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Plasma N-terminal pro-brain natriuretic peptide concentration predicts coronary events in men at work: a report from the BELSTRESS study

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Aims Increased levels of neurohormonal markers, including the N-terminal fragment of pro-brain natriuretic peptide (NT-pro-BNP), have been shown to be of prognostic significance in patients with heart failure or coronary heart disease (CHD). The aim of this study was to study the predictive value of NT-pro-BNP for coronary events in a middle-aged population of men at work.

Methods and results A nested case–control study was performed in a large cohort of over 10 000 men at work (aged 35–59) after a median follow-up of 2.66 years. In total, 66 individuals who developed coronary events were matched on a 3-to-1 basis to 198 controls free of coronary events during follow-up. Besides clinical characteristics and conventional cardiac risk factors, NT-pro-BNP (electrochemiluminiscence assay, Roche diagnostics) and serum creatinine levels were determined. In univariable analysis, cases were more frequently current smokers and diabetics, had more frequently a history of CHD, and had higher levels of total cholesterol and systolic blood pressure (SBP), and lower levels of HDL cholesterol. A highly significant difference ($P < 0.0001$) was noted for NT-pro-BNP levels between cases (median 48.5 pg/mL, interquartile range 26.4–116.6 pg/mL) and controls (30.0 pg/mL, 19.5–47.6 pg/mL). In multivariable conditional logistic regression analysis, NT-pro-BNP remained strongly associated with risk for coronary events [third vs. first tertile, odds ratio (95% CI) 3.24 (1.18–8.85)], independent of body mass index, smoking, diabetes, SBP, total and HDL cholesterol, creatinine, and previous CHD.

Conclusion NT-pro-BNP is a strong predictor of coronary events in men at work after a relatively short period, even after adjustment for conventional risk factors.

Introduction

Increased levels of neurohormonal markers, including brain natriuretic peptide (BNP) and the inactive N-terminal pro-BNP (NT-pro-BNP), have been shown to be of prognostic significance in patients with heart failure or coronary heart disease (CHD).[1–6] In addition, in the general population, it has been shown that levels of BNP and NT-pro-BNP are predictive for cardiac events, although most of these studies have focused on elderly subjects.[7–10] Recently, data from the Framingham Heart Study showed that BNP levels were strong predictors of cardiac morbidity and mortality even after adjustment for conventional cardiac risk factors and even when BNP levels were below the threshold used to identify patients with heart failure.[11] In addition, Kistorp *et al.*[12] reported that NT-pro-BNP provided prognostic information on mortality and first major cardiovascular events beyond traditional risk factors in a population-based prospective study of 626 participants aged 50–89. The prognostic value of NT-pro-BNP in younger populations, especially in middle-aged individuals at work, is, however, unknown.

BNP and NT-pro-BNP are predominantly released from ventricular myocardium as a response to ventricular dilatation and pressure overload.[13,14] It has, however, also been suggested that levels of BNP and NT-pro-BNP may not only reflect increased left ventricular wall stress but also result directly from myocardial ischaemia.[15–17] The relationship between NT-pro-BNP levels and subsequent coronary events in the general population has, however, not been studied in detail.

Therefore, we aimed to investigate the relationship between NT-pro-BNP levels and the occurrence of coronary events in a middle-aged population of men at work. We used a nested case–control study design in a large

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cohort of over 10 000 men at work (aged 35–59) who were included in the Belgian Job Stress Project (BELSTRESS).[18]

Methods

BELSTRESS study cohort

The BELSTRESS is a multi-disciplinary large-scale study focusing on the independent association of perceived job stress with health[18] and is part of the international JACE study (Job stress, Absenteeism and Coronary heart disease-European co-operative prospective study).[19] For a detailed description of the study protocol and study participants, we refer to previous publications.[18–21] In brief, the sample consists of middle-aged men and women at work in 25 large industries or administrations across Belgium. All 44 530 employees aged 35–59 received a personal invitation letter including a reply form and a return envelope. Invitation letters were distributed internally under the supervision of the occupational health service. The self-administered questionnaires were then distributed among the interested participants together with a personal invitation for the medical screening at the workplace. Participants were asked to complete questionnaires at home and bring them to the medical examination which took place at least a week later. There were no formal exclusion criteria. A total of 21 419 participants (16 329 men and 5090 women) complied with the study (participation rate 48%). Data collection was conducted in the period between 1994 and 1998.

Clinical examination and laboratory analysis

The clinical examination took place in the medical office at the workplace and was done in accordance with a manual of operations by centrally trained paramedics either from the occupational health service or from the research centre. Blood pressure was calculated as the average of two readings obtained by sphygmomanometry in a sitting position with a 5-min interval. Current smoking was considered as the current consumption of cigarettes, cigars, or pipes. Body mass index (BMI) was calculated as weight (in kilograms) divided by the squared height (in metres). Prevalent CHD at the clinical examination was defined as a history of myocardial infarction or angina pectoris according to the Rose questionnaire or a previous hospitalization for coronary angioplasty or bypass surgery or ischaemic-like abnormalities on the resting ECG [consisting of Q/QS patterns (Minnesota codes I_{1-3}) or ST segment depression (codes IV_{1-3}) or T-wave inversion (codes V_{1-3}) or complete left bundle branch block (code VII_1)].[22] Apart from the ECG information, all this information was self-reported in the medical history questionnaire but verified with the paramedics during clinical examination.

A non-fasting blood sample was taken at the worksite at the time of initial clinical examination and shipped to a central laboratory. Total cholesterol was determined using the CHOD-PAP High Performance Method (Boehringer) on a Hitachi 747 analyser, whereas HDL cholesterol was determined using the heparin–manganese precipitation method.[20,21] After initial lipid determinations, blood samples were frozen at -80°C for future analysis.

Follow-up of the BELSTRESS cohort

Regarding the low number of events expected among women, female employees did not participate in this short-term prospective study. The male subcohort was followed up until 31 December 1999 for incident clinical manifest coronary events. Because of organizational reasons, follow-up information was not gathered in seven of the smaller companies resulting in 14 987 male employees for inclusion for follow-up. Incident coronary events were defined as the occurrence of an acute myocardial infarction (AMI), unstable angina, and hospitalizations for coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). The incidence of CHD was carefully monitored according to the following procedure. For sickness absence spells of at least 3 weeks reported to the human resources department, the occupational health service in close collaboration with the co-ordinating research centre contacted the person's treating physician or hospital to check for a possible CHD diagnosis. In the case of a suspect coronary event, maximum efforts were put in accurately ascertaining the clinical diagnosis by following a formal diagnostic algorithm of gathering information on cardiac enzymes, electrocardiographic findings, and necropsy findings. After a median follow-up of 2.66 years, 82 subjects had developed coronary events. For 66 of these subjects, blood samples, taken at the initial visit, were still available to determine NT-pro-BNP and creatinine levels. These 66 subjects formed the cases and they were matched on a 3-to-1 basis to 198 controls free of coronary events during follow-up. Because controls were selected as subjects not having experienced a CHD event at the end of the study period, by default, controls were matched to cases for follow-up because at the time a case experienced an event, the control was free of an event. Cases and controls were matched for age. An exact match in age (within 1 year) was required. If more than three matches were found, the eligible controls were selected randomly. Given the large data pool of eligible controls, matched controls were found for all the cases. Because all studied individuals were men, no gender matching was performed.

The exclusion of 16 patients with missing blood samples probably did not introduce significant bias because the data availability was a random process which was caused by loss of blood samples that was not dependent on the status or progression of CHD. Furthermore, median age was comparable between the included cases and the missing cases (50 vs. 49 years, $P = 0.37$) as well as the prevalence of CHD (31.8 vs. 21.4%, $P = 0.75$). NT-pro-BNP levels were determined with an electrochemiluminiscence assay on a Modular E analyser (Roche diagnostics) and serum creatinine was determined using a rate-blanked compensated Jaffé method. The lower limit of detection was 5 pg/mL for the assay of NT-pro-BNP with an average interassay coefficient of variation of 3%. For data analysis, tertile cut points were pre-specified and were based on the distribution of NT-pro-BNP in the combined sample of cases and controls. Given the number of events, quartile or quintile analysis was expected to be inappropriate.

Statistical methods

Data are presented as median (interquartile range) or percentage (total number). Comparison of the characteristics between cases and matched controls was done by the Kruskal–Wallis test or Fisher's exact test. Spearman rank correlation coefficients were used to evaluate the association between NT-pro-BNP levels and quantitative characteristics among control subjects. NT-pro-BNP levels were compared between levels of categorical variables after age-adjustment according to analysis of covariance. To meet the model assumptions, NT-pro-BNP levels were logarithmically transformed in the latter analysis. Conditional logistic regression for matched sets was used for the multivariable analysis of the association between NT-pro-BNP and coronary events. Potential confounders chosen as covariates in multivariable modelling were smoking, diabetes, systolic blood pressure (SBP), total and HDL cholesterol, serum creatinine, prevalent CHD, and BMI all being established coronary risk factors which were indeed less favourable in our case series compared with the control subjects (*Table 1*). For continuous variables, the assumption of linearity was *a priori* checked by visual analysis of CHD odds after categorization according to their tertiles. An additional multivariable analysis was performed using NT-pro-BNP as a continuous variable to further strengthen the results and to rule out inflation of the type I error. All statistical analyses were performed using SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.). A two-sided *P*-value less than 0.05 was considered as indicating statistical significance.

Table 1 Characteristics of the cases and matched controls

	Cases ($n = 66$)	Controls ($n = 198$)	Significant *P*-values
Age (years)	50 (47–53)	50 (47–53)	0.97
BMI (kg/m^2)	27.2 (25.8–29.4)	26.8 (24.8–29.2)	0.10
Current smoking (%)	50.0% (33/66)	33.8% (67/198)	0.03
Former smoking (%)	36.4% (24/66)	35.9% (71/198)	0.94
Diabetes (%)	12.1% (8/66)	4.6% (9/198)	0.04
Prevalent CHD (%)	31.8% (21/66)	4.6% (9/198)	<0.0001
Low physical activity (%)	30.5% (18/59)	27.1% (51/198)	0.62
Alcohol intake (g/day)	17.1 (5.1–41.1)	21.9 (6.7–43.1)	0.64
SBP (mmHg)	135 (128–148)	131 (123–143)	0.06
Heart rate (b.p.m.)	70 (62–80)	70 (64–78)	0.81
Antihypertensive drug intake (%)	15.2% (10/66)	13.2% (26/197)	0.68
Total cholesterol (mg/dL)	240 (221–271)	228 (200–261)	0.02
HDL cholesterol (mg/dL)	42 (37–48)	48 (40–55)	0.0003
Lipid-lowering drug intake (%)	10.6% (7/66)	6.1% (12/198)	0.27
Serum creatinine (mg/dL)	1.26 (1.12–1.39)	1.22 (1.11–1.33)	0.36
NT-pro-BNP (pg/mL)	48.5 (26.4–116.6)	30.0 (19.5–47.6)	<0.0001

Results

Baseline characteristics

Median follow-up was 2.66 years (interquartile 2.12–3.69 years). During this follow-up period, 66 coronary events were registered including 36 cases of AMI (13 fatal cases), 22 cases of unstable angina, seven cases of PTCA, and one case of CABG. These 66 cases were matched on a 3-to-1 basis to 198 controls free of coronary events during follow-up.

Table 1 provides the baseline characteristics of the cases and controls. In total, 30 individuals had evidence for existing CHD at baseline: previous history of myocardial infarction ($n = 17$), previous coronary angioplasty or bypass surgery ($n = 1$), angina pectoris according tot the Rose questionnaire ($n = 2$), or ischaemic-like abnormalities on the resting ECG ($n = 10$). The prevalence of CHD at baseline was higher in the cases than in the controls. Regarding risk factors, cases were more frequently diabetics and had a higher blood pressure and total cholesterol levels as well as lower HDL cholesterol levels. Use of antihypertensive and lipid-lowering drugs was similar in both groups.

Association between NT-pro-BNP levels and other quantitative characteristics among control subjects

In 198 control subjects, NT-pro-BNP was only significantly correlated to age (r=0.14, P=0.04) but not to BMI, SBP or diastolic blood pressure, heart rate, or lipid levels. In addition, there was no significant correlation with serum creatinine ($r = -0.04$). *Table 2* shows the levels of NT-pro-BNP and serum creatinine according to smoking status, physical activity, diabetes, and treatment with antihypertensive or lipid lowering drugs. No significant differences were noted for NT-pro-BNP levels after age-adjustment.

Association between NT-pro-BNP levels and coronary events

As can be noted from *Table 1*, cases had significantly higher levels of NT-pro-BNP compared with controls, whereas serum creatinine levels were comparable. *Table 3* shows the association between NT-pro-BNP levels, divided into tertiles, and coronary events. The highest tertile (NT-pro-BNP levels >45.6 pg/mL) was associated with a significantly elevated matched odds ratio of 3.77 (95% CI 1.74–8.20). *Table 4* shows the results of the multivariable conditional logistic regression analysis for the association between NT-pro-BNP levels and coronary events. In this analysis, NT-pro-BNP remained associated with the risk for coronary events [third vs. first tertile odds ratio (95% CI) 3.24 (1.18–8.85)], independent of BMI, smoking, diabetes, SBP, total and HDL cholesterol, creatinine, and prevalent CHD. Additional analysis modelling NT-pro-BNP as a continuous variable (after log transformation of NT-pro-BNP) further confirmed the strength of the positive association between NT-pro-BNP and coronary events (matched OR 2.49, 95% CI 1.43–4.33, $P = 0.001$).

When the analysis was restricted to subjects with no prevalent CHD at baseline, the matched odds ratio for the highest tertile of NT-pro-BNP vs. the lowest tertile remained similar (OR=3.15, 95% CI 0.94–10.48, $P = 0.07$) in multivariable analysis.

Discussion

The main finding of this study is that NT-pro-BNP levels are strong predictors of coronary events in men at work, even after adjustment for conventional risk factors and the presence of CHD. NT-pro-BNP levels have shown to have a prognostic value in patients with acute coronary syndromes,[1,2] heart failure,[3,4] and even in stable coronary artery disease patients who are at 'intermediate' risk.[5,6] In the general population, NT-pro-BNP levels are also related to cardiovascular morbidity and mortality, but studies have mainly been restricted to elderly patients.[10,12] Recently, Kistorp *et al.*[12] reported that NT-pro-BNP predicted mortality and first major cardiovascular events in a population-based prospective study of individuals aged 50–89 from a community in Copenhagen, Denmark. Importantly, NT-pro-BNP remained a prognostic risk factor after adjustment for cardiovascular risk factors and was a stronger risk biomarker for cardiovascular disease and

Table 2 Association between NT-pro-BNP and serum creatinine levels and qualitative characteristics among control subjects

	NT-pro-BNP (pg/mL)	Serum creatinine (mg/dL)
Smoking		
Never	28.9	1.28
Former	30.0	1.21
Current	31.8	1.16
Significance	$P = 0.71$	$P = 0.01$
Diabetes		
No	30.0	1.23
Yes	31.6	1.15
Significance	$P = 0.13$	$P = 0.43$
Physical activity		
Low	28.9	1.22
<Low	31.6	1.24
Significance	$P = 0.34$	$P = 0.86$
Antihypertensive drugs		
No	29.4	1.21
Yes	33.2	1.26
Significance	$P = 0.30$	$P = 0.34$
Lipid-lowering drugs		
No	29.3	1.22
Yes	37.0	1.36
Significance	$P = 0.62$	$P = 0.09$

Data are presented as median values. Significance levels are given after age-adjustment.

Table 3 Association between NT-pro-BNP levels and coronary events

	Cases/ controls	Matched odds ratio (95% CI)
NT-pro-BNP		
Tertile 1 (<25.5 pg/mL)	16/72	1
Tertile 2 (25.5–45.6 pg/mL)	14/74	0.92 (0.41–2.05)
Tertile 3 (>45.6 pg/ml)	36/52	3.77 (1.74–8.20)

death than C-reactive protein. Similar to NT-pro-BNP, the prognostic value of BNP has also been documented in several clinical entities.[7–9] In the general population, Wang *et al.*[11] reported that BNP was a strong predictor of morbidity and mortality even when BNP levels were below the threshold of 100 pg/mL normally used to identify patients with heart failure. Similar to our study, the prognostic value of BNP levels remained after adjusted analyses for age, sex, the presence or absence of hypertension and diabetes, the ratio of total to HDL cholesterol, the BMI, the serum creatinine level, and smoking status. An important distinction between the present study and the studies by Kistorp *et al.*[12] and Wang *et al.*[11] is its focus on CHD events. We report a significant association between NT-pro-BNP levels and coronary events, whereas the other studies in the general population have not documented this association. This could be due to differences in study populations (focused on younger men in the present study), length of follow-up (shorter for the present study), choice of peptide (NT-pro-BNP in the present study), or other factors. For instance, the study by Kistorp *et al.*[12] only had 12 CHD events, leaving it underpowered to assess this specific outcome.

Several possibilities could explain our findings. First, levels of BNP and NT-pro-BNP are related to increased ventricular strain due to an increase of filling pressure and ventricular volume.[23–25] Although we did not perform echocardiography in this epidemiological study, the contribution of overt increases of ventricular strain was probably of minor importance in our population because all individuals were at work and the prognostic value of NT-pro-BNP levels remained after adjustment for prevalent coronary artery disease or restriction of the analysis to individuals without prevalent coronary artery disease. More subtle increases of ventricular strain due to increases of left ventricular mass could, however, have contributed to the elevated NT-pro-BNP levels because echocardiographic estimated left ventricular mass correlates with natriuretic peptide levels, even after adjustment for other cardiovascular risk factors.[26] Therefore, increases of ventricular strain and filling pressures could have contributed to higher myocardial oxygen demand and subsequent coronary events in our study population. Clearly, more studies incorporating echocardiography are needed to unravel the contribution of subtle abnormal loading conditions (including pressure and volume overload) to NT-pro-BNP levels in the younger, general population.

A second possible explanation could be that higher NT-pro-BNP levels are an indicator of ongoing myocardial ischaemia. Already in 1995, Hama *et al.*[27] showed a rapid induction of ventricular BNP gene expression in rats with AMI. Importantly, the BNP concentrations and BNP mRNA were increased in the non-infarcted region as well as in the infarcted region of the left ventricle. Goetze *et al.*[16] showed that myocardial ischaemia *per se* can cause an increase in plasma BNP and NT-pro-BNP concentrations in patients with coronary artery disease without overt heart failure. This mechanism most likely reflects an increased cardiac BNP gene expression in the ischaemic left ventricle, because plasma BNP and NT-pro-BNP concentrations were closely associated with ventricular BNP mRNA expression measured in biopsies from coronary artery disease patients undergoing CABG. Other studies in humans showed that circulating BNP and NT-pro-BNP increase after percutaneous coronary intervention, even when the intraventricular filling pressures remain unchanged[28] and that BNP levels increase after exercise in patients with known angina with a relationship between the degree of BNP elevation and the size of the ischaemic territory.[15] More recently, Bibbins-Domingo *et al.*[17] reported that in outpatients with stable coronary artery disease, elevated levels of BNP were associated with inducible ischaemia even after adjustment for measures of systolic and diastolic dysfunction. This association suggests not only a potential explanation for the increased risk of future coronary events associated with BNP elevations after acute coronary syndromes, but may also be part of the explanation of the association we found between elevated NT-pro-BNP levels and future coronary events in our study. Interestingly, in a recent study by Kragelund *et al.*[5] in patients with stable CHD, the increased risk of death associated with elevated NT-pro-BNP was independent of both left ventricular ejection fraction and left ventricular end-diastolic pressure, thus providing further evidence in support of the hypothesis that ischaemia

Table 4 Multivariable analysis of the association between NT-pro-BNP and coronary events: results of conditional logistic regression

	β (SE)	*P*-values	Matched OR (95% CI)
NT-pro-BNP			
T2 vs. T1	0.275 (0.524)	0.60	1.32 (0.47–3.68)
T3 vs. T1	1.175 (0.513)	0.02	3.24 (1.18–8.85)
BMI (kg/m^2)	0.078 (0.049)	0.11	1.08 (0.98–1.19)
Current smoking (yes vs. no)	1.059 (0.386)	0.006	2.88 (1.35–6.15)
Diabetes (yes vs. no)	0.382 (0.730)	0.60	1.46 (0.35–6.13)
SBP (10 mmHg)	0.141 (0.114)	0.22	1.15 (0.92–1.44)
Total cholesterol (40 mg/dL)	0.254 (0.150)	0.09	1.29 (0.96–1.73)
HDL Cholesterol (10 mg/dL)	−0.471 (0.178)	0.008	0.62 (0.44–0.88)
Serum creatinine (0.1 mg/dL)	0.149 (0.118)	0.21	1.16 (0.92–1.46)
Prevalent CHD (yes vs. no)	2.213 (0.636)	0.0005	9.14 (2.63–31.80)

directly promotes the release of NT-pro-BNP, in a manner that is independent of left ventricular wall stress.

Finally, the natriuretic peptides have a fundamental role in cardiovascular functioning and remodelling with varying documented effects ranging from endothelial regeneration,[29] increase of the effects of nitric oxide,[30] inhibition of oxidized LDL-induced migration of human coronary artery smooth muscle cells,[31] and augmentation of the parasympathetic tone.[32] Therefore, elevated NT-pro-BNP levels in patients without coronary artery disease could reflect an up-regulation of the natriuretic peptide axis in the setting of subclinical vascular disease and could therefore explain the increased risk for coronary events.

Our study potentially widens the spectrum of clinical usefulness of NT-pro-BNP as a prognostic marker because we studied a younger population of men at work. We report odds ratios of 3.15–3.77 which are comparable to those reported in other studies on older individuals in the general population. For instance, Kistorp *et al.*[12] reported adjusted hazard ratios for NT-pro-BNP levels of 1.96 for mortality and 3.24 for first major cardiovascular events. Similarly, Wang *et al.*[11] reported adjusted hazard ratios for BNP levels of 1.62 for mortality and 1.76 for first major cardiovascular events in the Framingham Offspring Study. However, in order to be useful for daily clinical work, further studies will be needed in larger populations of young individuals to define clinical useful cut-off values.

Study limitations

The lack of echocardiographic data made matching or adjustment for left ventricular systolic dysfunction or left ventricular mass impossible. However, most of our study individuals had no previous cardiac history and NT-pro-BNP levels remained predictive of coronary events after adjustment for prevalent CHD. In addition, in the previously mentioned study by Kistorp *et al.*,[12] measurements of NT-pro-BNP provided prognostic information on mortality and first major cardiovascular events after adjustment for left ventricular systolic dysfunction (left ventricular ejection fraction $<$50%) and left ventricular hypertrophy. Of note, the NT-pro-BNP levels in that study (lowest tertile $<$181.7 pg/mL, highest tertile $>$411.1 pg/mL) were higher when compared with the values in the present study (median value for the cases 48.5 pg/mL and median value for the controls 30 pg/mL). We studied only men during a relatively short follow-up period. Clearly, further studies are needed in the general population to confirm our findings, especially in women and during a longer-term follow-up. Finally, our study was not designed or powered to evaluate a threshold effect. Again, larger studies with longer-term follow-up are therefore needed.

Conclusions

This prospective study indicates that NT-pro-BNP levels are predictive of coronary events in men at work, even after adjustment for conventional risk factors. Therefore, this parameter may aid in the early detection of cardiovascular disease. However, additional studies are needed to confirm our results and to determine the value of natriuretic peptides when compared with other biomarkers (e.g. C-reactive protein) or measurements of atherosclerosis burden (e.g. intima-media thickness measurements) to risk stratify asymptomatic persons.

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