[REVIEW]

DEPRESSION AND CORONARY ARTERY DISEASE:

The Association, Mechanisms, and Therapeutic Implications

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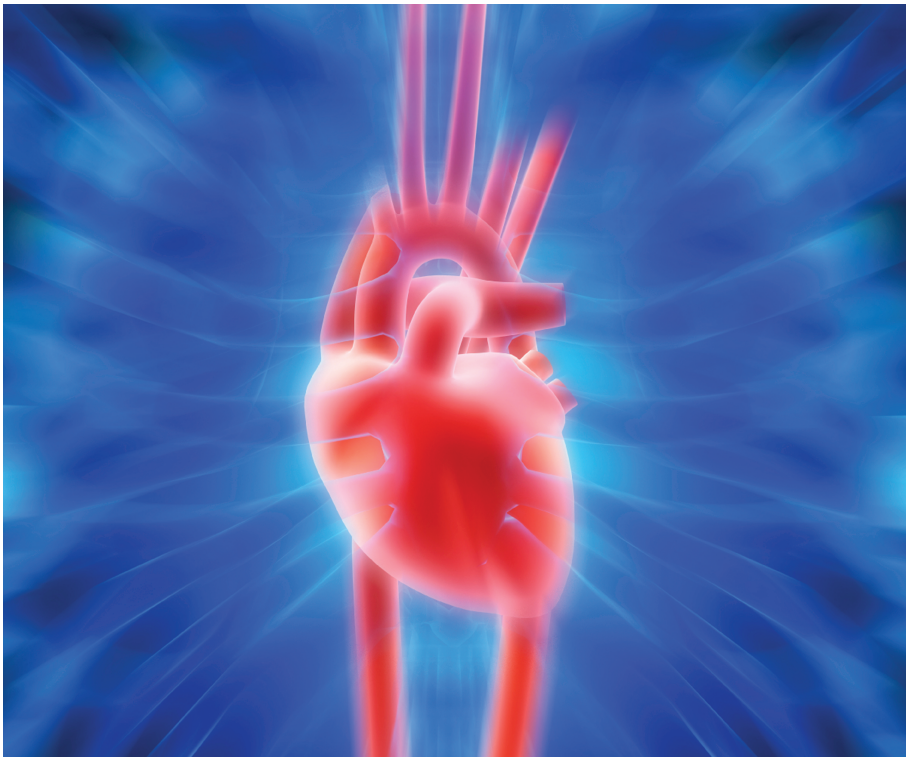
ABSTRACT

We performed a comprehensive review of the literature to determine whether or not a relationship between depression and coronary artery disease exists. Our literature search supports the following: Depression and coronary artery disease have a bidirectional relationship, i.e., coronary artery disease can cause depression and depression is an independent risk factor for coronary artery disease and its complications; depression may contribute to sudden cardiac death and increase all causes of cardiac mortality; and depression contributes to unhealthy lifestyle and poor adherence to treatment. We review various pathophysiological links between depression and coronary artery disease and screening for depression in at-risk patients for coronary artery disease. We also discuss pharmacological treatments, their implications, and various behavioral treatments.

INTRODUCTION

Coronary artery disease (CAD) has emerged as the leading cause of death and disability in the United States.



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According to an estimate by the World Health Organization (WHO), by the year 2020, both CAD and depression will be the two major causes of disability-adjusted life years.[1] CAD continues to be a major focus of clinical and epidemiological research. Nonmodifiable cardiovascular risk factors, such as age, gender, family history, and race, as well as modifiable risk factors, such as hypertension, weight, smoking, sedentary lifestyle, abnormal lipid profiles, inflammatory markers, diabetes, metabolic syndrome, and subclinical CAD, are associated with increased cardiovascular risk.[2–7]

Despite these findings, typically measured risk factors do not fully account for all the variation in outcomes.[8] There is a lack of a definitive correlation between high-risk profiles, biological profiles, and the occurrence of CAD. A number of psychological states and traits, such as depression, anxiety, anger, and stress, have also been implicated as potential risk factors for CAD.

BIDIRECTIONAL RELATIONSHIP OF DEPRESSION AND CAD

Cross-sectional and longitudinal data suggest a bidirectional link between depression and CAD.

CAD can cause major depressive disorder. In cross-sectional studies done in the past, between 19 and 66 percent of patients with myocardial infarction (MI) have some mental disorder, primarily depressive and anxiety states.[9,10,11–14] In several studies,[15–17] 17 to 44 percent of patients with CAD also have a diagnosis of major depression. Another study found that 27 percent of patients undergoing coronary artery bypass graft surgery (CABG) had depression after the surgery.[18]

In an another study,[19] a history of MI was independently associated with in-hospital depressive symptoms. Results of these studies with high prevalence of depression in this population of CAD patients gain more significance when they are compared to 6.6 percent one-year prevalence of major depressive disorder in a community sample.[20]

Depression is an independent risk factor for CAD and its complications. The role of depression in the pathogenesis of CAD has been examined in various longitudinal studies.[21–29] Studies summarized in Table 1 support the theory that depression is an independent risk factor for development of CAD and its complications.[22–28,30–32]

In the Baltimore cohort of the Epidemiologic Catchments Area (ECA) Study, patients with a history of dysphoria or depression have 4.5 times the relative risk of having an acute MI at follow up compared to nondepressed patients, independent of the coronary artery risk factors.[22]

Lesperance et al[33] examined 222 patients for depression after they were admitted to the hospital for acute MI. Patients were evaluated for depression using a modified version of the Diagnostic International Schedule (DIS). Depression ratings were completed at the initial hospitalization for MI and at one week, six months, and 12 months post-MI. This study controlled for patient's age and cardiovascular health. At six months, 6 to 12 months, and 13 to 18 months, there were six, seven, and eight deaths, respectively (total of 21 deaths), which were all associated with depression. Also patients who had depression during hospitalization were more likely to have had previous depression and to become depressed after discharge.

The onset of an MI is often observed to be preceded by a prodrome of decreasing energy, general malaise, and minor depression.[34] In a large, prospective, follow-up study[35] of 4,367 men and women older than 60 with isolated systolic hypertension, the risk of death (RR, 1.25; 95% CI, 1.15–1.36) and stroke or MI (RR, 1.18; 95% CI, 1.08–1.30) was associated with a progressive increase in depressive symptoms during an average follow-up time of 4.5 years

Previous history of depression is a predictor of congestive hear failure (CHF) after an acute MI.[36] In a multicenter trial, Lauzon et al[37] followed patients for a year to measure prevalence and prognostic effects of depression after acute MI. In recruited patients, a nurse practitioner documented acute MI within 2 to 3 days of admission. Patients completed Beck Depression Inventory (BDI) during their hospitalization and then at 30 days, six months, and one year post-MI.

Depressed patients had higher rates of cardiac complications, including recurrent ischemia, infarction, or CHF during their first hospital stay or readmission for angina, recurrent acute MI, CHF, or arrhythmias (adjusted HR 1.4, 95% CI 1.05–1.86) as compared to nondepressed patients.[38] These results were consistent across all demographic subgroups. These studies further add to the significance of depression and CAD relationship as they suggest that depression has an effect on CAD as well as on its complications.

DEPRESSION CAN CAUSE SUDDEN CARDIAC DEATH AND INCREASES ALL CAUSES OF CARDIAC MORTALITY

Depression and sudden cardiac death (SCD). Several studies suggest that patients who experience depression after an MI are at higher risk for SCD. In a Washington state health maintenance organization (HMO) study from 1980 to 1994, Empana et al[39] compared 2,228 patients with depression to a control group of 4,164 patients. Patients in both groups were ages 40 to 79. He found that presence and severity of clinical depression in patients is associated with higher risk of cardiac arrest resulting in death. In this case-controlled study, they found that clinically depressed patients had a higher odds ratio (OR) of a cardiac arrest (OR, 1.88; 95% CI, 1.59–2.23). This finding persisted even after adjustment for confounding factors, such as cigarette smoking, heavy alcohol consumption, diabetes, hypertension, prior MI, and prior CHF (OR, 1.43; 95% CI, 1.18–1.73). Compared with nondepressed patients, the risk of cardiac arrest increased in less severely depressed

TABLE 1. Depression as an independent risk factor for cardiovascular disease

RESEARCH	SAMPLE	SUMMARY OF FINDINGS
Barefoot and Schroll (1996)[32]	975 (730 Corrected)	Depression was associated in a Danish sample with a 1.7 relative risk of MI and 1.6 relative risk of all cause mortality over a 27-year follow up.
Pratt et al (1996)[22]	1,551	History of major depression was associated with a 4.5 relative risk of MI (Epidemiological Catchment Area Study).
Ford et al (1998)[23]	1,190	Former Johns Hopkins Medical students followed with annual self-reported depression for a mean of 35 years. Men with depression had a higher relative risk of developing CVD that was strongly related to MI not stroke.
Sesso et al (1998)[24] (Normative aging study)	1,305	Men with elevated depression scores on various MMPI-2 subscales had an increased relative risk (1.46-2.07) of incident coronary disease and angina over a 7-year follow up.
Pennix et al (1998)[25]	3,701	In men >70 years, those with newly depressed mood at baseline of study (diagnosed by CEDS) had an increase relative risk of 2.03 in developing new cardiac events during a 6-year period. Newly depressed men not women were approximately twice as likely to have CVD as those who were not depressed.
Mendes de Leon et al (1998)[27]	2,812	Among women, depressive symptomatogy, determined by CEDS, was associated with relative risk of 1.03 for cardiac mortality and total incidence of cardiac disease.
Whooley et al (1998)[26]	7,518	Women scoring high on Geriatric Depression Scale were at increased relative risk (1.8) during 7-year follow up.
Simonsick et al (1995)[31]	691	High depressive symptoms in older adults diagnosed with hypertension may place them at increased risk for cardiovascular disease over a 6-year period.
Sullivan et al (1997)[30]	198	Depression was a better predictor of physical function than the number of occluded vessels in patients undergoing cardiac catheterization over a 1-year period.
Fucc et al (2003)[28]	280	In a 12-year follow up, advanced age, type of household, marital status, and CEDS were significant predictors of mortality.

Abbreviations: MI: myocardial infarction; CV: Cardiovascular; CEDS: Center for Epidemiological Depression Scale

patients with an OR of 1.30 (95% CI, 1.04–1.63) and further increased in severely depressed patients with an OR of 1.77(95% CI, 1.28-2.45). *P* value was less than 0.001 for the trend. The authors concluded that depression is an independent risk factor for SCD and is not related to other previously determined cardiac risk factors. This association persisted across all demographic groups in this well-designed, case-control study. The study did not take into account the possibility of antidepressant use causing an increase in sudden cardiac arrest, nor did it mention the type of antidepressants used in these patients. However, these findings remained consistent when reanalyzed and adjusted for antidepressant use, suggesting that depression is an independent risk factor for SCD.[39]

In the Canadian Amiodarone MI Arrhythmia trial, Irvine et al[21] examined the impact of depressive symptoms and social support on the two-year SCD risk in 671 patients after controlling for fatigue symptoms. In the survival analysis of this study, elevated depressive symptoms were a predictor of increased SCD (RR, 2.45; 95% CI, 1.14–5.35; $p<0.020$) after controlling for significant factors like previous MI and CHF. Even after controlling for fatigue symptoms, there was a trend suggesting an association between cognitive/affective symptoms of depression and SCD (RR, 1.09; 95% CI, 0.99–1.10, $p<0.06$). Other studies summarized in Table 2[21,39–44] strongly support the conclusion that patients with histories of depression are more vulnerable to SCD.

Depression increases all causes of cardiac mortality. In the Mini-Finland Health Survey,[40] which examined the association between depression and cardiovascular disease (CVD), 8,000 healthy adults were followed for a mean time of 6.6 years. Patients with depression showed an increase in all-cause total mortality, which was twice as high compared to patients without depression (RR 2.05 for CVD and 1.95 CHD).

Depression affects all causes of mortality in CAD patients, and a number of studies[9,30,32,33,45–50] have examined the mortality rates of depressed patients with CAD. Studies

have shown that depression may have adverse effects on the prognosis of cardiac patients.[9,30,31,36,40,45–49,51] This section reviews studies pointing toward the relationship of depression and all causes of mortality in patients with CAD.

There is ample evidence that depression increases morbidity and mortality following MI.[33,38,43,49,50,52,54–57] In one landmark study of 222 patients by Frasure-Smith et al,[49] depression diagnosed 5 to 15 days following MI was associated with more than a four-fold increased risk of mortality during the six-month follow up. The impact of depression was sustained after controlling for left ventricular dysfunction and previous MI. A follow-up report published by the same authors demonstrated that depression was still a predictor of post-MI cardiac mortality at 18 months.[50]

In a subgroup analysis of patients enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, Carney et al[58] compared 358 depressed patients with acute MI to 408 nondepressed patients to see if depression was associated with a higher risk of mortality. Patients were assessed at six months after enrollment and then annually for up to 30 months. The major endpoints were all-cause mortality and recurrent, nonfatal, acute MI. In an adjusted analysis, the effects of depression occurred late. Patients with depression were 2.8 times more likely to die than nondepressed patients after 12 months of the initial MI. Depression did not predict nonfatal recurrent infarction in the sample.

de Jonge et al[59] utilized data from two studies in the Netherlands, namely the Myocardial Infarction Depression Intervention Trial (MIND IT) and Depression after Myocardial Infarction study. The authors studied the relationship between depressive symptom dimensions after an MI and both prospective cardiovascular prognosis and somatic health status. They related three depression symptom dimensions to baseline somatic health and cardiovascular prognosis. The cognitive/affective dimension was unrelated to baseline health status; whereas, somatic/affective and appetite dimensions were associated with cardiovascular events (OR 1.30). The somatic/affective symptoms had the strongest relationship with baseline health status.

Depression is an independent predictor of mortality and cardiovascular death or hospitalization after an acute MI complicated by CHF.[38] Rumsfeld et al[38] studied whether depression predicts mortality in patients with acute MI complicated by heart failure. In this trial, authors enrolled patients from Canada, the United Kingdom, and the United States. They used Medical Outcome Study-Depression questionnaire at baseline in addition to comprehensive clinical examination. Depressed patients had higher two-year mortality rates (29% vs. 18%, P=0.004) and cardiovascular death or hospitalization (42% vs. 33%, P=0.016). Depressive symptoms were significantly associated with mortality after adjusting for risk factors (HR 1.75, 95% CI 1.15–2, 68, P=0.01) and cardiovascular death or hospitalization (HR 1.41, 95% CI 1.03–1.93, P=0.03).

Studies focusing on various other aspects of depression and morbidity and mortality are summarized in Table 3 (depression and mortality and morbidity in patients with existing cardiac disease),[46–48,58,60–63] Table 4 (depression and mortality and morbidity in post-MI patients),[10,21,33,36,44,52,54,55,64] and Table 5 (depression and cardiac morbidity and mortality).[49,51,53,38,62,65] These studies further support the theory that depression increases mortality and morbidity rates in patients with CAD.

TABLE 2. Depression and sudden cardiac death

STUDY	SAMPLE	SUMMARY
Anda et al (1993)[43]	2,832	A depressed affect was associated with 1.5 times higher rate of cardiac death over a mean follow up of 12.4 years (National Health Examination Follow-up Study).
Aromaa et al (1994)[40]	8,000	Among Finnish adults initially free of CHD, depression was associated with 3.4 relative rate of cardiac death over a mean follow up of 6.6 years.
Empana et al (2006)[39]	2,228	Clinically depressed patients had higher odds ratio for cardiac arrest (OR 1.88; 95% CI, 1.59–2.23).
Everson et al (1995)[42]	2,396	Incidence of cardiac death was 1.9 times higher over 6-year follow up in Finish men with elevated depression scores on the MMPI.
Luukinen et al (2003)[41]	1,113	In patients 70 years or older, elevated depressive scores on short Zung scale was a significant predictor of sudden cardiac death (HR 2.67; 95%CI, 1.34–5.32).
Irvine at el (1999)[21] CAMIAT	671	There was an association between cognitive/affective symptoms of depression and SCD in placebo-treated patients after controlling for fatigue (RR=1.09; 95% CI=0.99–1.19, p<0.06).
Ahern et al (1990)[44]	Initial 502 (66% included)	Type B behavior pattern, higher levels of depression, and lower pulse rate reactivity to challenge was a significant risk factor for death or cardiac arrest, after adjusting for known predictors.

Abbreviations: CHD: coronary heart disease; MMPI: Minnesota Multiphasic Personality Inventory; RR: relative risk; CAMIAT: Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; SCD: sudden cardiac death.

TABLE 3. Depression and mortality/morbidity in patients with existing cardiac disease

STUDY	SAMPLE	SUMMARY
Kennedy et al (1987)[48]	88	Depression in patients evaluated for cardiac arrhythmias was associated with a 5-fold increase in all-cause mortality over an 18-month follow up.
Barefoot et al (1996)[46]	1,250	Among patients undergoing angiography, those with moderate-to-severe depression had 69% greater odds of cardiac mortality and 78% greater odds of all-cause mortality compared to nondepressed patients over a mean follow up of 19.4 years.
Carney et al (1988)[47]	52	Among patients undergoing angiography, patients with major depression were 2.2 times more likely than nondepressed patients to have a cardiac event over 1-year follow up.
Denollet et al (1995)[60]	303	Depressed patients assessed 2 months or longer after an MI or cardiac procedure had a 1.6 times higher risk of all-cause mortality than nondepressed patients over a 6-to 10-year follow up.
Levine et al(1996)[61]	210	Depression was a significant predictor of rehospitalization over a 6-month period in patients admitted for various cardiovascular procedures, such as MI, CABG, and PTCA.
Stewart et al (2003)[62]	1,130	No significant association between depressive symptoms and fatal or nonfatal event was found (negative study).
Blumenthal et al (2003)[63]	817	Patients having mild, moderate, and severe depression persisting for 6 months after CABG had higher rates of mortality even after 5.2 years
Carney et al (2003) (ENRICHD)[58]	358 from the 2,481 patients	Patients refractory to treatment for depression were at higher risk for late mortality. Patients with depression were 2.8 times more likely to die than patients without depression.

Key: MI=myocardial infarction; CABG=coronary artery bypass grafting; PTCA=percutaneous coronary angioplasty

DEPRESSION CONTRIBUTES TO UNHEALTHY LIFESTYLE AND POOR ADHERENCE TO TREATMENT

Depression is associated with poor medication adherence, which may have an impact on treatment outcomes for cardiovascular disease.[66] In an analysis of studies looking at depression and adherence, DiMatteo et al[67] concluded that depression exhibited a significant relationship to nonadherence with treatment recommendations with an OR of 3.03 (95% CI, 1.964–4.89).

Patients with depression are also more apt to have an unhealthy lifestyle, choosing behaviors like smoking, sedentary lifestyle, drinking, and nonadherence with prescribed medications.[68–70] Depression is also related to poor secondary prevention behaviors like exercise and quitting smoking in patients with acute coronary syndromes (ACS).[71] There is also a higher incidence of depression among severely obese patients,[72] which may have implications for changing to more healthy lifestyles.

THE PATHOPHYSIOLOGICAL LINK BETWEEN DEPRESSION AND CAD

There is growing evidence that several pathophysiological links exist that explain depression's effect on the cardiovascular system and may explain its role in CAD. Research is focusing on several mediators, seeking to identify how these mediators are activated by depression. Some of the more important mechanisms implicated are described in this section.

The hyperactivity of noradrenergic and hypothalamic pituitary adrenal corticol system. In CVD patients who are depressed, hyperactivity of the noradrenergic system is one important possible mechanism that may explain the association between depression and CAD.[73] Sympathetic outflow is increased in depressed patients as compared to nondepressed patients through negative stress effects of catecholamines on the heart, blood vessels, and platelets. Further support of the catecholamine association with depression is that increased urinary catecholamines levels are associated with negative emotions and decreased social support,[74,75] and high norepinephrine and low platelets serotonin are associated with MI and depression.[76]

Depression can also affect the hypothalamic pituitary-adrenocortical axis. Depressed patients have elevated corticotropin-releasing factor (CRF) in their cerebrospinal fluid. Depressed patients also fail to suppress cortisol secretion after dexamethasone administration.[77,78] Postmortem studies have shown that the brains of depressed patients have more neurons producing CRF as compared to controls.[79,80] These studies suggest that depression leads to heart disease by causing the hypothalamus to release CRF, which in turn increases the levels of corticosteroids, which may trigger atherosclerosis, hypercholesterolemia, hypertension, and hypertriglyceridemia.

Depression-induced altered autonomic tone associated with low heart rate variability leading to dysarrhythmias. Depressed patients may have decreased

parasympathetic nervous system (PNS) responses, leading to an imbalance between sympathetic nervous system (SNS) and PNS.[73]

Heart rate variability (HRV) refers to beat-to-beat alterations in the heart rate and is an objective measure of the dynamic response of the autonomic nervous system to react to physiological changes. A high degree of HRV is seen in patients with good cardiac function, whereas it is decreased in patients with severe CAD and CHF.[81] Low HRV, measured by power spectral analysis, has been observed in patients with major depression.[82,83] HRV is even lower in depressed patients with CAD as compared to nondepressed patients with CAD.[84] In the ENRICHD sub-study, Carney et al[85] concluded that low HRV partially mediate the effects of depression on survival after an acute MI.

Other evidence for cardiac autonomic dysfunction in depression, which include baroreflex dysfunction and QT variability, are less clearly understood. In depressed cardiac patients, QT variability was significantly higher when compared to age-matched and gender-matched nondepressed CHD patients during two of eight sampling periods over 24 hours of ambulatory monitoring.[86] The role of vagal nerve stimulation on cardiac rhythm is also not clear. One study suggests that left vagal nerve stimulation has little acute effect on cardiac rhythm.[87]

Inflammatory process and abnormal platelet functioning. Abnormal platelet functioning is associated with depression.[88] Enhanced platelet response to physiologic stress and depression might trigger platelet activation, increasing their adhesiveness, thus possibly triggering adverse coronary event.[88]

Berk and Plein[89] studied the response of intracellular calcium to thrombin stimulation. Intracellular calcium is a second messenger to platelet aggregation. They found that patients with major depressive disorder showed heightened sensitivity to thrombin stimulation. This suggests that platelet intracellular calcium response to thrombin stimulation might have a role in the pathogenesis of depression and CVD.

C reactive protein (CRP), a nonspecific marker of systemic inflammation, is consistently found elevated in depressed patients. The increased CRP can activate coronary endothelium and accumulates in the plaques. The increased CRP has a significant role as a predictor of incident and recurrent MI and cardiac death. The association of CRP and depression is not as strong as it is between CRP and exhaustion.[90]

Other possible mechanisms. Depression is associated with endothelial dysfunction, which in turn can cause or worsen a coronary artery event. In a recent study,[91] a marker of endothelial function was found to be significantly impaired in depressed patients compared to nondepressed patients.

TABLE 4. Depression and mortality/morbidity in the post-MI patients

STUDY	SAMPLE	SUMMARY
Ahern et al (1990)[44]	502	Patients who died within 1 year after MI had higher scores at index on BDI.
Schleifer et al (1991)[10]	108	Depression was associated with increased risks of reinfarction and death.
Silverstone (1986)[52]	108	Depressed patients were 8.5 times more likely than nondepressed controls to have a recurrent MI or die within 1 year.
Lesperance et al (1996)[33]	222	Patients immediately depressed after MI had an increased rate of mortality at 6 months
Ladwig et al (1994)[54]	377	Persistent postinfarction depression is an independent source of subsequent morbidity and long-acting, reduced quality of life
Dickens et al (2005)[36]	313	A previous episode of depression was independently associated with worse cardiac failure after first MI.
DeJonge et al (2006)[55]	468	Patients with post-MI depression were more likely to have poor quality of life, more health complaints, more cardiac complaints, and more disability at 12 months.
Dickens et al (2004)[57]	1,034	After controlling for demographic factors and severity of MI, patients with histories of depression prior to MI were not more likely to die or have further cardiac events as compared to controls. Lack of close confidante predicted further cardiac events.
Parashar et al (2006) (PREMIER)[64]	1,873	Depressive symptoms after an MI (irrespective of whether they persisted, subsided or developed newly) in the first month of hospitalization are associated with higher rates of rehospitalization rates or mortality rates, more frequent angina, more physical limitations, and worse quality of life. Adjustment hazard ratio for rehospitalization and mortality rates were 1.34, 1.71, and 1.42 for transient, new, and persistent depressive symptoms, respectively.
Irvine at al (1999) (CAMIAT)[21]	671	Elevated depressive symptoms was associated with 2-fold greater risk of mortality in patients after acute MI. When controlled for symptoms of dyspnea /fatigue, the affect did not remain significant.

Key: MI=myocardial infarction; BDI: Beck Depression Inventory

TABLE 5. Depression and cardiac morbidity and mortality

STUDY	SAMPLE	SUMMARY
Wassertheil-Smoller et al (2004) (The Women's Health Initiative Observational Study)[51]	93,676	Older women were followed for 4.1 years. Depression was significantly related to CVD risk and comorbidity. Among women without history of CVD, history of depression was an independent predictor of CVD and all-cause mortality.
Frasure-Smith et al (1993)[49]	222	Adjusted 6-month all-cause mortality was 4.2 times higher in patients with major depression than in nondepressed patients.
Ladwig et al (1991)[53]	560	Six-month cardiac mortality was 4.9 times higher in depressed than nondepressed patients.
Rumsfeld et al (2003)[65]	526	After adjusting for various risk factors, history of depression was a significantly associated with more angina, greater physical limitations and worse quality of life.
Stewart et al (2003)[62]	1,130	Modest association between depressive symptoms and cardiovascular events was found, but not for cardiovascular death (negative study).
Rumsfeld et al (2005)[38]	143	Depressed patients had a higher 2-year mortality, rate of CVD, or hospitalization. Even after risk adjustment, depression remained significantly associated with mortality, CVD, or hospitalization.

Abbreviations: MI=myocardial infarction; CABG=coronary artery bypass grafting; CVD=cardiovascular disease; PREMIER=Prospective Registry Evaluating Outcomes after Myocardial Infarction: Events and Recovery; CAMIAT=Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; ENRICHD=Enhancing Recovery in Coronary Heart Disease

There is some evidence that low red blood cell membrane levels of n-3 polyunsaturated fatty acids are associated with depression, which in turn can increase the risk of SCD.[92] Less is known about the triadic relationship among immune system parameters, psychological factors, and CVD.[90]

Other immunological markers like interleukin 6 and tumor necrosis factor are elevated in depressed patients and in patients with CAD.[90] Similarly, chronic infection and elevated levels of antibodies to several pathogens are associated with depression. However, another study suggested that the association may be confined to patients who are older and who are clinically depressed.[93]

SCREENING FOR DEPRESSION IN AT-RISK PATIENTS FOR CAD

It is our opinion that physicians should screen all CAD patients for depression. There is compelling evidence that depression affects cardiac mortality and morbidity, lifestyle, and medical adherence. Screening for depression in the primary care setting can improve clinical outcomes.[94] Moreover, rapid assessment of depression can also help identify patients at risk for poor secondary prevention outcomes.[71] Further, adding to the argument of screening is the evidence that treatment of depression with antidepressants is safe in patients with CAD.[95,97]

A recent nationwide survey[108] of cardiovascular physicians was conducted to determine their methods to diagnose depression, determine their beliefs about the association between depression and CVD, referral patterns for depressed patients, and the frequency of use and choice of antidepressant medications. This randomized, cross-sectional survey of 50 percent of US cardiovascular physicians revealed that 71.2 percent of the cardiovascular physicians ask less than half of their patients with CAD about depression and that 79 percent of them use no standard screening tool to diagnose depression. Of these physicians, 84.8 percent said that between 1 and 50 percent of their patients have depression; however only 49.2 percent stated that they treat depression.

Interestingly, this study also revealed that cardiovascular physicians are aware of the indirect association between depression and CAD, but surprisingly 49 percent were unaware of depression as an independent risk factor for CAD.

Some of the most frequently used depression screening instruments are PRIME MD® PHQ 9 (Primary Care Evaluation of Mental Disorders Patient Health Questionnaire), Hospital Anxiety and Depression Scale (HADS), Cardiac Depression Scale (CDS), and Cardiac Depression Visual Analogue Scale (CD-VAS). BDI, Hamilton Depression Scale (HAM-D), and Symptom Checklist 90 (SCL 90) can be used for diagnosing minor and major depression.[96]

HADS has 81-percent sensitivity and 54-percent specificity to determine a PRIME MD diagnosis of major depressive disorder.[98] The CDS is suitable to diagnose and screen for less severe depressive symptoms,[99] and the CD-VAS is also a useful tool for repeated assessments of depressive symptoms in cardiac patients.[100]

The authors recommend using PHQ-9 for screening for depression in CAD patients. It has been frequently used by primary care physicians to diagnose depression, and when used in a collaborative care model, can also help physicians treat depression more effectively.[101] There is also a trend by some large insurers to reimburse for these screenings.

One study recommended screening patients one month after coronary revascularization rather than at the time of revascularization, as two months and six months postrevascularization are stronger predictors of depression.[102] Table 6

reviews commonly used antidepressants with comorbid CAD, and Table 7 reviews the summary of recommendations.

PHARMACOLOGICAL TREATMENT OF DEPRESSION: CARDIOVASCULAR IMPLICATIONS

This section reviews the importance of treating depression in CAD patients and summarizes several studies addressing pharmacological treatment of depression in CAD patients.

Treating depression is critical in patients with CAD for several reasons. For example, in one study, reducing emotional distress in the short-term may improve long-term mortality in patients with CHD.[103] Liaison between psychiatrists and general practitioners, where psychiatrists give advice to the general practitioners, was helpful in reducing the depressive symptoms of patients with CVD in another study.[104]

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) and ENRICHD studies did not find the use of psychotherapy, i.e. interpersonal psychotherapy and cognitive behavioral therapy, substantially useful for the treatment of depression in CAD patients, thus highlighting the use of antidepressants in treatment of depression in this population.

We reviewed the Sequenced Treatment Alternatives to Relieve Depression (STAR* D) study and provide strategies for using antidepressants. STAR*D is the largest study (4,041 patients) done on "real-world patients" to assess the efficacy of antidepressant medications in patients with an average of three medical comorbidities and one psychiatric comorbidity. The study resulted in remission rates of approximately 47 percent at eight weeks of treatment with selective serotonin reuptake inhibitor (SSRI) monotherapy treatment.[105]

The study elicited risk factors for chronic depression as lower quality of life, lower level of work, and lower level social functioning. The study highlighted the impact of chronic depression on medical and socioeconomic burden. Phase 2 of this study[106] demonstrated that citalopram nonresponders had a comparable response rate of 25 percent when switched to venlafaxine, bupropion SR, or sertraline.

TABLE 6. Antidepressants commonly used with comorbid cardiovascular disease

GENERIC NAME	BRAND NAME	STARTING DOSE (mg/day)	THERAPEUTIC DOSE (mg/day)
Sertraline	Zoloft	25–50	50–200
Paroxetine	Paxil	10–20	10–40
Fluoxetine	Prozac	10–20	10–40
Fluvoxamine	Luvox	25–50	50–200
Citalopram	Celexa	10–20	20–40
Mirtazapine	Remeron	7.5–15	15–45
Venlafaxine	Effexor	37.5–75	75–375
Bupropion	Wellbutrin	150–450	50–150
Duloxetine	Cymbalta	15–30	30–60
Escitalopram	Lexapro	10	10–30

In the next level of the STAR*D study,[107] the authors randomly assigned 565 adult patients with nonpsychotic major depression who did not respond to SSRI monotherapy to augmentation of either bupropion SR or buspirone. Bupropion SR was slightly better tolerated and more effective in causing remission in 33 percent of the patients.

We learned from this study that treatment of depression is complicated and may involve close monitoring and switching of medications before patients achieve full remission. Physicians can start with an antidepressant, preferably an SSRI, and increase the medication to a therapeutic-maximum dose. If the patient is unable to tolerate the medication or does not respond to it after being on a maximum dose for 2 to 4 weeks, one can go to another medication from the same class or preferably from another class with a different mechanism of action. If the patient still does not respond and the physician feels comfortable, he or she can add another antidepressant with a different mechanism of action.

Various other guidelines, such as the Colorado Clinical Guidelines (*Major Depression Disorder in Adults: Diagnosis and Treatment Guidelines*), are being updated to reflect the STAR *D results. This guideline includes assessment and diagnosis and treatment planning, including medication and course of treatment. In addition, the guidelines have information about various antidepressant medications, screening, and treatment tracking log for the patient's chart, which can help with follow up. This information can be obtained at www.coloradoguidelines.org.

Depression is treated in many cardiac patients but there still remains a fear of cardiotoxicity of antidepressants.[108] The major classes of antidepressants and their potential for cardiotoxicity are discussed next.

Recommended first-line medications. SSRIs are the treatment of choice for patients with CAD since they are comparatively safe.[109] This class of medications includes fluoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®), fluvoxamine (Luvox®), citalopram (Celexa®) and escitalopram (Lexapro®).

SSRIs selectively inhibit serotonin reuptake by the presynaptic neurons, thus increasing serotonin levels in the synaptic cleft. There are case reports of SSRIs causing arrhythmias, atrial fibrillation and flutter, heart block, bradycardia, and supraventricular

TABLE 7. Summary of recommendations

1	Screen all patients with CAD for depressive symptoms.
2	Use PHQ-9 for screening for depression as it is easy to use and helps with follow up on progress
3	Medication use: Start with an SSRI medication and increase the dose to therapeutic-maximum dose. If patient does not tolerate the medication or does not show clinical improvement in 2–4 weeks of being on the therapeutic dose of an antidepressant, switch to another antidepressant from the same class or preferably another antidepressant from another class with a different mechanism of action. If the patient still does not show any improvement in another 2–4 weeks, consider adding another antidepressant with a different mechanism of action to the SSRI.
4	Patients who are smokers and want to quit smoking should be carefully watched for any symptoms of depression. If patient is a smoker, bupropion may be a good choice for its antidepressant and smoking cessation properties.

Key: CAD=coronary artery disease; PHQ-9=Patient Health Questionnaire-9; SSRI=selective serotonin reuptake inhibitor

tachycardia.[110–114] SSRIs, in general, are thought be cardio safe. Several small studies and some major studies like SAD HART and CREATE provided data regarding the safety of SSRIs in patients with CAD.[95,115–117]

In the well-known SAD HART study, Glassman et al[95] evaluated the safety and efficacy of sertraline treatment of major depressive disorder (MDD) in patients who were hospitalized for acute MI or unstable angina. The investigators enrolled 369 patients with MDD with either an MI or unstable angina in a randomized, double-blind, placebo-controlled trial. Patients were given a two-week, single-blind, placebo run and then were randomized to receive a flexible dose (50–200mg) of sertraline or placebo for 24 weeks. No changes were observed in various parameters, such as left ventricular ejection fraction (LVEF), prolonged QTc, or other cardiac measures. This supports sertraline being safe in patients with depression and comorbid CAD or unstable angina. However, sertraline was not very effective for the treatment of depression in this group of patients. It was statistically superior to placebo on Cognitive Global Impression (CGI) 1 scales over 24 weeks, but not on HAM-D scores at 16 weeks. However, when a predefined group of patients with severe depression was reviewed, sertraline was shown to be more effective than placebo in both CGI-1 and HAM-D scales (p=0.001). Treatment with sertraline was also found to be associated with significant improvement in quality of life and functioning in the severely depressed group.[118] Sertraline has been shown to improve HRV, an expression of cardiac autonomic function in post-MI patients who are depressed.[119] In a secondary analysis of 1,834 patients from the ENRICHD study, the risk of death or recurrent MI was significantly lower in patients taking SSRIs.[120] In another study,[116] fluoxetine was found to be effective in treating mild depression in patients with MI.

In another landmark trial, Lesperance et al[117] evaluated the treatment of depression in CAD patients. Authors simultaneously evaluated the short-term efficacy of an antidepressant medication and interpersonal psychotherapy for reducing depressive symptoms. It was a randomized, controlled trial in which 284 patients with CAD and depression were studied. All patients met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for the diagnosis of major depression of four-weeks duration or longer and had scores of 20 or higher on HAM-D scale.

Citalopram was superior to placebo in reducing HAM-D scores over the course of 12 weeks (mean difference, 3.3 points; 96.7 percent CI, 0.80–5.85; P=0.005). The reduction in BDI II scores also favored citalopram. Authors did not find any benefit of interpersonal psychotherapy over clinical management. This trial documented the efficacy of citalopram given in conjunction with weekly clinical management of major depression among patients with CAD.

SSRIs have various drug-drug interactions based on several pharmacokinetic actions.[121] For example some SSRIs, such as fluoxetine and paroxetine, inhibit cytochrome (CYP) P450-2D6 isoenzyme and can lead to increased levels of beta blockers, such as metoprolol, and 1C antiarrythmic drugs, such as encainide, propafenone, and flecainide.[121] SSRIs also have a high protein-binding affinity, which should be considered in patients given digoxin and warfarin. The only SSRI to demonstrate an interaction with digoxin is paroxetine, which significantly increases the area under the concentration curve for digoxin by 18 percent.[122] In addition, coadministration of fluoxetine with warfarin has been shown to affect the prothrombin time.[123] Based on these studies, sertraline or citalopram plus clinical management should be considered as first line of treatment for patients with depression and CAD. In addition, escitalopram and citalopram do not have any clinically significant activity at the cytochrome P 450 system.[121]

Medications considered safe for patients with CAD.

Triazolopyridines, another subclass of tricyclic antidepressants, include trazodone. Trazodone is rarely used as an antidepressant. It can, however, be used in low doses for insomnia. Its use is limited because of orthostatic hypotension; furthermore, if it is used to treat depression, it must be used at a higher dosage, which can be very sedating.

Venlafaxine is a dual-action medication that is well tolerated and has few anticholinergic effects.[124] It

does not have any significant effects on cardiac conduction, but can increase blood pressure at higher dosages. It can be used safely if the blood pressure is monitored closely. It has minimal CYP P450 interactions.[121]

Mirtazapine, a presynaptic alpha-2 antagonist, is a dual-action medication. It increases both nonadrenergic and serotonergic transmission.[125] Mirtazapine does not have significant cardiovascular effects, except postural hypotension at higher dosages, and can be used safely in patients with CAD. It can, however, cause sedation and weight gain, which can be a long-term risk for CAD.

Bupropion is classified as a monocyclic drug, which is a weak inhibitor of noradrenaline and dopamine reuptake inhibitor.[126] Bupropion is considered safe in patients with CAD, especially if their blood pressure and heart rate are monitored.

Duloxetine, one of the newer antidepressants, is an inhibitor of serotonin and norepinephrine reuptake. It has no significant affinity for cholinergic, adrenergic, or histaminergic receptors.[127] Duloxetine is both a substrate and moderately potent inhibitor of CYP 450-2D6 and warrants caution with beta blockers and 1-C antiarrythmic drugs, which are metabolized by this isoenzyme.[128] Not much is known about the cardiovascular safety of duloxetine at this time. It is associated with increased blood pressure.[129] Therefore, blood pressure monitoring is advised before and during treatment with duloxetine in patients with CAD.

In the MIND-IT study, which was a multicenter study of 2,177 patients with MI, antidepressant treatment with mirtazapine did not show improvement in long-term depression post-MI status or cardiac prognosis.[130]

Medications that can be used with extreme caution in patients with CAD. Tricyclic antidepressants have cardiovascular toxicity, which severely limits their use in patients with heart disease. These drugs also have anticholinergic, antiadrenergic, and antihistamine effects. They can cause sinus tachycardia, supraventricular tachyarrhythmias, ventricular tachycardia, and fibrillation, prolongation of PR, QRS, and QT intervals, first, second, and third degree heart block, and ST and T wave segment changes.[131] These drugs can be fatal in cases of overdose. Patients receiving cardiac medications, such as calcium channel blocker, alpha-adrenergic antagonist, diuretics, and beta-blockers, may be at risk of side effects.

Recently, a transdermal formulation of selegiline was approved for the treatment of MDD. Low dose (5–10mg/day) of oral selegiline does not need dietary restrictions, but is not an effective antidepressant. Compared with oral selegiline, selegiline transdermal system (STS) leads to steady plasma levels of the drug, increasing the amounts of the drug to the brain and decreasing metabolite production. STS specifically inhibits central nervous system monoamine oxidase (MAO) A and B enzymes, with minimal effects on MAO A in the gastrointestinal system and hepatic system, thus reducing the risk of interaction with foods rich in tyramine.[133] Not much data are available regarding the cardiovascular properties of this medication.

Medications to be avoided in patients with CAD. The MAO inhibitors, the oldest class of antidepressants, are used by physicians to treat depression and anxiety disorders. The use of these drugs has declined because of their potential interaction with foods rich in tyramine and other medications such as cold remedies and other antidepressants. This adverse interaction can lead to fatal adrenergic crisis or it may cause postural hypotension.[132] This side effect can be worsened in cardiac patients taking diuretics or other antihypertensives. Beta adrenergic blockers are also generally contraindicated in patients receiving MAO inhibitors because their predominant clinical effect in these patients may be to intensify vasoconstriction, leading to worsening hypertension. MAO inhibitors are rarely used in CVD patients.

BEHAVIORAL INTERVENTIONS

Even though behavioral interventions are useful in treatment of depression, the data are not very supportive of the use of behavioral therapies for treating depression in CAD patients.

Behavioral treatments for depression. There have been some clinical trials of psychosocial and behavioral interventions in patients with CHD that offer encouragement. In one open-label trial of 17 patients, Koszycki et al[134] found that medicated and unmedicated cardiovascular patients suffering from depression respond similarly to interpersonal psychotherapy.

The ENRICHD study[135] was a randomized, controlled trial of post-MI patients, which was designed to determine if treatment for depression and/or low perceived social support would reduce mortality and/or recurrent MI. Patients were randomized to either cognitive behavioral therapy (CBT) or usual care. Patients in the CBT group were supplemented with sertraline if their depression did not improve by five weeks (scores higher than 24 on the HAM-D or less than a 50-percent reduction on the BDI).

The intervention did not increase event-free survival.[136] The intervention improved depression, although the relative improvement in the psychosocial group compared with the usual care group was less than expected. The intervention did not seem to affect late mortality (29 months).

The selection criteria for the patients in this study may have contributed to the weaker findings, since those patients who were selected for the study had mild and transient depression. Also, patients were excluded if they had any other life-threatening illnesses, cognitive impairment, other major psychiatric illness, were too ill, were taking antidepressants, or undergone percutaneous coronary intervention or CABG surgery. The authors also suggested that psychopharmacological treatments might have helped patients in all the groups, thus decreasing the

difference in improvement between the groups.[136] One important finding in the study was that treatment-refractory patients were at a higher risk for late mortality than those patients who responded to treatment. Also the CREATE study reviewed in another section did not find interpersonal psychotherapy to be more effective than care as usual.

Behavioral treatments to reduce cardiovascular risks. Blumenthal et al[137] prospectively examined the relationship of exercise after MI to mortality and nonfatal reinfarction. They followed 2,078 individuals who were surveyed about their exercise habits six months after the initial MI and followed them for four years. After two years, the patients reporting exercise had less than half the events compared to patients who did not report regular exercise. They concluded that exercise is of potential value in reducing mortality and nonfatal reinfarction in acute MI patients at high risk for adverse effects because of being depressed or having low social support.

In a study by del Pino et al,[138] the investigators found that group CBT was superior to standard medical treatment and health education treatment in male patients with low social and educational levels to reduce certain aspects of physiological activation. It was also found useful for reducing depression at the two-year follow up.

Patients in a lifestyle change program, which incorporated a low-fat vegetarian diet, stress management training including yoga, meditation, and group therapy, and moderate exercise with weekly support group meetings, showed regression of their atherosclerotic lesions compared to a control group receiving usual care. Using angiography to monitor progression, these improvements were maintained at a four-year follow up.[139]

CONCLUSION

There is convincing evidence about the relationship between depression and CAD. However, it is not clear if treating depression can influence CAD prognosis and morbidity. Lack of a standardized measurement of depression, repeat publications from the same data set, and lack of standardization of outcome definitions and covariates tend to complicate the clarity of the association between depression and CAD. The National Heart and Lung Institute has organized a working group to recommend depression measurements for studies of depression in CVD.

Depression is common in patients with CAD. The data are consistent in supporting that depression is a risk factor for both the development and worsening of CAD. A number of pathophysiological mechanisms may explain this association. Because of the increasing evidence of these associations between depression and CAD, it is strongly recommended that physicians screen patients with CHD for depressive symptoms.

Several scales and tools can be used, such as PRIME-MD® PHQ-9, HADS, HAM-D, and CDS. We recommend using PHQ-9, as it is simple and easily administered.

Because of lack of studies supporting psychotherapy for treatment of depression in patients with CAD, use of antidepressants is the first line of treatment. The older drugs, such as MAO inhibitors and tricyclic antidepressants, have potential risks for patients with CAD. The newer classes of antidepressants are found to be safe and effective for treatment of depressive symptoms in these patients. These classes of medications include SSRIs, like sertraline, and other ones like venlafaxine, mirtazapine, and bupropion. Because there is more data supporting the use of SSRIs, these drugs should be considered as first-line treatment for depression in CAD patients. Some of the studies in progress may shed more light on the issue of whether treating depression in CAD patients can improve outcomes of the disease.

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