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Effect of antidepressants on death in patients with heart failure: a systematic review and meta-analysis

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Abstract

Depression is associated with an increased risk of death in patients with heart failure (HF); however, the association between the use of antidepressants and HF prognoses remains controversial. Therefore, this meta-analysis aimed to evaluate the effect of antidepressants on the risk of death in HF patients. We retrieved data from the PubMed and EMBASE databases until August 2019 for studies reporting the use of antidepressants in HF patients. Data were extracted from the eligible articles, and a random effects model was used to pool the effect estimates (risk ratios (RRs) and 95% confidence intervals (CIs)). A total of 8 studies were included in this meta-analysis. Overall, the use of antidepressants was associated with increased risks of all-cause death (RR = 1.27; 95% CI, 1.21–1.34) and cardiovascular death (RR = 1.14; 95% CI, 1.08–1.20) in HF patients with or without depression. Specifically, HF patients with depression taking antidepressants had increased risks of all-cause death (RR = 1.21; 95% CI, 1.16–1.27) and cardiovascular death (RR = 1.21; 95% CI, 1.13–1.30). Compared with nonusers, the use of selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and selective serotonin reuptake inhibitors (SNRIs) significantly increased the rate of all-cause death (SSRIs (RR = 1.26; 95% CI, 1.19–1.32), TCAs (RR = 1.30; 95% CI, 1.16–1.46), and SNRIs (RR = 1.17; 95% CI, 1.08–1.26)) but not cardiovascular death (SSRIs (RR = 1.03; 95% CI, 0.84–1.26), TCAs (RR = 1.02; 95% CI, 0.86–1.21), and SNRIs (RR = 0.92; 95% CI, 0.48–1.78)). Based on current publications, the use of antidepressants could increase the risk of all-cause death in HF patients, regardless of whether they have depression or the type of antidepressants they use. Further study is needed to determine the relationship between antidepressant use and cardiovascular death.

Keywords Heart failure · Depression · Antidepressant · Death

Introduction

Heart failure (HF) is associated with poor quality of life and frequent hospitalizations. Because of the increased risk of HF-related death, HF represents a heavy burden on both family and social health costs. Psychological disorders are prevalent in patients with HF, and these illnesses could lead to poor outcomes in HF [1, 2]. Prior meta-analyses have reported a 21.5% prevalence of depression among patients with HF [3]; further studies have demonstrated that depression in HF is associated with poorer prognoses and increased risk of death [3–5], particularly in elderly patients (age > 65 years) [4]. As such, the prescription of antidepressants is increasing in clinical practice [6].

Antidepressants are categorized as selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and others (tetracyclics, noradrenergic and specific serotonergic antidepressants (NaSSAs), selective serotonin reuptake inhibitors (SNRIs)). SSRIs and TCAs are the two major classes prescribed for cardiac patients with depression. However, the effect of antidepressant use on the risk of death in HF patients remains controversial. In patients with end-stage HF and depression, taking medications of β-blockers combined with SSRIs is associated with a reduced risk of cardiovascular death compared with the use of β-blockers without SSRIs [7]. Chung et al. [8] found that antidepressant use was not a

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predictor of cardiovascular hospital admission or all-cause death in HF patients when depressive symptoms remained. In contrast, several studies reported that antidepressants did not significantly reduce the risks of death or hospitalization in HF patients with or without depression [9–11]. Moreover, Brouwers et al. [12] and Fosb et al. [13] have proposed increased risks of death associated with antidepressants used in HF patients. Therefore, the role of antidepressants in HF patients should be further evaluated to guide treatment in clinical practice. We conducted a comprehensive meta-analysis to evaluate the effects of antidepressants on the risk of death in HF patients.

Methods

We performed this meta-analysis based on the protocol and reporting of the results from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [14].

Study search strategy

The PubMed and EMBASE computer-based databases were systematically searched from inception to August 2019 for studies that evaluated the use of antidepressants in HF patients. The following keywords were used and limited to retrieval in the titles and abstracts: *heart failure* AND (*psychological factors* OR *psychological distress* OR *emotional distress* OR *depression* OR *depressive symptom* OR *antidepressant*) AND (*mortality* OR *death*). We did not apply the language restrictions in the search. Non-English studies were translated into English by an author (JY-M) using Google's automatic-translation software. The literature search strategy is presented in Supplemental Table 1. The reference lists of all relevant studies were also searched to identify additional reports.

Eligibility criteria

Studies were included if they met the following criteria: (1) studies that reported antidepressant use and the consequent risk for all-cause death and cardiovascular death in HF patients; (2) randomized controlled trials (RCTs) or observational studies with comparison and control groups; and (3) studies that reported the unadjusted or adjusted risk ratios (RRs) with 95% confidence intervals (CIs). Reviews, letters to the editor, case reports, comments, editorials, and meeting abstracts were excluded. In the case of multiple publications analyzing the same population, the study with the longest follow-up time or with the largest sample size was selected.

Study selection and data extraction

According to the predefined criteria, study selection and data extraction were performed by two interdependent authors (WF-H and YH-F). All discrepancies were resolved through discussion. The first phase of study selection was based on the titles and abstracts. In the second phase, the full texts were assessed to detect whether the study met the inclusion criteria. For each study, the following information was recorded: the first author, publication year, geographic location, participant information (sex, age, and sample size), categories of antidepressants, follow-up time, and RRs with 95% CIs. When both unadjusted and adjusted RRs were presented in one study, the maximally adjusted RR value was extracted.

Quality assessment

The methodological quality of the RCTs was assessed independently by two authors (WF-H and YH-F) using the Cochrane Risk of Bias Tool [15]. We assessed the quality of observational studies using the Newcastle-Ottawa score [16, 17].

Statistical analysis

The RRs with 95% CIs were regarded as the common risk estimates. The consistency test was evaluated using Cochran's Q test complemented with the I^2 statistic, where $P < 0.1$ or $I^2 > 50\%$ indicated high heterogeneity. The effect measures were transformed to their natural logarithms (logRR), and the standard error (SElogRR) was calculated from the corresponding CIs. An inverse-variance weighted random effects model was used to pool these natural logarithms. In the sensitivity analysis, a fixed effects model was used to examine the robustness of the results. We performed a subgroup analysis based on the types of antidepressants (SSRIs, TCAs, and SNRIs). The publication bias was assessed using a funnel plot. All statistical analyses were performed using Review Manager version 5.3 software (Cochrane Collaboration 2014, Nordic Cochrane Center Copenhagen, Denmark).

Results

Study selection

The flowchart of electronic retrievals is shown in Supplemental Figure 1. Ultimately, a total of 8 studies (2 RCTs [9, 10] and 6 observational studies [11–13, 18–20]) published between 2007 and 2016 were included in this meta-analysis. The basic characteristics of the selected studies are shown in Table 1. Overall, 5 studies were from Europe, and 3 studies were from North America. The sample size of these

Table 1 Baseline characteristics of the included studies

Study	Country	Study design	Simple size (*n*)	Mean age (y)/sex	Follow-up time (y)	Type of antidepressants	Study quality*
Angermann-2016	Germany	RCT	372	62.3/both	1.5	SSRIs-Escitalopram	Low risk
O'Connor-2010	USA	RCT	469	62.2/both	2.2	SSRIs-Sertraline	Low risk
Brouwers-2016	Danish	Retrospective cohort	19,348	73.5/both	5.0	TCAs, SSRIs, others (tetracyclics, NaSSAs, SNRIs)	NOS = 7
Diez-Quevedo-2013	Spain	Prospective cohort	1017	68.0/both	5.4	SSRIs, TCAs	NOS = 7
Veien-2011	Danish	Prospective cohort	4012	69.1/both	1.5	Nonselective monoamine reuptake inhibitors, SSRIs, monoamine oxidase inhibitors (nonselective), monoamine oxidase A inhibitors, others (tetracyclics, NaSSAs, SNRIs)	NOS = 8
Fosbol-2009	Danish	Retrospective cohort	99,335	74.2/both	1.9	SSRIs, TCAs	NOS = 7
O'Connor-2008	USA	Prospective cohort	1006	69.1/both	2.7	SSRIs, TCAs, and others (bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine)	NOS = 8
Sherwood-2007	USA	Prospective cohort	204	56.8/both	3.0	SSRIs, TCAs, monoamine-oxidase inhibitors	NOS = 8

SSRIs, selective serotonin reuptake inhibitors; *TCAs*, tricyclics; *SNRIs*, selective serotonin reuptake inhibitors; *NaSSA*, noradrenergic and specific serotonergic antidepressant; *RCT*, randomized controlled trial; *y*, years; *NOS*, Newcastle-Ottawa score

*The quality of the RCTs and observational studies was assessed based on the Cochrane Risk of Bias Tool and the Newcastle-Ottawa score, respectively

studies ranged from 372 to 99,335, with a total of 125,763 participants. The mean age of patients ranged from 56.8 to 73.5 years. The follow-up duration varied from 1.4 to 5.0 years. The methodologic quality of all the included studies was acceptable.

Relationship between antidepressant use and death

A total of 8 and 5 studies reported the outcomes of all-cause death and cardiovascular death, respectively. As shown in Fig. 1, the use of antidepressants was associated with the risks of all-cause death (RR = 1.27; 95% CI, 1.21–1.34, $P < 0.00001$; $I^2 = 64\%$) and cardiovascular death (RR = 1.14, 95% CI, 1.08–1.20, $P < 0.00001$; $I^2 = 32\%$) in patients with HF with or without depression.

Sensitivity analysis In the sensitivity analysis, the aforementioned results remained stable after omitting 1 study at a time. In addition, only two RCTs focused on HF patients with depression [9, 10]. Consistent with the results of the main analyses, HF patients with depression taking antidepressants had increased risks of all-cause death (RR = 1.21; 95% CI, 1.16–1.27; $P < 0.00001$; $I^2 = 0\%$) and cardiovascular death (RR = 1.21; 95% CI, 1.13–1.30; $P < 0.00001$; $I^2 = 0\%$) compared with nonusers (Fig. 2). The results also did not change when we reperformed these analyses with fixed effects models. In addition, the included study of Veien et al. [19] specifically assessed the association between depression and mortality risk, and pharmacologically treated depression was defined as treatment with at least one antidepressant. We performed the sensitivity analysis and excluded this study, and the corresponding results did not change.

Subgroup analysis The subgroup analysis was performed based on the types of antidepressants (SSRIs, TCAs, SNRIs). As a result, compared with the corresponding nonusers, the use of SSRIs, TCAs, and SNRIs significantly increased the rates of all-cause death (SSRIs (RR = 1.26; 95% CI, 1.19–1.32; $P < 0.00001$), TCAs (RR = 1.30; 95% CI, 1.16–1.46; $P < 0.00001$), and SNRIs (RR = 1.17; 95% CI, 1.08–1.26; $P < 0.0001$); Fig. 3) but not cardiovascular death (SSRIs (RR = 1.03; 95% CI, 0.84–1.26; $P = 0.77$), TCAs (RR = 1.02; 95% CI, 0.86–1.21; $P = 0.85$), and SNRIs (RR = 0.92; 95% CI, 0.48–1.78; $P = 0.81$; Fig. 4).

Publication bias

As shown in Fig. 5, no obvious publication bias was observed by inspecting the funnel plot.

Discussion

To the best of our knowledge, we conducted the first meta-analysis to assess the relationship between antidepressant use and death in HF patients. With the use of data from 8 studies, our current meta-analysis suggested the following: (1) the use of antidepressants (SSRIs, TCAs, SNRIs) was associated with an increased risk of all-cause death in HF patients, regardless of whether the patients had clinical depression; and (2) there

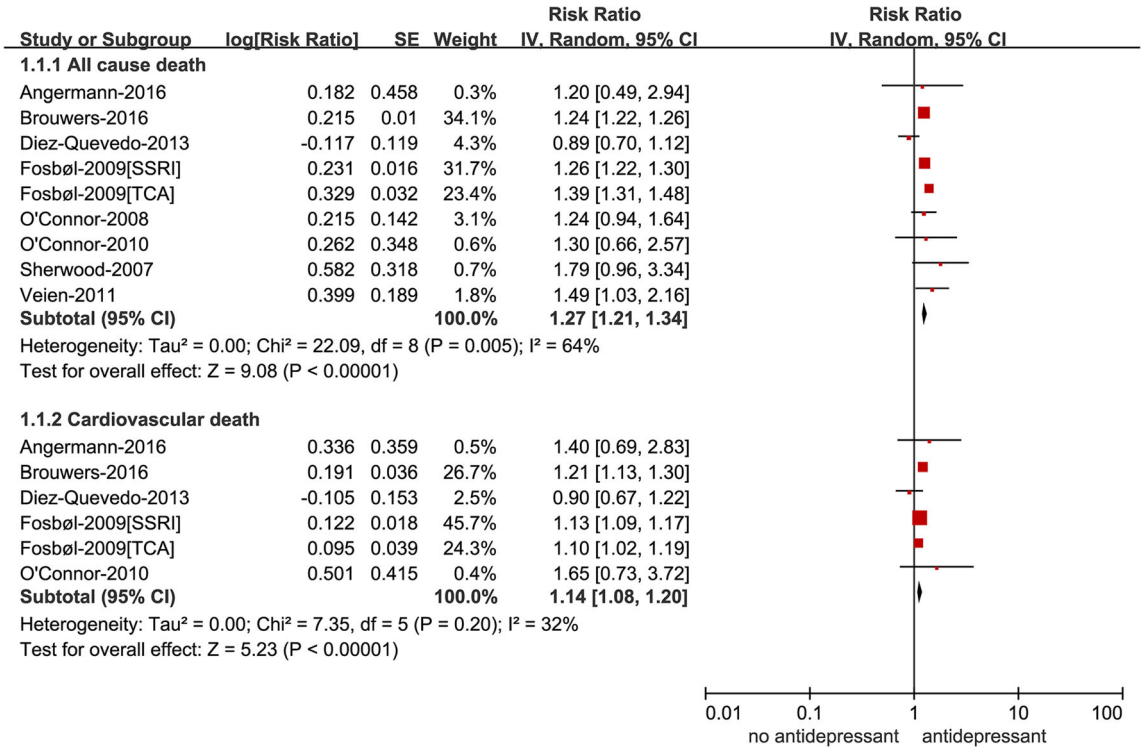

Fig. 1 Forest plot of antidepressant use on all-cause death and cardiovascular death in HF patients with or without depression. *HF*, heart failure; *RR*, risk ratio; *CI*, confidence interval; *SE*, standard error; *IV*, inverse of the variance

was a relatively weaker association (14% increased risk) between antidepressant use and cardiovascular death. However, the use of SSRIs, TCAs, or SNRIs was not associated with an increased rate of cardiovascular death when these drugs were analyzed separately.

Our current data found a significantly elevated risk of all-cause death in HF patients treated with antidepressants. The reasons for this finding are not yet clear, but different hypotheses have been proposed. In patients with HF, the use of antidepressants appears to improve depressive symptoms based on the validated measuring method of depression [21–24]. However, HF patients taking antidepressants still show high rates of at least mild-to-moderate depressive symptoms [25]. As such, antidepressants might not be capable of sufficiently alleviating depressive symptoms to reduce the risk of death. A prior meta-analysis indicated an increased risk of death in HF patients with major depression but not mild depression [26]. This finding might suggest that the use of

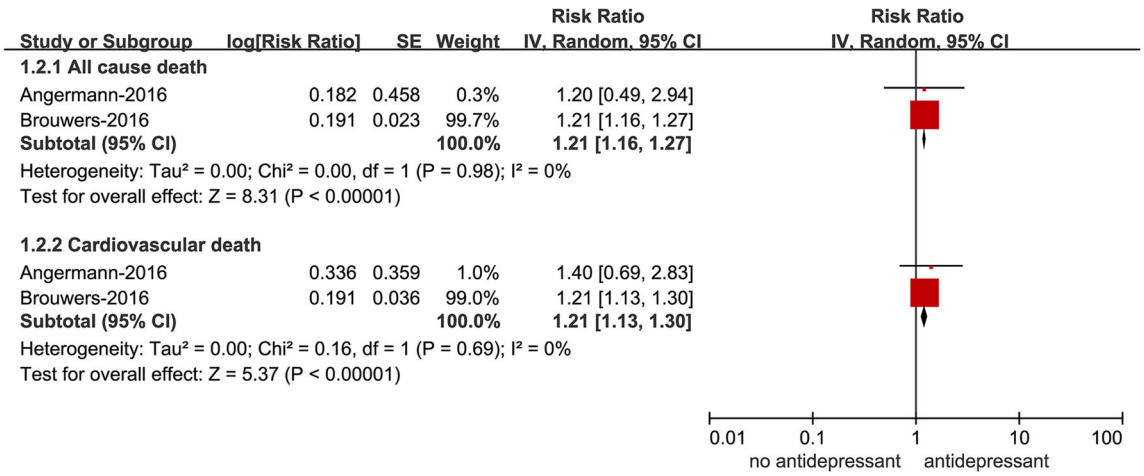

Fig. 2 Forest plot of antidepressant use antidepressants on all-cause death and cardiovascular death in HF patients with depression. *HF*, heart failure; *RR*, risk ratio; *CI*, confidence interval; *SE*, standard error; *IV*, inverse of the variance

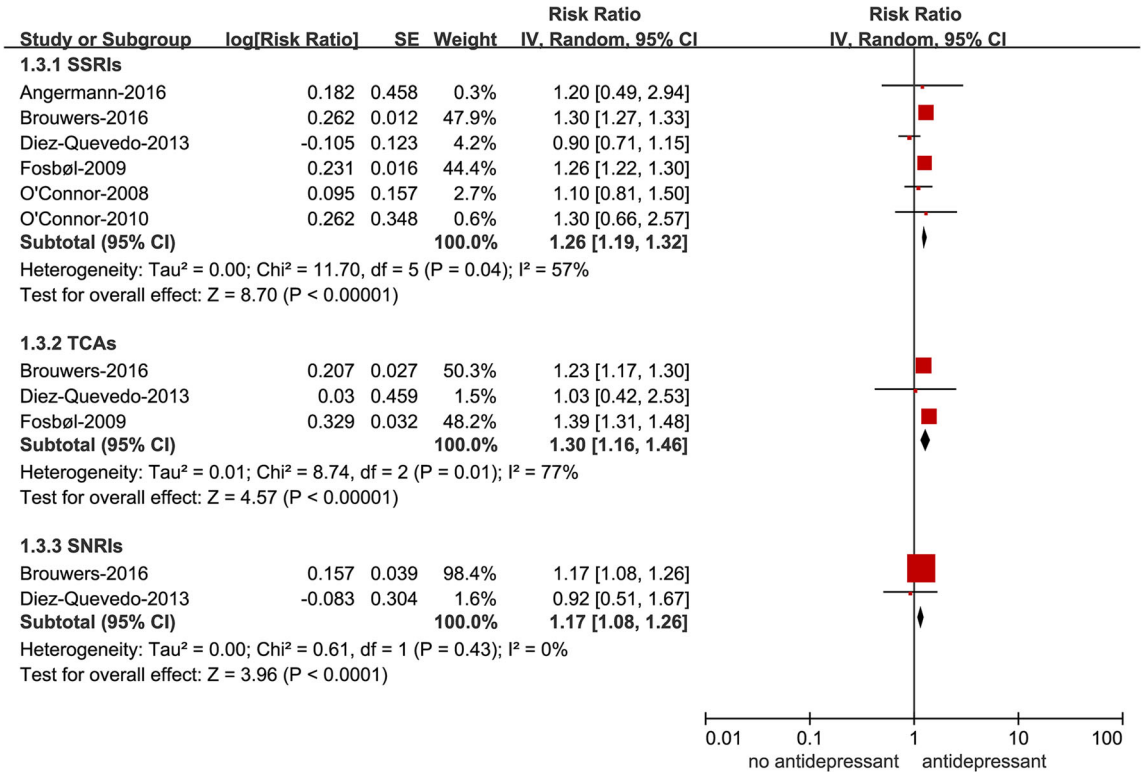

Fig. 3 Forest plot of SSRIs, TCAs, and SNRIs on all-cause death in HF patients with depression. *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclics; *SNRIs*, selective serotonin reuptake inhibitors; *HF*, heart failure; *RR*, risk ratio; *CI*, confidence interval; *SE*, standard error; *IV*, inverse of the variance

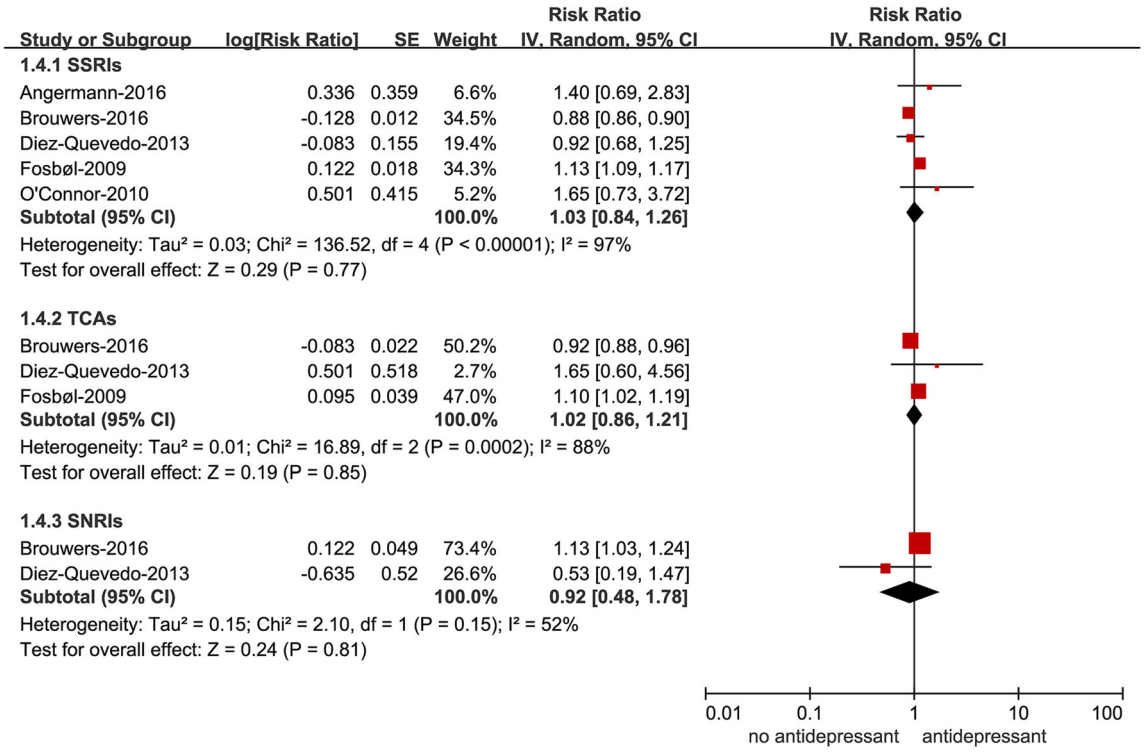

Fig. 4 Forest plot of SSRIs, TCAs, and SNRIs on cardiovascular death in HF patients with depression. *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclics; *SNRIs*, selective serotonin reuptake inhibitors; *HF*, heart failure; *RR*, risk ratio; *CI*, confidence interval; *SE*, standard error; *IV*, inverse of the variance

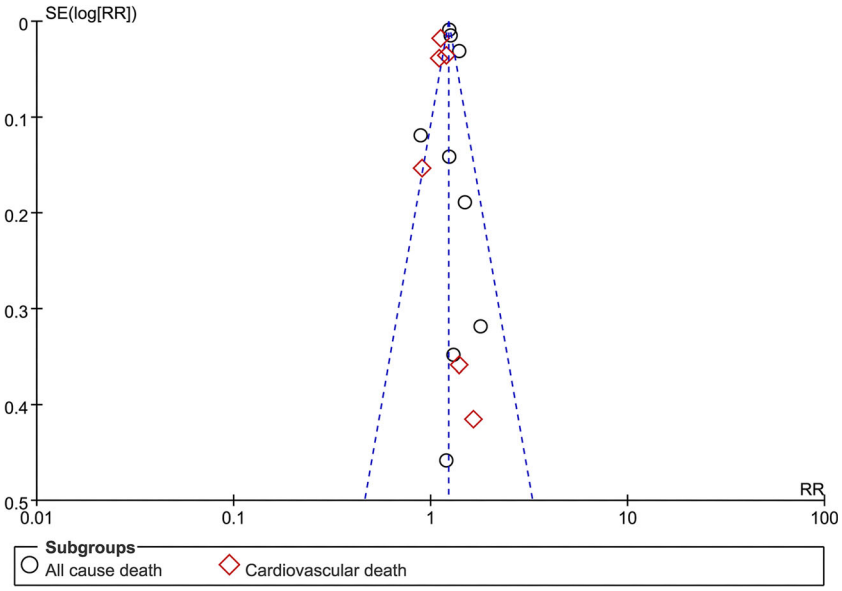

Fig. 5 Funnel plot of the reported outcomes (all-cause death and cardiovascular death) in the included studies. *RR*, risk ratio; *SE*, standard error

antidepressants would not reduce the risk of death in these patients with mild depression. Moreover, drug interactions could increase the risk of death by aggravating the side effects of drugs. For example, a case of bradycardia after the co-administration of paroxetine and metoprolol has been reported before [27]. In addition, β-blockers that are associated with reduced death risk are administered less frequently in HF patients with depression, contributing to the decreased survival rate [28]. Finally, some included studies might have patient selection bias, indicating that HF patients taking antidepressants actually suffered from more serious depression symptoms than nonusers did.

SSRIs were considered the standard pharmacological treatment of depression through the selective inhibition of the reuptake of 5-hydroxytryptamine (5-HT) by the presynaptic membrane in the central nervous system to increase the concentration of 5-HT in the synaptic cleft. Adverse cardiovascular responses during the administration of SSRIs are rare because of their high selectivity for therapeutic targets. TCAs can block the reuptake of noradrenaline and 5-HT by the presynaptic membranes of nerve endings and increase the concentration of monoamines at the synaptic cleft. In addition, TCAs can also retard the acetylcholine receptor, histamine H1 receptor, and noradrenalin α1 receptor, which can trigger adverse nervous system reactions, such as excessive sedation, delirium, extrapyramidal symptoms, and epileptic seizures, as well as an increased heart rate and postural hypotension. Current guidelines on the pharmacological management of depression in patients with cardiac disease also propose that SSRIs are relatively safer than TCAs [29]. TCAs could promote arrhythmias because of increased heart rate and prolonged QT intervals. These pharmacological characteristics could potentially increase the risk of cardiovascular death. However, interestingly, although a 14% increased risk of cardiovascular death was found in HF patients taking any antidepressants, SSRIs, TCAs, and SNRIs did not appear to increase the risk of cardiovascular death when they were analyzed separately. The overall increased risk of cardiovascular death in HF patients might be explained by other antidepressants, such as tetracyclics and NaSSAs that were potentially linked to a higher risk of cardiovascular death [12]. Our data in relation to the association between antidepressant use and cardiovascular death should be interpreted cautiously. Further study should confirm these findings in HF patients.

Since depression could increase the risk of death among HF patients, HF patients with depression symptoms are treated with antidepressants more frequently, even if the patients have no clinical depression. Consequently, antidepressants have been increasingly used by patients in recent years to alleviate depression symptoms. Our findings suggest that HF patients should be cautious when antidepressants are administered because of the increased risk of death. Antidepressant treatments for HF patients should be based on individual patient-level therapeutic strategies, such as the degree of patients' depression, HF severity, and general conditions.

Several limitations should be considered in this meta-analysis. First, residual confounders might exist given the nature of the observational data used in this study. Second, a higher prevalence of antidepressant use was observed in female patients with HF than in male patients, which raised the possibility that antidepressants might function differently depending on sex. However, the subgroup analysis based on sex could not be performed due to the limited data. Third, the number of included studies in some comparisons was relatively small, thus limiting the validity of these findings. Fourth, the major objective was pooling RCTs and observational studies; however, the results of our sensitivity analysis based on RCTs were consistent with the results of the main analyses.

Finally, the methods of clinically validated assessments of depression differed across studies, and the heterogeneous populations might limit the generalizability of the findings to all HF patients in clinical practice.

Conclusions

Based on current publications, the use of antidepressants was associated with an increased risk of all-cause death in HF patients, regardless of whether they have clinical depression or the type of antidepressants they use. Further study should confirm the association between antidepressant use and cardiovascular death in HF patients.

Contributors WF-H and YH-F performed the whole meta-analysis, including literature search, data extraction, statistical analysis, and writing the manuscript. Y-Z, B-W, and JY-M offered help in the process of revision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required.

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