Associations of Preexisting Depression and Anxiety With Hospitalization in Patients With Cardiovascular Disease

ALANNA M. CHAMBERLAIN, PhD, MPH; KRISTIN S. VICKERS, PhD; ROBERT C. COLLIGAN, PhD;
SUSAN A. WESTON, MS; TERESA A. RUMMANS, MD; AND VÉRONIQUE L. ROGER, MD, MPH

OBJECTIVE: To determine the risk of hospitalization and death in relation to preexisting depression and anxiety among patients with cardiovascular disease (CVD).

PATIENTS AND METHODS: The cohort consisted of 799 Olmsted County, MN, residents diagnosed with CVD (myocardial infarction or heart failure) from January 1, 1979, to December 31, 2009, who completed a Minnesota Multiphasic Personality Inventory (MMPI) prior to their event. The MMPI was used to identify depression and anxiety, and participants were followed up for hospitalizations and death during an average of 6.2 years.

RESULTS: Depression and anxiety were identified in 282 (35%) and 210 (26%) participants, respectively. After adjustment, depression and anxiety were independently associated with a 28% (95% confidence interval [CI], 8%-51%) and 26% (95% CI, 3%-53%) increased risk of being hospitalized, respectively. Depression also conferred an increased risk of all-cause mortality of similar magnitude, whereas the hazard ratio for anxiety was not statistically significant. The combined occurrence of depression and anxiety led to a 35% (95% CI, 8%-71%) increase in the risk of hospitalizations.

CONCLUSION: Among patients with CVD, both preexisting depression and anxiety, occurring on average 17 years before the CVD event, independently predict hospitalizations. In addition, the 2 conditions may act synergistically on increasing health care utilization in patients with CVD.

Mayo Clin Proc. 2011;86(11):1056-1062

CI = confidence interval; CVD = cardiovascular disease; HF = heart failure; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory

There has been recent interest in the association between psychosocial factors (depression, anxiety, hostility, type A behavior, and social isolation) and cardiovascular disease (CVD).¹ Depression, in particular, is approximately 3 times more common after myocardial infarction (MI) than in the general community,² and its presence increases the risk of cardiovascular events and mortality.³⁻⁵ These findings imply that identifying and treating depression are important for patients with CVD.⁶ However, most randomized controlled trials on cognitive behavioral therapy or antidepressant medications for depression have been disappointing because treatment did not confer a definite survival benefit.⁷

The apparent disconnect between the association of depression with CVD events and the lack of therapeutic benefit underscores the complexity of this issue and suggests that other constructs might be operating above and

beyond depression alone. Anxiety is one such factor that has been reported to increase the risk of incident MI⁸⁻¹¹ and may adversely influence outcomes in CVD.¹² Importantly, depression and anxiety, which sometimes coexist, could operate synergistically in the genesis of adverse events.¹³ This hypothesis, however, has not been adequately tested. Further, the influence of psychosocial risk factors on health care utilization among patients with CVD has rarely been studied. Addressing these issues is complex because it requires defined community cohorts to optimize the clinical relevance of these findings, complete longitudinal follow-up, and rigorous ascertainment of psychosocial constructs and CVD events, conditions that are seldom met. Using the resources of the Rochester Epidemiology Project,¹⁴ we undertook a study of Olmsted County, MN, residents with CVD to determine the risk of hospitalization and death in relation to preexisting depression and anxiety and to assess whether anxiety and depression potentiate each other in the genesis of adverse events.

PATIENTS AND METHODS

STUDY SETTING

This study was conducted in Olmsted County, MN. Population-based epidemiological research is feasible in Olmsted County because it is relatively isolated from other urban centers and only a few providers deliver nearly all health care to local residents. Each provider uses a comprehensive medical record system in which the details of every encounter are entered and can be easily retrieved. Review of medical records takes place under the auspices of the Rochester Epidemiology Project. This record-linkage sys-

From the Department of Health Sciences Research (A.M.C., S.A.W., V.L.R.), Department of Psychiatry and Psychology (K.S.V., R.C.C., T.A.R.), and Division of Cardiovascular Diseases (V.L.R.), Mayo Clinic, Rochester, MN.

Dr Roger is an Established Investigator of the American Heart Association.

This work was supported by grants from the National Institutes of Health (R01 HL59205 and R01 HL72435) and the National Institute on Aging (R01 AG034676). The funding sources played no role in the design, conduct, or reporting of this study.

Individual reprints of this article are not available. Address correspondence to Véronique L. Roger, MD, MPH, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (roger.veronique@mayo.edu).

© 2011 Mayo Foundation for Medical Education and Research

tem allows all medical records of Olmsted County residents to be indexed according to clinical and pathologic diagnoses, surgical procedures, and billing information. With this indexing system, all medical records can be retrieved for use in epidemiological studies, and complete capture of all health care–related events in Olmsted County is ensured.¹⁴ The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved this study.

IDENTIFICATION OF THE STUDY COHORT

This cohort consisted of Olmsted County residents aged 18 years or older given a diagnosis of incident MI or heart failure (HF) between January 1, 1979, and December 31, 2009. Possible MI events were identified by *International Classification of Diseases, Ninth Revision* (ICD-9), codes 410 and 411. Validation of an MI diagnosis included the presence of cardiac pain, biomarkers, and electrocardiographic findings.^{15,16} Possible HF diagnoses among Olmsted County residents were identified by ICD-9 code 428 assigned during either outpatient visits or hospitalizations. A random sample of incident diagnoses was selected for validation of the HF diagnosis based on the Framingham criteria.¹⁷ The procedures used to assemble the incident MI and HF cohorts have been previously described.^{18,19} If an individual had both a validated MI and a validated HF event, the earlier event was chosen as the index event.

CLINICAL DATA COLLECTION

The highest level of education attained, along with marital status and current (within the past 6 months) cigarette smoking status at the time of HF or MI, was obtained from medical records. Body mass index was calculated as weight (in kilograms from the last outpatient visit before diagnosis) divided by height (in meters from a first available outpatient value) squared. Information on comorbid conditions was abstracted from medical records, and a score was calculated using the Charlson comorbidity index.²⁰

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY

The original Minnesota Multiphasic Personality Inventory (MMPI) consisted of 550 unique true/false items covering physical and emotional symptoms, feelings, attitudes, and life experiences.²¹ The MMPIs were gathered from 3 sources: (1) an unbiased sample of consecutive medical outpatients seen between 1962 and 1965,²² (2) a clinical sample of patients who were asked to complete the MMPI by a Mayo consultant as part of the clinical evaluation, and (3) patients who were asked to complete the MMPI for a research study being conducted at Mayo Clinic. Responses to all MMPIs given at Mayo Clinic from 1962 until the date of MI or HF diagnosis were gathered for each patient.

Two scales from the MMPI were used: the 60-item Depression clinical scale and the 50-item Manifest Anxiety scale. The MMPI Depression scale has been previously shown to predict heart rate variability in patients with diagnosed coronary artery disease,²³ and the Manifest Anxiety scale has been previously shown to predict the onset of MI in a longitudinal study of initially healthy men.⁹ The Depression scale measures symptoms such as apathy, excessive sensitivity, isolation, and somatic symptoms such as sleep disturbances, loss of appetite, and gastrointestinal complaints.²¹ Women tend to endorse more items on the Depression scale than men; thus, we used sex-specific cut points for depression based on the raw score from the Depression scale. Men who score 25 or more points and women who score 30 or more points on the Depression scale exhibit a general sadness or depressed mood and tend to be withdrawn, guilty, and self-deprecating.²¹ These cut points were used to define depression in analyses.

The Manifest Anxiety scale measures subjective feelings of nervousness, tension, and anxiety, along with blushing, sweating, shakiness, and somatic complaints such as headaches, nausea, and stomach problems.²⁴ High scorers on the Manifest Anxiety scale tend to feel restless, unhappy, or useless; lack self-confidence; have difficulties concentrating; and report numerous physical complaints.²⁴ We dichotomized this scale at the 75th percentile, with men and women scoring 25 or more points defined as exhibiting anxiety.

ASCERTAINMENT OF HOSPITALIZATIONS AND DEATH

Participants were followed up through December 31, 2009, for hospitalizations and deaths. To ascertain hospitalizations, we used the Olmsted County Healthcare Expenditure and Utilization Database. This database includes information on hospitalization in Olmsted County from 1987 through 2009. If HF or MI was initially diagnosed during hospitalization, only that patient's subsequent hospitalizations were analyzed. If a patient was transferred in hospital or between Olmsted Medical Center and Mayo Clinic hospitals, this counted as a single hospitalization. Deaths among Olmsted County residents were obtained from inpatient and outpatient medical records and death certificates obtained on a yearly basis from Olmsted County and the state of Minnesota. In addition, the Mayo Clinic registration office records the obituaries and notices of death from the local newspapers.

STATISTICAL ANALYSES

All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute, Cary, NC). Cohort participants who took the MMPI were compared with those who did not take the MMPI, using χ^2 tests for categori-

TABLE 1. Characteristics of Persons Given the MMPI Compared With Persons Without an MMPI^a

	No MMPI (N=4852)	MMPI (N=799)	P value
Age (y), mean $\pm$ SD	71.0 $\pm$ 14.6	67.9 $\pm$ 13.9	<.001
Male, No. (%)	2607 (53.7)	443 (55.4)	.37
BMI (kg/m ²), median (25th, 75th percentile)	27.0 (23.7, 30.8)	27.2 (23.8, 31.2)	.13
Education, No. (%) ^b			.07
Less than high school	54 (28.0)	150 (19.5)	
High school degree	62 (32.1)	282 (36.8)	
Some college or college degree	63 (32.6)	263 (34.3)	
Graduate school	14 (7.3)	72 (9.4)	
Marital status at time of event, No. (%) ^b			.002
Single	13 (6.5)	50 (6.3)	
Married	110 (55.0)	495 (62.1)	
Divorced	13 (6.5)	90 (11.3)	
Widowed	64 (32.0)	162 (20.3)	
Current smoking status, No. (%)	1036 (21.4)	197 (24.7)	.04
Charlson comorbidity index, No. (%)			.03
0	1662 (34.4)	237 (29.8)	
1-2	1791 (37.0)	304 (38.2)	
≥ 3	1382 (28.6)	255 (32.0)	
Type of event, No. (%)			.001
Myocardial infarction	3054 (62.9)	551 (69.0)	
Heart failure	1798 (37.1)	248 (31.0)	
No. of MMPIs taken, mean $\pm$ SD	0	1.4 $\pm$ 0.8	...
Years between MMPI and event, mean $\pm$ SD	...	16.9 $\pm$ 9.9	...

^a BMI = body mass index; MMPI = Minnesota Multiphasic Personality Inventory.

^b Education and marital status were abstracted from a random sample of individuals with no MMPI (N=200) for comparison with those who had taken an MMPI.

cal variables, *t* tests for normally distributed continuous variables, and Mann-Whitney tests for skewed continuous variables. When multiple MMPIs were available for a participant, the responses from the first MMPI were used in the main analyses. Follow-up time was calculated from index date of MI or HF until death, last follow-up, or December 31, 2009, whichever came first. Outcomes were defined as hospitalizations and all-cause mortality and were compared for the following exposures: (1) depression vs non-depression, (2) anxiety vs non-anxiety, and (3) each of depression plus anxiety, depression only, and anxiety only vs no depression or anxiety. Cox proportional hazards regression was used to describe the associations between our exposures and all-cause mortality. For hospitalizations, Andersen-Gill modeling was used to model all hospitalizations after MI or HF in the subset of individuals with MI or HF events between 1987 and 2009. This analysis excluded 103 patients who had events before 1987 and 104 who died in hospital and thus had no time at risk for subsequent hospitalizations. Crude, demographic-adjusted (adjusted for age, sex, marital status, and education), and fully adjusted (adjusted for demographics, years between the MMPI and HF or MI event, and Charlson comorbidity index) models were run for both outcomes, with adjustment variables chosen a priori on the basis of assumptions of the potential confounding of these variables with the

exposure-outcome relationships. The proportional hazards assumption was tested using Schoenfeld residuals and found to be valid.

RESULTS

Between January 1, 1979, and December 31, 2009, we enrolled 3605 patients who had an MI and 2046 patients who had HF. Among these, 799 individuals had taken an MMPI before their CVD event. Individuals who had been given an MMPI were younger, more likely to be divorced, and exhibited a greater number of comorbidities at the time of their cardiovascular event compared with those who had never taken the MMPI (Table 1). On average, the first MMPI available had been given almost 17 years before the CVD event.

Of the 799 participants who had taken an MMPI, 282 (35%) were categorized as having marked depression, and 210 (26%) were considered to have high anxiety (Table 2). After a mean follow-up of 6.2 years (maximum, 29.5 years), individuals with depression or anxiety had, on average, more than one additional hospitalization compared with those without depression or anxiety. After adjustment for age, sex, marital status, education, years between the MMPI and cardiovascular event, and Charlson comorbidity index, persons with depression had a 28% (95% confi-

TABLE 2. Hazard Ratios for Hospitalizations and All-Cause Mortality by Depression and Anxiety^a

	Marked depression		Anxiety	
	No	Yes	Low	High
No. of patients	517	282	589	210
Mean hospitalizations (SD)	4.9 (5.1)	6.2 (6.7)	5.1 (5.5)	6.2 (6.5)
No. of deaths	265	169	321	113
HR (95% CI) for hospitalizations				
Crude	1.00 (ref)	1.36 (1.13-1.62) ^b	1.00 (ref)	1.23 (1.01-1.49) ^b
Demographic-adjusted ^c	1.00 (ref)	1.38 (1.16-1.65) ^b	1.00 (ref)	1.24 (1.01-1.52) ^b
Fully adjusted ^d	1.00 (ref)	1.28 (1.08-1.51) ^b	1.00 (ref)	1.26 (1.03-1.53) ^b
HR (95% CI) for all-cause mortality				
Crude	1.00 (ref)	1.22 (1.01-1.48) ^b	1.00 (ref)	0.94 (0.76-1.17)
Demographic-adjusted ^c	1.00 (ref)	1.46 (1.20-1.79) ^b	1.00 (ref)	1.16 (0.92-1.47)
Fully adjusted ^d	1.00 (ref)	1.23 (1.00-1.51)	1.00 (ref)	1.15 (0.91-1.45)

^a CI = confidence interval; HR = hazard ratio.^b *P* value <.05.^c Adjusted for age, sex, marital status, and education.^d Adjusted for age, sex, marital status, education, years between the Minnesota Multiphasic Personality Inventory and heart failure or myocardial infarction event, and Charlson comorbidity index.

dence interval [CI], 8%-51%) excess risk of hospitalization, whereas persons with anxiety had a 26% (95% CI, 3%-53%) excess risk of hospitalization. Depression was also associated with an increased risk of all-cause mortality; however, anxiety was not significantly associated with mortality. The combination of depression with anxiety appeared to be associated with a greater risk of hospitalization than either condition alone, although the interaction was not statistically significant. The hazard ratios for hospitalization were 1.35 (95% CI, 1.08-1.71) when depression and anxiety coexisted, 1.20 (95% CI, 0.93-1.57) for anxiety only, and 1.24 (95% CI, 0.98-1.57) for depression only compared with no depression or anxiety (Table 3).

In sensitivity analyses, the results for hospitalization and all-cause mortality did not differ when the models were further adjusted for the source of the MMPI or type of cardiovascular event. In addition, use of the MMPI closest to the cardiovascular event to categorize depression and

anxiety did not change the results. Finally, the exclusion of 35 hospitalizations due to anxiety or depression did not affect the hazard ratios for hospitalization (data not shown).

DISCUSSION

In this community-based cohort of individuals with CVD and extensive longitudinal follow-up, preexisting depression and anxiety, which occurred, on average, 17 years before the CVD event, were associated with a significant (28% and 26%, respectively) excess risk of hospitalization during an average of 6.2 years of follow-up after a CVD event. Depression also conferred an increased risk of all-cause mortality of similar magnitude, whereas the hazard ratio for anxiety was not statistically significant. Although not a statistically significant interaction, the combination of anxiety with depression led to an excess risk of hospitalization higher than either condition alone, suggesting

TABLE 3. Hazard Ratios for Hospitalizations and All-Cause Mortality Combining Depression and Anxiety^a

	Neither	Anxiety only	Depression only	Depression and anxiety
HR (95% CI) for hospitalizations				
Crude	1.00 (ref)	1.11 (0.85-1.45)	1.35 (1.06-1.71) ^b	1.40 (1.11-1.76) ^b
Demographic-adjusted ^c	1.00 (ref)	1.10 (0.85-1.42)	1.37 (1.08-1.73) ^b	1.42 (1.11-1.81) ^b
Fully adjusted ^d	1.00 (ref)	1.20 (0.93-1.57)	1.24 (0.98-1.57)	1.35 (1.08-1.71) ^b
HR (95% CI) for all-cause mortality				
Crude	1.00 (ref)	1.21 (0.86-1.72)	1.60 (1.26-2.04) ^b	0.99 (0.76-1.29)
Demographic-adjusted ^c	1.00 (ref)	1.16 (0.81-1.68)	1.59 (1.24-2.04) ^b	1.37 (1.04-1.82) ^b
Fully adjusted ^d	1.00 (ref)	1.23 (0.85-1.77)	1.30 (1.00-1.69)	1.21 (0.91-1.61)

^a CI = confidence interval; HR = hazard ratio.^b *P* value <.05.^c Adjusted for age, sex, marital status, and education.^d Adjusted for age, sex, marital status, education, years between the Minnesota Multiphasic Personality Inventory and heart failure or myocardial infarction event, and Charlson comorbidity index.

that the 2 conditions may act synergistically on increasing health care utilization in patients with CVD.

DEPRESSION AND CVD OUTCOMES

Depression contributes to both behavioral and physiologic changes, which increase the development and progression of CVD.^{1,25} In particular, psychosocial stressors contribute to a greater frequency of smoking and alcohol abuse, physical inactivity, poor dietary intake, and poor medication adherence.²⁵ In addition to behavioral modifiers, nervous system activation, hormonal variations, metabolic abnormalities, inflammation, hypercoagulability, increased platelet aggregation, and endothelial dysfunction are mechanisms that may play a role in the association between psychosocial factors and CVD.²⁶⁻²⁸

In observational studies, depression has been found to increase not only the incidence of CVD but also the risk of subsequent cardiovascular events and mortality in persons with a history of CVD. In a meta-analysis of 11 cohort studies, depression was associated with a 64% increased risk in development of fatal MI, nonfatal MI, or coronary heart disease death.⁴ Among the subset with clinical depression, the incidence of coronary heart disease was almost 3-fold higher than in those without clinical depression.⁴ Furthermore, depression is associated with an approximate doubling of new cardiovascular events or mortality in the 2 years after an MI, coronary artery bypass grafting, percutaneous transluminal angioplasty, or angiographic validation of coronary heart disease.^{3,5} Despite the strong associations of depression with CVD incidence and prognosis, several clinical trials implementing treatment with pharmacologic agents or cognitive behavioral therapy for depression in patients with CVD found only modest improvements in depressive symptoms and no significant effect of treatment on subsequent cardiovascular events or mortality.⁷ This apparent paradox is reminiscent of the challenges in assessing causation²⁹ and of the concept of programmatic research, whereby when a hypothesis meets a barrier, analyzing the elements of the theory can provide novel insights. Operationalizing this paradigm for depression requires, as was done herein, studying other psychosocial factors that, in combination with depression, may adversely affect outcomes in patients with CVD.

THE ROLE OF ANXIETY, IMPLICATIONS, AND FUTURE DIRECTIONS

Our community study evaluated the impact of anxiety as another psychosocial construct that adversely affects health care utilization and survival among patients with CVD. Although depression and anxiety individually increased the risk of hospitalization, the co-occurrence of depression and anxiety appeared to impart a greater adverse effect, augmenting the risk of hospitalization by 35% compared

with no depression or anxiety. Thus, psychosocial factors constitute important potential targets for interventions to reduce substantial and costly health care utilization, such as emergency department visits, outpatient visits, and office calls, in CVD.³⁰

Further, our study provides evidence that anxiety as another psychosocial dimension, distinct from depression, may interact synergistically with depression to increase hospitalizations and adversely affect overall survival after a CVD diagnosis. Although overlap between depression and anxiety has been demonstrated,^{31,32} only a few studies have investigated the combined effects of depression with anxiety on CVD.^{13,33-35} Among women, the joint effect of anxiety and depression symptoms predicted incident MI, HF, stroke, and death beyond individual symptom clusters.³⁴ The composite of depression and anxiety also conferred a larger risk of ventricular arrhythmias in patients with coronary disease than either condition alone.³⁵ In addition, comorbidity of major depressive disorder and generalized anxiety disorder predicted all-cause and cardiovascular mortality among Vietnam veterans.¹³ However, no added effect of anxiety and depression was detected in predicting clinical events during a limited follow-up period and among men only.³³ Our study results provide new knowledge indicating that depression and anxiety may have synergistic effects on outcomes in patients with CVD, including health care utilization.

A synergism in the effect of psychosocial factors on CVD outcomes may provide insights into the lack of benefit of treatment on survival in depressed patients with CVD. A post hoc analysis of the Enhancing Recovery in Coronary Heart Disease (ENRICH) trial found a 43% lower risk of death or recurrent MI among individuals taking a specific type of antidepressant, selective serotonin reuptake inhibitors, regardless of whether they were assigned cognitive behavioral therapy.³⁶ However, antidepressant use or cognitive behavioral therapy has not been shown to benefit survival in patients with CVD in most other studies.^{7,37} Targeting one specific psychosocial risk factor in patients with CVD may not be effective, and thus an inclusive approach targeting all psychosocial aspects collectively may be the best method for treatment interventions.³⁸

LIMITATIONS AND STRENGTHS

Some limitations should be acknowledged to help with data interpretation. The MMPI has a substantial participant burden and is less likely to be administered routinely in clinical practice compared with a shorter validated questionnaire, such as the 9-item depression module of the Patient Health Questionnaire (PHQ-9)³⁹ or the 7-item Generalized Anxiety Disorder Scale (GAD-7).⁴⁰ The MMPI was administered, on average, 17 years before the cardiovascular

event. Although it may have been ideal to have a measure closer to the time of CVD diagnosis, results did not differ when the MMPI closest to the event was used for the 23% of individuals who had been given more than one MMPI. Importantly, we have captured preexisting depression and anxiety instead of depression or anxiety that occurred as a result of the CVD event. Although it is likely that we have missed some individuals who developed depression and/or anxiety close to their CVD event, this misclassification would have resulted in our estimates being biased toward the null. We did not have information to adjust for any therapy for depression or anxiety, which may have attenuated our results and could have explained the lack of significant results for the association of anxiety with all-cause mortality. Although the characteristics of the Olmsted County, MN, population are similar to those of US whites, the generalizability of our results to other racial groups may be limited.

The strengths of this study include the defined community cohort of patients with CVD (including outpatients), rigorous validation of each event, and complete ascertainment of outcomes in Olmsted County through the record-linkage system. In addition, we have captured anxiety and depression that occurred before the CVD event, and thus our results reflect the impact of anxiety and depression that long predated the development of CVD, rather than occurring as a result of the development of CVD, on outcomes among patients after the development of CVD. Finally, we were able to assess the impact of these important psychosocial constructs, depression and anxiety, on health care utilization, seldom, if ever, evaluated in prior studies, and to delineate the combined effects of anxiety with depression on outcomes, areas of research that had not been adequately studied.

CONCLUSION

Both preexisting anxiety and depression are important risk factors for increased health care utilization in patients with CVD. In addition, the combined effect of anxiety with depression appeared to independently confer a greater impact on hospitalizations. Although further research is warranted to understand the mechanisms behind these observations, our data underscore the importance of a more comprehensive approach to assess multiple psychosocial constructs, including anxiety, to improve outcomes in patients with CVD.

We thank Susan Stotz, RN, Kay A. Traverse, RN, and Sheila M. McNallan, MPH, for their assistance in data collection; Ruoxiang Jiang for assistance with statistical analysis; and Kristie K. Shorter for secretarial assistance.

REFERENCES

1. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*. 1999;99(16):2192-2217.
2. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21(1):30-38.
3. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802-813.
4. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002;23(1):51-61.
5. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004;66(6):814-822.
6. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation*. 2008;118(17):1768-1775.
7. Thombs BD, de Jonge P, Coyne JC, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA*. 2008;300(18):2161-2171.
8. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. *Annu Rev Public Health*. 2005;26:469-500.
9. Shen BJ, Avivi YE, Todaro JF, et al. Anxiety characteristics independently and prospectively predict myocardial infarction in men: the unique contribution of anxiety among psychologic factors. *J Am Coll Cardiol*. 2008;51(2):113-119.
10. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56(1):38-46.
11. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol*. 2010;56(1):31-37.
12. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med*. 2010;72(6):563-569.
13. Phillips AC, Batty GD, Gale CR, et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam Experience Study. *Psychosom Med*. 2009;71(4):395-403.
14. Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996;71(3):266-274.
15. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108(20):2543-2549.
16. Prineas RJ, Crow RS, Blackburn HW. *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification*. Boston, MA: John Wright-PSG, Inc; 1982.
17. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993;88(1):107-115.
18. Dunlay SM, Weston SA, Redfield MM, Killian JM, Roger VL. Anemia and heart failure: a community study. *Am J Med*. 2008;121(8):726-732.
19. Roger VL, Weston SA, Gerber Y, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation*. 2010;121(7):863-869.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

21. Greene RL. *An MMPI Interpretive Manual*. New York, NY: Grune & Stratton, Inc; 1980:295.
22. Osborne D, Swenson WM, Pearson JS. *An MMPI Source Book: Basic Item, Scale, and Pattern Data on 50,000 Medical Patients*. Minneapolis, MN: University of Minnesota Press; 1973.
23. Krittayaphong R, Cascio WE, Light KC, et al. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosom Med*. 1997;59(3):231-235.
24. Graham JR. *The MMPI: A Practical Guide*. New York, NY: Oxford University Press; 1987.
25. Figueredo VM. The time has come for physicians to take notice: the impact of psychosocial stressors on the heart. *Am J Med*. 2009;122(8):704-712.
26. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. *Biol Psychiatry*. 2003;54(3):248-261.
27. Lippi G, Montagnana M, Favaloro EJ, Franchini M. Mental depression and cardiovascular disease: a multifaceted, bidirectional association. *Semin Thromb Hemost*. 2009;35(3):325-336.
28. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005;45(5):637-651.
29. Marmot M. Facts, opinions and affaires du couer. Presented at the Eighth Annual Meeting of the Society for Epidemiologic Research. Albany, NY: June 1975. Reprinted from *Am J Epidemiol*. 1975;103:519-526. *Int J Epidemiol*. 2009;38(4):903-907.
30. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115(5):e69-e171.
31. Denollet J, Strik JJ, Lousberg R, Honig A. Recognizing increased risk of depressive comorbidity after myocardial infarction: looking for 4 symptoms of anxiety-depression. *Psychother Psychosom*. 2006;75(6):346-352.
32. Martens EJ, Smith ORF, Denollet J. Psychological symptom clusters, psychiatric comorbidity and poor self-reported health status following myocardial infarction. *Ann Behav Med*. 2007;34(1):87-94.
33. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry*. 2008;65(1):62-71.
34. Rutledge T, Linke SE, Krantz DS, et al. Comorbid depression and anxiety symptoms as predictors of cardiovascular events: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *Psychosom Med*. 2009;71(9):958-964.
35. Watkins LL, Blumenthal JA, Davidson JRT, Babyak MA, McCants CB Jr, Sketch MH Jr. Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. *Psychosom Med*. 2006;68(5):651-656.
36. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*. 2005;62(7):792-798.
37. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women: the Women's Health Initiative (WHI). *Arch Intern Med*. 2004;164(3):289-298.
38. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull*. 2005;131(2):260-300.
39. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
40. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.