JACC: ADVANCES VOL. 2, NO. 10, 2023
© 2023 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ORIGINAL RESEARCH

OUTCOMES AND QUALITY

BNP and NT-proBNP Thresholds for the Assessment of Prognosis in Patients Without Heart Failure

Stefanie Jehn, MD, Amir A. Mahabadi, MD, Christian Pfohl, MD, Lukas Vogel, MD, Fadi Al-Rashid, MD, Peter Luedike, MD, Matthias Totzeck, MD, Tienush Rassaf, MD, Iryna Dykun, MD

ABSTRACT

BACKGROUND Brain natriuretic peptide (BNP)/N-terminal-pro hormone brain natriuretic peptides (NT-proBNP) enable risk stratification, diagnosing, and monitoring of heart failure patients. An additional prognostic value for BNP/NT-proBNP in nonheart failure patients and general population cohorts is described in the literature, but specific cut-off levels are only described for heart failure patients.

OBJECTIVES This study aimed to determine thresholds for risk stratification in nonheart failure patients.

METHODS Based on the Essen Coronary Artery Disease registry we excluded patients with known heart failure or elevated BNP/NT-pro BNP levels. The resulting cohort was divided into a derivation and validation cohort using random sampling. The prognostic value of BNP/NT-proBNP of incident mortality was evaluated in the derivation cohort using univariate and multivariable cox regression analysis. In receiver operating characteristic analysis and corresponding area under the curve the optimal threshold was determined using Youdens J index. The findings were verified in the validation cohort.

RESULTS A total of 3,690 patients (age 62.9 ± 12.5 years, 71% male, 68% patients with coronary artery disease) were included. During a mean follow-up of 2.6 ± 3.4 years (median 1.2 [IQR: 0.4-2.88]), 169 deaths of any cause occurred. Based on Youden's J index, BNP-thresholds of 9.6 and 29pg/ml and NT-proBNP thresholds of 65 and 77pg/ml for men and women, respectively, were determined. BNP/NT-proBNP levels above these thresholds were associated with increased mortality in the derivation cohort (HR: 2.44 [95% CI: 1.32-4.53], $P = 0.005$). The predictive value was confirmed in the validation cohort (HR: 2.78 [95% CI: 1.26-6.14], $P = 0.01$).

CONCLUSIONS We here describe sex-specific BNP/NT-proBNP thresholds that allow prediction of impaired survival in patients without heart failure, independent of traditional cardiovascular risk factors. (JACC Adv 2023;2:100688) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Natriuretic peptides are secreted in the atrium and ventricle due to mechanic wall stress and neurohormonal stimulation.[1] They play an important role in electrolyte and water homeostasis as well as lipolysis and blood pressure.[2,3] Concentrations of brain natriuretic peptide (BNP)/N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) are predominantly measured in patients

From the Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Hospital Essen, Essen, Germany.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 30, 2023; revised manuscript received September 6, 2023, accepted September 25, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100688

ABBREVIATIONS AND ACRONYMS

BNP = brain natriuretic peptide

CAD = coronary artery disease

ECAD = Essen Coronary Artery Disease

NT-pro BNP = N terminal pro hormone of natriuretic peptide

ROC = receiver-operating characteristic

with acute and chronic heart failure and predetermined cut-off values are specified in current heart failure guidelines for diagnosing, risk stratification, and therapy monitoring in heart failure cohorts.[4] Diverse data document a potential value of BNP/NT-proBNP serum levels also in the general population and nonheart failure patient cohorts as a predictor of cardiovascular disease manifestation and long-term prognosis in the absence of heart failure.[5-10] In a large meta-analysis of 66 prospective studies including over 89,000 patients, we demonstrate a similar association of BNP/NT-proBNP levels and incident cardiovascular events in patients with and without heart failure. In this meta-analysis the predictive value of BNP/NT-proBNP was found to be independent of the cut-off level used in the included studies.[11] For patients without heart failure, no thresholds are established for BNP/NT-proBNP in clinical routine to assess the patient's individual risk. Therefore, in the present large database of consecutive patients without heart failure, we aimed to determine the association of BNP/NT-proBNP with incident mortality an establish cut-off levels, applicable for routine risk stratification.

PATIENTS AND METHODS

STUDY SAMPLE. The present analysis is based on the cohort of the Essen Coronary Artery Disease [ECAD]-registry, including patients >18 years who were hospitalized between 2004 and 2019 in the West German Heart and Vascular Center, Essen, Germany. Details on the study have been previously reported.[12] In brief, the ECAD registry includes data from 40,461 coronary procedures (dataset as of July 2019). Data from 6,483 examinations were excluded due to missing follow-up information. For the present analysis, also patients with noncoronary exams were excluded (n = 3,117). Heart failure patients, defined by symptoms, echocardiography, and natriuretic peptides, were excluded based on clinical diagnosis. In addition, all patients with elevated natriuretic peptides (BNP >100 pg/nL, NT-proBNP >400 pg/nL) and missing information regarding BNP/NT-proBNP levels at admission (n = 27,171), were also excluded to control for any undiagnosed heart failure, leading to a final cohort of 3,690 patients for the present analysis. To derivate and subsequently validate a sex specific BNP/NT-proBNP cut-off value, we divided the cohort into a derivation and validation cohort by using random sampling. The derivation cohort consisted randomly assigned two-thirds of the cohort (n = 2,471) and the validation cohort of randomly assigned 1/3 of the cohort (n = 1,219). The study was approved by the local ethics committee (19-8956-BO).

CLINICAL CHARACTERISTICS AND COVARIATE ASSESSMENT. Information on traditional cardiovascular risk factors from the same hospital stay were automatically drawn from the hospital information system and merged into the database. Coronary artery disease was based on coronary angiogram, as defined by discretion of treating experienced interventional cardiologists. Valvular heart disease, hypertension, coronary artery disease, myocarditis, rhythm disorders, peripheral artery disorder, and aortic diseases were assessed based on clinical diagnosis and summarized as known cardiac conditions. Laboratory variables were assessed using standardized enzymatic methods (low- density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol, lipoprotein(a), creatinine). Diabetes was defined as hemoglobin A1c ≥6.5%. Self-reported information on current smoking status and family history of premature CAD was classified as present, absent, or unknown. In addition, medication information at time of admission was assessed (beta blockers, ACE inhibitors, Ca^{2+} inhibitors, diuretics, and aspirin).

ASSESSMENT OF BNP/NT-proBNP. Quantification of BNP/NT-proBNP-levels was performed in the central laboratory of the University Hospital Essen using standardized methods. Physiologically active BNP molecule was measured using the Siemens ADVIA Centaur BNP assay (Siemens) and NT-proBNP was quantified using the Roche Assay (Roche Diagnostics). The analytic functional sensitivity of the assay, which represents the lowest BNP and NT-proBNP concentration determined, were 2 pg/mL and 5 pg/mL, respectively. As either BNP or NT-proBNP was available for singular patients and to adjust for the skewed distribution, we standardized BNP and NT-proBNP levels based on the respective sex specific percentile rank in levels from 1 to 100.

ENDPOINT DEFINITION. All-cause mortality was defined as primary endpoint variable. Information on survival status was assessed from all available hospital records (including partner healthcare facilities) as well as insurance information. Any ambulatory or inpatient presentation to the West German Heart and Vascular Center, the University Hospital Essen or any partner health care facility after the coronary exam

was used for confirmation of survival status. Patients without confirmed death but no recurrent presentation to the health care provider were considered as missing follow-up and excluded from the present analysis.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD if normally distributed and as median (IQR) if nonnormally distributed. Discrete variables are given in frequency and percentiles. Continuous variables were compared using 2-sided *t*-test or Mann-Whitney U test (for nonnormal distributed variables) and discrete variables using the chi-square test.

Cox regression analysis was used to determine the association of BNP/NT-proBNP with all-cause mortality in unadjusted and risk factor adjusted (multivariable) models. Variables adjusted for in each multivariable model included age, sex, systolic blood pressure, LDL-C, diabetes, smoking status, and family history of premature CAD. In addition, a sensitivity analysis was performed excluding patients with impaired renal function, defined as creatinine levels >1.3 mg/dL, as well as excluding patients on diuretic medication. In further sensitivity analyses, we used several actual BNP/NT-proBNP numbers as threshold (20/70, 15/60, 30/100, and 50/150 pg/mL for BNP/NT-proBNP, respectively) to address a potential difference in the distribution of natriuretic peptides across the study population and to check for the robustness of the findings. Again, these sensitivity analyses were performed in fully adjusted Cox regression models. Data are expressed as HR (95% CI) per 1-SD change in BNP/NT-proBNP rank.

Kaplan-Meier curves illustrate the all-cause mortality stratified by the 29th percentile BNP/NT-proBNP threshold in the derivation and validation cohorts using the log-rank test.

Receiver-operating characteristic (ROC) curve analysis was performed with corresponding area under the curve for identifying specificity and sensitivity. Youden's J index was assessed to establish a threshold for prediction of survival. The association of this threshold with incident mortality was then tested in the derivation cohort and validated in the validation cohort using adjusted Cox regression analysis. Subgroup analyses were performed, stratifying by age-groups (<60 vs ≥60 years), sex, previous or known cardiac conditions, known CAD, systolic blood pressure (<140 vs ≥140 mm Hg), hypertension, renal function (creatinine <1.3 vs ≥1.3 mg/dL), and follow-up duration (<2.6 vs ≥2.6 years) in fully adjusted model. The *P* values for interaction were obtained by applying a Wald test to the coefficients of Cox regression models. All subgroup and sensitivity analyses followed the same methodology as outlined above.

Harrell's C statistics was calculated to obtain improvement in discrimination of incident mortality BNP/NT-proBNP above vs below the threshold over traditional cardiovascular risk factors (including age, sex, systolic blood pressure, LDL-C, diabetes, smoking status, and family history of premature CAD). Additionally, we analyzed the reclassification ability of elevated BNP/NT-proBNP using the category-free Net Reclassification Improvement index as well as Integrated Discrimination Improvement.[13]

All analyses were performed using SAS software (Version 9.4, SAS Institute Inc). A *P* value of <0.05 indicated statistical significance.

RESULTS

Overall, 3,690 patients (mean age 62.9 ± 12.5 years) were included in our analysis. 71% were male. Of these, 2,471 patients (mean age 62.9 ± 12.5 years, 70% men) were placed into the derivation cohort and 1,219 into the validation cohort (mean age 62.9 ± 12.6 years, 72% men). Baseline characteristics and frequency of coronary revascularization therapy did not differ between derivation and validation cohort. The present cohort includes 68% patients with coronary artery disease and 9% with other cardiac conditions.

Detailed patient characteristics depicted in **Table 1**. Median BNP level was 35.6 pg/mL (IQR: 18.9-61.8 pg/mL) and mean NT-proBNP level was 120 pg/mL (IQR: 61.0-219.0 pg/mL). In the derivation cohort the median BNP level was 35.2 pg/mL (IQR: 19.0-61.8 pg/mL) and the mean NT-proBNP level was 118.0 pg/mL (IQR: 61.0-217,5 pg/mL), respectively. In the validation cohort the median BNP level was 36.0 pg/mL (IQR: 18.9-60.8 pg/mL) and the mean NT-proBNP level was 124.0 pg/mL (IQR: 61.0-221.0 pg/mL).

ASSOCIATION OF BNP/NT-proBNP LEVELS AND ALL-CAUSE MORTALITY. During a mean follow-up of 2.6 ± 3.4 years (median 1.2 [IQR: 0.4-2.88]), 169 deaths of any cause occurred. Patients without fatal events had lower BNP/NT-proBNP rank compared to patients who died (48.4 ± 28.8 vs 58.4 ± 27.5, $P < 0.0001$). **Table 2** shows univariate and multivariate analyses of all-cause mortality based on the BNP/NT-proBNP rank in the derivation cohort. In fully

TABLE 1 Baseline Characteristics

	Overall cohort (N = 3,690)	Derivation cohort (n = 2,471)	Validation cohort (n = 1,219)	*P* Value
Demographics				
Age, y	62.9 ± 12.5	62.9 ± 12.5	62.9 ± 12.6	0.98
Male	2,604 (70.6)	1,726 (69.79)	878 (72.32)	0.11
Cardiovascular risk factors				
Diabetes mellitus	282 (7.6)	191 (7.7)	91 (7.5)	0.84
Family history of CAD	619 (16.8)	413 (16.7)	206 (16.9)	0.89
Current smoker	532 (14.4)	361 (14.6)	171 (14.0)	0.82
Systolic blood pressure (mm Hg)	138.9 ± 20.7	139.1 ± 21.1	138.6 ± 19.8	0.58
Hypertension	2,440 (66.1)	16,401 (66.4)	800 (65.6)	0.65
Laboratory parameters				
BNP (pg/mL)	35.6 (18.9-61.8)	35.2 (19.0-61.8)	36.0 (18.9-60.8)	0.77
NT-pro BNP (pg/mL)	120 (61.0-219.0)	118.0 (61.0-217.5)	124.0 (61.0-221.0)	0.68
Hb (g/dL)	13.9 ± 1.5	13.9 ± 1.5	13.9 ± 1.6	0.93
Creatinine (mg/dL)	1.07 (0.94-1.21)	1.07 (0.94-1.21)	1.07 (0.93-1.22)	0.63
LDL-C (mg/dL)	111.9 ± 40.1	112.2 ± 40.7	111.4 ± 40.0	0.61
HDL-C (mg/dL)	50.4 ± 15.4	50.4 ± 15.3	50.3 ± 15.4	0.90
HbA1c (%)	5.8 (5.4-6.4)	5.7 (5.4-6.4)	5.8 (5.4-6.4)	0.98
Clinical presentation				
Coronary artery disease	2,520 (68.3)	1,685 (68.2)	835 (68.5)	0.90
Chronic coronary syndrome	1,493 (40.5)	1,000 (40.5)	493 (40.4)	
Unstable angina	668 (18.1)	438 (17.7)	230 (18.9)	
NSTEMI	222 (6.0)	155 (6.3)	67 (5.5)	
STEMI	137 (3.7)	92 (3.7)	45 (3.7)	
Noncardiac diagnosis	836 (22.7)	554 (22.4)	282 (23.1)	
Other cardiac diagnosis	334 (9.1)	232 (9.4)	102 (8.4)	
Medication				
Beta-blockers	2,168 (58.8)	1,454 (58.8)	714 (58.6)	0.50
ACE inhibitors	1,642 (44.5)	1,087 (44.0)	555 (45.5)	0.12
Ca^{2+} inhibitors	768 (20.8)	522 (21.1)	246 (20.2)	0.72
Diuretics	1,233 (33.4)	828 (33.5)	405 (33.2)	0.81
Aspirin	1,988 (53.9)	1,350 (54.6)	638 (52.3)	0.45

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; BNP = brain natriuretic peptide; Hb = hemoglobin; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; NSTEMI = non-ST-segment-elevation-myocardial infarction; NT-proBNP = N terminal pro hormone of natriuretic peptide; STEMI = ST-segment elevation-myocardial infarction.

TABLE 2 Cox-regression Analysis for the Association of BNP/NT-proBNP With Incident All-cause Mortality in the Derivation Cohort

	HR (95% CI)	*P* Value
Unadjusted	1.56 (1.29-1.89)	<0.001
Adjusted for age, sex	1.46 (1.09-1.96)	0.01
Multivariable adjusted[a]	1.37 (1.08-1.80)	0.01

HR (95% CI) per SD for the BNP/NT-proBNP ranges were calculated using Cox proportional hazards regression models. [a]Multivariable model adjusted for sex, age, LDL-C, diabetes, systolic blood pressure, smoking status, family history for coronary artery disease.

BNP = brain natriuretic peptide; LDL-C = low-density lipoprotein-cholesterol; NT-proBNP = N terminal pro hormone of natriuretic peptide.

adjusted multivariable analyses, 1 SD increase in BNP/NT-proBNP was associated with 37% increased risk of mortality (Table 2).

Sensitivity analyses were performed to examine if similar associations were evident in several groups of interest. When excluding patients with impaired renal function, the prognostic value of natriuretic peptides was altered (HR: 1.6 [95% CI: 1.34-1.92], $P < 0.0001$). Likewise, effect size for the association of elevated natriuretic peptides with all-cause mortality was similar in patients without diuretic medication at baseline (HR: 1.39 [95% CI: 1.18-1.66], $P = 0.0001$). Testing the robustness of the

CENTRAL ILLUSTRATION **Natriuretic Peptides Associate With Long-term Mortality**

Step 1 Prognostic value of BNP/NT-proBNP as continuous variable in non-heart failure patients

	HR (95% CI)	*P* value
Unadjusted	1.43 (1.17-1.74)	0.0003
Multivariable adjusted*	1.25 (1.01-1.54)	0.04

*Multivariable adjustment controlling for age, sex, systolic blood pressure, LDL-cholesterol, smoking status, family history of premature CAD

Step 2 Optimal cut-off levels with Youden's J Index

BNP	NT-proBNP
29 pg/ml	77 pg/ml

BNP	NT-proBNP
9.6 pg/ml	65 pg/ml

Step 3 Cut-off levels in the derivation and validation cohort

	Derivation Cohort		Validation Cohort	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	3.19 (1.75-5.82)	<0.0001	3.02 (1.43-6.35)	0.004
Multivariable adjusted*	2.44 (1.32-4.53)	0.005	2.78 (1.26-6.14)	0.011

*Multivariable adjustment controlling for age, sex, systolic blood pressure, LDL-cholesterol, smoking status, family history of premature CAD

Jehn S, et al. JACC Adv. 2023;2(10):100688.

Evaluation of the prognostic value of BNP/NT-proBNP in nonheart failure patients: natriuretic peptides significantly associated with incident mortality with the 29th sex-specific percentile as optimal cut-off. BNP/NT-proBNP levels above this threshold were was associated with an approximately 2.5-fold increased mortality risk. BNP = brain natriuretic peptide; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

association of BNP/NT-proBNP with incident mortality, we further used different BNP/NT-proBNP thresholds, confirming the association of higher natriuretic peptides with increased mortality risk in nonheart failure cohorts (Supplemental Table 1). Effect sizes decreased with higher BNP/NT-proBNP thresholds.

DETERMINING BNP AND NT-proBNP THRESHOLDS. After demonstrating the significant and risk factor independent association of BNP/NT-proBNP levels with survival probability in patients without heart failure, we performed a ROC analysis in the derivation cohort to assess the predictive ability of BNP/NT-proBNP for long-term survival. For BNP/NT-proBNP alone, we observed an area under the curve of 0.622 (Supplemental Figure 1). Based on the ROC-analysis and Youden's J index, the 29th sex specific percentile was determined as optimal cut-off value, representing a BNP-threshold of 9.6 and 29 pg/mL and a NT-proBNP threshold of 65 and 77 pg/mL for men and women, respectively (**Central Illustration**). **Table 3** depicts the univariate and

TABLE 3 Cox-regression Analysis for BNP/NT-proBNP Thresholds as Predictor for All-cause Mortality

	Derivation Cohort		Validation Cohort	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	3.19 (1.75-5.82)	<0.001	3.02 (1.43-6.35)	0.004
Adjusted for age, sex	2.51 (1.36-4.64)	0.003	2.67 (1.23-5.81)	0.01
Multivariable adjusted[a]	2.44 (1.32-4.53)	0.005	2.78 (1.26-6.14)	0.01

HR (95% CI) per SD for the BNP/NT-proBNP ranges was calculated using Cox proportional hazards regression models. [a]Multivariable model adjusted for sex, age, LDL, diabetes, systolic blood pressure, smoking status, family history for coronary artery disease.

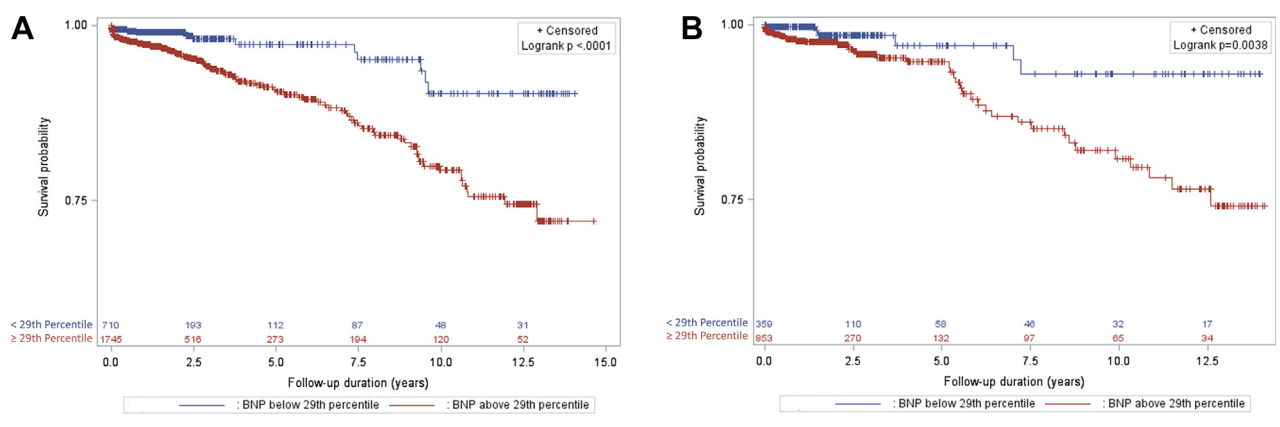
BNP = brain natriuretic peptide; LDL-C = low-density lipoprotein-cholesterol; NT-proBNP = N terminal prohormone of natriuretic peptide.

multivariable Cox regression analysis for the association of natriuretic peptides with mortality. When controlling for traditional risk factors, BNP/NT-proBNP levels above these thresholds were associated with increased mortality (derivation cohort: 2.44 [95% CI: 1.32-4.53], $P = 0.005$; validation cohort: 2.78 [95% CI: 1.26-6.14], $P = 0.01$). Figure 1 displays Kaplan-Meier curves illustrating the all-cause mortality among patients stratified by the 29th percentile BNP/NT-proBNP threshold in the derivation and validation cohorts (Figure 1).

In subgroup analyses, there was a trend toward a stronger association of BNP/NT-proBNP level above the threshold and all-cause mortality in patients older than 60 years, female patients and patients with known cardiac diagnosis, however, without significant interaction (Figure 2). No relevant association of elevated BNP/NT-proBNP levels with all-cause mortality was observed in patients with impaired renal function, while in patients with normal renal function, increased natriuretic peptides were strongly and independently associated with all-cause mortality. Stratifying by patients with shorter (0.87 ± 0.74 years; median 0.66 [IQR: 0.25-1.41] years) and longer follow-up duration (6.85 ± 3.80 years; median 5.68 [IQR: 3.22-10.19] years), we observed numerically slightly higher effect sizes for patients with shorter follow-up duration, while the difference did not reach statistical significance. In specific, BNP above the 29th percentile significantly associated with mortality in subgroups of shorter and longer follow-up. In subgroup analysis for patients with and without hypertension, effect sizes for the association of BNP/NT-proBNP levels above the threshold and all-cause mortality did not differ significantly. Effect sizes for patients with coronary artery disease compared to patients without coronary artery disease remained strong and independent for the association of BNP/NT-proBNP levels and all-cause mortality (Figure 2).

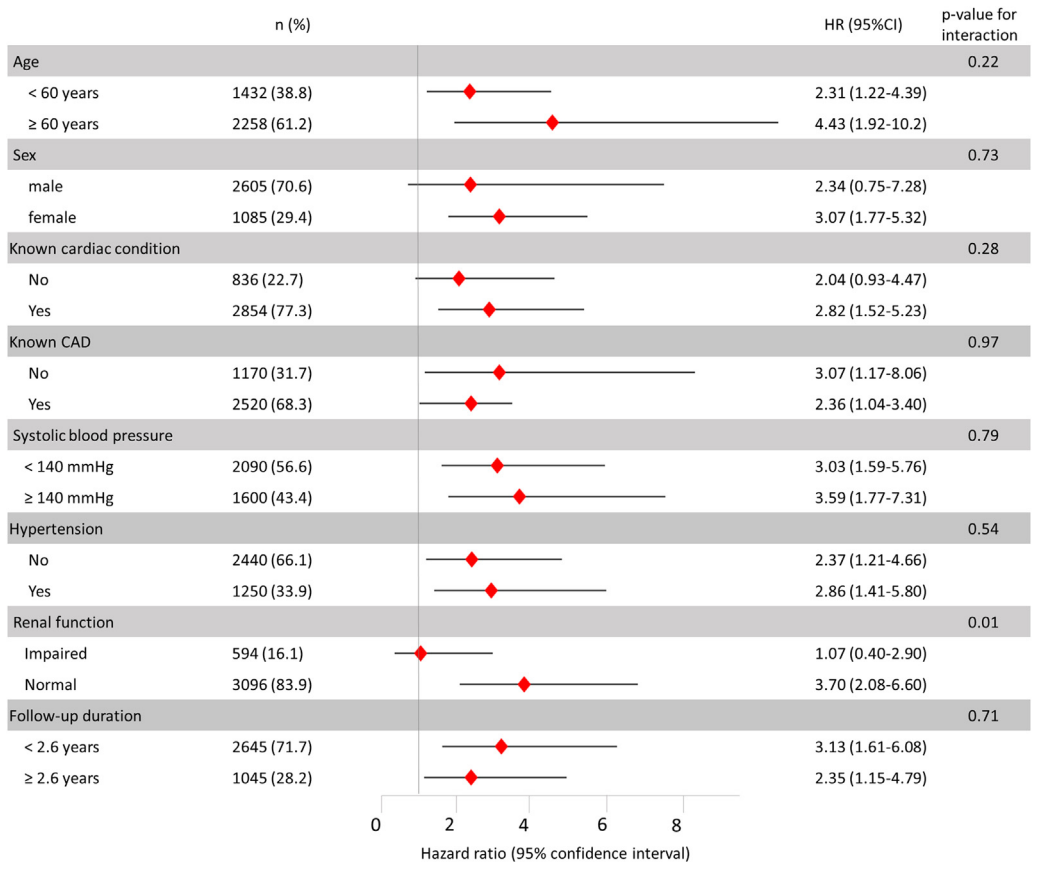
Adding above vs below the 29th percentile of BNP/NT-proBNP to a multivariable model including traditional cardiovascular risk factors led to significant improvement in Harrell's C statistic (Table 4). This was supported by an improvement in net reclassification (67% of events and 33% of nonevents were correctly reclassified) and a significant integrated discrimination improvement (Table 4).

FIGURE 1 Kaplan-Meier Curve for Survival of Patients With vs. Without Elevated Natriuretic Peptides



Kaplan-Meier-curve for survival stratified by the 29th percentile BNP/NT-proBNP threshold in the derivation (A) and validation cohort (B). The blue line depicts the patients With BNP/NT-proBNP levels below the 29th percentile, while the red line depicts the survival curve for patients with higher BNP/NT-proBNP-levels. Log-rank test confirmed a significant difference between both groups ($P < 0.0001$ for the derivation cohort; $P = 0.0038$ for the validation cohort). BNP = brain natriuretic peptide; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

FIGURE 2 Forest Plot for Appropriate Subgroups



Forrest Plot for subgroup analyses for the association of BNP/NT-proBNP thresholds with all-cause mortality, stratifying by other risk factors, clinical conditions, and follow-up duration. BNP = brain natriuretic peptide; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

DISCUSSION

In the present analysis of the ECAD-registry, we determined sex specific thresholds of BNP/NT-proBNP, which served as a predictor of all-cause mortality. In the present cohort, 70% of the included patients had diagnosed coronary artery disease and 15% had other cardiac conditions.

In a fully adjusted multivariable analysis, BNP/NT-proBNP levels above the defined thresholds were associated with an approximately 2.5-fold increase risk of all-cause mortality. These data suggest that the utilization of BNP threshold of 9.6 and 29 pg/mL and NT-proBNP thresholds of 65 and 77 pg/mL for men and women, respectively, can serve as novel sex-specific BNP/NT-proBNP cut-offs, qualifying for the detection of patients with impaired long-term prognosis.

Natriuretic peptides are well established in clinical routine for diagnosis and prognosis estimation as well as guiding therapy in heart failure.[4,14,15] It has been described that hypertensive patients have higher natriuretic peptides.[16] To evaluate, whether the presence of hypertension may have impacted our results, we performed a sensitivity analysis in patients with vs without elevated systolic blood pressure as

TABLE 4 Harrell's C Statistic, Net Reclassification Improvement, and Integrated Discrimination Improvement of the BNP Threshold Over Traditional Cardiovascular Risk Factors for Prediction of All-cause Mortality

	Effect size	*P* Value
Harrell's C for MV model without BNP	0.66952	–
Harrell's C for MV model with BNP	0.69346	–
Difference in AUC	0.0239 (0.00109-0.0468)	0.04
Category free net reclassification improvement	0.33701 (0.2206-0.4534)	<0.0001
Integrated discrimination improvement	0.006307 (0.0039-0.0087)	<0.0001

MV models include: age, sex, systolic blood pressure, low-density-lipoprotein-cholesterol, diabetes, smoking status, and family history of premature coronary artery disease.

AUC = area under the curve; BNP = brain natriuretic peptide; MV = multivariable.

well as with vs without hypertension, demonstrating that the association of elevated natriuretic peptides with impaired prognosis is independent of the presence of hypertension. In addition, previous data suggest that BNP/NT-proBNP may also be associated with increased cardiovascular risk and all-cause mortality in patients with coronary artery disease,[17-20] being in particular predictive of cardiac events in symptomatic patients[21] as well as in general population cohorts and nonheart failure patients.[9,22-25] In a healthy reference sample of a large European population-based study, the 90th percentile was described as a threshold, stratifying patients with and without future cardiovascular events.[9] While effect sizes using this approach were comparable to our findings, it led to slightly higher cut-off values for both BNP and NT-proBNP as compared to the present analysis. However, a validation of these thresholds has not been performed so far. In contrast, we stratified our cohort into a derivation and validation group, establishing the thresholds based on actual event rate in the derivation cohort. Subsequently we validated the thresholds in the validation cohort, observing similar predictive ability. In a recently performed meta-analysis on 66 studies with over 89,000 patients, we demonstrated that BNP/NT-proBNP levels are of prognostic value in patients with and without known heart failure as well as in the general population. We found that the effect sizes for the association of natriuretic peptides with MACE were independent of the predetermined cut-off values.[25] This meta-analysis underlined the need for validated cut-off values in nonheart failure patient cohorts that qualify for risk stratification. The present analysis provides such sex-specific thresholds that are associated with an increase in all-cause mortality and may qualify for the improving the risk assessment in clinical routine.

The circulating concentration of BNP/NT-proBNP is a well-established diagnostic tool for the detection of heart failure. However, other clinical conditions and diseases lead to elevated natriuretic peptides that need to be accounted for when interpreting BNP/NT-proBNP levels. BNP/NT-proBNP levels depend on age and sex, with higher values being described in the elderly and in women.[26-28] The present cohort is mostly representative of male sex; however, we found comparable results for male and female sex when using sex specific thresholds.

BNP/NT-proBNP are secreted by cardiomyocytes due to mechanic wall stress but also myocardial ischemia leads to augmented BNP gene expression, resulting in increased BNP/NT-proBNP levels,[1,29-32] while successful percutaneous coronary revascularization therapy decreases plasma concentrations.[33,34] In subgroup analysis, effect sizes for patients with coronary artery disease compared to patients without coronary artery disease remained strong and independent for the association of BNP/NT-proBNP levels and all-cause mortality. Impaired kidney function influences plasma concentrations of BNP[35] and in particular of NT-proBNP due to its renal elimination.[36] We found utilization of the here described threshold for BNP/NT-proBNP predicted outcome only in patients with normal renal function, while its application in patients with chronic kidney disease was not associated with future events. Further studies are needed to determine appropriate thresholds also for patients with concomitant renal impairment.

In the present analysis patients with heart failure were excluded. While we observed markedly lower BNP/NT-proBNP values as in heart failure cohorts, our results support the hypothesis that within normal range, elevated BNP/NT-proBNP values are a sign of multifactorial underlying diseases which is linked to poorer patient outcome. Therefore, if BNP/NT-proBNP is increased above the thresholds as established here, further workup of underlying diseases and subsequent therapy may improve the prognosis. Further studies are warranted to confirm our results and establish the mechanistic causality between underlying disease and prognosis.

STUDY LIMITATIONS. In the ECAD registry, only all-cause mortality is available as endpoint for longitudinal analyses. Therefore, we were not able to examine the association of natriuretic peptides with cardiovascular events, specifically. Our cohort represents a clinical and symptomatic cohort of patients undergoing invasive coronary angiography. The present findings are based on a predominantly male cohort. General population cohorts are needed to confirm, whether the here described thresholds also apply for asymptomatic and primary prevention cohorts. As part of the ECAD-registry, only the primary discharge diagnosis was assessed. Unfortunately, no further information on secondary diagnoses is available, ultimately limiting the understanding of the comorbidities of the patients in the cohort. Furthermore, body mass index was not available for the present cohort. When stratifying by duration of follow-up, we observed numerically higher effect sizes for patients with follow-up duration of <2.6 years as compared to ≥ 2.6 years, suggesting that elevated BNP-values associated stronger with short term mortality. However, also for patients with follow-up duration of ≥ 2.6 years (6.85 ± 3.80 years), we observed a significant association between

elevated natriuretic peptides and incident mortality, independent of other cardiovascular risk factors. Lastly, our results are based on a predominantly White population; hence generalization to other ethnic groups remains uncertain.

CONCLUSIONS

In a large cohort of patients with cardiovascular diseases but without heart failure, elevated natriuretic peptides levels were associated with increased long-term all-cause mortality. The majority of included patients had diagnosed coronary artery disease or other cardiac conditions. These data suggest the utilization of novel sex-specific BNP/NT-proBNP thresholds, which may qualify for the detection of patients with impaired long-term prognosis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Jehn was supported as a Junior Clinician Scientist within the University Medicine Essen Academy (UMEA) funded by the Faculty of Medicine, University of Duisburg-Essen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Amir A. Mahabadi, Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center, University Hospital Essen, Hufelandstr. 55, 45147 Essen, Germany. E-mail: amir-abbas.mahabadi@uk-essen.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Natriuretic peptides may qualify for the detection of patients with impaired long-term prognosis also in patient cohorts without heart failure.

TRANSLATIONAL OUTLOOK: General population cohorts are needed to confirm, whether the here described thresholds also apply for asymptomatic and primary prevention cohorts.

REFERENCES

1. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med*. 1998;339(5):321-328.

2. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. *Clin Endocrinol*. 1997;47(3):287-296.

3. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail*. 2004;6(3):257-260.

4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.

5. Volpe M, Rubattu S, Burnett J Jr. Natriuretic peptides in cardiovascular diseases: current use and perspectives. *Eur Heart J*. 2014;35(7):419-425.

6. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293(13):1609-1616.

7. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;52(6):450-459.

8. Berin R, Zafrir B, Salman N, Amir O. Single measurement of serum N-terminal pro-brain natriuretic peptide: the best predictor of long-term mortality in patients with chronic systolic heart failure. *Eur J Intern Med*. 2014;25(5):458-462.

9. Kara K, Lehmann N, Neumann T, et al. NT-proBNP is superior to BNP for predicting first cardiovascular events in the general population: the Heinz Nixdorf Recall Study. *Int J Cardiol*. 2015;183:155-161.

10. Pareek M, Bhatt DL, Vaduganathan M, et al. Single and multiple cardiovascular biomarkers in subjects without a previous cardiovascular event. *Eur J Prev Cardiol*. 2017;24(15):1648-1659.

11. Hendricks S, Dykun I, Balcer B, Totzeck M, Rassaf T, Mahabadi A. Higher BNP/NT-pro BNP levels stratify prognosis equally well in patients with and without heart failure: a meta-analysis with more than 89,000 patients. *ESC Heart Fail*. 2022;9(5):3198-3209.

12. Dykun I, Babinets O, Hendricks S, et al. Utilization of IVUS improves all-cause mortality in patients undergoing invasive coronary angiography. *Atherosclerosis Plus*. 2021;43:10-17.

13. Pencina MJ, Agostino RBD, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.

14. Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet*. 1997;350(9088):1349-1353.

15. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000;355(9210):1126-1130.

16. Takeda T, Kohno M. Brain natriuretic peptide in hypertension. *Hypertens Res*. 1995;18(4):259-266.

17. Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;352(7):666-675.

18. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA*. 2007;297(2):169-176.

19. Niccoli G, Conte M, Marchitti S, et al. NT-proANP and NT-proBNP circulating levels as predictors of cardiovascular outcome following coronary stent implantation. *Cardiovasc Revasc Med*. 2016;17(3):162-168.

20. Barbato E, Bartunek J, Marchitti S, et al. NT-proANP circulating level is a prognostic marker in stable ischemic heart disease. *Int J Cardiol*. 2012;155(2):311-312.

21. Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med*. 2002;39(2):131-138.

22. York MK, Gupta DK, Reynolds CF, et al. B-type natriuretic peptide levels and mortality in patients with and without heart failure. *J Am Coll Cardiol*. 2018;71(19):2079-2088.

23. Welsh P, Doolin O, Willeit P, et al. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J*. 2013;34(6):443-450.

24. Dietl A, Stark K, Zimmermann ME, et al. NT-proBNP predicts cardiovascular death in the general population independent of left ventricular mass and function: insights from a large population-based study with long-term follow-up. *PLoS One*. 2016;11(10):e0164060.

25. Hendricks S, Dykun I, Balcer B, Totzeck M, Rassaf T, Mahabadi AA. Higher BNP/NT-pro BNP levels stratify prognosis equally well in patients with and without heart failure: a meta-analysis. *ESC Heart Fail*. 2022;9(5):3198-3209.

26. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40(5):976-982.

27. Keyzer JM, Hoffmann JJ, Ringoir L, Nabbe KC, Widdershoven JW, Pop VJ. Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. *Clin Chem Lab Med*. 2014;52(9):1341-1346.

28. Rørth R, Jhund PS, Yilmaz MB, et al. Comparison of BNP and NT-proBNP in patients with heart failure and reduced ejection fraction. *Circ Heart Fail*. 2020;13(2):e006541.

29. Tenhunen O, Szokodi I, Ruskoaho H. Post-transcriptional activation of BNP gene expression in response to increased left ventricular wall stress: role of calcineurin and PKC. *Regul Pept*. 2005;128(3):187-196.

30. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail*. 2005;11(5 Suppl):S81-S83.

31. Volpe M, Gallo G, Rubattu S. Endocrine functions of the heart: from bench to bedside. *Eur Heart J*. 2023;44(8):643-655.

32. Burnett JC Jr, Kao PC, Hu DC, et al. Atrial natriuretic peptide elevation in congestive heart failure in the human. *Science*. 1986;231(4742):1145-1147.

33. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J*. 2003;17(9):1105-1107.

34. Gupta A, Beig JR, Tramboo NA, Afroze D, Hafeez I, Rather HA. The effect of percutaneous coronary revascularization on plasma N-terminal pro-B-type natriuretic peptide levels in stable coronary artery disease. *Indian Heart J*. 2018;70(2):282-288.

35. Santos-Araújo C, Leite-Moreira A, Pestana M. Clinical value of natriuretic peptides in chronic kidney disease. *Nefrologia*. 2015;35(3):227-233.

36. Panagopoulou V, Deftereos S, Kossyvakis C, et al. NTproBNP: an important biomarker in cardiac diseases. *Curr Top Med Chem*. 2013;13(2):82-94.

KEY WORDS brain natriuretic peptides, general population cohort, nonheart failure cohorts, risk stratification, thresholds

APPENDIX For a supplemental table and figure, please see the online version of this paper.

DuEPublico

Duisburg-Essen Publications online

UNIVERSITÄT DUISBURG ESSEN

Offen im Denken

ub | universitäts bibliothek

Dieser Text wird via DuEPublico, dem Dokumenten- und Publikationsserver der Universität Duisburg-Essen, zur Verfügung gestellt. Die hier veröffentlichte Version der E-Publikation kann von einer eventuell ebenfalls veröffentlichten Verlagsversion abweichen.

DOI: 10.1016/j.jacadv.2023.100688
URN: urn:nbn:de:hbz:465-20250107-140021-3

Dieses Werk kann unter einer Creative Commons Namensnennung - Nicht kommerziell - Keine Bearbeitungen 4.0 Lizenz (CC BY-NC-ND 4.0) genutzt werden.