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Worsening Depressive Symptoms are Associated with Adverse Clinical Outcomes in Patients with Heart Failure

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Abstract

OBJECTIVE—To assess the impact of changes in symptoms of depression over a 1-year time period on subsequent clinical outcomes in heart failure (HF) patients.

BACKGROUND—Emerging evidence shows that clinical depression, which is prevalent among patients with HF, is associated with a poor prognosis. However, it is uncertain how changes in depression symptoms over time may relate to clinical outcomes.

METHODS—147 HF outpatients, with ejection fraction (EF) <40%, were assessed for depressive symptoms using the Beck Depression Inventory (BDI) at baseline and again one year later. Cox Proportional Hazards regression analyses, controlling for established risk factors, were used to evaluate how changes in depressive symptoms were related to a combined primary endpoint of death or cardiovascular hospitalization over a median follow-up period of 5 years (with range of 4 to 7 years and no losses to follow-up).

RESULTS—1-year change in symptoms of depression, as indicated by higher BDI scores over a 1-year interval (BDI change (1-point) Hazard Ratio=1.07; 95% CI 1.02-1.12; p=.007), were associated with death or cardiovascular hospitalization after controlling for baseline depression (baseline BDI Hazard Ratio = 1.1; 95% CI 1.06-1.14, p<.001) and established risk factors, including HF etiology, age, EF, NT-proBNP, and prior hospitalizations.

CONCLUSIONS—Worsening symptoms of depression are associated with a poorer prognosis in HF patients. Routine assessment of symptoms of depression in HF patients may help guide appropriate medical management of these patients who are at increased risk for adverse clinical outcomes.

Keywords

Heart failure; Depression

With over five million Americans living with HF, and another 670,000 new cases being diagnosed each year, HF is the most costly diagnosis in the Medicare population, and is the most common cause for hospitalization in patients over the age of 65 years (1). Clinical

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depression also is common in HF, with prevalence estimates ranging from 24-42% (2). Studies from multiple investigative teams, including our own, have found that independent of HF disease severity, depressive symptoms are associated with adverse clinical outcomes for HF patients (3-8). Moreover, depressive symptoms that increase over time also have been associated with worse outcomes in post-myocardial infarction (MI) patients (9-11). Although changes in depressive symptoms have been assessed previously in HF patients (12,13), their relationship to HF clinical outcomes has not been evaluated. The present study extends our prior report (3), by evaluating the unique contribution of changes in depressive symptoms at 1 year follow-up, in the context of established risk factors including baseline depressive symptoms and established HF disease severity biomarkers, on subsequent clinical outcomes defined by hospitalization or death across an overall median follow-up period of 5-years.

METHODS

This is a prospective observational study of a non-hospitalized cohort of HF patients, recruited from outpatient HF clinics in central North Carolina. We performed medical and psychosocial assessments at baseline and at 1-year follow-up to evaluate their association with events, including mortality and hospitalizations over a median follow-up period of 5 years from baseline assessments (median of 4 years from the 1-year follow-up assessments with range of 3 to 6 years and no losses to follow-up).

Participants

The study sample was comprised of 147 patients recruited from the Heart Failure Programs at Duke University Medical Center and the University of North Carolina Health Care at Chapel Hill from January, 2000 through December, 2002. This sample represents a subset of the 204 participants whom we initially recruited (3); 27 patients died within the first year and 30 were alive but were unavailable to complete the depression assessment at one-year follow-up. Inclusion criteria were: left ventricular ejection fraction (LVEF) of 40% or less, documented within the last year by angiography, radionuclide ventriculography, or echocardiography; New York Heart Association (NYHA) functional classes I-IV for at least 3 months in duration. Exclusion criteria were: pacemaker dependence; uncontrolled hypertension; MI, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) within the last 3 months; and patients' first visit to the heart failure clinic. Pacemaker-dependence, <3 months post-MI, PCI and CABG were excluded because the study also was designed to evaluate autonomic nervous system regulation. The study was approved by the Institutional Review Board at Duke University Medical Center, where all assessments were performed. Written informed consent was obtained from all participants prior to their participation.

Baseline Assessments

Medical—Clinical information and medical history were obtained from medical records. Medications were documented as medications being taken at the time of baseline assessments, including both cardiac and psychotropic medications.

N-Terminal pro B-type Natriuretic Peptide (NT-proBNP)—Following 20-minutes of seated relaxation, blood was collected from an antecubital vein in 5 mL phlebotomy tube containing EDTA. Samples were placed on ice, cold-centrifuged at 1000 X g for 10 min. The resulting plasma was pipetted into plastic vials and frozen and maintained at –80°C until assay. On the day of NT-proBNP analysis, samples were thawed in a room temperature water bath then mixed thoroughly. NT-proBNP measurements were performed within 4 hours of thawing using an electrochemiluminescence immunoassay in accordance with the

manufacturer's instructions (Elecsys® proBNP, Roche Diagnostics Corporation, Indianapolis, IN). The analytical measurement range for the assay is 5-35000 pg/mL and typical day-to-day imprecision has a coefficient of variation <5%.

Left Ventricular Ejection Fraction (LVEF)—LVEF was determined by two-dimensional echocardiography. Apical 4-chamber and 2-chamber images of the heart were acquired by a single sonographer using an Acuson (Mountain View, California) ultrasound machine and were stored as digital loops. The endocardial borders of the LV in the 2 views were traced by a single experienced echocardiography specialist using customized off-line software (Access Point 2000, Freeland Systems, LLC, Westfield, Indiana), and ventricular volumes and LVEF were computed using the biapical Simpson's rule.

Depression—The Beck Depression Inventory (BDI) is a 21-item self-report measure of depressive symptomatology (14). A score of 10 or greater is considered indicative of clinically significant levels of depressive symptoms (15). Although the BDI is not used to diagnose clinical depression, it is a well-validated instrument for assessing the severity of depressive symptoms. Moreover, elevated symptoms of depression measured by the BDI are associated with increased risk of adverse events in cardiac patients, including patients with HF (3,7,16,17). These studies also document that the cut point of a BDI score of 10 or greater is applicable in cardiac patient populations, where it has been associated with poorer prognosis (3,16,17).

One Year Follow-Up Assessments—On the 1-year anniversary (± 2weeks) of participants' baseline assessments, 147 surviving participants repeated the BDI to re-assess their depression symptoms. Medical records also were examined to document current heath status, hospitalizations during the past year, and antidepressant medication use.

Long-term Follow-up of Vital Status and Hospitalizations—Participants' medical records were reviewed on a yearly basis, over a median period of 5 consecutive years from baseline (with range of 4 to 7 years and no losses to follow-up), on the anniversary of their baseline assessments, by trained research assistants blinded to patients' depression status. Patients also were contacted annually by mail and asked to indicate whether they had been hospitalized during the past year, and provided consent for retrieval of their hospitalization records. The primary endpoint was defined as the time to cardiovascular hospitalization or death (whichever occurred first) within the follow-up period. Patient mortality was verified through hospital and Emergency Medical Services records. Cardiovascular hospitalizations included hospitalizations for MI, stroke, treatment for worsening heart failure, cardiac surgery including coronary artery by-pass grafts (CABG), and heart transplantation. In order to develop a fuller understanding of the relation of depression and clinical outcomes, we also considered all-cause hospitalization or mortality as a secondary composite endpoint.

Statistical Methods—Cox proportional hazards regression models were used to examine the relationship between baseline characteristics and events (death and hospitalizations) during the median period of 5-year follow-up (with range of 4 to 7 years and no losses to follow-up). Age, HF etiology, NT-proBNP, LVEF, baseline BDI score, 1-year change in BDI score (BDI at 1 year minus baseline BDI), and antidepressant medication use had planned inclusion in the primary model. Hospitalizations occurring during the first year were used as an indicator of medical status for that year and also was included in the planned primary proportional hazards regression model to address the possibility that clinical events during the first year of follow-up could drive changes in depression symptoms during the interval between baseline and their reassessment one year later. In order to minimize the possible influence of clinical events during the first year on subsequent 1-year BDI scores,

outcomes were considered as clinical events occurring at least 1 year after initial baseline assessments. Thus, outcomes were defined as death or hospitalizations occurring only after the first year of follow-up data had been collected (including 1-year BDI score) for each participant. Secondary sensitivity analyses for the evaluation of robustness of findings from the planned model allowed other potential explanatory factors (including NYHA class, diabetes, hypertension, hypercholesterolemia, myocardial infarction, tobacco use, glomerular filtration rate (modified Cockroft-Gault equation), implantable defibrillator, and treatment with a beta-blocker, diuretic, angiotensin converting enzyme (ACE)-inhibitor, nitrate, warfarin, or statin) to be available for entry into the planned model by stepwise selection (SLE=.1). For Cox regression analyses, baseline NT-proBNP and BDI scores were trimmed at the 95th percentiles to prevent excessive influence of outliers; NT-proBNP was expressed as NT-proBNP/1000 and age was expressed as age/10. Descriptive statistics were means with standard deviations for continuous variables and counts with percentages for categorical variables. Also, student's t-tests and chi-square tests were used for the comparison of characteristics of study participants who died prior to, or were otherwise unavailable for reassessment of depressive symptoms, with those comprising the study sample (n=147) evaluated using the Cox regression analyses.

RESULTS

Baseline Characteristics

Demographic and clinical characteristics of the study sample are shown in Table 1. The mean age at baseline was 57 years, with a range of 27-88 years. Most patients were male (70%) and approximately half were minorities. The majority of patients were NYHA Class II (59%) or Class III (37%), and most patients were taking a beta-blocker (88%) and/or an ACE inhibitor (86%). Twenty percent of patients were taking antidepressant medication (serotonin reuptake inhibitors, tricyclic or tetracyclic agents, and monoamine-oxidase inhibitors) at baseline, and the average BDI score at baseline was 10 (SD=6; range 0-37). The study sample consisted of 147 patients, which represents 83% of the 177 patients who survived one year following baseline assessments from our original study (3). Compared to the survivors, patients who died during the first year of follow-up (n=27) had, at baseline, higher resting heart rates (p=.021), lower LVEFs (p=.028), higher NT-proBNP levels (p=.0001), and were less likely to be taking nitrates (p=.041). Cox proportional-hazards regression analyses revealed that only NT-proBNP and LVEF were related to death (p's<.01) within the first year following baseline assessments. There were few differences in any of the demographic or clinical characteristics of the 30 patients who survived at least one year, but who were unavailable for follow-up compared to the remaining 147 patients, with the exceptions of their having higher baseline systolic blood pressure (p=.011), higher NT-proBNP (p=.021), lower hemoglobin (p=.015) and being more likely to be diabetic (p=.024). It is of note that there were no differences in baseline BDI score between the present study sample (n=147) and those 30 patients who were unavailable for 1-year follow-up (10.2±6.9 versus 10.9±6.4 respectively, p=0.579).

The relationship of depression to cardiovascular hospitalizations and mortality

The median follow-up period from baseline was 5 years, with a range of 4 to 7 years; no patients were lost to follow-up. Of the 147 patients who survived at least one year and completed a second BDI assessment, 127 (88%) either died or were hospitalized at least once, including 112 (77%) such events due to cardiovascular reasons during the subsequent follow-up period (with median of 4 years). During the follow-up period 53 of the 147 participants died (36%), of which 40 deaths were due to cardiac causes; 15 of these 53 deaths occurred prior to any hospitalizations during the follow-up period. The planned multivariate Cox proportional-hazards regression analysis revealed that ischemic etiology

(Hazard Ratio=1.83; CI 1.22-2.75; p=.004), NT-proBNP (1000 pg/ml Hazard Ratio=1.17; 95% CI 1.01-1.36; p=.03), LVEF (Hazard Ratio=.97; CI 0.95-0.99; p=0.011), and hospitalization within the first year following baseline assessments (Hazard Ratio=2.4; CI 1.57-3.66, p<.001) were associated with cardiovascular hospitalization or mortality (Table 2). In this same model, the extent of baseline depression symptoms also was strongly related to risk for cardiovascular hospitalization or mortality (BDI (1-point) Hazard Ratio=1.1; 95% CI 1.06-1.14; p<.001), and so was change in BDI score at 1 year (BDI change [1-point] Hazard Ratio=1.07; 95% CI 1.02-1.12; p=.007). In secondary analyses, of the variables eligible for contributing further to the planned model through stepwise selection, current smoking status (Hazard Ratio=1.92; CI 1.14-3.23, p=0.014) and presence of an implantable defibrillator (Hazard Ratio=0.51; CI 0.28-0.92, p=.024) were added to the model. However, the addition of these factors did not influentially alter the results for the explanatory values of the variables in the original model, including baseline depression symptoms and 1-year change in depression symptoms, confirming that the original planned model was robust for its results.

The change in BDI score from baseline to 1-year follow-up ranged from a 14-point reduction to an increase of 19 points. In order to provide a better understanding of how changes in depressive symptoms were related to change in risk of adverse clinical outcomes, we created three descriptive categories. Ideally each of the categories would have about one third of the participants, and 25% at a minimum; moreover, one would like the middle category for a variable that is reflective of change to represent little or no change. Sixty-five participants (44%) showed a 2-point change or less in either direction in BDI score from baseline to one year follow-up, whereas 29% showed either an increase in BDI of 3-points or greater (n=43), and 27% showed a decrease of at least 3-points (n=39). In exploratory analyses, these BDI-change categories were entered into our planned regression model in place of the raw BDI-change score, in order to assess the nature of changing BDI effects on outcomes. Compared to patients showing minimal (≤2 point change) in BDI, those exhibiting a 3 or more point increase, indicating worsening depression symptoms, were at over twice the risk of adverse outcomes (Hazard Ratio=2.12; CI 1.31-3.43, p=.002); however, patients whose BDI scores were 3 or more points lower at 1 year follow up were at a relatively similar risk compared to those exhibiting a minimal BDI change (Hazard Ratio=0.87; CI 0.5-1.48; p=.59).

The relationship of depression to all-cause hospitalizations and mortality

In our planned model, age (10-year Hazard Ratio=1.25; CI 1.04-1.51, p=.019) and hospitalization within the first year following baseline assessments (Hazard Ratio=2.36; CI 1.59-3.51, p<.001) were associated with all-cause hospitalization or mortality over the subsequent follow-up period (Table 2). The extent of baseline depression symptoms also was related to increased risk for all-cause hospitalizations or mortality (BDI (1-point) Hazard Ratio=1.09; 95% CI, .1.05-1.13; p<.001), and so was change in BDI score at 1 year (BDI change (1-point) Hazard Ratio=1.06; 95% CI 1.01-1.11; p=.023). Secondary analyses showed no additional variables were added to the planned model through stepwise selection, confirming that the planned model was robust.

In exploratory regression analyses, we substituted our categorical variables indicating worsening, improving, or minimal change in BDI score for the continuous measure of 1-year change in BDI score. For all-cause hospitalizations there was a trend for increased risk associated with worsening depression symptoms compared to minimal or no change in depression symptoms (Hazard Ratio= 1.48; CI 0.96-2.29; p=0.077), whereas improving depression symptoms were not associated with altered risk compared to minimal or no change (Hazard Ratio= 0.78; CI 0.47-1.28; p=0.32).

DISCUSSION

The present findings confirm and extend our previous observations by showing that symptoms of depression are associated with adverse clinical outcomes, including cardiovascular (or all-cause) hospitalization and death, over a median of five years of follow-up from baseline (with range of 4 to 7 years and no losses to follow-up), even after controlling for the severity of HF disease and other established risk factors, and that worsening of depression was additionally associated with such adverse events compared to patients whose depressive symptoms remained relatively stable over the initial 1-year follow up period. To our knowledge, this is the first study to evaluate prospectively the clinical impact of changing depression symptoms in HF patients, and our observations demonstrate that such changes do indeed affect clinical outcomes. Specifically, a one-point change in BDI score was associated with a 7% alteration in risk (per unit of time) for cardiovascular hospitalizations and mortality. Importantly, the effects of change in depression symptoms were independent of baseline depression symptoms, and HF disease severity biomarkers, as well as hospitalizations occurring during the year over which depression symptoms were monitored. Exploratory analyses designed to better understand the latter finding suggest that worsening symptoms of depression in HF patients may be of particular concern; an increase in depressive symptoms of three or more BDI points over a 1-year follow-up period was associated with over a two-fold increased risk of cardiovascular hospitalization or death compared to minimal change (<2 BDI points). Our findings are consistent with observations in post-MI patients, in whom worsening symptoms of depression have been associated with greater risk of subsequent mortality (9-11).

Our study found no association between antidepressant use and clinical outcomes. However, because the study was not designed to assess the impact of antidepressant treatment on outcomes, the significance of this observation is unclear. There are currently no published data from randomized clinical trials (RCTs) of HF patients indicating whether interventions designed to modify depression symptoms may alter long-term clinical outcomes. Although the SADHART trial (18) was designed to be a safety and efficacy trial and was not powered to evaluate adverse clinical outcomes, the incidence of cardiovascular events in a subgroup of more severely depressed patients with acute coronary syndromes randomized to sertraline treatment was 14.5% compared to 22.4% among those receiving a placebo. In the ENRICHD trial, the rates of non-fatal MI and all cause mortality were similar between post-MI patients randomized to cognitive behavior therapy (CBT) and education controls (19), although a post-hoc analysis revealed that patients who received anti-depressant medication had improved survival compared to similar patients not receiving anti-depressants (20). Moreover, patients randomized to the CBT condition who exhibited an increase in depressive symptoms had higher event rates compared to those patients who showed an improvement in depressive symptoms (9). In a recently completed RCT in HF patients with depression (22), no antidepressant benefit of sertraline compared to placebo was observed, although remitting depression symptoms were found to be associated with improved health status and quality of life (23).

It is important to note that the observational data reported in the present study do not lend themselves to causal inferences nor to insights into the potential effects of interventions designed to modify symptoms of depression. Other limitations of the present study include absence of changes in depression during the follow-up period. However, changes in depression symptoms during the follow-up period would be difficult to interpret since such changes would be concomitant with changing HF disease severity. The reported analyses evaluate the role of change in depressive symptoms prior to the onset of the follow-up period and are therefore explanatory. The sample size of the present study also was relatively small, but a significant relationship between 1-year change in depression

symptoms and subsequent clinical outcomes was observed despite this limitation. It also should be noted that the HF disease severity biomarkers (NT-proBNP and LVEF) were assessed only at baseline, not at the time of the reassessment of depressive symptoms, one year later; however, our inclusion of hospitalizations during that one year period was designed to minimize this potential limitation.

In summary, elevated depression symptoms, and worsening depression symptoms, were found to be explanatory risk factors for adverse clinical outcomes in HF patients, independent of HF disease severity. Our findings support the recent American Heart Association's position encouraging depression screening (24), and would further suggest that it may be prudent for clinicians to routinely reassess symptoms of depression in HF patients, in order to better determine appropriate medical management of these patients who are at increased risk for adverse clinical outcomes and impaired quality of life.

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ABBREVIATIONS

BDI	Beck Depression Inventory
CABG	coronary artery bypass graft
CHD	coronary heart disease
HF	heart failure
HR	hazard ratio
ICD	implantable cardioverter defibrillator
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NT-proBNP	plasma N-terminal pro B-type Natriuretic Peptide
PCI	percutaneous coronary intervention
RCT	randomized clinical trial

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Table 1

Baseline characteristics (mean ± SD or %) for the study sample (n=147).

	Study Sample (n= 147)
Demographic & History	
Age, years	57±13
Sex (female, %)	30
Ethnicity (minority, %)	51
BMI (kg/m^2)	31.4±6.9
Etiology (ischemic, %)	45
NYHA Functional Class I (%)	3
NYHA Functional Class II (%)	59
NYHA Functional Class III (%)	37
NYHA Functional Class IV (%)	1
Implantable defibrillator (%)	11
Pacemaker (%)	10
SBP (mm Hg)	99±17
DBP (mm Hg)	60±10
HR (bpm)	66±11
Current smoker (%)	19
Time since HF diagnosis (years)	4.8±4.2
Baseline Assessments	
Left ventricular ejection fraction (%)	32±11
NT-proBNP (pg/ml)	1159±1466
Medications at Baseline	
Antidepressants (%)	20
Betablockers (%)	88
ACE Inhibitors (%)	86
ARBs (%)	7
Nitrates (%)	31
Warfarin (%)	26
Statins (%)	46
Aspirin (%)	55
Diuretics (%)	93
Laboratory Values at Baseline	
Total cholesterol, mg/dL	192±51
Sodium, mEq/L	140±3
Hemoglobin, g/dL	13.4±1.5
Creatinine, mg/dL	1.3±0.6
BUN, mg/dL	25.1±16.3
Medical Co-Morbidities	

	Study Sample (n= 147)
Diabetes (%)	41
Hypercholesterolemia (%)	48

Table 2

Multivariate Cox proportional hazards models assessing the association of baseline depression symptoms (BDI score) and 1-year change in depression symptoms (change in BDI score) with composite endpoints of Hospitalizations and Death (HR=Hazard Ratio; CI= Confidence Intervals).

Planned Model Characteristic	**Cardiac Hospitalization or Death (112 events)**		**All Cause Hospitalization Or Death (127 events)**	
	P value	**HR (95% CI)**	**P value**	**HR (95% CI)**
Age (yr/10)	.103	1.17 (0.97-1.41)	**.019**	**1.25 (1.04-1.51)**
Etiology (1=ischemic; 0= non-ischemic)	**.004**	**1.83 (1.22-2.75)**	.053	1.46 (0.99-2.14)
NT-ProBNP (pg/ml/1000)	**.031**	**1.17 (1.01-1.36)**	.129	1.12 (0.97-1.29)
LVEF (%)	**.011**	**0.97 (0.95-0.99)**	.098	.98 (0.96-1.00)
Baseline Depression Symptoms (BDI score)	**<.001**	**1.1 (1.06-1.14)**	**<.001**	**1.09 (1.05-1.13)**
1-year change in BDI Score	**.007**	**1.07 (1.02-1.12)**	**.023**	**1.06 (1.01-1.11)**
Antidepressant (1=yes; 0=no)	.092	0.63 (0.36-1.08)	.309	0.78 (0.48-1.26)
Hospitalization in first year (1=yes; 0=no)	**<.001**	**2.4 (1.57-3.66)**	**<.001**	**2.36 (1.59-3.51)**