Depression and Cardiovascular Disorders

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Abstract

During the past two decades, research in the field of depression and cardiovascular disorders has exploded. Multiple studies have demonstrated that depression is more prevalent in populations with cardiovascular disease, is a robust risk factor for the development of cardiovascular disease in healthy populations, and is predictive of adverse outcomes (such as myocardial infarction and death) among populations with preexisting cardiovascular disease. Mechanistic studies have shown that poor health behaviors, such as physical inactivity, medication nonadherence, and smoking, strongly contribute to this association. Small randomized trials have found that antidepressant therapies may improve cardiac outcomes. Based on this accumulating evidence, the American Heart Association has recommended routine screening for depression in all patients with coronary heart disease. This review examines the key epidemiological literature on depression and cardiovascular disorders and discusses our current understanding of the mechanisms responsible for this association. We also examine current recommendations for screening, diagnosis, and management of depression. We conclude by highlighting new research areas and discussing therapeutic management of depression in patients with cardiovascular disorders.

Contents

INTRODUCTION

By 2030, major depressive disorder (MDD) is projected to become the leading cause of worldwide disability, overtaking lower respiratory infections and diarrheal diseases (Mathers et al. 2008). Although some of this burden is due to the profound effects of MDD on human productivity and quality of life, a substantial portion relates to its association with medical illnesses, particularly cardiovascular disease. Cardiovascular disorders increase vulnerability to MDD because of their symptom burden, psychological stress, financial hardship, and functional limitations. Likewise, the presence of depression (defined here as either MDD or significant depressive symptoms with substantial functional impairment) increases risk of many cardiovascular disorders, including coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD), and heart failure (HF). This bidirectional relationship can result in a self-perpetuating cycle of poor mental and physical health.

MDD: major depressive disorder
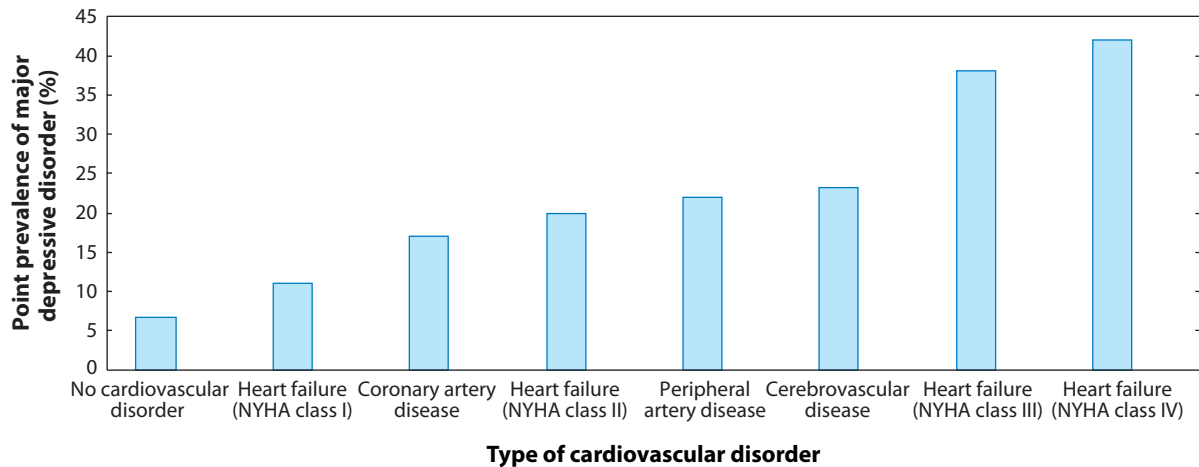
CAD: coronary artery disease

CVD: cerebrovascular disease

PAD: peripheral artery disease

HF: heart failure

Figure 1

Prevalence of depression among patients with cardiovascular disorders in the United States. NYHA, New York Heart Association.

The prevalence of depression is difficult to pinpoint because it varies by gender (female > male), age (younger > older), race (white > nonwhite), diagnostic criteria (self-reported symptoms > clinician interview), timeframe (lifetime > 12-month > current), socioeconomic status (lower > higher), geographic region (Simon et al. 2004), patient population (inpatient > outpatient > community dwelling) and the presence of comorbid medical illness. In the United States, MDD has a point prevalence around 6% to 7%, a 12-month prevalence around 10% to 12%, and a lifetime prevalence of 20% (Kessler et al. 2005a,b; Natl. Inst. Ment. Health 2012; Reeves et al. 2011). The prevalence of MDD is substantially higher among outpatients with cardiovascular disorders and among persons hospitalized for cardiovascular events such as acute coronary syndrome (ACS), acute myocardial infarction (MI), HF, coronary artery bypass grafting, CVD, or PAD (**Figure 1**).

CORONARY ARTERY DISEASE

In 1993, Frasure-Smith and colleagues demonstrated that MDD is an independent risk factor for mortality following MI (Frasure-Smith et al. 1993). Since then, dozens of epidemiological studies have examined the association between depression and cardiovascular outcomes in populations with and without preexisting CAD. Since depression cannot be randomly assigned, there is no way to prove that its association with CAD is causal, and controversy will always remain (Nicholson et al. 2006). However, the bulk of evidence indicates that depression is more prevalent in populations with CAD (Egede 2007, Rudisch & Nemeroff 2003), is a robust risk factor for the development of CAD in healthy populations (Lett et al. 2004), and is predictive of adverse cardiovascular outcomes among populations with preexisting CAD (Barth et al. 2004, van Melle et al. 2004).

Healthy Populations

In populations without evidence of preexisting cardiovascular disease, prospective studies have demonstrated that baseline depression is associated with an increased risk of incident CAD. The INTERHEART study sought to identify modifiable risk factors for incident MI in more than 15,000 cases versus age- and sex-matched controls worldwide (Yusuf et al. 2004). As expected,

ACS: acute coronary syndrome

MI: myocardial infarction

traditional risk factors such as dyslipidemia, diabetes, and smoking were all predictive of MI. However, even after multivariate adjustment for these and other patient characteristics, psychosocial risk factors, including depression, were as strongly predictive of MI as hypertension, diabetes, and obesity. More recently, Surtees and colleagues (2008) found an independent association between depression and incident CAD in a study sample of over 20,000 adults. Likewise, Whang and colleagues (2009) reported that depressive symptoms were associated with fatal CAD and sudden cardiac death in more than 60,000 women from the Nurses' Health Study. Cumulative evidence from meta-analytic reviews has also demonstrated a statistically significant association between depression and incident CAD (Lett et al. 2004).

Patients with Existing CAD

Following the landmark study by Frasure-Smith and colleagues demonstrating that MDD is an independent risk factor for death at six months after MI (Frasure-Smith et al. 1993), many subsequent studies have verified these findings. A 2011 meta-analysis reviewed 29 studies that investigated the impact of post-MI depression on cardiovascular outcomes and found that post-MI depression was associated with a 1.5-fold increased risk of cardiovascular events and a 2.3-fold increased risk of all-cause mortality during two years of follow-up (Meijer et al. 2011). These conclusions were comparable to those of prior meta-analyses (Barth et al. 2004, Nicholson et al. 2006).

Other studies have closely examined various subtypes of depression, hypothesizing that particular characteristics may be more cardiotoxic than others. A 2009 study by Glassman and colleagues from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) found that baseline MDD severity and failure of MDD to improve during treatment with sertraline or placebo were strongly associated with long-term mortality (Glassman et al. 2009). Individuals with treatment-resistant depression after ACS have been identified as a particularly high-risk subgroup in other clinical trial populations as well, including the Enhancing Recovery in Coronary Heart Disease (ENRICHD), the Myocardial Infarction and Depression Intervention Trial (MIND-IT), and the Montreal Heart Attack Readjustment Trial (MHART) (Carney & Freedland 2009). Some studies have suggested that somatic symptoms of depression (e.g., fatigue, change in appetite, sleep disturbance) may be more cardiotoxic than cognitive symptoms (e.g., anhedonia, poor concentration, feelings of worthlessness) (Hoen et al. 2010). However, the substantial overlap between somatic symptoms and cardiovascular disease severity makes it difficult to determine whether somatic symptoms truly represent depression versus worse underlying cardiovascular disease.

CEREBROVASCULAR DISEASE

Depression is also common after stroke and predictive of adverse outcomes among patients with existing cerebrovascular disease (inadequate blood flow to affected areas of the brain, usually due to arteriosclerosis or hypertension). Many prospective studies have reported a positive association between depression and incident stroke. However, the extent to which post-stroke depression results directly from cerebral ischemia or indirectly from the associated symptoms, psychological stress, and functional limitations is unknown. A 2011 meta-analysis reviewed 28 prospective cohort studies and found that depressed patients were 45% more likely to experience a stroke compared to those who were not depressed (Pan et al. 2011). Most studies (21/28) included in this meta-analysis excluded patients with baseline cerebrovascular disease. In post-stroke patients, depression is not associated with the location of stroke in the brain but remains a significant predictor of adverse outcomes (Carson et al. 2000).

PERIPHERAL ARTERY DISEASE

A growing body of evidence indicates that depression is a risk factor for the development of PAD and for adverse outcomes among patients with existing PAD (Grenon et al. 2012, McDermott et al. 2001, Smolderen et al. 2009). PAD is caused by the obstruction of larger peripheral arteries due to atherosclerosis, anatomic stenosis, or intravascular thrombus formation, and it most often affects the lower extremities. Classically, patients with PAD experience exertional leg pain or claudication caused by inadequate blood flow. McDermott and colleagues (2001) found that the prevalence of depression varies with the degree of PAD symptoms; patients with intermittent claudication were more likely to have depressive symptoms than those with atypical or absent exertional leg pain. Depressive symptoms have also been shown to correlate with the extent of reduced walking distance as a result of PAD (Smolderen et al. 2008). Although the mechanisms of association between depression and PAD have not been studied, it is likely that they are similar to those linking depression with CAD and CVD.

HEART FAILURE

Depression is associated with an increased risk of developing HF (Abramson et al. 2001, Guck et al. 2003, Jiang et al. 2002, MacMahon & Lip 2002, O'Connor & Joynt 2004, Rozzini et al. 2002, van den Broek et al. 2011, Whooley & Browner 1998, Williams et al. 2002) and with adverse outcomes among patients with existing HF (Faris et al. 2002, Jiang et al. 2001, Joynt et al. 2004, Koenig 1998, Murberg et al. 1999, Vaccarino et al. 2001), independent of CAD and other risk factors. HF is a clinical condition in which the heart has lost its ability to supply enough blood and oxygen to the body's tissues. This can result from an inability to pump blood forward (typically referred to as systolic dysfunction) and/or an inability to relax enough for blood to return (typically referred to as diastolic dysfunction). A comprehensive meta-analysis concluded that the presence of depression was associated with a twofold greater risk of death and secondary events among patients with HF (Rutledge et al. 2006). The relationship between depression and poor HF outcomes was consistent and strong across multiple endpoints, including rehospitalization and mortality.

MECHANISMS LINKING DEPRESSION TO CARDIOVASCULAR DISORDERS

The relationship between depression and cardiovascular disorders is complex and bidirectional (Lippi et al. 2009). Patients with both conditions suffer from a mutually reinforcing cycle that can worsen both mental and physical health (**Figure 2**). Polsky and colleagues (2005) examined the risk of future development of new depressive symptoms after a diagnosis of cancer, diabetes, hypertension, CAD, arthritis, or chronic lung disease. After eight years of follow-up, patients with CAD had consistently higher rates of depression than those with other diagnoses. More recently, Kendler et al. (2009) analyzed the time-dependent effects of CAD on MDD risk and vice versa. They concluded that the effect of CAD onset on future MDD risk was stronger than the reverse because MDD was sustained over time. In contrast, the effect of MDD on future CAD risk was more significant during the year following MDD onset than in subsequent years.

The mechanisms or combination of mechanisms responsible for the links between depression and cardiovascular disorders are not completely understood. Identifying precise mechanisms is challenging not only because of the complexity and bidirectional nature of this relationship, but also because of substantial differences across studies in the assessment of depression, definition of cardiovascular disorders, and inclusion of covariates for multivariate models. Although depression
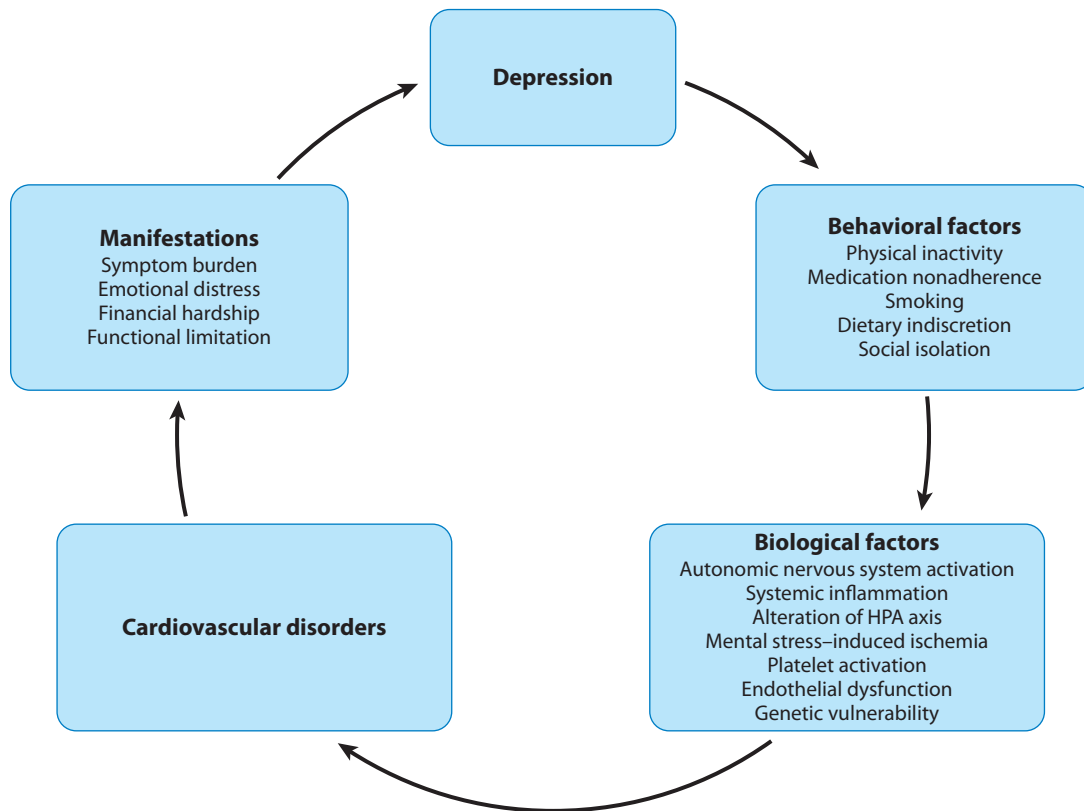
Figure 2

Conceptual model of the relationship between depression and cardiovascular disorders. HPA, hypothalamo-pituitary-adrenal.

may itself be triggered by cardiovascular disorders, the adverse outcomes associated with depression are not explained by worse clinical or subclinical cardiovascular disease (Diez Roux et al. 2006, Lett et al. 2008). Plausible pathways for the increased risk of cardiovascular disorders generally fall into two categories: biological and behavioral factors (see sidebar Mechanisms By Which Depression May Lead to Cardiovascular Events).

BEHAVIORAL FACTORS

Emerging evidence suggests that behavioral mechanisms are substantially involved in the relation between MDD and cardiovascular disorders. Generally, behavioral mechanisms considered as putative mediators include physical inactivity, nonadherence to medications, smoking, dietary indiscretion, and poor social support. Additionally, there is evidence that these poor health behaviors tend to cluster together in depressed patients (Bonnet et al. 2005). For example, Ziegelstein and colleagues (2000) determined that depressive symptoms were associated with poor adherence to diet, and lack of exercise, smoking cessation, and socializing in 144 post-MI patients. Although an increasing number of studies suggest that behavioral mechanisms play a significant role in the association between depression and cardiovascular disorders (Hamer et al. 2008a,b; Whooley et al. 2008; Win et al. 2011), it is challenging to demonstrate causality because the relationship between depression and health behaviors is bidirectional. Regardless of whether depression causes poor

MECHANISMS BY WHICH DEPRESSION MAY LEAD TO CARDIOVASCULAR EVENTS

Potential behavioral mechanisms for cardiovascular events include:

1. Physical inactivity (Whooley et al. 2008)
2. Medication nonadherence (Gehi et al. 2005)
3. Smoking (Whooley et al. 2008)
4. Dietary indiscretion (Ziegelstein et al. 2000)
5. Social isolation (Barefoot et al. 2003)

Potential biological mechanisms for cardiovascular events include:

1. Autonomic nervous system activation (Otte et al. 2005)
2. Systemic inflammation (Empana et al. 2005)
3. Activation of the hypothalamic-pituitary-adrenal (HPA) axis (Otte et al. 2004)
4. Mental stress–induced ischemia (Strike & Steptoe 2003)
5. Platelet activation and serotonergic dysfunction (Schins et al. 2004)
6. Endothelial dysfunction (Sherwood et al. 2005)
7. Common genetic vulnerability (McCaffery et al. 2006)

health behaviors or vice versa, improving health behaviors has become a key target for reducing the adverse cardiovascular outcomes associated with depression (Hamer et al. 2008a,b; Whooley et al. 2008; Win et al. 2011).

Physical Inactivity

Physical activity has important benefits for both physical health outcomes (Garber et al. 2011) and depressive symptoms (Herring et al. 2012, Krogh et al. 2010, Mead et al. 2009). A recent article from the Whitehall II study determined that regular physical activity was associated with a reduced likelihood of depressive symptoms and that individuals with baseline depressive symptoms had higher odds of not meeting recommended physical activity levels (Azevedo Da Silva et al. 2012). These bidirectional associations were also seen in a prospective study of adolescents (Stavrakakis et al. 2012).

Mounting evidence suggests that physical inactivity is a strong mediator in the relationship between MDD and secondary events among patients with existing cardiovascular disease (Blumenthal et al. 2004; Brummett et al. 2003; Hamer et al. 2008a,b; Whooley et al. 2008; Win et al. 2011). In a study of more than 1,000 outpatients with stable CAD, the Heart and Soul Study found that the association between depressive symptoms and subsequent cardiovascular events was largely explained by behavioral factors, in particular physical inactivity (Whooley et al. 2008). Several other studies have reported similar findings (Hamer et al. 2008a,b; Win et al. 2011). For example, Win and colleagues (2011) evaluated almost 6,000 patients from the Cardiovascular Health Study, a cohort that better generalizes to women, to African Americans, and to those without CAD. Using Cox regression analysis, they determined that depressive symptoms and physical inactivity were strongly associated with one another and that both of these factors independently increased the risk of cardiovascular mortality. Importantly, they also concluded that physical activity accounted for a significant proportion of the risk of cardiovascular mortality due to depressive symptoms.

Medication Nonadherence

Medication nonadherence is another health behavior that contributes to the relationship between MDD and cardiovascular disease. Depression has been associated with lower adherence to cardioprotective and other prescribed medications (Gehi et al. 2005, Rieckmann et al. 2006, Ziegelstein et al. 2000). Not surprisingly, patients with a history of MI who are not adherent to their medications have a higher risk of mortality (Gehi et al. 2007, Rasmussen et al. 2007). Medication nonadherence also predicts greater mortality in patients with hyperlipidemia (Coron. Drug Proj. 1980), diabetes mellitus (Ho et al. 2006a), HF (Granger et al. 2005), and MI (Ho et al. 2006b). In the Heart and Soul Study, medication nonadherence significantly attenuated the association between depressive symptoms and future cardiovascular events in patients with stable CAD, although the attenuation was not as large as for physical inactivity (Whooley et al. 2008).

Smoking

The relationship between smoking and depression has also received considerable attention. As many as 30% of all CAD deaths in the United States are attributed to cigarette smoking (Ockene & Miller 1997). Even nonsmokers who are exposed only to passive smoke have an increased risk of CAD compared to nonexposed individuals (He et al. 1999). Smoking cessation clearly reduces the risk of mortality in patients with CAD (Critchley & Capewell 2003, Gordon et al. 1974). Individuals with a history of depression are more than twice as likely to smoke as those without depression (Lasser et al. 2000), and the presence of depression may lower the success of smoking cessation efforts (Glassman et al. 1990).

In prospective studies, there is evidence of a bidirectional association between depression and smoking (Breslau et al. 1998). Breslau and colleagues found that daily smoking increased the risk for new-onset MDD by almost twofold and also that history of MDD was associated with a threefold increased risk for progression to daily smoking. The authors argued that separate causal mechanisms may be involved, where the depressed individual may attempt to self-medicate through smoking and smoking itself may cause neurologic changes in the dopaminergic systems that lead to depressed mood. If the link between smoking and MDD is indeed bidirectional, then smoking may act as both a mediator and confounder in the relationship between MDD and CAD. In patients with stable CAD, the Heart and Soul Study found that adjustment for smoking diminished the strength of association between depression and future cardiovascular events by more than 10%. The strength of association was reduced by 5% after adjustment for medication nonadherence and by 32% after adjustment for physical inactivity. After adjustment for all three health behaviors, the association between depressive symptoms and cardiovascular events was eliminated (Whooley et al. 2008).

Social Isolation

Social isolation has been associated with an increased risk of mortality in patients with CAD (Ruberman et al. 1984, Williams et al. 1992). Brummett and colleagues determined that CAD patients with three or fewer people in their social support network had more than twice the risk of cardiac mortality. They also found that social isolation was associated with lower income levels, higher hostility ratings, and higher smoking rates (Brummett et al. 2001). Furthermore, social isolation has been linked to depression (Barefoot et al. 2003) and may therefore represent a mechanism by which depressed patients are more likely to develop CAD and poor cardiovascular outcomes. These patients may be less likely to seek regular medical attention, adhere to their

prescribed medications, and get out of the house to exercise. Among women with CAD, both depressive symptoms and lack of social integration independently predict recurrent events five years after an acute coronary event (Horsten et al. 2000).

BIOLOGICAL FACTORS

Many biological factors have been implicated in the association between depression and cardiovascular disease. Candidate pathways include autonomic nervous system (ANS) dysfunction, inflammation, activation of the hypothalamic-pituitary-adrenal (HPA) axis, mental stress–induced ischemia, platelet activation or other disruptions to the clotting cascade, subclinical vascular changes (endothelial dysfunction), and common genetic factors. Since many of these biological changes can result from poor health behaviors, there is an emerging consensus that the biological changes associated with depression may be downstream effects of poor health behaviors rather than parallel mechanisms linking depression with cardiovascular disease (**Figure 2**).

Autonomic Nervous System Activation

The ANS is divided into the opposing sympathetic and parasympathetic divisions that act to control heart rate, cardiac contractility, vasodilation, and other critical functions. Conditions that cause sympathetic activation include physical activity, coronary ischemia, heart failure, and mental stress. Hyperactivity of the sympathetic system can increase the risk of poor cardiovascular outcomes, including death (Curtis & O'Keefe 2002). Depressed patients tend to have higher levels of circulating catecholamines, a marker of sympathetic activation (Carney et al. 2005b, Otte et al. 2005, Veith et al. 1994), which may contribute to the excess risk of cardiovascular disease associated with depression. In one study, however, adjustment for elevated levels of urinary catecholamines did not change the strength of association between depressive symptoms and cardiovascular events (Whooley et al. 2008).

Another marker of ANS dysfunction is decreased heart rate variability (HRV). Normally, the heart rate fluctuates from beat to beat, reflecting the balance between the sympathetic and parasympathetic inputs to the heart's conduction system. Lack of variability in heart rate (low HRV) is an independent predictor of mortality after MI (Kleiger et al. 1987). Decreased HRV has been associated with depression in patients after acute MI (Carney et al. 2001, 2005a), in patients with somatic depressive symptoms and stable CAD (de Jonge et al. 2007), and in a community-based sample of patients with depression who had low rates of CAD (Licht et al. 2008). In 907 patients from the Cardiovascular Health Study, Kop et al. (2010) reported that ANS dysfunction as measured by HRV and markers of inflammation contributed to the increased cardiovascular mortality risk associated with depression. However, another study found that adjustment for HRV did not change the strength of association between depressive symptoms and cardiovascular events (Whooley et al. 2008).

Systemic Inflammation

Inflammation is central to the process of atherosclerosis at every stage and is elevated in patients with obesity, insulin resistance, and diabetes (Rocha & Libby 2009). Increased levels of circulating inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin 6 (IL-6), predict incident cardiovascular disease in healthy populations (Engstrom et al. 2004, Ridker et al. 2001) and adverse cardiovascular events in diseased populations (Everett et al. 2006, Ridker 2007). It is uncertain whether these inflammatory markers directly contribute to cardiovascular disease, but

ANS: autonomic nervous system

HPA: hypothalamic-pituitary-adrenal

HRV: heart rate variability

CRP: C-reactive protein

IL-6: interleukin-6

they clearly reflect greater local arterial and tissue inflammation as well as overall plaque burden and thrombosis (Hansson 2005).

Observational studies have shown that depressed patients have higher levels of inflammatory biomarkers than do healthy controls (Empana et al. 2005, Howren et al. 2009, Vaccarino et al. 2007). In 2007, Frasure-Smith and colleagues reported that depression and CRP were largely overlapping prognostic risks for future cardiovascular events after 2 years of follow-up in patients who recently survived an ACS, suggesting that similar therapies may treat both conditions (Frasure-Smith et al. 2007). In fact, a double-blind study randomized 100 patients to sertraline or placebo for 20 weeks and found that the group receiving sertraline had improvements in depression and reductions in inflammatory biomarkers, including CRP, IL-6, and fibrinogen (Pizzi et al. 2009). Duivis and colleagues (2011) found a correlation between severity of depressive symptoms and elevated CRP and IL-6 levels in outpatients with stable CAD. However, this association was explained primarily through behavioral factors, specifically physical inactivity, smoking, and obesity.

Activation of the Hypothalamic-Pituitary-Adrenal Axis

Elevated cortisol levels as a result of enhanced activity of the HPA axis are another possible biological mechanism in the link between depression and cardiovascular disease (Brown et al. 2004). In response to stress or illness, the hypothalamus releases corticotropin-releasing hormone (CRH). CRH is transported to the anterior pituitary, which stimulates the secretion of adrenocorticotropin hormone-releasing hormone (ACTH). ACTH then enters the circulation and stimulates the adrenal gland to release cortisol. Depression in otherwise medically healthy (Posener et al. 2000, Vreeburg et al. 2009) and CAD patients (Otte et al. 2004) is associated with elevated cortisol levels.

There is also evidence that cortisol levels may be predictive of cardiovascular disease outcomes. Higher baseline serum cortisol predicted death caused by cardiovascular disease in inpatients with mood disorder (Jokinen & Nordstrom 2009), suggesting that HPA axis dysregulation may be involved in the association between depression and cardiovascular disease. However, the Heart and Soul Study found that adjustment for 24-hour urinary cortisol levels did not change the strength of association between depressive symptoms and adverse cardiovascular outcomes (Whooley et al. 2008).

Mental Stress–Induced Ischemia

Considerable evidence suggests that mental stress can contribute to the development of CAD and to adverse cardiovascular outcomes among patients with existing CAD (Gullette et al. 1997, Rozanski et al. 1988, Ziegelstein 2007). The physiologic effects of mental stress are thought to be mediated in part by catecholamine release (Becker et al. 1996, Goldberg et al. 1996), causing increases in heart rate and blood pressure while at the same time decreasing coronary blood flow and increasing systemic vascular resistance (Goldberg 1996, Jain et al. 1998, Kop et al. 2001, Strike & Steptoe 2003, Yeung et al. 1991). Current evidence indicates that mental stress–induced ischemia is a predictor of worse outcomes in patients with CAD (Jiang et al. 1996, Sheps et al. 2002, Specchia et al. 1991). Since depression is highly correlated with perceived stress, these episodes may contribute to the excess risk of cardiovascular disease associated with depression. Some have suggested that, regardless of depression, stress management in patients with CAD may be an important target leading to improved outcomes and decreased medical expenditures (Brosse et al. 2002).

Stress can also cause another cardiomyopathic condition called transient left ventricular apical ballooning syndrome (also known as takotsubo-like ventricular dysfunction, stress-induced

cardiomyopathy, ampulla cardiomyopathy, or broken heart syndrome). First described in Japan (Dote et al. 1991), takotsubo means pot with a round bottom and narrow neck and was named as such because of the appearance of the left ventricle on echocardiography (Gianni et al. 2006). This clinical syndrome is preceded by a severe emotional or physical stress, presumably through a surge of catecholamines (Abe et al. 2003). It is often misdiagnosed as acute coronary syndrome because it typically presents with chest pain, electrocardiographic changes, and elevated cardiac biomarkers. However, coronary angiography, which is used to visualize the coronary arteries, is normal in most patients. Postmenopausal females account for almost 90% of reported cases.

Platelet Activation and Serotonergic Dysfunction

Disruption in brain serotonergic signaling is believed to be involved in the pathophysiology of depression. It is well known that 99% of serotonin found in the human body is stored in platelets and that serotonin can induce downstream platelet aggregation and coronary vasoconstriction (Musselman et al. 1998). Therefore, over 20 years ago, investigators hypothesized that the association between depression and cardiovascular disease may be mediated by platelet dysfunction (Markovitz & Matthews 1991). Since then, many other investigators have reported that depression is associated with increased blood serotonin levels (Wulsin et al. 2009), platelet reactivity (Musselman et al. 1996, Schins et al. 2004), density of serotonin receptors, sensitivity to platelet aggregation in response to serotonin, and serotonin transporter dysfunction on the platelet cell surface (Ziegelstein et al. 2009). However, the Heart and Soul Study found no association of MDD with either platelet activation (Gehi et al. 2010) or levels of whole-blood serotonin and no evidence that adjustment for serotonin levels reduced the strength of association between depressive symptoms and cardiovascular events (Whooley et al. 2008).

In addition to their actions in the brain, selective serotonin reuptake inhibitors (SSRIs) inhibit platelet aggregation, likely by decreasing intracellular serotonin levels (Maurer-Spurej et al. 2004). Clinical studies have shown that SSRIs may attenuate platelet activation in depressed patients. In the SADHART study, Serebruany and colleagues (2003) studied the effect of SSRIs on platelet function in 64 patients who were randomized to sertraline or placebo after acute coronary syndrome. They found that treatment with sertraline was associated with substantially less release of platelet biomarkers compared to placebo. However, these findings were most likely due to the direct physiological effects of SSRIs on platelets rather than mediated through a reduction in depressive symptoms. In the Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE) trial, treatment with citalopram was not associated with a decrease in platelet activation markers (P-selectin, β-thromboglobulin, and sICAM-1) (van Zyl et al. 2009).

Endothelial Dysfunction

Vascular changes, such as endothelial dysfunction, reduced vasodilation, and decreased levels of nitric oxide may also be involved in the relationship between depression and cardiovascular disease (Sher et al. 2010), but the literature is mixed. A recent meta-analysis concluded that depression was associated with decreased vascular reactivity in cross-sectional studies (Cooper et al. 2011). However, Yang and colleagues (2007) found that depression was not associated with endothelial dysfunction in the coronary arteries of 759 patients without CAD. Chrapko and colleagues (2004) reported that nitric oxide was significantly lower in subjects with MDD compared to healthy controls. This was important because nitric oxide is a key mediator of endothelial function that regulates vascular tone, stabilizing low-density lipoproteins and inhibiting proliferation of smooth muscle cells, which helps to limit the process of atherosclerosis. In a follow-up study, they determined

that paroxetine treatment increased nitric oxide levels, although this was likely due to the direct effects of paroxetine rather than any reduction in depressive symptoms (Chrapko et al. 2006).

5-HTTLPR:
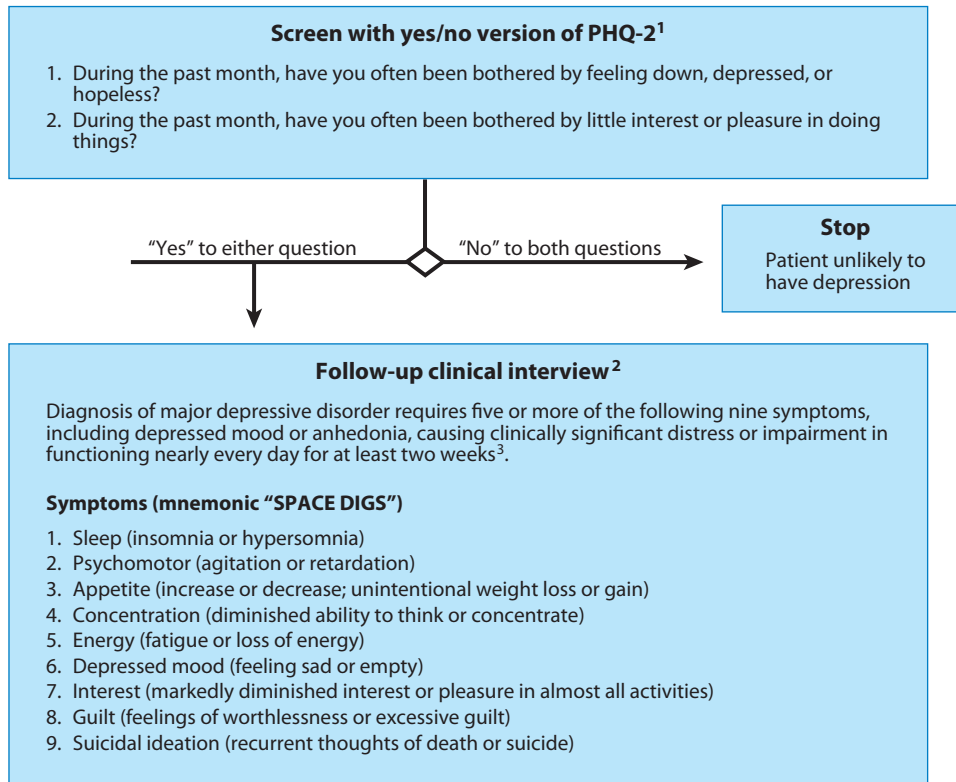promoter region of the serotonin transporter gene

Common Genetic Factors

Cardiovascular disease and traditional risk factors, such as hypertension and dyslipidemia, are known to have genetic determinants (Ordovas & Smith 2010). Since MDD can also be hereditary, it has been suggested that common genetic factors may increase vulnerability to both MDD and cardiovascular disease (Bozzini et al. 2009, McCaffery et al. 2009, Vaccarino et al. 2008). Many studies have focused on a specific variation in the polymorphic region of the serotonin transporter gene (5-HTTLPR) that may increase vulnerability to depression after a stressful life event (Caspi et al. 2003). Nakatani and colleagues (2005) reported that the S allele of 5-HTTLPR was associated with both depressive symptoms (OR = 2.2; 95% CI = 1.2–4.0) and risk of future cardiac events (hazard ratio = 1.7; 95% CI = 0.8–2.0) after MI. Another study by Otte and colleagues (2007) reported an association between the S allele and depression among patients with CAD. However, a subsequent meta-analysis concluded there was no evidence that the 5-HTTLPR polymorphism, either alone or in interaction with stressful life events, was associated with an elevated risk of depression (Risch et al. 2009). Thus, further research is necessary to determine whether genetic factors may increase vulnerability to both depression and cardiovascular disease.

Finally, recent research has pointed to telomere length as a possible link between depression and cardiovascular disease. Shortened telomeres, a biological marker of cellular aging, have been linked with both depression (Hoen et al. 2011, Wolkowitz et al. 2011) and adverse cardiovascular outcomes (Farzaneh-Far et al. 2008). Increased activity of telomerase, the enzyme that rebuilds telomere length, has also been linked to depression and may predict treatment response to SSRIs (Wolkowitz et al. 2012). However, Hoen and colleagues (2011) found that depression did not predict five-year change in leukocyte telomere length, suggesting that the previously observed association between depression and telomere length may be due to other factors, such as worse cardiovascular disease severity among depressed patients.

SCREENING AND DIAGNOSIS

Patients with cardiovascular disease should be screened for depression in health care settings that have collaborative care management programs in place to offer effective treatment and follow-up. Medicare currently reimburses for annual depression screening, but the optimal frequency of screening is unknown. In settings that do not have collaborative care management programs in place, neither the US Preventive Services Task Force nor the UK National Health Service recommends screening adults for depression (Natl. Inst. Health Clin. Excell. 2009, U.S. Prev. Serv. Task Force 2009). Since most cardiology practices are unable to provide the collaborative care management necessary for depression screening to provide benefit (Feinstein et al. 2006), it makes most sense for patients with cardiovascular disorders to be screened and treated for depression in the primary care setting.

Collaborative care is a team-based approach for managing depression that involves the primary care provider, a depression care manager, and a consulting psychiatrist (Katon et al. 2010). The care manager (usually a trained nurse) provides patient education and behavioral activation, close telephone follow-up, symptom monitoring, and timely stepped care for nonresponders. A consulting psychiatrist helps the care manager by supervising and assisting with patient management, including medication adjustment and augmentation of therapy. When a collaborative care

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Screen with yes/no version of PHQ-2[1]

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?

"Yes" to either question   "No" to both questions   ⟶   **Stop**

Patient unlikely to have depression

Follow-up clinical interview[2]

Diagnosis of major depressive disorder requires five or more of the following nine symptoms, including depressed mood or anhedonia, causing clinically significant distress or impairment in functioning nearly every day for at least two weeks[3].

Symptoms (mnemonic "SPACE DIGS")

1. Sleep (insomnia or hypersomnia)
2. Psychomotor (agitation or retardation)
3. Appetite (increase or decrease; unintentional weight loss or gain)
4. Concentration (diminished ability to think or concentrate)
5. Energy (fatigue or loss of energy)
6. Depressed mood (feeling sad or empty)
7. Interest (markedly diminished interest or pleasure in almost all activities)
8. Guilt (feelings of worthlessness or excessive guilt)
9. Suicidal ideation (recurrent thoughts of death or suicide)

Figure 3

Recommended algorithm for diagnosing depression in primary care patients (adapted from Whooley 2006). PHQ-2, two-item Patient Health Questionnaire. Footnotes: [1]Whooley et al. (1997), [2]Kroenke (2002), [3]Am. Psychiatr. Assoc. (2000).

program is in place, screening and treatment of depression can improve depressive symptoms and quality of life (Gilbody et al. 2006, Williams et al. 2007).

Because some symptoms of depression (e.g., lack of energy, loss of appetite, sleep disturbance) overlap with those of cardiovascular disorders, identifying depression in these patients can be challenging. Currently, the yes/no version of the two-item Patient Health Questionnaire (PHQ-2) is a simple and effective screening tool for identifying MDD in primary care patients (Whooley et al. 1997). It has excellent sensitivity in patients with cardiovascular disease and can be performed in less than one minute (McManus et al. 2005). As with all depression screening instruments, the specificity and positive predictive value of the PHQ-2 is relatively poor for MDD. Therefore, a clinical interview is necessary to confirm the diagnosis (**Figure 3**). As an alternative to a clinical interview, some practitioners administer the nine-item Patient Health Questionnaire (PHQ-9) (Kroenke et al. 2001), a self-report instrument that measures the frequency of each of the nine *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; Am. Psychiatr. Assoc. 2000) depressive symptoms over the previous two weeks (not at all = 0, several days = 1, more than half the days = 2, nearly every day = 3). Total scores range from 0 to 27 based on the number and frequency of depressive symptoms.

In clinical settings, it is reasonable to make a diagnosis and start therapy for MDD based on a PHQ-9 score of ≥10 if one of the two core symptoms (depressed mood or anhedonia) is present

PHQ: Patient Health Questionnaire

and the symptoms are associated with functional impairment. In research settings, the PHQ-9 is an excellent choice for measurement of depressive symptoms because it is much shorter than, yet has similar test characteristics to, other commonly used instruments (such as the Center for Epidemiological Studies Depression Scale and the Beck Depression Inventory) (Whooley et al. 1997). The PHQ-9 also provides a useful metric for monitoring response to therapy. However, it must be kept in mind that the PHQ-9 was developed as a depression severity measure (not a diagnostic instrument), and a cut point of ≥10 misses a small minority of cases of MDD that would be detected by a clinical interview.

There is considerable debate about the importance of differentiating a diagnosis of MDD from depressive symptoms that do not meet DSM-IV criteria for MDD. Most studies have found that MDD and the presence of depressive symptoms are associated with similar increases in risk of cardiovascular disease. In one study, patients with depressive symptoms (PHQ-9 score ≥10) and no MDD diagnosis actually had worse cardiovascular outcomes than patients with an MDD diagnosis alone (Elderon et al. 2011). This suggests that depressive symptoms may be even more important for cardiovascular prognosis than a DSM-IV diagnosis of MDD. We view depression as a continuum of illness that varies in severity and duration rather than as a rigid, criteria-based diagnosis (Judd & Akiskal 2000, Kendler & Gardner 1998).

The differential diagnosis of depression includes hypothyroidism, bipolar disorder, substance abuse, and medication toxicity. Problem drinking and substance abuse are important considerations, but the presence of these conditions should not preclude antidepressant therapy because stabilizing mood symptoms can help prevent relapse (Nunes & Levin 2004, Ostacher 2007). Some medications, such as interferon alpha, corticosteroids, and benzodiazepines, are associated with depression (Loftis & Hauser 2004, Patten & Love 1993), but the anecdotal belief that beta-blocker therapy causes depressive symptoms is not supported by data from clinical trials (Ko et al. 2002).

CLINICAL MANAGEMENT

Treatment options for depressed patients include self-management (empowering patients through education, counseling, and exercise), psychotherapy, and antidepressant medications. Choice of therapy depends on the severity of depressive symptoms, degree of functional impairment, availability of resources, and patient preference (Whooley 2012). Several randomized trials of depression treatment have been conducted in patients with cardiovascular disease (**Table 1**), including three suggesting that therapy may improve cardiovascular outcomes (Davidson et al. 2010, Gulliksson et al. 2011, Katon et al. 2010). However, regardless of its effects on cardiovascular outcomes, treatment of depression should be initiated to reduce depressive symptoms and improve quality of life.

Self-Management

Self-management strategies are recommended for all patients with depression. Critical to this approach is an emphasis on behavioral activation and physical activity, which can significantly improve depressive symptoms in addition to their beneficial effects on physical health (Blumenthal et al. 2012a,b; Cuijpers et al. 2007; Dimidjian et al. 2011). Recently, Herring and colleagues (2012) performed a systematic review demonstrating that exercise training improves depressive symptoms in patients with chronic illnesses. Among patients with cardiovascular disorders, pharmacotherapy and exercise interventions have shown similar effectiveness in improving depressive symptoms (Blumenthal et al. 2012a,b; Rimer et al. 2012).

Most adults should engage in moderate-intensity exercise for at least 150 minutes per week (e.g., walking for 30 minutes five times per week), or vigorous-intensity exercise for at least 75 minutes per week (e.g., running for 25 minutes three times per week), or a combination of moderate- and vigorous-intensity exercise (Garber et al. 2011). Although depression itself is often a barrier to physical exercise, the improvements in both depressive symptoms and physical health outcomes make it an imperative component of any treatment strategy. Coordinated support from health care providers, spouses, and family may be necessary to ensure adherence (Flynn et al. 2009, O'Connor et al. 2009).

Psychotherapy

In patients with mild to moderate depression, psychotherapy together with self-management is the most appropriate first-line treatment (Cuijpers et al. 2009, Whooley 2006). Benefits from cognitive behavioral therapy (CBT) have been demonstrated in two studies of patients with cardiovascular disease (Berkman et al. 2003, Gulliksson et al. 2011). In the ENRICHD trial, post-MI patients with depression or low social support who were randomized to CBT had significantly reduced depressive symptoms within six months compared to the group receiving usual care (Berkman et al. 2003). The Secondary Prevention in Uppsala Primary Health Care project (SUPRIM) trial randomly assigned 362 patients who were discharged from the hospital after a CAD event to traditional care versus traditional care plus a CBT program focused on stress management for one year. Although depression was not an inclusion criterion for this study, patients assigned to CBT had a 41% lower rate of recurrent cardiovascular events during a mean of 7.8 years of follow-up (p = 0.002), and there was a strong dose-response relationship between intervention group attendance and outcome.

Pharmacotherapy

In patients with moderate to severe MDD, antidepressant medications are effective at reducing depressive symptoms (Baumeister et al. 2011, Moncrieff et al. 2004, Rayner et al. 2010). Only a few studies have investigated the effectiveness of pharmacotherapy in patients with cardiovascular disease, but current evidence suggests that SSRIs are safe to use in this population and that tricyclics should be avoided (Roose 2003). In the SADHART-CAD trial, six months of sertraline was superior to placebo in improving depressive symptoms on the Clinical Global Improvement scale but not on the Hamilton Depression Rating Scale (HAM-D) (Glassman et al. 2002). In the CREATE trial, three months of citalopram was superior to placebo in reducing depressive symptoms after 12 weeks as measured by the HAM-D in patients with CAD (Lesperance et al. 2007). In the SADHART-CHF trial, sertraline was found to be no different than placebo in reducing depressive symptoms among patients with HF (O'Connor et al. 2010). However, both the intervention and control arms received a nurse-facilitated support intervention, making it difficult to detect any added benefit of sertraline over nurse-facilitated support alone.

Whether antidepressant medication reduces the risk of cardiovascular events in patients with cardiovascular disease is unknown. Although this should not be a factor in the decision to initiate treatment for depression, one small randomized trial has raised the possibility that depression treatment may actually improve cardiovascular outcomes. In the Coronary Psychosocial Evaluation Studies randomized controlled trial, Davidson and colleagues (2010) randomly assigned 157 postacute coronary syndrome patients with persistent depressive symptoms to a six-month interdisciplinary, stepped-care intervention adapted from the IMPACT model versus usual care. At the end of the trial, major adverse cardiac events had occurred in 4% (3/80) of intervention

Table 1   Randomized trials of antidepressant therapies in patients with cardiovascular disease (in chronological order)

Study	Reference	N	Patient population	Intervention	Control	Duration of intervention	Depression outcome	Cardiovascular outcome
M-HART*	Frasure-Smith et al. (1997)	1,376	Post-MI	Monthly telephone monitoring for psychological distress + home nursing support for distressed patients	Usual care	12 months	No benefit	No benefit; trend toward higher mortality in women
Strik et al.	Strik et al. (2000)	54	Post-MI + MDD	Fluoxetine	Placebo	6 months	No benefit	No adverse effects
SADHART-CAD	Glassman et al. (2002)	369	Post-MI or unstable angina + MDD	Sertraline	Placebo	6 months	Improvement	No adverse effects
Lincoln and Flannaghan	Lincoln & Flannaghan (2003)	123	Post-stroke + depressive symptoms	Cognitive behavioral therapy	Attention placebo or usual care	3 months	No benefit	Not reported
ENRICHD	Berkman et al. (2003)	1,834	Post-MI + MDD	Cognitive behavioral therapy ± sertraline	Usual care	3 months	Improvement	No benefit
MIND-IT	Honig et al. (2007), van Melle et al. (2007)	331	Post-MI + MDD	Mirtazapine ± stepped care	Placebo	6 months	Improvement	No adverse effects
CREATE	Lesperance et al. (2007)	284	Stable CAD + MDD	Citalopram	Placebo	3 months	Improvement	No adverse effects

CREATE	294	Stable CAD + MDD	Interpersonal therapy	Clinical management	3 months	Improvement	No adverse effects
SADHART-CHF	469	Heart failure + MDD	Nurse-facilitated support + sertraline	Nurse-facilitated support	3 months	No benefit	No benefit
TEAMcare	214	Poorly controlled CAD or diabetes + depressive symptoms	Collaborative care	Usual care	12 months	Improvement	Improved blood pressure, glycohemoglobin, and LDL cholesterol
COPES	157	Post-ACS + 3 months of depressive symptoms	Problem-solving therapy and/or antidepressant medication	Usual care	6 months	Improvement	Fewer cardiac events
SUPRIM*	362	Within 12 months of hospitalization for CAD event	Cognitive behavioral therapy	Usual care	12 months	Not reported	Fewer cardiac events

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

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; COPES, Coronary Psychosocial Evaluation Studies randomized controlled trial; CREATE, Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy; ENRICHD, Enhancing Recovery in Coronary Heart Disease Patients; LDL, low-density lipoprotein; MDD, major depressive disorder; M-HART, Montreal Heart Attack Readjustment Trial; MI, myocardial infarction; MIND-IT, Myocardial Infarction and Depression-Intervention Trial; SADHART-CAD, Sertraline Antidepressant Heart Attack Randomized Trial-Coronary Artery Disease; SADHART-CHF, Sertraline Against Depression and Heart Disease in Chronic Heart Failure; SUPRIM, Secondary Prevention in Uppsala Primary Health Care Project.

versus 13% (10/77) of usual care patients (p = 0.047). A subsequent cost-effectiveness analysis determined that the intervention was not only cost effective but was actually cost saving because the higher cost of mental health care in the intervention group was more than offset by reductions in subsequent hospitalization costs for cardiac events (Ladapo et al. 2012).

Several observational studies also point to a potentially protective effect of SSRIs. Ziegelstein and colleagues (2007) retrospectively studied more than 1,000 patients with ACS and found that those who received SSRIs had more in-hospital bleeding but were less likely to have recurrent MI, HF, or asymptomatic cardiac enzyme elevation. In a nursing home population of elderly patients, patients who responded to SSRIs had a 60% reduction in cardiovascular events over the following year (Santangelo et al. 2009). In a posthoc analysis of the ENRICHD trial, participants who received sertraline had a 42% reduction in risk of death or recurrent MI (Berkman et al. 2003). In the SADHART trial, the risk of death and recurrent MI was 20% lower in patients randomized to the sertraline group (Glassman et al. 2002). However, the study was not powered to evaluate cardiovascular events, and this difference was not statistically significant.

Follow-up

In addition to the details of individual antidepressant therapy for patients with cardiovascular disorders, the model of care delivery has been a research topic of increasing interest. Emerging evidence suggests that the best outcomes are achieved using a team-based approach in which a nurse case manager works with each patient's primary care provider and a supervising psychiatrist to simultaneously provide guideline-based management for both depression and cardiovascular disease. One key component of collaborative care is repeated monitoring of symptoms. Just as blood pressure, lipid, and glycohemoglobin levels must be measured and tracked for optimal titration of therapies, so too must depressive symptoms be monitored and tracked with timely stepped care and adjustment of therapy. Once remission is achieved, patients should continue antidepressant therapy for at least six months. Lifetime therapy may be necessary for patients with recurrent major depressive episodes.

The TeamCare study randomly assigned 214 patients with depressive symptoms and poorly controlled CAD or diabetes to a 12-month collaborative care intervention versus usual care (Katon et al. 2010). In the intervention group, a supervised nurse case manager worked with each patient's primary doctor to provide guideline-based management to control cardiac risk factors. In addition to following blood pressure, glycohemoglobin, and lipid levels, the nurse measured depressive symptoms every two to three weeks until patients achieved the targeted reduction in symptoms and every four weeks thereafter. As compared with controls, patients in the intervention group had greater overall 12-month improvement in glycohemoglobin levels, low-density lipoprotein cholesterol levels, systolic blood pressure, depression scores, quality of life, and satisfaction with care. Costs of the intervention were similar to those of usual care.

SUMMARY AND FUTURE DIRECTIONS

Over the past two decades, we have seen rapid growth in research relating to depression and cardiovascular disorders. Some of this research has contributed directly to significant changes in the way health providers approach depression in the setting of cardiovascular disease. Physical activity and other health behaviors have been identified as key mediators in this relationship. Guidelines have called for depression screening in all patients with CAD when it is combined with a collaborative care approach to treatment (Lichtman et al. 2008). Medicare now covers annual screening for depression in primary care settings (when collaborative care management is

in place), and specific funding strategies have been proposed to continue supporting the delivery of collaborative care (Bachman et al. 2006, Bao et al. 2011).

Despite these advances in our understanding of depression and cardiovascular disorders, important questions remain. We have identified five important directions that are most immediately critical toward meaningful progress in the field of depression and cardiovascular disease: (*a*) implement simultaneous management of both depression and cardiovascular disease using collaborative care (also known as TeamCare) models in the primary care setting; (*b*) determine the optimal frequency of depression screening; (*c*) measure the impact of new depression screening and management guidelines in clinical practice; (*d*) better understand how depression is related to cardiovascular disorders other than CAD, including cerebrovascular disease, peripheral arterial disease, atrial fibrillation, and other arrhythmias; and (*e*) identify methods to improve health behaviors, especially physical activity, medication adherence, and smoking, in all patients with cardiovascular disease.

DISCLOSURE STATEMENT

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Errata

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