Depression After Coronary Artery Disease Is Associated With Heart Failure

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Objectives The purpose of this study was to evaluate the influence of post-coronary artery disease (CAD) depression diagnosis on heart failure (HF) incidence.

Background Depression has been shown to be a risk factor for poor outcomes among CAD patients. However, little is known about the influence of depression on HF development in CAD patients.

Methods Patients (n = 13,708) without a diagnosis of HF and depression (International Classification of Diseases-Ninth Revision [ICD-9] codes: 296.2 to 296.36 and 311) and who were not prescribed antidepressant medication (ADM) at the time of CAD diagnosis (≥70% stenosis) were studied. For those with available medication records (n = 7,719), patients subsequently diagnosed with depression were stratified by use of ADM. Patients were followed until HF diagnosis (physician-diagnosed or ICD-9 code: 428) or death. Results were analyzed by Cox proportional hazards regression models.

Results A total of 1,377 patients (10.0%) had a post-CAD clinical depression diagnosis. The incidence of HF among those without a post-CAD depression diagnosis was 3.6 per 100 compared with 16.4 per 100 for those with a post-CAD depression diagnosis. Depression was associated with an increased risk for HF incidence (adjusted hazard ratio [HR]: 1.50, p < 0.0001). Results were similar among those with available follow-up medication information (vs. no depression: depression without ADM use [HR: 1.68, p < 0.0001]; depression with ADM use [HR: 2.00, p < 0.0001]). No difference was found between depressed patients with and without ADM treatment (HR: 0.84, p = 0.24).

Conclusions Depression diagnosis was shown to be associated with an increased incidence of HF after CAD diagnosis, regardless of ADM treatment. This finding suggests the need to further study the effect of depression on HF risk among CAD patients. (J Am Coll Cardiol 2009;53:1440–7) © 2009 by the American College of Cardiology Foundation

Depression has been shown to be a risk factor for poor outcomes among patients with coronary artery disease (CAD) (1–4). However, little is known about the influence that depression has on the development of heart failure (HF) in patients with CAD. Heart failure is a public health epidemic that affects more than 5 million people in the U.S. and has an incidence rate of 550,000 new cases per year (5). It is the only cardiovascular (CV) disease with increasing incidence, prevalence, and cost (both direct and indirect) (5). The First National Health and Nutrition Examination Survey reported that CAD, smoking, hypertension, being overweight, diabetes, myocardial infarction (MI), and valvular heart disease are risk factors for HF (6).

The World Health Organization now ranks major depression as one of the most burdensome diseases in the world (7). The prevalence of depression among the HF population is similar to post-MI patients. The authors of previous studies have shown that depression in patients with HF increases the risk of hospitalization and mortality (8–10). There may be some pathophysiological pathways (11–20) and/or behaviors (21–28) by which depression affects CV outcomes in patients with HF.

Although the authors of previous studies have reported depression to be a risk factor for adverse CV outcomes among those patients with HF, there are no reports on how depression influences HF development among patients with CAD. This study is the first to evaluate whether...
depression (defined as a depression diagnosis) in patients with angiographically defined CAD is associated with the development of HF.

Methods

Objectives. PRIMARY OBJECTIVE. Among those angiographically diagnosed with CAD, we sought to determine the incidence of HF among those with and without a clinical diagnosis of depression.

SECONDARY OBJECTIVE. We also sought to compare the incidence of HF among those treated with antidepressant medication (ADM) therapy who have a clinical diagnosis of depression; no ADM therapy, but have a clinical diagnosis of depression; and those with no clinical diagnosis of depression.

STUDY PATIENTS. Study patients were drawn from the cardiac catheterization registry of the Intermountain Heart Collaborative Study (29,30). Patients were included if they were determined to have CAD (stenosis >70%), no antecedent clinical diagnosis of depression or ADM use, and no antecedent clinical diagnosis of HF at index angiography. These patients were followed prospectively for the incidence HF, as determined by a subsequent hospitalization during which a clinical diagnosis of HF or a primary discharge diagnosis of HF (International Classification of Diseases-Ninth Revision [ICD-9] code: 428) was made (Fig. 1). This study was approved by the Intermountain Urban Central and the University of Utah institutional review boards.

DEPRESSION. Depression was defined as having a clinical diagnosis of depression (ICD-9 codes: 296.2 to 296.36 and 311) in an outpatient, inpatient, or emergent setting. Since ADM therapy can be prescribed for other indications, only those with an associated depression diagnosis were designated as “treated.” We assessed ADM therapy (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or other antidepressant [amoxapine, trazodone, venlafaxine, maprotiline, mirtazapine, nefazodone, bupropion]) at index hospitalization (angiography), at subsequent hospitalization(s) and, if available, for those who had their prescriptions filled at an Intermountain Healthcare pharmacy. The 2 cohorts, hospitalized and outpatient pharmacy, were combined to evaluate the association between ADM initiation and HF admission. Because not all patients can be tracked for future (post-angiography) ADM use through these ascertainment methods, analyses were limited to those patients in whom follow-up could be obtained.

OTHER RISK FACTOR, DEMOGRAPHIC, AND CLINICAL ASSESSMENTS. In addition to age and sex, patient information included the presence of diabetes (fasting blood glucose ≥126 mg/dl, clinical diagnosis of diabetes mellitus, or antidiabetic medication use), hypertension (systolic blood pressure ≥140 mm Hg, diastolic ≥90 mm Hg, or antihypertensive use), renal failure (clinical renal failure or calculated glomular filtration rate ≥15 ml/min), and hyperlipidemia (total cholesterol ≥200 mg/dl, low-density lipoprotein ≥130 mg/dl, or cholesterol-lowering medication use).
zyme inhibitors (ACEIs), digoxin, angiotensin II receptor blockers (beta-blockers), angiotensin-converting enzyme inhibitors, or coronary artery bypass surgery. Discharge medication included only, percutaneous coronary intervention, or coronary artery bypass surgery. Discharge medications were also recorded, including statins, beta-adrenergic receptor blockers (beta-blockers), angiotensin-converting enzyme inhibitors (ACEIs), digoxin, angiotensin II receptor blockers, diuretics, and ADMs.

**PATIENT FOLLOW-UP AND EVENT ASSESSMENT.** Patients were followed until a subsequent hospitalization, where they received a clinical diagnosis of HF or a primary discharge diagnosis of HF (ICD-9 code: 428), or until death. Patients were determined as having a depression-related HF diagnosis if the depression diagnosis occurred before the HF diagnosis or a nondepression related HF diagnosis if no depression diagnosis occurred or the depression diagnosis occurred post-HF diagnosis. Average length of follow-up was 5.6 ± 3.6 years among all the study patients and 6.1 ± 3.6 years for the hospitalized and outpatient pharmacy cohort (those with available follow-up medication information). Deaths were determined by telephone survey, hospital records, and Utah State Health Department records (death certificates) and were verified through Social Security death records. Patients not listed as deceased in any registry were considered to be alive (censor date: April 30, 2007).

**Statistical analysis.** The chi-square test and Student t test were used to examine univariable associations of a clinical diagnosis of depression to baseline and clinical characteristics. Analysis of variance was used to determine baseline characteristics of continuous variables among those with ADM use and depression, no ADM use and depression, and no depression or ADM use. To confirm the associations determined by univariable analysis, multivariable Cox regression analysis (version 15.0, SPSS Inc., Chicago, Illinois) was performed to determine hazard ratios (HRs) corrected for confounding factors. Kaplan-Meier survival estimates and the log rank test were used to determine initial associations with HF incidence. Available known baseline risk factors that were used in the modeling included age, gender, hypertension, hyperlipidemia, diabetes, smoking, family history of CAD, renal failure, body mass index, presentation (with stable angina, unstable angina, or acute MI), treatment type, EF, and discharge medications (statin, ACEI, beta-blocker, digoxin, and diuretic use). As intermediate end points, patients were evaluated for the occurrence of a MI (n = 241) or an atrial fibrillation (n = 249) admission (because both are risk factors for HF, overlap: n = 35). These intermediate end points were used as covariables in the primary outcome model. Final models entered significant (p < 0.05) and confounding (10% change in beta-coefficient) covariables. The proportional hazards assumption was evaluated by including a time-dependent covariate representing the interaction between depression and follow-up time.

A stratified analysis was performed to evaluate the selection bias that may be associated among those selected to receive (physician suspected decompensated heart function) and not receive an EF measurement. Two-tailed p values are presented with 0.05 designated as nominally significant.

**Results**

A total of 1,377 (10.0%) of 13,708 patients had a post-CAD clinical depression diagnosis. Baseline characteristics are described in Table 1. In summary, those diagnosed with depression were more likely to be female, have hypertension,
diabetes, and renal failure. A total of 674 patients had a follow-up HF diagnosis (no depression diagnosis: n = 448, depression diagnosis: n = 226). The incidence of HF among those without a post-CAD depression diagnosis was 3.6 per 100 compared with 16.4 per 100 for those with a post-CAD depression diagnosis.

Among those with available follow-up medication information (n = 7,719), baseline characteristics for those without a depression diagnosis, a depression diagnosis, but no ADM use, and those with a depression diagnosis and ADM use are shown in Table 2. Among those with a depression diagnosis, those treated with ADMs were more likely to be male (p = 0.007), have diabetes (p = 0.02), be younger (p = 0.03), have a greater EF (p = 0.05), and be less likely to smoke (p = 0.01). A total of 5.7% (n = 372), 18.6% (n = 129), and 16.1% (n = 73) of those without a depression diagnosis, a depression diagnosis but no ADM use, and those with a depression diagnosis and ADM use had a follow-up HF diagnosis, respectively.

The increase in the risk of a HF diagnosis was evident at the start of follow-up (angiography) for those with a post-CAD depression diagnosis as shown in the Kaplan Meier survival curve (Fig. 2A). However, this difference was not affected by ADM treatment (Fig. 2B). A depression diagnosis was associated with a 2-fold increased risk for the post-CAD depression diagnosis. The risk of HF remained when comparing those without depression (but with those on ADM treatment) to those with a depression diagnosis, with and without ADM use.

In a stratified analysis, those who did not receive an EF measurement and had a post–CAD diagnosis of depression had an even greater increase in risk for HF incidence (multivariable HR: 2.11, 95% CI: 1.30 to 3.43, p = 0.003). Although those receiving an EF measurement (multivariable HR: 1.54, 95% CI: 1.04 to 2.27, p = 0.03) had a similar risk to the entire cohort. Among those with available medication information, the associations were similar (data not shown).

There were some patients on ADM therapy (n = 486) who did not have a clinical diagnosis of depression. In an effort to determine whether their risk is similar to those with a clinical diagnosis of depression (ADM as a possible surrogate of depression), they were compared with the other patient groups. Interestingly, those with a depression diagnosis with ADM (HR: 2.86, p < 0.0001) and without ADM (HR: 2.24, p = 0.001) treatment had a substantial increase in the risk for HF development when compared with those on ADM treatment without a clinical diagnosis of depression. There was no increase in risk when comparing those without a depression diagnosis without ADM treatment (HR: 1.31, p = 0.26) to those with ADM and no depression diagnosis. The risk of HF remained when comparing those without depression (but with those on ADMs removed) to those with a depression diagnosis, with and without ADM treatment.

### Table 2 Baseline Characteristics Among Those Without a Depression Diagnosis; With Depression, But Without ADM Treatment; and With a Depression Diagnosis and ADM Use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Depression (n = 6,570)</th>
<th>Depression, No ADM Use (n = 696)</th>
<th>Depression, ADM Use (n = 454)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>76.9% (5,054)</td>
<td>68.3% (475)</td>
<td>60.8% (275)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.5 ± 11.5</td>
<td>64.2 ± 11.8</td>
<td>62.6 ± 12.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.7% (3,857)</td>
<td>62.4% (434)</td>
<td>65.2% (296)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>58.3% (3,829)</td>
<td>58.1% (404)</td>
<td>60.3% (273)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.9% (1,309)</td>
<td>26.8% (186)</td>
<td>33.3% (151)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>40.8% (2,679)</td>
<td>42.9% (298)</td>
<td>39.4% (179)</td>
<td>0.46</td>
</tr>
<tr>
<td>Smoking history</td>
<td>20.7% (1,361)</td>
<td>24.0% (167)</td>
<td>17.8% (81)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.7 ± 14.3</td>
<td>29.9 ± 16.1</td>
<td>30.5 ± 12.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Ejection fraction (n = 4,598)</td>
<td>61.1 ± 13.5</td>
<td>58.6 ± 14.8</td>
<td>60.7 ± 12.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.1% (73)</td>
<td>2.7% (19)</td>
<td>3.3% (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiography presentation</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
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<tr>
<td>Stable angina</td>
<td>41.9% (2,751)</td>
<td>48.9% (340)</td>
<td>47.1% (214)</td>
<td></td>
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<tr>
<td>Unstable angina</td>
<td>32.3% (2,122)</td>
<td>30.4% (211)</td>
<td>29.5% (134)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>25.8% (1,697)</td>
<td>20.7% (144)</td>
<td>23.3% (106)</td>
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ADM = antidepressant medication; CAD = coronary artery disease.
Discussion

This study is the first, to our knowledge, to show that a diagnosis of depression is a risk factor for the development of HF after a CAD diagnosis, even after adjustment by baseline characteristics, medications, and follow-up MI. This risk remained even when patients were treated with ADM therapy. It is particularly interesting that ADM treatment did not affect the risk of HF development. This finding indicates that ADM therapy may not alter the physiological and/or behavioral risks associated with depression and HF, despite a potential improvement in depressive symptoms (31). These results are consistent to findings in the Enhancing Recovery in Coronary Heart Disease study, in which the authors reported that post-MI patients treated with ADM had improved depressive symptoms but no reduction in the risk of mortality (32). This finding could have significant clinical impact in the treatment of depression. Although a person’s depressive symptoms have improved, the risks associated with negative CV outcomes have not.

Another important finding of this study is that treatment just by ADM without a depression diagnosis is not associated with an increase risk of developing HF. This was determined by comparing those treated with ADM therapy, but without a diagnosis of depression, to those with a depression diagnosis (treated and not treated by ADMs). In fact, this comparison resulted in an even increased risk for the incidence of HF among those with a depression diagnosis (treated and not treated). However, when compared with those without depression and ADM therapy, no difference in risk was found. It may be that the indication for ADM was not to treat depression, but rather some other ailment or that the attending health care provider thought that those with severe depressive symptoms warranted a clinical diagnosis, whereas those prescribed ADM medications without a depression diagnosis were done as precaution because they exhibited some particular characteristics or risk factors. Therefore, when designing future epidemiological studies, the use of ADM therapy as a surrogate for depression should be used with caution because the majority of depressed patients in this study were not treated with ADM therapy and a considerable number of those treated with ADMs did not have an associated depression diagnosis.

It is interesting to note that those who did not receive an EF measurement were found to have an increased risk of developing HF compared with those receiving an EF measurement. This finding indicates that those who were thought, as determined by their physician by not measuring an EF, to have the least risk of having systolic dysfunction were at an even greater risk of being hospitalized for HF. It has been reported that there is a strong relationship between depression and the functional severity of HF (New York Heart Association functional class) (33). It may be then that depression may exacerbate symptoms and increase the severity of functional impairment, since depression was shown to correlate with New York Heart Association

### Table 3 Multivariable Results for Those With Available Follow-Up Medication Information (n = 7,719)

<table>
<thead>
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<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Depression with no ADM use</td>
<td>1.68</td>
<td>1.36–2.07</td>
<td>&lt;0.0001</td>
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<tr>
<td>versus no depression</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Depression with ADM use</td>
<td>2.09</td>
<td>1.54–2.58</td>
<td>&lt;0.0001</td>
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<tr>
<td>versus no depression</td>
<td></td>
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<td></td>
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<tr>
<td>Depression versus depression</td>
<td>0.84</td>
<td>0.63–1.13</td>
<td>0.24</td>
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<tr>
<td>with ADM use</td>
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</table>

Comparisons include those with a clinical diagnosis of depression and no antidepressant medication (ADM) use to no clinical diagnosis of depression and no ADM use (referent); clinical diagnosis of depression and ADM use to no clinical diagnosis of depression and no ADM use (referent); and a clinical diagnosis of depression and no ADM use to a clinical diagnosis of depression and ADM use (referent).

CI = confidence interval.
functional class, but not with EF. Therefore, in patients with similar EF measurements, those who are depressed are more likely to report worse symptoms of HF and worse functional impairment in every day activities compared to those who are not depressed. This may be one of the reasons for not following prescribed treatments and interventions, which then may contribute to the development of HF.

A number of behavioral and physiological risks are associated with both depression and HF. Some of these risks include smoking, CAD, hypertension, diabetes, and being overweight (6). Because depressed individuals are less likely to properly take medications, not following a prescribed diet or exercise routine, or not attending scheduled appointments may be behavioral risks that lead to the development of HF. Depression has been shown to be a risk factor for poor medication adherence (28), and CV patients with poor adherence have worse outcomes (34). Depression also is associated with heart rate variability (11), blunted baroreflex sensitivity (12), heightened sympathetic nervous system activity (13), blood hypercoagulability (14), elevated inflammatory levels (15–18), and endothelial dysfunction (19). These physiological derangements are present in both depressed patients without CV disease and patients with a history of depression but are not currently depressed (35). These physiological dysfunctions are also associated with HF development (36–38). Thus, these depression-induced physiological dysfunctions are biologically plausible pathways that could explain the association between depression and HF development.

Two other studies have evaluated the association of depression with incidence HF, but among different patient populations (39,40). In a study by Abramson et al. (39), 4,538 persons ages 60 years and older with isolated systolic hypertension reported an almost 3-fold risk (HR: 2.82, p < 0.0001) in the development of HF among those depressed compared with those not depressed (39). Williams et al. (40) reported attenuated, while clinically important results (HR: 1.52, p = 0.09) among 2,501 in a community sample of persons ages ≥65 years. Both of these studies evaluated populations that had minimal CAD and were relatively older. These studies also identified depression differently through the use of Center for Epidemiological Studies Depression Scale, although with different depression thresholds. Although there are differences in methodologies and patient populations, results were similar to findings in this study.

Study limitations. A limitation of this study is the possibility of residual confounding. Although a strength of this study is the many baseline and follow-up risk factors that were available for adjustment, unmeasured confounding may still be present. For example, we did not have information on the severity of depressive symptoms (differences in severity of depression between the patients since all patients were deemed depressed or not depressed), change of depressive symptoms, start or stop of ADMs, socioeconomic status, behavioral changes, and functional impairment. However, functional impairment information was available in the studies by Abramson et al. (39) and Williams et al. (40), which produced similar results as this study. Like any other cohort study, the nonrandomized design of this study is unable to determine causality and temporality. It could be argued that the association of depression with heart disease was merely the result of the patient’s depressive reaction to the symptoms of heart disease. However, studies have shown that such an association does not explain the majority of the relationship between heart disease and depression (41–43).

Another limitation of this study is patient selection. First, the depression definition (ICD-9 codes) most likely resulted in an underestimation of the prevalence of depression (10% is lower than expected among a CAD population) and an attenuation of the results. We performed a random chart review of those with an ICD-9 diagnosis of depression within the entire registry in an effort to validate the ICD-9 diagnosis of depression using the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria (44). Of the 262 patient charts reviewed, 215 (82.1%) charts reported that the patient had depression, but only 8 of those charts described DSM-IV criteria. Of those 8 charts, none of the health care providers mentioned that the patient actually met the DSM-IV criteria or that they were evaluated by the DSM-IV criteria. Also, the ICD-9 diagnoses of depression were captured in a variety of places, which include outpatient (26.2%), inpatient (67.5%), and emergency (6.3%) settings. This may be a result of how depression was reported. Results of this chart review indicate that future studies should take a more prospective approach in the evaluation of depression. Second, when assessing ADM use, only those with a readmission or use of an Intermountain Healthcare pharmacy were evaluated. Finally, an HF diagnosis was only able to be determined if the patient was hospitalized. Therefore, it is likely that the incidence of HF was underestimated since only those with severe HF would be hospitalized.

Study strengths. Strengths of this study include its large sample size and long prospective follow-up. Data within this study were collected on standardized forms and by similar means. Not only did this study have a variety of baseline risk factors available for adjustment, it also had information on follow-up events. Myocardial infarction is a strong risk factor for the development of HF and by being able to adjust by the occurrence of follow-up MI in the analysis allows for the reduction of residual confounding, which accords greater credence for the association between depression and HF. Another strength of this study is its ability to identify a depression diagnosis during follow-up. In most studies, the identification of depression is made
through survey or interview at a single point in time. These assessments do not take into account the manifestation or diagnosis of depression after hospitalization. This study is able to identify a clinical diagnosis of depression at multiple time points and assess its impact on HF development.

Conclusions

After the development of CAD, the subsequent diagnosis of depression was associated with greater HF incidence, despite treatment with ADMs. Because both HF and depression are some of the most burdensome diseases in the world and are associated with high rates of health care utilization and severe limitations in daily functioning (5,32,45,46), this study’s finding of an association between these 2 diseases could increase use of health care services, thus multiplying the burden via resources and cost. Although this association needs further investigation, its consequences and future interventions could have a significant public health impact through the reduction of morbidity, mortality, quality of life, and health care expenditures.

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REFERENCES


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