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

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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

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Context It is uncertain whether intensified heart failure therapy guided by N-terminal brain natriuretic peptide (BNP) is superior to symptom-guided therapy.

Objective To compare 18-month outcomes of N-terminal BNP–guided vs symptom-guided heart failure therapy.

Design, Setting, and Patients Randomized controlled multicenter Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) of 499 patients aged 60 years or older with systolic heart failure (ejection fraction ≤45%), New York Heart Association (NYHA) class of II or greater, prior hospitalization for heart failure within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal. The study had an 18-month follow-up and it was conducted at 15 outpatient centers in Switzerland and Germany between January 2003 and June 2008.

Intervention Uptitration of guideline-based treatments to reduce symptoms to NYHA class of II or less (symptom-guided therapy) and BNP level of 2 times or less the upper limit of normal and symptoms to NYHA class of II or less (BNP-guided therapy).

Main Outcome Measures Primary outcomes were 18-month survival free of all-cause hospitalizations and quality of life as assessed by structured validated questionnaires.

Results Heart failure therapy guided by N-terminal BNP and symptom-guided therapy resulted in similar rates of survival free of all-cause hospitalizations (41% vs 40%, respectively; hazard ratio [HR], 0.91 [95% CI, 0.72-1.14]; $P=.39$). Patients' quality-of-life metrics improved over 18 months of follow-up but these improvements were similar in both the N-terminal BNP–guided and symptom-guided strategies. Compared with the symptom-guided group, survival free of hospitalization for heart failure, a secondary end point, was higher among those in the N-terminal BNP–guided group (72% vs 62%, respectively; HR, 0.68 [95% CI, 0.50-0.92]; $P=.01$). Heart failure therapy guided by N-terminal BNP improved outcomes in patients aged 60 to 75 years but not in those aged 75 years or older ($P<.02$ for interaction)

Conclusion Heart failure therapy guided by N-terminal BNP did not improve overall clinical outcomes or quality of life compared with symptom-guided treatment.

Trial Registration isrctn.org Identifier: ISRCTN43596477

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HEART FAILURE THERAPY guided by N-terminal brain natriuretic peptide (BNP) has been proposed to improve outcome compared with conventional therapy in patients with chronic heart failure in some studies.[1-4] However, these studies were small (n=69,[1] n=220,[2] n=130[3]), not conclusive,[3,4] had limited follow-up, focused on younger patients,[2,3] and/or have not yet been published in detail.[3,4] The concept of an intensified N-terminal BNP–guided therapy might be particularly attractive in older patients who are less physically active and in whom symptoms are less reliable, but they also may be more susceptible to drug-related adverse effects. Problems of heart failure increase with age.[5] Heart failure is the most common reason for hospitalization in patients aged 65 years or older.[6] Older patients are underrepresented in randomized controlled trials,[7] mainly be-

For editorial comment see p 432.

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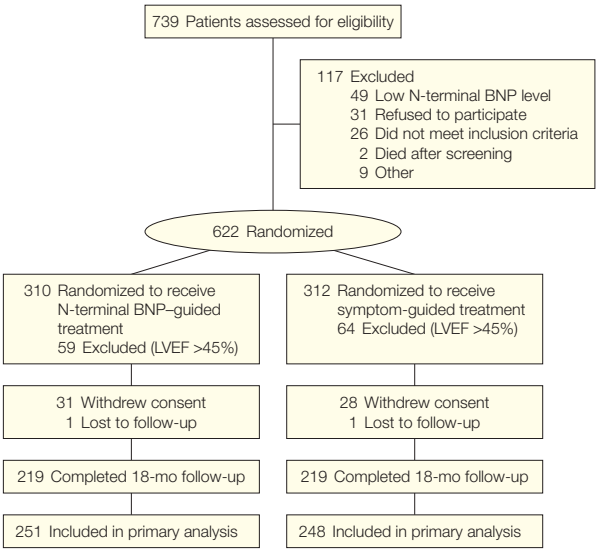
Figure 1. Flow of Participants Through the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure



BNP indicates brain natriuretic peptide; LVEF, left ventricular ejection fraction.

cause of the high rate of comorbidities leading to polypharmacy with multiple drug-drug interactions and adverse effects.[8] Despite the lack of specific evidence, current guidelines recommend similar medical management in this age group as in younger patients.[9,10]

Therefore, the aims of the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) were to compare an intensified N-terminal BNP–guided strategy with the standard symptom-guided therapy on 18-month outcome of patients with chronic symptomatic heart failure and to assess whether the N-terminal BNP–guided therapy is more effective than symptom-guided therapy in patients aged 75 years or older compared with patients with congestive heart failure who are aged 60 to 74 years.

METHODS

Patients

The study design and methods of the TIME-CHF study program have been reported in detail previously.[11] The study was conducted at 15 centers in Switzerland and Germany and included patients aged 60 years or older with dyspnea (New York Heart Association [NYHA] class ≥II with current therapy), a history of hospitalization for heart failure within the last year, and an N-terminal BNP level of 400 pg/mL or higher (to convert to ng/L, multiply by 1.0) in patients younger than 75 years and a level of 800 pg/mL or higher in patients aged 75 years or older.

Excluded were patients with dyspnea not mainly due to heart failure, with valvular disease requiring surgery, acute coronary syndromes within the previous 10 days, angina pectoris classified as being in the Canadian Cardiovascular Society Class higher than II, revascularization within the previous month, body mass index (calculated as weight in kilograms divided by height in meters squared) higher than 35, serum creatinine level higher than 2.49 mg/dL (to convert to μmol/L, multiply by 88.4), a life expectancy of less than 3 years for noncardiovascular diseases, unable to give informed consent, no follow-up possible, or participating in another study.

Based on these criteria, 622 outpatients consented to the TIME-CHF study[11] between January 2003 and December 2006 and were included. Of these 622 patients, 499 had systolic dysfunction (80%) defined as left ventricular ejection fraction of 45% or less by echocardiography by local assessment. This group was defined a priori as the main study group on which sample size was calculated.[11]

An independent clinical event committee and data and safety monitoring board adjudicated all events and supervised the study. The study was approved by the ethics committees of each center and each patient gave written informed consent before entering the study.

Study Design and End Point Definitions

Patients were randomized into 2 treatment strategies: symptom-guided or intensified N-terminal BNP–guided medical therapy in addition to symptom control (FIGURE 1). Both groups were stratified per protocol into 2 age groups of 60 to 74 years and 75 years or older. Randomization per center was performed by concealed central allocation in blocks of 8 patients, separately for both age groups. Patients, but not treating physicians, were blinded to group allocation. Patients were followed up in the outpatient clinics of each center with prespecified visits after 1, 3, 6, 12, and 18 months. Treatments were adjusted at all but the last visit with the attempt to achieve treatment goals by the 6-month visit (uptitration phase) followed by 12 months of outcome observation (follow-up period). The N-terminal BNP levels were determined centrally at every visit in all patients, but only results of patients in the N-terminal BNP–guided strategy group were sent to the investigators (treating physicians).

Two patients were lost to follow-up, known to be alive at 64 and 101 days, respectively, after inclusion. Fifty-nine patients withdrew consent (11.8%) (Figure 1) after a median follow-up of 96 days (interquartile range, 41-372 days), of which 40 allowed further contact by telephone (68%). Seventeen died during the study period of 18 months, 8 in the N-terminal BNP–guided group and 9 in the symptom-guided group. The other patients formally declined any further contact. These 59 patients

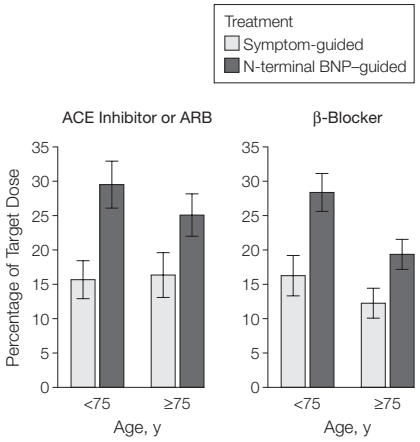
did not differ significantly from those who completed the study apart from history of dementia at baseline (12% vs 3%; $P=.01$; other data not shown). Importantly, treatment group allocation was similar (12% for the N-terminal BNP–guided group vs 11% for the symptom-guided group; $P=.71$). Follow-up was censored at the time of the

Table 1. Baseline Characteristics in Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure[a]

Characteristic	Treatment Group			Age Group, y		
	Symptom-Guided (n = 248)	N-Terminal BNP–Guided (n = 251)	*P* Value	60-74 (n = 210)	≥75 (n = 289)	*P* Value
Demographics						
Age, mean (SD), y	77 (8)	76 (7)	.16	69 (4)	82 (4)	<.001
Female	92 (37.1)	80 (31.9)	.22	53 (25.2)	119 (41.2)	<.001
Body mass index, mean (SD)[b]	25.3 (4.3)	25.4 (4.0)	.75	26.4 (4.5)	24.6 (3.7)	<.001
NYHA class ≥III	185 (74.6)	186 (74.1)	.53	138 (65.7)	233 (80.6)	.001
Atrial fibrillation	78 (31.5)	82 (32.7)	.94	56 (26.7)	104 (36.0)	.03
Primary cause of congestive heart failure[c]						
Coronary artery disease	149 (60.1)	138 (55.0)	.46	102 (48.6)	185 (64.0)	<.001
Hypertensive heart disease	47 (19.0)	60 (23.9)		40 (19.0)	67 (23.2)	
Dilated cardiomyopathy	42 (16.9)	46 (18.3)		59 (28.1)	29 (10.0)	
Other	10 (4.0)	7 (2.7)		9 (4.3)	8 (2.8)	
LVEF, mean (SD), %	29.7 (7.9)	29.8 (7.7)	.87	27.8 (7.2)	31.2 (7.9)	<.001
N-terminal BNP, median (IQR), pg/mL	4657 (2455-7520)	3998 (2075-7220)	.12	2998 (1691-5901)	5053 (2953-8589)	<.001
Creatinine, mean (SD), mg/dL	1.33 (0.42)	1.32 (0.45)	.69	1.26 (0.41)	1.37 (0.44)	.004
Heart rate, mean (SD), beats/min	77 (15)	75 (14)	.23	74 (14)	77 (15)	.03
Systolic blood pressure, mean (SD), mm Hg	119 (19)	119 (18)	.97	117 (18)	120 (18)	.04
Medical History						
Hypertension	179 (72.2)	175 (69.7)	.56	130 (61.9)	224 (77.5)	<.001
Diabetes mellitus	95 (38.3)	77 (30.7)	.08	79 (37.6)	93 (32.2)	.22
Insulin-dependent diabetes	22 (8.9)	33 (13.1)	.15	24 (11.4)	31 (10.7)	.89
Stroke/transient ischemic attack	40 (16.1)	36 (14.3)	.62	20 (9.5)	56 (19.4)	.002
COPD	44 (17.7)	60 (23.9)	.10	45 (21.4)	59 (20.4)	.82
Cancer	35 (14.1)	33 (13.1)	.80	18 (8.6)	50 (17.3)	.005
Kidney disease	135 (54.4)	140 (55.8)	.79	94 (44.8)	181 (62.6)	<.001
Arthritis	62 (25.0)	63 (25.1)	>.99	34 (16.2)	91 (31.5)	<.001
Quality of Life						
Minnesota Living With Heart Failure questionnaire, mean (SD) (n = 491) (range, 0-105; lower values = better quality of life)	40 (21)	40 (20)	.78	40 (21)	40 (20)	.94
Duke Activity Status Index, median (IQR) (n = 483) (range, 0-58.2; higher values = better quality of life)	7.2 (1.8-15.5)	7.2 (2.7-15.5)	.71	9.0 (2.7-19.0)	7.2 (1.8-12.9)	.007
Short Form 12, mean (SD) (n = 417) (range, 0-100; higher values = better quality of life)						
Mental component	46 (11)	46 (11)	.94	48 (11)	45 (11)	.02
Physical component	34 (9)	34 (10)	.92	35 (10)	33 (9)	.12
Medication/Devices						
Implantable cardioverter-defibrillator	12 (4.8)	13 (5.2)	.86	17 (8.1)	8 (2.8)	.01
ACE inhibitor or ARB	235 (94.8)	238 (94.8)	.95	199 (94.8)	274 (94.8)	.98
Target dose, mean (SD) (n = 499)[d]	50 (36)	53 (41)	.72	52 (38)	51 (39)	.56
β-Blocker	201 (81.0)	191 (76.1)	.19	176 (83.8)	216 (74.7)	.02
Target dose, median (IQR) (n = 499)[d]	25 (12.5-50)	25 (5-50)	.18	25 (12.5-50)	25 (0-50)	.06
Mineralocorticoid receptor antagonist	100 (40.3)	102 (40.6)	.92	98 (46.7)	104 (36.0)	.02
Loop diuretic	234 (94.4)	232 (92.4)	.47	191 (91.0)	275 (95.2)	.07
Dose, median (IQR) (n = 499)[e]	80 (40-115)	60 (40-80)	.06	40 (40-80)	80 (40-120)	.04
Nitrate	72 (29.0)	71 (28.3)	.92	44 (21.0)	99 (34.3)	.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
SI conversion factors: To convert BNP to ng/L, multiply by 1.0; creatinine to μmol/L, multiply by 88.4.
[a] Values are expressed as number (percentage) unless otherwise indicated.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Investigator's clinical diagnosis.
[d] Indicates percentage of target dose patients were receiving.
[e] A dose of 10 mg of torasemide is equivalent to 40 mg of furosemide.

Figure 2. Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin II Receptor Blocker (ARB) and β-Blocker Doses During the Study



BNP indicates brain natriuretic peptide. Error bars indicate standard error of the mean. $P < .001$ for the differences between the treatment groups for both age groups.

last contact with these patients and events per patient-year were normalized to time of follow-up. Two sensitivity analyses were performed and did not show any relevant influence on the results (data not shown). One analysis included deaths of patients who withdrew consent; the other analysis additionally considered all patients as dead who were lost to follow-up or did not allow further contact.

The primary end points were 18-month survival free of any hospitalization and quality of life measured at 18 months. Quality of life was assessed by structured, validated, and self-administered questionnaires: the Minnesota Living With Heart Failure,[12] the Short Form 12,[13] and the Duke Activity Status Index.[14] Secondary end points included (1) components of primary end points; (2) specific causes of death or hospitalizations such as heart failure, arrhythmia, etc; (3) effects of baseline characteristics on outcome; and (4) tolerability and effect of medication. Cancer-related deaths and hospitalizations, which are separate, clearly defined entities, were not considered (including these events did not alter the results; data not shown).

Treatment Strategies

Medical therapy was prescribed according to current European Society of Cardiology[10] and American College of Cardiology/American Heart Association[9] guidelines with predefined escalation rules simulating clinical practice to reduce either symptoms to dyspnea NYHA class of II or less (in the symptom-guided group) or N-terminal BNP levels to less than 2 times the upper limit of normal—less than 400 pg/mL in patients younger than 75 years and less than 800 pg/mL in patients aged 75 years or older—and NYHA class of II or less (in the N-terminal BNP–guided group[9]).

Patients were given angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and β-blockers. It was suggested to use agents only recommended by the guidelines in the appropriate dose.[9,10] Diuretics could be used as needed. Escalation of therapy was suggested as follows: addition of spironolactone, escalating doses of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers, loop diuretics, low-dose digoxin, long-acting nitrates, metalozone or another thiazide, molsidomide during nitrate-free intervals, and intravenous diuretics or inotropes. An escalation scheme could be individually adjusted as deemed appropriate by the investigator. Therapy was reduced in cases of significant adverse effects based on the investigator's discretion. Diuretics were recommended to be reduced prior to prognostically relevant medication. All other therapies also were left to the discretion of the treating physician.

Statistical Analysis

Based on previous studies and observations in patients aged 60 years or older, it was estimated that 471 patients with systolic dysfunction would have to be included to reach a relative risk reduction in the primary end point of 30% in the N-terminal BNP–guided group compared with the symptom-guided group at an α level of .05, a power level of 0.80, and a withdrawal rate of 10%.[11] Because the withdrawal rate was slightly higher, recruitment was stopped at 499 patients.

Results are presented as frequencies, mean (SD), or median (interquartile range), as appropriate. Between-group comparisons were performed using the *t* test, Mann-Whitney test, or Pearson χ^2. Changes over time were assessed using a generalized linear model for repeated measures. In case of lack of normal distribution, ranks instead of actual values were used. Kaplan-Meier curves were used for calculating time-dependent occurrences of events. For comparison between groups, the log-rank test was used. Hazard ratio (HR) was derived from univariate Cox regression and tested for independence from baseline characteristics using multivariate Cox regression entering all variables.

Interactions between intervention and patient characteristics were analyzed using bivariate Cox regression including interactions between the 2 covariates. Whereas the interaction between the 2 age groups was prespecified in the protocol, the other interactions are post hoc analyses and only exploratory.

Interactions between age groups were tested for independence in multivariate Cox regression including patient characteristics and other interactions that were significant in bivariate analysis.

Analyses were performed overall and for the 2 age groups separately (apart from interaction analyses), based on the intent-to-treat principle. A 2-sided *P* value of .05 was considered to be statistically significant. All calculations were performed with the use of the SPSS statistical package version 15.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Baseline Characteristics

Baseline characteristics of the 2 treatment groups are shown in TABLE 1. There were no relevant differences between the 2 treatment groups, reflecting randomized allocation. Patients in the older age group had an average age

of 82 years (vs 69 years in the younger group) and presented with more severe symptoms, higher N-terminal BNP levels, and lower quality-of-life scores despite higher ejection fractions.

Treatment and Achievement of Treatment Goals

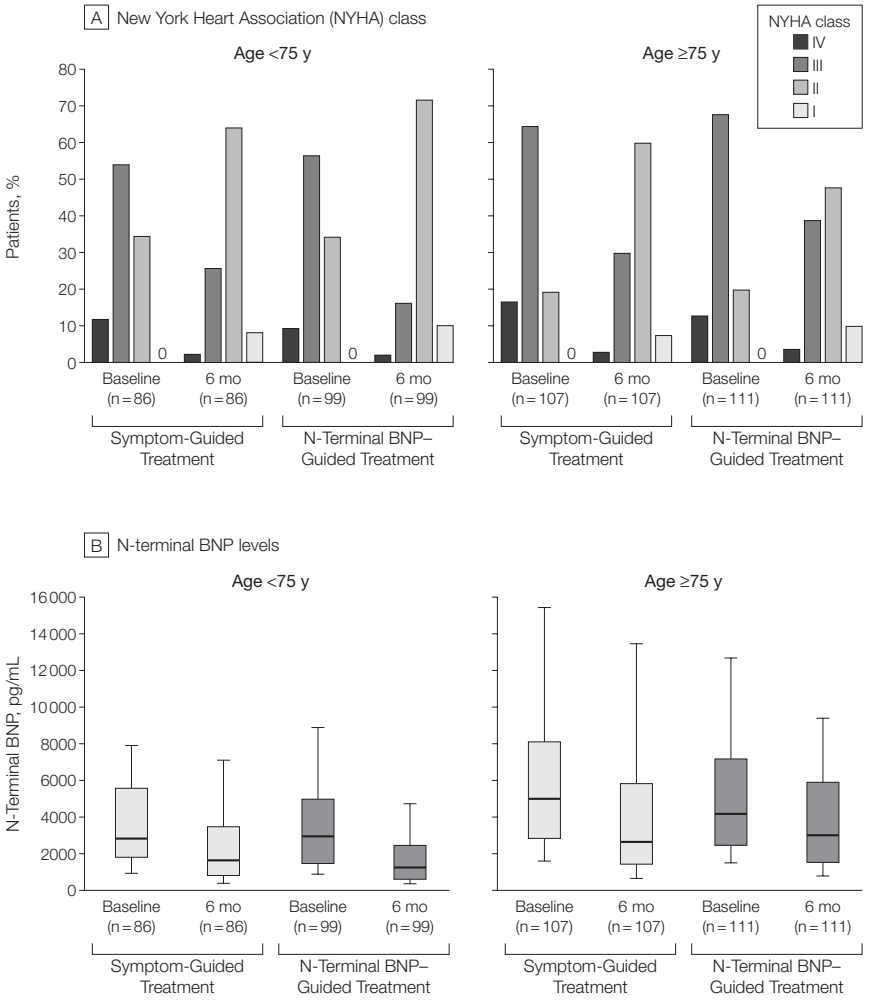
At baseline, a high percentage of patients were receiving the recommended heart failure therapy (Table 1). Uptitration of therapy to reduce symptoms was recommended in 192 patients in the symptom-guided group at baseline (77%), in 140 of 229 patients at visit month 1 (61%), in 111 of 210 patients at visit month 3 (53%), and in 101 of 194 patients at visit month 6 (52%). In patients in the N-terminal BNP–guided group, an increase in therapy was recommended in 213 patients at baseline (86%), in 221 of 232 patients at visit month 1 (95%), in 198 of 218 patients at visit month 3 (91%), and in 190 of 211 patients at visit month 6 (90%) ($P<.001$ between treatment groups at all follow-up visits and $P=.03$ at baseline).

Importantly, doses of drugs with proven prognostic efficacy were uptitrated to a significantly greater extent in the N-terminal BNP–guided group vs the symptom-guided group in both age groups (FIGURE 2). The dose increase in angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers did not differ between the age groups. There was less of a dose increase in β-blockers in patients aged 75 years or older ($P=.01$), but this was true for both treatment groups and the difference between them remained statistically significant (Figure 2).

Spironolactone and eplerenone were given more frequently in patients in the N-terminal BNP–guided group. Thus, 179 patients received spironolactone (or eplerenone) at any time during the study (72%) vs 156 in the symptom-guided group (63%; $P=.05$) with no significant differences between age groups. More patients in the N-terminal BNP–guided group started receiving spironolactone (n=76; 30%) than in the symptom-guided group (n=56; 23%) ($P=.05$). In contrast, changes in use of diuretics, nitrates, digoxin, and other treatments did not differ between the groups.

During the uptitration phase of the study (ie, first 6 months), dyspnea improved and BNP levels decreased significantly in both treatment groups with no significant differences between the groups (FIGURE 3A and Figure 3B). These treatment effects were similar for both age groups, although there was a significant interaction between treatment and age groups, ie, patients aged ≥75 years in the N-terminal BNP group had a smaller relative benefit on N-terminal BNP levels ($P=.04$) and symptoms ($P=.05$) than younger patients. After the uptitration phase, changes were small and not significant. There was a significant relationship between symptom severity and BNP levels (overall Spearman $r=0.36$; $P<.001$), but the variation of BNP levels at each NYHA class was wide (FIGURE 4), indicating that N-terminal BNP–guided therapy was the reason for increases in drug therapy (Figure 2) in patients with little or no dyspnea.

Figure 3. Symptoms and N-Terminal Brain Natriuretic Peptide (BNP) Levels at Baseline and Month 6



A, Symptoms expressed as NYHA class. B, N-terminal BNP levels. Boxes indicate interquartile range; horizontal lines, median; error bars, 10th and 90th percentiles. The improvements by both treatment strategies were significant in both age groups (all $P<.001$). There were no significant differences between the 2 treatment groups by age for symptoms ($P=.11$ for <75 years vs $P=.38$ for ≥75 years) or by N-terminal BNP level ($P=.06$ vs $P=.30$).

Outcomes With N-Terminal BNP–Guided vs Symptom-Guided Therapy

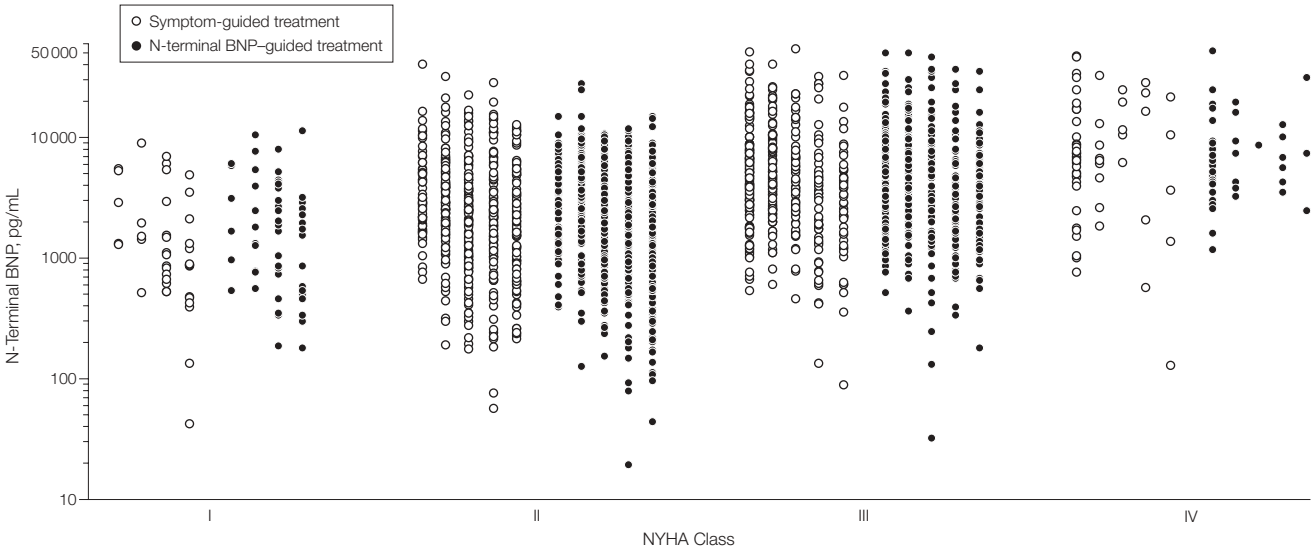
Compared with symptom-guided therapy, the N-terminal BNP–guided strategy did not improve 18-month survival free of any hospitalization, which was the primary end point of this trial (41% for N-terminal BNP–guided group vs 40% for symptom-guided group; FIGURE 5). Overall survival rates did not differ significantly (84% for N-terminal BNP–guided group vs 78% for symptom-guided group) (Figure 5). Survival free of hospitalizations for heart failure, a main secondary end point, was significantly improved with N-terminal BNP–guided therapy (72% for N-terminal BNP–guided group vs 62% for symptom-guided group) (Figure 5).

The prespecified interaction between treatment and age groups was significant for survival free of any hospitalization ($P=.02$), mortality ($P=.01$), and survival free of hospitalization for heart failure ($P=.01$) in Cox regression adjusted for baseline characteristics, indicating that the effects of the N-terminal BNP–guided treatment differed significantly between younger and older patients (FIGURE 6). Further exploratory subgroup analyses of treatment effects on primary and secondary end points are summarized in FIGURE 7, suggesting more favorable effects of N-terminal BNP–guided vs symptom-guided therapy with fewer comorbidities and a higher body mass index.

Quality of Life

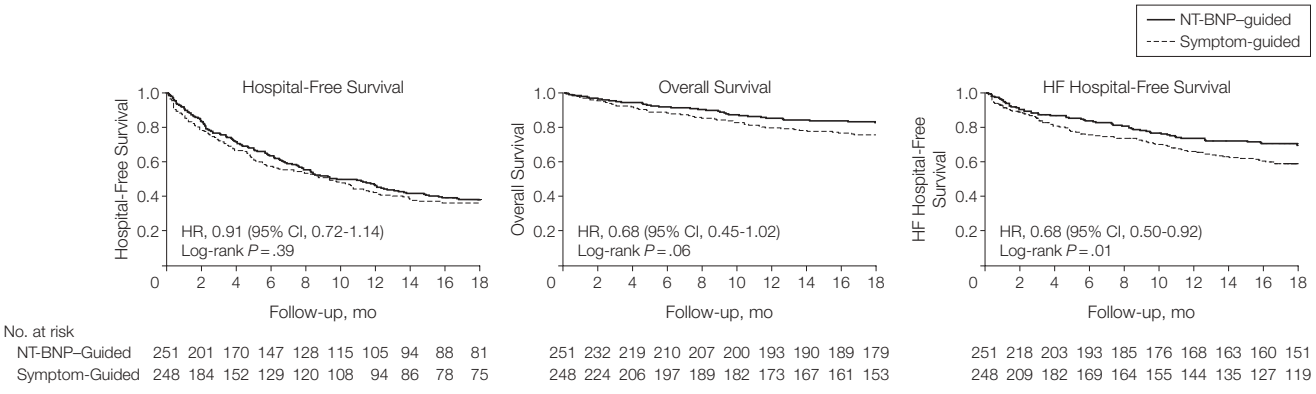
All measures of quality of life improved from baseline to month 12 ($P<.001$) in both treatment groups and

Figure 4. Relationship Between Symptoms and N-Terminal Brain Natriuretic Peptide (BNP) Levels



Relationship between New York Heart Association (NYHA) class and N-terminal BNP levels at visits from baseline to month 12 of all patients showing higher N-terminal BNP levels with higher NYHA class (Spearman $r=0.36$, $P<.001$) and a trend to lower N-terminal BNP levels within each NYHA class from baseline to month 12 (NYHA I: Spearman $r=0.34$, $P=.001$; NYHA II: Spearman $r=-0.21$, $P<.001$; NYHA III: Spearman $r=-0.15$, $P<.001$; NYHA IV: Spearman $r=0.04$, $P=.69$).

Figure 5. Primary and Secondary Outcomes in the 2 Treatment Groups



NT-BNP indicates N-terminal brain natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.

remained unchanged between month 12 and month 18 (TABLE 2). There were no significant differences in the magnitude of these improvements between the 2 treatment strategies.

Serious Adverse Events

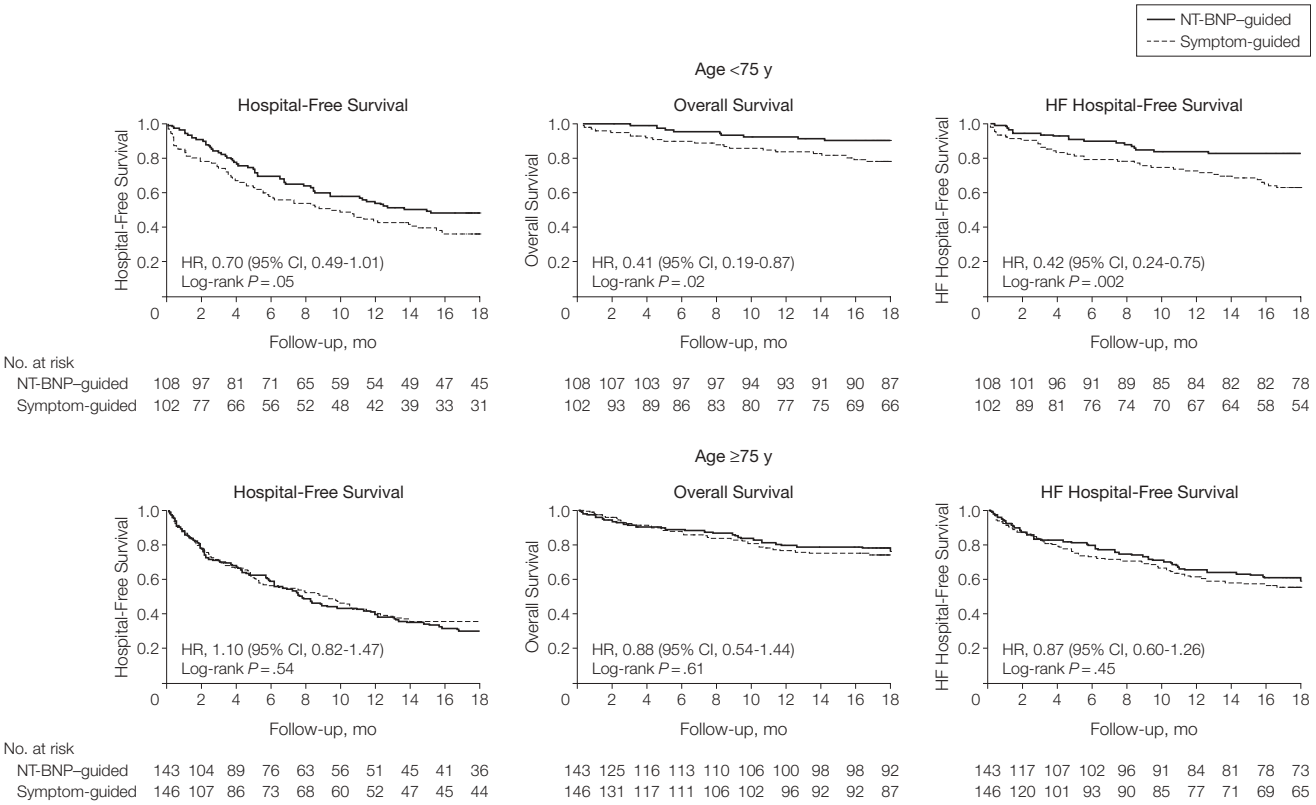
Overall, 236 patients had at least 1 serious adverse event (47.3%); 49.0% in the N-terminal BNP–guided group and 45.6% in the symptom-guided group ($P = .47$). Serious adverse events (mostly hospitalizations) related to renal impairment (3.2% vs 4.0%; $P = .64$) and hypotension (4.8% vs 2.4%; $P = .22$) did not differ between the N-terminal BNP–guided group and the symptom-guided group, respectively, or between the 2 age groups. However, incomplete adherence to the investigators' recommendations by general practitioners and/or patients due to hypotension or renal failure were more common in the N-terminal BNP–guided group ($P = .01$), both in younger patients (14.9% vs 11.7%), and in patients aged 75 years or older (17.5% vs 12.6%). Investigators judged more serious adverse events to be related to N-terminal BNP–guided therapy vs symptom-guided therapy in patients aged 75 years or older (10.5% vs 5.5%, respectively; $P = .12$), but not in patients aged 60 to 74 years (3.7% vs 4.9%; $P = .74$) (interaction between age and treatment groups, $P = .01$).

COMMENT

The TIME-CHF study demonstrated that intensified N-terminal BNP–guided heart failure therapy did not improve overall 18-month survival free of any hospitalizations or improve quality of life more than those receiving standard symptom-guided therapy. However, survival free of hospitalizations for heart failure was higher among those receiving N-terminal BNP–guided therapy. In contrast to our prespecified hypothesis, N-terminal BNP–guided therapy was not more beneficial in patients aged 75 years or older vs patients aged 60 to 74 years. In fact, patient age significantly interacted with N-terminal BNP–guided treatment group; with no benefit in patients aged 75 years or older compared with positive results in patients aged 60 to 74 years. Both treatment strategies improved symptoms and quality of life and reduced BNP levels similarly over time, although these effects tended to be lower in patients aged 75 years or older.

The TIME-CHF study is the largest prospective randomized study evaluating the value of N-terminal BNP–guided therapy of chronic heart failure. Previous smaller studies proposed that BNP guidance of therapy may be

Figure 6. Treatment Effects on Main Outcomes in Younger Compared With Older Patients

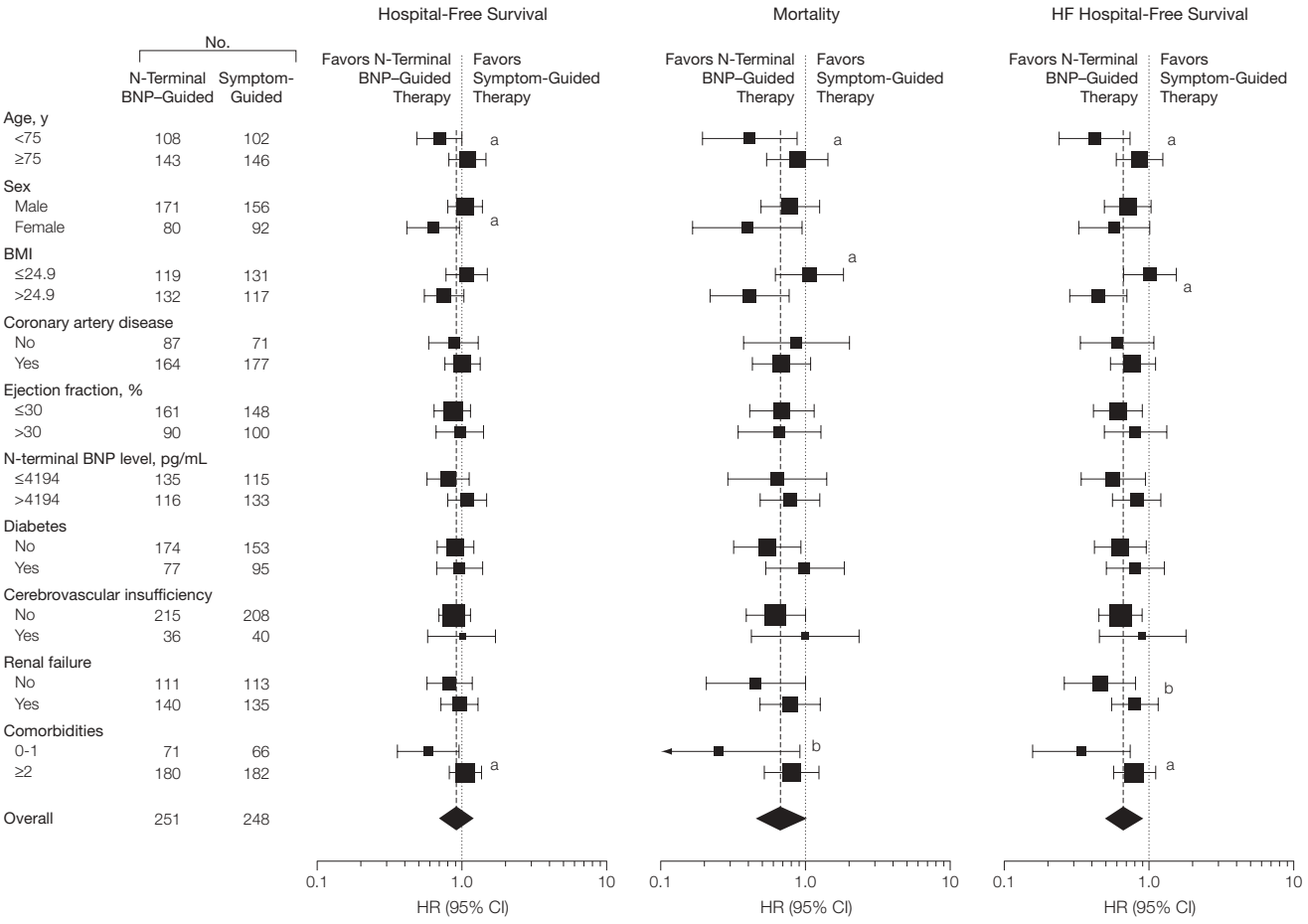


The differences between treatment groups were observed only in younger but not older patients. NT-BNP indicates N-terminal brain natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.

superior to clinically guided treatment,[1,2] although results were not entirely uniform.[3,4] Results of the TIME-CHF study relating to patients aged 60 to 74 years are in agreement with these findings with significant reductions in mortality and heart failure events. This was not the case, however, for patients aged 75 years or older, which is in agreement with previous preliminary data.[4] No noncardiovascular events were reported in one study[1] and no difference was reported in another study.[2] Interestingly, there was no significant difference in the reduction of N-terminal BNP levels between the 2 treatment groups in our study, similar to the previous study by Troughton et al[1] with BNP guidance that measured BNP levels in the control group. Thus, the value of BNP levels to guide therapy in addition to clinical symptom-based judgment seems limited despite their undisputed diagnostic[15] and prognostic importance.[16-18] Despite this, high BNP levels also were observed with little or no symptoms and lead to intensification of therapy in the N-terminal BNP–guided strategy.

With few exceptions,[19,20] previous large heart failure trials included only a few patients older than age 75 years, if any,[21-24] and patients with significant comorbidities were excluded. Registries of unselected heart failure patients[25-27] point to the discrepancy between real-world and trial data, indicating that evidence from trial data addresses only a minority of the total heart failure population. Still, recommendations in guidelines hardly consider age and comorbidities.[9,10] The TIME-CHF study addressed these complex interactions and highlights the need for solid data in patients older than 75 years. We found that those aged 75 years or older had no benefit from N-terminal BNP–guided therapy, but had greater adverse effects. Thus, in contrast to our original hypothesis, an N-terminal BNP–guided strategy is not

Figure 7. Interactions Between Baseline Characteristics and Treatments Relative to Main Outcomes



Subgroup analysis between the age groups was prespecified. Values for body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), N-terminal BNP, and creatinine were subdivided by median values. The size of the data markers represents the number of patients in each group. BNP indicates brain natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.
[a] $P < .05$ for interaction.
[b] $P < .10$ for interaction.

Table 2. Quality of Life in Patients With All 3 Treatment Month

Outcomes by Group	Baseline	Month 12	Month 18	*P* Value
Minnesota Living With Heart Failure questionnaire, mean (SD)[a]				
Symptom-guided	42.0 (20.3)	27.0 (18.6)	27.3 (21.5)	<.001
N-terminal BNP–guided	38.3 (20.2)	27.7 (17.9)	28.2 (17.6)	<.001
Duke Activity Status Index, median (IQR)[b]				
Symptom-guided	7.3 (2.7-15.4)	15.2 (7.2-27.5)	12.7 (4.9-27.0)	<.001
N-terminal BNP–guided	7.2 (2.7-18.6)	12.8 (7.2-27.0)	12.8 (4.5-25.7)	<.001
Short Form 12, mean (SD)[c]				
Physical component				
Symptom-guided	34.4 (9.1)	40.6 (10.3)	40.7 (10.2)	<.001
N-terminal BNP–guided	33.4 (9.8)	37.9 (10.1)	37.4 (10.2)	<.001
Mental component				
Symptom-guided	45.8 (10.5)	51.1 (9.5)	51.5 (9.9)	<.001
N-terminal BNP–guided	46.1 (11.0)	50.8 (10.4)	50.1 (10.3)	.001

Abbreviations: BNP, brain natriuretic peptide; IQR, interquartile range.
[a] Range of possible values is 0 to 105; lower values indicate better quality of life.
[b] Range of possible values is 0 to 58.2; higher values indicate better quality of life.
[c] Range of possible values is 0 to 100; higher values indicate better quality of life (a value of 50 is the average in the population).

helpful and may be harmful in patients aged 75 years or older.

The difference in all-cause and disease-specific outcomes in the TIME-CHF study is in agreement with results of previous large heart failure trials, which focused primarily on cardiovascular and/or heart failure end points.[20-22] The finding that survival free of all-cause hospitalizations was not significant in the TIME-CHF study may be explained by non–heart failure events and the lower than expected mortality reported elsewhere,[11,26,28,29] and by the high level of baseline therapy noted in the present study. The benefit in cardiovascular events (the main target of heart failure therapy) was offset by noncardiac events in previous trials.[20,30] Depending on the balance between cardiac and noncardiac risks, relative risk reduction on different outcomes may vary significantly. The TIME-CHF study suggests that the net benefit of heart failure therapy in daily practice may be smaller than that observed in randomized drug trials. This also may explain why improvements in prognosis in cohort studies were found to be smaller than expected.[29]

In the present study, there was a substantial improvement in symptoms and quality of life in both treatment and age groups despite a high level of heart failure therapy at baseline. This points to the fact that symptom-guided medical therapy can be improved in most patients in daily practice and it improves symptoms further. Importantly, drugs with proven prophylactic effects such as angiotensin-converting enzyme inhibitors and β-blockers could be increased more in patients receiving N-terminal BNP–guided therapy compared with symptom-guided therapy in this study. The findings of the TIME-CHF study suggest that persistence in intensifying medical therapy seems to be the key for an optimal clinical outcome in patients aged 60 to 74 years, whereas it may not be beneficial to push doses to the limits in patients aged 75 years or older.

There are limitations to this study. The TIME-CHF study was designed to compare 2 strategies and therefore, it is not possible to determine from this study which single drug treatment component added to the specific findings. Although, the strategies used may not completely reflect current standard of care according to the recommended guidelines, the use of evidence-based treatment was high and exceeded even that in recent large randomized controlled trials.[20,23,31] It also remains uncertain how much the knowledge of BNP levels contributed to the observed effect of the intensified treatment strategy. Because patients were recruited from clinics of large and small hospitals, they may be representative of a large part but not of all patients with heart failure seen in private practice. Sample size was calculated for the entire study population to detect an overall difference between N-terminal BNP–guided therapy compared with symptom-guided therapy; hence, findings of the 2 age groups are subgroup findings only; however, patients were stratified a priori into these 2 age groups by protocol. Together with the main results of the TIME-CHF study, this study underscores the need for new trials specifically addressing the large population of older heart failure patients.

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