ESC HEART FAILURE
ESC Heart Failure 2017; **4**: 232–240
Published online 21 April 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12150

ORIGINAL RESEARCH ARTICLE

Comparative accuracy of NT-proBNP and MR-proANP for the diagnosis of acute heart failure in dyspnoeic patients

Fabrice F. Darche, Christian Baumgärtner, Moritz Biener, Matthias Müller-Hennessen, Mehrshad Vafaie, Vitali Koch, Kiril Stoyanov, Rasmus Rivinius, Hugo A. Katus and Evangelos Giannitsis*

Department of Cardiology, Medical University Hospital Heidelberg, INF 410 D-69120, Heidelberg, Germany

Abstract

Aims To compare the performance of the natriuretic peptides (NPs) NT-proBNP and MR-proANP for the diagnosis of acute heart failure (AHF) in subsets of conditions potentially confounding the interpretation of NPs.

Methods and results We studied 312 patients, presenting to the emergency department with new onset of dyspnoea or worsening of chronic dyspnoea within the last 2 weeks. Performance of NPs for the diagnosis of AHF was tested and compared using C-statistics in the entire cohort and in conditions previously described to confound interpretation of NPs such as older age, renal failure, obesity, atrial fibrillation or paced rhythm, and in the NT-proBNP grey zone. AHF was diagnosed in 139 patients. In the entire cohort, the diagnostic performance of NT-proBNP was comparable with that of MR-proANP. Receiver operating characteristic analysis demonstrated that optimal diagnostic cut-offs were higher in the presence of older age, kidney failure or rhythm disorder. However, there were no statistically relevant differences between the receiver operating characteristic curves analysed in the total population and those studied in the pre-specified subsets severe kidney failure, advanced age, obesity, atrial fibrillation and paced rhythm, and grey zone NT-proBNP values. Moreover, the diagnostic performance of NT-proBNP was comparable with that of MR-proANP in the subsets.

Conclusions The performance of NT-proBNP and MR-proANP for AHF is comparable in the total population as well as in the subsets with potentially confounding characteristics such as older age, renal dysfunction, obesity, atrial fibrillation and paced rhythm, or those with NT-proBNP values in the grey zone.

Keywords NT-proBNP; MR-proANP; AHF; ROC curve; Clinical subsets

Received: 12 July 2016; Revised: 8 February 2017; Accepted: 17 February 2017
**Correspondence to: Prof. Dr Evangelos Giannitsis, Medizinische Klinik III, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. Tel: +49 6221 56 38686; Fax: +49 6221 56 5516. Email: evangelos_giannitsis@med.uni-heidelberg.de*

Introduction

In patients presenting with acute dyspnoea, accurate diagnosis of acute heart failure (AHF) is paramount in order to deliver early and appropriate treatment. For this purpose, brain-type natriuretic peptide (BNP), N-terminal pro brain-type natriuretic peptide (NT-proBNP) or atrial natriuretic peptide (ANP) collectively designated as natriuretic peptides (NPs) have been recommended by practice guidelines for rule-out used at pre-specified and validated cut-offs.[1–4] However, the performance of NP levels for the diagnosis of AHF has been reported to be less accurate in the setting of renal failure, and obesity as well as advanced age may confound interpretation of NP levels. While practice guidelines give no preference for the use of either NP, the biomarkers in acute heart failure (BACH) trial reported that ANP added to the utility of BNP levels in patients with intermediate BNP values and with obesity but not in renal insufficiency, the elderly, or patients with oedema.[5]

The present analysis was performed to test the relative performance of NT-pro-BNP and mid-regional (MR)-proANP for diagnosis of AHF in an independent study cohort and in clinical subsets where interpretation of levels might be confounded.

Methods

During a 22-month period from May 2013 to November 2014, patients presenting to the emergency department (ED) of the University of Heidelberg with acute onset of dyspnoea or pre-existing dyspnoea that deteriorated within the previous 14 days before admission were enrolled. Patients received routine evaluation including physical examination, a comprehensive laboratory testing including NT-proBNP, an ECG and chest radiography. Additional work-up was left at the discretion of the attending emergency physician.

Performance of NPs was tested in the overall cohort and in pre-specified subsets of particular interest including patients with a severe kidney failure (creatinine clearance $<$60 mL/min/1.73 m^2), age above or below 70 years, obesity defined as body mass index above or below 30 kg/m^2, rhythm other than sinus rhythm defined as either atrial fibrillation (AF) and paced rhythm, and among patients with NP levels within the grey zone, that is between the overall age-independent rule-out cut-off and the age-dependent rule-in cut-off for AHF. On the basis of the proBNP investigation of dyspnoea in the emergency department (PRIDE) study classification,[3] grey zone NT-proBNP values were defined as values above 300 ng/L but below 450 ng/L if age was below 50 years, from above 300 ng/L but below 900ng/L if age was between 50 and 75 years, and above 300 ng/L but below 1800 ng/L if age was 75 years or older.[5] Severe kidney failure was defined as an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or less using the modification of diet in renal disease formula.[6]

Confirmation of heart failure and adjudication of final diagnoses

Diagnosis of AHF was confirmed by two cardiologists (F.F.D. and C.B.) who independently reviewed all medical records and independently classified the diagnosis as dyspnoea due to heart failure or due to another cause. Adjudicators had access to data on chest radiography, lung computed tomography (CT) and/or multislice-CT angiography, 2D echocardiography, abdominal ultrasonography, and cardiac catheterization. In order to provide an objective diagnosis, the validated PRIDE score for AHF was retrospectively calculated for all study patients. The PRIDE score consists of eight factors: elevated NT-proBNP (4 points), interstitial oedema on chest X-ray (2 points), orthopnoea (2 points), absence of fever (2 points), loop diuretic use, age $>$75 years, rales, and absence of cough (all 1 point). The diagnosis of AHF was deemed very likely at a cut point of $\geq$6 points.[7] Patients were further reviewed for the presence of acute coronary syndrome (ACS), pulmonary embolism, infection of the lower respiratory tract, and systemic inflammatory response syndrome or sepsis. For patients with an infection as the sole cause of acute dyspnoea or as precipitant cause of AHF, records were reviewed for data on levels of C-reactive protein, leukocytes, temperature at presentation, location of infection, identification of pathogen agents, and need for and start of antimicrobial therapy.

Patients with ACS were classified according to the criteria of the universal myocardial infarction definition.[8] The diagnosis of acute pulmonary embolism required the identification of thrombotic material on a 256-multislice-CT angiography.

The study was observational and all medical decisions, therapies or further diagnostic work-up were left at the discretion of the attending emergency physician.

The study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee (Heidelberg, registration number S-117/2013). Written informed consent was obtained from all participating patients. Follow-up was accomplished via telephone contact or questionnaire at least 6 months after discharge.

Biomarker testing

N-terminal pro brain-type natriuretic peptide was measured by the Stratus® CS Acute Care™ NT-proBNP assay (Siemens AG, Berlin and Munich, Germany), whereas MR-proANP was analysed on a Kryptor (BRAHMS AG, Hennigsdorf Berlin, Germany). Both automated assays are based on the sandwich chemiluminescence assays, which are described in detail elsewhere[9,10] and which have been used in other studies.[9,11–13]

In addition, levels of procalcitonin and C-reactive protein were determined from the admission blood sample in all patients routinely, and results were available for interpretation by the attending physician during ED stay.

Statistical analysis

Continuous variables were tested for normal distribution using the D'Agostino-Pearson test and were presented either as means ± SD or as medians with 25th and 75th percentiles. Groups were compared using the χ^2-test for categorical variables and analysis of variance for continuous variables. Independent samples were compared using the

Mann–Whitney test. Alternatively, we used ANOVA after logarithmic transformation of the data. If the ANOVA test was found positive ($P < 0.05$), then Student–Newman–Keuls test for pairwise comparison of subgroups was applied. We determined diagnostic performance for diagnosis of AHF from receiver operating characteristic (ROC) curves on the basis of the continuously measured biomarker levels and compared areas under the curve (AUC) using the test of DeLong *et al.*[14] ROC-optimized cut-off values were calculated using the point closest to the upper left corner according to the method proposed by Zweig *et al.*[15] In addition, we calculated sensitivities, specificities, negative predictive and positive predictive values for the diagnosis of AHF.

The SPSS 15.0 (SPSS, Chicago, Illinois) and MedCalc 11.1 (MedCalc software, Mariakerke, Belgium) statistical software package were used. All tests were two-tailed and a *P*-value < 0.05 was considered statistically significant.

Results

A total of 312 patients were enrolled. Of these, the adjudicated diagnosis was AHF in 139 patients (44.6 %). The patient characteristics among the AHF and non-AHF groups are presented in *Table 1*. Patients with AHF were older and more often male, they had more comorbidities like diabetes mellitus, impaired LV function, impaired renal function and either paced rhythm or AF than patients without AHF.

The NT-proBNP ranged from 19.9 to 88 688 ng/L, with a median of 1472 ng/L and an intermediate quartile range (IQR) from 265 to 5748.5 ng/L. The MR-proANP ranged from 16.8 to 5868 pmol/L, with a median of 224.25 pmol/L and an IQR from 112.8 to 444.1 pmol/L. Spearman correlation between MR-proANP and NT-proBNP was 0.7327 (*Figure 1*).

Table 2 shows the sensitivity, specificity, positive predictive value and negative predictive value as well as the cut-off values for the diagnosis of AHF for both measurements.

The diagnostic performance was also evaluated by ROC analysis. The curves for MR-proANP and NT-proBNP are shown in *Figure 2A*. The AUCs for MR-proANP and NT-proBNP did not significantly differ (AUC MR-proANP = 0.842 vs. AUC NT-proBNP = 0.892, $P = 0.0839$).

Other diagnoses than acute heart failure

The diagnostic spectrum of causes for dyspnoea included respiratory infections including pneumonia (n = 25), pulmonary diseases without infection including asthma bronchiale (n = 31), ACS (n = 33) (ST-segment elevation myocardial infarction, n = 1; non-ST-segment elevation myocardial infarc-

Figure 1 Spearman correlation between MR-proANP and NT-proBNP. A base-10 log scale is used for the *x*-axis and the *y*-axis.

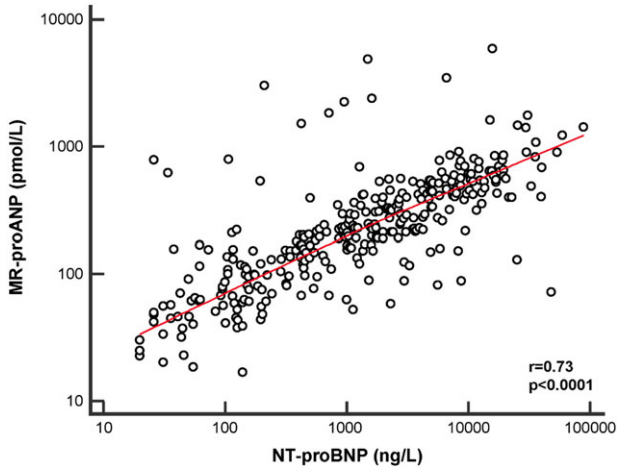


Table 1 Patients characteristics in the AHF and in the non-AHF group

Parameter	All patients n = 312	AHF group n = 139	Non-AHF group n = 173	*P*-value
Male gender	184 of 312 (59.0)	101 of 139 (72.7)	83 of 173 (48.0)	<0.0001*
Arterial hypertension, *n* (%)	243 of 312 (77.9)	115 of 139 (82.7)	128 of 173 (74.0)	0.0747
Dyslipidemia, *n* (%)	168 of 312 (53.8)	79 of 139 (56.8)	89 of 173 (51.4)	0.3623
Diabetes mellitus, *n* (%)	96 of 312 (30.8)	51 of 139 (36.7)	45 of 173 (26.0)	0.0486*
Nicotine consumption, *n* (%)	194 of 312 (62.2)	92 of 139 (66.2)	102 of 173 (59.0)	0.1986
Impaired LV function, *n* (%)	153 of 282 (54.3)	104 of 134 (77.6)	49 of 148 (33.1)	<0.0001*
Severe kidney failure (GFR<60/mL), *n* (%)	125 of 312 (40.1)	76 of 139 (54.7)	49 of 173 (28.3)	<0.0001*
Rhythm disorders, *n* (%)	106 of 312 (34.0)	76 of 139 (54.7)	30 of 173 (17.3)	<0.0001*
Advanced age (age ≥70), *n* (%)	176 of 312 (56.4)	94 of 139 (67.6)	82 of 173 (47.4)	0.0004*
Obesity (BMI ≥30), *n* (%)	101 of 308 (32.8)	47 of 138 (35.0)	54 of 170 (32.8)	0.7148

AHF, acute heart failure; BMI, body mass index; GFR, glomerular filtration rate; LV, left ventricular.
*Statistically significant ($P < 0.05$).

Table 2 Diagnostic test performance of NT-proBNP and MR-proANP

Biomarker	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Optimal cut-off	AUC (95% CI)
All patients						
NT-proBNP (ng/L)	89.21	75.72	74.70	89.70	1195	0.892 (0.852–0.924)
MR-proANP (pmol/L)	84.17	75.14	73.12	85.52	219.9	0.842 (0.796–0.880)
Severe kidney failure						
NT-proBNP (ng/L)	78.95	79.59	85.71	70.91	2775	0.839 (0.763–0.899)
MR-proANP (pmol/L)	81.58	73.47	82.67	72.00	315.2	0.808 (0.728–0.873)
Advanced age						
NT-proBNP (ng/L)	82.98	76.83	80.41	79.75	1716	0.868 (0.809–0.914)
MR-proANP (pmol/L)	73.40	81.71	82.14	72.82	315.2	0.834 (0.770–0.885)
Obesity						
NT-proBNP (ng/L)	95.74	66.67	71.43	94.73	747	0.858 (0.774–0.919)
MR-proANP (pmol/L)	91.49	74.07	75.43	90.91	167.7	0.888 (0.809–0.942)
Rhythm disorders						
NT-proBNP (ng/L)	63.16	90.00	94.12	49.09	3959	0.844 (0.761–0.907)
MR-proANP (pmol/L)	73.68	80.00	90.32	54.54	306.8	0.782 (0.691–0.856)
NT-proBNP grey zone						
NT-proBNP (ng/L)	71.43	82.61	55.55	90.48	868	0.731 (0.601–0.838)
MR-proANP (pmol/L)	91.49	74.07	75.43	90.91	229.9	0.685 (0.552–0.799)

AUC, areas under the curve; CI, confidence interval; NT-proBNP, N-terminal pro brain-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide.

tion, $n = 4$; unstable angina, $n = 28$), pulmonary embolism (n = 22), arrhythmias (n = 21), and miscellaneous including structural and congenital heart diseases, hypertensive crisis, malignomas, rheumatological, haematological and auto-immune diseases, atypical chest pain, trauma, neurological and psychosomatic diseases (n = 41).

The distributions of NT-proBNP and MR-proANP values across the diagnostic spectrum are shown in *Figure 3*.

Performance of NT-proBNP and MR-proANP in pre-specified subsets

The diagnostic performance of both biomarkers was tested in the subset of patients with severe kidney failure (76 of 125 (60.8%), advanced age (n = 94 of 176 (= 53.4%), obesity (n = 47 of 101 (= 46.5%), AF or paced rhythm (76 of 106 (= 71.7 %), and in the NT-proBNP grey zone (n = 14 of 60 (= 23.3%). The association between NT-proBNP/MR-proANP and either age, serum creatinine and body mass index is shown in *Figure 4A–C*.

Data on the diagnostic performance of both biomarkers in the different subsets are summarized in *Table 2*. AUCs for MR-proANP and NT-proBNP did not significantly differ from each other in the presence of severe renal failure (AUC 0.808 vs. 0.839, $P = 0.5683$), advanced age (AUC 0.868 vs. 0.834, P = 0.4087), obesity (AUC 0.888 vs. 0.858, $P = 0.5432$), AF or paced rhythm (AUC 0.782 vs. 0.844, $P = 0.3250$), and NT-pro BNP grey zone (AUC 0.685 vs. 0.731, P = 0.6927) (*Figure 2B–F*). Moreover, there was no statistically significant difference between the AUCs for MR-proANP and NT-proBNP in the pre-specified subsets compared with those in the total population for all subsets (*Figure 2*).

Prognosis of NT-proBNP and MR-proANP in patients with and without acute heart failure

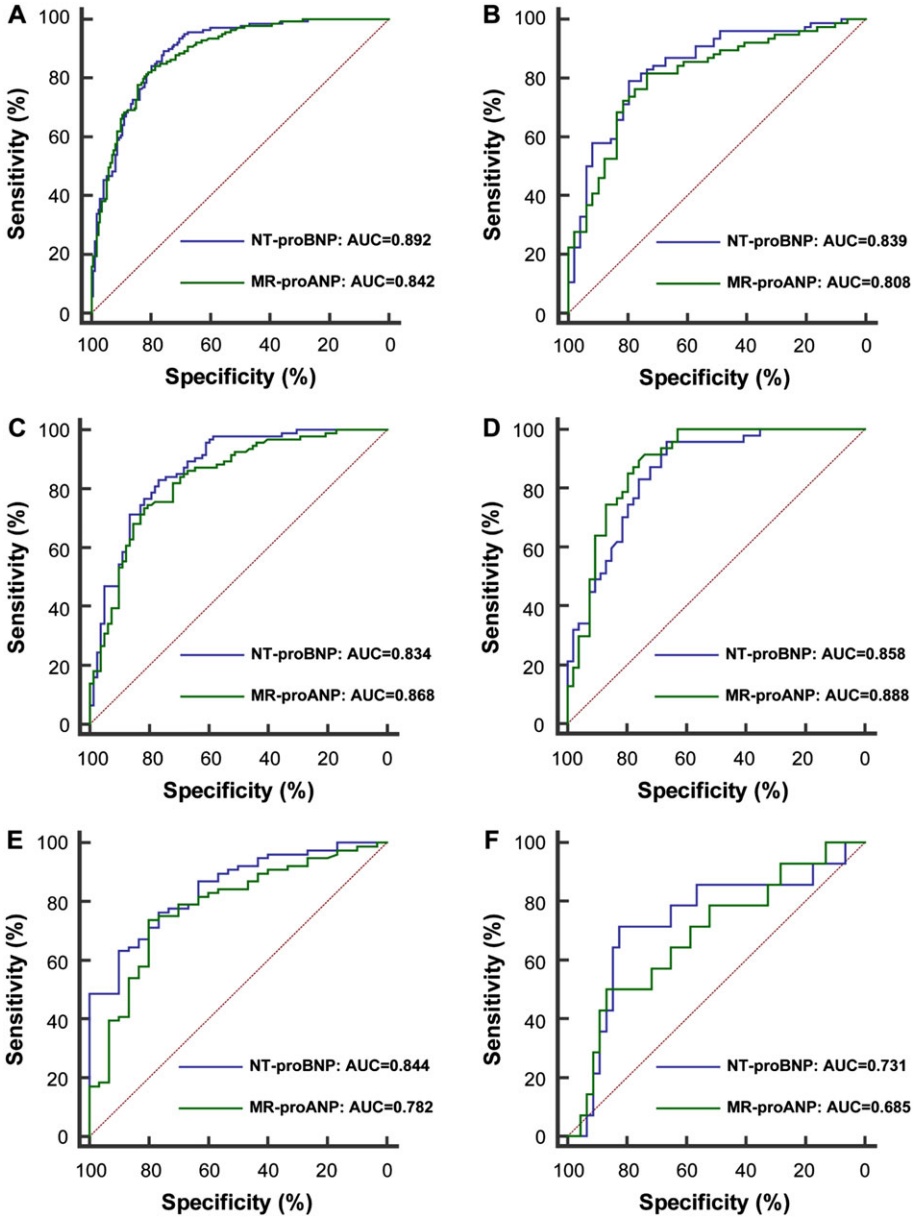
There were 25 deaths within 88.0 ± 23.5 days of follow-up. Of these, 16 deaths occurred among patients with a diagnosis of AHF and 9 deaths among those without AHF. Mortality was significantly higher in the group with AHF than in the group without AHF (P = 0.0316).

In the group with AHF, survivors had a median NT-proBNP of 4864 ng/L (IQR 1887.5–10 355.5 ng/L) and non-survivors had 16 723 ng/L (IQR 10 393–24 178 ng/L; P = 0.0008). Corresponding median MR-proANP values were 409.8 pmol/L (IQR 260.1–546.7 pmol/L) and 585.4 pmol/L (IQR 311.2–1081.9 pmol/L; P = 0.0077), respectively.

We classified advanced AHF as AHF with highly reduced left ventricular ejection fraction (LVEF) (LVEF $<$35%). In the group with advanced AHF (n = 59), survivors had a median NT-proBNP of 8525.5 ng/L (IQR 4062–15 245 ng/L) and non-survivors had 15 065.0 ng/L (IQR 10 864–19 197.3 ng/L; P = 0.0451). Corresponding median MR-proANP values were 490.7 pmol/L (IQR 344.2–648.6 pmol/L) and 755.8 pmol/L (IQR 565.3–1570.3 pmol/L; P = 0.013), respectively.

In the group without AHF, survivors had a median NT-proBNP of 422 ng/L (IQR 116–1174 ng/L) and non-survivors had 342 ng/L (IQR 125.5–957.3 ng/L; P = 0.613). Corresponding median MR-proANP values were 130.7 pmol/L (IQR 66.5–224 pmol/L) and 151.2 pmol/L (IQR 77.5–215.0 pmol/L; P = 0.6107), respectively.

Figure 2 Receiver operating characteristic curves of NT-proBNP and MR-proANP for the diagnosis of AHF**.** (A) Total population; (B) pre-specified subset severe kidney failure; (C) pre-specified subset advanced age; (D) pre-specified subset obesity; (E) pre-specified subset rhythm disorder; and (F) pre-specified subset NT-proBNP grey zone.



Discussion

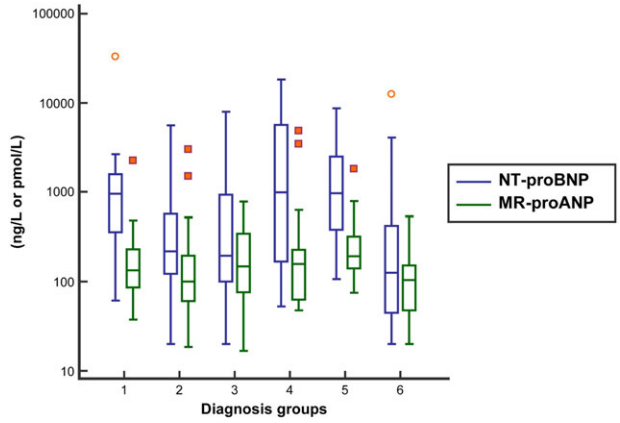
In this observational study, we compared the diagnostic and prognostic performance of NT-proBNP and MR-proANP for the diagnosis of AHF in consecutive patients presenting with acute dyspnoea and in pre-specified subsets that have been reported to confound and thus potentially limit the usefulness of NPs.

There were several findings that are important for interpretation of NT-proBNP and MR-proANP in clinical practice.

First, the diagnostic performance of both NT-proBNP and MR-proANP for the diagnosis of AHF is excellent (*Figure 2A*) confirming previous studies[1–3,16,17] and thus fully supporting current guideline recommendations on the use of NPs for rule-out of AHF.[18]

Second, non-survivor demonstrated significantly higher biomarker levels, and prediction of death with NT-proBNP and MR-proANP was similar, albeit less accurate than diagnostic performance.

Figure 3 Distributions of NT-proBNP and MR-proANP values across the diagnostic spectrum. Distributions of NT-proBNP and MR-proBNP values are represented by box-plots and whisker-plots. A base-10 log scale is used for the *y*-axis. The diagnostic spectrum comprises the diagnostic groups 1, respiratory infections including pneumonia; 2, pulmonary diseases without infection including asthma bronchiale; 3, acute coronary syndrome including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina; 4, pulmonary embolism; 5, arrhythmias; 6, miscellaneous including structural and congenital heart diseases, hypertensive crisis, malignomas, rheumatological, haematological and autoimmunological diseases, atypical thoracic pain, trauma, and neurological and psychosomatic diseases.



Third, the diagnostic performance of NT-proBNP and MR-proANP was not impaired in the subsets of patients with severe kidney failure, advanced age, obesity, AF or paced rhythm, and NT-proBNP grey zone values and remained comparable with that in the entire population (*Figure 2*).

Current guidelines recommend the use of NPs for rule-out of AHF without preference of any marker.

Previous data suggested differences with respect to the diagnostic performance of NPs in particular subgroups that may confound NP concentrations and thus limit interpretation. The BACH trial had reported that the performance of NT-proBNP for the diagnosis of AHF is impeded by severe kidney failure, advanced age, obesity, and intermediate NT-proBNP grey zone values.[5] They showed that testing for MR-proANP provided additional diagnostic utility regarding the diagnosis of AHF in patients with obesity and intermediate NT-proBNP values.[5] In patients with severe kidney failure and advanced age, however, testing for MR-proANP did not bring any further diagnostic utility.[5] By contrast, our findings demonstrated that the diagnostic performance of both NPs NT-proBNP and MR-proANP was not affected by severe kidney failure, advanced age, obesity, rhythm disorders, and intermediate NT-proBNP values (*Figure 2*). Diagnostic performances of NT-proBNP and MR-proANP did not differ statistically from each other (*Figure 2*), and both had a strong reciprocal correlation (*Figure 1*).

The characteristics of our study population show some similarities with the BACH trial.[5] First, the criteria of being eligible were similar to the BACH trial. Accordingly, only patients with acute shortness of breath as their primary complaint upon presentation to the ED were enrolled in the study. Second, the confirmation of diagnosis, as described under methods, was performed similarly to the BACH trial. Finally, the patients of our study had a lot of comorbidities like severe kidney failure and rhythm disorders (*Table 1*), comparable with the BACH trial.

However, there are also some differences to be considered. Compared with the study population of the BACH trial,[5] our patient cohort comprised a higher percentage of patients with AHF (44.6% vs. 34.6% in the BACH trial).

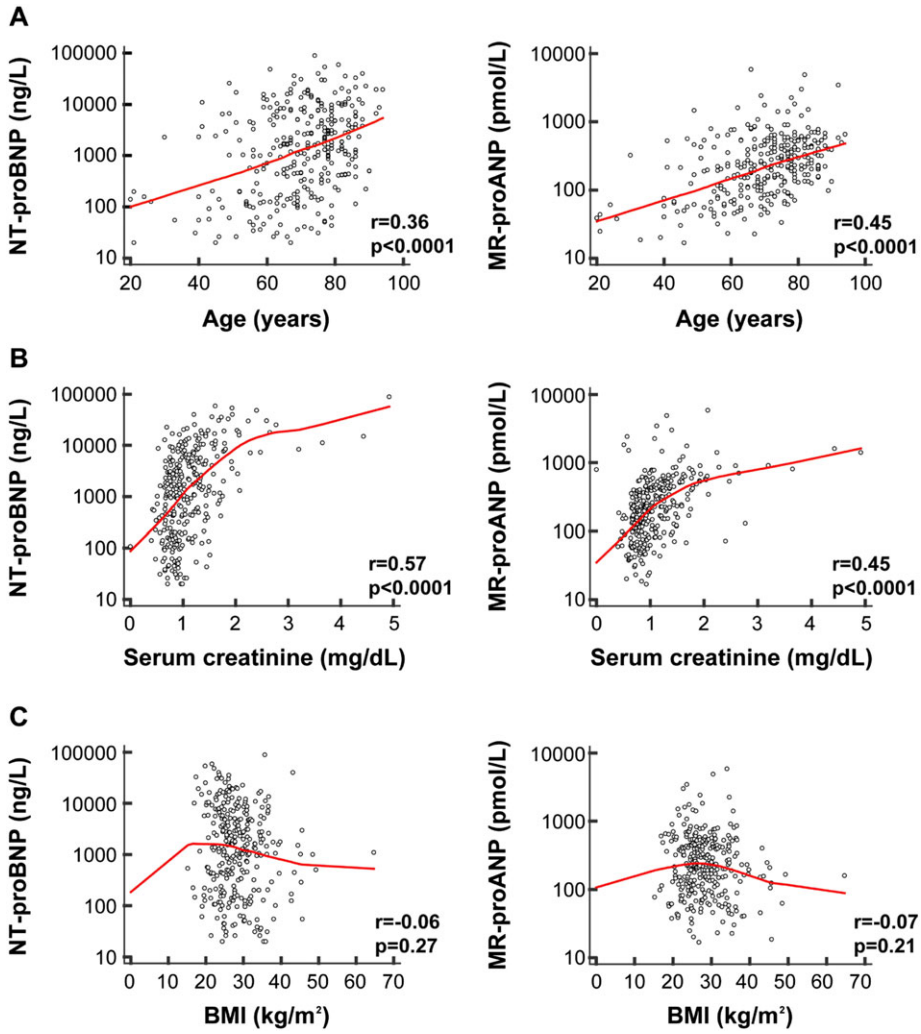
Our study also highlights the diagnostic challenge regarding accurate diagnosis of AHF among patients presenting with acute dyspnoea. A substantial proportion of patients were older than 70 years (53.4%), had severe impairment of kidney function (60.8%), were obese (46.5%), had rhythm disorders (71.7%), or had values in the grey zone (23.3%).

Similar to the BACH trial, less than 50% had a final diagnosis of AHF while the majority had other non-AHF diagnoses including respiratory tract infections, ACS, and pulmonary embolism.

Patients with severe kidney failure and rhythm disorders demonstrated significantly higher NT-proBNP and MR-proANP levels (*Figure 3*) and higher optimal cut-off values (*Table 2*), as derived from ROC analysis, than patients without severe kidney failure and those with preserved sinus rhythm. For kidney failure, an inverse relationship between NP and creatinine clearance has previously been reported consistently,[16] with some reporting that NT-proBNP values are more affected than BNP values.[19,20] Although NT-proBNP was reported to be more affected by renal function than BNP,[19,20] Anwaruddin *et al.* showed that the diagnostic performance of NT-proBNP was still acceptable.[16] Similar results could be found in our study. Even if a correlation between NP levels and serum creatinine could be identified (*Figure 4*), the performance of NPs for the diagnosis of AHF was not significantly impaired by severe kidney failure (*Figure 2*).

For AF, the findings of higher values of NT-proBNP and MR-proANP (*Figure 3* and *Table 2*) are in line with previously published data of patients with chronic heart failure and AF.[21,22] By contrast, the BACH trial[5] did not find any significant difference regarding NPs among patients with AHF and sinus rhythm as compared with those without sinus rhythm. Their explanation was that previous studies[21,22] were made on patients with chronic heart failure and not AHF. They stated that patients with AHF and AF had presumably a less impaired left ventricular (LV) function than patients with AHF alone.[5] According to them, AF probably caused the increase of NP levels in patients with AHF and AF, which, however, was counterbalanced by lower baseline levels of NPs because of a better LV function in those patients. Of note, they did not evaluate

Figure 4 Spearman correlation between NT-proBNP/MR-proANP and either age, serum creatinine, and body mass index (BMI). The graphs show the Spearman correlations between NT-proBNP (left)/MR-proANP (right) and either (A) age, (B) serum creatinine, and (C) BMI. A base-10 log scale is used for the *y*-axis.



the LV function by echocardiography. However, we found that patients with AHF and AF or paced rhythm had significantly higher NT-proBNP and MR-proANP cut-off values than patients with AHF alone (*Table 2*). Moreover, we were able to demonstrate that the LV function was not less impaired in patients with AHF and rhythm disorders (*Table 1*). Richards *et al.* showed that the diagnostic performance of NT-proBNP, BNP and MR-proANP was impaired by AF and that additional testing of MR-proANP did not bring any further diagnostic utility.[23] However, we could finally demonstrate that the diagnostic performance of the NPs was not impaired by rhythm disorders (*Figure 2*).

In summary, we could demonstrate that NT-proBNP and MR-proANP showed similar diagnostic performances. NT-proBNP and MR-proANP can hence be used equally. In case of NT-proBNP values in the grey zone, additional testing of MR-proANP, however, provides supplementary information for the diagnosis of AHF.

In this study, we also wanted to determine the prognostic value of NT-proBNP and MR-proANP for mortality in dyspnoeic patients with and without AHF. Our results showed that the rate of mortality was significantly higher in the AHF than in the non-AHF group (P = 0.0316). Concerning the prognostic value of NT-proBNP and MR-proANP, we could demonstrate that in the AHF group, both NPs were able to predict mortality. Similar results could be achieved in the group with advanced AHF. However, the level of statistical significance was higher for MR-proANP (P = 0.013) than for NT-proBNP (P = 0.0451). Hence, MR-proANP might be preferable to NT-proBNP for predicting mortality in patients with advanced heart failure. Given the relative small number of patients with

advanced heart failure (n = 59) and the fact that both NPs showed significant results for mortality prediction, it can yet not been deduced that MR-proANP is superior to NT-proBNP.

In the non-AHF group, NT-proBNP and MR-proANP were both not useful to determine mortality.

Conclusions

We presented a study with a lot of similarities to the BACH trial. One of the differences, however, consisted in the higher percentage of AHF patients in our study compared with the BACH trial, endorsing our study findings.

Despite the influence of comorbidities such as severe kidney failure or AF or paced rhythm on NPs, resulting in higher NP cut-off values, the performance of NPs for the diagnosis of AHF was not impaired. In fact, the ROC curves of NT-proBNP and MR-proANP for the diagnosis of AHF in the total population as well as in the pre-specified subsets severe kidney failure, advanced age, obesity, rhythm disorders, and intermediate NT-proBNP values showed no statistically relevant differences. Moreover, the diagnostic performances of both NPs NT-proBNP and MR-proANP were comparable.

Finally, the prediction of death with NT-proBNP and MR-proANP was similar, albeit less accurate than diagnostic performance.

In sum, the diagnostic performances of NT-proBNP and MR-proANP were similar. In case of NT-proBNP values in the grey zone, additional testing of MR-proANP can be helpful. Moreover, MR-proANP seems to be preferable but not superior to NT-proBNP for prediction of death in patients with advanced heart failure.

Acknowledgement

We thank B·R·A·H·M·S GmbH for having taken over the publication fee.

Conflict of interest

None declared.

References

1. Bayés-Genís A, Santaló-Bel M, Zapico-Muñiz E, López L, Cotes C, Bellido J, Leta R, Casan P, Ordóñez-Llanos J. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. *Eur J Heart Fail* 2004; **6**: 301–308.
2. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol* 2003; **42**: 728–735.
3. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *Am J Cardiol* 2005; **95**: 948–954.
4. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012; http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure European Society of Cardiology (ESC).
5. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010; **55**: 2062–2076.
6. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in renal disease study group. *N Engl J Med* 1994; **330**: 877–884.
7. Baggish AL, Siebert U, Lainchbury JG, Cameron R, Anwaruddin S, Chen A, Krauser DG, Tung R, Brown DF, Richards AM, Januzzi JL Jr. A validated clinical and biochemical score for the diagnosis of acute heart failure: the proBNP investigation of dyspnea in the emergency department (PRIDE) acute heart failure score. *Am Heart J* 2006; **151**: 48–54.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation* 2012; **126**: 2020–2035.
9. Mathewkutty S, Sethi SS, Aneja A, Shah K, Iyengar RL, Hermann L, Khakimov S, Razzouk L, Esquitin R, Vedanthan R, Benjamin TA, Grace M, Nisenbaum R, Ramanathan K, Ramanathan L, Chesebro J, Farkouh ME. Biomarkers after risk stratification in acute chest pain (from the BRIC Study). *Am J Cardiol* 2013; **111**: 493–498.
10. Morgenthaler NG, Struck J, Thomas B, Bergmann A. Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. *Clin Chem* 2004; **50**: 234–236.
11. von Haehling S, Jankowska EA, Morgenthaler NG, Vassanelli C, Zanolla L, Rozentryt P, Filippatos GS, Doehner W, Koehler F, Papassotiriou J, Kremastinos DT, Banasiak W, Struck J, Ponikowski P, Bergmann A, Anker SD.

Comparison of midregional pro-atrial natriuretic peptide with N-terminal pro-B-type natriuretic peptide in predicting survival in patients with chronic heart failure. *J Am Coll Cardiol* 2007; **50**: 1973–1980.
12. Gegenhuber A, Struck J, Poelz W, Pacher R, Morgenthaler NG, Bergmann A, Haltmayer M, Mueller T. Midregional pro-A-type natriuretic peptide measurements for diagnosis of acute destabilized heart failure in short-of-breath patients: comparison with B-type natriuretic peptide (BNP) and amino-terminal proBNP. *Clin Chem* 2006; **52**: 827–831.
13. Gegenhuber A, Struck J, Dieplinger B, Poelz W, Pacher R, Morgenthaler NG, Bergmann A, Haltmayer M, Mueller T. Comparative evaluation of B-type natriuretic peptide, mid-regional pro-A-type natriuretic peptide, mid-regional pro-adrenomedullin, and Copeptin to predict 1-year mortality in patients with acute destabilized heart failure. *J Card Fail* 2007; **13**: 42–49.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–845.
15. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993; **39**: 561–577.
16. Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL Jr. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *J Am Coll Cardiol* 2006; **47**: 91–97.
17. Wu AH, Tabas J, Stein J, Potocki M, Mueller C, McCord J, Richards M, Hartmann O, Nowak R, Peacock WF, Ponikowski P, Moeckel M, Hogan C, Filippatos GS, Di Somma S, Anand I, Ng L, Neath SX, Christenson R, Morgenthaler NG, Anker SD, Maisel AS. The effect of diabetes on the diagnostic and prognostic performance of mid-region pro-atrial natriuretic peptide and mid-region pro-adrenomedullin in patients with acute dyspnea. *Biomarkers* 2012; **17**: 490–497.
18. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, ESC Committee for Practice Guidelines. 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* 2012; **14**: 803–869.
19. McCullough PA, Sandberg KR. B-type natriuretic peptide and renal disease. *Heart Fail Rev* 2003; **8**: 355–358 Review.
20. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. *Rev Cardiovasc Med* 2003; **4**(Suppl 4): S13–S19 Review.
21. Rienstra M, Van Gelder IC, Van den Berg MP, Boomsma F, Van Veldhuisen DJ. Natriuretic peptides in patients with atrial fibrillation and advanced chronic heart failure: determinants and prognostic value of (NT-)ANP and (NT-pro)BNP. *Europace* 2006; **8**: 482–487.
22. Corell P, Gustafsson F, Kistorp C, Madsen LH, Schou M, Hildebrandt P. Effect of atrial fibrillation on plasma NT-proBNP in chronic heart failure. *Int J Cardiol* 2007; **117**: 395–402.
23. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH study (Biomarkers in Acute Heart Failure). *JACC Heart Fail* 2013; **1**: 192–199.