

Published in final edited form as:

*Psychosom Med*. 2009 September ; 71(7): 697–703. doi:10.1097/PSY.0b013e3181ad2abd.

# IS DEPRESSION AFTER AN ACUTE CORONARY SYNDROME SIMPLY A MARKER OF KNOWN PROGNOSTIC FACTORS FOR MORTALITY?

**Ian M. Kronish, MD, MPH**[1], **Nina Rieckmann, PhD**[2], **Joseph E. Schwartz, PhD**[3], **Daniel R. Schwartz, MD**[1], and **Karina W. Davidson, PhD**[3,4]

[1] Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY

[2] Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

[3] Departments of Medicine & Psychiatry, Columbia University Medical Centre, New York, NY

[4] Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY

## Abstract

**Objective—**Controversy remains over whether the association between depression and mortality in patients with acute coronary syndromes (ACS) is confounded by incomplete adjustment for measures of known prognostic markers. We assessed whether depression was associated with the most comprehensive empirically derived index of clinical mortality predictors: the Global Registry of Acute Coronary Events (GRACE) risk score for predicting 6-month mortality after discharge for ACS. We also assessed whether depression remained an independent predictor of all-cause mortality after adjustment for the GRACE score and left ventricular dysfunction.

**Methods—**We prospectively surveyed 457 ACS patients (aged 25–92 years; 41% women, 13% black, and 11% Hispanic), hospitalized between May 2003 and June 2005. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) and diagnosis of major depressive disorder (MDD) by a structured psychiatric interview, within one week of hospitalization.

**Results—**Despite differences in individual components of the GRACE score between depressed and non-depressed participants, neither depression measure was associated with overall GRACE score. For participants with MDD, the mean (SD) GRACE score was 84 (33), compared to 92 (31) for those without MDD (p=0.09). Using Cox proportional hazardsregression analysis, MDD and depressive symptom severity each predicted mortality after controlling for GRACE score and left ventricular dysfunction (adjusted hazard ratio for MDD, 2.51; 95% CI 1.45–4.37).

**Conclusion—**Depression is not simply a marker of clinical indicators that predict all-cause mortality after ACS. This strengthens the assertion that there is something unique in the association between depression and post-ACS prognosis, independent of known prognostic markers.

### Keywords

depression; myocardial infarction; unstable angina; prognosis

Correspondence: Ian M. Kronish, MD, MPH; Assistant Professor, Division of General Internal Medicine, Mount Sinai School of Medicine; One Gustave L. Levy Place, Box 1087; New York, NY; 10029; (212) 241-8641; fax (212) 831-8116; ian.kronish@msnyuhealth.org.

**Conflict of Interest:** none

## Introduction

Prospective observational studies have shown that depression is associated with increased mortality following hospitalization for acute coronary syndromes (ACS), consisting of myocardial infarction (MI) and unstable angina (1–4). Because depression is often assessed after the ACS event, some researchers have argued that the association between depression and mortality is due to *confounders* related to the ACS event; specifically, that depression is merely an indicator of known clinical markers that are themselves prognostic for an increased mortality risk after an ACS (5,6). In support of this contention, some studies have found that the association between depression and mortality was no longer significant, after adjusting for indicators of cardiac prognosis or other prognostic comorbidity measures in multivariate models (5,7).

A wide range of measures has been employed to account for prognosis in studies of depression and post-ACS mortality. In a meta-analysis assessing the association between depression and cardiovascular outcome after MI, only 12 of 22 studies made any adjustment for clinical variables (8). Studies that incorporated information about cardiac prognostic markers included different combinations of the following variables as potential confounders: prior history of MI, coronary artery bypass graft, or congestive heart failure; Killip class; left ventricular ejection fraction (LVEF); premature ventricular contractions; arrhythmia; type of MI (anterior or Q-wave); and prescription of angiotensin converting enzyme inhibitor after discharge. A more recent meta-analysis concluded that because of biased and incomplete adjustment for potential clinical confounders, depression cannot yet be viewed as an established, independent risk factor for coronary heart disease (9).

One strategy for addressing the issue of incomplete adjustment for potential clinical confounders is to utilize an evidence-based prediction tool to assess mortality risk after acute coronary events. Although prediction models do not necessarily incorporate information about all aspects of cardiac function, they do have the important advantage of documented predictive validity based on large registry samples for measuring mortality risk after an acute coronary event. Recently, the Global Registry of Acute Coronary Events (GRACE) risk index was developed as a validated model to predict 6-month mortality after ACS (10). The GRACE model, unlike other post-ACS prediction models, was developed from an internationally diverse and clinically representative population of patients from across the ACS spectrum. In head-to-head comparisons with two other prediction models, a model derived from the GRACE registry had the best predictive accuracy for death or MI recurrence at 12 months, even though the GRACE risk index was originally validated for predicting 6-month mortality (11). With its excellent predictive and content validity, the GRACE risk index provides an ideal measure by which to test whether depression is associated with the known clinical factors that empirically predict post-ACS mortality risk. In the present study, we assessed whether depression in ACS patients was correlated with a summary index of known ACS clinical mortality predictors, by testing the associations of the GRACE index with both depressive symptom severity and clinical depression during hospitalization for an ACS. If depressive symptoms and the GRACE index are highly associated, the association between depression and prognosis after ACS may merely be spurious. On the other hand, if depression or depressive symptoms and the GRACE index are not associated, then a unique set of behavioral or biological factors may place depressed ACS patients at increased mortality risk. As the GRACE investigators did not consider LVEF, another potential predictor of post-ACS outcome, in their model, we also tested whether depressive symptoms or status were associated with LVEF in our sample.

# Methods

## Setting

This was a substudy of the Coronary Psychosocial Evaluation Studies (COPES), a prospective observational cohort study that examines the association between depression and ACS prognosis. Details of this study have been previously described (12). The Institutional Review Boards of the three academic hospitals where patients were recruited approved this study.

## Medical Eligibility

In COPES, between May, 2003 and June, 2005, 457 patients, who were at least 18 years of age, were eligible for inclusion if they had been hospitalized for an ACS event. In agreement with the definition of ACS outlined by the GRACE investigators (10), our study defined ACS as either acute myocardial infarction (MI) or unstable angina, and required patients to have symptoms consistent with acute myocardial ischemia and at least one of the following: ischemic electrocardiographic changes, angiogram indicative of coronary artery disease on current admission, documented history of coronary artery disease, or acute rise in serum cardiac enzyme levels. A study cardiologist confirmed ACS eligibility for all patients.

## Assessment of Depression

In addition, patients were eligible if they scored between 0–4 (indicative of minimal depressive symptoms) or 10+ (indicative of at least mild depressive symptoms) on the original Beck Depression Inventory (BDI), within one week after the index ACS event (13). Patients with BDI scores of between 5 and 9 were excluded to more clearly delineate a depressed and nondepressed group at baseline. The BDI is a validated self-report instrument that has been used in prior studies of depression and ACS (2,14). Using a cutoff score of 10, the BDI had a sensitivity of 82% and specificity of 79% for diagnosing major depression by a clinical interview in patients diagnosed with myocardial infarctions (15).

Whereas we used the BDI as a measure of depressive symptom severity, we used a semi-structured diagnostic interview, known as the Diagnostic Interview Schedule with Hamilton Ratings (DISH), to diagnose major depression (MDD) (16). The DISH is based on a modified version of the National Institute of Mental Health Diagnostic Interview Schedule. It was developed to assess comorbid MDD in medically ill patients and has been used in some of the most important studies of depression in post MI and other cardiac populations, including the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study; we did not collect the Hamilton ratings (17). When trained interviewers use this interview, and quality assurance is conducted, the concordance with other structured psychiatric interviews is excellent (16). In our study, one clinical psychologist and one psychiatrist independently reviewed the trained interviewers' audiotapes and written notes for each interview and verified the diagnoses.

Patients who were diagnosed with MDD based on the psychiatric interview were then asked: "Have you ever been depressed before?" If patients said yes or were uncertain, they were then probed further to estimate whether they had fulfilled DSM-IV criteria for a positive history of MDD (18). This was evaluated by assessing whether a self-reported depressive episode was associated with DSM diagnostic symptoms, lasted at least 2 weeks, and was sufficiently severe to affect functioning. Patients with a diagnosis of MDD at time of the interview and a positive history of MDD were classified as "recurrent MDD"; those MDD patients without a history of MDD were classified as "initial MDD".

### Assessment of Prognostic Risk using GRACE Risk Index

We calculated the GRACE risk index to determine the patients' risk for all-cause mortality from the time of hospital discharge. Variables included in the GRACE risk index were obtained through a combination of chart review and self-report and included age (chart review), history of myocardial infarction or congestive heart failure (self-report and chart review), heart rate and systolic blood pressure at presentation (chart review), ST segment deviation (study cardiologist review of admission electrocardiogram), serum creatinine at admission (chart review), elevated serum cardiac enzymes on presentation (chart review), and percutaneous intervention during hospitalization (chart review). All variables have a positive correlation with GRACE score except systolic blood pressure at presentation which is inversely correlated. The GRACE score ranges from 1 to 263 points. A score of 80 predicts a 1% mortality rate at six months, 100 predicts a 2% mortality rate, and >210 predicts a >50% mortality rate (10).

### Assessment of Demographics and Clinical Variables

We used chart review and patient interview to collect information pertaining to demographic and clinical variables. The LVEF that was most proximate to the baseline cardiac event was abstracted from the chart. LVEF was not measured prospectively as part of the study protocol. LVEF could have been measured quantitatively by left ventriculogram, by echocardiogram, or by nuclear study. If multiple variables were available, research assistants were asked to record the value from the ventriculogram. Patients were then categorized into 4 groups: normal (LVEF≥60%); mild left ventricular dysfunction (LVEF 45%–59%); moderate left ventricular dysfunction (LVEF 30%–44%); and severe left ventricular dysfunction (LVEF<30%). LVEF data was available from left ventriculogram in 43% of patients, echocardiogram in 50% of patients, and nuclear study in 7% of patients. LVEF data was unavailable for 27 patients. Among patients with LVEF recorded, the date of LVEF measurement was unknown for 8% of patients; LVEF was measured more than 2 months after the ACS event for 7% of patients, and LVEF was only available prior to the ACS event for 6% of patients.

### Ascertainment of All-Cause Mortality (ACM)

At 1, 3, 6, and 18 months after enrollment, patients were proactively contacted and completed follow-up assessments either by telephone or in person. For patients who could not be contacted or who were reported by a relative to be deceased, the Social Security Death Index was searched to verify vital status.

### Cohort Development

Overall, 3,990 charts were screened. Out of 2515 charts with an ACS diagnosis, 287 (11.4%) patients were unavailable or refused to be screened for further eligibility. 677 patients were confirmed eligible for the study after completing the screening (no terminal illness, no alcoholism/drug addiction, no dementia, available for follow-up). Of these eligible patients, 211(21%) had BDI scores 5–9, 4 patients were suicidal and referred for treatment, and 5 withdrew before baseline was completed. This left 457 enrolled patients. Patients who were unavailable or refused to be screened differed significantly from patients who participated in the study: they were more likely to be Hispanic (24.3% versus 12.5%, respectively, $p = .01$) and older (mean age 65.2 (SD 11.9) years versus 61.5 (SD 12.2) years, respectively, $p<.001$).

### Statistical Analysis

We utilized student's t-test to compare the GRACE index score as well as its individual components according to depression category. We had 80% power to detect a 6-point

difference on the GRACE scale. We utilized chi-square and student's t-test to compare the GRACE individual components, as well as demographic and clinical variables according to depression category. We corrected for the family-wide alpha error by a Bonferroni correction within variable grouping (eg, demographic, clinical and GRACE component). When data were missing, we used a regression-based approach to impute the best linear-predicted score based on the non-missing items. As this occurred mainly for the GRACE index, the number of values available for each GRACE variable are listed in Table 1. For every pattern of missing data, the regression equation for estimating the GRACE risk score had an R-square >= 0.75. We used Pearson's r to test for a correlation between MDD status and LVEF.

We tested overall depression symptom severity and MDD diagnosis for their contribution to all-cause mortality risk at 12 months using Cox proportional hazards models. We also tested whether depression severity and depression status were significant hazards for mortality after adjustment for the GRACE score. We chose 12 months as our follow-up period, as the GRACE model has been validated to be a good predictor of mortality up to 12 months after ACS (11). We stratified all of our outcome analyses by hospital site. The proportional hazards assumption was met for all presented models. Analyses were performed using SPSS statistical software (version 13.0; SPSS Inc, Chicago, Ill).

## Results

The cohort is described in the Table 1. The mean age was 61 years (range 25–93), 41% were female, 11% were Hispanic, and 13% were Black. Forty-seven percent of patients (242/457) had elevated depressive symptoms when measured by self-report (BDI), and 11% of patients who completed a clinical interview (48/453) had current major depressive disorder (MDD).

With respect to socoiodemographic and other clinical characteristics, depressed patients, as measured by self report (BDI) or clinical interview, were significantly more likely with Bonferroni correction to be Hispanic and to have less education as compared to non-depressed patients. In terms of comorbid risk factors for cardiac disease, patients with MDD were more likely to have diabetes mellitus, hypercholesterolemia, and hypertension ($p<.05$), but these differences were not significant after Bonferroni correction. Patients with elevated depressive symptoms by BDI also had lower rates of cardiac catheterization -- which is not included in the GRACE index -- as compared to non-depressed patients (86% versus 93%, p=0.01). No significant association was found between left ventricular ejection fraction (4 categories, as recommended by Van Melle et al. [22]) and MDD status (Pearson's $r = -0.04$, p=0.37).

No significant differences were found in the mean overall prognostic score, as measured by the GRACE index between participants with elevated depressive symptoms (GRACE score = 91, SD 33) and without elevated depressive symptoms (GRACE score = 92, SD 30); p=0.83 (See Table 2). Similarly, GRACE scores among participants who met criteria for MDD by clinical interview (GRACE score = 84, SD 33) were not significantly different from GRACE scores among those who did not meet criteria for MDD (GRACE score = 92, SD 31); p=0.09. In fact, participants with MDD tended to have *lower* risk by GRACE score, although this difference was not statistically significant.

Data were available on participants' prior history of depression among 45 of 48 participants with MDD at hospitalization. One-third (15/45) of participants had initial MDD, whereas the other two-thirds (30/45) had recurrent MDD. No significant difference were found in GRACE scores between participants with initial MDD (GRACE score = 84, SD 34), as compared to those with recurrent MDD (GRACE score = 85, SD 31); p=0.92.

We further explored whether differences existed among depressed subgroups on the individual components of the GRACE index. The only factor that remained significantly different between depressive groups after making the Bonferroni correction was age; the unadjusted p values are provided in Table 2. Participants with current MDD tended to be younger (a protective factor for post-ACS clinical prognosis). If not including the Bonferroni correction for multiple comparisons, there was a trend toward a higher proportion of depressed subjects having prior MI and prior CHF. Interestingly, patients with elevated depressive symptoms as measured by BDI were less likely (but not significantly) to receive in-hospital percutaneous interventions, one component of the GRACE index indicating higher risk; however this trend was not evident when using the clinical interview definition of depression.

Finally, we tested whether depression was an independent predictor of mortality in our sample, even after adjustment for GRACE score. By 12 months after hospitalization, 18 confirmed deaths occurred (4%). Among patients with MDD in hospital, 17% (8/48) died by 12 months. In contrast, among patients without MDD in hospital, 3% (10/405) died by 12 months ($p<.001$). We examined different models that added depressive symptoms and MDD diagnosis to the covariate model that included the GRACE score (Table 3). These models showed that when only stratifying by hospital site, the GRACE score was a strong predictor of ACM (hazard ratio 1.04 per 1 point difference in GRACE score; 95% CI 1.02–1.05).

When MDD status was added to the model (adjusted for site and GRACE score), MDD status was a significant independent predictor of 12-month mortality (adjusted hazard ratio 2.53; 95%CI 1.54–4.16). When adjusted for site, GRACE, and LVEF, MDD status remained a significant predictor (adjusted hazard ratio 2.51; 95%CI 1.45–4.37). Similarly, when BDI score as a continuous variable was entered into a model adjusted for site and GRACE score, overall depressive symptom severity remained a significant predictor of mortality (adjusted hazard ratio, 2.23 per 10 point difference in BDI; 95% CI 1.48–3.36). In the final model adjusting for site, GRACE score, and LVEF, BDI score (adjusted hazard ratio, 1.80 per 10 point difference in BDI; 95% CI 1.13 – 2.89), was still statistically significant ($p<0.001$).

## Discussion

In our study, neither of two measures of depressive status (self-reported severity of depressive symptoms assessed with the BDI and clinical diagnosis of major depressive disorder), assessed within one week of hospitalization for ACS, was associated with the GRACE score, a well-validated measure of 6-month mortality risk. Moreover, even after adjustment for GRACE score, depressive symptom and disorder status remained significant independent predictors of mortality up to 12 months after ACS. Further, some investigators have shown that the elevated risk of depressive symptoms after ACS may be limited to patients with initial MDD after ACS (19,20). Yet again, according to our results, no significant differences exist in GRACE score when comparing patients with first episode of depression with patients who had recurrent depressive disorder. As a result, established clinical predictors after an acute coronary event are less likely to be a *confounder* of the relationship between depression and post-ACS mortality.

The range of potential predictors that the GRACE investigators tested for an association with post-ACS mortality included demographic characteristics, medical history of coronary risk factors, prior medical therapy, symptoms and signs at presentation, in-hospital treatments and complications, and medical therapy at discharge (21). The full set of over 39 tested variables was selected based on prior prediction models and expert opinion. Of note, our depressed patients had slightly increased rates of two comorbidities included in the final GRACE model, prior myocardial infarction and congestive heart failure, but this risk was

offset by their lower age for the calculation of their overall GRACE score, and was not significant when the family-wise alpha rate correction was applied.

The GRACE investigators were not able to assess all known clinical predictors. For example, the GRACE investigators did not incorporate LVEF into their prediction model, as their model sought to use clinical variables that would be readily available to all clinicians without requiring additional testing other than electrocardiography. Some studies have shown that depression may be associated with measures of cardiac function. For example, van Melle et al. showed that depression is associated with decreased LVEF (22). In our sample, we did not find a significant linear trend between LVEF and major depression status when using the same categorization as van Melle et al. Some possible reasons for the discrepancy include the fact that we collected data on LVEF using 3 different techniques. Further, we did not design our study to have power to find small but significant associations. Finally, our LVEFs were not all measured during the baseline hospitalization and this may have given our LVEFs less discriminating function. In contrast, van Melle et al. measured LVEF in hospital and depression 3 months later. Despite these limitations, when we included LVEF into our model testing whether depressive symptoms or MDD status contributed to the hazard of mortality at one year, they continued to significantly do so, although the point estimate was reduced.

What about other potential medical confounders? Our data confirmed the findings in prior studies that show higher rates of certain medical comorbidities, such as diabetes mellitus and hypercholesterolemia, among depressed as compared to non-depressed patients (23). Of note, however, when deriving their prediction tool, the GRACE investigators found that neither of these comorbidities was a significant predictor of post-ACS mortality when the final variable set was already considered.

Our research has some important limitations. First, the group who received the diagnostic psychiatric interview did not include patients with BDI scores between 5 and 9. The majority of these patients were likely to be non-depressed by clinical interview. The absence of patients with intermediate BDI scores may have subtly altered the individual associations between depression and the components of the GRACE score and may have affected the results of the proportional hazards analysis for determining whether depressive symptom severity was a significant predictor of ACM. Nevertheless, the absence of these intermediate BDI scores is unlikely to have altered the findings that depression was not associated with the overall GRACE score. If anything, the consequence of this “extreme groups design” would have been to inflate the estimated correlations between depressive symptoms and Grace scores, compared to estimates using a complete distribution.(24) In addition, our finding that depression independently predicted mortality after adjustment for GRACE score must be interpreted with caution as it was based on only 18 outcome events (deaths). Finally, we had missing data for some components of the GRACE score. However, we were able to account for these by our statistical imputation strategy.

We have one hypothesis-generating, but exploratory finding, from our study. Our analysis of the differences between depressed and non-depressed patients for the individual GRACE components demonstrated that depressed patients had (non-significantly) lower rates of percutaneous interventions. Further, we found that depressed patients had lower rates of cardiac catheterization as compared to non-depressed patients, despite having equivalent GRACE scores. These findings are consistent with the finding by Druss et al., that among a cohort of Medicare beneficiaries, patients with affective disorders were less likely to undergo cardiac catheterization during hospitalization for myocardial infarction (25). This is an interesting, but preliminary finding that raises the possibility that disparities in care may exist between depressed and non-depressed patients that may affect long-term clinical

outcomes. Many other important, novel mechanisms such as upregulated pro-inflammatory cytokine production, alterations in heart rate variability, or differences in adherence to medical treatment have also been proposed to explain the association between depression and post-ACS mortality, (26–27), and these mechanisms should be pursued when attempting to understand how depression confers its mortality risk post-ACS.

### Conclusion

Future studies of the association between depression and post-ACS mortality should incorporate the most current, validated clinical prognostic variables when testing whether depression is an independent marker of mortality risk in post-ACS patients. If all studies adopted one standardized, composite index of mortality risk, such as the GRACE index, comparisons across studies, cohorts, and different novel prognostic markers would be more easily accomplished.

Our data show that, even if depression is merely a marker of some cardiac disease severity markers, it is not a marker of cardiac disease prognosis as measured by GRACE 6-month post-discharge risk index. This leaves open the possibility that depression may add to our understanding of those who are at risk for adverse medical outcomes after ACS beyond what is explained by the established prognostic model.

## Acknowledgments

**Funding/Support:** Supported by contract HC25197 (IMK, NR, KWD, JES), by grants HL076857 (DS, KWD), HL084034 (KWD), and HL072866 (DS) from the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH)., and grant UL1 RR024156 (KWD) from the National Center for Research Resources (NCRR), NIH, and NIH Roadmap for Medical Research.

We thank Rebecca Straus and Dr. Daichi Shimbo for their assistance with this manuscript. We also thank our funder, the National Heart, Lung, and Blood Institute.

## Acronyms

| | |
|---|---|
| ACS | acute coronary syndrome |
| MI | myocardial infarction |
| LVEF | left ventricular ejection fraction |
| GRACE | Global Registry of Acute Coronary Events |
| COPES | Coronary Psychosocial Evaluation Studies |
| BDI | Beck Depression Inventory |
| MDD | major depressive disorder |

## References

1. Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. Arch Intern Med 2000;160:1354–1360. [PubMed: 10809041]
2. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;14:388–98.
3. Ladwig KH, Kieser M, König J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction: results from the post-infarction late potential study. Eur Heart J 1991;12:959–964. [PubMed: 1936008]
4. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. Am J Cardiol 2003;92:1277–1281. [PubMed: 14636903]

5. Lane D, Ring C, Lip GYH, Carroll D. Depression, indirect clinical markers of cardiac disease severity, and mortality following myocardial infarction. Heart 2005;91:531–2. [PubMed: 15772222]
6. Lane D, Carroll D, Lip GYH. Anxiety, depression and prognosis following myocardial infarction: is there a causal association? J Am Coll Cardiol 2003;42:1808–1810. [PubMed: 14642692]
7. Kaufmann MW, Fitzgibbons JB, Suusman EJ, Reed JF 3rd, Einfalt JM, Rodgers JK, Fricchione JL. Relation between myocardial infarction, depression, hostility, and death. Am Heart J 1999;138:549–554. [PubMed: 10467207]
8. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events : a meta-analysis. Psychosom Med 2004;66:814–822. [PubMed: 15564344]
9. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006;27:2763–2774. [PubMed: 17082208]
10. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–2733. [PubMed: 15187054]
11. De Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEACS. Eur Heart J 2005;26:865–72. [PubMed: 15764619]
12. Rieckmann N, Kronish IM, Haas D, Gerin W, Chaplin WF, Burg MM, Vorchheimer D, Davidson KW. Persistent depressive symptoms lower aspirin adherence after acute coronary syndromes. Am Heart J 2006;152:922–7. [PubMed: 17070160]
13. Beck AT, Ward CH, Mendelson M. An inventory for measuring depression. Archives of General Psychiatry 1961;4:561–571. [PubMed: 13688369]
14. Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105:1049–1053. [PubMed: 11877353]
15. Strik JJ, Honig A, Lousberg R, Denollet J. Sensitivity and specificity of observer and self report questionnaires in major and minor depression following myocardial infarction. Psychosomatics 2001;42:423–428. [PubMed: 11739910]
16. Freedland KE, Skala JA, Carney RM, Raczynski JM, Taylor CB, Mendes de Leon CF, Ironson G, Youngblood ME, Krishnan KR, Veith RC. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. Psychosom Med 2002;64:897–905. [PubMed: 12461195]
17. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease (ENRICHD) randomized trial. JAMA 2004;289:3106–3116. [PubMed: 12813116]
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, D.C: American Psychiatric Association; 1994.
19. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. J Am Coll Cardiol 2006;48:2204–2208. [PubMed: 17161246]
20. Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. Am J Cardiol 2005;96:1179–1185. [PubMed: 16253578]
21. Granger C, Goldberg R, Dabbous O Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003;163:2345–2353. [PubMed: 14581255]
22. van Melle J, de Jonge P, Ormel J, Crijns HJ, van Veldhuisen DJ, Honig A, Schene AH, van den Berg MP. MIND-IT investigators. Relationship between left ventricular dysfunction and

depression following myocardial infarction. Eur Heart J 2005;26:2550–2656. [PubMed: 16183686]

23. Watkins L, Scheiderman N, Blumenthal J, Sheps DS, Catellier D, Taylor CB, Freedland KE. ENRICHD Investigators. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. Am Heart J 2003;146:48–54. [PubMed: 12851607]
24. Preacher K, Rucker D, MacCallum R, Nicewander W. Use of extreme groups approach: a critical reexamination and new recommendations. Psychol Methods 2005;10:178–192. [PubMed: 15998176]
25. Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA 2000;283:506–511. [PubMed: 10659877]
26. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME. Coronary artery disease and depression. Eur Heart J 2004;25:3–9. [PubMed: 14683736]
27. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosom Med 2004;66:305–15. [PubMed: 15184688]

*Psychosom Med*. Author manuscript; available in PMC 2010 September 1.

**Table 1**

Demographic and Clinical Characteristics of Patients by Depression Status at Hospitalization*

| Characteristic | Non- depressed (BDI† 0–4) (n=242) | Depressed (BDI ≥ 10) (n=215) | P-value | No major depression by clinical interview (n=405) | Major depression by clinical interview (n=48) | P-value |
|---|---|---|---|---|---|---|
| ***Demographic***‡ | | | | | | |
| Mean (SD) years of education | 14.2(3.1) | 13.0(3.3) | <.001∫ | 13.8(3.2) | 12.3(3.7) | .002∫ |
| Female | 88 (36.4) | 101 (47.0) | .02 | 163 (40.2) | 25 (52.1) | .12 |
| Hispanic | 10 (4.1) | 39 (18.1) | <.001∫ | 29 (7.2) | 17 (35.4) | <.001∫ |
| Black | 30 (12.4) | 30 (14.0) | .62 | 53 (13.1) | 6 (12.5) | .91 |
| Lives alone | 47 (19.6) | 57 (27.0) | .06 | 90 (22.4) | 12 (26.1) | .58 |
| Unmarried/no partner | 82 (33.9) | 91 (42.3) | .06 | 149 (36.8) | 23 (47.9) | .13 |
| Unemployed | 106 (44.4) | 119 (56.7) | .009 | 193 (48.3) | 29 (64.4) | .04 |
| ***Clinical***‡ | | | | | | |
| Smoked at baseline | 36 (14.9) | 44 (20.5) | .12 | 75 (18.5) | 5 (10.4) | .16 |
| Hypertension | 164 (68.6) | 153 (72.5) | .37 | 275 (68.8) | 38 (82.6) | .05 |
| Diabetes mellitus | 58 (24.0) | 70 (32.6) | .04 | 107 (26.4) | 19 (39.6) | .05 |
| Hypercholesterolemia | 153 (65.4) | 155 (76.0) | .02 | 268 (68.4) | 36 (85.7) | .02 |
| History of depression | 40 (17.1) | 88 (43.1) | <.001∫ | 97 (24.9) | 30 (66.7) | <.001∫ |
| Mean (SD) baseline BDI† score | 2.0(1.4) | 16.8(7.5) | <.001∫ | 7.1 (7.0) | 24.1 (9.8) | <.001∫ |
| Cardiac catheterization during hospitalization | 225 (93.4) | 185 (86.0) | .01 | 366 (90.6) | 40 (83.3) | .12 |
| Left ventricle ejection fraction∫∫ | --- | --- | .46** | --- | --- | .37** |
| Normal (≥60%) | 107 (46.9) | 87 (43.1) | | 173 (45.3) | 21 (47.7) | |
| Mild decreased (45–59%) | 67 (29.4) | 66 (32.7) | | 121 (31.7) | 10 (22.7) | |
| Moderate decreased (30–44%) | 39 (17.1) | 31 (15.3) | | 63 (16.5) | 6 (13.6) | |
| Severe decreased (<30%) | 15 (6.2) | 18 (8.9) | | 25 (6.5) | 7 (15.9) | |

*Data are presented as number (%) of patients unless indicated otherwise. Denominators for variables vary slightly due to missing responses for all variables other than ejection fraction. Fewer than 5% of responses were missing for these variables.

†Beck Depression Inventory

‡Bonferroni correction for demographic variables is alpha< .003; Bonferroni correction for clinical variables is alpha< .004

$\int$ Significant difference between depression status groups after Bonferroni correction

** Refers to linear trend (df =1) for Chi-squared association between left ventricle ejection fraction and depression status

$\int\int$ N=430 for this last variable

**Table 2**

Association between Depression Status and GRACE Risk Score at Hospitalization*

| Characteristic of GRACE risk index‡ | Non-depressed (BDI† 0–4) (n=242) | Depressed (BDI ≥ 10) (n=215) | P- value | No major depression by clinical interview (n=405) | Major depression by clinical interview (n=48) | P-value |
|---|---|---|---|---|---|---|
| Age, mean (SD), years (missing data n= 0) | 62.4 (11.6) | 59.6 (13.2) | .01 | 61.8 (12.2) | 54.9 (12.8) | <.001∫ |
| Prior myocardial infarction (missing data n=7) | 57 (23.7) | 69 (33.0) | .03 | 107 (26.6) | 18 (40.0) | .06 |
| Prior congestive heart failure (missing data n = 0) | 27 (11.2) | 37 (17.2) | .06 | 53 (13.1) | 10 (20.8) | .14 |
| Initial heart rate, mean (SD) (missing data n = 38) | 75.9 (19.5) | 78.7 (17.7) | .13 | 76.5 (18.5) | 82.6 (17.6) | .04 |
| Initial systolic blood pressure, mean (SD) (missing data n = 33) | 145.6(31.9) | 138.7(25.3) | .01 | 143.5 (29.2) | 133.0 (24.8) | .02 |
| ST segment deviation (missing data n = 20) | 40 (16.9) | 32 (15.9) | .77 | 68 (17.5) | 4 (8.9) | .14 |
| Initial creatinine, mean (SD) (missing data n = 25) | 1.2 (0.7) | 1.2 (0.6) | .80 | 1.2 (0.6) | 1.2 (0.9) | .84 |
| Elevated cardiac enzymes (missing data n = 45) | 74 (33.5) | 61 (31.9) | .74 | 125 (34.2) | 10 (22.7) | .13 |
| No in-hospital percutaneous intervention (missing data n = 1) | 58 (24.0) | 69 (32.2) | .05 | 108 (26.7) | 17 (35.4) | .20 |
| GRACE risk score, missings imputed, mean (SD) (missing data n = 0) | 91.6 (29.9) | 90.9 (32.8) | .83 | 92.0 (30.9) | 83.9 (33.2) | .09 |

*Data are presented as number (%) of patients unless indicated otherwise. Denominators for variables vary slightly due to missing responses. The number of missing responses for each variable is listed in the first column.

†Beck Depression Inventory

‡Bonferroni correction for GRACE variables is alpha< .002; GRACE, Global Registry of Acute Coronary Events risk score

∫Significant difference between depression status groups after Bonferroni correction

## Table 3

Results of Cox Proportional Hazards Regression Analysis to All-Cause Mortality *

| Predictor | Number of subjects | Hazard Ratio for depression status (95% CI) | *P* Value |
|---|---|---|---|
| GRACE score only | 457 | 1.04 (1.02 – 1.05) | <.001 |
| Major Depressive Disorder status only | 453 | 2.13 (1.31 – 3.46) | .004 |
| Beck Depression Inventory (continuous per 10 point difference) | 457 | 1.99 (1.37 – 2.89) | .002 |
| LVEF (4 categories†) only | 430 | | .002 |
| normal vs. severe dysfunction | | 3.91 (1.76 – 8.65) | <.001 |
| normal vs. moderate dysfunction | | 1.82 (0.75 – 4.44) | .19 |
| normal vs. mild dysfunction | | 0.37 (0.12 – 1.14) | .08 |
| GRACE score | 453 | 1.04 (1.02 – 1.06) | <.001 |
| Major Depressive Disorder status | | 2.53 (1.54 – 4.16) | <.001 |
| GRACE score | 425 | 1.04 (1.02 – 1.05) | <.001 |
| Major Depressive disorder status | | 2.51 (1.45 – 4.37) | .001 |
| Left Ventricule Ejection Fraction (4 categories†) | | | .02 |
| normal vs. severe dysfunction | | 3.22 (1.44 – 7.17) | .004 |
| normal vs. moderate dysfunction | | 1.37 (0.55 – 3.36) | .50 |
| normal vs. mild dysfunction | | 0.47 (0.15 – 1.44) | .19 |
| GRACE score | 457 | 1.04 (1.02 – 1.06) | <.001 |
| Beck Depression Inventory (continuous per 10 point difference) | | 2.23 (1.48 – 3.36) | <.001 |
| GRACE score | 430 | 1.03 (1.02 – 1.05) | <.001 |
| Beck Depression Inventory (continuous per 10 point difference) | | 1.80 (1.13 – 2.89) | <.001 |
| Left Ventricule Ejection Fraction (4 categories†) | | | .25 |
| normal vs. severe dysfunction | | 1.86 (0.75 – 4.59) | .18 |
| normal vs. moderate dysfunction | | 1.77 (0.70 – 4.37) | .22 |
| normal vs. mild dysfunction | | 0.47 (0.15 – 1.47) | .20 |

*All analyses were adjusted for hospital site; abbreviations: CI, confidence interval; MDD, major depressive disorder; BDI, Beck Depression Inventory; LVEF, left ventricular ejection fraction

†normal, LVEF ≥60%; mild dysfunction, LVEF 45%–59%; moderate dysfunction, LVEF 30%–44%; severe dysfunction, LVEF<30%