Antidepressant Use, Depression, and Survival in Patients With Heart Failure

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Background: Recent studies suggest that the use of antidepressants may be associated with increased mortality in patients with cardiac disease. Because depression has also been shown to be associated with increased mortality in these patients, it remains unclear if this association is attributable to the use of antidepressants or to depression.

Methods: To evaluate the association of long-term mortality with antidepressant use and depression, we studied 1006 patients aged 18 years or older with clinical heart failure and an ejection fraction of 35% or less (62% with ischemic disease) between March 1997 and June 2003. The patients were followed up for vital status annually thereafter. Depression status, which was assessed by the Beck Depression Inventory (BDI) scale and use of antidepressants, was prospectively collected. The main outcome of interest was long-term mortality.

Results: Of the study patients, 30.0% were depressed (defined by a BDI score ≥10) and 24.2% were taking antidepressants (79.6% of these patients were taking selective serotonin reuptake inhibitors [SSRIs] only). The vital status was obtained from all participants at an average follow-up of 972 (731) (mean [SD]) days. During this period, 42.7% of the participants died. Overall, the use of antidepressants (unadjusted hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.03-1.69) or SSRIs only (unadjusted HR, 1.32; 95% CI, 0.99-1.74) was associated with increased mortality. However, the association between antidepressant use (HR, 1.24; 95% CI, 0.94-1.64) and increased mortality no longer existed after depression and other confounders were controlled for. Nonetheless, depression remained associated with increased mortality (HR, 1.33; 95% CI, 1.07-1.66). Similarly, depression (HR, 1.34; 95% CI, 1.08-1.68) rather than SSRI use (HR, 1.10; 95% CI, 0.81-1.50) was independently associated with increased mortality after adjustment.

Conclusion: Our findings suggest that depression (defined by a BDI score ≥10), but not antidepressant use, is associated with increased mortality in patients with heart failure.

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SUBSTANTIAL EVIDENCE SHOWS that depression is an independent risk factor for poor prognosis of patients with ischemic heart disease and heart failure (HF). Therefore, the use of antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), for depression has become more prevalent among these patients. Although the efficacy of antidepressant therapy for depression is generally well recognized, the safety of these medications in patients with ischemic heart disease and HF has been challenged. Data from the Cardiac Arrhythmia Suppression Trial demonstrated that the efficacy and safety of a medication are not necessarily linked; ie, a medication that demonstrates great efficacy may have an unsuitable safety profile. Tricyclic antidepressants (TCAs), which have some of the same pharmacologic properties as type IA antiarrhythmics, were found to increase mortality in the Cardiac Arrhythmia Suppression Trial; therefore, the use of these compounds has been discouraged among patients with cardiac disease. The safety of SSRIs has also been questioned in reports stating that use of SSRIs has been associated with increased occurrence of acute myocardial infarction and death. Randomized controlled trials examining the effects of antidepressants on cardiac prognosis at present have involved a modest number of patients with a limited number of events, precluding definitive conclusions regarding the safety and efficacy of these agents in patients with cardiovascular disease. In fact, the relationship between antidepressant and mortality remains far from settled at this...
time, with some studies linking their use to increased mortality and some showing decreased risk of death, while others have demonstrated no adverse effects. Also, almost all previous studies investigating the association between antidepressant use and prognosis failed to take into account the depression status of the study subjects, a factor also shown to increased mortality in these individuals. The current study represents an extension of our previously published data on the association of depression and mortality, seeking to evaluate the relationship of antidepressant use and depression on survival of patients with HF.

METHODS

Male and female patients aged 18 years and older who were admitted to the cardiology service between March 1, 1997, and July 31, 2003, were recruited for participation in the study. Eligibility criteria included clinically diagnosed HF, defined as a New York Heart Association (NYHA) classification of II or greater, a left ventricular ejection fraction (LVEF) of 39% or more (by radionuclide study, echocardiography, or angiography), or both. Patients were excluded because of pregnancy, active suicidal ideation, planned major surgery, or inability to provide informed consent. The study was conducted at Duke University Medical Center, Durham, North Carolina, after approval by the institution's review board. All participants provided informed consent according to review board guidelines.

During the hospitalization, all participants completed the Beck Depression Inventory (BDI), a self-administered, 21-item questionnaire for assessment of depressive symptoms. The BDI is the most commonly used instrument to screen for depression in various populations, including those with cardiac diseases. The psychometric properties of the BDI support its use to screen for depression. Internal consistency studies of the BDI have demonstrated correlation coefficients that range from 0.73 to 0.92, with a mean of 0.86 for test items, and the Spearman-Brown correlation for the reliability of the BDI yielded a coefficient of 0.93. Similarly, assessment of concurrent validity demonstrated moderate to high correlation, ranging from 0.55 to 0.96, with mean of 0.72, between the inventory and psychiatric rating. A patient with a total BDI score of 10 or more is considered to have depression, which has been associated with an increased risk of dying and recurrent cardiac events.

All study participants received standard care from their primary care physicians and cardiologists during and after the hospitalization. Intervention for depression was deferred to the clinical judgment of the primary care team.

Use of antidepressants during the index hospitalization was determined from inpatient pharmacy records as well as from discharge summaries. Detailed demographic data, which were collected from medical records or patient interviews, included age, race, sex, marital status, primary reason for admission, concomitant illnesses, vital signs, physical examination results, NYHA classification, and LVEF (lowest measurement during hospitalization). Patients were contacted by mail after discharge from the index hospitalization at 6 months and annually thereafter to obtain vital status. If patients did not respond within 4 to 6 weeks after the mailing or if clarification was needed, patients were contacted by telephone. The Duke Databank for Cardiovascular Disease was used to obtain missing data and contact information. In a few patients for whom survival status was not available, the National Death Index was queried to obtain this information.

Demographic and clinical characteristics were summarized as percentages or means (SDs), and were grouped according to antidepressant use and category as follows: (1) nonantidepressant group, patients who took no antidepressants; (2) SSRI-only group, patients who took only SSRIs; (3) TCA group, patients who took TCAs with or without SSRIs or other antidepressants; or (4) other group, patients who took other antidepressants with or without SSRIs or TCAs. Paired comparative analyses for survival were applied to nonantidepressant vs any antidepressant groups and nonantidepressant vs SSRI-only groups. Cox proportional hazards modeling was used to determine the ability of antidepressant use alone or in conjunction with depression and other risk factors associated with use of antidepressants and/or with increased mortality to predict survival during follow-up. Depression was defined as a BDI score of 10 or more for categorical analyses and regression modeling. The predictability of SSRI use (SSRIs only), alone and with adjustment for depression and the above-mentioned risk factors, to survival during follow-up was also evaluated. Furthermore, the BDI score, as a continuous variable, was used as a covariate in a separate multivariate analysis model to ascertain the predictability of antidepressant use or SSRI use only on survival. Association of TCAs or other antidepressant use with survival was not analyzed because of the very small number of participants who used these antidepressants. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). A P value of .05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

A total of 1006 patients out of 3852 patients with HF admitted to Duke University Medical Center met the study criteria, consented for the investigation, and were enrolled in the study. Because of 1 participant who did not complete the BDI assessment, the final analysis consisted of 1005 patients. Of these patients, 162 (16.1%) were taking some form of antidepressant during the index hospitalization. All patients who were receiving antidepressants during hospitalization were taking these drugs until discharge. The antidepressants used by our study population included amitriptyline, bupropion, citalopram, desipramine, doxepine, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone, triaval, and venlafaxine. Those medications were then categorized as SSRIs (citalopram, fluoxetine, paroxetine, and sertraline), TCAs (amitriptyline, desipramine, doxepine, nortriptyline, and triaval), and others (bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine). Of the 162 patients who were taking antidepressants, 129 (79.6%) took only SSRIs, 12 (7.4%) took TCAs, and 12 (7.4%) took others. Eight patients (4.9%) took a combination of TCA and SSRIs, and only 1 patient (0.6%) took an SSRI along with an “other” antidepressant. Table 1 summarizes the demographic and clinical characteristics of the study population categorized by use of antidepressants (nonantidepressants, SSRIs only, TCAs, or other). Compared with patients who were not taking any antidepressants, patients taking antidepressants were more likely to be white and married (Table 1).

Thirty percent of the total patient population (302 of 1005) had a BDI score of 10 or more and were considered depressed. Of those patients, 24.5% were taking antidepressants. In comparison, 12.3% of nondepressed pa-
patients (BDI score, <10) were taking antidepressants. Of the patients taking SSRIs only, TCAs, and others, 52.7%, 70.0%, and 46.2%, respectively, had BDI scores of less than 10 (Table 1). Nonetheless, antidepressant use incrementally increased along with the severity of depression (Figure).

### ANTIDEPRESSANT USE, DEPRESSION, AND OTHER RISK FACTORS FOR MORTALITY

The average duration of follow-up was 971 (730) (mean [SD]) days, with a median follow-up of 801 days. No patients were unavailable for follow-up with regard to collection of vital status. During the follow-up period, a total of 429 patients died (161 [53.3%] with a BDI score ≥10 vs 268 [38.1%] with a BDI score <10; P < .001). Those who died were significantly older (70.2 [10.3] vs 68.3 [10.6]; P = .005), less likely to be married (35.2% vs 51.6%; P < .001), and more likely to have been admitted for worsening HF than were survivors (39.7% vs 30.9%; P = .006). They also had a significantly lower average LVEF (28.9% vs 31.6%; P < .001), higher NYHA classification (71% vs 65.1% with NYHA class III or greater; P = .06), and higher mean BDI score. Patients with an ischemic cause of HF had higher rates of death than patients whose HF resulted from nonischemic cardiac diseases (68.2% vs 56.8%; P < .001). Higher rates of death were observed in patients taking antidepressants (76 deaths among 162 patients who were taking these drugs [46.9% overall, 44.2% in the SSRI-only group, 55.0% in the TCA group, and 61.5% in the other group]) compared with 353 deaths among 843 patients who were taking no antidepressants (41.9%). Information on the cause of death was available in 80.4% of the patients. The majority of the deaths were attributed to cardiovascular causes (94.4%), and the cause of death was similar between patients who were taking an antidepressant and those who were not.

Univariate analysis comparing the survival difference between patients taking antidepressants (n = 162) and patients not taking antidepressants (n = 843) revealed that the use of antidepressants was associated with significantly shortened survival (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.03-1.69; P = .03). The comparison of survival between patients taking SSRIs only (n = 129) and patients taking no antidepressants (n = 844) revealed a trend showing that patients taking SSRIs died sooner, but the difference between these 2 groups was not statistically significant (HR, 1.32; 95% CI, 0.99-1.74; P = .06).

After adjustment for depression, neither antidepressant use nor use of SSRIs only was associated with reduced survival (antidepressants: HR, 1.19; 95% CI, 0.84-1.67; P = .33) (SSRIs only: HR, 1.06; 95% CI, 0.69-1.62; P = .78). Nonetheless, depression remained associated with reduced sur-

### Table 1. Demographic and Clinical Characteristics of the Study Patients, by Categories of Antidepressant Use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None (n = 843)</th>
<th>SSRIs Only (n = 129)</th>
<th>TCAs (n = 20)</th>
<th>Others (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>69.2 (10.5)</td>
<td>70.3 (9.3)</td>
<td>59.0 (14.0)</td>
<td>67.9 (8.7)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>63.6</td>
<td>58.1</td>
<td>40.4</td>
<td>61.5</td>
</tr>
<tr>
<td>White race, %</td>
<td>71.2</td>
<td>83.7</td>
<td>80.0</td>
<td>84.6</td>
</tr>
<tr>
<td>Married, %a</td>
<td>44.4</td>
<td>45.5</td>
<td>31.3</td>
<td>55.6</td>
</tr>
<tr>
<td>Prior bypass surgery, %</td>
<td>46.1</td>
<td>54.3</td>
<td>36.8</td>
<td>57.1</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>41.1</td>
<td>49.5</td>
<td>26.3</td>
<td>55.6</td>
</tr>
<tr>
<td>Ischemic cause of HF, %</td>
<td>62.7</td>
<td>67.4</td>
<td>70.0</td>
<td>53.9</td>
</tr>
<tr>
<td>EF, mean (SD), %</td>
<td>30.5 (11.6)</td>
<td>31.6 (11.9)</td>
<td>41.5 (13.1)</td>
<td>27.7 (12.7)</td>
</tr>
<tr>
<td>NYHA classification III or IV, %</td>
<td>66.4</td>
<td>74.0</td>
<td>55.0</td>
<td>92.3</td>
</tr>
<tr>
<td>Reason for admission, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>34.0</td>
<td>34.9</td>
<td>50.0</td>
<td>46.2</td>
</tr>
<tr>
<td>Acute MI</td>
<td>14.2</td>
<td>11.6</td>
<td>15.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>19.6</td>
<td>20.9</td>
<td>15.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>10.0</td>
<td>7.8</td>
<td>10.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Other</td>
<td>22.2</td>
<td>24.8</td>
<td>10.0</td>
<td>30.8</td>
</tr>
<tr>
<td>BDI score ≥10</td>
<td>27.1</td>
<td>47.3</td>
<td>30.0</td>
<td>53.8</td>
</tr>
<tr>
<td>BDI score &lt;10</td>
<td>72.9</td>
<td>52.7</td>
<td>70.0</td>
<td>46.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>41.9</td>
<td>44.2</td>
<td>55.0</td>
<td>61.5</td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

a P < .05.

### Figure

Proportion of patients taking antidepressant medications according to the severity of depression as indicated by the Beck Depression Inventory (BDI) scale. Note that antidepressant use incrementally increased along with the severity of depression.

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suggest that depression is associated with increased long-term mortality, while antidepressants do not seem to decrease survival in these patients. Finally, while antidepressant use was not found to be associated with an increased risk of death in patients with HF in our study, the current study provides some evidence that the risk of depression on mortality is not significantly attenuated by the use of antidepressants.

The results of this study should be viewed in light of previous findings of many studies that have examined the impact of antidepressant use on cardiac mortality and morbidity. Some but not all studies have associated the use of antidepressants with increased risks of cardiovascular events. Xiong et al. found that patients who were treated with SSRIs before coronary artery bypass graft (CABG) surgery had increased mortality and rehospitalization after CABG surgery compared with patients who were not treated with SSRIs during a 4-year postsurgical follow-up. Even after adjustment for the propensity to receive SSRIs and for other clinical confounders, SSRIs on CABG surgery remained associated with increased adverse outcomes. Tata et al. conducted a case-controlled analysis using the United Kingdom General Practice Research Database records from 1988 to 2001 and reported that the use of both TCAs and SSRIs was significantly associated with acute myocardial infarction. In cases involving more than 28 days of antidepressant use, the odds ratio (OR) was 1.47 for patients taking SSRIs (95% CI, 1.41-1.54) and 1.40 for those taking TCAs (95% CI, 1.36-1.43). Similarly, Sherwood et al. recently showed that antidepressant medication use was associated with an increased likelihood of death or cardiovascular hospitalization (HR, 1.75; 95% CI, 1.14-2.08) after severity of depressive symptoms and established risk factors were controlled for.

In this large prospective cohort study, we found that 24.5% of depressed patients with HF (BDI score, ≥ 10) were taking antidepressants. The use of these agents was well correlated with the severity of depressive symptoms; ie, the more severe the depression was, the more likely the patients were receiving antidepressants (Figure), and this finding is consistent with prior observations.21 Also, our data on patients with HF and relatively large event rates suggest that depression is associated with increased long-term mortality, while antidepressants do not seem to decrease survival in these patients. Finally, while antidepressant use was not found to be associated with an increased risk of death in patients with HF in our study, the current study provides some evidence that the risk of depression on mortality is not significantly attenuated by the use of antidepressants.
In contrast to these findings, as well as ours, several other studies examining the impact of antidepressant use and cardiac outcome have reported no increase in adverse cardiovascular outcomes. For example, Cohen et al\(^{10}\) investigated the impact of TCAs and SSRIs on both acute myocardial infarction and death. They evaluated and compared 2247 working, union health plan members who received at least 1 prescription for an antidepressant during 1991 and 1992 with 52,750 members who did not receive any antidepressants for up to 4.5 years. After adjusting for age and sex, the authors found that the relative risk of myocardial infarction occurrence was 2.2 (95% CI, 1.2-3.8) among patients who used TCAs and 0.8 (95% CI, 0.2-3.5) among those who used SSRIs. Furthermore, the relative risk of death was 1.1 (95% CI, 0.7-1.6) in TCA users and 1.0 (95% CI 0.5-2.0) in SSRI users.\(^4\) Monster et al\(^{4}\) and Meier et al\(^{9}\) found no association between the use of SSRIs or TCAs and acute myocardial infarction. Similarly, no safety issues with SSRIs were identified in 2 large randomized clinical trials that enrolled patients with coronary heart disease: the Sertraline Antidepressant Heart Attack Randomized Trial\(^{10}\) and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial.\(^{11}\)

Yet, other studies have shown that the use of antidepressants, specifically SSRIs, can improve outcomes. Schlegier et al\(^{12}\) using the same data set and design as Tata et al\(^{12}\) but with a shorter study period (from 1995 to 2001), reported that SSRI use was associated with reduction of acute myocardial infarction, with an adjusted OR of 0.63 (95% CI, 0.43-0.91), whereas the use TCAs or other antidepressants was not.\(^{12}\) Two studies by Sauer et al\(^{13,14}\) found that the use of SSRIs reduced acute myocardial infarction and that the use of TCAs had no effect. It is clear from our data that if we had not measured depression our conclusions would have been similar to those of the above-mentioned studies, which found that the use of antidepressants or SSRIs is associated with increased mortality among patients with HF. Glassman et al\(^{10}\) have suggested that sertraline therapy might help prevent recurrent cardiac events in patients with recent acute coronary syndromes. Finally, Ziegelstein et al\(^{15}\) demonstrated that patients who received an SSRI were significantly less likely to experience recurrent myocardial ischemia, HF, or asymptomatic cardiac enzyme elevation while in the hospital (OR, 0.46; 95% CI, 0.22-0.99) but were significantly more likely to experience bleeding (OR, 1.65; 95% CI, 1.02-2.66), mainly minor bleeding. No differences were observed in death, myocardial infarction during the hospitalization, urgent revascularization, or major bleeding.

While the large number of event rates in our patient population allowed robust multivariate analysis, the findings have important limitations. The major drawback of our study is that it is observational, so caution is necessary when making definitive inferences regarding causality. Depression assessment and information on antidepressant use were available only during the index hospitalization, and compliance with long-term treatment could not be ascertained. Although evidence from studies involving patients with ischemic heart disease suggest that repeated measures of depressive symptoms during follow-up are not independent of the baseline depression level in terms of its relationship to survival, changes in severity of depressive symptoms may result in alteration of antidepressant use.\(^{21}\) Furthermore, all of our participants were recruited from a single tertiary care center where the impacts of depression as well as depression care among patients with cardiac diseases have been longitudinally and broadly studied. The influence of such studies on the clinical decision making of medical professionals should not be neglected. Therefore, the level of depression recognition and extent of antidepressant use simply may not reflect the current practice in the communities and other tertiary care places.

In conclusion, our findings suggest that depression (defined by a BDI score $\geq 10$), but not antidepressant use, is associated with increased mortality in patients with HF. Our data support the need for randomized clinical trials that are adequately powered to evaluate whether the use of SSRIs and/or other antidepressants may reduce mortality and other cardiac outcomes without raising safety concerns among depressed cardiac patients. The ongoing National Institute of Mental Health–funded Sertraline Antidepressant Heart Attack Randomized Trial–Chronic Heart Failure, a randomized double-blind placebo-controlled study of SSRI therapy in depressed patients with HF, is likely to provide further insight into this issue.

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