N-Terminal Pro-Brain Natriuretic Peptide
A Powerful Predictor of Mortality in Hypertension

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Abstract—Natriuretic peptides are co-regulatory hormones associated with cardiac remodeling, namely, left ventricular hypertrophy and systolic/diastolic dysfunction. We intended to address the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) in hypertension. We prospectively studied the relationship between plasma NT-proBNP and all-cause mortality in 684 hypertensive patients with no history or symptoms of heart failure referred for hypertension workup in our institution from 1998 to 2008. After a mean duration of 5.7 years, we observed 40 deaths (1.04 deaths per 100 patients per year). After adjustment for traditional cardiovascular risk factors, including ambulatory blood pressure and serum creatinine, the risk for all-cause mortality more than doubled with each increment of 1 log NT-proBNP (hazard ratio: 2.33 [95% CI: 1.36 to 3.96]). The risk of death of patients with plasma NT-proBNP ≥133 pg/mL (third tertile of the distribution) was 3.3 times that of patients with values <50.8 pg/mL (first tertile; hazard ratio: 3.30 [95% CI: 0.90 to 12.29]). This predictive value was independent of, and superior to, that of 2 ECG indexes of left ventricular hypertrophy, the Sokolov-Lyon index and the amplitude of the R wave in lead aVL. In addition, it persisted in patients without ECG left ventricular hypertrophy, which allowed refining risk stratification in this relatively low-risk patient category. In this large sample of hypertensive patients, plasma NT-proBNP appeared as a strong prognostic marker. This performance, together with the ease of measurement, low cost, and widespread availability of NT-proBNP test kits, should prompt a wide use of this marker for risk stratification in hypertension. (Hypertension. 2011;57:702-709.)

Key Words: hypertension ■ NT-proBNP ■ survival ■ risk stratification ■ left ventricular hypertrophy

In hypertension, detection of cardiac damages is critical for risk stratification. 1 This is usually done by searching for left ventricular hypertrophy (LVH), a major predictor of cardiovascular events. 2,3 However, in clinical practice, LVH detection is subject to various limitations. ECG is recommended by most guidelines but has a poor sensitivity and is rarely performed in clinical practice. 4 Echocardiography is extensively used but is time-consuming, expensive, and not always feasible for technical reasons. The cost-effectiveness of its systematic use in hypertensive patients is still widely debated. 5 Thus, there is still room for new cardiac markers to be used for risk stratification.

In response to volume expansion and pressure load, ventricular myocytes release a cardiac hormone, the B-type natriuretic peptide (BNP), together with its amino-terminal fragment, the N-terminal proBNP (NT-proBNP). 6 BNP and NT-proBNP are strong prognostic markers in advanced stages of cardiac diseases like heart failure 7 or coronary disease. 8 They are also closely related to cardiac geometry and mass, 9 and we have recently demonstrated the good performance of plasma NT-proBNP for the diagnosis of LVH. 10 However, few data are available as to the prognostic value of natriuretic peptides in hypertension. Olsen et al 11,12 showed that NT-proBNP had a significant prognostic value in 2 complementary analyses of the Losartan Intervention for End Point Reduction substudy, that is, in highly severe hypertensive subjects with electric LVH. In a subset of hypertensives from the general population, Pedersen et al 13 confirmed this finding after adjustment for traditional risk factors.

These promising features prompted us to test the prognostic value of NT-proBNP on top of traditional risk factors, ambulatory blood pressure (BP), renal function, and ECG in a large sample of hypertensives of various severities consecutively referred to our center.

Methods

We performed a cohort study among patients referred to our institution (Cardiology Department, Hôpital de la Croix-Rousse) for
hypertension workup. The association between NT-proBNP and all-cause mortality was sought using a multivariate Cox analysis. To further investigate a modifying effect of LVH on this association, we performed a separated analysis in patients without LVH.

**Participants**

From 1998 to 2008, 712 consecutive patients were considered for inclusion. The exclusion criteria were history or symptoms of heart failure (N=21) or unknown vital status at the time of censoring (N=7, patients born outside France). Thus, 684 patients were finally included. The study was approved by the local review board. In accordance with the current French legislation, an observational study that does not change routine management of patients does not need to be declared or submitted to the opinion of a research ethics board. Informed consent was obtained from every patient.

**Protocol**

In view of a workup for hypertension, and whenever possible, drugs interfering with hormonal regulations were withdrawn before hospitalization (6 weeks for spironolactone and 2 weeks for diuretics, β-blockers, and renin-angiotensin system inhibitors) and replaced by α-blockers or calcium antagonists as recommended.

Every patient filled out a questionnaire and underwent a medical examination. Over a 2-day hospital stay, each had a 24-hour BP and an ECG. Although the 24-hour BP recording was in progress, a blood sample was drawn after 1 night recumbence for NT-proBNP measurement (standardized NT-proBNP) and routine biological tests, including hormonal measurements, as described elsewhere. In a series of 60 consecutive patients, an extra blood sample was been taken the day before, that is, at patient arrival, to measure NT-proBNP and compared with the same sample. An echocardiography was performed with a Vivid 5 ultrasound device (GE Healthcare). In patients with an optimal recording, left ventricular ejection fraction was calculated according to the Teicholz formula. All of the tests performed were part of the department routine evaluation of hypertensive subjects. At discharge, patients usually resumed their previous treatment regimen.

Smoking status was based on current tobacco consumption. Diabetes mellitus and hyperlipidemia were defined as either a history or a current treatment of these conditions. Cardiovascular history includes any notion of myocardial infarction, angina pectoris, stroke, or transient ischemic attack. Renal disease was defined as a serum creatinine ≥133 μmol/L in men and 124 μmol/L in women.1

**Twenty-Four–Hour BP Recordings**

Twenty-four-hour BP recordings used SpaceLabs monitors. Daytime BP was recorded at 15-minute intervals from 7:00 AM to 10:00 PM and was considered for analysis. In 5% of the patients, the 24-hour BP could not be obtained; it was then replaced by a 1-hour BP measurement by an automatic device (Dinamap-1 measurement every 5 minutes in daytime).

**NT-proBNP Measurements**

Plasma concentrations of NT-proBNP were measured by an electrochemiluminescence immunoassay using an Elecsys 2010 analyzer (Roche Diagnostics). The range of values was 5 to 35 000 pg/mL, and the coefficient of variation was between 1.0% and 2.5%.15

**ECG Criteria of LVH**

For the first two thirds of the cohort, ECGs were analyzed manually, whereas amplitudes and durations of the ECGs of the last third were assessed automatically by dedicated software (Cardiosksoft Version 5, GE Medical Systems). Because it is undoubtedly the most widespread (even if not the best) index of LVH, the Sokolov-Lyon index (SV1+RV5 or V6) was considered as a criterion for LVH. It was used to estimate the prevalence of LVH with a 35-nV cutoff. The R-wave amplitude in lead AVL (RaVL), one of the two components of the Cornell voltage, was also considered as a significant prognostic factor in hypertension.16 Because there is no indisputable threshold yet, this index was used only as a continuous variable.

**Outcomes**

To avoid misclassification of causes of death17 and to collect enough events, all-cause mortality was selected as an objective end point. The vital status could be obtained for all of the participants either through standardized questionnaires filled out separately by the patients and their physicians or through the French office of civil registration.

**Data Analysis**

Continuous data are presented as medians (5th to 95th percentiles) and compared with the t test, 1-way ANOVA, Mann-Whitney, or Kruskall-Wallis test for independent samples. Categorical data were expressed as percentages, and differences in proportion were compared with the χ2 test, as appropriate. We examined the association between the baseline levels of plasma NT-proBNP and all-cause mortality. Because there is no definitive cutoff of NT-proBNP in the literature, we separated our population according to tertiles of NT-proBNP. We first analyzed the survival in these 3 groups by building event-free survival curves according to the Kaplan-Meier product limit method and using the Mantel (log-rank) test for comparisons across tertiles.

In a subsequent analysis, NT-proBNP was log-transformed and considered as a continuous variable. Hazard ratios (HRs) and their 95% CIs were assessed for overall mortality using Cox regression analysis. Multiplicative interactions with age (considered as a continuous variable), sex, ECG LVH (considered as a dichotomous variable), treatment, and secondary hypertension were tested in limited models, including log-transformed NT-proBNP, the potential modifying variable, and its multiplicative term with NT-proBNP. A “full adjustment model” was then built with the following large series of predefined potential confounders, significant or not in univariate analyses: age, systolic BP, sex, hyperlipidemic status (or total cholesterol), diabetic status (or blood glucose), smoking status, body mass index, history of cardiovascular disease, and renal/cardiac markers, that is, creatinine and Sokolov (or RaVL). The proportional hazards hypothesis was tested by introducing into the model a NT-proBNP-by-time interaction covariate (T × log NT-proBNP). To limit the number of events per variable tested, a restricted model was also built with only the variables found significantly associated with all-cause mortality in univariate analyses. To further rule out effect modification by LVH, these analyses were repeated in a subgroup of patients without ECG LVH. Statistical analyses were performed using SPSS 15 software (SPSS Inc). A P value <0.05 was considered to indicate statistical significance.

**Results**

**Baseline Characteristics**

Table 1 presents the general characteristics of the whole patient cohort and of the 3 groups of NT-proBNP defined by the following thresholds: (1) group 1, <50.8 pg/mL; group 2, 50.8 to 133 pg/mL (excluded); and (3) group 3, ≥133 pg/mL. The cohort was characterized, on average, by a moderately elevated BP and a rather low prevalence of LVH by ECG criteria. Twelve percent of the patients had a primary aldosteronism (defined by plasma aldosterone >416 pmol/L and aldosterone/active renin ratio >140 pmol/mg), whereas other etiologies (Cushing syndrome, pheochromocytoma, etc) concerned a very limited number of patients (∼1%). Plasma NT-proBNP was low but exhibited a wide interindividual variability. Globally, the cardiovascular risk profile worsened with increasing tertiles. The proportion of patients belonging to each tertile as a function of LVH, diabetes mellitus, and renal disease is given in Table S1 (available in the online Data
Supplement, please see http://hyper.ahajournals.org). Among patients with a reliable echocardiography, most had a normal ejection fraction (Figure S1, available in the online Data Supplement).

Reproducibility of NT-proBNP Tests
As illustrated in Figure S2, ambulatory NT-proBNP values and values after 1 night of recumbence were highly correlated (r=0.93; P<0.0001), and their medians were very close (72.8 versus 61.4 pg/mL, respectively). The coefficient of variation was 5.6%, in favor of a good reproducibility despite various sampling conditions.

Predictors of Outcomes in the Whole Cohort
The mean cohort follow-up was 5.7 years (3913 patient-years). During follow-up, 40 participants died (3 in group 1, 11 in group 2, and 26 in group 3), which corresponds with an incidence of 1.04 deaths per 100 patients per year. A comparison of the baseline characteristics of patients with and without outcome is presented in Table S2. Figure 1 shows
The survival curves relative to the 3 groups of NT-proBNP levels. It illustrates the deterioration of the prognosis associated with increasing NT-proBNP levels.

Table 2 displays both unadjusted and adjusted HRs for plasma NT-proBNP and for traditional risk factors, expressed either as a continuous or as a categorical variable. In univariate analyses, age, systolic BP, the presence of diabetes mellitus, and serum creatinine were significant predictors of all-cause mortality, whereas hyperlipidemia, smoking, or Sokolov index were not associated with the outcome. Considering blood glucose, total cholesterol, and RaVL instead of the Sokolov index, the RaVL was not found associated with the outcome (HR: 1.01 [95% CI: 0.92 to 1.10]). In any case, these changes in covariates had no impact on the significance of the association between log NT-proBNP and outcomes. When plasma NT-proBNP was used as a categorical variable, belonging to groups 2 and 3 was associated with 1.99 [95% CI: 0.53 to 7.51] and 3.30 [95% CI: 0.90 to 12.29] increased risks of death in comparison with group 1, respectively (Table 2).

Similar results were observed with the restricted model that included only age, creatinine, systolic BP, diabetic status, and log NT-proBNP. Age and log NT-proBNP were again the only significant predictors of mortality (HR: 1.084 [95% CI: 1.050 to 1.120] and HR: 1.700 [95% CI: 1.240 to 2.330], respectively).

Predictors of Outcomes in Patients Without ECG LVH

After exclusion of all of the patients presenting LVH by the Sokolov criteria, 569 patients were left for analysis. As shown in Table 3, these patients had the same risk profile as the entire group, although plasma NT-proBNP level was slightly lower than that of the whole group (78 versus 82 pg/mL). In this subset, 33 patients died during follow-up. Again, groups 2 and 3 were associated with a marked increase of all-cause mortality (Figure 2). After adjustment, log NT-proBNP remained a significant predictor of outcome in the group free from LVH, with HRs similar to those obtained with the whole cohort, whatever the model used, fully adjusted or restricted (data not shown).
Discussion

The present study shows that plasma NT-proBNP is a powerful prognostic indicator of mortality in hypertension, independent of (and superior to) 2 easily obtainable ECG markers, the Sokolov index and the RaVL amplitude. In addition, it can also be used in patients with no detectable ECG LVH, that is, in the majority of hypertensive patients seen in primary care, to improve risk stratification.

LVH detection is important for risk stratification; in all of the current guidelines, the first step relies on ECG that, by several indexes, allows for estimating the presence of this condition. Because our study aimed at evaluating a strategy for routine evaluation of hypertensive patients by noncardiologist physicians, echocardiography was not considered in the analysis. Moreover, we favored the use of a very widespread ECG index of hypertrophy, that is, the Sokolov-Lyon index. Because of its known limitations, like, for example, the interaction with body mass index,18 we also used the amplitude of R wave in lead aVL, proposed recently by Verdecchia et al16 as a simple marker of cardiovascular risk. The latter indicator appears to play a predominant role in the Cornell voltage, another ECG marker of LVH,16 less dependent on body mass index.18

In addition, as we and other groups have shown,10,19,20 natriuretic peptides are also able to spot LVH in hypertension. To our knowledge, there have been only 2 attempts to investigate other roles of these peptides than ventricular remodeling in hypertension. Pedersen et al13 reported that NT-proBNP predicts the risk of a composite end point made of death, stroke/transient ischemic attack, and myocardial infarction in a subset of hypertensives from an urban area of Copenhagen. However, the small size of the study did not permit a definite conclusion. An additional piece of evidence was obtained by Olsen et al11,12 based on 2 successive analyses of subgroups from the Losartan Intervention for End Point Reduction Study: NT-proBNP levels were strongly associated with cardiovascular events in patients with hypertension and LV hypertrophy. Yet, these findings were ham-

Table 3. Baseline Characteristics and Their Adjusted HRs in Patients Without LVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Values</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53 (30 to 75)</td>
<td>1.08 (1.04 to 1.12)†</td>
</tr>
<tr>
<td>History of cardiovascular disease, Y:1, N:0</td>
<td>13/87</td>
<td>1.15 (0.49 to 2.71)</td>
</tr>
<tr>
<td>Sex, M:1, F:0</td>
<td>50/50</td>
<td>1.77 (0.74 to 4.25)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>154 (124 to 192)</td>
<td>1.00 (0.96 to 1.02)</td>
</tr>
<tr>
<td>Diabetes mellitus, Y:1, N:0</td>
<td>13/87</td>
<td>1.78 (0.73 to 4.31)</td>
</tr>
<tr>
<td>Hyperlipidemia, Y:1, N:0</td>
<td>31/69</td>
<td>0.82 (0.37 to 1.79)</td>
</tr>
<tr>
<td>Smoking status, Y:1, N:0</td>
<td>21/79</td>
<td>0.55 (0.20 to 1.52)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>80.5 (56 to 121)</td>
<td>1.00 (0.99 to 1.02)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 (19.8 to 36.2)</td>
<td>0.90 (0.81 to 1.00)*</td>
</tr>
<tr>
<td>Sokolov, mm</td>
<td>23 (12 to 34)</td>
<td>0.96 (0.91 to 1.02)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL§</td>
<td>78 (17 to 562)</td>
<td>2.39 (1.26 to 4.55)†</td>
</tr>
<tr>
<td>Time×log NT-proBNP interaction</td>
<td>…</td>
<td>0.90 (0.80 to 1.01)</td>
</tr>
</tbody>
</table>

Baseline values are expressed as percentages for categorical variables and medians (5th to 95th percentiles) for continuous ones. Y indicates yes; N, no; M, male; F, female.

*P<0.05.
†P<0.01.
‡P<0.001.
§Log NT-proBNP was used for Cox regression analysis.

Figure 2. Survival curves relative to the 3 plasma NT-proBNP groups in patients free from ECG LVH (N=569).
pered by the fact that the study populations were highly selected; indeed, in terms of target organ damages, all of the subjects had an LVH by ECG criteria, whereas the prevalence of LVH in hypertensive cohorts is usually \(\approx 15\%\). In addition, according to the current guidelines, all of the patients considered in the Losartan Intervention for End Point Reduction substudies could already be considered at high risk, which reduces the interest of a further risk stratification.

Our study adds several important pieces of information: (1) it confirms the prognostic value of plasma NT-proBNP in a large sample of hypertensive patients for all-cause mortality; (2) it, thus, extends the results of previous studies to most hypertensive patients (indeed, our study cohort was comparable to other primary care cohorts, particularly concerning LVH prevalence, at 14.4% and 15.0%, respectively); (3) it confirms that the prognostic value of plasma NT-proBNP in predicting mortality is independent of a large series of traditional risk factors, including ambulatory BP or renal function; (4) it shows that this prognostic value is independent of, and superior to, 2 ECG indexes of LVH; and (5) it shows that plasma NT-proBNP keeps its prognostic significance after exclusion of patients with an LVH by ECG criteria, emphasizing the role of this marker in the very difficult task of improving risk stratification in patients with low risk (ie, with “normal ECG”).

**Plasma NT-proBNP and Outcomes**

BNP and NT-proBNP plasma levels are higher in hypertensive than in normotensive patients; they are also elevated with LVH. Because of its longer half-life, lower intra-individual variability, and ability to detect subtle preclinical cardiac changes, NT-proBNP was selected in the present study in accordance with the results of previous studies. We verified that the conditions of measurements (ambulatory or during a hospital stay after a night of recumbency) did not modify substantially the plasma levels of this natriuretic peptide, confirming its excellent intra-individual reproducibility and robustness. Secondary forms of hypertension, mainly primary aldosteronism, were not excluded, because they are also concerned by risk stratification when encountered in primary care. They did not interact with the association between NT-proBNP and outcome. The small number of lost-to-follow-up patients, mainly those born abroad, strengthens, of course, the validity of our results. Moreover, we considered 2 multivariate models. The restricted model led to 8 events per variable tested, which increased our confidence in the validity of the statistical model. We also performed an extensive adjustment for classic risk factors, including ambulatory BP and renal function, to take into account most major confounders. We then checked that the prognostic value of NT-proBNP was independent of ECG by including each of our 2 ECG markers of LVH in turn into the multivariate model and by looking for interactions. In all of the cases, after age, plasma NT-proBNP was the most powerful predictor of mortality without any modifying effect of ECG markers. Consistently, NT-proBNP kept its prognostic value after exclusion of patients with ECG LVH.

Having a plasma NT-proBNP level of \(\geq 133\) pg/mL (the highest tertile) is associated with a 3-fold increase of the risk of death in comparison with having levels \(< 50.8\) pg/mL, even after adjustment for confounders. In this respect, note that the former value is very close to the values reported previously by our group as diagnostic thresholds for LVH, that is, 111 pg/mL in men and 144 pg/mL in women. It is also close to the values reported in available prospective studies. Indeed, in a population free of heart failure, McKie et al showed that a threshold at \(109\) pg/mL was of prognostic value for mortality, a value close to that reported by Rutten et al in the Rotterdam Study. More specifically, in hypertension, Olsen et al demonstrated in the Losartan Intervention for End Point Reduction substudy the prognostic value of a 170-pg/mL cutoff, selected as the median value of this high-risk population. Taken as a whole, our results are coherent and confirm the powerful prognostic value of plasma NT-proBNP in a large hypertensive cohort fairly representative of that seen in primary care.

**Pathophysiological Link Between NT-proBNP and Prognosis**

Although we did not have cause-specific mortality data, we may reasonably assume that NT-proBNP is mostly related to cardiovascular outcomes and, consequently, to cardiovascular mortality. Natriuretic peptides are related to cardiac mass, systolic dysfunction, increased filling pressure, and myocardial ischemia. As a result, natriuretic peptides are related to the risk of atrial fibrillation. Natriuretic peptides also depend strongly on ventricular afterload, particularly BP and aortic stiffness. This may be translated into a strong association with the risks of future heart failure, coronary event, and stroke in the general population. In this respect, natriuretic peptides act as integrative markers able to predict outcomes beyond cardiac events.

**Limitations**

Although only a few patients had asymptomatic decreased ejection fraction, no information was available on diastolic function and filling pressure that could represent a confounder of our relationships. A significant proportion of the patients included in our study might have had asymptomatic diastolic dysfunction. Nevertheless, this would not have limited the value of NT-proBNP as a screening test, because patients with a diastolic dysfunction would have been detected and correctly identified as high-risk subjects.

The predictive value of NT-proBNP was independent of classic confounders, such as body mass index or serum creatinine, which suggests that overweight or mild renal alteration should not represent a major limitation of its performance, as suggested previously. Of course, an effect of severe obesity or advanced renal failure cannot be ruled out.

The study was performed in a tertiary healthcare institution, and most patients were treated, which might have diminished the generalizability of the results. However, the baseline characteristics indicated that the studied population had a fairly low-risk profile. Furthermore, no interaction was disclosed between treatment and NT-proBNP in terms of outcome prediction. Consequently, we believe that the patients included in the present study may well be taken as...
everyday hypertensive patients. Of note is the fact that renin-angiotensin system blockers were usually interrupted, whereas they have been shown to decrease natriuretic peptide levels.3,5 Further studies on standard therapy are thus needed to refine prognostic cutoffs.

Although the number of events was low, the statistical power was sufficient to disclose all of the strong relationships, thus strengthening the prognostic value of plasma NT-proBNP. However, cardiovascular mortality and morbidity could not be studied, which is of course a limitation in the assessment of the pathophysiological link between NT-proBNP and mortality.

Clinical Perspectives

Despite the guidelines, of which unequivocal statements recommend the use of ECG in every hypertensive, ECG is actually used routinely in only 11% of hypertensives. A systematic use of echocardiography, which is not recommended, would be neither feasible nor desirable on an economic basis. NT-proBNP adds significant prognostic information to the conventional Framingham-type risk factors and, in our hands, performed better than ECG. Thus, our results, together with other available reports, promote the use of NT-proBNP as an easy and powerful predictive marker that could be used in every hypertensive patient to improve the risk stratification. In this respect, it would probably perform better than the Sokolov index for 2 reasons: it was more predictive of mortality in our study, and it may be extended to all patients more easily than ECG. On basis of the literature and on the present results, a threshold of ~130 pg/mL may be proposed but has to be confirmed by other studies with different medications. Despite similar prognostic abilities in men and women, the usefulness of different thresholds cannot be excluded, as suggested previously for the diagnosis of LVH. Similarly, a higher threshold may be indicated in obese patients. Finally, the question of whether plasma levels of NT-proBNP may be used as surrogate end point for treatment adjustment is raised.

In conclusion, in a large group of hypertensive patients with various cardiovascular risk profiles, plasma NT-proBNP appears as a strong prognostic index. This performance, together with the ease of measurement, low cost, and widespread availability should prompt a wide use of this marker for risk stratification in hypertension, at least in patients with normal ECG, but also in most hypertensive patients.

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Disclosures

None.

References


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