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NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The getABI-study

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ABSTRACT

Background: Beside their role in the diagnosis of heart failure in symptomatic patients with dyspnea, natriuretic peptides have been suggested to improve risk prediction of cardiac events and mortality in asymptomatic cohorts. We aimed to evaluate the prognostic value of NT-proBNP for cardiovascular and all-cause mortality above traditional risk factors in a prospective cohort study of unselected elderly patients in a representative primary care setting.

Methods: We followed 6382 patients of the getABI-study for 7 years. Associations of NT-proBNP levels (≤125; 125–300; >300pg/ml for all) with all-cause and cardiovascular mortality were assessed using cox regression analysis.

Results: The incidence of all-cause and cardiovascular mortality was higher in subjects with higher levels of NT-proBNP (all-cause mortality/cardiovascular mortality: 35.4%/6% for NT-proBNP > 300 pg/ml; 16.2%/40% for NT-proBNP 125–300 pg/ml vs. 11.4%/4% for NT-proBNP ≤ 125 pg/ml. Participants with a NT-proBNP levels > 300pg/ml had increased incidence of hard endpoint (hazard ratio (HR) (95% confidence interval (CI)): 3.62 (3.15–4.17) for all-cause mortality, and 6.38 (4.84–8.41) for cardiovascular mortality). These associations remained after adjustment for traditional risk factors and cardiac medications and diseases (HR = 2.64 (2.26–3.08) for all-cause mortality, and HR = 3.93 (2.90–5.32) for cardiovascular mortality).

Conclusion: Our results show strong associations of higher NT-proBNP levels with cardiovascular and all-cause mortality in an unselected, large population of elderly patients in the primary care setting independent of traditional risk factors indicating that NT-proBNP can help identifying subjects at high risk for cardiac events.

1. Introduction

Cardiac risk stratification detecting silent cardiac damage remains a challenge in modern medicine. B-type natriuretic peptide (BNP) and N-terminal pro BNP (NT-proBNP) are secreted from cardiac myocytes in response to ventricular and atrial wall stress and serve as serum biomarkers for the diagnosis of heart failure [1].

Besides their established role in patients with heart failure, several studies have described the powerful prognostic role of natriuretic peptides for prediction of cardiovascular outcomes in asymptomatic cohort-studies [2–6].

Natriuretic peptides are increased in subjects with early stages of cardiac diseases such as diastolic dysfunction, left ventricular

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hypertrophy, and silent myocardial ischemia with plasma-levels markedly below the cut-off value used for the diagnosis of heart failure [4,7]. Thus, natriuretic peptides seem to reflect pancardiac functional heart disease also in early asymptomatic stages and thus may hereafter be useful in cardiac screening programs [4,7].

However, there is a lack of studies investigating the association of NT-proBNP levels with cardiac events in a large cohort from primary care setting.

Therefore, aim of this analysis was to determine the association of NT-proBNP with all-cause mortality and cardiovascular mortality above traditional risk factors in a prospective cohort study of unselected elderly patients in a representative primary care setting in Germany (getABI Study).

2. Methods

2.1. Participants

The German Epidemiological Trial on Ankle Brachial Index (getABI) is a prospective observational cohort study initiated in October 2001. Details about recruitment and study design have been previously published [8]. In brief, 34 vascular physicians trained and supervised 344 physicians throughout Germany. Patients were included in a prespecified week in October 2001 regardless of seeing the doctor. In total, 6880 elderly (>65 years) patients were recruited. Each practice included an average of 20 patients, the only exclusion criteria was life expectancy less than 6 month as judged by the doctor. At baseline, a medical history assessment including prescribed medications, physical examination, and blood sampling were performed. Follow-up included physician visits at one, three, five and seven years after baseline.

2.2. Measurement of NT-proBNP

Subjects blood samples were collected at baseline. NT-proBNP was determined using a chemoluminescent microparticle immunoassay (CMIA, Abbott Diagnostics, Chicago, Illinois, USA) on an Abbott Architect i200SR analyzer. Interassay CVs were 2.8% and 2.3% at mean values of 153 and 4849 pg/ml.

NT-proBNP was categorized into 3 levels as clinically established thresholds: minimum up to 125, 125 to 300, and>300 (unit pg/ml) [9]. GetABI participants with missing NT-proBNP values were excluded. Thus, 6382 patients comprised the analysis population for this work.

2.3. Cardiovascular diseases and endpoint definition

Cardiovascular diseases (CVDs) at baseline were defined as myocardial infarction, stroke, coronary revascularization, or revascularization of the carotid arteries. The endpoints death and death from cardiovascular cause were considered if declared by the physician (CRF) or via death certificate. If possible, they were verified by clinical reports. For lost to follow-up participants the registration office was asked for living status. Death from Cardiovascular cause comprised fatal myocardial infarction and cerebrovascular events.

2.4. Statistical analysis

On basis of the pre-determined NT-proBNP categories, characteristics of participants are presented descriptively with mean and standard deviations for continuous variables and counts and proportions for categorical variables. Survival analyses were done by means of Kaplan-Meier plots for the univariable analysis according to NT-proBNP categories, and by Cox proportional hazards regression for the adjusted models. Variables for adjustment of hazards were selected from previously published work of the getABI study group [10,11]. The Missing values for predictor variables were imputed by randomly selected values from the cohort. Results for predictors are given as hazard ratios (HR) and 95% confidence intervals (CI). Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics

A total of 6382 patients were included (mean age 72.5 ± 5.3, 42.2% female) in this analysis. The median NT-proBNP level was 143.15 pg/ml (Q1: 83.6; Q3: 271.8). In average, NT-proBNP levels were higher in male patients compared to female (304,6 pg/ml vs. 271,7 pg/ml).

The baseline characteristics were depicted in Table 1 stratified for NT-proBNP using 125 and 300 pg/ml as threshold [9].

3.2. Association of NT-proBNP with all-cause mortality and cardiovascular mortality

After a follow-up time of 41,873 person-years 1204 participants died from any cause and 347 patients had a fatal cardiovascular event.

The incidence of all-cause and cardiovascular mortality was higher in subjects with higher levels of NT-proBNP (all-cause mortality/cardiovascular mortality: 35.4%/13.6% for NT-proBNP > 300 p g/ml; 16.2%/4.0% for NT-proBNP 125–300 pg/ml vs. 11.4%/2.4% for NT-proBNP $\leq$ 125 pg/ml.

Table 2a and 2b show the Cox-regression analysis for all-cause mortality and fatal cardiovascular events. Unadjusted, subjects with a NT-proBNP level > 300 pg/ml had more than three-fold risk for all-cause mortality and more than six-fold increased risk for cardiovascular mortality. Associations were attenuated but remained statistically significant after further adjustment for age, sex, traditional risk factors, cardiac diseases and cardiac medications using NT-proBNP as continuous variable as well as using the defined thresholds. After further adjustment (full model) for cardiac diseases and cardiac medications associations remained unchanged as depicted in Table 3. In particular, when modelling NT-proBNP as a continuous variable, a 2-fold increase of it was associated with a 50% increase in the risk of cardiovascular death in the model M5. The ability of the model M5 to distinguish between alive and death was good, since the area under the curve (AUC) was determined as 0.77.

Further, we investigated if the associations between continuous NT-proBNP and endpoints were modified by sex. Regarding all-cause mortality, in females a one-unit change in log2-transformed NT-proBNP resulted in elevation of the hazard by 38,9%, and for men by 26,7% (p-value for interaction 0.015 in fully adjusted model), whereas for cardiovascular mortality, although hazards were still numerically different, that interaction was not significant (p-value 0.39, results not shown).

Fig. 1 displays the survival probability according to NT-proBNP levels, showing a significant difference in mortality rate in patients with a NT-proBNP level > 300 pg/ml.

4. Discussion

In this large prospective cohort study we examined the association of NT-proBNP with all-cause and cardiovascular mortality above traditional risk factors.

Table 1
Baseline characteristics.

	Overall	NT-proBNP ≤ 125 pg/ml	NT-proBNP 125–300 pg/ml	NT-proBNP > 300 pg/ml
N	6382	2780	2190	1412
Age (years)	72.51 (5.27)	71.23 (4.76)	72.71 (5.17)	74.68 (5.64)
Males (%)	2693 (42.20%)	1316 (47.34%)	763 (34.84%)	614 (43.48%)
Education: ISCED < 3 (%)	1586 (24.85%)	634 (22.81%)	576 (26.30%)	376 (26.63%)
Current Smoker (%)	578 (9.06%)	259 (9.32%)	205 (9.36%)	114 (8.07%)
Systolic blood pressure (mmHg)	143.72 (19.40)	142.10 (18.39)	144.45 (19.51)	145.78 (20.85)
Diastolic blood pressure (mmHg)	81.37 (9.58)	81.56 (9.40)	81.06 (9.43)	81.50 (10.12)
Vitamin D < 50 ng/ml (%)	4401 (68.96%)	1839 (66.15%)	1520 (69.41%)	1042 (73.80%)
CRP > 3 mg/L (%)	2468 (38.67%)	1009 (36.29%)	823 (37.58%)	636 (45.04%)
GGT > 3rd quartile (%)	1560 (24.44%)	667 (23.99%)	482 (22.01%)	411 (29.11%)
HCY > 15 μmol/L (%)	3188 (49.95%)	1247 (44.86%)	1072 (48.95%)	869 (61.54%)
PAD (%)	1319 (20.67%)	414 (14.89%)	468 (21.37%)	437 (30.95%)
Diabetes (%)	1626 (25.48%)	716 (25.76%)	487 (22.24%)	423 (29.96%)
Arterial hypertension (%)	4136 (64.81%)	1624 (58.42%)	1458 (66.58%)	1054 (74.65%)
LDL-C ≥ 130 mg/dl (%)	2736 (42.87%)	1309 (47.09%)	928 (42.37%)	499 (35.34%)
GFR < 60 ml/min (%)	1257 (19.70%)	317 (11.40%)	416 (19.00%)	524 (37.11%)
Lipid-lowering medication (%)	1499 (23.49%)	563 (20.25%)	556 (25.39%)	380 (26.91%)
Beta blocker (%)	1935 (30.32%)	516 (18.56%)	743 (33.93%)	676 (47.88%)
Diuretics (%)	1786 (27.98%)	626 (22.52%)	584 (26.67%)	576 (40.79%)
Digitalis (%)	516 (8.09%)	113 (4.06%)	140 (6.39%)	263 (18.63%)
Antihypertensive medication (%)	3284 (51.46%)	1259 (45.29%)	1102 (50.32%)	923 (65.37%)
Total Cholesterol (mg/dl)	212.29 (37.84)	215.09 (36.67)	213.46 (37.82)	204.95 (39.21)
HDL Cholesterol (mg/dl)	52.73 (17.58)	52.08 (16.03)	54.53 (19.57)	51.20 (16.99)
LDL Cholesterol (mg/dl)	125.23 (31.22)	127.96 (30.30)	124.91 (31.49)	120.37 (31.91)

ISCED: International Standard Classification of Education; CRP: C-reactive protein; GGT: Gamma-Glutamyl Transferase; HCY: Homocystein; PAD: peripheral artery disease; LDL; Low density lipoprotein; GFR: Glomerular filtration rate; HDL: High density lipoprotein.

Table 2a
Cox regression for the association of NT-proBNP with all-cause mortality.

	NT-proBNP as continuous variable (Log2-transformed)	NT-proBNP as categorical variable (in reference to the ≤ 125 pg/ml group)	
		125–300 pg/ml	> 300 pg/ml
Model	Hazard Ratio (95%-CI)	Hazard Ratio (95%-CI)	Hazard Ratio (95%-CI)
Unadjusted	1.51 (1.46; 1.57)	1.46 (1.25; 1.70)	3.62 (3.15; 4.17)
Model 1 (Age and gender)	1.41 (1.35; 1.46)	1.41 (1.21; 1.64)	2.90 (2.51; 3.35)
Model 2 (Model 1 + Cardiac medication)	1.37 (1.32; 1.43)	1.43 (1.22; 1.67)	2.74 (2.35; 3.19)
Model 3 (FRV)	1.43 (1.38; 1.49)	1.43 (1.23; 1.67)	3.09 (2.67; 3.56)
Model 4 (model 2 + Cardiac diseases)	1.36 (1.31; 1.42)	1.40 (1.20; 1.64)	2.64 (2.26; 3.08)
Model 5 (Full adjusted model)	1.31 (1.26; 1.37)	1.36 (1.17; 1.59)	2.34 (1.99; 2.74)

Cardiac diseases: cardiovascular diseases including coronary heart diseases, cerebral diseases and peripheral artery diseases.
Cardiac medication including beta-blocker, diuretics and digitalis.

Table 2b
Cox regression for the association of NT-proBNP with Cardiovascular mortality.

	NT-proBNP as continuous variable (Log2-transformed)	NT-proBNP as categorical variable (in reference to the ≤ 125 pg/ml group)	
		125–300 pg/ml	> 300 pg/ml
Model	Hazard Ratio (95%-CI)	Hazard Ratio (95%-CI)	Hazard Ratio (95%-CI)
Unadjusted	1.83 (1.71; 1.95)	1.62 (1.21; 2.29)	6.38 (4.83; 8.41)
Model 1 (Age and gender)	1.70 (1.60; 1.82)	1.64 (1.19; 2.25)	5.22 (3.93; 6.94)
Model 2 (Model 1 + Cardiac medication)	1.60 (1.49; 1.72)	1.58 (1.15; 2.18)	4.31 (3.19; 5.81)
Model 3 (FRV)	1.70 (1.59;1.81)	1.61 (1.17, 2.22)	5.06 (3.81,6.71)
Model 4 (Model 2 + Cardiac diseases)	1.58 (1.46; 1.69)	1.51 (1.10; 2.09)	3.93 (2.90; 5.32)
Model 5 (Fully adjusted model)	1.51 (1.39; 1.64)	1.48 (1.07; 2.04)	3.41 (2.51; 4.63)

Cardiac diseases: cardiovascular diseases including coronary heart diseases, cerebral diseases and peripheral artery diseases;
Cardiac medication including beta-blocker, diuretics and digitalis.

Increased NT-proBNP levels were associated with excessive prevalence of all-cause and cardiovascular mortality, resulting in an overall mortality of 35.4% and cardiovascular mortality of 13.6% in 7 years for patients with a NT-proBNP level > 300 pg/ml. The associations remained statistically significant after adjustment for traditional risk factors, cardiac diseases and medications.

Our results show strong associations of higher NT-proBNP levels with mortality in an unselected, large population of elderly patients in the primary care setting independent of traditional risk factors. Our results suggest that the mechanism involved in event manifestation and that are reflected in elevated NT-proBNP levels, are different from those mediated trough traditional risk factors.

Natriuretic peptides are commonly used for the diagnosis of heart failure in symptomatic patients with dyspnoea. Moreover, it was showed, that natriuretic guided treatment for chronic heart failure improves mortality. [12]

However, there is growing evidence, that higher levels of natriuretic peptides predict cardiac events and mortality in the general population and therefore serve as markers of cardiovascular risk.

Table 3
Predictors of all-cause mortality in the fully adjusted model, multivariable analysis.

Risk factor	Hazard-Ratio	95%-CI
Age (per year)	1.062	1.05–1.08
Sex	1.983	1.74–2.26
NT proBNP 125–300 pg/ml	1.363	1.17–1.59
NT proBNP > 300 pg/ml	2.335	1.99–2.74
Hypertension	0.918	0.80–1.05
Diabetes mellitus	1.445	1.27–1.64
Smoker (current)	2.027	1.72–2.39
LDL (≥130 mg/dl)	0.806	0.71–0.91
Lipid-lowering medication	0.722	0.62–0.84
CVD	1.267	1.09–1.47
ISCED 0–2 vs. 3–6	1.279	1.11–1.48
CRP (>3 mg/l)	1.186	1.05–1.33
GGT (>Q3)	1.302	1.14–1.48
GFR (per 10 ml/min/1.73 m^2)	0.923	0.89–0.96
Homocystein (>15 μmol/l)	1.171	1.04–1.32
Vitamin D (<50 nmol/l)	1.398	1.21–1.61
PAD	1.389	1.22–1.58
Use of Diuretics	1.220	1.07–1.39
Use of Beta blocker	0.836	0.73–0.96
Use of Digitalis	1.360	1.15–1.61

LDL: Low density lipoprotein; CVD: cardiovascular diseases; ISCED: International Standard Classification of Education; CRP: C-reactive protein; GGT: Gamma-Glutamyl Transferase; PAD: peripheral artery disease; LDL; Low density lipoprotein; GFR: Glomerular filtration rate; HDL: High density lipoprotein.

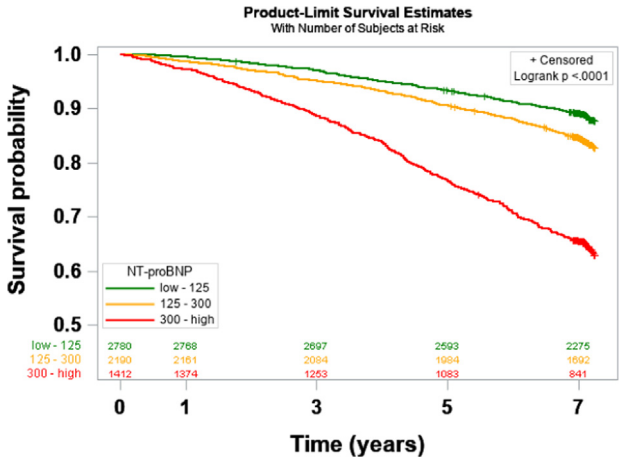

Fig. 1. Kaplan Meier Analysis for survival probability as stratified by a NT-pro-BNP-threshold of ≤ 125; 125–300; >300 pg/ml. Median follow up was 7.06 (Q1 7.00; Q3 7.14) years.

Wang et al. reported an association of BNP with all-cause mortality and cardiovascular events in a healthy population [3]. These results were confirmed in a *meta*-analysis with 87,747 subjects showing a 3-fold risk for cardiovascular events in subjects with a higher level of natriuretic peptides [13]. Another work of McKie et al including 2042 individuals showed that NT-proBNP independently predicted mortality and heart failure in the general population free of overt heart failure [14]. In another *meta*-analysis, recently published, on 25,715 subjects, elevated NT-proBNP levels appeared to be independently associated with increased risk for cardiovascular and all-cause mortality in the general population [15]. Participants in the highest NT-proBNP concentration had a significantly increased 3.77 fold cardiovascular mortality and 2.44 fold all-cause mortality, even after adjustment for traditional risk factors. In this setting, authors stated that higher NT-proBNP levels might reflect the degree of systemic atherosclerosis and/or an unknown initial cardiac overload.

Other studies demonstrated the prognostic value of natriuretic peptides in different settings:

Bibbings et al. showed, that elevated levels of NT-proBNP predict cardiovascular morbidity and mortality in patients with stable coronary heart disease independent of systolic and diastolic function assessed by echocardiography [16]. Paniagua et al. demonstrated the prognostic value of natriuretic peptide in dialysis patients. [17] and Tu et al. showed that NT-proBNP may be useful as independent prognostic markers in patients with ischemic stroke [18].

NT-proBNP is strongly associated with all-cause mortality also in hypertensive population. Paget et al. have demonstrated that plasma NT-proBNP levels ≥ 133 pg/mL were associated with a threefold increase of the risk of death in comparison with levels < 50.8 pg/ml, even after adjustment for confounders. Moreover, NT-proBNP resulted to be a stronger prognostic marker than ECG and its dosage has been proposed as first test for the cardiovascular stratification instead of ECG [19].

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 [2]. For the 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 [7].

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 [20].

Our here presented data revealed that elevated NT-proBNP levels in the primary care setting are able to identify patients at high risk for a future cardiac event.

4.1. Clinical Implications

In our study we describe a significant association of NT-proBNP with fatal cardiac events and all-cause mortality, suggesting that NT-proBNP is the first biomarker which may improve risk prediction independent of and complementary to traditional cardiovascular risk factors. Together with previously published results, these data suggest that NT-proBNP may improve risk discrimination for cardiac events above and beyond traditional cardiovascular risk factors and therefore may help to identify subjects that may profit from aggressive risk modification. Furthermore, subjects with higher NT-proBNP levels may benefit from a cardiological workup for detections of early stages of a systolic or diastolic heart dysfunction even in the absence of symptoms.

We emphasize that assessment of NT-proBNP is feasible using a simple blood.

5. Conclusion

In our study we describe a significant association of NT-proBNP with fatal cardiovascular events and all-cause mortality, suggesting that NT-proBNP is the first biomarker which may improve risk prediction for cardiovascular events in the primary care setting independent of traditional cardiovascular risk factors.

6. Limitations

A limitation of our study is that we did not perform an echocardiography at baseline to get more information und reasons for

elevated levels of NT-proBNP as heart failure. We presented heart failure medications and we included heart failure medication into Cox proportional hazard analyses.

Furthermore, our study includes the measurement of NT-proBNP only, not of BNP.

CRediT authorship contribution statement

Henrik Rudolf: Conceptualization, Methodology, Software, Writing - original draft. **Andreas Mügge:** Writing - review & editing, Supervision. **Hans J. Trampisch:** Investigation, Writing - review & editing, Supervision. **Hubert Scharnagl:** Investigation, Supervision. **W. März:** Investigation, Supervision. **Kaffer Kara:** Supervision, Conceptualization, Methodology, Software, Writing - original draft.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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