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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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 patients with acute coronary syndrome (ACS).\(^1\)\(^-\)\(^3\) Despite growing acceptance of depression as a cardiac risk factor,\(^4\) initial attempts to prevent mortality or recurrence by treating depression in ACS patients have not been successful.\(^5\)\(^-\)\(^6\)

To better understand how depression contributes to cardiac risk, some have suggested searching for subtypes of depression that are especially cardiotoxic.\(^7\)\(^-\)\(^8\) 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. 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 and had eligible scores (0-4, indicating minimal depressive symptoms, or ≥10, indicating at least mild depressive symptoms) on the Beck Depression Inventory (BDI) assessed within 1 week after the index ACS event. We chose the first version of the BDI as did the National Heart, Lung and Blood Institute consensus panel on this topic 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, later administration results in missing data on those who experience early cardiac events, a critical subgroup to include. Patients with BDI scores between 3 and 9 were excluded to more clearly delineate depressed and nondepressed groups at baseline. 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 to determine the presence of MDE according to the criteria of the DSM-IV. When trained interviewers use this interview and quality assurance is conducted, the concordance with other structured psychiatric interviews is excellent. 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. 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%. Data for the GRACE risk score, the Charlson comorbidity index, 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 ≥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) 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
inclusion.21,22 Based on published findings of factors that might
dictated MACE and ACM equally well.
repeated, using the patient-reported depressed mood and an-
score, or the BDI somatic scale score19; the last model was tested
anhedonia were better predictors of outcomes than MDE, BDI
els were tested to determine whether depressed mood and/or

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 sever-
ity, and MDE were tested separately. Several additional mod-
els were tested to determine whether depressed mood and/or
anhedonia were better predictors of outcomes than MDE. BDI
score, or the BDI somatic scale score19; 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 clin-
cal outcomes in post-MI patients.8,20 Finally, all analyses were
repeated, using the patient-reported depressed mood and an-
hedonia measures from the BDI instead of the respective me-
sures from the clinical interview, to see if these measures pre-
dicted MACE and ACM equally well.

We followed suggestions for a priori selection for covariate
inclusion.21,22 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 covar-
iates. We then repeated the primary analyses with the unique
individual components of the GRACE index to ensure that dif-
fences in individual components were tested. Finally, we re-
peated the primary analysis without the urgent/emergency re-
vascularizations 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 in-
terview. 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 sui-
cidal 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 com-
pleted within the designated time. Patients who were un-
available 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 pa-
tients were diagnosed with ST-segment elevation MI; 40%
with unstable angina; and 33% with MI without ST-

segment elevation. For the depression variables, 48 pa-
tients (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). An-
hedonia and depressed mood were highly associated
(φ = 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 (φ coefficients between MDE and
depressed mood and MDE and anhedonia were φ = 0.46
and φ = 0.51, respectively, both P < .001).

Demographic and medical variables at baseline ac-
cording to depressed mood and anhedonia status are
shown in Table 1. As can be seen, numerous significant
differences existed. Those with depressed mood were sig-
nificantly more likely to be female, to have higher Charl-
son comorbidity index scores, to be younger, to have an
MDE, to have higher rates of elevated depressive symp-
toms, and to have an antidepressant prescribed. They were
also significantly more likely to have higher admission
heart rates, lower systolic pressures, and to have re-
ceived significantly fewer percutaneous interventions
while in the hospital. Patients with anhedonia com-
pared with those without had the same significant dif-
fferences as were found between patients with and with-
out 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 revascular-
izations]), which is comparable with findings of previ-
ous research (15.1% MACE and ACM during 1 year).23

Table 2 displays age-adjusted associations of the co-
variates 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 de-
pressive symptom severity assessed by BDI were signifi-
cant predictors of age-adjusted MACE and/or ACM within
12 months, but only MDE remained a significant pre-
dictor after adjusting for age, sex, and the medical co-
variates (Table 3). The adjusted HR for MDE was com-
parable with that found in prior studies.24

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 signifi-
cantly predicted MACE and ACM in the age-adjusted
model (Table 3), but only anhedonia remained a signifi-
cant predictor of MACE and ACM after adjusting for age,
sex, and the medical covariates. When both anhedonia
Table 2. Age-Adjusted Association of Covariates With 12-Month Major Adverse Cardiac Events and All-Cause Mortality in 453 Patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M vs F</td>
<td>1.02 (0.80-1.31)</td>
<td>.87</td>
</tr>
<tr>
<td>Left ventricular ejection fraction,</td>
<td>1.39 (1.06-1.84)</td>
<td>.02</td>
</tr>
<tr>
<td>Charlson comorbidity index, per SDa</td>
<td>1.38 (1.16-1.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GRACE risk score, per SDb</td>
<td>1.45 (1.01-2.10)</td>
<td>.03</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>1.34 (1.03-1.74)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.
aOne SD = 1.57.
bOne 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, 1.17–3.40; P = .01).

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 significant predictor of outcome.

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-
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,\(^2\)^\(^-\)^\(^3\) even when adjusting for demographic characteristics and known medical prognostic disease markers and comorbid conditions.\(^2\)^\(^-\)^\(^3\) 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. In a previous study with post-MI patients, de Jonge and colleagues 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. 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, 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, 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. Anhedonia is not specific to depression; it occurs in other psychiatric disorders as well. Moreover, 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), 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. Hasler and colleagues 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. High catecholamine levels are toxic to cardiac myocytes, can trigger tachyarrhythmia, and promote platelet aggregation. Among patients with congestive heart failure, the extent of plasma catecholamine elevation correlates directly with cardiac mortality. 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. 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. 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. 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 and major clinical events after stent placement, 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.

Ascertaining 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. 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. This included ACM, infarction, and standardized criteria for unstable angina and urgent or emergency revascularization procedures. 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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REFERENCES


