Relationship of Depression to Death or Hospitalization in Patients With Heart Failure

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**Background:** Depression is widely recognized as a risk factor in patients with coronary heart disease. However, patients with heart failure (HF) have been less frequently studied, and the effect of depression on prognosis, independent of disease severity, is uncertain.

**Methods:** Two hundred four outpatients having a diagnosis of HF, with a ventricular ejection fraction of 40% or less, underwent baseline assessments including evaluation of depressive symptoms using the Beck Depression Inventory and of HF severity determined by plasma N-terminal pro–B-type natriuretic peptide. Cox proportional hazards regression analyses were used to examine the effects of depressive symptoms on a combined primary end point of death and hospitalizations because of cardiovascular disease (hereafter referred to as cardiovascular hospitalization) during a median follow-up of 3 years.

**Results:** Symptoms of depression (Beck Depression Inventory score) were associated with risk of death or cardiovascular hospitalization (P < .001) after controlling for established risk factors including HF disease severity, ejection fraction, HF etiology, age, and medications. Clinically significant symptoms of depression (Beck Depression Inventory score ≥10) were associated with a hazard ratio of 1.56 (95% confidence interval, 1.07-2.29) for the combined end point of death or cardiovascular hospitalization. Contrary to our expectation, antidepressant medication use was associated with increased likelihood of death or cardiovascular hospitalization (hazard ratio, 1.75; 95% confidence interval, 1.14-2.68, *P* = .01) after controlling for severity of depressive symptoms and for established risk factors.

**Conclusions:** Symptoms of depression were associated with an adverse prognosis in patients with HF after controlling for HF severity. The unexpected association of antidepressant medications with worse clinical outcome suggests that patients with HF requiring an antidepressant medication may need to be monitored more closely.

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**Heart Failure (HF) is characterized by markedly compromised cardiac function, high rate of complications, and decreased life expectancy.** Impaired cardiac function and neurohumoral activation are the defining characteristics of HF that contribute to clinical deterioration, and the focus of interventions has generally been on improving circulatory function and on blocking the renin-angiotensin and sympathetic nervous systems. Depression is widely considered a significant psychosocial risk factor in patients with coronary heart disease. Depression is associated with a substantially increased risk of developing HF in individuals at risk and has been associated with adverse outcomes in patients with established HF. In a study by Jiang et al of 374 hospitalized patients with HF who underwent screening for depression, those with major depression were approximately twice as likely to die or be rehospitalized within 1 year. Similarly, Vaccarino et al reported that severity of depressive symptoms was related to death or functional decline at 6-month follow-up in 391 hospitalized patients with HF. Murberg and Furuze recently reported findings of 6-year follow-up in 119 patients with HF in whom symptoms of depression at baseline were predictive of death. Because depression in patients with HF is related to disease severity, however, there remains uncertainty about the extent to which depression, independent of HF severity, is related to adverse clinical outcomes.

In the last few years, B-type natriuretic peptide (BNP)
and N-terminal proBNP (NT-proBNP), which are released from the cardiac ventricles and have vasodilator and diuretic effects, have emerged as standard diagnostic and prognostic markers of HF. In the present prospective study of 204 outpatients with HF, we used NT-proBNP to adjust for HF severity in evaluating whether symptoms of depression were related to death and hospitalizations during 3 years of follow-up.

Because depression has been associated with worse prognosis in various populations with cardiac disease, there also has been considerable interest in identifying effective treatments for depression in these patients. There is some evidence that antidepressant drugs are associated with reduced mortality after acute myocardial infarction (MI) and with improved cardiac function and fewer adverse events in patients with acute coronary syndromes. However, to our knowledge, the effects of antidepressant medication on outcomes in patients with HF have not been studied. Therefore, we also assessed whether antidepressant medication use at baseline was associated with death and hospitalization during 3 years of follow-up.

This was a prospective observational follow-up study of non-hospitalized patients with HF recruited from outpatient HF clinics in central North Carolina. We performed baseline medical and psychosocial assessments as potential predictors of events, including death and hospitalizations. Patients were followed up for a median of 3 years.

STUDY SUBJECTS

The study sample consisted of 204 patients recruited from HF programs at Duke University Medical Center, Durham, NC, and the University of North Carolina at Chapel Hill from January 19, 2000, through December 20, 2002. Inclusion criteria were as follows: left ventricular ejection fraction (LVEF) of 40% or less documented within the last year by angiography, nuclear wall motion study, or echocardiography; and New York Heart Association functional classes I through IV for at least 3 months. Exclusion criteria were as follows: pacemaker dependency, uncontrolled hypertension, MI, percutaneous coronary intervention, or coronary artery bypass grafting within the last 3 months. To enable stabilization of patients’ conditions with potentially new treatment regimens, a first visit to the HF clinic was also an exclusion criterion. Of the estimated 1000 patients with HF seen at the program clinics during the study enrollment period, only patients meeting eligibility criteria were invited to participate in the study, and more than 80% of these patients consented to participate. The study was approved by the institutional review board of Duke University Medical Center, where all assessments were performed. Written informed consent was obtained from all participants before the study.

BASELINE ASSESSMENTS

Medical Data

Clinical information and medical history were obtained from medical records. Current medications were documented as medications being taken at the time of baseline assessments and included both cardiac and psychotropic medications.

METHODS

Patients and Methods

The Beck Depression Inventory (BDI) is a 21-item self-report measure of depressive symptoms. A score of 10 or higher is indicative of clinically significant symptoms of depression. The BDI is not an instrument used to diagnose depression but to assess the severity of depressive symptoms. We selected the BDI because increase in depressive symptoms and not just major depressive disorder assessed by clinical interview is associated with greater risk of adverse events in patients with cardiac disease and in healthy individuals. Moreover, a BDI score of 10 or higher has been associated with poorer prognosis in a variety of populations with cardiac disease.

Follow-up

Patient medical records were reviewed yearly on the anniversary of obtaining baseline assessments by trained research assistants (K.S.J. and R.T.) blinded to the patients’ depression status. Patients also were contacted annually by mail and asked to indicate whether they had been hospitalized during the past year and to provide consent for retrieval of their medical records for each hospitalization. The primary end point was defined as the time to death or hospitalization because of cardiovascular disease (hereafter referred to as cardiovascular hospitalizations), whichever occurred first, during follow-up. Patient deaths were verified through hospital and emergency medical services records. Cardiovascular hospitalizations included the following: occurrence of MI or stroke, treatment of worsening HF, and cardiac surgery including coronary artery bypass grafting, heart transplantation, and defibrillator or pacemaker implantation. To develop a fuller understanding of the relation of depression and clinical outcomes, we also considered all-cause death or hospitalization as a secondary composite end point. In addition, because it is the most objective end point, we considered all-cause death separately, even though it involved fewer events and reduced statistical power than when it was combined with hospitalizations, to examine the extent to which findings for it were reflected in the composite end points of death or hospitalizations.

N-Terminal Pro-B-Type Natriuretic Peptide

After 20 minutes of seated relaxation, blood was collected from an antecubital vein in a 5-mL phlebotomy tube containing EDTA. Samples were placed on ice and cold centrifuged at 1000g for 10 minutes. The resulting plasma was pipetted into plastic vials and frozen and maintained at −80°C until assay. The NT-proBNP measurements were performed within 4 hours of thawing using an electrochemiluminescence immunoassay (Elecsys proBNP; Roche Diagnostics Corp, Indianapolis, Ind) in accord with the manufacturer’s instructions. The analytical measurement range for the assay is 5 to 35 000 pg/mL, and typical day-to-day imprecision has a coefficient of variation of less than 5%.

Left Ventricular Ejection Fraction

The LVEF was determined using 2-dimensional echocardiography. Apical 4-chamber and 2-chamber images of the heart were acquired by a single sonographer using an ultrasound machine and were stored as digital loops. The endocardial borders of the left ventricle in the 2 views were traced by a single experienced echocardiographer (A.L.H.) using customized software (Access Point 2000; Freeland Systems, Westfield, Ind), and ventricular volume and ejection fraction were computed using the biapical Simpson rule.
STATISTICAL ANALYSIS

Cox proportional hazards regression models were used to examine the relationship between baseline characteristics and events (death and hospitalizations) during follow-up. Heart failure etiology, NT-proBNP, LVEF, age, BDI score, and antidepressant medication use were evaluated in the originally planned models. To assess the robustness of the planned models, other potential factors (including race/ethnicity, sex, body mass index, and smoking status; New York Heart Association functional class; presence of diabetes mellitus, hypertension, or hypercholesterolemia; MI; blood pressure and heart rate; hemoglobin, serum urea nitrogen, total cholesterol, glomerular filtration rate [modified Cockcroft-Gault equation]; use of a defibrillator; and use of β-blocker, angiotensin-converting enzyme inhibitor, and nitrate concentrations; diuretic, or statin drugs or warfarin sodium) were eligible for entry into the models by stepwise selection (significance level for entry into the model = 0.1). For Cox regression analyses, NT-proBNP and BDI scores were trimmed at the 95th percentiles, NT-proBNP was expressed as NT-proBNP/1000 pg/mL, and age was expressed as age/10. Kaplan-Meier plots were constructed to illustrate the association between baseline characteristics and event-free survival.

RESULTS

BASELINE CHARACTERISTICS

Demographic and clinical characteristics of the study sample are given in Table 1. Patient mean age at baseline was 56.8 years (age range, 27-88 years). Of 204 patients, 31.9% were women, and approximately half (53.9%) were of minority race/ethnicity. Most patients were taking a β-blocker (88.7%) or an angiotensin-converting enzyme inhibitor (87.2%). The BDI score at baseline ranged from 0 to 37 (mean score, 10.3). Characteristics for patients with clinically significant depressive symptoms (BDI score ≥10) compared with minimal depression symptoms (BDI score <10) are given in Table 1, with associated P values comparing these 2 groups. At baseline, 21.1% of patients were taking antidepressant medications, including selective serotonin re-uptake inhibitors (n = 35), tricyclic or tetracyclic agents (n = 4), or monoamine-oxidase inhibitors (n = 4); most patients (75%) taking an antidepressant drug were receiving no more than the daily recommended dose. Patients taking an antidepressant at baseline (n = 43) were comparable to patients not taking an antidepressant (n = 161) for most of the characteristics in Table 1; however, patients taking an antidepressant drug evidenced more depressive symptoms (BDI score, 13.2 ± 7.2 vs 9.6 ± 5.6; P < .001), were more likely to be taking a β-blocker (97.7% vs 86.3%; P = .04), and had lower hemoglobin levels (12.8 ± 1.5 vs 13.4 ± 1.6; P = .02). All characteristics given in Table 1 were included as candidates for stepwise selection in the extended predictive models.

FOLLOW-UP ASSESSMENT OF THE RELATIONSHIP OF DEPRESSION TO DEATH OR CARDIOVASCULAR HOSPITALIZATIONS

The mean follow-up was 3 years (range, 2-5 years); no patients were lost to follow-up. During follow-up, 54 patients (26%) died and 126 (62%) were hospitalized at least once, including 98 (48%) hospitalized because of cardiovascular disease. Multivariate Cox proportional hazards regression analysis revealed that NT-proBNP was associated significantly with death or cardiovascular hospitalization (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.16-1.42; P < .001; note HR for 1000 pg/mL change in NT-proBNP) in the planned model comprising age, HF etiology, LVEF, NT-proBNP, BDI score, and antidepressant use (Table 2). Increase in depressive symptoms also was strongly associated with increased risk of death or cardiovascular hospitalization (BDI score HR, 1.06; 95% CI, 1.03-1.09; P < .001; HR for each 1-point change in total score on the BDI scale). Patients taking antidepressants (n = 43) were more likely to die or be hospitalized because of cardiovascular disease compared with patients not taking antidepressants (HR, 1.75; 95% CI, 1.14-2.68; P = .01).

The Figure compares patients with HF with clinically significant symptoms of depression (BDI score >10; n = 94) with patients with HF without symptoms of depression (BDI score <10; n = 110) for our primary end point of death and cardiovascular hospitalization (BDI score ≥10; HR, 1.56; 95% CI, 1.07-2.29; P = .02). For patients taking antidepressant drugs, NT-proBNP values were comparable to those in other patients (1479 ± 1693 pg/mL vs 1476 ± 1845 pg/mL). Although patients taking antidepressant drugs had higher BDI scores than patients not taking antidepressant drugs (13.2 ± 7.2 vs 9.6 ± 5.6; P < .001), the finding that antidepressant use was associated with increased risk for events included adjustment for depression severity in the statistical model. The stepwise selection of all other baseline characteristics extended the model by including resting heart rate (HR, 1.03; 95% CI, 1.02-1.05; P < .001) and anticoagulant medication use (HR, 1.59; 95% CI, 1.07-2.39; P = .02). However, the role of all variables in the planned model, including depressive symptoms (HR, 1.06; 95% CI, 1.03-1.10; P < .001) and antidepressant medication use (HR, 1.68; 95% CI, 1.06-2.64; P = .03), remained unaltered in the extended model, confirming that they were robust. Values for age, HF etiology, and LVEF are given in Table 2.

FOLLOW-UP ASSESSMENT OF THE RELATIONSHIP OF DEPRESSION TO ALL-CAUSE HOSPITALIZATIONS OR DEATH

In our planned model comprising age, HF etiology, LVEF, NT-proBNP, BDI score, and antidepressant use, elevated NT-proBNP (NT-proBNP/1000 pg/mL; HR, 1.23; 95% CI, 1.12-1.35; P < .001) and age (HR, 1.18; 95% CI, 1.00-1.39; P = .045) were associated with all-cause hospitalization or death (Table 2). Depressive symptoms and antidepressant use also were associated with increased risk for all-cause hospitalizations or death (BDI [1-point change in total score] HR, 1.06; 95% CI, 1.03-1.09; P < .001; antidepressant use HR, 1.57; 95% CI, 1.06-2.34; P = .024; Table 2). Resting heart rate (HR, 1.02; 95% CI, 1.01-1.04; P = .007) was subsequently added to the model through stepwise selection. However, its addition did not alter the role of the other variables in the planned model, including depressive symptoms (BDI HR, 1.06; 95% CI, 1.03-1.10; P = .002) and antidepressant use (HR, 1.50; 95% CI, 1.00-2.24; P = .055).
FOLLOW-UP ASSESSMENT OF THE RELATIONSHIP OF DEPRESSION TO DEATH

When we considered all-cause death as a single end point, NT-proBNP was strongly positively related (HR, 1.42; 95% CI, 1.24-1.64; P < .001). Both increased depressive symptoms (HR, 1.05; 95% CI, 1.00-1.10; P = .06) and antidepressant medication use (HR, 1.79; 95% CI, 0.96-3.34; P = .07) exhibited trends toward increased risk of death that were consistent with those noted for the primary end point of death or cardiovascular hospitalization. No additional variables were added to the model through step-wise selection. Values for age, HF etiology, and LVEF are given in Table 2.

COMMENT

In relatively stable outpatients with HF who were receiving contemporary medical treatment, symptoms...
of depression were associated with increased risk of death or cardiovascular hospitalization during a median 3-year follow-up. This observation is consistent with other recent reports that depression in patients with HF is associated with poorer prognosis.5-7 We observed depression to be associated with adverse clinical events over and above the severity of HF. N-terminal pro-B-type natriuretic peptide, a valuable marker of HF severity, also was found to be highly related to risk of death or hospitalization in our study sample. However, we observed that the effects of depressive symptoms on outcomes were present even after controlling for NT-proBNP, LVEF, and other established risk factors, indicating that depression is not simply a reflection of the severity of HF. Our observations also suggest that the presence of clinically significant depressive symptoms may have a notable effect on outcome, with approximately 50% increased risk (per unit of time) for death or hospitalization. Although our study was not designed to assess the mechanisms conferring adverse prognosis associated with depression, multiple pathways are likely involved. Depression may contribute to poor prognosis in patients with HF via adverse effects on health behaviors, including smoking, physical inactivity, and nonadherence to prescribed treatment plans. In addition, several pathophysiologic pathways have been identified by which depression may directly affect cardiovascular risk in patients with HF.18 Depression has been related to reduced heart rate variability,19 blunted baroreflex sensitivity,20 heightened sympathetic nervous system activity,21 blood hypercoagulability,22 increased inflammation,23 and endothelial dysfunction.24 Each of these disease pathways has been related to adverse outcomes and may act independently or synergistically to increase risk in patients with HF.

Clinically significant symptoms of depression (BDI score ≥10) were observed in 46% of our study sample, which is consistent with previous reports of the prevalence of depression in HF.25 The high prevalence of depression in patients with HF, coupled with its association with poorer outcomes, underscores the need to assess these patients for clinical depression and to develop and evaluate safe and efficacious treatments to ameliorate their depressive symptoms and improve clinical outcomes. To our knowledge, no prospective study to date has examined whether antidepressant treatment affects prognosis in patients with HF. In our cohort of patients with HF, antidepressant medication use was associated with increased likelihood of death or cardiovascular hospitalization. Although patients taking antidepressants were more depressed despite their medication use, they had worse outcomes even after controlling for depression severity. Moreover, patients taking antidepressant medications did not have more severe HF compared with other patients in our sample, as indicated by comparable ejection fractions and plasma NT-proBNP levels, and did not have more comorbidity; thus, worse outcomes could not be ascribed to more severe disease.

Our study provides no clear explanation for the observation that antidepressant use was associated with poorer HF prognosis, and limitations of the study de-
sign underscore the importance of interpreting this observation with caution. These limitations include a small sample size and the absence of propensity matching, which may preclude optimal control for potentially confounding variables. In our statistical models, antidepressant use may, in part, have served as an additional marker of depression in the sense of reflecting greater severity of depression and its associated pathophysiology than expressed by BDI score, thereby helping to capture more fully the effect of depression on cardiovascular outcomes. We did not have information about duration of antidepressant use, and we did not know whether depressive symptoms were stable, remitting, or worsening. Taking an antidepressant may be a marker for chronic, recurrent, or treatment-resistant depression. Carney et al\textsuperscript{26} found that, in a subset of participants in the Enhancing Recovery in Coronary Heart Disease study, patients with a history of depression after MI who remained depressed despite treatment had worse outcomes compared with patients successfully treated, which suggests that treatment-resistant depression may identify patients at especially high risk of poor outcomes. Although tricyclic antidepressants may increase the risk of life-threatening ventricular arrhythmias,\textsuperscript{27} in our study, more than 80% of patients with HF treated for depression were taking a selective serotonin reuptake inhibitor antidepressant. Preliminary data suggest that the use of selective serotonin reuptake inhibitor antidepressants in other patients with cardiac disease may improve survival. For example, in the Enhancing Recovery in Coronary Heart Disease study, patients with a recent MI who received antidepressant medication had improved survival compared with similar patients not receiving medication.\textsuperscript{11} In the SADHART (Sertraline Antidepressant Heart Attack Trial) study,\textsuperscript{12} the incidence of severe cardiac events was 14.5% in depressed patients with acute coronary syndromes randomized to the sertraline treatment group compared with 22.4% in the placebo group.

In summary, we observed that increased symptoms of depression are associated with worsened prognosis and that HF disease severity does not account for the association of depression with adverse outcomes. The effect size for depressive symptoms seems to be at least as great as traditional HF disease markers, including LVEF. Our observations associating antidepressant medication use with poorer prognosis in patients with HF were unexpected and should be interpreted cautiously because of their novelty and the absence of an established explanatory mechanism. Our observations do not imply that antidepressant treatment is contraindicated in patients with HF, nor do they suggest that antidepressant therapy is not useful. A larger observational cohort study, which might focus on the extent and history of antidepressant use, or a randomized clinical trial evaluating the safety and efficacy of antidepressant treatment in patients with HF with clinical depression is needed to more fully understand the potential effects of treating depression on clinical outcomes. In the interim, patients with HF requiring antidepressant medication may need to be monitored more closely.

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Author Contributions: Dr Sherwood had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sherwood, Blumenthal, O’Connor, Christenson, and Hinderliter. Acquisition of data: Sherwood, Trivedi, Johnson, O’Connor, Adams, Dupree, Waugh, Bensimhon, Gaulden, and Hinderliter. Analysis and interpretation of data: Sherwood, Blumenthal, Trivedi, Johnson, O’Connor, Dupree, Bensimhon, Christenson, Koch, and Hinderliter. Drafting of the manuscript: Sherwood, Blumenthal, Trivedi, Johnson, Gaulden, and Christenson. Critical revision of the manuscript for important intellectual content: Sherwood, Blumenthal, O’Connor, Adams, Dupree, Waugh, Bensimhon, Koch, and Hinderliter. Statistical analysis: Sherwood and Koch. Obtained funding: Sherwood, Blumenthal, and Waugh. Administrative, technical, and material support: Sherwood, Trivedi, Johnson, O’Connor, Adams, Waugh, Bensimhon, Gaulden, Christenson, and Hinderliter. Study supervision: Sherwood and Hinderliter. Patient recruitment: Adams, Dupree, Waugh, and Gaulden.

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REFERENCES


**Correction**

Y-Axis Incorrectly Labeled in Figure 1. In the original investigation titled “Prediction of Coronary Artery Calcium in Young Adults Using the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Risk Score: The CARDIA Study,” by Gidding et al published in the November 27th issue of the ARCHIVES (2006;166:2341-2347), the y-axis in Figure 1 on page 2345 should have read from top to bottom as follows: 10, 8, 6, 4, and 2.