Role of N-Terminal Pro-B-Type Natriuretic Peptide in Risk Stratification in Patients Presenting in the Emergency Room

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Background: Natriuretic peptides are promising markers in diagnosing acute and chronic heart failure and assessing prognosis in these patients. Increasing routine use to unselected patients is challenged by false-positive results. The aims of this study were to assess (a) the distributions of N-terminal B-type natriuretic peptide (NT-proBNP) values in various diagnostic groups, (b) factors that influence NT-proBNP, and (c) the value of NT-proBNP in risk stratification in unselected emergency room (ER) patients.

Methods: NT-proBNP was measured in 876 unselected consecutive patients [mean (SD) age, 58 (18) years; 53% male] attending the ERs of 2 university hospitals and 1 community hospital. Diagnoses, age, sex, hemoglobin, creatinine (CREA), C-reactive protein (CRP), troponin T, and intensity of care were documented. In a subset consisting of all 417 patients at 1 center, in-hospital follow-up was completed with respect to a complicated clinical course, including intensive care treatment and death.

Results: NT-proBNP was significantly increased in patients with cardiac diagnoses or histories compared with patients with only pulmonary or other diagnoses. In patients with other diagnoses, NT-proBNP values increased significantly with the number of atherosclerotic risk factors (P = 0.044). Age, renal function, CRP, and to a much lesser extent, hemoglobin significantly influenced NT-proBNP values. The amount of care was positively correlated with NT-proBNP (P < 0.001). Classification and regression tree analysis showed a superior impact of NT-proBNP for identification of high-risk patients.

Conclusions: NT-proBNP is a promising marker for identification of patients with structural heart disease in the ER and a suitable tool for risk stratification. Its use in the ER should be limited to clearly clinically defined patient groups at present to avoid a potential excess of additional diagnostic procedures in positive but asymptomatic patients.

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The incidence of acute and chronic heart failure has increased substantially during recent decades because of aging populations in the Western world arising, at least partially, from medical progress with extended life expectancies. On the other hand, dramatic improvements have been achieved in the pharmacotherapy of heart failure, including the use of angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, beta-blockers, and aldosterone antagonists. Recent international guidelines recommend treatment even in patients with asymptomatic structural heart disease (1).

The diagnosis and prognostic evaluation of heart failure is still a challenging problem in clinical medicine because simple and accurate diagnostic techniques are not available. In daily routine, diagnosis of heart failure is based mainly on the patient’s history and clinical findings.
and, occasionally, on echocardiographic evaluation of left ventricular (systolic) function and dimensions.

In an attempt to facilitate and improve diagnosis, biochemical markers have been suggested as additional diagnostic tools in this area. The natriuretic peptides, among which B-type natriuretic peptide (BNP) and its prohormone-derived amino-terminal split product (NT-proBNP) appear to be particularly promising. Concentrations of NT-proBNP are related to left ventricular filling pressures and wall stress. In a previous study by Groening et al. (2), NT-proBNP was identified as a promising diagnostic and prognostic marker for systolic heart failure and outcome in terms of survival, congestive heart failure (CHF) admissions, and other cardiac admissions. Most recently this has been confirmed by serial measurements in the FRISC study (3) and shown in patients with stable coronary artery disease (4). The value of BNP and NT-proBNP for diagnosing heart failure has been shown unequivocally (5, 6).

Studies of the prognostic value of NT-proBNP in unselected, routine patients in the emergency room (ER) are lacking, however, although this is where the most challenging and urgent need to distinguish between patients with heart failure and those with other acute diseases is encountered.

The purpose of the present study was to assess (a) distributions of NT-proBNP values in various diagnosis groups, (b) factors influencing NT-proBNP, and (c) the value of NT-proBNP in risk stratification in unselected ER patients.

**Patients and Methods**

A total of 876 consecutive patients from 3 German emergency departments (in 2 university hospitals and 1 large tertiary care community hospital) were enrolled. Laboratory analyses were done with lithium heparin-plasma samples taken for clinical purposes, and the attending physicians were blinded to the NT-proBNP results. No additional blood was taken, and history-taking, clinical variables, and follow-up were completed from the patients’ medical records. The Institutional Review Board approved the study protocol.

The characteristics of patients are listed in Table 1 according to the different diagnosis groups as defined below and the subgroup of Charité patients who underwent in-hospital follow-up.

Follow-up was performed in all patients treated in the internal medicine emergency room of the Charité University hospital; this subgroup consisted of 417 patients. The following variables were studied: death, intensive care therapy, and discharge status. A primary endpoint “complications/death” was defined, which included patients who had to be transferred to secondary or primary care hospitals or rehabilitation units after specific therapy in the tertiary care center had been completed. The secondary endpoint analyzed was “any intensive care therapy during the hospital stay”. The 2 endpoints overlapped in only 25% of patients. The follow-up subgroup did not differ from the whole population with respect to clinical characteristics (Table 1). Of all patients in the follow-up, 177 were admitted to hospital for more than 24 h. The mean duration of follow-up in this group was 10 days (range, 1–67 days).

Clinical variables, including assessment of atherosclerotic risk factors and diagnosis, were recorded. Diagnoses were grouped into 4 categories: (A), confirmed or suspected ischemic heart disease, including acute coronary syndrome and ischemic heart failure; (B), nonischemic heart disease, including arrhythmias without acute ischemic trigger, valvular heart disease, and cardiomyopathies; (C), lung disorders, including asthma, chronic obstructive and restrictive lung disease, and pulmonary embolism (n = 6); (D), all other disorders. Group D1 (subgroup of D) was defined as having no evidence of cardiac disorders and no risk factors for cardiac disorders.

Analytical variables included NT-proBNP, creatinine, high-sensitivity C-reactive protein (CRP), hemoglobin, and cardiac troponin T (cTnT; in patients of the follow-up group only). Analytes were measured in the central laboratories of the participating centers in accordance with national standard procedures. NT-proBNP and cTnT were measured by electrochemiluminescence immunoassays on the Elecsys® 2010 analyzer (Roche Diagnostics). The NT-proBNP method has been described in detail recently (7). The cutoff of 125 ng/L (97.5th percentile from healthy blood donors) was taken from the manufacturer’s package insert. The interassay CVs were 6.8% at 0.6 mg/L and 1.1% at 4.6 mg/L for CRP, 3.0% at 0.13 μg/L and 2.8% at 2.7 μg/L for cTnT, and 3.5% at 84.7 ng/L and 2.3% at 3265 ng/L for NT-proBNP.

The distributions of numerical variables were skewed. Consequently, medians and ranges were applied for descriptive statistics, and appropriate nonparametric statistical tests were used for bivariate testing (see figure legends). A 2-sided α-level of 5% was used for all tests. Categorical variables are given as percentages and with 95% confidence intervals (95% CIs) as appropriate. Chest pain, dyspnea, edema, heart noise, and heart insufficiency were analyzed as dichotomies (i.e., yes/no classifications).

Investigation of the overall distribution of the NT-proBNP values revealed a highly skewed distribution with an exponential or gaussian appearance. For NT-proBNP, the log-transformation was useful (7) and was consequently applied in Figs. 1–4. It seems worth noting that this monotonic transformation does not change any results of nonparametric analyses based on cutoffs or

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7 Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CHF, congestive heart failure; ER, emergency room; CRP, C-reactive protein; cTnT, cardiac troponin T; 95% CI, 95% confidence interval; CART, classification and regression tree; GFR, glomerular filtration rate; and RR, relative risk.
ranks. Graphical analyses treating age, renal function, and CRP as independent variables and NT-proBNP as the dependent variable were performed by nonparametric regression approaches based on smoothing splines (8, 9).

The relative value and hierarchy of potential prognostic variables were evaluated by classification and regression tree (CART) methodology. CART involves repeated subdivisions of a group of individuals on the basis of relatively optimal cut-points of binary, ordinal, or continuous covariates that maximizes a certain split criterion (10); CART has already been successfully applied in various clinical cardiovascular research studies (11, 12). In the present analysis, age, sex, diagnosis groups (see above), NT-proBNP, CRP, hemoglobin, creatinine, glomerular filtration rate (GFR) calculated from the Cockcroft–Gault formula, and cTnT were included and assessed for their relative value in classifying patients into homogeneous and clinically relevant “risk groups” according to clinical outcome after follow-up (available only for Charité data, n = 417).

Additionally, we performed a stepwise logistic regression analysis to assess the same variables used in the CART model. The main advantage of using CART was the direct and simple interpretation of CART results, which are observed incidences in actually observed groups as opposed to estimated odds ratios (which can be used to calculate estimated incidences) for often-hypothetical groups as obtained by logistic regression models. This fact clearly reflects the difference in emphasis of the 2 models: Although CART focuses on the impact and, therefore, the interpretation of results, the focus in logistic regression modeling is significance.

CART is also highly sensitive to interactions (i.e., combinatorial effects) between the examined factors. Although in general terms logistic regression is also able to identify significant interactions, it can estimate those effects only in the whole study group. CART is more sensitive in being able to probe for interactions in actually observed subgroups.

Results

Patients were enrolled between September 7 and November 11, 2003. Patients in the subgroup with follow-up did not differ from the whole study population (Table 1). The distribution of NT-proBNP in the different diagnosis groups is shown in Fig. 1. As can be seen in Fig. 2A, NT-proBNP values were significantly associated with different cardiac and pulmonary disorders. Patients with pulmonary disorders but no history of cardiac diseases or cardiovascular risk factors had the lowest NT-proBNP values. When we used the manufacturer-recommended NT-proBNP cutoff (125 ng/L) as a “diagnostic test” for cardiac diagnoses (diagnosis group A+B in Fig. 2A), sensitivity was 81.1% and specificity was 53%. The corresponding ROC curve is shown in Fig. 2B. The area under the curve was 0.74 (95% CI, 0.70–0.77; P < 0.001). The areas under the CRP and cTnT curves were 0.50 (0.45–0.54; P > 0.2) and 0.57 (0.50–0.63; P = 0.044), respectively.

The influences of age and GFR on NT-proBNP values is shown in Fig. 3 as spline smoothing graphs. NT-proBNP correlated significantly with CRP (Spearman r = 0.388; P < 0.001), age (r = 0.642; P < 0.001), and GFR (r = −0.533; P < 0.001). In particular, diminished renal function (Fig. 3B) seemed to have a strong association with NT-proBNP, whereas values in patients with GFR > 90 mL·min⁻¹·(1.73 m²)⁻¹ seemed to be unrelated.

Presenting diagnoses of patients who were enrolled in the study were acute coronary syndrome (n = 100); various arrhythmias, including tachycardia with atrial fibrillation (n = 84); acute CHF (n = 68); arterial hypertension (n = 32); pneumonia (n = 26); and chronic obstructive pulmonary disease or asthma (n = 20). Other diagnoses (n = 531) were most common and included a broad spectrum from infectious diseases to neurologic disorders. Other diagnoses were present in < 20 patients each. Acute bronchitis (n = 9) and pulmonary embolism (n = 6) were rare diagnoses.

The results of the CART analyses to assess the relative value and hierarchy of potential prognostic variables for the 2 outcome variables complications/death (9.4%; 39 cases, including 8 deaths) and intensive care therapy are detailed in panels A and B, respectively, of Fig. 4. At the upper starting point, the whole sample of patients with an incidence of an endpoint of 9.4% (Fig. 4A) or 9.6% (Fig. 4B) is displayed. For both outcome events, NT-proBNP (with an identical cutoff of 3806 ng/L) consistently possessed the highest impact in risk stratification in these unselected ER patients, splitting the whole sample into incidence subgroups of 6.4% and 35.7% [relative risk (RR) = 5.6] for complications/death and into incidence subgroups of 5.9% and 42.9% (RR = 7.3) for intensive care.

Additional significant splits with respect to the incidence of complications/death were found for CRP and age (Fig. 4A), defining potential extreme risk groups with incidences of 3.8% (n = 289) and 55.6% (n = 18).

For the endpoint intensive care, again NT-proBNP as well as CRP and hemoglobin (Fig. 4B) were identified as the most significant predictors, giving extreme risk groups of 2.0% (n = 200) and 66.7% (n = 18; RR = 14.6).

No other laboratory markers or diagnostic group and demographic variables (see Patients and Methods) that were included in the analysis achieved significant risk stratification. In this context, cTnT did not play an independent prognostic role in this overall ER population for either endpoint assessed.

Logistic regression analyses identified age, NT-proBNP, and CRP for death and NT-proBNP and CRP for intensive care as overall significant variables (Table 2).

Discussion

Although overwhelming evidence exists of the value of NT-proBNP in selected patients with cardiovascular dis-
Table 1. Characteristics of 876 unselected patients of the ER compared with the subgroup of 417 patients who were followed up.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Charité subpopulation</th>
<th>Total study population</th>
<th>Group A (ischemic)</th>
<th>Group B (nonischemic)</th>
<th>Group C (pulmonary disease)</th>
<th>Group D (other)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>417</td>
<td>876</td>
<td>151</td>
<td>150</td>
<td>84</td>
<td>491</td>
</tr>
<tr>
<td>Age, a, years</td>
<td>58 (41–69)</td>
<td>61 (44–73)</td>
<td>66 (58–75)</td>
<td>70 (58–78)</td>
<td>64 (42.5–75)</td>
<td>53 (38–67)</td>
</tr>
<tr>
<td>Male, b</td>
<td>50.4 (45.5–53.3)</td>
<td>53.2 (48.9–56.5)</td>
<td>68.9 (60.8–76.2)</td>
<td>54.7 (46.3–62.8)</td>
<td>60.7 (49.5–71.2)</td>
<td>46.6 (42.2–51.2)</td>
</tr>
<tr>
<td>Body mass index, a kg/m²</td>
<td>25.3 (22.1–28.3)</td>
<td>25.1 (22.5–28.4)</td>
<td>26.9 (23.7–29.4)</td>
<td>25.5 (23.7–29.1)</td>
<td>24.3 (21.6–28.3)</td>
<td>24.5 (21.8–27.8)</td>
</tr>
<tr>
<td>Smokers, b</td>
<td>17.3 (13.8–21.2)</td>
<td>17.6 (15.1–20.3)</td>
<td>21.2 (15.0–28.6)</td>
<td>12.7 (7.8–19.1)</td>
<td>20.2 (12.3–30.4)</td>
<td>17.5 (14.3–21.2)</td>
</tr>
<tr>
<td>Heart rate, a beats/min</td>
<td>80 (70–98)</td>
<td>80 (70–97)</td>
<td>74.5 (65–84.5)</td>
<td>92 (72–120)</td>
<td>94 (81–105)</td>
<td>80 (70–92)</td>
</tr>
<tr>
<td>Dyspnea, b</td>
<td>17.3 (13.8–21.3)</td>
<td>22.8 (20.1–25.8)</td>
<td>31.8 (24.5–39.9)</td>
<td>46.7 (38.5–55.0)</td>
<td>54.8 (43.3–65.7)</td>
<td>7.3 (5.2–10.0)</td>
</tr>
<tr>
<td>Edema, b</td>
<td>8.9 (6.3–12.0)</td>
<td>10.5 (8.6–12.7)</td>
<td>7.3 (3.7–12.7)</td>
<td>28.7 (21.6–36.6)</td>
<td>10.7 (5.0–19.4)</td>
<td>5.9 (4.0–8.4)</td>
</tr>
<tr>
<td>Chest pain, b</td>
<td>19.4 (15.7–23.6)</td>
<td>26.0 (23.2–29.1)</td>
<td>84.1 (77.3–89.5)</td>
<td>26.7 (19.8–34.5)</td>
<td>17.9 (10.4–27.7)</td>
<td>9.4 (6.9–12.3)</td>
</tr>
<tr>
<td>Heart noise, b</td>
<td>11.8 (8.8–15.2)</td>
<td>12.3 (10.2–14.7)</td>
<td>13.2 (8.3–19.7)</td>
<td>24.7 (18.0–32.4)</td>
<td>8.3 (3.4–16.4)</td>
<td>9.0 (6.6–11.8)</td>
</tr>
<tr>
<td>Heart insufficiency, b</td>
<td>13.4 (10.3–17.1)</td>
<td>14.3 (12.0–16.8)</td>
<td>18.5 (12.7–25.7)</td>
<td>36.7 (29.0–44.9)</td>
<td>10.7 (5.0–19.4)</td>
<td>6.7 (4.7–9.3)</td>
</tr>
<tr>
<td>History of AMI, c</td>
<td>12.0 (9.0–15.5)</td>
<td>12.7 (10.5–15.1)</td>
<td>32.5 (25.1–40.5)</td>
<td>16.7 (11.1–23.6)</td>
<td>9.5 (4.2–17.9)</td>
<td>5.9 (4.0–8.4)</td>
</tr>
<tr>
<td>Angina pectoris/CHD, b</td>
<td>24.5 (20.4–28.9)</td>
<td>25.0 (22.2–28.0)</td>
<td>63.6 (55.4–71.3)</td>
<td>35.3 (27.7–43.6)</td>
<td>14.3 (7.6–23.6)</td>
<td>11.8 (9.1–15.0)</td>
</tr>
<tr>
<td>Cardiac medication, b</td>
<td>25.9 (21.8–30.4)</td>
<td>39.3 (36.0–42.6)</td>
<td>65.6 (57.4–73.1)</td>
<td>68.0 (59.9–75.4)</td>
<td>34.5 (25.4–45.7)</td>
<td>23.2 (16.9–27.2)</td>
</tr>
<tr>
<td>Arterial hypertension, b</td>
<td>40.3 (35.5–45.2)</td>
<td>41.9 (38.6–45.2)</td>
<td>62.3 (54.0–70.0)</td>
<td>58.0 (49.7–66.0)</td>
<td>35.7 (25.6–46.9)</td>
<td>31.8 (27.7–36.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, b</td>
<td>14.6 (11.4–18.4)</td>
<td>15.9 (13.5–18.5)</td>
<td>23.2 (16.7–30.7)</td>
<td>28.0 (21.0–35.9)</td>
<td>11.9 (5.9–20.8)</td>
<td>10.6 (8.0–13.7)</td>
</tr>
<tr>
<td>Lung disease, b</td>
<td>14.1 (11.0–17.9)</td>
<td>16.0 (13.6–18.6)</td>
<td>10.6 (6.2–16.6)</td>
<td>18.0 (12.2–25.1)</td>
<td>72.6 (61.8–81.8)</td>
<td>7.3 (5.2–10.0)</td>
</tr>
<tr>
<td>Hb, a, g/L</td>
<td>135 (124–145)</td>
<td>134 (123–145)</td>
<td>136 (126–146)</td>
<td>135 (125–149)</td>
<td>130 (119–141)</td>
<td>134 (122–145)</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>9.2 (7.6–11.1)</td>
<td>9.0 (8.0–11.2)</td>
<td>9.4 (8.3–12.0)</td>
<td>10.3 (9.0–13.0)</td>
<td>10.0 (8.0–12.0)</td>
<td>9.0 (7.1–10.7)</td>
</tr>
<tr>
<td>Glucose, a, mg/L</td>
<td>1090 (970–1310)</td>
<td>1055 (910–1290)</td>
<td>1120 (950–1440)</td>
<td>1090 (920–1400)</td>
<td>1080 (900–1280)</td>
<td>1030 (910–1240)</td>
</tr>
<tr>
<td>CRP, a, mg/L</td>
<td>4.0 (1.3–14.3)</td>
<td>4.5 (2.6–17.0)</td>
<td>4.0 (2.6–9.0)</td>
<td>5.1 (4.0–15.5)</td>
<td>27.0 (5.2–106.0)</td>
<td>4.0 (2.0–15.2)</td>
</tr>
<tr>
<td>NT-proBNP, a, ng/L</td>
<td>136 (50–673)</td>
<td>196 (56–1090)</td>
<td>382 (103–1633)</td>
<td>1352 (476–3488)</td>
<td>269 (53–1074)</td>
<td>105 (44–323)</td>
</tr>
<tr>
<td>Discharge, b</td>
<td>46.8 (41.9–51.7)</td>
<td>40.9 (37.6–44.2)</td>
<td>21.2 (15.0–28.6)</td>
<td>24.7 (18.0–32.4)</td>
<td>33.3 (23.4–44.5)</td>
<td>53.2 (48.6–57.6)</td>
</tr>
<tr>
<td>General ward, b</td>
<td>21.3 (17.5–25.6)</td>
<td>39.8 (36.4–43.2)</td>
<td>39.1 (31.3–47.3)</td>
<td>55.3 (47.0–63.5)</td>
<td>47.6 (36.6–58.8)</td>
<td>34.0 (29.8–38.4)</td>
</tr>
<tr>
<td>ICU, b</td>
<td>31.9 (27.4–36.6)</td>
<td>18.8 (16.3–21.6)</td>
<td>39.1 (31.3–47.3)</td>
<td>20.0 (13.9–27.3)</td>
<td>17.9 (10.4–27.7)</td>
<td>12.4 (9.6–15.7)</td>
</tr>
</tbody>
</table>

*Median (25th–75th percentiles).%

Table 1 indicates the upper limit of the reference interval (125 ng/L).

Fig. 1. NT-proBNP values according to the different diagnosis groups as defined in the Patients and Methods section.

Values are displayed as box plots. The dashed line indicates the upper limit of the reference interval (125 ng/L).

Figures, only a few studies have been published on population samples and no data are available on unselected ER patients.

Our data confirmed results obtained in previous stud-
has prognostic importance; it can therefore be envisaged that even subsets of patients treated in hospital for non-cardiac reasons could be screened and seen by a cardiologist for further diagnostic tests and initiation of cardiac treatment if necessary.

The second issue is that because more patients than expected had substantially increased NT-proBNP values in a broad range (Fig. 1), the subject of an appropriate cutoff arises. In the CART analyses, 2 different cutoffs were seen to be useful (Fig. 4). This suggests the use of a high cutoff that applies to maximum risk detection and selection of candidates for intensive care. Because economic allocation of resources seems to be aided by BNP measurements (15), biochemical risk stratification may help admitting physicians to select the appropriate care for their patients.

The final issue is that although we confirmed the clear association of cardiac and noncardiac patients, which was one of the first (NT-pro)BNP issues (13, 16–18) (Fig. 2A), we also saw a significant overlap of values, as in the other published studies. The ROC curve in Fig. 2B shows that despite a highly significant association of diagnosis and NT-proBNP, discriminatory value remains critical. Additionally it has to be pointed out that the patients with a
primary pulmonary or other diagnosis but a cardiac history (Fig. 2A, diagnosis group C + D/Card) had intermediate values, with the median above the recommended upper limit of the reference interval (246 ng/L vs 125 ng/L; Fig. 2A). This limits the discriminatory value, although from other studies it could be speculated that these patients do have some cardiac pathology (19).

NT-proBNP values seemed to be influenced independently by age in our study, which means that they may reflect more than an increasing prevalence of cardiac pathology with increasing age. Thus, we suggest that age-dependent cutoffs be established to rule out relevant structural heart disease. Higher cutoffs may be used in the future to guide and optimize care and medication. From our analyses, definite cutoffs can not be deduced because not all patients underwent cardiovascular diagnostics. Nevertheless, it should be pointed out that in pulmonary diseases accompanied by pulmonary hypertension or primary hypertension, BNP concentrations were found to be increased and of prognostic significance (20–24). This may reflect right ventricular overload and cor pulmonale. Finally, clear differentiation of patients with pulmonary or cardiac diagnoses by NT-proBNP does not seem to be possible.

Age, renal function, and CRP were identified as influencing NT-proBNP concentrations. As can clearly be seen in Fig. 3, NT-proBNP values increased with these variables independent of the diagnosis group. This confirms data from other populations showing increased values in relation to age and reduced renal function (25). It should be kept in mind that cardiovascular morbidity is much higher in elderly renal patients than in age-matched controls and patients with high inflammatory activity, and therefore, increased NT-proBNP values probably reflect cardiovascular pathology in these patients (26).

In several studies, BNP was evaluated in selected ER patient populations. Most recently, the PRIDE Study showed that NT-proBNP was the strongest predictor of a

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**Table 2. Results of logistic regression analysis with respect to the death and therapy endpoints as outlined in the Patients and Methods section.**

<table>
<thead>
<tr>
<th></th>
<th>Complications/death [overall incidence, n = 39 (9.4%)]</th>
<th>Intensive care [overall incidence, n = 40 (9.6%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>ln(OR)*</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Constant</td>
<td>−3.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age 80+ years (baseline: up to 80 years)</td>
<td>1.57</td>
<td>4.80 (3.09–7.46)</td>
</tr>
<tr>
<td>NT-proBNP &gt;3806 ng/L (baseline: up to 3806 ng/L)</td>
<td>1.55</td>
<td>4.71 (3.09–7.19)</td>
</tr>
<tr>
<td>CRP &gt;23.6 mg/L (baseline: up to 23.6 mg/L)</td>
<td>1.33</td>
<td>3.80 (2.59–5.56)</td>
</tr>
<tr>
<td>Model fit (−2 log likelihood)</td>
<td>48.8 of 259</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model fit (−2 log likelihood)</td>
<td>52 of 263</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*OR, odds ratio.
final diagnosis of acute CHF in patients with dyspnea (27). Comparing the results obtained in that study with our data, it is evident that the patient populations are completely different. Acute CHF was the most common diagnosis in the PRIDE Study (prevalence, 35%) but was found in only 8% in our population. Therefore, the clinical preselection of patients clearly influences the value of NT-proBNP measurements in the ER. Consistently, previous studies using BNP showed sensitivities >90% (28), but decreasing specificities depending on the prevalence of acute CHF [76% in the largest studies by Maisel and coworkers (14, 16) and 53% in a community-based study by Nielsen et al. (19)]. On the other hand, the authors of the recently published REDHOT study (29) came to the conclusion that there is a lack of congruence between the severity of CHF as perceived by ER physicians and the “severity as determined by BNP levels”. The BNP concentrations in that study on patients arriving in the ER with shortness of breath did not differ among New York Heart Association functional classes (29).

In a systematic review of studies using BNP, Doust et al. (30) showed in pooled data that the diagnostic odds ratios in several clinical subgroups were mostly >10. They plotted the data from studies comparing BNP with a left ventricular ejection fraction ≤40% in an ROC curve, and BNP showed excellent diagnostic accuracy with an area under the curve of 0.83. Keeping this in mind, NT-proBNP may in fact be better than echocardiography for detecting mild and early forms of heart failure, which may have a high prevalence in patients admitted to the ER for other reasons.

Several studies have shown the prognostic value of NT-proBNP in various patient subpopulations (31–34). Although we investigated unselected ER patients with a broad range of cardiac and noncardiac diagnoses, we were able to show prognostic impact with respect to hard endpoints (Fig. 4). Because age, renal function, and CRP were associated with NT-proBNP concentrations, we included these variables in the CART analysis. We therefore could definitely confirm the superior prognostic value of NT-proBNP over both age and renal function in direct comparisons (Fig. 4). In fact, NT-proBNP consistently showed the strongest discriminating power in both analyses.

Our study included unselected ER patients from 3 participating centers in different regions of Germany whose characteristics were consistent. However, we did not carry out further cardiac diagnostic procedures in all NT-proBNP–positive patients and therefore do not have a “gold standard” for final cardiac diagnosis in all patients. Furthermore, we did not look at specific cardiovascular outcome variables. On the other hand, our data give unique insight into the spectrum of variables associated with NT-proBNP in the ER. To evaluate a suitable and economically feasible strategy for the use of NT-proBNP in the ER, additional prospective studies are needed. Because of the broad spectrum of patients presenting with increased NT-proBNP, studies are useful not only in the subgroup of patients with dyspnea, as shown in earlier strategy studies (15, 35), but also in other clinically defined subsets, such as the elderly or patients with multiple risk factors.

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