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Changes of Natriuretic Peptides Predict Hospital Admissions in Patients With Chronic Heart Failure

A Meta-Analysis

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Objectives The goal of this study was to explore the association between changes in B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) plasma levels and risk of hospital admission for heart failure (HF) worsening in patients with chronic HF.

Background The relationship between BNP and NT-proBNP plasma levels and risk of cardiovascular events in patients with chronic HF has been previously demonstrated. However, it is unclear whether changes in BNP and NT-proBNP levels predict morbidity in patients with chronic HF.

Methods The MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched for papers about HF treatment up to August 2013. Randomized trials enrolling patients with systolic HF, assessing BNP and/or NT-proBNP at baseline and at end of follow-up, and reporting hospital stay for HF were included in the analysis. Meta-regression analysis was performed to test the relationship between BNP and NT-proBNP changes and the clinical endpoint. Sensitivity analysis was performed to assess the influence of baseline variables on results. Egger's linear regression was used to assess publication bias.

Results Nineteen trials enrolling 12,891 participants were included. The median follow-up was 9.5 months (interquartile range: 6 to 18 months), and 22% of patients were women. Active treatments significantly reduced the risk of hospital stay for HF worsening. In meta-regression analysis, changes in BNP and NT-proBNP were significantly associated with risk of hospital stay for HF worsening. Results were confirmed by using sensitivity analysis. No publication bias was detected.

Conclusions In patients with HF, reduction of BNP or NT-proBNP levels was associated with reduced risk of hospital stay for HF worsening. (J Am Coll Cardiol HF 2014;2:148–58) © 2014 by the American College of Cardiology Foundation

Heart failure (HF) is a major and growing public health problem, affecting 1% of people aged 65 years and older. At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5; at 80 years of age, it remains at 20% despite shorter life expectancy (1). Despite significant advances in diagnosis and treatment, HF is currently the leading cause of hospital stays in people aged 65 years or older, with a rate of death increasing from about 10% after 1 year to about 50% after 5 years from diagnosis. Notably, health expenditures for the yearly 1.1 million hospital stays for chronic HF in the United States amount to nearly $29 billion, corresponding to 10% of total health expenditures.

Plasma concentrations of B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are useful for the diagnosis and management of patients with chronic HF. BNP is a cardiac hormone produced from ventricular muscle cells in response to ventricular dilation and pressure overload, and NT-proBNP is the inactive N-terminal fragment produced from the cleavage of proBNP (2,3). BNP and NT-proBNP levels are elevated in patients with left ventricular dysfunction and correlate to New York Heart Association functional class,

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left ventricular filling pressure, left ventricular ejection fraction assessed by using radionuclide angiography and echocardiography, and with other indices of HF (including pulmonary artery wedge pressure) (4–7). Furthermore, evidence exists supporting the use of BNP and NT-proBNP levels for hospital stay/discharge decision making and for identifying patients at risk of clinical events (8). In addition, it has been reported that, in patients hospitalized for decompensated HF, changes in natriuretic peptide levels from baseline to hospital discharge predict the composite outcome of death and hospital stay in the following 6 months (9) or 12 months (10). Similarly, changes in natriuretic peptide levels at 4 or 12 months from baseline assessment predict mortality and morbidity (11–13) and left ventricular remodeling (14) in outpatients with stable HF. However, a recent meta-analysis reported no association between changes in natriuretic peptides and mortality in HF patients, whereas in the same study, the relationship with the risk of hospital stay was not investigated (15). This information would be valuable in clinical practice for assessing and predicting the effects of new drugs or devices in HF.

The aim of the present study was therefore to investigate whether changes in BNP and/or NT-proBNP plasma levels reflect the risk of hospital stay for worsening HF in patients with chronic systolic HF.

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CI = confidence interval
DQS = Detsky Quality Score
HF = heart failure
NT-proBNP = N-terminal pro–B-type natriuretic peptide
OR = odds ratio
RC = regression coefficient

Methods

Data sources and searches. The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (16). The MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched for reports published in

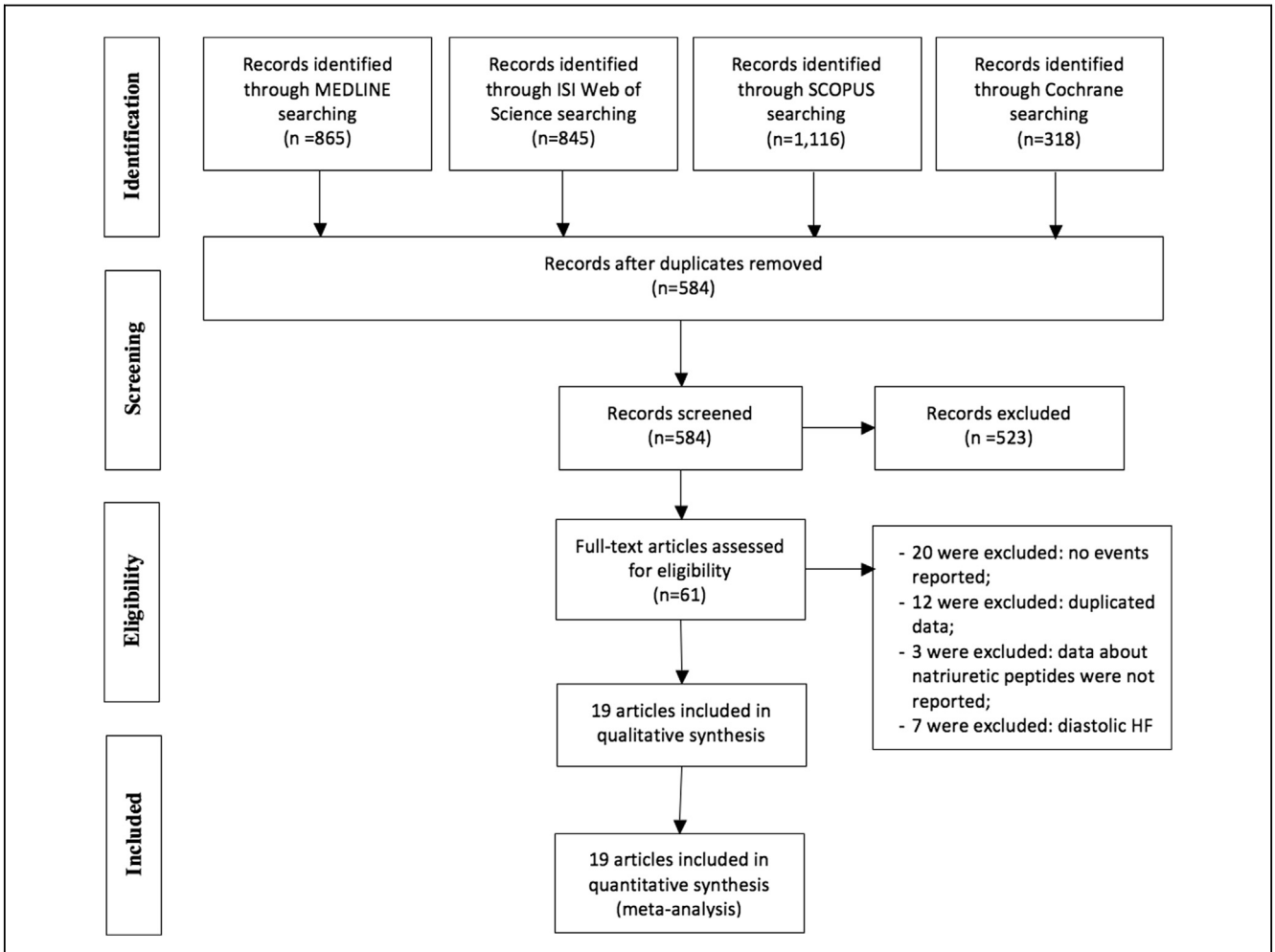

Figure 1 Meta-Analysis Flow Diagram

Flow diagram depicting the flow of information through the different phases of the systematic review. HF = heart failure.

JACC: Heart Failure Vol. 2, No. 2, 2014
April 2014:148–58

Table 1 Baseline Characteristics of Trials Included in Meta-Analysis

Trial Name/First Author (Ref. #)	Year	Treatment	Control	Treatment (n)	Controls (n)	Patients (n)	Follow-Up (mo)	Women (%)	Age (yrs)	SBP (mm Hg)
A-HEFT (26)	2004	Isosorbide dinitrate hydralazine	Placebo	518	532	1050	6	40	57	126
Abulhul et al. (27)	2012	Atorvastatin	Placebo	28	28	56	6	32	72	127
AREA IN-CHF (28)	2009	Canrenone	Placebo	231	236	467	6	16	63	128
ASTRONAUT (29)	2013	Aliskiren	Placebo	808	807	1615	11.3	23	65	123
Bielecka-Dabrowa (30)	2009	Atorvastatin	Placebo	41	27	68	6	15	57	NA
CARE-HF (31)	2005	Medical therapy, CRT	Medical Therapy	409	404	813	29.4	26	67	110
COPERNICUS (32)	2004	Carvedilol	Placebo	496	476	972	6.7	19	63	127
Krum et al. (33)	2007	Rosuvastatin	Placebo	40	45	85	6	20	62	119
NorthStar (34)	2013	Heart failure clinic	Usual care	460	460	920	30	25	69	126
Paterna et al. (35)	2005	Furosemide HSS	Furosemide	48	46	94	1	36	75	145
PROTECT (36)	2011	NT-proBNP guided	Standard of care	75	76	151	10	15	63	110
RESOLVD (37)	1999	Candesartan	Enalapril	327	109	436	9.9	18	63	NA
RESOLVD (37)	1999	Candesartan Enalapril	Enalapril	332	109	441	9.9	14	63	NA
TIME-CHF (38)	2009	NT-proBNP guided	Symptom-guided	251	248	499	18	34	76	119
Toblli et al. (39)	2011	Iron sucrose complex	Placebo	20	20	40	6	NA	75	139
Troughton et al. (40)	2000	NT-proBNP guided	Clinically guided	33	36	69	9.5	23	70	NA
VAL-HEFT (41)	2001	Valsartan	Placebo	2,511	2,499	5,010	23	20	63	123
Wojnicz et al. (42)	2006	LMWH	Placebo	52	150	102	12	15	38	NA
Wojnicz et al. (43)	2006	Atorvastatin	Placebo	36	38	74	6	19	38	NA
Yamada et al. (44)	2007	Atorvastatin	Placebo	19	19	38	36	8	66	122

ACE-Is = angiotensin-converting enzyme inhibitors; A-HEFT = African-American Heart Failure Trial; ARBs = angiotensin receptor blockers; AREA IN-CHF = Antiremodelling Effect of Aldosterone Receptors Blockade with Canrenone in Mild Chronic Heart Failure; ASTRONAUT = Aliskiren Trial on Acute Heart Failure Outcomes; BBs = beta-blockers; CARE-HF = Cardiac Resynchronization–Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; DM = diabetes mellitus; DQS = Detsky Quality Score; HR = heart rate; HSS = hypertonic saline solution; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; MRAs = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NA = not available; PROTECT = ProBNP Outpatient Tailored Chronic HF Therapy; RESOLVD = Ranodomized Evaluation of Strategies for Left Ventricular Dysfunction; SBP = systolic blood pressure; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; VAL-HEFT = Valsartan Heart Failure Trial.

Continued on the next page

all languages up to August 2013. Studies were identified, combining the following major Medical Subject Headings: "heart failure" AND "brain natriuretic peptide" AND "randomized," "heart failure" AND "N-terminal pro-BNP" AND "randomized." We also reviewed the bibliographies of selected trials, as well as more recent reviews and guidelines, and searched studies by the leading expert authors in HF to identify additional articles.

Study selection. Inclusion criteria were as follows: evaluation of BNP/NT-proBNP levels at baseline and at end of follow-up or report of changes in BNP/NT-proBNP levels from baseline to end of follow-up; report of endpoint (hospital stay for worsening of HF); comparison of active drug treatment versus placebo, or of different doses of active drugs; randomized protocol design; and chronic HF with reduced ejection fraction (ejection fraction <45%).

Data extraction and quality assessment. Two reviewers (G.S. and P.P.-F.) independently screened reports according to fulfillment of inclusion criteria by examination of the abstract or the published article. Reviewers compared the selected trials, and discrepancies were resolved by discussion and consensus. Data on baseline characteristics, BNP/NT-proBNP plasma levels at baseline and end of follow-up, and hospitalization for HF were abstracted and entered into Stata version 12.0 (StataCorp, College Station, Texas) by 1 author (G.S.) and checked by another author (P.P.-F.). The quality of the trials was evaluated according to the Detsky Quality Score (DQS) (17–19).

Data synthesis and analysis. Pre-specified outcome of the analysis was hospital stay for worsening of HF. Odds ratios (ORs) and 95% confidence intervals (CIs) for each outcome were separately calculated for each trial, with grouped data, by using the intention-to-treat principle. The choice to use ORs was adopted considering the retrospective design of the meta-analysis based on published studies that vary in design, subject population, treatment regimen, primary endpoints, and quality (19,20). The significance level for the overall estimates of effect and for meta-regression analyses was set at $p \leq 0.05$ (2-sided).

OUTCOME META-ANALYSIS. ORs of the effect of randomized treatments were calculated by using the metan routine (Stata

Table 1 Continued

DBP (mm Hg)	HR (beats/min)	DM (%)	Ischemic Etiology (%)	LVEF (%)	ACE-Is (%)	ARBs (%)	MRAs (%)	BBs (%)	Diuretics (%)	Digoxin (%)	DQS (%)
77	NA	41	23	24	69	17	39	74	90	60	95
70	71	23	64	35	79	27	18	80	96	NA	85
NA	67	20	52	43	80	18	NA	79	70	26	95
NA	78	41	64	28	NA	NA	57	82	96	39	95
NA	78	22	NA	29	94	9	88	87	93	29	75
70	69	NA	38	25	NA	NA	56	72	43	43	95
79	83	NA	66	20	93	6	26	51	99	58	95
72	67	7	12	29	84	15	38	85	81	NA	90
74	66	18	57	31	NA	NA	32	85	58	15	90
81	83	NA	49	30	NA	NA	NA	NA	NA	NA	80
66	73	41	56	27	66	15	42	96	91	31	90
NA	NA	NA	72	27	95	2	NA	17	83	72	80
NA	NA	NA	71	28	94	1	NA	16	85	68	80
NA	76	35	58	30	NA	NA	40	79	93	NA	90
74	80	NA	63	31	98	23	NA	100	95	63	80
NA	NA	13	NA	27	NA	NA	NA	NA	NA	NA	81
76	NA	26	57	27	89	NA	NA	35	85	67	95
NA	85	16	NA	29	NA	NA	NA	NA	NA	NA	80
NA	NA	NA	NA	28	NA	NA	NA	NA	NA	NA	85
70	71	22	53	35	76	21	NA	76	86	66	80

version 12.0) (21). Overall estimates of effect were calculated with a fixed or random effects model, as appropriate.

META-REGRESSION ANALYSIS. Weighted random effects meta-regression analysis was performed with the metareg command (STATA version 12.0) (17,22) to test the relationship between BNP/NT-proBNP changes from baseline to end of follow-up and incidence of HF hospital stay. For this analysis, the achieved differences (expressed as percentage of baseline values) between changes in BNP/NT-proBNP levels in active treatment and control groups were considered (17). For all meta-regression analyses, a random effects model was used. Tau^2 and the restricted maximum likelihood methods were used to explain residual heterogeneity not explained by potential effect modifiers (23).

Sensitivity analysis. To verify the consistency of outcome meta-analysis results, the influence of individual studies on the summary effect estimate (1 study was removed from the meta-analysis) was assessed by using the metaninf command (Stata version 12.0) (24).

To assess the influence of potential effect modifiers, meta-regression analyses were conducted to test the relationship between potential pre-specified confounding variables (mean age, sex, systolic arterial pressure, diastolic arterial pressure, heart rate, left ventricular ejection fraction, New York Heart Association class, HF etiology, concomitant HF therapy, DQS, duration of follow-up, type of study [intended or nonintended natriuretic peptide–lowering therapy]) and outcomes. The variables significantly correlated to outcomes were tested in a multivariate model including changes in natriuretic peptide levels.

The assumption of homogeneity between the treatment effects in different trials was tested by using the Q statistic and further quantified by using the I^2 statistic. A significant heterogeneity was defined by a p value <0.05 at Q statistic and by $I^2 \geq 50\%$, whereas $I^2 \leq 60\%$ might indicate only a moderate heterogeneity.

The presence of publication bias was assessed by using Egger's test. This assessment is a linear regression of the intervention effect estimates on their SEs, weighting by 1/(variance of the intervention effect estimate) (25).

Table 2 Data Regarding Baseline, End of Study, and Change in BNP or NT-proBNP as Reported in the Papers of Included Trials and Calculated %Delta

Trial Name/First Author (Ref. #)	Baseline		End of Study		Absolute Change		%Delta
	Treatment	Control	Treatment	Control	Treatment	Control	
A-HEFT (26)	283 ± 365 pg/ml	332 ± 446 pg/ml	243 ± 347 pg/ml	324 ± 444 pg/ml	−39 ± 305 pg/ml	−8 ± 305 pg/ml	−5
Abulhul et al. (27)	268 (190–441) pg/ml	336 (162–686) pg/ml	185 (144–344) pg/ml	246 (163–458) pg/ml	NA	NA	1
AREA IN-CHF (28)	90 (39–198) pg/ml	87 (34–172) pg/ml	NA	NA	−33.3 pg/ml	−6.96 pg/ml	−15
ASTRONAUT (29)	2,838 (1,516–5,235) pg/ml	2,674 (1,552–5,234) pg/ml	1,576 (681–3,156) pg/ml	1,792 (887–3,518) pg/ml	NA	NA	−7
Bielecka-Dabrowa et al. (30)	1,697 ± 1,613 pg/ml	2,665 ± 187 pg/ml	1,201 ± 1,146 pg/ml	3,197 ± 2,424 pg/ml	NA	NA	−25
CARE-HF (31)	1,920 (744–4,288) pg/ml	1,809 (719–3,949) pg/ml	NA	NA	NA	NA	30
COPERNICUS (32)	308 pmol/l	311 pmol/l	261 pmol/l	233 pmol/l	NA	NA	4
Krum et al. (33)	1,036 pg/ml	876 pg/ml	NA	NA	−111 pg/ml	3 pg/ml	−6
NorthStar (34)	793 (63–6,720) pg/ml	803 (58–7,517) pg/ml	NA	NA	181 (50–312) pg/ml	132 (30–235) pg/ml	3
Paterna et al. (35)	1,212 ± 491 pg/ml	1,265 ± 515pg/ml	312 ± 165 pg/ml	552 ± 284 pg/ml	NA	NA	−9
PROTECT (36)	2,344 pg/ml	1946 pg/ml	1,125 pg/ml	1844 pg/ml	NA	NA	−26
RESOLVD (37)	59 ± 4 pmol/l	50 ± 6 pmol/l	NA	NA	4	−6	8
RESOLVD (37)	52 ± 4 pmol/l	50 ± 6 pmol/l	NA	NA	4	−6	9
TIME-CHF (38)	3,998 (2,075–7,220) pg/ml	4,657 (2,455–7,520) pg/ml	NA	NA	NA	NA	−2
Toblli et al. (39)	256 ± 125 pg/ml	267 ±115 pg/ml	117 ± 87 pg/ml	451 ± 249 pg/ml	NA	NA	−61
Troughton et al. (40)	217 pmol/l	251 pmol/l	NA	NA	−79 pmol/l	−3 pmol/l	−15
VAL-HEFT (41)	183 ± 5 pg/ml	178 ± 5 pg/ml	NA	NA	−21 pg/ml	23 ± 5 pg/ml	−12
Wojnicz et al. (42)	1,125 (395–3,750) pg/ml	960 (294–2,835) pg/ml	489 (140–1,012) pg/ml	484 (120–2,265) pg/ml	NA	NA	−9
Wojnicz et al. (43)	739 (264–1,529) pmol/l	820 (294–2,770) pmol/l	314 (97–825) pmol/l	524 (171–1,962) pmol/l	NA	NA	−7
Yamada et al. (44)	84 (36–186) pg/ml	123 (36–252) pg/ml	55 (37–91) pg/ml	201 (54–302) pg/ml	NA	NA	−25

Values are mean ± SD or median (interquartile range).

BNP = B-type natriuretic peptide; other abbreviations as in Table 1.

Results

Characteristics of included trials. Of the 3,144 reports identified by the initial search, 61 were retrieved for more detailed evaluation, and 19 trials were included in the study (26–44) (Fig. 1). Eight reported BNP (26–28,33,35,37,41,44) and 11 reported NT-proBNP (29-32,34,36,38–40,42,43) assessments. Details of the included trials and populations are listed in Tables 1 and 2.

A total of 2,277 HF hospital stays were reported in 12,891 patients included in the analysis. Median follow-up was 9.5 months (interquartile range: 6 to 18 months). Mean age of patients was 63 ± 10 years, and 22% were women.

Methodological quality. Methodological aspects varied across trials, with some quality items of the DQS not fulfilled in some studies. The median DQS was 90% (interquartile range 80 to 95). No trial satisfied all DQS items. No trial was triple blinded; 14 (74%) of the 19 trials were double-blinded (26–29,31–33,35,37,39,40,41,43,44); 4 (21%) were open-label studies (34,36,38,42); and in 1 trial (5%), information about study blinding was not reported (30). In 10 (53%) of the 19 trials, information about the exclusion of patients was not reported in detail (27,30,33,35,37,39,40,42–44). Sample size was not calculated in 8 (42%) trials included in the analysis (30,35,37,39,40,42–44).

Outcome meta-analysis. Active treatments significantly reduced the risk of hospital stay for worsening of HF (OR: 0.678 [95% CI: 0.547 to 0.841]; comparison p = 0.000; heterogeneity p = 0.000; I^2 = 62.1%; random effect) (Fig. 2).

Meta-regression analysis. Meta-regression analysis showed no relationship between changes in natriuretic peptide levels (both BNP and NT-proBNP) and risk of HF hospital stay in the presence of significant heterogeneity (regression coefficient [RC]: 0.015 [95% CI: −0.006 to 0.035]; regression p = 0.146; heterogeneity p < 0.001; I^2 = 63.70%). Heterogeneity was due to the presence of only 1 study assessing nonpharmacological therapy (31), and it disappeared when the study was removed according to the Cochrane Handbook

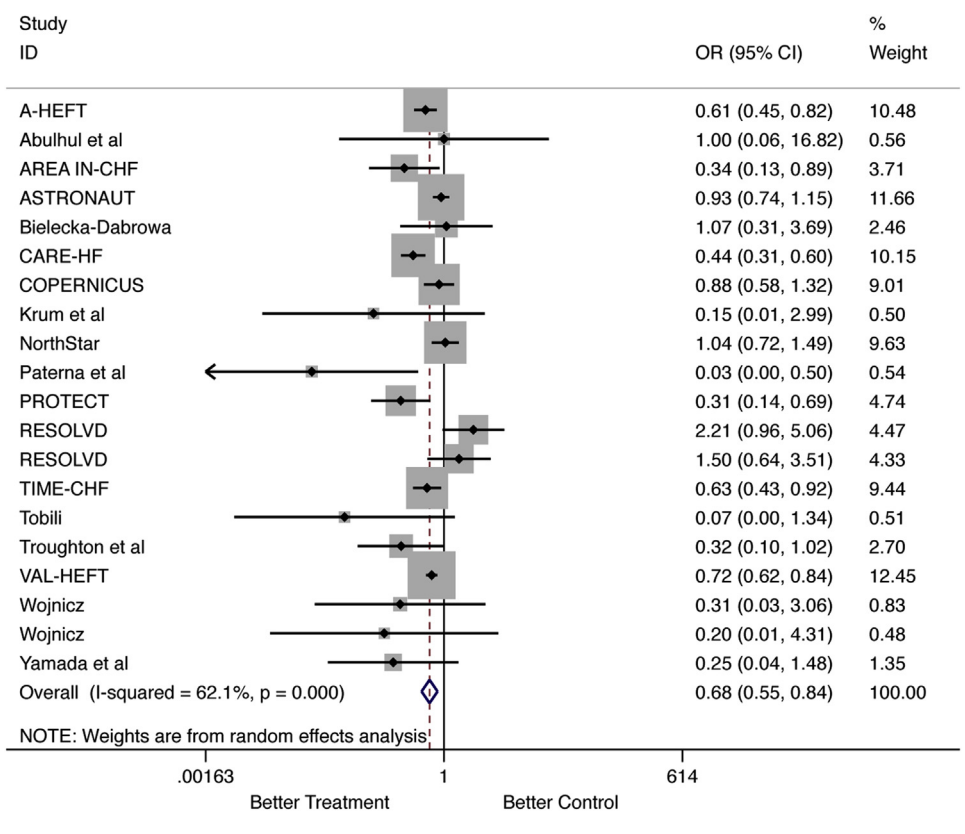

Figure 2 Meta-Analysis Outcomes

Odds ratios (ORs) of HF hospital stay. A-HEFT = African-American Heart Failure Trial; AREA IN-CHF = Antiremodelling Effect of Aldosterone Receptors Blockade with Canrenone in Mild Chronic Heart Failure; ASTRONAUT = Aliskiren Trial on Acute Heart Failure Outcomes; CARE-HF = Cardiac Resynchronization - Heart Failure; CI = confidence interval; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; PROTECT = ProBNP Outpatient Tailored Chronic HF Therapy; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; VAL-HEFT = Valsartan Heart Failure Trial; other abbreviation as in Figure 1.

for Systematic Reviews of Interventions (45). When heterogeneity was resolved, changes in natriuretic peptide levels significantly correlated with the outcome (RC: 0.036 [95% CI: 0.015 to 0.056]; regression p = 0.002; heterogeneity p = 0.056; I^2 = 37.43%) (Fig. 3A). In addition, tertiles of changes in natriuretic peptide levels correlated linearly with the risk of HF (RC: 0.459 [95% CI: 0.141 to 0.777]; regression p = 0.007; heterogeneity p = 0.023; I^2 = 44.17%), and the association was confirmed after adjustment for the potential effect modifier (percent of patients taking beta-blockers) (RC: 0.366 [95% CI: 0.010 to 0.723]; regression p = 0.045; heterogeneity p = 0.025; I^2 = 48.48%). After reporting the RC of the meta-regression analysis performed using continuous changes in natriuretic peptide levels and the one using tertiles of changes on the same scale, the use of continuous values of changes allowed to achieve higher predictive power compared with the tertiles of changes.

When changes in BNP and NT-proBNP levels were assessed separately, a relationship was found between risk of HF hospital stay and changes in BNP in the presence of significant heterogeneity (RC: 0.055 [95% CI: 0.007 to 0.104]; regression p = 0.031; heterogeneity p = 0.035; I^2 = 53.63%)(Fig. 3B). However, after adjustment for the potential effect modifier (percent of patients taking beta-blockers), significant heterogeneity was resolved, and results were confirmed (RC: 0.037 [95% CI: 0.003 to 0.070]; regression p = 0.038; heterogeneity p = 0.933; I^2 = 0.00%). NT-proBNP changes did not correlate with the outcome (RC: 0.006 [95% CI: −0.017 to 0.029]; regression p = 0.565; heterogeneity p < 0.001; I^2 = 64.44%). However, after significant heterogeneity was resolved by removal of the study identified as the source of heterogeneity (31), changes in NT-proBNP also significantly correlated with outcome (RC: 0.029 [95% CI: 0.001 to 0.568]; regression p = 0.046; heterogeneity p = 0.156; I^2 = 32.68%) (Fig. 3C).

Sensitivity analysis. Outcome meta-analysis results were confirmed when 1 study was removed from the meta-analysis (Fig. 4). Meta-regression analysis results were confirmed when potential effect modifiers were introduced as covariates in the meta-regression analysis. The results of sensitivity analysis are reported in Table 3.

No publication bias was detected according to Egger's test.

Discussion

The results of the present study indicate that changes in plasma levels of BNP or NT-proBNP predict risk of hospital stay for worsening HF in patients with chronic systolic HF. As recognized in guidelines (8), easy-to-measure, reproducible, and largely available predictors of therapy effects in patients with HF are needed, as availability of prognostic surrogate endpoints would be relevant for clinical investigations of new therapies in HF. In fact, if a relationship between effects of therapies and outcomes could be demonstrated, clinical studies testing surrogate endpoints would be relevant for planning large mortality/morbidity randomized trials. To date, only indexes of left ventricular remodeling have been reported to be associated with clinical outcomes in HF patients in large studies (46), but their implementation in clinical practice is substantially more complicated compared with the assessment of plasma biomarkers.

BNP and NT-proBNP levels are elevated in patients with HF and correlate with functional and morphological left ventricular parameters as well as independently predict prognosis in small cohorts of patients (5,6). In addition, widespread availability and nonoperator dependency of measurement candidate them as ideal predictors of therapeutic effects in patients with HF. The findings of the present analysis demonstrate a significant relationship between reduction of natriuretic peptide levels and rate of hospital

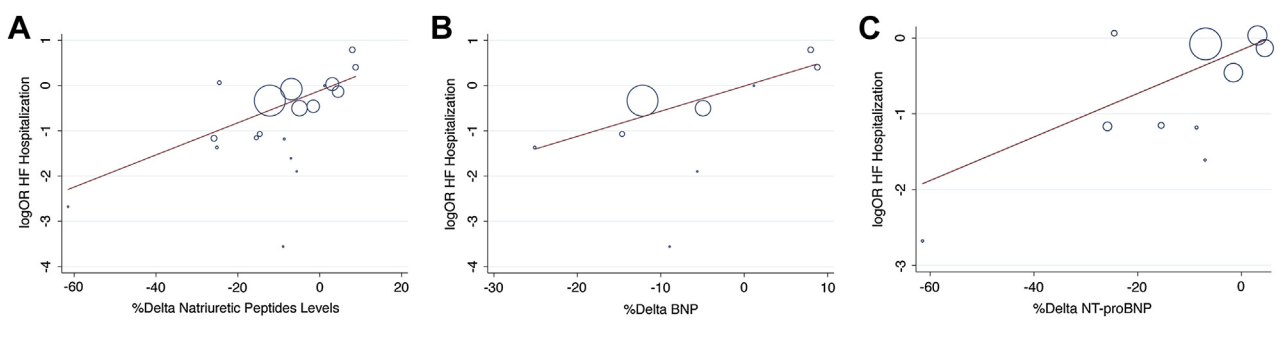

Figure 3 Meta-Regression Analysis

Meta-regression between HF hospital stay and changes in **(A)** natriuretic peptide levels, **(B)** B-type natriuretic peptide (BNP), and **(C)** N-terminal pro–B-type natriuretic peptide (NT-proBNP). Abbreviations as in Figures 1 and 2.

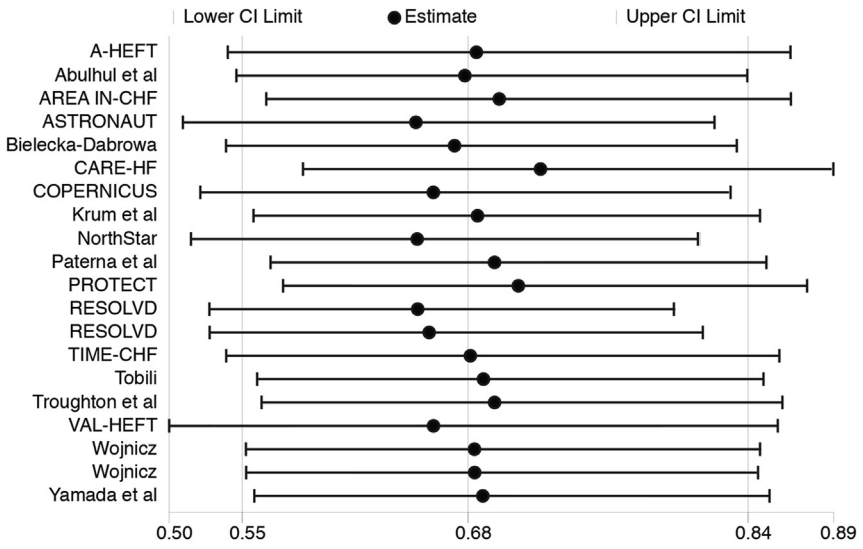

Figure 4 One Study Removed From Analysis for HF Hospitalization

Rows represent the results of meta-analysis of all studies except the omitted study named in that row. Abbreviations as in Figure 2.

stay for worsening of HF, which represents, together with death, the more commonly used endpoint in HF clinical trials. The effects of BNP- and NT-proBNP–guided therapy compared with clinically guided therapy on hospitalization rate for worsening HF was assessed in randomized clinical trials (36,38,40,47–50). The largest trial comparing NT-proBNP–guided therapy with symptom-guided therapy was conducted in 499 systolic HF patients and found reduced hospitalizations for HF in the NT-proBNP–guided group compared with the symptom-guided group (38). In contrast, other studies failed to demonstrate any benefit of BNP- or NT-proBNP–guided therapy on HF hospital stay (40,47,50). To our knowledge, the relationship observed in the present analysis was never reported because 1 previous meta-analysis that investigated whether changes of natriuretic peptide levels predict the effects of therapy on mortality in HF patients did not assess the relationship with HF hospital stay (15). In fact, the relationship between changes in natriuretic cardiac peptide levels and HF hospital stay was previously investigated by Felker et al. (51). In a meta-analysis of 6 studies enrolling patients randomized to receive peptide-guided therapy compared with clinically guided HF therapy, they reported a nonsignificant trend for reduction of HF hospital stay with biomarker-guided therapy. More recently, in a meta-analysis of 12 trials enrolling 2,686 patients, which compared clinically guided versus peptide-guided HF therapy, we reported a significantly reduced risk of all-cause death and HF hospital stay associated with NT-proBNP–guided therapy but not with BNP-guided therapy (52). Notably, however, in these trials, patients randomized to receive peptide-guided therapy had to reach a pre-defined peptide target level. Thus, on the basis of results of our and of previous analyses, it can be hypothesized that a continuous relationship exists between the clinical status of patients and levels of natriuretic peptides, that is consistent with the observation, in the present study, of a significant correlation between tertiles of reductions in peptide plasma levels and risk of hospital stay. In contrast, the relationship between changes in peptide levels and mortality becomes evident only when a substantial reduction of peptide levels is reached, as reported in our last meta-analysis.

Study limitations. The analysis was non–patient-level, and this represents a limitation of the study. In fact, the lack of patient-level data did not allow us to take into account the different follow-up times among patients within a trial and across trials. In addition, no studies included in the analysis were designed for assessing the relationship between peptide changes and our pre-specified outcome. It is known that substantial differences exist among commercially available BNP and NT-proBNP assay methods (53). However, because we used percent rather than absolute changes in peptide levels in the meta-regression analysis, it is unlikely that the heterogeneity of assay methods used in the different studies had an impact on the results. Finally, the short follow-up of the studies included in the analysis prevents verification of whether a relationship between changes in natriuretic peptide levels and clinical events could be demonstrated with longer follow-up. Despite these limitations, this analysis may be useful to generate hypotheses and foster collection of patients' longitudinal data.

Table 3 Sensitivity Analysis of Potential Effect Modifiers on Clinical Outcome

	Changes in Natriuretic Peptide Levels (Both BNP and NT-proBNP)								Changes in NT-proBNP							
	With Outliers				Without Outliers				With Outliers				Without Outliers			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value	Change in tau^2	p Value
Changes in natriuretic peptide levels	1.52	0.146	0.62	0.544	**3.58**	**0.002**	**2.96**	**0.012**	0.60	0.565	–	–	**2.36**	**0.046**	–	–
Women	−0.45	0.659	–	–	-0.08	0.935	–	–	0.24	0.820	–	–	0.42	0.685	–	–
Age	−0.20	0.841	–	–	0.27	0.794	–	–	0.21	0.839	–	–	0.22	0.830	–	–
SBP	1.23	0.242	–	–	0.27	0.794	–	–	3.62	0.015	–	–	1.82	0.143	–	–
DBP	1.59	0.147	–	–	1.07	0.316	–	–	1.73	0.183	–	–	1.09	0.391	–	–
Heart rate	0.30	0.767	–	–	0.07	0.949	–	–	0.21	0.840	–	–	-0.27	0.794	–	–
Diabetes	0.23	0.819	–	–	0.23	0.819	–	–	−0.13	0.899	–	–	−0.13	0.899	–	–
Ischemic etiology	2.11	0.053	–	–	1.69	0.114	–	–	1.77	0.137	–	–	0.69	0.528	–	–
NYHA I	−0.36	0.726	–	–	−0.36	0.726	–	–	1.24	0.433	–	–	1.24	0.433	–	–
NYHA II	0.46	0.653	–	–	0.46	0.653	–	–	−1.16	0.453	–	–	−1.16	0.453	–	–
NYHA III	0.33	0.747	–	–	0.33	0.747	–	–	1.11	0.466	–	–	1.11	0.466	–	–
NYHA IV	−2.05	0.067	–	–	−1.99	0.078		–	−0.75	0.530	–	–	−0.72	0.546	–	–
LVEF	−0.88	0.391	–	–	−1.06	−0.306	–	–	0.08	0.936	–	–	−0.15	0.888	–	–
ACE-Is and/or ARBs	−0.60	0.556	–	–	0.85	0.412	–	–	0.02	0.984	–	–	0.26	0.806	–	–
MRAs	−0.22	0.831	–	–	0.28	0.790	–	–	−0.18	0.865	–	–	0.19	0.859	–	–
BBs	**−2.30**	**0.038**	−2.04	0.063	**−2.19**	**0.047**	−1.20	0.255	−0.70	0.509	–	–	−0.88	0.421	–	–
Diuretics	0.66	0.520	–	–	−0.37	0.719	–	–	0.46	0.660	–	–	−0.62	0.565	–	–
Digoxin	0.69	0.503	–	–	0.58	0.574	–	–	−0.60	0.573	–	–	−0.41	0.706	–	–
DQS	−0.45	0.661	–	–	−0.24	0.811	–	–	0.72	0.490	–	–	1.24	0.249	–	–
Intended or nonintended NPL therapy	−1.30	0.211	–	–	−1.59	0.130	–	–	NA	NA	NA	NA	NA	NA	NA	NA

	Changes in BNP (No Outlier Trials in This Analysis)			
	Univariate Analysis		Multivariate Analysis	
	Change in tau^2	p Value	Change in tau^2	p Value
Changes in natriuretic peptide levels	**2.70**	**0.031**	**2.81**	**0.038**
Women	−0.51	0.627	–	–
Age	−1.05	0.328	–	–
SBP	−2.25	0.074	–	–
DBP	−0.10	0.923	–	–
Heart rate	−1.41	0.254	–	–
Diabetes	0.75	0.495	–	–
Ischemic etiology	1.57	0.161	–	–
NYHA I	−0.80	0.454	–	–

Continued on the next page

Table 3 Continued

	Changes in BNP (No Outlier Trials in This Analysis)			
	Univariate Analysis		Multivariate Analysis	
	Change in tau^2	p Value	Change in tau^2	p Value
NYHA II	0.71	0.505	-	-
NYHA III	0.28	0.787	-	-
NYHA IV	-1.94	0.101	-	-
LVEF	-1.08	0.316	-	-
ACE-Is and/or ARBs	0.94	0.384	-	-
MRAs	-0.31	0.807	-	-
BBs	**-2.65**	**0.038**	**-2.97**	**0.031**
Diuretics	0.70	0.508	-	-
Digoxin	1.69	0.166	-	-
DQS	-1.40	0.204	-	-
Intended or nonintended NPL therapy	NA	NA	NA	NA

Significant values are reported in bold.
NPL = natriuretic peptide lowering; NYHA = New York Heart Association; other abbreviations as given in Tables 1 and 2.

Conclusions

In these patients with HF, short-term changes in natriuretic peptide levels predicted hospital stay. These findings sustain the usefulness of BNP and NT-proBNP measurements in the management of patients with HF.

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