Longitudinal relationship between B-type natriuretic peptide and anxiety in coronary heart disease patients with depression

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Abstract

Objective

Patients with coronary heart disease (CHD) suffer from physical limitations, but also from psychological distress. Natriuretic peptides may be involved in the neurobiological processes that modulate psychological adaptation, as they are increased in heart disease and seem to have an anxiolytic-like function. Longitudinal data on this association are scarce.

Methods

To assess the relationship between NT-proBNP and anxiety (Hospital Anxiety and Depression Scale (HADS)), we used secondary data from a multicenter trial from baseline to 24 months. Patients (N = 308, 80.8% male, mean age 60.1 years) had stable CHD and moderate levels of depression (HADS ≥ 8).

Results

Multiple linear regression adjusted for age, sex, BMI, and physical functioning, revealed NT-proBNP as a significant predictor for anxiety at baseline, 1, 6, 12, 18, and 24 months (all $p < .05$). Linear mixed model analysis with the six anxiety measures as level-1 variable and NT-proBNP as fixed factor revealed a significant time*NT-proBNP interaction ($t(1535.99) = -2.669$, $p = .01$), as well as a significant time*NT-proBNP*sex interaction ($t(1535.99) = 3.277$, $p = .001$) when NT-proBNP was dichotomized into lowest vs. the three highest quartiles.

Conclusion

Our results indicate a stable negative association of baseline NT-proBNP with anxiety over two years. In men and women, different pathways modulating this relationship appear to be in effect. Female patients with very low NT-proBNP levels, despite their cardiac disease, show persistently higher levels of anxiety compared to women with higher levels of NT-proBNP and compared to men.

Trial name: Effects of a Psychotherapy Intervention in Depressed Patients With Coronary Artery Disease (SPIRR-CAD)

Trial registration: www.clinicaltrials.gov NCT00705965; www.isrctn.com ISRCTN76240576

Keywords: Anxiety, Coronary heart disease, Depression, Natriuretic peptide

1. Introduction

Patients with coronary heart disease (CHD) have an increased prevalence of psychological distress and mental disorders. It was reported that 20-50% of CHD patients show symptoms of depression and 20-30% fulfill the criteria for major depression (1-3). Since mental diseases, in particular depression, worsen the progression and prognosis of CHD, it is important to diagnose and treat these comorbidities appropriately. Studies reported that CHD patients with comorbid depression show higher numbers of complications and have a 1.6-2.5-fold increased risk of recurrent coronary events and all-cause death (1, 4). While depression is an established cardiac risk factor (5), the impact of anxiety is less clear, as there is conflicting evidence, whether anxiety increases or reduces the risk of mortality. In multiple studies anxiety was found to be independently associated with an increased risk of mortality in healthy individuals and CHD patients, while others reported no such association (6). In a study by Meyer and colleagues higher anxiety scores were associated with reduced mortality in 4864 patients undergoing an exercise test, including both CHD patients without myocardial infarction (MI) and patients without CHD (7).

The role of anxiety in cardiac disease may be confounded by the neurohumoral effects of natriuretic peptides. These peptides are typically elevated in heart failure and not only induce natriuresis, diuresis and vasodilation, but also attenuate the activity of the hypothalamic-pituitary-adrenal (HPA) axis and reduce sympathetic tone (8, 9). They might thus be regarded as antagonists to the sympatho-exitatory effect of anxiety. A-type natriuretic peptide (ANP) was found to exert anxiolytic effects in rodents and humans and has been negatively associated with anxiety in both cardiac patients and patients with alcohol withdrawal (10-14). While the effect of ANP on anxiety has been assessed in multiple studies, only few studies concerned the relationship between B-type natriuretic peptide (BNP) and psychological measures, even though BNP and its N-terminal prohormone (NT-proBNP) are frequently used as markers of illness severity and prognosis in patients with heart failure. Recent studies also suggest a role of BNP in emotion regulation, however these findings are inconsistent and longitudinal data are scarce.

In a recently published cross-sectional analysis, we found a link between high serum concentrations of NT-proBNP and lower levels of anxiety, depression and further measures of mental health (15). Patients with higher levels of NT-proBNP had a better overall mental health status, despite their somatic symptoms and worse physical functioning. To further assess the significance of NT-proBNP in the emotion regulation of CHD patients, we aimed at analyzing the longitudinal association of NT-proBNP and anxiety.

2. Methods

2.1. Study design

This is a post-hoc analysis of data from the Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD) trial to assess the longitudinal association of baseline NT-proBNP with anxiety. SPIRR-CAD, a randomized controlled trial, comparing usual care plus one individual information session to usual care plus a stepwise psychotherapy intervention, was conducted in ten tertiary care centers in Germany. The design of the study, recruitment path and main results are described in more detail elsewhere (16, 17). Briefly, the study tested whether a stepwise psychotherapy intervention added to usual care improves depressive symptoms more than a single information session. Primary endpoint was the change in depressive symptoms (Hospital Anxiety and Depression Scale (HADS)) from baseline to 18 months. The results showed that depressive symptoms decreased significantly in both groups with no significant difference between the groups or sexes. There was however a significant interaction with type D personality, i.e. patients with type D personality showed greater improvements in the stepwise psychotherapy group than in the usual care plus one information session group. The SPIRR-CAD trial further assessed multiple secondary endpoints, including additional biomarkers (high sensitivity C-reactive protein, cortisol, interleukin10, CD-40L, fibrinogen, creatinine, thyroid stimulating hormone). As these were not the focus of the present post-hoc analysis they were not analyzed. All ethics committees of the study sites approved the trial protocol and the study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice. All patients gave written informed consent before enrollment. The present analysis

used data at all time points of the SPIRR-CAD trial i.e., baseline (T0), 1 month (T1), 6 months (T2), 12 months (T2b), 18 months (T3) and 24 months (T4).

2.2. Participants

The main study enrolled 570 patients, 308 (54%) of whom had valid baseline NT-proBNP measures and HADS-anxiety measures at all six time points. Patients were eligible to participate when showing angiographic (coronary stenosis > 50%, as determined by a recent coronary angiogram) or clinical (history of percutaneous coronary intervention) evidence of CHD and a depression score ≥ 8 on the HADS-depression subscale. Inclusion in the study further required sufficient knowledge of the German language, and patients had to be free of symptoms of severe heart failure (left ventricular ejection fraction (LVEF) < 20% or New York Heart Association (NYHA) class IV) or other life-threatening mental or physical diseases at baseline. Due to ethical concerns, patients with severe depressive episodes (according to Structured Clinical Interview for DSM-IV (SCID)) had to be excluded from the study. Included patients were between 18 and 75 years of age.

2.3. Assessments

The patients' medical history, medication and sociodemographic data were collected from medical records and standardized interviews. Anxiety was assessed using the German version of the HADS questionnaire. This commonly used screening instrument has 14 items to assess symptoms of depression and anxiety in non-psychiatric hospitalized patients with seven items on each subscale (18, 19). It was developed to exclude symptoms that might equally arise from mental or somatic disease, such as fatigue. The scale shows good internal consistency and has been validated in numerous studies in CHD patients. According to the original publication, a cut-off of ≥ 8 should be used for each subscale to include all possible cases and have a low proportion of false negatives. A cut-off of ≥ 11should be used to only include cases of high symptomatology, thereby reducing the possibility of a misclassification of false positive cases (19).

To measure NT-proBNP levels, blood was drawn from a cubital vein in resting patients at baseline. The patients' blood was immediately centrifuged and stored at −80°C until analyzation at a central lab using electro-chemiluminescence immunoassay (Elecsys, Roche Diagnostics GmbH, Mannheim,

Germany). NT-proBNP is commonly used for research purposes and clinical diagnostics due to its longer half-live and higher stability as compared to BNP. Given that the precursor pro-BNP is hydrolytically cleaved in an equal stoichiometric ratio into the active BNP molecule and its biologically inactive N-terminal fragment, the NT-proBNP analyte can be used as a valid proxy for serum BNP concentration.

2.4. Data analysis

All raw data were tested for normality and log-transformed to approach normal distribution if they were severely skewed, such as laboratory measures of NT-proBNP. Pearson's correlations were calculated to characterize the sample in terms of sociodemographic data. To control for confounding factors, multiple regression models with baseline NT-proBNP as independent and anxiety as dependent variables were calculated adjusting for sex, age, BMI, and physical functioning, as determined from the corresponding subscale of the SF-36 questionnaire (Medical Outcomes Short Form Health Survey; 20). To assess the longitudinal association of NT-proBNP and anxiety, multilevel linear mixed models were calculated. The models included the six assessments of anxiety as level-1 variable, nested within participants as level-2 variable. In model A we included random intercepts for participants, as well as NT-proBNP as continuous measure, sex, randomization arm, time, and the interactions with time as fixed effects. In model B we entered the same factors into the model, however we dichotomized NT-proBNP into lowest vs. highest three quartiles. Differences between subgroups (e.g., sexes, quartiles of NT-proBNP) were assessed using χ^2-analysis for categorical measures and Student's *t*-test for continuous measures. For comparisons of non-parametric data, Mann-Whitney-*U* and Wilcoxon signed-rank tests were performed. All data were analyzed using SPSS (Version 25, IBM Corp., Armonk, NY, USA) and R (Version 3.5.1.).

3. Results

3.1. Baseline characteristics

The mean age of the sample was 60.1 (*SD* = 8.9) years. The majority of patients were male (80.8%), non-working (53.9%), and married (77.6%) and most patients had a medium or low socioeconomic status (Table 1). Patients had a mean HADS-depression score of 10.2, but the majority did not have a major depressive disorder (MDD) according to SCID (68.2%). The mean anxiety score on the HADS anxiety subscale was 10.2 (*SD* = 3.73) at baseline and 76.9% had clinically relevant scores ≥ 8. After 24 months, approximately half of the patients (49%) still had elevated anxiety scores, whereas the mean score had dropped to 7.7 (*SD* = 4.2). Separate analysis by sex showed that the prevalence of anxiety at baseline was 74.3% for men and 88.1% for women, which decreased to 47.4% and 55.9%, respectively, after 24 months. This reduction in the HADS-anxiety scores was significant in both male ($t(248) = 9.91$, $p < .001$) and female study participants ($t(58) = 6.34$, $p < .001$).

Comparison of the included versus the excluded sample revealed, that included patients were significantly older (mean (SD) = 60.1 (8.9) versus 58.0 (10.1)), had lower levels of NT-proBNP (median = 165.5 ng/l versus 261.3 ng/l) and higher LVEF (mean (SD) = 58.8 (13.8) versus 53.7 (14.6)). Moreover, they had a higher socioeconomic status (22.7% versus 15.1%) and a significantly higher percentage was married (75.0% versus 54.5%). The samples did not differ on baseline anxiety or other descriptive variables.

Comparison of patients with versus without MDD showed significantly different levels of NT-proBNP ($F(3, 304) = 3.35$, $p = .02$) with patients without MDD showing higher levels (median(IQR) = 188.55 (318.15)) compared to patients with mild or moderate MDD (median(IQR) = 123.9 (196.80) vs. 113.25 (203.33)). Patients in partial remission (N = 7) were not included in this analysis due to their small number.

Table 1. Baseline Characteristics.

	N/ valid *N*	%
Male sex	249/308	80.8
Married	225/300	75.0
Socioeconomic status		
Low	113/308	36.7
Medium	125/308	40.6
High	70/308	22.7
SCID major depression		
None	210/308	68.2
Mild	39/308	12.7
Moderate	52/308	16.9
Partial remission	7/308	2.3
NYHA class		
I	114/298	38.3
II	137/298	46.0
III	47/298	15.8
Beta-blocker medication	265/308	86.0
	M	*SD*
Age, y (*N* = 308)	60.1	8.9
LVEF (*N* = 176)	58.8	13.8
BMI (*N* = 303)	28.7	4.8
CCI (*N* = 308)	2.0	1.5
T0 NT-proBNP, median (IQR), ng/l (*N* = 308)	165.5	277.1
T0 HADS depression (*N* = 308)	10.2	2.5
T0 HADS anxiety (*N* = 308)	10.2	3.7
T1 HADS anxiety (*N* = 308)	9.2	4.1

T2 HADS anxiety (*N* = 308)	8.4	4.0
T2b HADS anxiety (*N* = 308)	8.4	4.1
T3 HADS anxiety (*N* = 308)	7.7	4.0
T4 HADS anxiety (*N* = 308)	7.7	4.2

BMI = body mass index (kg/m²), CCI = Charlson comorbidity index, HADS = Hospital Anxiety and Depression Scale, IQR = interquartile range, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, SCID = Structured Clinical Interview for DSM-IV.

3.2. Correlation analysis

Correlation analysis revealed significant negative associations between baseline log(NT-proBNP) and HADS-anxiety measures at all time points (Table 2). The associations remained significant at all time points in a multiple regression analysis adjusted for age, sex, BMI, and physical functioning (subscale of SF-36 questionnaire) (all $p < .05$).

Table 2. Correlation analysis.

HADS-anxiety measure		baseline	1 month	6 months	12 months	18 months	24 months
log(NT-proBNP)	Pearson correlation	-.198	-.159	-.151	-.223	-.129	-.152
	p-value (2-tailed)	.000	.005	.008	.000	.024	.007

3.3. Multilevel linear mixed model

The results of model A (continuous measure of NT-proBNP) revealed no significant interaction of any of the factors with time (all p > .05). In model B (lowest vs. three highest quartiles of NT-proBNP) we found a significant time*NT-proBNP interaction ($t(1535.99) = -2.669$, $p = .01$), as well as a significant time*NT-proBNP*sex interaction ($t(1535.99) = 3.277$, $p = .001$). Figures 1a and 1b show the different time course of anxiety for patients in the lowest versus the three highest quartiles of NT-proBNP, separately for the two genders. The mean values illustrate the significantly different course of anxiety in women with NT-proBNP levels < 86 ng/l versus ≥ 86 ng/l, and the similar course in men with low versus high NT-proBNP.

3.4. Sex-specific analysis

To further explore the unexpected sex difference that was found in model B, we performed an exploratory analysis to compare NT-proBNP levels of men and women at baseline. Overall, the median level of NT-proBNP did not differ significantly between men and women ($U = 7118.5$, $Z = -.396$, $p = .71$). Comparing the male ($N = 249$) and female ($N = 59$) sample, χ^2-analysis and

Student's *t*-test showed a significant difference in NYHA class ($\chi^2 = 6.79$, $p = .03$) and LVEF ($t(174) = -2.27$, $p = .03$), with women having both a higher LVEF and a higher NYHA class. Men and women did not differ in age, body mass index (BMI) and Charlson Comorbidity Index. As the sample of women was relatively small, more extensive analyses were not possible.

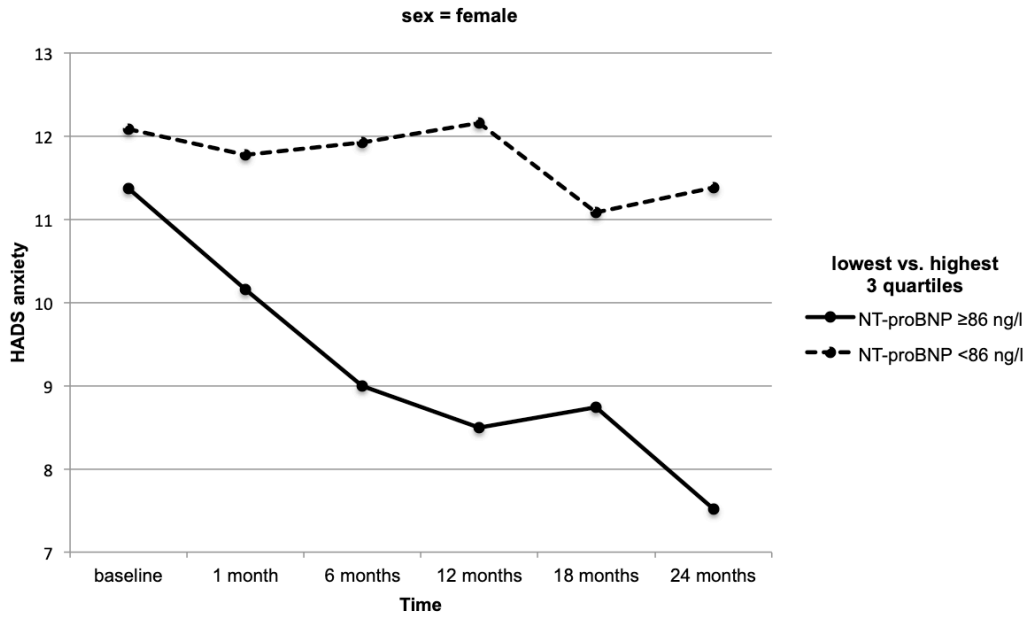

Figure 1. Mean values of HADS anxiety over 24 months for low and high baseline NT-proBNP in women. NTproBNP = N-terminal pro B-type natriuretic peptide.

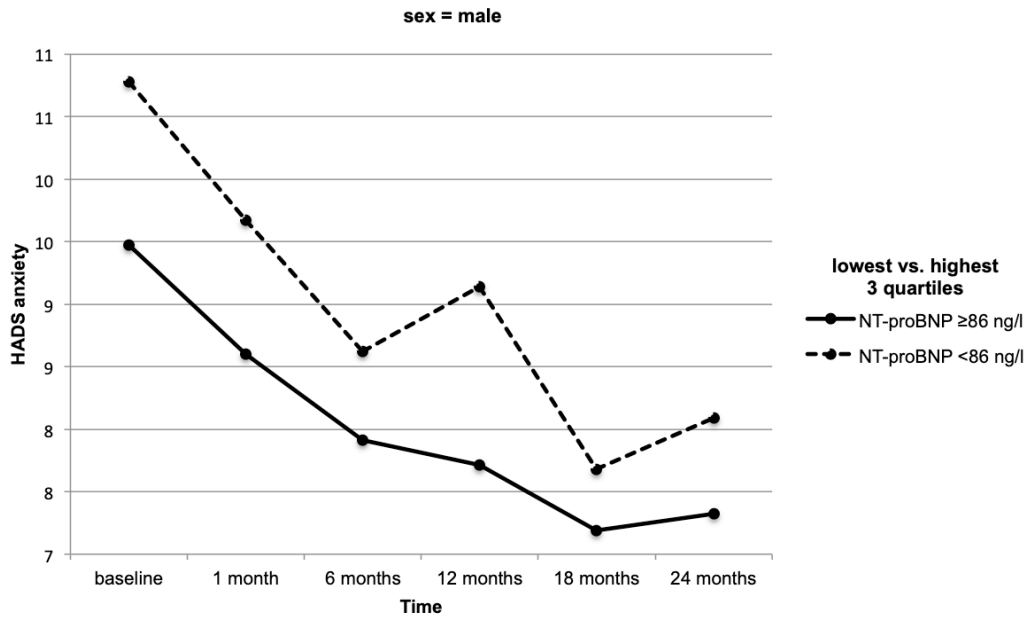

Figure 2. Mean values of HADS anxiety over 24 months for low and high baseline NT-proBNP in men. NTproBNP = N-terminal pro B-type natriuretic peptide.

1. Discussion

In the present secondary analysis of the SPIRR-CAD trial, we investigated the longitudinal association of anxiety and NT-proBNP in mildly to moderately depressed coronary artery disease patients. The results indicate that higher baseline levels of NT-proBNP were associated with persistently lower levels of HADS-anxiety measures over 24 months. To our knowledge, this is the first study with such a large sample and a follow-up of two years. Our results extend the findings of previous studies on natriuretic peptides and anxiety showing an inverse relationship (10, 12, 15, 21), however, they are in contrast to studies in patients with heart failure that found positive or no associations of (NT-pro)BNP and HADS-anxiety (22, 23). As these studies were conducted in a different patient population and either cross-sectional, or had a short follow-up period, they are not readily comparable to our findings. Brouwers and colleagues used anxiety as a predictor for the course of NT-proBNP over 9 months. In 94 heart failure patients they found no significant influence of baseline anxiety levels on the course of BNP. This supports our hypothesis that BNP affects the course of anxiety. Even though the present results do not prove causality, they support this notion. We hypothesize that an insufficient up-regulation of BNP, despite cardiac disease, results in more enduring anxiety than in patients with higher levels of this natriuretic peptide.

The results of linear mixed model A did not confirm a linear association of baseline NT-proBNP and anxiety over time and did not render a significant interaction effect. Model B, with dichotomized NT-proBNP values, detected a significant time*NT-proBNP and time*NT-proBNP*sex interaction term. The results show a significantly different course of anxiety for women with very low versus higher levels of NT-proBNP. While women with higher levels of NT-proBNP had a continuous decrease in anxiety over 24 months, women with very low levels of NT-proBNP did not exhibit such change and remained at a high level of anxiety over the entire course of the study, irrespective of their treatment assignment. Male patients with very low levels of NT-proBNP also exhibited higher levels of anxiety; however the course of anxiety over 24 months did not differ from that observed in men with higher

levels of NT-proBNP. These results point towards a non-linear association of NT-proBNP and anxiety with higher levels of anxiety, if the body is unable to up-regulate NT-proBNP despite a cardiac disease.

While the negative association of NT-proBNP and anxiety is in line with previous literature, the interaction with the patients' sex was unexpected. The results cannot be explained by the patients' age, BMI, comorbidity, or medication as these parameters did not differ between men and women. Further research with a more balanced representation of both sexes is needed to elaborate why this effect was only present in women.

Previous studies described sex differences in NT-proBNP levels, psychological conditions and cardiac disease separately, but the interaction of these factors has not been studied. Overall, female CHD patients seem to have a high prevalence of depression and anxiety (as women in epidemiological and other clinical samples); however few studies present data separated by sex and women are still underrepresented in most studies on cardiac diseases. A recent systematic review concluded that women experience more depressive symptoms than men shortly after a cardiac event as well as longitudinally (24). Moreover, women have naturally higher levels of BNP than men, possibly mediated by circulating free testosterone (25, 26). However, we found no significant difference in NT-proBNP levels for women compared to men. This might be due to 71% of women in our sample being post-menopausal, a state associated with decreasing levels of NT-proBNP (25, 27). Even though NT-proBNP is an established marker of disease severity in heart failure and other cardiac illnesses, the multitude of factors that influence its levels (including age, sex steroids, and BMI) call its prognostic value as an isolated predictor into question and warrants further sex-specific interventions.

1.1. Limitations

As the present results are a secondary-analysis of the SPIRR-CAD trial, in which NT-proBNP and anxiety were not primary endpoints and patients had moderate to high levels of depression, a study with a less preselected sample of heart patients would be more suitable. While the present results stem from a large multicenter trial, they have to be interpreted under the consideration that the number of

women in this sample was small, with the majority being male white Germans. The results are thus not readily generalizable to female cardiac patients or other races and ethnicities. Moreover, the inclusion criteria demanded stable CHD and HADS-depression score ≥ 8, thus we cannot assess the additional effects of the cardiac disease and the depressive symptoms on the association of anxiety and NT-proBNP. Additionally, many patients also had elevations in other dimensions of distress. The results thus cannot be generalized to patients with other somatic or mental illnesses or healthy subjects. Due to the nature of our data we cannot attribute the course of anxiety to changes in NT-proBNP. As 46% of the sample did not have valid measures for all 6 time points and had to be excluded for the present analysis, there is a possibility of a selection bias. Selected patients had higher ejection fraction and thus also lower levels of NT-proBNP, however with a long follow-up of two years it is common that mostly less severely ill patients have valid measures for all time points.

1.2. Conclusion

Our results show a stable negative association of baseline NT-proBNP and anxiety over two years. However, different pathways in men and women appear to modulate this relationship. Especially women who were not able to up-regulate their BNP at baseline despite their cardiac disease, exhibit persistently higher levels of anxiety, compared to women with higher levels of BNP and compared to men. In contrast, baseline anxiety did not predict the change in anxiety, arguing for a probable causal effect of BNP on anxiety rather than vice versa. However, measuring NT-proBNP levels at multiple time point (in parallel to anxiety scores) and using cross-lagged-model statistics could help clarify this issue. Nevertheless, our results suggest an anxiolytic-like function of BNP, acting as humoral feedback signal shielding the diseased heart from the adverse effects of overshooting anxiety.

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Appendix. Consort flow chart.