Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome

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TITLE PAGE

Brain natriuretic peptide guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure. Responders to treatment have a significantly better outcome.

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ABSTRACT

Aim: To determine if brain natriuretic peptide (BNP) -guided heart failure (HF) treatment improves morbidity and/or mortality when compared to conventional treatment.

Methods and Results:

UPSTEP was an investigator-initiated, randomized, parallel group, multicentre study with a PROBE design. Symptomatic patients with worsening HF, NYHA class II–IV, ejection fraction <40% and elevated BNP levels, were included. All patients (n=279) were treated according to recommended guidelines and randomized to BNP- guided (BNP) or to conventional (CTR) HF treatment.

The goal was to reduce BNP levels to < 150 ng/L in younger patients and < 300 ng/L in elderly patients, respectively. The primary outcome was a composite of death due to any cause, need for hospitalization and worsening HF. The study groups were well matched, including for BNP concentration at entry (mean: 808 ng/L vs. 899 ng/L; p=0.34).

There were no significant differences between the groups regarding either the primary outcome (p = 0.18) or any of the secondary endpoints. There were no differences for the pre-specified analyses; days out of hospital, and younger vs. elderly. A subgroup analysis comparing treatment responders (> 30% decrease in baseline BNP value) vs. non-responders found improved survival among responders (p<0.0001 for the primary outcome), and all of the secondary endpoints were also improved.

Conclusions: Morbidity and mortality were not improved by HF treatment guided by BNP levels. However, BNP responders had a significantly better clinical outcome than non-responders. Future research is needed to elucidate the responsible pathophysiological mechanisms in this sub-population.

Keywords: PROBE design; systolic heart failure; natriuretic peptides; BNP-guided treatment

Introduction

In recent years, the prevalence of heart failure (HF) in the western world has continued to increase, especially in patients older than 65 years. Recommended drugs are underutilized and only a small proportion of HF patients receive optimal treatment according to current guidelines (1). Moreover, patients with mild to moderate HF are sometimes not even diagnosed(2), leading to over- or under-treatment which might affect prognosis(3).

An increase in left ventricular filling pressures starts before patients develop signs or symptoms of HF, indicating that patients have an asymptomatic phase with depressed cardiac function prior to seeking medical attention (4, 5).

Clinical signs and symptoms are not the optimal way to guide treatment if we also wish to reduce morbidity and mortality. Natriuretic peptides are highly correlated to left ventricular filling pressure (4) and may serve as a useful tool in guiding the medical treatment of patients. Brain natriuretic peptide (BNP) is a useful prognostic marker for mortality and morbidity (6, 7), and prognosis of HF patients may be improved if therapy is guided by BNP levels rather than directed by clinical signs and symptoms and adherence to standardized medical therapy, as shown by Troughton et al (8). However, this study enrolled a limited number of patients (n=69) and results from subsequent studies have shown both positive (9) and negative findings, especially in elderly patients (10). There remains a need for further investigation, especially in elderly patients, to determine if BNP-guided treatment is beneficial and can be used in routine management of patients with HF.

The aim of this study was therefore to evaluate whether BNP-guided HF treatment improves morbidity and/or mortality when compared to therapy implemented by a treating physician at sites experienced in managing patients with HF according to guidelines. In this study we present new data on BNP-guided therapy in a well-treated elderly HF population

Methods

Patients

The study was conducted in 19 hospitals in Sweden (n=15) and Norway (n=4) by physicians experienced in managing HF (Appendix).

Inclusion criteria: Patients older than 18 years with verified systolic HF and a left ventricular ejection fraction (LVEF) < 40% (assessed within the last 6 months), NYHA class II-IV, signs and/or symptoms of worsening HF within the last month (requiring hospitalization and/or intravenous diuretic treatment, metolazone, or increased daily dosages of diuretics and/or need of intravenous inotropic support) were recruited. The patients were required to have elevated plasma concentrations of BNP (>150 ng/L for those aged <75 years, and >300 ng/L for those aged >75 years).

The patients were required to have ongoing standard HF treatment according to guidelines, defined as basic treatment with ACE-inhibitors (ACE I) or angiotensin II receptor blockers (ARB), beta blockers (BB), and diuretics, if fluid retention existed. In addition, they could also be treated with aldosterone antagonists (AA) and/or digoxin.

Exclusion criteria: Patients were ineligible for participation if any of the following conditions existed: haemodynamically unstable patients on the waiting list for cardiac surgery (cardiac transplantation, revascularization, or heart valve surgery); patients with a myocardial infarction within the last three months; patients with haemodynamically significant valvular heart disease; patients with impaired renal (s-creatinine > 250 μmol/L) or liver function (liver enzymes more than three times normal value); patients with severely decreased pulmonary

function; patients with a limited life expectancy; and patients unable to give informed consent or unable to follow the study schedule, as well as those patients participating in another trial.

Study design: UPSTEP (Use of PeptideS in Tailoring hEart failure Project) was an investigator- initiated, Scandinavian, randomized, parallel group multicentre study with a PROBE (prospective, randomized, open, blinded evaluation) design. After having met the inclusion criteria, patients were randomized into two treatment groups: the BNP-guided group (BNP-group) and the Control group (CTR-group). The randomization of patients was carried out in blocks of 12 within each centre.

BNP-guided group (BNP-group).

In the BNP-guided group, medical treatment was guided by the plasma concentration of BNP. The goal was to reduce BNP levels to <150 ng/L in patients aged <75 years and <300 ng/L in patients aged ≥75 years.

Treatment recommendations in order to reduce elevated BNP levels or signs/symptoms of worsening HF were suggested according to the following schedule**:** increase ACE I/ARB to maximally tolerated or to target dose according to guidelines; increase BB to maximally tolerated or to target dose according to guidelines; add AA in low dose (spironolactone 25 mg); add ARB and increase to target dose according to guidelines; increase ACE I /ARB to up to twice the target dose; increase BB to up to twice the target dose; increase spironolactone to up to 50 mg. The adjustment of loop diuretic dose was left to the discretion of the investigator.

The patients were made aware of their BNP value in order to increase motivation to adhere to treatment.

Control group (CTR-group):

In the CTR-group medical treatment was adjusted according to the discretion of the investigator and based on changes in clinical status and/or signs of worsening HF and in accordance with the guidelines (1). The physicians were not allowed to take blood samples for measurement of BNP during the study except at inclusion and at study end.

Study performance

Outpatient visits were scheduled at weeks 2, 6, 10, 16, 24, 36, 48 and then every 6 months as long as the study was ongoing. The last included patient was required to have a follow-up of at least 12 months. Every study visit included a history, physical examination, blood sampling for measurements of electrolytes and renal function, as well as measurement of BNP in the BNP-group.

Primary outcome variable: The primary outcome variable was a composite of death due to any cause, need for hospitalization and worsening HF. Worsening HF was defined as a need to increase diuretics orally or intravenously but no need for hospitalization.

Secondary outcome variables: Total mortality, cardiovascular mortality, HF-related death, all-cause hospitalization, cardiovascular hospitalization, HF-related hospitalization, worsening HF. All endpoints were adjudicated using a predefined endpoint protocol by a committee with two experienced cardiologists who did not participate in the study and were blinded to study results.

Prespecified analyses: Statistical analysis was performed on each of the following prespecified subgroups: age < 75 years vs. age $\geq$ 75 years; days in hospital; and responders vs. non-responders. Responders were defined as patients who demonstrated a fall in BNP level of

≥ 30% at the week 48 visit compared to baseline. Study patients who died before week 48 were classified as responders if any BNP value was 30% less than at baseline. Patients with a missing value at week 48 were defined as responders if any BNP value demonstrated a reduction of >30% during follow-up when compared to the baseline value.

Measurement of brain natriuretic peptide

Blood samples for BNP measurement were collected in EDTA-coated vials and analysed with a fluorescence immunoassay technique (Biosite Inc, San Diego, California, USA). This technique produces a measurement within 15 minutes and all centres were equipped with instruments for analysing BNP at the time of the patient visit. This analysis technique has been described in detail previously (11, 12). The coefficient of variation for intra-assay precision is 9.9% for 71.3 ng/l, 12.0% for 629.9 ng/l and 12.2 % for 4087.9 ng/l. The coefficient of variation for inter-assay precision was 10% for 28.8 ng/l, 12.4% for 584 ng/l and 14.8% for 1,180 ng/l, according to the manufacturer.

Ethics

The study protocol was approved by the Regional Ethical Review Board in Linkoping, Sweden. Every patient signed an informed consent before entering the trial.

Statistics

Analysis of treatment strategies was performed according to the intention-to-treat principle. Based on statistical calculations it was hypothesized that the incidence of the primary outcome would be 30% in the clinical group and 15% in the BNP-titrated group during a mean follow-up of one year. With 80% power at the 5% level of significance, 121 patients

were therefore needed in each group. With a withdrawal rate estimated at around 10%, 270 patients needed to be included in the trial.

Descriptive statistics with means and standard deviation (SD) values for continuous variables and percentages for categorical variables were calculated for baseline characteristics. Pearson's product-moment correlation coefficients or Spearman rank-order correlation coefficients where appropriate were used to examine the associations between the studied variables. Differences in mean values between groups were analyzed using the Student's two-tailed t-test for normally distributed data. For non-normally distributed variables, the non-parametric Mann-Whitney *U* test was used. Differences in proportions were tested using Chi-square test.

Interactions between intervention and patient characteristics were analysed using multivariate Cox regression. According to routine statistical procedures, centres with fewer than 5 patients were amalgamated into one group. Survival was evaluated with the Kaplan-Meier method. The cut-off point in the follow-up was set at 1,000 days, since at this time there were less than 25 patients in each group (post hoc decision). All calculations were performed on commercial statistical software packages (Statistica v9) (Statsoft Inc, Tulsa, OK, USA).

Results

Study population

The study population consisted of 279 patients, all with a diagnosis based on signs and symptoms of heart failure and echocardiographic confirmation of left ventricular systolic dysfunction (EF < 40%). Baseline characteristics (table 1) show that the two groups were well balanced according to sex, history, functional class, plasma concentration of BNP and drug treatment at the start of the study.

Eleven patients (7 patients in the BNP-group and 4 patients in CTR-group) dropped out during the study for various reasons, but mainly because of unwillingness to continue.

Most patients were in NYHA functional class III (55%) and IV (14%). Mean values of plasma concentrations of BNP were 808 ng/L versus 899 ng/L (Table 1) and median values were 631 ng/L versus 596 ng/L, in the BNP and CTR-groups, respectively. Both groups were well treated at baseline. For example, we found that 146/147 patients (99%) in the BNP-group vs. 129/132 patients (98%) in the CTR-group, were receiving treatment with RAS-blockers.

Medication doses during follow-up are given in table 2. There were no significant differences in medication doses between the groups during follow-up. We found a significant increase in ACEI and BB doses in both groups at study end compared to study start. Doses of ARBs were significantly increased in the BNP group but not in the CTR-group during the study. As shown in table 2, patients in both groups were already receiving medication according to given guidelines at the start of the study.

A substantial number of patients had renal dysfunction defined as an eGFR<60mL/min/1.73 m^2 (52% in the BNP-group vs 51% in the CTR-group, respectively). (Table 1)

Primary outcome variable

There was no significant difference in the primary outcome variable between groups. Even after univariate Cox proportional regression analysis, no significant difference in risk of the primary outcome variable was found between the BNP-group and the CTR-group; (HR 0.82, 95%CI 0,6-1,1; p = 0.18). The time course for the primary outcome is illustrated in Figure 1.

Secondary outcome variables

No difference was seen with regard to any of the secondary outcome variables between the BNP-group and CTR-group apart from worsening HF (Table 3). We analyzed time (days) to the first event of cardiovascular (CV) hospitalization, HF hospitalization, and all-cause hospitalization and also time to all-cause mortality, CV mortality and HF mortality. With BNP-guided therapy we found a significantly longer time to first event of worsening HF (table 3).

Prespecified subgroup analyses

(i) Age

For the prespecified subgroup, age < 75 years vs. age ≥ 75 years, we found no significant differences in risk for the primary outcome variable. For the group < 75 years there were 45 primary outcome events in the BNP-group (82 patients) compared to 51 events in the CTR-group (81 patients) (HR 0.86 95% CI 0.58-1.28, p= 0.46). For the group ≥ 75 years there were

40 primary outcome events in the BNP-group (58 patients) compared to 37 events in the CTR-group (47 patients) (HR 0.71 95% CI 0.45-1.11, p= 0.14).

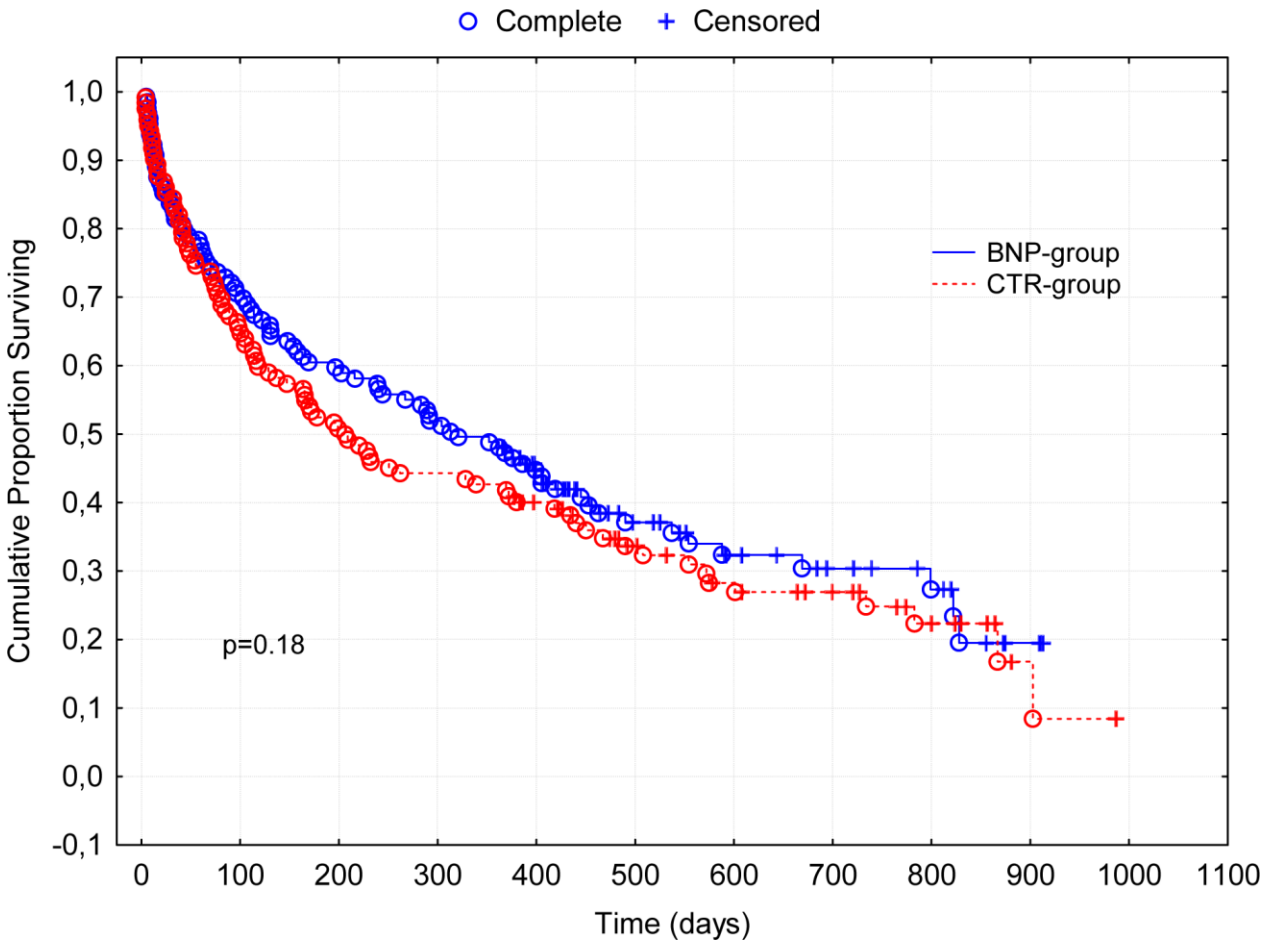

Figure 1. Kaplan-Meier analysis of primary outcome (death from any cause, need for hospitalization and worsening HF) in BNP-guided treatment (BNP-group) vs. control (CTR-group) in patients with systolic heart failure

(ii) Days in hospital

We found no significant differences between the groups for days in hospital, (HR 1.03 95% CI 0.77-1.39, p= 0.81) Overall 88 patients in the CTR-group and 90 patients in the BNP-group were hospitalized.

(iii) Responders and non-responders

In the BNP-guided group, 88 of 140 patients (60%) fulfilled the criteria for responders. Baseline characteristics (Table 4) of responders vs. non-responders showed that the non-responders were significantly older (69 ±10 years (SD) vs 75 ±8 years (SD), $p < 0.001$), and had significantly reduced renal function eGFR 68 ±20 (SD) vs. 52 ±20 (SD) mL/min/1.73 m^2 ($p<0.0001$).

Responders had a significantly lower risk in the univariate Cox proportional regression analysis for primary outcome events; (HR: 0.41; 95% CI 0.27- 0.63, $p<0.0001$), which was maintained after multivariate Cox regression analysis (HR 0.45; 95%CI 0.29-0.70, $p=0.0005$). The decrease in risk over time for the primary outcome in the responder group compared to the non-responder group is illustrated in Figure 2.

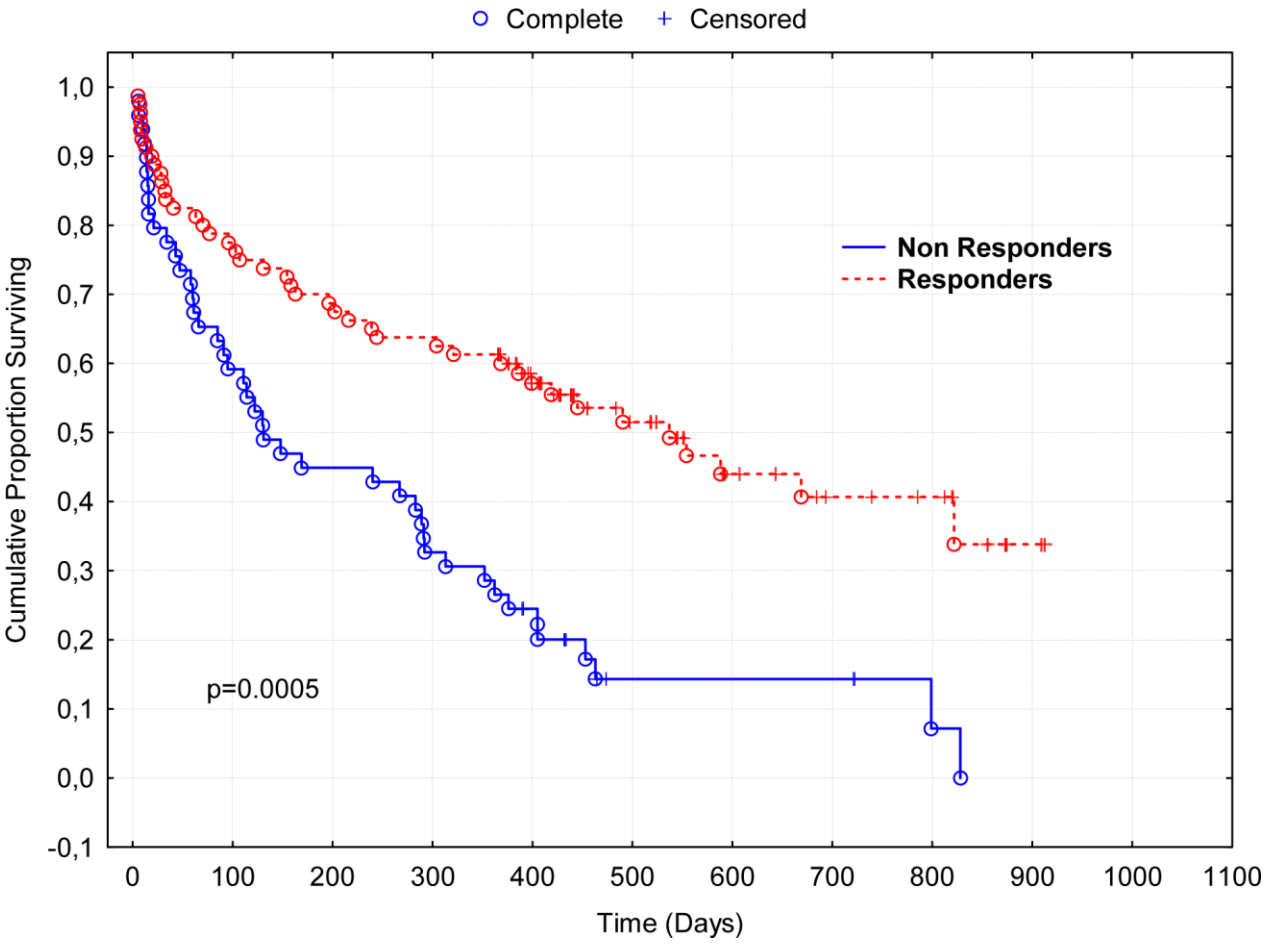

Figure 2**.** Kaplan-Meier analysis of primary outcome (death from any cause, need for hospitalization and worsening HF) in responders vs. non-responders

Significant changes in risk were found for all specified secondary outcome variables in univariate Cox proportional regression analysis between responders and non-responders (Table 5). In multivariate Cox regression analysis for each secondary outcome variable a similarly strong risk reduction was found after adjustment for the following variables: age> 75 years, male gender, NYHA III-IV, hypertension, ischaemic heart disease, eGFR<60 ml/min1.73 m^2, diabetes mellitus, and Hb<120g/l (data not shown).

Discussion

The main finding of the present study was the absence of any significant effect on morbidity and mortality by using a BNP-tailored regimen in our HF patients. The only exception to this was for the variable worsening HF, which is an important but rather "soft" variable compared with other treatment endpoints. What are the possible explanations to this and how well validated is the concept of tailored treatment based on natriuretic peptide values?

Brain natriuretic peptides have been shown to provide important prognostic information for cardiovascular mortality (6, 13, 14). Additionally, the plasma concentration of BNP is lowered with evidence-based pharmacological treatment of HF (15). Therefore, a logical conclusion would be to use plasma concentrations of BNP as a tool to tailor optimal treatment for patients with HF. This approach was first demonstrated by Troughton and colleagues (8). Although the study was small, it suggested a new approach to patient care which could be investigated further with larger studies in different patient populations. To date, three more substantial studies have been published (9, 10, 16) and the concept has also been evaluated in a meta-analysis (17).

Comparison with previously published data

There are four respects in which this study differs from other published studies of BNP/NT-proBNP-guided treatment of HF-patients.

First, the aim of our study to evaluate BNP guided treatment in an elderly population with systolic HF managed by experienced clinicians has never been done previously.

Second, in contrast to BATTLESCARRED and the TIME-CHF study, (10, 16) , we could not show any differences between the older (≥75 years) and younger (< 75 years) patient groups regarding mortality and morbidity outcomes.

Third, our study population differs from other published study populations in that our population was older (9) and, above all, had a baseline median BNP concentration that was higher than most other BNP/NT-proBNP guided trials (9, 10, 16). This implies that our population may have had a significantly higher disease burden when compared to other study populations. This is further emphasized by the fact that 70% of our patients were in NYHA class III or IV and 55% had a marked reduction in their systolic function.

Fourth, our study population was receiving more intensive background therapy at the time of randomization. Already at baseline, the majority of patients were receiving doses according to guidelines (Table 2). Despite this, there were significant increases in ACEIs, BBs, and also in ARBs in the BNP group, at study end compared to study start. We found more changes in the BNP group compared to the CTR-group during follow up: for ACEIs (130 changes in the BNP-group vs 64 in CTR, p-value< 0.0001), for ARBs (209 vs 81 changes, p-value <0.0001) and for AAs (122 vs 72 changes, p-value 0.001). However, BBs were not significantly altered (171 vs 155 changes, p-value 0.84).

This could be explained by the fact that the clinicians at the including centres handled severely diseased patients and, therefore, maximized all options for pharmacological treatment. This raises the question of whether it is possible to improve the patients' pharmacotherapy once they have already reached target doses according to guidelines. There is probably little room for further optimization in this patient group, even if the patient has an increased BNP concentration.

Therefore, pharmacological treatment of HF patients based on BNP/NT-proBNP levels seems, in general, to be an unsuccessful strategy according to the results of this study, particularly for those whose treatment has already been pushed as far as the guidelines recommend. However, in a subgroup analysis, our results indicate that the situation might be different for those who demonstrate a fall in BNP levels as a result of intensification of medical therapy. The underlying mechanism for this finding is still unidentified.

In these "responder" patients we found a highly significant reduction in the primary endpoint, as well as for all other secondary outcome variables. Total mortality and cardiovascular mortality were also significantly lower in responders, but as the number of patients was small we are cautious about drawing conclusions regarding these outcomes.

A significant problem in the analysis was the difference in baseline clinical parameters between responders and non-responders: the non-responder patients were older and had more impaired renal function. But even after adjusting for baseline differences in a Cox proportional hazard regression analysis including age, renal function and other important clinical variables (male gender, NYHA III-IV, hypertension, ischaemic heart disease, diabetes mellitus, Hb<120g/l), the responders still demonstrated a lower risk for the primary outcome

variable, as well as a longer time to first CV event, or time to first heart failure event compared with the non-responders.

Logeart and Bettencourt et al. also reported different BNP response capabilities among HF patients (18, 19). Patients who demonstrated a reduction in plasma concentration of BNP during hospitalization had a better outcome compared to those without a corresponding response, even if the two groups were treated in a similar way. Thus, the mechanisms responsible for the favourable response appear to be central in these patients.

In a retrospective analysis of the SURVIVE trial, Cohen-Solal et al. found that patients who were hospitalized due to acute heart failure and treated with levosimendan, who had a reduction in BNP concentration of 30% or more had a better outcome than those without a corresponding response (20).

These findings also suggest that patients who respond to treatment with a reduction in BNP levels might possess fundamental pathophysiological differences as compared to non-responders. Tools that aid in identifying BNP responders need to be investigated in future studies.

Limitations

The study design was intended to prevent treatment bias in the CTR-group. The vast majority of patients in both the BNP-group and the CTR-group were already optimally treated according to guidelines before the start of the study and this might have prevented us from showing any differences between the two groups, despite the fact that treatment of the patients in the BNP-group was guided by BNP levels. Our study is underpowered and a type II error cannot be excluded. Another limitation, which could also be regarded as a strength, is that most of the sites involved in this study were very experienced in managing patients with HF and had established the concept of HF clinics. In areas and settings without this

organization of heart failure management the value of BNP monitoring might be different to that found in our study.

We believe that the study design substantially impacted on our results by eliminating the opportunity to identify responders and non-responders in the CRT-group where BNP was only measured at baseline and at study end.

Conclusion

We found that morbidity and mortality were not improved by using HF treatment guided by BNP levels compared with treatment guided by signs or symptoms of HF. Neither were there any differences in the subgroups of patients aged below or above 75 years or according to the number of days in hospital.

However, in "BNP responders" to treatment there were significant reductions in all primary, as well as secondary, outcome variables. The findings suggest that a fundamental difference in pathophysiological mechanisms may exist and warrants further studies to increase our understanding of BNP response to treatment.

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Conflict of interests

One of the authors (Ulf Dahlström) has served as lecturer for Biosite.

No conflicts of interest for the other authors have been reported.

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Appendix

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Study Coordination and Monitoring

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Table 1 Baseline characteristics of patients in the BNP-guided group (BNP-group) and the control group (CTR-group).

	BNP-group (n=147)	***CTR-group*** (n=132)	***P-value***
Age years mean (SD)	71.6 (±9.7)	70.1(±10)	0.19
<75/>75 years	84/63	84/48	0.27
<75 years mean (SD)	64.7 (±8.6)	65.1 (±7.5)	0.77
>75 years mean (SD)	80.3 (±3.4)	79.5 (±3.0)	0.17
Male/Female n	107/40	96/36	0.99
Sex male (%)	73	73	
Hypertension n (%)	39 (27)	30 (23)	0.46
Diabetes mellitus n (%)	39 (27)	48 (36)	0.08
BMI kg/m² mean (SD)	27.2 (±4.6)	27.4 (±5)	0.68
NYHA II n (%)	47 (32)	36 (27)	0.39
NYHA III n (%)	76 (52)	78 (59)	0.22
NYHA IV n (%)	22 (15)	18 (14)	0.75
LVEF<30% n (%)	84 (57)	76 (58)	0.94
ACEI n (%)	113 (77)	92 (70)	0.17
ARB n (%)	51 (35)	46 (35)	0.98
BB n (%)	137 (93)	125 (95)	0.60
AA n (%)	81 (55)	78 (59)	0.50
Digoxin n (%)	33 (22)	28 (21)	0.80

Diuretics n (%)	128 (87)	121 (92)	0.22
BNP ng/l mean (SD)	808.2 (±676.1)	898.9 (±915.3)	0.34
Creatinine µmol/l mean (SD)	106.3 (±33.3)	109.2 (±34)	0.48
eGFR mL/min/1.73 m^2 mean (SD)	61.4 (±20.9)	60.1 (±20.9)	0.59
eGFR<60 mL/min/1.73 m^2 n (%)	77 (52)	67 (51)	0.79

Notes: AA=Aldosterone antagonist; ACEI=angiotensin converting enzyme inhibitor; ARB= Angiotensin receptor blocker; BB=Beta blocker; BNP = Brain natriuretic peptide; BMI=Body Mass Index; eGFR=estimated glomerular filtration rate (MDRD formula), LVEF = Left ventricular ejection fraction; NYHA = New York Heart Association functional class; SD=standard deviation.

Table 2 Medication during follow up in BNP-group and CTR-group at study start, week 48 and at study end.

Drug	Group	Start dose (mg/day)	p-value (start-w. 48)	Doses at w.48 (mg/day)	p-value (w. 48-end)	Doses at study end (mg/day)	p-value (start-end)
ACEI	CTR	17±7	0.009	20±6	0.81	20±6	0.03
	BNP	17±7	0.0002	21±8	0.69	21±9	0.0001
	p-value*	0.88		0.42		0.22	
BB	CTR	114±68	<0.0001	157±84	0.99	157±76	<0.0001
	BNP	128±71	0.005	155±81	<0.0001	156±89	0.009
	p-value*	0.09		0.90		0.90	
ARB	CTR	19±12	0.43	20±10	0.87	21±11	0.38
	BNP	17±10	0.0001	24±10	0.60	25±9	<0.0001
	p-value*	0.43		0.08		0.06	
AA	CTR	29±11	0.77	28±11	0.86	28±13	0.64
	BNP	27±11	0.80	28±12	0.59	29±15	0.44
	p-value*	0.40		0.86		0.64	
Diuretic	CTR	65±53	0.31	74±74	0.51	82±81	0.08
	BNP	62±55	0.11	74±53	0.99	74±87	0.22
	p-value*	0.65		1.0		0.56	

Notes: Data are shown as mean ±SD (Standard Deviation). *=p-value between groups. Mean doses are given for patients receiving the drug. ACEI are given in enalapril equivalents (10 mg ramipril=20 mg lisinopril= 150 mg captopril = 20 mg enalapril). Beta blockers are given in metoprolol equivalents (10 mg bisoprolol= 50 mg carvedilol= 100 mg atenolol= 200 mg metoprolol). ARB are given in candesartan equivalents (320 mg valsartan= 100 mg losartan= 300 mg irbesartan= 32 mg candesartan). Diuretics are given in furosemide equivalents (bumetanide 1mg= torasemide 10 mg= 40 mg furosemide). Aldosterone antagonist are given in spironolactone equivalents (50 mg eplerenone= 50 mg spironolactone). w.=week.

Table 3 Secondary outcome variables in BNP-guided treatment (BNP-group) vs. control group (CTR-group).

	BNP-group n=140	**CTR-group** n=128			
Variables	**Events (n)**	**Events (n)**	**Hazard ratio**	**CI 95 %**	**p-value**
Time to all-cause mortality	31	29	0.97	0.58-1.16	0.91
Time to CV mortality	25	26	1.02	0.59-1.76	0.95
Time to HF mortality	21	16	0.82	0.43-1.58	0.56
Time to first all cause hosp.	90	90	0.89	0.66-1.19	0.43
Time to first CV hosp.	81	76	0.93	0.68-1.27	0.75
Time to first HF hosp.	55	57	0.86	0.60-1.25	0.43
Time to first worsening HF	25	40	0.54	0.33-0.88	0.01

Notes: CV : Cardiovascular; HF : Heart failure; Hosp.: Hospitalization; Time to first hospitalization in days (defined as overnight stay in hospital); Time to mortality in days.

Table 4. Baseline characteristics of the 140 patients in the BNP-group divided into responders and non-responders.

	Responders	**Non Responders**	**P-value**
Number of patients	88	52	
Age years mean (SD)	69.2 (±10.2)	74.9 (±7.8)	<0.001
Male/Female n	66/22	37/15	0.62
Hypertension n (%)	20 (23)	15 (29)	0.42
Diabetes Mellitus n (%)	22 (25)	15 (29)	0.62
NYHA II n (%)	34 (39)	13 (25)	0.99
NYHA III n (%)	42 (48)	30 (58)	0.25
NYHA IV n (%)	11 (12)	9 (17)	0.43
LVEF<30% n (%)	55 (62)	27 (52)	0.22
RAS-b n (%)	88 (100)	51 (98)	0.19
BB n (%)	81 (92)	49 (94)	0.63
AA n (%)	44 (50)	34 (65)	0.58
Digoxin n (%)	21 (24)	11 (21)	0.77
Diuretics n (%)	75 (85)	46 (88)	0.59

BNP ng/l mean (SD)	778.7 (±663)	833 (±715.9)	0.65
Creatinine µmol/l mean (SD)	96.6 (±25.2)	122.3 (±38.5)	<0.0001
eGFR mL/min/1.73 m^2 mean (SD)	67.5 (±19.7)	52.1 (±19.9)	<0.0001

Notes: AA = Aldosterone antagonists; BB = beta blockers; BNP = Brain natriuretic peptide; eGFR=estimated glomerular filtration rate (MDRD formula); LVEF = Left ventricular ejection fraction; NYHA = New York Heart Association functional class; RAS-b = RAS blockade (ACE-inhibitors and/or Angiotensin II receptor blockers); SD= standard deviation

Responders were defined as patients who demonstrated a fall in BNP level of $\geq$ 30% at the week 48 visit compared to baseline.

Table 5 Secondary outcome variables, responders vs non-responders.

	Responders n=88	**Non responders** n=52			
Variables	***Events (n)***	***Events (n)***	***Hazard ratio***	***CI 95 %***	***p-value***
Time to all-cause mortality	8	23	0.18	0.08-0.41	<0.0001
Time to CV mortality	6	20	0.16	0.06-0.39	<0.0001
Time to HF mortality	3	18	0.09	0.03-0.30	<0.0001
Time to first all cause hosp.	44	46	0.35	0.23-0.53	<0.0001
Time to first CV hosp.	37	43	0.37	0.24-0.58	<0.0001
Time to first HF hosp.	22	33	0.31	0.18-0.53	<0.0001
Time to first worsening HF	7	18	0.21	0.09-0.49	0.0003

Notes: CV: Cardiovascular; HF : Heart failure; Hosp.: Hospitalization; Time to first hospitalization in days (defined as overnight stay in hospital); Time to mortality in days.

Responders were defined as patients who demonstrated a fall in BNP level of $\geq$ 30% at the week 48 visit compared to baseline.