



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Diagnostic Accuracy of Screening and Treatment of Post-Acute Coronary Syndrome Depression: A Systematic Review

Draft review available for public comment from April 27, 2017 to May 25, 2017.

Research Review Citation: Williams JW Jr, Nieuwsma JA, Namdari N, Washam JB, Raitz G, Blumenthal JA, Jiang W, Yapa R, McBroom AJ, Lallinger K, Schmidt R, Kosinski AS, Sanders GD. Diagnostic Accuracy of Screening and Treatment of Post–Acute Coronary Syndrome Depression: A Systematic Review. Comparative Effectiveness Review No. 200. (Prepared by the Duke University Evidence-based Practice Center under Contract No. 290-2015-00004-I.) AHRQ Publication No. 18-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2017.
www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI:
<https://doi.org/10.23970/AHRQEPCER200>.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.



#	Commentator & Affiliation	Section	Comment	Response
1.	TEP #1	Quality of Report	Superior	Thank you.
2.	TEP #2	Quality of Report	Superior	Thank you.
3.	TEP #3	Quality of Report	Good	Thank you.
4.	TEP #4	Quality of Report	Good	Thank you.
5.	TEP #5	Quality of Report	Good	Thank you.
6.	TEP #6	Quality of Report	Good	Thank you.
7.	Peer Reviewer #1	Quality of Report	Good	Thank you.
8.	Peer Reviewer #2	Quality of Report	Good	Thank you.
9.	Peer Reviewer #3	Quality of Report	Good	Thank you.
10.	Peer Reviewer #4	Quality of Report	Superior	Thank you.
11.	Edgar Weiss (Public Reviewer)	Quality of Report	Good	Thank you.
12.	TEP #1	General Comments	I think the report is an excellent and transparent summary and the key questions, which are defined quite explicitly, are clinically relevant and important.	Thank you.

Source: <https://effectivehealthcare.ahrq.gov/topics/acs-depression/research-review-final>

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13.	TEP #2	General Comments	This systematic reviews was expertly done, and addressed two important key questions. The report is clinically meaningful, and the target population was clearly articulated.	Thank you.
14.	TEP #3	General Comments	Overall terrific work.	Thank you.
15.	TEP #4	General Comments	This is a critical review of the literature concerning depression screening and depression treatment following acute coronary syndrome (ACS). It is the second review of this literature supported by the Agency for Healthcare Research and Quality (AHRQ). The first was published in 2005. In the present review, the authors examined the most significant, relevant resources and databases and followed appropriate procedures and guidelines for performing a comprehensive search of this literature. Finally, they followed established AHRQ guidelines for rating the strength of evidence. Thus, the review is comprehensive and balanced.	Thank you.
16.	TEP #4	General Comments	In the abstract and in the text, a difference in BDI score of 3.5 to 3.8 is declared “not considered clinically significant”. There is no reference or rationale provided for this claim. On page 29 they assert that a 5 point difference is clinically significant, again without a reference. What is clinically significant is somewhat subjective, but it is a critical question. It has been suggested that a 3 point difference on the HAM-D, which tracks fairly closely with the BDI-1, is clinically significant (Hegerl et al. <i>J Affect Disord</i> 2012;138:183-191; NICE. <i>National Clinical Practice Guideline 90</i> . National Institute for Health and Clinical Excellence, London; 2009). While the authors may have a different opinion, they should provide references or other support for their conclusions.	We evaluated further the evidence for a clinically important change on the BDI. Based on a review of 4 studies, there is evidence supporting a range of 3-5 points or a 17.5% reduction in baseline scores as the threshold for the minimum clinically important difference. We’ve modified our description, commented on the uncertainty of this estimate, and provided citations.

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17.	TEP #4	General Comments	<p>One may have questioned the need for another review of depression screening studies. Thombs et al. did an excellent review of this literature in 2008 (cited in this report), as did the American Heart Association (Lichtman et al. 2008 – also cited here). Although both are nearly ten years old, and there have been additional studies since those reviews, the findings over time have been remarkably consistent. One problem with not including the earlier (pre 2005) studies of depression screening in the present review can be seen in the attempt by these authors to compare the various depression screening instruments for sensitivity, specificity, and positive and negative predictive value, etc. (page 19). There are too few studies published since the last AHRQ review to reliably compare the instruments. This report could include all of the available studies, including those published before 2005, to provide more data for instrument comparison as a secondary analysis, if instrument comparison was a goal of the report. Without this, it is important to emphasize that there really are too few studies in this review to provide a reliable comparison or to make strong recommendations for one instrument over another.</p>	<p>Our review was an update to the prior review. As such, we examined the 2005 review and included studies that reported relevant findings. Only one study in the 2005 review reported performance characteristics (e.g., sensitivity) of a screening instrument, and we summarized these findings. Given the limited studies included in the 2005 report, including studies published before that date would not likely have substantially increased our capacity to compare instruments as employed in post-ACS populations.</p>
18.	TEP #5	General Comments	<p>The report is clinically meaningful and generally well-written. However, and I focus my comments on the section on interventions (KQ2) where my expertise is greater, I think the reviewers made too restrictive a review of the literature, missed several important reports, overemphasized one report (ENRICHHD), and limiting the usefulness of the overall report.</p>	<p>We respond to this reviewer's specific comments on these elements in subsequent sections.</p>

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19.	TEP #6	General Comments	1) Based upon the Key Questions as developed and the literature search performed in response to those questions, the report does provide clinically useful information which can be used in the further development of clinical guidelines.	Thank you.
20.	TEP #6	General Comments	2) The target population and intended audience for the report are adequately defined.	Thank you.
21.	TEP #6	General Comments	3) The key questions are appropriately delineated with comparators, time course and care options listed.	Thank you.

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22.	Peer Reviewer #1	General Comments	<p>Most of the standard components of an AHRQ evidence-reviews are included in report in a clear, consistent and transparent manner. The PICOS criteria are clearly stated. The intended audience is stated, but somewhat generically. The key questions could be clarified in two ways. First, the rationale for the time criterion of within 3 months of an ACS should be provided. Second, the analytic framework has 'adverse effects' as a box, but without either a key question or a contextual question articulated. This should be added, and a discussion of the adverse effects found, if any, should be added to the report. the report is marginally clinically meaningful--clinical recommendations about whether depression screening should occur, with what instrument, by when, and for whom, are not provided.</p>	<p>Thank you for this comment. 1- Rationale for 3 months within ACS was chosen for consistency with prior report, input from TEP/stakeholders, and to best understand the performance of screening instruments and treatment effects in the acute/subacute phase of coronary disease. This clarification is included in the methods section under "Inclusion/Exclusion Criteria".</p> <p>2-The adverse effect outcomes specified in the analytic framework are applicable to KQ 2. We have added an additional text label in the figure at the arrow connecting the KQ 2 treatment bar to the adverse effects oval to reinforce this relationship. We have also added in a similar labeling with the KQ 1 diagnostic accuracy outcomes. A discussion of the adverse outcomes are included in the detailed findings of the report and is one of the "Key Points" bullets.</p> <p>Note also that the EPC program does not make clinical recommendations but rather speaks clearly to the evidence and provides discussion of the implications for decision making in the discussion.</p>
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23.	Peer Reviewer #2	General Comments	<p>This evidence synthesis nicely summarizes the data available on the accuracy of depression screening tests and on the efficacy of depression treatments in post-ACS patients.</p> <p>Some comments that may be helpful for improving the manuscript are provided below:</p> <p>It was not clear why the authors were concerned with the diagnostic accuracy of screening test rather than focusing on their screening properties in which case the sensitivity would arguably be the most important property, and the positive predictive value less so, as screening tests often imply that a follow-up more extensive diagnostic test will follow. I agree with the authors conclusion that a 2-step process should be used (p.36) as is convention in general practice and is typical of other psychiatric diagnoses.</p>	<p>Thank you for this comment. We chose diagnostic accuracy because both sensitivity and specificity are important to understanding how a screening test will perform.</p>
24.	Peer Reviewer #2	General Comments	<p>Additionally, the authors should put in perspective the implications of a low Positive Predictive Value - for example, that this could lead to a large number of screens receiving time-consuming comprehensive depression evaluations.</p>	<p>We have elaborated on our discussion of PPV rates in the comparison with 2005 report section to more explicitly note this point.</p>

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25.	Peer Reviewer #2	General Comments	Another general concern is that there was a focus on understanding the utility of screening tests based on their accuracy in diagnosing MDD. However, in cardiac patients, even patients with subthreshold depressive symptoms are at elevated cardiac risk, and potentially deserving of enhanced depression treatment. Some published studies used elevated depressive symptoms rather than depression diagnosis as eligibility criteria. This has implications with respect to the screening tests. The authors didn't address these aspects in their manuscript.	We agree that subthreshold depressive symptoms can be important. However, MDD was identified by stakeholders, KI/TEP and public input as their focus. We have now more overtly noted this limitation within the limitations section. Note that the original report examined patients with MDD or depressive symptoms and so it was inclusive of subthreshold depression.
26.	Peer Reviewer #2	General Comments	Perhaps this is the standard approach to updating prior evidence syntheses, but it was somewhat challenging to review the updated literature separate from prior reviews, with only a paragraph at the end integrating the 2 reviews together.	We have inserted a table within the discussion that provides a summary look at how our current review compares with the original review – both in terms of the overlap of the key questions and the similarities/changes in the findings.
27.	Peer Reviewer #3	General Comments	Overall the review has been done well and meets all quality criteria for systematic reviews.	Thank you.

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28.	Peer Reviewer #3	General Comments	I would like to make a few comments. First I don't understand why this review is separate from the previous 2005 review. Depression has not changed over that period and evidence from before 2005 is just as valid as evidence after that year. So in my opinion the studies from before 2005 should have been included in this review too. That would also have given more statistical power to find significant pooled effects.	This review was designated as an update to the prior review. We attempted to address this limitation by synthesizing findings across reviews, and in the revised report we now specifically summarize the two reviews findings in tabular form in the discussion. Because our review focused on comparative effectiveness studies, most studies eligible for the earlier review were not eligible for the current review and, as such, quantitative synthesis between reviews was limited.
29.	Peer Reviewer #3	General Comments	The limits of the searches have reduced the number of trials. Especially the requirement that only studies were included in patients who had an ACS event within 3 months, has limited the number of studies. I think it would have been better to have broader inclusion criteria, so that more studies would have been available and then it could have been examined with subgroup analyses whether this inclusion criterion made a difference. By limiting the inclusion criteria the only conclusion can be that the evidence is limited.	We appreciate the concerns about the narrowness of the eligibility criteria. These criteria were developed in consultation with the stakeholders/TEP/KI and public input. Conceptually, we were interested in defining a post-ACS population that could be distinguished from patients with chronic coronary heart disease. Note that a narrower window (e.g. depression within one month post ACS) would have further limited the number of eligible studies.

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30.	Peer Reviewer #3	General Comments	I am not convinced that screening should be routinely recommended based on this report. Many of the patients who are screened already receive treatment and that overestimates the value of the screening considerably. Furthermore, it only looks whether these screening instruments are good at detecting depressive disorders. However, subthreshold depression can be clinically relevant as well and that complicates the results of this report further. I think it should first be shown in randomized trials that screening plus treatment has indeed a benefit over no screening. I am not convinced that this will be found in such trials.	KQ 1 addresses the accuracy of screening instruments and screening strategies. We found evidence for the accuracy but not for the effectiveness of screening. We do not make a recommendation for or against depression screening. In the introduction, we note that recommendations for screening are controversial.
31.	Peer Reviewer #4	General Comments	Yes.	No response needed.
32.	Edgar Weiss (Public Reviewer)	General Comments	Very helpful study and valuable information for those of us who are in clinical practice. In terms of policy implications, I would suggest that there is a need for studies that focus on other forms of psychotherapy and CBT. Therapies that focus on the impact of the ACS on the patient's interpersonal relationships with family. I would add to that therapies that use relaxation techniques such a deep muscle relaxation, biofeedback, and or meditation techniques. All of the above to be used to decrease the autonomic reactivity of the patient.	We have added in a callout to such interventions within the research recommendations section.
33.	TEP #1	Introduction	Clear.	Thank you.
34.	TEP #2	Introduction	I have no major comments.	Thank you.

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35.	TEP #3	Introduction	<p>The "PHQ" is mentioned numerous times throughout (e.g., pages 18-19). For example, "Data on the accuracy of screening instruments, including the PHQ, which is popular in general medical settings was very limited."</p> <p>Since there are 2 versions of the PHQ, use of the "PHQ" is ambiguous and confusing. All instances should be changed to the specific version (PHQ-2 or PHQ-9).</p>	We attended to this issue throughout the revised report and have added a clarification that is pertinent to the PHQ and other screening instruments included in this review where different item combinations and subscales were evaluated for the different versions of the instrument.
36.	TEP #5	Introduction	A summary effect sizes of the interventions should be added to the Introduction.	Where possible, we now include information on the effect sizes of the interventions throughout the report.
37.	TEP #5	Introduction	p. 2 line 25. "Alternative therapies". Alternative may have negative connotations. Consider a different word such as "Other therapies....".	We have replaced with "Other therapies."
38.	TEP #6	Introduction	The introduction appropriately outlines the previous research regarding the topic, the clinical background, the appropriate background material regarding depression screening instruments and treatment strategies as well the scope of the review and the key questions within the analytical framework. I have no suggested corrections or additions.	Thank you.
39.	Peer Reviewer #1	Introduction	Introduction is clear and succinct. No changes needed.	Thank you.
40.	Peer Reviewer #2	Introduction	The Introduction nicely introduces the topic and key questions.	Thank you.
41.	Peer Reviewer #3	Introduction	In the key messages it says that collaborative care and CBT improve depression but do not clearly improve cardiac outcomes. I think that should say that no evidence was found that they improve cardiac outcomes. The word "clearly" is confusing here and should be avoided.	The key message has been edited for clarity; "clearly" was removed.

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42.	Peer Reviewer #4	Introduction	Good.	Thank you.
43.	TEP #1	Methods	KQ2 did not address whether depression treatments aimed at individuals with high depression sx, but possibly not MDD or Persistent depressive disorder, are clinically effective in reducing depression sx.	Our eligibility criteria included patients with a criterion-based diagnosis of major depression or who had clinically important depressive symptoms using a validated depression scale. We included studies of patients with high or persistent depressive symptoms, but without a formal diagnosis of MDD or persistent depressive disorder. In KQ2 we describe the included population (See KQ2 – Evidence Summary – Table 9 for a summary).
44.	TEP #2	Methods	I suggest adding a few sentences why patients with heart failure were not included. This is a reasonable exclusion criteria but rationale should be included. The search strategies, study selection, and data extraction were all reasonable, and clearly articulated. The outcome measures were appropriate.	We thank the reviewer for this comment. We highlight in the text the included patient population and justification for this specific scope, but to aid in the readability/conciseness of the report do not explicitly list all other potential patient populations.

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45.	TEP #2	Methods	Minor comment (Appendix E): did any of the studies have multiple reasons for exclusion? If yes, how did the authors decide which exclusion was the "reason".	Yes, excluded studies may have failed to meet more than one criteria for inclusion. Articles were assessed against a hierarchical set of exclusion reason possibilities, and screeners were instructed to select the first applicable exclusion reason from the hierarchical list. The reasons are presented in that hierarchical order in the literature flow diagram and in Appendix E. We have added text to describe this process in the Methods section for Study Selection.
46.	TEP #3	Methods	<p>I do not think the "PHQ-10" should be mentioned (on page 25 or 26) because it has not been validated as a stand-alone instrument. Notably, the name "PHQ-10" was coined by McGuire et al in their 2013 article "Depression screening: utility of the patient health questionnaire in patients with ACS," which stated:</p> <p>"The PHQ-9 has a follow-up question: If you checked off any problems on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?" Possible answers are not difficult at all (0), somewhat difficult (1), very difficult (2), and extremely difficult (3). This question addresses the requirement for a functional impairment for a diagnosis of clinical depression. In this study, this follow-up question together with the first 9 items of the PHQ-9 was termed the PHQ-10".</p>	As suggested, we have removed reference to the PHQ-10 in the section of the discussion that described the PHQ as "popular in general medical settings." We do, however, retain discussion of the findings from the study that examined different versions of the PHQ but clarify which specific version is being evaluated.

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47.	TEP #4	Methods	<p>On page 7, the authors provide a nearly exhaustive list of antidepressants which were eligible for review if studied in a post ACS depression trial. However, most of these have not been studied in depressed post ACS patients, as the authors' later note, and some that have been studied, notably the tricyclics, are known to be cardiotoxic for some cardiac patients. It is important that this list should not be interpreted as an endorsement of any of these drugs so this point should be made the first time these drugs are mentioned. Otherwise the authors should consider simply noting that all major classes of antidepressants were considered in the review. The authors make it clear later in this report that the safety of the majority of these drugs has not been studied. However, they should draw attention to appendix A where they report potential problems with the antidepressants, and not wait until page 37 to mention the question of safety and possible side effects, etc.</p>	<p>Thank you for this caution. We have added a preamble to the table of inclusion and exclusion criteria that clarifies our choice of eligible interventions. In addition, we call attention to Appendix A in the section on treatment strategies (page 2 of the report).</p>
48.	TEP #4	Methods	<p>The authors only briefly note that there has been a strong negative response to routine screening by some cardiologists and other. Although the letters and editorials that have taken this position have been from a small but highly vocal group, some of these concerns (e.g. screening in a clinical setting that is not ready to respond to a positive screen by further evaluation and treatment, or the fact that there is little evidence for the benefit of depression screening) should be acknowledged and briefly discussed. If the authors wish to rebut these points they can add a brief paragraph to do so, but they should be acknowledged.</p>	<p>We state in the introduction that recommendations to screen this population are controversial (and include citations), and we added sentences to the discussion that address this issue.</p>

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49.	TEP #4	Methods	The intervention studies described as “collaborative care” interventions do not meet the conventional definition of collaborative care in which a mental health professional, usually a psychiatrist, makes recommendations for treatment to the patient’s primary care physician (PCP) who is coordinating the overall care of the patient. In both COPES and CODIACS, the study psychiatrist prescribed the drugs if the patient preferred an antidepressant, or the patient was provided problem solving therapy by study staff if that was preferred by the patient. The PCP was kept informed but did not oversee or coordinate the patient’s depression treatment. These differences may seem subtle, but these trials seem more like conventional trials in which interventions are provided by the study team, and do not rely on the PCP or cardiologist to provide or coordinate depression treatment.	Thank you for making this important point. We’ve revised the text to describe these interventions as “enhanced care” and given more detail on the components of this care. We’ve stated that the COPES trial was based on a large collaborative care model, and have pointed out how it differed from this collaborative care model.
50.	TEP #5	Methods	The reviewers state that their search strategy did not include papers included in the earlier 2005 AHRQ systematic review (ref #1). Indeed, the SADHART Trial of sertraline vs. placebo in ACS patients published in JAMA in mid-2002 (and its secondary reports on quality of life (Swenson 2003) long-term mortality outcomes (Glassman 2009) was excluded from the current report (N=369). However, the 2005 AHRQ report included the ENRICHD trial published in JAMA in mid-2003 that was also included in this report and heavily weighted the results (N=2,500 out of 3,119).	We included the ENRICHD study in this review because there were recent relevant secondary papers from ENRICHD that were published after the initial report’s search date. The inclusion of these secondary papers then necessitated us including the primary study to maintain cohesiveness. We do discuss the overlap of ENRICHD in the 2005 and 2017 reports in both the KQ 2 Results and Discussion. We also discuss consistency/inconsistency of the findings from the original report, which included the SADHART trial, with this new review.

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51.	TEP #5	Methods	Cost effectiveness was reported for COPES (see Ladpro paper on E10, that should be added to Appendix F) and within the original main COPES paper.	<p>The Ladpro cost effectiveness report was in a “research letter,” and as such was excluded from our review as it did not fit the inclusion requirement of being a full publication.</p> <p>For the CODIACS trial, effects on total costs are reported.</p>
52.	TEP #5	Methods	It is unclear why Jeff Huffman's MOSAIC Trial of collaborative care following an acute cardiac event was excluded (JAMA Internal Medicine 2014).	This study was identified in our search and excluded after review for the full text. Only 50% of the sample was post-MI. This did not meet our eligibility criteria.
53.	TEP #5	Methods	<p>Other important papers to consider adding:</p> <p>Ken Freedland's 2009 Arch Gen Psych report of cognitive behavioral therapy for depression following CABG Surgery.</p> <p>Bruce Rollman's 2009 JAMA report of collaborative care for post-CABG depression (and 2014 cost-effectiveness paper by Donohue).</p>	<p>We considered including patients following admission for CABG surgery in addition to patients post-ACS; however, this population was excluded based on recommendations from the TEP when establishing the scope of the review.</p> <p>These three suggested articles were screened and excluded. Although related, these papers are not germane to the topic of post-ACS.</p>



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54.	TEP #5	Methods	<p>Also, in Appendix E List of Excluded Studies. Several are the the "Methods" papers for relevant clinical trials, some published years ago, that would expected to have published results by now (e.g., Huffman's Positive Psychology Trial; Jolly's BRUM Trial; Kim K-DEPACS, O'Neil MoodCare; Hunger's KORINNA Trial, Jorstad's RESPONSE Trial; and Roncella's STEP-IN-AMI Trial, among others).</p> <p>For some of these reports, depression was not the primary outcome of interest, but it was reported so the authors may need to go back and review the papers more carefully or contact the PIs to get the data to include in this review.</p>	All of the suggested studies were identified in our search. We rechecked these studies for eligibility and all were appropriately excluded. Reasons for exclusion were depression was not an eligibility criteria for trial enrollment; the subsample with depression was <70% and results for subsample with depression were not reported separately; no eligible interventions; not eligible country; and not an RCT.
55.	TEP #6	Methods	1) The inclusion and exclusion criteria as outlined appear appropriate with all PICOTS elements appropriately listed with no elements overlooked or inappropriately excluded from my review.	Thank you.
56.	TEP #6	Methods	2) Search strategies are appropriately applied and outlined.	Thank you.
57.	TEP #6	Methods	3) The outcome measures for both KQs cover the pertinent criteria from this reviewer's standpoint.	Thank you.
58.	TEP #6	Methods	4) The statistical analysis including assessment of study quality and strength of evidence is appropriate.	Thank you.
59.	Peer Reviewer #1	Methods	All criteria, methods, and statistics, are reasonable. Search strategies are logical and reasonable.	Thank you.
60.	Peer Reviewer #2	Methods	The search strategy was appropriate. The decision to update the search to include UA and not just post-MI was appropriate.	Thank you.
61.	Peer Reviewer #3	Methods	I assume it is not the Cochrane Database of systematic reviews that was searched, but the Cochrane database of randomized trials?	The text is correct; the database searched was the Cochrane Database of Systematic Reviews.

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62.	Peer Reviewer #3	Methods	p.13, the requirement that at least 3 studies should be available to do a meta-analysis is arbitrary. It would be much better to do a power calculation to determine the number of needed studies.	The reviewer is correct that the minimal number of studies for a meta-analysis can be based on power calculations, consideration of the width of the confidence intervals, or the heterogeneity of the studies. We have added the inclusion of power to our methods description.
63.	Peer Reviewer #4	Methods	Detailed.	Thank you.
64.	TEP #1	Results	Good.	Thank you.
65.	TEP #2	Results	The results section was clear and easy to read. The tables and figures were excellent. I don't think any studies were missed. The only comment I have is that I would ask the authors to avoid vague or non-specific statements in the Results. For example, the term "generally" is used throughout the document. I would prefer the authors be more specific. On page 19 (3rd bullet point), I would avoid using "slightly", and be more specific. This term means different things to different people. Similarly, the term "nearly" is used on the same page (5th bullet point).	We have reviewed the specific uses of these terms and have modified many of them within the text. Some of the uses we have retained if we felt that the existing wording was important.
66.	TEP #3	Results	A sentence on page 38, line 27, states "the two-item version of the PHQ may perform as well as longer screening tools" and cites the problematic McGuire article mentioned above. Please note that "two item version of the PHQ" is a misnomer. The PHQ-2 (validated by Kroenke in 2003) is different than the "two-item instrument" (validated by Whooley in 1997). For an explanation, please see Whooley, Screening for depression—a tale of two questions. JAMA-IM 2016.	The PHQ-2 evaluated by the included study (McGuire, 2013) in the present review was assessing the version validated by Kroenke in 2003. We have revised the language of this sentence to help clarify.

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67.	TEP #4	Results	In Table 9, the UK is part of Europe (although soon not part of the European Union). It is not clear why it was mentioned separately. One of the four trials reported in this review, the MIND-IT trial, was completed in the Netherlands and perhaps could be recognized.	We have revised the categorization of countries to combine UK and Europe.
68.	TEP #4	Results	The authors note that the mean differences between intervention and control conditions, generally “usual care,” have been small, although usually statistically significant. However, they should mention that in every case the intervention groups showed significant improvement in depression from baseline to post treatment. Surprisingly perhaps, the control arms have also showed significant improvement, resulting in smaller than expected differences between groups. This small difference is unlikely to have a significant effect on cardiovascular outcomes, especially mortality, in the size of the trials that have been completed.	Because this is a comparative effectiveness review, we focused on the differences between intervention and control, rather than change within treatment arms.
69.	TEP #5	Results	It is difficult to understand the point changes since the studies described used a variety of scales. Presenting the results in effect size changes would be much more meaningful to readers. Rather than, or in addition to the changes in mood symptom scaled, can the authors add a Forrest Plot of effect sizes to the work to facilitate readers' understanding.	Where possible, we now include information on the effect sizes of the interventions throughout the report both within the text and within the summary Table 12.
70.	TEP #5	Results	p. 32. Outcomes not reported. It is mentioned that none of the trials included a cost-effectiveness. However, both CODIACS and COPES published C-E analyses, COIACS within the main report and Ladpro et al. for COPES in a separate paper.	The Ladpro cost effectiveness report was in a “research letter,” and as such was excluded from our review as it did not fit the inclusion requirement of being a full publication. For the CODIACS trial, effects on total costs are reported.

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71.	TEP #6	Results	1) The descriptive material included in the discussion of the KQs, the relevant studies and the descriptions of those studies appears adequate.	Thank you.
72.	TEP #6	Results	2) Yes, study characteristics including bias analysis, strength of evidence are appropriately delineated.	Thank you.
73.	TEP #6	Results	3) The key points from the research regarding the KQs are both explicitly defined. Applicability to possible guideline use will be determined after further review.	Thank you.
74.	TEP #6	Results	4) Tables and figures as included are adequate and included the additional subscripts needed for interpretation.	Thank you.
75.	TEP #6	Results	5) This reviewer is not aware of any studies inappropriately included or excluded at this time.	Thank you.
76.	Peer Reviewer #1	Results	Results should add one section on adverse events/harm for both KQ1 and KQ2. Even if almost no data on this topic was found, then this should be state. Potential harms should be stated, as appropriate (e.g. increased bleeding risk in those on SSRI). The sections on bias for KQ1 was excellent; both the visual graphic and the written results. Such a section should be added for KQ2. Authors just assert 'high' risk for many of the interventions, without a clear articulation of why, and the implications of this bias. Study inclusion/exclusion seems reasonable.	Noncardiac adverse effects were reported in only one study. The results and key points have been revised to clearly address major adverse cardiac effects (MACE) and noncardiac adverse effects A figure and table showing the risk of bias for KQ 2 studies has been added to the report.

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77.	Peer Reviewer #2	Results	The amount of detail provided was appropriate. The table showing the different amounts of time needed for each screening instrument was particularly helpful. Given the different sets of eligibility criteria for KQ1 and KQ2, I was expecting to see 2 separate literature flow diagrams (currently Fig 2) for each KQ.	Thank you for this comment. The literature flow diagram is presented in one figure to directly reflect the screening process followed. The searches presented in Appendix B were run and screened jointly. All articles returned across the entire search strategy (all search strings and all sources) were considered for both KQs.
78.	Peer Reviewer #2	Results	In Table 7, it seems as though some of the data not reported (e.g., PPV, NPV) could be calculated from the data provided using a 2X2 table.	Given that the PPV and NPV are dependent on the underlying prevalence of disease in the population, we did not calculate these outcomes unless reported within the study.
79.	Peer Reviewer #2	Results	I did not fully agree with the description of the COPES and CODIACS trials as representing collaborative care. While the patient-preference driven, measurement based, stepped care approach was borrowed from the quintessential collaborative care trial (IMPACT), treatment was not coordinated with the involvement of the primary care provider, but rather an enhanced depression care team made all treatment decisions with little to no involvement of participants usual treating providers.	Thank you for this comment. We agree and have revised the text to describe these interventions as “enhanced care” and given more detail on the components of this care. We’ve stated that the COPES trial was based on a large collaborative care model and have pointed out how it differed from this collaborative care model.



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80.	Peer Reviewer #2	Results	The description of the efficacy of depression treatments on depressive symptoms was primarily done using difference in depression scale scores (e.g., difference in BDI symptoms). Yet, for the casual reader, it is challenging to understand the magnitude of this difference score. It might be useful to describe this difference as a standardized effect size. A comparison with the effectiveness of these treatments in post-ACS patients versus the general population might also be useful for putting the findings in perspective. This is described as an issue in the introduction, but not followed up on.	Where possible, we now include information on the effect sizes of the interventions throughout the report. Note that we don't include a comparison of effect sizes, but rather compare overall effects in the post ACS population to patients with depression and cardiovascular risk factors and separately to patients with varying levels of depression.
81.	Peer Reviewer #2	Results	In the discussion of effectiveness of interventions, the authors did not classify the interventions as targeting patients with depressive symptoms in first week after ACS versus targeting patients with persistently elevated depressive symptoms - this is brought up in the discussion for the first time. It might be worth more clearly highlighting this in the results section as well.	Patients included are summarized in Table 9 and for each study in the results section.
82.	Peer Reviewer #3	Results	p.17, the overall description of included studies is not needed because these are two groups of completely different studies and a discussion of both of them together is not informative.	We thank the reviewer for the suggestion but feel that the overview of the complete set of included studies could be helpful to some readers. No change made.
83.	Peer Reviewer #4	Results	Very Detailed.	Thank you.
84.	TEP #1	Discussion/ Conclusion	Several studies have indicated benefit from exercise for both CAD and depression outcomes. These were outside the scope of this review, but this exclusion might have been revisited in the discussion--for example a trial of exercise + AD vs AD vs exercise + placebo might be a good future study.	Our eligibility criteria included structured aerobic exercise. However, we did not identify any studies evaluating this intervention.

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85.	TEP #2	Discussion/ Conclusion	The major findings were clearly stated. The Discussion is overall concise. Limitations were stated and what additional research needs to be done was clearly articulated. I have two suggestions: (1) on page 37, starting on line 32, for the following sentence: "Therefore, at present, evidence suggests that depression interventions will improve depression outcomes and at least not increase negative cardiovascular outcomes", I would suggest changing "will" to "may", and "at least" to "may".	We have changed the text to read "Therefore, at present, evidence suggests that depression interventions improve depression outcomes and may not increase negative cardiovascular outcomes."
86.	TEP #3	Discussion/ Conclusion	<p>: A sentence on page 25, line 4, is incorrect and poorly worded: "The PHQ versions 2 which included just 2 items (threshold>0), 9 (>4), and 10(>5) were compared in one study, with the three versions each demonstrating excellent AUC statistics and not performing significantly differently from one another with respect to sensitivity and specificity." Again, the problematic McGuire article is cited.</p> <p>Corrections: PHQ-2 has a threshold of >=3 (of 6 points) PHQ-9 has a threshold of >=10 (of 27 points) PHQ-10 is not a validated screening tool</p> <p>Notably, the 2013 McGuire article confused the PHQ-2 with the two-item screen (Whooley questions). McGuire et al incorrectly stated that the cutpoint on the PHQ-2 is >0.</p>	This sentence has been rewritten to clarify the thresholds that were used by the authors in their study and that these thresholds are non-traditional.



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87.	TEP #5	Discussion/ Conclusion	<p>Bottom line: the search strategy was too restrictive. Only 4 reports found, and one reported in 2005 AHRQ report on the topic dominates all.</p> <p>Consider "loosening" up the search criteria and more carefully reviewing the list of excluded studies and 'methods' reports to identify and include additional relevant trials, of which I believe there have been several published since 2005.</p>	The search strategy matches the eligibility criteria. We understand the reviewer's concern that the eligibility criteria were too restrictive, but they were developed with input from KI/TEP and public to match the size of the review authorized and the stakeholders needs.
88.	TEP #5	Discussion/ Conclusion	p. 37. lines 42-43. If treatment of post-ACS depression is going to occur, mention of the 4 new CMS payment codes to support collaborative care for depression should be added in the Intro and Executive Summary of the report.	The payment codes (G Codes) are described and cited. We do not think a detailed description (i.e., specific codes) adds to the discussion.
89.	TEP #5	Discussion/ Conclusion	p. 38. Research Recommendations. Many relevant trials should be referenced here for CABG (Rollman and Freedland), CHF (Mood-HF by Angermann and SADHART-CHF by O'Connor), the trials of exercise and cardiac rehabilitation for depressed patients with cardiac disease by Blumenthal.	We respectfully disagree. While these trials address patients with cardiac conditions, they do not address interventions in post-ACS patients.
90.	TEP #5	Discussion/ Conclusion	Given the findings in the report on collaborative care, it would be very important to highlight the trial of "blended" collaborative care for depression and co-morbid diabetes and CAD led by Katon et al. that reported particularly strong effect size improvements for mood symptoms as well as significant reductions in blood pressure, HgbA1c, and lipids (NEJM 2010). Their blended intervention may be more likely to be adopted into routine care than collaborative care interventions that are solely focused on patients' depression symptoms alone.	Thank you for this suggestion. This study has been described and cited.
91.	TEP #6	Discussion/ Conclusion	1) Study implications are clearly stated from the outcome measures that were addressed by the included studies.	Thank you.

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92.	TEP #6	Discussion/ Conclusion	2) Study limitations are outlined including the limited evidence base of studies which met the inclusion criteria as well the lack of studies addressing several of the interventions of interest.	Thank you.
93.	TEP #6	Discussion/ Conclusion	3) No omissions to my knowledge.	Thank you.
94.	TEP #6	Discussion/ Conclusion	4) In general, the future research topics are appropriate and appears to address most research needs. As a generalist, I question whether additional research should explore any differences between immediate depression screening in the hospital setting vs screening conducted at later stages in the outpatient setting and whether validity of the listed tools is different between the hospital setting and the subsequent outpatient (ie office) setting. This reviewer clearly would like to investigate the long-term effect (if any) of depression treatment regarding cardiac outcomes. This reviewer also would like to see more research into any sex and ethnicity differences regarding the various screening tools for the post ACS populations as well as the treatment options for this same population.	We thank the reviewer for his suggestion. We have added this suggested topic (immediate vs delayed screening) to the research recommendations section.
95.	Peer Reviewer #1	Discussion/ Conclusion	Implications of most major findings are clear and concise, with one major exception. The authors state in many places that the impact of the interventions on cardiac outcomes is insufficient (too few outcomes/too little power) but conclude that these interventions have either 'uncertain' impact on cardiac outcomes or that these interventions 'do not clearly improve cardiac outcomes'. The message should be consistent with the evidence--if there is insufficient evidence to draw a conclusion, then this should be stated. If the evidence is sufficient to draw a conclusion of no effect, then this should be stated.	We reviewed and edited our description of intervention impact on cardiac outcomes.

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96.	Peer Reviewer #2	Discussion/ Conclusion	In the abstract and results sections, the authors describe the improvement in depressive symptoms with collaborative care over usual care as being statistically but not clinically relevant. However, the conclusions suggest that collaborative care might be a good approach. The authors should seek to resolve this potential mixed message. In comparison with other depression treatments in the general population, the effect of collaborative care interventions was similarly if not more effective.	As described earlier, we reevaluated the MCID and now describe the interventions with at least a 3-point difference as being clinically significant. With this change and related edits, the message about statistical and clinical significance and the suggestion that enhanced care may be a good approach have been harmonized.
97.	Peer Reviewer #2	Discussion/ Conclusion	The authors might highlight that an NHLBI funded RCT of depression screening in post-ACS patients is underway. (<a 102="" 514="" 857="" 877"="" data-label="Text" href="https://urldefense.proofpoint.com/v2/url?u=https-3A_clinicaltrials.gov_ct2_show_NCT01993017&d=DwIFaQ&c=imBPVzF25OnBgGmVOlcsiEqHoG1i6YHLR0Sj_gZ4adc&r=bRvLhIBlwKo9K3-j2sdk9ss1M2GeSdXUBIDLVD9mXmE&m=1xr4Y3B9HLZz_CKcwXh4DA5o8Pe42I2ORq5-FdRAliQ&s=bz7UAkl88EVQPTe2D1DKpls84wtoy-uScmjuaQTR05Y&e=))</td> <td>We now cite this ongoing study in our research recommendations section.</td> </tr> <tr> <td>98.</td> <td>Peer Reviewer #2</td> <td>Discussion/
Conclusion</td> <td>In terms of research recommendations, the authors might recommend adequately powered studies to definitively answer whether enhanced depression care has an impact on CVD outcomes.</td> <td>We now include this suggestion within our research recommendations section.</td> </tr> <tr> <td>99.</td> <td>Peer Reviewer #2</td> <td>Discussion/
Conclusion</td> <td>The discussion also did not mention blended care depression interventions that address depression and CVD risk factors concurrently (ex: Katon et al. NEJM 2010). This might be a good approach to compare in post-ACS patients.</td> <td>Thank you for this suggestion. This study has been described and cited.</td> </tr> </tbody> </table> </div> <div data-bbox="> <p>Source: https://effectivehealthcare.ahrq.gov/topics/acs-depression/research-review-final</p> 	

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100.	Peer Reviewer #4	Discussion/ Conclusion	This is very detailed and clear. The authors, however, could include two recent papers in the American Journal of Medicine (Ernsten L et al AJM 2016;129:82-88 and Kachur S et al AJM 2016;129:1316-1321), as well as a recent one that could be included in the introduction (Lavie CJ et al Canadian Journal of Cardiology 2016;32:S365-S373).	Thank you for this comment. We have reviewed the suggested citations and considered either for inclusion in the introduction or as included articles. They did not meet our inclusion criteria. Specifically, the paper by Ernsten and Kachur are both observational studies and therefore do not meet our study design criteria. Lavie is a nonsystematic review. We did not feel that these additional citations contributed to the introduction sufficiently to warrant inclusion.
101.	TEP #1	Clarity and Usability	Yes. It was surprising and useful to me to learn that the BDI-II was the screening instrument best documented to have good screening performance characteristics.	Thank you.
102.	TEP #2	Clarity and Usability	I had no concerns. The document is well structured, and easy to read. The main points were clearly presented. The conclusions are directly relevant to policy AND practice decisions.	Thank you.
103.	TEP #3	Clarity and Usability	Congratulations on this Herculean effort!	Thank you.

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104.	TEP #5	Clarity and Usability	I think other reports have described the screening instruments more concisely (e.g. Lichtman et al., Circ 2008, McManus Am J Cardiology 2005, and Thombs JAMA 2008).	Only one of the cited studies is a systematic review. We report similar data on screening instruments but give additional information to inform readers about feasibility (e.g., response format, literacy level) and greater detail on performance at varying cutpoints. The additional information is needed to fully address the key question.
105.	TEP #5	Clarity and Usability	Highlighting the BDI-II in the "Key Messages" (p. 2) detracts from the fact that PHQ (-2/-9) that has become dominant in actual clinical practice at many health systems.	We have noted in the Key Messages that the BDI-II is the most studied, and we have added the need for more research on the PHQ-2/-9 in the future research section.
106.	TEP #6	Clarity and Usability	1) The report flows logically and in sequence with each section properly organized.	Thank you.
107.	TEP #6	Clarity and Usability	2) Yes.	Thank you.
108.	TEP #6	Clarity and Usability	3) The report as presented should enable further guideline development after proper incorporation of the material gained from review of the KQs.	Thank you.
109.	TEP #6	Clarity and Usability	4) Yes, the report supplies material regarding the KQs which should enhance diagnostic accuracy of the subject disorder and its subsequent treatment.	Thank you.

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110.	Peer Reviewer #1	Clarity and Usability	The report is well structured and organized. Conclusions are relevant to policy decisions, less so to practice decisions. An implementation lens or grid would be helpful for guiding clinicians as to what they should be concluding from this report. The report does contribute new information to this important topic.	We agree that incorporating the evidence summarized into tools for clinical providers to use would be helpful. The EPC program does not make clinical recommendations but rather speaks clearly to the evidence and provide discussion of the implications for decision making in the discussion.
111.	Peer Reviewer #2	Clarity and Usability	No issues. The report was well organized. The broadening of the inclusion criteria and incorporation of data from previously unconsidered intervention types adds novel information needed to understand the state of the evidence.	Thank you.
112.	Peer Reviewer #3	Clarity and Usability	yes, the report is well structured.	Thank you.
113.	Peer Reviewer #4	Clarity and Usability	This is quite lengthy but thorough.	Thank you.

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