Depression and heart disease: What do we know, and where are we headed?

ABSTRACT

Depression and heart disease have an intricate association and perhaps a causal relationship. We review the current status of depression and heart disease and provide an algorithm for diagnosing and treating depression in cardiac patients that internists and cardiologists can use in their daily patient encounters.

KEY POINTS

Depression is a risk factor for new cardiac disease and has a detrimental impact in established cardiac disease.

Numerous mechanistic pathways have been implicated.

In clinical trials, drug therapy and psychotherapy have not clearly decreased the rate of cardiac death in depressed cardiac patients, but they did improve depression, adherence to drug therapy, and quality of life.

Clinicians should routinely screen for depression in cardiac patients and should not hesitate to treat it.

Eligible patients should routinely be referred to cardiac rehabilitation programs.

Depression is a risk factor for heart disease, and in patients with heart disease, it is a risk factor for complications and death. Unfortunately, in the trials performed to date, treating depression in cardiac patients did not lead to lower rates of recurrent cardiovascular events or death. Nevertheless, we recommend that clinicians systematically screen for it in their heart patients, in view of the benefits of antidepressant therapy.

In this article we review key epidemiologic and psychosocial studies, the mechanistic links between depression and heart disease, and recent intervention trials. We also offer practical management advice and address the continued need for guidelines and risk stratification in the treatment of depressed cardiac patients.

After we submitted our review article, the American Heart Association (AHA) released a consensus document recommending that health care providers screen for and treat depression in patients with coronary heart disease. We will discuss the same screening tests that have been recommended by the AHA.

DEPRESSION AND HEART DISEASE: COMMON AND LINKED

Depression and heart disease are very common and often coexist: the prevalence of depression in various heart conditions ranges from 15% to 20%. According to data from the World Health Organization, by the year 2020 depression will be the second-leading cause of disability in developed countries (after heart disease).
The World Health Survey showed that depression worsens health more than angina, arthritis, asthma, or diabetes. Furthermore, patients with severe mental illness have a higher risk of dying from heart disease and stroke.

SOME HEART DISEASE RISK FACTORS ARE PSYCHOSOCIAL

In the 1980s, the “type A” personality (ambitious, aggressive, hostile, and competitive, with a chronic sense of urgency) was linked to heart disease. Later studies differed as to whether the entire set of features is valid as a collective risk factor for progressive heart disease, but hostility remains a validated risk factor and a focus of behavior modification.

Other psychosocial risk factors have been implicated, one of which is social isolation. Another is the “type D” personality, which includes a tendency to experience negative emotions across time and situations coupled with social inhibition and which is believed to be more valid than the type A personality as a risk factor for cardiac disease.

The INTERHEART study gathered data about attributable risk in the development of myocardial infarction (MI) in 52 countries in a case-control fashion. Psychosocial factors including stress, low generalized locus of control (ie, the perceived inability to control one’s life), and depression accounted for 32.5% of the attributable risk for an MI. This would mean that they account for slightly less attributable risk than that of lifetime smoking but more than that of hypertension and obesity.

Job stress increases the risk of initial coronary heart disease and also the risk of recurrent cardiac events after a first MI. Even though numerous psychosocial risk factors have been associated with coronary heart disease, including anxiety, depression is perhaps the best studied.

PROSPECTIVE STUDIES OF DEPRESSION AND HEART DISEASE

To examine the impact of depression in coronary heart disease, prospective studies have been done in healthy people and in patients with established cardiovascular disease who develop depression.

In healthy people, depression increases the risk of coronary disease

The 1996 Epidemiologic Catchment Area study found that people with major depression had a risk of MI four times higher than the norm, and people with 2 weeks of sadness or dysphoria had a risk two times higher.

A subsequent meta-analysis of 11 studies, which included 36,000 patients, found that the overall relative risk of developing heart disease in depressed but healthy people was 1.64.

A meta-analysis by Van der Kooy et al of 28 epidemiologic studies with nearly 80,000 patients showed depression to be an independent risk factor for cardiovascular disease.

Wulsin and Singal performed a systematic review to see if depression increases the risk of coronary disease. In 10 studies with a follow-up of more than 4 years, the relative risk in people with depression was 1.64, which was less than that in active smokers (2.5) but more than that in passive smokers (1.25).

Depression can also exacerbate the classic risk factors for coronary disease, such as smoking, diabetes, obesity, and physical inactivity.

A 2007 study from Sweden prospectively followed patients who were hospitalized for depression. The odds ratio of developing an acute MI was 2.9, and the risk persisted for decades after the initial hospitalization.

A prospective United Kingdom cohort study of people initially free of heart disease revealed major depression to be associated with a higher rate of death from ischemic heart disease. Specifically, patients who had depression currently or in the past 12 months had a 2.7 times higher risk of dying than those who had never had depression or who had had it more than 12 months previously.

In existing heart disease, depression predicts recurrent events, death

Carney et al found that patients with major depressive disorder had a higher incidence of new cardiac events in the 12 months after undergoing cardiac catheterization than those without major depressive disorder.

Frasure-Smith et al, in a landmark study, showed that patients who were depressed at 1 week after an MI were three to four times...
more likely to die in the next 6 months than nondepressed post-MI patients. Even after 18 months, depression remained an independent risk factor for cardiac-related death.32

In longer studies (with up to 19.4 years of follow-up), depression was associated with higher rates of death from cardiac and all causes in patients with coronary artery disease.33 Lésperance et al34 found that in MI patients, the higher the Beck Depression Inventory score at the time of hospital admission, the higher the 5-year death rate.

Using meta-analysis, Barth et al35 found the risk of dying in the first 2 years after initial assessment to be twice as high in depressed cardiac patients as in nondepressed cardiac patients (odds ratio 2.24).

Van Melle et al36 reviewed 22 studies and found that in the 2 years after an MI, depressed patients had a 2 to 2.5 times higher risk of dying of a cardiac or any other cause than did nondepressed patients.

Depression also predicts higher morbidity and mortality rates in patients undergoing coronary artery bypass grafting,37,38 patients with congestive heart failure,39 and heart transplant recipients.40

Medical illness can predispose to depression, and vice versa

Medical illnesses can predispose a patient to develop depression. Specifically, compared with healthy people, cardiac patients appear to be at greater risk of developing depression for many years after the initial medical diagnosis is made.41

Katon et al42 reviewed 31 studies involving 16,922 patients, that assessed the impact of depression and anxiety in chronic medical illnesses such as heart disease, diabetes, pulmonary disease, and arthritis. After the severity of the medical disorder was controlled for, patients with depression and anxiety reported a higher number of medical symptoms.

Depression worsens quality of life and adherence to treatment

Depressed patients perceive their health status and quality of life negatively. In the Heart and Soul study,43 depressive symptoms and low exercise capacity—but not low ejection fraction or ischemia—were significantly associated with perceived deterioration of health in patients with coronary artery disease.

After an MI, patients who take their cardiac drugs properly have a better chance of survival.44,45 Clinical depression can worsen compliance with cardiac medication regimens,46 and reducing depression increases medication adherence overall.47 Not surprisingly, depressed patients also adhere less well to other recommendations,48 including modifying the diet, exercising, stopping smoking, and attending cardiac rehabilitation programs.49

Plausible mechanisms link depression and heart disease

Traditional cardiac risk factors such as smoking, high cholesterol, hypertension, diabetes, and obesity tend to cluster in depressed patients.50 Other mechanisms linking depression and heart disease are reviewed below.51,52

Autonomic imbalance

Excessive sympathetic stimulation or diminished vagal stimulation or both are associated with higher rates of morbidity and death.53 Lack of variability in the heart rate reflects a sympathetic-vagal imbalance and is a risk factor for ventricular arrhythmias and sudden cardiac death in patients with cardiovascular disease.54 Carney et al55 reported that patients with coronary artery disease and depression had significantly less heart rate variability than nondepressed cardiac patients. Similarly, after an MI, depressed patients had significantly less heart rate variability than nondepressed patients,56 implying that low heart rate variability may mediate the adverse effect of depression on survival after an MI.57

In the Heart and Soul study, Gehi et al58 found no distinct relationship between heart rate variability and depression. However, in the same study, de Jong et al59 did find specific somatic symptoms of depression to be associated with lower heart rate variability, although cognitive symptoms were not.

Platelet activation, endothelial dysfunction

Depressed patients have been found to have
exaggerated platelet reactivity. Plasma levels of platelet factor IV and beta-thromboglobulin, markers of platelet activation, are higher in depressed patients with ischemic heart disease than in nondepressed patients with ischemic heart disease and in control patients. This activation of platelets can lead to vascular damage and thrombosis.

In a subset study of the Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART), depressed MI patients were treated with sertraline (Zoloft), a selective serotonin reuptake inhibitor (SSRI), and had substantially less platelet and endothelial biomarker release.

Depressed cardiac patients also have impaired flow-mediated dilation of the brachial artery, a sign of endothelial dysfunction. Although a recent study did not find coronary endothelial dysfunction in depressed patients who did not have cardiac disease, these patients had more clustering of other cardiac risk factors.

Hypothalamic-pituitary-adrenocortical and sympathetic adrenal medullary activation
High cortisol levels can accelerate the development of hypertension and atherosclerosis and result in endothelial vascular injury. Sympathoadrenal activation in turn can lead to higher levels of catecholamines, predisposing to vasoconstriction, a rapid heart rate, and platelet activation. Depressed patients have more activation of the hypothalamic-pituitary-adrenocortical and sympathetic adrenal medullary systems, yet another plausible mechanism for worse clinical outcomes in depressed cardiac patients.

Sudden emotional stress can cause transient left ventricular dysfunction, even in people without coronary disease, an effect that may be mediated by elevated plasma catecholamine levels.

Inflammatory cytokines
Inflammatory cytokines play a key role in the development of atherosclerosis. C-reactive protein, an acute-phase reactant produced in hepatocytes, can be induced by cytokines such as interleukin 6. Damage to endothelial tissues leads to the release of inflammatory cytokines, including interleukin 1, interleukin 6, and tumor necrosis factor alpha.

Depressed patients have higher levels of these inflammatory markers. A prospective study reported direct correlations between depression scores and C-reactive protein levels in post-MI patients. The Heart and Soul study, however, did not confirm that coronary patients have more inflammation if they have depression, indicating that the relationship is complex and is perhaps more evident in specific types of depression.

Anticholinergic inflammatory pathway
Tracey proposed a theory that vagal tone inhibits the release of inflammatory cytokines. This has important implications for treatment, as exercise, biofeedback, and meditation can stimulate the vagus nerve and therefore have beneficial anti-inflammatory effects.

Polymorphism in the serotonin transport promoter region gene
Research is focusing on the serotonin transport promoter region gene (5-HTTLPR). The gene exists in two forms, a long one and a less-effective short one that appears to predispose to depression. Nakatani et al showed that MI patients were more likely to become depressed and to have subsequent cardiac events if one or both of their alleles of this gene were short. Otte et al, using Heart and Soul study data, found that patients with a short allele had a higher likelihood of depression, higher perceived levels of stress, and higher urinary norepinephrine secretion. However, the long allele genotype may be associated with a higher risk of developing an MI.

Our knowledge of the genetic interplay of depression and cardiovascular disease is still in its infancy, and further studies are needed to clarify these findings.

IN TRIALS, LESS DEPRESSION BUT NO EFFECT ON DEATHS, RECURRENT MI

Major behavioral and drug trials conducted in the last 15 years have focused on how to best treat depression in cardiac patients. The Montreal Heart Attack Readjustment Trial (MHART) used telephone calls and home nursing visits to explore and monitor psychologi-
cal distress for up to 1 year after an MI. The overall trial did not show these interventions to have any impact on survival compared with usual care. In fact, in women receiving the telephone intervention, there was a trend toward higher rates of cardiac and all-cause death, which was quite unexpected. Uncovering stresses and problems without resolving them, rather than encouraging patients to place these on the “back burner,” may partially explain these results.

SADHART\(^2\) studied the safety of sertraline in depressed post-MI patients. No major differences in cardiac function were noted between the sertraline and placebo groups, showing that sertraline was safe for these patients. The sertraline group had fewer cardiovascular events, but the difference was not statistically significant.

**TABLE 1**

**Screening tests for depression: The Patient Health Questionnaire (PHQ-9)**

Over the last 2 weeks, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th></th>
<th>NOT AT ALL</th>
<th>SEVERAL DAYS</th>
<th>MORE THAN HALF THE DAYS</th>
<th>NEARLY EVERY DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble falling asleep or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>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</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thoughts that you would be better off dead, or thoughts of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
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Add columns

**TOTAL**

* A total score of 10 or higher indicates depression.

**Two screening questions (PHQ-2)**

During the past month, have you often been bothered by being feeling down, depressed, or hopeless?

During the past month, have you often been bothered by little interest or pleasure in doing things?

* An answer of yes to either question should be followed up with the PHQ-9, above.
The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study was primarily designed to see whether a psychosocial intervention would decrease deaths in depressed cardiac patients. Much to the chagrin of behavioral medicine, the group undergoing cognitive behavioral therapy did not have a higher rate of event-free survival, although the intervention had a favorable impact on depression and social support.

The Myocardial Infarction Depression Intervention Trial (MIND-IT) looked at whether the antidepressant mirtazapine (Remeron) would improve long-term depression and cardiovascular outcomes in depressed post-MI patients. In 18 months of follow-up, neither objective was obtained.

The Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial tested the efficacy of the SSRI citalopram (Celexa) and interpersonal therapy in a short-term intervention. Here, the antidepressant was superior to placebo in the primary outcome of treating depression, but interpersonal therapy had no advantage over "clinical management," ie, a shorter, 20-minute supportive intervention.

Common threads in these studies.

- In ENRICHD and MIND-IT, patients whose depression did not respond to treatment were at higher risk of cardiac events.
- In SADHART and CREATE, which used drug treatment, the antidepressant response was more robust in patients with a history of depression before their heart attacks, suggesting that a patient with recurrent depression at the time of a cardiac event should receive medication for it.

Clinical recommendations

Use a depression screening tool
Ziegelstein et al recently studied the ability of clinical personnel to detect depression in hospitalized MI patients. If a screening tool was not used, the results were abysmal, indicating the need to use formal screening for symptoms of depression in acute MI patients.

Many self-rating scales are available, among which are the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS). Others are:

- The Patient Health Questionnaire (PHQ-9) is a nine-item tool, easy to administer and score (TABLE 1). It has been well studied in both screening for and follow-up of depression in primary care. It was used in the Heart and Soul study and the Prospective Registry Evaluating Outcomes After Myocardial Infarction: Events and Recovery (PREMIER) study. It has also been used to identify and document depressive symptoms in patients with acute coronary syndrome. A cut-off score of 10 or higher on the PHQ-9 is diagnostic of depression.

The PHQ-2 consists of the two first questions of the PHQ-9, which deal with mood and lack of pleasure. A cut-off score of 3 or higher has a sensitivity of 83% and a specificity of 92%, fulfilling the need for a quick and reliable depression screening tool. The clinician can also ask for a yes-or-no answer to the two questions of the PHQ-2 (TABLE 1). A yes to either of the two questions is up to 90% sensitive and 75% specific.

When to suspect depression in cardiac patients
Cardiac patients may not realize they have the classic symptoms of depression, since they often ascribe somatic symptoms to their heart disease and overlook emotional associations. Lespérance and colleagues suggest that certain clues should make us suspect depression in cardiac patients (TABLE 2).

Which type of psychotherapy is best?
The negative results of psychosocial interventions (phone calls and home visits from a nurse) in MHART and of cognitive behavioral therapy in ENRICHD raise questions about which type of psychotherapy is best for depression in heart disease. CREATE found that 50-minute weekly sessions of interpersonal psychotherapy were no more beneficial than clinical management, ie, 20-minute weekly sessions that focused on compliance with treatment and education about depression and overall management. Perhaps a type of therapy akin to "clinical management" in this study or the brief behavior-based and targeted therapy used in the Improving Mood Promoting Access to Collaborative Care Treatment...
(IMPACT) trials of depression in primary care could be designed specifically to treat depression in cardiac disease. However, it is also quite possible that treatments that focus on uncovering stresses or problems may not be timely for these patients.

**Which therapy is best for women** is another area of consideration. In MHART, even after 5 years of follow-up, women who received the psychosocial support intervention did marginally worse. In the ENRICHD study, women did not experience a benefit from cognitive behavioral therapy. Further studies must address sex differences in response to different therapies.

SSRIs seem to be better than other antidepressants for cardiac patients

Before SSRIs were available, tricyclic antidepressants were the mainstays. Subsequent analysis showed the tricyclics to have an unfavorable risk-benefit profile in cardiac patients, and since other types of antidepressants are available, tricyclics should be avoided altogether in cardiac patients.

Whether the SSRIs actually decrease one’s risk of death in heart disease is still an issue of debate, but there are encouraging signs. In SADHART, the rate of death and recurrent nonfatal MI was 20% lower in the patients randomized to receive sertraline, although the difference was not statistically significant. In ENRICHD, patients who did not respond to cognitive behavioral treatment or had severe depression could receive sertraline or other antidepressant drugs on a nonrandomized basis, and those who did had a 42% lower incidence of death or recurrent MI.

The SADHART and CREATE trials provide convincing evidence of the cardiac safety and antidepressant efficacy of two SSRIs (sertraline and citalopram) in depressed cardiac patients. Mirtazapine, studied in MIND-IT, was not effective in treating depression in cardiac patients, although it had a better adverse effect and safety profile than tricyclic antidepressants.

Clinical observations indicate that SSRIs are associated with less risk of MI than non-SSRI drugs. During hospitalization for acute coronary syndromes, patients on SSRIs had lower rates of recurrent ischemia and heart failure but higher bleeding rates than patients not taking SSRIs. In a retrospective study of patients undergoing coronary artery bypass grafting, those on an SSRI before surgery had higher rates of death and rehospitalization. Being on antidepressant medication could be interpreted as a surrogate marker of having more severe depression before surgery; this issue clearly requires further study.

Given current observations and recent data from interventional trials coupled with the safe drug-interaction profile of sertraline and citalopram, these two SSRIs are recommended for treating depression in cardiac patients. If the patient is also receiving an anticoagulant, one should monitor for bleeding, as all SSRIs are associated with a prolonged bleeding time. Monitoring for rare cases of hyponatremia and bradycardia should also be part of early follow-up.

**Do cardiac drugs have psychiatric effects?**

Some concerns have arisen about cardiovascular drugs causing or aggravating psychiatric conditions.
Statins were once suspected of causing clinical depression or even suicide. However, subsequent studies have not substantiated this. In fact, long-term statin use has been associated with improved psychological well-being. Whether the favorable psychological profile is due to an improved lifestyle, a direct noncholesterol effect, or an immunomodulatory effect has yet to be determined.

Beta-blockers have been suspected of increasing depression and fatigue. Robust meta-analyses have shown no increased risk of depressive symptoms but a small increased risk of fatigue and sexual dysfunction. Observational trials in the first year post-MI have shown no differences between beta-blocker users and nonusers in depressive symptoms or depressive disorders.

Statins and beta-blockers offer both immense cardiac benefit and low risk, and both may be prescribed with confidence in depressed cardiac patients.

Refer patients for cardiac rehabilitation
The American Association of Cardiovascular and Pulmonary Rehabilitation strongly recommends screening cardiac patients for depression and referring them to cardiac rehabilitation programs. Typical programs run 12 weeks, affording an opportunity to further listen to and assess the patient and to promote general wellness via nutrition, stress management, and exercise.

These interventions by themselves can favorably affect depression. Blumenthal and colleagues, in the Standard Medical Intervention and Long-Term Exercise (SMILE) study, found that exercise was as effective as
Whether depression causes heart disease is up for debate

Can we predict the course of depression?
We need to identify better which patients will have a spontaneous remission of their depressive symptoms after a cardiac event, which patients will linger with depression, and which patients will best respond to treatment. Risk stratification, using the psychiatric history, symptoms and severity of depression, and genetic predisposition might allow improved targeted therapies.

Does depression cause cardiac disease?
The link between depression and heart disease can be seen as merely an association. In the interventional trials performed to date, we have not yet seen a reduction in cardiac deaths when depression was treated, challenging any assumption of a causal relationship between depression and heart disease. The debate about association vs cause is germane to behavioral medicine, and the better we understand the mechanistic pathways, the better we can advise patients and treat depression comorbid with heart disease.

Behavioral medicine is currently measuring the aspects of depression associated with cardiac disease, including the spectrum of somatic (body) and affective (mood) symptoms and specific areas such as sympathetic arousal and early morning insomnia. If we can determine the depression subtype that carries a worse cardiac prognosis, we may untangle the biobehavioral links that bidirectionally bridge clinical depression and cardiac disease.

Another area of interest, emotional vitality (a positive state associated with interest, enthusiasm, excitement, and energy for living) has been shown to protect against coronary heart disease and holds much promise.

In the plenary lecture of the Academy of Psychosomatic Medicine in 2006, Frasure-Smith spoke of the “pleiotropism” of our antidepressant interventions on the various risk factors in depressed cardiac patients. We need behavioral medicine studies that elucidate these mechanisms, guiding more precise treatments as well as novel therapies. Omega-3 fatty acids, which benefit heart disease and clinical depression, will be used in a randomized controlled trial by Lespérance and colleagues. We await the results of this exciting research.

Will treating depression help in other types of heart disease?
The SADHART-CHF trial is examining whether 12 weeks of sertraline therapy is better than placebo in preventing death and improving cardiac outcomes in patients with chronic heart failure and comorbid major depressive disorder. It was to be completed in the fall of 2008. The results and experience of this study will help in designing future interventional trials to reduce the risk of depression in cardiovascular diseases.

We also await the results of a National Heart, Lung, and Blood Institute (NHLBI) trial, “Bypassing the Blues,” which is studying the treatment of depression after cardiac bypass surgery. This study should provide further insights into management of the depressed cardiac patient. Further prognostic studies in cardiac patients are also needed using the PHQ-9 and its shorter version, PHQ-2.

Current and future guidelines
For years our European colleagues have been ahead of us in recognizing depression screening and stress management as key to cardiac disease-prevention strategies. The NHLBI nicely outlined recommendations on the assessment and treatment of depression in cardiovascular patients. The just-published AHA Science Advisory should further encourage clinicians to screen and treat depression in the patient population. As our knowledge grows, we look forward to future evidence-based guidelines for depressed cardiac patients.
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