Clinical research

Treatment of affective disorders in cardiac disease

Nicole Mavrides, MD; Charles B. Nemeroff, MD, PhD

Patients with cardiovascular disease (CVD) commonly have syndromal major depression, and depression has been associated with an increased risk of morbidity and mortality. Prevalence of depression is between 17% and 47% in CVD patients. Pharmacologic and psychotherapeutic interventions have long been studied, and in general are safe and somewhat efficacious in decreasing depressive symptoms in patients with CVD. The impact on cardiac outcomes remains unclear. The evidence from randomized controlled clinical trials indicates that antidepressants, especially selective serotonin uptake inhibitors, are overwhelmingly safe, and likely to be effective in the treatment of depression in patients with CVD. This review describes the prevalence of depression in patients with CVD, the physiological links between depression and CVD, the treatment options for affective disorders, and the clinical trials that demonstrate efficacy and safety of antidepressant medications and psychotherapy in this patient population. Great progress has been made in understanding potential mediators between major depressive disorder and CVD—both health behaviors and shared biological risks such as inflammation.

Dialogues Clin Neurosci. 2015;17:127-140.

Introduction

Cardiovascular disease (CVD) and depression are two very common health problems in developed and developing countries.[1] Coronary artery disease (CAD) is defined as ischemic symptoms associated with coronary angiographic evidence of 50% or more blockage in at least one major coronary artery, previous hospitalization for a myocardial infarct (MI), or angina.[2] Syndromal depression is extremely common in patients with CVD/CAD, and is associated with poor functional and cardiovascular outcomes.[3] In 1937, Maltzberg reported that patients with severe depression had a higher mortality rate when compared with the general population, and that those surplus deaths were largely attributable to CVD.[4,5] Anxiety disorders are commonly comorbid with depression and CAD as well as with adverse outcomes in patients with CVD.[6]

Over the past 20 years, many studies have analyzed the relationship between depression and CVD. Depression is not only associated with an increased risk of de-

Author affiliations: Department of Psychiatry and Behavioral Sciences, Center on Aging, University of Miami Miller School of Medicine, Miami, Florida, USA

Address for correspondence: Charles Nemeroff, 1120 NW 14th ST, 14th floor, Miami, FL 33136, USA (e-mail: cnemeroff@med.miami.edu)

Clinical research

veloping CAD, but is a predictor of increased morbidity and mortality in patients with CVD.[6,7] Depression has been identified as an independent risk factor for coronary heart disease, angina, heart failure, MI, and cardiac mortality, with anxiety being a risk factor for MI and heart failure.[6,8,9] Both anxiety and depression have been linked with poorer quality of life in both short-and long-term follow-up studies, being two to three times less likely to adhere to medical treatment than patients who are not depressed, as well as leading to an increase in hospital readmissions and greater health services use.[6,10-13] Relatively few studies have investigated the relationship between anxiety and CVD, or the co-occurrence of anxiety, depression, and CVD.[6]

The prevalence of major depression has been estimated to be 17% to 27% in hospitalized patients with CAD, and most studies have also documented a negative cardiac prognostic impact in patients with comorbid depression.[14] Treatment of depression and anxiety is imperative in this population, due to their high prevalence among patients with CAD/CVD, as well as the associated increase in both psychiatric and medical morbidity and mortality. Only a small number of trials have evaluated the use of antidepressants in patients with cardiac disease.[9,15,16] This review will describe the prevalence of depression and anxiety in patients with CVD and the pathophysiological links between depression (and other affective disorders) and CVD, and will focus on the treatment options based on the relevant clinical studies.

Epidemiology

Cardiovascular disease and affective disorders, especially depression, are common. The lifetime prevalence of major depressive disorder (MDD) is 16.6%, higher in woman than men, as reported in the National Comorbidity Study. Subsyndromal depression is also common in primary care clinics.[17] The lifetime risk of cardiovascular death by age 80 is 4.7% to 6.4% among people without cardiovascular risk factors and 20.5% to 29.6%, or about 17.3 million people, among those with two or more risk factors. Cardiovascular risk factors include: diabetes mellitus, obesity, smoking, elevated cholesterol level ≥180 mg/dL, and untreated hypertension.[18] The World Health Organization estimates that the number of deaths from CVD by 2030 will be approximately 30 million. The second leading cause of disability world-

wide after CVD will be depression.[5] Anxiety was also shown to increase the risk of CAD and cardiac death by 26% and 48%, respectively, in a meta-analysis of nearly 20 studies.[5,6]

The prevalence of MDD in patients with CAD, including stable and unstable angina or MI, is estimated to be between 15% to 20%, with another estimated 30% to 45% having clinically significant depressive symptoms without meeting *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth edition-revised) criteria for MDD.[18] In a meta-analysis of hospitalized patients with chronic heart failure (CHF), the prevalence rate for depression was 20% to 36%.[19] Depressive symptoms often persist in patients with CVD, due in part to underdiagnosis and lack of or inadequate treatment.[3,20]

In the National Health Examination Follow-up Study, 2832 adults aged 45 to 77 years with no history of CAD/CVD who demonstrated depressed mood and hopelessness at baseline exhibited an increased risk of both fatal ischemic heart disease (relative risk [RR] 1.5, 95% CI 1.0-2.3) and nonfatal ischemic heart disease (RR 1.5, 95% CI 1.11-4.06), even after controlling for demographics and other risk factors.[5,18] Other studies discovered that even after controlling for traditional risk factors of CAD (eg. physical inactivity, tobacco use, hypertension), depression is a significant independent risk factor for the development of CAD (RR 1.64, 95% CI 1.41-1.90).[17,21]

In the follow-up of the Hertfordshire Cohort Study in 2007, 2299 participants were evaluated to examine the relationship between depression and anxiety and CVD. It was found that 3.7% of men and 4.6% of women had scores on the HAD-D (Hospital Anxiety and Depression Scale) indicating possible depression, with probable depression being noted in 1.1% men and 1.4% women. In both men and women, higher HAD-D scores were associated with a higher prevalence of CVD (*P* value trend <0.001) with an odds ratio for CVD of 1.162 (95% CI 1.096-1.231, *P*<0.001) in men and 1.107 (95% CI 1.038-1.181, *P*=0.002) in women.[5] Depressive and anxiety symptoms were more common in men and women with CVD, and depression was an independent predictor of incident CVD, mortality, and cardiovascular mortality specifically in men.[5]

Windle and Windle[23] hypothesized that recurrent depression would significantly predict CVD, CVD risk, and diabetes in both the cross-sectional and longitudi-

nal analyses. The co-occurrence of diabetes and depression is high—those with type 2 diabetes have almost twice the rate of depression relative to those without diabetes (19.1% vs 10.7%) and depression is associated with a 60% increased risk of type 2 diabetes. Women with diabetes have a significantly higher relative risk of fatal coronary heart disease than do men with diabetes.[22]

The influential studies by Frasure-Smith and colleagues in the early 1990s at the Montreal Heart Institute demonstrated the negative impact of depression in patients with CVD. They confirmed that following an MI, patients with MDD had a 3- to 4-fold increased mortality rate within the 6- to 18-month post-MI period, with the vast majority of the increased mortality occurring in the first 6 months after the index MI. The findings were independent of left ventricular ejection fraction and index MI.[17,23] More recent studies have demonstrated that depression is associated with a 2- to 2.5-fold increased risk of poor cardiovascular outcome and mortality among patients hospitalized post-MI.[3,5,17]

This concatenation of data strongly supports the hypothesis that depression is an independent risk factor in the development and progression of CVD. The American Heart Association has issued recommendations for screening, referral, and treatment of depression in patients with CVD, indicating that early recognition and treatment of depression in patients with CVD is vital.[17,21]

Pathophysiology

Several mechanisms, behavioral and physiologic, have been implicated in the connection between depression and cardiac disease.[19]

Alterations in platelet activity

Platelets are responsible for thrombus formation, the ultimate cause of MI. Platelets are involved in recruiting inflammatory cells that can contribute to the development of atherosclerosis.[5] Depressive patients exhibit a state-dependent increase in platelet activation that may heighten their cardiovascular risk, particularly when combined with CAD. Plasma platelet factor-4 (PF4) and β-thromboglobulin (TG) levels are two markers of platelet activation that may contribute to the increased cardiovascular risk found in patients with major de-

pression.[24,25] CAD patients with comorbid depression have higher plasma levels of PF4 and TG than healthy controls or patients with CAD alone.[25] Markovitz and Matthews were the first to suggest that enhanced platelet response to physiological stress can trigger adverse coronary artery ischemic events.[17] Depressed patients exhibit exaggerated platelet reactivity as assessed by markers of platelet activation. Activated platelets are extremely adhesive, secondary to the expression of integrins and selectins, and they provide a unique interface between the injured arterial wall and circulating inflammatory cells.[3,17] Chiaie et al reported that maintenance of heightened platelet activation is determined by baseline severity of depression. This increased depression severity (for example observed in treatment-resistant depressed patients) prior to treatment may confer a particularly high risk for cardiac events. Such high levels of baseline severity likely increase the frequency of residual symptoms of depression, which may well explain the persistent of platelet hyperactivity.[24] In SADHART (Sertraline Antidepressant Heart Attack Randomized Trial), depressed post-MI patients had substantial increases in indices of platelet activity, which are reduced by sertraline treatment, but not associated with improved cardiovascular outcomes.[25,26] There is evidence that serotonergic mechanisms may provide the critical link between affective disorders and cardiovascular risk. Serotonin is incorporated rapidly into platelets, stored in the dense granules, and secreted during stimulation. Lopez-Vilchez et al investigated the existence of a prothombotic condition in depressed patients and its possible modulation during treatment with a selective serotonin uptake inhibitor (SSRI). Platelets from patients with MDD showed higher volumes ($P<0.01$), a significantly enhanced aggregation response to arachidonic acid, and augmented expression of fibrinogen, factor V, and anionic phospholipids by flow cytometry ($P<0.05$). Clot firmness and procoagulant activity of platelet-associated tissue factor were also significantly elevated ($P<0.05$). After 24 weeks of treatment with escitalopram, the majority of the alterations were normalized except for persistent alterations in thromboelastometic parameters.[27]

Inflammation

Inflammatory cytokines are associated with the formation of atherosclerosis, a major contributor to the

pathogenesis of CAD. C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-1 (IL-1) are independent risk factors for cardiovascular disease.[3] Depressed patients have been shown to exhibit a sustained inflammatory state with higher concentrations of CRP, IL-6, and tumor necrosis factor alpha (TNF α) than controls.[5,25] The Prospective Epidemiologic Study of Myocardial Infarction (PRIME), a study of healthy middle-aged men from France and Belfast, compared 335 future cases of CVD with 670 controls for 5 years and found a statistically significant correlation between depression severity and levels of IL-6 and CRP. Men with depression also had a 50% increase in the odds ratio of CVD.[5,17] Wium-Andersen showed in a cross-sectional analysis that a stepwise increase in fibrinogen was associated with a stepwise increase in risk of psychological distress, use of antidepressant medication, and hospitalization for depression (*P*< 0.005). When they examined patients with cardiovascular disease, the association between depression and fibrinogen was attenuated, which was opposite to what others have reported. Fibrinogen has been found to stimulate the synthesis of proinflammatory cytokines such as IL6, TNFα.[28]

Some studies suggest that the role of inflammation in linking depression and CVD may be influenced by physical activity. Depressed patients tend to exercise less than their healthy counterparts, and lower levels of exercise are associated with increased inflammatory markers. This suggests that physical inactivity and inflammation may synergistically work together on the causal pathway between depression and CVD.[29] In the Heart and Soul study, Duivis and colleagues found that in CVD patients increased levels of inflammatory markers were correlated with depression severity, mainly driven by physical inactivity, smoking, and obesity. These findings highlight the importance of health habits such as exercise, smoking, and medication adherence in the relationship between depression and CVD; as well as suggesting that inflammation in depressed patients may partly be the result of poor health behaviors.[3,5,28-30] In the Whitehall II Cohort Study, they examined the relationship between physical activity and CRP and IL6. They found that those patients who were more physically active had lower baseline levels of inflammatory markers, which remained stable over a 10-year follow-up period.[31]

Heart rate variability

Heart-rate variability (HRV) is a measure of the ability of the heart to respond to physiological demands, and reflects sympathetic-vagal balance.[5,25,30] Increases in HRV are associated with positive emotions, social connectedness, and longevity. Decreases in HRV are associated with depression, anxiety, CVD, and mortality, which may be attributable to a poorly functioning cholinergic anti-inflammatory reflex. Increases in resting heart rate and decreases in its variability are associated with substantial morbidity and mortality. Use of antidepressants in the ELSA-Brasil Cohort Baseline Study was associated with increases in heart rate and decreases in its variability. Effects were most evident for the tricyclic antidepressants, followed by the SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) relative to participants not receiving antidepressant therapy. Only those with generalized anxiety disorder showed increases in heart rate and decreases in its variability and vagal activity.[32] Carney et al first demonstrated that depressed patients had significantly lower HRV than controls. Post-MI, depressed patients had a significantly more reduced HRV than nondepressed patients, suggesting that decreased HRV may, in part, mediate the adverse effects of depression on survival post-MI. The Heart and Soul study indicated that somatic depressive symptoms in CVD patients were associated with reduced HRV.[33] The Twins Heart Study from the Vietnam Era Twin Registry revealed that both depressive symptoms and HRV were highly heritable, and that the association between depressive symptoms and reduced HRV is likely due to a shared genetic pathway. This suggests a common neurobiological dysregulation link between depression and autonomic dysfunction. Of the total genetic variation of depression and HRV indices, about 80% to 90% was found to be due to the same genetic factors, indicating that common genes contribute substantially to both depression and HRV.[34,35]

Lifestyle risk factors

The "type A" personality (ambitious, aggressive, hostile, competitive, chronic sense of urgency) was linked to heart disease 30 years ago. More recent studies differ in their findings as to whether all the symptoms of "type A" personality were a collective risk factor for heart disease, but hostility remains a validated risk factor.

"Type D" personality is a personality risk factor where patients experience negative emotions with social inhibition, which may be a more important risk factor of cardiac disease. The INTERHEART study is a case control study of attributable risk for myocardial infarction (MI) in 52 countries. Stress, low generalized locus of control, and depression accounted for 32.5% of the attributable risk for an MI, which is only slightly less than that of lifetime smoking, but greater than hypertension and obesity.[5,17,25] Rubin et al studied the association of depressive symptoms or antidepressants with CVD risk factor in the Look AHEAD (Action for Health in Diabetes) trial of weight loss in type 2 diabetes. The goal was to determine if increased depressive symptoms or antidepressant use were associated with an increase in CVD risk factors over 4 years in the type 2 diabetes population. They did find that elevated depression scores on the BDI or antidepressant use were associated with increased CVD risk, even when controlled for prior risk factor status. At least one indicator from the five domains assessed (glycemia, lipids, blood pressure, smoking, and BMI) was increased in the presence of depressive symptoms and medication use; more significant associations were observed with antidepressant use than with just elevated depressive symptoms. This suggests that depression and perhaps antidepressant treatment (a proxy for depression severity) may place patients at a higher risk of CVD; clinicians should be more attentive to diagnosing depression and use more aggressive treatment to control CVD risk factors.[36]

Women have a significantly higher prevalence rate of MDD relative to men, though heart disease continues to be the leading cause of death in men and women (25.4% and 24.5%). Windle and Windle thought that there might be a relationship between recurrent MDD and CVD and diabetes in women. They reported that recurrent MDD in middle-aged women significantly predicted an increase in CVD risk (hypertension and high cholesterol) and diabetes over a 5-year period, but a single episode of depression did not, even when controlling for age, BMI, and education level. Because most of the studies to date have been comprised of mainly men, this shows the importance of studies of women because of the increasingly high risk for both depression and cardiac disease.[22]

Genetic risk factors for both depression and cardiac disease have been a recent focus in the past few years, in both the young and middle-aged. Mannie et al studied young men and women who had a parent with depression but no personal history of depression, and healthy controls, and scrutinized their cardiac risk factors. The group with the family history of depression showed increased peripheral and central blood pressure, increased arterial stiffness, and decreased insulin sensitivity. They did not differ from the controls in their plasma lipids, C-reactive protein (CRP), or waking cortisol concentrations. This study demonstrated that individuals with an increased familial risk of depression show evidence of altered cardiovascular risk in young adulthood, in the absence of depressive symptoms. The authors hypothesized that genetic factors are likely to explain both the increased risk of familial depression and cardiac risk factors, though no specific genes have been identified to date.[37]

In the Twins Heart Study, the extent to which a common genetic pathway was involved in the relationship between depressive symptoms and inflammation was sought.[34] As noted above, depression is associated with increased levels of IL-6 and CRP, though the causal direction of the association is unknown. In their sample from the Vietnam Twins Registry, they found a correlation between the severity of depressive symptoms and increased levels of IL-6 ($P<0.001$). They also demonstrated there was a shared genetic vulnerability that accounted for most of this association, which suggests that depression and inflammation may be the expression of a common biological pathway that is genetically driven.[34,35]

Overview of antidepressant therapy

The Food and Drug Administration (FDA) approved and evidence-based effective treatments for depression include pharmacologic (SSRIs, tricyclic antidepressant [TCAs], monamine oxidase inhibitors [MAOIs], SNRIs, etc), nonpharmacological somatic (electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation) and evidence-based psychotherapy techniques (cognitive behavioral therapy, interpersonal therapy, etc). SSRIs are the first line of treatment for depression in patients with and without cardiac disease. With treatment of MDD, 60% respond to antidepressants (defined as a 50% decline in depressive symptom severity) with potentially a 40% relapse rate after 1 year.[31,38] Remission rates are significantly lower. The TCAs are used less commonly because of their multi-

ple potential cardiac side effects.[5] Antidepressants are believed to act predominantly by increasing the availability and/or signal transduction of one or more of the monoamine neurotransmitters, ie, norepinephrine, dopamine, and serotonin.[18] Cardiovascular side effects such as orthostatic hypotension, hypertension, and conduction abnormalities can also occur with certain antidepressants, including TCAs and MAOIs.[31,39]

Treatment of depression in cardiovascular disease: pharmacotherapy

Although MDD, depressive symptoms, and anxiety are highly prevalent in the population with heart disease, and have been associated with a poorer prognosis for survival and quality of life, few of these patients actually receive treatment. Although measures have improved since 2008 when the American Heart Association recommended screening for depression,[40] usually the lack of treatment is due to poor recognition of depression, partly because of the overlap of symptoms associated with hospitalization (fatigue, sleep changes, decreased appetite, guilty feelings, preoccupation with death). Depression can also present atypically, characterized by hypersomnia and hyperphagia, which can be difficult to diagnose as well. Cardiologists and internists may be uncomfortable treating depression due to unease about antidepressant safety, possible cardiac adverse effects, or potential medication interactions.[41]

Selective serotonin reuptake inhibitors

SSRIs inhibit the reuptake of serotonin at presynaptic terminals, resulting in increased serotonin concentrations in the synaptic cleft. Serotonin can cause coronary artery vasoconstriction in patients with atherosclerosis and an increase in platelet aggregation. Potential cardiovascular side effects of SSRIs are largely because some members of this class are associated with drug-drug interactions secondary to inhibition of certain of the isoenzymes of the cytochrome p450 enzyme system.[15] Those with the least drug-drug interactions are citalopram, escitalopram, and sertraline.[17,42] There are case reports demonstrating cardiac side effects of SSRIs such as bradycardia, tachycardia, heart block, and heart failure, but these are effective antidepressants with minimal cardiovascular side effects in healthy patients.[1,43] SSRIs appear to be safe in cardiac populations

and have been suggested to improve cardiovascular prognosis following MI, but this has not been reliably replicated.[10,44]

Many of the clinical trials have sought to demonstrate the effectiveness and safety of SSRIs in the cardiac population, compared with TCAs or psychotherapy. We reviewed 14 studies that evaluated SSRIs in the cardiac population, and the majority found them to be effective and safe, though none have suggested any one agent as superior over the others. Roose et al led two studies, one double-blind randomized controlled trial and one a historical controlled study that compared paroxetine and fluoxetine, respectively, with nortriptyline.[45-47] The comparison between paroxetine and nortripytline was a 6-week trial with 81 patients; no significant difference was found between the two medications in treating the depression, but there was significantly greater cardiac side effects with the nortriptyline. Indeed 10 of the 40 patients (25%) receiving nortriptyline discontinued the medication. Nortriptyline also demonstrated a statistically significant increase in heart rate compared with baseline (83 beats/min vs 75 beats/min, $P<0.001$).[15,46,48] In the historical control study, Roose et al studied 27 patients treated with fluoxetine and 60 patients treated with nortriptyline, all of whom had significant cardiac disease, and again found that although they both improved depression, nortriptyline had significant cardiac side effects when compared with the SSRI.[49] Strik et al demonstrated a greater antidepressant response to fluoxetine compared with placebo in a randomized double-blind placebo controlled trial using 54 patients with depression and recent myocardial infarction. There were no differences in cardiac adverse events between the placebo and fluoxetine, which allowed the authors to conclude that fluoxetine was a safe and effective antidepressant in patients post-MI.[15,50]

The SADHAT trial was a 16-week open study of 26 patients post-MI with depressive symptoms that demonstrated that sertraline improved depressive symptoms without any increase in adverse cardiac events.[3,15,51] In the follow-up study, the Sertraline Antidepressant Heart Randomized Trial (SADHART), 369 patients post-MI (n=294) or with unstable angina (n=75) were randomized to receive either sertraline (n=186) or placebo (n=183) for a total of 24 weeks. Sertraline numerically improved scores on the Clinical Global Impression (CGI) scale and Hamilton Depression Scale (HAM-D) compared with placebo. In

the group with recurrent depressive episodes, sertraline was significantly superior to placebo in both the CGI and HAM-D measures, though in the new onset depression following the cardiac event, sertraline was only significantly superior to placebo on the CGI.[5,51-53] In the Sertraline Antidepressant Heart Randomized Trial of CHF patients (SADHART-CHF), 469 patients with CHF were randomized to receive either sertraline or placebo for 12 weeks. There was no statistical difference in reduction of depressive symptoms between the sertraline and placebo and no difference in all-cause mortality either.[3,54,55]

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) was a 12-week 2x2 factorial designed trial testing the efficacy of interpersonal therapy (IPT) or citalopram on depression symptom severity in cardiac patients. The patients underwent two randomizations— once to receive IPT vs clinical management only and once to receive citalopram vs placebo. This resulted in four groups: IPT plus clinical management and citalopram, IPT plus clinical management and placebo, clinical management with citalopram, and clinical management with placebo.[14,56] IPT was chosen because it had been reported to be more effective than cognitive behavioral therapy (CBT) in treating depression in patients with HIV.[14] Citalopram was superior in improving depressive symptoms when compared with placebo across all measures. There was no difference between citalopram and placebo on measures of cardiac safety, which suggested that citalopram was safe and effective in patients with CAD.[14,50] IPT was not significantly better at improving depressive symptoms compared with clinical management, a somewhat surprising result.[56]

Two larger multicenter trials, ENRICHD and MIND-IT, assessed the treatment of depression in patients with MDD and CAD. In the Enhancing Recovery in Coronary Heart Disease (ENRICHD), 2481 patients with an acute MI and MDD, depressive symptoms, or dysthymia were randomized to CBT or treatment as usual and if their scores on the HAM-D were greater than 24, they also received an SSRI. CBT was found to significantly improve depression with no effect on cardiac outcomes. The antidepressant use was associated with a decreased risk of death or nonfatal MI at the 6-month mark in the study.[57,58] MIND-IT (Myocardial Infarction Depression Intervention Trial) randomized depressed patients post-MI to receive either mirtazap-

ine or citalopram. There was no difference between the two medications on their efficacy on depression when compared with placebo. Those patients who did not respond to antidepressants had a higher rate of cardiac events in the 27 months of follow up than those who did.[59,60]

In more recent studies, investigators have evaluated escitalopram versus placebo, sertraline versus citalopram, paroxetine versus placebo, and SSRIs compared with TCAs. Each study showed that SSRIs improve depressive symptoms when compared with placebo and some have demonstrated a decrease in cardiac events and improvements in cardiovascular disease prevention.[5,25,26,60-62]

In the Hertforshire Cohort Study the relationship between anxiety and depression and CVD in a large, well-characterized population study was examined in both men and women. Data was extracted from 1578 men and 1417 women; 59 (3.7%) men and 65 (4.6%) women had HAM-D scores indicating possible depression, with probable depression in 17 (1.1%) men and 20 (1.4%) women. They also found 154 (9.8%) men and 209 (14.8%) women with possible anxiety and 78 (4.9%) men and 146 (10.3%) women with probable anxiety. Of note, 281 men (18.3%) and 158 (11.5%) women had cardiovascular disease. This study demonstrated that depression and anxiety symptoms are more common in men and women with CVD, and moreover that depressive symptoms are an independent predictor of incident CVD, all-cause mortality, and cardiovascular mortality in men. Depression appears to contribute to the onset of CVD and worsen its severity, with depression increasing the risk of mortality following an MI. This study did not demonstrate that anxiety symptoms predicted the development of CVD or incident mortality, which is discordant with previous studies.[5]

In 2011, the FDA regulated that citalopram should not be used at doses above 40 mg/day because the higher dose can unfavorably alter the electrical activity of the heart, and that higher doses did not provide any additional benefit in the treatment of depression. In the elderly it was advised that no doses of citalopram over 20 mg/day be used for the same risk consideration. There was no convincing evidence that citalopram above 40 mg/day was associated with an increased risk of QTc interval prolongation or torsade de pointes. A clinical safety study of over 3000 patients across 24 separate trials did not identify cardiac adverse effects or EKG

abnormalities. A multicenter double-blind placebo-controlled study with crossover design studied the QT prolongation examined differences between placebo, citalopram 20 mg, and citalopram 60 mg in 119 people. In comparison with placebo, the 20 mg and 60 mg doses caused QT prolongation by 8.5 ms (90% CI, 6.2 to 10.8 ms) and 18.5 ms (16 to 21 ms), respectively. This demonstrated to the regulatory authorities that citalopram was capable of evoking dose-dependent QT interval prolongation, and there is insufficient data to support the efficacy of citalopram in doses higher than 40 mg/day and its maximal effect are observed after 20 to 40 mg/day.[63]

The Bureau of National Health Insurance in Taiwan conducted a cost-effectiveness and cost-utility study based on the National Health Insurance Research Database (NHIRD) of patients with depression in Taiwan. They compared the cost-effectiveness and cost-utility between antidepressants and to determine how the presence of CVD affected the economics of pharmacologic depression treatment. SSRIs were shown to be the most cost-effective treatment option for depressed patients, over SNRIs and TCAs, in both CVD and non-CVD population. Patients with CVD had poorer treatment response rates in this study, similar to findings in other studies. Of the SSRI studies that were reviewed, the majority (7 out of 12) demonstrated efficacy compared with placebo or other antidepressants in treating depression in the CVD population, three showed no difference in efficacy when compared with placebo, and two showed no improvement in depressive symptoms. SSRIs improved quality of life to a greater effect than TCAs in patients with depression, regardless of their CVD status.[64]

Tricyclic antidepressants

TCAs act primarily by blocking the reuptake of norepinephrine and/or serotonin.[56] Norepinephrine binds peripherally to α- and β-adrenergic receptors, which can lead to an increase in blood pressure, heart rate, and cardiac and vascular contractility. In patients with CVD, this could increase ischemia, chest pain, hypertension, and arrhythmias.[15]

The effects of TCAs on the heart are similar to class I antiarrhythmic medications, which can prolong intraventricular conduction secondary to sodium channel blockade, an effect associated with many cardiac adverse events.[65] TCAs also inhibit the fast inactivating rapid component of potassium channels, which prolongs the QT interval. Excessive prolongation of QT can lead to torsades de pointes, which can occur when TCAs are used with other medications that also prolong the QT interval. In addition, TCAs can cause first- and second-degree atrioventricular block, asystole, and sudden cardiac death.[15,66] The most common cardiovascular side effect of TCAs is tachycardia; postural hypotension occurs in up to 20% of patients due to the combined effects of TCAs including α-adrenergic receptor blockade in the CNS.[15]

The studies with TCAs in the cardiac population have been many, but are comprised of a small number of patients. The largest of the studies was completed by Roose et al, a randomized controlled trial of 196 patients over a 10-year period. They surveyed the difference in the rates of cardiovascular complications and orthostatic hypotension in patients with cardiac conduction disease treated with either imipramine or nortriptyline. Both medications were effective antidepressants and both caused significant cardiac adverse events, but nortriptyline caused fewer side effects, specifically not causing any orthostatic hypotension compared with 9 of 122 patients (7%) receiving imipramine.[45,47,67] There were seven other studies of TCAs worth mentioning—most with impiramine, nortriptyline, or a combination of the two. Roose et al had conducted two studies, one of nortriptyline in depressed patients with decreased left ventricular ejection fraction and one a double-blind crossover study with imipramine and buproprion. Only one patient in the former study developed orthostatic hypotension and nortriptyline was found to be effective in treating depression.[15,67] In the crossover study, each of the 10 heart failure patients with depression received 3 weeks of imipramine followed by 3 weeks of bupropion. Although both were equally efficacious in treating depression, bupropion had significantly fewer cardiac side effects than imipramine and was safer for use in patients with depression and heart failure than imipramine.[15,46] The summary of the other five studies showed that although TCAs are efficacious in treating depressive symptoms in patients with significant cardiac disease, they exert significant adverse effects that many patients find intolerable. The most notable side effect was orthostatic hypotension, noted in all of the imipramine trials.[15,42,44,52,53,68-70] The only study that found no evidence of orthostatic hypotension was the Cohen

et al's study of trimipramine in 22 depressed patients with mild heart disease; the medication was found to be effective and safe.[43,71]

The side effect of most concern about TCAs in depressed patients with CVD, as evidenced by the above eight trials, is orthostatic hypotension. No long-term studies have been completed, so it is not known if the short-term studies that demonstrate no left ventricular depression or conduction abnormalities would be the case with long-term use. Nortriptyline does appear to possess a more favorable side effect profile than imipramine or the other TCAs studied. The TCAs can be used safely, but with significantly more side effects than the SSRIs and are of course lethal in overdose. Thus they are not considered the first-line treatment for depressed patients with cardiac comorbidity.[15,45,67,68,71]

SSNRIs and other antidepressants

The selective serotonin/norepinephrine reuptake inhibitors (SSNRIs), venlafaxine, desmethylvenlafaxine, and duloxetine, as well as the "other" antidepressants including bupropion (whose pharmacological mechanism of action remains obscure), mirtazapine, trazodone, nefazodone, vilazodone, and monoamine oxidase inhibitors (MAOIs), have hardly been studied at all compared with both SSRIs and TCAs in terms of their cardiovascular effects and in patients with comorbid cardiac disease. Venlafaxine has been frequently associated with dose-dependent increases in blood pressure and decreases in heart rate variability.[5] Mirtazapine can cause weight gain and increase body fat mass, which is not associated with improved cardiac outcomes, so it would not represent a first-line treatment for depression in this cardiac population. Neither duloxetine nor the new antidepressant vortioxetine have been studied in clinical trials of depressed cardiac patients. Bupropion may increase systolic blood pressure at high doses, which is already common in many patients with CVD, though it has been studied, as noted above, in small randomized controlled trials in cardiac patients.[10,46,72]

Treatment of depression in cardiovascular disease patients: psychotherapy

CBT and IPT are the evidence-based psychotherapies that have been extensively studied in cardiac patients. Cognitive behavioral therapy focuses on altering cognitions and behavioral activation whereas interpersonal therapy focuses on resolving interpersonal issues characteristic of depression.[10] Both are effective treatments for depression, and unlike antidepressants exert no cardiovascular side effects in cardiac patients. Social support interventions and self-management, as well as cardiac rehabilitation programs, have also been studied have some benefit without negative cardiovascular effects.[10,15,54,55,73]

There is also evidence that positive psychological factors may improve longevity and decrease morbidity and mortality from cardiac disease. Because depressive symptoms have been shown to independently predict adverse outcomes in CVD, it was postulated that improved survival and health behaviors might be associated with positive affect. In the Heart and Soul Study, investigators focused mainly on psychosocial factors and health outcomes in a prospective cohort study. Over a thousand patients with stable cardiac disease were recruited into the study; positive affect was not significantly associated with cardiovascular events, but each standard deviation (8.8 points) increase in positive affect score was associated with a 16% decreased risk of all-cause mortality (HRL 0.84l 95% CI 0.76-0.92, P=0.001). Positive affect was associated with a 27% reduction in mortality during a 7-year follow-up period, though this effect was no longer significant when adjusted for behavioral factors, specifically physical activity. This study suggests that patients with a positive attitude may have longer lives because they successfully adopt a healthier lifestyle and exercise more than those without a positive attitude.[40]

Investigators in the REGARDS (Reason for Geographic and Racial Differences in Stroke) study examined the possible role alcohol use, smoking, physical inactivity, and medication nonadherence play in the association between depression and MI or death in patients with CVD. This was a population-based cohort study of over 4000 participants of stroke incidence and cognitive decline in patients with CVD. Patients with depression were more likely to have hypertension, diabetes mellitus, and a history of stroke. They also were more likely to be taking an antidepressant and less likely to be taking a statin at baseline. The depressed patients were less likely to report alcohol use but more likely to be current smokers (27.6% vs 13.8%, P<0.001), be physically inactive (51.9% vs 36.1%, P<0.001), and to have worse medication adherence (5.8% vs 2.3%,

$P<0.0010$) (80). The most substantial contributors to excess risk of MI were smoking and physical inactivity, contributing to one fifth of the relationship between increased depression and cardiac risk. These results were similar to those observed in the Heart and Soul Study cited above, which suggests that interventions developed to encourage exercise and stop smoking would be imperative to decreasing both depressive symptoms and the risk of death in cardiac patients.[40,74] A small study, the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) trial, demonstrated a 4-month exercise intervention to reduce depressive symptoms in CVD. No differences in cardiac outcomes were noted because the study was underpowered.[38,74]

The IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) randomized controlled trial is an 8-year follow-up study of elderly depressed patients who received either usual care or a 12-month collaborative stepped care program for late-life depression comprised of antidepressants and psychotherapy. For patients with baseline CVD, there was no difference in reduction of depressive symptoms between the IMPACT and usual care group. IMPACT patients were more likely to have received psychotherapy. In the 8-year follow-up period, in the IMPACT patients with baseline CVD, the CVD event rate was 86% (30/35) for IMPACT versus 81% (26/32) for the usual care group ($P=0.52$). The IMPACT intervention was associated with a significant CVD risk reduction for men without baseline CVD (70%, $P=0.037$), though not significant for women (37%, $P=0.12$). IMPACT patients without CVD had a significantly lower risk of fatal/nonfatal MI or stroke (53%, $P=0.030$ and 75%, $P=0.014$). This study demonstrated that collaborative care for depression received before the onset of clinical CVD reduced the risk of subsequent cardiac events in elderly depressed patients. This buoys up the evidence that depression is a risk factor for CVD and that treatment of depression can lower cardiac events.[75]

The Coronary Psychosocial Evaluation Studies Randomized Controlled Trial (COPES) studied patients with persistent depression following an acute coronary syndrome. Patients either received problem-solving therapy +/- pharmacotherapy or usual care and were compared with a control group of nondepressed patients. The problem-solving group was more satisfied with their care (54% vs 19%; 95% CI 2.2-12.9, $P<0.001$)

than the usual care group and had lower BDI scores (95% CI -7.6- -3.8, $P=0.005$). Freedland et al demonstrated the efficacy of CBT in depressed patients with CAD, specifically those post-CABG. Patients were randomized to either receive 12 weeks of CBT, supportive stress management, or usual care. Those in the CBT and supportive stress management groups had significantly higher remissions rates of depression compared with the usual care group (71% vs 57% vs 33%, $P=0.002$). In long term follow-up at 9 months, only the patients from the CBT group continued to show remission of their depression.[76-78]

The Bypassing the Blues study showed the effectiveness of telephone-delivered collaborative care over the usual care for depression after coronary artery bypass graft. The intervention group showed better improvements in mental and physical quality of life and had a larger rate of depression remission than the usual care group ($P=0.09$).[79] More recently, Glozier et al studied an Internet-delivered CBT intervention for adults with mild-to-moderate depression and high-risk CVD. This was a randomized-controlled trial with the iCBT group (Internet-based CBT) and a usual care group. Although participants in both groups exhibited symptom improvement, it was greater in the iCBT group (3.66, 95% CI 3.05-4.27) compared with the control group (2.60, 95% CI 2.05-3.16). The iCBT group also showed significantly reduced anxiety symptoms (2.44, 95% CI 1.87-3.02) compared with the control group (1.48, 95% CI 0.97-1.99). In addition, adherence rates were improved in the iCBT group. These results indicate that an iCBT program can improve both mood and adherence in patients with depression and a comorbid medical disorder, specifically CAD. This Internet-based intervention has the potential to be applied to large numbers of patients and as a low intensity psychosocial intervention in the future.[80]

Discussion

Cardiovascular disease is the leading cause of death, disability, and disease burden in the developed world. Depression is a major public health concern with severe morbidity (a leading cause of disability) and mortality that remains insufficiently addressed. Depression is associated with poor functional and cardiac outcomes, including more than a 2-fold increase in mortality following MI.[3,18] When cardiovascular comorbidity is added,

morbidity and mortality worsen.[8,9] It is imperative that patients with the cardiac risk factors of recent history of MI, CAD, heart failure, conduction abnormalities, and preexisting postural hypotension, be evaluated and treated for depression.[15]

There is strong evidence for a bidirectional association between depression and cardiovascular disease, both genetically and environmentally. Patients post-MI are at considerable risk for depression and suicide, and depressed patients are at increased risk for development of CAD and for poor outcome post-MI.[3,17] There have been studies suggesting that treatment of depression improves cardiovascular outcome, but these effects are relatively small and the findings are equivocal. Depression is associated with decreased adherence with medications/medical appointments, dietary and exercise regimens, in short, an unhealthy lifestyle. There is evidence that the introduction of exercise, psychotherapy, and antidepressant medications reduce depressive symptoms. Modifiable health behaviors, specifically physical inactivity, smoking, and medication non-adherence appear to be the most critical of the biological factors that are associated with both CVD and depression. The available treatments for depression, antidepressants (SSRIs, TCAs, SNRIs) and psychotherapy (specifically CBT) have been shown to be relatively safe and effective in cardiac patients. Collaborative care management which incorporates mental health treatment, problem solving and exercise, and optimal medical treatment is likely the area where future research will lie, with the goal of improving and modifying health behaviors to improve both physical and mental health conditions. Another area of possible research implication is in the area of genetic susceptibility and heritability, and would include the possible shared vulnerability genes for depression, cardiac risk factors (hypertension/diabetes/cholesterol levels), and the inflammatory markers that all increase the risk of CAD in patients. ❑

REFERENCES

1. Halaris A. Comorbidity between depression and cardiovascular disease. *Int Angiol*. 2009;28:92-99.
2. Dowlati Y, Herrmann N, Swardfager WL, Reim EK, Lanctot KL. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: A meta-analysis. *Can J Psychiatry*. 2010;55(2):91-99.
3. Celano CM, Huffman JC. Depression and cardiac disease. A review. *Cardiol Rev*. 2011;19(3):130-142.
4. Maltzberg B. Mortality among patients with involution melancholia. *Am J Psychiatry*. 1937;93:1231-1238.
5. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak – the link between depression and cardiovascular disease. *Nat Rev Cardiol*. 2012;9(9):1-14.
6. Garfield LD, Scherrer JF, Hauptman PJ, et al. Association of anxiety disorders and depression with incident heart failure. *Psychosom Med*. 2014;76:128-136.
7. Bucknall C, Brooks D, Curry PV, Bridges PK, Bouras N, Ankier SI. Mianserin and trazodone for cardiac patients with depression. *Eur J Clin Pharmacol*. 1988;33(6):565-569.
8. Scherrer JF, Chrusciel T, Garfield LD, et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. *Br J Psychiatry*. 2012;200:137-142.
9. Sowden GL, Huffman JC. The impact of mental illness on cardiac outcomes: A review for the cardiologist. *Int J Cardiol*. 2009;132:30-37.
10. Scherrer JF, Garfield LD, Lustman PJ, et al. Antidepressant drug compliance: reduced risk of MI and mortality in depressed patients. *Am J Med*. 2011;124:318-324.

11. Ramasubbu R, Beaulieu S, Taylor VH, Schaffer A, McIntylre RS. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid medical conditions: Diagnostic, assessment, and treatment principles. *Ann Clin Psychiatry*. 2012;24(1):82-90.
12. Taylor D, Meader N, Bird V, Pilling S, Creed F, Goldberg D. Pharmacological interventions for people with depression and chronic physical health problems: Systematic review and meta-analysis of safety and efficacy. *Br J Psychiatry*. 2011;198:179-188.
13. Van Melle JP, de Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry*. 2007;190:460-466.
14. Lesperance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial. *JAMA*. 2007;297:367-379.
15. Alvarez W, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: A review of the literature. *Pharmacotherapy*. 2003;23(6):754-771.
16. McIntyre RS, Schaffer A, Beaulieu S. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid conditions. *Ann Clin Psychiatry*. 2012;24(1):1-3.
17. Cowles MK, Musselman DL, McDonald W, Nemeroff CB. Effects of mood and anxiety disorders on the cardiovascular system. In: *Hurt's Heart.* 13th ed: two volume set. New York, NY: McGraw-Hill Publishers; 2010;Chapter 96:2128-2145
18. Holt RIG, Phillips DIW, Jameson KA, Cooper C, Dennison E, Peveler RC. The relationship between depression, anxiety, and cardiovascular disease: Findings from the Hertfordshire Cohort Study. *J Affect Disord*. 2013;150:84-90.

Clinical research

El tratamiento de los trastornos afectivos en la enfermedad cardíaca

Habitualmente los pacientes con enfermedad cardio-vascular (ECV) tienen depresión mayor sindromática y la depresión se ha asociado con un aumento del riesgo de morbilidad y mortalidad. La prevalencia de la depresión en los pacientes con ECV está entre 17% y 47%. Desde hace tiempo se han estudiado las intervenciones farmacológicas y psicoterapéuticas, las que en general son seguras, pero poco eficaces en la reducción de los síntomas depresivos en pacientes con ECV. El impacto en los resultados cardíacos no está claro. La evidencia a partir de los ensayos clínicos controlados y randomizados señala que los antidepresivos, especialmente los inhibidores selectivos de la recaptura de serotonina, son ampliamente seguros y tienen una alta probabilidad de ser efectivos en el tratamiento de la depresión en pacientes con ECV. Esta revisión describe la prevalencia de la depresión en pacientes con ECV, las relaciones fisiológicas entre depresión y ECV, las opciones terapéuticas para los trastornos afectivos y los ensayos clínicos que demuestran la eficacia y la seguridad de los fármacos antidepresivos y de la psicoterapia en este grupo de pacientes. Se han realizado grandes progresos en la comprensión de los potenciales mediadores entre el trastorno depresivo mayor y la ECV (tanto en el estilo de vida como en los riesgos biológicos que comparten, como es el caso de la inflamación).

Traitement des troubles de l'humeur dans la maladie cardiaque

Les patients souffrant de maladie cardiovasculaire (MCV) présentent couramment un syndrome de dépression caractérisée, la dépression étant associée à un risque accru de morbidité et de mortalité. Chez les patients atteints de MCV, la prévalence de la dépression varie de 17 % à 47 %. Les traitements psychothérapeutiques et pharmacologiques sont étudiés depuis longtemps et généralement bien tolérés, assez efficaces pour diminuer les symptômes dépressifs chez ces patients. L'impact sur l'issue cardiaque demeure obscur. Des études cliniques contrôlées randomisées montrent que les antidépresseurs, surtout les inhibiteurs sélectifs de la recapture de la sérotonine, sont en grande majorité bien tolérés et vraisemblablement efficaces dans le traitement de la dépression des patients atteints de MCV. Cet article décrit la prévalence de la dépression chez ces patients, les liens physiologiques entre dépression et MCV, les possibilités thérapeutiques pour les troubles de l'humeur et présente les études cliniques montrant l'efficacité et la tolérance des antidépresseurs et de la psychothérapie dans cette population de patients. De grands progrès ont été faits pour comprendre les liens éventuels entre les troubles dépressifs majeurs et la MCV, à la fois l'hygiène de vie et les risques biologiques communs comme l'inflammation.

19. Iosifescu DV, Clementi-Craven N, Fraguas R, et al. Cardiovascular risk factors may moderate pharmacological treatment effects in major depressive disorder. *Psychosom Med*. 2005;67:703-706.

20. Smoller JW, Allison M, Cochrane BB, et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the women's health initiative study. *Arch Intern Med*. 2990;169(22):2128-2139.

21. Taylor CB, Conrad A, Wilhelm FH, et al. Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? *J Psychiatr Res*. 2009;43:1246-1252.

22. Windle M, Windle RC. Recurrent depression, cardiovascular disease, and diabetes among middle-aged and older adult women. *J Affect Disord*. 2013;150:895-902.

23. Frasure-Smith N, Lesperance F., Talajic M. Depression following myocardial infarction. Impact on 6 month survival. *JAMA*. 1993;270:1819-1825.

24. Chiaie RD, Capra E, Salviati M, et al. Persistence of subsyndromal residual symptoms after remission of major depression in patients without cardiovascular disease may condition maintenance of elevated platelet factor 4 and β-thromboglobulin plasma levels. *J Affect Disord*. 2013;150:664-667.

25. Paslakis G, Kopf D, Westphal S, et al. Treatment with paroxetine, but not amitriptyline, lowers levels of lipoprotein(a) in patients with major depression. *J Psychopharmacol*. 2011;25(10):1344-1346.

26. Pozuelo L, Zhang J, Franco K, Tesar G, Penn M, Jiang W. Depression and heart disease: What do we know, and where are we headed? *Cleve Clin J Med*. 2009;76(1):59-70.

27. Lopez-Vilchez I, Serra-Millas M, Navarro V, et al. Prothrombotic platelet phenotype in major depression: Downregulation by antidepressant treatment. *J Affect Disord*. 2014;159:39-45.

28. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated plasma fibrinogen, psychological distress, antidepressant use, and hospitalization with depression: Two large population-based studies. *Psychoneuroendocrinology*. 2013;38:638-647.

29. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. *J Am Coll Cardiol*. 2012;60:1053-1063.

30. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health related quality of life: the Heart and Soul Study. *JAMA*. 2003;290:215-221.

31. Hamer M, Batty GD, Seldenrijk A, Kivimaki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Study. *Eur Heart J*. 2010;32(4):737-442.

32. Kemp AH, Brunoni AR, Santos IS, et al. Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability An ELSA-Brasil cohort baseline study. *Am J Psychiatry*. 2014;171(2):1328-1334.

33. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med*. 2005;165(21):2508-2513.

34. Su S, Lampert R, Lee F, et al. Common genes contribute to depressive symptoms and heart rate variability: The Twins Heart Study. *Twin Res Hum Genet*. 2010;13(1):1-9.

35. Su S, Miller AH, Sneider H, et al. Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: The Twins Heart Study. *Psychosom Med*. 2009;71:152-158.

36. Rubin RR, Peyrot M, Gaussoin SA., et al. Four-year analysis of cardiovascular disease risk factors, depression symptoms, and antidepressant medicine use in the Look AHEAD (Action for Health in Diabetes) clinical trial of weight loss in diabetes. *Diabetes Care*. 2013;36:1088-1094.

37. Mannie ZN, Williams C, Diesch J, Steptoe A, Leeson P. Cardiovascular and metabolic risk profile in young people at familial risk of depression. *Br J Psychiatry*. 2013;203(1):18-23.

38. Blumenthal JA. New frontiers in cardiovascular behavioral medicine: Comparative effectiveness of exercise and medication in treating depression. *Cleve Clin J Med*. 2011;78:S35-S43.

39. Baumeister H, Hutter N, Bengel K. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev*. 2011;9:CD008012.

40. Hoenr PW, Denollet J, de Jonge P, Whooley MA. Positive affect and survival in patients with stable coronary heart disease: Findings from the Heart and Soul Study. *J Clin Psychiatry*. 2013;74(7):716-722.

41. Van den Brink RHS, Van Melle JP, Honig A, et al. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: Rationale and outline of the Myocardial Infarction and Depression-Intervention Trial. *Am Heart J*. 2002;144(2):219-225.

42. Santangelo A, Testai M, Barbagallo P, et al. Use of specific serotonin reuptake inhibitors (SSRIs) (sertraline or citalopram) in the treatment of depression reduces the cardiovascular risk in the elderly. Evidence from a Sicilian population >80 years recovered in the assisted sanitary residences (RSA). *Arch Gerontol Geriatr*. 2009;48:350-352.

43. Cohen JB, Wilcox CS, Goodman L. Antidepressant efficacy and safety of trimipramine in patients with mild heart disease. *Clin Ther*. 1993;15:114-126.

44. Nelson JC, Kennedy JS, Pollock BG, et al. Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. *Am J Psychiatry*. 1999;156(7);1024-1028.

45. Roose SP, Glassman AH. Antidepressant choice in the patient with cardiac disease: lessons from the cardiac arrhythmias suppression trials (CAST) studies. *J Clin Psychiatry*. 1994;55(suppl A):83-87.

46. Roose SP, Glassman AH, Giardina EV, Johnson LL, Resovsky K, Le Winter M. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol*. 1987;7:247-251.

47. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA*. 1998;279(4):287-291.

48. Yeragani VK, Roose S, Mallavarapu M, Radhakrishna RK, Pesce V. Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on measures of nonlinearity and chaos of heart rate. *Neuropsychobiology*. 2002;46(3):125-135.

49. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EV, Bigger JT. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry*. 1998;155:660-665.

50. Strik JJ, Honig A, Lousberg R. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind placebo-controlled trial. *Psychosom Med*. 2000;62:783-789.

51. Shapiro PA, Lesperance F, Frasure-Smith N. An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (SAHDAT trial). Sertraline Anti-Depressant Heart Attack Trial. *Am Heart J*. 1999;37:1100-1106.

52. Glassman AH, O'Connor CM, Califf RM etal. Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):401-709.

53. Glassman AH, Bigger, JT. Depression and cardiovascular disease: The safety of antidepressant drugs and their ability to improve mood and reduce medical morbidity. In: *Depression and Heart Disease*. New York, NY: Wiley and Sons; 2011; Chapter 5.

54. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure. Results of the SAD-HART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) Trial. *J Am Coll Cardiol*. 2010;56(9):692-699.

55. O'Connor CM, Jiang W, Kuchibhatla M, et al. Antidepressant use, depression, survival in patients with heart failure. *Arch Int Med*. 2008;168(2):2232-2237.

56. Habra ME, Baker B, Frasure-Smith N, et al. First episode of major depressive disorder and vascular factors in coronary artery disease. Baseline characteristics and response to antidepressant treatment in the CREATE trial. *J Psychosom Res*. 2010;69(2):133-141.

57. Bekke-Hansern S, Trockel M, Burg MM, Taylor CB. Depressive symptom dimensions and cardiac prognosis following myocardial infarction: results from the ENRICHD clinical trial. *Psychol Med*. 2012;42:51-60.

58. Enriched Investigators: Carney RM. et al. Enhancing recovery in coronary heart disease (ENRICHD) study interventions: Rationale and design. *Psychosom Med*. 2001;63:747-755.

59. Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infacrtion depressive disorder: a randomized, placebo-controlled trial with mirtazapine. *Psychosom Med*. 2007;69:606-613.

60. Weeke P, Jensen A, Folke F, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: A nationwide case–time–control study. *Clin Pharmacol Ther*. 2012;92:72.

61. Gottlieb SS, Kop WJ, Thomas SA, et al. A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. *Am Heart J*. 2007;153:868-873.

62. Hansen BH, Hanash JA, Rasmussen A, et al. Effects of escitalopram in prevention of depression in patients with acute coronary syndrome (DECARD). *J Psychosom Res*. 2012;72:11-16.

63. Rasmussenr SL, Overo KF Tanghoj P. Cardiac safety of citalopram: prospective trials and retrospective analyses. *J Clin Psychopharmacol*. 1999;19:407-415.

64. Pan YJ, KuoKH, Chan HY, McCrone P. Cost-effectivesness and cost-utility of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants in depression with comorbid cardiovascular disease. *J Psychiatr Res*. 2014;54:70-78.

65. Veith RC, Raskind MA, Caldwell JH, Barnes RF, Gumbrecht G, Ritchie JL. Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. *N Engl J Med*.1982;306:954-959.

66. Hoc J. The clinical efficacy and side-effects of mianserin and nortriptyline in depressed outpatients: a double-blind randomized trial. *Curr Med Res Opin*. 1982;8(4):107-115.

67. Roose SP, Glassman AH, Giardina EV. Nortriptyline in depressed patients with left ventricular impairment. *JAMA*. 1986;256:3253-3257.

68. Dietch JT, Fine M. The effect of nortriptyline in elderly patients with cardiac conduction disease. *J Clin Psychiatry*. 1987;44:273-275.

69. Glassman AH, Johnson LI, Giardina EV. The use of imipramine in depressed patients with congestive heart failure. *JAMA*. 1983;250:1997-2001.

70. Raskind M, Veith R, Barnes R, Gumbrecht G. Cardiovascular and antidepressant effects of imipramine in the treatment of secondary depression in patients with ischemic heart disease. *Am J Psychiatry*. 1982;139:1114-1117.

71. Cohen BE, Panguluri P, Na B, Whooley MA. Psychological risk factors and the metabolic syndrome in patients with coronary heart disease: findings from the Heart and Soul Study. *Psychiatry Res*. 2010; 175;133-137.

72. Kiev A, Masco HL, Wenger TL, Johnston JA, Batey SR, Holloman LC. The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. *Ann Clin Psychiatry*. 1994;6(2):107-115.

73. Milani RV, Lavie CJ. Impact of cardiac rehabilitation on depression and its associated mortality. *Am J Med*. 2007;120:799-806.

74. Ye S, Muntner P, Shimbo D, et al. Behavioral mechanisms, elevated depressive symptoms, and the risk for myocardial infarction or death in individuals with coronary heart disease. *J Am Coll Cardiol*. 2013;61(6):622-630.

75. Stewart JC, Perkinds A, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: Data from the IMPACT randomized controlled trial. *Psychosom Med*. 2014;76:29-37.

76. Davidson KW, Rieckmann N, Clemow L, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms. Coronary Psychosocial Evaluation Studies Randomized Controlled Trial. *Arch Intern Med*. 2010;120(7):600-608.

Clinical research

77. Freedland KE, Skala JA, Carney RM, et al. Treatment of depression after coronary artery bypass surgery. *Arch Gen Psychiatry*. 2009;66(4):387-396.

78. Whang W, Shimbo D, Kronish IM, et al. Depressive symptoms and all-cause mortality in unstable angina pectoris (from the Coronary Psychosocial Evaluation Studies [COPES]. *Am J Cardiol*. 2010;106(8):1104-1107.

79. Rollman BL, Herbeck, BB. The Bypassing the Blues Trial: Collaborative care for post-CABG depression and implications for future research. *Cleve Clin J Med*. 2011;78(suppl 1):S4-12.

80. Glozier N, Christensen H, Naismith S, et al. Internet-delivered cognitive behavioral therapy for adults with mild to moderate depression and high cardiovascular disease risks: A randomized attention-controlled trial. *PLoS ONE*. 2013;8(3):e59139.