Published in final edited form as:

Am J Cardiol. 2011 March 1; 107(5): 723–729. doi:10.1016/j.amjcard.2010.10.055.

Predictive Value of Depressive Symptoms and B-Type Natriuretic Peptide for New-Onset Heart Failure and Mortality

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Abstract

Depression and natriuretic peptides predict heart failure (HF) progression, but the unique contributions of depression and biomarkers associated with HF outcomes are not known. The present study determined the additive predictive value of depression and aminoterminal pro-B-type natriuretic peptide (NT-proBNP) for new-onset HF in HF-free subjects and mortality in patients with HF. The participants in the Cardiovascular Health Study were assessed for depressive symptoms using the Center for Epidemiologic Studies Depression Scale and NT-proBNP using an electrochemiluminescence immunoassay. The validated cutoff values for depression (Center for Epidemiologic Studies Depression Scale ≥ 8) and NT-proBNP (≥ 190 pg/ml) were used. The risks of incident HF and mortality (cardiovascular disease-related and all-cause) were examined during a median follow-up of 11 years, adjusting for demographics, clinical factors, and health behaviors. In patients with HF ($n = 208$), depression was associated with an elevated risk of cardiovascular disease mortality (hazard ratios [HR] 2.07, 95% confidence interval [CI] 1.31 to 3.27) and all-cause mortality (HR 1.49, 95% CI 1.05 to 2.11), independent of the NT-proBNP level and covariates. The combined presence of depression and elevated NT-proBNP was associated with substantially elevated covariate-adjusted risks of cardiovascular disease mortality (HR 5.42, 95% CI 2.38 to 12.36) and all-cause mortality (HR 3.72, 95% CI 2.20 to 6.37). In the 4,114 HF-free subjects, new-onset HF was independently predicted by an elevated NT-proBNP level (HR 2.27, 95% CI 1.97 to 2.62) but not depression (HR 1.08, 95% CI 0.92 to 1.26) in covariate-adjusted analysis. In conclusion, depression and NT-proBNP displayed additive predictive value for mortality in patients with HF. These associations can be explained by complementary pathophysiologic mechanisms. The presence of both elevated depression and NT-proBNP levels might improve the identification of patients with HF with a high risk of mortality.

Depression has been associated with poor clinical outcomes in patients with heart failure (HF); however, the pathophysiologic mechanisms and potential synergy between depression and biomarkers in relation to an adverse HF prognosis are insufficiently understood.^{1,2}

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A full list of the principal Cardiovascular Health Study investigators and institutions can be found at www.chs-nhlbi.org/pi.htm.

Research findings regarding the relation between depressive symptoms and B-type natriuretic peptide or aminoterminal pro-B-type natriuretic peptide (NT-proBNP) levels have been inconsistent.^{3–8} The objectives of the present study were to determine whether depression was associated with elevated NT-proBNP levels in subjects with and without HF; to investigate whether depression and NT-proBNP are additive predictors of increased risk of new-onset HF in those free of HF; and to determine the additive predictive value of depression and NT-proBNP for cardiovascular and all-cause mortality in patients with HF.

Methods

The design of the Cardiovascular Health Study (CHS) has been previously described.⁹ In brief, CHS was a prospective, community-based, observational study of subjects aged ≥ 65 years, with the main objective to determine the factors related to the onset and course of coronary heart disease (CHD) and stroke.⁹ The participants were enrolled in 4 geographically distinct communities across the United States. The institutional review boards of the participating hospitals approved the CHS, and all patients gave written informed consent. The institutional review board of the University of Maryland (Baltimore, Maryland) approved the present analysis.

The initial main CHS cohort included 5,201 participants recruited from 1989 to 1990 and an additional minority cohort of 687 participants recruited from 1992 to 1993. To enable simultaneous assessment of the echocardiographic data (obtained in 1994 to 1995 for the added minority cohort), the assessment visit obtained in 1994 to 1995 of the minority cohort was considered their baseline evaluation for depression, NT-proBNP level, and covariates.

The present study stratified participants by HF status, because depression and NT-proBNP could have differential roles for new-onset HF versus mortality in patients with pre-existing HF. Of the 5,888 participants in the CHS, 5,565 did not have prevalent HF at baseline. Of these 5,565 patients, 4,114 (74%) had complete data for depression, NT-proBNP level, and covariates. Of the 295 participants with prevalent HF at baseline, 208 (71%) with complete data were included in the analyses. The main reason for excluding the participants from the analyses was missing data for NT-proBNP resulting from the unavailability of stored samples in the blood repository (1,332 participants [24%] free of HF and 76 participants [26%] with HF at screening). As described previously, the differences between those with and without NT-proBNP data were minimal.¹⁰

The 10-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to measure the symptoms of depression.^{11–13} The CES-D items cover the previous week using a 4-point Likert scale ranging from 0, rarely or none of the time (<1 day), to 3, all of the time (5 to 7 days). The CES-D has good psychometric properties.¹¹ The total score can range from 0 to 30, with a score ≥ 8 indicating clinically relevant depression,^{11,12} similar to the ≥ 16 cutoff for the 20-item version of the CES-D.

NT-proBNP was measured in serum using an electro-chemiluminescence immunoassay (ECIA, Elecsys 2010 System, Roche Diagnostics, Indianapolis, Indiana), as described previously.¹⁰ The coefficient of variation for the NT-proBNP assay was 2% to 5%, and the analytic measurement range for NT-proBNP was 5 to 35,000 pg/ml. All samples were stored at -70° to -80°C before testing (maximum of 3 freeze-thaw cycles). The measurements of NT-proBNP using this assay did not change after 5 freeze-thaw cycles.¹⁴ The cutoff NT-proBNP level of >190 pg/ml was applied to indicate a high NT-proBNP level, because we have previously shown that this cutoff corresponds to the inflection point for an increased risk of new-onset HF in the CHS.¹⁰

The demographic and clinical data were obtained by trained interviewers and physical examination. The demographic variables included age, gender, and race (white vs black and other). The clinical risk factors for cardiovascular disease (CVD), including HF and CHD, were systolic blood pressure, diabetes mellitus status, and cholesterol level. The measures related to health behaviors included current smoking status, body mass index, and physical activity. Physical activity was assessed using self-reported activity levels, which were converted to kcal/wk.¹⁵ Because of the non-normal distribution of this measure, the median level was used (<1,072 kcal/wk) to indicate those with low physical activity levels.¹⁶ The indexes of CHD status at study entry were a history of CHD at baseline (e.g., history of myocardial infarction, coronary revascularization by angioplasty or bypass surgery, or angina pectoris), echocardiographically defined ejection fraction (normal vs borderline and abnormal), and electrocardiographically determined left ventricular hypertrophy. Two-dimensional echocardiograms were obtained using a standardized protocol and interpreted at a centralized core laboratory by 2 trained and independent readers, who were unaware of the clinical information.

The assessment protocol for cardiovascular outcomes has been previously described in detail.¹⁷ In brief, the participants were asked whether they had experienced cardiovascular outcomes during the semiannual interviews and annual examinations. The hospital discharge summaries, outpatient physician notes, and results of diagnostic tests were obtained for the participants who reported these outcomes. The Events Subcommittee adjudicated the outcomes by review of the medical records, including interview, physical examination, and diagnostic study data.¹⁷

New-onset HF was confirmed if a physician diagnosis of HF had been made and the subjects had received medical therapy for HF.^{17–19} The documentation of HF signs and symptoms and supporting diagnostic data were considered sufficient, but not necessary, to validate a diagnosis of HF.¹⁸ CVD mortality and all-cause mortality were examined by the Events Subcommittee and adjudicated for cardiovascular cause by review of the medical records, death certificate, or autopsy reports and the Medicare database.¹⁷

The data are presented as the mean $\pm$ SD or median with the interquartile range for variables with a non-normal skewed distribution. Chi-square tests and *t* tests for independent samples were applied to examine the differences between the depressed and nondepressed participants in baseline characteristics. The distribution of CES-D scores was positively skewed, and a square root transformation was applied before the parametric analyses, as described previously.¹² The NT-proBNP levels were positively skewed, and logarithmic transformations were applied before the analyses.¹⁰ Transformed scores of depression and NT-proBNP were used in the analyses of continuous depression and NT-proBNP measures. The association between continuous depression and NT-proBNP levels was examined with Pearson's correlation, and hierarchical linear regression analyses were used to determine whether the relation between depression and NT-proBNP was independent of the covariates.

To test the additive independent value of depression and NT-proBNP for adverse clinical outcomes (new-onset HF in HF-free subjects and mortality in participants with HF at screening), hierarchical Cox regression analyses were performed. Four hierarchical sets of covariates were consecutively used in the multivariate models. These variables were selected, because they have been associated with depression, HF, and/or CHD progression. The first set of covariates included depression, NT-proBNP level, and demographics (i.e., age, gender, and race). The second set included CVD risk factors (i.e., systolic blood pressure, diabetes mellitus, and cholesterol). The third set contained factors related to health behaviors (i.e., smoking status, body mass index, and physical activity levels). The final set included indexes of cardiac disease status (CHD at baseline, left ventricular ejection

fraction, and left ventricular hyper-trophy). The role of cardiac medications was explored in separate models. The medications included β blockers, angiotensin-converting enzyme inhibitors, and diuretics. Using Cox proportional hazards analyses, the combined effect of depression and elevated NT-proBNP level on the outcomes was investigated by forming 4 groups according to the depression (CES-D ≥ 8) and NT-proBNP (≥ 190 pg/ml) status. For all multivariate Cox proportional hazards models, graphic and formal methods were used to test the assumption of proportionality. We also examined whether the analyses using continuous CES-D depression scores and NT-proBNP levels revealed the same results as those obtained when evaluating the dichotomized measures. To investigate whether multiplicative effects between depression and NT-proBNP were observed, the interaction between these 2 factors was examined. The analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, Illinois). A 2-sided p value of <0.05 was used to indicate statistical significance.

Results

The baseline data for participants free of HF at study entry with complete data on depression, NT-proBNP level, and covariates ($n = 4,114$) are listed in Table 1. A total of 840 (20%) participants without HF reported clinically relevant levels of depressive symptoms (CES-D ≥ 8). Depression in those without HF was associated with female gender, black race, diabetes mellitus, current smoking status, reduced physical activity levels, CHD at baseline, left ventricular hypertrophy, and the use of angiotensin-converting enzyme inhibitors, diuretics, and antidepressive medications compared to nondepressed participants.

The baseline data of those with HF ($n = 208$) are listed in Table 2. Of these subjects, 36% were classified as having clinically relevant levels of depression. The patients with HF and depression were more often women, black, and current smokers, had lower physical activity levels, and were more often taking angiotensin-converting enzyme inhibitors and diuretics than did the patients with HF but without depression.

The median NT-proBNP value in those without HF was 112 pg/ml (interquartile range 57 to 222 pg/ml). The participants without HF but with depression tended to have a greater median NT-proBNP level than those without HF and without depression (118 pg/ml, interquartile range 62 to 242, vs 110 pg/ml, interquartile range 56 to 218; $p = 0.069$). Greater continuous depression scores correlated weakly with greater NT-proBNP levels ($r = 0.03$, $p = 0.043$) in those without HF. However, this association lost significance when adjusting for demographics ($\beta = 0.03$, $p = 0.070$) and remained nonsignificant when additionally adjusting for CVD risk factors, health behaviors, and CHD indexes ($\beta = 0.01$, $p = 0.61$). In patients with HF at baseline, the mean NT-proBNP levels did not differ between those with and without depression (median 496 pg/ml, interquartile range 159 to 1,632 vs median 520 pg/ml, interquartile range 148 to 1,716, $p = 0.85$). Similarly, no associations were found between the continuous depression scores and NT-proBNP levels ($r = 0.001$, $p = 0.99$), which remained nonsignificant in multivariate analyses.

New-onset HF developed in 970 participants (24%) who were free of HF at screening (median follow-up 10.7 years, range 0.01 to 14). Depression (CES-D ≥ 8) was associated with an increased odds of incident HF when adjusting for demographics (hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.04 to 1.42). The results remained similar when additionally adjusting for NT-proBNP (Table 3). However, this elevated depression-related risk was attenuated and nonsignificant after adjustment for CVD risk factors and remained nonsignificant after additional adjustment for health behaviors and indexes of CHD (Table 3) and cardiac medications (HR 1.13, 95% CI 0.96 to 1.32). The analyses of the continuous depression scores revealed the same pattern of results (demographic- and NT-

proBNP- adjusted HR 1.09, 95% CI 1.02 to 1.17 per square root CES-D unit). No interaction was found between depression status and NT-proBNP level in the prediction of new-onset HF ($p = 0.11$, adjusting for demographics).

When comparing 4 groups according to the presence or absence of depression status and elevated NT-proBNP levels at baseline, the results of the demographic-adjusted models showed an elevated risk of new-onset HF in the depressed/high NT-proBNP group (HR 2.91, 95% CI 2.32 to 3.65, $n = 282$), nondepressed/high NT-proBNP group (HR 2.81, 95% CI 2.42 to 3.27, $n = 948$), and depressed/low NT-proBNP group (HR 1.33, 95% CI 1.07 to 1.64, $n = 558$), using the nondepressed/low NT-proBNP group as the reference ($n = 2,326$). Depression did not add to the effect of high NT-proBNP levels (nondepressed/high NT-proBNP group vs depressed/high NT-proBNP group, $p = 0.76$). Figure 1 shows that similar results were found when adjusting for all covariates.

Of the 208 participants with HF at screening, 168 (81%) died during follow-up, with 97 patients dying from CVD-related causes. The median duration until death was 5.8 years (range 0.06 to 14). The demographic-adjusted predictive value of depression for CVD-related mortality was significantly elevated (HR 2.17, 95% CI 1.41 to 3.32) and remained significant when adjusting for NT-proBNP, CVD risk factors, health behaviors, and cardiac disease indexes (Table 4). When adding cardiac medications, the predictive value of depression also remained significant (HR 1.76, 95% CI 1.08 to 2.88). The results were comparable in the model with continuous depression scores (HR 1.26, 95% CI 1.01 to 1.56 per square root CES-D unit, adjusting for demographics and NT-proBNP). No interaction was found between depression status and elevated NT-proBNP for increased CVD mortality risk ($p = 0.78$ in the demographic-adjusted model).

The combined risks of depression and NT-proBNP status for CVD-related mortality, adjusting for demographics, were as follows. The depressed/high NT-proBNP group showed the greatest risk of CVD death (HR 6.02, 95% CI 2.86 to 12.67, $n = 56$), followed by the nondepressed/high NT-proBNP group (HR 3.03, 95% CI 1.46 to 6.26, $n = 95$) and the depressed/low NT-proBNP group (HR 2.32, 95% CI 0.85 to 6.31, $n = 19$) compared to the nondepressed/low NT-proBNP group ($n = 38$). The risk of participants with both depression and high NT-proBNP levels was significantly greater than the risk of participants with high NT-proBNP but no depression ($p = 0.004$). When adjusting for all covariates, the results remained basically similar (Figure 2).

Among the patients with HF, depression was also associated with a significantly increased risk of all-cause mortality (HR 1.59, 95% CI 1.14 to 2.22), after adjusting for demographics. Depression remained associated with a significant all-cause mortality risk (Table 5), after additional adjustment for NT-proBNP, CVD risk factors, health behaviors, and CHD indexes. The addition of cardiac medications decreased the predictive value of depression (HR 1.43, 95% CI 0.99 to 2.07). Continuous depression scores were also associated with an increased all-cause mortality risk (HR 1.21, 95% CI 1.02 to 1.43 per square root CES-D unit), adjusting for NT-proBNP and demographics. The interaction between an elevated depression status and increased NT-proBNP levels was not significant ($p = 0.79$ in the demographic-adjusted model).

Investigating the combined effect of depression status and NT-proBNP showed that the depressed/high NT-proBNP group had a 3.7-fold increased risk (95% CI 2.20 to 6.37, $n = 56$) for all-cause mortality, followed by the nondepressed/high NT-proBNP (HR 2.50, 95% CI 1.51 to 4.12, $n = 95$) compared to the reference category of non-depressed/low NT-proBNP levels ($n = 38$), adjusting for demographics. The depressed/low NT-proBNP group ($n = 19$) was not at a significantly elevated risk of all-cause mortality (HR 1.67, 95% CI 0.81

to 3.45). Of the participants with high NT-proBNP levels, depression significantly added to the risk of all-cause mortality ($p = 0.031$). The risks in the model with all covariates were similar (Figure 3).

Discussion

The results of the present investigation have shown that depression and NT-proBNP are independent and additive predictors of cardiovascular mortality and all-cause mortality in patients with HF during a median follow-up of 10 years. In contrast to the predictive value of mortality in patients with HF, depression did not independently predict new-onset HF in the covariate-adjusted models.

Investigation of the association between depressive symptoms and NT-proBNP in a large sample of the general population aged ≥ 65 years who were free of HF is a unique component of the present study. Previous studies have largely focused on patients with HF in clinical settings and found positive results, including those by Parissis et al³ and Laederach-Hofmann et al,⁴ as well as an absence of marked relationships.^{4–8} The psychological factors that partially overlap with depression, such as anxiety, negative affectivity, social inhibition, and type D personality (i.e., the joint presence of negative affectivity and social inhibition), have also not revealed significant associations with natriuretic peptide levels.^{8,20} One study found that pro-atrial natriuretic peptide correlated negatively with anxiety in patients with HF.²¹ Thus, the evidence regarding psychological factors and BNP and NT-proBNP has been mixed, but most studies have suggested that these factors are minimally related. Depression and NT-proBNP might therefore adversely affect HF progression by way of independent pathophysiologic pathways.

Depression at baseline was an important predictor of mortality among patients with HF, consistent with the results from previous studies¹ (for a meta-analysis, see the study by Nicholson et al²²). The CHS has also confirmed a positive relation between depression and all-cause mortality in adults aged ≥ 65 years from the general population.¹³ The elevated risk associated with depression in the present study occurred over and above the risk of the simultaneously obtained NT-proBNP levels. Exploratory analyses revealed that depression and NT-proBNP were independently predictive of mortality in patients with HF with preserved left ventricular function. In contrast, the predictive value of depression was nonsignificant in patients with systolic HF (data not shown). The results of the present study have extended the current published data by demonstrating that depression adds to the risk of mortality in patients with HF over and above the effects of NT-proBNP.

Depression was not independently associated with new-onset HF, corroborating the results of previous studies that indicated that the role of depression for new-onset HF might be less strong in community-based samples²³ than in samples with hypertension²⁴ or coronary artery disease.²⁵ It is possible that the association between depression and new-onset HF is primarily mediated by cardiovascular co-morbidities that predispose patients to developing HF, including myocardial infarction and hypertension.

The results of the present study should be interpreted in light of the following limitations. It is possible that depression reflects underlying clinical or subclinical disease processes. The present study adjusted for multiple possible “common factors,” such as CHD status and diabetes, which attenuated the risks of depression for incident HF. However, the common indexes of cardiac disease severity were not related to depression in those with HF (Table 2). In addition, the associations between depression and mortality in those with HF remained significant when taking these co-morbidities into account. Additional studies are needed to examine changes in depression and NT-proBNP (either in response to treatment or in

observational studies) to elucidate the time trajectories and causal pathways linking depression and plausible biologic pathways of HF progression to adverse clinical outcomes. Selective survival might have resulted in an underestimation of the observed associations between depression and NT-proBNP, particularly in patients with HF, because high levels of both factors might have been associated with increased mortality risk before study enrollment. Because all participants with available data were included at study entry, selective survival was not likely to have been a primary factor in the observed relations between depression and NT-proBNP. Finally, depression and NT-proBNP were evaluated at one point (i.e., baseline) only, and no information was available on the long-term psychological treatment of depression.

In conclusion, depression and NT-proBNP are independent risk factors for CVD-related and all-cause mortality in elderly individuals with HF. Recent evidence suggests that the detrimental effect of depression may be attributable to behavioral factors, such as physical inactivity and lack of compliance, as well as biological factors.²⁶ Data from this investigation suggest that depression may add to the risk stratification of HF patients over and above HF-related biomarkers.

Acknowledgments

This research was supported by the National Heart, Lung, and Blood Institute (Bethesda, Maryland) grants N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133, U01 HL080295, and R01 HL62181 and HL079376 (to W.J. Kop), with additional contribution from the National Institute of Neurological Disorders and Stroke, Bethesda, Maryland and Roche Diagnostics, Indianapolis, Indiana, and a travel grant, 2009R001, from the Dutch Heart Foundation, The Hague, The Netherlands (to K.C. van den Broek).

Dr. deFilippi received research grant support (>\$10,000) and honorarium/consulting fees (>\$10,000) from Siemens, Glasgow, Delaware, Roche Diagnostics, Indianapolis, Indiana, BG Medicine, Waltham, Massachusetts, and Critical Diagnostics, San Diego, California. Dr. Christenson reports that funding from Roche Diagnostics, Indianapolis, Indiana was supplied for NT-proBNP testing. Siemens Healthcare Diagnostics, Glasgow, Delaware, and Response Biomedical, Vancouver, Canada have supported research efforts and market NT-proBNP assays. Dr. Seliger received a research grant from Roche, Inc, Indianapolis, Indiana.

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Figure 1.

Predictive value of depression and NT-proBNP for incident HF. Fully adjusted HR 2.33 (95% CI 1.85 to 2.95) for depressed/high NT-proBNP group; HR 2.36 (95% CI 2.02 to 2.76) for nondepressed/high NT-proBNP group; and HR 1.18 (95% CI 0.95 to 1.46) for depressed/low NT-proBNP group using participants with low depression and low NT-proBNP levels as reference group.

Figure 2.

Predictive value of depression and NT-proBNP for cardiovascular-related mortality in patients with HF. Fully adjusted HR 5.42 (95% CI 2.38 to 12.36) for depressed/high NT-proBNP group; HR 2.58 (95% CI 1.14 to 5.84) for nondepressed/high NT-proBNP group; and HR 1.91 (95% CI 0.65 to 5.64) for depressed/low NT-proBNP group using participants with low depression/low NT-proBNP levels as reference group.

Figure 3.

Predictive value of depression and NT-proBNP for all-cause mortality in patients with HF. Fully adjusted HR 3.15 (95% CI 1.75 to 5.69) for depressed/high NT-proBNP group; HR 2.05 (95% CI 1.16 to 3.65) for nondepressed/high NT-proBNP group; and HR 1.32 (95% CI 0.60 to 2.88) for depressed/low NT-proBNP group using participants with low depression and low NT-proBNP levels as reference group.

Table 1

Baseline characteristics of patients at risk of new-onset heart failure (HF) stratified by depression status

Variable	Total (n = 4,114)	Depression		p Value
		No (n = 3,274; 79.6%)	Yes (n = 840; 20.4%)	
Age (years)	72.9 ± 5.5	72.8 ± 5.4	73.1 ± 5.6	0.12
Men	1,677 (40.8%)	1,427 (43.6%)	250 (29.8%)	<0.001 *
Black race	584 (14.2%)	407 (12.4%)	177 (21.1%)	<0.001 *
Systolic blood pressure (mm Hg)	136.4 ± 21.4	136.3 ± 21.1	136.7 ± 22.4	0.64
Diabetes mellitus	729 (17.7%)	553 (16.9%)	176 (21.0%)	0.006 *
Total cholesterol (mg/dl)	212.0 ± 39.0	211.5 ± 38.9	214.2 ± 39.5	0.068
Body mass index (kg/m ²)	26.6 ± 4.6	26.6 ± 4.4	26.9 ± 5.0	0.071
Current smoker	449 (10.9%)	332 (10.1%)	117 (13.9%)	0.002 *
Reduced physical activity	2,020 (49.1%)	1,520 (46.4%)	500 (59.5%)	<0.001 *
Coronary heart disease	728 (17.7%)	532 (16.2%)	196 (23.3%)	<0.001 *
Reduced left ventricular ejection fraction (<55%)	315 (7.7%)	248 (7.6%)	67 (8.0%)	0.70
Left ventricular hypertrophy	181 (4.4%)	129 (3.9%)	52 (6.2%)	0.005 *
β blocker	550 (13.4%)	430 (13.2%)	120 (14.3%)	0.39
Angiotensin-converting enzyme inhibitor	264 (6.4%)	197 (6.0%)	67 (8.0%)	0.039 *
Diuretics	1,020 (24.8%)	777 (23.8%)	243 (28.9%)	0.002 *
Antidepressants	145 (3.5%)	83 (2.5%)	62 (7.4%)	<0.001 *

Data are presented as mean ± SD, unless otherwise stated.

* Statistically significant.

Table 2

Baseline characteristics of participants with heart failure (HF) stratified by depression status

Variable	Total (n = 208)	Depression		p Value
		No (n = 133; 63.9%)	Yes (n = 75; 36.1%)	
Age (years)	75.2 ± 6.1	75.3 ± 5.9	74.9 ± 6.5	0.63
Men	102 (49.0%)	77 (57.9%)	25 (33.3%)	0.001*
Black race	45 (21.6%)	23 (17.3%)	22 (29.3%)	0.043*
Systolic blood pressure (mm Hg)	136.7 ± 24.9	136.1 ± 24.9	137.9 ± 25.0	0.61
Diabetes mellitus	77 (36.1%)	43 (32.3%)	32 (42.7%)	0.14
Total cholesterol (mg/dl)	195.2 ± 37.8	195.3 ± 34.5	195.2 ± 43.3	0.98
Body mass index (kg/m ²)	27.5 ± 6.0	27.0 ± 5.1	28.4 ± 7.1	0.13
Current smoker	19 (9.1%)	8 (6.0%)	11 (14.7%)	0.038*
Reduced physical activity [†]	140 (67.3%)	83 (62.4%)	57 (76.0%)	0.045*
Coronary heart disease	130 (62.5%)	84 (33.2%)	46 (61.3%)	0.79
Reduced left ventricular ejection fraction	76 (36.5%)	49 (36.8%)	27 (36.0%)	0.90
Left ventricular hypertrophy	30 (14.4%)	21 (15.8%)	9 (12.0%)	0.46
β Blocker	31 (14.9%)	19 (14.3%)	12 (16.0%)	0.74
Angiotensin-converting enzyme inhibitor	66 (31.7%)	35 (26.3%)	31 (41.3%)	0.025*
Diuretics	139 (66.8%)	80 (60.2%)	59 (78.7%)	0.006*
Antidepressants	8 (3.8%)	3 (2.3%)	5 (6.7%)	0.12

Data are presented as mean ± SD, unless otherwise stated.

* Statistically significant.

[†] <1,072 kcal/wk.

Table 3

Hierarchical Cox model for new-onset heart failure in participants free of heart failure at study entry (n = 4,114)

Variable	Adjusted			
	Demographics [*]	Demographics [*] and CVD Risk Factors [†]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡] , CHD Indexes [§]
Depression	1.18 (1.01–1.37) [¶]	1.15 (0.99–1.35)	1.12 (0.96–1.31)	1.08 (0.92–1.26)
Elevated NT-proBNP	2.66 (2.33–3.04) [¶]	2.63 (2.30–3.02) [¶]	2.62 (2.29–3.01) [¶]	2.27 (1.97–2.62) [¶]

^{*} Including age, gender, and race.

[†] Including systolic blood pressure, cholesterol, and diabetes mellitus status.

[‡] Including body mass index, smoking, and reduced physical activity.

[§] Including CHD at baseline, reduced left ventricular ejection fraction, and left ventricular hypertrophy.

[¶] HR (95% CI), Statistically significant.

Table 4

Multivariate Cox model for interval to cardiovascular-related mortality in patients with heart failure (HF) at study entry (n = 208)

Variable	Adjusted			
	Demographics [*]	Demographics [*] , CVD Risk Factors [†]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡] , CHD Indexes [§]
Depression	2.04 (1.33–3.14)	2.19 (1.40–3.42)	2.08 (1.33–3.27)	2.07 (1.31–3.27)
Elevated NT-proBNP	2.83 (1.64–4.90)	3.03 (1.75–5.25)	3.17 (1.80–5.58)	2.70 (1.47–4.95)

All data statistically significant, HR (95% CI).

^{*} Including age, gender, and race.

[†] Including systolic blood pressure, cholesterol, and diabetes mellitus status.

[‡] Including body mass index, smoking, and reduced physical activity.

[§] Including CHD at baseline, reduced left ventricular ejection fraction, and left ventricular hypertrophy.

Table 5

Multivariate Cox model for interval to all-cause mortality in patients with heart failure (HF) at study entry (n = 208)

Variable	Adjusted			
	Demographics [*]	Demographics [*] , CVD Risk Factors [†]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡]	Demographics [*] , CVD Risk Factors [†] , Health Behaviors [‡] , CHD Indexes [§]
Depression	1.53 (1.10–2.13)	1.53 (1.08–2.15)	1.50 (1.07–2.12)	1.49 (1.05–2.11)
Elevated NT-proBNP	2.40 (1.61–3.57)	2.49 (1.67–3.72)	2.42 (1.59–3.66)	2.19 (1.40–3.43)

All data statistically significant, HR (95% CI).

^{*} Including age, gender, and race.

[†] Including systolic blood pressure, cholesterol, and diabetes mellitus status.

[‡] Including body mass index, smoking, and reduced physical activity.

[§] Including CHD at baseline, reduced left ventricular ejection fraction, and left ventricular hypertrophy.