Pre-admission NT-proBNP improves diagnostic yield and risk stratification – the NT-proBNP for Evaluation of dyspnoeic patients in the Emergency Room and hospital (BNP4EVER) study

Simcha R Meisel¹, James L Januzzi², Margarita Medvedovski¹,
Moshe Sharist³, Michael Shochat¹, Jalal Ashkar¹,
Pavel Peschansky¹, Shmuel Bar Haim³, David S Blondheim¹,
Michael Glikson⁴ and Avraham Shotan¹

Abstract

Background: Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) level is useful to diagnose or exclude acutely decompensated heart failure (ADHF) in dyspnoeic patients presenting to the emergency department (ED).

Aim: To evaluate the impact of ED NT-proBNP testing on admission, length of stay (LOS), discharge diagnosis and long-term outcome.

Methods: Dyspnoeic patients were randomized in the ED to NT-proBNP testing. Admission and discharge diagnoses, and outcomes were examined.

Results: During 17 months, 470 patients were enrolled and followed for 2.0 ± 1.3 years. ADHF likelihood, determined at study conclusion by validated criteria, established ADHF diagnosis as unlikely in 86 (17%), possible in 120 (24%), and likely in 293 (59%) patients. The respective admission rates in these subgroups were 80, 91, and 96%, regardless of blinding, and 61.9% of blinded vs. 74.5% of unblinded ADHF-likely patients were correctly diagnosed at discharge ($p=0.029$), with similar LOS. 2-year mortality within subgroups was unaffected by test, but was lower in ADHF-likely patients with NT-proBNP levels below median (5000 pg/ml) compared with those above median ($p=0.002$). Incidence of recurrent cardiac events tracked NT-proBNP levels.

Conclusion: ED NT-proBNP testing did not affect admission, LOS, 2-year survival, or recurrent cardiac events among study patients but improved diagnosis at discharge, and allowed risk stratification even within the ADHF-likely group. (ClinicalTrials.gov#NCT00271128)

Keywords

Acute heart failure, diagnosis, dyspnoea, NT-proBNP

Received: 26 December 2011; accepted: 11 April 2012

Introduction

Studies have established B-type natriuretic peptide (BNP) and amino-terminal proBNP (NT-proBNP) assays as effective tests that reliably evaluate for acutely decompensated heart failure (ADHF) in patients presenting to the emergency department (ED) with dyspnoea.^{1–4} Testing for BNP or NT-proBNP was useful in ADHF patients with impaired as well as with preserved systolic left ventricular function.⁵

¹Hillel Yaffe Medical Center, Hadera, Israel.

²Massachusetts General Hospital, Boston, MA, USA.

³Assaf Harofeh Medical Center, Zerifin, Israel.

⁴Chaim Sheba Medical Center, Tel Hashomer, Israel.

Corresponding author:

Simcha R Meisel, Heart Institute, Hillel Yaffe Medical Center, Hadera 38100, Israel

Email: meisel@hy.health.gov.il

Mueller et al.⁶ have shown that the application of a point-of-care BNP assay in the ED decreased admission rate, shortened length of stay (LOS), and saved healthcare resources. In the prospective multicentre IMPROVE-CHF study,⁷ NT-proBNP testing in a central laboratory was associated with higher diagnostic accuracy, cost savings, and improved selected outcomes. Post-hoc analysis of patients with blinded ED results showed that natriuretic peptide level was also indicative of short- and long-term prognosis.^{8,9} However, overall experience with respect to the impact of natriuretic peptide testing in the ED on hospital diagnosis at discharge and on long-term outcome is lacking.

Based on available data, we assumed that measuring NT-proBNP level, even in a central laboratory set up, in patients presenting to the ED with dyspnoea would improve the accuracy of ADHF diagnosis affecting admission. Moreover, we hypothesized that the availability of NT-proBNP level in the ED may also increase the diagnostic accuracy at discharge in admitted patients. This, in turn, could possibly affect outcomes following index admission by improving management. We, therefore, conducted a prospective, randomized, two-centre study [the NT-proBNP for Evaluation of dyspnoeic patients in the Emergency Room and hospital (BNP4EVER) study, Clinical Trial registration NCT00271128], to evaluate the impact of a central laboratory NT-proBNP testing in the ED on admission rate and on discharge diagnosis and therapy of ADHF in hospitalized patients. We also assessed in a post-hoc analysis the associations between NT-proBNP testing in the ED and 2-year outcome in terms of mortality and readmissions for cardiac events.

Patients and methods

Study design and population

The present study (BNP4EVER) was an investigator-initiated, prospective, randomized, two-centre study with no extramural funding and approved by the local institutional review board. The study population included consecutive patients with objective evidence of dyspnoea presenting to the ED of participating medical centres during daytime hours. Exclusion criteria were age <18 years or the presence of other overt disease known to cause acute dyspnoea, such as trauma, chronic obstructive pulmonary disease exacerbation, acute myocardial infarction, or pneumonia. Informed consent was obtained from eligible patients in the ED and a blood sample for NT-proBNP was immediately drawn and sent to the central laboratory for analysis.

A provisional diagnosis of either ADHF or a non-ADHF aetiology as the cause of dyspnoea was determined in the ED by attending physicians prior to receipt of NT-proBNP results. Blood samples were processed for NT-proBNP at the central laboratory of each centre and randomized in four-patient blocks to blinded or unblinded test results.

When unblinded, test results were immediately reported to the ED and to the medical ward in case of admission. During hospitalization, attending physicians based the diagnosis of ADHF or non-ADHF aetiology as the cause of dyspnoea on history, physical examination, and auxiliary testing (chest radiography, electrocardiography, and echocardiogram) and on NT-proBNP level when unblinded. After study launch, we decided to evaluate post hoc the impact of NT-proBNP testing in the ED on all-cause mortality and readmission for cardiac events at 2-year follow up.

NT-proBNP analysis

NT-proBNP level was measured with a commercially available immunoassay (Elecsys proBNP; Roche Diagnostics, Indianapolis, Indiana). In short, a 10- μ l serum sample was incubated with biotinylated polyclonal capture antibodies and polyclonal ruthenium-complexed detection antibodies directed against NT-proBNP. These were bound to streptavidin-coated paramagnetic microparticles and quantitated by electrochemoluminescence. The NT-proBNP assay does not cross react with the 32 amino acid BNP molecule (<0.001%). The planned turnaround time of test to result report was 2 hours.

NT-proBNP-based diagnosis of ADHF

In the final analysis of study results and for the diagnosis or exclusion of ADHF, we employed the NT-proBNP cutpoint strategy validated by Januzzi et al.⁹ Briefly, an NT-proBNP level <300 pg/ml, regardless of age, denoted an unlikely diagnosis of ADHF and was termed 'ADHF-unlikely'. Patients whose NT-proBNP level was between this rule-out cutpoint and their age-adjusted rule-in cutpoint were termed 'ADHF-possible'. An NT-proBNP level above age-adjusted rule-in cutpoint was denoted 'ADHF-likely'. A diagnosis of ADHF determined according to NT-proBNP level was the standard against which the accuracy of the clinical diagnosis was appraised. This scale was found to be valid even in patients with reduced renal function.¹⁰ After the introduction of the NT-proBNP test into the central laboratory, ED and medical ward physicians were trained in its use.¹¹

Data collection, diagnosis, and heart failure-specific therapy

Following recruitment and admission, patient details, LOS, blood test results, and medications prescribed and diagnosis at discharge were documented. A diagnosis of ADHF at hospital discharge was defined in this study with fulfilment of either (1) heart failure explicitly specified as a discharge diagnosis or (2) heart failure listed as major cause for admission in discharge report, with discharge medications include at least three of the drug categories used to treat heart failure. These drug categories comprise the angiotensin-converting enzyme inhibitors or angiotensin receptor

blockers (grouped as angiotensin antagonists; AA), heart failure-specific beta-blockers (including carvedilol, bisoprolol, and extended-release metoprolol; BB), furosemide, aldosterone antagonists, digoxin, and nitrates. If these conditions were not fulfilled, an alternative diagnosis was established according to main discharge diagnosis, heart failure-specific medical treatment, i.e. AA and heart failure-specific BB, at discharge were recorded.

Mortality and follow up events

We followed patients for 2 years and obtained all-cause mortality by matching patient identification numbers with the records of the national population registry. Admissions for recurrent cardiac events (heart failure, coronary events, or arrhythmia) were documented according to hospital records.

Statistical analysis

Chi-squared test with Pearson correction was applied to evaluate the significance of difference in the rate of ADHF diagnosis between blinded and unblinded ADHF-likely patients. The Kruskal–Wallis test was applied to evaluate the association between admission rate and NT-proBNP levels among study groups. Kaplan–Meier curves were drawn for comparison of overall survival and cardiac event-free survival intervals between groups and within the ADHF-likely subgroups. A multivariable Cox regression model using the Forward Wald method to determine predictors of survival was applied to identify significant univariate variables. Hazard ratios (HR) with 95% confidence interval (CI) and *p*-values by likelihood ratio test were presented. *p*≤0.05 was significant. Analyses were performed using SPSS 11.5 (SPSS, Chicago, Illinois, USA).

Results

Patients

Study population comprised 470 patients (mean age 72.3±13.8 years) who presented 499 times to the ED and included 371 patients at the Hillel Yaffe Medical Center, Hadera, between October 2005 and March 2007, and 99 patients at Asaf Harofeh Hospital, Zerifin between March 2006 and January 2007 (Figure 1). Study population included 232 men (70.1±14.5 years) and 238 women (74.4±12.9 years, *p*<0.001 compared with males). Time from ED presentation to blood sampling was 11±13 minutes, and time from sampling to assay processing and report was 150±104 minutes. Study subgroups according to blinding were comparable. No difference was detected by blinding within the entire study population or within the largest subgroup of ADHF-likely patients (Table 1). Study patients were followed for 2±1.3 years (median 2, range 0–3.9 years) after discharge, with 245, 221, 199, 186, 172, 165,

Figure 1. Consort diagram of BNP4EVER study design
ED, emergency department.

and 162 ADHF-likely patients followed for 6, 12, 18, 24, 30, 36, and 42 months, respectively.

Diagnosis of ADHF and admission rate

Diagnosis rates of ADHF in the ED and at discharge, and admission rates by groups and blinding are shown in Table 2. Most patients were admitted to the hospital. Twenty-four ADHF-unlikely patients (27% of subgroup), 13 ADHF-possible patients (11%), and 13 ADHF-likely patients (4%) were discharged at the ED. No difference was observed in the admission rate between blinded and unblinded patients within each group. Admission rate within the entire study population was 90.9% in blinded and 93.4% in unblinded patients (*p*=0.32). The pre-test alternative diagnoses in undiagnosed ADHF-likely patients were mostly of pulmonary aetiology (51%).

LOS and discharge diagnosis

LOS in blinded study patients was 4.8±3.8 days (median 3) vs. 5.3±4.3 (median 4, *p*=0.13) in unblinded patients. LOS was 4.4±3.6 (median 3), 3.6±2.2 (median 3), and 5.5±4.3 days (median 4) in the blinded unlikely, possible, and likely ADHF patients, compared with 3.7±3.1 (median 3, *p*=NS), 5.5±5.4 (median 4, *p*<0.027), and 5.7±4 days (median 5, *p*=NS) in the unblinded subgroups, respectively. When stratifying the ADHF-likely patients by median NT-proBNP level (5000 pg/ml), LOS was 5.4±4.2 days (median 4) in the below-median ADHF-likely patients, and 5.7±4.1 days (median 5, *p*=0.43) in the above-median patients. Among all patients admitted, ADHF was diagnosed at discharge in 54.7% of unblinded vs. 44% of blinded patients (*p*=0.049). No difference in the diagnosis of ADHF at discharge

Table 1. Characteristics of ADHF-likely patients by blinding

Variable	Blinded patients (n=147)	Unblinded patients (n=146)	p-value
Males	72 (49)	75 (51)	0.72
Age (years)	75.5±11.2 (77)	74±12.1 (76)	0.26
Weight (kg)	75.9±17.2 (74)	76.6±16.3 (75)	0.76
Height (cm)	164.8±9.6 (165)	164.6±8.2 (165)	0.87
Body mass index (kg/m ²)	27.6±5.4 (26.7)	28.3±5.1 (28.0)	0.34
Diabetes mellitus	74 (57)	75 (59.5)	0.80
Smoking	23 (20)	22 (19)	1.00
Hyperlipidaemia	66 (51)	73 (57)	0.38
Hypertension	120 (91)	114 (87)	0.33
Obesity	44 (30)	59 (40)	0.067
Angina pectoris	43 (34)	40 (31)	0.69
S/P AMI	42 (36)	43 (38)	0.78
S/P PCI	40 (35)	39 (35)	1.00
S/P CABG	33 (29)	33 (29)	1.00
Systolic blood pressure (mmHg)	144±28 (142)	141±28 (140)	0.52
Diastolic blood pressure (mmHg)	80±16 (77)	80±15 (80)	0.96
Heart rate (beats/min)	83±21 (80)	85±18 (83)	0.47
Killip class			
I	21 (15)	13 (10)	0.19
II	79 (58)	76 (56)	0.91
III	34 (25)	36 (27)	0.78
IV	3 (2)	10 (7)	0.05
Beta-blocker	75 (56)	57 (45)	0.11
Angiotensin-converting enzyme inhibitor	68 (55)	66 (54)	1.00
Angiotensin receptor blocker	18 (15)	16 (14)	0.85
Furosemide	82 (73)	85 (77)	0.54
Haemoglobin (g/dl)	12.3±1.8 (12.1)	12.4±1.7 (12.2)	0.76
Urea (mg/dl)	39±27 (31)	40±27 (33)	0.71
eGFR <60 ml/min	60 (41)	66 (45)	0.34
eGFR <30 ml/min	24 (16)	19 (13)	0.45
Cholesterol (mg%)	164±38 (161)	167±41 (168)	0.77

Values are n (%) or mean±SD (median). AMI, acute myocardial infarction; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; S/P, state post.

Table 2. Diagnostic subgroups and blinding, rates of diagnosis of acute decompensated heart failure (ADHF) in the emergency department, admission rate, and final diagnosis of ADHF upon discharge from hospital in study subgroups according to blinding

Test status	ADHF-unlikely group			ADHF-possible group			ADHF-likely group		
	Blinded (n=41)	Unblinded (n=45)	Total (n=86)	Blinded (n=66)	Unblinded (n=54)	Total (n=120)	Blinded (n=147)	Unblinded (n=146)	Total (n=293)
Men	21 (51)	26 (58)	47 (55)	23 (35)	27 (50)	50 (42)	72 (49)	75 (51)	147 (50)
Age (years)	59.3±17.8 ^a	61.6±17.5 ^a	60.5±17.6 ^a	75±9.8	75.4±10.6	75.2±10.1	75.5±11.2	74±12.1	75±11.7
NT-proBNP level	86 (45–195)	91 (25–153)	88 (32–184)	699 (523–942)	736 (483–1123)	713 (512–1003)	5093 (2624–11,762)	5093 (2955–11,583)	5093 (2910–11,622)
ED diagnosis of ADHF	8 (19.5)	7 (15.6)	15 (17.4)	34 (51.5)	30 (56.6)	64 (53.8)	106 (72.1) ^b	116 (80.0) ^b	222 (76.0) ^b
Admission rate	32 (78.0)	37 (82.2)	69 (80.2)	59 (89.4)	49 (92.5)	108 (90.8)	138 (95.2) ^b	141 (97.2) ^b	279 (96.2) ^b
Discharge diagnosis of ADHF	2 (6.3)	5 (13.2)	7 (10)	14 (23.3)	12 (24.5)	26 (23.9)	86 (61.9) ^b	105 (74.5) ^{b,c}	191 (68.2) ^b

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

^{a-c}Diagnosis of ADHF at the ED prior to test results: ^ap<0.001 compared with ADHF-possible and likely groups, p=NS between blinded and unblinded subgroups for all ADHF categories; ^bp<0.001 between ADHF-likelihood subgroups; ^cp=0.029 compared with blinded patients.

Table 3. Survival and rate of use of heart failure-specific beta-blockers and angiotensin antagonists in acute decompensated heart failure (ADHF)-likely patients according to study subgroups

Study group	n	NT-proBNP	BB	AA	2-year survival	Cardiac event-free 2-year survival
Blinded ADHF-likely patients	147	5093 (2624–11,762)	31	67	41	19
Unblinded ADHF-likely patients	146	5093 (2955–11,583)	31.5	68	37	24
ADHF-likely patients undiagnosed as ADHF	89	4444 (2358–8421) ^a	13.5 ^b	62	42	31 ^c
ADHF-likely patients diagnosed as ADHF	191	6140 (2966–12,476) ^a	41 ^b	71	39	17 ^c
ADHF-likely patients with NT-proBNP ≤ median	144	2897 (1973–3768) ^b	21.5 ^d	72	51 ^e	29 ^f
ADHF-likely patients with NT-proBNP > median	149	11,490 (7566–17,226) ^b	41 ^d	62	31 ^e	13 ^f
Undiagnosed ADHF-likely patients NT-proBNP < median	50	2711 (1740–3797)	6 ^g	71	46	36
Diagnosed ADHF-likely patients NT-proBNP < median	84	2897 (1991–3783)	31 ^g	75	52	25
Undiagnosed ADHF-likely patients with NT-proBNP > median	39	9218 (7256–14,616)	23 ^h	50	41	17
Diagnosed ADHF-likely patients with NT-proBNP > median	107	11,701 (7748–17,402)	49 ^h	67	27	11

Values are median (interquartile range) or %.

^a $p=0.029$; ^b $p<0.0001$; ^c $p=0.01$; ^d $p=0.0004$; ^e $p=0.002$; ^f $p=0.003$; ^g $p=0.005$; ^h $p=0.0075$.

AA, angiotensin antagonists; BB, beta-blockers.

between blinded and unblinded patients in the ADHF-unlikely and ADHF-possible subgroups was observed (Table 2). In contrast, there was an increased rate of correct recognition of ADHF in unblinded (74.5%) compared with blinded ADHF-likely patients (61.9%, $p=0.029$). Discharge diagnosis in 56% of undiagnosed ADHF-likely patients involved pulmonary disease.

Mortality and follow-up events

Sixteen patients (3.5%) died during admission, including 13 ADHF-likely patients (5.9%, six among the blinded and seven among the unblinded patients, $p=NS$) and three ADHF-possible patients (3.3%) died during admission. The 2-year survival and recurrent cardiac event-free survival analysis showed a significant difference between the ADHF-unlikely, -possible, and -likely groups ($p<0.0001$) with an even more pronounced effect observed on recurrent cardiac events. Table 3 shows cumulative overall survival and recurrent cardiac event-free survivals, as well as rates of BB and AA therapy at discharge in the ADHF-likely patient subsets. The cumulative and recurrent cardiac event-free survival curves for all study patients (Figure 2) and for the ADHF-likely patients (Figure 3) according to blinding, as well as that for the ADHF-likely patients by discharge diagnosis of ADHF (Figure 4) and median NT-proBNP (Figure 5) are presented.

Availability of NT-proBNP level in the ED was not associated with improved 2-year survival in ADHF-likely patients (Table 3). Furthermore, even in ADHF-likely patients stratified by discharge diagnosis of ADHF, the survival curves showed, surprisingly, only a trend toward a benefit in the appropriately diagnosed patients (Figure 4). In contrast, cardiac event incidence was significantly higher

in the latter compared with that in the undiagnosed ADHF patients. Examination of these subgroups revealed a significant NT-proBNP level difference, with higher NT-proBNP levels in patients appropriately diagnosed with ADHF (6140 pg/ml) compared with undiagnosed ADHF-likely patients (4444 pg/ml, $p=0.029$, Table 3). The correctly diagnosed ADHF-likely patients experienced more recurrent cardiac events putatively because of their more advanced disease, which likely offset any possible therapeutic benefit resulting from proper diagnosis. Given the finding that not all ADHF-likely patients fared similarly, we examined survival in ADHF-likely patients by median NT-proBNP (5000 pg/ml). This analysis showed that survival at 2 ± 1.3 years was 51% for patients with below median NT-proBNP level compared with 31% for those with above-median NT-proBNP level (Figure 5, Table 3, $p=0.002$), underscoring the prognostic importance of NT-proBNP level even within the ADHF-likely group. Consequently, we evaluated as a post-hoc analysis the impact of correct diagnosis in ADHF-likely patients according to median NT-proBNP value. This demonstrated that correct diagnosis in patients with below median NT-proBNP values was associated with better survival at 16 months ($p<0.01$) but not at 3 years (Figure 6A) when a ‘catch-up’ phenomenon occurred resulting in similar survival. This effect was not observed in ADHF-likely patients with above-median NT-proBNP values (Figure 6B).

The ADHF-likely patients were, in general, older and sicker patients with more concomitant illnesses reflected in their high mortality and rate of recurrent cardiac events (Table 3). There was a significant difference between the use of heart failure-specific BB in the undiagnosed and in

Figure 2. Kaplan-Meier cumulative (A) and recurrent cardiac event-free (B) survival curves of all study patients according to test blinding in the emergency department. Solid line, blinded patients; broken line, unblinded patients. There are no significant differences.

the appropriately diagnosed ADHF-likely patients in both the below-median NT-proBNP subgroup (6% vs. 31%, $p < 0.005$, Table 3) and the above-median NT-proBNP subgroup (23% vs. 49%, $p < 0.0075$). No difference in use of AA between subgroups was observed.

Predictors of survival

Multivariable Cox regression analysis of the significant univariate predictors yielded diastolic blood pressure (hazard ratio, HR, 0.97, 95% CI 0.95–0.99, $p = 0.001$), urea concentration (HR 1.02, 95% CI 1.002–1.02, $p = 0.023$), and AA use (HR 0.58, 95% CI 0.35–0.98, $p = 0.04$), but not age, creatinine level, or systolic blood pressure, as predictors of survival.

Discussion

The prevalence of heart failure during the last decade is on the rise and it is a common cause for ED referrals and hospitalizations. Accurate diagnosis of heart failure in the hospital is essential to guide therapy, to improve symptoms and prognosis, and to save on mounting health expenditure.¹² Uncertainty in making the diagnosis while evaluating dyspnoea is associated with more hospital resource utilization and longer LOS, in addition to worse outcomes.¹³ Thus, the NT-proBNP test that may reduce uncertainty in the evaluation of acute dyspnoea is helpful, although little is known about its impact on discharge diagnosis and outcomes. We have assessed the effect of ED NT-proBNP testing in dyspnoeic patients on admission, discharge diagnosis, and outcomes using the age-stratified NT-proBNP scale, shown to yield 88% positive predictive value for diagnosis of ADHF,⁹ as a benchmark to evaluate ADHF probability.

Diagnosis of ADHF in the ED

Despite a primary diagnosis of ADHF in the ED prior to test results in 17, 54, and 76% of patients in the three study subgroups, admission rates were high in all three subgroups regardless of pre-test clinical likelihood (Table 2). The percentage of patients not admitted to the hospital seemed to correspond with the degree of symptom severity, i.e., patients with milder symptoms, such as the ADHF-unlikely patients, were more readily discharged at the ER. On the other hand, a higher percentage of the more symptomatic ADHF-likely patients were admitted. Despite a difference in admission rate among subgroups, probably reflecting symptom severity, we observed no difference in admission rate by blinding within subgroups. Hence, in the present setup, availability of test results did not affect the decision to admit these symptomatic patients, as observed also in the IMPROVE-CHF study⁷ and by Schneider et al.¹⁴ Both these studies demonstrated similar admission rates to those in the present study, in contrast to a possible reduction reported in a recent relatively large meta-analysis.¹⁵ This neutral finding could plausibly be the result of central laboratory testing involving a necessary turnaround time. However, it may also reflect the fact that physicians are generally more likely to discharge mildly symptomatic patients but not the very symptomatic ones. Robaei et al.¹⁶ have shown in 68 patients presenting to the ED with dyspnoea and possible heart failure that NT-proBNP testing improved diagnostic accuracy, however, they did not report the effect on admission. It seems that in practice when older and sicker patients are concerned, such as those enrolled in the present study, uncertainty dictates the need to admit whether the problem is ADHF or not.

Figure 3. Cumulative (A) and cardiac event-free (B) survival curves for the acutely decompensated heart failure-likely patients according to test blinding in the emergency department. Solid line, blinded patients; broken line, unblinded patients. There are no significant differences.

Effect of test on LOS

We have not observed a difference in LOS according to blinding among all study subgroups including the sicker ADHF-likely patients with the exception of the ADHF-possible patients. It is feasible that an intermediately elevated NT-proBNP level in unblinded ADHF-possible patients prompted a more extensive work up. Murtagh et al.¹⁷ have evaluated the effect of the NT-proBNP assay on hospital LOS and in-hospital mortality in 574 patients admitted to an acute medical admission unit. They found that a significantly elevated NT-proBNP level, in the ADHF-likely range, was associated with prolonged hospitalization with a median LOS of 9 days in patients diagnosed with heart failure. An NT-proBNP level >5000 pg/ml was predictive of both LOS >9 days (odds ratio, OR, 1.54 (95% CI 1.06–2.24, $p=0.02$) and LOS >14 days (OR 1.87, 95% CI 1.29–2.71, $p=0.0009$). A recent meta-analysis

Figure 4. Cumulative (A) and cardiac event-free (B) survival curves for acutely decompensated heart failure (ADHF)-likely patients according to discharge diagnosis of ADHF. Solid line, appropriately diagnosed patients; broken line, undiagnosed ADHF patients. No significant differences in survival was observed but a difference in cardiac events was recorded (B, $p=0.01$) between these populations differing in NT-proBNP level.

analysing five heterogeneous trials found a modest benefit, of about 1-day reduction in LOS in tested patients.¹⁵ However, variability in the LOS was large, ranging from 6 to 11 days, reflecting trial diversity, while LOS reduction was particularly seen in trials with longer hospitalization, such as the study by Murtagh et al.¹⁷ In the present study, median LOS across all subgroups was about 4–5 days, which may explain the lack of observed benefit.

In-hospital mortality

Murtagh et al.¹⁷ showed in 574 admitted patients that of the 396 patients with NT-proBNP <5000 pg/ml, 8.1% died during admission compared with 22.5% of the 178

Figure 5. Cumulative (A) and cardiac event-free (B) survival curves for acutely decompensated heart failure-likely patients according to median NT-proBNP level (5000 pg/ml). Solid line, patients with NT-proBNP < 5000 pg/ml; broken line, patients with NT-proBNP > 5000 pg/ml. A, significant difference ($p=0.002$); B, significant difference ($p=0.013$).

patients with NT-proBNP values > 5000 pg/ml ($p<0.0001$). Similarly, of the 16 patients in the present study who died during hospitalization, most were among the ADHF-likely subgroup irrespective of blinding. This is in accordance with the meta-analysis by Lam et al.,¹⁵ which found that testing did not affect conclusively hospital mortality rates.

Diagnosis of ADHF at discharge

Among ADHF-likely patients admitted to the hospital, a discharge diagnosis of ADHF was determined in only 61.9% of blinded compared with 75% of unblinded patients ($p<0.029$). This suggests that, when NT-proBNP was unknown, one ADHF patient in three was missed. Thus, the

Figure 6. Cumulative survival curves for acutely decompensated heart failure (ADHF)-likely patients with NT-proBNP < 5000 pg/ml (A) and > 5000 pg/ml (B) according to discharge diagnosis of ADHF.

Solid line, misdiagnosed patients; broken line, properly diagnosed patients. There are no significant differences. There was a significant survival benefit at 16 months after discharge in patients with below-median NT-proBNP ($p<0.01$) that cancelled out at the end of follow up.

availability of the NT-proBNP test resulted in improved accuracy of ADHF diagnosis at discharge. Yet, even when NT-proBNP was known, one of four subjects was still undiagnosed, possibly due to an atypical presentation, concomitant diseases, or inexperience in interpretation of NT-proBNP values. It is possible that the gap between rates of correct diagnosis in the blinded and unblinded groups could increase further with experience.

Therapy at discharge and 2-year outcome

We did not prove the hypothesis that knowledge of NT-proBNP during admission would improve long-term outcomes in the entire cohort or in ADHF-likely patients.

As NT-proBNP values generally track with severity of ADHF symptoms, it seems that patients in the blinded group with higher NT-proBNP values were more likely to be correctly diagnosed and treated, obscuring benefit derived from knowledge of higher NT-proBNP levels. This effect was demonstrated in the similar 2-year outcome of the appropriately diagnosed and the misdiagnosed ADHF-likely patients. Notably, these patient groups were not identical with regard to NT-proBNP level (Table 3) which generally reflects disease severity and prognosis (Figure 5). This was demonstrated in a post-hoc analysis of our data that suggests that ADHF-likely patients with below median (NT-proBNP <5000 pg/ml) fared better than their above-median counterparts. It is possible that the misdiagnosed ADHF-likely patients were not as sick as those in the former group, as shown by their lower NT-proBNP level, and were, therefore, less likely to be properly diagnosed. Of note, the present study median NT-proBNP value (5000 pg/ml) is identical to the NT-proBNP threshold found by Murtagh et al.¹⁷ to stratify in-hospital mortality and LOS.

Correct diagnosis of ADHF in the below-median group was associated with a better outcome at 16-months, showing a short-term 'salvage' effect not observed in those with higher values. There was no significant difference in rate of AA therapy between diagnosed and undiagnosed ADHF-likely patients of both below- and above-median NT-proBNP subgroups. However, more BB were used in both subgroups of the properly diagnosed ADHF-likely patients ($p < 0.01$). These findings suggest the vital need to combine correct diagnosis and proven therapy with long-term clinic visits, as implemented in clinical trials, in order to assure optimal therapy and prognosis.

Limitations

NT-proBNP was measured in a central laboratory with a turnaround time of approximately 2 hours. Although beneficial for diagnosis and prognosis, NT-proBNP testing might have been even more valuable in the present study if results were available more rapidly, as feasible with a point-of-care assay. Clinicians might have been less likely to admit subjects with results more rapidly available, thus influencing admission rate. The observation that median NT-proBNP level can be used to further stratify ADHF-likely patients was a post-hoc finding, requiring prospective powering and validation. Although therapy at discharge is known to affect treatment during follow up, failure to up-titrate therapy during follow up could also be a cause for lack of benefit in unblinded ADHF-likely patients.

In summary, the present study has shown that NT-proBNP testing performed in a central laboratory in patients presenting to the ED with dyspnoea did not affect admission rate or long-term survival. Yet, NT-proBNP testing did improve the accuracy of ADHF diagnosis in admitted patients. The findings raise the possibility that patients with

ADHF presenting with dyspnoea are underdiagnosed, which may adversely affect their outcome. NT-proBNP testing will make the recognition of these patients easier, especially those with milder disease, and at the same time identify patients with very high NT-proBNP values who are at considerable risk for adverse outcome. Study results suggest that in the absence of outpatient clinic visits, a correct diagnosis at hospital discharge in ADHF-likely patients may not ensure the expected long-term benefit.

Funding

This work was supported by Roche Diagnostics, Siemens Diagnostics, and the Balson Clinical Scholar Fund.

References

1. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001; 37: 379–385.
2. Maisel A, Krishnaswamy P, Nowak RM, et al.; for the Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347: 161–167.
3. Lainchbury JG, Campbell E, Frampton CM, et al. 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.
4. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *Am J Cardiol* 2005; 95: 948–954.
5. Maisel AS, McCord J, Nowak RM, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol* 2003; 41: 2010–2017.
6. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004; 350: 647–654.
7. Moe GW, Howlett J, Januzzi JL, Zowall H; Canadian Multicenter Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation* 2007; 115: 3103–3110.
8. Bettencourt P, Ferreira S, Azevedo A, et al. Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. *Am J Med* 2002; 113: 215–219.
9. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. The International collaborative of NT-proBNP Study. *Eur Heart J* 2006; 27: 330–337.
10. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. 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.
11. Mark DB and Felker GM. B-type natriuretic peptide – a biomarker for all seasons? *N Eng J Med* 2004; 350: 718–720.
 12. Fang J, Mensah GA, Croft JB, et al. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol* 2008; 52: 428–434.
 13. Green SM, Martinez-Rumayor A, Gregory SA, et al. Clinical uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. *Arch Intern Med* 2008; 168: 741–748.
 14. Schneider HG, Lam L, Lokuge A, et al. B-type natriuretic peptide testing, clinical outcomes, and health services use in emergency department patients with dyspnea: a randomized trial. *Ann Intern Med* 2009; 150: 365–372.
 15. Lam LL, Cameron PA, Schneider HG, et al. Meta-analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 2010; 153: 728–735.
 16. Robaei D, Koe L, Bais R, et al. Effect of NT-proBNP testing on diagnostic certainty in patients admitted to the emergency department with possible heart failure. *Ann Clin Biochem* 2011; 48(Pt 3): 212–217.
 17. Murtagh G, Canniffe C, Mahgoub M, et al. Introduction of an NT-proBNP assay to an acute admission unit – a 2-year audit. *Eur J Intern Med* 2009; 20: 58–62.