



Published in final edited form as:

Harv Rev Psychiatry. 2018 ; 26(4): 175–184. doi:10.1097/HRP.0000000000000162.

Depression and Anxiety in Heart Failure: a Review

Christopher M. Celano, M.D.^{1,2}, Ana C. Villegas, M.D.², Ariana M. Albanese, B.A.², Hanna K. Gaggin, M.D., M.P.H.^{1,3}, and Jeff C. Huffman, M.D.^{1,2}

¹Harvard Medical School, Boston, MA

²Department of Psychiatry, Massachusetts General Hospital, Boston, MA

³Department of Medicine, Division of Cardiology, Massachusetts General Hospital, Boston, MA

Abstract

Background—In patients with heart failure (HF), depression and anxiety disorders are common and associated with adverse outcomes such as reduced adherence to treatment, poor function, increased hospitalizations, and elevated mortality. However, despite the adverse impact of these disorders, anxiety and depression remain underdiagnosed and undertreated in HF patients.

Methods—We performed a targeted literature review to (1) identify associations between depression, anxiety, and HF, (2) examine mechanisms mediating relationships between these conditions and medical outcomes, (3) identify methods for accurately diagnosing depression and anxiety disorders in HF, and (4) review current evidence for treatments of these conditions in this population.

Results—Both depression and anxiety disorders are associated with the development and progression of HF, including increased rates of mortality, likely mediated through both physiologic and behavioral mechanisms. Given the overlap between cardiac and psychiatric symptoms, accurately diagnosing depression or anxiety disorders in HF patients can be challenging. However, adherence to formal diagnostic criteria and utilization of a clinical interview comprise the best course of action in the evaluation process. There is limited evidence for the efficacy of pharmacologic and psychotherapy in patients with HF. However, cognitive behavioral therapy has been shown to improve mental health outcomes in patients with HF, and selective serotonin reuptake inhibitors appear safe in this cohort.

Conclusions—Depression and anxiety disorders in HF patients are common, underrecognized, and linked to adverse outcomes. Further research to improve detection and develop effective treatments for these disorders in HF patients is badly needed.

Keywords

Depression; anxiety; heart failure; diagnosis; treatment

Heart failure (HF), a chronic impairment of cardiac function typically characterized by shortness of breath, edema, and/or fatigue,¹ affects over 5 million Americans, with

prevalence expected to rise to 8 million by 2020.² Associated with poor functioning and impaired health-related quality of life (QoL), as well as frequent hospitalizations and high healthcare costs, HF represents a serious burden to both patients and the healthcare system.^{3,4} Mortality remains high despite advances in treatment, with roughly 50% of HF patients dying within 5 years of diagnosis.²

Psychiatric illnesses are prevalent in patients with HF, and prior work suggests that these disorders lead to negative health and cardiovascular outcomes in these patients. Depression and anxiety disorders—including generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and panic disorder—are the most common psychiatric conditions in HF patients. We performed a targeted review to determine: the associations between depression/anxiety and HF incidence and outcomes, potential mechanisms underlying these relationships, and methods for diagnosing and treating depression and anxiety disorders in this high-risk population.

Search strategy

We performed focused literature searches using PubMed and Google Scholar to identify relevant original research and review articles. Search terms focused on epidemiology (e.g., “heart failure depression prevalence”), associations between psychiatric symptoms and HF outcomes (e.g., “panic disorder heart failure mortality”), pathophysiological and health behavior mechanisms (e.g., “depression inflammation,” “post-traumatic stress disorder physical activity”), and treatments of depression and anxiety disorders in HF (e.g., “cognitive behavioral therapy depression heart failure”). Titles and abstracts from these searches were reviewed, full text articles were obtained for relevant manuscripts, and reference lists were reviewed to identify additional manuscripts appropriate for review.

Prevalence of depression and anxiety in HF

Among patients with HF, depression and anxiety disorders are common, with prevalence rates markedly higher than in the general population. A meta-analysis of 36 studies found that clinically significant depressive symptoms affect 21.5% of HF patients, with one-third of HF patients reporting elevated depressive symptoms on questionnaires and 19% meeting criteria for a depressive disorder (typically major depressive disorder, but some studies have included dysthymia and minor depression⁵) based on a diagnostic interview.⁶ These prevalence rates are similar in studies of inpatients and outpatients,⁶ and they are approximately two-to-three times higher compared to the general population.^{7,8} Anxiety too is highly prevalent in this population, with about 13% of HF patients fulfilling diagnostic requirements for a formal anxiety disorder (usually GAD, though one study included panic disorder and unspecified anxiety disorder⁹), and nearly 30% of patients endorsing clinically significant levels of anxiety (based on anxiety questionnaires).¹⁰ These rates appear to be higher than those in older adults and other medical populations,¹⁰ though the method by which anxiety is measured and the overlap between anxiety and HF symptoms may impact reported prevalence rates.

Links between depression/anxiety and adverse medical outcomes in HF

Depression has been linked to the development and progression of HF and other cardiovascular diseases. In a recent prospective observational study of nearly 2 million healthy adults, depression (defined by a billing diagnosis of depression or prescription of an antidepressant) was prospectively associated with an 18% increased risk of HF development over the subsequent 7 years (median), even after controlling for other cardiovascular risk factors.¹¹ In another study of over 80,000 veterans without heart disease, a diagnosis of major depression (defined as 1 inpatient or 2 outpatient ICD-9 codes for major depressive disorder) was linked to a 21% increased risk of HF development over the next 5.8 years in HIV negative veterans, when taking other medical factors into account.¹² In patients with a diagnosis of HF, depression is a poor prognostic marker as well. In this group, both elevated depressive symptoms and depressive disorders has been prospectively linked to frequent hospitalizations, recurrent cardiac events, and mortality.^{6,13} In a meta-analysis of eight studies examining the prospective associations between elevated depressive symptoms or a depressive disorder and HF outcomes, Rutledge and colleagues found that depressive symptoms or a depressive disorder led to a 2-fold increased risk of death or cardiac events.⁶

In contrast, associations between anxiety and health outcomes in patients with HF are less clear. To date, five studies have examined the link between anxiety and HF outcomes; four of these examined the relationship between anxiety symptoms and mortality in patients with HF,^{14–17} while one focused on the links between PTSD and subsequent development of HF.¹⁸ In the studies focused on anxiety symptoms, when controlling for relevant demographic and medical variables, there were no significant associations between anxiety and mortality.^{14–17} However, in the longitudinal prospective PTSD study, a diagnosis of PTSD (diagnosed based on ICD-9 codes for PTSD) at enrollment conferred a 47% increased risk of incident HF over the subsequent seven years.¹⁸ This raises the possibility that anxiety disorders may pose a significantly greater risk to cardiac health than the symptom of anxiety alone, consistent with prior work finding that anxiety disorders confer a much clearer risk of adverse cardiac outcomes than anxiety alone in coronary artery disease (CAD).^{19–21} Further studies are needed to examine the links between anxiety disorders and health outcomes in patients with established HF.

Though the literature linking anxiety to HF-related health has been mixed, several factors highlight the importance of identifying anxiety disorders in HF patients. First, anxiety has been associated with poor heart health and higher rates of mortality in patients with CAD, which often co-occurs with HF.^{20–22} Similarly, in patients with or without cardiac disease, anxiety disorders such as GAD, PTSD, and panic attacks/panic disorder are associated with poor cardiac outcomes.^{20,23–27} Furthermore, in patients who have HF and elevated depressive symptoms, the presence of comorbid anxiety increases the risk of poor cardiac outcomes, including rehospitalizations and mortality.^{28,29} Finally, in patients with major depression, the presence of anxiety may reduce antidepressant efficacy and lead to depression persistence.^{30–32}

Mechanisms linking depression/anxiety and adverse health outcomes in HF

Both physiologic and behavioral mechanisms may help to explain the associations between negative psychological states and outcomes in patients with HF (Figure 1).

Regarding behavioral mechanisms, adherence to healthy behaviors is critical to cardiac health. In patients without pre-existing HF, physical inactivity is prospectively linked to the development of HF.³³ Among patients with HF, poor self-care—including nonadherence to physical activity, a low sodium diet, and pharmacologic treatment—is associated with worse outcomes, including reduced QoL, higher rates of hospitalizations, and mortality.³⁴

Depression and anxiety may make it more challenging for patients with heart disease to adhere to health behavior recommendations. For example, depressed patients with CAD are less likely to maintain a healthy diet,³⁵ exercise regularly,^{35,36} adhere to medications,^{35,37} or complete cardiac rehabilitation, compared to those without depression.³⁸ In addition, patients with depression are less able to lower their cholesterol than non-depressed individuals.³⁹ Likewise, depressed patients with HF and other cardiovascular diseases are less likely to complete cardiac rehabilitation.⁴⁰

There is also evidence that anxiety is associated with unhealthy behaviors and cardiovascular risk, though the evidence is less robust than that for depression. Anxiety disorders are linked to smoking, physical inactivity, binge drinking, and heavy drinking,⁴¹ and PTSD in particular is linked to reduced physical activity and smoking.⁴² Like depression, anxiety is associated with poorer adherence to risk-reducing health behaviors, such as physical activity or smoking cessation following MI.⁴³

Physiological factors may also play a major role in the connection between psychiatric symptoms and adverse outcomes in HF. For example, inflammation is implicated in the pathogenesis of several different subtypes of HF^{44,45} and may be a driver of ventricular remodeling that leads to increasing fibrosis and the progression of cardiac dysfunction.⁴⁶ Among patients with known HF, interleukin-6—a marker of inflammation—is linked to both short- and longer-term cardiovascular mortality.⁴⁷

Depressive symptoms and major depression are linked to elevated levels of inflammatory biomarkers. In a recent meta-analysis including patients with and without cardiovascular disease, depression was associated with increased levels of C-reactive protein (CRP), interleukin (IL)-1, and IL-6,⁴⁸ and other studies have found links between depression and tumor necrosis factor-alpha (TNF- α) and monocyte chemoattractant protein-1 (MCP-1).⁴⁹ Likewise, an analysis of data from the Cardiovascular Health Study found that depression was linked to higher levels of inflammatory and fibrosis markers.⁵⁰ Finally, in a study of individuals with both major depression and HF, depression was associated with multiple inflammatory markers.⁵¹

Relationships between anxiety and inflammatory markers are less clear. While some studies have found links between anxiety and higher levels of CRP, TNF- α , IL-6, homocysteine, IL-17, and fibrinogen levels in non-cardiac populations,^{52,53} others have not.^{53,54} The evidence for links between anxiety *disorders* and inflammation, however, are more

consistent. In patients with CAD, GAD has been associated with elevated levels of CRP.⁵⁵ Similarly, compared to healthy controls, patients with PTSD have higher levels of IL-6, IL-1 β , and interferon- γ .⁵⁶ Thus, inflammation may be one physiologic mechanism through which anxiety and depression are associated with cardiac outcomes in HF.

Changes to the autonomic nervous system are also implicated in the relationships between depression, anxiety, and cardiac outcomes. Cardiac activity and vascular tone are modulated by the sympathetic and parasympathetic nervous systems, with the sympathetic nervous system typically promoting increased heart rate and vasoconstriction and the parasympathetic nervous system promoting bradycardia and vasodilation. In HF, an imbalance in autonomic nervous system function, characterized by relative hyperactivity of the sympathetic nervous system and hypoactivity of the parasympathetic nervous system, is common.⁵⁷ This imbalance can lead to cardiac remodeling and arrhythmias, and it has been linked to mortality in HF.⁵⁷

Negative psychological states are associated with sympathetic hyperactivity and parasympathetic hypoactivity. For example, both depression and anxiety have been associated with reduced heart rate variability, a sign of abnormal autonomic function, in patients with and without heart disease. This suggests the autonomic dysfunction described above.^{58–61} These reductions in heart rate variability are most pronounced in patients with more severe depressive symptoms, suggesting that patients with formal major depression may be at particularly high risk for autonomic dysfunction.⁶⁰

Endothelial function may also be important. Proper function of the endothelium (the dynamic layer of cells lining blood vessels) is critical for heart health, as it helps to ensure adequate perfusion of the heart and other organs and reduces strain on the heart. In patients with HF, endothelial dysfunction is prospectively linked to increased HF-related events and all-cause mortality.^{62–64} Both depression and anxiety are associated with endothelial dysfunction in patients with and without HF. In patients with HF, depressive symptoms are associated with a lower L-arginine/ADMA ratio, indicating reduced nitric oxide availability, leading to endothelial dysfunction.⁶⁵ Similarly, in patients with CAD, depressive symptoms are associated with impairments in flow-mediated dilation, another marker of endothelial function.⁶⁶

Anxiety is also associated with impaired endothelial function—measured by flow-mediated dilation—in patients with and without heart disease.^{67,68} Furthermore, PTSD is associated with elevated markers of endothelial dysfunction, including soluble intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and soluble tissue factor in some, but not all, studies.^{69,70}

Diagnosis of depression and anxiety disorders in patients with HF

Despite the high rates of depression and anxiety in HF, and their links to adverse outcomes in this population, these psychiatric symptoms often are overlooked in clinical practice. For example, inpatient providers only succeed in identifying half of post-MI patients who have elevated anxiety,⁷¹ and the majority of depressed individuals are not recognized as such.^{71,72}

Accurate psychiatric diagnosis may prompt clinicians to offer psychiatric treatment, which in turn could improve health behaviors, enhance engagement in cardiac treatment, and ultimately improve clinical outcomes.

Due to the significant overlap in symptoms shared between HF and major depression and anxiety disorders, making an accurate psychiatric diagnosis in patients with HF can be challenging. However, accurately diagnosing these disorders when present—and excluding them when absent—is critical, as both over- and under-diagnosis can have significant consequences (i.e., overdiagnosis may lead to inappropriate exposure to medications and side effects, while underdiagnosis may lead to worse psychiatric health and functioning). Given the complexities inherent to this diagnostic process, it is highly recommended that clinicians carefully examine HF patients to assess whether they meet full Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for major depression or an anxiety disorder.⁷³ This includes endorsing the cardinal symptoms of the disorders under question, such as depressed mood or anhedonia most of the day, nearly every day, for two consecutive weeks. Adhering to DSM-5 criteria helps to ensure that symptoms leading to diagnosis, such as isolated problems with sleep, concentration, or energy, are not simply manifestations of HF.

Use of screening tools to improve recognition

To increase recognition of depression and anxiety disorders in patients with cardiovascular disease, some organizations have recommended systematic screening for common psychiatric illnesses. For example, the American Heart Association (AHA) recommends two-step depression screening of all patients with heart disease using the 2-item Patient Health Questionnaire (PHQ-2),⁷⁴ followed by the 9-item Patient Health Questionnaire (PHQ-9) for positive-screen patients.⁷⁵ This two-step procedure is highly specific (91%) but relatively insensitive (52%) in patients with stable CAD,⁷⁶ suggesting that it is a good screening tool but that positive screens should be followed by a more thorough assessment to confirm diagnosis. Though this two-step screening procedure has not been examined specifically in HF patients, the PHQ-9 has adequate sensitivity and specificity (70% and 92%, respectively) for major depression in this group of patients.⁷⁷

Although universal screening for anxiety disorders has not yet been recommended, it may be useful to screen for GAD. This disorder is not only prospectively associated with poor cardiac outcomes in post-MI patients,²⁰ but may be as prevalent as major depression in hospitalized cardiac patients.⁷⁸ In addition, comorbid anxiety can reduce the effectiveness of depression treatment and has been linked to worse cardiovascular health.^{28–32} Easy to administer GAD screening tools, such as the two- and seven-item GAD-2 and GAD-7, have demonstrated adequate specificity and sensitivity for identifying GAD.^{79–81}

Despite the potential benefits of screening for depression and anxiety disorders, the practical details of when and where to screen are less clear. For instance, while screening for psychiatric disorders following an acute cardiac event may be highly efficient and identify many patients with elevated depressive or anxiety symptoms, these symptoms may dissipate following the cardiac events and may not represent full-fledged psychiatric disorders.

Similarly, screening for psychiatric conditions when dedicated treatment is not available has demonstrated little benefit,^{82,83} and thus screening for depression and GAD in HF patients should only occur in programs that have a clear process to ensure that treatment can be initiated and monitored. If screening is performed in acute care settings, deferring the final diagnosis to a period of clinical stability may be advisable if the diagnosis is new in onset during the admission or is unclear.

Management of depression and anxiety disorders in HF

Both psychotherapeutic and medication treatments are available for depression and anxiety disorders in patients with HF. Psychotherapy offers several advantages over pharmacotherapy. First, it can be customized for individual patients. Second, it has no known side effects or interactions with patients' cardiac medications. Finally, it may help patients to develop long-term skills to improve symptoms and prevent relapse. Despite these potential advantages, few studies have been performed to examine the efficacy of psychotherapy in HF patients.

Cognitive-behavioral therapy (CBT) is the only psychotherapeutic treatment that has been tested systematically in HF patients, with beneficial effects.^{84–87} In a single-arm trial of 23 patients with elevated depressive or anxiety symptoms and a history of HF or chronic obstructive pulmonary disease, a 6-week CBT intervention led to large improvements in HF-related QoL and moderate improvements in depressive symptoms.⁸⁴ In a larger (N=74), four-arm randomized pilot trial comparing CBT and exercise training vs. CBT alone vs. exercise training alone vs. usual care in patients with major depression (diagnosed using DSM-IV criteria) and HF, the combined treatment group showed the greatest—but non-significant—improvements in depression-related outcomes.⁸⁶ This suggests that CBT could be used in concert with other health behavior-enhancing interventions.

The largest CBT trial to date for patients with HF was the Depression and Self-Care of HF trial. In this study, the efficacy of a 6 month CBT intervention was tested in 158 patients diagnosed with major depression (diagnosed using DSM-IV-TR criteria) and HF.⁸⁸ Compared to enhanced usual care, the CBT intervention led to greater improvements in depression (reduction in depressive symptoms and higher rates of remission) and greater improvements in anxiety, fatigue, and life satisfaction. However, it did not lead to changes in physical functioning or self-care.

Regarding medications, for major depression, GAD, PTSD, and panic disorder, antidepressants—particularly selective serotonin re-uptake inhibitors (SSRIs)—are first-line treatment.^{89–91} While these agents are effective in patients without heart disease, the evidence for their use in HF is mixed. Two early randomized trials of depressed patients (one diagnosed using the structured clinical interview for the DSM-IV, one requiring BDI score 10) with HF (N=37, N=28), found that both citalopram and controlled-release paroxetine led to significantly greater reductions in depressive symptoms compared to placebo.^{92,93} However, two larger randomized trials examining the efficacy of escitalopram and sertraline for depression in HF did not replicate these findings. In the Mood and Mortality in Depressed HF Patients (MOOD-HF) study of 372 patients with MDD (diagnosed using

structured clinical interview for the DSM-IV), both escitalopram and placebo led to significant reductions in depressive symptoms, but there were no significant between-group differences.^{94,95} Similarly, in the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial (N=469; major depressive disorder diagnosis made using DSM-IV criteria), sertraline was no more effective than placebo at reducing depressive symptoms at 3 months.⁹⁶

Several factors may account for the findings of the MOOD-HF and SADHART-CHF trials. One possible explanation relates to the overlap between the somatic symptoms of HF and those of depression or anxiety. While we would expect antidepressants to improve somatic symptoms caused by depression, those related to HF generally will not improve (and likely will worsen) over time. Since many depression scales are comprised of a combination of both cognitive and somatic symptoms,^{97,98} the apparent inefficacy of antidepressant treatments may be related to a failure to impact somatic symptoms. A second possible explanation for the negative findings of these trials is that some instances of major depression in HF patients may be biologically distinct from typical depression and therefore may not respond as well to antidepressant treatment. In both MOOD-HF and SADHART-CHF, participants had a mean age of 62 years, and in both studies, over 80% of participants were experiencing their first depressive episode at the time of enrollment. Given that the incidence of major depression peaks between 30 and 40 years,⁹⁹ the depression in these patients may have been physiologically distinct from that in the general population and less responsive to treatment.

Despite the lack of clear efficacy for SSRIs in patients with HF, we still recommend their use for treatment given their known efficacy for depression and anxiety disorders in other populations.⁸⁹⁻⁹¹ However, we would recommend frequent monitoring, titration, and switching of medications/treatments if patients are not responding initially to treatment in order to maximize the likelihood of response.

Regarding safety, SSRIs appear to be associated with few adverse cardiac side effects. They cause mild increases in norepinephrine and have minimal affinity for adrenergic receptors, and are thus less likely to cause orthostatic hypotension or tachycardia compared to the older tricyclic antidepressants (TCAs).¹⁰⁰ In addition, SSRIs have little effect on intraventricular conduction.¹⁰⁰ However, SSRIs induce three noteworthy side effects in patients with HF and other cardiovascular conditions. First, through their inhibition of platelet aggregation/activation and enhancement of gastric acid secretion, SSRIs can increase bleeding risk, especially in patients receiving antiplatelet or anticoagulant medications.^{101,102} Second, SSRIs can cause QTc prolongation, which increases the risk of potentially lethal ventricular arrhythmias.¹⁰³ In a recent meta-analysis, SSRIs as a class prolonged the QTc interval by an average of 6.10 milliseconds, although these changes varied by the specific agent: citalopram and escitalopram caused the greatest QTc prolongation, and other agents led to minimal or no prolongation.¹⁰³ Of note, though the SSRIs do lead to QTc prolongation, they do so to a significantly lesser degree than TCAs.¹⁰³ Finally, certain SSRIs may lead to changes in cardiovascular and antidepressant medication levels through interactions with other cardiovascular agents (e.g., warfarin, antiarrhythmics, angiotensin receptor blockers), which could lead to side effects.¹⁰⁴ Of the SSRIs, sertraline, citalopram, and escitalopram

have a low risk of interactions, while fluvoxamine, fluoxetine, and paroxetine have a higher risk.¹⁰⁴

Other antidepressants have been evaluated for safety and efficacy in patients with heart disease. One randomized placebo-controlled trial conducted in post-MI patients found mirtazapine to be an effective and safe treatment to reduce depressive symptoms.¹⁰⁵ Although never studied for the management of depression in patients with cardiovascular disease, bupropion has been found to have minimal cardiovascular side effects in patients with cardiac disease (including HF).^{100,106,107} Venlafaxine and duloxetine have less clear evidence regarding their safety. One large epidemiologic study in older adults found that venlafaxine led to no increase in risk of cardiovascular events compared to sertraline and was linked to a lower risk of HF.¹⁰⁸ However, venlafaxine causes mild increases in blood pressure and heart rate, and several cases of acute HF have been linked to venlafaxine overdose.^{109,110} In addition, case reports suggest that in patients with HF, venlafaxine and duloxetine may worsen symptoms of HF.¹¹¹ Given this mixed evidence, venlafaxine and duloxetine should be used with caution in patients with HF. Finally, due to their propensity to cause cardiovascular side effects, such as tachycardia, orthostasis, and conduction abnormalities, TCAs are generally avoided in patients with HF or other cardiovascular disease when alternatives are available.

Integrated care models in the management of depression and anxiety disorders in patients with heart disease

A promising method for delivering psychiatric care for patients with depression or anxiety disorders is collaborative care. This model involves the use of a non-physician care manager—supervised by a psychiatrist—to screen for psychiatric disorders and coordinate the treatment of these disorders within the patient's current medical treatment. In primary care settings, where these programs have most commonly been studied and implemented, collaborative care programs have led to improvements in depression, anxiety, and health-related QoL.¹¹² Collaborative care programs are similarly effective in depressed patients with cardiovascular disease,^{113–117} and one program that focused on treating both depression and cardiovascular risk factors led to improvements in both mental and physical health outcomes, including blood pressure, hemoglobin A1c, and low density lipoprotein (LDL) cholesterol.¹¹⁵ The Patient-Centered Disease Management study—the only prior study of collaborative care exclusively in patients with HF—examined the efficacy of a multi-component collaborative care intervention focused on the management of HF symptoms and depressive symptoms (if present).¹¹⁸ While this study did not find the intervention to be superior to enhanced usual care on improving HF-related QoL (the study's primary outcome), patients with depression experienced greater improvements in depressive symptoms.¹¹⁸

Treatment selection

Choosing a treatment for an HF patient with depression or an anxiety disorder depends on multiple factors including patient preference, treatment and provider availability, and other patient and system-related factors. In cases of relatively straightforward major depression or

anxiety disorders, collaborative care programs may be ideal, given that these programs often allow for the use of either pharmacologic or psychotherapeutic interventions within the framework of existing medical treatment. Of course, collaborative care programs are not available in many settings, where reimbursement for these programs remains an important issue.

When collaborative care programs are unavailable, an initial treatment of an SSRI or CBT is sensible. CBT may be preferable, given stronger evidence for efficacy in this population and the lack of potential side effects. However, many patients are not able or willing to attend regular psychotherapy sessions, and here too the limited availability of an experienced CBT clinician may be an issue. Given these issues, medication treatment, especially an SSRI, is often a straightforward option. In terms of selecting a specific SSRI, sertraline is often preferred given its established safety in patients with heart disease (including those with HF) and relatively few drug-drug interactions. Citalopram and escitalopram may be additional options due to their prior use in studies of patients with heart disease and few drug-drug interactions, though an alternative SSRI may be preferable in those with known QTc prolongation or risk factors for such prolongation. Though it is reasonable to initiate treatment at low doses to ensure tolerability, it is important to ensure that effective doses are reached and that ongoing adjustment of treatment occurs until remission is reached.

Limitations

This article has several notable limitations. First, the literature on the topic of depression and anxiety in HF is highly variable, with studies using different criteria for diagnosing depression, anxiety disorders, and HF. As a result, interpreting the results of these studies (e.g., the directionality of the relationships between depression/anxiety and HF) is challenging, and comparing findings between studies may be difficult or impossible. Second, studies examining the associations between psychiatric symptoms and cardiovascular health may have included different covariates in their analyses, which adds to the heterogeneity of the literature. Third, many of the treatment studies (especially the medication studies) were relatively small, which limited their power to detect significant between-group differences and may have contributed to their negative findings. Finally, given the breadth of topics covered and the goal of providing a broad overview of depression and anxiety disorders in HF, we chose to perform a narrative review, rather than a systematic review. As a result, it is possible that not all articles published on this subject were included in this manuscript.

Conclusions

In patients with HF, major depression and anxiety disorders—especially GAD—are highly prevalent, and these psychiatric illnesses have been linked to poor medical and functional outcomes. Though diagnosing a psychiatric illness can be challenging given the significant overlap between psychiatric and HF-related symptoms, doing so can help to identify those who are at higher risk for poor cardiac outcomes and allow for the treatment of these disorders. The use of SSRIs or CBT appear safe but have had somewhat limited effects on psychiatric and cardiac outcomes. It is likely that an aggressive, multimodal treatment

approach—such as collaborative care models or stepped care from a mental health professional—will be needed to improve psychiatric and cardiac health in this high-risk population.

Acknowledgments

Source of Funding:

Time for article preparation was funded by the National Heart Lung and Blood Institute through grant K23HL123607 (to Dr. Celano) and R01HL113272 (to Dr. Huffman). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

References

1. Rogers C, Bush N. Heart Failure: Pathophysiology, Diagnosis, Medical Treatment Guidelines, and Nursing Management. *Nurs Clin North Am*. 2015; 50:787–99. [PubMed: 26596665]
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014; 129:e28–e292. [PubMed: 24352519]
3. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. *JAMA*. 2011; 306:1669–78. [PubMed: 22009099]
4. Coelho R, Ramos S, Prata J, Bettencourt P, Ferreira A, Cerqueira-Gomes M. Heart failure and health related quality of life. *Clin Pract Epidemiol Ment Health*. 2005; 1:19. [PubMed: 16202163]
5. Sullivan M, Levy WC, Russo JE, Spertus JA. Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. *J Card Fail*. 2004; 10:390–6. [PubMed: 15470649]
6. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006; 48:1527–37. [PubMed: 17045884]
7. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003; 289:3095–105. [PubMed: 12813115]
8. [Accessed 11/22/2016, 2016] Major Depression Among Adults 2014 at <http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml>
9. Muller-Tasch T, Frankenstein L, Holzapfel N, et al. Panic disorder in patients with chronic heart failure. *J Psychosom Res*. 2008; 64:299–303. [PubMed: 18291245]
10. Easton K, Coventry P, Lovell K, Carter LA, Deaton C. Prevalence and measurement of anxiety in samples of patients with heart failure: meta-analysis. *J Cardiovasc Nurs*. 2016; 31:367–79. [PubMed: 25930162]
11. Daskalopoulou M, George J, Walters K, et al. Depression as a Risk Factor for the Initial Presentation of Twelve Cardiac, Cerebrovascular, and Peripheral Arterial Diseases: Data Linkage Study of 1.9 Million Women and Men. *PLoS One*. 2016; 11:e0153838. [PubMed: 27105076]
12. White JR, Chang CC, So-Armah KA, et al. Depression and human immunodeficiency virus infection are risk factors for incident heart failure among veterans: Veterans Aging Cohort Study. *Circulation*. 2015; 132:1630–8. [PubMed: 26358261]
13. Frasure-Smith N, Lesperance F, Habra M, et al. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. *Circulation*. 2009; 120:134–40. [PubMed: 19564557]
14. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. *Am Heart J*. 2006; 152:940e1–8. [PubMed: 17070164]
15. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation*. 2004; 110:3452–6. [PubMed: 15557372]

16. Konstam V, Salem D, Pouleur H, et al. Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure. SOLVD Investigations. Studies of Left Ventricular Dysfunction Investigators. *Am J Cardiol.* 1996; 78:890–5. [PubMed: 8888661]
17. Pelle AJ, Pedersen SS, Schiffer AA, Szabo B, Widdershoven JW, Denollet J. Psychological distress and mortality in systolic heart failure. *Circ Heart Fail.* 2010; 3:261–7. [PubMed: 20071656]
18. Roy SS, Foraker RE, Girton RA, Mansfield AJ. Posttraumatic stress disorder and incident heart failure among a community-based sample of US veterans. *Am J Public Health.* 2015; 105:757–63. [PubMed: 25713943]
19. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry.* 2008; 65:62–71. [PubMed: 18180430]
20. Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10-year follow-up. *Br J Psychiatry.* 2012; 200:324–9. [PubMed: 22403086]
21. Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis. *Am Heart J.* 2015; 170:1105–15. [PubMed: 26678632]
22. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med.* 2010; 72:563–9. [PubMed: 20410247]
23. Ahmadi N, Hajsadeghi F, Mirshkarlo HB, Budoff M, Yehuda R, Ebrahimi R. Post-traumatic stress disorder, coronary atherosclerosis, and mortality. *Am J Cardiol.* 2011; 108:29–33. [PubMed: 21530936]
24. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. *Psychosom Med.* 2008; 70:668–76. [PubMed: 18596248]
25. Edmondson D, Cohen BE. Posttraumatic stress disorder and cardiovascular disease. *Prog Cardiovasc Dis.* 2013; 55:548–56. [PubMed: 23621964]
26. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. *Eur Heart J.* 2008; 29:2981–8. [PubMed: 18948354]
27. Smoller JW, Pollack MH, Wassertheil-Smoller S, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women’s Health Initiative Observational Study. *Arch Gen Psychiatry.* 2007; 64:1153–60. [PubMed: 17909127]
28. Alhurani AS, Dekker RL, Abed MA, et al. The association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. *Psychosomatics.* 2015; 56:371–80. [PubMed: 25556571]
29. Suzuki T, Shiga T, Kuwahara K, et al. Impact of clustered depression and anxiety on mortality and rehospitalization in patients with heart failure. *J Cardiol.* 2014; 64:456–62. [PubMed: 24755202]
30. Howland RH, Wilson MG, Kornstein SG, et al. Factors predicting reduced antidepressant response: experience with the SNRI duloxetine in patients with major depression. *Ann Clin Psychiatry.* 2008; 20:209–18. [PubMed: 19034753]
31. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. *Arch Gen Psychiatry.* 2008; 65:870–80. [PubMed: 18678792]
32. Celano CM, Mastromauro CA, Lenihan EC, Januzzi JL, Rollman BL, Huffman JC. Association of baseline anxiety with depression persistence at 6 months in patients with acute cardiac illness. *Psychosom Med.* 2012; 74:93–9. [PubMed: 22210240]
33. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med.* 2001; 161:996–1002. [PubMed: 11295963]
34. Riegel B, Moser DK, Anker SD, et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation.* 2009; 120:1141–63. [PubMed: 19720935]

35. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med.* 2000; 160:1818–23. [PubMed: 10871976]
36. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA.* 2008; 300:2379–88. [PubMed: 19033588]
37. May HT, Sheng X, Catinella AP, Horne BD, Carlquist JF, Joy E. Antilipidemic adherence post-coronary artery disease diagnosis among those with and without an ICD-9 diagnosis of depression. *J Psychosom Res.* 2010; 69:169–74. [PubMed: 20624515]
38. Casey E, Hughes JW, Waechter D, Josephson R, Rosneck J. Depression predicts failure to complete phase-II cardiac rehabilitation. *J Behav Med.* 2008; 31:421–31. [PubMed: 18719990]
39. Huffman JC, Smith FA, Fricchione GL, Januzzi JL, Nadelman S, Pirl WF. Depression and failure of cholesterol lowering after acute myocardial infarction. *Prim Care Companion J Clin Psychiatry.* 2010; 12 PCC 08m00766.
40. McGrady A, McGinnis R, Badenhop D, Bentle M, Rajput M. Effects of depression and anxiety on adherence to cardiac rehabilitation. *J Cardiopulm Rehabil Prev.* 2009; 29:358–64. [PubMed: 19940639]
41. Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry.* 2008; 30:127–37. [PubMed: 18291294]
42. Chwastiak LA, Rosenheck RA, Kazis LE. Association of psychiatric illness and obesity, physical inactivity, and smoking among a national sample of veterans. *Psychosomatics.* 2011; 52:230–6. [PubMed: 21565594]
43. Kuhl EA, Fauerbach JA, Bush DE, Ziegelstein RC. Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. *Am J Cardiol.* 2009; 103:1629–34. [PubMed: 19539067]
44. Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. *Eur Heart J.* 1998; 19:761–5. [PubMed: 9717010]
45. Kania G, Blyszczuk P, Eriksson U. Mechanisms of cardiac fibrosis in inflammatory heart disease. *Trends Cardiovasc Med.* 2009; 19:247–52. [PubMed: 20447565]
46. Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a Driver of Adverse Left Ventricular Remodeling After Acute Myocardial Infarction. *J Am Coll Cardiol.* 2016; 67:2050–60. [PubMed: 27126533]
47. Kell R, Haunstetter A, Dengler TJ, Zugck C, Kubler W, Haass M. Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. *Eur Heart J.* 2002; 23:70–8. [PubMed: 11741364]
48. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med.* 2009; 71:171–86. [PubMed: 19188531]
49. Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. *J Affect Disord.* 2014; 169:15–20. [PubMed: 25128861]
50. Kop WJ, Kuhl EA, Barasch E, Jenny NS, Gottlieb SS, Gottdiener JS. Association between depressive symptoms and fibrosis markers: the Cardiovascular Health Study. *Brain Behav Immun.* 2010; 24:229–35. [PubMed: 19800964]
51. Xiong GL, Prybol K, Boyle SH, et al. Inflammation Markers and Major Depressive Disorder in Patients With Chronic Heart Failure: Results From the Sertraline Against Depression and Heart Disease in Chronic Heart Failure Study. *Psychosom Med.* 2015; 77:808–15. [PubMed: 26186432]
52. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. *Atherosclerosis.* 2006; 185:320–6. [PubMed: 16005881]
53. Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *Int J Rheum Dis.* 2012; 15:183–7. [PubMed: 22462422]
54. Kheirabadi GR, Toghiani F, Kousha M, et al. Is there any association of anxiety-depressive symptoms with vascular endothelial function or systemic inflammation? *J Res Med Sci.* 2013; 18:979–83. [PubMed: 24523785]

55. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. *Eur Heart J*. 2008; 29:2212–7. [PubMed: 18603621]
56. Passos IC, Vasconcelos-Moreno MP, Costa LG, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry*. 2015; 2:1002–12. [PubMed: 26544749]
57. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. *Heart*. 2004; 90:1248–55. [PubMed: 15486114]
58. Francis JL, Weinstein AA, Krantz DS, et al. Association between symptoms of depression and anxiety with heart rate variability in patients with implantable cardioverter defibrillators. *Psychosom Med*. 2009; 71:821–7. [PubMed: 19661191]
59. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am J Cardiol*. 1995; 75:882–5. [PubMed: 7732994]
60. Stein PK, Carney RM, Freedland KE, et al. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *J Psychosom Res*. 2000; 48:493–500. [PubMed: 10880671]
61. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. *Cleve Clin J Med*. 2009; 76(Suppl 2):S13–7. [PubMed: 19376975]
62. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. *Eur Heart J*. 2005; 26:65–9. [PubMed: 15615801]
63. Fujisue K, Sugiyama S, Matsuzawa Y, et al. Prognostic Significance of Peripheral Microvascular Endothelial Dysfunction in Heart Failure With Reduced Left Ventricular Ejection Fraction. *Circ J*. 2015; 79:2623–31. [PubMed: 26489455]
64. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. *Circulation*. 2005; 111:310–4. [PubMed: 15655134]
65. Mommersteeg PM, Schoemaker RG, Eisel UL, Garrelds IM, Schalkwijk CG, Kop WJ. Nitric oxide dysregulation in patients with heart failure: the association of depressive symptoms with L-arginine, asymmetric dimethylarginine, symmetric dimethylarginine, and isoprostane. *Psychosom Med*. 2015; 77:292–302. [PubMed: 25790241]
66. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *J Am Coll Cardiol*. 2005; 46:656–9. [PubMed: 16098431]
67. Narita K, Murata T, Hamada T, et al. Association between trait anxiety and endothelial function observed in elderly males but not in young males. *Int Psychogeriatr*. 2007; 19:947–54. [PubMed: 17147843]
68. Narita K, Murata T, Hamada T, et al. Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. *J Psychiatr Res*. 2007; 41:418–27. [PubMed: 16494899]
69. Serrani Azcurra D. Early markers of endothelial dysfunction posttraumatic stress disorder. Role in atherogenesis. *Rev Psiquiatr Salud Ment*. 2010; 3:128–36. [PubMed: 23446035]
70. von Kanel R, Hepp U, Traber R, et al. Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. *Psychiatry Res*. 2008; 158:363–73. [PubMed: 18252265]
71. Huffman JC, Smith FA, Blais MA, Beiser ME, Januzzi JL, Fricchione GL. Recognition and treatment of depression and anxiety in patients with acute myocardial infarction. *Am J Cardiol*. 2006; 98:319–24. [PubMed: 16860016]
72. Ziegelstein RC, Kim SY, Kao D, et al. Can doctors and nurses recognize depression in patients hospitalized with an acute myocardial infarction in the absence of formal screening? *Psychosom Med*. 2005; 67:393–7. [PubMed: 15911901]
73. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders : DSM-5*. Washington, D.C: American Psychiatric Association; 2013
74. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003; 41:1284–92. [PubMed: 14583691]

75. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001; 16:606–13. [PubMed: 11556941]
76. Elderon L, Smolderen KG, Na B, Whooley MA. Accuracy and prognostic value of American Heart Association: recommended depression screening in patients with coronary heart disease: data from the Heart and Soul Study. *Circ Cardiovasc Qual Outcomes.* 2011; 4:533–40. [PubMed: 21862720]
77. Hammash MH, Hall LA, Lennie TA, et al. Psychometrics of the PHQ-9 as a measure of depressive symptoms in patients with heart failure. *Eur J Cardiovasc Nurs.* 2013; 12:446–53. [PubMed: 23263270]
78. Celano CM, Suarez L, Mastromauro C, Januzzi JL, Huffman JC. Feasibility and utility of screening for depression and anxiety disorders in patients with cardiovascular disease. *Circ Cardiovasc Qual Outcomes.* 2013; 6:498–504. [PubMed: 23759474]
79. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006; 166:1092–7. [PubMed: 16717171]
80. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med.* 2007; 146:317–25. [PubMed: 17339617]
81. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry.* 2016; 39:24–31. [PubMed: 26719105]
82. Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ.* 2008; 178:997–1003. [PubMed: 18390942]
83. Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002; 136:765–76. [PubMed: 12020146]
84. Cully JA, Stanley MA, Deswal A, Hanania NA, Phillips LL, Kunik ME. Cognitive-behavioral therapy for chronic cardiopulmonary conditions: preliminary outcomes from an open trial. *Prim Care Companion J Clin Psychiatry.* 2010:12.
85. Dekker RL, Moser DK, Peden AR, Lennie TA. Cognitive therapy improves three-month outcomes in hospitalized patients with heart failure. *J Card Fail.* 2012; 18:10–20. [PubMed: 22196836]
86. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. *J Psychosom Res.* 2010; 69:119–31. [PubMed: 20624510]
87. Tully PJ, Selkow T, Bengel J, Rafanelli C. A dynamic view of comorbid depression and generalized anxiety disorder symptom change in chronic heart failure: the discrete effects of cognitive behavioral therapy, exercise, and psychotropic medication. *Disabil Rehabil.* 2015; 37:585–92. [PubMed: 24981015]
88. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH. Cognitive Behavior Therapy for Depression and Self-Care in Heart Failure Patients: A Randomized Clinical Trial. *JAMA Intern Med.* 2015:1–10.
89. [Accessed August 3, 2016] Practice guideline for the treatment of patients with acute stress disorder and post-traumatic stress disorder. 2004 at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf
90. [Accessed April 29, 2016] Practice guideline for the treatment of patients with panic disorder 2009 at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf
91. [Accessed March 14, 2011, 2011] Practice guideline for the treatment of patients with major depressive disorder 2010 at http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
92. Fraguas R, da Silva Telles RM, Alves TC, et al. A double-blind, placebo-controlled treatment trial of citalopram for major depressive disorder in older patients with heart failure: the relevance of the placebo effect and psychological symptoms. *Contemp Clin Trials.* 2009; 30:205–11. [PubMed: 19470312]
93. 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; 153:868–73. [PubMed: 17452166]

94. Angermann CE, Gelbrich G, Stork S, et al. Rationale and design of a randomised, controlled, multicenter trial investigating the effects of selective serotonin re-uptake inhibition on morbidity, mortality and mood in depressed heart failure patients (MOOD-HF). *Eur J Heart Fail.* 2007; 9:1212–22. [PubMed: 18029292]
95. Angermann CE, Gelbrich G, Stork S, et al. Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial. *JAMA.* 2016; 315:2683–93. [PubMed: 27367876]
96. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol.* 2010; 56:692–9. [PubMed: 20723799]
97. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56–62. [PubMed: 14399272]
98. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961; 4:561–71. [PubMed: 13688369]
99. Eaton WW, Anthony JC, Gallo J, et al. Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. *Arch Gen Psychiatry.* 1997; 54:993–9. [PubMed: 9366655]
100. Alvarez W Jr, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. *Pharmacotherapy.* 2003; 23:754–71. [PubMed: 12820818]
101. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am J Med.* 2006; 119:113–6. [PubMed: 16443409]
102. Serebruany VL, Glassman AH, Malinin AI, et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation.* 2003; 108:939–44. [PubMed: 12912814]
103. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry.* 2014; 75:e441–9. [PubMed: 24922496]
104. Guck TP, Elsasser GN, Kavan MG, Barone EJ. Depression and congestive heart failure. *Congest Heart Fail.* 2003; 9:163–9. [PubMed: 12826775]
105. Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. *Psychosom Med.* 2007; 69:606–13. [PubMed: 17846258]
106. Roose SP, Glassman AH, Giardina EG, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987; 7:247–51. [PubMed: 3114333]
107. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry.* 1991; 148:512–6. [PubMed: 1900980]
108. Ho JM, Gomes T, Straus SE, Austin PC, Mamdani M, Juurlink DN. Adverse cardiac events in older patients receiving venlafaxine: a population-based study. *J Clin Psychiatry.* 2014; 75:e552–8. [PubMed: 25004195]
109. Batista M, Dugernier T, Simon M, et al. The spectrum of acute heart failure after venlafaxine overdose. *Clin Toxicol (Phila).* 2013; 51:92–5. [PubMed: 23301719]
110. Fangio P, De Jonghe B, Appere-De-Vecchi C, et al. Acute heart failure associated with venlafaxine poisoning. *Am J Emerg Med.* 2007; 25:210–1. [PubMed: 17276818]
111. Colucci VJ, Berry BD. Heart failure worsening and exacerbation after venlafaxine and duloxetine therapy. *Ann Pharmacother.* 2008; 42:882–7. [PubMed: 18445706]
112. Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. *Cochrane Database Syst Rev.* 2012; 10:CD006525. [PubMed: 23076925]
113. Davidson KW, Bigger JT, Burg MM, et al. Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. *JAMA Intern Med.* 2013; 173:997–1004. [PubMed: 23471421]

114. Rollman BL, Belnap BH, LeMenager MS, et al. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA*. 2009; 302:2095–103. [PubMed: 19918088]
115. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2010; 363:2611–20. [PubMed: 21190455]
116. Huffman JC, Mastromauro CA, Sowden GL, Fricchione GL, Healy BC, Januzzi JL. Impact of a depression care management program for hospitalized cardiac patients. *Circ Cardiovasc Qual Outcomes*. 2011; 4:198–205. [PubMed: 21386067]
117. Huffman JC, Mastromauro CA, Beach SR, et al. Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized clinical trial. *JAMA Intern Med*. 2014; 174:927–35. [PubMed: 24733277]
118. Bekelman DB, Plomondon ME, Carey EP, et al. Primary Results of the Patient-Centered Disease Management (PCDM) for Heart Failure Study: A Randomized Clinical Trial. *JAMA Intern Med*. 2015; 175:725–32. [PubMed: 25822284]

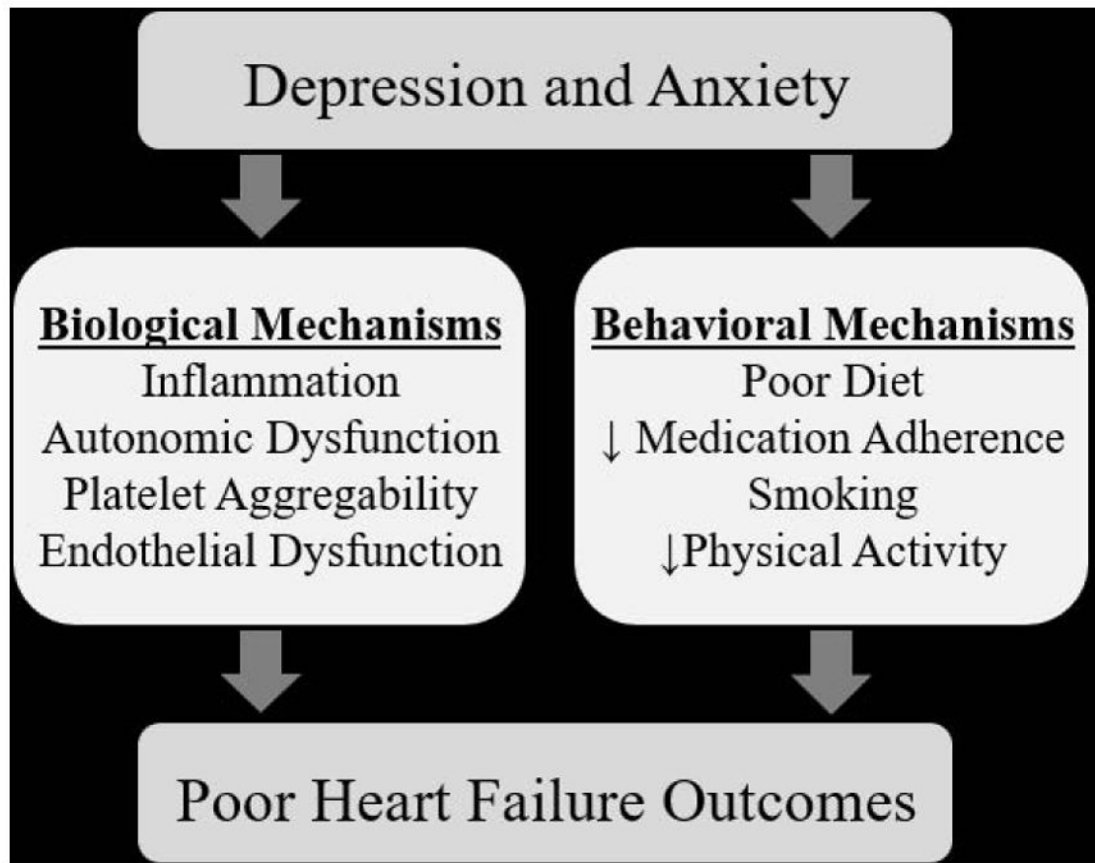


Figure 1. Potential Mechanisms Linking Depression, Anxiety, and Heart Failure Outcomes