HHS Public Access

Author manuscript

Curr Psychiatry Rep. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Curr Psychiatry Rep. 2016 November ; 18(11): 101. doi:10.1007/s11920-016-0739-5.

Anxiety disorders and cardiovascular disease

Christopher M. Celano, M.D.[1,2], **Daniel J. Daunis, M.D.**[1,2], **Hermioni N. Lokko, M.D.**[2,3], **Kirsti A. Campbell, B.S.**[1,2], and **Jeff C. Huffman, M.D.**[1,2]

[1]Harvard Medical School, Boston, MA

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

[3]Department of Psychiatry, Brigham and Women's Hospital, Boston, MA

Abstract

Anxiety and its associated disorders are common in patients with cardiovascular disease and may significantly influence cardiac health. Anxiety disorders are associated with the onset and progression of cardiac disease, and in many instances have been linked to adverse cardiovascular outcomes, including mortality. Both physiologic (autonomic dysfunction, inflammation, endothelial dysfunction, changes in platelet aggregation) and health behavior mechanisms may help to explain the relationships between anxiety disorders and cardiovascular disease. Given the associations between anxiety disorders and poor cardiac health, the timely and accurate identification and treatment of these conditions is of the utmost importance. Fortunately, pharmacologic and psychotherapeutic interventions for the management of anxiety disorders are generally safe and effective. Further study is needed to determine whether interventions to treat anxiety disorders ultimately impact both psychiatric and cardiovascular health.

Keywords

Anxiety; generalized anxiety disorder; panic disorder; post-traumatic stress disorder; cardiovascular disease

Introduction

Negative psychological states are commonly experienced among patients with cardiovascular disease. To date, depression has received the most attention in this population, given its high prevalence and association with poor cardiac health, especially in patients who have experienced a major cardiac event, such as an acute coronary syndrome (ACS). However, anxiety has recently emerged as another important psychological construct that is highly prevalent, frequently co-occurs with depression and impedes response to depression treatment, and may ultimately influence the course of cardiovascular disease independent of depression. In this article, we aim to review the recent literature on anxiety—and its associated disorders—in cardiovascular disease.

Corresponding Author and Address for Correspondence: Christopher M. Celano, M.D., Massachusetts General Hospital / Blake 11, 55 Fruit Street Boston, MA 02114, Phone: 617-726-6485 Fax: 617-724-9150, ccelano@partners.org.

Anxiety in patients with cardiovascular disease

Epidemiology

Anxiety is common in patients with cardiovascular disease, such as coronary artery disease (CAD). Following an ACS, 20-30% of patients experience elevated levels of anxiety [1, 2]. While post-ACS anxiety may be transient for some patients, in half of cases anxiety persists for up to 1 year post-event [1], suggesting that for many patients with heart disease, anxiety is a chronic condition. Research has revealed similar prevalence rates in patients with CAD awaiting coronary artery bypass graft (CABG) surgery. In this population, 25% of patients experience elevated levels of anxiety pre-procedure, with many having a reduction in symptoms in the months following surgery [3].

Anxiety is common in patients with other forms of heart disease as well. In a recent meta-analysis of 38 studies, Easton and colleagues estimated that 32% of patients with heart failure (HF) experience elevated levels of anxiety, and 13% meet criteria for an anxiety disorder [4]. Anxiety also affects approximately 20% of patients with more advanced HF who require implantation of a left ventricular assist device to support their cardiac function [5, 6]. Finally, among patients who have undergone implantation of an implantable cardioverter defibrillator to prevent the development of lethal arrhythmias, elevated anxiety is present in approximately 20-40% [7].

Associations between anxiety and cardiovascular health

The relationship between anxiety and cardiovascular health is complex. Anxiety may be a normal response to a stressful situation, such as an acute cardiac event, and if anxiety prompts an individual to engage more in treatment (e.g., exercise regularly, adhere to medications), it may be beneficial. However, when present in excess or for extended periods of time, anxiety is considered to be detrimental for psychiatric and overall health.

Anxiety has been associated with the incidence, and in some cases progression, of cardiovascular disease. In patients without existing cardiac disease, anxiety has been linked to the subsequent development of CAD. In a 2010 meta-analysis including 20 studies and nearly 250,000 patients, Roest and colleagues found that anxiety, controlling for other medical variables when possible, led to a 26% increased risk of incident CAD [8•]. While the overall findings were significant, it should be noted that only 10 of the 20 studies found a significant relationship between anxiety and incident CAD in multivariate analyses, suggesting that there are heterogeneous findings in the literature regarding this relationship.

In patients with established CAD, the literature regarding the relationship between anxiety and cardiac outcomes is similarly mixed. In a recent meta-analysis of 44 studies, anxiety was significantly associated with poor cardiac outcomes, including recurrent cardiac events and mortality, in unadjusted analyses [9•]. However, when adjusting for medical and psychological covariates, nearly all of these relationships became non-significant, suggesting that while anxiety may be a good marker of poor cardiac health, other medical and psychological factors may actually explain much of the relationship between anxiety and outcomes. In sensitivity analyses, there were no significant relationships between anxiety and cardiac health when anxiety was measured in the 2 months following an ACS; however,

when anxiety was measured in patients with stable CAD, anxiety was associated with poor outcomes in nearly all analyses [9•]. Ultimately, it may be that anxiety following an ACS may be more likely to be transient than anxiety measured during a period of clinical stability. These findings argue that measuring anxiety in a stable period may be much more useful for predicting future cardiac health.

The relationship between anxiety and cardiac outcomes is relatively weak in patients with HF. To date, four prospective trials have examined the relationship between anxiety and cardiac health in HF patients [10-13]. In a prospective study of 153 adult outpatients with HF, anxiety was marginally associated with mortality in unadjusted analyses; however, when controlling for relevant covariates, this relationship became non-significant [10]. A second study of 643 patients with chronic HF followed patients for an average of 3 years to examine the prospective relationship between psychological distress (a combination of depression and anxiety) and mortality [13]. In unadjusted analyses, depression/anxiety was marginally associated with mortality; however, this relationship again became non-significant when controlling for demographic and medical factors [13]. In the other two studies, there were no significant relationships between anxiety and cardiac health in adjusted or unadjusted analyses [11, 12]. Similar to the trials in patients with CAD, it appears that while anxiety may be a good marker for adverse outcomes in patients with cardiac disease, the actual relationship between anxiety and outcomes may in some cases be explained by other factors.

Finally, anxiety and anxiety disorders are also common in patients who present in cardiac settings but who do not have heart disease, such as those who have so-called non-cardiac chest pain. Rates of GAD and PD are substantially higher in this population than in those in the general population [14, 15], and this is an important public health issue because such patients have impairment of function and quality of life that is greater than those with confirmed heart disease [16]. Furthermore, the repeated utilization of healthcare services by patients with non-cardiac chest pain leads to a substantial financial burden, with the annual cost of such patients' evaluations measured in the billions [17].

Anxiety disorders in patients with cardiovascular disease

While much of the literature to date has focused on the associations between anxiety as a symptom and cardiovascular health, it may be more important to examine the links between anxiety *disorders* and heart health. By definition, anxiety in the setting of anxiety disorders is chronic and persistent, and therefore it may have greater physiologic consequences than transient anxiety. Furthermore, effective treatments are available for anxiety disorders.

Generalized anxiety disorder (GAD)

Generalized anxiety disorder (GAD) is highly prevalent in patients with cardiac disease. A recent meta-analysis found an 11% point prevalence and 26% lifetime prevalence of GAD in CAD patients [18], and a similar meta-analysis in HF patients found GAD prevalence to be 14% [4]. These rates are significantly higher than the 3-7% lifetime prevalence of GAD in the general U.S. population [19, 20].

GAD is independently associated with poor outcomes in patients with established cardiac disease, especially CAD. Though one study found that GAD was protective in the post-ACS period [21], most studies suggest that GAD is associated with poor cardiac health in all stages of CAD [22-24]. Following myocardial infarction (MI), GAD has been linked to a nearly two-fold increased risk of mortality over the subsequent ten years [23], and in patients with stable CAD, GAD is associated with a two-fold increased risk of major adverse cardiac events over the next two years [22]. In a prospective study of 158 patients undergoing CABG surgery, GAD was associated with incident major adverse cardiac events over the subsequent 5 years [24]. The associations between GAD and outcomes in HF have not yet been studied.

Panic disorder (PD)

PD also is common in patients with heart disease. Among patients with CAD, studies have varied, with one review providing PD prevalence estimates of 10-50% [25], though another analysis and a recent cross-sectional study estimated PD prevalence of 5-8% in patients with established CAD [26, 27]. These latter studies are likely closer to the true estimate, as a study of post-ACS patients found PD to be significantly less prevalent than GAD or depression [28].

While less common than GAD, PD significantly increases the risk of the development and progression of cardiac disease. In a cohort study of nearly 80,000 individuals without pre-established CAD (and half with PD), PD was associated with a nearly two-fold increased risk of incident CAD [29]. In another cohort study of 57,615 patients with PD and nearly 350,000 age- and sex-matched controls, patients with PD had a significantly higher risk of the development of CAD but a lower risk of CAD-related mortality [30]. Finally, a systematic review and meta-regression analysis of over 1 million patients found that PD was significantly associated with incident CAD, major adverse cardiac events, and MI [31••].

Post-traumatic stress disorder (PTSD)

PTSD symptoms and formal PTSD diagnoses also are common in patients with cardiac disease. In a prospective cohort study of 105 patients attending cardiac rehabilitation, 24% reported symptoms of PTSD [32], and a recent cohort study of veterans revealed a PTSD prevalence of 6% [33].

PTSD is associated with the development of both CAD and HF. In a study of 637 veterans without known CAD, a diagnosis of PTSD was associated with the presence and extent of CAD, as well as higher rates of mortality over the subsequent three years [34]. Similarly, in a study involving 281 twin pairs, a diagnosis of PTSD led to a two-fold increase in risk for incident CAD over the next 13 years [35]. A recent meta-analysis confirmed the relationship between PTSD and incident CAD [36••]. Finally, in a longitudinal study of 8,000 veterans in outpatient settings, veterans with PTSD had a 47% greater risk of developing HF over a seven-year follow-up period compared to veterans without PTSD [37].

While PTSD is clearly associated with the development of cardiac disease, the relationship between PTSD and cardiac outcomes is less clear. In patients without pre-established CAD, PTSD has been linked to increased rates of mortality [34, 38]. Among patients with

implantable cardioverter-defibrillators, elevated PTSD symptoms also were associated with a greater than three-fold increase in mortality risk, even after controlling for relevant covariates [39]. However, among patients with established CAD undergoing angiography or revascularization, two studies of veterans have found that PTSD is associated with a reduced rate of mortality at one year post procedure [40, 33]. The cause of this discrepancy is unclear, and further research would help to clarify these relationships and determine whether these findings can be generalized outside of the veteran population.

Mechanisms mediating the relationships between anxiety disorders and cardiac health

There are several mechanisms that may explain the underlying association between anxiety disorders and cardiac disease. Though no definitive model exists, these hypotheses include both behavioral and physiologic factors (see Figure 1).

Health behaviors

Health behaviors may explain part of the link between anxiety disorders and cardiac health. Adherence to a number of healthy behaviors, such as maintaining a healthy diet, healthy level of physical activity, and medication adherence, is clearly linked to improved outcomes in patients with cardiac disease [41-43]. Further, for patients with stable HF or following MI, attendance at cardiac rehabilitation programs is an important step to improving health-related-quality of life (HRQoL) and reducing the risk of future hospitalization [44]. In contrast, unhealthy behaviors can lead to the development or worsening of risk factors including diabetes, hypertension, elevated cholesterol, obesity, and smoking, all which increase mortality in patients with cardiac disease [45].

Though the evidence is mixed, individuals who experience anxiety appear less likely to engage in health behaviors. Anxious individuals tend to have increased dietary cholesterol intake, elevated total energy intake, sedentary lifestyle, and decreased physical activity [46], consistent with the finding that patients with PD and GAD have increased odds of dyslipidemia, obesity, diabetes, and substance use [47, 48]. Patients with PTSD have poor diet quality (with most energy obtained from fatty acids), decreased physical activity, increased obesity, and increased rates of smoking [49]. Among cardiac patients, anxiety is associated with a lower likelihood of adhering to a number of risk-reducing recommendations after MI, including smoking cessation, social support utilization, and stress reduction [50]. Patients with anxiety disorders also are less likely to both attend and complete cardiac rehabilitation programs [51, 52]. These behavioral factors in patients with anxiety disorders could increase the likelihood of cardiovascular morbidity and mortality.

Physiologic mechanisms

Inflammation—Inflammatory pathways play a key role in both the development and progression of cardiac disease [53]. Inflammatory pathways involving interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) have all been implicated in the development of atherosclerosis and heart disease including CAD, HF, and unstable angina [54, 55]. In patients with unstable CAD, inflammatory

markers such as CRP have been associated with increased long-term mortality [56]. Similarly, inflammatory pathways have been associated with worsening function, increased hospitalization rates, and poor survival in HF patients [57, 58].

Both anxiety and anxiety disorders are associated with increased inflammatory markers. In one large study of healthy adults, individuals with elevated anxiety were found to have higher levels of CRP, TNF-α, IL-6, homocysteine, and fibrinogen [59]. Further, anxiety disorders, including GAD, PTSD, and PD, have all been linked to increased inflammation, most notably CRP [60, 61]. In addition, PTSD has been linked to increased levels of circulating TNF-α, IL-1, IL-6, interleukin-1β, and interferon-γ [62, 63]. Thus the association between anxiety disorders and inflammation could be a process by which anxiety disorders are associated with the development of cardiac disease.

Endothelial Dysfunction—The vascular endothelium plays a key role in the health and maintenance of the circulatory system via regulation of platelet activity, thrombosis, vascular tone, and leukocyte adhesion [64]. Its dysfunction leads to the development of atherosclerosis [65] and has been shown to increase the incidence of hospitalization, cardiac transplantation, and death in patients with HF [66, 65, 64].

Anxiety and anxiety disorders have been linked to changes in the vascular endothelium. Patients with anxiety have impaired flow-mediated dilation of the vasculature, which suggests greater endothelial dysfunction [66-69]. Patients with GAD, PD, and obsessive compulsive disorder have decreased levels of circulating endothelial progenitor cells that are vital to healthy endothelial function and prevent progression of CAD [70]. Furthermore, patients with PTSD—especially those with active symptoms—have increased levels of soluble tissue factor and von Willebrand Factor, two substances that are secreted by endothelial cells and have been implicated in inflammation, thrombosis, and ultimately the development of atherosclerosis [71].

Platelet Dysfunction—Increased activity and activation of platelets by inflammatory triggers has been shown to play a critical role in atherothrombosis and myocardial ischemia [72]. Interestingly, serotonin has been shown to increase platelet aggregation and may be a method by which anxiety disorders are associated with increased cardiac events, as anxiety disorders have been associated with abnormalities in the serotonin system [73, 74]. Serotonin binds 5-hydroxytryptamine-2 (5HT-2) receptors on platelets and precipitates the release of factors enhancing platelet aggregation. In healthy vessels, prevention of thrombus formation is mediated by the release of nitrous oxide by endothelial cells and subsequent vasodilation. However, when the endothelial cell is damaged by atherosclerotic disease, the vessel is unable to properly dilate, and exposure to serotonin results in vasoconstriction. This serves as an underlying mechanism which links increased serotonin blood levels in CAD with cardiac events [75, 76].

In general, patients with anxiety and acute stress have greater platelet aggregation [77, 78], and anxiety disorders, including PTSD and PD, may also be associated with changes in platelet activity. In individuals with PTSD, changes in circulating catecholamines and a hyperactive sympathoadrenal system could lead to increased platelet activation [79].

Moreover, individuals with PTSD have increased platelet reactivity and aggregation ex vivo in response to exposure to adenosine-diphosphate and epinephrine [72]. In patients with PD, platelet aggregation has been shown to be elevated via changes in nitrous oxide and homocysteine levels [80]. Finally, patients with PD have larger mean platelet volume, a marker of increased platelet reactivity [81].

Autonomic dysfunction—Disruption in cardiovascular autonomic homeostasis, particularly as it relates to the body's ability to maintain stable beat-to-beat changes and blood pressure, has been shown to be important in overall cardiovascular health and risk of mortality. Patients with a history of cardiovascular disease, diabetes, and hypertension who are found to have a decreased ability to maintain autonomic stability are at increased risk of all-cause mortality [82]. Specifically, disrupted heart rate variability (a measure of beat-to-beat variability of the heart) and baroreflex sensitivity have been linked to increased adverse outcomes and mortality in post-MI and HF patients [83-85]. Decreased heart rate variability has been associated with phobic anxiety [86], GAD [87], PD [88], and PTSD [89]. Thus dysfunction in the body's ability to regulate autonomic function in patients with anxiety disorders could be a mechanism linking anxiety disorders to cardiac health.

Diagnosis of anxiety disorders

Diagnosing anxiety disorders in patients with cardiovascular disease is difficult given the substantial overlap between the symptoms of anxiety disorders and those of cardiovascular disease. Many symptoms of GAD, such as restlessness, fatigue, poor concentration, and sleep disturbance, are very common in patients with cardiac disease, especially HF. Similarly, nearly all the symptoms of a panic attack (e.g., palpitations, diaphoresis, dyspnea, nausea, chest pain) could potentially be experienced in the setting of an arrhythmia, ACS, or paroxysmal nocturnal dyspnea. If one relies too heavily on these overlapping symptoms, there is a significant risk of attributing cardiac symptoms to anxiety.

However, making a diagnosis of an anxiety disorder when one is present is critical. As noted, anxiety disorders are persistent, pervasive, and function-limiting, and they are associated with poor cardiac and psychiatric health. Accurate diagnosis will allow for the proper treatment of these disorders, and this hopefully can reduce their impact on psychiatric and cardiac health. To improve the likelihood of making an accurate diagnosis, we recommend focusing on the cardinal psychological symptoms of the disorders (e.g., chronic worry and difficulty controlling worry about a number of subjects for GAD), and following closely the DSM-5 criteria for these disorders [90], including the requirements regarding duration of symptoms and effects on function. Information from family members or close friends can also be helpful for clarifying the course of symptoms over time. Finally, if there is a significant question about the duration of symptoms and whether they exist only in the context of an acute exacerbation of cardiac symptoms (e.g., an ACS or episode of decompensated HF), it can be helpful to re-evaluate the patient during a period of medical stability to see if those symptoms persist. Using this approach, it is possible to make an accurate clinical diagnosis to ensure treatment for those who need it and avoid unnecessary treatment for those without a formal disorder.

Management of anxiety disorders

Pharmacotherapy

Antidepressants—Antidepressant medications are the most commonly used pharmacologic treatments for a variety of anxiety disorders, including GAD, PTSD, and PD. While there is evidence that selective serotonin reuptake inhibitors (SSRIs), some serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) are effective for the management of GAD, PTSD, and PD [91-93], no studies have been conducted to examine their efficacy for treating these disorders in patients with cardiovascular disease. However, these agents have been studied in depressed cardiac patients, providing data on their safety and tolerability in this population.

Of the antidepressant medications, SSRIs are the best studied and most frequently used agents in cardiac patients. Due to minimal affinity for adrenergic receptors and sodium channels, SSRIs typically do not cause orthostatic hypotension or affect intraventricular conduction, unlike TCAs [94]. In patients with CAD, sertraline, citalopram, and fluoxetine have been shown to be safe and effective for depression [95-97]. In HF, sertraline, paroxetine, citalopram, and escitalopram also have been well-tolerated, though they may have lesser efficacy for depression than in other populations [98-102].

SSRIs have been associated with several relevant side effects. First, some SSRIs are associated with a modest effect on the QT interval, with citalopram and escitalopram appearing to cause the greatest QTc prolongation [103]; prolongation of this interval has been associated with risk of torsades de pointes, a ventricular arrhythmia. However, the overall magnitude of QT prolongation is very small and has little clinical significance in the vast majority of patients [104]; furthermore, sertraline, paroxetine, and fluoxetine appear to have essentially no effect on the QT interval [103, 105]. Second, certain SSRIs, such as fluvoxamine, fluoxetine, and paroxetine, can interact with cardiovascular medications (e.g., metoprolol, captopril), which can affect blood levels of these agents and impact therapeutic response or side effects [106]. Finally, SSRIs are known to inhibit platelet aggregation/activation, and this can increase the risk of bleeding, especially for patients who are prescribed other anticoagulant medications [107, 108]. Conversely, there has been indirect evidence that SSRIs—potentially independent of their effects on mood—may be associated with superior cardiac outcomes. This includes a pair of epidemiologic studies finding SSRIs to be associated with lower cardiac mortality and lower rates of first MI [109, 110], and a post hoc analysis of a large cognitive behavioral therapy (CBT) trial in post-MI patients that found no effect of CBT on cardiac outcomes but that those also receiving SSRIs had lesser cardiac mortality [111].

SNRIs, such as venlafaxine and duloxetine, are sometimes used for the management of anxiety disorders, though there is less data on their use in heart disease. Venlafaxine is known to cause mild dose-dependent increases in heart rate and blood pressure. Venlafaxine has also been associated with the development of acute HF in overdose [112, 113], and both duloxetine and venlafaxine have been linked to worsening HF symptoms in case reports [114]. These reports are countered by a large retrospective cohort study, in which venlafaxine was associated with a lower risk of HF and no increase in risk of cardiac events

compared to sertraline [115]. Given these results and the overall lack of rigorous study in patients with heart disease, venlafaxine and duloxetine should be considered second-line agents for anxiety disorders in patients with cardiovascular disease, especially HF.

Finally, while TCAs can be used for the management of anxiety disorders, they typically are not recommended in patients with cardiovascular disease. In contrast to SSRIs, TCAs—especially tertiary amines (e.g., amitriptyline, clomipramine)—have effects on adrenergic receptors and sodium channels, and may cause tachycardia, orthostatic hypotension, and conduction abnormalities [94]. TCAs also appear to prolong the QT interval to a greater degree than SSRIs [104, 103]. Finally, an observational study found that patients receiving TCAs had higher rates of new MI compared to patients not treated with antidepressants, and that patients taking SSRIs had lower MI rates than either group [116]. Due to their lack of superiority in terms of treatment efficacy and their significantly worse cardiac side effect profile, these medications are considered second- or third-line in patients with heart disease.

Benzodiazepines—Despite only being approved for the management of PD [91], benzodiazepines frequently are prescribed as augmentation agents for other anxiety disorders, as well as standalone treatments for the management of acute anxiety. These agents may have beneficial cardiovascular effects, including lowering of left ventricular end diastolic pressure and antiarrhythmic effects [117]. While never studied formally in patients with cardiac disease, these medications have been associated with a reduced risk of HF hospitalization and cardiac mortality in patients with a history of MI [118], suggesting potential benefit in these patient groups. Benzodiazepines can cause respiratory depression, so they likely should be used cautiously in patients with acute HF exacerbations, and they have been linked to falls in the elderly and confusion [119-121]. Finally, there is the risk of abuse or dependence in patients with substance use disorders. For these reasons, benzodiazepines are often well-used for short-term acute anxiety or very specific indications (e.g., PD), but are less indicated for patients with chronic low-grade anxiety or other anxiety disorders.

Psychotherapy

Psychotherapy, especially CBT, is a reasonable alternative to pharmacotherapy in cardiac patients and in some cases may be preferable to pharmacologic treatment. In contrast to antidepressant and anxiolytic medications, psychotherapy has no side effects or medication interactions and so can be utilized in patients regardless of illness severity or medication use.

CBT has been the most studied psychotherapy in patients with heart disease. To date, nearly all studies examining the use of CBT in cardiac patients have focused on the management of depression, not anxiety disorders [122-127]. In patients with CAD (post-MI or post-CABG surgery) or HF, CBT leads to significantly greater improvements in psychological symptoms (typically depression and anxiety) compared to usual care or enhanced usual care [126, 128, 127]. While these studies targeted patients with depression, they are important because they demonstrate that CBT is feasible in patients with cardiac disease and can lead to improvement in psychological health.

Only one study has examined the impact of CBT for anxiety in patients with cardiovascular disease. This study enrolled 29 patients with comorbid major depression and GAD who were participating in a HF self-care program [125•]. Patients chose whether to receive CBT focused on GAD or depression, then received CBT focused on that disorder for 12 weeks. Both interventions led to nonsignificant improvements in depression and anxiety scores, with minimal differences between groups, though the GAD-focused CBT group had fewer unplanned admissions during the follow-up period than the MDD-focused group [125•]. Limitations of this study include the small sample size, lack of randomization, and the presence of pharmacologic intervention concurrent with CBT. However, it does suggest that CBT focused on anxiety disorders may be effective.

From a practical standpoint, we most often prescribe SSRIs, and specifically sertraline, in cardiac patients with anxiety disorders. Sertraline has been the most-studied SSRI in patients with heart disease, has few drug-drug interactions or QT effects, and treats comorbid depression and anxiety (unlike benzodiazepines). Though starting at lower doses (e.g., 25-50mg/day) may be reasonable, it is important to continue to push the dose upward to obtain a therapeutic effect. CBT, when available, is another excellent option.

Conclusions

Among patients with cardiovascular disease, anxiety and formal anxiety disorders are common and associated with poor cardiovascular health, including the development and progression of CAD and HF. The relationships between anxiety disorders and cardiac outcomes likely are mediated by both behavioral and physiologic mechanisms, including autonomic dysfunction, inflammation, and platelet aggregation. Given their links to poor outcomes, the diagnosis and treatment of anxiety disorders is critical. Diagnosis generally should adhere to the DSM-5 criteria as closely as possible, and treatment with SSRIs, benzodiazepines, and CBT appear safe and generally efficacious in this population. With careful diagnosis and appropriate treatment, anxious patients could have improved quality of life, functioning, and cardiac health.

Acknowledgements

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 or other funders.

References

1. Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. Psychother Psychosom. 2004; 73(6):344–52. doi:10.1159/000080387. [PubMed: 15479989]
2. Hanssen TA, Nordrehaug JE, Eide GE, Bjelland I, Rokne B. Anxiety and depression after acute myocardial infarction: an 18-month follow-up study with repeated measures and comparison with a reference population. Eur J Cardiovasc Prev Rehabil. 2009; 16(6):651–9. doi:10.1097/HJR.0b013e32832e4206. [PubMed: 19707149]
3. Koivula M, Tarkka MT, Tarkka M, Laippala P, Paunonen-Ilmonen M. Fear and anxiety in patients at different time-points in the coronary artery bypass process. Int J Nurs Stud. 2002; 39(8):811–22. doi:S0020748902000226 [pii]. [PubMed: 12379299]

4. 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. 2015 doi:10.1097/JCN.0000000000000265.

5. Brouwers C, Denollet J, Caliskan K, de Jonge N, Constantinescu A, Young Q, et al. Psychological distress in patients with a left ventricular assist device and their partners: an exploratory study. Eur J Cardiovasc Nurs. 2015; 14(1):53–62. doi:10.1177/1474515113517607 1474515113517607 [pii]. [PubMed: 24351334]

6. Modica M, Ferratini M, Torri A, Oliva F, Martinelli L, De Maria R, et al. Quality of life and emotional distress early after left ventricular assist device implant: a mixed-method study. Artif Organs. 2015; 39(3):220–7. doi:10.1111/aor.12362. [PubMed: 25205291]

7. Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, et al. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: a systematic review. J Psychosom Res. 2011; 71(4):223–31. doi:10.1016/j.jpsychores.2011.02.014 S0022-3999(11)00088-2 [pii]. [PubMed: 21911099]

8•. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010; 56(1):38–46. doi:10.1016/j.jacc.2010.03.034. [PubMed: 20620715] This meta-analysis, including 249,846 healthy adults who were followed over an average of 11 years, found that anxiety was associated with an increased risk of incident coronary artery disease and cardiac death, independent of relevant covariates.

9•. 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] This meta-analysis examined the relationship between anxiety and adverse cardiac outcomes in over 30,000 individuals with established coronary artery disease. In unadjusted analyses, anxiety was associated with a moderately increased risk of adverse cardiac events; however, these relationships were attenuated in adjusted analyses. The relationship between anxiety and outcomes appeared to be stronger when anxiety was measured during a period of clinical stability, compared to after an acute coronary syndrome.

10. 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(5): 940, e1–8. doi:10.1016/j.ahj.2006.05.009. [PubMed: 17070164]

11. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation. 2004; 110(22): 3452–6. doi:10.1161/01.cir.0000148138.25157.f9. [PubMed: 15557372]

12. Konstam V, Salem D, Pouleur H, Kostis J, Gorkin L, Shumaker S, et al. SOLVD Investigations. Studies of Left Ventricular Dysfunction Investigators. Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure. Am J Cardiol. 1996; 78(8):890–5. doi:S0002914996004638 [pii]. [PubMed: 8888661]

13. 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(2):261–7. doi:10.1161/circheartfailure.109.871483. [PubMed: 20071656]

14. Al-Ani M, Winchester DE. Prevalence and Overlap of Noncardiac Conditions in the Evaluation of Low-risk Acute Chest Pain Patients. Crit Pathw Cardiol. 2015; 14(3):97–102. doi:10.1097/HPC.0000000000000050 00132577-201509000-00003 [pii]. [PubMed: 26214812]

15. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. Am J Med. 1996; 101(4):371–80. doi:S0002-9343(96)00224-0 [pii] 10.1016/S0002-9343(96)00224-0. [PubMed: 8873507]

16. Ortiz-Garrido O, Ortiz-Olvera NX, Gonzalez-Martinez M, Moran-Villota S, Vargas-Lopez G, Dehesa-Violante M, et al. Clinical assessment and health-related quality of life in patients with non-cardiac chest pain. Rev Gastroenterol Mex. 2015; 80(2):121–9. doi:10.1016/j.rgmx.2015.03.005 S0375-0906(15)00054-3 [pii]. [PubMed: 26148745]

17. Hutter AM Jr. Amsterdam EA, Jaffe AS. 31st Bethesda Conference. Emergency Cardiac Care. Task force 2: Acute coronary syndromes: Section 2B--Chest discomfort evaluation in the hospital. J Am Coll Cardiol. 2000; 35(4):853–62. [PubMed: 10732881]

18. Tully PJ, Cosh SM. Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: a meta-analysis. J Health Psychol. 2013; 18(12):1601–16. doi: 10.1177/1359105312467390. [PubMed: 23300050]

19. Hoge EA, Ivkovic A, Fricchione GL. Generalized anxiety disorder: diagnosis and treatment. BMJ. 2012; 345:e7500. doi:10.1136/bmj.e7500. [PubMed: 23187094]

20. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62(6):617–27. doi:10.1001/archpsyc.62.6.617. [PubMed: 15939839]

21. Parker G, Hyett M, Hadzi-Pavlovic D, Brotchie H, Walsh W. GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome. Psychiatry Res. 2011; 188(3):383–9. doi:S0165-1781(11)00384-2 [pii] 10.1016/j.psychres.2011.05.018. [PubMed: 21652086]

22. 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(1):62–71. doi:65/1/62 [pii] 10.1001/archgenpsychiatry.2007.4. [PubMed: 18180430]

23. Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10-year follow-up. Br J Psychiatry. 2012; 200(4):324–9. doi:10.1192/bjp.bp.111.103549. [PubMed: 22403086]

24. Tully PJ, Winefield HR, Baker RA, Denollet J, Pedersen SS, Wittert GA, et al. Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. Biopsychosoc Med. 2015; 9:14. doi: 10.1186/s13030-015-0041-541 [pii]. [PubMed: 26019721]

25. Fleet R, Lavoie K, Beitman BD. Is panic disorder associated with coronary artery disease? A critical review of the literature. J Psychosom Res. 2000; 48(4-5):347–56. doi:S0022-3999(99)00101-4 [pii]. [PubMed: 10880657]

26. Todaro JF, Shen BJ, Raffa SD, Tilkemeier PL, Niaura R. Prevalence of anxiety disorders in men and women with established coronary heart disease. J Cardiopulm Rehabil Prev. 2007; 27(2):86–91. doi:10.1097/01.HCR.0000265036.24157.e7 01273116-200703000-00006 [pii]. [PubMed: 17558244]

27. Huffman JC, Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. Psychosomatics. 2003; 44(3):222–36. doi:S0033-3182(03)70292-8 [pii] 10.1176/appi.psy.44.3.222. [PubMed: 12724504]

28. 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(4):498–504. doi:10.1161/circoutcomes.111.000049. [PubMed: 23759474]

29. Gomez-Caminero A, Blumentals WA, Russo LJ, Brown RR, Castilla-Puentes R. Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. Psychosom Med. 2005; 67(5):688–91. doi:67/5/688 [pii] 10.1097/01.psy.0000174169.14227.1f. [PubMed: 16204424]

30. 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(24):2981–8. doi:10.1093/eurheartj/ehn477. [PubMed: 18948354]

31••. Tully PJ, Turnbull DA, Beltrame J, Horowitz J, Cosh S, Baumeister H, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1131612 persons and 58111 cardiac events. Psychol Med. 2015; 45(14):2909–20. doi:10.1017/S0033291715000963. [PubMed: 26027689] This systematic review and meta-regression found that panic disorder was significantly associated with incident coronary artery disease and major adverse cardiac events, even when controlling for depression.

32. Perkins-Porras L, Joekes K, Bhalla N, Sutherland C, Pollard M. Reporting of posttraumatic stress disorder and cardiac misconceptions following cardiac rehabilitation. J Cardiopulm Rehabil Prev. 2015; 35(4):238–45. doi:10.1097/HCR.0000000000000100. [PubMed: 25689163]

33. Copeland LA, Sako EY, Zeber JE, Pugh MJ, Wang CP, MacCarthy AA, et al. Mortality after cardiac or vascular operations by preexisting serious mental illness status in the Veterans Health

Administration. Gen Hosp Psychiatry. 2014; 36(5):502–8. doi:10.1016/j.genhosppsych.2014.04.003 S0163-8343(14)00120-0 [pii]. [PubMed: 24957928]

34. 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(1):29–33. doi:10.1016/j.amjcard.2011.02.340 S0002-9149(11)01138-6 [pii]. [PubMed: 21530936]
35. Vaccarino V, Goldberg J, Rooks C, Shah AJ, Veledar E, Faber TL, et al. Post-traumatic stress disorder and incidence of coronary heart disease: a twin study. J Am Coll Cardiol. 2013; 62(11):970–8. doi:10.1016/j.jacc.2013.04.085 S0735-1097(13)02506-0 [pii]. [PubMed: 23810885]
36••. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J. 2013; 166(5):806–14. doi:10.1016/j.ahj.2013.07.031 S0002-8703(13)00533-4 [pii]. [PubMed: 24176435] This meta-analysis, which included over 400,000 individuals, found that post-traumatic stress disorder was associated with an increased risk of incident coronary artery disease, independent of medical variables and depression.
37. 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(4):757–63. doi:10.2105/AJPH.2014.302342. [PubMed: 25713943]
38. 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(6):668–76. doi:10.1097/PSY.0b013e31817bccaf PSY.0b013e31817bccaf [pii]. [PubMed: 18596248]
39. Ladwig KH, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry. 2008; 65(11):1324–30. doi:10.1001/archpsyc.65.11.1324 65/11/1324 [pii]. [PubMed: 18981344]
40. Bradley SM, Stanislawski MA, Bekelman DB, Monteith LL, Cohen BE, Schilling JH, et al. Invasive coronary procedure use and outcomes among veterans with posttraumatic stress disorder: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Am Heart J. 2014; 168(3):381–90. e6. doi:10.1016/j.ahj.2014.05.015 S0002-8703(14)00343-3 [pii]. [PubMed: 25173551]
41. Duncan K, Pozehl B. Effects of an exercise adherence intervention on outcomes in patients with heart failure. Rehabil Nurs. 2003; 28(4):117–22. [PubMed: 12875144]
42. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. Prog Cardiovasc Dis. 2013; 55(6):590–600. doi:10.1016/j.pcad.2013.02.001 S0033-0620(13)00040-6 [pii]. [PubMed: 23621969]
43. McDermott MM, Schmitt B, Wallner E. Impact of medication nonadherence on coronary heart disease outcomes. A critical review. Arch Intern Med. 1997; 157(17):1921–9. [PubMed: 9308504]
44. Anderson LJ, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. Int J Cardiol. 2014; 177(2):348–61. doi:10.1016/j.ijcard.2014.10.011 S0167-5273(14)01938-X [pii]. [PubMed: 25456575]
45. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993; 16(2):434–44. [PubMed: 8432214]
46. Bonnet F, Irving K, Terra JL, Nony P, Berthezene F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis. 2005; 178(2):339–44. doi:S0021-9150(04)00468-X [pii] 10.1016/j.atherosclerosis.2004.08.035. [PubMed: 15694943]
47. Kinley DJ, Lowry H, Katz C, Jacobi F, Jassal DS, Sareen J. Depression and anxiety disorders and the link to physician diagnosed cardiac disease and metabolic risk factors. Gen Hosp Psychiatry. 2015; 37(4):288–93. doi:10.1016/j.genhosppsych.2015.03.022 S0163-8343(15)00066-3 [pii]. [PubMed: 25896947]
48. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006; 63(7):824–30. doi:63/7/824 [pii] 10.1001/archpsyc.63.7.824. [PubMed: 16818872]

49. Gavrieli A, Farr OM, Davis CR, Crowell JA, Mantzoros CS. Early life adversity and/or posttraumatic stress disorder severity are associated with poor diet quality, including consumption of trans fatty acids, and fewer hours of resting or sleeping in a US middle-aged population: A cross-sectional and prospective study. Metabolism. 2015; 64(11):1597–610. doi:10.1016/j.metabol.2015.08.017 S0026-0495(15)00250-4 [pii]. [PubMed: 26404481]
50. 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(12):1629–34. doi:10.1016/j.amjcard.2009.02.014 S0002-9149(09)00595-5 [pii]. [PubMed: 19539067]
51. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Predictors of attendance at cardiac rehabilitation after myocardial infarction. J Psychosom Res. 2001; 51(3):497–501. doi:S0022-3999(01)00225-2 [pii]. [PubMed: 11602219]
52. 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(6):358–64. doi:10.1097/HCR.0b013e3181be7a8f 01273116-200911000-00003 [pii]. [PubMed: 19940639]
53. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340(2):115–26. doi:10.1056/NEJM199901143400207. [PubMed: 9887164]
54. Moyer CF, Sajuthi D, Tulli H, Williams JK. Synthesis of IL-1 alpha and IL-1 beta by arterial cells in atherosclerosis. Am J Pathol. 1991; 138(4):951–60. [PubMed: 2012178]
55. Hohensinner PJ, Niessner A, Huber K, Weyand CM, Wojta J. Inflammation and cardiac outcome. Curr Opin Infect Dis. 2011; 24(3):259–64. doi:10.1097/QCO.0b013e328344f50f. [PubMed: 21378564]
56. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000; 343(16):1139–47. doi:10.1056/NEJM200010193431602. [PubMed: 11036119]
57. Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. Eur Heart J. 1998; 19(5):761–5. doi:S0195668X97908587 [pii]. [PubMed: 9717010]
58. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation. 2003; 107(11):1486–91. [PubMed: 12654604]
59. 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(2):320–6. doi:10.1016/j.atherosclerosis.2005.06.001. [PubMed: 16005881]
60. Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry. 2013; 3:e249. doi:10.1038/tp.2013.27 tp201327 [pii]. [PubMed: 23612048]
61. 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(18):2212–7. doi:ehn326 [pii] 10.1093/eurheartj/ehn326. [PubMed: 18603621]
62. von Kanel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res. 2007; 41(9):744–52. doi:S0022-3956(06)00123-3 [pii] 10.1016/j.jpsychires.2006.06.009. [PubMed: 16901505]
63. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2(11):1002–12. doi:10.1016/S2215-0366(15)00309-0 S2215-0366(15)00309-0 [pii]. [PubMed: 26544749]
64. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation. 2001; 104(22):2673–8. [PubMed: 11723017]
65. Drexler H. Endothelial dysfunction: clinical implications. Prog Cardiovasc Dis. 1997; 39(4):287–324. doi:S0033-0620(97)80030-8 [pii]. [PubMed: 9050817]

66. Narita K, Murata T, Hamada T, Takahashi T, Omori M, Suganuma N, et al. Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. J Psychiatr Res. 2007; 41(5):418–27. doi:S0022-3956(06)00015-X [pii] 10.1016/j.jpsychires.2006.01.003. [PubMed: 16494899]

67. Narita K, Murata T, Hamada T, Takahashi T, Kosaka H, Yoshida H, et al. Association between trait anxiety and endothelial function observed in elderly males but not in young males. Int Psychogeriatr. 2007; 19(5):947–54. doi:S1041610206004571 [pii] 10.1017/S1041610206004571. [PubMed: 17147843]

68. Mercer DA, Lavoie KL, Ditto B, Pelletier R, Campbell T, Arsenault A, et al. The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients. Biol Psychol. 2014; 102:44–50. doi:10.1016/j.biopsycho.2014.07.012 S0301-0511(14)00159-8 [pii]. [PubMed: 25058195]

69. Harris KF, Matthews KA, Sutton-Tyrrell K, Kuller LH. Associations between psychological traits and endothelial function in postmenopausal women. Psychosom Med. 2003; 65(3):402–9. [PubMed: 12764213]

70. Felice F, Di Stefano R, Pini S, Mazzotta G, Bovenzi FM, Bertoli D, et al. Influence of depression and anxiety on circulating endothelial progenitor cells in patients with acute coronary syndromes. Hum Psychopharmacol. 2015; 30(3):183–8. doi:10.1002/hup.2470. [PubMed: 25784019]

71. von Kanel R, Hepp U, Traber R, Kraemer B, Mica L, Keel M, et al. Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. Psychiatry Res. 2008; 158(3): 363–73. doi:10.1016/j.psychres.2006.12.003. [PubMed: 18252265]

72. Vidovic A, Grubisic-Ilic M, Kozaric-Kovacic D, Gotovac K, Rakos I, Markotic A, et al. Exaggerated platelet reactivity to physiological agonists in war veterans with posttraumatic stress disorder. Psychoneuroendocrinology. 2011; 36(2):161–72. doi:10.1016/j.psyneuen.2010.08.005 S0306-4530(10)00213-1 [pii]. [PubMed: 20863624]

73. Garvey MJ, Noyes R, Woodman C, Laukes C. The association of urinary 5-hydroxyindoleacetic acid and vanillylmandelic acid in patients with generalized anxiety. Neuropsychobiology. 1995; 31(1):6–9. [PubMed: 7535900]

74. Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, et al. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci. 2004; 24(3):589–91. doi: 10.1523/JNEUROSCI.4921-03.2004 24/3/589 [pii]. [PubMed: 14736842]

75. Miyata K, Shimokawa H, Higo T, Yamawaki T, Katsumata N, Kandabashi T, et al. Sarpogrelate, a selective 5-HT2A serotonergic receptor antagonist, inhibits serotonin-induced coronary artery spasm in a porcine model. J Cardiovasc Pharmacol. 2000; 35(2):294–301. [PubMed: 10672864]

76. Vikenes K, Farstad M, Nordrehaug JE. Serotonin is associated with coronary artery disease and cardiac events. Circulation. 1999; 100(5):483–9. [PubMed: 10430761]

77. Strike PC, Magid K, Brydon L, Edwards S, McEwan JR, Steptoe A. Exaggerated platelet and hemodynamic reactivity to mental stress in men with coronary artery disease. Psychosom Med. 2004; 66(4):492–500. doi:10.1097/01.psy.0000130492.03488.e7 66/4/492 [pii]. [PubMed: 15272093]

78. Levine SP, Towell BL, Suarez AM, Knieriem LK, Harris MM, George JN. Platelet activation and secretion associated with emotional stress. Circulation. 1985; 71(6):1129–34. [PubMed: 2986876]

79. Bedi US, Arora R. Cardiovascular manifestations of posttraumatic stress disorder. J Natl Med Assoc. 2007; 99(6):642–9. [PubMed: 17595933]

80. Yapislar H, Aydogan S, Ozum U. Biological understanding of the cardiovascular risk associated with major depression and panic disorder is important. Int J Psychiatry Clin Pract. 2012; 16(1):27–32. doi:10.3109/13651501.2011.620127. [PubMed: 22122655]

81. Kokacya MH, Copoglu US, Kivrak Y, Ari M, Sahpolat M, Ulutas KT. Increased mean platelet volume in patients with panic disorder. Neuropsychiatr Dis Treat. 2015; 11:2629–33. doi:10.2147/NDT.S94147 ndt-11-2629 [pii]. [PubMed: 26508858]

82. Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care. 2001; 24(10): 1793–8. [PubMed: 11574444]

83. Buccelletti E, Gilardi E, Scaini E, Galiuto L, Persiani R, Biondi A, et al. Heart rate variability and myocardial infarction: systematic literature review and metanalysis. Eur Rev Med Pharmacol Sci. 2009; 13(4):299–307. [PubMed: 19694345]
84. La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. Circulation. 2001; 103(16):2072–7. [PubMed: 11319197]
85. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. Heart. 2004; 90(11):1248–55. doi:90/11/1248 [pii] 10.1136/hrt.2003.026146. [PubMed: 15486114]
86. 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(14):882–5. doi:S0002914999806808 [pii]. [PubMed: 7732994]
87. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry. 1996; 39(4):255–66. doi:0006-3223(95)00136-0 [pii] 10.1016/0006-3223(95)00136-0. [PubMed: 8645772]
88. Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA. Altered heart rate variability in panic disorder patients. Biol Psychiatry. 1995; 37(1):18–24. doi:0006-3223(94)00130-U [pii] 10.1016/0006-3223(94)00130-U. [PubMed: 7893854]
89. Cohen H, Kotler M, Matar MA, Kaplan Z, Loewenthal U, Miodownik H, et al. Analysis of heart rate variability in posttraumatic stress disorder patients in response to a trauma-related reminder. Biol Psychiatry. 1998; 44(10):1054–9. doi:S0006-3223(97)00475-7 [pii]. [PubMed: 9821570]
90. American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5. American Psychiatric Publishing; Washington, DC: 2013.
91. American Psychiatric Association. [Accessed April 29 2016] Practice guideline for the treatment of patients with panic disorder. 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf
92. American Psychiatric Association. [Accessed August 3 2016] Practice guideline for the treatment of patients with acute stress disorder and post-traumatic stress disorder. 2004. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf
93. Stein MB, Sareen J. Clinical practice: generalized anxiety disorder. N Engl J Med. 2015; 373(21): 2059–68. doi:10.1056/NEJMcp1502514. [PubMed: 26580998]
94. Alvarez W, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. Pharmacotherapy. 2003; 23(6):754–71. [PubMed: 12820818]
95. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002; 288(6): 701–9. doi:joc11572 [pii]. [PubMed: 12169073]
96. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, 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(4):367–79. doi:297/4/367 [pii] 10.1001/jama.297.4.367. [PubMed: 17244833]
97. Strik JJ, Honig A, Lousberg R, Lousberg AH, Cheriex EC, Tuynman-Qua HG, et al. 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(6): 783–9. [PubMed: 11138997]
98. Fraguas R, da Silva Telles RM, Alves TC, Andrei AM, Rays J, Iosifescu DV, 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(3):205–11. doi:10.1016/j.cct.2009.01.007 S1551-7144(09)00008-1 [pii]. [PubMed: 19470312]
99. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, Greenberg N, 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(5):868–73. doi:S0002-8703(07)00159-7 [pii] 10.1016/j.ahj.2007.02.024. [PubMed: 17452166]

100. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, 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(9):692–9. doi:10.1016/j.jacc.2010.03.068 S0735-1097(10)02238-2 [pii]. [PubMed: 20723799]
101. Pellicori P, Clark AL. Clinical trials update from the European Society of Cardiology-Heart Failure meeting 2015: AUGMENT-HF, TITRATION, STOP-HF, HARMONIZE, LION HEART, MOOD-HF, and renin-angiotensin inhibitors in patients with heart and renal failure. Eur J Heart Fail. 2015; 17(9):979–83. doi:10.1002/ejhf.340. [PubMed: 26289928]
102. Angermann CE, Gelbrich G, Stork S, Fallgatter A, Deckert J, Faller H, 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(12):1212–22. doi:S1388-9842(07)00428-X [pii] 10.1016/j.ejheart.2007.10.005. [PubMed: 18029292]
103. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014; 75(5):e441–9. doi:10.4088/JCP.13r08672. [PubMed: 24922496]
104. Beach SR, Celano CM, Noseworthy P, Januzzi J, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. 2013; 54(1):1–13. [PubMed: 23295003]
105. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013; 346:f288. doi: 10.1136/bmj.f288 bmj.f288 [pii]. [PubMed: 23360890]
106. Guck TP, Elsasser GN, Kavan MG, Barone EJ. Depression and congestive heart failure. Congest Heart Fail. 2003; 9(3):163–9. [PubMed: 12826775]
107. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med. 2006; 119(2):113–6. doi:S0002-9343(05)00357-8 [pii] 10.1016/j.amjmed.2005.03.044. [PubMed: 16443409]
108. Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, 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(8):939–44. doi: 10.1161/01.CIR.0000085163.21752.0A 01.CIR.0000085163.21752.0A [pii]. [PubMed: 12912814]
109. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006; 63(12):1358–67. doi:63/12/1358 [pii] 10.1001/archpsyc.63.12.1358. [PubMed: 17146010]
110. Kimmel SE, Schelleman H, Berlin JA, Oslin DW, Weinstein RB, Kinman JL, et al. The effect of selective serotonin re-uptake inhibitors on the risk of myocardial infarction in a cohort of patients with depression. Br J Clin Pharmacol. 2011; 72(3):514–7. doi:10.1111/j.1365-2125.2011.04008.x. [PubMed: 21557758]
111. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry. 2005; 62(7):792–8. doi:62/7/792 [pii] 10.1001/archpsyc.62.7.792. [PubMed: 15997021]
112. Batista M, Dugernier T, Simon M, Haufroid V, Capron A, Fonseca S, et al. The spectrum of acute heart failure after venlafaxine overdose. Clin Toxicol (Phila). 2013; 51(2):92–5. doi: 10.3109/15563650.2012.763133. [PubMed: 23301719]
113. Fangio P, De Jonghe B, Appere-De-Vecchi C, Lacherade JC, Terville JP, Outin H, et al. Acute heart failure associated with venlafaxine poisoning. Am J Emerg Med. 2007; 25(2):210–1. doi:S0735-6757(06)00306-8 [pii] 10.1016/j.ajem.2006.08.007. [PubMed: 17276818]

114. Colucci VJ, Berry BD. Heart failure worsening and exacerbation after venlafaxine and duloxetine therapy. Ann Pharmacother. 2008; 42(6):882–7. doi:10.1345/aph.1L031 aph.1L031 [pii]. [PubMed: 18445706]

115. 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(6):e552–8. doi:10.4088/JCP.13m08508. [PubMed: 25004195]

116. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med. 2000; 108(1):2–8. doi:S0002-9343(99)00301-0 [pii]. [PubMed: 11059434]

117. Huffman JC, Stern TA. The use of benzodiazepines in the treatment of chest pain: a review of the literature. J Emerg Med. 2003; 25(4):427–37. doi:S0736467903002464 [pii]. [PubMed: 14654185]

118. Wu CK, Huang YT, Lee JK, Jimmy Juang JM, Tsai CT, Lai LP, et al. Anti-anxiety drugs use and cardiovascular outcomes in patients with myocardial infarction: a national wide assessment. Atherosclerosis. 2014; 235(2):496–502. doi:10.1016/j.atherosclerosis.2014.05.918 S0021-9150(14)01168-X [pii]. [PubMed: 24953489]

119. Zaal IJ, Devlin JW, Hazelbag M, Klein Klouwenberg PM, van der Kooi AW, Ong DS, et al. Benzodiazepine-associated delirium in critically ill adults. Intensive Care Med. 2015; 41(12): 2130–7. doi:10.1007/s00134-015-4063-z 10.1007/s00134-015-4063-z [pii]. [PubMed: 26404392]

120. Serafim RB, Dutra MF, Saddy F, Tura B, de Castro JE, Villarinho LC, et al. Delirium in postoperative nonventilated intensive care patients: risk factors and outcomes. Ann Intensive Care. 2012; 2(1):51. doi:10.1186/2110-5820-2-51 2110-5820-2-51 [pii]. [PubMed: 23272945]

121. de Jong MR, Van der Elst M, Hartholt KA. Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. Ther Adv Drug Saf. 2013; 4(4):147–54. doi: 10.1177/2042098613486829 10.1177_2042098613486829 [pii]. [PubMed: 25114778]

122. 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(4) doi:10.4088/PCC.09m00896blu PCC.09m00896 [pii].

123. 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(1):10–20. doi:10.1016/j.cardfail.2011.09.008 S1071-9164(11)01194-8 [pii]. [PubMed: 22196836]

124. 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(2):119–31. doi:10.1016/j.jpsychores.2010.01.013 S0022-3999(10)00018-8 [pii]. [PubMed: 20624510]

125•. 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(7):585–92. doi:10.3109/09638288.2014.935493. [PubMed: 24981015] The only study examining the efficacy of CBT for anxiety disorders in HF, this trial enrolled 29 HF patients with both GAD and depression, then allowed patients to choose whether they preferred anxiety- or depression-focused CBT. Depression and anxiety appeared to improve in both groups, but patients receiving anxiety-focused CBT were less likely to have unplanned admissions during the follow-up period.

126. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA. 2003; 289(23):3106–16. doi:10.1001/jama.289.23.3106 289/23/3106 [pii]. [PubMed: 12813116]

127. Freedland KE, Skala JA, Carney RM, Rubin EH, Lustman PJ, Davila-Roman VG, et al. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. Arch Gen Psychiatry. 2009; 66(4):387–96. doi:10.1001/archgenpsychiatry.2009.7 66/4/387 [pii]. [PubMed: 19349308]

128. 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. doi:10.1001/jamainternmed.2015.5220 2443368 [pii].

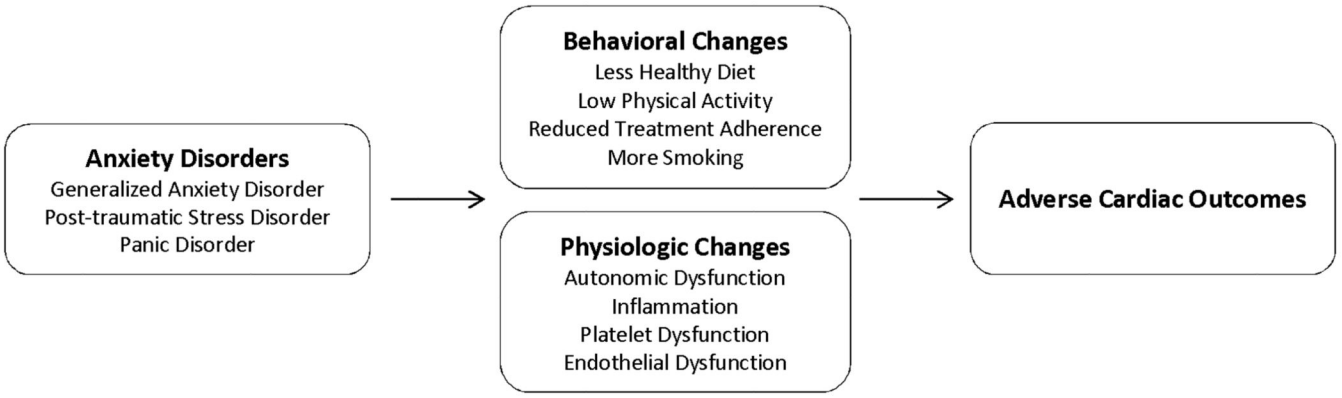

Figure 1. Potential mechanisms mediating the relationships between anxiety disorders and cardiac health