

# History of Depression and Survival After Acute Myocardial Infarction

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**Objective:** To compare survival in post-myocardial (MI) participants from the Enhancing Recovery In Coronary Heart Disease (ENRICHD) clinical trial with a first episode of major depression (MD) and those with recurrent MD, which is a risk factor for mortality after acute MI. Recent reports suggest that the level of risk may depend on whether the comorbid MD is a first or a recurrent episode. **Methods:** Survival was compared over a median of 29 months in 370 patients with an initial episode of MD, 550 with recurrent MD, and 408 who were free of depression. **Results:** After adjusting for an all-cause mortality risk score, initial Beck Depression Inventory score, and the use of selective serotonin reuptake inhibitor antidepressants, patients with a first episode of MD had poorer survival (18.4% all-cause mortality) than those with recurrent MD (11.8%) (hazard ratio (HR) = 1.4; 95% Confidence Interval (CI) = 1.0–2.0;  $p = .05$ ). Both first depression (HR = 3.1; 95% CI = 1.6–6.1;  $p = .001$ ) and recurrent MD (HR = 2.2; 95% CI = 1.1–4.4;  $p = .03$ ) had significantly poorer survival than did the nondepressed patients (3.4%). A secondary analysis of deaths classified as probably due to a cardiovascular cause resulted in similar HRs, but the difference between depression groups was not significant. **Conclusions:** Both initial and recurrent episodes of MD predict shorter survival after acute MI, but initial MD episodes are more strongly predictive than recurrent episodes. Exploratory analyses suggest that this cannot be explained by more severe heart disease at index, poorer response to depression treatment, or a higher risk of cerebrovascular disease in patients with initial MD episodes. **Key words:** depression, depression history, acute myocardial infarction, mortality.

**MI** = myocardial infarction; **MD** = major depression; **ENRICHD** = Enhancing Recovery In Coronary Heart Disease; **DISH** = Depression Interview and Structured Hamilton; **BDI** = Beck Depression Inventory; **HR** = hazard ratio; **SSRI** = selective serotonin reuptake inhibitor; **HAM-D** = Hamilton Rating Scale for Depression; **UC** = usual care; **LVEF** = left ventricular ejection fraction; **ACS** = acute coronary syndrome; **HADS** = Hospital Anxiety and Depression Scale.

## INTRODUCTION

Numerous studies have established depression as a risk factor for mortality post acute myocardial infarction (MI) (1–3), although a few studies have failed to replicate these findings (3). One possible explanation for the negative findings is that not all patients with depression are at high risk for mortality, and the proportion of truly high-risk depressed patients may vary across samples. One of the factors that may affect the level of risk is whether the major depressive episode at the time of the MI is the patient's first; that is, whether a patient has a history of major depressive episodes before their index MI, or whether the episode occurring in conjunction with the MI is the first episode (4,5).

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In the first study to address this question, Lespérance and colleagues found that patients with recurrent major depression (MD) tended to be at higher risk for mortality than those with an initial episode (6). This finding was not unexpected: the more exposure to a risk factor, the higher the risk. Having hypertension for 10 years, for example, is associated with a higher risk than having it for 1 year. Thus, depressed patients with a history of earlier depressive episodes, and therefore more exposure to its cardiotoxic effects, should be at greater risk for cardiac events than those with a first episode. However, three recent studies have found that initial episodes of depression may carry more risk than recurrent depression (7–9).

Recent clinical trials have provided evidence that patients with a recurrent depressive episode post MI may respond better to antidepressants than those with an initial episode (10,11). It is possible, therefore, that patients with a first episode of depression have a form of depression that is less responsive to standard treatments. These patients may be at higher risk for mortality post MI because their depressions are more likely to persist even if treated.

The primary purpose of this study was to examine the relationship between initial versus recurrent MD and survival in post-MI patients who were enrolled in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) clinical trial. The secondary aims were to explore medical, demographic, and psychiatric differences between these subgroups to generate hypotheses about why medical prognosis may differ because of depression history and to determine whether depression history affects response to treatment.

## METHODS

### Subjects

Patients admitted between October 1996 and October 1999 to coronary care units at eight ENRICHD clinical trial sites (Washington University, St. Louis, Missouri; Duke University, Durham, North Carolina; Harvard University, Boston, Massachusetts/Yale University, New Haven, Connecticut [combined]; Stanford University, Stanford, California; University of Miami, Miami, Florida; University of Alabama, Birmingham, Alabama; University of Washington, Seattle, Washington; and Rush Presbyterian Hospital, Chicago, Illinois) for an acute MI were screened for eligibility within 28 days after hospital admission. The study protocol was approved by the Institutional Review Boards from each

participating site. MI was documented by cardiac enzymes and by chest pain compatible with acute MI, characteristic evolutionary ST-T changes, or new Q waves. Details of the methods and design of the ENRICHD clinical trial are available elsewhere (12,13). Patients were excluded from the ENRICHD trial if they:

- a) had other life-threatening medical illnesses, cognitive impairment, other major psychiatric disorders, or were at imminent risk of suicide;
- b) were too ill or unable to participate due to logistical barriers;
- c) had been taking an antidepressant for <14 days; or
- d) were exempted by their cardiologist from participating in the study.

## Procedures

Patients who fulfilled the eligibility criteria and provided their informed consent were administered the ENRICHD social support instrument (12) and the Depression Interview and Structured Hamilton (DISH) (14). The DISH is a semistructured interview that was developed for ENRICHD to diagnose current depressive episodes in cardiac patients according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, to determine the severity of depression using the 17-item Hamilton Rating Scale for Depression (HAM-D), and to screen for other psychiatric disorders. The interview also is designed to differentiate between first and recurrent major depressive episodes. There is a high level of diagnostic agreement between DISH interviews administered to cardiac patients by trained research nurses and structured interviews administered by trained clinicians (weighted  $\kappa = 0.86$ ) (14). Patients also completed the Beck Depression Inventory (BDI) (15), a 21-item measure of the self-reported severity of depression.

Medically eligible patients who met the symptom criteria for either major or minor depressive episode for at least 7 rather than the usual 14 days could be enrolled in ENRICHD if they had a prior episode of MD. However, only patients who met the full DSM-IV criteria for MD, including a  $\geq 14$ -day duration, were included in the analysis.

Patients who met all medical inclusion criteria, but who did not meet the depression criteria of the ENRICHD trial, were recruited for a nondepressed comparison group for an ancillary study from three of the ENRICHD sites (Washington University, St. Louis, Missouri; Duke University, Durham, North Carolina; Harvard University, Boston, Massachusetts/Yale University, New Haven, Connecticut). Additional criteria for enrollment in the comparison group included a score of <10 on the BDI and no previous episodes of MD.

Patients enrolled in the clinical trial were assigned randomly to either the study intervention or to usual care (UC). Intervention patients received individual, and in some cases, group cognitive behavior therapy weekly for up to 6 months. Patients with severe depression (HAM-D score of  $>24$ ), and those who did not show at least a 50% decrease in BDI scores after 5 weeks, were referred to study psychiatrists for consideration of pharmacotherapy. Most of these patients were started on 50 mg/day sertraline, and the dosage was subsequently adjusted up to a maximum of 200 mg/day, if needed. Nearly all of these patients received the antidepressant for 12 months (13). The nondepressed comparison patients did not receive a study-related intervention, but they were followed for the duration of the study.

Follow-up assessments were performed annually beginning 6 months after enrollment. The primary outcome of the ENRICHD trial was the combined end point of all-cause mortality or recurrent nonfatal acute MI. Standardized, group-masked classification of the major end points, including probable cardiovascular and noncardiovascular death, was performed by the ENRICHD Medical Endpoints Committee. Death certificates were obtained to document all deaths. The primary end point for the present study was all-cause mortality. Suspected cardiovascular mortality was also evaluated as a secondary end point.

## Statistical Analyses

$\chi^2$  tests and analyses of variance were used to compare demographic and medical variables across the three groups (i.e., initial episode of depression, recurrent depression, nondepressed controls). Kaplan-Meier estimates and covariate-adjusted Cox proportional hazards regression models were used to describe the relationship between depression subgroup and survival. Schoenfeld (16) and Martingale residuals (17) were used to test the Cox model

assumptions of proportional hazards and linearity of continuous covariates, respectively. Variable-by-time interaction terms were also calculated to test the proportional hazards assumption. Kaplan-Meier survival curves for the three groups were compared with the log rank statistic (18).

A previously published, weighted index of independent risk factors for all-cause mortality in the ENRICHD trial was used to adjust for possible confounders (19). All major risk factors and cardiac treatments were initially considered in this model, including smoking, hypertension, gender, current heart failure, and being discharged on  $\beta$  blockers. The final risk score, representing the best set of independent predictors for all-cause mortality for the participants in the ENRICHD clinical trial, included age, diabetes, left ventricular ejection fraction (LVEF), creatinine level, prior MI, history of pulmonary disease, prior transient ischemic attack or stroke, history of heart failure, Killip class at time of the index MI, and treatment with vasodilators. Baseline BDI scores, and selective serotonin reuptake inhibitor (SSRI) antidepressant use during the study, which was previously shown to be associated with improved survival in the ENRICHD trial (20), were also included in the adjusted models. Because SSRI use varied throughout the follow-up period, it was modeled as a time-dependent covariate, as described by Taylor and colleagues (20).

Multiple imputation (SAS Proc MI) was used to impute missing data, which occurred in 3% to 10% of cases for the covariables included in the statistical models (21). Survival outcomes were not included in the imputation model. All analyses were performed on 50 complete 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, North Carolina) was used to perform all statistical analyses.

## RESULTS

A total of 920 patients enrolled in the ENRICHD study who met the full DSM-IV criteria for major depression at the time of enrollment, including the  $\geq 14$ -day episode duration criterion, and 408 patients who were free of depression but otherwise eligible for the ENRICHD study, were included in the present analyses. Three hundred seventy (40%) of the patients who met the criteria for MD at enrollment reported this to be their first depressive episode, and 550 (60%) reported having one or more previous episodes. Comparisons of the medical and demographic characteristics of the three groups are presented in Table 1. There are many demographic and medical differences between both of the depressed groups and the nondepressed patients, including a higher proportion of women and a higher prevalence of diabetes. These differences have been reported in earlier studies (22,23).

During a median follow-up of 29 months, 3.4% of the nondepressed patients died, compared with 18.4% of the patients with first-time MD, and 11.8% of those with recurrent MD. There was no difference in survival between intervention versus UC arms for either first depressive episode (20% versus 17%,  $p = .23$ ) or recurrent depression cases (11% versus 12%,  $p = .61$ ). Consistent with the results of the ENRICHD trial (13), there were no differences in survival overall between patients who received the intervention and those in the UC arm (log rank:  $\chi^2 = 0.17$ ;  $df = 1$ ;  $p = .68$ ). Thus, treatment arm assignment was not included in the primary analyses.

Kaplan-Meier survival curves for the three groups are presented in Figure 1. The omnibus test of differences in survival among the groups was significant (log rank test:  $\chi^2 = 38.4$ ;

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**TABLE 1. Demographic, Depression, and Medical Characteristics<sup>a</sup>**

Characteristic	First Episode Major Depression (n = 370)	Recurrent Major Depression (n = 550)	No Depression (n = 408)	p		
				1 versus 3	2 versus 3	1 versus 2
<b>Demographics</b>						
Women	44.3%	54.2%	32.1%	.001	<.001	.003
Married	60.4%	55.0%	78%	<.001	<.001	.10
Education (>12 years)	68.4%	71.2%	77.0%	.008	.05	.37
Age (years)	60.7 ± 12.4	58.4 ± 12.2	61.1 ± 10.6	.86	.001	.01
PSS	60.2 ± 15.2	57.6 ± 16.2	NA <sup>b</sup>			.02
<b>Depression</b>						
BDI (Base)	19.4 ± 8.2	22.2 ± 8.4	3.9 ± 2.9	<.001	<.001	<.001
BDI (6 months)	10.5 ± 9.6	13.7 ± 9.5	NA <sup>b</sup>	—	—	<.001
Change in BDI (B - 6 months)	8.3 ± 9.8	8.5 ± 10.2	—	—	—	.81
No. prior depression episodes	0	3.1 ± 3.9	0	—	—	—
Baseline antidepressants	5%	15.5%	1.8%	.01	<.001	<.001
Antidepressants at any time	19.5%	34.6%	5.7%	<.001	<.001	<.001
Family history of depression	16.8%	42.7%	14.9%	.51	<.001	<.001
<b>Risk factors/history</b>						
Total cholesterol (mg/dl)	198 ± 47.9	202 ± 61.1	184 ± 47.3	.02	.0002	.75
BMI (kg/m <sup>2</sup> )	28.4 ± 5.8	29.5 ± 6.4	28.4 ± 4.8	.99	.02	.02
Systolic blood pressure (mm Hg)	126.7 ± 20.2	122.9 ± 20.0	122.2 ± 18.1	.005	.86	.01
Diabetes mellitus	37.4%	38.2%	22.3%	<.001	<.001	.80
History hypercholesterolemia	61.3%	66.4%	49.1%	.001	<.001	.13
Heart disease in 1st degree relatives	70.1%	70.2%	67.2%	.40	.33	.97
History CHF	18.8%	17.9%	4.4%	<.001	<.001	.73
History PVD	13.0%	17.7%	5.6%	.004	<.001	.06
Previous AMI	29.1%	29.2%	20.3%	.005	.002	.98
History CABG	16.4%	13.4%	10.5%	.02	.18	.20
History PTCA	17.5%	17.1%	10.3%	.004	.003	.90
History stroke/TIA	9.1%	11.3%	5.8%	.08	.003	.29
Cigarette smoker (current)	29.2%	37.5%	26.1%	.35	.002	.01
History of hypertension	63.3%	65.0%	52.4%	.002	<.001	.61
<b>Post-MI medical status</b>						
ENRICHD all-cause mortality risk score	3.9 ± 1.1	3.8 ± 1.1	3.7 ± 0.9	.002	.02	.57
Q wave	27%	29%	32%	.09	.24	.51
Creatinine >1.3 mg/dl	18.0%	17.6%	15.4%	.33	.37	.87
LVEF (<40%)	27.6%	27.5%	23.0%	.17	.15	.97
Killip class III-IV	10.3%	9.8%	4.4%	.002	.002	.82
Post-MI CABG	21.2%	15.8%	13.0%	.003	.25	.04
Post-MI PTCA	43.8%	46.6%	67.3%	<.001	<.001	.40
Thrombolytic therapy	49.6%	32.5%	33.6%	<.001	.74	<.001

PSS = Perceived Social Support; BDI = Beck Depression Inventory; BMI = body mass index; CHF = coronary heart failure; PVD = peripheral vascular disease; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; TIA = transient ischemic attack; MI = myocardial infarction; ENRICHD = Enhancing Recovery In Coronary Heart Disease; LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminal coronary angioplasty.

<sup>a</sup> Continuous variables are reported as (mean ± standard deviation); categorical variables are percentage of subjects with the characteristic.

<sup>b</sup> Not administered to nondepressed patients.

$df = 2; p = .001$ ). Post hoc comparisons of survival among the three groups with a Tukey adjustment for multiple comparisons showed that both recurrent ( $\chi^2 = 10.4; df = 1; p = .004$ ) and first-time ( $\chi^2 = 38.2; df = 1; p < .001$ ) depressed groups differed from the nondepressed group. First-time and recurrent depression groups also differed from each other ( $\chi^2 = 5.8; df = 1; p = .04$ ).

Unadjusted hazard ratios (HRs) were estimated from a Cox proportional regression model for patients with first-time MD and those with recurrent MD, each compared with the reference group of nondepressed patients. Both first-time MD

(HR = 5.2; 95% Confidence Interval (CI) = 2.9–9.3;  $p < .001$ ) and recurrent MD (HR = 3.3; 95% CI = 1.8–5.9;  $p < .001$ ) predicted shorter survival. Patients with a first time depression were at higher risk than those with recurrent depression (HR = 1.6; 95% CI = 1.2–2.2;  $p = .008$ ). Adjusting for the ENRICHD all-cause mortality risk score, initial BDI score, and SSRI antidepressant use, the difference in adjusted survival between those with recurrent MD and those with a first episode of MD remained significant (HR = 1.4; 95% CI = 1.0–2.0;  $p = .05$ ). Similarly, after adjustment for covariates, survival time for those with first-time (HR = 3.1;



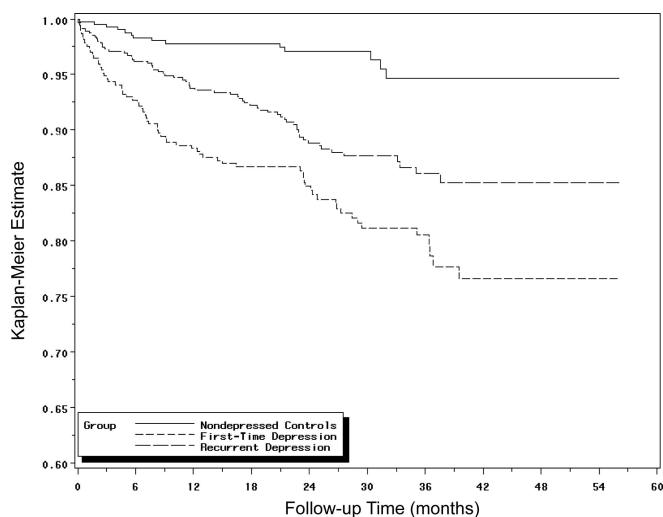


Figure 1. Kaplan-Meier survival curves for initial major depression, recurrent major depression, and no depression.

95% CI = 1.6–6.1;  $p = .001$ ) and recurrent MD (HR = 2.2; 95% CI = 1.1–4.4;  $p = .03$ ) remained significantly less than for nondepressed patients.

In a secondary analysis, unadjusted HRs for cardiovascular-specific mortality were again estimated using Cox regression. Death likely due to cardiovascular causes occurred in 2.5% of the nondepressed patients, 11.1% of the patients with first-time MD, and 7.6% of those with recurrent MD. First-time MD (HR = 4.5; 95% CI = 2.3–9.0;  $p < .001$ ) and recurrent MD (HR = 3.0; 95% CI = 1.5–6.1;  $p = .002$ ) predicted shorter survival from cardiovascular-related mortality, although the difference in survival between the two groups only approached significance (HR = 1.5; 95% CI = 0.97–2.3;  $p = .07$ ). After adjusting for the ENRICHD all-cause mortality risk score, initial BDI score, and SSRI antidepressants, the effects for first-time MD remained significant (HR = 2.7; 95% CI = 1.2–6.0;  $p = .02$ ), whereas the effect for recurrent MD was only marginal (HR = 2.1; 95% CI = 0.9–4.9;  $p < .09$ ). Cardiovascular-related mortality did not differ between the recurrent MD (reference group) and first episode of MD subgroups (HR = 1.3; 95% CI = 0.80–2.0;  $p = .31$ ).

To determine whether 6-month depression remission rates differed between the two depressed groups,  $\chi^2$  analyses were performed separately for patients in the intervention and UC groups. Remission of depression was defined in the ENRICHD trial as a BDI score of  $\leq 7$  at the 6-month assessment. The 6-month BDI was completed by 80% of the ENRICHD participants. In the intervention group, 57% of those with first-time depression remitted by 6 months, compared with 41% of those who enrolled with recurrent depression ( $\chi^2 = 8.4$ ,  $df = 1$ ;  $p = .004$ ). In the UC group, 40% of the patients with first-time depression and 20% of those who enrolled with recurrent depression remitted at 6 months ( $\chi^2 = 16.0$ ,  $df = 1$ ;  $p = .001$ ). However, the difference between the intervention and UC groups in 6-month BDI change scores did not differ by initial (mean = 3.3) versus recurrent major depressive episode (mean = 3.9;  $F = 0.18$ ;  $df = 1$ ;  $p = .67$ ), although the baseline levels did (first =  $19.4 \pm 8.2$  versus

recurrent =  $22.2 \pm 8.4$ ), suggesting that the difference in remission rates may be due to lower baseline depression scores in the group with an initial depressive episode.

## DISCUSSION

Participants in the ENRICHD clinical trial with a first episode of MD had poorer survival (18.4% all-cause mortality) than those with recurrent MD (11.8%), and both groups had significantly poorer survival than did the nondepressed patients (3.4% all-cause mortality). These differences persisted after adjusting for baseline BDI score, SSRI antidepressant use, and other medical and demographic predictors of mortality. The results of a secondary analysis of cardiovascular deaths found similar results, but the two depression groups did not differ even though the hazard was similar to that for all-cause mortality (1.3 versus 1.4). Only 83 of the 133 total deaths were classified as being clearly cardiovascular-related, suggesting that insufficient statistical power may explain the lack of significance.

The findings of the primary analysis differ somewhat from those of five other studies of first-time versus recurrent depression and survival post MI. In a secondary analysis, Lespérance and colleagues found an 18-month post-MI mortality rate of 40% in 15 patients with recurrent MD, compared with 10% in 20 patients with first-time depression (6). In a more recent study of a cohort of 750 post-acute coronary syndrome (ACS) patients, Grace et al. found that depression (BDI score of  $\geq 10$ ) at the time of the MI was a significant predictor of all-cause mortality, but only in patients who had never before been depressed (9). Thus, only new-onset depression without prior depression predicted survival. It is not clear, however, whether these patients were depressed before or only after the MI.

In a study of 468 patients, de Jonge and colleagues administered a depression interview at 3 and 12 months after an acute MI (7). They found that, of the patients who became depressed in the year post MI, only those who were depressed for the first time after the MI were at increased risk of cardiovascular mortality and cardiovascular readmissions. As in Grace et al. (9), those who became depressed but who had a history of earlier episodes of depression were not at greater risk for cardiac events.

Dickens and colleagues studied 588 patients with a recent MI (8). Patients who were depressed at 12 months after the MI, but not those who reported having been depressed in the week before the MI (HADS score of  $> 17$ ), were at greater risk for cardiovascular-related death during the follow-up period. It is not clear from this report whether patients were depressed at or some time during the previous 12 months.

In the most recent report, Parker and colleagues administered a depression interview to 489 patients post ACS, and interviewed them again by phone at 1 and 12 months (24). Neither a history of depression before the MI nor depression at the time of the MI was found to be associated with a combined end point of cardiovascular mortality or cardiac hospitalization. However, similar to Grace et al. and de Jonge et al., depression that began after an ACS admission was a risk

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factor for future cardiac events. However, unlike Grace et al. and de Jonge et al., the risk was present in patients with a depression after the event regardless of whether there were prior episodes of depression. That is, the timing of the onset of depression in relationship to the MI, and not whether it was an initial or recurrent depressive episode, determined its impact. Unfortunately, the ENRICHD interviewers did not determine the precise onset of the current depressive episode so this could not be evaluated in the present study.

Although there are methodological differences among these five studies of post-MI or ACS patients, including the use of interview-based depression diagnostic criteria versus self-report inventories, different end points (all-cause mortality, cardiovascular-related mortality, and cardiac events), and different time points for assessment of depression, none of these differences seem to explain the contradictory findings. Determining depression history is difficult, at best, and often unreliable (25). It seems likely that this difficulty is magnified when interviewing someone who just experienced a life-threatening medical event. Thus, it is possible that differences in depression history ascertainment may at least partially explain some of the variation in the findings.

Nevertheless, the preponderance of evidence now seems to suggest that an initial episode of depression after an acute MI carries a higher risk of death than does a recurrent episode, especially if its onset occurs after the acute cardiac event. Why patients with an initial depressive episode would tend to be at higher risk than those depressed patients with prior depressive episodes is not clear.

Two earlier studies found that patients who were having their first major depressive episode at the time of diagnostic coronary angiography had more severe coronary artery disease than did those patients with a recurrent episode of depression (26,27). Furthermore, first episodes of depression relatively late in life could be manifestations of cerebrovascular disease in some cases (28,29). Late-life depression has been associated with white matter hyperintensities on magnetic resonance imaging (MRI) scans, suggesting cerebrovascular abnormalities, and with mild-to-moderate cognitive impairment (30). Thus, one explanation for the present findings is that patients with an initial episode of depression may have more significant coronary artery disease or cerebrovascular disease than those with recurrent MD, placing them at higher risk for mortality.

Coronary angiography, MRI scans, and tests of cognitive functioning were not routinely performed on ENRICHD participants before or after the index MI. However, risk factors for coronary artery disease and cerebrovascular disease were determined from systematic chart reviews. ENRICHD patients with initial depressive episodes were younger than those with recurrent depression by an average of 2 years. Mean systolic blood pressure was slightly higher (4 mm Hg), but well within normal limits (mean =  $126.7 \pm 20.2$  mm Hg). Patients with initial episodes were more likely to have coronary bypass surgery after their MI, but were no more likely to have coronary angioplasty. On the other hand, they were less likely

to smoke and slightly less likely to have had a history of peripheral vascular disease than were those with recurrent depression. There were no differences between the groups in history of stroke, prior MI, revascularization, hypercholesterolemia, total serum cholesterol levels, or family history of stroke or heart disease. Thus, there was little evidence that these patients were at higher risk for cerebrovascular disease, or that they had more significant coronary artery disease before the index MI. Nevertheless, neither of these possibilities can be entirely ruled out.

It has also been suggested that acute MI patients with initial depressive episodes may have more severe coronary heart disease, compared with those with recurrent depression (7,31). However, little evidence was found for this in the present study. There were no differences between these groups in Killip class, LVEF, heart failure, prior MI, the ENRICHD all-cause mortality risk score, or the presence of other medical comorbidities. One interesting and unexpected finding was that a higher proportion of patients with initial major depressive episodes had received thrombolytic therapy, compared with patients with recurrent MD. There were no differences between these subgroups in the proportion of patients with documented Q-wave MIs. In any case, receiving thrombolytic therapy was not associated with survival in this study.

Patients with recurrent depression had slightly more severe depression, were more likely to have a family history of depression, to be female, to have less perceived social support, and to be on antidepressants at the baseline assessment. Although the data were only available for about 80% of cases, patients with initial or recurrent major depression experienced similar changes in depression severity over the first 6 months after the acute MI. However, because their depressions were slightly more severe at baseline, those with recurrent depression also remained slightly more depressed than those with first-time depression.

Initial major depressive episodes were more likely to remit than were recurrent episodes, both in the intervention and in the UC groups. However, this may have been due to lower baseline depression scores in the patients who were depressed for the first time. In any case, this finding is not consistent with the results of two recent antidepressant clinical trials.

Unlike our study, Lespérance et al. (11) found no difference in HAM-D scores at baseline between initial and recurrent depressive episodes ( $29.6 \pm 6.8$  versus  $29.8 \pm 6.7$ ), but patients with recurrent depression showed a larger response to citalopram than did patients in their first major depressive episode. Glassman et al. (10) reported a better response to sertraline in patients with recurrent MD compared with patients experiencing an initial major depressive episode. Although about 20% of patients in the ENRICHD intervention arm received sertraline, most patients were treated solely with cognitive behavior therapy. It is possible that patients with initial major depressive episodes after an acute MI respond better to psychotherapy, and those with recurrent depression respond better to antidepressant therapy. However, the study

by Lespérance et al. found that interpersonal psychotherapy had little effect on either type of depressive episode.

One possible explanation for the finding that a first episode of depression is a greater risk for mortality than a recurrent depression is that those patients with prior episodes of depression at greatest risk died as a result of the index MI. Those who survived the index MI may have been at lower risk for reasons that are not presently known. These patients may remain at lower risk in the months after the index MI.

One of the limitations of this study is that the sample was composed of participants enrolled in a clinical trial or in an ancillary study of that 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 were excluded. Furthermore, 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 total follow-up period for either group of depressed patients. This is a shortcoming of this and of most previous studies. A better understanding of the course of depression after acute MI and its relationship to mortality risk remains one of the most important goals in this area of study (32). Finally, it is possible that high-risk patients with prior episodes of depression were less likely to volunteer for the study than those with a first episode of depression, although we have no evidence for this. More than half of the patients in our sample had recurrent depression, similar to that reported in a previous study of depression in post-MI patients (31).

In summary, in a large sample of well-characterized post-MI patients with interview-based depression diagnoses, those with initial episodes of MD tended to have poorer survival than those with recurrent major depression, but both had poorer survival than did patients without depression. Exploratory analyses suggest that the greater risk of mortality seen among patients with an initial episode of MD cannot be explained by more severe cardiac illness at index or by being at higher risk for more severe coronary artery or cerebrovascular disease. Future research should attempt to confirm this finding and seek to identify the factors contributing to a greater risk of mortality after acute MI in this common subtype of MD.

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