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Depression and Cardiovascular Disease

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ABSTRACT

Approximately one out of every five patients with cardiovascular disease (CVD) suffers from major depressive disorder (MDD). Both MDD and depressive symptoms are risk factors for CVD incidence, severity and outcomes. Great progress has been made in understanding potential mediators between MDD and CVD, particularly focusing on health behaviors. Investigators have also made considerable strides in the diagnosis and treatment of depression among patients with CVD. At the same time, many research questions remain. In what settings is depression screening most effective for patients with CVD? What is the optimal screening frequency? Which therapies are safe and effective? How can we better integrate the care of mental health conditions with that of CVD? How do we motivate depressed patients to change health behaviors? What technological tools can we use to improve care for depression? Gaining a more thorough understanding of the links between MDD and heart disease, and how best to diagnose and treat depression among these patients, has the potential to substantially reduce morbidity and mortality from CVD.

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Major depressive disorder (MDD) is present in approximately 1 out of every 5 patients with cardiovascular disease (CVD).[1] Beyond its frequent co-occurrence with CVD, MDD has been associated with both increased incidence and worse outcomes of coronary heart disease (CHD), even after controlling for traditional CVD risk factors. The presence of depressive symptoms (with or without a clinical diagnosis of MDD) predicts incident CHD in healthy individuals,[2] secondary events in patients with known CHD,[3–6] and adverse outcomes among individuals who have undergone coronary artery bypass grafting.[7] MDD was the 4th leading cause of worldwide disability in 2002 and is expected to become the 2nd leading cause of worldwide disability by 2030.[8] In recent years, researchers have shed light not only on what mechanisms link MDD and CVD, but also on how to best screen and treat patients with both conditions. This manuscript reviews some of these important discoveries and highlights future directions that we hope will lead to new treatment strategies for these diseases.

Is depression an independent risk factor of CVD?

Historically, age, gender, family history of CVD, smoking, hypertension, diabetes, cholesterol levels, obesity and physical inactivity have been recognized as "traditional risk factors" for CVD. In recent decades, studies have demonstrated that psychosocial factors play an equal role in predicting CVD

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Abbreviations and Acronyms

AHA = American Heart Association

BDI = Beck Depression Inventory

CBT = Cognitive-Behavioral Therapy

CHD = Coronary Heart Disease

COPES = Coronary Psychosocial Evaluation Study

CVD = Cardiovascular Disease

ENRICHD = Enhancing Recovery in Coronary Heart Disease

HF = Heart Failure

IPT = Interpersonal Therapy

MDD = Major depressive disorder

PHQ-2 = 2-Item Patient Health Questionnaire

PHQ-9 = 9-Item Patient Health Questionnaire

PST = Problem-Solving Therapy

PAD = Peripheral Arterial Disease

SSRI = Selective Serotonin Reuptake Inhibitor

morbidity and mortality. The INTERHEART study, a case–control study which examined modifiable risk factors for acute myocardial infarction (MI) in over 25,000 patients from 52 different counties, found that psychosocial factors were stronger risk factors for incident MI than were diabetes, smoking, hypertension and obesity.[9] The psychosocial factors examined in this study included depression, locus of control, perceived stress, and life events. Based on the findings of this and other studies, depression was officially recognized as a CHD risk factor in the 2010 Global Burden of Disease Study.[10]

In addition to CHD, depression (defined here as either MDD or significant depressive symptoms with substantial functional impairment) is associated with an increased risk of—and adverse outcomes among patients with—heart failure (HF), stroke,[11] and peripheral artery disease (PAD).[11–13] One study of 4500 patients with HF found that the relative risk of HF in depressed patients as compared to non-depressed patients was 2.6, even after adjustment for traditional CVD risk factors.[14] Depression has also been shown to be an independent predictor of mortality and re-hospitalization among patients with established HF.[15]

Similarly, depression increases risk of recurrent total stroke, fatal stroke and ischemic stroke in patients with existing cerebrovascular disease.[11] In the reverse direction, stroke survivors have a 33% greater pooled frequency of depressive symptoms compared to that of the general population, with higher rates found when more formal depression scales were used.[16,17] As one might expect, worse functional status and inability to work following stroke were associated with an even higher risk of depression in these patients.[16] As compared with other forms of CVD, cerebrovascular disease is unique in that depression may be directly linked to cerebral ischemia through patterns of blood flow in the central nervous system. This contrasts to MI or HF, which are thought to be related to depression more indirectly through symptom burden, emotional distress and functional impairment. The mechanisms relating depression to cerebral ischemia, and vice-versa, will provide interesting areas for future research and may aid in risk factor modification.

Many studies have sought to determine how depression interacts with other CVD risk factors. A study published by Rutledge and colleagues followed 620 women for a median of 5.9 years of follow-up, and found that the relationship between modifiable CVD risk factors and CVD outcomes varied with depression status. The authors concluded that, in addition to influencing CVD as an independent risk factor, depression also intensifies the influence of other risk factors on cardiac outcomes. This finding points to the need for further research to understand the complex interactions among the numerous pathways leading to CVD.[18] While most researchers recognize that depression is an independent risk factor for CVD, an aim in future years will be to understand the interrelationship of various behavioral and biological pathways that contribute to cardiac risk.

How does depression contribute to CVD?

The finding that depression predicts CVD incidence and severity has prompted the question of precisely how depression causes or exacerbates CVD. Multiple potential biological and behavioral mediators have been identified, including smoking, physical inactivity,[19] medication nonadherence,[20,21] lower heart rate variability,[22] toxicity from antidepressants,[23] enhanced activity of the hypothalamo-pituitary-adrenal (HPA) axis,[24] greater catecholamine levels,[25] poor diet, low omega-3 fatty acid levels,[26] platelet activation,[27] and inflammatory processes.[28,29] However, most of these factors have been identified based on separate linkages with both depression and CVD. Health behaviors, inflammatory processes and heart rate variability are the only candidate mechanisms that have actually been shown to mediate the association.

The bulk of evidence suggests that poor health behaviors, particularly physical inactivity, are largely responsible for the excess risk of CVD associated with depression.[30–38] In the Heart and Soul Study, a prospective cohort study of 1024 subjects with stable coronary heart disease, patients with depressive symptoms had a 50% greater rate of adverse cardiovascular events than those without depressive symptoms. The increase in risk was attenuated, but still significant, following adjustment for comorbid conditions and left ventricular ejection fraction. However, the difference in outcomes was no longer significant following adjustment for smoking, medication adherence, and especially physical activity.[32] Several other cohort studies have reported similar findings.[30,31,33–36]

Inflammation is another potential mediator of interest. Certain inflammatory biomarkers such as C-reactive protein, interleukin 1, and interleukin 6 have been associated with atherosclerosis and depression alike, both in healthy subjects and in cardiac patients.[29,39–45] However, previous studies have suggested both that inflammation increases risk of depression[42,46] and that depression causes inflammation in patients with CHD.[47] Thus, it is difficult to determine whether such markers serve as triggers of both depression and CVD, act on the causal pathway between them, or result from both conditions.[28]

Some studies suggest that the role of inflammation in linking depression and CVD may be intertwined with the role of physical activity. Depressed individuals tend to exercise less than their healthy counterparts, and lower levels of exercise have been associated with increased inflammation.[48–53] Given the well-studied association between inflammation and CVD pathogenesis, these findings suggest that physical activity and inflammation may act together on the causal pathway between depression and CVD. In a cohort of patients with stable CHD, Duivis and colleagues found that the association between depressive symptoms and subsequent inflammation was no longer significant following adjustment for health behaviors. These findings highlight the importance of health habits such as exercise, smoking, and medication adherence in the relationship between depression and CVD, and suggest that inflammation in depressed patients may be partly the result of associated poor health behaviors.[54]

Using data from the Whitehall II Cohort Study, Hamer and colleagues followed 4289 individuals over a period of 10 years, examining the relationship between physical activity and the inflammatory markers CRP and IL-6. The authors found that subjects who were physically active had lower baseline levels of inflammatory markers, and that this remained stable over the 10 years of follow-up.[55] These results support the importance of physical activity in preventing the development of pro-inflammatory states that are associated with increased risk of CVD. Other studies have shown that inflammation itself may contribute to decreased physical activity, suggesting a bidirectional relationship between health behaviors and inflammation.[55,56]

Another piece of evidence relating inflammation and health behaviors to CVD and depression involves heart rate variability (HRV). Lower HRV is a marker of cardiac risk. Both physical inactivity and inflammation have been associated with reduced HRV,[57,58] suggesting that low HRV may be a downstream effect of depression and its associated health behaviors. In 907 patients from the Cardiovascular Health Study, Kop et al. reported that both low HRV and markers of inflammation contributed to the increased cardiovascular mortality risk associated with depression.[59] Another study by Carney and colleagues demonstrated that adjusting for heart rate variability (HRV) diminished (but did not eliminate) the effect size of depression on survival in 311 post-MI patients suffering from depression.[22] These findings further emphasize the likely inter-connections between health behaviors, inflammation and HRV on the pathway between depression and CVD (Fig 1).

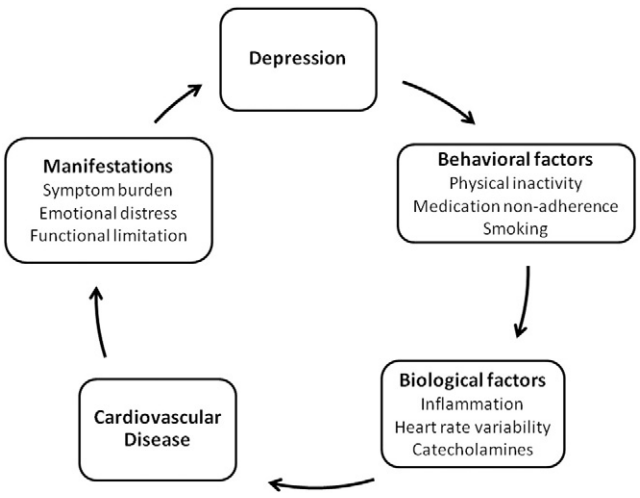

Fig 1 – Relationship between depression and cardiovascular disorders.

Screening for depression in CVD patients

The strong association between depression and adverse cardiac outcomes highlights the importance of identifying and treating MDD in this population. The essential feature of a major depressive episode is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities.[60] The gold standard for diagnosing a major depressive episode is a clinician interview assessing the extent to which a patient meets the criteria outlined in the Diagnostic and Statistical Manual.[60] As it is not practical to administer a diagnostic interview to all patients with CVD, several shorter screening tools have been developed, and many of these tools have been validated specifically in cardiac patients.[61–63]

Screening for depression is straightforward. A yes/no version of the 2-Item Patient Health Questionnaire (PHQ-2) is a simple instrument that takes less than a minute to complete.[64] A "yes" response to one or both questions constitutes a positive screen, and is 90% sensitive and 69% specific for MDD in patients with heart disease.[61] This screen is excellent for ruling out depression in patients who answer no to both questions. However, the low specificity and positive predictive value of this instrument make it necessary to perform a diagnostic interview in patients who screen positive (Fig 2). As an alternative to the clinical interview, some providers administer the 9-item Patient Health Questionnaire (PHQ-9). This is a self-report questionnaire that takes less than 3 minutes to complete, and can be scored by an office assistant. Although a score of 10 or higher misses about half of depression cases in CHD patients, the test's 90% specificity and high PPV make it virtually diagnostic of depression in those who screen positive.[61,66,67]

In light of the utility of both the PHQ-2 and PHQ-9, the American Heart Association (AHA) issued a recommendation that all patients with CVD be screened for depression using these questionnaires in a 2-step screening process, with the PHQ-9 administered only to those patients who screened positive on the PHQ-2.[68] In one study of over 1000 patients with CHD, the sensitivity of this 2-step approach was limited (52%), but it was highly specific (91%) and had a high negative predictive value (87%) for the diagnosis of MDD. Furthermore, the test was found to carry prognostic value even in the absence of MDD.[69] Patients who screened positive had a 41% greater long-term risk of cardiovascular events than those who did not screen positive, regardless of their interview-based diagnosis of MDD.[69] These results suggest that, although the AHA-recommended screening method does not capture all CHD patients with a comorbid diagnosis of MDD, the instrument does identify patients at higher

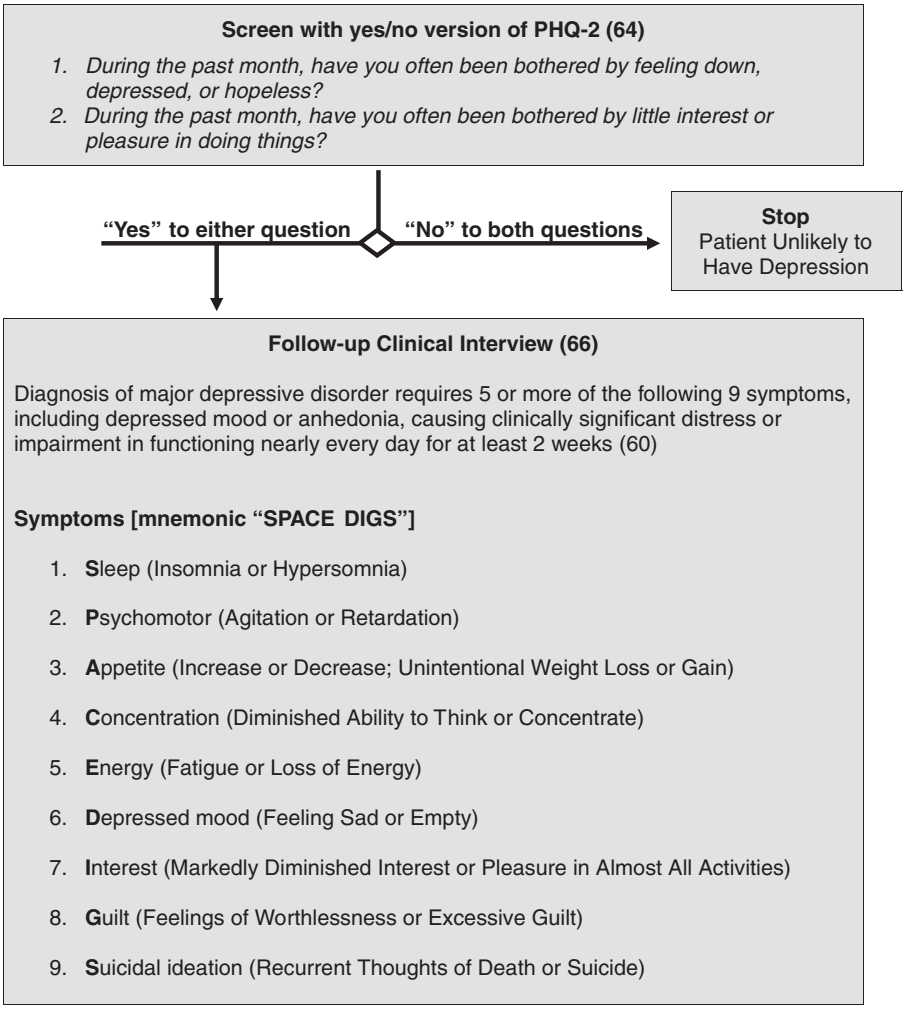

Fig 2 – Algorithm for diagnosing depression in primary care patients.[65]

risk for adverse cardiovascular outcomes. By identifying CHD patients whose depressive symptoms put them at increased risk of cardiovascular events, clinicians can better prioritize and personalize the treatment of these patients.

Treating depression in CVD patients: psychotherapy

The AHA recommendation to screen for MDD leads to the question of what constitutes appropriate depression treatment in cardiac patients. As for any patient with depression, first-line treatment options include self-management, psychotherapy, pharmacotherapy, or a combination. Choice of treatment can be guided by severity of depressive symptoms, degree of functional impairment, and patient preference, along with research on the safety and efficacy of treatments specifically in patients with CVD.

Self-management involves patient education about the diagnosis of MDD, brief counseling, and prescribed exercise.[70,71] A key feature of self-management is teaching patients the skills of behavioral activation, which involves increasing and focusing attention on pleasant activities, modifying negative self-perceptions, and activating social networks. Exercise, which is one component of self-management, not only reduces depressive symptoms[72–74] but also improves cardiovascular health.[75] Thus, the importance of physical activity should be emphasized for all patients with CVD, regardless of depression.

Evaluation of specific psychotherapy interventions is important for patients with CVD because, as with any treatment, psychotherapy carries risks in addition to benefits.[76] The Montreal Heart Attack Readjustment Trial examined a group of 1376 patients who had suffered an MI, and followed them with monthly telephone calls. The calls consisted of monitoring symptoms in all patients, and providing additional support for patients with psychological distress. One year later, survival and psychological outcomes were similar between the intervention and control groups, but women who had received psychological intervention demonstrated higher cardiac and all-cause mortality. The authors hypothesized that patients in this group

may have suffered from increased distress based on lowered perceived health status. This result shows the importance of continuing to study the efficacy and safety of psychotherapy techniques in patients with CHD.

Cognitive-behavioral therapy (CBT) was the first form of psychotherapy shown to be safe and effective in treating MDD in patients with CVD.[77] Cognitive-behavioral therapy works by helping patients increase the frequency of pleasant activities, activate social networks, focus on accomplishments, and identify and challenge pessimistic or self-critical thoughts that cause or perpetuate depression.[78] This therapeutic intervention was evaluated in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, in which 2481 patients who had been hospitalized for an MI in the past 30 days were randomized to receive CBT or usual care. Nine hundred fifty eight of these patients met criteria for MDD, 811 had minor depression, 66 had dysthymia, and 647 had low social support but no depression. The study found no significant difference in cardiac outcomes between the 2 groups, but depressive symptoms improved more in the CBT group than in the usual care group.

Although the ENRICHD trial showed only a small difference in depressive symptom improvement between intervention and control subjects, the size of this difference was similar to that seen in trials of pharmacotherapy for depression in medically healthy individuals. Thus, the results of the ENRICHD trial are consistent with findings in the general population that CBT and pharmacotherapy are equally effective in treatment of depression.[79,80] It has also been shown that the benefits of CBT may last even beyond the duration of treatment.[81]

Interpersonal therapy (IPT) has also been evaluated in patients with CVD. IPT focuses on helping patients manage interpersonal situations that may contribute to depression. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial compared the acute phase efficacies of IPT, citalopram, a combination of the two, and usual care. Study subjects were 284 patients with CHD, and the outcome of interest was depression reduction. The results of this study supported the efficacy of citalopram in reducing depression, but revealed no increased value of IPT over usual care.[82] The authors noted that this was not the first study which failed to show a clear benefit of IPT when compared to a control population, and suggested this may be related to the difficulty of creating inert control conditions when studying IPT.

Problem-solving therapy (PST) is the form of psychotherapy most recently shown to be safe in patients with CVD. PST helps patients identify everyday life problems that contribute to depression and develop skills to manage them. In the Coronary Psychosocial Evaluation Study (COPES), patients with persistent depression 3 months following hospitalization for acute coronary syndrome were randomly assigned to receive either usual care or an intervention that consisted of PST and/or pharmacologic therapy. After 6 months, the intervention group showed significantly higher patient satisfaction ratings, greater average reduction in depressive symptoms, and lower rates of adverse cardiac outcomes.[83]

Treating depression in CVD patients: pharmacotherapy

For patients who cannot or do not wish to receive psychotherapy, pharmacotherapy provides an excellent alternative option for treatment of MDD. In patients with severe depressive symptoms causing substantial functional impairment, psychotherapy plus pharmacotherapy is generally more effective than either one alone.[78,84] Selective serotonin reuptake inhibitors (SSRIs) have been shown to be both safe and effective in treating depression among heart disease patients,[85] with no one agent showing superiority to the others.[86] Some early studies suggested that SSRIs may be associated with serious cardiovascular events when used in CHD patients. However, a recent meta-analysis of the topic by Pizzi and colleagues concluded that SSRIs are in fact safe and favorable to use in this population, and that the adverse events in these studies were better explained by underlying cardiac disease.[87] Thus, SSRIs are now considered first-line agents for treatment of MDD in patients with CVD.

When choosing an SSRI, it is important to consider that many cardiac patients are on multiple medications. Among the SSRIs, those with the fewest drug-drug interactions are citalopram and sertraline. These are the least likely to inhibit the CYP450 enzymes, and are thus the least likely to cause pharmacokinetic interactions.[88] Individual medication regimens and tolerance of side effects should also be taken into account prior to choosing a medication because these factors can substantially affect adherence. As with other patients taking SSRIs, cardiac patients taking SSRIs should receive thorough education on the potential adverse effects of their medications, and the >4 week duration of treatment necessary to experience antidepressant effects.[89]

Bupropion is another antidepressant that has been shown to be safe and effective in cardiac patients.[90,91] In the general population, this medication is effective in smoking cessation as well as depression treatment. Unfortunately, it does not appear to enhance smoking cessation after acute coronary syndrome.[92] Bupropion may be taken in conjunction with SSRIs, and indeed has been used to help offset adverse effects of SSRIs. Importantly for cardiac patients, however, bupropion has been associated with minor increases in blood pressure, so this parameter should be monitored.[90]

Multiple other medications exist to treat depression; however, they should not be used as first-line therapy in patients with CVD. Although mirtazapine is safe in CVD patients,[93] it is not first-line due to its association with weight gain[94] and the risk of hypertensive urgency when administered with clonidine.[95] Whenever possible, tricyclic antidepressants should be avoided based on the risk of altered cardiac conduction and associated adverse cardiovascular events.[96] Hypericum perforatum (St John's wort) should similarly be avoided based on potential interaction with cardioactive medications.[97]

In addition to considering the safety and efficacy of long term psychotherapy and pharmacotherapy, it is important to consider that patients with depression (with or without comorbid CVD) are prone to psychiatric emergencies. If a patient has a history of mania or psychosis, referral to a

psychiatrist is recommended. It is also critical to ask patients specifically about any thoughts of hurting themselves or others, and to seek emergent psychiatric evaluation for any patient with a suicidal plan.

Does treating depression affect risk of adverse cardiovascular events?

While much of the research on depression treatment in cardiac patients has focused on the psychiatric consequences of medications or psychotherapy, another outcome of interest is of course the incidence of adverse cardiovascular events. Several studies have examined the effects of antidepressant therapies on cardiovascular outcomes, with mixed results. Most of these studies are relatively small (Table 1), making it difficult to draw any definitive conclusions. However, a large trial of antidepressant therapy vs. placebo would be unethical because depression deserves treatment regardless of any cardiovascular benefits of the treatment. Therefore, the impetus to study the effect of antidepressant therapies on cardiovascular outcomes is in demonstrating safety and helping providers choose the most appropriate intervention for each patient.

Three recent trials of antidepressant therapies and cardiovascular outcome deserve particular mention. In the COPES trial, published in 2010, 156 patients with persistent depression 3 months following hospitalization for ACS were randomized to receive either usual care or a stepped care intervention that included pharmacotherapy and/or psychotherapy.[83] After 6 months, the intervention group showed significantly higher patient satisfaction ratings, greater average reduction in depressive symptoms, and a lower rate of cardiovascular events.[83] The Secondary Prevention in Uppsala Primary Health Care (SUPRIM) trial evaluated 362 patients who were within 12 months of hospitalization for a coronary heart disease event. Patients (with or without depression) were randomly assigned to usual care vs. a year-long CBT program focused on stress management.[100] Those randomized to a year-long CBT program showed a 41% lower rate of fatal and nonfatal CVD events over a mean 94 months of follow-up, and 45% fewer recurrent myocardial infarctions. In the TeamCare study, 214 patients with depression plus poorly controlled diabetes and/or coronary heart disease risk factors were randomly assigned to usual care vs. a collaborative care intervention in which a nurse care manager worked with the patient's primary care doctor to improve treatment of both depression and cardiovascular risk factors. After 12 months, the intervention group showed greater improvement in all measures, including glycated hemoglobin, lipid levels, systolic blood pressure, and depression scores. As in the COPES trial, the intervention group also reported greater patient satisfaction and quality of life.[102]

Subtypes of depression in CVD patients

One hypothesis that could explain the mixed results regarding depression treatment and CVD outcomes involves the presence of various subtypes of depression, such that the optimal treatment for one patient may be ineffective for the next patient, should they have different subtypes of the disease.[106] Proponents of this hypothesis posit that certain features in the timing and/or quality of each patient's depression may be associated with better or worse cardiovascular outcomes. Differentiating features that have been suggested include timing of depression onset (before vs. after myocardial infarction), chronicity of depressive symptoms (continuing vs. recurrent vs. new), specific types of symptoms (cognitive vs. somatic), and treatment resistance.

Data from the CREATE and SADHART trials have suggested that SSRIs are more beneficial for cardiac patients suffering from recurrent episodes of depression than for those experiencing a first episode.[82,107] This makes sense because depression is typically a chronic disorder with recurrent episodes that occur over the lifespan. Others have shown that the presence of depressive symptoms is less predictive of cardiac events if assessed within two weeks of (vs. more than two weeks after) an acute coronary event.[108] Patients who experience depressive symptoms for the first time after myocardial infarction may be more likely than those with continuing or recurrent depression to have transient depressive symptoms that resolve over time. Thus, when evaluating the relationship between depression and CVD, it is important to differentiate major depression from adjustment disorder with depressed mood (depressive symptoms that persist for no more than 6 months following an identifiable stressor[60]).

Some investigators have suggested that somatic symptoms of depression may be more strongly predictive of CVD prognosis than cognitive symptoms.[109–117] Given the overlap between depressive symptoms and somatic symptoms of CVD, it is not surprising that somatic symptoms of depression (e.g., fatigue, appetite problems, difficulty sleeping) would be more strongly associated with adverse CVD outcomes than cognitive symptoms of depression (e.g., poor concentration, anhedonia, sense of worthlessness). The key question is whether these findings are independent of CVD severity. Although studies have attempted to control for CVD severity, multivariable adjustment rarely captures all potential confounding. Thus, it has been difficult to determine whether the somatic symptoms that predict adverse cardiac outcomes result from depression or from worse underlying CVD. Furthermore, substantial variability in methodology between studies has made findings difficult to compare to one another and to replicate.[117] Given these issues, there is insufficient evidence to conclude that somatic and cognitive symptoms of depression are more or less strongly predictive of CVD events.

Others have suggested that treatment-resistant depression may be a stronger predictor of subsequent mortality than treatment-responsive depression.[93,118] However, it is unclear how comparing treatment-resistant vs. treatment-responsive depression differs from comparing depressed vs. non-depressed patients. One trial found that lack of response to antidepressant treatment more strongly predicted mortality than lack of response to placebo (i.e., persistent depression).[118] In this study, treatment-responders had lower mortality than treatment non-responders, but mortality did not differ between

Table 1 – Selected randomized trials of antidepressant therapies in patients with cardiovascular disease.

Study	Reference	N	Patient Population	Intervention	Control	Duration of Intervention	Depression Outcome	Cardiovascular Outcome
ENRICHD	[77]	1834	Post-MI + MDD	Cognitive behavioral therapy ± sertraline	Usual care	3 months	Improvement	No benefit
M-HART*	[98]	1376	Post-MI	Monthly telephone monitoring + home nursing support for distressed patients	Usual care	12 months	No benefit	No benefit; trend toward higher mortality in women
SADHART–CHF	[99]	469	Heart failure + MDD	Nurse-facilitated support + sertraline	Nurse-facilitated support	3 months	No benefit	No benefit
SADHART–CAD	[79]	369	Post-MI or unstable angina + MDD	Sertraline	Placebo	6 months	Improvement	No adverse effects
SUPRIM*	[100]	362	Within 12 months of hospitalization for CHD event	Cognitive behavioral therapy	Usual care	12 months	Not reported	Fewer cardiac events
MIND-IT	[93,101]	331	Post-MI + MDD	Mirtazapine ± stepped care	Placebo	6 months	Improvement	No adverse effects
CREATE	[82]	294	Stable CHD + MDD	Interpersonal Therapy	Clinical management	3 months	Improvement	No adverse effects
CREATE	[82]	284	Stable CHD + MDD	Citalopram	Placebo	3 months	Improvement	No adverse effects
TeamCare	[102]	214	Poorly controlled CHD or diabetes + depressive symptoms	Collaborative care	Usual care	12 months	Improvement	Improved blood pressure, glyco-hemoglobin and LDL cholesterol
COPES	[83]	157	Post-ACS + 3 months of depressive symptoms	Problem-solving therapy and/or antidepressant medication	Usual care	6 months	Improvement	Fewer cardiac events
Strik et al.	[103]	54	Post-MI + MDD	Fluoxetine	Placebo	6 months	No benefit	No adverse effects
McFarlane et al.	[104]	27	Post-MI + depressive symptoms	Sertraline	Placebo	5.5 months	Improvement	Improved heart rate variability
Mohapatra et al.	[105]	17	Post-MI + depressive symptoms	Sertraline	Usual care	6 months	Improvement	Not reported

Abbreviations: CREATE, Cardiac Randomization Evaluation of Antidepressant and Psychotherapy Efficacy; ENRICHD, Enhancing Recovery in Coronary Heart Disease Patients; M-HART, Montreal Heart Attack Readjustment Trial; MIND-IT, Myocardial Infarction and Depression-Intervention Trial; SADHART-CAD, Sertraline Antidepressant Heart Attack Randomized Trial; SADHART-CHF, Sertraline Against Depression and Heart Disease in Chronic Heart Failure; SUPRIM, Secondary Prevention in Uppsala Primary Health Care Project; COPES, Coronary Psychosocial Evaluation Studies Randomized Controlled Trial; MDD, Major Depressive Disorder; CAD, Coronary Artery Disease; MI, Myocardial Infarction.

* Presence of depressive symptoms was not an inclusion criterion for M-HART or SUPRIM.

placebo responders and placebo non-responders. Therefore, the investigators concluded that the increased mortality associated with treatment resistance was due to more than just persistent depression. However, comparing patients with treatment-responsive vs. treatment-resistant depression is not necessarily analogous to comparing patients with placebo-responsive vs. placebo-resistant depression. In addition, fewer patients responded to placebo than to treatment, leaving less power to detect an association between change in symptoms and mortality in the control group.

Future directions

Despite these considerable advances in our understanding of the relationship between depression and CVD, many important questions remain. Some investigators have advocated for a large randomized trial to determine whether treatment of depression improves cardiovascular outcomes. The results of such a trial would of course be of great academic interest. However, they would not change clinical management

because depression treatment is necessary whether or not it improves cardiovascular outcomes. Evaluating the safety of antidepressant therapies in patients with cardiovascular disease will likely be the primary focus of future comparative effectiveness trials.

In what settings is depression screening most effective for patients with CVD?

Screening for depression in the primary care setting is important because it can improve both depression and cardiovascular outcomes when staff-assisted care supports are in place. However, screening unselected patients for depression in the absence of staff-assisted care support has no proven benefit. Although screening increases recognition and treatment of depression, screening itself has no effect on future mental health or cardiac outcomes because many patients do not fill prescriptions, take prescribed antidepressant medications, or follow through with mental health referrals. The Cochrane Collaboration and US Preventive Services Task Force have specifically recommended against screening unless a designated depression care manager, in consultation with a supervising psychiatrist, is available to work closely with the patient's provider to offer patient activation, follow-up, symptom monitoring, and treatment intensification when necessary.[119,120]

Whether depression screening is useful in the outpatient cardiology setting has not been specifically evaluated. However, most cardiology practices do not have a dedicated depression care manager who can provide the level of support necessary for screening to be beneficial. As with diabetes, cardiologists recognize and understand the importance of depression as a risk factor for CVD. However, treatment decisions are rarely straight-forward, responses to therapy are extremely varied, treatment must be tailored to each patient, and close monitoring is an important component of treatment. Given these complexities, the best thing a cardiologist can do is refer patients (regardless of depression) to a primary care provider who can oversee all appropriate health screenings and consultations.

What is the optimal frequency for depression screening in patients with CVD?

The optimal frequency of depression screening is unknown. Currently, Medicare covers annual screening for depression in primary care settings that have staff-assisted depression care supports in place to assure accurate diagnosis, effective treatment and follow-up. The relative benefits of more or less frequent screening have not been evaluated empirically. It would certainly be possible to randomly assign primary care patients (or practices) to different frequencies of depression screening. As an outcome measure, all patients could complete the PHQ-9 once per month for five years. We could then evaluate whether frequency of depression screening was associated with any difference in average PHQ-9 depression scores during those 5 years.

How can we better integrate the care of mental health conditions and cardiovascular disease?

Although we have yet to gain a complete understanding of what mediates the relationship between CVD and depression, we have enough knowledge of this relationship to begin translating it to clinical practice. The possibility for common therapeutic strategies to help both depression and CVD makes depression care essential to cardiac care, and vice-versa. To maximize care of patients with either disease, integration of psychiatric and physical health care will be critical,[102] with team-based care as a potential strategy to achieve this integration. Team-based care (also known as collaborative care) involves a nurse case manager who works with the patient's primary care provider to provide guideline-based management for the patient's chronic conditions (in this case, CVD and depression). Key components include repeated monitoring of symptoms and timely adjustments of medications to achieve treatment targets.

Such monitoring has been growing in the realm of CVD, diabetes and HTN, but has been slower to develop for depression care.[102] The TeamCare trial was performed to examine this type of care particularly for patients with depression and either diabetes or CVD. Subjects randomly assigned to TeamCare management (vs. usual care) experienced greater improvement in glycated hemoglobin, lipid levels, systolic blood pressure, depression scores, and quality of life.[102] The improvements in outcome observed in the TeamCare study were even greater in magnitude than those observed in other trials of collaborative care, where care was designed to help only one chronic condition (i.e., depression or CVD, but not both).[121–123] The high rate of patient satisfaction was especially notable.[124] Although the TeamCare study was not powered to examine differences in cardiovascular events between groups, its findings suggest that this approach could be effective in attenuating risk factors for CVD and depression alike.

How do we motivate depressed patients to change health behaviors?

Exercise interventions can be as effective as pharmacotherapy at improving depressive symptoms.[125,126] Given the multiple benefits and relatively low cost of exercise and self-care training in general, this is promising news. However, achieving motivation to begin and sustain behavioral change is difficult for all individuals, particularly those with depression. Future research in this area should focus on how to engage and motivate patients in behavioral change plans, and how to coordinate support for these patients from health care providers, family, and social networks.[127,128]

What technological tools can we use to improve care for both depression and CVD?

Technological advances provide many potential tools to help engage patients in behavioral change. Various mobile phone

programs, typically based around automated text messaging, have been developed as adjunct treatments for depression, behavioral activation, CVD, and related diseases.[129,130] Such applications are very promising, as they can provide health reminders and improve adherence to treatment recommendations between patient visits to the provider. Furthermore, these applications are low cost and very easy to disseminate. Although text messaging programs are a recent development, they have already been shown to be highly effective for behavior change.

In a 2010 review of the literature, 8 of 9 mobile phone applications intended for disease prevention or management were found to be more effective than usual care.[131] While all of the trials included in this review were studying applications for diabetes management, other studies have also found positive results for mobile applications on physical activity,[132] hypertension management,[133] smoking cessation,[134] and depression care.[130] The proliferation of smartphones provides an even wider array of possible applications and ways to reach patients.[135] Particularly relevant to patients with comorbid depression and CVD are smartphone applications being developed for cardiac rehabilitation, an intervention that targets both physical and psychosocial health improvement.[136]

Further development of mobile programs to enhance patient adherence could allow providers to reach a vast number of patients with only slightly more time and effort. Notably, while a multitude of programs exist for the monitoring of a single health behavior or category of symptoms, few if any combine health behaviors, depression measures and cardiac care. Development of such programs will be an important step as we learn more about the interconnectedness of physical and mental health. Larger trials, and assessment of long-term outcomes, will be needed to fully assess the utility of these applications.

Summary

In summary, research has clearly demonstrated that depression is a risk factor for both incident and recurrent coronary heart disease, as well as stroke, PAD and HF.[11–13] Although several biological factors have been associated with both CVD and depression, modifiable health behaviors, particularly physical inactivity, smoking, and medication non-adherence, appear to be the most critical mediators.[35–38] Many standard treatments for depression, such as SSRIs and CBT, have been shown to be safe in cardiac patients. Recently, small randomized trials have suggested that mental health treatment may even improve cardiovascular outcomes.[83,100,102] Integrating treatment of both depression and CVD risk factors through TeamCare management is the next frontier. Future research in this area should focus on how to engage, motivate and empower patients to modify health behaviors that will simultaneously improve outcomes of both mental and physical health conditions.

Statement of conflict of interest

All authors declare that there are no conflicts of interest.

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