JAMES A. BLUMENTHAL, PhD
Department of Psychiatry and Behavioral Sciences,
Duke University Medical Center, Durham, NC

Depression and coronary heart disease: Association and implications for treatment

ABSTRACT

Growing evidence indicates that depression is an important primary and secondary risk factor for coronary heart disease (CHD). Depression is quite common among patients with CHD: prevalence estimates are 14% or higher, and an additional 20% of patients have subclinical or minor depression. This review summarizes evidence that depression is a risk factor for cardiac events in patients with established CHD, suggests potential mechanisms underlying the relationship between depression and adverse cardiac outcomes, and provides evidence for the efficacy of exercise in improving both depression and clinical outcomes in depressed patients with CHD.

Depression refers to an emotional condition ranging from a transient negative mood state of sadness or mild dysphoria to a chronic and severe psychiatric illness. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) identifies two depressive disorders: major depressive disorder (MDD) and dysthymic disorder.[1] The essential feature of MDD is a clinical course characterized by one or more major depressive episode (whose diagnostic criteria are presented in **Table 1**) without a history of manic, mixed, or hypomanic episodes. The diagnosis requires the presence of a total of at least five symptoms over a period of at least 2 weeks, which must include either depressed mood or loss of interest or pleasure. Dysthymic disorder is marked by mild depressive symptoms that are more chronic in nature, lasting at least 2 years.[1]

Minor depressive disorder (mDD) is not an official DSM-IV diagnosis but is used for research purposes; it is similar to MDD in duration but requires that only two to four symptoms be present.

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EPIDEMIOLOGY OF DEPRESSION

Depression is a widespread and often chronic condition. Lifetime prevalence estimates for MDD are approximately 15% to 20%;[2,3] 1-year prevalence estimates are 5% to 10%;[2,4] and point prevalence estimates range from 4% to 7%.[3,5] Moreover, MDD is characterized by high rates of relapse: 22% to 50% of patients suffer recurrent episodes within 6 months after recovery.[6]

Women are twice as likely as men to be diagnosed with MDD, with lifetime prevalence rates of 10% to 25% in women versus 5% to 12% in men.[1]

Although rates of depression do not appear to increase with age, MDD often goes undertreated in older adults[3] and in cardiac patients.[7]

DIAGNOSING AND ASSESSING DEPRESSION

The gold standard for diagnosing MDD is a clinical interview. Commonly used instruments include the Diagnostic Interview Schedule[8] and the Composite International Diagnostic Interview.[9] The Structured Clinical Interview for DSM-IV Axis I Disorders[10] and the Schedule for Affective Disorders and Schizophrenia[11] are frequently used semistructured interviews.

The most common clinical instruments for assessing the severity of depressive symptoms are the Hamilton Rating Scale for Depression (HAM-D),[12] which is a clinician-rated scale, and various psychometric questionnaires, including the Beck Depression Inventory (BDI)[13,14] and the Center for Epidemiological Studies Depression Scale (CES-D).[15]

THE DEPRESSION–HEART DISEASE LINK

Depression as a primary risk factor

Evidence that depression is a primary risk factor for coronary heart disease (CHD) in healthy individuals has been reviewed previously.[16] A recent meta-analysis of 11 prospective cohort studies of initially healthy individuals indicated that depression (either depressive mood or clinical MDD) conferred a relative risk of 1.64 for adverse cardiac events, including myocardial infarction (MI) and cardiac death; the presence

TABLE 1
DSM-IV criteria for major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). *Note:* In children and adolescents, can be irritable mood.
   (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
   (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
   (4) Insomnia or hypersomnia nearly every day.
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   (6) Fatigue or loss of energy nearly every day.
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
E. The symptoms are not better accounted for by bereavement, ie, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

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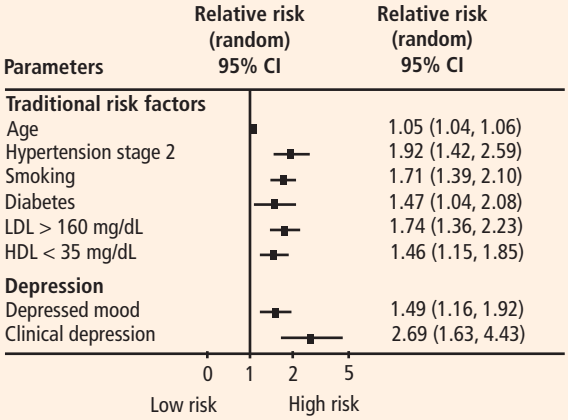

FIGURE 1. Risk ratios of traditional risk factors for coronary heart disease (CHD) observed in the Framingham study as compared with risk ratios of depressive symptoms and depressed mood as derived from the recent meta-analysis by Rugulies.[17] The risk of CHD conferred by depressive symptoms is comparable to that conferred by traditional risk factors, and the presence of clinical depression appears to raise this risk. For traditional risk factors, risk ratios were calculated for cardiac death, myocardial infarction, coronary artery insufficiency, and angina. For depressed mood and clinical depression, risk ratios were calculated for cardiac disease and myocardial infarction.[18]

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of MDD was associated with the greatest risk (relative risk of 2.69).[17] **Figure 1** shows that clinical depression is comparable to traditional risk factors for CHD, such as smoking and elevated blood lipid levels, as observed in the Framingham study.[18]

Depression as a secondary risk factor

Depression is an even stronger risk factor for cardiac events in patients with established CHD. Point estimates range from 14% to as high as 47%, with higher rates in patients with unstable angina and in patients awaiting coronary artery bypass graft (CABG) surgery; an additional 20% of patients exhibit elevated depressive symptoms or minor depression (mDD).[19–25]

Prospective studies have shown that depression increases the risk for death or nonfatal cardiac events approximately 2.5-fold in patients with CHD. For instance, Frasure-Smith et al followed 896 patients with a recent acute MI and found that the presence of depressive symptoms as indicated by an elevated BDI score was a significant predictor of cardiac mortality after controlling for multivariate predictors of mortality (odds ratio [OR] = 3.29 for women and 3.05 for men).[26]

Two recent meta-analyses confirmed the association between depression and adverse clinical outcomes in patients with CHD.[27,28] For example, van Melle et al reported that post-MI depression was associated with a 2- to 2.5-fold increase in the risk of adverse health outcomes.[28] In this analysis, depression's effect on cardiac mortality and all-cause mortality was especially pronounced in older studies (before 1992) (OR = 3.2) compared with more recent studies (after 1992) (OR = 2.01).[28]

Duke University researchers have conducted several

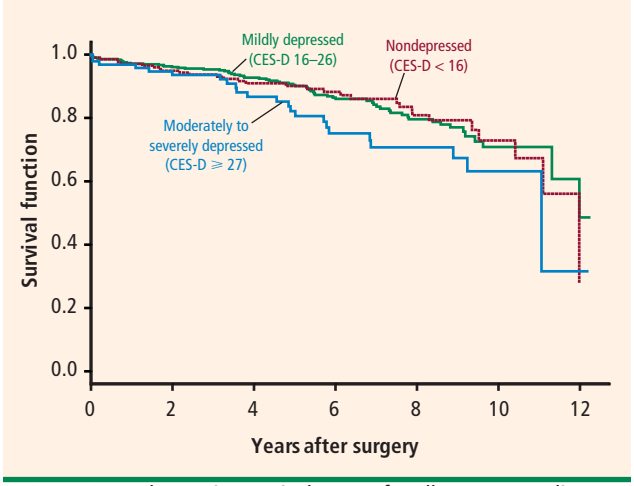

FIGURE 2. Kaplan-Meier survival curves for all-cause mortality among coronary surgery patients according to their presurgery (baseline) depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale (CES-D). Compared with the absence of depressive symptoms, the presence of moderate to severe symptoms was associated with a hazard ratio of 2.4 (95% CI = 1.40 to 4.00; $P = .001$) for all-cause mortality. Mild symptoms were associated with no difference in risk relative to the absence of symptoms (hazard ratio = 1.08, 95% CI = 0.70 to 1.67; $P = .723$).[30]

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prospective studies in various cardiac populations.[29–31] Barefoot et al assessed 1,250 patients with documented CHD using the Zung Self-Rating Depression Scale at the time of diagnostic coronary angiography and followed them for up to 19.4 years.[29] Results showed that patients with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all-cause death than were their nondepressed counterparts.

In a prospective study of patients undergoing CABG surgery, we assessed the effect of depression on mortality in 817 patients followed for up to 12 years (mean, 5.2 years).[30] Using the CES-D instrument, patients were categorized on the day before surgery as having either no depression (CES-D score < 16), mild depression (score of 16 to 26), or moderate to severe depression (score ⩾ 27). We found that moderate to severe depression was independently associated with a twofold to threefold increase in the risk of death, even after controlling for age, gender, number of grafts, diabetes, smoking, left ventricular ejection fraction, and history of acute MI **(Figure 2)**. Moreover, patients who exhibited persistent depression, with CES-D scores of 16 or greater at baseline and after 6 months, had more than a doubling in risk relative to patients who were never depressed.

We also recently reported results from a prospective study that followed 204 patients with heart failure over a median interval of 3 years.[31] Clinically significant symptoms of depression (BDI score ⩾ 10) were associated with a hazard ratio of 1.56 (95% CI, 1.07 to 2.29) for the combined end point of death or cardiovascular hospitalization. These observations included adjustment for plasma NT-proBNP level, ejection fraction, and other established risk factors, suggesting that heightened risk of adverse clinical outcomes associated with depressive symptoms is not simply a reflection of the severity of heart failure.

In summary, a number of observational studies have demonstrated that depression is associated with increased risk of morbidity and mortality both in healthy populations and in a variety of populations with established cardiac disease.

BIOBEHAVIORAL MECHANISMS LINKING DEPRESSION AND CHD

A number of biobehavioral mechanisms have been hypothesized to underlie the relationship between depression and CHD. Most evidence is derived from cross-sectional studies and suggests that depression is associated with traditional risk factors for CHD, such as hypertension, diabetes, and insulin resistance,[32,33] as well as changes in platelet reactivity,[34] dysregulation of the autonomic nervous system[35] and hypothalamic-pituitary-adrenal axis,[36] and alterations in the immune response/inflammation.[37] Depression is also associated with behavioral factors that are in turn associated with CHD risk, such as reduced treatment adherence,[38] smoking,[39] and physical inactivity.[40]

STUDIES OF DEPRESSION TREATMENT IN CARDIAC PATIENTS

Successful treatments for depression in patients with CHD may have the potential to improve not only quality of life but also cardiovascular and physical health. Several treatments for depression exist for use in the general population, such as antidepressant medication or psychotherapy.[41] However, only three studies have tested the efficacy of these treatments in patients with CHD: SADHART, ENRICHD, and CREATE.[42–44]

SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) was a safety and efficacy evaluation of antidepressant medication in patients with MDD and a recent MI or unstable angina.[42] It showed only modest differences in reductions in depressive symptoms between sertraline recipients and placebo recipients, and it lacked statistical power

to examine the impact of treatment on hard clinical end points.

ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) assessed the effect of psychosocial treatment on survival among more than than 2,400 post-MI patients.[43] Although this trial found that cognitive behavior therapy resulted in significant, albeit small, improvements in depressive symptoms compared with usual care, it failed to demonstrate that treating depression and low social support was associated with increased survival.

CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy), a recent placebo-controlled trial, assessed the value of antidepressant medication and clinical management in patients with CHD.[44] The study's 284 patients, all of whom had CHD as well as MDD and a HAM-D score of 20 or greater, underwent two separate randomizations: (1) to 12 weeks of interpersonal therapy plus clinical management or 12 weeks of clinical management alone, and (2) to 12 weeks of citalopram therapy or matching placebo. There was no difference between interpersonal therapy and clinical management alone; however, citalopram was superior to placebo in reducing HAM-D scores and demonstrated better remission rates (35.9% with citalopram vs 22.5% with placebo). The same therapists who provided interpersonal therapy also performed the clinical management, so it could be argued that this was why additional interpersonal therapist time did not result in greater reductions in depressive symptoms than did clinical management alone. Furthermore, this study did not examine the effects of depression therapy on clinical outcomes.

EXERCISE AS A TREATMENT FOR DEPRESSION

There is growing evidence that exercise may be an effective treatment for depression.[45] Most of the existing studies of exercise for depression have focused on aerobic exercise.

In the relatively large SMILE study (Standard Medical Intervention and Long-term Exercise),[46] conducted at Duke University, 156 adult noncardiac patients with MDD were randomized to 4 months of treatment with supervised aerobic exercise, antidepressant medication (sertraline), or a combination of exercise and medication. Although antidepressant medication was associated with faster reductions in depression in the first 4 weeks of treatment among mildly depressed patients, exercise was as effective as antidepressant medication in treating depression by the end of the 16-week intervention for all participants.

Six-month follow-up among patients from the SMILE study who had achieved remission revealed that those who had been randomized to exercise were less likely to have relapsed than those randomized to the medication or combination-therapy groups **(Figure 3)**.[47] Moreover, across the entire follow-up population, those patients who reportedly engaged in regular aerobic exercise during the 6-month follow-up period were only half as likely to have relapsed compared with those who did not engage in regular exercise.

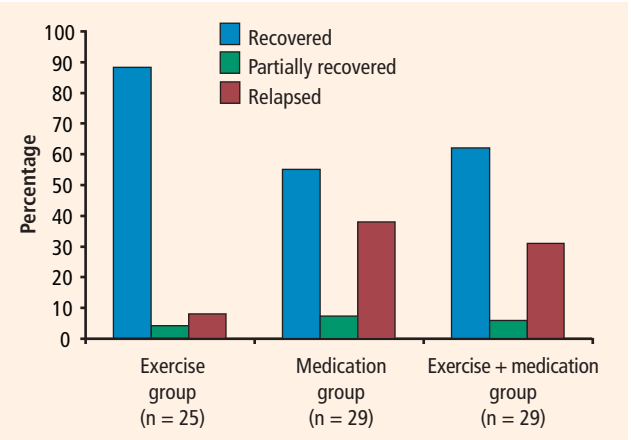

FIGURE 3. Clinical status at 10 months (6 months after end of treatment) among 83 patients who achieved remission from major depressive disorder following 4 months of treatment in the SMILE study,[46] according to the three treatment groups. Compared with participants in the other treatment groups, those in the exercise group were more likely to remain fully or partially recovered and less likely to have relapsed.[47]

Reprinted, with permission, from Babyak MA, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med 2000; 62:633–638.

Exercise generally is considered safe for most patients with stable CHD.[48] Some studies of exercise treatments for patients with CHD have tracked depressive symptoms and thus have provided insight into the potential efficacy of exercise as a treatment for depression in this population. Although most of these studies have reported significant improvements in depression after completion of an exercise program, many have had important methodologic limitations, including absence of a control group. In one of the few controlled studies in this area, Stern et al[49] randomized 106 men who had a recent acute MI and elevated depression, anxiety, or low fitness to 12 weeks of exercise training, group therapy, or usual care (control). At 1-year follow-up, subjects in both the exercise and counseling groups showed improvements in depression relative to controls.

EFFECT OF EXERCISE ON CARDIOVASCULAR RISK FACTORS AND OUTCOMES

Exercise is a particularly promising intervention for depression in patients with CHD because it has well-

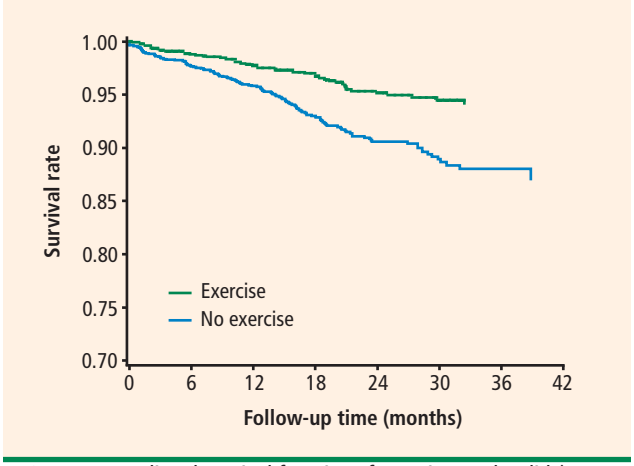

FIGURE 4. Predicted survival functions for patients who did (n = 952) and did not (n = 1,096) exercise regularly during the 6 months following an index myocardial infarction in the ENRICHD trial. There were a total of 187 fatal events; the mortality rate was 5.7% among the exercisers compared with 12.0% among the nonexercisers.[52]

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documented cardiovascular benefits. In addition to the well-established role of exercise interventions in primary prevention, such interventions have been shown to improve outcomes for patients with CHD.[50]

Jolliffe et al conducted a meta-analysis comparing exercise-only interventions, comprehensive rehabilitation (including educational and behavioral components such as dietary changes and stress reduction in addition to exercise), and usual care.[51] Exercise-only interventions were associated with reductions in both all-cause and cardiac mortality relative to usual care. Comprehensive rehabilitation, on the other hand, was not associated with statistically significant reductions in all-cause mortality relative to usual care, but it was associated with a decreased risk for cardiac mortality, to a slightly lesser extent than exercise-only interventions.

Recent data from the ENRICHD trial suggest that exercise may reduce rates of death and recurrent nonfatal infarction in post-MI patients with depression or low levels of social support.[52] Self-reported data were used to categorize participants as exercising regularly or not exercising regularly. After adjustment for medical and demographic variables, regular excercise was found to be associated with a nearly 40% reduction in the risk of death and a nearly 30% reduction in the risk of recurrent nonfatal infarction. **Figure 4** depicts the Kaplan-Meier survival curves for patients who did and did not exercise regularly.

The evidence that exercise affects depression, CHD risk factors, and CHD outcomes suggests that exercise is a particularly promising intervention for depression in this population.

UPBEAT trial promises further insight

A new Duke University study known as UPBEAT (Understanding Prognostic Benefits of Exercise and Antidepressant Treatment) is randomizing 200 patients with elevated depressive symptoms to exercise, antidepressant therapy (sertraline), or placebo for 4 months.[53] A variety of "biomarkers" of risk are being assessed, including measures of heart rate variability, vascular function, inflammation, and platelet aggregation. Results of this 5-year trial should be available by 2011.

CONCLUSIONS

Although depression has emerged as an important risk factor for CHD, there is no consensus on the optimal way to treat depression in patients with CHD. Interventions that are guided by an understanding of the mechanisms linking depression to CHD may prove to be most effective in improving both depression and physical health outcomes.

Exercise targets many of the mechanisms by which depression may be associated with increased risk, including autonomic nervous system activity, hypothalamic-pituitary-adrenal axis function, platelet activation, vascular function, and inflammation. Moreover, a growing body of evidence suggests that exercise is an effective treatment for depression that may be comparable in effect to antidepressant medication, at least in select subgroups (eg, patients who are receptive to exercise as a treatment for depression). The value of exercise training—not only for improving quality of life, but also for improving "biomarkers" of risk and other relevant health outcomes—is the focus of our current research efforts.

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Correspondence: *James A. Blumenthal, PhD, Box 3119, Duke University Medical Center, Durham, NC 27710; blume003@mc.duke.edu.*