Relation of N-terminal pro-brain natriuretic peptide levels and their prognostic power in chronic stable heart failure to obesity status

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Aims
To investigate the relationship between body mass index (BMI) and N-terminal pro-brain natriuretic peptide (NTproBNP) level and resultant prognostic capacity in chronic heart failure (CHF) controlled for known confounders.

Methods and results
We formed 206 triplets of patients (n = 618) with stable systolic CHF matched with respect to age, sex, renal function (MDRD, modification of diet in renal disease formula), and NYHA class, each with a BMI > 30 kg/m² (group 3), 20–24.9 kg/m² (group 1), and 25–29.9 kg/m² (group 2). BMI conveys a 4% drop in NTproBNP per unit increase. This influence remained significant after correction for age, sex, MDRD, NYHA, heart rate, rhythm, and ejection fraction. NTproBNP remained an independent predictor of adverse outcome after correction for age, sex, BMI, NYHA, MDRD, and ejection fraction. Despite numerical differences, prognostic power was comparable between BMI groups (log-transformed NTproBNP; group 1: hazard ratio (HR) 1.435, 95% CI 1.046–1.967, \( \chi^2 = 5.02, P = 0.03 \); group 2: HR 1.604, 95% CI 1.203–2.138, \( \chi^2 = 10.36, P = 0.001 \); group 3: HR 1.735, 95% CI 1.302–2.313, \( \chi^2 = 14.12, P = 0.0002 \) (\( P = \text{NS, all} \)). An NTproBNP correction factor was calculated.

Conclusion
Even matched for NYHA, age, sex, and renal function, BMI exerts a significant and independent inverse influence on NTproBNP in patients with stable CHF. NTproBNP retained equal statistical power in all three BMI groups.

Keywords
Chronic heart failure • NTproBNP • Obesity • Body mass index • Prognosis

Introduction
Over the past, both chronic heart failure (CHF) and obesity exhibited an almost epidemic increase¹,² and will probably continue to do so. Furthermore, there is increasing data on a higher prevalence of heart failure in obese patients.³ As natriuretic peptides are elevated in heart failure,⁴ they are commonly used to screen for heart failure,⁵ stratify the risk,⁶ and guide medical therapy in such patients.⁷,⁸

An inverse relationship of blood levels of natriuretic peptides with body mass index (BMI) has been described⁹,¹⁰ in healthy individuals, but this notion has already been questioned by recent data.¹¹ Not only could these peptides be more related to lean mass rather than fat mass,¹² but there appears to be a difference between brain natriuretic peptide (BNP) and the aminoterminal cleavage product (NTproBNP, N-terminal pro-brain natriuretic peptide)¹² as to the influence of BMI on the respective hormone.

With respect to heart failure, only few studies focused on this problem. As for BNP, an inverse relation with BMI has recently been described in both the acute¹³,¹⁴ and chronic¹⁵,¹⁶ setting. But again, this has already been contradicted.¹⁷ And although reports on NTproBNP in acute heart failure confirmed the inverse relation to BMI,¹³,¹⁴,¹⁸ only few studies have¹⁹,²⁰ addressed this issue in CHF.

Given the growing importance of both CHF and adiposity as well as the widespread use of NTproBNP, it is crucial to understand the possible confounding influence of BMI on the validity of NTproBNP to allow correct and adequate application of this...
valuable tool in CHF. Furthermore, some of the above controversies might in part be due to heterogeneous cohorts examined. We therefore adopted a matched approach for the major influencing factors (NYHA, age, sex, and renal function) in patients with stable CHF from a university hospital outpatient’s department.

Methods

Study population
The registry of the specialized heart failure clinic of the University Hospital Heidelberg, Germany, formed the basis for this study. All patients attending the clinic for the evaluation of heart failure were asked to participate in the registry and provide written informed consent for data storage and evaluation. The decline rate was <1% of patients asked. The proceedings were approved by the local Ethics Committee and conformed to the principles outlined in the Declaration of Helsinki. The diagnosis of heart failure was based on the ESC criteria of symptoms compatible with the diagnosis in the presence of objective abnormalities of cardiac function21 on echocardiography or left heart catheter.

For inclusion in the present study, all patients with stable chronic systolic dysfunction and the assessment of NTproBNP during initial presentation were selected. The etiology of heart failure was either ischaemic or idiopathic dilated cardiomyopathy and patients were on stable medication for at least 1 month prior to inclusion. Patients with a history of primary pulmonary disease, valvular heart disease, and decompensation of heart failure requiring inotropic support within the last 3 months prior to study inclusion were not included. If multiple visits were present, only the first visit was chosen (n = 1743). These patients were separated according to BMI into three groups [group 1 (BMI 20–24.9 kg/m^2; n = 522); group 2 (BMI 25–29.9 kg/m^2; n = 774); group 3 (BMI >30 kg/m^2; n = 447)] and matched according to the following strategies.

Measurements of N-terminal pro-brain natriuretic peptide
Blood samples were taken from a peripheral venous catheter using EDTA vacutainers, immediately centrifuged for 10 min at 4000 r.p.m. at 4°C, subdivided and frozen at −30°C. Testing was performed for plasma NTproBNP levels (Elecsys46, Roche Diagnostics, Mannheim, Germany). NTproBNP results are presented in pg/mL. To convert to pmol/L, results need to be multiplied by 0.118.

Matching
Each patient of group 3 was individually matched using calliper matching according to renal function (as estimated through the simplified modification of diet in renal disease (MDRD) formula,22 age, sex, and NYHA functional class to two individual patients, one from group 1 and one from group 2. For age and MDRD, calliper was defined as 0.25 x standard deviation of the respective variable. For each patient, the matching routine first identified sex and NYHA class matches. From this cohort, all patients within age-calliper were selected, and from this cohort the first patient within MDRD-calliper.

In a first step, individual pairs from groups 3 and 1 were obtained. Then, to each patient of group 3, an individual, matched patient was identified from group 2. This patient was retained as a match only if the patient represented a match to the corresponding patient of group 1 within this triplet of patients. If not, the next available matched patient from group 2 was tested. After the first matching step, 232 pairs of patients from groups 3 and 1 were retained. After the second step, 206 nested triplets were retained for final analysis.

Follow-up and endpoint
The determination of survival status and follow-up were performed—in hierarchical order—by scheduled visits to the outpatient clinic, telephone calls either to the patient’s home or to their physician, or hospital electronic records. The predefined endpoint for the purpose of this analysis was all-cause mortality. Patients receiving cardiac transplantation during follow-up were followed until their surgical procedure and censored thereafter. All survivors were followed up for a minimum of 1 year. No patient underwent implantation of left ventricular assist devices during follow-up.

Statistics
To compare frequencies, χ^2 analysis was performed. To test for significant differences between means, two-sample Wilcoxon test, Kruskal–Wallis test and one-way analysis of variance were used where appropriate. All tests are two-tailed and a P-value <5% was regarded statistically significant. For multiple pairwise testing, this P-value was adjusted to <1.7% according to the Bonferroni correction for the testing of the three groups. The data are presented as mean ± SD, except where specified otherwise. Univariable and multivariable linear regressions were performed using transformed NTproBNP values23 as dependent variables. All baseline variables were entered into the univariable analysis. Covariates that were strongly associated with NTproBNP levels (P < 0.10) were included in the multivariable analysis. Baseline model assumptions were proportionality of hazard, linearity, and non-influential observations. Assumptions of proportional hazards were assessed by visual judgement of the logarithm of minus logarithm of the survival estimates, obtained from stratified Cox regression. To check the proportional hazards assumption, the score process (which is a transformed partial sum process of the Martingale residuals) is compared with the simulated processes under the null hypothesis that the proportional hazards assumption holds.24 Proportionality was not rejected for any variable included in the final model other than NTproBNP. Therefore, trans-NTproBNP values23 were used. Martingale residuals from the full Cox model were plotted against covariates of interest. No violation of linearity was detected. In addition, cumulative Martingale residuals were compared with simulated residual patterns under the null hypothesis that linearity holds.24 Influential observations were assessed by plotting the deviance residual against the linear predictor.25 To test for differences between Cox regression coefficients of NTproBNP and trans-NTproBNP of the BMI strata, z-test was performed as described previously.26 Finally, we directly obtained a correction factor for NTproBNP of obese patients by using the ratio of β-coefficients from separately stratified Cox analysis.

Results
Surviving patients were followed for a median of 37 (21–58) months, with no significant differences between the BMI groups [35 (21–49) vs. 38 (21–61) vs. 37 (23–66) months for groups I, II, III, with P = 0.27, P = 0.63, and P = 0.12 for group I vs. II, II vs. III, and III vs. I, respectively].

Between groups, differences were seen for left ventricular ejection fraction, prevalence of diabetes, mean blood pressure, the distance walked during 6 min walk test, and the use of β-blockers (Table 1). With respect to the etiology of heart failure, patients
Table 1  Baseline clinical characteristics according to body mass index group

<table>
<thead>
<tr>
<th></th>
<th>P-value for overall trend</th>
<th>Group I (BMI 20–24.9, n = 206)</th>
<th>P-value vs. Group II</th>
<th>Group II (BMI 25–29.9, n = 206)</th>
<th>P-value vs. Group III</th>
<th>Group III (BMI &gt;30, n = 206)</th>
<th>P-value vs. group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year mortality, n (%)</td>
<td>&lt;0.01</td>
<td>28 (14)</td>
<td>0.07</td>
<td>17 (8)</td>
<td>0.30</td>
<td>10 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2 year mortality, n (%)</td>
<td>0.01</td>
<td>43 (21)</td>
<td>0.08</td>
<td>28 (14)</td>
<td>0.44</td>
<td>23 (11)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3 year mortality, n (%)</td>
<td>0.02</td>
<td>47 (23)</td>
<td>0.16</td>
<td>34 (17)</td>
<td>0.48</td>
<td>29 (14)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>23.2 ± 1.4</td>
<td>27.4 ± 1.4</td>
<td>33.5 ± 3.2</td>
<td></td>
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</tr>
<tr>
<td>Age, years</td>
<td></td>
<td>64 ± 11</td>
<td>62 ± 11</td>
<td>62 ± 11</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td></td>
<td>186 (90)</td>
<td>186 (90)</td>
<td>186 (90)</td>
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<td></td>
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<tr>
<td>NYHA</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>I, n (%)</td>
<td></td>
<td>27 (13)</td>
<td>27 (13)</td>
<td>27 (13)</td>
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<tr>
<td>II, n (%)</td>
<td></td>
<td>113 (55)</td>
<td>113 (55)</td>
<td>113 (55)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>III, n (%)</td>
<td></td>
<td>66 (32)</td>
<td>66 (32)</td>
<td>66 (32)</td>
<td></td>
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</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td></td>
<td>101 ± 28</td>
<td>102 ± 28</td>
<td>102 ± 29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRD, mL/min/1.73 m²</td>
<td></td>
<td>72 ± 20</td>
<td>73 ± 21</td>
<td>72 ± 21</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>iCMP, n (%)</td>
<td>0.13</td>
<td>108 (52)</td>
<td>0.61</td>
<td>101 (49)</td>
<td>&lt;0.05</td>
<td>126 (61)</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>&lt;0.01</td>
<td>28 ± 11</td>
<td>0.08</td>
<td>31 ± 10</td>
<td>0.22</td>
<td>33 ± 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SR, n (%)</td>
<td>0.98</td>
<td>151 (73)</td>
<td>0.56</td>
<td>156 (76)</td>
<td>0.56</td>
<td>151 (73)</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>&lt;0.001</td>
<td>21 (10)</td>
<td>0.02</td>
<td>40 (19)</td>
<td>0.04</td>
<td>57 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP mean, mmHg</td>
<td>&lt;0.001</td>
<td>89 ± 14</td>
<td>&lt;0.05</td>
<td>93 ± 14</td>
<td>&lt;0.01</td>
<td>97 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, b.p.m.</td>
<td>0.56</td>
<td>73 ± 16</td>
<td>0.36</td>
<td>74 ± 16</td>
<td>0.95</td>
<td>74 ± 17</td>
<td>0.34</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>0.04</td>
<td>403 ± 134</td>
<td>0.40</td>
<td>415 ± 148</td>
<td>&lt;0.05</td>
<td>380 ± 129</td>
<td>0.10</td>
</tr>
<tr>
<td>NTproBNP, pg/mL</td>
<td>&lt;0.001</td>
<td>1502 (724–3569)</td>
<td>&lt;0.001</td>
<td>1110 (387–2597)</td>
<td>&lt;0.001</td>
<td>623 (247–1496)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE/ARB, n (%)</td>
<td>0.88</td>
<td>181 (88)</td>
<td>0.62</td>
<td>185 (90)</td>
<td>0.62</td>
<td>182 (88)</td>
<td>0.88</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>0.03</td>
<td>131 (64)</td>
<td>&lt;0.01</td>
<td>163 (79)</td>
<td>0.19</td>
<td>151 (73)</td>
<td>0.06</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>0.08</td>
<td>59 (29)</td>
<td>0.10</td>
<td>76 (37)</td>
<td>0.92</td>
<td>76 (37)</td>
<td>0.10</td>
</tr>
<tr>
<td>Loop diuretics, n (%)</td>
<td>0.53</td>
<td>139 (67)</td>
<td>0.24</td>
<td>126 (61)</td>
<td>0.07</td>
<td>145 (70)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

iCMP, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; MDRD, glomerular filtration rate as estimated through the modified diet in renal disease formula; BP, blood pressure; 6MWT, 6 min walk test; ACE/ARB, ACE-inhibitor or angiotensin receptor blocker.
with ischaemic heart disease were older (66.5 ± 10.5 vs. 58.1 ± 10.0; P < 0.001), had slightly higher ejection fraction (28.4 ± 5.0 vs. 27.6 ± 4.4; P < 0.05), and BMI (32 ± 9 vs. 29 ± 12; P < 0.01) with no difference as to NYHA class distribution (P = 0.65) and sex (P = 0.13).

**Body mass index and N-terminal pro-brain natriuretic peptide**

Plasma levels of NTproBNP differed significantly between the matched BMI groups (Table 1 and Figure 1). NTproBNP was moderately inversely correlated with BMI both as uncorrected (r = −0.22; 95% CI −0.30 to −0.15; P < 0.001) and as log-transformed value (r = −0.29; 95% CI −0.36 to −0.22; P < 0.001), with BMI considered as a continuous variable (Figure 2). The same results were obtained for uncorrected and log-transformed NTproBNP values, with BMI considered as a categorical variable (r = −0.30; 95% CI −0.37 to −0.23; P < 0.001 and r = −0.30; 95% CI −0.37 to −0.23; P < 0.001).

**Determinants of N-terminal pro-brain natriuretic peptide**

When considered as a continuous variable, BMI was a significant univariable predictor of NTproBNP levels, with a 4% decrease in NTproBNP per unit increase of BMI. When considered as a categorical variable, BMI category, too, was a significant univariable predictor of NTproBNP levels, with a 52.2 and 38.2% decrease in NTproBNP for BMI groups 2 and 3, respectively. Further significant predictors of NTproBNP levels were age (P < 0.001), renal function (P < 0.001), left ventricular ejection fraction (P < 0.001), NYHA functional class (P < 0.001), rhythm (P < 0.001), heart rate (P < 0.001), mean blood pressure (P < 0.001), 6 min walk test distance (P < 0.01), and the aetiology of heart failure (P < 0.05). Diabetic status (P = 0.29) or sex (P = 0.14) were not significant predictors of NTproBNP levels in this analysis.

When entered into a common multivariable regression analysis with the above significant variables, BMI—both as a continuous and a categorical variable—remained an independent predictor of NTproBNP levels (Tables 2 and 3).

**Prognostic significance of N-terminal pro-brain natriuretic peptide and body mass index**

Although BMI as a continuous variable was not a significant univariable predictor of adverse outcome, it was, however, significant

**Table 2 Multivariable linear regression for N-terminal pro-brain natriuretic peptide as dependent variable using body mass index as a categorical variable**

<table>
<thead>
<tr>
<th>R² = 0.472</th>
<th>β-Coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI group 2+a</td>
<td>−0.522</td>
<td>0.133</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI group 3a</td>
<td>−0.382</td>
<td>0.129</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>−0.048</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, 1/min</td>
<td>0.013</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0.254</td>
<td>0.088</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.015</td>
<td>0.006</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.288</td>
<td>0.131</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MDRD, mL/min/1.73 m²</td>
<td>−0.007</td>
<td>0.003</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; MDRD, glomerular filtration rate as estimated through the modified diet in renal disease formula; BP, blood pressure.

aReference is group 1.
Tables 3 and 4 provide detailed statistical analyses that support the text. Table 3 shows a multivariable linear regression for the trans-N-terminal pro-brain natriuretic peptide (NTproBNP) as a dependent variable using body mass index (BMI) as a continuous variable. Table 4 presents univariable Cox proportional hazard models for NTproBNP retention in the context of various factors.

In the Discussion section, the authors discuss the implications of their findings, considering both clinical and physiological contexts.
non-obese patients with regard to age and sex distribution in one of these studies.\textsuperscript{19}

In order to eliminate the possibly confounding influence of cardiac cachexia, patients with a BMI \(<20\text{ kg/m}^2\) were not included in the present study. Also, we formed three distinct groups of patients—normal weight, overweight, and obese—to account for a possible categorical (class) effect of BMI. We consider it as a strong point of the present analysis that matching was performed with respect to all known anthropometric influences on NTproBNP (age, sex, and renal function) and in addition to NYHA to account for subjective disease severity. As we were still able to reproduce the above-described independent influence of BMI on NTproBNP levels in this matched setting, the present study strongly supports the notion of an intrinsic influence of adipose tissue on NTproBNP levels rather than confounding co-morbid conditions.

The influence of BMI on survival is still controversial. Though BMI is a risk factor towards the evolution of heart failure,\textsuperscript{34} in CHF a paradoxical survival benefit has been described,\textsuperscript{35} which apparently was replicated in our study. A recent sub-analysis of the CHARM programme showed a U-shaped mortality curve for BMI,\textsuperscript{36} and others found the influence of BMI on mortality to be complex and dependent on co-variates.\textsuperscript{37} As for previous studies,\textsuperscript{35, 36} there were differences in baseline clinical variables in our study, too, possibly explaining certain aspects of this survival benefit.

As far as the validity of natriuretic peptides as a prognostic marker is concerned, only a few studies have focused on this issue.\textsuperscript{16, 18} Since Bayes-Genis et al.\textsuperscript{18} addressed this question for NTproBNP in the setting of acute heart failure and Horwich et al.\textsuperscript{16} for BNP in the setting of CHF, this study significantly extends their findings. Our results do not support the notion brought about by Horwich et al.,\textsuperscript{16} that the prognostic value of NTproBNP appears to change with respect to BMI group. It must, however, be emphasized that this study was primarily designed to investigate a possible independent influence of BMI on NTproBNP levels, and less, in order to compare the individual prognostic performance within each BMI class or across the BMI continuum. To do so, an alternative matching strategy would have to include NTproBNP itself to account for its intrinsic prognostic information. This, however, would render the analysis of influence of BMI on NTproBNP levels—the goal of the present study—impossible. Consequently, we urge caution as to any correction factor. The variables of our matching strategy explained \(\sim47\%\) of total variance of NTproBNP, and the BNP promoter is responsive not only to wall stress but also to neuroendocrine activation, as well as to growth signals and pro-inflammatory signal transduction.\textsuperscript{38} Therefore, this would need to be taken into account for such a factor—which unfortunately goes beyond our study.

**Limitations**

Our patients reflect the average population at a tertiary reference centre which accounts for the low proportion of women and ischaemic cardiomyopathy in this study. Therefore, our results might not be fully transferable to all patients. Though only 10\% of the cohort, a total of 60 women were included. We would therefore be inclined to assume that even though generalizability is limited, this number is important enough to allow a sample-specific statement. Furthermore, we cannot completely exclude a certain pre-selection bias. Recruitment depends on referring physicians deeming their patients appropriate for attendance at our university hospital clinic. Also, the number of patients included might still represent a handicap. This might have precluded more detailed analyses, e.g. separate for sex or age groups.

**Conclusion**

Even when matched for NYHA, age, sex, and renal function, BMI exerts a significant and independent inverse influence on NTproBNP in patients with chronic stable CHF. NTproBNP retained equal statistical power in all three BMI groups.

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**Conflict of interest:** none declared.

**References**


