Usefulness of NT-ProBNP as a Biomarker of Clinical Status in Outpatients With Chronic Heart Failure

Jesús M. Casado,[a] Ana Díaz,[b] and Carmen Suárez[a]

[a]Servicio de Medicina Interna, Hospital Universitario de La Princesa, Madrid, Spain
[b]Servicio de Análisis Clínicos, Hospital Universitario de La Princesa, Madrid, Spain

The role of the amino-terminal fragment of probrain natriuretic peptide (NT-proBNP) in monitoring the clinical status of outpatients with chronic heart failure has not yet been fully established. Fifty-nine patients with chronic heart failure were followed up at an outpatient clinic. The serum NT-proBNP level was measured and clinical status was assessed according to New York Heart Association (NYHA) functional class and Framingham clinical criteria. A positive correlation was found between the NT-proBNP level, NYHA functional class and Framingham score (*P*<.001). Patients who presented with a Framingham score> 2 were more likely to be readmitted to hospital (31.8% vs 0%; *P*<.001), to visit an emergency department (36.4% vs 5.4%; *P*=.002), or to die (13.6% vs 0%; *P*=.021). The NT-proBNP level was higher in patients who needed to be readmitted to hospital (*P*=.004) and in those who attended an emergency department for decompensation (*P*=.002).

Key words: *Natriuretic peptide. Heart failure. Framingham.*

Utilidad del NT-proBNP como marcador biológico de la situación clínica en pacientes con insuficiencia cardiaca crónica seguidos de forma ambulatoria

El papel del fragmento aminoterminal del péptido natriurético tipo B (NT-proBNP) en la determinación de la situación clínica ambulatoria de pacientes con insuficiencia cardiaca crónica no está bien establecido. Se evaluó a 59 pacientes con insuficiencia cardiaca seguidos en consulta para determinar la concentración de NT-proBNP y la situación clínica mediante clase funcional según la New York Heart Association (NYHA) y los criterios clínicos de Framingham. Se obtuvo una correlación positiva entre NT-proBNP, NYHA y Framingham (p < 0,001). Los pacientes que presentaban una puntuación de Framingham > 2 tenían mayor tasa de reingresos (el 31,8 y el 0%; p < 0,001), visitas a urgencias (el 36,4 y el 5,4%; p = 0,002) y muertes (el 13,6 y el 0%; p = 0,021). El NT-proBNP estaba más elevado en pacientes que precisaron reingreso (p = 0,004) o visita a urgencias por descompensación (p = 0,002).

Palabras clave: *Péptidos natriuréticos. Insuficiencia cardiaca. Framingham.*

INTRODUCTION

Heart failure has a great impact on health systems and society as a whole; indeed, it is the most common cause of hospitalization in people over 65 years of age.[1] The outpatient management of this disease is conditioned by the patient's New York Heart Association (NYHA) functional class or Framingham score.

The determination of type-B natriuretic peptide (BNP) and its aminoterminal fragment (NT-proBNP) represents an advance in the management of heart failure.[2,3] The concentration of these molecules strongly reflect ventricular function[4] and are of prognostic value.[5] The aim of this study was to determine whether the serum NT-proBNP concentration correlates with the Framingham score during the follow-up of outpatients with chronic heart failure, and to determine whether the concentration of this marker can predict which patients are likely to require readmission —or at least a visit to the emergency room— because of decompensation.

METHODS

This prospective study involved patients with heart failure, all of whom had been admitted to hospital at least once for this problem in the previous year. All were being monitored at outpatient internal medicine clinics. Patients

Correspondence: Dr. J.M. Casado Cerrada.
Servicio de Medicina Interna. Hospital Universitario de La Princesa.
Diego de León, 62. 28006 Madrid. España.
E-mail: casadocerrada@hotmail.com

Received February 11, 2007.
Accepted for publication August 27, 2007.

with active myocarditis or pericarditis were excluded, as were those with severe lung or liver disease, a creatinine concentration of >2.5 mg/dL, severe valve disease, and those who had suffered a myocardial infarction in the previous 3 months.

Patients were enrolled over a 6 month period and followed up for 1 year. Appointments were attended every 3 months, during which patient functional class was determined according to the NYHA system and Framingham criteria. A Framingham score table was kept for each patient. One point was assigned for each of the major Framingham criteria met, and half a point for each of the minor criteria; patients were considered unstable when they obtained a score of >2.[6] During the same appointments patient kidney function was checked and serum ion and NT-proBNP concentrations determined, the latter via the proBNP chemiluminescence assay (Roche Diagnostics) using an Elecsys 2010 analyzer.

All patients received treatment according to the guidelines of the European Society of Cardiology[7]; their physicians modified this therapy with the aim of obtaining a Framingham score of <2 without knowledge of the NT-proBNP results. The patients were classified into different groups according to their Framingham score (above or below 2) and NYHA class.

All patients provided written consent to be included.

Statistical Analysis

The results for numerical variables are presented as means (standard deviations); those for categorical variables are presented as percentages. The Mann-Whitney *U* test was used to compare the former and the χ^2 test to compare the latter.

The differences between the groups of patients with respect to their NT-proBNP concentration were examined using the Kruskal-Wallis test. Spearman correlation coefficients were calculated to detect any correlation between the NT-proBNP concentration and the NYHA class and Framingham score. A *P* value less than .05 was considered significant. All calculations were made using SPSS software v.11.0.

RESULTS

The patient sample included 59 individuals, of whom 12% were eventually readmitted and 17% had to visit the emergency room for decompensation during the follow-up period (mean, 11.5 months). Three patients died during this time.

Table 1 shows the baseline characteristics of the patients. The LVEF was preserved in 61% of patients. A significant correlation was seen between the serum NT-proBNP concentration and the NYHA class (*P*<.001; data not shown) and Framingham score (*P*<.001; Figure 1). The correlation coefficient between the NT-proBNP concentration and Framingham score was 0.63 (Figure 2).

TABLE 1. **Patient Characteristics (n=59)**

Characteristic	Total Patients
Women, %	52.5
Age, mean (SD), y	75.2 (8.8)
Hypertension, %	79.7
Diabetes mellitus, %	32.2
Dyslipidemia, %	57.6
Active smokers, %	15.3
Alcoholics, %	5.1
Number of prior admissions, mean (SD)	1.9 (1.4)
Etiology of heart failure, %	
Hypertensive heart disease	30.5
Valve disease	28.8
Ischemic heart disease	23.7
Mixed etiology	13.6
Idiopathic dilated heart disease	3.4
Left ventricular ejection fraction, mean (SD)	48.8 (15.4)
Initial Framingham score, mean (SD)	2.1 (1.0)
Framingham score during follow-up, mean, (SD)	1.92 (0.73)
COPD, %	23.7
Hemoglobin, mean (SD), mg/dL	13.1 (1.8)
Creatinine, mean (SD), mg/dL	1.1 (0.4)
NT-proBNP, mean (SD), pg/mL	2168 (4780)
Angiotensin converting enzyme inhibitors, %	67.8
Angiotensin II receptor antagonists, %	28.8
Diuretics, %	91.5
Spironolactone, %	40.2
Beta-blockers, %	30.5

COPD indicates chronic obstructive pulmonary disease.

Among those patients whose Framingham score increased by 0.5 points between any 2 visits, the NT-proBNP concentration was seen to increase by a mean of 65% (95% confidence interval [95% CI], 50.23-79.74). Among those patients who experienced no increase in their Framingham score, or who saw it decrease, reductions in the NT-proBNP concentration were recorded (*P*<.001) (Figure 3).

Patients with a Framingham score of >2 during follow-up were more likely to be readmitted to hospital due to decompensation (31.8% of those with such a score compared to 0% of those with a score of <2; *P*<.001), to have to visit the emergency room (36.4% compared 5.4%; *P*=.002), and to suffer death of cardiac origin (13.6% compared to 0%; *P*=.021). The mean NT-proBNP concentration was higher among readmitted patients compared to those who did not need to be readmitted (6660 [7762] compared to 1377 [2106] pg/mL; *P*=.004), among those who suffered decompensation and had to visit the emergency room (5154 [6790] compared to 1360.5 [2167] pg/mL in those who did not; *P*=.002), and in those who died (6574 [3650] compared to 1759 [3483] pg/mL in those still alive; not significant).

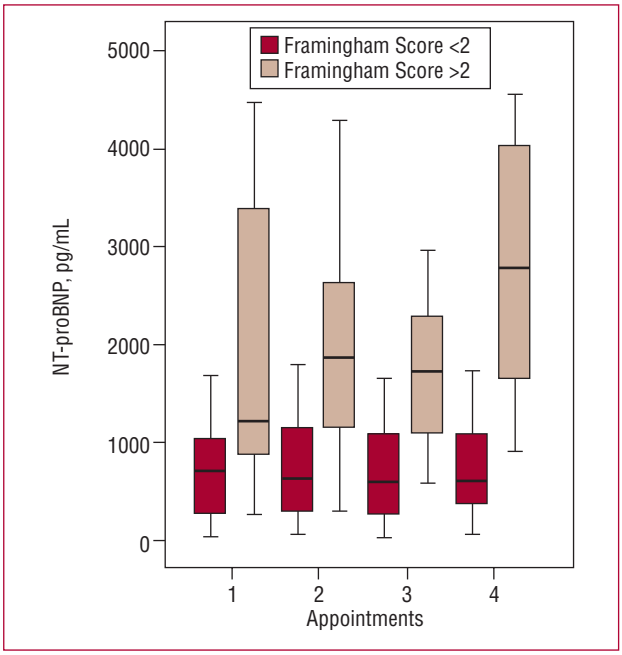

Figure 1. Distribution of NT-proBNP concentrations at the different appointment times with respect to Framingham scores. Comparisons were made using the non-parametric Kruskal-Wallis test (*P*<.001).

DISCUSSION

The present results show that NT-proBNP can be used as a biological marker of the need for readmission or a visit to the emergency room because of decompensation in the monitoring of outpatients with chronic heart failure whose characteristics are similar to those of the present study. A positive correlation was seen between the NT-proBNP concentration and the Framingham score. Most studies in this area have investigated the use of NT-proBNP in the differential diagnosis of acute dyspnea[8,9] or in post-admission prognosis[10]; only a few have examined the usefulness of natriuretic peptide determination in patients with chronic heart failure attending outpatient clinics.[11-13] One of these[11] found that variations in BNP concentration were related to NYHA functional class. The characteristics of the patients, however, were different to those of the present study; the majority were men <75 years of age who mainly suffered heart failure of ischemic etiology and who showed a depressed LVEF. In a study with patients of characteristics similar to those of the latter study, Bayés-Genís et al[12] reported the NT-proBNP concentration of those with decompensation due to heart failure who did not need to be admitted to hospital to be related to short-term prognosis. In an important study which examined the relationship between the NT-proBNP concentration and chronic heart failure, Troughton et al[6] used a modified Framingham score to determine the clinical status of patients, as in the present study. The aim was to determine whether NT-proBNP could be used to guide the treatment of patients with heart failure in the outpatient setting. The results showed that the likelihood of suffering a cardiovascular event was reduced among patients whose treatment was guided in this way (19 of these patients suffered such an event compared to 54 patients whose treatment was not thus guided; *P*=.02).

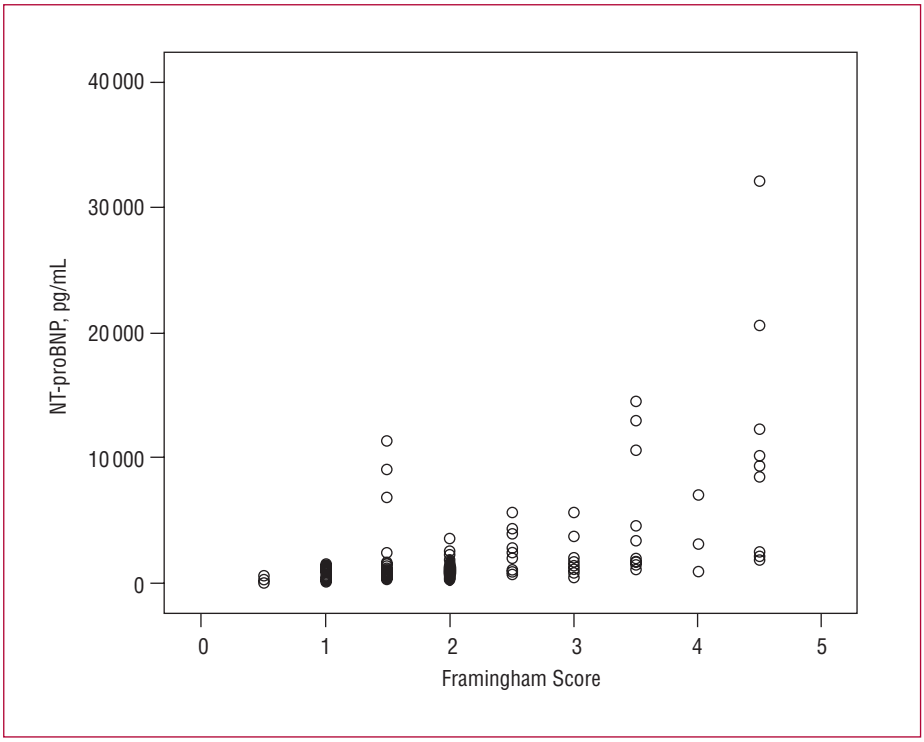

Figure 2. Correlation between Framingham score during follow-up and serum NT-proBNP concentration. As the Framingham score increases so does the NT-proBNP concentration. Spearman correlation coefficient=0.63.

Figure 3. Change in NT-proBNP concentration according to changes in Framingham score during follow-up. Comparisons were made using the non-parametric Kruskal-Wallis test (*P*<.001).

The clinico-demographic characteristics of the present patients reflect the situation commonly encountered in internal medicine departments.[14] The etiology of heart failure does not seem to influence the NT-proBNP concentration.[15] Some studies suggest sex has no influence on these concentrations[8] while others suggest that in women they are normally higher.[16] With respect to the LVEF, the NT-proBNP concentration is higher in patients with a value of <45%; however, patient prognosis does not seem to depend entirely on this variable.[17] Age certainly influences the NT-proBNP concentration as well as the cut-offs established for the differential diagnosis of acute dyspnea.[8]

The originality of the present study lies in that to date there have been no Spanish data available regarding the use of NT-proBNP in the follow-up of patients with chronic heart failure monitored at internal medicine outpatient departments. NTproBNP concentrations should not be used as a substitute for appropriate clinical examination, even though the use of the Framingham score involves checking for certain signs that is not without difficulty for inexpert physicians. Rather, adding a more objective variable for the assessment of this disease could be useful in refining the treatment of patients.

The present study has a number of limitations such as its small sample size and short follow-up time (and consequently the small number of cardiovascular events recorded). For this reason no regression analysis of the possible relationship between NT-proBNP as an independent predictor of the need for readmission or a visit to the emergency room was performed. The small sample size also precludes the establishment of any relationship between mortality and NT-proBNP concentration or LVEF; death was only seen in 3 patients.

Studies with larger numbers of patients and longer follow-up times are needed to further investigate the degree to which determining the NT-proBNP concentration may help in the clinical assessment of patients with chronic heart failure attending outpatient clinics.

REFERENCES

1. Heart disease and stroke statistics—2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007;115:e69-171.
2. Bettencourt P, Ferreira A, Dias P, Castro A, Martins L, Cerqueira-Gomes M. Evaluation of brain natriuretic peptide in the diagnosis of heart failure. Cardiology. 2000;93:19-25.
3. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure. BMJ. 2002;324:1498-502.
4. Richards AM, Crozier IG, Yandle TG, Espiner EA, Ikram H, Nicholls MG. Brain natriuretic factor: regional plasma concentrations and correlations with haemodynamic state in cardiac disease. Br Heart J. 1993;69:414-7.
5. Doust JA, Pietrzak E, Dobson A, Glasziuo P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005;330:625-32.
6. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide concentrations. Lancet. 2000;355:1126-30.
7. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure:executive summary (update 2005). EU Heart Tour. 2005;26:1115-40.

8. Januzzi J, Kimmenade R, Lainchbury J, Bayés-Genís A, Ordóñez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. EU Heart Tour. 2006;27:330-7.
9. Pascual-Figal DA, Cerdán-Sánchez MC, Noguera-Velasco JA, Casas-Pina T, Muñoz-Gimeno L, García-Rodríguez R, et al. Utilidad del NTproBNP en el manejo urgente del paciente con disnea severa y diagnóstico dudoso de insuficiencia cardiaca. Rev Esp Cardiol. 2005;58:1155-61.
10. O'Brien R, Squire IB, Demme B, Davies JE, Ng LL. Pre-discharge, but not admission, levels of NTproBNP predict adverse prognosis following acute LVF. Eur J Heart Fail. 2003;5:499-506.
11. Lee S, Stevens T, Sandberg S, Heublein D, Nelson S, Jougasaki M, et al. The potential of brain natriuretic peptide as a biomarker for NYHA class during the outpatient treatment of heart failure. J Car Fail. 2002;8:149-54.
12. Bayés-Genís A, Pascual-Figal D, Fabregat J, Domingo M, Planas F, Casas T, et al. Serial NT-proBNP monitoring and outcomes in outpatients with decompensation of heart failure. Int J Cardiol. 2007;120:338-43.
13. Cortés R, Rivera M, Salvador A, Bertomeu V, García de Burgos F, Roselló-Lletí E, et al. Variability of NT-proBNP plasma and urine levels in stable heart failure patients. a two-year follow-up study. Heart. 2007;93:957-62.
14. Grupo de Trabajo de Insuficiencia Cardíaca de la Sociedad Española de Medicina Interna. La insuficiencia cardíaca en los servicios de medicina interna. Med Clin (Barc). 2002;118:605-10.
15. Richards M, Troughton RW. NTproBNP in heart failure: therapy decisions and monitoring. Eur J Heart Fail. 2004;6:351-4.
16. Chang AY, Abdullah SM, Jain T, Stanek HG, Das Sr, Mc Guire DK, et al. Associations among androgens, estrogens, and natriuretic peptides in young women. J Am Coll Cardiol. 2007;49: 109-16.
17. Smith GL, Masoudi FA, Vaccarino C, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction. J Am Coll Cardiol. 2003;41:1510-8.