REVIEW ARTICLE

B-Type Natriuretic Peptide–Guided Heart Failure Therapy

A Meta-analysis

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Background: The use of plasma levels of B-type natriuretic peptides (BNPs) to guide treatment of patients with chronic heart failure (HF) has been investigated in a number of randomized controlled trials (RCTs). However, the benefits of this treatment approach have been uncertain. We therefore performed a meta-analysis to examine the overall effect of BNP-guided drug therapy on cardiovascular outcomes in patients with chronic HF.

Methods: We identified RCTs by systematic search of manuscripts, abstracts, and databases. Eligible RCTs were those that enrolled more than 20 patients and involved comparison of BNP-guided drug therapy vs usual clinical care of the patient with chronic HF in an outpatient setting.

Results: Eight RCTs with a total of 1726 patients and with a mean duration of 16 months (range, 3-24 months) were included in the meta-analysis. Overall, there was a significantly lower risk of all-cause mortality (relative risk [RR], 0.76; 95% confidence interval [CI], 0.63-0.91; *P*=.003) in the BNP-guided therapy group compared with the control group. In the subgroup of patients younger than 75 years, all-cause mortality was also significantly lower in the BNP-guided group (RR, 0.52; 95% CI, 0.33-0.82; *P*=.005). However, there was no reduction in mortality with BNP-guided therapy in patients 75 years or older (RR, 0.94; 95% CI, 0.71-1.25; *P*=.70). The risk of all-cause hospitalization and survival free of any hospitalization was not significantly different between groups (RR, 0.82; 95% CI, 0.64-1.05; *P*=.12 and RR, 1.07; 95% CI, 0.85-1.34; *P*=.58, respectively). The additional percentage of patients achieving target doses of angiotensin-converting enzyme inhibitors and β-blockers during the course of these trials averaged 21% and 22% in the BNP group and 11.7% and 12.5% in the control group, respectively.

Conclusions: B-type natriuretic peptide–guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care, especially in patients younger than 75 years. A component of this survival benefit may be due to increased use of agents proven to decrease mortality in chronic HF. However, there does not seem to be a reduction in all-cause hospitalization or an increase in survival free of hospitalization using this approach.

Arch Intern Med. 2010;170(6):507-514

HEART FAILURE (HF) IS A leading cause of death, hospitalization, and rehospitalization worldwide.[1] Despite advances in the treatment of HF, including use of drugs, devices, and heart transplantation, the condition remains associated with substantial morbidity and mortality.

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A likely contributor is inadequate dose titration of HF medications[2] such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-adrenergic blockers, and spironolactone, all of which have been shown to improve outcomes and are recommended by international guidelines.[3,4]

B-type natriuretic peptide (BNP) is a neurohormone secreted predominantly from the ventricle of the heart in response to intracardiac volume loading.[5] B-type natriuretic peptide functions as a counterregulatory hormone to angiotensin II, norepinephrine, and endothelin, having vasodilatorary and diuretic effects.[5] The precursor of BNP is pro-BNP, stored in secretory granules in myocytes. Pro-BNP is split by a protease enzyme into BNP and *N*-terminal pro-BNP (NT-pro-BNP). Compared with BNP, NT-pro-BNP is a longer peptide sequence than BNP (76 vs 32 amino acids) and has a longer half-life (60-120 minutes vs 15-20 minutes).[6] Both BNP and NT-pro-BNP plasma concentration have been shown to be useful in the diagnosis of acute decompensated HF.[7] In addition, these peptides can be used as prognostic indicators in prediction of mortality and clinical outcome in patients with chronic HF. Specifi-

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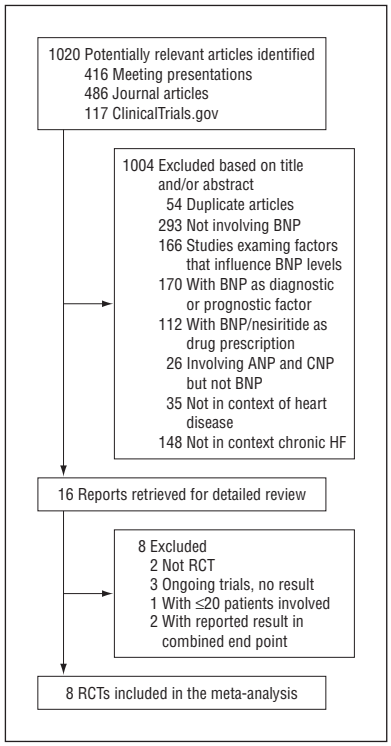

Figure 1. Quality of Reporting of Meta-analyses (QUOROM) flow diagram. ANP indicates atrial natriuretic; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; HF, heart failure; RCT, randomized controlled trial.

cally, lower plasma BNP levels are predictive of a reduced likelihood of future major cardiovascular events.[8,9]

B-type natriuretic peptide plasma concentrations can be reduced considerably in patients with acute decompensated HF after aggressive treatment with ACE inhibitors,[10] ARBs,[11] and aldosterone antagonists.[12] B-type natriuretic peptide plasma levels also fall following long-term treatment with β-adrenergic blockers, although levels may increase temporarily in the short term.[13] Titration of ACE inhibitors or β-blockers after comprehensive treatment resulting in further reduction of BNP levels may reflect a reverse remodeling process on the ventricle of the heart.[14] Thus, lowering of BNP plasma levels by use of proven HF medications represents a putative therapeutic target (BNP-guided therapy).

This hypothesis has been investigated in a number of prospective randomized controlled trials (RCTs). To date, however, the therapeutic benefit of this approach remains uncertain. In particular, individual studies have generally been underpowered in the evaluation of the impact of BNP-guided therapy on major cardiovascular and mortal events. In addition, the ability of individual studies to ascertain reasons by which BNP-guided therapy may influence such outcomes is also limited. Furthermore, there has been some variability in the findings reported in these studies. The aim of the present study was therefore to assess the potential clinical benefits of BNP-guided therapy in chronic HF, by performing a meta-analysis of RCTs comparing BNP-guided treatment and usual clinical care.

METHODS

DATA SOURCES AND SEARCHES

Clinical RCTs were identified via MEDLINE (source, PubMed, 1966 to December 2008), EMBASE (1974 to December 2008), the Cochrane Controlled Clinical Trials Register Database (through December 2008), and the ClinicalTrials.gov Web site (through December 2008). Each search query included the keywords and corresponding MeSH terms for *brain natriuretic peptide*, *pro-brain natriuretic peptide*, *heart failure*, and *therapy*. Manual reference checking of the bibliographies of all retrieved articles was also performed. To identify studies reported only at scientific meetings, searches were undertaken both manually and electronically of the abstracts of annual scientific sessions of the American Heart Association (2005-2008), the European Society of Cardiology (2005-2009), the American College of Cardiology (2005-2009), the European Heart Failure Society, and the Heart Failure Society of America (through 2009). Eligibility assessment and data abstraction were both performed independently in an unblinded[15] standardized manner by 2 reviewers (P.P. and P.P.)

STUDY SELECTION

Only prospective RCTs conducted in outpatients with a history of HF were considered for inclusion in this meta-analysis. An RCT was defined according to the National Library of Medicine.[16] Trials with a total of 20 or fewer patients[17] or with end points that were reported only in a single study[18,19] were excluded.

DATA EXTRACTION AND QUALITY ASSESSMENT

All qualifying studies were assessed for patient characteristics as well as for adjustment of medications in both the clinical usual care and BNP-guided groups. Clinical outcomes assessed included all-cause mortality, all-cause hospitalization, survival free of any hospitalization, mortality in patients younger than 75 years or 75 years or older, number of days alive outside of hospital, and additional percentage of patients prescribed adjusted HF medication (diuretics, aldactone, β-blockers, and ACE inhibitors or ARBs), and whether target doses of ACE inhibitors and β-blockers were achieved during the study. We were unable to assess hospitalization for HF owing to differences between studies in the method of reporting used (ie, number of hospitalization events vs number of patients hospitalized).

DATA SYNTHESIS AND ANALYSIS

Results were pooled with Stata statistical software (version 10; StataCorp, Cary, North Carolina) using the Mantel-Haenszel fixed-effects model. In the Mantel-Haenszel model, we used Stata software to calculate a weighting for every study in accordance with the number of events that occurred in every study to form an average overall outcome statistic and 95% confidence interval (CI). Heterogeneity among studies was analyzed by χ^2 and sensitivity analyses were performed to determine the influence of individual trials on the results. Statistical significance was set at the .05 level for both χ^2 test for heterogeneity and *z*-test for relative risk (RR).

RESULTS

SEARCH RESULTS

Detailed search steps are summarized in a flowchart illustrating the mechanisms of exclusion for certain studies (**Figure 1**) in accordance with the Quality of Reporting of Meta-analyses (QUOROM) recommendations.[20] We initially identified 1020 potentially relevant articles. Sixteen articles were considered to be of interest and were retrieved for detailed evaluation. Eight articles that did not meet our criteria were excluded, and the remaining 8 studies were included in the meta-analysis.

QUALITATIVE FINDINGS

Eight trials, with a total of 1726 patients, met the specified criteria for meta-analysis. Trials included were those by Troughton et al,[21] Beck-da-

Table 1. Patient Characteristics in Included Trials

Source	Patients, No.		Duration of Follow-up, Mo.	Age, y[a]		Male, %		NYHA FC, Mean[a]		NYHA FC Class II, %		NYHA FC Class >III, %	
	NH	C		NH	C	NH	C	NH	C	NH	C	NH	C
Troughton et al[21]	33	36	9.5	68	72	78	75	2.3	2.3	72	67	NA	NA
Beck-da-Silva et al[22]	21	20	3	64.5 (15.2)	65.6 (13.5)	33.33	35	2.6 (0.7)	2.4 (0.6)	NA	NA	NA	NA
Esteban et al[23]	30	30	18	Similar in both groups		Similar in both groups		NA	NA	NA	NA	NA	NA
STARS-BNP[24]	110	110	15	65 (5)	66 (6)	59	56	2.29 (0.60)	2.21 (0.62)	NA	NA	NA	NA
TIME-CHF[25]	251	248	18	76 (7)	77 (8)	68.1	62.9	NA	NA	NA	NA	74.1	74.6
BATTLESCARRED[26]	121	121	24	76	76	63	67	NA	NA	69	66	20	27
PRIMA[27]	174	171	24	71 (12)	73 (12)	55	60	NA	NA	64.9	70.8	23.6	19.3
SIGNAL-HF[28]	126	124	9	>18[b]	>18[b]	NA	NA	2-4	2-4	NA	NA	NA	NA

Source	EF, %[a]		HT, %		DM, %		Renal Function (Cr or CCr)[a]		Type of NH Use	Method of Assay: NH	Baseline BNP-NT-BNP[c]	
	NH	C	NH	C	NH	C	NH	C			NH	C
Troughton et al[21]	28	26	64	67	12	14	CCr, 1.0 (0.7)[d]	CCr, 0.9 (0.7)[d]	NT-pro-BNP	NA	NT-pro-BNP, 1844	NT-pro-BNP, 2133
Beck-da-Silva et al[22]	23.8 (8.8)	20.9 (9.2)	NA	NA	24	25	Cr <200[e]		BNP	Triage, Biosite Inc[f]	BNP, 502	BNP, 702
Esteban et al[23]	Similar in both groups		NA	NA	NA	NA	NA		BNP	NA	NA	NA
STARS-BNP[24]	31.8 (8.4)	29.9 (7.7)	30	30	16	19	Cr, 97 (40)[e]	Cr, 92 (40)[e]	BNP	Imm, Biosite Inc[f]	NA	NA
TIME-CHF[25]	29.8 (7.7)	29.7 (7.9)	69.7	72.2	30.7	38.3	Cr, 1.32 (0.45)[g]	Cr, 1.33 (0.42)[g]	NT-pro-BNP	NA	NT-pro-BNP, 3998	NT-pro-BNP, 4657
BATTLESCARRED[26]	37	37	NA	NA	NA	NA	CCr, 57[h]	CCr, 56[h]	NT-pro-BNP	Immunoassay	NT-pro-BNP, NT-pro-BNP, 2012	NT-pro-BNP, 1996
PRIMA[27]	31	35	48	49	25	28	Cr, 121[i]	Cr, 126[i]	NT-pro-BNP	NA	NT-pro-BNP, 2958	NT-pro-BNP, 2932
SIGNAL-HF[28]	<50	<50	NA	NA	NA	NA	NA	NA	NT-pro-BNP	NA	Male >800 Female >1000[e]	

Abbreviations: BATTLESCARRED, NT-pro-*B*NP-*A*ssis*T*ed *T*reatment to *LE*ssen *S*erial *CAR*diac *RE*admissions and *D*eath; BNP, B-type natriuretic peptide; C, control group; CCr, creatinine clearance; Cr, creatinine; Imm, Immunofluorometric; NA, not available; NH, neurohormonal group; NT-pro-BNP, pro-BNP split by a protease enzyme into BNP and *N*-terminal pro-BNP; PRIMA, *PR*o-brain-natriuretic peptide–guided therapy of chronic heart failure *IM*prove heart failure morbidity *A*nd mortality; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; TIME-CHF, *T*rial of *I*ntensified vs standard *M*edical therapy in *E*lderly Patients with *C*ongestive *H*eart *F*ailure.

[a] Values are expressed as mean (SD).

[b] Inclusion criteria, patients older than 18 years.

[c] Data are given in picograms per milliliter.

[d] Data are given in milliliters per second per meters squared.

[e] Data are given in millimoles per liter.

[f] San Diego, California.

[g] Data are given as miligrams per deciliter.

[h] Data are given as milliliters per minute per 1.73 m^2.

[i] Data are given as micromoles per liter.

Silva et al,[22] Esteban et al,[23] the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) study,[24] the TIME-CHF study (*T*rial of *I*ntensified vs standard *M*edical therapy in *E*lderly Patients with *C*ongestive *H*eart *F*ailure),[25] the BATTLESCARRED study (NT-pro-*B*NP-*A*ssis*T*ed *T*reatment to *LE*ssen *S*erial *CAR*diac *RE*admissions and *D*eath),[26] the PRIMA study[27] (*PR*o-brain-natriuretic peptide guided therapy of chronic heart failure to *IM*prove heart failure morbidity *A*nd mortality) and the SIGNAL-HF study.[28]

Patient characteristics in these trials are summarized in **Table 1**. The studies varied in terms of number of patients, duration of the intervention, and primary end points. In studies where all-cause mortality or all-cause hospitalization was not the primary end point, they were included as secondary end points. The total number of patients in each study ranged from 41 to 499, and the duration of follow-up time varied from 3 to 24 months (mean duration, 17 months). All studies were performed in patients with New York Heart Association (NYHA) class II or greater and left ventricular ejection fraction less than 50%. The participants' ages ranged from 18 to 85 years. Most were men, with the exception of the study by Beck-da-Silva et al,[22] in which the percentage of males was around 35% in each group. Three studies, including those by Beck-da-Silva et al[22] and Esteban et al[23] and the STARS-BNP study,[24] used the BNP level as a monitor to guide medication doses in the intervention group, whereas the other 4 studies (Troughton et al,[21] the BATTLESCARRED study,[26] the TIME-CHF study,[25] the PRIMA study,[27] and the SIGNAL-HF study[28]) used NT-pro-BNP levels.

Target plasma BNP or NT-pro-BNP level in the intervention group and clinical aims in the control group of each trial are summarized in **Table 2**. In the BATTLESCARRED study,[29] there were 3 study arms: hormone-guided care, intensive clinical care, and usual care. "Usual care" in this trial involved no adjustment of medication or further contact with the research team other than an enquiry after 3 months to document medications, adverse events, readmissions to hospital, and death. Consequently, this

Table 2. Treatment Group Targets in Included Trials

Source	Target BNP/NT-Pro-BNP–Guided Therapy	Target Control Group	Medical Adjustment Involved
Troughton et al[21]	NT-pro-BNP <1700 pg/mL	HF score[a] <2 (based on Framingham criteria)	ACEI, diuretic, digoxin, aldactone, metolazone then additional vasodilator (isosorbide dinitrate and felodipine)
Beck-da-Silva et al[22]	Based first on BNP level and then clinical status evaluation; BB up-titrated when: 1. BNP level is lower + unchanged or better clinical status 2. There are mild signs of congestion but BNP level >10% lower than previous value 3. BNP is within ±10% previous level, clinical signs were primarily considered	Up-titrate medication when no sign of deterioration (worsening FC, HR <55, BP <80, increase congestion)	Only BB (ACEI or ARB and digoxin were unchanged)
Esteban et al[23]	NA	Framingham score	NA
STARS-BNP[24]	BNP <100 pg/mL	Based on PE + usual paraclinical + biological parameter	BB, ACEI, aldactone, diuretic
TIME-CHF[25]	NT-pro-BNP + FC ≤II <400 pg/mL (<75 y), <800 pg/mL (≥75 y)	FC ≤ II	BB, ACEI, or ARB, aldactone, diuretic, nitrate
BATTLESCARRED[26]	NT-pro-BNP <1300 pg/mL	HF score[a] <2	BB, ACEI, aldactone, diuretic, digoxin, metolazone
PRIMA[27]	Individual NT-pro-BNP target (lowest level during the first 2 wk after treatment of HF) together with clinical assessment	Clinical assessment	BB, ACEI, or ARB, aldactone, diuretic, digoxin
SIGNAL-HF[28]	NT-pro-BNP plus clinical symptoms and signs	Clinical symptoms and signs	BB, ACEI, or ARB, aldactone

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; BNP, B-type natriuretic peptide; BP, blood pressure; FC, functional class; HF, heart failure; HR, heart rate; NA, not available; NT-pro-BNP, pro-BNP split by a protease enzyme into BNP and *N*-terminal pro-BNP; PE, physical examination. See Table 1 footnote for study name abbreviations.

[a] Heart failure score based on Framingham data for a diagnosis of HF with major criteria each scoring 1 point and minor criteria each scoring 0.5 point.

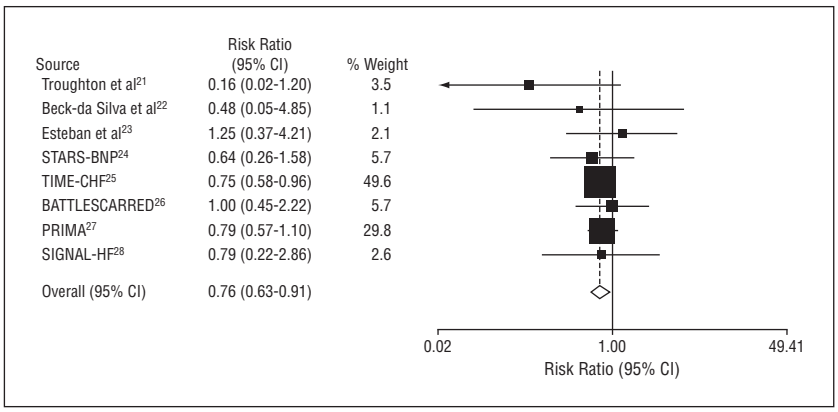

Figure 2. All-cause mortality meta-analysis of individual trials. Fixed-effects model (χ^2=3.75; *P*=.59). CI indicates confidence interval.

group was not used in the subsequent meta-analysis. The intensive clinical care group was similar to the clinical usual care groups of the other trials used in this meta-analysis and thus was used as such. In the TIME-CHF study,[25] the authors reported the overall survival outcomes instead of all-cause mortality. We therefore used these data to calculate all-cause mortality for the purpose of our analysis. Only 2 studies, the TIME-CHF study[25] and BATTLESCARRED studies,[26] presented data according to age group (<75 years or ≥75 years). One-year all-cause mortality data in patients younger than 75 years or 75 years or older from the BATTLESCARRED[26] trial were used, because insufficient data were available at the 2-year time point. The STARS-BNP study[24] and the PRIMA study[27] reported the numbers of patients whose doses of the HF medication were up-titrated during the studies, and only the STARS-BNP[24] and TIME-CHF[25] studies provided details of the percentages of patients achieving the target dose of medications proven to decrease morbidity and mortality.

QUANTITATIVE FINDINGS

The risk of all-cause mortality was significantly lower in the neurohormonal (BNP)-guided treatment group (RR, 0.76; 95% CI, 0.63-0.91; *P*=.003) (**Figure 2**) compared with the clinical-guided treatment group. This effect was dominated by the TIME-CHF study,[25] which contributed 49.6% of the weight. There was no significant heterogeneity between the trials (heterogeneity χ^2_7 of 3.81; *P*=.80). Funnel plot analysis suggested that there was little in the way of publication bias in this result (**Figure 3**).

A subgroup analysis was performed in the TIME-CHF[25] and BATTLESCARRED[26] studies, which provided data on patients younger than 75 years or 75 years or older. All-cause mortality was significantly lower in younger patients treated with BNP-guided therapy (RR, 0.52; 95% CI, 0.33-0.82; *P*=.005) than in those in the clinical guided group with a heterogeneity χ^2_1 of 0.57 (*P*=.45). In contrast, all-cause mortality of those 75 years or older was not significantly different between groups (RR, 0.94; 95% CI, 0.71-1.25; *P*=.70 [heterogeneity χ^2_1 of 1.14; *P*=.29]).

HOSPITALIZATION

Three studies[21,22,24] provided data on all-cause hospitalization. There was no significant difference seen in the BNP-guided therapy group on all-cause hospitalization vs clinical guidance (RR, 0.82; 95% CI, 0.64-1.05; $P=.12$) (**Figure 4**A), with a heterogeneity χ^2_2 of 0.78 ($P=.68$). For this end point, the effect was dominated by the STARS-BNP study[24] with around 80.4% of the weight.

Survival free of any hospitalization was reported in 2 trials. There was a nonsignificant difference in survival free of any hospitalization between the 2 groups (RR, 1.07; 95% CI, 0.85-1.34; $P=.58$) (Figure 4B), with a heterogeneity of χ^2_1 0.00 ($P=.98$). This was predominated by the TIME-CHF study,[25] with approximately 81.6% of the weight.

NUMBER OF DAYS ALIVE AND NOT HOSPITALIZED

The STARBRITE[18] and PRIMA[27] studies provided data on the number of days that patients were alive and not hospitalized. The number of days they were alive and not hospitalized was higher in the BNP-guided group than in the clinical control group, but the difference was not significant in both studies (mean [SD], 85 [12.1] days vs 80.4 [20.6] days in the STARBRITE study [18] and 685 days vs 664 days in the PRIMA study[27]). Unfortunately, we are unable to perform a formal meta-analysis of this outcome because of differences in the presentation of data.

DRUG THERAPY

The STARS-BNP[24] and PRIMA[27] studies presented the percentages of patients having medical treatment adjustment during the study period. Patients in the BNP-guided group had doses of their HF medication adjusted more than those in the clinical care group (**Figure 5**A; 75% vs 58% in diuretics, 13.4% vs 8.2% in aldactone, 49.6% vs 30.9% in ACE inhibitors or ARBs, and 51.1% vs 41.6% in β-blockers).

The mean percentage of patients reaching their target dose of ACE inhibitors and β-blockers during the study were calculated from the STARS-BNP[24] and TIME-CHF studies.[25] Approximately double the number of patients in the BNP-guided therapy group had their doses up-titrated and reached their target level of ACE inhibitors and β-blockers compared with the clinical usual care group (Figure 5B) (21.% and 22.0% in the BNP group vs 11.7% and 12.5% in the usual care group, respectively).

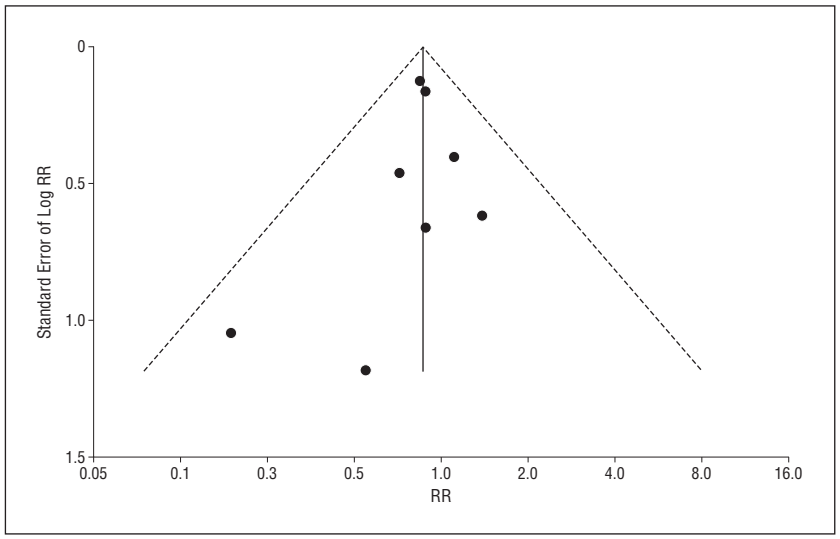

Figure 3. Funnel plot of individual trials (filled circles) contributing to all-cause mortality meta-analysis. RR indicates relative risk.

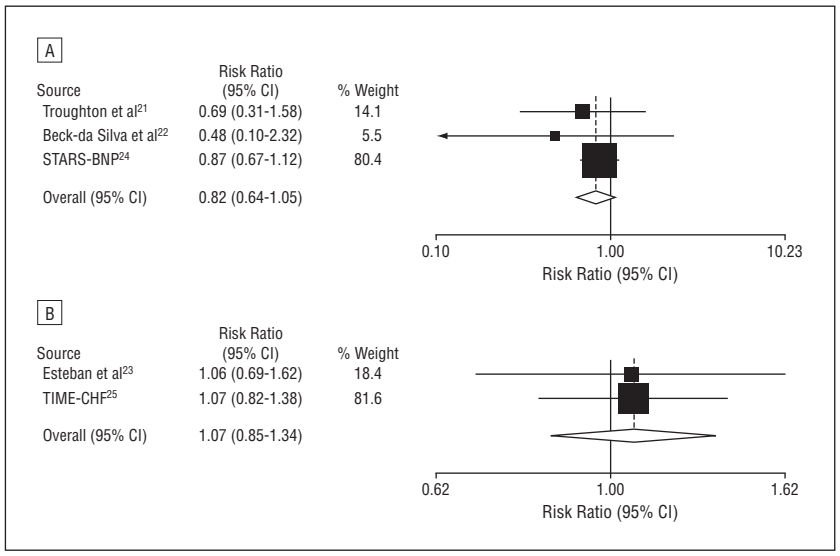

Figure 4. Fixed-effects models. A, All-cause hospitalization meta-analysis of individual trials ($\chi^2=0.78$; $P=.68$); B, survival free of any hospitalization meta-analysis of individual trials ($\chi^2=0.00$; $P=.98$). CI indicates confidence interval. The size of squares reflects weighting for each study. The diamonds indicate the overall results, with the middle being the RR and the outer tips reflecting the 95% CIs around the result.

OTHER PARAMETERS

Change of functional class, quality-of-life (QOL), and left ventricular (LV) ejection fraction (LVEF) could not be meta-analyzed. In terms of functional class, the TIME-CHF[25] and STARS-BNP[24] studies showed improvement in both groups; however, Beck-da-Silva et al[22] and Esteban et al[23] found no change. The TIME-CHF[25] study reported a significant improvement in both the BNP and control groups on QOL, particularly during the first 12 months, but the difference between the 2 groups was not significant. However, statistical improvement in QOL in the BNP-guided therapy group ($P=.03$) was observed in the study by Beck-da-Silva et al[22] ($P=.03$). Troughton et

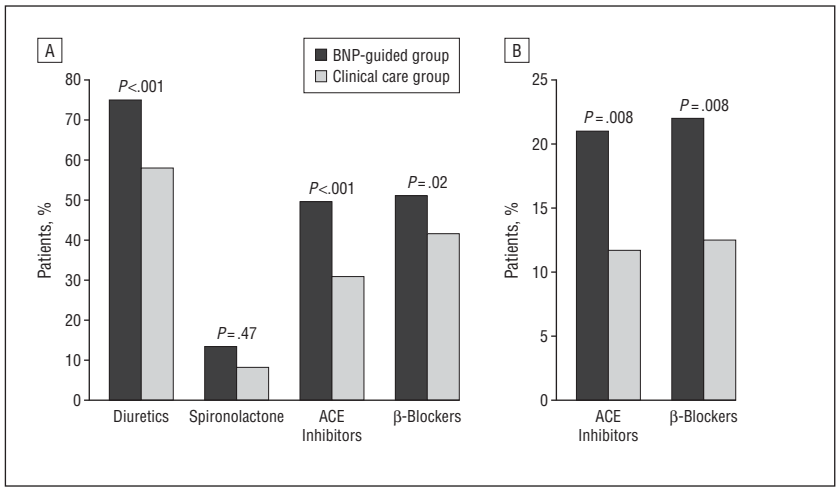

Figure 5. Patients having medical treatment adjustment. A, Percentage of patients having doses of medication increased; B, percentage change of patients reaching target dose. ACE indicates angiotensin-converting enzyme; BNP, B-type natriuretic peptide.

al[21] and Beck-da-Silva et al[22] found significant improvement in LVEF in both treatment groups but no significant difference between the 2 groups ($P=.23$ and $P=.40$, respectively).

SENSITIVITY ANALYSIS

We performed sensitivity analysis to determine the effect of plausible changes in assumptions on the association between BNP-guided therapy and all-cause mortality (**Table 3**). With the exclusion of the TIME-CHF study,[25] the point estimate changed to become nonsignificant ($P=.052$; RR, 0.76; 95% CI, 0.58-1.00). All-cause mortality significance was not affected by exclusion of the other individual trials, including the PRIMA study.[27] Therefore, only the TIME-CHF study[25] among studies evaluated had a major impact on the point estimate of the pooled data.

Sensitivity analysis was also performed for the end point of all-cause hospitalization (Table 3). The point estimates for all-cause hospitalization were stable under a range of assumptions, and although studies favored BNP-guided therapy, significance was not achieved under any scenario.

COMMENT

We performed a meta-analysis of clinical RCTs of BNP-guided therapy in the outpatient treatment of HF. We found that using this approach can decrease all-cause mortality of these patients significantly compared with usual clinical care, particularly in patients younger than 75 years. The number of days that patients were alive and not hospitalized was also significantly higher in the BNP-guided group; nevertheless, all-cause hospitalization and survival free of hospitalization between the 2 groups were not significantly different.

One case report[30] and 1 case series[31] of 76 patients with LV dysfunction showed promising results regarding the potential clinical benefits of measuring the plasma BNP level to guide the treatment. Larger studies[18,19,21,24] using BNP monitoring in the treatment of patients with chronic HF suggested the effectiveness of this approach, with demonstrable improvements in clinical outcomes, including rates of death and rehospitalization. However, subsequent RCTs of this therapy, including those used in this meta-analysis, have found variable results. The overall findings of our study suggest that BNP-guided treatment reduces all-cause mortality in patients with chronic HF. This observation is supported by a recently published evaluation[32] that included some (but not all) of the studies used in the present meta-analysis.

We found that the mortality benefit observed with BNP-guided therapy was restricted primarily to those patients in a younger age group (<75 years). In general, these patients have high mortality rates despite use of proven medications and/or devices. Use of ACE inhibitors,[33] β-blockers,[34] and spironolactone[35] reduce morbidity and mortality in patients with chronic HF. As a result of treatment using BNP-guided modification, it was shown that there is an increase in prescribing of these HF medications (spironolactone, ACE inhibitors, and β-blockers) compared with clinically guided treatment. Specifically, the percentage of patients achieving their target dose of ACE inhibitors and β-blockers in the BNP-guided group were increased to approximately 2-fold higher than those in the control group. Therefore, mechanisms underlying decreased mortality in the BNP-guided therapy group could relate to the higher percentage of patients achieving the target dose of drugs with proven prognostic efficacy. Alternatively, there may be other, as-yet unidentified factors contributing to the mortality benefit.

The BATTLESCARRED[26] and TIME-CHF[25] studies showed that the group of patients younger than 75 years derived considerable clinical benefit from BNP-guided therapy, including decreased all-cause mortality. In contrast, in the older age group (≥75 years), the mortality benefit was not substantive. The reason for this is uncertain. Older patients may have more comorbid diseases, including hypertension, chronic kidney disease, diabetes mellitus, and dysrhythmia, that make them less able tolerate target doses of medication than those in younger age group. They may also be less responsive to these therapies. In the TIME-CHF study,[25] patients in the older age group had a mean age of 82 years (compared with 69 years in the younger group) and had more prevalent comorbidities (eg, hypertension [77% vs 61%], atrial fibrillation [36% vs 26.7%], and kidney disease [62% vs 44%]), and more were classified as having NYHA functional class III disease (80% vs 65%). The TIME-CHF[25] study also suggested that the less severe the comorbidities, the more favorable the effects of NT-pro-BNP–guided therapy. Older patients are also more likely to have noncardio-

Table 3. Sensitivity Analysis of the Effect of BNP-Guided Medical Therapy on All-Cause Mortality and All-Cause Hospitalization

Source	Trials, No.	Patients Evaluated, No.	All-Cause Mortality, RR (95% CI)	*P* Value
All-cause mortality: analysis with all studies except				
Troughton et al[21]	7	1657	0.78 (0.65-0.94)	.008
Beck-da-Silva et al[22]	7	1685	0.76 (0.63-0.92)	.004
Esteban et al[23]	7	1666	0.75 (0.62-0.90)	.002
STARS-BNP[24]	7	1506	0.76 (0.63-0.92)	.005
TIME-CHF[25]	7	1227	0.76 (0.58-1.00)	.052
BATTLESCARRED[26]	7	1484	0.74 (0.61-0.89)	.002
PRIMA[27]	7	1381	0.74 (0.59-0.93)	.009
SIGNAL-HF[28]	7	1476	0.76 (0.63-0.91)	.003
All-cause hospitalization: analysis with all studies except				
Troughton et al[21]	2	261	0.84 (0.65-1.09)	.19
Beck-da-Silva et al[22]	2	289	0.84 (0.65-1.08)	.18
STARS-BNP[24]	2	110	0.63 (0.31-1.31)	.22

Abbreviations: BNP, B-type natriuretic peptides; CI, confidence interval; RR, relative risk. See Table 1 footnote for study name abbreviations.

vascular diseases such as cancers[36] and chronic lung[37] and liver diseases.[38] Thus, these may contribute to mortality in patients of advanced age, and BNP-guided therapy would not alter these outcomes.

The optimal target level of BNP to which therapy should be guided is difficult to decide on. Confounding effects include age, sex, and weight; BNP levels are higher in females and those of advanced age.[39,40] Furthermore, too aggressive a reduction in BNP levels by uptitration of diuretics, ACE inhibitors, and β-blockers may potentially result in worsening rather than improvement in clinical outcomes, especially in elderly individuals, by causing hypotension and worsening renal failure.

Rates of all-cause hospitalization and survival free of hospitalization were not significantly different between the 2 study groups (Figure 4). However, there was a trend toward lower risk of all-cause hospitalization and more survival free of any hospitalization in this group. This may be explained in part by the contribution of non–HF events on which BNP-guided therapy would not have an impact. Unfortunately, we could not calculate the impact on HF hospitalization owing to a lack of data.

A major limitation of this evaluation of BNP-guided therapy is that we were not able to meta-analyze some key clinical end points on which this approach may have a beneficial impact. In particular, hospitalization for HF is one such end point, where BNP-guided therapy and accompanying intensification of use of standard HF pharmacological therapies should theoretically have a favorable impact on this outcome.

We identified 3 ongoing trials of BNP-guided therapy: the NorthStar study,[41] the PROTECT trial,[42] and the EXIMPROVE CHF trial.[43] The NorthStar study[41] is a clinical RCT conducted in Denmark and involving 720 patients with follow-up for 30 months, in which there were 3 arms: treatment in general practice, a standard follow-up program in an HF clinic, and follow-up with plasma NT-pro-BNP levels monitored in an HF clinic. The PROTECT trial[42] is an RCT in Massachusetts General Hospital, Boston, that includes 300 patients with follow-up for 1 year. There are 2 arms: standard of care and NT-pro-BNP–guided groups. The EXIMPROVE CHF (Improvement of patients with Chronic Heart Failure Using NT-pro-BNP) study [43] is an RCT in St Michael's Hospital, Toronto, Ontario, Canada, using NT-pro-BNP–guided care, with follow-up for 2 years.

Based on the findings of the present meta-analysis, future studies will require a larger number of patients and careful matching of age, sex, and other key clinical variables to definitively address the true effectiveness of BNP-guided treatment in the treatment of chronic HF. Prospective evaluation of relevant study end points for which BNP-guided therapy may be expected to have a beneficial impact on outcomes (eg, hospitalization for HF) would also be of great importance.

In summary, the present study demonstrates that BNP-guided therapy can significantly lower all-cause mortality rate in patients with chronic HF compared with those receiving usual clinical care, particularly in patients younger than 75 years but not in those of advanced age. However, this approach does not seem to either reduce all-cause hospitalization or increase survival free of hospitalization.

Accepted for Publication: October 8, 2009.

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Financial Disclosure: None reported.

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