N-Terminal Pro B-Type Natriuretic Peptide Guided, Intensive Patient Management in Addition to Multidisciplinary Care in Chronic Heart Failure: A 3-Arm, Prospective, Randomized Pilot Study

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N-Terminal Pro–B-Type Natriuretic Peptide–Guided, Intensive Patient Management in Addition to Multidisciplinary Care in Chronic Heart Failure

A 3-Arm, Prospective, Randomized Pilot Study

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Objectives This study was designed to investigate whether the addition of N-terminal pro–B-type natriuretic peptide–guided, intensive patient management (BM) to multidisciplinary care (MC) improves outcome in patients following hospitalization due to heart failure (HF).

Background Patients hospitalized due to HF experience frequent rehospitalizations and high mortality.

Methods Patients hospitalized due to HF were randomized to BM, MC, or usual care (UC). Multidisciplinary care included 2 consultations from an HF specialist who provided therapeutic recommendations and home care by a specialized HF nurse. In addition, BM included intensified up-titration of medication by HF specialists in high-risk patients. NT-proBNP was used to define the level of risk and to monitor wall stress. This monitoring allowed for anticipation of cardiac decompensation and adjustment of medication in advance.

Results A total of 278 patients were randomized in 8 Viennese hospitals. After 12 months, the BM group had the highest proportion of antineurohormonal triple-therapy (difference among all groups). Accordingly, BM reduced days of HF hospitalization (488 days) compared with the hospitalization for the MC (1,254 days) and UC (1,588 days) groups ($p < 0.0001$; significant differences among all groups). Using Kaplan-Meier analysis, the first HF rehospitalization (28%) was lower in the BM versus MC groups (40%; $p = 0.06$) and the MC versus UC groups (61%; $p = 0.01$). Moreover, the combined end point of death or HF rehospitalization was lower in the BM (37%) than in the MC group (50%; $p < 0.05$) and in the MC than in the UC group (65%; $p = 0.04$). Death rate was similar between the BM (22%) and MC groups (22%), but was lower compared with the UC group (39%; vs. BM: $p < 0.02$; vs. MC: $p < 0.02$).

Conclusions Compared with MC alone, additional BM improves clinical outcome in patients after HF hospitalization. (BNP Guided Care in Addition to Multidisciplinary Care; NCT00355017) (J Am Coll Cardiol 2010;55:645–53)

Despite advances in therapy, about 30% of chronic heart failure (CHF) patients are readmitted within 60 to 90 days following heart failure (HF) hospitalization, and about 10% of them are dying within this time span (1). These poor discharge outcomes can be attributed to suboptimal care associated with the patients' lack of understanding of their condition, poor treatment compliance, as well as inadequate medical prescription and follow-up (2). For optimizing outpatient care, the involvement of specialized HF nurse care and the increased accessibility to clinicians trained in HF are crucial in reducing rehospitalization rate and mortality (3). Despite variations in the role of HF nurses in different health care settings, the basic principles are similar. The nurses are usually responsible for history taking, clinical assessment, and patient management, which includes adjustment and titration of medication (4); the associated HF clinicians provide titration plans and get involved in the management of patients with clinical deterioration and cardiac decompensation.

Disease management programs focus on patients discharged after HF hospitalization, as these patients are at higher risk for readmission. Despite severe cardiac dysfunction, these patients report few or no symptoms after recompensation. This finding may result from patients' perception that symptoms have improved or from the fact that patients do not return to their

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Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
BM = N-terminal pro–B-type natriuretic peptide-guided, intensive patient management
BNP = B-type natriuretic peptide
CHF = chronic heart failure
HF = heart failure
MC = multidisciplinary care
NP = natriuretic peptide
NT-proBNP = N-terminal pro–B-type natriuretic peptide
UC = usual care

usual daily activities during hospitalization or immediately after discharge (5). In contrast to symptoms, B-type natriuretic peptide (BNP) is an objective prognostic marker that better predicts survival than traditional prognostic indicators in HF (6). Patients with high risk for early rehospitalization and death can be effectively identified by assessing levels of natriuretic peptides (NPs) at discharge, as recently shown (7,8). This prognostic capacity of NPs might improve the management of discharged patients by identifying those requiring more intensive outpatient care.

Moreover, NPs may also be useful in objectively detecting short-term improvement or deterioration. A recent study demonstrated that in high-risk patients, as identified by high N-terminal pro–B-type natriuretic peptide (NT-proBNP), short-term changes of NT-proBNP add significant prognostic information to its absolute value (9). These changes of NT-proBNP correlate with hemodynamic alterations (10) and seem to be a reliable diagnostic tool for monitoring changes in fluid status and/or cardiac function.

NT-proBNP measurement offers 2 diagnostic opportunities for the management of HF patients: 1) global risk assessment, which allows the intensive patient treatment by HF specialists to be focused on patients with the highest risk for decompensation; and 2) monitoring of short-term changes in wall stress, which allows for anticipation of cardiac decompensation and adjustment of medication in advance. We used these 2 diagnostic opportunities for NT-proBNP–guided, intensive management (BM) of patients discharged after HF hospitalization. Therefore, we investigated whether the benefit of multidisciplinary care (MC) compared with usual care (UC) can be increased by adding BM.

Methods

The study was conducted in 8 Viennese hospitals and included patients who met the following criteria: 1) clinical signs and symptoms of cardiac decompensation during the present hospitalization; 2) New York Heart Association functional class III or IV at admission; and 3) cardiothoracic ratio >0.5 or left ventricular ejection fraction <40% as documented by echocardiography. This 3-arm pilot study was approved by relevant ethical committees for each participating hospital. Written informed consent was obtained from all patients.

At discharge, concealed allocation was performed by sending the baseline characteristics of each patient to an independent medical project management institute (RESULT CRO Data GmbH, Vienna, Austria). Using computer-generated permuted block randomization (6 patients per block), patients were randomized to the 3 groups: 1) BM in addition to MC; 2) MC alone; and 3) UC. Patients were monitored for a maximum period of 18 months. Follow-up was closed when the last patient included in the study completed the 12-month visit.

UC. For patients assigned to UC, their management plan was sent to the appropriate primary care physician, who was asked to implement it. Based on this management plan, the primary care physician was responsible for the patient evaluation and treatment as well as judging the need for readmission. In hospitals in which the usual patient management offered visits for selected patients at the cardiac outpatient clinic, the discharging physician was allowed to arrange such visits as usual. Contact with the HF specialists of the research team was discouraged. Neither a structured follow-up nor specialized HF nurses were available for patients in the UC group. A phlebotomist collected blood samples and tracked medical therapy 1, 3, 6, and 12 months after discharge for scientific reasons. In case of questions concerning HF management, patients were asked to contact their primary care physician.

MC. MC comprised care by a specialized CHF nurse, which included 4 home visits and telephone contact, 2 pre-scheduled consultations from the CHF specialist 10 days and 2 months after discharge, and consultations on demand that were performed if any deterioration in the patient's status was noted by the HF nurse. During the first consultation, the full clinical history was evaluated. Each consultation consisted of a physical examination (including measurement of blood pressure and body weight) where functional status and HF medication were documented and a 12-lead electrocardiogram was reviewed. Moreover, laboratory testing including blood chemistry and blood cell count was performed. Based on these data, a tailored recommendation for the optimization of medical therapy was provided. This included a preparation of an individual titration plan, adjustment of diuretics, and recommendations for discontinuation of inappropriate medication. Furthermore, the HF specialist scheduled laboratory tests checking electrolytes and renal parameters at least 1 week after each dose adaptation or addition of medication and 3 months after optimization of medical therapy.

Nurse care consisted of 4 home visits at 1, 3, 6, and 12 months after discharge by a nurse specialized in caring for CHF patients. The nurse checked and recorded weight, symptoms and signs of HF, and heart rate and blood pressure, as well as organized and reviewed blood analyses on demand (particularly electrolytes and renal parameters). In coordination with the HF specialist, the nurse checked for and implemented guideline-based HF medication. Additionally, the nurse was in charge of individualized patient and caregiver education and enhancement of self-management. When necessary (as judged by the nurse), additional visits were performed. If any deterioration in the patient's status was noted, the nurse either reported to the HF specialist or immediately advised the patient to seek consultation.

BM. In patients with a discharge NT-proBNP level >2,200 pg/ml, ambulatory visits at a CHF specialist were performed at least every 2 weeks (except at scheduled nurse visits) in addition to MC to optimize medical therapy as quickly as possible. When NT-proBNP fell below 2,200 pg/ml 3 or 6 months after discharge, patients were followed similarly to those in the MC group. In patients with an ongoing elevated NT-proBNP >2,200 pg/ml, the every-2-weeks visits were continued until maximal recommended or tolerated dosages of CHF therapy were established, following which the time interval between visits was increased to 3 months. The HF specialist used NT-proBNP in addition to other clinical and laboratory parameters for integrated clinical management (e.g., adaptation of diuretic regimen, rate of dose increase for neurohormonal antagonists, schedule of visits) according to the recommendations given in Figure 1.

NT-proBNP levels. Blood samples for measurement of NT-proBNP (Roche Diagnostics, Mannheim, Germany) were drawn at 1, 3, 6, and 12 months following discharge in all available patients. The NT-proBNP levels were analyzed immediately in all patient samples; however, only the results from the BM group were delivered immediately to the HF specialists, whereas the results from the other 2 groups were not made available for clinical use.

In 2 studies, the pre-discharge BNP cutoff values were calculated to be 350 pg/ml and 430 pg/ml for prediction of HF rehospitalization and death, respectively (7,8). However, no data are available for NT-proBNP. We converted the lower BNP value of 350 pg/ml to an NT-proBNP value. A conversion factor of 9 was used, which resulted from an analysis of our own data on simultaneous determination of BNP and NT-proBNP in CHF patients (D. Moertl and R. Berger, unpublished data, October 2002). This factor was also confirmed by Richards et al. (11). Due to the known intraindividual variability of 30% (12), we used a safety margin adjusted to the known intraindividual variability of 30% (12). Overall, the cutoff value for NT-proBNP of 2,200 pg/ml was based on a converted BNP cutoff of 350 pg/ml and a safety margin of 30%.

Outcome data. The analyzed end points included HF rehospitalization, duration of time it takes to reach the combined end point of death and HF rehospitalization, the first HF rehospitalization, and death. Independent data collectors obtained information from medical reports and from interviews with relatives during the follow-up at least every 3 months. During a consensus reading, 2 cardiologists, who were blinded to the treatment groups, classified the cause of rehospitalization as being a result of cardiac decompensation or not. If the cause of rehospitalization was classified unclear by 1 cardiologist, the data collector provided the appropriate hospital charts for final classification.

Statistical analysis. Data analyses were performed according to the intention-to-treat principle. Continuous variables are expressed as mean ± SD. Continuous variables were compared using a 1-factor analysis of variance followed by Fisher *t* test. Ordinal data were compared using a Kruskal-Wallis test followed by Shaffer-corrected *U* tests. Categorical data were compared using a chi-square test. For calculations, NT-proBNP values were log-transformed due to the nonparametric distribution. A paired *t* test was performed to estimate changes in the log-transformed NT-proBNP values between discharge and follow-up. Mean, median, lower and upper quartiles, and 95% confidence intervals (box plot) were computed on the log-scale and back-transformed to the original scale. Follow-up data were defined as those collected from the 12-month visit or the last available visit. Kaplan-Meier analyses with log-rank test were calculated for comparison of time-dependent outcomes. Cox proportional hazards models were used to determine independent predictors of the first HF rehospitalization, death, and the combined end point of HF rehospitalization and death. The full models included patient characteristics given in Table 1 and treatment allocation. The models were carried out using a stepwise approach. Each variable was required to meet the criterion p value of 0.05 in order to enter and remain in the model. Simple models that included treatment allocation, age, and an interaction term (treatment allocation × age) tested whether the effect of treatment strategy was influenced by age.

Results

Patients. Between July 2003 and September 2004, 278 of 441 eligible patients were randomized (Fig. 2). Patients who participated were on average 5 years younger than nonparticipants were. The study ended in September 2005, after a 1-year follow-up of the last patient included in the study. Sixty-three percent of patients completed the 18-month observation period, whereas the remaining 37% were followed for a median of 15 months (interquartile range 13 to 16 months). Their characteristics are given in Table 1; no differences could be detected among groups.

Ambulatory visits and telephone contacts. The total number of consultations of the HF specialist was similar in the BM (n = 564) and MC (n = 511) groups. This was due to the fact that in the BM group repeated scheduled visits were performed only in high-risk but not in low-risk patients. At the same time, the number of unscheduled visits was slightly higher in the MC group. In contrast, the total number of visits was significantly lower in the UC group (n = 229; $p < 0.0001$ among groups) (Table 2).

Medical therapy. Table 3 lists medical therapy at discharge and at follow-up. The proportion of patients treated with antineurohormonal triple therapy including spironolactone and ≥50% of the target doses of an angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker and of a beta-blocker was higher in the BM group than in the MC group (Fig. 3). During outpatient care, the furosemide dose was adjusted more frequently in the BM group (sum of dose changes = 273) than in the MC group (n = 231) and the UC (n = 150) groups ($p < 0.0001$; significant differences among all groups).

NT-proBNP levels. The proportion of patients with an NT-proBNP level above 2,200 pg/ml was similar among patients in the BM (53%), MC (56%), and UC (56%)

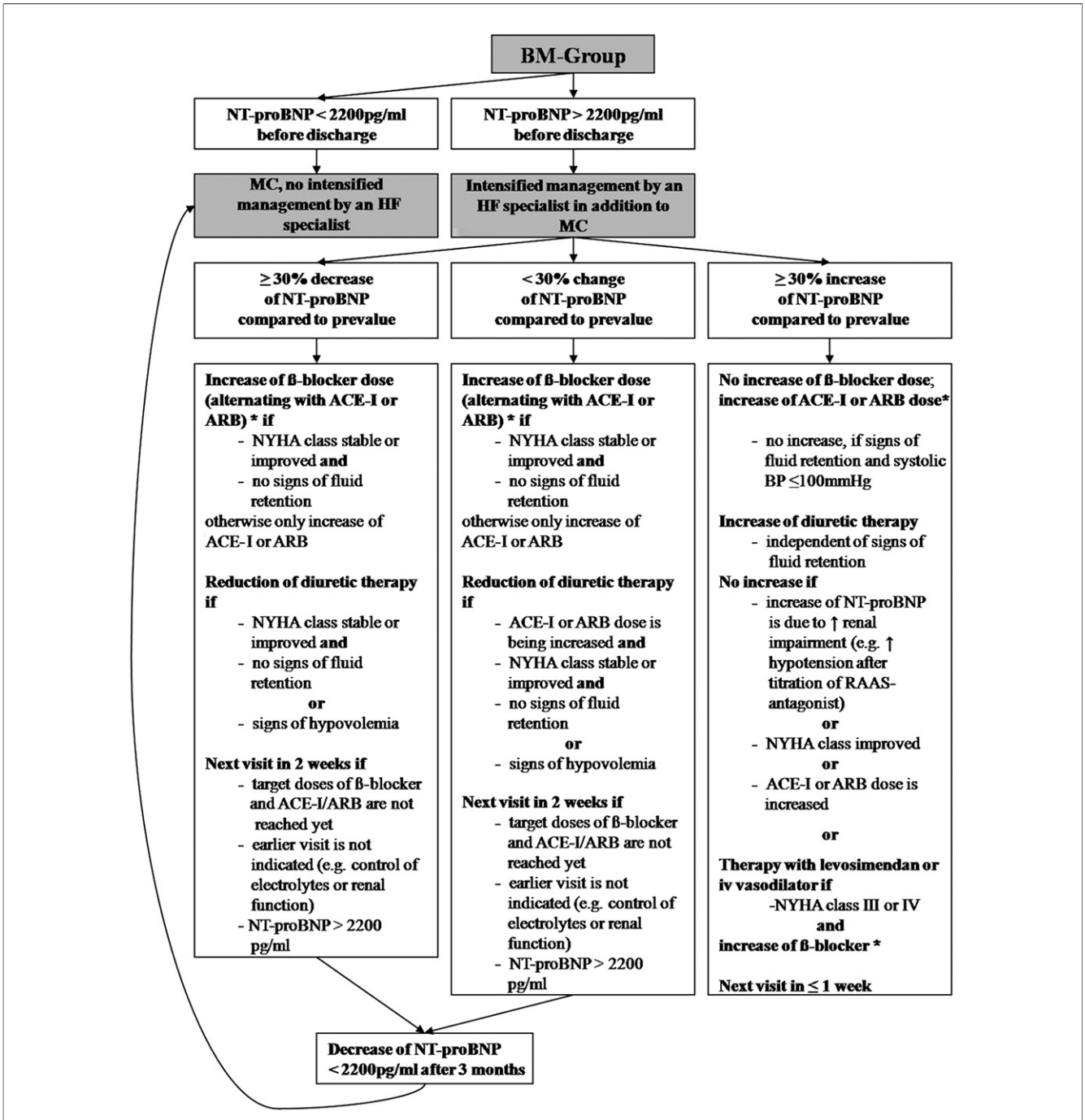

Figure 1 **Recommendations for BM**

N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels were used to determine the intensity of care during medical optimization, thereby selecting high-risk patients (NT-proBNP >2,200 pg/ml) for intensified care by heart failure (HF) specialists and discharging them from this care in case of a decrease of NT-proBNP <2,200 pg/ml after 3 or 6 months. In high-risk patients, the course of NT-proBNP levels was used in addition to other clinical and laboratory parameters for integrated clinical management (e.g., adaptation of diuretic regimen, speed of dose-increase of neurohormonal antagonists, schedule of visits). *Increase of angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) or beta-blocker only in the absence of: 1) symptomatic hypotension; 2) significant increase of serum creatinine (>0.3 mg/dl or >50% of serum creatinine >2.5 mg/dl); and 3) for beta-blocker, heart rate ≥60 beats/min. BM = N-terminal pro–B-type natriuretic peptide-guided, intensive patient management; BP = blood pressure; iv = intravenous; MC = multidisciplinary care; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system.

groups. The decrease of NT-proBNP levels from discharge to follow-up was more pronounced in the BM group than in the MC group. No decrease was observed in the UC group (Fig. 4).

Outcome. BM reduced days of HF hospitalization (488 days) when compared with hospitalization for the MC (1,254 days) and UC groups (1,588 days) ($p = 0.0001$; significant differences among all groups). Using Kaplan-

Table 1 Patient Characteristics

Variable	UC (n = 90)	Nurse-Led MC (n = 96)	BM (n = 92)
Mean age, yrs	71 ± 13	73 ± 11	70 ± 12
Women	31	30	37
Primary cause of heart failure			
Coronary artery disease	68	64	61
Hypertension	21	25	23
Valve-related	2	5	2
Other	9	6	14
Comorbidities			
Previous myocardial infarction	46	49	42
Hypertension	67	69	65
Atrial fibrillation	31	33	30
Stroke	14	10	12
Chronic obstructive lung disease	21	17	15
Diabetes	33	47	45
Left ventricular systolic function			
Preserved	8	9	2
Mild to moderately reduced	31	18	20
Severely reduced	61	73	76
NT-proBNP, pg/ml*	2,359 (355–15,603)	2,469 (355–18,487)	2,216 (355–9,649)
Systolic blood pressure, mm Hg	123 ± 21	122 ± 18	119 ± 19
Diastolic blood pressure, mm Hg	71 ± 14	72 ± 12	72 ± 13
Heart rate, beats/min	77 ± 16	80 ± 17	79 ± 19
Serum creatinine >2 mg/dl	17	17	15

Values are mean ± SD or % unless otherwise indicated. *Mean and 95% confidence intervals were computed on the log-scale and back-transformed to the original scale.

BM = N-terminal pro–B-type natriuretic peptide-guided, intensive patient management; MC = multidisciplinary care; NT-proBNP = N-terminal pro–B-type natriuretic peptide; UC = usual care.

Meier analysis, the first HF rehospitalization (28%) was lower in the BM group than in the MC group (40%; $p = 0.06$), and in the MC versus UC group (61%; $p = 0.01$). Moreover, the combined end point of death or HF rehospitalization (Fig. 5) was lower in the BM (37%) than in the MC group (50%; $p < 0.05$), and in the MC versus UC group (65%; $p = 0.04$). Death rate was similar between the BM (22%) and MC groups (22%), but was lower than the UC group (39%; vs. BM: $p < 0.02$; vs. MC: $p < 0.02$).

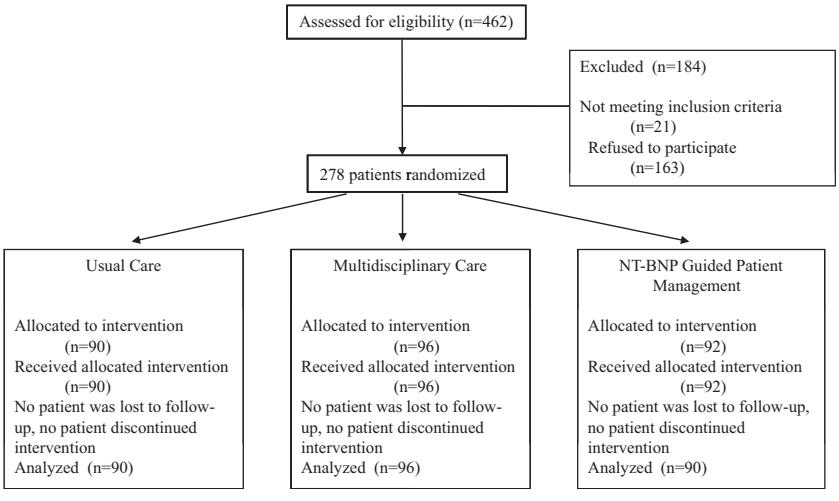

Figure 2 Consort Diagram

A total of 462 patients were screened for the study, of which 21 patients never met eligibility criteria. Of 441 eligible patients, 163 refused to participate, and the remaining 278 patients were randomized to BM (n = 92), MC (n = 96), and usual care (n = 90). Abbreviations as in Figure 1.

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Table 2 Interventions and Days in Hospital Due to HF

Variable	UC (n = 90)	Nurse-Led MC (n = 96)	BM (n = 92)
Ambulatory visits at the CHF specialist			
All visits*	229	511†	564†
Scheduled visits		220	336‡
In patients with NT-proBNP >2,200 pg/ml		116	215‡
In patients with NT-proBNP <2,200 pg/ml		104	121
Unscheduled visits	229	291	228
Telephone contacts with the CHF specialist		103	263‡
Days in hospital due to HF*	1,588	1,254†	488†‡

*Significant difference among groups (for all visits and for days in hospital due to heart failure [HF]: $p < 0.0001$). †Significant difference compared with UC (for all visits: MC vs. UC and BM vs. UC, $p < 0.001$; for days in hospital due to UC: MC vs. UC, $p < 0.04$; BM vs. UC, $p < 0.001$). ‡Significant difference compared with MC (for scheduled visits: $p = 0.0005$; for scheduled visits in patients with NT-proBNP >2,200 pg/ml: $p = 0.0002$; for telephone contacts with the chronic heart failure [CHF] specialist: $p < 0.0001$; for days in hospital due to HF: $p < 0.04$).
Abbreviations as in Table 1.

In the multivariable model, NT-proBNP was the strongest independent predictor, with treatment allocation providing additional prognostic information for first HF rehospitalization, death, and the combination of these end points. Left ventricular systolic function and diabetes were other independent predictors of first HF rehospitalization, whereas chronic obstructive lung disease independently predicted death. Treatment allocation and age were univariate predictors of each end point. Using a simple model including age, treatment allocation, and an interaction term between these 2, we found no interaction between age and treatment allocation indicating that treatment allocation predicted outcome irrespective of age.

Discussion

This is the first study utilizing the prognostic power of discharge NPs for individualized post-discharge management. Patients with high discharge NT-proBNP were referred to multidisciplinary management with intensified care by a CHF specialist and transferred to a nurse-led multidisciplinary management as soon as NT-proBNP fell below the limit. This approach ensured rapid up-titration of therapy guided by NT-proBNP in patients at highest risk for cardiac decompensation. Consequently, such treatment, when compared with nurse-led multidisciplinary management alone, was associated with a higher proportion of antineurohormonal triple therapy, more frequent adjustments of diuretics, a more pronounced decrease in NT-proBNP levels, and an improved outcome. The intensified patient management, as used in the high NT-proBNP subgroup in BM, was not accompanied by an increase in total visits to the HF specialist. This was because of the shift of intensified treatment from decompensated patients in MC to patients with imminent decompensation in BM, which obviously served as a preventive strategy.

NT-proBNP for treatment monitoring. Ambulatory medical HF treatment includes antineurohormonal (and vasodilator) treatment as well as diuretic therapy. Both treatment principles reduce ventricular wall stress, either by reducing pre-load and afterload and stopping and even reversing ventricular remodeling, or by achieving and maintaining euvolemia. Natriuretic peptides allow for direct assessment of this ventricular wall stress. Up to now, various studies used NPs as guidance for HF therapy, thereby aiming to decrease NP levels below a certain cutoff value: BNP 50 pg/ml (13), BNP 200 pmol/ml (14), BNP 100 pg/ml (15), or NT-proBNP 2 times or less the upper limit of normal (16,17). One study titrated ACE-Is up to doses exceeding target doses and further added angiotensin-receptor blockers if necessary (13). Other studies intensified drug treatment according to a stepwise protocol. One protocol started with maximization of ACE-Is, followed by an increase in loop diuretic, then addition of digoxin, another diuretic, and finally addition of vasodilators (first isosorbide mononitrate, then felodipine) (14). The protocol of the TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart

Table 3 Medical Therapy: Discharge and Follow-Up

Variable	UC (n = 90)	Nurse-Led MC (n = 96)	BM (n = 92)
Discharge			
ACE-Is or ARBs	89	88	91
% of target dose	52 ± 38	50 ± 39	51 ± 37
Beta-blockers	73	76	82
% of target dose	35 ± 32	32 ± 32	36 ± 23
Spironolactone	37	42	45
Dose, mg/day	63 ± 43	55 ± 32	52 ± 31
Triple therapy	7	4	7
Combination of ACE-I and ARB	0	0	0
Furosemide	81	78	85
Dose, mg/day	65 ± 40	74 ± 44	66 ± 50
Follow-up			
ACE-Is or ARBs	87	88	92
% of target dose*	54 ± 38	97 ± 62†	100 ± 64†
Beta-blockers	76	92	88
% of target dose*	38 ± 27	58 ± 35†	73 ± 39†‡
Spironolactone	46	49	53
Dose, mg/day	48 ± 35	36 ± 19	42 ± 20
Triple therapy	9	20†	37†‡
Combination of ACE-I and ARB*	0	39†	44†
Furosemide	79	72	76
Dose, mg/day*	76 ± 90	62 ± 68	47 ± 45†

Values are % or mean ± SD. Triple therapy is spironolactone and ≥50% of the target dose of an ACE-I/ARB and of a beta-blocker. *Significant difference among groups (% of ACE-I or ARB target dose: $p < 0.0001$; % of beta-blocker target dose: $p < 0.0001$; furosemide dose: $p < 0.05$). †Significant difference compared with UC (for triple therapy: MC vs. UC, $p = 0.03$; BM vs. UC, $p < 0.0001$; for the combination of ACE-I and ARB: MC vs. UC, $p < 0.0001$; BM vs. UC, $p < 0.0001$). ‡Significant difference compared with MC (for triple therapy: BM vs. UC, $p = 0.009$).
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; other abbreviations as in Table 1.

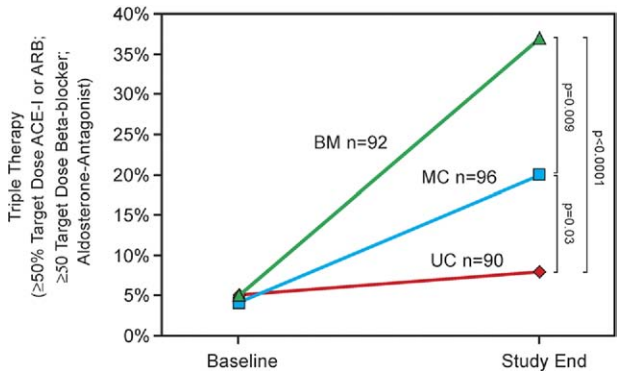

Figure 3 **Effect of UC, MC, and BM on Heart Failure Therapy**

The proportion of triple therapy (spironolactone and ≥50% of the target dose of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and of a beta-blocker) was similar among groups at baseline, but was higher in the BM group versus the MC group, and higher in the MC versus the usual care (UC) group at follow-up. Abbreviations as in Figure 1.

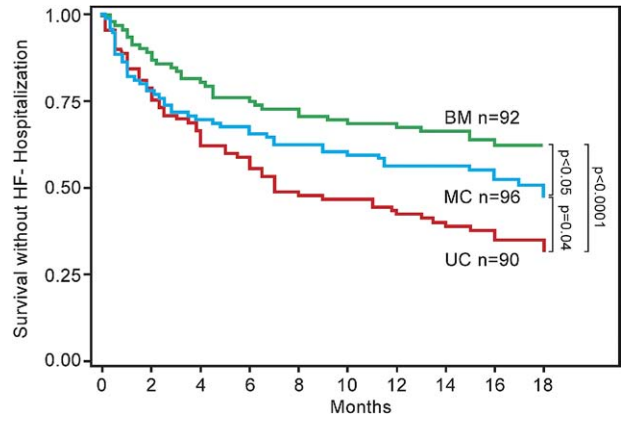

Figure 5 **Survival Without HF Hospitalization**

Up to 18 months, the combined end point of death or heart failure (HF) hospitalization was lower in the BM (37%) versus MC group (50%; $p < 0.05$) and in the MC versus UC group (65%; $p = 0.04$). Abbreviations as in Figures 1 and 3.

Failure) (16) started with adding spironolactone and continued with up-titration of ACE-Is, angiotensin-receptor blockers, and beta-blockers; addition of loop diuretics; low-dose digoxin; long-acting nitrates; metolazone or another thiazide; molsidomide during nitrate-free intervals; and intravenous diuretics or inotropes. In the STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) study, medical treatment was intensified according to the judgment of the investigator, an approach that resulted in a change of furosemide in 55% versus 26% of the patients, spironolactone in 17% versus 7%, ACE-Is or angiotensin-receptor blockers in 21% versus 9%, and beta-blockers in 36% versus 20% of the patients (15). In these various studies, the NP-guided strategies were compared either with up-titration of neurohormonal therapy to target doses independent of symptoms or with symptom-guided up-titration of neurohormonal therapy as well as adjustment of diuretics targeting clinical stability. The key objective of the STARBRITE (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide versus the Clinical Congestion Score) study (17) was to test 2 different outpatient fluid-management strategies, 1 strategy guided by BNP levels as well as clinical targets and another strategy using clinical targets alone.

Regarding symptom- or NP-guided up-titration of neurohormonal antagonists, 1 major criticism was that neurohormonal antagonists should be up-titrated to target doses proven to prolong life or to maximally tolerated doses in all CHF patients, irrespective of symptoms or NP levels (18), especially as their effects on outcome are dose-dependent (19). In some

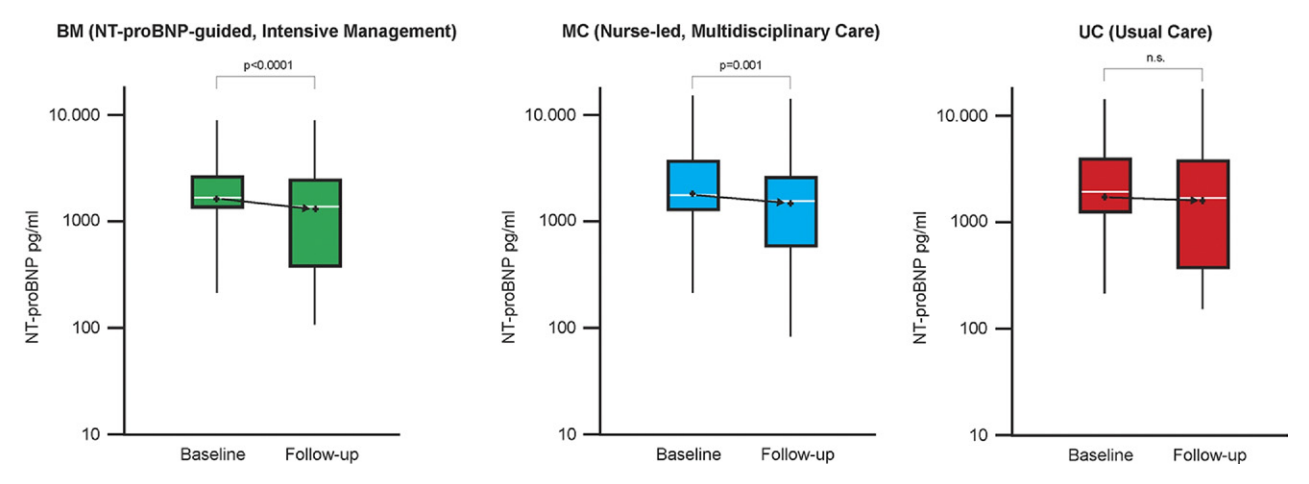

Figure 4 **Baseline and Follow-Up Values of NT-ProBNP**

Box plot with mean [+], median, lower and upper quartiles, and 95% confidence intervals: the decrease of NT-proBNP levels from discharge to follow-up was more pronounced in the BM group than in the MC group. No decrease was observed in the UC group. Abbreviations as in Figures 1 and 3.

studies evaluating NP-guided therapy, patients under conventional (i.e., non–NP-guided) therapy tended to be undertreated. In contrast, our study assessed NT-proBNP primarily as guidance of patient management instead of medical therapy by selecting high-risk patients for intensified management. This concept of NP-guided management has now been taken over by a Danish group of investigators, who are testing the effects of close monitoring of high-risk patients (defined by NP) despite clinical stability under optimized medical therapy (20). In addition to the guidance of patient management, our HF specialists used NT-proBNP together with other clinical and laboratory parameters for integrated clinical management (e.g., adaptation of diuretic regimen, rate of dose-increase of neurohormonal antagonists, or schedule of visits) in patients with levels >2,200 pg/ml. According to the recommendations presented in Figure 1, they reacted to increasing NT-proBNP levels by intensifying the diuretic regimen (depending on renal function) and by interrupting or slowing further up-titration of beta-blockers. In case of stable or decreasing NT-proBNP levels, they fastened the up-titration of beta-blockers and reduced doses of diuretics. Patients whose NT-proBNP level decreased to <2,200 pg/ml within 3 or 6 months were discharged from intensified up-titration management by CHF specialists but still received ongoing care by the nurse-led multidisciplinary approach. With this management design, optimization of CHF therapy was achieved in all patients within months, but intensified care by CHF specialists was reserved only for patients at highest risk of cardiac decompensation as estimated by high NT-proBNP levels. Thereby, BM improved the outcome of CHF patients, even when compared with nurse-led MC alone, which is currently regarded as optimal care for ambulatory CHF patients.

We decided not to change the treatment strategy in response to NT-proBNP until 3 months had elapsed, which we believed was necessary for medical up-titration in high-risk patients. Moreover, a significant decrease of NT-proBNP could not be expected before 3 months, as treatment with renin-angiotensin-aldosterone system antagonists as well as beta-blockers had to be optimized in most patients. During alternate up-titration, the decrease of natriuretic peptides by renin-angiotensin-aldosterone system antagonists is counterbalanced by the opposing effect of beta-blockers on plasma NPs (21).

Role of CHF specialists in multidisciplinary management. Medical up-titration in severe CHF patients with the highest risk is the most challenging. A subgroup analysis from the COPERNICUS (Effect of Carvedilol on Survival in Severe Chronic Heart Failure) trial revealed that the most severe patients at the highest risk had the highest rate of carvedilol withdrawal (20%) and failure of reaching target doses (50%). However, they also had the highest absolute benefit from carvedilol (22). It is difficult to up-titrate beta-blockers in these patients, as side effects such as hypotension and associated renal dysfunction or decompensation are likely to occur. Similarly, the up-titration of renin-angiotensin-aldosterone system antagonists and their combined use can cause acute renal failure and hyperkalemia (23). The important role of specialist care in severe CHF patients at the highest risk has been recently suggested (24). Therefore, in these patients the potential for medical up-titration in usual and ambulatory nurse care must be limited due to safety concerns. This suggestion was confirmed by our findings.

Intensity of care. We cannot differentiate whether intensified patient management provided to high-risk patients of the BM group or NT-proBNP–guided management contributed more to improving outcomes, as this was not the aim of our study. However, recently, a large multicenter trial (the COACH [Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure]) demonstrated that increasing the intensity of care from moderate to intensive disease management has no beneficial effect (25). As also shown in other studies, the intensive care strategy even tended to increase the number of HF rehospitalizations. The reason for this may be the low-threshold access to care providers, resulting in relatively easy hospital admission in case of clinical deterioration. In contrast, our approach in the BM group led to a decrease in the number of rehospitalizations. The assessment of NT-proBNP allowed for the monitoring of short-term changes in cardiac wall stress and, thereby, the anticipation of cardiac decompensation, which facilitated medical adjustment in advance. Interestingly, the increase in the number of scheduled contacts for the BM group did not significantly increase overall contacts with HF specialists, as unscheduled contacts due to clinical deterioration decreased in trend when compared with MC alone.

Study limitations. Of 441 eligible patients, 163 (37%) refused to participate in the study. This phenomenon has been described previously (26) and can be attributed to patients' inability to attend scheduled ambulatory visits due to reduced mobility (comorbidities, high age, reduced social contacts), the unwanted intrusion into patients' privacy during home visits, and negative psychology associated with being a test subject. As a result, study subjects may have been more motivated than those refusing to participate may have been, a fact that might have positively influenced the outcome in the intervention groups but also in the UC group. However, as a similar selection bias can be expected in real-world multidisciplinary programs, we can assume that the results of this study also apply to daily clinical practice. Another limitation represents the fact that both the patients and providers knew they were in an intervention group (BM and MC). This awareness might have resulted in a competitive stimulus with optimal dedication of the providers and compliance of the patients. In reality, effects might be lower. Moreover, the study group consists almost entirely of patients with systolic dysfunction. Therefore, our study does not provide information regarding the effect of BM in the large subgroup of CHF patients with preserved ejection fraction.

Cost-effectiveness. Cost-effectiveness is an important factor in the context of HF management programs. Although the number of programs increased during the last few years, health care insurance covers the costs in only a small proportion of programs. Many HF programs are financed partly or completely by the pharmaceutical industry, a fact

that imposes a threat for their continuity (27). Therefore, the question faced is how to focus limited resources on the patients who are in need of such an intervention. Our study does not only demonstrate that MC improves outcome but also shows that focusing intensified care to high-risk patients improves outcome without further increasing the consumption of resources. Thereby, this concept might improve the cost-effectiveness ratio of HF programs.

Conclusions

Our study proves the concept of applying intensified treatment to patients at high risk for cardiac decompensation selected via NT-proBNP levels and of adjusting medical treatment in advance according to short-term changes in NT-proBNP levels. However, deployment of this concept (BM) using ambulatory HF specialists and home nurses may not be feasible in all health care systems, and further adaptation of this approach will be necessary in different settings. As primary care is not very effective in the management of these patients, BM may only be successful in combination with other disease management programs. Most European and North American countries have established HF units, which could use BM to select high-risk patients for intensified care and discharge them to less intensive care following stabilization. It could be expected that BM combined with a disease management program, such as an HF unit, improves the outcome of the HF population without the use of increasing personal and financial resources. It will be worthwhile to study such possibilities, especially in light of the current financial strain on most health care systems.

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REFERENCES

1. Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007;297:61–70.
2. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admissions with decompensated heart failure. Heart 1998;80:437–41.
3. McAlister FA, Stewart S, Ferrua S, McMurray JJV. Multidisciplinary strategies for the management of heart failure patients at high risk for admission. J Am Coll Cardiol 2004;44:810–9.
4. Blue L, McMurray J. How much responsibility should heart failure nurses take? Eur J Heart Fail 2005;7:351–61.
5. Cleland JGF, Louis AA, Rigby AS, Janssens U, Balk AHMM. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death. J Am Coll Cardiol 2005;45:1654–64.
6. Berger R, Hülsmann M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392–7.
7. Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol 2004;43:635–41.
8. Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure. J Am Coll Cardiol 2001;37:386–91.
9. Moertl D, Hammer A, Huelsmann M, Pacher R, Berger R. Prognostic value of sequential measurements of amino-terminal prohormone of B-type natriuretic peptide in ambulatory heart failure patients. Eur J Heart Fail 2008;10:404–11.
10. Knebel F, Schimke I, Pliet K, et al. NT-proBNP in acute heart failure: correlation with invasively measured hemodynamic parameters during recompensation. J Card Fail 2005;11:S38–41.
11. Richards M, Nicholls MG, Espiner EA, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. J Am Coll Cardiol 2006;47:61–4.
12. Wu AH, Smith A, Wieczorek S, et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am J Cardiol 2003;92:628–31.
13. Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1999;138:1126–32.
14. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide. Lancet 2000;355:1126–30.
15. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure. J Am Coll Cardiol 2007;49:1733–9.
16. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383–92.
17. Shah MR, on behalf of the STARBRITE Investigators. STARBRITE: a randomized pilot trial of BNP-guided therapy in patients with advanced heart failure. Circulation 2006;114:II-528 (Abstract).
18. Packer M. Should B-type natriuretic peptide be measured routinely to guide the diagnosis and management of chronic heart failure? Circulation 2003;108:2950–3.
19. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807–16.
20. Schou M, Gustafsson F, Videbaek L, et al. Design and methodology of the NorthStar Study: NT-proBNP stratified follow-up in outpatient heart failure clinics—a randomized Danish multicenter study. Am Heart J 2008:154:649–55.
21. Davis ME, Richards M, Nicholls G, Yandle TG, Framton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. Circulation 2006;113:977–85.
22. Rouleau JL, Roecker EB, Tendera M, et al. Influence of pre-treatment systolic blood pressure on the effect of Carvedilol in patients with severe chronic heart failure. J Am Coll Cardiol 2004;43:1423–9.
23. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 2004;351:543–51.
24. Jong P, Gong Y, Liu PP, Austin PC, Lee DS, Tu JV. Care and outcomes of patients newly hospitalized for heart failure in the community treated by cardiologists compared with other specialists. Circulation 2003;108:184–91.
25. Jaarsma T, van der Wal MHL, Lesman-Leegte I, et al. Effect of moderate or intensive disease management program on outcome in patients with heart failure. Arch Intern Med 2008;168:316–24.
26. Ekman I, Andersson B, Ehnforst M, Matejkat G, Persson B, Fagerberg B. Feasibility of a nurse-monitored, outpatient-care programme for elderly patients with moderate-to-severe, chronic heart failure. Eur Heart J 1998;19:1254–60.
27. Jaarsma T, Tan B, Bos RJ, Veldhuisen DJ. Heart failure clinics in the Netherlands in 2003. Eur J Cardiovasc Nurs 2004;3:271–4.

Key Words: chronic heart failure ■ multidisciplinary care ■ nurse ■ natriuretic peptide.

N-Terminal Pro B-Type Natriuretic Peptide Guided, Intensive Patient Management in Addition to Multidisciplinary Care in Chronic Heart Failure: A 3-Arm, Prospective, Randomized Pilot Study

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