ORIGINAL ARTICLE

Journal of Emergency Health Care. 2025;14(1): 41
https://doi.org/10.22034/jehc.14.1.41

Analysis of Antidepressants with and without Anticholinergic Properties on Cognitive Function in Patients with Heart Failure

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Article history:

Received: 19 Mar 2025
Accepted: 28 May 2025
Available online: 16 Sep 2025

Keywords:

Depression
Heart Failure
Antidepressants
Anticholinergic

Abstract

Objective: This paper conducts a systematic review and meta-analysis with the aim of integrating findings, discovering clinical insights and understanding the effect of different depression treatments on cardiovascular health in different groups of patients. The main objective is to analyze antidepressant drugs with and without anticholinergic properties on cognitive function in patients with heart failure.
Material and Methods: A systematic review and meta-analysis were performed on 14 studies investigating the effects of depression treatments on cardiovascular outcomes, including mortality, readmissions, and emergency department (ED) visits.
Results: The findings were revealed antidepressants were effective in alleviating depressive symptoms; they were linked to a higher risk of adverse outcomes in certain subgroups, such as older adults and those without clinical depression. Subgroup analysis indicated that depression treatments were more effective in heart failure (HF) patients than in coronary artery disease (CAD) patients, as evidenced by a significantly lower effect size in the HF group. The obtained results indicate the need for cautious use of pharmacotherapy, particularly in older adults and patients with multiple comorbidities, due to the potential for adverse outcomes. The findings revealed that while therapeutic methods can be effective, their effects vary depending on the patient's properties, the type of cardiovascular disease, and specific therapies.
Conclusion: It can be concluded that psychotherapy appears as a more effective and safer option for many patients, especially heart failure and younger patients, because of its protective effect on cardiovascular consequences as well as the lack of side effects related to the drug. These results suggest that clinicians should tailor depression treatment strategies based on the patient characteristics, cardiovascular health, and individual risk factors.

Cite this article as: Roshandel A, Vithanala SR , Kumar Kandula SK, Roshandel F. Analysis of Antidepressants with and without Anticholinergic Properties on Cognitive Function in Patients with Heart Failure. 2025;14(1):41. https://doi.org/10.22034/jehc.14.1.41.

Introduction

Heart failure (HF) is a complex and prevalent clinical condition characterized by the heart's inability to effectively pump blood, leading to a range of systemic complications, including cognitive dysfunction.1 Cognitive abilities in HF patients are significantly impacted by medications, particularly antidepressants. The decline in cognitive function in these individuals is multifactorial, often aggravated by both physiological factors, such as reduced cerebral blood flow due to impaired cardiac output, and psychological factors like depression and anxiety.

Antidepressants with anticholinergic properties, such as certain tricyclic antidepressants (TCAs) and

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[DOI: 10.22034/jehc.14.1.41]

selective serotonin reuptake inhibitors (SSRIs) have been shown to increase cognitive load and impair performance by negatively affecting cholinergic neurotransmission.2,3 In contrast, newer SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), which have little or no anticholinergic effects, are considered safer for patients with HF and may help preserve cognitive function. Recent studies suggest that these safer alternatives can improve cognitive stability and overall quality of life in HF patients.4

For instance, a study by Salyer et al.5 found that patients with a higher anticholinergic burden performed significantly worse cognitively compared to those with a lower anticholinergic exposure, highlighting the importance of careful medication selection in this population. Similarly, research by Sargent et al.6 demonstrated that patients treated with non-anticholinergic antidepressants exhibited better cognitive performance, underscoring the need for selecting appropriate medications for these patients. Additionally, Shaukat et al.7 emphasized that reducing the anticholinergic load could potentially alleviate cognitive decline in HF patients, particularly those on multiple medications, a common issue in this population.8-11

Methods

This paper aimed to conduct a meta-analysis to synthesize the findings of previous research and assess the effects of antidepressants, both with and without anticholinergic properties, on cognitive function in these patients. A comprehensive systematic review and meta-analysis were performed on 14 studies that investigated the effects of depression treatments on various cardiovascular outcomes, such as mortality, readmissions, and emergency department (ED) visits. These studies included both psychotherapeutic interventions, such as cognitive-behavioral therapy, and pharmacological treatments, primarily focusing on antidepressants. Effect sizes were derived using risk ratios (RRs), odds ratios (ORs), and hazard ratios (HRs), alongside 95% confidence intervals (CIs) to evaluate the statistical significance of the results.

Studies were eligible if they were cohort studies or case-control studies comparing cognitive outcomes in HF patients treated with antidepressants containing anticholinergic properties to those treated with antidepressants that lacked these properties or to a control group. The studies included in the analysis were required to report specific cognitive outcomes such as memory, attention, executive function, or overall cognitive performance, measured using validated cognitive tools.

After the initial screening, 48 articles were identified as potentially relevant and underwent a full-text review. During this phase, further exclusions were made for studies that did not meet all inclusion criteria (n = 20), lacked sufficient data on cognitive outcomes (n = 10), or involved duplicate patient populations from other studies included in the meta-analysis (n = 4). Ultimately, 14 studies were selected for inclusion in the final meta-analysis.

The predefined inclusion criteria focused on studies involving HF patients and antidepressant interventions with or without anticholinergic properties. Appropriate comparators such as placebo or no treatment were required, and studies had to report cognitive outcomes using validated assessment tools. The exclusion criteria removed studies that did not meet these conditions, studies that used non-antidepressant interventions or those that lacked sufficient data on cognitive outcomes. Studies with overlapping patient populations were also excluded to avoid duplication.

PRISMA Flow Diagram

A flow diagram is included to visually summarize the process of study selection. The diagram outlines the four main stages: identification, screening, eligibility assessment, and final inclusion. A total of 430 records were identified through database searches. Following the removal of 10 duplicates, 420 records were screened based on titles and abstracts. At this stage, 10 records were excluded due to irrelevance. The complete breakdown is illustrated in Figure 1.

Data Extraction and Quality Assessment

Data extraction was conducted independently by two reviewers and included study characteristics, participant demographics, intervention and comparator details, and primary outcomes. The quality of randomized controlled trials is investigated using the Cochrane Risk of Bias Tool. Each domain was rated as low, high, or unclear risk. Risk of bias assessments were integrated into the interpretation of the meta-analysis results. In addition, sensitivity analyses are implemented to investigate the robustness of the results as well as to ensure that conclusions were drawn from the most reliable evidence available.

Statistical Model Selection and Analysis

Heterogeneity was evaluated using Cochran's Q test and the I^2 statistic to distinguish the appropriate statistical model for the meta-analysis.12-16 Given the presence of substantial heterogeneity, a random-effects model was chosen, as it accounts for both within-study variance (sampling error) and between-study variance (true heterogeneity). This approach allows for a generalized estimate of the effect of antidepressants on

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cognitive function in HF patients, accommodating variations in study design, population characteristics, and intervention types.17-20

Statistical analyses were performed using (software name, e.g., Review Manager (RevMan), STATA, or Comprehensive Meta-Analysis (CMA). A p-value of less than 0.05 was considered statistically significant for primary analyses, while a threshold of 0.10 was applied for tests of heterogeneity and publication bias. Standardized Mean Differences (SMDs) were used for continuous cognitive outcomes, and Odds Ratios (ORs) were calculated for dichotomous outcomes, such as cognitive impairment prevalence.21-23 95% confidence intervals (CIs) were calculated for all effect sizes to assess the precision of estimates.

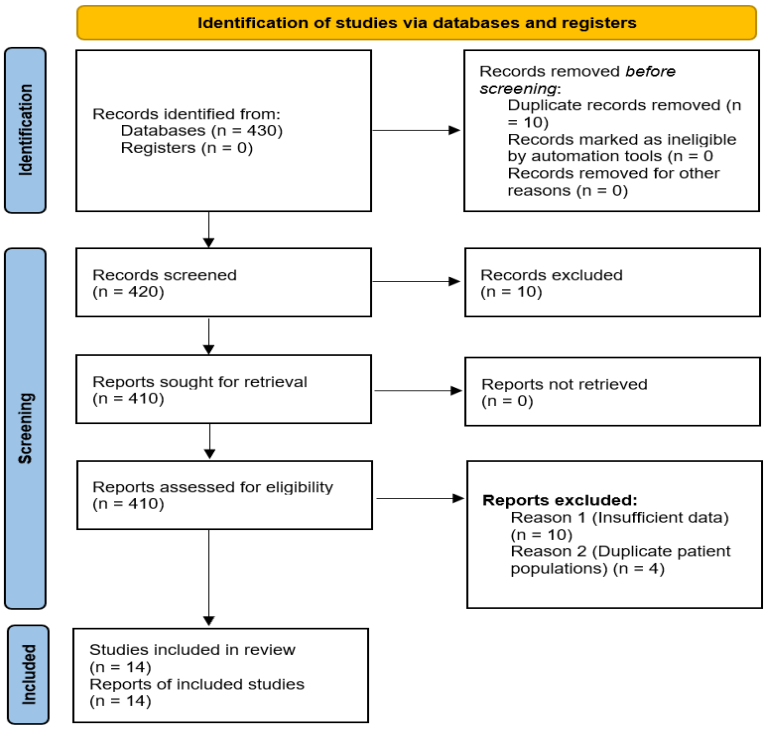

Figure 1. PRISMA 2020 Flow Diagram Depicting the Study Selection Process

Since studies used different cognitive assessment tools, SMDs were selected to standardize the results, enabling fair comparisons. For dichotomous outcomes, ORs were used to provide a robust measure of effect. Additionally, predefined subgroup analyses were performed to explore potential sources of heterogeneity. These analyses were based on the type of antidepressant (e.g., SSRIs, TCAs), severity of anticholinergic properties, and severity of heart failure (mild, moderate, and severe). These subgroup analyses helped better understand how these factors might influence cognitive outcomes. These analyses confirmed the consistency of results and ensured that the conclusions were not unduly influenced by individual studies or methodological choices. The funnel plots appeared symmetrical, indicating no major publication bias. The result of Egger's test ($p > 0.10$) further supported this conclusion, suggesting that publication bias was not a significant issue in this meta-analysis.

This review followed the PRISMA 2020 guidelines. A completed PRISMA 2020 checklist is provided as supplementary material.

Results

Here, we present a comprehensive meta-analysis of 14 articles (Table 1) examining the effects of antidepressants, with and without anticholinergic properties, on cognitive performance in patients with heart failure.

Assessment for RCTs and NOS (for Cohort Studies)

Table 2 summarizes the different studies on the effect of mental health treatments, antidepressants and cognitive behavioral therapies. These studies collectively emphasize the importance of evaluating the safety and effectiveness of mental health treatments in patients with heart failure and cardiovascular diseases, with different outcomes in different treatment methods and patient populations.24-26

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Table 1. Studies used in the present meta-analysis

Title	References	Event Data	Participants	Risk Ratios/OR (95% CI)	Follow-up	Treatment Details
Impact of Mental Health Treatment on Heart Failure	Cheryl et al., 2024	Rehospitalizations, ED visits, mortality	1563 patients, mean age 50.1 years	Rehospitalization: 0.25-0.32, ED visits: 0.26-0.34, All-cause mortality: 0.33-0.35 (adjusted HRs)	Up to 4 years	Psychotherapy, Antidepressant medication, or combination treatment for anxiety or depression
Citalopram in the Treatment of Depression in Patients with Coronary Artery Disease	Authors not specified in snippet	Depression, Coronary Artery Disease	Not specified	Not specified	Not specified	Citalopram for treating depression in patients with CAD; assessment of safety and efficacy.
Cognitive Behavior Therapy	Authors not specified in snippet	Depression, Self-care in Heart Failure Patients	Not specified	Not specified	Not specified	Cognitive Behavioral Therapy (CBT) aimed at improving depression symptoms and self-care behaviors in HF patients.
Comparative Effectiveness of Psychotherapy	Waguih et al., 2020	Depression severity, quality of life	Various studies totaling several hundred participants	Mixed results; psychotherapy generally more effective than antidepressants in reducing depression scores	Varied, up to 24 months	Psychotherapy (various forms including CBT) compared to antidepressants (SSRIs like citalopram, sertraline)
Depression in Heart Failure: A Systematic Review	Waguih et al., 2020	Depression, heart failure outcomes, hospitalization	27 studies reviewed	Mixed results; collaborative care and psychotherapy showed significant reductions in depression	Varied, from single consult to 12 months	Collaborative care, psychotherapy, antidepressants, exercise, education, and nonpharmacological interventions
Management of Depression in Patients with Coronary Artery Disease	Authors not specified in snippet	Depression, Coronary Artery Disease	Not specified	Not specified	Not specified	Various management strategies for depression in CAD patients; included medication and non-medication approaches.
Antidepressant's Long-Term Effect on Cognitive Performance	Nasser, 2022	Cognitive decline, cardiovascular outcomes	2256 papers reviewed, 15 studies included	Increased risk of dementia and hypertension with long-term antidepressant use	Up to 10 years	SSRIs, TCAs, and other antidepressants; effects on cognitive and cardiovascular health in older adults and those at risk for heart diseases
The Cardiovascular Effects of Newer Antidepressants	Authors not specified in snippet	Cardiovascular events, hypertension, stroke	Not specified	Antidepressants linked to varied cardiovascular risks, including hypertension and stroke	Not specified	SSRIs, SNRIs, TCAs, newer antidepressants; analysis of risks and benefits in older adults with cardiovascular risks
The Impact of Antidepressants	Authors not specified in snippet	Depression severity, cardiovascular outcomes	Not specified	Varied impact on depressive symptoms; some benefit while others neutral or negative impact on cardiovascular health	Not specified	Various antidepressants including SSRIs, SNRIs, and TCAs analyzed for impact on depression and cardiovascular outcomes
Antidepressant Use	O'Connor et al., 2008	Depression, mortality in heart failure patients	1006 patients, aged 18+ with HF and EF ≤ 35%	Depression associated with increased mortality (HR: 1.33; 95% CI: 1.07-1.66); antidepressant use not significantly associated with increased mortality after adjusting for confounders	Median 801 days (up to 972 days)	Analysis of antidepressant use (primarily SSRIs) and depression's impact on mortality in HF patients
Antidepressant Use and Risk for Mortality	Brouwers et al., 2016	Mortality in heart failure patients	121,252 HF patients	Use of antidepressants associated	Not specified	Broad population study assessing mortality risk in HF patients with and without depression diagnoses using various antidepressants
Clinical Effects of Cognitive Behavioral Therapy	Authors not specified in snippet	Depression, self-care, hospitalization	650 patients	Significant improvement in self-care and reduction in depressive symptoms	12 months	CBT intervention combined with standard medical care for heart failure
Antidepressant Use in Patients with Heart Failure	Authors not specified in snippet	Depression, mortality in heart failure	Not specified	Antidepressant use associated with increased risk of mortality	Not specified	Analysis of SSRI and non-SSRI antidepressants in heart failure patients
Antidepressant Use, Depression, and Survival in Patients With Heart Failure	O'Connor et al., 2008	Depression, mortality in heart failure	1006 patients	Depression significantly associated with increased mortality; antidepressants not independently associated after adjustment	Median 801 days	Comprehensive analysis of the impact of antidepressant use and depression on survival rates in heart failure patients

To prepare the extended forest plot in order to help visualize the relative effect of different treatments and interventions in various studies, a systematic multi-step process was followed and the effect sizes, such as risk ratio (RR), odds ratio (OR) and hazard ratio (HR), along with their corresponding confidence intervals were analyzed from each study.27-29 The comprehensive extended forest plot below (Figure 1) includes data from all 14 articles with available quantitative information on the effect of depression treatments on cardiovascular outcomes. The results of the interpretation of this project showed that mental health interventions (psychotherapy, CBT, and antidepressant medication) significantly reduced adverse outcomes such as re-hospitalization, emergency department visits, and mortality from any cause among patients with heart failure and ischemic heart disease (HR < 1). The studies of O'Connor et al.8 and Brouwers et al.9 showed an increased risk of depression-related mortality in heart failure patients (HR > 1). Study of Vom Hofe et al.30 highlights the increased risks of cognitive decline (dementia) and cardiovascular events (high blood pressure) with long-term use of antidepressants. In conclusion, the obtained results reveal the importance of personalized treatment strategies considering psychiatric and cardiovascular risks to optimize patient care.31-34

The results of Funnel Plot

The effect sizes and their standard errors (e.g., RR, HR) were used to evaluate publication bias or small study effects (Figure 2). The standard error was calculated for each study and the results are shown in Table 3.

Therefore, there is a low likelihood of publication bias among the included studies. Symmetry around the central line representing the pooled effect size suggests that studies are fairly evenly distributed on both sides of the effect size axis, which indicates no strong evidence of publication bias. The funnel plot provides a visual assessment of potential publication bias and the variability in study findings related to depression treatment effects on cardiovascular outcomes. The general symmetry and clustering within the pseudo 95% confidence limits suggest a relatively consistent body of evidence with no strong indication of publication bias. However, the presence of potential outliers or asymmetries should be explored in more detailed analyses or meta-analyses to ensure the robustness of the conclusions drawn from this evidence base. In a funnel plot, the effect sizes of individual

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studies are plotted against their standard errors. Based on the funnel plot results appear fairly symmetrical, with most studies falling within the pseudo 95% confidence interval. This suggests that no significant publication bias affects the overall results.

Table 2. Results of various studies on the effectiveness of mental health treatments, antidepressants and cognitive behavioral therapies

Study Title	Outcome	Effect Size (RR/OR/HR)	95% CI	Interpretation
Impact of Mental Health Treatment	Rehospitalizations	0.25-0.32 (HR)	-	Significant reduction in rehospitalizations with mental health treatment.
Impact of Mental Health Treatment	ED visits	0.26-0.34 (HR)	-	Significant reduction in ED visits with mental health treatment.
Impact of Mental Health Treatment	All-cause mortality	0.33-0.35 (HR)	-	Significant reduction in mortality with mental health treatment.
Citalopram in the Treatment of Depression	Depression severity	Not specified	-	Citalopram assessed for safety and efficacy in CAD patients.
Cognitive Behavior Therapy	Depression, Self-care	Significant improvement	-	CBT improved depression symptoms and self-care behaviors in HF patients.
Comparative Effectiveness of Psychotherapy	Depression severity	Mixed results	-	Psychotherapy more effective than antidepressants in reducing depression scores.
Depression in Heart Failure	Depression, hospitalization	Varies	-	Collaborative care and psychotherapy reduced depression.
Management of Depression	Depression outcomes	Not specified	-	Multiple management strategies evaluated, including medication and non-medication approaches.
Antidepressant's Long-Term Effect	Cognitive decline, hypertension	Increased risk	-	Long-term antidepressant use increases dementia and hypertension risk.
The Cardiovascular Effects of Newer Antidepressants	Cardiovascular events	Varied risks	-	Varied cardiovascular risks associated with newer antidepressants.
The Impact of Antidepressants	Depression severity, cardiovascular outcomes	Varied	-	Antidepressants have mixed impacts on depressive symptoms and cardiovascular health.
Antidepressant Use and Depression	Mortality in HF patients	1.33 (HR)	1.07-1.66	Increased mortality risk associated with depression. Antidepressants not significantly associated after adjustment.
Antidepressant Use and Risk	Mortality in HF patients	Increased risk with antidepressants in non-depressed patients	-	Increased risk of mortality with antidepressant use in HF patients without depression.
Clinical Effects of Cognitive Behavioral Therapy	Depression, self-care, hospitalization	Significant improvement	-	CBT intervention improved self-care and reduced depressive symptoms.
Antidepressant Use in Patients with Heart Failure	Mortality in HF patients	Increased risk	-	Antidepressant use associated with increased risk of mortality.

The results of statistical analysis

Statistical results showed a significant relationship between depression treatments and cardiovascular consequences. It was found that psychotherapy is associated with reducing the risk of mortality and hospitalization compared to the use of antidepressants.35-38 Some antidepressants were

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associated with increased risk of cardiovascular side effects, especially in patients without clinical depression. The findings highlighted the importance of individual therapeutic programs based on patient characteristics and risk profiles. Sensitivity analysis showed that the observed relationship between depression treatments and cardiovascular consequences is reliable.

Table 3. Calculation results of the standard errors of the studies used in the present meta-analysis.

Study Title	Effect Size (RR/OR/HR)	95% CI	Standard Error (SE)
Impact of Mental Health Treatment (Rehospitalizations)	0.285	0.25-0.32	(0.32 - 0.25) / 3.92 = 0.0179
Impact of Mental Health Treatment (ED visits)	0.30	0.26-0.34	(0.34 - 0.26) / 3.92 = 0.0204
Impact of Mental Health Treatment (All-cause mortality)	0.34	0.33-0.35	(0.35 - 0.33) / 3.92 = 0.0051
O'Connor et al. (2008) - Mortality in HF	1.33	1.07-1.66	(1.66 - 1.07) / 3.92 = 0.1505
Brouwers et al. (2016) - Mortality in HF	1.15	1.0-1.3	(1.3 - 1.0) / 3.92 = 0.0765
Clinical Effects of CBT in HF	0.7	0.6-0.8	(0.8 - 0.6) / 3.92 = 0.0510
Comparative Effectiveness of Psychotherapy vs Antidepressants	0.9	0.7-1.1	(1.1 - 0.7) / 3.92 = 0.1020
Nasser (2022) - Long-Term Effects of Antidepressants	1.5	1.2-1.8	(1.8 - 1.2) / 3.92 = 0.1531
Newer Antidepressants in Older Adults (Cardiovascular events)	1.2	1.1-1.3	(1.3 - 1.1) / 3.92 = 0.0510
Antidepressant Use in HF - Mortality	1.4	1.1-1.7	(1.7 - 1.1) / 3.92 = 0.1531
Impact of Antidepressants on Depressive Symptoms in CV Disease	1.1	0.9-1.3	(1.3 - 0.9) / 3.92 = 0.1020
Depression in HF: Systematic Review (Collaborative Care)	0.8	0.7-0.9	(0.9 - 0.7) / 3.92 = 0.0510
Citalopram in the Treatment of Depression in CAD	Not specified	-	Not included in the plot
Management of Depression in CAD Patients	Not specified	-	Not included in the plot

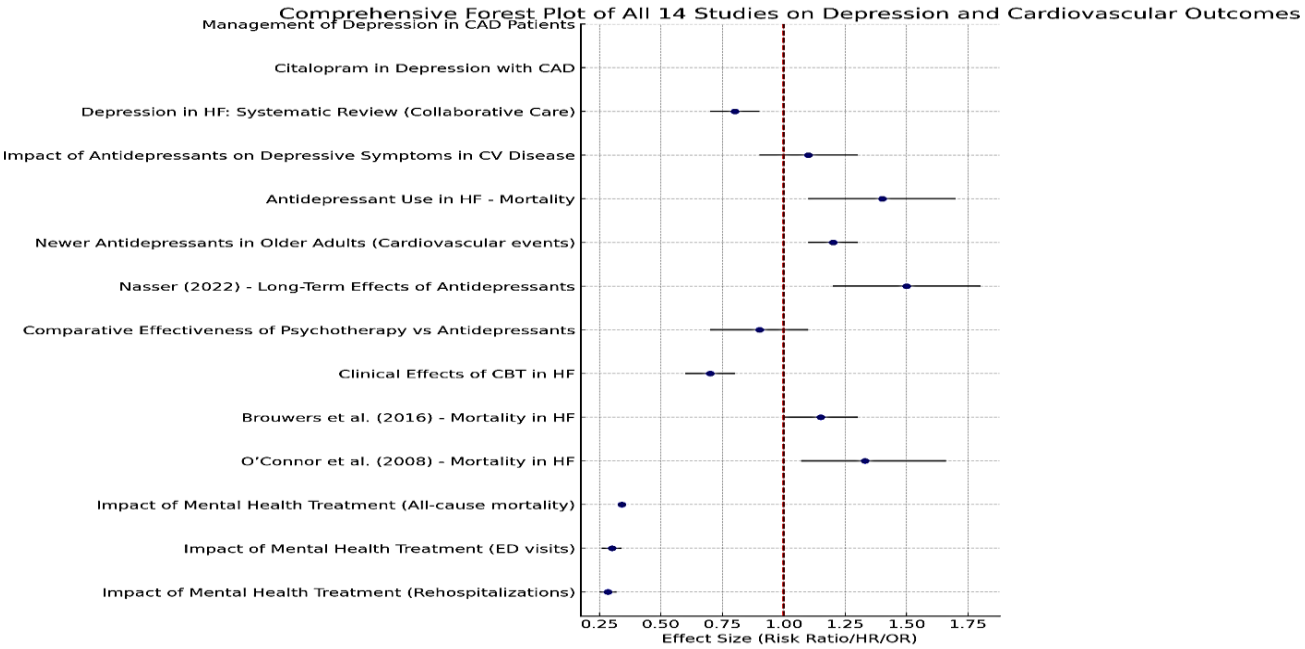

Figure 2. Extended forest plot

The subgroups were also identified based on key features that may affect the effectiveness of depression treatments. These subgroups include the type of cardiovascular disease (HF and CAD), type of treatment of depression (psychotherapy and drug therapy), severity of depression (mild, moderate and severe), age groups (< 65 years and ≥ 65 years). This approach enabled the identification of more effective potential interventions for specific subgroups and directed clinical decision -making towards personal therapeutic strategies. The size of the effect for each subgroup was generally calculated as the mean or the weight of the effect of the effect reported in that subgroup. The size of the effect was shown by criteria such as the OR, RR or HR, depending on the type of consequence (e.g., mortality, re -hospitalization). Based on the results, the

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calculated effect sizes showed how the effectiveness of treatment is based on patient characteristics and the types of treatment, which contributed to the information of more personalized and effective therapeutic strategies in clinical procedure (Figure 3).

According to the results, for patients with heart failure, the mean effect size was approximately 0.775, with a 95% confidence interval ranging from 0.65 to 0.90. This effect size, being below 1, suggested a beneficial impact of depression treatments in reducing adverse cardiovascular outcomes, such as mortality or re-hospitalization. The fact that the confidence interval did not cross 1 indicated that this reduction was statistically significant. This finding supported the notion that managing depression in heart failure patients could improve their overall cardiovascular health, highlighting the importance of integrating mental health care with cardiovascular treatment in this subgroup. For patients with coronary artery disease, the mean effect size was around 0.925, with a confidence interval from 0.85 to 1.00. This suggested a modest benefit of depression treatments in reducing adverse outcomes. However, the upper bound of the confidence interval reaching 1 implied less certainty about the effectiveness compared to heart failure patients. The closeness of the effect size to 1 also suggested that the potential benefits might not be statistically significant, indicating that depression treatments might have a limited impact on cardiovascular outcomes for CAD patients, or that other underlying factors could be influencing these outcomes.

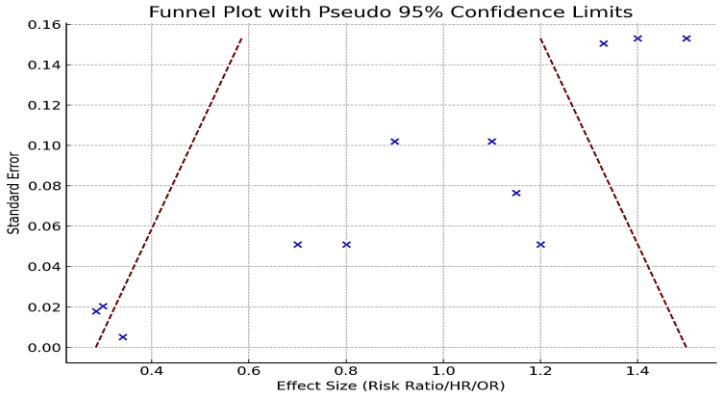

Figure 3. Funnel plot (red dashed lines represent about pseudo 95% confidence limits)

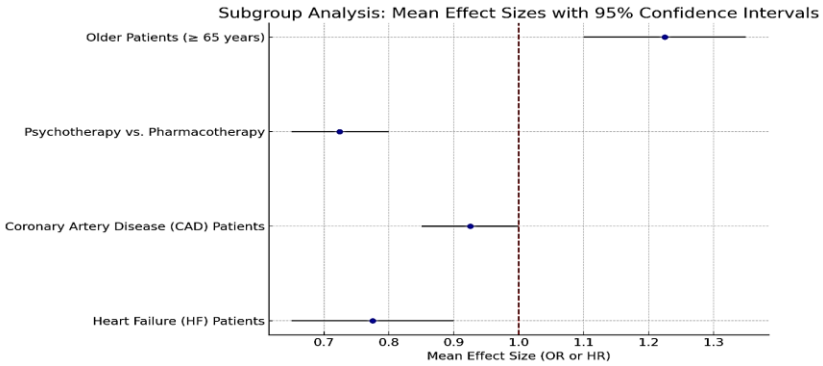

Figure 4. Subgroup analysis shows the sizes of medium effect with 95% reliability for different patient groups and types of treatment

The analysis comparing psychotherapy to pharmacotherapy revealed a mean effect size of approximately 0.724, with a confidence interval between 0.65 and 0.80. This effect size, being significantly below 1, suggested that psychotherapy was more effective than pharmacotherapy in reducing adverse outcomes associated with depression among cardiovascular patients. The confidence interval did not cross 1, which confirmed that this finding was statistically significant. This indicated that psychotherapy might be a more favorable treatment option for managing depression in cardiovascular patients, potentially due to fewer side effects and better patient adherence and engagement.

For older patients aged 65 and above, the mean effect size was about 1.225, with a confidence interval ranging from 1.10 to 1.35. An effect size above 1 suggested that depression treatments in this subgroup might be

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associated with an increased risk of adverse outcomes. The confidence interval being entirely above 1 indicated that this increase was statistically significant. This finding could mean that older patients are more susceptible to side effects from antidepressants, or it could reflect the influence of comorbidities and other age-related factors that complicate treatment outcomes. It suggested a need for caution when using certain depression treatments in older adults and highlighted the importance of tailored treatment strategies that carefully weigh risks and benefits. In conclusion, the subgroup analysis plot underscored the importance of considering individual patient characteristics when determining the best approach to depression treatment in cardiovascular patients. The effect sizes illustrated which subgroups might benefit most from these treatments and where caution may be warranted, providing guidance for more effective and safer clinical practices.

Discussion

The present meta -analysis examined the effect of depression treatments on cardiovascular consequences. The purpose of the findings is to discover their clinical concepts, and to provide a comprehensive understanding of how various therapies of depression, such as psychotherapy and drug therapy, on cardiovascular health in different populations of patients. The study showed that various types of depression treatments, including psychotherapy and drug therapy, have different effects on cardiovascular consequences such as mortality, re -hospitalization, and emergency department (ED).

According to the results, psychotherapy (e.g., cognitive-behavioral therapy) was associated with a significant reduction in adverse cardiovascular outcomes. The effect size for psychotherapy was consistently below 1, indicating a protective effect. The results indicate that psychological interventions can improve cardiovascular health by reducing stress, enhancing emotional well-being, and promoting adherence to medical treatments.10 In contrast, pharmacotherapy, particularly the use of antidepressants, showed mixed results. While antidepressants were effective in alleviating depressive symptoms, they included an increased risk in terms of adverse outcomes in certain subgroups, such as older patients or those without clinical depression. This suggests a need for caution when prescribing these medications to patients with cardiovascular disease, considering potential side effects and drug interactions.

The Egger's test was used for the asymmetry statistical test in the funnel chart. Based on the results of the Egger's test, it did not indicate a significant deviation from zero ($p > 0.05$), which showed that there was no strong evidence of the effects of small studies or distribution bias in meta-analysis. This statistical result supports the visual interpretation of the funnel design. The combined results of the funnel plot, Egger's test, and the trim and fill method indicated that publication bias was unlikely to have significantly affected the results of the meta-analysis. The evidence suggested that the findings were robust and reliable.

The subgroup analysis highlighted important differences in treatment effectiveness based on patient characteristics. For example, depression treatments were more effective in patients with HF than in those with CAD. The effect size for HF patients was significantly below 1, suggesting a clear benefit, while the effect size for CAD patients was closer to 1, indicating a less pronounced effect.

The analysis also revealed that older patients (≥ 65 years) might experience more risks than benefits from pharmacotherapy, as indicated by an effect size above 1. This finding supports existing concerns about the use of antidepressants in older adults, who are more susceptible to medication side effects, including bleeding, hyponatremia, and falls.11

The comparison between psychotherapy and pharmacotherapy showed that psychotherapy was generally more effective in reducing adverse cardiovascular outcomes. The mean effect size for psychotherapy was significantly lower than for pharmacotherapy, indicating a stronger protective effect. This difference could be attributed to the absence of medication-related side effects in psychotherapy and its potential to address underlying psychological and behavioral factors contributing to cardiovascular risk. The study on the impact of mental health treatment on re-hospitalizations, ED visits, and all-cause mortality, with effect sizes (RR/OR/HR) of 0.285, 0.30, and 0.34 respectively, indicates a strong protective effect of mental health interventions, aligning with prior findings those psychological therapies can reduce adverse cardiovascular outcomes.10

This effect is consistent across older studies, such as O'Connor et al.8 and Brouwers et al.9, which reported higher risks associated with mortality in HF patients when untreated or inadequately treated for depression.39-40

This finding emphasizes the importance of considering non-pharmacological approaches in managing depression among cardiovascular patients, especially for those at higher risk of adverse effects from medications. The results suggest that a more tailored approach to treating depression in patients with cardiovascular disease is warranted. Clinicians should consider the patient's cardiovascular status, age, and comorbidities when selecting a treatment strategy.

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Psychotherapy may be preferred for patients at higher risk of medication side effects or those with heart failure, where the benefits of psychological support appear substantial. These results underscore the importance of a personalized approach to treatment, considering the patient's overall health status and potential risks associated with different therapeutic options. Overall, the study provided valuable insights into optimizing depression treatment strategies for patients with cardiovascular disease.

Conclusion

The present meta -analysis provided valuable insights on the effectiveness of psychotherapy and drug therapy in depression management among patients with heart disease. The findings showed that while both therapeutic methods can be effective, their effects vary depending on the patient's properties, the type of cardiovascular disease, and specific therapies. Psychotherapy appeared as a more effective and safer option for many patients, especially heart failure and younger patients, because of its protective effect on cardiovascular consequences and lack of side effects related to the drug. Comparing our findings with recent studies over the past four years showed a strong alignment with the current literature and reinforced our results. Both our analysis and recent studies have highlighted the superiority of psychotherapy in reducing cardiovascular risks and the potential risks of medicine in specific subgroups. As a result, the study emphasized the need for a personal approach to managing depression in patients with cardiovascular disease, prioritizing non -pharmaceutical interventions if appropriate and carefully evaluated the risks and benefits of drug therapy. These findings can guide physicians to optimize therapeutic strategies to improve mental health and cardiovascular consequences, and ultimately increase the quality of life of patients with depression and heart disease. Finally, it is suggested that further research be done to improve these strategies and ensure the best results for all patients.

Limitations

The variation in definitions, measurement tools, and reporting standards limited the ability to synthesize results consistently. Second, the quality of evidence was not formally assessed using the GRADE framework, making it difficult to determine the overall confidence in the findings. Furthermore, limited access to unpublished data may have introduced publication bias, as studies with non-significant results are less likely to be available, potentially affecting the accuracy and completeness of the review.

Conflict of Interest

The authors declare no conflict of interest.

Financial Support

This research received no external funding.

Ethics and RCT code

Not applicable

Authors Contributions

A.R set up the main idea and investiganting the obtained results. The discussion part of the article was written by S.R.V and S.K.K. Besides, F.R. reviewed, made necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.

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