Diagnostic and Prognostic Performance of N-Terminal ProBNP in Primary Care Patients With Suspected Heart Failure

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ABSTRACT

Background: The value of N-terminal pro-brain natriuretic peptide (NT-proBNP) in terms of diagnosis and prognosis in congestive heart failure (CHF) and left ventricular systolic dysfunction (LVSD) has been demonstrated previously in various populations, but data on primary care patients are sparse. The aim of this study was to evaluate the diagnostic and prognostic performance of NT-proBNP in primary care patients with suspected CHF.

Methods and Results: Three hundred sixty-seven consecutive patients (mean age, 68.8 years; range, 39.0–84.0 years) who had been referred by their general practitioner for echocardiographic evaluation because of suspected CHF. In all patients, NT-proBNP was measured at baseline and left ventricular ejection fraction (LVEF) was estimated with echocardiography. LVSD (LVEF ≤0.40) was found in 9% of the patients. NT-proBNP was significantly higher in patients with LVSD (P < .0001). With predefined cut off values for NT-proBNP (125 pg/mL), the sensitivity, specificity, positive predictive value, and negative predictive value for the detection of LVSD were 0.97, 0.46, 0.15 and 0.99, respectively. Area under the receiver operating characteristic curve was 0.87. The application of an age-differentiated cut-off value for NT-proBNP (125 pg/mL for <75 years old and 450 pg/mL for ≥75 years old) did not increase diagnostic performance. Patients were followed for a median of 778 days; 8% of the patients died during the follow-up period. The mortality rate was higher in patients with NT-proBNP of >125 pg/mL than in patients with normal values (P < .002, log rank), and the difference persisted after controlling for age, gender, and LVEF (hazard ratio per unit increase in log NT-proBNP, 2.2; range, 1.2–4.1; P = .015).

Conclusion: In primary care patients who were referred for echocardiography because of suspected CHF, NT-proBNP values <125 pg/mL effectively rule out LVSD. Furthermore low NT-proBNP values are associated with a lower risk of death, independently of age, gender, and LVEF.

Key Words: General practitioner, echocardiography, death, diagnosis.
eficacy of natriuretic peptides in the diagnosis of LVSD have been conducted in hospitalized patients or in epidemiologic cohort studies. It appears, however, that the most obvious need for aid in the diagnosis of LVSD is present in primary care patients who have possible symptoms of CHF. Few studies have evaluated natriuretic peptides in this setting, and study populations are small or moderate. Furthermore, the prognostic significance of natriuretic peptides has not been tested in this group of patients.

Thus, the purpose of the current study was to (1) determine the sensitivity and specificity of a commercially available NT-proBNP assay to detect LVSD in consecutive primary care patients with suspected CHF who were referred for echocardiography and to (2) determine the ability of NT-proBNP to predict death in this clinically well-defined population.

Methods

Patients

The study population consisted of patients in whom heart failure was suspected clinically by their general practitioner (GP) and who had been referred for echocardiography at the Copenhagen General Practitioners’ Laboratory between May 1 and October 15, 2002. Patients with acute heart failure are not referred to this echocardiographic service. The Laboratory provides an echocardiographic diagnosis to the GP, and patients are treated subsequently at the discretion of the GP (ie, GP treatment or referral to a cardiologist or a hospital).

For all patients, a medical history was taken, and their medications were recorded. Furthermore, an electrocardiogram and an echocardiogram were recorded, and blood was drawn for hormone analysis. Mortality data were obtained from a national computer registry in which all deaths are recorded within 2 weeks of occurrence. All patients provided written consent for participation in the study, which was conducted in accordance with Helsinki Declaration.

NT-proBNP Analysis

Blood samples were centrifuged, and plasma was frozen at −80°C. Analysis of NT-proBNP was performed with a commercially available kit (Elecsys proBNP immunoassay; Roche Diagnostics Corporation, Indianapolis, Indiana). The method is a sandwich-type quantitative immunoassay that is based on polyclonal antibodies against epitopes in the N-terminal part of proBNP (amino acids, 1–76). The coefficient of variance of the Elecsys proBNP analysis in pooled human plasma samples with mean NT-proBNP values that varies from 175 to 6781 pg/mL is 2.2% to 3.2%. We applied the cut off value for NT-proBNP using Elecsys of 125 pg/mL, which has been approved by the Food and Drug Administration and separately applied the further recommendation to increase the cut-off value to 450 pg/mL for patients older than 75 years.13

Echocardiography

For all patients, a full echocardiographic and Doppler-echocardiographic study was performed by 1 of 2 experienced investigators (J.B., F.S-H.), who used a Sonos 4500 apparatus (Hewlett-Packard, Andover, Massachusetts). Left ventricular ejection fraction (LVEF) was estimated with the wall motion score index in patients with regional wall motion abnormalities.12 In patients with homogenous regional wall motion, LVEF was estimated by fractional shortening that was based on M-mode scans of the long-axis parasternal view.13 In either case, the results were controlled with an estimate of LVEF by means of measurement of atrioventricular plane displacement.14 Normal systolic function was defined as an LVEF in the range of 0.55 to 0.75. Echocardiograms were primarily classified as belonging to 1 of 3 categories: LVEF ≤0.30 (severe LVSD), LVEF ≤0.40 (moderate or severe LVSD), or LVEF >0.40 (normal systolic function or mild LVSD). The investigator who performed the echocardiographic study was blinded to the result of the NT-proBNP analysis.

Statistics

Values are presented as medians and 5th and 95th percentiles. NT-proBNP values are not normally distributed and therefore medians, rather than geometric means, were compared with the use of the Mann-Whitney U test. Sensitivity, specificity, and positive and negative predictive values were calculated with standard formulas. Receiver operating characteristic (ROC) curves were generated to illustrate the ability of NT-proBNP to detect the different levels of LVSD over the entire range of peptide cut-off values. The overall diagnostic accuracy of the test was estimated with the area under the ROC curve.15 To test the ability of NT-proBNP to predict death, Kaplan-Meier plots were generated by the dichotomization of patients at an NT-proBNP value of 125 pg/mL; statistical difference between the curves was tested by a log-rank test. Because NT-proBNP levels are known to depend on age and gender, the effect of NT-proBNP on mortality rates was further tested in a multivariable Cox analysis, with adjustment for the effect of age and gender. Furthermore, a model that contained the presence or absence of LVSD (LVEF ≤0.40) was constructed. In these models, NT-proBNP was log-transformed. All statistical calculations were performed with SPSS software (version 10.0.5; SPSS Inc, Chicago, Illinois). A probability value of <.05 was considered significant.

Results

Clinical Characteristics of the Study Population

A total of 367 patients were enrolled in the study. Their clinical characteristics are presented in Table 1. In 89% of the patients, the indication for referral was dyspnea; in 5% of the patients, an increased cardiothoracic ratio was the cause for referral, and in 3% of the patients, abnormal Q-waves on ECG prompted the referral. The remaining 3% were referred for other or no given reasons. Patients were elderly, with a slight predominance of female patients. Few patients were diagnosed previously with ischemic heart disease, atrial fibrillation, or diabetes mellitus, and the prevalence of known hypertension was modest. The relatively low prevalence of known existing cardiovascular disease was reflected in a low proportion of patients who used drugs such as diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. LVSD (LVEF ≤0.40) was found in 9% of the patients. Male gender (76% vs 43%; P < .0001) and ischemic heart disease (42% vs 10%; P < .0001) was more prevalent among patients with LVSD than among patients without LVSD.

Diagnosis

NT-proBNP was significantly higher in both the group with LVEF ≤0.30 and the group with LVEF ≤0.40 than in
the group with normal or near normal LVEF ($P < .0001$ for both). The sensitivity and specificity for the test to detect LVEF $\leq 0.30$ and LVEF $\leq 0.40$ are given in Table 2. The test proved fully sensitive to detect LVEF $\leq 0.30$, irrespective of whether the supplementary cut-off value for the elderly patients was used. Sensitivity to detect LVEF $=0.40$ was also high with the 125-pg/mL limit but was clearly lower when the age differentiated cut-off value was used. In either case, negative predictive value was close to 100%. The area under the ROC curve was 0.93 and 0.87 for the detection of LVEF $\leq 0.30$ and LVEF $=0.40$, respectively (Fig. 1). Elevated NT-proBNP (>125 pg/mL) was found in 180 patients with LVEF $>0.40$. In 22% of these patients, a normal echocardiogram was recorded. In the remaining 78% of patients, a number of different abnormalities were noted, the most common of which were mitral valve insufficiency (43%), aortic valve sclerosis (36%), and slightly reduced LVEF (range, 0.41–0.55; 23%).

### Prognosis

One patient was lost to follow-up because of immigration; therefore, the total number of patients for whom survival was available was 366. Median follow-up time was 778 days. During follow-up, 31 patients died (8%). NT-proBNP values of >125 pg/mL were associated with an increased risk of death ($P = .02$, log rank; Fig. 2). This result was not changed significantly if the differentiated cut-off value was used (<125 pg/mL at <75 years of age and 450 pg/mL at $\geq$75 years of age). Because the levels of natriuretic peptides depend on age and gender to some extent, these variables were entered together with logNT-proBNP into a Cox regression model. In this model logNT-proBNP significantly predicted death, with a hazard ratio of 2.2 (range, 1.2–3.8) per 1 unit increase in logNT-proBNP ($P = .009$). Adding to the model whether the LVEF was $<0.40$ did not change the results significantly (hazard ratio for logNT-proBNP, 2.2; range, 1.2–4.1; $P = .015$).

Of the 31 patients who died, 7 patients (23%) had NT-proBNP of $<125$ pg/mL. None of the patients with low NT-proBNP had LVSD on echocardiography at baseline. A review of the medical records of these 7 patients revealed that 6 of the patients had a malignant diagnosis at the time of death and thus presumably died of malignancy (1 pulmonary, 1 pancreatic, 2 colonic, 1 laryngeal, and 1 disseminated cancer without known primary tumor). The last patient died of heart disease.

### Discussion

The principal finding of the study is that NT-proBNP has a very high negative predictive value for ruling out LVSD in primary care patients with suspected heart failure. Further, it has demonstrated that NT-proBNP provides prognostic information in this group of patients independently of age, gender, and LVEF.

Several previous studies have validated the diagnostic performance of NT-proBNP in different populations compared with echocardiography, radionuclide ventriculography, and magnetic resonance imaging. The ability of brain natriuretic peptides to detect LVSD appears to be superior to that of atrial natriuretic peptides. A few medium-sized studies have compared BNP and NT-proBNP.
for diagnosis of LVSD, but so far no statistically significant differences in the diagnostic performance between BNP and NT-proBNP have been reported. However, in theory, NT-proBNP may have analytic advantages over BNP because of a longer half-life that results in higher plasma concentrations.

The present study demonstrates that low NT-proBNP levels effectively rule out significant LVSD in primary care patients with suspected CHF. In contrast, positive predictive values were modest and reflected the low prevalence of LVSD in the study population. These findings should be compared with diagnostic performance findings of B-type natriuretic peptide that previously were obtained in primary care patients. The results regarding positive and negative predictive values of natriuretic peptides agree well with 2 previous studies that were conducted in similar populations. In contrast, the diagnostic performance of NT-proBNP in our study was superior to that of BNP in stable patients who were treated for heart failure or long-term survivors after myocardial infarction. These 2 studies are, however, somewhat different from the current investigation. In contrast to the patients in our cohort, the patients in the 2 latter studies had been symptomatic for a longer time, and they generally were receiving more drug treatment. In our study, few patients were receiving cardiovascular drug therapy at baseline because, in most instances, no diagnosis had been made at that time. It has been shown that long-term treatment with beta-blockers and angiotensin-converting enzyme inhibitors lower levels of natriuretic peptides, which could in turn decrease diagnostic sensitivity. Thus, it is possible that the better diagnostic performance of NT-proBNP in the present study may relate to either the shorter duration of heart failure symptoms or the lower degree of drug treatment.

The prevalence of LVSD in the referred population of the current study was rather low (<10%), which implies that >10 echocardiograms must be performed to detect 1 patient with LVSD. Although slightly higher, this number is not very different from the results of previous echocardiographic studies of primary care patients with possible heart failure. When the results of the present study are applied, it appears that, among patients who are referred for echocardiography because the GP suspects CHF, a normal NT-proBNP value would be detected in 56% of the patients (using the
age-differentiated cut-off value); and in this group of patients, LVSD is very unlikely. However, despite of the high negative predictive value of NT-proBNP that was shown in our study, it is too early to say that echocardiography can safely be omitted in more than one half of the patients who are referred for evaluation. In particular, there are unresolved issues regarding the sensitivity of natriuretic peptide for the detection of other types of cardiac dysfunction that potentially require specific intervention (such as valvular disease and hypertrophic cardiomyopathy). Although good diagnostic performance of natriuretic peptides in aortic stenosis has been demonstrated recently, it is evident that more research on diagnostic sensitivity in these complex patient populations is needed. NT-proBNP analyzes cannot stand alone but must be interpreted in the clinical context of the patient. Thus, in patients with low NT-proBNP values but who have a high a priori risk of LVSD, the physician must proceed with further cardiologic evaluation.

The results of the present study indicate that NT-proBNP levels in primary care patients with suspected CHF carry prognostic information in terms of death risk. This was true even after controlling for potential confounders such as age and gender. Although, the prognostic significance of NT-proBNP has been demonstrated in several populations, both with and without heart failure, to our knowledge, it has not been reported previously for primary care patients with suspected CHF. Further, NT-proBNP appeared to add prognostic information when LVEF was entered into the model. Because of a limited number of events, it was not possible to control for more potential confounders such as diabetes mellitus or ischemic heart disease. Few patients with “normal” levels of NT-proBNP died during the follow-up period. None of these patients had LVSD, and most of them apparently died of malignant disease. NT-proBNP would not be expected to provide prognostic information in this group of patients, and the finding underlines the specificity of natriuretic peptides as a marker for cardiovascular disease and prognosis. On the basis of the data, it appears reasonable to conclude that primary care patients with suspected CHF who have normal NT-proBNP have a low cardiovascular mortality rate.

Conclusion

The present study demonstrated that NT-proBNP is highly effective in ruling out LVSD in primary care patients with suspected CHF. Moreover, NT-proBNP predicts subsequent death in this population, independently of other clinical variable such as age, gender, and LVEF.

References


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