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Psychological and pharmacological interventions for depression in patients with coronary artery disease (Review)

Tully PJ, Ang SY, Lee EJL, Bendig E, Bauereiß N, Bengel J, Baumeister H

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[Intervention Review]

Psychological and pharmacological interventions for depression in patients with coronary artery disease

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ABSTRACT

Background

Depression occurs frequently in individuals with coronary artery disease (CAD) and is associated with a poor prognosis.

Objectives

To determine the effects of psychological and pharmacological interventions for depression in CAD patients with comorbid depression.

Search methods

We searched the CENTRAL, MEDLINE, Embase, PsycINFO, and CINAHL databases up to August 2020. We also searched three clinical trials registers in September 2021. We examined reference lists of included randomised controlled trials (RCTs) and contacted primary authors. We applied no language restrictions.

Selection criteria

We included RCTs investigating psychological and pharmacological interventions for depression in adults with CAD and comorbid depression. Our primary outcomes included depression, mortality, and cardiac events. Secondary outcomes were healthcare costs and utilisation, health-related quality of life, cardiovascular vital signs, biomarkers of platelet activation, electrocardiogram wave parameters, non-cardiac adverse events, and pharmacological side effects.

Data collection and analysis

Two review authors independently examined the identified papers for inclusion and extracted data from the included studies. We performed random-effects model meta-analyses to compute overall estimates of treatment outcomes.

Main results

Thirty-seven trials fulfilled our inclusion criteria. Psychological interventions may result in a reduction in end-of-treatment depression symptoms compared to controls (standardised mean difference (SMD) −0.55, 95% confidence interval (CI) −0.92 to −0.19, I^2 = 88%; low certainty evidence; 10 trials; n = 1226). No effect was evident on medium-term depression symptoms one to six months after the end of treatment (SMD −0.20, 95% CI −0.42 to 0.01, I^2 = 69%; 7 trials; n = 2654). The evidence for long-term depression symptoms and depression response was sparse for this comparison. There is low certainty evidence that psychological interventions may result in little to no difference in end-of-treatment depression remission (odds ratio (OR) 2.02, 95% CI 0.78 to 5.19, I^2 = 87%; low certainty evidence; 3 trials; n = 862). Based on one to two trials per outcome, no beneficial effects on mortality and cardiac events of psychological interventions versus

control were consistently found. The evidence was very uncertain for end-of-treatment effects on all-cause mortality, and data were not reported for end-of-treatment cardiovascular mortality and occurrence of myocardial infarction for this comparison.

In the trials examining a head-to-head comparison of varying psychological interventions or clinical management, the evidence regarding the effect on end-of-treatment depression symptoms is very uncertain for: cognitive behavioural therapy compared to supportive stress management; behaviour therapy compared to person-centred therapy; cognitive behavioural therapy and well-being therapy compared to clinical management. There is low certainty evidence from one trial that cognitive behavioural therapy may result in little to no difference in end-of-treatment depression remission compared to supportive stress management (OR 1.81, 95% CI 0.73 to 4.50; low certainty evidence; n = 83). Based on one to two trials per outcome, no beneficial effects on depression remission, depression response, mortality rates, and cardiac events were consistently found in head-to-head comparisons between psychological interventions or clinical management.

The review suggests that pharmacological intervention may have a large effect on end-of-treatment depression symptoms (SMD −0.83, 95% CI −1.33 to −0.32, I^2 = 90%; low certainty evidence; 8 trials; n = 750). Pharmacological interventions probably result in a moderate to large increase in depression remission (OR 2.06, 95% CI 1.47 to 2.89, I^2 = 0%; moderate certainty evidence; 4 trials; n = 646). We found an effect favouring pharmacological intervention versus placebo on depression response at the end of treatment, though strength of evidence was not rated (OR 2.73, 95% CI 1.65 to 4.54, I^2 = 62%; 5 trials; n = 891). Based on one to four trials per outcome, no beneficial effects regarding mortality and cardiac events were consistently found for pharmacological versus placebo trials, and the evidence was very uncertain for end-of-treatment effects on all-cause mortality and myocardial infarction.

In the trials examining a head-to-head comparison of varying pharmacological agents, the evidence was very uncertain for end-of-treatment effects on depression symptoms. The evidence regarding the effects of different pharmacological agents on depression symptoms at end of treatment is very uncertain for: simvastatin versus atorvastatin; paroxetine versus fluoxetine; and escitalopram versus Bu Xin Qi.

No trials were eligible for the comparison of a psychological intervention with a pharmacological intervention.

Authors' conclusions

In individuals with CAD and depression, there is low certainty evidence that psychological intervention may result in a reduction in depression symptoms at the end of treatment. There was also low certainty evidence that pharmacological interventions may result in a large reduction of depression symptoms at the end of treatment. Moderate certainty evidence suggests that pharmacological intervention probably results in a moderate to large increase in depression remission at the end of treatment. Evidence on maintenance effects and the durability of these short-term findings is still missing. The evidence for our primary and secondary outcomes, apart from depression symptoms at end of treatment, is still sparse due to the low number of trials per outcome and the heterogeneity of examined populations and interventions. As psychological and pharmacological interventions can seemingly have a large to only a small or no effect on depression, there is a need for research focusing on extracting those approaches able to substantially improve depression in individuals with CAD and depression.

PLAIN LANGUAGE SUMMARY

Treatments for depression in individuals with coronary artery disease

This review examined clinical trials on psychological treatments and antidepressant drugs in individuals with coronary artery disease and depression. The objective was to determine the effects of these treatments on depression, mortality, cardiac events such as another heart attack, or heart surgery.

We identified 37 trials as relevant for the review. Fifteen trials investigated psychological treatments, and 21 trials investigated pharmacological interventions including antidepressant drugs.

Generally, psychological treatments compared to controls, and antidepressant drugs compared to placebo (inactive drug), may result in a reduction in depression symptoms at the end of treatment; however, the evidence is generally of low certainty. The evidence is very uncertain as to whether psychological treatments compared to control and antidepressant drugs compared to placebo reduce mortality and cardiovascular events.

The evidence is current to August 2020.

Summary of findings 1. Summary of findings table - Psychological treatment compared to control for depression in patients with coronary artery disease

Psychological treatment compared to control for depression in patients with coronary artery disease

Patient or population: health problem or population
Setting: cardiology in- and outpatient
Intervention: Psychological treatment
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Psychological treatment				
Depression symptoms - short-term assessed with: objective and self-reported measures of depression symptoms, higher scores indicate more severe symptoms	-	SMD **0.55 SD lower** (0.92 lower to 0.19 lower)	-	1226 (10 RCTs)	⊕⊕⊖⊖ Low[a,b]	There is low certainty evidence that psychological treatment may result in a moderate reduction in depression symptoms at the end of treatment.
Depression remission - short term assessed with: below cut-points on objective and self-report measures of depression	319 per 1000	**486 per 1000** (267 to 708)	**OR 2.02** (0.78 to 5.19)	862 (3 RCTs)	⊕⊕⊖⊖ Low[b,c]	There is low certainty evidence that psychological treatment may result in no difference in depression remission at the end of treatment.
All-cause mortality - short-term assessed with: mortality records	25 per 1000	**8 per 1000** (1 to 50)	**OR 0.31** (0.05 to 2.02)	324 (2 RCTs)	⊕⊖⊖⊖ Very low[d,e]	The evidence is very uncertain about the effect of psychological treatment on all-cause mortality at the end of treatment.
Cardiovascular mortality - long-term assessed with: cause of death according to standardised criteria on mortality records	85 per 1000	**72 per 1000** (54 to 93)	**OR 0.83** (0.62 to 1.10)	2720 (2 RCTs)	-	No data for cardiovascular mortality at end of treatment in trials comparing psychological interventions versus usual care

Myocardial infarction - short term (end of treatment) - not reported	-	-	-	-	-	No data for occurrence of myocardial infarction at end of treatment in trials comparing psychological interventions versus usual care

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427596582080189491.

[a] Risk of bias rated down one level - trials that contributed to this outcome were rated as unclear risk of bias
[b] Inconsistency rated down one level - though confidence intervals generally overlapped, there was considerable unexplained statistical heterogeneity
[c] Imprecision rated down one level - confidence intervals encompass an adverse effect to beneficial effect
[d] Risk of bias rated down two levels - most trials that contributed to this outcome were rated as high or unclear risk of bias
[e] Imprecision rated down two levels - sparse events and wide confidence intervals encompass an adverse effect to beneficial effect

Summary of findings 2. Summary of findings table - Psychological treatment 1 compared to psychological treatment 2 for depression in patients with coronary artery disease

Psychological treatment 1 compared to psychological treatment 2 for depression in patients with coronary artery disease

Patient or population: health problem or population
Setting: cardiology outpatient settings
Intervention: Psychological Treatment 1
Comparison: Psychological Treatment 2

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Psychological Treatment 2	Risk with Psychological Treatment 1				

Depression symptoms - short term (end of treatment) assessed with: objective and self-reported measures of depression symptoms; higher scores indicate more severe symptoms	Not pooled	Not pooled	Not pooled	219 (3 RCTs)	-	No meta-analysis performed due to clinical heterogeneity. The evidence is very uncertain as to whether different psychological interventions may result in a reduction in depression symptoms at the end of treatment for: cognitive-behavioural therapy compared to supportive stress management (Freedland 2009); behaviour therapy compared to person-centred therapy (Brown 1993); cognitive-behavioural therapy and well-being therapy compared to clinical management (TREATED-ACS 2020).
Depression remission - short term (end of treatment) assessed with: below cut-off on Hamilton Rating Scale for Depression	571 per 1000	**707 per 1000** (493 to 857)	**OR 1.81** (0.73 to 4.50)	83 (1 RCT)	⊕⊕⊖⊖ Low[a]	There is low certainty evidence from one trial that cognitive-behavioural therapy may result in no difference in depression remission at the end of treatment compared to supportive stress management (Freedland 2009).
All-cause mortality - short term (end of treatment) - not reported	-	-	-	-	-	No data for all-cause mortality at end of treatment in trials comparing psychological intervention versus another psychological intervention/clinical management
Cardiovascular mortality - short term (end of treatment) - not reported	-	-	-	-	-	No data for cardiovascular mortality at end of treatment in trials comparing psychological intervention versus another psychological intervention/clinical management
Myocardial infarction - short term (end of treatment) - not reported	-	-	-	-	-	No data for the occurrence of myocardial infarction at end of treatment in trials comparing psychological intervention versus another psychological intervention/clinical management

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427665509108780589.

[a] Imprecision rated down two levels - wide confidence intervals from one trial encompass an adverse effect to beneficial effect

Summary of findings 3. Summary of findings table - Pharmacological treatment compared to placebo for depression in patients with coronary artery disease

Pharmacological treatment compared to placebo for depression in patients with coronary artery disease

Patient or population: health problem or population
Setting: cardiology in- and outpatient settings
Intervention: Pharmacological
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Pharmacological				
Depression symptoms - short term assessed with: objective and self-reported measures of depression; higher scores indicate more severe symptoms	-	SMD **0.83 lower** (1.33 lower to 0.32 lower)	-	750 (8 RCTs)	⊕⊕⊖⊖ Low[a,b]	There is low certainty evidence that pharmacological intervention may result in a large reduction in depression symptoms at the end of treatment
Depression remission - short term assessed with: below cut-point on objective measure of depression (Hamilton Rating Scale for Depression)	323 per 1000	**496 per 1000** (412 to 580)	**OR 2.06** (1.47 to 2.89)	646 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	There is moderate certainty evidence that pharmacological intervention probably results in a moderate to large increase in depression remission at the end of treatment.
All-cause mortality - short term assessed with: mortality records	36 per 1000	**14 per 1000** (4 to 53)	**OR 0.38** (0.10 to 1.47)	437 (2 RCTs)	⊕⊖⊖⊖ Very low[a,c]	The evidence is very uncertain about the effect of pharmacological intervention on all-cause mortality at the end of treatment. In addition to the pooled results, data could not be extracted from 2 studies where no deaths occurred and from 1 trial which remained unclear.

Cardiovascular mortality - short term (end of treatment) - not reported	-	-	-	-	-	No data for cardiovascular mortality at end of treatment in trials comparing pharmacological intervention versus placebo
Myocardial infarction - short term assessed with: standardised criteria for fatal or non-fatal myocardial infarction	22 per 1000	**17 per 1000** (6 to 45)	**OR 0.74** (0.26 to 2.09)	728 (3 RCTs)	⊕⊖⊖⊖ Very low[a,c]	The evidence is very uncertain about the effect of pharmacological intervention on myocardial infarction at the end of treatment.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427666962988765745.

[a] Risk of bias rated down one level - trials that contributed to this outcome were rated as unclear or high risk of bias
[b] Inconsistency rated down one level - though confidence intervals generally overlapped, there was considerable unexplained statistical heterogeneity
[c] Imprecision rated down two levels - sparse events and wide confidence intervals encompass an adverse effect to beneficial effect

Summary of findings 4. Summary of findings table - Pharmacological treatment 1 compared to pharmacological treatment 2 for depression in patients with coronary artery disease

Pharmacological treatment 1 compared to pharmacological treatment 2 for depression in patients with coronary artery disease

Patient or population: health problem or population
Setting: cardiology in- and outpatient settings
Intervention: Pharmacological intervention 1
Comparison: Pharmacological intervention 2

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with Pharmacological intervention 2	Risk with Pharmacological intervention 1				
Depression symptoms - short term (end of treatment) assessed with: objective measure of depression (Hamilton Rating Scale for Depression); higher scores indicate more severe symptoms	Not pooled	Not pooled	Not pooled	442 (4 RCTs)	-	No meta-analysis performed due to clinical heterogeneity. The evidence is very uncertain as to whether different pharmacological interventions may result in a reduction in depression symptoms at the end of treatment for: simvastatin compared to atorvastatin (Abbasi 2015); sertraline plus omega-3 compared to sertraline plus placebo (Carney 2009); paroxetine compared to fluoxetine (Tian 2016); escitalopram compared to Bu Xin Qi (Wang 2020).
Depression remission - short term (end of treatment) assessed with: below cut-points on objective and self-report measures of depression	Not pooled	Not pooled	Not pooled	243 (3 RCTs)	-	No meta-analysis performed due to clinical heterogeneity. The evidence is very uncertain about the effect of pharmacological treatment compared to another pharmacological treatment on depression remission at the end of treatment .
All-cause mortality - short term (end of treatment) assessed with: mortality records	26 per 1000	**68 per 1000** (14 to 281)	**OR 2.72** (0.51 to 14.49)	149 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	The evidence from 1 trial is very uncertain about the effect of sertraline vs Shugan Jieyu on all-cause mortality at the end of treatment (Liu 2016).
Cardiovascular mortality - short term (end of treatment) - not reported	-	-	-	-	-	No data for cardiovascular mortality at end of treatment in trials comparing a pharmacological intervention versus another pharmacological intervention
Myocardial infarction - short term (end of treatment) assessed with: standardised criteria for fatal and non-fatal myocardial infarction	Not pooled	Not pooled	Not pooled	396 (3 RCTs)	-	No meta-analysis performed due to clinical heterogeneity. The evidence is very uncertain about the effect of pharmacological treatment compared to another pharmacological treatment on the occurrence of myocardial infarction at end of treatment for: sertraline plus omega-3 compared to sertraline plus placebo (Carney 2009); paroxetine compared to fluoxetine (Tian 2016); escitalopram compared to Bu Xin Qi (Wang 2020).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_428037497253281678.

[a] Risk of bias rated down one level - the trial(s) that contributed to this outcome were rated as unclear or high risk of bias
[b] Imprecision rated down two levels - sparse events and wide confidence intervals encompass an adverse effect to beneficial effect

BACKGROUND

Coronary artery disease (CAD) is amongst the leading causes of death for both men and women in middle- and high- income countries (Roth 2017). A strong association between CAD and comorbid depression has been consistently reported (Baune 2012; Kendler 2009; Scherrer 2003; Schulman-Marcus 2016; Stenman 2014), which is similar to the association observed in other chronic disease populations (Chen 2019; Härter 2007; Matte 2016; Mezuk 2015; Petrak 2015). Results from the World Mental Health Surveys, Ormel 2007, indicate a twofold increased risk of depression for individuals with heart disease compared to those without heart disease and conversely, an increased risk of developing incident heart disease in individuals with depression compared to those without depression (Scott 2013). Prevalence rates of major depression in CAD populations, including those undergoing coronary revascularisation procedures, range from 15% to 20% (Nieuwsma 2017; Thombs 2008; Tully 2012), and are thus disproportionate to that observed in the general community (Kessler 2010).

The increased prevalence rates raise the issue of the impact of comorbid depression on the lives of these individuals and the healthcare system. Several original studies and systematic reviews document a significant prognostic association between comorbid depression and increased mortality, morbidity, and healthcare costs, as well as diminished quality of life and adherence to treatment regimen (Abberger 2017; Barth 2004; Baumeister 2011c; Frasure-Smith 2003a; Frasure-Smith 2008; Lichtman 2014; Nicholson 2006).

Description of the condition

Coronary artery disease is one of the most common forms of heart disease. One of the main underlying problems in cardiovascular disease is atherosclerosis, a process that obstructs blood vessels with deposits of fat, cholesterol, and other substances (WHO 1992). It is most serious when it restricts the blood supply to the heart itself (myocardial ischaemia). Clinical manifestations of CAD are acute coronary syndrome comprising myocardial infarction (MI) and unstable angina (Antman 2004), as well as stable angina pectoris (Fox 2006). MI refers to what is commonly known as a 'heart attack'. It occurs when prolonged myocardial ischaemia leads to myocardial cell death (necrosis) (Alpert 2000).

Depression is an emotional state characterised by strong feelings of sadness, worthlessness and guilt, withdrawal from others, sleeplessness, and loss of appetite, sexual desire, and interest in usual activities (Davison 2003), occurring in several subtypes (Baune 2012). Two key diagnostic criteria for major depression are depressed mood and loss of pleasure or interest in activities (anhedonia; APA 2013). Depressive disorders can be reliably diagnosed through structured clinical interviews. The severity of depressive symptoms is usually assessed by patient- or clinician-administered rating scales that have undergone psychometric validation. Cut-off scores have been validated for these scales that correspond to the likelihood of an indication of depression (Sadock 2009). Recommendations for the assessment of depression in individuals with cardiovascular disease are available (Davidson 2006; Lichtman 2014; Nieuwsma 2017; Thombs 2008).

Description of the intervention

Psychological interventions comprise cognitive behavioural therapy (CBT), psychodynamic psychotherapy, interpersonal therapy (IPT), other approaches such as problem-solving therapy, non-directive or supportive therapy and counselling as well as single techniques of these interventions (Davison 2003). Other interventions comprise acceptance and commitment therapy, mindfulness-based cognitive therapy and mindfulness-based stress reduction, emotion-focused therapy, and metacognitive therapy (Australian Psychological Society 2018). The mode of delivery comprises individual, group, or family (including couple) therapy carried out by a healthcare professional.

A network meta-analysis comparing seven psychotherapeutic approaches concluded that most approaches were equally effective, with IPT being more effective than supportive therapy (Cohen's d = −0.30, 95% confidence interval (CI) −0.54 to −0.05) (Barth 2013). However, this conclusion needs to be considered preliminary, as single trials lack statistical power, and meta-analyses are limited by the heterogeneous methodological standards of primary studies (Cuijpers 2016). This might be even more true regarding psychological depression interventions for individuals with CAD, given the diversity of psychological interventions offered, from nurse-led and low-intensive, two-session interventions to regular psychotherapies with at least 12 to 16 therapy sessions, offered at varying time points post-cardiac event (Baumeister 2011c; Baumeister 2012b; Doyle 2021).

Antidepressant drugs are commonly used treatments in people with depression. In general, the available medications do not differ in their overall efficacy and effectiveness, but differ substantially with regard to short- and long-term side effects (NICE 2009; Sadock 2009). Antidepressant treatment selection depends on the type of depressive disorder and the presence of comorbid somatic or mental disorders. The main pharmacological classes of antidepressant medications are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). For CAD patients with moderate, severe, or recurrent depression, SSRIs are viewed as safe and effective pharmacological agents (Lichtman 2008). In contrast, TCAs and MAOIs are contraindicated in CAD patients because of their cardiac side effects such as prolongation of the QT interval on electrocardiogram (Lichtman 2008). Other potential pharmacological interventions include repurposing vascular drugs intended to lower cholesterol or blood pressure for the treatment of depression (Cipriani 2016; Taragano 2005). In addition, interventions may explore diet and supplements such as n-3 polyunsaturated fatty acids, also known as omega-3 oils (Appleton 2015).

A systematic review experimentally comparing psychological or psychotherapy and pharmacological approaches indicated that overall, psychological and pharmacological interventions are equally effective for treating depression, with pharmacotherapy seemingly being superior in dysthymia (Hedges' g = 0.3) as well as compared to non-directive counselling (Hedges' g = 0.33), and psychotherapy being superior to tricyclic antidepressants (Hedges' g = 0.21) (Cuijpers 2013). Combining both pharmacotherapy and psychotherapy is superior to pharmacotherapy alone at six months or longer postrandomisation (odds ratio (OR) 2.93). However, and conversely, psychotherapy alone compared to combined therapy

resulted in equal depression effects at six months follow-up and longer (Karyotaki 2016).

How the intervention might work

Many biological and behavioural mechanisms linking CAD and depression have been proposed (Carney 2017; Härter 2007a; Joynt 2003; Musselman 1998; Skala 2006), comprising pathophysiological pathways such as decreased heart rate variability, platelet activation, and endothelial dysfunction in depressed CAD patients (Antman 2004). Furthermore, an accumulation of behavioural (smoking, physical inactivity, and imbalanced diet) and medical risk factors (hypertension, diabetes, and obesity) in depressed patients might affect the development and course of CAD (Joynt 2003; Whooley 2008). Psychosocial stress constitutes a risk factor for both CAD and depression (Joynt 2003).

A review concluded that pharmacological interventions for depression might influence physiological pathways linking depression and CAD (Carney 2017). Psychological treatments may also affect physiological processes, but the interrelations between behavioural and physiological mechanisms remain less clear (Carney 2017). Psychological interventions might improve not only depression outcomes in CAD patients with comorbid depressive disorder, but also medical outcome parameters, by encouraging behaviour changes towards a healthier lifestyle in these patients (Firth 2019; Richards 2017).

Why it is important to do this review

Due to high prevalence rates and the impact of comorbid depression on both medical and psychosocial outcomes, there is a need for effective depression treatments in CAD. In various systematic reviews, psychological and psychopharmacological interventions have proven to be effective interventions for the treatment of major depression (Cuijpers 2008a; Cuijpers 2008b; Cuijpers 2013; Karyotaki 2016; NICE 2009; Sadock 2009). However, the evidence on the effectiveness of psychological and pharmacological depression interventions for people with CAD and depression is far less conclusive (Baumeister 2011c), and prone to bias in the literature (Doyle 2021), which argues for an update of our Cochrane Review. Several clinical guidelines recommend depression intervention in CAD populations whilst noting the limited efficacy in preventing major adverse cardiac events, based on few trials to date (Hillis 2011; Lichtman 2014).

Another Cochrane Review examined the effects of non-specific psychological interventions in CAD patients and found small to moderate reductions in depression, anxiety, and stress symptoms as well as a 22% reduction in MI compared to usual care (Richards 2017). However, the review did not study the effects of depression-specific treatment in the population of CAD patients with a comorbid depressive disorder or depression symptoms. Furthermore, the review included non-specific psychological interventions and interventions delivered in combination with cardiac rehabilitation, whereas the focus of our review is on depression-specific psychological or pharmacological interventions explicitly used for treating depression in populations with depression. Some randomised controlled trials may be included in both reviews, but the research questions remain different owing to the focus of our review on the effects of depression treatments in depressed CAD patients.

The current review will permit the drawing of conclusions on the effects of depression treatment in CAD patients with comorbid depressive disorders. Depending on the number of primary studies, conclusions may be drawn concerning differential effects of type of intervention on depression and mortality or cardiovascular events, as well as on participant quality of life (QoL), thus providing a basis for treatment recommendations. Furthermore, follow-up data may be examined concerning the healthcare costs of the interventions. Sources of heterogeneity in the results of the primary studies can be explored and could help provide suggestions for the design of future studies.

OBJECTIVES

To determine the effects of psychological and pharmacological interventions for depression in CAD patients with comorbid depression.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials (RCTs) of any length of treatment and any length of follow-up. Both individually and cluster-randomised clinical trials were eligible. We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

Adults (18 years or older) with CAD (International Statistical Classification of Diseases and Related Health Problems (ICD-10): I20-I25, WHO 1992, or later versions of the ICD) and comorbid depressive disorder (ICD-10: F32/33/34.1 (WHO 1992); *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*): 296.xx; 300.4, APA 1987, or later versions of diagnostic classification systems; including subthreshold conditions) assessed by standardised interviews, self-reports, medical records, or physicians' diagnosis. Studies comprised of individuals with non-CAD conditions were ineligible. Inclusion of primary studies was not further limited to specific clinical subgroups in order to increase the generalisability of the results of the review.

With regard to comorbid depression, studies comprising mixed study samples (e.g. both depressed CAD patients and CAD patients with low social support (ENRICHD 2003)) were included in the review.

Types of interventions

Psychological interventions comprise CBT, psychodynamic psychotherapy, IPT, non-directive or supportive therapy and counselling (Davison 2003), acceptance and commitment therapy, mindfulness-based cognitive therapy, mindfulness-based stress reduction, emotion-focused therapy, and metacognitive therapy (Australian Psychological Society 2018). In the first instance, we pooled all psychological interventions together, conducted analyses of heterogeneity, and took this into consideration when adjudicating the strength of evidence. The mode of delivery was defined as individual, group, or family (including couple) therapy carried out in whole or in part by a healthcare professional. The comparison group was defined consistent with a similar

review of type 1 diabetes interventions (Winkley 2020): 'no intervention', 'usual care', 'wait-list control', 'attention-control' or 'clinical management' (CM).

With regard to differential or incremental effects of different treatment approaches, we also considered trials with a control group receiving pharmacological treatment or another psychological treatment (Comparison 2 and Comparison 4). In accordance with the previous review (Baumeister 2011c), we grouped separately studies using CM as a comparator intervention or other psychological intervention. The rationale for this was that CM, which consists of information about depression and depression treatment, provides a more concerted approach to depression management than does usual care (CREATE 2007), with CM delivered by health professionals and often for equal intensity as an intervention. By contrast, usual care commonly involves no depression treatment at all, even when incentives are provided (Jani 2013; Rollman 2009). In head-to-head comparison trials of psychological interventions or CM, we abstained from pooling across different treatments, consistent with the original review (Baumeister 2011c), owing to the heterogeneity in clinical interventions and their heterogenous comparators.

Pharmacological interventions included all antidepressant medications and other drug therapies used explicitly for treating depressive disorders (Sadock 2009). The control group was placebo. In the first instance, we pooled all pharmacological interventions and conducted analyses of heterogeneity. We included pharmacological treatments compared to other pharmacological medications, as well as add-on therapies or augmentation strategies, or by comparison to psychological interventions, to determine differential or incremental effects. In accordance with the previous review (Baumeister 2011c), we grouped separately head-to-head comparison trials of pharmacological interventions. We abstained from pooling across different studies owing to the heterogeneity in clinical interventions and their heterogenous comparators.

Types of outcome measures

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review. Where a published report did not appear to report one of these outcomes, we accessed the trial protocol and contacted the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials that measured these outcomes but did not report the data at all, or not in a useable format, were included in the review as part of the narrative.

We assessed outcomes at three follow-up periods, consistent with the previous review by Baumeister 2011c:

- short term (at the end of treatment), which was the primary time point of clinical interest for the review;
- medium term (one to six months after the end of treatment);
- long term (more than six months after the end of treatment).

Multiple observations in primary studies were allocated to separate analyses by different time frames, which reflect short-, medium-, and long-term follow-up. The rationale for subdividing outcomes by time was to assess the durability of interventions, given that evidence was sparse for longer-term outcomes in the previous review (Baumeister 2011c).

Primary outcomes

- Depression (measured either dimensionally or categorically) following the intervention, as assessed by validated self-report questionnaires or standardised interviews. Depression may be quantified categorically as 'remitted' or 'response', the latter defined as a 50% or more reduction in severity from baseline.
- All-cause mortality.
- Cardiovascular mortality.
- Non-fatal cardiac events according to standardised criteria (e.g. WHO 1992 or subsequent iterations):
  - myocardial infarction (MI);
  - angina;
  - heart failure;
  - arrhythmia;
  - stroke;
  - Coronary revascularisation for CAD: coronary artery bypass graft (CABG) and/or percutaneous coronary intervention (PCI) or angioplasty.

We analysed the primary outcomes separately and abstained from pooling a composite outcome, with two exceptions: 1) acute coronary syndromes (inclusive of ST and non-ST elevated MI, and/or unstable angina) were collapsed into MI (for one study, U-CARE 2018); and 2) coronary revascularisation for CAD was inclusive of CABG and/or PCI or angioplasty. Here we grouped coronary revascularisation for CAD under cardiac events, as opposed to healthcare utilisation, in line with common definitions of major adverse cardiac events (Bosco 2021).

Secondary outcomes

- Healthcare costs or resource utilisation, including:
  - hospitalisations;
  - emergency department visits;
  - length of stay.
- Health-related quality of life.
- Cardiovascular vital signs:
  - systolic blood pressure (BP) measured in mmHg;
  - diastolic BP measured in mmHg;
  - heart rate measured in beats per minute (bpm).
- Biomarkers of platelet activation:
  - β-thromboglobulin (βTG);
  - platelet factor 4 (PF4);
  - P-selectin;
  - platelet/endothelial cell adhesion molecule-1 (PECAM-1);
  - thromboxane B_2 (TxB_2).
- Electrocardiogram (ECG) wave recording in milliseconds:
  - PR interval;
  - QRS interval;
  - QT interval;
  - QTc interval.
- Non-cardiac adverse events (psychiatric admission, suicide, worsening depression). In pharmacological interventions side effects were also assessed.

Analysis of the secondary outcomes cardiovascular vital signs and biomarkers of platelet activation was considered in the previous review but not reported (Baumeister 2011c). We also

added important adverse effects (ECG wave recording, non-cardiac adverse events, and pharmacological side effects) to this updated review, which we define as post hoc outcomes. We analysed the secondary outcomes separately and abstained from pooling any composite outcomes apart from pharmacological side effects, which we considered as a composite of any quantified side effect by self-report scale, checklist, or adverse outcome.

Search methods for identification of studies

Electronic searches

We searched the following databases for RCTs of treatment of depressive disorders in CAD patients on 3 August 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library, Issue 8 of 12, 2020);
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 31 July 2020);
- Embase (Ovid, 1980 to 2020 Week 31);
- PsycINFO (Ovid, 1806 to July Week 4 2020);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO, 1937 to 3 August 2020);
- Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (EED) (Cochrane Library, Issue 2 of 4, 2015);
- Health Technology Assessment Database (HTA) (Cochrane Library Issue 4 of 4, 2016).

The Cochrane sensitivity-maximising RCT filter was used for MEDLINE, and for Embase, terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* were applied (Lefebvre 2011). Adaptations of these RCT filters were applied to the other databases, except CENTRAL. See Appendix 1 for details of the 2009 search strategies and Appendix 2 for the updated 2020 search strategies. No language restrictions were applied.

Searching other resources

We searched the World Heath Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/), ISRCTN registry (http://isrctn.org/), and ClinicalTrials.gov (clinicaltrials.gov) on 2 September 2021 (Appendix 2). We also examined the reference lists of all included trials to identify other potentially relevant studies. We contacted corresponding authors of the included trials to ask about other RCTs, published or unpublished, which might be relevant to the review. We handsearched the list of included and excluded studies in the Cochrane Review by Richards 2017 and the network meta-analysis by Doyle 2021.

Data collection and analysis

Selection of studies

Two review authors independently in pairs selected studies for inclusion (original review: NH, HB; update: SYA, EJLL, EB, NB). We examined a list of titles and abstracts; if title and abstract contained sufficient information to determine exclusion, the article was rejected. We retrieved the full papers of all remaining articles, which two review authors independently reviewed. In addition, any other potentially relevant articles identified by checking the reference lists or personal communications were also reviewed. We kept a record of all rejected papers and the reasons for rejection. We used this information to construct a PRISMA flow diagram (Figure 1), and reported the reasons for exclusion of excluded studies in the Characteristics of excluded studies table. Important parts of foreign language papers of included studies (i.e. not English, German, or Chinese) were translated into English. If the two review authors disagreed about the inclusion of an article, a third review author (original review: JB; update: PJT) was asked to review the article. Any disagreements were resolved by consensus discussion.

Figure 1. Summary of the 2020 literature search update and study selection.

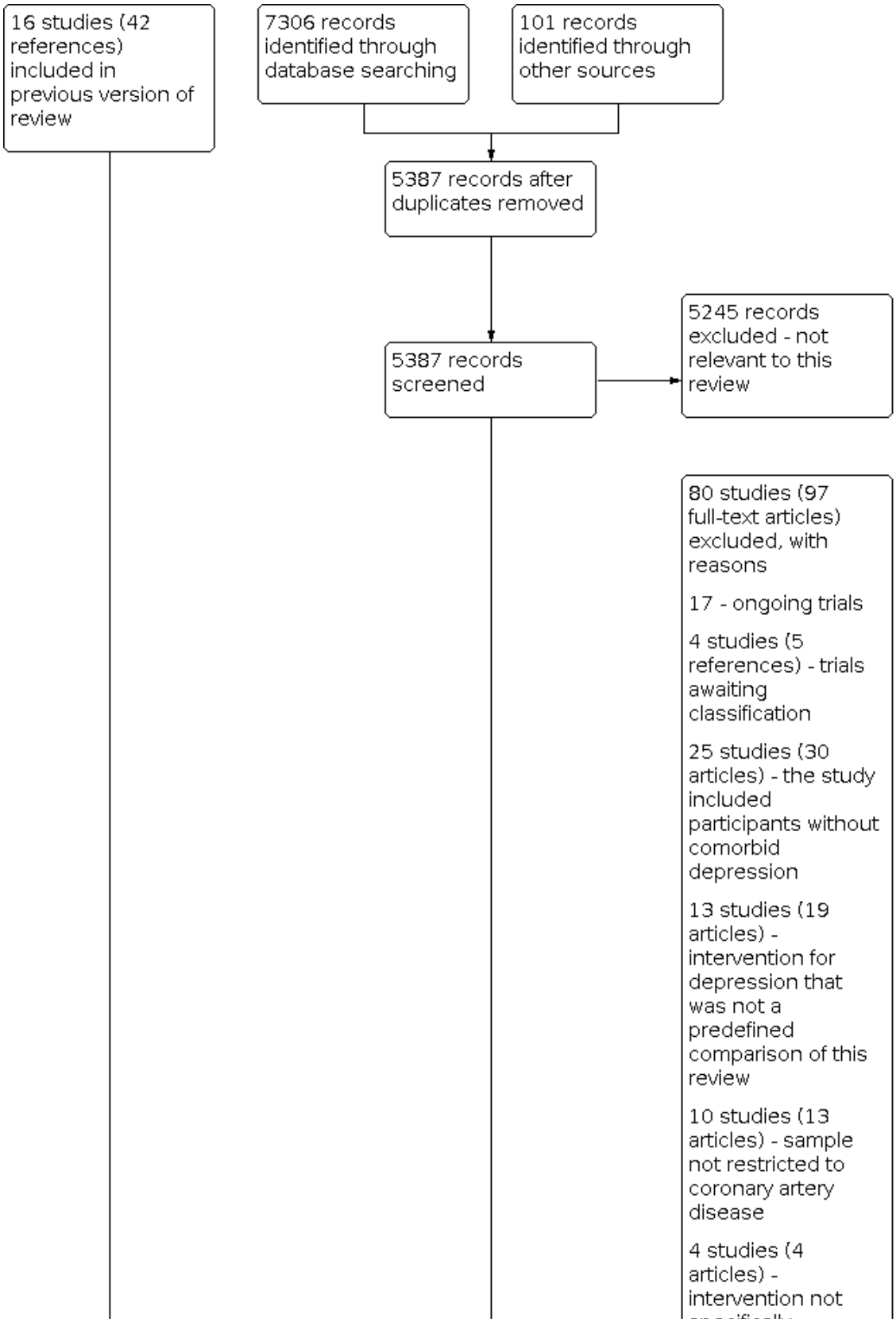
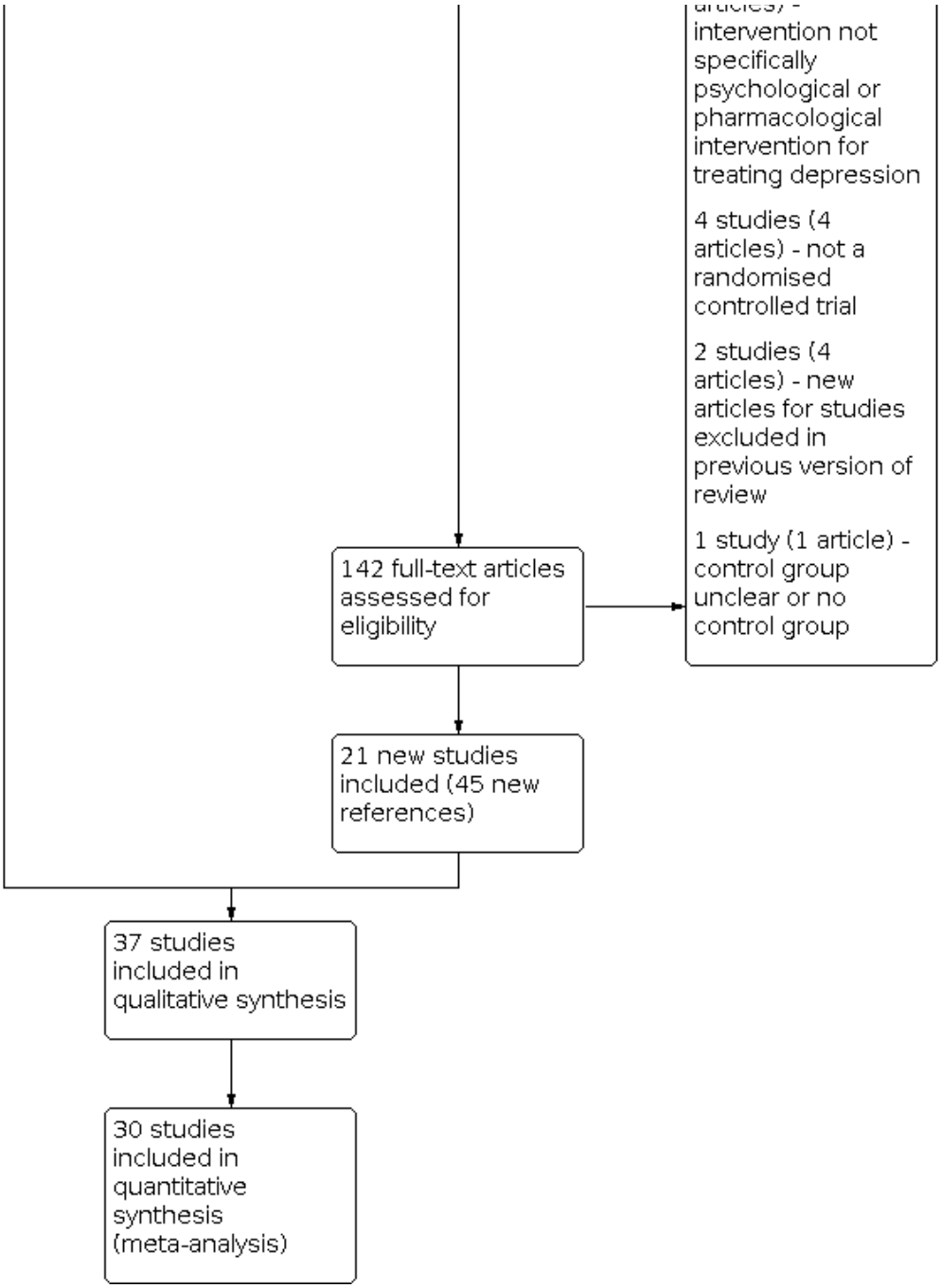


Figure 1. (Continued)



Data extraction and management

Two review authors (original review: HB, NH; update: PJT, SYA, EJLL, NB, EB) independently in pairs extracted data from the full copies of primary studies using a data extraction form. We extracted study characteristics including participants (sample size at baseline and follow-up, type of CAD, gender, age), type of depression (major depression, minor depression or dysthymic disorder), assessment method (standardised diagnostic interview, self-report questionnaire, medical record or physician's diagnosis), cut-off used to indicate depression on self-report questionnaire, type of intervention (type of psychological treatment versus type of pharmacological treatment), comparison group (usual care, other control, another psychological treatment or pharmacological treatment), length of follow-up, descriptive statistics of primary and secondary outcomes, effect sizes and confidence intervals.

Assessment of risk of bias in included studies

Two review authors (original review HB, NH; update: PJT, SYA, EJLL, EB, NB) independently in pairs assessed risk of bias in the included studies using Cochrane's tool for assessing risk of bias (Higgins 2011). We described sequence generation, allocation concealment, blinding, incomplete outcome data,

selective outcome reporting, and other sources of bias. With regard to psychological interventions, blinding of healthcare providers or participants to the treatment is not feasible. In pharmacological trials blinding is possible for participants, personnel, and outcome assessors, and was evaluated accordingly. We considered a trial as having an overall high risk of bias when four domains out of six were assessed as high or unclear for: allocation (sequence generation and concealment), blinding (participants, personnel, and outcome assessors), incomplete outcome data, and selective reporting. In the event that we identified an other source of bias at high risk, this also contributed to the overall adjudication of a trial at high risk of bias.

Measures of treatment effect

Continuous outcomes measured using different scales necessitated the standardisation of the results of the studies to a uniform scale. We computed standardised mean differences (SMD) with 95% confidence intervals (CIs) for continuous outcomes measured using different scales. As a first preference we analysed the mean scores of final assessment, followed by mean change scores from baseline to final assessment if only these scores were available. If no measures of variability were provided in the study reports, we used exact P values as well as t-statistic or Chi^2 statistic to compute an SMD.

For dichotomous variables, we computed odds ratios (OR) with 95% CI. For continuous primary and secondary outcomes assessed by the same method (i.e. Hamilton Depression Rating Scale (HAM-D), BP, heart rate, ECG parameters), we used a mean difference (non-standardised).

Several strategies have been proposed to help readers interpret results presented as SMDs (e.g. re-expressing SMDs using Cohen's rules of thumb for effect sizes (Cohen 1988), re-expressing SMDs by transformation to OR, re-expressing SMDs using a familiar instrument, reporting the ratio of the means, or expressing as minimal important difference units; see also Section 15.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). However, all of these strategies have substantial disadvantages and introduce imprecision. For example, re-expressing SMDs by means of familiar instruments does not account for between-study heterogeneity. An SMD of a specific magnitude translates into different scores (e.g. on the Beck Depression Inventory (BDI)) depending on, for example, the baseline severity of depression. Conclusions based on this strategy might thus be substantially misleading. We decided to use the rule of thumb proposed by Cohen 1988 and suggested by the *Cochrane Handbook* to re-express SMDs (Higgins 2011). Based on the assumptions of Cohen 1988, SMDs around 0.2 must be regarded as small, 0.5 as moderate, and 0.8 as large. As previously mentioned, this strategy also comprises substantial disadvantages, as a small, moderate, or large effect size depends on the specific outcome and the assessment instrument being used. Moreover, *patient* importance of a finding is context-dependent and not amenable to generic statements (Higgins 2011). When interpreting the results (Baumeister 2012b), readers should keep this limitation of the rules of thumb in mind (Cohen 1988).

Unit of analysis issues

The unit of analysis in the primary studies was the participant, which is randomised to either the treatment or control group. The number of observations thus matches the number of units that are randomised. In instances where observational units were correlated (e.g. by cluster), we planned to reduce the sample to an 'effective sample size', dividing the original sample size by the ‘design effect’ (Higgins 2021).

Dealing with missing data

We requested missing information from published RCTs from the corresponding authors or obtained it from trial data repositories. Of 18 authors contacted for missing data, five replied, and three were able to provide at least some of the requested data. No imputation methods were used due to the small amount of trials per outcome.

Assessment of heterogeneity

We tested for statistically significant heterogeneity using the Q-statistics with a 95% CI. We computed the I^2 to examine the extent of heterogeneity. Meta-analytically pooled effect estimates should be interpreted in accordance with any substantial clinical or methodological or statistical heterogeneity. We planned to specifically examine heterogeneity with the I^2 statistic quantifying inconsistency across studies to assess the impact of heterogeneity on the meta-analysis. Interpretation of heterogeneity would include the magnitude and direction of effects, the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test), and the I^2 statistic where:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2021).

A meta-regression was considered to explore potential sources of heterogeneity but was not performed owing to the small amount of trials per outcome.

Assessment of reporting biases

We did not create funnel plots to investigate reporting bias due to the limited number of trials per outcome (Higgins 2021). To examine outcome reporting bias, we analysed discrepancies in reported outcomes between published protocols and original papers. Where no protocol was available, we contacted the corresponding trial authors for published or unpublished protocols.

Data synthesis

We performed random-effects meta-analyses to compute overall estimates of treatment outcomes based on the assumption of high clinical and methodological heterogeneity between RCTs. Both SMD and OR effect sizes were pooled using the inverse-variance method, which is best suited to random-effects meta-analysis (Higgins 2011). The effect sizes of the primary studies are presented in forest plots. In the case of considerable methodological heterogeneity owing to different intervention types and their heterogenous comparators, we abstained from meta-analytical pooling of trial results (Comparison 2: psychological versus psychological/CM; Comparison 4: pharmacological versus pharmacological). Where no dichotomous events occurred in both arms of a trial, we described the finding narratively in the text and in the summary of findings tables.

In the case of multiple assessment tools used for the same outcome, we followed a hierarchical approach to decide which assessment to use in the meta-analyses. Clinician-rated assessments were given priority over patient self-report questionnaires. In the case of assessment tools on the same hierarchical level, we chose the most frequently used assessment tool across the included studies, followed by the measure with the least missing data (per-protocol), followed by random selection of one of the assessment tools.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to examine the impact of sex (men versus women), CAD subtype, time of onset of depression (pre-existing versus new-onset depression), CAD severity, and risk of bias of included studies on the results, but did not conduct them due to the sparseness of trial data. We will reconsider these subgroup analyses in future updates of the review.

Sensitivity analysis

Because pooling results across different types of psychological interventions may level out specific treatment effects and be potentially misleading (Baumeister 2011c), we conducted sensitivity analysis on depression symptoms at end of treatment to update the results of Baumeister 2011c for Comparison 1: psychological versus control and Comparison 3: pharmacological versus placebo. For Comparison 1, we performed sensitivity analysis in CBT-only trials, and similarly in Comparison 3 conducted sensitivity analysis restricted to serotonergic antidepressant interventions. Specifically, the sensitivity analysis included SSRIs and mirtazepine, which can be classed as a noradrenergic and specific serotonergic antidepressant and tetracyclic analogue (see Types of interventions) (de Boer 1995). We also performed sensitivity analyses according to depressive disorders and secondly by depression-only trials (e.g. excluding mixed depression/anxiety studies).

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence for the primary outcomes (short-term) using the GRADE approach (GRADEpro GDT), which takes into consideration risk of bias (see Assessment of risk of bias in included studies), consistency of effect, imprecision, indirectness, and publication bias (Schünemann 2019). We constructed a summary of findings table for the primary outcomes (short-term, end of treatment) for five outcomes: depression symptoms, depression remission, all-cause mortality, cardiovascular mortality, and occurrence of MI. We made comments narratively to qualitatively describe the certainty of the evidence for the five end-of-treatment outcomes per comparison.

RESULTS

Description of studies

See: PRISMA flow chart (Figure 1), Characteristics of included studies; Table 1; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The database and trial registry search resulted in 7407 references (101 from trial registries), 5387 of which were unique references. We excluded 5245 articles at the title/abstract level, and 80 studies (97 articles) after full-text review, most commonly because the study did not investigate participants without comorbid depression (25 studies, 30 articles), the intervention for depression was not a predefined comparison of this review (13 studies, 19 articles), the sample was not restricted to CAD (10 studies, 13 articles), the intervention not specifically psychological or pharmacological intervention for treating depression (4 studies, 4 articles), the study was not an RCT (4 studies, 4 articles), the control group was unclear or there was no control group (1 study, 1 reference), or new citations to studies already excluded in the previous review (2 studies, 4 references). We also identified 17 ongoing studies (17 references) and 4 trials awaiting classification (5 references). Twenty-one new studies were found to be eligible in this updated review (45 new references) and included in the narrative review or synthesis. See the study flow chart for details of the study selection process (Figure 1).

Included studies

Thirty-seven trials fulfilled the inclusion criteria of the review (Abbasi 2015; ANDROS 2015; Barth 2005; Brown 1993; Carney 2009; CREATE 2007; Dao 2011; Divsalar 2018; Doering 2007; ENRICHD 2003; EsDEPACS 2014; Fang 2003; Freedland 2009; Freeman 1986; Kennedy 2005; Li 2005; Liu 1999; Liu 2016; Ma 2019; McFarlane 2001; McLaughlin 2005; MIND-IT 2007; MoodCare 2011; Pizzi 2009; Roose 1998; SADHART 2002; Shahmansouri 2014; SPIRR-CAD 2011; Strik 2000; Tian 2016; TREATED-ACS 2020; U-CARE 2018; UPBEAT 2012; Wang 2020; WIDeCAD 2017; Yang 2019; Zarea 2014).

Fifteen trials investigated psychological interventions, which comprised CBT (Dao 2011; Doering 2007; ENRICHD 2003; MoodCare 2011; U-CARE 2018; WIDeCAD 2017), resource-orientated psychotherapy (Barth 2005), telephone counselling (McLaughlin 2005; Yang 2019), individual and group psychotherapy (SPIRR-CAD 2011), therapeutic communication sessions (Zarea 2014), and an intervention comprising health education and various psychological treatments (Fang 2003). One three-arm trial examined CBT, supportive stress management, and usual care (Freedland 2009). One trial examined eight sessions of CBT in combination with four sessions of well-being therapy versus CM (TREATED-ACS 2020). One trial examined behaviour therapy versus person-centred therapy (Brown 1993). Two psychological therapy trials delivered the CBT intervention entirely online with therapist or eCoach support (U-CARE 2018; WIDeCAD 2017); all others delivered the intervention face-to-face.

Twenty-one trials investigated the effects of pharmacological depression treatments with sertraline (ANDROS 2015; McFarlane 2001; Pizzi 2009; SADHART 2002; UPBEAT 2012), mirtazapine (MIND-IT 2007), fluoxetine (Liu 1999; Strik 2000), escitalopram (EsDEPACS 2014; Kennedy 2005), paroxetine and nortriptyline (Roose 1998), paroxetine and fluoxetine (Tian 2016), alprazolam (Freeman 1986), sertraline plus omega-3 (Carney 2009), sertraline plus red yeast rice (Divsalar 2018), St John's wort (Li 2005), simvastatin compared to atorvastatin (Abbasi 2015), Xinkeshu (Ma 2019), saffron compared to fluoxetine (Shahmansouri 2014), Shugan Jieyu compared to sertraline (Liu 2016), Bu Xin Qi compared to escitalopram (Wang 2020).

One trial had a 2 x 2 factorial design (CREATE 2007). In accordance with our inclusion criteria, we restricted analyses to the citalopram and CM versus placebo and CM arms of the trial. The IPT plus citalopram plus CM, and IPT plus placebo plus CM arms of the trial were ineligible and are not described further.

The trial size in psychological intervention studies ranged from 15 participants in Doering 2007 to 2481 participants in ENRICHD 2003. In the pharmacological intervention studies, the trial size ranged from 2 participants in ANDROS 2015 to 369 participants in SADHART 2002.

The mean age of participants ranged from 52.6 in Shahmansouri 2014 to 64.0 years in UPBEAT 2012. The percentage of female participants ranged from 10% in Brown 1993 to 56.8% in Shahmansouri 2014. One study was restricted to female participants only (Doering 2007).

Ten studies originated from the USA (Brown 1993; Carney 2009; Dao 2011; Doering 2007; ENRICHD 2003; Freedland 2009; Freeman 1986; McLaughlin 2005; Roose 1998; UPBEAT 2012), eight from China (Fang 2003; Li 2005; Liu 1999; Liu 2016; Ma 2019; Tian 2016; Wang 2020; Yang 2019), four from Iran (Abbasi 2015; Divsalar 2018; Shahmansouri 2014; Zarea 2014), three from Germany (Barth 2005; SPIRR-CAD 2011; WIDeCAD 2017), two from Canada (CREATE 2007; McFarlane 2001), two from the Netherlands (MIND-IT 2007; Strik 2000), two from Italy (Pizzi 2009; TREATED-ACS 2020), one from Australia (MoodCare 2011), one from Korea (EsDEPACS 2014), one from France (ANDROS 2015), and one from Sweden (U-CARE 2018). Two studies were performed across multiple sites in different countries, taking place in the USA, Europe, Canada, and Australia in SADHART 2002 and Denmark, Estonia, and Norway in Kennedy 2005.

Sixteen studies investigated individuals with MI or acute coronary syndromes (ANDROS 2015; ENRICHD 2003; EsDEPACS 2014; Fang 2003; Kennedy 2005; Liu 1999; Liu 2016; McFarlane 2001; McLaughlin 2005; MIND-IT 2007; MoodCare 2011; SADHART 2002; Strik 2000; Tian 2016; TREATED-ACS 2020; U-CARE 2018). Twelve trials studied diverse CAD populations comprising MI, angina pectoris, and patients undergoing cardiac procedures (Barth 2005; Brown 1993; Carney 2009; CREATE 2007; Ma 2019; Pizzi 2009; Roose 1998; SPIRR-CAD 2011; UPBEAT 2012; Wang 2020; WIDeCAD 2017; Yang 2019). Seven trials investigated patients awaiting or after CABG (Abbasi 2015; Dao 2011; Doering 2007; Freedland 2009; Freeman 1986; Li 2005; Zarea 2014), and two trials investigated patients after PCI (Divsalar 2018; Shahmansouri 2014).

We also identified 17 ongoing trials (Ahmadi 2018; Ardakani 2020; COMBAT-DS 2021; eMindYourHeart 2021; Firouzjaei 2017; Geng 2018; Hamzehpour 2020; Irfan 2020; Jazayeri 2017; Luberto 2021; Ma 2014; Mohammadian 2018; Moudi 2016; Qiaoning 2019; Sourizahi 2017; Wang 2015; Yang 2020). Three studies are awaiting classification, two of which were identified as conference abstracts in our search of the databases, without any contact information available (Ahangarezaiezadeh 2017; Cai 2012; Gu 2017).

Excluded studies

A total of 96 studies (118 articles) that appeared to be relevant to the review were excluded after careful examination of eligibility criteria (see Characteristics of excluded studies for reasons for exclusion). Sixteen studies (21 references) were excluded in the previous review reported by Baumeister 2011c, and 80 studies (97 references) were excluded from the 2020 updated literature search.

Risk of bias in included studies

Risk of bias in the included studies varied across studies (see Figure 2; Figure 3). The information available after translating parts of three trials published in Chinese was insufficient to determine risk of bias in these studies (Fang 2003; Li 2005; Liu 1999). We assessed risk of bias for the two trials that were terminated early by the investigators based on information reported in the clinical trial registries (ANDROS 2015; Kennedy 2005).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

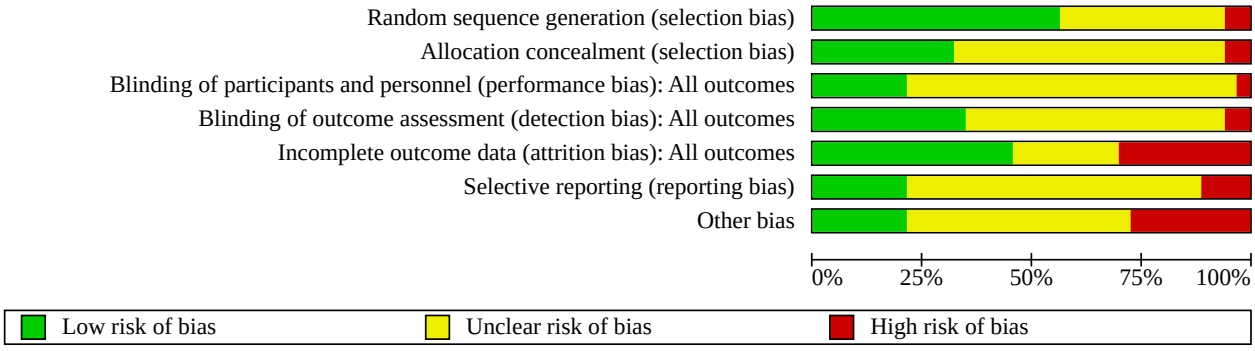


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

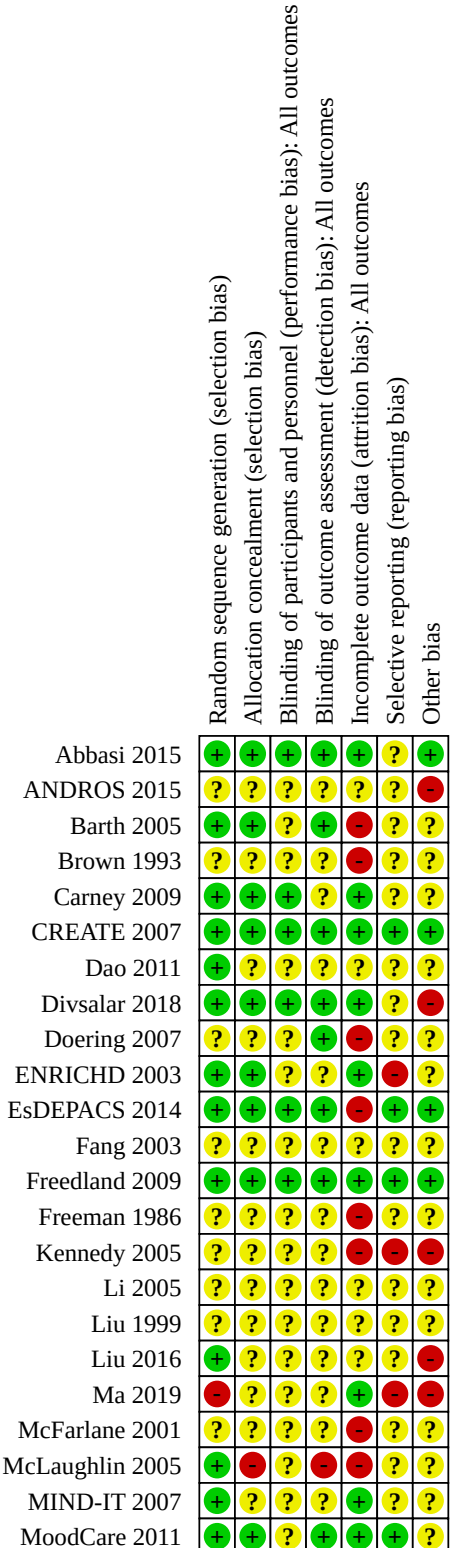
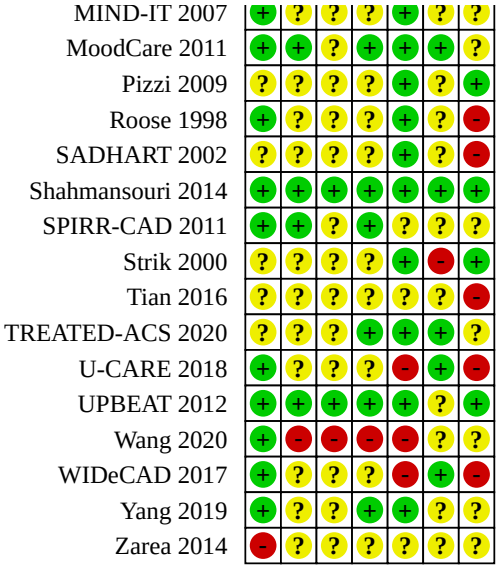


Figure 3. (Continued)



Allocation

Twelve trials used an appropriately generated and adequately concealed randomisation procedure (Abbasi 2015; Barth 2005; Carney 2009; CREATE 2007; Divsalar 2018; ENRICHD 2003; EsDEPACS 2014; Freedland 2009; MoodCare 2011; Shahmansouri 2014; SPIRR-CAD 2011; UPBEAT 2012). The generation of the randomisation sequence appeared to be appropriate in eight trials; however, they did not sufficiently describe the concealment of the allocation, Dao 2011; Liu 2016; MIND-IT 2007; Roose 1998; U-CARE 2018; WIDeCAD 2017; Yang 2019, or failed to conceal the allocation adequately (McLaughlin 2005). Two trials used an inappropriate randomisation procedure and provided insufficient information on concealment (Ma 2019; Zarea 2014). One trial described a sufficient sequence generation but was an open-label trial (Wang 2020). Details regarding sequence generation and allocation concealment were unclear for the remaining 14 trials (ANDROS 2015; Brown 1993; Doering 2007; Fang 2003; Freeman 1986; Kennedy 2005; Li 2005; Liu 1999; McFarlane 2001; Pizzi 2009; SADHART 2002; Strik 2000; Tian 2016; TREATED-ACS 2020).

Blinding

No trial of psychological interventions utilised an attention-control design, thus we judged participants in all psychological intervention trials as unblinded to treatment allocation. The outcome assessor was blinded in seven psychological intervention trials (Barth 2005; Doering 2007; Freedland 2009; MoodCare 2011; SPIRR-CAD 2011; TREATED-ACS 2020; Yang 2019). Seven trials did not report sufficient details regarding blinding to make a judgement of low or high risk (Brown 1993; Dao 2011; ENRICHD 2003; Fang 2003; U-CARE 2018; WIDeCAD 2017; Zarea 2014). We assessed one psychological trial as high risk and unblinded, as the outcome was assessed using patient self-report without sufficient information regarding blinding (McLaughlin 2005).

In six pharmacological trials blinding was adequately realised and described (Abbasi 2015; CREATE 2007; Divsalar 2018; EsDEPACS 2014; Shahmansouri 2014; UPBEAT 2012). Four pharmacological trials reported using a double-blind method but did not describe who was blinded (MIND-IT 2007; Roose 1998; SADHART 2002; Strik 2000). One trial was described as open-label trial and hence unblinded (Wang 2020). The remaining 11 trials did not report sufficient information regarding blinding of staff, participants, and outcome assessors (ANDROS 2015; Carney 2009; Freeman 1986; Kennedy 2005; Li 2005; Liu 1999; Liu 2016; Ma 2019; McFarlane 2001; Pizzi 2009; Tian 2016).

Incomplete outcome data

Fourteen trials provided intention-to-treat (ITT) analyses for primary outcomes (Carney 2009; CREATE 2007; Divsalar 2018; Freedland 2009; MIND-IT 2007; MoodCare 2011; Roose 1998; SADHART 2002; SPIRR-CAD 2011; Strik 2000; TREATED-ACS 2020; UPBEAT 2012; WIDeCAD 2017; Yang 2019). One trial reported both ITT and per-protocol analyses simultaneously (SPIRR-CAD 2011). Depression outcomes were analysed per-protocol in two trials that reported cardiovascular mortality and cardiac events as ITT (ENRICHD 2003; U-CARE 2018). Conversely, Strik 2000 reported ITT analyses for depression outcomes and per-protocol analyses for cardiac events, cardiovascular vital signs, and ECG waves. Fourteen trials reported per-protocol analyses (Abbasi 2015; Barth 2005; Brown 1993; Doering 2007; EsDEPACS 2014; Freeman 1986; Kennedy 2005; Ma 2019; McFarlane 2001; McLaughlin 2005; Pizzi 2009; Shahmansouri 2014; Tian 2016; Wang 2020). The remaining seven studies provided insufficient information to make a determination (ANDROS 2015; Dao 2011; Fang 2003; Li 2005; Liu 1999; Liu 2016; Zarea 2014).

Selective reporting

We judged eight studies as free of selective reporting based on the comparison of outcomes reported in published study protocols, methods sections, and original papers (CREATE 2007; EsDEPACS 2014; Freedland 2009; MoodCare 2011; Shahmansouri 2014; TREATED-ACS 2020; U-CARE 2018; WIDeCAD 2017). Three trials have as yet not reported the results of all the outcomes mentioned in published protocols (Carney 2009; MIND-IT 2007;

SPIRR-CAD 2011). We assessed four trials as high risk of bias due to incomplete or inadequate outcome reporting (ENRICHD 2003; Kennedy 2005; Ma 2019; Strik 2000). Furthermore, in UPBEAT 2012, we rated selective reporting as unclear risk bias, as measures of variance (standard deviation (SD) or standard error (SE)) were not reported, and P values were reported for active treatment (sertraline group, exercise group), thereby combining two separate interventions. No published or unpublished trial protocols were available other than trial registries for the remaining 21 trials (Abbasi 2015; ANDROS 2015; Barth 2005; Brown 1993; Dao 2011; Divsalar 2018; Doering 2007; Fang 2003; Freeman 1986; Li 2005; Liu 1999; Liu 2016; McFarlane 2001; McLaughlin 2005; Pizzi 2009; Roose 1998; SADHART 2002; Tian 2016; Wang 2020; Yang 2019; Zarea 2014), thus it remains unclear whether or not there is a risk of selective reporting in these trials.

Other potential sources of bias

We judged eight studies as free of other sources of bias (Abbasi 2015; CREATE 2007; EsDEPACS 2014; Freedland 2009; Pizzi 2009; Shahmansouri 2014; Strik 2000; UPBEAT 2012). The risk of other sources of bias remains unclear for the three trials translated from Chinese (Fang 2003; Li 2005; Liu 1999). Ten psychotherapy studies may exhibit performance bias because the adherence of therapists in the treatment group was unclear (Barth 2005; Brown 1993; Doering 2007; McLaughlin 2005; TREATED-ACS 2020; U-CARE 2018; WIDeCAD 2017; Yang 2019; Zarea 2014), or was undertaken differently from the protocol (MoodCare 2011). In two trials there was evidence of statistically significant differences between groups at baseline on depression (Brown 1993; MIND-IT 2007), or differences at baseline were not established (ENRICHD 2003; Wang 2020). In McFarlane 2001 (p 619 and p 620) and McLaughlin 2005 (discrepancy between text and figure of depression score on Hospital Anxiety and Depression Scale (HADS)), results were inconsistently reported. In three trials (Carney 2009; SPIRR-CAD 2011; U-CARE 2018), there was a change in the inclusion criteria.

In two trials there was evidence of high risk of bias (selection bias), with eligible participants not recruited (Divsalar 2018; WIDeCAD 2017). There was evidence of high risk of other bias in two internet CBT interventions that were terminated early by investigators with ITT results reported (U-CARE 2018; WIDeCAD 2017). Similarly, a high risk of other bias was evident in two drug trials terminated early with results not reported (ANDROS 2015), or partially reported per protocol in redacted form (Kennedy 2005). A high risk of other bias was evident in two trials that either did not register the trial (Tian 2016), or did so retrospectively after recruitment had commenced (Ma 2019). A high risk of other bias was evident in two drug trials that included pharmaceutical company employees in the trial design, conduct, analysis, and reporting of results (Roose 1998; SADHART 2002). A high risk of other bias was evident in Liu 2016, where the primary results were reported mid-treatment.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Psychological treatment compared to control for depression in patients with coronary artery disease; **Summary of findings 2** Summary of findings table - Psychological treatment 1 compared to psychological treatment 2 for depression in patients with coronary artery disease; **Summary of findings 3** Summary of findings table - Pharmacological treatment compared to placebo for depression in patients with coronary artery disease; **Summary of findings 4** Summary of findings table - Pharmacological treatment 1 compared to pharmacological treatment 2 for depression in patients with coronary artery disease

Comparison 1: Psychological intervention versus control

Thirteen trials studied the effects of a psychological intervention versus control (Barth 2005; Dao 2011; Doering 2007; ENRICHD 2003; Fang 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; U-CARE 2018; WIDeCAD 2017; Yang 2019; Zarea 2014).

1.1 Primary outcome: depression symptoms

Twelve studies investigated the effects of psychological interventions on short-term depression symptoms (i.e. the end of treatment) (Barth 2005; Dao 2011; Doering 2007; Fang 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; U-CARE 2018; WIDeCAD 2017; Yang 2019; Zarea 2014). One study did not report sufficient information to compute effect sizes (Doering 2007). Three studies reported data as change scores (Fang 2003; SPIRR-CAD 2011; Yang 2019), of which two studies reported end-of-treatment scores that could be pooled in analysis of standardised mean difference (SMD) (Fang 2003; SPIRR-CAD 2011). Meta-analysis of 10 trials showed that psychological interventions may result in a reduction in depression symptoms at the end of treatment compared to control groups (pooled SMD −0.55, 95% confidence interval (CI) −0.92 to −0.19) (n = 1226) (Analysis 1.1) (Barth 2005; Dao 2011; Fang 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; U-CARE 2018; WIDeCAD 2017; Zarea 2014). Heterogeneity was considerable (I^2 = 88%). One trial reported a significant change in the depression subscale of the HADS for patients' intensive telephone-based care (Δ −2.20, SD 2.61) compared to usual care (Δ −1.04, SD 2.89) (n = 212) (Yang 2019), which could not be pooled. Sensitivity analyses for Analysis 1.1 (Table 2) indicate minimal change to the pooled SMD and heterogeneity in analyses restricted to non-major depressive disorder trials and CBT trials. By contrast, analyses restricted to depression-only trials resulted in an attenuation of the SMD that was no longer significant.

Eight studies investigated the effects of psychological interventions on medium-term depression symptoms (i.e. one to six months after treatment) (Dao 2011; Doering 2007; ENRICHD 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; Zarea 2014). One study did not report sufficient information to compute effect sizes (Doering 2007). Meta-analysis of seven psychotherapy trials showed no benefit compared to control on medium-term depression symptoms (pooled SMD −0.20, 95% CI −0.42 to 0.01) (n = 2620) (Analysis 1.2) (Dao 2011; ENRICHD 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; Zarea 2014). Heterogeneity was substantial (I^2 = 69%).

Two trials investigated the effects of psychological interventions on long-term depression symptoms (i.e. more than six months after treatment) (Freedland 2009; U-CARE 2018). CBT was not superior to control on long-term depression symptoms (SMD −0.46, 95% CI −0.96 to 0.04) (n = 282) (Analysis 1.3). There was evidence of considerable heterogeneity (I^2 = 72%).

1.2 Primary outcome: depression remission and response

Three studies reported on depression remission in the short term (i.e. end of treatment) (n = 862) (Freedland 2009; SPIRR-CAD 2011;

Yang 2019). CBT was beneficial compared to usual care (odds ratio (OR) 5.02, 95% CI 1.95 to 12.90) in the study by Freedland 2009. An intensive telephone-based care programme was beneficial compared to usual care (OR 2.25, 95% CI 1.22 to 4.15) in the study by Yang 2019. Stepwise, fully manualised individual and group psychotherapy was not superior compared to usual care (n = 569) (SPIRR-CAD 2011). A pooled analysis suggests that psychological intervention results in little to no difference in depression remission at the end of treatment (OR 2.02, 95% CI 0.78 to 5.19) (n = 862) (Analysis 1.4). Statistical heterogeneity remained considerable between studies (I^2 = 87%).

One trial included only participants with depressive disorders and re-evaluated participants in the medium term (four months) for depression disorders, but did not report these data (Doering 2007). Only Freedland 2009 (n = 81) reported on medium- and long-term depression remission. No effect was observed in the medium term (i.e. one to six months after end of treatment) (Analysis 1.5). In the same trial, the effect was significant in the long term (i.e. more than six months after end of treatment; OR 5.06, 95% CI 1.96 to 13.08) (Analysis 1.6).

No trials reported depression response at any time point.

1.3 Primary outcome: all-cause and cardiovascular mortality

Two trials reported loss to follow-up attributable to all-cause mortality in the short term (McLaughlin 2005; Yang 2019). Few events were recorded (five deaths), and neither trial showed a significant increase or decrease in probability of mortality in the short term. Pooled analysis of the two trials was very uncertain regarding the effect of psychological interventions on all-cause mortality at end of treatment (OR 0.31, 95% CI 0.05 to 2.02; I^2 = 0%) (n = 324) (Analysis 1.7).

The SPIRR-CAD 2011 trial reported all-cause mortality in the medium term and did not find a significant increase or decrease in probability of mortality (OR 0.66, 95% CI 0.23 to 1.88) (n = 570) (Analysis 1.8).

The ENRICHD 2003 (n = 2481) and Yang 2019 (n = 189) trials reported all-cause mortality in the long term as an endpoint. No effect between psychotherapy versus usual care was observed in the two trials, and the pooled effect was not significant (OR 0.83, 95% CI 0.48 to 1.42) (n = 2670) (Analysis 1.9). There was evidence of moderate heterogeneity (I^2 = 46%).

No psychological intervention trial reported the short-term cardiovascular mortality outcome. The SPIRR-CAD 2011 trial (n = 570) reported cardiovascular mortality in the medium term and did not find a significant increase or decrease in probability of cardiovascular mortality (Analysis 1.10). Two trials reported on cardiovascular mortality in the long term (ENRICHD 2003; U-CARE 2018). No effect between CBT versus usual control was observed (OR 0.83, 95% CI 0.62 to 1.10) (n = 2720) (Analysis 1.11). There was no evidence of heterogeneity (I^2 = 0%).

1.4 Primary outcome: cardiac events

No psychological intervention trial reported MI as an outcome in the short or medium term. Two trials (n = 2720) reported on MI (ENRICHD 2003; U-CARE 2018). In U-CARE 2018, the endpoint was inclusive of acute coronary syndromes (ST and non-ST elevated MI, and unstable angina). No effect between CBT and control was observed on MI outcome in the long term (OR 1.09, 95% CI 0.73 to 1.65) (n = 2720) (Analysis 1.12). There was no evidence of heterogeneity (I^2 = 27%). Only U-CARE 2018 reported the primary outcomes of heart failure and stroke in the long term (n = 239). U-CARE 2018 did not report a significant increase or decrease in probability of heart failure (OR 3.82, 95% CI 0.78 to 18.77) (Analysis 1.13) or stroke (OR 2.10, 95% CI 0.19 to 23.52) (Analysis 1.14) in the long term (n = 239), though the number of events were sparse. Two trials reported coronary revascularisation procedure as an outcome in the long term (OR 0.91, 95% CI 0.75 to 1.11) (n = 2780) (Analysis 1.15) without heterogeneity (I^2 = 0%) (ENRICHD 2003; U-CARE 2018). No psychological intervention trial reported angina or arrhythmia as an outcome in the short, medium, or longer term.

1.5 Secondary outcome: healthcare and resource utilisation

One trial reported data on the effect of a brief CBT intervention compared to usual care on hospital length of stay after a CABG procedure (mean difference (MD) −1.30, 95% CI −2.53 to −0.07) (n = 97) (Analysis 1.17) (Dao 2011). One trial reported data on the effect of a CBT intervention compared to usual care on hospitalisation for cardiovascular causes (OR 0.92, 95% CI 0.78 to 1.09) (n = 2481) (Analysis 1.16) (ENRICHD 2003).

1.6 Secondary outcome: quality of life

Three studies investigated the effects of psychological interventions on short-term quality of life (QoL) (Freedland 2009; MoodCare 2011; WIDeCAD 2017). The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the Medical Outcomes Study Short-Form 12/36-item Health Survey (SF-12 and SF-36) were used in MoodCare 2011 and Freedland 2009, respectively. The WIDeCAD 2017 trial utilised the Assessment of Quality of Life scale (AQoL-8D) at end of treatment, where higher scores indicate lower QoL, therefore these data were not pooled with data from the trials utilising the SF-12 and SF-36 (Freedland 2009; MoodCare 2011).

There was no beneficial effect of CBT versus usual care on PCS score (SMD 0.22, 95% CI −0.06 to 0.50) (n = 202) (I^2 = 0%). (Analysis 1.18). There was an effect favouring CBT versus usual care on MCS in Freedland 2009. No effect on MCS was reported in MoodCare 2011. The pooled effect of the two trials indicated a moderate effect on MCS favouring CBT versus usual care (SMD 0.51, 95% CI 0.07 to 0.94) (n = 202), with substantial heterogeneity (I^2 = 57%) (Analysis 1.19). There was no difference between internet CBT (M = 63.87 ± 16.43) and wait-list control (M = 63.78 ± 14.42; Cohen's *d* = 0.00) on total AQoL-8D scores at end of treatment in the WIDeCAD 2017 trial (n = 34).

Three studies investigated the effects of psychological interventions on medium-term QoL, using the PCS and MCS scores of the SF-12/36 (Freedland 2009; MoodCare 2011), and the overall score of the SF-12 (Dao 2011). The pooled effect of two trials indicated no effect on PCS for psychotherapy (both CBT) versus usual care (SMD 0.18, 95% CI −1.29 to 1.65) (n = 202), without evidence of heterogeneity (I^2 = 25%) (Analysis 1.20) (Freedland 2009; MoodCare 2011). The pooled effect of two trials indicated no effect on MCS for psychotherapy (both CBT) versus usual care (SMD 1.21, 95% CI −1.09 to 3.52) (n = 202), with evidence of moderate heterogeneity (I^2 = 41%) (Analysis 1.21) (Freedland 2009; MoodCare 2011). In the trial by Dao 2011, no effect for brief CBT versus usual care was found for the SF-12 overall score (MD −4.00, 95% CI −8.48

to 0.48) (n = 96) (Analysis 1.22). One trial investigated the effects of psychological interventions on long-term QoL using the PCS and MCS scores of the SF-36 quantified at nine months (n = 81) (Freedland 2009). No effect was observed on the PCS score in the long term (MD 0.70, 95% CI −3.60 to 5.00) (Analysis 1.23). An effect was reported for the MCS score of the SF-36 QoL measure (MD 6.70, 95% CI 1.29 to 12.11) (n = 81) (Analysis 1.24). One further study did not report sufficient information to compute effects sizes regarding QoL (ENRICHD 2003).

1.7 Secondary outcome: cardiovascular vital signs, biomarkers of platelet activation, ECG wave recording

No trial comparing psychological interventions with control reported cardiovascular vital signs, biomarkers of platelet activation, or ECG wave recording at any follow-up time point.

1.8 Post hoc outcome: non-cardiac adverse events

One trial comparing CBT with wait-list control reported a non-cardiac adverse event (suicide intent) during the eight-week intervention and did not attribute this to the intervention (WIDeCAD 2017). One trial reported insufficient information on newly diagnosed severe mental illness (e.g. severe depression, suicide attempt, and psychosis) (SPIRR-CAD 2011). Otherwise, data were sparse for non-cardiac adverse effects of psychological interventions for depression in individuals with CAD.

Comparison 2: Psychological intervention versus psychological intervention

In three trials with a total of 219 participants the effects of a specific psychological intervention were compared with the effects of another psychological intervention or clinical management (Brown 1993; Freedland 2009; TREATED-ACS 2020). Brown 1993 compared 12 weekly sessions of behaviour therapy for patients and their partners by Lewinsohn versus 12 weekly sessions of person-centred therapy by Rogers. Freedland 2009 compared 12 weekly sessions of CBT versus 12 weekly sessions of supportive stress management. TREATED-ACS 2020 compared an intervention comprising eight sessions of CBT and four sessions of well-being therapy versus CM. We could not report pooled estimates for this comparison due to the heterogeneous interventions and different comparators examined in the trials (see Types of interventions). Data are therefore reported as mean differences and described qualitatively in text.

2.1 Primary outcome: depression score

Three studies investigated the effects of psychological intervention compared to another psychological intervention on short-term depression symptoms (i.e. end of treatment) (Brown 1993; Freedland 2009; TREATED-ACS 2020). The evidence is very uncertain regarding the effect on end-of-treatment depression symptoms for behaviour therapy compared to person-centred therapy on the BDI (n = 40) (Brown 1993); CBT compared to supportive stress management on the HAM-D (n = 83) (Freedland 2009); and the combination of CBT and well-being therapy compared to CM on symptoms measured by the Clinical Interview for Depression (CID) (n = 100) (Analysis 2.1) (TREATED-ACS 2020).

Three studies investigated the effects of psychological intervention compared to another psychological intervention or CM on medium-term depression symptoms (i.e. one to six months after treatment) (Brown 1993; Freedland 2009; TREATED-ACS 2020). No effect was observed for CBT compared to supportive stress management on symptoms measured by the HAM-D depression score (n = 83) (Freedland 2009). Behaviour therapy showed a beneficial effect compared to person-centred therapy on symptoms measured by the BDI (SMD −0.65, 95% CI −1.28 to −0.01) (n = 40) (Brown 1993). No effect was observed for the combination of CBT and well-being therapy compared to CM on symptoms measured by the CID (n = 100) (Analysis 2.2) (TREATED-ACS 2020).

Three studies investigated the effects of psychological intervention compared to another psychological intervention or CM on long-term depression symptoms (i.e. more than six months after treatment) (Brown 1993; Freedland 2009; TREATED-ACS 2020). No effect was observed for CBT compared to supportive stress management on symptoms measured by the HAM-D (n = 83) (Freedland 2009). Behaviour therapy resulted in a large effect compared to person-centred therapy on symptoms measured by the BDI (SMD −0.69, 95% CI −1.33 to −0.05) (n = 40) (Brown 1993). No effect was observed for the combination of CBT and well-being therapy compared to CM on symptoms measured by the CID (n = 100) (Analysis 2.3) (TREATED-ACS 2020).

2.2 Primary outcome: depression remission and response

One trial investigated the effects of psychological intervention compared to another psychological intervention on short-term depression remission (i.e. end of treatment) (Freedland 2009). No effect was observed for CBT compared to supportive stress management on the HAM-D (n = 83) (Analysis 2.4) (Freedland 2009). No effect was observed for CBT compared to supportive stress management on HAM-D depression remission in one study (n = 83) in the medium term (i.e. one to six months after end of treatment) (Analysis 2.5) and the long term (i.e. more than six months after end of treatment) (Analysis 2.6) (Freedland 2009). One trial reported depression relapse, but as remission and response rate was unclear data were not extracted (TREATED-ACS 2020).

2.3 Primary outcome: all-cause and cardiovascular mortality

No trials reported all-cause mortality at any length of follow-up for this comparison. One trial comparing the combination of CBT and well-being therapy versus CM reported cardiac death as a cause of attrition or dropout from the study from 18 to 30 months (TREATED-ACS 2020), though events were sparse (Analysis 2.7) (n = 100).

2.4 Primary outcome: cardiac events

One trial reported composite cardiac events to 30 months of follow-up but did not differentiate cardiac events, therefore data could not be analysed (n = 100) (TREATED-ACS 2020).

2.5 Secondary outcome: healthcare and resource utilisation

No trials reported healthcare and resource utilisation at any length of follow-up for this comparison.

2.6 Secondary outcome: quality of life

Only Freedland 2009 (n = 83) reported QoL using mean final scores of the SF-36 subscales PCS and MCS. No effects were observed for CBT compared to supportive stress management in the short term (i.e. end of treatment) for the PCS (Analysis 2.8) (n = 83) and MCS (Analysis 2.9) (n = 83). No effects were observed for CBT compared to supportive stress management in the medium term (i.e. one to six months after end of treatment) for the PCS (Analysis 2.10) (n = 83)

and MCS (Analysis 2.11) (n = 83). Likewise, no effects were reported for the PCS (Analysis 2.12) and MCS (Analysis 2.13) in the long term (i.e. more than six months after end of treatment) (n = 83).

2.7 Secondary outcome: cardiovascular vital signs, biomarkers of platelet activation, ECG wave recording

One trial quantified biomarkers of platelet activation (i.e. platelet count, D-dimer level) at three months but did not report sufficient information to compute effect sizes (TREATED-ACS 2020).

2.8 Post hoc outcome: non-cardiac adverse events

Non-cardiac adverse events were inconsistently and sparsely reported for this comparison. In Freedland 2009, one participant in the supportive stress management group dropped out due to psychiatric complications.

Comparison 3: Pharmacological intervention versus placebo

Thirteen trials studied the effects of a pharmacological intervention versus placebo (ANDROS 2015; CREATE 2007; EsDEPACS 2014; Freeman 1986; Li 2005; Liu 1999; Ma 2019; McFarlane 2001; MIND-IT 2007; Pizzi 2009; SADHART 2002; Strik 2000; UPBEAT 2012). Minimal information could be extracted from the trial registry of the two trials that were terminated early (ANDROS 2015; Kennedy 2005). Data from CREATE 2007 were restricted to the citalopram and CM versus placebo and CM arms of this trial, thereby excluding data from the arms randomised to psychotherapy (IPT).

3.1 Primary outcome: depression score

Twelve studies investigated the effects of pharmacological interventions on short-term depression symptoms (i.e. end of treatment) (CREATE 2007; EsDEPACS 2014; Freeman 1986; Li 2005; Liu 1999; Ma 2019; McFarlane 2001; MIND-IT 2007; Pizzi 2009; SADHART 2002; Strik 2000; UPBEAT 2012). Two trials did not report sufficient information to compute effects sizes (Freeman 1986; MIND-IT 2007). A pooled analysis of eight trials indicated that pharmacological intervention may result in a large reduction in depression symptoms at the end of treatment versus placebo (SMD −0.83, 95% CI −1.33 to −0.32) (n = 750) (Analysis 3.1) (CREATE 2007; EsDEPACS 2014; Li 2005; Liu 1999; Ma 2019; McFarlane 2001; Pizzi 2009; UPBEAT 2012). There was evidence of considerable heterogeneity between studies (I^2 = 90%). Sensitivity analyses for Analysis 3.1 (Table 3) indicated that heterogeneity remained. The pooled SMD was attenuated and no longer significant in three trials undertaken in participants with depressive disorders. There was no attenuation of the pooled SMD in analyses restricted to seven trials undertaken in depression-only samples (i.e. excluding mixed depression/anxiety). The pooled SMD was modestly attenuated in analyses restricted to six serotonergic antidepressant trials.

Two studies reported depression change scores that could not be pooled in the main meta-analysis of end-of-treatment SMDs (SADHART 2002; Strik 2000), and one trial reported both end-of-treatment scores and change scores (UPBEAT 2012). A pooled analysis of change scores suggested a small change in depression symptoms (SMD −0.18, 95% CI −0.36 to −0.00) compared to placebo (Analysis 3.2) (n = 482). Heterogeneity was low (I^2 = 0%). No trials reported depression symptoms in the medium or long term.

3.2 Primary outcome: depression remission and response

Four studies investigated the effects of pharmacological interventions on short-term depression remission (i.e. end of treatment) (CREATE 2007; EsDEPACS 2014; MIND-IT 2007; Strik 2000). One study reported insufficient information on "depressive reductive rate" which was unclear and not extracted (Li 2005). Citalopram showed a beneficial effect compared to placebo in two studies (CREATE 2007; EsDEPACS 2014). Mirtazapine, MIND-IT 2007 (n = 91), and fluoxetine, Strik 2000 (n = 54), did not show a beneficial effect compared to placebo. Pooled meta-analysis of four studies indicated that pharmacological intervention probably results in a moderate to large increase in depression remission at the end of treatment versus placebo (OR 2.06, 95% CI 1.47 to 2.89; I^2 = 0%) (Analysis 3.3) (n = 646) (CREATE 2007; EsDEPACS 2014; MIND-IT 2007; Strik 2000).

Five trials investigated the effects of pharmacological intervention on depression response, defined as a 50% reduction in depression scores, in the short term (i.e. end of treatment) (CREATE 2007; EsDEPACS 2014; Liu 1999; Pizzi 2009; SADHART 2002). No significant effect was found in one trial (CREATE 2007). An effect favouring pharmacological intervention for depression response versus placebo was found in the other four trials (EsDEPACS 2014; Liu 1999; Pizzi 2009; SADHART 2002). The pooled effect from five trials indicated an effect favouring pharmacological intervention treatment versus placebo (OR 2.73, 95% CI 1.65 to 4.54) (n = 891) with considerable heterogeneity (I^2 = 62%) (Analysis 3.4). No trials reported depression remission or depression response in the medium or long term for this comparison.

3.3 Primary outcome: all-cause and cardiovascular mortality

Five studies reported all-cause mortality (EsDEPACS 2014; Liu 1999; McFarlane 2001; MIND-IT 2007; SADHART 2002). No deaths occurred in two studies in the short term (MIND-IT 2007 (n = 91); (McFarlane 2001) (n = 27)), and in two trials no effect was observed (Liu 1999; SADHART 2002). Data from one trial after translation remained unclear and could not be extracted (Li 2005). The evidence is very uncertain regarding the effect of pharmacological intervention on all-cause mortality at end of treatment in two trials (OR 0.38, 95% CI 0.10 to 1.47; I^2 = 0%) (n = 437) (Analysis 3.5). Medium-term all-cause mortality data was not reported. Two studies reported long-term all-cause mortality (EsDEPACS 2014 (n = 300); SADHART 2002 (n = 361)), neither of which showed a survival benefit from pharmacological intervention versus placebo. The pooled effect was not significant (OR 0.89, 95% CI 0.64 to 1.25) (n = 661) (Analysis 3.6) and without heterogeneity (I^2 = 0%). One trial reported long-term cardiovascular mortality and did not find a survival benefit from escitalopram versus placebo (Analysis 3.7) (n = 300) (EsDEPACS 2014).

3.4 Primary outcome: cardiac events

Four studies analysed cardiac events (CREATE 2007; EsDEPACS 2014; Liu 1999; SADHART 2002). One trial reported specific cardiac events occurring by the end of treatment in groups randomised to mirtazapine or placebo (MIND-IT 2007). Serious adverse events were described in the terminated trial (Kennedy 2005). Insufficient information was provided in one trial to adjudicate whether cardiac events were assessed or had occurred (Ma 2019). Three studies reported the occurrence of MI in the short term (CREATE 2007; EsDEPACS 2014; SADHART 2002). The evidence is very uncertain

regarding the effects of pharmacological intervention on MI at end of treatment from tree trials (OR 0.74, 95% CI 0.26 to 2.09; I^2 = 0%) (n = 728) (Analysis 3.8). Longer-term MI was not significantly decreased in one trial comparing escitalopram versus placebo (Analysis 3.9) (n = 300) (EsDEPACS 2014).

There was little to no difference in angina at the end of treatment in trials of sertraline (SADHART 2002) (n = 369), mirtazapine (MIND-IT 2007) (n = 91), citalopram (CREATE 2007) (n = 142), and escitalopram (EsDEPACS 2014) (n = 217). Meta-analysis of four studies indicated little to no difference with pharmacological intervention versus placebo in angina pectoris (OR 0.75, 95% CI 0.44 to 1.28; I^2 = 0%) (Analysis 3.10) (n = 819) (CREATE 2007; EsDEPACS 2014; MIND-IT 2007; SADHART 2002). Angina was not reported in the medium to long term for this comparison.

There was little to no difference in heart failure in trials of sertraline (SADHART 2002) (n = 369), mirtazapine (MIND-IT 2007) (n = 91), and citalopram (CREATE 2007) (n = 142), though the number of events was sparse. Meta-analysis of three studies indicated little to no difference with pharmacological intervention versus placebo in heart failure in the short term (OR 0.93, 95% CI 0.33 to 2.62; I^2 = 0%) (Analysis 3.11) (n = 602) (CREATE 2007; MIND-IT 2007; SADHART 2002).

Arrhythmias were decreased in one trial of fluoxetine compared to placebo at the end of treatment (Liu 1999). Atrial fibrillation was reported as a serious adverse event in the terminated trial (Kennedy 2005). The pooled estimate from two trials showed little to no difference in arrhythmia at end of treatment (OR 0.46, 95% CI 0.01 to 17.06) (Analysis 3.12) (n = 87). The number of events was sparse, and there was considerable heterogeneity between studies (I^2 = 71%). Changes to ECG waves, Kennedy 2005; Strik 2000, and heart rate variability, McFarlane 2001, were reported but could not be extracted due to uncertainty in the assessment of arrhythmia endpoints. Ventricular function assessment and endpoints were unclear after translation of one trial, and data could not be extracted (Li 2005).

There was little to no difference in stroke in one trial comparing sertraline to placebo, SADHART 2002 (n = 369), and one trial comparing escitalopram to placebo, EsDEPACS 2014 (n = 217). One trial of citalopram compared to placebo reported no stroke events in either group (n = 142) (CREATE 2007). The pooled probability estimate of stroke at the end of treatment from the two trials with events indicated little to no difference in stroke (OR 0.99, 95% CI 0.20 to 4.96) (Analysis 3.13) (n = 586). The number of events was sparse, and there was no heterogeneity between studies (I^2 = 0%). There was little to no difference in percutaneous coronary intervention procedures in the long term in one trial of escitalopram versus placebo (Analysis 3.14) (n = 300) (EsDEPACS 2014). Evidence of coronary revascularisation interventions for CAD was sparse and not reported in the short and medium term.

3.5 Secondary outcome: healthcare and resource utilisation

There was little to no difference in healthcare costs at the end of treatment, excluding antidepressant medication with sertraline, in SADHART 2002 (Analysis 3.15) (n = 369). Meta-analysis of three studies (n = 514) indicated that pharmacological interventions may reduce hospitalisations compared to placebo (OR 0.58, 95% CI 0.39 to 0.85) (Analysis 3.16) without evidence of heterogeneity (I^2 = 0%) (MIND-IT 2007; SADHART 2002; Strik 2000). Any possible effect on hospitalisation was largely attributed to a trial of sertraline (OR 0.59, 95% CI 0.38 to 0.91) (n = 369) (SADHART 2002), whereas no effect was observed in the trials of mirtazapine, MIND-IT 2007 (n = 91), and fluoxetine, Strik 2000 (n = 54). Emergency room visits at the end of treatment were not reduced in a trial of sertraline (OR 0.58, 95% CI 0.34 to 1.00) (Analysis 3.17) (n = 369) (SADHART 2002).

3.6 Secondary outcome: quality of life

Two trials examined quality of life (EsDEPACS 2014; SADHART 2002). The SADHART 2002 trial (n = 369) investigated quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the SF-36 comparing sertraline with placebo. Data for the SF-36 were not reported sufficiently to compute effects sizes. No effect was observed for the Q-LES-Q (Analysis 3.18). EsDEPACS 2014 (n = 213) examined short- and medium-term QoL using the WHOQOL-BREF questionnaire. Escitalopram compared to placebo (n = 213) showed possible short-term end-of-treatment effects on the following WHOQOL-BREF subscales: physical (MD 6.80, 95% CI 2.77 to 10.83) (Analysis 3.19), psychological (MD 5.60, 95% CI 1.54 to 9.66) (Analysis 3.20), social relationship (MD 4.00, 95% CI 0.03 to 7.97) (Analysis 3.21), and environmental (MD 6.50, 95% CI 2.90 to 10.10) (Analysis 3.22) (EsDEPACS 2014). End-of-treatment effects on social and occupational functioning, as well as disability, were reported for a subset of participants in EsDEPACS 2014 (n = 217), but were not extracted here.

Escitalopram compared to placebo showed possible medium-term treatment effects on the WHOQOL-BREF subscales physical (MD 6.10, 95% CI 1.25 to 10.95) (Analysis 3.23), social relationship (MD 4.80, 95% CI 0.17 to 9.43) (Analysis 3.25), and environmental (MD 5.80, 95% CI 1.54 to 10.06) (Analysis 3.26), but not on the psychological subscale (MD 4.70, 95% CI −0.33 to 9.73) (n = 213) (Analysis 3.24) (EsDEPACS 2014).

3.7 Secondary outcome: cardiovascular vital signs, biomarkers of platelet activation, ECG wave recording

Three trials reported all BP and heart rate cardiovascular vital signs post-treatment (CREATE 2007; EsDEPACS 2014; SADHART 2002), and a fourth trial reported heart rate and not BP (McFarlane 2001). Pooled analysis from three trials indicated that pharmacological intervention may result in little to no difference in end-of-treatment systolic BP versus placebo (MD −0.24, 95% CI −3.52 to 3.05) (Analysis 3.27) in three trials (n = 675) without substantial heterogeneity (I^2 = 32%). Likewise, pharmacological intervention may result in little to no difference in end-of-treatment diastolic BP (MD 0.60, 95% CI −1.55 to 2.74) (Analysis 3.28) in three trials (n = 675). There was evidence of moderate heterogeneity between studies (I^2 = 43%). Pharmacological intervention may result in little to no difference in end-of-treatment heart rate (MD −0.80, 95% CI −2.40 to 0.79) (Analysis 3.29) in four trials (n = 662). There was no evidence of heterogeneity between studies (I^2 = 0%).

Seven studies reported platelet biomarkers post-treatment (CREATE 2007; EsDEPACS 2014; Ma 2019; MIND-IT 2007; Pizzi 2009; SADHART 2002; UPBEAT 2012), generally from a smaller subset of participants from each trial arm. Two studies reported insufficient data to calculate effect sizes (EsDEPACS 2014; UPBEAT 2012), and additional data for PF4 could be extracted from an online trial data repository (UPBEAT 2012). Two studies reported platelet biomarkers outside of the outcomes of this review (Ma 2019; Pizzi 2009), which may be considered in a future update. Meta-analysis

of three trials showed that pharmacological treatment may reduce βTG at end of treatment (SMD −0.54, 95% CI −0.99 to −0.09) versus placebo (n = 141) (Analysis 3.30). There was evidence of possible heterogeneity (I^2 = 36%).

Meta-analysis of three trials showed that pharmacological treatment may result in little to no difference in reduction in PF4 (SMD −0.14, 95% CI −0.48 to 0.19) versus placebo (n = 144) (Analysis 3.31). There was no evidence of heterogeneity between studies (I^2 = 0%). Meta-analysis of two trials showed that pharmacological treatment may result in little to no difference in P-selectin (SMD −0.31, 95% CI −1.12 to 0.50) versus placebo (n = 121) (Analysis 3.32). There was evidence of considerable between-study effect sizes (I^2 = 79%). Only SADHART 2002 reported PECAM-1 and TxB_2 in a subset of trial participants. SADHART 2002 did not find an effect of pharmacological treatment versus placebo on PECAM-1 (MD −8.30, 95% CI −18.12 to 1.52) (n = 64) (Analysis 3.33). No effect was observed in SADHART 2002 of pharmacological treatment versus placebo in TxB_2 (MD −6.20, 95% CI −15.78 to 3.38) (n = 64) (Analysis 3.34).

Six studies performed end-of-treatment ECGs and reported wave parameters comparing pharmacological intervention versus placebo at end of treatment (CREATE 2007; EsDEPACS 2014; MIND-IT 2007; SADHART 2002; Strik 2000; UPBEAT 2012). Three studies reported insufficient data to calculate effect sizes (MIND-IT 2007; Strik 2000; UPBEAT 2012). A reduction in PR interval was found in the SADHART 2002 trial of sertraline when compared to placebo (MD −6.00, 95% CI −11.84 to −0.16). The pooled effect for PR interval from three studies indicated that pharmacological intervention may result in a small reduction in PR interval (MD −4.35, 95% CI −8.40 to −0.31) (Analysis 3.35) (n = 635) without evidence of heterogeneity (I^2 = 0%) (CREATE 2007; EsDEPACS 2014; SADHART 2002). The pooled effect of ECG findings also suggested that pharmacological intervention may result in little to no difference in the QRS interval at the end of treatment (MD 2.37, 95% CI −0.41 to 5.15) (Analysis 3.36) (n = 635) without evidence of heterogeneity (I^2 = 0%). Only CREATE 2007 (n = 142) reported the QT interval, finding no evidence of a difference between citalopram and placebo (MD 2.40, 95% CI −9.11 to 13.91). Pooled meta-analysis from three trials indicated that pharmacological intervention probably results in little to no difference in QTc interval at the end of treatment (MD 2.76, 95% CI −1.96 to 7.47) (Analysis 3.38) (n = 635) without evidence of heterogeneity between studies (I^2 = 20%).

3.8 Post hoc outcome: non-cardiac adverse events and pharmacological side effects

One trial reported worsening depression in one participant receiving placebo and CM (CREATE 2007). Otherwise, non-cardiac adverse events were sparsely reported. Ten studies reported pharmacological side effects (CREATE 2007; EsDEPACS 2014; Kennedy 2005; Li 2005; Ma 2019; MIND-IT 2007; Pizzi 2009; SADHART 2002; Strik 2000; UPBEAT 2012). Two studies reported insufficient data to calculate effect sizes (Li 2005; Ma 2019). Pharmacological intervention may be associated with an increase in side effects (OR 1.44, 95% CI 1.07 to 1.92) versus placebo (Analysis 3.39) in eight trials (n = 1193) (CREATE 2007; EsDEPACS 2014; Kennedy 2005; MIND-IT 2007; Pizzi 2009; SADHART 2002; Strik 2000; UPBEAT 2012), without evidence of heterogeneity (I^2 = 0%).

Comparison 4: Pharmacological intervention versus pharmacological intervention

4.1 Primary outcome: depression symptoms

Eight trials compared two active pharmacological interventions against each other (Abbasi 2015; Carney 2009; Divsalar 2018; Liu 2016; Roose 1998; Shahmansouri 2014; Tian 2016; Wang 2020). We did not report pooled estimates for this comparison due to the heterogeneous interventions and comparators examined in the trials. The trials made the following comparisons:

- Abbasi 2015 (n = 46) simvastatin versus atorvastatin (each 20 mg/d);
- Carney 2009 (n = 122) the add-on effect of sertraline (50 mg/d) plus omega-3 (2 g/d) versus sertraline (50 mg/d) and placebo;
- Divsalar 2018 (n = 56) sertraline (200 mg/d) plus red yeast rice (2400 mg/d) versus sertraline (200 mg/d) plus placebo;
- Liu 2016 (n = 146) Shugan Jieyu plus sertraline placebo versus sertraline plus Shugan Jieyu placebo;
- Roose 1998 (n = 81) paroxetine versus nortriptyline;
- Shahmansouri 2014 (n = 40) saffron (15 to 30 mg/d) versus fluoxetine (20 to 40 mg/d);
- Tian 2016 (n = 46) paroxetine versus fluoxetine (each 20 mg/d); and
- Wang 2020 (n = 228) escitalopram (5 to 10 mg/d) versus Bu Xin Qi concoction (400 mL twice a day).

Eight studies examined the differential effects of two pharmacological interventions on short-term depression symptoms, all using the HAM-D clinician rating scale (Abbasi 2015; Carney 2009; Divsalar 2018; Liu 2016; Roose 1998; Shahmansouri 2014; Tian 2016; Wang 2020). The evidence is very uncertain as to whether different pharmacological interventions may result in a reduction in depression symptoms at end of treatment (Analysis 4.1) for: simvastatin versus atorvastatin (SMD −0.66, 95% CI −1.25 to −0.06) (n = 46) (Abbasi 2015); paroxetine versus fluoxetine (SMD −1.05, 95% CI −1.67 to −0.43) (n = 46) (Tian 2016); and escitalopram versus Bu Xin Qi (SMD −1.02, 95% CI −1.30 to −0.74) (n = 228) (Wang 2020). The evidence is very uncertain as to whether the add-on effect of sertraline (50 mg/d) plus omega-3 (2 g/d) versus sertraline (50 mg/d) and placebo may result in a reduction in depression symptoms at end of treatment (n = 122) (Carney 2009).

Four trials reported end-of-treatment depression change scores (Divsalar 2018; Liu 2016; Roose 1998; Shahmansouri 2014). In the study by Liu 2016, we assumed the data were reported as standard errors and not standard deviation as stated in the article to remain consistent with the P values reported. The evidence is very uncertain regarding the effects of different pharmacological strategies on end-of-treatment depression change scores in the four trials (Analysis 4.2) (Divsalar 2018 (n = 50), Liu 2016 (n = 149), Roose 1998 (n = 81), and Shahmansouri 2014 (n = 40)). No trials for this comparison reported medium- or longer-term durability of interventions on depression symptoms.

4.2 Primary outcome: depression remission and response

Three studies examined the differential effects of two pharmacological interventions on depression remission (Carney 2009; Roose 1998; Shahmansouri 2014). In all three trials no differences were observed between groups using the clinician-rated HAM-D, Carney 2009; Shahmansouri 2014, or the BDI-II,

Roose 1998 (Analysis 4.3), and the evidence is very uncertain regarding the effects of different pharmacological strategies on end-of-treatment depression remission. Four studies examined the differential effects of two pharmacological interventions on depression response (Abbasi 2015; Carney 2009; Roose 1998; Shahmansouri 2014). No differences were observed using the clinician-rated HAM-D, Abbasi 2015; Carney 2009; Shahmansouri 2014, or the BDI-II, Roose 1998 (Analysis 4.4). The study by Liu 2016 (n = 149) reported the number needed for treatment for non-inferiority, but not depression response nor remission, therefore no data were extracted.

4.3 Primary outcome: all-cause and cardiovascular mortality

The evidence from one trial is very uncertain regarding the effect of Shugan Jieyu plus sertraline placebo compared to sertraline plus Shugan Jieyu placebo on all-cause mortality at the end of treatment (n = 149) (Analysis 4.5) (Liu 2016). No trials for this comparison reported medium- or longer-term all-cause mortality. Likewise, no trials for this comparison reported cardiovascular mortality at any time point.

4.4 Primary outcome: cardiac events

Four studies reported the differential effects of two pharmacological interventions on cardiac events at the end of treatment (i.e. short term) (Carney 2009; Roose 1998; Tian 2016; Wang 2020). The number of events were sparse for MI, heart failure, and arrhythmia, whilst no study reported stroke. The evidence is very uncertain regarding the occurrence of MI at end of treatment in trials of: sertraline plus omega-3 versus sertraline plus placebo (n = 122) (Carney 2009); paroxetine versus fluoxetine (n = 46) (Tian 2016); and escitalopram versus Bu Xin Qi concoction (n = 228) (Wang 2020) (Analysis 4.6). No differences were reported between different pharmacological strategies on end-of-treatment angina in the trials by Roose 1998 (n = 81), Tian 2016 (n = 46), or Wang 2020 (n = 228) (Analysis 4.7). No differences were observed between pharmacological interventions in end-of-treatment heart failure in the trials reported by Carney 2009 (n = 122) and Wang 2020 (n = 228) (Analysis 4.8). Likewise, no differences were observed between pharmacological interventions in end-of-treatment arrhythmia in the trials reported by Carney 2009 (n = 122), Roose 1998 (n = 81), and Wang 2020 (n = 228) (Analysis 4.9). No studies reported the occurrence of MI, angina, heart failure, arrhythmia, or stroke in the medium to longer term. Coronary revascularisation procedure for CAD (angioplasty) at end of treatment did not differ between groups in the trial reported by Carney 2009 (Analysis 4.10) (n = 122).

4.5 Secondary outcome: healthcare and resource utilisation

One trial reported emergency room visits, finding no effect for sertraline plus omega-3 versus sertraline plus placebo (n = 122) (Analysis 4.11) (Carney 2009).

4.6 Secondary outcome: quality of life

No trials evaluating this comparison reported QoL at any time point.

4.7 Secondary outcome: cardiovascular vital signs, biomarkers of platelet activation, ECG wave recording

Three studies reported the differential effects of pharmacological interventions on cardiovascular vital signs in the short term (Liu 2016; Roose 1998; Tian 2016). Paroxetine may result in a lower systolic BP (MD −10.00, 95% CI −17.10 to −2.90) compared to nortriptyline (n = 63) (Analysis 4.12) (Roose 1998). Systolic BP may not differ for pharmacological strategies employing paroxetine versus fluoxetine (n = 46) (Tian 2016), or Shugan Jieyu versus sertraline (n = 149) (Liu 2016). No differential effects were evident between pharmacological interventions for diastolic BP in the trials by Roose 1998 (n = 63), Tian 2016 (n = 46), and Liu 2016 (n = 149) (Analysis 4.13). Two studies reported heart rate. Paroxetine may result in a lower heart rate (MD −11.00, 95% CI −14.31 to −7.69) compared to nortriptyline (n = 63) (Analysis 4.14) (Roose 1998). No difference in heart rate was observed between Shugan Jieyu plus sertraline placebo and sertraline plus Shugan Jieyu placebo (n = 149) (Liu 2016). No trials reported medium- to longer-term assessment of cardiovascular vital signs for this comparison.

No head-to-head comparison of two pharmacological interventions reported on biomarkers of platelet activation.

Two studies reported the differential effects of two pharmacological interventions on ECG waves in the short term (Liu 2016; Roose 1998). Paroxetine may result in a lower PR interval (MD −9.00, 95% CI −16.77 to −1.23) compared to nortriptyline (n = 63) (Analysis 4.15) (Roose 1998). Shugan Jieyu plus sertraline placebo versus sertraline plus Shugan Jieyu placebo was not associated with differences in PR interval (n = 146) (Liu 2016). There may be little to no differences between pharmacological interventions for the QRS (Analysis 4.16) and QTc intervals (Analysis 4.17). No trial reported end-of-treatment QT intervals. One trial reported ventricular premature depolarisations (Roose 1998), which was not considered in this review.

4.8 Post hoc outcome: non-cardiac adverse events and pharmacological side effects

In Shahmansouri 2014, one participant allocated to fluoxetine withdrew from treatment due to suicidal ideation. In two trials (Liu 2016 ; Wang 2020), the definition of non-cardiac adverse events was unclear. Otherwise, non-cardiac adverse events were sparsely reported. Seven studies reported pharmacological side effects (Abbasi 2015; Carney 2009; Divsalar 2018; Liu 2016; Roose 1998; Shahmansouri 2014; Wang 2020). There may be little to no difference between different pharmacological intervention strategies on side effects at end of treatment in seven trials (Analysis 4.18) (n = 716).

Comparison 5: Psychological intervention versus pharmacological intervention

We found no trials evaluating psychological intervention versus pharmacological intervention. No analyses were performed.

Subgroup analyses

We planned subgroup analyses to take into account variables such as the population, sex, CAD subtype, time of onset of depression, CAD severity, and risk of bias. Lack of primary data per outcome precluded these analyses. However, as Cochrane Reviews are meant to be updated on a regular basis, these analyses may be feasible in future updates of this review.

DISCUSSION

The current systematic review investigated the effects of psychological and pharmacological interventions on depression outcomes, mortality, cardiac events, healthcare costs and

utilisation, health-related QoL, cardiovascular vital signs, biomarkers of platelet activation, ECG wave parameters, non-cardiac adverse events, and side effects in CAD patients with comorbid depressive disorder. Our comprehensive search strategy identified 37 RCTs fulfilling the inclusion criteria of the review. Fifteen trials examined psychological interventions, and 21 trials examined pharmacological interventions.

Summary of main results

The results of the current review provide evidence that psychological interventions may result in lower depression symptoms compared to control at end of treatment. However, psychological intervention may result in little to no difference in depression remission in the short term based on three trials. The findings of one trial favoured psychological intervention for depression remission in the long term but not in the medium term. Based on one to two trials per outcome, the evidence is uncertain or sparse for the effects of psychological interventions versus usual care on mortality and cardiac events in the short to longer term. Regarding our secondary outcomes, one trial reported that psychological intervention may result in a reduction in resource utilisation (i.e. length of hospital stay). Though an improved mental QoL favouring psychological intervention versus usual care was found in the short term, no effect on end-of-treatment physical QoL was observed.

The evidence base for the comparison of psychological intervention versus other psychological intervention or CM was sparse, and the evidence is very uncertain. Based on four trials, the evidence is very uncertain as to whether there may be differences between the varying approaches (behavioural therapy versus person-centred therapy; CBT versus supportive stress management; IPT versus CM; CBT and well-being therapy versus CM) on our primary outcomes. Statistical and methodological heterogeneity precluded the pooling of results to determine effect sizes.

Regarding the comparison pharmacological intervention versus placebo, we found low-certainty evidence that pharmacological intervention may result in a large reduction in depression symptoms at the end of treatment. There was moderate-certainty evidence that pharmacological intervention probably results in a moderate to large increase in depression remission at the end of treatment. The evidence is very uncertain regarding the effects of pharmacological intervention on mortality and cardiac events, and no consistent findings were reported. The evidence for our secondary outcomes of hospitalisation rates, emergency room visits, and QoL was sparse but points in the direction of a possible beneficial effect of pharmacological intervention compared to placebo. Evidence on cardiovascular vital signs, platelet biomarkers, and ECG waves was mixed and based on small substudies from the main trials. Pooled meta-analysis of one to three trials indicated a possible small beneficial effect of pharmacological interventions for βTG and lower PR interval on ECG at the end of treatment. A possible increase in non-cardiovascular side effects was observed with the pharmacological intervention compared with placebo.

The comparison of pharmacological intervention versus other pharmacological intervention comprised eight trials. The evidence was very uncertain for the effect of different pharmacological agents on depression symptoms at the end of treatment for: simvastatin compared to atorvastatin (Abbasi 2015); sertraline plus omega-3 compared to sertraline plus placebo (Carney 2009); paroxetine compared to fluoxetine (Tian 2016); and escitalopram compared to Bu Xin Qi (Wang 2020). Statistical and methodological heterogeneity precluded the pooling of results to determine effect sizes.

Overall, there is evidence for a possible beneficial effect of both psychological and pharmacological interventions on depression outcomes at end of treatment. However, the evidence base is still small and did not permit conclusions about the effects of these interventions on most other outcomes, as well as on specific types of psychological approaches and pharmacological agents. Moreover, the settings, samples, interventions, and outcome measures were heterogeneous across the included studies, which hampered the interpretation of meta-analytical synthesis. Sensitivity analyses for end-of-treatment depression symptoms provided mixed results that could not explain heterogeneity between psychological trials (versus control) and pharmacological trials (versus placebo). Moreover, our pre-planned subgroup analyses were not feasible due to the low number of studies per outcome and methodological and clinical heterogeneity between studies.

Overall completeness and applicability of evidence

This review summarises the evidence regarding depression treatments in a variety of settings. The included trials comprised different CAD samples (MI, CABG, PCI); investigated various types of psychological and pharmacologic interventions; and were located in different countries with different healthcare systems, thus increasing the generalisability of the results. However, the overall completeness is limited, and the applicability of evidence restricted due to four aspects.

Firstly, most of the primary and secondary outcomes were investigated or reported insufficiently. Hence, evidence of treatment effects on these outcomes needs to be interpreted carefully. Moreover, most trials were underpowered to detect effects of depression treatments on mortality and specific cardiac events and were below the optimal information size.

Secondly, we found no studies comparing psychological and pharmacological interventions. Consequently, no conclusions could be drawn on the differential effects of these treatment approaches. A systematic review experimentally comparing the two approaches indicated that overall psychological and pharmacological interventions were equally effective for treating depression, with pharmacotherapy seemingly superior in dysthymia (g = 0.3), as well as compared to non-directive counselling (g = 0.33), and psychotherapy superior to tricyclic antidepressants (g = 0.21) (Cuijpers 2013). Combining both pharmacotherapy and psychotherapy was superior to pharmacotherapy alone at six months or longer postrandomisation (OR = 2.93), whilst psychotherapy alone resulted in equal depression effects when compared to combined therapy at six months and longer follow-up (Karyotaki 2016). However, the National Institute for Health and Care Excellence (NICE) guideline on depression in adults with a chronic physical health problem favours the use of psychological interventions as first-line interventions in patients with minor and mild to moderate depression due to adverse effects of antidepressants and the resulting poor risk-benefit ratio (NICE 2009). An increase in side

effects was observed in trials of antidepressants versus placebo for patients with CAD and depression symptoms.

Thirdly, the samples of the included trials most likely differed regarding subtypes and severity of depression. The included trials comprised participants with a wide range of depressive symptomatology and different aetiology (e.g. dysthymia, minor and major depression, adjustment disorder with depressed mood; Baumeister 2012a). Depressive disorders were present immediately following the cardiac event or up to 12 months after the event. Furthermore, diverse methods and cut-off points were used to determine trial eligibility and determine depression remission and depression response. The inclusion of mixed samples and those with different depression disorders may have levelled potential effects of depression treatments in participants with specific subtypes of depression (Baumeister 2012a; Baune 2012). For example, when these factors were considered, sensitivity analyses showed changes to the strength and significance of end-of-treatment depression symptoms effect sizes. Other research suggests that the onset of depression was previously shown to be a moderator of treatment outcomes in CAD patients (Dickens 2008). Another trial on depression treatment in general highlighted differential responses to psychotherapy versus pharmacotherapy in chronic depressed patients with childhood trauma compared to those without a history of childhood trauma (Nemeroff 2003). Moreover, a patient-level meta-analysis concluded that the effects of antidepressant medication are associated with the severity of depressive symptoms, showing minimal effects in mild to moderate depression and substantial benefit in severe depression (Fournier 2010).

Fourthly, the length of psychotherapies examined in the included trials ranged from short-term four-session therapies, Barth 2005; Dao 2011, to 12 sessions, Freedland 2009; TREATED-ACS 2020; single- and group-therapies, Brown 1993; SPIRR-CAD 2011; and 12-month telephone support counselling, Yang 2019. The number and intensity of sessions needed to show substantial benefit in psychotherapy should be higher or more specifically tailored to the needs, problems and treatment response of individual patients in order to exploit the full potential of psychological interventions (Carr 2017; Harnett 2010). Hence, the effects found in the included psychological intervention trials may be limited in part due to an insufficient number or intensity of sessions.

Quality of the evidence

The included trials differed with regard to methodological shortcomings (see Risk of bias in included studies) and quality of reporting. Many trials did not adequately describe design aspects such as randomisation procedure, allocation concealment, and blinding. Furthermore, some trials did not report ITT analyses, missing data was common, and selective reporting may have occurred. However, published protocols were not always available, and we were unable to quantify publication bias for our primary outcomes. Low-quality studies have been associated with exaggerated effects (Cuijpers 2010; Moher 1999). The treatment effects summarised in this review may therefore be overestimated due to poor methodological quality of some of the included trials as well as uncertainty in study quality.

Most pharmacological studies were supported by pharmaceutical industry, and two trials included pharmaceutical company employees in the design, conduct, analysis, and reporting of trial outcomes. It has been shown that studies sponsored by pharmaceutical companies are more likely to have outcomes favouring the sponsor than studies with other sponsors (Lexchin 2003). Furthermore, selective reporting of null findings in industry-funded RCTs of antidepressant trials has been documented (Turner 2008). Despite our comprehensive search strategy, there may be unpublished trials with non-significant results or additional trials terminated prematurely.

Another source of bias results from selective reporting of negative findings for prespecified primary outcomes, whilst emphasising positive results from secondary or new outcomes of antidepressant medication trials (Pigott 2010). We were not able to obtain published protocols for all trials included in this review and thus were not able to judge the risk of selective reporting for these studies.

Meta-analyses regarding depressive outcomes were hampered because depressive symptoms were assessed by a heterogeneous set of clinician-rated tools and self-report questionnaires. Furthermore, the included trials reported either final mean scores or mean change scores from baseline to final assessment or did not report sufficient information to compute effect estimates.

The GRADE assessment of primary outcomes in the short term resulted in a range of ratings of certainty of evidence. We assessed the evidence for only one outcome as moderate certainty (depression remission at end of treatment in pharmacological versus placebo trials). Otherwise, the certainty of evidence was very low, low, or could not be determined. The certainty of evidence must be taken into consideration when interpreting the findings of the review (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Potential biases in the review process

In the review process we decided to consider the ENRICHD 2003 and Barth 2005 studies as psychological intervention trials, disregarding the fact that participants in these trials were allowed to receive adjunct pharmacologic treatments in addition to the assigned psychological intervention. Hence, it remains unclear to what degree the effects of these studies were impacted by additional pharmacological treatments. Conversely, we excluded the psychological arms (IPT) in the CREATE 2007 trial who received citalopram, placebo, or CM. The results might also be biased by the inclusion of mixed study samples of CAD patients with depression and/or low social support, ENRICHD 2003, and patients with depression and/or anxiety (Brown 1993; Dao 2011; Fang 2003; Freeman 1986; Ma 2019; McLaughlin 2005; U-CARE 2018; Zarea 2014). As a result of including these trials with mixed study samples and methodological uncertainties, the presented findings might be biased. Moreover, the inclusion of such heterogeneous samples without depression may spuriously increase or decrease the pooled effect sizes. Another source of potential bias may result from the translation process of the included Chinese trials (Fang 2003; Li 2005; Liu 1999). Despite our efforts to translate the Chinese trials accurately, the translations did not result in unambiguous results. Moreover, the limited information provided resulted in unclear risk of bias for these trials (Fang 2003; Li 2005; Liu 1999). Another potential source of bias in the review process concerns the pooling of outcomes by time frame (short, medium, and long term) in accordance with the original review (Baumeister 2011c). This likely results in data below the optimal information size when pooling

uncommon cardiovascular events (e.g. stroke). Future updates to this review may consider pooling all time frames together in dichotomous but infrequent primary outcomes of mortality and cardiovascular events. Likewise, combining end-of-treatment depression symptom effect sizes with the medium-term data may result in increased certainty of evidence.

Agreements and disagreements with other studies or reviews

Differences in the trials included in this review compared to previous reviews are attributable to our focus on trials investigating depression treatments in CAD patients with depression. Two psychological intervention trials included in the current review, CREATE 2007; ENRICHD 2003, were also included in the review of Van Straten 2010, which investigated the effects of psychological treatments on depressive symptoms in medical diseases. The authors conducted a meta-analysis of 23 studies with 10 different medical diseases and concluded that depressive symptoms could be effectively treated with psychological interventions. The results of our review were in a similar direction for CAD patients with depression. However, the evidence is still sparse given the high within-review variance of findings regarding psychological interventions.

Rayner 2010, a Cochrane Review, systematically reviewed trials investigating the effects of antidepressant medication in treating depression in physically ill people. They concluded that antidepressants were superior to placebo in a meta-analysis of 51 studies. The evidence of the current review agrees with this finding for the specific group of CAD patients with comorbid depression. Four trials were included in both reviews (CREATE 2007; MIND-IT 2007; SADHART 2002; Strik 2000).

One systematic review examined collaborative care interventions for patients with CAD and depression (Tully 2015). Based on six included trials, the authors reported a reduction in major cardiac events in the short but not long term, and a small-to-moderate effect on depression severity and an increased depression remission rate. A direct comparison of the findings on collaborative care (Tully 2015) with the stand-alone psychological or pharmacological interventions here is difficult since the methodological heterogeneity between the respective included trials is substantial. There is as yet insufficient evidence to recommend one treatment option over another, suggesting that psychological interventions and pharmacological interventions and more complex collaborative care are recommendable for the treatment of depression in patients with CAD and depression. A network meta-analysis compared different depression interventions for CAD patients at eight weeks from baseline (Doyle 2021). Both psychological therapy (versus usual care) and antidepressant therapy (versus placebo and usual care) displayed significantly better effects. The strongest effects were evident for combination therapy and exercise; however, only single trials were available. Moreover, the network meta-analysis included antidepressant versus usual care interventions, which was a prespecified exclusion criterion for the current review, where we only included pharmacological versus placebo trials (Doyle 2021).

Several trials included in our review, Brown 1993; ENRICHD 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011, were included in a Cochrane Review on the effects of psychological interventions in CAD patients in general (i.e. not restricted to depressed CAD patients) (Richards 2017). Overall, psychological interventions had no effect on mortality, but a beneficial effect on depression symptoms (Richards 2017), which is comparable to the current review. Also, Richards 2017 found a 22% reduction in MI for psychological interventions, which cannot be confirmed for the depression-specific interventions for depressed CAD patients examined in the current review.

The systematic review by Swenson 2006 reported the side effects from antidepressant drug versus placebo trials performed in individuals with chronic illness. No difference was observed between SSRI and placebo for serious and non-serious cardiovascular events. Swenson 2006 also reported higher dropout due to side effects in participants receiving SSRIs versus placebo. A direct comparison with the current review indicates some consistent results on pharmacological side effects. We found evidence that pharmacological intervention may result in an increase in side effects compared to placebo at end of treatment. However, the evidence is very uncertain as to whether there are differences between different pharmacological agents in end-of-treatment side effects.

AUTHORS' CONCLUSIONS

Implications for practice

Psychological interventions may result in a reduction in depression symptoms at end of treatment. Pharmacological interventions may result in a reduction in depression symptoms and probably result in a moderate to large increase in depression remission at end of treatment. The National Institute for Health and Care Excellence (NICE) guideline on depression in adults with a chronic physical health problem favours the use of psychological interventions as first-line interventions in patients with minor and mild-to-moderate depression due to the adverse effects of antidepressants and the resulting poor risk-benefit ratio (NICE 2009). In the primary studies of the current review, antidepressant medications compared to placebo were associated with increased rates of dizziness, diarrhoea, somnolence, sweating, palpitations, libido reduction or sexual difficulties in CREATE 2007; fatigue, appetite changes and weight gain in MIND-IT 2007; fatigue and increased sexual problems in UPBEAT 2012; and nausea and diarrhoea in SADHART 2002. Nortriptyline had a higher rate of adverse events compared to paroxetine in Roose 1998. These side effects must be weighted against the positive effects on depression outcomes when considering initiating pharmacological treatment in depressed coronary artery disease (CAD) patients. The trials conducted by Carney 2009, Abbasi 2015, Shahmansouri 2014, Divsalar 2018, and Ma 2019 reported no meaningful adverse events for omega-3 add-on therapy, simvastatin versus atorvastatin (with a few side effects reported for simvastatin but not for atorvastatin), saffron versus fluoxetine, sertraline augmented with red yeast rice, and Xinkeshu tablets. Conversely, more side effects were observed with escitalopram versus Bu Xin Qi (Wang 2020). There was insufficient evidence to make recommendations on the relative safety of serotonergic drugs with regard to electrocardiogram (ECG) wave parameters. Prolongation of the QTc interval is a possible side effect of selective serotonin reuptake inhibitor (SSRI) drugs (Rochester 2018), and have received a warning from the US Food and Drug Administration (Gerlach 2017). Data from three serotonergic drug versus placebo trials indicated that further investigation is warranted, as two trials did not report sufficient data (MIND-IT 2007;

UPBEAT 2012). The evidence for more specific recommendations is scarce.

There is no evidence to recommend a particular type of psychological intervention (e.g. cognitive-behavioural therapy (CBT)) on the basis of this review. Specifically, comparable effect sizes were found for psychological interventions and those for CBT-only interventions on end-of-treatment depression symptoms. There was modest attenuation in effect size but still considerable heterogeneity, thereby precluding differential conclusions between CBT and non-CBT approaches. Similarly, with regard to pharmacological interventions, there is comparable evidence from sensitivity analyses for pharmacological interventions and specifically for serotonergic antidepressants. However, an insufficient number of studies investigating TCAs and the small evidence base regarding cardiac endpoints in the included studies precluded recommendations on the benefits and risks of SSRIs versus other antidepressant drug classes, such as tricyclic antidepressants (TCAs), for the treatment of depression in CAD patients. The TCAs are viewed as highly cardiotoxic in overdose and may therefore worsen outcomes in CAD patients (Lichtman 2008; Taylor 2008).

With regard to initiating treatment for CAD patients with depression, this review focused on psychological and pharmacological interventions as stand-alone approaches, which neither permit any conclusions on collaborative care (Tully 2015), nor on other treatment options such as exercise (Anderson 2016). For example, UPBEAT 2012 conducted a three-arm trial comparing sertraline and aerobic exercise with placebo, finding no differences between the active trial arms except for heart rate variability in favour of exercise. It may thus be worth considering evidence-based alternatives beyond the frequently suggested two psychological and pharmacological approaches, taking patient preferences into account.

Implications for research

The presence of depression in CAD patients is associated with a high additional burden and a negative medical prognosis (Baumeister 2005; Baumeister 2011a; Baumeister 2015; Dempe 2013; Frasure-Smith 2003; Haschke 2012; Herrmann-Lingen 2006; Lichtman 2014). Furthermore, the rather sparse evidence regarding the durability of depression interventions on depression and other outcomes in CAD populations leads to uncertainty in the evidence base. Accordingly, there is a need for further trials focusing on outcomes not yet sufficiently examined. Alternatively, past trials could improve the standard of evidence by reporting long-term outcomes based on intention-to-treat (ITT). Several post hoc analyses of trials included in this review were no longer in ITT or per-protocol groups, and were ineligible for inclusion in long-term analyses of depression, mortality, and cardiac events. Rather, post hoc analyses were based on responders to depression treatment and participants with major depression versus those without major depression. This applies at least to medium- and long-term depression, quality of life, mortality, specific cardiac events, and healthcare costs. Moreover, to examine differential effects of depression treatments, more comparative trials of psychological and pharmacological interventions are needed. Finally, there is a need for trials of psychological interventions examining the minimum dose required for a clinical meaningful treatment response.

With regard to the divergent effects of both psychological and pharmacological interventions for depression in CAD patients contingent on depression disorder and mixed samples, a change in the current research agenda away from generic depression patient samples regardless of their specific depression subtype and severity may also be needed (Baumeister 2009a; Baumeister 2009b; Baumeister 2012a; Baune 2012; Bech 2010; Pigott 2010). As summarised earlier (Baumeister 2010b; Lichtenberg 2010), the effectiveness of depression treatments may vary depending on depression subtypes. The evidence of depression treatment in general emphasises that treatment effectiveness should at least be examined for different levels of depression severity (Baumeister 2011b; Fournier 2010; NICE 2009), taking clinical significance of depression into account (Baumeister 2008; Baumeister 2010a; Wakefield 2010). In CAD patients the need for subtyping depression might particularly apply to the differentiation of new-onset depression, recurrent depression, atypical depression, and treatment-resistant depression (Dickens 2008; Scherrer 2012).

The current evidence also argues for research efforts beyond the standard treatments that better align with patient needs (Collopy 2021), with a focus on alternatives that improve accessibility, availability, efficacy, and attrition of depression interventions for individuals with CAD and depression. Uncertainty remains regarding the optimal delivery of psychotherapy for depression in CAD via individual or group therapy, or new ways of providing psychological care such as by means of internet- and mobile-based interventions (Bendig 2018; U-CARE 2018; WIDeCAD 2017). Alternatives to improve accessibility and availability might apply to new biological interventions (Kaster 2016), such as examining the drug-repurposing potential of standard cardiovascular medications like lipid- or blood pressure-lowering agents (Abbasi 2015; Cipriani 2016), or add-on therapies using cardiovascular health-promoting agents such as omega-3 (Carney 2009).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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* Indicates the major publication for the study

Abbasi 2015

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 58 Length of follow-up: no follow-up Analysis: per-protocol (6 dropouts in the simvastatin group, 6 dropouts in the atorvastatin group)
Participants	Location: Iran Number of study centres and setting: patients who had undergone CABG from Psychiatric Clinic of Tehran Heart Center CAD criteria: history of post-CABG in the last 6 months Depression criteria: patients who met the DSM IV-TR criteria for diagnosis of MDD, confined to patients with mild-to-moderate depression and a HAM-D score of ≤ 19 Other entry criteria: patients aged 18 to 50 years Exclusion criteria: participants with any diagnosis other than MDD on the DSM-IV-TR axis I or II, on any psychotropic medications or presence of any psychotic features, receiving any antidepressant medication in the last month, receiving electroconvulsive therapy during the last 2 months, serum low-density lipoprotein level of < 80, history of hypothyroidism, hepatic diseases, alcohol or substance (with exception of nicotine) dependence, receiving any statins or any other lipid-lowering agent during the last 2 months, hypersensitivity to statins, presence of any serious medical condition or neurological problem, high levels of liver aminotransferases, pregnancy and lactations, behavioural intervention therapy

Abbasi 2015 *(Continued)*

	Treatment N: 23 (30.4% female, mean age: 56.87 (SD: 6.90))
	Control N: 23 (34.8% female, mean age: 57.70 (SD: 7.26))
	Comparability of groups: no significant baseline differences
Interventions	Treatment: 1 tablet of simvastatin once daily (20 mg tablets)
	Control: 1 tablet of atorvastatin once daily (20 mg tablets)
	Duration of treatment: 6 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression response (50% reduction on HAM-D), cardiac events, pharmacological side effects (checklist)
Funding	Tehran University of Medical Sciences
Notes	The title says "...placebo-controlled, randomized trial...", but both groups received a drug treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Computer generated block randomisation carried out by an independent party
Allocation concealment (selection bias)	Low risk	Comment: Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants, research investigators, rater and statistician blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: primary outcome (HAMD) rater blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: per-protocol analysis and authors reported reasons for early drop-out per group
Selective reporting (reporting bias)	Unclear risk	Comment: trial registry measurement points (week 2, 4, 6) differ from reported measurement points (week 3, 6)
Other bias	Low risk	Comment: no indication of other bias

ANDROS 2015

Study characteristics

Methods	RCT design: 3-arm parallel-group trial
	Total N randomised: 2
	Length of follow-up: 6 months

ANDROS 2015 *(Continued)*

	Analysis: unclear from trial registry (no analysis was reported, information on dropouts unclear)
Participants	Location: France Number of study centres and setting: unclear, affiliated with Hôpitaux de Paris CAD criteria: ACS with elevated cardiac enzymes (above the 99th percentile of the upper limit of normal of the laboratory) Depression criteria: depressive symptoms on the BDI short form Other entry criteria: age 18 years and older, without antidepressant therapy for 3 months (valid only for the sertraline and placebo groups), affiliated to a social security scheme (beneficiary or assignee), signed a free and informed consent Exclusion criteria: psychosis, bipolar illness, dementia (Mini-Mental State Examination score < 23), uncontrolled epilepsy, severe depression (score > 15) with suicidal risk identified by a psychiatrist (urgent treatment for depression needed), patient experienced depression and treated in the last 3 months or currently receiving treatment, treatment with selective and non-selective monoamine oxidase inhibitors of the group A within 14 days prior to the introduction of sertraline, prothrombin time > 1.5 seconds, platelet rate < 100,000/mm^3, hypersensitivity to the active substance or to any of the excipients (anhydrous lactose, pregelatinised corn starch, sodium laurilsulfate, magnesium stearate), treatment with pimozide, genetic galactose intolerance, malabsorption of glucose and galactose, lactase deficiency, women without effective contraception or pregnant or lactating or desiring pregnancy or within 6 months after randomisation, participation in biomedical research on other drugs during the period of participation, unable to follow the treatment Treatment: unclear Control: unclear Comparability of groups: unclear
Interventions	Intervention 1: sertraline 50 mg/d, which can be increased up to 200 mg/d (maximum dose) Intervention 2: placebo 1 capsule per day, which can be increased up to 4 capsules per day (maximum dose) Control: no depression, no treatment Duration of treatment: 6 months
Outcomes	Review outcomes: depression symptoms (BDI short form), platelet biomarkers (β-thromboglobulin) Other outcomes: maximal platelet aggregation (ADP, arachidonic acid, collagen), markers of platelet activation (CD40s), inflammatory markers (interleukin-6, C-reactive protein, Fg, myeloperoxydase), tobacco addiction (Fargenström test), bleeding risk (haemoglobin, haematocrit, and follow-up of haemorrhage)
Funding	Assistance Publique - Hôpitaux de Paris
Notes	Comment: this study was terminated early after recruitment of 2 participants. No data were reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported

ANDROS 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: Double blind (Participant, Investigator), not further specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No details reported
Selective reporting (reporting bias)	Unclear risk	Comment: No details reported; trial terminated early after recruitment of two participants
Other bias	High risk	Comment: The trial was terminated early by the Investigator after recruitment of two participants. The sample size target was 225

Barth 2005

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 59 Length of follow-up: no follow-up Analysis: per-protocol (4 participants in the control group dropped out)
Participants	Location: Germany Number of study centres and setting: 3 cardiac inpatient rehabilitation clinics CAD criteria: patients with MI, CABG, PTCA, unstable angina pectoris; diagnosis based on physician's report; time to randomisation unclear Depression criteria: MDD, dysthymia and depressive adjustment disorder assessed in a 2-stage procedure: 1) HADS and 2) Structured Clinical Interview for DSM-IV in all patients with a HADS score of 17 or higher Other entry criteria: none stated Exclusion criteria: poor general health, language and cognitive deficits, bipolar disorder, psychotherapy at residence, psychotic symptoms Treatment: 27 (18.5% female, mean age: 60.8 (SD: 11.1)) Control: 32 (28.1% female, mean age: 55.6 (SD: 10.1)) Comparability of groups: no significant baseline differences
Interventions	Treatment: brief, individualised, resource-orientated psychotherapy (4 to 6 sessions of 50 minutes each) comprising patient education, motivation, goal setting, crisis management, modification of dys-

Barth 2005 *(Continued)*

	functional cognitions and behaviour, and written recommendations for further outpatient treatment; participants with severe depression were also treated with sertraline Control: usual care Duration of treatment: 3 to 4 weeks during inpatient rehabilitation
Outcomes	Review outcomes: depression symptoms (Bech Rafaelsen Melancholia Scale, also BDI and HADS) Other outcomes: HADS anxiety score
Funding	Ministry for Education and Research, Germany, Federal Insurance Authority, Baden-Württemberg, Germany
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Randomisation carried out by methodology center (independent from study staff)
Allocation concealment (selection bias)	Low risk	Comment: By sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Participants and interventionists unmasked. Blinding to psychopharmacological interventions unclear. Possible performance bias with regard to manual adherence of therapists in treatment group, which remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: primary outcome (BRMS) interviewers blinded to allocation. All other outcomes patient self-report
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: Table 2 (pg. 6/7): "Only patients with data at both assessments were included in the analysis."
Selective reporting (reporting bias)	Unclear risk	Comment: Outcomes as stated in methods section. No protocol or design paper available
Other bias	Unclear risk	Comment: In inpatient studies, therapists and clinic staff are not blind to the patients' allocation, which might impact the inpatient treatment of the intervention and the control group

Brown 1993

Study characteristics

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 54 Length of follow-up: 15 months Analysis: per-protocol (6 dropouts in intervention arm, 8 dropouts in control arm at 15 months)

Brown 1993 *(Continued)*

Participants	Location: USA Number of study centres and setting: patients recruited from 5 cardiac rehabilitation departments of medical centres and by newspaper advertisements CAD critieria: MI and/or coronary bypass surgery 4 to 24 months before study; diagnosis based on physician's report; prognosis of no worse than 3.3 based on the New York Heart Association criteria for moderately compromised cardiac status; stable cardiac status with no medical contraindications to increased physical activity according to their physician's report Depression criteria: new-onset depression and/or anxiety on the SADS; scores of > 13 on the BDI or > 70 on the SCL 90-R Other entry criteria: spouses, friends, or relative who was willing to participate; age between 43 and 75 years Exclusion criteria: unstable medical condition; chronic, severe depression and/or anxiety preceding the cardiac event; suicidal ideation; changes in county residence; unwillingness or inability to include a partner; pre-existing psychiatric disorder Treatment N: 20 (45% female, mean age: 63.55 (SD: 7.43)) Control N: 20 (10% female, mean age: 57.65 (SD: 7.82)) Comparability of groups: significant baseline differences regarding age, religion, SCL 90-R, BDI (with control being more distressed on SCL 90-R and BDI)
Interventions	Treatment: behaviour therapy for participants and their partners by Lewinsohn (weekly 1-hour sessions) in which participants should increase and intensify adaptive behaviours (pleasant activities, relaxation, cognitive restructuring, assertion/anger management, time management) and partners practise positive reinforcement of adaptive behaviours and ignore maladaptive behaviours Control: person-centred therapy by Rogers (weekly 1-hour sessions) Duration of treatment: 12 sessions (treatment and control)
Outcomes	Outcomes: depression symptoms (BDI) Other outcomes: SADS-C, SCL 90-R, Minnesota Multiphasic Personality Inventory-168 (MMPI-168), Pleasant Events Schedule (PES), Unpleasant Events Schedule (UES), Locke Wallace Marital Adjustment Test, Katz Adjustment Scale
Funding	Study supported in part by a grant from the American Heart Association.
Notes	Study investigated effects of behaviour therapy of participants and their partners on depression *and/or* anxiety in comparison to person-centred therapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Blinding of patients not stated Comment: therapists supervision provided

Brown 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: Regarding Schedule of Affective Disorders and Schizophrenia (SADS) "None of the therapists conducted the post-treatment interviews." (p.203) Comment: All other outcomes patient self-report
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Per-protocol analysis and no drop-out analysis (14 of 54 patients dropped-out from baseline to 15-month follow-up). Missing data present
Selective reporting (reporting bias)	Unclear risk	Comment: Outcomes reported as stated in the methods section; no protocol or design paper available
Other bias	Unclear risk	Comment: significant baseline imbalance between groups in baseline depression (BDI) and age Comment: therapists rated and monitored for quality; no efforts regarding therapy quality mentioned; therapist quality analaysis provided

Carney 2009

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 122 Length of follow-up: no follow-up Analysis: ITT with multiple imputation for missing data
Participants	Location: USA Number of study centres and setting: cardiology practices in St Louis, Missouri and from cardiac diagnostic laboratories affliliated with Washington University School of Medicine CAD criteria: CHD documented by at least 50% stenosis in at least 1 major coronary artery, a history of revascularisation or hospitalisation for an acute coronary syndrome Depression criteria: patients who fullfilled DSM-IV criteria for current major depressive episode (DISH) and scored 16 or higher on the BDI-II Other entry criteria: none Exclusion criteria: cognitive impairment, comorbid psychiatric disorders, psychosis, high risk of suicide, current substance abuse, acute coronary syndrome within the previous 2 months, a left ventricular ejection fraction of less than 30%, advanced malignancy or physical inability to participate, use of any antidepressants, anticonvulsants, lithium, or omega-3 supplements, sensitivity to sertraline or omega-3, physician or patient refusal Treatment N: 62 (35.5% female, mean age: 58.1 (SD: 9.4)) Control N: 60 (31.7% female, mean age: 58.6 (SD: 8.5)) Comparability of groups: no significant baseline differences between groups except for a higher proportion of aspirin use in the placebo group
Interventions	Treatment 1: sertraline (50 mg/d) + omega-3 (2 g/d) Treatment 2: sertraline (50 mg/d) + corn oil capsules (placebo)

Carney 2009 *(Continued)*

	Duration of treatment: 10 weeks
Outcomes	Review outcomes: depression score (HAM-D, also BDI-II), depression response (50% symptom reduction BDI-II) and depression remission (BDI-II ≤ 8), cardiac events, resource utilisation (emergency room visits), pharmacological side effects Other outcomes: anxiety symptoms (Beck Anxiety Inventory), treatment adherence, omega-3 index
Funding	Study funded by the National Heart, Lung, and Blood Institute. Other support: GlaxoSmithKline Inc supplied omega-3 and placebo capsules; Pfizer Inc supplied sertraline
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: permuted-block-randomisation (SAS institute, Cary, North Carolina)
Allocation concealment (selection bias)	Low risk	Comment: assignments sealed envelopes opened at enrolment by a pharmacist blinded to all assessments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the study pharmacist and the chair of the data and safety monitoring committee were unblinded to group assignment during the trial." (p.1652)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Only the study pharmacist and the chair of the data and safety monitoring committee were unblinded to group assignment during the trial." (p.1652) Quote: "An independent cardiologist, the study investigators, and the study nurses met quarterly to review adverse events. The study pharmacist and the independent cardiologist were informed immediately about serious adverse events and quarterly about routine adverse events" (pg. 1653) Comment: Unclear how HAMD was rated and by whom
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT, reasons for drop-out given (drop-out: 4 patients in the sertraline+placebo, 3 patients in the sertraline+Omega-3)
Selective reporting (reporting bias)	Unclear risk	Comment: Secondary outcomes (biomarkers) were not reported ITT
Other bias	Unclear risk	Comment: in- and exclusion criteria differ from the trial registry

CREATE 2007

Study characteristics

Methods	RCT design: 2 x 2 factorial trial Total N randomised: 284

CREATE 2007 *(Continued)*

	Length of follow-up: no follow-up Analysis: ITT with last-observation-carried-forward applied for missing data
Participants	Location: Canada Number of study centres and setting: 9 hospitals with patients being referred from physicians, responded to media advertisements or targeted posters CAD criteria: evidence of CAD based on hospital chart, evidence of a previous hospitalisation for acute MI, or coronary angiographic evidence of 50% or more blockage in at least 1 major coronary artery, or previous revascularisation; patients were not randomised less than 1 week following discharge Depression criteria: current major depressive episode based on the SCID with at least 4 weeks' duration; baseline score of > 19 on the HAM-D Other entry criteria: adult patients (18 years or older), stable CAD according to physician's clinical judgement Exclusion criteria: coronary bypass surgery planned during the next 4 months, CCS angina class = 4, bipolar disorder, major depression with psychotic features, or evidence of substance abuse or dependency during the previous 12 months, serious suicide risk based on clinical judgement, use of antidepressants, lithium, or anticonvulsants for mood disorder, currently undergoing any form of psychotherapy, absence of response to a previous adequate trial of citalopram or IPT, 2 previous unsuccessful trials of treatment for depression for the index episode, lifetime history of early termination (< 8 weeks) of citalopram because of adverse events or side effects, lifetime history of early termination (< 8 weeks) of 2 other SSRI antidepressants because of adverse events or side effects, significant cognitive problems, depression due to a general medical condition based on clinical judgement, participation in other trials, inability to speak English or French, unable or unwilling to comply with the study regimen Treatment 1 N: 142 (31.0% female, mean age: 59.0 (SD: 9.81)) Treatment 2 N: 142 (23.2% female, mean age: 57.9 (SD: 9.15)) Control 1 N: 142 (18.3% female, mean age: 57.3 (SD: 8.35)) Control 2 N: 142 (26.1% female, mean age: 58.4 (SD: 9.16)) Comparability of groups: significantly more women in IPT compared to CM groups
Interventions	Treatment 1: IPT + citalopram (20 mg/d to 40 mg/d, tablets) + CM. IPT provided weekly dealing with common problems in CAD patients, including interpersonal conflicts, life transitions, grief, loss, and social isolation (ineligible for this review) Treatment 2: citalopram (20 mg/d to 40 mg/d, tablets) + CM with 20- to 25-minute visits including information about depression and medication use, reassurance, and encouragement of adherence to medication and the study protocol, review of side effects and progress Control 1: IPT + CM + placebo (ineligible for this review) Control 2: placebo administration matched to citalopram condition + CM Duration of treatment: 12 weeks
Outcomes	Outcomes: depression symptoms (HAM-D, also BDI-II), depression remission (HAM-D ≤ 8), depression response (50% reduction on HAM-D), cardiovascular vital signs (BP, HR), platelet biomarkers (P-selectin), ECG waves, pharmacological side effects Other outcomes: Interpersonal Relationships Inventory (IPRI), Functional Performance Inventory (FPI), biomarkers (nitric oxide)
Funding	Canadian Institute of Health Research; Fondation du Centre Hospitalier de l'Université de Montréal; Fondation de l'Institut de Cardiologie de Montréal

CREATE 2007 *(Continued)*

	Other support: citalopram and matching placebo donated by Lundbeck Canada Inc
Notes	Factorial design did not allow for 2 randomised comparisons of main effects: 1) IPT vs CM, 2) citalopram vs placebo. Only citalopram vs placebo was included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Computer generated block randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Concealed in sequentially numbered, site-specific, sealed opaque envelopes stored at the coordinating center until randomization" (p. 369)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: therapists, patients, site psychiatrists, telephone raters for primary outcome, and other personnel blinded to assignment regarding citalopram treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: therapists, patients, site psychiatrists, telephone raters for primary outcome, and other personnel blinded to assignment regarding citalopram treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat (ITT) analysis with last-observation-carried-forward
Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes reported in accordance with the study protocol (ISRCTN15858091)
Other bias	Low risk	Comment: no indication of other bias

Dao 2011

Study characteristics

Methods	RCT design: nested, 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: no follow-up Analysis: unclear (method of analysis not explicitly stated; analysis not based on total N randomised; 2 dropouts in intervention arm, 2 dropouts in control arm)
Participants	Location: USA Number of study centres and setting: single centre, Veterans Affairs hospital CAD criteria: patients undergoing first-time CABG wtihout concomitant valve procedures Depression criteria: BDI-II of 14 or higher (or anxiety, State–Trait Anxiety Inventory-Trait score ≥ 40) Other entry criteria: none Exclusion criteria: serious medical illness other than CAD, psychiatric instability (suicidality), schizophrenia, bipolar disorder, active alcoholism or substance abuse, severe cognitive impairment, non-car-

Dao 2011 *(Continued)*

	diac illnesses with a poor 1-year prognosis, previous exposure to CBT within the past year, receiving psychotherapeutic services, unstable antidepressant medication (less than 4 weeks) Treatment N: 48 (22.9% female, mean age: 62.8 (SD: 11.8)) Control N: 49 (20.4% female, mean age: 64.2 (SD: 11.9)) Comparability of groups: no significant baseline differences between groups on demographic variables and measures of depression and anxiety, significantly more diabetes patients in the control group than in the treatment group (Cohen's d = 0.443)
Interventions	Treatment: brief CBT intervention (Managing Anxiety and Depression using Education and Skills (MADES)). MADES uses a manualised approach to address the needs of patients who have CAD with preoperative depression and/or anxiety. Duration of treatment: 2 sessions before surgery, 1 session after surgery, 1 session 5 days after surgery Control: usual care
Outcomes	Review outcomes: depression symptoms (BDI-II), healthcare and resource utilisation (length of stay), quality of life (12-item Short Form Health survey) Other outcomes: anxiety symptoms (STAI-Trait)
Funding	Mental illness research, education and clinical centre
Notes	Mixed study sample (patients with high depression and/or anxiety scores eligible)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Random numbers table
Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Low drop-out, but reasons for missing data not mentioned
Selective reporting (reporting bias)	Unclear risk	Comment: No study protocol available. Uncertainties regarding data analysis and degrees of freedom (pg.112)
Other bias	Unclear risk	Comment: In inpatient studies, therapists and clinic staff are not blind to the patients' allocation, which might impact the inpatient treatment of the intervention and the control group Comment: manualised treatment; all treatment sessions video-taped and reviewed by lead investigator for adherence and compliance

Divsalar 2018

Study characteristics	
Methods	RCT design: 2-arm parallel trial Total N randomised: 101 Length of follow-up: no follow-up Analysis: ITT with last-observation-carried-forward (3 dropouts from sertraline/red yeast arm, 3 dropouts from sertraline/placebo arm)
Participants	Location: Iran Number of study centres and settings: Imam Hospital and Tehran Heart Center CAD criteria: history of coronary angioplasty Depression criteria: diagnosis of major depressive disorder (MDD) based on DSM-V and HAM-D score of ≥ 20 Other entry criteria: aged 18 to 60 years old Exclusion criteria: other DSM-V disorders other than MDD; presence of psychotic features or suicidal ideation; inability to communicate; consumption of psychotropic or antidepressant medications in the last month prior to the study; electroconvulsive therapy in the last 2 months prior to study; lipid-lowering agents (e.g. statins) in the last 2 weeks prior to the study; hypersensitivity to statins; presence of neurological diseases or serious medical condition or history of hepatic disease or hypothyroidism; elevated serum aminotransferases to serum LDL (80 mg/dL); pregnancy or lactation Treatment: 25 (28% women, mean age: 43.52 (SD: 6.36)) Control: 25 (40% women, mean age: 44.32 (SD: 5.47)) Comparability of groups: no significant baseline differences
Interventions	Intervention 1: sertraline (200 mg/day) and red yeast rice (2500 mg/day) Intervention 2: sertraline (200 mg/day) and placebo Duration of treatment: 6 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), pharmacological side effects (25-item checklist)
Funding	Tehran University of Medical Sciences (TUMS)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: Computerized random number generation was used
Allocation concealment (selection bias)	Low risk	Quote pg. 71 "Computerized random number generation was used by one of the personnel different from raters" Comment: Allocation was achieved using sealed opaque envelopes with sequential numbers

Divsalar 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: All healthcare providers, participants, and caregivers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote pg. 71 "An independent rater was responsible for administration of the HDRS at weeks 0, 3, and 6." Comment: unclear blinding for other outcomes including biomarkers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: The reasons for patients who did not complete the intervention were reported
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol or design paper available
Other bias	High risk	Comment: selection bias evident with 14.9% of participants who were eligible for the study but were excluded prior to randomisation

Doering 2007

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: not stated Length of follow-up: 4 months Analysis: per-protocol (number of participants who dropped out of nested trial unclear; 23 participants did not finish study)
Participants	Location: USA Number of study centres and setting: 2 urban medical centres CAD criteria: patients undergoing first-time CABG; time to randomisation not specified Depression criteria: diagnosis of major depression during inpatient treatment or 2 to 4 weeks after hospital admission or minor depression at both interviews diagnosed by the Diagnostic Interview and Structured Hamilton (DISH) Other entry criteria: <= 75 years old, English-speaking, Mini-Mental State Examination score of >= 24, available for 6 months follow-up Exclusion criteria: malignancies or autoimmune disorders Treatment N: 7 (100% female, mean age: 58.6 (SD: 7.6)) Control N: 8 (100% female, mean age: 60.9 (SD: 9.4)) Comparability of groups: treatment group participants had a significantly higher rate of depression history
Interventions	Treatment: CBT (weekly 1-hour sessions) by a trained nurse therapist including establishing therapeutic relationship, behavioural activation, active problem-solving, identification of automatic thoughts, reframing automatic thoughts, learning self-therapy and relapse prevention

Doering 2007 *(Continued)*

	Control: usual care comprising usual medical and nursing follow-up after CABG and an assessment by a psychiatrist who recommended individualised treatment options Duration of treatment: 8 weeks
Outcomes	Review outcomes: depression symptoms (BDI), depression disorders (DISH), postoperative illnesses (Modified Health Review) Other outcomes: biomarkers (natural killer cell cytotoxicity, interleukin-6, C-reactive protein)
Funding	Not stated
Notes	Study investigated depressed post-CABG women; intervention trial was nested in a study inclusive of a non-depressed comparator group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No details reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Outcome assessed by a research assistant blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Only those patients who completed all study measures were included in this report." (p. 19)
Selective reporting (reporting bias)	Unclear risk	Comment: depression disorders were assessed at follow-up (DISH) and this data was not reported for intervention and control group who all met criteria for baseline depression disorder. No protocol or design paper available
Other bias	Unclear risk	Comment: No efforts regarding nurse therapists protocol adherence reported. Usual care comprised psychiatrists' recommendations for individualised treatment options, but utilised treatments in the control group were not assessed

ENRICHD 2003

Study characteristics

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 2481 Length of follow-up: evaluations after 6 months and annually thereafter (follow-up duration 18 to 54 months)

ENRICHD 2003 *(Continued)*

	Analysis: ITT for mortality and cardiac events (93 participants in the intervention arm did not receive the intervention)
Participants	Location: USA Number of study centres and setting: Outpatients from 73 hospitals affiliated with 8 clinical centres CAD criteria: acute MI with elevation in 1 or more biomarkers as well as MI-compatible symptoms or characteristic ECG ST-T changes or new Q waves; randomisation within 28 days after MI Depression criteria: major depression or dysthymia diagnosis based on the DISH according to modified DSM-IV criteria Other entry criteria: low perceived social support assessed through the ENRICHD Social Support Instrument (ESSI) Exclusion criteria: patients with acute MI following PCI or CABG, receiving psychotherapy or taking an antidepressant for longer than 14 days but remained depressed, non-cardiac conditions likely to be fatal within 1 year, too ill to participate, participating in another trial, major psychiatric disorder (including schizophrenia, bipolar disorder, severe dementia, or active substance abuse), at risk for suicide, refusal of participation or physician disallowed participation, could not be enrolled within 28 days, inaccessible for intervention or follow-up Treatment N: 1238 (43% female, mean age: 61 (SD: 12.6)) Control N: 1243 (44% female, mean age: 61 (SD: 12.5)) Comparability of groups: no significant baseline differences except for the use of ACE inhibitors
Interventions	Treatment: individual (at least six 1-hour sessions weekly) and group (weekly 2-hour sessions) CBT by Beck supplemented by techniques based on social learning theory for participants with low perceived social support; participants with scores > 24 on the HAM-D or those with less than 50% reduction in BDI score after 5 weeks were referred to study psychiatrist for consideration of pharmacotherapy with sertraline (50 to 200 mg/d) Control: usual care Duration of treatment: individual behavioural intervention up to 6 months with additional 12 weeks for group therapy, adjunctive pharmacotherapy up to 12 months
Outcomes	Review outcomes: depression symptoms (HAM-D), all-cause mortality, cardiovascular mortality, cardiac events, healthcare and resource utilisation (cardiovascular hospitalisation), quality of life (12-item Short Form Health survey) Other outcomes: social support and social networks, life satisfaction, change in cardiac risk factor profile, perceived stress, self-efficacy
Funding	National Heart, Lung, and Blood Institute Other support: Pfizer Inc provided sertraline for the study
Notes	Mixed study sample (patients with depression *and/or* low perceived social support were enrolled)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Automated telephone randomization system using permuted blocks with varying sizes, stratified by clinical center; test for selection bias potentially resulting from unmasking of previous assignments (participants and interventionists were unblinded) with nonsignificant results

ENRICHD 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Comment: Allocation obtained by an automated telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Participants and interventionists unmasked Quote: "Psychosocial interventions including those used in ENRICHD cannot be fully blinded" (protocol paper, pg. 4)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Conflicting information reported for blinded outcome assessment. Quote: "Staff who collected, verified, or classified end point data or follow-up assessments were masked as much as possible" (Berkman, 2003). Quote: "End point data collection, verification and classification, and follow-up psychosocial assessments are conducted by staff who are blinded to treatment assignment." (protocol paper, 2000)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Depression outcomes analysed per protocol, all other reported outcomes ITT
Selective reporting (reporting bias)	High risk	Comment: results of main outcomes reported as described in the design papers of the trial. Secondary outcomes (change in cardiac risk factor profile, perceived stress and self-efficacy) were not reported per protocol or ITT
Other bias	Unclear risk	Comment: Therapy quality and adherence to treatment protocol were monitored by an external organisation (the Beck Institute) Comment: QoL was not assessed at baseline and it thus remains unclear whether or not QoL was balanced in the two groups at baseline

EsDEPACS 2014

Study characteristics	
Methods	RCT design: nested, 3-arm parallel-group trial Total N randomised: 300 Length of follow-up: 6 months Analysis: per-protocol. ITT stated in protocol paper, and no imputation was performed for end-of-treatment results (42 dropouts in intervention group, 45 dropouts in control group including 3 for protocol violation)
Participants	Location: Korea Number of study centres and setting: Department of Cardiology of Chonnam National University Hospital CAD criteria: patients 2 to 14 weeks after a confirmed ACS episode Depression criteria: diagnosis of major or minor depressive disorder (participants with BDI > 10 and clinically evaluated depression via Mini-International Neuropsychiatric Interview (MINI) Other entry criteria: unclear Exclusion criteria: unclear

EsDEPACS 2014 *(Continued)*

	Treatment N: 149 (40.9% female, mean age: 60.0 (SD: 11.2)) Control N: 151 (38.4% female, mean age: 60.1 (SD: 10.5)) Comparability of groups: no significant baseline differences
Interventions	Treatment: flexible doses of daily escitalopram (5, 10, 15, or 20 mg); dose was 10 mg/day (5 mg/day if age ≥ 65) at baseline and could be changed after 4 weeks Control 1: placebo Control 2: usual care (ineligible for this review) Duration of treatment: 24 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D, also Montgomery-Asperg Depression Rating Scale, BDI), depression remission (HAM-D ≤ 7), depression response (50% reduction on HAM-D), all-cause mortality, cardiac mortality, cardiac events, quality of life (WHOQOL-BREF), cardiovascular vital signs (BP, HR), platelet biomarkers, ECG waves, pharmacological side effects (unclear how assessed) Other outcomes: clinical global impressions, echocardiography (left ventricular ejection fraction, wall motion), weight, blood biomarkers (troponin I, creatine kinase-MB, cholesterol, brain derived neurotrophic factor methylation), Big Five Inventory (3 months)
Funding	Korean Ministry of Health & Welfare; National Research Foundation of Korea; Korean Ministry of Science, ICT and future Planning; National Institute for Health Research Biomedical Research Centre and Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust and King's College London Other support: escitalopram and placebo provided by H. Lundbeck A/S
Notes	EsDEPACS is a nested placebo-controlled trial within the Korean Depression in ACS (K-DEPACS) study. In K-DEPACS, depressed participants received no treatment; this comparator was ineligible for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computerized random number generator (blocks of four, allocation ratio 1:1), independent party was responsible for generation
Allocation concealment (selection bias)	Low risk	Comment: randomization codes provided by a statistician independent of the recruiting clinicians
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome measurement (by nurses) and adverse event monitoring (by psychiatrists) were carried out blind to treatment allocation" (pg. 63)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high drop-out rate immediately after randomisation including protocol violations
Selective reporting (reporting bias)	Low risk	Comment: outcomes from study protocol reported; only personality assessed mid-treatment is not reported to date

EsDEPACS 2014 *(Continued)*

Other bias	Low risk	Comment: no indication of other bias

Fang 2003

Study characteristics	
Methods	RCT design: parallel-group trial Total N randomised: 57 Length of follow-up: 8 weeks Analysis: unclear
Participants	Location: China Number of study centres: patients selected from 2 hospitals CAD criteria: MI) confirmed by an electronic radiograph Depression criteria: Sung's self-rating depressive scale score > 43 Other entry criteria: Sung's self-rating anxiety scale score > 38 Exclusion criteria: unclear Treatment N: 27 (sex and age distribution unclear) Control N: 30 (sex and age distribution unclear) Comparability of the groups: unclear
Interventions	Treatment: health education and psychological intervention in addition to standard medication. Health education included basic MI knowledge and related subjects such as healthy diet, exercise, and cholesterol control. Psychological intervention comprised support (5 times a week, 30 to 40 minutes per meeting), various psychological treatments tailored according to the participant's needs (twice a week for 30 to 40 minutes), and mind and body relaxation time using breathing exercises and various relaxation techniques (twice daily, 15 to 20 minutes) Control: usual care Duration of treatment: 8 weeks
Outcomes	Review outcomes: depression symptoms (Sung's self-rating depressive scale) Other outcomes: Sung's self-rating anxiety scale score, New York Heart Association functional class, left ventricular ejection fraction
Funding	Unclear
Notes	Comment: translated paper; possible mixed study sample (patients with depression and/or anxiety)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No sufficient information provided

Fang 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Selective reporting (reporting bias)	Unclear risk	Comment: No sufficient information provided
Other bias	Unclear risk	Comment: translated paper

Freedland 2009

Study characteristics	
Methods	RCT design: 3-arm parallel-group trial Total N randomised: 123 Length of follow-up: 6 months Analysis: ITT with multiple imputation
Participants	Location: USA Number of study centres and setting: patients who had undergone CABG from 3 hospitals CAD criteria: CABG, randomisation within 12 months after surgery Depression criteria: BDI score of 10 or higher and current major or minor depressive episode assessed with the DISH Other entry criteria: patients aged 21 years or older Exclusion criteria: severe psychiatric comorbidities (schizophrenia or bipolar disorder), active alcoholism or substance abuse, severe cognitive impairment, non-cardiac illnesses with a poor 1-year prognosis, being too medically ill or living too far away to participate, unable to communicate in English, or receiving ongoing psychotherapeutic services Treatment 1 (CBT) N: 41 (56% female, mean age: 62 (SD: 11)) Treatment 2 (SSM) N: 42 (50% female, mean age: 59 (SD: 10)) Control N: 40 (43% female, mean age: 61 (SD: 9)) Comparability of groups: proportion of African-American participants in treatment 2 (SSM) was significantly higher than in the other study arms

Freedland 2009 *(Continued)*

Interventions	Treatment 1: individual CBT (weekly 1-hour sessions) including target problem identification, problem-solving, behavioural activation, cognitive techniques (challenging distressing automatic thoughts, changing dysfunctional attitudes), self-therapy and relapse-prevention skills Treatment 2: SSM (weekly 1-hour sessions) including patient education regarding stress and coping, practice in progressive muscle relaxation training, controlled breathing and relaxing imagery Control: usual care for depression Duration of treatment: 12 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D, also BDI-II), depression remission (HAM-D ≤ 6), quality of life (36-Item Short Form Health Survey) Other outcomes: anxiety symptoms (Beck Anxiety Inventory), hopelessness (Beck Hopelessness Scale), stress (Perceived Stress Scale), Heart Surgery Questionnaire (HSQ), cognitive function (digit symbol test, Trail Making Test-part B, paragraph recall, Short Blessed Test)
Funding	National Institute of Mental Health, USA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Computer-generated random allocation sequence with block sizes of 3 and 6
Allocation concealment (selection bias)	Low risk	Comment: Concealed in sealed envelopes and revealed to the study coordinator immediately after the participant completed all of the baseline assessments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: single-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome assessors were masked to the participants' group assignments" (p. 389)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: Missing data "plausibly missing at random" (p. 389) Comment: Missing outcome data imputed
Selective reporting (reporting bias)	Low risk	Comment: Outcomes reported in accordance to the study protocol
Other bias	Low risk	Comment: 94% of intervention sessions taped for quality assurance; trial fidelity quantified by a Treatment Process Scale after each session. The measure was developed for the study; Comment: manualised CBT treatment with weekly supervision; SSM intervention not manualised

Freeman 1986

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 107 Length of follow-up: no follow-up Analysis: per-protocol (60 of 107 participants completed the trial)
Participants	Location: USA Number of study centres and setting: patients from 1 hospital CAD criteria: patients undergoing CABG (assessment method and time to randomisation not specified) Depression criteria: a score of 13 or greater on the Center for Epidemiological Studies - Depression Scale (CES-D) or a score of 36 or greater on the Spielberger State Anxiety Inventory (SSAI), or both; presence of clinically significant anxiety or depression was confirmed by a semistructured psychiatric interview Other entry criteria: under 65 years of age Exclusion criteria: females of childbearing potential, patients with a history of sensitivity to benzodiazepines, patients with prior or existing evidence of substance abuse, antisocial personality, psychosis, significant uncontrolled systemic disease, cerebral infarction, dementia, or insufficient English Treatment N: 32 (sex and age distribution unclear) Control N: 28 (sex and age distribution unclear) Comparability of groups: treatment group had significantly higher anxiety scores at baseline; no further information regarding group comparability
Interventions	Treatment: alprazolam (tablets, 2.5 mg/d at bedtime, maximum dose 4.5 mg/d) Control: placebo Duration of treatment: 1 month
Outcomes	Review outcomes: depression symptoms (CES-D score, also Zung Self-Rating Depression Scale) Other outcomes: anxiety symptoms (SSAI, Zung Self-Rating Anxiety Scale), Global Impression Scale, structured psychiatric semistructured interviews (signs and symptoms of psychosis, cognitive dysfunction, depression, anxiety, and somatisation)
Funding	Upjohn Company
Notes	Mixed study sample (participants with depression and/or anxiety)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: No details reported

Freeman 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Only 60 of 107 patients completed the trial Comment: 22 early drop-outs in the alprazolam group (with noncompleters being less distressed than completers preoperatively) Comment: 25 early drop-outs in the placebo group (with noncompleters being more distressed than completers preoperatively)
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol or design paper available Comment: psychiatric semistructured interviews were performed at all assessment time points (signs and symptoms of psychosis, cognitive dysfunction, depression, anxiety, and somatization) but were not reported
Other bias	Unclear risk	Comment: unclear if selection bias present. 60% of 459 patients met entrance criteria and 23% were included. "The remainder were excluded from entering the drug trial by semistructured interview or were rendered ineligible because of surgical complications or withdrawal of consent." (p. 39) Comment: possible baseline imbalance. Treatment group significantly higher anxiety scores at baseline; no further information regarding comparability of groups

Kennedy 2005

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 19 Length of follow-up: no follow-up Analysis: per-protocol, all randomised participants who took at least 1 dose of investigational medical product (4 of 19 participants completed the trial)
Participants	Location: Denmark, Estonia, and Norway Number of study centres and setting: multinational and multicentre CAD criteria: had been admitted for chest pains (or other MI symptom) with a diagnosis of evolving MI not less than 3 weeks and not more than 24 weeks prior to screening, as evidenced by either an elevation of biochemical markers of MI (troponin and creatine kinase-MB fraction) or ECG changes that were unequivocally consistent with an acute, evolving MI, i.e. development of a significant Q-wave in at least 2 continuous leads Depression criteria: a score of 20 or greater on the SCL-90-R at screening and at baseline Other entry criteria: male or female outpatient between 40 and 75 years of age, on the basis of a physical examination, medical history, ECG, and the results of blood biochemistry and haematology tests

Kennedy 2005 *(Continued)*

carried out at the screening visit; the patient is, in the investigator's opinion, healthy, otherwise than what is part of the MI and its sequelae

Exclusion criteria:

1. Patients who have previously participated in this study.
2. CABG or PTCA within 3 weeks of screening or CABG or PTCA during the duration of the study.
3. Known Class IV rating as defined by the CCS classification for angina, based on investigator judgement or medical chart.
4. Known Class IV rating as defined by the Congestive Heart Failure Classification of the New York Heart Association, based on investigator judgement or medical chart.
5. Ongoing myocardial ischaemia diagnosed with presence of ST-segment elevation or ST-segment depression on screening visit ECG.
6. Cardiac arrhythmias (except for atrial fibrillation) necessitating other antiarrhythmic treatment than beta-blockers or calcium-channel blockers.
7. Uncontrolled high blood pressure: diastolic above or equal to 100 mmHg or systolic above or equal to 180 mmHg.
8. Bipolar I and II disorders, major depressive episode with psychotic features, or evidence of substance abuse or dependency during the previous 12 months based on investigator judgement or medical chart.
9. Patients with a baseline MADRS total score above or equal to 40.
10. Serious suicide risk based on investigator judgement or a score above or equal to 3 on item 15 of the SCL-90-R or a score above or equal to 5 on item 10 of the MADRS.
11. Use of disallowed recent or concomitant medications or treatments:
    a. IMAO or RIMA within 2 weeks prior to screening.
    b. Fluoxetine within 5 weeks and other SSRIs or TCAs or SNRIs within the past 2 weeks prior to screening.
    c. Herbal remedies that are psychoactive (including St John's wort, S-adenosylmethionine (SAMe), kava kava, valerian, ginkgo biloba) within 2 weeks prior to screening.
    d. Tryptophan within 2 weeks prior to screening.
    e. Any drug used for the augmentation of antidepressant action within 2 weeks prior to screening.
    f. Any other antidepressants within the 2 weeks prior to screening.
    g. Mood stabilisers/antimanic drugs/anticonsulvants (e.g. lithium, lamotrigine, valproic acid, gabapentine, carbamazepine, phenytoin) within the 2 weeks prior to screening.
    h. Oral antipsychotics in the 2 weeks or depot antipsychotics in the 6 months prior to screening.
    i. Electroconvulsive therapy within the 6 months prior to screening.
    j. Benzodiazepines were only allowed if the patient was on stable treatment prior to screening with a maximum daily dose of diazepam 10 mg (or its equivalent). This dose should remain fixed for the duration of the study.
    k. During the course of the study period, the use of hypnotics (zolpidem, zaleplon, or zopiclone) was allowed if needed for a maximum of 3 evenings per week.
    l. Dopamine antagonists (e.g. metoclopramide) for any indication within 2 weeks prior to screening.
    m. Serotonergic agonists (e.g. triptans) within 2 weeks prior to screening.
    n. Any other drugs with potential psychotropic effects within 2 weeks prior to screening.
12. Patient was receiving, within 4 weeks prior to screening, formal behaviour therapy or systematic psychotherapy, or was planning to initiate such therapy during the study.
13. Patient has a serious illness or serious sequelae thereof, including liver or renal insufficiency, or a pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance.
14. Patient has laboratory values outside the normal ranges and considered by the investigator to be clinically sign

Treatment N: 9 (sex and age distribution unclear)

Control N: 10 (sex and age distribution unclear)

Comparability of groups: unclear as no results shown. Reported "There were no clinically relevant differences in age, sex, weight, or BMI between the treatment groups. At baseline, there were no clinically

Kennedy 2005 *(Continued)*

	relevant differences between the placebo and escitalopram groups with respect to medical history or the use of concomitant medication."
Interventions	Treatment: flexible doses of daily escitalopram (10 or 20 mg); dose was fixed at 10 mg/day at baseline (to 8 weeks) and could be changed to 20 mg/day at 9 weeks according to the participant's response to treatment, as judged by the investigator Control: placebo Duration of treatment: 24 weeks
Outcomes	Review outcomes: cardiac events, ECG waves (rhythm, QRS complex, ST-segment, and T-wave inversion), pharmacological side effects
Funding	H. Lundbeck A/S, Lundbeck Austria GmbH Other support: study drugs provided by H. Lundbeck A/S Denmark
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This is a double-blind study; insufficient information provided on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This is a double-blind study. Insufficient information provided on blinding and detection
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 83.3% of participants did not complete the study
Selective reporting (reporting bias)	High risk	Comment: efficacy data not reported for depressive symptoms; trial was terminated early by the Investigator
Other bias	High risk	Comment: trial was terminated early by the Investigator Comment: Protocol reported for Finland, Austria and Denmark. Study recruitment undertaken in Denmark, Estonia, and Norway

Li 2005

Study characteristics	
Methods	RCT design: parallel-group trial

Li 2005 *(Continued)*

	Total N randomised: 87 Length of follow-up: 6 weeks Analysis: unclear (2 cases dropped out in the intervention group, 3 cases dropped out in the control group)
Participants	Location: China Number of study centres and setting: hospitalised patients (number of centres unclear) CAD criteria: undergone CABG Depression criteria: self-rated HAM-D score > 18 Other entry criteria: unclear Exclusion criteria: unclear Treatment N: 43 (sex and age distribution unclear) Control N: 39 (sex and age distribution unclear) Comparability of groups: unclear
Interventions	Treatment: St John's wort extract (300 mg, 3 times a day) Control: placebo Duration of treatment: 6 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D score), depressive reductive rate (unclear from translation), pharmacological side effects Other outcomes: ventricular function (Tei-Index)
Funding	Unclear
Notes	Comment: translated paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No sufficient information provided
Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided Quote from translation: "placebo-control and blind evaluation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided. HAMD was described as a self-rated measure of depression Quote from translation: "placebo-control and blind evaluation"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias)	Unclear risk	Comment: No sufficient information provided

Li 2005 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Comment: No sufficient information provided
Other bias	Unclear risk	Comment: translated paper

Liu 1999

Study characteristics	
Methods	RCT design: parallel-group trial Total N randomised: unclear Length of follow-up: 4 weeks Analysis: unclear
Participants	Location: China Number of study centres and setting: patients from 1 hospital CAD diagnosis: MI as confirmed by electrocardiography Depression diagnosis: Center for Epidemiologic Studies - Depression Scale (CES-D), HAM-D, diagnosis according to Chinese Classification of Mental Disorders, Second Edition, Revised (CCMD-2-R) Other entry criteria: unclear Exclusion criteria: unclear Treatment N: 31 (32% female, mean age unclear) Control N: 37 (27% female, mean age unclear) Comparability of groups: no significant differences
Interventions	Treatment: fluoxetine Control: placebo Duration of treatment: 4 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression response, all-cause mortality, cardiac events Other outcomes: heart rate variability
Funding	Unclear
Notes	Comment: translated paper

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No sufficient information provided

Liu 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided Quote: "double-blind controlled trial" (pg. 210)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Selective reporting (reporting bias)	Unclear risk	Comment: No sufficient information provided
Other bias	Unclear risk	Comment: translated paper

Liu 2016

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 149 Length of follow-up: no follow-up Analysis: unclear (27 dropouts in the treatment group, 28 dropouts in the control group)
Participants	Location: China Number of study centres and setting: single centre, Cardiology of Harbin Medical University Hospital Department CAD criteria: MI in the past month (diagnosis of acute MI according to the Braunwald standard of cardiology); MI patients must comply with symptomatic myocardial ischaemia, and the ECG appears to ischaemic ST-segment decline or the ST segment elevation or the new pathological Q wave, myocardial enzyme changing observed, such as elevated serum creatine kinase CK-MB, increased lactate dehydrogenase (LDH1), increased CK (CPK) Depression criteria: depression score HAM-D ≥ 18 Other entry criteria: none Exclusion criteria: (1) Those suffering from cardiovascular disease: (1.1) acute MI caused by non-atherosclerotic disease; (1.2) uncontrollable hypertension (systolic BP > 180 mmHg or diastolic BP > 100 mmHg); (1.3) less than 3 months after arterial bypass surgery; (1.4) suffering from arrhythmia; (1.5) suffering from non-arterial sclerosis (such as anaemia). (2) Those suffering from other somatic diseases: (2.1) an obvious laboratory examination exception; (2.2) distinct hepatic and renal dysfunction; (2.3) with a history of allergies to sertraline, hyperforin, and acanthopanax.

Liu 2016 *(Continued)*

	(3) Those suffering from mental illness: (3.1) with alcohol or other substance abuse in the last 6 months; (3.2) with psychotic symptoms, psychiatric history or suffering from bipolar disorder, organic mental disorder, dementia, and other diseases; (3.3) frequently receiving benzodiazepines; (3.4) receiving psychological treatment in the last 3 months; (3.5) with suicide attempts; (3.6) receiving monoamine oxidase inhibitor in the last 4 weeks; (3.7) if the patient has a suicide attempt or the depressive symptoms are aggravated in the course of treatment, the psychiatrist would advise the patient to quit the experiment; (3.8) with a history of depression and the HAM-D24 score higher than 35 before MI. Treatment N: 73 (43.4% female, mean age: 53.4 (SD: 10.3)) Control N: 76 (41.1% female, mean age: 54.1 (SD: 10.8)) Comparability of groups: no significant baseline differences
Interventions	Treatment: sertraline + placebo of Shugan Jieyu capsule treatment Control: Shugan Jieyu capsule + sertraline placebo Duration of treatment: 24 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), all-cause mortality, cardiovascular vital signs (BP, HR), ECG waves, pharmacological side effects Other outcomes: clinical global impression, number needed to treat for non-inferiority
Funding	None
Notes	Inconsistency in HAM-D change scores. No significant differences between trial arms were reported, but the data suggest otherwise (likely standard error instead of standard deviation reported). No contact possible in order to clarify results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients were numbered chronologically and then labeled by a random number." (p.535) Comment: Group allocation via odd or even number
Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided Quote: "We used the double-blind experiment..." (pg. 537)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: data-analysis paragraph is missing, insufficient information on data-analysis (ITT/per protocol) and missing data handling procedure
Selective reporting (reporting bias)	Unclear risk	Comment: No study protocol available; assessment points described (see below) do not correspond with results

Liu 2016 *(Continued)*

Other bias	High risk	Comment: data on assessments at 4, 8 and 24 weeks are missing; available results are based on week 12 (middle of the treatment). End of treatment (week 24) not reported

Ma 2019

Study characteristics	
Methods	RCT design: 2-arm parallel trial Total N randomised: 312 Length of follow-up: no follow-up Analysis: per-protocol (3 dropouts in treatment group, 2 dropouts in control group)
Participants	Location: China Number of study centres and settings: patients who were in hospital cardiac centre CAD criteria: CAD confirmed by coronary angiography Depression entry criteria: HADS Anxiety or HADS Depression score ≥ 8 Other entry criteria: Han ethnicity, at least junior middle school level of education Exclusion criteria: chest pain originating from a stomach complaint; sympathetic ganglia compression in the neck; atrial fibrillation; rapid arrhythmia; ejection fraction < 35% by echocardiography; severe liver, kidney, nerve, or coagulation dysfunction; pregnant or lactating women; suspected aortic dissection; previously diagnosed psychiatric patients (including bipolar disorder, manic depression, psychosis, schizophrenia, suicidal tendencies); allergy to Xinkeshu Treatment: 30 (66.67% male, mean age: 61 (SD: 11)) Control: 30 (56.67% male, mean age: 66 (SD: 11)) Comparability of groups: no significant baseline differences
Interventions	Treatment: Xinkeshu (4 tablets, 3 times a day) Control: placebo Duration of treatment: 12 weeks
Outcomes	Review outcomes: depression symptoms (HADS Depression, PHQ-9), platelet biomarkers, pharmacological side effects Other outcomes: HADS Anxiety, cytokine levels
Funding	National Natural Science Fund and Guangdong Provincial People's Hospital Fund
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Conflicting report of randomization in the study "random number table" and trial registration "expert bronze camel random envelope method"

Ma 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information provided on allocation concealment Quote: "Randomization was blinded to both the patient and investigator" (pg. 2)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Insufficient information provided on performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Depression outcome is self-reported. Otherwise, insufficient information provided on outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Out of 60 patients, 2 patients did not complete the intervention (1 patient in each group). 3 patients did not complete the intervention (2 patients in the intervention group, and 1 patient in the control group. The reasons for patients who did not complete the intervention were stated in the result section
Selective reporting (reporting bias)	High risk	Comment: drug safety data reported inadequately and cytokine data not reported as either per protocol or ITT
Other bias	High risk	Comment: this trial was registered retrospectively after recruitment had commenced ChiCTR-IPR-17010940

McFarlane 2001

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 38 Length of follow-up: no follow-up Analysis: per-protocol (6 dropouts in the intervention group, 5 dropouts in the control group)
Participants	Location: Canada Number of study centres and setting: patients admitted to 1 coronary care unit CAD criteria: acute MI; assessment method and time to randomisation not specified Depression criteria: score > 15 on the Inventory to Diagnose Depression (IDD) questionnaire on 2 occasions (just before hospital discharge and 2 weeks later) Other entry criteria: none stated Exclusion criteria: predischarge 24-hour Holter recordings showing either atrial fibrillation or ventricular etopic beats greater than 100 per hour, congestive heart failure, any life-threatening comorbid condition, inability to complete the questionnaire, and taking antidepressant medication Treatment N: 12 (33% female, mean age: 56 (SD: 11)) Control N: 15 (47% female, mean age: 56 (SD: 12)) Comparability of groups: no significant baseline differences

McFarlane 2001 *(Continued)*

Interventions	Treatment: sertraline (50 mg/d) Control: placebo Duration of treatment: 22 weeks
Outcomes	Review outcomes: depression symptoms (IDD), all-cause mortality, cardiovascular vital signs (HR) Other outcomes: HR variability (SD of all 24-hour N-N intervals, root mean square of the SD of successive N-N intervals, low frequency/high frequency ratio, low frequency power in normalised units)
Funding	Heart and Stroke Foundation of Ontario, Canada
Notes	The intervention trial was nested in a study inclusive of a non-depressed comparator group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No sufficient information provided
Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided Quote: "double-blind, randomized, placebo-controlled trial" (pg. 618)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 11 drop-outs (3 had side-effects, 7 non-compliant, 1 with ectopy)
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol or design paper available Comment: Outcomes reported according to methods section
Other bias	Unclear risk	Comment: Inconsistent description of depression change results (p. 619 and p. 620)

McLaughlin 2005

Study characteristics

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: 4 months Analysis: per-protocol (8 treatment participants dropped out, 12 control participants dropped out)

McLaughlin 2005 *(Continued)*

Participants	Location: USA Number of study centres and setting: patients with ACS from 2 hospitals CAD diagnosis: ACS assessed by medical chart review in the coronary care unit; time to randomisation not specified Depression diagnosis: score of 7 and more on either subscale of the HADS Other entry criteria: 35 years of age or older, able to speak English, access to a touch-tone phone Exclusion criteria: mental health care in the prior 3 months, psychoactive drug use during the past year, and diagnosis of substance abuse during the past year Treatment N: 45 (31.1% female, mean age: 59.9 (SD: 10.2)) Control N: 34 (35.3% female, mean age: 60.7 (SD: 9.8)) Comparability of the groups: significantly higher anger scores amongst females in the treatment group, significantly more participants with MI in the treatment group
Interventions	Treatment: 6 telephone counselling sessions (30 minutes each) with clinicians (psychiatrist, clinical psychologist, internist) comprising review of common fears experienced by those living with chronic medical conditions and identification and management of barriers to adjustment to medical illness; participants with HADS score > 15 were referred for emergent care Control: usual care (received a booklet on coping with cardiac illness typical of those given at hospital discharge and were instructed to contact their primary care physician if they experienced any warning signs of depression; advised to continue follow-up with their primary care and specialist physicians) Duration of treatment: 8 weeks
Outcomes	Review outcomes: depression symptoms (HADS), all-cause mortality Other outcomes: anxiety symptoms (HADS), Work and Social Adjustment Scale (WSAS), State-Trait Anger Expression Inventory (STAXI), clinical global impressions
Funding	National Institute of Mental Health, USA; Robert Wood Johnson Foundation
Notes	Mixed study sample (patients with depression and/or anxiety)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "by coin flip" (p. 1085 in McLaughlin et al., 2005)
Allocation concealment (selection bias)	High risk	Quote: "The study coordinator conducted the coin flip and assigned patients to a treatment arm when she contacted study participants by telephone and enrolled consenting participants." (p. 540 in Bambauer et al., 2005)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No sufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Primary outcome was patient self-report measure (HADS); other blinding not stated

McLaughlin 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: The authors describe that multiple imputation methods were used to examine if data were missing at random. But all analyses were reported for the final cohort of 79 patients
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol and design paper available Comment: outcomes consistent in methods and results sections
Other bias	Unclear risk	Comment: weekly meetings and supervision of counsellors; monitoring quality not otherwise specified Comment: depression data reported as β value unit change and final HADS depression scores post-treatment

MIND-IT 2007

Study characteristics	
Methods	RCT design: nested, 3-arm parallel-group trial Total N randomised: 91 Length of follow-up: no follow-up Analysis: ITT (10 dropouts in the intervention group, 3 dropouts in the placebo group during the first 8-week acute treatment phase; 23 dropouts in the intervention group, 15 dropouts in the placebo group during the entire treatment (24 weeks))
Participants	Location: Netherlands Number of study centres and setting: patients with a MI from 8 hospitals CAD criteria: MI with typical clinical picture, increase of cardiac enzymes, ECG changes and chest pain for > 20 minutes; time to randomisation 3 to 12 months (to exclude adjustment disorders) Depression criteria: 2-stage procedure, in which those with 1) score of 10 or more on the BDI were 2) interviewed with the Composite International Diagnostic Interview (CIDI) for major or minor depression diagnosis (psychiatrist confirmed CIDI diagnosis) Other entry criteria: age >= 18 years Exclusion criteria: occurrence of MI whilst hospitalised for another reason except for unstable angina pectoris, lacking capability to participate in study procedures, any disease likely to influence short-term survival, already receiving psychiatric treatment for depressive disorder, participation in any clinical trial that might intervene with the study, hyperthyroidism, suicidality Treatment N: 47 (12.8% female, mean age: 56.6 (SD: 11.1)) Control N: 44 (18.2% female, mean age: 57.9 (SD: 9.7)) Comparability of groups: no significant baseline differences
Interventions	Treatment: mirtazapine (30 to 45 mg/d); participants who did not respond and those with relapse were offered open treatment with citalopram Control 1: placebo Control 2: care as usual, pharmacological treatment, non-pharmacological treatment, or no treatment (not eligible for this review)

MIND-IT 2007 *(Continued)*

	Duration of treatment: 24 weeks (8 weeks acute plus 16 weeks continuation treatment)
Outcomes	Review outcomes: depression symptoms (HAM-D, also BDI, depression scale of the SCL 90), depression remission (HAM-D ≤ 7), all-cause mortality, cardiac events, hospitalisations, cardiovascular vital signs (BP, HR), platelet biomarkers, ECG waves, pharmacological side effects Other outcomes: clinical global impression, concurrent medication, weight
Funding	Netherlands Heart Foundation; Organon (Netherlands); Lundbeck (Denmark)
Notes	MIND-IT trial investigated antidepressant treatment in general versus usual care in patients following MI (N = 331). The intervention arm consisted of double-blind mirtazapine, open pharmacological treatment, non-pharmacological treatment, or no treatment. The care-as-usual arm comprised pharmacological treatment, non-pharmacological treatment, or no treatment. We used data for the nested trial investigating mirtazapine versus placebo (n = 91) in this review consistent with the predefined comparisons (i.e. pharmacological intervention vs placebo).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Central randomization service (computer-generated blocks of four)
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Insufficient information provided Quote: "double-blind" (Honig 2007, pg. 607)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information provided in primary nested-trial paper (Honig 2007). Quote: From protocol " A blinded end point committee will judge all possible primary end points" (van den Beek 2002, pg. 223)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT with last observation carried forward
Selective reporting (reporting bias)	Unclear risk	Comment: Results and methods section consistent in Honig (2007) Comment: Analysis of nested-study trial data not stated in protocol paper (van den Brink, 2002)
Other bias	Unclear risk	Comment: in the paper by Honig patients randomised to mirtazapine had higher baseline scores on depression (HAM-D, p = 0.05) which suggests possible baseline imbalance

MoodCare 2011

Study characteristics

Methods	RCT design: 2-arm parallel-group trial

MoodCare 2011 *(Continued)*

	Total N randomised: 121 Length of follow-up: 6 months, 18 months Analysis: ITT with last-observation-carried-forward (8 dropouts in intervention group, 7 dropouts in control group at 6-month follow-up)
Participants	Location: Australia Number of study centres and setting: multicentre; 6 metropolitan hospitals in the states of Victoria (Austin, St. Vincent's, Geelong, Royal Melbourne Hospitals) and Queensland (Royal Brisbane and Women's and The Prince Charles Hospitals). CAD criteria: clinical diagnosis of ACS (MI (ST segment elevation MI, STEMI or non-STEMI) or unstable angina confirmed by angiogram) Depression criteria: depression (PHQ-9) score of 5 to 19 Other entry criteria: age between 21 and 85, fluency in English, availability via the telephone for the duration of the study Exclusion criteria: regular psychological therapy with a mental health professional at the time of admission for ACS, diagnosis of mental health condition which may impact on involvement (including bipolar disorder, psychotic illness of any type, dementia, acute suicidality, severe personality disorder), cognitive impairment impacting ability to participate in the study, diagnosed with a terminal illness, unable to participate in a tele-based unsupervised mood and lifestyle intervention as confirmed by treating clinician Treatment N: 61 (26.2% female, mean age: 61.0 (SD: 10.2)) Control N: 60 (23.3% female, mean age: 58.9 (SD: 10.7)) Comparability of groups: no significant baseline differences except for a significantly higher proportion of participants in the treatment group being born in Australia and had visited a general practitioner in the past 6 months
Interventions	Treatment: CBT intervention with structured counselling sessions (2 weeks baseline screening delivered by qualified psychologists, intervention aims to manage depression as well as CHD risk factor behaviours using a tele-based care management model incorporating CBT counselling; psychologists with at least 2 years of experience deliver the intervention, content: cognitive restructuring, behavioural activation, goal setting, motivational interviewing techniques); participants received 10 sessions lasting 30 to 40 minutes, unless target recovery was achieved prior to programme completion (in this event, the interventionists reviewed the individual case with the senior clinical consultant, and if the participant produced a PHQ score in the normal range for 3 consecutive counselling sessions, after completing at least 4 sessions, the participant was considered to have met target recovery). Additonally, participants received a brief National Heart Foundation of Australia education pamphlet on MI recovery. Control: usual care and a brief National Heart Foundation of Australia education pamphlet on MI recovery Duration of treatment: 6 months
Outcomes	Review outcomes: depression symptoms (PHQ-9), quality of life (12-Item Short Form Health Survey) Other outcomes: cardiac depression (Cardiac Depression Scale), acceptability, feasibility
Funding	Australian Government Department of Health and Ageing
Notes	
Risk of bias	

MoodCare 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: automatically generated separate block randomization (integrated into web-based database), process concealed from investigators
Allocation concealment (selection bias)	Low risk	Comment: automatic group allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: randomisation schedule was concealed from investigators, participants were asked not to reveal the group to which they were randomised
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: project staff who administered telephone questionnaires were blinded to participans´study group. Primary outcome was a self-report measure (PHQ-9)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT
Selective reporting (reporting bias)	Low risk	Comment: Study protocol available and congruent
Other bias	Unclear risk	Comment: manualised intervention and therapist quality assessed by Cognitive Therapy Scale Comment: therapist adherence monitored by audiotape of phonecalls; only 17% reviewed by expert psychiatrist as specified in protocol

Pizzi 2009

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: 5 months Analysis: per-protocol (method of analysis not explicitly stated; 3 dropouts in the treatment group, 2 dropouts in the control group)
Participants	Location: Italy Number of study centres and setting: secondary care referral to visit the Department of International Medicine, Aging and Nephrological Diseases CAD criteria: documented CAD (diagnosis of at least 1 of the following: previous MI, previous or current angina with objective evidence of atherosclerosis, and a previous surgical procedure for coronary revascularisation) Depression criteria: symptoms of depression (BDI ≥ 10) Other entry criteria: none

Pizzi 2009 *(Continued)*

	Exclusion criteria: neoplasms, kidney or liver failure, systemic inflammatory disease, uncontrolled hypertension (systolic BP > 180 mmHg or diastolic BP > 100 mmHg), recent AMI or unstable angina, ejection fraction < 50%, current antidepressant treatment, current psychotherapy Treatment N: 47 (53.2% female, mean age: 57.4 (SD: 8.7)) Control N: 48 (47.9% female, mean age: 56.3 (SD: 8.2)) Comparability of groups: no significant baseline differences
Interventions	Treatment: sertraline (week 1 to 6: 50 mg daily, week 7 to 12: gradually increase to attain a maximum daily dose of 200 mg, depending on each participant's clinical response and tolerance, week 13 to 20: constant dose (= maximum of milligrams reached at the end of week 12) Control: placebo Duration of treatment: 20 weeks
Outcomes	Review outcomes: depression symptoms (BDI), depression response, platelet biomarkers, pharmacological side effects Other outcomes: inflammatory markers, flow-dependent endothelium-mediated dilation
Funding	No information provided.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Randomisation carried out by a central office, no other information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: No sufficient information provided, steps taken to conceal the allocation unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Double-blind trial, researchers were blind to patients group allocation during recruitment, data collection and data analyses, physicians who were not involved in the study design performed treatment assignment and implementation of the therapy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Self-reported primary outcome (BDI); no other information on blinded outcome assessments for biomarkers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Low drop-out, authors reported reasons for early drop-out per group
Selective reporting (reporting bias)	Unclear risk	Comment: No study protocol available but mentioned (p.531)
Other bias	Low risk	Comment: No indication of other bias

Roose 1998

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 81 Length of follow-up: no follow-up Analysis: ITT (4 paroxetine participants discontinued, 10 nortriptyline participants discontinued)
Participants	Location: USA Number of study centres and setting: outpatients from 4 hospitals CAD criteria: MI, CABG, coronary angioplasty, positive stress test, or angiographic evidence of a 75% or greater luminal narrowing of a major coronary artery; time to randomisation unclear Depression criteria: meeting DSM-IV criteria for major depressive disorder, unipolar subtype, with a score of 16 or greater on the 17-item HAM-D Other entry criteria: age >= 18 Exclusion criteria: MI within the past 3 months, a baseline QTc interval of 460 milliseconds or greater, unstable or crescendo angina, receiving drugs with class 1 antiarrhythmic activity or warfarin Treatment 1 N: 41 (12% female, mean age: 57.8 (SD: 11.0)) Treatment 2 N: 40 (22% female, mean age: 57.9 (SD: 12.7)) Comparability of groups: no significant baseline differences
Interventions	Treatment 1: paroxetine (+ dummy placebo at night) (age < 65: 20 mg/d for the first 3 weeks; age > 65: 10 mg/d for the first week, 20 mg/d for week 2 and 3; if no response (HAM-D reduction 50% or HAM-D <= 8), 30 mg/d at week 4 and 40 mg/d at end of week 5) Treatment 2: nortriptyline (+ dummy placebo in the morning) (25 mg for the first 2 days; 50 mg on day 3; on day 7 plasma level measurement and adjustment of the dose to achieve a nortriptyline plasma level between 203 and 456 nmol/L (80 to 120 ng/mL)) Duration of treatment: 6 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression remission (HAM-D ≤ 8), depression response (50% reduction on HAM-D), cardiac events, cardiovascular vital signs (BP, HR), ECG waves, pharmacological side effects Other outcomes: heart rate variability (SDNN, pNN50), ventricular premature depolarisations
Funding	Smith-Kline Beecham Pharmaceuticals (GlaxoSmithKline)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized by permuted blocks of 10" (p. 288)
Allocation concealment (selection bias)	Unclear risk	Comment: Reported as a double-blind study; no other details reported

Roose 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Reported as a double-blind study; with "double dummy" blinding described for patients and physicians and other raters Quote: "To ensure that the treating physician and other raters remained unaware of drug administration, the nortriptyline dose was adjusted by a physician who was not involved in the study" and "the blind was maintained by selecting, on a random basis, patients receiving active paroxetine to have their nortriptyline placebo increased or decreased to mimic the dose adjustment for patients re3cigving active nortriptyline" (Roose 1998, pg. 288)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Reported as a double-blind study; no other details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT with last observation carried forward
Selective reporting (reporting bias)	Unclear risk	Comment: Results and methods section consistent Comment: No protocol or design paper available
Other bias	High risk	Comment: authors of the study involved in design, analysis and reporting were employees of SmithKline Beecham Pharmaceuticals PA

SADHART 2002

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 369 Length of follow-up: no follow-up Analysis: ITT (53 discontinued treatment, 46 discontinued placebo)
Participants	Location: USA, Europe, Canada, Australia Number of study centres and setting: outpatients from 40 cardiology centres and psychiatry clinics CAD criteria: patients hospitalised for MI or unstable angina in the past 30 days. Criteria for acute MI: at least 1 criterion from each of the following 2 categories: Category A: 1) creatine kinase isoenzyme MB (CK-MB) level greater than the upper limit of normal, 2) CK or troponin T or troponin 1 level more than 2 times the upper limit of normal, 3) a total lactate dehydrogenase (LDH) level more than 1.5 times the upper limit of normal (with LDH 1 greater than LDH 2). Category B: 1) typical ischaemic symptoms (chest pain or shortness of breath) lasting for more than 10 minutes, 2) ECG evidence of ischaemic ST-segment depression, ST-segment elevation, or new pathological Q waves. Criteria for unstable angina: 1) experienced angina of anginal equivalent symptoms at rest, with episodes lasting for at least 10 minutes and leading to hospitalisation, and had ECG documentation of transient ST-segment elevation or depression of more than 0.5 mm, or had T wave inversion of greater than 1 mm within 12 hours of an episode of chest pain; 2) were hospitalised for symptoms of unstable angina and had known CAD with a documented history of a prior MI, had undergone a prior revascularisation procedure, or had documented coronary artery stenosis greater than 75% in 1 of the major epicardial vessels Depression criteria: major depression according to structured Diagnostic Interview Schedule (DIS) for DSM-IV, BDI score of 10 or greater Other entry criteria: none

SADHART 2002 *(Continued)*

	Exclusion criteria: uncontrolled hypertension, cardiac surgery anticipated during the next 6 months, MI or unstable angina developed less than 3 months after CABG, resting heart rate of less than 40/min, MI or unstable angina of non-atherosclerotic aetiology, Killip class III or IV status, persistent clinically significant laboratory abnormalities, renal dysfunction, hepatic dysfunction, other significant non-cardiac disease, women of childbearing potential not using adequate contraception, current use of class 1 antiarrhythmic medications, use of reserpine, guanethidine, clonidine, methyldopa, anticonvulsants, neuroleptics, antidepressants, benzodiazepines, initiation of psychotherapy in the 3 months prior to study entry, alcohol or substance abuse or dependence in past 6 months, psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, dementia, significant suicide risk Treatment N: 186 (37% female, mean age: 56.8 (SD: 11.1)) Control N: 183 (36% female, mean age: 57.6 (SD: 10.4)) Comparability of groups: no significant baseline differences
Interventions	Treatment: sertraline 50 mg/d for the first 6 weeks, up to 100 mg/d for weeks 6 to 10, up to 150 mg/d for weeks 10 to 12, up to 200 mg/d for weeks 12 to 24 Control: placebo Duration of treatment: 24 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression response, all-cause mortality, cardiac events, healthcare costs, hospitalisations, quality of life (Quality of Life Enjoyment and Satisfaction scale (Q-LES-Q, Medical Outcomes Study Short-Form 36), cardiovascular vital signs, platelet biomarkers, ECG waves, pharmacological side effects Other outcomes: left ventricular function, ventricular premature complexes, heart rate variability, clinical global impression
Funding	Pfizer Inc; Suzanne C. Murphy Foundation; Thomas and Caroline Royster Research Fund; Perry and Martin Granoff Family Foundation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: Single-blind placebo treatment preceded double-blind randomization to intervention or placebo
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Single-blind placebo treatment preceded double-blind randomization to intervention or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Serious adverse events and ECG reporting blinded to treatment allocation; other outcomes unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Last observation carried forward

SADHART 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: No protocol or design paper available
Other bias	High risk	Comment: author involved in design, analysis and reporting of data was an employee of Pfizer

Shahmansouri 2014

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 44 Length of follow-up: 6 weeks Analysis: per-protocol, method of analysis not explicitly stated (4 dropouts, 2 in each group)
Participants	Location: Iran Number of study centres and setting: Psychiatric Clinic of Tehran Heart Center CAD criteria: PCI in the last 6 months Depression criteria: patients who met DSM IV-TR criteria for diagnosis of MDD (mild-moderate); HAM-D = 14 to 22 Other entry criteria: 20 to 65 years of age Exclusion criteria: diagnosis of any other psychiatric disorder on the DSM-IV axis I or II; patients receiving any other psychotropic medications; patients at high risk for suicide (score ≥ 2 on the suicide item of HAM-D) were referred to a psychiatrist and were not enrolled in this study. Patients were also excluded if they had received psychotropic agents, alternative medicine, or psychotherapy within 4 weeks or electroconvulsive therapy within 8 weeks prior to entry. Other exclusion criteria were substance abuse or dependence (other than nicotine) within 3 months, serious or life-threatening illness, thyroid disease, hepatic or renal dysfunction, hypersensitivity to fluoxetine or herbal compounds, pregnancy, lactation, and oral contraception use. Women of child-bearing age were excluded if they were willing to get pregnant. Treatment N: 22 (50.0% female, mean age 52.05 (SD: 8.92)) Control N: 22 (63.6% female, mean age: 53.10 (SD: 8.47)) Comparability of groups: no significant baseline differences
Interventions	Treatment 1: saffron (SaffroMood, IMPIRAN, containing 15 mg of saffron extract); participants would receive 1 capsule every other day for the first week followed by 1 capsule daily for the second week and 2 capsules per day for the rest of the study, for a maximum dose of 30 mg/day Treatment 2: fluoxetine (Abidi, Iran, 20 mg capsule); participants would receive 1 capsule every other day for the first week followed by 1 capsule daily for the second week and 2 capsules per day for the rest of the study, for a maximum dose of 40 mg/day Duration of treatment: 6 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression response (50% HAM-D symptom reduction), depression remission (HAM-D < 8), pharmacological side effects
Funding	Tehran University of Medical Sciences; IMPIRAN company donated the capsules of SaffroMood

Shahmansouri 2014 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Random permuted blocks of four, patients were randomly and equally assigned to two groups (fluoxetine or SaffroMood) in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	Comment: An independent person who was not involved elsewhere in the research project generated the randomization codes by Excel software. Assignments were kept in sequentially numbered, sealed, opaque envelopes and were opened sequentially only after participant details were written on the envelope. Separate persons were responsible for rating and random allocation of the patients.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: The patients and their caregivers, the clinician who referred them, the research team investigators who rated the participants and prescribed the medications, and the statistician were all blind to the treatment group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: The patients and their caregivers, the clinician who referred them, the research team investigators who rated the participants and prescribed the medications, and the statistician were all blind to the treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Low attrition, no ITT
Selective reporting (reporting bias)	Low risk	Comment: Study protocol available and congruent with reported outcomes
Other bias	Low risk	Comment: No indication of other bias

SPIRR-CAD 2011

Study characteristics

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 570 Length of follow-up: 6 months Analysis: ITT (last-observation-carried-forward) and per-protocol analysis (24 did not receive intervention; 174 dropouts in intervention group, 90 dropouts in usual care group)
Participants	Location: Germany Number of study centres and setting: multicentre; 10 tertiary care centres in Germany CAD criteria: documented CAD with recent coronary angiograms Depression criteria: HADS Depression > 7 Other entry criteria: none

SPIRR-CAD 2011 *(Continued)*

	Exclusion criteria: inability to speak German; severe heart failure (NYHA class IV); scheduled cardiac surgery within the next 3 months; severe depressive episodes according to Structured Clinical Interview for DSM-IV (SCID) or other severe life-threatening physical or mental illness Treatment N: 285 (21.4% female, mean age 59.1 (SD: 9.8)) Control N: 285 (20.7% female, mean age 59.3 (SD: 9.3)) Comparability of groups: no baseline-differences in sociodemographic, clinical, and psychological data
Interventions	Treatment: stepwise, fully manualised individual and group psychotherapy in addition to usual care by primary physicians or cardiologist, or both. All participants were offered 3 individual supportive-expressive psychotherapy sessions. Participants' partners were invited for the third session. All participants were reassessed with the HADS after the third session (4 to 6 weeks after inclusion), and those who were still depressed were offered 25 90-minute sessions of group psychotherapy in closed groups of 6 to 10 participants for approximately 10 months, usually starting 3 to 6 months after randomisation. Control: usual care by primary physicians and/or cardiologist and 1 manualised individual information session, 30 to 45 minutes delivered by trained staff (content of information session: healthy behaviours and psychosocial factors in CAD) Duration of treatment: 18 months
Outcomes	Review outcomes: depression symptoms (HAM-D, also HADS), depression remission (HADS ≤ 7), all-cause mortality, cardiovascular mortality Other outcomes: type D personality
Funding	German Research Foundation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Online randomization service, ALEA, 1:1 ratio
Allocation concealment (selection bias)	Low risk	Comment: sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "blinding of the intervention to patients and therapists was not possible" Comment: control participants received information session
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Outcome assessments were performed by patients self report (HADS) and face-to-face interviews (HAMD, SCID) with trained raters who where masked regarding patients treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: analyses ITT with and without imputation LOC method (per-protocol also reported, not extracted) Comment: imbalance in loss to follow-up between groups (174 drop-outs in intervention group (61.3%), 90 drop-outs in usual care group (31.7%))
Selective reporting (reporting bias)	Unclear risk	Comment: not all secondary outcomes are reported as yet

SPIRR-CAD 2011 *(Continued)*

Other bias	Unclear risk	Comment: changes made from protocol during trial to intervention of implementation i.e. group psychotherapy could commence more than 8 weeks after randomisation Comment: trial fidelity and therapist adherence described in Albus 2011

Strik 2000

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 54 Length of follow-up: no follow-up Analysis: ITT for primary outcomes (9 withdrawn from control group, 5 withdrawn from treatment group), per-protocol for cardiologic safety variables
Participants	Location: Netherlands Number of study centres and setting: patients from 2 hospitals CAD criteria: MI diagnosed by a cardiologist with a clinical picture typical of MI, electrocardiographic changes specific for MI, and a maximum plasma concentration of aspartate aminotransferase (ASAT) of twice the upper normal range (80 units/litre); enrolment 3 to 12 months after MI Depression criteria: patients with a score above the cut-off on the SCL-90 Depression Scale (> 22 for men and > 28 for women) were interviewed with the Schedules for Clinical Assessment in Neuropsychiatry; patients meeting DSM-III-R criteria for major depressive episode and having a HAM-D score of > 17 were included Other entry criteria: 18 to 75 years of age Exclusion criteria: any concurrent psychosocial or therapeutic intervention, psychotic symptomatology, a second psychiatric diagnosis, history of mania, current pregnancy or lactation, life-threatening non-cardiac physical illness, concurrent use of psychotropic drugs, hypersensitivity to fluoxetine, liver or severe kidney dysfunction, right ventricular filling pressure > 30 mmHg and a low systolic volume or an ATVI < 10 cm Treatment N: 27 (22% female, mean age: 54.1 (SD: 11.3)) Control N: 27 (37% female, mean age: 58.7 (SD: 10.1)) Comparability of groups: no significant baseline differences
Interventions	Treatment: fluoxetine (acute treatment period of 9 weeks and continuation period of 16 weeks; 20 to 60 mg/d) Control: placebo Duration of treatment: maximum of 25 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), depression remission (HAM-D < 7), cardiac events, resource utilisation (hospitalisation), cardiovascular vital signs (BP, HR), ECG waves, pharmacological side effects Other outcomes: SCL-90 Hostility Scale score, concurrent use of medications, cognitive performance, echocardiography (LVEF, ATVI, E/A ratio)

Strik 2000 *(Continued)*

Funding	Eli Lilly, Dutch Prevention Fund, Maastricht University Hospital Research Fund
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No details reported
Allocation concealment (selection bias)	Unclear risk	Comment: No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" (pg. 785)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" (pg. 785)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 14 patients meeting inclusion criteria did not complete the trial, but did not differ from participants in age, gender, or maximum ASAT Comment: Intention-to-treat for primary outcomes
Selective reporting (reporting bias)	High risk	Comment: Many outcomes not or only partially reported Comment: No protocol or design paper available
Other bias	Low risk	Comment: No indication of other bias

Tian 2016

Study characteristics

Methods	RCT design: 3-arm parallel-group trial nested within observational cohort Total N randomised: 46 (not including inactive comparator) Length of follow-up: no follow-up Analysis: per-protocol (attrition per group allocation not specified; 16/308 recruited patients dropped out)
Participants	Location: China Number of study centres and setting: patients from Coronary Care Unit in Qian Fo Shan Hospital of Shandong University Medical School CAD criteria: acute MI with: ischaemic chest pain for > 30 minutes but < 24 hours, persistent ST-segment elevation >= 0.1 mV, ST-segment depression or T-wave inversion in 2 adjacent electrocardiography leads, and significantly elevated blood levels of biomarkers for myocardial injury (creatine kinase-MB and troponin I)

Tian 2016 *(Continued)*

	Depression criteria: patients with a score above the cut-off on the HAM-D-17 and a self-test score using the Self-Rating Depression Scale (cut-off not specified) Other entry criteria: none specified Exclusion criteria: more than 85 years old, infection, allergic disorder, endocrine disease, malignancy, autoimmune disease, rheumatic heart disease, severe liver disease, renal failure, history of drug abuse, or having been prescribed an anti-inflammatory or immunosuppressant drug except aspirin in the past 3 weeks prior to MI. Other comorbid heart diseases ineligible (atrial fibrillation, myocarditis, endocarditis, valvular heart disease, or requirement of an implanted pacemaker) Treatment 1: paroxetine N: 27 (43% female, mean age: 63.4 (SD: 10.7)) Treatment 2: fluoxetine N: 27 (48% female, mean age: 61.7 (SD: 10.4)) Comparability of groups: no significant baseline differences evident
Interventions	Treatment 1: paroxetine: 10 mg/d initially and increased to 20 mg/d within 1 week Treatment 1: fluoxetine: 10 mg/d initially and increased to 20 mg/d within 1 week Duration of treatment: 8 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), cardiac events, cardiovascular vital signs (BP)
Funding	Tackle Key Problems in Science and Technology Program of Shandong Province
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: No sufficient information provided
Allocation concealment (selection bias)	Unclear risk	Comment: stated as randomized, double-blind study with no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: stated as randomized, double-blind study with no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Psychiatrists rated depression (HAMD) at baseline after myocardial infarction, no information provided on follow-up assessments or blinding to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No flow chart or reasons for attrition provided
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol paper or trial registry
Other bias	High risk	Comment: no trial registry provided for this trial

TREATED-ACS 2020

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: 30 months Analysis: ITT and imputation not specified (8 dropouts from intervention group, 10 dropouts from CM group)
Participants	Location: Italy Number of study centres and setting: Maggiore Hospital in Bologna and San Giovanni Battista Hospital in Torino CAD criteria: first episode of acute MI or unstable angina. MI defined by cardiac symptoms (presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent non-cardiac source) and signs (acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes) associated with ECG findings (characteristic evolutionary ST-T changes or new Q waves) and/or cardiac biomarkers (blood measures of myocardial necrosis, specifically CK, CK-MB, CK-MBm, or troponin, cTn). Unstable angina defined by cardiac symptoms (chest pain lasting less than 20 minutes) with likely ECG findings (ST-segment depression and abnormal T-wave) in the absence of myocardial necrosis biomarkers Depression criteria: a current diagnosis of at least 1 of the following: major or minor depression, dysthymia according to DSM-IV criteria, and demoralisation according to Diagnostic Criteria for Psychosomatic Research criteria Other entry criteria: Mini-Mental State Examination score higher than 24, written informed consent provided by the patient to participate Exclusion criteria: history of bipolar disorder (DSM-IV criteria), major depression with psychotic features, history of substance abuse or dependency during the previous 12 months, serious suicide risk, current use of antidepressants, current treatment with any form of psychotherapy
Interventions	Intervention 1: CBT in combination with WBT and lifestyle modification. CBT involves: identifying and correcting inaccurate thoughts associated with depressed feelings (cognitive restructuring); helping participants to engage in enjoyable activities more often (behavioural activation); enhancing problem-solving skills; providing instruction and guidance in specific strategies for solving problems. WBT involves techniques to overcome impairments in environmental mastery, purpose in life, personal growth, autonomy, self-acceptance, and positive relations with others. Lifestyle modification not further specified. Intervention 2: clinical management, consisting of reviewing the participant's clinical status and providing the participant with support and advice if necessary
Outcomes	Primary: depression symptoms measured by Paykel's 20-item change version of the Clinical Interview for Depression (CID). Depressive symptoms subscale of Kellner's Symptom Questionnaire Secondary outcomes: frequency of negative cardiac outcomes, such as rehospitalisations due to cardiac complications, acute MI, unstable angina, angioplasty, cardiac surgery, and cardiac mortality occurring after the first episode of ACS
Funding	Compagnia di San Paolo di Torino, Italy
Notes	https://clinicaltrials.gov/ct2/show/NCT00998400

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

TREATED-ACS 2020 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: Treatment allocation was accomplished through random computerized assignment that allocated 50% of the patients to each treatment group, not further specified
Allocation concealment (selection bias)	Unclear risk	Comment: Assignment concealed until the time of group assignment, not further specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Outcomes included self-report and structured interviews, as well as biomarkers. Assignment concealed until the time of group assignment; blinding not further specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Patients were assessed by 2 clinical psychologists, who were blind to treatment assignment, at pretreatment and posttreatment, and 3, 6, 12, and 30 months after the end of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 of 48 patients in each group dropped-out from baseline to end of treatment, and 22 patients total dropped-out before 30-month follow-up Comment: All analyses were performed by using intention-to-treat analysis, where missing values were managed by means of a multiple-imputations procedure
Selective reporting (reporting bias)	Low risk	Comment: All outcomes stated in the methods section and trial registry NCT00998400 were reported Comment: Biomarker analyses included in the paper were not stated in the trial registry NCT00998400 Comment: No design paper available
Other bias	Unclear risk	Comment: exact p values not reported for baseline comparisons between intervention groups. Possible imbalance at baseline, psychotherapy group taking less cardiac medications and reporting more personal growth; psychotherapy group reporting more depression + demoralisation Comment: therapists trained in intervention; no efforts regarding therapy quality mentioned

U-CARE 2018

Study characteristics	
Methods	RCT design: 2-arm parallel design Total N randomised: 3928 Length of follow-up: 14 weeks Analysis: ITT with multiple imputation by chained equations for depression, ITT without missing data for cardiovascular mortality and cardiac events (28 dropouts intervention group, 10 dropouts control group at 12 months)
Participants	Location: Sweden Number of study centres and settings: 25 Swedish hospitals CAD criteria: recent MI < 3 months

U-CARE 2018 *(Continued)*

	Depression entry criteria: > 7 on 1 or both of the 2 HADS subscales Other entry criteria: < 75 years old Exclusion criteria: scheduled for coronary artery bypass surgery; unable to use computer, internet, email, or mobile phone; unable to read Swedish; expected to live < 1 year; anticipated to show poor compliance (e.g. substance abuse or not showing up to the cardiac nurse visit); self-reported severe depression or suicidal ideation (MARDS-S total score > 34 or MARDS-S item 9 > 3); participating in another behavioural intervention trial Treatment: 117 participants (44% women, mean age: 58.4 (SD: 9)) Control: 122 participants (36% women, mean age: 60.8 (SD: 7.8)) Comparability of groups: no significant baseline differences
Interventions	Treatment: therapist-guided internet CBT treatment Control: usual treatment Duration of treatment: 14 weeks
Outcomes	Review outcomes: depression symptoms (Montgomery–Åsberg Depression Rating Scale, also HADS), cardiovascular mortality, cardiac events Other outcomes: anxiety symptoms (HADS Anxiety), behavioural activation (Behavioral Activation for Depression Scale), cardiac anxiety (Cardiac Anxiety Questionnaire), adherence to treatment
Funding	Swedish Research Council
Notes	Mixed study sample (patients with symptoms of depression or anxiety were recruited)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: sequence generation with stratification by clinical centre Quote "1:1 allocation, using a computer-generated code"
Allocation concealment (selection bias)	Unclear risk	Comment: Randomization occurred automatically in the internet-based portal
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: technical and telephone support staff blind to allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no details on outcome assessment blinding; primary outcomes self-reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Intention-to-treat as the main analysis. Reasons for drop-out not provided in Norlund or Humphries
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes reported (depression and anxiety) Comment: secondary endpoints in protocol not yet reported - quality of life, stress behaviors, fatigue, sleep pattern, posttraumatic stress, posttraumatic

U-CARE 2018 *(Continued)*

		growth, health economy aspects, cost-effectiveness of the intervention, major adverse cardiac events
Other bias	High risk	Comment: There was a change in the inclusion criteria during the study due to low recruitment numbers. The HADS threshold was lowered from ≧10 to >7 on any subscale of the HADS. The recruitment target in the protocol was 500 (eventual recruitment n = 239) Comment: manualised treatment (online) and therapist support was provided for the online modules in patients allocated to treatment; no information on therapists adherence or quality Comment: email and telephone prompts provided; unclear if to intervention and control groups

UPBEAT 2012

Study characteristics	
Methods	RCT design: 3-arm parallel-group trial Total N randomised: 101 Length of follow-up: no follow-up Analysis: ITT with multiple imputation (4 dropouts from intervention group, 1 dropout from control group)
Participants	Location: USA Number of study centres and setting: physician referrals, community-based screenings, mass media advertisements CAD criteria: documented CHD (e.g. prior MI, revascularisation procedure, or significant (> 70% stenosis) coronary atherosclerosis) Depression criteria: BDI ≥ 7 Other entry criteria: age 35 years or older Exclusion criteria: presence of another primary mental disorder diagnosis; medical comorbidities that would preclude participation in the trial (e.g. significant musculoskeletal disease, cancer); current psychotherapy; use of antidepressants or other psychotropic medications; history of inability to tolerate or benefit from sertraline; use of dietary supplements or herbal therapies with psychoactive indications; current active alcohol or drug abuse or dependence; active suicidal intent; participation in regular exercise > 1 day/week Treatment N: 40 (63% male, mean age: 63.4 (SD: 10.2)) Control N: 37 (65% male, mean age: 64.7 (SD: 11.0)) Comparability of groups: no baseline differences
Interventions	Treatment: sertraline once daily, dosage dependent on clinical response, but participants usually started at 50 mg and progressed up to 200 mg, contingent on therapeutic response and the presence of side effects Control 1: placebo Control 2: aerobic exercise (3 classes per week, 16 weeks); ineligible for inclusion in this review

UPBEAT 2012 *(Continued)*

	Duration of treatment: 4 months
Outcomes	Review outcomes: depression symptoms (HAM-D), platelet biomarkers, ECG waves, pharmacological side effects
Funding	National Heart, Lung, and Blood Institute Other support: sertraline and matching placebo pills were supplied by Pfizer Inc NY
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants assigned to exercise, sertraline, or placepo in a pre-determined 2:2:1 ratio. Randomization was performed centrally by computer with conditional randomization (stratified by age [35 to 59 vs ≥60], CHD status (prior MI vs. no MI) and depression severity [HAM-D score > 18 vs. ≤ 18)]; patients were provided with sealed envelopes containing their group assignments" Comment: no
Allocation concealment (selection bias)	Low risk	Comment: sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: treating psychiatrist blinded to pill condition; only research pharmacist was aware of which patients were assigned to sertraline or to placebo Comment: group randomized to exercise were unblinded and not used in this review
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: primary HAMD assessments were performed blinded to treatment allocation Quote: "Outcome assessors were unaware of patients' treatment assignments" (pg. 1056)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Reasons for drop-out provided; 1 patient randomized to sertraline and 4 patients randomized to placebo did not complete the study Quote: "unless otherwise indicated, treatment effects were analyzed following the intent-to-treat principle..." (pg. 1056)
Selective reporting (reporting bias)	Unclear risk	Comment: predetermined endpoints are reported; no protocol paper available Comment: measures of variance (e.g. SD or SE) not reported for biomarkers in paper, only p values for between group comparisons - e.g. active treatment vs. placebo, thereby incorporating the exercise group which were not relevant to this review. Biomarker data obtained from trial repository
Other bias	Low risk	Comment: No indication of other bias

Wang 2020

Study characteristics

Methods	RCT design: 2-arm parallel-group trial

Wang 2020 *(Continued)*

	Total N randomised: 280 Length of follow-up: 4 weeks after the 8-week intervention Analysis: per-protocol (27 dropouts from intervention group, 25 dropouts from control group)
Participants	Location: China Number of study centres and setting: outpatient clinic and hospitalised patients from the Cangzhou Center Hospital, the Tangshan Hospital of Traditional Chinese Medicine, and the Beijing Huilongguan Hospital CAD criteria: angina pectoris diagnosed according to the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina, and standardisation of diagnosis and treatment of unstable angina pectoris published by the Chinese Medical Association in 2000 Depression criteria: depression was diagnosed according to the *Chinese Classification and Diagnostic Criteria of Mental Disorders, Third Edition*, and depression symptoms were assessed with the HAM-D, total score 20 or higher CAD and depression standardised in *Guidelines for Diagnosis and Treatment of Common Disease in Traditional Chinese Internal Medicine, First Edition*: “Xiong Bi and Xin Tong syndrome”, “palpitation”, “insomnia”, “hysteria”, “depressive psychosis”, “consumptive disease”, and “sweating syndrome” Other entry criteria: age 40 years or older; TCM criteria for "Qi deficiency and blood stasis"; not yet received antidepression drugs, or received antidepression treatment but discontinued for at least 1 month; agreement to participate in the study; without any other acute diseases and severe complications Exclusion criteria: MI or acute or severe heart failure; advanced malignancy; a physical impairment that would prevent participation; cognitive impairment, comorbid major psychiatric disorders, psychosis, a high risk of suicide or current substance abuse; severe arrhythmia such as atrial fibrillation, atrial flutter, high atrioventricular block, sick sinus syndrome, frequent ventricular premature or ventricular tachycardia; history of epilepsy; current use of an antidepressant or anticonvulsant; patient with a HAM-D score of > 35; physician or patient refusal
Interventions	Intervention 1: flexible doses of daily escitalopram (Lexapro): 5 mg/d for mild depression HAM-D 20 to 23, and 10 mg/d for moderate depression HAM-D > 24 Intervention 2: Bu Xin Qi herbal decoction 400 mL orally (2 times per day); Dang shen Codonopsis pilosula (root) 15 mg/d, Fu lin Poria cocos 15 mg/d, Bai zhu Bighead atractylodes rhizome (rhizome) 15 mg/d, Huang qi Astragalus membranaceus (Fisch) Bge. (root) 12 mg/d, Dang gui Angelica sinensis (root) 20 mg/d, Gui zhi Cassia twig (dried twigs) 10 mg/d, Gan cao Radix liquiritiae (root) 18 mg/d Duration of treatment: 8 weeks
Outcomes	Review outcomes: depression symptoms (HAM-D), cardiac events, pharmacological side effects
Funding	Supported by the Scientific Research Plan Project of Administration of Traditional Chinese Medicine of Hebei Province of China (Project No. 2016117) and Scientific Research Plan Project of Cangzhou City of Hebei Province of China (Project No. 151302047)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Wang 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: Randomization was carried out by using random-number tables with a block size of 4. The assignment was carried out at the trial coordination center.
Allocation concealment (selection bias)	High risk	Comment: Described as an open-label trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: Described as an open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding not described for depression, major adverse cardiac events or biomarkers; described as open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: per-protocol analysis that excluded patients for non-compliance, adverse events Comment: reason for drop-out described - 27 drop-outs in escitalopram and 25 in Bu Xin Qi decoction
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol paper available
Other bias	Unclear risk	Comment: unclear how study drugs were obtained Comment: p values for between group baseline differences in comorbidities were not reported

WIDeCAD 2017

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 34 Length of follow-up: no follow-up Analysis: ITT with multiple imputation (5 dropouts from intervention arm, 3 dropouts from control arm)
Participants	Location: Germany, Switzerland, and Austria Number of study centres and setting: not specified. Recruitment involved medical specialists in clinics, heart institutions and foundations, self-help and groups for people living with CAD. CAD criteria: self-reported diagnosis of CAD Depression criteria: PHQ-9 score ≥ 5 Other entry criteria: age 18 years or older, access to internet, sufficient German language skills Exclusion criteria: acute suicidality; concurrent or lifetime diagnosis of schizophrenia, psychosis or bipolar disorder Treatment: not specified Control: not specified All participants: 34 (35% female, mean age: 56.4 years (SD: 10.2)

WIDeCAD 2017 *(Continued)*

	Comparability of groups: no comparisons performed
Interventions	Intervention 1: participants received treatment as usual and immediate access to a guided (e-coach; trained psychologists) internet- and mobile-based cognitive-behavioural self-help programme. The programme consisted of 7 lessons, 6 out of 9 optional lessons and 1 booster session after 4 weeks; participants worked on 1 to 2 lessons per week and received feedback after each lesson by e-coaches (trained psychologists); the main components of the programme included psychoeducation, behavioural activation, problem-solving, and cognitive restructuring Wait-list control group: participants received standard care and were given access to the same programme as the intervention group after a waiting time (2 months); participants in the wait-list control group worked on the programme without guidance
Outcomes	Review outcomes: depression symptoms (PHQ-9), quality of life (Assessment of Quality of Life), non-cardiac adverse events (negative effects of psychotherapy) Secondary outcomes: anxiety symptoms (GAD-7), satisfaction (Client Satisfaction Questionnaire-8), adherence (discontinuation rate), fear of disease progression (Fear of Progression Questionnaire)
Funding	No external financing
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was created by an automated web-based program, sealed envelope (https://www.sealedenvelope.com)"
Allocation concealment (selection bias)	Unclear risk	Quote: "There was no way that researchers involved in the study could foresee allocation of individual participants." Quote: "Not otherwise to the study associated staff enrolled and assigned participants (Laura Simmelbauer, LS and Karolin Bauer, KB)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "There was no way that researchers involved in the study could foresee allocation of individual participants."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no details on outcome assessment blinding; primary outcomes self-reported. Quote: All surveys were conducted online via the “Unipark” platform (www.unipark.de)."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 15 of 18 (83.3%) patients randomised to the intervention did not continue the intervention at 8 weeks
Selective reporting (reporting bias)	Low risk	Comment: Outcomes as stated in methods section. No protocol or design paper available
Other bias	High risk	Comment: 53% of eligible participants were excluded after not providing consent

WIDeCAD 2017 *(Continued)*

	Comment: the trial was terminated after recruitment of 34 participants and deemed unfeasible; target sample 122

Yang 2019

Study characteristics	
Methods	RCT design: 2-arm parallel group Total N randomised: 224 Length of follow-up: 12 months Analysis: ITT with last-observation-carried-forward
Participants	Location: China Number of study centres and settings: 1 hospital CAD criteria: at least 1 coronary artery having a stenosis greater than the cutoff point of 50% by coronary angiography Depression entry criteria: HADS Depression > 8 and SDS score > 50 Other entry criteria: > 18 years of age; life expectancy > 1 year; available to be followed up regularly Exclusion criteria: treated with antidepressants within 3 months before enrolment; history of other mental disorders (e.g. dementia, schizophrenia, schizotypal affective disorder, delusional disorder, bipolar affective disorder, alienation, schizoid personality disorders, etc.); imminent risk of suicide and risk of suicide attempts; uncontrolled hypertension, cardiac arrhythmia, or unstable angina pectoris; history of severe pulmonary and renal comorbidities, heart failure, tumours, or other life-threatening diseases; pregnancy or lactation Treatment: 112 (27.7% female, mean age: 61.25 (SD: 8.6)) Control: 112 (28.6% female, mean age: 60.85 (SD: 10.8)) Comparability of groups: no significant baseline differences
Interventions	Treatment: patients' intensive telephone-based care program Control: usual care Duration of treatment: 12 months
Outcomes	Review outcomes: depression symptoms (HADS Depression), depression remission (HADS Depression), all-cause mortality
Funding	Unclear
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: Block-randomization generated in SAS

Yang 2019 *(Continued)*

		Comment: Randomization was performed by an independent analyzer who was not involved in other parts of the study
Allocation concealment (selection bias)	Unclear risk	Comment: Allocation was done by a randomized module by a medical and statistical service company (Shanghai Qeejen Bio-tech Co) Comment: Randomization was performed by an independent analyzer who was not involved in other parts of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Participants unblinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Nurses who were in charge of the primary depression outcome (HADS-D) were blinded to allocation Comment: Unclear whether outcome assessor for death and cardiac events were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Reasons for drop-out described for both groups during treatment phase and longer-term follow-up Comment: Analyses were ITT with last observation carried forward
Selective reporting (reporting bias)	Unclear risk	Comment: Results of all main outcomes reported as described in the methods. No protocol available. Comment: there is a discrepancy between the all-cause mortality reported in the CONSORT flow chart and the survival analyses reported in the results section. No numbers at risk were reported with the Kaplan-Meier survival plot
Other bias	Unclear risk	Comment: no monitoring of intervention quality was reported for study-trained counsellors

Zarea 2014

Study characteristics	
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 74 Length of follow-up: 2 and 4 months' post-treatment Analysis: per-protocol (method of analysis not stated, also no information on participant flow chart)
Participants	Location: Iran Number of study centres and setting: Al-Zahra Heart Hospital CAD criteria: all patients who were candidates for coronary artery bypass referred to the research environment on a non-emergency basis (being in a bypass list) Depression criteria: moderate to severe depression and anxiety scores (HADS) Other entry criteria: no history of mental illness, interested in participating in the study (i.e. the tendency of the patient and their family to participate in the intervention), lack of previous bypass surgery, aged between 35 and 70 years, ability to communicate verbally and ability to speak Persian

Zarea 2014 *(Continued)*

	Exclusion criteria: lack of co-operation of patients and families during the intervention, failure to perform coronary artery bypass surgery for various reasons, mortality during the study, failure to attend therapeutic communication sessions (absence of 2 or more sessions) Treatment N: 37 (29.7% female, 100% aged 51 to 70 years) Control N: 37 (51.4% female, 100% aged 51 to 70 years) Comparability of groups: not stated. Different gender distribution
Interventions	Treatment: therapeutic communication sessions were held for the intervention group based on Peplau's model at 4 stages, including orientation, identification, exploitation, and resolution. In total, 7 sessions were held individually with the consent of the participant and their family at the hospital and the participant's home. It should be noted that during therapeutic communication, duration of each session varied given the location and participant's needs. Control: not stated Duration of treatment: not stated. Quote: "...duration of each session was variable..." (p 161), total treatment duration unclear
Outcomes	Review outcomes: depression symptoms (HADS Depression) Other outcomes: anxiety symptoms (HADS Anxiety)
Funding	None
Notes	Mixed study sample (patients with depression and/or anxiety were enrolled)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: The subjects were randomly divided into test and control groups using a coin toss
Allocation concealment (selection bias)	Unclear risk	Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Participants and therapists unblinded Comment: Unclear the number and type of staffs involved in the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The procedures for obtaining outcome data are unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No information on participant flow or attrition
Selective reporting (reporting bias)	Unclear risk	Comment: Trial registry congruent with reported outcomes for depression and anxiety (HADS) Comment: Depression and anxiety (HADS) data reported as unadjusted means and analysis of covariance across all timepoints
Other bias	Unclear risk	Comment: No indication of intervention fidelity and monitoring

ACE: angiotensin-converting enzyme
ACS: acute coronary syndrome
BDI: Beck Depression Inventory
BMI: body mass index
BP: blood pressure
CABG: coronary artery bypass graft
CAD: coronary artery disease
CBT: cognitive-behavioural therapy
CCS: Canadian Cardiovascular Society Angina Class
CHD: coronary heart disease
CK-MB: creatine kinase myocardial band
CM: clinical management
DISH: Depression Interview and Structured Hamilton
ECG: electrocardiogram
HADS: Hospital Depression and Anxiety Scale
HAM-D: Hamilton Rating Scale for Depression
HR: heart rate
IPT: interpersonal psychotherapy
ITT: intention-to-treat
LDL: low-density lipoprotein
LVEF: left ventricular ejection fraction
MI: myocardial infarction
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
PHQ-9: Patient Health Questionnaire
PTCA: percutaneous transluminal coronary angioplasty
RCT: randomised controlled trial
SADS: Schedule of Affective Disorders and Schizophrenia
SCID: Structured Clinical Interview for Depression
SCL 90-R: Symptom Checklist 90-Revised
SD: standard deviation
SSM: supportive stress management
SSRI: selective serotonin reuptake inhibitor
STAI: State-Trait Anxiety Inventory
TCM: Traditional Chinese Medicine
WBT: well-being therapy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abedimanesh 2017	Study included participants without comorbid depression.
ACHD-CARE 2015	Study investigated a sample of heart disease patients that was not restricted to CAD.
ACTonHEART 2014	Study included participants without comorbid depression.
Beating Heart Problems 2014	Study included participants without comorbid depression.
Black 1998	Study included participants without comorbid depression. The study investigated psychologically distressed patients (depression was not explicitly assessed).
Boese 2013	Intervention not specifically a psychological or pharmacological treatment for depression. Intervention not delivered by a trained professional ("Peer counselor with CAD trained in attentive listening and sharing experiences").
BraveHeart 2013	Study investigated a sample of heart disease patients that was not restricted to CAD.
Bucknall 1988	Study investigated a sample of heart disease patients that was not restricted to CAD.

Study	Reason for exclusion
BY.PASS Study 2013	Study included participants without comorbid depression.
CADENCE 2016	Study investigated collaborative interventions for depression treatment versus usual care, which was not a predefined comparison of this review.
Carney 2012	Study investigated collaborative interventions for depression treatment versus usual care, which was not a predefined comparison of this review.
Carney 2019	Study investigated a sample of heart disease patients that was not restricted to CAD.
CHAMPS 2016	Study investigated a sample of heart disease patients that was not restricted to CAD.
Chang 2020	Study included participants without comorbid depression.
Child 2010	The psychological intervention was not allocated as part of an RCT.
CHIP 2011	Study included participants without comorbid depression.
Chung 2010	Intervention not specifically a psychological or pharmacological treatment for depression (home-based deep breathing).
CODIACS 2013	Study investigated patient-preference, stepped-care depression treatment versus usual care, which was not a predefined comparison of this review.
COINCIDE 2012	Study investigated collaborative interventions for depression treatment versus usual care, which was not a predefined comparison of this review.
COPES 2010	Study investigated patient-preference, stepped-care depression treatment (including no treatment, problem-solving therapy and/or pharmacotherapy) versus usual care, which was not a predefined comparison of this review.
Doering 2013	Study investigated a sample of heart disease patients that was not restricted to CAD.
ENHANCED 2016	Study included participants without comorbid depression.
Fu 2006	Control group unclear (treatment with "Shierkang tablets")
Giltay 2011	Study included participants without comorbid depression.
González-Jaimes 2003	Study included participants without comorbid depression. The study investigated patients with acute myocardial infarction and adjustment disorder with depressed mood (DSM-IV: 309.0), but not depression.
Haberka 2013	Study included participants without comorbid depression.
Haybar 2018	Study included participants without comorbid depression.
Huffman 2011	Study investigated collaborative care versus usual care, which was not a predefined comparison of this review.
I-CARE 2018	Study included participants without comorbid depression.
InterHerz 2012	Study investigated a sample of heart disease patients that was not restricted to CAD.
Jang 2018	Intervention not specifically a psychological or pharmacological treatment for depression (mindfulness-based art therapy).

Study	Reason for exclusion
Kachkovskii 2006	Control group unclear
Keeping-Burke 2013	Study included participants without comorbid depression.
Li 2014	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.
Li 2020	Study included participants without comorbid depression.
Liang 2019	Study included participants without comorbid depression.
Lin 2014	Study investigated collaborative care versus usual care, which was not a predefined comparison of this review.
Lv 2016	Study compared a combination of psychotherapy and pharmacological interventions (CBT, escitalopram, and alprazolam) versus a combination of pharmacological interventions (escitalopram and alprazolam), which was not a predefined comparator of this review.
Ma 2010	Control group unclear
Malik 2002	The pharmacological intervention was not allocated as part of an RCT.
Mazereeuw 2016	Study included participants without comorbid depression.
MindfulHeart 2014	Study included participants without comorbid depression.
Mohapatra 2005	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.
MOSAIC 2013	Study investigated collaborative care versus enhanced usual care, which was not a predefined comparison of this review.
MOTIV-CABG 2013	Study included participants without comorbid depression.
Nikrahan 2019	Study included participants without comorbid depression.
Norris 2009	Intervention not specifically a psychological or pharmacological treatment for depression. The study investigated the effectiveness of providing follow-up information regarding mental health services to depressed patients after cardiac catheterisation.
Oldridge 1991	Intervention not specifically a psychological or pharmacological treatment for depression (cardiac rehabilitation).
Oranta 2010	Study included participants without comorbid depression.
O'Doherty 2015	Not a randomised trial; allocation to intervention or wait-list control group was not by randomisation
Park 2013	Study included participants without comorbid depression.
PATHWAY Group MCT	Study investigated a sample of heart disease patients that was not restricted to CAD.
PATHWAY Home MCT	Study investigated a sample of heart disease patients that was not restricted to CAD.
Pogosova 2004	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.

Study	Reason for exclusion
Pogosova 2009	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.
Rakowska 2015	Study included participants without comorbid depression.
Rollman 2009	Study investigated telephone-delivered collaborative care versus usual care, which was not a predefined comparison of this review.
Schneider 2020	Study included participants without comorbid depression. Quote: "The inclusion of people below clinical thresholds of depression and/or general anxiety may have weakened the results and limited generalizability among clinical settings"
Schrader 2005	Study investigated the effectiveness of different forms of communication between hospital psychiatric services and general practitioners of depressed cardiac patients; sample of heart disease patients not restricted to CAD.
Sogolitappeh 2009	The psychological intervention was not allocated as part of an RCT.
Soucy 2019	Study investigated behavioural activation for depression versus physical activity, which was not a predefined comparison of this review.
STEP-IN-AMI-2013	Study included participants without comorbid depression.
Stern 1983	Study compared counselling versus exercise therapy, which was not a predefined comparison of this review.
Strokova 2012	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.
SU.FOL.OM3 2012	Study investigated a sample of heart disease patients that was not restricted to CAD.
SUPRIM 2011	Study included participants without comorbid depression.
TAKE Heart 2010	Intervention not specifically a psychological or pharmacological treatment for depression.
TEAMcare 2010	Study investigated a collaborative intervention for depression versus usual care, which was not a predefined comparison of this review.
Tsai 2012	Study included participants without comorbid depression.
UPBEAT-UK 2014	Intervention consisted of collaborative care (case management, information provision and referral to other health professionals via the Improving Access to Psychological Therapy programme, and behaviour change techniques), which was not a predefined comparison of this review.
Vasiuk 2010	The pharmacological intervention was not allocated as part of an RCT.
Veith 1982	Study investigated a sample of heart disease patients that was not restricted to CAD.
WELL.ME 2012	Study investigated a sample of heart disease patients that was not restricted to CAD.
Zeng 2001	Study compared pharmacological treatment versus usual care, which was not a predefined comparison of this review.

CAD: coronary artery disease
CBT: cognitive-behavioural therapy

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Ahangarezaiezadeh 2017

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 60 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: heart clinic in Takab city CAD criteria: diagnosis of coronary heart disease by a physician cardiologist Depression criteria: unclear. Depression Anxiety and Stress Scales-21 used to compare groups pre and post intervention. Other entry criteria: 20 to 65 years of age, provides written informed consent Exclusion criteria: concurrent participation in educational programmes or other treatment; antianxiety or antidepression medication and tranquilisers; drug abuse; other mental disorder; chronic disease (progressive neurologic diseases such as Parkinson's, Alzheimer's, multiple sclerosis, cancer, diabetes); undergoing open-heart surgery
Interventions	Intervention: positive-thinking training delivered as group therapy in 8 sessions (90 min each) over 8 weeks Control: not specified
Outcomes	Depression, anxiety and stress, not further specified
Notes	http://www.who.int/trialsearch/trial2.aspx?Trialid=irct2016022026347n2

Cai 2012

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 126 Length of follow-up: 4 weeks of intervention with no follow-up Analysis: unclear (method of analysis not explicitly stated; dropouts unclear)
Participants	Location: China Number of study centres and setting: unclear CAD criteria: unstable angina, not further specified Depression criteria: unclear. Clinical Global Impression used to quantify change. Other entry criteria: unclear Exclusion criteria: unclear

Cai 2012 *(Continued)*

	Treatment N: 66 (no demographics reported) Control N: 60 (no demographics reported) Comparability of groups: no comparisons reported
Interventions	Treatment: flupentixol melitracen (trade name Deanxit), 1 or 2 pieces for 4 weeks Control: unclear Duration of treatment: 4 weeks
Outcomes	Cinical global improvement in depression and anxiety, incidence of angina pectoris and malignant cardiovascular events
Notes	Conference abstract only. Department of Cardiology, Affiliated Hospital of Gannan Medical College, JiangXi, GanZhou, China

CoroDep 2019

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 150 Length of follow-up: length of intervention unclear, follow-up 6 months after PCI Analysis: unclear (method of analysis not explicitly stated; dropouts unclear)
Participants	Location: Croatia Number of study centres and setting: unclear, affiliated with Klinički Bolnički Centar Zagreb CAD criteria: percutaneous coronary intervention due to angina pectoris or myocardial infarction Depression criteria: unclear Other entry criteria: 18 to 70 years old, without antidepressant drugs or major tranquilisers more than 1 year Exclusion criteria: symptoms of myocardial infarction lasting more than 12 hours, left ventricular ejection fraction less than 40%, earlier presence of cardiomyopathy, acute infection Treatment N: not specified (no demographics reported) Control N: not specified (no demographics reported) Comparability of groups: no comparisons reported
Interventions	Treatment 1: sertraline, from 50 to 200 mg/day Treatment 2: escitalopram, from 10 to 20 mg/day Duration of treatment: not specified
Outcomes	Montgomery Asberg Depression Scale, Hamilton Rating Scale for Depression, Beck Depression Inventory, EuroQol, other outcomes not relevant to this review (GRACE score, Duke Activity Index, Seattle Angina Questionnaire, brain-derived neurotrophic factor)
Notes	Described as an unmasked trial and that the two interventions will be reported as a single group

Gu 2017

Methods	RCT design: 2-arm parallel-group trial Total N randomised: 146 Length of follow-up: no follow-up Analysis: unclear (method of analysis not explicitly stated; dropouts unclear)
Participants	Location: China Number of study centres and setting: unclear CAD criteria: stable ischaemic heart disease and exercise-induced myocardial ischaemia Depression criteria: unclear. General distress and BDI-II measured Other entry criteria: unclear Exclusion criteria: unclear Treatment N: sample size unclear (no demographics reported) Control N: sample size unclear (no demographics reported) Comparability of groups: no comparisons reported
Interventions	Treatment: mindfulness-based stress reduction programme for 2.5 hours 2 times per week Control: usual care Duration of treatment: 12 weeks
Outcomes	Depression measured by the BDI-II, ECG quantified wall motion abnormalities and HRV
Notes	Clinical College, Hainan Medical University Affiliated Hospital, Hainan, China

BDI: Beck Depression Inventory
CAD: coronary artery disease
ECG: electrocardiogram
PCI: percutaneous coronary intervention
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Ahmadi 2018

Study name	Effectiveness of Rumination-Focused Cognitive-Behavioral Therapy on improvement depression and anxiety in patients with coronary heart disease
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 32 Length of follow-up: 8 weeks Analysis: not specified
Participants	Location: Iran

Ahmadi 2018 *(Continued)*

	Number of study centres and setting: not stated, affiliated with Taleghani Educational Hospital, Tehran, Iran CAD criteria: coronary heart disease Depression criteria: major depressive disorder, single episode, moderate, criteria not further specified Other entry criteria: 20 to 80 years of age, ability to read and write and do homework treatment Exclusion criteria: drug addiction, severe mental disorder, psychiatric medication, attending other psychotherapy
Interventions	Intervention group: CBT based on rumination. This treatment was introduced by Edward Watkins and includes 10 sessions of 45 minutes. Duration of treatment: 8 weeks Control group: no treatment other than conventional treatments
Outcomes	Depression: at the beginning of the intervention, 8 weeks after the intervention, quantified by the BDI-II
Starting date	22 June 2018
Contact information	Dr Abbas MasjediArani Taleghani Educational Hospital, Tabnak St Velenjak Region, Chamran High Way, Tehran, Iran 1985711151 Tehran Iran (Islamic Republic of) T: +98 912 575 2870 E: doctormasjedi@yahoo.com Affiliation: Shahid Beheshti University of Medical Sciences Seyed Mojtaba Ahmadi Taleghani Educational Hospital, Tabnak St Velenjak Region, Chamran High Way, Tehran, Iran 1985711151 Tehran Iran (Islamic Republic of) T: +98 930 640 7071 E: mojtabakmahmadi@yahoo.com Affiliation: Shahid Beheshti University of Medical Sciences
Notes	

Ardakani 2020

Study name	The study of of escitalopram's effectiveness on treatment of mild to moderate depressive disorder and improvement of quality of life in patients who are undergone coronary artery bypass graft surgery (CABG): a randomized double blind placebo controlled trial
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 41 Length of follow-up: end of treatment, 8 weeks

Ardakani 2020 *(Continued)*

	Analysis: not specified
Participants	Location: Iran Number of study centres and setting: 1, Tehran Heart Center Hospital, Tehran, Iran CAD criteria: undergone coronary artery bypass graft surgery Depression criteria: BDI scores between 10 and 20, confirmed through clinical interview by a psychiatrist (ICD F32.8) Other entry criteria: 18 to 75 years of age Exclusion criteria: previous history of intolerance to SSRI, psychosis or dementia or cognitive impairment, severe liver disease, high risk of postoperative cardiac complications such as bleeding, participating in other trials, history of bipolar disorder, patients treated with escitalopram or another antidepressant during the previous month, recent alcohol and substance abuse, pregnancy and lactation
Interventions	Intervention: escitalopram 10 mg/d Control: placebo, not further specified Duration of treatment: 8 weeks
Outcomes	Primary: change in depressive symptoms as a result of intervention effects on BDI-II, quality of life quantified with the 36-Item Short Form Health Survey Secondary: checklist of drug side effects
Starting date	22 November 2020
Contact information	Dr Mohammad Reza khodaie Ardakani Razi Psychiatric Hospital, Shahre Rey, Tehran, Iran T: +98 21 3340 1604 E: kh.ardakani@uswr.ac.ir
Notes	

COMBAT-DS 2021

Study name	Online cognitive behavioral therapy for depressive symptoms in rural patients with cardiac disease (COMBAT-DS)
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 500 (also states 150 per group; stratified by sex) Length of follow-up: 12 months from baseline Analysis: not specified
Participants	Location: USA Number of study centres and setting: not specified, affiliated with University of Kentucky, University of California, Patient-Centered Outcomes Research Institute CAD criteria: physician-documented acute coronary syndrome event

COMBAT-DS 2021 *(Continued)*

	Depression criteria: at least moderate depressive symptoms (PHQ-9 ≥ 10) Other entry criteria: rural dwelling Exclusion criteria: cognitive impairment, major psychiatric comorbidities that might require additional treatment, presence of non-CHD conditions likely to be fatal within next year
Interventions	Intervention 1: video-conferenced CBT (vcCBT) consisting of 8 face-to-face video-conferencing sessions via tablet computers lasting approximately 45 minutes each Intervention 2: iCBT is self-directed cognitive-behavioural therapy using an interactive internet programme, MoodGYM, which does not include direct interactions with a therapist Duration of treatment: 3 months
Outcomes	Primary: change in depressive symptoms as a result of intervention effects on PHQ-9 Seconday: all-cause hospitalisation rates
Starting date	3 August 2021
Contact information	Debra K Moser PhD, RN Professor and Linda C Gill Endowed Chair of Nursing University of Kentucky, Lexington, Kentucky, United States T: 859-323-6687 E: dmoser@uky.edu Misook Chung University of Kentucky, Lexington, Kentucky, United States T: 8593236687 E: misook.chung@uky.edu Rana Rahman, PhD, RN University of Kentucky, Lexington, Kentucky, United States T: 8593236656 E: rana.lindsay-rahman@uky.edu
Notes	

eMindYourHeart 2021

Study name	eMindYourHeart
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 188 Length of follow-up: 3 and 9 months after end of treatment or usual care Analysis: "modified" ITT
Participants	Location: Denmark

eMindYourHeart 2021 *(Continued)*

	Number of study centres and setting: cardiac rehabilitation settings at hospitals and municipalities delivering cardiac rehabilitation across 5 regions in Denmark CAD criteria: diagnosis of ischaemic heart disease (ICD codes I20 to I25) Depression criteria: score ≥ 8 on depression or anxiety or both scales of the HADS Other entry criteria: ≥ 18 years of age, access to a computer or smartphone, ability to use a computer or smartphone, and proficient in the Danish language Exclusion criteria: severe psychiatric disorders (i.e. borderline personality disorder, schizophrenia, bipolar disorder), severe cognitive difficulties (e.g. severe brain damage, mental retardation, or dementia) that would prevent patients from participating, endorsement of suicidal ideation with daily suicidal thoughts (PHQ-9 item 9 > 2), participating in other intervention studies (unless they are clinical studies (e.g. medication trials)), or seeing a psychologist or mental health professional for the treatment of depression and anxiety
Interventions	Intervention: between 10 and 12 sessions of CBT and includes aspects of acceptance and commitment therapy and compassion-focused therapy (i.e. an introductory module, 9 core treatment modules, 2 optional modules related to sleep and lifestyle changes) with telephone support from a psychologist Control group: no treatment other than usual care (cardiac rehabilitation) Duration of treatment: 3 months
Outcomes	Primary: symptoms of depression, measured with HADS at the end of the intervention (i.e. 3 months) Secondary: symptoms of anxiety measured with HADS at 3 months; symptoms of depression and anxiety at 6 and 12 months' follow-up; quality of life (HeartQoL) at 3, 6, and 12 months' follow-up; trial dropout (number of participants who dropped out in either arm at 3 months); and cost-effectiveness/cost-utility Other measures reported in protocol: Cardiac Anxiety Questionnaire (CAQ-18), PHQ-9, UCLA Loneliness Scale, Multidimensional Scale of Perceived Social Support (MSPSS), Brief Illness Perceptions Questionnaire (B-IPQ), quality of life (HeartQoL), Perceived Stress Scale, Health Complaints Scale, physical activity, patient engagement in cardiac rehabilitation, Negative Effects Questionnaire
Starting date	1 June 2020
Contact information	Susanne S Pedersen, PhD T: +4565507992 E: sspedersen@health.sdu.dk Affiliation: Department of Psychology, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark
Notes	

Firouzjaei 2017

Study name	Cognitive-behavioral therapy for cardiovascular disease
Methods	RCT design: 2-arm parallel-group trial. Study described as randomised controlled design comparing a problem-solving therapy with usual care group (control group); also stated as "not randomized". Unclear group allocation

Firouzjaei 2017 *(Continued)*

	Total N randomised: 24 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: single centre, Shahid Modarres Hospital, Tehran CAD criteria: ischaemic heart disease, ICD-10 codes I20 to I25 Depression criteria: meeting the diagnostic criteria for depression due to other medical condition according to DSM-5 and a minimum score of 10 on the BDI-II Other entry criteria: sufficient knowledge of the Persian language, age under 70 years, minimum diploma education, minimum score of 26 on the Dysfunctional Attitudes Scale-26 Exclusion criteria: already receiving psychotherapy for mental health problems, taking psychiatric drugs during the last 6 months, the presence of severe depressive symptoms (indicated by a score above 40 on the items of the BDI-II)
Interventions	Intervention: problem-solving therapy based on Robert Leahy protocol. No further details provided. Usual care: 2 educational sessions on cardiovascular disease and a depression brochure. Educational sessions under the supervision of cardiologist included: 1) medical education about heart disease and CABG surgery; 2) general education about health care after heart bypass surgery; 3) having a good diet programme; 4) having a daily walking programme Duration of treatment: 50 days
Outcomes	Depression measured by the BDI-II Dysfunctional attitudes measured by the Dysfunctional Attitudes Scale-26 Social support measured by the Multidimensional Scale of Perceived Social Support All outcomes assessed pre- and postintervention.
Starting date	13 August 2017
Contact information	Nima Hajitabar Firouzjaei Shahid Beheshti University of Medical Science Teharan - Evin - Student bouleward- Arabi street- Medical College, Shahid Beheshti University of Medical Science Tehran T: +98 21 6670 5780 E: nimahajitabar@yahoo.com
Notes	

Geng 2018

Study name	Effect of guanxin danshen dropping pill on clinical anxiety, depression, heart rate variability and cardiovascular prognosis in patients with coronary heart disease after PCI combined with anxiety or depression
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: China Number of study centres and setting: Guangdong General Hospital CAD criteria: CHD, any stable angina pectoris, unstable angina pectoris, non-ST-elevation myocardial infarction, acute ST-segment elevation myocardial infarction, PCI patients (completed or required) Depression criteria: patients who scored between 5 to 14 points on the PHQ-9, or score of between 5 and 14 points on the Generalized Anxiety Disorder-7 Other entry criteria: voluntarily participate in the trial, signed informed consent and ability to understand and voluntarily sign informed consent, aged between 18 and 75 years, can co-operate with the treatment Exclusion criteria: cachexia state; or combined lung, liver, kidney, haematopoietic system, immune system, and other serious primary disease and dysfunction, angina pectoris not relieved or NYHA cardiac function grade IV, recurrent anxiety, depression patients, electrolyte imbalance acid-base imbalance, history of epilepsy, or patients with organic mental disorders, other mental illness such as: bipolar affective disorder, schizophrenia, and other patients, alcohol and drug abuse and addiction within 1 year, use of other antidepressant and anxiolytic drugs within 4 weeks before assessment, pregnant or lactating women, or planned pregnancy, had previous coronary revascularisation, participated in other drug clinical trials within 3 months, researchers believe that patient is not suitable for clinical trials, patients with cognitive impairment, patients with suicidal tendencies
Interventions	Guanxin danshen drop pills. No further information available. Duration of treatment: not specified
Outcomes	Symptoms of anxiety and depression Heart rate variability during cardiopulmonary exercise Major adverse cardiovascular events (MACE)
Starting date	1 August 2017
Contact information	Qingshan Geng 106 Second Zhongshan Road, Guangzhou, Guangdong, China T: +86 13922205818 E: mahuannovel@163.com
Notes	http://www.chictr.org.cn/showproj.aspx?proj=20507

Hamzehpour 2020

Study name	Treatment of depressive symptoms in patients after coronary artery bypass graft surgery
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 100 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: 1 Ayatollah Rouhani Hospital, Iran CAD criteria: undergoing coronary artery bypass graft surgery Depression criteria: unclear. Depression measured with BDI. ICD code stated in health conditions studied (F32.0) Major depressive disorder, single episode, mild Other entry criteria: willingness to participate in the study Exclusion criteria: cognitive impairment, history of substance use, bipolar disorder
Interventions	Intervention 1: bupropion 75 mg/d increased to 150 mg/d Intervention 2: unclear from text. Likely citalopram or escitalopram 5 mg/d increased to 20 mg/d Duration of treatment: 8 weeks
Outcomes	Primary: BDI measured at baseline and end of therapy; no other outcomes specified
Starting date	25 July 2020
Contact information	Romina Hamzehpour Ayatollah Rouhani Hospital, Daneshgah Square, Ganjafrooz Avenue T: +98 11 3233 8301 E: r.hamzehpour@mubabol.ac.ir
Notes	

Irfan 2020

Study name	The effect of culturally adapted CBT-based guided self help in depressed patients with myocardial infarction
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 140 Length of follow-up: 8 weeks Analysis: ITT with last-observation-carried-forward
Participants	Location: Pakistan Number of study centres and setting: Punjab Institute of Cardiology, Lahore

Irfan 2020 *(Continued)*

	CAD criteria: myocardial infarction Depression criteria: score of 8 or more on HADS and fulfilling criteria of Major Depressive Disorder using DSM-5 Other entry criteria: 18 to 65 years of age Exclusion criteria: patients using alcohol or drugs, significant cognitive impairment (intellectual disability or dementia), active psychosis, patients who have received CBT during the previous 12 months
Interventions	Intervention: culturally adapted cognitive-behavioural therapy (CaCBT)-based guided self-help (using the book *Khushi Aur Khatoon*) Usual care: not specified Duration of treatment: 8 weeks
Outcomes	Change in HADS Depression Subscale score from baseline to end of therapy Change in World Health Organization Disability Assessment Schedule (WHODAS 2.0) score from baseline to end of therapy
Starting date	22 October 2019
Contact information	Muhammad Irfan, Professor of Psychiatry and Director Research, Peshawar Medical College Farooq Naeem, PhD, University of Toronto
Notes	

Jazayeri 2017

Study name	Effect of hesperidin supplementation on depressive symptoms, serum levels of BDNF and cortisol in patients after myocardial infarction
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 70 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: not specified, affiliated with Iran University of Medical Sciences, Tehran CAD criteria: myocardial infarction in past 6 weeks Depression criteria: BDI score of 10 or higher Other entry criteria: willingness to co-operate and signed informed consent, no use of supplements during the last 3 months (including omega-3, Q10, antioxidants, and vitamins), absence of any allergies (gastrointestinal and skin) to any type of antioxidant supplements and vitamins, age 30 to 70 years, do not use more than 1 blood orange or more than 2 other citrus fruits a day, body mass index between 25 to 40

Jazayeri 2017 *(Continued)*

	Exclusion criteria: major psychiatric disorder history, treatment of depression within past 12 months, consumes more than 500 mL per day of flavonoid-rich beverages include tea, coffee, or citrus juice, major cognitive disorders or impaired cognitive function, lack of follow-up after discharge, tobacco smoking, uncontrolled metabolic disease, pregnancy and lactation, use of heparin or warfarin, uncontrolled chronic diseases (hepatic failure, renal failure, diabetes, etc.), digestive disorders, compliance below 80%
Interventions	Intervention 1: hesperidin capsules 200 mg/d Control: placebo containing starch Duration of treatment: 3 months
Outcomes	Primary: depression measured by the BDI Secondary: serum levels of BDNF and cortisol
Starting date	5 May 2017
Contact information	Dr Shima Jazayeri Vice chancellor for research, Iran University of Medical Sciences, Besides Milad Tower, Hemmat, Tehran, Iran (Islamic Republic of) T: +98 21 8670 4805 E: Jazayeri.sh@iums.ac.ir; sh_jaz@yahoo.com
Notes	

Luberto 2021

Study name	MBCT via group videoconferencing for acute coronary syndrome patients with depressive symptoms: a pilot RCT
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 50 Length of follow-up: 3 months Analysis: not specified
Participants	Location: USA Number of study centres and setting: Department of Psychiatry, Massachusetts General Hospital CAD criteria: acute coronary syndrome specified by medical records or patient confirmation, or both Depression criteria: current elevated depression symptoms (PHQ-9 greater than or equal to 5) Other entry criteria: 35 to 85 years of age, access to high-speed internet Exclusion criteria: active suicidal ideation or past-year psychiatric hospitalisation (per patient report or medical record review, or both); non-English-speaking; cognitive impairments preventing informed consent per medical record review and/or cognitive screen less than or equal to 4; patient deemed to be unable to complete the study protocol or has a condition that would likely interfere with the study

Luberto 2021 *(Continued)*

Interventions	Intervention 1: 8 virtually delivered MBCT sessions (approximately 1.5 hours each) to regulate distress and choose healthy behaviours, as well as learn about cardiac health Intervention 2: attention-matched control comprising 8 weekly virtual group sessions that focus on cardiac health and depression education Duration of treatment: 8 weeks
Outcomes	Depression measured by the HADS and PHQ-9 Quality of life measured by PROMIS-Physical Function and 1 item of 12-Item Short Form Health Survey Inflammatory biomarkers, interleukin 6, tumour necrosis factor-α, and C-reactive protein measured by whole dried blood spot sample collection All outcomes measured 1 week before and after the intervention and at 3 months postintervention.
Starting date	April 2021
Contact information	Christina Luberto, Assistant Professor, Department of Psychiatry, Harvard Medical School; Massachusetts General Hospital T: 617-643-9453 E: cluberto@mgh.harvard.edu Elyse Park, PhD, MPH T: 617-724-6836 E: epark@mgh.harvard.edu
Notes	

Ma 2014

Study name	The therapeutic effect of statins on patients with depression after acute coronary syndrome
Methods	RCT design: 3-arm parallel-group trial Total N randomised: 180 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: China Number of study centres and setting: Tongji Hospital affiliated to Tongji University, Shanghai CAD criteria: diagnostic criteria of ACS based on guidelines, including ST elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina Depression criteria: based on PHQ, not further specified Other entry criteria: between 30 and 90 years of age

Ma 2014 *(Continued)*

	Exclusion criteria: previous history of mental illness, suicidal tendencies, severe hepatic and renal dysfunction, anxiety state (HADS Anxiety score more than 7), left ventricular ejection fraction less than 0.45, haemodynamic instability, LDL-c more than 3.37 mmol/L, allergic to statins or sertraline
Interventions	Intervention 1: rosavastatin calcium 20 mg/d Intervention 2: sertraline 25 to 50 mg/d Intervention 3: rosavastatin calcium 5 mg/d Duration of treatment: not specified
Outcomes	Not specified
Starting date	14 December 2014
Contact information	Wenlin Ma NO.389 Xincun Rd, Putuo district, Shanghai, China T: +86 18621892703 E: mawenlin@medmail.com.cn
Notes	

Mohammadian 2018

Study name	The efficacy of cognitive-behavioral therapy based on rumination on depression, anxiety and hostility in cardiac patients
Methods	RCT design: 3-arm parallel-group trial Total N randomised: 48 Length of follow-up: 2 months Analysis: not specified
Participants	Location: Iran Number of study centres and setting: not stated, affiliated with Shahid Beheshti University of Medical Sciences CAD criteria: open-heart surgery for coronary heart disease Depression criteria: a mild or moderate score on the depression questionnaire (PHQ-9 total score greater than 5) or anxiety questionnaire (Beck Anxiety Inventory total score greater than 8) or aggression questionnaire (Buss-Perry Aggression Questionnaire total score greater than 40) Other entry criteria: 40 to 70 years of age, ability to participate in the rehabilitation programme and doing assignments with a diagnosis of cardiologist and rehabilitation specialist, reading and writing skills, no other physical illness that limits attendance at meetings, no change in psychiatric medications from 1 month before intervention, no history of receiving psychotherapy before intervention Exclusion criteria: cognitive disorders such as Alzheimer's and dementia, severe mental disorder (personality disorders, psychotic disorders, and dissociative disorders), thyroid problems
Interventions	Intervention 1 (intervention group): 12 sessions of CBT based on rumination devised to treat depression for 1 session per week

Mohammadian 2018 *(Continued)*

	Intervention 2 (rehabilitation group): 40 sessions of rehabilitation, with 3 sessions per week. Intervention 3 (control group): this group will be selected from the waiting list and will not receive any intervention Duration of treatment: 12 weeks in Intervention 1; 13 weeks in Intervention 2
Outcomes	Depression pre- and postintervention quantified by the BDI. Unclear if PHQ-9 is captured at end of treatment
Starting date	15 July 2018
Contact information	Rasoul Mohammadian 10th Alley, Resalat street 5981944451 Shahindezh Iran (Islamic Republic of) T: +98 44 4632 1250 E: rasoul.2828@gmail.com Shahid Beheshti University of Medical Sciences
Notes	

Moudi 2016

Study name	The efficacy of citalopram in depression and quality of life in the patients with cardiac disease
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 40 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: 2 cardiac care units affiliated to Babol University of Medical Sciences, Babol CAD criteria: admission in cardiac care units because of acute coronary syndrome, including acute myocardial infarction or unstable angina, ICD-10 code I121 Depression criteria: not specified Other entry criteria: age more than 18 years, informed consent Exclusion criteria: past history of intolerance to SSRIs, severe and life-threatening medical conditions that inhibit participation of the patient in the duration of the study, severe congestive heart failure with diagnosis of the cardiologist, dependence on alcohol or other drugs, psychosis or dementia or intellectual disability, pregnancy, lactation, or planned pregnancy during study, history of elevated mood
Interventions	Intervention: citalopram 20 mg/d Control: weekly psychiatric visit without any antidepressant drug Duration of treatment: 8 weeks
Outcomes	Depression measured by the HADS

Moudi 2016 *(Continued)*

	Quality of life measured by the 36-Item Short Form Health Survey Quality of Life Questionnaire
Starting date	
Contact information	Sussan Moudi Department of Psychiatry, Shahid Yahyanejad Hospital Babol, Iran T: +98 11323268823 E: sussan.mouodi@gmail.com
Notes	

Qiaoning 2019

Study name	Effect of guanxindanshen dropping pills on quality of life and cardiovascular prognosis of patients with depression or anxiety after PCI for coronary heart disease
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 200 Length of follow-up: not specified Analysis: not specified
Participants	Location: China Number of study centres and setting: 6 hospital recruitment sites: Xiyuan Hospital, CACMS (Beijing); Shanghai Tongji Hospital (Shanghai); Fuwai Hospital, CAMS & PUMC (Beijing); Guangdong Provincial People's Hospital (Guangzhou); Beijing First Hospital of Integrated Chinese and Western Medicine (Beijing); The Affiliated Hospital of Changchun University of TCM (Changchun) CAD criteria: diagnostic criteria of CHD (not specified) and complete PCI procedure Depression criteria: PHQ-9 score 5 to 14 or Generalized Anxiety Disorder-7 Scale score 5 to 14, or both Other entry criteria: voluntary participation and informed consent, age 18 to 75 years, able to co-operate with examination and treatment Exclusion criteria: 1. Quote: "wicked liquid condition" 2. Unalleviated angina attack or NYHA cardiac function grade IV 3. Electrolyte disorder, acid-base imbalance 4. Complicated with pulmonary, liver, kidney, haematopoietic system, immune system, and other serious primary diseases and dysfunction 5. Organic mental disorders, depression caused by other mental disorders such as schizophrenia or somatic diseases, etc. 6. Bipolar disorder, rapid circulatory seizures 7. History of epilepsy 8. Alcohol or drug abuse within 1 year 9. Other antidepressants and antianxiety drugs used within 4 weeks before the trial 10. Pregnant or lactating women or planned pregnancies

Qiaoning 2019 *(Continued)*

	11.Those who have participated in clinical trials of other drugs within 3 months 12.Researcher does not consider it appropriate for patient to participate in clinical trials 13.Suicide-prone patients
Interventions	Intervention: guanxin danshen dropping pills, therapeutic dose or intake not specified Control: placebo, unclear
Outcomes	Primary: depression measured by the PHQ-9, major adverse cardiac events, angina measured by the Seattle Angina Questionnaire Secondary: quality of life measured with the 12-Item Short Form Health Survey, blood pressure, vital signs, microcirculation and inflammatory-related indicators, adverse events
Starting date	1 March 2017
Contact information	Yang Qiaoning Xiyuan Hospital, CACMS 1 Xiyuan Caochang, Haidian District, Beijing, China T: +86 15101072110 E: 15101072110@126.com
Notes	

Sourizahi 2017

Study name	Comparison of therapeutic effect of sertraline and supportive psychotherapy in comparison with placebo in coronary heart disease patients with mild to moderate depression
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 90 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: Iran Number of study centres and setting: not specified. Investigators are affiliated with Zahedan University of Medical Sciences. CAD criteria: coronary heart disease, not further specified Depression criteria: patients mild or moderate depression who fulfill ICD criteria for any: F32 Depressive episode, F32.0 Mild depressive episode, or F32.1 Moderate depressive episode Other entry criteria: no serious medical illness, no use of psychiatric drugs Exclusion criteria: heart medications affecting the mood
Interventions	Intervention: sertraline 50 mg/d with weekly dose 150 to 200 mg per week, plus supportive supportive psychotherapy consisting of: discussion about depression in response to the diagnosis of heart disease, controlled diaphragmatic breathing and gradual muscle relaxation training, exposure and cognitive therapy, behavioural activation, pleasant activity scheduling

Sourizahi 2017 *(Continued)*

	Control: sertraline placebo (vitamin C)
Outcomes	Depression level measured by the HAM-D
Starting date	22 December 2017
Contact information	Mohammadislam Sourizahi Zahedan University of Medical Sciences Zahedan, Dr Hesabi square 9816743463 Zahedan Iran (Islamic Republic of) T: +98 54 3329 5715 E: dr.sourizahi58@zaums.ac.ir
Notes	

Wang 2015

Study name	Intervention study of the patients with mild depressive mood after percutaneous coronary intervention in the treatment of the patients with collateral vessels
Methods	RCT design: 2-arm parallel-group trial Total N randomised: sample size and allocation ratio not specified Length of follow-up: not specified Analysis: not specified
Participants	Location: China Number of study centres and setting: not specified, affiliated with Dongzhimen Hospital CAD criteria: previous PCI surgery for coronary heart disease Depression criteria: accordance with the diagnostic criteria of TCM syndrome differentiation of depression, accordance with the diagnostic criteria of depressive episode of Western medicine; depression symptoms defined by score of 8 to 35 on the HAM-D Other entry criteria: stable vital signs, the consciousness is clear, has certain expression ability, aged 18 to 80 years old, patient is willing to try and co-operate, provides informed consent Exclusion criteria: suicide risk, language difficulties, disturbance of consciousness, dementia, aphasia, deafness, agnosia influence emotional expression and not according to the prescribed medication, patients with severe or unstable heart, liver, kidney, endocrine, thyroid dysfunction, blood, and other diseases in the department of internal medicine; history of epilepsy, cerebral trauma; alcohol and drug dependence in the past year; depressive episode secondary to other mental illness or physical disease; serious psychiatric symptoms, such as hallucinations, paranoia, and other symptoms; pregnant women or likely to become pregnant during the trial; history of allergy to paroxetine hydrochloride; participation in other clinical trials of drugs; cannot take medication according to doctor's advice
Interventions	Intervention: paroxetine hydrochloride, not further specified Control: placebo, not further specified
Outcomes	Primary: 5-HT content, HAM-D scores

Wang 2015 *(Continued)*

	Secondary: Seattle Angina Questionnaire
Starting date	1 January 1990
Contact information	Wang Zhen 11 North 3rd Ring Road, Chaoyang District, Beijing, China Dongzhimen Hospital T: +86 13001240944 E: 1282174720@qq.com
Notes	

Yang 2020

Study name	The efficacy and safety of Ginkgo biloba dropping pills in the treatment of coronary heart disease with stable angina pectoris and depression
Methods	RCT design: 2-arm parallel-group trial Total N randomised: 72 Length of follow-up: no follow-up Analysis: not specified
Participants	Location: China Number of study centres and setting: not specified, affiliated with Foshan Chancheng Central Hospital (Guangdong), The First Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong), Luohu District People's Hospital (Guangdong), and The Second Affiliated Hospital of Guizhou University of Chinese Medicine (Guizhou) CAD criteria: coronary heart disease and at least 1 of (history of myocardial infarction; coronary artery revascularisation; coronary radiography or coronary angiography with at least 1 coronary artery stenosis and lumen stenosis ≥ 50%; or cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging or cardiac color Doppler diagnosis coronary heart disease with myocardial ischaemia); stable angina pectoris treated for at least 4 weeks Depression criteria: diagnostic criteria for depressive episode in the ICD-10 (World Health Organization) Other entry criteria: 18 to 75 years of age, informed consent, not used any food that has an impact on intestinal flora such as foods containing probiotics (e.g. yogurt) or drugs (e.g. antibiotics) in the past 7 days Exclusion criteria: acute myocardial events, unstable angina pectoris, severe heart failure; serious arrhythmia; severe or poorly controlled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg); sitting blood pressure and systolic blood pressure ≤ 85 mmHg or symptomatic hypotension, severe primary diseases such as liver, kidney, and haematopoietic system, or serious diseases affecting patient's survival (such as tumour, etc.); serious suicidal tendency (HAM-D item 3 ≥ 3); bipolar disorder depressive episode in patients with epilepsy history, or depression secondary to other mental or physical diseases; alcohol and drug dependence within 1 year; abnormal liver and kidney function (ALT and/or AST > 3 times of the upper normal limit, and/or CRE > 2 times of the upper normal limit); patients who are currently taking antianxiety drugs; pregnant women, lactating women, women of child-bearing age who do not take effective contraceptive measures, or who plan to conceive during the trial, and whose pregnancy test results are

Yang 2020 *(Continued)*

	positive before the test; those who have participated in clinical trials of other new drugs within 30 days before screening; other reasons unsuitable to participate (researcher determined); allergic to the ingredients contained in Ginkgo biloba dropping pills
Interventions	Intervention: sertraline 50 mg/d with weekly dose 150 to 200 mg per week Ginkgo biloba dropping 63 mg x 5 pills, x 3 per day (total 945 mg/d) Control: matching placebo, not further specified
Outcomes	Primary: 1. Seattle Angina Questionnaire 2. Frequency of angina pectoris-related symptoms Secondary: 1. 36-Item Short Form Health Survey 2. HAM-D-17
Starting date	20 September 2020
Contact information	Zhongqi Yang T: 0086-020-36591222 E: Yang_zhongqi@163.com
Notes	

BDI: Beck Depression Inventory
BDNF: brain-derived neurotrophic factor
CABG: coronary artery bypass graft
CAD: coronary artery disease
CBT: cognitive-behavioural therapy
CHD: coronary heart disease
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HADS: Hospital Anxiety and Depression Scale
HAM-D: Hamilton Depression Rating Scale
ICD: International Classification of Diseases
ITT: intention to treat
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
PHQ-9: Patient Health Questionnaire
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomised controlled trial
SSRI: selective serotonin reuptake inhibitor
TCM: Traditional Chinese Medicine

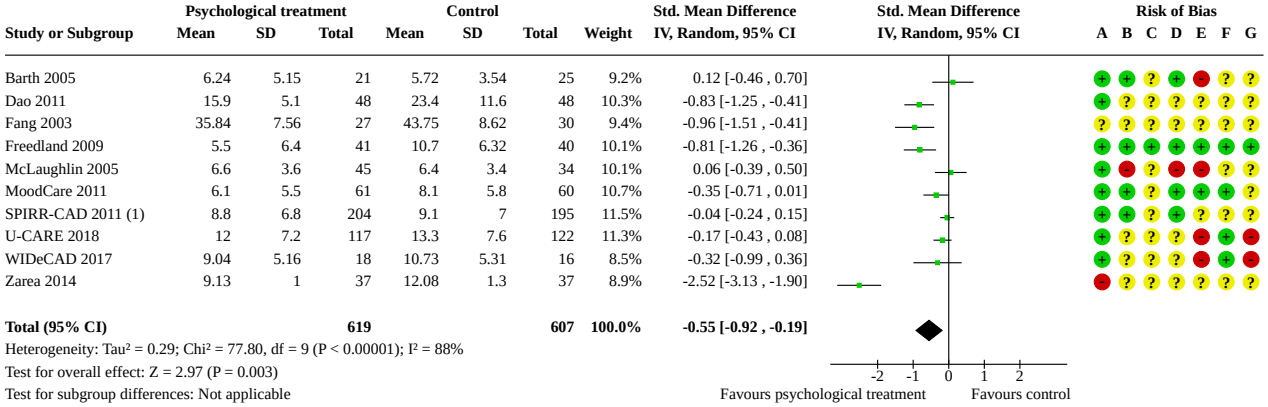
DATA AND ANALYSES

Comparison 1. Psychological intervention versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Depression symptoms - short term	10	1226	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.92, -0.19]
1.2 Depression symptoms - medium term	7	2620	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.42, 0.01]
1.3 Depression symptoms - long term	2	282	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.96, 0.04]
1.4 Depression remission - short term	3	862	Odds Ratio (IV, Random, 95% CI)	2.02 [0.78, 5.19]
1.5 Depression remission - medium term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.6 Depression remission - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.7 All-cause mortality - short term	2	324	Odds Ratio (IV, Random, 95% CI)	0.31 [0.05, 2.02]
1.8 All-cause mortality - medium term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.9 All-cause mortality - long term	2	2670	Odds Ratio (IV, Random, 95% CI)	0.83 [0.48, 1.42]
1.10 Cardiovascular mortality - medium term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.11 Cardiovascular mortality - long term	2	2720	Odds Ratio (IV, Random, 95% CI)	0.83 [0.62, 1.10]
1.12 Myocardial infarction - long term	2	2720	Odds Ratio (IV, Random, 95% CI)	1.09 [0.73, 1.65]
1.13 Heart failure - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.14 Stroke - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.15 Coronary revascularisation procedure - long term	2	2780	Odds Ratio (IV, Random, 95% CI)	0.91 [0.75, 1.11]
1.16 Hospitalisations - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.17 Length of stay - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.18 Quality of life SF-12/36 physical - short term	2	202	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.06, 0.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.19 Quality of life SF-12/36 mental - short term	2	202	Std. Mean Difference (IV, Random, 95% CI)	0.51 [0.07, 0.94]
1.20 Quality of life SF-12/36 physical - medium term	2	187	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-1.29, 1.65]
1.21 Quality of life SF-12/36 mental - medium term	2	187	Std. Mean Difference (IV, Random, 95% CI)	1.21 [-1.09, 3.52]
1.22 Quality of life SF-12 total - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.23 Quality of life SF-36 physical - long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.24 Quality of life SF-36 mental - long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Psychological intervention versus control, Outcome 1: Depression symptoms - short term



Heterogeneity: Tau² = 0.29; Chi² = 77.80, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Not applicable

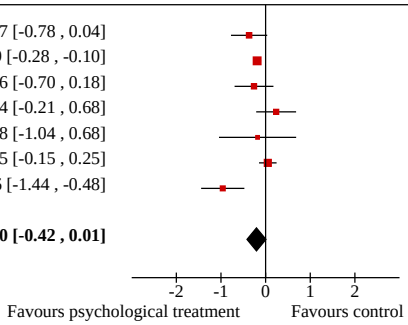
Footnotes
(1) 18 months post-randomisation is assumed as the post-treatment score

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Psychological intervention versus control, Outcome 2: Depression symptoms - medium term

Study or Subgroup	SMD	SE	Psychological Treatment Total	Usual Care Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dao 2011	-0.37	0.207	48	48	13.3%	-0.37 [-0.78 , 0.04]
ENRICHD 2003	-0.19	0.045	916	869	25.0%	-0.19 [-0.28 , -0.10]
Freedland 2009	-0.26	0.222	41	40	12.4%	-0.26 [-0.70 , 0.18]
McLaughlin 2005	0.2361	0.228	45	35	12.1%	0.24 [-0.21 , 0.68]
MoodCare 2011	-0.18	0.441	53	53	4.9%	-0.18 [-1.04 , 0.68]
SPIRR-CAD 2011 (1)	0.049292	0.100287	195	203	21.3%	0.05 [-0.15 , 0.25]
Zarea 2014	-0.96	0.247	37	37	11.0%	-0.96 [-1.44 , -0.48]
Total (95% CI)			**1335**	**1285**	**100.0%**	**-0.20 [-0.42 , 0.01]**

Heterogeneity: Tau² = 0.04; Chi² = 19.48, df = 6 (P = 0.003); I² = 69%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable

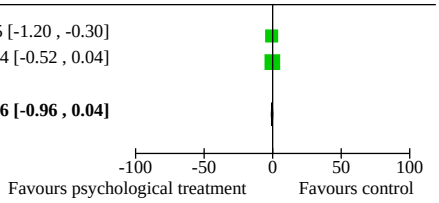


Footnotes
(1) 24 months post-randomisation is assumed as the medium term outcome

Analysis 1.3. Comparison 1: Psychological intervention versus control, Outcome 3: Depression symptoms - long term

Study or Subgroup	Psychological treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Freedland 2009	5.5	6.4	41	10.3	6.32	40	43.7%	-0.75 [-1.20 , -0.30]
U-CARE 2018	11	7.2	89	12.8	7.9	112	56.3%	-0.24 [-0.52 , 0.04]
Total (95% CI)			**130**			**152**	**100.0%**	**-0.46 [-0.96 , 0.04]**

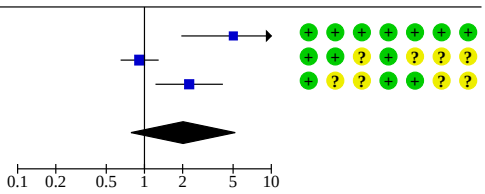
Heterogeneity: Tau² = 0.09; Chi² = 3.57, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Psychological intervention versus control, Outcome 4: Depression remission - short term

Study or Subgroup	Psychological treatment Events	Total	Control Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Freedland 2009	29	41	13	40	28.4%	5.02 [1.95 , 12.90]
SPIRR-CAD 2011 (1)	96	284	102	285	37.6%	0.92 [0.65 , 1.29]
Yang 2019	40	107	22	105	34.0%	2.25 [1.22 , 4.15]
Total (95% CI)		**432**		**430**	**100.0%**	**2.02 [0.78 , 5.19]**
Total events:	165		137			

Heterogeneity: Tau² = 0.59; Chi² = 14.92, df = 2 (P = 0.0006); I² = 87%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable

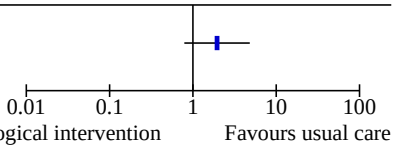


Footnotes
(1) 18 months post-randomisation is assumed as the post-treatment score

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

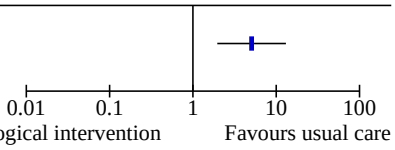
Analysis 1.5. Comparison 1: Psychological intervention versus control, Outcome 5: Depression remission - medium term

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Freedland 2009	28	41	21	40	1.95 [0.79 , 4.81]	



Analysis 1.6. Comparison 1: Psychological intervention versus control, Outcome 6: Depression remission - long term

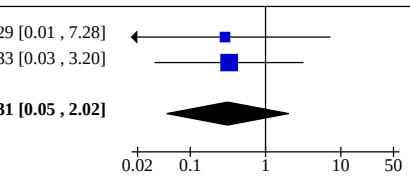
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Freedland 2009	30	41	14	40	5.06 [1.96 , 13.08]	



Analysis 1.7. Comparison 1: Psychological intervention versus control, Outcome 7: All-cause mortality - short term

Study or Subgroup	Psychological Events	Psychological Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
McLaughlin 2005	0	53	1	47	33.3%	0.29 [0.01 , 7.28]		+ - ? - - ? ?
Yang 2019 (1)	1	112	3	112	66.7%	0.33 [0.03 , 3.20]		+ ? ? + + ? ?
Total (95% CI)		**165**		**159**	**100.0%**	**0.31 [0.05 , 2.02]**		
Total events:	1		4					

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable

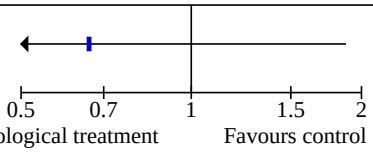


Footnotes
(1) From flow-chart

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Psychological intervention versus control, Outcome 8: All-cause mortality - medium term

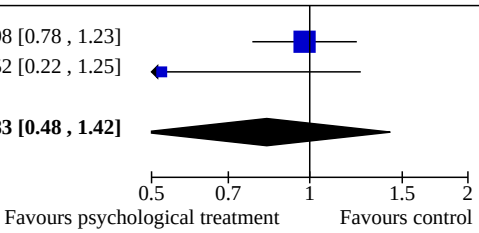
Study or Subgroup	Psychological Events	Psychological Total	Control Events	Control Total	Odds Ratio IV, Random, 95% CI
SPIRR-CAD 2011	6	285	9	285	0.66 [0.23 , 1.88]



Analysis 1.9. Comparison 1: Psychological intervention versus control, Outcome 9: All-cause mortality - long term

Study or Subgroup	Psychological Events	Psychological Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
ENRICHD 2003	168	1238	172	1243	73.5%	0.98 [0.78 , 1.23]
Yang 2019 (1)	9	94	16	95	26.5%	0.52 [0.22 , 1.25]
Total (95% CI)		**1332**		**1338**	**100.0%**	**0.83 [0.48 , 1.42]**
Total events:	177		188			

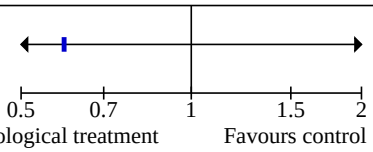
Heterogeneity: Tau² = 0.09; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Footnotes
(1) From flow-chart

Analysis 1.10. Comparison 1: Psychological intervention versus control, Outcome 10: Cardiovascular mortality - medium term

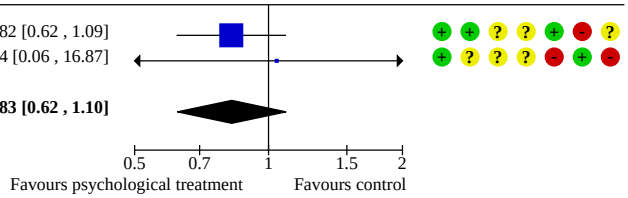
Study or Subgroup	Psychological Events	Psychological Total	Control Events	Control Total	Odds Ratio IV, Random, 95% CI
SPIRR-CAD 2011	3	285	5	285	0.60 [0.14 , 2.52]



Analysis 1.11. Comparison 1: Psychological intervention versus control, Outcome 11: Cardiovascular mortality - long term

Study or Subgroup	Psychological Events	Psychological Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
ENRICHD 2003	96	1238	115	1243	99.0%	0.82 [0.62 , 1.09]
U-CARE 2018	1	117	1	122	1.0%	1.04 [0.06 , 16.87]
Total (95% CI)		**1355**		**1365**	**100.0%**	**0.83 [0.62 , 1.10]**
Total events:	97		116			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.19)
Test for subgroup differences: Not applicable

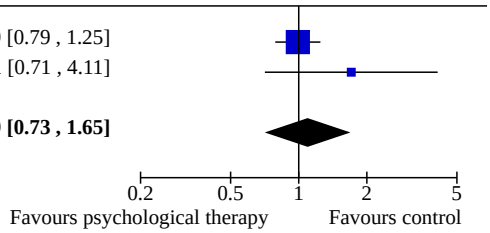


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: Psychological intervention versus control, Outcome 12: Myocardial infarction - long term

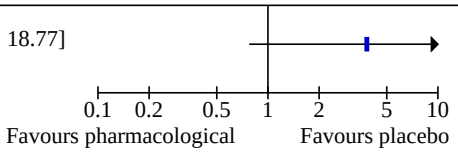
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
ENRICHD 2003	168	1238	170	1243	81.7%	0.99 [0.79 , 1.25]
U-CARE 2018	14	117	9	122	18.3%	1.71 [0.71 , 4.11]
Total (95% CI)		**1355**		**1365**	**100.0%**	**1.09 [0.73 , 1.65]**
Total events:	182		179			

Heterogeneity: Tau² = 0.04; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



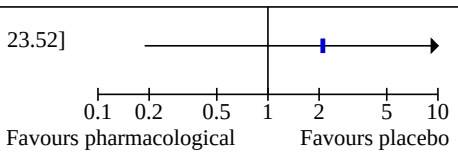
Analysis 1.13. Comparison 1: Psychological intervention versus control, Outcome 13: Heart failure - long term

Study or Subgroup	Psychological Events	Psychological Total	Usual Care Events	Usual Care Total	Odds Ratio IV, Random, 95% CI
U-CARE 2018	7	117	2	122	3.82 [0.78 , 18.77]



Analysis 1.14. Comparison 1: Psychological intervention versus control, Outcome 14: Stroke - long term

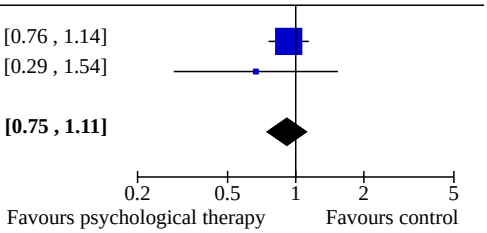
Study or Subgroup	Psychological Events	Psychological Total	Usual Care Events	Usual Care Total	Odds Ratio IV, Random, 95% CI
U-CARE 2018	2	117	1	122	2.10 [0.19 , 23.52]



Analysis 1.15. Comparison 1: Psychological intervention versus control, Outcome 15: Coronary revascularisation procedure - long term

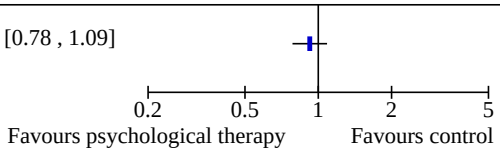
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
ENRICHD 2003	216	1238	230	1243	94.3%	0.93 [0.76 , 1.14]
U-CARE 2018	12	177	12	122	5.7%	0.67 [0.29 , 1.54]
Total (95% CI)		**1415**		**1365**	**100.0%**	**0.91 [0.75 , 1.11]**
Total events:	228		242			

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



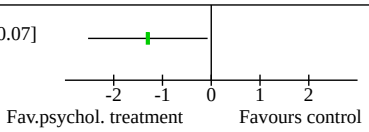
Analysis 1.16. Comparison 1: Psychological intervention versus control, Outcome 16: Hospitalisations - long term

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio IV, Random, 95% CI
ENRICHD 2003	442	1238	467	1243	0.92 [0.78 , 1.09]



Analysis 1.17. Comparison 1: Psychological intervention versus control, Outcome 17: Length of stay - short term

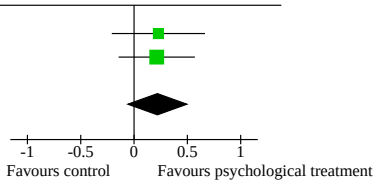
Study or Subgroup	Psychological Treatment Mean	Psychological Treatment SD	Psychological Treatment Total	Control Mean	Control SD	Control Total	Mean Difference IV, Random, 95% CI
Dao 2011	7.9	2.6	48	9.2	3.5	49	-1.30 [-2.53 , -0.07]



Analysis 1.18. Comparison 1: Psychological intervention versus control, Outcome 18: Quality of life SF-12/36 physical - short term

Study or Subgroup	Psychologcal Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Freedland 2009	38	9.6	41	35.8	9.49	40	40.1%	0.23 [-0.21 , 0.67]
MoodCare 2011	38	9.2	61	35.9	10.4	60	59.9%	0.21 [-0.14 , 0.57]
Total (95% CI)			**102**			**100**	**100.0%**	**0.22 [-0.06 , 0.50]**

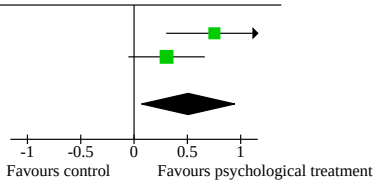
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Psychological intervention versus control, Outcome 19: Quality of life SF-12/36 mental - short term

Study or Subgroup	Psychologcal Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Freedland 2009	52.5	12.17	41	43.3	12.02	40	45.1%	0.75 [0.30 , 1.20]
MoodCare 2011	44.8	11	61	41.3	11.8	60	54.9%	0.30 [-0.05 , 0.66]
Total (95% CI)			**102**			**100**	**100.0%**	**0.51 [0.07 , 0.94]**

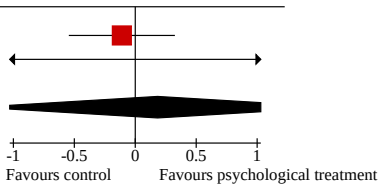
Heterogeneity: Tau² = 0.06; Chi² = 2.32, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 2.27 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Psychological intervention versus control, Outcome 20: Quality of life SF-12/36 physical - medium term

Study or Subgroup	SMD	SE	Psychological Treatment Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Freedland 2009	-0.11	0.222	41	40	86.7%	-0.11 [-0.55 , 0.33]
MoodCare 2011	2.1	1.9073	53	53	13.3%	2.10 [-1.64 , 5.84]
Total (95% CI)			**94**	**93**	**100.0%**	**0.18 [-1.29 , 1.65]**

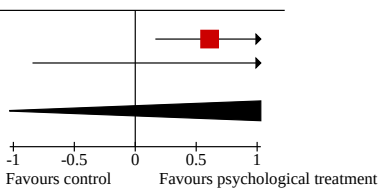
Heterogeneity: Tau² = 0.60; Chi² = 1.32, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



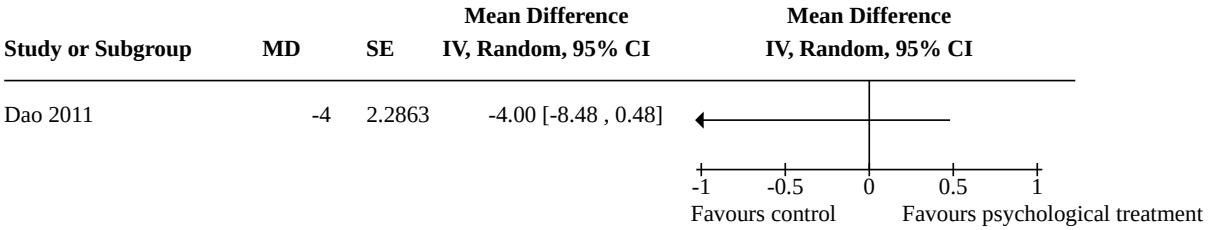
Analysis 1.21. Comparison 1: Psychological intervention versus control, Outcome 21: Quality of life SF-12/36 mental - medium term

Study or Subgroup	SMD	SE	Psychological Treatment Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Freedland 2009	0.61	0.227	41	40	79.1%	0.61 [0.17 , 1.05]
MoodCare 2011	3.5	2.2159	53	53	20.9%	3.50 [-0.84 , 7.84]
Total (95% CI)			**94**	**93**	**100.0%**	**1.21 [-1.09 , 3.52]**

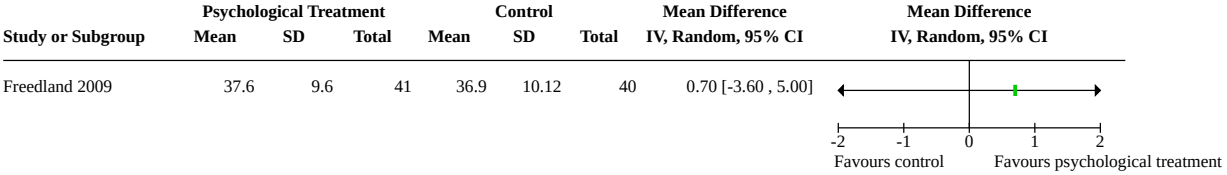
Heterogeneity: Tau² = 1.70; Chi² = 1.68, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



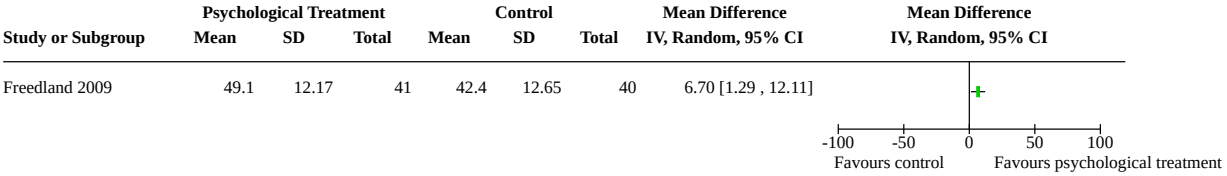
Analysis 1.22. Comparison 1: Psychological intervention versus control, Outcome 22: Quality of life SF-12 total - medium term



Analysis 1.23. Comparison 1: Psychological intervention versus control, Outcome 23: Quality of life SF-36 physical - long term



Analysis 1.24. Comparison 1: Psychological intervention versus control, Outcome 24: Quality of life SF-36 mental - long term



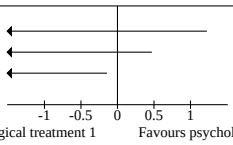
Comparison 2. Psychological intervention versus psychological intervention/clinical management

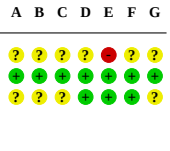
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Depression symptoms - short term	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Depression symptoms - medium term	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3 Depression symptoms - long term	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4 Depression remission - short term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2.5 Depression remission - medium term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2.6 Depression remission - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 Cardiovascular mortality - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2.8 Quality of life SF-36 physical - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.9 Quality of life SF-36 mental - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.10 Quality of life SF-36 physical - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.11 Quality of life SF-36 mental - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.12 Quality of life SF-36 physical - long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.13 Quality of life SF-36 mental - long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 1: Depression symptoms - short term

Study or Subgroup	Psychological Treatment 1 Mean	SD	Total	Psychological Treatment 2 Mean	SD	Total	Mean Difference IV, Random, 95% CI
Brown 1993	6.9	4.3	20	9.35	7.2	20	-2.45 [-6.13 , 1.23]
Freedland 2009	5.5	6.4	41	7.8	6.48	42	-2.30 [-5.07 , 0.47]
TREATED-ACS 2020	29.39	6.55	48	32.3	7.26	48	-2.91 [-5.68 , -0.14]

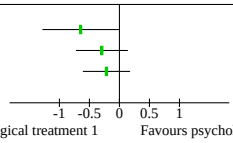




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

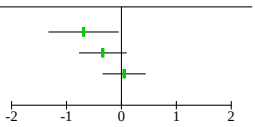
Analysis 2.2. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 2: Depression symptoms - medium term

Study or Subgroup	Psychological Treatment 1 Mean	SD	Total	Psychological Treatment 2 Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Brown 1993	6.3	2.9	20	9.7	6.7	20	-0.65 [-1.28 , -0.01]
Freedland 2009	6.6	6.4	41	8.5	6.48	42	-0.29 [-0.72 , 0.14]
TREATED-ACS 2020	30.48	5.81	50	31.89	7.11	50	-0.22 [-0.61 , 0.18]



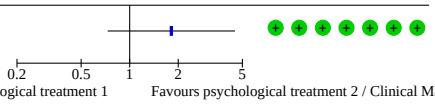
Analysis 2.3. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 3: Depression symptoms - long term

Study or Subgroup	Psychological Treatment 1 Mean	SD	Total	Psychological Treatment 2 Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Brown 1993	5.6	4.4	20	10.5	8.8	20	-0.69 [-1.33 , -0.05]
Freedland 2009	5.5	6.4	41	7.7	6.48	42	-0.34 [-0.77 , 0.10]
TREATED-ACS 2020	30.64	7.02	50	30.3	6.82	50	0.05 [-0.34 , 0.44]



Analysis 2.4. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 4: Depression remission - short term

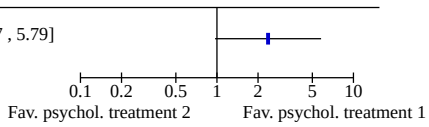
Study or Subgroup	Psychological treatment 1 Events	Total	Psychological treatment 2 Events	Total	Odds Ratio IV, Random, 95% CI
Freedland 2009	29	41	24	42	1.81 [0.73 , 4.50]



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

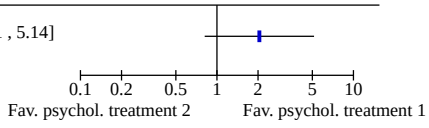
Analysis 2.5. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 5: Depression remission - medium term

Study or Subgroup	Psychological treatment 1 Events	Total	Psychological treatment 2 Events	Total	Odds Ratio IV, Random, 95% CI
Freedland 2009	28	41	20	42	2.37 [0.97 , 5.79]

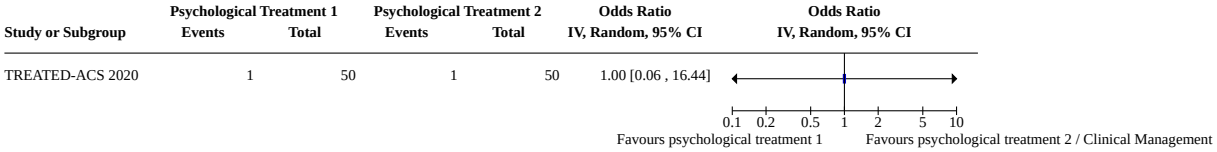


Analysis 2.6. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 6: Depression remission - long term

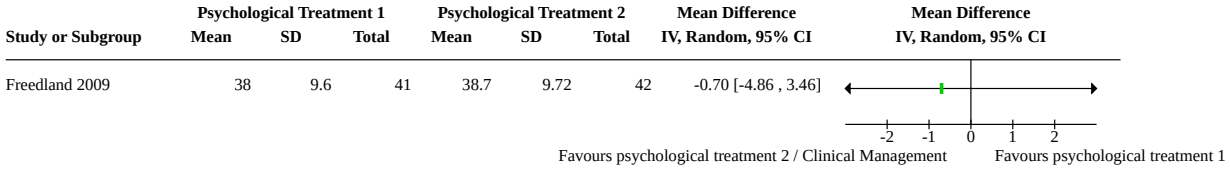
Study or Subgroup	Psychological treatment 1 Events	Total	Psychological treatment 2 Events	Total	Odds Ratio IV, Random, 95% CI
Freedland 2009	30	41	24	42	2.05 [0.81 , 5.14]



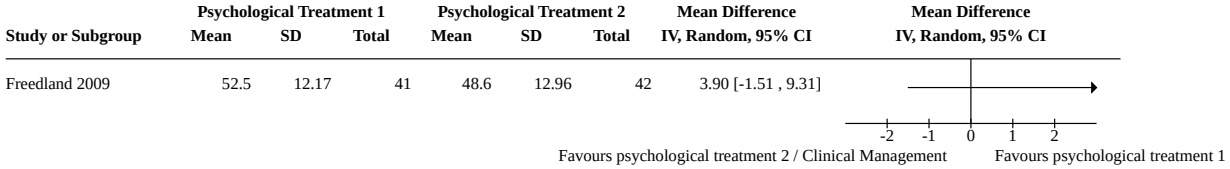
Analysis 2.7. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 7: Cardiovascular mortality - long term



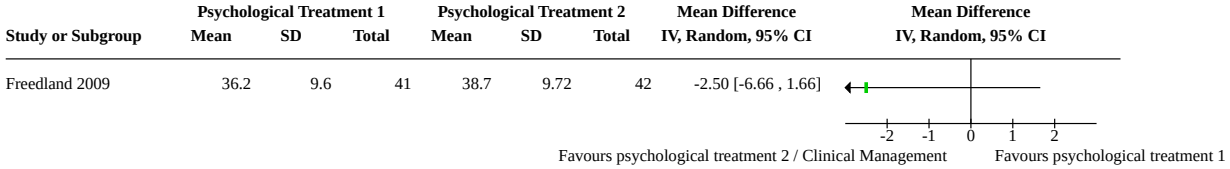
Analysis 2.8. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 8: Quality of life SF-36 physical - short term



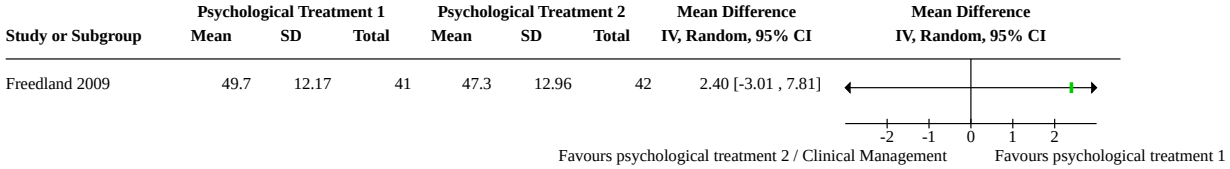
Analysis 2.9. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 9: Quality of life SF-36 mental - short term



Analysis 2.10. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 10: Quality of life SF-36 physical - medium term

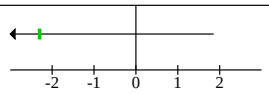


Analysis 2.11. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 11: Quality of life SF-36 mental - medium term



Analysis 2.12. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 12: Quality of life SF-36 physical - long term

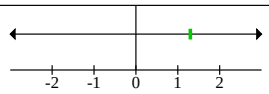
Study or Subgroup	Psychological Treatment 1 Mean	SD	Total	Psychological Treatment 2 Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Freedland 2009	37.6	9.6	41	39.9	9.72	42	-2.30 [-6.46 , 1.86]	



Favours psychological treatment 2 / Clinical Management Favours psychological treatment 1

Analysis 2.13. Comparison 2: Psychological intervention versus psychological intervention/clinical management, Outcome 13: Quality of life SF-36 mental - long term

Study or Subgroup	Psychological Treatment 1 Mean	SD	Total	Psychological Treatment 2 Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Freedland 2009	49.1	12.17	41	47.8	12.96	42	1.30 [-4.11 , 6.71]	



Favours psychological treatment 2 / Clinical Management Favours psychological treatment 1

Comparison 3. Pharmacological intervention versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Depression symptoms - short term	8	750	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.33, -0.32]
3.2 Depression symptoms change score - short term	3	482	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.36, -0.00]
3.3 Depression remission - short term	4	646	Odds Ratio (IV, Random, 95% CI)	2.06 [1.47, 2.89]
3.4 Depression response - short term	5	891	Odds Ratio (IV, Random, 95% CI)	2.73 [1.65, 4.54]
3.5 All-cause mortality - short term	2	437	Odds Ratio (IV, Random, 95% CI)	0.38 [0.10, 1.47]
3.6 All-cause mortality - long term	2	661	Odds Ratio (IV, Random, 95% CI)	0.89 [0.64, 1.25]
3.7 Cardiovascular mortality - long term	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
3.8 Myocardial infarction - short term	3	728	Odds Ratio (IV, Random, 95% CI)	0.74 [0.26, 2.09]
3.9 Myocardial infarction - long term	1		Odds Ratio (IV, Random, 95% CI)	Subtotals only
3.10 Angina - short term	4	819	Odds Ratio (IV, Random, 95% CI)	0.75 [0.44, 1.28]

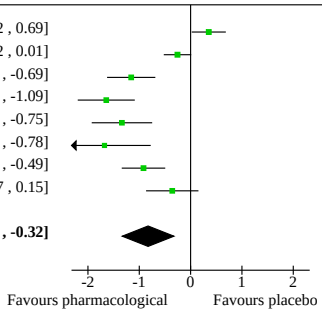
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11 Heart failure - short term	3	602	Odds Ratio (IV, Random, 95% CI)	0.93 [0.33, 2.62]
3.12 Arrhythmia - short term	2	87	Odds Ratio (IV, Random, 95% CI)	0.46 [0.01, 17.06]
3.13 Stroke - short term	2	586	Odds Ratio (IV, Random, 95% CI)	0.99 [0.20, 4.96]
3.14 Coronary revascularisation procedure - long term	1	300	Odds Ratio (IV, Random, 95% CI)	0.59 [0.32, 1.10]
3.15 Healthcare costs - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.16 Hospitalisations - short term	3	514	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.39, 0.85]
3.17 Emergency department visits - short term	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.18 Quality of life Q-LES-Q - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.19 Quality of life WHOQOL-BREF Physical - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.20 Quality of life WHOQOL-BREF Psychological - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.21 Quality of life WHOQOL-BREF Social relationships - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.22 Quality of life WHOQOL-BREF Environmental - short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.23 Quality of life WHOQOL-BREF Physical - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.24 Quality of life WHOQOL-BREF Psychological - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.25 Quality of life WHOQOL-BREF Social Relationships - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.26 Quality of life WHOQOL-BREF Environmental - medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.27 Systolic BP - short term	3	675	Mean Difference (IV, Random, 95% CI)	-0.24 [-3.52, 3.05]
3.28 Diastolic BP - short term	3	675	Mean Difference (IV, Random, 95% CI)	0.60 [-1.55, 2.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.29 Heart rate - short term	4	662	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.40, 0.79]
3.30 Platelet biomarker βTG - short term	3	141	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.99, -0.09]
3.31 Platelet biomarker PF4 - short term	3	144	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.48, 0.19]
3.32 Platelet biomarker P-selectin - short term	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-1.12, 0.50]
3.33 Platelet biomarker PECAM-1 - short term	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.34 Platelet biomarker TxB_2 - short term	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.35 ECG PR interval - short term	3	635	Mean Difference (IV, Random, 95% CI)	-4.35 [-8.40, -0.31]
3.36 ECG QRS interval - short term	3	635	Mean Difference (IV, Random, 95% CI)	2.37 [-0.41, 5.15]
3.37 ECG QT interval - short term	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.38 ECG QTc interval - short term	3	635	Mean Difference (IV, Random, 95% CI)	2.76 [-1.96, 7.47]
3.39 Non-cardiac adverse events and side effects - short term	8	1193	Odds Ratio (M-H, Random, 95% CI)	1.44 [1.07, 1.92]

Analysis 3.1. Comparison 3: Pharmacological intervention versus placebo, Outcome 1: Depression symptoms - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
CREATE 2007	16.1	9.96	75	12.6	9.7	67	13.6%	0.35 [0.02 , 0.69]
EsDEPACS 2014	8.6	6	108	10.1	5.7	109	13.8%	-0.26 [-0.52 , 0.01]
Li 2005	13	4	43	19.3	6.6	39	12.8%	-1.16 [-1.63 , -0.69]
Liu 1999	15.5	5.2	31	24.7	5.8	37	12.3%	-1.64 [-2.20 , -1.09]
Ma 2019	3.2	2.1	28	6.4	2.6	27	12.0%	-1.34 [-1.93 , -0.75]
McFarlane 2001	16.5	1.5	12	27	8	15	9.9%	-1.68 [-2.58 , -0.78]
Pizzi 2009	13	7	47	21	10	48	13.1%	-0.92 [-1.34 , -0.49]
UPBEAT 2012	7.8	5.1	40	9.7	5.5	24	12.6%	-0.36 [-0.87 , 0.15]
Total (95% CI)			**384**			**366**	**100.0%**	**-0.83 [-1.33 , -0.32]**

Heterogeneity: Tau² = 0.46; Chi² = 70.64, df = 7 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable

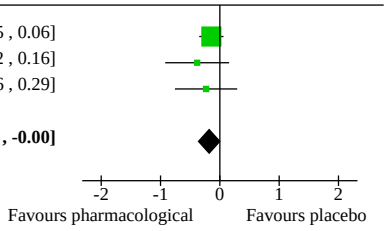


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Pharmacological intervention versus placebo, Outcome 2: Depression symptoms change score - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
SADHART 2002	-8.4	5.59	186	-7.6	5.55	183	77.2%	-0.14 [-0.35 , 0.06]
Strik 2000	-9.65	7.17	27	-6.92	6.91	27	11.1%	-0.38 [-0.92 , 0.16]
UPBEAT 2012	-6.1	6.64	36	-4.5	7.05	23	11.7%	-0.23 [-0.76 , 0.29]
Total (95% CI)			**249**			**233**	**100.0%**	**-0.18 [-0.36 , -0.00]**

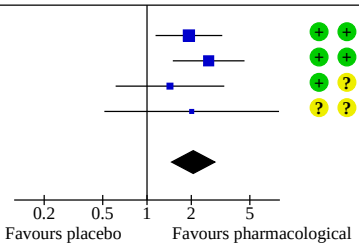
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable

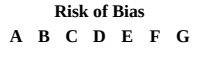


Analysis 3.3. Comparison 3: Pharmacological intervention versus placebo, Outcome 3: Depression remission - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
CREATE 2007	51	142	32	142	41.9%	1.93 [1.14 , 3.25]
EsDEPACS 2014	77	108	53	109	36.2%	2.62 [1.50 , 4.60]
MIND-IT 2007	20	47	15	44	15.8%	1.43 [0.61 , 3.35]
Strik 2000	7	27	4	27	6.1%	2.01 [0.51 , 7.89]
Total (95% CI)		**324**		**322**	**100.0%**	**2.06 [1.47 , 2.89]**
Total events:	155		104			

Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)
Test for subgroup differences: Not applicable



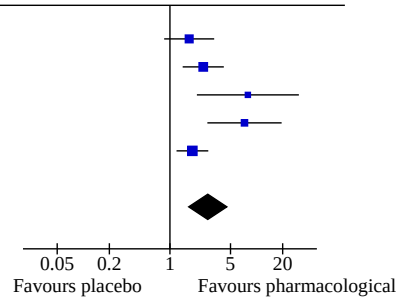


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Pharmacological intervention versus placebo, Outcome 4: Depression response - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
CREATE 2007	42	75	29	67	21.9%	1.67 [0.86 , 3.24]
EsDEPACS 2014	69	108	46	109	24.9%	2.42 [1.40 , 4.19]
Liu 1999	28	31	20	37	10.0%	7.93 [2.05 , 30.75]
Pizzi 2009 (1)	26	47	7	48	15.0%	7.25 [2.70 , 19.45]
SADHART 2002	125	186	97	183	28.2%	1.82 [1.19 , 2.77]
Total (95% CI)		**447**		**444**	**100.0%**	**2.73 [1.65 , 4.54]**
Total events:	290		199			

Heterogeneity: Tau² = 0.19; Chi² = 10.55, df = 4 (P = 0.03); I² = 62%
Test for overall effect: Z = 3.89 (P < 0.0001)
Test for subgroup differences: Not applicable

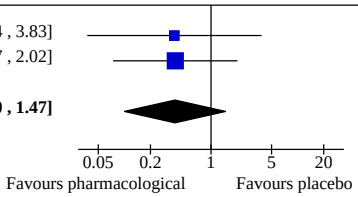


Footnotes
(1) Includes “improved” defined as change to a lower category of depression on BDI

Analysis 3.5. Comparison 3: Pharmacological intervention versus placebo, Outcome 5: All-cause mortality - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Liu 1999	1	31	3	37	33.7%	0.38 [0.04 , 3.83]
SADHART 2002	2	186	5	183	66.3%	0.39 [0.07 , 2.02]
Total (95% CI)		**217**		**220**	**100.0%**	**0.38 [0.10 , 1.47]**
Total events:	3		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

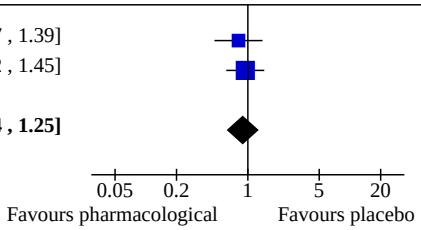


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.6. Comparison 3: Pharmacological intervention versus placebo, Outcome 6: All-cause mortality - long term

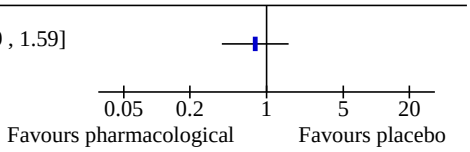
Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
EsDEPACS 2014	31	149	37	151	38.4%	0.81 [0.47 , 1.39]
SADHART 2002	115	184	113	177	61.6%	0.94 [0.62 , 1.45]
Total (95% CI)		**333**		**328**	**100.0%**	**0.89 [0.64 , 1.25]**
Total events:	146		150			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

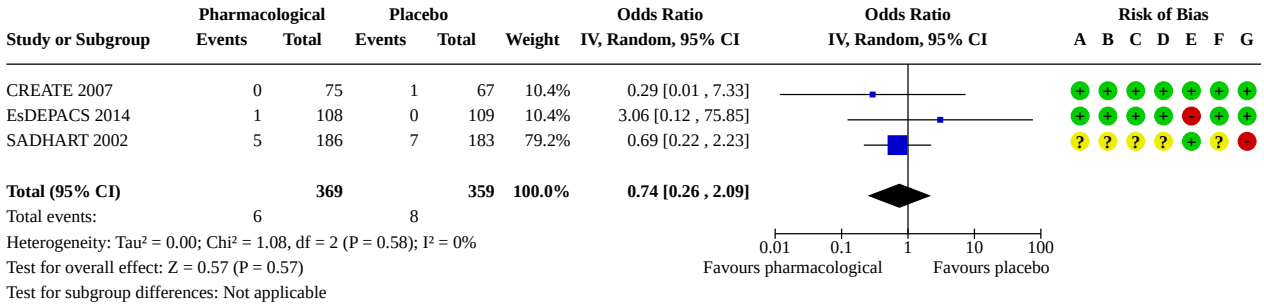


Analysis 3.7. Comparison 3: Pharmacological intervention versus placebo, Outcome 7: Cardiovascular mortality - long term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Odds Ratio IV, Random, 95% CI
EsDEPACS 2014	16	149	20	151	0.79 [0.39 , 1.59]



Analysis 3.8. Comparison 3: Pharmacological intervention versus placebo, Outcome 8: Myocardial infarction - short term

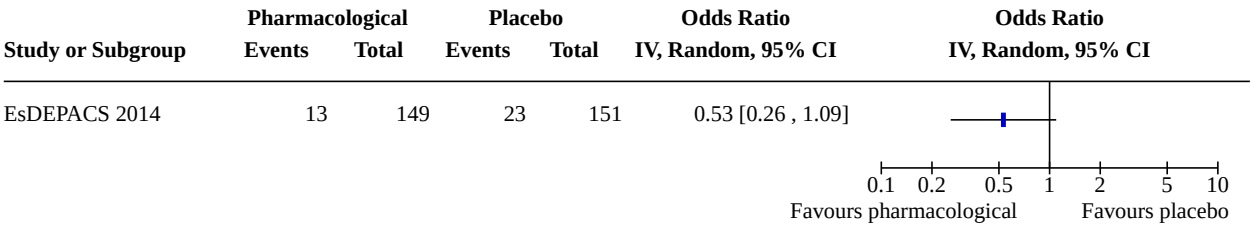


Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
CREATE 2007	0	75	1	67	10.4%	0.29 [0.01 , 7.33]
EsDEPACS 2014	1	108	0	109	10.4%	3.06 [0.12 , 75.85]
SADHART 2002	5	186	7	183	79.2%	0.69 [0.22 , 2.23]
Total (95% CI)		**369**		**359**	**100.0%**	**0.74 [0.26 , 2.09]**
Total events:	6		8			

Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable

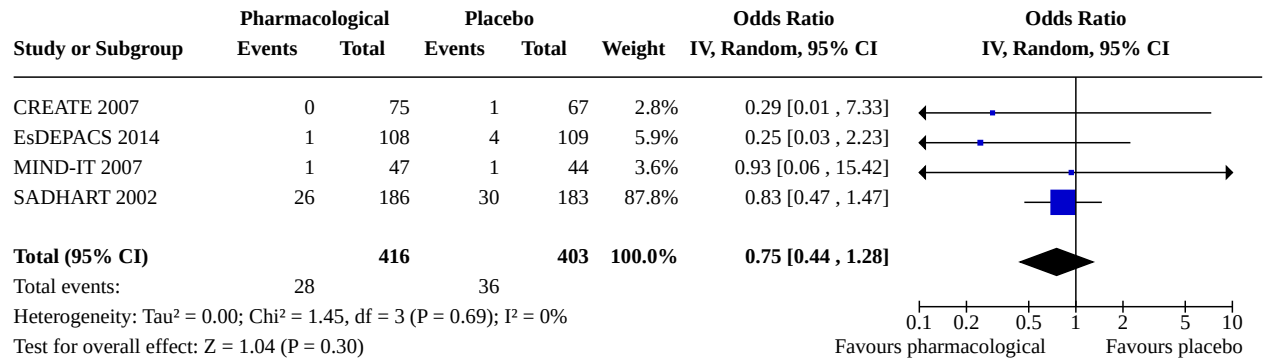
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.9. Comparison 3: Pharmacological intervention versus placebo, Outcome 9: Myocardial infarction - long term



Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Odds Ratio IV, Random, 95% CI
EsDEPACS 2014	13	149	23	151	0.53 [0.26 , 1.09]

Analysis 3.10. Comparison 3: Pharmacological intervention versus placebo, Outcome 10: Angina - short term



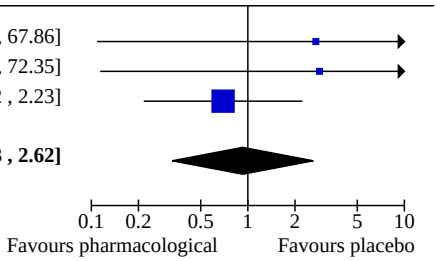
Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
CREATE 2007	0	75	1	67	2.8%	0.29 [0.01 , 7.33]
EsDEPACS 2014	1	108	4	109	5.9%	0.25 [0.03 , 2.23]
MIND-IT 2007	1	47	1	44	3.6%	0.93 [0.06 , 15.42]
SADHART 2002	26	186	30	183	87.8%	0.83 [0.47 , 1.47]
Total (95% CI)		**416**		**403**	**100.0%**	**0.75 [0.44 , 1.28]**
Total events:	28		36			

Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable

Analysis 3.11. Comparison 3: Pharmacological intervention versus placebo, Outcome 11: Heart failure - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
CREATE 2007	1	75	0	67	10.4%	2.72 [0.11 , 67.86]
MIND-IT 2007	1	47	0	44	10.4%	2.87 [0.11 , 72.35]
SADHART 2002	5	186	7	183	79.2%	0.69 [0.22 , 2.23]
Total (95% CI)		**308**		**294**	**100.0%**	**0.93 [0.33 , 2.62]**
Total events:	7		7			

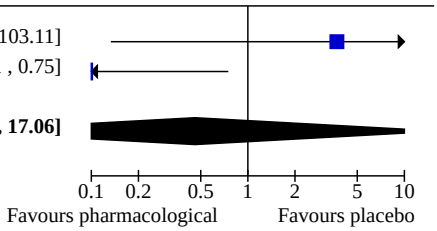
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Pharmacological intervention versus placebo, Outcome 12: Arrhythmia - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Kennedy 2005	1	9	0	10	43.8%	3.71 [0.13 , 103.11]
Liu 1999	1	31	10	37	56.2%	0.09 [0.01 , 0.75]
Total (95% CI)		**40**		**47**	**100.0%**	**0.46 [0.01 , 17.06]**
Total events:	2		10			

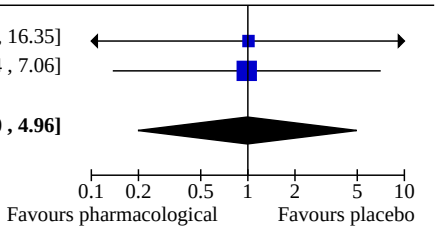
Heterogeneity: Tau² = 4.89; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 3.13. Comparison 3: Pharmacological intervention versus placebo, Outcome 13: Stroke - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
EsDEPACS 2014	1	108	1	109	33.4%	1.01 [0.06 , 16.35]
SADHART 2002	2	186	2	183	66.6%	0.98 [0.14 , 7.06]
Total (95% CI)		**294**		**292**	**100.0%**	**0.99 [0.20 , 4.96]**
Total events:	3		3			

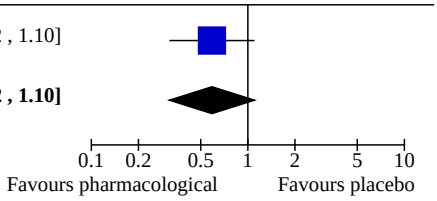
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 3.14. Comparison 3: Pharmacological intervention versus placebo, Outcome 14: Coronary revascularisation procedure - long term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
EsDEPACS 2014 (1)	19	149	30	151	100.0%	0.59 [0.32 , 1.10]
Total (95% CI)		**149**		**151**	**100.0%**	**0.59 [0.32 , 1.10]**
Total events:	19		30			

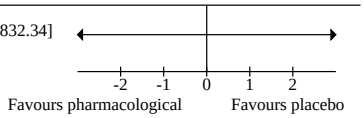
Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Footnotes
(1) PCI only

Analysis 3.15. Comparison 3: Pharmacological intervention versus placebo, Outcome 15: Healthcare costs - short term

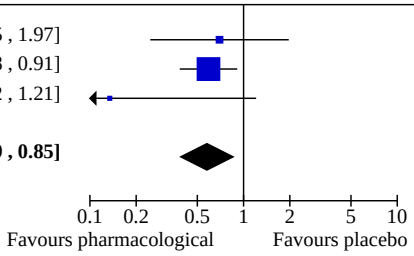
Study or Subgroup	Pharmacological Mean [USD]	Pharmacological SD [USD]	Pharmacological Total	Placebo Mean [USD]	Placebo SD [USD]	Placebo Total	Mean Difference IV, Random, 95% CI [USD]
SADHART 2002	2733	6764	186	3326	7195	183	-593.00 [-2018.34 , 832.34]



Analysis 3.16. Comparison 3: Pharmacological intervention versus placebo, Outcome 16: Hospitalisations - short term

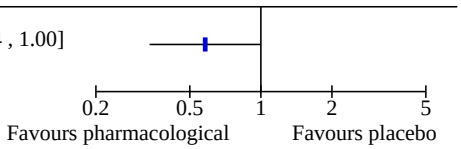
Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
MIND-IT 2007	8	47	10	44	14.2%	0.70 [0.25 , 1.97]
SADHART 2002	55	186	76	183	82.6%	0.59 [0.38 , 0.91]
Strik 2000	1	27	6	27	3.2%	0.13 [0.02 , 1.21]
Total (95% CI)		**260**		**254**	**100.0%**	**0.58 [0.39 , 0.85]**
Total events:	64		92			

Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable



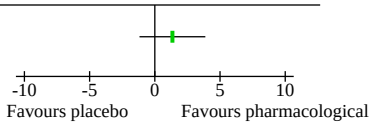
Analysis 3.17. Comparison 3: Pharmacological intervention versus placebo, Outcome 17: Emergency department visits - short term

Study or Subgroup	Pharmacological Events	Pharmacological Total	Placebo Events	Placebo Total	Odds Ratio M-H, Random, 95% CI
SADHART 2002	26	186	40	183	0.58 [0.34 , 1.00]



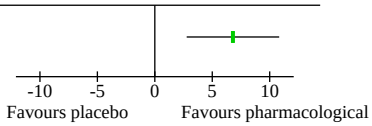
Analysis 3.18. Comparison 3: Pharmacological intervention versus placebo, Outcome 18: Quality of life Q-LES-Q - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
SADHART 2002	9.03	11.84	170	7.68	11.8	167	1.35 [-1.17 , 3.87]



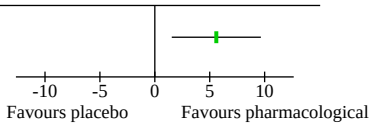
Analysis 3.19. Comparison 3: Pharmacological intervention versus placebo, Outcome 19: Quality of life WHOQOL-BREF Physical - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	51.6	16.1	107	44.8	13.8	106	6.80 [2.77 , 10.83]



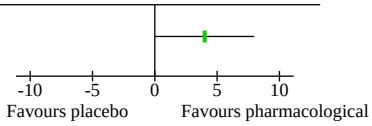
Analysis 3.20. Comparison 3: Pharmacological intervention versus placebo, Outcome 20: Quality of life WHOQOL-BREF Psychological - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	47.5	14.9	107	41.9	15.3	106	5.60 [1.54 , 9.66]



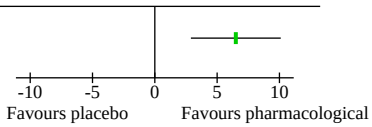
Analysis 3.21. Comparison 3: Pharmacological intervention versus placebo, Outcome 21: Quality of life WHOQOL-BREF Social relationships - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	53.2	14.1	107	49.2	15.4	106	4.00 [0.03 , 7.97]



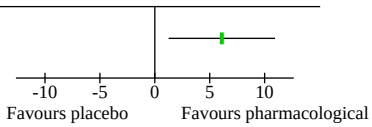
Analysis 3.22. Comparison 3: Pharmacological intervention versus placebo, Outcome 22: Quality of life WHOQOL-BREF Environmental - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	50.4	12.7	107	43.9	14.1	106	6.50 [2.90 , 10.10]



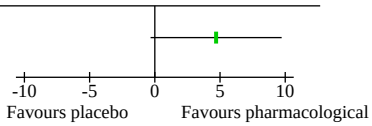
Analysis 3.23. Comparison 3: Pharmacological intervention versus placebo, Outcome 23: Quality of life WHOQOL-BREF Physical - medium term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	51.3	18.2	107	45.2	17.9	106	6.10 [1.25 , 10.95]



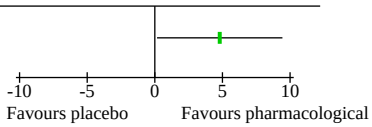
Analysis 3.24. Comparison 3: Pharmacological intervention versus placebo, Outcome 24: Quality of life WHOQOL-BREF Psychological - medium term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	54.5	18.2	107	49.8	19.2	106	4.70 [-0.33 , 9.73]



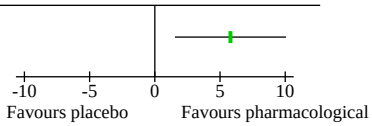
Analysis 3.25. Comparison 3: Pharmacological intervention versus placebo, Outcome 25: Quality of life WHOQOL-BREF Social Relationships - medium term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	57.1	15.9	107	52.3	18.5	106	4.80 [0.17 , 9.43]



Analysis 3.26. Comparison 3: Pharmacological intervention versus placebo, Outcome 26: Quality of life WHOQOL-BREF Environmental - medium term

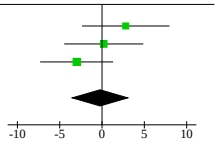
Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
EsDEPACS 2014	55.6	14.6	107	49.8	17	106	5.80 [1.54 , 10.06]



Analysis 3.27. Comparison 3: Pharmacological intervention versus placebo, Outcome 27: Systolic BP - short term

Study or Subgroup	Pharmacological Mean [mmHg]	Pharmacological SD [mmHg]	Pharmacological Total	Placebo Mean [mmHg]	Placebo SD [mmHg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
CREATE 2007	126.5	15.24	75	123.7	16.06	67	29.1%	2.80 [-2.37 , 7.97]
EsDEPACS 2014	122.2	17.3	108	122	17.8	109	33.6%	0.20 [-4.47 , 4.87]
SADHART 2002 (1)	127	18	159	130	21	157	37.3%	-3.00 [-7.31 , 1.31]
Total (95% CI)			**342**			**333**	**100.0%**	**-0.24 [-3.52 , 3.05]**

Heterogeneity: Tau² = 2.68; Chi² = 2.93, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

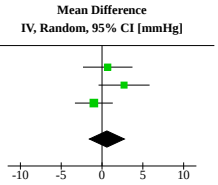


Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.28. Comparison 3: Pharmacological intervention versus placebo, Outcome 28: Diastolic BP - short term

Study or Subgroup	Pharmacological Mean [mmHg]	Pharmacological SD [mmHg]	Pharmacological Total	Placebo Mean [mmHg]	Placebo SD [mmHg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
CREATE 2007	74.9	9.22	75	74.2	9.18	67	30.3%	0.70 [-2.33 , 3.73]
EsDEPACS 2014	78.5	11.7	108	75.8	11.8	109	29.2%	2.70 [-0.43 , 5.83]
SADHART 2002 (1)	76	10	159	77	11	157	40.5%	-1.00 [-3.32 , 1.32]
Total (95% CI)			**342**			**333**	**100.0%**	**0.60 [-1.55 , 2.74]**

Heterogeneity: Tau² = 1.55; Chi² = 3.52, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

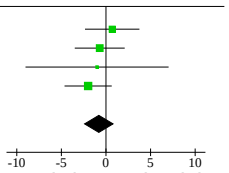


Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.29. Comparison 3: Pharmacological intervention versus placebo, Outcome 29: Heart rate - short term

Study or Subgroup	Pharmacological Mean [bpm]	Pharmacological SD [bpm]	Pharmacological Total	Placebo Mean [bpm]	Placebo SD [bpm]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [bpm]
CREATE 2007	62.4	8.1	75	61.7	10.18	67	27.3%	0.70 [-2.35 , 3.75]
EsDEPACS 2014	67.5	10	91	68.2	9	86	32.4%	-0.70 [-3.50 , 2.10]
McFarlane 2001	64	11	12	65	10	15	4.0%	-1.00 [-9.02 , 7.02]
SADHART 2002 (1)	64	12	159	66	12	157	36.3%	-2.00 [-4.65 , 0.65]
Total (95% CI)			**337**			**325**	**100.0%**	**-0.80 [-2.40 , 0.79]**

Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.32)
Test for subgroup differences: Not applicable

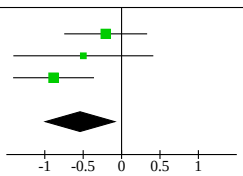


Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.30. Comparison 3: Pharmacological intervention versus placebo, Outcome 30: Platelet biomarker βTG - short term

Study or Subgroup	Pharmacological Mean	Pharmacological SD	Pharmacological Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
CREATE 2007	370.04	143.2	36	402.75	176	21	39.7%	-0.21 [-0.75 , 0.33]
MIND-IT 2007	49.6	15.7	8	61	25.1	12	19.4%	-0.50 [-1.41 , 0.41]
SADHART 2002	42.8	22.8	25	65.1	26.1	39	40.9%	-0.89 [-1.41 , -0.36]
Total (95% CI)			**69**			**72**	**100.0%**	**-0.54 [-0.99 , -0.09]**

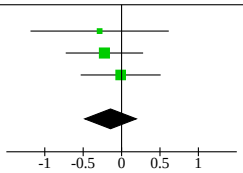
Heterogeneity: Tau² = 0.06; Chi² = 3.13, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.31. Comparison 3: Pharmacological intervention versus placebo, Outcome 31: Platelet biomarker PF4 - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
MIND-IT 2007	7.1	5.5	8	10.5	13.9	12	13.9%	-0.29 [-1.19 , 0.61]
SADHART 2002	37.4	36.1	25	43.6	20.1	39	44.4%	-0.22 [-0.73 , 0.28]
UPBEAT 2012	34	38	37	34.4	23	23	41.6%	-0.01 [-0.53 , 0.51]
Total (95% CI)			**70**			**74**	**100.0%**	**-0.14 [-0.48 , 0.19]**

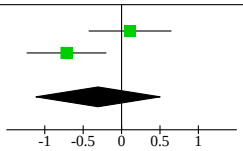
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 3.32. Comparison 3: Pharmacological intervention versus placebo, Outcome 32: Platelet biomarker P-selectin - short term

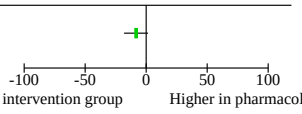
Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
CREATE 2007	82.75	28.1	36	79.83	22.3	21	49.6%	0.11 [-0.43 , 0.65]
SADHART 2002	70.4	22.5	25	87.4	24	39	50.4%	-0.72 [-1.23 , -0.20]
Total (95% CI)			**61**			**60**	**100.0%**	**-0.31 [-1.12 , 0.50]**

Heterogeneity: Tau² = 0.27; Chi² = 4.70, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



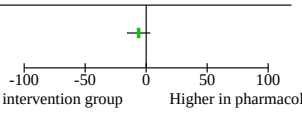
Analysis 3.33. Comparison 3: Pharmacological intervention versus placebo, Outcome 33: Platelet biomarker PECAM-1 - short term

Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
SADHART 2002	39.7	17.8	25	48	22	39	-8.30 [-18.12 , 1.52]



Analysis 3.34. Comparison 3: Pharmacological intervention versus placebo, Outcome 34: Platelet biomarker TxB_2 - short term

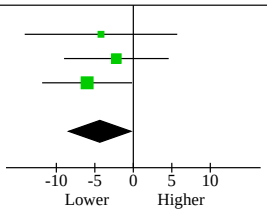
Study or Subgroup	Pharmacological Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
SADHART 2002	42.7	15.2	25	48.9	23.9	39	-6.20 [-15.78 , 3.38]



Analysis 3.35. Comparison 3: Pharmacological intervention versus placebo, Outcome 35: ECG PR interval - short term

Study or Subgroup	Pharmacological Mean [ms]	Pharmacological SD [ms]	Pharmacological Total	Placebo Mean [ms]	Placebo SD [ms]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [ms]
CREATE 2007	167.3	28.96	75	171.5	31.03	67	16.7%	-4.20 [-14.11 , 5.71]
EsDEPACS 2014	163.9	24.5	91	166.1	21.6	86	35.4%	-2.20 [-9.00 , 4.60]
SADHART 2002 (1)	167	27	159	173	26	157	47.9%	-6.00 [-11.84 , -0.16]
Total (95% CI)			**325**			**310**	**100.0%**	**-4.35 [-8.40 , -0.31]**

Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable

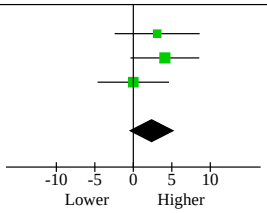


Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.36. Comparison 3: Pharmacological intervention versus placebo, Outcome 36: ECG QRS interval - short term

Study or Subgroup	Pharmacological Mean [ms]	Pharmacological SD [ms]	Pharmacological Total	Placebo Mean [ms]	Placebo SD [ms]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [ms]
CREATE 2007	97.3	19.47	75	94.2	13.88	67	25.4%	3.10 [-2.42 , 8.62]
EsDEPACS 2014	97.7	16.3	91	93.6	14	86	38.7%	4.10 [-0.37 , 8.57]
SADHART 2002 (1)	98	20	159	98	22	157	35.9%	0.00 [-4.64 , 4.64]
Total (95% CI)			**325**			**310**	**100.0%**	**2.37 [-0.41 , 5.15]**

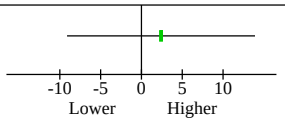
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.37. Comparison 3: Pharmacological intervention versus placebo, Outcome 37: ECG QT interval - short term

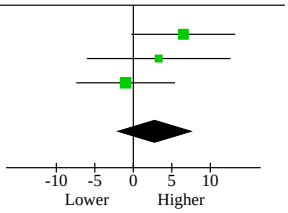
Study or Subgroup	Pharmacological Mean [ms]	Pharmacological SD [ms]	Pharmacological Total	Placebo Mean [ms]	Placebo SD [ms]	Placebo Total	Mean Difference IV, Random, 95% CI [ms]
CREATE 2007	413	35.72	75	410.6	34.24	67	2.40 [-9.11 , 13.91]



Analysis 3.38. Comparison 3: Pharmacological intervention versus placebo, Outcome 38: ECG QTc interval - short term

Study or Subgroup	Pharmacological Mean [ms]	Pharmacological SD [ms]	Pharmacological Total	Placebo Mean [ms]	Placebo SD [ms]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [ms]
CREATE 2007	418.4	25.2	75	411.9	15.12	67	37.4%	6.50 [-0.26 , 13.26]
EsDEPACS 2014	424.4	29.8	91	421.1	33.3	86	22.1%	3.30 [-6.03 , 12.63]
SADHART 2002 (1)	418	27	159	419	31	157	40.5%	-1.00 [-7.41 , 5.41]
Total (95% CI)			**325**			**310**	**100.0%**	**2.76 [-1.96 , 7.47]**

Heterogeneity: Tau² = 3.60; Chi² = 2.51, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable

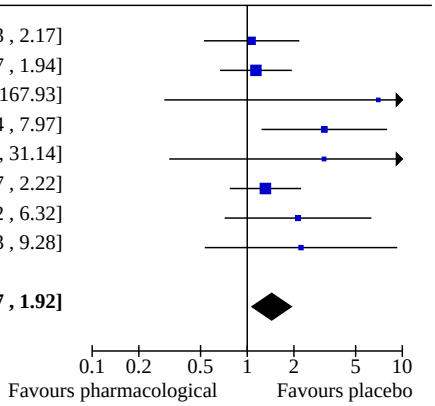


Footnotes
(1) Week 16 observations or end of treatment observations (week 24)

Analysis 3.39. Comparison 3: Pharmacological intervention versus placebo, Outcome 39: Non-cardiac adverse events and side effects - short term

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
CREATE 2007	18	142	17	142	16.8%	1.07 [0.53 , 2.17]
EsDEPACS 2014	55	108	52	109	29.7%	1.14 [0.67 , 1.94]
Kennedy 2005	2	9	0	10	0.8%	7.00 [0.29 , 167.93]
MIND-IT 2007 (1)	21	47	9	44	9.7%	3.14 [1.24 , 7.97]
Pizzi 2009	3	50	1	50	1.6%	3.13 [0.31 , 31.14]
SADHART 2002 (2)	38	186	30	183	30.1%	1.31 [0.77 , 2.22]
Strik 2000	17	27	12	27	7.1%	2.13 [0.72 , 6.32]
UPBEAT 2012 (3)	9	36	3	23	4.1%	2.22 [0.53 , 9.28]
Total (95% CI)		**605**		**588**	**100.0%**	**1.44 [1.07 , 1.92]**
Total events:	163		124			

Heterogeneity: Tau² = 0.00; Chi² = 6.50, df = 7 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable



Footnotes
(1) Most common side-effect - fatigue
(2) Most common side-effect - headache
(3) Most common side-effect - sexual problems

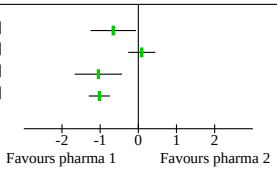
Comparison 4. Pharmacological intervention versus pharmacological intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Depression symptoms - short term	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4.2 Depression symptoms change score - short term	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4.3 Depression remission - short term	3		Odds Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Depression response - short term	4		Odds Ratio (IV, Random, 95% CI)	Totals not selected
4.5 All-cause mortality - short term	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.6 Myocardial infarction - short term	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.7 Angina - short term	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.8 Heart failure - short term	2		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.9 Arrhythmia - short term	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.10 Coronary revascularisation procedure - short term	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.11 Emergency department visits - short term	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.12 Systolic BP - short term	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.13 Diastolic BP - short term	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.14 Heart rate - short term	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.15 ECG PR interval - short term	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.16 ECG QRS interval - short term	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.17 ECG QTc interval - short term	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.18 Non-cardiac adverse events and side effects - short term	7		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 1: Depression symptoms - short term

Study or Subgroup	Pharmacological intervention 1 Mean	SD	Total	Pharmacological intervention 2 Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Abbasi 2015 (1)	4.95	3.98	23	8.56	6.5	23	-0.66 [-1.25 , -0.06]
Carney 2009 (2)	9.7	6.5	62	9.1	6.7	60	0.09 [-0.26 , 0.45]
Tian 2016 (3)	11.2	4	23	15.9	4.8	23	-1.05 [-1.67 , -0.43]
Wang 2020 (4)	7.25	3.25	113	10.63	3.35	115	-1.02 [-1.30 , -0.74]

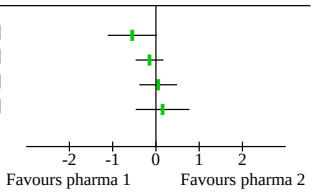


Footnotes
(1) Simvastatin vs. Atorvastatin
(2) sertraline plus omega-3 vs. sertraline plus placebo
(3) Paroxetine vs. Fluoxetine
(4) Escitalopram vs. Bu Xin Qi

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 2: Depression symptoms change score - short term

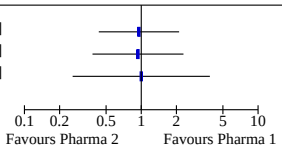
Study or Subgroup	Pharmacological intervention 1 Mean	SD	Total	Pharmacological intervention 2 Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Divsalar 2018 (1)	-14.56	2.43	25	-13.32	2.01	25	-0.55 [-1.11 , 0.02]
Liu 2016 (2)	-11.02	6.1896	76	-10.13	5.8099	73	-0.15 [-0.47 , 0.17]
Roose 1998 (3)	-12.7	7.8	41	-13.1	7.4	40	0.05 [-0.38 , 0.49]
Shahmansouri 2014 (4)	-11.65	4.39	20	-12.3	3.94	20	0.15 [-0.47 , 0.77]

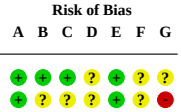


Footnotes
(1) Sertraline plus Red Yeast Rice vs. Sertraline + Placebo
(2) Sertraline vs. Shugan Jieyu
(3) paroxetine vs. notriptyline
(4) saffron vs. fluoxetine

Analysis 4.3. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 3: Depression remission - short term

Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio IV, Random, 95% CI
Carney 2009 (1)	17	62	17	60	0.96 [0.43 , 2.11]
Roose 1998	25	41	25	40	0.94 [0.38 , 2.30]
Shahmansouri 2014	14	20	14	20	1.00 [0.26 , 3.87]



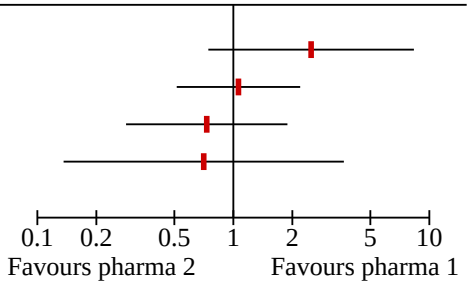


Footnotes
(1) sertraline plus omega-3 vs. sertraline plus placebo

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 4: Depression response - short term

Study or Subgroup	log[OR]	SE	Odds Ratio IV, Random, 95% CI
Abbasi 2015 (1)	0.9137	0.6161	2.49 [0.75 , 8.34]
Carney 2009 (2)	0.06	0.37	1.06 [0.51 , 2.19]
Roose 1998	-0.3126	0.4836	0.73 [0.28 , 1.89]
Shahmansouri 2014	-0.348	0.84	0.71 [0.14 , 3.66]



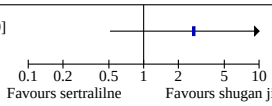
Footnotes

(1) Simvastatin vs. Atorvastatin

(2) sertraline plus omega-3 vs. sertraline plus placebo

Analysis 4.5. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 5: All-cause mortality - short term

Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Liu 2016 (1)	5	73	2	76	2.72 [0.51 , 14.49]	+ ? ? ? ? ? -



Footnotes

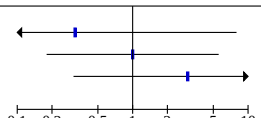
(1) Sertraline vs. Shugan Jieyu

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.6. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 6: Myocardial infarction - short term

Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Carney 2009 (1)	0	62	1	60	0.32 [0.01 , 7.94]	+ + + ? + ? ?
Tian 2016 (2)	3	23	3	23	1.00 [0.18 , 5.56]	? ? ? ? ? ? -
Wang 2020 (3)	3	115	1	113	3.00 [0.31 , 29.28]	+ - - - - ? ?



Footnotes

(1) sertraline plus omega-3 vs. sertraline plus placebo

(2) Paroxetine vs. Fluoxetine

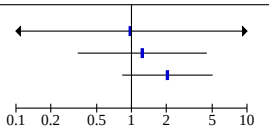
(3) Escitalopram vs. Bu Xin Qi

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.7. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 7: Angina - short term

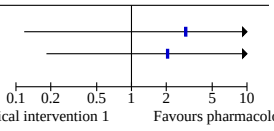
Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI
Roose 1998 (1)	1	41	1	40	0.97 [0.06 , 16.14]
Tian 2016 (2)	7	23	6	23	1.24 [0.34 , 4.49]
Wang 2020 (3)	15	113	8	115	2.05 [0.83 , 5.04]



Footnotes
(1) Paroxetine vs. nortriptyline
(2) Paroxetine vs. Fluoxetine
(3) Escitalopram vs. Bu Xin Qi

Analysis 4.8. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 8: Heart failure - short term

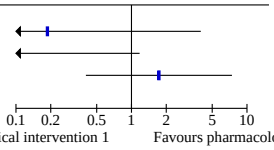
Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI
Carney 2009 (1)	1	62	0	60	2.95 [0.12 , 73.88]
Wang 2020 (2)	2	113	1	115	2.05 [0.18 , 22.98]



Footnotes
(1) sertraline plus omega-3 vs. sertraline plus placebo
(2) Escitalopram vs. Bu Xin Qi

Analysis 4.9. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 9: Arrhythmia - short term

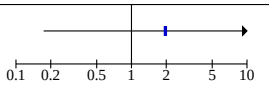
Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI
Carney 2009 (1)	0	62	2	60	0.19 [0.01 , 3.98]
Roose 1998 (2)	0	41	6	40	0.06 [0.00 , 1.18]
Wang 2020 (3)	5	113	3	115	1.73 [0.40 , 7.41]



Footnotes
(1) sertraline plus omega-3 vs. sertraline plus placebo
(2) Paroxetine vs. nortriptyline
(3) Escitalopram vs. Bu Xin Qi

Analysis 4.10. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 10: Coronary revascularisation procedure - short term

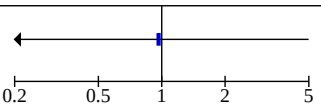
Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI
Carney 2009 (1)	2	62	1	60	1.97 [0.17 , 22.28]



Footnotes
(1) sertraline plus omega-3 vs. sertraline plus placebo

Analysis 4.11. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 11: Emergency department visits - short term

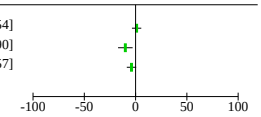
Study or Subgroup	Pharmacological 1 Events	Pharmacological 1 Total	Pharmacological 2 Events	Pharmacological 2 Total	Odds Ratio M-H, Random, 95% CI
Carney 2009 (1)	3	62	3	60	0.97 [0.19 , 4.99]



Footnotes
(1) sertraline plus omega-3 vs. sertraline plus placebo

Analysis 4.12. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 12: Systolic BP - short term

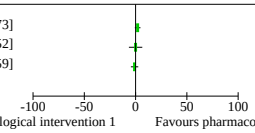
Study or Subgroup	Pharmacological intervention 1 Mean [mmHg]	SD [mmHg]	Total	Pharmacological intervention 2 Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]
Liu 2016 (1)	116	13.7	73	115	14.6	76	1.00 [-3.54 , 5.54]
Roose 1998 (2)	76	11	37	86	16	26	-10.00 [-17.10 , -2.90]
Tian 2016 (3)	115	7.6	23	119	8.2	23	-4.00 [-8.57 , 0.57]



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline (standing measure)
(3) Paroxetine vs. Fluoxetine

Analysis 4.13. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 13: Diastolic BP - short term

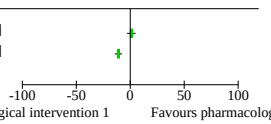
Study or Subgroup	Pharmacological intervention 1 Mean [mmHg]	SD [mmHg]	Total	Pharmacological intervention 2 Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]
Liu 2016 (1)	77	8.6	73	75	8.4	76	2.00 [-0.73 , 4.73]
Roose 1998 (2)	78	13	37	78	13	26	0.00 [-6.52 , 6.52]
Tian 2016 (3)	72	6	23	73	6.4	23	-1.00 [-4.59 , 2.59]



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline (standing measure)
(3) Paroxetine vs. Fluoxetine

Analysis 4.14. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 14: Heart rate - short term

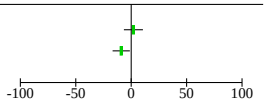
Study or Subgroup	Pharmacological intervention 1 Mean [bpm]	SD [bpm]	Total	Pharmacological intervention 2 Mean [bpm]	SD [bpm]	Total	Mean Difference IV, Random, 95% CI [bpm]
Liu 2016 (1)	65	12.3	73	64	12.1	76	1.00 [-2.92 , 4.92]
Roose 1998 (2)	72	6	37	83	7	26	-11.00 [-14.31 , -7.69]



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline (standing measure)

Analysis 4.15. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 15: ECG PR interval - short term

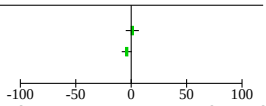
Study or Subgroup	Pharmacological intervention 1 Mean [ms]	SD [ms]	Total	Pharmacological intervention 2 Mean [ms]	SD [ms]	Total	Mean Difference IV, Random, 95% CI [ms]	Mean Difference IV, Random, 95% CI [ms]
Liu 2016 (1)	168	26.9	73	166	26.5	76	2.00 [-6.58 , 10.58]	
Roose 1998 (2)	164	11	37	173	18	26	-9.00 [-16.77 , -1.23]	



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline

Analysis 4.16. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 16: ECG QRS interval - short term

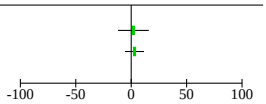
Study or Subgroup	Pharmacological intervention 1 Mean [ms]	SD [ms]	Total	Pharmacological intervention 2 Mean [ms]	SD [ms]	Total	Mean Difference IV, Random, 95% CI [ms]	Mean Difference IV, Random, 95% CI [ms]
Liu 2016 (1)	97	18.3	73	96	18.6	76	1.00 [-4.93 , 6.93]	
Roose 1998 (2)	100	5	37	104	11	26	-4.00 [-8.52 , 0.52]	



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline

Analysis 4.17. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 17: ECG QTc interval - short term

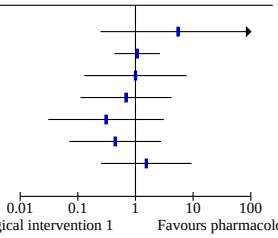
Study or Subgroup	Pharmacological intervention 1 Mean [ms]	SD [ms]	Total	Pharmacological intervention 2 Mean [ms]	SD [ms]	Total	Mean Difference IV, Random, 95% CI [ms]	Mean Difference IV, Random, 95% CI [ms]
Liu 2016 (1)	420	43.6	73	418	42.9	76	2.00 [-11.89 , 15.89]	
Roose 1998 (2)	419	14	37	416	19	26	3.00 [-5.58 , 11.58]	



Footnotes
(1) Sertraline vs. Shugan Jieyu; 12 week observations
(2) Paroxetine vs. nortriptyline

Analysis 4.18. Comparison 4: Pharmacological intervention versus pharmacological intervention, Outcome 18: Non-cardiac adverse events and side effects - short term

Study or Subgroup	Pharmacological intervention 1 Events	Total	Pharmacological intervention 2 Events	Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Abbasi 2015 (1)	2	23	0	23	5.47 [0.25 , 120.37]	
Carney 2009 (2)	12	62	11	60	1.07 [0.43 , 2.65]	
Divsalar 2018 (3)	2	25	2	25	1.00 [0.13 , 7.72]	
Liu 2016 (4)	2	73	3	76	0.69 [0.11 , 4.23]	
Roose 1998 (5)	1	41	3	40	0.31 [0.03 , 3.10]	
Shahmansouri 2014 (6)	2	20	4	20	0.44 [0.07 , 2.76]	
Wang 2020 (6)	3	113	2	115	1.54 [0.25 , 9.40]	



Footnotes
(1) Simvastatin vs. Atorvastatin
(2) sertraline plus omega-3 vs. sertraline plus placebo
(3) Sertraline plus Red Yeast Rice vs. Sertraline + Placebo
(4) Sertraline vs. Shugan Jieyu
(5) Paroxetine vs. nortriptyline
(6) Fluoxetine vs. Saffron

ADDITIONAL TABLES

Table 1. Overview of study population

Study ID	Intervention	[n]screened	[n] randomised	[n] ITT	[n] finishing study	[%] of randomised participants finishing study	Comments
Abbasi 2015	Intervention 1 (I1): simvastatin Intervention 2 (I2): atorvastatin	Total: 206	I1: 29 I2: 29 Total: 58	I1: NR I2: NR Total: NR (per-protocol)	I1: 23 I2: 23 Total: 46	I1: 79.3% I2: 79.3% Total: 79.3%	
ANDROS 2015	Intervention (I): sertraline Control (C): placebo	Total: ?	I: ? C: ? Total: 2	I: ? C: ? Total: ?	I: ? C: ? Total: ?	I: ? C: ? Total: ?	Comment: trial terminated early, no results posted
Barth 2005	Intervention (I): resource-orientated psychotherapy Control (C): usual care	Total: 1709	I: 27 C: 32 Total: 59	I: 27 C: 32 Total: 59 (per-protocol)	I: 27 C: 28 Total: 55	I: 100% C: 87.5% Total: 93.2%	
Brown 1993	Intervention 1 (I1): behaviour therapy Intervention 2 (I2): person-centred therapy	Total: 107	I1: NR I2: NR Total: 54	I1: NR I2: NR Total: NR (per-protocol)	I1: 20 I2: 20 Total: 40	I1: ? I2: ? Total: 74.1%	Comment: dropout reported in text, no flow chart
CREATE 2007	Intervention 1 (I1): interpersonal psychotherapy, citalopram, clinical management Intervention 2 (I2): citalopram, clinical management Control 1 (C1): interpersonal psychotherapy, placebo, clinical management	Total: 1897	I1: 67 I2: 75 C1: 75 C2: 67 Total: 284	I1: 67 I2: 75 C1: 75 C2: 67 Total: 284	I1: 59 I2: 72 C1: 59 C2: 47 Total: 237	I1: 88.1% I2: 96.0% C1: 78.7% C2: 70.1% Total: 83.5%	Comment: 2 x 2 factorial trial; only I2 and C2 data are eligible for this review

Table 1. Overview of study population *(Continued)*

	Control 2 (C2): placebo, clinical management						
Carney 2009	Intervention 1 (I1): sertraline plus omega-3 Intervention 2 (I2): sertraline plus placebo	Total: 941	I1: 62 I2: 60 Total: 122	I1: 62 I2: 60 Total: 122	I1: 59 I2: 56 Total: 115	I1: 95.2% I2: 93.3% Total: 94.3%	
Dao 2011	Intervention (I): cognitive- behavioural therapy C: usual care	Total: 513	I: 50 C: 50 Total: 100	I: NR C: NR Total: NR (per-protocol)	I: 48 C: 48: Total: 96	I: 96% C: 96% Total: 96%	
Divsalar 2018	Intervention 1 (I1): sertraline plus red yeast rice Intervention 2 (I2): sertraline plus placebo	Total: 101	I1: 28 I2: 28 Total: 56	I1: NR I2: NR Total: NR	I1: 25 I2: 25 Total: 50	I1: 89.3% I2: 89.3% Total: 89.3%	
Doering 2007	Intervention (I): cognitive- behavioural therapy Control (C): usual care	Total: 117	I: NR C: NR Total: NR	I: NR C: NR Total: NR (per-protocol)	I: 7 C: 8 Total: 15	I: ? C: ? Total: ?	Comment: reasons for dropout not stated, no flow chart Comment: nested trial within observational study (non-depressed cohort)
EsDEPACS 2014	Intervention (I): escitalopram Control (C): placebo	Total: 4809	I:149 C: 151 Total: 300	I: 108 C: 109 Total: 217 (per-protocol)	I: 78 C: 79 Total: 157	I: 52.3% C: 52.3% Total: 52.3%	Comment: nested trial within observational study (depressed cohort receiving usual care)
ENRICHD 2003	Intervention (I): cognitive- behavioural therapy Control (C): usual care	Total: 33780	I: 1238 C: 1243 Total: 2481	I: 1238 C: 1243 Total: 2481	I: 983 C: 985 Total: 1968	I: 79.4% C: 79.2% Total: 79.3%	

Table 1. Overview of study population *(Continued)*

Fang 2003	Intervention (I): health education and psychological intervention Control (C): usual care	Total: ?	I: 27 C: 30 Total: 57	I: ? C: ? Total: ?	I: ? C: ? Total: ?	I: ? C: ? Total: ?	Comment: translated paper
Freedland 2009	Intervention 1 (I1): cognitive- behavioural therapy Intervention 2 (I2): supportive stress management Control (C): usual care	Total: 2955	I1: 41 I2: 42 C1: 40 Total: 123	I1: 41 I2: 42 C1: 40 Total: 123	I1: 40 I2: 33 C1: ? Total: ?	I1: 98% I2: 79% C1: ? Total: ?	
Freeman 1986	Intervention (I): alprazolam Control (C): placebo	Total: 459	I: 54 C: 53 Total: 107	I: NR C: NR Total: NR (per-protocol)	I: 32 C: 28 Total: 60	I: 59.3% C: 52.8% Total: 56.1%	Comment: no flow chart
Kennedy 2005	Intervention (I): escitalopram Control (C): placebo	Total: NR	I: 9 C: 10 Total: 19	I: NR C: NR Total: NR (per-protocol)	I: 2 C: 2 Total: 4	I: 22.2% C: 20.0% Total: 21.1%	Comment: trial terminated early, redacted results posted
Li 2005	Intervention (I): St John's wort extract Control (C): placebo	Total: ?	I: ? C: ? Total: 87	I: ? C: ? Total: ?	I: 43 C: 39 Total: 82	I: ? C: ? Total: 94.3%	Comment: translated paper
Liu 1999	Intervention (I): fluoxetine Control (C): placebo	Total: ?	I: ? C: ? Total: ?	I: ? C: ? Total: ?	I: 31 C: 37 Total: ?	I: ? C: ? Total: ?	Comment: translated paper
Liu 2016	Intervention 1 (I1): sertraline and Shugan Jieyu Intervention 2 (I2): sertraline and placebo	Total: 3907	I1: 76 I2: 73 Total: 149	I1: 76 I2: 73 Total: 149	I1: 48 I2: 46 Total: 94	I1: 63.2% I2: 63.0% Total: 63.1%	Comment: no flow chart, reasons for dropout reported in text

Table 1. Overview of study population *(Continued)*

MIND-IT 2007	Intervention (I): mirtazapine Control (C): placebo	Total: 2177	I: 47 C: 44 Total: 91	I: 47 C: 44 Total: 91	I: 22 C: 18 Total: 40	I: 46.8% C: 40.9% Total: 44.0%	Comment: nested trial within observational study (depressed cohort receiving usual care)
Ma 2019	Intervention (I): Xinkeshu Control (C): placebo	Total: 312	I: 30 C: 30 Total: 60	I: NR C: NR Total: NR	I: 28 C: 27 Total: 55	I: 93.3% C: 90% Total: 91.7%	
McFarlane 2001	Intervention (I): sertraline Control (C): placebo	Total: 238	I: 18 C: 20 Total: 38	I: NR C: NR Total: NR (per-protocol)	I: 12 C: 15 Total: 27	I: 66.7% C: 75.0% Total: 71.1%	Comment: no flow chart, reasons for dropout reported in text
McLaughlin 2005	Intervention (I1): telephone counselling Control (C): usual care	Total: 700	I: 53 C: 47 Total: 100	I: NR C: NR Total: NR (per-protocol)	I: 45 C: 34 Total: 79	I: 84.9% C: 72.3% Total: 79%	
MoodCare 2011	Intervention (I): cognitive- behavioural therapy Control (C): usual care	Total: 3071	I: 61 C: 60 Total: 121	I: NR C: NR Total: NR	I: 53 C: 53 Total: 106	I: 86.9% C: 88.3% Total: 87.6%	
Pizzi 2009	Intervention (I): sertraline Control (C): placebo	Total: 630	I: 50 C: 50 Total: 100	I: NR C: NR Total: NR (per-protocol)	I: 47 C: 48 Total: 95	I: 94% C: 96% Total: 95%	
Roose 1998	Intervention 1 (I1): paroxetine Intervention 2 (I2): nortriptyline	Total: NR	I1: 41 I2: 40 Total: 81	I1: 41 I2: 40 Total: 81	I1: 37 I2: 30 Total: 67	I1: 90.2% I2: 75.0% Total: 82.7%	Comment: no flow chart, reasons for dropout reported in text

Table 1. Overview of study population *(Continued)*

SADHART 2002	Intervention (I): sertraline Control (C): placebo	Total: 11546	I: 186 C: 183 Total: 369	I: 186 C: 183 Total: 169	I: 133 C: 137 Total: 270	I: 71.5% C: 74.9% Total: 73.1%	
SPIRR-CAD 2011	Intervention (I): stepwise psychotherapy intervention Control (C): usual care	Total: 21780	I: 285 C: 285 Total: 570	I: 284 C: 284 Total: 568	I: 110 C: 194 Total: 304	I: 38.6% C: 68.1% Total: 53.3%	
Shahmansouri 2014	Intervention 1 (I1): fluoxetine Intervention 2 (I2): *Crocus sativus* L. (saffron)	Total: 75	I1: 22 I2: 22 Total: 44	I1: NR I2: NR Total: NR (per-protocol)	I1: 20 I2: 20 Total: 40	I1: 90.9% I2: 90.9% Total: 90.9%	
Strik 2000	Intervention (I): fluoxetine Control (C): placebo	Total: 556	I: 27 C: 27 Total: 54	I: 27 C: 27 Total: 54	I: 22 C: 18 Total: 40	I: 81.5% C: 66.7% Total: 74.1%	
Tian 2016	Intervention 1 (I1): paroxetine Intervention 2 (I2): fluoxetine	Total: ?	I1: 23 I2: 23 Total: 46	I1: 23 I2: 23 Total: 46 (per-protocol)	I1: 23 I2: 23 Total: 46	I1: 100% I2: 100% Total: 100%	Comment: no flow chart was reported. It is unclear whether 16 participants who did not finish the study were from I1 or I2 groups, or non-treatment or non-depressed groups.
TREATED-ACS 2020	Intervention 1 (I1): cognitive-behavioural therapy and well-being therapy Intervention 2 (I2): clinical management	Total: 740	I1: 50 I2: 50 Total: 100	I1: 50 I2: 50 Total: 100	I1: 42 I2: 40 Total: 82	I1: 84% I2: 80% Total: 82%	
U-CARE 2018	Intervention (I): internet cognitive-behavioural therapy Control (C): usual care	Total: 3928	I: 117 C: 122	I: 117 C: 122	I: 96 C: 115	I: 82.1% C: 94.3%	

Table 1. Overview of study population *(Continued)*

			Total: 239	Total: 239	Total: 211	Total: 88.3%	
UPBEAT 2012	Intervention 1 (I1): sertraline Intervention 2 (I2): exercise Control (C): placebo	Total: 1680	I1: 40 I2: 37 C: 24 Total: 101	I1: NR I2: NR C: NR Total: NR	I1: 36 I2: 36 C: 23 Total: 95	I1: 90% I2: 97.3% C: 95.8% Total: 94.1%	Comment: only I1 sertraline and C placebo are eligible for this review
Wang 2020	Intervention 1 (I1): escitalopram Intervention 2 (I2): Bu Xin Qi decoction	Total: 300	I1: 140 I2: 140 Total: 280	I1: NR I2: NR Total: NR (per-protocol)	I1: 113 I2: 115 Total: 228	I1: 80.7% I2: 82.1% Total: 81.4%	Comment: reasons for dropout not stated in flow chart
WIDeCAD 2017	Intervention (I): internet cognitive-behavioural therapy Control (C): wait-list control	Total: 72	I: 18 C: 16 Total: 34	I: 18 C: 16 Total: 34	I: 13 C: 13 Total: 26	I: 72.2% C: 81.3% Total: 76.5%	
Yang 2019	Intervention (I): intensive telephone-based care Control (C): usual care	Total: 354	I: 112 C: 112 Total: 224	I: NR C: NR Total: NR	I: 107 C: 105 Total: 212	I: 95.5% C: 93.8% Total: 94.6%	
Zarea 2014	Intervention (I): Peplau's therapeutic communication model Control (C): usual care	Total: ?	I: ? C: ? Total: ?	I: ? C: ? Total: ? (per-protocol)	I: 37 C: 37 Total: 74	I: ? C: ? Total: ?	Comment: total sample estimated from degrees of freedom in Table 3

ITT = intention-to-treat; NR = not reported; ? = unclear

Table 2. Sensitivity analyses for depression symptoms at end of treatment in psychological versus control trials

Comparison	Sensitivity analysis	Study references [n]	SMD	I^2
Psychological vs control	None (Analysis 1.1)	Barth 2005; Dao 2011; Fang 2003; Freedland 2009; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; U-CARE 2018; WIDeCAD 2017; Zarea 2014 (n = 1226)	−0.55 (95% CI −0.92 to −0.19)	88
Psychological vs control	Constrained to trials without depression disorders as part of the inclusion criteria	Barth 2005; Dao 2011; Fang 2003; McLaughlin 2005; MoodCare 2011; SPIRR-CAD 2011; U-CARE 2018; WIDeCAD 2017; Zarea 2014 (n = 1145)	−0.53 (95% CI −0.92 to −0.13)	89
Psychological vs control	Constrained to depression (e.g. excluding trials with mixed depression and/or anxiety as part of the inclusion criteria)	Barth 2005; Freedland 2009; MoodCare 2011; SPIRR-CAD 2011; WIDeCAD 2017 (n = 681)	−0.27 (95% CI −0.58 to 0.03)	65
Psychological vs control	Constrained to cognitive-behavioural therapy trials	Dao 2011; Freedland 2009; MoodCare 2011; U-CARE 2018; WIDeCAD 2017 (n = 571)	−0.48 (95% CI −0.77 to −0.19)	61

CI = confidence interval; SMD = standardised mean difference

Table 3. Sensitivity analyses for depression symptoms at end of treatment in pharmacological versus placebo trials

Comparison	Sensitivity analysis	Study references [n]	SMD	I^2
Pharmacological vs placebo	None (Analysis 3.1)	CREATE 2007; EsDEPACS 2014; Li 2005; Liu 1999; Ma 2019; McFarlane 2001; Pizzi 2009; UPBEAT 2012 (n = 750)	SMD −0.83 (95% CI −1.33 to −0.32)	90
Pharmacological vs placebo	Constrained to trials with major depressive disorders as part of the inclusion criteria	CREATE 2007; EsDEPACS 2014; Liu 1999 (n = 427)	SMD −0.48 (95% CI −1.38 to 0.42)	95
Pharmacological vs placebo	Constrained to depression (e.g. excluding trials with mixed depression and/or anxiety as part of the inclusion criteria)	CREATE 2007; EsDEPACS 2014; Li 2005; Liu 1999; McFarlane 2001; Pizzi 2009; UPBEAT 2012 (n = 695)	SMD −0.76 (95% CI −1.29 to −0.23)	90
Pharmacological vs placebo	Constrained to serotonergic antidepressant trials	CREATE 2007; EsDEPACS 2014; Liu 1999; McFarlane 2001; Pizzi 2009; UPBEAT 2012 (n = 613)	SMD −0.69 (95% CI −1.27 to −0.11)	91

CI = confidence interval; SMD = standardised mean difference

APPENDICES

Appendix 1. Search strategies 2009

CENTRAL, DARE, HTA and EED on The Cochrane Library

#1 MeSH descriptor myocardial ischemia explode all trees
#2 MeSH descriptor Myocardial Revascularization explode all trees
#3 (ischemi* in All Text near/3 heart in All Text)
#4 (ischaemi* in All Text near/3 heart in All Text)
#5 (coronary in All Text near/3 disease* in All Text)
#6 angina in All Text
#7 myocardial next infarct* in All Text
#8 heart next infarct* in All Text
#9 (coronary in All Text near/3 bypass in All Text)
#10 (heart in All Text near/3 disease in All Text)
#11 (cardiac in All Text near/3 disease in All Text)
#12 chd in All Text
#13 cad in All Text
#14 (coronary in All Text near/3 angioplasty in All Text)
#15 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#16 (#11 or #12 or #13 or #14)
#17 (#15 or #16)
#18 MeSH descriptor depression explode all trees
#19 MeSH descriptor Depressive Disorder explode all trees
#20 MeSH descriptor Mood Disorders this term only
#21 "depression" in Keywords
#22 "depressive" in Keywords
#23 "Dysthymia" in Keywords
#24 dysthymi* in All Text
#25 (depressi* in All Text near/3 disorder* in All Text)
#26 (depressi* in All Text near/3 symptom* in All Text)
#27 mood next disorder* in All Text
#28 depression in Record Title
#29 antidepress* in All Text
#30 anti-depress* in All Text
#31 (#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27)
#32 (#28 or #29 or #30)
#33 (#31 or #32)
#34 (#17 and #33)

MEDLINE (OVID)

1 exp Myocardial Ischemia/
2 exp Myocardial Revascularization/
3 (isch?emi$ adj3 heart).tw.
4 (coronary adj3 disease).tw.
5 angina.tw.
6 myocardial infarct$.tw.
7 heart infarct$.tw.
8 (coronary adj3 bypass$).tw.
9 (heart adj3 disease).tw.
10 (cardiac adj3 disease).tw.
11 chd.tw.
12 CAD.tw.
13 (coronary adj3 angioplasty).tw.
14 or/1-13
15 Depression/
16 exp Depressive Disorder/
17 Mood Disorders/
18 dysthymi$.tw.
19 (depressi$ adj3 disorder$).tw.
20 (depressi$ adj3 symptom$).tw.

21 mood disorder$.tw.
22 affective disorder$.tw.
23 antidepress$.tw.
24 anti-depress$.tw.
25 or/15-24
26 14 and 25
27 randomized controlled trial.pt.
28 controlled clinical trial.pt.
29 randomized.ab.
30 placebo.ab.
31 drug therapy.fs.
32 randomly.ab.
33 trial.ab.
34 groups.ab.
35 or/27-34
36 (animals not humans).sh.
37 35 not 36
38 26 and 37

EMBASE (OVID)

1 exp ischemic heart disease/
2 exp coronary artery surgery/
3 exp percutaneous coronary intervention/
4 (isch?emi$ adj3 heart).tw.
5 (coronary adj3 disease).tw.
6 angina.tw.
7 myocardial infarct$.tw.
8 heart infarct$.tw.
9 (coronary adj3 bypass$).tw.
10 (heart adj3 disease).tw.
11 (cardiac adj3 disease).tw.
12 chd.tw.
13 CAD.tw.
14 (coronary adj3 angioplasty).tw.
15 or/1-14
16 exp depression/
17 affective neurosis/
18 Mood Disorder/
19 dysthymi$.tw.
20 (depressi$ adj3 disorder$).tw.
21 (depressi$ adj3 symptom$).tw.
22 mood disorder$.tw.
23 affective disorder$.tw.
24 antidepress$.tw.
25 anti-depress$.tw.
26 or/16-25
27 15 and 26
28 controlled clinical trial/
29 random$.tw.
30 randomized controlled trial/
31 follow-up.tw.
32 double blind procedure/
33 placebo$.tw.
34 placebo/
35 factorial$.ti,ab.
36 (crossover$ or cross-over$).ti,ab.
37 (double$ adj blind$).ti,ab.
38 (singl$ adj blind$).ti,ab.
39 assign$.ti,ab.
40 allocat$.ti,ab.
41 volunteer$.ti,ab.

42 Crossover Procedure/
43 Single Blind Procedure/
44 or/28-43
45 (exp animals/ or nonhuman/) not human/
46 44 not 45
47 27 and 46

PsycINFO

1 exp heart disorders/
2 heart surgery/
3 (isch?emi$ adj3 heart).tw.
4 (coronary adj3 disease).tw.
5 angina.tw.
6 myocardial infarct$.tw.
7 heart infarct$.tw.
8 (coronary adj3 bypass$).tw.
9 (heart adj3 disease).tw.
10 (cardiac adj3 disease).tw.
11 chd.tw.
12 CAD.tw.
13 (coronary adj3 angioplasty).tw.
14 or/1-13
15 exp affective disorders/
16 "depression (emotion)"/
17 dysthymi$.tw.
18 (depressi$ adj3 disorder$).tw.
19 (depressi$ adj3 symptom$).tw.
20 mood disorder$.tw.
21 affective disorder$.tw.
22 antidepress$.tw.
23 anti-depress$.tw.
24 or/15-23
25 14 and 24
26 random$.tw.
27 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or dummy or mask$)).tw.
28 placebo$.tw.
29 crossover.tw.
30 assign$.tw.
31 allocat$.tw.
32 ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)).tw.
33 placebo/
34 treatment effectiveness evaluation/
35 mental health program evaluation/
36 experimental design/
37 clinical trials/
38 or/26-37
39 25 and 38

CINAHL (EBSCO)

((MH "Affective Disorders+") or (TI depression) or dysthymi* or (mood disorder*) or (affective disorder*) or antidepress* or anti-depress* or (depressi* N3 disorder*) or (depressi* N3 symptom*)) and ((MH "Myocardial Ischemia+") or (MH "Myocardial Revascularization+") or Angina or (myocardial infarct*) or (heart infarct*) or coronary or cardiac or chd or CAD or (heart disease)) and ((MH "Clinical Trials+") or randomi* or randomly or placebo* or trial)

Appendix 2. Search strategies 2021

CENTRAL, DARE, HTA and EED on The Cochrane Library

#1 MeSH descriptor: [Myocardial Ischemia] explode all trees

#2 MeSH descriptor: [Myocardial Revascularization] explode all trees

#3 (ischemi* near/3 heart)

#4 (ischaemi* near/3 heart)

#5 (coronary near/3 disease*)

#6 angina

#7 myocardial next infarct*

#8 heart next infarct*

#9 (coronary near/3 bypass)

#10 (heart near/3 disease)

#11 (cardiac near/3 disease)

#12 chd

#13 cad

#14 (coronary near/3 angioplasty)

#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Depression] explode all trees

#17 MeSH descriptor: [Depressive Disorder] explode all trees

#18 MeSH descriptor: [Mood Disorders] this term only

#19 depression:kw

#20 depressive:kw

#21 Dysthymia:kw

#22 dysthymi*

#23 (depressi* near/3 disorder*)

#24 (depressi* near/3 symptom*)

#25 mood next disorder*

#26 depression:ti

#27 antidepress*

#28 anti-depress*

#29 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

#30 #15 and #29

MEDLINE OVID

1. exp Myocardial Ischemia/

2. exp Myocardial Revascularization/

3. (isch?emi$ adj3 heart).tw.

4. (coronary adj3 disease).tw.

5. angina.tw.

6. myocardial infarct$.tw.

7. heart infarct$.tw.

8. (coronary adj3 bypass$).tw.

9. (heart adj3 disease).tw.

10. (cardiac adj3 disease).tw.

11. chd.tw.

12. CAD.tw.

13. (coronary adj3 angioplasty).tw.

14. or/1-13

15. Depression/

16. exp Depressive Disorder/

17. Mood Disorders/

18. dysthymi$.tw.

19. (depressi$ adj3 disorder$).tw.

20. (depressi$ adj3 symptom$).tw.

21. mood disorder$.tw.

22. affective disorder$.tw.

23. antidepress$.tw.

24. anti-depress$.tw.

25. or/15-24

26. 14 and 25

27. randomized controlled trial.pt.

28. controlled clinical trial.pt.

29. randomized.ab.

30. placebo.ab.

31. drug therapy.fs.

32. randomly.ab.

33. trial.ab.

34. groups.ab.

35. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36. exp animals/ not humans.sh.

37. 35 not 36

38. 26 and 37

39.(200907* or 200908* or 200909* or 200910* or 200911* or 200912* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).ed.

40. 38 and 39

Embase OVID

1. exp ischemic heart disease/
2. exp coronary artery surgery/
3. exp percutaneous coronary intervention/
4. (isch?emi$ adj3 heart).tw.
5. (coronary adj3 disease).tw.
6. angina.tw.
7. myocardial infarct$.tw.
8. heart infarct$.tw.
9. (coronary adj3 bypass$).tw.
10. (heart adj3 disease).tw.
11. (cardiac adj3 disease).tw.
12. chd.tw.
13. CAD.tw.
14. (coronary adj3 angioplasty).tw.
15. or/1-14
16. exp depression/
17. affective neurosis/
18. Mood Disorder/
19. dysthymi$.tw.
20. (depressi$ adj3 disorder$).tw.
21. (depressi$ adj3 symptom$).tw.
22. mood disorder$.tw.
23. affective disorder$.tw.
24. antidepress$.tw.
25. anti-depress$.tw.
26. or/16-25
27. 15 and 26
28. random$.tw.
29. factorial$.tw.
30. crossover$.tw.
31. cross over$.tw.
32. cross-over$.tw.
33. placebo$.tw.
34. (doubl$ adj blind$).tw.

35. (singl$ adj blind$).tw.

36. assign$.tw.

37. allocat$.tw.

38. volunteer$.tw.

39. crossover procedure/

40. double blind procedure/

41. randomized controlled trial/

42. single blind procedure/

43. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42

44. (animal/ or nonhuman/) not human/

45. 43 not 44

46. 27 and 45

47. (2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dd.

48. 46 and 47

PsycINFO

1. exp heart disorders/

2. heart surgery/

3. (isch?emi$ adj3 heart).tw.

4. (coronary adj3 disease).tw.

5. angina.tw.

6. myocardial infarct$.tw.

7. heart infarct$.tw.

8. (coronary adj3 bypass$).tw.

9. (heart adj3 disease).tw.

10. (cardiac adj3 disease).tw.

11. chd.tw.

12. CAD.tw.

13. (coronary adj3 angioplasty).tw.

14. or/1-13

15. exp affective disorders/

16. "depression (emotion)"/

17. dysthymi$.tw.

18. (depressi$ adj3 disorder$).tw.

19. (depressi$ adj3 symptom$).tw.

20. mood disorder$.tw.

21. affective disorder$.tw.

22. antidepress$.tw.

23. anti-depress$.tw.

24. or/15-23

25. 14 and 24

26. random$.tw.

27. factorial$.tw.

28. crossover$.tw.

29. cross-over$.tw.

30. placebo$.tw.

31. (doubl$ adj blind$).tw.

32. (singl$ adj blind$).tw.

33. assign$.tw.

34. allocat$.tw.

35. volunteer$.tw.

36. control*.tw.

37. "2000".md.

38. or/26-37

39. 25 and 38

40. (200907* or 200908* or 200909* or 200910* or 200911* or 200912* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).up.

41. 39 and 40

CINAHL

S43 S41 AND S42

S42 EM 20090715-20200803

S41 S22 AND S40

S40 S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39

S39 TX cross-over*

S38 TX crossover*

S37 TX volunteer*

S36 (MH "Crossover Design")

S35 TX allocat*

S34 TX control*

S33 TX assign*

S32 TX placebo*

S31 (MH "Placebos")

S30 TX random*

S29 TX (doubl* N1 mask*)

S28 TX (singl* N1 mask*)

S27 TX (doubl* N1 blind*)

S26 TX (singl* N1 blind*)

S25 TX (clinic* N1 trial?)

S24 PT clinical trial

S23 (MH "Clinical Trials+")

S22 S10 AND S21

S21 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20

S20 (heart disease)

S19 CAD

S18 chd

S17 cardiac

S16 coronary

S15 (heart infarct*)

S14 (myocardial infarct*)

S13 Angina

S12 MH "Myocardial Revascularization+"

S11 MH "Myocardial Ischemia+"

S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 S9 (depressi* N3 symptom*)

S8 (depressi* N3 disorder*)

S7 anti-depress*

S6 antidepress*

S5 (affective disorder*)

S4 (mood disorder*)

S3 dysthymi*

S2 TI depression

S1 MH "Affective Disorders+"

The WHO International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/)

1. Myocardial Ischemia
2. Myocardial Revascularization
3. coronary artery disease
4. angina
5. myocardial infarction

6. heart infarction
7. coronary artery bypass
8. heart disease
9. coronary heart disease
10. coronary angioplasty
11. or/1-10
12. Depression
13. Depressive disorder
14. Mood disorder
15. dysthymia
16. depressive
17. mood disorder
18. affective disorder
19. antidepressant
20. anti-depressant
21. or/12-20
22. 11 and 21

International Standard Randomized Controlled Trial Number Register (ISRCTN, http://isrctn.org)

1. Myocardial Ischemia.tw
2. Myocardial Revascularization.tw
3. coronary artery disease.condition
4. angina.condition
5. myocardial infarction.condition
6. heart infarction.tw
7. coronary artery bypass.condition
8. heart disease.condition
9. coronary heart disease.condition
10. coronary angioplasty.tw
11. or/1-10
12. Depression.condition
13. Depressive disorder.condition
14. Mood disorder.condition
15. dysthymia.tw
16. depressive.tw
17. mood disorder.tw
18. affective disorder.tw
19. antidepressant.tw
20. anti-depressant.tw
21. or/12-20
22. 11 and 21
23. randomized controlled trial.tw
24. controlled clinical trial.tw
25. randomized interventions.tw

U.S. National Library of Medicine ClinicalTrials.gov (clinicaltrials.gov)

1. Myocardial Ischemia.other term
2. Myocardial Revascularization.other term
3. coronary artery disease.condition/disease
4. angina.condition/disease
5. myocardial infarction.condition/disease
6. heart infarction.other term

7. coronary artery bypass.condition/disease
8. heart disease.condition/disease
9. coronary heart disease.condition/disease
10. coronary angioplasty.other term
11. or/1-10
12. Depression.condition/disease
13. Depressive disorder.condition/disease
14. Mood disorder.condition/disease
15. dysthymia.other term
16. depressive.other term
17. mood disorder.other term
18. affective disorder.other term
19. antidepressant.other term
20. anti-depressant.other term
21. or/12-20
22. interventional studies (clinical trials)
23. 11 and 21 and 22

WHAT'S NEW

Date	Event	Description
3 August 2020	New citation required and conclusions have changed	Updated literature search, 27 new trials included, including new analyses (cognitive-behavioural therapy (CBT) versus non-CBT interventions), new outcomes (cardiovascular vital signs and platelet biomarkers as per protocol), new adverse outcomes included (arrhythmia, stroke, electrocardiogram parameters, and drug side effects), conclusions changed.
26 July 2019	New search has been performed	First updated search for studies and content updated

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 9, 2011

CONTRIBUTIONS OF AUTHORS

Phillip Tully: trials search and selection, data extraction, entering data into review, data analysis, GRADE classification, drafting the updated review

Ser Yee Ang: trials search and selection, data extraction, entering data into review, data analysis, drafting the updated review

Emily Jo Lynn Lee: trials search and selection, data extraction, entering data into review, data analysis, drafting the updated review

Eileen Bendig: trials search and selection, data extraction, entering data into review, data analysis, drafting the updated review

Natalie Bauereiss: trials search and selection, data extraction, entering data into review, data analysis, drafting the updated review

Jürgen Bengel: drafting of protocol, trials search and selection, drafting the original Cochrane Review

Harald Baumeister: drafting of protocol, developing of search strategy, trials search and selection, data extraction, entering data into review, data analysis, drafting the review, updating the review

DECLARATIONS OF INTEREST

Phillip Tully: Dr Tully reports receiving salary from the National Health and Medical Research Council of Australia. Dr Tully reports receiving salary and his institution received grant payment from the Alzheimer's Drug Discovery Foundation. Dr Tully has received royalties from Springer and Lambert Academic Publishing. Dr Tully reports receiving payment for development of educational presentations from the Mental Health Professionals Network. Dr Tully reports receiving payment for editorial services from Elsevier.

Ser Yee Ang: none to declare.

Emily JL Lee: none to declare.

Eileen Bendig: EB is an author of an included study, but was not involved in the data extraction or ratings of bias or quality for that study.

Natalie Bauereiss: NB is an author of an included study, but was not involved in the data extraction or ratings of bias or quality for that study.

Jürgen Bengel: JB is an author of an included study, but was not involved in the data extraction or ratings of bias or quality for that study.

Harald Baumeister: HB is an author of an included study, but was not involved in the data extraction or ratings of bias or quality for that study.

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- No sources of support provided

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- Freemasons Foundation Centre for Men's Health, Australia

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We omitted subgroup analyses due to the small numbers of trials investigating the various outcomes. For the same reason we did not create funnel plots or test them for asymmetry.
- We included new adverse outcomes (arrhythmia, stroke) in the current review that were not reported in the previous version (Baumeister 2011c).
- We reported secondary outcomes, including the effects of depression treatment on cardiac parameters (e.g. vital signs, platelet biomarkers), that were not reported in the previous version of the review (Baumeister 2011c), but that were prespecified in the protocol.
- We added new secondary outcomes (adverse effects) for electrocardiogram (ECG) parameters, adverse mental health outcomes, and pharmacological side effects in this update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Coronary Artery Disease [complications]; *Depression [therapy]; Escitalopram; Psychotherapy; Quality of Life

MeSH check words

Adult; Humans