

# Association of Anhedonia With Recurrent Major Adverse Cardiac Events and Mortality 1 Year After Acute Coronary Syndrome

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**Context:** Depression consistently predicts recurrent events and mortality in patients with acute coronary syndrome (ACS), but it has 2 core diagnostic criteria with distinct biological correlates—depressed mood and anhedonia (loss of pleasure or interest).

**Objective:** To determine if depressed mood and/or anhedonia predict 1-year medical outcomes for patients with ACS.

**Design:** Observational cohort study of post-ACS patients hospitalized between May 2003 and June 2005. Within 1 week of admission, patients underwent a structured psychiatric interview assessing clinically impairing depressed mood, anhedonia, and major depressive episode (MDE). Also assessed were the Global Registry of Acute Coronary Events risk score, Charlson comorbidity index, left ventricular ejection fraction, antidepressant use, and depressive symptom severity using the Beck Depression Inventory.

**Setting:** Cardiac units of 3 university hospitals in New York and Connecticut.

**Participants:** Consecutive sample of 453 patients with ACS (age, 25-93 years; 42% women).

**Main Outcomes Measures:** All-cause mortality (ACM) and documented major adverse cardiac events (MACEs)—myocardial infarction, hospitalization for unstable angina, or urgent/emergency coronary revascularization—actively surveyed for 1 year after admission.

**Results:** There were 67 events (16 deaths and 51 MACEs; 14.8%): 108 (24%) and 77 (17%) patients had anhedonia and depressed mood, respectively. Controlling for sex, age, and medical covariates, anhedonia (adjusted hazard ratio, 1.58; 95% confidence interval, 1.16-2.14;  $P < .01$ ) was a significant predictor of combined MACE and ACM, but depressed mood was not. Anhedonia continued to significantly predict outcomes ( $P < .05$ ) when additionally controlling for MDE diagnosis or depressive symptom severity. Findings were confirmed using depressed mood and anhedonia subscores from the Beck Depression Inventory in place of clinician interview ratings.

**Conclusions:** Anhedonia identifies risk of MACE and ACM beyond that of established medical prognostic indicators, including MDE and depressive symptom severity. Correlates of anhedonia may add to the understanding of the link between depression and heart disease.

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**S**YSTEMATIC REVIEWS HAVE concluded that depression, identified either by self-reported depressive symptom severity or by psychiatric interview, confers an independent mortality and morbidity risk in patients with acute coronary syndrome (ACS).<sup>1-3</sup> Despite growing acceptance of depression as a cardiac risk factor,<sup>4</sup> initial attempts to prevent mortality or event recurrence by treating depression in ACS patients have not been successful.<sup>5,6</sup>

To better understand how depression contributes to cardiac risk, some have suggested searching for subtypes of depres-

sion that are especially cardiotoxic.<sup>1,7,8</sup> Major depression is a complex phenotype encompassing a wide range of symptoms, not all of which are present in all patients. Furthermore, to receive a diagnosis of major depression, 1 of 2 core functionally impairing criteria must be present—depressed mood (sadness and the report of feeling depressed) or anhedonia (markedly diminished interest or pleasure in all, or almost all, activities). Evidence suggests that these 2 key components have distinct biological correlates. While depressed mood is typically associated with central serotonergic dysfunction, anhedonia has recently been linked

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to catecholaminergic dysfunction.<sup>9</sup> Thus, depressed mood and/or anhedonia may differentially predict clinical outcomes in post-ACS patients.

The hypothesis of the present study was that 1 of the 2 core criteria of depression independently predicts major adverse cardiac events (MACEs)—myocardial infarction (MI), hospitalization for unstable angina, or urgent revascularization—or all-cause mortality (ACM) in ACS patients, independent of standard medical covariates. In addition, we tested whether depressed mood and/or anhedonia carried independent prognostic risk beyond that associated with previously established markers of depression—clinical diagnosis of major depressive episode (MDE) and self-reported depressive symptom severity.

## METHODS

### STUDY SAMPLE

The study included post-ACS patients who were admitted to the coronary care and cardiac care telemetry units of 3 university hospitals (Mount Sinai Hospital, New York, New York, and Yale–New Haven Hospital and Hospital of St Raphael, New Haven, Connecticut) between May 2003 and June 2005. The institutional review boards of each hospital approved the study.

### INCLUSION CRITERIA

Patients who were aged 18 years or older and spoke English or Spanish were asked to provide informed consent within 1 week of admission to the hospital for the index ACS event. Patients were eligible if they met the criteria for ACS (either acute MI with or without ST-segment elevation or unstable angina) verified by the study cardiologists using standard ACS criteria<sup>10</sup> and had eligible scores (0–4, indicating minimal depressive symptoms, or  $\geq 10$ , indicating at least mild depressive symptoms) on the Beck Depression Inventory (BDI)<sup>11</sup> assessed within 1 week after the index ACS event.<sup>12</sup> We chose the first version of the BDI as did the National Heart, Lung and Blood Institute consensus panel on this topic<sup>12</sup> over the second version, which is preferred for cardiology epidemiology studies. We chose the timing of within 1 week, as this is when the BDI predicts 1-year MACE and ACM<sup>4,13</sup>; later administration results in missing data on those who experience early cardiac events, a critical subgroup to include. Patients with BDI scores between 5 and 9 were excluded to more clearly delineate depressed and nondepressed groups at baseline.<sup>1</sup> Patients were also ineligible for study participation if they had a terminal illness (life expectancy <1 year), were active alcohol and/or substance abusers, or had cognitive impairment; if the screening could not be completed within 1 week of the initial hospitalization date; or if they were unavailable for follow-up visits.

### DEPRESSION MEASURES

All patients underwent the semi-structured diagnostic interview developed for the Enhancing Recovery in Coronary Heart Disease Patients trial<sup>14</sup> to determine the presence of MDE according to the criteria of the *DSM-IV*.<sup>15</sup> When trained interviewers use this interview and quality assurance is conducted, the concordance with other structured psychiatric interviews is excellent.<sup>14</sup> In our study, interviews were conducted by trained research staff, and 1 clinical psychologist and 1 psychiatrist independently reviewed the trained interviewers' audiotapes and

written notes for each interview and verified all diagnoses. As patients were often interviewed on nights and weekends, it was not feasible for mental health specialists to be present at the time of the live interviews. The presence of depressed mood and anhedonia was determined for patients according to the standard criteria used in psychiatric interviews: that the symptom be clinically impairing and present for at least 2 weeks.

Depressed mood and anhedonia were also assessed by patient report with the BDI. Items 1 (sadness) and 10 (crying) of the BDI were summed, yielding a depressed mood score ranging from 0 (low depressed mood) to 6 (high depressed mood). The BDI items 4 (loss of enjoyment) and 12 (loss of interest in others), which assessed anhedonia, were also summed into a score from 0 to 6. Scores on both subscales were categorized to create 2 groups: low or medium (0 or 3) and high (4–6), the latter indicating severe depressed mood or anhedonia.

### MEDICAL COVARIATES

#### GRACE Risk Score, Charlson Comorbidity Index, and Antidepressant Use

We used the Global Registry of Acute Coronary Events (GRACE) risk score to measure established mortality risk factors in post-ACS patients.<sup>16</sup> Prognostic markers in the final GRACE model are 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 evident on electrocardiogram at presentation, and percutaneous coronary intervention performed in the hospital. The GRACE risk score ranges from 1 to 263 points, with higher scores indicating higher mortality risk. A GRACE risk score of 80 predicts a 1% mortality rate at 6 months; 100, a 2% mortality rate; and higher than 210, a mortality rate greater than 50%.<sup>16</sup> Data for the GRACE risk score, the Charlson comorbidity index,<sup>17,18</sup> and antidepressant use at discharge from the hospital were collected from medical records or patient history.

#### Left Ventricular Ejection Fraction

Values for left ventricular ejection fraction (LVEF) were measured quantitatively by left ventriculography during cardiac catheterization (43% of patients), by echocardiography (50% of patients), or by nuclear study (7% of patients). If multiple variables were available, the value from the ventriculogram was used. Values for LVEF were then categorized into 2 groups: normal to mild dysfunction (LVEF  $\geq 40\%$ ) and moderate to severe dysfunction (LVEF < 40%).

#### Ascertainment of MACE and ACM

The primary end point of the study was either the first occurrence of a MACE (hospitalization for nonfatal MI, unstable angina, or urgent/emergency coronary revascularization procedures [percutaneous coronary intervention, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty] using standardized cardiology classification)<sup>10</sup> or ACM by 12 months. Study participants were proactively contacted to complete follow-up assessments at 1, 3, 6, and 18 months either by telephone or in person. For any patient-reported hospitalization, supporting documentation of the event was secured from the hospital's records. Additionally, all recruitment hospitals were proactively searched for any possible MACE hospitalization and death. An end point committee consisting of 2 board-certified cardiologists, blinded to

depression status, independently reviewed and classified each hospitalization; in case of disagreement, a third board-certified cardiologist adjudicated the final end point. For participants who could not be contacted or were reported deceased by a relative, the Social Security Death Index was searched to verify vital status.

## STATISTICAL ANALYSIS

The *t* test for continuous variables and  $\chi^2$  test for categorical variables was used to compare those with and without depressed mood or anhedonia at baseline. When some items of a scale or index were missing, a regression-based approach was used to impute the best linear-predicted score based on the non-missing items.

Cox proportional hazards models were used to estimate the hazard ratio (HR) for MACE and ACM, stratified by hospital. First, depressed mood, anhedonia, depressive symptom severity, and MDE were tested separately. Several additional models were tested to determine whether depressed mood and/or anhedonia were better predictors of outcomes than MDE, BDI score, or the BDI somatic scale score<sup>19</sup>; the last model was tested (1) to ensure that anhedonia and/or depressed mood were not simply marking this dimension of depression, and (2) because the somatic subscale has previously been found to predict clinical outcomes in post-MI patients.<sup>8,20</sup> Finally, all analyses were repeated, using the patient-reported depressed mood and anhedonia measures from the BDI instead of the respective measures from the clinical interview, to see if these measures predicted MACE and ACM equally well.

We followed suggestions for a priori selection for covariate inclusion.<sup>21,22</sup> Based on published findings of factors that might confound the depression–MACE/ACM association, age, sex, LVEF, medical comorbidities (Charlson), clinical prognostic index (GRACE), and antidepressant use were treated as covariates. We then repeated the primary analyses with the unique individual components of the GRACE index to ensure that differences in individual components were tested. Finally, we repeated the primary analysis without the urgent/emergency revascularizations considered to be part of the outcome measure, as we found that the anhedonic patients had significantly fewer baseline revascularizations than nonanhedonic patients.

Follow-up was censored at 12 months after the baseline interview. All analyses were performed using SPSS, version 16 (SPSS Inc, Chicago, Illinois).

## RESULTS

Medical eligibility screening identified 677 patients. Of these, 211 (31%) had BDI scores of 5 to 9, 4 were suicidal and were referred for treatment, and 5 withdrew before the baseline examination was completed. Of the 457 enrolled patients, 4 were excluded from the current analysis because the psychiatric interview was not completed within the designated time. Patients who were unavailable or refused to be screened differed significantly from patients who participated in the study; they were older (mean [SD] age, 65.2 [11.9] vs 61.5 [12.2] years;  $P < .001$ ) and more were Hispanic by self-report (24.3% vs 12.5%;  $P = .01$ ). No other differences were noted.

The remaining 453 patients had a mean age of 61 years (range, 25–93 years); 42% were women; 80% were white; and 10% were Hispanic. Twenty-one percent of the patients were diagnosed with ST-segment elevation MI; 46% with unstable angina; and 33% with MI without ST-

segment elevation. For the depression variables, 48 patients (11%) met the criteria for MDE, 108 (24%) were rated by clinical interview as having depressed mood, and 77 (17%) were rated as having anhedonia (**Table 1**). Anhedonia and depressed mood were highly associated ( $\phi = 0.74$ ,  $P < .001$ ). Of 108 patients with depressed mood, 36 (33.3%) did not have anhedonia. Of 77 patients with anhedonia, 5 (6.5%) did not have depressed mood. In patients with MDE, 81.3% had depressed mood, and 72.9% had anhedonia ( $\phi$  coefficients between MDE and depressed mood and MDE and anhedonia were  $\phi = 0.46$  and  $\phi = 0.51$ , respectively, both  $P < .001$ ).

Demographic and medical variables at baseline according to depressed mood and anhedonia status are shown in Table 1. As can be seen, numerous significant differences existed. Those with depressed mood were significantly more likely to be female, to have higher Charlson comorbidity index scores, to be younger, to have an MDE, to have higher rates of elevated depressive symptoms, and to have an antidepressant prescribed. They were also significantly more likely to have higher admission heart rates, lower systolic pressures, and to have received significantly fewer percutaneous interventions while in the hospital. Patients with anhedonia compared with those without had the same significant differences as were found between patients with and without depressed mood; additionally they had significantly lower GRACE scores (less cardiac risk).

During a mean follow-up of 10.4 months (range, <1–12 months), there were 67 confirmed events (14.8%; 17 deaths and 50 MACEs [11 MIs, 25 hospitalizations for unstable angina, and 14 urgent/emergency revascularizations]), which is comparable with findings of previous research (15.1% MACE and ACM during 1 year).<sup>23</sup>

**Table 2** displays age-adjusted associations of the covariates and MACE and ACM. As expected, all medical covariates were significant bivariate predictors of MACE and ACM within 12 months.

Major adverse cardiac events and/or ACM occurred in 17 of 48 patients (35.4%) with MDE, compared with 50 of 405 patients (12.3%) without MDE. To compare our sample with previous samples, we conducted some preliminary analyses. Major depressive episode and depressive symptom severity assessed by BDI were significant predictors of age-adjusted MACE and/or ACM within 12 months, but only MDE remained a significant predictor after adjusting for age, sex, and the medical covariates (**Table 3**). The adjusted HR for MDE was comparable with that found in prior studies.<sup>24</sup>

## CLINICIAN-RATED DEPRESSED MOOD AND ANHEDONIA AS PREDICTORS OF CLINICAL OUTCOMES

Table 1 shows that the 1-year outcome rates differed by anhedonia and depressed mood groups and that there were few urgent or emergency revascularizations in either group. Both depressed mood and anhedonia significantly predicted MACE and ACM in the age-adjusted model (Table 3), but only anhedonia remained a significant predictor of MACE and ACM after adjusting for age, sex, and the medical covariates. When both anhedonia

**Table 1. Demographic and Clinical Characteristics and Outcomes of 453 Patients With Acute Coronary Syndrome<sup>a</sup>**

Characteristic	Depressed Mood, No. (%)			Anhedonia, No. (%)		
	Absent (n = 345)	Present (n = 108)	P Value	Absent (n = 376)	Present (n = 77)	P Value
Demographic characteristic						
Female sex	132 (38.3)	56 (51.9)	.01	146 (38.9)	42 (55.5)	.01
Age, mean (SD), y	62 (12.2)	58 (12.6)	.001	62 (12.3)	55 (11.6)	<.001
Medical covariate						
LVEF < 40%	51 (14.8)	18 (16.7)	.63	56 (14.9)	13 (17)	.66
Charlson comorbidity index, mean (SD)	1.21 (1.4)	1.85 (1.9)	.002	1.28 (1.5)	1.79 (1.8)	.009
GRACE risk score, mean (SD)	92.2 (30.6)	88.0 (33.0)	.23	92.5 (31.2)	84.64 (30.8)	.04
Prior MI	90 (26.1)	41 (37.9)	.06	105 (27.9)	26 (33.7)	.15
Prior congestive heart failure	33 (9.6)	10 (9.9)	.92	35 (9.4)	8 (11.0)	.68
Heart rate at admission, mean (SD), beats/min	76.1 (18.6)	80.7 (17.6)	.03	76.3 (18.5)	81.42 (18.0)	.03
SBP at admission, mean (SD), mm Hg	143.9 (30.0)	137.2 (24.2)	.046	143.6 (29.5)	136.1 (24.7)	.046
ST-segment deviation	57 (17.1)	15 (15.0)	.62	61 (16.8)	11 (15.9)	.87
Serum creatinine level at admission, mean (SD), mg/dL	1.18 (0.6)	1.17 (0.7)	.94	1.18 (0.6)	1.16 (0.7)	.84
Elevated serum cardiac enzyme levels at admission	106 (33.8)	29 (30.5)	.56	111 (32.6)	24 (34.8)	.73
PCI during hospitalization	250 (72.9)	60 (58.8)	.007	269 (72.5)	41 (55.4)	.003
Antidepressant prescribed at discharge	58 (16.8)	43 (39.8)	<.001	64 (17.0)	37 (48)	<.001
SSRI	38 (11.0)	31 (28.7)	<.001	42 (11.1)	27 (35)	<.001
Non-SSRI	20 (5.8)	12 (11.1)	.06	22 (5.9)	10 (13)	.03
Depression variable						
MDE	9 (2.6)	39 (36.1)	<.001	13 (3.5)	35 (45)	<.001
BDI score ≥ 10	110 (31.9)	102 (94.4)	<.001	138 (36.7)	74 (96)	<.001
1-Year MACE/ACM	40 (11.6)	27 (25.0)	<.001	44 (11.7)	23 (29.9)	<.0001
1-Year ACM	8 (2.3)	9 (8.3)		9 (2.4)	8 (10.3)	
1-Year MI	7 (2.0)	4 (3.7)		8 (2.1)	3 (3.9)	
1-Year urgent/emergency revascularization	9 (2.6)	5 (4.6)		11 (2.9)	3 (3.9)	
1-Year hospitalization for unstable angina	16 (4.6)	9 (8.3)		16 (4.3)	9 (11.7)	

Abbreviations: ACM, all-cause mortality; BDI, Beck Depression Inventory; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MDE, major depressive episode; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor.

SI conversion rate: To convert creatine to micromoles per liter, multiply by 76.25.

<sup>a</sup>Denominators for variables vary slightly owing to missing responses for some variables.

**Table 2. Age-Adjusted Association of Covariates With 12-Month Major Adverse Cardiac Events and All-Cause Mortality in 453 Patients**

Predictor	Age-Adjusted HR (95% CI)	P Value
Sex, M vs F	1.02 (0.80-1.31)	.87
Left ventricular ejection fraction, <40 vs ≥40	1.39 (1.06-1.84)	.02
Charlson comorbidity index, per SD <sup>a</sup>	1.38 (1.16-1.64)	<.001
GRACE risk score, per SD <sup>b</sup>	1.45 (1.01-2.10)	.03
Antidepressant use	1.34 (1.03-1.74)	.02

Abbreviations: CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.

<sup>a</sup>One SD = 1.57.

<sup>b</sup>One SD = 31.21.

and depressed mood were in the multivariable-adjusted model, only anhedonia was a significant predictor of MACE and ACM (adjusted HR, 1.69; 95% confidence interval [CI], 1.07-2.68;  $P = .03$ ; **Figure**). This association was strengthened when 1-year urgent or emergency revascularization events were not considered part of the MACE/ACM outcome (HR, 2.17; 95% CI, 1.26-3.73;  $P = .005$ ), whereas depressed mood continued to be unrelated to outcomes (Table 3). Anhedonia remained a significant predictor after adjusting for MDE (HR, 1.45; 95%

CI, 1.03-2.05;  $P = .04$ ). Similarly, anhedonia remained significant when adjusting for severity of depressive symptoms (HR, 1.52; 95% CI, 1.09-2.11;  $P = .01$ ). Furthermore, with anhedonia in the model, neither MDE (HR, 1.25; 95% CI, 0.87-1.79;  $P = .23$ ) nor depressive symptom severity (HR, 1.09; 95% CI, 0.81-1.47;  $P = .57$ ) were significant predictors of outcome. Finally, after adjusting for covariates and the somatic subscale of the BDI, anhedonia remained a significant predictor (HR, 1.99; 95% CI, 1.17-2.40;  $P = .01$ ). With MDE, depressive symptom severity, or BDI somatic subscale in the model, depressed mood was not a significant predictor of outcome.

When the analyses were repeated with individual medical covariates from the GRACE score as covariates, rather than using the GRACE composite index, the results were the same. Anhedonia was significant (HR, 1.79; 95% CI, 1.01-3.17;  $P = .048$ ), while depressed mood was not (HR, 0.74; 95% CI, 0.42-1.32;  $P = .31$ ).

#### PATIENT-REPORTED DEPRESSED MOOD AND ANHEDONIA AS PREDICTORS OF CLINICAL OUTCOMES

When anhedonia and depressed mood as assessed with the BDI were used as predictors instead of the clinician-diagnosed criteria, the results were again similar; patient-



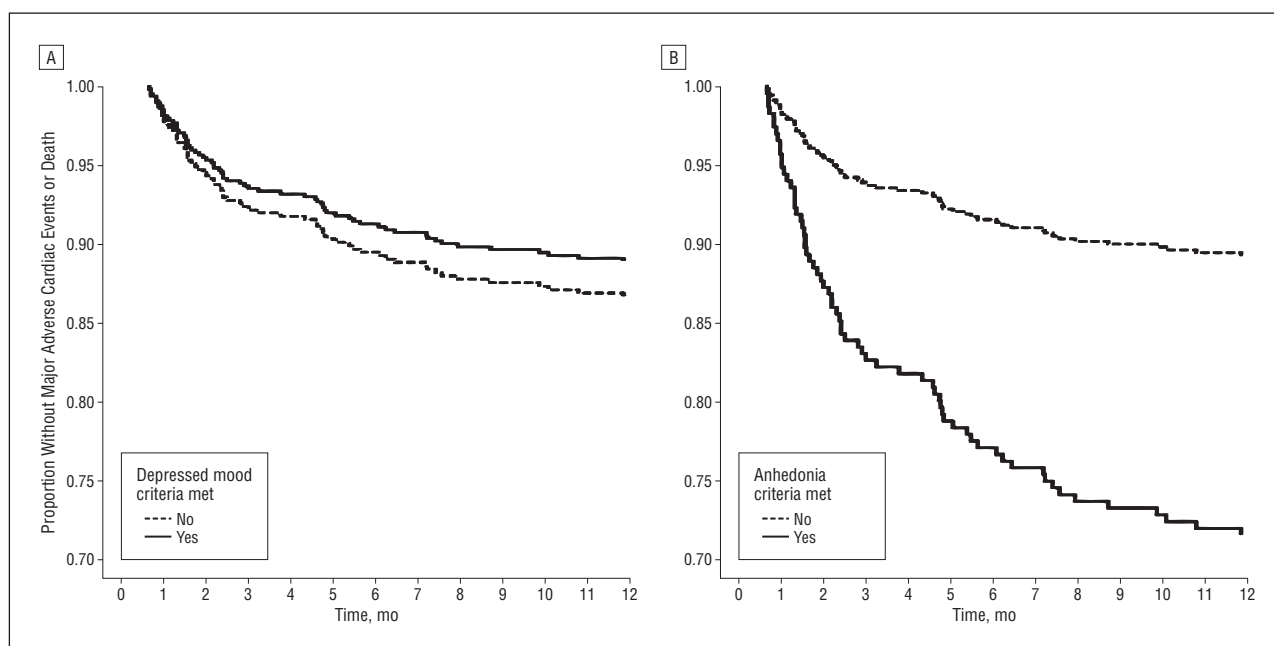
**Table 3. Adjusted HRs for 12-Month Major Adverse Cardiac Events and All-Cause Mortality**

Predictor	Age-Adjusted HR (95% CI)	P Value	Multivariable-Adjusted HR (95% CI) <sup>a</sup>	P Value
Depressive symptom severity, BDI score <5 vs ≥10	1.33 (1.03-1.72)	.03	1.23 (0.94-1.62)	.14
Major depressive episode	1.71 (1.27-2.29)	<.001	1.48 (1.07-2.04)	.02
Entered in model alone				
Depressed mood	1.41 (1.08-1.85)	.01	1.28 (0.96-1.71)	.09
Anhedonia	1.69 (1.28-2.24)	<.001	1.58 (1.16-2.14)	<.01
Entered in same model				
Depressed mood	0.99 (0.65-1.51)	.95	0.92 (0.59-1.43)	.70
Anhedonia	1.71 (1.10-2.65)	.02	1.69 (1.07-2.68)	.03
Depressed mood <sup>b</sup>	0.89 (0.54-1.47)	.64	0.80 (0.47-1.35)	.40
Anhedonia <sup>b</sup>	2.12 (1.27-3.55)	.004	2.17 (1.26-3.73)	.005

Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; HR, hazard ratio; GRACE, Global Registry of Acute Coronary Events.

<sup>a</sup>Adjusted for age, sex, Charlson comorbidity index score, GRACE risk score, left ventricular ejection fraction, and antidepressant use at discharge.

<sup>b</sup>The final model is repeated after recoding urgent/emergency revascularizations as no longer being part of the medical outcome measure.



**Figure.** Cox regression predicted curves for patients with and without clinician-rated depressed mood (left) or anhedonia (right). Adjusted for site, age, sex, Charlson comorbidity index score, Global Registry of Acute Coronary Events risk score, left ventricular ejection fraction, and antidepressant use at discharge and the other depression core criteria.

reported anhedonia was a significant predictor of MACE/ACM after controlling for demographic and medical covariates (HR, 2.26; 95% CI, 1.33-3.82;  $P = .002$ ) and also after controlling for the somatic subscale of the BDI (data not shown), while patient-reported depressed mood was not (HR, 0.86; 95% CI, 0.51-1.43;  $P = .55$ ).

#### COMMENT

The present study replicates and augments the finding of previous research in patients with established heart disease, that depression is a significant risk factor for adverse clinical outcomes,<sup>2,3</sup> even when adjusting for demographic characteristics and known medical prognostic disease markers and comorbid conditions.<sup>25</sup> We further demonstrated that of the 2 core criteria of depression—

depressed mood and anhedonia—only anhedonia predicts the risk of MACE and ACM independent of the usual covariates and other depression indices.

#### IMPROVING RISK STRATIFICATION

Major depressive episode is a heterogeneous clinical entity with diverse somatic and cognitive symptoms that include fatigue, feelings of guilt, sleep problems, and weight gain or loss. Not all of these symptoms may mark individuals at increased risk of MACE or ACM. Also, because MDE criteria can be met through varying symptom patterns, the resulting heterogeneity may in part explain why previous depression treatment and observational studies in ACS patients have inconsistent results. As others have pointed out, it is important to move

beyond the broad phenotype of depression and delineate its “cardiotoxic” components.<sup>26</sup> In a previous study with post-MI patients, de Jonge and colleagues<sup>27</sup> identified 3 symptom dimensions of the BDI—somatic/affective, cognitive/affective, and appetitive—and found that only somatic or affective symptoms predicted future death or cardiac events after controlling for somatic health indicators. The somatic/affective dimension, however, still contained symptoms that were clinically (and likely, etiologically) distinct, such as insomnia, indecisiveness, and both depressed mood and anhedonia. Recent analyses from the Women’s Ischemia Syndrome Evaluation study used a similar approach to evaluate the cardiac prognostic impact of symptom dimensions from BDI in women with suspected myocardial ischemia.<sup>28</sup> This study revealed that somatic/affective symptoms of depression predicted cardiovascular events and mortality, and cognitive/affective did not. We chose a different approach of analyzing the 2 core symptoms of depression that are also known as *endophenotypes* of depression in the psychiatry literature,<sup>9</sup> which are thought to be clinically distinguishable and possibly have unique biological bases. Furthermore, when we controlled for the somatic depression subscale, anhedonia continued to predict MACE and ACM, while depressed mood did not.

Anhedonia is described as the loss of ability to experience pleasure in all or almost all activities,<sup>29</sup> whereas depressed mood is marked by sadness, tearfulness, and sometimes visible distress. This clinical distinction within the complex phenotype of major depression has been noted for centuries.<sup>30,31</sup> Anhedonia is not specific to depression; it occurs in other psychiatric disorders as well.<sup>32</sup> Moreover, as with all symptoms of psychiatric disease, not all patients with anhedonia fulfill the diagnostic criteria for MDE. In fact, almost half the patients with anhedonia in our sample did not have MDE, yet anhedonia proved to be the most accurate predictor of MACE and ACM, better even than the clinical diagnosis of MDE.

When we created patient-reported subscales of anhedonia and depressed mood from the BDI, we replicated this finding, that anhedonia, not depressed mood, is uniquely predictive of medical outcomes. Other patient-report measures may assess anhedonia and depressed mood more accurately than post hoc subsets of the BDI (eg, Patient Health Questionnaire 2<sup>33</sup>), and these more easily administered self-report measures should be tested for their usefulness in risk-stratifying cardiac patients. Should the present finding be confirmed in other samples, assessments of patient-reported anhedonia could easily be implemented in clinical practice.

Of note, when controlling for depressive symptom severity, anhedonia still predicted MACE or ACM, ruling out the possibility that patients with anhedonia are at increased risk merely because they have more severe depressive symptoms overall. These findings suggest that examining the particular criteria of anhedonia might provide new insights concerning mechanisms and treatments that increase the risk of adverse cardiac events and death in post-ACS patients.

## BIOLOGICAL AND BEHAVIORAL CORRELATES OF ANHEDONIA IN PSYCHIATRIC PATIENTS

Psychiatric patients with anhedonia tend to have perturbations of sleep, satisfaction, appetite, weight, and libido. Perturbations in the dopaminergic system, inflammatory processes, circadian rhythms, and melatonin production have also been observed in anhedonic patients.<sup>30,34,35</sup> Hasler and colleagues<sup>9</sup> suggest that anhedonia, but not depressed mood, is associated with catecholaminergic dysfunction, a mechanism that has been proposed to explain increased morbidity and mortality owing to cardiovascular disease.<sup>36,37</sup> High catecholamine levels are toxic to cardiac myocytes,<sup>38</sup> can trigger tachyarrhythmia,<sup>39-41</sup> and promote platelet aggregation.<sup>42,43</sup> Among patients with congestive heart failure, the extent of plasma catecholamine elevation correlates directly with cardiac mortality.<sup>44</sup> It is also possible that the risk conferred by anhedonia in cardiac patients is mediated through behavior. A relatively stable feature of anhedonia is an impaired responsiveness to reinforcing, rewarding stimuli.<sup>9</sup> This suggests that patients with anhedonia may be less likely to perceive the benefits of and engage in healthy cardioprotective behaviors, such as exercising, attending cardiac rehab, adhering to a healthy diet, and taking their medications regularly. It is even possible that anhedonia predicts less symptom reporting at the time of the ACS event. This might in turn impact physician behavior, because less urgency of symptom reporting sometimes leads to less aggressive medical or surgical management. More studies are therefore needed to understand the behavioral and biological aspects of anhedonia in cardiac patients.

## IMPLICATIONS FOR CARDIAC PATIENTS WITH ANHEDONIA

Thus far, studies that have applied standard pharmacological and nonpharmacological depression treatments to cardiac patients with MDE have achieved modest reductions in depressive symptoms.<sup>24</sup> They have failed, however, to significantly improve the cardiac prognosis of these patients. The present study shows that it is not only patients with MDE that are at increased risk, but that the endophenotype of anhedonia is a potent predictor, irrespective of the severity of depressive symptoms. To date, there are no studies that have directly compared the efficacy of various forms of antidepressant treatments in patients with and without anhedonia.

Understanding the behavioral and biological mechanisms underlying anhedonia in cardiac patients may provide insights into which treatments to best apply in these patients. For example, interventions involving behavioral activation may be a good choice for treatment should future studies show marked decreases in cardioprotective health behavior that is associated with the presence of anhedonia in cardiac patients. It may also be the case that patients with anhedonia need to be more rapidly treated with antidepressant medication, as the effects of pharmacotherapy on this specific feature of depression may take longer than on other features.<sup>45</sup> Whether reducing anhedonia in post-ACS patients will reduce their risk of MACE or ACM is not yet known.

## STUDY LIMITATIONS

There are a number of limitations in the present study. Although anhedonia has previously been found to predict in-hospital mortality in medical patients<sup>46</sup> and major clinical events after stent placement,<sup>47</sup> our finding that anhedonia is uniquely associated with increased risk of MACE and ACM in post-ACS patients must be replicated. Furthermore, the current study was insufficiently powered to rule out the possibility that depressed mood is a moderate predictor of medical outcomes. However, its HR in this sample was below 1, so it was trending toward being a protective, rather than a risk, factor. Events or deaths within this study occurred primarily within the first 3 months after discharge, so the association of depressed mood and anhedonia with longer-term outcomes was also not determined.

Ascertainment of cardiac events that required hospitalization was largely dependent on patients' reports, and there is a possibility that some patients may not have reported a hospitalization. We did search recruitment hospital records for all admissions, but patients readmitted to outside hospitals would not be found with this process.

It is possible that the post-ACS patients who reported loss of interest in activities are those with the most severe forms of heart disease and that it is the severity of their disease that is causing a poor prognosis, rather than a particular symptom of depression—anhedonia. Some doubt remains about the predictive power of depression, or its components, as an independent risk marker beyond the power of established clinical disease markers, as many prognostic studies have not adequately controlled for clinical and cardiovascular covariates, such as LVEF.<sup>25</sup> In our study, anhedonic patients had higher medical comorbidities, as indicated by the Charlson comorbidity index score and differences in components of the GRACE risk score, but these differences were controlled for in the analyses. Furthermore, the significant differences found in resting heart rate and other cardiac risk factors were small and are not considered clinically significant within cardiology research. It remains possible, however, that anhedonia is a marker for some medical confounder not assessed in the current study that predicts clinical outcome.

We also excluded ACS patients with mild BDI scores (5-9) to more clearly delineate depression groups. It is possible that many patients within this range of depressive symptoms might have met criteria for anhedonia. In a small subsequent study (for which outcomes are not yet available), however, only 2% of ACS patients with BDI scores in this range meet clinical criteria for anhedonia. Nonetheless, this is a limitation of the study, and future studies should include the full range of BDI scores in their cohorts.

Finally, we used an a priori, composite medical outcome as is now common in cardiology clinical trials and registries.<sup>48</sup> This included ACM, infarction, and standardized criteria for unstable angina and urgent or emergency revascularization procedures.<sup>10</sup> Outcomes that incorporate coronary revascularization are at risk of

including "softer" outcomes, such as target vessel revascularization, angiographic stenosis, and nonurgent revascularizations. To a certain extent, these latter outcomes can represent physician bias and variable practice patterns. Thus, we chose to include only urgent or emergency coronary revascularizations as part of the primary composite outcome, and excluded these others. When we tested our findings with urgent and emergency revascularizations removed from our 1-year outcome measure, the independent association between anhedonia and medical outcomes was strengthened; depressed mood remained nonsignificantly associated. Our inability to examine each outcome separately (because there were too few in each category) remains a limitation. A future study should examine whether the association of anhedonia is primarily with death or recurrent coronary events, as this too would suggest differential mechanistic pathways.

This study replicates the finding of prior research that MDE is a significant and independent risk factor for adverse clinical outcomes in patients with ACS. It also demonstrates that, of the 2 core criteria of MDE (depressed mood and anhedonia), only anhedonia was a significant predictor before and after adjusting for depression severity and MDE diagnosis. Focusing on anhedonia in post-ACS patients may better identify those at risk, may provide insight into the mechanisms underlying the association between depression and poor outcomes in patients with heart disease, and ultimately may inform the design of novel treatments to improve post-ACS prognosis.

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