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ORIGINAL PAPER

B-type natriuretic peptide: distribution in the general population and the association with major cardiovascular and coronary events—The Heinz Nixdorf Recall Study

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Abstract
Background A B-type natriuretic peptide (BNP) threshold of 100 pg/ml is used in practice for identification of heart failure, but data about the "normal" distribution of BNP in a large population in primary prevention are rare. We aimed to characterize the BNP distribution in a healthy subset of a population-based cohort and to evaluate the association of elevated BNP levels with major events.
Methods In a first step, we determined gender-specific distribution and 90th percentiles of BNP in participants who were at baseline free from known determinants of increased BNP, i.e. cardiovascular disease, hypertension or chronic kidney disease. Consecutively, the association of BNP levels above these 90th percentiles with subsequent cardiovascular and coronary events was assessed in the entire cohort.
Results In the BNP-normal sub-sample ($n = 1{,}639$), we defined gender-specific 90th percentile of BNP (31.3 pg/ml for men, 45.5 pg/ml for women). From overall 3,697 subjects (mean age 59.4, 52.4 % female), 194 subjects developed a major cardiovascular event and 122 myocardial infarction during a mean follow-up period of 8.0 ± 1.5 years. The 90th percentiles derived from the normal subset as threshold showed strong associations with major events in the entire cohort even after adjusting for traditional risk factors: hazard ratio (95 % CI): 1.86 (1.37; 2.53), $p < 0.0001$ for cardiovascular, and 1.77 (1.19; 2.62), $p = 0.005$ for coronary events.
Conclusion The gender-specific 90th percentile of BNP (31 pg/ml for males and 45 pg/ml for females) obtained from a BNP-normal sub-sample is associated with incident major cardiovascular and coronary events, suggesting that even BNP values lower than 100 pg/ml could imply prognostic information in the general population.

Keywords Natriuretic peptides · Prevention · Risk factors · Heinz Nixdorf Recall Study

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Introduction

Detecting silent cardiac damage and thereby predicting cardiac risk remain a challenge in modern medicine. Besides its role in the diagnosis for heart failure [1–4], BNP was suggested to reflect silent "pancardiac" damage in early stages including left ventricular dysfunction, silent ischemia and left ventricular hypertrophy [5–8]. It is associated with severity of coronary atherosclerosis and predicts cardiac morbidity and all-cause mortality even in subjects without known cardiovascular disease [5, 6, 9–14]. Therefore, measurements of BNP may help to identify

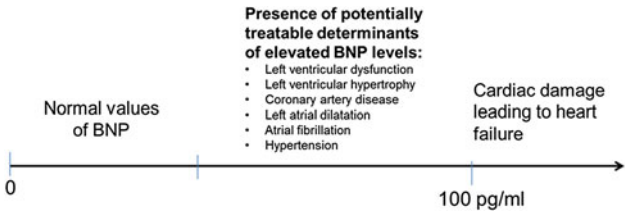

Fig. 1 Schematic relation of BNP to stages of cardiovascular diseases

those who need further examination to achieve better risk stratification [7].

For the diagnosis heart failure in patients with dyspnea cutoff value of 100 pg/ml is widely accepted in clinical practice. Heart failure is the final stage of many cardiac diseases and mostly irreversible, thus there is a raising interest in BNP levels below the established value of 100 pg/ml, specially the distribution of BNP (Fig. 1) in healthy subjects. In the last 10 years some determinants of increased BNP, e.g. hypertension, cardiovascular diseases (CVD), or chronic kidney disease (CKD), have been identified [9, 12, 15, 16]. Furthermore BNP levels are higher in female population [9, 12–16]. To date there is a lack of studies investigating the gender-specific distribution of BNP levels in the general population without determinants of increased BNP. Therefore, aim of this analysis was to determine (1) distribution of BNP in a subsample of a population-based cohort including subjects without CVD, hypertension, or CKD, (2) gender-specific 90th percentile of BNP in this subset and (3) to evaluate the association of elevated BNP levels according to this 90th percentile with incident major cardiovascular and coronary events in the entire population.

Methods

Participants

The Heinz Nixdorf Recall Study is a population-based, prospective cohort study, designed to assess the predictive value of novel markers for risk stratification in addition to traditional risk factors. The participants were randomly selected from mandatory city registries from Bochum, Essen and Muelheim, three adjacent cities in the West German Ruhr area. Details about recruitment and study design have been previously published [17–20]. In brief, 4,814 subjects (50.3 % females) aged 45–75 years were recruited between 2000 and 2003 with a baseline response of 55.6 % [21]. For this analysis, we excluded participants with known coronary artery disease ($n = 327$) and prior stroke ($n = 105$) at baseline examination. All participants provided written informed consent, and the study was approved by the institutional ethical committee at the University Essen, Germany.

Cardiovascular risk factors and covariate definitions

Traditional cardiovascular risk factors were measured at baseline examination with details being previously reported [22]. For blood pressure measurement, the mean of second and third measure was calculated. Body mass index (BMI) was calculated as body weight divided by square of height. Serum levels of HDL-, LDL- and total cholesterol as well as serum glucose levels were analyzed utilizing standard enzymatic methods. Smoking history was classified in current and former smokers and no history of smoking was assessed by computer assisted interview [23]. Diabetes was defined as a history of diabetes, being on medical treatment or based on blood glucose levels as previously published [24] We used the modification of diet and renal disease (MDRD) formula to calculate the estimated GFR (eGFR) : $\text{eGFR}\ (\text{ml/min/1.73m}^2) = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203}[\times 0.742\ \text{if female}]$. An eGFR $\leq$ 60 ml/min/1.73 m^2 was considered as impaired renal function.

Measurement of BNP

Plasma samples obtained from EDTA blood were aliquoted and stored at −80 °C until further use. We measured the physiologically active BNP molecule using the Siemens ADVIA Centaur BNP assay (Siemens, Erlangen, Germany). The analytic functional sensitivity of the assay which represents the lowest BNP concentration determined was 2.5 pg/ml.

Electron-beam computed tomography (EBCT)

To quantify coronary artery calcification (CAC), EBCT scans were performed with a C-100 and C-150 scanner (GE Imatron, South San Francisco, California) without the use of contrast media. Images were prospectively triggered at 80 % of the RR interval. Contiguous 3-mm-thick slices from the right pulmonary artery to the apex of the heart were obtained at an image acquisition time of 100 ms. Coronary artery calcium was defined as a focus of at least four contiguous pixels with a CT density >130 Hounsfield units. CAC was quantified using the Agatston method and computed by the sum of all foci in the epicardial coronary system [20, 25].

Follow-up and end point definition

Annually, questionnaires on the current state of health including questions about medication, hospital admissions

and outpatient diagnosis of cardiovascular disease were sent to the participants. Any hint to incident cardiovascular morbidity, whether from self-reports of events or from reported contacts to the medical system or medication, and fatal events was validated by review of hospital records and records of the attended physicians. Coronary events (fatal and nonfatal) and major cardiovascular events (incident myocardial infarction, stroke, or cardiovascular death) were considered as end points. Event status was classified by an external end point committee, blinded to the risk factor status and the CAC score. Myocardial infarction was defined based on symptoms, electrocardiographic signs, and enzymes (levels of creatine kinase [CK-MB]) as well as troponin T or I, and necropsy as: (1) nonfatal acute myocardial infarction; and (2) coronary death, according to predefined study criteria [17, 26]. Stroke was defined as focal neurological deficits over a period of >24 h of presumed cerebrovascular origin.

Statistical analysis

Subject characteristics are presented as mean ± standard deviation (SD) for continuous variables and as *N* (%) for dichotomous traits. BNP was not normally distributed (Kolmogorov–Smirnow test: $p < 0.01$). For a better characterization of BNP, also median, quartiles and 90th percentiles are reported.

To identify BNP levels in a population without known determinants for elevated BNP we formed a sub-sample with subjects without known hypertension, a blood pressure measurement higher or equal to 140/90 mmHg, intake of anti-hypertensive medication, a low glomerular filtration rate (GFR $\leq$ 60 ml/min/1.73 m^2), and participants without known cardiovascular diseases (including heart valve disease, open heart surgery, atrial fibrillation or flutter, having a pacemaker of defibrillator, or prior stroke).

In the defined sub-sample (BNP-normal sub-sample) we used quantile regression of log(BNP) on age per gender. The results are displayed after retransformation together with BNP median, 75th and 90th percentiles in 5-year age classes. Furthermore, we determined the 90th gender-specific percentile of BNP in this BNP-normal sub-sample. BNP levels >90th percentile were defined as high BNP level. Consecutively, using these percentiles as thresholds, association of elevated BNP levels with incident first major CV events (defined as incident myocardial infarction, stroke, or cardiovascular death) and coronary events (fatal and nonfatal) in the entire population was assessed. This method was established in large population studies investigating novel reference values or thresholds assuming that subjects with values equal or less the 90th percentile were deemed to have "normal" values [27–29].

We used cox proportional hazard regression to calculate unadjusted and adjusted hazard ratios using BNP as binary variable (BNP $\leq$ 90th percentile vs. BNP > 90th percentile). For adjusted regression, the following models were used: model 1 includes age and gender, model 2 Framingham risk variables (FRV, including model 1 + systolic blood pressure, HDL-cholesterol, LDL-cholesterol, diabetes, and present smokers), model 3 uses additionally anti-hypertensive and lipid-lowering medication, BMI, and former smoking, and model 4 additionally CAC (as log(-CAC + 1)). Analysis of Schoenfeld residuals [30] and a Kolmogorov-type supremum test (based on [31]) confirmed validity of the proportional hazard assumption. The Harrell's c statistic was used to estimate the increase in risk prediction accuracy for time-to-event data, comparable to the area under the receiver-operator characteristic curve (c-statistic) in logistic regression analysis.

All analyses were performed using SAS software (Version 9.2, SAS Institute Inc), except comparison of Harrell's c, which was evaluated using Stata/IC version 11.2. A p value of <0.05 indicated statistical significance.

Results

Baseline characteristics

From the total 4,814 participants of the Heinz Nixdorf Recall Study, 327 subjects were initially excluded due to coronary heart disease at baseline and 105 due to prior stroke. Of the remaining 4,382 participants, BNP or at least one risk factor was missing in 685 subjects. Thus, the analysis sample comprises 3,697 subjects (mean age 59.4 ± 7.7 years, 52.4 % female).

The baseline characteristics in the entire population stratified by gender-specific 90th percentile of BNP, defined in a sub-sample without predictors of increased BNP, are shown in Table 1. Median and quartiles of BNP were higher in women as compared to men [median (Q1; Q3): 21.7 pg/ml (12.0; 36.8) vs. 13.8 pg/ml (7.4; 25.5)]. Overall, 2.1 % of the participants had a BNP >100 pg/ml.

Regarding baseline characteristics as well as outcome measures, the analyzed subset (n = 3,697) did not differ from those excluded (n = 685, data not shown).

Distribution of BNP in the BNP-normal sub-sample and the 90th percentile of BNP

From the entire cohort (n = 3,697), 1,639 subjects had no known determinants of increased BNP with median (Q1; Q3) BNP level 15.1 pg/ml (8.7; 26.0). The age- and gender-specific distribution of BNP is shown in Fig. 2. The

Table 1 Baseline characteristics (stratified by gender-specific 90th percentile of BNP, as defined in a subgroup without predictors of increased BNP)

	Overall	≤90th percentile of BNP	>90th percentile of BNP	*p* value
n	3,697	3,049	648	
Age	59.4 ± 7.7	58.5 ± 7.6	63.6 ± 7.1	<0.0001
Males (%)	1,759 (47.6)	1,610 (52.8)	328 (50.6)	0.31
BNP (median (Q1; Q3))	17.8 (9.5; 32.1)	14.2 (8.2; 23.0)	55.9 (46.3; 75.1)	n.a.*
BMI (kg/m^2)	27.8 ± 4.5	27.6 ± 4.4	28.7 ± 4.8	<0.0001
Systolic blood pressure (mmHg)	132.9 ± 20.9	131.6 ± 20.1	139.3 ± 23.4	n.a.
Diastolic blood pressure (mmHg)	81.6 ± 10.9	81.4 ± 10.6	82.4 ± 12.0	n.a.
Anti-hypertensive medication (%)	1,153 (31.2)	821 (26.9)	332 (51.2)	n.a.
Diabetes (%)	264 (7.1)	201 (6.6)	63 (9.7)	0.005
Lipid-lowering medication (%)	327 (9.5)	257 (9.1)	70 (11.4)	0.08
Smokers				
Never (%)	1,619 (43.8)	1,307 (42.9)	312 (48.2)	
Former (%)	1,221 (33.0)	990 (32.5)	231 (35.6)	
Current (%)	857 (23.2)	752 (24.6)	105 (16.2)	<0.0001
Framingham Risk Score	11.4 ± 8.4	10.9 ± 8.0	13.8 ± 10.0	n.a.
CV Events	194 (5.3)	126 (4.1)	68 (10.5)	<0.0001
Coronary Events	122 (3.2)	82 (2.7)	40 (6.2)	<0.0001

BMI body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CV Events* cardiovascular events including myocardial infarction, stroke, or cardiovascular death

* Non applicable due to selection of non-hypertensive subjects in the BNP-normal sub-sample

determined gender-specific 90th percentile in this sub-sample was 31.3 pg/ml for men and 45.5 pg/ml for women.

Prevalence of BNP levels above the 90th gender-specific percentile in the entire population for women was 16.9 %, for men 18.2 % (Table 2). Subjects with a BNP level above the 90th percentile were older, and had higher BMI (Table 1).

Association of increased BNP levels with major events in the entire population

During a mean follow-up time of 8.0 ± 1.5 years, 194 participants developed major CV events and 122 subjects experienced coronary events. Incidence of major CV events and coronary events was higher at increased BNP levels (CV events/coronary events: 4.1/2.7 % for BNP ≤90th percentile vs. 10.5/6.2 % for BNP >90th percentile, respectively).

Cox-regression analyses for major CV events and coronary events are shown in Table 3. In unadjusted models, subjects with a BNP >90th percentile had more than twofold increased risk for major CV events and coronary events. Associations were slightly attenuated but remained highly statistically significant after further adjustment for age, gender, traditional cardiovascular risk factors in multivariable analysis (model 3). After further adjustment for CAC Score, associations for major CV events remained unchanged.

Adding the dichotomous BNP variable to traditional cardiovascular risk factors did not lead to a significant increase in Harrell's c for major events.

Discussion

In this population-based study, we determined gender-specific distribution of plasma BNP and described its 90th percentile in a sub-sample of subjects without prevalent cardiovascular disease, hypertension, and chronic kidney disease as known determinants for increased BNP. Applying the elevated BNP levels as thresholds to the entire population, a strong association with CV events and coronary events was observed.

This effect was independent of traditional cardiovascular risk factors. Notably, the BNP values of 31 pg/ml for males and 45 pg/ml for females for the 90th percentile were relevantly lower than the established threshold of 100 pg/ml in heart failure, indicating that BNP values clearly below this established threshold could imply prognostic value in the general population.

There is a growing evidence that in a pre-clinical setting, measurement of BNP may improve risk prediction in the

general population. Elevated levels of BNP (e.g. using the 80th percentile as threshold) are associated with high risk for cardiac morbidity and mortality, as Wang et al. [9] reported an association of BNP with all-cause mortality and cardiovascular events in a healthy population. These results were confirmed in a meta-analysis with 87,747 subjects [11]. In our previously published work we demonstrated an association of BNP with coronary events and all-cause mortality, with BNP significantly improving prediction of risk in the general population above and complementary to coronary artery calcification and traditional risk factors [32]. For risk prediction in the general population, it was suggested that BNP reflects early stages of systolic and diastolic dysfunction; additionally it was hypothesized that BNP is linked with asymptomatic chronic cardiac ischemia. These suggestions were confirmed in a recently published study showing that BNP screening—in asymptomatic treated primary prevention patients—is able to identify existing left ventricular hypertrophy, systolic and diastolic dysfunction, left atrial enlargement, and ischemia [8]. Notably, BNP screening levels for detecting cardiac diseases were clearly below 100 pg/ml.

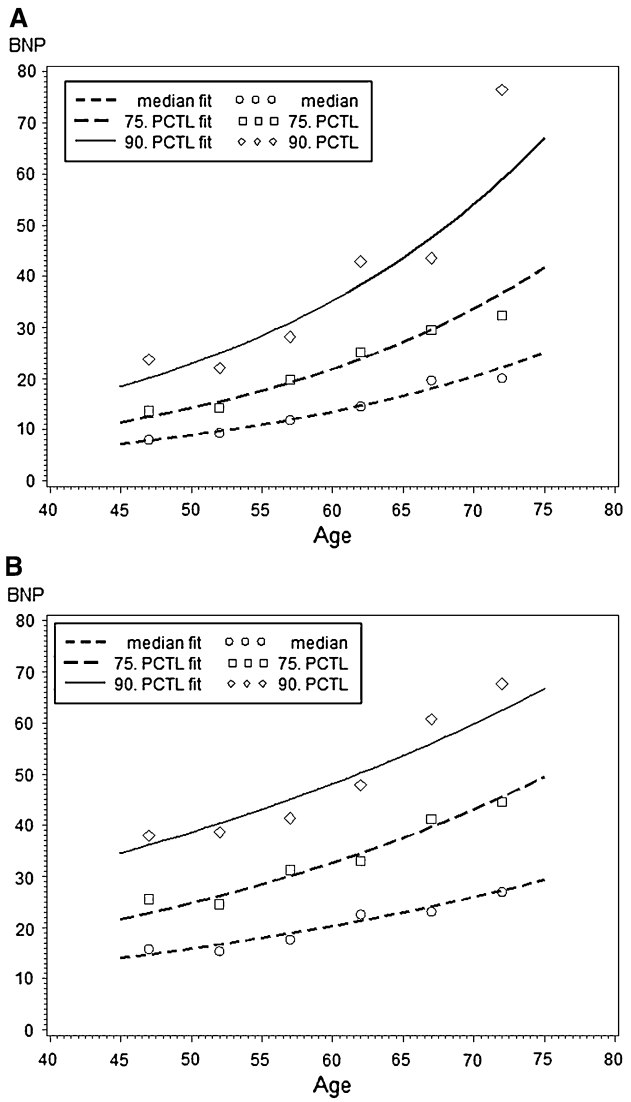

Fig. 2 Median, 75th and 90th percentiles of BNP and *fit lines* as functions of age, determined in subjects free from known determinants of increased BNP in men (**a**) and women (**b**)

As a conclusion, it has been suggested that BNP may reflect "pancardiac" damage in early stages and that measurements of BNP may help to identify those who need closer examination and further risk stratification [7]. This finding was confirmed by our results of 90th percentile of BNP in a population without cardiovascular disease being notably lower than the established 100 pg/ml and higher in women as compared to men.

Wang et al. were first showing a predictive value of BNP in the general population using tertiles of BNP from the entire population. Since 2004, many studies confirmed these findings. However, yet there are no established thresholds of BNP for cardiac screening.

Moreover, in the last years there have been identified some determinants of increased BNP, e.g. hypertension, cardiovascular diseases, or chronic kidney disease. Excluding these factors led to establishing thresholds of BNP that enables identification of subjects at increased risk for cardiovascular morbidity and mortality. Furthermore BNP levels are higher in female population, clarifying the need for gender-specific thresholds [9, 12–16]. Despite the predictive value of BNP with the potential of a biomarker as screening parameter for cardiac diseases there is a lack of studies investigating the distribution of BNP in a cohort free of determinants of increased BNP. This is the first study, taking these finding from the last years into account, determining gender-specific thresholds in a large "BNP-normal" sub-sample, which identify subjects at higher risk for cardiac events.

Implications

Identifying cardiac diseases in early stages remains a challenge in modern medicine. Echocardiography is a precise method to identify cardiac abnormalities, but it is

Table 2 Subjects with a BNP > 90th in the entire population

		45–54 years	55–64 years	65–75 years	Total
Male	>90th percentile (%)	8.3	15.8	33.5	18.2
Female	>90th percentile (%)	7.4	16.6	27.7	16.9

Table 3 Cox regression for the association of BNP (gender-specific 90th percentile in the BNP-normal sub-sample) with the combined end point in the entire population

	BNP as binary variable (BNP ≤90th percentile vs. BNP >90th percentile)			
	Major cardiovascular events		Coronary events	
Model	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
Unadjusted	2.67 (1.99; 3.59)	<0.0001	2.40 (1.64; 3.50)	<0.0001
Model 1 (age and gender)	1.86 (1.37; 2.53)	<0.0001	1.77 (1.19; 2.62)	0.005
Model 2 (FRV)	1.82 (1.34; 2.49)	0.0002	1.78 (1.20; 2.65)	0.005
Model 3*	1.68 (1.21; 2.33)	0.002	1.67 (1.10; 2.52)	0.02
Model 4 (model 3 + CAC)	1.57 (1.13; 2.18)	0.007	1.52 (1.00; 2.30)	0.050

CAC coronary artery calcium

* Adjusted for Framingham risk variables (FRV), anti-hypertensive medication, lipid-lowering medication, BMI, former smoking

expensive and also rarely available in primary prevention, and therefore, not established in widely screening programmes. In contrast, assessment of a biomarker is feasible using a simple blood.

We describe the distribution and determined the 90th percentile of BNP in a "BNP-normal" sub-sample in the European general population. BNP seems to be a biomarker which reflects pancardiac damage in early stages. Using the determined gender-specific 90th percentile of BNP—which are clearly lower than 100 pg/ml—may identify subjects which could profit from an aggressive risk modification.

As a result, these data may help clinicians and primary care practitioners to better interpret BNP values and potentially identify asymptomatic subjects via BNP with increased risk for future cardiovascular events who are missed by current risk stratification algorithms. BNP could be established in screening programmes to detect silent cardiac diseases, and therefore, subjects with a higher BNP level may qualify from a cardiological workup for detection of early stages of a systolic or diastolic heart dysfunction even in the absence of symptoms.

Strength and limitations

The strengths of our study include its population-based sample without known cardiovascular disease. Traditional cardiovascular risk factors were measured using highly standardized protocols. A limitation of our study is that the participants are predominantly Caucasians, hence generalization to other ethnic groups might be limited. Lastly, our study includes the measurement of BNP only, but not of N-terminal pro–B-type natriuretic peptide.

Conclusion

We describe the age and gender-specific distribution and determine 31 pg/ml for males and 45 pg/ml for females as gender-specific 90th percentiles of BNP obtained in a subsample from a European general population cohort, without CV disease, hypertension, and chronic kidney disease as known determinants of increased BNP levels. These BNP values as threshold are associated with incident major cardiovascular and coronary events, and therefore, may help for primary prevention purposes. Using the accepted BNP threshold of 100 pg/ml may lead to a considerable miss of persons at increased risk.

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Conflict of interest The authors declare that they have no conflict of interest.

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