Heart Failure

Predischarge B-Type Natriuretic Peptide Assay for Identifying Patients at High Risk of Re-Admission After Decompensated Heart Failure

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OBJECTIVES	The aim of this study was to determine the value of serial B-type natriuretic peptide (BNP) assay for predicting post-discharge outcome of patients admitted for decompensated congestive heart failure (CHF).
BACKGROUND	Patients hospitalized for decompensated CHF are frequently re-admitted. Thus, identification of high-risk patients before their discharge is a major issue that remains challenging. B-type natriuretic peptide measurement could be useful.
METHODS	Serial BNP measurements were performed from admission to discharge in two samples of consecutive patients. Survivors were monitored for six months; the main end point combined death or first re-admission for CHF.
RESULTS	Among the 105 survivors of the derivation study, all serial BNP values, percentage change in BNP levels, and predischarge Doppler mitral pattern correlated with the outcome. In contrast, clinical variables and left ventricular ejection fraction were poorly predictive. The predischarge BNP assay had the best discriminative power (area under the receiver operating characteristic [ROC] curve = 0.80) and remained the lone significant variable in multivariate analysis (hazard ratio [HR] = 1.14 [95% confidence interval {CI}, 1.02 to 1.28], p = 0.027). Among the 97 survivors of the validation study, the predischarge BNP assay was also the most predictive parameter (area under the ROC curve = 0.83). The risk of death or re-admission increased in stepwise fashion across increasing predischarge BNP ranges (p < 0.0001). After adjustment for baseline covariables, the HRs were 5.1 [95% CI 2.8 to 9.1] for BNP levels between 350 and 700 ng/l and 15.2 [95% CI 8.5 to 27] for BNP levels >700 ng/l, compared with BNP <350 ng/l.
CONCLUSIONS	High predischarge BNP assay is a strong, independent marker of death or re-admission after decompensated CHF, more relevant than common clinical or echocardiographic parameters and more relevant than changes in BNP levels during acute cares. (J Am Coll Cardiol 2004; 43:635–41) © 2004 by the American College of Cardiology Foundation

Heart failure (HF) is a major reason for hospitalization and represents a huge cost for national health care budgets. Hospitalization for decompensated congestive heart failure (CHF) carries a poor vital prognosis, with frequent subsequent re-admissions (1–5). It has recently been shown that outcome can be improved in high-risk patients by treatment intensification and home-based interventions (6,7). However, there is currently no simple clinical criterion or score for predicting early outcome after discharge (8) and, thus, for identifying patients who require such caution. Doppler echocardiography is largely used in hospitalized patients and can help to stratify patients. Indeed, Doppler analysis of left ventricular (LV) filling parameters has been linked to outcome after myocardial infarction and in dilated cardiomyopathy (9,10), including in the setting of hospitalization (11).

The B-type natriuretic peptide (BNP) serum level is a promising cardiac marker in various HF settings, especially because of the advent of rapid assays. Indeed, BNP is secreted by overloaded LV, and its blood level is related to severity of LV dysfunction and CHF. B-type natriuretic peptide has diagnostic value in acute dyspnea (12–14); BNP also has prognostic value after myocardial infarction (15,16), as well as in outpatients with chronic CHF and systolic dysfunction (17–19). Despite potential interest, the prognostic relevance of BNP assay has been poorly investigated in the setting of patients admitted for decompensated CHF.

The aims of this study were to determine the prognostic value of serial BNP assay in consecutive patients hospitalized for severely decompensated CHF for the prediction of early death or re-admission for CHF, and to compare it to common clinical and echocardiographic characteristics.

METHODS

Study design. The study was approved by local ethics committees. Consecutive patients admitted to the cardiol-

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CHF = congestive heart failure
DTE = deceleration time of E-wave
HF = heart failure
HR = hazard ratio
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
ROC = receiver operating characteristic

ogy department for decompensated CHF were enrolled, except in the following circumstances: acute myocardial infarction, severe valve disease, surgical patients, or poor adherence to therapy. The diagnosis of decompensated CHF was confirmed by two senior cardiologists using the generally accepted Framingham criteria and corroborative information including the hospital course and results of further cardiac tests. On admission, a blood sample was collected for BNP measurement. Standard treatment was prescribed daily by senior cardiologists. Blood samples were also collected every day for serial BNP assay. A final blood sample was collected either on the day of discharge or on the day before discharge (predischarge values). B-type natriuretic peptide assays were performed after discharge of patient, and results were kept blinded until the end of the study. Doppler echocardiograms were performed before discharge, in order to assess LV ejection fraction (LVEF) as well as Doppler mitral inflow pattern and systolic pulmonary artery pressure. The discharge was decided by two senior cardiologists in charge of the HF unit, using clinical examination, biological tests (except BNP measurements), electrocardiogram, and chest radiograms. Patients were discharged when they presented no more sign of decompensation, stable blood pressure as well as renal function, and optimal achievement of diuretics and angiotensin-converting enzyme inhibitor dosages. Outcome during the six months after discharge was determined in every case, by telephoning the patient or the general practitioner. The main end point combined death or first unscheduled re-admission for CHF. Re-admission for CHF was defined by hospitalization for decompensated CHF.

Patients. In the derivation study, 127 patients were enrolled in a single center (Beaujon Hospital); 13 were subsequently excluded because of requirement for emergent transplantation, transfer to another hospital, absence of predischarge BNP measurement, or rectified non-CHF diagnosis, and, thus, 114 patients were finally included in the derivation study. In the validation study, 109 patients were included in another center (Pontoise Hospital).

BNP assay. Blood was collected into tubes containing potassium EDTA (1 mg/ml blood), and plasma was stored at $-80°C$ for blinded BNP assay with the Triage BNP test (Biosite Diagnostics Inc., San Diego, California). Triage is a point-of-care method based on fluorescence immunoas-

say, and can be used to quantify BNP in whole blood or plasma. At time of the study, the working range of the Triage BNP assay was 5.0 to 1,300 ng/l, and samples with values exceeding 1,300 ng/l were, thus, diluted with normal plasma and retested.

Doppler echocardiography. Doppler echocardiographic examinations were performed with a Hewlett Packard (Andover, Massachusetts) Sonos 5500 machine equipped with a 2.5-MHz probe. Each examination was recorded on videotape for subsequent blind analysis. Pulsed Doppler analysis of mitral inflow included measurements of the mitral valve early peak filling velocity (E), the late peak filling velocity (A), the E to A ratio, and the deceleration time of E-wave (DTE), and yielded three patterns: 1) an "impaired relaxation" pattern (E/A ratio <1); 2) a "restrictive" pattern when the E/A ratio was >2, or between 1 and 2 with an E-wave deceleration time (DT) ≤130 ms, or DT ≤130 ms alone in case of atrial fibrillation; and 3) a "pseudonormal" or "normalized" pattern when the E/A ratio was between 1 and 2 and the E-wave DT >130 ms. The mitral Doppler pattern was unavailable in eight patients because of poor echogenicity, tachycardia, permanent pacing, or mitral prosthesis. Systolic pulmonary arterial pressure was calculated from the velocity of tricuspid regurgitation, when present. The LVEF was estimated by Simpson's method.

Statistical analysis. Categorical data are presented as numbers (percent), and continuous data as means ± SD. Log-transformed values for BNP were used in these analyses to reduce the effects of skewness in the distribution of BNP values. Student *t* test and Fisher exact test were used when indicated. Group comparisons of BNP values were made by using analysis of variance with the Newman-Keuls post hoc test. We used Cox proportional hazards regression models to examine the relation of clinical variables, BNP levels, and echocardiographic findings with the incidence of primary end point (death or re-admission for CHF) or alone re-admission for CHF within the first month and at six months after discharge. B-type natriuretic peptide levels were evaluated both as a continuous variable (with increases in risk calculated per increment of 100 ng/l) and as a categorical variable (based on distribution quartiles). Percentage change in BNP level ([BNP "admission" − "predischarge" BNP] × 100/BNP "admission") was also evaluated as a continuous variable (with decreases in risk calculated per decrease of 10%) and as a categorical variable. Analyses were adjusted for the following baseline covariables: age, diabetes mellitus, and LVEF (well-known predictors of mortality), inotropic drug use, and Doppler mitral pattern (associated with outcome in this study). Receiver operating characteristics (ROC) curves were constructed to illustrate various cut-off values of BNP. P values <0.05 were considered significant. Analyses were performed using STATA 8.0 software for Windows (Stata Corporation, College Station, Texas).

Table 1. Main Characteristics of the Patients in the Two Groups and Adverse Events After Discharge

	Derivation Study (n = 114)	Validation Study (n = 109)	p Value
Age (yrs)	69.4 ± 14.4	70.9 ± 13.3	0.45
Age ≥75 yrs (n, %)	50 (44%)	32 (43%)	0.85
Gender (male/female)	79/35	56/53	0.003
Ischemic etiology (n, %)	44 (39%)	45 (42%)	0.50
LVEF	37.5 ± 14.9	31.8 ± 14.5	0.17
Use of inotropes (n, %)	25 (22%)	34 (32%)	0.07
In-hospital death (n, %)	9 (8%)	12 (11%)	0.64
BNP at admission (ng/ml)	1,015 ± 604	941 ± 526	0.68
BNP at discharge (ng/ml)	457 ± 451	441 ± 501	0.80
Outcome after discharge	n = 105	n = 97	
Cardiac death (n, %)	12 (11%)	9 (9%)	0.64
First re-admission (n, %)	39 (37%)	26 (27%)	0.21

BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction.

RESULTS

Derivation study: outcome and predictors of outcome.
All the 114 patients were admitted because of severely decompensated CHF (New York Heart Association class IV); 83 patients had pulmonary edema, 12 had cardiogenic shock, and 24 required inotropic agents and/or mechanical ventilation. Main characteristics are summarized in Table 1. Nine patients died of refractory CHF during the initial hospital stay. The 105 surviving patients were discharged home in New York Heart Association class II to III and had no more symptoms at rest, no rales, no gallop, no severe hypotension (defined as systolic blood pressure <80 mm Hg). Mean BNP levels were 1,015 ± 604 ng/l at admission, 881 ± 615 ng/l at 24 h, 638 ± 560 ng/l at 48 h, and 457 ± 402 ng/l predischarge (Fig. 1). B-type natriuretic peptide levels did not decrease, or fell by <50 ng/l, in 11 patients between admission and discharge. Predischarge Doppler-echocardiographic examination showed a systolic dysfunction (LVEF <45%) in 70% of patients, "impaired relaxation," "pseudonormal," and "restrictive" mitral patterns in 38%, 33%, and 29% of patients, respectively.

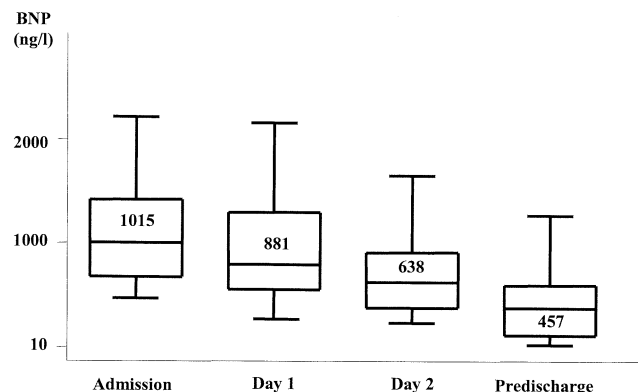During the six months of follow-up, 12 patients died, and

39 were re-admitted for unscheduled CHF; 29% of these events occurred during the first month, and the mean time from discharge to the first event was 72 ± 48 days. Table 2 shows the results of univariate Cox analysis for each clinical variable, creatininemia, echocardiographic findings, and serial BNP measurements as predictors of death or re-admission. Among clinical variables, only the use of inotropic drugs was associated with adverse outcome. Among echocardiographic variables, LVEF was poorly predictive while the predischarge Doppler mitral pattern was strongly associated with death or re-admission. Serial BNP measurements were also predictive of outcome as well the percentage change between admission and subsequent assays. The predischarge BNP level was the value most strongly associated with death or re-admission and the most discriminative (area under ROC curve = 0.80 [0.71 to 0.89] vs. 0.69 and 0.68 for previous BNP assays and 0.76 for percentage change).

In multivariate analysis including clinical variable, echocardiographic findings, the predischarge BNP level, and the percentage change in BNP levels, only the predischarge BNP level remained significant (hazard ratio [HR] = 1.14 [1.02 to 1.28], p = 0.027). Using the predischarge BNP level (as a continuous variable and after adjustment for covariables), similar results were obtained for: 1) death or re-admission at one month (HR = 1.17 [1.06 to 1.28], p = 0.002); and 2) re-admission at six months (HR = 1.25 [1.16 to 1.34], p < 0.001). At last, a BNP level of 350 ng/l was found to have the best compromise between sensitivity and specificity for predicting death or re-admission at six months (Fig. 2).

Validation study. Main characteristics of the validation sample are summarized in Table 1. Patients enrolled in this sample differed from those enrolled in the derivation sample only for gender and inotropic drugs use. Among the 109 included patients, 12 died during the hospitalization, nine died during the six months follow-up, and 26 were rehospitalized for decompensated HF. Mean BNP levels were 941 ± 526 ng/l at admission, 693 ± 440 ng/l at day 1, and 441 ± 501 mg/l at discharge. Among serial BNP measurements, predischarge BNP level remains a strong predictor of death or re-admission in the validation sample (area under ROC curve = 0.83 [0.69 to 0.97]). Event-free patients had mean predischarge BNP levels of 247 ± 201 ng/l compared with 908 ± 809 ng/l for patients with adverse events (p < 0.001). Applying the predefined BNP cut-off level of 350 ng/l, death or re-admission at six months was predicted with a sensitivity of 80% and a specificity of 88%.

Figure 3 shows Kaplan-Meier curves according to predefined BNP cut-off (350 ng/l); predischarge BNP levels >350 ng/l strongly related to death or re-admission (HR = 12.6 [5.7 to 28.1], p = 0.0001), and the rate of events reached 23.5% at one month and 79.4% at six months, compared with 0% and 12.7% for predischarge BNP levels <350 ng/l.

Figure 1. Box plots showing median predischarge levels of B-type natriuretic peptide (BNP) from admission to discharge (derivation study). Mean levels are indicated in the **box**.

Table 2. Univariate Cox Analysis Showing the Association Between Various Variables and the Risk of Death or Re-Admission During the Six Months of Follow-up in the Derivation Study

Variables	HR	95% CI	p Value
Age (yrs), per five-year increase	1.03	0.93–1.13	0.6
Gender (male)	0.87	0.49–1.56	0.6
Ischemic	1.14	0.65–2.0	0.6
Diabetes	1.16	0.58–2.32	0.7
Atrial fibrillation	0.61	0.30–1.26	0.2
Creatininemia	1.02	0.98–1.06	0.3
Inotropic use	2.34	1.26–4.34	0.007
LVEF	0.95	0.78–1.16	0.6
Doppler mitral pattern			
"Abnormal relaxation" pattern	1		
"Pseudo-normal" pattern	3.27	1.43–7.49	0.005
"Restrictive" pattern	6.30	2.78–14.25	0.0001
Serial BNP			
BNP admission, per 100 ng/l increase	1.06	1.03–1.10	0.0001
BNP day 2, per 100 ng/l increase	1.07	1.03–1.11	0.0001
BNP predischarge, per 100 ng/l increase	1.22	1.15–1.30	0.0001
Percentage decrease BNP, per 10% decrease	0.84	0.77–0.90	0.0001
BNP predischarge (per quartile of distribution)			
First quartile (0–130)	1		
Second quartile (130–370)	2.94	0.92–9.37	0.07
Third quartile (370–660)	4.42	1.45–13.45	0.009
Fourth quartile (660–1,725)	13.77	4.71–40.23	0.0001
Percentage decrease BNP (per quartile of distribution)			
First quartile (<38%)	1		
Second quartile (38%–63%)	0.94	0.49–1.81	0.85
Third quartile (63%–79%)	0.40	0.19–0.87	0.02
Fourth quartile (>79%)	0.18	0.07–0.48	0.001

BNP = B-type natriuretic peptide; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; Percentage decrease BNP = (BNP admission − predischarge BNP)/BNP admission.

Graded relation between predischarge BNP levels and outcome. We constructed Kaplan-Meier curves with the predischarge BNP values from the whole population (i.e., derivation and validation samples) (Fig. 4). The risk of death or re-admission increased in stepwise fashion across increasing predischarge BNP ranges: <350 ng/l, 350 to 700 ng/l, >700 ng/l (p < 0.001); this relation was unchanged after adjustment for age, LVEF, diabetes mellitus, and the use of inotropic drugs. Patients with BNP <350 ng/l had the best outcome (16.2% of events at 6 months) compared with patients with BNP between 350 and 700 ng/l (60.0%, HR 5.1 [2.8 to 9.1]) and patients with BNP >700 ng/l (92.7%, HR 15.2 [8.5 to 27]).
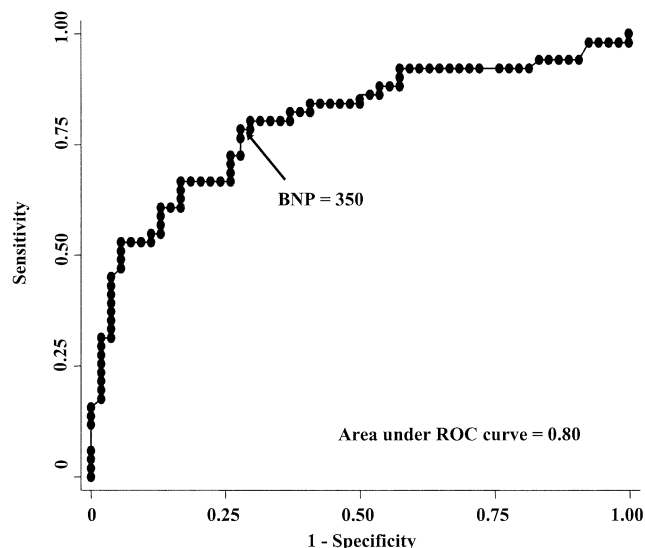
DISCUSSION

This prospective study documents and validates that high predischarge blood BNP levels are a strong predictor of short-term death or re-admission after acute hospital care for decompensated CHF. This relationship between predischarge BNP and outcome is graded. The prognostic information of predischarge BNP assay is greater than are common clinical variables, BNP change during the in-hospital stay, and Doppler echocardiographic findings. The two samples consisted of unselected patients with a wide range of ages and LVEF values (preserved LVEF, i.e., >0.45, in 30% of patients), similar to that encountered in routine practice, and successively included in two different hospitals. The very high rate of post-discharge adverse events was in keeping with the results of other studies of unselected community-dwelling patients (1–5,20). Stratification for subsequent treatment (titration of medications such as diuretics, visits, and so forth) is, therefore, impor-
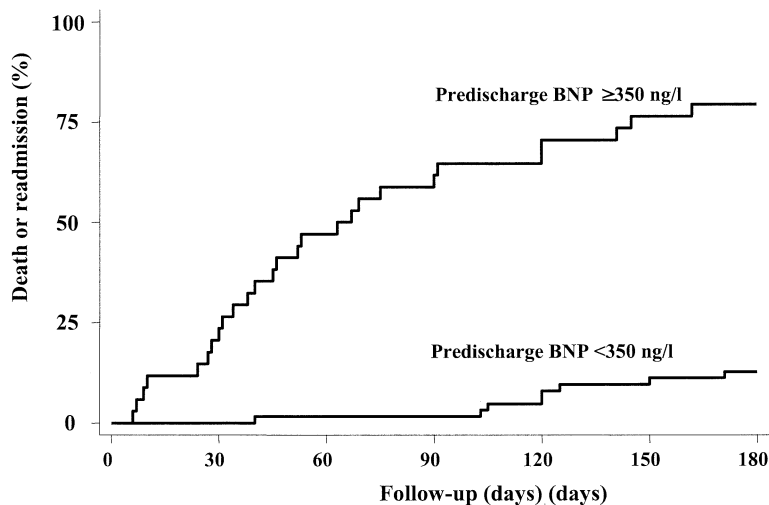

Figure 2. Receiver operating characteristic (ROC) curve for predischarge B-type natriuretic peptide (BNP) cut-off values and association with death or re-admission at six months (derivation study).

Figure 3. Kaplan-Meier curves showing the cumulative incidence of death or re-admission according to predischarge B-type natriuretic peptide (BNP) cut-off value of 350 ng/l in the validation study; p = 0.0001.

tant. In our study, clinical variables were poorly predictive of post-discharge outcome, with the exception of inotropic use during acute care. All patients were judged to be stable at discharge, even though, respectively, 15% of them were re-admitted or died during the first month and more than 40% during the first six months after discharge. In practice it is difficult to evaluate, using clinical criteria, the stability of such weakened and sometimes bedridden patients after several days of aggressive treatment. Indeed, clinical judgment correlates poorly with tests of cardiac function (21,22). Moreover, a number of tests with known prognostic value, such as invasive hemodynamic measurements and stress testing of aerobic capacity, are unusable in many of these patients. Nevertheless, Doppler-echocardiographic examination results in criteria of prognostic significance, which can be easily obtained, even in this setting, and are widely

admitted. While LVEF had poor prognostic value in the two population samples of our study, the Doppler mitral inflow pattern was predictive, and "restrictive" and "pseudo-normal" patterns before discharge were associated with adverse outcome. The "restrictive" pattern is a widely used prognostic index in various settings (9,10,23–25), whereas a "pseudonormal" pattern has rarely been linked to poor outcome of CHF (11).

B-type natriuretic peptide measurement, a simple biological test, is appropriate to this acute setting. In univariate Cox analysis, all BNP measurements from admission to discharge, as well as the percentage change, were significantly associated with the risk of death or re-admission after discharge, but the predischarge assay was the most valuable. After adjustment for age, diabetes mellitus, and LVEF (usual predictors of mortality), and for inotropic drug
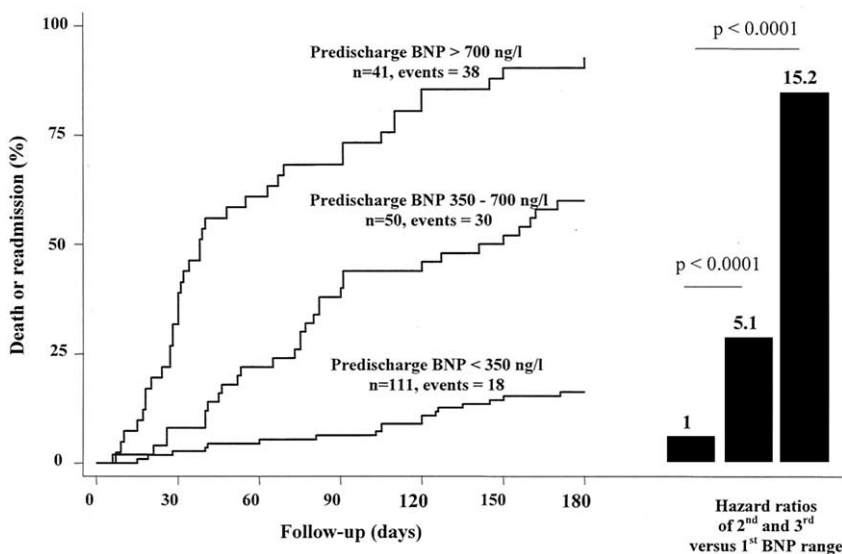

Figure 4. Kaplan-Meier curves showing the cumulative incidence of death or re-admission according to predischarge B-type natriuretic peptide (BNP) ranges (<350, 350 to 700, >700 ng/l) in the whole population; p < 0.001 for the trend among BNP ranges. On the **right**, hazard ratios are shown for each BNP range.

requirements (the only predictive clinical variable found here), predischarge BNP levels remained strongly predictive of death or re-admission after both one month and six months of follow-up. Recently, changes in the BNP level during early aggressive treatment were closely associated with falling pulmonary wedge pressure in patients treated for decompensated CHF (26). In addition, Cheng et al. (27) reported that changes in serial BNP levels during hospital care were predictive of outcome, but BNP was not compared with other parameters, and end points combined in-hospital deaths and post-discharge events. In this study, very high mean BNP levels at discharge (more than 1,500 ng/l) and no decrease during treatment in patients who died or were re-admitted suggest that the patients were very severely sick. In our study, the percentage change in BNP levels during acute care had less prognostic value than the predischarge measurement alone. B-type natriuretic peptide levels are mainly determined by LV wall stress. The predischarge BNP level may, thus, reflect the decrease in LV filling pressure and the degree of hemodynamic stability, which is achieved after acute treatment, as well as the severity of underlying diastolic dysfunction, and is a major predictor of early outcome. Interestingly, BNP level and Doppler mitral pattern have similar significance from a mechanistic point of view, as LV filling pressure and LV wall stress are major determinants of both BNP levels (28) and Doppler mitral pattern (29,30). The E-wave DT correlated negatively with BNP levels in our study (data not shown), and the predischarge "restrictive" Doppler pattern (suggesting lasting high LV filling pressure or severe diastolic dysfunction) was associated with the highest BNP levels at discharge. Finally, Doppler analysis of mitral inflow added no significant prognostic information to BNP measurement when the two parameters were included in multivariate Cox models. A predischarge BNP level at 350 ng/ml appeared the more relevant cut-off to predict adverse outcome in our two samples of patients. In fact, the risk of death or re-admission increased in stepwise fashion across increasing predischarge BNP ranges; a dramatic increase in the risk of events was observed from 350 ng/l, and BNP >700 ng/l was associated with a major risk (31% of death or re-admission for CHF at one month and 93% at six months). These levels, like those reported by Cheng et al. (27), are higher than the values generally reported in outpatients (17,18). Among 85 selected outpatients with symptomatic CHF and systolic dysfunction, Tsutamoto et al. (17) found that the median BNP level (73 ng/l) distinguished subsequent survivors from nonsurvivors. Berger et al. (19) recently proposed a cut-off of 130 ng/l. These differences in BNP cut-offs reflect differences in the duration of follow-up and in the study populations (e.g., hospitalized patients vs. outpatients).

Clinical implications. The high rates of early re-admission observed in this study suggest that many CHF patients are discharged without sufficient circulatory stabilization, despite the clinician's impression to the contrary. The single predischarge BNP assay is strongly predictive of early outcome, regardless of the initial BNP level (and in-hospital changes) and echocardiographic findings; thus, it appears to be a simple and reliable test to identify the highest risk patients. Further studies are required to determine if serial BNP assay can improve patient management, for example by determining the optimal timing of discharge and subsequent care requirements, as recently suggested (31).

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