Depressive Symptoms, Cardiac Disease Severity, and Functional Status in Patients With Coronary Artery Disease (from the Heart and Soul Study)

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Patient-reported health status is highly valued as a key measure of health care quality, yet little is known about the extent to which it is determined by subjective perception compared with objective measures of disease severity. We sought to compare the associations of depressive symptoms and objective measures of cardiac disease severity with perceived functional status in patients with stable coronary artery disease. We assessed depressive symptoms, severity of cardiovascular disease, and perceived functional status in a cross-sectional study of 1,023 patients with stable coronary artery disease. We compared the extent to which patient-reported functional status was influenced by depressive symptoms versus objective measures of disease severity. We then evaluated perceived functional status as a predictor of subsequent cardiovascular hospitalizations during 8.8 years of follow-up. Patients with depressive symptoms were more likely to report poor functional status than those without depressive symptoms (44% vs 17%; p <0.001). After adjustment for traditional risk factors and co-morbid conditions, independent predictors of poor functional status were depressive symptoms (odds ratio [OR] 2.68, 95% confidence interval [CI] 1.89 to 3.79), poor exercise capacity (OR 2.30, 95% CI 1.65 to 3.19), and history of heart failure (OR 1.61, 95% CI 1.12 to 2.29). Compared with patients who had class I functional status, those with class II functional status had a 96% greater rate (hazard ratio 1.96, 95% CI 1.15 to 3.34) and those with class III or IV functional status had a 104% greater rate (hazard ratio 2.04, 95% CI 1.12 to 3.73) of hospitalization for HF, adjusted for baseline demographic characteristics, co-morbidities, cardiac disease severity, and depressive symptoms. In conclusion, depressive symptoms and cardiac disease severity were independently associated with patient-reported functional status. This suggests that perceived functional status may be as strongly influenced by depressive symptoms as it is by cardiovascular disease severity. Published by Elsevier Inc. (Am J Cardiol 2016;118:1287−1292)

Depression is particularly prevalent in patients with cardiovascular disease, and screening is recommended for all patients with coronary artery disease (CAD).[1] Identification of depressive symptoms in patients with CAD is important because these patients have a worse prognosis.[2,3] Depressive symptoms contribute to an increased burden of cardiovascular and functional impairment.[4] Depression has a significant negative influence on self-rated functional status in CAD.[5] Previous studies have demonstrated that functional impairment is associated with more severe symptoms and worse health in patients with CAD.[6] Poor functional classification is also a risk factor for future cardiac events including stroke,[7] HF hospitalization,[8] and mortality.[8,9] However, determining the degree of influence depression has in comparison with objective measures of disease on symptoms burden in patients with stable CAD is unknown. Therefore, understanding how depression and severity cardiac disease relate to quality of life and perception of symptoms is important. We sought to test the hypothesis that depressive symptoms are associated with patients' perceived symptom burden even after adjusting for objective markers of CAD severity using a cross-sectional study of a cohort of patients with stable CAD. In addition, we evaluated the association between

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See page 1291 for disclosure information.

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Box 1
Functional status classification questionnaire

Which one of the following statements best describes the symptoms associated with your heart condition:

I. I have no limitation of physical activity. Ordinary physical activity does not cause fatigue, shortness of breath, or chest pain.
II. I have slight limitation of physical activity. Ordinary physical activity results in fatigue, shortness of breath, or chest pain.
III. I have marked limitation of physical activity. Less than ordinary activity causes fatigue, shortness of breath, or chest pain.
IV. I am unable to engage in any physical activity without discomfort. Fatigue, shortness of breath, or chest pain may be present even at rest.

functional status as a predictor of subsequent cardiovascular hospitalizations both before and after adjustment for depressive symptoms.

Methods

The Heart and Soul Study is a prospective cohort study that was originally designed to investigate the effects of psychosocial factors on health outcomes in patients with stable CAD. Methods have been previously described.[10] Patients were eligible if they had at least one of the following: history of myocardial infarction (MI), angiographic evidence of $\geq$50% stenosis in $\geq$1 coronary vessels, evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, a history of coronary revascularization, or a diagnosis of coronary disease. Patients were excluded if they were unable to walk at least 1 block, had an acute coronary syndrome within the previous 6 months, or were likely to move from the area within 3 years.

From September 2000 to December 2002, 1,024 subjects were recruited from 12 outpatient clinics in the San Francisco Bay Area, including 1,023 with assessment of functional status. All participants completed a full-day study including medical history and physical examination, health status questionnaires, and an exercise treadmill test with baseline and stress echocardiograms. Institutional review boards at each site approved this study protocol. All participants provided written informed consent.

The primary outcome was perceived functional status that was obtained by self-report questionnaire.[11–13] Assessment of functional status was performed using a scale combining elements of the New York Heart Association functional classification and the Canadian Cardiovascular Society angina score which are both well-established prognostic tools in patients with cardiovascular disease.[9,11,12] Participants were asked to grade the severity of their cardiac symptom burden, which could include chest discomfort, dyspnea, or fatigue, ranging from minimal (I) to mild (II) to moderate (III) to severe (IV) (Box 1).

To assess depressive symptoms, all participants completed the 9-item Patient Health Questionnaire (PHQ-9).[14] The PHQ-9 is a well-studied and validated diagnostic tool for identifying depression with a score of $\geq$10 representing 88% specificity and 88% sensitivity.[14,15] Patients were categorized as "depressed" if they scored a 10 or greater on the PHQ-9, which represented an estimate of the burden of depressive symptoms.

Participants underwent symptom-limited exercise stress testing according to a standard Bruce protocol (those unable to complete the standard protocol were converted to a manual protocol) with continuous 12-lead electrocardiogram monitoring. Immediately before and after exercise, participants underwent complete 2-dimensional echocardiograms at rest with all standard views using an Acuson Sequoia Ultrasound System (Siemens Medical Solutions, Mountain View, California) with a 3.5-MHz transducer and Doppler ultrasound examination. Left ventricular ejection fraction, diastolic function, and left ventricular mass were assessed as previously described.[16–18] We defined exercise-induced ischemia as the presence of $\geq$1 new wall motion abnormalities at peak exercise that was not present at rest. Each of the 16 wall segments in the left ventricle was scored based on the contractility visualized at peak exercise (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysm). The wall motion score index was defined as the sum of wall motion scores divided by the number of segments visualized.[17] A single experienced cardiologist, who was blinded to the results of all laboratory values and clinical histories, interpreted all echocardiograms.

Demographic characteristics, medical history, and smoking status were assessed by self-report questionnaire. Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT-C).[19] We measured weight and height and calculated the body mass index (kg/m^2). Participants were asked to bring their medication bottles to the study appointment, and research personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, California). Lipid values were measured by standard laboratory techniques. Cystatin C was measured using the Siemens assay, and estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation.[20]

To identify hospitalizations for HF or MI, we conducted annual telephone interviews with participants or their proxies regarding recent emergency room visits, hospitalizations, or death. Two independent and blinded adjudicators each reviewed any reported events, medical records, death certificates, or coroner's reports. If the adjudicators agreed on the outcome classification, their classification was binding. If they disagreed, a third blinded adjudicator reviewed the event and determined the outcome classification. MI was defined using standard diagnostic criteria.[21] Hospitalization for HF has been previously defined.[22]

Baseline characteristics between prespecified groups were compared using ANOVA for continuous variables and chi-square test for dichotomous variables. We used ordinal logistic regression for cross-sectional analyses with functional status (severe vs moderate vs mild vs minimal symptoms) as the outcome. Because there were only 49 participants with severe limitation of functional status, they were combined with participants with moderate limitation of functional status for all models. Cox proportional hazards models were used for longitudinal analyses. As a subgroup analysis, subjects with a diagnosis of HF at baseline were defined as subjects who self-reported a history of HF, had a left ventricular ejection fraction <50%, or had diastolic dysfunction (pseudonormal or restrictive pattern) on baseline echocardiogram at rest. We checked for

interaction of depressive symptoms with gender, age, marital status, exercise capacity, presence of inducible ischemia, and HF. Analyses were performed using Stata (version 12.1; Statacorp, College Station, Texas).

Results

At baseline, among 1,023 participants, 199 (19.4%) had depressive symptoms (PHQ-9 score ≥10). Compared with nondepressed participants, those who were depressed were younger and less likely to be male or married (Table 1). Patients with depression had lower income and were more likely to smoke than those without depression. They were also more likely to have a history of diabetes, myocardial infarction, heart failure, and/or increased body mass index. Participants with depressive symptoms had lower exercise capacity, greater left ventricular mass, and were more likely to be taking a statin medication.

Participants with depression were more likely to report poor (class III or IV) functional status than those without depression (44% vs 17%; p <0.001; Figure 1). Of the 199 participants with depression, 38 (17%) had minimal, 78 (39%) had mild, and 87 (44%) had moderate or severe limitation of functional status (p <0.001). Of the 824 participants without depression, 343 (42%) had minimal, 338 (41%) had mild, and 143 (17%) had moderate or severe limitation of functional status (p <0.001).

Perception of higher symptom burden was associated with greater LV mass index, higher wall motion score index, worse exercise capacity, and greater inducible ischemia (Table 2). Compared with those with minimal symptoms, participants with greater functional status limitation did not have significant differences in left ventricular ejection fraction or presence of diastolic dysfunction (Table 2). The prevalence of depressive symptoms ranged from 9.0% in patients with mild symptoms to 46.9% in patients with severe symptoms (p <0.001).

Multivariate analysis of the association between depression and perceived functional status was significant after adjustment for baseline demographics (age, gender, income, marital status), co-morbidities (history of diabetes, myocardial infarction, heart failure, use of statin medication, body mass index, smoking), left ventricular systolic function, and cardiac disease severity (exercise capacity, left ventricular mass, inducible ischemia, wall motion index score at rest; Table 3). Participants with depression had 2.7 times greater odds of having worse perceived functional status compared with those without depressive symptoms. Other predictors of worse functional status included poor treadmill exercise capacity (<5 metabolic equivalents of task [METs]), current smoking, annual income of <20,000 USD per year, and history of HF (Table 4). There were no significant interactions of depression with gender, marital status, inducible ischemia, or exercise capacity.

During a mean of 8.8 years follow-up, HF hospitalization occurred in 10% (39 of 374) of patients with class I functional status, 18% (75 of 416) of patients with class II functional status, and 26% (59 of 229) of patients with class III/IV functional status (Figure 2). Overall, there was a greater risk of HF hospitalization in participants with class II functional status (hazard ratio [HR] 1.87, 95% CI 1.27 to 2.76, p = 0.001) and class III/IV functional status (HR 2.93, 95% CI 1.95 to 4.39, p <0.001) compared with those with class I functional status. Impaired functional status remained predictive of HF hospitalization after extensive adjustment for demographics, co-morbidities, left ventricular systolic

Table 1
Baseline characteristics of 1023 participants by presence or absence of depressive symptoms (Patient Health Questionnaire score ≥10)

Variables*	Depressive Symptoms		p value
	Yes (n=199)	No (n=824)	
Age (years)	62.6 (±11.9)	67.8 (±10.4)	<0.001
Men	152 (76.4%)	688 (83.4%)	0.021
White	110 (55.3%)	505 (61.2%)	0.125
High school graduate	166 (83.4%)	725 (88.1%)	0.077
Annual income <$20K	128 (64.3%)	370 (45.2%)	<0.001
Married	66 (33.2%)	370 (45.0%)	0.002
Hypertension	151 (76.3%)	572 (69.5%)	0.060
Diabetes mellitus	68 (34.3%)	197 (23.9%)	0.003
Myocardial infarction	121 (61.7%)	426 (51.9%)	0.013
Heart failure	49 (24.8%)	130 (15.9%)	0.003
eGFR (ml/min)	70.6 (±21.3)	70.9 (±25.1)	0.840
Stroke	33 (16.8%)	115 (14.0%)	0.320
Coronary revascularization	109 (55.3%)	493 (59.8%)	0.249
LV ejection fraction (%)	60.5 (±10.1)	61.9 (±9.5)	0.062
Diastolic dysfunction†	22 (12.7%)	94 (12.8%)	0.984
LV mass (g/m^2)	102.6 (±29.9)	97.2 (±25.5)	0.011
Resting wall motion index score	1.2 (±0.4)	1.2 (±0.3)	0.178
Exercise capacity (METs)	6.5 (±3.2)	7.5 (±3.3)	<0.001
Inducible ischemia	41 (24.0%)	187 (24.4%)	0.904
BMI (kg/m2)	29.2 (±5.7)	28.2 (±5.2)	0.016
Current smoker	67 (33.8%)	134 (16.3%)	<0.001
Regular alcohol use	55 (27.8%)	238 (29.1%)	0.713
Anti-platelet	145 (74.0%)	596 (73.1%)	0.809
B-blocker	119 (60.7%)	474 (58.2%)	0.514
ACE-I or ARB	104 (53.1%)	420 (51.5%)	0.701
Statin	113 (57.7%)	544 (66.8%)	0.017

* Number (percent) for dichotomous variables; mean ± standard deviation for continuous variable.

† Diastolic dysfunction = pseudonormal or restrictive pattern on echo.

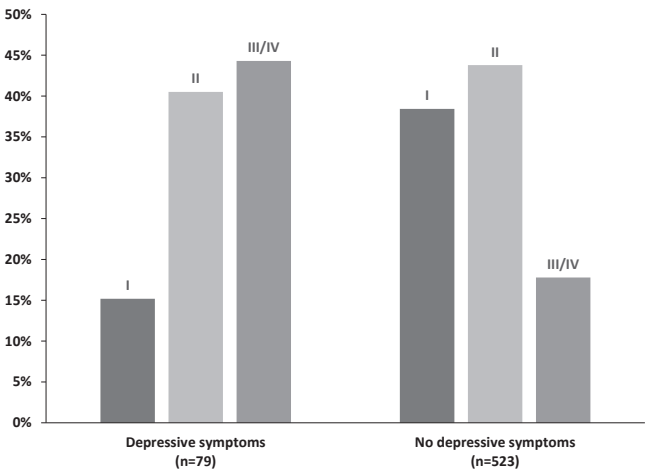

Figure 1. Distribution of functional status by the presence or absence of depressive symptoms in 1,023 participants with CAD.

Table 2
Association of cardiac disease severity with functional classification

Variable	Functional status classification				p value
	Minimal I (n=347)	Mild II (n=416)	Moderate III (n=181)	Severe IV (n=49)	
LV ejection fraction	62.2 (±9.1)	61.7 (±9.5)	60.9 (±10.5)	60.5 (±11.1)	0.405
Diastolic dysfunction*	36 (10.8%)	56 (15.0%)	18 (11.3%)	6 (14.3%)	0.369
LV mass index (g/m^2)	95.4 ± 25.0	98.0 ± 25.9	101.3 ± 27.9	111.6 ± 33.0	<0.001
Resting wall motion index	1.1 (±0.3)	1.2 (±0.4)	1.2 (±0.4)	1.2 (±0.4)	0.045
Exercise capacity (METs)	9.0 (±3.6)	6.6 (±2.7)	5.7 (±2.6)	5.0 (±2.6)	<0.001
Inducible ischemia	67 (18.8%)	102 (26.7%)	48 (26.5%)	11 (29.7%)	0.016
Depressive symptom score	3.2 (±4.3)	5.3 (±5.1)	7.9 (±6.1)	9.6 (±6.8)	<0.001
Depression (PHQ-9 score ≥10)	34 (9.0%)	78 (18.8%)	64 (35.4%)	23 (46.9%)	<0.001

* Diastolic dysfunction = pseudonormal or restrictive pattern on echocardiogram.

Table 3
Multivariate association of depressive symptoms (PHQ9 ≥10) with worse functional classification using ordinal logistic regression

Model	Worse functional classification	
	OR (95% CI)	p value
Unadjusted	3.61 (2.67, 4.87)	<0.001
Model 1	3.32 (2.45, 4.51)	<0.001
Model 2	2.78 (2.02, 3.82)	<0.001
Model 3	2.68 (1.89, 3.79)	<0.001

Model 1 = adjusted for age, male gender, income <$20000, married.
Model 2 = adjusted for above + diabetes mellitus, myocardial infarction, heart failure, use of statin, BMI >25 kg/m^2, smoker.
Model 3 = adjusted for above + LV ejection fraction ≤50%, exercise capacity <5 METs, LV mass index >90 g/m^2, inducible ischemia, resting wall motion index score >1.

Table 4
Multivariable model of association between each covariate and functional classification

Variable	Worse functional classification	
	OR (95% CI)	p value
Depression (PHQ≥10)	2.68 (1.89, 3.79)	<0.001
Exercise capacity <5 METs	2.30 (1.65, 3.19)	<0.001
Current smoker	2.26 (1.59, 3.22)	<0.001
Annual income <$20K	1.98 (1.48, 2.64)	<0.001
Heart failure	1.61 (1.12, 2.29)	0.009
Inducible ischemia	1.46 (1.06, 2.00)	0.019
Age >mean	1.38 (1.01, 1.89)	0.046
BMI >25 kg/m^2	1.32 (0.98, 1.77)	0.071
LVEF ≤50%	1.32 (0.82, 2.12)	0.251
Married	1.29 (0.97, 1.71)	0.081
Diabetes mellitus	1.25 (0.97, 1.69)	0.158
Myocardial infarction	1.18 (0.90, 1.55)	0.224
Use of statin	1.09 (0.82, 1.44)	0.559
Left ventricular mass >90 g/m^2	1.01 (0.76, 1.34)	0.945
Men	0.74 (0.52, 1.05)	0.091
Resting wall motion index score >1	0.93 (0.66, 1.31)	0.681

function, cardiac disease severity, and depressive symptoms for participants with class II functional status (Table 5). Depression was also predictive of HF hospitalization (HR 1.44, 95% CI 1.01 to 2.03, p = 0.04). However, adjusting for functional status eliminated this association (HR 1.10, 95% CI 0.77 to 1.59, p = 0.60). During follow-up, MI occurred in 10% of patients (37 of 374) with class I functional status, 12% of patients (48 of 416) with class II functional status, and 17% of patients (38 of 229) with class III/IV functional status. Compared with those with class I functional status, there was a greater risk of MI in participants with class III/IV functional status (HR 1.90, 95% CI 1.21 to 3.00, p = 0.005) but not class II functional status (HR 1.24, 95% CI 0.81 to 1.91, p = 0.32).

Discussion

In a cohort of 1,023 older adults with stable CAD, we found that perceived functional status was as strongly associated with depressive symptoms as objective measures of cardiac disease severity. Subjects with depression were more likely to report worse cardiac symptom burden compared with those without depression. Also, we found those with worse symptoms were more likely to be hospitalized over a long-term follow-up period. These findings suggest that (a) depressive symptoms should be considered in the differential diagnosis of more severe symptom burden in patients with CAD and (b) that perceived functional status may be as reflective of depressive symptoms as it is of cardiac disease severity. Thus, treatment of depression in patients with poor functional status may be as important as more aggressive medical management of their cardiac disease to improve symptom burden. Identifying depressive symptoms can be done by administering simple screening questions that is inexpensive and not overly time consuming.[23,24] Recognizing depressive symptoms is important in patients with CAD because they are associated with worse cardiovascular outcomes.[2,3,25] We also know that more severe cardiac disease can lead to depressive symptoms and that depressive symptoms are a risk factor for cardiac events.[10,26]

We believe our study is the first to demonstrate that depressive symptoms are strongly predictive of poor self-reported functional status in subjects with stable CAD even after considering numerous objective measures of the severity of cardiac disease. Patient perception of symptoms is essential because of the strong association with poor

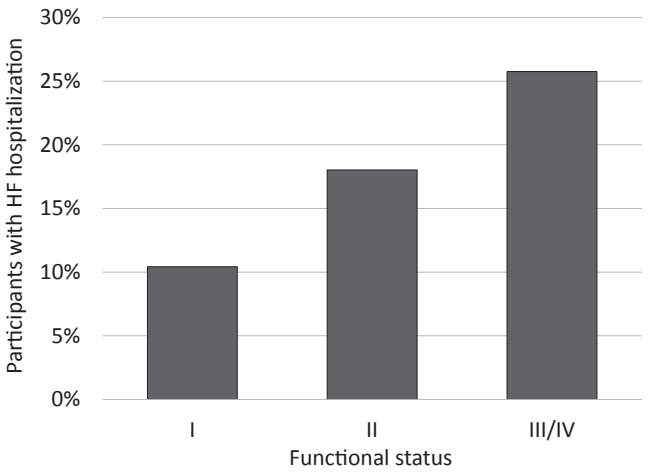

Figure 2. Incidence of heart failure hospitalization by functional status.

Table 5
Multivariable association of patient-reported functional status and baseline cardiac disease severity with subsequent heart failure hospitalization

Variable	Risk of Heart Failure Hospitalization	
	HR (95% CI)*	p value
Class I functional status	1.0	–
Class II functional status	1.96 (1.15, 3.34)	0.014
Class III/IV functional status	2.04 (1.12, 3.73)	0.020
Diastolic dysfunction	2.68 (1.65, 4.37)	<0.001
Left ventricular mass >90 g/m^2	2.59 (1.47, 4.54)	0.001
LVEF ≤50%	1.92 (1.11, 3.31)	0.019
Resting wall motion index score >1	1.88 (1.14, 3.10)	0.013
Inducible ischemia	1.68 (1.08, 2.61)	0.021
Exercise capacity <5 METs	1.59 (0.98, 2.48)	0.062

* Adjusted for baseline depressive symptoms and for all variables in Table 1.

outcomes. These findings are critical because we have shown that identifying depressive symptoms may be as important as traditional objective markers of cardiac disease severity, such as left ventricular ejection fraction, exercise capacity, and ischemia.

As the field of medicine begins to more effectively and appropriately incorporate patient-centered outcomes in studies, it is essential that providers understand which factors play the greatest role in these outcomes. Our results show that more common markers of disease, and recommended performance measures, are not as strongly associated with patients' clinical symptoms and health status as that measured by functional status. Our measure of functional status assessed the most common and burdensome symptoms of cardiac disease, angina and dyspnea, into a single scale and was chosen because it is so easily and frequently used in clinical practice, it is well understood, and relevant to numerous cardiac diseases. Our findings support that to improve cardiovascular outcomes, as assessed by symptom burden, then identifying and addressing depression is important.

In addition to depressive symptoms, exercise capacity and current smoking status were also associated with functional status. Interventions that focus on improving exercise capacity and smoking cessation will be necessary to maximize patients' reported symptom burden and quality of life. It has been well known that exercise training to increase exercise capacity reduces depressive symptoms in patients after ischemic coronary events in addition to improvement in other cardiac risk factors.[27,28] Treatments must be focused on both simultaneously improving depressive symptoms and functional impairment.

It is important to recognize that depressive symptoms were associated with subsequent hospitalization for HF in our cohort of stable patients including many with normal systolic and diastolic functions. Therefore, depressive symptoms were especially useful in risk-stratifying stable patients with CAD who at higher risk of developing HF and may benefit from more intensive monitoring, treatment, and follow-up. However, depressive symptoms were not associated after controlling for symptom burden that suggests that depressive symptoms and functional status have overlapping characteristics that capture the same element of risk. The presence of depression and poor functional status lessened each other's associations with hospitalization. Because depressive symptoms are so strongly associated with a patient's perception of cardiac symptoms, both of these may be helpful in guiding appropriate therapy to maximize patients' outcomes.

A number of limitations must be considered in interpreting our results. The association between depressive symptoms and functional status was a cross-sectional study; therefore, we cannot determine causality, although we believe it is a bidirectional relation as both depression leads to greater cardiac symptoms and worse cardiac disease increases the risk of depression. However, our goal was not to determine causality but to investigate the relation between depressive symptoms and perceived symptom burden. Second, our cohort was among patients with stable CAD and did not specifically include stage B or C HF, although many did have a history of HF, reduced systolic function, or abnormal diastolic function at baseline; however, all patients had stage A HF due to CAD. The association between severity of symptoms and severity of cardiac disease has been well established. Third, data for this study were collected 15 years ago and some treatments and diagnostic tests available today were not in use at that time; therefore, it is unclear how much the independent association reported between depression and functional impairment applies to patients today. Fourth, although we included many markers of disease severity, others were not included (e.g., angiography results, recent hospitalization) that may have reduced the association between depression and functional impairment in adjusted models. Last, interobserver variability of functional classification has been reported because of the subjective nature of symptom severity.[29] However, in our study, patients completed a self-report questionnaire regarding their functional status assessing cardiac symptoms.

Disclosures

The authors have no conflicts of interest to disclose.

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