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# B-type natriuretic peptides for the prediction of cardiovascular events and mortality in patients living with HIV: Results from the HIV-HEART study

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ABSTRACT

*Aims:* B-type natriuretic peptide (BNP) has been suggested to improve risk prediction of cardiovascular (CV) events and mortality. We aimed to evaluate the value of BNP to predict the composite primary endpoint of CV events and mortality alongside traditional and HIV specific risk factors in a HIV-infected population.
*Methods:* In this prospective multicenter HIV-HEART study we followed 808 HIV-positive subjects in the German Ruhr area for a median follow up of 120 (IQR:113–129) months since 2004. Association of BNP with the composite primary endpoint was assessed using Cox regression adjusting for traditional cardiovascular and HIV specific risk factors.
*Results:* At baseline, median BNP was 10.3 (IQR 5.4–18.9) pg/ml. The composite endpoint occurred in 158 (19.6%) patients. Subjects with high BNP levels showed significantly increased frequencies of CV events and death (22% for BNP ≤5 pg/ml, 30% for BNP >5 up to ≤20 pg ml, 38% for BNP >20 up to ≤35 pg ml, 59% for BNP >35 up to ≤100 pg ml and 86% for BNP >100 pg/ml, p-value < 0.01). In the fully adjusted model that included traditional CV risks as well as HIV specific factors, after a $\log_2$ transformation, doubling of BNP was significantly associated with increased risk for the composite endpoint (HR:1.16 (95%CI 1.01–1.33); p = 0.031). Comparing BNP of <5 pg/ml to BNP > 100 pg/ml, HR in the fully adjusted model was 3.25 (95%CI 1.50–7.08; p < 0.001).
*Conclusions:* Increased BNP is associated with significant excess of incident CV events and mortality in HIV-infected patients. BNP is a valuable marker to improve the prediction of CV events and mortality.


## 1. Introduction

Significantly improved combined antiretroviral treatment (cART) and progress in the management of human immunodeficiency virus-1 (HIV-1) infection changed the clinical course of HIV-infection to a chronic disease with approximately normal life-expectancy. The reconstitution of the immune system and a decreased rate of HIV-associated diseases have greatly reduced mortality among HIV-infected patients [1]. Cardiovascular disease (CVD) is now one of the leading causes of morbidity and mortality in countries with established cART [2,3]. Individuals with HIV have higher rates of CVD than uninfected subjects [4], likely because of a combination of traditional CV risk factors as well as independent effects of HIV itself such as inflammatory and immunologic factors and toxicities of cART [5,6]. The longer life expectancy of HIV-infected populations due to a reduced death rate of HIV-specific causes after the introduction of cART coupled with the increased risk for CVD makes CV risk assessment an important part of HIV care. However, CV risk stratification remains a challenge in HIV-infected subjects. The accuracy of established CVD risk prediction underestimates the observed incidence of cardiovascular events and diseases [7]. Brain

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natriuretic peptide (BNP) is one of the important biomarkers with a proven role in the diagnosis of congestive heart failure [8,9] and has recently been associated with CV disease and all-cause mortality in patients even without known CV disease [10–12]. The potency of BNP has also been researched in myocardial ischemia, cor pulmonale and acute pulmonary embolism [13]. However, the prognostic utility to predict CV events and mortality in HIV-infected patients is still unclear. Therefore, the aim of this study was to assess, whether BNP improves risk prediction of CV events and mortality in a German cohort of HIV-positive subjects in the HIV-HEART study.

## 2. Methods

### 2.1. Study population

The HIV-HEART study is an ongoing, prospective multicenter trial that is being conducted to assess the incidence, prevalence and clinical course of CV diseases in HIV-infected patients. We consecutively included 875 subjects, all ≥18 years of age with documented HIV infection, enrolled between 05/2004 and 05/2006 in HIV-outpatient clinics of the German Ruhr-region. The study is registered at Clinical Trials (NCT01119729) and the design of the study has been previously published [14]. Informed consent was obtained from all subjects included in this study. The study was approved by the Institutional Review Board and performed in compliance with GCP (good clinical practice) guidelines according to the Declaration of Helsinki. Furthermore, the study was approved by appropriate national regulatory authorities and ethics committees for the participating centers.

Therapy-naïve and cART-receiving males and females with known HIV-1 infection, were included in a consecutive manner. Patients were requested to have a stable disease within 4 weeks prior to inclusion in the study. Exclusion criteria for this longitudinal study were: (1) an instable CV status in the last four weeks prior to the screening visit or current hospitalization; (2) inability or unwillingness to give informed consent; (3) age <18 years; or (4) pregnancy. In addition, subjects with prior coronary artery disease (coronary artery bypass surgery and/or interventional revascularization procedures and history of prior myocardial infarction) and atherosclerotic non-coronary heart disease (stroke/TIA and peripheral artery disease) at baseline were excluded from the analysis.

### 2.2. Clinical data collection and risk factor classification

The standardized examinations included a targeted assessment of medical history, regarding sociodemographics, access to care information, chronic illness, behaviors associated with HIV acquisition, medications, HIV treatment, and disease characteristics, physical examination, a single office blood pressure and heart rate measurement, an electrocardiogram (ECG) and a transthoracic echocardiography with details being described elsewhere [14]. In brief, body mass index (BMI) was calculated as body weight divided by square of height. Smoking behavior was assessed in detail. Use of lipid lowering drugs as well as antihypertensive and antidiabetic medication was documented. Hypertension was defined as systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively, or documented use of antihypertensive medication. Dyslipidemia was defined as total cholesterol > 4.92 mmol/l, HDL cholesterol < 1.04 mmol/l in male and <1.16 mmol/l in female, or fasting triglycerides >1.69 mmol/l. Diabetes mellitus was defined as anamnestic definite diagnosis or documented antidiabetic drug or insulin. A family history for CHD was defined as myocardial infarction or stroke before the age of 50 years in any first-degree relative. Obesity was defined as Body Mass Index (BMI) > 30 kg/m$^2$. The Framingham risk equation was used to predict the 10-year probability of coronary heart disease (10-year CHD risk) at baseline and follow-up [15]. Blood was drawn for comprehensive laboratory tests including HIV-specific parameters (CD4 cell count, HIV-1 RNA viral levels) and CV markers (lipid concentrations, BNP values and renal parameters) using standard methods. The physiologically active BNP levels were measured from blood samples using Triage ® MeterPlus BNP assay (Biosite, Au-Wädenswill, Switzerland).

### 2.3. Follow up and end point definition

Clinical follow-up was scheduled in an ambulatory setting including complete baseline evaluation as described above and questions about new medications, hospital admissions and an outpatient diagnosis of CVD. During the trial, patients were followed for the occurrence of endpoint events. All analyses were on a time-to-first event basis. CV events—fatal and nonfatal—including death were considered as the composite primary endpoint. CV events were defined as myocardial infarction, new diagnosis of coronary artery disease, coronary artery bypass grafting, coronary revascularisation and atherosclerotic non-coronary heart disease (stroke/TIA and peripheral artery disease). 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.

### 2.4. Statistical analysis

Data management for the study was coordinated by the Clinical Trial Centre Leipzig (Leipzig, Germany), which independently managed the database and performed primary statistical analyses. Statistical analysis was performed using the statistical opensource software R (R Core Team Vienna). Continuous parameters were represented as mean ± SD or median (25th percentile, Q1; 75th percentile, Q3). Accordingly, (univariate) tests for group differences in continuous parameters were performed using the Student *t*-test or Mann-Whitney *U* test. Nominal parameters were given as n (percentage, %); group differences were evaluated by using the $\chi^2$ or Fisher's exact test. To evaluate the association between BNP and the risk of mortality and CV events defined as time to first event (one row per patient), we calculated unadjusted, age and sex-adjusted, and multivariable adjusted hazard ratios (HRs), and 95% confidence intervals (CIs) using Cox proportional hazards regression models. In multivariable models, we mutually adjusted relevant predictors of CV mortality and morbidity. A p-value of $p < 0.05$ indicated statistical significance. The proportional Hazard Assumption was tested for all models using the function cox.zph out of the survival Package of R. Before the inclusion of the BNP variable into the models we log transformed the BNP to base 2. This means, one step on the log scale of BNP represents a doubling of BNP values. The given Hazard Ratio (HR) in Table 2 (and the text) is the risk of a patient with a doubled BNP value. For adjusted regression, the following models were used: model 1 included age and gender; model 2 included age, gender, smoking, diabetes mellitus, total cholesterol, LDL, arterial hypertension or use of antihypertensive drugs; model 3 included model 2 and clinical HIV CDC stadium III (AIDS) and CD4/CD8 ratio. We also used a model with HIV specific risk factors only, notably HIV duration (in months) as well as HIV RNA below the detection limit. At the beginning of the HIVH Trial in 2004, the detection limit was set to 50 c/ml due to logistic reasons. To assess the performance of the different models, time-dependent discrimination was estimated by Uno's C-statistic. To evaluate the additional predictive value of a model with and without BNP, we calculated the Average Positive Prediction (AP) Values for either model with and without BNP. To compare the additional predictive value of BNP we used prediction accuracy metrics. This measurement is appropriate for population-based studies. To evaluate the impact of BNP we calculated the AP-ratio of the models with and without BNP, whereas the model with BNP is the numerator and the AP of the model without BNP is the denominator. AP ratios above 1 suggest better performance of the model with BNP. Afterwards, we compared the APs of the models with BNP with the models without BNP.

## 3. Results

### 3.1. Demographic characteristics

A total of 875 cohort subjects were included in the analysis. 67 of 875 subjects (7%) were excluded because of invalid BNP measurements or CV events prior to inclusion. The baseline characteristics stratified by BNP levels in 5 groups (≤5 pg/ml, >5 to ≤20 pg/ml, >20 to ≤35 pg/ml, >35 to ≤100 pg/ml, >100 pg/ml) are shown in Table 1. The cohort was predominantly male (83.2%) with an average age of 43.8 ± 10.3 years and of Caucasian ethnicity in 89% of individuals. The duration of known HIV-infection was 8.2 ± 7.0 years with 29.6% of the subjects were late presenters with a HIV CDC stadium C. At baseline, average BNP levels were 19.4 ± 32.4 (median 10.3; IQR: 5.4–18.9) pg/ml. We observed substantial differences in the CV risk factors between those groups with low versus high BNP-levels. Subjects with low BNP-levels had a more favorable CV risk profile compared to those with increased BNP-levels, resulting in a significantly lower Framingham risk score (FRS: 4.7 ± 6.1; 5.5 ± 6.5; 6.3 ± 6.9; 10.2 ± 9.5; 13.7 ± 9.8; $p < 0.001$). Besides, the systolic and diastolic blood pressure was higher in patients with increased BNP-levels. The proportion of patients with an LVEF of >50% and >55% was similar between the 5 BNP groups (Table 1). In the univariate model adjusting both for the cutoff of 50% and 55%, the LVEF did not influence the predictive value of BNP (data not shown). Furthermore, increased BNP levels were associated with lower CD4 cells and longer time since HIV diagnosis. However, there was no difference in the duration of cART.

### 3.2. Association of BNP with cardiovascular events and mortality

We studied 808 patients in this study. During a median follow up of 120 (IQR: 113–129) months, an overall period of 7924 patient years, the composite endpoint occurred in 158 (19.6%) patients. Time to first event was significantly shorter in those with higher BNP-levels. From those, 46 patients died of CV or sudden death. Overall, 91 subjects died from any other or unknown cause. Subjects with increased BNP

**Table 1**
Demographics.

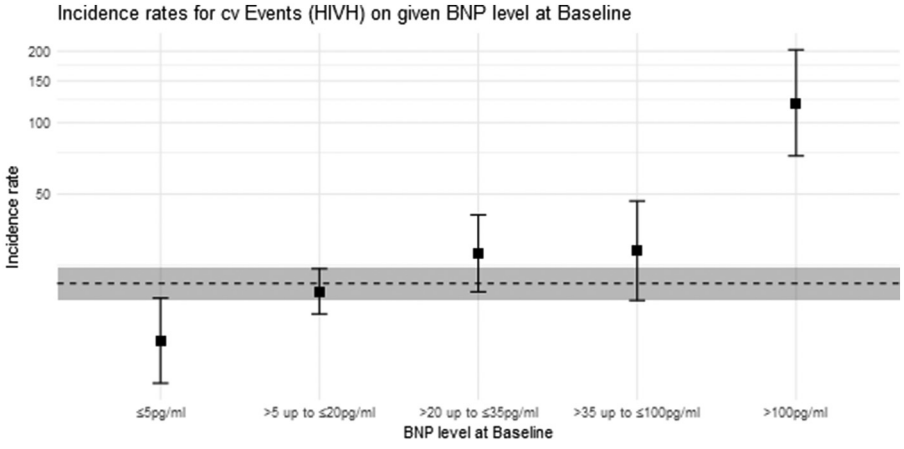
| BNP in groups | Overall | ≤5 pg/ml | >5 up to ≤20 pg ml | >20 up to ≤35 pg ml | >35 up to ≤100 pg ml | >100 pg/ml | P-value |
|---|---|---|---|---|---|---|---|
| | (N = 808) | (N = 187) | (N = 430) | (N = 106) | (N = 64) | (N = 21) | |
| Age (yrs) | 43.8 ± 10.3 | 40.5 ± 8.3 | 43.0 ± 9.6 | 46.0 ± 10.8 | 50.1 ± 10.6 | 57.5 ± 14.5 | <0.001 |
| Sex (male) n (%) | 672 (83.2) | 170 (90.9) | 359 (83.5) | 77 (72.6) | 48 (75.0) | 18 (85.7) | <0.001 |
| Framingham risk (%) | 6.0 ± 7.1 | 4.7 ± 6.1 | 5.5 ± 6.5 | 6.3 ± 6.9 | 10.2 ± 9.5 | 13.7 ± 9.8 | <0.001 |
| Diabetes n (%) | 35 (4.3) | 6 (3.2) | 14 (3.3) | 4 (3.8) | 5 (7.8) | 6 (28.6) | <0.001 |
| Hypertension n (%) | 167 (20.7) | 33 (17.7) | 70 (16.3) | 28 (26.4) | 27 (42.2) | 9 (42.9) | <0.001 |
| Present smoking n (%) | 417 (51.7) | 108 (57.8) | 228 (53.0) | 46 (43.4) | 29 (46.0) | 6 (28.6) | 0.15 |
| Former smoking n (%) | 149 (18.5) | 33 (17.6) | 77 (17.9) | 21 (19.8) | 12 (19.0) | 6 (28.6) | 0.15 |
| Body mass index [kg/m$^2$] | 24.0 ± 3.7 | 24.2 ± 3.4 | 23.9 ± 3.8 | 24.2 ± 4.0 | 24.4 ± 3.0 | 24.0 ± 3.9 | 0.79 |
| Systolic BP [mm Hg] | 128.6 ± 20.6 | 128.4 ± 17.2 | 125.8 ± 19.2 | 133.7 ± 24.7 | 137.5 ± 26.1 | 135.0 ± 23.4 | <0.001 |
| Diastolic BP [mm Hg] | 83.3 ± 12.2 | 84.8 ± 11.8 | 82.2 ± 11.6 | 83.8 ± 13.8 | 86.9 ± 13.7 | 79.4 ± 11.3 | 0.007 |
| Total cholesterol [mg/dl] | 207.4 ± 49.0 | 207.2 ± 46.9 | 206.8 ± 47.7 | 213.7 ± 57.8 | 203.2 ± 43.3 | 204.2 ± 63.0 | 0.69 |
| LDL-C [mg/dl] | 112.5 ± 45.6 | 110.4 ± 44.9 | 114.7 ± 43.5 | 106.7 ± 59.6 | 113.0 ± 33.8 | 115.5 ± 45.8 | 0.63 |
| Creatinine [mg/dl] | 1.04 ± 0.18 | 1.04 ± 0.15 | 1.03 ± 0.16 | 1.01 ± 0.17 | 1.11 ± 0.32 | 1.08 ± 0.26 | 0.4 |
| BNP [pg/ml], median (Q1, Q3) | 10.3 (5.4–18.9) | 5.0 (5.0–5.0) | 10.2 (7.5–13.8) | 25.1 (22.8–29.2) | 49.2 (40.4–61.2) | 162.0 (135.0–235.0) | <0.001 |
| HIV stadium C n (%) | 239 (29.6) | 52 (27.8) | 125 (29.1) | 32 (30.2) | 20 (31.2) | 10 (47.6) | 0.45 |
| HIV RNA <50 copies n (%) | 423 (53.7) | 106 (57.6) | 221 (52.7) | 54 (52.4) | 32 (52.5) | 10 (50.0) | 0.82 |
| CD4/CD8-ratio - mean ± SD | 0.62 ± 0.53 | 0.66 ± 0.41 | 0.62 ± 0.62 | 0.57 ± 0.39 | 0.61 ± 0.36 | 0.55 ± 0.49 | 0.70 |
| CD4/CD8-ratio - median (IQR) | 0.50 (0.30 to 0.80) | 0.60 (0.40 to 0.80) | 0.50 (0.30 to 0.80) | 0.50 (0.30 to 0.72) | 0.50 (0.30 to 0.80) | 0.40 (0.20 to 0.80) | 0.08 |
| CD4 cells [%] | 25.6 ± 10.9 | 27.7 ± 11.2 | 25.3 ± 10.3 | 24.2 ± 11.5 | 25.6 ± 11.0 | 21.7 ± 13.5 | 0.022 |
| HIV duration [years] | 8.2 ± 7.0 | 8.2 ± 6.7 | 7.8 ± 6.7 | 7.7 ± 5.5 | 10.5 ± 11.0 | 9.3 ± 6.1 | 0.05 |
| ART duration [years] | 4.4 ± 3.7 | 4.4 ± 3.3 | 4.4 ± 3.9 | 4.1 ± 3.8 | 4.1 ± 3.3 | 5.6 ± 3.6 | 0.47 |
| LVEF [%] - median (IQR) | 57 (53 to 62) | 56 (53.to 60) | 57 (53 to 62) | 58 (54 to 64) | 57 (54 to 60) | 59 (53 to 62) | 0.06 |
| LVEF > 55% - N (%) | 467 (58.2) | 96 (51.3) | 254 (59.3) | 68 (64.8) | 36 (58.1) | 13 (61.9) | 0.22 |
| LVEF > 50% - N (%) | 689 (85.8) | 156 (83.4) | 367 (85.7) | 91 (86.7) | 57 (91.9) | 18 (85.7) | 0.58 |
| CV events n (%) | 266 (32.9) | 42(22.4) | 128(29.8) | 40 (37.7) | 38 (59.4) | 18 (85.7) | <0.001 |
| Time to 1st CV event (months) | 111.7 ± 32.1 | 117.3 ± 27.0 | 113.3 ± 30.0 | 108.8 ± 33.4 | 104.2 ± 36.0 | 66.2 ± 53.1 | <0.001 |

Abbreviations; yrs. = years; BP = blood pressure; LDL = low density lipidoprotein; ART = antiretroviral therapy; LVEF = left ventricular ejection fraction; IQR = interquartile range; CV = cardiovascular. Data are presented as mean ± SD if not otherwise presented.

had higher frequencies of the composite primary endpoint (22% for BNP ≤ 5 pg/ml, 30% for BNP > 5 up to ≤20 pg/ml, 38% for BNP > 20 up to ≤35 pg/ml, 59% for BNP >35 up to ≤100 pg/ml and 86% for BNP > 100 pg/ml).

Incidence rates of the composite primary endpoint were higher in subjects with increased BNP, 12.0 (95%CI 8.0–18.2) for BNP ≤ 5 pg/ml, 19.5 (95%CI 15.6–24.2) for BNP > 5 to ≤20 pg/ml, 28.1 (95%CI 19.4–40.9) for BNP > 20 to ≤35 pg/ml and 28.8 (95%CI 17.8–46.7) >35 to ≤100 pg/ml, 120.8 (95%CI 72.5–202.8) for BNP > 100 pg/ml (Fig. 1).

Cox-regression analyses for the composite primary endpoint are shown in Table 2. Doubling of the BNP value was associated with CV events and mortality [HR: 1.14 (95%CI 1.00–1.29); p = 0.05]. These associations were slightly enhanced after adjustment for CV risk factors [HR: 1.19 (95%CI 1.04–1.36); p = 0.010]. In the fully adjusted model that included traditional CV risks as well as HIV specific parameters, doubling of the BNP value was still significantly associated with increased risk for the composite primary endpoint [HR: 1.16 (95%CI 1.01–1.33); p = 0.031]. For sensitive reason, we repeated the analyses




| | ≤5pg/ml | >5 up to ≤20pg/ml | >20 up to ≤35pg/ml | >35 up to ≤100pg/ml | >100pg/ml |
|---|---|---|---|---|---|
| N with event | 22 | 79 | 27 | 16 | 14 |
| # of events | 42 | 128 | 40 | 38 | 18 |
| Incidence [95% CI] | 12.0 [8.0;18.2] | 19.5 [15.6;24.2] | 28.1 [19.4;40.9] | 28.8 [17.8;46.7] | 120.8 [72.5;202.8] |

**Fig. 1.** Incidence rates for CV events (HIVH) on BNP levels at baseline. N = number of patients; # = number of cardiovascular events.

**Table 2**
Cox regression for the association of BNP with cardiovascular events and mortality (Model 1 (age and gender); Model 2 (Model 1 + CV risks: diabetes, hypertension, smoking behavior); Model 3 (Model 2 + HIV specific factors: HIV CDC stadium C (aids) and CD4/CD8 ratio)).

| Model | Model 1 | P value | Model 2 | P value | Model 3 | P value |
|---|---|---|---|---|---|---|
| BNP [pg/ml] | Hazard ratio (95% CI) | | Hazard ratio (95% CI) | | Hazard ratio (95% CI) | |
| per doubling | 1.14 [1.00 to 1.29] | 0.05 | 1.19 [1.04 to 1.36] | 0.010 | 1.16 [1.01 to 1.33] | 0.031 |
| BNP in 5 groups | | <0.001 | | <0.001 | | <0.001 |
| >5 up to ≤20 vs. ≤5 | 1.39 [0.86 to 2.24] | | 1.44 [0.88 to 2.34] | | 1.38 [0.85 to 2.25] | |
| >20 up to ≤35 vs. ≤5 | 1.66 [0.93 to 2.96] | | 1.75 [0.96 to 3.16] | | 1.64 [0.91 to 2.98] | |
| >35 up to ≤100 vs. ≤5 | 1.39 [0.71 to 2.71] | | 1.50 [0.76 to 2.95] | | 1.59 [0.81 to 3.13] | |
| >100 vs. ≤5 | 2.93 [1.38 to 6.22] | | 4.34 [1.98 to 9.50] | | 3.25 [1.50 to 7.08] | |

using BNP grouped as above mentioned, still showing association of CV events and mortality with elevated BNP. Comparing BNP of <5 pg/ml to BNP > 100 pg/ml, HR in the fully adjusted model was 3.25 (95%CI 1.50–7.08; p < 0.001). BNP values between 5 and 100 pg/ml were also associated with higher HRs, although this was not significant (Table 2). After 12 months the model with BNP (per doubling) had an AP of 0.16 (95%CI 0.06–0.31) while the AP for the model without BNP was lower [AP 0.11 (95%CI 0.05–0.24)]. This is the greatest difference of APs [0.05 (95%CI 0.01–0.10)]. The AP-ratio between the two models was best at 12 months [1.48 (95%CI 1.04–1.80)]. When BNP was included in the model, a 1.5 times increased prediction for early CV events resulted and Uno's C-index was improved (0.721 vs. 0.734). After adjustment for CV risk factors, the C-index remained increased (0.774 vs. 0.786). In the fully adjusted model including both CV and HIV-specific risk factors, the C-index still was slightly improved for the model including BNP (0.795 vs. 0.800). Overall, these models display at least moderate ability to detect HIV-infected patients with increased risk for CV events, when including BNP into the model.

### *3.3. BNP for prediction of first cardiovascular event and mortality*

The Kaplan-Meier curve for BNP in Fig. 2 displays the event-free probability for coronary events and survival probability over time, showing a significant higher event rate in subjects with increased BNP, especially for those >100 pg/ml. The event rate in individuals >100 pg/ml within the first twelve months was extraordinary high. BNP < 5 pg/ml was associated with much lower rates of CV events over the next ten years.

## 4. Discussion

In this cohort study, we investigated the value of BNP to predict CV events and mortality in HIV-infected subjects and found that increased BNP levels were associated with adverse CV events and mortality. This increased risk persisted even after adjustment for CV risk factors and HIV specific parameters.

In the general population BNP has been established as a marker for heart failure diagnosis. Moreover, there is growing evidence that elevated levels of natriuretic-peptides may improve CV risk prediction in the general population above traditional risk factors [16–18]. In the STOP-HF trial, BNP-based screening and cardiological work-up in patients with BNP > 50 pg/ml significantly reduced the rate of incident heart failure [19]. Our findings in an HIV-infected cohort support the previous observations in HIV-negative individuals (or in general populations), that increased BNP-levels are independently associated with CV events and mortality, even after adjusting for traditional CV risk factors and HIV specific parameters. Especially, BNP-levels of >100 pg/ml are linked to significantly increased risk. Recently, several published

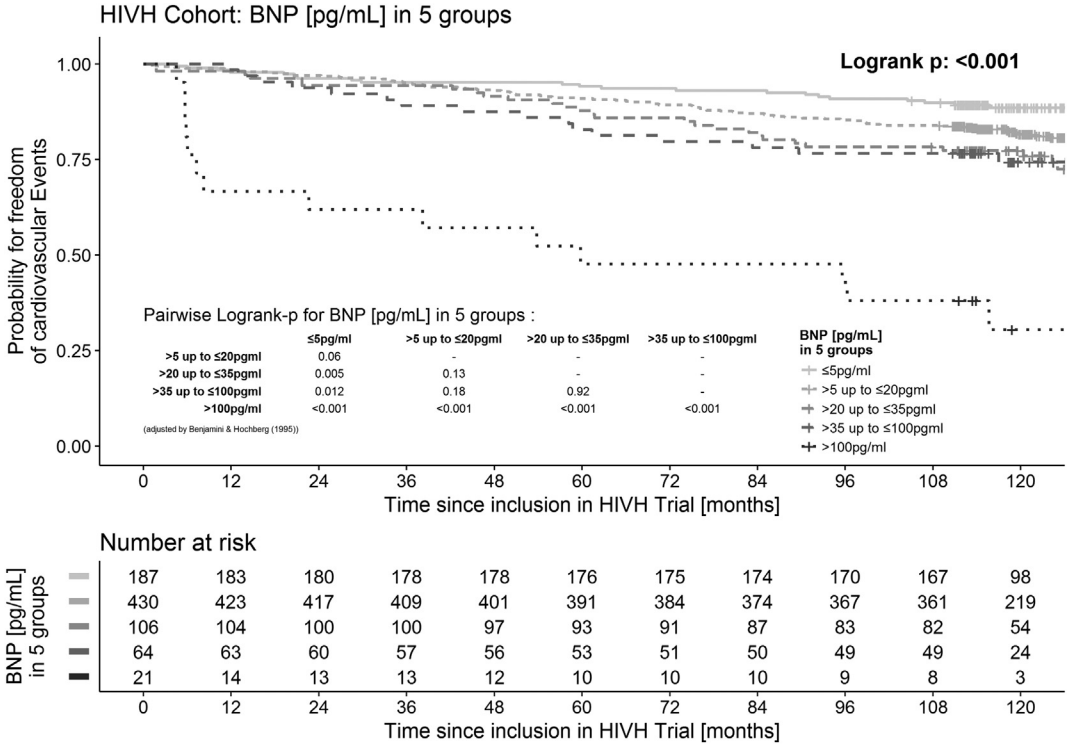



**Fig. 2.** Kaplan-Meier plot on probability for freedom of cardiovascular events based on BNP levels.

studies in small cohorts showed that high BNP levels are associated with an increased risk and burden of CVD in HIV-infected patients [20–22]. However, data on long-term follow-up evaluating the prognostic value of BNP in HIV positive patients are lacking. To our knowledge, this is the first study, to assess the association of BNP, CV events and mortality over a prospective follow-up of 10 years in an HIV-positive cohort, demonstrating BNP to have a high impact on the incidence of CV events and mortality.

Moreover, until now, for primary prevention purposes there are no established thresholds for BNP. In patients with dyspnea and suspected heart failure the current guidelines of the European Society of Cardiology recommend measurement of BNP with different thresholds for acute and chronic symptoms (BNP: 35 and 100 pg/ml) [23]. Therefore, we evaluated the predictive value of these thresholds and found relevant associations with CV events. We additionally determined BNP thresholds based on our cohort of <5 pg/ml, >5 to ≤20 pg/ml and >20 to ≤35 pg/ml which were associated with a lower CV morbidity. These risk prediction thresholds may also help to identify patients at higher risk for CV events, even if there is no heart failure present.

### 4.1. Clinical implications

Identifying subjects with cardiac diseases in early stages remains a challenge in modern medical care. Prior work already demonstrated that BNP is elevated in HIV-infected subjects with known heart dysfunction [24,25]. In our study we describe an association of BNP with CV events and mortality in subjects of unknown CV disease, suggesting that BNP is an appropriate biomarker, which may improve risk prediction in HIV-infected subjects independent of traditional CV risk factors and HIV specific parameters. While current guidelines do not recommend the use of biomarkers to assess risk [26], there is increasing evidence for their role in the prediction of CV events. In addition to previously published data, our data suggest that BNP may help to identify subjects that may profit from aggressive risk modification [21,24,27–29]. Refining risk prediction, measurement of BNP-levels in screening programs of HIV-infected subjects could help to detect silent CV disease and therefore, subjects with a high BNP-level may qualify for a cardiological workup for detection of early stage disease. Indeed, studies have shown the superiority of this peptide in the regard over conventional risk factors [12,30]. As the incidence of events is significantly increased with a doubling of BNP, we consider this value a suitable parameter to detect patients with an increasing CV risk during the outpatient follow-up. A threshold of >100 pg/ml could also be used as a single measure for high-risk patients because the rate of CV events above this threshold was increased dramatically especially within the first 12 months.

### 4.2. Strengths and limitations of the study

The strength of our study is the population-based design with follow-up over >10 years and benefits from a well-characterized and prospectively followed cohort of HIV-infected subjects. Traditional CV risk factors and HIV specific parameters were measured using highly standardized protocols. Since we studied mainly male individuals of Caucasian ethnicity, our results probably may not be generalizable to other ethnic groups and female patients, respectively. Our study includes only the measurement of BNP only, not of NT-pro BNP because of different values in healthy subjects and disproportionate rise of both peptides, there is no simple conversion factor to compare BNP and NT-proBNP levels. In addition, cardiac comorbidities like pulmonary hypertension, cardiac arrhythmias, right heart failure or valvular disease may influence the BNP level and CV endpoints as possible confounders. However, the total amount of patients with these comorbidities was too low, to be considered in our analyses. Also, further research is warranted to establish age- and gender-adjusted distribution as well as thresholds to define increased BNP-levels.

## 5. Conclusions

Elevated levels of BNP are associated with significant excess of incident CV events and mortality in HIV-infected patients. BNP measurement significantly and complementary improves the prediction of CV events and mortality in the HIV-infected population in addition to traditional risk factors and HIV specific parameters. Elevated BNP in HIV-infected subjects may be a useful marker for risk stratification of CVD in order to target intensified risk management and to predict mortality in HIV-infected patients.

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## Conflict of interest

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

## References

[1] F.J.J. Palella, K.M. Delaney, A.C. Moorman, et al., Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators, N. Engl. J. Med. 338 (1998) 853–860.
[2] N. Friis-Moller, C.A. Sabin, R. Weber, et al., Combination antiretroviral therapy and the risk of myocardial infarction, N. Engl. J. Med. 349 (2003) 1993–2003.
[3] N. Obel, H.F. Thomsen, G. Kronborg, et al., Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study, Clin. Infect. Dis. 44 (2007) 1625–1631.
[4] V.A. Triant, HIV infection and coronary heart disease: an intersection of epidemics, J. Infect. Dis. 205 (Suppl. 3) (2012) S355–S361.
[5] F.C. Frerichs, K.P. Dingemans, K. Brinkman, Cardiomyopathy with mitochondrial damage associated with nucleoside reverse-transcriptase inhibitors, N. Engl. J. Med. 347 (2002) 1895–1896.
[6] V.A. Triant, H. Lee, C. Hadigan, et al., Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease, J. Clin. Endocrinol. Metab. 92 (2007) 2506–2512.
[7] V.A. Triant, J. Perez, S. Regan, et al., Cardiovascular risk prediction functions underestimate risk in HIV infection, Circulation 137 (2018) 2203–2214.
[8] J.L.J. Januzzi, C.A. Camargo, S. Anwaruddin, et al., The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study, Am. J. Cardiol. 95 (2005) 948–954.
[9] A.S. Maisel, P. Krishnaswamy, R.M. Nowak, et al., Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure, N. Engl. J. Med. 347 (2002) 161–167.
[10] E. Di Angelantonio, R. Chowdhury, N. Sarwar, et al., B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies, Circulation 120 (2009) 2177–2187.
[11] G.C. Linssen, S.J. Bakker, A.A. Voors, et al., N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population, Eur. Heart J. 31 (2010) 120–127.
[12] T.J. Wang, M.G. Larson, D. Levy, et al., Plasma natriuretic peptide levels and the risk of cardiovascular events and death, N. Engl. J. Med. 350 (2004) 655–663.
[13] M. Namdari, A. Eatemadi, B. Negahdari, Natriuretic peptides and their therapeutic potential in heart failure treatment: an updated review, Cell. Mol. Biol. (Noisy-le-Grand) 62 (2016) 1–7.
[14] T. Neumann, S. Esser, A. Potthoff, et al., Prevalence and natural history of heart failure in outpatient HIV-infected subjects: rationale and design of the HIV-HEART study, Eur. J. Med. Res. 12 (2007) 243–248.
[15] R.B.S. D'Agostino, R.S. Vasan, M.J. Pencina, et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study, Circulation 117 (2008) 743–753.
[16] J.L. Januzzi, R. van Kimmenade, J. Lainchbury, et al., NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study, Eur. Heart J. 27 (2006) 330–337.
[17] K. Kara, A.A. Mahabadi, M.H. Berg, et al., Predicting risk of coronary events and all-cause mortality: role of B-type natriuretic peptide above traditional risk factors and coronary artery calcium scoring in the general population: the Heinz Nixdorf Recall Study, Eur. J. Prev. Cardiol. 21 (2014) 1171–1179.
[18] K. Kara, N. Lehmann, T. Neumann, H. Kälsch, S. Möhlenkamp, I. Dykun, M. Broecker-Preuss, N. Pundt, S. Moebus, K.H. Jöckel, R. Erbel, A.A. Mahabadi, NT-proBNP is superior to BNP for predicting first cardiovascular events in the general population: the Heinz Nixdorf Recall Study, Int. J. Cardiol. 183 (2015) 155–161.
[19] M. Ledwidge, J. Gallagher, C. Conlon, et al., Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial, JAMA 310 (2013) 66–74.

[20] T. Berg, D. Zdunek, J. Stalke, et al., N-terminal pro-B-type natriuretic peptide (NT-proBNP) in HIV-1 infected individuals on HAART, Eur. J. Med. Res. 12 (2007) 152–160.
[21] D.A. Duprez, J. Neuhaus, R. Tracy, et al., N-terminal-proB-type natriuretic peptide predicts cardiovascular disease events in HIV-infected patients, AIDS 25 (2011) 651–657.
[22] A. Mansoor, K. Althoff, S. Gange, et al., Elevated NT-pro-BNP levels are associated with comorbidities among HIV-infected women, AIDS Res. Hum. Retrovir. 25 (2009) 997–1004.
[23] J.J. McMurray, S. Adamopoulos, S.D. Anker, et al., ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 14 (2012) 803–869.
[24] F. Breuckmann, K. Nassenstein, J. Kondratieva, et al., MR characterization of cardiac abnormalities in HIV+ individuals with increased BNP levels, Eur. J. Med. Res. 12 (2007) 185–190.
[25] U.S. Kristoffersen, A.M. Lebech, J. Gerstoft, et al., Right and left cardiac function in HIV-infected patients investigated using radionuclide ventriculography and brain natriuretic peptide: a 5-year follow-up study, HIV Med. 9 (2008) 180–186.
[26] M.F. Piepoli, A.W. Hoes, S. Agewall, et al., European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2381.
[27] M.R. Gingo, Y. Zhang, K.B. Ghebrehawariat, et al., Elevated NT-pro-brain natriuretic peptide level is independently associated with all-cause mortality in HIV-infected women in the early and recent HAART eras in the Women's Interagency HIV Study cohort, PLoS One 10 (2015), e0123389.
[28] T. Neumann, N. Reinsch, K. Neuhaus, et al., BNP in HIV-infected patients, Herz 34 (2009) 634–640.
[29] J. Olalla, E. Crespo, J. De la Torre, et al., Factors related to NT-proBNP levels in HIV patients aged over 40 years, AIDS Res. Ther. 12 (2015) 17.
[30] P. Welsh, C. Hart, O. Papacosta, et al., Prediction of cardiovascular disease risk by cardiac biomarkers in 2 United Kingdom cohort studies: does utility depend on risk thresholds for treatment, Hypertension 67 (2016) 309–315.