

Usefulness and Predictive Value of Circulating NT-proBNP Levels to Stratify Patients for Referral and Priority Treatment in a Specialized Outpatient Heart Failure Center

Offer Amir MD, Hagar Paz RN, Ronny Ammar MD, Nisan Yaniv MD, Jorge E. Schliamser MD and Basil S. Lewis MD FRCP

Heart Failure Center, Department of Cardiovascular Medicine, Lady Davis Carmel and Lin Medical Centers and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Key words: natriuretic peptides, chronic heart failure, outpatient management, prognosis

Abstract

Background: Serum natriuretic peptide levels are useful diagnostic and prognostic markers in patients with acute decompensated heart failure, but have been little used to stratify urgency of treatment in the outpatient situation.

Objectives: To examine the use of natriuretic peptide to guide priority of patient referral to a heart failure center.

Methods: We analyzed data from 70 consecutive patients with chronic heart failure (NYHA class 2-4) referred for first evaluation in a specialized outpatient heart failure center. Serum NT-proBNP was measured at the initial patient visit. We examined correlates and predictive value of mid- and upper tertile NT-proBNP for mortality in comparison with other known prognostic indicators using univariate and multivariate logistic regression analysis.

Results: Mortality at 6 months was 26.0% in patients with upper tertile (> 1958 pg/ml) NT-proBNP, 8.7% in the middle tertile group and 0% in the lowest tertile ($P = 0.017$). Patients with upper tertile serum NT-proBNP levels (group 3) had lower left ventricular ejection fraction, were more often in atrial fibrillation ($P = 0.04$) and more often had renal failure ($P = 0.03$). Age-adjusted logistic regression analysis identified upper tertile serum NT-proBNP level as the strongest independent predictor of 6 month mortality with a sixfold risk of early death (adjusted odds ratio 6.08, 95% confidence interval 1.58–47.13, $P = 0.04$). NT-proBNP was a more powerful predictor of prognosis than ejection fraction and other traditional outcome markers.

Conclusions: In heart failure patients referred to an outpatient specialized heart failure center, an upper tertile NT-proBNP level identified patients at high risk for mortality. A single high > 550 pg/ml NT-proBNP measurement appears to be useful for selecting patients for care in a heart failure center, and a level > 2000 pg/ml for assigning patients to high priority management.

IMAJ 2008;10:109–112

For Editorial see page 152

Circulating levels of N-terminal pro-brain natriuretic peptide and other natriuretic peptides are useful in the diagnosis [1], response to device therapy [2] and overall prognosis [3] of patients with heart failure [3,4], but most studies have been conducted in the setting of acute decompensated heart failure [5] or in patients with an acute coronary syndrome [6-8] or acute myocardial infarction [9]. Gardner et al. [10] showed that both

an NT-proBNP concentration above the median and an absolute increase in NT-proBNP were independent predictors of mortality, and that subjects who had the highest NT-proBNP concentration at 4 months were at the greatest risk of death.

With the increasing burden of heart failure on the health-care system, there has been a considerable shift to outpatient management and the establishment of specialized heart failure centers and clinics. Outpatient management results in a lower number of hospital admissions, but the patient referral load is high. We tested the hypothesis that an initial NT-proBNP blood level, measured at the index visit to a heart failure clinic, may allow risk stratification of patients so that treatment resources may be suitably allotted and prioritized.

Patients and Methods

Patient population

The study included 70 consecutive patients referred to a specialized outpatient heart failure center during a 12 month period. Apart from one patient there were no admissions for heart failure at least 3 weeks prior to the NT-proBNP analysis.

Patients underwent routine physical examination as well as laboratory, electrocardiographic and echocardiographic tests. Patients completed the Minnesota Living with Heart Failure Quality of Life questionnaire and underwent a 6 minute corridor walk test to document functional disability. We noted background drug therapy, especially the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta blockers.

On the index visit to the clinic, a blood sample for NT-proBNP was drawn. Serum NT-proBNP was measured with the Elecsys proBNP electro-chemiluminescence immunoassay run on the Elecsys 1010 (Roche Diagnostics, Indianapolis, IN, USA).

Patient follow-up

Patient follow-up was conducted by direct structured telephone interview and frontal communication with the patient and family, with additional review of electronic hospital and governmental databases. The study was approved by the Helsinki Committee of the Lady Davis Carmel Medical Center and all the participants signed a written informed consent form prior to inclusion in any study procedure.

NT-proBNP = N-terminal pro-brain natriuretic peptide

Statistical analysis

Statistical analysis was performed using a Statistix 8 software package (Analytical Software, Tallahassee, FL). We used chi-square test, Student's unpaired *t*-test, Fisher test and Mann-Whitney tests in univariate analysis. To assess the clinical and laboratory parameters in the different patient groups, we used one-way ANOVA. Then, in a multivariate logistic regression analysis model for mortality we tested the parameters including parameters that were statistically significant and variables that were considered to have a potential influence on short-term outcome. A *P* value of < 0.05 was considered to represent statistical significance.

Results

Patient characteristics

The study cohort included 53 men and 17 women (age 69 ± 13 years) [Table 1] who were in New York Heart Association class 2-4). The etiology of heart failure was ischemic in 37 patients (53%). Associated diseases included systemic hypertension in 63%, diabetes mellitus in 53%, and chronic renal failure in 21%. Atrial fibrillation was present in 44% of the patients. Echocardiographic left ventricular ejection fraction was 35 ± 15%. Background treatment included ACEI/ARB in 52 patients (74%), and beta blockers in 55 patients (79%).

Clinical characteristics in relation to serum NT-proBNP values

Serum NT-proBNP level ranged from 23 to 20,323 pg/ml (mean 2849). We divided patients into three groups: 24 patients with NT-proBNP ≤ 534 pg/ml (lower tertile, group 1), 23 patients with NT-proBNP 535–1958 pg/ml (middle tertile, group 2) and 23 patients with NT-proBNP > 1958 pg/ml (upper tertile, group 3).

Patients in the upper tertile NT-proBNP group (group 3) were slightly older (72 ± 2 years), with lower body mass index and lower ejection fraction [Table 1]. Etiology of heart failure (ischemic/non-ischemic) was similar in the three groups, as was the prevalence of diabetes mellitus and hypertension. There were no differences in NYHA grade or Minnesota questionnaire score. Group 3 patients tended to have a lower 6 minute walk distance. Atrial fibrillation (*P* = 0.04) and chronic renal failure (defined as persistent serum creatinine level of > 2 mg/dl) (*P* = 0.03) were more frequent in group 3 patients. Most patients were treated with beta-blocking drugs (not significant), but there was a lower usage of ACEI/ARB in group 3 patients (52% vs. 83% and 85%, *P* = 0.01).

Mean serum NT-proBNP level was by definition higher in group 3 patients (7154 ± 5105 pg/ml). Group 3 patients had higher levels of blood urea (*P* = 0.02), serum creatinine (*P* < 0.001) and high sensitive-C reactive protein (*P* = 0.026) and lower hemoglobin levels (*P* < 0.001) [Table 2].

Mortality and determinants

Eight patients died (11.4%) – 6 (26.0%) in group 3, 2 (8.7%) in group 2 and none in group 1 (odds ratio 7.94, 95% confidence interval 1.45–43.2, *P* = 0.02 for group 3 patients vs. lower 2 tertiles). Four patients died due to progressive heart failure: two had sudden cardiac death and two due to sepsis. In the group of the

Table 1. Patient characteristics in relation to serum NT-proBNP levels

Demographic and clinical data	Total group (N=70)	Group 1 (N=24)	Group 2 (N=23)	Group 3 (N=23)	<i>P</i> *
Age (yrs)	69 ± 13	62 ± 2	74 ± 2	72 ± 2	0.001
Gender (males/females)	53/17	18/6	19/4	16/7	0.58
Body mass index (kg/m ²)	29 ± 6	31 ± 1	30 ± 1	27 ± 1	0.05
NYHA Class 3-4	46 (66)	13 (54)	16 (70)	17 (74)	0.32
Ischemic etiology	37 (53)	10 (42)	15 (65)	12 (52)	0.27
Left ventricular ejection fraction (%)	35 ± 15	41 ± 3	34 ± 3	28 ± 3	0.02
6 minute walk distance (m)	173 ± 145	213 ± 32	177 ± 33	124 ± 33	0.15
QOL Minnesota questionnaire	60 ± 23	66 ± 5	51 ± 5	64 ± 5	0.69
Systolic blood pressure (mmHg)	123 ± 23	124 ± 5	123 ± 5	121 ± 5	0.9
QRS duration (msec)	124 ± 37	114 ± 8	124 ± 8	134 ± 8	0.19
Atrial fibrillation	51 (44)	7 (29)	9 (39)	15 (65)	0.04
Associated diseases					
Systemic hypertension	44 (63)	13 (54)	16 (70)	15 (65)	0.52
Diabetes mellitus	37 (53)	11 (46)	16 (70)	10 (43)	0.14
Chronic renal failure	15 (21)	2 (8)	4 (17)	9 (39)	0.03
Pharmacotherapy					
Beta blocker	55 (79)	18 (75)	19 (83)	18 (78)	0.81
ACEI and/or ARB	52 (74)	20 (83)	20 (85)	12 (52)	0.01

* Differences between groups (analysis of variance)

Numbers in parentheses are percentages

QOL = quality of life

Table 2. Laboratory values in relation to serum NT-proBNP level

	Total group	Group 1	Group 2	Group 3	<i>P</i> *
NT-proBNP (pg/ml)	2849 ± 4211	300 ± 163	1202 ± 481	7154 ± 5105	< 0.001
Blood urea level (mg/dl)	78 ± 54	56 ± 10	82 ± 11	99 ± 11	0.02
Serum creatinine (mg/dl)	1.5 ± 0.6	1.1 ± 0.1	1.6 ± 0.1	1.8 ± 0.1	< 0.001
Creatinine clearance (ml/min)	63 ± 36	91 ± 6	52 ± 6	43 ± 6	< 0.001
Hemoglobin (g/dl)	12 ± 1.8	13.1 ± 0.3	11.8 ± 0.3	11 ± 0.3	< 0.001
hs-CRP (mg/L)	2 ± 4	1.1 ± 0.8	1.1 ± 0.8	3.4 ± 0.8	0.026
Serum sodium level (mEq/dl)	139 ± 4	140 ± 1	139 ± 1	138 ± 1	0.77
Total cholesterol (mg/dl)	154 ± 31	157 ± 6	157 ± 6	148 ± 6	0.56

* Differences between groups (analysis of variance)

highest NT-proBNP serum level, four died due to heart failure, one due to sudden cardiac death and one due to sepsis.

Death occurred on average after the first 4 months (range 1–6) of follow-up. By univariate analysis, patients who died were slightly older (not significant) [Table 3] and had a larger left ventricular dimension with lower systolic blood pressure. LV ejection fraction tended to be lower. There was no difference with respect to body mass index, ischemic etiology, atrial fibrillation, diabetes mellitus, serum renal function tests, QRS width, hemoglobin

ACEI = angiotensin-converting enzyme inhibitors

ARB = angiotensin receptor blockers

NYHA = New York Heart Association

LV = left ventricular

Table 3. Characteristics of patients who died

	Alive (N=62)	Dead (N=8)	P
Age (yrs)	68 ± 2*	73 ± 4	0.38
Female gender	15 (88)	2 (12)	1.00
Body mass index (kg/m ²)	30 ± 1	27 ± 2	0.18
Diabetes mellitus	35 (95)	2 (5)	0.09
Systemic hypertension	41 (93)	3 (7)	0.23
NYHA class 3-4	40 (65)	6 (75)	0.04
Left ventricular end-diastolic diameter (mm)	55 ± 1	65 ± 4	0.01
Left ventricular ejection fraction (%)	36 ± 2	28 ± 5	0.15
6 minute walk distance (m)	179 ± 20	127 ± 55	0.38
Ischemic etiology	33 (53)	4 (50)	0.86
Systolic blood pressure (mmHg)	124 ± 3	106 ± 8	0.03
Chronic renal failure	13 (21)	4 (50)	0.07
Atrial fibrillation	24 (39)	6 (75)	0.05
QRS width (msec)	120 ± 5	153 ± 13	0.02
QOL (Minnesota questionnaire)	60 ± 3	65 ± 8	0.56
Beta blocker	50 (81)	3 (38)	0.007
ACEI and/or ARB	49 (79)	3 (38)	0.01

Numbers in parentheses are percentages

Table 4. Laboratory findings in relation to mortality

	Alive (N=62)	Dead (N=8)	P
NT-proBNP (pg/ml)	2566 ± 529*	5040 ± 1472	0.12
Blood urea level (mg/dl)	76 ± 7	95 ± 19	0.34
Serum creatinine (mg/dl)	1.44 ± 0.08	1.59 ± 0.22	0.52
Hemoglobin (g/dl)	12.1 ± 0.2	11.4 ± 0.6	0.32
hs-C reactive protein (mg/L)	1.6 ± 0.5	4.2 ± 1.3	0.07
Serum sodium level (mEq/dl)	139 ± 1	138 ± 1	0.41
Serum potassium level (mEq/dl)	5.2 ± 0.7	4.4 ± 1.8	0.71
Uric acid (mg/dl)	8.4 ± 0.4	9.8 ± 1.0	0.19

* Mean ± SE

level, sodium level. Serum pro-BNP and hs-CRP tended to be higher (NS) in patients who died [Table 4].

The logistic regression model examined predictors of mortality with adjustment for age and included body mass index, LV ejection fraction, NYHA class, QRS width, ischemic etiology, presence of atrial fibrillation, blood urea level, serum creatinine level, hemoglobin level, hs-CRP, and serum NT-proBNP level in the upper tertile (> 1958 pg/ml). Serum NT-proBNP level > 1958 pg/ml (upper tertile group) was the only significant independent predictor of mortality (adjusted OR 7.6, 95%CI 1.4–40.8, *P* = 0.01).

Discussion

The study showed the prognostic importance of a single high (> 2000 pg/ml) serum NT-proBNP level at the index visit to a heart

hs-CRP = high sensitive C-reactive protein

OR = odds ratio

CI = confidence interval

failure center. Serum NT-proBNP was the strongest independent predictor of adverse outcome, with a sixfold increased risk of 6 month mortality. Patients with high NT-proBNP had more advanced cardiac disease, including a lower ejection fraction, higher prevalence of atrial fibrillation and renal dysfunction and shorter 6 minute walk test distance. There was a graded and consistent effect, and patients with even mild (mid-range) elevation of NT-proBNP (> 500 pg/ml) had a relatively high, almost 10%, mortality in the early months of treatment.

There is no consensus regarding a single cutoff value of NT-proBNP for mortality prediction. A variable range, from 1500 to 5000 pg/ml, was suggested by different groups [11-13]. We chose levels by tertiles. The upper third tertile cutoff (> 1958 pg/ml) has on the receiver operating curve, a sensitivity of 75% and a specificity of 28% for mortality prediction.

In the acute situation, high levels of NT-proBNP result from a surge in NT-proBNP production in reaction to acute myocardial dysfunction and increased wall stress [14]. In contrast, in the outpatient setting, current guidelines concentrate mainly on the ability of the natriuretic peptides to “rule out” significant cardiac disease in breathless patients [15-18]. Several studies did show that NT-proBNP, in combination with other measures such as oxygen consumption [19] or QT interval [20], may be a useful prognostic marker in ambulatory heart failure patients or in the community [21]. In the COPERNICUS trial [11] and in the EuroHeart Failure Survey [22], mean natriuretic peptide values were markedly increased, and NT-proBNP was a strong predictor of all-cause mortality or hospitalization for heart failure. Rothenburger and co-authors [12] showed that patients who were candidates for heart transplantation had higher levels of NT-proBNP. The present study extends these observations to outpatient heart failure patient management and the specialized center management program. It also suggests that NT-proBNP may be a useful and simple test that may guide the timing of patient referral to the heart failure specialist.

Potential limitations of the study

We report a single center experience with a relatively small number of patients, and the findings should be confirmed on a broader level. The small number of patients may explain the lack of formal statistical correlation for certain univariate predictors of adverse outcome, but does not negate the ranking of NT-proBNP as the most powerful predictor of mortality. The mortality in this patient cohort may be higher than that for heart failure patients seen in the general population, but these are the patients whose management and prognosis are in question.

Clinical implications

In chronic heart failure patients, a single high serum NT-proBNP level of > 550 pg/ml is a simple and important marker for increased mortality and a level of > 2000 pg/ml for very high early mortality in patients referred to a heart failure center. Patients with very high NT-proBNP levels should be assigned a high priority intensive management strategy, since a quarter of them may not survive the first 6 months of treatment.

References

- Latour-Perez J, Coves-Orts FJ, Abad-Terrado C, Abraira V, Zamora J. Accuracy of B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction and heart failure: a systematic review. *Eur J Heart Fail* 2006;8:390–9.
- Glick A, Michowitz Y, Keren G, George J. Neurohormonal and inflammatory markers as predictors of short-term outcome in patients with heart failure and cardiac resynchronization therapy *MAJ* 2006;8:391–5.
- Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005;352:666–75.
- Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005;293:1609–16.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
- James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;108:275–81.
- Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation* 2004;110:3206–12.
- James SK, Lindahl B, Timmer JR, et al. Usefulness of biomarkers for predicting long-term mortality in patients with diabetes mellitus and non-ST-elevation acute coronary syndromes (a GUSTO IV substudy). *Am J Cardiol* 2006;97:167–72.
- Bjorklund E, Jernberg T, Johanson P, et al. Admission N-terminal pro-brain natriuretic peptide and its interaction with admission troponin T and ST segment resolution for early risk stratification in ST elevation myocardial infarction. *Heart* 2006;92:735–40.
- Gardner RS, Chong KS, Morton JJ, McDonagh TA. A change in N-terminal pro-brain natriuretic peptide is predictive of outcome in patients with advanced heart failure. *Eur J Heart Fail* 2007;9:266–71.
- Hartmann F, Packer M, Coats AJ, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. *Circulation* 2004;110:1780–6.
- Rothemburger M, Wichter T, Schmid C, et al. Aminoterminal pro type B natriuretic peptide as a predictive and prognostic marker in patients with chronic heart failure. *J Heart Lung Transplant* 2004; 23:1189–97.
- Stanton E, Hansen M, Wijesundera HC, Kupchak P, Hall C, Rouleau JL. A direct comparison of the natriuretic peptides and their relationship to survival in chronic heart failure of a presumed non-ischaemic origin. *Eur J Heart Fail* 2005;7:557–65.
- Fried I, Bar-Oz B, Perles Z, Rein AJ, Zonis Z, Nir A. N-terminal pro-B-type natriuretic peptide levels in acute versus chronic left ventricular dysfunction. *J Pediatr* 2006;149:28–31.
- Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24:1710–18.
- Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:384–416.
- Battaglia M, Pewsner D, Juni P, Egger M, Bucher HC, Bachmann LM. Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure: systematic review of test accuracy studies. *Arch Intern Med* 2006;166:1073–80.
- Mueller C, Laule-Kilian K, Schindler C, et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;166:1081–7.
- Gardner RS, Henderson G, McDonagh TA. Combination of B-type natriuretic peptide and peak oxygen consumption improves risk stratification in outpatients with chronic heart failure. *J Heart Lung Transplant* 2005;24:303–9.
- Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Eur Heart J* 2003;24:1735–43.
- Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–63.
- Hulsmann M, Berger R, Sturm B, et al. Prediction of outcome by neurohumoral activation, the six-minute walk test and the Minnesota Living with Heart Failure Questionnaire in an outpatient cohort with congestive heart failure. *Eur Heart J* 2002;23: 886–91.

Correspondence: Dr. B.S. Lewis, Dept. of Cardiovascular Medicine, Heart Hospital at Lady Davis Carmel Medical Center, 7 Michal Street, Haifa 34362, Israel.
 Phone: (972-4) 825-0288
 Fax: (972-4) 834-3755
 email: lewis@tx.technion.ac.il