Linssen GC, Bakker SJ, Voors AA, *et al*. N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. *Eur Heart J* 2010;31:120–7.
- Wannamethee SG, Welsh P, Lowe GD, *et al*. N-terminal pro-brain natriuretic Peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. *J Am Coll Cardiol* 2011;58:56–64.
- Di AE, Chowdhury R, Sarwar N, *et al*. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation* 2009;120:2177–87.
- Maisel AS, Krishnaswamy P, Nowak RM, *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
- Davis M, Espiner E, Richards G, *et al*. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;343:440–4.
- McCullough PA, Nowak RM, McCord J, *et al*. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416–22.
- Dinh W, Futh R, Nickl W, *et al*. Elevated plasma levels of TNF-alpha and interleukin-6 in patients with diastolic dysfunction and glucose metabolism disorders. *Cardiovasc Diabetol* 2009;8:58.
- Leli C. Utility of brain natriuretic peptide as prognostic marker in community-acquired pneumonia and chronic obstructive pulmonary disease exacerbation patients presenting to the emergency department. *Infez Med* 2011;19:235–40.
- Perman SM, Chang AM, Hollander JE, *et al*. Relationship between B-type natriuretic peptide and adverse outcome in patients with clinical evidence of sepsis presenting to the emergency department. *Acad Emerg Med* 2011;18:219–22.
- Post F, Weilemann LS, Messow CM, *et al*. B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. *Crit Care Med* 2008;36:3030–7.
- Rivers EP, McCord J, Otero R, *et al*. Clinical utility of B-type natriuretic peptide in early severe sepsis and septic shock. *J Intensive Care Med* 2007;22:363–73.
- Ueda S, Nishio K, Akai Y, *et al*. Prognostic value of increased plasma levels of brain natriuretic peptide in patients with septic shock. *Shock* 2006;26:134–9.
- Maeder M, Fehr T, Rickli H, *et al*. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. *Chest* 2006;129:1349–66.

## Clinical and epidemiological research

- 17 Witthaut R, Busch C, Fraunberger P, *et al*. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. *Intensive Care Med* 2003;29:1696–702.
- 18 Goodson NJ, Wiles NJ, Lunt M, *et al*. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum* 2002;46:2010–19.
- 19 Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:871–83.
- 20 Maradit-Kremers H, Crowson CS, Nicola PJ, *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005;52:402–11.
- 21 Maradit-Kremers H, Nicola PJ, Crowson CS, *et al*. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52:722–32.
- 22 vina-Zubieta JA, Choi HK, Sadatsafavi M, *et al*. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis and Rheumatism* 2008;59:1690–7.
- 23 Meune C, Touze E, Trinquart L, *et al*. High risk of clinical cardiovascular events in rheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253–61.
- 24 Maradit-Kremers H, Nicola PJ, Crowson CS, *et al*. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:76–80.
- 25 Crowson CS, Myasoedova E, Myasoedova E, *et al*. Use of B-type natriuretic peptide as a screening tool for left ventricular diastolic dysfunction in rheumatoid arthritis patients without clinical cardiovascular disease. *Arthritis Care Res (Hoboken)* 2011;63:729–34.
- 26 Solus J, Chung CP, Oeser A, *et al*. Amino-terminal fragment of the prohormone brain-type natriuretic peptide in rheumatoid arthritis. *Arthritis Rheum* 2008;58:2662–9.
- 27 Armstrong DJ, Gardiner PV, O’Kane MJ. Rheumatoid arthritis patients with active disease and no history of cardiac pathology have higher Brain Natriuretic Peptide (BNP) levels than patients with inactive disease or healthy control subjects. *Ulster Med J* 2010;79:82–4.
- 28 Targonska-Stepniak B, Majdan M. Amino-terminal pro-brain natriuretic peptide as a prognostic marker in patients with rheumatoid arthritis. *Clin Rheumatol* 2011;30:61–9.
- 29 Provan S, Angel K, Semb AG, *et al*. NT-proBNP predicts mortality in patients with rheumatoid arthritis: results from 10-year follow-up of the EURIDISS study. *Ann Rheum Dis* 2010;69:1946–50.
- 30 Peters MJ, Welsh P, McInnes IB, *et al*. Tumour necrosis factor {alpha} blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. *Ann Rheum Dis* 2010;69:1281–5.
- 31 Ahmad Y, Shelmerdine J, Bodill H, *et al*. Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology (Oxford)* 2007;46:983–8.
- 32 Sidhu PS, Desai SR. A simple and reproducible method for assessing intimal-medial thickness of the common carotid artery. *Br J Radiol* 1997;70:85–9.
- 33 Li R, Duncan BB, Metcalf PA, *et al*. B-mode-detected carotid artery plaque in a general population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994;25:2377–83.
- 34 Bramer GR. International statistical classification of diseases and related health problems. Tenth revision. *World Health Stat Q* 1988;41:32–6.
- 35 Kumar A, Thota V, Dee L, *et al*. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. *J Exp Med* 1996;3:949–58.
- 36 Devlin J, Gough A, Huissoon A, *et al*. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. *J Rheumatol* 1997;1:9–13.
- 37 Wang TJ, Wang TJ, Larson MG, *et al*. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109:594–600.
- 38 Pfister R, Sharp S, Luben R, *et al*. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med* 2011;8:e1001112.
- 39 Reinhard H, Reinhard H, Wiinberg N, *et al*. NT-proBNP levels, atherosclerosis and vascular function in asymptomatic type 2 diabetic patients with microalbuminuria: peripheral reactive hyperaemia index but not NT-proBNP is an independent predictor of coronary atherosclerosis. *Cardiovasc Diabetol* 2011;10:71.
- 40 Lorenz MW, Polak JF, Kavousi M, *et al*. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012;379:2053–62.
- 41 Den Ruijter HM, Peters SA, Anderson TJ, *et al*. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;308:796–803.
- 42 Welsh P, Welsh P, Doolin O, *et al*. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J* 2012;Aug:1–8.
- 43 Mansoor A, Althoff K, Gange S, *et al*. Elevated NT-pro-BNP levels are associated with comorbidities among HIV-infected women. *AIDS Res Hum Retroviruses* 2009;25:997–1004.





## N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: results from the Norfolk Arthritis Registry (NOAR)

Hoda Mirjafari, Paul Welsh, Suzanne M M Verstappen, et al.

*Ann Rheum Dis* 2014 73: 684-690 originally published online March 19, 2013

doi: 10.1136/annrheumdis-2012-202848

---

Updated information and services can be found at:

<http://ard.bmj.com/content/73/4/684.full.html>

---

*These include:*

- |                               |  |
|-------------------------------|--|
| <b>References</b>             | This article cites 43 articles, 13 of which can be accessed free at:<br><a href="http://ard.bmj.com/content/73/4/684.full.html#ref-list-1">http://ard.bmj.com/content/73/4/684.full.html#ref-list-1</a>  |
| <b>Open Access</b>            | This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <a href="http://creativecommons.org/licenses/by-nc/3.0/">http://creativecommons.org/licenses/by-nc/3.0/</a> |
| <b>Email alerting service</b> | Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.   |
- 

### Topic Collections

Articles on similar topics can be found in the following collections

- [Open access](#) (390 articles)
  - [Epidemiology](#) (1138 articles)
  - [Degenerative joint disease](#) (3860 articles)
  - [Musculoskeletal syndromes](#) (4133 articles)
- 

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>

## Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>