Depression and Cardiovascular Disease : A Call For Recognition

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Editorial

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A Call For Recognition

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For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.

— William Harvey

In 1628, William Harvey defined the circulatory system as we know it and proposed a link between the mind and the heart. This potential association received little attention for >300 years, until Frasure-Smith and colleagues[1] published a study demonstrating that patients who are depressed at the time of an acute myocardial infarction (MI) have markedly elevated mortality as compared with patients who are not depressed. Since then, >100 studies have investigated this relationship, providing evidence that depression is prevalent (≈20% to 35%) in populations with cardiovascular disease, is predictive of developing cardiovascular disease, and is predictive of adverse outcomes among patients with existing cardiac disease.[2,3] Depression, however, remains largely off the radar screen of cardiac care, in large part because of confusion about the nature of the association between depression and cardiovascular disease and the role of cardiovascular clinicians with regard to depressed patients.

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In this issue of *Circulation*, Mallik et al[4] add to our understanding of the relationship between depression and outcome in cardiac patients. Prospectively evaluating 963 coronary artery bypass graft (CABG) surgery patients, they found that 25% had substantial perioperative depressive symptoms. A graded, inverse relationship was noted between the severity of perioperative depressive symptoms and improvement in physical functional status 1 year after surgery. Patients with moderate to severe depressive symptoms were one third less likely to experience improvement in physical function after the operation, even after adjustment for >20 clinical variables. In other words, perioperative depressive symptoms appear to diminish the functional benefits of CABG surgery.

The study by Mallik et al is an important contribution for several reasons. First, depressive symptoms were a stronger predictor of lack of functional improvement than were variables such as previous MI, diabetes, and ejection fraction. This argues for the clinical importance of the association. Second, the relationship was more pronounced in women than it was in men. This may explain why women may derive less functional benefit from CABG surgery[5] and suggests the particular importance of considering depression as a cofactor among women undergoing cardiac surgery. Third, the focus on health status outcomes is to be commended. The vast majority of patients survive CABG surgery, and symptom burden, functional status, and quality of life outcomes are of central importance. These outcomes are arguably as important as any potential survival benefit of surgery because survival gain is limited to specific patient subsets and many patients express a desire for quality of life equal to or greater than their desire for quantity of life.[6]

This study, however, does not resolve the nature of the relationship between depression and cardiac disease. Is depression a causal risk factor, directly related to cardiovascular disease and outcome? Or is depression a risk marker, indirectly related to cardiovascular disease through behavioral variables? Or is depression a secondary event, elicited by major medical events such as cardiac surgery?

Depression is associated with several physiological derangements that could contribute to adverse cardiac outcomes.[2,3] Patients with depression have high sympathetic tone, hypercortisolemia, elevated catecholamine levels, abnormal platelet activation, increased inflammatory markers, and endothelial dysfunction. Importantly, these physiological derangements are present in depressed patients who do not have cardiac disease (ie, these mechanisms are linked to depression itself), and even when not actively depressed, patients with a history of depression have at least some of these abnormalities (eg, platelet activation) as compared with patients who are not depressed.[7]

Studies proposing various physiological mechanisms linking depression and cardiac disease tend to stand alone, begging the question of how these findings might be unified. One possible unifying hypothesis relates to emotional stress. Stress has been shown to be one of the most potent triggers or inducers of depression.[8] With stress, the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary (SA) system are activated. With resolution of stress, these 2 systems should return to their basal states. Genetic predisposition, such as specific serotonin transporter gene polymorphisms, coupled with gene–environment interaction may explain why some individuals recover from life stressors and others develop the disease of depression.[9]

In essence, patients with depression are in a constant state of perceived stress, with continuous upregulation of the HPA

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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

Total Score: 1-4 Minimal depression; 5-9 Mild depression; 10-14 Moderate depression; 15-19 Moderately severe depression; 20-27 Severe depression

axis and the SA system. In animal models, stress causes serotonin dysregulation, leading to decreased brain monoaminergic activity and the state of depression.[10,11] In turn, persistent HPA and SA activation lead to the observed downstream abnormalities in platelet function, autonomic tone, inflammation, and endothelial function. This unifying stress-response hypothesis suggests how depression could be a direct risk factor for both the development of cardiovascular disease and the increased morbidity and mortality for patients with preexisting disease.

Despite the evidence for physiological mechanisms, it is equally likely that behavioral mechanisms partially or wholly explain the association between depression and cardiovascular outcomes.[2,3] Compared with patients who are not depressed, patients who are depressed are significantly less likely to adhere to prescribed medications, follow lifestyle recommendations (eg, smoking cessation, exercise), practice self-management (eg, monitor weight and adjust diuretics in heart failure), and even follow up or receive recommended cardiac testing. It is disconcerting that when clinicians recommend a cardiac care plan and prescribe the best guideline-indicated therapies for our patients (eg, aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins), patients with substantial depressive symptoms simply may not adhere, thereby increasing their risk of adverse outcomes. In this scenario, depression itself is not a direct cause of adverse outcome but serves as a barrier to the delivery of optimal cardiac care.

Another possibility is that depression is a secondary development in cardiac patients, whereby patients with more severe cardiac disease or a heavier burden of comorbid conditions may become depressed in reaction to their illnesses. In this case, adverse outcome is the result of the greater disease burden but not of depression itself. Several factors mitigate against this explanation, at least as a sole mechanism for the association between depression and cardiovascular outcomes. Multiple studies, including that by Mallik et al,[4] have used robust risk adjustment for cardiac and noncardiac disease burden in their analyses. Accounting for these variables does not appear to eliminate the relationship, supporting the conclusion that depression is an independent predictor of outcome. Furthermore, depression precedes cardiovascular disease in multiple studies. In healthy cohorts, depression is predictive of first MI and cardiac death.[2,3]

We simply do not know at this time which mechanisms account for the relationship between depression and cardiovascular outcomes. Unfortunately, the intense focus on mechanistic relationships appears to be detracting from a clinical, patient-focused reality—the need for improved recognition and treatment of depression in cardiovascular populations. Irrespective of mechanism, several arguments can be made that depression should be detected and treated in cardiac patients:

- As a comorbid illness, depression is prevalent in cardiac patients and in and of itself is characterized by tremendous morbidity (eg, hopelessness, poor quality of life), as well as increased mortality risk through suicide.
- Depression is woefully underrecognized and undertreated in medical populations overall and certainly within cardiovascular populations.
- If depression is linked to cardiovascular disease through physiological mechanisms, then recognition and treatment may lead to improved patient outcomes through modification of the adverse physiological changes that accompany depression.

- If depression is linked to cardiovascular disease through behavioral mechanisms, then appropriate recognition and treatment may help remove the "depression barrier" and improve adherence to medications, lifestyle changes, self-management, and receipt of appropriate testing and follow-up.

To move past this point, 2 important questions must be addressed: (1) Does treatment of depression in cardiac patients make a difference? (2) To what degree should the recognition and treatment of depression be incorporated into cardiovascular care?

With regard to treatment, selective serotonin reuptake inhibitors (SSRIs) appear to be safe for use in cardiac patients and can improve both depressive symptoms and quality of life.[12,13] SSRIs increase brain monoaminergic levels and appear to reverse many of the physiological derangements associated with depression, as evidenced by normalization of urinary cortisol excretion, improved heart rate variability, reduced platelet activation, and reduced inflammatory markers.[12,14–16] Cognitive therapy also can be an effective treatment for depression when applied as an adjunctive therapy or as an alternative when drug therapy is not desired.[17]

Studies to date have not proven that treating depression can improve cardiovascular mortality and morbidity (eg, recurrent MI). However, the amount of investigation of this hypothesis has been minimal and lack of evidence is not proof of ineffectiveness. SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial) was a small safety study that found a trend toward reduced cardiovascular mortality and morbidity with SSRIs but was not powered for these outcomes.[12] The ENRICHD (Enhancing Recovery in Coronary Heart Disease) trial found that a post-MI cognitive therapy intervention improved depressive symptoms but did not reduce mortality.[17] In post-hoc analysis, however, patients in the ENRICHD trial who were treated with SSRIs had significantly lower overall and cardiovascular mortality. Observational data also suggest that SSRIs may be associated with a reduction in MI.[18] Clearly, further studies are needed to determine whether treatment of depression, particularly with SSRIs, can improve cardiovascular outcomes.

Importantly, this should not preclude the appropriate screening and treatment of depression in cardiac patients with the goal of improving depression itself. Depression is the third leading cause of morbidity in the world, and organizations such as the Institute of Medicine emphasize that depression screening and treatment should be a priority for US medicine in the 21st century.[19] By treating depression, we can improve the quality of life of our patients and we may improve adherence to cardiac care recommendations.

The next question is how to incorporate the recognition and treatment of depression into cardiovascular practice. Psychiatric diagnoses can carry a significant stigma in the perceptions of both patients and clinicians. Given the challenges of cardiovascular care, it is also difficult to promote the recognition and treatment of an additional condition. Nevertheless, as the population ages, multiple comorbid conditions are becoming the norm in cardiac patients. Because comorbid conditions strongly influence treatment plans and prognosis, it makes no sense to treat cardiovascular disease in a silo. Cardiologists should not become generalists, but modifying systems of care to facilitate the recognition of key comorbidities, including depression, can lead to the delivery of more patient-centric, higher-quality care. The availability of simple patient surveys for depressive symptoms suggests that depression screening can be integrated into routine cardiac care.

Recently developed depression screening questionnaires, such as the Patient Health Questionnaire (PHQ-9), are easy to administer and take ≤5 minutes for patients to complete (see the Figure).[20] A PHQ-9 score of ≥10 is 88% sensitive and specific for depression. Patients scoring above this level deserve consideration for treatment of depression. This tool can be administered in clinics, in waiting rooms, and before discharge from the hospital (eg, after CABG), and can be integrated into cardiac rehabilitation and disease management programs. Concern that screening for depression will cause patients to become depressed or suicidal is unfounded and cannot excuse the failure to screen.

Once significant depressive symptoms are identified, establishing a system to ensure appropriate consideration for treatment and follow-up is essential. Primary care clinicians can manage >75% of cases of depression, with psychiatric referral reserved for complicated cases (eg, depression with psychosis) and the most severe cases (eg, suicidal ideation).[21] Currently, if a cardiovascular clinician realizes that a patient has a comorbid condition such as diabetes or chronic obstructive pulmonary disease, the clinician either refers the patient to his or her primary care physician or the clinician initiates treatment and refers for follow-up. The same can and should be done for depression.

Future research will help us fully understand the mechanisms that link depression and cardiovascular disease, and studies should be designed to answer whether treatment of depression can improve cardiovascular mortality and morbidity. In the meantime, current American College of Cardiology/American Heart Association guidelines for CABG surgery, acute MI, and chronic angina all recommend evaluation for symptoms of depression and consideration of treatment of depression. The failure to recognize depression in patients with cardiovascular disease is a failure to provide the best care for our patients.

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