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N-Terminal Pro–B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure

Results From the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial

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Objectives The purpose of this study was to compare the effects of N-terminal pro–B-type natriuretic peptide (NT-proBNP)-guided therapy with those of intensive clinical management and with usual care (UC) on clinical outcomes in chronic symptomatic heart failure.

Background Initial trial results suggest titration of therapy guided by serial plasma B-type natriuretic peptide levels improves outcomes in patients with chronic heart failure, but the concept has not received widespread acceptance. Accordingly, we conducted a longer-term study comparing the effects of NT-proBNP–guided therapy with those of intensive clinical management and with UC of patients with heart failure.

Methods Three hundred sixty-four patients admitted to a single hospital with heart failure were randomly allocated 1:1:1 (stratified by age) to therapy guided by NT-proBNP levels or by intensive clinical management, or according to UC. Treatment strategies were applied for 2 years with follow-up to 3 years.

Results One-year mortality was less in both the hormone- (9.1%) and clinically-guided (9.1%) groups compared with UC (18.9%; $p = 0.03$). Three-year mortality was selectively reduced in patients ≤75 years of age receiving hormone-guided treatment (15.5%) compared with their peers receiving either clinically managed treatment (30.9%; $p = 0.048$) or UC (31.3%; $p = 0.021$).

Conclusions Intensive management of chronic heart failure improves 1-year mortality compared with UC. Compared with clinically guided treatment and UC, hormone-guided treatment selectively improves longer-term mortality in patients ≤75 years of age. (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death [BATTLESCARRED]; Australian New Zealand Clinical Trials Registry 12605000735651) (J Am Coll Cardiol 2010;55:53–60) © 2010 by the American College of Cardiology Foundation

Proven treatments in chronic heart failure (CHF) include angiotensin-converting enzyme inhibitors (ACEIs) (1), angiotensin receptor blockers (ARBs) (2), beta-adrenergic blockers (BBs) (3), and spironolactone (4). Whether drug doses should be the same for all or individually "tailored" is unclear. Individualized treatment may be optimal for patients with few limiting factors but impossible for others, including elderly, hypotensive, or renally impaired patients. Testing of tailored therapy has hitherto been limited by the absence of a reliable, readily accessible index of cardiac dysfunction. Plasma B-type natriuretic peptide (BNP) measurements reflect left ventricular function (5,6) and prognosis in CHF (7). Drug- and device-induced improvements in cardiac status are paralleled by falls in peptide levels (8–10).

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Therefore, serial measurements of plasma BNP or N-terminal pro–B-type natriuretic peptide (NT-proBNP) might prove useful in optimizing pharmacotherapy for CHF. Two trials have reported that hormone-guided treatment of CHF improves outcomes compared with conventional, clinically-guided (CG) therapy (11,12). These trials have excluded patients with CHF and preserved left ventricular

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
BB = beta-adrenergic blocker
BNP = B-type natriuretic peptide
CG = clinically guided
CHF = chronic heart failure
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro–B-type natriuretic peptide
NYHA = New York Heart Association
UC = usual care

ejection fraction (LVEF), have not included a parallel group of patients cared for in the community by primary care physicians, and have been relatively small and brief. One such trial was carried out before BBs were in widespread use for the treatment of CHF (11).

Uncertainty surrounding this issue is encapsulated by the 2007 guidelines for the clinical utilization of cardiac biomarker testing in heart failure, which state: "...the concept of natriuretic peptide-guided management of heart failure is still debated, and there is no general consensus in expert opinion regarding this issue" (13). We designed the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial, a randomized, controlled trial that compared usual care (UC), intensive standardized clinical management, and NT-proBNP–guided therapy for CHF.

Methods

Trial design and methods have been published (14) and registered with the Australian Clinical Trials Registry. Three hypotheses were addressed: First, that titration of medication aimed at reducing plasma levels of NT-proBNP to <150 pmol/l (≈1,300 pg/ml) or based on intensive standardized clinical assessment would result in outcomes superior to those of UC. Second, that drug treatment titrated according to plasma NT-proBNP levels would improve clinical outcomes compared with treatment guided by intensive standardized clinical assessment. Third, that the clinical efficacy of NT-proBNP–guided therapy would be influenced by age.

Study population. Inclusion required age >18 years and symptomatic CHF, defined by Framingham criteria (15) and satisfying European Society of Cardiology diagnostic guidelines (16), precipitating admission, and ability to give informed consent. Immediate pre-randomization plasma NT-proBNP levels had to exceed 50 pmol/l (≈400 pg/ml). Exclusion criteria included active myocarditis/pericarditis, life expectancy due to noncardiovascular disease of <24 months, severe hepatic or pulmonary disease (forced expiratory volume in 1 s of <1 l), severe renal impairment (plasma creatinine >250 μmol/l), severe valvular disease, or candidacy for cardiac transplantation. Recruitment deliberately included elderly patients and patients with a preserved LVEF.

Procedures. During index admissions, treatment was according to the usual practice of the admitting physician. Qualifying patients attended a research outpatient clinic within 2 weeks of discharge from hospital and were randomly assigned, in a double-blind fashion, to 1 of 3 treatments in a 1:1:1 ratio, stratified by age (≤75 or >75 years) in permuted blocks of 30. The UC group had no further contact with the research team beyond 3-monthly documentation of medications, readmissions, and death. Their management was undertaken in primary care with or without additional attendance of hospital cardiology or specialist heart failure clinics as requested by their primary care physician. Patients randomly allocated to the hormone-guided (NT-proBNP) and CG groups were seen at 3-monthly intervals in a dedicated research clinic. At each visit, clinical assessment was undertaken by staff blinded to the patient's assigned trial group to ascertain a heart failure score, derived by assigning a value to variables included in the Framingham method for the diagnosis of heart failure, with major criteria scoring 1 point and minor criteria, 0.5 points (Table 1) (11,14,15). Clinical end points were documented and blood drawn for NT-proBNP (17) and biochemistry, including plasma creatinine for estimation of the glomerular filtration rate (18). New York Heart Association (NYHA) functional class (3-monthly), 6-min walk tests (baseline and 6 and 12 months), Minnesota Living With Heart Failure quality of life scores (baseline and 6 and 12 months), blood pressure, and heart rate (all visits) were documented. Both groups received instructions on monitoring weight, dietary sodium restriction, rest after diuretic administration, exercise, avoidance of licorice, nonsteroidal anti-inflammatory drugs, and alcohol, and the need for influenza vaccination.

For the CG group, we aimed to establish trial-based drug doses. This included the equivalent of enalapril 10 mg twice daily adjusted for renal function. Beta-blockers were introduced with standard titration at 2-weekly intervals toward doses of carvedilol 25 mg twice daily or a sustained-release preparation of metoprolol to 190 mg daily. Heart failure scores ≥2.0 triggered escalation of drug therapy according to a pre-set algorithm.

For the NT-proBNP group, adjustments in medications and additional follow-up visits were triggered by an NT-

Table 1 Heart Failure Score

Symptom/Sign	Value	Score
Orthopnea	0.5	
Paroxysmal nocturnal dyspnea	1.0	
Reduction in exercise tolerance	0.5	
Resting sinus tachycardia (>100 $^{-1}$)	0.5	
Jugular venous pressure >4 cm	0.5	
Hepatojugular reflux positive	1.0	
Third heart sound present	1.0	
Basal crackles	1.0	
Hepatomegaly	0.5	
Peripheral edema	0.5	
Total score		

proBNP level >150 pmol/l and/or a heart failure score ≥2.0 according to instructions by 1 investigator (J.G.L.) who did not undertake the clinical assessments. When results fell below both thresholds, treatment was not altered. Serial assessments were conducted as for the CG group.

Trial treatment protocols were applied for 2 years from randomization after which patients were returned to standard management. Outcomes were documented at 1 and 2 years and, for the coprimary end points, also at 3 years.

Outcomes. Primary outcomes included all-cause mortality and the composite of death plus hospitalization for heart failure. Secondary outcomes were death plus hospital admission for any cardiovascular event plus episodes of outpatient decompensated heart failure requiring increased medications; any episode of heart failure decompensation; total admissions to hospital; and changes in NT-proBNP levels, NYHA status, 6-min walk distance, and Minnesota Living With Heart Failure quality of life scores.

Statistical analysis. Data are presented as mean ± SD (when normally distributed) or median and interquartile range. The appropriateness of parametric analyses was confirmed by visual inspection of the normality and variability of residual plots. When these assumptions were not met, data were log transformed before analyses or nonparametric tests were employed. Baseline variables were compared between treatment groups using *t* tests, Mann-Whitney *U* statistic, chi-square test, and Fisher exact test as appropriate. Variables undergoing serial measurements were analyzed by analysis of variance with repeated measures including time, group, and time by group interaction terms. Where significant main or interaction effects were detected, these were further explored as within subject and between subject effects using post-hoc paired and independent *t* tests.

Clinical outcomes were tested on an intention to treat basis using the Cox proportional hazards regression models, including treatment arm, age (≤75 and >75 years), and age by treatment interactions. Event-free survival was analyzed by the Kaplan-Meier method comparing treatments by the log-rank test. A p value <0.05 (2-tailed) was taken to indicate statistical significance.

Results

Between July 1, 2001, and August 31, 2006, 3,576 patients admitted to Christchurch Hospital with heart failure were screened. In all, 998 met inclusion criteria; 823 patients were approached, and 448 consented to participate. Eighty-four were subsequently excluded because NT-proBNP levels were <50 pmol/l. Three hundred sixty-four patients were randomized.

Treatment groups were well matched for relevant baseline variables and test results (Table 2). Median ages were 75 to 76 years, and 75% of patients fell within NYHA functional classes II and III. A broad spectrum of LVEF was present (38 ± 16%).

At randomization, the proportion of patients receiving key drugs was similar across groups (furosemide in 94%, 98%, and 91%; ACEI/ARB in 84%, 84%, and 77%; BB in 65%, 70%, and 71%; and spironolactone in 12%, 12%, and 17% of NT-proBNP, CG, and UC groups, respectively). Initial doses did not differ between groups but subsequent doses of furosemide, ACEI, and BB were less in UC patients than in either the NT-proBNP group or the CG group ($p < 0.001$ for all) (Table 3). Accordingly, target drug doses were met less often in the UC group compared with the NT-proBNP and CG groups for both ACEI (28%, 48%, and 46%, respectively, at 12 months; $p < 0.001$) and BB (15%, 21%, and 27%; $p < 0.001$). Furosemide doses rose significantly ($p < 0.001$) above baseline in both the NT-proBNP and CG groups but not in the UC group ($p < 0.05$ for UC vs. NT-proBNP group or CG group) (Table 3). Final achieved doses of furosemide were similar in the NT-proBNP and CG groups, but the proportion of visits in which furosemide doses were increased was significantly greater in the NT-proBNP group than in either the CG group or the UC group (17% vs. 14% and 9%; $p = 0.02$ and $p < 0.001$, respectively). The ACEI doses did not alter significantly over time in any group. The BB doses rose over initial follow-up similarly in NT-proBNP and CG groups (both $p < 0.001$) but not in the UC group. Spironolactone doses fell significantly within the NT-proBNP group of patients ($p < 0.001$ over follow-up) but were unchanged in the CG and UC groups (Table 3).

Drugs were frequently decreased, predominantly reflecting either symptomatic hypotension or azotemia (85% of occasions). Loop diuretic, ACEI, and BB doses were reduced at ≈9%, 7%, and 6% of reviews, respectively, with little difference between treatment groups except in the case of BBs, which were both increased and decreased significantly less often in the UC group than in either intensively managed group.

Plasma NT-proBNP levels fell similarly within 6 months of randomization in both the NT-proBNP and CG groups (by 20% and 23%, respectively; $p < 0.001$). Levels remained above 150 pmol/l in more than one-half of the patients in the NT-proBNP and CG groups at 2 years (Table 3).

Minnesota scores improved significantly and similarly in both groups (both $p < 0.001$), whereas 6-min walk distance tended to improve in both groups (p = NS) (Table 3). The proportions of patients in NYHA functional classes I, II, III, and IV did not differ significantly among NT-proBNP, CG, and UC at baseline (5.7%, 76.1%, 18.2%, and 0% vs. 11.1%, 72.2%, 16.7%, and 0% vs. 8.4%, 74.3%, 17.3%, and 0%, respectively) nor between NT-proBNP and CG groups over follow-up (11.1%, 63.6%, 20.2%, and 5.1% vs. 11.0%, 59.0%, 25.0%, and 5.0%, respectively, at 12 months). The NT-proBNP and CG patients attended for similar numbers of scheduled and extra clinic visits (totaling 1,145 and 1,131 visits for NT-proBNP and CG, respectively).

Mortality at 1 year was 18.9% in UC patients and 9.1% in the NT-proBNP and CG groups ($p = 0.028$ overall, $p = 0.03$

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Table 2 Demographic and Clinical Characteristics of Patients According to Subgroup

	Group		
	NT-proBNP–Guided (n = 121)	Clinically-Guided (n = 121)	Usual Care (n = 122)
Age, yrs	76 (44–89)	76 (34–89)	75 (31–89)
Sex, % male	63	67	62
Blood pressure, mm Hg			
Systolic	125 ± 22	123 ± 24	125 ± 22
Diastolic	72 ± 13	70 ± 12	73 ± 14
Heart rate, beats/min	71 ± 13	71 ± 13	69 ± 13
Weight, kg	76 ± 16	75 ± 16	76 ± 15
Diabetes mellitus	23	20	22
Hypertension	55	42	62
Coronary artery disease	70	72	73
History of myocardial infarction	42	47	44
Dilated cardiomyopathy	19	23	27
Stroke	23	20	21
Peripheral vascular disease	14	11	14
COPD	23	20	16
Plasma creatinine, μmol/l	120 ± 42	122 ± 49	119 ± 44
LVEF, %	40 ± 15	39 ± 15	37 ± 15
NYHA functional class			
I	12	7	7
II	68	66	67
III	18	25	25
IV	2	2	1
Heart failure admissions			
0	69	67	71
≥1	31	32	29
Plasma NT-proBNP			
pmol/l	238 (61–1,210)	236 (50–779)	238 (50–1,250)
pg/ml	2,012 (516–10,233)	1,996 (425–6,588)	2,012 (425–10,571)

Data are shown as median (interquartile range), %, or mean ± SD. Baseline variables did not differ between treatment groups as assessed by *t* tests, Mann-Whitney *U* statistic, chi-square test, and Fisher exact test, applied as appropriate.

COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

for both pairwise comparisons between UC and the other 2 groups). Univariate Kaplan-Meier analysis showed no overall difference in survival among groups at 2 and 3 years, but on Cox regression (allowing for time to event, age ≤75 or >75 years, and time by age interactions), an overall treatment effect spanned the 3 years ($p = 0.033$), driven primarily by a significant difference between the NT-proBNP and UC groups ($p = 0.011$) (Fig. 1). We observed interactions ($p \leq 0.025$) between treatment group and age with respect to mortality (Fig. 2). At 1, 2, and 3 years among patients ≤75 years of age, cumulative all-cause mortality was 1.7%, 7.3%, and 15.5%, respectively, in the NT-proBNP group; 7.3%, 20.0%, and 30.9%, respectively, in CG patients; and 20.3%, 23.4%, and 31.3%, respectively, in the UC group. Three-year mortality was significantly lower for the younger NT-proBNP patients than for their peers in either the CG or the UC group ($p = 0.048$ and 0.021, respectively), whether analysis included all patients randomized ($p = 0.03$) (Fig. 2) or was confined to subjects with follow-up of at least 3 years ($n = 215$) from randomization ($p = 0.008$).

For the coprimary end point of death and/or readmission with heart failure, Cox regression indicated reduced rates in both the NT-proBNP group ($p = 0.05$) and the CG group ($p < 0.043$) compared with UC patients at 1 year for those ≤75 years of age (Table 4). By 3 years, benefit was confined to younger NT-proBNP patients ($p = 0.044$; cumulative event rates of 39%, 51%, and 55% for younger NT-proBNP, CG, and UC groups, respectively). Accordingly, a comparison of "days alive and not in hospital with heart failure" for patients with potential follow-up of 1, 2, and 3 years favored patients ≤75 years in the NT-proBNP group: totals at 1, 2, and 3 years averaged 360, 690, and 1,012 days, respectively, in the younger NT-proBNP patients; 352, 655, and 896 days, respectively, for their peers in the CG group; and 318, 584, and 806 days, respectively, for patients receiving UC. The difference between the NT-proBNP and UC groups in this regard was sustained ($p = 0.04$, $p = 0.07$, and $p = 0.04$, respectively, at 1, 2, and 3 years) whereas CG patients differed from patients in the UC group only for the first year ($p = 0.04$) but not at 2 or 3 years ($p = 0.11$ and $p = 0.23$, respectively). On average over 3 years

Table 3 Medications and Serial Measures

Drug	Treatment Group	Time (Months) 0	3	6	12	24
Furosemide, mg/day	NT-proBNP*	128 ± 23	138 ± 20	140 ± 22	182 ± 22	200 ± 27
	CG*	149 ± 23	144 ± 21	134 ± 21	166 ± 23	197 ± 28
	UC†	124 ± 22	121 ± 21	119 ± 21	123 ± 22	140 ± 25
ACEI, mg/day	NT-proBNP	12.7 ± 6	13.0 ± 6	13.3 ± 6	13.1 ± 6	12.4 ± 7
	CG	13.3 ± 6	14.7 ± 6	14.6 ± 6	14.2 ± 6	14.0 ± 7
	UC	10.3 ± 6	11.3 ± 6	11.0 ± 6	11.0 ± 6	10.8 ± 6
Beta-blocker, mg/day	NT-proBNP‡	76 ± 11	83 ± 9	95 ± 9	95 ± 10	94 ± 11
	CG‡	80 ± 11	91 ± 9	95 ± 9	99 ± 10	99 ± 12
	UC†	73 ± 10	74 ± 9	75 ± 9	73 ± 10	72 ± 10
Spironolactone, mg/day	NT-proBNP§	20 ± 6	22 ± 4	22 ± 4	20 ± 5	16 ± 7
	CG	21 ± 6	22 ± 5	24 ± 5	23 ± 5	20 ± 6
	UC	20 ± 2	20 ± 2	21 ± 2	21 ± 2	21 ± 3
6-min walk distance, m	NT-proBNP	337 ± 103		356 ± 106	364 ± 109	
	CG	337 ± 98		369 ± 93	369 ± 97	
	UC	345 ± 95				
Quality of life score	NT-proBNP‖	36.5 ± 22.7		28.9 ± 24.5	28.8 ± 21.6	
	CG‖	36.6 ± 23.1		27.5 ± 20.0	26.5 ± 22.0	
	UC	36.5 ± 24.0				
NT-proBNP >150 pmol/l	NT-proBNP§	66	67	58	57	51
	CG§	79	71	57	63	68
Heart failure score ≥2.0	NT-proBNP§¶	14	5	3	9	4
	CG§	14	9	13	10	4
eGFR, ml/min	NT-proBNP§	57 ± 18	56 ± 18	56 ± 18	55 ± 17	52 ± 16
	CG§	61 ± 20	59 ± 20	60 ± 20	59 ± 19	56 ± 19
BP systolic, mm Hg	NT-proBNP§	125 ± 14	124 ± 13	125 ± 15	123 ± 12	122 ± 12
	CG§	123 ± 13	122 ± 12	122 ± 13	119 ± 15	119 ± 13
BP diastolic, mm Hg	NT-proBNP§	72 ± 12	71 ± 12	70 ± 11	70 ± 11	69 ± 10
	CG§	70 ± 12	70 ± 12	70 ± 12	69 ± 12	68 ± 12

Data are shown as mean ± SD or %. Mean doses are for patients receiving drug. Angiotensin-converting enzyme inhibitor (ACEI) doses are given in enalapril equivalents. Beta-blocker (BB) doses are given in metoprolol equivalents. *Dose increased over follow-up, $p < 0.001$. †No significant change in dose, and either average dose or increment in dose over follow-up is less than in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) group and clinically-guided (CG) group, $p < 0.05$. ‡BB doses rise in first 6 months, $p < 0.001$. §Significant falls over 24 months, $p < 0.001$. ‖Quality of life score improves, $p < 0.001$. ¶NT-proBNP group less than CG group over 24 months, $p = 0.04$.

BP = blood pressure; eGFR = estimated glomerular filtration rate; UC = usual care.

among younger patients, the NT-proBNP group had 206 more days (of a possible 1,076) alive and not in hospital with heart failure than did the UC group ($p = 0.04$).

Overall hospitalizations for heart failure (Table 4) did not differ among groups (cumulative event rates over 3 years of 36%, 40%, and 34% for NT-proBNP, CG, and UC groups, respectively) although a nonsignificant reduction was observed among younger NT-proBNP patients (29% vs. 40% and 36%) (Table 4). No difference was seen for other secondary outcomes, including death plus hospital admission for any cardiovascular event or for total admissions (data not shown).

The percentage of patients with heart failure scores ≥2.0 at clinic assessments fell in both the NT-proBNP and CG groups ($p < 0.001$) (Table 3). The fall was more pronounced in NT-proBNP patients (over all visits, 6.6% vs. 12.1%, respectively; $p = 0.03$).

No significant benefit was observed from NT-proBNP or CG over UC among patients >75 years of age. Patients >75 years of age received lower drug doses (88%, 79%, and 50% of doses at 12 months for patients ≤75 years of age for furosemide, ACEI, and BB, respectively; $p < 0.001$ for all) and met target doses less often (in 30% vs. 50% and 12% vs. 27% for ACEIs and BBs, respectively, at 12 months; $p < 0.001$ for both), had higher baseline (296 ± 179 pmol/l vs. 265 ± 233 pmol/l; $p = 0.001$) and subsequent plasma NT-proBNP levels that remained above 150 pmol/l more often (66% to 84% vs. 48% to 57% of serial 3-monthly measurements; $p < 0.001$), and had poorer renal function (baseline estimated glomerular filtration rate 52 ± 17 ml/min/1.73 m^2 vs. 60 ± 21 ml/min/1.73 m^2; $p < 0.001$) than did patients ≤75 years of age. Notably, LVEF was higher in older patients (42.1 ± 12.7% vs. 34.7 ± 12.6%; $p = 0.001$). LVEF was preserved (i.e., >40%) in 29% and 53% of patients age ≤75 years and >75 years, respectively. All age-associated differences were similar across treatment groups.

Discussion

Tailored treatment is accepted for many disorders, including diabetes mellitus and hypertension. For CHF, the issue remains unsettled. Whereas a single-center study (11) and a

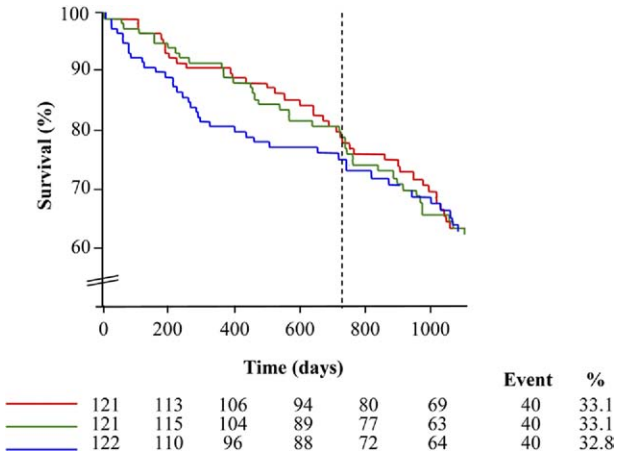

Figure 1 **3-Year Survival of Patients With Chronic Symptomatic Heart Failure**

Three-year survival of patients with chronic symptomatic heart failure receiving hormone-guided treatment **(red line)**, clinically-guided treatment **(green line)**, or usual care **(blue line)**. All patients irrespective of age are included. An overall treatment effect was confirmed by Cox hazards analysis at 1, 2, and 3 years ($p < 0.05$ for all analyses), driven mainly by a significant difference between hormone-guided and usual care groups ($p = 0.011$ over 3 years). The **vertical dashed line** indicates cessation of management strategy and return to standard clinical practice for all surviving participants at 2 years.

multicenter trial (12) documented outcome benefits from pharmacotherapy guided by BNP peptides, they have been criticized on a number of grounds, guidelines have yet to endorse the concept, and the view exists that clinicians do not need "such a crutch" (19). The present trial was designed to overcome current uncertainties by including a larger number of patients, less selected than in the 2 reported studies (11,12), in other words, typical of patients admitted with CHF in Western countries. Follow-up was longer than in earlier studies, and we compared the efficacy of NT-proBNP–guided treatment not only with intensive clinical management but also with UC.

Survival at 1 year was superior in both groups followed up intensively compared with UC. These observations support previous reports regarding the effectiveness of systematic multidisciplinary care employing a variety of monitoring strategies for CHF in which reduced mortality has been the most consistently improved end point (20–23). Survival benefit at 1 year was driven by patients ≤75 years of age, and for those >75 years of age, the 1-year mortality did not differ among groups (Fig. 2). The same applies to 2- and 3-year data except that, at these time points, survival among ≤75-year-old patients was significantly greater in the NT-proBNP group versus both of the other 2 groups.

The NT-proBNP patients (all ages) were significantly less likely to have heart failure scores ≥2 during 2 years of follow-up than were CG patients. For the coprimary end point of death and/or readmission to hospital with CHF at 1 year, the 2 intensively managed groups had a significantly better outcome than did UC patients among those ≤75 years of age, but not among older patients. Again, by 3 years, this outcome favored NT-proBNP–guided patients over those in the other 2 groups (again, only among patients ≤75 years of age). Hence, our second hypothesis, that pharmacotherapy titrated according to plasma levels of NT-proBNP would result in clinical outcomes superior to management guided by a heart failure score based on intensive standardized clinical assessment, can be answered in the affirmative—but with age- and time-related caveats. We cannot fully explain the late-emerging advantage of hormone-guided treatment over intensive clinical manage-

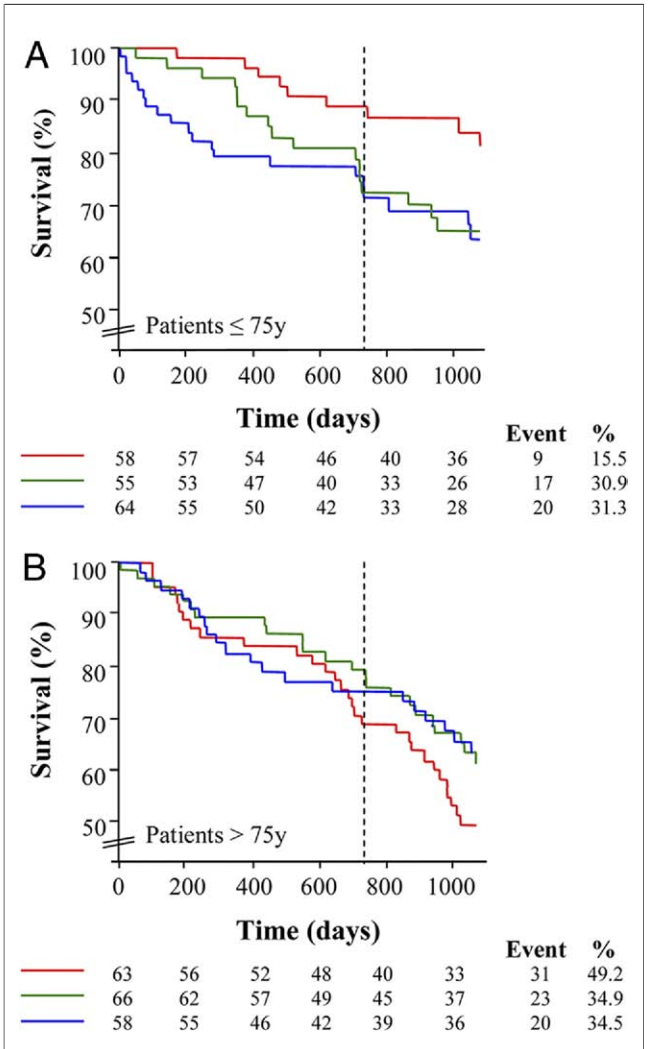

Figure 2 **Survival of Patients ≤75 and >75 Years of Age With Chronic Symptomatic Heart Failure**

Survival among patients **(A)** ≤75 years of age and **(B)** >75 years of age with chronic symptomatic heart failure receiving hormone-guided treatment **(red lines)**, clinically-guided treatment **(green lines)**, or usual care **(blue lines)**. **Vertical dashed lines** indicate cessation of treatment strategy and return to standard clinical practice for all surviving participants at 2 years. At 1 year, in the ≤75-year-old group, both hormone-guided and clinically managed groups had lower mortality than did the usual care group ($p < 0.05$ for both comparisons). At 3 years, the younger hormone-guided group had lower mortality than both other groups ($p < 0.05$ for both comparisons), and mortality in the clinically managed group no longer differed from that in the usual care group.

Table 4 Clinical Outcomes

Treatment Group	Age Group (yrs)	Year 1	Year 2	Year 3
Death ± heart failure admission				
NT-proBNP	All	36 (30)	52 (43)	64 (53)
	≤75*	14 (24)	20 (34)	23 (39)
	>75	22 (35)	32 (51)	41 (65)
CG	All	36 (30)	57 (47)	66 (55)
	≤75	15 (27)	25 (45)	28 (51)
	>75	21 (32)	32 (48)	38 (58)
UC	All	42 (34)	57 (47)	66 (54)
	≤75	25 (39)	31 (48)	35 (55)
	>75	17 (29)	26 (45)	31 (53)
Heart failure admission				
NT-proBNP	All	29 (24)	38 (31)	44 (36)
	≤75	13 (22)	16 (28)	17 (29)
	>75	16 (25)	22 (35)	27 (43)
CG	All	30 (25)	44 (36)	49 (40)
	≤75	14 (25)	21 (38)	22 (40)
	>75	16 (24)	23 (35)	27 (41)
UC	All	26 (21)	37 (30)	41 (34)
	≤75	18 (28)	22 (34)	23 (36)
	>75	8 (14)	15 (26)	18 (31)

Values are n (%). *Significantly less than UC at 3 years ($p = 0.044$).
Abbreviations as in Table 3.

ment. However, increments in loop diuretics were instituted significantly more frequently and may have been more optimally matched to individual patient needs in the NT-proBNP group even in the absence of differences in final mean doses between the NT-proBNP and UC groups. The data suggest sustained benefit, and no net harm, accrues from increased loop diuretic doses when added to maximally tolerated doses of ACEI and BB for patients with persistent elevation of plasma NT-proBNP but without bedside signs or symptoms of cardiac decompensation. The CG patients received more intensive follow-up and frequent adjustment of therapy than would be expected in routine clinical practice, but at 3 years this conferred no advantage, in contrast to UC. That may reflect cessation of this management strategy at 2 years from randomization with loss of effect within the following 12 months (Fig. 2). The hormone-guided approach may have allowed establishment of more effective individualized therapy within the 2-year window with longer-lasting beneficial effects.

At the time of writing, the TIME-CHF (Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) trial of NT-proBNP–guided versus symptom-guided therapy was published (24,25). The trial was conducted with 499 patients >60 years of age randomly allocated to the 2 treatment strategies and followed up for 18 months. The results are in striking parallel to the current report, with improvement in outcomes among patients 60 to 75 years of age but not among those 75 years of age or older.

It is evident from our results and the foregoing discussion that patient age has a modulating effect on the clinical efficacy of NT-proBNP–guided therapy. Benefits were confined to patients ≤75 years of age, broadly consistent with the 2 previous studies in which the average age of patients was considerably younger, age ≈70 years (11) and ≈66 years (12), than in the present trial, age 76 years. Patients age >75 years of age were less able to tolerate full trial-based doses of drugs, and had reduced renal function. In addition, older patients included a higher proportion with preserved LVEF, a group in which the efficacy of established heart failure therapy is uncertain (26,27). These factors presumably underlie, or at least contribute to, the lack of benefit in this subgroup.

In the subgroup for which mortality benefit was most apparent (i.e., patients ≤75 years of age receiving hormone-guided treatment), achieved doses of loop diuretics were higher than in UC patients and dose adjustments were more frequent than in both the UC and CG groups. Furosemide has no fixed, trial-based, standard or target dose and has a broad therapeutic range between 20 mg and 3 g daily. Clearly, this is where most flexibility resides for altering heart failure therapy once a full attempt has been made to achieve trial-based doses of ACEIs/ARBs and BBs. Younger versus older patients with adequate renal reserve and preserved autonomic function are likely to be better able to compensate for any adverse hemodynamic effects of increasing doses of loop diuretic.

Patients in the NT-proBNP–guided group and the CG group had a similar total number of visits to the outpatient clinic. This finding suggests that the benefit of hormone guidance does not reflect differences in frequency of patient contact with attendant increased opportunity for promotion of drug compliance, better education, and/or promotion of nonpharmacological measures.

We utilized a single level of plasma NT-proBNP (150 pmol/l) in our NT-proBNP group as a target for pharmacotherapy independent of patient age. Because levels of the B-type peptides increase with age, it might in retrospect have been logical to have used age-adjusted peptide levels or even individualized target peptide levels for guiding treatment.

Conclusions

We have shown that, compared with UC in the community, intensive management with or without guidance from serial measurements of plasma NT-proBNP improves mortality at 1 year among patients with CHF. Hormone-guided treatment was associated with a lower mortality rate (and also reduced mortality plus hospitalization rate) at 3 years compared with either intensive clinical management or UC for patients ≤75 years of age.

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