
Depression— An independent risk factor for cardiovascular disease

The author describes how to screen for depression in patients with CVD and summarizes what studies say about why it is essential that you do so.

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Which of the following are risk factors for cardiovascular disease (CVD): (a) dyslipidemia; (b) cigarette smoking; (c) hypertension; (d) obesity; (e) depression; (f) all of the above? The correct answer is (f), all of the above. Physicians, PAs, and popular medical textbooks¹⁻⁵ all recognize the first four choices as important risk factors for cardiovascular disorders. However, major depressive disorder (MDD) remains an often unrecognized risk factor for the development of coronary artery disease (CAD) (see Table 1, page 42).

In numerous studies, depression has been shown to be associated with an increased risk of developing CAD.⁶⁻¹¹ MDD is also associated with higher morbidity and mortality in patients who have acute coronary syndromes (ACS); who have a history of MI,¹² coronary artery bypass grafting (CABG),¹³ or stroke,¹⁴ or who have heart failure (HF).¹⁵ Although MDD is present in approximately 20% of patients with CVD,¹⁶ most health care professionals do not routinely screen for depression or prescribe antidepressant treatment for patients experiencing this potentially deadly disorder. Recent studies have demonstrated that using the selective serotonin reuptake inhibitor (SSRI) class of antidepressants to treat depression in patients with CVD is safe and may actually help to improve outcomes in those patients.^{17,18}

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Depression and cardiovascular risk

Multiple studies have shown that depression is an independent risk factor for the development of CAD. The Cardiovascular Health Study followed 5,888 subjects older than 65 years without known current or prior CVD for up to 6 years.⁶ Results showed that risk for CVD and death increased by 40% and 60%, respectively, in those with high scores on a modified version of the Center for Epidemiological Studies Depression (CES-D) Scale. Higher depression scores were associated with higher morbidity and mortality. This study showed depression as an independent risk factor for cardiovascular events in elderly men and women.⁶

Another study reviewed data on 2,391 subjects older than 65 from the Established Populations for the Epidemiologic Studies of the Elderly, 1982-1991. Patients with a known prior MI were excluded, and other CVD risk factors were adjusted for. The investigators found that elderly women who had depressive symptoms had a higher incidence of cardiovascular events.⁷

A subgroup of the first National Health and Nutrition Examination Survey (NHANES) included 5,946 women and 3,560 men not known to have CAD who underwent screening for depression. Patients were followed for up to 10 years for development of cardiovascular events and cardiac-related deaths; these were found to be greater among the depressed subjects.⁹

Recently published results from the Women's Health Initiative (WHI) Observation Study followed 93,676 postmenopausal women for an average of 4.1 years. CVD had not been diagnosed previously in any of the participants. After adjustment for other cardiac risk fac-

tors, results showed that depression was an independent risk factor for developing and dying from CVD.¹⁰

Depression during hospitalization for CVD In one study, hospitalized patients with MI were screened, interviewed for depression, and followed for 6 and 18 months. After adjusting for other post-MI risk factors, the death rate was higher in those with depression.^{19,20} In a similar study of 430 patients with unstable angina, 41% were identified as depressed. Depression was associated with an increase in cardiac events and/or mortality during the 1-year follow-up.²¹

Depression increases morbidity and mortality Romanelli found that depressed patients older than 65 years who were hospitalized for acute MI were more likely to die within the first 4 months than were those who were not depressed.¹² At Duke University, Durham, NC, 1,250 persons undergoing cardiac angiography for CAD were screened for depression. This 19-year study showed that moderately to severely depressed patients had a 69% greater chance of death from CVD and that mildly depressed patients had a 38% greater chance of death from CVD than did those without depression.¹¹ Thus, not only is depression a risk factor for cardiovascular events, but the severity of the depression impacts the outcome.

Depression and HF Persons with HF and depression had more than twice the mortality of those with HF without depression. In one study, rehospitalization rates were also significantly higher in the depressed group.¹⁵ Jiang and colleagues followed 357 patients with HF for 1 year and found higher mortality and rehospitalization among the depressed group. The readmission rate was directly proportional to the severity of depression.²² Depression resulted in a 2.5-fold increase in the risk of developing HF among 4,538 patients in the Systolic Hypertension in the Elderly Program.²³

Depression after CABG At Duke University, depression was identified in 310 of 817 patients undergoing CABG. Depression status was evaluated again 6 months after surgery. At the 1-year follow-up, deaths were higher in the persistently depressed group than in those without depression.¹³

Depression and stroke Hass and colleagues evaluated 308 healthy subjects for depressive symptoms. None had a history of CVD. At 10-year follow-up, 219 of the participants underwent carotid ultrasonography. After adjusting for other cardiovascular risk factors, the depressed group was twice as likely to have carotid atherosclerosis as the nondepressed group.²⁴ Carotid atherosclerosis has also been closely associated with CAD.

Patients with CAD and its sequelae are not the only ones affected adversely by depression. The Multiple Risk Factor Intervention Trial enrolled 12,866 men without known CVD but at risk for it. After 6 years,

IN THIS ARTICLE

Key Points

- Major depressive disorder (MDD) remains an often unrecognized risk factor for the development of cardiovascular disease.
- MDD is also associated with higher morbidity and mortality in patients who have acute coronary syndromes; who have a history of MI, coronary artery bypass grafting, or stroke; or who have heart failure.
- Most health care professionals do not routinely screen for depression or prescribe antidepressant treatment for patients experiencing this potentially deadly disorder.
- Recent studies have demonstrated that using the selective serotonin reuptake inhibitor (SSRI) class of antidepressants to treat depression in patients with CVD is safe and may actually improve outcomes in those patients.

Competencies

Medical knowledge	◆◆◆◆
Interpersonal & communication skills	◆◆
Patient care	◆◆◆
Professionalism	◆
Practice-based learning and improvement	◆
Systems-based practice	◆

For an explanation of competencies ratings, see the table of contents.

there was both a higher stroke incidence and higher stroke mortality in the depressed group.¹⁴

Understanding the association

There is evidence supporting many theories of possible causes for the association between depression and CVD. One of them is medication noncompliance. Patients who suffer from depression and CAD adhere less well to their medication regimens than do those who are not depressed. One study showed that 69% of nondepressed subjects were adherent, while only 45% of the depressed group were.²⁵ Maximal medical therapy is well accepted as an important factor in the recovery of patients with CVD, and depression-related noncompliance can contribute to disease progression.⁵

Lifestyle The WHI Observation Study, which showed depression as an independent risk factor for CVD, also observed lifestyles. Obesity and smoking were significantly more prevalent in women who were depressed. Physical inactivity was also higher in this group.¹⁰

Heart rate variability Decreased heart rate variability has been shown to increase the risk of death in post-MI

patients, possibly due to increases in sympathetic tone and decreases in vagal tone that raise the potential for ventricular fibrillation. Depression has been associated with decreased heart rate variability. Carney and colleagues monitored variability in 100 patients screened for depression who had CAD by angiography. Interestingly, the depressed group had more severe CAD, which was controlled for in the study. Results showed that the depressed group had significantly lower heart rate variability, suggesting a higher risk of dying.²⁶ Carney also assessed heart rate variability in patients with and without depression in the ENRICH (Enhancing Recovery in Coronary Heart Disease) study, finding that depressed patients had significantly lower variability than those without depression.²⁷

Increased platelet activation/aggregation Higher levels of platelet factor IV and beta thromboglobulin have been demonstrated in depressed patients.¹⁶ Serotonin has been shown to increase platelet cytosolic calcium, which leads to an exaggerated platelet response and enhanced platelet aggregation.²⁸ Treating patients with CAD and depression with SSRIs may decrease this platelet alteration, thereby reducing cardiac risk.²⁹

Elevated C-reactive protein (CRP) This inflammatory marker is thought to be a predictor of CAD.³⁰ Ladwig and colleagues, using data from the MONICA-KORA Augsburg Cohort Study, found that the combination of depressed mood and an elevated CRP value was a predictor of MI in men.³¹ An analysis of data from NHANES III found that men with a history of depression were more than twice as likely to have elevated CRP levels than were those with no history of depression and that the more recent the depressive episode, the higher the odds of having elevations. In women, this association was quite weak.³² In contrast, Suarez found elevated CRP associated with depressive symptoms in both men and women.³³

Depression screening and diagnosis of MDD

Identifying MDD in patients with acute coronary events is challenging because symptoms of depression—fatigue, diminished energy, sleep disturbances, changes in weight or appetite—overlap with those of medical illness. In addition, patients with major depression often present with anxiety, irritability, complaints of pain, and excessive

worries about their physical health. Patients often fail to recognize their own depression, attributing symptoms to the cardiovascular event. A simple diagnostic tool can be helpful in screening for depression.

Screening instruments Several screening instruments for depression, based on the presence and severity of symptoms, are available and have recently been reviewed.³⁴ These include the Beck Depression Inventory, CES-D Scale, Depression Scale, Duke Anxiety-Depression Scale, Geriatric Depression Scale, Hopkins Symptoms Checklist, Primary Care Evaluation of Mental Disorders, Patient Health Questionnaire (PHQ), Symptom Driven Diagnostic System—Primary Care, and Zung Self-Rating Depression Scale. Williams and colleagues evaluated these instruments based on reviews of multiple studies that used them and validated the results with comparisons of assessments by mental health professionals. They concluded that there were no significant differences among the various screening instruments reviewed and that

all were useful for depression case finding.

In order to make a diagnosis of MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, the clinician must establish the presence of at least five out of nine diagnostic criteria, including at least one of the first two criteria listed below.³⁵ These nine diagnostic criteria for MDD are

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day
- Insomnia or hypersomnia nearly every day
- Substantial change in appetite nearly every day or unintentional weight loss or gain
- Fatigue or loss of energy nearly every day
- Psychomotor agitation or retardation nearly every day
- Diminished ability to think or concentrate, or indecisiveness nearly every day
- Feelings of worthlessness or excessive guilt nearly every day
- Recurrent thoughts of death or suicide.³⁵

Symptoms must be present for at least 2 weeks and must cause significant distress or impaired functioning to merit a diagnosis of MDD.³⁵ *Continued on page 44*

TABLE 1
Risk factors for cardiovascular disease

Advanced age
Anxiety
Atherogenic diet
Cigarette smoking
Depression
Dyslipidemia
Family history
Gender
Homocysteine level
Hypertension
Insulin resistance
Obesity
Physical inactivity
Postmenopausal status
Stress
Type 2 diabetes

Data from Fuster V, Alexander RW, O'Rourke RA, et al. *Hurst's The Heart*. 10th ed. New York, NY: McGraw-Hill; 2001.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)						
Name	Date					
Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day		
1. Little interest or pleasure in doing things	0	1	2	3		
2. Feeling down, depressed, or hopeless	0	1	2	3		
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3		
4. Feeling tired or having little energy	0	1	2	3		
5. Poor appetite or overeating	0	1	2	3		
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3		
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3		
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3		
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3		
Add columns		<input type="text"/>	+	<input type="text"/>	+	<input type="text"/>
Total		<input type="text"/>				
10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?		Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____				

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B. W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. PHQ-9 copyright © 1999 Pfizer Inc. All rights reserved. Reproduced with permission.

The PHQ-9 is a self-administered questionnaire that assesses each of the nine diagnostic criteria for MDD (see this page). A score of less than 5 represents a very low likelihood of depression; a score higher than 15 usually suggests the presence of major depression.³⁶ A study of 580 patients who completed the PHQ-9 and were then interviewed by a mental health professional who was blinded to the results showed that the test discriminates well between patients with major depression and those without depression.³⁶ PAs and other nonpsychiatric health care professionals can easily use an instrument

such as the PHQ-9 to screen patients for depression in any setting. A positive result on the screening instrument merits a clinical interview to confirm the diagnosis and determine appropriate treatment.

Treating MDD in patients with CAD

Although there have been no randomized, controlled clinical trials of antidepressant medication in patients with CAD that were adequately powered to demonstrate a meaningful cardiovascular risk reduction associated with the treatment of depression, there is some evidence that

treatment of depression post-MI with SSRIs may reduce the risk of mortality and subsequent cardiac events.

Two multicenter studies have looked at the treatment of depression in patients with ACS.

The Sertraline AntiDepressant Heart Attack Randomized Trial randomized 369 patients with MDD diagnosed during hospitalization for an acute MI or unstable angina to treatment with the SSRI sertraline or with placebo for 16 to 24 weeks. Patients assigned to sertraline had a significant improvement of depression compared to patients treated with placebo. There were no adverse effects on ejection fraction, BP, heart rate, or ECG intervals and no between-group differences in cardiovascular adverse events. The sertraline group developed slightly fewer cardiac events, but the difference was not statistically significant. The sample size in this study was too small to assess cardiac outcomes such as mortality or reinfarction rates.¹⁷

The ENRICH study, sponsored by the National Heart, Lung, and Blood Institute, randomized 2,481 patients with social isolation or depression following an acute MI to either cognitive behavior therapy (CBT) or usual care. Patients receiving CBT had modest improvements in depression. There were no significant differences in cardiac events or mortality between treatment groups.³⁷

A population-based case-control investigation using data from the United Kingdom General Practice Database compared 8,688 patients who had an MI between 1995 and 2001 with 33,923 selected controls. Current use of an SSRI was associated with a decreased risk of MI.¹⁸ Another case-control study evaluated first-time MI patients in 36 hospitals from 1998 to 2001 and found that treatment of depression with an SSRI was associated with a significant reduction in future MI.³⁸

Conclusion

Major depression is associated both with the development of CVD and with worse outcomes of existing CVD. MDD is prevalent but underrecognized and undertreated in patients with CVD, often resulting in greater morbidity and mortality. The AAPA reported in the 2005 PA Census that 89% of PAs work in clinical settings.³⁹ This puts the PA in an excellent position to screen for and identify depression in patients with CVD. In addition to providing relief for a painful illness that impairs function and quality of life, clinicians who enhance their recognition and treatment of depression may reduce the associated cardiovascular risk and improve overall cardiac outcomes. □

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