Heart Failure

Prognostic Value of Changes in N-Terminal Pro-Brain Natriuretic Peptide in Val-HeFT (Valsartan Heart Failure Trial)

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Objectives	This study sought to evaluate the association between changes over time of N-terminal pro-brain natriuretic peptide (NT-proBNP) expressed in different ways and outcome in patients with stable and chronic heart failure (HF).
Background	Although previous studies examined the prognostic value of repeated determinations of BNP in HF, there are only limited data on the clinical utility of serial measurements of the inactive peptide NT-proBNP in a large population of ambulatory patients with chronic HF with sufficient follow-up time.
Methods	The NT-proBNP was measured at randomization and after 4 months in 1,742 patients enrolled in the placebo arm of Val-HeFT (Valsartan Heart Failure Trial). Changes in NT-proBNP concentrations over 4 months were expressed as absolute change from baseline, percent relative changes, or categorical changes across a threshold value and related to subsequent mortality.
Results	A single determination of NT-proBNP (area under the curve at 4 months: 0.702, 95% confidence interval [CI]: 0.669 to 0.735) showed a higher prognostic discrimination than continuous changes of concentrations, expressed either as absolute (0.592, 95% CI: 0.549 to 0.634) or relative changes (0.602, 95% CI: 0.566 to 0.639). A Cox proportional hazards model showed that stratification of patients into 4 categories according to NT-proBNP levels at 2 time points 4 months apart with respect to a threshold concentration provided prognostic information in patients with chronic HF beyond that of a single determination.
Conclusions	Serial determinations of NT-proBNP concentration and classification into few categories of changes according to threshold levels may be a superior strategy for risk stratification of patients with chronic and stable HF. (J Am Coll Cardiol 2008;52:997–1003) © 2008 by the American College of Cardiology Foundation

A single measurement of a natriuretic peptide at any time during the progression of chronic heart failure (HF) provides a clinically useful tool for risk stratification in different clinical settings (1,2). Elevation of natriuretic peptides concentration (brain natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]), in particular in patients with acutely decompensated HF, predicts adverse outcomes such as death or readmission in hospital for HF. Both peptides

are the strongest prognostic circulating biomarkers, even in the presence of robust clinical risk factors in HF, such as age, New York Heart Association (NYHA) functional class, or ischemic etiology (3–5). There are, however, fewer reports on the clinical utility of serial biomarker testing in ambulatory patients

with chronic HF. In the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) pilot study (6), baseline and 17-week changes in N-terminal pro-atrial natriuretic peptide were independently associated with death and HF hospitalization in 768 patients with left ventricular (LV) systolic dysfunction and HF. In addition, elevation of BNP at any time during clinical follow-up predicted an increased risk of events in 190 ambulatory patients with chronic HF (7).

In Val-HeFT (Valsartan Heart Failure Trial), serial measurements and changes in BNP concentration over time

**Abbreviations
and Acronyms**

AUC = area under the
receiver-operator
characteristic curve

BNP = brain natriuretic
peptide

CI = confidence interval

cTnT = cardiac troponin T

HF = heart failure

HR = hazard ratio

LV = left ventricular

LVEF = left ventricular
ejection fraction

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

NYHA = New York Heart
Association

ROC = receiver-operator
characteristic

were associated with outcomes in a large population of patients (~4,000) with chronic and symptomatic HF (3,8). In the same trial, the amino-terminal fragment of BNP (NT-proBNP) showed only subtle differences in terms of prognostic value when compared with the active hormone BNP (9). Here, we aimed at determining whether serial determinations of NT-proBNP can also provide useful clinical information in a large, well-characterized population of patients with chronic, stable, and symptomatic HF with sufficient follow-up time.

Methods

Study design and patients. The Val-HeFT study was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial. A total of 5,010 patients with stable, symptomatic HF who were on prescribed HF therapy and had left ventricular ejection fraction (LVEF) <40% and left ventricular diameter in diastole adjusted for body surface area ≥2.9 cm/m^2 were enrolled in the study (10). To avoid the confounding effect of the randomized active treatment (valsartan) on the concentrations of NT-proBNP over time, the present analyses were performed on patients enrolled in the placebo arm of the trial who had NT-proBNP measured at study entry and after 4 months of follow-up (n = 1,742).

Measurement of NT-proBNP. Blood samples were collected on potassium-ethylenediaminetetracetic acid at study entry and after 4 months for measurement of NT-proBNP with an electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Rotkreuz, Switzerland), as reported (9). The intra-assay coefficient of variation was 2.9%, and the interassay coefficient of variation was 3.6%. The reference value in 377 age-matched apparently healthy volunteers (mean age 60 ± 4 years, 76% male) was a median of 38 pg/ml (range of Q1 to Q3: 20 to 73 pg/ml, 95th percentile = 157 pg/ml).

Statistical methods. Outcome was adjudicated by a central end point committee. The independent prognostic contribution of baseline and 4-month concentrations of NT-proBNP (considered log-transformed variables), in addition to the variables that were clinically relevant and statistically significant, was assessed in incremental Cox proportional hazards models by the likelihood ratio test.

Changes in NT-proBNP concentration from baseline to 4 months were expressed by 3 different methods: absolute change from baseline, percent relative change from baseline, and categorical changes. Absolute and percent relative changes from baseline were analyzed by quartiles for subsequent mortality. For categorical changes, patients with NT-proBNP measurements available at baseline and 4 month follow-up were divided into 4 groups, based on changes in NT-proBNP concentrations from baseline to 4 months across a threshold level. This level was calculated as the concentration of NT-proBNP at baseline that gave the highest prognostic accuracy for mortality (product of specificity and sensitivity) by univariate time-dependent receiver-operator characteristic (ROC) curve (1,078 pg/ml, specificity 0.619, sensitivity 0.619). We defined 4 categories:

1. low→low (patients with NT-proBNP below the threshold concentration of 1,078 pg/ml at baseline and after 4 months)
2. high→high (patients with NT-proBNP above the threshold at baseline and after 4 months)
3. high→low (patients with NT-proBNP above the threshold at baseline and below after 4 months)
4. low→high (patients with NT-proBNP below the threshold at baseline and above after 4 months)

Cumulative survival estimates were presented as Kaplan-Meier curves for the 4 categories and compared using the log-rank test.

The prognostic discrimination of a single determination (baseline or 4 months) or continuous changes over time (absolute or percent) of NT-proBNP concentration was assessed by time-dependent univariate ROC curves (11). This was evaluated by the area under the ROC curve, which is equivalent to the C-index. Comparisons between the areas under the ROC curves were performed by pairwise method with the use of U statistics (12). A Cox proportional hazards model was used to compare the risk of death in each category using the low→low group as a reference category. Baseline or 4-month concentrations of NT-proBNP were also included in the model because they were the strongest predictors of outcome. The model was adjusted for all variables that were found to be statistically significant in the univariate analysis (age, body mass index, serum creatinine at baseline, ischemic etiology of HF, NYHA functional class, LV ejection fraction and diameter, and prescription of digoxin and diuretics).

All probability values are 2-tailed at 5% significance level. Analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, North Carolina) and the libraries Hmisc and survivalROC of the R language (13).

Results

Baseline characteristics. Table 1 summarizes the clinical and demographic features of the patients at baseline. The population was predominantly male (80.6%) with a mean age of 63 ± 11 years. Over 37% of patients were in NYHA functional classes III and IV; the mean LVEF was 27%. Median (Q1 to Q3) concentrations of NT-proBNP were

Table 1	Baseline Demographic and Clinical Characteristics
	n = 1,742
Age (yrs), mean ± SD	63 ± 11
Male, n (%)	1,404 (80.6)
NYHA functional classes III to IV, n (%)	647 (37.1)
Ischemic etiology, n (%)	1,004 (57.6)
LVEF (%), mean ± SD	27 ± 7
BMI ≤22 kg/m^2, n (%)	174 (10.0)
LVIDd (cm), mean ± SD	6.93 ± 0.91
Heart rate (beats/min), mean ± SD	73 ± 11
Sitting SBP (mm Hg), mean ± SD	125 ± 19
Serum creatinine (μmol/l), mean ± SD	112 ± 26
Serum bilirubin (μmol/l), mean ± SD	11.3 ± 5.9
ACEi, n (%)	1,635 (93.9)
Beta-blockers, n (%)	664 (38.1)
Digoxin, n (%)	1,177 (67.6)
Diuretics, n (%)	1,461 (83.9)
NT-proBNP at entry (pg/ml), median (Q1–Q3)	861 (368–1,803)
NT-proBNP at 4 months (pg/ml), median (Q1–Q3)	783 (327–1,781)

ACEi = angiotensin-converting enzyme inhibitor; BMI = body mass index; LVEF = left ventricular
ejection fraction; LVIDd = left ventricular internal diameter in diastole; NT-proBNP = N-terminal
pro-brain natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure;
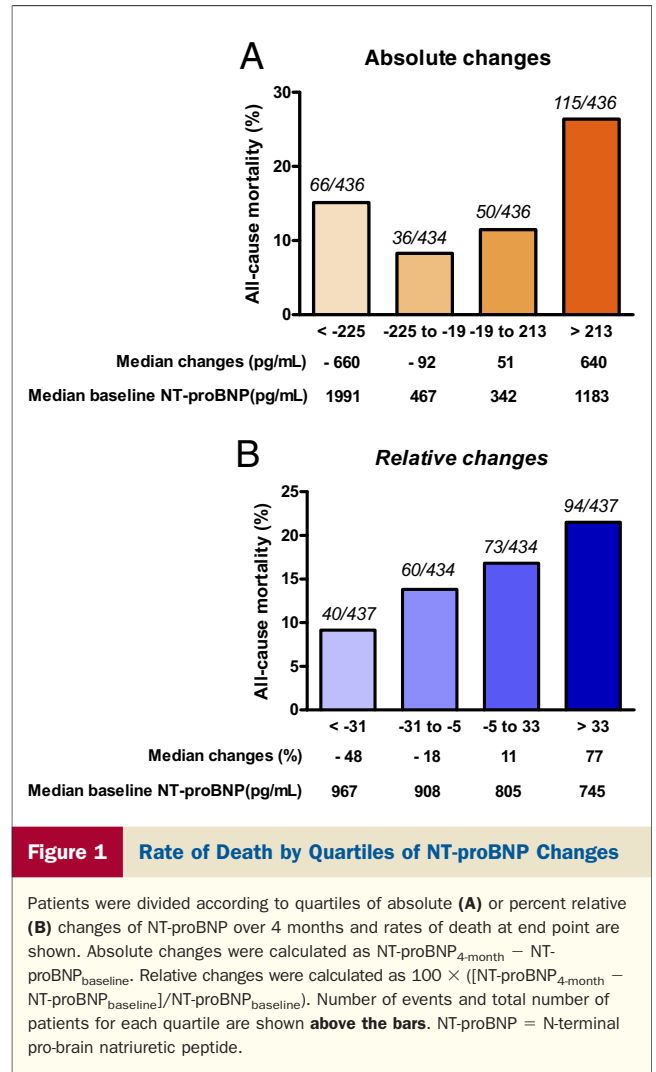Q = quartile.

861 (368 to 1,803) pg/ml at baseline and 783 (327 to 1,781) pg/ml after 4 months of follow-up (n = 1,742).

Two hundred and sixty-seven patients died during a median follow-up time of 24.5 months. Patients who died before 4 months of follow-up (n = 117) were excluded from the analysis related to changes in NT-proBNP concentration and subsequent mortality. Baseline NT-proBNP, entered as a continuous log-transformed variable, was the strongest independent predictor of mortality in a multivariate model that included all of the significant clinical risk factors (hazard ratio [HR]: 1.403, 95% confidence interval [CI]: 1.241 to 1.585, chi-square: 29.47, p < 0.0001) (Table 2). The other significant variables in this model were (by decreasing order of chi-square): LV internal diameter, prescription of beta-blockers, NYHA functional class, and ischemic etiology of HF. Addition of the concentration of NT-proBNP measured at 4 months in the previous model provided incremental prognostic value as evaluated by the likelihood ratio test (increment of chi-square by 42, p < 0.0001 for 1° of freedom). In this new model, NT-proBNP at 4 months was associated with a significant risk of all-cause mortality (HR:

Table 2	Predictors of All-Cause Mortality by Multivariable Cox Regression Analysis		
Variable	HR (95% CI)	Chi-Square	p Value
Baseline NT-proBNP (1 increment on log scale)	1.403 (1.241–1.585)	29.47	<0.0001
Left ventricular internal diameter >6.8 cm	1.696 (1.305–2.204)	15.61	<0.0001
Prescription of beta-blockers	0.589 (0.444–0.781)	13.52	0.0002
NYHA functional classes III to IV	1.560 (1.216–2.001)	12.21	0.0005
Ischemic etiology of heart failure	1.447 (1.118–1.872)	7.87	0.0050

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

| Figure 1 | Rate of Death by Quartiles of NT-proBNP Changes |

Patients were divided according to quartiles of absolute **(A)** or percent relative **(B)** changes of NT-proBNP over 4 months and rates of death at end point are shown. Absolute changes were calculated as NT-proBNP$_{4\text{-month}}$ − NT-proBNP$_{baseline}$. Relative changes were calculated as $100 \times$ ([NT-proBNP$_{4\text{-month}}$ − NT-proBNP$_{baseline}$]/NT-proBNP$_{baseline}$). Number of events and total number of patients for each quartile are shown **above the bars**. NT-proBNP = N-terminal pro-brain natriuretic peptide.

1.993, 95% CI: 1.616 to 2.459, chi-square: 41.43, p < 0.0001). When the concentration of NT-proBNP at 4 months was entered in the model, baseline NT-proBNP remained a marginal predictor (HR: 0.776, 95% CI: 0.623 to 0.965, chi-square: 5.18, p = 0.0228). These models did not include other circulating biomarkers, such as BNP. However, in a separate multivariate analysis considering BNP instead of NT-proBNP, the strongest predictor for the risk of death was BNP (for each increment of 50 pg/ml, HR: 1.072, 95% CI: 1.050 to 1.095, chi-square: 43.57, p < 0.0001).

Absolute and relative changes of NT-proBNP at 4 months and prognosis. Because 4-month NT-proBNP was strongly associated with 2-year mortality, we assessed whether changes in NT-proBNP between baseline and 4 months would be a better predictor of outcome than a single determination. Three different methods, commonly used for expressing changes of concentrations, were compared in the same patient cohort. Figure 1A shows the relationship between quartiles of absolute change in NT-proBNP from baseline to 4 months and subsequent death. Patients who

had the greatest absolute decrease (<-225 pg/ml) or greatest absolute increase ($>+213$ pg/ml) in NT-proBNP over the 4-month period had the highest mortality (15.1% and 26.4%, respectively). Conversely, patients with intermediate changes, between -225 and $+213$ pg/ml over the 4 months, had the lowest mortality (8.3% and 11.5%, respectively). This is probably explained by the fact that patients with the greatest absolute changes (either positive or negative) had the highest baseline concentrations of NT-proBNP, compared with the 2 groups of patients with intermediate absolute changes (Fig. 1A). On the other hand, there was a progressive increase in the rate of all-cause mortality (Fig. 1B) across quartiles of percent relative changes in NT-proBNP, from 9.2% in quartile 1 (reduction >31%) to 21.5% in quartile 4 (increase >33%, chi-square: 27.2, $p < 0.0001$). To further test the association between relative changes in NT-proBNP and outcome across the whole range of NT-proBNP concentrations, we divided patients into quartiles of baseline NT-proBNP concentration. The independent predictive value (from baseline concentration) of relative changes of NT-proBNP over 4 months was estimated separately in each quartile with multivariate Cox models, including the variables associated with outcome in univariate analyses (Table 3). In these models, relative changes in NT-proBNP resulted as robust and significantly independent predictors of subsequent mortality in all of the 4 quartiles of NT-proBNP concentration.

We compared the prognostic discrimination of a single determination of NT-proBNP (baseline or 4 months) versus continuous changes, expressed as either relative (percent) or absolute changes, using time-dependent ROC analyses (Fig. 2). The single determination of NT-proBNP at 4 months had the greatest prognostic accuracy (area under the receiver-operator characteristic curve [AUC]: 0.702, 95% CI: 0.669 to 0.735, $p < 0.0001$ versus baseline NT-proBNP) followed by baseline NT-proBNP levels (AUC: 0.659, 95% CI: 0.624 to 0.690). Absolute and relative (percent) changes from baseline had overall lower prognostic discrimination (AUC: 0.592, 95% CI: 0.549 to 0.634, $p = 0.026$; and AUC: 0.602, 95% CI: 0.566 to 0.639, $p = 0.046$, respectively).

Categorical changes of NT-proBNP. Kaplan-Meier survival curves for patients classified by categorical changes are
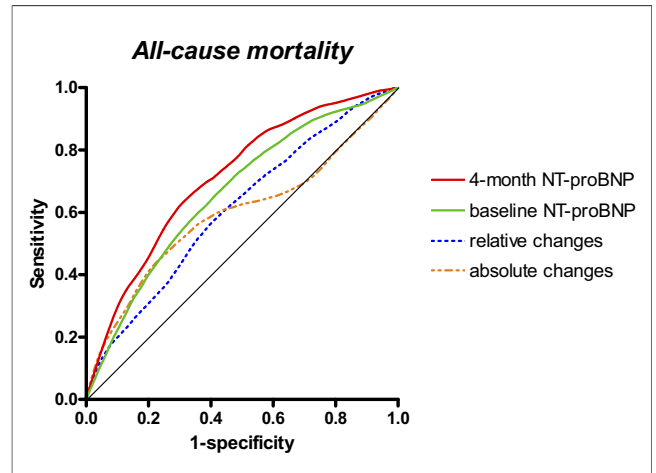

Figure 2 **Time-Dependent Receiver-Operator Characteristic Curves for All-Cause Mortality**

Curves are based on univariate models of the prediction of risk at 24 months with single determinations of NT-proBNP at baseline or 4 months or as percentage relative or absolute changes from baseline. Areas under the curves were compared with the C-index. NT-proBNP = N-terminal pro-brain natriuretic peptide.

presented in Figure 3. The outcome of the 125 patients who had an NT-proBNP concentration above the ROC's optimal prognostic cutoff value (1,078 pg/ml) at baseline but below this level at 4 months (high→low) was comparable with those 904 patients who had levels below the cutoff value at the 2 time-points (low→low, end point mortality 7.2% vs. 8.9%). Likewise, outcome was similar in patients who maintained high levels of NT-proBNP (n = 599, mortality 25.7%) compared with those with worsened level of NT-proBNP (low→high, n = 114, mortality 21.1%).

To evaluate the independent contribution of categorical NT-proBNP changes over time to outcome, a multivariate Cox regression analysis was performed in a model considering the 4 categories of NT-proBNP changes, baseline NT-proBNP, and the clinical variables associated with outcome (Fig. 4). Patients who improved their NT-proBNP at 4 months (high→low) had a risk for all-cause mortality (HR: 0.614, 95% CI: 0.290 to 1.302, $p = 0.2036$) that was not significantly different from that of patients in the reference category (low→low). On the contrary, patients

Table 3 **Predictive Values of Relative (Percent) Changes in NT-proBNP Across Quartiles of Baseline Concentrations**

Quartile of Baseline NT-proBNP Concentration (n)	Baseline NT-proBNP Concentration (pg/ml), Median (Minimum–Maximum)	Number (Rate) of Deaths	Predictive Value of Changes in NT-proBNP	
			HR (95% CI)	p Value
Q1 (436)	199 (12–368)	34 (7.8%)	1.143 (1.025–1.274)	0.0165
Q2 (435)	571 (369–859)	44 (10.1%)	1.390 (1.075–1.798)	0.0121
Q3 (436)	1,210 (862–1,803)	79 (18.1%)	1.615 (1.405–1.865)	<0.0001
Q4 (435)	2,982 (1,807–24,428)	110 (25.3%)	1.352 (1.060–1.724)	0.0151

Patients were divided into quartiles of baseline concentration of NT-proBNP, and the independent predictive value for risk of mortality of relative changes of NT-proBNP over 4 months was estimated separately in each quartile with multivariate Cox models, including the variables associated with outcome in univariate analyses. Hazard ratios and 95% CIs are presented for relative increments of 1 unit (%) of changes in NT-proBNP concentrations. Abbreviations as in Tables 1 and 2.
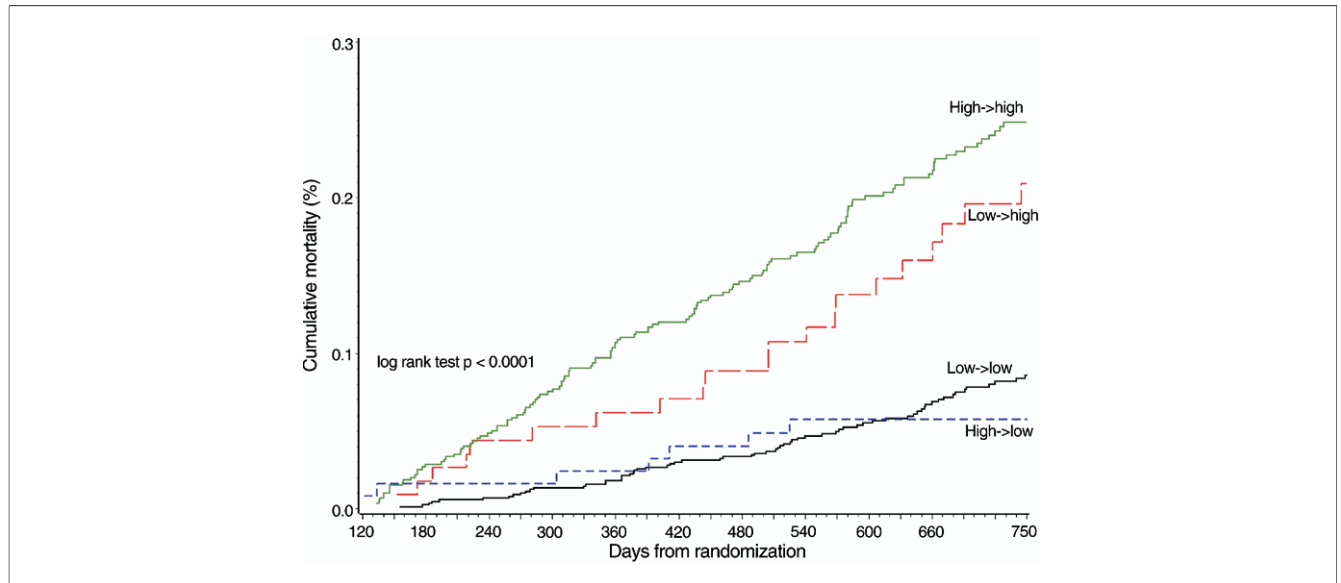
Figure 3   **Kaplan-Meier Curves for All-Cause Mortality in the 4 Categories of Patients**

Patients were divided into 4 categories according to NT-proBNP concentrations at baseline and 4 months relative to a threshold (1,078 pg/ml) determined by ROC curves. Low→low (patients with NT-proBNP below threshold at baseline and 4 months, n = 904 patients), high→high (patients with NT-proBNP above threshold at baseline and 4 months, n = 599), high→low (NT-proBNP above to below threshold, n = 125), and low→high (NT-proBNP below to above threshold, n = 114). Log-rank test, chi-square = 96.5, p < 0.0001. NT-proBNP = N-terminal pro-brain natriuretic peptide; ROC = receiver-operator characteristic.

who worsened in their NT-proBNP over 4 months (low→high) had a significantly elevated risk of death (HR: 1.699, 95% CI: 1.051 to 2.745, p = 0.00305), close to that of patients with elevated NT-proBNP at baseline and at 4 months (high→high, HR: 1.877, 95% CI: 1.180 to 2.986, p = 0.0079) (Fig. 4). In this model, baseline concentration of NT-proBNP (log-transformed) was not significantly associated with mortality (HR: 1.174, 95% CI: 0.964 to 1.430, p = 0.1101).

Discussion

In the present study, which included a large and well-controlled population of ambulatory patients with chronic, stable, and symptomatic HF, we found that: 1) changes over 4 months of NT-proBNP concentrations in patients with chronic and stable HF are associated with long-term outcome; 2) the relationship between outcome and changes in NT-proBNP depends largely on the way these changes are expressed (i.e., as absolute differences of concentrations or as relative changes with respect to a baseline concentration); and 3) a single determination of NT-proBNP shows a higher prognostic discrimination during the course of a strict clinical monitoring period than continuous changes of concentrations, expressed either as absolute or relative changes, whereas categorical changes of NT-proBNP concentration across a threshold value predict outcome independently of a single determination. The size and representativeness of the sample studied allows epidemiological translation of several fragmented observations from smaller studies.

Since their initial discovery (14,15), there has been considerable evidence showing that a single determination of a natriuretic peptide (BNP or NT-proBNP) at any time during the progression of the disease has prognostic value in patients with chronic HF, even on top of robust clinical variables. The importance of changes over time in natriuretic peptide concentrations as a prognostic marker in patients with chronic HF has previously been investigated
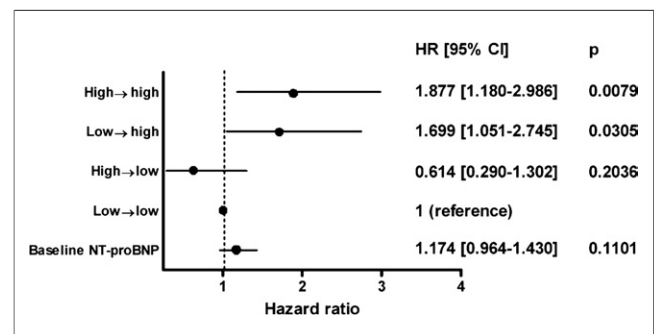

Figure 4   **Risk of Death by Baseline NT-proBNP and Categories of Changes Over 4 Months**

Patients were divided into 4 categories according to NT-proBNP concentration at baseline and 4 months relative to a threshold of 1,078 pg/ml. A multivariate Cox proportional hazards model was used to compare the risk of death among the 4 categories of patients and by baseline NT-proBNP concentration (log-transformed) using the low→low group as a referent. The model was adjusted for clinical variables with statistically significant association to outcome (age, body mass index, serum creatinine at baseline, ischemic etiology of heart failure, New York Heart Association functional class, left ventricular ejection fraction and diameter, and prescription of digoxin and diuretics). Data are presented as hazard ratio (HR) and 95% confidence interval (CI). NT-proBNP = N-terminal pro-brain natriuretic peptide.

(3,6,8,16). In a recent study, a cohort of 190 ambulatory patients with chronic HF (NYHA functional class III to IV) was prospectively enrolled, and BNP and cardiac troponin T (cTnT) were measured at baseline and every 3 months for 2 years (7). Elevation of BNP or cTnT detected at any time during clinical follow-up was highly associated with an increased risk for adverse events (death, cardiac transplantation, or hospitalization). Interestingly, whereas a new elevation of BNP from normal to above normal concentration was associated with an incremental risk, once elevated at any time, subsequent changes in BNP (increase or decrease) did not translate into a modulation of risk category, in contrast to what was observed for cTnT (7).

As observed previously with BNP in the Val-HeFT trial, we confirm here that changes over time in the concentration of the inactive fragment NT-proBNP are similarly associated with outcome in patients with chronic HF when expressed either as continuous absolute or relative changes (8) or as categorical changes across a threshold value (3). The relationship between outcome and continuous changes of BNP, as well as NT-proBNP, depends largely on whether these changes are expressed as absolute differences [concentration at time$_{i+1}$ − concentration at time$_i$] or relative differences (absolute changes normalized by initial level). It is intuitive that the same absolute decrease in a patient with a very high initial concentration is unlikely to have the same prognostic significance than in a patient with a low initial NT-proBNP concentration. Normalizing the absolute differences by the initial concentration yielded an almost linear relationship between quartiles of BNP (8) or NT-proBNP and mortality (Fig. 1B).

Changes across pre-defined threshold values have been alternatively proposed. Definition of the threshold level may be on a statistical basis (median concentrations of the population studied, ROC-derived optimal cutoff value) or clinical basis (upper limit of the reference value in healthy individuals, diagnostic cutoff values). In a substudy of the COMET (Carvedilol Or Metoprolol European Trial) study, 309 patients with chronic HF (NYHA functional class II to IV, LVEF <0.35) had NT-proBNP measured at randomization and at a follow-up time varying between 12 and 36 months (17). A threshold of 400 pg/ml (upper reference value in elderly healthy women) was chosen to divide patients according to baseline NT-proBNP level. In this study, it was shown that among patients with a baseline concentration of NT-proBNP ≥400 pg/ml, subsequent mortality was significantly lower in those who reached a level below this threshold at follow-up (risk ratio: 0.35, 95% CI: 0.15 to 0.82, p = 0.017) (17). We have previously shown that stratification of patients into 4 categories according to BNP levels at 2 time points with respect to a median concentration provided prognostic information in patients with chronic HF beyond that of a single determination (3). The same approach and conclusion can be found in a prospective study that enrolled 133 patients with severe HF referred for consideration of cardiac transplantation

(18). In the present study, the threshold level was derived from an ROC analysis and the calculated optimal cutoff concentration (1,078 pg/ml) is in fact close to the median concentration at study entry (861 pg/ml), so that our findings should be relatively independent of the way the threshold was calculated. We showed that most patients in the placebo arm had stable low (51.9%) or high (34.4%) levels of NT-proBNP over 4 months of follow-up, in agreement with the definition of the population studied. Nevertheless, changes of category were associated with marked modification of the prognosis. In other words, similar concentrations of NT-proBNP at a given time can have profoundly different prognostic values, depending on the subsequent trend in these patients. For instance, patients with an initial NT-proBNP concentration below the threshold level have, on average, markedly divergent outcomes depending on whether they maintain (mortality rate 8.9%) or worsen their level of NT-proBNP (21.1%). Conversely, mortality rate is drastically different in patients with stable high levels of NT-proBNP (25.7%) compared with those with decreasing NT-proBNP (7.2%). Further, the prognostic value of categorical changes in NT-proBNP was independent of and incremental to a single determination of NT-proBNP in multivariate models that also included robust clinical risk factors. Finally, the categorical changes seem to be more easily understood than continuous absolute or relative changes and may be transferred more readily into clinical practice. Although not formally tested in the present study, major differences in the prognostic value of repeated determinations of BNP and NT-proBNP in chronic HF are unlikely, as already reported in patients presenting with chest pain (19).

To the best of our knowledge, this is the first evaluation and head-to-head comparison of the prognostic discrimination of different strategies for risk stratification using a natriuretic peptide in a large population of patients with stable and chronic HF. In a different setting, acute HF, NT-proBNP was serially determined in 116 patients at the time of initiation of intravenous therapy (baseline) and at different intervals until discharge from the hospital (20). It was shown, comparing the AUC of time-dependent ROC curves, that single absolute concentrations of NT-proBNP (in particular at discharge) had the highest prognostic accuracy, ahead of absolute or relative changes from baseline. With different statistical approaches, other studies also concluded the superiority of single-measurement over absolute or relative changes in advanced (18) or decompensated HF (21). Our data confirm and extend these observations to patients with chronic and stable HF. They also support the hypothesis that serial determinations of natriuretic peptide (BNP or NT-proBNP) concentration and classification into few categories of changes according to threshold levels may be a superior strategy for risk stratification of patients with chronic and stable HF, and thus offer an aid in monitoring these patients or actively guiding titration of treatment (22,23).

Study limitations. Natriuretic peptide elevation may reflect the progression of the underlying disease that negatively influences prognosis, but also superimposed volume expansion and worsening of symptoms, which may not have the same impact on outcomes. A decrease in natriuretic peptide may reflect the effect of therapy, such as more diuretic, without any improvement in outcomes or the resolution of an initial elevation caused by volume overload, although outcome is dependent on underlying severity of myocardial disease. All of these possibilities should be borne in mind when interpreting changes in natriuretic peptide concentrations over time. However, the lack of a reliable estimate of volume overload makes it difficult to fully interpret the changes observed. Finally, ROC curves and C-statistics, although widely used, may not be the optimal tool for assessing the impact of a new marker in risk prediction models containing standard risk factors (24,25).

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