

# Depression and Anxiety as Predictors of 2-Year Cardiac Events in Patients With Stable Coronary Artery Disease

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**Context:** Anxiety and depression are associated with mechanisms that promote atherosclerosis. Most recent studies of emotional disturbances in coronary artery disease (CAD) have focused on depression only.

**Objective:** To assess the 2-year cardiac prognostic importance of the *DSM-IV*-based diagnoses of major depressive disorder (MDD) and generalized anxiety disorder (GAD) and self-report measures of anxiety and depression and their co-occurrence.

**Design, Setting, and Patients:** Two-year follow-up of 804 patients with stable CAD (649 men) assessed using the Beck Depression Inventory II (BDI-II), the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), and the Structured Clinical Interview for *DSM-IV* (masked to self-reports) 2 months after acute coronary syndromes.

**Main Outcome Measures:** Major adverse cardiac events (MACEs) (cardiac death, myocardial infarction, cardiac arrest, or nonelective revascularization) in the 2 years after baseline.

**Results:** Of the 804 patients, 57 (7.1%) met the criteria for MDD and 43 (5.3%) for GAD (11 [1.4%] had comorbidity); 220 (27.4%) had elevated BDI-II scores ( $\geq 14$ ), and 333 (41.4%) had elevated HADS-A scores ( $\geq 8$ ), with 21.1% overlap. MDD (odds ratio [OR], 2.85; 95% confidence interval [CI], 1.62-5.01), GAD (OR, 2.09; 95% CI, 1.08-4.05), elevated BDI-II (OR, 1.75; 95% CI, 1.21-2.54), elevated HADS-A score (OR, 1.67; 95% CI, 1.18-2.37), and continuous standardized scores on the BDI-II (OR, 1.34; 95% CI, 1.11-1.62) and the HADS-A (OR, 1.38; 95% CI, 1.16-1.63) all predicted MACEs. After covariate control, only the *P* value associated with the continuous BDI-II score increased to above .10. Most of the risk associated with elevated symptoms was in patients with psychiatric disorders. However, patients with comorbid MDD and GAD or elevated anxiety and depression symptoms were not at greater MACE risk than those with only 1 factor.

**Conclusion:** Anxiety and depression predict greater MACE risk in patients with stable CAD, supporting future research into common genetic, environmental, and pathophysiologic pathways and treatments.

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SEVERAL OF THE PATHOPHYSIOLOGIC correlates of anxiety and depression may contribute to atherosclerosis,<sup>1,2</sup> but many recent studies<sup>3</sup> of patients with coronary artery disease (CAD) have focused only on depression. Furthermore, most of the existing literature on anxiety as a predictor of prognosis in patients with CAD has involved self-report measures.<sup>4</sup> Although some attention has been given to panic disorder,<sup>5</sup> to our knowledge, the potential importance of anxiety disorders, in particular generalized anxiety disorder (GAD), has been ignored, as has the question of whether the co-occurrence of anxiety and depression has prognostic importance.

The overlap between anxiety and depression has long been discussed by theoreticians and health care professionals alike,<sup>6</sup> and it is well known that self-report measures of these concepts are

highly interrelated.<sup>7</sup> Although the diagnosis of GAD is based on the presence of continuous and excessive worry, and the diagnosis of major depressive disorder (MDD) requires depressed mood or loss of interest, these conditions have much in common. The *DSM-IV* criteria for MDD and GAD share 4 symptoms (restlessness/agitation, fatigue, concentration difficulties, and sleep problems),<sup>8</sup> with a fifth GAD symptom (irritability) often used clinically as a substitutive symptom<sup>9</sup> for diagnosing MDD in medically ill patients.

Estimates of comorbidity between anxiety and mood disorders vary from 25% to 50% or more.<sup>10</sup> Research<sup>11,12</sup> in non-medically ill patients suggests that those with dual diagnoses may be particularly difficult to treat and are likely to experience a chronic course. A recent report<sup>13</sup> from the STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) project indicated that close to half of the patients

had anxious depression (MDD with high levels of anxiety symptoms) and that they had more severe depressions of longer duration than patients with MDD alone.

Although some previous research<sup>14</sup> suggested that GAD often precedes the development of MDD, a recent prospective study<sup>15</sup> following up individuals from age 11 to 32 years observed that in approximately one-third of patients, MDD preceded GAD, with GAD preceding MDD approximately as often. Thus, the 2 disorders may follow a fluctuating and alternating pattern across time. In fact, several studies<sup>16,17</sup> have observed a common genetic component. Finally, antidepressant agents have demonstrated efficacy in both conditions.<sup>18,19</sup>

Suls and Bunde<sup>4</sup> reviewed 17 studies published before 2003 that considered the long-term prognostic impact of anxiety in patients with CAD. They concluded that the evidence linking anxiety symptoms to cardiac outcomes was sparse. All the studies used self-report measures, with most administering the State-Trait Anxiety Inventory.<sup>20</sup> Most studies observed no relationship between anxiety and prognosis. One large study<sup>21</sup> of more than 2000 patients with CAD assessed before routine stress tests found that anxiety, measured using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A),<sup>22</sup> was associated with lower mortality rates. The researchers speculated that anxiety might be related to increased tendencies to seek medical attention or alter risk factors. Another study<sup>23</sup> that administered the HADS to 344 patients after myocardial infarction (MI) reported no relationship between either anxiety or depression and 1-year mortality. However, the mortality rate was low (4%). In fact, only 3 of the studies<sup>24-26</sup> reviewed by Suls and Bunde<sup>4</sup> showed that anxiety symptoms predicted worse long-term prognosis. All 3 studies administered the State-Trait Anxiety Inventory. Two of these studies<sup>25,26</sup> assessed patients who participated in cardiac rehabilitation programs with psychological treatment components during follow-up, making it difficult to interpret the results. There were also relatively few cardiac events, limiting the ability to control covariates. In the third study,<sup>24</sup> we examined 222 patients during hospitalization for MI who received usual care for 1 year. There was an increase in risk associated with anxiety symptoms that was independent of depression symptoms (assessed using the Beck Depression Inventory I [BDI-I]<sup>27</sup>), history of major depression, previous MI, and prescription of angiotensin-converting enzyme inhibitors.<sup>24</sup> With an expanded cohort of 896 usual-care patients followed up for 5 years, we performed more extensive control for cardiac disease severity. Covariates entirely explained the long-term impact of anxiety symptoms, whereas the impact of depression symptoms continued to remain significant.<sup>28</sup>

Recently a few other publications have appeared,<sup>29-33</sup> but differences in the measures used, timing of measurement, variations in sample sizes, and consequent ability to control covariates, as well as publication bias in favor of small studies with positive findings, mean that the prognostic value of self-reports of anxiety remains unclear. Furthermore, to our knowledge, there is no information about the role of GAD or the cardiac prognostic importance of co-occurring MDD and GAD.

Two of the aims of the Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions (ESCAPE) study,<sup>34,35</sup> the subject of this article, were to evaluate the prognostic importance of *DSM-IV* diagnoses in patients with stable CAD and to assess the relative predictive value of self-report symptom scales and diagnoses based on structured interviews. In this article we (1) examine the relationship between *DSM-IV*-based diagnoses and self-report measures of anxiety and depression assessed approximately 2 months after hospital discharge for an acute coronary syndrome (ACS) and the occurrence of major adverse cardiac events (MACEs) during the subsequent 2 years and (2) explore whether the combination of anxiety and depression confers an increased risk of 2-year MACEs compared with that conferred by only 1 of the 2 factors.

## METHODS

The ESCAPE study has been described previously.<sup>34,35</sup> With previous ethics approval, we recruited patients from the Montreal Heart Institute and Hôpital du Sacré-Coeur de Montréal (Montreal, Quebec, Canada) who had cardiac catheterizations during ACS admissions. The ACSs included acute Q-wave MI (electrocardiographic evidence of new Q waves in 2 consecutive leads), non-Q-wave MI (peak creatine kinase [CK] enzyme level  $\geq 1.5$  times the hospital norm, or a CK-MB value greater than 5% of a simultaneous CK value greater than normal before revascularization; after angioplasty, the lower limit CK-MB mass level was at least 3 times greater than the reference range, and after coronary artery bypass graft surgery, the lower limit was at least 10 times greater than the reference range), or an episode of unstable angina with elevated troponin T levels (according to each hospital's norms). Exclusion criteria included ACS secondary to noncardiac conditions, likely survival less than 2 years due to another illness, living too far away to return for baseline evaluation, and inability to speak and read English or French. Eligible patients received letters about the project containing a telephone number to call if they did not want additional information about the study. Between August 31, 1999, and August 2, 2001, 1577 patients were contacted by telephone, and 965 agreed to attend appointments for baseline interviews. Of these patients, 811 (55.3% of eligible men and 40.4% of eligible women) signed informed consent forms and completed baseline assessments.

## MEASURES OF DEPRESSION AND ANXIETY

Approximately 2 months after hospital discharge, participants arrived at the research center after an overnight fast, had their vital signs measured, and had baseline blood samples collected. They brought all current medications with them for recording purposes. Other baseline medical variables were abstracted from hospital medical records. We used the definition of metabolic syndrome from the Adult Treatment Panel III of the National Cholesterol Education Program.<sup>36</sup>

Participants completed the 21-item BDI-II<sup>37</sup> and the 7-item HADS-A.<sup>22</sup> The HADS-A was included because of its brevity, item content (tension, fear, worry, apprehension, agitation, and panic feelings), and psychometric properties.<sup>38</sup> The depression subscale of the HADS was not administered because of inclusion of the BDI-II.

After the self-reports, a trained psychologist, masked to self-report results, administered the Structured Clinical Interview for *DSM-IV*,<sup>39</sup> including modules for current and past mood dis-

orders, panic disorder with and without agoraphobia, social phobia, GAD, and alcohol and substance abuse and dependence. The full *DSM-IV* criteria for MDD were applied, including requiring at least a 2-week duration for depression symptoms and functional impairment.

## CARDIAC EVENTS

Patients received biannual telephone calls assessing hospital readmissions for the subsequent 2 years. With written permission from patients or next of kin, records for admissions outside of study hospitals were obtained from archives departments. Study hospital records were reviewed for the 2-year period, and we obtained Quebec Medicare data for hospitalizations, procedures, and last dates of physician contacts (to establish 2-year survival status) for all participants. Cardiac events were blindly and independently coded by a cardiologist and a psychiatrist (F.L.) with extensive cardiac experience. Disagreements were resolved by discussion. The primary outcome was the occurrence of 1 or more MACEs (cardiac death, survived MI, survived cardiac arrest, or nonelective revascularization) in the 730 days after the baseline interview. Cardiac deaths were classified as ischemic, arrhythmic, due to pump failure, or due to cardiac procedure complications.<sup>40</sup> The MIs were defined by elevation of the CK-MB level accompanied by chest pain lasting longer than 30 minutes or by ST-T changes (any of the following in 2 contiguous leads: new persistent or transient ST-segment depression  $>0.1$  mV or T-wave inversion or transient [ $<20$ -minute] ST-segment elevation  $>0.1$  mV). Nonelective revascularizations included coronary artery bypass graft surgery and angioplasty during admissions directly after emergency department visits. Nonelective revascularizations during hospital admissions with other MACE diagnoses were not counted separately.

## STATISTICAL ANALYSES

A software program (SPSS for Windows version 15.0; SPSS Inc, Chicago, Illinois) was used for all analyses. Statistical tests were 2-sided. We performed receiver operating characteristic curve analyses to assess the sensitivity and specificity for each self-report measure in predicting each *DSM-IV* diagnosis. The relationships between background factors and measures of anxiety and depression were assessed using Pearson product moment correlations for pairs of continuous variables and between continuous and dichotomous variables. Contingency coefficients were calculated for pairs of dichotomous variables. Logistic regression was used to evaluate the odds ratios (ORs) for experiencing 1 or more MACEs during the 2-year follow-up associated with each measure of anxiety and depression. Because of skewness, BDI-II scores were analyzed using natural log transformations. The ORs for the HADS-A and log-transformed BDI-II were calculated per standard deviation increase. For comparability with previous research and to allow assessment of comorbidity using the self-reports, both scales were dichotomized using cutoff points suggested in the literature. Scores of 14 or greater on the BDI-II were considered indicative of at least mild to moderate symptoms of depression (elevated depression symptoms),<sup>37</sup> and scores of 8 or greater on the HADS-A defined elevated anxiety symptoms.<sup>22</sup>

The limiting factor for the number of covariates in studies with dichotomous outcomes is the smaller of the outcome frequencies,<sup>41</sup> in this case the number of MACEs, with the rule-of-thumb limit being approximately 8 to 10 events per covariate.<sup>42</sup> With 115 MACEs, we were able to use the approach recommended by Steyerberg et al<sup>43</sup> to select covariates. Baseline variables were entered together into a logistic regression analysis to predict MACEs. Those with adjusted  $P < .50$  were

retained as covariates. These variables were entered together in the first step of a logistic regression analysis, followed by the measure being evaluated. The likelihood ratio test was used to assess the covariate-adjusted  $P$  value. Body mass index and blood pressure measurements were missing for 1 participant, and owing to technical problems, baseline blood test results were not available for 11 patients. We substituted the overall mean values for the missing variables in the covariate modeling, and we also used a regression model based on the complete cases to estimate values for the missing data. The 2 approaches yielded almost identical results, and the analyses substituting mean values are presented in this article.

## RESULTS

### SAMPLE

Only 7 of the 811 participants ( $<1\%$ , including 1 with GAD and none with MDD) were lost to follow-up or died of noncardiac causes without having 1 or more MACEs in 2 years, resulting in a final sample of 804. Overall, 110 (13.7%) of the patients in the final sample met the *DSM-IV* criteria for 1 or more current mood, anxiety, or substance abuse or dependence disorders. This included 57 (7.1%) who met the criteria for current MDD (22 [2.7%] with past depression), whereas GAD was diagnosed in 43 (5.3%) (17 [2.1%] with past depression). Other diagnoses occurring in more than 1% of the sample included past MDD (not currently depressed,  $n=123$ ; 15.3%), bipolar disorder ( $n=21$ ; 2.6%), panic disorder ( $n=16$ ; 2.0%), and alcohol abuse or dependence ( $n=23$ ; 2.9%). Using the cutoff score of at least 14 on the BDI-II, 220 (27.4%) had elevated depression symptoms, and 333 (41.4%) had HADS-A scores of 8 or greater. **Table 1** includes participants' background characteristics.

### PSYCHOMETRICS

Internal consistency was acceptable for both self-reports (BDI-II:  $\alpha = .90$ ; HADS-A:  $\alpha = .83$ ). Both showed some departure from normality. The BDI-II showed more pronounced skewness (1.35) and kurtosis (2.13) than the HADS-A (skewness=0.64; kurtosis=-0.07). Analyses for the continuous BDI-II score were based on natural log-transformed data (skewness=-0.69; kurtosis=0.17). Log-transformed continuous BDI-II and HADS-A scores were moderately highly correlated ( $r=0.61$ ;  $P < .001$ ). This degree of interrelationship is approximately in the middle of the range reported previously ( $r=0.45-0.83$ ).<sup>38,44,45</sup>

We performed receiver operating characteristic curve analyses to compare the ability of each self-report measure to predict the *DSM-IV* diagnoses of MDD and GAD (**Table 2**). The area under the curve (AUC) for the BDI-II for predicting MDD was greater than its AUC for GAD, indicating that the BDI-II is a better screening tool for depression than for anxiety. This is also reflected in the higher sensitivity of elevated BDI-II scores for detecting MDD than GAD. The AUC for MDD predicted by the HADS-A, although lower than that for the BDI-II, was approximately the same as the AUC for the HADS-A as a predictor for GAD. Although the sensitivity of the HADS-A for detecting GAD was as high as that of the

**Table 1. Sample Characteristics and Relationships Between Background Factors and Measures of Depression and Anxiety in Patients Assessed 2 Months After Acute Coronary Syndrome**

Characteristic	Overall Sample (N=804)	Correlations With Depression, <i>r</i> (P Value)			Correlations With Anxiety, <i>r</i> (P Value)		
		MDD	BDI-II Score <sup>a</sup>	BDI-II Score ≥ 14	GAD	HADS-A Score	HADS-A Score ≥ 8
Age, y, mean (SD)	60.0 (10.6)	-0.08 (.03) <sup>b</sup>	-0.06 (.12)	-0.08 (.03) <sup>b</sup>	-0.10 (.004) <sup>b</sup>	-0.17 (<.001) <sup>b</sup>	-0.16 (<.001) <sup>b</sup>
Female sex, No. (%)	155 (19.3)	0.12 (<.001) <sup>b</sup>	0.13 (<.001) <sup>b</sup>	0.08 (.02) <sup>b</sup>	-0.004 (.91)	0.17 (<.001) <sup>b</sup>	0.12 (.001) <sup>b</sup>
Education, y, mean (SD)	11.4 (4.3)	-0.05 (.21)	-0.07 (.04) <sup>b</sup>	-0.05 (.17)	-0.01 (.86)	-0.03 (.36)	-0.04 (.26)
Married, No. (%)	601 (74.8)	-0.04 (.25)	-0.08 (.03) <sup>b</sup>	-0.07 (.06)	0.09 (.01) <sup>b</sup>	-0.01 (.81)	-0.03 (.42)
Sedentary, No. (%)	398 (49.5)	-0.03 (.38)	0.05 (.14)	0.05 (.15)	0.008 (.82)	0.04 (.28)	0.08 (.02) <sup>b</sup>
Current daily smoker, No. (%)	138 (17.2)	0.07 (.06)	0.13 (<.001) <sup>b</sup>	0.14 (<.001) <sup>b</sup>	0.04 (.28)	0.14 (<.001) <sup>b</sup>	0.11 (.001) <sup>b</sup>
Diabetes mellitus, No. (%) <sup>c</sup>	203 (25.2)	0.03 (.41)	0.01 (.88)	0.01 (.79)	-0.06 (.08)	-0.07 (.06)	-0.08 (.02) <sup>b</sup>
Previous MI, coronary bypass, or angioplasty, No. (%)	266 (33.1)	0.06 (.07)	0.10 (.007) <sup>b</sup>	0.09 (.01) <sup>b</sup>	0.01 (.80)	0.08 (.02) <sup>b</sup>	0.02 (.56)
Left ventricular ejection fraction <45%, No. (%)	166 (20.6)	0.05 (.15)	0.03 (.35)	0.03 (.48)	0.002 (.96)	-0.02 (.50)	-0.01 (.89)
CABG surgery, No. (%)	154 (19.2)	-0.04 (.31)	-0.06 (.07)	-0.04 (.22)	-0.03 (.37)	-0.06 (.09)	-0.08 (.02) <sup>b</sup>
Coronary angioplasty, No. (%)	498 (61.9)	0.01 (.84)	-0.01 (.80)	0.02 (.54)	0.04 (.28)	-0.02 (.65)	0.004 (.91)
≥1 Coronary vessels with ≥50% blockage after index revascularization, No. (%)	432 (53.7)	0.03 (.35)	0.07 (.04) <sup>b</sup>	0.06 (.09)	-0.02 (.51)	0.01 (.75)	0.02 (.56)
BMI, mean (SD) (n=803)	28.3 (4.3)	0.03 (.41)	0.02 (.66)	0.04 (.26)	-0.09 (.01) <sup>b</sup>	-0.03 (.38)	-0.02 (.56)
Waist, mean (SD), cm (n=801)	100.6 (11.8)	-0.01 (.84)	-0.01 (.80)	0.01 (.69)	-0.10 (.006) <sup>b</sup>	-0.10 (.005) <sup>b</sup>	-0.08 (.03) <sup>b</sup>
Fasting triglyceride level, mean (SD), mg/dL (n=793)	165 (90)	0.15 (<.001) <sup>b</sup>	0.09 (.01) <sup>b</sup>	0.13 (<.001) <sup>b</sup>	0.02 (.60)	0.15 (<.001) <sup>b</sup>	0.12 (.001) <sup>b</sup>
Fasting HDL cholesterol level, mean (SD), mg/dL (n=793)	42 (10)	-0.01 (.80)	-0.004 (.92)	-0.01 (.79)	0.01 (.89)	0.05 (.13)	0.04 (.31)
Systolic blood pressure, mean (SD), mm Hg (n=803)	135.1 (23.2)	-0.03 (.41)	-0.02 (.63)	-0.01 (.78)	-0.01 (.85)	-0.02 (.49)	-0.01 (.71)
Diastolic blood pressure, mean (SD), mm Hg (n=803)	74.6 (10.6)	0.01 (.89)	-0.02 (.58)	0.02 (.65)	0.06 (.10)	0.05 (.19)	0.04 (.29)
Metabolic syndrome, No. (%) <sup>d</sup>	391 (48.6)	0.08 (.02) <sup>b</sup>	0.09 (.01) <sup>b</sup>	0.08 (.03) <sup>b</sup>	-0.04 (.22)	0.006 (.87)	-0.02 (.67)
Medications used, No. (%)							
Aspirin	715 (88.9)	0.04 (.31)	-0.02 (.58)	0.02 (.55)	-0.04 (.26)	-0.02 (.59)	-0.03 (.35)
β-Blockers	621 (77.2)	-0.01 (.74)	-0.01 (.68)	<0.0001 (.99)	-0.03 (.41)	-0.01 (.72)	0.01 (.89)
Angiotensin-converting enzyme inhibitors	413 (51.4)	-0.05 (.15)	-0.02 (.65)	-0.03 (.43)	-0.02 (.51)	-0.04 (.30)	-0.04 (.25)
Calcium channel blockers	175 (21.8)	0.01 (.84)	0.12 (.001) <sup>b</sup>	0.03 (.43)	0.05 (.17)	0.11 (.001) <sup>b</sup>	0.10 (.004) <sup>b</sup>
Statins	569 (70.8)	0.03 (.42)	-0.01 (.85)	0.01 (.69)	-0.01 (.88)	0.03 (.37)	0.03 (.40)
Long-acting nitrates	136 (16.9)	0.018 (.62)	0.14 (<.001) <sup>b</sup>	0.07 (.04) <sup>b</sup>	0.03 (.47)	0.11 (.002) <sup>b</sup>	0.10 (.005) <sup>b</sup>
Antidepressants	68 (8.5)	0.25 (<.001) <sup>b</sup>	0.18 (<.001) <sup>b</sup>	0.18 (<.001) <sup>b</sup>	0.11 (.003) <sup>b</sup>	0.24 (<.001) <sup>b</sup>	0.21 (<.001) <sup>b</sup>
Benzodiazepines	212 (26.4)	0.15 (<.001) <sup>b</sup>	0.25 (<.001) <sup>b</sup>	0.22 (<.001) <sup>b</sup>	0.06 (.10)	0.25 (<.001) <sup>b</sup>	0.21 (<.001) <sup>b</sup>
Total No., mean (SD)	6.0 (2.5)	0.18 (<.001) <sup>b</sup>	0.23 (<.001) <sup>b</sup>	0.14 (<.001) <sup>b</sup>	0.03 (.39)	0.22 (<.001) <sup>b</sup>	0.17 (<.001) <sup>b</sup>

Abbreviations: BDI-II, Beck Depression Inventory II; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft; GAD, generalized anxiety disorder; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein; MDD, major depressive disorder; MI, myocardial infarction.

SI conversion factors: To convert fasting triglycerides to millimoles per liter, multiply by 0.0113; fasting HDL cholesterol to millimoles per liter, multiply by 0.0259.

<sup>a</sup>Natural log transformed.

<sup>b</sup>Significant at *P* < .05.

<sup>c</sup>Defined as a fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or taking hypoglycemic medication.

<sup>d</sup>Based on the definition from the Adult Treatment Panel III of the National Cholesterol Education Program,<sup>36</sup> participants with more than 2 of the following components were classified as having the metabolic syndrome: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (fasting serum triglycerides >150 mg/dL), low fasting HDL cholesterol level (<40 mg/dL in men and <50 mg/dL in women), high blood pressure (≥130/85 mm Hg) or use of diuretics, and high fasting glucose level (≥110 mg/dL) or use of hypoglycemic medications.

BDI-II for detecting MDD, the cutoff score of at least 8 on the HADS-A had a specificity of 84.2% for detecting MDD. In this sample, the HADS-A was more likely to reflect both depression and anxiety than was the BDI-II, which is a more pure index of depression.

#### BASELINE VARIABLES ASSOCIATED WITH DEPRESSION AND ANXIETY

Table 1 shows the correlations between baseline characteristics and measures of depression and anxiety. The

only baseline variables not significantly related to any psychological measures were left ventricular ejection fraction less than 45%, coronary angioplasty at baseline, high-density lipoprotein cholesterol level, systolic and diastolic blood pressure, and prescription of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins. Measures of depression and anxiety were higher in younger participants. Women were more likely to meet the criteria for MDD (5.5% of men and 13.5% of women; *P* < .001) and had higher scores on the BDI-II and the HADS-A, but they did not differ from men in their preva-

lence of GAD (5.4% of men and 5.2% of women;  $P = .91$ ). Metabolic syndrome was related to measures of depression but not anxiety. Most measures of anxiety and depression were significantly linked to smoking, triglyceride levels, and use of antidepressants and benzodiazepines. Long-acting nitrates were linked to self-report measures but not to the diagnostic categories.

### PREDICTORS OF CARDIAC EVENTS

During the 2 years after the baseline interview, 115 participants (14.3%) experienced at least 1 MACE (11 cardiac deaths, 54 survived MIs, 3 survived cardiac arrests, and 47 nonelective revascularizations). All diagnostic and self-report symptom measures of anxiety and depression significantly predicted MACEs (**Table 3**). Although the ORs associated with psychological factors were numerically higher for men than for women, none of the interactions between sex and baseline anxiety and depression were significant in predicting MACEs ( $P \geq .25$  for all depression measures;  $P \geq .13$  for all anxiety measures). However, the number of women was too small to reliably detect sex-related differences. For example,

with a prevalence of 50% for elevated anxiety symptoms and a 17% event rate, the sample of 155 women had a power of less than 25% to detect a doubling in risk associated with this factor.

Other significant predictors of MACEs included older age, previous cardiac history, higher systolic and diastolic blood pressure, and more prescribed medications, plus several variables reflecting ischemic risk, including having 1 or more major cardiac vessels remaining blocked after index revascularization procedures and being prescribed long-acting nitrates (**Table 4**).

### COVARIATE CONTROL

The method suggested by Steyerberg et al<sup>43</sup> was used to select covariates. Table 2 includes multivariate-adjusted ORs for MACEs associated with each measure of depression and anxiety. The final multivariate model is illustrated in **Table 5** using the standardized HADS-A score. Although the final covariates included age, left ventricular ejection fraction less than 45%, coronary artery bypass graft surgery at index, having 1 or more coronary vessels with 50% or greater blockage after index revascularization, diastolic blood pressure, triglyceride levels, and several other variables, most results remained statistically significant after covariate adjustment. The only  $P$  value increasing to  $>.10$  was for the log-transformed BDI-II score.

**Table 2. Receiver Operating Characteristic Curve Analyses for the BDI-II and HADS-A in Predicting DSM-IV Diagnoses of MDD and GAD in 804 Patients Assessed 2 Months After Acute Coronary Syndrome**

Self-report Scale and Measure of Performance	DSM-IV Diagnosis	
	MDD (n=57)	GAD (n=43)
<b>BDI-II</b>		
Sensitivity of score $\geq 14$ , %	91.2	60.5
Specificity of score $\geq 14$ , %	77.5	74.5
Continuous score AUC (95% CI)	0.92 (0.89-0.95)	0.72 (0.63-0.80)
<b>HADS-A</b>		
Sensitivity of score $\geq 8$ , %	84.2	90.7
Specificity of score $\geq 8$ , %	61.8	61.4
Continuous score AUC (95% CI)	0.86 (0.80-0.91)	0.85 (0.79-0.91)

Abbreviations: AUC, area under the curve; BDI-II, Beck Depression Inventory II; CI, confidence interval; GAD, generalized anxiety disorder; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; MDD, major depressive disorder.

### COMPARATIVE PROGNOSTIC IMPORTANCE OF DIAGNOSES AND SELF-REPORTS

In Table 3, the ORs associated with DSM-IV diagnoses are numerically greater than those associated with elevated self-report scores. We wondered whether there was an increased risk of MACEs in patients with elevated self-report symptoms who did not fulfill the criteria for MDD or GAD. Two 3-category variables were created, 1 for depression and 1 for anxiety. The highest category included patients meeting the criteria for the DSM-IV diagnosis. The middle category included those with elevated self-report scores not meeting the DSM-IV criteria, and

**Table 3. Relationships Between Measures of Depression and Anxiety in 804 Patients Assessed 2 Months After Acute Coronary Syndrome and MACEs in the Subsequent 2 Years**

	Unadjusted OR (95% CI)	P Value	Covariate-Adjusted OR (95% CI) <sup>a</sup>	P Value
<b>Depression</b>				
Current MDD	2.85 (1.62-5.01)	<.001	2.27 (1.15-4.47)	.02
Elevated depression symptoms (BDI-II score $\geq 14$ )	1.75 (1.21-2.54)	.003	1.61 (1.03-2.50)	.04
Continuous BDI-II score <sup>b</sup>	1.34 (1.11-1.62) <sup>c</sup>	.002	1.18 (0.94-1.47) <sup>c</sup>	.15
<b>Anxiety</b>				
GAD	2.09 (1.08-4.05)	.03	2.29 (1.07-4.88)	.04
Elevated anxiety symptoms (HADS-A score $\geq 8$ )	1.67 (1.18-2.37)	.004	1.45 (0.95-2.22)	.08
Continuous HADS-A score	1.38 (1.16-1.63) <sup>c</sup>	<.001	1.36 (1.11-1.68) <sup>c</sup>	.003

Abbreviations: BDI-II, Beck Depression Inventory II; CI, confidence interval; GAD, generalized anxiety disorder; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; MACEs, major adverse cardiac events; MDD, major depressive disorder; OR, odds ratio.

<sup>a</sup>Adjusted for age, female sex, years of education, current daily smoker, previous myocardial infarction, coronary artery bypass graft surgery or angioplasty, left ventricular ejection fraction  $< 45\%$ , coronary artery bypass graft surgery during index hospitalization,  $\geq 1$  coronary vessels with  $\geq 50\%$  blockage after index revascularization, body mass index, fasting triglyceride level, diastolic blood pressure, calcium channel blockers, angiotensin-converting enzyme inhibitors, and statins.

<sup>b</sup>Natural log transformed.

<sup>c</sup>Per standard deviation increase.

**Table 4. Baseline Characteristics Associated With MACEs Across 2 Years in 804 Patients Assessed 2 Months After Acute Coronary Syndrome**

Characteristic	No MACEs (n=689)	MACEs (n=115)	Odds Ratio (95% CI)	P Value
<b>Demographic variables</b>				
Age, y, mean (SD)	59.6 (10.5)	62.2 (11.4)	1.29 (1.05-1.57) <sup>a</sup>	.01
Female sex, No. (%)	128 (18.6)	27 (23.5)	1.35 (0.84-2.16)	.23
Education, mean (SD), y	11.5 (4.4)	10.8 (4.0)	0.84 (0.68-1.03) <sup>a</sup>	.09
Married, No. (%)	517 (75.0)	84 (73.0)	0.90 (0.58-1.41)	.65
<b>Risk factors and cardiac history, No. (%)</b>				
Sedentary	336 (48.8)	62 (53.9)	1.23 (0.83-1.83)	.31
Current daily smoker	115 (16.7)	23 (20.0)	1.25 (0.76-2.06)	.39
Diabetes mellitus <sup>b</sup>	169 (24.5)	34 (29.6)	1.29 (0.84-2.00)	.26
Previous MI, coronary bypass or angioplasty	211 (30.6)	55 (47.8)	2.08 (1.39-3.10)	<.001
Left ventricular ejection fraction < 45%	137 (19.9)	29 (25.2)	1.36 (0.86-2.15)	.20
<b>Intervention at index hospitalization, No. (%)</b>				
CABG surgery	145 (21.0)	9 (7.8)	0.32 (0.16-0.64)	<.001
Coronary angioplasty	422 (61.2)	76 (66.1)	1.23 (0.81-1.87)	.32
≥1 Coronary vessels with ≥50% blockage after index revascularization	343 (49.8)	89 (77.4)	3.45 (2.18-5.48)	<.001
<b>Baseline indicators of metabolic syndrome, mean (SD)</b>				
BMI	28.4 (4.4) (n=688)	28.1 (4.7)	0.95 (0.78-1.16) <sup>a</sup>	.63
Waist, cm	100.7 (11.7) (n=687)	100.1 (12.1) (n=114)	0.82 (0.38-1.81) <sup>a</sup>	.63
Fasting triglyceride level, mg/dL	163 (87) (n=682)	180 (108) (n=111)	1.18 (0.99-1.41) <sup>a</sup>	.08
Fasting HDL cholesterol level, mg/dL	42 (10) (n=682)	42 (10) (n=111)	0.99 (0.81-1.22) <sup>a</sup>	.95
Systolic blood pressure, mm Hg	134.3 (23.2) (n=688)	139.7 (23.2)	1.24 (1.03-1.50) <sup>a</sup>	.03
Diastolic blood pressure, mm Hg	74.3 (10.5) (n=688)	76.4 (10.9)	1.22 (1.00-1.48) <sup>a</sup>	.047
Metabolic syndrome, No. (%) <sup>c</sup>	329 (47.8)	62 (53.9)	1.28 (0.86-1.90)	.22
<b>Medications used at baseline interview, No. (%)</b>				
Aspirin	613 (89.0)	102 (88.7)	0.97 (0.52-1.82)	.93
β-Blockers	528 (76.6)	93 (80.9)	1.29 (0.78-2.12)	.32
Angiotensin-converting enzyme inhibitors	344 (49.9)	69 (60.0)	1.50 (1.01-2.25)	.045
Calcium channel blockers	134 (19.4)	41 (35.7)	2.30 (1.50-3.51)	<.001
Statins	493 (71.6)	76 (66.1)	0.78 (0.51-1.18)	.24
Long-acting nitrates	95 (13.8)	41 (35.7)	3.46 (2.23-5.37)	<.001
Antidepressants	58 (8.4)	10 (8.7)	1.04 (0.51-2.09)	.92
Benzodiazepines	176 (25.5)	36 (31.3)	1.33 (0.86-2.04)	.20
Total No., mean (SD)	5.9 (2.5)	6.6 (2.5)	1.32 (1.09-1.59) <sup>a</sup>	.004

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft; CI, confidence interval; HDL, high-density lipoprotein; MACEs, major adverse cardiac events; MI, myocardial infarction.

SI conversion factors: To convert fasting triglycerides to millimoles per liter, multiply by 0.0113; fasting HDL cholesterol to millimoles per liter, multiply by 0.0259.

<sup>a</sup>Per standard deviation increase.

<sup>b</sup>Defined as a fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or taking hypoglycemic medication.

<sup>c</sup>Based on the definition from the Adult Treatment Panel III of the National Cholesterol Education Program,<sup>36</sup> participants with more than 2 of the following components were classified as having the metabolic syndrome: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), hypertriglyceridemia (fasting serum triglycerides > 150 mg/dL), low fasting HDL cholesterol level (< 40 mg/dL in men and < 50 mg/dL in women), high blood pressure (≥ 130/85 mm Hg) or use of diuretics, and high fasting glucose level (≥ 110 mg/dL) or use of antidiabetic medications.

the lowest category included those with low self-report scores who also did not meet the diagnostic criteria. The ORs for MACEs associated with each of these 3-category variables appear in **Table 6** before and after covariate control.

After covariate adjustment, the ORs for MACES remained significant only for patients meeting diagnostic criteria vs those in the lowest category. Those with elevated symptoms who did not meet the diagnostic criteria were not at significantly increased risk compared with those with a low level of symptoms. With the observed group sizes and event rates, we had greater than 80% power to detect ORs of approximately 1.7 associated with elevated symptoms without *DSM-IV* diagnoses compared with a low level of symptoms. Thus, the increase in MACE risk in patients who have elevated symptoms only is not likely to be greater than this.

## COMORBID ANXIETY AND DEPRESSION

Although 19.3% of patients with MDD and 25.6% of those with GAD met the criteria for the other disorder ( $\kappa=0.17$ ;  $P<.001$ ), there were only 11 patients with comorbid diagnoses (1.4% of the total sample). The dichotomized self-report scores showed a greater degree of overlap ( $\kappa=0.43$ ;  $P<.001$ ), with 21.1% of the sample ( $n=170$ ) having elevated scores on both self-reports. Approximately 77.3% of patients with elevated BDI-II scores had HADS-A scores of 8 or greater, and 51.1% of the patients with anxiety also had elevated BDI-II scores.

To determine whether patients with comorbid depression and anxiety experienced an increased risk of MACES compared with those with only 1 condition, we performed logistic regression analyses comparing the ORs for MACES for patients with both conditions, those hav-

ing only depression, and those having only anxiety. As illustrated in the **Figure**, approximately the same percentage of patients with both GAD and MDD experienced MACEs as those with only 1 diagnosis (comparison of 3 groups:  $P = .99$ ). Although we had 80% power to detect an increase in risk of approximately 2.6 associated with comorbid *DSM-IV* disorders in contrast to a single disorder, results from the self-report scales corroborate these findings, with greater than 80% power for

detecting a doubling in risk. Patients with elevated depression and anxiety symptoms did not experience a doubling in risk compared with those with elevated scores on only 1 measure (comparison of 3 groups:  $P = .68$ ). Thus, this sample provided little evidence that co-occurring anxiety and depression lead to an augmentation in MACE risk across 2 years above that conferred by either anxiety or depression alone.

Given the lack of increased risk in patients with co-occurring anxiety and depression, we considered the ORs associated with having 1 or more diagnoses or with having elevated symptoms on 1 or more of the self-report scales (Table 6). Patients with either *DSM-IV* diagnosis were at significantly greater risk than those with elevated symptoms of either type who did not meet the diagnostic criteria, a difference that remained significant after covariate control. The sample size was large enough to conclude that patients with elevated symptoms without diagnoses did not experience an increase in the OR of MACEs of more than approximately 1.7 compared with those with a low level of symptoms.

**Table 5. Multivariate Model of 115 Major Adverse Cardiac Events Across 2 Years in 804 Patients Assessed 2 Months After Acute Coronary Syndrome**

Predictor	Odds Ratio (95% CI)	P Value
Age	1.21 (0.95-1.56) <sup>a</sup>	.13
Female sex	1.07 (0.63-1.80)	.81
Years of education	0.94 (0.75-1.17) <sup>a</sup>	.58
Current daily smoker	1.33 (0.75-2.35)	.33
Previous MI, CABG surgery, or angioplasty	1.31 (0.83-2.08)	.25
Left ventricular ejection fraction <45%	1.30 (0.78-2.17)	.31
CABG surgery during index hospitalization	0.52 (0.24-1.13)	.10
≥1 Coronary vessels with ≥50% blockage after index revascularization	2.45 (1.46-4.11)	.001
Body mass index	0.85 (0.94-1.03) <sup>a,b</sup>	.16
Fasting triglyceride level	1.11 (0.91-1.35) <sup>a,b</sup>	.30
Diastolic blood pressure	1.24 (1.01-1.53) <sup>a,b</sup>	.04
Calcium channel blockers	1.57 (0.96-2.56)	.07
Angiotensin-converting enzyme inhibitors	1.38 (0.89-2.13)	.15
Statins	0.81 (0.52-1.27)	.36
HADS-A score	1.42 (1.14-1.75) <sup>a</sup>	.001

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; MI, myocardial infarction.

<sup>a</sup>Per standard deviation increase.

<sup>b</sup>Means substituted for missing values.

#### COMMENT

We found that in patients with stable CAD, diagnostic and dichotomous self-report measures of anxiety and depression predict increased odds of experiencing MACEs across 2 years, even after adjustment for multiple background and cardiac disease severity measures. Although before covariate adjustment there was evidence of increased risk with elevated self-report symptoms, even in the absence of meeting *DSM-IV* criteria, after covariate control only the increased risks associated with MDD and GAD remained significant. Most of the increased risk associated with elevated depression and anxiety symp-

**Table 6. Odds Ratios for MACEs Across 2 Years in Patients With *DSM-IV* Diagnoses or Elevated Self-report Scores in the Absence of Meeting *DSM-IV* Diagnostic Criteria**

	Prevalence, No. (%) (N=804)	Unadjusted Odds Ratio (95% CI)	P Value	Covariate-Adjusted Odds Ratio (95% CI) <sup>a</sup>	P Value
Measures of depression					
MDD	57 (7.1)	2.88 (1.54-5.42) <sup>b</sup>	.001	2.54 (1.27-5.09) <sup>b</sup>	.008
Elevated depression symptoms (BDI-II score ≥ 14) without MDD	168 (20.9)	1.61 (1.01-2.57) <sup>b</sup>	.047	1.46 (0.89-2.39) <sup>b</sup>	.13
Low level of depression symptoms (BDI-II score < 14) without MDD	579 (72.0)	1 [Reference]	NA	1 [Reference]	NA
Measures of anxiety					
GAD	43 (5.3)	2.90 (1.41-5.98) <sup>c</sup>	.004	2.58 (1.18-5.66) <sup>c</sup>	.02
Elevated anxiety symptoms (HADS-A score ≥ 8) without GAD	294 (36.6)	1.46 (0.96-2.22) <sup>c</sup>	.08	1.30 (0.83-2.02) <sup>c</sup>	.25
Low level of anxiety symptoms (HADS-A score < 8) without GAD	467 (58.1)	1 [Reference]	NA	1 [Reference]	NA
Measures of depression or anxiety					
MDD or GAD	89 (11.1)	3.29 (1.88-5.74) <sup>d</sup>	<.001	2.95 (1.60-5.43) <sup>d</sup>	.001
Elevated depression and anxiety symptoms without <i>DSM-IV</i> diagnoses	301 (37.4)	1.52 (0.97-2.36) <sup>d</sup>	.07	1.35 (0.85-2.15) <sup>d</sup>	.21
Low level of depression and anxiety symptoms without <i>DSM-IV</i> diagnoses	414 (51.5)	1 [Reference]	NA	1 [Reference]	NA

Abbreviations: BDI-II, Beck Depression Inventory II; CI, confidence interval; GAD, generalized anxiety disorder; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; MACEs, major adverse cardiac events; MDD, major depressive disorder; NA, not applicable.

<sup>a</sup>See variables listed in Table 5.

<sup>b</sup>Odds ratios vs low level of depression symptoms for current major depression vs BDI-II score of at least 14 without *DSM-IV* diagnosis: unadjusted, 1.80 (95% CI, 0.89-3.61),  $P = .10$ ; adjusted, 1.74 (95% CI, 0.82-3.70),  $P = .15$ .

<sup>c</sup>Odds ratios vs low level of anxiety symptoms for GAD vs HADS-A score of at least 8 without *DSM-IV* diagnosis: unadjusted, 1.98 (95% CI, 0.95-4.14),  $P = .07$ ; adjusted, 1.99 (95% CI, 0.90-4.38),  $P = .09$ .

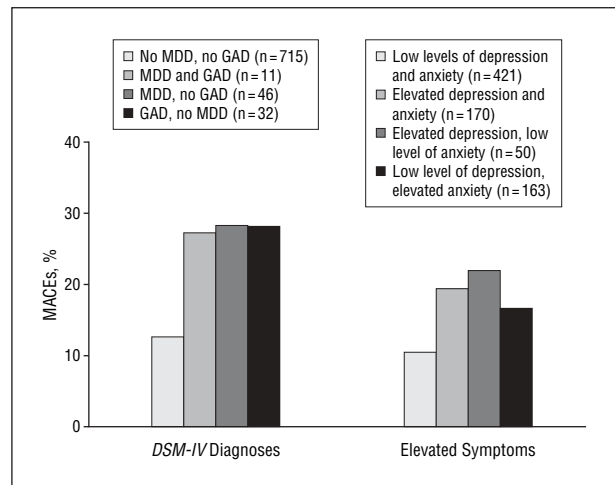
<sup>d</sup>Odds ratios vs low level of depression and anxiety symptoms for MDD/GAD vs elevated symptoms without *DSM-IV* diagnoses: unadjusted, 2.17 (95% CI, 1.24-3.79),  $P = .007$ ; adjusted, 2.11 (95% CI, 1.20-3.40),  $P = .01$ .

toms occurred in those meeting the diagnostic criteria. The results suggest that medical and background factors play a greater confounding role in self-report data than in diagnostic assessments. This may in part account for the inconsistent results in the literature on the prognostic importance of anxiety in patients with CAD and underscore the importance of covariate adjustment. The use of diagnostic measures is likely to produce larger and more robust risk estimates for anxiety and depression.

We observed 20% to 25% comorbidity between MDD and GAD, on the low side of estimates from cross-sectional community studies.<sup>10</sup> However, patients with comorbid diagnoses were not at greater risk for MACEs than those with only 1 of these factors. Results were the same when comorbidity was defined by the self-reports. It is possible that patients with comorbid conditions were less likely to survive the index ACS episode or may not even have survived to be hospitalized. However, the distinction between the conditions may not matter much in terms of cardiac prognosis in patients with established CAD. Approximately 40% of those with each diagnosis had past episodes of depression. This is similar to data recently reported<sup>15</sup> in a much younger cohort followed up prospectively since childhood. For some patients, the presentation of emotional difficulties may vary between anxiety and depression across their lifetimes. In others, anxiety or depression may remain the predominant observable negative emotion, but both may share common genetic, environmental, and pathophysiologic bases. It has been suggested that because of their overlap, MDD and GAD should probably be considered as part of the same broad diagnostic classification in the DSM-V, perhaps as part of a “distress disorder” category.<sup>46</sup> This may be particularly true for patients with CAD.

Receiver operating characteristic curve analyses of the BDI-II and the HADS-A for predicting diagnoses of MDD and GAD also supported the overlapping nature of anxiety and depression in patients with CAD. The HADS-A was almost as good at predicting MDD as GAD. The BDI-II was a more psychometrically pure measure of depression but did as well at detecting GAD as many screening indices. When considered as continuous measures, the HADS-A, but not the BDI-II, remained a significant predictor of increasing MACE risk after covariate control. This likely reflects its ability to tap both factors and thus better identify patients for whom emotional symptoms increase the risk of cardiac events.

Although most recent research on pathophysiologic links between negative emotions and CAD has involved depression, evidence indicates that anxiety is also related to several mechanisms involved in CAD events,<sup>1</sup> including increased catecholamine levels,<sup>47</sup> indicators of autonomic dysfunction (increased heart rate, decreased heart rate variability, and decreased baroreceptor sensitivity),<sup>48-51</sup> increased platelet activity,<sup>52</sup> and subacute chronic inflammation.<sup>53</sup> It has also been suggested that depression and anxiety have common genetic predispositions<sup>16,17</sup> and that the biological mechanisms linking depression with CAD may result from shared genetic factors.<sup>54</sup> For example, dysregulation of the serotonin system,<sup>55,56</sup> which is likely to be partially



**Figure.** Percentage of major adverse cardiac events (MACEs) across 2 years associated with *DSM-IV* diagnoses of major depressive disorder (MDD) and generalized anxiety disorder (GAD) and their comorbidity, and elevated levels of depression and anxiety symptoms and their comorbidity in 804 patients assessed 2 months after an acute coronary syndrome.

determined by genetic factors, may predispose to depression or anxiety or CAD, with the predominant clinical phenotype(s) being the result of multiple genetic-environmental interactions yet to be determined.

In the present sample, assessed approximately 2 months after hospital discharge for ACS, the rate of MDD was only 7.1%, approximately one-third of that reported for patients interviewed during hospitalization for MI.<sup>57</sup> Previous studies have varied in the proportion of women, and evidence suggests that female cardiac patients are approximately twice as likely to be depressed as their male counterparts. In the ESCAPE study, 13.5% of women but only 5.5% of men met the criteria for MDD, and only 19.3% of the patients were women. A more probable explanation for the low prevalence of depression is that some patients who meet the criteria for MDD during hospitalization have an adjustment disorder or a less severe mood disorder that is no longer present 2 months later. Most structured interview studies in patients with CAD have administered the Diagnostic Interview Schedule<sup>58</sup> or the Depression Interview and Structured Hamilton.<sup>59</sup> In contrast, ESCAPE study psychologists administered the Structured Clinical Interview for *DSM-IV*.<sup>39</sup> To qualify for MDD, ESCAPE study patients had to note sadness or loss of interest “most of the day, nearly every day” for 2 weeks or more during the past month and have experienced significant social, occupational, or other impairment. The Diagnostic Interview Schedule requires sadness or loss of interest most days and, when administered in the hospital, has often been modified to exclude the impairment criterion and to require less than 2 weeks of symptoms. Thus, the stricter application of the *DSM-IV* criteria in the ESCAPE study is at least partially responsible for the lower prevalence of MDD.

This study has other limitations. We do not know the refusal rates in patients with *DSM-IV* diagnoses or elevated self-report symptoms. Depression and anxiety were assessed at baseline only. We do not know whether patients with co-occurring anxiety and depression had different psychological outcomes than those with a single



condition. There were 68 patients (8.5%) taking antidepressant agents, and 212 (26.4%) had benzodiazepine prescriptions. However, neither was related to MACEs. Despite the 2-year follow-up, the number of cardiac events was lower than in earlier studies, likely a positive consequence of improvements in medical treatment coupled with the fact that patients were recruited 2 months after an ACS episode rather than during hospitalization. The outcome, MACEs, was a composite of cardiac deaths, MIs, survived cardiac arrests, and emergency revascularizations, all events signaling a worsening cardiovascular condition and associated with major health care costs and long-term prognostic burden. However, this sample was not large enough to assess the separate components and ensure adequate covariate adjustment.

Anxiety and depression have prognostic importance in patients with stable CAD, and the risks are fairly equivalent. At first glance, the inclusion of patients with elevated anxiety or depression symptoms seems to be a good strategy for recruitment in clinical trials aimed at preventing the cardiac consequences of psychological risks. However, we found that most of the increased risk of cardiac events associated with self-report symptoms is in those with either GAD or MDD. Because there is evidence that 2 selective serotonin reuptake inhibitor antidepressants (sertraline<sup>60</sup> and citalopram<sup>61</sup>) are efficacious and safe for patients with CAD and MDD, randomization to placebo use for long periods is not likely to be ethically acceptable. In addition, although there are no specific trial data supporting their use for GAD in patients with CAD, several selective serotonin reuptake inhibitors have demonstrated efficacy for medically healthy patients with GAD.<sup>62</sup> Thus, long-term randomization to placebo therapy is also questionable in patients with CAD and GAD. Placebo treatment is probably acceptable for patients with CAD and elevated symptoms who do not meet the criteria for a disorder, but their rate of cardiac events is likely to be low, requiring a substantially larger sample size. This adds yet another challenge to designing a cardiac prevention trial based on reduction of risks linked to psychiatric factors and suggests that efforts would be better placed at improving the efficacy of existing treatments.

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