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Impact of Depression on Prognosis in Heart Failure

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Synopsis

Depression is a common comorbid condition in heart failure, and there is growing evidence that it increases the risks of mortality and other adverse outcomes, including rehospitalization and functional decline. The prognostic value of depression depends, in part, on how it is defined and measured. The few studies that have compared different subsets of depressed patients suggest that major (or severe) depression is a stronger predictor of mortality than is minor (or mild) depression. Whether depression is a causal risk factor for heart failure mortality, or simply a risk marker, has not yet been established, but mechanistic research has identified several plausible behavioral and biological pathways. Further research is needed to clarify the relationships among depression, heart failure, and adverse outcomes, as well as to develop efficacious interventions for depressive disorders in patients with heart failure.

Keywords

depression; major depressive disorder; heart failure; prognosis; mortality

Depression is a common comorbid condition in patients with heart failure (HF), and it is associated with a poor prognosis. Whether the prognosis of HF can be improved by treating depression has not yet been established, but depression deserves clinical attention nevertheless. This article discusses the definition and measurement of depression in patients with HF, research on the relationship between depression and HF outcomes, some candidate mechanisms that may help to explain this relationship, and the status of depression as a risk factor for adverse outcomes in HF. It concludes by considering the implications of these issues for further research and for the assessment and treatment of depression in HF.

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DEFINITIONS AND MEASURES OF DEPRESSION IN HEART FAILURE

The prognostic importance of depression depends on how it is defined and measured. In the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[2], a *major depressive episode* is defined as the presence of a particular constellation of depressive symptoms (Box 1). Over the course of an individual's lifetime, there may be only a single episode of major depression (MD), or there may be recurrent episodes. The first (or only) episode may occur in childhood, adolescence, or adulthood, and for any given episode, the duration may vary from as little as a few weeks to a few years or even longer. The durations of interepisode intervals are highly variable as well. Consequently, major depressive disorder (MDD) can follow very different lifetime courses in different individuals.

Box 1

DSM-IV-TR criteria for major depressive episode

- At least 5 of the following 9 symptoms persist for at least 2 weeks and represent a change from the individual's previous level of functioning:
  - Depressed mood (feels sad, down blue, etc.)
  - Loss of interest or pleasure in most or all usual activities
  - Significant change in appetite or weight, whether decreased or increased
  - Insomnia or hypersomnia (excessive sleepiness)
  - Agitation (restlessness, excessive motor activity) or psychomotor retardation (slowing of movements or speech)
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive guilt
  - Inability to concentrate, think clearly, or make decisions
  - Suicidal ideation, wishes to die, or thoughts of being better off dead
- Depressed mood and loss of interest or pleasure are cardinal symptoms of major depression; at least one of these symptoms must be present.
- The depressive symptoms are associated with significant impairment in one or more important areas of functioning (social, occupational, recreational, etc.)
- The symptoms are not due solely to the direct, physiological effects of a medical condition (e.g., an endocrine disorder), a medication, or substance abuse.

The criteria for a *minor* depressive episode (md) are the same as for an MD episode, except that there are only 2 to 4 symptoms rather than 5 to 9. When MD episodes resolve, they usually do so gradually. Consequently, an individual who had 7 or 8 symptoms during a MD episode may have only 3 or 4 symptoms when the episode is in partial remission. If a cross-sectional assessment of depression is performed at this time, without regard to the history of the episode or whether there is a past history of MD episodes, then a major depressive episode in partial remission may be misdiagnosed as an episode of minor depression. As will be discussed in a later section, relatively severe depression may have worse prognostic implications in heart failure than milder forms of depression. Thus, when evaluating patients with heart failure, one should to try to avoid misdiagnosing an episode of MD in partial

remission as an episode of minor depression. Unfortunately, this is easier said than done; many patients are unable to provide accurate details about symptoms that have already abated.

Because the lifetime course of major depressive disorder is highly variable, some patients experience their first depressive episode sometime after the onset of chronic heart failure. When this occurs, the onset of depression may occur soon after, or long after, the onset of heart failure. In other cases, the first episode of depression may have occurred years or even decades before the onset of heart failure, as well as before the onset of HF precursors such as hypertension or coronary heart disease. Furthermore, some patients have multiple episodes of depression long before they develop heart failure. If comorbid major depression were simply a psychological reaction to heart failure, it would be tempting to dismiss its apparent prognostic implications as epiphenomenal. Clearly, however, the temporal relationship between these conditions is far too complex to assume that depression is always, or even usually, an emotional reaction to heart failure.

In clinical settings, many patients are diagnosed as having major depression without regard to whether they actually meet the DSM-IV-TR criteria. According to a recent survey, the majority of nonpsychiatrist physicians and even a substantial minority of psychiatrists do not use the DSM-IV criteria when diagnosing major depressive disorder.[55] As a result, some patients with minor depression, or with no recognized depressive disorder, are misdiagnosed as having major depression. This is usually avoided in research studies by following the DSM-IV-TR criteria and utilizing a standardized interview such as the Depression Interview and Structured Hamilton (DISH)[19] to ensure that all of the criterion symptoms of MDD are carefully assessed.

However, depression can also be defined by self-report questionnaires such as the Beck Depression Inventory (BDI)[4] or a new version of this instrument, the BDI-II[3;48]. Total scores on instruments such as the BDI are often used to measure the severity of depressive symptoms, and standard cutoff scores such as 10 on the BDI or 14 on the BDI-II are often used to define “depression” or “clinically significant depression”. When administered to patients with carefully diagnosed depressive disorders, the scores on such measures indeed reflect the severity of depression. In contrast, when they are administered to patients who have not had a diagnostic evaluation, elevated scores may or may not indicate the presence of a depressive disorder. In patients with heart failure, many of whom have multiple medical comorbidities, endorsement of symptoms such as fatigue or insomnia may indicate depression, but these symptoms may also be due at least in part to medical illness or its treatment. Consequently, it is important to exercise caution in interpreting nonspecific symptoms such as fatigue when evaluating the prognostic importance of depression in patients with heart failure.

DEPRESSION AS A PREDICTOR OF MORTALITY IN HEART FAILURE

In the first prospective study of major depression as a predictor of mortality in heart failure, Freedland et al.[16] enrolled 60 patients who were 70 years or older at the time of hospital admission for heart failure. Seventeen percent of the patients met criteria for a major depressive episode, according to a standardized diagnostic interview. Vital status was determined one year after the index hospitalization, with no patients lost to follow-up. During follow-up, 50% of the depressed patients died, compared to 29% of the nondepressed patients. This study provided the first evidence that major depression may have adverse prognostic implications in patients hospitalized for heart failure. When the investigators sought to replicate this finding in a larger (n=682) sample of hospitalized patients with heart failure, they found that major depression was an independent predictor of

survival over one year, after adjusting for left ventricular ejection fraction (LVEF) and other covariables.[15]

Subsequent research has confirmed that depression increases the risk of mortality in patients with heart failure. The studies that have been conducted to date are strikingly heterogeneous with respect to the medical and demographic characteristics of the samples, the measures used to assess depression, the duration of follow-up, and the potential confounders that were included in the statistical models. Despite these differences, most of the published evidence shows that the presence of depression alters the risk of mortality and other adverse outcomes in heart failure.

One of the earliest prospective studies was conducted in Norway. In this study[33], 119 clinically stable outpatients with symptomatic HF (71% men, mean age 66±10 years) were recruited from a cardiology practice and followed for two years. Most of the patients were in New York Heart Association (NYHA) class II (41%) or III (46%) heart failure at enrollment. Depression was measured by the Zung Depression Scale.[56] Twenty (17%) of the patients died during a two-year follow-up period. A Cox proportional hazards regression analysis was conducted to model the effect of depression on survival, adjusting for gender, age, and, as an index of the severity of heart failure, the prohormone of atrial natriuretic factor (pro-ANF). In this model, the hazard ratio (HR) for a one-point increase on the Zung scale was 1.08 (p=.002). The participants also completed several other questionnaires assessing heart-failure related emotional distress, quality of life, and perceived health. A factor analysis of the scores on these questionnaires and the Zung scale yielded two factors, “depressed mood” and “subjective health”. When these factors were entered into a Cox regression model along with the same covariates as before, depressed mood emerged as an even stronger inverse predictor of two-year survival (HR, 1.90; p=.002). This study provided the first evidence that depression increases the risk of mortality among outpatients with heart failure.

Murberg and Furze[34] subsequently published a six-year follow-up of this cohort. They found that depression at baseline continued to predict mortality over this period (RR per point on the Zung Scale, 1.05; 95% C.I., 1.00 to 1.08; p=.02), after adjustment for gender, age, and pro-ANP, as well as for the personality trait of neuroticism. The strength of the association was somewhat smaller than the investigators had reported in their earlier two-year follow-up study, but it was still detectable years after the index hospitalization and the baseline assessment of depression.

Koenig[27] enrolled a consecutive sample of 107 older (age ≥60 years) patients with heart failure who were hospitalized at a university teaching hospital. The National Institute of Mental Health Diagnostic Interview Schedule (DIS)[42] was administered to diagnose major depression at baseline, and minor depression was identified by a combination of criterion symptoms and scores on two different depression scales, the Center for Epidemiological Studies – Depression (CES-D)[40] scale and the 17-item Hamilton Rating Scale for Depression (HAM-D)[21]. Thirty-nine (36%) of the patients had MD at baseline, 23 (22%) had md, and 45 (42%) had no depressive disorder. Over a median 46 week follow-up, 28% of the patients with major depression, 30% of those with minor depression, and 20% of those with no depression died. Although a higher proportion of depressed than nondepressed participants died during the follow-up, the difference was not statistically significant in this relatively small sample.

A larger study by Vaccarino and colleagues[52] was the first to examine the effect of depression on a composite outcome of functional decline or death. A cohort of 391 patients (49% women) who were at least 50 years old on hospital admission for decompensated heart

failure were assessed for depression and followed prospectively for 6 months. The 15-item short form of the Geriatric Depression Scale (GDS)[53] was used to assess depression at baseline. Functional decline was defined as an increase in the number of limitations in activities of daily living (ADLs) between baseline and 6 months, as assessed by the Katz ADL scale[26]. In a series of multivariable models, GDS scores were adjusted for demographic factors, medical history, baseline functional status, clinical characteristics at enrollment (systolic blood pressure, serum creatinine, heart rate) and LVEF. Twenty-nine percent of the patients had an ejection fraction of 55% or higher at baseline. Functional decline or death occurred in 159 (41%) of the participants, and the event rate increased as the level of depression increased (nondepressed, 31%; mildly depressed, 34%; moderately depressed, 49%; severely depressed, 60%; p=.001). In the fully adjusted model, the rates corresponded to risk ratios (RRs) of 1.00 (referent), 1.10, 1.39, and 1.82, respectively; p=.004. Unlike the mildly and moderately depressed group, the confidence interval around the RR did not include 1.00 in the severe group, indicating that this group was clearly at high risk of functional decline or death.

When Vaccarino et al. decomposed the outcome, they found that increasing levels of depression were significantly associated in univariate analyses with functional decline (p=.004) based on event rates of 22%, 22%, 34%, and 46% in the nondepressed and mildly, moderately, and severely depressed groups, respectively, and with death from any cause (p=.02), based on event rates of 11%, 16%, 22%, and 26%. The association with functional decline persisted in the fully adjusted model (RR, 1.00, 1.15, 1.65, and 2.16; p=.01), but the association with death was not statistically significant (RR, 1.00, 1.07, 1.25, and 1.68; p=.27). Because functional decline often precedes death in chronic heart failure, it is possible that the multivariable association with death would have been significant if the follow-up had been extended to one year. Regardless, this study replicated earlier findings that depression has prognostic importance in elderly patients who have been hospitalized with heart failure, but it did so with a different measure of depression and a composite outcome that had not been examined in previous studies.

Jiang and colleagues[23] were the first to publish a study of the prognostic value of depression in patients hospitalized with heart failure that was not restricted to elderly participants. They screened a series of patients who were at least 18 years old at admission and who had an LVEF of 35% or less and/or were in NYHA class II or higher heart failure. Patients who scored 10 or higher on the Beck Depression Inventory were asked to undergo a modified version of the DIS interview to identify major depression. The outcomes included all-cause mortality and rehospitalization 3 months and 1 year after baseline. Of 357 patients who completed the BDI, 126 (35%) scored at or above the cutoff score. One hundred (79%) of these patients completed the DIS, and 46 met criteria for major depression. Patients who scored 10 or higher on the BDI but who did not have major depression according to the DIS were classified as having “mild depression”. The ages (mean ± standard deviation) of the nondepressed, mild depression, and major depression groups were 64 ± 13, 63 ± 13, and 63 ± 13 years, respectively. Thus, most of the participants were at least 60 years old, despite the fact that younger patients were eligible.

The mortality rates were 6%, 7%, and 13% at 3 months in the nondepressed, mild depression, and major depression groups, respectively, and 14%, 11%, and 26% at one year. Readmission rates were 37%, 43%, and 52% at 3 months, and 52%, 56%, and 80% at one year. In univariate analyses, major depression predicted mortality at one year (odds ratio [OR] = 2.23, 95% C.I., 1.04 to 4.77), p=.04), but not at 3 months, and minor depression did not predict mortality at either point. The association with one-year mortality was no longer significant after adjustment for age, NYHA class, baseline LVEF, and cause of heart failure. In contrast, major depression was a significant predictor of rehospitalization within 3 months

(OR=1.90, 95% C.I., 1.00 to 3.59, p=.04) and one year (OR=3.07, 95% C.I., 1.41 to 6.66, p=.005), and the one-year effect persisted after multivariable adjustment (OR=2.57, 95% C.I., 1.16 to 5.68, p=.02). The results provided only equivocal evidence that major depression increases the risk of one-year mortality in patients hospitalized with heart failure, but it yielded clear evidence that patients with major depression are more likely than their nondepressed counterparts to be rehospitalized.

In a secondary analysis of data from the same cohort, Hedayati et al.[22] stratified the sample according to the presence or absence of chronic kidney disease (CKD). They reported that major depression was more prevalent among patients with (22%) than without (13%) severe CKD, as was depression defined by a BDI score of 10 or higher (55% vs. 13%). After adjustment for age and severe CKD, major depression remained an independent predictor of one-year mortality when compared to mild depression (OR, 3.13; 95% C.I., 1.02 to 9.26), although not when compared to the nondepressed reference group (OR, 2.07; 95% C.I., 0.93 – 4.63). Overall, these findings suggest that major depression may have prognostic importance in heart failure, including patients with severe CKD.

Most of the studies in this area have been based on samples with diverse heart failure etiologies. A study from the UK was the first to focus exclusively on patients with non-ischemic heart failure. Based on hospital records and a clinical echocardiography database, Faris et al.[12] retrospectively identified 396 consecutive adult patients (mean age, 53 ± 15 years, 74% men) at a tertiary cardiac care hospital in London with a principal discharge diagnosis of heart failure due to non-ischemic dilated cardiomyopathy. Unlike the preceding studies, the retrospective design of this study precluded the use of standardized depression questionnaires or interviews. Instead, patients were classified as clinically depressed if a diagnosis of depression was listed in their medical record. At enrollment, 33% of the patients were in NYHA class I heart failure, 37% in class II, 20% in class III, and 10% in class IV. Eighty-three (21%) of the patients were classified as depressed.

The duration of follow-up varied considerably (mean, 48 ± 35 months, range 3 to 84 months). During follow-up, there were 83 deaths (21% mortality), and 15 (4%) of the patients underwent heart transplantation. There were 660 hospital readmissions; rehospitalizations occurred at a rate of 1.7 per patient-year on average. Clinical depression predicted mortality in both an unadjusted model (HR, 2.1; 95% C.I., 1.4 to 3.2; p=.0005) and after multivariable adjustment (HR, 3.0; 95% C.I., 1.4 to 6.6; p=.004). It also predicted hospital readmissions in both univariate (p=.01) and multivariable (p=.03) models.

Sullivan and colleagues[49] were the first to examine depression in relation to the combined endpoint of heart transplantation or death in outpatients with advanced heart failure. They recruited a consecutive series of 142 patients (age, 53 ± 10 years; 78% men; mean NYHA class, 2.7 ± 0.7) from a heart failure/pre-transplant specialty clinic at a university teaching hospital. A structured interview based on the DSM-IV criteria for mood disorders, the Primary Care Evaluation of Mental Disorders (PRIME-MD)[47] was administered to identify major and minor depression. The 24-item version of the HAM-D and the 20-item Symptom Checklist (SCL-20) Depression scale[9] were used to assess the severity of depression, and extensive data were collected at baseline to document the severity of heart failure and other medical conditions. The cohort was followed with regularly scheduled contacts over a mean of 3 years ± 7 months. During this period, 15 (11%) of the patients died and 24 (17%) received a heart transplant. Thirteen of the deaths were due to cardiovascular causes, and two were from cancer.

In a univariate Cox regression analysis, having any depression diagnosis at baseline (whether MD, md, or dysthymia, which is a chronic, relatively mild form of depression)

significantly increased the hazard of the primary combined endpoint (HR, 2.54; 95% C.I., 1.16 to 5.55; p=.02). This effect persisted (HR, 2.41; 95% C.I., 1.24 to 4.68; p<.01) after multivariable adjustment for age, serum sodium, NYHA class, systolic blood pressure, and a geriatric version of the Cumulative Illness Rating Scale[32]. Although the study was underpowered to examine mortality and transplantation as separate endpoints, the investigators did so in exploratory univariate analyses. Depression diagnosis did not have a significant effect in the time-to-death analysis (HR, 1.65; 95% C.I., 0.51 to 5.28; p=.40), but it did in the transplant analysis (HR, 3.29; 95% C.I., 1.31 to 8.27; p=.01). These effects were specific to depression diagnosis; neither the HAM-D nor the SCL-20 predicted any of these outcomes. In additional multivariable analyses, the investigators found that patients with a depression diagnosis had a higher number of HF-related hospitalizations during the first year of follow-up (1.5 ± 1.8 vs. 0.6 ± 1.4; p=.04), as well as more HF clinic visits (2.4 ± 1.7 vs. 1.7 ± 1.8; p=.04). Taken together, the findings from this study suggest that depression may increase the likelihood of rehospitalization and heart transplantation, but they do not provide evidence that depression increases the risk of mortality.

A European study by Jünger and colleagues[25] was the first to utilize the Hospital Anxiety and Depression Scale (HADS)[54] in a study of heart failure mortality. The HADS omits somatic symptoms of depression such as fatigue, which presumably makes it a more specific measure of comorbid depression in medically ill patients compared to other depression scales. In this study, 209 outpatients (age, 54 ± 10 years; 86% male), with stable NYHA class I – III heart failure were enrolled and followed for an average of approximately 2 years. The endpoint was all-cause mortality, and observations were censored at the time of heart transplantation if it occurred. Forty-five patients died during the follow-up period. Depression was a significant predictor of survival in a univariate Cox regression analysis (HR, 1.09; 95% C.I., 1.02 to 1.17; p=.007), and remained significant (HR, 1.08; 95% C.I., 1.01 to 1.15; p=.02) after adjustment for LVEF and peak VO_2 obtained from cardiopulmonary exercise testing.

In a secondary analysis, the investigators explored whether the mortality risk associated with depression is stable over time. They found, to the contrary, that the risk increases over time. During the first 6 months of observation, the hazard ratio for depression, as defined by a score of 6 or higher on the HADS Depression scale, was 1.0 (95% C.I., 0.44 to 2.39; p=.95). It increased steadily over each subsequent 6-month period, reaching a peak at 30 months (HR, 8.22; 95% C.I., 2.62 – 25.84; p<.001). Prior studies had suggested that even if depression is assessed at a single and perhaps arbitrary point in the course of heart failure, it can have a durable influence on survival. This study went beyond these findings to show that the risk due to depression may increase over time.

As noted above, the majority of studies have not focused on patients with a particular heart failure etiology. A study by Rumsfeld and colleagues[44] was the first to examine the prognostic importance of depression in patients with an acute myocardial infarction (MI) complicated by heart failure. The prognostic value of comorbid depression in acute MI was already well established[14] when this study appeared, but Rumsfeld et al. went beyond the existing literature to study the subset of patients whose acute MIs are complicated by HF. The findings were based on a planned substudy of the Epleronone Post-Acute Myocardial Infarction heart Failure Efficacy and Survival Study (EPHESUS). It employed yet another self-reported depression scale, the Medical Outcomes Study Depression (MOS-D) questionnaire[5]. Of 634 patients included in this analysis, 143 (23%) scored above the depression cutoff on the MOS-D at baseline. The primary outcome was all-cause mortality over a mean follow-up period of 16 months, and cardiovascular death or hospitalization was examined as a composite endpoint. In univariate analyses, the depressed patients had a significantly higher all-cause mortality rate than the nondepressed patients (29% vs. 18%,

p=.004), as well as a higher rate of cardiovascular death or rehospitalization (42% vs. 33%, p=.02). These relationships remained significant in multivariable regression models after adjustment for a large set of demographic, cardiac, other medical, and treatment variables, including for all-cause mortality (HR, 1.78; 95% C.I., 1.11 to 2.63; p=.01) and for cardiovascular death or rehospitalization (HR, 1.41; 95% C.I., 1.03 to 1.93; p=.03). The results were consistent across a number of subgroups defined by demographic and medical characteristics, although there was a trend toward a higher depression-associated risk of mortality among patients with a prior history of myocardial infarction.

A study by Sherwood and colleagues was one of the first to prospectively examine whether depression predicts death or rehospitalization in heart failure when taking the effects of antidepressant medications into account. It was also one of the first studies of depression in HF to use NT-proBNP as a marker of the severity of heart failure. In this study, 204 outpatients with heart failure and an LVEF of 40% or less completed the BDI at enrollment. Participants were followed for a mean of 3 years, and none were lost to follow-up. During this period, 54 (26%) of the patients died and 126 (62%) were hospitalized at least once; 98 (48%) were hospitalized at least once for cardiovascular reasons. In a Cox regression model adjusting for age, HF etiology, LVEF, and NT-proBNP, both the baseline BDI score (HR, 1.06; 95% C.I., 1.03 to 1.09; p<.001) and antidepressant medications at baseline (HR, 1.75; 95% C.I., 1.14 to 2.68; p=.01) were independent predictors of the primary combined endpoint of death or cardiovascular rehospitalization. In a secondary model of time to death or all-cause hospitalization, the BDI effect was identical to that found in the primary model, but the effect of antidepressant medication weakened slightly (HR, 1.57; 95% C.I., 1.06 to 2.34; p=.02). The magnitude of the effects of depression and antidepressants in relation to all-cause mortality were similar to those found in the primary model, but they were not statistically significant. These data demonstrate that depression is associated with a worse HF prognosis even among patients receiving antidepressant medications.

A more recent and larger study by O'Conner and colleagues[35] sought to clarify whether the apparent prognostic value of depression in HF is attributable to the use of antidepressants, or whether it is better explained by depression per se. They enrolled 1006 hospitalized patients with clinically diagnosed HF who were in NYHA class II or higher, who had an LVEF of 35% or lower, or both. The participants completed the BDI during the index hospitalization. Use of antidepressants at the index hospitalization was determined from inpatient pharmacy records and hospital discharge summaries. One hundred sixty-two (16%) of the patients were taking an antidepressant at enrollment. One hundred twenty-nine (80%) of them were taking a selective serotonin reuptake inhibitor (SSRI) alone; 8 (5%) were taking an SSRI in combination with a tricyclic antidepressant (TCA); and 24 (15%) were taking a TCA alone or other antidepressants. Thirteen percent of the nondepressed patients were taking an antidepressant medication. In comparison, 25% of the patients who scored 10 or higher on the BDI were taking an antidepressant, and the proportion increased along with the severity of depression such that 34% of those with a BDI score of 19 or higher were on an antidepressant. Patients taking an antidepressant were more likely to be white and married.

The mean duration of follow-up was 2.7 + 2.0 years (median, 2.2 years). During this period, 429 patients died, including 161 (53%) who were depressed at baseline and 268 (38%) who scored in the nondepressed range on the BDI. Among patients who were not taking an antidepressant at baseline, 42% died; in contrast, death occurred in 44% of the patients who were taking an SSRI only, 55% of those who were taking a TCA, and 62% of those who were taking other antidepressants. In univariate analyses, both depression as defined by a BDI score of 10 or higher (HR, 1.39; 95% C.I., 1.12 to 1.74; p=.003) and any type of antidepressant use (HR, 1.32; 95% C.I., 1.03 to 1.69; p=.03) predicted shorter survival. When adjusted for demographic factors, baseline LVEF, NYHA class, and HF etiology,

antidepressant use was no longer a significant predictor of shorter survival (HR, 1.24; 95% C.I., 0.94 to 1.64; p=.13) but depression remained significant (HR, 1.33; 95% C.I., 1.07 to 1.66; p=.01). When the analysis was restricted to SSRI antidepressants, depression continued to predict shorter survival in both univariate and multivariable models, but SSRIs did not predict outcomes in either model. These findings helped to allay concerns about potential adverse effects of antidepressants in patients with HF, and pointed to the need for controlled clinical trials to evaluate the safety and efficacy of these agents in patients with heart failure and comorbid depression.

In most of the preceding studies, the multivariable models adjusted for gender as a potential confounder. None of them, however, examined whether the effects of depression on HF prognosis differ between men and women. This was the aim of a study conducted in German by Faller and colleagues[11]. The investigators enrolled a consecutive series of 231 patients (age, 64 ± 13 years; 29% women) presenting with heart failure (25% in NYHA class I, 44% in class II, 25% in class III, and 6% in class IV), without restrictions as to etiology and with no exclusion criteria except refusal to participate. Depression was assessed with the PHQ-9[29], a well-established depression screening tool that has the advantage of providing both a total severity score and an algorithm to identify probable cases of DSM-IV major or minor depression.

Cox proportional hazards regression was used to model survival over a median follow-up period of 2.7 years. None of the participants were lost to follow-up, and 59 (26%) of the patients died. In the overall sample, probable major depression predicted shorter survival both in a univariate analysis (HR, 3.3; 95% C.I., 1.8 to 6.1; p<.001) as well as in a multivariable analysis adjusting for sex, age, etiology, NYHA class, LVEF, and the presence or absence of systolic dysfunction (HR, 2.4; 95% C.I., 1.3 to 4.6; p<.01). Probable minor depression did not have a significant effect on survival. The gender subgroup analyses were limited by small sample sizes (only 12 women and 19 men had probable major depression). Nevertheless, probable major depression had a strong effect on survival among women (adjusted HR, 4.5; 95% C.I., 1.3 to 15.8; p=.02). The hazard ratio was smaller, and statistically nonsignificant, in men (adjusted HR, 2.1; 95% C.I., 0.9 to 4.6; p=.08). Unfortunately, this study was not adequately powered to definitively determine whether gender moderates the effect of depression on survival in HF, and it did not formally test for a depression by gender interaction, but it did suggest that depression may have worse prognostic implications in women than in men.

Given the multiplicity of depression measures that have been used in HF research, it would be useful to know whether they differ with respect to their ability to predict adverse outcomes if administered to the same patients. In one of the first studies to address this question, Parissis and colleagues[39] administered both the Zung Depression scale and the BDI to 155 hospitalized patients with heart failure (83% male; age, 65 + 12 years; 9%, 33%, 51%, and 17% in NYHA class I, II, II, and IV, respectively). The patients were followed for 6 months, during which time 61 (39%) were either rehospitalized or died, and 10 (16%) died. In univariate logistic regression analyses, the Zung scale predicted death or rehospitalization (OR, 1.06; 95% C.I., 1.03 to 1.10; p<.001), but the BDI did not. The Zung scale remained a significant predictor of rehospitalization or death (OR, 1.07; 95% C.I., 1.01 to 1.14; p=.03) after multivariable adjustment for NYHA class, BNP, and 6-minute walk test performance. Thus, in this particular study, the Zung scale predicted clinical outcomes of HF but the BDI did not. Unfortunately, it is not clear why the BDI predicted clinical outcomes in previous studies but not in this one.

Some of the most recent research has involved much larger samples than were enrolled in many of the earlier studies. Macchia et al.[31] linked hospital discharge records, medication

prescription databases, and vital statistics from 6 local health districts in Italy to identify 48,117 patients with heart failure. It was not possible to assess depression directly, so the investigators defined depressed cases as patients who were exposed to antidepressant medications during the 12 months preceding the index date. These cases were subclassified as "occasionally" exposed if at least one antidepressant prescription was filled during the pre-index year (n=3,328; 6.9%), and as "chronically" exposed if three or more prescriptions were filled (n=1,632; 3.4%). The depressed patients were slightly older (median age, 79 years) than the nondepressed patients (78 years), and they were more likely to be female (68% vs. 58%). Patients were followed for up to one year or until the occurrence of all-cause mortality, nonfatal cardiovascular events, hospitalization for HF, or hospitalization for any reason. The effects of depression on these outcomes were analyzed in Cox regression models, adjusting for age, sex, and medical comorbidities, as well as an antidepressant treatment propensity score in order to reduce the potential for residual confounding. Depression was associated with a higher risk of all-cause mortality (HR, 1.20; 95% C.I., 1.08 to 1.33; p=.0006) and a composite cardiovascular endpoint including myocardial infarction, stroke, and transient ischemic attack (HR, 1.23; 95% C.I., 1.13 to 1.34; p<.0001). Depression did not predict higher rates of rehospitalization for HF or for any cause. Despite its large size, these findings must be interpreted with caution because utilization of antidepressants is only a proxy for depression, and it misclassifies patients who are depressed but not on an antidepressant. Nevertheless, the study provides additional support for the adverse prognostic effect of depression in patients with heart failure.

Albert and colleagues[1] conducted a 60–90 day follow-up of a sample of 5,791 elderly patients (mean age, 73 ± 14 years) from among 48,612 participants in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry. Approximately 14% of the sample were classified as depressed on the basis of hospital records. Sixty percent of the depressed patients were women, compared to 51% of the nondepressed patients. Depression predicted all-cause mortality in both unadjusted (HR, 1.36; 95% C.I., 1.04 to 1.79; p=.03) and adjusted models (HR, 1.46; 95% C.I., 1.05 to 2.03; p=.03).

Using data from the Coordinating study evaluating Outcomes of Advising and Counseling in HF patients (COACH) multicenter randomized trial in the Netherlands, Lesman-Leegte and colleagues[30] studied 958 patients in NYHA class II-IV heart failure (37% women, age 71 ± 11 years, 51% in class II HF and 49% in class III or IV) who completed the CES-D depression questionnaire at baseline. Based on a CES-D score of 16 or higher, 377 (39%) of the patients had depression, and 200 (21%) were classified as having severe depression based on a CES-D score of 24 or higher. The patients were followed for 18 months, during which time 40% of the patients reached the primary composite endpoint of HF readmission or death; 26% survived the follow-up but with at least one HF readmission, and 27% of the patients died.

In a univariate analysis, depression predicted the primary composite endpoint (HR per 10-point increase on the CES-D, 1.10; 95% C.I., 1.01 to 1.20; p=.04), and this remained significant after multivariable adjustment for age, sex, and BNP (HR, 1.13; 95% C.I., 1.02 to 1.26; p=.02). In secondary analyses, depression also predicted HF readmission (adjusted HR, 1.17; 95% C.I., 1.02 to 1.33; p=.02) and mortality (adjusted HR, 1.17; 95% C.I., 1.03 to 1.34; p=.02). Post hoc analyses suggested that the risk of HF readmission or death increases in linear fashion along with the severity of depression.

Finally, Frasure-Smith and colleagues[13] recently published the first study of the prognostic importance of depression in patients with both HF and atrial fibrilliation (AF). Their sample consisted of 974 participants (18% women, age 66 ± 11 years) in the AF-CHF trial, which

compared rate-control vs. rhythm control strategies for AF. Three-hundred twelve (32%) of the participants were classified as depressed on the basis of a BDI-II score of 14 or higher. The participants were followed for a mean of 39 ± 18 months, during which time there were 302 all-cause deaths. Of these, 246 were judged to be cardiovascular deaths, and 111 of those were presumed to be arrhythmic. The dichotomous BDI-II classification predicted cardiovascular deaths in both an unadjusted model (HR, 1.59; 95% C.I., 1.24 to 2.05; p<. 001) and in a model adjusted for demographic and medical covariates (HR, 1.57; 95% C.I., 1.20 to 2.07; p=.001). It was an even stronger predictor of arrhythmic deaths (univariate HR, 1.82; 95% C.I., 1.25 to 2.65; p=.002; adjusted HR, 1.69; 95% C.I., 1.13 to 2.53; p=.01) The continuous BDI-II scores were also significant predictors of these outcomes, and both the dichotomous and continuous BDI-II scores predicted all-cause mortality as well. Furthermore, a secondary analysis suggested that patients who are both depressed and unmarried may comprise a group at especially high risk of cardiovascular mortality.

In addition to the findings summarized above, a number of other studies have also investigated the effect of depression on heart failure outcomes.[e.g., 20;24;36;43;51] Despite many differences among these studies, all of them add to the growing evidence that depression does have independent prognostic value in heart failure.

CAUSAL MODELS AND CANDIDATE MECHANISMS

Numerous studies have investigated biobehavioral mechanisms that may help to explain the well-documented effects of depression on cardiovascular morbidity and mortality in patients with coronary heart disease (CHD).[46] There has been much less research on mechanisms that may account for the adverse prognostic effects of depression in heart failure, but there is substantial overlap between the candidate mechanisms in CHD and CHF.[38]

It must be acknowledged that the search for mechanisms implies that depression is a *causal* risk factor for adverse outcomes in heart failure, not merely a risk marker. However, the causal status of depression in HF is unknown. There have not yet been any well-designed, adequately powered trials to determine whether treating depression can improve medical outcomes in heart failure. It is possible, although unlikely, that when depression is observed in patients with heart failure, it is simply a byproduct of HF (or its treatment) rather than a comorbid condition in its own right. If so, the increased risks associated with depression should be attributed to the depression-inducing aspects of the heart failure rather than to depression per se. As discussed in a previous section, the lifetime courses of heart disease and depression are far too complex and vary too much across individuals to dismiss the latter as a direct consequence of the former. In addition, studies that have examined relationships among depression, heart failure, and outcomes have not provided any compelling evidence that the apparent adverse effects of depression are better explained by associated characteristics of heart failure.[27;28] It is also possible that depression and heart failure could share genetic substrates that could explain why these disorders are so highly coprevalent, but there is as yet little empirical basis for speculation about this.

If depression actually does complicate heart failure in ways that increase the risk of death or other adverse medical outcomes, then both behavioral and biological mechanisms must be considered. In many different patient populations, depression has been identified as a strong predictor of noncompliance with prescribed medications[10], physical inactivity[50], and smoking[17]. In patients with heart failure, depression has been identified as one of the most important barriers to effective HF self-care.[41]

In addition to these behavioral pathways, some of the physiological concomitants of depression might have adverse effects on the course and outcome of HF. For example, depression is associated with sleep apnea syndromes[7] and with low heart rate variability

(HRV)[6], a marker of sympathetic-parasympathetic imbalance that may predispose to arrhythmias and ischemia. Both sleep apnea[37] and low HRV[45] have adverse prognostic implications in HF. Depression may worsen these and other physiological risk markers in heart failure.

IMPLICATIONS FOR RESEARCH AND TREATMENT

It seems clear that depression is an independent risk marker for mortality, hospitalization, and other adverse medical outcomes in heart failure. However, the studies that have been reviewed herein are quite heterogeneous with respect to the composition of the samples, their design and methodological rigor, the methods used to assess depression, the potential confounders for which the models were adjusted, and the duration of follow-up. A systematic review and meta-analysis is needed to evaluate the impact of these factors on the predictive value of depression in patients with heart failure.

Whether depression is a causal risk factor, or merely a risk marker, for mortality and other adverse outcomes in heart failure has not been determined. Research on the mechanistic connections between depression and heart failure outcomes is at a very early stage, and it lags behind similar research on depression in CHD. There have not yet been any large RCTs designed to determine whether treatment of depression can reduce medical morbidity and mortality in heart failure. In fact, there have been very few trials of treatments for comorbid depression per se in heart failure. The largest antidepressant trial to date, SADHART-CHF, recently concluded with no difference in depression outcomes between heart failure patients treated with sertraline compared to patients treated with a placebo.[8]

Our research group recently conducted a randomized, controlled pilot study of cognitive behavior therapy (CBT) for outpatients with heart failure. The results suggested that CBT may be an efficacious treatment for depression in these patients[18], and they were sufficiently promising to warrant replication and extension. In an ongoing randomized trial, we are combining CBT for depression with an intervention to enhance self-care in heart failure. It is possible that this sort of combined approach could affect multiple behavioral and physiological mechanisms, and thereby improve the prognosis of depression patients. Additional research is needed to test other psychotherapeutic interventions, other antidepressant medications, and other intervention strategies such as preference-based, stepped, or collaborative care for comorbid depression in heart failure. Although it is not yet known whether any form of depression treatment can affect cardiac outcomes, major depression deserves clinical attention in patients with heart failure, just as it does in other patient populations.

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