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Comparison of treatment options for depression in heart failure: A network meta-analysis

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ABSTRACT

Background: Depression independently predicts poor outcomes in heart failure (HF) patients, including increased mortality, morbidity and 30-day re-hospitalization. In this network meta-analysis, we compared different interventions designed to treat depression in HF.

Materials and methods: Electronic searches were conducted using Ovid MEDLINE, EMBASE, CINAHL, Web of Science, and PsycINFO up to November 2016. Included randomized clinical trials (RCTs) compared interventions (Exercise therapy (ET), cognitive behavioral therapy (CBT) or antidepressant (AD) medications) for depression in heart failure patients. The primary outcome was change in depressive symptoms based on validated measures of depression. Network meta-analysis based on random effects model estimating standardized mean difference (SMD) with 95% confidence interval (CI), compared the effects of the 3 classes of interventions with respect to usual care or placebo control conditions.

Results: A total of 21 RCTs (including 4563 HF patients) reporting the effects of treating depression in HF patients were included in the analysis. In comparison to placebo or usual standard of care, ET (SMD -0.38; 95% CI -0.54 to −0.22) and CBT (SMD -0.29; 95% CI -0.58 to −0.01) were associated with reduction in depressive symptoms whereas AD (SMD -0.16; 95% CI -0.44 to 0.11) was less effective.

Conclusions: This meta-analysis is suggestive of therapeutic benefit of ET and CBT in comparison to usual standard of care in treating depression in HF patients. However, comparison among the three interventions was not conclusive. Future randomized clinical trials are warranted to compare the therapeutic effects of ET, CBT and AD in such patients.

1. Introduction

With 550,000 new cases of heart failure (HF) diagnosed annually in US alone, heart failure has fueled a worldwide pandemic (Fishman et al., 2010; WRITING GROUP MEMBERSLloyd-Jones et al., 2010; McMurray, 2010). Depression is an independent prognostic factor in HF patients and is associated with greater mortality (Friedmann et al., 2006; Vaccarino et al., 2001; Jiang et al., 2004; Faris et al., 2002), morbidity (Joynt et al., 2004; Gottlieb et al., 2004; Depression: Are We Ignori, 2017) and reduced quality of life (QoL) (Heo et al., 2009; DeWolfe et al., 2012; Mårtensson et al., 2003). In a seminal meta-analysis by Rutledge and colleagues, the prevalence of clinically significant depression was shown to be almost 3 times higher among patients with HF compared to the general population (Rutledge et al., 2006). Notably, the 2014 American Heart Association (AHA) guidelines on depression and coronary heart disease recommended that depression should be considered as an independent risk factor for poor prognosis in acute coronary syndrome (ACS) which is a leading cause of HF

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(Lichtman et al., 2014). Several interventions have been used to treat depression in HF, but antidepressants (ADs), exercise training (ET) and cognitive behavioral therapy (CBT) have been studied most often. A recent study by Angermann et al. (2016) reported a small and non-significant effect of ADs on depression and cardiovascular outcomes in HF patients with a follow-up period of 12 months. CBT represents an additional intervention for depression in HF, but its efficacy is uncertain because of a limited number of randomized clinical trials (RCTs). Several studies have shown that ET can have a beneficial effect for depressive symptoms (Rimer et al., 2012; Cooney et al., 2013), as well as clinical outcomes in HF patients (Anderson et al., 2016; Sagar et al., 2015; Pandey et al., 2015). A secondary analysis from the HF-ACTION study (Blumenthal et al., 2012a) and subsequent meta-analysis have demonstrated the beneficial effects of ET on depressive symptoms in HF patients (Tu et al., 2014), making ET a viable therapeutic alternative for patients with HF (Tu et al., 2014). However, the relative benefits of ET compared to AD or CBT remain unclear. Although no single study compared the effectiveness of AD, ET and CBT, we performed a network meta-analysis to explore the comparative benefit of antidepressant medications (AD), cognitive behavioral therapy (CBT) and exercise training (ET) with respect to usual care or placebo control conditions in treating depressive symptoms in HF patients.

2. Methods

2.1. Study design

A systematic review with network meta-analysis with frequentist approach was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs (Moher, 2009). We used a predefined study protocol and our study is registered in PROSPERO (42016049005).

2.2. Search strategy

Electronic searches were conducted of Ovid MEDLINE, EMBASE, CINAHL, Web of Science and PsycINFO up to November 2016. The full database search strategies are provided in Appendix 1. The searches were limited to studies published in English and animal studies were excluded. All identified studies were combined in a single reference manager file (EndNote) and uploaded in an online software (Covidence). Duplicates were discarded, and the title and abstracts were reviewed by two authors independently (AD and BR) to exclude studies that did not report the interventional outcomes related to depression in HF patients. The full texts of the remaining articles were examined to determine whether they contained relevant information. Disagreements were harmonized by consensus, in conjunction with the senior investigator (SD). Second, the reference lists from included original articles and recent reviews and meta-analyses on related topics were hand searched to identify additional studies. When necessary, the original investigators were contacted to clarify data or provide additional data. Fig. 1 summarizes the study identification and selection process.

2.3. Study selection

Eligibility criteria for the inclusion of studies were (i) RCTs; (ii) included patients with HF (any etiology) in the control and in the intervention group (diagnosis based on LVEF or clinical findings); (iii) if patients received ADs (tricyclic antidepressants or selective serotonin receptor inhibitor); (iv) if patients received ET of any form (either alone or as part of a comprehensive cardiac rehabilitation program); (v) if patients received CBT (either alone or as part of a comprehensive cardiac rehabilitation program); (vi) compared with a standard medical treatment or education placebo control group (clubbed together as control); and (vii) assessed the effect of interventions (before and after the interventions) on depression or depressive symptoms in terms of validated measures of depression (MADRS,BDI,HAM-D/HDRS, PHQ-9,HADS, ZDRS,CES-D,GDS,CBA-H, MAACL, Hare-Davis Cardiac Depression Scale). A detailed account of PICOS element of inclusion and exclusion is shown in Appendix 2.

2.4. Data abstraction

Two reviewers (AD and OZ) independently abstracted data on the following study and patient-related characteristics onto a standardized form: (a) study characteristics – last name of primary author, time period of study/year of publication, country/region of the population studied and type of study, (b) patient characteristics – total number of participants and number of patients receiving intervention and number of patients receiving placebo, gender of the patients, duration of follow-up of the studies, type of active interventions, clinical characteristics (age, New York Heart Association (NYHA) classification, Left Ventricular Ejection Fraction (LVEF).

2.5. Outcomes assessed

Our primary outcome was the change in depressive symptoms, based on the reported depression scale score. Attrition bias was taken into consideration and patients who completed the trials were taken in our analysis. In cases where the clinical trials reported multiple standardized depressive scoring systems, we used a predefined hierarchy, based on psychometric properties, frequency of use in HF patients and consistency of use across included trials (Appendix 3).

2.6. Quality assessment

The risk of bias in these individual clinical trials was assessed by 2 authors (AD and BR) independently using the Cochrane collaboration's tool for assessing the risk of bias, which evaluates validity and bias in studies of prognostic factors across 7 domains: random sequence generation bias, allocation concealment, blinding of participants/personnel, outcome assessor blinding, incomplete outcome data, selective reporting (reporting bias) and other bias (Cochrane Handbook for Sys, 2017). (Appendix 4).

2.7. Data synthesis and statistical analysis

R software version 3.4.1 and RStudio version 1.0.136 were used to perform statistical analysis. As studies have used different depression rating score, standardized mean difference (SMD) was calculated as the effect size (Furukawa et al., 2002). We performed a network meta-analysis using the R package netmeta (meta.pdf [Internet]. [cit, 2017). R-code used for the network meta-analysis and subgroup analysis is provided in Appendix 5. Additionally, the contribution of direct and indirect evidence in the network meta-analysis was assessed using the GRADE framework which characterises the quality of a body of evidence incorporating study limitations inconsistency, imprecision, indirectness, and publication bias for the primary outcomes (Working Group app, 2017). Estimation of the proportion of total variation across studies was due to heterogeneity rather than chance, inconsistency index (I^2 statistic) was calculated; quartiles of $< 30\%$, 30%–59%, 60%–75%, and $> 75\%$ were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively (Baujat et al., 2002). We used Begg and Mazumdar' rank correlation test to evaluate publication bias where P-scores are calculated to rank intervention according to their treatment effect (Rücker and Schwarzer, 2016). Qualitative assessment of publication bias was conducted through visualization of funnel plot.

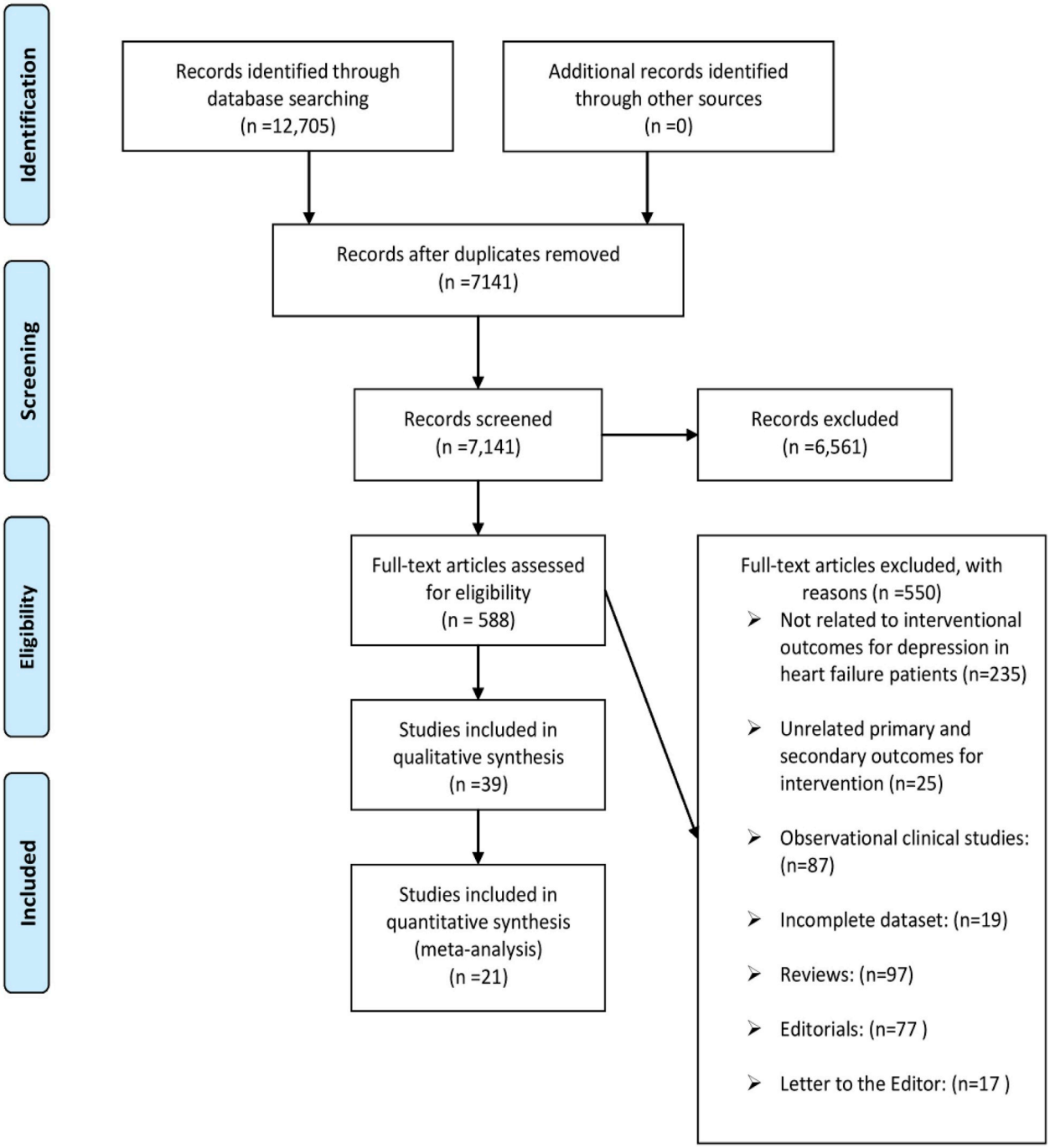

Fig. 1. Study selection flow chart.

2.8. Subgroup and sensitivity analyses

Despite randomization, covariates like age, duration of study and LVEF results in heterogeneity between different interventions and control groups. To circumvent this issue and assess robustness of the analysis and also to verify the consistency of primary outcome subgroup analysis was performed based on the duration of follow-up after intervention (> 3 months or ≤3 months), mean age of the patients (> 65 years or ≤65 years) and left ventricular ejection fraction (LVEF) (> 50% or ≤50%).

3. Results

Overall, 12,705 citations were identified by the search and 588 potentially eligible articles were retrieved in full-text (Fig. 1). A total of 21 RCTs were identified and included for quantitative synthesis in our meta-analysis (Fig. 1).

3.1. Characteristics and quality of included studies

The included 21 RCTs randomized 4563 HF patients with depression. Appendix 6 shows a list of included studies in our analysis. The median follow-up duration was 3.5 months after treatment initiation, with the minimum being 1.5 months (Table 1). The mean sample size is 208 patients, ranging between 24 and 2322 participants. The mean age of the study population was 62.9 ± 6.5 years and 60.85% subjects were men. 10 trials (47%) recruited patients from North America, 9 (43%) from Europe, and 1 (5%) each from South America and Australia.

Table 1
Characteristics of included studies.

Study	Year	Location of the study	Design Type	Mean Age (years)	Male/ Females (%)	Mean NYHA	NYHA (Experimental Group)	NYHA (Control Group)	LVEF (%)	Total Participants	Interventions	Duration of follow-up	Primary and secondary outcome
Giannuzzi[21]	1997	Italy	RCT	53.5	95/5	I/III	N/A	N/A	34	80	Exercise vs Usual care	6 months	**Primary Outcome:** work capacity, left ventricular volumes (end diastolic volume), ejection fraction **Secondary Outcome:** Changes in Cognitive Behavior
Berg-Emons[16]	2004	Netherlands	RCT	58.6	73/27	II/III	II:10 III:8	II:10 III:6	25.6	34	Exercise vs Usual care	3 months	**Primary Outcome:** everyday physical activity (PA, novel accelerometry-based activity monitor) and quality of life **Secondary Outcome:** exercise capacity, fear of movement, satisfaction with everyday PA, feelings of being disabled, depression, anxiety
Gary[14]	2004	United States of America	RCT	68	0/100	II-III	II: 6 III: 10	II: 7 III: 9	55.5	32	Exercise vs Usual care	3 months	**Primary outcome:** Functional performance in terms of Six Minute Walk Test (6MWT) **Secondary outcome:** Quality of Life and changes in geriatric depression
Kulcu[19]	2006	Portugal	RCT	59.4	73/27	II/III	II:9 2.5: 6 III:6	II:1 2.5: 11 III:11	N/A	53	Exercise vs Usual care	2 months	**Primary Outcome:** Ergospirometric exercise test, change in depression, Health Related Quality of Life **Secondary Outcome:** N/A
Witham[13]	2006	United States of America	RCT	80.5	80/20	I-II	II:37 III:16	II:48 III:6	57.8	107	Exercise vs Usual care	6 months	**Primary Outcome:** change in 6 MW distance **Secondary Outcome:** markers of physical function, quality of life
Dracup[12]	2007	United States of America	RCT	54	72/28	II-IV	II: 28, III: 52, IV: 7	II: 19, III: 57 IV: 10	26.4	173	Exercise vs Usual care	12 months	**Primary outcome:** all-cause hospitalizations, emergency department admissions, urgent transplantation and death **Secondary outcome:** functional status, quality of life and psychological states
Jolly[17]	2008	United Kingdom	RCT	68	75/25	I-III	I:4, II:63 III:17	I: 6, II:62 III:17	≤40	169	Exercise vs Usual care	12 months	**Primary Outcome**: disease-specific quality of life **Secondary Outcome**: composite outcome of death or admission with heart failure or myocardial infarction; incremental shuttle walking test (ISWT), psychological wellbeing, self-reported physical activity blood pressure a generic measure of health-related quality of life; and health care utilization.
Fraguas[2]	2009	Brazil	RCT	> 65	48/52	N/A	N/A	N/A	< 50	37	AD(Citalopram) vs Placebo	2 months	**Primary Outcome:** changes in depression **Secondary Outcome:** N/A
Gary[7]	2010	United States of America	RCT	65.8	42/58	II/III II:32 III:42	N/A	N/A	≥15	39	CBT vs Exercise	6 months	**Primary Outcome:** reduction in depression, changes in 6MWT distances, improvement in Health-related Quality of Life **Secondary Outcome:** N/A
Gary[7]	2010	United States of America	RCT	65.8	42/58	II/III II:32 III:42	N/A	N/A	≥15	37	Exercise vs Usual care	6 months	**Primary Outcome:** reduction in depression, changes in 6MWT distances, improvement in Health Related Quality of Life **Secondary Outcome:** N/A
Gary[7]	2010	United States of America	RCT	65.8	42/58	II/III II:32 III:42	N/A	N/A	≥15	36	CBT vs Usual Care	6 months	**Primary Outcome:** reduction in depression, changes in 6MWT distances, improvement in Health Related Quality of Life **Secondary Outcome:** N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Location of the study	Design Type	Mean Age (years)	Male/ Females (%)	Mean NYHA	NYHA (Experimental Group)	NYHA (Control Group)	LVEF (%)	Total Participants	Interventions	Duration of follow-up	Primary and secondary outcome
O'Connor[3]	2010	United States of America	RCT	62.1	59/41	II-IV	II:71 III:109 IV:54	II:61 III:114 IV:60	30.4	469	AD(Sertraline) vs Placebo	3 months	**Primary Outcome:** severity of depression and composite cardiovascular status, cardiovascular events and survival during the short-term treatment phase and long-term follow-up were also assessed. **Secondary Outcome**
Bosnak-Gulcu[9]	2011	Turkey	RCT	67.6	80/20	II-III	II:11 III:5	II: 9 III:5	34.8	30	Exercise vs Usual care	1.5 months	**Primary Outcome:** Functional capacity and balance, respiratory muscle strength, quadriceps femoris muscle strength, pulmonary function, dyspnea, fatigue, quality of life, and depression **Secondary Outcome:** N/A
Dekker[5]	2011	United States of America	RCT	66	54/46	II-IV	II: 6 III: 15 IV:0	II:2 III:16 IV:3	39.5	41	CBT vs Usual care	3 months	**Primary Outcome:** Depressive symptoms, **Secondary Outcome:** negative thinking and health-related quality of life
Årgen[4]	2012	Sweden	RCT	68.4	75/25	II-IV	II:25, III:39, IV:7	II:25 III:43 IV:16	N/A	155	CBT(Psychoeducation) vs Usual care	3 months	**Primary Outcome:** perceived control, perceived health, depressive symptoms, self-care, and caregiver burden. **Secondary Outcome:** N/A
Blumenthal[8]	2012	United States of America	RCT	59	70/30	III/IV	II: 723 III-IV:435	II:748 III-IV:416	25	2322	Exercise vs Usual care	12 months (for depression)	**Primary Outcome**: all-cause mortality or all-cause hospitalization; change in depression **Secondary Outcome:** cardiovascular (CV) mortality and hospitalization and HF mortality and hospitalization served as combined secondary medical endpoints.
Gary[15]	2012	United States of America	RCT	50	50/50	II/III	II:4 III:8	II:6 III:6	25	24	Exercise vs Usual care	3 months	**Primary Outcome:** 10-item Continuous Scale Physical Functional Performance Test (CS-PFP10), health-related quality of life **Secondary Outcome:** Depression, Charlson Comorbidity Index
Smart[20]	2012	Australia	RCT	64.5	53/47	I-III	II:4 III:8	II:5 III:8	57.8	38	Exercise vs Usual care	4 months	**Primary Outcome:** functional capacity, quality of life, and echocardiography responses of heart failure with preserved ejection fraction (HFpEF) patients **Secondary Outcome:** N/A
Chrysohoou[10]	2013	Greece	RCT	59.2	79/21	I-III	I:52 II:36 III:12	I: 39 II:51 III: 9	33.6	100	Exercise vs Usual Care	3 months	**Primary Outcome:** quality of life (QoL) **Secondary Outcome:** depression status
Kitzman[18]	2013	United States of America	RCT	69.5	13/87	II/III	II:15 III:17	II:17 III:14	≥50	63	Exercise vs Usual care	4 months	**Primary Outcome:** endothelial dependent flow-mediated arterial dilation (FMD) and carotid artery stiffness and their potential contributions to the training-related increase in peak exercise oxygen consumption (VO2) in older patients with heart failure with preserved ejection fraction (HFPEF). **Secondary Outcome** health-related quality-of-life and depression
Nolte[11]	2013	Multicentered	RCT	65	44/56	II/III	N/A	N/A	67.7	64	Exercise vs Usual care	3 months	**Primary Outcome:** QoL and depression **Secondary Outcome:** N/A
Freedland[6]	2015	United States of America	RCT	55.8	54/46	I-III	I-II: 46 III:33	I-II: 45 III:34	38.9	158	CBT vs Usual care	12 months	**Primary Outcome:** change in depression, Self-Care Maintenance and Confidence

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Location of the study	Design Type	Mean Age (years)	Male/ Females (%)	Mean NYHA	NYHA (Experimental Group)	NYHA (Control Group)	LVEF (%)	Total Participants	Interventions	Duration of follow-up	Primary and secondary outcome
													subscale scores
Angermann[1]	2016	Germany	RCT	62	76/24	III/IV	II:97 III-IV:88	II: 79 III-IV:108	34.8	372	AD (Escitolopram) vs Placebo	12 weeks	**Secondary Outcome:** health-related quality of life, 6-min walk test distance and average daily activity level on wrist actigraphy. **Primary Outcome:** time to a first event of the composite of all-cause death or hospitalization **Secondary Outcome: change in** depressionr and health-related quality of life

Superscript above each study author in Study column denotes the corresponding RCT in Appendix 6.

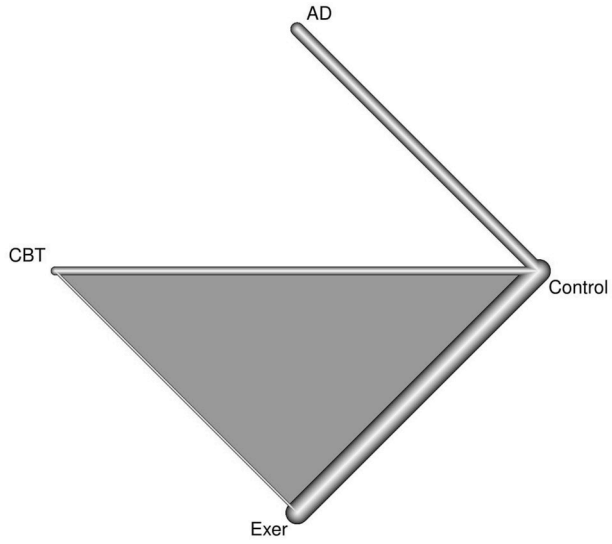

Fig. 2. Network meta-analysis for depression in HF.

3 RCTs randomizing 878 patients compared AD with placebo, 4 RCTs randomizing 390 patients compared CBT with Usual Care, 15 RCTs randomizing 3309 patients compared ET with Usual Care (Table 1). Overall, 1989 patients who received active intervention (AD or CBT or ET) and 1826 patients from control group (Usual Care or placebo) were analysed in our study.

3.2. Risk of bias assessment

Risk of bias assessment of individual studies was undertaken according to the Cochrane risk of bias assessment tool (Assessing Risk of Bias in, 2017). Failure to report intention-to-treat analysis in respective studies was not considered as a potential risk of bias in our analysis. Overall, the risk of bias was high or unclear for random sequence generation in 1 trials (4.8%); concealment of treatment allocation in 9 trials (42.9%); masking of participants, masking of investigators, or both in 8 trials (38.1%); masking of outcome assessment, completeness of outcome reporting and selective reporting of outcomes in none of the trials. A detailed account of risk of bias assessment of individual studies is illustrated in Appendix 4.

3.3. Outcomes for depression in HF patients

Network of eligible comparisons for depressive symptoms in HF patients is shown in Fig. 2. Overall, comparison between ET and control (SMD -0.38; 95% CI -0.54 to −0.22) and CBT and control (SMD -0.29; 95% CI -0.58 to −0.01) showed decrease in depressive symptoms between individual intervention and control. We observed no differences in reduction of depressive symptoms in heart failure patients treated with AD compared to control (SMD -0.16; 95% CI -0.44 to 0.11). Comparison of individual intervention with control for depression in heart failure is shown in Fig. 3B. All treatment comparisons for the primary outcome in the network meta-analysis are presented in the league table Fig. 3A. Network meta-analysis showed no difference in reduction of depressive symptoms in ET vs CBT (SMD -0.08; 95% CI -0.23 to 0.40), ET vs AD (SMD -0.21; 95% CI -0.10 to 0.53) and CBT vs AD (SMD -0.13; 95% CI -0.26 to 0.53) (Fig. 3B). The effect of individual clinical trial on our analysis, expressed as weighted distribution, is shown in Appendix 7. There was no significant skewing of the weight (< 25% of the total) among different interventions and control in each group, duly reflected in our analysis. Heterogeneity was moderate among the clinical trials (I^2 = 40.67%) (Appendix 8). The rank probability of all interventions for the treatment of depression in HF patients

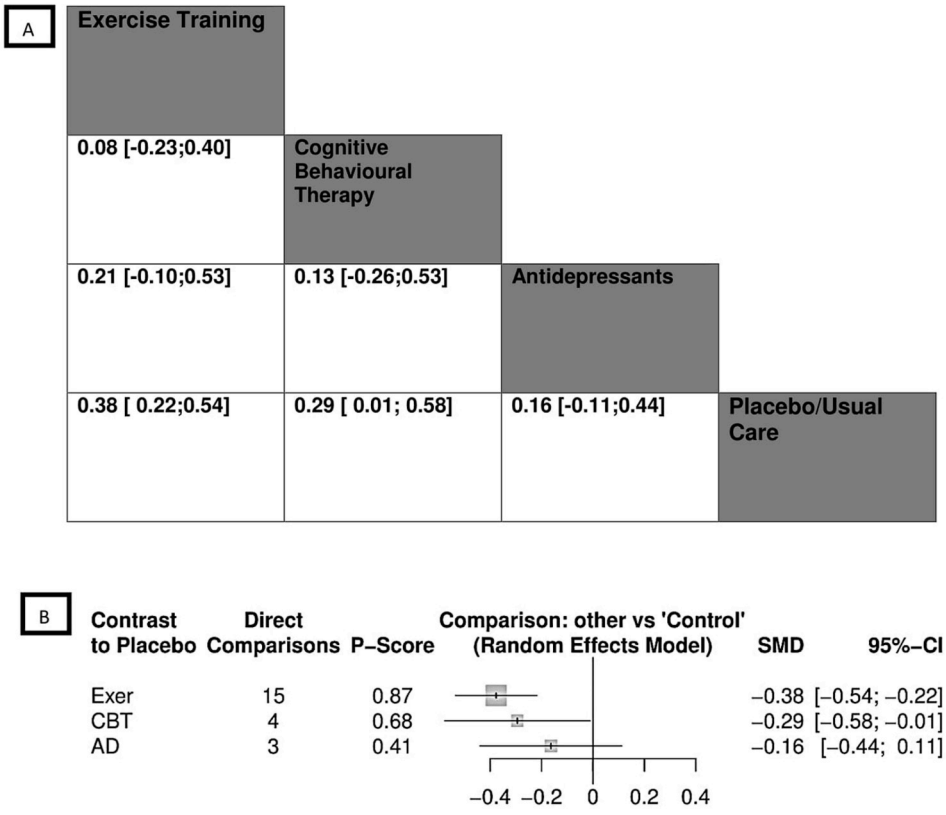

Fig. 3. Network meta-analysis of change in depressive symptoms due to interventions in HF patients with depression, expressed in terms of Standardized Mean Difference (SMD); A: League table demonstrating the effects of the interventions in changing the depressive symptoms B: Forest Plot demonstrating the comparative effects of the interventions on the depressive symptoms.

is shown in Appendix 9. Additionally, the assessment of direct and indirect evidence in the network meta-analysis was assessed using the GRADE framework is shown in Appendix 10.

3.4. Subgroup analysis

Considering our subgroup analysis, ET appeared to have better therapeutic effect in treating depression in the younger patients (age ≤ 65 years) compared to their older counterparts (age > 65 years) (SMD -0.3725; 95% CI -0.5484 to −0.1965] **(p < 0.0001)** (Appendix 11). We observed no significant difference in the effect of any of interventions in treatment of depressive symptoms with duration of follow-up after intervention (> 3 months or ≤3 months), and LVEF (> 50% or ≤50%).

3.5. Publication bias

Based on the visual inspection of the 'comparison-adjusted' funnel plot (Chaimani et al., 2013) as well as on quantitative measurement using the Begg's rank correlation test, there was no evidence of publication bias (p-value = 0.895) (Appendix 12).

4. Discussion

Although there is good evidence that HF patients with depression have worse prognosis (Depression: Are We Ignori, 2017; DeWolfe et al., 2012), evidence regarding the therapeutic benefit of various interventions is limited. Furthermore, there are no large RCTs directly comparing the effects of the different types of interventions in reducing depressive symptoms in HF patients. Our network meta-analysis employs mixed treatment comparison on a frequentist approach as an effort to fill this void. To our knowledge, this is the first network meta-analysis that examines three common interventions related to the treatment of depression in HF patients (Anderson et al., 2016; Tu et al., 2014). We found that ET and CBT had significant reductions in depressive symptoms in HF patients while AD did not provide any significant therapeutic benefit compared with placebo or usual care.

Burgeoning evidence points towards the role of ET in improving functional capacity, reducing cardiovascular risk factors and improving clinical outcomes in patients with HF. Data that supports the cardiovascular benefits of ET in terms of improvements in functional parameters like peak VO_2 and 6 min walk test remains widely documented in literature (Sagar et al., 2015; Pandey et al., 2015; O'Connor et al., 2009). Our results highlight that the beneficial role of exercise can be further extended in the domain of depression in HF patients. Similar results demonstrating beneficial effect of ET in the treatment of depression in ischemic heart disease has been reported (Blumenthal et al., 2012b). Several plausible mechanisms have been proposed as being responsible for the therapeutic benefits of exercise on depressive symptoms (Tang et al., 1981; Post et al., 1973; Ebert et al., 1972; Morgan, 1985; deVries, 1981). The physiology and molecular mechanism of the beneficial role of ET in HF patients has been linked to its neuro-humoral effects (Piepoli, 2013; Malliani and Montano, 1979; Ponikowski et al., 1997; Jankowska et al., 2006), which suggests that ET can simultaneously affect both depressive and cardiovascular outcomes in HF patients.

CBT, which is an empirically supported intervention used to treat depression successfully, demonstrates a slightly beneficial effect in reducing depressive symptoms in HF patients when compared with usual care. Although CBT has been shown to be as effective as ET in treating depression (Fremont and Craighead, 1987), the anti-depressant and cardiovascular effects of combinatorial treatment of ET and CBT has been documented to be higher than CBT or ET alone (Gary et al., 2010). A thorough mechanistic insight could help further our understanding for the basis of the synergistic outcomes with ET and CBT in these patients.

In contrast, evidence has demonstrated that AD has no significant benefit in treating depression and clinical cardiovascular outcomes in HF patients (Angermann et al., 2016; O'Connor et al., 2010). Our results support this claim that AD is not effective in the treatment of depression

in HF patients. The prevalence of HF patients has been documented to be higher in geriatric population (aged > 65 years). Using AD in these population is challenging, given the burden of polypharmacy in geriatric population (Garfinkel and Mangin, 2010; Fournier et al., 2010). Moreover, effect of AD in treating depression in HF patients is negligible with concurrent burden of the cardiotoxic profile of these drugs (QTc prolongation, arrythmia, orthostatic hypotension etc) (Depression in heart failu, 2018; Moir et al., 1972; Pacher and Kecskemeti, 2004). Moreover, effect of AD in treating depression in HF patients is negligible. ET provides a suitable alternative in treating depression in HF patients and circumvent this barrier.

There are certain limitations in our study. First, Cochrane risk of bias was high/unclear for some studies thus restricting the interpretation of these results. There was imprecision between the studies in our network meta-analysis which can be attributed to the inherent heterogeneity between the 21 RCTs. Because the samples were heterogenous in their clinical characteristics including stages of HF, etiology of HF (ischemic vs non-ischemic HF) and differences in follow-up duration, we believe the heterogeneity in the comparison stems from lack of uniformity among RCTs. In addition, changes in depression were not the primary outcomes in 10 out of 21 RCTs (47.62%) which may have resulted in inclusion of patients with variable risk factors of depression (sex, medication for hypertension, sleep and socio-economic background) in individual studies, thus contributing heavily to the overall heterogeneity in depressive outcomes with the different interventions, in our meta-analysis. Furthermore, quantitative analysis identified four RCTs (Blumenthal et al., 2012a; O'Connor et al., 2009; Kulcu et al., 2007; Chrysohoou et al., 2014) which have a high evidence of intra-study heterogeneity and contributed to the overall heterogeneity. Baseline characteristics of patients in terms of their previous history of depression and treatment for the depression before the development of heart failure, another potential factor of inter and intra-study heterogeneity, was not also reported in the included studies, which needs to be accounted for when interpreting the results in our meta-analysis. Additionally, most of the patients included in our study were NYHA II-IV and the data regarding cardiovascular outcomes in patients were not provided in those clinical studies where they received AD and CBT. Hence we cannot compare the cardiovascular outcomes of these interventions in our study. Furthermore, our analysis regarding the outcomes of depression was based on SMD to normalize the change across multiple scales of depression. Clinical interpretation of a small change in SMD can be ambiguous and require symptom validation. RCTs relating to AD and CBT were limited by their small sample size. Furthermore, a plausible argument about the effectiveness of AD can be made on the basis of the variable duration of follow-up of the included RCTs (12 months for Angermann's, 3 months for O'Connor and 2 months for Fraguas) and longer duration of follow-up have been associated with more robust outcomes for AD in the treatment of depression (Machado-Vieira et al., 2010). Future RCTs comparing AD to control should be designed to address this limitation. Although the type of ET can be a determining factor in its effect (Sagar et al., 2015; Pandey et al., 2015), we were unable to examine this issue due to the lack of adequate power in most RCTs.

In conclusion, treatment of depression in HF patients with ET and CBT demonstrated a superior effect compared to placebo or usual care. Given the additional beneficial cardiovascular outcomes of ET, ET alone or in combination with CBT, appears to be a reasonable intervention to treat depression in HF. Large randomized clinical trials are warranted to compare the therapeutic effects of these three interventions in such patients.

Funding sources

None

Conflicts of interest

None.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.10.007.

Appendix 1. Database Search Strategies

1. MEDLINE via Ovid

1	exp Depression/
2	depressive disorder/or depressive disorder, major/or depressive disorder, treatment-resistant/
3	(depression or depressive).ti,ab.
4	1 or 2 or 3
5	exp Heart Failure/
6	("heart failure" or CHF).ti,ab.
7	5 or 6
8	4 and 7
9	"ST segment depression".ti,ab.
10	animals/not humans/
11	8 not (9 or 10)
12	limit 11 to english language

2. PsycInfo via EBSCO

S1	TI (depression or depressive) OR AB (depression or depressive)
S2	(DE "Major Depression" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Depression (Emotion)")
S3	S1 OR S2
S4	TI ("heart failure" or CHF) OR AB ("heart failure" or CHF)
S5	DE "Heart Disorders"
S6	S4 OR S5
S7	S3 AND S6
S8	TI "ST segment depression" OR AB "ST segment depression"
S9	DE "Animals" OR DE "Animal Personality" OR DE "Companion Animals" OR DE "Female Animals" OR DE "Infants (Animal)" OR DE "Invertebrates" OR DE "Male Animals" OR DE "Vertebrates"
S10	S7 NOT (S8 OR S9)
S11	S7 NOT (S8 OR S9) Limits: English Language

3. CINAHL Complete via EBSCO

S1	TI (depression or depressive) OR AB (depression or depressive)
S2	(MH "Depression") OR (MH "Depression, Reactive")
S3	S1 OR S2
S4	TI ("heart failure" or CHF) OR AB ("heart failure" or CHF)
S5	(MH "Heart Failure")
S6	S4 OR S5
S7	S3 AND S6
S8	TI "ST segment depression" OR AB "ST segment depression"
S9	MH animals + NOT MH humans
S10	S7 NOT (S8 OR S9)
S11	S7 NOT (S8 OR S9) Limits: English Language

4. Embase via Elsevier

#1	depression:ab, ti OR depressive:ab,ti
#2	depression'/mj OR 'major depression'/mj OR 'agitated depression'/mj OR 'atypical depression'/mj OR 'endogenous depression'/mj OR 'involutional depression'/mj OR 'late life depression'/mj OR 'masked depression'/mj OR 'melancholia'/mj OR 'postoperative depression'/mj OR 'reactive depression'/mj OR 'treatment resistant depression'/mj OR 'recurrent brief depression'/mj
#3	#1 OR#2
#4	heart failure':ab, ti OR chf:ab,ti
#5	heart failure'/mj OR 'acute heart failure'/exp/mj OR 'congestive heart failure'/exp/mj OR 'forward heart failure'/exp/mj OR 'heart ventricle failure'/exp/mj OR 'high output heart failure'/exp/mj
#6	#4 OR#5
#7	#3 AND#6
#8	st segment depression':ab,ti
#9	[animals]/lim NOT [humans]/lim
#10	#7 NOT (#8 OR#9)
#11	#7 NOT (#8 OR#9) AND [english]/lim

5. Web of Science via Thomson Reuters

#1	TOPIC: (depression or depressive) NOT TOPIC: ("st segment depression")
#2	TOPIC: ("heart failure" or CHF)
#3	((#3 AND#2) NOT TS=(animals OR rats OR rat OR mice OR pigs OR animal OR rat OR mouse OR pig)) AND LANGUAGE: (English)

Appendix 2. PICOS Elements

PICOS Element	Inclusion Criteria	Exclusion Criteria
Population	• Heart failure patients with a diagnosis of depression after the onset of heart failure	• Patients with a history of diagnosed depression • Patients treated for depression prior to the onset of heart failure
Interventions	• Antidepressants (SSRIs and TCAs) • Exercise training (home and hospital-based) • Cognitive behavioral therapy including psycho-education • Placebo/Usual Care	• Traditional form of Exercise training (Yoga, Tai-chi etc)
Comparators	Patients who are treatment-naïve for depression and received either of the above mentioned interventions	

Outcomes	Change in depressive symptoms expressed in terms of depression measurement scales	
Timing	Duration of follow-up of individual studies	
Setting	All clinical settings (inpatient as well as outpatient)	
Study Design	• Original data • Any study size • Randomized controlled trials	• Editorials, • Reviews • letters, • case series, case reports • abstract only
Publications	• English language only • Inception of database to November 2016. • Relevant meta-analysis	

Appendix 3. Hierarchy of depression symptom severity measurement scale

Hierarchy	Depressive Scales	Abbreviation
1	Montgomery Asberg Depression Rating Scale	MADRS
2	Beck Depression Inventory-II	BDI
3	Hamilton Depression Rating Scale	HAM-D/HDRS
4	Patient Health Questionnarie	PHQ-9
5	Hospital Anxiety and Depression Scale	HADS
6	Zung Depression Rating Scale	ZDRS
7	Center for Epidemiological Studies Depression Scale	CES-D
8	Geriatric Depression Score	GDS
9	Cognitive Behavioral Assessment (Hospital)	CBA-H
10	Multiple Affect Adjective Checklist	MAACL
11	Hare-Davis Cardiac Depression Scale	CDS

Appendix 4. Risk of Bias assessment of individual studies using Cochrane risk of bias tool

Study	Random sequence generation bias	Allocation concealment	Blinding of participants/ personnel	Outcome assessor blinding	Incomplete Outcome data	Selective reporting (Reporting bias)	Other bias
Fraguas 1997	Low	Unclear	Low	Low	Low	Low	Low
O'Connor 2010	Low	Low	Low	Low	Low	Low	Low
Årgen 2012	Low	Unclear	Unclear	Low	Low	Low	Low
Bluementhal 2012	Low	Low	Low	Low	Low	Low	Low
Dekker 2011	Low	Low	Low	Low	Low	Low	Low
Chrysohoou 2013	Low	Low	Unclear	Low	Low	Low	Low
Nolte 2013	Low	Unclear	Unclear	Low	Low	Low	Low
Freedland 2015	Low	Low	High	Low	Low	Low	Low
Angermann 2016	Low	Low	Low	Low	Low	Low	Low
Dracup 2007	Unclear	Unclear	Low	Low	Low	Low	Low
Witham 2006	Low	Low	Low	Low	Low	Low	Low
Gary 2004	Low	Low	Low	Low	Low	Low	Low
Bosnak-Gulcu 2011	Low	Low	Low	Low	Low	Low	Low
Berg-Emons 2004	Low	Unclear	Unclear	Low	Low	Low	Low
Jolly 2008	Low	Low	Low	Low	Low	Low	Low
Kitzman 2011	Low	Unclear	High	Low	Low	Low	Low
Gary 2012	Low	Unclear	Unclear	Low	Low	Low	Low
Gary 2010	Low	Unclear	Low	Low	Low	Low	Low
Kulcu 2006	Low	Low	Unclear	Low	Low	Low	Low
Smart 2012	Low	Low	Low	Low	Low	Low	Low
Giannuzzi 1997	Low	Unclear	Low	Low	Low	Low	Low

Appendix 5. R-Code

```
library(netmeta)


## Conduct network meta-analysis (using control as reference group)

net1 <- netmeta(TE, seTE, treat1, treat2, studlab,
                data=dat1, sm = "SMD", tol = 0.0002,
                comb.fixed = FALSE, comb.random = TRUE,
                ref = "Control",
                seq = c("AD", "CBT", "Exer", "Control"))


net1


decomp.design(net1)


oldopts <- options(width = 100)
netleague(net1, digits = 2, seq = netrank(net1))
options(oldopts)


print(netsplit(net1), ci = TRUE)


netrank(net1)



pdf("netgraph-depression-hf.pdf")
netgraph(net1)
dev.off()


pdf("forest-depression-hf.pdf", width = 7, height = 2)
forest(net1,
       leftcols=c("studlab", "k", "Pscore"),
       leftlabs=c("Contrast\nto Placebo",
                  "Direct\nComparisons", "P-Score"),
       drop = TRUE, sortvar = -Pscore)
dev.off()







## Model code for Subgroup analysis
```

```
dat2.young <- subset(dat2, age == "<65")
dat2.old   <- subset(dat2, age == ">65")


##
## Conduct separate network meta-analysis within subgroups
## (with between-study variance of overall network meta-analysis,
##  see argument 'tau.preset')
##
net.young <- netmeta(TE, seTE, treat1, treat2, studlab,
                     data = dat2.young, sm = "SMD", tol = 0.0002,
                     comb.fixed = FALSE, comb.random = TRUE,
                     ref = "Control",
                     tau.preset = net1$tau)
##
net.old <- netmeta(TE, seTE, treat1, treat2, studlab,
                   data = dat2.old, sm = "SMD", tol = 0.0002,
                   comb.fixed = FALSE, comb.random = TRUE,
                   ref = "Control",
                   tau.preset = net1$tau)

## Three treatments (AD missing)
##
summary(net.young)

## Four treatments
##
summary(net.old)


##
## Comparison of CBT and Control in younger and older patients
##
TE.y   <- net.young$TE.random["CBT", "Control"]
seTE.y <- net.young$seTE.random["CBT", "Control"]
##
TE.o   <- net.old$TE.random["CBT", "Control"]
seTE.o <- net.old$seTE.random["CBT", "Control"]
##

## Test for subgroup difference: "Test of heterogeneity",

metagen(c(TE.y, TE.o), c(seTE.y, seTE.o), sm = "SMD",
        studlab = c("young", "old"))
##
## Test for subgroup difference:
## Difference unequal to zero (same p-value: p = 0.6685)
##
metagen(TE.y - TE.o, sqrt(seTE.y^2 + seTE.o^2), sm = "SMD")


## Comparison of Exer and Control in younger and older patients
##
```

```
TE.y   <- net.young$TE.random["Exer", "Control"]
seTE.y <- net.young$seTE.random["Exer", "Control"]
##
TE.o   <- net.old$TE.random["Exer", "Control"]
seTE.o <- net.old$seTE.random["Exer", "Control"]
##
##
metagen(c(TE.y, TE.o), c(seTE.y, seTE.o), sm = "SMD",
        studlab = c("young", "old"))
##
## Test for subgroup difference:
metagen(TE.y - TE.o, sqrt(seTE.y^2 + seTE.o^2), sm = "SMD")
```

```
## Comparison of AD and Control in younger and older patients
TE.y   <- net.young$TE.random["AD", "Control"]
seTE.y <- net.young$seTE.random["AD", "Control"]
##
TE.o   <- net.old$TE.random["AD", "Control"]
seTE.o <- net.old$seTE.random["AD", "Control"]
##
## Similar overall results for random-effects model (see above)
## Test for subgroup difference: "Test of heterogeneity",
## i.e., non-significant (p = 0.6685)
##
metagen(c(TE.y, TE.o), c(seTE.y, seTE.o), sm = "SMD",
        studlab = c("young", "old"))
##
## Test for subgroup difference:
## Difference unequal to zero (same p-value: p = 0.6685)
##
metagen(TE.y - TE.o, sqrt(seTE.y^2 + seTE.o^2), sm = "SMD")
```

Appendix 6. List of included studies

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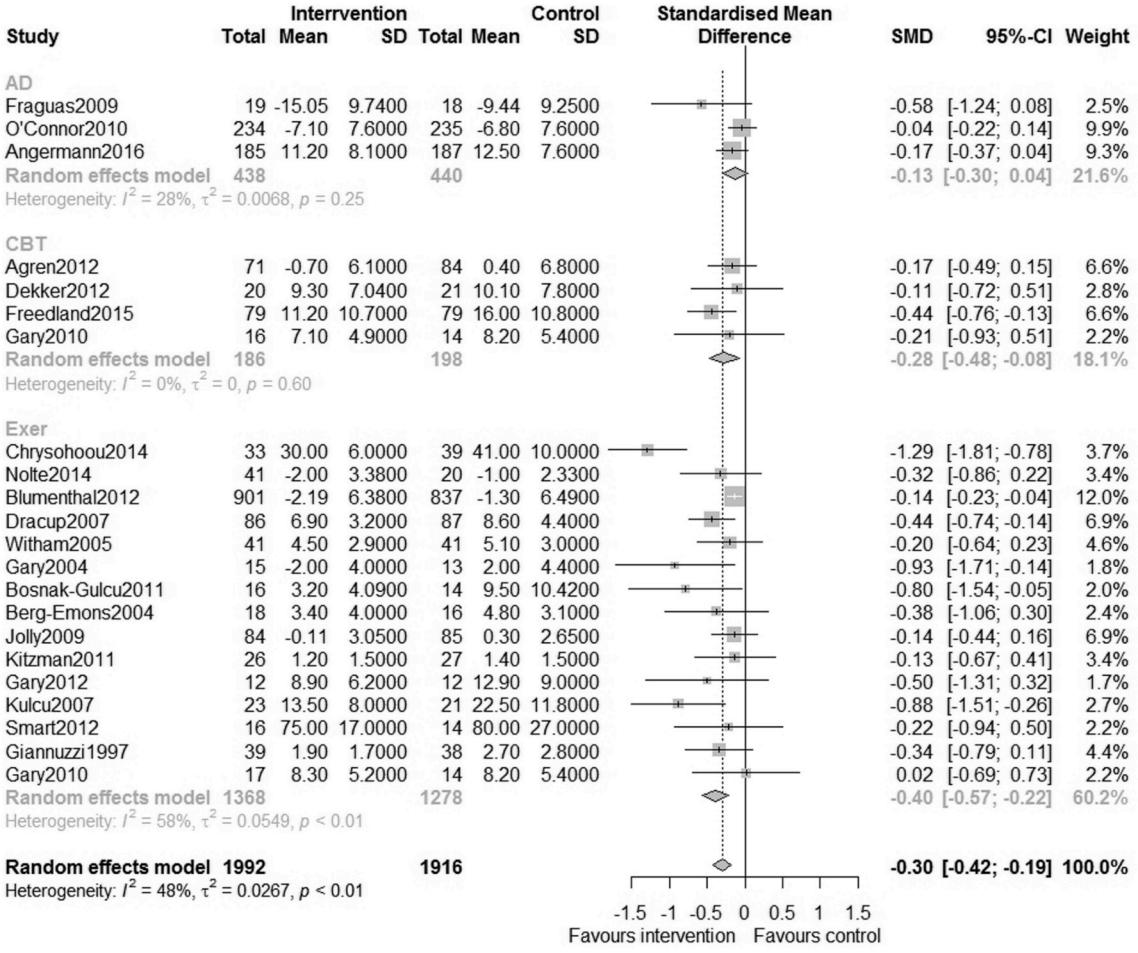
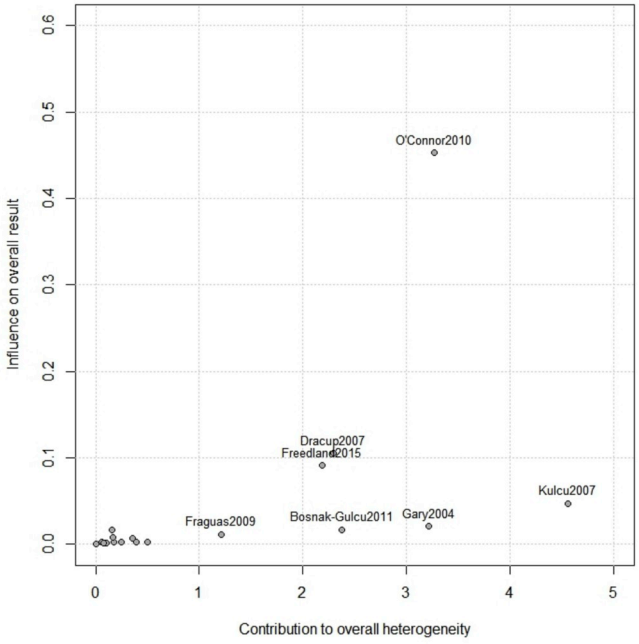
Appendix 7

Distribution of weight of individual clinical trial.



Appendix 8

Contribution of individual clinical trial to overall heterogeneity.



Appendix 9. Rank probability of interventions for the treatment of depression in heart failure patients

Treatment	
Exercise Training	0.8671
Cognitive Behavioral Therapy	0.6755
Antidepressants	0.4099
Placebo/Usual Care	0.0474

Appendix 10. Detailed GRADE Quality of Evidence Assessment from Network Meta-analysis

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	SMD(95 CrI)	Quality of evidence	SMD(95 CrI)	Quality of evidence	SMD(95 CrI)	Quality of evidence
Antidepressants *vs* Control	0.4261 [0.1136; 0.7387]	Low[1,2]	N/A	N/A	0.4261 [0.1136; 0.7387]	Low
Antidepressants *vs* Exercise Training	N/A	N/A	0.0152 [-0.3415; 0.3719]	Low[1,3]	0.0152 [-0.3415; 0.3719]	Low
Antidepressants *vs* Cognitive behavioral therapy	N/A	N/A	0.0682 [-0.3681; 0.5045]	Low[1,3]	0.0682 [-0.3681; 0.5045]	Low
Cognitive behavioral therapy *vs* Control	0.3216 [0.0096; 0.6336]	Moderate[1]	1.0743 [-0.3108; 2.4593]	Low[1,3]	0.3580 [0.0536; 0.6624]	Moderate[1]
Cognitive behavioral therapy *vs* Exercise Training	0.2269 [-0.5805; 1.0342]	Low[1,3]	−0.1138 [-0.4903; 0.2626]	Low[1,3]	−0.0530 [-0.3942; 0.2882]	Low
Control vs Exercise Training	−0.4135 [-0.5865; −0.2405]	Very Low[1,2,3]	−0.2278 [-1.6957; 1.2402]	Low[1,3]	−0.4110 [-0.5828; −0.2391]	Low

1- Risk of Bias, 2-Inconsistency, 3-Imprecision.

Appendix 11. Subgroup analysis

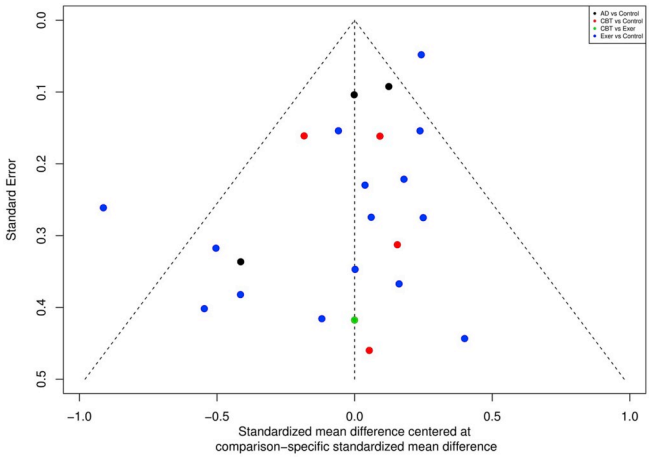
Age	ET	CBT	AD
≤65 years	−0.4517 [-0.6601; −0.2432]	−0.4444 [-0.9312; 0.0424]	−0.1007 [-0.3959; 0.1944]
> 65 years	−0.2707 [-0.5139; −0.0275]	−0.2038 [-0.5528; 0.1452]	−0.5775 [-1.3339; 0.1790]
Group difference	−0.3725 [-0.5484; −0.1965] **(p < 0.0001)**	−0.2854 [-0.5691; −0.0018] (p = 0.0486)	−0.2067 [-0.5951; 0.1818] (p = 0.2970)
Duration	**ET**	**CBT**	**AD**
> 3 months	−0.2113 [-0.4018; −0.0207]	−0.3117 [-0.6201; −0.0032]	−0.1652 [-0.5880; 0.2575]

≤3 months	−0.7483 [-1.0320; −0.4646]	−0.1055 [-0.8216; 0.6107]	−0.1627 [-0.5247; 0.1994]
Group difference	−0.4691 [-0.9949; 0.0568] (p = 0.0804)	−0.2794 [-0.5627; 0.0039] (p = 0.0533)	−0.1637 [-0.4387; 0.1112] (p = 0.2432)

EF	EF	CBT	AD
> 50%	−0.3052 [-0.6124; 0.0019]	N/A	N/A
≤50%	−0.3724 [-0.5634; −0.1815]	−0.3580 [-0.7062; −0.0098]	−0.1637 [-0.4387; 0.1112]
Group difference	−0.0467 [-0.4226; 0.3293] (p = 0.8078)	N/A	N/A

Appendix 12

Funnel plot Contribution of individual clinical trial to overall heterogeneity.



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