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Hybrid Systematic Review and Network Meta-Analysis of Randomized Controlled Trials of Interventions for Depressive Symptoms in Patients With Coronary Artery Disease

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ABSTRACT

Objective: Depression is common in patients with coronary artery disease (CAD) and is associated with poor outcomes. Although different treatments are available, it is unclear which are best or most acceptable to patients, so we conducted a network meta-analysis of evidence from randomized controlled trials (RCTs) of different depression treatments to ascertain relative efficacy.

Methods: We searched for systematic reviews of RCTs of depression treatments in CAD and updated these with a comprehensive search for recent individual RCTs. RCTs comparing depression treatments (pharmacological, psychotherapeutic, combined pharmacological/psychotherapeutic, exercise, collaborative care) were included. Primary outcomes were acceptability (dropout rate) and change in depressive symptoms 8 week after treatment commencement. Change in 26-week depression and mortality were secondary outcomes. Frequentist, random-effects network meta-analysis was used to synthesize the evidence, and evidence quality was evaluated following Grading of Recommendations, Assessment, Development and Evaluations recommendations.

Results: Thirty-three RCTs (7240 participants) provided analyzable data. All treatments were equally acceptable. At 8 weeks, combination therapy (1 study), exercise (1 study), and antidepressants (10 studies) yielded the strongest effects versus comparators. At 26 weeks, antidepressants were consistently effective, but psychotherapy was only effective versus usual care. There were no differences in treatment groups for mortality. Grading of Recommendations, Assessment, Development and Evaluations ratings ranged from very low to low.

Conclusions: Overall, the evidence was limited and biased. Although all treatments for post-CAD depression were equally acceptable, antidepressants have the most robust evidence base and should be the first-line treatment. Combinations of antidepressants and psychotherapy, along with exercise, could be more effective than antidepressants alone but require further rigorous, multiarm intervention trials.

Systematic Review Registration: CRD42018108293 (International Prospective Register of Systematic Reviews)

Key words: network meta-analysis, depression, coronary artery disease, intervention, randomized controlled trial.

INTRODUCTION

Depressive symptoms are a common presentation in patients with coronary artery disease (CAD), with a documented prevalence of elevated symptoms ranging between 12% and 38%, and are associated with increased mortality, morbidity, poor quality of life, high health service utilization, and increased health care costs (1–4). Many randomized controlled trials (RCTs) have evaluated the treatments of post-CAD depression and have been summarized in systematic reviews (3,5–12). However, these reviews are difficult to interpret. They typically combine studies with different durations of follow-up, the included participants do not always have elevated depressive symptoms, the content of psychological interventions can be highly variable and can

be delivered by untrained interventionists (5,9,10,13), and comparator groups are not always well delineated, which can have direct implications for the obtained summary effect sizes (5,12,14). There are also other outcomes of interest to patients, such as the acceptability of treatments, which have been omitted from these reviews (15,16). A further complication is that treatments are seldom compared directly with each other; hence, clinicians lack vital information about efficacy and acceptability. Therefore,

CAD = coronary artery disease, GRADE = Grading of Recommendations, Assessment, Development and Evaluations, NMA = network meta-analysis, OR = odds ratio, RCTs = randomized controlled trials, RoB = risk of bias, SMD = standardized mean difference

SDC Supplemental Digital Content

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the current evidence is difficult to interpret both scientifically and clinically.

Although few studies have directly compared interventions, there are sufficient RCTs to allow for indirect comparisons (17). Network meta-analysis (NMA) is an advanced technique that enables both direct and indirect comparisons for treatments that have not been directly tested against each other. It is recommended for evaluations of competing interventions, such as pharmacotherapies, psychotherapies, behavioral interventions, and exercise (11,15–23). Indeed, in the absence of direct head-to-head studies, NMA is acknowledged as the best available approach (17,24). It facilitates clinical decision making by accounting for multiple outcomes and providing a ranking of treatments where there is sufficient evidence (15). A recent NMA of antidepressants excluded studies of patients with serious concomitant medical illness (15), thereby leaving a significant gap in the psychosomatic literature.

Therefore, it is an opportune time to conduct an NMA to summarize interventions for depression in people with CAD, in terms of both efficacy and acceptability, to provide vital scientific and clinical evidence. We report the results of an NMA of pharmacotherapeutic, psychotherapeutic, exercise, collaborative care, and combination treatments of depression in CAD (25).

We compared established treatments for post-CAD depression for acceptability, and efficacy (for placebo-controlled-trials) or effectiveness (for other comparator groups), in an NMA, with the following participants, interventions, comparators, and outcomes:

- Participants: patients with CAD and elevated depressive symptoms enrolled in RCTs for depression treatment in any setting, excluding cardiac rehabilitation
- Interventions: any established treatment of depression, including pharmacotherapy, psychotherapy, combination therapy, exercise, and collaborative care
- Comparison: placebo groups, usual care, or (active or inactive) treatment control groups
- Outcomes:
 - o Primary: 8-week change in depressive symptoms, acceptability (% of patients who discontinue treatment)
 - o Secondary: 26-week depression change

The outcome durations were chosen to mirror those of Cipriani et al. (15), with a focus on testing treatments that work in a clinically feasible period.

METHODS

The protocol for this analysis has been published previously (25) and registered on the International Prospective Register of Systematic Reviews (CRD42018108293). This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for NMA guidelines (24,26), whereas changes to the protocol are summarized in Supplemental Digital Content, section A1 (Table A1, <http://links.lww.com/PSYMED/A738>).

Eligibility Criteria

Study and Intervention Types

We included all randomized trials of interventions for depression in patients with CAD. Interventions included pharmacotherapy (selective serotonin

reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, anxiolytics, etc), psychotherapy (as delivered by trained therapists: e.g., cognitive-behavioral therapy, interpersonal psychotherapy, and counseling), combination psychotherapies and pharmacotherapies, exercise (specifically targeting depression), and collaborative care (programs that meet the accepted criteria (8,27,28), including all of the following: multiprofessional approach, structured management plan, scheduled follow-up, and enhanced interprofessional communication). It was assumed that included patients were equally likely to have been randomized to any such intervention (24). A validated depression scale or diagnostic interview had to be used as an outcome measure, and studies had to report a (potential) change in depressive symptoms from baseline (or pretreatment) to posttreatment. Crossover or cluster RCTs were considered for inclusion, but the following were excluded: quasi-experimental trials, interventions focusing on cardiac rehabilitation, and psychological interventions that were not established psychotherapies delivered by trained therapists. Studies that reported depression outcomes for either of the prespecified follow-up durations were included, not only those reporting results at 26 weeks. Included studies were published peer-reviewed journals, in English.

Participants

Results from participants 18 years or older were included if they met the following criteria: depression treatment RCTs (scoring above threshold on a validated scale or clinician-diagnosed) and having a depression score at baseline and postintervention from which to calculate change or outcome scores, in which at least 70% of the participants had a diagnosis of CAD (including acute coronary syndrome, angina, and angiographically confirmed coronary disease, treated with percutaneous coronary intervention or coronary bypass graft).

Comparison Groups

RCTs that compared other interventions or a range of comparator groupings were included (29). Comparator groupings followed previous recommendations (30), as follows: a) placebo (for drug trials); b) no treatment, waitlist, or treatment as usual; and c) treatment control (defined as minimal treatment control, active comparator, and specific and nonspecific factor treatment control).

Outcomes

Primary Outcomes

Two primary outcomes were adopted (5,8,15):

1. Efficacy (effectiveness) response: between-group differences in depressive symptoms change (a continuous score as measured by validated tools and summarized with standardized mean difference [SMD]) at week 8 after intervention commencement (or closest measure to 8 weeks that is available, between 4 and 16 weeks)
2. Acceptability: the proportion of participants who discontinue treatment (for any reason)

Secondary Outcome

1. Efficacy (effectiveness) response (continuous): between-group differences in depressive symptom change (as measured by validated tools and summarized with SMD) at week 26 after intervention commencement (or closest available estimate between 20 and 30 weeks)
2. Mortality: proportion of participants who die during or after treatment, for the longest duration of available data

Other secondary outcomes, including quality of life, morbidity, and health services use, are not included because of lack of data (Supplemental Digital Content A1, <http://links.lww.com/PSYMED/A738>).

Search Strategy and Study Selection

We adopted a hybrid umbrella review and systematic review methodology (25,31,32), which incorporates two stages: a) search for relevant systematic reviews (umbrella review) and extraction of relevant references from the same reviews and b) a supplemental search for individual RCTs within a given time frame (e.g., 2–6 years, depending on dates of systematic reviews). We searched, from inception to September 11, 2020, the Cochrane Library, CINAHL, MEDLINE, EMBASE, MEDLINE In-Process, and PsycInfo for systematic reviews. This was supplemented with MEDLINE and Cochrane Library searches for recent RCTs published since January 1, 2014 (to September 11, 2020). The World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov platforms were also searched. The reference lists for included systematic reviews and RCTs were appraised for any other relevant RCTs. All search terms are provided in the protocol (25) and in Supplemental Digital Content A1, <http://links.lww.com/PSYMED/A738>. References were downloaded into EndNote with duplicates removed using the software tools. Titles, abstracts, and full texts were screened and appraised independently by F.D. and M.D., with discussion as needed.

Data Extraction

RCT data were independently extracted (F.D., M.D.), with discrepancies resolved by discussion. Extracted data included the following: study characteristics (author/year, setting), participant characteristics (sample size, age, % women, CAD inclusion criteria, depression inclusion criteria), and intervention details (dosing and duration for pharmacotherapies; using the Template for Intervention Description and Replication checklist for psychotherapies (33)). The *metareff* command in Stata was used to calculate SMDs and associated standard errors and 95% confidence intervals (CIs) from available data for continuous outcomes (34). Acceptability, defined as the numbers of participants who discontinued for any reason at any point during follow-up, was extracted.

Duration of RCTs and Outcome Assessments

For the synthesis of depression as a primary outcome, we adopted the closest available data to 8 weeks (between 4 and 16 weeks) after treatment commencement to indicate a time frame for interventions that could work in a clinically reasonable period of time. Data on acceptability were not restricted to this time period. Twenty-six-week (range, 20–30 weeks) depression assessment was the secondary outcome. For mortality, data from the longest available follow-up were used.

Missing RCT Outcome Data

We adopted the results as reported originally, but also cross-checked results from the published meta-analyses. Because not all trials reported change scores, we combined change and end-of-trial scores only, to have sufficient data to generate the network.

Risk of Bias and Quality Ratings

Where available, we extracted the Cochrane risk-of-bias (RoB) tool (35) ratings from prior reviews (e.g., Refs. (5,8)) and used these to inform the RoB 2 tool ratings, conducted independently by F.D. and M.D. (36). We followed the recommendations for NMA, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework summary findings table for obtained results (15,37,38), and used the Confidence in Network Meta Analysis Web application to facilitate this (39). GRADE ratings incorporate information from the study limitations, imprecision, inconsistency, indirectness, and publication bias, which can lead to downgraded quality ratings for evidence (40).

Statistical Analysis

Descriptive statistics were used to profile the RCTs. Network diagrams were plotted, with node size indicating the number of patients per grouping, width of the edges (lines) indicative of the numbers of studies, and edge color/pattern indicative of the modal bias rating for that comparison (17). Influential network comparisons were evaluated using a contribution matrix, describing the proportion of the contribution to the entire network of each direct meta-analysis (41). Two main networks, corresponding to the primary outcomes, were evaluated using random-effects frequentist multivariate meta-analysis (using *network meta*) in Stata 15 (42). Continuous outcomes are reported as SMDs, with binary outcomes reported as odds ratios (ORs), both with associated 95% CIs. Pairwise meta-analytic estimates were also calculated where possible and are reported in addition to the network estimates as recommended (24). Inconsistency (or incoherence (i.e., the disagreement between direct and indirect evidence (37))) was assessed using local and global methods (17,24,41,43). Evaluations used loop-specific and node-splitting methods, with the global networks assessed using design-by-treatment interaction models. Because of network incoherence (inconsistency), two studies were dropped from the network for 8-week depression efficacy, which allowed consistency models to be analyzed instead (as outlier trial results can be overly influential for final estimates and violate underlying assumptions (42)). We report inconsistency factors as recommended (17). The analyses used the groupings as outlined previously (i.e., placebo, usual care, minimal treatment control, pharmacotherapy, psychotherapies, exercise, collaborative care, combination therapies). We also presented the overall treatment model when omitting stringently imputed data from three studies. Treatment rankings were obtained using rankograms and surface under the cumulative ranking (Surface Under the Cumulative Ranking curve) curves (17) for the primary depression outcome only. Stata 15 was used to conduct the main reported analyses, with the online Confidence in Network Meta Analysis application used to support GRADE ratings (39).

The transitivity assumption (37) was initially addressed by the inclusion of patients with CAD only, and it was assumed that all participants had an equal opportunity to be randomized to any trial arm. To ascertain possible small-study effects, we computed several funnel plots: for overall effects, including any intervention versus any comparator, then investigating antidepressants and psychotherapy versus all or specific comparators, as these were the most commonly used interventions (24,41).

RESULTS

We identified 7412 citations, from which data were extracted from 33 RCTs (with 72 trial arms and 7240 participants; see flowchart depicted in Supplemental Digital Content, section A2, Fig. A1, <http://links.lww.com/PSYMED/A738>). Not all studies provided estimates for each primary outcome (see Table A2 – Supplemental Digital Content A2, <http://links.lww.com/PSYMED/A738>; 30 study estimates were available for acceptability, 24 study estimates for depression efficacy at 8 weeks, with total participants reduced accordingly). In terms of treatment and comparator arms, these numbered as follows: 10, placebo; 16, usual care; 5, treatment control; 15, pharmacotherapy; 15, psychotherapy; 4, collaborative care; 1, exercise; and 1, combination. Full study characteristics are detailed in Table A2 (Supplemental Digital Content A2, <http://links.lww.com/PSYMED/A738>), with detailed psychotherapy descriptions according to Template for Intervention Description and Replication (Supplemental Digital Content A2; Table A3, <http://links.lww.com/PSYMED/A738>). Publication years ranged from 1982 to 2020, with studies from various countries (13 United States; 4 China; 3 Australia; 2 the Netherlands; 2 South Korea; 2 Italy; 1 each from Germany, India, Iran, and Sweden; and 1 international

study). Of the listed settings, 27 were in hospital/outpatient settings, with 1 online, 1 telephone, 1 in Medical College, 1 in various settings, and 2 unclear. Mean age of participants was reported to be 59.1 years (range, 52–65.3 years), with an average of 33.3% (range, 0%–100%) of participants being women. Five studies enrolled patients 6 months or more after event or assessed depression on at least two occasions before enrollment; 2 studies provided treatment choice to patients; and 7 studies provided insufficient or unclear data so depression outcomes were imputed to maximize the evidence base, as per our protocol (25) (see Table A2).

Primary Outcomes

Figure 1 shows the network of comparisons for both primary outcomes for the consistency models. The modal direct comparisons were indicated to have a low risk of bias (RoB) in the majority of instances. Specifically, for acceptability, the modal RoB rating for direct comparisons was low, except for antidepressant–placebo or psychotherapy–usual care (both rated as “some concerns”), and antidepressant–usual care and antidepressant–treatment control—both of which were rated as having high RoB. There was no comparison possible for combination therapies for acceptability. For efficacy, again the modal RoB assessment was “low” for the majority of comparisons. The modal psychotherapy–usual care comparisons were rated as “some concerns,” whereas the antidepressant–combination and antidepressant–treatment control comparisons were rated as having high RoB.

Supplemental Digital Content B, <http://links.lww.com/PSYMED/A738> provides detailed results of all relevant pairwise meta-analyses. Substantial heterogeneity was evident for acceptability (placebo versus antidepressants; treatment control versus psychotherapy) and 8-week efficacy (psychotherapy versus usual care). For NMA of acceptability, potential evidence of incoherence was found using the node-splitting techniques, such that direct and indirect evidence for two comparisons were inconsistent. However, NMA inconsistency model suggested no issues ($\chi^2 = 5.81$, $p = .325$; see Supplemental Digital Content C1, <http://links.lww.com/PSYMED/A738>).

com/PSYMED/A738). Results of the consistency model are therefore presented in Figure 3. There were no statistically significant differences among any of the treatments in terms of acceptability, which was also found for the inconsistency model (an interval plot is available in Figure 2A). Because there were no significant differences for acceptability, a treatment ranking was not conducted.

For the NMA of 8-week depression treatment effects, node-splitting results suggested an inconsistent model, with strong incoherence for three comparisons. Although the NMA inconsistency model was nonsignificant ($\chi^2 = 8.26$, $p = .143$), there were two clear outliers visible in the forest plot (see Supplemental Digital Content C, Fig. C2, <http://links.lww.com/PSYMED/A738>; Tian et al. Study 50; Nikrahan et al. Study 38). Once these were removed, there was no remaining evidence of inconsistency ($\chi^2 = 0.96$, $p = .916$). Figure 3 contains results of the consistency model for 8-week depression treatments, whereas the contribution plot and associated RoB graph are available in Supplemental Digital Content C, <http://links.lww.com/PSYMED/A738>. The strongest effects are evident for combination therapies and exercise; however, only single trials have evaluated these therapies. Otherwise, antidepressants have significantly better effects than placebo and usual care and marginally better effects than treatment controls, whereas psychotherapy is superior to usual care (with a larger effect size than seen for the pairwise meta-analysis – see Supplemental Digital Content B6, <http://links.lww.com/PSYMED/A738>). There are also statistically significant differences between comparator groups: usual care is inferior to both placebo and treatment control. Figure 2B contains the interval plots for 8-week efficacy. Because stringent assumptions for imputation were made for three studies, we present the results of the NMA for 8-week depression in Supplemental Digital Content C (Table C1, <http://links.lww.com/PSYMED/A738>)—no substantial differences were evident.

For 8-week depression efficacy, treatment rankograms are available in Supplemental Digital Content D, <http://links.lww.com/PSYMED/A738>. The probable best treatments were in the following order, respectively: combination therapies (best), exercise,

Network comparisons for primary outcomes

FIGURE 1. Network of comparisons for primary outcomes acceptability (left panel) and efficacy (right panel). Larger node size indicates higher patient numbers in that category. Wider edges indicate higher numbers of studies in comparisons. Edge color indicates modal risk of bias assessment for comparisons (green [solid line], low risk; yellow [dash-dot], some concerns; red [dash], high risk). Color image is available online only at www.psychosomaticmedicine.org.

FIGURE 2. Interval plots, with 95% confidence intervals (CIs; black lines) and predictive intervals (PrI; red, dashed lines), for acceptability (A: top, with odds ratios) and efficacy (B: bottom, with standardized mean differences). Color image is available online only at www.psychosomaticmedicine.org.

and antidepressants, with treatment control, placebo, psychotherapy, collaborative care, usual care all having a mean ranking of 5 or greater (with usual care the lowest ranked [worst]).

Small study effects were evident when analyzing efficacy data, from when using all comparators or the most common ones—funnel plots displayed in Supplemental Digital Content E, <http://links.lww.com/PSYMED/A738>.

Secondary Outcomes

Sixteen RCTs reported analyzable results for the secondary depression outcome at 26 weeks after treatment commencement (none for

exercise or combination care). Modal RoB was low for psychotherapy–usual care and collaborative care–usual care comparisons, with all other comparisons being rated as having at least some concerns (Supplemental Digital Content F; Fig. F1, <http://links.lww.com/PSYMED/A738>). Comparative efficacy is available in Supplemental Digital Content F (Table F1, <http://links.lww.com/PSYMED/A738>). Antidepressants had the strongest and most consistent effects. Psychotherapy and collaborative care were better than usual care but significantly worse than antidepressants, with strong effect sizes.

Fifteen RCTs reported mortality rates (none for exercise or combination care; Supplemental Digital Content F; Fig. F2,

Placebo	0.81 (0.25,2.61)	1.13 (0.44,2.89)	1.07 (0.63,1.82)	0.86 (0.30,2.49)	0.96 (0.23,3.96)	0.34 (0.03,3.83)	-
0.53 (0.03,1.03)	Usual Care	1.40 (0.49,3.99)	1.33 (0.41,4.25)	1.07 (0.63,1.80)	1.19 (0.55,2.59)	0.42 (0.03,5.95)	-
0.05 (-0.34,0.44)	-0.48 (-0.92,-0.05)	TrtControl	0.95 (0.39,2.33)	0.76 (0.31,1.89)	0.85 (0.23,3.16)	0.30 (0.02,3.85)	-
-0.28 (-0.51,-0.05)	-0.81 (-1.30,-0.32)	-0.33 (-0.69,0.04)	Antidepressant	0.80 (0.28,2.29)	0.90 (0.22,3.67)	0.31 (0.03,3.49)	-
0.09 (-0.35,0.54)	-0.44 (-0.68,-0.20)	0.05 (-0.31,0.40)	0.37 (-0.05,0.8)	Psychotherapy	1.12 (0.44,2.86)	0.39 (0.03,5.33)	-
0.21 (-0.43,0.85)	-0.32 (-0.73,0.08)	0.16 (-0.43,0.75)	0.49 (-0.15,1.12)	0.12 (-0.36,0.59)	Collaborative Care	0.35 (0.02,5.60)	-
-0.52 (-1.12,0.09)	-1.05 (-1.81,-0.29)	-0.56 (-1.26,0.13)	-0.24 (-0.84,0.36)	-0.61 (-1.33,0.11)	-0.73 (-1.59,0.14)	Exercise	-
-1.07 (-1.78,-0.36)	-1.60 (-2.43,-0.77)	-1.12 (-1.88,-0.36)	-0.79 (-1.46,-0.12)	-1.16 (-1.96,-0.37)	-1.28 (-2.20,-0.36)	-0.55 (-1.45,0.34)	Combination

FIGURE 3. Comparative effects of interventions and comparators on depression (at 8 weeks) and acceptability. Note: The pink quadrant (shaded area top right) contains result for acceptability, with values <1 for odds ratios indicating greater dropout rate for the row treatment compared with the column treatment; the blue quadrant (shaded area bottom left) contains effect sizes for efficacy, with negative standardized mean differences indicating better treatment effects for depression for the row treatment compared with the column treatment, whereas positive standardized mean differences indicate better treatment effects for the column treatment in comparison to the row treatment. Estimates in bold and underlined indicate statistically significant values. Color image is available online only at www.psychosomaticmedicine.org.

<http://links.lww.com/PSYMED/A738>), with only the collaborative care–usual care comparisons having a modal RoB rated as low. Only treatment control showed differences (Table F1), versus usual care (OR = 8.1, 95% CI = 1.2–54.3), and versus psychotherapy (OR = 0.13, 95% CI = 0.02–0.89), but due to low numbers and RoB, these results are likely spurious.

GRADE

GRADE ratings for depression at 8 weeks are summarized in Supplemental Digital Content G, <http://links.lww.com/PSYMED/A738>. For mixed direct and indirect evidence, ratings ranged from “very low” (including antidepressants versus placebo; psychotherapy versus placebo, usual care, or treatment control; exercise versus antidepressants; antidepressants versus combination) to “low” (placebo versus exercise, collaborative care versus usual care, antidepressants versus treatment control, antidepressants versus psychotherapy). Because of limited numbers of trials, we rated all indirect evidence as “low” and downgraded this rating to “very low,” where there were any major concerns around bias.

DISCUSSION

We report the first NMA to provide a ranking of treatments for depression in those with CAD, for several clinically important outcomes. All interventions were equally acceptable to patients, whereas for short-term depression efficacy, the best evidence existed for antidepressants, with very promising effects for combination therapies and exercise. For secondary outcomes, the results mostly favored antidepressants. However, the evidence base was limited and biased, with mostly low evidence ratings for all treatment comparisons because of the sparsity of eligible trials.

That there were no differences in acceptability, defined as dropout from a study for any reason, is a clinically important finding. Although other measures of acceptability might be preferred, dropout is typically used (e.g., Refs. (15,16)) and is most commonly reported in RCTs. Because some of the attrition in the included trials

may be due to morbidity or mortality, because of the broad definition adopted, it could be argued that these attrition reasons do not necessarily reflect low acceptability of the interventions, especially as reasons for dropout were not consistently reported. However, because treating depression in CAD has not been consistently associated with a reduction in these outcomes (5,8,12), it is likely that the results are not biased by these events. Acceptability of pharmacotherapy has been reported to be lower than combination therapies and psychotherapy in more general populations with depression (16), possibly because of the adverse effects of antidepressants, but this was not evident in the present findings. One reason for this equivalence in acceptability may be that patients are already prescribed numerous medications for CAD, so there is limited increased treatment burden for a typical single tablet per day antidepressant treatment, in comparison to attending psychotherapy sessions.

For short-term depression treatment, a combination of psychotherapy and pharmacotherapy, or exercise, showed the strongest effects. However, these treatments were investigated in single trials only. Antidepressants and psychotherapies provided a more robust evidence base. Antidepressants were shown to be effective against placebo and usual care, whereas psychotherapies were effective in comparison to usual care, but not placebo. Although not reaching statistical significance for the primary depression outcome, there was a marginal effect for antidepressants to be superior to psychotherapy. This was confirmed in the secondary depression outcome at 26 weeks, where although psychotherapy was again shown to be superior to usual care, it was *worse* than antidepressants, with a large difference in effect size between the two. This discrepancy between antidepressants is in stark contrast to other research in patients with depression but no CAD (16). These results may be attributed, at least in part, to a number of elements, including the heterogeneity of overall psychotherapy types, or the ability of psychotherapy to show efficacy over the short-term of 8 weeks. Alternatively, it may be that biological elements such

as inflammatory processes may play a role in both CAD and depression (44), which would not necessarily be amenable to psychotherapy.

The combined psychotherapy results are also in contrast to the recent TREATED-ACS study, which showed that a combination of cognitive-behavioral and well-being therapy was superior to a treatment control group (clinical management) (45). The heterogeneity in this treatment grouping is highlighted by contrasting findings in previous high-quality studies. For example, the CREATE trial showed that interpersonal psychotherapy was inferior to the treatment control group (also termed clinical management) (46), whereas the SPIRR-CAD trial of supportive-expressive psychotherapy showed null effects at 8 weeks when compared with usual care (47). Future research should consider carefully the actual components of psychotherapies that obtain the largest effects in this population. It is notable that the one psychotherapy study that was omitted from the summary results as it was clearly an outlier (SMD, -3.04), although it was rated as having a low RoB, was also based on well-being therapy (48). Well-being therapy may prove a promising avenue of future research for this population.

Data on secondary outcomes were sparser than primary outcomes, although some interesting findings emerged. Collaborative care emerged as having a significant effect on depression at 26 weeks, although antidepressants had stronger effects than collaborative care or psychotherapy. Mortality seemed to be reduced from usual care to treatment control but increased from treatment control to psychotherapy, whereas there was no difference in psychotherapy and usual care. The small number of studies, low mortality rates, contradictory findings, and very wide CIs suggest that these may be spurious findings. In any case, we failed to replicate the recent finding that antidepressants reduced mortality rates in people with depression and CAD (12). This may be due to the categorization of comparator groups, but also the fact that we only included participants with elevated depression and within delineated follow-up time frames.

Overall, when using GRADE, we conclude that the evidence base for treating post-CAD depression is modest at best, despite decades of research, with, for example, comparisons with the most (antidepressants and psychotherapy) evidence obtaining “very low” ratings, due largely to reporting bias and heterogeneity. Although, of course, there are several examples of excellent studies with low bias within these categories, the modal RoB assessments show concerns, which is also evident from the network plots for the primary outcomes. These ratings, along with the relative sparsity of evidence, preclude strong statements about treatment rankings and clinical recommendations.

One important element of the present study is the fact that comparator groups were demonstrably different, supporting previous observations (29,30), so that accounting for these differences is vital for both researchers and clinicians to determine the true effects of interventions. For example, for short-term depression, usual care was significantly worse than both placebo and treatment controls, whereas there were also similar differences evident for some secondary outcomes. Previous pairwise meta-analyses have grouped all comparators together and will therefore find effect sizes that are difficult to interpret (5,12). Furthermore, even usual care can differ substantially across settings, thereby masking or moderating effect sizes of interventions (49–51), which may be especially pertinent for the psychotherapy research

included in these analyses. Similarly, the purpose of an RCT will dictate the chosen comparator group (14), but this is not often accounted for in pairwise meta-analyses. Future work should investigate the effects of different intervention and comparator group classifications on treatments for depression in those with CAD. Researchers and funders need to carefully consider the purpose of the trial; carefully document and report the content of the comparator group care, including placebo comparators; and consider multiarm trials investigating exercise and combination therapies, to determine the true efficacy of these interventions. Such a trial is likely to require international collaboration and large-scale funding.

Strengths and Limitations

The adopted hybrid overview and systematic review methodology allowed for more rapid collection of relevant articles than a standard systematic review—for example, we estimate that from Medline alone, we reviewed >1100 fewer abstracts than if we had used standard methodologies. This methodology may interest future systematic reviewers. An overall limitation of the evidence is that relatively low numbers of RCTs met the inclusion criteria, especially head-to-head trials, and especially those of combination therapies and exercise. Future research should address these gaps. These low numbers did not allow for building networks that could account for specific psychotherapies and antidepressants, or exploration of the impact of coronary disease severity on treatment effects. They also precluded analysis of predefined secondary outcomes, detailed sensitivity analyses, and network meta-regression. Further studies could consider other sophisticated techniques, such as individual patient data NMA and application of cost-effectiveness modeling. The majority of studies had at least some concerns about bias and could also vary in ways that have not been reported, although we have attempted to describe these in detail and assess transitivity appropriately. However, there may still be differences among the studies, which affected the findings (e.g., recruitment criteria differing substantially among studies, such as recruiting participants who had lower-than-usual exercise levels, or the diversity of offered treatments yielding differential participation), resulting in estimates that were not truly comparable. Findings for depression may be different for longer-term outcomes, and it is possible, for example, that psychotherapy may outperform other interventions if studied for longer durations (16). This is especially important given that in some studies, for example, SPIRR-CAD (47), the planned treatment extended beyond the primary outcome of 8 weeks. Although acceptability, as used here, is similar to the definitions from other reviews (e.g., Refs. (15,16)), it is arguable whether dropout is truly comparable across groups; for example, medication adverse effects may cause dropout in antidepressant trials, which may not be comparable to acceptability of psychotherapies.

In conclusion, the current evidence suggests that, although all treatments for post-CAD depression are equally acceptable, the most robust evidence base is for antidepressants, which should be the first treatment option. Combinations of antidepressants and psychotherapy, along with exercise, could be even more effective than antidepressants alone but require further research before this can be established. Researchers should consider the comparator groups carefully and report them in detail for future evidence synthesis.

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