Anhedonia Predicts Major Adverse Cardiac Events and Mortality in Patients 1 Year After Acute Coronary Syndrome

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Abstract

Context—Depression is a consistent predictor of recurrent events and mortality in ACS patients, but it has 2 core diagnostic criteria with distinct biological correlates—depressed mood and anhedonia.

Objective—To determine if depressed mood and/or anhedonia (loss of pleasure or interest) predict 1-year medical outcomes for patients with Acute Coronary Syndrome (ACS).

Design—Observational cohort study of post-ACS patients hospitalized between May 2003 and June 2005. Within one week of admission, patients underwent a structured psychiatric interview to assess 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.

Setting—Coronary care and cardiac care step-down units of 3 university hospitals in New York and Connecticut.

Participants—Consecutive sample of 453 ACS patients (aged 25–93 years; 42% women).

Main Outcomes Measures—All-cause mortality (ACM) and documented major adverse cardiac events (MACE; myocardial infarction, hospitalization for unstable angina, or urgent revascularization) were actively surveyed for 1 year after admission.

Results—There were 67 events (16 deaths and 51 MACE; 14.8%). 108 (24%) and 77 (17%) patients with anhedonia and depressed mood, respectively. After controlling for sex, age, and medical covariates, anhedonia (adjusted hazard ratio, 1.58; 95% confidence interval, 1.16–2.14; *P*<.01) and MDE (adjusted hazard ratio, 1.48; 95% confidence interval, 1.07–2.04; *P*=.02) were significant predictors of combined MACE/ACM, but depressed mood was not. Anhedonia continued to significantly predict outcomes controlling for MDE diagnosis and depressive symptom severity, each of which were no longer significant.

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Conclusions—Anhedonia identifies risk for MACE/ACM beyond that of established medical prognostic indicators. Biological correlates of anhedonia may add to the understanding of the link between depression and heart disease.

Keywords

Acute coronary syndromes; mortality; depressio; anhedonia

INTRODUCTION

Systematic 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 acute coronary syndrome (ACS) patients.[1⁻3] Moreover, in patients with established coronary heart disease (CHD), the presence of a depression diagnosis is more important than CHD severity in predicting quality of life and overall perceived health. [4, 5] This risk has been observed in recent studies and meta-analyses, despite continued improvement in cardiology interventions, medications, and care.[3, 6⁻14] Recent calls have been made for the recognition of depression as an independent risk marker for ACS patients, [15] and evidence-based patient grand rounds[16] are now being provided to assess and manage this predictor of poor cardiac prognosis. Despite growing acceptance of depression as a cardiac risk factor,[17] initial attempts to prevent mortality or recurrence by treating depression in ACS patients have not been successful.[18, 19] In addition, some doubt remains about the power of depression as an independent risk marker beyond the power of established clinical disease markers, since many prognostic studies have not adequately controlled for clinical and cardiovascular covariates such as left ventricular ejection fraction. [13]

To better understand how depression predicts cardiac risk, some have suggested searching for subtypes of depression that are particularly cardiotoxic.[1, 14, 20] Major depression is a complex phenotype encompassing a wide range of symptoms, not all of which are present in all patients. 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). These symptoms must be present most of the day, nearly every day. Depressed mood and anhedonia have been posited to have distinct biological correlates; while depressed mood is typically associated with central serotonergic dysfunction, anhedonia has recently been linked to catecholaminergic dysfunction.[21] Thus, it is possible that depressed mood and/or anhedonia may differentially predict clinical outcomes in post-ACS patients.

The aim of the present study was to determine the independent prognostic significance the 2 core criteria of depression, as judged by a trained psychiatric interviewer, for major adverse cardiac events (MACE; myocardial infarction [MI], hospitalization for unstable angina, or urgent revascularization) or all-cause mortality (ACM) in ACS patients. We chose as covariates established clinical prognostic markers of recurrent clinical events and mortality in ACS patients:[13, 22, 23] the Global Registry of Acute Coronary Events (GRACE) risk score, a composite prediction score recently shown to predict the 12-month risk of MACE or ACM in post-ACS patients discharged from the hospital[24, 25]; the Charlson comorbidity index[23]; left ventricular ejection fraction (LVEF); age; sex; and antidepressant use. In addition, we assessed whether depressed mood and 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 step-down units of 3 university hospitals (Mount Sinai Hospital, New York, NY, and Yale–New Haven Hospital and Hospital of St. Raphael, New Haven, CT) 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 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[26] and had valid scores (0–4, indicating minimal depressive symptoms, or ≥10, indicating at least mild depressive symptoms) on the Beck Depression Inventory (BDI)[27] assessed within 1 week after the index ACS event.[28] Patients with BDI scores between 5 and 9 were excluded to more clearly delineate depressed and nondepressed group at baseline. Patients were also ineligible for study participation if they had a terminal illness (life expectancy <1 year), were active 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

In addition to the self-report measure of depressive symptom severity (BDI), all patients underwent the semistructured diagnostic interview developed for the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial[29] to determine the presence of MDE according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.[30] When trained interviewers use this interview and quality assurance is conducted, the concordance with other structured psychiatric interviews is excellent.[29] In our study, one clinical psychologist and one psychiatrist independently reviewed the trained interviewers' audiotapes and written notes for each interview and verified all diagnoses. 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, most of the day, nearly every day.

Medical Covariates

GRACE Risk Score, Charlson Comorbidity Index, and Antidepressant Use—
We employed the GRACE risk score to measure established mortality risk factors in post-ACS patients.[25] 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 hospital, elevated initial serum creatinine level, elevated initial cardiac enzyme level, ST-segment depression evident on electrocardiogram at presentation, and percutaneous coronary intervention (PCI) performed in 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%. [25] Data for the GRACE risk score, the Charlson comorbidity index,[23, 31] and antidepressant use at discharge from hospital were collected from the medical records or patient history.

Left Ventricular Ejection Fraction Values—Values for LVEF were measured quantitatively by left ventriculogram during cardiac catheterization (43% of patients), by

echocardiogram (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 ≥40%) and moderate to severe dysfunction (LVEF <40%).

Ascertainment of MACE and ACM—The primary endpoint of the study was either the first occurrence of a MACE (hospitalization for nonfatal MI, urgent cardiac revascularization, or unstable angina) 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 requested from the hospital's records. An endpoint committee consisting of 2 board-certified cardiologists independently reviewed and classified each hospitalization; in case of disagreement, a third board-certified cardiologist adjudicated the final endpoint. All cardiologists were unaware of the participants' depression status. 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, and death certificates were obtained.

Statistical Analysis—The *t* test for continuous variables and χ^2 analysis for categorical variables tested baseline variables for differences between those with and without depressed mood or anhedonia. The familywide α error underwent Bonferroni correction within variable grouping (eg, demographic variables, Charlson comorbidity index, and GRACE risk score components). When baseline medical covariate data were missing, a regression-based approach was used to impute the best linear-predicted score based on the nonmissing items.

Cox proportional hazards models were used to estimate the hazard ratios for MACE/ACM, stratified by hospital. The depression predictors (depressed mood, anhedonia, and MDE) were first tested separately, adjusting for specified covariates: GRACE risk score, Charlson comorbidity index, LVEF value (<40% vs ≥40%), antidepressant use, age, and sex. We followed suggestions for apriori selection for covariate inclusion.[32, 33] First, we listed the covariates from published findings that might confound the Depression—MACE/ACM association: age, sex, left ventricular ejection fraction, medical comorbidities (Charlson), clinical prognostic index (GRACE), and anti-depressant use. We then calculated how many covariates we could include in the model based on a ratio of at least 10 events per covariate; as we had 67 events, we could include up to 6 covariates. Depressed mood and anhedonia were then tested to determine if they predicted outcomes over and above the power of MDE and the selected covariates. This was followed by tests of these 2 predictors over and above BDI scores to rule out the possibility that they are simply markers of depressive symptom severity.

The proportional hazards assumption was met for all presented models. Follow-up was censored at 12 months after the baseline interview. All analyses were performed using SPSS (version 16; SPSS Inc, Chicago, IL).

RESULTS

During medical eligibility screening (no terminal illness, no alcoholism/drug addiction, no dementia, available for follow-up), we identified 677 patients for the study. 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 an average age of 61 years (range, 25–93 years), and 42% were women, 80% white, and 10% Hispanic. Twenty-one percent of the patients were diagnosed with myocardial infarction with ST-segment elevation; 46%, unstable angina; and 33%, myocardial infarction with non–ST-segment elevation. For the depression variables, 48 patients (11%) met the criteria for MDE, 108 (24%) were rated as having depressed mood, and 77 (17%) were rated as having anhedonia. Furthermore, 39 patients (36%) with depressed mood and 35 patients (45%) with anhedonia met the criteria for MDE. Anhedonia and depressed mood were highly intercorrelated (*r* = .74, *P* < .001).

Demographic and medical variables at baseline according to depressed mood and anhedonia are shown in Table 1. 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 depressive symptoms, and to have an antidepressant prescribed. Patients with anhedonia were significantly more likely to be female and to have a higher Charlson comorbidity index score. They did not differ from patients without anhedonia on GRACE risk score, but they did receive significantly fewer percutaneous interventions while in the hospital, and they were significantly younger. Finally, they were significantly more likely to have an MDE, to have more severe depressive symptoms, and to have an antidepressant prescribed.

During a mean follow up of 10.4 months (range, <1–12 months), there were 67 confirmed events (16 deaths and 51 ACS recurrences; 14.8%), which is comparable to the finding of another study (15.1% over 1 year).[24] Table 2 displays age-adjusted associations between the covariates and MACE and ACM. All medical covariates were significant predictors of MACE and ACM within 12 months. Major adverse cardiac events or ACM occurred in 23 patients (29.9%) with anhedonia compared with 44 patients (11.7%) without anhedonia; in 27 patients (25.0%) with depressed mood compared with 40 patients (11.6%) without depressed mood; and in 17 patients (35.4%) with MDE compared with 50 patients (12.3%) without MDE.

Major depressive episode and depressive symptom severity assessed by BDI were significant predictors of age-adjusted MACE and ACM within 12 months, but only MDE remained a significant predictor after adjusting for age, sex, and medical covariates (Table 3). Furthermore, 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 medical covariates. When both anhedonia and depressed mood were in the multivariable adjusted model, only anhedonia was a significant predictor of MACE/ACM (adjusted hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.07–2.68; *P*=.03; see Figure 1).

Anhedonia remained a significant predictor after adjusting for all covariates and MDE (HR, 1.45; 95% CI, 1.03–2.05; *P*=.04), and it also remained significant after adjusting for covariates and severity of depressive symptoms (HR, 1.52; 95% CI, 1.09–2.11; *P*=.01). With either MDE or depressive symptom severity in the model, depressed mood was not a significant predictor of outcome. 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) was a significant predictor of outcome. A final model with anhedonia and all covariates as well as PCI, the only GRACE risk score component that significantly differed between those with and without anhedonia, and anhedonia remained a significant predictor of outcome (*P*= .002).

DISCUSSION

The finding in 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,[2, 3] even when adjusting for demographic characteristics and known medical prognostic disease markers and comorbid conditions.[13] We further demonstrated that of the 2 core criteria of depression—depressed mood and anhedonia—only anhedonia predicted the risk of MACE and ACM beyond the power of all 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 these symptoms may mark those at increased risk of MACE or ACM. As others have pointed out, it is important to move beyond the broad phenotype of depression and delineate its "cardiotoxic" components.34 In a previous study with post-MI patients, de Jonge and colleagues35 identified 3 symptom dimensions of the BDI—somatic or affective, cognitive or affective, and appetitive—and found that only somatic or affective symptoms predicted future death or cardiac events after controlling for somatic health indicators. However, the somatic or affective dimension still contained symptoms that are clinically (and likely, etiologically) distinct, such as insomnia, indecisiveness, and both depressed mood and anhedonia. Recent analyses from the Women's Ischemia Syndrome Evaluation (WISE) study used a similar approach to evaluate the cardiac prognostic impact of symptom dimensions from the Beck depression inventory (BDI) in women with suspected myocardial ischemia.[36] This study revealed that somatic symptoms of depression predicted cardiovascular events and mortality, and cognitive/affective did not. Interestingly, the two BDI items that assess anhedonia, had low factor loadings (< .50) on the somatic factor as well as the cognitive/affective factor, indicating that anhedonia is neither a purely 'cognitive', nor a purely 'somatic' depression symptom in their analyses. We chose a different approach by analyzing the two core symptoms of depression that are also known as 'endophenotypes' of depression21 that are clinically distinct and may have distinct biological bases.

Anhedonia is described as the loss of the ability to experience pleasure in all or almost all activities[37] and is viewed as different from depressed mood, which is marked by sadness, tearfulness, and sometimes visible distress. This clinical distinction within the complex phenotype of major depression has been noted for centuries.[38, 39] A diagnosis of MDE requires the presence of either anhedonia or depressed mood, and excellent screening tools for MDE exist that assess just these 2 criteria.[40, 41] Anhedonia is not specific to depression; it occurs in other psychiatric disorders as well.[42] 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 severe anhedonia in our sample did not have MDE, yet anhedonia proved to be the most persistent predictor of MACE and ACM, better even than the clinical diagnosis of MDE. When we controlled for depression 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 the possibility that examining the particular criteria of anhedonia can provide new insights concerning mechanisms that increase risk of adverse cardiac events in post-ACS patients.

Understanding Mechanisms

Numerous biological and behavioral mechanisms have been proposed for the link between depression and adverse cardiovascular events in post-ACS patients [43, 44]. For example, we found increased platelet reactivity in depressed patients [45], and others found hypercoaguability, inflammatory activation, and endothelial or autonomic dysfunction among depressed patients with cardiac disease.[46–50] More recently, we demonstrated that depressed post-ACS patients comply less well with recommended medications and other treatments.[51, 52] The mechanisms for the relationship between anhedonia (as opposed to the more complex phenotype of MDE) and poor outcome after ACS have not yet been studied.

Patients with anhedonia tend to have perturbations of sleep, satisfaction, appetite, weight, and libido. Animal models of experimentally induced anhedonia suggest that cytokine profiles are disrupted.[53] A recent comparison of MDE patients and interferon-alpha induced depressed patients determined that anhedonia was more prevalent in the latter, as were other neurovegetative symptoms.[54] Perturbations in the dopaminergic system, inflammatory processes, circadian rhythms, and melatonin production have also been observed in anhedonic patients.[38, 55, 56] Hasler and colleagues suggested that anhedonia, but not depressed mood, is associated with catecholaminergic dysfunction,[21] a mechanism that has been proposed to explain increased morbidity and mortality due to cardiovascular disease.[46, 57] High catecholamine levels are toxic to cardiac myocytes,[58] can trigger tachyarrhythmia,[53, 59, 60] and promote platelet aggregation.[61, 62] Among patients with congestive heart failure, the extent of plasma catecholamine elevation correlates directly with cardiac mortality.[63] Further study of these mechanisms is needed in anhedonic cardiac patients.

Directions for Future Treatments

If previous depression trials had already demonstrated that depression treatment offsets the increased risk of adverse cardiac events found for depressed patients, it would be moot to explore the type of depression symptom that increases MACE/ACM risk. Two previous trials, SADHART, which used sertraline,[64] and ENRICHD, which predominantly used cognitive behavioral therapy,[65] demonstrated a statistically significant (but not large) reduction of depressive symptoms in post-MI patients. Although the ENRICHD study was sufficiently powered to determine whether depressive symptom reduction improved post-MI survival, it was unable to do so. A recent trial of antidepressant medication use in depressed post-MI patients also did not show a reduction in mortality risk.[66] Depressed patients with anhedonia have long been thought to respond well to antidepressant treatment,[67] but evidence for this clinical intuition is limited to a few studies in psychiatric patient samples.[68] Mechanisms of action in antidepressant treatments are not fully understood. A recent study of experimentally induced myocardial infarction in rats found that sertraline blocked the anhedonia and despair equivalent in this animal model, and modulated the inflammatory response to the infarction; the effect was also noted with desipramine.[69] If we hypothesize that a cytokine release precipitates anhedonia in some ACS patients, then rapid treatment may be indicated, as it is possible that the timing of the depression treatment is critical for preventing the anhedonia comorbidity we discovered in humans. Treatments that focus on reducing anhedonia through modulating upregulated proinflammatory cytokines may be of particular interest.[56, 70, 71] More recent efforts have focused on the functional interaction between the serotonergic and dopaminergic systems[72, 73] and these may also offer new treatments to test in anhedonic ACS patients. 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[74] and major clinical events

after stent placement,[75] 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 not sufficiently powered to rule out the possibility that depressed mood is not a moderate prognostic marker, and its usefulness in this regard should be retested with a larger sample size. 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.

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 it is the severity of their disease that is causing a poor prognosis, rather than a particular symptom of depression—anhedonia. As shown in Table 1, patients with anhedonia were significantly younger than those without anhedonia, and there were no significant differences between the 2 groups in GRACE risk score variables other than the frequency of PCI. When frequency of PCI was added to the model, anhedonia remained a significant predictor of clinical outcomes. Anhedonic patients also had higher Charlson comorbidity index scores, but this difference was controlled for in analyses. It remains possible, however, that anhedonia is a marker for some medical confounder not assessed in the current study that predicts clinical outcome.

CONCLUSIONS

The current finding 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 criteria of MDE, depressed mood and anhedonia, only anhedonia was a significant predictor, after adjusting for severity of depression and clinical diagnosis of MDE. 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.

Abbreviations list

ACS	Acute Coronary Syndrome
GRACE	Global Registry of Acute Coronary Events
MACE	Major Adverse Cardiac Events
MDE	Major Depressive Episode

Acknowledgments

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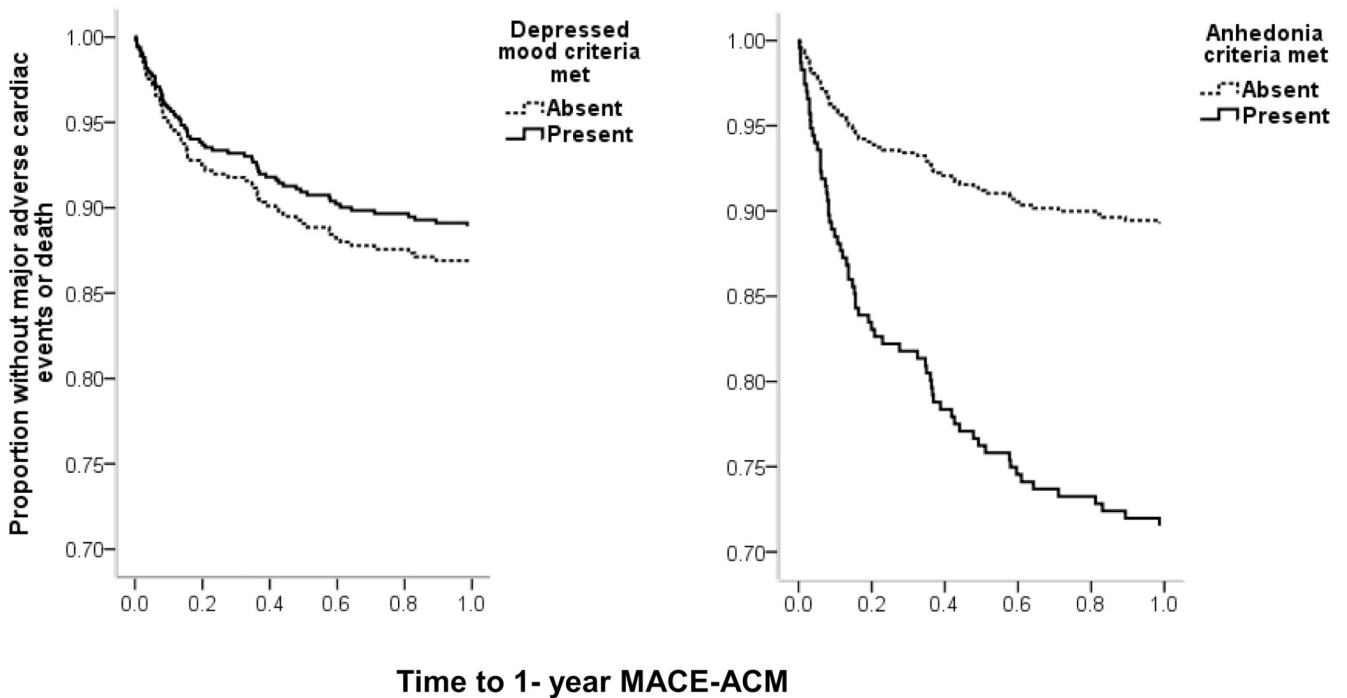
Figure 1.
Kaplan-Meier curves for patients with and without clinically impairing anhedonia (left; markedly diminished interest or pleasure in all or almost all activities) or depressed mood (right; sadness and the report of feeling depressed) most of the day, nearly every day. Adjusted for site, age, sex, Charlson comorbidity index score[23], GRACE [Global Registry of Acute Coronary Events] risk score,[25] left ventricular ejection fraction, and antidepressant use at discharge and the other depression core criteria. Abbreviations: MACE, major adverse cardiac events; ACM, all-cause mortality. Time is percentage of one year.

Table 1

Demographic and Clinical Characteristics of 453 Patients with Severe Anhedonia or Depressed Mood[a]

Characteristic	Depressed Mood			Anhedonia		
	Absent (n=345)	Present (n=108)	P	Absent (n=376)	Present (n=77)	P
Demographic Characteristics[c]						
Women, No. (%)	132 (38.3)	56 (51.9)	.01	146 (38.9)	42 (555)	.01
Age, y	62 (12.3)	58 (12.6)	.001	62 (12.3)	55 (11.6)	<.001
Medical Covariates						
LVEF <40%	51 (14.8)	18 (16.7)	.63	56 (14.9)	13 (17)	.66
Charlson comorbidity index[23]	1.21 (1.4)	1.85 (1.9)	.002[b]	1.28 (1.5)	1.79 (1.8)	.009
GRACE[24, 25] risk score[c]	92.2 (30.6)	88.0 (33.0)	.23	92.5 (31.2)	84.64 (30.8)	.04
Prior MI	0.35 (0.7)	0.50 (0.8)	.06	0.37 (0.7)	0.47 (0.8)	.15
Prior congestive heart failure	33 (9.6)	10 (9.9)	.92	35 (9.4)	8 (11.0)	.68
Heart rate at admission	76.1 (18.6)	80.7 (17.6)	.03	76.3 (18.5)	81.42 (18.0)	.03
Systolic blood pressure at admission	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	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[b]
Antidepressant prescribed at discharge, No. (%)	58 (16.8)	43 (39.8)	<.001	64 (17.0)	64 (17.0)	<.001
Depression Variables						
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
MDE, No. (%)	9 (2.6)	39 (36.1)	<.001	13 (3.5)	35 (45)	<.001
BDI[28] score ≥10, No. (%)	110 (31.9)	102 (94.4)	<.001	138 (36.7)	74 (96)	<.001

Abbreviations: BDI, Beck Depression Inventory; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; MDE, major depressive episode; MI, myocardial infarction; PCI, percutaneous coronary intervention; SSRI, selective serotonin reuptake inhibitor.

[a] Values are mean (SD) unless otherwise indicated. Denominators for variables vary slightly due to missing responses for some variables.

[b] Significant difference between groups after Bonferroni correction.

[c] Bonferroni correction for demographic variables, $\alpha \leq .003$; Bonferroni correction for GRACE risk components, $\alpha \leq .004$

Table 2

Age- Adjusted Association of Each Covariate with 12Month MACE or ACM in 453 Patients

Predictor	Category of Exposure	Age-Adjusted Hazard Ratio 95% Confidence Interval)	P
Demographic Characteristic			
Sex	Men (vs women)	1.02 (0.80–1.31)	.87
Medical Covariates			
Left ventricular ejection fraction	< 40 (vs ≥ 40)	1.39 (1.06–1.84)	.02
Charlson comorbidity index[23]	Per SD (1 SD = 1.57)	1.38 (1.16–1.64)	<.001
GRACE[24, 25] risk score	Per SD (1 SD = 31.21)	1.45 (1.01–2.10)	.03
Antidepressant use	Yes	1.34 (1.03–1.74)	.02

Abbreviations: ACM, all-cause mortality; GRACE, Global Registry of Acute Coronary Events; MACE, major adverse cardiac event.

Table 3

Adjusted Hazard Ratios for Anhedonia and Depressed Mood

Predictor	Age-Adjusted Hazard Ratio (95% Confidence Interval)	P	Multivariable Adjusted Hazard Ratio (95% Confidence Interval)[a]	P
Depressive symptom severity (BDI[28] 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
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
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

Abbreviations: BDI, Beck Depression Inventory; GRACE, Global Registry of Acute Coronary Events.

[a]Adjusted for age, sex, Charlson comorbidity index score,[23] GRACE risk score,[25] left ventricular ejection fraction, and antidepressant use at discharge.