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Diagnostic Accuracy of Screening Tests and Treatment of Post-Acute Coronary Syndrome (ACS) Depression: A Systematic Review

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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 diagnosed with depression

Key Messages

- 10 new studies have been published since the last review in 2005
- Available depression-screening tools produce acceptable diagnostic accuracy, but <50% of those who screen positive have depression
- BDI-II tool has diagnostic accuracy comparable to use in other populations
- Collaborative care interventions that integrate psychiatric treatment into other clinical settings improve depression symptoms but do not clearly improve cardiac outcomes
- Strategy that combines cognitive behavioral therapy and antidepressant medication may improve depression outcomes but does not clearly improve cardiac outcomes

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None of the investigators has 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

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) to see draft research questions and reports or to join an e-mail 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 Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Diagnostic Accuracy of Screening Tests and Treatment of Post-Acute Coronary Syndrome (ACS) Depression: A Systematic Review

Structured Abstract

Objective: 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 and who are within 3 months of an ACS event.

Data Sources: We searched PubMed®, Embase®, PsycINFO®, CINAHL®, and the Cochrane Database of Systematic Reviews for English-language studies published from January 1, 2003, to August 22, 2016, for studies 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. For treatment effectiveness, outcomes of interest included clinical outcomes (both related to depression or cardiovascular conditions), quality of life, cost effectiveness, utilization of healthcare services, discontinuation of treatment, and adverse effects of treatment.

Review Methods: Two investigators individually screened each abstract and full-text article for inclusion; abstracted data; and performed quality ratings, applicability ratings, and evidence grading. Where appropriate, random-effects models were used to compute summary estimates of effects.

Results: We identified a total of 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 6 studies evaluating 4 instruments involving 1,755 post-ACS patients, evidence suggests that a range of different depression screening instruments produce generally acceptable levels for diagnostic sensitivity, specificity, and negative predictive values (70% to 100%) but produce low (below 50%) positive predictive values (i.e., percentage of patients who screen positive that actually have the condition). A meta-analysis of 4 studies (N=1,576 patients) estimated the Beck Depression Inventory (BDI)-II diagnostic screening performance characteristics to have a sensitivity of 90% and specificity of 80%. For treatment effectiveness, collaborative 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), which although demonstrates a statistically significant improvement is not considered clinically significant. One trial compared second-generation antidepressants with usual care and found no effect on depression symptoms or quality of life although when taken together with studies included in the prior review, these trials support 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, n=2,481, SOE=high). Evidence supporting effects on cardiovascular and other outcomes of interest was insufficient.

Conclusions: Among several depression screening instruments with acceptable performance characteristics, the BDI is the most studied, but positive predictive values are low (<50%) for diagnostic certainty. Collaborative 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. The effects of depression interventions on cardiovascular outcomes is uncertain.

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Introduction

Background

In 2005, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on depression in patients following myocardial infarction (MI).[1] 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 and who are within 3 months of an ACS event.

Condition: Post-Acute Coronary Syndrome (ACS) Depression

Heart disease is the leading cause of death worldwide.[2] 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% of deaths from all causes.[3] Over 25 million adults in the United States are currently estimated to be living with a diagnosis of heart disease,[4] and over 1 million Americans are estimated to be hospitalized for an acute coronary syndrome (ACS) each year.[5]

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.[6] 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%,[7] but studies have found that as many as 20% of post-ACS patients have MDD and 65% of post-MI patients experience elevated symptoms of depression.[8-10] 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)[11-15] and are estimated as the second largest cause of loss in disability-adjusted life years.[16] 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.[17,18]

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.[19] 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."[20] However, other guidelines recommend targeted screening for patients at increased risk of depression[21] or against routine screening.[22] 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.[23,24] 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,[17] 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.[25] 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.[26] Alternative therapies also have been demonstrated to have beneficial effects for emotional health[27] and cardiovascular health.[28] In particular, aerobic exercise has been shown to improve survival in post-ACS patients and also may reduce depression.[29,30] 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.[25]

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 follow-up visits, communication amongst the members of the treatment team, and measurement-based care.

Scope and Key Questions

Scope of the Review

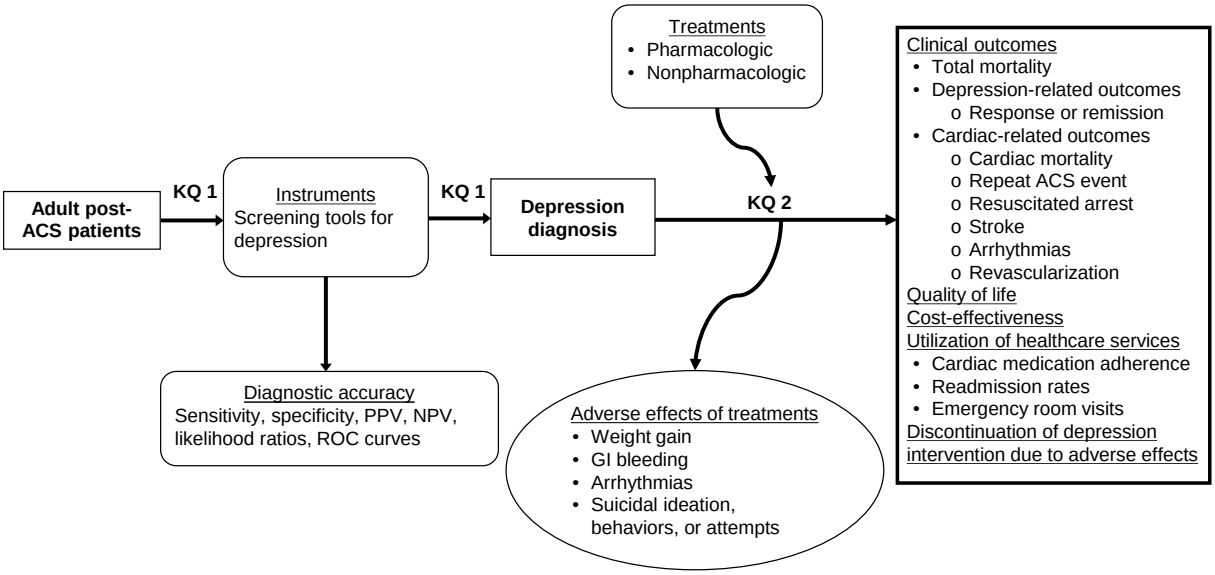
This review evaluates (1) the diagnostic accuracy of selected depression screening instruments and strategies versus a validated criterion standard in adult patients within 3 months of an ACS event, and (2) the comparative safety and effectiveness of a broad range of pharmacologic and nonpharmacologic treatments for depression in adult patients who have received a criterion-based diagnosis of depression 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 (Table 6 in the Results chapter).

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.

Appendices 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.[31] Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[32] 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) website 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 website (www.effectivehealthcare.ahrq.gov). The PROSPERO registration is CRD42016047032.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched MEDLINE® (via PubMed), Embase®, PsycINFO®, CINAHL®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to articles published from January 1, 2003, to August 22, 2016. 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.[1] 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[1] published in 2005 (which had an electronic search date through March 2004). The overlap in search dates follows EPC methods guidance.[31]

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.[33-47] 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® Version X7; Thomson Reuters, Philadelphia, PA).

While the draft report is under peer review, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

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.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	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. 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. Subgroups of interest: • Age (KQ 1, KQ 2) older adults (≥ 65 years) versus adults younger than 65 years of age • Race/ethnicity (KQ 1, KQ 2) • Sex (KQ 1, KQ 2) • Inpatient vs outpatient (KQ 1)	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. KQ 2: Depression diagnosis made by unstructured clinical diagnosis, chart diagnosis, or based on administrative codes (rather than DSM) or prescription for an antidepressant.

Interventions	KQ 1:
	• Screening tools for depression, limited to:
	  o Beck Depression Inventory (BDI) (multiple versions)
	  o Center for Epidemiologic Studies-Depression (CES-D20 and CES-D10)
	  o Distress Questionnaire 5
	  o Duke Anxiety and Depression Scale
	  o Geriatric Depression Scale (GDS-15) [2 versions, long and short]
	  o Hospital Anxiety and Depression Scale (HADS and HADS-D)
	  o Diagnostic Inventory for Depression (DID)
		KQ 2: Combination interventions that include an ineligible intervention

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	o Kessler Psychological Distress Scale (K10 and K6) o Patient Health Questionnaire (PHQ-8/9 and 2) o Primary care rapid evaluation of mental disorders (PRIME-MD, including Whooley questions) o PROMIS® (Patient-Reported Outcomes Measurement Information System) o Quick Inventory of Depressive Symptomatology o Symptom Checklist 20 and Hopkins Symptom Checklist o WHO-5 (World Health Organization-5) o Zung Self-Rating Depression Scale • Screening strategies that differ by setting (i.e, inpatient vs outpatient, general medicine vs cardiology) or timing (i.e., duration post-ACS event) KQ 2 (considered singly or in combination): • Medical Therapy o Antidepressant medications (SSRI, SNRI, etc.) limited to second-generation medications which have been FDA-approved for treatment of major depressive disorder: ▪ Bupropion ▪ Citalopram ▪ Desvenlafaxine ▪ Duloxetine ▪ Fluoxetine ▪ Escitalopram ▪ Levomilnacipran ▪ Mirtazapine ▪ Nefazodone ▪ Paroxetine ▪ Sertraline ▪ Trazodone ▪ Venlafaxine ▪ Vilazodone ▪ Vortioxetine o Atypical antipsychotics – limited to those that are FDA-approved for treatment of major depressive disorder: ▪ Aripiprazole ▪ Olanzapine ▪ Quetiapine o Tricyclic antidepressants – limited to those that are FDA-approved for	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	treatment of major depressive disorder: ▪ Amitryptiline ▪ Amoxapine ▪ Desipramine ▪ Doxepin ▪ Imipramine ▪ Nortryptiline ▪ Protryptiline ▪ Trimipramine • Psychotherapy o Cognitive behavioral therapy, limited to: cognitive behavioral therapy (CBT), cognitive therapy, behavioral therapy, cognitive behavioral analysis system of psychotherapy, and behavioral activation o Problem solving therapy o Interpersonal psychotherapy o Short-term psychodynamic therapy o "Third wave" cognitive behavioral psychotherapies, limited to: acceptance and commitment therapy, dialectical behavior therapy, mindfulness, mindfulness-based cognitive therapy (MBCT), and functional analytic psychotherapy • Other Treatments o 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. o St John's Wort o Fish oil/ omega-3 fatty acids o S-Adenosylmethionine o 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). o Education/psychoeducation o Stress management: mindfulness meditation, progressive muscle relaxation, qigong meditation, spiritual medication, guided imagery-based approaches, paced	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	respiration, Roll breathing, 4-7-8 breath technique o Psychosocial support: interventions to help a person cope with stress that do not involve formal therapy o Transcranial magnetic stimulation o Electroconvulsive therapy • Enhanced Care Delivery o 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 follow-up visits, communication amongst the members of the treatment team, and measurement-based care."[48])	
Comparators	KQ 1: Validated criterion standard (e.g., DSM or ICD criteria) administered by a trained interviewer KQ 2: Active comparator from listed interventions; usual care	KQ 2: Same treatment comparisons that vary by dose; Combination comparators that include an ineligible intervention
Outcomes	KQ 1: • Diagnostic accuracy, as measured by: o Sensitivity o Specificity o Negative predictive value (NPV) o Positive predictive value (PPV) o Likelihood ratios o Receiver operating characteristic (ROC) curves KQ 2: • Clinical outcomes o Total mortality o Depression-related outcomes ▪ Response or remission of depressive symptoms using validated continuous or categorical measures o Cardiac-related outcomes ▪ Cardiac mortality ▪ Repeat ACS event (repeat	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	MI or unstable angina) ▪ Resuscitated arrest ▪ Stroke ▪ Arrhythmias ▪ Revascularization • Quality of life (QOL) • Cost-effectiveness • Utilization of health care services o Cardiac medication adherence o Readmission rates due to cardiac and non-cardiac reasons o Emergency room visits: all visits, cardiac-related, and psychiatric-related • Discontinuation of depression intervention due to adverse effects • Adverse effects of treatment (excluding clinical outcomes listed above) o Weight gain o Gastrointestinal bleeding o Arrhythmias o Suicidal ideation, behaviors or attempts	
Timing	KQ 1: Within 3 months of an identifying ACS event KQ 2: At least 6 weeks of followup	
Settings	• Primary, specialty, and inpatient settings • 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	
Study design	• Original peer-reviewed data • KQ 1: Observational studies, sample size ≥50 subjects • KQ 2: Randomized controlled trials (RCTs), sample size ≥20 subjects	Editorials, nonsystematic reviews, systematic reviews, meta analyses, letters, case series, case reports, abstract-only or poster publications, articles that have been retracted or withdrawn Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality,[49,50] we have excluded them from our review. For observational studies, we require at least 50 subjects.
Publications	• English-language only • Published on or after January 1, 2003	Non-English language articles[a]

[a]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. Disagreements 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,[31] 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://srdr.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[51] tool for randomized studies and the Quality Assessment of

Diagnostic Accuracy Studies-2 (QUADAS-2)[52] for observational studies. We supplemented these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ's Methods Guide.[31] Observational studies were rated on each individual quality criterion without a summary rating. For each 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 RCTs

Rating	Definition
Good (low risk of bias)	These studies had the least bias, and the results were considered valid. These 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.
Fair	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.
Poor (high risk of bias)	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, and completeness of the reporting of results. 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% 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.

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.[31,53] 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.[54] 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
High	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.
Moderate	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.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this

Rating	Definition
	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.
Insufficient	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.[31,55] 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 (Draft Report)

This draft report will be posted on the AHRQ EHC website for 4 weeks to elicit public comment. Experts in the fields of internal and family medicine, cardiovascular medicine, mental health, clinical trial and systematic review methodology, and health services research have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The authors will address all reviewer comments, revising the text as appropriate, and document the 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 website.

Results

Introduction

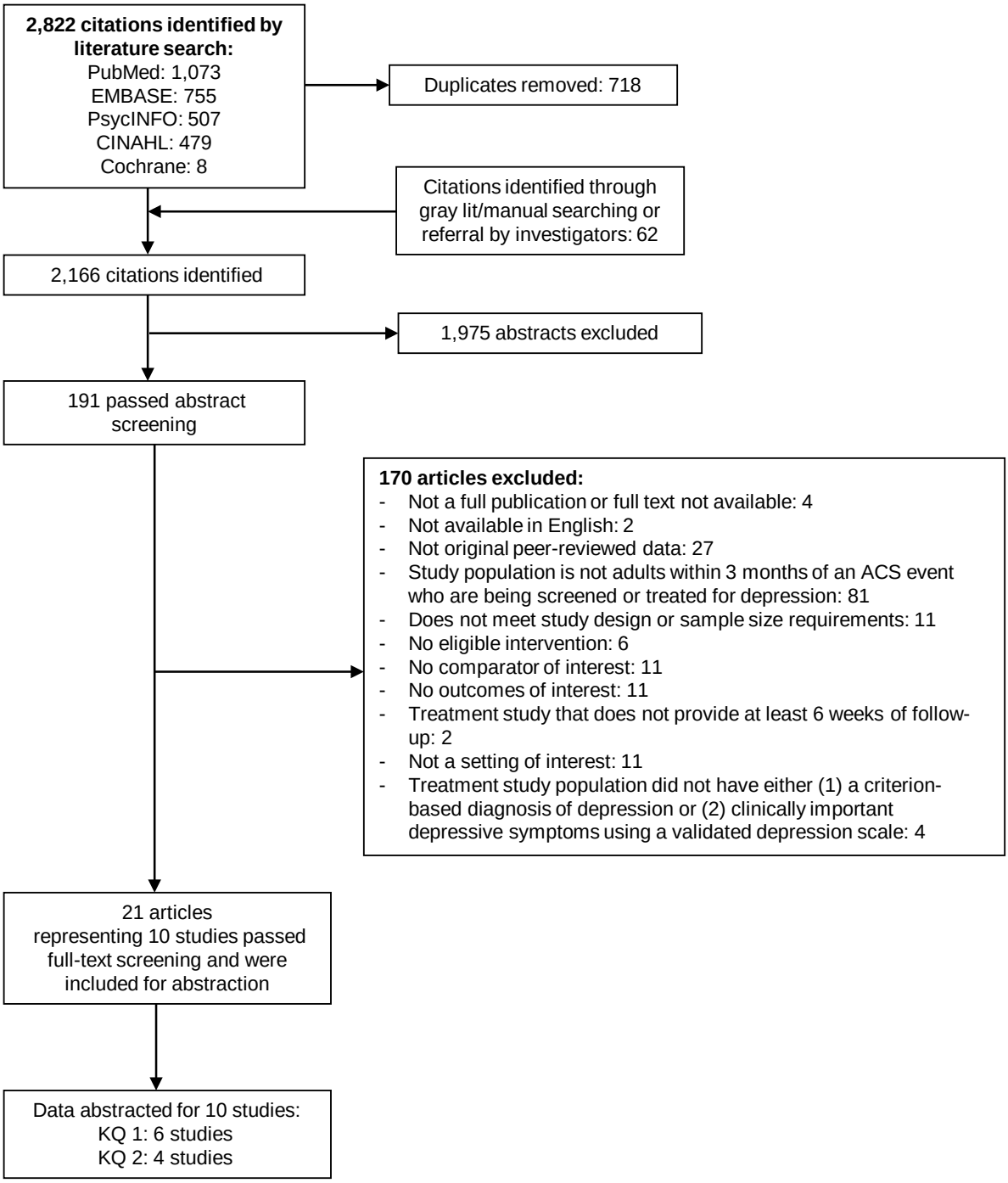
In what follows, we begin by describing the results of our literature searches. We then provide an overall description of the included studies. The remainder of the chapter is organized by key question (KQ). Under both KQs, we begin with a brief description of the included studies, followed by a bulleted 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®, Embase®, PsycINFO®, CINAHL®, and the Cochrane Database of Systematic Reviews yielded 2,822 citations, 2,104 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 2,166 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, 191 full-text articles were retrieved and screened. Of these, 170 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; KQ=key question; RCT=randomized controlled trial

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 (5 studies; 50%), Canada (2 studies; 20%), or both the United States and Canada (1 study; 10%). 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 57 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-ACS Patients

Description of Included Studies

For KQ 1, we identified 7 articles[56-62] representing 6 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[58] and a companion paper.[59]

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,[60] while the remaining five were all conducted at a single center. Three studies were conducted solely in the United States,[56,58,61] one study in the UK/Europe,[62] and two studies in Canada.[57,60] Three studies did not report the funding source or the source was unclear,[56,60,62] one study reported a mixture of government, industry, and nongovernment/nonindustry funding,[57] one study reported a mixture of government and nongovernment, nonindustry funding,[61] and one study reported nongovernment, nonindustry funding.[58] MDD served as the criterion standard for studies, with one study[56] describing the criterion standard as "clinical depression" based on DSM-IV-TR criteria (correspondence with the authors indicated that most of these patients had MDD, though some had minor depression).

Table 4. KQ 1 evidence summary

Number of studies: 6
Study publication years: 2005-2013
Date of literature search: August 22, 2016
Number of patients: 1,755
Men: 1,343 (77%)
Women: 412 (23%)
Mean age range: 57 to 63 years
Race/ethnicity: Unavailable
Settings: Inpatient (5); cardiac rehabilitation clinic (1)
Countries: USA (3), Canada (2), UK/Europe (1)
Screening instruments: Beck Depression Inventory-II (BDI-II); Hospital Anxiety and Depression Scale (HADS); Patient Health Questionnaire (PHQ); Geriatric Depression Scale (GDS)
Criterion standard: DSM III-IV major depressive disorder (MDD)

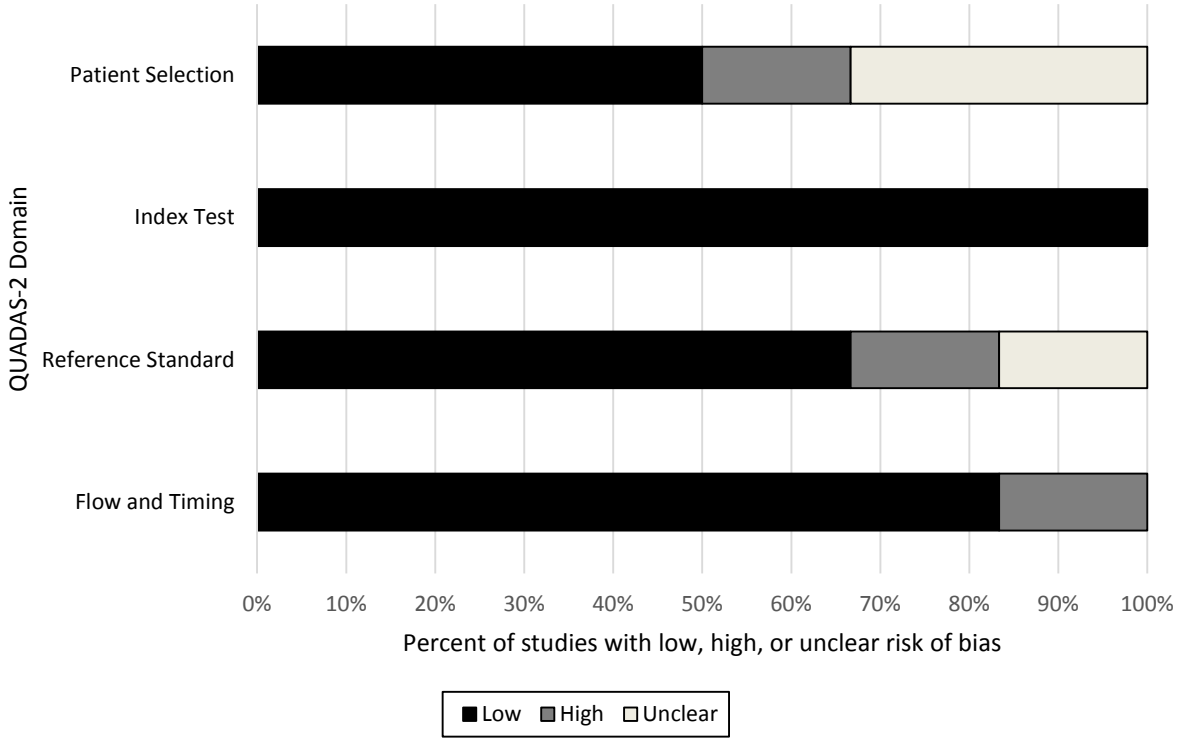
We used the QUADAS-2 tool to evaluate the quality of the included studies and their risk of bias (Table 5 and Figure 3).[52] For the domain of patient selection, three studies were ranked as low risk of bias, one as high risk of bias, and two as unclear risk of bias. For the domain of index tests, all 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[61]	H	L	U	H
Bunevicius, 2012[62]	L	L	L	L
Frasure-Smith, 2008[57]	L	L	L	L
Huffman, 2006[58]	U	L	H	L
Low, 2008[60]	L	L	L	L
McGuire, et al., 2013[56]	U	L	L	L

Abbreviations: L=Low risk, H=High risk, U=Unclear risk

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



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 generally acceptable levels for diagnostic sensitivity, specificity, and negative predictive values (70% to 100% for each characteristic) but produce low (below 50%) positive predictive values (i.e., percentage of patients who screen positive that actually have the condition) (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 specificity that compares to the variable values produced by different HADS scales/subscales, and the GDS demonstrated better specificity and positive predictive values than the BDI-II in one small study (3 head to head comparative studies).
- 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 nearly as effective 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[a]

Instrument	N items	Response format	Score range	Usual cut-point for diagnosing depression	Literacy level[b]	Time to complete (minutes)[c]	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[d]
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[d]
GDS	15	Yes or no	0-15	≥6	Easy	2-5	No
HADS-T <u>Subscales</u> HADS-A HADS-D	14	4-point Likert scale 0-3	0-42 0-21 0-21	8-10 = mild 11-15 = moderate ≥16 = severe	Easy	1-2	Yes[e]
PHQ-2	2	4 frequency ratings	0-6	≥3	Average	<1	Yes[f]
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[f]

[a] 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.
[b] Easy=3rd to 5th grade reading level; average=6th to 9th grade reading level.

[c] With the exception of BDI-II, which is based on oral administration, all estimates of time to complete are based on self-administration.
[d] Copyright, Pearson Assessments, 19500 Bulverde Road, San Antonio, TX. The BDI-II instrument requires licensing.
[e] Copyright, GL Assessment, The Chiswick Centre, 414 Chiswick High Road, London, W4 5TF, UK.
[f] 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	Threshold Reasoning as Specified in Study	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	P
Bambauer, 2005[61] PRIME-MD DMS-IV N=79 Prevalence=34%	HADS	≥7	NR	NR	NR	34.2	NR	NR	NR
Huffman, 2006[58] Huffman, 2010[59] 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	Optimal cutoff	88.2	92.1	62.5	98.1	0.96 (0.92-1.0)	<.0001
		≥14	Traditionally accepted values	88.2	84.2	45.5	98		
Low, 2007[60] SCID-I/NP N=119 Prevalence=5.90%	BDI-II	≥14	Generally accepted for instrument	83	88	28	99	0.91	0.06
		≥10	Threshold considered optimal by authors	100	75	18	100		
	GDS	≥11	Generally accepted for instrument	100	83	25	100	0.97	
		≥14	Threshold considered optimal by authors	100	94	50	100		

Study Criterion Standard N Patients Prevalence of Post-ACS Depression	Tool	Chosen Threshold	Threshold Reasoning as Specified in Study	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	P
Frasure-Smith, 2008[57] Structured Clinical Interview for DSM-IV N=804 Prevalence=7.10%	BDI-II	≥14	A priori specified	91.2	77.5	NR	NR	0.92 (0.89-0.95)	
	HADS-A	≥8	A priori specified	84.2	61.8	NR	NR	0.86 (0.80-0.91)	
Bunevicius, 2012[62] Structured MINI N=522 Prevalence=11%	HADS	≥14	Optimal cutoff	82 (69-91)	79 (75-83)	32 (25-41)	97 (95-99)	0.87 (0.81-0.92)	
	HADS-A	≥8	Traditionally accepted values	86 (73-93)	72 (67-76)	27 (21-34)	98 (95-99)	0.86 (0.80-0.92)	
		≥8	Optimal cutoff	86 (73-93)	72 (67-76)	27 (21-34)	98 (95-99)		
	HADS-D	≥8	Traditionally accepted values	41 (28-55)	90 (87-93)	34 (23-46)	93 (90-95)	0.79 (0.73-0.85)	
		≥5	Optimal cutoff	77 (63-87)	69 (65-73)	23 (17-30)	96 (93-98)		
	BDI-II	≥14	Traditionally accepted values	89 (95% CI 77-96)	74 (70-78)	29 (23-37)	98 (96-99)	0.90 (0.86-0.94)	
		≥14	Optimal cutoff	89 (95% CI 77-96)	74 (70-78)	29 (23-37)	98 (96-99)		
McGuire, 2013[56] Depression interview Structured Hamilton N=100 Prevalence=23%	PHQ-2	>0	Optimal cutoff	95.65	71.43	NR	NR	0.912 (0.0336 SE)	Vs 9 = 0.66 Vs 10 = 0.49
	PHQ-9	>4	Optimal cutoff	95.65	72.73	NR	NR	0.926 (0.0257 SE)	Vs 2 =-0.66 Vs 10 = 0.07
	PHQ-10	>5	Optimal cutoff	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

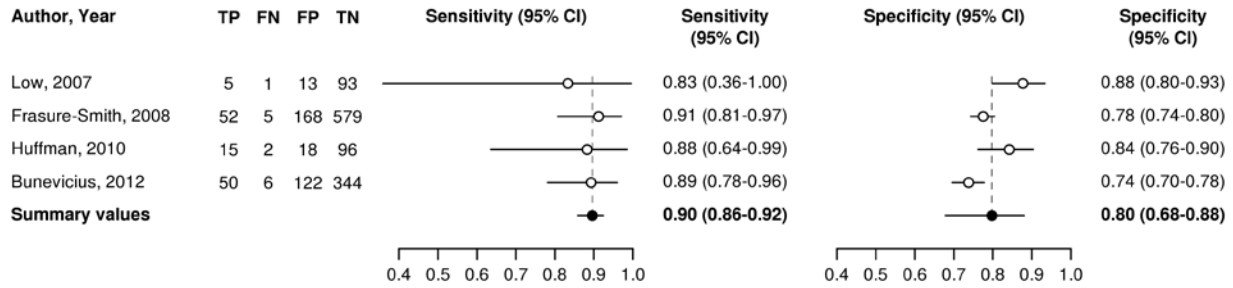
Beck Depression Inventory-II

Four of the six included studies examined the BDI-II for use in depression screening among post-ACS patients[57,58,60,62] (Figure 4). In the four studies that examined the generally accepted cutoff of ≥14 on the BDI-II to screen for MDD, sensitivity ranged from 83% to 91% and specificity from 74% to 88%. Three of these studies reported PPV and NPV, with PPV ranging from 28% to 46% and NPV from 98% to 99%. We were able to combine quantitatively the findings from the 4 studies that evaluated the BDI-II with a cutoff of ≥14. The meta-analysis of these 4 studies indicated an overall sensitivity of 90% (95% CI 86% to 92%) and specificity of 80% (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 ≥14.[58-60,62] 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[58] found that using the one sadness item alone from the BDI-II (score ≥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 ≥ 14.[59]

Figure 4. Forest plot of diagnostic accuracy of BDI-II for major depressive disorder (cutpoint ≥14)



Abbreviations: CI=confidence interval; FN=false negative; FP=false positive; TN=true negative; TP=true positive

Hospital Anxiety and Depression Scale (HADS)

Three of the six studies tested the HADS or a HADS subscale to screen for depression among post-ACS patients.[57,61,62] One study found optimal cutoff values of ≥14 for the full HADS, ≥5 for the HADS depression subscale, and ≥8 for the HADS anxiety subscale.[62] The depression subscale slightly underperformed the full HADS, HADS anxiety subscale, and BDI-II.

Two studies examined the depression screening characteristics of both the HADS anxiety subscale (threshold of ≥8) and the BDI-II (threshold of ≥14).[57,62] One study found the scales to perform comparably,[62] and one found the HADS anxiety subscale to not perform as well as the BDI-II.[57] One study found a PPV of 34% for the full HADS (threshold ≥7).[61]

Other Screening Instruments

Depression screening instruments other than the BDI-II or HADS were examined in two studies.[56,60] The Geriatric Depression Screen (GDS) was compared with the BDI-II in one study and was found to have similar sensitivity but somewhat better specificity and PPV.[60] A threshold

of ≥10 for the GDS was considered optimal for the post-ACS population, as opposed to the traditional ≥14. The Patient Health Questionnaire (PHQ) versions 2 which included just two items (threshold >0), 9 (>4), and 10 (>5) were compared in one study, with the three versions each demonstrating excellent AUC statistics (91.2% to 93.4%) and not performing significantly differently from one another with respect to sensitivity (95.7% to 96.7%) and specificity (71.4% to 77.9%).[56]

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% to 30%.[9,63-66] 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%[57-60,62]; one study of "clinical depression" (included some patients with minor depression per correspondence with authors) found a rate of 23%[56]; and one poor-quality study had a rate of 34%.[61] 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,[59] and another for having a known current depressive disorder.[62] Depression is highly comorbid with other psychiatric disorders[67] and is most highly correlated with a history of past depressive episodes,[68] 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.[9] 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),[58,59] whereas the remaining five studies had samples in which post-MI patients constituted approximately 30% to 70% 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.[60] While two studies had sample sizes above 500[57,62]—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.[62] Even for this study that had a relatively large sample size, the 95% confidence interval surrounding sensitivity for the BDI-II at threshold of ≥14 still ranged from 77% to 96%. 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 that were reported.[69]

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.[70,71] 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,[72] 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.[73-76]

Three studies in the present review compared screening instruments head-to-head, with these studies considering the BDI-II in comparison to the GDS,[60] the HADS (full version and two subscales[62]), and the HADS anxiety subscale.[57] 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 ≥14 (which is the generally accepted threshold[62]), one four points below this,[60] and one two points above this traditional threshold.[59] 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 (≥14 suggested vs. the traditional ≥11[60]) and subscale cutoffs on the HADS of ≥8 for the anxiety subscale (same as traditional threshold) and ≥5 for the depression subscale (vs. ≥ 8 as traditional[62]).

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 nearly as well as the entire scale,[58,59] with the same being true for the PHQ-2 when compared with the 9- and 10-item versions of the PHQ.[56] 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[77] and (2) PPV in the included studies remains around or below 50%, indicating the need for follow-up assessment to arrive at a diagnosis.

Comparison with the 2005 Post-MI Depression Report Findings

The 2005 AHRQ report "Post-Myocardial Infarction Depression" (AHRQ publication no. 05-E018-2[1]) 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.[78] 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.[56,57,60-62] Findings from the present review are consistent with the prior review's concern with respect to PPV rates. PPV was consistently below 50%, 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.

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. Given the lack of direct comparisons of screening versus no screening, the evidence requires us to make inferences based on the available data about the downstream consequences. Per guidance from the GRADE literature,[79] we therefore report the individual components for the BDI-II tool but do not make a summary strength of evidence rating.

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

Test result	Study design (N)	Study quality	Indirectness	Inconsistency	Test property (95% CI) Precision	Test result	Number per 1,000 tested for 10% prevalence[a]	Number per 1,000 tested for 20% prevalence[a]
Sensitivity[b]	4 cross-sectional (1,576)	Low risk of bias	Direct	Consistent	0.90 (0.86 to 0.92) Precise	True positives False negatives	90 10	180 20
Specificity[c]	4 cross-sectional (1,576)	Low risk of bias	Direct	Inconsistent	0.80 (0.68 to 0.88) Precise	False positives True negatives	180 720	160 640

[a] Number per 1,000 tested for given prevalence of major depressive disorder. Prevalence was based on the range observed in included studies.
[b] Sensitivity=true positive + false negative.
[c] Specificity=false positive + true negative.
Abbreviations: CI=confidence interval

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[80-93] representing 4 studies[83,85,88,92] 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 to diverse for quantitative analysis.

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

- ENRICHD (Enhancing Recovery In Coronary Heart Disease): Primary report[92] and seven companion papers[80,82,86,87,89-91]
- COPES (Coronary Patients Evaluation Study): Primary report[85] and two companion papers[81,84]
- MIND-IT (Myocardial Infarction and Depression–Intervention Trial): Primary report[88] and one companion paper[93]

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). Two studies were conducted solely in the United States,[85,92] one study in the UK/Europe,[88] and one study conducted in both the United States and Canada.[83] Two studies reported government funding,[83,85] one reported a mixture of government and industry funding,[92] and one reported a mixture of industry and nongovernment/nonindustry funding.[88] Finally, of the four studies relevant to KQ 2, three were rated as good quality[83,85,92] and one was rated as fair quality.[88] 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. KQ 2 evidence summary

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

- For post-ACS patients, collaborative care interventions which integrates psychiatric treatment in to other clinical settings improve depression symptoms more than usual care (mean difference in Beck Depression Inventory [BDI] ranged from -3.5 to -3.8) which was statistically significant but not clinically different (2 trials, SOE=moderate).
- One trial compared second-generation antidepressants with usual care and found no effect on 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, when taken with results from the previous review, these studies support a small positive effect of antidepressants in this patient population.
- A large RCT found that a combination strategy, including cognitive behavioral therapy (CBT) plus antidepressant medication for severe symptoms or 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).
- Based on all four studies evaluated, we found evidence that 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 and ACS event.
- Based on all four studies evaluated, the evidence did not show increased adverse events among post-ACS individuals treated with collaborative care, CBT, or antidepressant medications compared with usual care.
- In general, the strength of evidence was stronger for depression than for cardiovascular outcomes, and stronger for CBT with antidepressants than for other interventions.

Detailed Synthesis

Collaborative Care Versus Usual Care

Two trials including 307 patients compared collaborative care with usual care and reported on depression, cardiovascular, economic, and adverse effect outcomes: Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS)[83] and Coronary Patients Evaluation Study (COPES).[85] Both studies enrolled patients who were post-ACS with persistent depressive symptoms on the BDI scale. Persistent depressive symptoms were defined by a BDI ≥10 on two occasions between 2 and 6 months post-ACS,[83] or at 1 week and 3 months post-ACS,[85] or by a single BDI score >15.[83] The COPES study[85] reported criterion standard diagnoses; only 33% met criteria for major depressive disorder (MDD). Patients with major psychiatric comorbidity (e.g., psychosis, substance abuse) or suicidal ideation were excluded. Collaborative 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 (stepped care). Treatments offered included antidepressant therapy and/or psychotherapy.

In the CODIACS trial,[83] a significantly greater decrease in depression symptoms (BDI score [21 questions, 0-63 score with higher scores=greater severity]) was seen in the collaborative care group with a between-group difference of -3.5 (95% CI -6.1 to -0.7) at 6 months' followup. Note that a 5-point change is generally described as the meaningful clinically important difference for the BDI score and so although this finding is statistically different, it is not considered clinically

different. There was also a significantly greater depression remission (BDI <10) rate in the collaborative 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).[83] Total healthcare costs were not significantly different between the collaborative care and usual care groups. Rates of hospitalization for any cause and revascularization were similar between the two groups.[83] 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.

In the COPES trial,[85] patients assigned to collaborative care had a greater decrease in depression symptoms (mean difference -3.8 in BDI score, 95% CI -6.5 to -1.2) 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 collaborative 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 collaborative care group experienced death or MACE (HR 2.91, 95% CI 0.80 to 10.56).[81] 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).[84] However, the 95% 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 collaborative 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 ENRICHD trial[92] was included in the 2005 AHRQ report,[1] but is described in detail in this systematic review because additional outcomes and subgroup analyses were reported subsequently. That trial[92] 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% 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% 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) and HRSD (between-group difference -1.7, 95% CI -2.5 to -0.9).[92] 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).[89] There was no significant difference in major cardiac events, all-cause mortality, cardiovascular mortality, repeat ACS, revascularization, or cardiovascular hospitalization between groups (Table 10).[92] 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.[90] 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).[92] 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 10. Major cardiovascular outcomes in the ENRICHD 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 to1.18)
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; MI=myocardial infarction

Antidepressants Versus Usual Care

The MIND-IT trial[88] 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), physical or mental health complaints, and disability or quality of life at 18 months' followup.[88] 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.[88] 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).[93] 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.

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

Table 11 summarizes the strength of evidence 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 collaborative 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 11. Strength of evidence for KQ 2

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
KQ 2: Collaborative care versus usual care						
Depression symptoms	2 (307)	RCT/High	Consistent Direct	Imprecise[b] None detected	Mean difference -3.5 to -3.8 BDI	Moderate
Mental health–related function	1 (150)	RCT/High	NA Direct	Imprecise[b] None detected	OR 1.08 (CI 0.73 to 1.42)	Low
MACE	2 (307)	RCT/High	Inconsistent Direct	Imprecise[b] None detected	Inconsistent results, No effect to short-term benefit (HR 0.25) that was not sustained in long-term followup	Insufficient
Adverse effects	1 (157)	RCT/High	NA Direct	Imprecise None detected	No difference, findings not reported by specific adverse effects	Insufficient
KQ 2: CBT and second-generation antidepressant versus usual care						
Depression symptoms	1 (2481)	RCT/High	NA Direct	Precise None detected	Mean difference -2.7 (CI -3.7 to -1.7) BDI	High
Mental health–related function	1 (2481)	RCT/High	NA Direct	Precise None detected	Mean difference -2.2 (CI 1.2 to 3.2) SF-12 MCS	High

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
MACE	1 (2481)	RCT/High	NA Indirect[a]	Precise None detected	HR 1.01 (CI 0.86 to 1.18) for death or nonfatal MI	Moderate
Adverse effects	NR	–	–	–	–	Insufficient
KQ 2: Antidepressant medication versus usual care						
Depression symptoms	1 (331)	RCT/Fair	NA Direct	Precise None detected	Mean BDI 11.0 vs. 10.2	Moderate
Mental health–related function	1 (331)	RCT/Fair	NA Direct	Imprecise None detected	Mean at 18 months 44.5 vs. 43.4 SF-36 MCS	Low
MACE	1 (331)	RCT/Fair	NA Direct	Imprecise None detected	OR 1.07 (0.57 to 2.0) for MACE	Low
Adverse effects	NR	–	–	–	–	Insufficient

[a]Rated as indirect since 20.1% of patients enrolled for low perceived social support rather than depression.
[b]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; KQ=key question; MACE=major adverse cardiovascular event; MCS=mental component summary; MI=myocardial infarction; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Comparison with the 2005 Post-MI Depression Report Findings

The original 2005 AHRQ report[1] 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 there was insufficient power to assess the impact on survival. Seven studies (6 RCTs, 1 prospective cohort study) assessed psychosocial interventions 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 collaborative care. The additional studies identified in the current review builds upon these findings to show benefit from collaborative 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-ACS patients (KQ 1) and the comparative safety and effectiveness of depression treatment strategies in post-ACS patients (KQ 2). Major depressive disorder is a common comorbid illness post-ACS and is associated with worse cardiovascular outcomes and higher mortality than in patients without ACS.[17,18] Identification and effective treatment for patients who are depressed post-ACS has the potential to improve depressive symptoms, quality of life, and cardiovascular outcomes. 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. Our findings are based on those 10 studies that met these criteria and addressed the clinical questions of diagnosis of depression and treatment in post-ACS patients.

Key Findings and Strength of Evidence

This present review is an update of the original 2005 AHRQ systematic review,[1] which found insufficient evidence to support the comparative effectiveness of interventions for improving cardiovascular outcomes, although it recognized the effectiveness of psychosocial interventions and 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 ENRICHD 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 What is Already Known

Both the 2008 AHA[24] and 2009 AAFP Clinical Practice Guidelines[94] recommend screening for depression in post-MI patients at regular intervals, including during the initial hospitalization, albeit such recommendations have been met with some controversy.[95,96] Although no specific screening instruments were recommended by these guidelines, the PHQ-9 was used as an example of how screening instruments could be used in clinical practice. Our present review finds that the BDI-II has good sensitivity (90%) and specificity (80%) for MDD during hospitalization for 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 diagnostic screening accuracy metrics that approach those evidenced when using longer screens (e.g., the full BDI-II, PHQ-9, and PHQ-10). 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 follow-up and monitoring of their treatment response and adherence to treatment."[94] The present systematic review did not find any new studies comparing directly SSRIs with tricyclic antidepressants but found two trials supporting collaborative care for patients post-ACS with severe or persistently elevated (two positive depression screens) depressive symptoms. The 2005 AHRQ review[1] 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 ACP policy recommendations[97] for integrated behavioral healthcare. Also it should be noted that our findings are generally consistent across sex and ethnic groups.[85,92] The CODIACS study focusing on collaborative care did find stronger effects in women.[83] 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 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.

Note that the prior 2005 AHRQ review[1] and guidelines[24,83,85,94] have focused on patients post-MI, but our review extends the population of interest to post-ACS patients.

Applicability

We assessed the applicability of our included studies for both key questions. For KQ 1, all studies assessed the performance of screeners 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 [83,85]with the BDI (first edition), an instrument that does not reflect important changes first made to the criterion standard diagnosis of MDD in the DSM-IIIR (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.

Table 12 summarizes the applicability scores across KQs.

Table 12. Potential issues with applicability of included studies

Issues	Key Question	
	KQ 1 N=6	KQ 2 N=4
Population (P)		
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
Intervention (I)		
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
Follow-up not reflective of current practice	0	0
Comparator (C)		
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
Outcomes (O)		
Composite outcomes that mix outcomes of different significance	0	0
Short-term follow-up	0	0
Surrogate outcomes	0	0
Setting (S)		
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.[17,18] 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.

Our systematic review has several implications for clinical and policy decisionmaking. Specifically, in KQ 1 we found good performance characteristics for the BDI-II diagnostic tool, which was the screening instrument used most often among included studies. Data on the widely used PHQ 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.[98] 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[56,58] 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[99] 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[83,85] 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.[83] The USPSTF used this type of evidence and logic model to conclude that evidence supports depression screening in primary care.[20]

Within KQ 2, secondary analyses from the treatment trials showed generally consistent benefit of interventions on depression outcomes by sex and ethnicity.[85,92] 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.[100]

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.[92] Second, two post-hoc analyses suggest the possibility that antidepressant use may be associated with lower cardiovascular events.[83,85] In addition, the follow-up 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 at least not increase negative cardiovascular outcomes.

Data from other studies including individual patient-level meta-analyses[101] 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, CMS introduced four new payment codes (G codes) that support collaborative care for depression.[102] 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.[1] 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, NSTEMI, and 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

addition, our inclusion criteria limited studies for KQ 1 to those with a criterion standard, while the original report used any psychometric study. 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 an 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.[99,103,104]

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[58] or the two-item version of the PHQ[56] 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,[105,106] 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 include exploration of how our results for both KQ 1 and KQ 2 apply to highly related patients, such as those post-CABG or post-PCI done electively or in congestive heart failure patients. We also identified gaps in evidence for depression treatments with demonstrated benefit in patients without heart disease. Some of these treatments, such as exercise,[107] cardiac rehabilitation and omega-3 fatty acid supplements[95,108,109] 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.

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.[110] 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.

Current general MDD guidelines,[97] 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 instruments with acceptable performance characteristics, the BDI is the most studied, but positive predictive values are low (<50%) for diagnostic certainty. Collaborative 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. The effects of depression interventions on cardiovascular outcomes is uncertain.

Acronyms and Abbreviations

ACS	Acute coronary syndrome
AUC	Area under the curve
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory, 2nd 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, 3rd edition
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
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, 10th 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, 2nd edition

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

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