

The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study

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The utility of aminoterminal pro-brain natriuretic peptide (NT-proBNP) testing in the emergency department to rule out acute congestive heart failure (CHF) and the optimal cutpoints for this use are not established. We conducted a prospective study of 600 patients who presented in the emergency department with dyspnea. The clinical diagnosis of acute CHF was determined by study physicians who were blinded to NT-proBNP results. The primary end point was a comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF. The median NT-proBNP level among 209 patients (35%) who had acute CHF was 4,054 versus 131 pg/ml among 390 patients (65%) who did not ($p < 0.001$). NT-proBNP at cutpoints of >450 pg/ml for patients <50 years of age and >900 pg/ml for patients ≥ 50 years of age were highly sensitive and

specific for the diagnosis of acute CHF ($p < 0.001$). An NT-proBNP level <300 pg/ml was optimal for ruling out acute CHF, with a negative predictive value of 99%. Increased NT-proBNP was the strongest independent predictor of a final diagnosis of acute CHF (odds ratio 44, 95% confidence interval 21.0 to 91.0, $p < 0.0001$). NT-proBNP testing alone was superior to clinical judgment alone for diagnosing acute CHF ($p = 0.006$); NT-proBNP plus clinical judgment was superior to NT-proBNP or clinical judgment alone. NT-proBNP measurement is a valuable addition to standard clinical assessment for the identification and exclusion of acute CHF in the emergency department setting. ©2005 by Excerpta Medica Inc.

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Brain-type natriuretic peptide (BNP) is a 32-amino acid protein synthesized by the myocardium. BNP is derived from an intracellular 108-amino acid precursor protein, which is cleaved into 2 fragments and released by the myocyte, yielding BNP, and a 76-amino acid N-terminal fragment, NT-proBNP. Although BNP has been widely used as an important biomarker for diagnosis and evaluation of acute congestive heart failure (CHF),¹⁻³ clinical measurement of NT-proBNP has only recently become available. NT-proBNP levels tend to be much higher than BNP levels, and only limited data are available to guide physicians in their interpretation.^{4,5} We therefore undertook the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, the largest prospective trial of NT-proBNP testing to date, to definitively establish the role of NT-proBNP testing for the diagnosis of acute CHF in patients who present with dyspnea in the emergency department.

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METHODS

Study population: The institutional review board approved all procedures involved in the PRIDE study. The PRIDE study is similar in design to the Breathing Not Properly Multinational study,^{3,6} which assessed the use of BNP for patients who presented with dyspnea in the emergency department. The PRIDE study population was drawn from consenting patients ≥ 21 years of age who presented to the emergency department of the Massachusetts General Hospital (Boston, Massachusetts) with a complaint of dyspnea. Exclusion criteria for the study were severe renal insufficiency (serum creatinine level >2.5 mg/dl), dyspnea after chest trauma, dyspnea secondary to severe coronary ischemia that was identified as >0.1 mV ST-segment elevation or ST-segment depression on a 12-lead electrocardiogram if performed at presentation), >2 -hour delay after urgent intravenous loop diuretic administration (above any baseline maintenance dose), and unblinded natriuretic peptide level measurement.

Data collection: After enrollment, clinical characteristics of each patient were recorded, including demographics, symptoms (including New York Heart Association symptom severity), signs, medical history, medication use, and diagnostic studies in the emergency department, such as electrocardiography,

chest x-ray, and standard blood tests. An additional blood sample was collected for NT-proBNP measurement, which was performed after patient enrollment had been completed. After collection, blood samples were processed and frozen at -80°C for later NT-proBNP analysis.

At the end of standard clinical assessment and with knowledge of the results of all clinical tests except NT-proBNP levels, the managing emergency department attending physician was asked to estimate (on a scale from 0% to 100%) the likelihood that acute CHF was the cause of the patient's dyspnea. This estimate was recorded for future comparison with NT-proBNP results. The emergency department discharge diagnosis was also recorded.

If the patient was admitted to the hospital, the hospital course, the results of any laboratory testing, outcomes of diagnostic tests, and pertinent discharge information (including discharge diagnoses made by in-hospital physicians and discharge medications) were recorded.

A 60-day follow-up was performed on every patient and included attempts to contact each patient and a chart review of electronic hospital records, physician's notes, and test results to determine whether any clinical events occurred during the period since the index presentation.

Determination of diagnosis: To determine the diagnosis for each patient at presentation, study cardiologists were provided with all hospital records (including admit/discharge notes, results of laboratory and radiologic testing, cardiac tests such as echocardiograms, and clinical notes) that pertained to the subject, starting from the time of emergency department presentation to the results of the 60-day follow-up. These records included all data regarding index presentation, those related to subsequent hospitalization at index presentation (if applicable), those related to any repeat presentations between the index presentation and 60 days, and all available outpatient clinical records for each patient. In addition, results of the 60-day phone contact with each patient were made available to physicians. By using all available data from presentation through the 60-day review, a clinically rendered diagnosis for each patient's presentation was assigned without knowledge of the results of NT-proBNP testing. Patients were stratified by diagnosis at presentation into 1 of 3 categories: acute CHF, noncardiac dyspnea in a patient who had previous CHF, or no CHF previously or currently. In addition to these categories, a clinical diagnosis (when available) was assigned. Acute coronary syndromes were classified as previously described.⁷ In the 10% of cases in which the diagnosis was unclear or in doubt or when disagreement as to the final diagnosis existed, an adjudicated diagnosis was rendered in accordance with Framingham Heart Study criteria for diagnosis of CHF.⁸

NT-proBNP analysis: NT-proBNP analysis was performed with a commercially available immunoassay (Elecys proBNP, Roche Diagnostics, Indianapolis, Indiana) on an Elecys 1010 analyzer according to estab-

lished methods. This assay is reported to have $<0.001\%$ cross reactivity with bioactive BNP. Briefly, 20 μl of the sample was incubated with biotinylated polyclonal capture antibodies and polyclonal ruthenium-complexed detection antibodies, which were directed against NT-proBNP. After incubation, the captured NT-proBNP, which was bound to streptavidin-coated paramagnetic microparticles, was quantified by electrochemiluminescence. In the PRIDE study, this assay had an inter-run coefficient of variation of $<1.0\%$.

Statistical analysis: Comparisons of clinical characteristics between patients who had acute CHF and those who did not were performed with chi-square tests for categorical data and Wilcoxon's rank-sum test for continuous data. Comparisons of NT-proBNP levels across diagnostic categories were performed with nonparametric Kruskal-Wallis testing. Comparisons of NT-proBNP levels across patients based on New York Heart Association classification were performed using similar methods.

Cut-point analyses: Receiver-operating characteristic curve analysis using Analyze-It software (Analyze-It, Ltd., Leeds, United Kingdom) was performed for NT-proBNP using the final blinded diagnosis as the reference standard. The sensitivity and specificity of NT-proBNP for prediction of CHF in PRIDE study subjects were determined across numerous age groups to independently evaluate for optimal rule-in cutpoints. To address the question of ruling out acute CHF, we examined the manufacturer-recommended cutpoints and evaluated independently generated cutpoints.

Independent predictors of acute CHF: Multivariable analysis with stepwise logistic regression was used to identify independent predictors of acute CHF, with a p value <0.05 for entry into the model and a p value >0.10 for removal. Goodness of fit was verified with the Hosmer-Lemeshow test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Primary end point: NT-proBNP versus clinical judgment: Receiver-operating characteristic curves for NT-proBNP and clinician-estimated likelihood of acute CHF (as continuous variables) were plotted, and areas under the curve for each were calculated and compared with univariate Z score testing. A logistic regression model that contained a combination of NT-proBNP and clinician-estimated likelihood was analyzed in a similar fashion and compared with the results of receiver-operating characteristic analyses of each patient component. The sensitivity and specificity of NT-proBNP testing were examined at various levels of the clinician-estimated likelihood for acute CHF (0% to 25%, 26% to 75%, and $>75\%$).

RESULTS

Patients: Six hundred eligible patients were enrolled over 4 months. One patient withdrew consent at 60-day follow-up, leaving a final cohort of 599 patients. Of the 599 patients in the study, 209 (35%) had a final diagnosis of acute CHF, 35 (6%) had noncardiac dyspnea with a history of CHF, and the remaining

| Characteristic | Acute CHF (n = 209) | No Acute CHF (n = 390) | p Value |
|--|----------------------|------------------------|---------|
| Demographics | | | |
| Age (mean ± SD; range) (yrs)* | 72.8 ± 13.6 (27–94) | 56.9 ± 16.3 (22–95) | <0.001 |
| Men | 51% | 51% | 0.70 |
| Caucasian | 90% | 86% | 0.21 |
| Symptoms/signs | | | |
| Paroxysmal nocturnal dyspnea | 23% | 7% | <0.001 |
| Orthopnea | 32% | 9% | <0.001 |
| Lower extremity edema | 32% | 9% | <0.001 |
| Chest pain | 36% | 46% | 0.05 |
| Cough | 31% | 40% | 0.02 |
| Fever | 5% | 12% | 0.009 |
| Increased sputum production | 6% | 11% | 0.007 |
| Change in sputum quality | 4% | 7% | 0.08 |
| Medical history | | | |
| Cardiomyopathy | 20% | 6% | 0.001 |
| Arrhythmia | 32% | 9% | <0.001 |
| Systemic hypertension | 64% | 41% | <0.001 |
| Coronary artery disease | 42% | 20% | 0.001 |
| Mitral valve disease | 15% | 3% | <0.001 |
| Aortic valve disease | 14% | 3% | 0.001 |
| Previous acute myocardial infarction | 21% | 9% | 0.004 |
| Previous CHF | 54% | 9% | <0.001 |
| Chronic obstructive pulmonary disease | 25% | 42% | <0.001 |
| Medications | | | |
| β Blocker | 56% | 29% | <0.001 |
| Loop diuretic | 56% | 16% | <0.001 |
| Hydrochlorothiazide | 9% | 7% | 0.87 |
| Digoxin | 23% | 4% | <0.001 |
| Angiotensin-converting enzyme inhibitor | 33% | 15% | <0.001 |
| Aspirin | 44% | 23% | 0.002 |
| Hydralazine | 2% | 0.5% | 0.257 |
| Nitroglycerin | 15% | 7% | 0.05 |
| Physical examination | | | |
| Pulse rate (mean ± SD; range)/(beats/min) | 86.5 ± 23.5 (30–172) | 88.2 ± 22.3 (18–170) | 0.85 |
| Jugular venous distension | 19% | 4% | <0.001 |
| S ₃ gallop | 2% | 0.3% | 0.05 |
| S ₄ gallop | 2% | 1% | 0.41 |
| Murmur | 19% | 7% | <0.001 |
| Lower extremity edema | 40% | 16% | <0.001 |
| Rales | 48% | 14% | <0.001 |
| Wheezing | 18% | 28% | 0.001 |
| Diagnostic Studies | | | |
| Cardiac troponin T >0.03 ng/ml | 26% | 5% | <0.001 |
| Electrocardiogram with normal sinus rhythm | 58% | 77% | <0.001 |
| Interstitial edema on chest x-ray | 42% | 4% | <0.001 |

355 (59%) did not have CHF previously or the time of presentation.

Clinical characteristics: Comparisons of clinical characteristics at presentation between those patients who had acute CHF (n = 209) and those who did not (n = 390) are presented in Table 1.

Clinical diagnoses: As expected, there were a variety of diagnoses as the etiology of dyspnea in our patient cohort (Figure 1), with acute CHF being the most prevalent. Only 31 patients overall (5.2%) had an acute coronary syndrome. Among patients who had acute CHF, 12 (5.7%) had concomitant acute myocardial infarction. In 116 subjects (grouped into the “other” category in Figure 1), dyspnea was attributed in <10 patients each to allergic reactions, anxiety, ascites, atrial fibrillation, fever, fibrothorax, gram-negative sepsis, herpes zoster, hypertension, lung carcinoma, pericarditis, supraventricular tachycardia, or unknown etiology.

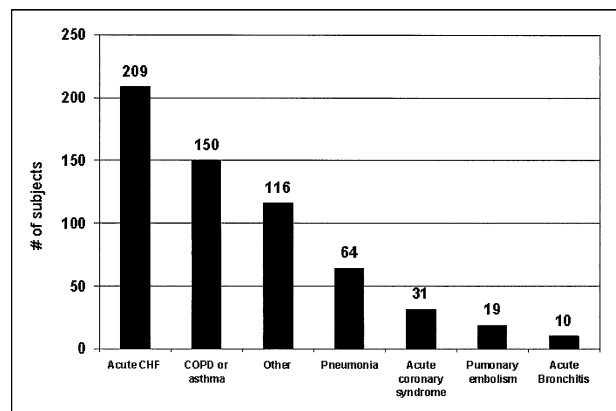


FIGURE 1. Presenting diagnoses of patients who were enrolled in the PRIDE study. Acute CHF was most common, followed by exacerbation of chronic obstructive pulmonary disease (COPD) or asthma. In 116 patients, other diagnoses (outlined in text) were present in <10 patients each.

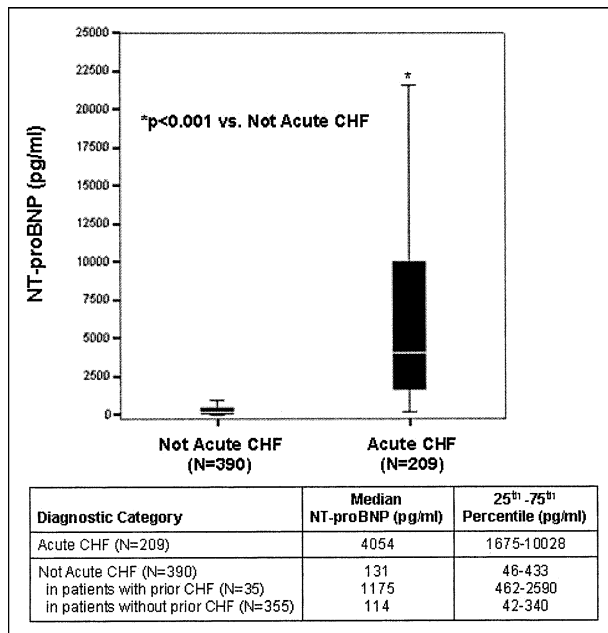


FIGURE 2. Median NT-proBNP levels among patients who had acute CHF ($n = 209$) and those who did not ($n = 390$; $p < 0.001$ for difference). Boxes, interquartile ranges; whiskers, 5th and 95th percentiles.

NT-proBNP results: Median NT-proBNP levels among patients who had acute CHF and those who did not are shown in Figure 2. Among patients who had acute CHF, the median NT-proBNP level was 4,054 pg/ml (interquartile range 1,675 to 10,028) compared with 131 pg/ml (interquartile range 46 to 433) among patients who did not have acute CHF ($p < 0.001$). The difference remained significant when comparing NT-proBNP levels of those who had acute CHF with those who had noncardiac dyspnea and previous CHF (whose median NT-proBNP level was 1,175 pg/ml, $p = 0.02$). Among patients who had acute CHF, NT-proBNP levels correlated with CHF symptom severity ($p = 0.001$; Figure 3).

Receiver-operating characteristic analyses (Figure 4) demonstrated NT-proBNP to be highly sensitive and specific for the diagnosis of acute CHF, as indicated by an overall age-independent area under the receiver-operating characteristic curve of 0.94 ($p < 0.0001$), with an optimal cutpoint of 900 pg/ml, which was sensitive and specific for ruling in the diagnosis of acute CHF (Table 2). Importantly, although this cutpoint was optimal overall, we observed an age-related variation in sensitivity and specificity, i.e., in younger patients (< 50 years old), an NT-proBNP cutpoint of 900 pg/ml was only 73% sensitive (and 96% specific), but the same cutpoint was 91% sensitive and 80% specific in older patients. After thorough age-stratified analyses, we determined that an optimal cutpoint strategy for patients in the PRIDE study was using an age categorization of < 50 years ($n = 144$) and ≥ 50 years ($n = 455$); the optimal cutpoints for ruling in acute CHF were 450 and 900 pg/ml, respectively, for these age strata (Table 2). In the 2 age categories, an excellent area under each receiver-operating characteristic

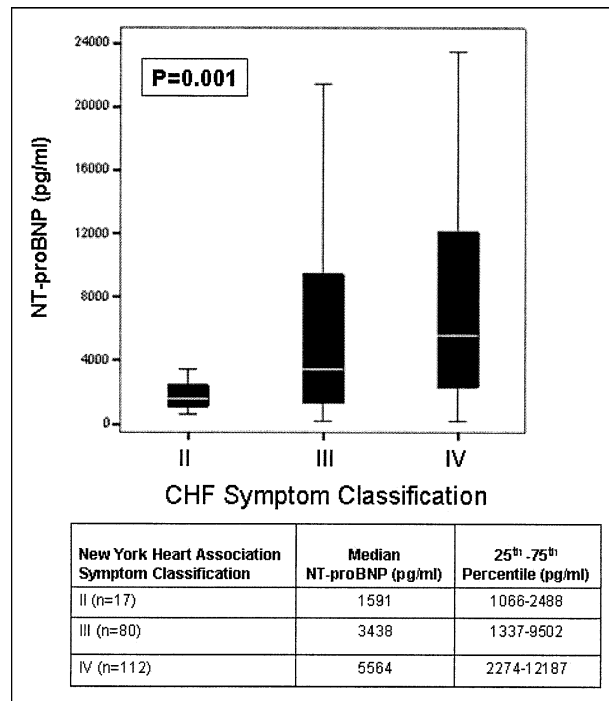


FIGURE 3. Correlation between median NT-proBNP levels and symptom severity based on New York Heart Association symptom classification. Boxes, interquartile ranges; whiskers, 5th and 95th percentiles.

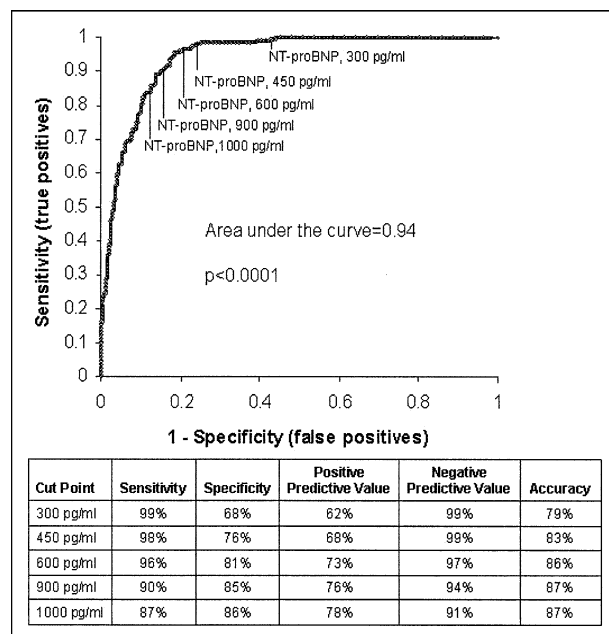


FIGURE 4. NT-proBNP was highly sensitive and specific for the diagnosis of acute CHF, with a highly significant area under the curve. A strategy of partitioning patients in age categories of < 50 and ≥ 50 years (with cutpoints of 450 and 900 pg/ml, respectively) was optimal, with areas under the curve of 0.98 and 0.93, respectively ($p < 0.0001$ for the 2 categories).

curve was observed (0.98 and 0.93, respectively; $p < 0.0001$ for the 2 categories; Figure 4). Using this age-stratified approach, the sensitivity of NT-proBNP

| | Optimal Cutpoint (pg/ml) | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Accuracy (%) |
|--------------------------|--------------------------|-----------------|-----------------|-------------------------------|-------------------------------|--------------|
| Rule-in cutpoints | | | | | | |
| All patients (n = 599) | 900 | 90 | 85 | 76 | 94 | 87 |
| <50 yrs old (n = 144) | 450 | 93 | 95 | 67 | 99 | 95 |
| ≥50 yrs old (n = 455) | 900 | 91 | 80 | 77 | 92 | 85 |
| Rule-out cutpoint | | | | | | |
| All patients (n = 599) | 300 | 99 | 68 | 62 | 99 | 83 |

*NT-proBNP testing was of value to identify and exclude acute CHF with high accuracy. In the PRIDE study, the optimal rule-in strategy using NT-proBNP was an age-stratified approach with 2 cutpoints, whereas a single cutpoint of 300 pg/ml was of value for excluding the diagnosis.

among younger patients was outstanding, with preserved specificity in the 2 groups (Table 2).

With regard to rule-out thresholds, the manufacturer-recommended age-stratified cutpoints of 125 pg/ml for patients who were <75 years old and 450 pg/ml for those who were ≥75 years old yielded a high sensitivity (99%) and negative predictive value (100%), thus emphasizing the value of these cutpoints for ruling out the diagnosis of CHF and extending their value to the emergency department setting. Importantly, we found similar results in our study when using a single age-independent cutpoint of 300 pg/ml (Table 2).

Multivariable predictors of acute CHF: By multivariable analysis, the strongest predictor of acute CHF was an increased NT-proBNP level (when using the age-stratified cutpoints; OR 44.0, 95% CI 21.0 to 91.0, $p < 0.0001$). Other independent predictors of CHF were interstitial edema on chest x-ray (OR 11, 95% CI 4.5 to 26.0, $p < 0.0001$), orthopnea (OR 9.6, 95% CI 4.0 to 23.0, $p < 0.0001$), loop diuretic use before presentation (OR 3.4, 95% CI 1.8 to 6.6, $p = 0.01$), rales on pulmonary examination (OR 2.4, 95% CI 1.2 to 5.2, $p = 0.05$), and age (OR per year 1.03, 95% CI 1.01 to 1.05, $p = 0.01$). Cough (OR 0.43, 95% CI 0.23 to 0.83, $p = 0.05$) and fever (OR 0.17, 95% CI 0.05 to 0.50, $p = 0.03$) independently predicted diagnoses other than CHF.

NT-proBNP versus clinical estimation for diagnosis of CHF: Among the 209 patients who had a final diagnosis of acute CHF, the most frequent emergency department discharge diagnosis was undifferentiated dyspnea (in 44%) followed closely by acute CHF (in 43%). A wide range of estimates of likelihood for CHF were provided by the managing attending emergency department physicians. Using these estimates, receiver-operating characteristic curves that compared the sensitivity and specificity of NT-proBNP results with those of clinician-estimated likelihood for diagnosis of acute CHF are shown in Figure 5. NT-proBNP alone was superior to clinician-estimated likelihood of CHF alone (area under the curve 0.94 vs 0.90, $p = 0.006$). Adding the results of NT-proBNP to those of clinician estimation for the presence of acute CHF improved the sensitivity and specificity further, with an area under the curve of 0.96, which was significantly better compared with NT-proBNP results alone ($p = 0.04$) and particularly with clinical estimation alone ($p < 0.0001$).

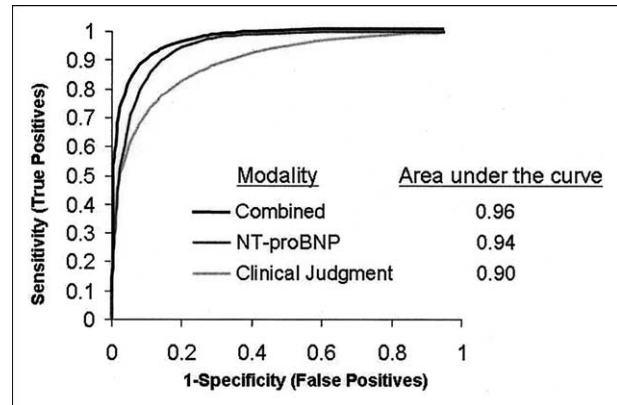


FIGURE 5. Receiver-operating characteristic curve comparison of NT-proBNP versus clinician-estimated likelihood for the emergency department diagnosis of acute CHF. Results of NT-proBNP testing were superior to those of clinical judgment, with significantly greater area under the curve (0.94 vs 0.90, $p = 0.006$). The area under the curve from NT-proBNP testing plus clinical judgment (0.96) was superior to each diagnostic modality alone.

NT-proBNP results discriminated those patients who had acute CHF from those who did not equally well across all ranges of clinician-estimated likelihood for acute CHF. At a range of 0% to 25% estimated likelihood for acute CHF, NT-proBNP testing (using optimal cutpoints) had a sensitivity of 96% and a specificity of 88%. In the estimated likelihood range >75%, the sensitivity of NT-proBNP testing was 93% and the specificity was 84%; in the range of 25% to 75% estimated likelihood (corresponding to the area of poorest performance by the managing physicians for identifying CHF), the sensitivity of NT-proBNP testing for the diagnosis of acute CHF was 93%, with a specificity of 85%.

DISCUSSION

Despite worldwide use of NT-proBNP testing, prospective data that examine its role in diagnosis of acute CHF in the emergency department has been limited to 2 reports with a relatively small number of patients.^{4,5} In addition, although NT-proBNP is approved for ruling out CHF in the outpatient setting, the utility of the assay in the emergency department setting (for diagnosis and exclusion of acute CHF) remained unclear. Thus, the PRIDE study was prospectively performed to definitively establish the clinical

utility of NT-proBNP for the urgent diagnosis or exclusion of acute CHF in patients who have dyspnea and the role of NT-proBNP compared with standard clinical assessment. Our results definitively establish the value of NT-proBNP testing in the emergency department setting. Despite the superiority of NT-proBNP testing to standard clinical assessment in our study, we agree with the suggestion that laboratory testing for BNPs should not supplant clinical acumen,^{9,10} and it is reassuring to note that the combination of NT-proBNP testing plus standard clinical assessment was superior to either diagnostic modality alone.

Previous studies using NT-proBNP have largely focused on the exclusion of CHF.^{11–13} In our study, we confirm the importance of NT-proBNP to rule out acute CHF and suggest the consideration of an age-independent rule-out cutpoint of 300 pg/ml for this indication. Importantly, we also demonstrate that NT-proBNP can be used to “rule in” acute CHF. Because natriuretic peptide levels increase significantly with age in normal subjects,¹⁴ we hypothesized that a single reference range for NT-proBNP-based diagnosis of acute CHF would be insufficient. As expected, the optimal cutpoint for patients who were <50 years of age was lower (450 pg/ml) than the optimal cutpoint in older patients (900 pg/ml). This is presumably due to a higher prevalence of co-morbidities known to influence NT-proBNP levels in the older age category, including chronic structural heart disease, acute coronary syndromes, and deteriorating renal function. Thus, partition into distinct age categories allowed maximum sensitivity (and preserved specificity) in the younger patients and preserved the specificity demonstrated with 900 pg/ml when evaluating older patients. Whether a third cutpoint would be necessary for elderly patients (e.g., >75 years of age) remained unclear in our dataset; and we are currently undertaking a large pooled analysis of several clinical trials of NT-proBNP to address this question. To our knowledge, ours is the first demonstration of age stratification for optimal cutpoints for any BNP test.

It is worthwhile to note that the specificity of NT-proBNP in the PRIDE study was in part influenced by the presence of several disease processes that increase NT-proBNP levels. Among these were acute coronary syndromes^{15–17} and pulmonary thromboembolism.¹⁸ Although not specifically related to acute CHF, detection of high NT-proBNP levels in patients who have acute coronary syndromes or pulmonary thromboembolism adds powerful prognostic information.^{15–18} In addition, abnormal renal function is a factor with known effects on BNP levels due to decreased clearance of the marker and increased prevalence of concomitant cardiovascular abnormalities in patients who have abnormal renal function.¹⁹ We enrolled patients who had a wide range of renal function in the PRIDE study; although we are currently exploring the value of NT-proBNP testing for patients who have abnormal renal function in the PRIDE study, preliminary results indicate preserved sensitivity and specificity of the marker to a serum creatinine level of

2.5 mg/dl. Moreover, significant overlap in NT-proBNP values existed among those patients who had previous CHF (but without acute destabilized CHF at enrollment) and those patients who had acute destabilized CHF at presentation. This has been demonstrated previously with BNP³ and reflects constitutive upregulation of the neurohormonal system in patients who have previous heart failure. To best manage this issue, we emphasize the importance for knowledge of each patient’s “dry” NT-proBNP value during periods of clinical stability, so that correct interpretation of such high levels in the acute setting would be facilitated. In sum, to optimally interpret NT-proBNP results, we emphasize the importance of integrating the results of NT-proBNP testing with factors from clinical history, physical examination, imaging studies, and previous NT-proBNP testing.

Our study is limited because it occurred in a single center from a large urban teaching hospital. However, the prevalence of CHF in our patient population and the clinical characteristics of our patients are similar to those of other trials of BNP testing.^{1–5,20,21} In addition, the skill of the physicians in identifying acute CHF was high. Despite the excellent performance of the physicians in our study, NT-proBNP testing alone was superior and might be even more valuable when used by a broader array of caregivers. We did not compare NT-proBNP with BNP. Although small studies have demonstrated NT-proBNP to be at least comparable to⁴ and possibly more sensitive than^{22–24} BNP, the goal of the PRIDE study was to prospectively establish the utility of NT-proBNP testing in the emergency department. That NT-proBNP is used worldwide without such large-scale prospective data underscores the importance of our data.

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