Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure

The STARS-BNP Multicenter Study

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Objectives
The aim of this multicenter study was to evaluate the prognostic impact of a therapeutic strategy using plasma brain natriuretic peptide (BNP) levels.

Background
The prognosis of chronic heart failure (CHF) remains poor, even among patients treated in specialized departments.

Methods
A total of 220 New York Heart Association functional class II to III patients considered optimally treated with angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and diuretics by CHF specialists were randomized to medical treatment according to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels <100 pg/ml (BNP group). Outpatient visits were scheduled every month for 3 months, then every 3 months. The primary combined end point was CHF-related death or hospital stay for CHF.

Results
Both groups were similar for baseline clinical and biological characteristics. Left ventricular ejection fraction was slightly lower in the BNP group than in the clinical group (29.9 ± 7.7% vs. 31.8 ± 8.4%, p = 0.05). At the end of the first 3 months, all types of drugs were changed more frequently in the BNP group. Mean dosages of ACEIs and beta-blockers were significantly higher in the BNP group (p < 0.05), whereas the mean increase in furosemide dosage was similar in both groups. During follow-up (median 15 months), significantly fewer patients reached the combined end point in the BNP group (24% vs. 52%, p < 0.001).

Conclusions
In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages. (J Am Coll Cardiol 2007;49:1733–9) © 2007 by the American College of Cardiology Foundation

Optimal treatment of heart failure includes angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, spironolactone, and diuretics, as recommended by the international guidelines (1,2). Treatment optimization is currently based on physician experience and patient tolerance.

Chronic heart failure (CHF) remains the main reason for hospital stay among patients >65 years of age and is associated with high mortality (3,4). However, implementation of guidelines remains imperfect (5).

Brain natriuretic peptide (BNP) is a 32-amino acid protein secreted by cardiac ventricles (6–9). The diagnostic and prognostic value of BNP plasma levels in CHF is supported by many studies (10–15). Most drugs used to treat heart failure significantly reduce BNP plasma levels (16–18). In the Val-HeFT (Valsartan Heart Failure Trial), only patients receiving valsartan in addition to conventional therapy presented with a significant reduction in plasma BNP levels compared with the placebo group (19). Recent data from RALES (Randomized Aldactone Evaluation Study) showed that spironolactone can also markedly reduce BNP levels in patients with severe heart failure (20). The effect of beta-blockers on BNP remains controversial. In
randomized trials, patients with the most marked neurohormonal activation and the highest BNP levels at enrollment seemed to benefit most from beta-blocker therapy (21–23). More recent data showed a significant N-terminal pro-BNP reduction in patients receiving carvedilol or metoprolol (24).

Plasma BNP level monitoring has been proposed for treatment optimization in patients with heart failure (25–27). However, these studies included few patients, most of whom did not receive beta-blocker therapy. Thus, the aim of this French multicenter randomized study was to evaluate the benefit of BNP-guided therapy on outcome in CHF patients in clinical practice.

Methods

Study population. The patients were included by CHF specialists from 17 university hospitals. All investigators had expertise in CHF management and were members of the Working Group on Heart Failure (WGHF) of the French Society of Cardiology.

The inclusion criteria were as follows: patients older than 18 years with symptomatic (New York Heart Association [NYHA] functional class II to III) systolic heart failure defined by left ventricular ejection fraction (LVEF) <45% assessed by echocardiography using the American Society of Echocardiography guidelines, in stable condition (no hospital stay in the previous month), and treated by optimal medical therapy according to the European guidelines at the time of the study (1); dosages of medications were to be stable for at least 1 month before inclusion. Patients had to receive diuretics, ACEIs, or angiotensin II-receptor blockers (ARB) at the maximal tolerated dosage unless documented intolerance and beta-blockers approved for CHF (carvedilol, bisoprolol, and metoprolol XR-CL), at the maximal tolerated dosage unless documented intolerance or specific contra-indication. All patients signed informed consent.

The exclusion criteria were as follows: acute coronary syndrome within 3 months, chronic renal failure (plasma creatininemia >250 μmol/l), documented hepatic cirrhosis, asthma, or chronic obstructive pulmonary disease.

Study design. Patients were randomized into 2 groups:

- BNP group: medical therapy was increased with the aim of lowering plasma BNP levels (target <100 pg/ml) (1,10); each class of therapy could be modified according to the judgment of the investigator.
- Clinical group: medical therapy was adjusted according to the opinion of the investigator, on the basis of the physical examination and usual paraclinical and biologic parameters. The investigators were not allowed to measure plasma BNP level.

Outpatient visits were scheduled every month for the first 3 months and every 3 months thereafter. During the titration phase (3 months), each visit included physical examination, electrocardiogram recording, and blood sample measurements. Plasma sodium levels, renal function, and hemoglobin were measured in both groups, whereas plasma BNP level was measured only in patients belonging to BNP group. During the follow-up phase, each visit included a clinical examination. The BNP was systematically measured only in the BNP group.

The protocol of the study was written by the WGHF of the French Society of Cardiology and approved by the CCPRPB (French legal ethics committee). Each patient gave written informed consent.

Plasma BNP level measurement. Venous blood sample was taken after 20 min of rest in the supine position and collected on an EDTA tube. The BNP was immediately measured with the immunofluorometric triage method (28) (Biosite Inc., San Diego, California). The BNP triage assay variability was 10% for a threshold of 800 pg/ml and 15% for a threshold of 100 pg/ml.

Primary and secondary end points. The primary composite end point was defined as unplanned hospital stays for heart failure or death related to heart failure. Hospital stays were decided by the physician in the emergency room, not involved in the study, and unaware of plasma BNP levels. The BNP plasma levels were kept in a specific patient chart and accessible only to investigator. Patients also were blinded for BNP results. The secondary end points were all-cause death, death related to heart failure, all-cause hospital stay, and hospital stay for heart failure.

Statistical analysis. Intent-to-treat principles were used. Continuous variables are presented as mean ± SD. Comparisons between continuous variables were made with Student parametric unpaired t test for between group comparison and paired t test for 6-month versus baseline comparison. Proportions were compared with the chi-square test. A statistical difference was considered significant if p < 0.05. Survival was evaluated with the Kaplan-Meier method. Differences in survival between the 2 groups were compared with log-rank analysis. Statistical analyses were performed with the SPSS version 11.0 software (SPSS Inc., Chicago, Illinois).

Results

Baseline. Each group included 110 patients. Mean age of the patients was 65 ± 5 years; 73% were male. Complete baseline patient characteristics are reported in Table 1. Patients had severe heart failure with a mean LVEF of 30 ± 8% and a mean left ventricular end-diastolic diameter of 67 ± 12 mm.

The 2 groups were comparable in terms of left ventricular end-diastolic diameter, NYHA functional class, hemody-

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin II-receptor blockers
BNP = brain natriuretic peptide
CHF = chronic heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
namic parameters, QRS duration, and biological parameters. However, percentage of active smokers (p = 0.03) and mean LVEF (p = 0.05) were lower in the BNP group than in the clinical group. Both groups were also similar for background medical therapies. At baseline, medical treatment was optimized in the population: 99% of patients received an ACEI or an ARB at 94% of the recommended dosage (Table 1). Similarly, 94% of patients received a beta-blocker at 58% of the recommended dosage. All the patients received furosemide. Therefore, the background therapy was truly optimized before entry into the study.

**Titration phase: treatment adjustment during the first 3 months.** Changes in treatment occurred more frequently in the BNP group compared with the clinical group, 134 versus 66 occasions (p < 0.05). In the BNP group, the treatment was adjusted according to the plasma BNP level in 79% of the cases (106 of 134 treatment changes) (Fig. 1).

The most frequently changed pharmacological drugs were diuretics (41% of the changes in the BNP group vs. 39% of the changes in the clinical group, p = NS) (Fig. 2). The mean increase in furosemide dosage was 9 ± 20 mg and was similar in both groups. However, all types of drugs were changed more frequently in the BNP group (furosemide: 55% vs. 26% of the patients; spironolactone: 17% vs. 7% of the patients; ACEI or ARB: 21% vs. 9% of the patients; beta-blockers: 36% vs. 20% of the patients).

During the first 3 months, the mean daily dosage of ACEI increased in the 2 groups (from 94% to 98% of the recommended dosage in the clinical group, p = NS, and from 94% to 106% of the recommended dosage in the BNP group, p < 0.05) as well as the mean daily dosage of beta-blockers (from 57% to 67% of the recommended dosage in the clinical group, p < 0.05, and from 58% to 77% of the recommended dosage in the BNP group, p < 0.05). However, at the end of the first 3 months, the mean dosages of ACEIs and beta-blockers, expressed as percentage of

| Table 1 | Population Characteristics at Baseline According to the Group Allocation |
|---------|-----------------|-----------------|----------|
|          | Clinical (n = 110) | BNP (n = 110) | p Value |
| Age (yrs) | 66 ± 6          | 65 ± 5          | NS       |
| Male/female patients (n) | 62/48           | 65/45           | NS       |
| Smoking (%) | 53               | 39              | 0.03     |
| Hypertension (%) | 30              | 30              | NS       |
| Diabetes (%) | 19               | 16              | NS       |
| Dyslipidemia (%) | 60              | 46              | NS       |
| Duration of heart failure (months) | 29              | 31              | NS       |
| Ischemic heart failure (%) | 48              | 55              | NS       |
| Weight (kg) | 77 ± 17          | 76 ± 18         | NS       |
| NYHA functional class | 2.21 ± 0.62     | 2.29 ± 0.60     | NS       |
| Heart rate (beats/min) | 69 ± 13          | 68 ± 13         | NS       |
| QRS duration (ms) | 118 ± 40         | 119 ± 43        | NS       |
| Natremia (mmol/l) | 137 ± 13         | 137 ± 13        | NS       |
| Creatininemia (μmol/l) | 97 ± 40          | 92 ± 40         | NS       |
| LVEF (%) | 31.8 ± 8.4       | 29.9 ± 7.7      | 0.05     |
| LVEDD (mm) | 69 ± 11          | 67 ± 12         | NS       |
| ACEI or ARB (%) | 99              | 99              | NS       |
| At recommended daily dose (1) (%) | 94              | 94              | NS       |
| Beta-blocker (%) | 97              | 99              | NS       |
| At recommended daily dose (1) (%) | 58              | 59              | NS       |
| Spironolactone (%) | 22              | 25              | NS       |
| Furosemide (%) | 100             | 100             | NS       |
| Mean daily dose (mg) | 52 ± 60          | 50 ± 48         | NS       |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

![Figure 1](http://content.onlinejacc.org/) Number of Changes in Medical Therapy During the First 3 Months

Changes were related to high brain natriuretic peptide (BNP) value according to protocol or clinical reasons.
recommended dosage, were significantly higher in the BNP group than in the clinical group (p < 0.05).

**Titration phase: clinical and biological variations.** During the first 3 months, NYHA functional class improved in both groups. There was no difference for mean NYHA class for the 2 groups at the end of the titration phase (2.1 ± 0.5 vs. 2.0 ± 0.4, p = NS). Blood pressure, heart rate, and weight decreased in a comparable way in the 2 groups (Fig. 3). Similar clinical adverse events rates occurred in the 2 groups.

Creatininemia (Fig. 3) and azotemia tended to increase during the titration phase in the 2 groups (p = NS). Increase in creatininemia by more than 30% was observed in 9% of the control group and in 7% of the BNP group (p = NS). There was no significant variation in potassium or sodium levels.

**Follow-up.** No patient was lost to follow-up (Fig. 4). During follow-up (minimum 6 months, median 15 months), the primary composite end point (unplanned hospital stays for heart failure or death related to heart failure) was observed in 83 occasions in the 220 patients (38%) (25 of 110 [24%] in the BNP group vs. 57 of 110 [52%] in the clinical group, p < 0.001). By log-rank analysis, event-free survival was also significantly better in

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**Figure 2** Changes in Medical Therapy During the Titration Phase in BNP Group and Clinical Group

Therapeutic modifications during titration phase. ACEI = angiotensin-converting enzyme inhibitor; BNP = brain natriuretic peptide.

**Figure 3** Evolution of Systolic Blood Pressure, Heart Rate, Weight, and Creatininemia During the First 3 Months

Hemodynamic and biological variations during titration phase. BNP = brain natriuretic peptide; M = month.
the BNP group (84%) than in the clinical group (73%) (p < 0.01) (Fig. 4).

All-cause death was not significantly different between the groups (7 in the BNP group vs. 11 in the clinical group, p = NS). Death related to heart failure was observed in 3 patients in the BNP group versus 9 patients in the clinical group. Six patients died from non–CHF-related causes (2 of cancer, 3 of pulmonary embolism, 1 of endocarditis).

All-cause hospital stays were not significantly different between the 2 groups: 60 patients in the clinical group versus 52 in the BNP group (p = NS).

Hospital stays for heart failure were observed in 22 patients in the BNP group versus 48 patients in the clinical group (p < 0.0001). Two patients in the BNP group versus 10 patients in the clinical group were hospitalized twice or more for acute heart failure decompensation (p < 0.02).

In the BNP group, mean plasma BNP levels significantly decreased during follow-up from 352 ± 260 pg/ml at baseline to 284 ± 180 pg/ml at 3-month follow-up (p = 0.03). Accordingly, the target (<100 pg/ml) was reached in 16% of patients at baseline to 33% at 3-month follow-up (p = 0.04) (Fig. 5).

Discussion

This study has shown that CHF treatment optimization based on plasma BNP levels is associated with a lower risk of death related to heart failure or hospital stay related to heart failure than the usual strategy based on clinical expertise. The benefit was observed despite optimization of therapy in both groups by cardiologists specialized in congestive heart failure before entry into the study (more than 95% of the patients received a recommended triple therapy: ACEI or ARB + beta-blocker + furosemide).

Suboptimal dosages of beta-blockers were reported in the EuroHeart Failure Survey (29), much lower than that prescribed at baseline in our study. However, in our study, dosage at baseline remained below those reached during recent multicenter beta-blocker trials (30,31), and inclusion into the study led to significant increase in diuretics, ACEIs, and beta-blockers in both groups. Optimization is actually a long-term aim, and a patient’s condition varies from time to time. Beta-blocker and ACEI increases were well tolerated.

Previous studies have examined BNP variations and their prognostic implications during medical therapy. In the first landmark study, Throughton et al. (26) observed a significant reduction in all-cause mortality and in heart failure-related hospital stay with BNP-guided medical therapy. However, the sample size was limited (69 patients), and medical therapy mainly consisted of ACEI and diuretics without beta-blockers.

Brain natriuretic peptide is a noninvasive marker of ventricular myocyte stretch and correlates with left end-diastolic pressure (9,32). High BNP values can identify patients with high left end-diastolic pressures who would benefit from medical optimization (32). Interestingly, in our study, diuretic dosages and weight variations were similar in both groups, whereas plasma BNP level is dependent on blood volume.
It had been expected that a high plasma BNP level would lead to an increase in diuretic dosage. In fact, the use of plasma BNP levels led also to an increase in ACEI and beta-blockers. During the trial, we found that the association of abnormal BNP levels plus clinical examination was more meaningful to the cardiologist and led to more optimization in medications than clinical examination alone. Whether knowledge of BNP plasma level is beneficial through better evaluation of the CHF status of the patient or acts as a supplementary stimulus for increasing all drugs remains to be determined.

**Study limitations.** In our study, the benefit of the BNP-guided strategy was tested after medical therapy had been optimized by highly qualified cardiologists. The benefit might actually be larger in routine clinical practice.

Similarly, baseline LVEF tended to be lower in the BNP group, which would be expected to increase the number of clinical events. This actually strengthens the results of our study.

As in other randomized studies, our population was young, mostly male, and limited to systolic dysfunction (LVEF <45%). Medical registers demonstrate that CHF patients are older and frequently female and diastolic dysfunction is increasingly prevalent. Our results only apply to the selected population included.

**Conclusions**

In optimally treated CHF patients with left ventricular systolic dysfunction, a BNP-guided strategy reduces the incidence of a combined end point (death and hospital stay related to heart failure) compared with a standard strategy. The result is mainly obtained through an increase in ACEI and beta-blocker dosages.

**Acknowledgments**

The following is a list of the French investigators involved in the STARS-BNP study: National Coordinator: Patrick Jourdain (Pontoise); Investigators: Marie-Claude Aumont (Paris), Jean-François Aupertit (Lyon), Jean-Marc Davy (Montpellier), Michel Desnos (Paris), Erwan Donal (Poitiers), Jean-Christophe Eicher (Dijon), François Funck (Pontoise), Pascal De Groote (Lille), Michel Galinier (Toulouse), Pierre Gibelin (Nice), Jean-Yves Gueffet (Nantes), Guillaume Jondeau (Boulogne-Billancourt), Yves Jullièbre, Chairman of the French Working Group on Heart Failure (Nancy), Yves Kettelers (Armentières), Michel Komajda (Paris), Alain Le Helloco (Rennes), and Damien Logeart (Clichy).

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