

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



## *Comparative Effectiveness Review*

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Number 200

# Diagnostic Accuracy of Screening and Treatment of Post–Acute Coronary Syndrome Depression: A Systematic Review

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# Key Messages

## **Purpose of Review**

Evaluate the comparative accuracy of tools for diagnosing depression in patients after an acute coronary syndrome event and the effectiveness of treatments in these patients.

## **Key Messages**

- The Beck Depression Inventory (BDI)-II screen tool is the most studied and is as accurate in this population as in others.
- Available depression-screening tools may miss 3 percent of people with depression, but less than 50 percent of those who screen positive have clinically confirmed depression.
- Enhanced care interventions that integrate psychiatric treatment into cardiology and primary care settings improve depression symptoms. Current evidence is insufficient to determine if enhanced care improves cardiac outcomes.
- Combining cognitive behavioral therapy and antidepressant medication may improve depression outcomes but does not clearly improve cardiac outcomes.

This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00004-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

**None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.**

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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- Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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

## Structured Abstract

**Objectives.** To evaluate (1) the diagnostic accuracy of selected depression screening instruments and strategies versus a validated criterion standard in adult patients within 3 months of an acute coronary syndrome (ACS) event and (2) the comparative safety and effectiveness of a broad range of pharmacologic and nonpharmacologic treatments for depression in adult patients who have received a criterion-based diagnosis of depression or had clinically important depressive symptoms using a validated depression scale and who are within 3 months of an ACS event.

**Data sources.** We searched PubMed<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, and the Cochrane Database of Systematic Reviews for English-language studies published from January 1, 2003, to August 15, 2017, that evaluated the accuracy of tools for diagnosing depression in patients after ACS or that evaluated interventions for treating post-ACS patients identified with depression.

**Review methods.** Two investigators individually screened each abstract and full-text article for inclusion; abstracted data; and rated quality, applicability, and strength of evidence. Where appropriate, random-effects models were used to compute summary estimates of effects.

**Results.** We identified 21 primary articles describing 10 unique studies that met our inclusion criteria: 6 studies relevant to diagnostic accuracy and 4 studies relevant to treatment effectiveness. For diagnostic accuracy, based on six studies evaluating four instruments involving 1,755 post-ACS patients, evidence suggests that a range of different depression screening instruments produce high (97%) negative predictive values (i.e., percentage of patients who screen negative who do not have the condition) but produce low (<50%) positive predictive values (i.e., percentage of patients who screen positive who actually have the condition). Sensitivity and specificity are greater than 70 percent. A meta-analysis of four studies (1,576 patients) estimated the diagnostic screening performance characteristics of the Beck Depression Inventory (BDI)-II: sensitivity of 90 percent (SOE=high) and specificity of 80 percent (SOE=moderate). For treatment effectiveness, enhanced care interventions that integrate psychiatric treatment into other clinical settings improve depression symptoms more than usual care (mean difference in BDI, -3.5 to -3.8; 2 trials; SOE=moderate); adverse effects did not differ. One trial compared second-generation antidepressants with usual care and found no effect on depression symptoms or quality of life, although, when combined with studies included in the original review, it showed a small positive effect of antidepressants. A large trial found that a combination strategy including cognitive behavioral therapy (CBT) and antidepressant medication improved depression symptoms, mental health-related function, and overall life satisfaction more than usual care (1 trial, 2,481 patients, SOE=high) but had no consistent effect on cardiovascular outcomes (SOE=moderate). Evidence supporting effects of enhanced care interventions on cardiovascular and other outcomes of interest was insufficient.

**Conclusions.** Among several depression screening tools, the BDI is the most studied. Existing tools miss less than 3 percent of patients with depression, but only 50 percent of patients who screen positive actually have clinically confirmed depression. Enhanced care interventions and a strategy using CBT plus second-generation antidepressants for patients with severe depression or partial response to CBT improved depressive outcomes more than usual care. The effects of depression interventions on cardiovascular outcomes are uncertain.

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# Evidence Summary

## Objectives and Rationale for Review

Patients who are diagnosed with acute coronary syndrome (ACS) are at increased risk for mental health problems—including major depressive disorder (MDD) and elevated symptoms of depression. For the purpose of this review, ACS refers to clinical symptoms compatible with acute myocardial ischemia and includes unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).

The objectives of the systematic review are:

- To evaluate the diagnostic accuracy of selected depression screening instruments.
- To assess the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for depression in adult patients within 3 months of an ACS event.

## Post-ACS Screening Strategies

A number of screening tools for depression have been developed. This review sought to evaluate tools, which were feasible to use and have been validated in general populations. These tools and strategies were compared against the gold standard of a validated criterion standard (e.g., Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases [ICD] criteria) administered by a trained interviewer.

## Post-ACS Treatment Strategies

Pharmacologic treatments included second-generation antidepressants (e.g., selective serotonin reuptake inhibitor [SSRIs], serotonin-norepinephrine reuptake inhibitor [SNRIs]), atypical antipsychotics, and tricyclic antidepressants.

Nonpharmacologic treatments included various types of psychotherapy, aerobic exercise, selected dietary supplements, cardiac rehabilitation, education/psychoeducation, stress management, psychosocial support, transcranial magnetic stimulation, electroconvulsive therapy, and combinations of these approaches.

Enhanced care delivery strategies, which integrate psychiatric treatment into other clinical settings, also were evaluated. In such strategies, patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (e.g., psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (e.g., patient education or cognitive-behavioral therapy), scheduled followup visits, communication among the members of the treatment team, and measurement-based care.

## Key Questions and Scope of Review

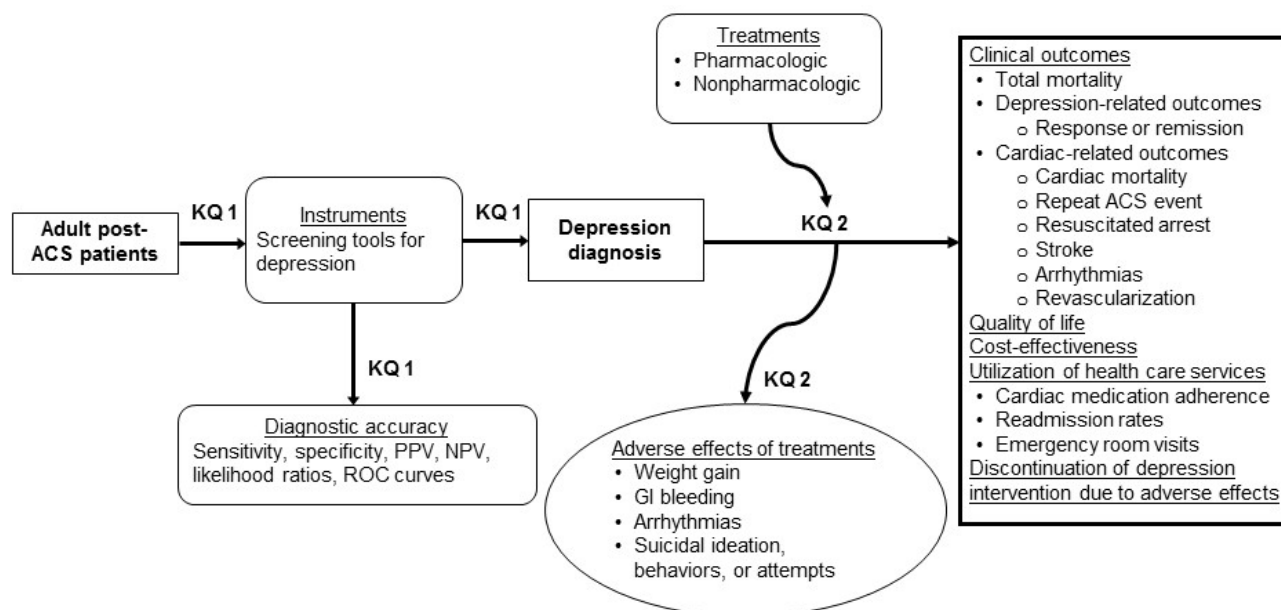
The Key Questions (KQs) follow:

**KQ 1:** What is the accuracy of depression screening instruments or screening strategies compared to a validated criterion standard in post-ACS patients?

## KQ 2: What are the comparative safety and effectiveness of pharmacologic and nonpharmacologic depression treatments in post-ACS patients?

Figure A shows the scope of the review.

**Figure A. Analytic framework**



Abbreviations: ACS=acute coronary syndrome; GI=gastrointestinal; KQ=Key Question; NPV=negative predictive value; PPV=positive predictive value; ROC=receiver operating characteristic

## Data Sources

MEDLINE<sup>®</sup> (via PubMed<sup>®</sup>), Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, and the Cochrane Database of Systematic Reviews (CDSR), bibliographic databases from January 1, 2003, to August 15, 2017; hand searches of references of relevant studies and [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

The finalized protocol is posted on the EHC Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)). The PROSPERO registration is CRD42016047032.

## Results

### KQ 1: Diagnostic Accuracy of Depression Screening Tests in Post-ACS Patients

We identified seven articles representing six studies that examined the accuracy of depression screening instruments or screening strategies in post-ACS patients (Table A).

**Table A. Key Question 1 evidence summary**

<b>Number of studies:</b> 6
<b>Study publication years:</b> 2005-2013
<b>Number of patients:</b> 1,755
<b>Men:</b> 1,343 (77%)
<b>Women:</b> 412 (23%)
<b>Mean age range:</b> 57 to 63 years
<b>Race/ethnicity:</b> Unavailable
<b>Settings:</b> Inpatient (5); cardiac rehabilitation clinic (1)
<b>Countries:</b> USA (3), Canada (2), UK/Europe (1)
<b>Screening instruments:</b> <sup>a</sup> Beck Depression Inventory-II (BDI-II); Hospital Anxiety and Depression Scale (HADS); Patient Health Questionnaire (PHQ); Geriatric Depression Scale (GDS)
<b>Criterion standard:</b> Diagnostic and Statistical Manual of Mental Disorders III-IV major depressive disorder (MDD)

<sup>a</sup> Some studies examined different numbers of items and subscales for the BDI-II, HADS, and PHQ. Specific versions, subscales, and item combinations are noted where applicable, and the generic scale is referenced for statements that apply across different versions and item combinations for the scale (e.g., 2-item, 9-item, and 10-item versions of the PHQ).

### Key Findings

- Four depression screening instruments have a high negative predictive value (97%) but have low (below 50%) positive predictive values. This means the instruments would miss less than 3 percent of those who have depression, but only 50 percent of patients who screen positive actually have the condition.
- The Beck Depression Inventory (BDI)-II has a sensitivity of 90 percent and a specificity of 80 percent.
- Thresholds for screening in post-ACS patient populations are comparable to thresholds used in general populations (4 studies, 1,576 patients).
- One or two specific items from validated screening scales (BDI-II, Patient Health Questionnaire [PHQ]) may be almost as accurate for diagnostic screening as using the full instrument.

## Strength of Evidence

Table B shows the strength of evidence for KQ 1 findings.

**Table B. Strength of evidence for the BDI-II depression tool**

Test Result Strength of Evidence	Study Design (N patients)	ROB/ Directness	Inconsistency	Test Property (95% CI) Precision	Test Result	Number per 1,000 Tested for 10% Prevalence <sup>a</sup>	Number per 1,000 Tested for 20% Prevalence <sup>a</sup>
Sensitivity <sup>b</sup> High	4 cross-sectional (1,576)	Low/ Direct	Consistent	0.90 (0.86 to 0.92)  Precise	True positives	90	180
					False negatives	10	20
Specificity <sup>c</sup> Moderate	4 cross-sectional (1,576)	Low/ Direct	Inconsistent	0.80 (0.68 to 0.88)  Precise	False positives	180	160
					True negatives	720	640

<sup>a</sup> Number per 1,000 tested for given prevalence of major depressive disorder. Prevalence was based on the range observed in included studies.

<sup>b</sup> Sensitivity=true positive + false negative.

<sup>c</sup> Specificity=false positive + true negative.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; ROB=risk of bias

## KQ 2: Comparative Safety and Effectiveness of Depression Treatments in Post-ACS Patients

We identified 14 articles representing 4 studies that examined the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments and enhanced care delivery approaches to usual care for the treatment of depression in post-ACS patients (Table C).

No studies were identified that evaluated nutritional supplements, aerobic exercise, cardiac rehabilitation, stress management or atypical antipsychotics, transcranial magnetic stimulation and electroconvulsive therapy.



**Table C. Key Question 2 evidence summary**

<b>Number of randomized clinical trials:</b> 4
<b>Number of patients:</b> 3,119
<b>Men:</b> 58%
<b>Women:</b> 42%
<b>Race/ethnicity:</b> (2 studies, 307 patients): Hispanic, 33%; African American, 26%
<b>Mean age range:</b> 57.6 to 61.1 years
<b>Depressive disorders:</b> Persistent depressive symptoms, major or minor depressive disorder, dysthymia, or ICD-10 depressive disorder (diagnoses 29 days to 12 months post-ACS)
<b>Cardiac conditions:</b> Post-ACS (2 studies) or post-myocardial infarction (MI) (2 studies)
<b>Settings:</b> Multicenter outpatient specialty and primary care clinics
<b>Countries:</b> USA, UK/Europe
<b>Interventions:</b> Enhanced care (2 studies), CBT and antidepressants (1 study), antidepressants only (1 study)
<b>Comparator:</b> Usual care
<b>Primary outcome:</b> Decrease in depression symptoms
<b>Secondary outcomes:</b> Major adverse cardiac event (MACE) or death, quality of life, treatment adherence

Abbreviations: ACS=acute coronary syndrome; CBT=cognitive behavioral therapy; ICD-10=International Classification of Disease, 10th edition

## Key Findings

- Collaborative care interventions, which integrate psychiatric treatment into other clinical settings, improve depression symptoms more than usual care
- Collaborative care, CBT, or antidepressant medications were similar to usual care in reducing major adverse cardiovascular event (MACE) cardiac mortality, all-cause mortality, repeat ACS, revascularization, or hospitalization in individuals following an ACS event
- Evidence did not show increased adverse events among post-ACS individuals treated with collaborative care, CBT, or antidepressant medications compared with usual care

## Strength of Evidence

Tables D–F show the strength of evidence for KQ 2 findings.

**Table D. Strength of evidence for Key Question 2: Enhanced care versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	2 studies	RCT	Consistent	Imprecise <sup>a</sup>	Mean difference -3.5 to -3.8 BDI SMD -0.42 (CI -0.75 to -0.10) to -0.45 (CI -0.77 to -0.14)	Moderate
	307 patients	Low	Direct	None detected		
Mental health–related function	1 study	RCT	Unknown	Imprecise <sup>a</sup>	OR 1.08 (CI 0.73 to 1.42)	Low
	150 patients	Low	Direct	None detected		

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
MACE	2 studies	RCT	Inconsistent	Imprecise <sup>a</sup>	Inconsistent results; no effect to short-term benefit (HR 0.25); short-term benefit was not sustained in long-term followup	Insufficient
	307 patients	Low	Direct	None detected		
Adverse effects	1 study	RCT	Unknown	Imprecise <sup>a</sup>	No difference, findings not reported by specific adverse effects	Insufficient
	157 patients	Unclear	Direct	None detected		

<sup>a</sup>Imprecision based on broad confidence interval or confidence interval which crosses the decisional threshold combined with few events.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; RCT=randomized controlled trial; ROB=risk of bias; SMD=standardized mean difference; SOE=strength of evidence

**Table E. Strength of evidence for Key Question 2: CBT and second-generation antidepressant versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	1 study	RCT	Unknown	Precise	Mean difference -2.7 (CI -3.7 to -1.7) BDI SMD -0.31 (CI -0.42 to -0.20)	High
	2,481 patients	Low	Direct	None detected		
Mental health-related function	1 study	RCT	Unknown	Precise	Mean difference 2.2 (CI 1.2 to 3.2) SF-12 MCS SMD 0.24	High
	2,481 patients	Low	Direct	None detected		
MACE	1 study	RCT	Unknown	Precise	HR 1.01 (CI 0.86 to 1.18) for death or nonfatal MI	Moderate
	2,481 patients	Low	Indirect <sup>a</sup>	None detected		
Adverse effects	NR	–	–	–	–	Insufficient

<sup>a</sup>Rated as indirect since 20.1% of patients enrolled for low perceived social support rather than depression.  
 Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MCS=mental component summary; MI=myocardial infarction; NR=not reported; RCT=randomized controlled trial; ROB=risk of bias; SF-12=Short Form Health Survey; SMD=standardized mean difference; SOE=strength of evidence

**Table F. Strength of evidence for Key Question 2: Antidepressant medication versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	1 study	RCT	Unknown	Precise	Mean BDI 11.0 vs 10.2 SMD 0.12 (CI -0.10 to 0.34)	Moderate
	331 patients	Unclear	Direct	None detected		
Mental health–related function	1 study	RCT	Unknown	Imprecise <sup>a</sup>	Mean at 18 months 44.5 vs 43.4 SF-36 MCS SMD 0.14	Low
	331 patients	Unclear	Direct	None detected		
MACE	1 study	RCT	Unknown	Imprecise	OR 1.07 (0.57 to 2.0) for MACE	Low
	331 patients	Unclear	Direct	None detected		
Adverse effects	NR	–	–	–	–	Insufficient

<sup>a</sup>Imprecision based on broad confidence interval or confidence interval which crosses the decisional threshold combined with few events.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; MACE=major adverse cardiovascular event; NR=not reported; MCS=mental component summary; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SF-12=Short Form Health Survey; SMD=standardized mean difference; SOE=strength of evidence

## Discussion

This present review is an update of the original 2005 Agency for Healthcare Research and Quality systematic review.<sup>1</sup> Both reviews found insufficient evidence to support the comparative effectiveness of interventions for improving cardiovascular outcomes, and both reviews recognized the effectiveness of psychosocial interventions and SSRIs on improving depression symptoms in patients after myocardial infarction.

Our systematic review has several implications for clinical and policy decisionmaking. We found that BDI-II was the most often used screening instrument among included studies. BDI-II has a high sensitivity (90%) and specificity (80%) for identifying patients requiring treatment across a range of prevalences. The performance characteristics for the BDI-II in post-ACS patients were similar to the performance in general medical and psychiatric populations. This suggests that other screening instruments that may be more feasible for use in general medical

settings (e.g., shorter, easier to administer and score, no licensing fee) may also perform well in post-ACS patients. Some data within our review also suggest that very short questionnaires (1-2 questions) may perform similarly to full instruments although the evidence is currently sparse.

For treatment effectiveness, enhanced care interventions that integrate psychiatric treatment into other clinical settings, second-generation antidepressants, and a combination strategy including cognitive behavioral therapy (CBT) and antidepressant medication improved depression symptoms more than usual care but had no consistent effect on cardiovascular outcomes. Secondary analyses from the treatment trials showed generally consistent benefit of interventions on depression outcomes by sex and ethnicity. Importantly, these trials use second-generation antidepressants and/or cognitive behavioral therapy. Thus, recommendations should be limited to these interventions and not generalized to all antidepressants (e.g., tricyclic antidepressants), which may have adverse cardiovascular effects. The included studies did not show a clear beneficial effect of depression treatment on cardiovascular outcomes in this post-ACS population.

## Conclusions

Among several depression screening tools, the BDI is the most studied. Existing tools miss less than 3 percent of patients with depression (high negative predictive value: 97%), but less than 50 percent of patients who screen positive actually have the condition (low positive predictive value: <50%). Enhanced care interventions and a strategy using CBT plus second-generation antidepressant medication for patients with severe depression or partial response to CBT improve depressive outcomes more than usual care. Given the inconsistency and imprecision of findings, and the small number of studies evaluating cardiovascular outcomes, the effects of depression interventions on such cardiovascular outcomes is uncertain.

## Reference

1. Bush DE, Ziegelstein RC, Patel UV, et al. Post-myocardial infarction depression. *Evid Rep Technol Assess (Summ)*. 2005 May(123):1-8. PMID: 15989376.

# Introduction

## Background

In 2005, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on depression in patients following myocardial infarction (MI).<sup>1</sup> That review addressed six Key Questions spanning the prevalence of depression during initial hospitalization and following discharge, the association of post-MI depression with outcomes of interest, the comparison of outcomes of post-MI patients with and without depression, the performance characteristics of instruments used for screening for depression post MI, and the use of cardiac treatments in this patient population. This current review builds on that original review but focuses on the questions and populations currently of greatest clinical uncertainty. Specifically, it evaluates (1) the diagnostic accuracy of selected depression screening instruments and strategies versus a validated criterion standard in adult patients within 3 months of an acute coronary syndrome (ACS) event, and (2) the comparative safety and effectiveness of a broad range of pharmacologic and nonpharmacologic treatments for depression in adult patients who have received a criterion-based diagnosis of depression or had clinically important depressive symptoms using a validated depression scale, and who are within 3 months of an ACS event.

## Condition: Post–Acute Coronary Syndrome Depression

Heart disease is the leading cause of death worldwide.<sup>2</sup> In the United States, where it is the leading cause of death for both men and women, heart disease accounts for more than 600,000 deaths annually, or 23.5 percent of deaths from all causes.<sup>3</sup> Over 25 million adults in the United States are currently estimated to be living with a diagnosis of heart disease,<sup>4</sup> and over 1 million Americans are estimated to be hospitalized for an acute coronary syndrome (ACS) each year.<sup>5</sup>

For the purpose of this review, ACS refers to clinical symptoms compatible with acute myocardial ischemia and includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Patients who are diagnosed with ACS are at risk for a range of negative health outcomes. Among these, post-ACS patients may be at increased risk for mental health problems—including major depressive disorder (MDD) and elevated symptoms of depression.<sup>6</sup> Major depressive disorders are characterized by persistent depressed mood or anhedonia, along with other associated symptoms such as sleep disturbance or decreased energy, feelings of worthlessness and functional impairment for at least 2 weeks. In the general population, lifetime prevalence of major depressive disorder is approximately 17 percent,<sup>7</sup> but studies have found that as many as 20 percent of post-ACS patients have MDD and 65 percent of post-MI patients experience elevated symptoms of depression.<sup>8-10</sup> Major depressive disorder, persistent depressive disorder (Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV dysthymia), and subsyndromal depression are highly prevalent in general medical populations (2-16% within the United States)<sup>11-15</sup> and are estimated as the second largest cause of loss in disability-adjusted life years.<sup>16</sup> Depressive disorders are associated with chronic medical illness, including cardiovascular disease, and worse general medical outcomes. Patients with depression post-ACS have significantly increased risk of death.<sup>17, 18</sup>

Despite the high prevalence of depression, the association with cardiovascular disease, and the impact of depression on quality of life (QOL), there is considerable uncertainty about whether and how to screen patients for depression post-ACS.<sup>19</sup> Guidelines for screening for

depression in primary care settings vary. The 2016 guidelines from the U.S. Preventive Services Task Force (USPSTF) recommend that depression screening for the general population in primary care be “implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow up.”<sup>20</sup> However, other guidelines recommend targeted screening for patients at increased risk of depression<sup>21</sup> or against routine screening.<sup>22</sup> Individuals post-ACS are at higher risk for depression, and some professional societies recommend routine screening during and after the post-MI hospitalization, but these guidelines are controversial.<sup>23, 24</sup> It is unclear how well standard instruments for detecting depression perform in this medically ill group and whether this group would benefit from targeted screening.

It is also unclear whether post-ACS patients with depression respond any differently than people in the general population with depression to commonly used, empirically validated treatments for depression. Such treatments include pharmacotherapy and psychotherapy, with second-generation antidepressants and cognitive behavioral therapy (CBT) being among the most widely supported, evidence-based depression treatment approaches. Both pharmacotherapy and psychotherapy have been shown to be effective,<sup>17</sup> although it is unclear whether combination therapy is superior to pharmacotherapy or psychotherapy alone. It is possible, though not clearly established, that some of these treatments for depression may function differently in post-MI patients.<sup>25</sup> For instance, behavioral activation, a core component of many CBT-based approaches, might encourage the adoption of new behavioral repertoires that not only improve mood but also medical outcomes.<sup>26</sup> Other therapies also have been demonstrated to have beneficial effects for emotional health<sup>27</sup> and cardiovascular health.<sup>28</sup> In particular, aerobic exercise has been shown to improve survival in post-ACS patients and also may reduce depression.<sup>29, 30</sup> Alternatively, it may be that certain depression treatments that are usually effective in the general population are less so among post-ACS patients, or carry certain risks that might be of particular concern in this population.<sup>25</sup>

## Screening Strategies

A number of screening tools for depression have been developed. This review sought to evaluate tools (described in the Results chapter), which were selected because they are feasible to use and have been validated in general populations. We also evaluated screening strategies that differ by setting (e.g., inpatient vs. outpatient, general medicine vs. cardiology) or timing (e.g., duration post-ACS). These tools and strategies were compared against the gold standard of a validated criterion standard (e.g., DSM or International Classification of Diseases [ICD] criteria) administered by a trained interviewer.

## Treatment Strategies

Pharmacologic treatments considered for patients with depression included second-generation antidepressants (e.g., selective serotonin reuptake inhibitor [SSRIs], serotonin-norepinephrine reuptake inhibitor [SNRIs]), atypical antipsychotics, and tricyclic antidepressants. For all three categories, the specific medications evaluated were limited to those that are Food and Drug Administration (FDA)-approved for treatment of MDD. Information on the FDA status and warnings for use the medications considered in this review are provided in Appendix A.

Nonpharmacologic treatments considered included various types of psychotherapy, aerobic exercise, selected dietary supplements, cardiac rehabilitation, education/psychoeducation, stress

management, psychosocial support, transcranial magnetic stimulation, electroconvulsive therapy, and combinations of these approaches. Collaborative care, a method to improve care delivery which integrates psychiatric treatment into other clinical settings, also was evaluated. In such strategies, patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (e.g., psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (e.g., patient education or cognitive-behavioral therapy), scheduled followup visits, communication amongst the members of the treatment team, and measurement-based care.

## **Scope and Key Questions**

### **Scope of Review**

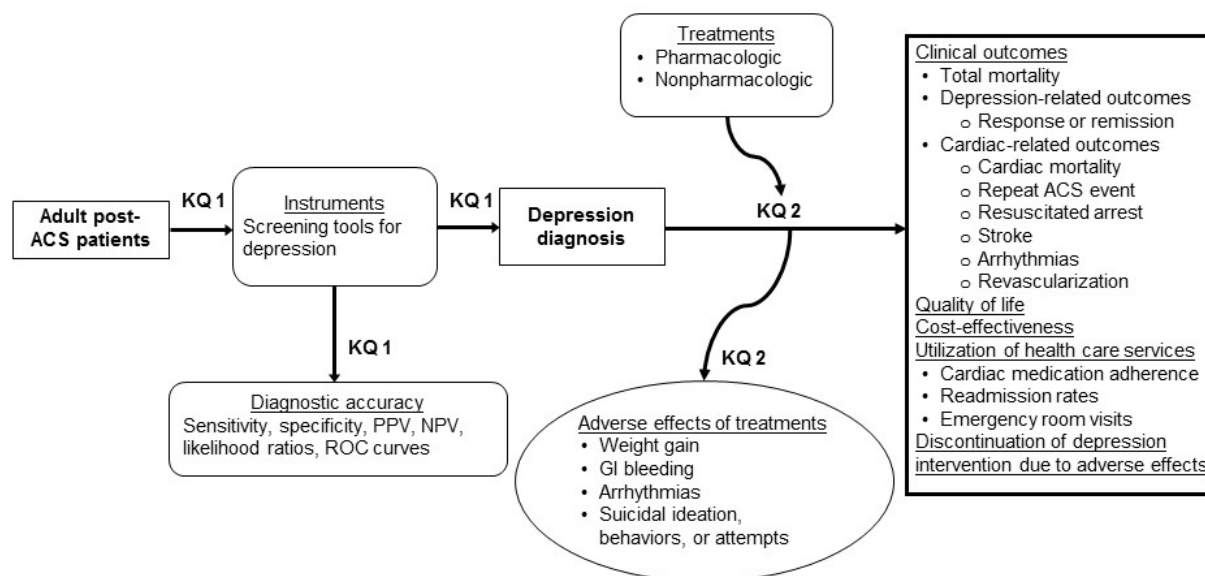
This review evaluates (1) the diagnostic accuracy of selected depression screening instruments and strategies versus a validated criterion standard in adult patients within 3 months of an ACS event, and (2) the comparative safety and effectiveness of a broad range of pharmacologic and nonpharmacologic treatments for depression in adult patients who have received a criterion-based diagnosis of depression or had clinically important depressive symptoms using a validated depression scale, and who are within 3 months of an ACS event. As noted above, we use ACS to include unstable angina, NSTEMI, and STEMI.

### **Key Questions**

The specific Key Questions (KQs) addressed in this review are listed below, and Figure 1 displays the analytic framework that guided our work.

- KQ 1: What is the accuracy of depression screening instruments or screening strategies compared to a validated criterion standard in post-ACS patients?
- KQ 2: What are the comparative safety and effectiveness of pharmacologic and nonpharmacologic depression treatments in post-ACS patients?

**Figure 1. Analytic framework**



Abbreviations: ACS=acute coronary syndrome; GI=gastrointestinal; KQ=Key Question; NPV=negative predictive value; PPV=positive predictive value; ROC=receiver operating characteristic

Figure 1 depicts the KQs within the context of the population, interventions, comparators, outcomes, timing, and settings (PICOTS) considered in this review. In general, the figure illustrates how individuals who are post-ACS may be screened and treated for depression, and how treatment is associated with a range of potential adverse effects and outcomes. Separate KQs address the accuracy of screening (KQ 1) and the effectiveness and risk of adverse events associated with pharmacologic and/or nonpharmacologic treatments (KQ 2).

It should be noted that the scope of the review does not explicitly address the linkage between the use of screening tools in KQ 1 and downstream clinical outcomes. This limitation in scope is addressed in the discussion of the findings and highlighted as an area for potential future research later in the report. Also, although ease of use and user burden are not listed within KQ 1 as specific outcomes of interest, we include a summary table of included screening tool characteristics (e.g., number of items, ease of use, availability) to aid in the comparison and interpretation of our findings.

## Organization of This Report

The remainder of the report details our methodology and presents the results of our literature synthesis, with summary tables and strength of evidence grading for major comparisons and outcomes. In the discussion section, we offer our conclusions, summarized findings, and other information that may be relevant to translating this work for clinical practice and future research.

Appendixes provide further details on our methods and the studies we assessed, as follows:

- Appendix A. FDA Status and Warnings for Drugs Included in This Review
- Appendix B. Exact Search Strings
- Appendix C. Data Abstraction Elements
- Appendix D. List of Included Studies
- Appendix E. List of Excluded Studies
- Appendix F. Key to Included Primary and Companion Articles



- Appendix G. Characteristics of Included Studies

A list of acronyms and abbreviations is provided at the end of the report.

## Methods

We followed the methods for this comparative effectiveness review provided by the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide) for the Evidence-based Practice Center (EPC) program.<sup>31</sup> Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>32</sup> All methods and analyses were determined a priori.

### Topic Refinement and Review Protocol

During topic refinement, we generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). Initially a panel of key informants representing medical professionals and researchers with expertise in areas of cardiology, cardiovascular and pulmonary rehabilitation, psychiatry, psychology, and family medicine; and patients/caregivers gave input on the KQs to be examined; these KQs were posted on AHRQ's Effective Health Care (EHC) Web site for public comment from May 26, 2016 to June 15, 2016, and were revised to refine the screening tools, interventions, and outcomes of interest. These revisions were made prior to seeing the results of any studies. We then drafted a protocol for the systematic review and recruited a panel of technical experts (TEP) to provide high-level content and methodological expertise and finalized the review protocol. The TEP included medical professionals, researchers, and topic experts from other Health and Human Services agencies. The finalized protocol is posted on the EHC Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)). The PROSPERO registration is CRD42016047032.

### Literature Search Strategy

#### Search Strategy

To identify relevant published literature, we searched MEDLINE<sup>®</sup> (via PubMed), Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to articles published from January 1, 2003, to August 15, 2017. These databases were selected based on (1) expert opinion that they would identify most of the relevant literature on this topic and (2) the approaches of prior related systematic reviews.<sup>1</sup> We believe that the evidence published from 2003 both represents the current standard of care for the population of interest in this review and allows this report to build on the previous AHRQ systematic review<sup>1</sup> published in 2005 (which had an electronic search date through March 2004). The overlap in search dates follows EPC methods guidance.<sup>31</sup>

We used a combination of medical subject headings and title and abstract keywords, focusing on terms to describe the relevant population and interventions of interest. Exact search strings used for each KQ are in Appendix B. Where possible, we used existing validated search filters. An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.<sup>33-47</sup> The reference list for identified pivotal articles was hand-searched and cross-referenced against our database, and additional relevant manuscripts were retrieved. All citations were imported into an electronic bibliographical database (EndNote<sup>®</sup> Version X7; Thomson Reuters, Philadelphia, PA).

To identify relevant gray literature, the EPC Scientific Resource Center notified stakeholders that the EPC was interested in receiving information that the stakeholders would consider relevant to the KQs. We also searched ClinicalTrials.gov for two purposes: (1) to identify relevant articles from completed studies that may not have appeared in our other search strategies and (2) as one mechanism to ascertain publication bias in recent studies. For the latter goal, we sought to identify completed but unpublished studies that could impact the findings of the review. Search terms used for ClinicalTrials.gov are provided in Appendix B. We also explored the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques such as a funnel plot when appropriate.

## Inclusion and Exclusion Criteria

We specified our inclusion and exclusion criteria based on the PICOTS identified for each question. Table 1 specifies inclusion and exclusion criteria. In brief, eligibility criteria were designed to include patients with clinically important depressive symptoms, occurring within 3 months post ACS. The 3-month post-ACS criterion was chosen for consistency with the original report, and to identify a post-ACS population that could be distinguished from patients with chronic coronary heart disease. Studies evaluating screening instruments had to compare an eligible questionnaire to a criterion standard diagnosis. Studies evaluating intervention effects had to evaluate any FDA-approved antidepressant, an inclusive list of psychotherapies and other treatments, or an enhanced care model.

**Table 1. Inclusion and exclusion criteria**

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	<p>KQ 1: Adults who have acute coronary syndrome (ACS) [which includes both unstable angina and myocardial infarction (MI)] and are within 3 months of an identifying ACS event</p> <p>KQ 2: Adults who received a criterion-based diagnosis of depression or had clinically important depressive symptoms using a validated depression scale, and are within 3 months of an acute ACS event</p> <p>Subgroups of interest:</p> <ul style="list-style-type: none"> <li>• Age (KQ 1, KQ 2) older adults (≥65 years) versus adults younger than 65 years of age</li> <li>• Race/ethnicity (KQ 1, KQ 2)</li> <li>• Sex (KQ 1, KQ 2)</li> <li>• Inpatient vs outpatient (KQ 1)</li> </ul>	<p>KQs 1 and 2: Individuals younger than 18 years of age. Studies including mixed samples (e.g., both adults and patients under 18, or a mixture of patients within 3 months of an ACS event and those who are more than 3 months post-event) were excluded unless data for the target population were reported separately.</p> <p>KQ 2: Depression diagnosis made by unstructured clinical diagnosis, chart diagnosis, or based on administrative codes (rather than DSM) or prescription for an antidepressant</p>
Interventions	<p>KQ 1:</p> <ul style="list-style-type: none"> <li>• Screening tools for depression, limited to: <ul style="list-style-type: none"> <li>○ Beck Depression Inventory (BDI) (multiple versions)</li> <li>○ Center for Epidemiologic Studies-Depression (CES-D20 and CES-D10)</li> <li>○ Distress Questionnaire 5</li> <li>○ Duke Anxiety and Depression Scale</li> <li>○ Geriatric Depression Scale (GDS-15) [2 versions, long</li> </ul> </li> </ul>	<p>KQ 2: Combination interventions that include an ineligible intervention</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<p>and short]</p> <ul style="list-style-type: none"> <li>○ Hospital Anxiety and Depression Scale (HADS and HADS-D)</li> <li>○ Diagnostic Inventory for Depression (DID)</li> <li>○ Kessler Psychological Distress Scale (K10 and K6)</li> <li>○ Patient Health Questionnaire (PHQ-2, 8, 9, 10)</li> <li>○ Primary care rapid evaluation of mental disorders (PRIME-MD, including Whooley questions)</li> <li>○ PROMIS® (Patient-Reported Outcomes Measurement Information System)</li> <li>○ Quick Inventory of Depressive Symptomatology</li> <li>○ Symptom Checklist 20 and Hopkins Symptom Checklist</li> <li>○ WHO-5 (World Health Organization-5)</li> <li>○ Zung Self-Rating Depression Scale</li> </ul> <ul style="list-style-type: none"> <li>● Screening strategies that differ by setting (i.e, inpatient vs outpatient, general medicine vs cardiology) or timing (i.e., duration post-ACS event)</li> </ul> <p>KQ 2 (considered singly or in combination):</p> <ul style="list-style-type: none"> <li>● Medical Therapy <ul style="list-style-type: none"> <li>○ Antidepressant medications (SSRI, SNRI, etc.) limited to second-generation medications that have been FDA-approved for treatment of major depressive disorder: <ul style="list-style-type: none"> <li>▪ Bupropion</li> <li>▪ Citalopram</li> <li>▪ Desvenlafaxine</li> <li>▪ Duloxetine</li> <li>▪ Fluoxetine</li> <li>▪ Escitalopram</li> <li>▪ Levomilnacipran</li> <li>▪ Mirtazapine</li> <li>▪ Nefazodone</li> <li>▪ Paroxetine</li> <li>▪ Sertraline</li> <li>▪ Trazodone</li> <li>▪ Venlafaxine</li> <li>▪ Vilazodone</li> <li>▪ Vortioxetine</li> </ul> </li> <li>○ Atypical antipsychotics – limited to those that are FDA-approved for treatment of major depressive disorder: <ul style="list-style-type: none"> <li>▪ Aripiprazole</li> <li>▪ Olanzapine</li> <li>▪ Quetiapine</li> </ul> </li> <li>○ Tricyclic antidepressants – limited to those that are FDA-approved for treatment of major depressive disorder: <ul style="list-style-type: none"> <li>▪ Amitriptyline</li> <li>▪ Amoxapine</li> <li>▪ Desipramine</li> <li>▪ Doxepin</li> <li>▪ Imipramine</li> <li>▪ Nortriptyline</li> </ul> </li> </ul> </li> </ul>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> <li>▪ Protryptiline</li> <li>▪ Trimipramine</li> <li>• Psychotherapy <ul style="list-style-type: none"> <li>○ Cognitive behavioral therapy, limited to: cognitive behavioral therapy (CBT), cognitive therapy, behavioral therapy, cognitive behavioral analysis system of psychotherapy, and behavioral activation</li> <li>○ Problem solving therapy</li> <li>○ Interpersonal psychotherapy</li> <li>○ Short-term psychodynamic therapy</li> <li>○ “Third wave” cognitive behavioral psychotherapies, limited to: acceptance and commitment therapy, dialectical behavior therapy, mindfulness, mindfulness-based cognitive therapy (MBCT), and functional analytic psychotherapy</li> </ul> </li> <li>• Other Treatments <ul style="list-style-type: none"> <li>○ Structured aerobic exercise: Structured exercise is defined as regular physical activity done with the intention of improving or maintaining physical fitness or health, or performed as part of a class or with support from a health professional.</li> <li>○ St John’s Wort</li> <li>○ Fish oil/ omega-3 fatty acids</li> <li>○ S-Adenosylmethionine</li> <li>○ Cardiac rehabilitation which typically includes supervised exercise training in conjunction with other secondary prevention interventions (e.g., psychosocial support, stress management, nutrition counseling, education on medication adherence).</li> <li>○ Education/psychoeducation</li> <li>○ Stress management: mindfulness meditation, progressive muscle relaxation, qigong meditation, spiritual medication, guided imagery-based approaches, paced respiration, Roll breathing, 4-7-8 breath technique</li> <li>○ Psychosocial support: interventions to help a person cope with stress that do not involve formal therapy</li> <li>○ Transcranial magnetic stimulation</li> <li>○ Electroconvulsive therapy</li> </ul> </li> <li>• Enhanced Care Delivery <ul style="list-style-type: none"> <li>○ Collaborative care in primary care or cardiology settings (Note that such care integrates psychiatric treatment into other settings. “Patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (e.g., psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (e.g., patient education or cognitive-behavioral therapy), scheduled followup visits, communication amongst the members of the treatment team, and measurement-based care.”<sup>48</sup>)</li> </ul> </li> </ul>	
Comparators	KQ 1: Validated criterion standard (e.g., DSM or ICD criteria) administered by a trained interviewer	KQ 2: Same treatment comparisons that vary by

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	KQ 2: Active comparator from listed interventions; usual care	dose; combination comparators that include an ineligible intervention
Outcomes	<p>KQ 1:</p> <ul style="list-style-type: none"> <li>• Diagnostic accuracy, as measured by: <ul style="list-style-type: none"> <li>○ Sensitivity</li> <li>○ Specificity</li> <li>○ Negative predictive value (NPV)</li> <li>○ Positive predictive value (PPV)</li> <li>○ Likelihood ratios</li> <li>○ Receiver operating characteristic (ROC) curves</li> </ul> </li> </ul> <p>KQ 2:</p> <ul style="list-style-type: none"> <li>• Clinical outcomes <ul style="list-style-type: none"> <li>○ Total mortality</li> <li>○ Depression-related outcomes <ul style="list-style-type: none"> <li>▪ Response or remission of depressive symptoms using validated continuous or categorical measures</li> </ul> </li> <li>○ Cardiac-related outcomes <ul style="list-style-type: none"> <li>▪ Cardiac mortality</li> <li>▪ Repeat ACS event (repeat MI or unstable angina)</li> <li>▪ Resuscitated arrest</li> <li>▪ Stroke</li> <li>▪ Arrhythmias</li> <li>▪ Revascularization</li> </ul> </li> </ul> </li> <li>• Quality of life (QOL)</li> <li>• Cost-effectiveness</li> <li>• Utilization of health care services <ul style="list-style-type: none"> <li>○ Cardiac medication adherence</li> <li>○ Readmission rates due to cardiac and non-cardiac reasons</li> <li>○ Emergency room visits: all visits, cardiac-related, and psychiatric-related</li> </ul> </li> <li>• Discontinuation of depression intervention due to adverse effects</li> <li>• Adverse effects of treatment (excluding clinical outcomes listed above) <ul style="list-style-type: none"> <li>○ Weight gain</li> <li>○ Gastrointestinal bleeding</li> <li>○ Arrhythmias</li> <li>○ Suicidal ideation, behaviors or attempts</li> </ul> </li> </ul>	
Timing	<p>KQ 1: Within 3 months of an identifying ACS event</p> <p>KQ 2: At least 6 weeks of followup</p>	
Settings	<ul style="list-style-type: none"> <li>• Primary, specialty, and inpatient settings</li> <li>• Studies conducted in countries with similar cardiac care and similar concept of depressive disorders to that of the United States: North America, European Union and the UK, Australia, New Zealand</li> </ul>	
Study design	<ul style="list-style-type: none"> <li>• Original peer-reviewed data</li> </ul>	Editorials, nonsystematic reviews, systematic reviews,

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> <li>• KQ 1: Observational studies, sample size ≥50 subjects</li> <li>• KQ 2: Randomized controlled trials (RCTs), sample size ≥20 subjects</li> </ul>	<p>meta analyses, letters, case series, case reports, abstract-only or poster publications, articles that have been retracted or withdrawn</p> <p>Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality,<sup>49,50</sup> we have excluded them from our review. For observational studies, we require at least 50 subjects.</p>
Publications	<ul style="list-style-type: none"> <li>• English-language only</li> <li>• Published on or after January 1, 2003</li> </ul>	Non-English language articles <sup>a</sup>

<sup>a</sup>Non-English language articles were excluded due to: (1) the high volume of literature available in English language publications, (2) the focus of our review on applicability to populations in the United States, and (3) the scope of our KQs.

Abbreviations: ACS=acute coronary syndrome; CBT=cognitive behavioral therapy; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases; FDA=U.S. Food and Drug Administration; KQ=Key Question; MBCT=mindfulness-based cognitive therapy; MI=myocardial infarction; NPV=negative predictive value; PICOTS=Populations, Interventions, Comparators, Outcomes, Timing, Settings; PPV=positive predictive value; QOL=quality of life; ROC=receiver operating characteristic; RCTs=randomized controlled trials; SNRI=serotonin–norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitors

## Study Selection

For citations retrieved from MEDLINE, Embase, PsycINFO, CINAHL, and the CDSR, two reviewers used the prespecified inclusion/exclusion criteria to review titles and abstracts for potential relevance to the research questions. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers were required to agree on a final inclusion/exclusion decision. In recording reasons for exclusion, articles were assessed against a hierarchical list of exclusion reason possibilities; these options are presented in order in the literature flow diagram (Figure 2) and Appendix E. Screeners were instructed to select the first applicable exclusion reason encountered in that order. Disagreements in inclusion/exclusion or exclusion reason decisions were resolved by a third expert member of the team. Articles meeting eligibility criteria were included for data abstraction. At random intervals during screening, quality checks by senior team members were made to ensure that screening and abstraction were consistent with inclusion/exclusion criteria and abstraction guidelines. All results were tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

Appendix D provides a list of all articles included for data abstraction. Appendix E provides a list of articles excluded at the full-text screening stage, with reasons for exclusion.

## Data Extraction

The research team created abstraction forms that were programmed into DistillerSR software or excel to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes

(intermediate, final, and adverse events outcomes). Particular attention was given to describing the details of the screening approach (e.g., instrument version, administration mode), details of the treatment (e.g., pharmacotherapy dosing, methods of behavioral interventions, co-interventions), patient characteristics (e.g., depressive disorder, age) that may be related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes were framed to help identify adverse events, including those from drug therapies and those resulting from misdiagnosis and labeling. Data necessary for assessing quality and applicability, as described in the Methods Guide,<sup>31</sup> were also abstracted. A list of data abstraction elements is provided in Appendix C.

All data abstraction form templates were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles.

Based on clinical and methodological expertise, a pair of researchers abstracted data from each of the eligible articles, with one researcher abstracting the data and the second over-reading the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer’s opinion if consensus was not reached. To avoid duplication of patient cohorts, we linked related studies.

Final abstracted data will be uploaded to AHRQ’s Systematic Review Data Repository (<https://srdhr.ahrq.gov/>).

## Quality Assessment of Individual Studies

We assessed the methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias<sup>51</sup> tool for randomized studies and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)<sup>52</sup> for observational studies. Observational studies were rated on each individual quality criterion without a summary rating. For each randomized controlled trial (RCT), one investigator assessed methodological quality, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement was not reached. Individual components of the Cochrane tool were rated as low, high, or unclear risk of bias. We then rated each RCT as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies following the definitions in the AHRQ Methods Guide. The rating was outcome-specific such that a given study that analyzed its primary outcome well but did an incomplete analysis of a secondary outcome could be assigned a different quality grade for each of the two outcomes. We applied this outcome-specific quality assessment to groups of outcomes that have lower risk of detection bias (e.g., mortality) and those at higher risk of detection bias (e.g., depression symptoms).

Studies of different designs were evaluated within the context of their respective designs. RCT quality was summarized as good, fair, or poor. Table 2 defines these quality ratings, which are presented in the Results section, Appendix G, and the strength of evidence tables in the Discussion section of the report. Observational studies were graded using QUADAS-2 methodology with graphics showing judgments for each quality item.

**Table 2. Definition of quality assessment ratings for randomized controlled trials**

Rating	Definition
<b>Good (low risk of bias)</b>	These studies had the least bias, and the results were considered valid. These



Rating	Definition
	studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
<b>Fair (unclear risk of bias)</b>	These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
<b>Poor (high risk of bias)</b>	These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

## Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We ordered our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized.

We reviewed and highlighted studies using a hierarchy-of-evidence approach. The best evidence available was the focus of our synthesis for each KQ. If high-quality evidence was not available, we described any lower quality evidence we were able to identify, but we underscored the issues that made it lower quality and the uncertainties in our findings. We assessed and stated whether the inclusion of lower quality studies would change any of our conclusions and performed sensitivity analyses excluding this evidence where appropriate.

We then determined the feasibility of completing quantitative syntheses (i.e., meta-analyses). Feasibility was dependent on the volume of relevant literature (we required 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, completeness of the reporting of results, and the power of the proposed meta-analysis. When a meta-analysis was appropriate, we used random-effects models (DerSimonian-Laird estimator with Knapp-Hartung standard error adjustment) to synthesize the available evidence quantitatively. For KQ 1, proportions were summarized on the logit (log odds) scale and then converted back to a proportion. Individual study sensitivities and specificities were calculated with exact 95 percent confidence intervals. Sensitivities and specificities were summarized separately as proportions because a joint model, which would have summarized these together, did not converge.

For KQ 2, we anticipated that intervention effects may be heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation were associated with the intervention effects. We planned subgroup analyses and/or meta-regression analyses to examine these hypotheses, but quantitative analyses were not feasible because of the small number of studies with diverse comparisons. Where possible we calculated effect sizes using standardized mean differences.

## Strength of the Body of Evidence

We selected a specific set of comparisons and outcomes for strength of evidence grading. The aim was to identify and grade those outcomes that are critical for decisionmaking. We graded the strength of evidence for each selected outcome separately.

We assessed the strength of evidence using the approach described in AHRQ’s Methods Guide.<sup>31, 53</sup> We graded the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. These grades are presented in the strength of evidence tables in the Discussion section of the report. In brief, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias. For intervention trials, these domains affect the confidence in treatment effects. For diagnostic test studies, these factors affect the confidence in estimates of test accuracy and effects on patient management.<sup>54</sup> These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned for each outcome after independent assessment and then discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of “insufficient” was assigned. Table 3 defines the four-level grading scale.

**Table 3. Definition of strength of evidence grades**

Rating	Definition
<b>High</b>	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
<b>Moderate</b>	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
<b>Low</b>	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
<b>Insufficient</b>	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## Applicability

We assessed applicability across our KQs using the method described in AHRQ’s Methods Guide.<sup>31, 55</sup> In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, depression severity, psychiatric and medical comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We used a checklist to guide assessment of the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models

currently in use, and clinical relevance and timing of the outcome measures (Appendix C). We summarized issues of applicability qualitatively.

## **Peer Review and Public Commentary**

Experts in the fields of mental health, cardiology, primary care, and systematic review methodology were invited to provide external peer review of the draft report. AHRQ, an associate editor, and members of the TEP were also given the opportunity to provide comments. In addition, the draft report was posted on the AHRQ EHC Web site for public comment from April 27, 2017, to May 25, 2017. We have addressed all reviewer comments, revising the text as appropriate, and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

# Results

## Introduction

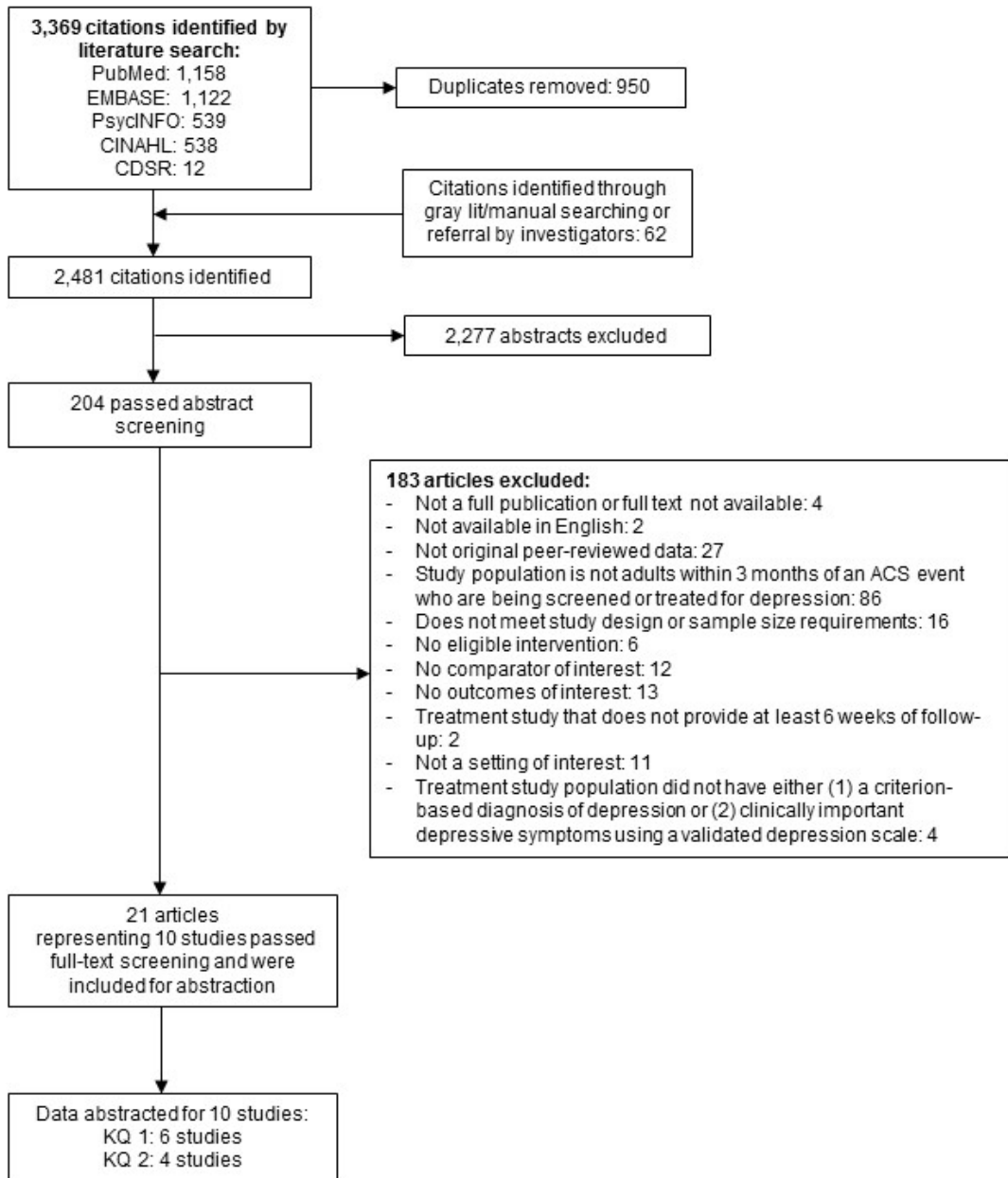
In what follows, we begin by describing the results of our literature searches. We then provide an overall description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under both KQs, we begin with a brief description of the included studies, followed by a bulleted list of the key points of the findings and a detailed synthesis of the evidence. The detailed syntheses are organized first by treatment comparison and then by outcome. We conducted quantitative syntheses where possible, as described in the Methods chapter. Each KQ results section concludes with a summary of the strength of evidence for the main findings.

## Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, and the Cochrane Database of Systematic Reviews yielded 3,369 citations, 2,419 of which were unique. Manual searching of gray literature databases and bibliographies of key articles or referral by investigators identified 62 additional citations, for a total of 2,481 citations. No responses were received through public notification to manufacturers of requests for supplemental evidence. After applying inclusion/exclusion criteria at the title-and-abstract level, 204 full-text articles were retrieved and screened. Of these, 183 were excluded at the full-text screening stage, leaving 21 articles for data abstraction. These 21 articles described 10 unique studies. The relationship of studies to the review questions is as follows: 6 studies relevant to KQ 1 and 4 studies relevant to KQ 2.

Appendix D provides a detailed listing of included articles. Appendix E provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix F provides a “study key” table listing the primary and companion publications for the 10 included studies.

**Figure 2. Literature flow diagram**



Abbreviations: ACS=acute coronary syndrome; CDSR=Cochrane Database of Systematic Reviews; KQ=Key Question

## Description of Included Studies

Overall, we included 10 studies described in 21 publications: 6 studies were relevant to KQ 1 and 4 studies to KQ 2. Studies were conducted wholly or partly in continental Europe or the United Kingdom (2 studies; 20%), the United States (6 studies; 60%), and Canada (2 studies; 20%). Further details on the studies included for each KQ are provided in the relevant results sections below and in Appendix G.

We searched the ClinicalTrials.gov registry of clinical studies as a mechanism for ascertaining publication bias by identifying studies that have been completed but are as yet unpublished. This registry provided the most relevant information to the populations and interventions of interest in this review. Our search yielded 64 records of completed trials for screening (see Appendix B for details). Manual review identified 7 of these records as potentially relevant to the KQs. We identified publications for all 7 of these studies, thus finding no indication of publication bias that would impact the results of this review. Note that we did not compare ClinicalTrials.gov records or protocols listing intended/pre-specified outcomes against published findings.

## Key Question 1: Diagnostic Accuracy of Depression Screening Tests in Post–Acute Coronary Syndrome Patients

### Description of Included Studies

For KQ 1, we identified seven articles<sup>56-62</sup> representing six studies that examined the accuracy of depression screening instruments or screening strategies in post-ACS patients. One study, Huffman, 2006 was described in two publications: the primary report<sup>58</sup> and a companion paper.<sup>59</sup>

In this opening section, we refer only to the primary publications; the companion paper is cited where relevant under “Detailed Synthesis” below. In addition, Appendix F provides a key to primary and companion articles.

All 6 included studies were observational, representing a total of 1,763 prospectively enrolled (1,755 completed) patients (Table 4). One study was conducted in multiple centers,<sup>60</sup> while the remaining five were all conducted at a single center. Three studies were conducted solely in the United States,<sup>56, 58, 61</sup> one study in the UK/Europe,<sup>62</sup> and two studies in Canada.<sup>57, 60</sup> Three studies did not report the funding source or the source was unclear,<sup>56, 60, 62</sup> one study reported a mixture of government, industry, and nongovernment/nonindustry funding,<sup>57</sup> one study reported a mixture of government and nongovernment, nonindustry funding,<sup>61</sup> and one study reported nongovernment, nonindustry funding.<sup>58</sup> Major depressive disorder (MDD) served as the criterion standard for studies, with one study<sup>56</sup> describing the criterion standard as “clinical depression” based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR criteria (correspondence with the authors indicated that most of these patients had MDD, though some had minor depression).

**Table 4. Key Question 1 evidence summary**

<b>Number of studies:</b> 6
<b>Study publication years:</b> 2005-2013
<b>Date of literature search:</b> April 27, 2017
<b>Number of patients:</b> 1,755
<b>Men:</b> 1,343 (77%)
<b>Women:</b> 412 (23%)
<b>Mean age range:</b> 57 to 63 years
<b>Race/ethnicity:</b> Unavailable
<b>Settings:</b> Inpatient (5); cardiac rehabilitation clinic (1)
<b>Countries:</b> USA (3), Canada (2), UK/Europe (1)
<b>Screening instruments<sup>a</sup>:</b> Beck Depression Inventory-II (BDI-II); Hospital Anxiety and Depression Scale (HADS); Patient Health Questionnaire (PHQ); Geriatric Depression Scale (GDS)
<b>Criterion standard:</b> Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-IV major depressive disorder (MDD)

<sup>a</sup> Some studies examined different numbers of items and subscales for the BDI-II, HADS, and PHQ. Specific versions, subscales, and item combinations are noted where applicable, and the generic scale is referenced for statements that apply across different versions and item combinations for the scale (e.g., 2-item, 9-item, and 10-item versions of the PHQ).

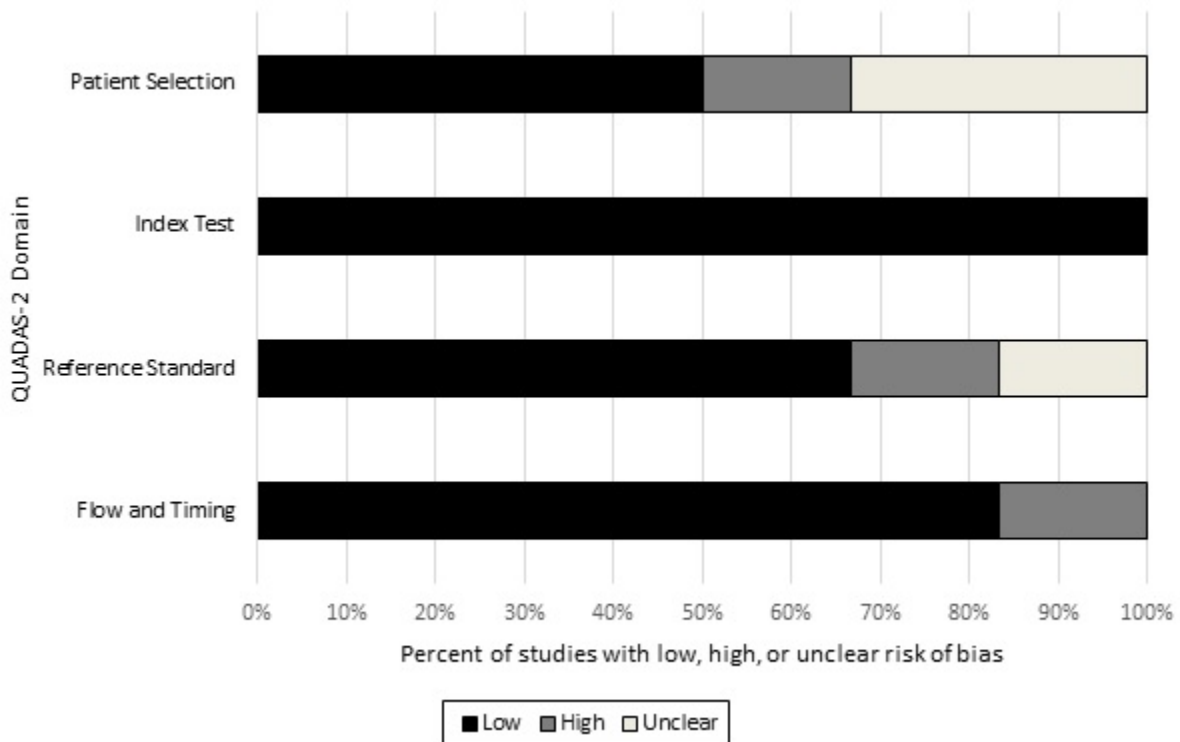
We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to evaluate the quality of the included diagnostic accuracy studies and their risk of bias (Table 5 and Figure 3).<sup>52</sup> For the domain of patient selection, three studies were ranked as low risk of bias, one as high risk of bias, and two as unclear risk of bias. For the domain of index tests, all studies were ranked as low risk of bias. For the domain of reference standards, four studies were ranked as low risk of bias, one as high risk of bias, and one as unclear risk of bias. For the domain of flow and timing, five studies were ranked as low risk of bias and one as high risk of bias. Details of the study characteristics of the included studies are in Appendix G.

**Table 5. QUADAS-2 risk of bias assessment for diagnostic accuracy studies**

Study	Patient Selection	Index Test	Reference Standard	Flow and Timing
Bambauer, 2005 <sup>61</sup>	High	Low	Unclear	High
Bunevicius, 2012 <sup>62</sup>	Low	Low	Low	Low
Frasure-Smith, 2008 <sup>57</sup>	Low	Low	Low	Low
Huffman, 2006 <sup>58</sup>	Unclear	Low	High	Low
Low, 2008 <sup>60</sup>	Low	Low	Low	Low
McGuire, 2013 <sup>56</sup>	Unclear	Low	Low	Low

Abbreviation: QUADAS=Quality Assessment of Diagnostic Accuracy Studies

**Figure 3. Percent of studies with low, high, or unclear risk of bias across QUADAS-2 domains**



Abbreviation: QUADAS=Quality Assessment of Diagnostic Accuracy Studies

## Key Points

- Four depression screening instruments (Beck Depression Inventory II [BDI-II], Geriatric Depression Scale [GDS], Hospital and Anxiety Depression Scale [HADS], and Patient Health Questionnaire [PHQ]), produce high negative predictive value (97%) (i.e. will miss less than 3% of those who have depression) but produce low (below 50%) positive predictive values (i.e., percentage of patients who screen positive that actually have the condition). Overall sensitivity and specificity are over 70 percent. (6 studies, 1,755 patients).
- BDI-II has diagnostic screening performance characteristics (sensitivity 90%, specificity 80%) comparable to those found when this instrument is used in other patient populations (4 studies, 1,576 patients).
- The Beck Depression Inventory II (BDI-II) is slightly more sensitive than the HADS (including the full version, depression subscale, and anxiety subscale) and demonstrates comparable specificity (based on two head-to-head comparative studies). The GDS demonstrated better specificity and positive predictive values than the BDI-II in one small study.
- Diagnostic thresholds for screening in post-ACS patient populations are comparable to those thresholds generally used in general populations (4 studies, 1,576 patients).
- One or two specific items from validated screening scales (BDI-II, PHQ) may be almost as accurate for diagnostic screening as using the full instrument (2 studies, 231 patients).



## **Detailed Synthesis**

Table 6 presents a summary of the characteristics of the depression screening tools evaluated within our included studies. Table 7 presents a summary of the included studies and their diagnostic accuracy results. We then discuss in more detail the findings for specific instruments and synthesize across the included studies.

**Table 6. Characteristics of validated depression screening tools<sup>a</sup>**

Instrument	N Items	Response Format	Score Range	Usual Cutpoint for Diagnosing Depression	Literacy Level <sup>b</sup>	Time to Complete (Minutes) <sup>c</sup>	Copyright
BDI	21	4-point scale indicating degree of severity; items are rated from 0 (not at all) to 3 (extreme form of each symptom)	0-63	10-19 = mild 20-29 = moderate ≥30 = severe	Easy	2-5	Yes <sup>d</sup>
BDI-II	21	4-point scale indicating degree of severity; items are rated from 0 (not at all) to 3 (extreme form of each symptom)	0-63	0-13 = minimal range 14-19 = mild 20-28 = moderate 29-63 = severe recommended cutpoint ≥16	Easy	5-10	Yes <sup>d</sup>
GDS	15	Yes or no	0-15	≥6	Easy	2-5	No
HADS-T	14	4-point Likert scale 0-3	0-42	8-10 = mild 11-15 = moderate ≥16 = severe	Easy	1-2	Yes <sup>e</sup>
<u>Subscales</u> HADS-A HADS-D			0-21 0-21				
PHQ-2	2	4 frequency ratings	0-6	≥3	Average	<1	Yes <sup>f</sup>
PHQ-9	9	4 frequency ratings	0-9 for diagnosis 0-27 for response	<u>Diagnosis</u> 5 symptoms <u>Severity</u> 0-4 = none 5-9 = mild 10-14 = moderate 15-19 = major 20-27 = severe	Average	<2	Yes <sup>f</sup>

<sup>a</sup> Table adapted from Williams JW, Jr. Update: Depression. In: The Rational Clinical Examination: Evidence-based Clinical Diagnosis, Simel DL, Rennie D (Eds), McGraw-Hill, New York, 2009. Adapted with permission.

<sup>b</sup> Easy=3rd to 5th grade reading level; average=6th to 9th grade reading level.

<sup>c</sup> With the exception of BDI-II, which is based on oral administration, all estimates of time to complete are based on self-administration.

<sup>d</sup> Copyright, Pearson Assessments, 19500 Bulverde Road, San Antonio, TX. The BDI-II instrument requires licensing.

<sup>e</sup> Copyright, GL Assessment, The Chiswick Centre, 414 Chiswick High Road, London, W4 5TF, UK.

<sup>f</sup> Copyright, Pfizer Inc., no licensing fee.

Abbreviations: BDI=Beck Depression Inventory; GDS=Geriatric Depression Scale; HADS-A=Hospital Depression and Anxiety Scale (anxiety subscale); HADS-D=Hospital Depression and Anxiety (depression subscale); HADS-T=Hospital Depression and Anxiety Scale (combined scales); PHQ=Patient Health Questionnaire

**Table 7. Accuracy of tools for diagnosis of major depressive disorder**

Study Criterion Standard N Patients Prevalence of Post- ACS Depression	Tool	Chosen Threshold to Diagnose MDD	Threshold Reasoning as Specified in Study	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	P
Bambauer, 2005 <sup>61</sup>  PRIME-MD DMS-IV  N=79  Prevalence=34%	HADS	≥7	NR	NR	NR	34.2	NR	NR	NR
Huffman, 2006 <sup>58</sup> Huffman, 2010 <sup>59</sup>  SCID-I/NP  N=131  Prevalence=13%	BDI-II	Item 1 ≥1	A priori specified	82.4	86.8	48.3	97.1	NR	
		Item 4 ≥1	A priori specified	88.2	76.3	35.7	97.8	NR	
		Item 12 ≥1	A priori specified	82.4	84.2	43.8	97	NR	
		Item 1 or 4 ≥1	A priori specified	94.1	70.2	32	98.8	NR	
		Item 1 or 12 ≥1	A priori specified	94.1	76.3	37.2	98.9	NR	
		≥16	Threshold considered optimal by authors	88.2	92.1	62.5	98.1	0.96 (0.92-1.0)	<.0001
≥14	Traditionally accepted for instrument	88.2	84.2	45.5	98				
Low, 2007 <sup>60</sup>  SCID-I/NP  N=119  Prevalence=5.90%	BDI-II	≥14	Traditionally accepted for instrument	83	88	28	99	0.91	0.06
		≥10	Threshold considered optimal by authors	100	75	18	100		
	GDS	≥11	Traditionally accepted for instrument	100	83	25	100	0.97	
		≥14	Threshold considered optimal by authors	100	94	50	100		

<b>Study Criterion Standard N Patients Prevalence of Post- ACS Depression</b>	<b>Tool</b>	<b>Chosen Threshold to Diagnose MDD</b>	<b>Threshold Reasoning as Specified in Study</b>	<b>Sens (%)</b>	<b>Spec (%)</b>	<b>PPV (%)</b>	<b>NPV (%)</b>	<b>AUC</b>	<b>P</b>
Frasure-Smith, 2008 <sup>37</sup>	BDI-II	≥14	A priori specified	91.2	77.5	NR	NR	0.92 (0.89-0.95)	
Structured Clinical Interview for DSM-IV  N=804  Prevalence=7.10%	HADS-A	≥8	A priori specified	84.2	61.8	NR	NR	0.86 (0.80-0.91)	
Bunevicius, 2012 <sup>62</sup>	HADS	≥14	Threshold considered optimal by authors	82 (69-91)	79 (75-83)	32 (25-41)	97 (95-99)	0.87 (0.81-0.92)	
Structured MINI  N=522  Prevalence=11%	HADS-A	≥8	Traditionally accepted for instrument	86 (73-93)	72 (67-76)	27 (21-34)	98 (95-99)	0.86 (0.80-0.92)	
≥8		Threshold considered optimal by authors	86 (73-93)	72 (67-76)	27 (21-34)	98 (95-99)			
	HADS-D	≥8	Traditionally accepted for instrument	41 (28-55)	90 (87-93)	34 (23-46)	93 (90-95)	0.79 (0.73-0.85)	
		≥5	Threshold considered optimal by authors	77 (63-87)	69 (65-73)	23 (17-30)	96 (93-98)		
	BDI-II	≥14	Traditionally accepted for instrument	89 (95% CI 77-96)	74 (70-78)	29 (23-37)	98 (96-99)	0.90 (0.86-0.94)	
		≥14	Threshold considered optimal by authors	89 (95% CI 77-96)	74 (70-78)	29 (23-37)	98 (96-99)		
McGuire, 2013 <sup>36</sup>	PHQ-2	>0	Threshold considered optimal by authors	95.65	71.43	NR	NR	0.912 (0.0336 SE)	Vs 9 = 0.66 Vs 10 = 0.49
Depression interview Structured Hamilton  N=100  Prevalence=23%	PHQ-9	>4	Threshold considered optimal by authors	95.65	72.73	NR	NR	0.926 (0.0257 SE)	Vs 2 = -0.66 Vs 10 = 0.07
	PHQ-10	>5	Threshold considered optimal by authors	96.65	77.92	NR	NR	0.934 (0.0237 SE)	Vs 2 = 0.49 Vs 9 = 0.07

Abbreviations: ACS=acute coronary syndrome; AUC=area under the curve; BDI=Beck Depression Inventory; CI=confidence interval; DSM-Diagnostic and Statistical Manual of Mental Disorders; GDS=Geriatric Depression Scale; HADS-A=Hospital Depression and Anxiety Scale (anxiety subscale); HADS-D=Hospital Depression and Anxiety (depression subscale); HADS-T=Hospital Depression and Anxiety Scale (combined scales); NPV=negative predictive value; NR=not reported; P=p value; PHQ=Patient Health Questionnaire; PPV=positive predictive value; PRIME-MD=Primary care Rapid Evaluation of Mental Disorders; SCID-I/NP=Structured Clinical Interview for DSM-IV Axis I Disorders (Non-Patient); SE=standard error; Sens=sensitivity; Spec=specificity

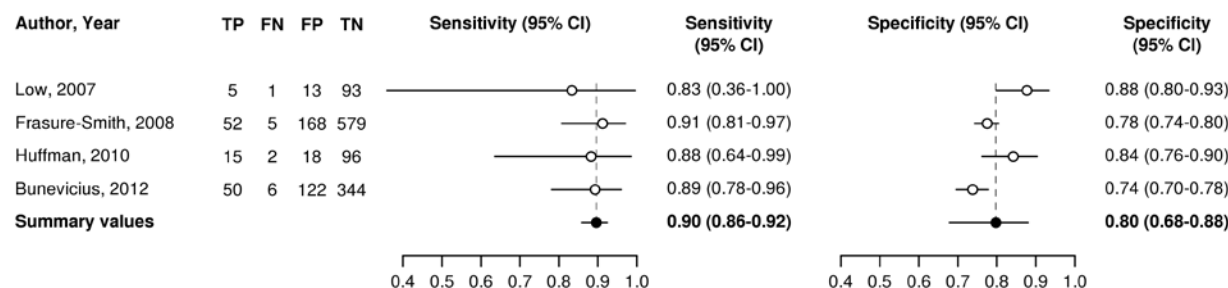
## Beck Depression Inventory-II

Four of the six included studies examined the BDI-II for use in depression screening among post-ACS patients<sup>57, 58, 60, 62</sup> (Figure 4). In the four studies that examined the traditionally accepted cutoff of  $\geq 14$  on the BDI-II to screen for MDD, sensitivity ranged from 83 percent to 91 percent and specificity from 74 percent to 88 percent. Three of these studies reported PPV and NPV, with PPV ranging from 28 percent to 46 percent and NPV from 98 percent to 99 percent. We were able to combine quantitatively the findings from the 4 studies that evaluated the BDI-II with a cutoff of  $\geq 14$ . The meta-analysis of these 4 studies indicated an overall sensitivity of 90 percent (95% CI 86% to 92%) and specificity of 80 percent (95% CI 68% to 88%).

Three of the four studies that examined the BDI-II sought to determine if there was a more optimal cutoff for depression screening among post-ACS patients than the traditionally used score of  $\geq 14$ .<sup>58-60, 62</sup> The optimal greater-than-or-equal-to thresholds indicated by these studies were 10, 14, and 16—with higher thresholds generally corresponding to increases in specificity and PPV and decreases in sensitivity and NPV. Studies varied with respect to whether they suggested that these different thresholds should be employed clinically.

One study of 131 post-ACS patients<sup>58</sup> found that using the one sadness item alone from the BDI-II (score  $\geq 0$  on single item), or this one item in combination with the anhedonia item from the BDI-II (2 items total), resulted in screening test values approximately comparable to those produced from employing the full 21-item BDI-II with a threshold of  $\geq 14$ .<sup>59</sup>

**Figure 4. Forest plot of diagnostic accuracy of BDI-II for major depressive disorder (cutpoint  $\geq 14$ )**



Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; FN=false negative; FP=false positive; TN=true negative; TP=true positive

## Hospital Anxiety and Depression Scale

Three of the six studies tested the HADS or a HADS subscale to screen for depression among post-ACS patients.<sup>57, 61, 62</sup> Note that the HADS instrument screens for both depression and anxiety, but not all of the included studies tested HADS as a screening instrument for depression and anxiety but all did assess its ability to screen for depression. One study found optimal cutoff values of  $\geq 14$  for the full HADS,  $\geq 5$  for the HADS depression subscale, and  $\geq 8$  for the HADS anxiety subscale.<sup>62</sup> The depression subscale slightly underperformed as compared to the full HADS, HADS anxiety subscale, and BDI-II.

Two studies examined the depression screening characteristics of both the HADS anxiety subscale (threshold of  $\geq 8$ ) and the BDI-II (threshold of  $\geq 14$ ).<sup>57, 62</sup> One study found the scales to perform comparably,<sup>62</sup> and one found the HADS anxiety subscale to not perform as well as the BDI-II.<sup>57</sup> One study found a PPV of 34 percent for the full HADS (threshold  $\geq 7$ ).<sup>61</sup>

## Other Screening Instruments

Depression screening instruments other than the BDI-II or HADS were examined in two studies.<sup>56, 60</sup> The GDS was compared with the BDI-II in one study and was found to have similar sensitivity but somewhat better specificity and PPV.<sup>60</sup> A threshold of  $\geq 10$  for the GDS was considered optimal for the post-ACS population, as opposed to the traditional  $\geq 14$ . The PHQ was evaluated in another study, with the authors using nontraditional thresholds of  $> 0$  for the PHQ-2,  $> 4$  for the PHQ-9, and  $> 5$  for the PHQ-10. The three versions each demonstrated excellent AUC statistics (91.2% to 93.4%) and did not perform significantly differently from one another with respect to sensitivity (95.7% to 96.7%) and specificity (71.4% to 77.9%).<sup>56</sup>

## Depression Prevalence and Implications for Screening in Post-ACS Patients

Prior research has suggested that the prevalence rate for MDD among post-ACS patients ranges from 10 percent to 30 percent.<sup>9, 63-66</sup> Prevalence rates in most of the studies included in this review clustered near the lower end of that estimate: four studies found prevalence rates within three percentage points of 10 percent;<sup>57-60, 62</sup> one study of “clinical depression” (included some patients with minor depression per correspondence with authors) found a rate of 23 percent<sup>56</sup>; and one poor-quality study had a rate of 34 percent.<sup>61</sup> This clustering near the lower end of prior prevalence estimates may be in part due to the exclusionary criteria used in some of the studies, with one excluding patients for substance use/dependence diagnoses,<sup>59</sup> and another for having a known current depressive disorder.<sup>62</sup> Depression is highly comorbid with other psychiatric disorders<sup>67</sup> and is most highly correlated with a history of past depressive episodes,<sup>68</sup> and so these criteria likely excluded a number of post-ACS patients with depression from participating.

Another reason for the tendency toward lower prevalence rates in included studies may be that the current review considered studies of patients post-ACS, whereas prior prevalence estimates have often been based on the narrower population of exclusively post-MI patients.<sup>9</sup> One study in this review focused exclusively on this narrower population (MDD prevalence was 13%, though this study also had broader exclusionary criteria as previously noted),<sup>58, 59</sup> whereas the remaining five studies had samples in which post-MI patients constituted approximately 30 percent to 70 percent of the total.

The lower MDD prevalence rates in many of the included studies have implications for the precision of estimates on screening accuracy of the examined measures. One study had only six patients who were diagnosed with MDD per the criterion standard.<sup>60</sup> While two studies had sample sizes above 500<sup>57, 62</sup>—each of these having at least 50 patients diagnosed with MDD—the remaining four studies had sample sizes ranging from 79 to 131 and MDD diagnoses in 27 or fewer patients. Further, only one study, which had a sample of 522 patients, provided confidence intervals surrounding estimates of sensitivity, specificity, PPV, and NPV.<sup>62</sup> Even for this study that had a relatively large sample size, the 95 percent confidence interval surrounding sensitivity for the BDI-II at threshold of  $\geq 14$  still ranged from 77 percent to 96 percent. Although confidence intervals were not provided for the other studies, those studies with smaller sample sizes and limited numbers of patients with MDD would clearly have much larger confidence intervals surrounding the screening accuracy estimates than were reported.<sup>69</sup>

## Depression Screening Properties in Post-ACS Patients

In general, the criterion-oriented diagnostic validity metrics of depression screening scales as tested in post-ACS patients are comparable to those produced from studies of these measures in other more general populations.<sup>70, 71</sup> Estimates of sensitivity, specificity, and NPV for the BDI-II from studies included in this review are in line with those found in other studies,<sup>72</sup> with PPV estimates from included studies in this review near the lower range but generally consistent with PPV estimates produced in other medical samples. The GDS, HADS, and PHQ did not have uniform versions (i.e., they differed in either items assessed or cutpoint used) employed in more than two studies in the present review, limiting comparability with other research, though in general the reported metrics from presently included studies appear broadly consistent with those reported from studies that have examined these measures in other non-post-ACS populations.<sup>73-76</sup>

Three studies in the present review compared screening instruments head-to-head, with these studies considering the BDI-II in comparison to the GDS,<sup>60</sup> the HADS (full version and two subscales<sup>62</sup>), and the HADS anxiety subscale.<sup>57</sup> Both studies looking at the BDI-II in comparison with versions of the HADS concluded that the BDI-II was superior, evidencing slightly better sensitivity than the HADS full version, anxiety subscale, and depression subscale (specificity comparisons were mixed depending on the scale/subscale). The study examining the BDI-II and the GDS found in favor of the GDS, noting that it demonstrated better specificity and PPV.

Considered collectively, evidence from the studies examined in this review does not provide robust support for employing different depression screening thresholds for post-ACS patients than those thresholds that are generally employed for depression screening measures. The three studies that examined different thresholds for the BDI-II came to three different conclusions on this matter—one finding the optimal threshold to be  $\geq 14$  (which is the traditionally accepted threshold<sup>62</sup>), one four points below this,<sup>60</sup> and one two points above this traditional threshold.<sup>59</sup> Only two other studies compared traditional thresholds to levels considered optimal for the post-ACS study samples, resulting in a higher suggested cutoff for the GDS ( $\geq 14$  suggested vs. the traditional  $\geq 11$ <sup>60</sup>) and subscale cutoffs on the HADS of  $\geq 8$  for the anxiety subscale (same as traditional threshold) and  $\geq 5$  for the depression subscale (vs.  $\geq 8$  as traditional<sup>62</sup>).

The two studies in the present review that examined extremely brief screening instruments (i.e., 1-2 items), as described above, indicate that such an approach may be both efficient and relatively effective. A single item from the BDI-II (sadness) performed almost as well as the entire scale,<sup>58, 59</sup> with the same being true for the PHQ-2 when compared with the 9- and 10-item versions of the PHQ.<sup>56</sup> While such brief screening entails clear efficiencies, it bears noting that (1) research indicates that screening performed in the absence of adequate depression care support systems does not improve patient outcomes<sup>77</sup> and (2) PPV in the included studies remains around or below 50 percent, indicating the need for followup assessment to arrive at a diagnosis.

## Comparison With the 2005 Post-MI Depression Report Findings

The 2005 Agency for Healthcare Research and Quality (AHRQ) report “Post-Myocardial Infarction Depression” (AHRQ Publication No. 05-E018-2<sup>1</sup>) addressed the performance characteristics of instruments used to screen for depression after an acute MI. Six studies published between 1988 and 2003 were considered, with most of these focusing on psychometric properties of different instruments (e.g., reliability and validity), and only one of these reporting useful information on an instrument’s diagnostic utility when compared to a criterion standard.<sup>78</sup>



Only this one study would be included in our current review based on the updated inclusion/exclusion criteria. Reported diagnostic utility metrics for measures that were also considered in the present review (i.e., BDI-II) were near or within the range of those found in the current review. The authors of the 2005 review expressed particular concern over the low PPV rates found for all depression screening measures.

By expanding the population under consideration from post-MI patients to post-ACS patients, the present review was able to consider a wider breadth of literature, allowing for a fuller analysis of depression screening measures. Five of the six included studies in the present review examined a post-ACS patient population broader than post-MI alone.<sup>56, 57, 60-62</sup> Findings from the present review are consistent with the prior review's concern with respect to PPV rates. PPV was consistently below 50 percent, even when optimal thresholds were employed, strongly suggesting that the depression screening measures evaluated in this review be employed as the first step in a two-step process when employed in clinical practice. As a second step, a more careful diagnostic assessment needs to be conducted on post-ACS patients who screen positive for MDD before determining a diagnosis and implementing a treatment plan. While such a two-step process is relevant when screening for most diseases and disorders, the low PPV rates produced by depression screening instruments do indicate that a substantial percentage of the more time-intensive full clinical assessments for depression (step 2) are likely to yield a negative result—an important consideration for clinical practice settings.

## **Strength of Evidence**

Table 8 summarizes the strength of evidence for the findings described above. The BDI-II is the only tool with sufficient evidence to support strength of evidence.

**Table 8. Strength of evidence for the BDI-II depression tool**

Test result Strength of Evidence	Study Design (N Patients)	ROB	Indirectness	Inconsistency	Test Property (95% CI) Precision	Test Result	Number per 1,000 Tested for 10% Prevalence <sup>a</sup>	Number per 1,000 Tested for 20% Prevalence <sup>a</sup>
Sensitivity <sup>b</sup> High	4 <sup>57, 58, 60, 62</sup> cross-sectional (1,576)	Low	Direct	Consistent	0.90 (0.86 to 0.92) Precise	True positives	90	180
						False negatives	10	20
Specificity <sup>c</sup> Moderate	4 <sup>57, 58, 60, 62</sup> cross-sectional (1,576)	Low	Direct	Inconsistent	0.80 (0.68 to 0.88) Precise	False positives	180	160
						True negatives	720	640

<sup>a</sup> Number per 1,000 tested for given prevalence of major depressive disorder. Prevalence was based on the range observed in included studies.

<sup>b</sup> Sensitivity=true positive + false negative.

<sup>c</sup> Specificity=false positive + true negative.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; ROB=risk of bias

## Key Question 2: Comparative Safety and Effectiveness of Depression Treatments in Post-ACS Patients

### Description of Included Studies

For KQ 2, we identified 14 articles<sup>79-92</sup> representing 4 studies<sup>82, 84, 87, 91</sup> that examined the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments and enhanced care delivery approaches to usual care for the treatment of depression in post-ACS patients. No studies were identified that evaluated nutritional supplements, aerobic exercise, cardiac rehabilitation, stress management or atypical antipsychotics, transcranial magnetic stimulation and electroconvulsive therapy. Studies were synthesized qualitatively because studies were too few and interventions too diverse for quantitative analysis.

Three studies were described in more than one publication as follows:

- ENRICHED (Enhancing Recovery In Coronary Heart Disease): Primary report<sup>91</sup> and seven companion papers<sup>79, 81, 85, 86, 88-90</sup>
- COPEs (Coronary Patients Evaluation Study): Primary report<sup>84</sup> and two companion papers<sup>80, 83</sup>
- MIND-IT (Myocardial Infarction and Depression–Intervention Trial): Primary report<sup>87</sup> and one companion paper<sup>92</sup>

In this opening section, we refer only to the primary publications; the companion papers are cited where relevant in the Detailed Synthesis section below. In addition, Appendix F provides a key to map primary with companion articles.

All 4 included studies were RCTs, representing a total of 3,119 enrolled patients, and were conducted in multiple centers (Table 9). Three studies were conducted solely in the United States<sup>82, 84, 91</sup> and one study in the UK/Europe.<sup>87</sup> Two studies reported government funding,<sup>82, 84</sup> one reported a mixture of government and industry funding,<sup>91</sup> and one reported a mixture of industry and nongovernment/nonindustry funding.<sup>87</sup> Finally, of the four studies relevant to KQ 2, three were rated as good quality<sup>82, 87, 91</sup> and one was rated as fair quality.<sup>84</sup> Details of the study characteristics of the included studies (including descriptions of the usual care strategies used in the different studies) are in Appendix G.

**Table 9. Key Question 2 evidence summary**

<b>Number of randomized clinical trials:</b> 4
<b>Number of patients:</b> 3,119
<b>Men:</b> 58%
<b>Women:</b> 42%
<b>Race/ethnicity:</b> (2 studies, 307 patients): Hispanic, 33%; African American, 26%
<b>Mean age range:</b> 57.6 to 61.1 years
<b>Depressive disorders:</b> Persistent depressive symptoms, major or minor depressive disorder, dysthymia, or ICD-10 depressive disorder (diagnoses 29 days to 12 months post-ACS)
<b>Cardiac conditions:</b> Post-ACS (2 studies) or post-myocardial infarction (MI) (2 studies)
<b>Settings:</b> Multicenter outpatient specialty and primary care clinics
<b>Countries:</b> USA, UK/Europe
<b>Interventions:</b> Enhanced care (2 studies), CBT and antidepressants (1 study), antidepressants only (1 study)
<b>Comparator:</b> Usual care
<b>Primary outcome:</b> Decrease in depression symptoms
<b>Secondary outcomes:</b> Major adverse cardiac event (MACE) or death, quality of life, treatment adherence

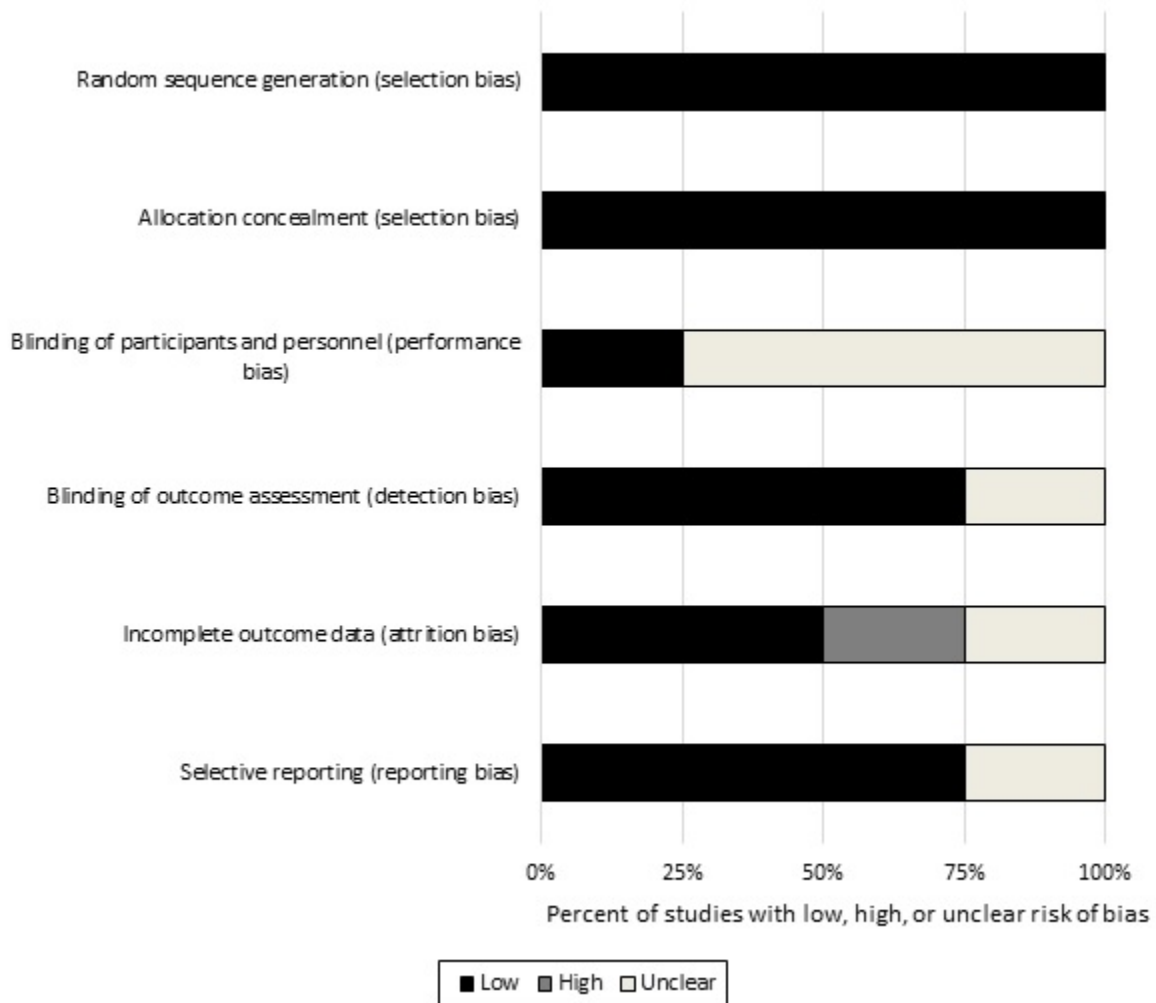
Abbreviations: ACS=acute coronary syndrome; CBT=cognitive behavioral therapy; ICD-10=International Classification of Disease, 10<sup>th</sup> edition

We used the Cochrane Risk of Bias tool to evaluate the quality of the included studies and their risk of bias (Table 10 and Figure 5).<sup>51</sup> For the domain of selection bias (both random sequence and allocation concealment) all studies were ranked low risk of bias. For performance bias, one study was ranked as low risk of bias, while the other three were rated as unclear risk of bias. For detection bias, three studies were ranked as low risk of bias while one was of unclear risk. For attrition bias, two studies were ranked as low risk of bias, one as unclear, and one as high risk. Finally, for potential reporting bias, three studies were ranked as low risk of bias while one was considered unclear risk. Details of the study characteristics of the included studies are in Appendix G.

**Table 10. Cochrane risk of bias assessment for treatment studies**

Study	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Berkman, 2003 <sup>91</sup>	Low	Low	Unclear	Unclear	Low	Low
Davidson, 2010 <sup>84</sup>	Low	Low	Unclear	Low	High	Unclear
Davidson, 2013 <sup>82</sup>	Low	Low	Unclear	Low	Low	Low
van Melle, 2007 <sup>87</sup>	Low	Low	Low	Low	Unclear	Low

**Figure 5. Percent of studies with low, high, or unclear risk of bias across Cochrane risk of bias domains**



## Key Points

- For post-ACS patients, enhanced care interventions which integrates psychiatric treatment in to other clinical settings improve depression symptoms more than usual care (mean difference in BDI ranged from -3.5 to -3.8) which was statistically and clinically significant (2 trials, SOE=moderate).
- One trial compared second-generation antidepressants with usual care and found no difference in the outcomes of depression symptoms or quality of life. The original AHRQ review found that selective serotonin reuptake inhibitors (SSRIs) improved depressive symptoms more than placebo (5 trials, n=3308). Although the one trial included in this update found no improvement with antidepressants compared to usual care, when taken with results from the previous review, these studies support a small positive effect of antidepressants in this patient population.
- A combination strategy, including cognitive behavioral therapy (CBT) plus antidepressant medication for patients with severe symptoms or with a partial response to

CBT, improved depression symptoms, mental health– related function, and overall life satisfaction more than usual care (1 trial, n=2481, SOE=high).

- A combination strategy, including CBT plus antidepressant medications did not show a consistent difference from usual care in effects on MACE, cardiac mortality, all-cause mortality, repeat ACS, revascularization, or cardiac hospitalization in individuals following an ACS event. (SOE = moderate)
- Evidence for enhanced care interventions on cardiovascular outcomes was insufficient.
- Rates of physical or psychiatric adverse effects were reported in one study and similar in the enhanced care and usual care arms. Other than MACE, adverse effects were not reported for any other interventions.
- Strength of evidence was stronger for depression than for cardiovascular outcomes, and stronger for CBT with antidepressants than for enhanced care strategies or antidepressant treatment.

## Detailed Synthesis

### Enhanced Care Versus Usual Care

Two trials including 307 patients compared enhanced care with usual care and reported on depression, cardiovascular, economic, and adverse effect outcomes: Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS)<sup>82</sup> and Coronary Patients Evaluation Study (COPES).<sup>84</sup> Both studies enrolled patients who were post-ACS with persistent depressive symptoms on the BDI scale. Persistent depressive symptoms were defined by a BDI  $\geq 10$  on two occasions between 2 and 6 months post-ACS,<sup>82</sup> or at 1 week and 3 months post-ACS,<sup>84</sup> or by a single BDI score  $> 15$ .<sup>82</sup> The COPES study<sup>84</sup> reported criterion standard diagnoses; only 33 percent met criteria for major depressive disorder (MDD). Patients with major psychiatric comorbidity (e.g., psychosis, substance abuse) or suicidal ideation were excluded. In the COPES trial, enhanced care was based on a collaborative care model, previously tested in a large primary care trial.<sup>93</sup> Care was delivered by a clinical nurse specialist, psychologist, social worker and/or psychiatrist, and patients were offered preference-based treatments; response was assessed with the PHQ-9 and treatment plans were reviewed and modified based on symptom severity (stepped-care). In the CODIACS trial, enhanced care included 6 months of centralized, team-based care with patient preference–based treatments and routine monitoring with escalation of care as needed for non-response. Treatments offered included antidepressant therapy and/or psychotherapy. Both trials differed from primary care-based collaborative care interventions in that the interventions were provided by the study team and did not rely on a primary care physician or cardiologist to provide or coordinate depression treatment.

In the CODIACS trial,<sup>82</sup> a significantly greater decrease in depression symptoms (BDI score [21 questions, 0-63 score with higher scores=greater severity]) was seen in the enhanced care group with a between-group difference of -3.5 (95% CI -6.1 to -0.7; effect size [standardized mean difference] = -0.42, 95% CI -0.75 to -0.10) at 6 months' followup. Note that a 3 to 5-point change or  $\geq 17.5$  percent reduction from baseline is generally described as a meaningful clinically important difference for the BDI score.<sup>94,95</sup> There was also a significantly greater depression remission (BDI  $< 10$ ) rate in the enhanced care group (risk ratio [RR] 1.7, 95% CI 1.04 to 2.40) but no difference in depression response (RR 1.11, 95% CI 0.83 to 1.30), with response defined as  $> 0.5$  standard deviation (SD) improvement in BDI score. There was no difference in the proportion of patients achieving at least moderate improvement in mental

health-related functioning (SF-12 Mental Health) between the two groups (RR 1.08, 95% CI 0.73 to 1.42).<sup>82</sup> Total health care costs were not significantly different (MD -\$325, 95% CI -\$2639 to \$1989) between the enhanced care and usual care groups. Rates of hospitalization for any cause and revascularization were similar between the two groups.<sup>82</sup> Post-hoc analyses showed greater intervention effects on depressive symptoms for women (BDI -6.4, 95% CI -10.1 to -2.6) than for men (BDI -1.6, 95% CI -6.7 to 3.6). Intervention effects did not differ for Hispanic or African American ethnic groups. Adverse effects were not reported.

In the COPES trial,<sup>84</sup> patients assigned to enhanced care had a greater decrease in depression symptoms (mean difference -3.8 in BDI score, 95% CI -6.5 to -1.2; effect size [standardized mean difference] = -0.45, 95% CI -0.77 to -0.14) than usual care at 9 months' followup. Intervention effects on depressive symptoms were also reported by sex and Hispanic and African American subgroups. Intervention effects were similar across these subgroups, but a formal statistical test for differences in treatment effects across subgroups was not performed. Mental health-related function and quality of life were not assessed. Patient-reported adverse events were similar between groups. The enhanced care group had a significantly lower rate of death or a major adverse cardiac event (MACE) during the 6-month intervention period (hazard ratio [HR] 0.25 for the intervention, 95% CI 0.07 to 0.9). However, during the 12-month observational period following the intervention, more patients in the enhanced care group experienced death or MACE (HR 2.91, 95% CI 0.80 to 10.56).<sup>80</sup> There was no difference in the number of patients reporting never missing their daily aspirin (OR 1.6, 95% CI 0.74 to 3.45).<sup>83</sup> However, the 95 percent CI for MACE and adherence outcomes were broad and do not rule out an important beneficial or harmful effect.

Collectively, these two trials showed that enhanced care improves depression symptoms (SOE=moderate) but did not show a consistent effect on cardiovascular outcomes (SOE=insufficient).

## **Sequenced Cognitive Behavioral Therapy and Antidepressants Versus Usual Care**

The ENRICH trial<sup>91</sup> was included in the 2005 AHRQ report,<sup>1</sup> but is described in detail in this systematic review because additional outcomes and subgroup analyses were reported subsequently. That trial<sup>91</sup> compared a sequenced strategy of CBT therapy and antidepressant medications to usual care in patients who were post-MI and met modified DSM-IV criteria for major or minor depression or dysthymia, or low perceived social support. Of the 2,481 patients enrolled, 1,784 (71.9%) met criteria for depression, with approximately 52 percent meeting criteria for MDD and the remainder meeting criteria for minor depression or dysthymia. The key modification to the DSM-IV criteria was that patients with a prior history of MDD were eligible if they had depressive symptoms for a week instead of the usual requirement of 2 weeks. Patients with major psychiatric comorbidity (e.g., psychosis, substance abuse) or suicidal ideation were excluded. All intervention patients began with individual then group CBT; patients with severe depression (i.e., Hamilton Rating Scale for Depression [HRSD] >24) and patients who had <50 percent reduction in depression scores at 5 weeks were considered for antidepressant medication (typically sertraline). CBT was given for up to 6 months and adjunctive antidepressant treatment for up to 12 months.

A significantly greater decrease in depression symptoms was seen in the intervention group when measured by both the BDI (between-group difference -2.7, 95% CI -3.7 to -1.7; effect size [standardized mean difference] = -0.31, 95% CI -0.42 to -0.20) and HRSD (between-group

difference -1.7, 95% CI -2.5 to -0.9).<sup>91</sup> At the end of the intervention, patients in the intervention group reported significantly higher mental health–related functioning (SF-12 mental health, 2.2 points higher) and overall life satisfaction (Life Satisfaction Scale, 1 point higher). However, there was no significant difference in physical health–related functioning (SF-12 physical health).<sup>88</sup> There was no significant difference in major cardiac events, all-cause mortality, cardiovascular mortality, repeat ACS, revascularization, or cardiovascular hospitalization between groups (Table 11).<sup>91</sup> Adverse effects were not reported.

Prespecified subgroup analyses showed a consistent intervention effect on depressive symptoms for white men and women and minority men and women.<sup>89</sup> Intervention effects on death or nonfatal MI were greater for women than men (p=0.03), but this interaction effect was attenuated after adjustment for age and Charlson Comorbidity Index (p=0.20).<sup>91</sup> Intervention effects on cardiovascular outcomes did not vary by ethnic group. In post-hoc analyses, not adjusted for multiple comparisons, use of antidepressant medication was associated with a lower risk of death or nonfatal MI (HR 0.63, 95% CI 0.46 to 0.87). Since patients were not assigned randomly to antidepressant medication, these findings should be considered hypothesis-generating.

**Table 11. Major cardiovascular outcomes in the ENRICH trial**

Event	# Events Usual Care (N=1243)	# Events Intervention (N=1238)	HR (95% CI)
Major cardiac events (death or nonfatal MI)	300	299	1.01 (0.86 to 1.18)
All-cause mortality	172	168	0.98 (0.79 to 1.21)
Cardiovascular mortality	115	96	0.83 (0.64 to 1.10)
Repeat ACS	170	168	0.90 (0.78 to 1.14)
Revascularization	230	216	0.94 (0.78 to 1.14)
Cardiovascular hospitalization	467	442	0.95 (0.83 to 1.08)

Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; ENRICH= Enhancing Recovery In Coronary Heart Disease; HR=hazard ratio; MI=myocardial infarction

## Antidepressants Versus Usual Care

The MIND-IT trial<sup>87</sup> compared antidepressant treatment with usual care in 331 patients meeting International Classification of Disease (ICD-10) criteria for depression at least 3 months post-MI. Patients with suicidal ideation were excluded. Intervention patients were offered first-line treatment with mirtazapine followed by citalopram as second-line therapy and tailored personalized antidepressant treatment by a psychiatrist as third-line treatment. Treatment was continued for 6 months. There was no significant difference between groups with respect to depression symptoms (mean BDI of 11 in intervention vs. 10.2 in usual care; p=0.68, effect size [standardized mean difference] = 0.12, 95% CI -0.10 to 0.34), physical or mental health complaints, and disability or quality of life at 18 months' followup.<sup>87</sup> Additionally, there was no difference in the rate of major cardiac events (14% vs. 13%, OR 1.07, 95% CI 0.57 to 2.00) a composite outcome that included cardiac death, nonfatal MI, heart failure, myocardial ischemia, coronary revascularization, and ventricular tachycardia.<sup>87</sup> Event rates for specific cardiac outcomes (e.g., myocardial ischemia) were low and did not differ between groups. Rates of cardiac-related hospitalization did not differ between treatment groups (39% vs. 41%, p=0.34)

Hypothesizing that effects on cardiovascular outcomes may be delayed, the authors reported outcomes at a mean of 4 to 5 years' followup. There was no intervention effect on the combined endpoint of cardiovascular-related hospital readmissions and cardiac mortality (HR 0.97, 95% CI 0.67 to 1.40) or all-cause mortality (HR 0.74, 95% CI 0.41 to 1.33). A secondary analysis from



this RCT found that patients who received antidepressant treatment, without regard to random assignment, had lower all-cause mortality (HR 0.52, 95% CI 0.28 to 0.97).<sup>92</sup> This finding is consistent with the secondary analysis in the ENRICHD trial, showing lower risk of death or nonfatal MI in patients who used antidepressants. Adverse effects were not reported.

## Outcomes Not Reported

None of the trials reported intervention effects on stroke, gastrointestinal bleeding, emergency department visits, or suicidal ideation, behaviors or attempts. No study reported a cost-effectiveness analysis.

## Strength of Evidence

Tables 12-14 summarizes the strength of evidence (SOE) for the findings described above. In general, the strength of evidence was stronger for depression than for cardiovascular outcomes, and stronger for CBT with antidepressants than for other interventions. A common limitation across all comparisons was the small number of studies. For enhanced care and antidepressant medication, the small number of patients enrolled and relatively few cardiovascular events led to imprecise estimates and lower SOE. Note that selective outcomes reporting was part of the risk of bias assessment rating below, which was incorporated into the overall SOE rating.

**Table 12. Strength of evidence for Key Question 2: Enhanced care versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	2 studies	RCT	Consistent	Imprecise <sup>a</sup>	Mean difference -3.5 to -3.8 BDI SMD -0.42 (CI -0.75 to -0.10) to -0.45 (CI -0.77 to -0.14)	Moderate
	307 patients	Low	Direct	None detected		
Mental health-related function	1 study	RCT	Unknown	Imprecise <sup>a</sup>	OR 1.08 (CI 0.73 to 1.42)	Low
	150 patients	Low	Direct	None detected		
MACE	2 studies	RCT	Inconsistent	Imprecise <sup>a</sup>	Inconsistent results; no effect to short-term benefit (HR 0.25); short-term benefit was not sustained in long-term followup	Insufficient
	307 patients	Low	Direct	None detected		
Adverse effects	1 study	RCT	Unknown	Imprecise <sup>a</sup>	No difference, findings not reported by specific adverse effects	Insufficient
	157 patients	Unclear	Direct	None detected		

<sup>a</sup>Imprecision based on broad confidence interval or confidence interval which crosses the decisional threshold combined with few events.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SMD=standardized mean difference; SOE=strength of evidence

**Table 13. Strength of evidence for Key Question 2: CBT and second-generation antidepressant versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	1 study	RCT	Unknown	Precise	Mean difference -2.7 (CI -3.7 to -1.7) BDI SMD -0.31 (CI -0.42 to -0.20)	High
	2,481 patients	Low	Direct	None detected		
Mental health-related function	1 study	RCT	Unknown	Precise	Mean difference 2.2 (CI 1.2 to 3.2) SF-12 MCS SMD 0.24	High
	2,481 patients	Low	Direct	None detected		
MACE	1 study	RCT	Unknown	Precise	HR 1.01 (CI 0.86 to 1.18) for death or nonfatal MI	Moderate
	2,481 patients	Low	Indirect <sup>a</sup>	None detected		
Adverse effects	NR	–	–	–	–	Insufficient

<sup>a</sup>Rated as indirect since 20.1% of patients enrolled for low perceived social support rather than depression.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MCS=mental component summary; MI=myocardial infarction; NR=not reported; RCT=randomized controlled trial; ROB=risk of bias; SF-12=Short Form Health Survey; SMD=standardized mean difference; SOE=strength of evidence

**Table 14. Strength of evidence for Key Question 2: Antidepressant medication versus usual care**

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
Depression symptoms	1 study	RCT	Unknown	Precise	Mean BDI 11.0 vs 10.2 SMD 0.12 (CI -0.10 to 0.34)	Moderate
	331 patients	Unclear	Direct	None detected		
Mental health–	1 study	RCT	Unknown	Imprecise	Mean at 18 months 44.5 vs	Low

Outcome	Number of Studies/ Number of Patients	Study Design/ ROB	Consistency/ Directness	Precision/ Publication Bias	Effect Estimate (95% CI)	SOE
related function	331 patients	Unclear	Direct	None detected	43.4 SF-36 MCS SMD 0.14	
MACE	1 study	RCT	Unknown	Imprecise	OR 1.07 (0.57 to 2.0) for MACE	Low
	331 patients	Unclear	Direct	None detected		
Adverse effects	NR	–	–	–	–	Insufficient

<sup>a</sup>Rated as indirect since 20.1% of patients enrolled for low perceived social support rather than depression.

<sup>b</sup>Imprecision based on broad confidence interval or confidence interval which crosses the decisional threshold combined with few events.

Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; MACE=major adverse cardiovascular event; MCS=mental component summary; NR=not reported; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SF-12=Short Form Health Survey; SMD=standardized mean difference; SOE=strength of evidence

## Comparison With the 2005 Post-MI Depression Report Findings

The original 2005 AHRQ report<sup>1</sup> addressed the effects of depression treatments, including antidepressants, CBT, interpersonal psychotherapy, psychosocial support, and cardiac rehabilitation on depression and cardiovascular outcomes. This previous report differed from the current review in that it was restricted to post-MI patients and included placebo-controlled studies. A total of 12 studies published between 1991 and 2003 were included in that review. Five placebo-controlled RCTs evaluated the efficacy of antidepressant medications for myocardial infarction patients with depression. The report concluded that SSRIs improved depression and some surrogate markers of cardiac risk compared with placebo, but statistical power was not adequate to assess the impact on survival. Seven studies (6 RCTs, 1 prospective cohort study) compared psychosocial interventions to controls for myocardial infarction patients with depression. The report concluded these interventions improved depression compared with usual care or attention control but did not improve other outcomes. The 2005 report did not identify any studies evaluating enhanced care delivery strategies such as enhanced care. The additional studies identified in the current review builds upon these findings to show benefit from enhanced care and consistent improvements in depression outcomes across important patient subgroups.

## Discussion

In this comparative effectiveness review, we reviewed 10 studies described in 21 publications that compared the accuracy of depression screening instruments in post-acute coronary syndrome (ACS) patients (Key Question [KQ] 1) and the comparative safety and effectiveness of depression treatment strategies in post-ACS patients (KQ 2).

This present review is an update of the original 2005 Agency for Healthcare Research and Quality (AHRQ) systematic review,<sup>1</sup> both reviews found insufficient evidence to support the comparative effectiveness of interventions for improving cardiovascular outcomes, and both reviews recognized the effectiveness of psychosocial interventions and selective serotonin reuptake inhibitors (SSRIs) on improving depression symptoms in patients after myocardial infarction (MI). The original review found insufficient evidence to adequately assess the accuracy of depression screening instruments during the initial hospitalization. In the decade since the 2005 review called for additional research, there are still only 9 more studies added to the evidence base that focus on the broader post-ACS patient population. Both our review and the 2005 review included the Enhancing Recovery In Coronary Heart Disease (ENRICH) trial since some publications from this trial were included in our current review. We summarize here new evidence and its implications for clinical practice, policy, and needed future research.

### Findings in Relation to Other Reviews on Depression Screening and Treatment After ACS

Both the 2008 American Heart Association (AHA)<sup>24</sup> and 2009 American Association of Family Physicians (AAFP) Clinical Practice Guidelines<sup>23</sup> recommend screening for depression in post-MI patients at regular intervals, including during the initial hospitalization, although such recommendations have been met with some controversy.<sup>96, 97</sup> Other guidelines, such as those from U.S. Preventive Services Task Force (USPSTF) on depression screening in primary care,<sup>20</sup> recommend implementing screening with “adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow up.” Whether the clinical settings where post-ACS patients are seen can be equipped with such “adequate systems” is an important health care system consideration. Although no specific screening instruments were recommended by the AHA or AAFP guidelines, the Patient Health Questionnaire (PHQ)-9 was used as an example of how screening instruments could be used in clinical practice. Our present review finds that the Beck Depression Inventory (BDI)-II has good sensitivity (90%) and specificity (80%) for major depressive disorder (MDD) during hospitalization after ACS, suggesting that screening can be accomplished in this setting with reasonable accuracy. Data on the accuracy of other screening instruments, including the PHQ, which is popular in general medical settings as well outpatient settings, was very limited. However, the limited available evidence from this review on very brief screenings for depression, including 1-2 items from the BDI-II and 2 items from the PHQ, suggests that such brief screenings may produce comparable diagnostic screening accuracy metrics when using longer screens (e.g., the full BDI-II and PHQ-9). Although we sought evidence on the timing of diagnostic assessment, our findings did not inform the timing of post-ACS depression assessment except to indicate that in-hospital assessment appears to be reasonably accurate in terms of its diagnostic sensitivity and specificity.

Clinical practice guidelines also have recommended that patients “post-MI with a diagnosis of depression” be treated with SSRIs preferentially over tricyclic antidepressants, and that treatment be given “with systems in place to ensure regular followup and monitoring of their

treatment response and adherence to treatment.”<sup>23</sup> The present systematic review did not find any new studies directly comparing SSRIs with tricyclic antidepressants but found two trials supporting enhanced care for patients post-ACS with severe or persistently elevated (two positive depression screens) depressive symptoms. A trial of collaborative care addressing both depression and cardiovascular risk factors (hyperlipidemia, hypertension, diabetes mellitus) improved depression outcomes and intermediate outcomes (e.g., lipid values, blood pressure).<sup>98</sup> The 2005 AHRQ review<sup>1</sup> also found that SSRIs and psychosocial interventions improved depression outcomes but not cardiovascular outcomes. Thus, our findings provide support for the recommendation to have systems in place to ensure high-quality treatment, a recommendation that is consistent with the USPSTF recommendation for screening on general medical populations and the American College of Physicians (ACP) policy recommendations<sup>99</sup> for integrated behavioral health care. Also it should be noted that our findings are generally consistent across sex and ethnic groups.<sup>84, 91</sup> The Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS) study focusing on enhanced care did find stronger effects in women.<sup>82</sup> Although current evidence does not show an overall effect on of depression treatment on cardiovascular events, post-hoc analyses from two studies did show lower major adverse cardiovascular events (MACE) in patients treated with antidepressants, demonstrating a signal that such treatment may lower cardiovascular events. This signal should be considered a hypothesis-generating finding because the analyses did not preserve randomization, and the observed association could be due to chance or biased by unrecognized confounders. Other potential adverse effects (e.g., suicidality, nausea) were not well reported in these studies and it is uncertain if they would differ in post-ACS patients compared to the general adult population.

Note that the prior 2005 AHRQ review<sup>1</sup> and guidelines<sup>23, 24, 82, 84</sup> have focused on patients post-MI, but our review extends the population of interest to post-ACS patients. Table 15 summarizes this current review as compared to the prior 2005 AHRQ review.

**Table 15. Differences in scope and findings between the 2005<sup>1</sup> and current evidence reports**

	<b>2005 Report</b>	<b>Current Report</b>
<b>Scope of Key Questions (KQs)</b>	KQs spanned: the prevalence of depression during initial hospitalization and following discharge the association of post-MI depression with outcomes of interest the comparison of outcomes of post-MI patients with and without depression the performance characteristics of instruments used for screening for depression post MI, and the use of cardiac treatments in this patient population.	This current review builds on that original review but focuses on: the diagnostic accuracy of selected depression screening instruments and strategies versus a validated criterion standard in adult patients within 3 months of an ACS event the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for depression in adult patients who have received a criterion-based diagnosis of depression or had clinically important depressive symptoms using a validated depression scale, and who are within 3 months of an ACS event
<b>Publication dates for included studies</b>	Inception to 2004	2003-2017
<b>Depression diagnosis</b>	Depression defined as symptoms meeting established clinical threshold criteria for depression as measured by validated questionnaires or standardized psychiatric interviews	Depression defined as a criterion-based diagnosis of depression or having clinically important depressive symptoms using a validated depression scale
<b>Cardiac population</b>	Adults who have undergone an acute MI	Adults who have acute coronary syndrome (ACS), which includes both unstable angina and myocardial infarction (MI), and are within 3 months of an identifying ACS event
<b>Prevalence of depression in patients with acute MI</b>	Major depression was reported in approximately 20% of patients during the initial hospitalization for an MI  Insufficient data were available to address the question of the prevalence of depression during the initial hospitalization for an acute MI in patients with and without a history of previous depression  Most patients with depression during the initial MI hospitalization continued to have depression 1 to 4 months after experiencing an MI	Not addressed
<b>Association of post-MI depression with outcomes</b>	Post-MI depression is associated with a significantly increased risk of death following an MI	Not addressed
<b>What is the performance/accuracy of depression screening instruments in</b>	The BDI tended to be more sensitive to lower levels of depressive symptoms but less sensitive to more severe depression compared to the Hospital and Anxiety Depression Scale (HADS) and the Symptom Checklist-90 Depression scale for depression diagnosis following an acute MI	Four depression screening instruments (Beck Depression Inventory II [BDI-II], Geriatric Depression Scale [GDS], HADS, and Patient Health Questionnaire [PHQ]) produce generally acceptable levels for diagnostic sensitivity, specificity, and negative predictive values

	<b>2005 Report</b>	<b>Current Report</b>
<b>patients with MI/ACS</b>	Insufficient data were available to address the performance characteristics of instruments/methods to screen for depression (1) following an acute MI during hospitalization and (2) within 3 months after an acute MI hospitalization	The BDI-II diagnostic screening performance characteristics were found to have a sensitivity of 90% and specificity of 80%
<b>Do depression treatments improve outcomes in post-MI patients with depression</b>	<p>In post-MI patients with depression, psychosocial interventions improve depression but not other clinical outcomes</p> <p>Selective serotonin reuptake inhibitors improve depression and some surrogate markers of cardiac risk, but no studies of sufficient power address the question of whether this treatment improves survival</p>	<p>Collaborative care interventions, which integrate psychiatric treatment into other clinical settings, improve depression symptoms more than usual care</p> <p>Collaborative care, CBT, or antidepressant medications were similar to usual care in reducing MACE, cardiac mortality, all-cause mortality, repeat ACS, revascularization, or hospitalization in individuals following an ACS event</p> <p>Evidence did not show increased adverse events among post-ACS individuals treated with collaborative care, CBT, or antidepressant medications compared with usual care</p>
<b>Is the use of cardiac medications different in MI patients with and without depression?</b>	Findings were inconsistent with 2 studies showing decreased prescription of beta-blockers and aspirin and 2 studies showing no difference in rates of prescribed discharge medications	Not addressed

Abbreviations: ACS=acute coronary syndrome; BDI=Beck Depression Inventory; CBT=cognitive behavioral therapy; GDS=Geriatric Depression Scale; HADS=Hospital and Anxiety Depression Scale; KQ=Key Question; MACE=major adverse cardiovascular events; MI=myocardial infarction; PHQ=Patient Health Questionnaire

## Applicability

Many studies initially identified in our review either included patients who were not within 3 months from their identifying ACS event, or had not been diagnosed either through a criterion standard or through demonstration of clinically important depressive symptoms using validated depression instruments. We assessed the applicability of our included studies for both Key Questions. For KQ 1, all studies assessed the performance of screening tools for major depressive disorder, and thus are directly applicable to the specific question of interest although have potentially limited applicability to depressive episodes that do not meet criteria for major depression. The strongest evidence was for the BDI-II, a 21-item instrument that takes somewhat longer to complete compared with other commonly used depression screeners (see Table 8). The BDI-II may be feasible to use during hospitalizations but shorter instruments, such as the PHQ-2, are more commonly used in outpatient settings. Further, the BDI-II requires a license to use, which could be a barrier to uptake in practice.

For KQ 2, patients were enrolled with persistently elevated depressive symptoms or after a criterion-based diagnosis of MDD. Study eligibility was determined in two studies<sup>82, 84</sup> with the BDI (first edition), an instrument that does not reflect important changes first made to the criterion standard diagnosis of MDD in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R (1987) and later DSM-IV. The BDI-II (which was evaluated in KQ 1) was updated to reflect these changes. The other two studies used criterion-based diagnoses of MDD. In general medical practice, depression diagnoses are often made without the use of formal criteria. Clinicians would need to use criterion-based diagnoses or document persistently elevated depressive symptoms with a validated instrument, to replicate the outcomes observed in these trials.

Table 16 summarizes the applicability scores across KQs. Note that 3 of the 6 included studies for KQ 1 were described as having narrow eligibility criteria or exclusion of those with comorbidities.

**Table 16. Potential issues with applicability of included studies**

Category	Issue	Key Question 1 N=6	Key Question 2 N=4
<b>Population</b>	Narrow eligibility criteria and exclusion of those with comorbidities	3	0
	More complex patients than typical of the community	0	1
	Run-in period with high exclusion rate for non-adherence or side effects	0	0
<b>Intervention</b>	Diagnostic tools used differently than as recommended or commonly used in practice	0	0
	Dosing not reflective of current practice	0	0
	Co-interventions that are likely to modify the effectiveness of therapy	0	2
	Highly selected intervention team or level of training/proficiency not widely available	0	2
	Followup not reflective of current practice	0	0
<b>Comparator</b>	Diagnostic tools used differently than as recommended or commonly used in practice	0	0
	Comparator unclear	0	0
	Inadequate comparison therapy or use of a substandard alternative therapy	0	0
<b>Outcomes</b>	Composite outcomes that mix outcomes of different significance	0	0
	Short-term followup	0	0
	Surrogate outcomes	0	0
<b>Setting</b>	Level of care different from that in the community	0	0



## Implications for Clinical and Policy Decisionmaking

MDD is a common comorbid illness post-ACS and is associated with worse cardiovascular outcomes and higher mortality.<sup>17, 18</sup> The bio-behavioral mechanisms are uncertain but include potential effects on the neuroendocrine system, platelet function, autonomic nervous system activity, adherence to medications, and lifestyle factors such as physical activity. Effective depression treatment may not only improve depression outcomes but also improve quality of life. The impact of depression treatment on cardiovascular outcomes remains uncertain. With the exception of a sequenced approach of CBT plus antidepressants that found no benefit on MACE, depression interventions have not been evaluated in trials with sufficient power to determine effects on cardiovascular outcomes.

Our systematic review has several implications for clinical and policy decisionmaking. Specifically, in KQ 1 we found good performance characteristics for negative predictive value for the BDI-II diagnostic tool across a range of prevalences, which was the screening instrument used most often among included studies. Data on the widely used PHQ (2-, 9-, and 10-item versions) were presented in only one study, which did not compare the PHQ directly to any other screening instruments but found sensitivity and specificity values within a comparable range of those generally reported for the BDI-II. The performance characteristics for the BDI-II in post-ACS patients were similar to the performance in general medical and psychiatric populations.<sup>100</sup> This suggests that other screening instruments that may be more feasible for use in general medical settings (e.g., shorter, easier to administer and score, no licensing fee) may also perform well in post-ACS patients. Some data within our review<sup>56, 58</sup> also suggest that very short questionnaires (1-2 questions) may perform similarly to full instruments although the evidence is currently sparse. Both these assumptions need to be confirmed through additional studies. We did not identify studies that directly addressed the timing of screening, and thus there remains uncertainty about the performance of screeners at various times post-ACS.

Our review did not address the effects of depression screening<sup>101</sup> versus no-screening on downstream depressive or cardiovascular outcomes. However, all intervention studies within KQ 2 identified patients initially by depression screening, and two trials<sup>82, 84</sup> relied on persistent depressive symptoms to determine eligibility. Thus, coupling screening for identification (using a validated instrument and showing persistent symptoms) with effective treatment seems to improve depressive outcomes.<sup>82</sup> The USPSTF used this type of evidence and logic model to conclude that evidence supports depression screening in primary care.<sup>20</sup>

Within KQ 2, secondary analyses from the treatment trials showed generally consistent benefit of interventions on depression outcomes by sex and ethnicity.<sup>84, 91</sup> Importantly, these trials use second-generation antidepressants and/or cognitive behavioral therapy. Thus, recommendations should be limited to these interventions and not generalized to all antidepressants (e.g., tricyclic antidepressants), which may have adverse cardiovascular effects.<sup>102</sup>

The included studies did not show a clear beneficial effect of depression treatment on cardiovascular outcomes in this post-ACS population. However, only one study had sufficient patients and events—and therefore the needed statistical power—to identify a clinically important effect.<sup>91</sup> Second, two post-hoc analyses suggest the possibility that antidepressant use may be associated with lower cardiovascular events.<sup>82, 84</sup> In addition, the followup time was limited in the included studies. Clinically, a key issue is that all trials used second-generation antidepressants, and while cardiovascular events were not lower, there was no consistent signal for higher cardiovascular event rates. Therefore, at present, evidence suggests that depression

interventions will improve depression outcomes and may not increase negative cardiovascular outcomes.

Data from other studies of unselected patients with depressive disorders, including individual patient-level meta-analyses<sup>103</sup> show a relationship between greater treatment benefits among patients with more severe depressive symptoms. These data, coupled with the diagnostic approaches in the intervention trials we studied, support a recommendation for careful criterion-based diagnoses and/or diagnoses using validated instruments that show persistent depressive symptoms.

Finally, starting January 1, 2017, the Centers for Medicare and Medicaid Services (CMS) introduced four new payment codes (G codes) that support collaborative care for depression.<sup>104</sup> The payment by CMS for collaborative care should lower financial barriers to implementing integrated behavioral health for depressed patients, including those post-ACS.

## **Limitations of the Systematic Review Process and Evidence Base**

Several aspects of the review process may have affected the results. We limited the search to papers published after the cut-off date (March 2004) of the previous AHRQ evidence report on depression post-MI, but incorporated studies from this review.<sup>1</sup> Our systematic review, however, expanded the patient population of interest to include patients within 3 months of an ACS event (including patients with unstable angina, non-ST-segment elevation myocardial infarction [NSTEMI], and ST-segment elevation myocardial infarction [STEMI]). This meant that studies completed prior to 2004 that targeted the broader post-ACS population might have met our new inclusion criteria but were excluded in the original review. In addition, while the original report included any study which assessed psychometric characteristics, our inclusion criteria limited studies for KQ 1 to those with a criterion standard; however, identifying and treating subthreshold depression in post-ACS patients may still be clinically prudent. Given broad changes in clinical practice over the past decade in both cardiac care (e.g., greater early intervention increased use of dual antiplatelets, greater use of rehabilitation) and depression care (e.g., introduction of new drugs, more behavioral health integration), the impact of missing earlier studies on conclusions about comparative effectiveness of currently used treatment alternatives is unclear, but these changes in populations of interest and required criterion standard made integrating our findings with the previous report challenging.

Our review did not address directly the effectiveness of depression screening in post-ACS patients. To address this issue optimally would require a randomized controlled trial (RCT) that compared the effects of screening with no screening on depression and cardiovascular outcomes. There are few trials of depression screening in any patient population, and the effects of screening alone have been quite limited.<sup>101, 105, 106</sup>

Finally, we did not include studies published in languages other than English, primarily due to resource limitations. However, given the focus of our review on applicability to populations in the United States, and the scope of our KQs, we believe this restriction to be valid.

In addition to the limitations of the systematic review process, the evidence base itself provided additional challenges. The main limitation of the evidence base is the small number of studies directly performed in the post-ACS population of interest using defined criterion standards for comparison (KQ 1) or for identification of patients for assessment of treatment effectiveness (KQ 2). Within these studies, limited data suggest that very short screens such as item 1 (sadness) from the BDI-II<sup>58</sup> or the two items from the PHQ-2<sup>56</sup> may perform as well as

longer screening tools. If future studies confirm these findings, this could greatly improve the feasibility of screening for depression in post-ACS patients. Secondly, the included KQ 1 studies assessed several cutoff points, either targeting commonly used cutoffs or those determined to be optimal for diagnostic accuracy by the study itself. It is unclear whether the cutoffs should differ for post-ACS patients, although the limited available data suggests this not to be the case.

The evidence for KQ 2 was limited to only four studies. Most of these were underpowered for cardiovascular outcomes, and no studies evaluated several of the interventions identified by key informants and our technical expert panel as being of interest (specifically exercise,<sup>107, 108</sup> cardiac rehab, nutritional supplements). Some of these interventions may improve cardiac outcomes. For some other interventions also without evidence (e.g., atypical antipsychotics), there are concerns about adverse effects and so studies of these interventions are needed to inform the evidence base. Note that we did not include evidence from observational studies for KQ 2.

## Research Recommendations

Future clinical research, especially comparative effectiveness research—which helps resolve current uncertainties regarding clinical or policy decisions—should receive priority. For both KQs, there are multiple areas of remaining uncertainty based on the existing evidence. Some potential areas for future research informed by our engagement with stakeholders during the topic refinement phase include exploration of how our results for both KQ 1 and KQ 2 apply to highly-related patients; for example, in patients after electing to have coronary artery bypass grafting or percutaneous coronary intervention surgery, or in patients with congestive heart failure. These patient populations were not prioritized for this review but identified as being of interest for future work. Studies on depression screening could focus on differences between screening immediately after an ACS event in the hospital setting compared with later in the outpatient setting, as well as differences based on demographics (e.g., sex, age, ethnicity). More research on the widely used PHQ is also warranted (one study of the PHQ-8 is ongoing<sup>109</sup>).

We also identified gaps in evidence for depression treatments with demonstrated benefit in patients without heart disease. Some of these treatments, such as exercise,<sup>110</sup> cardiac rehabilitation and omega-3 fatty acid supplements<sup>96, 111, 112</sup> have the potential to benefit both depression and cardiac outcomes. Interventions that have the evidence to directly benefit both conditions may be particularly promising interventions to prioritize for future research. In addition, evidence from studies that explore other interventions such as other forms of psychotherapy and CBT are needed.

As noted above, our review signaled that antidepressants may benefit cardiovascular outcomes in addition to depression, but these findings are observational and not definitive. Further trials however—and specifically longer-term studies—are needed which have cardiovascular outcomes as the primary outcome of interest with the appropriate statistical power to detect an effect. Such trials will need to be relatively large and so value-of-information studies done in advance could help prioritize such studies and inform their design.<sup>113</sup> Given the scarcity of evidence from RCTs, insight from large high-quality observational studies may also inform the remaining uncertainties and help prioritize needed future research. Similar to KQ 1, research studies which focused on specific subgroups of interest (e.g., older patients, women, minorities) is needed.

Current general MDD guidelines,<sup>99</sup> although not specific to post-ACS patients, recommend second-generation antidepressant or CBT as first line treatment for depression. All of our studies

compared treatment strategies to usual care. We therefore were unable to make direct head-to-head comparisons of the active interventions. Although such studies would increase the strength of evidence, possibly more valuable research would focus on the comparisons of antidepressant treatment with CBT compared to antidepressant treatment alone. Some data suggest this may be more effective for depression in general, and given the psychosocial stress of post-ACS and the signal for possible cardiovascular benefit from secondary analyses on antidepressant, testing this combination might be a high priority.

## **Conclusions**

Among several depression screening tools, the BDI is the most studied. Existing tools miss less than 3 percent of patients with depression (high negative predictive value: 97%), but less than 50 percent of patients who screen positive actually have the condition (low positive predictive value: <50%). Enhanced care interventions and a strategy using CBT plus second generation antidepressant medication for patients with severe depression or partial response to CBT improve depressive outcomes more than usual care. Given the inconsistency and imprecision of findings, and the small number of studies evaluating cardiovascular outcomes, the effects of depression interventions on such cardiovascular outcomes is uncertain.

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## Acronyms and Abbreviations

<b>Acronym</b>	<b>Definition</b>
ACS	Acute coronary syndrome
AUC	Area under the curve
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory, 2 <sup>nd</sup> edition
CBT	Cognitive behavioral therapy
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CKD	Chronic kidney disease
CODIACS	Comparison of Depression Interventions after Acute Coronary Syndrome
COPEs	Coronary Patients Evaluation Study
DISH	Depression Interview and Structured Hamilton
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3 <sup>rd</sup> edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> edition, Text Revision
ENRICHD	Enhancing Recovery in Coronary Heart Disease study
GAD	Generalized anxiety disorder
GDS	Geriatric Depression Scale
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
HR	Hazard ratio
HRSD	Hamilton Rating Scale for Depression
ICD-10	International Classification of Disease, 10 <sup>th</sup> edition
LPSS	Low perceived social support
MACE	Major adverse cardiac events
MBCT	Mindfulness-based cognitive therapy
MCS	Mental component summary
MDD	Major depressive disorder
MI	Myocardial infarction
MIND-IT	Myocardial Infarction and Depression-Intervention Trial
MINI	Mini International Neuropsychiatric Interview
NPV	Negative predictive value
OR	Odds ratio
PHQ	Patient Health Questionnaire
PPV	Positive predictive value
PROMIS	Patient-Reported Outcomes Measurement Information System
PRIME-MD	Primary Care Evaluation of Mental Disorders
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies, 2 <sup>nd</sup> edition

<b>Acronym</b>	<b>Definition</b>
ROC	Receiver operating characteristic
RR	Risk ratio
SCID-I/NP	Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient edition
SD	Standard deviation
SE	Standard error
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

# Appendix A. FDA Status and Warnings for Drugs Included in This Review

**Appendix Table A1. Second-generation antidepressant medications that are FDA approved for treatment of major depressive disorder<sup>1</sup>**

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
<b>Warnings:</b>		
All antidepressants have a black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age.		
There is also a risk of withdrawal symptoms if discontinued abruptly.		
Other risks of SSRI/SNRIs: bleeding, fracture, narrow angle glaucoma, serotonin syndrome, sexual dysfunction, syndrome of inappropriate antidiuretic hormone secretion (SIADH). Many antidepressants have cautions for use in patients with angle-closure glaucoma, bipolar disorder, pregnancy in 3 <sup>rd</sup> trimester, or seizure disorders.		
<b>Atypical antidepressants</b>		
Bupropion	Yes	Contraindicated in seizure disorders or eating disorders
Mirtazapine	Yes	–
Nefazodone	Yes	Hepatic failure
Trazodone	Yes	–
Vilazodone <sup>2</sup>	Yes	–
Vortioxetine <sup>3</sup>	Yes	–
<b>SSRIs</b>		
Citalopram	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF; Reduce dose if age >60
Fluoxetine	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF
Escitalopram	Yes	Bradycardia, Ventricular arrhythmias, QT prolongation, Recent MI, CHF
Paroxetine	Yes	–
Sertraline	Yes	–
<b>SNRIs</b>		
Desvenlafaxine	Yes	Cardiovascular disease
Duloxetine	Yes	Hypertension
Levomilnacipran <sup>4</sup>	Yes	Cerebrovascular disease, Cardiovascular disease, Hypertension, ≥ Stage 3 CKD
Venlafaxine	Yes	Heart failure, recent MI

Abbreviations: MI=myocardial infarction; CHF=congestive heart failure; CKD=chronic kidney disease; SIADH=syndrome of inappropriate antidiuretic hormone secretion; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin-norepinephrine reuptake inhibitors

**Appendix Table A2. Atypical antipsychotics that are FDA approved for treatment of major depressive disorder<sup>1</sup>**

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
<p><b>Warnings:</b>                      Black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age (Aripiprazole and Quetiapine).                      Black box warning for increased risk of death in elderly patients with dementia-related psychosis.                      Other risks related to atypical antipsychotics: altered cardiac conduction (prolonged QTc), blood dyscrasia, increased stroke in dementia related psychosis, CNS depression, anticholinergic effect, dyslipidemia, hyperlipidemia, aspiration, extrapyramidal symptoms, neuroleptic malignant syndrome, orthostatic hypotension, pathologic gambling, impaired temperature regulation, weight gain and metabolic side effects.</p>		
Aripiprazole <sup>5</sup>	Yes, as an adjunct with an antidepressant	FDA safety alert: uncontrollable urges to gamble, binge eat, shop or have sex. Other risks: akathisia, restlessness, sedation, headache, nausea and vomiting
Olanzapine <sup>6</sup>	For bipolar depression and treatment resistant depression, only in combination with fluoxetine	FDA safety alert: DRESS (drug reaction with eosinophilia and systemic symptoms) FDA black box: delirium/sedation syndrome with long acting injection (likely not relevant to use in depression) Other risks: akathisia, sedation, dizziness, headache, increased prolactin Risk of suicidal thoughts and behavior but does not have black box.
Quetiapine <sup>7</sup>	Yes, as an adjunct with an antidepressant	Other risks: sedation, hypertension, cataracts, hypothyroidism, headache, tachycardia, increased prolactin

Abbreviations: CNS=central nervous system; QTc=corrected QT interval

**Appendix Table A3. Tricyclic antidepressants that are FDA approved for treatment of major depressive disorder<sup>1</sup>**

Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
<p><b>Warnings:</b>                      All antidepressants have a black box warning for increased risk of suicidal thinking and behavior in children, adolescents and adults 18-24 years of age.                      Contraindicated for use with or within 14 days of concomitant monoamine oxidase inhibitor (MAOI) therapy.                      Tricyclic antidepressants are contraindicated during the acute recovery period following a myocardial infarction.                      There is also a risk of withdrawal symptoms if discontinued abruptly.                      Tricyclic antidepressants should be used with caution in patients with a history of cardiovascular disease due to the risk of conduction abnormalities. Other risks related to tricyclic antidepressants include altered cardiac conduction (prolonged QTc), orthostatic hypotension, anticholinergic effects (including but not limited to constipation, urinary retention and blurred vision) and CNS depression including sedation. Tricyclic antidepressants should be used with caution in individuals with bipolar disorder, the elderly and those with hepatic impairment or a history of seizures.</p>		
Amitriptyline <sup>8-9</sup>	Yes	–
Amoxapine <sup>10-11</sup>	Yes	History of neuroleptic malignant



Drug	FDA-Labeled Indication for Depressive Disorders	Additional Warnings and Cautions relevant to Adults with Cardiovascular disease
		syndrome, high environmental temperatures
Desipramine <sup>12-13</sup>	Yes	–
Doxepin	Yes	–
Imipramine <sup>14-15</sup>	Yes	–
Nortryptiline <sup>16-17</sup>	Yes	–
Protryptiline <sup>18-19</sup>	Yes	–
Trimipramine	Yes	–

Abbreviations: CNS=central nervous system; MAOI=monoamine oxidase inhibitor; QTc=corrected QT interval

## Notes to Appendix Tables A1, A2, and A3

1. Depression: Medicines to Help You. FDA office of women's Health. <http://www.fda.gov/downloads/ForConsumers/ByAudience/ForWomen/FreePublications/UCM182083.pdf>
2. Vilazodone: Drug Information. [http://www.uptodate.com/contents/vilazodone-drug-information?source=search\\_result&search=vilazodone&selectedTitle=1%7E13#F11595949](http://www.uptodate.com/contents/vilazodone-drug-information?source=search_result&search=vilazodone&selectedTitle=1%7E13#F11595949)
3. Vortioxetine: Drug Information. [http://www.uptodate.com/contents/vortioxetine-drug-information?source=search\\_result&search=vortioxetine&selectedTitle=1%7E8](http://www.uptodate.com/contents/vortioxetine-drug-information?source=search_result&search=vortioxetine&selectedTitle=1%7E8)
4. Levomilnacipran: Drug Information. [http://www.uptodate.com/contents/levomilnacipran-drug-information?source=search\\_result&search=levomilnacipran&selectedTitle=1%7E6](http://www.uptodate.com/contents/levomilnacipran-drug-information?source=search_result&search=levomilnacipran&selectedTitle=1%7E6)
5. Aripiprazole: Drug Information. [http://www.uptodate.com/contents/aripiprazole-short-acting-oral-and-injectable-and-long-acting-injectable-abilify-maintena-drug-information?source=search\\_result&search=abilify&selectedTitle=1%7E62](http://www.uptodate.com/contents/aripiprazole-short-acting-oral-and-injectable-and-long-acting-injectable-abilify-maintena-drug-information?source=search_result&search=abilify&selectedTitle=1%7E62)
6. Olanzapine: Drug Information. [http://www.uptodate.com/contents/olanzapine-drug-information?source=search\\_result&search=zyprexa&selectedTitle=1%7E121](http://www.uptodate.com/contents/olanzapine-drug-information?source=search_result&search=zyprexa&selectedTitle=1%7E121)
7. Quetiapine: Drug Information. [http://www.uptodate.com/contents/quetiapine-drug-information?source=search\\_result&search=quetiapine&selectedTitle=1%7E105](http://www.uptodate.com/contents/quetiapine-drug-information?source=search_result&search=quetiapine&selectedTitle=1%7E105)
8. Amitriptyline: Product Information: amitriptyline hcl oral tablets, amitriptyline hcl oral tablets. Vintage Pharmaceuticals, LLC, Huntsville, AL, 2006.
9. Amitriptyline: Drug Information. [http://www.uptodate.com/contents/amitriptyline-drug-information?source=search\\_result&search=Amitriptyline&selectedTitle=1~139](http://www.uptodate.com/contents/amitriptyline-drug-information?source=search_result&search=Amitriptyline&selectedTitle=1~139)
10. Amoxapine: Product Information: amoxapine oral tablets, amoxapine oral tablets. Watson Pharma, Inc. (per DailyMed), Parsippany, NJ, 2014.
12. Amoxapine: Drug Information. [http://www.uptodate.com/contents/amoxapine-drug-information?source=search\\_result&search=amoxapine&selectedTitle=1~8](http://www.uptodate.com/contents/amoxapine-drug-information?source=search_result&search=amoxapine&selectedTitle=1~8)
12. Desipramine: Product Information: NORPRAMIN(R) oral tablets, desipramine HCl oral tablets. Sanofi-Aventis U.S. LLC (per FDA), Bridgewater, NJ, 2014
13. Desipramine: Drug Information. [http://www.uptodate.com/contents/desipramine-drug-information?source=search\\_result&search=Desipramine&selectedTitle=1~74](http://www.uptodate.com/contents/desipramine-drug-information?source=search_result&search=Desipramine&selectedTitle=1~74)
14. Imipramine: Product Information: Tofranil-PM(TM) oral capsules, imipramine pamoate oral capsules. Mallinckrodt Inc. (per FDA), Hazelwood, MO, 2014.
15. Imipramine: Drug Information. [http://www.uptodate.com/contents/imipramine-drug-information?source=search\\_result&search=Imipramine&selectedTitle=1~76](http://www.uptodate.com/contents/imipramine-drug-information?source=search_result&search=Imipramine&selectedTitle=1~76)

16. Nortriptyline: Product Information: Pamelor(TM) oral solution, nortriptyline HCl oral solution. Mallinckrodt Inc. (per FDA), Hazelwood, MO, 2014.

17. Nortriptyline: Drug Information. [http://www.uptodate.com/contents/nortriptyline-drug-information?source=search\\_result&search=Nortriptyline&selectedTitle=1~92](http://www.uptodate.com/contents/nortriptyline-drug-information?source=search_result&search=Nortriptyline&selectedTitle=1~92)

18. Protriptyline: Product Information: VIVACTIL(R) film-coated tablets, protriptyline HCl film-coated tablets. Teva Pharmaceuticals USA, Inc. (per FDA), Horsham, PA, 2014.

19. Protriptyline: Drug Information. [http://www.uptodate.com/contents/protriptyline-drug-information?source=search\\_result&search=Protriptyline&selectedTitle=1~19](http://www.uptodate.com/contents/protriptyline-drug-information?source=search_result&search=Protriptyline&selectedTitle=1~19)

## Appendix B. Exact Search Strings

### PubMed® Search Strategy (August 15, 2017)

#### KQ 1:

Search Number	Search String
#1	"Myocardial Infarction"[Mesh] OR "myocardial infarction"[tiab] OR "myocardial infarct"[tiab] OR "myocardial infarctions"[tiab] OR "heart infarction"[tiab] OR "heart infarct"[tiab] OR "heart infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab]
#2	"Acute Coronary Syndrome"[Mesh] OR "acute coronary syndrome"[tiab]
#3	"Depression"[Mesh] OR "Mental Disorders"[Mesh] OR depression[tiab] OR depressive[tiab] OR "mood disorder"[tiab] OR "mood disorders"[tiab] OR "psychiatric disorder"[tiab] OR "psychiatric disorders"[tiab]
#4	"Depression/diagnosis"[Mesh] OR mass screening[mesh] OR questionnaires[mesh] OR Interviews as Topic[Mesh] OR Psychometrics[Mesh] OR Psychiatric Status Rating Scales[Mesh] OR questionnaire[tiab] OR questionnaires[tiab] OR screening[tiab] OR screen[tiab] OR scale[tiab] OR instrument[tiab] OR instruments[tiab] OR inventory[tiab] OR BDI[tiab] OR "beck depression inventory"[tiab] OR CES-D20[tiab] OR CES-D10[tiab] OR "Center for Epidemiologic Studies Depression Scale"[tiab] OR HADS[tiab] OR "HADS-D"[tiab] OR "Hospital Anxiety and Depression Scale"[tiab] OR PHQ-9[tiab] OR "Patient Health Questionnaire-9"[tiab] OR PHQ-8[tiab] OR "Patient Health Questionnaire-8"[tiab] OR "Zung SDS"[tiab] OR "Zung Self-Rating Depression Scale"[tiab] OR "Zung Self Assessment Depression Scale"[tiab] OR "symptom checklist 20"[tiab] OR "Hopkins symptom checklist"[tiab] OR "Kessler psychological distress scale"[tiab] OR "distress questionnaire 5"[tiab] OR "geriatric depression scale"[tiab] OR "gds-15"[tiab] OR "primary care rapid evaluation of mental disorders"[tiab] OR "prime-md"[tiab] OR "duke anxiety and depression scale"[tiab] OR "inventory to diagnose depression"[tiab] OR "IDS"[tiab] OR "world health organization 5"[tiab] OR "who-5"[tiab] OR "Quick Inventory of Depressive Symptomatology"[tiab] OR promis[tiab] OR "patient reported outcomes measurement information system"[tiab]
#5	(systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "Cross-Sectional Studies"[Mesh] OR "cross sectional"[tiab]"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh]) AND English[la] AND ("2003/01/01"[Date - Publication] : "3000"[Date - Publication])
# 6	(#1 OR #2) AND #3 AND #4 AND #5

**KQ 2:**

Search Number	Search String
#1	"Myocardial Infarction"[Mesh] OR "myocardial infarction"[tiab] OR "myocardial infarct"[tiab] OR "myocardial infarctions"[tiab] OR "heart infarction"[tiab] OR "heart infarct"[tiab] OR "heart infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab]
#2	"Acute Coronary Syndrome"[Mesh] OR "acute coronary syndrome"[tiab]
#3	"Depression"[Mesh] OR "Mental Disorders"[Mesh] OR depression[tiab] OR depressive[tiab] OR "mood disorder"[tiab] OR "mood disorders"[tiab] OR "psychiatric disorder"[tiab] OR "psychiatric disorders"[tiab]
#4	"Depression/therapy"[Mesh] OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "Antidepressive Agents, Second-Generation" [Pharmacological Action] OR "Aripiprazole"[Mesh] OR "olanzapine"[Supplementary Concept] OR "Quetiapine Fumarate"[Mesh] OR "Fish Oils"[Mesh] OR "Psychotherapy"[Mesh] OR "Exercise"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Cardiovascular Diseases/rehabilitation"[Majr] OR "Hypericum"[Mesh] OR "Health Education"[Mesh] OR "Stress, Psychological"[Mesh] OR "Adaptation, Psychological"[Mesh] OR "Electroconvulsive Therapy"[Mesh] OR "continuity of patient care"[mesh] OR "Delivery of Health Care, Integrated"[Mesh] OR "Patient Care Team"[Mesh] OR "Patient Care Planning"[Mesh] OR "Disease Management"[Mesh] OR "Comprehensive Health Care"[Mesh:NoExp] OR "Patient Care Management"[Mesh:NoExp] OR "Transcranial Magnetic Stimulation"[Mesh] OR "S-Adenosylmethionine"[Mesh] OR amitriptyline[tiab] OR bupropion[tiab] OR citalopram[tiab] OR Desipramine[tiab] OR desvenlafaxine[tiab] OR Doxepin[tiab] OR duloxetine[tiab] OR fluoxetine[tiab] OR escitalopram[tiab] OR Imipramine[tiab] OR levomilnacipran[tiab] OR mirtazapine[tiab] OR nefazodone[tiab] OR paroxetine[tiab] OR Protriptyline[tiab] OR sertraline[tiab] OR trazodone[tiab] OR Trimipramine[tiab] OR venlafaxine[tiab] OR vilazodone[tiab] OR vortioxetine[tiab] OR aripiprazole[tiab] OR nortriptyline[tiab] OR olanzapine[tiab] OR quetiapine[tiab] OR Amoxapine[tiab] OR antidepressants[tiab] OR antidepressant[tiab] OR "fish oil"[tiab] OR "fish oils"[tiab] OR "fatty acid"[tiab] OR "fatty acids"[tiab] OR "omega 3"[tiab] OR "psychotherapy"[tiab] OR "behavior therapy"[tiab] OR "behavioral therapy"[tiab] OR "behaviour therapy"[tiab] OR "behavioural therapy"[tiab] OR "cognitive therapy"[tiab] OR "problem solving therapy"[tiab] OR "psychodynamic therapy"[tiab] OR mindfulness[tiab] OR "acceptance and commitment therapy"[tiab] OR "behavioral activation"[tiab] OR "behavioural activation"[tiab] OR "behavioral action"[tiab] OR "behavioural action"[tiab] OR exercise[tiab] OR psychosocial[tiab] OR "cardiac rehabilitation"[tiab] OR "physical therapy"[tiab] OR hypericum[tiab] OR "st john's wort"[tiab] OR "saint john's wort"[tiab] OR education[tiab] OR psychoeducation[tiab] OR stress[tiab] OR "collaborative care"[tiab] OR "care management"[tiab] OR "case management"[tiab] OR "disease management"[tiab] OR "enhanced care"[tiab] OR "managed care"[tiab] OR multidisciplinary[tiab] OR interprofessional[tiab] OR "team care"[tiab] OR "team consultation"[tiab] OR "team treatment"[tiab] OR "shared care"[tiab] OR "Transcranial Magnetic Stimulation"[tiab] OR "S-Adenosylmethionine"[tiab]
#5	(systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) AND English[la] AND ("2003/01/01"[Date - Publication] : "3000"[Date - Publication])
#6	(#1 OR #2) AND #3 AND #4 AND #5

## Embase® Search Strategy (August 15, 2017)

Platform: Embase.com

### KQ 1:

Search Number	Search String
#1	'heart infarction'/exp OR "myocardial infarction":ab,ti OR "myocardial infarct":ab,ti OR "myocardial infarctions":ab,ti OR "heart infarction":ab,ti OR "heart infarct":ab,ti OR "heart infarctions":ab,ti OR "heart attack":ab,ti OR "heart attacks":ab,ti
#2	'acute coronary syndrome'/exp OR 'acute coronary syndrome':ab,ti
#3	'mental disease'/exp OR depression:ab,ti OR depressive:ab,ti OR "mood disorder":ab,ti OR "mood disorders":ab,ti OR "psychiatric disorder":ab,ti OR "psychiatric disorders":ab,ti
#4	'depression'/exp/dm_di OR 'screening'/exp OR 'questionnaire'/exp OR 'interview'/exp OR 'Beck Depression Inventory'/exp OR 'Center for Epidemiological Studies Depression Scale'/exp OR 'Hospital Anxiety and Depression Scale'/exp OR 'psychometry'/exp OR 'psychological rating scale'/exp OR questionnaire:ab,ti OR questionnaires:ab,ti OR screening:ab,ti OR screen:ab,ti OR scale:ab,ti OR instrument:ab,ti OR instruments:ab,ti OR inventory:ab,ti OR BDI:ab,ti OR "beck depression inventory":ab,ti OR "CES D20":ab,ti OR "CES D10":ab,ti OR "Center for Epidemiologic Studies Depression Scale":ab,ti OR HADS:ab,ti OR "HADS D":ab,ti OR "Hospital Anxiety and Depression Scale":ab,ti OR "PHQ 9":ab,ti OR "Patient Health Questionnaire 9":ab,ti OR "PHQ 8":ab,ti OR "Patient Health Questionnaire 8":ab,ti OR "Zung SDS":ab,ti OR "Zung Self Rating Depression Scale":ab,ti OR "Zung Self Assessment Depression Scale":ab,ti OR "symptom checklist 20":ab,ti OR "Hopkins symptom checklist":ab,ti OR "Kessler psychological distress scale":ab,ti OR "distress questionnaire 5":ab,ti OR "geriatric depression scale":ab,ti OR "gds 15":ab,ti OR "primary care rapid evaluation of mental disorders":ab,ti OR "prime md":ab,ti OR "duke anxiety and depression scale":ab,ti OR "inventory to diagnose depression":ab,ti OR "world health organization 5":ab,ti OR "who 5":ab,ti OR "Quick Inventory of Depressive Symptomatology":ab,ti OR promis:ab,ti OR "patient reported outcomes measurement information system":ab,ti
#5	('evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR 'cross-sectional study'/exp OR 'cross sectional':ab,ti OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim) AND [2003-2017]/py AND [english]/lim AND [humans]/lim AND [embase]/lim NOT [medline]/lim
#6	(#1 OR #2) AND #3 AND #4 AND #5

### KQ 2:

Search Number	Search String
#1	'heart infarction'/exp OR "myocardial infarction":ab,ti OR "myocardial infarct":ab,ti OR "myocardial infarctions":ab,ti OR "heart infarction":ab,ti OR "heart infarct":ab,ti OR "heart infarctions":ab,ti OR "heart attack":ab,ti OR "heart attacks":ab,ti
#2	'acute coronary syndrome'/exp OR 'acute coronary syndrome':ab,ti
#3	'mental disease'/exp OR depression:ab,ti OR depressive:ab,ti OR "mood disorder":ab,ti OR

Search Number	Search String
	"mood disorders":ab,ti OR "psychiatric disorder":ab,ti OR "psychiatric disorders":ab,ti
#4	'depression'/exp/dm_dt,dm_th,dm_rh,dm_dm,dm_pc OR 'antidepressant agent'/exp OR 'psychotherapy'/exp OR 'exercise'/exp OR 'physical medicine'/exp OR 'heart rehabilitation'/exp OR 'Hypericum'/exp OR 'fish oil'/exp OR 'omega 3 fatty acid'/exp OR 'health education'/exp OR 'mental stress'/exp OR 'adaptive behavior'/exp OR 'electroconvulsive therapy'/exp OR 'transcranial magnetic stimulation'/exp OR 's adenosylmethionine'/exp OR bupropion:ab,ti OR citalopram:ab,ti OR desvenlafaxine:ab,ti OR duloxetine:ab,ti OR fluoxetine:ab,ti OR escitalopram:ab,ti OR levomilnacipran:ab,ti OR mirtazapine:ab,ti OR nefazodone:ab,ti OR paroxetine:ab,ti OR sertraline:ab,ti OR trazodone:ab,ti OR venlafaxine:ab,ti OR vilazodone:ab,ti OR vortioxetine:ab,ti OR amitriptyline:ab,ti OR Desipramine:ab,ti OR Doxepin:ab,ti OR Imipramine:ab,ti OR Protriptyline:ab,ti OR Trimipramine:ab,ti OR nortriptyline:ab,ti OR Amoxapine:ab,ti OR antidepressants:ab,ti OR antidepressant:ab,ti OR "fish oil":ab,ti OR "fish oils":ab,ti OR "fatty acid":ab,ti OR "fatty acids":ab,ti OR "omega 3":ab,ti OR "psychotherapy":ab,ti OR "behavior therapy":ab,ti OR "behavioral therapy":ab,ti OR "cognitive therapy":ab,ti OR "problem solving therapy":ab,ti OR "psychodynamic therapy":ab,ti OR mindfulness:ab,ti OR "acceptance and commitment therapy":ab,ti OR "reminiscence therapy":ab,ti OR "behavioral action":ab,ti OR "compassion-based therapy":ab,ti OR exercise:ab,ti OR psychosocial:ab,ti OR "cardiac rehabilitation":ab,ti OR "physical therapy":ab,ti OR hypericum:ab,ti OR "st john* wort":ab,ti OR "saint john* wort":ab,ti OR education:ab,ti OR psychoeducation:ab,ti OR stress:ab,ti OR "collaborative care":ab,ti OR "Transcranial Magnetic Stimulation":ab,ti OR "S Adenosylmethionine":ab,ti
#5	('evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross overs':ab,ti OR placebo*:ab,ti OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim) AND [2003-2017]/py AND [english]/lim AND [humans]/lim AND [embase]/lim NOT [medline]/lim
#6	(#1 OR #2) AND #3 AND #4 AND #5

## Cochrane Search Strategy (August 15, 2017)

Platform: Wiley

Database searched: Cochrane Database of Systematic Reviews

Search Number	Search String
#1	[mh "Myocardial Infarction"]
#2	"myocardial infarction":ab,ti OR "myocardial infarct":ab,ti OR "myocardial infarctions":ab,ti OR "heart infarction":ab,ti OR "heart infarct":ab,ti OR "heart infarctions":ab,ti OR "heart attack":ab,ti OR "heart attacks":ab,ti
#3	#1 OR #2
#4	[mh "Acute Coronary Syndrome"]
#5	"acute coronary syndrome":ab,ti
#6	#4 OR #5
#7	[mh Depression] OR [mh "Mental Disorders"]
#8	depression:ab,ti OR depressive:ab,ti OR "mood disorder":ab,ti OR "mood disorders":ab,ti OR "psychiatric disorder":ab,ti OR "psychiatric disorders":ab,ti
#9	#7 OR #8

<b>Search Number</b>	<b>Search String</b>
#10	(#3 OR #6) AND #9

## PsycINFO Search Strategy (August 15, 2017)

### KQ 1:

Search Number	Search String
#1	DE "Myocardial Infarctions" OR TI ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" ) OR AB ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" )
#2	TI ("acute coronary syndrome") OR AB ("acute coronary syndrome")
#3	(DE "Depression (Emotion)") OR (DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression") OR TI ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" ) OR AB ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" )
#4	DE "Screening" OR DE "Screening Tests" OR DE "Psychological Screening Inventory" OR DE "Rating Scales" OR DE "Inventories" OR DE "Psychological Assessment" OR DE "Psychodiagnosis" OR DE "Psychodiagnostic Interview" OR DE "Questionnaires" OR DE "General Health Questionnaire" OR ((DE "Beck Depression Inventory") OR (DE "Zungs Self Rating Depression Scale")) OR TI (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR inventory OR BDI OR "beck depression inventory" OR CES-D20 OR CES-D10 OR "Center for Epidemiologic Studies Depression Scale" OR HADS OR HADS-D OR "Hospital Anxiety and Depression Scale" OR PHQ-9 OR PHQ-8 OR "Patient Health Questionnaire" OR "Zung SDS" OR "Zung Self-Rating Depression Scale" OR "Zung Self Assessment Depression Scale" OR "symptom checklist 20" OR "Hopkins symptom checklist" OR "Kessler psychological distress scale" OR "distress questionnaire 5" OR "geriatric depression scale" OR "gds-15" OR "primary care rapid evaluation of mental disorders" OR "prime-md" OR "duke anxiety and depression scale" OR "inventory to diagnose depression" OR "world health organization 5" OR "who-5" OR "Quick Inventory of Depressive Symptomatology" OR promis OR "patient reported outcomes measurement information system") OR AB (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR inventory OR BDI OR "beck depression inventory" OR CES-D20 OR CES-D10 OR "Center for Epidemiologic Studies Depression Scale" OR HADS OR HADS-D OR "Hospital Anxiety and Depression Scale" OR PHQ-9 OR PHQ-8 OR "Patient Health Questionnaire" OR "Zung SDS" OR "Zung Self-Rating Depression Scale" OR "Zung Self Assessment Depression Scale" OR "symptom checklist 20" OR "Hopkins symptom checklist" OR "Kessler psychological distress scale" OR "distress questionnaire 5" OR "geriatric depression scale" OR "gds-15" OR OR "primary care rapid evaluation of mental disorders" OR "prime-md" OR "duke anxiety and depression scale" OR "inventory to diagnose depression" OR "world health organization 5" OR "who-5" OR "Quick Inventory of Depressive Symptomatology" OR promis OR "patient reported outcomes measurement information system")
#5	ZC "meta analysis" OR ZC "systematic review" OR DE "Meta Analysis" OR TI ("meta-analysis" OR "meta-analyses" OR "systematic review" OR "systematic reviews") OR AB ("meta-analysis" OR "meta-analyses" OR "systematic review" OR "systematic reviews") OR ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "prospective study" OR ZC "retrospective study" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR TI ("evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study") OR AB ("evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies")



Search Number	Search String
	OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study") AND (ZZ "journal article")
#6	(S1 OR S2) AND S3 AND S4 AND S5 Limits: English, 2003 – present, Human

**KQ 2:**

Search Number	Search String
#1	DE "Myocardial Infarctions" OR TI ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" ) OR AB ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" )
#2	TI ("acute coronary syndrome") OR AB ("acute coronary syndrome")
#3	(DE "Depression (Emotion)") OR (DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression") OR TI ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" ) OR AB ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" )
#4	DE "Antidepressant Drugs" OR DE "Bupropion" OR DE "Citalopram" OR DE "Fluoxetine" OR DE "Fluvoxamine" OR DE "Iproniazid" OR DE "Isocarboxazid" OR DE "Lithium Carbonate" OR DE "Methylphenidate" OR DE "Mianserin" OR DE "Moclobemide" OR DE "Molindone" OR DE "Nefazodone" OR DE "Nialamide" OR DE "Nomifensine" OR DE "Paroxetine" OR DE "Phenelzine" OR DE "Pheniprazine" OR DE "Pipradrol" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Sertraline" OR DE "Sulpiride" OR DE "Tranlycypromine" OR DE "Trazodone" OR DE "Tricyclic Antidepressant Drugs" OR DE "Venlafaxine" OR DE "Zimeldine" OR DE "Psychotherapy" OR DE "Adlerian Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Affirmative Therapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Brief Relational Therapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Conversion Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Geriatric Psychotherapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Network Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Rational Emotive Behavior Therapy" OR DE "Reality Therapy" OR DE "Relationship Therapy" OR DE "Solution Focused Therapy" OR DE "Supportive Psychotherapy" OR DE "Transactional Analysis" OR DE "Exercise" OR DE "Aerobic Exercise" OR DE "Weightlifting" OR DE "Yoga" OR DE "Physical Therapy" OR DE "Rehabilitation" OR DE "Hypericum Perforatum" OR DE "Health Education" OR DE "Stress" OR DE "Psychological Stress" OR DE "Stress and Coping Measures" OR DE "Electroconvulsive Shock Therapy" OR DE "Continuum of Care" OR DE "Transcranial Magnetic Stimulation" OR TI ( bupropion OR citalopram OR desvenlafaxine OR duloxetine OR fluoxetine OR escitalopram OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR amitriptyline OR Desipramine OR Doxepin OR Imipramine OR Protriptyline OR Trimipramine OR nortriptyline OR Amoxapine OR antidepressants OR

Search Number	Search String
	antidepressant OR "psychotherapy" OR "behavior therapy" OR "behavioral therapy" OR "cognitive therapy" OR "problem solving therapy" OR "psychodynamic therapy" OR mindfulness OR "acceptance and commitment therapy" OR "reminiscence therapy" OR "behavioral action" OR "compassion-based therapy" OR exercise OR psychosocial OR "cardiac rehabilitation" OR "physical therapy" OR hypericum OR "st john's wort" OR "saint john's wort" OR education OR psychoeducation OR stress OR "collaborative care" OR "Transcranial Magnetic Stimulation" OR "S-Adenosylmethionine" OR "fish oil" OR "fish oils" OR "fatty acid" OR "fatty acids" OR "omega 3") OR AB ( bupropion OR citalopram OR desvenlafaxine OR duloxetine OR fluoxetine OR escitalopram OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR amitriptyline OR Desipramine OR Doxepin OR Imipramine OR Protriptyline OR Trimipramine OR nortriptyline OR Amoxapine OR antidepressants OR antidepressant OR "psychotherapy" OR "behavior therapy" OR "behavioral therapy" OR "cognitive therapy" OR "problem solving therapy" OR "psychodynamic therapy" OR mindfulness OR "acceptance and commitment therapy" OR "reminiscence therapy" OR "behavioral action" OR "compassion-based therapy" OR exercise OR psychosocial OR "cardiac rehabilitation" OR "physical therapy" OR hypericum OR "st john's wort" OR "saint john's wort" OR education OR psychoeducation OR stress OR "collaborative care" OR "Transcranial Magnetic Stimulation" OR "S-Adenosylmethionine" OR "fish oil" OR "fish oils" OR "fatty acid" OR "fatty acids" OR "omega 3")
#5	ZC "treatment outcome/clinical trial" OR DE "Clinical Trials" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials) OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials) OR ZC "meta analysis" OR ZC "systematic review" OR DE "Meta Analysis" OR TI (OR "meta-analysis" OR "meta-analyses" OR "systematic review" OR "systematic reviews) OR AB (OR "meta-analysis" OR "meta-analyses" OR "systematic review" OR "systematic reviews) AND (ZZ "journal article")
#6	(S1 OR S2) AND S3 AND S4 AND S5 Limits: English, 2003 – present, Human

## CINAHL Search Strategy (August 15, 2017)

### KQ 1:

Search Number	Search String
#1	(MH "Myocardial Infarction+") OR TI ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" ) OR AB ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" )
#2	(MH "Acute Coronary Syndrome") OR TI "Acute Coronary Syndrome" OR AB "Acute Coronary Syndrome"
#3	(MH "Affective Disorders+") OR TI ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" ) OR AB ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" )
#4	(MH "Depression+/DI") OR (MH "Health Screening+") OR (MH "Questionnaires+") OR (MH "Interviews+") OR (MH "Psychometrics") OR (MH "Psychological Tests+") OR (MH "Behavior Rating Scales") OR (MH "Scales") OR (MH "Beck Depression Inventory, Revised Edition") OR (MH "Center for Epidemiological Studies Depression Scale") OR (MH "Geriatric Depression Scale") OR TI (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR inventory OR BDI OR "beck

Search Number	Search String
	depression inventory" OR CES-D20 OR CES-D10 OR "Center for Epidemiologic Studies Depression Scale" OR HADS OR HADS-D OR "Hospital Anxiety and Depression Scale" OR PHQ-9 OR PHQ-8 OR "Patient Health Questionnaire" OR "Zung SDS" OR "Zung Self-Rating Depression Scale" OR "Zung Self Assessment Depression Scale" OR "symptom checklist 20" OR "Hopkins symptom checklist" OR "Kessler psychological distress scale" OR "distress questionnaire 5" OR "geriatric depression scale" OR "gds-15" OR "primary care rapid evaluation of mental disorders" OR "prime-md" OR "duke anxiety and depression scale" OR "inventory to diagnose depression" OR "world health organization 5" OR "who-5" OR "Quick Inventory of Depressive Symptomatology" OR promis OR "patient reported outcomes measurement information system") OR AB (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR inventory OR BDI OR "beck depression inventory" OR CES-D20 OR CES-D10 OR "Center for Epidemiologic Studies Depression Scale" OR HADS OR HADS-D OR "Hospital Anxiety and Depression Scale" OR PHQ-9 OR PHQ-8 OR "Patient Health Questionnaire" OR "Zung SDS" OR "Zung Self-Rating Depression Scale" OR "Zung Self Assessment Depression Scale" OR "symptom checklist 20" OR "Hopkins symptom checklist" OR "Kessler psychological distress scale" OR "distress questionnaire 5" OR "geriatric depression scale" OR "gds-15" OR OR "primary care rapid evaluation of mental disorders" OR "prime-md" OR "duke anxiety and depression scale" OR "inventory to diagnose depression" OR "world health organization 5" OR "who-5" OR "Quick Inventory of Depressive Symptomatology" OR promis OR "patient reported outcomes measurement information system")
#5	MH "Systematic Review" OR MH "Meta Analysis" OR TI ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses") OR AB ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses") OR (MH "Retrospective Design") OR (MH "Empirical Research") OR (MH "Nonexperimental Studies+") OR TI ("evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study") OR AB ("evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study") AND (ZT "journal article")
#6	(S1 OR S2) AND S3 AND S4 AND S5

**KQ 2:**

Search Number	Search String
#1	(MH "Myocardial Infarction+") OR TI ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" ) OR AB ( "myocardial infarction" OR "myocardial infarct" OR "myocardial infarctions" OR "heart infarction" OR "heart infarct" OR "heart infarctions" OR "heart attack" OR "heart attacks" )
#2	(MH "Acute Coronary Syndrome") OR TI "Acute Coronary Syndrome" OR AB "Acute Coronary Syndrome"
#3	(MH "Affective Disorders+") OR TI ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" ) OR AB ( depression OR depressive OR "mood disorder" OR "mood disorders" OR "psychiatric disorder" OR "psychiatric disorders" )
#4	(MH "Depression+/TH") OR (MH "Antidepressive Agents+") OR (MH "Psychotherapy+") OR (MH "Exercise+") OR (MH "Physical Therapy+") OR (MH "Rehabilitation, Cardiac+") OR (MH "St. John's Wort") OR (MH "Health Education+") OR (MH "Adaptation, Psychological+") OR (MH "Stress Management") OR (MH "Electroconvulsive Therapy") OR (MH "Continuity of Patient Care+") OR (MH "Fish Oils+") OR (MH "Transcranial Magnetic

Search Number	Search String
	Stimulation") OR (MH "S-Adenosylmethionine") OR TI ( bupropion OR citalopram OR desvenlafaxine OR duloxetine OR fluoxetine OR escitalopram OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR amitriptyline OR Desipramine OR Doxepin OR Imipramine OR Protriptyline OR Trimipramine OR nortriptyline OR Amoxapine OR antidepressants OR antidepressant OR "psychotherapy" OR "behavior therapy" OR "behavioral therapy" OR "cognitive therapy" OR "problem solving therapy" OR "psychodynamic therapy" OR mindfulness OR "acceptance and commitment therapy" OR "reminiscence therapy" OR "behavioral action" OR "compassion-based therapy" OR exercise OR psychosocial OR "cardiac rehabilitation" OR "physical therapy" OR hypericum OR "st john's wort" OR "saint john's wort" OR education OR psychoeducation OR stress OR "collaborative care" OR "Transcranial Magnetic Stimulation" OR "S-Adenosylmethionine" OR "fish oil" OR "fish oils" OR "fatty acid" OR "fatty acids" OR "omega 3") OR AB ( bupropion OR citalopram OR desvenlafaxine OR duloxetine OR fluoxetine OR escitalopram OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR amitriptyline OR Desipramine OR Doxepin OR Imipramine OR Protriptyline OR Trimipramine OR nortriptyline OR Amoxapine OR antidepressants OR antidepressant OR "psychotherapy" OR "behavior therapy" OR "behavioral therapy" OR "cognitive therapy" OR "problem solving therapy" OR "psychodynamic therapy" OR mindfulness OR "acceptance and commitment therapy" OR "reminiscence therapy" OR "behavioral action" OR "compassion-based therapy" OR exercise OR psychosocial OR "cardiac rehabilitation" OR "physical therapy" OR hypericum OR "st john's wort" OR "saint john's wort" OR education OR psychoeducation OR stress OR "collaborative care" OR "Transcranial Magnetic Stimulation" OR "S-Adenosylmethionine" OR "fish oil" OR "fish oils" OR "fatty acid" OR "fatty acids" OR "omega 3")
#5	(ZT "randomized controlled trial") OR MH "Randomized Controlled Trials" OR TI ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomized" OR "randomization" OR "randomization" OR "placebo" OR "randomly" OR "trial" OR "groups") OR AB ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomized" OR "randomization" OR "randomization" OR "placebo" OR "randomly" OR "trial" OR "groups") OR MH "Systematic Review" OR MH "Meta Analysis" OR TI ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses") OR AB ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses") OR (MH "Empirical Research") AND (ZT "journal article")
#6	(S1 OR S2) AND S3 AND S4 AND S5

## Gray Literature Search

### ClinicalTrials.gov (May 9, 2017):

Search Number	Search String
Search Terms	("Myocardial Infarction" OR "myocardial infarctions" OR "heart attack" OR "heart attacks" OR "Acute Coronary Syndrome") AND (Depression OR "Mental Disorders" OR depressive OR "mood disorder" OR "mood disorders" OR psychiatric)
Recruitment	Completed studies

Total number of results: 64

# Appendix C. Data Abstraction Elements

## Study Characteristics

- Study Identifiers
  - Study Name or Acronym
  - NCT number or other trial registry identifier
  - Last name of first author
- Additional Articles Used in This Abstraction
- Purpose of the Study
- Key Question Applicability (Select all that apply):
  - KQ1, KQ2
- Study Sites:
  - Single center, Multicenter, Unclear/Not reported
- Geographic Location (Select all that apply):
  - US, Canada, UK/Europe, Latin America, Middle East (includes Israel), Asia, Africa, Australia/New Zealand, Unclear/Not reported
- Study Design:
  - Observational
  - RCT
  - Cluster RCT
- Funding Source (Select all that apply):
  - Government, Industry, Non-government/non-industry, Unclear/Not reported
- Setting (Select all that apply):
  - Outpatient, Inpatient, Other (specify), Unclear/Not reported
- Study Enrollment/Study Completion
  - Is the entire population of the study relevant to this review, or only a portion?:
    - Entire study population, Only a portion of the study population
  - For the relevant population:
    - N enrolled/included
    - N completed (those who completed the final outcome assessment of the primary study publication)
  - Data reported for any subgroups of interest? (Select all that apply):
    - Age (older adults  $\geq 65$  years] versus adults younger than 65 years of age), Race/ethnicity, Sex, In- vs outpatient, None
  - Is the study population entirely composed of a population that falls into a subgroup of interest?: (Select all that apply)
    - No, Yes
    - If yes, specify the subgroup category.
- Cardiac-related inclusion criteria used in the study
- Comments

## Baseline Characteristics

- Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, Arm 4, and Arm 5 (as applicable)

- Number of Patients (N; and for individual arms, %)
- Age in Years
  - Mean
  - Median
  - Standard Deviation
  - Min
  - Max
  - 25% IQR
  - 75% IQR
  - Categorical (describe)
  - Other, specify
- Proportion of Women and Men (N and %)
- Race/Ethnicity (N and %)
  - Hispanic or Latino
  - Black/African American
  - American Indian or Alaska Native
  - Asian
  - Native Hawaiian or Pacific Islander
  - White
  - Multiracial
  - Other (specify)
  - Unknown
- Socioeconomic Factors (Indicate elements reported and describe data)
  - Insurance Status
  - Income Level
  - Social Class
  - Level of Education
  - Other
  - Unclear or NR
- Depression Severity (Indicate elements reported and describe data)
  - PHQ-9 Continuous Measure
  - Other Continuous Measures
  - Categorical Measures
  - Unclear or NR
- Cardiac Severity (Indicate elements reported and describe data)
  - Type of ACS Event
  - Functional Class
  - LV function
  - Unclear or NR
- Renal Function
  - If reported - list measure and describe data
  - Unclear or NR
- Comments

## **KQ 1 Intervention Characteristics and Outcomes**

- For Each Tool of Interest Assessed, Specify:
  - Tool name

- Number of questions
- Mode of administration
- N patients assessed
- Criterion Standard (Specify the following):
  - Tool/ type
  - N patients assessed
  - Mode of administration
- Prevalence of Post-ACS Depression in the Population
- Timing of Screening
- Threshold(s) Considered
- Record the following for selected thresholds and populations assessed:
  - Major Depressive Disorder
    - Chosen threshold
    - Threshold rationale
    - Sensitivity (%)
    - Sensitivity (%)
    - PPV (%)
    - NPV (%)
    - AUC
    - p value
  - Major Depressive Disorder and Dysthymic Disorder
    - Chosen threshold
    - Threshold rationale
    - Sensitivity (%)
    - Sensitivity (%)
    - PPV (%)
    - NPV (%)
    - AUC
    - p value
  - Major Depressive Disorder (MDD), MDD and Dysthymic Disorder, Minor Depressive Disorder, Partial Remission of MDD, or Dysthymic Disorder
    - Chosen threshold
    - Threshold rationale
    - Sensitivity (%)
    - Sensitivity (%)
    - PPV (%)
    - NPV (%)
    - AUC
    - p value

## **KQ 2 Intervention Characteristics**

- High Level Intervention/Comparison (Select all that apply):
  - KQ 2: Medical therapy vs Medical therapy
  - KQ 2: Medical therapy vs Psychotherapy
  - KQ 2: Medical therapy vs Other treatment
  - KQ 2: Medical therapy vs Enhanced care delivery

- KQ 2: Medical therapy vs Usual care
- KQ 2: Psychotherapy vs Psychotherapy
- KQ 2: Psychotherapy vs Other treatment
- KQ 2: Psychotherapy vs Enhanced care delivery
- KQ 2: Psychotherapy vs Usual care
- KQ 2: Other treatment vs Other treatment
- KQ 2: Other treatment vs Enhanced care delivery
- KQ 2: Other treatment vs Usual care
- KQ 2: Enhanced care delivery vs Enhanced care delivery
- KQ 2: Enhanced care delivery vs Usual care
- KQ 2: Combination of categories vs a single category or another combination (describe)
- If applicable, describe the Usual care intervention
- Intervention Descriptors (For each arm)
  - Describe the intervention received by the patient group.
  - Categorize the Depression-Focused Intervention (Select all that apply):
    - Medical Therapy
    - Psychotherapy
    - Enhanced Care Delivery
    - Other treatments (e.g., aerobic exercise, fish oils) - specify
    - Usual Care
  - Provide a Descriptive Label for the Depression-Focused Intervention
- Comments

## **KQ 2 Outcomes**

- Select the Category of Outcome Reported:
  - Clinical outcomes, Quality of Life, Cost-effectiveness, Utilization of healthcare services, Discontinuation of depression intervention due to adverse effects, Adverse effects of treatment
- Select the Specific Outcome Reported:
  - Clinical outcomes
    - Total mortality
    - Depression related outcomes: Response or remission of depressive symptoms using validated continuous or categorical measures
    - Cardiac mortality
    - Repeat ACS event (repeat MI or unstable angina)
    - Resuscitated arrest
    - Stroke
    - Arrhythmias
    - Revascularization
    - MACE composite
  - Quality of Life
  - Cost-effectiveness
  - Utilization of healthcare services
    - Cardiac medication adherence
    - Readmission rates due to cardiac and non-cardiac reasons



- Emergency room visits: all visits
    - Emergency room visits: cardiac-related
    - Emergency room visits: psychiatric-related
    - Hospitalization
  - Discontinuation of depression intervention due to adverse effects
  - Adverse effects of treatment
    - Weight gain
    - GI bleeding
    - Arrhythmias
    - Suicidal ideation, behaviors, or attempts
- Describe the outcome measure represented on this form
- Categorize timing of the outcome:
  - During hospitalization/at discharge
  - Within 30 days of hospitalization for an acute ACS event
  - Within 3 months of hospitalization for an acute ACS event
  - Beyond 3 months of hospitalization for an acute ACS event
  - Unclear
- Record the specific timepoint for this outcome
- Select outcome type (Continuous or Categorical)
  - If Continuous:
    - Label intervention
    - Label comparator
    - Record available baseline data:
      - Intervention
        - N
        - Baseline Average (mean, median, NR)
        - Baseline Variability (SD, IQR, Range, SE, NR)
      - Comparator
        - N
        - Baseline Average
        - Baseline Variability
        - NR
      - NR
    - Record available follow-up data:
      - Intervention
        - N analyzed
        - Average (mean at follow-up, median at follow-up, within group difference, NR)
        - Variability (SD, IQR, Range, SE, 95% CI, NR)
      - Comparator
        - N analyzed
        - Average
        - Variability
        - NR
      - Effect Estimate
        - N analyzed

- Effect size (mean difference, regression coefficient, Cohen's d, Hedges' g, NR)
    - Variability (95% CI, SE, value, Other, NR)
  - If Categorical
    - Label intervention
    - Label comparator
    - Intervention
      - N with event
      - N denominator
      - NR
    - Comparator
      - N with event
      - N denominator
      - NR
    - Effect Estimate
      - Between group effect (OR, RR, HR, NR)
      - Variance (95% CI, SE, p value, NR)
- Comments

## Quality

- Applicable KQ (select one):
  - KQ 1 (QUADAS-2 Tool)
  - KQ 2 (Cochrane Tool)
- If KQ 1, rate each individual element as Yes/No/Unclear, then rate each domain as Low/High/Unclear risk of bias.
  - Patient Selection
    - Individual Elements:
      - Was a consecutive or random sample of patients enrolled?
      - Was a case-control design avoided?
      - Did the study avoid inappropriate exclusions?
    - Domain summary: Could the selection of patients have introduced bias? (Indicate risk: Low/High/Unclear)
  - Index Tests
    - Individual Elements:
      - Were the index test results interpreted without knowledge of the reference standard?
      - If a threshold was used, was it pre-specified?
    - Domain summary: Could the conduct or interpretation of the index test have introduced bias? (Indicate risk: Low/High/Unclear)
  - Reference Standards
    - Individual Elements:
      - Is the reference standard likely to correctly classify the target condition?
      - Were the reference standard results interpreted without knowledge of the results of the index test?

- Domain summary: Could the reference standard, its conduct, or its interpretation have introduced bias? (Indicate risk: Low/High/Unclear)
    - Flow and Timing
      - Individual Elements:
        - Was there an appropriate interval between index test(s) and reference standard?
        - Did all patients receive a reference standard?
        - Did all patients receive the same reference standard?
        - Were all patients included in the analysis?
      - Domain summary: Could the patient flow have introduced bias? (Indicate risk: Low/High/Unclear)
- If KQ 2, rate each domain item listed as Low/High/Unclear risk and describe:
  - Random sequence generation
  - Allocation concealment
  - Blinding of participants and personnel
  - Blinding of outcome assessment
  - Incomplete outcome data
  - Selective reporting
  - Other Bias
- If KQ2, rate the overall study risk of bias (Good/Fair/Poor)
  - **Good** (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
  - **Fair**. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
  - **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.
  - **If the study is rated as “Fair” or “Poor,” provide rationale.**
- **Outcome-specific quality rating**
  - **Should any of the outcomes abstracted for this study should be assigned a quality rating different from the overall study rating? (No/Yes)**
    - **If yes, provide the outcome(s), rating(s), and rationale(s).**
- **Comments**

## Applicability

Use the PICOS format to identify specific issues, if any, which may limit the applicability of the study.

- Population (P)

- Narrow eligibility criteria and exclusion of those with comorbidities
- More complex patients than typical of the community
- Run-in period with high exclusion rate for non-adherence or side effects
- Intervention (I)
  - Diagnostic tools used differently than as recommended or commonly used in practice
  - Dosing not reflective of current practice
  - Co-interventions that are likely to modify the effectiveness of therapy
  - Highly selected intervention team or level of training/proficiency not widely available
  - Follow-up not reflective of current practice
- Comparator (C)
  - Diagnostic tools used differently than as recommended or commonly used in practice
  - Comparator unclear
  - Inadequate comparison therapy or use of a substandard alternative therapy
- Outcomes (O)
  - Composite outcomes that mix outcomes of different significance
  - Short-term follow-up
  - Surrogate outcomes
- Setting (S)
  - Level of care different from that in the community
- Any other concerns regarding the applicability of this study? (Yes/No)
  - If yes, describe.
- Comments

## Appendix D. List of Included Studies

Bambauer, Kara Zivin, Locke, Steven E, Aupont, Onesky, Mullan, Mariquita G, McLaughlin, Thomas J. Using the Hospital Anxiety and Depression Scale to screen for depression in cardiac patients. *General Hospital Psychiatry* 2005;27(4):275-284. DOI: 10.1016/j.genhosppsy.2005.03.002. PMID: 2005-08290-009.

Banankhah, SK, Friedmann, E, Thomas, S. Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol* 2015;7(4):215-23. DOI: 10.4330/wjc.v7.i4.215. PMID: 25914790.

Berkman, LF, Blumenthal, J, Burg, M, Carney, RM, Catellier, D, Cowan, MJ, Czajkowski, SM, DeBusk, R, Hosking, J, Jaffe, A, Kaufmann, PG, Mitchell, P, Norman, J, Powell, LH, Raczynski, JM, Schneiderman, N. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) Randomized Trial. *Jama* 2003;289(23):3106-16. DOI: 10.1001/jama.289.23.3106. PMID: 12813116.

Bunevicius, A, Staniute, M, Brozaitiene, J, Bunevicius, R. Diagnostic accuracy of self-rating scales for screening of depression in coronary artery disease patients. *J Psychosom Res* 2012;72(1):22-5. DOI: 10.1016/j.jpsychores.2011.10.006. PMID: 22200518.

Carney, RM, Blumenthal, JA, Freedland, KE, Youngblood, M, Veith, RC, Burg, MM, Cornell, C, Saab, PG, Kaufmann, PG, Czajkowski, SM, Jaffe, AS. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICH) study. *Psychosom Med* 2004;66(4):466-74. DOI: 10.1097/01.psy.0000133362.75075.a6. PMID: 15272090.

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## Appendix E. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

### **Not a full publication, article retracted/withdrawn, or full publication not available**

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## Appendix F. Key to Included Primary and Companion Articles

\*Companion articles marked with an asterisk (n=3) did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

**Appendix Table F1. Key to included primary and companion articles**

Study Designation	Primary Abstracted Article	Companion Articles
CODIACS (Comparison of Depression Interventions after Acute Coronary Syndrome)	Davidson, 2013 <sup>1</sup>	*Whang, 2012 <sup>2</sup>
COPEs (Coronary Patients Evaluation Study)	Davidson, 2010 <sup>3</sup>	Ye, 2014 <sup>4</sup> Kronish, 2012 <sup>5</sup>
ENRICHd (Enhancing Recovery In Coronary Heart Disease)	Berkman, 2003 <sup>6</sup>	Banankhah, 2015 <sup>7</sup> Roest, 2013 <sup>8</sup> Saab, 2009 <sup>9</sup> Cowan, 2008 <sup>10</sup> Mendes de Leon, 2006 <sup>11</sup> Schneiderman, 2004 <sup>12</sup> Carney, 2004 <sup>13</sup> *ENRICHd investigators, 2001 <sup>14</sup>
ESCAPE (Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions)	Frasure-Smith, 2008 <sup>15</sup>	None
MIND-IT (Myocardial INfarction and Depression–Intervention Trial)	van Melle, 2007 <sup>16</sup>	Zuidersma, 2013 <sup>17</sup> *van den Brink, 2002 <sup>18</sup>
None	Bambauer, 2005 <sup>19</sup>	None
None	Bunevicius, 2012 <sup>20</sup>	None
None	Huffman, 2006 <sup>21</sup>	Huffman, 2010 <sup>22</sup>
None	Low, 2007 <sup>23</sup>	None
None	McGuire, 2013 <sup>24</sup>	None

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## Appendix G. Characteristics of Included Studies

**Appendix Table G1. Characteristics of included studies for KQ 1**

<b>Study Companion Article</b>	<b>Study Design Location Setting</b>	<b>Patient Demographics</b>	<b>Purpose</b>	<b>Criterion Standard versus Tool(s) Assessed</b>	<b>Diagnostic Accuracy Measures</b>
Bambauer, 2005 <sup>1</sup>	Observational U.S. Inpatient	N completed: 79 Mean age: Arm 1: 60.7 (SD 9.8) Arm 2: 59.9 (SD 10.2) % Female: Arm 1: 35% Arm 2: 31%	To determine the effects of providing post-ACS depression care on depressive symptoms and healthcare costs.	<u>Criterion standard</u> PRIME-MD, DSM-IV  <u>Tool assessed</u> Hospital Anxiety and Depression Scale-14 (HADS-14)	PPV
Bunevicius, 2012 <sup>2</sup>	Observational U.K./Europe Cardiac rehabilitation clinic	N completed: 522 Mean age: 58 % Female: 28%	To evaluate the internal consistency and psychometric properties of the HADS and the BDI-II for screening of major depressive episodes in patients with coronary artery disease undergoing rehabilitation.	<u>Criterion standard</u> Structured Mini International Neuropsychiatric Interview, DSM-IV  <u>Tools assessed</u> Hospital Anxiety and Depression Scales: HADS-14 HADS-Anxiety Subscale HADS-Depression Subscale BDI-II	Sensitivity Specificity  PPV NPV AUC
Frasure-Smith, 2008 <sup>3</sup>	Observational Canada Inpatient	N completed: 804 Mean age: 60 (SD 10.6) % Female: 19.3%	To assess the 2-year cardiac prognostic importance of the DSM-IV–based diagnoses of major depressive disorder and generalized anxiety disorder and self-report measures of anxiety and depression and their co-occurrence.	<u>Criterion standard</u> Structured Clinical Interview for DSM-IV  <u>Tools assessed</u> HADS-Anxiety Subscale BDI-II	Sensitivity Specificity  AUC
Huffman, 2006 <sup>4</sup>  <u>Companion</u> Huffman, 2010 <sup>5</sup>	Observational U.S. Inpatient	N completed: 131 Mean age: 62.2 (SD 12.6) % Female: 20%	To determine the ability of 3 questions from the BDI-II to detect major depressive disorder in a cohort of patients hospitalized for acute myocardial infarction.	<u>Criterion standard</u> Structured Clinical Interview for DSM-IV-TR Axis I Disorders  <u>Tool assessed</u> BDI-II	Sensitivity Specificity  PPV NPV AUC

Study Companion Article	Study Design Location Setting	Patient Demographics	Purpose	Criterion Standard versus Tool(s) Assessed	Diagnostic Accuracy Measures
Low, 2007 <sup>6</sup>	Observational Canada Inpatient	N completed: 119 Mean age: 62.9 (SD 11.6) % Female: 25%	To examine the sensitivity and specificity for participants' scores on 2 widely-used depression inventories with older adults relative to the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, as well as recommend appropriate cut scores for the 2 measures for identifying post-myocardial infarction or unstable angina patients with depression.	<u>Criterion standard</u> PRIME-MD, DSM-IV  <u>Tools assessed</u> Geriatric Depression Scale BDI-II	Sensitivity Specificity  PPV NPV AUC
McGuire, 2013 <sup>7</sup>	Observational U.S. Inpatient	N completed: 100 Mean age: Depressed: 56.6 (SD 13.4) Nondepressed: 65.52 (SD 11.2) % Female: 31%	To evaluate nurse-administered versions of the Patient Health Questionnaire for depression screening in patients hospitalized for acute coronary syndrome.	<u>Criterion standard</u> Depression interview Structured Hamilton Scale, DSM-IV  <u>Tools assessed</u> Patient Health Questionnaire: PHQ-2 PHQ-9 PHQ-10	Sensitivity Specificity  PPV NPV AUC

Abbreviations: ACS=acute coronary syndrome; AUC=area under the curve; BDI=Beck Depression Inventory; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; HADS=Hospital Anxiety and Depression Scale; KQ=key question; NPV=negative predicted value; PHQ=Patient Health Questionnaire; PPV=positive predicted value; PRIME-MD=Primary Care Evaluation of Mental Disorders; SD=standard deviation.

**Appendix Table G2. Characteristics of included studies for KQ 2**

Study Acronym Companion Article(s)	Study Design Location Patient Demographics Quality Rating	Purpose Criteria for Diagnosis of Depression	Intervention versus Comparator	Outcomes Subgroups
Berkman, 2003 <sup>8</sup>  ENRICH  <u>Companions</u> Banankhah, 2015 <sup>9</sup> Roest, 2013 <sup>10</sup> Saab, 2009 <sup>11</sup> Cowan, 2008 <sup>12</sup> Mendes de Leon, 2006 <sup>13</sup> Schneiderman, 2004 <sup>14</sup> Carney, 2004 <sup>15</sup>	RCT  U.S.  N enrolled: 2,481 Mean age: Arm 1: 61 (SD 12.5) Arm 2: 61 (SD 12.5) % Female: Arm 1: 44% Arm 2: 43%  Good quality	<u>Purpose</u> To determine whether mortality and recurrent infarction are reduced by treatment of depression and low perceived social support with CBT supplemented with an SSRI antidepressant when indicated, in patients enrolled within 28 days post-MI.  <u>Diagnosis</u> The Depression Interview and Structured Hamilton (DISH) was used to diagnose current depressive episodes according to DSM-IV) criteria. The DISH also yields a depression severity score on the 17-item Hamilton Rating Scale for Depression (HRSD). In addition to the DISH, the BDI was administered. A score of 10 or higher is the threshold for considering clinical depression.	<u>Enhanced care delivery</u> Individual CBT sessions plus group therapy when feasible, with SSRIs for patients scoring higher than 24 on HRSD or having <50% reduction in the BDI scores after 5 weeks.  <u>Usual care</u> Patients in usual care received only the care provided by their physicians. This included antidepressant use at baseline in 4.8% of patients, 13.4% at 6 months and 20.6% by the end of the study.	<u>Clinical outcomes</u> MACE composite (death or nonfatal MI) Total mortality Cardiac mortality Repeat ACS event Revascularization procedures Depression-related outcomes: response or remission of depressive symptoms  <u>Healthcare utilization</u> Cardiovascular hospitalizations  <u>Quality of life</u> SF-12 Physical Component Summary SF-12 Mental Component Summary Life Satisfaction Scale (8 items; score range 0-24)  <u>Subgroups</u> Race/ethnicity Sex



Study Acronym Companion Article(s)	Study Design Location Patient Demographics Quality Rating	Purpose Criteria for Diagnosis of Depression	Intervention versus Comparator	Outcomes Subgroups
Davidson, 2013 <sup>16</sup>  CODIACS	RCT U.S.  N enrolled: 150 Mean age Arm 1: 59.2 (SD 9.7) Arm 2: 60 (SD 11.1) % Female Arm 1: 41% Arm 2: 43%  Good quality	<u>Purpose</u> To determine the effects of providing post-ACS depression care on depressive symptoms and health care costs.  <u>Diagnosis</u> BDI $\geq 10$ on 2 occasions or $>15$ on one occasion.	<u>Enhanced care delivery</u> Centralized, stepped, patient-preference-based depression care; team care; centralized patient services team and/or local MD/nurse practitioner prescribed antidepressants. Symptom monitoring with PHQ-9 and stepped care.  <u>Usual care</u> Primary care physician and/or cardiologist notified by letter of depression symptoms. No restrictions on care.	<u>Clinical outcomes</u> Revascularization procedures Depression-related outcomes: response or remission of depressive symptoms  <u>Healthcare utilization</u> All hospitalizations  <u>Costs</u> Total healthcare costs  <u>Subgroups</u> Sex

Study Acronym Companion Article(s)	Study Design Location Patient Demographics Quality Rating	Purpose Criteria for Diagnosis of Depression	Intervention versus Comparator	Outcomes Subgroups
Davidson, 2010 <sup>17</sup>  COPES  <u>Companions</u> Ye, 2014 <sup>18</sup> Kronish, 2012 <sup>19</sup>	RCT  U.S.  N enrolled: 157 Mean age Arm 1: 61.1 (SD 10.6) Arm 2: 59.3 (SD 10.6) % Female Arm 1: 53% Arm 2: 54%  Fair quality	<u>Purpose</u> To determine the acceptability and efficacy of enhanced depression treatment in patients with ACS.  <u>Diagnosis</u> Trial eligibility required a score of 10 or higher on the BDI on assessments within 1 week of hospitalization for ACS and 3 months later.	<u>Enhanced care delivery</u> Collaborative care including enhanced care by a team of providers (nurse specialist, psychologist, social worker, and/or psychiatrist), patient choice of pharmacotherapy and/or psychotherapy (problem-solving therapy), stepped care approach with symptom severity reviewed every 8 weeks and treatment augmented by protocol, and routine monitoring of depression symptoms using a standardized instrument.  <u>Usual care</u> For patients randomized to usual care only: The control condition for the trial was usual care, as defined by the patient's treating physicians. Physicians of the intervention and usual care patients were informed that their patients were participating in a trial and that they had elevated depressive symptoms; physicians were also told whether the patient met the criteria for a major depressive episode.	<u>Clinical outcomes</u> MACE events MACE composite (hospitalization for ACS) Depression-related outcomes: response or remission of depressive symptoms  <u>Healthcare utilization</u> Cardiac medication adherence  <u>Adverse effects of treatment</u>  <u>Subgroups</u> Race/ethnicity Sex

Study Acronym Companion Article(s)	Study Design Location Patient Demographics Quality Rating	Purpose Criteria for Diagnosis of Depression	Intervention versus Comparator	Outcomes Subgroups
van Melle, 2007 <sup>20</sup>  MIND-IT  <u>Companion</u> Zuidersma 2013 <sup>21</sup>	RCT  U.K./Europe  N enrolled: 331 Mean age Arm 1: 58.6 (SD 11.5) Arm 2: 57.5 (SD 10.6) % Female Arm 1: 24% Arm 2: 26%  Good quality	<u>Purpose</u> To evaluate the effects of antidepressant treatment compared with usual care in an effectiveness study.  <u>Diagnosis</u> BDI $\geq 10$ plus met WHO ICD-10 criteria for current depressive episode [CIDI interview].	<u>Medical therapy</u> First-choice treatment: mirtazapine. If refusal or insufficient treatment response after 8 weeks, open treatment with citalopram was offered. Treatment response $\geq 50\%$ reduction on the HDRS or a HDRS score at 8 weeks of $\leq 9$ . The third option was "tailored treatment," which was at the discretion of the clinical psychiatrist (e.g., SSRI, psychotherapy). Scheduled to visit the psychiatrist on average once a month during the treatment period of 6 months.  <u>Usual care</u> Psychiatric treatment outside the study was recorded, but no treatment was offered by the MIND-IT investigators. Patients NOT informed of diagnosis.	<u>Clinical outcomes</u> MACE composite (death or nonfatal MI) Total mortality Cardiac mortality Repeat ACS event Revascularization procedures Depression-related outcomes: response or remission of depressive symptoms  <u>Healthcare utilization</u> Cardiovascular hospitalizations  <u>Quality of life</u> Health Complaints Scale Physical health (RAND-36) score Mental health (RAND-36) score Complete disability Partial disability  <u>Subgroups</u> None

Abbreviations: ACS=acute coronary syndrome; BDI=Beck Depression Inventory; CBT=cognitive behavioral therapy; CIDI=Composite International Diagnostic Interview; CODIACS=Comparison of Depression Interventions after Acute Coronary Syndrome; COPES=Coronary Patients Evaluation Study; DISH=Depression Interview and Structured Hamilton; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ENRICHD=Enhancing Recovery in Coronary Heart Disease study; HCS=Health Complaints Scale; HDRS=Hamilton Depression Rating Scale; HRSD=Hamilton Rating Scale for Depression; ICD-10=International Classification of Disease, Tenth Edition; MACE=major adverse cardiac events; MI=myocardial infarction; MIND-IT=Myocardial Infarction and Depression-Intervention Trial; PHQ=Patient Health Questionnaire; RCT=randomized controlled trial; SD=standard deviation; SSRI=selective serotonin reuptake inhibitor; WHO=World Health Organization.

## References to Appendix G

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