ORIGINAL ARTICLE

Utility of NT-proBNP for Diagnosing Heart Failure in a Heterogeneous Population of Patients With Dyspnea. Spanish Multicenter Study

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Introduction and objectives. Recent studies have shown that brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are useful in the diagnosis of heart failure in patients presenting with dyspnea. However, the cutoff values used with these markers vary according to patient characteristics and dyspnea severity. The aim of this study was to investigate the diagnostic accuracy of using the plasma NT-proBNP level for identifying heart failure in a heterogeneous population of patients with dyspnea.

Methods. A multicentre study involving 247 consecutive patients with recent-onset dyspnea was carried out at 12 Spanish hospitals. Patients previously diagnosed with heart failure or any other condition known to cause dyspnea were excluded.

Results. Of the 247 patients, 161 (65%) had heart failure. The remaining 86 (35%) presented with dyspnea of non-cardiac origin. Plasma NT-proBNP levels were higher in patients with heart failure (5600 [7988] pg/mL vs 1182 [4406] pg/mL; *P*=.0001), and increased as functional status deteriorated (*P*=.036). The area under the receiver operating characteristic curve was 0.87 (0.02) (95% CI, 0.81-0.91) for the optimum cutoff value of 1335 pg/mL. The sensitivity of this cutoff value for diagnosing heart failure was 77% (95% CI, 70%-83%), the specificity was 92% (95% CI, 84%-97%), the positive predictive value was 94%, and the negative predictive value was 68%.

Conclusions. The plasma NT-proBNP concentration provides an accurate means of diagnosing heart failure. However, the negative predictive value found in this study was somewhat lower than the values found in previous studies involving more homogeneous patient populations.

Key words: *Natriuretic peptides. NT-proBNP. Heart failure. Diagnosis.*

Utilidad del NT-proBNP para el diagnóstico de insuficiencia cardiaca en una población heterogénea de pacientes con disnea. Estudio multicéntrico español

Introducción y objetivos. En estudios recientes se ha demostrado la utilidad de los péptidos natriuréticos cerebrales (BNP) para el diagnóstico de insuficiencia cardiaca. Sin embargo, los valores de corte de estos marcadores difieren según las características de los pacientes y la severidad de la disnea. El objetivo de nuestro estudio fue evaluar la eficacia diagnóstica de los valores plasmáticos de la fracción N-terminal del BNP (NT-proBNP) en una población heterogénea de pacientes con disnea.

Métodos. Realizamos un estudio multicéntrico en 12 hospitales españoles en el que se incluyó a 247 pacientes que consultaron de forma consecutiva por disnea de reciente comienzo. Se excluyó a los pacientes previamente diagnosticados de insuficiencia cardiaca u otras causas conocidas de disnea.

Resultados. De los 247 pacientes, 161 (65%) fueron diagnosticados de insuficiencia cardiaca y 86 (35%) presentaron disnea de origen no cardiaco. Los valores plasmáticos de NT-proBNP fueron más elevados en los pa-

*The appendix contains a list of all the Spanish Muticenter NT-proBNP-IC Study researchers and participating hospitals.

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ABBREVIATIONS

BNP: brain natriuretic peptide.
LVEF: left ventricular ejection fraction.
CHF: congestive heart failure
NT-proBNP: N-terminal proBNP.

cientes con insuficiencia cardiaca (5.600 ± 7.988 frente a 1.182 ± 4.406 pg/ml; p = 0,0001), y fueron mayores con peor clase funcional (p = 0,036). El área bajo la curva ROC fue 0,87 ± 0,02 (intervalo de confianza [IC] del 95%, 0,81-0,91), para un valor de corte óptimo de 1.335 pg/ml. La sensibilidad de este valor de corte para diagnosticar insuficiencia cardiaca fue del 77% (IC del 95%, 70-83%); la especificidad, del 92% (IC del 95%, 84-97%); el valor predictivo positivo, del 94%, y el valor predictivo negativo del 68%.

Conclusiones. Las concentraciones plasmáticas de NT-proBNP son útiles para el diagnóstico de insuficiencia cardiaca en este tipo de pacientes, aunque el valor predictivo negativo es algo más bajo que en estudios previos que incluyeron a pacientes más homogéneos.

Palabras clave. *Péptidos natriuréticos. NT-proBNP. Insuficiencia cardiaca. Diagnóstico.*

INTRODUCTION

The diagnosis of congestive heart failure (CHF)—an increasingly common condition[1]—is usually based on clinical data and echocardiographic findings.[2] Errors in the diagnosis of CHF, however, are relatively common, especially in the primary care situation and the emergency room; indeed, it is thought that between and 25% and 50% of all clinical diagnoses of CHF pronounced in these settings are incorrect.[3] In recent years, the determination of brain natriuretic peptide (BNP and its N-terminal fraction known as NT-proBNP) levels has been shown useful in the diagnosis of CHF. Studies performed in primary care centers and hospital emergency rooms have confirmed the excellent diagnostic precision of these markers.[4,5] However, their routine determination has still to become widely adopted; the cost of this procedure and doubts still not clarified by experimental work appear to be among the main reasons responsible.[6-12] With respect to the latter, most of the studies performed in this area have been single-center in nature, and have involved selected centers and very homogeneous patients—usually with reduced systolic function[10-12] (quite different from the everyday picture of CHF seen in clinical practice). In addition, they offer cut-off values that vary greatly from one another and that depend on the severity of dyspnea suffered, the healthcare setting (hospital emergency room or other environments), and patient age. The present paper reports a study of the diagnostic usefulness of measuring NT-proBNP levels in a more heterogeneous population of patients, i.e., in a population more similar to that seen in routine practice. The study involved 12 Spanish hospitals representing different levels of healthcare attention. All the patients presented with dyspnea (of differing severity) at either hospital emergency rooms or specialist outpatients clinics; some had preserved systolic function, others showed reduced systolic function.

METHODS

The study subjects were 247 consecutive patients who presented at the emergency room or cardiology or internal medicine clinics of 12 Spanish hospitals (see appendix) with dyspnea of recent onset. Patients previously diagnosed with heart failure or other problems associated with dyspnea (normally significant bronchopulmonary disease) were excluded, as were those with kidney failure (in dialysis), and those with acute coronary syndrome at presentation. The patients included all belonged to dyspnea functional classes II, III, or IV. All were explained the aims of the study, and all gave their consent to take part. Blood was taken from all patients to determine the plasma NT-proBNP concentration. The diagnosis of CHF was always finally pronounced by a specialist physician (who was always "blind" to the NT-proBNP concentrations detected) when the criteria of the European Society of Cardiology regarding clinical symptoms and Doppler echocardiography results[2] were met. The medical history of each patient was examined, and all underwent Doppler echocardiography, a physical examination and a chest x-ray before such a diagnosis was reached. To reduce the diagnostic variability between centers, a number of meetings were held by the participating physicians with the aim of homogenizing diagnostic criteria.

At the participating clinics, patient blood samples were taken between 08.00 and 09.00 h; for those who presented at the emergency room, blood samples were taken at an appropriate moment during their visit, but always before starting treatment for CHF. The samples were centrifuged at 1500 rpm and stored at –80ºC until analysis. Plasma NT-proBNP levels (pg/mL) were determined using an Elecsys 1010 analyzer (Roche Diagnostics).

Demographic, clinical, analytical, and echocardiographic data were collected from each patient, introduced into a database, and analyzed by an independent company using SAS v. 8.02 software for Windows.

The patients were divided into 2 groups, those with dyspnea due to CHF and those with dyspnea of non-

cardiac origin. The results for the variables measured were expressed as means ± standard deviation (SD). Qualitative variables were compared by the χ^2 test and the McNemar test for independent and paired data respectively. The NT-proBNP levels did not show a normal distribution and were therefore compared using the Mann-Whitney or Wilcoxon test (for independent and paired data respectively). The Kruskal-Wallis test was used to compare more than 2 groups of non-paired data. Receiver operating characteristic (ROC) curves were produced for the NT-proBNP values in relation to the diagnosis of CHF. Diagnostic precision was determined by calculating the sensitivity, specificity and the positive and negative predictive powers of the cut-off NT-proBNP values. Significance was set at $P<.05$.

RESULTS

The mean age of the patients was 70±11 years; 131 (57%) were men and 116 (43%) were women. Congestive heart failure was diagnosed in 161 patients (65%); in the remaining 86 (35%), dyspnea was due to a non-cardiac cause. Among those with CHF, 44% fell into functional class II, another 44% fell into class III, and 12% fell into class IV. Among those with non-cardiac origin dyspnea, 89% fell into functional class II, 8% into class III, and 3% into class IV; the primary cause of dyspnea in these patients was bronchopulmonary disease (57 patients [66%]), followed by anemia (10 patients [11%]), anxiety (8 patients [9%]), severe obesity (7 patients [8%]), and dyspnea of multifactorial origin (age, obesity, sedentary lifestyle, etc) (4 patients [6%]).

Differences in the Clinical, Analytical, and Physical Examination Results of Patients With and Without Congestive Heart Failure

Table 1 shows the demographic characteristics and relevant medical backgrounds of the 2 groups of patients. The age of the patients with CHF was significantly higher, with no difference with respect to sex. The prevalence of cardiovascular risk factors was similar in both groups, except for a slightly higher prevalence of hyperlipidemia in the patients with non-cardiac origin dyspnea (36% compared to 22%; $P=.02$). Table 2 shows the results of the physical examination of both groups of patients. No significant differences were seen in terms of body weight, height or blood pressure. The heart rate was higher in the patients diagnosed with CHF ($P<.001$), as was the incidence of leg edema, crackles, and third heart sound, or murmur (Table 2). However, it should be highlighted that these very specific signs of CHF were observed very infrequently. For instance, crackles were heard in only 15% of these patients (compared to 1% in patients with non-cardiac origin dyspnea; $P<.01$), and a third heart sound was heard in only 26% (compared to 3% in patients with non-cardiac origin dyspnea; $P<.01$).

Table 3 shows the main biochemical and analytical results. No significant differences were seen between the groups in terms of hemoglobin, serum ion or creatinine kinase concentrations, although the patients with CHF had higher levels of blood sugar and bilirubin and a higher serum creatinine concentration.

Table 4 shows the electrocardiographic, x-ray and echocardiographic results for both groups of patients. Those with CHF more commonly had an abnormal electrocardiogram (93% compared to 46%; $P<.0001$), an abnormal chest x-ray (94% compared to 45%; $P<.0001$), cardiomegaly (60% compared 40%; $P<.01$), and an interstitial pattern in their chest x-ray (40% compared to 16%; $P<.001$). Atrial fibrillation was also more common among those with CHF (40% compared

TABLE 1. **Demographic Background of Patients With Congestive Heart Failure and Non-Cardiac Origin Dyspnea***

	CHF (n=161)	Non-Cardiac Origin (n=86)	*P*
Age, y	72±11	67±18	.01
Sex			NS
Men	97 (60%)	44 (51%)	
Women	64 (40%)	42 (49%)	
Smokers	77 (48%)	38 (44%)	NS
High blood pressure	97 (60%)	61 (71%)	NS
Hyperlipidemia	35 (22%)	30 (36%)	.02
Diabetes	45 (28%)	23 (25%)	NS
Ischemic heart disease	27 (17%)	12 (14%)	NS
Mild COPD	28 (18%)	24 (27%)	NS

*CHF indicates congestive heart disease; NS, not significant; COPD, chronic obstructive pulmonary disease.

TABLE 2. **Semiologic Findings in Patients With Congestive Heart Failure and Non-Cardiac Origin Dyspnea***

	CHF (n=161)	Non-Cardiac Origin (n=86)	*P*
Body weight, kg	78±14	79±14	NS
Height, cm	164±8	165±7	NS
Heart rate, beats/min	92±25	79±19	<.001
SBP, mm Hg	141±24	138±22	NS
DBP, mm Hg	83±14	78±12	NS
Leg edema	84 (52%)	22 (24%)	<.001
Pulmonary crackles	24 (15%)	1 (1%)	<.001
Third heart sound	43 (26%)	2 (3%)	<.001
Murmur	63 (39%)	13 (15%)	<.001

*CHF indicates congestive heart disease; NS, not significant; DBP, diastolic blood pressure; SBP, systolic blood pressure.

to 14%; *P*<.001). The incidence of an alveolar pattern in the chest x-ray was similar in both groups (Table 4). The Doppler echocardiogram results (Table 4) showed the patients with CHF to have larger left ventricular diameters (both systolic and diastolic) and a smaller left ventricular ejection fraction (LVEF), although the mean for the latter variable was almost within normal limits (49±18% compared to 65±11% in the patients with non-cardiac origin dyspnea). Among the patients with CHF, 67 (41%) had an LVEF of <45%, and 91 (59%) had an LVEF of 45% or greater. No significant differences were seen between the patient groups in terms of the thickness of the left ventricular wall. The left ventricular isovolumetric relaxation time was longer in the patients diagnosed with CHF, who also more commonly showed an abnormal diastolic pattern (Table 4).

Although the specificities of the Framingham criteria clinical parameters for the diagnosis of CHF were high (98% for pulmonary crackles, 96% for third heart sound, and 76% for cardiomegaly), their diagnostic sensitivity was low: 15% for crackles, 25% for a third heart sound, and 45% for cardiomegaly. The overall sensitivity of the Framingham criteria was just 52%.

TABLE 3. **Biochemical and Analytical Data of Patients With Congestive Heart Failure and Non-Cardiac Origin Dyspnea***

	CHF (n=161)	Non-Cardiac Origin (n=86)	*P*
Hemoglobin, g/dL	13.2±1.6	13.6±1.7	NS
Serum creatinine, mg/dL	1.2±0.5	1.0±0.3	<.001
Serum bilirubin, mg/dL	2.1±2.8	1.0±1.7	<.01
Creatine kinase, U/L	87±41	77±44	NS
Troponin T, ng/mL	0.19±0.67	0.04±0.16	<.001
Positive troponin T	46 (29%)	6 (7%)	<.001
Glycemia, mg/dL	127±46	117±39	.03
Oxygen saturation, %	93±4	95±4	<.001
PCO_2, mm Hg	38±11	42±10	.038
CRP highly sensitive, mg/dL	3.39±3.62	4.64±3.14	NS

*CHF indicates congestive heart failure; PCO_2, partial pressure of carbon dioxide; NS, not significant; CRP, C-reactive protein.

TABLE 4. **Electrocardiographic, Radiological, and Echocardiographic Findings in Patients With Congestive Heart Failure and Non-Cardiac Origin Dyspnea***

	CHF (n=161)	Non-Cardiac Origin (n=86)	*P*
Abnormal ECG	150 (93%)	40 (46%)	<.0001
Atrial fibrillation	64 (40%)	12 (14%)	<.001
Abnormal chest x-ray	151 (94%)	39 (45%)	<.001
Cardiomegaly	97 (60%)	35 (40%)	<.01
Interstitial pattern	64 (40%)	14 (16%)	<.001
Alveolar pattern	19 (12%)	7 (8%)	NS
IV septal thickness, mm	11.2±3.9	11.2±4.1	NS
Posterior wall thickness, mm	10.4±3.5	10.3±3.1	NS
LV diastolic diameter, mm	47±17	39±15	<.001
LV systolic diameter, mm	40±16	32±13	<.001
LV ejection fraction, %	49±18	65±11	<.001
LVIRT, ms	108±40	103±28	<.003
Abnormal diastolic pattern	96 (59%)	46 (54%)	.04

*ECG indicates electrocardiogram; CHF, congestive heart disease; IV, interventricular; NS, no significant; LVIRT, left ventricular isovolumetric relaxation time; LV, left ventricular.

Diagnostic Usefulness of the NT-proBNP Level in the Diagnosis of CHF

The plasma NT-proBNP levels recorded were significantly higher in the patients with CHF (5600±7988 pg/mL compared to 1182±4104 pg/mL in those with non-cardiac origin dyspnea; *P*=.0001) (Figure 1). Among the patients with CHF, NT-proBNP increased with functional class (*P*=.036; Figure 1). However, no significant differences were seen in these values between patients with CHF plus an LVEF of above or below 45%, nor between those with or without left ventricular hypertrophy (Figure 2). Those patients with an impaired ventricular diastolic pattern, as determined from their Doppler echocardiograms, had higher NT-proBNP levels than those with a normal diastolic pattern (5991±6672 pg/mL compared to 3141±5237 respectively; *P*=.002).

Figure 3 shows the area under the ROC curve for plasma NT-proBNP in relation to the diagnosis of CHF. The mean area under the curve was 0.87±0.02 (95% confidence interval [CI], 0.82-0.91). The cut-off NT-proBNP value of 1335 pg/mL showed a sensitivity of 77%, a specificity of 92%, a positive predictive power of 94%, and a negative predictive power of 68% for the diagnosis of CHF. This means that 94% of patients with dyspnea who had an NT-proBNP value of >1335 pg/mL had CHF, although almost a third of those with lower values also had CHF. The value of 76 pg/mL appeared as a cut-off value with a very high negative predictive power. The sensitivity of this value for the diagnosis of CHF was 98%, specificity a very low 16%, the positive predictive power 70%, and the negative predictive power 93%. Thus, patients with dyspnea with NT-proBNP values of <76 pg/mL nearly never have CHF, although the specificity of this value is very low.

DISCUSSION

It is well known that a diagnosis of CHF made in primary attention centers and emergency rooms is often wrong—in fact, some 25%-50% of all diagnoses of CHF pronounced in such settings are incorrect.[3] One of the reasons for this is the scant diagnostic

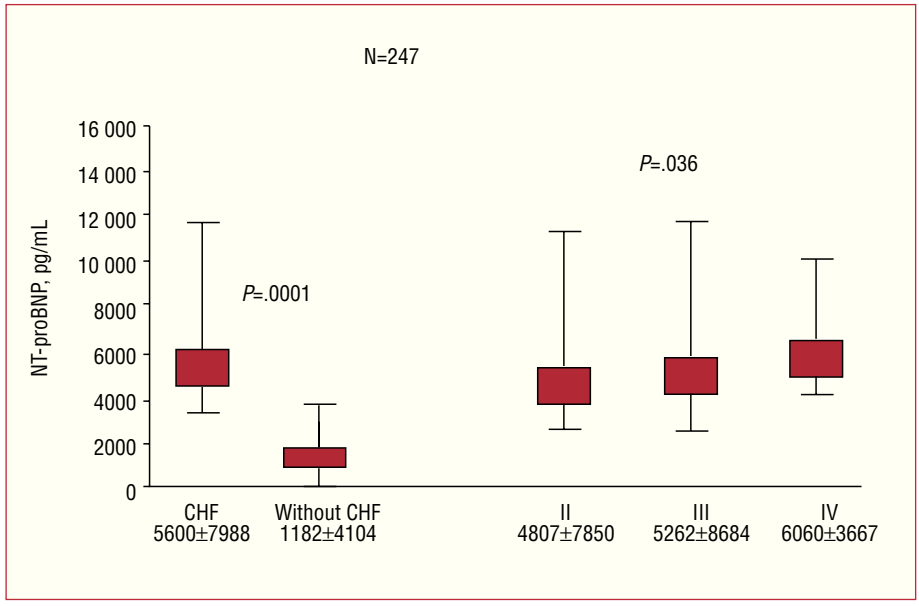

Figure 1. Mean plasma N-terminal BNP and NT-proBNP levels in patients with and without congestive heart failure, and in patients with congestive heart failure stratified by dyspnea functional class.

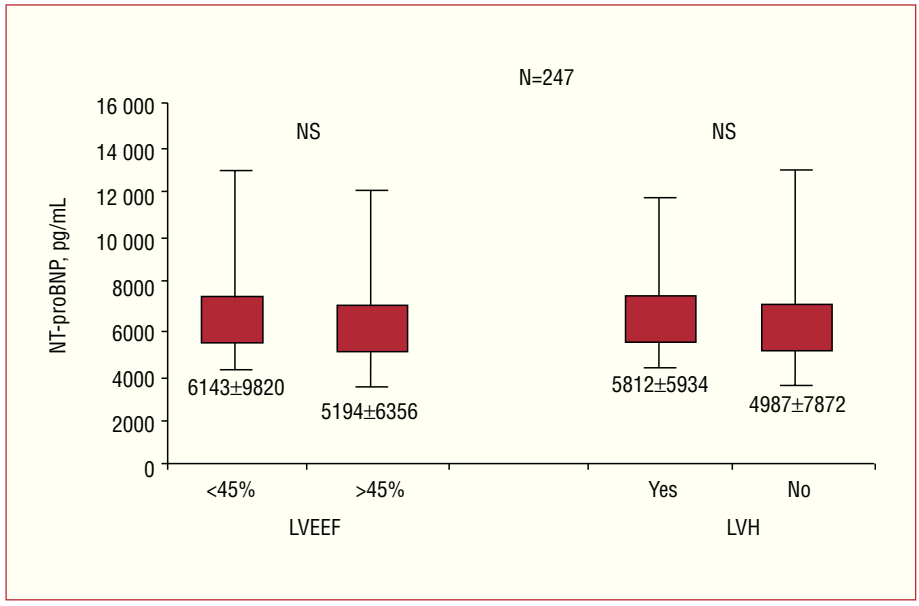

Figure 2. Mean plasma N-terminal BNP and NT-proBNP levels in patients with congestive heart failure according to left ventricular ejection fraction (LVEF) (above or below 45%), and the presence or absence of left ventricular hypertrophy (LVH). NS indicates not significant.

precision of the symptoms, signs and electrocardiographic and radiological findings associated with CHF. This is confirmed by the present results. Table 2 shows that crackles were heard in just 15% of patients diagnosed with CHF, and that a third heart sound was heard in just 26%. Although these findings are very specific for the diagnosis of CHF (they were only heard in 1% and 3% respectively of the patients with non-cardiac origin dyspnea) their sensitivity is very low. The opposite is true of x-ray and electrocardiographic findings, which have a higher sensitivity but very low specificity. Another reason for so many incorrect diagnoses is the scant access to echocardiographic equipment in the emergency room and primary care setting, along with problems in the interpretation of the results. It is therefore very important that new, reliable, simple and accessible diagnostic techniques become available if we are to improve our accuracy in the diagnosis of CHF. One such technique is the determination of plasma BNP and NT-proBNP. Several studies have shown the excellent precision of these biochemical markers in the diagnosis of CHF,[6-12] which has led to their inclusion in the diagnostic algorithm of the European Society of Cardiology.[2] These peptides also seem to be useful in prognostic stratification,[13,14] in the selection of heart transplant candidates,[15] and in the monitoring of CHF treatment.[16] Other studies have shown these peptides

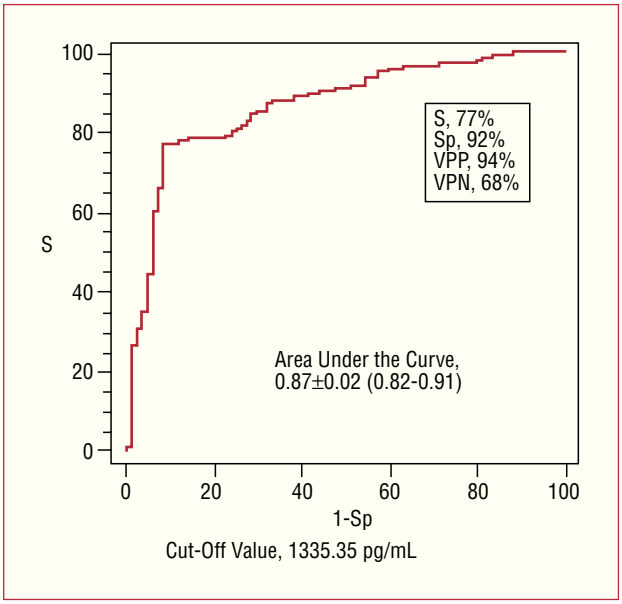

Figure 3. ROC curve for the diagnostic value of NT-proBNP. S indicates sensitivity; Sp, specificity; PPP, positive predictive power; NPP, negative predictive power.

to be important in determining the prognosis of patients who have undergone a heart transplant,[17] in the prognostic assessment of acute coronary syndromes,[18,19] and even in that of aortic stenosis.[20]

However, despite the evidence regarding the advantages of determining BNP and NT-proBNP levels, this is not widely practiced. To some degree this might be due to the costs involved, but a further influence may be the doubts and controversies that still surround the results of the above-mentioned studies. The majority have been single center studies —often involving specialized and selected CHF units—which naturally raises concerns about whether the results obtained are applicable to a more general population of CHF patients. In several studies, for example, only patients with systolic dysfunction were included[10-12]—a condition that is only seen in 50%-60% of patients with CHF.[1] Another source of doubt for the general clinician is the diversity of units used (ng/L, pg/mL, pmol/L),[7-10] making the cut-off values different depending on the units in which they are expressed (recently, consensus has been reached that the units pg/mL should be used). Another possible problem is the variability of the cut-off values recommended by each study (even when they use the same units); depending on bodyweight and age, BNP and NT-proBNP levels can vary for the same degree of heart failure and intraventricular pressure.[10] In addition, the cut-off values recommended are lower when these peptides are used in CHF screening in the general population or in the primary care setting than in the emergency room when dealing with patients with more severe dyspnea.[6,10-12]

The present work attempts to clarify some of these doubts by having a multicenter design involving 12 Spanish hospitals (representing different levels of healthcare), by involving patients presenting at emergency rooms and cardiology or internal medicine clinics with dyspnea of recent onset and with no previously diagnosed disease that might give rise to such symptoms. The mean age of the population studied was 70 years, almost half the patients were women, the severity of the dyspnea was very variable (44% of patients were in functional class II, another 44% in class III, and 12% in class IV), and the mean LVEF was almost normal at 49±18% (meaning a good proportion of the patients had preserved systolic function). The studied population was therefore representative of the general population of patients with CHF or dyspnea. Importantly, the results appear to confirm previous findings. Plasma NT-proBNP levels were significantly higher in patients with CHF than in those with non-cardiac origin dyspnea (Figure 1), and showed very good diagnostic precision (area under the ROC curve 0.87 0.02; 95% CI, 0.82-0.91) (Figure 3). The NT-proBNP level increased with the severity of dyspnea (Figure 1), confirming the results of other studies.[6,10,11] Interestingly, the NT-proBNP values were similar in patients with CHF and an LVEF of above or below 45% (Figure 2). This indicates that NT-proBNP levels are useful in the diagnosis of CHF with preserved systolic function. Further supporting this is the fact that the patients with an impaired ventricular diastolic pattern had significantly higher NT-proBNP levels than those who had normal diastolic function—something also reported in earlier studies.[21]

Another interesting feature of the present study is that the diagnostic precision, although notable, was somewhat lower than that recorded in other studies that involved more homogeneous patients. In the present study, the area under the ROC curve was 0.87±0.02, while in the majority of other studies it has been above 0.90.[6-12] The optimum cut-off value in the present study was 1335 pg/mL; this was associated with a negative predictive power of 68%, while in other studies this figure was >90%. The positive predictive power of the NT-proBNP level in the present sample was very high (94%). This means that, in a population with the characteristics of the present sample, nearly all (94%) those who present at an emergency room or outpatient clinic with NT-proBNP values of >1335 pg/mL have CHF. However, some 32% of patients with lower values also have CHF. If the lower cut-off value of 76 pg/mL is used, nearly 100% of the patients with lower values would not have CHF, although the specificity of this cut-off value is very low. In a recent Spanish study involving patients presenting at the emergency room with dyspnea of unknown origin, Pascual et al[22] found an area under

the curve (0.72) lower than that of the present study, although these authors obtained a higher negative predictive power (92%). The optimum cut-off proposed in this earlier study was 900 pg/mL.[22] As Bayés-Genís postulates in the editorial accompanying this article, determining the levels of these peptides would be of greatest use in patients with dyspnea of doubtful origin, and least useful when the results of the physical examination and other initial findings clearly point towards a definite cause of dyspnea.[23]

CONCLUSIONS

Determining plasma NT-proBNP levels is very important in the diagnosis of CHF in the general population of patients with suspected CHF. However, the present results show some differences with respect to previously published results involving more selected patients. The diagnostic precision, though good, was somewhat lower than in previous studies, and 2 cut-off values seem to be required, a CHF *rule in* value, and a CHF *rule out* value. The present results show that the optimum cut-off value is more efficient in terms of confirming a diagnosis of CHF (very high positive predictive power) than for ruling it out (lower negative predictive power, the opposite of that reported in earlier studies). The fact that more than half of the patients in the present sample had an LVEF of 45% or greater (i.e., most of the population diagnosed with CHF had preserved systolic function) may have influenced the present findings; recent studies indicate that the natriuretic peptides are associated with increased ventricular diameters.[24] It may therefore be necessary to study the diagnostic value of determining the NT-proBNP levels in patients with CHF with preserved and reduced systolic function.

The main limitation of the present study is that the sample size allowed no analysis of the different age groups to be made—and cut-off values can vary with patient age.[25] Neither could the patients with severe dyspnea presenting at the emergency room be separated from those with less severe dyspnea who presented at outpatient clinics. In addition, the effect of body weight[26] on the results could not be studied. However, the results confirm the diagnostic usefulness of determining NT-proBNP levels in non-selected patients suspected of suffering CHF. The determination of these markers should be included in the overall assessment of such patients, as indicated in the recent guidelines published by the European Society of Cardiology.[2]

APPENDIX. PARTICIPATING CENTERS AND RESEARCHERS

Hospital de Cruces (Vizcaya): P. Montes, I. Eguía, M. Rueda. Hospital Universitario de Elche: A. Jordá, F. García de Burgo, J. Luján, J.F. Sánchez. Hospital Reina Sofía (Córdoba): M. Anguita, S. Ojeda, C. Aguilera, T. Pérez. Hospital San Agustín de Avilés: G. Casares, I. Fernández, A. Fernández, R. Ventas. Hospital Clínico Universitario de Santiago: I. Gómez, D. López, F. Soto. Hospital Vall d'Hebron (Barcelona): J. Recio, E. Ruiz, J. Alegre, R. Segura. Hospital Virgen del Rocío (Sevilla): A. Martínez, C. Sevillano, D. Fatela. Hospital de Galdácano (Vizcaya): J. Zumalde, F. Izquierdo, I. Lecuona. Hospital Miguel Servet (Zaragoza): J. Povar, J.M. Franco, M. Sanz, A. García de Jalón. Hospital General Universitario de Valencia: F. Ridocci, P. Federico, V. Manzó. Hospital Clinico de Barcelona: E. Roig, J.L. Marín, O. Miró. Hospital Fundación Alcorcón (Madrid): E. Batlle, E. España, J. Jiménez.

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