Background—The increasing prevalence of heart failure (HF) and high associated costs have spurred investigation of factors leading to adverse outcomes in patients with HF. Studies to date report inconsistent evidence on the link between depression and outcomes with only limited data on emergency department and outpatient visits.

Methods and Results—Olmsted, Dodge, and Fillmore county, Minnesota residents with HF were prospectively recruited between October 2007 and December 2010 and completed a 1-time 9-item Patient Health Questionnaire for depression categorized as: none to minimal (Patient Health Questionnaire score, 0–4), mild (5–9), or moderate to severe (≥10). Andersen-Gill models were used to determine whether depression predicted hospitalizations and emergency department visits, whereas negative binomial regression models explored the association of depression with outpatient visits. Cox proportional hazards regression characterized the relationship between depression and all-cause mortality. Among 402 patients with HF (mean age, 73±13 years; 58% men), 15% had moderate to severe depression, 26% mild, and 59% none to minimal depression. During a mean follow-up of 1.6 years, 781 hospitalizations, 1000 emergency department visits, 15,515 outpatient visits, and 74 deaths occurred. After adjustment, moderate to severe depression was associated with nearly a 2-fold increased risk of hospitalization (hazard ratio, 1.79; 95% confidence interval, 1.30–2.47) and emergency department visits (hazard ratio, 1.83; 95% confidence interval, 1.34–2.50), a modest increase in outpatient visits (rate ratio, 1.20; 95% confidence interval, 1.00–1.45), and a 4-fold increase in all-cause mortality (hazard ratio, 4.06; 95% confidence interval, 2.35–7.01).

Conclusions—In this prospective cohort study, depression independently predicted an increase in the use of healthcare resources and mortality. Greater recognition and management of depression in HF may optimize clinical outcomes and resource utilization. (Circ Heart Fail. 2013;6:387-394.)

Key Words: cardiovascular outcomes • depression • healthcare utilization • heart failure • psychosocial factors

Heart failure (HF) affects ≈6 million Americans and remains the most common cause of hospitalization in the Medicare population, with readmission rates approaching 50% within 6 months after initial hospitalization. As such, HF is one of the most costly healthcare problems in the United States, with estimated direct and indirect costs of $39.2 billion in 2010, an increase of 163% compared with 2000. These costs continue to rise with the aging population and improvements in survival after cardiovascular events.

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Due to its high prevalence, associated costs, and relatively poor prognosis, factors contributing to adverse outcomes in HF are targets of investigation. Among such factors, depression has been given special attention, as it is often underdiagnosed and potentially modifiable. Although depression rates are consistently higher in HF than the general population, estimated at 5% to 10%, the exact prevalence and severity of depression in HF varies considerably across studies, ranging from 11% to 25% in outpatients to 35% to 70% among inpatients. These discrepancies leave uncertainties about the importance of depression in HF, from both a clinical and a public health standpoint.

Several studies have reported an increased risk of death and hospitalizations in patients with HF and depressive symptoms, whereas others have failed to identify significant associations with rehospitalizations or mortality. Still others have demonstrated mixed results, with significant associations only in the most severely depressed.

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As most studies have focused on mortality and rehospitalization, the impact of depression on other forms of healthcare utilization, such as outpatient or emergency department (ED) visits, is unknown. This study was designed to address, in a prospective community-based cohort study, the aforementioned knowledge gaps by examining the prevalence and severity of depression among HF patients, as well as its impact on hospitalizations, ED visits, outpatient visits, and survival.

Methods

Study Setting
This was a prospective cohort study conducted in southeast Minnesota, which constitutes a unique environment because there are a small number of medical providers, including Mayo Clinic, Olmsted Medical Center, and a few private practitioners. Each provider uses comprehensive medical records, which are indexed through the Rochester Epidemiology Project. This record linkage system enables virtually complete capture of outcomes and healthcare utilization in Olmsted County. This system captures outcomes and utilization for non-Olmsted County residents who are seen by an Olmsted County provider, but nonresidents may also seek care in their own counties with providers that do not participate in the Rochester Epidemiology Project. Therefore, capture of utilization for these patients may be less comprehensive than that of Olmsted County residents. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Identification of the Study Cohort
Patients with either incident or prevalent HF during an inpatient or outpatient visit were identified using natural language processing of the electronic medical record, and the diagnoses were manually validated by trained nurse abstractors using the Framingham criteria, as described previously. Participants meeting the following criteria were prospectively recruited between October 2007 and December 2010: (1) aged ≥18 years, (2) residents of Olmsted, Dodge, or Fillmore counties, Minnesota, and (3) completed a 9-item Patient Health Questionnaire (PHQ-9) for depression on study enrollment. Written informed consent was obtained from all participants before enrollment.

Clinical Data Collection
Patient characteristics, including age, sex, education, marital status, current or former cigarette smoking status, and medications at index, were obtained from patient records. Body mass index was calculated from the outpatient weight and height recorded in the medical record closest to study enrollment. Hypertension was defined from outpatient weight and height recorded in the medical record, and the diagnoses were validated by trained nurse abstractors using the Framingham criteria, as described previously. Participants meeting the following criteria were prospectively recruited between October 2007 and December 2010: (1) aged ≥18 years, (2) residents of Olmsted, Dodge, or Fillmore counties, Minnesota, and (3) completed a 9-item Patient Health Questionnaire (PHQ-9) for depression on study enrollment. Written informed consent was obtained from all participants before enrollment.

Depression Measurement
Depression was assessed once using a PHQ-9 administered by a registered nurse during a face-to-face interview conducted during a return visit within 6 weeks of consent. This brief questionnaire has been validated and assessed each of the 9 criteria in the Diagnostic and Statistical Manual of Mental Disorders for clinical depression on a scale from 0 (not at all) to 3 (nearly every day). According to Kroenke et al., PHQ-9 scores of ≥10 were 88% sensitive and 88% specific for detecting major depression, and scores of 5, 10, 15, and 20 corresponded well to mild, moderate, moderately severe, and severe depressive symptoms, respectively, as measured by diagnostic interview. Taking the results of this study into consideration, depressive symptoms were categorized as none to minimal (PHQ-9 score, 0–4), mild (5–9), or moderate to severe (≥10).

Ascertainment of Healthcare Utilization and Death
Participants were followed from study enrollment through December 31, 2010, for death and healthcare utilization. Deaths were obtained from inpatient and outpatient medical records and death certificates received from the state of Minnesota. Hospitalizations, ED visits, and outpatient office visits were ascertained through the Olmsted County Healthcare Expenditure and Utilization Database, which contains healthcare utilization information from 1987 to present. For patients enrolled during hospitalization, only subsequent hospitalizations were included in the analysis. In-hospital transfers or transfers between Olmsted Medical Center and Mayo Clinic were analyzed as a single hospitalization. ED visits that resulted in admission and hospitalization were counted as both an ED visit and a hospitalization. Outpatient visits for psychiatric care, tests, imaging, or outpatient procedures were not included.

Statistical Analysis
Baseline patient characteristics are reported as a frequency (%) for categorical variables and mean (SD) for continuous variables. Mantel–Haenszel $\chi^2$ tests and generalized linear models were used to test differences in baseline characteristics between depression categories. Follow-up was calculated from HF date until death, last follow-up visit, or December 31, 2010, whichever came first. Kaplan–Meier plots were constructed to illustrate the association of depression severity with all-cause mortality. Cox proportional hazards regression was used to describe associations between severity of depressive symptoms and mortality after adjustment for age, sex, Charlson Comorbidity Index, and incident versus prevalent HF status. The proportional hazards assumption was tested using Schoenfeld residuals and found to be valid. Andersen–Gill modeling, which allows for modeling of multiple outcome events, was used to explore associations of depressive symptoms with hospitalizations and ED visits. Because outpatient visits during follow-up may cluster together (eg, multiple outpatient visits on a given day or within in a span of several days as part of the diagnostic process or for yearly physical examinations), a time-to-event analysis, such as the Andersen–Gill model, is not appropriate. Thus, the association between depression and outpatient office visits was evaluated by calculating the number of visits per person-year for each patient. A likelihood ratio test for overdispersion in the Poisson regression model examining the association between depression severity and rate of outpatient visits indicated that overdispersion existed; therefore, the negative binomial regression model was used.

Several sensitivity analyses were also conducted. First, in an attempt to reduce the possible impact of residual confounding on the association of depression with healthcare utilization and mortality, we also adjusted for left ventricular ejection fraction, estimated glomerular filtration rate, serum sodium, hypertension, use of antidepresants or HF medications, and hospitalizations within the last year in our fully adjusted models. Second, because responses to 2 of the questions of the PHQ-9 may be reflective of a patient’s symptoms due to their HF and not due to depression, we deleted the responses to questions 4 and 5, which asked participants how often they were bothered by feeling tired or having little energy, and poor appetite or overeating. The totals were recalculated after deleting these 2 questions, but the same cut points were used to define none to minimal, mild, and moderate to severe levels of depression. All analyses were then repeated to determine the robustness of our results. Analyses
were conducted using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Baseline Patient Characteristics

Between October 2007 and December 2010, we identified 902 patients with HF of which 402 patients (mean age, 73±13 years; 58% men; 41% incident HF) were enrolled and completed all necessary components of this study (Figure 1). Of these 402 patients, 189 (47%) were identified during an inpatient visit, whereas 213 (53%) were identified during an outpatient visit. Furthermore, ≈60% of the HF patients enrolled had prevalent HF, with a median duration of HF of 4.9 years. Greater than 50% of all patients, regardless of depression status, had a reduced ejection fraction (<50%). Sixty-two (15%) had moderate to severe depressive symptoms, 104 (26%) mild symptoms, and 236 (59%) none to minimal symptoms. Among the inpatients, 11%, 28%, and 61% had moderate to severe, mild, and none to minimal depression, respectively; the respective proportions were 19%, 24%, and 56% in the outpatients. No significant differences in baseline characteristics were observed between depression categories, with the exception of an increasing proportion of diabetes mellitus and current or former smoking status in those with more severe depression (Table 1). As expected, there was an increased use of antidepressants among patients with more severe depression. Interestingly, only 37.1% of patients with moderate to severe depression were on antidepressant medication.

Depression and Healthcare Utilization

During a mean follow-up of 1.6 years, 781 hospitalizations, 1000 ED visits, and 15,515 outpatient office visits occurred. Hospitalizations after HF ranged from 0 to 18 (median 1) per person, ED visits ranged from 0 to 32 (median 2), and outpatient office visits ranged from 1 to 189 (median 30). Sixty-seven percent of hospitalizations were preceded by ED visits, whereas 53% of ED visits resulted in hospitalizations. There were more hospitalizations and ED visits with increasing severity of depressive symptoms, contrasting with a more modest effect on outpatient office visits (Table 2). Compared with patients with none to minimal depression, patients with mild depressive symptoms demonstrated a marginal increase in hospitalizations (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.88–1.53), ED visits (HR, 1.35; 95% CI, 1.00–1.83), and outpatient visits (rate ratio, 1.04; 95% CI, 0.89–1.21) after adjustment for age, sex, comorbidity, and incident versus prevalent HF status. Patients with moderate to severe depression demonstrated nearly a 2-fold increased risk of hospitalizations (HR, 1.79; 95% CI, 1.30–2.47) and ED visits (HR, 1.83; 95% CI, 1.34–2.50) compared with those with none to minimal depression (P for trend, 0.001 and <0.001, respectively). A modest increase in outpatient office visits was also apparent among moderate to severely depressed HF patients, keeping in mind that psychiatric care–related visits were excluded (rate ratio, 1.20; 95% CI, 1.00–1.45; P for trend=0.068).

Depression and Mortality

Within the 402 study participants, 74 deaths occurred. There was a strong positive and graded association between depressive symptom severity and mortality (P for trend <0.001; Figure 2). In fully adjusted models, moderate to severe depression was associated with a 4-fold increased risk of all-cause mortality compared with none to minimal depression (HR, 4.06; 95% CI, 2.35–7.01). Mild depression was associated with a more modest increased risk of mortality (HR, 1.59; 95% CI, 0.89–2.83; Table 3).

Figure 1. Heart failure participant enrollment. PHQ-9 indicates 9-item Patient Health Questionnaire.
Sensitivity Analyses

Additional adjustment for left ventricular ejection fraction, estimated glomerular filtration rate, serum sodium, hypertension, hospitalizations within the last year, and the use of antidepressants or HF-related medications, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or statins, did not alter results for healthcare utilization or all-cause mortality. After the removal of 2 questions on the PHQ-9 that may be related to symptoms of HF, 306 people were classified as none to minimal depression, 69 had mild depression, and only 27 patients remained in the moderate to severe depression category. Although the associations of depression with each measure of healthcare utilization remained the same, the HR for all-cause mortality became higher for those categorized as mildly depressed (HR, 3.07; 95% CI, 1.80–5.22 for mild and moderate depression).
Table 2. Rates and Hazard Ratios* (95% Confidence Interval) or Rate Ratios† (95% Confidence Interval) for Healthcare Utilization by Severity of Depression

<table>
<thead>
<tr>
<th>Severity of Depressive Symptoms</th>
<th>None to Minimal</th>
<th>Mild</th>
<th>Moderate to Severe</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate‡</td>
<td>1.05</td>
<td>1.23</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.00 (ref)</td>
<td>1.20 (0.91–1.59)</td>
<td>1.90 (1.36–2.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted§</td>
<td>1.00 (ref)</td>
<td>1.16 (0.88–1.53)</td>
<td>1.79 (1.30–2.47)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Emergency department visits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate‡</td>
<td>1.43</td>
<td>1.93</td>
<td>2.66</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.00 (ref)</td>
<td>1.36 (1.02–1.82)</td>
<td>1.83 (1.36–2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted§</td>
<td>1.00 (ref)</td>
<td>1.35 (1.00–1.83)</td>
<td>1.83 (1.34–2.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Outpatient visits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate‡</td>
<td>23.46</td>
<td>25.66</td>
<td>28.37</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
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<td>1.05 (0.90–1.23)</td>
<td>1.24 (1.03–1.50)</td>
<td>0.029</td>
</tr>
<tr>
<td>Fully adjusted§</td>
<td>1.00 (ref)</td>
<td>1.04 (0.89–1.21)</td>
<td>1.20 (1.00–1.45)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Outpatient visits exclude psychiatric care, tests, imaging, and outpatient procedures.
*For hospitalizations and emergency department visits.
†For outpatient visits.
‡Crude event rate per person-year.
§Adjusted for: age, sex, Charlson Comorbidity Index, and incident vs prevalent heart failure status.

Discussion

Depression Prevalence in HF

In this community-based HF cohort, depression was frequent in HF patients, with 26% of patients reporting mild depressive symptoms and 15% reporting moderate to severe depressive symptoms, and its presence and severity was not related to HF characteristics. Although reported prevalence of depression in HF is variable, our findings are similar to the 15% to 20% rate of major depression cited in studies of coronary artery disease. Importantly, the rate of depression in our HF patients was 2 to 3x the estimated rate in the general population. Interestingly, despite the high prevalence of depression in patients with HF, of those reporting mild and moderate to severe depressive symptoms at study enrollment, only approximately one third were on antidepressant medications at that time. Although it is possible that some patients were receiving a nonpharmacological therapy, this finding raises the possibility that depression might be under-recognized and undertreated in these patients.

Depression, Healthcare Utilization, and Mortality in HF

Within our cohort, patients with moderate to severe depression had nearly double the rate of hospitalizations and ED visits, in contrast with only a modest increase in outpatient visits compared with those with none to minimal depression. Depression is known to have a strong impact on patient behaviors, particularly among the more severely depressed. Psychosocial stressors contribute to increased smoking and alcohol abuse, poor diet, physical inactivity, and poor medication adherence, all behaviors that are risk factors for cardiovascular deterioration. These behavioral changes could at least partially explain why these patients have increased healthcare utilization.

In addition, patients with moderate to severe depression had a 4-fold increased risk of all-cause mortality compared with

Figure 2. All-cause mortality in heart failure (HF) patients by severity of depression.
none to minimal depression. Just as depression is associated with negative behavioral changes, it can also cause deleterious physiological and hormonal changes. Depressed states have been shown to induce sympathetic activation, hypercortisolism, and other metabolic abnormalities, increased heart rhythm disturbances, hypercoagulability, endothelial dysfunction, and a state of elevated proinflammatory cytokines, including interleukin-6, tumor necrosis factor-α, and interleukin-1β. The effects of neurohormonal dysregulation and a proinflammatory state over time have been hypothesized to adversely affect the failing heart which could be part of the mechanism underlying the increased cardiovascular mortality in depressed patients with HF. However, other causes of mortality were also increased in these patients, suggesting that the physiological changes occurring in depression negatively affect other organ systems as well. Finally, as the hypothetical pathways are complex, the elevation of cytokines that occurs in HF may play a role in the genesis of depression. In this scenario, depression itself may not have a strong impact on survival, as depression may be a symptom of cytokine activation rather than a cause.

The finding of higher rates of hospitalizations and mortality among depressed patients with HF is congruent with findings from several prior studies of patients with HF and coronary artery disease. However, only limited data exist for ED and outpatient office visits. Although hospitalizations are considered to be one of the largest expenditures in patients with HF, outpatient and ED visits are also important contributors to the excess cost associated with depression in HF, and ED visits denote care seeking behaviors often leading to hospitalizations.

Clinical Implications
In this study, only about one third of patients with mild and moderate to severe depression were on antidepressants. These data resonate with prior reports suggesting that depression is under-recognized and undertreated in practice. We acknowledge that the most effective ways to assess and manage depression in HF remain to be fully defined, as there are limited data investigating options to treat depression in HF and uncertainties about impact on outcomes. A trial of the antidepressant sertraline showed relative efficacy with 44.5% remission, as well as decreased hospitalizations and nonfatal cardiovascular events. However, nonpharmacological treatments may also be helpful, as exercise programs have been shown to favorably impact cytokines, which are elevated with depression. It is likely that clinical approaches will be most effective when tailored to individual patients’ profiles. Regardless of uncertainties surrounding the optimal treatment approach, the present data underscore that depression is a key driver of healthcare utilization in HF, thereby delineating an opportunity for a greater emphasis on managing depression to reduce acute care use.

Limitations and Strengths
Several limitations should be acknowledged. Depressive symptoms were measured only at enrollment and, therefore, we cannot account for temporal changes in depressive symptoms. Likewise, medications were only available at baseline, and treatments for depression other than antidepressant medications were unavailable. Some of the symptoms of depression overlap with common symptoms of HF, including fatigue, low energy, psychomotor retardation, and difficulty sleeping or insomnia, a limitation that is common to all studies of depression in HF. In addition, participants willing to enroll in the study and complete questionnaires may differ from nonparticipants. Although it is possible that some healthcare utilization may have occurred outside of Olmsted County, in our experience such underascertainment is minimal and would not have impacted our results. Finally, the population of southeastern Minnesota is chiefly white and thus, our results should be examined in other racial groups.

Despite potential limitations, this study has several unique strengths, including its defined cohort of patients with HF prospectively recruited from the community with validated HF diagnoses. In addition, through the record-linkage system of the Rochester Epidemiology Project, we captured most healthcare utilization among participants, allowing us to analyze ED and outpatient office visits, indicators of health resource use rarely evaluated in prior studies. This enabled the categorization of healthcare utilization patterns into chronic (outpatient visits) and acute (ED and hospitalization) care. In doing so, we identified that the striking impact of depression on acute care use contrasted with a more modest increase in chronic care. This adds support for recasting care models for depression in HF toward more proactive management in primary care, as had been done in some settings.

Conclusions
Depression is frequent among patients with HF in the community and is associated with a large increase in acute healthcare utilization and mortality. Further research is warranted to develop more effective clinical approaches for management of depressed patients with HF.
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Disclosures
None.

References

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Heart failure (HF) affects ≈6 million Americans and is one of the most costly healthcare problems in the United States. Depression is a potentially modifiable risk factor that may increase the risk of healthcare utilization and death in patients with HF. However, results from previous studies are inconsistent and information on the association of depression with healthcare utilization measures other than hospitalizations, such as outpatient and emergency department visits, are lacking. Therefore, this study was designed to address the impact of depression on hospitalizations, emergency department visits, outpatient visits, and mortality in a prospective community-based cohort study of 402 patients with HF from southeast Minnesota from 2007 to 2010. Among the 402 HF patients, 62 had moderate to severe depressive symptoms, 104 had mild symptoms, and 236 had none to minimal symptoms. During a mean follow-up of 1.6 years, 781 hospitalizations, 1000 emergency department visits, 15 515 outpatient office visits, and 74 deaths occurred. Patients with HF with moderate to severe depression exhibited a nearly a 2-fold increased risk of hospitalizations and emergency department visits, a modest 20% increase in outpatient visits, and a 4-fold increase in all-cause mortality compared with patients with none to minimal depression. Thus, greater recognition and management of depression in HF may optimize clinical outcomes and resource utilization in these patients.