

## Magnitude and Relationship between Depression and Cardiovascular Diseases - A Review

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**Abstract:** The association between depression and cardiovascular diseases (CVD) is well established and is suggested to be bidirectional. Depression is common, persistent and associated with worse health related quality of life, recurrent events and mortality. Numerous clinical and epidemiological studies investigating the association of depression and CVD have suggested that depression independently increases the risk of CVD 1.5-fold on average, and that patients with coronary artery disease and depression have a two- to threefold increased risk of future non-fatal and fatal cardiac events compared with those cardiac patients without depression. Both physiological and behavioral factors- including inflammation, endothelial dysfunction, platelet abnormalities, neurohormonal and autonomic nervous system dysfunction and reduced engagement in health-promoting activities- may link depression with adverse cardiac outcomes. We outline the associations between depression and cardiac outcomes, as well as the mechanisms that may mediate these links.

**Keywords:** depression, cardiovascular diseases, cardiac events.

### I. Introduction

The association between depression and cardiovascular disease is well established and is suggested to be bidirectional. Depression in cardiac disease is common, persistent, under recognized, and deadly. Over the past 20 years, research has found that not only is depression more common in cardiac patients than in the general population, but depression is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors. This link between depression and cardiac morbidity likely involves both physiologic and behavioral effects of depression. In this paper, we will review the epidemiology, course, impact and pathogenesis of depression in patients with cardiovascular disease (CVD).

#### Prevalence of depression in cardiac patients

Clinically significant depressive symptoms have been reported between 31–45% of patients with coronary artery disease (CAD), including those with stable CAD, unstable angina, or myocardial infarction (MI)<sup>1</sup>. Furthermore, 15–20% of patients with CAD meet criteria at any given time for the full syndrome of MDD<sup>2-6</sup>; this rate of MDD is roughly threefold higher than in the general population<sup>7</sup> and is similar to the rates of MDD in patients with chronic kidney disease<sup>8</sup> and cancer<sup>9</sup>. Patients with heart failure (HF), atrial fibrillation (AF) and those undergoing implantable cardioverter-defibrillator (ICD) placement are similarly at increased risk for elevated depressive symptoms and for MDD<sup>10-12</sup>. A meta-analysis of patients with HF found prevalence rates of 36% for increased depressive symptoms and 20% for MDD [11]. Furthermore, a recent systematic review of ICD patients found depressive disorders (e.g., MDD, dysthymic disorder) to be present in 11–28% of patients [10]. Finally, among patients undergoing coronary artery bypass graft (CABG) surgery, approximately 30–40% of patients meet criteria for dysthymia, minor or major depression, with roughly 15% of patients meeting full MDD criteria on diagnostic interview<sup>13</sup>.

#### Course of illness

Depression tends to be chronic and recurrent in patients with CVD. About 50–70% patients were found to have ongoing depressive symptoms prior to their cardiac event<sup>14-16</sup>; this finding is consistent with literature that describes persistent depression in patients with stable CAD<sup>17</sup>. Depression is found to exist for months or years before and persists long after the cardiac event<sup>14-21</sup> while studies found that in post-MI depression, depressive symptoms remain at steady levels of severity over the 12 months after an MI<sup>18, 19</sup>. Similar results have been observed in patients with chronic CVD, such as those with ICDs; in this cohort, 80% of patients who are depressed at the time of ICD placement continue to suffer from depressive symptoms 2 years later<sup>21</sup>. Finally, among patients admitted with a HF exacerbation and diagnosed with MDD, less than half have a remission of symptoms at 5-month followup<sup>20</sup>.

The above studies shows that depression is present in a significant portion of patients across the spectrum of cardiac disease, and such symptoms, when present, are likely to persist unless treated. These

findings underscore the need to find better methods for identifying and managing depression in patients with CVD.

### **Risk factors for depression in cardiac patients**

There are several risk factors established for depression in cardiac patients. Most studies reports that younger patients, women, and patients with premorbid histories of depression are more likely to have depression in the context of CVD though some literature report different findings<sup>22-26</sup>. Among patients suffering from an acute coronary syndrome (ACS), in addition to the previous factors, social isolation, prior ACS, and in some cases, comorbid diabetes may also increase depression risk<sup>24,25,27-29</sup>. These factors, as well as poor functional status or worse New York Heart Association (NYHA) HF severity class, have also been linked to depression in patients with HF<sup>30-32</sup>. Among CABG patients, depression pre-CABG is predicted by female gender, younger age, living alone, and less education<sup>33</sup>, and post-CABG depression is best predicted by pre-CABG depressive symptoms and anxiety<sup>34</sup>. Similarly, among patients with an ICD for ventricular arrhythmias, younger age and female gender predict depression<sup>8</sup>; there is some suggestion, though not definitive evidence, that ICD shocks are linked to higher rates of depression<sup>8,35</sup>.

### **Association between depression and cardiac outcomes**

Over the past 15 years, a multitude of studies have confirmed that depression is associated with adverse cardiovascular outcomes, independent of traditional risk factors. In healthy individuals, depression has been independently associated with the development and progression of CAD<sup>36-39</sup> and with CVD-related mortality<sup>40</sup>. In fact, two separate systematic quantitative reviews have found depression (diagnosed with a diagnostic interview or self-report measure) to be a significant and independent risk factor for the development of cardiac disease, with a relative risk of 1.6 (relative risk 1.64 [95% Confidence Interval (CI) = 1.41–1.90] and 1.60 [95% CI 1.34–1.92], resp.) in depressed patients compared to those persons who were never depressed<sup>38,41</sup>.

Depressed patients with unstable CAD appear to be at even greater risk for poor cardiac outcomes. The presence of post-MI depression predicts recurrent cardiac events<sup>42</sup>, cardiac-related death<sup>42-45</sup>, and all-cause mortality<sup>42,46</sup>. Indeed, a recent meta-analysis revealed that depressed post-MI patients have a 2.4-fold increased risk (unadjusted) for all-cause mortality (odds ratio 2.38; 95% CI = 1.76– 3.22) [42]. Likewise, among patients with a wider range of unstable or angiographically validated CAD, a meta-analysis of 20 studies found depressive symptoms and MDD to be associated with mortality (Hazard ratio 1.76 [95% CI = 1.27–2.43], adjusted for other risk factors) in the two years following an event<sup>46</sup>. Furthermore, depressive symptoms following MI have been associated with increased hospital readmissions, particularly cardiac readmissions, and with reduced adoption of secondary prevention behaviors, including smoking cessation, physical activity, and cardiac rehabilitation<sup>47-50</sup>.

A meta-analysis done in 2012 found that depression was independently predictive of mortality and cardiac morbidity after an ACS, regardless of whether the depression was present prior to or after the onset of cardiac illness; however, first-onset depression within 30 days of an acute cardiac event was potentially more strongly linked to morbidity and mortality<sup>51</sup>. Conversely, following an acute cardiac event, prior history of depression, without current depression, was not associated with adverse outcomes<sup>51</sup>. Depression also appears to substantially impact cardiovascular outcomes in patients with other forms of CVD. Clinically significant depression increases the risk of incident HF, especially in those already at increased risk for its development; in patients with established HF, it is also related to increased health care utilization, more frequent hospitalizations, and a 2-fold increase in mortality risk<sup>11,52</sup>. Increased depressive symptoms are also linked to recurrence of AF in patients following cardioversion<sup>53</sup> and with cardiovascular mortality in patients with comorbid AF and HF<sup>54</sup>.

Depression has been associated with longer hospitalization<sup>55</sup>, poorer functional outcomes<sup>56,57</sup>, more perioperative complications<sup>55</sup>, worse health-related quality of life (HRQoL)<sup>58</sup>, progression of atherosclerotic disease<sup>59</sup>, higher rates of rehospitalization<sup>58</sup>, and mortality<sup>13,60,61</sup> in patients undergoing CABG.

Finally, depression has been associated with mortality, independent of covariates, in patients with an ICD<sup>62</sup>. Several studies have evaluated the characteristics of psychiatric illness and its treatment that may contribute to poor cardiac outcomes in depressed cardiac patients. Non-response to treatment for depression, for instance, appears to put depressed post-ACS patients at greater risk for recurrent cardiac events<sup>63</sup> and for all-cause mortality<sup>64</sup>. Poor outcomes may be exacerbated by the presence of co-occurring anxiety, which is independently associated with recurrent cardiac events and mortality<sup>65</sup> and which has been linked with poor response to treatment for depression<sup>66-68</sup>. Other patients who appear to be at particularly high risk for poor outcomes include those with prominent anhedonia (the inability to experience pleasure)<sup>69-71</sup> and those with type D personality (a personality structure characterized by negative affectivity and social inhibition)<sup>18</sup>, though the latter association is controversial<sup>72</sup>. Thus, not only is depression common and persistent in patients with CVD, but it also may have a negative impact on multiple aspects of the course of cardiovascular illness, including physical functioning, quality of life, health care utilization, re-hospitalization and mortality.

## **Potential Mechanisms Linking Depression and Cardiac Disease**

There are a number of mechanisms that are potentially implicated in the connection between depression and adverse cardiac outcomes.

### **i. Inflammation.**

The contribution of inflammation to the overall development of cardiac disease—and especially to acute cardiac events—is well documented. Inflammatory cytokines have been associated with atherosclerotic plaque formation, progression, and rupture; as such they are major contributors to the pathogenesis of CAD, unstable angina, and MI<sup>73,74</sup>. Furthermore, inflammation plays a key role in the pathogenesis of certain types of HF<sup>75,76</sup>. Overall, inflammatory cytokines i.e., C-reactive protein (CRP) in CAD and interleukin-6 (IL-6) in HF have been predictive of cardiovascular mortality and disease progression in healthy individuals<sup>40</sup> and in patients with CAD<sup>77</sup> and HF<sup>78-80</sup>.

Depression also has been linked to increased levels of cytokines (specifically CRP, IL-1, and IL-6), both in patients with and without a history of cardiac disease<sup>36,81-83</sup>. Two studies provide evidence that inflammation associated with elevated depressive symptoms or MDD is associated with the development of cardiac disease and cardiovascular mortality. In a population cohort study of 908 patients without known CVD, Kop and associates<sup>40</sup> found that depression predicted cardiovascular mortality; controlling for inflammatory markers reduced the association by 12.7%, suggesting that inflammation partially contributed to the effects of depression on cardiovascular mortality. Similarly, in a study of 559 women with suspected cardiac ischemia, Vaccarino and associates found that depression predicted cardiovascular events; controlling for inflammatory factors (CRP, IL-6) reduced this association by 20%, again suggesting a small but meaningful contribution to the effects of depression on cardiac events<sup>84</sup>.

Inflammation, depression, and cardiovascular disease may be linked by at least two potential mechanisms. First, neural-immune interaction may occur. In animal models of induced fatigue, levels of the inflammatory cytokine interferon alpha increase, while extracellular levels of serotonin increase in the medial prefrontal cortex. Furthermore, treatment with a serotonin (5HT-1A) receptor agonist reduces the effects of fatigue<sup>85,86</sup>. Hence, in depression, reduced serotonin actions on these receptors may be linked to increased cytokines and the subsequent effects on cardiovascular outcome. Second, elevated levels of inflammatory cytokines (e.g., interferon-gamma) are associated with increased activity of an enzyme that degrades tryptophan (a serotonin precursor) to kynurenine in patients with CVD<sup>87</sup>. This is likely to result in lower levels of serotonin and may represent another mechanistic link that connects inflammation to depression in patients with cardiac disease.

### **ii. Endothelial Dysfunction.**

Endothelial dysfunction and its role in the development of ischemic CAD in patients with atherosclerosis have been established<sup>88</sup>. While a normal endothelium typically releases nitric oxide in response to serotonin to ensure adequate blood flow through the coronary arteries, in atherosclerotic arteries it fails to do so. This results in vasoconstriction in areas of atherosclerosis and may provide a mechanism for myocardial ischemia and coronary thrombosis<sup>89</sup>. Inflammation, which has been associated with CAD, also impairs endothelial nitric oxide release and may represent a mechanism explaining the finding of endothelial dysfunction in cardiac patients<sup>90</sup>. In addition to its role in cardiac ischemia in patients with CAD, endothelial dysfunction independently predicts mortality in patients with HF<sup>91,92</sup>.

Depression has been associated with impaired endothelial function in healthy patients<sup>93,94</sup> in those at risk for CVD<sup>95</sup>, and in those with established CVD<sup>96</sup>. Treatment of depression with selective serotonin reuptake inhibitors (SSRIs) has led to improved endothelial function in patients with depression and established CAD, further suggesting that endothelial dysfunction may be linked to depression's effects on cardiac outcomes<sup>97</sup>.

### **iii. Increased Platelet Activity and Aggregation.**

Platelet adhesion, activation, and aggregation are important components of cardiac disease, and increased platelet activity may lead to coronary events on this basis. Serotonin plays a key role in platelet biology through its binding with 5-hydroxytryptamine (5-HT) receptors on platelets. In atherosclerotic arteries, as described in the previous section, serotonin leads to platelet aggregation<sup>98,99</sup>. Furthermore, elevated levels of blood serotonin predict CAD and future ischemic cardiac events in patients with suspected CAD<sup>98</sup>. SSRIs, which theoretically deplete platelet serotonin stores by inhibiting platelet uptake of serotonin, have also been shown to decrease platelet aggregation and activity in vitro and in patients with CAD<sup>99,100</sup>. Taken together, these findings lend credence to the theory that serotonin, through its activity on platelet aggregation, is associated with myocardial ischemia and other cardiac events.

Platelet dysfunction also occurs in patients suffering from major or minor depression; depressed patients have abnormalities in whole blood and platelet serotonin levels<sup>101</sup>, increased platelet serotonin receptor

concentrations<sup>102,103</sup> and abnormally low platelet serotonin transporter levels<sup>104</sup>, suggesting that their platelets are both more sensitive to serotonin and less able to remove it from the bloodstream. Furthermore, there is evidence—albeit mixed—suggesting that the platelets of depressed patients are hyperactive<sup>101,105–107</sup>. This serotonergic and platelet dysfunction could mediate the increased risk for ischemic events in these patients. At this stage, much less is known about the association between platelet hyperaggregability and other forms of CVD.

#### **iv. Neurohormonal and Autonomic Nervous System Dysfunction.**

Neurohormonal activation may also play a particularly important role in the connection between depression and outcomes in HF. Levels of circulating catecholamines (e.g., epinephrine and norepinephrine) are elevated in patients with HF, especially in those with decompensated HF, and higher levels of norepinephrine have been linked to greater mortality in this illness<sup>108,109</sup>. Furthermore, increases in plasma as well as cerebrospinal fluid levels of norepinephrine have been observed in patients with MDD to the extent of being capable of causing increased mortality in HF<sup>110</sup>. Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis may also play a substantial role, as cortisol (and aldosterone) are independently linked with mortality in HF, and patients with depression have elevated levels of cortisol<sup>80</sup>. Such hypercortisolemia and other HPA-related abnormalities in depression may impact medical outcomes in other cardiac illnesses, as these abnormalities are associated with the development and progression of the metabolic syndrome, a condition characterized by dyslipidemia, truncal obesity, and insulin resistance and linked to cardiac morbidity and mortality.

Other abnormalities in the autonomic nervous system may also contribute to the relationship between depression and cardiac disease. Since the heart is innervated by both sympathetic and parasympathetic nervous systems, the interplay between these two opposing forces helps the heart make changes in response to stressors. Patients with a history of ischemic heart disease or HF typically exhibit a pattern of increased sympathetic and decreased parasympathetic activity; this is manifested by decreased baroreflex sensitivity and decreased heart rate variability (HRV)<sup>111</sup>. This pattern of autonomic dysfunction has been associated with increased mortality in patients with HF<sup>111</sup> and a history of MI<sup>111–113</sup> and with increased rates of recurrent AF after cardioversion<sup>53</sup>. In animal studies, such a pattern of autonomic dysfunction was associated with increased rates of ventricular fibrillation during recurrent ischemic episodes<sup>114</sup> and may represent a mechanism by which autonomic dysfunction leads to increased morbidity and mortality in cardiac patients.

Studies have found that depressed patients (with and without cardiac disease) also have reduced HRV<sup>115–117</sup>, suggestive of the same imbalance between sympathetic and parasympathetic nervous systems described previously. This reduction appears to be linearly associated with depression severity, with more severe depression resulting in greater reductions in HRV<sup>115</sup>. Furthermore, patients with both CAD and depression have greater decreases in HRV compared to patients with depression or CAD alone, suggesting that the effects of depression and CAD on HRV are additive<sup>117</sup>. This increased autonomic dysfunction in depressed patients may therefore lead to worse cardiac outcomes in patients with co-occurring HF.

#### **v. Effects of Brain-Derived Neurotrophic Factor (BDNF) and Related Factors.**

BDNF may also play an important role in the connection between depression and cardiac outcomes. Depression has been strongly and consistently linked to low levels of BDNF<sup>118</sup>, and it is thought that BDNF signaling mediates the hippocampal neurogenesis that has been linked to depression recovery<sup>119</sup>. Indeed, SSRI antidepressants have been associated with increased levels of BDNF<sup>120</sup> and with hippocampal neurogenesis<sup>121</sup>. BDNF also has an important role in several physiologic processes important to cardiovascular health. BDNF is expressed by endothelial cells, and it leads to angiogenesis in, and survival of, endothelial cells (primarily mediated via the phosphatidylinositol-3-kinase-Akt pathway), with increased BDNF expression during hypoxia<sup>122</sup>. Endothelial cells are vital to vascular health and, as noted, endothelial function is independently associated with cardiac outcomes.

BDNF expression is up-regulated by neural signals from the heart after experimentally induced MI (interestingly, BDNF expression is increased in brain but not heart), and such expression was linked to reduced cardiomyocyte death and improved systolic function<sup>123</sup>. Such heart-brain connections are similarly seen with the brain sigma-1 receptor (S1R)<sup>124</sup>. Brain S1R appears to be associated with depression, as S1R knockout mice display depressive phenotypes<sup>125</sup>, and S1R agonists improve such behavior<sup>126</sup>. A recent mouse model study showed that induced heart failure was associated with reduction in brain S1R, consistent with the investigators' hypothesis that reduced brain S1R exacerbates heart failure<sup>127</sup>.

In addition, BDNF may be an important mediator of the previously noted HPA axis effects on depression and cardiovascular disease. The glucocorticoid receptor interacts with the specific receptor of BDNF, TrkB, and excessive glucocorticoid interferes with BDNF signaling<sup>128</sup>; therefore excess glucocorticoids may be associated with adverse outcomes via BDNF-mediated effects on endothelial cells and cardiomyocytes.

## vi. Behavioral Factors.

Behavioral factors play a vital role in the relationship between depression and cardiac disease. Depressed patients are less likely to engage in health promoting behaviors, including maintenance of a healthy diet<sup>66,129</sup> regular exercise<sup>66,130</sup> adherence to medications<sup>66,129,131</sup> stress reduction<sup>66</sup> and completion of cardiac rehabilitation programs<sup>132, 133</sup> following MI. These patients also have more difficulty lowering their cholesterol following MI<sup>134</sup>. Medication nonadherence and lower physical fitness are associated with an increased risk of cardiovascular events in certain populations<sup>135,136</sup> and this additionally suggests that the behavioral changes associated with depression may be associated with the progression of CAD and poor cardiac outcomes in patients with and without established CVD. Fortunately, in a study of hospitalized patients with a variety of cardiac conditions, those who met criteria for clinical depression during admission had improvement of adherence (to diet, exercise, and medication) if their depression improved following hospitalization<sup>130</sup>. This suggests that reduced adherence to key secondary prevention behaviors in depressed cardiac patients may be modifiable with treatment of the depressive symptoms.

## Summary

The association between CVDs and depression using the latter as a single diagnostic entity is well established and suggested to be bidirectional. Additionally, although depression may be a factor that predisposes a patient to the development of CVD, it may not necessarily be the factor that maintains the development of CVD. Systemic immune activation may be stimulated by one depressive episode and ongoing regardless of the episode going into remission through treatment. This review implicates the need for development of timely and appropriate measures for detection, prevention and treatment for CVD and depression.

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