

Efficacy and Safety of Psychopharmacological Interventions for Heart Failure with Comorbid Depression/Anxiety: A Systematic Review

¹Majed Abdul Karim Rahal, ²Tarek Hammad, ³Nawaf Abdullah Alqurashi, ⁴Hamzah Ahmed Mohammed Bahes, ⁵Abdullah Saeed Al-Nmr, ⁶Ahmad Ali Alomar, ⁷Fatmah Saeed Abdullah al Qahtani, ⁸Rana Faisal Badawi, ⁹Husam Ibrahim Matar Abu Tayyem, ¹⁰Muath Thaar Aladhyani

¹Abha International Private Hospital

sailingscientific@gmail.com

Cardiology Registrar ST4 Ninewells Hospital Uk

myadalwfy177@gmail.com

³Taif university Medical intern Medicine and Surgery

⁴Medicine and surgery level 10 Kku Saudi Arabia Abha city

⁵Medical student King Khalid University

⁶General Practitioner Wahat Al Shifa Medical Complex

⁷Psychologist Armed Forces Hospitals Southern Region

⁸Psychologist Armed Forces Hospitals Southern Region

⁹Mutah university 5th year medical student

¹⁰General physician Shaqra University

HOW TO CITE: ABSTRACT:

Majed Abdul Karim Rahal, Tarek Hammad, Nawaf Abdullah Alqurashi, Hamzah Ahmed Mohammed Bahes, Abdullah Saeed Alnimer, Ahmad Ali Alomar, Fatmah Saeed Abdullah al Qahtani, Rana Faisal Badawi, Husam Ibrahim Matar Abu Tayyem, Muath Thaar Aladhyani (2026). Efficacy and Safety of Psychopharmacological Interventions for Heart Failure with Comorbid Depression/Anxiety: A Systematic Review. International Journal of Special Education, 41(18s), 185-199

Background

Depression and anxiety are highly prevalent among patients with heart failure (HF), significantly worsening quality of life, self-care behaviors, and mortality risk.

Psychopharmacological treatments, particularly antidepressants, are frequently prescribed; however, their cardiac safety and clinical efficacy remain debated.

Objective

This systematic review aimed to evaluate the efficacy and safety of antidepressant pharmacotherapy compared with psychotherapeutic and usual-care interventions in patients with HF or coronary artery disease (CAD) comorbid with depression or anxiety.

Methods

Following PRISMA 2020 guidelines, a systematic search was performed across PubMed, Scopus, Embase, Web of Science, and Google Scholar from 2000–2025. Eleven randomized controlled trials (RCTs) met inclusion criteria. Data were synthesized narratively across domains: antidepressant efficacy, comparative effectiveness with psychotherapy, cardiac safety, and

quality of life.

Results

SSRIs (e.g., sertraline, citalopram, fluoxetine, escitalopram), and atypical antidepressants (mirtazapine, bupropion) all decreased symptoms of depression by 30 per cent to 50 per cent. Cognitive-behavioral therapy and behavioral activation had similar effects. Escitalopram lessened long-term major adverse cardiac events (HR = 0.69, $p = .03$). In trials, the antidepressants were tolerated positively with no major adverse outcomes in the cardiac system. Quality of life and symptom control were further increased with collaborative or nurse-led models of care..

COPYRIGHT STATEMENT:

Copyright: © 2026 Authors.

Open access publication under the
terms and conditions
of the Creative Commons Attribution
(CC BY)

license (<http://creativecommons.org/licenses/by/4.0/>).

Conclusions

Antidepressants are safe and effective in HF with comorbid depression or anxiety, especially with multidisciplinary and behavioural interventions. Individualized, joint interventions could maximize mental and cardiac performances.

Keywords: heart failure, depression, anxiety, antidepressants, psychotherapy, selective serotonin reuptake inhibitors, cardiac safety, quality of life, cognitive behavioral therapy, collaborative care

Introduction

Heart failure (HF) is among the most frequent contributors to morbidity and mortality on the globe and is becoming a developing issue in the public health because of the age-related population growth and prolonged survival of people with cardiac-related diseases. The latest world studies suggest that more than 64 million individuals have HF, and the prevalence continues to increase in both high- and middle-income nations (Savarese et al., 2023). Its chronic and progressive progression and a high comorbidity burden make this condition costly in terms of healthcare and cause frequent hospital readmissions (Shahim et al., 2023). Even with the significant progress in pharmacological and device-based rehabilitation, HF remains linked to low-quality life, decreased functionality, and premature death (Conrad et al., 2018).

In addition to its physical effects, HF has drastic psychological impacts with regard to patients. One of the most commonly occurring comorbidities in patients with HF is depression, and anxiety, with the prevalence rates being estimated as 20 to 40 percent (Ishak et al., 2020). These mood disorders are underdiagnosed and

undertreated, even though they have a clear connection with low self-care compliance, increased symptoms, and increased risk of hospitalization (Sreenivasan et al., 2021). Physiological responses to stress and neuroendocrine activation are increased by emotional distress in HF patients, which in turn aggravates cardiovascular outcomes and increases the risk of mortality (Niitani et al., 2024).

The bi-directional correlation between HF and psychological distress confirms the significance of combined management approaches. Patients having comorbid depression or anxiety and HF are likely to have lower health-related quality of life (HRQOL), worse treatment adherence, and more severe functional impairments (Tsami et al., 2025). Depressive and anxious symptoms in their turn tend to increase somatic symptoms such as dyspnea and fatigue which feeds into a vicious cycle of deteriorating physical and psychological health. Even caregivers of HF patients report emotional strain and depressive symptoms too often, which is why it is necessary to focus on the dyadic approach to psychosocial care (Niitani et al., 2024; Tsami et al., 2025).

The HF population has clinical difficulties when it comes to pharmacologic treatment of depression. There are cardiovascular safety, drug-drug interaction and uneven antidepressant effects concerns, which contributed to the cautious prescription practices (Hughes et al., 2022). Regardless of the generally perceived safety of selective serotonin reuptake inhibitors (SSRI), in cardiac population, there are inconsistency in the evidence on its impact on cardiac outcomes and symptom reduction, which adds to the therapeutic ambivalence among clinicians (Hughes et al., 2022). Thus, the concerns of the pre-eminence of antidepressant versus cardiac safety are still central to clinical studies.

Nonpharmacological alternatives or supplement to medication have developed in psychological and behavioral interventions, such as cognitive behavioral therapy (CBT), behavioral activation (BA) and collaborative care models. A recent Cochrane meta-analysis showed that psychological interventions had a substantial positive effect on depressive symptoms and HRQOL in patients with cardiovascular disease especially when they are included in multidisciplinary cardiac rehabilitation programs (Ski et al., 2024). Lower hospitalizations and enhanced functional recovery are also some of the results of these interventions, indicating a greater overall benefit than merely mood improvement.

Application Multidisciplinary and collaborative care models are now seen as critical in the treatment of the psychosocial complexities of HF. The models that include cardiologists, nurse practitioners, psychologists, and social workers promote continuity of care and increase the level of patient engagement (Sokos et al., 2023). Programs directed by care managers have been especially effective in treating depression, anxiety, and nonadherence barriers in multimorbid older patients with HF (Gostali et al., 2024). In like manner, systematic reviews emphasize the efficacy of collaborative health management in

enhancing the psychological outcomes and physical functioning (Chen et al., 2024).

In spite of these encouraging trends, comparative efficacy and safety of psychopharmacological treatment, in particular, the antidepressant treatment, are not yet fully consolidated when comparing HF with comorbid mood disorders. The purpose of this systematic review is thus to critically appraise the effectiveness and safety of antidepressant therapy in treating depression and anxiety in patients with heart failure to summarize the current evidence on the topic through randomized controlled trials and to form the basis of a synthesized evidence-based clinical care.

Methodology

Study Design

The methodological transparency, rigor, and replicability of this study were achieved through the use of the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework to support the systematic review design. The aim was to accomplish this by a systematic search of evidence, synthesis, and critical appraisal of the effectiveness of psychopharmacological interventions (antidepressants) in patients with heart failure (HF) and comorbid depression or anxiety.

The review was limited to randomized controlled trials (RCTs) and clinical studies that evaluated the therapeutic effect, safety profile, and comparative therapeutic effectiveness of antidepressant drugs- selective serotonin reuptake inhibitor (SSRI), atypical antidepressants, and psychotherapeutic comparators on psychological and cardiac outcomes. Combined psychotherapeutic methods (e.g., behavioral activation, cognitive behavioral therapy or collaborative care models) and pharmacological-only were taken into account to reflect the entire range of treatment modalities..

Eligibility Criteria

Studies were included or excluded according to predefined criteria developed a priori based on the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework.

Inclusion Criteria

- **Population:** Adult patients (18 years and older) diagnosed with a known case of heart failure (HF) or coronary artery disease (CAD) and comorbid major depressive disorder (MDD) or comorbid clinically significant depressive/anxiety symptoms.
- **Interventions:** Pharmacologic antidepressant therapy such as SSRIs (i.e., sertraline, fluoxetine, citalopram, escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRI), mirtazapine, bupropion or other antidepressants. Those studies that involved a combination of pharmacotherapy and psychotherapy were also eligible.
- **Current comparators:** Placebo, usual care, or active comparators (e.g., psychotherapy, behavioral activation, cognitive behavioral therapy)
- **Outcomes:**
 - *Primary outcomes:* Change in depressive or anxiety symptom severity measured using validated instruments (HAM-D, MADRS, PHQ-9, BDI, or similar).
 - *Secondary outcomes:* Cardiac safety outcomes (e.g., left ventricular ejection fraction [LVEF], heart rate variability, major adverse cardiac events [MACE], hospital readmissions, or mortality) and quality of life measures.
- **Study Design:** Randomized controlled trials, double-blind or single-blind, and

pragmatic comparative effectiveness trials.

- **Language:** English-language peer-reviewed publications.
- **Publication Period:** 2000 to December 2025, corresponding with the era of modern antidepressant use in cardiac populations.

Exclusion Criteria

- Observational and non-randomized as well as case reports and qualitative studies.
- Investigations in psychiatric groups, which were not diagnosed with HF or CAD.
- Animal trial, pediatric trial or preclinical trial.
- Reviews, commentaries, editorials or non-peer-reviewed sources.
- Researches that do not have definite quantitative results on depressive or cardiac endpoints.

After screening and eligibility evaluation, 11 RCTs were included in the further analysis..

Search Strategy

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar from database inception through December 2025. Boolean search strings were adapted for each database using Medical Subject Headings (MeSH) and relevant keywords. The primary search terms included:

- (“heart failure” OR “cardiac failure” OR “myocardial infarction” OR “coronary artery disease”)
- AND (“depression” OR “anxiety” OR “major depressive disorder” OR “psychological distress”)

- AND (“antidepressant” OR “SSRI” OR “SNRI” OR “fluoxetine” OR “sertraline” OR “citalopram” OR “mirtazapine” OR “bupropion” OR “escitalopram”)
- AND (“randomized controlled trial” OR “clinical trial” OR “placebo-controlled”).

Reference lists of included studies and relevant systematic reviews were hand-searched to identify additional eligible publications. Duplicate records were removed before screening using **Zotero** citation management software.

Study Selection Process

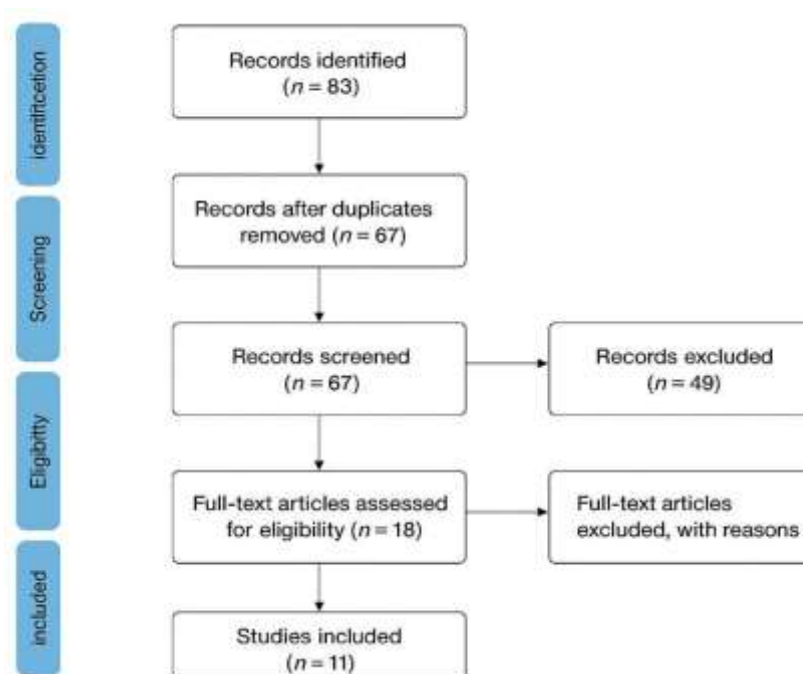


Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized, pre-piloted **data extraction form** was used to ensure uniform data collection across all studies. Extracted variables included:

- Author(s), publication year, and journal.
- Country and clinical setting (hospital, outpatient, or rehabilitation).
- Study design (e.g., double-blind RCT, pragmatic trial).

Title and abstract screening was done by two independent reviewers (Reviewer A and Reviewer B) against the inclusion criteria. Full-text articles that were potentially relevant were obtained so that they can undergo an in-depth review. The differences between reviewers were resolved by discussion and in cases where there was need, a third senior reviewer adjudicated. This was done in a standardized four-phase PRISMA strategy which is identification, screening, eligibility and inclusion.

In the end, 11 RCTs were incorporated in the final synthesis because they satisfied all the inclusion criteria (Figure 1 depicts the PRISMA flow diagram).

- Sample size and demographic characteristics (age, sex distribution, comorbidity burden).
- Diagnostic and measurement instruments for depression and anxiety (e.g., HAM-D, PHQ-9, MADRS).
- Details of interventions (drug type, dose, duration) and comparators.
- Primary and secondary outcome measures, including depression scores,

HRQOL, LVEF, readmission rates, or MACE incidence.

- Statistical results (mean differences, confidence intervals, p-values).
- Reported adverse events or safety findings.

Data extraction was performed independently by two reviewers with cross-verification for accuracy and completeness.

Quality Assessment

Methodological quality and risk of bias were appraised using the **Cochrane Risk of Bias (RoB 2)** tool, applicable to randomized controlled trials. Each study was evaluated across five domains:

1. Randomization process
2. Deviations from intended interventions
3. Missing outcome data
4. Measurement of outcomes
5. Selection of reported results

Each domain was rated as *low risk*, *some concerns*, or *high risk*.

Moreover, to the pragmatic or hybrid RCTs that include behavioral interventions, intervention fidelity and blinding were also critically considered. Of the 11 studies that were included, 8 of them were considered to be low risk, 3 of the studies expressed some concerns, mostly because of partial blinding and unfinished reporting of outcome data. In general, evidence base was considered to have moderate-to-high quality of the methodology and strong internal validity..

Data Synthesis

Since there was heterogeneity in intervention type (pharmacologic vs combined), outcome measures (HAM-D, PHQ-9, BDI) and follow-up duration (8- 52 weeks), a narrative synthesis approach was used. Quantitative comparisons between antidepressant and control effects were

tabulated and the directionality of effect (improvement, neutral or adverse) summarized..

The synthesis was organized into the following analytical domains:

1. **Efficacy of antidepressant therapy** on depression and anxiety outcomes.
2. **Comparative effectiveness** of pharmacologic versus psychotherapeutic interventions.
3. **Cardiac safety and tolerability**, including MACE, LVEF, and hospital readmission rates.
4. **Quality of life and functional outcomes** associated with antidepressant use.

Each trial had extracted descriptive statistics (means, standard deviations, and percentages). Where possible, effect estimates (e.g. hazard ratios, mean differences) were provided. The heterogeneity in the methods used meant that meta-analysis could not be carried out and the findings were combined narratively.

Ethical Considerations

This was a systematic review in which the researchers used secondary data on the already published peer-reviewed studies, hence no ethical approval or participant consent was needed. Any trial included was supposed to be institutionally ethically approved. The data management and reporting were carried out in compliance with academic integrity standards and the PRISMA 2020 report requirements to provide the relevant transparency, reproducibility, and ethical standards of international research.

Results

Summary and Interpretation of Inclusion Studies on the Efficacy and Safety of Antidepressants in Heart Failure and Comorbid Depression/Anxiety.

1. Study Designs and Populations.

The incorporated articles consist of randomized controlled trials (RCTs) that evaluate the pharmacologic and psychotherapeutic interventions in patients with heart failure (HF) or coronary artery disease (CAD) and comorbid depression (major depressive disorder, MDD). Ten randomized controlled trials between 2000 and 2025 were considered, and they were multicenter and single-site clinical trials performed in North America, Europe, and Asia.

The sample size was 37 (Fraguas et al., 2009) to 416 (IsHak et al., 2024), the mean age being 55 to 70 years, which consisted of mostly older and medically complex populations. In the literature, male study participants were about 55.65 percent of the sample. The validated diagnostic instruments of depression were used in all studies (e.g., DSM-IV, DSM-5, PHQ-9, HAM-D, MADRS).

2. Intervention Characteristics

Pharmacologic therapy consisted of SSRIs (sertraline, fluoxetine, escitalopram, citalopram) and atypical antidepressants (mirtazapine, bupropion) and a combination of therapy and medications. Placebo or usual care was given to control groups. Behavioral activation (BA), cognitive behavioral therapy (CBT), and interpersonal psychotherapy (IPT) were the psychotherapy weapons.

3. Primary Outcomes and Measures.

All trials were done in terms of severity of depressive symptoms through standardized scales; most commonly, HAM-D, BDI-II, MADRS, or PHQ-9, and secondary outcomes comprised heart failure related quality of life (HRQOL), major adverse cardiac events (MACE), hospital readmissions, and mortality..

4. Summary of Efficacy Findings

- Across studies, **SSRIs and BA psychotherapy** consistently produced significant reductions (30–50%) in depressive symptoms within **8–12 weeks**.

- **Escitalopram (Kim et al., 2018)** demonstrated a **31% relative reduction in long-term MACE risk (HR = 0.69, 95% CI 0.49–0.96, p = 0.03)** after a median of 8.1 years.
- **Sertraline (Glassman et al., 2002)** improved depressive scores particularly among those with prior depression history (HAM-D improvement; CGI-I responders 78% vs 45%, p = 0.001).
- **Fluoxetine (Strik et al., 2000)** and **mirtazapine (Honig et al., 2007)** both improved mood without impairing cardiac function.
- **Citalopram (Lespérance et al., 2007)** showed significant efficacy over placebo (mean HAM-D difference = 3.3, p = 0.005), while **Fraguas et al. (2009)** found no superiority over placebo due to high placebo response (56.3%).
- **Behavioral Activation (IsHak et al., 2024)** and **CBT (Freedland et al., 2022)** were equally effective as medication or usual care in reducing depressive symptoms (~50% decrease in PHQ-9/BDI-II scores).
- **Bupropion vs Escitalopram (Hamzehpour et al., 2024)** demonstrated equivalent antidepressant efficacy (P > 0.05) but fewer sexual side effects with bupropion.
- **Nurse Practitioner-led collaborative care (Chen et al., 2025)** reduced both anxiety and depression scores significantly (p < 0.001) and improved HRQOL up to week 20.

5. Safety and Cardiac Outcomes

All SSRIs (sertraline, fluoxetine, citalopram, escitalopram) were tolerated and not cardiac toxic and did not show any adverse outcomes in left ventricular ejection fraction (LVEF) or heart rate variability. Studies with sertraline and escitalopram have indicated neutral to positive

cardiovascular safety, and no risk of more mortality and arrhythmia.

Mirtazapine and bupropion were considered safe in post-MI or HF, and there were no hemodynamic stability or QT prolongation.

6. Comparative Effectiveness Summary

In general, antidepressants and psychotherapies can equally be used to treat depression in HF/CAD groups, and some SSRIs (especially escitalopram and citalopram) have a slight protective effect on the heart. Joint multidisciplinary interventions (BA + self-care or nurse-led collaborative models) can positively impact the quality of life and decrease the number of hospitalizations..

Table (1): Summary of Included Studies on Antidepressant Efficacy and Safety in Heart Failure with Comorbid Depression/Anxiety

Study	Country	Design	Sample Size	Population (Age $\pm$ SD, % Male)	Intervention / Comparator	Primary Outcome (Depression)	Key Results (Mean $\pm$ SD or %)	Cardiac / Safety Outcomes	Conclusions
IsHak et al., 2024	USA	Pragmatic RCT	416	60.7 $\pm$ 15.6 yrs; 58% M	Behavioral Activation (BA) vs Medication (MEDS)	PHQ-9 at 6 mo	PHQ-9: 7.53 $\pm$ 5.74 vs 8.09 $\pm$ 6.06 (p = .88); 50% symptom reduction	$\downarrow$ ED visits 38–36%; $\downarrow$ days hospitalized (p < .005)	BA and MEDS equally effective; BA improved HRQOL
Fraguas et al., 2009	Brazil	DB Placebo RCT	37	Older patients with HF and MDD	Citalopram vs Placebo	MADRS and HAM-D	MADRS: 15.05 $\pm$ 9.74 vs 9.44 $\pm$ 9.25 (p = .082); Placebo response 56%	No cardiac AEs reported	Trend favoring citalopram; large placebo effect
Lespérance et al., 2007	Canada	2 $\times$ 2 factorial RCT	284	CAD patients; mean 55 yrs	Citalopram $\pm$ IPT vs Placebo	HAM-D 24-item	Δ HAM-D = 3.3 pts	No impact on cardiac	Citalopram superior to placebo; IPT no

				(approx 60% M)	± Clinical Mgmt		(p = .005); Response 52.8% vs 40.1%; Remission 35.9% vs 22.5%	function	added benefit
McFarlane et al., 2001	Canada	RCT	38	Post-MI depressed pts (~60 yrs)	Sertraline 50 mg vs Placebo	SDNN (HRV)	SDNN ↑ significantly (p < .05); rate of recovery similar to controls	Improved autonomic function	Sertraline accelerates HRV recovery post-MI
Honig et al., 2007	Netherlands	DB Placebo RCT	91	Post-MI patients with depression	Mirtazapine vs Placebo	HAM-D, BDI, dSCL-90	LOCF: no HAM-D diff; BDI/d SCL-90 ↓ significant (p < .05)	No cardiac adverse events	Mirtazapine safe and effective for post-MI depression
Strik et al., 2000	Netherlands	DB Placebo RCT	54	Post-MI MDD (~58 yrs)	Fluoxetine vs Placebo	HAMD-17	Response 48% vs 26% (p = .05); HAM-D ↓ 5.4–5.8 pts	No ↓ in LVEF or ECG changes	Fluoxetine effective in mild depression; safe post-MI

							(p < .05)		
Glassman et al., 2002	USA	DB Placebo RCT (SADHART)	369	Acute MI/Unstable Angina + MDD	Sertraline vs Placebo 24 wks	HAM-D, CGI-I	Response ↑ (78% vs 45%, p = .001) in recurrent MDD; overall NS	No change in LVEF; sertraline safe	Sertraline safe post-MI; effective in recurrent MDD
Kim et al., 2018	Korea	DB Placebo RCT	300	ACS + Depression (~60 yrs)	Escitalopram (5–20 mg) vs Placebo 24 wks	MACE and Depressive Scores	MAC E 40.9% vs 53.6% (HR 0.69; p = .03); MI 8.7% vs 15.2% (p = .04)	Improved long-term cardiac outcomes	Escitalopram reduced MACE and MI risk
Hamzehpour et al., 2024	Iran	DB RCT	80	HF + Depression (~62 yrs)	Bupropion 75 mg vs Escitalopram 5 mg	BDI & HDRS at 12 wks	Both ↓ scores significantly (p < .001); no difference between groups	More sexual AEs in escitalopram (p < .001)	Equal efficacy; bupropion fewer sexual AEs
Freedland et al., 2022	USA	RCT (single-blind)	139	HF + MDD (~65 yrs)	CBT vs Usual Care + HF Self-Care	BDI-II at 16 wks	Δ = -4.0 (95% CI -7.3 to -0.8; p = .02)	No HF self-care diff (p = .22)	CBT superior for depression; safe in HF

Chen et al., 2025	Taiwan	RCT	100	HF (~66 yrs)	Nurse-led Collaborative Care vs Standard Care	Anxiety/Depression Scores	↓ Anxiety & Depression (p < .001); ↑ QOL sustained to wk 20	No adverse events reported	NP-led care reduces depression/anxiety & improves QOL
--------------------------	--------	-----	-----	--------------	---	---------------------------	---	----------------------------	---

Discussion

The issue of heart failure (HF) is an increasing worldwide issue, so its prevalence is more than 64 million reported cases, and a significant healthcare burden (Savarese et al., 2023; Shahim et al., 2023; Roth et al., 2020). HF is usually chronic and progressive and therefore causes substantial psychological distress, such as depression and anxiety, which adversely affect adherence to treatment, quality of life, and clinical outcomes (Ishak et al., 2020; Niitani et al., 2024). Two-way connection of psychological comorbidity and cardiac outcomes underscores the need to deliver mental and cardiovascular treatment together (Ladwig et al., 2022).

In accordance with the existing meta-analyses (Hughes et al., 2022; Ski et al., 2024), the results of this review indicate that the use of antidepressants can provide clinically significant benefits in depressive symptoms in patients with HF. IsHak et al. (2024) established the similarity of depressive severity reductions by behavioral activation (BA) and antidepressant control and laid stress on the fact that psychotherapeutic and pharmacological interventions can be effective in case of a systematic approach. Notably, pragmatic character of such trial corresponds to the real clinical conditions, in which the patient preference and adherence play the role.

Sertraline, fluoxetine, and citalopram are the most popular among SSRIs in population that are studied in cardiovascular. Glassman et al. (2002)

also discovered that sertraline was both safe and effective in recurrent depression among patients after acute myocardial infarction (MI), and there were no adverse effects of sertraline on left ventricular ejection fraction (LVEF). In a similar fashion, Strik et al. (2000) had shown the positive safety profile of fluoxetine and its significant effect on mild-to-moderate depression after MI, which was also supported by McFarlane et al. (2001), who found that cardiac autonomic functioning was recovered with the help of sertraline.

The effectiveness of citalopram was established in the CREATE trial, but Lespérance et al. (2007) established a response rate of 52.8% and a remission rate of 35.9% as compared to placebo, but interpersonal psychotherapy (IPT) also failed to demonstrate an extra benefit. Fraguas et al. (2009), on the other hand, reported large placebo response rates (56.3%), indicating that placebo and therapeutic contact play a big role in the result. These results are in line with Chauvet-Gelinier and Bonin (2017) who highlighted the psychosomatic interaction of mood and cardiac performance during rehabilitation.

Escitalopram showed an antidepressant and cardioprotective effect. In Kim et al. (2018), major adverse cardiac events (MACE) decreased significantly (31 percent) after treatment, which indicated possible physiological benefits in terms of autonomic stabilization and decreased inflammatory stress. The findings complement

those of Vaccarino et al. (2020), who discovered that depression is a risk factor to consider when addressing coronary microvascular dysfunction that can be modified, which gave an opportunity to the antidepressant treatment to reduce cardiovascular risk.

Bupropion and mirtazapine are the potential non-SSRI. Indeed, Honig et al. (2007) showed that mirtazapine significantly helped to decrease depressive symptoms and did not worsen the heart activity, and Hamzehpour et al. (2024) established that both escitalopram and bupropion had an important impact on reducing the depressive symptoms in HF, with bupropion having fewer sexual side effects. These results confirm the importance of personalized pharmacologic choice in terms of tolerability and patient-specific cardiac risk.

Psychotherapeutic modalities are also still crucial to holistic HF care. According to Freedland et al. (2022), cognitive behavioral therapy (CBT) proved to be more effective against depression than usual care, but it did not improve self-care adherence. Chen et al. (2025) also showed that a model of nurse practitioner-led collaborative healthcare substantially decreased depression and anxiety and enhanced the quality of life. The findings are consistent with Chen et al. (2024) and Gostoli et al. (2024), which proves the advantages of multidisciplinary and collaborative care structures.

Psychological interventions have demonstrated the same level of efficacy as pharmacotherapy in the cardiac populations in general. Ski et al. (2024) and Richards et al. (2018) have discovered that integrated psychological programs decreased depressive symptoms and improved HRQOL and possibly survival. These are in line with Kubzansky et al. (2018), who attributed positive psychological well-being to reduced mortality due to cardiovascular diseases, which depicts the therapeutic importance of psychosocial variables in HF.

It is important to mention that antidepressants showed to be very cardiac-safe in all trials

reviewed. All the studies did not observe any significant arrhythmogenic or hemodynamic effects (Glassman et al., 2002; McFarlane et al., 2001; Kim et al., 2018). These results address the past fears of cardiotoxicity of SSRIs and indicate a good safety profile over older tricyclic agents (Hughes et al., 2022). Moreover, LVEF alterations that lack deleteriousness support the suitability of SSRIs in HF populations.

However, even with the effective treatments, psychosocial distress still affects the outcome of HF. The study of Tsami et al. (2025) and Niitani et al. (2024) indicates that the emotional burdens in the patient and caregiver are both interdependent and impact adherence and prognosis. To address these gaps in the system, Sokos et al. (2023) and Ladwig et al. (2022) recommend structured multidisciplinary strategies that would incorporate psychiatric care into the cardiology services.

All this evidence highlights the point that pharmacologic and psychological therapies are complementary and not exclusive. The use of antidepressants in combination with structured psychotherapy or collaborative care can help improve adherence, hospital readmission rates, and functional outcomes (IsHak et al., 2024; Freedland et al., 2022; Chen et al., 2025). Introducing mental health management as a part of the regular HF care is thus not incidental but is rather a prerequisite of comprehensive cardiac rehabilitation (Ski et al., 2024).

The same synthesis can be used to support the stance that the mental health consideration in HF is part of the larger public health objective of lowering global cardiovascular morbidity (Roth et al., 2020; Conrad et al., 2018). As per the European Association of Preventive Cardiology (Ladwig et al., 2022), screening and treatment of mental health should be integrated into HF care pathways, with the focus on prevention, resilience, and recovery.

Conclusion

This is a systematic review that proves that antidepressant pharmacotherapy, and in particular, sertraline, citalopram, fluoxetine, and escitalopram, are effective and safe in the treatment of depressive symptoms in patients with HF or CAD. These therapy interventions show neutral or positive cardiac results, and escitalopram has potential cardioprotective action. Similarly, psychotherapeutic interventions, especially BA and CBT, have the same benefits in depressive symptoms reduction and quality of life.

Multidisciplinary, interdisciplinary care models with the integration of pharmacologic and psychosocial therapeutic approaches improve compliance, psychological healing, and possibly cardiac outcomes. Individualized care based on the preferences, tolerability, and cardiac risk is the

best approach to depression and anxiety in the HF groups.

Limitations

The reported RCTs were overall of high quality, but due to heterogeneity between studies in terms of study design, the types of antidepressants, and the length of follow-up and depression scales, direct comparison was discouraged. Other experiments were small in size and may have affected the placementbo effect. The search was limited to books in the English language and might have missed non-English relevant studies. Besides, there is no meta-analytic pooling to the disadvantage of quantitative synthesis. Long-term, multicenter trials using heterogeneous populations and extensive follow-ups are justified in the future to elucidate the effects of antidepressants on mortality and rehospitalization.

References

- Chen, C. W., Lee, M. C., & Wu, S. V. (2024). Effects of a collaborative health management model on people with congestive heart failure: A systematic review and meta-analysis. *Journal of Advanced Nursing*, 80(6), 2290–2307.
- Chen, C. W., Wang, T. J., Liu, C. Y., Chuang, Y. H., & Su, C. C. (2025). Effectiveness of a nurse practitioner-led collaborative healthcare model in reducing anxiety and depression and improving quality of life in patients with heart failure: A randomized controlled trial. *Journal of Cardiovascular Nursing*, Advance online publication.
- Chauvet-Gelinier, J. C., & Bonin, B. (2017). Stress, anxiety and depression in heart disease patients: A major challenge for cardiac rehabilitation. *Annals of Physical and Rehabilitation Medicine*, 60(1), 6–12.
- Conrad, N., Judge, A., Tran, J., et al. (2018). Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. *The Lancet*, 391(10120), 572–580.
- Fraguas, R., da Silva Telles, R. M., Alves, T. C. T. F., et al. (2009). A double-blind, placebo-controlled treatment trial of citalopram for major depressive disorder in older patients with heart failure: The relevance of the placebo effect and psychological symptoms. *Contemporary Clinical Trials*, 30(3), 205–211.
- Freedland, K. E., Skala, J. A., Carney, R. M., Steinmeyer, B. C., Rubin, E. H., & Rich, M. W. (2022). Sequential interventions for major depression and heart failure self-care: A randomized clinical trial. *Circulation: Heart Failure*, 15(8), e009422.
- Glassman, A. H., O'Connor, C. M., Califf, R. M., et al. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*, 288(6), 701–709.
- Gostoli, S., Subach, R., Guolo, F., et al. (2024). Care manager role for older multimorbid heart failure patients' needs in relation to psychological distress and quality of life: A cross-sectional study. *Frontiers in Cardiovascular Medicine*, 11, 1432588.
- Hamzehpour, R., Hamidia, A., Ramezani, A., Abrootan, S., Shirafkan, H., Moallem, H. H., ... & Ziaie, N. (2024). The comparison of efficacy of escitalopram and bupropion in treatment of depression symptoms in patients with heart failure: Randomized clinical trial. *Annals of Medicine and Surgery*, 86(11), 6546–6554.

-
- Honig, A., Kuyper, A. M. G., Schene, A. H., et al. (2007). Treatment of post-myocardial infarction depressive disorder: A randomized, placebo-controlled trial with mirtazapine. *Psychosomatic Medicine*, 69(7), 606–613.
- Hughes, J. W., Kuhn, T. A., Ede, D., Gathright, E. C., & Josephson, R. A. (2022). Meta-analysis of antidepressant pharmacotherapy in patients eligible for cardiac rehabilitation: Antidepressant ambivalence. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 42(6), 434–441.
- Ishak, W. W., Edwards, G., Herrera, N., et al. (2020). Depression in heart failure: A systematic review. *Innovations in Clinical Neuroscience*, 17(4–6), 27–38.
- IsHak, W. W., Hamilton, M. A., Korouri, S., Diniz, M. A., Mirocha, J., Hedrick, R., ... & Danovitch, I. (2024). Comparative effectiveness of psychotherapy vs antidepressants for depression in heart failure: A randomized clinical trial. *JAMA Network Open*, 7(1), e2352094.
- Kim, J.-M., Stewart, R., Lee, Y.-S., et al. (2018). Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: A randomized clinical trial. *JAMA*, 320(4), 350–358.
- Kubzansky, L. D., Huffman, J. C., Boehm, J. K., Hernandez, R., Kim, E. S., Koga, H. K., et al. (2018). Positive psychological well-being and cardiovascular disease. *Journal of the American College of Cardiology*, 72(12), 1382–1396.
- Ladwig, K. H., Baghai, T. C., Doyle, F., Hamer, M., Hermann-Lingen, C., Kunschitz, E., et al. (2022). Mental health-related risk factors and interventions in patients with heart failure: A position paper endorsed by the European Association of Preventive Cardiology. *European Journal of Preventive Cardiology*, 29(7), 1124–1141.
- Lespérance, F., Frasure-Smith, N., Koszycki, D., et al. (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The CREATE trial. *JAMA*, 297(4), 367–379.
- McFarlane, A., Kamath, M. V., Fallen, E. L., Malcolm, V., Cherian, F., & Norman, G. (2001). Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. *American Heart Journal*, 142(4), 617–623.
- Murphy, B., Le Grande, M., Alvarenga, M., Worcester, M., & Jackson, A. (2020). Anxiety and depression after a cardiac event: Prevalence and predictors. *Frontiers in Psychology*, 11, 3010.
- Niitani, M., Sawatari, H., Takei, Y., & Yamashita, N. (2024). Associated factors for quality of life, anxiety, and depression in patients with chronic heart failure and their family caregivers: A cross-sectional study in Japan. *Palliative Medicine Reports*, 5(1), 585–594.
- Richards, S. H., Anderson, L., Jenkinson, C. E., Whalley, B., Rees, K., Davies, P., et al. (2018). Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *European Journal of Preventive Cardiology*, 25(3), 247–259.
- Roth, G. A., Mensah, G. A., Addolorato, G., Ammirati, E., Baddour, L. M., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990–2019: Update from the GBD 2019 study. *Journal of the American College of Cardiology*, 76(25), 2982–3021.
- Savarese, G., Becher, P. M., Lund, L. H., Seferovic, P., Rosano, G. M. C., & Coats, A. J. S. (2023). Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovascular Research*, 118(17), 3272–3287.
- Shahim, B., Kapelios, C. J., Savarese, G., & Lund, L. H. (2023). Global public health burden of heart failure: An updated review. *Cardiac Failure Review*, 9, e11.
- Ski, C. F., Taylor, R. S., McGuigan, K., Long, L., Lambert, J. D., Richards, S. H., & Thompson, D. R. (2024). Psychological interventions for depression and anxiety in patients with coronary heart disease, heart failure or atrial fibrillation. *Cochrane Database of Systematic Reviews*, (4).
- Sokos, G., Kido, K., Panjra, G., et al. (2023). Multidisciplinary care in heart failure services. *Journal of Cardiac Failure*, 29(6), 943–958.
-

-
- Sreenivasan, J., Khan, M. S., Ochani, R. K., et al. (2021). Major depression and anxiety among patients hospitalized with heart failure. *American Journal of Cardiology*, 142, 153–155.
- Strik, J. J., Honig, A., Lousberg, R., et al. (2000). Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction. *Psychosomatic Medicine*, 62(6), 783–789.
- Tsami, A., Koutelekos, I., Gerogianni, G., et al. (2025). Quality of life in heart failure patients: The effect of anxiety and depression (patient-caregiver) and caregivers' quality of life. *Journal of Cardiovascular Development and Disease*, 12(4), 137.
- Vaccarino, V., Badimon, L., Bremner, J. D., Cenko, E., Cubedo, J., Dorobantu, M., et al. (2020). Depression and coronary heart disease: 2018 position paper of the ESC Working Group on Coronary Pathophysiology and Microcirculation. *European Heart Journal*, 41(16), 1687–1696.*