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Depression and Five Year Survival Following Acute Myocardial Infarction

Robert M. Carney, PhD^{1,4}, Kenneth E. Freedland, PhD^{1,4}, Brian Steinmeyer, MS^{1,4}, James A. Blumenthal, PhD^{1,5}, Lisa F. Berkman, PhD^{3,6}, Lana L. Watkins, PhD^{1,5}, Susan M. Czajkowski, PhD⁷, Matthew M. Burg, PhD^{2,8}, and Allan S. Jaffe, MD^{2,9}

^{1,4}Department of Psychiatry, Washington University School of Medicine, St. Louis, MO ^{1,5}Department of Psychiatry, Duke University Medical Center, Durham, NC ^{2,8}Department of Medicine, Yale University School of Medicine, New Haven, CT ^{2,9}Department of Medicine, Mayo Clinic, Rochester, MN ^{3,6}Department of Epidemiology, Harvard University, Boston MA ⁷National Heart, Lung, and Blood Institute, Bethesda, Maryland

Abstract

Background—Depression has been shown to be a risk factor for mortality during the 12 months following an acute myocardial infarction (MI), but few studies have examined whether it is associated with increased risk over longer periods. Most of the existing studies utilized depression questionnaires rather than diagnostic interviews, the gold standard for clinical depression diagnosis. The purpose of this study was to determine whether interviewed-diagnosed clinical depression affects survival for at least 5 years after an acute MI.

Methods—Vital status was determined for 163 patients with major depression, 195 with minor depression or dysthymia, and 408 nondepressed patients, during a median follow-up period of 58 months after an acute MI. Survival analysis was used to model time from the index MI to death.

Results—There were 106 deaths during the follow-up. After adjusting for other risk factors for mortality, patients with either major or minor depression (HR = 1.76; 95% CI: 1.19 to 2.60), major depression alone (HR = 1.87; 95% CI: 1.17 to 2.98), or minor depression alone (HR = 1.67; 95% CI: 1.06 to 2.64) were at higher risk for all-cause mortality compared to the nondepressed patients.

Conclusions—Depression is an independent risk factor for death 5 years after an acute MI. Even minor depression is associated with an increased risk. Although it is not known whether treating depression can improve survival, patients with depression should be recognized as being at increased risk long after their acute MI.

Keywords

Depressive Disorder; Acute Myocardial Infarction; Mortality

Address for reprints: Robert M. Carney, PhD, Behavioral Medicine Center, 4625 Lindell Blvd. Suite 420, St. Louis, MO, 63108. Telephone: 314-286-1300. Fax: 314-286-1301. Email: carneyr@bmc.wustl.edu.

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Introduction

Depression is a risk factor for mortality following an acute myocardial infarction (MI). (Barth et al., 2004; Carney & Freedland, 2003; Glassman & Shapiro, 1998; van Melle et al., 2004) Most studies of depression and mortality after MI have followed patients for 12 months or less after the acute event. However, clinical depression is often chronic or recurrent. Therefore, the adverse effects of depression might continue for months or even years after an MI.

A few studies have included longer follow-ups of depressed post-MI patients. However, most of them have used self-report inventories to assess depression (Grace et al., 2005; Lane et al., 2002; Strik et al., 2003; Lesperance et al., 2002), and they have provided mixed support for a long term effect of depression on mortality. For example, using the Beck Depression Inventory (BDI) (Beck et al., 1979), Lesperance and his colleagues found a significant dose-response relationship between BDI scores in the days following the MI and mortality over a five year period. (Lesperance et al., 2002) Lane et al., on the other hand, found no relationship between BDI scores following an acute MI and three year mortality (Lane et al., 2002), although they also reported no relationship after one year in the same cohort. (Lane et al., 2001) One of the problems in defining depression by self-report questionnaires like the BDI is that they are not highly specific for clinical depression. Another is that they assess the patient's current mood state but not the chronicity or history of depression. Thus, an elevated score may reflect transient sadness, anxiety, other psychiatric disorders, general distress secondary to a life-threatening experience, or even the symptoms of the medical illness. (Strik et al., 2001)

The gold standard for defining clinical depression is a diagnostic interview. However, only a few interview-based studies have examined the relationship between depression and long term survival following an acute MI. Dickens and colleagues did not find a significant relationship between depression prior to an acute event and 8 year mortality, using either the Hospital Anxiety and Depression Survey (HADS) self report inventory, or a diagnostic interview that was administered to a subset of these patients. (Dickens et al., 2007) However, they identified patients who were depressed *prior* to rather than immediately *following* the acute MI, in contrast to previous investigations. On the other hand, Drago and colleagues found that an interview-based diagnosis of depression following an acute MI predicted 5 year mortality, but this was a small study with only 15 patients who met criteria for major depression. (Drago et al., 2007) Furthermore, it did not address the question of whether minor depression also poses a risk.

We previously reported the results of a 24-month follow-up of a cohort of 356 post-MI patients with an interview-based diagnosis of either major or minor depression, and 403 nondepressed patients. (Carney et al., 2003) This paper reports the results of a 5 year follow-up of this cohort.

Methods

Subjects

Patients admitted for an acute MI to hospitals at four enrollment sites of the ENhancing Recovery In Coronary Heart Disease (ENRICHD) clinical trial (Washington University, St. Louis, MO; Duke University, Durham, NC; Harvard University, Boston, MA; Yale University, New Haven, CT) between October 1997 and January 2000 were screened for eligibility within 28 days following hospital admission. Myocardial infarction was documented by cardiac enzymes, and either chest pain consistent with acute MI, or characteristic evolutionary ST-T changes or new Q waves. Patients were excluded if they: 1) had other life-threatening medical illnesses, cognitive impairment, or other major psychiatric disorders; 2) were too ill or logistically unable to participate; 3) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants; or 4) refused to provide written informed consent to participate.

Patients were eligible for enrollment in this ancillary study if they scored 10 or higher on the Beck Depression Inventory (BDI)(Beck et al., 1979), and met the Diagnostic and Statistical Manual-IV (DSM-IV) diagnostic criteria for either major depression, or minor depression or dysthymia(ENRICHD Investigators, 2000) on the Depression Interview and Structured Hamilton (DISH).(Freedland et al., 2002) Following the ENRICHD protocol(ENRICHD Investigators, 2000; Berkman et al., 2003), medically eligible patients with a prior episode of major depression could be enrolled if they met the symptom criteria for a major or minor depressive episode for at least 7 rather than the usual 14 days. The DSM-IV duration criterion for dysthymia was not changed.

Patients were enrolled in the ancillary study as nondepressed controls if they met all medical eligibility criteria for ENRICHD, but not the trial's criteria for depression or low perceived social support (ENRICHD Investigators, 2000), had no prior episodes of major depression, and scored < 10 on the BDI. The first eligible nondepressed patient to have been screened after the enrollment of a depressed patient was enrolled as a control subject. If no depressed patients were identified on a given day, the first eligible nondepressed patient was enrolled.

A total of 358 depressed patients and 408 nondepressed patients were enrolled. One hundred sixty-three of the depressed patients met the criteria for major depression, and 195 met the criteria for either minor depression (192) or dysthymia only (3). Patients with both major depression and dysthymia were included in the major depression group, and those with dysthymia only were added to the group with minor depression. One hundred sixty of the depressed patients were randomized to the ENRICHD intervention, and 182 were randomized to the usual care arm. More detailed accounts of recruitment, enrollment, and the demographic and medical characteristics of the participants in the ENRICHD trial and this ancillary study are available elsewhere.(ENRICHD Investigators, 2000; Berkman et al., 2003; Carney et al., 2001; Carney et al., 2003)

Follow-up

The primary endpoint for this study was all-cause mortality. Vital status was determined for all participants by searching the National Death Index, using name, social security number, gender, date of birth, and last known residence. National Death Index searches of this type have been shown to be highly accurate in determining vital status and date of death.(Cowper et al., 2002)

Statistical Analyses

Chi-square tests and analyses of variance were used to determine whether demographic and medical characteristics differed between depressed and nondepressed patients. Univariate and covariate-adjusted Cox proportional hazards regression models were used to describe the relationship between depression and survival. Schoenfeld (Schoenfeld, 1982) and Martingale residuals (Therneau et al., 1990) were used to test the Cox model assumptions of proportional hazards and linearity of continuous covariates, respectively. Variable-by-time interaction terms were also used to test the proportional hazards assumption. Survival curves were generated by the Kaplan-Meier method and were then compared with the log rank statistic.(Hosmer & Lemeshow, 1999)

A composite index of independent risk factors for all-cause mortality in the ENRICHD trial was used to adjust for possible confounders.(Jaffe et al., 2006) All major positive and negative risk factors and cardiac treatments were initially considered in the model, including smoking, hypertension, gender, being discharged on beta blockers, etc. The risk score represents a weighted sum of the independent predictors, including age, diabetes, LVEF, creatinine level,

prior MI, history of pulmonary disease, prior transient ischemic attack or stroke, history of heart failure, Killip class at time of index MI, and treatment with vasodilators.

Multiple imputation (SAS Proc MI) was used to impute missing data.(Rubin, 1990) Survival outcomes were not included in the imputation model. All analyses were performed on 50 completed data sets in which missing values were replaced with values estimated from observed variables. The resulting model estimates were then combined for statistical inference. SAS 9.1.3 software (SAS Institute, Inc., Raleigh, NC) was used to perform all statistical analyses.

Results

The medical and demographic characteristics of the subjects are presented in Table 1. The depressed patients were slightly younger (mean age 57 ± 12 vs. 61 ± 11 years), more likely to be female (48% vs. 32%), to have diabetes (33% vs. 22%), to be a current cigarette smoker (41% vs. 26%), and less likely to be on β -blockers (21% vs. 15%), than the nondepressed patients.

The patients were followed for a median of 58 months. A total of 106 patients died during the follow-up, including 62 of the initially depressed patients and 44 of the nondepressed. There were no differences in the rates of death between the ENRICHD participants who received the intervention and those in the usual care arm (log rank $p = 0.82$). Thus, treatment arm assignment was not included in further analyses. The hazard of death was proportional over time for depression but not for the ENRICHD risk score. This was corrected in the Cox model by median split stratification.(Hosmer & Lemeshow, 1999)

The unadjusted hazard ratio for either major or minor depression was 1.61 (95% CI: 1.09 to 2.36; $p=0.02$). The unadjusted hazard ratios for major and minor depression separately were 1.70 (95% CI: 1.07 to 2.70; $p=0.03$) and 1.53 (95% CI: .97 to 2.41; $p=0.07$), respectively. The adjusted hazard ratios were 1.76 (95% CI: 1.19 to 2.60) for either major or minor depression, 1.87 (95% CI: 1.17 to 2.98) for major depression alone, and 1.67 (95% CI: 1.06 to 2.64) for minor depression alone, compared to the nondepressed patients (Table 2). Kaplan-Meier estimates of survival for the depressed and nondepressed patient groups are presented in Figure 1. The depressed patients had less favorable survival than the nondepressed patients over the follow-up period (log-rank statistic: $\chi^2 = 5.88$; $df = 1$; $p = .02$).

Discussion

To our knowledge, this study includes the largest sample of depressed patients, as determined by a structured clinical interview, and one of the longest follow-up periods, of any prognostic study of depression in post-MI patients conducted to date. The results confirm that depression is associated with an increased risk of all-cause mortality, even after adjustment for multiple potential confounders and other predictors of survival. The hazard for major depression was higher than that for minor depression, consistent with the previous observation of a dose-response relationship between depression severity and survival in post MI patients.(Bush et al., 2001; Lesperance et al., 2002) However, patients with minor depression were nevertheless at significant risk.

About 80% of patients in this study completed a BDI at 12 months. There was a trend toward improvement in depression among the depressed group after 12 months (mean BDI at baseline = 17.5 vs. 10.0 at the 12 month follow-up), while the nondepressed patients remained at about the same low level of depression (mean baseline BDI = 3.9 vs. 3.5 at 12 months). However, we know little about the duration of the depression episodes that were identified at baseline, the rates of relapse and recurrence, peak severity, or the cumulative exposure to depression

over the entire follow-up period. A better understanding of the course of depression following acute MI and its relationship to mortality risk remains one of the most important goals in this area of study.(Carney & Freedland, 2007)

One of the study's limitations is that the depressed sample was composed of participants enrolled in a clinical trial. As a result, the findings may not generalize to all post-MI patients, as patients who were too sick or debilitated to participate in the trial intervention were not enrolled. A second limitation concerns the size of the sample. Even though this is one of the largest studies of its kind to date, both the sample size and number of events were small compared to many studies of other major cardiovascular risk factors for post-MI mortality.

In conclusion, clinical depression was found to be an independent risk factor for death 5 years after the acute MI. Even minor depression increased the risk of dying. Although it is not yet known whether treating depression can improve survival(Carney & Freedland, 2007), depression should be recognized as a risk factor for mortality well after an acute MI.

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Figure 1.
Kaplan-Meier group survival curves for nondepressed and major/minor depressed participants

Table 1

Medical and demographic characteristics by depression status *

Characteristic	Depressed (n=358)	Nondepressed (n=408)	p-value
Age (years)	56.8 ± 12.7	60.9 ± 10.9	<.0001
Beck Depression Inventory	17.5 ± 7.6	3.9 ± 2.9	<.0001
Women	48.3%	31.9%	<.0001
Systolic blood pressure	123.4 ± 20.0	122.2 ± 18.1	.43
Diabetes mellitus	32.9%	22.3%	.001
Cigarette smoker (current)	40.7%	26.2%	<.0001
LVEF (<40%)	23.9%	22.4%	.90
Killip class III–IV	5.7%	4.4%	.43
Creatinine (mg/dl)	1.1 ± 0.8	1.1 ± 0.6	.67
Prior MI	22.2%	20.0%	.47
Coronary bypass post MI	14.4%	12.7%	.48
Beta blocker	78.8%	85.2%	.02
ACE inhibitor	46.4%	49.5%	.41

* Continuous variables are reported as means ± standard deviations; categorical variables are listed as column-wise percentage.

Table 2

The Effect of Depression on 5 Year Survival

Model	Any Depression	Parameter Major Depression	Minor Depression
Unadjusted ¹	1.61 CI(1.09, 2.36) p = .016	1.70 CI(1.07, 2.70) p = .025	1.53 CI(.97, 2.41) p = .068
Adjusted ²	1.76 CI(1.19, 2.60) p = .004	1.87 CI(1.17, 2.98) p = .009	1.67 CI(1.06, 2.64) p = .028

¹ Estimated hazard ratio (HR) compared to nondepressed participants, 95% confidence interval (CI), and p-value.

² Estimated HR adjusted for mortality risk score.