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Depression in Heart Failure

A Meta-Analytic Review of Prevalence, Intervention Effects, and Associations With Clinical Outcomes

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This article describes a meta-analysis of published associations between depression and heart failure (HF) in regard to 3 questions: 1) What is the prevalence of depression among patients with HF? 2) What is the magnitude of the relationship between depression and clinical outcomes in the HF population? 3) What is the evidence for treatment effectiveness in reducing depression in HF patients? Key word searches of the Medline and PsycInfo databases, as well as reference searches in published HF and depression articles, identified 36 publications meeting our criteria. Clinically significant depression was present in 21.5% of HF patients, and varied by the use of questionnaires versus diagnostic interview (33.6% and 19.3%, respectively) and New York Heart Association–defined HF severity (11% in class I vs. 42% in class IV), among other factors. Combined results suggested higher rates of death and secondary events (risk ratio = 2.1, 95% confidence interval 1.7 to 2.6), trends toward increased health care use, and higher rates of hospitalization and emergency room visits among depressed patients. Treatment studies generally relied on small samples, but also suggested depression symptom reductions from a variety of interventions. In sum, clinically significant depression is present in at least 1 in 5 patients with HF; however, depression rates can be much higher among patients screened with questionnaires or with more advanced HF. The relationship between depression and poorer HF outcomes is consistent and strong across multiple end points. These findings reinforce the importance of psychosocial research in HF populations and identify a number of areas for future study. (J Am Coll Cardiol 2006;48: 1527–37) © 2006 by the American College of Cardiology Foundation

Over the past 2 decades, associations between clinical depression and cardiovascular disease risk have become an increasingly common, if not always consistent, finding in the cardiovascular literature (1–4). Meta-analytic reviews of the depression relationship with heart disease outcomes provide strong evidence for prospective connections between depression and the incidence of coronary artery disease (CAD) (5,6), between depression and premature mortality among patients with documented CAD (7,8), and between depression and all-cause mortality in populations with and without CAD (9). However, despite these associations, there has yet to be a successful randomized intervention trial for depression affecting objective clinical outcomes (10), raising important questions about the biological role of depression in CAD.

The surge of research interest in depression and CAD has carried over into related cardiovascular diseases. Heart failure (HF), a condition affecting nearly 5 million patients in the U.S. alone, has become a major focus of depression research in recent years, with a growing number of publications suggesting poorer clinical outcomes for HF patients reporting symptoms of depression (11–14). Research interest in the psychosocial dimensions of HF is reinforced by the enormous health care costs associated with the condition (15,16), as well as by the high rates of clinical depression reported among patients with HF in numerous studies (17,18).

Although recent literature reviews of depression and HF identify important themes (19,20), quantitative methods are necessary to precisely define the magnitude of the relationship between clinical depression and HF. To our knowledge, this article is the first meta-analytic review of depression and HF. The focus was guided by 3 primary questions: 1) What is the prevalence of clinically significant depression in HF? To what extent is the heterogeneity in reported prevalence estimates explained by differences in depression assessment methods, HF severity, age, gender composition, or other demographic characteristics? 2) What is the evidence for longitudinal associations between depression and objective clinical outcomes in HF, including HF incidence, mortality and cardiovascular events, and hospitalization? 3) What are the effects of pharmacologic and nonpharmacologic interventional efforts on depression among patients with HF?

METHODS

Article selection and literature search. Using the Medline and PsycInfo databases, two of the authors (V.R. and S.L.) independently identified relevant articles published in peer-reviewed journals by September 12, 2005. Primary key words included depression and HF, congestive heart failure, depressive disorder, depressive symptoms, quality of life,

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Abbreviations and Acronyms

BDI = Beck Depression Inventory
CAD = coronary artery disease
HF = heart failure
IL = interleukin
NYHA = New York Heart Association

psychosocial factors, stress, cardiomyopathy, emotional factors, psychological distress, and mental health. Subsequently, these abstracts were reviewed for inclusion based on assessments of the published article. We identified additional eligible articles using references from the articles collected through the database search. Criteria for selection included the following: 1) reporting a rate of depression using either clinical interview or a validated questionnaire; 2) describing prospective relationships between depression and mortality, secondary cardiovascular events, rehospitalization, or health care costs; and 3) documenting changes in depression, measured before and after treatment, attributed to an intervention. In cases in which articles contained insufficient statistics, we attempted to contact the study's primary investigators to provide additional information. All studies required the use of a sample composed exclusively of patients diagnosed with HF, or the reporting of statistics specifically for a patient subgroup with HF. Using the aforementioned methods, we identified a total of 36 independent articles. These include 27 articles reporting depression prevalence information, 14 describing prospective associations between depression and HF outcomes, and 6 reporting depression changes from treatment (some contained multiple association types, accounting for the nonadditive article total).

Depression measures. Depression diagnostic methods fell into 3 primary categories: 1) clinical interviews, including the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (21), Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Nonpatient Edition (22), Diagnostic Interview Schedule for Depression (23), Modified Diagnostic Interview Schedule for Depression (24), Composite International Diagnostic Interview Short Form (25), and Primary Care Evaluation of Mental Disorders (26); 2) depression symptom inventories, including the Beck Depression Inventory (BDI) (27), Zung Self-Rating Depression Scale (28), Geriatric Depression Scale (29), Center for Epidemiological Studies–Depression scale (30), Hospital Anxiety and Depression Scale (31), Inventory to Diagnose Depression (32), Hamilton Rating Scale for Depression (33), the depression scale from the Hopkins Symptom Checklist (34), Medical Outcomes Study–Depression (35), and the Multiple Affect Adjective Checklist (36); and 3) a diagnosis of depression based on the patient's medical record (e.g., International Classification of Diseases, 9th Edition code) or use of antidepressant medication.

In several cases, investigators used more than 1 of the previously mentioned criteria. For example, a number of articles used questionnaires as screening tools, and higher-scoring patients were subsequently interviewed for evidence of a major depressive disorder.

Database construction and coding. Because of the relative independence of our review questions, we developed separate databases for the prevalence, clinical outcome, and treatment effects themes. Some studies contributed to more than 1 database (e.g., by reporting baseline depression prevalence in addition to a prospective or intervention component).

From studies describing depression prevalence, we coded depression rates by HF severity, gender, minority status, study location, depression assessment method, mean age, and inpatient/outpatient status, as available. Several studies included sample information regarding HF subtypes (e.g., ischemic vs. nonischemic HF), however, there were not sufficient data from which to make depression comparisons across different forms of HF. The coding scheme defined depression assessment methods according to the use of questionnaires, clinical interviews, or patient medical records/patient use of antidepressants. We also categorized prevalence rates from individual studies as either "conservative" or "liberal" depending on the rigor of their criteria for classifying participants as depressed. To qualify as conservative, a prevalence rate had to meet one or more of the following criteria: included an interview component, examined patients' medical records for evidence of a formal diagnosis of depression, or used a questionnaire with a cutoff that explicitly screened for moderate to severe depression (representative of a DSM diagnosis) as opposed to mild depression or depressive symptoms. An example of a conservative versus a liberal cutoff is a score of 17 versus 10 on the BDI. All other rates were classified as liberal: most of them were determined from using a lower cutoff on a validated questionnaire, whereas 1 rate (15) was based on evidence of an antidepressant prescription without an accompanying diagnosis of depression in the patients' medical records, and therefore, could have included patients taking antidepressants for other reasons (e.g., sleep or smoking cessation). Studies that used 2 cutoffs (1 conservative and 1 liberal) and reported separate rates for each were represented in both categories.

The categorization of treatment studies included sorting by intervention type and study duration. Because of the small number of available treatment studies, we did not exclude studies based on qualitative factors. All of the identified treatment studies assessed depressive symptoms via questionnaires before and after treatment; treatment effects were determined, in part, by comparing changes in scores between these 2 time periods.

From the longitudinal outcome studies, we categorized studies by duration, study method, level of covariate adjustment, and type of clinical outcome, among other variables. Clinical outcomes included HF incidence, health care costs

associated with HF, hospitalization, and combined clinical outcomes in the form of death and secondary events. As with the prevalence articles, the sorting of depression assessment methods used categories reflecting the use of questionnaires, diagnostic interviews, or patient medical records. The coding of all articles included demographic information (i.e., gender, age, and minority composition), sample size, inpatient and outpatient sample type, and study location (e.g., U.S., Europe).

Quantitative methods. The software SPSS, version 11.5 (SPSS Inc., Chicago, Illinois), and Comprehensive MetaAnalysis, Version 2 (BioStat Software, Engelwood, New Jersey), served as the statistical platforms for completing all statistical tests and associated graphic results. For the summation of the prevalence findings, we computed prevalence point estimates and 95% confidence intervals using the formulas Logit Event Rate = Log [Event Rate / (1 − Event Rate)], Logit Event Rate SE = $\sqrt{1/(\text{Event Rate} \times \text{Num Tot}) + 1 / [(1 - \text{Event Rate}) \times \text{Num Tot}]}$, and 95% confidence intervals as Lower Limit = Logit Event Rate − (1.96 × Logit Event Rate SE) and Upper Limit = Logit Event Rate + (1.96 × Logit Event Rate SE). To standardize results for meta-analytic summary in the clinical outcomes articles, we converted reported odds ratios into risk ratio values using the formula: risk ratio = odds ratio/([1 − P_0] + [1 × P_0]), where P_0 represents the incidence of the outcome in the nonexposed (nondepressed) group (37).

We centered the display of prevalence estimates around a point of 0.50 to provide a reference standard for purposes of illustration. In addition to the overall random effects model, sensitivity analyses broke down prevalence results across a number of methodologic factors to assess evidence of moderation. These factors included gender, minority status, depression assessment method, HF severity, and use of inpatient versus outpatient HF patient samples.

The small number of overall treatment studies and the mixed nature of the interventions prohibited the use of meta-analytic tests for this section. Descriptive summaries of the treatment articles divided studies on the basis of using pharmacologic versus nonpharmacologic interventions. We calculated effects sizes for the treatment studies in the form of Cohen d values according to the formula $d = M_1 - M_2/s_{pooled}$. To address the issue of publication bias, a fail-safe N was calculated using the Comprehensive Meta-Analysis software program (BioStat).

Heterogeneity assessments preceded all meta-analytic tests concerning depression prevalence and clinical outcomes. In each case regarding prevalence rate analysis, there was significant heterogeneity, hence we calculated results using a random effects model and reported corresponding p values and I^2 values. Clinical outcome article categories included HF incidence, health care use and hospitalization, and mortality and clinical events. The number of mortality-specific findings was insufficient to assess this outcome independently. Log-transformed risk ratios and 95% confidence intervals were calculated for each study using the reported effect size and estimates of the standard error of each effect drawn from data reported in the article. When articles reported multiple models, we selected the model with the highest level of covariate adjustment. In cases in which parallel models from different time points were available, we used the model with the longest time estimate, except in cases in which we extracted both short-term and longer-term model results for comparisons as described.

RESULTS

Prevalence. Figure 1 shows the prevalence rates of clinically significant depression among HF patients reported for each of the 27 studies and an aggregated estimate of approximately 21.5%, determined using meta-analytic tests (previously described). The failsafe N statistic indicated that an additional 8,680 missing studies were required to bring the p value from 0.00 to 0.05. The prevalence rates reported across these studies varied widely, ranging from 9% (38) to 60% (39).

Sixteen of the 27 studies included sufficient data regarding gender to analyze prevalence rates of depression in male and female HF patients (12,15,17,18,38–60). The aggregated prevalence rate for women was higher than that for men, with point estimates of 32.7% ($p < 0.000$; $I^2 = 89.2\%$) and 26.1% ($p < 0.000$; $I^2 = 94.4\%$), respectively. Reported ranges again varied widely, with a range of 11% (40) to 67% (41) for women and 7% (15) to 63% (42) for men.

Ten of the 27 studies provided prevalence rates of depression among HF patients broken down by race or ethnicity. The range of minority prevalence rates was 7% to 44% with an aggregated estimate of 18.7% ($p < 0.000$; $I^2 = 85.2\%$). In comparison, Caucasian HF patients within the same 10 studies had a depression prevalence range of 9% to 54% with an aggregated estimate of 25.3% ($p < 0.000$; $I^2 = 91.2\%$). Thus, there was some evidence of depression differences between minority and nonminority ethnic groups. Minority groups included within these 9 studies were African Americans, Afro-Caribbeans, Asians, Native Americans, and Pacific Islanders. An attempt to break these data down further for analysis by ethnicity was not feasible because of the heterogeneity of groups and small sample sizes.

An analysis of the reported prevalence rates of depression in HF patients based on 5 studies that presented sufficient data for analysis by New York Heart Association (NYHA) functional class showed an aggregated estimate of 27.8% ($p < 0.001$; $I^2 = 92.1\%$) and higher prevalence rates associated with higher NYHA functional class (Table 1). Although the differences between prevalence rates for patients within classes I or II and classes III or IV are similar, the rate of depression in patients with class III HF was nearly double that of patients with class II HF. We further

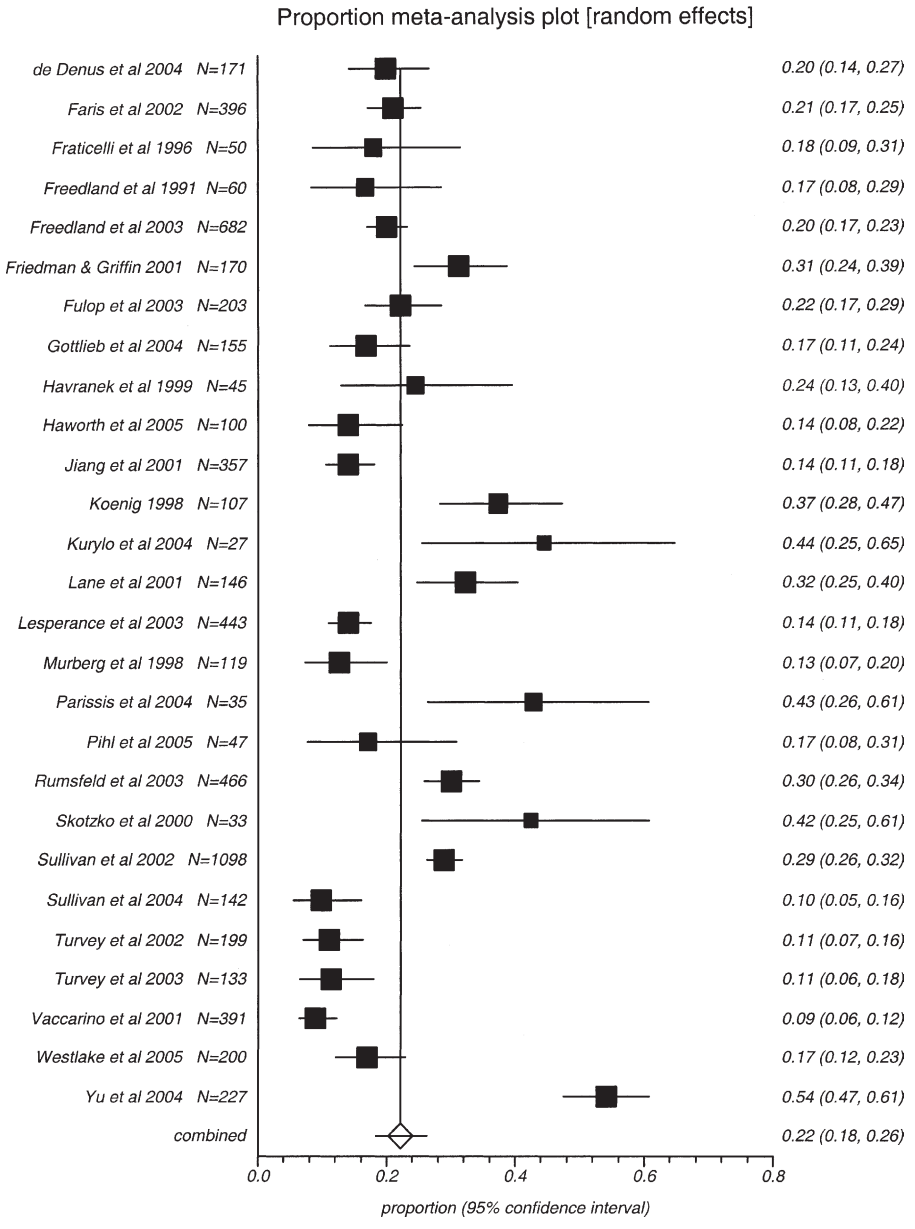

Figure 1. Prevalence of depression in heart failure patients, and 95% confidence intervals (27 studies).

observed a nearly 4-fold increase in depression rates between patients with class I and class IV HF. The depression and HF class relationship may further be affected by age, as shown by Freedland et al. (17), with younger patients (<60 years) being more vulnerable to depression.

Table 1. Depression Prevalence Reported by NYHA Functional Class in Patients With HF

NYHA Functional Class	n*	Depression Rate
I	222	0.11
II	774	0.20
III	638	0.38
IV	155	0.42

*Estimates compiled from 5 studies reporting depression rates among specific NYHA functional classes of HF patients.
HF = heart failure; NYHA = New York Heart Association.

Prevalence rates by the type of assessment measure used ranged from 10% to 54%. The method of assessment was then dichotomized into "questionnaires" or "interview included." Compared with the aggregate depression rate of approximately 22%, prevalence estimates for patients assessed solely with questionnaires versus those whose assessment included an interview were 33.6% (heterogeneity $p < 0.001$, $I^2 = 90.3\%$) and 19.3% ($p < 0.001$, $I^2 = 94.1\%$), respectively. Depression was assessed with both a self-report questionnaire and an interview component in 9 of the 26 studies, solely an interview in 2 of the 26 studies; the combined prevalence rate reported in these studies was approximately 17.7%, nearly 25% less than the overall aggregate rate. The remaining studies used self-report questionnaires alone to assess depression and reported prevalence rates ranging from 30% to 44%. When

Table 2. Depression Rates Among Heart Failure Patients by Inpatient/Outpatient Status and Diagnostic Threshold

Depression Prevalence Rates Among Patient Classifications Using Conservative Cutoffs*			Depression Prevalence Rates Among Patient Classifications Using Liberal Cutoffs*		
Patient Classification	Prevalence Rate (SD)	Number of Studies, (Patients)	Patient Classification	Prevalence Rate (SD)	Number of Studies, (Patients)
Inpatient	0.16 (0.09)	8 (2,921)	Inpatient	0.38 (0.13)	7 (2,667)
Outpatient	0.14 (0.02)	8 (1,095)	Outpatient	0.38 (0.11)	11 (1,036)
Combined	0.14 (0.06)	3 (1,037)	Combined	0.32 (0.06)	5 (1,673)

*Conservative depression definitions included protocols with a structured interview, diagnosis by an MD or PhD mental health professional, or use of a stringent questionnaire cutoff in the case of measures with multiple cutoff points.

the studies that used the same depression measure were combined and compared with each other, the rates differed.

The overall weighted conservative prevalence depression rate mean (based on 9 studies with 5,053 participants) was 20.3% ($p < 0.000$; $I^2 = 86.7\%$), whereas the overall weighted liberal prevalence depression rate mean (based on 13 studies with 5,376 participants) was 35.5% ($p < 0.000$; $I^2 = 95.5\%$).

The data were also analyzed for differences in depression prevalence rates among inpatient and outpatient HF patients. Five of the 27 studies included for prevalence data were designed to measure participants' depression levels over time and hence captured data while participants were both inpatients and outpatients; thus, these studies were coded as "combined" for this portion of the analysis. Of the 22 studies with participants who were not considered combined, 10 fell into the inpatient category and 12 fell into the outpatient category.

Although overall results suggested no important differences between inpatient and outpatient samples, we were concerned about the risk of measurement bias such that outpatients may have been more likely to be assessed with questionnaires. As shown in Table 2, we addressed this concern formally by examining 14 studies that reported depression rates using either a conservative cutoff, a liberal cutoff (e.g., 17 vs. 10 on the BDI), or both. Even broken down by depression assessment method, rates of depression remained similar for inpatient and outpatient samples.

Analyses based on geographic location showed nearly identical point estimates of prevalence of depression rates in HF patients in the U.S. and Canada (20.3%) and Europe (21%).

Clinical outcomes. Table 3 provides a description of the 14 prospective investigations reporting associations between depression and HF-related events (11–15,38,44,48–50,58,60–63). The studies included a range of depression assessment tools, protocol lengths, and sample sizes. Women composed a significant percentage of most study samples. Outcome categories included: 1) the relationship between depression and HF incidence in a healthy or at-risk sample; 2) depression effects among HF patient samples on measures of health care cost or health care system use; and 3) the impact of depression on mortality and/or secondary events not including hospitalization.

HF incidence. Two studies reported data concerning depression and HF development. Covariate adjusted hazard ratios (including age and disease severity) were 1.5 and 2.6 in these studies, which followed up participants for 4.5 and 14 years, respectively. The stronger relationship between depression and HF incidence was noted in the protocol enrolling "high risk" patients with systolic hypertension (61).

Table 3. A Description of HF Studies Reporting Relationships Between Depression and Clinical Outcomes

Study	Depression Measure	Duration	Sample Size	% Women	Outcome(s)
Abramson et al. (61)	CES-D	4.5 yrs	4,538	57	Incident HF
Williams et al. (44)	CES-D	14 yrs	2,501	58	Incident HF
Himelhoch et al. (62)	Medical records	1 yr	139,089	NA	Health service use, hospitalization
Sullivan et al. (15)	Medical records	3 yrs	1,098	53	Health care costs, clinical events
Fulop et al. (58)	SCID interview	6 months	203	53	Hospitalization
Koenig et al. (48)	DIS interview	1 yr	107	52	Hospitalization
Rumsfeld et al. (14)	MOS-D	6 weeks	466	24	Hospitalization
De Denus et al. (49)	Medical records	7.5 months	171	36	Clinical events
Faris et al. (50)	Medical records	4 yrs	396	26	Hospitalization, clinical events
Freedland et al. (60)	DIS interview	1 yr	60	57	Hospitalization, mortality
Jiang et al. (12)	DIS interview	1 yr	357	36	Hospitalization, clinical events
Junger et al. (13)	HADS-D	24 months	209	28	Clinical events
Murberg et al. (63)	Zung	2 yrs	119	29	Clinical events
Sullivan et al. (11)	PRIME-MD interview	3 yrs	142	23	Clinical events
Vaccarino et al. (38)	Geriatric depression	6 months	391	49	Clinical events

CES-D = Center for Epidemiological Studies–Depression; DIS = Diagnostic Interview Schedule; HADS-D = Hospital Anxiety and Depression Scale; HF = heart failure; MOS-D = Medical Outcomes Study–Depression; NA = not available; PRIME-MD = Primary Care Evaluation of Mental Disorders; SCID = Structured Clinical Interview for DSM-IV.

Health care use and hospitalization. A total of 7 studies reported information concerning relative rates of health care use among HF patients with lower versus higher levels of depression, including 6 studies comparing rates of rehospitalization. Despite the wide range of use variables, the data indicate a consistent pattern of increased health care usage for patients with depression. These end points included a more than 2-fold risk of emergency room visits for depressed versus nondepressed patients (62); a 29% increase in total health care costs (aggregated from separate measures of mental health visits, and inpatient and outpatient treatments) for patients with a depression diagnosis or receiving treatment for depression versus those without depression (11); and increases in both short-term (4-week) and longer-term (6-month) medical encounters (58).

Among studies reporting hospitalization comparisons, protocol lengths varied from 6 weeks to more than 4 years. Protocol length influenced the relationship between depression severity and rehospitalization rates. Briefer studies typically suggested no or small differences during the initial months after discharge (60), compared with more substantial differences appearing by 1 year of follow-up. The study by Koenig (48) provides an illustration of this theme. Among 39 HF patients with high scores on the Center for Epidemiologic Studies–Depression scale, inpatient readmission rates were 31.6%, 54.8%, 40.7%, and 25% at 3, 6, 9, and 12 months, respectively. Rates over the same intervals among 45 nondepressed patients in this sample were 35.7%, 27.8%, 17.7%, and 16.1%.

Mortality and associated clinical events. Eight independent cohort studies, ranging in length from 6 months to more than 4 years, tracked the incidence of mortality and associated cardiac events (e.g., heart transplantation, new cardiac events) in association with depression. Figure 2 illustrates the range of effects from these studies.

Study protocols included a variety of definitions of depression, including elevated questionnaire scores, diagnoses based on information in the patients' medical records, and the administration of a diagnostic interview. The number of studies including an interview-based diagnosis was insufficient to make comparisons between depression symptoms and mood disorders in the prediction of clinical outcomes.

The aggregated risk estimate from the 8 studies suggested a greater than 2-fold risk of death and associated clinical events for HF patients with heightened depressive symptoms or a depressive disorder (relative risk = 2.1, 95% confidence interval 1.7 to 2.6). Despite the variation across studies noted above, this estimation is based on homogenous results (heterogeneity $p = 0.87$; $I^2 = 0\%$). Overall, the combined evidence did not indicate that the relationship between depression and HF outcomes differed by length of follow-up, however, the results of individual studies suggest that this is an area requiring additional study. Junger et al. (13) reported depression and mortality associations by 6-month intervals across 30 months of follow-up, indicating a strong, graded relationship over time. In contrast, differences in death rates between depressed and nondepressed HF patients were stable across 1-, 2-, and 3-year estimates in a separate protocol (50). Few if any of the studies to date included samples sizes that were adequately powered to detect differences in short-term mortality and clinical event rates.

Treatment effects. Table 4 summarizes the methodologic characteristics and intervention outcomes for the 6 articles included as treatment studies (56,64–68). Each study comprised a pre-post design using HF patients among whom depression severity was assessed using a validated questionnaire to gauge treatment effectiveness. Two studies also

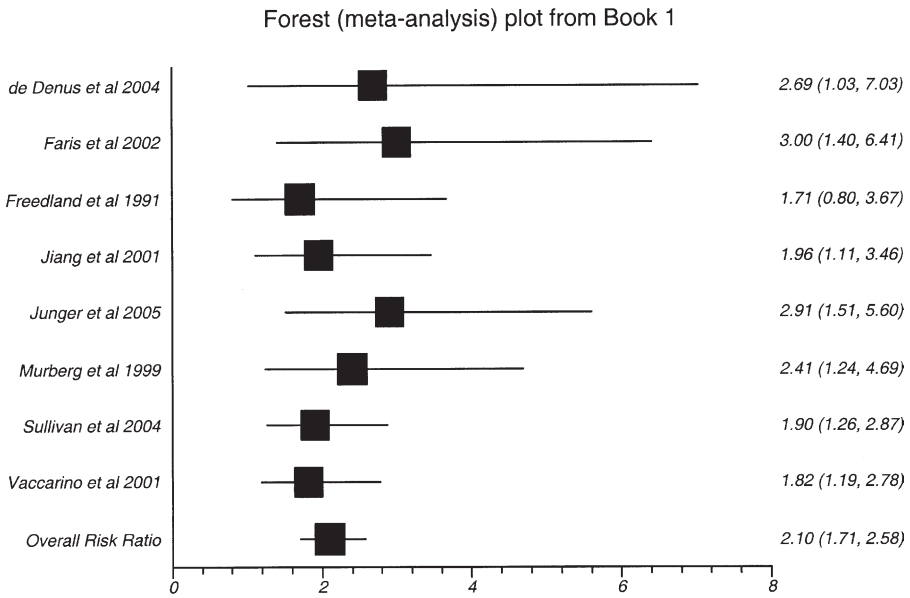

Figure 2. Effect sizes and 95% confidence intervals among studies reporting associations between depression and mortality and secondary events (8 studies).

Table 4. A Summary of HF Intervention Studies Describing Changes in Depression Severity

Authors	n (Women)	Mean Age, yrs (SD)	Intervention	Duration	Depression Measure	Outcomes
Corvera-Tindel et al. (64)	39 (NA)	63.2 (10.1)	Home walking exercise program	12 weeks	Multiple Affect Adjective Checklist (MAACL)	MAACL compliant vs. non-compliant completers: d = −0.21 MAACL compliant completers vs. drop-outs: d = 0.14
Kostis et al. (65)	20 (6)	65.7 (6.1)	Combined exercise, dietary control, & group CBT vs. digoxin vs. placebo	12 weeks	Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS)	Mean depression change (combined BDI & HDRS) Nonpharmacologic tx: d = −0.64 Digoxin tx: d = 0.35 Placebo: d = 0.35
Lader et al. (66)	589 (156)	64.6 (11.7)	Digoxin vs. placebo	4 and 12 months	Center for Epidemiologic Studies–Depression Scale (CES-D)	Depression score change nonsignificant, same in both groups: 8 to 7 Digoxin 6 MWT: d = 0.16 Placebo 6 MWT: d = 0.14
Lesperance et al. (56)	28 (8)	59.6 (NA)	Nefazodone	12 weeks	BDI or PRIME-MD & SCID & HDRS	HDRS change: d = −2.20 BDI change: d = −1.54
Luskin et al. (67)	33 (20)	66 (9)	Group stress management training vs. control	10 weeks	Geriatric Depression Scale (GDS)	Tx GDS change: d = −0.16 Control GDS change: d = 0.03 Tx 6 MWT change: d = 0.12 Control 6 MWT change: d = −0.02
Radzewitz et al. (68)	88 (21)	65.8 (8.2)	Muscle strength and bicycle ergometer training; 6-min walk	4 weeks	Hospital Anxiety & Depression Scale–Depression (HADS)	HADS-D change: d = −0.13 6 MWT change: d = 0.99

CBT = cognitive behavior therapy; 6 MWT = 6 minute walk test; Tx = treatment group; other abbreviations as in Table 3.

reported patients' results on the 6-min walk test before and after treatment to determine whether objective measures of ability were affected by the intervention. In addition, some of the studies also reported results of other variables on which HF patients experienced changes attributed to the intervention, such as physical abilities (e.g., Vo_{2max}, weight lifted), physiological measurements (e.g., weight, blood pressure, QT intervals), and scores on other questionnaires (e.g., quality of life, anxiety).

The treatment studies generally suffered from 1 or more methodologic flaws, including small samples, brief treatment durations, and a lack of a placebo or control group comparison. The mean decrease in depression scores, expressed in Cohen *d* units, was 0.42, translating to just over 40% of a standard deviation difference between groups. However, this result was skewed by large depression symptom reductions observed in 1 study (56). The median Cohen *d* value across all studies was 0.16 (i.e., 16% of a standard deviation difference between treated and untreated groups, a modest difference by most standards). Assessing depression symptom reductions separately for studies that used a nonpharmacologic intervention yielded a mean Cohen *d* value of 0.29 in depression reduction.

DISCUSSION

This meta-analysis provides evidence supporting a moderate to high prevalence of depression among patients with HF, an increased risk of mortality and clinical events among HF patients with depressive symptoms, and reductions in depressive symptoms resulting from a variety of treatment interventions. The relationship between depression and HF is a relatively new but rapidly expanding area of interest in cardiology research. In fact, very few articles were published on this topic before 1990, but the key word searches used identified more than 100 articles published on the topics of depression and other psychosocial factors in HF patients since that time. This increase in research attention coincides with the growth in HF as a health care problem in the U.S. During the past 10 years, HF was the fastest growing form of cardiovascular disease, and accounted for more than 1 million annual hospital admissions and an estimated $60 billion in annual health care expenses (69). Because patients with HF face high rates of debilitation and mortality, the study of depression characteristics in this population is a critical research area in the pursuit of improved quantity and quality of their lives. Abundant evidence suggests that depression is under-recognized and undertreated in cardiac populations (3,10,70); this review begins to address some of the consequences of this treatment milieu.

Depression prevalence in HF. The overall aggregated point estimate prevalence rate calculated in this study (21.6%) indicates that HF patients experience clinically significant depression at a rate similar to the 15% to 20% levels cited for CAD patients (71,72), and at 2 to 3 times the rate of the general population (73). Considering the

typically worse prognosis for individuals with HF as opposed to CAD or myocardial infarction, this rate of depression may seem modest. However, this combined depression estimate is much lower than that suggested in a number of HF studies (48), a discrepancy that seems from this review to be a result of defining depression on the basis of elevated symptom severity from questionnaires rather than a diagnostic interview. Individual study prevalence estimates ranged from 9% to 60%, suggesting a considerable degree of heterogeneity.

Explaining the heterogeneity of reported depression rates was a secondary goal of this review. The moderators explored in association with depression prevalence included depression assessment method, conservative versus liberal cutoff used to classify depression's presence, inpatient versus outpatient samples, HF severity, ethnicity, age, and gender. From these analyses, depression assessment methods (i.e., questionnaire versus diagnostic interview) and the liberality of their cutoffs as well as HF severity seem to have the largest impact on reported depression rates. With one exception (17), differences in depression and HF severity based on patient age were not reported in a form that could provide an effective assessment of this relationship. Mean ages between study samples were likewise too similar to identify age-related trends. Depression rates may also differ according to HF characteristics that affect symptom severity or degree of disability (e.g., systolic vs. diastolic HF, or HF with preserved vs. depressed ejection fraction). At present, we have almost no information concerning depression differences across subclasses of HF patients. Although interactions among the above moderator factors are potentially very interesting for understanding depression prevalence in HF and could be approached using multilevel modeling methods (74), we were not able to address these questions systematically because of inconsistent reporting of the moderator factors across studies.

Awareness of which demographic characteristics and/or methods of assessment are likely to result in a higher or lower detection rate of depression may help researchers and clinicians alike. For example, researchers examining this relationship could design their studies with greater precision to answer their specific research questions. Likewise, clinicians (e.g., primary care physicians, cardiologists, psychiatrists, and psychologists) would be equipped with the knowledge of the idiosyncrasies associated with the identification of major depression versus depressive symptoms among their patients; hence, clinicians could assess their patients with different criteria depending on the severity of depression they intend to identify and attempt to treat. Numerous studies from the depression and CAD literature indicate that depression severity is linearly associated with clinical outcomes (3–5), suggesting that the presence of a major depressive episode is not necessary as a standard for intervening. No single method or cutoff is necessarily the best; rather, each is different and should be used with appreciation of its implications and limitations.

Depression and clinical outcomes. Across a range of mortality, health care use, and associated clinical event outcomes investigated in the prospective studies of depression and HF, aggregate results indicated a substantially worse prognosis for HF patients with more severe depressive symptoms. Nearly all of the clinic outcome studies of depression adjusted for multiple covariates (e.g., age, NYHA functional class, ejection fraction), suggesting that depression effects are reasonably robust to demographic and disease severity characteristics. Although these findings are consistent with depression effects on mortality in cardiac disease patients described in recent reviews (7,8), the mortality results were further reinforced by equally large differences in hospital readmission and health care use by depressed versus nondepressed HF patients. This pattern suggests that any interventional efforts targeting depression in HF should consider a broad category of clinical outcomes to accurately assess potential benefits. Importantly, the increased event risk associated with depression within the HF population has only been examined in studies with relatively small sample sizes, many of which were marginally powered to detect clinically significant effects, particularly over shorter time intervals. We can likewise only speculate at this stage regarding differences in the depression and HF outcomes relationship based on factors such as NYHA class, treatment adherence, or age. Thus, although this meta-analysis was able to quantify a more precise magnitude of the increased risk of clinical events among depressed patients, a clear need for additional research remains.

Unfortunately, outcome variables of interest such as HF incidence and health care costs did not lend themselves to meta-analytic procedures because of an insufficient number of studies. The data from existing studies are suggestive of a higher risk of HF development among those with more severe depressive symptoms, as well as higher costs resulting from an increased use of health care services. We hope that drawing attention to the current paucity of data regarding these topics will provide direction to researchers working in this area. Finally, in the context of prospective studies, almost no information concerning changes in depression over time is available. Because individuals' depression symptoms are likely to change over time, depression should ideally be assessed at multiple intervals throughout studies' durations to understand possible biobehavioral pathways linking depression with HF events (75,76). Heart failure and depression share several biological mechanisms. Heart failure (75–77) and depression (78–81) are associated with sympathetic activation and elevated proinflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor alpha, and IL-1β. The additive effects of the inflammation found in depression likely adversely affect the heart (82–84). Exercise programs reduce IL-6 and tumor necrosis factor alpha levels in HF (85,86). Pharmacologic and exercise treatments for depression reduce depressive symptoms and might reduce accompanying inflammation (87–89), potentially producing more favorable HF-related clinical out-

comes in the patients. At the very least, reducing symptoms of depression could be expected to improve adherence to HF treatment regimens (90,91).

Depression treatment studies among HF patients. Finally, the treatment/intervention section proved to be the most difficult to quantify because of the following factors: small number of identified studies documenting changes in pretreatment versus posttreatment depression severity, brief durations, small sample sizes (many were pilot studies), and substantial heterogeneity in the types of interventions. We were not able to quantify the quality or appropriateness of the interventions for the target patient groups. Some of the pharmacologic interventions used, such as digoxin, do not have specific antidepressant effects, and may underestimate potential treatment benefits achievable via interventions focused more specifically on depression symptoms. Unlike the larger depression and CAD literature (10,92), no study to date has investigated the effects of a depression intervention on objective clinical outcomes such as survival or secondary cardiac events in an HF population. Despite these limitations, a general pattern of decreased depressive symptoms and increased physical abilities (as measured by the standard 6-min walk test) was observed across the treatment studies. Although these preliminary results are promising, the most important aspect of this section is the need for more studies with larger sample sizes, replicable interventions (especially interventions with a behavioral or psychosocial component), and longer durations.

Study limitations. A large number of articles describe psychosocial characteristics other than depression among HF patients. Anxiety, social support and social isolation, and quality of life are each examples of other topics of psychosocial research in the HF literature (93–95) that merit review but that are beyond the scope of this review.

We did not include unpublished articles or articles from non–peer-reviewed journals, which are more likely to contain negative associations (96). Additional articles that contain findings relevant to the areas covered in this article may have been missed because of a mismatch between our key word and abstract searches and the key words in their titles or abstracts. Lastly, the protocol descriptions in a number of studies suggested that additional information that could have been useful in the meta-analytic tests was collected, but we were limited to the data as reported because of incomplete reporting or inability to contact the study investigators.

Summary. We conducted a focused quantitative review of the depression and HF literature concerning questions about depression prevalence, clinical outcomes, and treatment impact. This article is among the first to apply meta-analytic methods to the growing field of depression and HF. Across published studies concerning depression prevalence, associations with clinical outcomes, and changes resulting from treatment interventions, several general conclusions can be drawn: 1) depression is common among patients with HF, with approximately 1 in 5 patients meeting criteria for major depression based on interview methods, and substantially higher rates of clinically significant depression are present among patients assessed with questionnaires (vs. diagnostic interviews) or with more severe HF; 2) rates of mortality, clinical events, rehospitalization, and general health care use are markedly higher among HF patients reporting more severe depression; and 3) studies describing depression treatments among HF patients are too small and heterogeneous to permit definitive conclusions regarding intervention effectiveness. These results identify areas requiring further development, raise novel questions, and provide information on depression prevalence that can help researchers design studies with appropriate depression measures and adequately powered sample sizes.

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