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Depressive Symptoms and All-cause Mortality in Unstable Angina Pectoris (From the Coronary Psychosocial Evaluation Studies [COPES])

William Whang, MD[a], **Daichi Shimbo, MD**[a], **Ian M. Kronish, MD**[a,b], **W. Lane Duvall, MD**[b], **Howard Julien, MD**[a], **Padmini Iyer, BA**[a], **Matthew M. Burg, PhD**[a,c], and **Karina W. Davidson, PhD**[a]

[a] Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY

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

[c] Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT

Abstract

While depression is clearly associated with increased mortality after acute myocardial infarction, there is a paucity of data examining the impact of depression on patients with unstable angina (UA). We analyzed the relationship between depressive symptoms and all-cause mortality (ACM) among patients with UA who were enrolled in a prospective multi-center study of depression and acute coronary syndrome (ACS). Depressive symptoms were measured with the Beck Depression Inventory (BDI) within 1 week of the ACS event, and patients were selected for BDI score 0 to 4, or ≥10. Our sample included 209 UA patients, with 104 (50%) having BDI score ≥10. Proportional hazards analyses adjusted for variables including left ventricular ejection fraction, GRACE risk score, and Charlson comorbidity index. In multivariable analyses, BDI score ≥10 was associated with increased risk of 42-month ACM (HR=2.04, 95% CI 1.20–3.46, p=0.008) compared with BDI score 0 to 4. In conclusion, our results confirm and extend prior evidence linking depression to worse outcomes in UA, and suggest that interventions that address depression may be worth examining across the spectrum of risk in ACS.

Keywords

depression; acute coronary syndrome

Introduction

Depression is associated with increased mortality risk after acute myocardial infarction (MI), with an approximate relative risk of 2.4 for all-cause mortality (ACM) according to a meta-analysis of 22 studies.[1] However, there have been relatively few published studies of depression as a predictor of mortality in unstable angina (UA).[2] UA patients comprise about

Corresponding author: Karina W. Davidson, PhD, Center for Behavioral Cardiovascular Health, 622 West 168th St, PH9 Room 948, Columbia University Medical Center, New York, New York, 10032, kd2124@columbia.edu, Work: 212-342-4493; Fax: 212-342-3431.

26 percent of hospitalized patients with acute coronary syndrome (ACS),[3] and although long-term prognosis is more favorable compared with MI patients,[4] early invasive revascularization strategies are less beneficial for prevention of recurrent events in UA patients.[5] In light of differences in pathophysiology and outcomes in UA compared with MI, there may also be differences in the impact of risk factors such as depression on long-term prognosis in UA patients. Given the relative paucity of data regarding the relationship between depressive symptoms and mortality in UA patients, we sought to examine this association in a prospective multi-center study of depression in ACS patients.

Methods

We performed an analysis of the Coronary Psychosocial Evaluation Studies (COPES), a multi-site, observational cohort study designed to investigate the etiology and naturalistic course of depressive symptoms after an ACS event.[6,7] Participants were recruited from among patients admitted to 3 university hospitals (Mount Sinai Hospital, New York, New York, and Yale–New Haven Hospital and Hospital of St Raphael, New Haven, Connecticut) for an ACS event between May 2003 and June 2005. The institutional review board of each hospital approved the study. ACS events were defined according to AHA/ACC criteria[8] as either acute MI (with or without ST segment elevation) or UA. UA patients had symptoms consistent with acute myocardial ischemia and at least one of the following: ischemic electrocardiographic changes (i.e. ST depression and/or T-wave abnormalities), an angiogram indicative of coronary artery disease on current admission, and/or documented history of coronary artery disease. Patients with an acute rise in serum cardiac enzyme levels were excluded. A study cardiologist confirmed ACS eligibility for all patients.

The Beck Depression Inventory (BDI),[9] a self-report measure of depressive symptom severity, was administered within one week after the index ACS event,[10] and patients who scored between 0 and 4 (indicative of no depressive symptoms) or ≥10 (at least mild depressive symptoms) were included. Patients with BDI scores between 5 and 9 were excluded to delineate more clearly depressed and non-depressed groups at baseline.[11] For this analysis, depressive symptoms were categorized into two groups according to BDI score: ≥10, versus 0 to 4.

In addition to the assessment of depressive symptom severity with the BDI, a diagnosis of major depression was also determined using the Diagnostic Interview with Structured Hamilton (DISH), an interview format developed for the (Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) clinical trial.[12] Interviews were conducted by trained research staff, and 1 clinical psychologist and 1 psychiatrist independently reviewed audiotapes and written notes for each interview to verify all diagnoses.

Medical risk factors for long-term mortality were measured with the Global Registry of Acute Coronary Events (GRACE) risk score[13] and the Charlson comorbidity index.[14] The GRACE model includes advanced age, history of MI and heart failure, elevated pulse rate and systolic blood pressure at presentation to the hospital, elevated initial serum creatinine level, elevated initial cardiac enzyme level, ST-segment depression on electrocardiogram at presentation, and percutaneous coronary intervention (PCI) performed in the hospital. The GRACE risk score ranges from 1 to 263 points, with higher scores indicating higher mortality risk. A score from 1 to 80 predicts a 1% mortality rate at 6 months; 100, a 2% mortality rate; and higher than 210, a mortality rate greater than 50%.[13] The Charlson index includes 12 chronic conditions with weights according to their association with one-year mortality, and has been associated with long-term survival in patients with coronary artery disease.[15]

Left ventricular ejection fraction (LVEF) was measured quantitatively by left ventriculogram during cardiac catheterization (48% of patients), echocardiogram (38%), or radionuclide study (12%). If multiple measures were available, the value from the ventriculogram was used first, followed by the value from the echocardiogram. LVEF was then classified as normal to mild dysfunction (LVEF ≥0.40) and moderate to severe dysfunction (LVEF < 0.40). Data on LVEF were missing for 19 patients.

The primary end point was all-cause mortality (ACM). At 1, 3, 6, 18, 30, and 42 months after enrollment, patients were contacted and follow-up assessments were completed 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.

Fisher exact chi-squared tests and 2-sample t-tests were used to compare categorical and continuous measurements between the depressed (BDI ≥10) and non-depressed (BDI 0 to 4) groups. Actuarial survival curves were plotted according to BDI score category. Cox proportional hazards models were used to estimate the hazard ratio (HR) for ACM associated with BDI score ≥10, stratified by hospital. Based on published findings of factors that might confound the depression–ACM association, age, sex, LVEF, medical comorbidities (Charlson index), and clinical prognostic index (GRACE) were included in multivariable analyses. All analyses were performed using SPSS, version 16 (SPSS Inc, Chicago, Illinois).

Results

Of the 457 enrolled ACS patients in COPES, 4 were excluded from the current analysis because the psychiatric interview was not completed within the designated time. Of the remaining 453 patients, 209 who met study criteria for UA were included in the analysis (Table 1). Of this sample, 104 patients scored ≥10 on the BDI, indicating meaningful levels of depressive symptoms. Compared to patients with minimal depressive symptoms (BDI<5), those with meaningful symptoms were younger, more likely to be female, and had higher Charlson comorbidity scores. Major depressive disorder by diagnostic interview was present in 1 patient in the group with BDI<5 and in 29 patients in the group with BDI ≥10.

During an average follow-up of 30.5 + 11.5 months, 9 deaths occurred by 1 year and 23 deaths occurred by 42 months (Figure 1). In age- and sex-adjusted analyses, depression (BDI score ≥10) was associated with 1-year ACM (HR 2.15, 95% CI 0.96–4.83, p=0.063) and was significantly associated with 42-month ACM (HR 1.79, 95% CI 1.13–2.85, p=0.014). In analyses that also included LVEF<0.40, Charlson score, and GRACE score, there remained a trend toward increased 1-year mortality associated with BDI score ≥10, and the relationship to 42-month ACM remained statistically significant without attenuation (Table 2). Baseline major depressive disorder was not associated with 1-year or 42-month ACM in multivariable analyses (HR=1.16 for 12-month ACM, HR=1.18 for 42-month ACM, p>0.28 for both).

Discussion

In this prospective cohort study performed across 3 centers, UA patients with meaningful depressive symptoms measured by BDI at the time of index hospitalization were at increased risk for 42-month ACM, and the relative magnitude of risk was similar to that for patients with acute MI. This relationship held despite multivariable adjustment for LVEF, GRACE risk score, and Charlson comorbidity index. The great majority of research on depression and post-ACS prognosis has focused on the population of patients admitted to hospital with acute MI.[1] Indeed, our results join those of only one prior study of which we

aware, by Lesperance and colleagues,[2] who in 2000 showed in a cohort of 430 UA patients that those with elevated depressive symptoms were at higher risk for 1-year mortality. The definitions for unstable angina and depressive symptoms used by both studies were similar. Interestingly, depressive symptoms predict 1-year mortality in patients with MI, but not mortality over a longer observation period.[16] Our findings revealed that depressive symptoms in UA patients conferred mortality risk at 42 months, but this relationship was not statistically significant for 1-year mortality. Our results contribute to a broadening of our understanding of the importance of depression, and are consistent with the concept that depressive symptoms are associated with mortality in ACS cases across the spectrum of cardiac risk.

The current findings are important to consider as research efforts to treat depression and to offset cardiovascular risk are undertaken. ENRICHD, the largest randomized trial of depression treatment for cardiac patients conducted to date, enrolled only patients meeting criteria for acute MI and did not show a reduction in cardiovascular events associated with the intervention.[17] The recently completed COPES Phase I Randomized Trial[18] enrolled patients with both acute MI and UA. The results of this study demonstrated a trend to reduced risk of major cardiovascular events and ACM associated with treatment for persistent depressive symptoms in the months after the index ACS event. While the COPES Trial was small and focused primarily on safety and patient satisfaction associated with a collaborative care approach to depression treatment, the finding of reduced risk in the intervention group raises important questions for future, larger scale treatment efforts. Together with the recent trial data, the current analysis suggests that future large scale depression interventions in cardiac populations should include patients with UA as well as MI.

The prospective, multi-center study design and the systematic assessment of depressive symptom severity represent important strengths of the current study. The few events and relatively small cohort represent study limitations, although we were still able to detect a relationship between depressive symptoms and ACM at 42 months in multivariable analyses. In addition, we did not collect standardized measures of anxiety in our study, and cannot compare the ACM risk between depression and anxiety. Furthermore, with few patients demonstrating major depression, there was limited power to detect a significant relationship between this level of depression severity and ACM risk. Nonetheless, our results highlight the potential importance for post-ACS depression intervention trials that target cardiovascular risk to include UA as well as acute MI.

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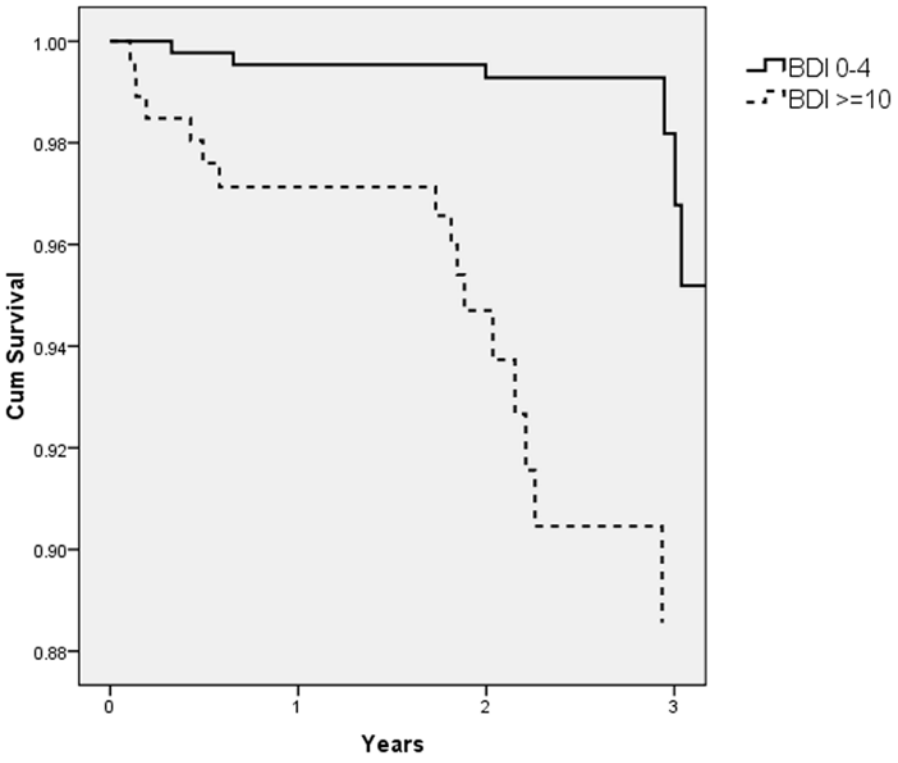

Figure 1.
Actuarial survival according to Beck Depression Inventory (BDI) score category.

Table 1

Baseline characteristics of unstable angina patients according to Beck Depression Inventory (BDI) category.

Variable	BDI 0–4 (n=105)	BDI ≥10 (n=104)	P value
Age (years) (std. dev.)	63.7 (10.9)	58.5 (13.5)	0.003
Female	37 (35%)	60 (62%)	0.001
Non-white	23 (22%)	28 (27%)	0.42
LVEF<0.40	8 (8%)	12 (12%)	0.23
Mean GRACE score (std. dev.)	87.8 (27.5)	85.9 (32.8)	0.65
Mean Charlson score (std. dev.)	1.3 (1.5)	1.8 (1.6)	0.03
PCI during index admission	64 (54%)	54 (46%)	0.32
MDD at baseline	1 (3%)	29 (28%)	0.001

GRACE= Global Registry of Acute Coronary Events; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; MDD=major depressive disorder

Table 2

Multivariable Cox regression for all-cause mortality among unstable angina patients (n=209).

	1-year ACM (d=9)		42-month ACM (d=23)	
	Hazard Ratio (95% CI)	**P value**	**Hazard Ratio (95% CI)**	**P value**
Age	1.02 (0.92–1.13)	0.74	1.04 (0.98–1.10)	0.21
Female	0.28 (0.09–0.91)	0.03	0.61 (0.37–1.02)	0.06
Charlson Score	1.52 (1.06–2.20)	0.02	1.62 (1.30–2.03)	<0.01
Grace Score	1.03 (0.98–1.08)	0.29	1.01 (0.98–1.03)	0.72
LVEF <0.40	0.77 (0.09–6.53)	0.81	1.87 (0.62–5.63)	0.27
BDI score ≥10	1.91 (0.81–4.50)	0.14	2.04 (1.20–3.46)	0.008

d=deaths; ACM=all-cause mortality; CI=confidence interval; LVEF=left ventricular ejection fraction; BDI=Beck Depression Inventory