Title

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Journal

Academic Emergency Medicine, 28(7)

ISSN

1069-6563

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Publication Date

2021-07-01

DOI

10.1111/acem.14296

Peer reviewed

HHS Public Access

Author manuscript

Acad Emerg Med. Author manuscript; available in PMC 2022 May 18.

Published in final edited form as:

Acad Emerg Med. 2021 July ; 28(7): 718–744. doi:10.1111/acem.14296.

Guidelines for reasonable and appropriate care in the emergency department (GRACE): Recurrent, low-risk chest pain in the emergency department

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AUTHORS CONTRIBUTIONS

All authors participated in the writing and review of this manuscript.

CONFLICT OF INTERESTS

Paul Musey, MD—Research funding from SAEM Foundation and PCORI. Jeffrey Kline, MD—Consultant to Janssen, Stago Diagnostica, Research funding from NIH, Mallingkrodt, Roche Diagnostics. Christopher Carpenter, MD—Research funding from John A. Hartford Foundation, Gary and Mary West Foundation, and National Institute of Aging. Bryn Mumma, MD, MAS—Research funding from Roche Diagnostics and Alpha Phi Foundation. Marc Probst, MD, MS—Research funding from NIH/NHLBI. Anna Marie Chang, MD MSCE—Research funding from Abbott, Roche, Siemens, Entegrion, Beckman Coulter, Ortho Diagnostics, NIH, Pennsylvania Medical Society. Deborah Diercks, MD: Research funding from Stago Diagnostica, Ortho Clinical Diagnostics, Abbott, Siemens.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Abstract

This first Guideline for Reasonable and Appropriate Care in the Emergency Department (GRACE-1) from the Society for Academic Emergency Medicine is on the topic: Recurrent, Low-risk Chest Pain in the Emergency Department. The multidisciplinary guideline panel used The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence and strength of recommendations regarding eight priority questions for adult patients with recurrent, low-risk chest pain and have derived the following evidence based recommendations: (1) for those >3 h chest pain duration we suggest a single, high-sensitivity troponin below a validated threshold to reasonably exclude acute coronary syndrome (ACS) within 30 days; (2) for those with a normal stress test within the previous 12 months, we do not recommend repeat routine stress testing as a means to decrease rates of major adverse cardiac events at 30 days; (3) insufficient evidence to recommend hospitalization (either standard inpatient admission or observation stay) versus discharge as a strategy to mitigate major adverse cardiac events within 30 days; (4) for those with non-obstructive (<50% stenosis) coronary artery disease (CAD) on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation; (5) for those with no occlusive CAD (0% stenosis) on prior angiography within 5 years, we recommend referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation; (6) for those with a prior coronary computed tomographic angiography within the past 2 years with no coronary stenosis, we suggest no further diagnostic testing other than a single, normal high-sensitivity troponin below a validated threshold to exclude ACS within that 2 year time frame; (7) we suggest the use of depression and anxiety screening tools as these might have an effect on healthcare use and return emergency department (ED) visits; and (8) we suggest referral for anxiety or depression management, as this might have an impact on healthcare use and return ED visits.

Keywords

acute coronary syndrome; chest pain; low risk; recurrent

INTRODUCTION

Chest pain is the second most common chief complaint in the emergency department (ED), accounting for 5% of visits[1] with an estimated cost up to $10 billion annually.[2–4] The differential diagnosis for chest pain is broad. While providers often prioritize the exclusion of cardiac causes of chest pain such as acute coronary syndromes (ACS), other causes such as acute aortic syndromes, pericarditis, myocarditis, pulmonary embolism, pneumothorax, pneumonia, and perforated peptic ulcer also cause chest pain. However, only 5% of chest pain visits are diagnosed with one of these acute life-threatening conditions, most commonly ACS.[5,6]

Despite this low prevalence, missed acute myocardial infarction (AMI) and associated adverse events rank as frequent causes of malpractice lawsuits, and consequently, emergency

physicians are loath to miss these conditions.[7,8] In addition, significant inter-physician and inter-emergency department variation occurs in the evaluation (diagnostic testing and admission) of these patients. Clinical practice guidelines can aid clinicians in the evaluation of low-risk chest pain,[9] but significant practice variation persists and is often subject to the available local resources or lack thereof.[10] For example, one recent study found physician-level admission rates varied from 54% to 96% for chest pain patients at a single facility.[11] Recurrent ED visits for chest pain are common, with up to 40% of patients returning to the ED for chest pain within 1 year.[12,13] The ED evaluation of patients with chest pain is further complicated by patients' varying degrees of prior diagnostic evaluations. Patients can also develop new or multiple contributing etiologies for recurrent or evolving symptoms, or symptom quality and character can fluctuate under the influence of psychosocial factors, without any progression of underlying physical disease. These factors create a diagnostic dilemma of particular importance for the emergency clinician. Clinical practice guidelines for the diagnosis and management of ACS exist, but neglect the preponderance of ED chest pain patients who are low risk, as well as the subset of those who present with recurrent chest pain.[14,15] The lack of guidelines specific to the ED population with recurrent chest pain reflects the diagnostic uncertainty associated with this condition and raises several critical questions including but not limited to (1) does a revisit represent a previously missed diagnosis; (2) does the revisit warrant an escalation in diagnostic approach; (3) what if the patient has already had what can be considered a recent, reasonable and thorough diagnostic evaluation; (4) and for how long is this prior evaluation valid? The objective of these guidelines is to provide an evidence-based framework intended to support patients, clinicians, and other health-care professionals in their decisions about the evaluation and management of patients with recurrent, low-risk chest pain in the ED.

SCOPE AND PURPOSE

The target audience includes all practicing ED clinicians (physicians and advanced practice providers) responsible for the evaluation and management of undifferentiated chest pain in community and academic settings, as well as healthcare systems and hospitals responsible for care pathways in this population.

METHODS

Group composition

The panel was composed of several geographically, ethnically, and gender diverse ED clinicians, a cardiologist, a patient representative and three methodologists. The Society for Academic Emergency Medicine (SAEM) provided financial support for the development of this guideline.

Group interaction and processes

Starting in May 2019, the panel met regularly through in-person, online, and telephone meetings. The methodologists attended a 3-day in-person Grading of Recommendations Assessment, Development and Evaluation (GRADE) training before the development of this guideline. Content experts were selected among known emergency medicine

(EM) physicians with relevant publications in the field. As a quality/trustworthiness check, the final manuscript was analyzed using the recently published AHRQ National Guideline Clearinghouse Extent of Adherence to Trustworthiness Standards (NEATS) instrument[16] to ensure best possible adherence to Institute of Medicine 2011 guideline trustworthiness standards (see Table S1). An introduction to the GRADE process of creating and weighting clinical recommendations was delivered to all panel members and it can be viewed at the following link. (https://drive.google.com/drive/folders/1ov_mmUZwFu752yKzuxKUWA_ycq6gH6lZ) (Figure 1).

Declaration and management of competing interests

The conflict of interest (COI) review group included one of the methodologists who reviewed, evaluated, and approved all disclosures. All members of the expert panel complied with the COI process for reviewing and managing conflicts of interest, which required disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. The assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The COI review group ensured that the majority of the panel and chair were without potential relevant (related to the topic) conflicts. The chair and all members of the team were determined to have no significant conflicts of interest by the SAEM Executive Board.

Selection of questions and outcomes of interest

Clinical questions were developed into a PICO format (Population, Intervention, Comparison, Outcomes) prior to the first panel meeting.[17] Panel members prioritized questions and patient-important outcomes such as 30-day major adverse cardiac events (MACE) defined as AMI, need for percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and death.

Evidence review and development of clinical recommendations

Data sources and search strategies—A comprehensive search of several databases from inception to August 16, 2019, limited to English language only, and excluding animal studies, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced medical librarian with input from the methodologists. Controlled vocabulary supplemented with keywords was used to search for studies on recurrent chest pain. The full search strategy is available in Appendix 1.

Screening and study selection—The database found 5252 articles. The titles and abstracts were reviewed independently and in duplicate in Phase 1 by the three methodologists. A total of 334 full-text articles from the search were retrieved and reviewed in triplicate in Phase 2. Forty-four additional articles were provided by content experts and

38 were included. See Figure 2 for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies.

The matched PICO articles were reviewed by an independent team to assess for feasibility for conduction of a systematic review. Most of the PICO questions had no relevant literature from the initial literature search that would provide an answer, and no systematic review was performed. A list of articles and reasons for exclusion is available in Appendix 2 through 6.

The studies included to inform these guidelines included systematic reviews, interventional studies and observational studies. For several interventions, no direct evidence was available, and indirect evidence was sought by all panel members. The panel either decided to include plausible indirect evidence and make a recommendation (e.g., from studies of low-risk chest pain with single troponin measurement instead of studies with a comparison arm with serial troponins) or to provide a short narrative discussion of the intervention.

Data collection and analysis—Data extracted from the available evidence included outcomes of AMI, MACE, mortality, health care use, and return ED visits. Where applicable, data were pooled using random effects model using RevMan™ or OpenMeta™. Risk of bias and certainty of evidence was assessed using the Cochrane risk-of-bias tools for randomized clinical trials (RCTs) and observational studies with modified domains used for assessing confounding bias, selection bias, and misclassification bias.[18] The certainty of evidence was assessed using the GRADE approach.[19] Within GRADE, the body of evidence across each outcome is assessed for domains that may reduce or increase one's certainty in the evidence and corresponding strength of recommendation. Factors that may reduce one's certainty include risk of bias (study limitations), inconsistency (unexplained heterogeneity across study findings), indirectness (applicability or generalizability to the research question), imprecision (the confidence in the estimate of an effect to support a particular decision) or publication bias (selective publication of studies). One's certainty in the evidence may be strengthened if the following considerations are present: large or very large magnitude of effect, evidence of a dose-response gradient, or opposing residual confounding. GRADE summary of findings tables were developed using the GRADEpro Guideline Development Tool (https://gradepro.org/).

Evidence to recommendations

The panel considered core elements of the GRADE evidence in the decision process, including certainty of evidence and balance between desirable and undesirable effects. Additional domains were acknowledged where applicable (feasibility, resource use, acceptability). For all recommendations, the expert panelists reached consensus. Voting rules were agreed on prior to the panel meetings for situations when consensus could not be reached. The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects. As per GRADE methodology, recommendations are labeled as "strong" or "conditional." The words "we recommend" indicate strong recommendations, and "we suggest" indicate conditional recommendations (Figure 3; Table 1).

Use of indirect evidence

A recommendation associated with a diagnostic question follows from an evaluation of the balance between the desirable and undesirable consequences of the diagnostic test or pathway. Ideally, evidence should come from a systematic review addressing the clinical question. Inferring from accuracy data that a diagnostic test or strategy improves a patient-important outcome usually requires access to effectiveness studies.[21,22] Alternatively, even with no effective treatment being available, using an accurate test may be beneficial if it reduces adverse effects, cost, or anxiety through excluding an ominous diagnosis or if confirming a diagnosis improves patient well-being from the prognostic information it imparts.[23]

The first Guidelines for Reasonable and Appropriate Care in the Emergency Department (GRACE-1) writing committee identified the eight questions summarized in Box 1.

In deriving those questions, the GRACE-1 writing committee used the following definitions:

Recurrent chest pain—This was defined as patients who have had a previous visit to an ED with chest pain that led to a diagnostic protocol for its evaluation that did not demonstrate evidence of ACS or flow-limiting coronary stenosis. This included two or more ED visits for chest pain in a 12-month period.

Low risk—Low risk was defined by HEART score <4 points[24–26] (and other scores validated in the ED setting such as the HEART pathway[2] or TIMI score[27]) for disease-related poor outcomes within 30 days all of which require an electrocardiogram (ECG) for risk stratification.

There are several key differences between the HEART score and the HEART pathway. The HEART score was developed as an easy-to-use, 0–10 score to risk stratify ED patients with chest pain. Use of the HEART score yields a ~2% MACE rate among patients with a low-risk score of 0–3.[25,26] In derivation work, the HEART score incorporated a single conventional (not high-sensitivity) troponin measure, and, although rare, patients with an elevated troponin level can have a low-risk score. In addition, the HEART score can indicate low risk in patients with acute ischemic changes on ECG or known CAD. Finally, the HEART score uses subjective criteria and is manually calculated, which decreases inter-physician reliability.[2] In contrast, the HEART pathway is an accelerated diagnostic protocol, which uses a modified-HEART (mHEART) score and serial troponin measurements. To be low risk by the HEART pathway, patients must meet all of the following criteria: a HEART score of 0–3, no troponin elevation on serial testing, no ischemic ECG changes, and no prior CAD (prior MI, CABG, or PCI). The HEART pathway replaces subjective components of the History and ECG components of the HEART score with objective binary questions and uses an algorithm to determine component scores. Implementation of the HEART pathway is associated with decreased hospitalizations and death and MI rates <0.5% among low-risk patients, which meets the international standard for ‘acceptable” clinical practice.[28,29] One important note: the term “low risk” in GRACE-1 refers specifically to the risk for ACS or MACE in ED patients with recurrent chest pain. Thus, clinicians should continue to maintain patient-specific pretest probability for other cardiopulmonary and non-

cardiac causes of chest pain such as aortic dissection, pulmonary embolism, pneumothorax, pneumonia, pancreatitis, and perforated peptic ulcer until adequately excluded to avoid anchoring bias and premature diagnostic closure.[30]

Expedited—This time period was defined as 3–5 days.

After synthesizing the evidence for each question in Box 1, the GRACE-1 writing committee used the GRADE Evidence to Decision Framework to formulate the recommendations summarized in Box 2. These represent reasonable and appropriate care with the understanding that individual clinicians should always use their clinical judgement in the application of these recommendations.

QUESTION 1

In adult patients with recurrent, low-risk chest pain, is a single troponin versus serial troponins needed for ACS outcomes within 30 days?

Summary of the evidence—There were no studies with direct evidence to answer this question. Additional searches for indirect evidence yielded no relevant studies that evaluated a single troponin in ED patients with recurrent chest pain with 30-day MACE outcome. Additional search for indirect evidence yielded nine studies[31–39] that evaluated a single troponin in ED patients with low-risk chest pain with 30-day MACE outcome. (Appendix 2) Nearly all of these studies evaluated the use of a single high-sensitivity troponin measurement, with only one small, single-center study evaluating a single conventional troponin measurement.[33] Thus, insufficient evidence exists to recommend for or against a single conventional troponin measurement in patients with recurrent, low-risk chest pain. High-sensitivity troponin assays measure cTn levels within the normal range in at least 50% of healthy individuals with high precision, defined as a coefficient of variance (CV) ≤ 10% at the 99th percentile.[40,41] Among the nine studies with indirect evidence, 72 out of 15,715 patients (0.5%) with low-risk chest pain had an AMI or MACE within 30 days (each of the 9 studies had variable definitions of normal troponin, for details please see appendix 2). These studies did not address the “recurrence” of chest pain, and it is possible that patients who are low risk with recurrent chest pain are likely to have even lower risks of AMI or MACE. Several additional studies were found with indirect evidence for the use of a single troponin in a mixed-risk group of ED patients with 30-day MACE outcomes; however, these studies did not address the question of recurrent chest pain or low-risk populations, so were not included (Table 2).

Benefits—The most substantial benefit to both patients and hospitals in performing a single troponin is shorter ED length of stay.[42] Patients are also spared serial phlebotomy, and hospitals may have lower healthcare costs by performing fewer troponin tests. These benefits were not addressed by the included studies.

Harms and burden—The harms are missed AMI and MACE that could potentially be diagnosed if serial troponins were drawn instead of a single troponin. We calculated the pooled incidence of 30-day AMI or MACE following a single, normal high sensitivity

troponin using indirect evidence as 3.4 per 1000 patients (95% confidence interval [CI] 2.0–4.8 per 1000) as shown in the Forest plot section of Appendix 2.

Decision criteria and additional considerations—Patients prefer shorter ED lengths of stay. Identifying AMI is essential for patients, clinicians, and policymakers. Patients with missed or delayed AMI diagnosis may develop complications such as conduction disturbances, arrhythmias, heart failure, myocardial rupture, ventricular aneurysm, pericarditis, and death. Clinicians may be subject to medical malpractice suits for missed or delayed diagnoses of AMI as AMI is one of the most common diagnoses in lawsuits against EM physicians.[8] Professional societies such as the American Heart Association (AHA) and European Society of Cardiology (ESC) currently differ in their guidelines for the use of a single troponin, with the AHA recommending serial troponins and the ESC providing an option for a single troponin to exclude AMI,[15,43,44] and physicians are using single conventional and high-sensitivity cardiac troponin testing in clinical practice.[45,46] These differences in guidelines likely reflect differences in the adoption of high-sensitivity troponin assays, which have been used internationally for nearly a decade but only approved for use in the United States in 2017. Despite the increased incorporation of high-sensitivity troponin into accelerated diagnostic protocols, the authors acknowledge that many EDs may currently only have access to conventional troponin at this time. Additionally, timing of chest pain onset relative to troponin testing was agreed to be an important criterion for using a single troponin strategy, as ESC guidelines recommend chest pain duration of at least 3 h from symptom onset to troponin testing.[44,47]

Conclusions and research needs—The use of a single troponin with result below a validated threshold appears to be sufficient to decrease the risk of AMI or MACE to a clinically acceptable threshold in patients with low-risk chest pain as measured by clinical prediction scores such as the mHEART score.

Recommendation 1: In adult patients with recurrent, low-risk chest pain, for >3 h duration we suggest a single, high-sensitivity troponin below a validated threshold to reasonably exclude ACS within 30 days. (Conditional, For) [Low level of evidence].

QUESTION 2

In adult patients with recurrent, low-risk chest pain, and normal or non-diagnostic stress testing within the last 12 months, does repeat stress testing versus no stress test have an effect on MACE within 30 days?

Summary of the evidence—The authors assessed literature pertaining to stress testing in general (both exercise and pharmacologic). There were no studies with direct evidence to answer this question. An additional literature search for indirect evidence focusing on stress testing for adult ED patients with non-high-risk chest pain, not necessarily recurrent and without recent testing specified, yielded two randomized studies.[48,49] Neither of these two studies used MACE as a primary outcome but did report on a similar, more broadly defined outcome termed “cardiac events” at 30 days. An additional literature search for indirect evidence focusing on outpatient stress testing for adult patients discharged from the ED after a visit for chest pain, not necessarily recurrent and without recent testing specified, yielded

one multicenter, retrospective study.[50] This study sought to compare the incidence of MACE at 30 days between patients who completed an outpatient stress test within 3 days, 4–30 days, or not at all.

Among the three studies with indirect evidence, zero out of 4906 ED patients (0%) with chest pain died at 30 days, while 91 out of 4906 patients (1.9%) experienced a non-fatal, significant cardiac event. These significant cardiac events included MI, ventricular fibrillation, acute pulmonary edema requiring intubation, cardiogenic shock, coronary revascularization (i.e. PCI or CABG), and significant CAD on coronary angiogram (Table 3).

Several additional studies were found with indirect evidence for the use of stress testing in a mixed-risk group of ED patients with chest pain.[51–54] However, these studies lacked a control group or were limited to patients under age 40. For these reasons, these studies were not included (Appendix 3).

Benefits—The potential benefit of stress testing for ED patients with recurrent, low-risk chest pain would be to identify intervenable CAD to reduce the incidence of MACE. The two randomized studies that indirectly addressed this question in a similar but not identical population of ED chest pain patients did not demonstrate a reduction in significant cardiac events (described above), including MACE, at 30 days.[48,49] The multicenter, retrospective cohort study evaluating the incidence of MACE at 30 days in patients who completed an outpatient stress test did not demonstrate any associated benefit of stress testing within 3 days, nor within 30 days, compared with not undergoing a stress test at all.[50]

Harms and burden—The harms of stress testing for ED patients with recurrent, low-risk chest pain include the potential for an allergic reaction, radiation exposure, procedural risks, and indirect harm from downstream testing and procedures. The burdens on the patient could include avoidable out-of-pocket expenses (depending on health insurance benefits); the inconvenience of time spent in the ED, observation unit, or hospital waiting for the test; psychological stress associated with false-positive test results; and additional burdens associated with downstream testing, such as coronary angiography. From a resource utilization perspective, stress testing in an observation unit led to greater total charges at 30 days as compared with direct discharge from the ED.[48]

Decision criteria and additional considerations—Additional considerations include the financial incentives around stress testing that may impact health systems and thus decision-making for this cohort of patients. Perceived medico-legal risk by ED clinicians may also promote the ordering of low-yield stress testing.[55] Patient preferences could also influence this decision since certain patients may only be reassured by repeat stress testing, while others may prefer to be discharged home after laboratory and ECG testing has reasonably excluded a myocardial infarction.[56] Thus, shared decision-making may be reasonable in this clinical scenario.[57] A majority (~85%) of men and women with potential ACS would accept a stress test if recommended by their physician and most preferred a stress test over cardiac catheterization.[58]

Different types of cardiac stress testing (e.g., exercise, pharmacological, nuclear, echocardiographic) exhibit different accuracies,[59] and thus a different type of stress testing or other evaluation modality such as coronary computed tomographic angiography (CCTA) or angiography may be considered if there is concern for false-negative results on a previous stress test. Although most included studies did not define all parameters for a normal or negative test, to be conservative we are defining a normal stress test as achieving target heart rate for an exercise test or an imaging test without ischemic ECG or imaging abnormalities. Similarly, if the previous stress test was deemed inadequate (as locally defined) or was ended prematurely, repeat stress testing may be considered.

Access to care is also a consideration since outpatient stress testing may be more difficult to obtain for certain patients based on socioeconomic factors.[60] Clinicians may be more likely to offer same-day stress testing or admission, hospital or observation, for patients who are at higher risk of loss to follow-up.

Conclusions and research needs—Although no studies directly addressed the exact PICO question above, the three studies included in this review indirectly addressed a similar question. Extrapolating from these studies' results, repeated provocative stress testing is unlikely to reduce the risk of MACE at 30 days in patients with recurrent, low-risk chest pain. Further research to answer this exact question would need to focus specifically on ED patients with recurrent, low-risk chest pain with normal stress testing within the last 12 months.

Recommendation 2: In adult patients with recurrent, low-risk chest pain, and a normal stress test within the previous 12 months, we do not recommend repeat routine stress testing as a means to decrease rates of MACE at 30 days. (Conditional, Against) [Low level of evidence].

QUESTION 3

In adult patients with recurrent, low-risk chest pain, is admission to the hospital versus stay in the ED observation unit versus outpatient follow up recommended for ACS outcomes within 30 days?

Summary of the evidence—No articles were available, and no indirect evidence was found.

Conclusions and research needs—The acceptable miss rate of ACS outcomes in patients who are deemed low risk is largely agreed to be <1%.[29] Healthcare costs associated with the ED evaluation of chest pain are significant and it may be worthwhile to consider that cost when making disposition decisions. The cost of admission for the evaluation of chest pain has been shown to be greater than that of evaluation provided in an observation unit with the most significant cost benefit associated with discharge from the ED.[61–63]

Recommendation 3: In adult patients with recurrent, low-risk chest pain, there is insufficient evidence to recommend hospitalization (either standard inpatient admission or observation

stay) versus discharge as a strategy to mitigate major adverse cardiac events within 30 days. [No evidence].

Note that there is no GRADE software evidence table for this question in the appendix due to lack of evidence.

QUESTION 4

In adult patients with recurrent, low-risk chest pain and a negative cardiac catheterization defined as less than 50% stenosis what is their risk of subsequent ACS and time to ACS?

Cardiac catheterizations are frequently performed procedures and are indicated for several reasons, including the diagnosis of coronary stenosis and occlusion in the setting of ACS. However, there are no clearcut guidelines for if and when catheterization should be performed in the setting of recurrent chest pain. There is variation in how often this procedure is performed, and even debate as to the appropriateness of these procedures in some cases.[64,65] In fact, some studies suggest that high rates of normal or negative diagnostic catheterizations indicate opportunities for improved patient selection for the procedure.[66] On an individual level, both patient and physician preferences influence the decision to undertake this procedure. Females are less likely to be recommended for cardiac catheterization by their physicians, and are also less likely to prefer this as a diagnostic test for their chest pain symptoms.[58,67] These factors may have contributed to the lack of direct evidence for this series of PICO questions.

Summary of evidence—The evidence informing this question is based on data from one meta-analysis and a few retrospective observational studies. Only the meta-analysis by Radico[68] (2018, 54 studies with 35,039 patients, 99,770 person-years and median follow-up 5 years) separately analyzed those patients with non-obstructive CAD (<50%) versus those with 0% stenosis (which is the next question addressed by this guideline). Statistical heterogeneity was high (I^2 = 93%) for studies with less-than-obstructive CAD patients. It should be noted that this meta-analysis included studies using both invasive cardiac catheterization (the topic of questions 4 and 5) as well as CCTA (the topic of question 6), thus each article in the meta-analysis was reviewed and we extracted the relevant articles using cardiac catherization for inclusion as evidence for this question (Table 4).

The incidence of all-cause mortality and MI was 1.32/100 person-years, (95% CI 1.02–1.62), meaning 1.32 cases are expected for 100 patients followed for 1 year, or 0.66 cases for 100 patients followed for 2 years.[69–73]

The other observational studies did not separately analyze those without any stenosis versus those with <50% stenosis.[69–73] The data available suggest that the likelihood of non-fatal MI or all-cause mortality within 5 years is very low in this group of patients with coronary stenosis between 1% and 49% (Appendix 4).

Benefits—The potential benefit of cardiac catheterization for ED patients with recurrent, low-risk chest pain would be to potentially detect a structural cause of chest pain. Stress testing and cardiac catheterization provide functional versus structural/anatomical

information regarding cardiac causes of chest pain. In addition, a cardiac catheterization allows for an intervention if a stenotic lesion is found. Finally, catheterization may provide some reassurance to the patient and provide the perception that their symptoms have been fully evaluated.[56]

Harms and burden—The harms of cardiac catheterization for ED patients with recurrent, low-risk chest pain include the potential for an allergic reaction to contrast, radiation exposure of fluoroscopy, procedural risks, and complications. These risks include bruising, bleeding, perforation, arrhythmias and contrast nephropathy, and very rarely, death. The burdens on the patient could include avoidable out-of-pocket expenses, travel time, and recovery time.

Conclusions and future research needs—The data available suggest that the likelihood of non-fatal MI or all-cause death within 5 years is low in this group. It is reasonable to avoid low-yield admission or inpatient observation for such patients and they could be referred for expeditious outpatient evaluations after discharge. Ongoing research is needed to follow outcomes in such patients, using standard definitions for the outcomes of interest (MACE, death) and timeframes for follow-up. Incorporating patient values, preferences, and equity considerations into such research is also important, as are the resource utilization issues with such lower-risk populations.[74]

Recommendation 4: In adult patients with recurrent, low-risk chest pain and non-obstructive (<50% stenosis) CAD on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, For) [Low level of evidence].

QUESTION 5

In adult patients with recurrent, low-risk chest pain and a negative cardiac catheterization defined as no coronary disease (0% stenosis) what is their risk of subsequent ACS and time to ACS?

Summary of evidence—The data available suggest that the likelihood of non-fatal MI or all-cause death within 5 years is very low in this group. The evidence informing this question is based on data from one meta-analysis, and a number of retrospective studies. Only the meta-analysis by Radico (2018, 54 studies, 35,039 patients, 99,770 person-years and median follow-up 5 years) separately analyzed those patients with non-obstructive CAD (<50%) versus those with 0% stenosis. It should be noted that this meta-analysis included studies using both invasive cardiac catheterization (the topic of questions 4 and 5) as well as CCTA (the topic question 6), thus each article in the meta-analysis was reviewed and we extracted the relevant articles using cardiac catherization for inclusion as evidence for this question (Table 5).

The incidence of all-cause mortality and MI was 0.52/100 person-years, (95% CI 0.34–0.71), meaning 0.52 cases are expected for 100 patients followed for 1 year, or 0.26 cases for 100 patients followed for 2 years. Statistical heterogeneity was moderate (I^2 = 64%) for studies of patients with normal coronary arteries. The other observational studies did not

separately analyze those without any stenosis versus those with <50% stenosis. (Appendix 4).

Benefits—The potential benefit of cardiac catheterization for ED patients with recurrent, low-risk chest pain would be to potentially detect a structural cause of chest pain. Stress testing and cardiac catheterization provide functional versus structural/anatomical information regarding cardiac causes of chest pain. In addition, a cardiac catheterization allows for an intervention if a stenotic lesion was found. Finally, catheterization may provide some reassurance to the patient and provide the perception that their symptoms have been fully evaluated.

Harms and burden—The harms of cardiac catheterization for ED patients with recurrent, low-risk chest pain include the potential for an allergic reaction to contrast, radiation exposure of fluoroscopy, procedural risks, and complications, as described previously. The burdens on the patient could include avoidable out-of-pocket expenses, travel time, and recovery time.

Conclusions and future research needs—Given the low 5-year rates of non-fatal MI and all-cause mortality in patients with a negative cardiac catheterization (0% stenosis), it is advisable to avoid low-yield admission or inpatient observation for such patients, and they could be referred for expeditious outpatient evaluations after discharge. Ongoing research is needed to follow outcomes in such patients, using standard definitions for outcomes of interest (MACE and death) and timeframes for follow-up. Incorporating patient values, preferences, and equity considerations into such research is also important, as are the resource utilization issues with such low-risk populations.[74]

Recommendation 5: In adult patients with recurrent, low-risk chest pain and no occlusive CAD (0% stenosis) on prior angiography within 5 years, we recommend referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, For) [Low level of evidence].

QUESTION 6

In adult patients with recurrent, low-risk chest pain and a negative coronary CT angiogram what is their risk of subsequent ACS and time to ACS?

Summary of the evidence—There were no studies with direct evidence to answer this question. Additional searches for indirect evidence yielded 18 relevant studies that evaluated the prognostic value of CCTA for predicting long-term coronary events in patients who had previously undergone CCTA for evaluation of potential ischemic symptoms. Data were derived from randomized trials evaluating CCTA versus standard of care or another imaging technique (stress myocardial perfusion imaging or stress echocardiography), ED observation studies, and registries that included patients who underwent CCTA for assessing patients with possible ischemic symptoms. In general, the studies excluded patients who had known coronary disease and those who had contraindications to CCTA such as renal failure and arrhythmias. Consideration as to how a “negative” CCTA is defined is important. Most studies separated results into those with normal scans (0% stenosis), and those with mild

stenosis (1%–49% stenosis). Assessing long-term outcomes is difficult, as almost all ED trials focused on outcomes based on the specific CCTA strategy used for evaluating low to intermediate-risk patients as opposed to reporting outcomes based on the degree of stenosis present on the CCTAs. Two studies that included patients who underwent outpatient evaluation for possible myocardial ischemia reported long term results. The CONFIRM Registry[75] reported that patients who had a normal (negative) CCTA were at very low-risk, with a rate of MI of 0.08%, all-cause mortality of 0.4%, and a MACE rate of 0.6% at a median of 2.1 years follow-up. Patients who had 1%–49% stenosis had corresponding event rates of 1.3%, 0.5%, and 2.4%, respectively. In the PROMISE Trial,[76] patients with a normal CCTA had a rate of cardiovascular death and MI of 0.3% during a median follow-up of 26 months. Those who had a mildly abnormal CCTA (1%–49% stenosis) had a corresponding event rate of cardiovascular death and MI of 1.6%.

In the PROMISE Trial, among the subset of 3800 patients who had a negative test, 8% subsequently underwent secondary noninvasive testing within 90 days of the CCTA, while 4% had coronary angiography.[76] However, the results of the secondary test results were not reported. These studies did not address the “recurrence” of chest pain; it would be expected that patients who are low risk with an initial negative ischemic evaluation, including CCTA, would likely have even lower risks of AMI or MACE than observed in CONFIRM and PROMISE (Table 6).

Benefits—The benefits of a negative ED CCTA are to accurately exclude 30-day MACE rates and decrease admission to the hospital or observation unit. Longer-term benefits are that patients who have a normal CCTA or one with only mild stenosis who return with recurrent symptoms do not require extensive ischemic evaluation, thereby reducing costs. The indirect evidence supports this benefit, as the risk for later MI and death is very low.

Harms and burden—The harms of ED CCTA are associated with possible contrast reactions as well as radiation exposure. Multiple epidemiological studies have shown an increased risk of breast, blood and thyroid cancers after a single computed tomography (CT) scan of the chest, especially in young persons. Longitudinal, population-based studies estimate that for every 10,000 CT scans done in patients under 40 years of age, approximately 35 will develop cancer.[77–83] This risk is increased with repeated CT scans, female sex and younger age.[83–85] At the patient level, one study has estimated a 0.07% increased lifetime risk of cancer for a single CT scan of the chest and a 0.12% increased lifetime risk of cancer for nuclear myocardial perfusion imaging.[86] Simulation modeling has estimated the life-time cancer risk for a standard CCTA to vary from 1 in 143 for a 20-year-old woman to 1 in 3261 for an 80-year-old man.[87] The burdens are higher charges and longer ED length of stay, compared to a no testing strategy, which likely exacerbate patient’s healthcare bills and ED crowding.

Decision criteria and additional considerations—Defining the optimal testing strategy for patients who had a prior negative CCTA who return with recurrent chest pain is important. Accurately identifying the time period during which a negative CCTA remains valid is also important.

Conclusions and research needs—Based upon indirect evidence, we do not recommend routine repeat evaluation other than a troponin and ECG for patients with recurrent, low-risk chest pain after a negative CCTA within 2 years. Additional research explicitly evaluating the risk of ischemic events in patients who have recurrent, low-risk chest pain after negative ischemic testing is important.

Recommendation 6: In adult patients with recurrent, low-risk chest pain and prior CCTA within the past 2 years with no coronary stenosis, we suggest no further diagnostic testing other than a single, high-sensitivity troponin below a validated threshold to exclude ACS within that 2-year time frame. (Conditional, For) [Moderate level of evidence].

QUESTION 7

In adult patients with recurrent, low-risk chest pain, what is the yield of depression and anxiety screening tools in healthcare use and return ED visits?

Summary of the evidence—With regard to depression screening, we were unable to identify any studies with direct evidence to answer this question. We were able to identify one study for inclusion to provide indirect evidence.[88] This prospective cohort study of low-to-moderate cardiac risk ED patients admitted to a chest pain observation unit showed an increased risk of chest pain recurrence among ED chest pain patients who screened positive for clinically significant depression (odds ratio [OR] 2.11; 95% CI 1.18–3.79), as well as increased ED return visits and increased healthcare use.[89] However, this study had a small sample size (n = 365). The depression screening tool used in this study was the validated 8-item Patient Health Questionnaire depression scale (PHQ-8), which has been shown to have a sensitivity and specificity for major depressive disorder in the general population of 100% and 95% respectively for a PHQ-8 score ≥10 along with a likelihood ratio of a positive test of 28.[89]

For anxiety screening, three studies were included to provide indirect evidence.[88,90,91] Each was a prospective observational cohort study of low-to-moderate risk chest pain patients evaluated in the ED or ED observational unit. One study[88] reported no increased risk of chest pain recurrence among patients with anxiety (adjusted OR 1.59; 95% CI 0.80–3.79), while another study[90] found increased risk of chest pain recurrence with an OR of 2.36 (95% CI 1.09–5.15). Regarding return ED visits, two studies[88,90] showed increased risk of ED return in patient screening positive for anxiety, while one study[91] showed no difference in return visits. Regarding overall healthcare use, one study[91] showed no significant difference among the two groups (18.2% vs. 24.8%) (Tables 7 and 8).

Kim et al. used the clinical anxiety scale (CAS),[92] a 25-item self-administered tool to determine anxiety symptoms over the 2 weeks prior to assessment with a cutoff score ≥30 as predictive of clinical anxiety. Musey et al. used the validated hospital anxiety and depression scale-anxiety subscale (HADS-A), which is a 7-item self-reported scale with a scoring range of 0–21 with a cutoff of ≥8 as borderline abnormal anxiety.[93] Finally, Schwarz et al. used the validated generalized anxiety disorder 7-item scale (GAD-7) to identify anxiety symptoms over the prior 2 weeks with scores ≥15 denoting severe anxiety.[94] (Appendix 5).

Benefits—These observational cohort studies demonstrated that screening for depression and/or anxiety in a population of ED patients with low-to-moderate risk chest pain uncovered a higher prevalence of clinically relevant depression and/or anxiety symptoms compared with what is seen in the general population.

Harms and burden—The screening tools used in these studies were all self-administered, and ranged in length from 7 to 25 questions depending upon the domain assessed. It is unclear if incorporating these screening tools into the clinical workflow would cause an undue burden to either the provider or patient. However, it should be noted that many departments and health systems already mandate screening of suicidal ideation, and, depending upon the screening tool used, may also screen for significant depression, as well. Moreover, these observational studies also provided no information as to what to do with this added screening information with respect to patient communication or disposition. It should be clearly stated that the presence of a mental health problem, in this case either depression or anxiety (to be discussed in question 8) does not minimize the risk that the patient under evaluation may be in the midst of a cardiac event. Indeed, there is evidence supporting the assertion that untreated anxiety and depression are independent risk factors for the development of CAD.[95–98] Additionally, impaired mental health, particularly post-traumatic stress disorder, depression, and anxiety are associated with increased mortality and poorer health outcomes in survivors of ACS.[99] Thus, when taking screening into account, clinicians will need to guard against premature closure and anchoring bias, which represent two types of cognitive error that can threaten patient safety by failing to consider potentially life-threatening etiologies of chest pain attributed to psychiatric causes.[30]

Decision criteria and additional considerations—Currently, our healthcare systems and EDs are encouraged by the Joint Commission to implement universal screening for suicidality, for all patients, irrespective of whether they are presenting with psychiatric complaints of suicidality.[100] This is an acknowledgment of the fact that it is well-established that undiagnosed or under-addressed psychological factors, such as anxiety and depression, are prevalent (possibly >40%) and may complicate or contribute directly to medical problems and somatic complaints.[101] However, it must be stated that the primary imperative of emergency medicine is to evaluate for and manage conditions that pose immediate threats of morbidity and mortality. Thus, of paramount relevance to EM providers is the notion that “EM should not take on any non-core initiatives until ED care itself is adequately resourced.”[102] Therefore, the barriers to screening for psychological conditions in some cases and ED environments are myriad: (1) optimal timing regarding when in the time course such screening is appropriate and whether it can or should occur in triage or in the treatment area; (2) what specific screening tool(s) should be used and how should they be administered (e.g., verbal, paper, electronic) and who should administer (e.g., self-administered, nursing personnel, social workers, ED providers); and (3) should screening be universal or triggered by an overt action such as a physician order?

Additionally, the decisions about how to deal with the results of screening results pose serious consideration (i.e. how are results provided to both clinicians and patients and how does this translate into the next step in care). There also must be an acknowledgment

of the role of gender and race in the historical context of labeling patients as hysterical in the case of females or under-diagnosis in the case of minorities.[103,104] Finally, it has been documented that ED providers do not often address these psychological issues even when informed, which may be a result of the lack of sufficient available resources, such as directed outpatient psychiatric follow-up.[105,106] Thus, there is a need to determine what the responsibility of the treating clinician is with regard to specifically addressing the screening results, especially in the landscape of medicolegal considerations. While individual providers are free to use their clinical judgment and pursue targeted screening for their patients, for the reasons outlined above, the decision to embrace a more comprehensive screening paradigm should be made at the level of the department where appropriate system resources should be coordinated to support such an effort.

Conclusions and research needs—Indirect evidence from a single site prospective observational study found increased chest pain recurrence, ED utilization, and healthcare use among patients screening positive for clinically relevant depression among a population of low-to-moderate risk chest pain patients. While indirect evidence from three studies found that, despite a high prevalence of clinically relevant anxiety among low-to-moderate risk chest pain patients, there are mixed results for this association with chest pain recurrence, ED utilization and healthcare use. To provide specific direct evidence to answer this question, prospective studies are needed which (1) include a measure of recurrent chest pain visits prior to enrollment; (2) include a clear description of ACS risk stratification in the ED and specifically include those with low-risk; (3) screen for the presence of clinically significant anxiety and depression at the time of enrollment using an instrument validated for use in the ED; and (4) assess specifically for outcomes of ED utilization and health care utilization (with a clear breakdown of the number of visits specifically for chest pain versus other reason for visit), as well as methods for determining chest pain recurrence which minimize recall bias.

Recommendation 7: In adult patients with recurrent, low-risk chest pain, we suggest depression and anxiety screening as these might have an effect on healthcare use and return ED visits. (Conditional, Either) [Very low level of evidence].

QUESTION 8

In adult patients with recurrent, low-risk chest pain, what is the role of referral for anxiety or depression in healthcare use and return ED visits?

Summary of the evidence—There were no studies to provide direct evidence for this question. However, there were two systematic reviews available to provide indirect evidence for this question. No additional studies were found. Kisely et al.[107] evaluated psychological interventions in 17 RCTs with 1006 participants for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. Interventions included cognitive behavioral therapy, relaxation therapy, hyperventilation control, hypnotherapy, and other psychotherapy/counseling. There was a reduction in reports of chest pain in the first 3 months following the intervention (relative risk [RR] 0.70; 95% CI 0.53–0.92). There was an increase in the number of chest pain-free days up to 3 months following the intervention

(mean difference [MD] 3.00; 95% CI 0.23–5.77) and reduced chest pain frequency (MD −2.26; 95% CI −4.41 to −0.12). There was no effect on the severity of chest pain (Table 9).

Wang et al.[108] evaluated antidepressants for symptomatic management of functional chest pain (defined as normal coronary angiography). The authors included seven RCTs of 319 patients. There was an association between antidepressants and pain reduction (standardized mean difference [SMD] −1.26; 95% CI −2.34 to −0.19) and psychological symptoms (SMD −0.87; 95% CI −1.67 to −0.08), as well as increased side effects (OR 0.34; 95% CI 0.15–0.78). There was no significant improvement in health-related quality of life (weighted mean difference 2.00; 95% CI −2.54 to −6.65) (Appendix 6).

Benefits—These systematic reviews of trials of psychological interventions in patients with nonspecific or functional chest pain (one looking at multi-component psychological interventions and one assessing an anti-depressant intervention) demonstrated a reduction in chest pain frequency and an improvement in psychological symptoms.

Harms and burden—The indirect evidence presented here is based upon interventions of which only a portion was initiated in the ED setting. Similar to the discussion of the addition of screening tools for anxiety and/or depression in PICO question 7, the effect of referral for behavioral or pharmacologic interventions on ED flow/throughput cannot be quantified. Thus, it is unclear if this step represents an undue burden to providers or patients; however, it should be noted that ED clinicians often make referrals for outpatient evaluation and management of non-emergent conditions which is similar to this. The adverse events associated with behavioral events were not assessed/reported; however, antidepressants were associated with an increased risk of non-serious side effects, such as drowsiness and fatigue.

Decision criteria and additional considerations—The decision to refer for management of anxiety and or depression in patients with low-risk chest pain is directly related to the discussion of additional considerations in PICO question 7 above. In summary of that discussion, while the decision to screen a particular patient is at the discretion of the clinical provider, initiation of broad-based screening in this population of interest is likely best operationalized, resourced, and backstopped at the level of the hospital or healthcare system. As such, the decision regarding how to handle the results of this screening should be operationalized in such a manner that there is consistency and ease of access. An example of a specific consideration would be what to do with a patient that screens positive for severe anxiety or depression. Should behavioral health or social work be notified automatically; can this happen independent of the provider; do discharge instructions automatically get populated with referral instructions to specific clinics or clinicians? Clearly, this topic and these determinations require system-level support and are affected by the local resources available.

Conclusions and research needs—Evidence suggests modest benefit for psychological interventions (particularly cognitive behavioral therapy) within the first 3 months after the intervention. Antidepressant medications might be associated with improvements in pain and psychological symptoms, but no difference in health-related quality of life. A number of significant questions remain unanswered and should be further

investigated, specifically in the population of patients with recurrent, low-risk chest pain. As a practical note, probably the most important question for ED clinicians aside from screening implementation is: how does patient receptivity and preference impact the referral for further behavioral health evaluation and intervention in this population? Is the current pragmatic access to mental health resources sufficient, or are more resources required for implementation? How does insurance status affect the ability to follow up as an outpatient? How does documentation of previously unrecognized depression impact malpractice risk? Are these psycho-behavioral interventions equivalent and interchangeable, or are there some recurrent chest pain subtypes that respond differently to various modalities? What effect does referral for anxiety and depression management have on patient perceptions of stress? Additional research to provide direct evidence on the numbers needed to treat and harm, cost-effectiveness, and healthcare disparities are of paramount importance.

Recommendation 8: In adult patients with recurrent, low-risk chest pain, we suggest referral for anxiety/depression management, as this might have an impact on healthcare use and return ED visits. (Conditional/Either) [Low level of evidence].

The GRADE Evidence to Decision Framework tables are located in Appendix 7.

GENER AL ISSUES NECESSARY FOR CORREC T INTERPRETATION AND IMPLEMENTATION OF RECOMMENDATIONS

Limitations

Given the topic of these guidelines, the panel rightly included ED clinicians, a cardiologist, a patient with lived experiences, and methodologists. However, stakeholders representing primary care, mental health, and the medicolegal perspective were not a part of this panel at its inception. It is possible that these perspectives may have provided further insight particularly with regard to the decision criteria and additional considerations sections for each question.

The NEATS analysis performed for this guideline is limited by a single assessment by a NEATS-experienced rater (SU), who is also part of this project Methods team, and was completed before distribution for external stakeholder/audience review. Ideally, future GRACE guideline draft manuscripts will be independently rated using NEATS, and feedback incorporated by panel writers when completing final manuscripts.

Assumed values and preferences

Limited data exist on patient preferences regarding the management of recurrent, low-risk chest pain. In the Chest Pain Choice multicenter trial, ED patients with low-risk chest pain had a better understanding of their risk of ACS, were less likely to agree to admission, and received fewer advanced cardiac imaging tests when a decision aid was used to explain their risk level and options for care.[109,110] Men and women are equally likely to prefer noninvasive over invasive evaluation and management for CAD, and the vast majority (85%) would accept their physician’s recommendation for stress testing. However, women and Black patients were less likely than men and non-Black patients to say they would

accept a physician's recommendation for cardiac interventions.[58] At 30-day follow up, women were less likely than men to receive any cardiac diagnostic testing and to undergo cardiac catheterization.[58] Taken together, these data highlight the importance of shared decision-making and considering patients' values and preferences in the ED management of low-risk chest pain.[74] Although the panel acknowledges that the method of communicating with patients about their chest pain was not evaluated as a specific PICO question, a patient information sheet (Appendix 8) was created in an effort to make our recommendations more accessible to the average ED patient. It was vetted by our patient representative. It could be useful as a dissemination tool, and could even be printed out and given to patients while they are in the ED.

Shared decision-making works best when there is equipoise in decisions and given how preference and value-sensitive many of these clinical decisions are, and since most of the recommendations fall into the conditional category, shared decision making should be considered when operationalizing these recommendations into practice. Specific steps to operationalize the implementation of these guidelines are beyond our scope. Suggestions include provider education on these recommendations, understanding of local resources available at each center including outpatient follow up, access to cardiology clinics, availability of stress testing, use of decision aids, etc. Furthermore, involving patients in their healthcare decisions has shown that patients prefer less invasive choices, with the potential to decrease costs and increase satisfaction. We created an accessible 1-page infographic for physician education and to facilitate shared decision-making conversations with patients at the bedside (Supplemental Material 2).

Plans for updating these guidelines

Evidence is constantly growing. These guidelines should be updated within 5 years, or when significant new relevant high-quality research requires reassessment and revision of the relevant recommendation(s). Adoption of these guidelines should be tailored to local policies and practices. Availability of cardiology consultation, stress test, CCTA and type of troponin test might differ in each hospital.

Monitoring criteria for audit/feedback of implementation

Based on the recommendations of this guideline being Conditional with Very Low/Low/Moderate levels of supporting evidence, we cannot offer monitoring criteria for audit/feedback purposes with prospective implementation of any/all of these recommendations at this time. Should future evidence and updates warrant a Strong recommendation for an intervention with High level supporting evidence, we will suggest potential monitoring/audit criteria at that time.

CONCLUSIONS

These guidelines outline and summarize the evidence and strength of GRACE recommendations regarding eight priority questions of interest to emergency clinicians, other healthcare professionals, patients, and policymakers with regard to the evaluation and management of patients with recurrent, low-risk chest pain seen in the ED. Direct evidence

for the selected priority questions in this population is lacking, which highlights areas which will benefit from further robust prospective investigation in this specific population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Information

This study was funded by the Society for Academic Emergency Medicine.

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BOX 1

Key questions

1 (P) In adult patients with recurrent, low-risk chest pain, (I) is a single troponin versus (C) serial troponins needed for (O) ACS outcomes within 30 days?

2 (P) In adult patients with recurrent, low-risk chest pain, and normal or non-diagnostic stress testing within the last 12 months, (I) does repeat stress testing versus (C) no stress test have an effect on (O) MACE within 30 days?

3 (P) In adult patients with recurrent, low-risk chest pain, is (I) admission to the hospital versus (C) stay in the ED observation unit versus (C) outpatient follow up recommended for (O) ACS outcomes within 30 days?

4 (P) In adult patients with recurrent, low-risk chest pain and a negative cardiac catheterization defined as less than 50% stenosis (E) what is their risk of subsequent ACS and time to ACS?

5 (P) In adult patients with recurrent, low-risk chest pain and a negative cardiac catheterization defined as no coronary disease (0% stenosis) (E) what is their risk of subsequent ACS and time to ACS?

6 (P) In adult patients with recurrent, low-risk chest pain and a negative coronary CT angiogram (E) what is their risk of subsequent ACS and time to ACS?

7 (P) In adult patients with recurrent, low-risk chest pain, (I) what is the yield of depression and anxiety screening tools in (O) healthcare use and return ED visits?

8 (P) In adult patients with recurrent, low-risk chest pain, (I) what is the role of referral for anxiety/depression in (O) healthcare use and return ED visits?

BOX 2

Recommendations

Recommendation 1:

In adult patients with recurrent, low-risk chest pain, for >3 h duration we suggest a single, high-sensitivity troponin below a validated threshold to reasonably exclude ACS within 30 days. (Conditional, For) [Low level of evidence].

Recommendation 2:

In adult patients with recurrent, low-risk chest pain, and a normal stress test within the previous 12 months, we do not recommend repeat routine stress testing as a means to decrease rates of MACE at 30 days. (Conditional, Against) [Low level of evidence].

Recommendation 3:

In adult patients with recurrent, low-risk chest pain, there is insufficient evidence to recommend hospitalization (either standard inpatient admission or observation stay) versus discharge as a strategy to mitigate major adverse cardiac events within 30 days. [No evidence].

Recommendation 4:

In adult patients with recurrent, low-risk chest pain and non-obstructive (<50% stenosis) CAD on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, For) [Low level of evidence].

Recommendation 5:

In adult patients with recurrent, low-risk chest pain and no occlusive CAD (0% stenosis) on prior angiography within 5 years, we recommend referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, For) [Low level of evidence].

Recommendation 6:

In adult patients with recurrent, low-risk chest pain and prior CCTA within the past 2 years with no coronary stenosis, we suggest no further diagnostic testing other than a single, high-sensitivity troponin below a validated threshold to exclude ACS within that 2-year time frame. (Conditional, For) [Moderate level of evidence].

Recommendation 7:

In adult patients with recurrent, low-risk chest pain, we suggest the use of depression and anxiety screening tools as these might have an effect on healthcare use and return ED visits. (Conditional, Either) [Very low level of evidence].

Recommendation 8:

In adult patients with recurrent, low-risk chest pain, we suggest referral for anxiety or depression management, as this might have an impact on healthcare use and return ED visits. (Conditional/Either) [Low level of evidence].

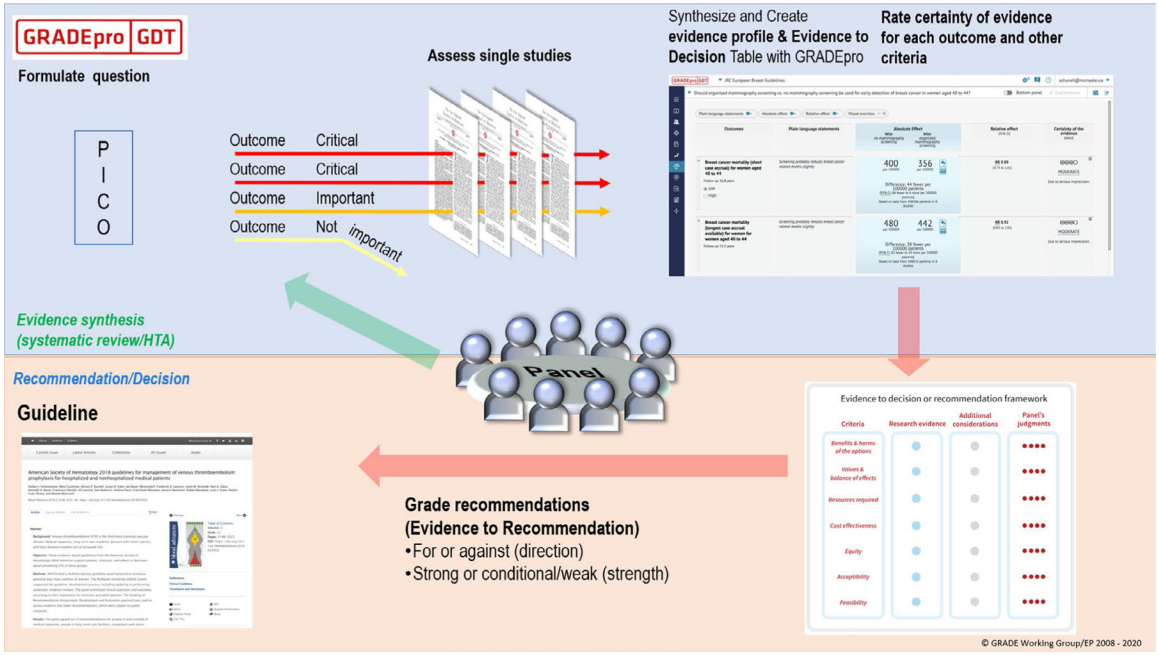

FIGURE 1.

A schematic view of the GRADE approach for synthesizing evidence and developing recommendations. The upper half describe steps in the process common to systematic reviews and making health care recommendations and the lower half describe steps that are specific to making recommendations including steps from panel members to make recommendations. *Reproduced with permission by the U.S. GRADE Network. GRADE, Grading of Recommendations Assessment, Development and Evaluation

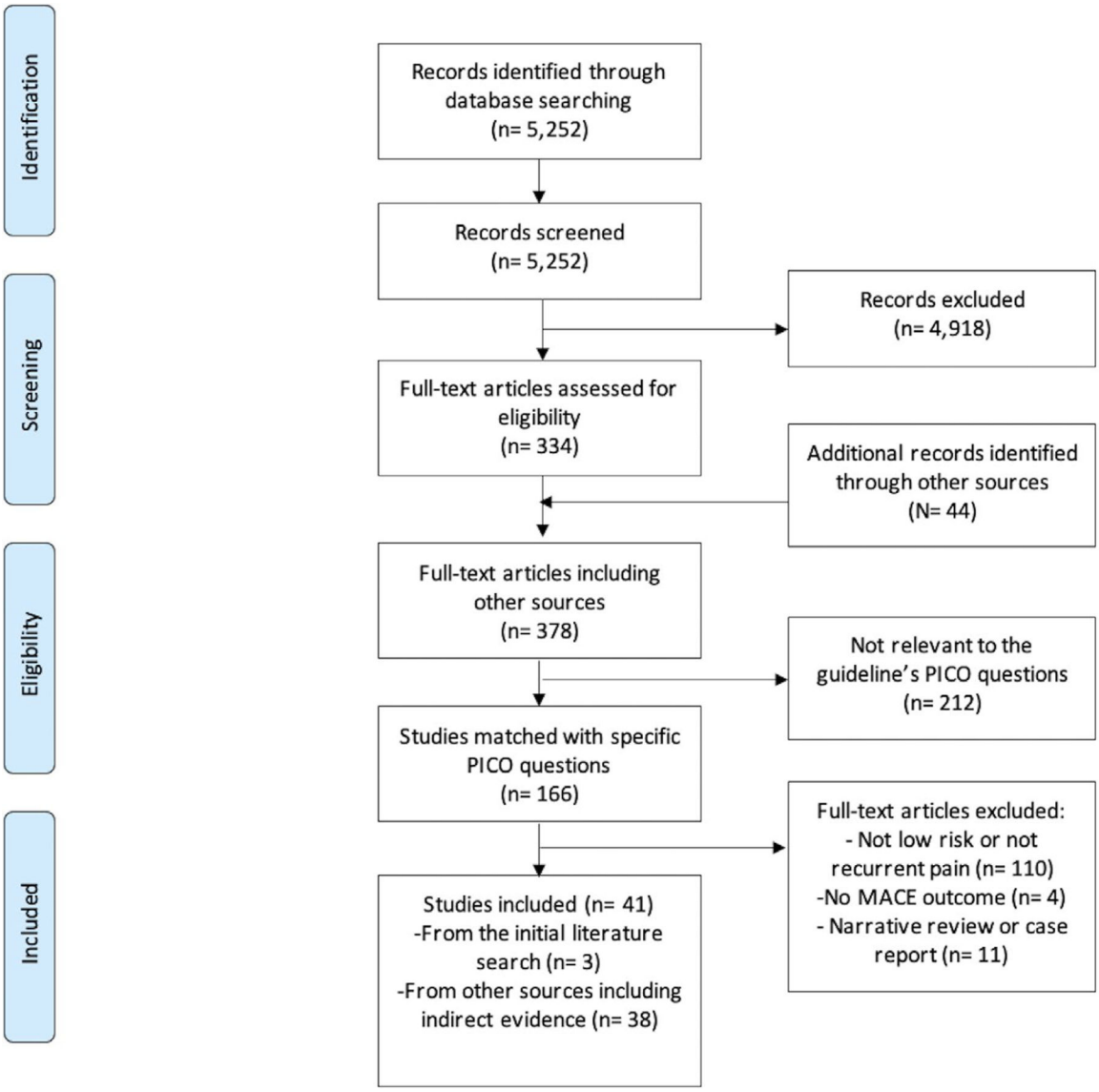

FIGURE 2.

PRISMA flow diagram of studies included in this clinical guideline on emergency department patients with recurrent, low risk chest pain

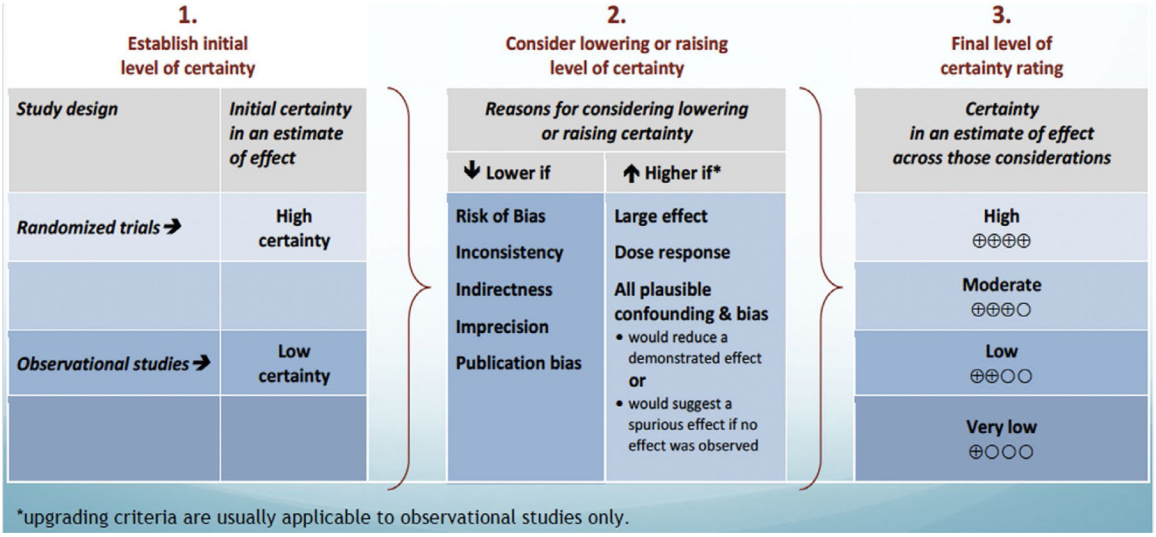

FIGURE 3.

Rating the quality of evidence using the GRADE methodology. *Reproduced with permission granted by the U.S. GRADE Network

TABLE 1

Interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers

Implications of strong and weak recommendations for different users of guidelines

	Strong recommendation	**Conditional Weak recommendation**
For patients	Most individuals in this situation would want the *recommended* course of action and only a small proportion would not.	The majority of individuals in this situation would want the *suggested* course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Note: Reproduced with permission from the GRADE Handbook.[20] https://gdt.gradepro.org/app/handbook/handbook.html#h.svwngs6pm0f2

TABLE 2

Evidence table for Question 1–In adult patients with recurrent, low-risk chest pain, is a single troponin versus serial troponins needed for acute coronary syndrome outcomes within 30 days?

Certainty assessment							No. of patients	Effect	Certainty	Importance
No. of Studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Single troponin**	**Outcome rate (95% CI)**		
9	Observational	Not serious[a]	Not serious	Serious[b]	Not serious	Strong association	72/15,717 (0.5%)[c]	3.4 per 1000 patients (2.0–4.8 per 1000)	⨁⨁◯◯ LOW	IMPORTANT

Abbreviation: CI, confidence interval.

[a]For guideline panels: The quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation. Guideline panels must make judgments about the quality of evidence relative to the specific context for which they are using the evidence.

[b]Studies do not compare single troponin versus serial troponin, but report the outcome of cohorts where a single troponin was measured with different negative thresholds.

[c]Outcome rate is 3.4 per 1,000 patients (95%CI 2.0 to 4.8 per 1,000)

TABLE 3

Evidence table for Question 2–In adult patients with recurrent, low-risk chest pain, and normal or non-diagnostic stress testing within the last 12 months, does repeat provocative stress testing versus no stress test have an effect on major adverse cardiac events within 30 days?

Certainty assessment							No. of patients		Effect			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Repeat provocative stress testing**	**No stress testing**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Death (follow up: 30 days)												
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	0/1056 (0.0%)	0/557 (0.0%)	Not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
Death (follow up: 30 days)												
1	Observational	Serious[a]	Not serious	Serious[a]	Not serious	None	0/2497 (0.0%)	0/796 (0.0%)	Not estimable		⨁⨁◯◯ LOW	CRITICAL
Cardiac event (follow up: 30 days)												
1	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	4/1004 (0.4%)	4/504 (0.8%)	OR 0.50 (0.13–2.00)	4 fewer per 1000 (from 7 fewer to 8 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Significant CAD												
1	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	36/1004 (3.6%)	15/504 (3.0%)	OR 1.20 (0.61–2.17)	6 more per 1000 (from 11 fewer to 33 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
MACE (follow up: 30 days)												
2	Randomized trials	Serious[b]	Not serious	Serious[a]	Not serious	None	27/2549 (1.1%)	5/849 (0.6%)	OR 1.81 (0.69–4.71)	5 more per 1000 (from 2 fewer to 21 more)	⨁⨁◯◯ LOW	CRITICAL

Abbreviations: CAD, coronary artery disease; CI, confidence interval; MACE, major adverse cardiac events; OR, odds ratio.

[a]Not recurrent low-risk chest pain and does not assess this outcome for those with previous stress testing within 12 months.

[b]One non-randomized interventional trial.

TABLE 4

Evidence table for Question 4–In adult patients with recurrent, low-risk chest pain and a cardiac catheterization with <50% stenosis what is their risk of subsequent acute coronary syndrome?

	Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
All-cause mortality and MI							
23[a]	Observational studies	Serious[b]	Very serious[c]	Not serious[d]	Not serious	Strong association	⨁⨁◯◯ Low
Non-fatal MI							
23	Observational studies	Serious[b]	Very serious[e]	Not serious	Not serious	Strong association	⨁⨁◯◯ LOW
All-cause mortality							
23	Observational studies	Serious[b]	Very serious[e]	Not serious	Not serious	Strong association	⨁⨁◯◯ LOW

Abbreviations: CT, computed tomography; MI, myocardial infarction.

[a] Median follow-up of 5 years (interquartile range 3–7 years; range 1–10 years)

[b] Most included studies were considered as high .risk of bias.

[c] The authors included studies using diagnostic angiograms as well as coronary CT angiograms. There was variable follow up from 1 to 10 years. Studies with follow up <1 year were excluded.

[d] Overall included population had higher cardiovascular risk (enough to require an angiography).

[e] I^2 = 91% very heterogeneous results.

TABLE 5

Evidence table for Question 5–Inadult patients with recurrent, low-risk chest pain and a negative cardiac catheterization defined as no coronary disease (0% stenosis) what is their risk of subsequent acute coronary syndrome?

	Certainty assessment						
No.of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
All-cause mortality and MI							
27	Observational studies	Serious[a]	Very serious[b]	Not serious[c]	Not serious	Strong association[d]	⨁⨁◯◯ LOW
Non-fatal MI							
24	Observational studies	Serious[a]	Very serious[e]	Not serious	Not serious	Strong association	⨁⨁◯◯ LOW
All-cause mortality							
24	Observational studies	Serious[a]	Very serious[e]	Not serious	Not serious	Strong association	⨁⨁◯◯ LOW

Abbreviation: MI, myocardial infarction.

[a]Most included studies were considered as high risk of bias.

[b]The authors included studies using diagnostic angiograms as well as coronary CT angiograms. There was variable follow up from 1 to 10 years. Studies with follow up <1 year were excluded.

[c]Overall included population had higher cardiovascular risk (enough to require an angiography).

[d]Median follow up was 5 years (interquartile range 3–7 years).

[e]I^2 = 91% very heterogeneous results.

TABLE 6

Evidence table for Question 6–In adult patients with recurrent low risk chest pain and a negative coronary computed tomography angiogram what is their risk of subsequent acute coronary syndrome/time to acute coronary syndrome?

Certainty assessment							No. of patients		Certainty
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**MACE**	**NO MACE**	
Coronary CT with no disease (follow-up 30 days to 2 years) MACE									
6	Observational	Serious	Not serious	Serious	Not serious	None	3	1444	⊕⊕⊕◯ MODERATE
Coronary CT with 1%–49% stenosis (follow-up 30 days to 2 years) MACE									
9	Observational	Serious	Not Serious	Serious	Not Serious	None	6	2377	⊕⊕⊕◯ MODERATE
Coronary CT with no disease (follow-up 30 days to 2 years) MACE									
2	Randomized trials	Not serious	Not serious	Serious	Not serious	None	2	468	⊕⊕⊕◯ MODERATE
Coronary CT with 1%–49% stenosis (follow-up 30 days to 2 years) MACE									
2	Randomized trials	Not serious	Not serious	Serious	Serious	None	1	828	⊕⊕⊕◯ MODERATE
Coronary CT with no disease (follow-up 2 years) MACE non-ED patients									
2	Observational	Serious	Not serious	Serious	Not serious	None	33	5679	⊕⊕⊕◯ MODERATE
Coronary CT with 1%–49% stenosis (2 years) MACE non-ED patient									
2	Observational	Serious	Not serious	Serious	Not serious	None	119	4382	⊕⊕⊕◯ MODERATE

Abbreviations: CT, computed tomography; ED, emerhency department; MACE, major adverse cardiac events.

TABLE 7

Evidence tables for Question 7–In adult patients with recurrent, low-risk chest pain, what is the yield of depression and anxiety screening tools in healthcare use and return ED visits?

Question 7a—What is the yield of depression screening for adult patients with recurrent low-risk chest pain

Certainty assessment							No. of patients		Effect		
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Depression**	**No Depression**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Healthcare use/30 day hospital return											
1[a]	Observational	Serious[b,c]	Not serious[d]	Serious[e]	Not serious	None	5/131 (3.8%)	0/234 (0.0%)	OR 19.60 (1.08–357.60)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Return ED visits											
1	Observational	Serious[b,c]	Not serious[d]	Serious[e]	Not serious	None	10/131 (7.6%)	0/234 (0.0%)	OR 37.50 (2.18–644.30)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Chest pain recurrence											
1	Observational	Serious[b,c]	Not serious[d]	Serious[e]	Not serious	None			OR 2.11 (1.18–3.79)	2 fewer per 1000 (from 4 fewer to 1 fewer)	⊕◯◯◯ VERY LOW
Healthcare use/primary care physician follow up											
1[a]	Observational	Serious[b]	Not serious	Not serious	Not serious	None	91/131 (69.5%)	151/234 (64.5%)	OR 1.08 (0.77–1.51)	17 more per 1000 (from 62 fewer to 88 more)	⊕◯◯◯ VERY LOW

Abbreviations: CI, confidence interval; ED, mergency department; OR, odds ratio.

[a] Kim et al.[88]

[b] Kim et al.[88]: Stratified by recurrent chest pain (CP) versus non-recurrent chest pain (NRCP) not by anxiety–depression screening status. Selection bias of subjects admitted to observation unit with low-mod risk (not all comers with CP). Excludes very low-risk CP. Self-reported chest pain recurrence. Potential recall bias.

[c] Depression/anxiety tools are self-administered questionnaires. 90% of recurrent and 84% of non-recurrent CP had anxiety.

[d] Inconsistency is low or not applicable when there is only one study involved.

[e] Kim et al.[88]: The population is adequate (recurrent low-risk chest pain) however the study is looking at association of depression with outcome and not at screening for depression, so it is more indirect evidence.

TABLE 8

Evidence tables for Question 7–In adult patients with recurrent, low-risk chest pain, what is the yield of depression and anxiety screening tools in healthcare use and return ED visits?

Question 7b—What is the yield of anxiety screening for adult patients with recurrent low-risk chest pain

Certainty assessment							No. of patients		Effect		
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anxiety**	**No Anxiety**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Healthcare use/PCP follow up											
1[a]	Observational	Serious[b]	Not serious	Serious[b]	Serious[c]	None	4/22 (18.2%)	32/129 (24.8%)	OR 0.73 (0.24–2.28)	54 fewer per 1000 (from 175 fewer to 181 more)	⊕◯◯◯ VERY LOW
ED return											
2	Observational	Serious[d]	Not serious	Not serious	Not serious	None			OR 3.22 (1.53–6.80)	3 fewer per 1000 (from 7 fewer to 2 fewer)	⊕◯◯◯ VERY LOW
Chest pain recurrence											
1[e]	Observational	Serious[f]	Not serious	Not serious	Serious[g]	None	38/56 (67.9%)	25/53 (47.2%)	OR 1.59 (0.80–3.79)	115 more per 1000 (from 55 fewer to 300 more)	⊕◯◯◯ VERY LOW

Abbreviations: CI, confidence interval; ED, emergency department; OR, odds ratio.

[a] Schwarz et al.[91]

[b] Schwarz et al.[91]: Outcomes divided by severe anxiety.

[c] Imprecision: The decision will differ across boundaries of the CI.

[d] Cohorts (anxiety/depression vs. not anxiety/depression) are comparable in all three studies and representative of the population of interest. The outcomes are mostly self-reported. Lost of follow up.

[e] Musey et al.[90]

[f] Musey et al.[90]: Follow up assessed by patient report and chart review. Potential recall bias.

[g] Musey et al.[90]: Follow up data available in only 109 subjects.

TABLE 9

Evidence table for Question 8–In adult patients with recurrent, low-risk chest pain, what is the role of referral for anxiety or depression in healthcare use and return emergency department visits?

Certainty assessment							No. of patients		Effect		
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Referral for anxiety/ depression**	**No Referral**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Psychotherapy interventions vs. control, any chest pain (follow up: 30 days)											
3	Randomized trials	Very serious[a,b]	Not serious	Not serious	Not serious	None	57/90 (63.3%)	76/82 (92.7%)	RR 0.70 (0.53–0.92)	278 fewer per 1000 (from 436 fewer to 74 fewer)	⊕⊕◯◯
Psychotherapy interventions vs. control, any chest pain (follow up: range 3)											
2	Randomized trials	Very serious[a,b,c]	Not serious	Not serious	Not serious	None	27/50 (54.0%)	57/61 (93.4%)	RR 0.59 (0.45–0.76)	383 fewer per 1000 (from 514 fewer to 224 fewer)	⊕⊕◯◯ LOW[d]
Psychotherapy interventions vs. control, chest pain frequency (follow up: 3 months)											
7	Randomized trials	Serious[a,b]	Serious[e]	Not serious	Not serious	None	154	140	–	MD 2.26 lower (4.41 lower to lower)	⊕⊕◯◯ LOW
Psychotherapy interventions vs. control, chest pain frequency (follow up: range 3–12 months)											
4	Randomized trials	Serious[a,b]	Not serious	Not serious	Serious	None	84	80	–	MD 0.81 lower (2.35 lower to 0.74 higher)	⊕⊕◯◯ LOW
Antidepressants vs. placebo, reduction of chest pain											
7	Randomized trials	Serious	Serious	Not serious	Not serious	None	161	158	–	MD 1.26 lower (2.43 lower to 0.13 lower)	⊕⊕◯◯ LOW

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio.

[a] In 10 studies there was a low-risk of random sequence generation and/or selection bias. In seven there was unclear risk for both of these biases. Due to the nature of the main interventions (counselling or CBT), it was not possible to blind the people delivering the treatment as to whether the participant was in the intervention or control arm. The SR considered all studies to be at high risk of performance and outcome assessment bias.

[b] One exception was van Beek et al., which assessed disease severity with the Clinical Global Inventory (CGI) rated by a blinded independent rater. Most studies did not discuss intention-to-treat (ITT) analysis, but most studies appeared to have analyzed data based on ITT analysis. We considered three studies to be at high risk of outcome bias because of a high loss or differential loss from baseline to follow-up. The other trials were at low-risk of bias for this domain. Two studies had unclear risk.

[c] There is significant differences in results between individual studies. High I^2 94%. Small sample studies.

[d] Decision will differ if the truth is in the lower versus upper boundary of the CI.

[e] Large heterogeneity I^2 94%.