Depression and Cardiac Disease

A Review

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Abstract: Depression is highly prevalent in cardiac patients, with 20% to 40% of patients meeting criteria for major depressive disorder or experiencing an elevation in depressive symptoms. These depressive symptoms are often chronic and persistent, and they have been associated with the development and progression of coronary artery disease, worse health-related quality of life, poor physical functioning, recurrent cardiac events, and a 2- to 2.5-fold increased risk of mortality. Impaired adherence to health behaviors and adverse physiological effects of depression, including inflammation, endothelial dysfunction, platelet hyperactivity, and autonomic nervous system abnormalities, may link depression with adverse cardiac outcomes. Pharmacologic and psychotherapeutic interventions appear to be safe and effective at reducing depressive symptoms in patients with cardiovascular disease and may impact cardiac outcomes. Unfortunately, depression often is unrecognized and untreated in this population, despite the availability of brief screening tools that can be used for this purpose. We recommend the routine screening of cardiac patients for depression when there are adequate mechanisms for management and referral, such as available consulting psychiatrists or care management programs that facilitate the delivery of pharmacologic and psychotherapeutic treatments in this vulnerable population.

Key Words: depression, cardiac disease, coronary artery disease, congestive heart failure, collaborative care

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Depression commonly afflicts patients with cardiovascular disease (CVD) and contributes to poor psychiatric, functional, and cardiovascular outcomes. Despite the availability of safe and effective treatments in cardiac patients, depression remains under-recognized and undertreated in this population. This review will focus on the prevalence of depression in patients with CVD and its effects on psychiatric and cardiac outcomes, the potential physiological and behavioral links between depression and CVD, and the treatment options and models of care for depressed cardiac patients. Recommendations for the identification and treatment of depression in this population will be provided.

THE RELATIONSHIP BETWEEN DEPRESSION AND CARDIAC DISEASE

Depression is highly prevalent in cardiac patients. Between 31% and 45% of patients with coronary artery disease (CAD), including those with stable CAD, unstable angina, or myocardial infarction (MI), suffer from clinically significant depressive symptoms. Furthermore, 15% to 20% of patients with CAD meet full criteria for major depressive disorder (MDD),[1–5] a condition characterized by ≥2 weeks of depressed mood or loss of pleasure and multiple somatic symptoms (including abnormalities in sleep, interest, energy, concentration, guilt, appetite, psychomotor functioning, and/or suicidal ideation).[6] This rate of MDD is 2- to 3-fold higher in patients with CVD than in the general population[7] and similar to the rates of MDD in patients with chronic kidney disease,[8] cancer,[9] and diabetes mellitus.[10] Patients with congestive heart failure (CHF) and those undergoing implantable cardioverter defibrillator (ICD) placement are similarly at increased risk for elevated depressive symptoms and for MDD.[11–13] A recent meta-analysis of patients with CHF found a conservative (ie, MDD equivalent) prevalence rate of 20% and a liberal (ie, increased depressive symptoms) prevalence rate of 36%[11]; recent studies of ICD patients found depression prevalence to be 24% to 33%.[12,13]

In patients with CVD, depression is often chronic and recurrent. Among patients with CVD hospitalized for acute cardiac events and who were found to meet criteria for depression during or shortly after admission, approximately 50% to 70% have a history of depression that predates their cardiac events.[14,15] This finding is consistent with literature that describes persistent depression in patients with stable CAD[17] and suggests that for many patients, depression exists for months or years before a cardiac event, rather than being a transient reaction to the event. Furthermore, depressive symptoms often persist in patients with CVD. In studies that examine the course of post-MI depression, depressive symptoms remain at steady levels of severity over a 12-month follow-up period.[18,19] Similar results have been observed in patients with chronic CVD, such as those with ICD devices; in this cohort, 80% of patients who are depressed at the time of ICD placement continue to suffer from depressive symptoms 2 years later.[13]

In summary, depression is present in a significant portion of cardiac patients across the spectrum of cardiac disease, and such symptoms, when present, are likely to persist unless treated. These findings underscore the need to find better methods for identifying and managing depression in patients with CVD.

EFFECTS OF DEPRESSION ON PATIENTS WITH CARDIAC DISEASE

Depression is not only common in cardiac patients, but also associated with adverse cardiovascular outcomes, independent of traditional risk factors. In healthy individuals, depression has been associated with the development and progression of CAD[20–23] and with CVD-related mortality.[24] In patients with acute episodes of CAD who require intervention, depression is linked with inferior cardiac and functional outcomes. For instance, depression in patients undergoing coronary artery bypass graft (CABG) surgery has been associated with poorer functional outcomes,[25,26] worse health-related quality of life (HRQoL),[27] progression of atherosclerotic disease,[28] higher rates of rehospitalization,[26] and mortality.[29,30]

Patients with unstable CAD in particular seem to be at increased risk for poor outcomes as a result of depression. The presence of post-MI depression is a predictor for recurrent cardiac events,[31] for cardiac-related death,[31–34] and for all-cause mortality.[31,35] In fact, 2 recent meta-analyses revealed that depressed post-MI patients have a 2- to 2.5-fold increased risk (unadjusted) for all-cause mortality[31,35]; a significantly elevated risk remains (odds ratio, 1.76) even after adjusting for other

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cardiac risk factors.[35] The possible arrhythmogenic effects of depression may explain these findings—at least in part—because depression in patients with CAD has been associated with ventricular arrhythmias,[36] and ventricular ectopy in post-MI patients has been associated with mortality.[37]

Depression may also impact CV outcomes in patients with other forms of CVD. Depression increases the risk of incident CHF, especially in those already at increased risk for its development; it is also related to increased health care utilization, more frequent hospitalizations, and a 2-fold increase in mortality risk in patients with established CHF.[11] Increased depressive symptoms are also linked with recurrence of atrial fibrillation (AF) in patients following cardioversion[38] and with CV mortality in patients with comorbid AF and CHF.[39]

Several studies have evaluated the characteristics of psychiatric illness and its treatment that may contribute to poor cardiac outcomes in depressed cardiac patients. Nonresponse to treatment for depression, for instance, seems to put depressed postacute coronary syndrome (ACS) patients at greater risk for recurrent cardiac events[40] and for all-cause mortality.[41] Poor outcomes may be exacerbated by the presence of co-occurring anxiety, which is independently associated with recurrent cardiac events and mortality[42] and which has been linked with poor response to treatment for depression.[43,44] Other patients who seem to be at particularly high risk for poor outcomes include those with prominent anhedonia (the inability to experience pleasure)[45] and those with type D personality (a personality structure characterized by negative affectivity and social inhibition).[18]

Thus, not only is depression common and persistent in patients with CVD, but it also may have a negative impact on the course of their CV illness as manifested by physical functioning, quality of life, health care utilization, rehospitalization, and mortality. Treatment-resistant depression, in particular, appears to be associated with poor psychiatric and CV outcomes; this makes it crucial to accurately identify depression in patients with CVD.

POTENTIAL MECHANISMS LINKING DEPRESSION AND CARDIAC DISEASE

Several mechanisms, both behavioral and physiologic, may be implicated in the connection between depression and adverse cardiac outcomes.

Inflammation

The contribution of inflammation to the development of cardiac disease, and especially to acute cardiac events, is well-documented. Inflammatory cytokines have been associated with atherosclerotic plaque formation, progression, and rupture; as such they are major contributors to the pathogenesis of CAD, unstable angina, and MI.[46,47] Furthermore, inflammation plays a key role in the pathogenesis of certain types of CHF.[48,49] Thus, it is not surprising that inflammatory cytokines (ie, C-reactive protein [CRP] in CAD and interleukin-6 [IL-6] in CHF) have been independently predictive of cardiovascular mortality in healthy individuals[24] and in patients with CAD[50] and CHF.[51]

Depression has also been linked to increased levels of cytokines (specifically CRP, IL-1, and IL-6), both in patients with and without a history of cardiac disease.[20,52–54] Two studies provide evidence that inflammation associated with depression predicts the development of cardiac disease and CV mortality. In a population cohort study of 908 patients without known CVD, Kop et al[24] found that depression predicted cardiovascular mortality; controlling for inflammatory markers reduced the association by 12.7%, suggesting that inflammation modestly contributed to the effects of depression on CV mortality. Similarly, in a study of 559 women with suspected cardiac ischemia, Vaccarino et al found that depression predicted CV events; inflammatory factors (CRP, IL-6) reduced this association by 20%, again suggesting modest contributions to the effects of depression on cardiac events.[55] It, therefore, appears that inflammation plays at least a minor role in the mediation of depression's effects on cardiac outcomes.

Endothelial Dysfunction

Endothelial dysfunction has been linked with the development of ischemic CAD in patients with atherosclerosis.[56] Although a normal endothelium typically releases nitric oxide in response to serotonin, in atherosclerotic arteries it fails to do so; this results in vasoconstriction in areas of atherosclerosis and may provide a mechanism for coronary thrombosis.[57] Inflammation, which has been associated with CAD, also impairs endothelial nitric oxide release and may represent a mechanism explaining the finding of endothelial dysfunction in cardiac patients.[58] In addition to its role in cardiac ischemia in patients with CAD, endothelial dysfunction independently predicts mortality in patients with CHF.[59,60]

Depression has also been associated with impaired endothelial function in healthy patients,[61] in those at risk for CVD,[62] and in those with established CVD.[63] Evidence that treatment of depression with selective serotonin reuptake inhibitors (SSRIs) improves endothelial function in patients with depression and established CAD may provide further evidence that endothelial dysfunction is linked with a portion of depression's effects on cardiac outcomes.[64]

Increased Platelet Activity and Aggregation

Platelet aggregation and activity are also important components of cardiac disease, especially myocardial ischemia. Serotonin, a substance often implicated in the pathogenesis of depression, may play a key role in the formation of myocardial ischemia through its binding with 5-hydroxytryptamine receptors on platelets. In atherosclerotic arteries, whose endothelial cells are unable to release nitric oxide in response to serotonin, serotonin leads to platelet aggregation and to paradoxical vasoconstriction.[56,57] The finding that elevated levels of blood serotonin predicts CAD and future ischemic cardiac events in patients with suspected CAD provides suggestive evidence of serotonin's involvement in the development of myocardial ischemia in patients with CAD.[65] Furthermore, SSRIs, which theoretically deplete platelet serotonin stores by inhibiting platelet uptake of serotonin, have been shown to decrease platelet aggregation and activity in vitro and in patients with CAD.[66,67] Taken together, these findings lend credence to the theory that serotonin, through its activity on platelet aggregation, is associated with myocardial ischemia and other cardiac events.

Serotonergic and platelet dysfunction also occur in patients suffering from depression. Depressed patients have abnormalities in whole blood and platelet serotonin levels,[68] increased platelet serotonin receptor concentrations[69,70] and abnormally low platelet serotonin transporter levels,[71] suggesting that their platelets are both more sensitive to serotonin and less able to remove it from the bloodstream. Furthermore, there is evidence—albeit mixed—suggesting that the platelets of depressed patients are hyperactive.[68,72–74] This serotonergic and platelet dysfunction could mediate the increased risk for ischemic events in these patients.

Although much less is known about the association between platelet hyperaggregability and other forms of CVD, activity of depression through platelet hyperactivity and myocardial ischemia could contribute to the development of certain types of CHF, AF, and ventricular arrhythmias. Further research is needed to clarify the potential relationship between dysfunction of the serotonergic and coagulation systems in these patients.

Autonomic Nervous System Dysfunction

Abnormalities in the autonomic nervous system may also contribute to the relationship between depression and cardiac disease. As the heart is innervated by nerves from both the sympathetic

and parasympathetic nervous systems, the interplay between these 2 opposing forces helps the heart make changes in response to stressors and other situational factors. Patients with a history of ischemic heart disease or CHF typically exhibit a pattern of increased sympathetic and decreased parasympathetic activity, which is manifested by decreased heart rate variability (HRV) and decreased baroreflex sensitivity.[75] This pattern of autonomic dysfunction has been associated with increased mortality in patients with CHF[75] and a history of MI[75–77] and with increased rates of recurrent AF after cardioversion.[38] In animal studies, such a pattern of autonomic dysfunction was associated with increased rates of ventricular fibrillation during recurrent ischemic episodes[78] and may represent a mechanism by which autonomic dysfunction leads to increased morbidity and mortality in cardiac patients.

Depressed patients (with and without cardiac disease) also have reduced HRV,[79–81] suggestive of the same imbalance between sympathetic and parasympathetic nervous systems described previously. This reduction appears to be linearly associated with depression severity, with more severe depression resulting in greater reductions in HRV.[79] Furthermore, patients with CAD and depression have greater decreases in HRV compared with patients with depression or CAD alone, suggesting that the effects of depression and CAD on HRV are additive.[81] This increased autonomic dysfunction may be one mechanism whereby depression results in increased mortality in cardiac patients. Unfortunately, one recent meta-analysis found that antidepressant medications do not cause HRV to normalize in these patients.[79] This suggests that patients in remission from their depressive symptoms may remain at increased risk for adverse cardiac outcomes.

In addition to its effects on the heart, autonomic dysfunction may have an effect on the vasculature, including the coronary arteries. Depression has been linked to sympathetic nervous system dysregulation, with depressed patients having elevated levels of plasma epinephrine and norepinephrine (when compared with controls).[82] Increased sympathetic activity, which leads to elevated circulating catecholamines in the periphery (including the coronary vasculature), could lead to vasoconstriction, hypertension, platelet activation, and arrhythmia, all of which could lead to poor cardiac outcomes. Autonomic dysfunction has also been linked to increased levels of inflammatory cytokines in depressed patients[24,83]; because inflammatory cytokines are involved in progression of atherosclerosis, it is possible that these 2 mechanisms interact to increase morbidity and mortality in depressed cardiac patients.

Behavioral Factors

A number of behavioral factors are almost undoubtedly involved in the relationship between depression and cardiac disease. Depressed patients are less likely to engage in health-promoting behaviors, including maintenance of a healthy diet,[84] regular exercise,[84,85] adherence to medications,[84,86] stress reduction,[84] and completion of cardiac rehabilitation programs,[87,88] following MI. These patients also have more difficulty in lowering their cholesterol after MI[89] and may be at higher risk for recurrent cardiac events. The finding that medication nonadherence and lower physical fitness are associated with an increased risk of CV events in certain populations also suggests that the behavioral changes associated with depression may be associated with the progression of CAD and poor cardiac outcomes, both in patients with and without established CVD.[90,91]

TREATMENT OF DEPRESSION IN CARDIAC PATIENTS

Pharmacologic Interventions

Several pharmacologic interventions have been studied in depressed patients with CVD. Tricyclic antidepressants (TCAs), which act by increasing brain levels of serotonin, dopamine, and norepinephrine in addition to antagonizing histaminic, muscarinic, and alpha$_1$-adrenergic receptors, are among the oldest antidepressant agents.[92] Although these medications are effective for the treatment of depression, they are suboptimal in cardiac patients, given their propensity to cause orthostatic hypotension,[93,94] conduction disturbances,[93,94] and arrhythmias.[94] In fact, TCAs have been linked with significantly more frequent adverse cardiac events in patients with ischemic heart disease as compared with SSRIs.[95] Therefore, they should be avoided if safer alternative treatments are available.

Contrary to TCAs, SSRIs appear to be safe and effective in patients with both unstable[96–99] and stable CAD.[15,95] As their name implies, SSRIs block neuronal reuptake of serotonin, leading to elevated synaptic levels of the neurotransmitter. Unlike TCAs, SSRIs have minimal or no affinity for muscarinic, histaminic, and alpha$_1$-adrenergic receptors[92]; this likely accounts for their improved safety profile in patients with CVD.

Most studies of SSRIs in patients with CVD have focused on patients recruited during or shortly after hospitalization for an acute coronary event (ie, unstable angina or MI). Initial evidence that SSRIs might be helpful and safe in cardiac patients came in 1999, when Shapiro et al[98] performed an open-label study evaluating the safety, tolerability, and efficacy of sertraline in post-MI patients and learned that sertraline led to improvement in depressive symptoms without any increased risk of adverse cardiac events. Further suggestion of the potential efficacy of SSRIs in CVD patients came from a randomized, placebo-controlled trial of fluoxetine, which found higher 25-week response rates of fluoxetine-treated patients as compared with placebo-treated patients (48% vs. 26%, $P \leq 0.05$).[99] These 2 small studies sparked further investigation into the efficacy of SSRIs in patients with CAD (see Table 1 for a listing of major studies involving SSRIs).

The first large-scale study of SSRIs in patients with CAD was the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) trial, a randomized, double-blind, placebo-controlled trial of sertraline in post-ACS patients. This study found no significant differences between sertraline and placebo on left ventricular ejection fraction, premature ventricular contractions, QTc prolongation, or major adverse cardiac events.[97] It also noted higher depression response rates in the sertraline-treated group, especially in those patients with more severe depressive symptoms and in those with a history of depressive episodes. These findings suggested that sertraline was safe and effective for the treatment of depressive symptoms in post-ACS patients.

Further evidence for the efficacy of SSRI medications in depressed CAD patients came from the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) study, a 2 × 2 factorial trial that evaluated the efficacy of interpersonal therapy (IPT) and citalopram in 284 patients with stable CAD over 12 weeks.[15] In this study, citalopram was found to be superior to placebo in terms of decreasing depressive symptoms, increasing functional status, and improving interpersonal relationships. There were no differences between citalopram or placebo on any cardiac safety measure, suggesting that citalopram was safe and tolerable for patients with stable CAD.[15]

Although the efficacy of SSRIs for improving depressive symptoms in CAD patients is fairly well established, there is less data about its ability to improve cardiac outcomes. The SADHART study did find lower rates of cardiac events in sertraline-treated patients when compared with placebo, but these findings were not statistically significant.[97] The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study,[96] which evaluated the efficacy of cognitive behavioral therapy (CBT) in post-MI patients with minor or major depression, was more promising. Although the primary

TABLE 1. Major SSRI Treatment Trials for Depression in Patients With CVD

Study Name	Study Design	Study Size	Type of Cardiac Disease	Method for Depression Diagnosis	Intervention	Length of Follow-up	Psychiatric Outcomes	Cardiac Outcomes	Findings
Sertraline Antidepressant Heart Attack Trial (SADHAT)[98]	Open-label; no comparison group	N = 26 (all received sertraline)	CAD (post-MI)	Structured interview (DIS or SCID), with repeat SCID after 1 wk of placebo treatment to confirm diagnosis	Sertraline 50–200 mg daily (mean dose 79.8 ± 38.7 mg/d)	16 wk	17-item HRS-D, BDI, CGI	Heart rate, blood pressure, LVEF, arrhythmias, PR interval, QRS interval, QT interval, CV symptoms, PT, PTT, bleeding time	Sertraline led to depression response rates (50% reduction in HRS-D score) of 17% after 1 wk, 52% after 4 wk, and 74% after 16 wk and significant improvements on all depression scales.* There were no significant changes in cardiac outcome variables. Three patients (11.6%) withdrew early for mild adverse events. Two patients had MI during study, and 2 more had UA. Neither MI was attributed to study medication.
Strik et al[99]	Randomized, double-blind, placebo-controlled	N = 54 (27 fluoxetine, 27 placebo); patients enrolled 3–12 mo after event	CAD (post-MI)	HRS-D > 17, diagnostic checklist based on DSM-III-R criteria from SCAN	Fluoxetine 20–60 mg daily (mean dose 47.3 ± 19.1 mg/d)	25 wk	17-item HRS-D†, SCL-90 hostility score‡	Blood pressure, height, weight, LVEF, ATVI, EA ratio, HR, PR interval, QRS interval, QTc interval, cardiac rehospitalization, adverse events	At 25 wk, there were greater rates of response to fluoxetine compared to placebo.‡ Overall change in HRS-D score was not significant between groups. There were no significant differences in adverse effects between fluoxetine and placebo groups. At 25 wk, placebo-treated patients had greater increase in ATVI,‡ and fluoxetine-treated patients had a greater decrease in QRS interval.‡

(*Continued*)

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Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)[97]	Randomized, double-blind, placebo-controlled	N = 369 (186 sertraline, 183 placebo)	CAD (post-MI or UA)	Structured interview (DIS), with repeat after 2 wk of placebo treatment to confirm diagnosis	Sertraline 50–200 mg daily (mean dose 68.8 ± 40.1 mg/d)	24 wk	BDI,17-item HRS-D, CGI	LVEF†, HR, BP, PR interval, QRS interval, QTc duration, arrhythmias, HRV, laboratory studies, CV events	Sertraline led to superior CGI-I scores at 24 wk compared to placebo.§ In patients with recurrent depression, sertraline was better than placebo on both the CGI and HRS-D§. Sertraline also caused more response (CGI-I of "much improved" or "very much improved") in this subset of patients at 24 wk.§ There were no differences in LVEF or other CV variables between groups.
Canadian Citalopram Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE)[15]	Randomized, double-blind, controlled, parallel group 2 × 2 factorial design	N = 284 (142 citalopram, 142 placebo)	Stable CAD (h/o MI, revascularization procedure, or CABG)	Structured interview (SCID) with 4 wk duration and HRS-D ≥20	IPT plus clinical management vs. clinical management alone; citalopram vs. placebo	12 wk	24-item HRS-D†, BDI-II, IDS, FPI, IPRI	Blood pressure, EKG, adverse cardiac events	At 12 wk, citalopram was superior to placebo on all measures of depression (HRS-D§, BDI-II§, IDS‡, FPI‡, and IPRI§). There were no differences on EKG changes, blood pressure changes, or adverse cardiac events between citalopram and placebo groups.
Enhancing Recovery in Coronary Heart Disease (ENRICHD)[96]	Randomized, placebo-controlled	N = 2481 (1238 CBT, 1243 usual care)	CAD (post-MI)	Structured interview (DIS-H)	CBT (plus antidepressant if indicated) vs. usual care	6 mo of active treatment, minimum 18 mo follow-up (average 29 mo)	BDI, 17-item HRS-D, ESSI, PSSS	Recurrent MI†, all-cause mortality†, revascularization procedures, EKG, cardiac rehospitalization	CBT modestly but significantly improved BDI, HRS-D, ESSI, and PSSS compared to usual care.* CBT intervention had no effect on cardiac outcomes. Antidepressant use was associated with decreased risk of death or nonfatal MI.‡

(*Continued*)

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Study Name	Study Design	Study Size	Type of Cardiac Disease	Method for Depression Diagnosis	Intervention	Length of Follow-up	Psychiatric Outcomes	Cardiac Outcomes	Findings
Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF)[100]	Randomized, double-blind, placebo-controlled	N = 469 (234 sertraline, 235 placebo)	CHF (LVEF ≤ 45%, NYHA class II to IV)	DSM-IV criteria	Sertraline 50–200 mg daily (mean dose 65 ± 29 mg/d)	12 wk	17-item HRS-D†, somatic side effects	Composite CV score‡, adverse cardiac events	Both placebo and sertraline caused significant decreases in HRS-D scores*, but there were no differences between treatments on psychiatric outcomes. There were no differences between groups on CV composite score, CV adverse events, or other serious adverse events.

BDI indicates Beck Depression Inventory; BDI-II, Beck Depression Inventory II; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CBT, cognitive behavioral therapy; CGI, Clinical Global Impression Scale; CGI-I, Clinical Global Impression, Improvement Subscale; DSM-IV, Diagnostic Statistical Manual, fourth edition; DIS, Diagnostic Interview Schedule; DIS-H, Diagnostic Interview Schedule with Hamilton Rating Scale; EKG, electrocardiogram; ESSI, Enhancing Recovery in Coronary Heart Disease Patients Social Support Instrument; FPI, Functional Performance Inventory; CHF, congestive heart failure; HR, heart rate; HRS-D, Hamilton Rating Scale for Depression; IDS, Inventory of Depression Severity; IPRI, Interpersonal Relationships Inventory; IPT, interpersonal psychotherapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PSSS, Perceived Social Support Scale; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID, Structured Clinical Interview for DSM-IV Diagnosis.

*$P \leq 0.001$.
†Primary outcome variable.
‡$P \leq 0.05$.
§$P \leq 0.01$.

focus of the study was on a psychotherapeutic intervention, patients were allowed to start on antidepressant treatment in an open fashion if their depressive symptoms failed to respond after 5 weeks of CBT treatment or if their depression was severe (Hamilton Rating Scale for Depression ≥24) at the study's outset; in addition, subjects in the usual care arm may have received antidepressants from their primary medical providers. At 6 months, patients in either study arm who were taking antidepressants (most commonly an SSRI) had significantly lower rates of death and recurrent MI as compared with those who were taking no antidepressants.[96] These findings must be interpreted with caution, however, as the administration of antidepressants in this study was neither randomized nor blinded. Most other studies have not found significant decreases in recurrent cardiac events and mortality in SSRI-treated patients but were not sufficiently powered to do so.[98,99] With respect to population studies, one epidemiologic study found a significant mortality benefit associated with SSRIs. In a study of 15,390 Finnish patients with a history of a suicide attempt, SSRIs significantly decreased the mortality risk associated with CV and cerebrovascular disease when compared with no antidepressant use (relative risk, 0.42; 95% confidence interval, 0.24–0.71; $P = 0.001$).[100] This finding suggests that SSRIs may improve cardiac outcomes in patients with CVD and highlights the need for further investigation in this area.

There has been less formal study of antidepressant efficacy in patients with CHF. The SADHART-CHF trial, the only study designed to answer this question, was a randomized, double-blinded, placebo-controlled study that found that sertraline along with nurse-facilitated support did not improve psychiatric or cardiac outcomes compared with nurse-facilitated support alone.[101] Although another study evaluating the efficacy of citalopram in CHF patients is underway,[102] there is not enough evidence to make recommendations regarding the utility of antidepressant treatment in these patients at this time.

Fewer data are available about the efficacy and safety of other antidepressants in the treatment of cardiac patients with depression. Mirtazapine, a 5HT-2 and alpha-2 receptor antagonist, was found (in a randomized trial of post-MI patients) to provide some benefit for depressive symptoms without significant CV side effects, but it did not impact mortality or rates of recurrent cardiac events.[103,104] Mirtazapine has been associated with weight gain and hyperlipidemia, making it a less-than-ideal medication in those with established cardiac disease. Bupropion, a dopamine and norepinephrine reuptake inhibitor, has been studied for smoking cessation in post-ACS patients and has been found safe in this population at full antidepressant doses.[105] However, it has not been studied for depression in these patients and therefore is a second-line treatment as well. Venlafaxine and duloxetine, both serotonin and norepinephrine reuptake inhibitors, have not been formally studied for depression in cardiac patients; given the propensity of venlafaxine to increase blood pressure, it should not be considered unless SSRIs have failed to treat a patient's symptoms.

Psychotherapeutic Interventions

There is also evidence for the efficacy of psychotherapeutic interventions in depressed cardiac patients. One recent meta-analysis evaluating the benefits of psychological treatments in this population revealed significant short-term reductions in mortality, particularly among men; these reductions in mortality decreased over time.[106] However, this meta-analysis included numerous studies with different modalities of psychotherapy, making it difficult to identify one particular type of therapy that is helpful in reducing mortality. Therefore, more recently, researchers have gravitated toward studying more regimented psychotherapeutic interventions. IPT and CBT, forms of short-term, manualized psychotherapy, often are used in the treatment of depression. IPT focuses on improving depressive

symptoms, self-esteem, and interpersonal relationships, whereas CBT focuses on improving the patient's ability to recognize how their thoughts, feelings, and behaviors interact to cause depression or other symptoms.[92,107,108] Both treatments are time-limited (typically lasting for 12–16 sessions) and have been shown to be effective in the treatment of depression in patients without cardiac disease.[92,107,108] More recently, these forms of psychotherapy have been studied in cardiac patients as well. In the ENRICHD study,[96] 2481 post-MI patients with major or minor depression or low perceived social support were randomized to either receive usual care or CBT for a maximum of 6 months. Depressed patients and those with low perceived social support in the intervention group experienced modest, statistically significant improvements in depressive symptoms and social support scores during the initial 6-month treatment period. However, these improvements faded over time. Furthermore, no significant differences between groups were found in terms of recurrent MI or death.[96]

Freedland et al[109] also studied the efficacy of CBT in the treatment of depressed patients with CAD. They recruited 123 patients with major or minor depression who had undergone CABG surgery within the past year and randomized them to receive CBT, supportive stress management, or usual care. Patients in the CBT and supportive stress management groups experienced significantly higher rates of remission from depressive symptoms at 3 months compared with the usual care group (71% vs. 57% vs. 33%, respectively; $P = 0.002$), but only the patients in the CBT group had higher rates of remission at 9 months. The CBT intervention also resulted in greater improvements in anxiety, hopelessness, perceived stress, and mental HRQoL compared with usual care.[109] These findings suggest that CBT is an effective treatment for depression in post-CABG patients.

The CREATE trial evaluated the efficacy of citalopram and IPT, using clinical management as a control, in patients with moderate to severe depression and stable CAD.[15] While both IPT and clinical management caused reductions in depressive symptoms, clinical management appeared to be more effective at doing so than IPT, particularly in patients with few social supports and poor function at home.[15] These findings call into question not only the effectiveness of IPT in patients with depression and CVD, but also suggest that certain aspects of clinical management may be beneficial for depressed patients at risk for recurrent cardiac events. Further research is needed to determine which aspects of clinical management (eg, increased number of treatment contacts, supportive relationships with treatment team) are helpful for patients.

Further evidence for the efficacy of psychotherapy in cardiac patients comes from the collaborative care literature (described later). Collaborative care interventions and other care management programs, which often contain a psychotherapy component (eg, problem-solving therapy, behavioral activation, motivational interviewing) as part of their treatments, have led to improvements in depressive symptoms, anxiety, mental-HRQoL, and functional status.[109a,110–112] Many patients receiving collaborative care do not receive medications; therefore, it can be inferred that the psychotherapy components of the interventions are responsible for some of the beneficial effects seen in patients receiving these treatments.

CLINICAL MODELS FOR THE MANAGEMENT OF DEPRESSION IN CARDIAC PATIENTS

Identification of Depression in Cardiac Patients

Despite the existence of effective and safe treatments for depression in cardiac patients, it still remains under-recognized and under-treated in this population.[113,114] In one study of post-MI patients, less than 15% of depressed patients were accurately identified as such by their treatment teams, and only 11% received treatment with antidepressants.[113] Given the increased morbidity and mortality associated with depression, it is important that these patients be more consistently identified.

Routine screening of cardiac patients for depression is one possible way to improve detection of depression in this patient population. The American Heart Association recommends such screening using the 2- and 9-item Patient Health Questionnaires (PHQ-2 and PHQ-9, respectively),[115–117] 2 brief screening tools for depression. Both screening tools focus on the frequency that patients suffer from specific depressive symptoms, with the PHQ-2 focusing on depressed mood and anhedonia and the PHQ-9 focusing on the 9 criteria of MDD (Tables 2 and 3). The PHQ-9 has been found to be both sensitive and specific for diagnosing MDD, and it has been used successfully on inpatient cardiac units with good acceptance by staff and patients.[118] Both screening tools are time-efficient and could be integrated into standard inpatient and outpatient evaluations.

At the present time, there has been minimal study from randomized controlled trials (RCTs) to ascertain whether depression screening followed by referral to treatment affects cardiovascular or psychiatric outcomes.[4] Critics of universal screening have, therefore, suggested that the recommendations of the American Heart Association be reconsidered.[4,119] Specific concerns have included potential misdiagnosis of patients with screening tools if patients with positive screens do not undergo confirmatory psychiatric interviews, unnecessary stigma for patients who may be misdiagnosed, and lack of evidence regarding the cost-effectiveness of screening programs.[119]

Although there is no evidence that systematic depression screening in cardiac patients alone is beneficial, there is evidence for efficacy when screening is paired with a collaborative care program to treat depression.[110–112] Therefore, some proponents of universal screening suggest that screening could be performed when a collaborative care treatment program is available for patients who might screen positive.[120] Such a policy would ensure that those patients would undergo a more thorough evaluation for depression and would have resources available for treatment.

TABLE 2. Patient Health Questionnaire 2 (PHQ-2)[117]*

	Not At All	Several Days	More Than Half the Days	Nearly Every Day
Over the past 2 wk, how often have you				
Lost interest or had little pleasure in doing things	0	1	2	3
Felt down, depressed, or hopeless	0	1	2	3

Total score = sum of 2 items.

PHQ-2 score ≥3 is suggestive of elevated symptoms of depression.

*The PHQ-2 was developed by Dr. Robert L. Dr. Spitzer, Dr. Janet B.W. Williams, Dr. Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc.

TABLE 3. Patient Health Questionnaire 9 (PHQ-9)[116]*

	Not At All	Several Days	More Than Half the Days	Nearly Every Day
Over the past 2 wk, how often have you been bothered by the following?				
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
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
Thoughts that you would be better off dead, or of hurting yourself in some way.	0	1	2	3
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

Total score = sum of 9 items.

*The PHQ-9 was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc.

Care Management Programs

Collaborative care and related care management programs are one way to improve the identification and treatment of depression in patients with cardiac disease. Although each program is unique, most collaborative care programs usually involve a nurse or social work case manager who interacts with the patient, a consulting psychiatrist, and primary medical care provider to coordinate the patient's treatment among several providers. Collaborative care programs that focus on depression treatment have been effective in a variety of patient populations, including primary care patients,[121] the elderly,[122] and those with chronic medical problems, such as diabetes mellitus,[123] arthritis,[122] or cancer.[124] Furthermore, studies generally find that collaborative care interventions do not significantly increase costs compared with usual care.[122,125,126]

The use of collaborative care programs for the treatment of depression in cardiac patients has also been studied. (Table 4). In a RCT of collaborative care treatments in post-CABG patients, Rollman and coworkers[111] created a telephone-based, collaborative care depression treatment that resulted in greater improvements in mental HRQoL, physical function, mood symptoms, and rates of depression response at 8 months.[111]

Huffman et al[112] performed a similar telephone-based, RCT in patients admitted to inpatient units after an acute cardiac event (defined as unstable angina, MI, CHF exacerbation, or arrhythmia). Depressed patients randomized to the collaborative care group were contacted by a social work care manager, who discussed the patient's symptoms as well as treatment options including pharmacotherapy or a referral for psychotherapy. This intervention was associated with improvement of depressive symptoms, less anxiety, better mental HRQoL, fewer cognitive symptoms of depression, and higher rates of depression response, at 6 and 12 weeks. At 6 months, the intervention also resulted in reduction in the number and intensity of cardiac symptoms and greater self-reported adherence to specific health behaviors.[112]

Finally, Davidson et al[110] performed an RCT of another care management model in post-ACS patients. Patients randomized to collaborative care could choose to start pharmacotherapy, in which case they were seen by study psychiatrists every 1 to 2 weeks until on a stable dosage of a medication, or problem-solving therapy in which case they were followed by another mental health clinician on a weekly basis. The collaborative care intervention led to greater reductions in depressive symptoms (change in Beck Depression Inventory score: −5.7 in collaborative care, −1.9 in usual care, $P = 0.005$) and fewer major adverse cardiac events at 9 months (4% in collaborative care, 13% in usual care, $P < 0.05$).[110]

These studies illustrate the usefulness of collaborative care interventions and suggest the need for future studies to evaluate their efficacy in patients with other cardiac problems, such as CHF. Although cost-effectiveness analyses of these studies are not yet available, collaborative care programs in depressed patients with chronic medical illnesses (eg, diabetes mellitus) tend to be as cost-effective as usual care, with the increased costs associated with the intervention being offset by decreases in general medical costs over 2 to 5 years.[122,125,126] This topic will, however, need further study. Studies should also evaluate other models for collaborative care, such as stepped-care models; one such study already is underway.[127] Finally, studies with longer follow-up periods should be performed to determine whether the effects of collaborative care last well beyond the intervention period.

CONCLUSIONS AND TREATMENT RECOMMENDATIONS

MDD and depressive symptoms are highly prevalent in patients with a range of CVD diagnoses and have been associated with poor psychiatric, functional, and cardiac outcomes, including a greater than 2-fold increase in mortality in certain populations. Given the potential health consequences of untreated depression,

TABLE 4. Collaborative Care Studies in Depressed Cardiac Patients

Study Name	Study Size	Type of Cardiac Disease	Method for Depression Diagnosis	Method of Delivery	Staff Delivering Treatment	Treatment Options	Length of Follow-up	Psychiatric Outcomes	Cardiac Outcomes	Findings
Bypassing the Blues[111]	N = 302 (150 intervention, 152 usual care)	CAD (post-CABG)	PHQ-9 score ≥10; diagnosis confirmed at 2 wk	Telephone	Nurse (supervised by psychiatrist and primary care physician)	Workbook, antidepressant therapy, watchful waiting, referral to mental health clinician	8 mo	SF-36 MCS* and PCS, DASI, HRS-D	Rehospitalization	Intervention led to greater improvements on SF-36 MCS†, DASI‡, and HRS-D‡ at 8 mo. Intervention led to greater rates of depression response (50% reduction in depressive symptoms).‡ There were no differences between groups on rates of rehospitalization.
Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial[110]	N = 157 (80 intervention, 77 usual care)	CAD (post-ACS admission)	BDI ≥10 one week and 3 mo after cardiac event	In-person and by telephone	Clinical nurse specialist, psychologist, social worker, and/or psychiatrist	Problem-solving therapy and/or antidepressant	9 mo	Satisfaction with care*, BDI	Rehospitalization, mortality, adverse events	Intervention led to greater satisfaction at 9 mo§ but not at 3 mo. Intervention led to lower BDI scores at 9 mo and greater improvements in BDI overall compared to usual care.§ Intervention led to fewer adverse cardiac events compared to usual care.†

(*Continued*)

TABLE 4. (*Continued*)

Study Name	Study Size	Type of Cardiac Disease	Method for Depression Diagnosis	Method of Delivery	Staff Delivering Treatment	Treatment Options	Length of Follow-up	Psychiatric Outcomes	Cardiac Outcomes	Findings
SUCCEED[109a,112]	N = 175 (90 intervention, 85 usual care)	Unstable angina, MI, arrhythmia, CHF	PHQ-9 ≥10, with at least 5 of 9 symptoms present, with one of those being depressed mood or anhedonia	Telephone	Social work care manager (supervised weekly by psychiatrist)	Antidepressant treatment or psychotherapy referral	6 mo	PHQ-9*, SF-12 MCS and PCS, HADS-A, CPFQ, MOS-A	Cardiac symptoms, rehospitalization	Intervention led to greater improvements in PHQ-9[§], SF-12 MCS[‡], HADS-A[†], and CPFQ[†] at 6 and 12 wk and improvement in cardiac symptoms at 6 mo.[†] Intervention led to increased depression response at 6[§] and 12 wk[†], greater adherence at 6 mo[†], and greater satisfaction at 6 mo.[§]
TEAMcare[127]	N = 214 (106 intervention, 108 usual care)	DM, CAD	PHQ-9 score ≥10	In-person and/or by telephone 1–2 times per month	Nurse (supervised weekly by psychiatrist and primary care physician or internist)	Behavioral activation strategies, antidepressants, depression helpbook, physical activity, and social support	12 mo	SCL-20*, depression response, satisfaction with care	HbA1C*, SBP*, LDL*	Study ongoing

ACS indicates acute coronary syndrome; BDI, Beck Depression Inventory; CAD, coronary artery disease; CPFQ, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; DASI, Duke Activity Scale Index; DM, diabetes mellitus; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HbA1C, Hemoglobin A1C; CHF, congestive heart failure; HRS-D, Hamilton Rating Scale for Depression; LDL, low density lipoprotein; MI, myocardial infarction; MOS-A, Medical Outcomes Study Specific Adherence Scale; PHQ-9, Patient Health Questionnaire-9; SBP, systolic blood pressure; SCL-20, 20-item version of the Symptom Checklist-90; SF-12 MCS, Medical Outcomes Study Short Form-12 Mental Component Scale; SF-12 PCS, Physical Component Scale.

*Primary outcome variable.

[†]$P \leq 0.05$.

[‡]$P \leq 0.001$.

[§]$P \leq 0.01$.

accurate identification of depression and referral for treatment is advised. Screening tools such as the PHQ-2 and PHQ-9, which are easy to use and time-efficient, have been effective at identifying those patients with elevated depressive symptoms or MDD and—when possible—should be used in both inpatient and outpatient settings when there is adequate next-step evaluation and treatment available. This could include the availability of a consulting psychiatrist to consult with or follow the patient, or a more comprehensive care management type program.

In patients who are diagnosed with MDD, both antidepressants and psychotherapeutic interventions are effective at alleviating depressive symptoms. Standard doses of SSRIs are safe and effective in patients with cardiac disease and may be considered first-line if pharmacologic treatment is appropriate. Psychotherapeutic interventions, especially those that are supportive and work to improve adherence to rehabilitation programs, cardiac treatments, and psychiatric medications may also be helpful. As coordinated care programs appear to be effective at delivering these interventions, such a model should be adopted in cardiology practices and inpatient cardiology units when possible. If such a model does not exist, relationships with psychiatrists, therapists, and primary care physicians should be cultivated to create a treatment model that resembles collaborative care as much as possible.

Further research on all issues related to understanding and treating depression in cardiac patients is needed. More thorough knowledge of the mechanisms mediating the link between depression and cardiac disease could help to develop treatments targeting the underlying pathophysiology that leads to worse cardiac outcomes. Evaluation of the efficacy of antidepressant medications in patients with CHF and arrhythmias would be useful to ensure their safety and efficacy in those populations. Furthermore, study of other antidepressants (eg, duloxetine, and bupropion) would be helpful to ensure their safety in those patients who might not tolerate SSRIs. Larger studies of SSRIs with enough power to evaluate their effect on cardiac outcomes and mortality and can assess the ability of those medications to impact cardiac outcomes would allow us to understand their full utility. Finally, further studies of collaborative care programs that include measures of cost effectiveness and are integrated into existing disease management programs (such as CHF management programs) may lead to the development of appropriate screening and treatment programs to improve outcomes while reducing healthcare costs.

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