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TREATMENT OF COMORBID DEPRESSION AFTER ACUTE CORONARY SYNDROME: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Depression post-acute coronary syndrome (ACS) increases cardiac risk; however, the efficacy of antidepressant therapies for its treatment has not been sufficiently demonstrated. Our aim is to meta-analyze controlled trials with homogeneous samples that allow us to explain the inconsistency of the results obtained so far. After reviewing 1525 articles, two independent reviewers identified 7 studies that met very restrictive criteria to ensure homogeneity of the samples. The results indicated that patients treated with interventions of proven efficacy for the depression, reduce their levels of depressive disorder significantly more than subjects without this treatment and that there are significant differences in the number of patients who reduce depressive symptoms in a clinically relevant way. In addition, fewer adverse cardiovascular events were observed during treatment, although this difference was minimally significant and was not maintained after the follow-up. These results suggest that the inconsistency of the currently available data could be due to methodological difficulties evidencing the need for further research to clarify the effect of depression treatment on post-ACS prognosis.
KEY WORDS: *coronary heart disease, acute coronary syndrome, depression treatment, meta-analysis.*

Resumen

La depresión postsíndrome coronario agudo (post-SCA) aumenta el riesgo cardíaco; sin embargo, la eficacia de las terapias antidepresivas para su tratamiento no está suficientemente demostrada. Nuestro objetivo es metaanalizar ensayos controlados con muestras homogéneas que permitan explicar la inconsistencia de los resultados obtenidos hasta el momento. Tras revisar 1525 artículos, dos revisores independientes identificaron 7 estudios que cumplían criterios muy restrictivos para asegurar la homogeneidad de las muestras. Los resultados indicaron que los pacientes tratados con intervenciones de eficacia demostrada para la depresión, reducen sus niveles de trastorno depresivo significativamente más que los sujetos sin este tratamiento, y que existen diferencias significativas en el número de pacientes que reducen los síntomas depresivos de forma clínicamente relevante. Además, se observaron menos eventos cardiovasculares adversos durante el tratamiento, aunque esta

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diferencia fue mínimamente significativa y no se mantuvo tras el seguimiento. Estos resultados sugieren que la inconsistencia de los datos actualmente disponibles podría deberse a dificultades metodológicas que evidencian la necesidad de nuevas investigaciones que aclaren el efecto del tratamiento de la depresión sobre el pronóstico post-SCA.
PALABRAS CLAVE: *enfermedad cardiocoronaria, síndrome coronario agudo, tratamiento de la depresión, metaanálisis.*

Introduction

In recent decades, a remarkable body of scientific literature suggests that depression increases the risk of coronary heart disease (CHD) and subsequent acute coronary events in patients with established CHD (Vaccarino et al., 2020). In this line, a recent review of meta-analytical studies (Carney, & Freedland, 2017) concludes that clinically significant depression, defined both by interview-based diagnoses of major depression and questionnaire scores, increases the risk of developing CHD, and is also associated with increased risk of cardiac morbidity and mortality after the onset of a first acute coronary syndrome (ACS). More specifically, the largest meta-analytical study comparing patients with and without depression after myocardial infarction (MI) found that this comorbid depression was associated with a 2.71-fold increased risk of cardiac mortality, and 1.59-fold increased risk of new cardiac events; this association has remained relatively stable over the 25 years investigated (Meijer et al., 2011).

Furthermore, the adverse effects of depression appear to be independent of other coronary risk factors, as there are data (Kronish et al., 2009; Meurs et al., 2013) showing that depression remains a significant risk factor, even when adjusted for the Global Registry of Acute Coronary Events score, considered a useful adjustment alternative for the large number of risk factors that may compromise the results of studies on depression as a risk factor for cardiac mortality after ACS.

The importance of depression as a risk factor for CHD is even greater if we take into account that its prevalence in these patients is up to three-fold higher than in the general population (Amin et al., 2006; Kang et al., 2015; Lichtman et al., 2014; Thombs et al., 2006). Numerous studies agree that major depressive disorder is present in around 20% of coronary heart patients (Celano, & Huffman, 2011; Doyle et al., 2015), and it is also estimated that more than 40% report significant depressive symptomatology (Carney, & Freedland, 2008).

The foregoing has led to include in the clinical guidelines published by the American Heart Association (AHA) (Lichtman et al., 2008) and the European Society of Cardiology (ESC) (Vaccarino et al., 2020) the recommendation to assess and treat depression in all patients with CHD; however, to date, neither the efficacy of antidepressant treatments, or their effect on cardiac prognosis in post-ACS patients, has not been consistently demonstrated (Fernandes et al., 2021),

and the need to invest healthcare resources for depression screening in cardiovascular care has been questioned (Thombs et al., 2013).

In order to clarify this issue, several randomized controlled trials (RCTs) have investigated the effects of pharmacological interventions with selective serotonin reuptake inhibitors (SSRIs) (Glassman et al., 2002; Kim et al., 2015; Strik et al., 2000), and with mirtazapine (Honig et al., 2007), a noradrenergic and specific serotonergic antidepressant, drugs of choice due to the cardiotoxic effects of tricyclic antidepressants (Raj et al., 2009), as well as cognitive-behavioral programs of proven efficacy in the depressive disorder treatment (Davidson et al., 2010; ENRICHD Investigators, 2003; O'Neil et al., 2014). However, the number of RCTs, aimed at investigating the efficacy of depression treatment in CHD patients and its impact on cardiac outcomes, has been limited and does not seem to yield conclusive results (Fernandes et al., 2021).

In view of this lack of conclusive evidence, in the last decade, at least 9 meta-analytical studies of RCTs have been carried out on the effects of pharmacological and/or psychological interventions in CHD patients with comorbid depression. In 4 meta-analyses, the effect of pharmacological treatment has been investigated (Dowlati et al., 2010; Fernandes et al., 2021; Mazza et al., 2010; Pizzi et al., 2011); in another 3, psychological treatment was reviewed (Dickens et al., 2013; Reavell et al., 2018; Ski et al., 2016) and, in the remaining 2, pharmacological and/or psychological intervention was studied (Baumeister et al., 2011; Tully, & Baumeister, 2015).

The number of RCTs identified and meta-analyzed in each of these works has ranged between 4 (Dowlati et al., 2010; Mazza et al., 2010) and 7 (Dickens et al., 2013), given that in Reavell's work (Reavell et al., 2018), although 12 studies are included, in 5 of them, the participants had depression or anxiety. The results of these meta-analytical studies are contradictory; of the 8 meta-analyses that evaluate the effect of treatments on depression scores, compared with control groups (placebo or non-intervention), in 3 there were no significant effect of treatment (Baumeister et al., 2011; Dickens et al., 2013; Mazza et al., 2010) and in 5 there were (Dowlati et al., 2010; Pizzi et al., 2011; Reavell et al., 2018; Ski et al., 2016; Tully, & Baumeister, 2015).

The inconsistency of these results has led some authors to propose the need to investigate the existence of a subtype of depression, or depressive symptoms specifically related to the post-ACS prognosis (Carney, & Freedland, 2012a; Carney, & Freedland, 2012b; Martens et al., 2010; Smolderen et al., 2009), whereas other researchers question whether depression treatment is an adequate therapeutic objective in these patients (Rafanelli et al., 2013).

However, before initiating research studies in this direction, perhaps several limitations of the studies carried out so far should be taken into account.

First, the eligibility criteria used for the selection of the studies has allowed the pooled analysis of patient samples, categorized globally as CHD, but with very different forms and severities with respect to the cardiac condition; from coronary

artery bypass graft to simply presence of significant coronary atherosclerosis, and even, samples that include patients with heart failure; this fact is an important limitation, if we take into account the repeatedly stated recommendation that, in patients with cardiovascular disease, screening and treatment of depression should be performed for specific populations, since the results of a group of patients cannot be generalized to others (US Preventive Services Task Force, 2002). Similarly, the samples have been highly heterogeneous with respect to the level of depression of the participants, from standard diagnostic criteria of major depressive disorder, to increased depressive symptomatology, and even, samples in which only 80% of subjects had comorbid depression (Baumeister et al., 2011; Mazza et al., 2010), which implies the study of samples that do not present, strictly speaking, the risk characteristic to be investigated.

Second, the results of the meta-analyses show high levels of statistical heterogeneity; specifically, in 5 of 7 meta-analyses reporting this data, the heterogeneity was greater than 50%, which makes the comparability of the meta-analyzed studies questionable. It was only less than 20% in two works (Ski et al., 2016; Tully, & Baumeister, 2015), but in one of them (Ski et al., 2016) not all participants had depression and, in the other (Tully, & Baumeister, 2015), patients with CHD and diabetes were included.

In short, the high clinical heterogeneity of the samples, together with the equally high statistical heterogeneity of the meta-analytical results, greatly compromises the research findings, without determining whether the inconsistency of the results is due to the absence of evidence supporting the hypothesis under study or, on the contrary, is due to the disparity of the included studies. In fact, when the statistical heterogeneity index is greater than 50%, the pooled analysis of studies results is questionable (Higgins, & Thompson, 2002).

Regarding the effect of depression treatment on morbidity and mortality in patients with established CHD, none of the 6 meta-analyses, including these variables, pooled more than 5 studies (Dowlati et al., 2010; Fernandes et al., 2021; Mazza et al., 2010; Pizzi et al., 2011; Ski et al., 2016; Tully, & Baumeister, 2015), and only 2 of them showed a reduction in major adverse cardiac events (MACEs) in the short term, which was not sustained in the longer term (Fernandes et al., 2021; Tully, & Baumeister, 2015).

This meta-analytical review aims to overcome the above limitations and provide data that contribute to a better understanding of the effect of depression treatments in patients with CHD. Our objective is to carry out a meta-analysis of RCTs with very restrictive eligibility criteria to identify a set of studies including very homogeneous samples that will help to clarify the reasons for the inconsistency in the efficacy results of antidepressant treatments in patients with CHD so far found and, likewise, contribute to explain why, despite the fact that depression has been recognized as a risk factor for poor prognosis in these patients (Vaccarino et al., 2020), the procedures with recognized efficacy for the depression treatment have not yet been shown to be more useful than no treatment or placebo interventions,

neither for the significant reduction of depression, nor for the reduction of risk of cardiac morbidity and mortality.

Method

This work has been carried out in accordance with the standards of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

Eligibility criteria

To be included in the meta-analysis, the studies had to meet the following requirements: a) RCTs comparing intervention group and control group (usual care, placebo or no treatment); b) patients hospitalized for ACS, including MI or unstable angina, with comorbid depression, identified by clinical diagnosis according to standardized criteria, or by the presence of clinically significant depressive symptomatology according to predefined cut-off points in validated questionnaires; c) psychological and/or pharmacological intervention of proven efficacy in the treatment of depression, including Cognitive Behavioral Therapy (CBT) and/or antidepressant medication of choice; d) reporting at least baseline and post-treatment measure of depression.

Studies that included other cardiac diagnoses together with ACS, or mixed samples of patients with and without depression, were excluded, unless it was possible to extract data for the subgroup of patients only with ACS and comorbid depression.

Search strategy and study selection

For the studies identification on the effectiveness of depression treatment in post-ACS patients, in October 2022 three different searches were carried out.

First, a search in the MEDLINE and PsycINFO databases, combining the key words: [depress*] and [(myocardial infarction) or (heart attack) or (unstable angina) or (acute coronary syndrome)] was performed. No date or language restrictions were applied.

Second, additional studies were sought by reviewing the references included in systematic reviews and meta-analytical studies identified in the previous search.

Finally, the clinical trials on depression treatment in patients post-ACS with comorbid depression, included in the following registers were reviewed: Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, and U.S. National Library of Medicine Clinicaltrials.gov.

After eliminating duplicities, the titles and abstracts of the articles found were reviewed, and those in which the efficacy of any treatment was not studied were eliminated.

Full text reports of studies that were potentially relevant were screened to determine eligibility. The inclusion criteria were applied by two independent reviewers (first and second author) to identify studies meeting the criteria. The Cohen's kappa concordance index (κ) was calculated. Disagreements were solved by consensus discussion.

Data extraction

The full text of each study was analyzed and the following data were gathered: number of randomized participants, ACS diagnosis (MI or unstable angina), depression diagnosis (method and time post-ACS), depression treatment (type and duration), comparison group (no treatment, usual care, placebo), outcome measurement (types and time post-ACS). Data were extracted by two independent reviewers; any discrepancies were discussed in consensus meeting.

Risk of bias in included studies

The risk of bias in the studies included in the meta-analysis was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011). In each study, a risk of bias "high", "low" or "unclear" was assigned in the following domains: "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other bias".

For the psychological intervention trials, in the blinding domains, only the blinding of outcome assessment was taken into account, since the blinding of participants and personnel is not feasible in this type of studies.

Data analysis and synthesis

For continuous variables, measured with different scales, the effect size was determined from the means and standard deviations post-intervention corresponding to the experimental and control groups, calculating the standardized mean differences (SMD) and 95% confidence intervals (CI). These final scores were not mixed with pre-post change scores, since this is only adequate if the non-standardized mean difference is used as effect size index, a valid method only if the variable in question is measured, in all cases, with the same instrument. Data were pooled together with random effects model using the inverse variance method.

For dichotomous variables, odds ratio (OR) and 95% CI were computed from the proportions of events corresponding to the experimental and control groups. In this case, for each variable, the meta-analysis was carried out, with random effect model, using Mantel-Haenszel method, since this procedure has shown better statistical properties with scarce data and low event rates, whereas in other situations it offers a similar result to the inverse variance method.

For each meta-analysis, the statistical heterogeneity was computed using the χ^2 test, and the inconsistency of the results (impact of heterogeneity) using the I^2 index.

All analyses were performed with the Cochrane Review Manager software RevMan 5.3.

Risk of bias across studies

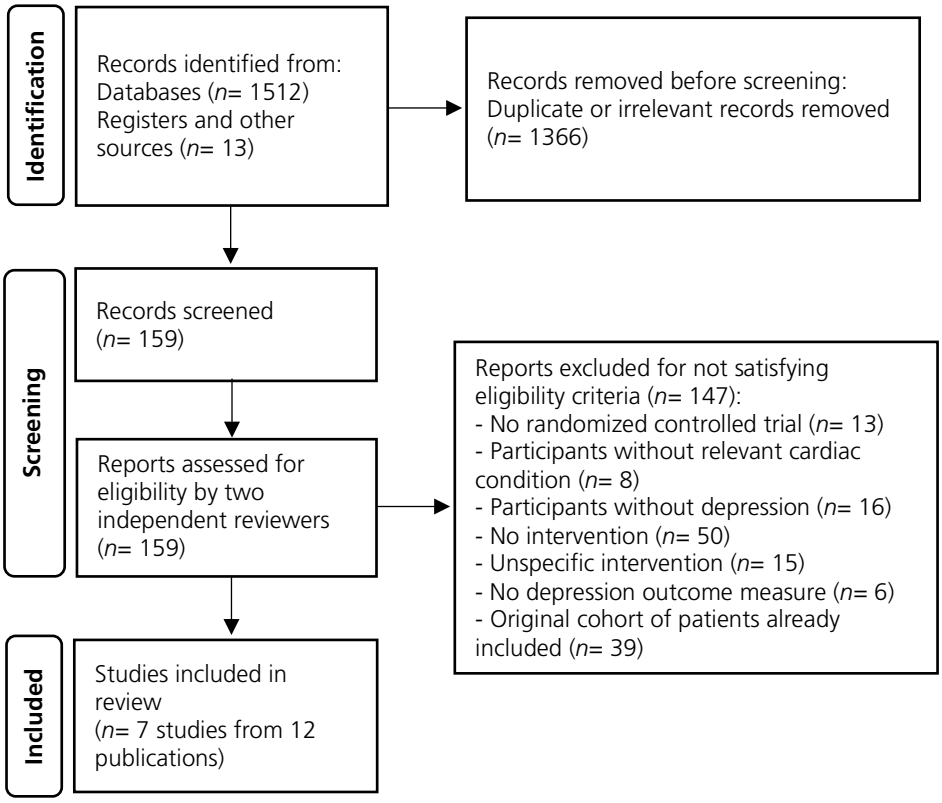
With regard to methodological quality, the risk of bias across studies was assessed by calculating the percentage of studies rated as "high", "low", or "unclear" risk in each of the six domains of risk of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011). Because the number of meta-analyzed studies was fewer than ten, no tests for funnel plot asymmetry were used for publication bias assessment.

Results

Search results and study selection

By searching databases, 1512 articles were identified; 13 additional articles were found through other sources (clinical trial records and references from other meta-analyses). After an initial review of the titles and abstracts of the 1525 articles found, 1366 were excluded because they were not related to the objective of our work. Of the remaining 159 articles, after the application of the eligibility criteria, carried out by two independent reviewers, 147 were excluded for not meeting all the previously established criteria; the agreement between reviewers was 95% (κ= .72), agreement categorized as "substantial" on the rating scale of κ index (Landis, & Koch, 1977); discrepancies were resolved by consensus among reviewers. Finally, 7 studies, included in 12 articles, met all the criteria and were included in the meta-analysis. The flowchart describing the study selection process can be seen in Figure 1.

Figure 1
Flowchart of study selection



Study characteristics

The studies included in the present meta-analysis were: Coronary Psychosocial Evaluation Study (COPES; Davidson et al., 2010), Enhancing Recovery in Coronary Heart Disease Randomized Trial (ENRICHD; ENRICHD Investigators, 2003), Escitalopram for Depression in Acute Coronary Syndrome (EsDEPACS; Kim et al., 2015), Myocardial Infarction and Depression - Intervention Trial (MIND-IT; Honig et al., 2007), "MoodCare" randomized controlled trial (O'Neil et al., 2014), Sertraline Antidepressant Heart Attack Randomized Trial (SADHART; Glassman et al., 2002), and the Strik study (Strik et al., 2000). Table 1 summarizes the characteristics of these studies.

Table 1
Characteristics of the included studies

Study	Number of patients	ACS diagnosis hospitalization	Depression diagnosis (time post-hospitalization)	Treatment (duration)	Control group	Outcomes (time post-ACS)
COPES (Davidson et al., 2010; Ye et al., 2014)	TG: 80 CG: 77	MI; unstable angina	BDI score ≥ 10 (3 months)	SSRI or CBT (6 months)	Usual care	BDI score (9 months) Treatment response (9 months) MACE (9 months; 21 months)
ENRICHD* (Enrichd Investigators, 2003; Carney et al., 2004)	TG: 697 CG: 635	MI	DSM-IV criteria (1st month)	CBT with or without SSRI (6 months)	Usual care	BDI score (6 months) Treatment response (6 months) MACE (12 months)
EsDEPACS (Kim et al., 2015; Kim et al., 2018)	TG: 108 CG: 109	MI; unstable angina	DSM-IV criteria BDI score ≥ 10 (1st 3 months)	SSRI (6 months)	Placebo	BDI score (6-9 months) Treatment response (6-9 months) MACE (6-9 months; 8 years)
MIND-IT* (Honig et al., 2007)	TG: 47 CG: 44	MI	DSM-IV criteria BDI score ≥ 10 (1st 12 months)	Mirtazapine (6 months)	Placebo	BDI score (6-18 months) Treatment response (6-18 months) MACE (6-18 months)
"MoodCare" (O'Neil et al., 2014; O'Neil et al., 2015)	TG: 61 CG: 60	MI; unstable angina	PHQ-9 score 5 – 19 (during hospitalization)	CBT (6 months)	Usual care	PHQ-9 score (6 months)
SADHART (Glassman et al., 2002; Glassman et al., 2009)	TG: 186 CG: 183	MI; unstable angina	DSM-IV criteria (1st month)	SSRI (6 months)	Placebo	HAM-D score (6 months) Treatment response (6 months) MACE (6 months; 7 years)
Strik et al., 2000	TG: 27 CG: 27	MI	DSM-III-R criteria HAM-D > 17 (3 – 12 months)	SSRI (6 months)	Placebo	HAM-D score (9-18 months) Treatment response (9-18 months) MACE (9-18 months)

Notes: *Subgroup of patients meeting the inclusion criteria. COPES= Coronary Psychosocial Evaluation Study; ENRICHD= Enhancing Recovery in Coronary Heart Disease; EsDEPACS= Escitalopram for Depression in Acute Coronary Syndrome; MIND-IT= Myocardial Infarction and Depression-Intervention Trial; SADHART= Sertraline Antidepressant Heart Attack Randomized Trial. ACS= acute coronary syndrome; TG= treatment group; CG= control group; MI= myocardial infarction; BDI= Beck Depression Inventory; SSRI= selective serotonin reuptake inhibitor; CBT= cognitive behavioral therapy; MACE= major adverse cardiac event; DSM= Diagnostic and Statistical Manual; PHQ-9= Patient Health Questionnaire-9; HAM-D= Hamilton Depression Scale.

Sample sizes ranged from 54 to 1332 participants. The percentage of male in the investigated groups, ranged from 46% to 87.2%, and the mean age from 54.1 ± 11.3 to 61.1 ± 10.6. In 3 studies, the participants were patients hospitalized for MI (ENRICHD Investigators, 2003; Honig et al., 2007; Strik et al., 2000), whereas in 4 trials (Davidson et al., 2010; Glassman et al., 2002; Kim et al., 2015; O'Neil et al., 2014) they were a mixed sample of patients hospitalized for MI or unstable angina. For the selection of the sample of patients with depression, a validated questionnaire was used in 2 studies (Davidson et al., 2010; O'Neil et al., 2014), diagnosis based on standard criteria in 2 others (ENRICHD Investigators, 2003; Glassman et al., 2002), or both methods in the remaining 3 (Honig et al., 2007; Kim et al., 2015; Strik et al., 2000).

Four studies investigated the efficacy of depression pharmacological treatment using SSRIs (Glassman et al., 2002; Kim et al., 2015; Strik et al., 2000) or mirtazapine (Honig et al., 2007), in one trial (O'Neil et al., 2014) only CBT was used, and in the remaining 2 studies, the intervention included CBT with pharmacological support in patients who did not respond to psychological treatment (ENRICHD Investigators, 2003) or CBT combined with drug treatment (Davidson et al., 2010). In all cases, the duration of the intervention was approximately 6 months. Control groups received usual care (Davidson et al., 2010; ENRICHD Investigators, 2003; O'Neil et al., 2014) or placebo treatment (Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000).

For the depression assessment pre-post treatment, in 4 studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Honig et al., 2007; Kim et al., 2015) the *Beck Depression Inventory* (BDI; Beck, & Steer, 1993) was used, in one study (O'Neil et al., 2014) the *Patient Health Questionnaire-9* (PHQ-9; Kroenke et al., 2001) was administered, and in the remaining 2 (Glassman et al., 2002; Strik et al., 2000) the *Hamilton Depression Rating Scale* (HAM-D; Hamilton, 1960) was applied. The pre-treatment assessment was carried out in the first month post-ACS (ENRICHD Investigators, 2003; Glassman et al., 2002; O'Neil et al., 2014), between 1-3 months post-ACS (Kim et al., 2015), after 3 months from hospitalization by ACS (Davidson et al., 2010) or during the first year post-ACS (Honig et al., 2007; Strik et al., 2000). In all studies, the post-treatment depression was measured approximately 6 months after the pre-treatment assessment, and in 6 trials (Davidson et al., 2010; ENRICHD Investigators, 2003; Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000) the percentage of subjects who showed response to treatment (including remission or significant reduction of depressive symptomatology) was recorded. In no case follow-up assessment of depression scores were carried out.

The MACEs including death or requiring hospitalization, occurred during treatment, was reported in 6 studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000); in addition, 4 of them (Davidson et al., 2010; ENRICHD

Investigators, 2003; Glassman et al., 2002; Kim et al., 2015) report MACEs after follow-up periods of 6 months (see Carney et al., 2004), 1 year (see Ye et al., 2014), 7 years (see Glassman et al., 2009) and 8 years (see Kim et al., 2018).

Risk of bias within studies

The risk of bias of each study can be seen in Table 2. A "high" risk of bias was assigned to 2 studies due to "selective reporting" (ENRICHD Investigators, 2003; Strik et al., 2000), and to 4 studies (ENRICHD Investigators, 2003; Glassman et al., 2002; Honig et al., 2007; Strik et al., 2000) due to potential conflict of interest, within the "other bias" domain. An "unclear" risk of bias was assigned to 2 studies in the "random sequence generation" domain (Glassman et al., 2002; Strik et al., 2000), to 4 studies in the "allocation concealment" domain (Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000), to 2 studies in the "selective reporting" domain (Glassman et al., 2002; Honig et al., 2007), and to one study in the "other bias" domain, due to potential conflict of interest (O'Neil et al., 2014).

Table 2
Risk of bias within studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other bias
COPES	Low	Low	Not applicable	Low	Low	Low	Low
ENRICHD	Low	Low	Not applicable	Low	Low	High	High
EsDEPACS	Low	Unclear	Low	Low	Low	Low	Unclear
MIND-IT	Low	Unclear	Low	Low	Low	Unclear	High
"MoodCare"	Low	Low	Not applicable	Low	Low	Low	Low
SADHART	Unclear	Unclear	Low	Low	Low	Unclear	High
Strik study	Unclear	Unclear	Low	Low	Low	High	High

Notes: COPES= Coronary Psychosocial Evaluation Study; ENRICHD= Enhancing Recovery in Coronary Heart Disease; EsDEPACS= Escitalopram for Depression in Acute Coronary Syndrome; MIND-IT= Myocardial Infarction and Depression-Intervention Trial; SADHART= Sertraline Antidepressant Heart Attack Randomized Trial.

Depression symptoms and treatment response

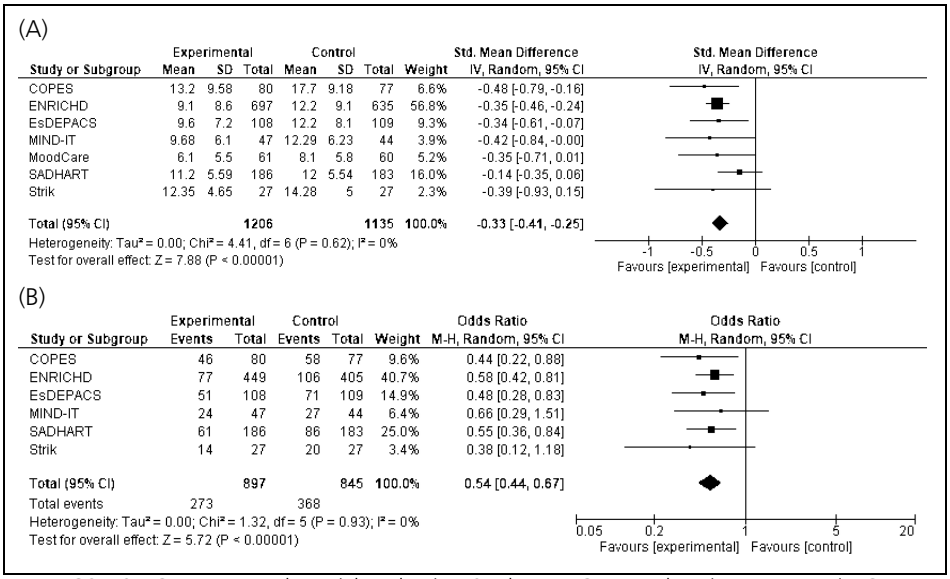
The 7 studies analyzed included 2341 participants, 1206 in the treatment groups and 1135 in the control groups. In all cases, at the end of the intervention period, the depression score was lower in the treatment group than in the control condition, with effect sizes ranging from 0.14 to 0.48, although in only 4 studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Honig et al., 2007; Kim et al., 2015) the difference was statistically significant. The pooled effect size was statistically significant in favor of the treatment group vs control condition (SMD= -

0.33, 95% CI [-0.41, -0.25], p< .001). Heterogeneity was not significant (χ^2= 4.41, p= .62; I^2= 0%). A forest plot of effect size and 95% confidence limits for all interventions can be seen in Figure 2.

Six studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000), including 1742 participants, report data on response to treatment. At the end of the intervention period, a higher proportion of participants in the control condition were still showing symptoms of clinically significant depression (OR= 0.54, 95% CI [0.44-0.67], p< .001); the heterogeneity was not significant (χ^2= 1.32, p= .93, I^2= 0%) (Figure 2).

Figure 2

Forest plots of studies for depression post-treatment scores (A) and for participants without treatment response (B)



Notes: COPES= Coronary Psychosocial Evaluation Study; ENRICHD= Enhancing Recovery in Coronary Heart Disease; EsDEPACS= Escitalopram for Depression in Acute Coronary Syndrome; MIND-IT= Myocardial Infarction and Depression-Intervention Trial; SADHART= Sertraline Antidepressant Heart Attack Randomized Trial.

Major Adverse Cardiovascular Events (MACEs)

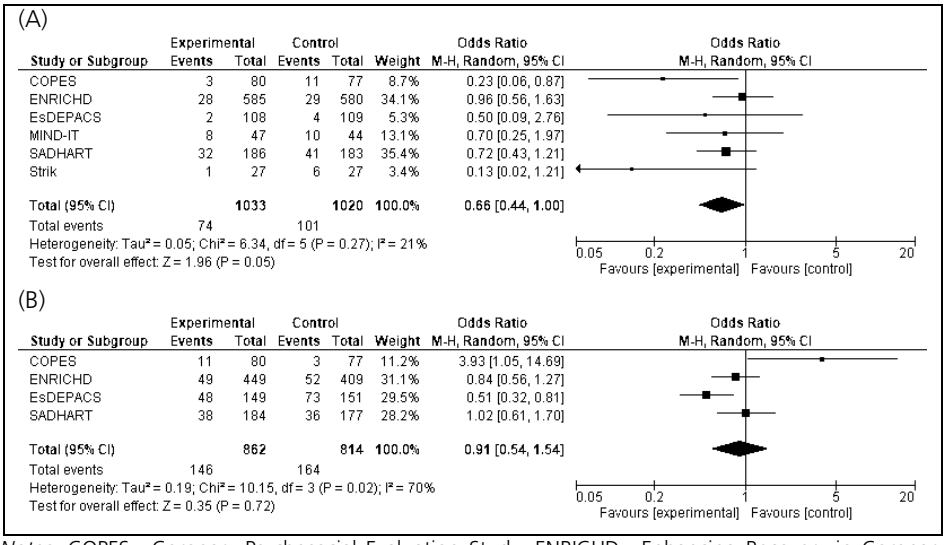
Six studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Glassman et al., 2002; Honig et al., 2007; Kim et al., 2015; Strik et al., 2000), involving 2053 participants, reported MACEs after treatment. In all studies, the scores showed fewer cardiovascular events in the treatment group compared with controls, although this difference was only significant in one study (Davidson et al., 2010).

The pooled scores showed fewer events in the treatment group vs controls; this was minimally significant (OR= 0.66, 95% CI [0.44-1.00], *p*= .05); the heterogeneity was not significant (χ^2= 6.34, *p*= .27, I^2= 21%) (Figure 3).

Only 4 studies (Davidson et al., 2010; ENRICHD Investigators, 2003; Glassman et al., 2002; Kim et al., 2015) report MACEs after follow-up periods, ranging from 1 to 8 years. The results showed, in 2 studies more MACEs in experimental group (see Glassman et al., 2009; Ye et al., 2014), and in 2 others, more MACEs in control group (see Carney et al., 2004; Kim et al., 2018). Pooled scores showed fewer events in the intervention condition compared with control groups; this difference was not significant (OR= 0.91, 95% CI [0.54-1.54], *p*= 0.72). Heterogeneity was statistically significant (χ^2= 10.15, *p*= .02, I^2= 70%) (Figure 3).

Figure 3

Forest plots of studies for major adverse coronary events (MACE) at the post-treatment (A) and for MACE at the follow-up (B)



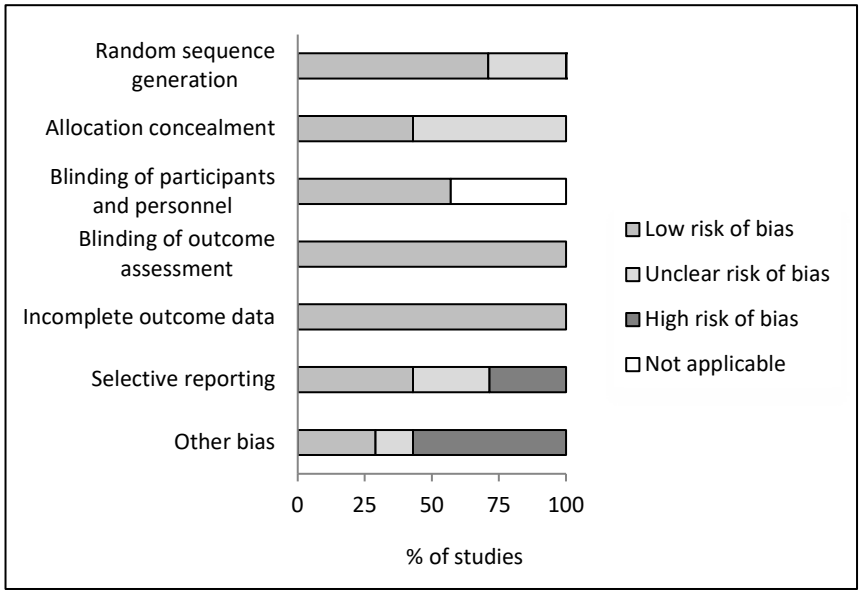
Notes: COPES= Coronary Psychosocial Evaluation Study; ENRICHD= Enhancing Recovery in Coronary Heart Disease; EsDEPACS= Escitalopram for Depression in Acute Coronary Syndrome; MIND-IT= Myocardial Infarction and Depression-Intervention Trial; SADHART= Sertraline Antidepressant Heart Attack Randomized Trial.

Risk of bias across studies

The application of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011) showed that no studies was rated as high risk of bias in the domains "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", and "incomplete outcome data", although, in 57% of the trials the information about "allocation concealment" was unclear. Some results were not

reported, or only partially reported, in 28.5% of the studies and, finally, in 57% there was a potential conflict of interest (Figure 4).

Figure 4
Risk of bias across studies



Discussion

This meta-analytical review has investigated the effects of psychological and/or pharmacological interventions for the treatment of depression and their impact on post-ACS morbidity and mortality. Using a comprehensive search strategy, after reviewing 1525 articles, 7 RCTs have been identified with very restrictive eligibility criteria, overcoming the limitation of previous meta-analyses that have not been able to answer the question investigated here because the levels of clinical heterogeneity of the included studies, and statistical heterogeneity of the results obtained, call into question the feasibility of combining the meta-analyzed data.

As far as we have been able to trace from the exhaustive review carried out, this would be the first meta-analysis of RCTs results on the efficacy of depression treatment with samples of patients hospitalized exclusively with ACS (MI or unstable angina) and comorbid depression as determined by standard diagnostic criteria and/or cut-off points on validated questionnaires.

The results obtained meta-analyzing a similar number of studies to those included in previous meta-analyses indicate, with 0% statistical heterogeneity, that post-ACS patients with comorbid depression treated with psychological and/or

pharmacological interventions of choice for the therapeutic management of depression reduce their levels of depressive disorder significantly more than subjects without this treatment. Likewise, with total homogeneity of results, the meta-analysis shows significant differences between the experimental group and the control group in the number of patients who reduce their depressive symptoms in a clinically relevant way. Therefore, the inconsistency in the results, observed in previous studies on the efficacy of comorbid depression treatment in post-ACS patients, is not confirmed in our meta-analysis; conversely, the results consistently indicate that the intervention is superior to non-intervention or placebo.

However, in accordance with previous meta-analytical studies, it is important to note that the difference, although very consistent, is clinically modest, mainly due to the improvement of depressive symptomatology in the control group. This result could be due to the fact that, although the selection criteria of studies in our meta-analysis, overcoming the limitation of previous works, have greatly reduced clinical heterogeneity with respect to the level of depression severity of the participants, there is a notable difference between the characteristics of depression in subjects participating in RCTs on treatment of post-ACS depression and those included in RCTs on the efficacy of antidepressant treatments in population without this coronary pathology. As noted by Glassman et al. (2002), in general, trials of efficacy of antidepressant treatments include subjects who seek treatment, score at least 18 on the HAM-D, and have mostly been depressed for many months, whereas patients in trials on efficacy of antidepressant treatments after ACS, typically, do not seek treatment, are approached in the coronary care unit days after hospitalization and screened for depression, and their symptoms are not only less severe but, more importantly, they have been depressed for only 2-3 weeks prior to randomization; under these conditions it can be problematic to demonstrate the efficacy of antidepressant treatments. In fact, when the results have been analyzed by subgroups according to the severity and persistence of depressive symptoms, significant differences with respect to the control groups have been found only in subjects with more severe and persistent depression (Kim et al., 2015; O'Neil et al., 2014).

In addition, it is very important to point out that the results of our meta-analysis show that the number of patients in whom a relevant remission of depressive symptomatology is observed after treatment, is consistently and significantly higher in the group of treated subjects, but a percentage between 26-75% of the subjects in the control group, and between 18-58% in the experimental group, have no response to treatment. We believe that the explanation for this finding is particularly important, because it may be due to the fact that most studies have not paid sufficient attention to a variable of great relevance in this field which is discussed below.

In post-ACS patients is very frequent an adjustment reaction with depressive symptomatology that has a spontaneous remission of more than 50% at three

months, whereas approximately another half of post-ACS subjects with comorbid depression persist with depressive disorder or relapse one year later (Glassman et al., 2002). The confusion and the mixture of these two courses of depressive symptomatology in the samples of studies that have tried to determine the efficacy of depression treatment and its impact on post-ACS morbidity and mortality could explain the results obtained. Thus, it could be that, in effect, the treatment reduces the depressive symptomatology and achieves remission in some patients, but with no effect other than spontaneous remission (which would be clearly observed in the subjects of the control group), while, in parallel, in other patients the treatment would have a significantly greater effect than the non-treatment; in this way, when taking the results of both types of patients together, the modest effect of the treatment found in most of the studies carried out to date would be obtained (Thombs et al., 2008), leading some authors to suggest the need to investigate the existence of a subtype of depression or specific high-risk depressive symptomatology in patients with CHD (Carney, & Freedland, 2012a; Carney, & Freedlad, 2012b; Martens et al., 2010; Smolderen et al., 2009), or to consider, on the contrary, that depression is not a therapeutic target of interest for these patients (Rafanelli et al., 2013).

On the other hand, regarding the effect of treatment on short-term post-SCA morbidity and mortality, only one study (Davidson et al., 2010) found a small significant difference between the intervention group and the control condition in the MACEs recorded at the end of treatment, whereas in the rest, although in all of them the number of events was greater in the control group, the difference did not reach statistical significance, so that the meta-analytical result does not allow firm conclusions to be drawn in this regard. Furthermore, only 4 studies evaluated MACEs after prolonged periods of follow-up, finding significant differences in 2 of them; but while in one, greater morbidity was found in the control group (Kim et al., 2018), in the other, greater morbidity was recorded in the experimental group (Ye et al., 2014). Thus, the meta-analysis shows no significant differences in this variable, being the inconsistency of the results very high, despite the clinical homogeneity of the samples studied.

These results, coinciding with those found in previous meta-analyses, do not allow us to draw conclusions about the relationship between treatment of depression and cardiac prognosis in post-ACS patients, probably due to the important methodological limitations of the studies regarding this issue. In this sense, together with the small number of studies carried out, it is important to keep in mind that, if the disorder that has been shown to be a risk factor for re-MI and death is the major depressive disorder (persistent and recurrent) and not the adjustment reaction with depressive symptomatology frequently found in post-ACS patients, then it is possible that the treatment of depression may not show significant effects in reducing risk, because some patients included in the studies do not have the risk characteristic under investigation. Moreover, this is exacerbated by the fact that research carried out to determine the effect of the

depression treatment in post-ACS patients (short-term) on mortality in later years (long-term) has surprisingly not included follow-up measures of depressive symptomatology which, with high probability, will have occurred and acted as a factor of poor prognosis at least in some subjects of the experimental group, for whom the adequate treatment for patients with severe and recurrent depression, that constitute the risk group for post-ACS morbidity and mortality, has not been implemented. In fact, it has already been pointed out in this direction that the efficacy of depression treatments in cardiac patients included in the research in this field could be strengthened if the treatment were longer (Davidson et al., 2010).

The small number of available RCTs and the impossibility to analyzing the publication bias of meta-analyzed studies are limitations of our work that should be taken into account; nevertheless, the results obtained here seem to support the conclusion of Carney and Freedland (2017) that it may be premature to initiate a research line to identify subtypes of depression of particular risk of cardiac events, and specific treatments for them. Instead, future research should perhaps focus on studies of the efficacy of currently available treatments for depression that, overcoming the limitations of previous work, include sufficiently large and clinically homogeneous samples of patients with diagnosis of depressive disorder persisting at least two months post-ACS. Furthermore, following the recommendation of Carney and Freedland (2017), future work should include repeated measures of depression over long post-ACS follow-up periods; this would allow to determine how much exposure to depression is necessary to increase the risk of MACEs and to analyze the efficacy of treatment of recurrent depressive episodes during that follow-up period. In this way, conclusions could be drawn about the effect of depression treatment on post-ACS morbidity and mortality that, to date, has not been conclusively demonstrated.

In short, as the European Society of Cardiology has recently pointed out in its document on depression and coronary heart disease "whether effective and safe treatment of depression may improve CHD outcomes, and whether specific patient subgroups may benefit more from such treatments, require further evaluation" (Vaccarino et al., 2020, p.1695). In this sense, if the hypotheses presented here are confirmed, the recommendation to assess comorbid depression in all post-ACS patients could be justified in order to identify, among the high percentage of them with depressive symptoms, those who may benefit from a minimal antidepressant treatment in the first months after hospitalization, and apply more powerful interventions only in those patients with more severe and persistent depressive disorder associated with increased risk of morbidity and mortality cardíaca.

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