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Review Article

Sertraline in depressed patients with or at risk for coronary heart disese: a systemic review

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Abstract: Background and Aims: Depression is a prevalent comorbidity among patients with coronary heart disease (CHD). While recent studies have hinted at a possible association between CHD and antidepressant medications like sertraline, the existing evidence remains inconclusive. To investigate this potential link, we conducted a comprehensive systematic review. Methods: We systematically searched PubMed, Google Scholar, and Scopus for relevant articles published up to March 2023. After a thorough screening of titles and abstracts, 12 studies were included in our review. Results: The included studies, spanning from 1999 to 2021, comprised 11 randomized controlled trials (RCTs) and one pilot study. A total of 2767 participants with major depressive disorder and a history of cardiovascular disease or at risk for such events were included. The majority of these studies demonstrated improvements in mood status among patients treated with serotonin-targeting antidepressants and a reduced risk of cardiovascular events, as measured by various outcomes. While some cardiac adverse effects were observed with serotonin treatment, these did not reach statistical significance. Conclusion: Our findings provide evidence supporting the beneficial effects of serotonin-targeting antidepressants for both depressive symptoms and the prevention of coronary adverse outcomes. These results highlight the potential value of serotonin-based treatments for depression in high-risk populations.

Keywords: Depression, coronary heart disease, sertraline, cardiac disease, SSRIs

Introduction

Depression, a prevalent neuropsychiatric condition characterized by persistent low mood and anhedonia, significantly impacts all facets of an individual's life [1]. Approximately 3.8% of the global population experiences depression, with higher rates observed in adults and older adults. The substantial burden of depression on mental health is underscored by its ranking

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as the second leading cause of years lived with disability (YLDs) and thirteenth among the top 25 leading causes of disability-adjusted life years (DALYs) globally in 2019 [2]. Depression is closely intertwined with physical health and influenced by a complex interplay of biological, psychological, and social factors. Stress, smoking, alcohol consumption, and physical inactivity are notable contributors to depression. Furthermore, these factors have been identified as significant risk factors for various physical health conditions, including diabetes mellitus, cardiovascular diseases, respiratory diseases, and cancers [1, 3].

Depression and coronary heart disease (CHD) are two interconnected conditions with significant implications for health outcomes. Individuals with depression or at risk for CHD have a heightened risk of experiencing adverse cardiac events, including increased morbidity and mortality. The frequent co-occurrence of these conditions underscores their substantial burden on global health [4]. The complex interplay between depression and CHD highlights depression as a critical independent psychosocial risk factor for CHD [5]. Additionally, individuals with depression who have experienced or are at risk for CHD face a poorer prognosis and increased likelihood of adverse outcomes [6-10]. Several factors contribute to the comorbidity of depression and CHD, including early childhood fearful-avoidant personality attachment styles [11], sympathetic dysregulation, and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis [12, 13], all of which are associated with poor prognosis in both conditions. Depression can exacerbate the sympathetic nervous system, as evidenced by elevated levels of catecholamines in the urine. This heightened sympathetic activity can lead to damage to the myocardium, coronary arteries, and platelets [14]. Hyperactive platelets and decreased platelet serotonin have been implicated in the development and progression of depression [14], CHD [4], diabetes [4, 15], HPA-axis dysfunction [12, 15], and systematic inflammation [16].

Given the adverse outcomes associated with depression in patients with or at risk for CHD, including poor prognosis, reduced quality of life, and increased risk of complications, effective management of depression is crucial in this population [8]. Appropriate treatment for depression can potentially mitigate the negative impacts of this condition on cardiovascular health [17, 18]. Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) have emerged as effective, safe, and first-line medications for depressive disorders in patients with CHD. SSRIs have demonstrated their ability to significantly reduce CHD-associated morbidity and mortality [19]. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial further solidified the efficacy of SSRIs in reducing the risk of myocardial infarction [20]. Sertraline, a specific SSRI, stands out as a particularly promising treatment option due to its favorable cardiovascular safety profile, tolerability, and demonstrated effectiveness in improving depressive symptoms, cardiovascular outcomes, and quality of life. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) provided compelling evidence for the importance of treating depression in patients with CHD, highlighting the significant association between untreated depression and increased mortality risk [21]. While further research is warranted to fully elucidate the effects of sertraline on cardiovascular outcomes in patients with CHD, the available evidence suggests that it is a promising treatment option with potential benefits beyond the management of depression [22]. To the best of our knowledge, this is the first systematic review to comprehensively examine the effects of sertraline in depressed patients with or at risk for CHD. Our review will provide a critical analysis of the available evidence, shedding light on the potential benefits of sertraline treatment in this population.

Methods

Search strategy

This systematic review was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The design protocol was registered in OSF (available at https://osf.io/bjqku). A comprehensive search was performed on March 14, 2023, across electronic databases including PubMed, Google Scholar, and Scopus. We employed advanced search strategies with appropriate Boolean operators tailored to each database to retrieve relevant articles. We com-

Table 1. Search strategies for Pubmed, Scopus and Google scholar Databases

Search engine	Search strategy	Additional filters
PubMed	("Sertraline"[Mesh]) AND (("Depression"[Mesh]) OR ("depressed"[tiab])) AND (("Coronary Disease"[Mesh]) OR ("Heart"[Mesh]))	English March 13th, 2023 25 results
Scopus	((TITLE-ABS-KEY (depressed) OR TITLE-ABS-KEY (depression))) AND ((TITLE-ABS-KEY (coronary AND heart AND disease) OR TITLE-ABS-KEY (heart))) AND (TITLE-ABS-KEY (sertraline))	English March 13th, 2023 1675 results
Google scholar	All in title: sertraline depressed OR depression "coronary heart disease"	English March 13th, 2023 90 results

bined search terms and MeSH headings related to "sertraline", "depression", "coronary heart disease", and "heart" (**Table 1**). No restrictions were placed on publication date or language. Reference lists of identified articles and relevant reviews were also hand-searched for additional studies. Titles and abstracts of retrieved articles were screened for eligibility based on pre-defined criteria. Studies were included if they: 1. Investigated the use of sertraline in depressed patients. 2. Assessed the impact of sertraline on coronary heart disease outcomes. 3. Employed any study design (e.g., randomized controlled trial, observational study).

Two independent reviewers assessed the eligibility of studies. Discrepancies were resolved through discussion or by consulting a third reviewer. Data extraction forms were used to collect relevant information from included studies, including study design, participant characteristics, interventions, and outcomes.

Inclusion and exclusion criteria

Articles meeting the following inclusions were included: 1) Randomized control trial studies that assessed the effect of sertraline on depressed patients with or at risk of cardiovascular disease. 2) Studies that provided adequate information on study design, participant characteristics, and outcomes. 3) Articles written only in English. Articles meeting the following criteria were excluded: 1) Studies based on cell lines and animals. 2) Reviews case reports, abstracts, book chapters, and letters to the editor.

Quality assessment and data extraction

The Cochrane Risk of Bias assessment tool's RCT bias checklist was utilized to evaluate the methodological quality of included studies. First, Titles and abstracts were reviewed to identify studies that aligned with the research question. Eligible studies underwent a thorough examination of their full text to confirm their suitability for inclusion. For each selected study, the following information was extracted: the author and year of publication, country, sample size, mean age and sex of participants, the dose of sertraline, follow-up time, adjustments, and outcomes.

Results

A total of 2767 studies were initially identified through the search strategy. After removing duplicates, 1682 articles remained for further review. Following a thorough assessment of abstracts, 1615 studies were excluded for not meeting the inclusion criteria. Subsequent full-text screening led to the exclusion of an additional 55 studies, primarily due to methodological limitations or lack of relevant data. Ultimately, only 12 studies met all inclusion criteria and were included in the systematic review (**Figure 1**).

The included studies were published between 1999 and 2021 and comprised 11 randomized controlled trials (RCTs) and one pilot study. A total of 2767 participants diagnosed with major depressive disorder and a history of cardiovascular disease or at risk for such events were included. Detailed methodological and outcome data for each study are presented in **Table 2**.

Patient characteristics and treatment

Nine studies [21, 23-30] included patients who were diagnosed with both depression and ACS in the last 30 days prior to the start of treat-

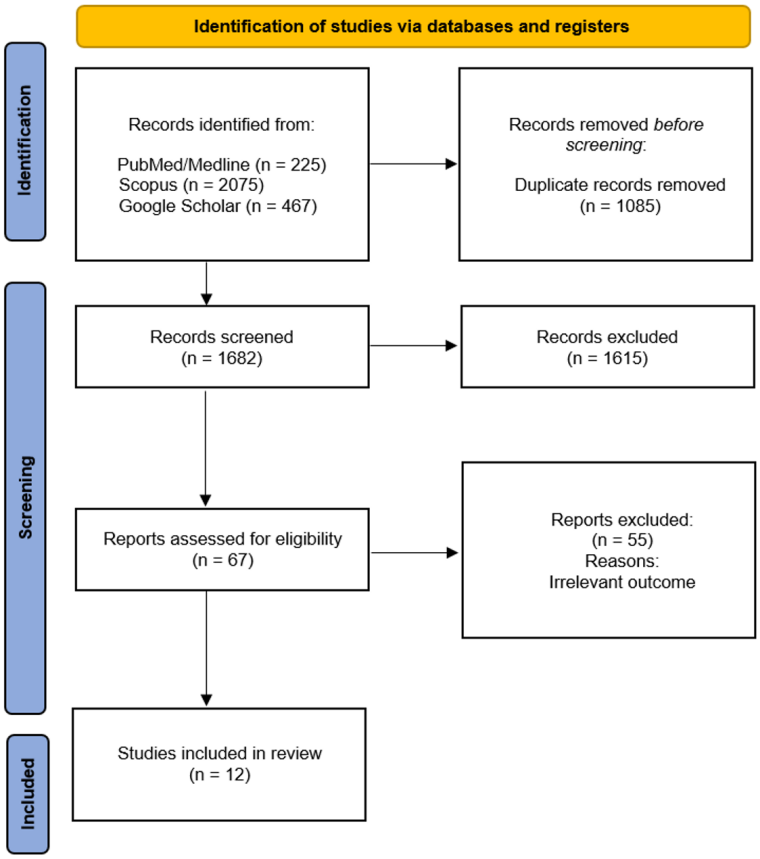

Figure 1. PRISMA flow diagram of study.

ment. One study [31] included depressed patients with heart failure, and two other studies enrolled depressed diabetic patients and measured factors that could be interpreted in light of predisposition to cardiovascular events [32, 33]. Women comprised the majority (more than 50%) in four studies [21, 29, 32, 33], and the mean age of patients fell between 51.8 to 62.9.

In all studies except for three [23, 32, 33], serotonin was given to participants as sertraline, initiating from 50 mg/day to 200 mg/day throughout treatment. The follow-up duration ranged from 2 months to 6 months. Only two studies lacked the placebo group [28, 33]. Moreover, three studies [21, 24, 31] discussed the worsening effect of serotonin (fatal or non-fatal) on the cardiovascular status of patients. Overall, among 680 sertraline recipients, 46 deaths occurred. Of other cardiovascular adverse outcomes, angina and exacerbation of HF were the most prevalent; however, none of these events were significantly different from the placebo group.

Effectiveness of serotonin in treating depression

As for the effectiveness of serotonin in treating depression, nine studies [21, 24-26, 28, 30-33] reported improved depressed mood evaluated by Hamilton Depression Rating Scale (HAM-D) or Beck's Depression Inventory (BDI), or clinical global impression - improvement scale (CGI-I). Two studies [23, 30] reported improved quality of life in those given sertraline assessed by the 36-Item Short Form Health Survey.

Potential benefits of serotonin in reducing the risk of heart disease

As for the potential benefits of serotonin in reducing the risk of heart disease, studies have used different measures. According to the evidence, significant improvement was seen in the following parameters: flow-mediated dilation of the brachial artery (increased) [26, 29], Atherosclerotic cardiovascular disease (ASCVD) score (decreased) [29], intima-media thickness (decreased) [29], standard deviation of the NN (R-R) intervals (increased) [25], Platelet/Endothelial Biomarkers (only beta-thromboglobulin and E-selectin which were decreased) [27], inflammatory biomarkers (decreased IL-6 and CRP) [26]. One study supported the relationship between the effectiveness of treatment for depression and the improvement of cardiovascular indices [26].

Adjustment for potential confounders

Finally, four studies mentioned adjusting outcomes for potential confounders, detailed in **Table 2**.

Discussion

Existing research has established a strong link between depression and heart failure. A shared neuroendocrine basis may contribute to the co-occurrence of these two conditions. Evidence

Table 2. Characteristics of included studies

Author (year)	Country	Study design	Participants	Completed the study	Mean age	Sex (number of female)	Dose of sertraline	Duration of follow up	Cardiovascular adverse events following treatment	Adjustment for	Outcome
Sherwood et al. (2016) [29]	USA	RCT	MDD without known CHD (49 sertraline/49 placebo)	42/35	S: 51.8 Placebo: 51.2	76% (37) 78% (38)	50-200 mg/d	4 months	None	Age, sex, severity of depression, respective pretreatment level of each outcome, baseline arterial diameter for FMD	Cardiovascular indices: Up FMD, Down IMT, Down ASCVD
Pizzi et al. (2009) [26]	Italy	RCT	CHD patients with depression (50 sertraline/50 placebo)	47/48	Sertraline: 57.4 Placebo: 56.3	53.1% (25) 47.9% (23)	50-200 mg/d	20-Week	None	Age, BMI, medication (for blood pressure and lipid control), blood Pressure, lipid levels	Mood: down BDI (compared to both placebo and baseline) Inflammatory markers: down CRP, down IL-6 Cardiovascular: up FMD Note: all outcomes were significant in relation to each other
Khameslo et al. (2021) [23]	Iran	RCT	Depressed patients with a history of CABG (8 sertraline/8 placebo)	8/8	53.87	Not mentioned	25-50 mg/d	2 months	None	Not mentioned	Quality of life: up SF-36 score Cardiovascular disease biomarker: no significant change in TPN-1 and CK-MB levels
Glassman et al. (2002) [21]	7 countries	RCT	Depressed patients with ACS in last 30 days (186 sertraline/183 placebo)	133/137	Sertraline: 56.8 Placebo: 57.6	69 (37%) 66 (36%)	50-200 mg/d	24 weeks	2 deaths, 5 MI, 5 CHF, 2 stroke, 26 anginas (NS)	Not mentioned	Mood: down HAM-D (not significant in those with moderate depression and no history of symptoms prior to ACS) Sertraline was safe regarding cardiac indices: no significant change in LVEF, HR, BP, ECG intervals, SDNN
Swenson et al. (2003) [30]	USA	RCT	Depressed patients with ACS in last 30 days (184 sertraline, 183 placebo)	184/183	56.8 57.6	37% (68) 36% (66)	50-200 mg/d	24 weeks	Not mentioned	Age, baseline HAM-D total score, previous episodes of depression, index cardiac syndrome (AMI vs unstable angina), and Killip class	Quality of life: up SF-36 Up Q-LES-Q (significant only in cases of recurrent depression) Mood: down HAM-D Down BDI Down CGI
Mcfarlane et al. (2001) [25]	Canada	RCT	Depressed patients with MI in last 30 days (19 sertraline, 19 placebo)	12/15	62	33% (4) 47% (7)	50 mg/d	22 weeks	Not mentioned	Age, sex, BMI, LVEF, previous MI, smoker, diabetes, hypertension, Anti-hypertensive medication, PTCA, CABG, IDD score	Mood: down IDD Cardiac indices: up SDNN No significant change in MSSD, LF/HF ratio, LF power *Note: mood improvement and increase of SDNN were not related

Serebruany et al. (2003) [27]	USA	RCT	Depressed patients with ACS in last 30 days (25 sertraline, 39 placebo)	25/39	57.8 57.4	44% (11) 38.5% (15)	50-200 mg/d	24 weeks	Not mentioned	Not mentioned	Down E-selectin, down beta TG level, no significant change in PF4, PECAM-1, P-selectin, Tx, 6-Keto-PG-F1alpha (*Note: there was an overall trend of decrease in all parameters)
Carney et al. (2004) [24]	USA	RCT	Depressed patients who survived at least 6 months after MI (585 sertraline, 508 usual care)	409/449	58.50 59.26	47.9% 52.6%	50-200 mg/d	12 months	28 Deaths (NS)	Age, minority status, diabetes, LVEF, creatinine level, prior MI, history of pulmonary disease, prior TIA or stroke, history of CHF, and CABG	Mortality: No significant change in mortality rate
Shapiro et al. (1999) [28]	Canada	Pilot study	Depressed patients with MI in last 30 days (26 sertraline)	19	57.9	42.3% (11)	50-200 mg/d	16 weeks	None	Not mentioned	Mood: down HAM-D, down BDI, down CGI Cardiovascular parameters: no significant change in HR, BP, LVEF, ECG components Coagulation parameters: no significant change in PTT, INR, BT
Echeverey et al. (2009) [32]	USA	RCT	Depressed diabetic patients (45 sertraline, 44 placebo)	39/36	52 53	73.3% (33) 72.7% (32)	50-100 mg/d	6 months	None	Not mentioned	Mood: down HAM-D, down pain Scale (Note: only to baseline and not to placebo) Risk factors for cardiovascular events: down HbA1c, down BP
Rachdi et al. (2009) [33]	Tunisia	RCT	Depressed diabetic patients (38 sertraline)	33	58.4	63.6% (21)	50 mg/d	12 weeks	None	Not mentioned	Mood: down HAM-D Anthropometric parameters: down weight, down waist circumference, down BMI, down FBS, down PPG
O'Connor et al. (2010) [31]	USA	RCT	Depressed patients with CHF (234 sertraline, 235 placebo)	138/96	62.9 61.4	43.2% (101) 37.9% (89)	50-200 mg/d	12 weeks, 6 months	12 weeks follow up: 16 deaths, 1 AMI, 4 arrhythmia, 2 CVA, 19 exacerbation of HF, 7 UA (NS) 6 months follow up: 10 AMI, 17 arrhythmias, 6 cardiac syncope, 10 CVA, 64 exacerbations of HF, 23 UA	Not mentioned	Mood: down HDRS total score (only to baseline)

suggests that the presence of major depression in patients with heart failure can adversely affect clinical outcomes and increase treatment costs [34]. This systematic review of 1692 participants is conducted to assess the efficacy and cardiovascular safety of sertraline in patients with depression.

Several mechanisms may contribute to this association. Behavioral patterns commonly observed in depressed individuals, such as unhealthy lifestyle choices, can contribute to the development or exacerbation of traditional cardiac risk factors. Depressed cohorts often exhibit elevated levels of C-reactive protein and other markers of immune dysfunction, which can lead to endothelial dysfunction and altered platelet aggregability. Additionally, depression and stress may induce dysregulation of the autonomic nervous system. The psychological stress associated with depression can trigger the activation of cardiac sympathetic nerves [6]. Activation of these nerves has been linked to reduced blood circulation, an elevated heart rate, enlargement of the left ventricle, heart attacks, and sudden cardiac death [35-38]. Depression may also cause imbalances in the hypothalamic-pituitary axis, with depressed patients typically showing higher cortisol levels, a known risk factor for metabolic syndrome [39]. Metabolic syndrome contributes to abnormalities such as glucose intolerance, high cholesterol, and weight gain [40, 41]. These factors reinforce the idea that depression may contribute to the onset of cardiovascular disease, as demonstrated in the results of our study. Moreover, inflammation was shown as a common mediator between depression and cardiovascular disease [42]. Depression may contribute to cardiovascular disease by increasing hypercoagulability, inflammation, and the development of traditional risk factors like obesity and medication noncompliance [43].

Several studies have demonstrated the positive effects of sertraline on cardiovascular outcomes in depressed patients with or at high risk for coronary heart disease. A randomized, double-blind, placebo-controlled trial of 100 patients with coronary heart disease and depression revealed a significant improvement in flow-dependent endothelium-mediated dilation (FMD) among patients treated with sertraline compared to the placebo group. Previous research has established a link between FMD and an increased risk of cardiovascular disease [26, 44].

A randomized controlled trial of 500 patients with major depressive disorder (MDD) and heart failure (HF) were randomly assigned to receive sertraline or placebo. Patients treated with sertraline experienced lower rates of adverse cardiac events, including death, myocardial infarction (MI), stroke, worsened angina, and onset of congestive heart failure [45]. Compared to non-use of antidepressants or non-SSRI antidepressants, patients receiving SSRIs, such as sertraline, were significantly less likely to experience acute myocardial infarction (AMI) [45, 46]. Additional studies have suggested that SSRIs may also be associated with a slight reduction in the risk of ischemic stroke [47, 48]. However, some studies have not found a clear link between SSRI use and the risk of AMI or stroke [49, 50]. The potential mechanisms underlying the reduced risk of AMI associated with SSRI use may involve either their effects on platelet activation or their ability to improve depressive symptoms. While both mechanisms may contribute, the latter is more likely based on the available evidence. It's important to note that the risk of AMI may increase one month after discontinuing SSRI therapy. This could be attributed to withdrawal symptoms such as dizziness, anxiety, fatigue, and nausea [22, 51-54].

Standard deviation of all 24-hour NN intervals (SDNN) is a recognized predictor of cardiac mortality. In post-MI patients with depression, treatment with sertraline was associated with a significant increase in SDNN [25]. These findings suggest that antidepressants can effectively improve heart rate variability (HRV) parameters [25, 55, 56]. This positive impact on HRV may lead to improved clinical outcomes. The cardiovascular effects of antidepressants likely play a crucial role in this regard. SSRIs like sertraline generally do not exhibit anticholinergic or peripheral autonomic side effects, such as postural hypotension or proarrhythmic effects.

Enhanced cardiac contractility without an excessive calcium burden, attributed to the hyperactivation of 5-HT2A receptors, improved endothelial function resulting from increased

nitric oxide bioavailability, and the myocyte-rescue effect associated with serotonergic receptors are potential mechanisms underlying the beneficial clinical outcomes observed in HF patients treated with SSRIs and beta-blockers [34].

A combination of sertraline and aerobic exercise can lead to a reduction in troponin I and CK-MB levels, indicating less myocardial injury. Sherwood et al. demonstrated that both sertraline and exercise can improve CHD risk factors, including enhanced vascular endothelial function (brachial artery), reduced atherosclerosis development, and decreased 10-year risk of atherosclerotic cardiovascular disease (ASCVD) progression [23]. Carotid intima-media thickness (IMT) is a well-established marker of atherosclerosis and a potential predictor of cardiovascular events. Each 0.1-mm increase in IMT is associated with a 10-15% increase in the risk of myocardial infarction and a 13-18% increase in the risk of stroke [29, 57]. Swenson et al. observed that sertraline can positively impact the quality of life and functional status of patients who have recently experienced acute coronary syndrome and are diagnosed with major depression [30].

A study on 26 patients with severe depression following MI. Cardiovascular measures were assessed at baseline and at the end of sertraline treatment. No significant changes were observed in PR or QRS intervals, suggesting no impairment of the cardiac conduction system [28]. SSRIs can have a modest effect on heart rate [58]. A study reported a decrease in baseline heart rate by 3-4 beats/min during treatment with fluoxetine and paroxetine [59]. In a reported case, systematic bradycardia was observed with the combined use of fluoxetine and metoprolol [60]. However, in Shapiro et al.'s study, the average heart rate did not decrease, and significant bradycardia occurred in only one patient, even prior to initiating antidepressant therapy. Blood pressure remained stable during sertraline therapy, and there were no signs of orthostatic hypotension [28, 32]. Additionally, sertraline did not exhibit any antiarrhythmic effects on the heart. Depression occurs frequently after MI, with a prevalence of 15-20%. Notably, nearly half of all mortalities within the first six months post-MI occur in patients with depression. Therefore, effective treatment of depression is crucial to reduce cardiac mortality [28]. Based on the findings of this study, sertraline appears to be a suitable antidepressant option with minimal effects on heart rate and blood pressure.

A randomized, double-blind, placebo-controlled trial evaluated the cardiovascular safety of sertraline in post-MI patients with major depression. The study found no significant differences between the sertraline and placebo groups in cardiovascular measures, including blood pressure, heart rate, arrhythmias, left ventricular ejection fraction, and 24-hour ECG-derived SDNN [61]. Importantly, the rate of life-threatening cardiovascular events was numerically lower among patients treated with sertraline, although this difference did not reach statistical significance. Sertraline did not lead to any adverse medical conditions [21, 62]. In contrast to SSRIs, tricyclic antidepressants have been associated with an increased risk of MI in patients.

In the SADHART-CHF trial, sertraline was found to be safe for use in patients with heart failure. However, when compared to placebo, sertraline treatment did not demonstrate a significant improvement in cardiovascular events or a reduction in cardiovascular status among patients with heart failure and depression [31].

This systematic review provides a comprehensive overview of randomized controlled trials published between 1999 and 2021 that investigated the effects of sertraline in depressed patients with or at high risk for coronary heart disease. To our knowledge, this is the first systematic review to collate the available evidence on this topic. Due to the heterogeneity among the included studies, meta-analysis was not feasible.

A substantial body of evidence supports the association between depression and an increased risk of CVD and MI. Depression is a prevalent comorbidity in patients with heart disease and is linked to adverse cardiovascular outcomes. Sertraline is often considered a first-line antidepressant for patients with a history of heart disease due to its favorable cardiovascular safety profile. Additionally, sertraline has been shown to have beneficial effects on various cardiovascular measures in depressed patients.

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None.

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