International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	THE RELATIONSHIP BETWEEN DEPRESSION AND CARDIOVASCULAR DISEASES: A REVIEW OF PSYCHOCARDIOLOGICAL MECHANISMS
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3901
RECEIVED	14 August 2025
ACCEPTED	25 September 2025
PUBLISHED	30 September 2025
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THE RELATIONSHIP BETWEEN DEPRESSION AND CARDIOVASCULAR DISEASES: A REVIEW OF PSYCHOCARDIOLOGICAL MECHANISMS

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ABSTRACT

Background and Aim: Depression and cardiovascular diseases (CVDs) are major global health burdens with significant overlap. Increasing evidence supports a bidirectional relationship between them, driven by shared mechanisms such as HPA axis dysregulation, inflammation, autonomic imbalance, and behavioral risk factors. Depression increases the risk of cardiovascular events and worsens outcomes in CVD patients. This review explores psychocardiological mechanisms behind this comorbidity and assesses the efficacy of pharmacological and behavioral treatments—including cognitive behavioral therapy (CBT), cardiac rehabilitation programs (CRPs), and consultation-liaison psychiatry (CLP)—in improving patient outcomes.

Materials and Methods: A narrative review was conducted using sources from PubMed, Scopus, and ClinicalTrials.gov, including meta-analyses, cohort studies, and clinical guidelines. The review focused on the comorbidity of depression and CVD, underlying mechanisms, and the effects of interventions.

Results: Depression affects up to 25% of coronary artery disease patients and elevates the risk of adverse cardiac events. Mechanisms include chronic stress, HPA axis hyperactivity, systemic inflammation, and autonomic dysfunction. CBT and positive psychology interventions were associated with reduced myocardial infarction incidence and angina symptoms. CRPs improved quality of life and reduced depression and anxiety. CL psychiatry helped manage psychiatric comorbidities and enhanced adherence in hospitalized patients.

Conclusions: Depression is a modifiable, independent risk factor for CVD. Early screening and integrated interventions—including CBT, CRPs, and CL psychiatry—are effective in improving psychological and cardiovascular health. Personalized, multidisciplinary care is essential for optimal outcomes in patients with comorbid depression and CVD.

KEYWORDS

Depression, Cardiovascular Disease, Psychocardiology, Brain–Heart Axis, Inflammation, Mental Health Integration

CITATION

Kinga Dyndał, Marcelina Broda, Patrycja Jędrzejewska-Rzezak, Aleksandra Mokrzycka, Adam Żuczek, Katarzyna Urbańska, Izabela Szczap, Anna Hawryluk, Olga Żuczek, Kamil Marzec. (2025) The Relationship Between Depression and Cardiovascular Diseases: A Review of Psychocardiological Mechanisms. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3901

1. Introduction

Depression is one of the most prevalent and clinically recognized mental disorders worldwide, affecting individuals across all age groups, genders, and social backgrounds. It is characterized by a persistently low mood and a marked loss of interest or pleasure, often lasting for extended periods [1]. Globally, depression affects an estimated 280 million people, accounting for approximately 3.8% of the general population, with a prevalence of about 5% among adults [2]. The consequences of depression can be chronic or recurrent and often lead to significant impairments in social, occupational, and family functioning. Moreover, depressive disorders are strongly associated with an increased risk of suicidal ideation, which may result in suicide attempts or death by suicide [3]. More than 700, 000 people die by suicide each year globally [2]. Although the precise pathophysiology of depression remains incompletely understood, it is widely accepted to be a multifactorial condition arising from complex interactions between biological, genetic, environmental, and psychosocial factors.

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels. They include: coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. CVDs are the leading cause of death globally. In 2019, cardiovascular diseases (CVDs) were responsible for an estimated 17.9 million deaths, accounting for approximately 32% of all global deaths. Of these, 85% were due to heart attacks and strokes. Among the 17 million premature deaths (occurring before the age of 70) attributed to noncommunicable diseases in the same year, CVDs were the leading cause, contributing to 38% of cases [4].

CVDs and mental health disorders are among the most significant health challenges of our time, affecting both physical and psychological well-being. When symptoms of CVDs coexist with mental illnesses, the condition is often referred to as a psychocardiological disorder. CVDs remain one of the leading causes of disability and premature death worldwide. In terms of disability-adjusted life years (DALYs), ischemic heart disease and stroke consistently rank among the top contributors to the global burden of disease, occupying the first and third positions, respectively [5].

2. Methods

This narrative review was conducted through a comprehensive search of PubMed, Scopus, and ClinicalTrials.gov for studies published between January 2000 and June 2025. Keywords and MeSH terms included ‘depression', ’major depressive disorder', ’cardiovascular disease', ’coronary artery disease', ’myocardial infarction', ’heart failure', ’psychocardiology', and ’cognitive behavioral therapy'. Eligible sources comprised systematic reviews, meta-analyses, randomized controlled trials, cohort studies, and clinical guidelines, while conference abstracts, and non-English articles were excluded. Data extraction focused on epidemiological links, pathophysiological mechanisms, behavioral factors, and therapeutic interventions. Given the heterogeneity of the evidence, findings were synthesized qualitatively and organized into thematic domains.

3. Results

4. Epidemiological Links Between Depression and Cardiovascular Diseases

Depression and CVDs are among the most prevalent and burdensome non-communicable conditions worldwide. Numerous epidemiological studies have demonstrated a strong and bidirectional relationship between these two diseases.

Depression is highly prevalent among individuals with cardiovascular conditions. According to position papers of the American Heart Association and the European Society of Cardiology, depression may be a modifiable prognostic factor for coronary heart disease (CHD) [6]. Moreover, depression has been identified as an independent risk factor for CHD, not only reducing quality of life in affected patients but also significantly increasing the incidence of major adverse cardiac events [7]. Meta-analyses indicate that the overall estimated prevalence of depression in patients with CVD was 20.8%. Subgroup analyses revealed that the prevalence of depression was 19.8% in patients with coronary artery disease (CAD), and 24.7% in patients with heart failure. The prevalence of anxiety in patients with CVD was found to be 23.2% [8]. Several studies have documented that women with CAD are particularly prone to developing depression. In the general population, depression in women is roughly twice as prevalent as in men—a pattern mirrored among CAD patients [9]. Notably, young women under 60 who have experienced an MI are at especially high risk, with up to 40–50% meeting criteria for major depressive disorder [10]. A recent meta-analysis using structured psychiatric interviews found a pooled prevalence of depression at 23.6% and anxiety at 12.0% in patients post-acute MI. Further pooled prevalence subgroup analysis of depression and anxiety revealed significantly higher rates in the female sex (29.89%) [11]. In many cases, these symptoms manifest for the first time during hospitalization for acute coronary syndrome (ACS). Furthermore, the incidence of psychological distress increases following percutaneous coronary intervention (PCI) or surgical revascularization procedures [12]. Yunlong et al. demonstrated that women with a high polygenic risk score for major depression also had a higher risk of coronary artery disease, myocardial infarction, heart failure, and small vessel stroke, independent of whether they were clinically diagnosed with depression. Additionally, type 2 diabetes mellitus and smoking demonstrated significant mediation effects in the association of depression with coronary artery disease and myocardial infarction [13].

In a random-effect model, depressive symptoms were associated with an increased unadjusted all-cause mortality rate compared with non-depressed patients [8]. Depression is a strong and independent risk factor for the development of coronary heart disease, particularly in women, with a magnitude of risk that may exceed that of traditional cardiovascular factors. Early identification and treatment of depressive symptoms could play a critical role in primary prevention strategies for cardiovascular disease. Due to, two-times greater prevalence of major depression in women than men with CAD, women may warrant greater emphasis in efforts to identify and treat depression [14]. Integrating mental health assessments into cardiovascular care is increasingly recognized as a crucial step in improving prognosis.

5. Pathophysiological Mechanisms Connecting Depression and Cardiovascular Diseases

Cardiovascular disease (CVD) and major depressive disorder (MDD) are both chronic conditions that demonstrate a clinically supported bidirectional relationship. Several pathophysiological factors may explain the development of MDD in CVD patients, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system imbalance, inflammation, platelet activation, EC vasodilator dysfunction, genetic disorders and epigenetic factors [15]. The activation of stress-related physiological pathways plays a central role in the bidirectional relationship between major depressive disorder MDD and CVD. Patients affected by both conditions typically exhibit poorer clinical outcomes compared to those without comorbid MDD [16].

5.1. Neuroendocrine Dysregulation

Evidence suggests the association between dysregulation of the HPA axis and the pathophysiology of MDD [17]. Dysregulation of the HPA axis has a profound impact on the production and activity of corticotropin-releasing factor (CRF). In individuals with MDD, the HPA axis is often hyperactive, leading to increased secretion of CRF from the paraventricular nucleus of the hypothalamus. Elevated CRF levels stimulate the anterior pituitary to release adrenocorticotropic hormone (ACTH), which subsequently increases cortisol production by the adrenal glands [18]. Normally, high cortisol levels trigger a negative feedback loop that suppresses further hormone release. However, in depression, this feedback mechanism is disrupted—often due to glucocorticoid receptor (GR) resistance—which results in sustained cortisol elevation. Studies have shown that people with depression, including those who died by suicide, exhibit increased CRH expression and altered CRH receptor activity, especially in prefrontal brain regions [19]. Animal studies confirm that chronic stress heightens the sensitivity of hypothalamic neurons to excitatory input, amplifying ACTH release and weakening glucocorticoid feedback [20]. This overactivation of the HPA axis contributes not only to hormonal imbalances but also to changes in gene expression and neurotransmitter systems (glutamate and GABA). Morover, elevated corstisol levels disrupt neurogenesis in the hippocampus—a brain region critically involved in the pathophysiology of depression [21]. These changes are thought to underlie many of the emotional and cognitive symptoms seen in major depression.

Prolonged hypercortisolemia exerts several deleterious effects on the cardiovascular system. Elevated cortisol levels contribute to endothelial dysfunction, increased arterial stiffness, and enhanced sympathetic nervous system activity, all of which promote hypertension and atherosclerosis [22]. Moreover, cortisol impairs glucose metabolism, promotes central adiposity, and worsens lipid profiles—factors that collectively increase the risk for coronary artery disease and heart failure [23]. Dysregulated cortisol circadian rhythm, such as flattened or reversed secretion patterns, have also been associated with increased cardiovascular mortality [24]. In a large cohort of patients undergoing coronary angiography, elevated morning serum cortisol was associated with an adverse cardiovascular risk profile and increased mortality, though the mortality risk was no longer significant after adjusting for conventional cardiovascular risk factors—suggesting that cortisol's effects may be mediated through these factors and potentially balanced by cardioprotective mechanisms [25].

Thus, chronic HPA axis activation and cortisol excess play a central role in linking psychological stress and mood disorders to the pathophysiology of cardiovascular diseases.

5.2. Autonomic Nervous System Imbalance

Imbalance in autonomic nervous system (ANS) regulation—marked by enhanced sympathetic tone and reduced parasympathetic (vagal) activity—is a central mechanism linking major depressive disorder (MDD) to cardiovascular disease (CVD). A key biomarker of this imbalance is heart rate variability (HRV) [26, 27]. The mechanisms underlying alterations in HRV in mental disorders are complex and multifactorial. Reduced HRV is commonly associated with an imbalance between sympathetic and parasympathetic nervous system activity, reflecting a dysregulated physiological response to stress. Chronic stress—prevalent across many psychiatric conditions—may lead to sustained sympathetic activation and parasympathetic withdrawal, ultimately resulting in lower HRV. In addition, neuroinflammation and structural brain changes, particularly within the prefrontal cortex and amygdala, have been implicated in autonomic dysfunction [28, 29]. These brain regions play a central role in emotional regulation and autonomic control, and their impairment may contribute to both the onset and progression of mental disorders [30]. Recent umbrella reviews confirm that individuals with depression consistently exhibit significantly lower HRV, a pattern strongly associated with

increased cardiovascular morbidity and mortality. Moreover, HRV is emerging as a predictive biomarker for depression and may serve as a target for early intervention [26, 27].

In the context of cardiovascular health, chronic sympathetic overactivation contributes directly to disease progression by increasing heart rate, raising blood pressure, inducing endothelial damage, and promoting arterial stiffness [31]. Parasympathetic withdrawal further compromises cardiac resilience and anti-inflammatory regulation, both of which are essential for cardiovascular health [32]. Neuroimaging studies reinforce this link by showing structural and functional changes within central autonomic networks (e.g. in the amygdala, cingulate cortex and prefrontal cortex), which regulate both emotional and cardiac responses [33].

Collectively, these evidences underscore that ANS dysregulation is not merely a bystander but an active contributor to the pathogenesis of both depression and CVD, making it a promising focus for integrated diagnostics and therapeutic interventions.

5.3. Inflammatory and Immune Pathways

Both MDD and CVD are chronic conditions in which inflammation plays a key pathogenic role. Individuals with MDD frequently show elevated levels of pro-inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor (TNF). For instance, a study of 6, 126 participants aged 45–69 in the Czech Republic found that those with significant depressive symptoms had higher plasma CRP levels than healthy controls [34]. A similar association between CRP levels and depression Osimo et al. observed in another study of 13 541 depressed patients. About a quarter of patients with depression show evidence of low-grade inflammation, and over half of patients show mildly elevated CRP levels [35]. Elevated levels of inflammatory markers, may result from increased concentrations of CRF in plasma and saliva observed in individuals with MDD [36].

The association between depression and inflammatory markers, notably CRP levels, has been extensively investigated, with meta-analysis highlighting the significance of IL-1β. Growing evidence supports a bi-directional relationship between inflammation and MDD, with elevated plasma levels of CRP, IL-6, and IL-1β correlating with a heightened risk of major cardiac events. Bai et al. found that among patients with CHD, the coexistence of elevated depression and high hs-CRP levels significantly increases the risk of noncardiac readmissions and composite adverse events, compared to either condition alone. Anxiety, however, did not influence these outcomes, underscoring the importance of prioritizing depression and systemic inflammation in CHD prognosis and management [37].

TNF-α, IL-6 and CRP play key roles in the inflammatory cascade driving atherosclerosis, promoting endothelial dysfunction, plaque buildup, and destabilization. Elevated levels of these biomarkers are strongly associated with increased risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death [38]. Fibrinogen (FIB), IL-6, CRP, and galectin-3 (Gal-3) are significantly associated with increased risk of developing cardiovascular disease (CVD) and may serve as valuable biomarkers for early identification and risk stratification in the general adult population. The combined use of multiple inflammatory biomarkers enhances predictive accuracy for CVD compared to individual markers alone, supporting their integration into future preventive and diagnostic strategies—though further studies across diverse populations are still needed [39].

5.4. Platelet Activation and Coagulation

The link between MDD and CVD is increasingly attributed to heightened platelet activation and a dysregulated coagulation cascade. Platelets, which store large amounts of serotonin (5-HT) in dense granules, become activated following a calcium influx, triggering the release of β-thromboglobulin, serotonin, platelet factor 4, and Ca^{2+}—which in turn promotes irreversible aggregation and thrombus formation. In MDD, abnormalities such as increased platelet serotonin receptors, reduced serotonin transporter function, and elevated platelet reactivity have been consistently reported [40]. Interestingly, selective serotonin reuptake inhibitors (SSRIs) demonstrate mixed in vitro effects on platelet function: while some studies show enhanced aggregation, others report inhibition—overall reflecting uncertain clinical significance [41]. Furthermore, activated platelets in MDD exhibit increased expression of integrins (e.g., GPIIb/IIIa), selectins, and adhesive proteins, enhancing endothelial binding and recruitment of inflammatory cells. These cells, including monocytes that differentiate into macrophages, uptake oxidized LDL and form foam cells, contributing to early atherogenesis and plaque formation [42]. Compounding these processes, dysregulation of the HPA axis—elevated cortisol and CRF—further sensitizes platelets, augmenting prothrombotic mediator release such as thromboxane A_2 [43]. Notably, MDD patients exhibit a prothrombotic platelet phenotype: larger mean platelet

volume, heightened aggregating responses, increased fibrinogen receptor expression, and elevated β-thromboglobulin (β-TG) and platelet factor 4 (PF4)—particularly in those with comorbid coronary artery disease [44]. Significantly, both PF4 and β-TG were higher in depressed compared to non-depressed CAD patients, as well as in depressed CAD patients compared to CAD- and depression-free controls [45]. Furthermore, an increased oxidative stress and hyperaggregability were observed in platelets of MMD cases compared to controls [46]. This persistent prothrombotic state likely contributes to their increased risk of myocardial infarction, stroke, and other cardiovascular events.

6. Behavioral and Lifestyle Factors

Depression is not only a psychological condition — it also drives patterns of behavior that significantly increase cardiovascular risk. Individuals suffering from MDD are more likely to engage in unhealthy behaviors such as smoking, physical inactivity, poor diet, excessive alcohol consumption, and irregular sleep patterns. These lifestyle choices contribute directly to well-established cardiovascular risk factors like obesity, hypertension, dyslipidemia, and insulin resistance.

Physical activity constitutes an established protective factor while sedentary behavior is increasingly recognized as an independent risk factor for cardiovascular diseases. Physical inactivity is more common in depressed individuals. A meta-analysis of over 191, 000 participants and more than 2 million person-years of follow-up demonstrated a clear inverse curvilinear dose-response relationship between physical activity and the risk of depression. The strongest protective effects were observed at lower levels of activity: adults engaging in just half of the recommended physical activity volume (4.4 mMET-hours/week) had an 18% lower risk of developing depression compared to inactive individuals. Meeting the full recommended amount (8.8 mMET-hours/week) was associated with a 25% reduction in depression risk. However, beyond this threshold, the benefits appeared to level off, and the certainty of further protection decreased. Importantly, the study estimated that if all less active individuals met current physical activity guidelines, approximately 11.5% of depression cases could be prevented [47]. Furthermore, chronic elevated cortisol, often observed in MDD patients, contributes to the accumulation of visceral fat by disrupting carbohydrate metabolism and promoting insulin resistance. This visceral adiposity not only increases the risk of obesity but also significantly elevates the likelihood of cardiovascular disease by fostering systemic inflammation, dyslipidemia, and endothelial dysfunction. Stress further exacerbates this risk by stimulating appetite and encouraging unhealthy eating behaviors, both of which intensify metabolic burden [48]. Prolonged sedentary behavior and increased cortisol levels may lead to endothelial dysfunction and impaired metabolic regulation, both of which accelerate atherosclerosis [49].

Conversely, many risk factors of CVDs promote the endothelial expression of chemokines, cytokines, and adhesion molecules. The resultant endothelial activation can lead to endothelial cell dysfunction (ECD). Endothelial dysfunction is a central mechanism in the development of cardiovascular disease (CVD), largely resulting from reduced production or impaired activity of endothelium-dependent hyperpolarization factors. Various pathological conditions—such as smoking, hypoxia, hyperlipidemia, and diabetes—can trigger or exacerbate endothelial dysfunction, thereby increasing cardiovascular risk [50]. The assessment of biomarkers related to endothelial function plays a crucial role in the early detection and prevention of CVD. Notably, based on the findings of studies, peripheral endothelial dysfunction (PED) appears to be a significant and independent predictor of developing major depressive disorder MDD. Among patients undergoing cardiovascular risk assessment, those who were later diagnosed with MDD had a notably higher prevalence of PED. Specifically, individuals with PED were more than twice as likely to develop MDD compared to those with normal endothelial function (OR = 2.3; 95% CI: 1.4–3.8). These results suggest a potential vascular contribution to the pathophysiology of depression and highlight PED as a clinically relevant biomarker [51]. Early identification of endothelial dysfunction may allow for the proactive management of at-risk individuals, potentially mitigating the onset or severity of depressive symptoms through earlier interventions.

Sleep disturbances — frequently comorbid with depression — add another layer of risk. Shortened sleep duration heightens sympathetic nervous system activity, reduces leptin secretion, and increases circulating ghrelin levels, resulting in persistent hunger and overeating [52]. These hormonal shifts, along with disrupted circadian regulation, overactivate the HPA axis and elevate glucocorticoid secretion, further impairing systemic inflammation, autonomic imbalance, and higher blood pressure, which is compounding cardiovascular risk. Collectively, these factors create a feedback loop linking depression, obesity, and heightened cardiovascular risk, as supported by recent evidence from large-scale cohort studies [48].

Additionally, depression can reduce motivation for medication adherence and engagement in preventive care, worsening prognosis in patients with existing CVD.

While these behavioral and lifestyle factors explain part of the link between depression and heart disease, they do not account for it entirely. Importantly, depression itself remains an independent predictor of adverse cardiovascular outcomes, even when controlling for lifestyle risks. This suggests a multifaceted relationship that combines behavioral, neuroendocrine, inflammatory, and psychosocial mechanisms.

7. Brain-Heart Axis and Psychocardiology

The concept of the brain–heart axis has gained increasing recognition in psychocardiology, highlighting the bidirectional communication between neural circuits and cardiovascular function. Central to this axis are cortical and limbic structures—particularly the anterior cingulate cortex (ACC) and the amygdala—which are critically involved in the regulation of emotional processing and autonomic output.

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or”broken heart syndrome, " is a transient left ventricular dysfunction typically triggered by acute emotional or physical stress. It mimics acute coronary syndrome but occurs in the absence of obstructive coronary artery disease. Stress is a core component of depressive disorders, both as a contributing factor to their onset and as a mechanism that exacerbates their course. The comprehensive analysis by Khan et al. offers indirect support for the hypothesis that brain responses to stress—particularly those involving pathways linking the thalamus, amygdala, and insula—contribute to sympathetic hyperactivity and subsequent cardiac dysfunction. Structural and functional variability within these neural circuits may underlie individual vulnerability to takotsubo syndrome in the context of acute stress. Among these regions, the insular cortex has been identified as a critical neuroanatomical link between the brain and the heart [53]. Compared to patients with acute coronary syndrome (ACS), those with takotsubo had a significantly higher prevalence of neurological or psychiatric disorders (55.8% vs. 25.7%) and a lower left ventricular ejection fraction at admission (40.7% vs. 51.5%, $P<0.001$) [54]. The left insula is predominantly involved in parasympathetic regulation, while the right insula governs sympathetic output; disruption of this balance due to neurological injury can precipitate cardiac complications. Notably, electrical stimulation of anatomically intact right and left insulae in epilepsy patients has been shown to significantly decrease heart rate and cardiac output while increasing stroke volume [55]. Recent evidence further underscores the clinical relevance of these findings. In a cohort of 415 patients with middle cerebral artery infarction, those with left hemispheric strokes involving the insula exhibited elevated cardiac injury biomarkers and transient cardiac dysfunction resembling takotsubo cardiomyopathy. Notably, the incidence of new-onset atrial fibrillation was tenfold higher in patients with right-sided insular strokes compared to left-sided cases [56]. Moreover, takotsubo syndrome may share pathophysiological mechanisms with other neurologically mediated stress-related conditions—such as depression.

Beyond acute syndromes, growing evidence supports the notion of the heart as an”emotional organ.” Emotional stress, through its neural correlates in the limbic system, can directly modulate cardiovascular parameters such as heart rate, contractility, and rhythm via autonomic pathways. Chronic dysregulation within this axis—manifested, for example, in persistent sympathetic overactivity and reduced vagal tone—has been associated with endothelial dysfunction, inflammation, reduced heart rate variability, and increased cardiovascular morbidity and mortality [57].

These findings underline the importance of integrating neuropsychological assessment into cardiovascular care. Understanding the mechanisms underlying the brain–heart interaction may improve prevention and treatment strategies for stress-related cardiac disorders.

8. Clinical Implications and Treatment Considerations

8.1. Antidepressant Use in CVD Patients

Pharmacological treatment of depression in patients with cardiovascular risk requires careful consideration. Although antidepressants—particularly SSRIs—are generally regarded as safer alternatives to older agents like tricyclic antidepressants, they are not entirely free from cardiovascular effects. Certain antidepressants may influence heart rate, blood pressure, cardiac conduction, or platelet function, and these effects can be clinically significant in individuals with pre-existing cardiovascular conditions. Therefore, when initiating antidepressant therapy in patients with known or suspected cardiovascular disease, clinicians should carefully weigh the benefits of symptom relief against potential cardiac risks, monitor for adverse effects, and consider individual patient factors such as age, comorbidities, and concomitant medications. Regular

cardiovascular monitoring and a personalized treatment approach are key to optimizing both mental and physical health outcomes in this population [58-72].

Table 1. Cardiovascular effects of common antidepressants.

Antidepressant drug	CV Safety Profile/Cardiac Effects	References
Sertraline	Well tolerated in post-MI, HF, and CHD patients; First-line in CVD + depression ↑ Flow-mediated dilation (FMD) – Improvement in endothelial function ↓ Major adverse cardiac events (MACE) – Lower rates of MI, stroke, angina, and HF onset ↓ Acute myocardial infarction (AMI) – Reduced risk compared to non-users and non-SSRI antidepressants ↓ Troponin I and CK-MB – Lower levels when combined with aerobic exercise ↓ Intima-media thickness (IMT) – Slower progression of atherosclerosis ↔ Heart rate, blood pressure – Stable ↔ Arrhythmias / 24h SDNN – No increase; ↓ CV mortality in post-MI depression – Depression = high mortality risk; treatment may reduce deaths by up to 50%	[58-61]
Citalopram	Pro-arrhythmic effects observed at therapeutic concentrations; QTc prolongation Age-related risk: ↓ drug clearance → ↑ serum levels with age (20% of patients >65 yrs on 10 mg escitalopram may exceed pro-arrhythmic threshold) ↑ LVEF, ↓ NT-proBNP Depression severity (↓ HAMD-24) in patients with elderly chronic HF and depression	[62-64]
Fluoxetine	May cause arrhythmias (AF, bradycardia), inhibits Na^{+}/Ca^{2+} channels, and may impair autonomic control in HF ↓ CHD Risk – Fluoxetine associated with 21% reduced risk of CHD relative to other SSRI prescriptions	[65, 66]
Venlafaxine	↑ CV Risk with High-Dose Venlafaxine (VEN) – Higher VEN doses linked to increased risk of arrhythmias, QT prolongation, IHD, heart failure, and cardiomyopathy. Elderly (≥75), males, comorbidities, and co-medication (e.g. quetiapine) raise risk of CV death. Standard doses not associated with higher mortality	[67, 68]
Amitriptyline	Use with caution in elderly / CVD patients ↑ MI risk (observational data) ↑ All-cause mortality in HF patients ↑ Trend toward sudden cardiac death (elderly) ↑ High cardiotoxicity in overdose orthostatic hypotension, heart rate variability, slow intracardiac conduction, induce various arrhythmias, and cause QTc (corrected QT) prolongation	[69, 70]
Bupropione	Anti-inflammatory vascular effects Effective for smoking cessation; neutral cardiovascular profile Minimal cardiac impact (modest rises in heart rate and blood pressure at higher doses); considered safe in stable coronary artery disease (CAD)	[71, 72]

8.2. Psychotherapy and Behavioral Interventions, Integrated Care Models

CVDs remain a leading global cause of morbidity and mortality, with substantial health and economic burdens. They are frequently associated with risk factors such as hypertension, central adiposity, and dyslipidemia, which are influenced not only by biological determinants but also by behavioral and psychosocial factors. Recognizing this, major professional bodies such as the European Society of Cardiology (ESC) and the American Heart Association (AHA) emphasize the importance of preventive strategies targeting lifestyle and psychological well-being to reduce cardiovascular risk and improve long-term outcomes. A growing body of evidence highlights the role of psychosocial factors, such as depression or anxiety, not only in the onset of CVD but also in its progression and prognosis. Psychological distress has been associated with increased risk of recurrent cardiac events, poor adherence to treatment, and higher mortality rates. In response, current ESC and AHA guidelines advocate for routine screening of psychological symptoms in individuals with CVD to ensure comprehensive, patient-centered care [73]. To address the psychological burden in CVD populations and promote behavior change, a range of psychological interventions have been implemented, including cognitive behavioral therapy (CBT). CBT interventions in CVD populations aim to reduce psychological distress, improve treatment adherence, and facilitate lifestyle changes that support cardiovascular health. Core techniques include cognitive restructuring, behavioral activation, problem-solving, and relaxation training. Regarding physiological risk factors, elevated blood pressure and dyslipidemia are critical contributors to CVD development and progression. Hypertension, often linked with psychological distress, is one area where CBT may offer benefit. Meta-analytic evidence suggests that CBT can reduce blood pressure in hypertensive CVD patients, though it appears less effective in individuals with established CHD. Similarly, while CBT may reduce total cholesterol (TC) in hypertensive patients, it does not significantly impact lipid levels in those with CHD. These findings indicate that while CBT may help manage certain cardiovascular risk factors, its effects on lipid profiles in CVD populations require further study. CBT's influence on health-related behaviors in CVD patients was also examined. Modifiable lifestyle factors—such as smoking, diet, physical inactivity, and poor sleep—are well-established contributors to cardiovascular risk. CBT appears effective in improving sleep quality and promoting healthier behaviors in hypertensive individuals. However, its impact on exercise capacity, medication adherence, or self-care behaviors in patients with heart disease is inconsistent [74]. These mixed outcomes may reflect methodological limitations of the included meta-analyses, such as small sample sizes and variability in CBT intervention design (e.g., duration, content, delivery method). Moreover, the meta-analysis by Yu et al., which included 11 studies (1, 259 patients) found that CBT significantly reduced cardiovascular adverse events, depression, and anxiety scores in patients who have ACS with anxiety and depression [75]. Meta-analysis of 25 trials (n = 8119) showed that psychological interventions, particularly those based on CBT and Positive Psychology Therapy (PPT), significantly reduced the risk of adverse cardiovascular outcomes in patients with CAD. Specifically, these interventions lowered the risk of any cardiovascular event, MI, and the duration and intensity of angina symptoms compared to control groups. However, no significant effects were observed on other primary clinical outcomes, laboratory values, or anthropometric measures [76]. Furthermore, findings from other studies suggesting that targeted psychological interventions can support dietary modifications in patients with CVD, potentially serving as a valuable component of public health strategies [77].

Cardiac rehabilitation programs (CRPs) are comprehensive, structured interventions aimed at supporting recovery in patients with cardiovascular disease, including those with myocardial infarction, heart failure, or following procedures such as coronary artery bypass grafting. By combining supervised exercise, health education, and psychological support, CRPs serve as a key component of secondary prevention, effectively reducing mortality and hospital readmissions while enhancing functional capacity and health-related quality of life (HRQoL). Findings highlight a strong link between psychological health and cardiovascular outcomes—patients experienced significant reductions in anxiety and depression following CRP, in line with AHA recommendations for integrated cardiac care. The studies showed that individuals with higher baseline anxiety and depression benefitted less in terms of HRQoL, emphasizing the need to address mental health early in rehabilitation. Adaptive coping strategies were associated with better psychological outcomes, reinforcing the value of psychological support within CRP. Improvements in anxiety mirrored previous findings showing exercise therapy's role in reducing psychological distress in cardiac patients. However, depressive symptoms at baseline strongly predicted worse long-term mental health outcomes, underlining the importance of early screening and intervention. HRQoL significantly improved post-rehabilitation, particularly in social and mental domains, supporting the dual benefit of CRPs for both physical and psychological health. Studies confirms that integrating psychological care into CRP enhances recovery [78].

Consultation-liaison psychiatry (CLP), also known as psychosomatic medicine, is a subspecialty of psychiatry focused on the diagnosis and management of psychiatric conditions in medically ill patients. CL psychiatrists work within general hospitals, collaborating closely with medical teams to address the psychological and behavioral aspects of physical illness. In the context of cardiovascular disease, CLP is particularly important, as conditions such as depression, anxiety, and adjustment disorders are highly prevalent among cardiac patients and can significantly worsen prognosis. CL psychiatrists assess and treat these comorbidities, support medication adherence, and help patients adjust to chronic illness or disability. They also contribute to decision-making in complex cases, evaluate capacity for informed consent, and assist in managing emotional distress in acute settings such as post-myocardial infarction or during rehabilitation. Integrating CLP into cardiovascular care improves patient outcomes, enhances quality of life, and supports holistic treatment approaches [79].

9. Discussion and Conclusions

Depression and CVDs are two of the most prevalent and burdensome health conditions worldwide, with a well-documented bidirectional relationship rooted in shared biological, behavioral, and psychosocial mechanisms. The overlap between these disorders is mediated by neuroendocrine dysregulation, autonomic nervous system imbalance, inflammation, and platelet activation, as well as by maladaptive health behaviors such as smoking, poor diet, and physical inactivity. These factors contribute to both the development and progression of CVD in individuals with depression and vice versa. Given this complex interplay, early recognition and integrated management of depression in patients with cardiovascular risk are essential. Antidepressant treatment—particularly with SSRIs—can be safely used in most CVD patients, but should be tailored carefully with cardiovascular monitoring. Psychotherapeutic interventions, especially CBT, have demonstrated efficacy in reducing psychological distress, improving adherence to healthy behaviors, and lowering cardiovascular event rates. CRPs, which combine physical training with psychological support, represent a valuable secondary prevention tool that can improve both HRQoL and mental health outcomes. Evidence suggests that individuals with higher baseline depression or anxiety may require more targeted psychological support to fully benefit from rehabilitation. Moreover, CLP plays a key role in bridging the gap between mental and physical healthcare in hospital settings. By addressing psychiatric comorbidities in patients with CVD, CLP contributes to improved prognosis, greater adherence to treatment, and better long-term outcomes. Collectively, integrating mental health care into cardiovascular prevention and treatment strategies is not only clinically justified but essential for holistic, patient-centered care. Further research should focus on refining multidisciplinary interventions and identifying biomarkers that can personalize treatment approaches in psychocardiology.

Declarations

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All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Ethical Approval: This study did not involve human participants or animals. Therefore, approval by an ethics committee was not required.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflict of Interest Statement: No conflicts of interest to declare.

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